The Valsartan Antihypertensive Long-term Use Evaluation (VALUE) Trial of Cardiovascular Events in Hypertension. Rationale and Design

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Essential hypertension is a major Public Health issue. Although the number of treated hypertensive patients has increased, only 25% of treated patients have their blood pressure levels under control. The benefit of treating hypertension has been proven, but cardiovascular morbidity and mortality rates remain high. The ideal antihypertensive drug should not only normalize blood pressure levels, but also reduce the associated cardiovascular morbidity and mortality rates. The role of angiotensin II in systemic hypertension and its complications has been recently redefined. The potent trophic effects of angiotensin II on blood vessels and on cardiac cells have been well demonstrated, especially the role of angiotensin II in left ventricular hypertrophy, vascular hypertrophy, endothelial dysfunction, and congestive heart failure. Of all ongoing mortality and morbidity trials in systemic hypertension, VALUE (Valsartan Antihypertensive Long-term Use Evaluation) is the only one comparing an angiotensin II antagonist (valsartan) with a third-generation calcium channel blocker (amlodipine). The main hypothesis of the VALUE trial is that, for an equivalent decrease in blood pressure, valsartan will be more effective than amlodipine in decreasing cardiac mortality and morbidity. VALUE is a prospective, multinational, multicentre, double-blind, randomized, active-controlled, 2-arm parallel group comparison with a response-dependent dose titration scheme. VALUE involves 14 400 patients in over 30 countries, who will be followed for 4 years or until 1450 patients experience a primary endpoint. The population to be included in VALUE consists of hypertensive men and women, aged 50 years or older, and at a relatively high risk of sustaining a cardiovascular event. The high risk profile is defined taking into account age, gender, and a list of cardiovascular risk factors and disease factors. Risk factors are cigarette smoking, hypercholesterolaemia, diabetes mellitus, uncomplicated left ventricular hypertrophy, proteinuria, and high serum creatinine. Disease factors include documented history of myocardial infarction, peripheral vascular disease, stroke or transient ischaemic attack, or the presence of left ventricular hypertrophy with strain on the ECG. A unique feature of VALUE is the assessment of the predictive power of this cardiovascular risk factor scale in a large population of treated hypertensive patients. The trial started on 10 September 1997. Key words: amlodipine, angiotensin II antagonist, angiotensin receptor blocker, cardiovascular, cardiovascular risk, hypertension, intervention, mortality–morbidity, valsartan.

INTRODUCTION

Essential hypertension is the most prevalent cardiovascular disease in the world, and a major public health issue [1, 2]. In the US, for instance, hypertension is present in nearly 75% of the African–American population and in 50% of the Caucasian population aged 60 to 74 years [3]. The worldwide increase in the use of antihypertensive drugs has led to an impressive reduction in cardiovascular morbidity and mortality [4]. The effect of antihypertensive drugs on cardiovascular morbidity and mortality, however, is far from homogeneous. The first inkling of a differential effect came from the VA study in the USA [5] where the frequency of stroke (20 instances in controls vs 5 instances in treated patients) and of congestive heart failure (11 vs 0) in treated hypertensive patients and controls respectively decreased dramatically, but the frequency of coronary events did not change significantly (13 in the control group vs 11 in the treated group). Two decades later, a meta-analysis by Collins et al. [4] showed a decrease in stroke of 42% in 37 000 hypertensive patients treated for 5 years. During the same time interval, the decrease in coronary events was only 14%. These data triggered a reappraisal of cardiovascular events in hypertension, and led to appreciation of other factors, besides high blood pressure, which are conducive to cardiovascular events in hypertension. Amongst these other factors, the renin-angiotensin system has been suggested to play a key role [6].

