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International Heart Journal (2012.08) 53巻4号:244～248.

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Investigation (CAMUI) Trial
Rationale and Design

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Rationale and Design

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SUMMARY

Angiotensin receptor blockers (ARBs) with calcium channel blockers (CCBs) or diuretics are a widely used combination therapy for hypertensive patients. The present study aimed to determine which combination was better for elderly hypertension patients aged ≥ 65 years.

We designed a multicentre, randomized, open-label, parallel comparison study. Hypertensive outpatients aged ≥ 65 years who did not achieve the target blood pressure (BP < 140/90 mmHg) with usual dosages of ARBs were randomly assigned to switch treatment to losartan 50 mg/hydrochlorothiazide 12.5 mg or amlodipine 5 mg in addition to ARBs. The primary endpoint was a change in the systolic blood pressure (SBP) and diastolic blood pressure (DBP) after the 3-month treatment period, while secondary endpoints were changes in the BP, albuminuria, laboratory values, and cognitive function with the mini-mental state examination (MMSE) at baseline and after one year. The results from the CAMUI trial should provide new evidence for selecting optimal combination therapies for elderly hypertensive patients. (*Int Heart J* 2012; 53: 244-248)

Key words: Antihypertensive agents, Combination therapy, Cognitive function

Optimal blood pressure control is essential for treating hypertensive patients. According to recent reports, the attainment rate of a target blood pressure by anti-hypertensive monotherapy is relatively low.¹⁾ Therefore, recent guidelines for the treatment of hypertension recommend combination therapy to achieve optimal blood pressure control. Indeed, according to the JSH 2009, ESH-ESC guideline 2007, and the American Society of Hypertension Writing Group, both an angiotensin receptor blocker (ARB) with a calcium channel blocker (CCB), and an ARB with diuretics are the recommended combination therapy for hypertension since each drug has evidence of reducing cardiovascular events and renoprotective effects, and it is expected that the antihypertensive effects will become additive while the adverse effects can cancel each other out.^{2,4)} However, which combination is better, especially for elderly hypertension patients aged ≥ 65 years, remains to be determined.

From the pathophysiological point of view, it has been shown that salt sensitivity is more frequent and more pronounced in older than in younger subjects.³⁾ On the other hand, arteriosclerotic changes leading to cerebrovascular or cardiovascular events are expected to be frequently associated with elderly hypertensive patients.

Thus, the evidence described above provides us with the questions: "which combination therapy is suitable as an initial combination therapy for hypertensive patients who do not attain their blood pressure goal with monotherapy?" and "which

combination therapy is optimal and safe, especially for elderly hypertensive patients with occult organ damage?"

From a different viewpoint, one of the biggest problems being faced in Japan now is how to cope with the coming super-aging society. As the Japanese society ages, we will be obliged to deal with not only increases in medical needs, but also problems with the medical related economy and its management, insurance regimes, shortages of doctors, need for enhanced services, and political intervention.

Hypertension needs to be classified as a typical disease whose incidence increases with age. Henceforth, when we perform clinical trials with hypertensive patients, we will need to verify various associated complications such as impaired cognitive function and a reduction in the patient's income as well as blood pressure control, and thereby come up with a more realistic approach to hypertensive patients and the social problems related to the condition.

Recently, a fixed-dose ARB/CCB combination has become available following the development of an ARB/diuretic in Japan, and the opportunity to use these drugs is increasing. Hence, we designed a multicenter, randomized, open-label, parallel comparison study in an attempt to obtain answers to the aforementioned questions and identify new evidence for selecting the optimal combination therapy for elderly hypertensive patients. Another aim was to investigate the relationship between antihypertensive therapy and cognitive function in consideration of the looming problem of a rapidly aging society.

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Received for publication March 15, 2012.

Accepted May 11, 2012.

