



# Critical Appraisal

## Heart attack patients with complications

### *Treat with valsartan, captopril, or both?*

Anne Nguyen, PHARM D Sudheer Sharma, MD, FRCPC

Pfeffer MA, McMurray JJ, Velazquez EJ, Rouleau JL, Kober L, Maggioni JA, et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med* 2003;349(20):1893-906. Erratum in: *N Engl J Med* 2004;350(2):203.

### Research question

Should patients with acute myocardial infarction (MI) complicated by heart failure (HF) or left ventricular systolic dysfunction (LVSD) be treated with valsartan, captopril, or both for better survival?

### Type of article and design

Randomized, double-blind, multicentre trial. Superiority trial and noninferiority trial. Noninferiority trials aim to demonstrate that new treatments are not worse than existing ones.

### Relevance to family physicians

Angiotensin-converting enzyme (ACE) inhibitors have been shown to reduce death and major cardiovascular events after MI in patients with HF or LVSD, and have been the mainstay of therapy.<sup>1</sup> Angiotensin-converting enzyme inhibitors do not completely block production of angiotensin II; angiotensin receptor blockers (ARBs) block angiotensin II action at the AT<sub>1</sub> receptor directly. Only one trial has evaluated use of ARBs after MI with HF; it failed to demonstrate the benefit of ARBs

over ACE inhibitors.<sup>2</sup> Hence, until another trial proves otherwise, ARBs are second-line therapy for patients after MI with HF or LVSD and are reserved for those unable to tolerate ACE inhibitors.

### Overview of study and outcomes

The VALsartan In Acute myocardial iNfarcTion (VALIANT) trial was designed to compare survival rates of patients with acute MI complicated by HF or LVSD. Patients were recruited from 931 centres in 24 countries; Canada had the third highest enrolment with 65 sites.<sup>3</sup> Eligible subjects had had acute MIs (between 12 hours and 10 days before) complicated by HF (clinical or radiologic signs), LVSD (evidence on echocardiography, angiography, or radionuclide ventriculography), or both. Patients were excluded if they had been previously intolerant of ACE inhibitors or ARBs, had clinically significant valvular disease, or had diseases known to limit life expectancy severely. Patients were randomized to one of three arms. All medications were taken by mouth.

- Valsartan: start at 20 mg once daily and titrate to 160 mg twice daily at 3 months;
- Valsartan plus captopril: start at 20 mg of valsartan plus 6.25 mg of captopril once daily and titrate to 80 mg of valsartan twice daily and 50 mg of captopril three times daily at 3 months; or
- Captopril: start at 6.25 mg once daily and titrate to 50 mg three times daily at 3 months.

Dr Nguyen is a pharmacist at the British Columbia Community Drug Utilization Program ([www.cdup.org](http://www.cdup.org)) and at Lions Gate Hospital in Vancouver. Dr Sharma is a cardiologist at Lions Gate Hospital.

## Critical Appraisal

Data were processed and managed independently of the sponsor (Novartis Pharmaceuticals). Analyses were performed independently but verified by the sponsor.

### Results

Of 14 703 patients randomized to three arms, 4989 were given valsartan, 4885 were given valsartan plus captopril, and 4909 were given captopril. Patients were on average 64.8 years old (25% were older than 74), white, and had a mean body mass index of 27.3 kg/m<sup>2</sup>; 31.1% were women.<sup>3</sup> Cardiac risk factors included hypertension (55.1%), diabetes mellitus (23%), hyperlipidemia (29.9%), and current smoking (31.8%).<sup>3</sup> Median number of days from MI to randomization was 4.9.<sup>3</sup> Median duration of follow up was 24.7 months.

For the primary end point, mortality, the three regimens were equally effective. For the secondary end point, death from cardiovascular causes, recurrent MI, or hospitalization for HF, no differences appeared when both valsartan groups were compared with captopril alone. A post hoc analysis for hospitalization rates for either MI or HF revealed a difference between the valsartan plus captopril group and the captopril only group in proportion of patients (17.1% vs 19.3%,  $P < .05$ , number needed to harm [NNH] 46) and number of admissions (1297 in the valsartan plus captopril group vs 1437 in the captopril group,  $P < .05$ ). These results can generate hypotheses.

For the noninferiority analysis, valsartan met criteria for noninferiority to captopril.

Cough has always been a reason to consider switching patients from ACE inhibitors to ARBs. Although data from this study support this, the number of people *able* to tolerate ACE inhibitor cough is surprisingly higher than would be suspected clinically. Proportions of patients with cough resulting in dose reduction were 1.7% for valsartan and 5.0% for captopril ( $P < .05$ , NNH 30).

