

# Heart Failure: Is There a Role for Angiotensin II Receptor Blockers?

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## ABSTRACT

Angiotensin-converting enzyme (ACE) inhibitors are currently considered the mainstay of treatment for heart failure because of their effects in decreasing morbidity and mortality. However, up to 10% of patients with heart failure may be intolerant of ACE inhibitor therapy because of intractable cough caused by these agents. The use of angiotensin II receptor blockers (ARBs) is now emerging for the management of heart failure in such patients. A literature review was undertaken to assess the clinical evidence available on the use of ARBs in the treatment of heart failure. Comparisons of these agents with ACE inhibitors in heart failure are growing but still limited. In particular, the effect of ARBs on morbidity and mortality is not clear. A recent meta-analysis of 17 clinical trials did not reveal any superiority of ARBs over ACE inhibitors in reducing either mortality or admission to hospital among patients with heart failure. On the basis of preliminary evidence, ARBs may be used in patients with heart failure who are intolerant of ACE inhibitors because of cough. Further research is required to more clearly define the role of these agents in the management of heart failure.

**Key words:** angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, heart failure

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## RÉSUMÉ

Les inhibiteurs de l'enzyme de conversion de l'angiotensine (ECA) sont considérés actuellement comme la pierre angulaire du traitement de l'insuffisance cardiaque, parce qu'ils réduisent la morbidité et la mortalité. Cependant, jusqu'à 10 % des patients souffrant d'insuffisance cardiaque peuvent présenter une intolérance aux inhibiteurs de l'ECA, se manifestant par une toux rebelle. On a donc de plus en plus recours chez ces patients aux antagonistes des récepteurs de l'angiotensine II (ARA). Une revue de la littérature a été effectuée pour évaluer les données cliniques sur l'utilisation des ARA dans le traitement de l'insuffisance cardiaque. On trouve un nombre croissant, quoique limité, de données comparant ces agents aux inhibiteurs de l'ECA dans le traitement de l'insuffisance cardiaque. Plus précisément, les effets des ARA sur la morbidité et la mortalité ne sont pas clairs. D'ailleurs, une méta-analyse récente de 17 essais cliniques n'a pu démontrer que les ARA exerçaient un effet supérieur aux inhibiteurs de l'ECA sur la réduction de la mortalité ou des hospitalisations chez les patients atteints d'insuffisance cardiaque. Ces données préliminaires permettent de conclure que les ARA peuvent être utilisés chez les patients souffrant d'insuffisance cardiaque et qui présentent une intolérance aux inhibiteurs de l'ECA se manifestant par une toux. D'autres recherches sont nécessaires pour définir plus clairement le rôle de ces agents dans le traitement de l'insuffisance cardiaque.

**Mots clés :** inhibiteurs de l'enzyme de conversion de l'angiotensine, antagonistes des récepteurs de l'angiotensine II, insuffisance cardiaque

## INTRODUCTION

Heart failure affects more than 400 000 Canadians, with over 50 000 new cases occurring each year.<sup>1</sup> The 1-year mortality rate ranges from 25% to 40%.<sup>2</sup> An aging population, combined with improvements in survival after cardiovascular events, has contributed to the rising prevalence and incidence of heart failure.<sup>3</sup>

Angiotensin-converting enzyme (ACE) inhibitors are currently considered the mainstay of treatment for heart

failure because of their effects in decreasing morbidity and mortality.<sup>4</sup> These effects may derive from their ability to suppress neurohormonal activation in the renin-angiotensin-aldosterone system.<sup>4</sup> Direct inhibition of the angiotensin II type 1 receptor by angiotensin II receptor blockers (ARBs) carries the potential for additional benefits in the treatment of heart failure.<sup>4</sup> In addition, unlike ACE inhibitors, ARBs do not suppress the breakdown of bradykinin. This suppression may be



associated with intractable cough in up to 10% of patients with heart failure, because of the resulting increase in bradykinin levels.<sup>4</sup> Such intolerance may prevent the use of ACE inhibitors in these patients.

Six ARBs are currently approved for the treatment of hypertension in Canada: candesartan cilexetil (Atacand, AstraZeneca Canada, Mississauga, Ontario), eprosartan mesylate (Teveten; Solvay Pharma Inc., Markham, Ontario), irbesartan (Avapro; Bristol-Myers Squibb [Montreal, Quebec]/Sanofi-Synthelabo [Markham, Ontario]), losartan (Cozaar; Merck Frosst Canada Ltd, Dorval, Quebec), telmisartan (Micardis; Boehringer Ingelheim [Canada] Ltd, Burlington, Ontario), and valsartan (Diovan; Novartis Pharmaceuticals Canada Inc, Dorval, Quebec). Although none is yet approved for the treatment of heart failure in Canada, consensus guidelines suggest that ARBs may be considered an alternative in patients intolerant of ACE inhibitor therapy because of cough.<sup>2</sup> In the United States, valsartan was recently approved for the treatment of heart failure in patients intolerant of ACE inhibitors.<sup>5</sup>