The last decade has seen a large number of cardiovascular morbidity and mortality trials comparing old with new drugs in hypertension. These trials involve over 100 000 patients worldwide. Most of them compare calcium channel blockers with diuretics and/or beta-blockers.
[7, 8], others compare angiotensin converting enzyme (ACE) inhibitors with diuretics alone or with combinations of diuretics and beta-blockers [9, 10]. These studies will show—at least—equivalence to the old “gold standard” of diuretics and beta-blockers. The newest trials involve the latest addition to the therapeutic armamentarium of hypertension, angiotensin II antagonists such as valsartan, candesartan, and losartan. The LIFE [11] trial compares the relative effects of losartan and atenolol on cardiovascular morbidity and mortality in patients with essential hypertension and left ventricular hypertrophy; the SCOPE trial investigates the effect of candesartan on cardiovascular morbidity and mortality in elderly hypertensive patients.

The Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial is the first to compare the angiotensin II antagonist valsartan to a third-generation calcium channel blocker, amlodipine. The driving scientific hypothesis of the VALUE trial is that for the same level of blood pressure control, valsartan will be significantly more effective than the calcium channel blocker amlodipine in decreasing acute myocardial infarction, congestive heart failure, and cardiac mortality. Despite recent challenges to the safety of calcium channel blockers [12, 13], convincing evidence is accruing that these compounds are clinically at least as useful as the older generation gold standard beta-blockers and diuretics. In the large Syst-Eur study the overall decrease in cardiovascular mortality and the overall mortality rates in patients treated with a long-acting dihydropyridine [14] were practically identical with those reported using a diuretic beta-blocker treatment in a similar population in the USA [15]. In addition to being effective antihypertensive agents, the calcium channel blockers may, in fact, have some useful ancillary cardiovascular protective properties. In animal experiments they improve outcomes after myocardial infarction [16, 17]; this cardioprotective mechanism has been investigated in some detail [18, 19]. Based on animal studies, it has been suggested that calcium channel blockers may also exert an antiatherogenic effect, but the angiographic outcomes in clinical studies range from positive [20] to negative [21].

Although some retrospective studies have suggested an increased risk in coronary deaths in calcium channel blocker treated hypertensives [22], this observation seems to relate only to short-acting agents. It is generally accepted that if there are any negative effects, these relate to sympathetic counter-regulation elicited by sudden blood pressure decreases observed with short-acting preparations. Amlodipine is a long-acting calcium channel blocker which does not trigger sympathetic activation during chronic use. The choice of amlodipine as the comparator for the VALUE trial is not based on any weaknesses of the compound, but on the belief that antagonizing the renin-angiotensin system may offer clinical advantages.

RATIONALE

Angiotensin II has a well-defined trophic effect on vascular and cardiac cells [23], cardiac matrix [24, 25] and other cell lines [26]. Folkow [27] showed that vascular hypertrophy accelerates hypertension by amplifying vasoconstriction and decreasing vasodilation. This concept has been validated for angiotensin II by Schiffrin & Deng [28] in a study of gluteal fat biopsies, where regression of vascular hypertrophy was assessed in patients chronically treated with either the ACE inhibitor cilazapril or the beta-blocker, atenolol. Significant ($p < 0.05$) regression of vascular hypertrophy was observed only in the group which received the ACE inhibitor.

Left ventricular hypertrophy is a cardiovascular risk factor in itself [29, 30]. Angiotensin II stimulates division of fibroblasts by an as yet unknown mechanism, although the level of intracellular Ca$^{++}$ seems to play a role. This Ca$^{++}$ pathway is also involved in the trophic action of angiotensin II on vascular smooth muscle cells. In experimental animals, left ventricular hypertrophy decreases when the animals are treated with an angiotensin converting enzyme inhibitor, but not with a Ca$^{++}$ antagonist or a vasodilator such as hydralazine [31]. Clinical studies suggest that a similar difference in the effect of drugs on the left ventricular mass may also occur during the chronic treatment of hypertension. Dahlo¨f’s meta-analysis [32] was the first to show that ACE inhibitors are the pharmacological class with the most pronounced effect on reduction of left ventricular mass. In 1996, Schmieder et al. [33] published a meta-analysis of double-blind trials looking at regression of left ventricular hypertrophy in hypertensive patients, where ACE inhibitors appeared as the most potent drug class to achieve regression of LVH. Gottdiener et al. [34] confirmed these data in a study with 1105 male veterans. On the other hand, the randomized prospective study of mild hypertension (TOMHS) found no difference in the effects of a diuretic, a beta-blocker, an alpha-blocker, and an ACE inhibitor on the left ventricular mass [35]. The RACE study showed the ACE inhibitor ramipril to be superior to atenolol in decreasing left ventricular hypertrophy [36]. Recent data assessing the effect of the angiotensin II antagonist valsartan in hypertensive patients have shown a significant decrease in LV mass index with valsartan [37].

