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 regimens 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.


Introduction

Substantial benefits in prevention of major cardiovascular morbidity and mortality in high-risk populations have been reported with calcium antagonists1–3 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.5–7 The LIFE study8 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 study9 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. VALUE10–20 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.10,11,15

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

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 at high cardiovascular risk. The complete study design has been published.10,11

A computer-generated randomisation list was prepared centrally by the sponsor, using appropriate blocks and guaranteeing that in study centres patients were assigned
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
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 amiodipine 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, 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 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), 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
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. Adverse experiences were analysed with intention-to-treat analysis, although rates of events were available only up to the date of local circumstances, and 90 patients maturely closed their operation because of good clinical practice deficiencies, and therefore included in the analysis. 11 centres pre-randomised eligible patients in 31 countries from 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 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 chi-squared 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.

**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.

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

<table>
<thead>
<tr>
<th>Event</th>
<th>Valsartan (n=7649)</th>
<th>Amlodipine (n=7596)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite</td>
<td>810 (10.6%) 25-5</td>
<td>799 (10.4%) 24-7</td>
<td>1.04 (0.94–1.15) 0.49</td>
</tr>
<tr>
<td>Cardiac mortality</td>
<td>304 (4.0%)</td>
<td>304 (4.0%) 9.2</td>
<td>0.91 (0.86–1.18) 0.49</td>
</tr>
<tr>
<td>Cardiac morbidity</td>
<td>586 (7.7%) 18-4</td>
<td>578 (7.6%) 18-1</td>
<td>1.02 (0.91–1.15) 0.71</td>
</tr>
<tr>
<td>Myocardial infarction*</td>
<td>369 (4.8%) 11-4</td>
<td>313 (4.1%) 9.6</td>
<td>0.89 (0.77–1.03) 0.29</td>
</tr>
<tr>
<td>Stroke*</td>
<td>354 (4.6%) 11.0</td>
<td>400 (5.3%) 12.4</td>
<td>0.89 (0.77–1.03) 0.12</td>
</tr>
<tr>
<td>All-cause death</td>
<td>841 (11.0%) 25.6</td>
<td>818 (10.8%) 24.8</td>
<td>1.04 (0.94–1.14) 0.45</td>
</tr>
<tr>
<td>New onset diabetes</td>
<td>690 (13.1%) 32-1</td>
<td>845 (16.4%) 41-1</td>
<td>0.77 (0.69–0.86) &lt;0.0001</td>
</tr>
</tbody>
</table>

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

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**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 10.6% to 9.2% with 14400 patients. All endpoints and BP values were analysed using the intention-to-treat approach...

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

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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

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

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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,
Closer the odds ratio trends for myocardial infarction were consistent with our original hypothesis and with published findings. 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.

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 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. 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 some6,8,10,12 but not all studies. Meta-analyses 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.

In the LIFE study, 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. In the SCOPE trial, substantial BP differences between the study groups might largely explain the observed stroke reduction in the candesartan arm. It has been suggested that even small reductions in BP might be important in stroke reduction. The time 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, and calcium antagonists at the doses used had equal effects. Finally, recent findings showed no difference in coronary heart disease between angiotensin-receptor blockers and comparator groups.

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### Table 5: Adverse events

<table>
<thead>
<tr>
<th></th>
<th>Valsartan (n=7622)</th>
<th>Amlodipine (n=7576)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre-specified adverse events</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral oedema</td>
<td>1135 (14-9%)</td>
<td>2492 (32-9%)</td>
<td>&lt;0-0001</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1257 (16-5%)</td>
<td>1083 (14-3%)</td>
<td>&lt;0-0001</td>
</tr>
<tr>
<td>Headache</td>
<td>1120 (14-7%)</td>
<td>947 (12-5%)</td>
<td>&lt;0-0001</td>
</tr>
<tr>
<td>Fatigue</td>
<td>739 (9-7%)</td>
<td>674 (8-9%)</td>
<td>0-0750</td>
</tr>
<tr>
<td><strong>Additional common adverse events</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhoea*</td>
<td>670 (8-8%)</td>
<td>515 (6-8%)</td>
<td>&lt;0-0001</td>
</tr>
<tr>
<td>Angina pectoris*</td>
<td>708 (9-3%)</td>
<td>485 (6-4%)</td>
<td>&lt;0-0001</td>
</tr>
<tr>
<td>Oedema other*</td>
<td>345 (4-4%)</td>
<td>234 (3-1%)</td>
<td>&lt;0-0001</td>
</tr>
<tr>
<td>Hypokalaemia*</td>
<td>243 (3-2%)</td>
<td>462 (6-1%)</td>
<td>&lt;0-0001</td>
</tr>
<tr>
<td>Atrial fibrillation†</td>
<td>182 (2-4%)</td>
<td>151 (2-0%)</td>
<td>0-1197</td>
</tr>
<tr>
<td>Syncope†</td>
<td>129 (1-7%)</td>
<td>75 (1-0%)</td>
<td>&lt;0-0001</td>
</tr>
</tbody>
</table>

*With an incidence >5% and a difference between treatment groups >1%. †Reported as serious.

### Table 6: Laboratory values

<table>
<thead>
<tr>
<th></th>
<th>Valsartan (n=7622)</th>
<th>Amlodipine (n=7576)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Haemoglobin (g/L)</strong></td>
<td>14-0 (13-3)</td>
<td>13-7 (15-5)</td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>14-0 (7-2)</td>
<td>14-1 (3-2)</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>4-4 (0-4)</td>
<td>4-4 (0-5)</td>
</tr>
<tr>
<td>Urate (µmol/L)</td>
<td>372 (9)</td>
<td>394 (0)</td>
</tr>
</tbody>
</table>

Data are mean (SD). AAT=alanine aminotransferase.
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.35,36 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 amiodipine-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 diuretics or β blockers, however, even uncomplicated hypertension is frequently treated with drugs that increase total cardiovascular risk seems illogical. In studies like VALUE, treatment regimens rather than individual drugs are compared. Bearing in mind that in studies like VALUE, treatment from the outset.35,36

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. 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. Achieving adequate blood-pressure control in high-risk patients will often require combination therapy from the outset.35,36

VALUE investigators


VALUE committees

Executive committee — Stevo Julius (Chair, USA), Sverre E Kjeldsen (Associate Chair, Norway), John H Laragh (USA), Michael A Weber (USA), Hans R Brunner (Switzerland), Gordon McNInnes (UK), Alberto Zanchetti (Italy), Anthony Schork (USA), Lennart Hansson (Sweden).

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