Other pharmacological interventions for the management of heart failure include  $\beta$ -blockers, which have also been shown to reduce morbidity and mortality.<sup>2,4,6</sup> Spironolactone has shown similar benefits but only in patients with severe heart failure.<sup>2</sup> Diuretics are used to alleviate symptoms in selected patients, whereas digoxin may improve symptoms and reduce the need for hospital admission.<sup>2,7</sup>

Given the emerging interest in using ARBs as a therapeutic option in heart failure, a comprehensive literature search was conducted to assess the clinical evidence available on the use of ARBs for this indication. Databases searched included MEDLINE, EMBASE, Pascal, BIOSIS Previews, the Cochrane Library, and Pharmaceutical News Index. The National Library of Medicine's PubMed database was also searched to identify in-process citations and additional studies. Finally, trial registries such as the National Research Register and Current Controlled Trials were searched to identify ongoing trials. This article summarizes the findings of all major published clinical trials assessing the effect of ARBs in heart failure and attempts to define the role of these agents in the management of this condition.

## REVIEW OF THE EVIDENCE

The first long-term (48 weeks) clinical trial evaluating the use of an ARB in patients with heart failure was the Evaluation of Losartan in the Elderly (ELITE) trial, published in 1997.<sup>8</sup> Although this study was designed to compare the effects on renal function of losartan and

captopril in 722 elderly patients with heart failure, a statistically significant reduction in all-cause mortality was observed for patients receiving losartan. To further investigate this possible effect, another study was conducted.

The Losartan Heart Failure Survival Study ELITE II was similar in design to ELITE, but it had sufficient power to determine whether a survival benefit of losartan over captopril truly existed.<sup>9</sup> A total of 3152 patients with heart failure who had never received ACE inhibitor or ARB therapy were randomly assigned to receive either losartan or captopril; the mean follow-up period was 1.5 years. The primary endpoint was all-cause mortality, and the secondary endpoint was a composite of sudden cardiac death or resuscitation after cardiac arrest. In contrast to the results of ELITE, no significant differences between the losartan and captopril groups were found for the primary endpoint (280 deaths [17.7%] versus 250 deaths [15.9%]; hazard ratio 1.13, 95.7% confidence interval [CI] 0.95–1.35) or the composite secondary endpoint (9.0% versus 7.3%; hazard ratio 1.25, 95% CI 0.98–1.60).<sup>9</sup> Losartan was better tolerated than captopril in terms of discontinuation rates related to adverse effects, including cough. There were no significant differences in rates of heart failure, changes in blood pressure, or heart rate. However, the results failed to show any superiority of losartan over captopril in terms of mortality rate. This lack of superiority of losartan should not be interpreted as equivalence of losartan and captopril, in that this study was not designed to test equivalency or noninferiority.

The hypothesis that ARBs may provide additional benefit when combined with ACE inhibitors and other conventional heart failure therapies has been investigated in a number of short-term outcome trials.<sup>10</sup> Among these, the Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) pilot study, which investigated the effects of candesartan on physiological outcomes (e.g., exercise tolerance), had the longest analytic horizon (43 weeks).<sup>11</sup> This randomized, double-blind study had 3 treatment arms: candesartan alone, candesartan plus the ACE inhibitor enalapril, and enalapril alone. The combination of candesartan and enalapril appeared more beneficial for preventing left ventricular dilatation.<sup>11</sup> However, similar benefits in terms of neurohormonal changes were not observed. Although a larger decrease in plasma aldosterone concentrations was observed with the combination of candesartan and enalapril than with enalapril alone, there were no between-group differences in terms of changes in plasma norepinephrine or epinephrine concentrations. Also, plasma renin concentrations increased, with the smallest increase occurring with candesartan monotherapy.<sup>11</sup>



The Valsartan Heart Failure Trial (Val-HeFT) was the first study designed to measure morbidity and mortality rates in patients receiving an ARB combined with conventional heart failure therapy.<sup>12</sup> This randomized, double-blind, placebo-controlled trial was designed to assess the efficacy and safety of adding valsartan to conventional therapy in 5010 patients with heart failure. The 2 primary endpoints were all-cause mortality and the combined endpoint of all-cause mortality and morbidity. At baseline, 93% of all patients were receiving an ACE inhibitor, and 35% were on a  $\beta$ -blocker. At a mean follow-up period of 23 months, no significant difference in all-cause mortality was observed between the valsartan group (495 deaths, 19.7%) and the control group (484 deaths, 19.4%) (relative risk 1.02, 98% CI 0.88–1.18). However, the combined endpoint was significantly lower among patients receiving valsartan (723 events, 28.8%) than in the control group (801 events, 32.1%) (relative risk 0.87, 97.5% CI 0.77–0.97).<sup>12</sup> However, this effect was later determined to be largely driven by the 7% of patients not receiving an ACE inhibitor (hazard ratio 0.51, 95% CI 0.35–0.73); among patients using such therapy, the hazard ratio was 0.92 (95% CI 0.82–1.02).<sup>5</sup> The modest favourable trend in the group receiving an ACE inhibitor was mainly derived from the patients receiving less than the recommended dose, so there may be little further benefit in adding valsartan to an adequate dose of ACE inhibitor.<sup>5</sup> A recently published subgroup analysis<sup>13</sup> of the 7% of patients enrolled in the Val-HeFT study who were not receiving an ACE inhibitor reported benefit with valsartan in terms of all-cause mortality and combined mortality and morbidity, relative to placebo (17.3% versus 27.1%,  $p = 0.017$ , and 24.9% versus 42.5%,  $p < 0.001$ , respectively). Morbidity benefit included fewer hospital admissions for heart failure.<sup>13</sup> Finally, a *post hoc* subgroup analysis of the Val-HeFT trial found that among the 1610 patients who were being treated with both an ACE inhibitor and a  $\beta$ -blocker at baseline, the addition of valsartan was associated with an increase in mortality ( $p = 0.009$ ) and a nonsignificant trend toward an increase in the combined endpoint of mortality and morbidity ( $p = 0.10$ ).<sup>12</sup> It is not known if this was a reproducible effect or a chance occurrence.<sup>5</sup>

