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

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Summary

Background The Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial was designed to test the hypothesis that for the same blood-pressure control, valsartan would reduce cardiac morbidity and mortality more than amlodipine in hypertensive patients at high cardiovascular risk.

Methods 15 245 patients, aged 50 years or older with treated or untreated hypertension and high risk of cardiac events participated in a randomised, double-blind, parallel-group comparison of therapy based on valsartan or amlodipine. Duration of treatment was event-driven and the trial lasted until at least 1450 patients had reached a primary endpoint, defined as a composite of cardiac mortality and morbidity. Patients from 31 countries were followed up for a mean of 4·2 years.

Findings Blood pressure was reduced by both treatments, but the effects of the amlodipine-based regimen were more pronounced, especially in the early period (blood pressure 4·0/2·1 mm Hg lower in amlodipine than valsartan group after 1 month; 1·5/1·3 mm Hg after 1 year; p<0·001 between groups). The primary composite endpoint occurred in 810 patients in the valsartan group (10·6%, 25·5 per 1000 patient-years) and 789 in the amlodipine group (10·4%, 24·7 per 1000 patient-years; hazard ratio 1·04, 95% CI 0·94–1·15, p=0·49).

Interpretation The main outcome of cardiac disease did not differ between the treatment groups. Unequal reductions in blood pressure might account for differences between the groups in cause-specific outcomes. The findings emphasise the importance of prompt blood-pressure control in hypertensive patients at high cardiovascular risk.

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Introduction

Substantial benefits in prevention of major cardiovascular morbidity and mortality in high-risk populations have been reported with calcium antagonists[1–3] and angiotensin-converting enzyme (ACE) inhibitors.[4] However, large hypertension trials have failed to show significant differences between treatment regimens based on diuretics, β blockers, calcium antagonists, ACE inhibitors, or α blockers.[5–15] The LIFE study[16] showed advantages for the angiotensin-receptor blocker losartan over the β blocker atenolol in hypertensive patients with left ventricular hypertrophy, primarily a 25% reduction in strokes. Subsequently, the second National Australian Blood Pressure study[17] reported fewer cardiovascular events in patients treated with ACE inhibitor compared with diuretics. Therefore, the issue of whether the mechanism of action of antihypertensive drugs might influence their clinical effect remains unresolved.

The Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial offered a further opportunity to test this hypothesis by comparing the effects of two contemporary agents. VALUE[18–20] was designed to compare the effects of treatment regimens based on the angiotensin-receptor blocker valsartan or on the calcium antagonist amlodipine on cardiac morbidity and mortality in patients with essential hypertension and at high risk for cardiac disease. The study hypothesis was that for the same level of blood-pressure (BP) control, valsartan-based treatment would be superior to amlodipine-based treatment in reduction of cardiac morbidity and mortality. There is strong evidence that raised concentrations of angiotensin II are an independent risk factor for cardiac disease.[21] Valsartan was expected to reduce cardiac morbidity beyond its BP-lowering effect. Amlodipine was chosen as comparator because it effectively lowers BP but has not been proven to have specific cardioprotective properties.[10,15]

The trial used a specific predefined algorithm dependent on age, risk, and disease factor to recruit a population of patients with hypertension at high risk of cardiac disease. In this article we report the main outcome results.

Methods

Study design

VALUE was an investigator-designed, prospective, multinational, double-blind, randomised, active-controlled, parallel-group trial. The primary objective was, at the same level of achieved BP, to compare the long-term effects on the incidence of cardiac morbidity and mortality, of antihypertensive therapy started with once-daily valsartan or amlodipine, in hypertensive patients with high cardiovascular risk. The complete study design has been published.[18]

A computer-generated randomisation list was prepared centrally by the sponsor, using appropriate blocks and guaranteeing that in study centres patients were assigned

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	Valsartan (n=7649)	Amlodipine (n=7596)
Sex (number [%] women)	3240 (42·4%)	3228 (42·5%)
Age (years)	67·2 (8·21)	67·3 (8·1)
Body-mass index (kg/m²)	28·6 (5·1)	28·7 (5·0)
Systolic blood pressure (mm Hg)	154·5 (19·0)	154·8 (19·0)
Diastolic blood pressure (mm Hg)	87·4 (10·9)	87·6 (10·7)
Heart rate (beats per min)	72·3 (10·8)	72·5 (10·7)
Race		
White	6821 (89·2%)	6796 (89·5%)
Black	325 (4·3%)	314 (4·1%)
Oriental	272 (3·6%)	261 (3·4%)
Other	231 (3·0%)	225 (3·0%)
Antihypertensive medication taken at time of randomisation		
Previously treated for hypertension	7088 (92·7%)	6989 (92·0%)
ACE inhibitor	3148 (41·3%)	3135 (41·4%)
Angiotensin-receptor blocker	812 (10·7%)	800 (10·6%)
α blockers	540 (7·1%)	495 (6·5%)
β blocker	2496 (32·7%)	2551 (33·7%)
Calcium-channel antagonist	3181 (41·7%)	3048 (40·2%)
Diuretics as monotherapy	2047 (26·9%)	2020 (26·7%)
Fixed-dose diuretic combinations	686 (9·0%)	634 (8·4%)
Qualifying disease factors		
Coronary heart disease	3490 (45·6%)	3491 (46·0%)
Peripheral arterial disease	1052 (13·8%)	1062 (14·0%)
Stroke or TIA	1513 (19·8%)	1501 (19·8%)
LVH with strain pattern*	454 (5·9%)	462 (6·1%)

Data are shown as numbers of patients (%) or mean (SD). TIA=transient ischaemic attack. LVH=left ventricular hypertrophy.*LVH including left bundle branch block.

Table 1: **Baseline characteristics**

to one of both treatment groups. The study medication was provided in externally indistinguishable capsules. Hydrochlorothiazide tablets were administered unblinded.

