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A REPORT BY THE DIVISION OF CARDIOLOGY
ST. MICHAEL'S HOSPITAL, UNIVERSITY OF TORONTO, CANADA

Scientific Update™

Optimal Inhibition of the Renin-angiotensin System in Patients with High-risk Myocardial Infarction: the Valsartan in Acute Myocardial Infarction Trial (VALIANT)

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Angiotensin-converting enzyme inhibitors (ACEIs) have been shown to improve mortality and morbidity in a broad spectrum of patients following myocardial infarction (MI). The most pronounced benefits were observed in high-risk patients with MI complicated by left ventricular systolic dysfunction (LVSD) and/or acute heart failure. Angiotensin receptor blockers (ARBs) provide an alternative approach to block the renin-angiotensin system. Until recently, it was unclear whether ARBs were superior, the same, or inferior to ACEIs. Furthermore, the combination of an ARB and an ACEI is a theoretically attractive approach. The principal aim of the multinational Valsartan in Acute Myocardial Infarction Trial (VALIANT) was, therefore, to compare with sufficient statistical power the effect of an ARB, versus a combination of an ARB with an ACEI versus an optimal dose of an ACEI on mortality in patients with high-risk MI complicated by LVSD and/or heart failure.

Patients who suffer an MI complicated by the development of LVSD and/or acute or transient congestive heart failure (CHF) are at a particularly high risk of death and recurrent morbid events.[1-3] Even though ACEIs have been shown to reduce mortality, recurrent MI, and CHF, both mortality and morbidity in these patients remain exceedingly high.[1,4] Effective additional pharmacologic strategies, including novel approaches to block the renin-angiotensin-aldosterone system (RAAS) are therefore required. ARBs provide an alternative approach for blocking the RAAS,[5] potentially providing a more complete blockade of angiotensin II, but without the theoretically beneficial bradykinin-preserving effects of ACEIs.[6,7] Based on these considerations, ARBs may be superior, equal, or inferior to ACEIs, and combining ARBs and ACEIs may be theoretically superior to ACEIs alone.

Although ACEIs are of proven clinical value in a broad spectrum of patients with MI,[8-10] the relative and absolute benefits of ACEIs are most pronounced when administered long-term to patients at higher risk based on LVSD and/or clinical signs of CHF, as demonstrated in the SAVE, AIRE, and TRACE studies (Figure 1).[11-13] VALIANT was a multinational, multicentre, double-blind, randomized, active-controlled, parallel group study comparing the efficacy and safety of long-term treatment with the ARB, valsartan, the ACEI, captopril, and their combination, in high-risk patients

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Figure 1: All-cause mortality from a meta-analysis of SAVE, AIRE, and TRACE[1]

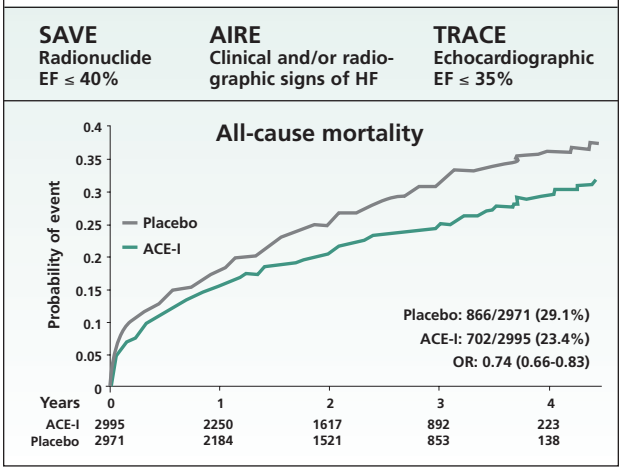
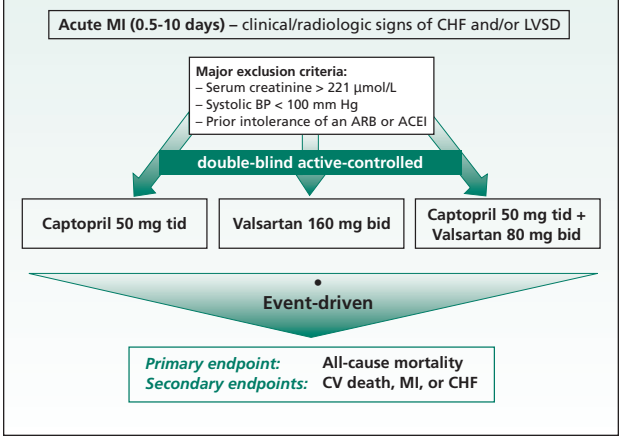