Patients with hypertension can present with angina in the absence of coronary artery disease. One explanation is the presence of left ventricular hypertrophy, which impairs coronary vasodilator reserve. However, there
are still some hypertensive patients without left ventricular hypertrophy who will present with angina. In these patients, the anginal pain is due to myocardial ischaemia related to the increase in coronary resistance at the microvascular level [38]. Furthermore, endothelial-dependent relaxation is impaired at the level of resistance vessels in patients with hypertension. High angiotensin II levels trigger endothelin activation, which is one of the most potent endogenous vasoconstrictors [39]. When the endothelium is damaged, acetylcholine does not trigger vasodilation. Hypertensive patients have been shown to have a decreased response to acetylcholine [40], which confirms dysfunction of the endothelium. The TREND study [41] has shown the beneficial effect of ACE inhibition on endothelial dysfunction. Although the patients included in the TREND study were patients with established coronary artery disease and no history of hypertension, there is no reason to believe that the use of ACE inhibitors in hypertensive patients would have a different effect on endothelial dysfunction.

Angiotensin II stimulates hypertrophy of vascular smooth muscle cells [42], which play a key role in atherosclerotic lesions. ACE inhibitors have been shown to decrease atherosclerosis in Watanabe heritable hyperlipidaemic rabbits [43], although the results are not consistent for different ACE inhibitors. Captopril, for instance, decreases the cholesterol content of the thoracic aorta, as well as the number of smooth muscle cells. High-dose trandolapril causes a decrease in the percentage of aortic surface involved with atherosclerotic plaques [44]. Low dose trandolapril, on the other hand, decreases aortic ACE activity by 80% but does not modify the degree of aortic atherosclerosis in the same species [45].

Congestive heart failure (CHF) studies have provided the clearest evidence of the role of the renin-angiotensin system in cardiovascular diseases. Angiotensin-converting enzyme inhibitors limit the degree of ventricular remodelling seen after a myocardial infarction, and help preserve a certain level of left ventricular function [46]. Treatment with ACE inhibitors significantly improves survival rate in patients with left ventricular dysfunction regardless of whether it is related to acute myocardial infarction. The SAVE study showed a 21% reduction in the risk of cardiovascular death, a 25% reduction in recurrence of myocardial infarction, and a 37% decrease in the risk of development of severe congestive heart failure compared with placebo in patients treated with captopril [47]. The AIRE study showed a 30% reduction in the risk of sudden death in patients with heart failure secondary to acute myocardial infarction [48]. Quite recently, the ELITE study [49] comparing the angiotensin II antagonist losartan with the ACE inhibitor captopril showed an unexpected significantly lower mortality with losartan than with captopril. Since the ELITE study had not been designed to investigate cardiac mortality, the validity of this preliminary finding will be assessed in a trial designed to evaluate this outcome.

Thus, the effect of angiotensin II on vascular hypertrophy, left ventricular hypertrophy, endothelial function, atherosclerosis, and congestive heart failure can be viewed in the light of Laragh's visionary statement that high plasma renin activity in hypertension causes cardiovascular damage [50].

