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Original article

The design of a prospective, randomized, open-labeled study to compare the efficacy of lercanidipine with amlodipine on renal function in hypertensive patients aged at least 55 years (LEADER study)

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ABSTRACT

Background: Although all classes of antihypertensive treatment can successfully reduce morbidity and mortality of cardiac pathology, prevention of target organ damages is of great importance beyond blood pressure lowering. Unlike most dihydropyridines, lercanidipine dilates both afferent and the efferent arterioles of nephrons, so it may provide renoprotective effects, which other CCBs may not have. The main purpose of this study is to compare the renoprotective effect of lercanidipine and amlodipine among hypertensive people aged 55 years and older with newly diagnosed hypertension or those who were treatment-naïve for one month.

Methods: The study is a prospective, open-labelled, randomized, controlled trial to enrol 232 hypertensive patients aged ≥55 years. Subjects will be randomized into lercanidipine arm (10–20 mg/day) and amlodipine arm (5–10 mg/day) by 1:1 ratio. The dosage can be up-titrated to 20 mg/day (lercanidipine group) and 10 mg/day (amlodipine group), respectively, at week 4 or any following visit thereafter. Efficacy and safety data will be collected at week 4, 12 and 24 by evaluating the blood pressure lowering, estimated glomerular filtration rate, creatinine clearance, and urine albumin-creatinine ratio.

Conclusions: The reno-protective effects of new generation of CCBs such as lercanidipine administered to patients with hypertension are not investigated well. After all, this study will bring benefit to older patients who need drugs with both excellent anti-hypertensive and reno-protective efficacy. And the results will be provided for future treatment guideline of elder population in Taiwan.

1. Introduction

Hypertension is the most common cardiovascular condition in the world and is the leading preventable cause of morbidity and mortality from coronary heart diseases, heart failure, stroke, and chronic renal failure. Hypertension is highly prevalent in both developed and developing countries (more than 30% of adult populations) and constitutes one of the major cardiovascular risk factors and accounts for more than 5% of total deaths worldwide.[1] The economic impact of hypertension is huge not only because of blood pressure control but also the treatment of target organ damages. The kidney is involved in the pathophysiology of hypertension and is damaged by hypertension.[2] Renal hypertensive injury is mainly caused by microcirculatory changes determining hypoperfusion, glomerular hypertension, and hyperfiltration. Approximately 70% of patients with an elevated serum creatinine have hypertension; and in 26.8% of patients, end-stage renal disease was caused by hypertension.[3,4]

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The prevalence of hypertension rises as advancing age, which makes most hypertensive patients to be older adults. Older hypertensive patients have 3- to 4-fold higher mortality than those with normal blood pressure. Renin-profiling studies have shown that people younger than 55 years tend to have higher renin levels relative to people aged 55 years or older. Thus, the treatment with angiotensin-converting enzyme (ACE) inhibitors/angiotensin-receptor blockers (ARBs) or β-blockers, which reduce blood pressure at least in part by suppressing the rennin-angiotensin system at one point or another, are generally more effective in younger patients. In contrast, calcium channel blockers (CCBs) and diuretics are better used as first-line agents in older patients.[5] High blood pressure will accelerate the decline in glomerular filtration rate (GFR) in diabetic and nondiabetic kidney disease.[6] Although all classes of antihypertensive drugs can significantly reduce the morbidity and mortality of cardiac pathology, not all antihypertensive drugs are the same in terms of end-organ protection. It is well known that treatment with ACE inhibitors or ARBs normalizes systemic blood pressure and glomerular capillary pressure and counters both glomerulosclerosis and albuminuria in hypertensive patients. However, renoprotective effect of CCBs in hypertension treatment is controversial that the African American Study on Kidney Disease and Hypertension clearly showed the inferiority of amlodipine in renoprotection than other classes of antihypertensive drugs.[7] A newly synthesized dihydropyridine, that is, lercanidipine, presents the advantage of vasodilation both in afferent and efferent arterioles, which exerts a favorable effect in renoprotection.

A multicenter trial disclosed that lercanidipine not only provided a remarkable antihypertensive effect but also an additional improvement in renal function in patients treated with either ACE inhibitor or ARB.[8] Creatinine clearance was significantly increased from 41.8 ± 16.0 mL/min to 48.5 ± 18.0 mL/min after 6-month treatment period.[8] Moreover, another study, which recruited patients aged 60–85 years, reported the antihypertensive effect and safety of lercanidipine in elderly patients without causing reflex tachycardia.[9] In addition, lercanidipine undergoes extensive hepatic metabolism and processes a gradual and long-lasting effect that encourages the better compliance with once-daily regimen and suggests the use in patients with impaired renal function. On the other hand, other long-acting dihydropyridines, amlodipine, has been shown to have an unfavorable renoprotective profile.[7] Therefore, the main purpose of this study is to evaluate the safety, efficacy, and renoprotective effects of lercanidipine compared with amlodipine in people aged 55 years and older in Taiwan.

