

VALIANT trial results support use of valsartan in acute myocardial infarction*

The Valsartan in Acute Myocardial Infarction (VALIANT) study results, announced last week at the American Heart Association Meeting, confirmed the value of using valsartan (Diovan®) in early post-MI heart failure or left ventricular dysfunction, while also adding additional pharmacological insights into this acute cardiac condition.^{1,2}

The VALIANT trial that started in 2000 compared the effects of the angiotensin receptor blocker valsartan, the ACE inhibitor captopril, and the combination of valsartan and captopril, in a population of high-risk patients with clinical or radiological evidence of heart failure, evidence of left ventricular systolic dysfunction, or both, after acute myocardial infarction. South Africa participated in the trial, contributing 58 patients to the total of 14 808 patients.

Captopril (titrated to 50 mg three times daily) and valsartan (titrated to 160 mg twice daily) were given from within 12 hours to 10 days after myocardial infarction. The combination used was valsartan titrated to 80 mg twice daily and captopril titrated to 50 mg three times daily.

During a median follow-up of 24.7 months, mortality from any cause was 19.9 per cent in the valsartan group, 19.5 per cent in the captopril group and 19.3 per cent in the valsartan and captopril group. The hazard ratio for death in the valsartan group, compared with the captopril group was 1.00 (97.5 per cent confidence interval, 0.90 to 1.11; $p = 0.98$), and the hazard ratio for death in the valsartan and captopril group, compared with the captopril group was 0.98 (97.5 per cent confi-

dence interval, 0.89 to 1.09; $p = 0.73$). The trial showed that valsartan was at least as good as captopril when overall mortality and the composite end point of fatal and non-fatal cardiovascular events were examined (Fig. 1).²

The lack of observed difference in benefits achieved with ACE inhibition and with angiotensin II blockade does not imply there was none. This debate is taken up in the interviews with Dr Anthony Dalby, Cardiologist in private practice, Johannesburg, and Dr John McMurray of the University of Glasgow, Scotland.

The VALIANT study demonstrates that valsartan is well tolerated in post-MI patients who have left ventricular dysfunction and/or heart failure. Discontinuations due to adverse events were lowest in the valsartan group and highest in the combination group. The rates of hypotension and renal dysfunction were slightly higher in the valsartan group than in the captopril group. Overall, there was a statistically significant higher rate of patient discontinuation due to adverse events in the captopril group, where more treatment-limiting side effects occurred, including cough, rash and taste disturbance, than in the valsartan group.

The overall findings are interesting, notes Dr John McMurray. 'Combination treatment should not be written off. Patients showed significantly greater reduction in blood pressure with combination therapy. Overall, admissions for heart failure and myocardial infarction were significantly reduced in VALIANT with the combination therapy.'

For further information, call Werner Rooseboom of Novartis on (011) 929-9111

References

1. Mann DL, Derwel A. Angiotensin-receptor blockade in acute myocardial infarction – A matter of dose (editorial). *N Engl J Med* 2003; **349**(20): 1963-1964.
2. Pfeffer MA, McMurray JJV, 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): 1843-1906.

* Please note that these results are brought to you in the interests of furthering the dissemination of new scientific information. Please consult the South African package insert for prescribing information

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Dr AJ Dalby, cardiologist in private practice, Milpark Hospital, Johannesburg.



[Click here for Dr Dalby's comments.](#)

Dr J McMurray, senior investigator of VALIANT study, and Professor of Medicine, University of Glasgow, UK.

[Click here for Dr McMurray's comments.](#)

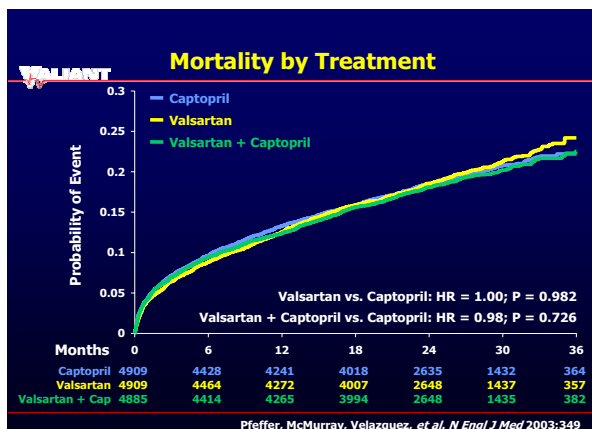


Fig. 1A. Kaplan-Meier estimates of the rate of death from any cause, according to treatment group.