HYPOTHESIS
The driving scientific hypothesis behind VALUE is that for the same level of blood pressure control, the angiotensin II receptor antagonist valsartan will be more effective in decreasing the frequency of acute myocardial infarction, congestive heart failure and cardiac death than the third-generation, long-acting calcium channel blocker amlodipine.

Design of the trial
VALUE is a prospective, multinational, multicentre, double-blind, randomized, active, controlled 2-arm parallel group comparison trial with a response-dependent dose titration scheme. Patients entering the trial will be randomized to either valsartan 80 mg once daily or amlodipine 5 mg once daily. After 4 weeks on the initial dose, patients will be titrated up to valsartan 160 mg or amlodipine 10 mg once daily, depending on blood pressure response. The third and fourth steps on the VALUE trial involve the addition of hydrochlorothiazide at 12.5 and 25 mg doses, respectively. The fifth step of the protocol allows for free add-on of antihypertensive drugs, with the exception of ACE inhibitors, calcium channel blockers, angiotensin II antagonists or diuretics other than hydrochlorothiazide. The only exception is the replacement of thiazide diuretics by loop diuretics in patients with impaired renal function or with congestive heart failure.

Patient population
The eligible population consists of women and men, of any racial background, aged 50 years and over, with a high-risk cardiovascular profile, and essential systolic and/or diastolic arterial hypertension.

For inclusion into the trial, patients will be grouped as those newly diagnosed and never treated for hypertension, and those already on antihypertensive treatment. For previously untreated patients, hypertension is defined as a mean sitting systolic blood pressure between 160 and 210 mmHg (inclusive), and a mean sitting diastolic blood pressure below 115 mmHg, or a mean sitting diastolic blood pressure between 95 and 115 mmHg (inclusive) and a mean sitting systolic blood pressure up to 210 mmHg.
For patients already on antihypertensive treatment, there is no lower limit of mean systolic or diastolic blood pressure. However, the upper limit of mean sitting systolic blood pressure should not exceed 210 mmHg, and the mean sitting diastolic blood pressure should not exceed 115 mmHg. Patients already receiving antihypertensive treatment will be directly rolled over to one of the two VALUE arms, discontinuing previous drugs and starting with either valsartan 80 mg or amlodipine 5 mg, without a placebo run-in period.

RISK ASSESSMENT

The Framingham study [51] was the milestone study which helped identify the relative importance of cardiovascular risk factors in the assessment of epidemiological cardiovascular risk profiles. Cigarette smoking, diabetes mellitus, hypercholesterolaemia and left ventricular hypertrophy have all been identified as cardiovascular risk factors. More recently, increases in serum creatinine and proteinuria have also been shown to bear a relationship to cardiovascular morbidity and mortality [52]. Some of these risk factors carry a greater weight as predictive factors than others. It is well known, for instance, that a patient who has already had an acute coronary event is at a very high risk of having—and even dying of—a second event [53]. VALUE introduces a new concept in clinical trials, namely the assessment of cardiovascular risk by risk factors or predisposing conditions, and by disease factors, i.e. target organ damage which can be documented and confirmed by invasive and/or non-invasive techniques. The combination of risk factors and disease...
factors, together with age and gender, will give VALUE one of its unique features, the possibility of assessing the predictive power of an up-to-date cardiovascular risk scale in a large population of treated hypertensive patients traditionally considered to be at high risk of a cardiovascular event.

The risk factors to be used in the VALUE trial include diabetes mellitus, cigarette smoking, hypercholesterolaemia, left ventricular hypertrophy without strain diagnosed on electrocardiogram, proteinuria, and serum creatinine above 1.7 mg/dl. Disease factors include: documented history of myocardial infarction, peripheral vascular disease, stroke or transient ischaemic attack, or the presence of left ventricular hypertrophy with strain on ECG (Table I).

The age/risk stratification runs as follows:

—For male patients aged between 50 and 59 years, at least three (3) risk factors or one (1) disease factor is required to be entered into the trial. For female patients between 50 and 59 years, at least two (2) risk factors AND one (1) disease factor are required. This is due to the lower risk profile of women of perimenopausal age.