Figure 2: VALIANT study design[14]



after MI complicated by LVSD and/or CHF. Details of the rationale behind VALIANT have been previously published.[14] By targeting a population in whom ACEI therapy had been clearly established, and comparing valsartan against a *proven* agent and dose regimen, VALIANT determined whether valsartan offered additional clinical advantages over standard therapy with an ACEI. The principal aims were to determine:

- if the ARB, valsartan, is superior to captopril in improving survival and, with *equal* statistical power
- if the addition of valsartan to captopril is superior to the proven dose of captopril in improving survival
- if the results demonstrate that valsartan is not superior to captopril, a non-inferiority analysis was prespecified to determine whether valsartan could be considered "as effective as" captopril.

Study design

VALIANT involved 931 centres in 24 countries. In brief, men and women aged ≥18 years with acute MI (between 12 hours and 10 days) complicated by either clinical or radiographic signs of CHF and/or LVSD, were eligible for inclusion. At randomization, patients were required to have systolic blood pressure >100 mm Hg and a serum creatinine <221 µmol/L.

Patients were permitted to have received an ACEI or an ARB up to 12 hours before randomization. The study design is summarized in Figure 2. LVSD was defined as ejection fraction (EF) <40% on radionuclide ventriculography or ≤ 35% on echocardiography. Consenting patients were randomized in a 1:1:1 manner to:

- captopril using the clinically proven beneficial SAVE study regimen[13,14] (target dose of 50 mg t.i.d)
- valsartan (target to 160 mg b.i.d.), or
- a combination of captopril (SAVE regimen) plus valsartan (target to 80 mg b.i.d).

Captopril was chosen as a comparator because it was the most studied ACEI with the most extensive evidence of clinical benefit. Importantly, no head-to-head trial had an appropriate design to show a benefit or an "as good as" captopril outcome. The primary outcome was total (all-cause) mortality and the secondary endpoint was combined cardiovascular (CV) mortality, MI, and CHF hospitalization.

Results

The results of the VALIANT study were recently presented at the American Heart Association Scientific Sessions and published.[15] From December 1988 through June 2001, a total of 14,808 patients were enrolled from 24 countries. Patients from Canada and the United States comprised nearly 35% of the trial cohort. The 1092 patients at 65 Canadian sites comprised the third largest national enrollment among the 24 participating countries.[16] In the study, 14,703 patients consented and were randomized. Vital status was ascertained in over 99% and was similar in the 3 arms. Baseline characteristics are shown in Table 1. Close to one-third of the patients were Killip class 1, qualifying by ejection fraction (EF) criteria, and over three-quarters had some degree of

Table 1: Baseline characteristics[15]

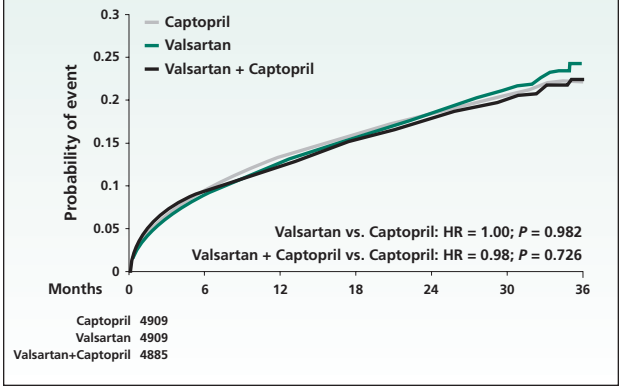
Mean age (years)		64.8
Women (%)		31.1
Mean blood pressure (mm Hg)		123/72
Killip class (%)	I	28.0
	II	48.3
	III	17.3
	IV	6.4
Mean LV ejection fraction (%)*		35.3
Time to randomization (days)		4.9
Thrombolytic therapy (%)		35.2
Primary percutaneous coronary intervention		14.8
Qualifying MI site (%)	anterior	59.4
	inferior	34.4
Diabetes (%)		23.1
Hypertension (%)		55.2
Prior MI (%)		27.9
Prior heart failure (%)		14.8
ACE inhibitor (%)**		39.6
ARB (%)**		1.2
Beta-blocker (%)		70.4
Aspirin (%)		91.3
Statin		34.1

