Original Article

Valsartan in Elderly Isolated Systolic Hypertension (VALISH) Study: Rationale and Design

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Although antihypertensive therapy has been proven to reduce cardiovascular morbidity and mortality, it is unclear how much blood pressure should be decreased in elderly patients with hypertension. The Valsartan in Elderly Isolated Systolic Hypertension (VALISH) study is a multicenter parallel-group study comparing the incidence of cardiovascular events between two target systolic blood pressure levels, below 140 mmHg and below 150 mmHg, under treatment with valsartan, an angiotensin II receptor blocker, as an initial antihypertensive drug in elderly patients with isolated systolic hypertension. The number of patients to be recruited is 3,000 and the duration of follow-up is at least 2 years. This 3,000-patient trial was designed with a two-sided level of 0.05 and 80% power to detect the difference in incidence of cardiovascular events between the target blood pressure levels based on estimation of the cardiovascular events ratio as 21.5/1,000 patient-years and 29.1/1,000 patient-years for the two blood pressure levels. The VALISH study, a large-scale investigator-initiated trial in Japan, will determine whether age should be considered in setting target blood pressure in treatment of isolated systolic hypertension in elderly patients. (Hypertens Res 2004; 27: 657–661)

Key Words: isolated systolic hypertension, cardiovascular events, clinical trial, valsartan

Introduction

The population of hypertensive patients is growing along with the aging of the general population in Japan, and numerous epidemiological studies have reported that hypertension is a significant risk factor for cardiovascular diseases such as stroke, myocardial infarction and heart failure (I). In the elderly, the incidence of isolated systolic hypertension (ISH) is increased and augmentation of systolic blood pressure (SBP) and pulse pressure are considered risk factors for the onset of cardiovascular diseases (2, 3). A number of studies have indicated that aggressive antihypertensive therapy could reduce the incidence of cardiovascular diseases (4–6).

The usefulness of aggressive antihypertensive therapy for elderly patients with ISH has been questioned because the elevation of SBP is an age-related phenomenon and because elderly patients often have complications of various organ dysfunctions. However, several large-scale trials in elderly hypertensive patients have suggested that appropriate blood

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pressure (BP) control could prevent the onset of cardiovascular diseases (7–10). In accordance with the results of these trials, target BP levels were determined in the Joint National Committee (JNC) 7 and European Society of Hypertension (ESH)–European Society of Cardiology (ESC) guidelines irrespective of the age of patients (11, 12). In contrast, the Japanese guideline for treatment of hypertension specifies target BP levels by age group (13). Determination of the appropriate target BP in elderly hypertensive patients is therefore important. However, only a few studies on elderly patients have been conducted in Japan (9, 10).

Angiotensin II receptor blockers (ARBs) are a new class of antihypertensive agents that selectively antagonize the binding of angiotensin II to angiotensin II type 1 receptors. Valsartan is an ARB that is highly selective for angiotensin II type 1 receptors, and its BP-lowering effect is sustained for 24 h after a single oral administration (14–16). In addition, its effect on BP is the same as those of other antihypertensive agents, including Ca antagonists, angiotensin converting enzyme inhibitors (ACEIs), and others (17, 18). ARBs have recently become first-line agents for the treatment of hypertensive patients because they are associated with a lower rate of occurrence of adverse reactions than ACEIs and Ca antagonists.

It would be useful to determine the incidence of cardiovascular diseases in elderly ISH patients receiving first-line antihypertensive therapy and also to evaluate how low BP needs to be to reduce cardiovascular events. We are therefore conducting the Valsartan in Elderly Isolated Systolic Hypertension (VALISH) study, a multicenter parallel-group study, to compare the incidence of cardiovascular events between two target SBP levels, below 140 mmHg and below 150 mmHg, under treatment with an ARB, valsartan, as an initial antihypertensive drug in elderly ISH patients.

Methods

Study Design

Study Subjects and Recruitment

A total of 3,000 patients diagnosed with ISH will be recruited within 1.5 years and randomly divided into 2 groups to receive valsartan for initial treatment. The patients to be recruited satisfy the inclusion criteria and meet none of the exclusion criteria (Tables 1 and 2). Randomization of target BP levels, i.e., SBP of <140 mmHg (L group) or ≥140 mmHg and <150 mmHg (M group), will be performed with a minimization method based on the following assignment factors using a computer program: Sex: male or female; Age: younger than 75 years or 75 years or older; Seated SBP: less than 175 mmHg or 175 mmHg or higher; Antihypertensive therapy: not being treated or being treated; and Institution.

All patients for the study will provide written informed consent to the study investigators.