The trial protocol was approved by all involved ethics committees and the trial was undertaken in accordance with the Declaration of Helsinki. All patients gave written, informed consent. An independent data and safety monitoring board monitored safety. The executive committee had full access to the data, was responsible for the data analysis, and had full control over the right to publish. A statistician on the executive committee independently analysed data to validate and further explore the analyses done by statisticians employed by the sponsor.

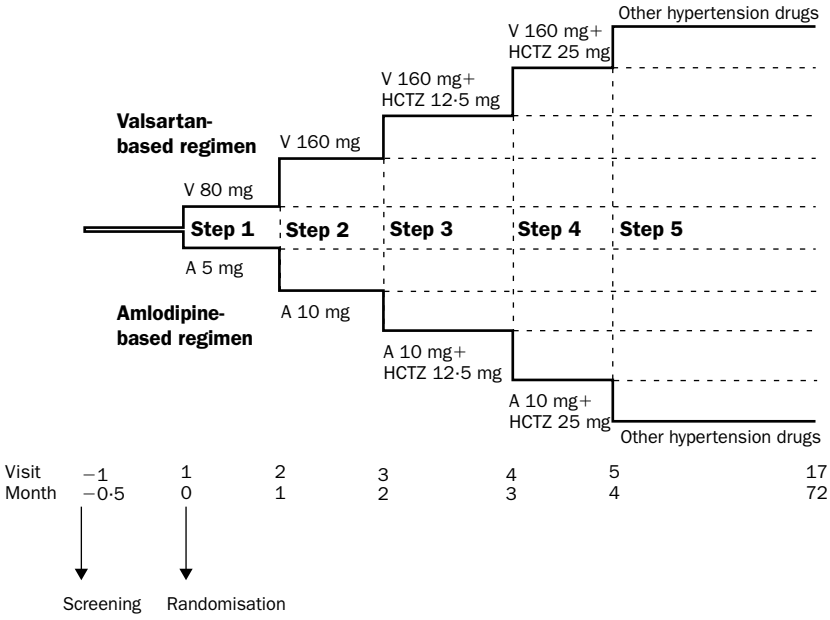

Figure 1: **Study design**
V=valsartan. A=amlodipine. HCTZ=hydrochlorothiazide.

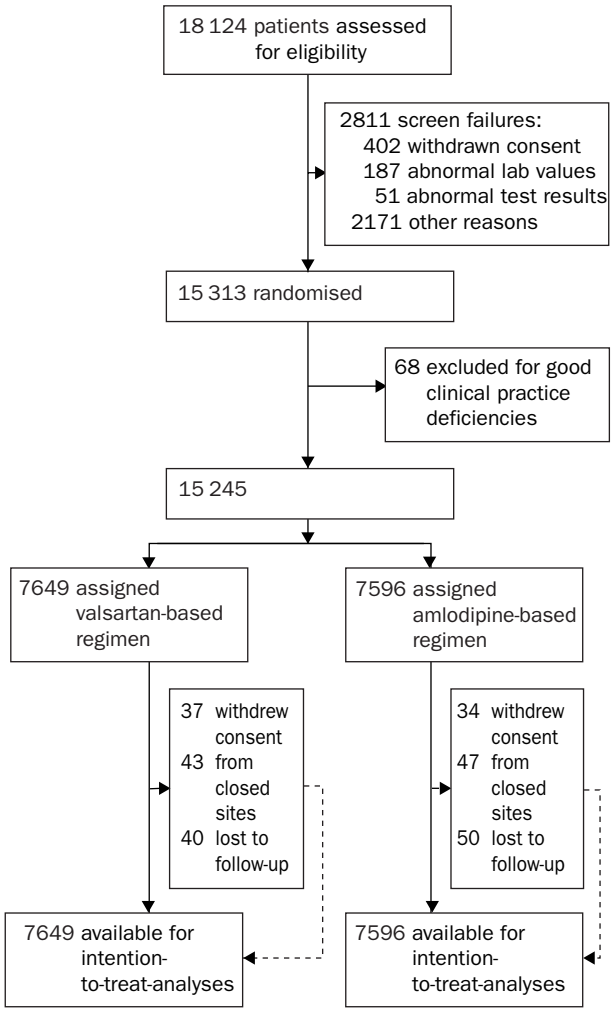

Figure 2: **Trial profile**

Population and treatment

VALUE included patients 50 years or older, with treated or untreated hypertension at baseline and predefined combinations of cardiovascular risk factors and cardiovascular disease. Additional inclusion criteria were: men or women of any racial background, 50 years of age and older, and presence of cardiovascular risk factors or disease according to an algorithm based on age and sex.[18]

The qualifying risk factors were male sex, age older than 50 years, verified diabetes mellitus, current smoking, high total cholesterol, left ventricular hypertrophy by electrocardiogram, proteinuria on dipstick and raised serum creatinine between 150 and 265 μmol/L (if >265 μmol/L patients were judged to have severe renal failure and were excluded). The qualifying diseases were verified coronary disease, cerebrovascular disease or peripheral arterial occlusive disease, or left ventricular hypertrophy with strain pattern.

Exclusion criteria were: renal artery stenosis, pregnancy, acute myocardial infarction, percutaneous transluminal

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	Valsartan	Amlodipine
Patients on study medication at primary endpoint including stroke or at final visit for patients without event (ITT population)	n=7649	n=7596
Valsartan 80 mg or amlodipine 5 mg	1213 (15·9%)	1583 (20·8%)
Valsartan 160 mg or amlodipine 10 mg	852 (11·1%)	1105 (14·5%)
Valsartan 80 mg or amlodipine 5 mg plus HCTZ	159 (2·1%)	329 (4·3%)
Valsartan 160 mg or amlodipine 10 mg plus HCTZ	1719 (22·5%)	1481 (19·5%)
Other combinations or drugs	1758 (23·0%)	1279 (16·8%)
No study therapy*	1948 (25·5%)	1819 (23·9%)
Patients on concomitant therapy (safety population)	n=7622	n=7576
ACE inhibitors	1574 (20·7%)	1461 (19·3%)
α blockers	1856 (24·4%)	1385 (18·3%)
β blockers	3656 (48·0%)	3295 (43·5%)
Diuretics as monotherapy	1023 (13·4%)	1137 (15·0%)
Diuretics as part of combination therapy	318 (4·2%)	319 (4·2%)
Statins	3553 (46·6%)	3516 (46·4%)
Aspirin	5570 (73·1%)	5505 (72·7%)

Data are number (%). ITT=intention-to-treat. HCTZ=hydrochlorothiazide.
*Patients who did not have a primary event including stroke and permanently discontinued the study medication or patients who did not take the study medication during the trial or patients for whom the last study medication taken before the event or at final visit is not recorded.