METHODS

The CAMUI (Combination of Antihypertensive therapy in the elderly, Multicenter Investigation) trial was a multicentre, randomized, open-label, parallel comparison study in Japanese hypertensive patients, who had not attained their blood pressure goal with a monotherapy with usual dosages of ARBs, and then were assigned to receive either a thiazide diuretic or amlodipine as a second combination drug. This trial was registered with the University Hospital Medical Information Network-Clinical Trials Registry (UMIN-CTR) under the trial identification number UMIN000001688. It was approved by the Institutional Review Board of Asahikawa Medical University and by the review boards of all the other participating hospitals, and the trial was undertaken in accordance with the Declaration of Helsinki Principles. Subsequently, written informed consent was obtained after the patients received a full explanation of the trial from the investigators.

Participants: Enrollment of eligible patients began in November 2008 and continued until November 2010, and follow-up continued until November 2011. The subjects of the study were hypertensive patients who did not attain their optimal blood pressure in response to the usual dosage of ARBs. The inclusion criteria were 1) patients with essential hypertension, who had been previously treated with an ARB monotherapy (losartan 50 mg, candesartan 8 mg, valsartan 80 mg, telmisartan 40 mg, or olmesartan 20 mg) for more than a month and whose blood pressure had not been adequately controlled with the treatment (systolic blood pressure (SBP) > 140 mmHg and/or diastolic blood pressure (DBP) > 90 mmHg; In the case of diabetes or renal disease, an SBP > 130 mmHg and/or DBP > 80 mmHg), 2) patients aged 65 years or more, 3) both males and females, 4) outpatients, and 5) the patient understands the study procedure and agrees to participate in the study by giving written informed consent prior to the study start. The exclusion criteria were 1) patients with secondary hypertension, 2) patients with heart failure (above NYHA grade III), 3) patients with a history of severe hepatic or renal disease (serum

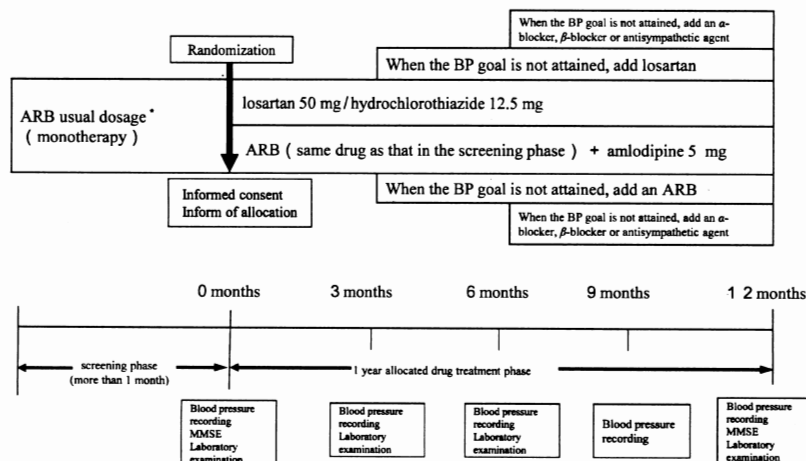
Cr \geq 2.0 mg/dL), 4) patients with critical liver damage (aspartate aminotransferase (AST) or alanine transaminase (ALT) levels that were \geq 3 times the upper limit of normal), 5) patients with a history of hypersensitivity to losartan, 6) patients with a history of hypersensitivity to components of thiazide or similar compounds, and 7) patients who were considered not to be eligible for the study by the investigator due to medical reasons.

Study design: All patients were required to be treated with the usual dosage of an ARB monotherapy for at least 4 consecutive weeks during the screening and run-in phases. If the blood pressure level at the last baseline visit was equal to or more than 140/90 (in the case of diabetes or renal disease, an SBP > 130 mmHg and/or DBP > 80 mmHg), the patients were randomly assigned to receive either a fixed-dose combination of losartan (50 mg) plus hydrochlorothiazide (12.5 mg) or a combination of amlodipine (5 mg) plus the usual dosage of ARBs as step 1 (Figure). Eligible patients were randomly assigned to one of the two study arms. The randomization was conducted at the CAMUI trial data center by the dynamic allocation method after stratification by gender, age, and the SBP as adjusting factors in the minimization calculation.

