

RAPID APPRAISAL

Name of Trial: Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial.

Reference: Julius S, Kjeldsen SE, Weber M et al. Lancet 2004;363:2022-31

Question: For the same level of blood pressure control, does valsartan reduce cardiac morbidity and mortality more than amlodipine in hypertensive patients at high cardiovascular risk?

Did the study ask a clearly focussed question?

Yes. This trial was designed to compare the effects of treatment with the angiotensin-receptor blocker (ARB) valsartan with the calcium channel blocker (CCB) amlodipine on cardiac morbidity and mortality in hypertensive patients at high risk of cardiac disease. The hypothesis was that valsartan would reduce cardiac morbidity beyond its blood pressure (BP) lowering effect.

A predefined algorithm based on age, risk and disease factors was used to recruit a population with hypertension at high risk of cardiovascular disease (CVD). Qualifying CVD risk factors were male sex, age ≥ 50 yrs, diabetes mellitus, current smoker, hypercholesterolaemia, left ventricular hypertrophy, proteinuria, or serum creatinine between 150 and 265 micromol/L. Qualifying diseases were left ventricular hypertrophy (LVH) with strain pattern or coronary, cerebrovascular or peripheral arterial disease.¹ The algorithm stated that to enter the trial, patients over 70 yrs were required to have ≥ 1 risk factor or ≥ 1 disease factor; patients aged 60-69, ≥ 2 risk factors or ≥ 1 disease factor; men aged 50-59 required ≥ 3 risk factors or ≥ 1 disease factor and women aged 50-59 required ≥ 2 risk factors AND ≥ 1 disease factor.²

Hypertension was defined as a mean sitting BP of 160-210/ <115 mmHg in patients without prior antihypertensive drug therapy. In those receiving current drug therapy, treatment was discontinued and patients were allocated to either valsartan 80 mg or amlodipine 5 mg daily without a placebo run-in period. All patients were then titrated in a stepwise fashion to a target BP of $<140/90$ mmHg. (Table).

Step	Valsartan Arm	Amlodipine Arm
1	80mg	5mg
2	160mg	10mg
3	160mg + HCTZ 12.5mg	10mg + HCTZ 12.5mg
4	160mg + HCTZ 25mg	10mg + HCTZ 25mg
5	160mg + HCTZ 25mg + other antihypertensive*	10mg + HCTZ 25mg + other antihypertensive*

HCTZ = open-label hydrochlorothiazide

*Not ARBs or CCBs unless separate clinical indication

The primary outcome measure was time to first cardiac event defined as a composite of sudden cardiac death, fatal myocardial infarction (MI), death during or after coronary artery bypass graft or percutaneous coronary intervention, death due to heart failure, and death associated with recent MI on autopsy, heart failure requiring hospital management, non-fatal MI or emergency procedures to prevent MI.

Pre-specified secondary endpoints were fatal and non-fatal MI, heart failure and stroke. Analysis of all-cause mortality and new-onset diabetes (diagnosed if serum glucose concentration >7.8 mmol/L) were also pre-specified.

Was the study design appropriate?

Yes. The trial was a prospective, multi-centre, multi-national, double-blind, randomised, active-control, parallel-group comparison. To achieve equal BP in both groups a response-dependent dose titration scheme was used.

However, throughout the study there was a discrepancy between the BP lowering effects of the two treatments with the amlodipine based regime reducing BP more effectively than the valsartan based regime. This precluded a valid assessment of the primary hypothesis. The authors went on to perform a posthoc analysis using serial median matching,³ a technique of unproven reliability.⁴

Were participants appropriately allocated to intervention and control groups?

Yes. 15,313 patients in 31 countries were centrally randomised by computer in appropriate blocks and assigned to one of two groups, the intervention group, valsartan, or the active control group, amlodipine. There were no significant differences in baseline characteristics between the control and intervention groups, including severity of hypertension, prior antihypertensive drug use or prevalence of co-existing cardiovascular conditions. At baseline 33% of patients had a serum cholesterol >6.2 mmol/L, 24% were current smokers and 31.7% had diabetes (mostly type 2).⁵

Were participants, staff and study personnel 'blind' to participants study group?

Yes. The study was conducted in a double-blind fashion with regard to the study drug and active control. However, the addition of hydrochlorothiazide and other antihypertensive treatments was not blinded. At the end of the study, the proportion of patients receiving valsartan monotherapy was significantly less than those receiving amlodipine monotherapy, and a larger proportion of patients in the valsartan group received the highest dose of study drug plus hydrochlorothiazide plus other antihypertensive drugs than in the amlodipine group. However, these differences were not expected making it highly unlikely that the investigator was unblinded during the study.

Were all of the participants who entered into the trial accounted for at its conclusion?

Yes. A flow diagram was provided which accounts for all randomised patients up to entry into the intention to treat analysis. Forty patients were lost to follow up in the valsartan group and fifty patients in the amlodipine group making up only 0.6% of the entire cohort. These patients were included in the intention to treat analysis although life status at studies end was not available. Other reasons for withdrawal were similar between groups.

Were the participants in all groups followed up and data collected in the same way?

Yes. Data was collected at the same intervals in both study groups. 73.7% in the valsartan group and 74.9% in the amlodipine group remained on blinded study therapy for the entire follow-up period. The study was due to run for 72 months (mean 50.4 months) with upward titration of medication in five steps until the target BP was reached. It is stated that most patients who discontinued study medication continued to attend for follow up.

Was the study large enough?

