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VALUE Trial: Long-Term Blood Pressure Trends in 13,449 Patients With Hypertension and High Cardiovascular Risk

Stevo Julius, Sverre E. Kjeldsen, Hans Brunner, Lennart Hansson, Francis Platt, Steffan Ekman, John H. Laragh, Gordon McInnes, Anthony M. Schork, Beverly Smith, Michael Weber, and Alberto Zanchetti, for the VALUE Trial

Background: The Valsartan Antihypertensive Long-term Use Evaluation (VALUE) study compares cardiovascular outcomes in 15,314 eligible patients from 31 countries randomized to valsartan or amlodipine-based treatment.

Methods: The blood pressure (BP) trends are analyzed in 13,449 of VALUE study patients who had baseline BP and 24 months BP and treatment data.

Results: In a cohort of 12,570 patients, baseline 24 and 30 months BP, but not 30 months treatment data, were available. Of 13,449 patients, 92% (N = 12,398) received antihypertensive therapy at baseline. The baseline BP was 153.5/86.9 mm Hg in treated compared to 168.1.8/95.3 mm Hg in 1051 untreated patients. After 6 months both groups had indistinguishable BP values. At 12 months the BP decreased to 141.2/82.9 mm Hg ($P < .0001$ for systolic BP and diastolic BP versus baseline), at 24 months to 139.1/80 mm Hg ($P < .0001$ *v* 12 months), and to 138/79 mm Hg at 30 months ($P < .0001$ *v* 24 months). The systolic BP control (<140 mm Hg) at 30 months increased from 21.9% at baseline to 62.2%, the diastolic BP (< 90 mm Hg) from 54.2% to 90.2% and the combined control (<140 and <90 mm Hg) from 18.9% to 60.5%. At 24 months 85.8% of patients were on protocol drugs: monotherapy = 39.7%, added hydrochlorothiazide = 26.6%, add-on drugs = 15.1%, and protocol drugs in nonstandard doses = 4.3%.

Conclusions: The achieved BP control exceeds values reported in most published large-scale trials. The VALUE study is executed in regular clinical settings and 92% of the patients received antihypertensive drugs at baseline. When an explicit BP goal is set, and a treatment algorithm is provided, the physicians can achieve better control rates than in their regular practice. Am J Hypertens 2003;16: 544–548 © 2003 American Journal of Hypertension, Ltd.

Key Words: Valsartan, amlodipine, blood pressure response to drugs, pulse pressure.

The Valsartan Antihypertensive Long-term Use Evaluation (VALUE) study is one of the largest ongoing trials investigating whether various antihypertensive agents might have different effects on cardiovascular outcomes. Such trials are based on the concept that blood pressure (BP) elevation is only one, albeit the most visible, sign of multiple pathophysiologic abnormalities in the syndrome of hypertension. Many of these abnormalities might independently cause damage to the cardiovascular (CV) system. When properly dosed, most antihypertensive agents decrease BP to the same extent but often have divergent effects on vascular function, coagulation, and associated metabolic, neurohumoral, and hemodynamic correlates of hypertension. Specifically, the VALUE study investigates whether lowering BP with the angiotensin receptor blocking agent valsartan (Diovan; Novartis, Basel, Switzerland), which antagonizes multiple negative effects of angiotensin, would yield better CV outcomes than treatment with the calcium antagonist amlodipine (Norvasc; Pfizer, New York, NY). The trial hypothesis states that for the same level of BP control valsartan-

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From the Department of Internal Medicine (SJ), Division of Hypertension, University of Michigan Health System, Ann Arbor, Michigan; Division of Cardiology (SEK), Ullevaal University Hospital, Oslo, Norway; Hypertension Division (HB), University of Lausanne, Lausanne, Switzerland; Department of Geriatrics (LH), University of Uppsala, Uppsala, Sweden; Cardiovascular Clinical Research (FP, SE), Novartis Pharma AG, Basel, Switzerland; Hypertension and Cardiovascular Center (JHL), New York Presbyterian Hospital-Weill Medical College, New York, New York; Department of Medicine and Therapeutics (GM), University of Glasgow, Glasgow, United Kingdom; Department of Medicine (MW), SUNY Downstate College of Medicine, New York, New York; Department of Biostatistics (AMS), University of Michigan School of Public Health, Ann Arbor, Michigan; Cardiovascular Clinical Research (BS), Novartis Pharmaceuticals Corporation, East Hanover, New Jersey; Centro di Fisiologia Clinica e Ipertensione (AZ), University of Milan, Instituto Auxologico Italiano, Milan, Italy.