A recent meta-analysis combined data on all-cause mortality and hospital admissions related to heart failure from 17 clinical trials.<sup>10</sup> Most of the included trials assessed short-term endpoints such as left ventricular ejection fraction and exercise tolerance. In total, 12 469 patients and 5 ARBs (candesartan, eprosartan, irbesartan, losartan, and valsartan) were tested. The results indicated that ARBs are not superior to ACE inhibitors in reducing all-cause mortality or hospital admission for patients

with heart failure. Combination therapy involving an ARB and an ACE inhibitor carries the potential for additional benefits in terms of hospital admissions, but not in terms of mortality rate.<sup>10</sup>

## DISCUSSION

Evidence currently available on the use of ARBs in patients with heart failure is still limited and does not allow clear definition of a role for ARBs at this time. In particular, the effect of these drugs on mortality and morbidity is not clear. There is a possible exception in the case of patients with heart failure who cannot tolerate ACE inhibitors. Indeed, mortality and morbidity benefits observed in patients enrolled in the Val-HeFT study who were not using an ACE inhibitor<sup>13</sup> represent preliminary evidence supporting the use of ARBs as alternatives to ACE inhibitors in this specific subpopulation. However, this evidence is based on a small number of patients and is derived from a subgroup analysis. Furthermore, the subgroup analysis concerned a specific ARB, valsartan. Accordingly, further research is required to confirm the benefits of ARBs as a class in patients with heart failure who are intolerant of ACE inhibitors. Also, although substitution of ACE inhibitors with ARBs may be considered reasonable in the case of intolerance because of cough, such substitution in patients who have suffered an episode of angioedema induced by ACE inhibitors requires further assessment and should be done cautiously. This recommendation is based on the potentially life-threatening nature of angioedema, and the fact that although the occurrence of this condition is expected to be lower with ARBs than with ACE inhibitors, it might still occur.<sup>14</sup> Prior recommendations to use ARBs as substitutes for ACE inhibitors in patients with heart failure who were intolerant of ACE inhibitors were probably based on the effect of angiotensin II on the pathophysiology of cardiovascular disease.

Additional studies will also be required to confirm whether ARBs are in fact equivalent in effect to ACE inhibitors and whether the combination of an ARB and an ACE inhibitor carries additional benefit or harm, compared with either agent used alone, in the treatment of heart failure. Such studies would also better define the appropriate dosage, target population, and cost of therapy. Whereas dosing regimens in hypertension are well established, the optimal dosage of ARBs in heart failure has not yet been clearly defined. Losartan titrated to 50 mg once daily<sup>9</sup> and valsartan titrated to 160 mg twice daily<sup>12</sup> have been studied in clinical trials of heart failure. These dosing regimens translate into daily drug costs ranging from \$1.16 to \$2.22. By comparison, a regimen of the ACE inhibitor captopril



(generic product) at 50 mg 3 times per day costs \$1.68.<sup>15</sup> Two long-term trials are currently under way, the results of which are expected to be available later in 2003. The Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) trial is evaluating the role of candesartan in a broad spectrum of patients with heart failure (i.e., intolerant of ACE inhibitors, with or without systolic dysfunction),<sup>16</sup> whereas the Irbesartan in Heart Failure with Preserved Systolic Function (I-PRESERVE) study is comparing irbesartan with placebo in heart failure patients with preserved left ventricular function.<sup>17</sup>

## CONCLUSIONS

Evidence currently available on the use of ARBs in the treatment of heart failure, though growing, is still limited. The effect of these agents on mortality and morbidity is unclear. Preliminary evidence suggests that ARBs may be considered for patients intolerant of ACE inhibitors because of cough. However, further research is required to more clearly define the role of ARBs in the management of patients with heart failure. Until such evidence becomes available, ACE inhibitors will continue to be the mainstay of drug therapy in heart failure.

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