—Above the age of 60, gender as a cardiovascular risk factor does not differ between men and women. Thus, for men and women between 60 and 69, at least two (2) risk factors or one (1) disease factor is required. Finally, for patients above the age of 70, the predictive value of age as a risk factor increases significantly, and thus only one (1) risk factor or one (1) disease factor is required to enter the trial.

Main exclusion criteria are: renal artery stenosis; pregnancy; acute myocardial infarction, percutaneous transluminal coronary angioplasty (PTCA) or Coronary artery bypass (CABG) within the last 3 months; clinically relevant valvular disease; cerebrovascular accident in the last 3 months; severe hepatic disease; severe chronic renal failure; CHF requiring ACE inhibitor therapy; patients on monotherapy with beta-blockers for both coronary artery disease and hypertension (Table II).

The primary variable to be assessed at the end of the VALUE trial is the time to the first cardiac morbidity or mortality event. Cardiac mortality is defined as sudden cardiac death, fatal acute myocardial infarction, death during or post PTCA or CABG, death due to congestive heart failure, and evidence of recent acute myocardial infarction on autopsy. Cardiac morbidity is defined as new or chronic congestive heart failure requiring hospitalization, non-fatal acute myocardial infarction, emergency thrombolysis or any other interventional procedure performed in order to prevent a full-blown myocardial infarction.

Secondary variables include all cause mortality, cardiac mortality defined as for the primary endpoint, cardiac morbidity defined as for the primary endpoint, cardiac morbidity defined as for the primary endpoint plus worsening of chronic stable angina or unstable angina, routine interventional procedures, potentially lethal arrhythmias, syncope or near-syncope, stroke, silent myocardial infarction, and endstage renal failure.

Table II. Main exclusion criteria in the VALUE trial

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<th>Exclusion Criteria</th>
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<td>Renal artery stenosis</td>
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<td>Pregnancy</td>
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<td>Acute myocardial infarction, PTCA or CABG within the past three months</td>
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<tr>
<td>Clinically relevant valvular disease</td>
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<td>Cerebrovascular accident in the past 3 months</td>
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<td>Severe hepatic disease</td>
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<td>Severe chronic renal failure</td>
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<td>Congestive heart failure requiring ACE inhibitor therapy</td>
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<td>Patients on monotherapy with beta-blockers for both coronary artery disease</td>
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Abbreviations: ACE: angiotensin converting enzyme; CABG: coronary artery bypass grafting; PTCA: percutaneous transluminal coronary angioplasty.

cardiac morbidity defined as for the primary endpoint plus worsening of chronic stable angina or unstable angina, routine interventional procedures, potentially lethal arrhythmias, syncope or near-syncope, stroke, silent myocardial infarction, and endstage renal failure.

Statistical analysis

A total of 14 400 patients, equally allocated to each of the two treatment arms, is required. The total trial duration is planned to be 6 years, including a 2-year recruitment period. It is projected, based on studies of hypertensive patients with at least one risk or disease factor, that the 5-year event rate for cardiac mortality or morbidity in the amlodipine group will be 12.5%. A total of 1450 patients reaching an endpoint is needed to give 90% power for detecting at least a 15% reduction to 10.63% in the primary endpoint rate for patients randomized to the valsartan arm, with a two-sided 0.05 significance level. The sample size was calculated, as described by Lachin [54], under the assumption that time to survival is exponentially distributed.

Two interim analyses of the primary endpoint, time to cardiac mortality or cardiac morbidity are planned. These are planned to be equally spaced in terms of the accumulating number of patients reaching an endpoint. The exact nominal significance levels to be used for the interim analysis and final analysis will be obtained using the Lan-DeMets [55] alpha spending function approximating an O’Brien-Fleming boundary. The results of the interim analysis will be reviewed by an independent Data and Safety Monitoring Board.