Proportions of patients with cough requiring discontinuation of drug were 0.6% for valsartan and 2.5% for captopril ( $P < .05$ , NNH 53). Interestingly, renal conditions also led to more decreases in dose of valsartan than of captopril (4.9% vs 3.0%,  $P < .05$ , NNH 53). Incidence of drug discontinuation for any reason was highest in the combination arm compared with captopril (9.0% vs 7.7%, NNH 77) and lower with valsartan than captopril (5.8% vs 7.7%, NNH 53).

At 1 year, drop-out rates were 15.3% for valsartan, 19% for valsartan plus captopril, and 16.8% for captopril. Discontinuation of treatment was highest among those in the combination arm and lowest among those taking captopril (23.4% vs 21.6%,  $P < .05$ , NNH 56).

### Analysis of methodology

This trial had sufficient power to detect a difference for the primary end point, mortality. We can have confidence in these results. So why was there a noninferiority trial?

With increasing data showing benefit of using ACE inhibitors for patients' post-MI complications of HF or LVSD, it is unethical to conduct placebo-controlled trials. When comparing active treatments (eg, ACE inhibitors versus ARBs), large patient populations are usually required to provide enough power to demonstrate a difference. It is not always feasible to conduct trials with a large sample size; in this case, it was. These authors wanted to ensure that, if valsartan was not demonstrably superior to captopril, it could at least be proven not inferior. They were able to do this by using both intention-to-treat analysis (ie, including all patients) and per-protocol analysis (ie, including patients who met inclusion criteria and who had received at least one dose of study medication).

The companion editorial suggests that the dose of valsartan was not high enough to be effective compared


with the dose of captopril, and the authors cite other trials that favoured ACE inhibitors because doses of ARBs were inadequate.<sup>4</sup> Interestingly, the 2003 *Compendium of Pharmaceuticals and Specialities* (CPS) lists the maximum dose of valsartan at 160 mg by mouth *daily* (for hypertension). The VALIANT study used a dose double that, and mortality benefits were similar to mortality benefits from ACE inhibitors.

### Application to clinical practice

Therapy is usually chosen based on efficacy, toxicity, and cost. There was no difference in efficacy. Combination therapy is thus unnecessary and leads to more drug discontinuation due to adverse effects. This result conflicts with results of the CHARM-Added trial supporting combination therapy with an ACE inhibitor and an ARB<sup>5</sup>; however, CHARM-Added was for patients with HF, not patients who have had acute MIs complicated by HF. The CHARM-Added trial used candesartan at a target dose of 32 mg once daily, which is also double the CPS's recommended dose for hypertension. Compared with ACE inhibitors, there are fewer discontinuations with ARBs because there are fewer adverse effects.

For patients able to tolerate the doses recommended in the VALIANT trial, monthly cost is approximately \$76 for valsartan and \$59 for captopril. Although this trial used specific agents, practically speaking, clinicians tend to consider ACE inhibitors and ARBs to have a class effect.

### Bottom line

- This trial does not change current clinical practice, but we now have evidence to support what we have been doing all along.
- For patients who have had acute MIs complicated by HF or LVSD and who cannot tolerate ACE inhibitors, we now have data to support use of ARBs. 

### Points saillants

- Cette étude ne conclut pas qu'il faille changer la pratique clinique actuelle, mais nous avons maintenant les données scientifiques à l'appui de ce que nous avons toujours fait.
- Pour les patients souffrant d'un infarctus du myocarde aigu compliqué par une insuffisance cardiaque ou une dysfonction systolique ventriculaire gauche et qui ne tolèrent pas les inhibiteurs de l'enzyme de conversion, nous avons maintenant des données appuyant le recours à des bloqueurs des récepteurs de l'angiotensine.

### References

1. Flather MD, Yusuf S, Kober L, Pfeffer M, Hall A, Murray G, et al. Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. ACE-Inhibitor Myocardial Infarction Collaborative Group. *Lancet* 2000;355:1575-81.
2. Dickstein K, Kjekshus J. Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomised trial. *Lancet* 2002;360:752-60.
3. Velazquez EJ, Pfeffer MA, McMurray JJ, Maggioni AP, Rouleau JL, Van de Werf F, et al. VALsartan In Acute myocardial iNfarctiOn (VALIANT) trial: baseline characteristics in context. *Eur J Heart Fail* 2003;5(4):537-44.
4. Mann DL, Deswal A. Angiotensin-receptor blockade in acute myocardial infarction—a matter of dose [editorial]. *N Engl J Med* 2003;349(20):1963-5.
5. McMurray JJ, Ostergren J, Swedberg K, Granger CB, Held P, Michelson EL, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. *Lancet* 2003;362:767-71.

**Critical Appraisal reviews important articles in the literature relevant to family physicians. Reviews are by family physicians, not experts on the topics. They assess not only the strength of the studies but the "bottom line" clinical importance for family practice. We invite you to comment on the reviews, suggest articles for review, or become a reviewer. Contact Coordinator Michael Evans by e-mail michael.evans@utoronto.ca or by fax (416) 603-5821.**