Address correspondence and reprint requests to Professor Stevo Julius, University of Michigan Health System, Department of Internal Medicine, Division of Hypertension, 3918 Taubman Center, Ann Arbor, MI 48109-0356; e-mail: sjulius@umich.edu

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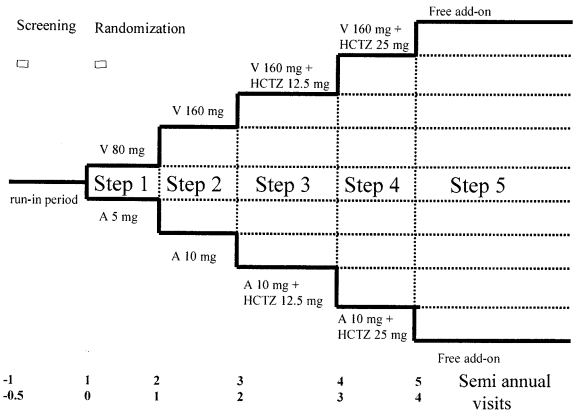

FIG. 1. Valsartan Antihypertensive Long-term Use Evaluation study design. A = amlodipine; HCTZ = hydrochlorothiazide; V = valsartan.

based treatment would be superior to amlodipine-based treatment in reduction of cardiac morbidity and mortality among hypertensive patients with a high CV risk.[1]

Methods

The rationale and design of the VALUE trial, including outcome measures, statistical methods and baseline characteristics of patients, CV risk profile, and definition of events have been published in detail elsewhere.[1,2] Patients of both genders with hypertension, 50 years of age or older were included. Previously untreated patients had to have a mean sitting systolic BP (SBP) of 160 to 210 mm Hg and a diastolic BP (DBP) of 95 to115 mm Hg. No lower BP limit was set for patients already receiving antihypertensive treatment, but the upper safety limit was set at ≤210/115 mm Hg. In addition to qualifying BP criteria the investigators used a specific predefined age-risk factor-dependent algorithm to recruit high CV risk patients into the study.[1]

The VALUE study is a multicenter, double-blind, randomized, prospective, active-controlled parallel group trial of the effect of two treatment modalities on BP and on CV end points in hypertension. An angiotensin receptor blocking agent, valsartan, in doses of 80 or 160 mg/day is compared to a calcium antagonist, amlodipine, in doses of 5 or 10 mg/day (steps 1 and 2). Additional treatment may be given as open label hydrochlorothiazide, 12.5 or 25 mg (steps 3 and 4). Initial dose adjustments were made in monthly intervals. If needed, added antihypertensive medication except other angiotensin I receptor blockers, angiotensin converting enzyme inhibitors, or calcium antagonists may be added (step 5) to reach a target BP of <140/90 mm Hg (Fig. 1).

Patients were randomized to one of the treatment regimens and will be followed for 4 to 6 years or until 1450 patients have experienced a primary event.[1] This study is end point-driven and it has been calculated that 14,400 enrolled patients are needed to detect a 15% between-group difference in CV outcomes with a 90% power and a significance of $P < .05$ during an average of 5 years of treatment. When the enrollment into the study was closed, a large number of patients had already given written informed consent and eventually 914 more patients than planned were included. All patients read and signed informed consents approved by appropriate Local Institutional Review Boards.

Differences between groups were analyzed by a Wilcoxon's two-sample test or, when appropriate, by a two-tailed Fisher's exact test.