Table 1. Inclusion Criteria for the VALISH Study

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<td>1) Outpatients aged over 70 years and less than 85 years, regardless of sex</td>
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<td>2) Patients with a stable seated systolic blood pressure of ≥160 mmHg and diastolic blood pressure of &lt;90 mmHg at two visits within 2 to 4 weeks</td>
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<td>3) Previously untreated patients or patients who are on other therapy that can be converted to valsartan</td>
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Patients who satisfy the blood pressure level criteria mentioned above despite previous treatment with one or two antihypertensive drugs

For patients who have been treated with one or two antihypertensive drugs other than valsartan, these drugs will be switched to valsartan

Table 2. Exclusion Criteria for the VALISH Study

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<td>1) Patients with secondary hypertension or malignant hypertension</td>
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<td>2) Patients with a seated systolic blood pressure of ≥200 mmHg</td>
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<tr>
<td>3) Patients with a seated diastolic blood pressure of ≥90 mmHg</td>
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<td>4) Patients with a history of cerebrovascular disorder or myocardial infarction within 6 months prior to enrolment in the study</td>
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<td>5) Patients who underwent coronary arterioplasty within 6 months prior to enrolment in the study or patients who will undergo coronary arterioplasty within 6 months after entry</td>
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<td>6) Patients with severe heart failure (≥NYHA functional classification III)</td>
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<td>7) Patients with severe aortic stenosis or valvular disease</td>
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<td>8) Patients with atrial fibrillation, atrial flutter, or serious arrhythmia</td>
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<td>9) Patients with renal dysfunction with a serum creatinine level of ≥2 mg/dl</td>
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<td>10) Patients with serious liver dysfunction</td>
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<td>11) Patients with a history of hypersensitivity to valsartan</td>
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<td>12) Other patients who are judged to be inappropriate for the study by the investigator or subinvestigator</td>
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Subject Visit and Assessment

Subjects will be orally administered valsartan at doses of 40 to 80 mg once daily, which will be increased up to 160 mg/day if the target BP cannot be achieved within 1 to 2 months. In addition, if the antihypertensive effect of valsartan is inadequate, other antihypertensive agents (except other ARBs) may be added—i.e., low-dose diuretics, Ca antagonists and so on. Use of other drugs for complications is not prohibited. Since the subjects are elderly patients, BP should be gradually lowered and the target BP level should be reached over 3
months.

Before randomization, data will be recorded for height, weight, heart rate, smoking status, alcohol consumption, medical history, and concomitant drugs and treatments. After randomization, BP, heart rate, concomitant drugs, and serious adverse events, including the study endpoints, will be recorded every 3 months. In addition, laboratory-test, chest X-ray, and ECG results will be recorded every 6 months after randomization. Study visits will be made every 3 months for at least 2 years. All data will be reported to the VALISH Data Center (Data Center) via the Internet or fax.

**Study Endpoints**

The primary endpoint of the study is a composite of cardiovascular events including the following: sudden death (acute onset and intrinsic death within 24 h), fatal or nonfatal stroke (new onset or recurrence), fatal or nonfatal myocardial infarction (new onset or recurrence), death due to heart failure, other cardiovascular death, unplanned hospitalization for cardiovascular disease (excluding hospitalization for examination) and renal disorder (as indicated by a serum creatinine level that is at least doubled to over 2 mg/dl or introduction of dialysis). Secondary endpoints consist of each component of the primary endpoint, total mortality and new onset or exacerbation of angina pectoris.

**Adverse Events**

Adverse events are any unfavorable medical signs, symptoms, or diseases that occur during the study, whether or not considered related to the study drug. Among adverse events, those for which a causality with drugs administered cannot be ruled out should be regarded as adverse reactions. If any serious adverse event occurs, its time of onset, time of disappearance, severity, treatments given, and causality with the study drug should be reported to the Data Center.

**Statistical Methods**

**Rationale for the Number of Study Subjects**

Based on domestic and foreign clinical studies in elderly hypertensive patients, the incidence of cardiovascular events is calculated to be about 20 to 30 cases per 1,000 patient-years in patients treated with Ca-antagonist or ACEI (10). Although few studies have examined in detail the incidence of cardiovascular events in the range of the target BP level set in this study, based on the results of the Framingham Heart Study (19), the incidence of cardiovascular events in the SBP level of <140 mmHg was estimated as 21.4 per 1,000 patient-years, and in the level of ≥140 mmHg to <150 mmHg the incidence was estimated to be 29.1 per 1,000 patient-years. Recently, the JMIC-B study has revealed that the incidence of those cardiovascular events that are also the focus of the VALISH study was 24 to 32 per 1,000 patient-years under Ca-antagonist or ACEI treatment (20). This result means that the method of the Framingham Heart Study used to estimate the number of patients should also be acceptable for estimating the required subjects for a study in Japanese patients. At the two-sided α level of 5% and with a power (1 - β) of 80%, 2,674 subjects (1,337 subjects for each target BP level) would permit differences to be detected by observing for 2.5 years, and thus, after allowing for dropouts, 3,000 subjects (1,500 subjects for each target BP level) may be appropriate as the number of subjects.