Table 2: **Antihypertensive and other medications in the study**

coronary angioplasty or coronary artery bypass graft within the past 3 months, clinically relevant valvular disease, cerebrovascular accident in the past 3 months, severe hepatic disease, severe chronic renal failure, congestive heart failure requiring ACE inhibitor therapy, patients on monotherapy with β blockers for both coronary artery disease and hypertension.

Patients already receiving antihypertensive treatment discontinued taking previous drugs and were directly rolled over to one of the two VALUE arms starting with either valsartan 80 mg or amlodipine 5 mg, without a placebo run-in period (figure 1). For previously untreated patients, hypertension was defined as a mean sitting systolic BP between 160 and 210 mm Hg (inclusive), and a mean sitting diastolic BP of less than 115 mm Hg. The upper limit of BP for patients already on antihypertensive treatment was 210 and/or 115 mm Hg. Patients with well-controlled hypertension were also accepted into the study, and no lower BP limit was set for treated patients.

Patients were followed up for 4–6 years with regular visits. Upward-titration of medication was implemented in five steps to reach a target BP of less than 140/90 mm Hg. Further antihypertensive drugs excluding angiotensin-receptor blockers could be given to achieve BP control. ACE inhibitors or calcium antagonists were allowed only if these drugs were clinically indicated for reasons other than hypertension. BP and heart rate were recorded 24 h post-dose with recommended BP-measurement techniques after patients had been seated for 5 min.

Outcome measures

The primary endpoint was time to first cardiac event (a composite of sudden cardiac death, fatal myocardial infarction, death during or after percutaneous coronary intervention or coronary artery bypass graft, death due to heart failure, and death associated with recent myocardial infarction on autopsy, heart failure requiring hospital management, non-fatal myocardial infarction, or emergency procedures to prevent myocardial infarction). Pre-specified secondary endpoints were fatal and non-fatal myocardial infarction, fatal and non-fatal heart failure, and fatal and non-fatal stroke. Analyses of all-cause mortality and new-onset diabetes were also pre-specified.

When VALUE was designed, meta-analysis[22] suggested that reduction of strokes entirely depended on the degree of BP reduction. Since we planned to achieve similar BP in both groups we did not expect to find any difference in strokes. Consequently, in this trial, strokes were categorised as secondary endpoints.

To detect new-onset diabetes (defined according to 1999 WHO criteria[23]) we first excluded all patients who at entry were diagnosed with diabetes, received anti-diabetic agents, or had abnormal glucose levels. In the remaining group, individual patient study forms and adverse events databases were monitored for new use of antidiabetic drugs and for newly reported diabetes. A blood chemistry report was mandatory at the end of the trial, and the diagnosis of new onset diabetes was made if the serum glucose concentration exceeded 7·8 mmol/L.

An endpoint committee, blinded to therapy allocation, reviewed the

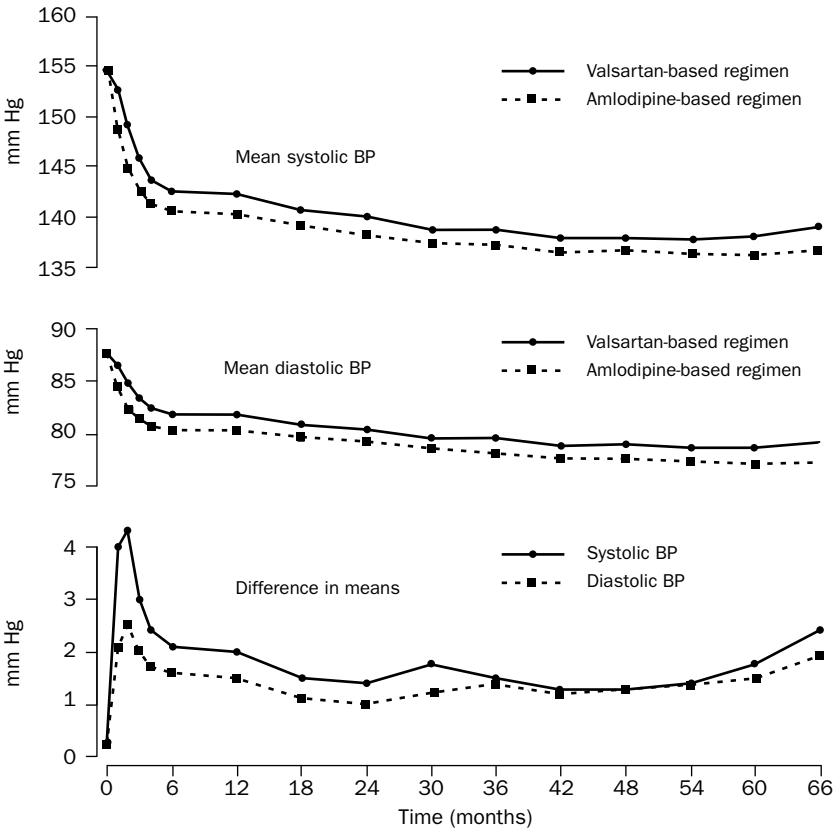

Figure 3: **Systolic and diastolic BP and differences (valsartan–amlodipine) in BP between treatment groups during follow-up**
BP difference between the two groups was significant (<0·000) at every time point. Overall differences in systolic BP=2·23 mm Hg (SE 0·18); overall differences in diastolic BP 1·59 mm Hg (SE 0·11). SDs of average BP at various time points in the amlodipine and valsartan groups are shown in table 4.