Results

Although 15,314 eligible patients in 30 countries were randomized by December 31, 1999, this paper reports on 13,449 patients who 1) had complete BP records at baseline; 2) had in-study BP at each point up to 24 months; and 3) had information about the treatment status at 24 months. In addition we summarize 30 months of BP status for those 12,570 patients whose records presently contain baseline, 24, and 30 months BP data but their treatment status at 30 months BP data had not yet been entered into the records. Consequently, we report on BP trends and achievement of BP control after 24 and 30 months but analyze the utilization of blinded drugs only after 24 months of treatment.

From the total of 15,314 original patients, 1864 were excluded from the 24-month report as a result of death ($N = 524$), discontinuation for other reasons than death ($N = 1012$), and nonavailability of 24 months reports ($N = 328$). Among the patients with 30 months of data there were 2744 fewer subjects than originally randomized for the following reasons: deaths ($N = 529$), discontinuation for other reasons than death ($N = 1080$), and nonavailability of 30 months reports ($N = 1135$). The apparent small increase of deaths from 24 to 30 months most likely reflects the degree of completeness of the 30-month data set at time of writing of this paper. As indicated earlier the data set contained BP data only. It is likely that this number will increase when 1135 patients in whom 30 months of data were not available are accounted for and when a fully completed data set becomes available.

The SBP Initiative

We took note of the fact that the BP changed very little from the sixth month (when the initial medication uptitration could be completed) to 12 months. A large number of patients at that point had uncontrolled SBP. Consequently, we mounted a concentrated effort to improve SBP control. In addition to discussion of the problem at investigator meeting and communications with newsletters, we informed each investigator about specific patients who had uncontrolled SBP in their clinic. Thereafter, throughout the duration of the study, with the help of physicians in charge of each country (national coordinators), we closely monitored the BP trends.

BP Trends in the Study

Fig. 2 illustrates the BP trends in the cohort of 13,499 patients that had 24 months of BP data. The broken line at the end of the graph illustrates the BP trend in 12,570 patients who had BP recordings at 24 and 30 months. A majority of 13,499 patients with 24 months of BP data (*n*

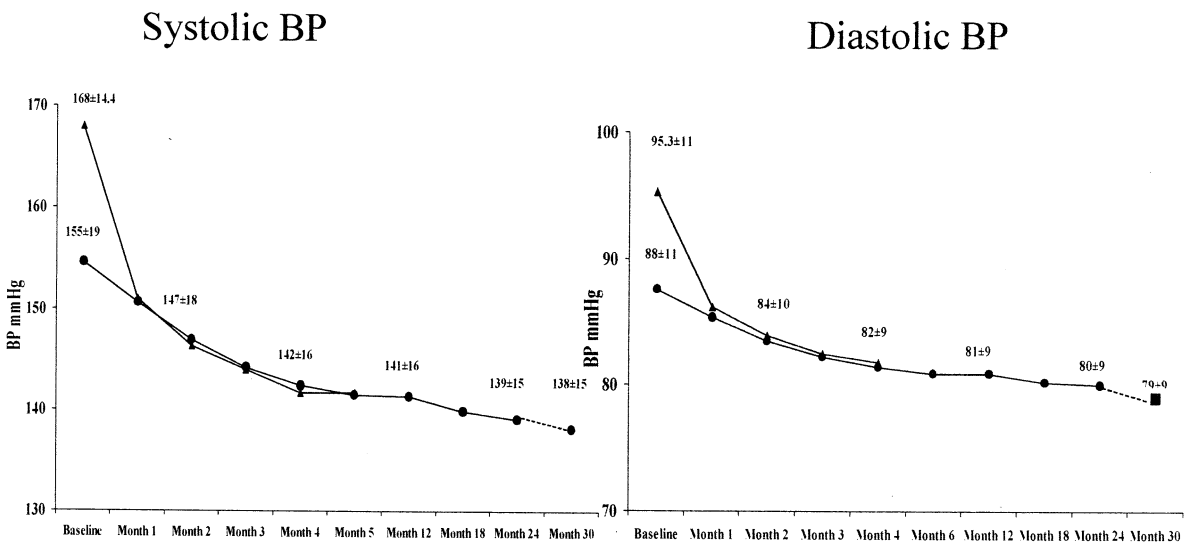

FIG. 2. Blood pressure (BP) trends in the cohort of 13,449 patients who had baseline and 24 months of data (**dots**) and in 12,750 patients who also have 30 months of data (**broken line**). **Triangles** denote the pressures in 1051 patients who were not receiving antihypertensive treatment before the enrollment.