Yes. Power calculations indicated that 1,450 primary endpoints would be needed to detect a 15% reduction in endpoint rate from 12.5% to 10.63% with 90% power. This would require the inclusion of 14,400 patients. The study ended with 1,599 primary endpoint events in 15,245 randomised patients each followed up for between 4 and 6 years (mean 4.2). All tests were two sided with a significance level of 5%.

How are the results presented and what is the main result?

Mean daily doses were 151.7 mg for valsartan and 8.5 mg for amlodipine.

Blood pressure

Blood pressure was consistently less well controlled in the valsartan arm compared with the

amlodipine arm. Mean reductions over the entire study were 15.2/8.2 and 17.3/9.9 mmHg in the valsartan and amlodipine groups respectively ($p < 0.0001$). The differences persisted throughout the study but were largest during the first few months. Fewer valsartan than amlodipine patients achieved target BP (56% v 62%) or were controlled with monotherapy (27% v 35%) and a larger proportion of patients in the valsartan group received the highest dose of study drug plus hydrochlorothiazide plus other antihypertensive drugs (23%) than in the amlodipine group (16.8%). At study end or final visit the mean BP was 139.3/79.2 mmHg in the valsartan group and 137.5/77.7 mmHg in the amlodipine group. The BP difference between the two groups was significant ($p < 0.0001$) at every time point.

Primary endpoint

The first occurrence of a cardiac event (composite primary endpoint) was recorded in 10.6% (n=810) of valsartan patients and 10.4% (n=789) of amlodipine patients (hazard ratio [HR] 1.04, 95% CI: 0.94 - 1.15; $p = 0.49$). This shows that there was no significant difference between the valsartan or amlodipine groups in the primary outcome of cardiac mortality and morbidity.

Secondary endpoints

MI was significantly more frequent in the valsartan group ($p = 0.02$; NNH=143), but new-onset diabetes was less common in this group ($p < 0.0001$; NNT=30).

Posthoc analysis

Due to the persistent discrepancy between the BP lowering effects of the two treatments, the authors performed a posthoc analysis using serial median matching.³

A computer was programmed to select the patient closest to the median (based on systolic BP) within the valsartan group and then pair this patient with one from the amlodipine group matched for systolic BP (within 2 mmHg), age, sex and the presence or absence of previous coronary heart disease (CHD), stroke, and diabetes. This was repeated until all eligible patients were included and 5,006 matched valsartan-amlodipine cohort pairs, with a mean systolic BP of 139.9 mmHg in each drug group, were created. The primary endpoint (composite of cardiac events) again showed no significant differences between the two arms. Fewer hospitalisations for heart failure occurred in the valsartan group, just reaching statistical significance (HR 0.81, 95% CI: 0.66 - 0.99, $p = 0.04$). This method of data analysis is of unproven reliability.⁴

How safe were the regimens?

The pre-specified adverse events significantly more common in either group were peripheral oedema with amlodipine ($p < 0.0001$) and dizziness and headache with valsartan ($p < 0.0001$ for both).

The lower incidence rate of new-onset diabetes in the valsartan group suggests a potential beneficial effect of renin-angiotensin blockade.

This effect was also seen in the LIFE study where patients randomised to the ARB losartan were less likely to develop diabetes than those taking atenolol.⁶

However, there was a significantly greater incidence of angina pectoris with valsartan than with amlodipine (9.3 vs. 6.4%; $p < 0.0001$), with 4.4% episodes reported as serious in the valsartan group compared to 3.1% in the amlodipine group ($p < 0.0001$). This effect was also demonstrated in one of the pre-specified analyses in diabetic patients in the LIFE study where chest pain was more frequent with losartan than with atenolol (NNT of 25),⁷ although this was non-significant for the entire cohort.⁶ These results are however, not surprising as beta blockers and CCBs are effective for angina prophylaxis, while ARBs have no such action.

How precise are the results?

The 95% confidence interval of the hazard ratio for the primary endpoint crosses the line of no effect (0.94 to 1.15) suggesting no difference between valsartan and amlodipine in reducing the composite primary endpoint. The inequalities in blood pressure in favour of amlodipine throughout the trial prevent reliable assessment of the primary hypothesis.

Can the results be applied to the local population?

Randomised patients had a mean age of 67yrs, 58% were men, 46% had existing CHD, 31.7%

had diabetes (mostly type 2), 24% were current smokers, 33% had a serum cholesterol of > 6.2 mmol/L and most (92%) were previously treated for hypertension with a mean BP of 155/87 mmHg representing a wide range of independent risk factors.

The benefits to be gained from a reduction in new-onset diabetes by valsartan in this high-risk cohort APPEAR to be outweighed by a smaller BP reduction, which was associated with a higher risk of stroke in the early months of the study when control was poorest and an increased incidence of angina and MI.

This trial does not indicate that valsartan should be prescribed in preference to amlodipine in high-risk hypertensive patients.

Valsartan and other ARBs are more expensive than ACE inhibitors (and amlodipine). Their increased cost is not justified by this trial.

For the same level of blood pressure control, does valsartan reduce cardiac morbidity and mortality more than amlodipine in hypertensive patients at high cardiovascular risk?

The trial did not demonstrate superiority of valsartan over amlodipine with regard to the reduction of cardiac mortality and morbidity in hypertensive patients at high cardiovascular risk. It was shown that amlodipine was more effective at reducing blood pressure in these high-risk individuals.

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KEY RCT - randomised controlled trial, MA - meta analysis, E - editorial, L – letter, P - paper

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