left ventricular (LV) diastolic dysfunction is strongly related to LV structural abnormalities, such as LV hypertrophy and fibrosis, and is associated with a poor prognosis. Hypertension is a major underlying disease for LV diastolic dysfunction, even without LV systolic dysfunction, and antihypertensive treatments are effective in causing regression of such LV structural abnormalities, although the relation between depressor response and changes in LV structure is not necessarily intimate. Activation of the cardiac renin–angiotensin system (RAS) plays a crucial role in the development of LV hypertrophy and fibrosis, and many previous experimental studies have shown that angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II type 1 receptor blockers (ARB) can attenuate LV structural alterations independently of their depressor effects. Recent clinical studies showed that losartan, an ARB, causes greater regression of LV hypertrophy and fibrosis than atenolol, a β-blocker. In contrast, theValsartan Antihypertensive Long-term Use Evaluation (VALUE) trial failed to demonstrate the benefits of valsartan, an ARB, compared with amlodipine, a third-generation calcium-channel blocker (CCB) in hypertensive patients with a high-risk cardiovascular profile. It should be noted, however, that LV diastolic dysfunction is not necessarily associated with echocardiographic abnormalities of LV geometry. Thus, it still remains unclear whether blockade of RAS by an ARB has superior effects on LV diastolic function in hypertensive patients compared with other antihypertensive drugs.

Aims

The aim of the present multicenter trial, the Effect of Losartan and Amlodipine on Left Ventricular Diastolic Function in Patients With Mild-to-Moderate Hypertension (J-ELAN) study, is to compare the effects of an ARB, losartan, with those of a CCB, amlodipine, on LV diastolic function in hypertensive patients with LV diastolic dysfunction in the absence of systolic dysfunction. CCB is the most widely used hypertensive treatment in Japan, and the results of the VALUE trial have caused discussion about the superiority of blockade of RAS. In addition, the Japanese β-Blockers and Calcium Antagonists Myocardial Infarction (JBCMI) study suggested benefits of CCB as compared with β-blockers in Japanese patients with myocardial infarction. Thus, we chose losartan and amlodipine for a head-to-head comparison of effects on LV diastolic function.

Study Design and Ethical Issues

The study is a multicenter, prospective, randomized, open, blinded endpoint trial that will be conducted in accordance with the principles stated in the Declaration of Helsinki, 1964, and revised in South Africa in 1996. The Ethical Committee of Osaka University Graduate School of Medicine approved this study on December 27, 2004 (No. 436) and written informed consent will be given by all pa-

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The J-ELAN Investigators
Eligibility

Inclusion Criteria
- Age 20 years or older.
- Mild to moderate hypertension (systolic blood pressure ≥140 mmHg and ≤200 mmHg, diastolic blood pressure ≥90 mmHg and ≤110 mmHg).
- Presence of LV hypertrophy (ratio of LV mass to body surface area (LV mass index) ≥120 g/m² in men and ≥105 g/m² in women or LV wall thickness >11 mm).
- LV mass is calculated following the formula derived from the American Society of Echocardiography.
- LV diastolic dysfunction (ratio of peak early to late diastolic filling velocities (E/A) <1.0 or >1.5, an E-wave deceleration time <160 ms or >280 ms, isovolumic relaxation time <60 ms or > 105 ms).
- LV ejection fraction ≥50% (echocardiographic screening will be performed when symptoms, physical examination, chest X-ray or electrocardiography suggests the presence of cardiac abnormalities).

Exclusion Criteria
- History of a life-threatening adverse event induced by ARB or CCB.
- Pregnancy.
- Serious liver dysfunction (aspartate aminotransferase or alanine aminotransferase >10-fold normal upper limit).
- Serum creatinine >1.8 mg/dl, known bilateral renal artery stenosis, single kidney, nephrosclerosis.
- Secondary hypertension, malignant hypertension, hypertensive encephalopathy.
- Cardiovascular or cerebrovascular accident within the past 6 months.
- Patients with angina pectoris who need CCB or -blocker.
- Significant aortic stenosis (peak transaortic valve pressure gradient >20 mmHg).
- Significant aortic or mitral regurgitation in the investigator's opinion.
- Patients with other diseases that affect the serum levels of the carboxy-terminal telopeptide of collagen type I (CTIP) and the carboxy-terminal of procollagen type III (PIIIP).
- Prescription of ACEI or ARB within the past 5 months.
- Prescription of -blocker or CCB within the past 4 weeks.

Randomization, Up-Titration and Maintenance Phase

After screening for eligibility and giving of written informed consent, patients will be randomized to either losartan 50 mg once daily or amlodipine 2.5 mg once daily. After 4 weeks on the initial dose, patients will be titrated up to losartan 100 mg or amlodipine 5 mg once daily, depending on blood pressure response. The target blood pressure will be systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg. The third and fourth steps involve the addition of thiazide diuretics or -blockers.

The planned maximum follow-up period for each patient is 18 months, and Doppler echocardiography and blood sampling (creatinine, uric acid, PIIIP, CTIP, brain natriuretic peptide and high-sensitivity C-reactive protein) will be conducted at study entry and every 6 months after randomization. Carotid ultrasonography will be conducted at study entry and 12 and 18 months after randomization.

Statistical Considerations

Sample Size
We estimate that the improvement of E-wave deceleration time will occur in 62% of losartan-treated patients and in 44% of amlodipine-treated patients based on a previous study. The power calculation was based on a 2-sided log-rank test for comparison between the groups treated with losartan and amlodipine at a significance level of 0.05. A total of 240 patients (120 patients in each group) is necessary to achieve a power greater than 80%. Assuming further that approximately 10% of patients will be ineligible after randomization, the total sample size needed in this trial is 300 patients (150 patients in each group).