* Data were available for 11,338 patients,
** Stopped at least 12 hours prior to randomization

pulmonary congestion. It is important to note that these high-risk patients did receive contemporary therapy; 50% of patients received reperfusion therapy and a relatively great number were treated with ß-blockers, aspirin, and statins. The baseline characteristics were comparable in the 3 arms.

Results of the primary endpoint – total mortality – are shown in Figure 3. In this active-controlled, randomized trial, the mortality of the captopril group served as the comparator. Those randomized to the valsartan arm experienced a very similar incidence of death due to any cause, with a hazard ratio (HR) of 1.00. Patients randomized to the combination of valsartan plus captopril also had a very similar incidence of death, with a HR of 0.98. Neither group had results that were significantly different from the captopril event rate. To demonstrate non-inferiority, the HR for total mortality in the valsartan group compared to captopril had to meet the pre-specified margin of 1.13 (Figure 4). This threshold was chosen because it preserves at least 55% of the

Figure 3: Primary endpoint: total mortality[15]



survival benefit of the ACE inhibitor. The point estimate for valsartan compared to captopril, as stated, was 1.00 and, importantly, the upper limit of the 97.5% confidence interval was well within the non-inferiority range. A per protocol analysis of a population of 14,285 patients (all had received study medication and met stricter cardiac marker-based inclusion criteria for MI) was also conducted to provide another validation of the non-inferiority test. The criteria for non-inferiority were again met in this more restricted population. Using the methods of Fisher, Hasselblad, and Kong, an estimate of the effectiveness of valsartan, as compared to imputed placebo, was derived. It was estimated that valsartan had an effect that was 99.6% (95% confidence interval, 60-139) of that of captopril (Figure 5).

Data for the secondary endpoint, combined CV mortality, MI or CHF, are shown in Figure 6. The event rate for the valsartan monotherapy group was similar to captopril

Figure 4: Total mortality: non-inferiority analyses[15]

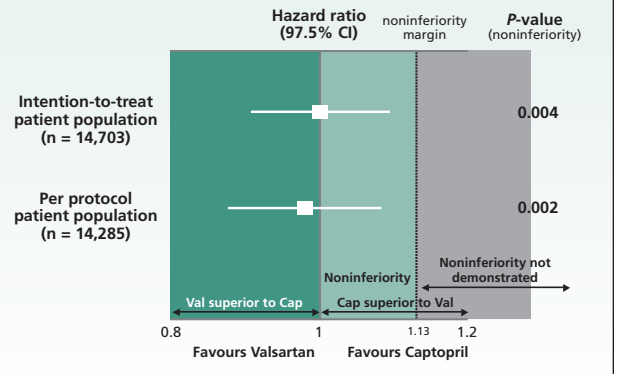


Figure 5: Mortality in SAVE, TRACE, AIRE and VALIANT[15]

