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Combining Angiotensin Receptor Blockers With ACE Inhibitors in Elderly Patients

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Angiotensin-converting enzyme (ACE) inhibitors decrease mortality and cardiovascular events in patients with cardiovascular disease or high-risk diabetes and slow the progression of chronic kidney disease (CKD) in patients with proteinuria.^{1,2} Dual blockade of the renin-angiotensin pathway with ACE inhibitors in combination with angiotensin receptor blockers (ARBs) has a physiologic basis as standard doses of ACE inhibitors do not fully block the vasoconstrictor response to angiotensin II. Additionally, during long-term ACE-inhibitor therapy, increases in angiotensin II levels may occur, blunting efficacy.³ Accordingly, blockade of the angiotensin receptor can further decrease angiotensin II-induced vasoconstriction.

Two indications for combination therapy with ACE inhibitors and ARBs are prominently cited in the literature: heart failure and CKD with proteinuria.^{4,5} In patients with heart failure, several randomized controlled trials have shown that combination therapy, compared with ACE-inhibitor monotherapy, decreases cardiovascular morbidity.⁴ Conversely, ONTARGET (Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial), conducted in patients with vascular disease or diabetes with end-organ damage, suggested that combination therapy did not decrease death or cardiovascular events and also was associated with higher rates of adverse events, including hyperkalemia and acute kidney failure requiring dialysis.⁶ Although there is no definitive evidence that combination therapy improves clinically meaningful outcomes in patients with proteinuria, it is speculated to be beneficial in this setting based on a meta-analysis of small trials.⁵

When evidence from clinical trials is conflicting or incomplete, carefully designed observational studies can fill knowledge gaps about the comparative effectiveness of different treatment strategies. A recent study by McAlister et al,⁷ published in 2011 in the

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Commentary on McAlister FA, Zhang J, Tonelli M, Klarenbach S, Manns BJ, Hemmelgarn BR; on behalf of the Alberta Kidney Disease Network. The safety of combining angiotensin-converting-enzyme inhibitors with angiotensin-receptor blockers in elderly patients: a population-based longitudinal analysis. *CMAJ*. 2011;183(6):655-662.

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Canadian Medical Association Journal, evaluated the indications for and outcomes of combination therapy in elderly patients living in Alberta, Canada.

What does this Important Study Show?

Taking advantage of administrative data from a large provincial health care system, McAlister et al⁷ identified ~32,000 patients 66 years and older who received a new prescription for an ACE inhibitor, ARB, or both between 2002 and 2006. The investigators compared the incidence of doubling of serum creatinine level, initiation of long-term dialysis therapy, or death within 6 months of starting therapy and the incidence of hyperkalemia (serum potassium ≥ 6 mEq/L) in users of monotherapy versus combination therapy. Mean age of the study cohort was 76 years, and mean serum creatinine level was 1.1 mg/dL. Most patients (61%) received monotherapy with ACE inhibitors, 29% received monotherapy with ARBs, and 5% received combination therapy.

Their findings provide several useful insights about the real-world application of combination therapy. First, 86% of those prescribed combination therapy did not have heart failure or proteinuria, the 2 indications best supported by clinical trials. Prevalences of heart failure, diabetes, and albuminuria were similar between monotherapy versus combination-therapy users, although hypertension (64.4% vs 60.5%) and nephrotic-range proteinuria (6.7% vs 4.0%) were more common in combination-therapy users. Second, combination therapy was linked to a small but significantly higher risk of hyperkalemia, and there was no clear benefit in terms of mortality or progression of CKD. Specifically, combination therapy was linked to a 2-fold higher rate of the composite primary outcome of death, initiation of long-term dialysis therapy, or doubling of serum creatinine level (Table 1), and excluding the serum creatinine end point, combination therapy tripled the risk of death or initiation of long-term dialysis therapy. Third, and perhaps most importantly, combination therapy generally was short lived; only 12% remained on combination therapy for longer than 6 months, whereas most of the remaining patients switched to monotherapy. Curiously, most patients who discontinued combination therapy did not experience hyperkalemia or decreasing kidney function, suggesting that other factors influenced the decision to curtail treatment. Because the benefits take longer to accrue than the risks or adverse events, this prescribing pattern would suggest that many patients were exposed to the small but serious risks of combination therapy without having an opportunity to experience the potential benefits.

The analysis has several strengths, including the use of prescription data from a large comprehensive health care system, ascertainment of kidney outcomes over several years, and a “new-user” design that minimizes a potential bias in which sicker individuals who experience early adverse events are eliminated from the analysis. However, there also are some limitations. Because this was an observational study, it is possible that confounding by indication may still exist despite adjustment for multiple confounding factors. The higher prevalence of hypertension and nephrotic-range proteinuria in the combination-therapy group may support this possibility. Doses of each drug were not evaluated and other important outcomes were not studied, such as heart failure hospitalizations (the outcome

most consistently shown to improve with combination therapy), changes in albuminuria, or symptomatic hypotension.

How does this Study Compare with Prior Studies?