2. Methods

2.1. Objectives

This study aims to compare the renoprotective effect of lercanidipine with amlodipine in hypertensive patients at least 55 years old, which is evaluated by the change in estimated GFR (eGFR) at Week 12. Secondary objectives of this study are as follows: (1) the change in eGFR at Week 24; (2) the change in serum/urine creatinine and the estimation of creatinine clearance (eC_{Cr}) at Week 12 and 24; (3) the change in microalbuminuria, expressed as the urine albumin-creatinine ratio at Week 12 and 24; (4) the change in sitting systolic and diastolic blood pressure by visits; and (5) the proportion of responding that is defined as systolic blood pressure reduction at least 10 mmHg at Week 24.

2.2. Study design and treatment plan

This is a prospective, open-labeled, randomized, controlled, multicenter trial that contains two treatment groups. It is estimated to recruit 232 hypertensive patients aged 55 years and older. Table 1 lists the main eligibility criteria for all the subjects enrolled in this study. Eligible patients will be 1:1 randomly assigned to receive lercanidipine 10 mg/d or amlodipine 5 mg/d treatment. There will be 116 patients for each treatment group (lercanidipine) in the trial

Table 1
Main study subject selection criteria of LEADER study

Inclusion Criteria	Exclusion Criteria (Patients will be excluded from the study for any of the following reasons)
● Females or males aged 55 years or older	● Females who are pregnant, breast-feeding, or intent to be pregnant during study period
● Patients who fulfill one of the following criteria	● Known secondary, or accelerated, or malignant hypertension within 6 months before enrollment
● Hypertension without medication treatment within 1 month before the initiation of study prescription and with blood pressure level of 140/90 mmHg or higher (fit any one of them) but lower than 180/105 mmHg (fit both of them) at baseline	● Patients with unstable cardiovascular disease, such as myocardial infarction, unstable angina pectoris, valvular heart disease, arrhythmia, severe heart failure (New York Heart Association Class III–IV), stroke, and so on, or coronary bypass surgery or any percutaneous coronary intervention within 6 months before enrollment
● Newly diagnosed or treatment-naïve hypertensives with blood pressure level of 140/90 mmHg or higher (fit any one of them) but lower than 180/105 mmHg (fit both of them) at baseline	● Patient with diabetes mellitus according to definition of American Diabetes Association
● Willing and able to provide informed consent	● Patients with chronic kidney disease Stage 4–5 (defined as eGFR level higher than 30 mL/min/1.73 m^2)
	● History or presence of malignancy other than nonmelanoma skin cancer within 5 years before enrollment.
	● Patient with urine albumin-creatinine ratio higher than 300 mg/g, ALT and/or AST more than two times the upper limit of normal, total bilirubin higher than 2.0 mg/dL, serum potassium level higher than 5.5 mmol/L or less than 3.5 mmol/L.
	● Known hypersensitivity to the active ingredient or to any of the excipients of lercanidipine or amlodipine
	● Patients on immunosuppressive therapy and active nephrotic syndrome
	● Patients who have received any investigational product within 30 days before enrollment
	● History of alcohol or substance abuse

ALT = alanine aminotransferase; AST = aspartate aminotransferase; eGFR = estimated glomerular filtration rate.

treatment group and amlodipine as regimen in the control group. These patients have to be directly enrolled in the clinical coordinating centers of the study, located in the Center for Geriatrics and Gerontology of Taipei Veterans General Hospital, Center for Geriatrics and Gerontology of Taichung Veterans General Hospital, Geriatric Medicine Center of Kaohsiung Veterans General Hospital, Department of Family Medicine, Yuanshan Veterans Hospital, and Department of Medicine of Kaohsiung Medical University Hospital.

For all participants, the dosage used could be escalated to 20 mg/d of lercanidipine and 10 mg/d of amlodipine at Week 4 or any following visit thereafter, in those who do not reach the treatment target based on the best judgment of the investigators. If the blood pressure still cannot be controlled well at Week 12 postdose escalation, investigator may discontinue the study treatment earlier for add-on or switching to other antihypertensive agents. Efficacy and safety data will be collected at Week 4, 12, and 24. Data about safety, efficacy, physical, and biochemical parameters will also be collected individually for the defined time points (Fig. 1).