= 12,398, 92.2%) received antihypertensive drugs before enrollment and were "rolled over" to study drugs (circles). The baseline BP of the 1051 patients who were not receiving treatment before enrollment (triangles) was 14.6/8.4 mm Hg higher than in the previously treated patients. However, both the treated and untreated groups achieved similar BP levels already at 4 months and past the sixth month point the BP readings of both groups were identical. The BP changed very little between 4 and 12 months, but after initiation of the SBP initiative (see Methods) the BP of the entire population started to decrease. The readings (SBP/DBP) at 24 months were 1.3/1.0 mm Hg lower than at 12 months ($P < .0001/.0001$) and at 30 months 1.0/1.0 mm Hg lower than at 24 months ($P < .0001/.0001$).

BP Control and Drug Utilization

Blood pressure control at baseline, after 6 months (when the initial medication up-titration should have been completed), and semiannually thereafter (Fig. 3). At baseline 21.9% of patients had SBP <140 mm Hg, at 24 months the SBP control increased to 59.5%, and at 30 months to 62.2%. The DBP control increased from 54.2% to 88.6% and 90.2%, respectively. Combined SBP and DBP control at 30 months was 60.5%. As Fig. 3 shows the better rates of BP control were mirrored by the drug utilization: The percentage of patients on lowest dose of monotherapy decreased, whereas the utilization of the highest step of titration (step 5) increased.

The degree of BP control at 30 months is shown in Fig. 4. Whereas 62.2% of patients had controlled SBP, an additional 20.6% had "nearly controlled" (≥140 to <150 mm Hg) SBP readings, 9.3% had "inadequate" SBP control (≥150 to <160 mm Hg), and 7.9% had "uncontrolled" systolic hypertension (≥160 mm Hg). In parallel the DBP control at 30 months (<90 mm Hg) was 90.2%, an additional 6.5%, had "near control" values (≥90 to

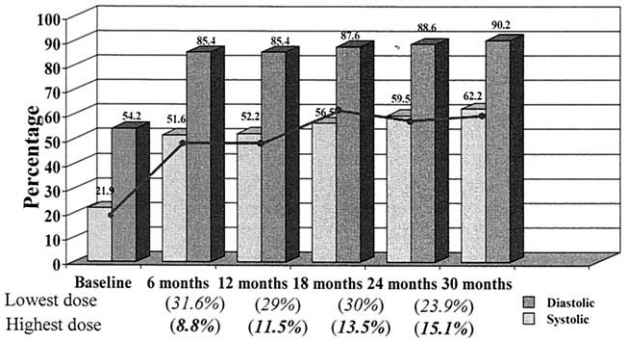

FIG. 3. Blood pressure control rates (percentage <140 or <90 mm Hg) from baseline to 30 months. Up to 24 months N = 13,449; at 30 months, N = 12,570. The line shows the percentage of combined (systolic and diastolic) blood pressure control. The percentage utilization of the lowest dose of monotherapy and of the highest titration step (step 5) from 6 to 24 months is shown under the figure.

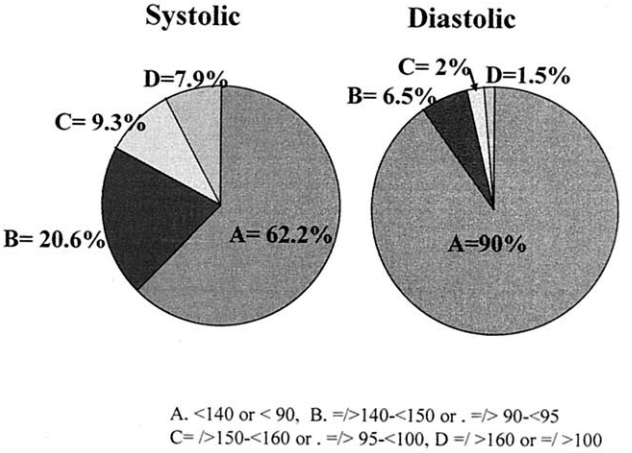

FIG. 4. Distribution of degrees of blood pressure control at 30 months (N = 12,750).