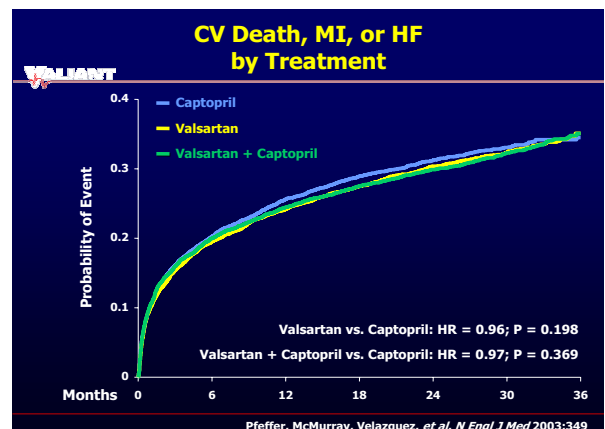


Fig. 1B. Kaplan-Meier estimates of the rate of death from cardiovascular causes, reinfarction or hospitalisation for heart failure, according to treatment group.

Comments on the VALIANT trial

Interview with Dr Anthony Dalby, cardiologist in private practice, Milpark Hospital, Johannesburg, and lead investigator for the VALIANT study in South Africa.

Q: Why is VALIANT important?

A. VALIANT is a very important study. Firstly, with 14 000 patients, it is the largest trial ever to be carried out on heart failure. Secondly, it is the first major trial to investigate angiotensin receptor blockade in patients immediately post-MI who have heart failure or depressed ejection fraction.

Q: What makes VALIANT different from other trials with ARBs?

A. VALIANT patients had incurred their left ventricular dysfunction acutely. This makes it very different from trials in chronic heart failure, such as the CHARM study, whose patients had had time for the chronic adaptive responses in cardiac tissue to occur. This I shall term the pathophysiological difference.

Next, the way patients were treated in VALIANT was different; patients were randomised to the ACE inhibitor captopril, or to the ARB valsartan, or to the combination of both agents that were started at the same time. The trial did not allow for the chronic adaptive responses to ACE inhibition before the ARB was started. So there was also a pharmacological difference. Chronic use of an ACE inhibitor upregulates chymase and other pathways that allow angiotensin II to reach its receptor without needing its converting enzyme. So, giving an angiotensin receptor blocker at a later stage may have a different effect from starting an ACE and an ARB at the same time.

Q: What were the main findings?

A. VALIANT shows that there is no difference between the benefits

observed with captopril ACE inhibition and with valsartan angiotensin receptor blockade in this particular group of patients. This is not to say there is no difference in effect – but there was no difference in the benefits. Angiotensin receptor blockade with valsartan was ‘at least as good as’ treatment with the ACE inhibitor and fulfilled the statistical requirements for non-inferiority.

The study did not include a placebo group, so the results do not show the magnitude of the benefit with valsartan compared to placebo – only the benefit compared to the best current treatment, captopril. The results showed that valsartan worked as well as captopril in the group of patients tested.

Q: What are the implications for clinical practice?

A. Valsartan may be used henceforth as an alternative to ACE inhibition in patients with any contraindication to ACE inhibitors and in those who develop side-effects on ACEI. The most frequent side-effect with ACE inhibitors is cough – so valsartan can be used in patients who cough when taking an ACE inhibitor, or for other fairly common ACE inhibitor side-effects such as skin rash or taste disturbance.

Q: How common is ACE intolerance in clinical practice?

A. ACE intolerance is a significant problem in routine clinical practice – much more frequent than was revealed in VALIANT. ACE inhibitor cough usually affects 6 to 10 per cent of patients, which is much higher than in VALIANT, where the rate of cough was only about 2 per cent. In the real world, patients are unwilling to pay for a medicine that causes them to cough. ACE-inhibitor cough can take some time to develop – up to 6 months in some patients.

It is important to remember that angio-oedema with an ACE inhibi-

tor can be fatal, so it is useful to know that now we have another drug, from a different class, that is unlikely to cause the same serious, acute side-effects.

It is always helpful to have a ‘second string to our bow’. Valsartan offers an effective alternative for patients who can’t take ACE inhibitors.

Q: What were the side-effects of the high dose of valsartan?

