

## Combining angiotensin-receptor blockers with angiotensin-converting-enzyme inhibitors

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See related research article by McAlister and colleagues at [www.cmaj.ca/cgi/doi/10.1503/cmaj.101333](http://www.cmaj.ca/cgi/doi/10.1503/cmaj.101333).

In this issue, McAlister and colleagues looked at the safety of combining angiotensin-receptor blockers with angiotensin-converting-enzyme (ACE) inhibitors (combination therapy) using a retrospective cohort study.<sup>1</sup> The authors employed a central laboratory repository with linked administrative data to assess adverse drug effects.<sup>1</sup> They found that of the 1750 patients (5.4% of the study population) who received combination therapy, 86.4% did not have trial-established indications such as heart failure or proteinuria. Combination therapy, compared with ACE inhibitors alone, was associated with significant increases in renal dysfunction and hyperkalemia (serum potassium levels  $\geq 6.0$  mmol/L). Moreover, combination therapy was poorly tolerated, and 88.1% of patients who stopped it were given monotherapy instead.

Despite the limitations associated with analysing administrative data sets, McAlister and colleagues appropriately defined exposure and outcome variables, assessed temporal relationships and accounted for potential major confounding factors.<sup>1</sup> The strength of their observational study is its consistency with the adverse drug effects reported in clinical trials.

Activation of the renin–angiotensin–aldosterone system is a major neurohormonal driver of adverse cardiovascular and renal remodeling.<sup>2</sup> This results in significant increases in morbidity and mortality among patients with heart failure, chronic kidney disease and left ventricular dysfunction in the setting of acute myocardial infarction.<sup>2</sup> Treatment with ACE inhibitors is recommended based on several decades of scientific evidence that show significant reductions in morbidity and mortality, as well as the reversal of many of the deleterious effects of activation of the renin–angiotensin–aldosterone system.<sup>3–5</sup> However, subsequent increases in angiotensin-II levels (angiotensin-II reactivation) during prolonged treatment with ACE inhibitors (prevalence estimates of 18%–45% have been reported) may blunt the long-term efficacy of ACE inhibitors.<sup>6</sup>

Combination therapy may provide opportunities for adjunctive blockade of the renin–angiotensin–aldosterone system and a viable clinical alternative for certain patients.<sup>7–11</sup> The Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) pilot study compared the efficacy of combining candesartan (an angiotensin-receptor blocker) and enalapril (an ACE inhibitor) with monotherapy among patients with chronic heart failure ( $n = 768$ , mean left ventricular ejection fraction 27% and 48 weeks of follow-up).<sup>7</sup> The authors reported that there were no significant differences in mortality or morbidity and stated that larger trials were needed to assess the effects of combination therapy on major clinical outcomes.<sup>7</sup>

Several large clinical trials have been subsequently published affirming that combination therapy significantly reduces morbidity, but not mortality.<sup>8–11</sup> These benefits have been observed among patients with chronic heart failure,<sup>8,9</sup> patients with acute myocardial infarction complicated by symptomatic left ventricular dysfunction<sup>10</sup> and patients with chronic kidney disease.<sup>11,12</sup>

The magnitude of benefit has been summarized in several systematic reviews.<sup>11,12</sup> Kuenzli et

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### KEY POINTS

- Combining angiotensin-converting-enzyme (ACE) inhibitors with angiotensin-receptor blockers should be considered for patients with heart failure and reduced left ventricular ejection fraction who have persistent or progressive worsening of symptoms despite treatment with an ACE inhibitor and a  $\beta$ -blocker.
- McAlister and colleagues suggest that 5.4% of patients prescribed combination therapy do not have clear indications such as proteinuria or heart failure.
- Patients who receive combination therapy are more likely than patients who receive monotherapy to stop taking their medications because of adverse drug effects; these effects do not include overt renal dysfunction or hyperkalemia.
- Better risk-to-benefit assessment, appropriate patient selection and close clinical monitoring may preserve the long-term viability of combination therapy.

al. performed a systematic review using all available studies of combination therapy versus monotherapy in heart failure with or without acute myocardial infarction and found significant incremental reductions in admissions to hospital (relative risk [RR] 0.81 [95% confidence interval (CI) 0.72–0.91]).<sup>13</sup> In addition, the Ongoing Telmisartan Alone and in Combination with Ramipril Global End-point Trial, targeting patients with renal dysfunction, showed modest incremental renovascular protection with combination therapy versus monotherapy (RR 1.09 [95%CI, 1.01–1.18]).<sup>11</sup>

Using the scientific evidence available, the Heart Failure Society of America has given combination therapy a class 1A recommendation. The Society states that the addition of an angiotensin-receptor blocker should be considered for patients with heart failure due to reduced left ventricular ejection fraction who have persistent symptoms, or a progressive worsening of symptoms, despite therapy with an ACE inhibitor and a  $\beta$ -blocker.<sup>4</sup> Consensus recommendations for the use of combination therapy in other clinical settings are evolving, and clinical enthusiasm appears to be growing.<sup>3–5</sup>

Emerging concerns about the tolerability of, and the adverse drug events associated with, combination therapy may limit its prescription to certain patients.<sup>13–15</sup> A meta-analysis of pooled data from four of the largest clinical trials to study patients given combination therapy versus a control group given background treatment with an ACE inhibitor initially showed significant increases in the proportions of patients stopping treatment due to adverse drug events (11% v. 15%,  $p < 0.001$ ; number needed to treat [NNT] 25), worsening renal function (1.5% v. 2.4%,  $p < 0.001$ ; NNT 111), hyperkalemia (0.8% v. 1.6%,  $p < 0.001$ ; NNT 125) and symptomatic hypotension (2.4% v. 4.1%,  $p < 0.001$ ; NNT 59).<sup>14</sup> These findings have been confirmed in recently published reports.<sup>13,14</sup>

When should physicians prescribe combination therapy, to whom should it be given, and when should patients stop receiving it? First, prescribing decisions concerning combination therapy should be driven by clinical guidelines and knowledge of the potential risks of adverse drug effects. Second, the available evidence supports combination therapy for patients with symptomatic left ventricular dysfunction (despite optimal therapy with an ACE inhibitor or angiotensin-receptor blocker) and patients with proteinuria. Third, careful clinical monitoring coupled with identification of alternative causes of progressive renal dysfunction and hyperkalemia may provide more objective determi-

nants for withdrawal from combination therapy.

The study by McAlister and colleagues also showed that most of the patients who stopped taking combination therapy had relatively minor changes in their glomerular filtration rate and serum potassium levels.<sup>1</sup> This was despite the authors' projected estimates of a 0.52% monthly risk of adverse renal outcomes.<sup>1</sup> Data from four of the largest clinical trials to study combination therapy have shown that this strategy can be sustained for long periods when prescribed to eligible patients.<sup>13–15</sup> Therefore, a decline in renal function may not have been the primary reason for patients to stop taking their medications.

Persistent concerns among physicians about symptomatic hypotension and severe or life-threatening hyperkalemia affecting patients given combination therapy may be barriers to this regimen being prescribed clinically. Better risk–benefit assessments that include patient eligibility, appropriate clinical indications, tests for baseline renal function and determination of angiotensin-II levels during prolonged treatment with ACE inhibitors may improve patient selection. Knowledge of adverse drug effects and closer monitoring could reassure prescribing clinicians that combination therapy remains a viable option for certain patients.

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