The primary null hypothesis tested is that the distribution of survival time to the primary endpoint of cardiac mortality or morbidity is the same for valsartan and amlodipine versus the two-sided alternative hypothesis that the distribution of survival time for valsartan is different from that of amlodipine. Cox regression analysis
will be used to compare the treatment groups. The analysis will be based on the intention-to-treat approach, i.e., all randomized patients will be included in the analysis.

VALUE is a “maximum information” trial. The trial will end when 1450 patients have reached a primary endpoint, thus maintaining the power of the trial regardless of the actual event rate. The trial may be completed early if statistical significance is observed at either of the two interim analyses for the primary endpoint, cardiac mortality or cardiac morbidity.

ORGANIZATION

The VALUE trial involves 14,400 patients who will be recruited in 32 countries (see Appendix). More than 1000 centres worldwide are involved. The first patient was recruited in September 1997.

The Executive Committee consists of 8 members, including a Chair (S. Julius) and a Secretary (S. Kjeldsen). Employees of Novartis (see Appendix) can take part in the Executive Committee sessions, but have no voting right. The role of the Executive Committee is to disseminate information to the Steering Committee and to supervise the overall execution of the study.

The Data and Safety Monitoring Board is independent of Novartis Pharma AG and consists of 4 members, including a Chair (S. MacMahon). Its role is to oversee the welfare of patients enrolled in the trial, to review the compliance and trial progress at specified intervals and as requested by the Executive Committee, and to make recommendations to the Executive Committee should any problems arise.

The Endpoint Committee includes a Chair (L. M. Ruilope), 4 cardiologists and 1 neurologist.

The Operations Committee consists of 9 members, 2 from the Executive Committee and 7 from Novartis Pharma AG, who are involved with the day-to-day operational and logistic aspects of the trial.

The Steering Committee includes all the National Coordinators from the 33 participating countries, as well as the Executive Committee. The Steering Committee is blinded to the study data; its function is to review study progress and communicate periodically with all investigators; to act on the recommendations of the Data and Safety Monitoring Board and the Endpoint Committee, and to review publications.

APPENDIX

Executive Committee: Stevo Julius (Chairman, US), Hans Brunner (Switzerland), Lennart Hannson (Sweden), Sverre Kjeldsen (Secretary, Norway), John Laragh (US), Gordon McInnes (United Kingdom), Michael Weber (US), Alberto Zanchetti (Italy); Novartis representatives: Steffan Ekmans, Marc Henis, Jessica Mann, Jillian Pincus.

Data and Safety Monitoring Board: Stephen MacMahon (Chair, New Zealand), Henry Black (US), Tom Flemming (US), Peter Sleight (UK).

Endpoint Committee: Luis Ruilope (Chair, Spain), Enrico Agabiti Rosei (Italy), G. W. Albers (US), M. Weinberger (US), Per Omvik (Norway), William Parmley (US), Sven Strandgaard (Denmark), A Manin’t Veld (The Netherlands).


Steering Committee: F. Martinez (Argentina), D. Magometschnigg (Austria), L. Howes (Australia), J. P. Degauve (Belgium), W. Oigman (Brazil), P. Larochelle (Canada), Z. Zhu (China), J. Widimsky (Czech Republic), O. Lederballe Pedersen (Denmark), S. Majahalme (Finland), X. Girerd (France), R. Schmieder (Germany), K. Siomopoulos (Greece), B. Herczeg (Hungary), I. Graham (Ireland), G. Mancia (Italy), C. Calvo-Vargas (Mexico), P. W. de Leeuw (The Netherlands), M. Rostrup (Norway), R. Seabra Gomes (Portugal), A. Cieslinski (Poland), J. Kobolava (Russia), I. Balazovjech (Slovak Republic), G. Cassel (South Africa), A. Coca Payeras (Spain), E. Battegay (Switzerland), N. Koylan (Turkey), T. McDonald (UK), K. Jamerson (USA), as well as all the Executive Committee members.

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