Valsartan plus captopril did not improve survival more than captopril alone after myocardial infarction

Pfeffer MA, McMurray JJ, Velazquez EJ, et al. **Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both.** N Engl J Med. 2003;349:1893-906.

QUESTION

In patients with myocardial infarction (MI), does the angiotensin-receptor blocker (ARB) valsartan, alone or combined with the angiotensin-converting enzyme (ACE) inhibitor captopril, reduce mortality more than captopril alone?

DESIGN

Randomized (allocation concealed*), blinded (clinicians, patients, and outcome assessors),* controlled trial with median 25-month follow-up (Valsartan in Acute Myocardial Infarction Trial [VALIANT] trial).

SETTING

931 centers in 24 countries.

PATIENTS

14 703 patients ≥ 18 years of age (mean age 65 y, 69% men) who had had an acute MI in the previous 0.5 to 10 days that was complicated by clinical or radiologic signs of heart failure (HF), left ventricular systolic dysfunction, or both; systolic blood pressure > 100 mm Hg; and serum creatinine level < 2.5 mg/dL (221 µmol/L). Exclusion criteria included previous intolerance or contraindication to ACE inhibitors or ARBs, valvular disease, and other diseases known to limit life expectancy. Follow-up was 99%.

INTERVENTION

Patients were allocated to valsartan monotherapy, 20 mg increased to 160 mg twice daily (n = 4909); valsartan plus captopril 6.25 mg, increased to 80 mg twice daily and 50 mg 3 times daily, respectively (n = 4885); or captopril monotherapy, 6.25 mg increased to 50 mg 3 times daily (n = 4909).

MAIN OUTCOME MEASURE

All-cause mortality and drug-related adverse events.

MAIN RESULTS

Analysis was by intention to treat. Valsartan alone or combined with captopril did not differ from captopril alone for all-cause mortality (Table). Valsartan combined with captopril was associated with more adverse events leading to permanent discontinuation than captopril alone (Table).

CONCLUSIONS

In patients with myocardial infarction complicated by left ventricular systolic dysfunction, heart failure, or both, valsartan combined with captopril increased adverse events without improving survival more than captopril alone. Valsartan alone was similar to captopril alone for all-cause mortality.

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*See Glossary.

Valsartan alone or combined with captopril vs captopril alone in patients at high risk for cardiovascular events after myocardial infarction†

Outcomes	Comparisons	Event rates	Hazard ratio (97.5% CI)	NNT
All-cause mortality	Valsartan vs captopril	19.9% vs 19.5%	1.00 (0.90 to 1.11)	Not significant
	Valsartan plus captopril vs captopril	19.3% vs 19.5%	0.98 (0.89 to 1.09)	Not significant
			RRI (95% CI)	NNH (95% CI)
Any adverse event leading to discontinuation	Valsartan plus captopril vs captopril	23.4% vs 21.6%	8% (0.6 to 17)	56 (29 to 694)

†Abbreviations defined in Glossary; RRI, NNH, and CI calculated from data in article.

COMMENTARY

The VALIANT trial was a large, randomized trial comparing the effects of the ARB valsartan with the ACE inhibitor captopril, and the combination of valsartan and captopril with captopril alone in patients who had acute MI with left ventricular systolic dysfunction, signs or symptoms of HF, or both. Although the comparison of valsartan with captopril satisfied the trial's noninferiority criteria for decreased mortality, the combination of valsartan and captopril did not improve survival compared with captopril alone.

The VALIANT trial outcome was different from that of the Optimal Therapy in Myocardial Infarction with Angiotensin II Antagonist Losartan (OPTIMAAL) trial (1), in which losartan, up to 50 mg/d, was not proven to be as effective as captopril, 50 mg 3 times/d, in patients who had MI with cardiac dysfunction or symptomatic HF. In VALIANT, although valsartan was not found to be superior to captopril, it was shown to be as effective as captopril. An HF trial is currently ongoing in which losartan doses of 50 and 150 mg/d are being compared.

VALIANT was the first large, randomized controlled trial comparing the combination of an ARB and ACE inhibitor with an ACE inhibitor in early post-MI patients with left ventricular systolic dysfunction, HF, or both. These results were different from those of the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM)-Added trial (2), in which candesartan combined with an ACE inhibitor reduced mortality and morbidity in patients with stable HF compared with an ACE inhibitor alone. The patient populations are a major distinction between these trials. In the CHARM-Added trial, patients were clinically stable but remained symptomatic despite optimal HF therapy, whereas in the VALIANT trial patients were given combination therapy early after MI. In addition, in the VALIANT trial valsartan and captopril were simultaneously uptitrated, whereas in the CHARM-Added trial only candesartan was uptitrated in patients receiving an optimal ACE inhibitor dose.

In Canada, the ranges of cost are similar for ACE inhibitors and ARBs, but certain ACE inhibitors remain less expensive than valsartan. The results of VALIANT would not support using an ARB where an ACE inhibitor is tolerated but would support ARB use in patients intolerant of ACE inhibitors. The role of combination therapy remains unresolved.

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References

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2. **McMurray JJ, Ostergren J, Swedberg K, et al.** Lancet. 2003;362:767-71.