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	Valsartan (n=7649)		Amlodipine (n=7596)		Hazard ratio (95% CI)	p
	n (%)	Per 1000 patient years	n (%)	Per 1000 patient years		
Primary composite	810 (10·6%)	25·5	789 (10·4%)	24·7	1·04 (0·94–1·15)	0·49
Cardiac mortality	304 (4·0%)	9·2	304 (4·0%)	9·2	1·01(0·86–1·18)	0·90
Cardiac morbidity	586 (7·7%)	18·4	578 (7·6%)	18·1	1·02 (0·91–1·15)	0·71
Myocardial infarction*	369 (4·8%)	11·4	313 (4·1%)	9·6	1·19 (1·02–1·38)	0·02
Heart failure*	354 (4·6%)	11·0	400 (5·3%)	12·4	0·89 (0·77–1·03)	0·12
Stroke*	322 (4·2%)	10·0	281 (3·7%)	8·7	1·15 (0·98–1·35)	0·08
All-cause death	841 (11·0%)	25·6	818 (10·8%)	24·8	1·04 (0·94–1·14)	0·45
New onset diabetes	690 (13·1%)	32·1	845 (16·4%)	41·1	0·77† (0·69–0·86)	<0·0001

*Fatal and non-fatal. †Odds ratio. Incidence rates are based on patients without diabetes at baseline.

Table 3: **Endpoints (first time occurrence in each category)**

clinical records of all cardiovascular events reported by clinical centres and adjudicated according to the protocol criteria. If necessary, resolution was achieved by joint in-person reviews. The endpoint committee rejected 379 (19%) of submitted cardiac morbidity cases, 72 (12%) of cardiac mortality cases, and 314 (30%) of strokes. A diagnosis of congestive heart failure was confirmed if the patient met the predefined criteria used by the endpoint committee and an admission to hospital was required either for new onset or for management of chronic heart failure.

Routine laboratory tests were done by core laboratories. All electrocardiograms were assessed at two reading centres using standard parameters.[24,25] Adverse experiences and prespecified safety parameters were monitored throughout the trial.

The study closure lasted from Sept 5 through Dec 5, 2003. During this period all patients were recalled for a final clinic visit or a final life status was obtained in patients who prematurely discontinued the study. The database was locked on March 26, 2004. Endpoints that occurred before the final clinic visit or Dec 5 were included in the primary analysis.

Statistical methods

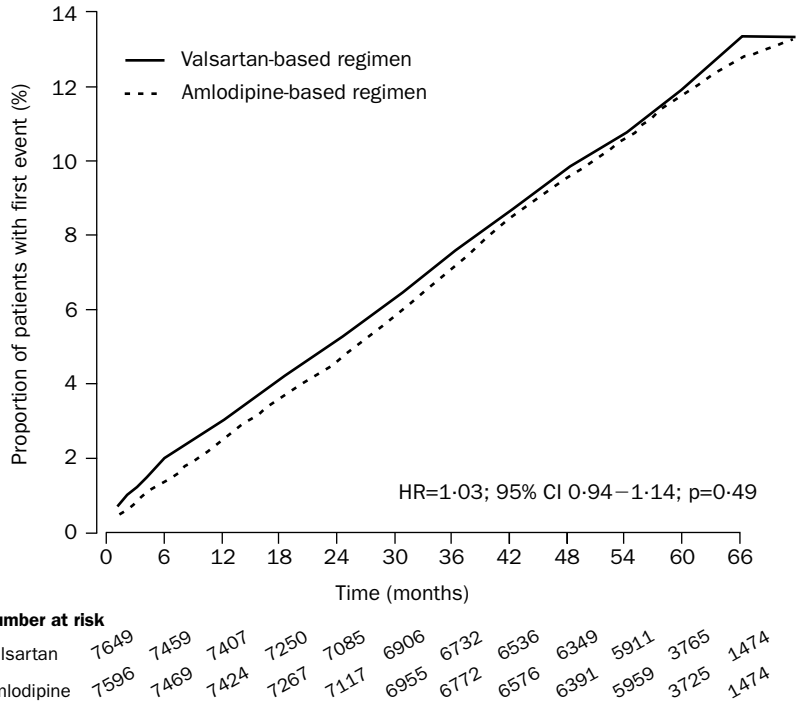
The study was endpoint-driven; 1450 patients with primary event were required to provide 90% power to detect a 15% reduction in the primary endpoint rate from 12·5% to 10·63% with 14 400 patients. All endpoints and BP values were analysed using the intention-to-treat approach.

Cox regression models were used to assess clinical events differences between treatment arms. Age, the presence of coronary heart disease, and the presence of left ventricular hypertrophy at baseline were used as a priori covariates to account for the effects of key risk predictors at baseline. Treatment effects were measured by hazard ratios and their 95% CIs based on Cox regression models. Event rates over time are presented as Kaplan-Meier curves. For analyses within time-specific intervals, odds ratios were calculated.

Only the time to the first cardiac event was considered in the composite primary endpoint. For secondary analyses, only the first event was counted in each category but a single patient could have multiple first events across all event categories. The safety population included all randomised patients who received at least one dose of the study medication. Differences between groups in frequency of adverse experiences were analysed with χ^2 test. All tests were 2-sided and significance level was set at 5%.

Role of the funding source

The study was designed interactively between an advisory board (later the VALUE executive committee) and the sponsor. The sponsor managed the data and did all final analyses. The executive committee had full access to all data and the statistician of the executive committee independently verified results. The study chairman and the associate chairman prepared the first draft and the executive committee wrote the final version of the paper.