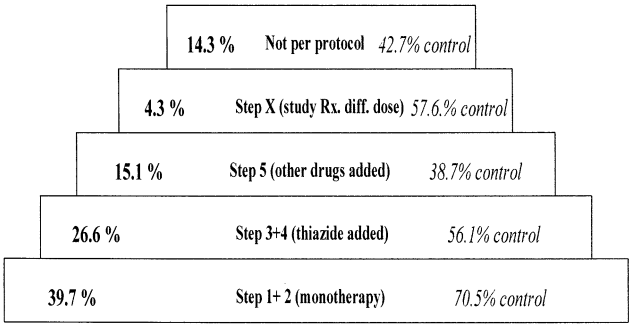

FIG. 5. Drug utilization and blood pressure control at 24 months in the Valsartan Antihypertensive Long-term Use Evaluation study (*N* = 13,449). The numbers in bold are the percentages of all patients at various drug (Rx.) steps. The numbers in italics describe the percentage of patients whose blood pressure was controlled (<140 and 90 mm Hg) within each category.

<95 mm Hg), "inadequate" readings (≥95 to <100 mm Hg) were present in 2%, and "uncontrolled" DBP (≥100 mm Hg) was seen in 1.3% of patients.

The relationship of treatment status to BP control at 24 months is illustrated in Fig. 5. Here the percentage of patients on a given treatment step is given in bold letters and the percentage of BP control is given in italics. After 2 years in the study, 66.3% of patients received active monotherapy or addition of a diuretic. In another 15.1% other antihypertensive drugs permitted by the protocol were added. In an additional 4.3% of patients the physicians prescribed drugs defined by the protocol but in different doses than stipulated (for example, diuretic added already to the first step of monotherapy, or one treatment component down-titrated from a protocol step). Thus, a total of 81.4% of patients adhered to the study protocol and 85.8% received drugs investigated in the VALUE study. The remaining 18.5% patients were followed in our clinics but did not receive per protocol treatment. Among them 6.3% received added drugs not foreseen by the protocol, 3.7% were not taking the study drug at 24 months ("temporary discontinuation"), 8.3% permanently discontinued study drugs, and in 0.3% information was missing.

Fig. 5 also shows that at 24 months 39.7% of patients still received monotherapy and among them almost 30% had uncontrolled BP levels but additional steps of the protocol were not used. At 24 months 23.9% of patients received only the first step of monotherapy. In this group the BP was not at goal in 25% but they were not further up-titrated. Similarly, in the diuretics-added group the BP was not at goal in approximately 44% of patients but the fifth step of the protocol had not been used.

Discussion

The baseline status of 12,398 patients who received antihypertensive treatment before enrollment in the VALUE study gives an insight on how hypertension is treated in routine clinical practice. Among patients treated for high BP at the entry into the study, the baseline SBP was controlled (<140 mm Hg) only in 21.9% subjects compared to a 54.2% control rate (<90 mm Hg) of the DBP. These findings confirm other observations that practicing physicians are more successful in controlling the DBP than SBP.[3–9] After 24 months in the study the control rates increased to 59.3% for SBP and 88.5% for DBP. A further improvement in SBP control to 62.2% and of DBP to 90.2% has been noticed in patients who completed the 30 months examination (Fig. 3). Because the VALUE study is executed in regular clinical settings the results demonstrate that physicians can achieve much better control rates when they work in a structured environment, which sets explicit BP goals, provides a simple algorithm to achieve these goals, and educates the patient and the personnel alike about the importance of achieving a good BP control.