Statistical Analysis
All analyses will be performed according to the intention-to-treat principle. All study data will be stratified by treatment group. All baseline variables will be presented using appropriate descriptive summary tables. Chi-square tests will be used for analyzing changes in LV diastolic function. Differences between the groups in changes in other parameters derived from echocardiography, serum markers, symptoms of heart failure (New York Heart Association functional classification) and indices derived from carotid ultrasonography will be analyzed with appropriate methods. P value judges less than 5% will be considered to be meaningful. Statistical analysis will be performed using SAS software (Cary, NC, USA).

Safety Monitoring
The independent Data Safety and Monitoring Committee will monitor all adverse events during the course of the trial and advise the Executive and Steering Committee members on the appropriateness of continuing the trial.

Status of the Study
The first patient was enrolled in March 2005.
Discussion

Heart failure has 2 subtypes: systolic heart failure and diastolic heart failure, and the ratio of their prevalence is almost 3:2.23,24 Although reducing the ejection fraction is associated with poor prognosis in patients with systolic dysfunction, LV diastolic function is another independent determinant of prognosis.25,26 Diastolic heart failure is not accompanied by reduced ejection fraction and is mainly attributed to diastolic dysfunction. Its incidence increases with aging, and diastolic dysfunction leads to poor outcomes even in the general elderly population.3,4 Thus, there is a growing interest in LV diastolic dysfunction as a therapeutic target, but therapeutic strategies have not been established.

Hypertension is well recognized as a major underlying disease of diastolic dysfunction. Blood pressure control is mandatory in the treatment of hypertension, but is not sufficient to achieve an improved prognosis. Antihypertensive therapies have been associated with regression of LV hypertrophy in some hypertensive populations but not in others in which the prognosis was poorer. Structural alterations, such as LV hypertrophy and fibrosis, are well-known complications of LV diastolic dysfunction2 and the Losartan Intervention For Endpoint Reduction in Hypertension (LIFE) study showed an association between improvement of LV diastolic filling dynamics and regression of LV hypertrophy.27 However, Aeshbacher et al showed that a decrease in the E/A ratio precedes LV hypertrophy in hypertensive patients,10 and a subanalysis of the LIFE study reported a high prevalence of abnormal isovolumic relaxation time even in hypertensive patients with normal LV geometry.17 Those results indicate that LV diastolic dysfunction occurs even without LV remodeling, and thus, the effects of pharmacological interventions on LV diastolic function may not be assessable from their effects on LV structure alone, and remain to be clarified in clinical practice.

Previous experimental studies report beneficial effects of ARB on LV diastolic function.10,12 The administration of ARB, if initiated at an early stage of hypertensive heart disease, prevented LV relaxation abnormality and myocardial stiffening, and, if initiated at a later stage, improved the abnormal LV relaxation. A previous experimental study also demonstrated that administration of CCB was effective in the prevention of LV relaxation abnormality and myocardial stiffening28 A clinical trial reported that administration of ARB reduced the hospitalization rate for patients with diastolic heart failure, but there was not a significant reduction in the primary outcomes.29 As such, clinical evidence of the effects of these drugs on LV diastolic function in patients with LV diastolic dysfunction has not been established yet. Thus, the aim of the J-ELAN study is to compare the effects of an ARB, losartan, and a CCB, amiodipine, on LV diastolic function in hypertensive patients.

There are many clinical trials that have assessed the effects of drugs in hypertensive patients. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) demonstrated comparable benefits of diuretics, CCB and ACEI in hypertensive patients;30 but other clinical trials, eg, the second Australian National Blood Pressure Study (ANBP2) reported that anti-hypertensive drugs provided different clinical outcomes in hypertensive patients.31 The LIFE demonstrated benefits of ARB as compared with β-blockers;2 but the Study on Cognition and Prognosis in the Elderly (SCOPE) and VALUE failed to show benefits of ARB.32 The results of these clinical trials do not give consistent conclusions, particularly on the effects of pharmacological interventions on LV diastolic function.

Querejeta et al reported that LV fibrosis plays a crucial role in the development of heart failure in hypertensive patients;2 and LV fibrosis determines myocardial stiffness, one of the important determinants of LV diastolic function.25 Diez et al demonstrated that losartan caused regression of LV fibrosis and improved myocardial stiffness in hypertensive patients. If pharmacological interventions alter LV diastolic function, their effects may be partly explained by their modulation of the extracellular matrix. Myocardial biopsy is the sole established method of assessing the degree of LV fibrosis, but is not easy to conduct routinely. To address this issue, the serum levels of PiNP, an index for the production of collagens, and CITP, an index for the degradation of collagens, will be assessed in J-ELAN.

This study will also assess the effects of each drug on carotid artery atherosclerosis as assessed by carotid ultrasoundography. Atherosclerosis is frequently associated with hypertension, and leads to ischemic events. The Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial (PREVENT) demonstrated that amiodipine-induced attenuation of progressive carotid artery atherosclerosis,34 and it has also been shown that losartan has a protective effect against the acceleration of atherosclerosis.35 The difference in the effects on atherosclerosis, if present, may also affect the choice of therapeutic regimen.

In spite of recent progress in the treatment of hypertension according to a number of clinical trials during the past decades, the management of the LV diastolic dysfunction that is frequently associated with hypertension remains to be established. This clinical study will contribute to better drug choice in the treatment of hypertension.

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References


Appendix 1

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