Number at risk

Valsartan	7649	7459	7407	7250	7085	6906	6732	6536	6349	5911	3765	1474
Amlodipine	7596	7469	7424	7267	7117	6955	6772	6576	6391	5959	3725	1474

Figure 4: **Kaplan Meier curves for primary composite endpoint**

Results

15 313 eligible patients in 31 countries were randomised between September, 1997 and November, 1999. The two treatment groups were similar in terms of demographic characteristics, severity of hypertension, antihypertensive drug use before enrolment, and prevalence of coexisting cardiovascular conditions (table 1). 68 patients in nine centres were excluded because of good clinical practice deficiencies, and therefore 15 245 randomised patients were included in the analysis. 11 centres prematurely closed their operation because of local circumstances, and 90 patients from these centres were included in the intention-to-treat analysis, although results were available only up to the date of the closure. No life-status could be obtained at study closure for 71 patients

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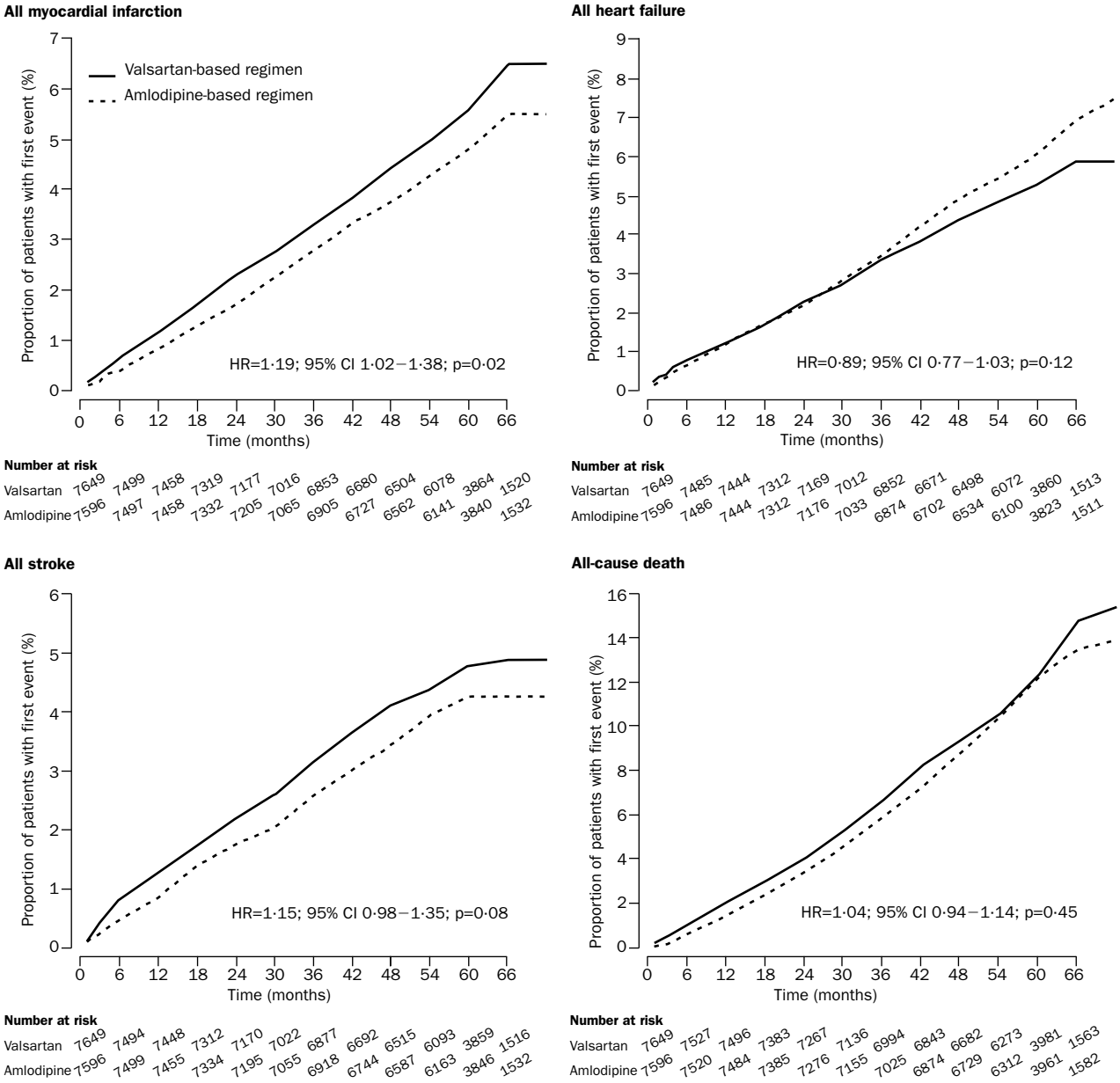

Figure 5: **Kaplan Meier curves for secondary endpoints and all-cause death**

who withdrew consent to participate in the study. Only 90 patients (0·6%) were lost to follow-up (figure 2).

Mean follow-up time was 4·2 years (SD 1·2 years, interquartile range [IQR] 4·0–4·9). The study accumulated 63 631 patient-years of follow-up. 5636 (73·7%) patients in the valsartan group and 5691 (74·9%) in the amlodipine group remained on blinded study therapy throughout the entire follow-up period. In none of the patients who discontinued the study was the code of the study drug broken. Most of these patients continued to return for clinic visits. The mean duration of exposure to study medication was 3·6 years (SD 1·7; IQR 2·8–4·3) in the valsartan-based group and 3·6 years (1·7; 2·8–4·3) in the amlodipine-based group. The proportion of patients receiving valsartan monotherapy as the last recorded study medication was significantly smaller than that of patients 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 (table 2). The median daily doses were 151·7 mg (IQR 83·2–158·5) for valsartan and 8·5 mg (IQR 5·0–9·9) for amlodipine. When study drug interruptions were included, the median doses were 149·3 mg (80·2–158·5) and 8·2 mg (5·0–9·9), respectively.