**Statistical Analysis**

All study patients who are registered and assigned to treatment will be analyzed on an intention-to-treat (ITT) basis, regardless of the actual drugs administered, treatment compliance, or premature conversion to other drugs. In addition, an additive analysis will be performed on the full analysis set (FAS). In the FAS, an analysis will be performed using patients who fit into the protocol. In other words, patients should be excluded from the FAS according to judging criteria drawn up by the Statistical Committee of this study. The Statistical Committee independent of this study will perform the analysis. Interim analysis will be performed on the incidence of cardiovascular events and adverse events at the completion of patient registration and 1 year after registration. The primary and secondary endpoint incidences at the target BP levels should be evaluated as a primary analysis.

As an additive analysis, the relationships between the incidences of primary and secondary endpoints, and final BP measurements, pulse pressure, age, concomitant drugs and complications should be evaluated. Based on the ITT analysis set, interval estimation of the cumulative event-free rate will be performed by Greenwood’s formula using the Kaplan-Meier method. The log-rank test will be used for comparison among the factors. The adjusted odds ratio for background factors will be tested for proportional hazards and determined by a Cox’s proportional hazards model with consideration of expandability. For changes with time in each test parameter, the changes from baseline values will be adjusted and evaluated by ANCOVA. An ANOVA model will be used for changes in BP rate between measurement time points and changes in each parameter.

**Ethics Committee**

Prior to performance of the study, the Ethics Committee, which is independent of the study, should evaluate the ethical and safety aspects of the protocol, and patient explanation documents and informed consent forms at the request of the study representatives. Prior to participation in the study, each participant must be approved by an Ethics Committee of the participating medical institution. If an individual institution is unable to convene an Ethics Committee, the investigator responsible for the study must obtain the permission to participate in the study from the Ethics Committee (VALISH Ethics Committee; see Fig. 1).
**Study Organization and Management**

The study is coordinated by the Data Center and the Ethics Committee independently, and is managed by committees organized with independent experts (Fig. 1). These committees consist of a Steering Committee headed by the study chairpersons, a Protocol Committee, a Safety Committee, an Endpoint Committee, and a Statistical Committee. The responsibilities and activities of these committees are as follows. **Steering Committee**: This committee is responsible for the study design and makes final decisions about the study. **Protocol Committee**: This committee is responsible for drawing up of the protocol, the case report form and informed consent documents, and revising these documents based on the instructions of the Steering Committee. **Safety Committee**: This committee is responsible for the evaluation of adverse events, and for recommendations to the Steering Committee if a serious adverse event occurs. **Endpoint Committee**: This committee is responsible for evaluation of the primary and secondary endpoints. **Statistical Committee**: This committee is responsible for drawing up of the statistical analysis plan and determination of the validity of the results of analysis.

**Discussion**

The Japanese Society of Hypertension issued the guideline for treatment of hypertensive patients in 2000 (JSH 2000) (13). In the guideline for elderly patients with hypertension, target BP levels are milder, and are different from those of the JNC 7 and ESH-ESC guidelines (11, 12). There is no clear evidence that more aggressive antihypertensive therapy is more beneficial for elderly than for non-elderly patients (21). To reduce SBP to less than 140 mmHg might be ideal for decreasing the occurrence of cardiovascular events in hypertensive patients (22, 23). However, in reducing SBP to less than 140 mmHg in the elderly, it must be considered whether the elderly are at risk of cerebral infarction due to the decrease in cerebral blood flow induced by excessive antihypertensive treatment. In fact, several studies have revealed a J-shape phenomenon in antihypertensive treatment, in which an increased cardiovascular event ratio was observed with lower BP levels below 130 mmHg (10). A questionnaire survey of clinical specialists in the treatment of hypertension in Japan showed that most of them approved of the JSH 2000 guideline (24).

The PROGRESS study reported that aggressive antihypertensive therapy reduced the incidence of cardiovascular events, particularly cerebrovascular events, and that a J-shape phenomenon did not occur even below 140 mmHg on treatment with an ACEI plus diuretic (25). However, the mean BP at the pretreatment period was 147/86 mmHg in that study. Re-analysis of the SHEP study revealed the usefulness of antihypertensive therapy for patients who are older, who have risk factors for diabetes mellitus, or who smoke, etc. (7). Staessen reported that numbers needed to treat (NNT) to prevent cardiovascular events for 5 years are lower for patients over 70 years old than for patients 60-69 years old (5). These results suggest that aggressive antihypertensive treatment for the elderly could reduce the occurrence of cardiovascular events.

With regard to the issue of what agent should be prescribed first to hypertensive patients, all guidelines recommend that the physician choose from among diuretics, β-blockers, Ca antagonists, ACEIs and ARBs as the first-line treatment according to the condition of each patient. However, it is unclear what type of agents is favorable not only to reduce BP but also to protect against the incidence of cardiovascular events. In fact, in order to compare the protective effects against cardiovascular events in hypertensive patients, an investigator-initiated trial, the CASE-J study, is currently being performed in elderly hypertensive subjects in Japan (26).

The VALISH study was begun in October 2003 to compare the incidence of cardiovascular events between two target BP levels. In this study, 3,000 elderly patients with ISH will be recruited within 1.5 years and will be followed-up for a minimum of 2 years. The results of this study, together with those of the CASE-J study, should be useful for determining the appropriate target BP in elderly patients with ISH.
References


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