The study protocol will be approved by the Institutional Review Board (IRB) of all participating hospitals. The principal investigators' agreements were provided to the IRB or ethics committee with all appropriate material, including the informed consent document. This trial would not be initiated until appropriate IRB approvals of the protocol, the informed consent documents, the receiving confirming of investigator(s), those received copies of the submitted documents, and the approval letter had been exactly organized. Appropriate reports on the progress of this study by the principal investigator will be made to the IRB in a timely manner in accordance with applicable government regulations and in agreement with policy established by each center.

Other treatment may be continued during the trial and whenever possible at fixed dose. This should be noted in the case report form. Subjects were prohibited treatments of other antihypertensive and investigational drug during the study period. Subjects' condition in this trial would be evaluated according to the endpoints of change in laboratory results, adverse events (AEs), and serious AEs (SAEs).

The aforementioned "change in laboratory results" contains laboratory results, such as eGFR, eC_{cr}, serum/urine creatinine, and urine albumin-creatinine ratio thereof. Here, the occurrence of AEs were determined by any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to possess a causal relationship with this treatment. SAEs were any experience that suggests a signification hazard, contraindication, serious side effect, or precaution. AEs were coded with Medical Dictionary for Regulatory Activities and a summary frequency table of AEs was provided. The severity and relationship to study medication of AEs was summarized as well. The brief summary about SAEs was also described. SAEs will be listed and described in tables. Meanwhile, the record of the efficacy/safety data and the vital signs will be collected in this study.

2.3. The study population

All participants need to be newly diagnosed with hypertension or treatment naïve within 1 month before the initiation of study and with their blood pressure level of 140/90 mmHg or higher (fit any one of them) but lower than 180/105 mmHg (fit both of them) at baseline were diagnosed. For all participants, the therapeutic goal of blood pressure control is stratified by their age: (1) age of 55–69 years at systolic blood pressure higher than 140 mmHg and diastolic blood pressure lower than 90 mmHg; (2) age of 70–79 years at systolic blood pressure higher than 150 mmHg and diastolic blood pressure lower than 90 mmHg; and (3) age 80 years or older at systolic blood pressure lower than 160 mmHg and diastolic blood pressure lower than 90 mmHg.[10]

Patients will be excluded from the study if they are pregnant female, with known secondary hypertension, or with unstable cardiovascular diseases. In addition, those who were diagnosed with diabetes mellitus, chronic kidney disease Stage 4–5, malignancies, or serious abnormality in urinary were also excluded. At last, people who were alcohol/drug abusers or allergic to any excipients of lercanidipine or amlodipine were excluded. The subjective study population design described above can be understood clearly by the inclusion/exclusion criteria as shown in Table 1.

2.4. Statistical analysis plan

This study is designed to demonstrate that the study drug is superior to active drug, and the statistical power had to achieve 80% under 0.05 confidence level. At least 232 patients will be enrolled in a 1:1 ratio to therapy of lercanidipine (116 patients) or amlodipine (116 patients). The sample size estimation assumes that the true mean difference between a test drug and an active control drug is 4 mL/min. Assumed mean change of GFR from baseline to Month 3 in amlodipine is −0.16 mL/min/1.73 m^2 (standard deviation = 13.6) and mean change of GFR from baseline to Month 3 in ramipril is

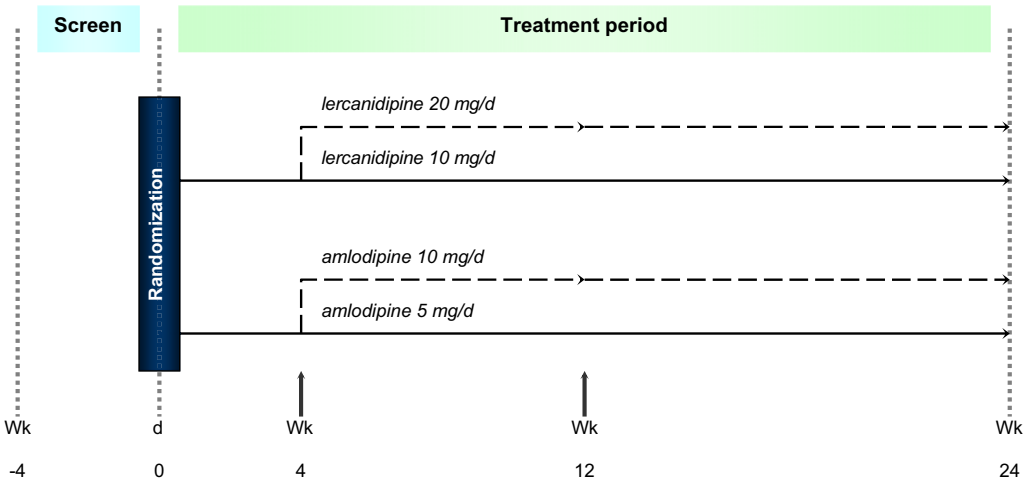

Fig. 1. Study design of the LEADER study.