To place the findings by McAlister et al⁷ into context, it is useful to review the adverse-event and discontinuation rates reported in clinical trials of combination therapy. In a meta-analysis of combination therapy versus monotherapy in patients with acute or chronic left ventricular dysfunction, rates of discontinuation were 15% versus 11% in studies of chronic heart failure and 9% versus 8% in studies of myocardial infarction over an average of 2 years of follow-up.⁸ These investigators estimated that for every 1,000 patients with left ventricular dysfunction treated with combination therapy, 36 would experience hypotension, 8 would experience hyperkalemia, and 17 would experience an increase in serum creatinine concentration. However, higher rates of drug therapy discontinuation and adverse events associated with combination therapy in these clinical trials were tempered by an average 20% decrease in cardiovascular morbidity.⁴

In ONTARGET, rates of drug therapy discontinuation, hyperkalemia, hypotensive symptoms, and dialysis for acute kidney failure were higher for combination therapy versus monotherapy (Table 1).⁶ However, unlike previous heart failure trials, combination therapy did not decrease mortality and cardiovascular events or slow progression of kidney disease. Because it is speculated that patients with CKD may be more likely to benefit from combination therapy, the ONTARGET investigators tested this hypothesis in post hoc analyses; the findings were consistent with the main trial results. That is, in participants with CKD defined by the presence of albuminuria or low glomerular filtration rate (GFR; ie, <60 mL/min/1.73 m²), combination therapy did not decrease mortality or slow the progression of CKD.⁹ In participants with low GFR and macroalbuminuria, combination therapy was linked to a 63% higher risk of long-term dialysis therapy or doubling of serum creatinine level versus monotherapy (2.9 vs 2.2 events/100 person-years), whereas this risk was not significantly different from monotherapy for subgroups with GFR ≥ 60 mL/min/1.73 m² or those with normo- or microalbuminuria.

In sum, compared with previous clinical trials, combination therapy in elderly patients in Alberta, Canada, was linked to substantially higher rates of discontinuation, slightly higher rates of hyperkalemia, and no observed benefit with respect to mortality or progression of CKD. Two clinical trials are underway to examine whether combination therapy decreases proteinuria and slows CKD progression in patients with type 2 diabetes. The VA NEPHRON-D study ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00555217) identifier NCT00555217) plans to enroll 1,850 patients with type 2 diabetes and CKD accompanied by overt proteinuria (albuminuria with albumin excretion >300 mg/g), with the primary outcomes of time to decrease in estimated GFR by at least 50%, initiation of dialysis therapy, or death.¹⁰ A smaller open-label study also is underway in Italy (VALID; [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00494715) identifier NCT00494715).

What should Clinicians and Researchers do?

Is this an example of efficacious therapy that has been lost in clinical translation? Possibly so. When clinical trial results are translated into practice, some liberalization of the inclusion

criteria used in clinical trials is expected. However, if most patients do not have a recognized indication for therapy, this prompts questions about whether prescribing patterns represent educated clinical judgment or poor understanding of the evidence base. In the Alberta sample, rates of dialysis therapy and death were an order of magnitude lower than those observed in ONTARGET, suggesting that patients were less likely to benefit even if therapy was sustained.

Clinical practice guidelines can help synthesize and disseminate the evidence base; however, discrepancies among guidelines may promote confusion rather than clarity. For example, American Heart Association guidelines classify the addition of an ARB in patients with persistently symptomatic heart failure who are “already on conventional therapy” as a Class IIB recommendation (therapy may be considered based on evidence that suggests benefits may be greater than risk), whereas the Heart Failure Society provides a stronger Class IA recommendation.^{1, 11} The National Kidney Foundation's KDOQI (Kidney Disease Outcomes Quality Initiative) guidelines note that although combination therapy can be used with a goal of decreasing proteinuria or blood pressure, use of monotherapy is preferred.² Providing clearer recommendations about the indications and contraindications to combination therapy, dose titration and monitoring, and use of adjunctive therapies may help attenuate some of the risks and optimize tolerability. In particular, evidence-based strategies to minimize hyperkalemia and manage acute increases in serum creatinine concentration would be especially useful for clinicians.

However, we also might ask whether the evidence base before publication of ONTARGET could be extrapolated easily to clinical practice. In heart failure, clinical trials of combination therapy have enrolled patients an average of 10 years younger than the typical patient who is hospitalized with heart failure. CKD is present in >60% of patients with hospitalized heart failure, but in <30% of participants enrolled in combination-therapy clinical trials.¹² Trials often have close surveillance for adverse events, and run-in periods eliminate patients who are most prone to these events. Implementing these strategies in practice may be difficult except in closely monitored circumstances. Finally, when study outcomes are disease specific, such as cardiovascular hospitalizations or decrease in proteinuria, it becomes difficult to estimate the risks and benefits of therapies with the potential to decrease morbidity of one chronic condition, but at the expense of another. Clinicians in Alberta, Canada, may have considered these factors during their early experience using combination therapy and concluded that for most of their elderly patients, the benefits of combination therapy did not outweigh the risks.

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Table 1
Adverse-Event Rates Associated With ACEi and ARB Combination Therapy in
ONTARGET and the Alberta Study

Adverse Event	ONTARGET ⁶		Alberta Study ⁷	
	Monotherapy With ACEi or ARB	Combination Therapy	Monotherapy With ACEi or ARB	Combination Therapy
Discontinuation of therapy	23.0%-24.5%	29.3%	NR ^a	88%
Hyperkalemia ^b	0.6 events/1,000 patient-mo	1.1 events/1,000 patient-mo	0.9 events/1,000 patient-mo	2.5 events/1,000 patient-mo
Doubling of SCr, long-term dialysis, or death	13.5%	14.5%	2.7 events/1,000 patient-mo	5.2 events/1,000 patient-mo
Death	11.6%	12.5%		0.7% ^c
Long-term dialysis	0.3%	0.4%		0.06% ^c
Acute dialysis	0.2%	0.34%		NR

Note: Median follow-up was 56 months in ONTARGET. It was not reported in the Alberta study.

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; NR, not reported; ONTARGET, Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial; SCr, serum creatinine.

^a Median duration of therapy was 13 months for patients receiving monotherapy versus 3 months for patients receiving combination therapy.

^b Hyperkalemia was defined as serum potassium level >5.5 mEq/L in ONTARGET and >6 mEq/L in the Alberta study.

^c NR according to treatment group.