Patient follow-up: Following the randomization, the patients received follow-up visits every 3 months, during which the safety parameters were checked annually. Adverse events, classed as drug related or nondrug related and serious or non-serious, were observed throughout the study. If a blood pressure target of < 140/90 mmHg (in the case of diabetes or renal disease, < 130/80 mmHg) was not obtained, a dose-titration was performed as shown in the Figure.

Schedule for the data collection: Table I shows the schedule for the data collection in the CAMUI trial. The blood pressure and heart rate were checked at least every 3 months. Laboratory tests were measured at baseline and at 3, 6, and 12 months. The MMSE was examined at baseline and after one year. Echocardiography and cervical ultrasonography were done if possible.

The primary endpoint was a change in the SBP/DBP after



* ARB usual dosage : losartan 50 mg/day, candesartan 8 mg/day, valsartan 80 mg/day, telmisartan 40 mg/day, olmesartan 20 mg/day

Figure. Protocol of the CAMUI study.

Table I. Schedule for Data Collection

Period	Screening phase	1 year allocated drug treatment phase				
		0 months	3 months	6 months	9 months	12 months
Informed consent						
Patient profile	○					
Blood pressure, heart rate	○	○	○	○	○	○
Home BP				← △ →		
Complete blood count test		○	○	○		○
Blood chemistry test		○	○	○		○
Urine test		○	○	○		○
Fasting insulin concentration • HbA1c	(*)	○ or △	○ or △	○ or △		○ or △
Echocardiography, PWV, IMT		△				△
MMSE		○				○
Drug compliance		○	○	○	○	○
Adverse effect				← ○ →		

○: indispensable, △: optional, (*): indispensable for DM patients, otherwise optional. PWV indicates pulse wave velocity; IMT, intima media thickness; and MMSE, mini-mental state examination.

Table II. Baseline Characteristics of The Two Groups

	Losartan/hydrochlorothiazide group (n = 68)	ARB/amlodipine group (n = 74)
Male, n (%)	32 (47.1)	36 (48.6)
Age (years)	74.5 ± 5.8	74.1 ± 6.6
SBP (mmHg)	155.3 ± 11.4	155.9 ± 15.6
DBP (mmHg)	83.0 ± 10.0	82.3 ± 11.1

a 3 month treatment. The secondary endpoints were 1) changes in the MMSE score before and one year after a combination antihypertensive therapy, 2) the rate of achieving the target blood pressure, 3) changes in the laboratory test results including the HbA1c, HOMA-R, FBS, urine protein, microalbuminuria, potassium, and uric acid, 3) the rate of continued treatment and compliance with the treatment, and 4) the safety of the combination compound (losartan 50 mg/hydrochlorothiazide 12.5 mg) and ARB/Ca channel blocker combination therapy.

Sample size determination: A sample size of 92 patients in each group was required to achieve an 80% power to detect the noninferiority using a one-sided, two-sample *t*-test. The significance (alpha) of the test was 0.025. The noninferiority margin of the systolic and diastolic blood pressures was ≤ 5 mmHg and the true differences between the means were assumed to be zero (mmHg). A standard deviation (SD) of ± 12.0 was estimated. We estimated there would be an 8 percent loss-to-follow up. Thus, we estimated a total of 200 participants would be required. The baseline characteristics of the two groups in the registration are summarized in Table II.

Statistical analysis: For the primary endpoint, the differences in the systolic and diastolic blood pressures between the two groups were analyzed using Student's *t*-test. The analysis was performed on the intention-to-treat (ITT) basis, but those who never took the trial drug were not included. The data analysis for the primary endpoint was determined if the effect of the treatment with a single pill combination of losartan (50 mg)

plus hydrochlorothiazide (12.5 mg) lied within the prior defined noninferiority margin (± 5 mmHg) and the null effect (0 mmHg) of a one-sided alpha of 0.025 as compared to the treatment with amlodipine (5 mg) plus the usual dosage of an ARB.

To compare the secondary endpoint, an analysis of covariance was performed to adjust the baseline values. The urea albumin/creatinine and HOMA-R were logarithmically-transformed because of their skewed distribution.