At study end (72 months) or final visit the mean BP was 139·3/79·2 mm Hg (SD 17·6/9·8) with valsartan-based regimens and 137·5/77·7 mm Hg (15·0/9·0) with amlodipine-based regimens (BP reduction from baseline until the study end 15·2/8·2 and 17·3/9·9 mm Hg in the valsartan and amlodipine arms, respectively; p<0·0001 between groups; figure 3). After 1 month of treatment, BP in the amlodipine group was substantially (4·0/2·1 mm Hg) lower than in the valsartan group. At 6 months the difference decreased to 2·1/1·6 mm Hg. Thereafter, the average BP difference was about 2·0/1·6 mm Hg. From the sixth month until the end of the study BP decreased in both treatment groups: valsartan-based regimens by 3·3/2·6 mm Hg, and amlodipine-based regimens by 3·0/2·5 mm Hg. BP control was achieved in 4392 (58%) of patients on valsartan and 4793 (64%) of those on amlodipine for systolic pressure (<140 mm Hg) and in 6652 (88%) and 6940

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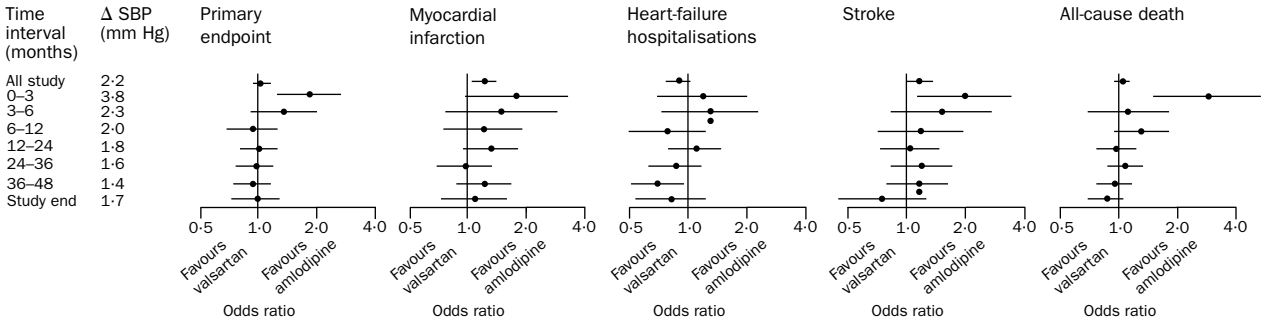

Figure 6: **Differences in BP between treatment groups with odds ratios for primary endpoint, secondary endpoints, and all-cause death during consecutive time periods in the study**
Bars show 95% CI.

(92%), respectively, for diastolic pressure (<90 mm Hg). The target BP (both <140 mm Hg systolic and <90 mm Hg diastolic) was achieved in 4274 (56%) patients in the valsartan group and 4694 (62%) in the amlodipine group.

Major findings are shown in table 3. The frequency of the main outcome, a composite of cardiac mortality and morbidity, did not differ significantly between the two treatment groups. Of the secondary outcomes, myocardial infarction was significantly (p=0·02) more frequent in the valsartan group, but rates of heart-failure admissions and stroke (fatal and non-fatal) were similar between the two groups. Rates of total cardiovascular events including stroke were 1074 in the valsartan versus 1021 in the amlodipine group (hazard ratio 1·06, 95% CI 0·98–1·16, p=0·17). Rates of all-cause death did not differ significantly between the groups. New-onset diabetes arose in significantly fewer patients on valsartan than on amlodipine (p<0·0001).

The Kaplan-Meier curves for the primary and secondary endpoints are shown in figures 4 and 5. Figure 6 and table 4 show BP differences and odds ratios for time periods of the trial for primary and secondary endpoints. Higher odds ratios in favour of amlodipine were noted for all endpoints during the first 6 months, when BP differences between the treatment groups were greatest. In the following months, there was an attenuation in odds ratios. For heart-failure hospital admission there was a trend in favour of valsartan during the last 4 years.

Both treatment strategies were well tolerated with few severe adverse events (table 5). The most frequently reported adverse event—oedema, including peripheral oedema—was twice as common in amlodipine-treated patients as in valsartan-treated patients. Hypokalaemia was more frequent in the amlodipine group. However, dizziness, headache, and diarrhoea were more frequently reported in patients on valsartan-based regimens, although the frequency of these events was low. Angina was reported more frequently in the valsartan-treated group. 911 patients in the valsartan group (11·9%) and 983 (12·9%) in the amlodipine group discontinued treatment because of adverse events. Descriptive laboratory values at baseline and end of study are reported in table 6.

Discussion

The VALUE trial was designed to test the hypothesis that, for the same level of BP control, a valsartan-based regimen would be better than an amlodipine-based regimen for cardioprotection in patients with hypertension. For the primary composite endpoint of cardiac morbidity and mortality and for all-cause mortality, no significant differences were noted between the treatment groups. The amlodipine group had a significantly lower incidence of myocardial infarction and higher rate of new-onset diabetes than in the valsartan group. The most consistent and statistically significant difference between the groups was in BP control: amlodipine-based therapy was significantly more efficacious in reducing BP, especially during the early phases of treatment. The differences in BP between the drug regimens were 4·0/2·1, 4·3/2·5, 3·0/2·0, 2·4/1·7, 2·1/1·6 and 2·0/1·5 mm Hg after 1, 2, 3, 4, 6, and 12 months, respectively, and stabilised at about 1·5/1·3 mm Hg thereafter.