Despite considerable improvement of BP management in the VALUE study our 24 and 30 months of BP outcome is still not ideal. However, the results reported herein are substantially better than in most published studies. The average achieved SBP level in VALUE is 16 mm Hg lower than in the Stroke Prevention Trial 2 (STOP-2)[10] and Nordic Diltiazem (NORDIL)[11] studies, 12 mm Hg below the value in Systolic Hypertension in Europe Trial (SYST-EUR),[12] and 11 mm Hg below the Captopril Prevention Project (CAPP) study.[13] The 30 months results in VALUE are a few millimeters lower compared to final results of the Systolic Hypertension in Elderly Patients (SHEP) study[14] and Hypertension Optimal Treatment (HOT)[15] studies. The final average SBP in the recently published Losartan Intervention For Endpoint reduction (LIFE) study[16] was 6 mm Hg higher in the losartan and 7.3 mm Hg higher in the atenolol group than the average SBP achieved at the 30-month point in the VALUE study. Our average SBP results at 30 months are similar to values reported at the end of the Intervention as a Goal in Hypertension Treatment (INSIGHT) study.[17]

Admittedly all of the studies quoted had a washout period previous to the entry into the study, whereas in VALUE most patients were "rolled over" from active treatment to our study protocol. This makes it difficult to compare our entry BP values to entry BP readings in other studies. However, we can compare our results to the Anti-hypertensive and Lipid-lowering Treatment to Prevent Heart Attack Trial (ALLHAT) study, which also used the rollover method. When the data in the ALLHAT study[18] average SBP are compared to the VALUE results at a similar time point (2 years in both studies), the achieved BP in the ALLHAT is lower than in VALUE. The VALUE SBP at 2 years was 139 mm Hg compared to 135.9, 137.1, and 138.4 mm Hg in the chlorthalidone, amlodipine, and lisinopril ALLHAT groups, respectively. However, this comparison might not be appropriate as the baseline SBP in ALLHAT (146.2 mm Hg) was substantially lower than in the VALUE study (155.2 mm Hg). In fact, in the ALLHAT chlorthalidone group, which achieved the lowest in-treatment SBP, the decrease from the baseline was 10.3 mm Hg compared to a 16 mm Hg SBP decrease in the VALUE study.

Whereas all papers report on achieved BP levels in their

study, only few discuss the results in terms of BP control rates. At the end of the LIFE study,[16] a 48% SBP control rate (≤140 mm Hg) was reported, whereas defined more strictly (<140 mm Hg) the control rate in VALUE was 62.2% at 30 months. This is of particular interest because LIFE is the first trial to use an angiotensin receptor blocking agent for control of the BP in a long-term outcome trial in hypertension. The ALLHAT study reported after 2 years of treatment a control rate (<140 and <90 mm Hg) of 61%, 57.4%, and 54.1% for chlorthalidon, amlodipine, and lisinopril, respectively. At the same time point the control rate in VALUE was 57.6%.

In national surveys[7] about 75% of treated hypertensive subjects remain on monotherapy, even in the face of poor control, predominantly with respect to SBP. It is encouraging to see (Fig. 5) that at 24 months our physicians retained a smaller proportion of patients on monotherapy (39.7%) compared to 66% reported in national surveys.[7] Among 5342 patients who at 24 months still received monotherapy, 70.5% had adequate BP control (<140 and <90 mm Hg.). However, almost 30% continued to receive monotherapy in spite of inadequate BP control (≥140 and 90 mm Hg.) Among these patients 27.9% had uncontrolled SBP and only 6.5% had not achieved the DBP goal. In some of these patients the physicians might have exercised proper clinical judgment but we argue that more VALUE patients could be up-titrated to diuretics. Clinical trials[15] underscore the need for combination therapy to achieve rigorous BP targets and the VALUE protocol called for addition of diuretics in such cases. Nevertheless, the physicians in our study took that directive more seriously with regard to DBP than SBP control. Surely in the VALUE study there are some subjects whose SBP is genuinely resistant to treatment. For example, among patients who received "add-on" therapy on top of full dose of treatment drugs and diuretics (step 5), the BP was too high in 61.3%. Nevertheless, the true proportion and the clinical characteristics of patients whose SBP is resistant to treatment will be known only after all therapeutic options for controlling BP provided by the VALUE protocol have been fully used.

The results presented demonstrate that organizational and educational efforts to improve the SBP control can be efficacious. Our BP-lowering initiative has been well received by the study physicians and BP in the study continues decreasing. We believe that setting a fixed stepwise algorithm of drug usage was an important component in the improvement of BP control in the VALUE study.

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