Organization structure: The CAMUI trial was an independent academic study designed, undertaken, and monitored by "The Elderly Hypertension Research Association". The organization and members of the committee of the CAMUI trial are listed in the Appendix. Any protocol changes or premature termination of the study was determined by the Principal Study Coordinator and Steering Committee who had the responsibility for conducting the trial. The study design and any protocol changes were the responsibility of the Protocol Committee. The execution of the trial, fund and data management, and general affairs were performed by the Executive Study Coordinator. Evaluation of the safety, endpoints, and adverse events were performed by the Data Monitoring and Safety Committee, and they gave their recommendations to the Steering Committee if any problems occurred. The design of the statistical analysis plan was carried out by the Study Statistician, who determined the validity of the analysis results and independently analyzed the study data. The CAMUI data center was responsible for the patient registry and data management.

This trial was performed based on funding received from The Waksman Foundation of Japan INC. The corresponding author has full access to all the data in the study and has the final responsibility for the decision to submit for publication.

DISCUSSION

The primary endpoint of this trial is to compare the antihypertensive effects of combination therapies consisting of an ARB/diuretic and an ARB/CCB in elderly hypertensive pa-

tients. Combinations consisting of one of the 5 representative ARBs available in Japan (losartan, valsartan, candesartan, telmisartan and olmesartan) and the most frequently prescribed CCB, amlodipine, for the ARB/CCB group, and a single pill combination of losartan plus hydrochlorothiazide for the ARB/diuretic group were used in this trial. A fixed-dose combination of losartan (50 mg) plus hydrochlorothiazide (12.5 mg) was the first combination drug available in Japan and was reported to be well tolerated and more efficacious in lowering the SBP and DBP than a monotherapy.⁶ Furthermore, losartan plus hydrochlorothiazide was shown to improve hypokalemia and hyperuricemia to a greater extent than monotherapy with a thiazide diuretic.⁶ In addition, a lot of evidence of a positive cardiovascular outcome and renoprotection with losartan has been provided.^{7,8} Therefore, we selected this combination as the ARB/diuretic arm.

Shimosawa compared combination therapy with losartan 50 mg/hydrochlorothiazide 12.5 mg and candesartan 8 mg/amlodipine 5 mg and reported the hypotensive effects were very similar.⁹ On the other hand, it is possible that a combination therapy with a CCB may be much more potent in terms of the antihypertensive effect. However, some randomized clinical trials have shown not only a blood pressure dependent effect but also a blood pressure independent effect on renoprotection and cardioprotection.^{8,10,11} Hence, it would be meaningful to compare the changes in the laboratory test results including urine protein and albuminuria as a secondary outcome in addition to the antihypertensive effect. Guidelines for the treatment of hypertension recommend a CCB or thiazide diuretic as a second choice in combination with RAS inhibitors to treat CKD.^{2,3,12} However, in ARB-based combination therapy, it is still unknown as to what kind of drugs should be added as the second-line therapy. ACCOMPLISH (Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension) showed that the benazepril-amlodipine combination was superior to the benazepril-hydrochlorothiazide combination in reducing cardiovascular events in patients with hypertension who were at high risk for such events.¹³ Therefore, it might be better to select an ARB with a CCB to reduce the cardiovascular events in hypertensive patients. On the other hand, which combination is superior in terms of the renoprotective effects is still controversial. An ACCOMPLISH substudy demonstrated that the progression of kidney disease, which was defined as doubling of the serum creatinine concentration, was lower in the benazepril plus amlodipine group than in the benazepril plus hydrochlorothiazide group, although it did not differ between each treatment group with diabetic nephropathy.¹⁴ In contrast, GUARD (Gauging Albuminuria Reduction with Loterel in Diabetic Patients with Hypertension) showed that treatment with hydrochlorothiazide plus benazepril resulted in a greater reduction in albuminuria compared to the group with amlodipine plus benazepril, although the mean decrease in the estimated glomerular filtration rate (eGFR) was less in the latter group than in the former group.¹⁵ Thus, with respect to the antialbuminuric effect, RAS inhibitors plus diuretics might be superior, while RAS inhibitors plus a CCB might be better able to maintain the eGFR. Needless to say, both the maintenance of the eGFR and antialbuminuric effects are considered to be important in the renoprotection from antihypertensive agents. However, their effects are not always concordant, namely, a reduced