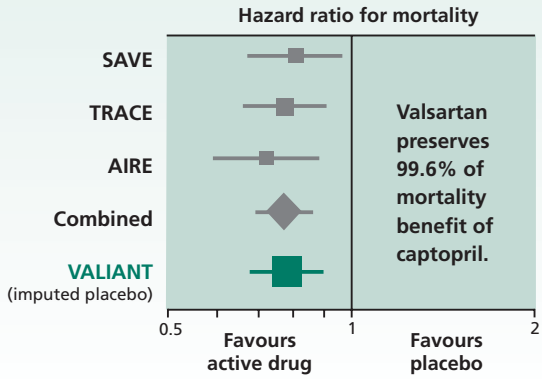
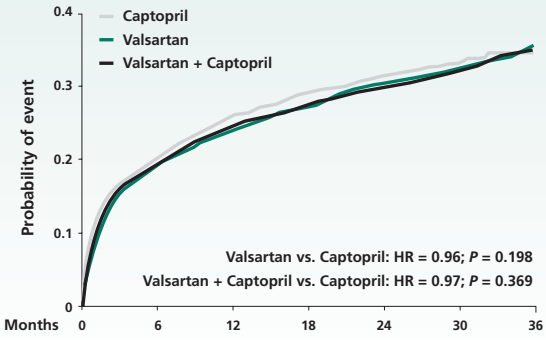


Figure 6: Secondary endpoint: CV death, MI or CHF[15]



with a HR of 0.96. The rate for the combination of valsartan plus captopril was not different from that for captopril alone, with a HR of 0.97. The effects of valsartan relative to captopril were compared for a hierarchy of CV events (Figure 7). For each of the composites, the point estimates favoured valsartan and, more importantly, the upper limit of the 97.5% confidence intervals were within the pre-specified non-inferiority range.

The relative effectiveness of valsartan compared to captopril, or the combination compared to captopril, on both the primary and secondary endpoints was not influenced by pre-specified demographic factors, past medical history, the severity of the MI, or use of concurrent medications. Beta-blocker use was a subgroup of interest because a previous post-hoc subgroup analysis of the Val-HeFT trial raised potential concerns when valsartan was used with both an ACEI and ß-blocker.[17] In VALIANT, over 70% (or 10,000 patients) were on a ß-blocker at randomization. There were no adverse interactions for either total mortality or the composite outcome when valsartan was administered concomitantly with a ß-blocker either alone or in combination with an ACEI.

The dose titration of the study medication was similar for valsartan and captopril, with about 55% of patients achieving target dose in both arms. On the other hand, the proportion of patients on combined therapy that achieved target dose was consistently lower, with about 45% of patients achieving target dose. Furthermore, those randomized to combined therapy were more likely to discontinue study medication from any adverse event (valsartan 5.8%, captopril 7.7%, and combined therapy 9.0%).[15] Discontinuation of study medications increased as a function of time in all arms. Compared to captopril, valsartan-treated patients were less likely to discontinue due to an adverse event attributed to study medication. Conversely, patients on combined therapy were more likely to discontinue their study medication and more likely to experience study drug-related adverse effects that required discontinuation. Adverse experiences leading to study drug discontinuation are shown on Figure 8. The patterns of adverse experiences leading to discontinuation of study medication differed. For valsartan, which lowered blood pressure slightly more, discontinuation was more likely to be associated with hypotension or renal concerns, whereas captopril discontinuation was

Figure 7: CV mortality and morbidity[15]

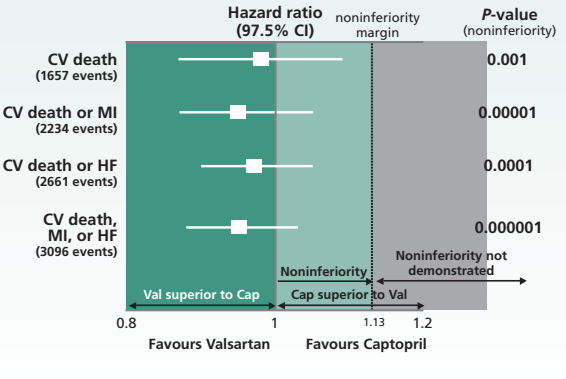
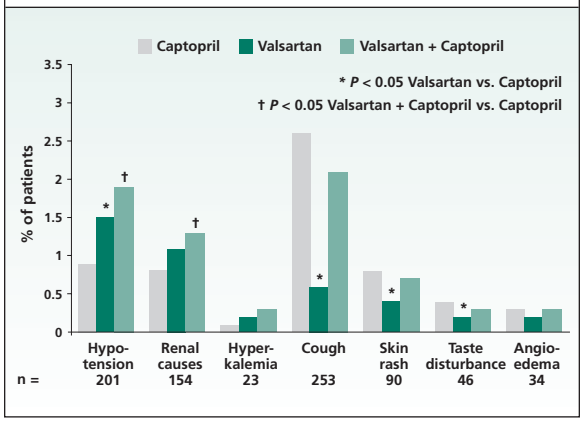


Figure 8: Adverse effects leading to study drug discontinuation[15]



more frequently attributed to rash, cough, or taste disturbance. Combined therapies resulted in additive adverse experiences of the single agents.

