

## EDITORIAL



## ACE Inhibitors in Cardiovascular Disease — Unbeatable?

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The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET, NCT00153101), reported by Yusuf et al.<sup>1</sup> in this issue of the *Journal*, has important lessons for clinical practice and also illustrates the complexities of designing, conducting, analyzing, and interpreting trials comparing new treatments that act in a manner similar to that of established therapies. As the fourth and largest comparative trial, the ONTARGET study confirms, beyond doubt, that angiotensin-receptor blockers (ARBs) are not better than angiotensin-converting-enzyme (ACE) inhibitors at reducing fatal and nonfatal cardiovascular events. Of course, physicians and patients might still choose to use an ARB if it is as effective as an ACE inhibitor but better tolerated or less costly.

However, proving that one drug is as effective as another is extremely difficult from a statistical and regulatory perspective. The closest we can realistically get to this goal is to show “noninferiority,” a concept that sometimes worries physicians. One concern is the definition of the noninferiority “margin.” This margin can be thought of simply as the proportion of the benefit of the comparator gold-standard treatment — a benefit proved in at least one historical, randomized, placebo-controlled trial — that is retained by the new treatment.<sup>2,3</sup> The concern is that a common definition of noninferiority requires the preservation of as little as half this benefit. There are other concerns about noninferiority testing — for example, the assumption that the gold-standard comparator has the same effect in a contemporary group of patients as it had in the historical population. For this and other reasons, the design and analysis of noninferiority trials must follow rigorous criteria that differ from the usual in-

tervention-to-treat analysis of conventional, placebo-controlled, “superiority” trials.<sup>2,3</sup>

The ONTARGET study provides an example of a high-quality noninferiority trial. In this trial, Yusuf et al. show that telmisartan (at a target dose of 80 mg once daily) preserved 94% (95% confidence interval [CI], 83 to 105) of the benefit of 10 mg of ramipril daily, as reported in the Heart Outcomes Prevention Evaluation (HOPE) trial.<sup>4</sup> In a previous study with an almost identical design, the Valsartan in Acute Myocardial Infarction Trial (VALIANT), valsartan (at a dose of 160 mg twice daily) preserved 100% (95% CI, 60 to 139) of the putative benefit of 50 mg of captopril three times daily, as shown in a meta-analysis of three trials in patients with acute myocardial infarction.<sup>5</sup>

Of note, noninferiority was not confirmed in two other trials comparing losartan (at a dose of 50 mg once daily) with captopril (at a dose of 50 mg three times daily), findings that emphasize the importance not only of the drug selected but also of the dose and dosing interval.<sup>6,7</sup> In this context, the similar or greater reduction in blood pressure and the tendency toward more hypotension and renal dysfunction in patients receiving telmisartan and valsartan in both the ONTARGET and VALIANT studies suggest that the ARB regimen in these trials was at least as effective at inhibiting the renin-angiotensin system as the evidence-based regimen of the comparator ACE inhibitors.

Less important from a clinical perspective but of interest from a scientific one, the similar effectiveness of the two different types of drugs in preventing cardiovascular events also raises questions about the putative roles of bradykinin and the angiotensin II type 2 receptor in drug efficacy.<sup>8,9</sup>

The ONTARGET study is also the fourth trial comparing the effects of the combination of an ACE inhibitor and an ARB with those of an ACE inhibitor alone. The designs of the four trials differed in some crucial aspects. The VALIANT and ONTARGET studies added an ARB to an evidence-based dose of an evidence-based ACE inhibitor, whereas the other two studies — the Valsartan Heart Failure Trial and the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity-Added (CHARM-Added, NCT00634309) study — combined an ARB with the physicians' choice of the type and regimen of ACE inhibitor.<sup>10,11</sup> Of note, the last two trials were both carried out in patients with heart failure. The addition of an ARB to a full dose of an ACE inhibitor in the VALIANT study (80 mg of valsartan twice daily added to 50 mg of captopril three times daily) and the ONTARGET study (80 mg of telmisartan added to 10 mg of ramipril daily) was associated with additional adverse effects, including hypotension and renal dysfunction. However, despite the increased lowering of blood pressure, these combinations did not reduce the risk of cardiovascular events, as compared with an ACE inhibitor alone, a finding that merits further analysis and discussion.

In contrast, the addition of either 160 mg of valsartan twice daily in the Valsartan Heart Failure Trial or 32 mg of candesartan once daily in the CHARM-Added study to an ACE inhibitor reduced the risk of hospital admission for heart failure in both trials and decreased mortality from cardiovascular causes in the CHARM-Added study. Whether this difference was due to the condition studied (heart failure) or the type or regimen of ACE inhibition is uncertain, although there is evidence from a retrospective analysis of the CHARM-Added study that the combination of an ARB with a full-dose ACE inhibitor is of benefit to patients with heart failure.<sup>12</sup>

In summary, both the ONTARGET and the VALIANT studies show that telmisartan and valsartan provide a benefit similar to that of a proven ACE inhibitor. However, because ARBs are more costly than ACE inhibitors and have more side effects, their primary value is as an alternative for patients who cannot tolerate ACE inhibitors because of cough. The addition of an ARB to an ACE

inhibitor has no benefit and causes an increased number of adverse events in patients with arterial disease but seems to be beneficial in patients with heart failure, although the trials in heart failure did not test the addition of an ARB to a full dose of a proven ACE inhibitor.

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