albuminuria is often associated with a reduction in the eGFR^{10,11,14,16-19} and this phenomena is explained by a decreased effective blood pressure volume and a loss of the kidney's ability to autoregulate the pressure through the nephrons.¹⁷ On the other hand, as was demonstrated in the RENAAL (Reduction in End Points in Noninsulin-Dependent Mellitus with the Angiotensin II antagonist, losartan, in patients with diabetic nephropathy) trial, the specific (beyond blood pressure lowering) renoprotective effect of the ARB, which can be explained by its antialbuminuric effect, has also been suggested.¹⁰ The aim of the present study was to analyze the renoprotective effects of each combination therapy taking into consideration the baseline GFR and level of proteinuria or albuminuria.

According to the guidelines for hypertension in the elderly published by the Japanese Society of Hypertension (JSH2009), a CCB, ARB, angiotensin-converting enzyme (ACE) inhibitor, or a low-dose diuretic should be the first choice, and if the antihypertensive effect is insufficient, these drugs should be used in combination.² Similar to the aforementioned discussion, it is still undetermined what kind of combination therapy should be selected as the first line for elderly hypertensive patients since elderly patients might have latent organ damage such as brain, heart and kidney damage. Shimosawa performed a subanalysis of the efficacy and safety between a combination therapy with losartan/hydrochlorothiazide and candesartan/amlodipine in aged patients over 65 years and found that the percentage of patients who attained the treatment goal was higher in the elderly patients than in the younger patients.⁹ Since salt sensitivity is expected to increase with age,⁵ it may imply the importance of combination therapy using diuretics for elderly patients. We attempted to perform a subanalysis to determine what subclass of patients could be responders to an ARB/diuretic or ARB/CCB.

Another important issue is comparing the cognitive function with the mini-mental state examination (MMSE) at baseline and after one year in our trial. Considerable evidence has been reported indicating there is a strong association between hypertension and cognitive function. In elderly people with isolated systolic hypertension, antihypertensive treatment was found to be associated with a lower incidence of dementia.²⁰ In the Hypertension in the Very Elderly trial (HYVET), antihypertensive treatment, when included in a meta-analysis, was shown to reduce incident dementia.²¹ It has also been demonstrated that hypertension in midlife is a risk factor for a cognitive decline and dementia. In fact, in the Honolulu-Asia Aging Study, it was shown that midlife SBP was the strongest blood pressure component predicting incident dementia.²² On the other hand, recently, great attention has been paid to the association between the renin-angiotensin system and cognitive function or Alzheimer's dementia.²³ Indeed, there have been reports regarding the beneficial effects of ARBs on cognitive function in hypertensive patients.²⁴⁻²⁶ In addition, it has been suggested that some ACE inhibitors and ARBs might have benefits not only for the prevention but also for the treatment of mild to moderate Alzheimer disease progression.²⁷⁻²⁹ Thus the association between an antihypertensive treatment and cognitive function is becoming an important topic. In this trial, we hope to elucidate the relationship between blood pressure or drug combination and cognitive function.

In conclusion, the CAMUI trial will provide new evi-

dence concerning optimal combination therapy and its effects on renal outcome and cognitive function in elderly hypertensive patients.

APPENDIX

The CAMUI (Combination of Antihypertensive therapy in the elderly, Multicenter Investigation)

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Executive Study Coordinator: Nobuyuki Sato, Department of Cardiology, Asahikawa Medical University

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Data Monitoring and Safety Committee: Takahiko Yoshida, Division of Community Medicine and Epidemiology, Department of Health Science, Asahikawa Medical University

Advisory Board for Statistical Analyses (The Study Statistician): Yasuaki Saijo, Division of Community Medicine and Epidemiology, Department of Health Science, Asahikawa Medical University

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