Discussion

Left ventricular dysfunction and/or HF are common following MI and account for a large proportion of in-hospital MI mortality. The preliminary results of the VALIANT Registry – a nested registry involving 85 hospitals across 9 countries that enrolled 5,573 patients, including 2,347 with CHF and/or LV dysfunction – demonstrated an overall in-hospital mortality rate of 6.91%.[3] The in-hospital mortality rate of patients with CHF and/or LV dysfunction, the "VALIANT-like" patients, was 6 times higher than in those without these complications. In patients with MI complicated by LVSD and/or CHF, the VALIANT study demonstrated the following key findings:

- Valsartan is as effective as a proven dose of captopril in reducing the risk of death or CV death or non-fatal MI or CHF admission
- Combined therapy with valsartan and a proven dose of captopril produces no further reduction in mortality, but is accompanied by more adverse drug effects.

The VALIANT trial is the first study to demonstrate convincing non-inferiority of an ARB, valsartan, over an ACEI in high-risk patients post-MI. Indeed, it is the only trial to date that was sufficiently powered to test for non-inferiority of an ARB, valsartan, over an ACEI in any patient population. The next obvious question is: Does this benefit of valsartan represent a class effect of the ARBs? In this regard, it is useful to review 2 studies that compared an ARB with an ACEI head-to-head.

In the Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan (OPTIMAAL),[18] the ARB, losartan, at a dose of 50 mg/day, was compared with captopril at 150 mg/day in high-risk patients with acute MI. There was a strong trend in favour of captopril with respect to the primary endpoint of total mortality (p=0.07). A similar trend in favour of the same dose of captopril over the same dose of losartan was observed in patients with chronic heart failure in the Evaluation of Losartan in the Elderly II (ELITE-II) trial.[19] While it is almost impossible to prove or disprove minute pharmacologic differences between agents within the same class, results of VALIANT highlight the importance of choosing the right agent at the right dose in high-risk patients with CV disease.

The lack of benefit of combination treatment with valsartan and captopril was unexpected, particularly given the benefits observed with this approach on CHF hospitalizations in CHARM and Val-HeFT.[17,20] The following are possible explanations.

- First, the patient population of VALIANT (patients had LVSD and experienced acute CHF following MI) is likely to be very different, with some overlapping but likely differing pathophysiology, from those of CHARM and Val-HeFT, who had chronic stable CHF.
- Second, the dose of the background ACEI therapy used in CHARM and Val-HeFT was lower than the prespecified dose of the ACEI, captopril, used in VALIANT.
- Third, only 30% of patients in VALIANT were on ACEIs at the time of randomization, whereas almost all patients were on long-term ACEI therapy at the time of randomization in CHARM and Val-HeFT.

In summary, results of the VALIANT study carry the following clinical implications. In patients with MI complicated by LVSD and/or CHF, an optimal dose of the ARB, valsartan, will reduce mortality and morbid CV events to the same extent as an optimal dose of an ACEI, but with better tolerability than an ACEI. Unlike chronic CHF, the combined use of an ARB and ACE inhibitor cannot be recommended in patients post-MI complicated by LV dysfunction and/or CHF. Indeed, in patients post-MI with both LV dysfunction *and* acute CHF, the addition of an aldosterone receptor antagonist to an ACEI or ARB

can be considered, based on the results of the EPHESUS study.[20,21] All of these patients should also receive other secondary preventive therapy including ASA, ß-blockers, and statins. The choice between an ARB and an ACE inhibitor will ultimately depend on the physician's experience with the agents, as well as individualized considerations of the cost and tolerability; however, the choice of the proper agent and the right dose will be crucial in order to accrue maximal survival benefit.

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