Disparity in BP control in the comparator groups in VALUE confounds the interpretation of the results. Failure to achieve equivalent BP levels, particularly for systolic BP,

	Mean blood pressure (SD)*		Time-specific interval odds ratios (95% CIs)				
Visit	Valsartan	Amlodipine	Primary endpoint	Stroke	Myocardial infarction	Heart failure	All-cause mortality
Baseline	154·5 (19·0) 87·4 (10·9)	154·8 (19·0) 87·6 (10·7)					
0–3 months	149·2 (19·5) 84·8 (10·4)	145·4 (16·1) 82·6 (9·3)	1·78 (1·22–2·60)	1·94 (1·10–3·42)	1·74 (0·94–3·22)	1·18 (0·70–2·00)	2·84 (1·51–5·34)
3–6 months	143·2 (16·8) 82·1 (9·3)	140·9 (14·3) 80·4 (8·6)	1·32 (0·89–1·96)	1·50 (0·82–2·72)	1·47 (0·76–2·83)	1·29 (0·73–2·28)	1·12 (0·70–1·81)
12 months	142·3 (16·9) 81·7 (9·3)	140·3 (14·4) 80·2 (8·5)	0·93 (0·69–1·26)	1·18 (0·71–1·95)	1·19 (0·74–1·90)	0·78 (0·49–1·24)	1·30 (0·93–1·83)
24 months	140·0 (16·2) 80·4 (9·0)	138·2 (13·8) 79·2 (8·6)	0·99 (0·80–1·24)	1·03 (0·73–1·45)	1·30 (0·94–1·80)	1·09 (0·78–1·50)	0·98 (0·78–1·23)
36 months	138·7 (16·1) 79·5 (9·2)	137·2 (13·5) 78·1 (8·6)	0·97 (0·78–1·19)	1·18 (0·83–1·68)	0·96 (0·69–1·34)	0·85 (0·63–1·16)	1·08 (0·88–1·33)
48 months	137·9 (15·6) 78·8 (9·0)	136·6 (13·6) 77·5 (8·6)	0·93 (0·745–1·15)	1·13 (0·79–1·61)	1·20 (0·86–1·67)	0·69 (0·51–0·94)	0·95 (0·78–1·15)
Study end	139·3 (17·6) 79·2 (9·8)	137·5 (15·0) 77·7 (9·0)	0·98 (0·74–1·29)	0·75 (0·45–1·25)	1·07 (0·72–1·59)	0·81 (0·53–1·22)	0·87 (0·70–1·09)

*Upper values systolic, lower values diastolic.

Table 4: **Blood pressure and odds ratios throughout the study**

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	Valsartan (n=7622)	Amlodipine (n=7576)	p
Pre-specified adverse events			
Peripheral oedema	1135 (14·9%)	2492 (32·9%)	<0·0001
Dizziness	1257 (16·5%)	1083 (14·3%)	<0·0001
Headache	1120 (14·7%)	947 (12·5%)	<0·0001
Fatigue	739 (9·7%)	674 (8·9%)	0·0750
Additional common adverse events			
Diarrhoea*	670 (8·8%)	515 (6·8%)	<0·0001
Angina pectoris*	708 (9·3%)	485 (6·4%)	<0·0001
Angina pectoris†	335 (4·4%)	234 (3·1%)	<0·0001
Oedema other*	243 (3·2%)	462 (6·1%)	<0·0001
Hypokalaemia*	266 (3·5%)	469 (6·2%)	<0·0001
Atrial fibrillation†	182 (2·4%)	151 (2·0%)	0·1197
Syncope†	129 (1·7%)	75 (1·0%)	<0·0001

*With an incidence >3% and a difference between treatment groups >1%.
†Reported as serious.

Table 5: **Adverse events**

in the treatment arms has been a frequent feature of comparative outcome trials of antihypertensive therapy. Favourable BP trends in particular treatment groups might have amplified or explained the apparent outcome benefits in some trials[4,7,10,26–28] and masked differences in others.[5,8,26] A meta-regression analysis concluded that the results of contemporary outcome trials can be attributed mainly to observed differences in systolic BP,[14] which in some instances might reflect chosen doses of study drugs. The lack of BP comparability at the end of a blinded study largely reflects the limited range of available drug dosage. Usable doses are further narrowed by regulatory differences in international studies. When VALUE was conceived, a dose range of 80–160 mg of valsartan was approved worldwide for treatment of hypertension. A linear BP dose-response relation was documented for valsartan in the range of 40–160 mg without any signs of a plateau[29] and it stood to reason that in VALUE higher doses would be useful. However, the 320 mg dose which has been used with success in outcome trials seeking registration for new indications (heart failure and in left-ventricular dysfunction[30,31]), was not authorised for use in hypertension.

Total composite cardiac morbidity and mortality was not different between the two VALUE treatment arms. Significantly more myocardial infarctions were seen in the valsartan-based treatment group. However, in the high coronary risk population in VALUE, 79% of the excess of infarctions on valsartan occurred during the first 2 years of the study. Thereafter, when the BP of the two groups was closer, the odds ratio trends for myocardial infarction were less consistent. Early[22] and later[15] placebo-controlled trials showed that BP lowering reduces the incidence of coronary heart disease endpoints to the same degree, regardless of the type of drug used. However, the same degree of BP lowering resulted in a substantially lesser reduction of myocardial infarction compared with the reduction of strokes. This observation supported the notion that something other than BP might be involved in the excessive coronary risk in hypertension. This belief, in turn, fuelled hopes that new drugs might offer better protection against myocardial infarction. Published findings failed to confirm such additional effects. In direct drug comparisons, diuretics, β blockers, ACE inhibitors,[5,6,10,17] and calcium antagonists at the doses used[6,8–12,32] had equal effects. Finally, recent findings showed no difference in coronary heart disease between angiotensin-receptor blockers[16,24] and comparator groups. In VALUE, as in previous studies, the benefit of BP lowering was clearer for strokes than for myocardial infarction. Most of the excess stroke in the valsartan group appeared in the first year when the difference in BP between the two groups was largest. However, a decrease of the excess myocardial infarction was seen a year later than for strokes. We do not know whether this finding means that it took a longer time for vascular healing to occur, or whether it reflects some pressure-unrelated differences between the drugs.