A. Valsartan up to 320 mg daily was generally well tolerated in the VALIANT study. Only 20 per cent of all withdrawals from treatment were due to adverse events, while the rest were for a range of patient-motivated reasons. In VALIANT, experience in giving valsartan at the chosen dose exposed an association with hypotension and renal dysfunction that was reversible when the dose was reduced. So when this treatment is used, clinicians should be on the look-out for symptomatic hypotension and signs of renal dysfunction. Notwithstanding, the study’s steering committee felt that, with sufficient encouragement, even more patients could be helped to take this effective therapy.

Q: Is this an ARB class effect?

A. This trial tested specific drugs. Captopril is the gold-standard treatment in this setting, and it was tested at the gold-standard dose (50 mg tds). It was compared with valsartan, titrated up to a dose of 160 mg bd. To ensure the same clinical benefit in practice as that seen in the trial, clinicians should use the same agents, titrated to the same doses. For instance, one can’t simply make the assumption that any ARB at any dose will work as well. OPTIMAAL was a similar trial that used losartan and it is unclear why it failed to show efficacy. On the other hand, VALIANT showed that valsartan at a dose of 160 mg bd is an effective alternative to captopril.

Q: Were there specific benefits for diabetics?

- A. Patients with diabetes did just as well as all other patients, showing no significant difference between the benefits with captopril or valsartan.

Q: What about costs?

- A. Cost is always an issue, but the bottom line is that valsartan offers an effective therapeutic alternative. The question is whether or not we can afford it. In reality, it is likely that valsartan will be used selectively in patients for whom captopril is inappropriate, because captopril, available as a generic, is very inexpensive. This means that it may be most cost effective to reserve valsartan for treating ACE-intolerant post-MI patients.

Q: How should the combination arm that got ACE plus ARB be viewed?

- A. This was a proof-of-concept trial to test whether adding an ARB to an ACE would be of benefit. The answer was a resounding no. I am surprised by this result. There was a sound theoretical basis for proposing that combination ARB-ACE should be beneficial. However, in this instance, the results indicate that it did not matter whether or not the angiotensin receptor was blocked (ARB effect) and whether or not bradykinin accumulated (ACEI effect). Results from VALIANT suggest that there is no benefit in combining these agents in patients with recent onset of heart failure. The CHARM Added

study showed a minor benefit when combining an ARB with an ACE in patients with chronic heart failure. Therefore, if I had a patient who developed more severe heart failure while already on an effective dose of an ACE inhibitor, I would then consider adding an ARB as add-on therapy.

Interview with Dr John McMurray, Professor of Medicine, University of Glasgow, Glasgow, Scotland.**Q: Why were the results of VALIANT different from those of CHARM**

- A. There are four possible reasons why we found different results in VALIANT from those seen in CHARM. All may be part of the explanation.

First, we were looking at a different disease – because of the natural history of heart failure. In VALIANT, patients were early post-MI. They had increased risk of acute events, including another MI, increased risk of mortality and requirement for revascularisation. In contrast, CHARM included patients with chronic heart failure, at high risk of hospital admission due to worsening of their heart failure. The way events occur in these patients is different. Post-MI patients have an early risk of events, while chronic heart failure patients have a more long-term risk. Overall, the two groups of patients are at risk of different events and have a different course of events. These differences may help to explain the lack of effect of combination therapy in VALIANT.

Secondly, treatment regimens

were different – comparing starting two treatments together, with adding one after the other. Patients with heart failure have a more active renin-angiotensin system. After some time on an ACE inhibitor, the body finds ways to bypass the blocked ACE. So patients with heart failure on long-term ACE inhibitors develop RAS escape. If you add an ARB at this point, you might expect to find more effect than in a patient not previously treated with an ACE inhibitor.

Thirdly, VALIANT was designed to test if an ARB could do something different from a high-dose ACE. The mean dose achieved in VALIANT was 117 mg at one year – compared to an average dose of only 80 mg in VALHeFT. So you might expect less ARB effect with such a high dose of ACE.

Fourthly, the dose of valsartan in the combination arm may have been too low (80 mg valsartan twice daily). VALHeFT tested a dose of 160 mg twice daily. The dose was chosen because of concern about reducing blood pressure too much in patients with heart failure. We saw some intolerance, even with 80 mg, so I don't know if we could have got patients up to 160 mg daily.

Overall, the findings are interesting. Combination treatment should not be written off. Patients showed significantly greater reduction in blood pressure with combination therapy. Overall, heart failure hospital admissions and MI admissions were significantly reduced in VALIANT with combination therapy. There was a hint of additional benefit with combination therapy.