	Valsartan (n=7622)		Amlodipine (n=7576)	
	Baseline	End of study	Baseline	End of study
Haemoglobin (g/L)	140·8 (13·4)	137·5 (15·5)	140·9 (13·3)	140·8 (15·1)
Sodium (mmol/L)	140·7 (2·7)	141·2 (3·4)	140·7 (2·7)	141·4 (3·3)
Potassium (mmol/L)	4·4 (0·4)	4·4 (0·5)	4·4 (0·5)	4·2 (0·5)
AAT (IU/L)	23·5 (14·0)	22·5 (18·6)	23·3 (11·8)	23·1 (14·9)
Glucose (mmol/L)	6·9 (2·9)	6·7 (2·6)	6·9 (2·8)	6·9 (2·7)
Total cholesterol (mmol/L)	5·7 (1·2)	5·2 (1·1)	5·7 (1·2)	5·3 (1·1)
Uric acid (μmol/L)	372·9 (95·7)	394·0 (104·7)	373·4 (94·6)	373·4 (100·5)
Creatinine (μmol/L)	101·2 (23·9)	108·1 (45·0)	100·9 (23·6)	103·2 (48·1)

Data are mean (SD). AAT=alanine aminotransferase.

Table 6: **Laboratory values**

In the second half of VALUE there was a persistent trend for fewer admissions for heart-failure in the valsartan group but the overall difference did not reach statistical significance. Patients on calcium antagonists are prone to develop drug-related peripheral oedema, which could be mistaken for heart failure. In VALUE, the validity of the diagnosis of heart failure was adjudicated by a panel of experts. In no case was the diagnosis of heart failure made solely on the basis of ankle oedema, which was reported in 2179 patients in the amlodipine group, whereas heart failure was diagnosed in only 400 patients.

A meta-analysis of antihypertensive trials[14] suggested a reduction in heart failure favouring drugs which block the renin-angiotensin system compared with other drugs, including calcium antagonists. Prolonged use of enalapril in human hypertension reduces, whereas amlodipine increases, sympathetic nervous tone.[33] It is speculated that such radically different physiological responses to BP lowering might lead to different long-term cardiovascular outcomes. Although the difference did not reach statistical significance, the steady trend for greater heart failure reduction with valsartan-based regimens in VALUE is consistent with our original hypothesis and with published findings.

In VALUE, stroke incidence was lower in the amlodipine group than in the valsartan group. Compared with other antihypertensives, greater reduction in stroke risk has been reported with calcium antagonists in some[6,8,10,12] but not all studies.[9] Meta-analyses[14,15] showed an overall greater reduction in stroke with calcium antagonists. However, across a wide range of studies, including those with calcium antagonists, the incidence of stroke seems to be directly related to the observed differences in BP between active drugs and placebo, between more or less intensive therapy, or between different antihypertensive agents.[14]

In the LIFE study,[16] losartan-based therapy was better than atenolol-based therapy in reducing strokes, despite almost identical BP control. However, it cannot be determined whether this reduction in stroke reflected only positive effects of angiotensin-receptor blockers or whether negative vascular effects of the β blocker contributed.[34] In the SCOPE trial,[26] substantial BP differences between the study groups might largely explain the observed stroke reduction in the candesartan arm. It has been suggested[14] that even small reductions in BP might be important in stroke reduction. The time

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relationship of excess strokes in the valsartan group of VALUE can be best explained by between-group differences in BP, which were largest in the first year. 63% of the entire observed excess of strokes occurred in the first 6 months, and this value grew to 76% at the end of the first year.

Control of BP at the end of VALUE largely met current standards.[35–37] At the end of the study, good control of BP had been achieved in both treatment groups.

The incidence of new-onset diabetes in VALUE was significantly lower with valsartan-based than with amlodipine-based regimens. Compared with diuretics or β blockers, a reduction of new-onset diabetes has been seen with ACE inhibitors,[4,5,10] calcium antagonists,[9,10] and with angiotensin-receptor blockers.[6,26] Diuretics and β blockers each negatively affect glucose balance, whereas ACE inhibitors and calcium antagonists are thought to be metabolically neutral. In VALUE's comparison of a calcium antagonist and an angiotensin-receptor blocker, the 23% reduction of new-onset diabetes with valsartan suggests an active positive effect of this drug on long-term glucose metabolism. A similar reduction was seen with lisinopril compared with amlodipine in ALLHAT,[10] suggesting that this effect might be related to blockade of biological effects of angiotensin II.

Diabetes greatly increases the cardiovascular consequences of hypertension. In high-risk patients, an immediate benefit of BP lowering could override long-term negative effects of diabetes induced by diuretics and β blockers. However, even uncomplicated hypertension is frequently associated with insulin resistance.[38] Committing such a large population of patients to decades of treatment with drugs that increase total cardiovascular risk seems illogical. At a time when there is a pandemic of type 2 diabetes, these findings from VALUE are especially relevant.

Patients in each treatment group of VALUE had few adverse effects. Oedema was more frequent and angina was less common in the amlodipine group than in the valsartan group, as might be expected from amlodipine's pharmacological profile. Some of the less common adverse events were more often reported in patients randomised to valsartan. This finding may appear to contradict the general opinion of the placebo-like tolerability of angiotensin-receptor blockers.[39] However, since BP was less well-controlled in the valsartan arm, more non-study drugs for hypertension were used in these patients, which might account for the observed adverse effect profiles, bearing in mind that in studies like VALUE, treatment regimens rather than individual drugs are compared.

The findings of VALUE may provide important, pragmatic lessons about the design, conduct, and analysis of future outcome trials in hypertension. To further investigate these issues, additional analyses have been undertaken.[40] The results of the trial could also give new insights into the clinical importance of the rate of achieving BP control—the findings suggest that recommended BP goals need to be reached within a relatively short time (weeks rather than months), at least in patients with hypertension who are at high cardiovascular risk. Furthermore, the results draw attention to the clinical relevance of apparently minor differences in BP within the high-to-normal range. Acheiving adequate blood-pressure control in high-risk patients will often require combination therapy from the outset.[35,36]

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Conflict of interest statement

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