4.03 mL/min/1.73 m^2 (standard deviation = 13.2). Using two-sample *t* test will have 80% power to show a statistical difference between arms.

The primary endpoint is the change in eGFR at Week 12. Descriptive statistical analysis will be provided and the comparison between arms will be tested by using two-sample *t* test. The secondary endpoint are the change in eGFR, serum/urine creatinine, and eC_{Cr}; microalbuminuria and sitting blood pressure will be summarized at 4, 12, and 24 weeks after initiation of study prescription. In addition, the difference between treatment groups will be analyzed by using *t* test or analysis of variance. For the proportion, analyses will be summarized as frequency table and χ^2 test or Fisher's exact test will be used to compare between arms. For the safety analysis, the summary results of laboratory at the baseline and the end of study visit, and the change from baseline to end of study visit will be summarized by descriptive statistics and paired *t* test. The AEs will be summarized by frequency tables. In Table 2, the calculated sample sizes within each different arm with different δ (milliliter/min) from the aforementioned equation are listed.

2.5. Data collection and study traits

The data collected from laboratorial examinations and the records of vital signs are executed step by step as the chart shown as Table 3. Laboratory tests are implemented according to the protocols, such as pregnancy tests, biochemical examinations, and the urology testing. However, pregnancy test will be only conducted in female subjects of childbearing potential. The investigator should counsel the patient and inform the risks of continuing with the pregnancy and the possible effects on the fetus. All female patients should be instructed to immediately inform the investigator if she becomes pregnant during study period. Blood sample will be drawn for biochemistry examinations in all patients at every visit. At each visit, both eGFR and eC_{Cr} will be determined from the serum creatinine using the biostatistical formula.[11] In the beginning, the value of eGFR will be calculated by Modification of Diet in Renal Disease formula or by Cockcroft-Gault formula,[12]and the last parameter in the aforesaid equations will be chosen from one of the numbers: 1.233 (if Chinese) and 1.21 (if Black).[13] During the screening period, patients with fasting glucose level higher than 126 mg/dL on two different occasions or random glucose level higher than 200 mg/dL should be excluded. Urine sample will be collected for routine urinalysis, such as urine creatinine and spot urine albumin, will be conducted at screening, baseline, and at Visit 4 and 5. The microalbuminuria will be determined by spot urine albumin and be presented by the albumin-creatinine ratio.

3. Discussion

CCB and thiazide diuretics both are the recommended starting antihypertensive agents among patients aged older than 55 years by the British Hypertension Society. However, geriatricians do worry about the adverse effect of diuretics in hypertension treatment for older patients because of the postural hypotension and increased tendency to fall. This trial is designed to compare the renoprotective effects of different CCBs whose effects are much different toward the efferent arterioles, and this research especially focused on the observation of the difference between lercanidipine and another CCB, amlodipine. It is well known that treatment with ACE inhibitors/ARBs can be administered to hypertensive patients and these two categories of medicines will present protective effect upon the renal function, especially the glomerular microcirculatory system. Most CCBs dilate afferent but not efferent arterioles, which might be associated with worsening of glomerular injury.[14] Patients treated with all those aforesaid antihypertensive agents can significantly reduce the morbidity and mortality of cardiac pathology, but only limited results were obtained in patients with end-stage renal disease.

Experts in the field of cardiovascular disease have noticed that those who used antihypertensive drugs somehow have disadvantages for those with unhealthy renal function. Compared with the old generations of CCBs, which dilate afferent but not efferent arterioles, the new generation of CCBs can dilate not only the afferent but also the efferent arterioles, so physicians have started to find out the antihypertensive drugs those offer better nephroprotection.[9,14] Most researchers try to sieve the study targets from the third generation of the antihypertensive drugs of CCBs. But whether CCBs will prevent the glomerular microcirculation from damage caused by huge difference between afferent and efferent arterioles or not is studied much little in this field. Newly synthesized dihydropyridine, such as lercanidipine, present the advantages of vasodilation both in afferent and efferent arterioles. Among various new antihypertensive CCBs, lercanidipine reveals to have less adverse side effect, especially peripheral edema toward elder patients.[15,16] As human generation grows older all around the world, it is important to find out a regimen, which can not only

Table 2
Endpoint-series sample size of arms with different δ (milliliter/min)

Per arm	δ(mL/min)				
	2	1.5	1	0.5	0
13	261	167	116	85	65

The number of the probable sample size in each treatment group was 167.

Table 3
Flow chart of LEADER study

Visit number	Screening	Baseline	Treatment		
	1	2	3	4	5/ET
Time of visit (wk ± d)	−4, 0	0	4 ± 4	12 ± 1	24 ± 1
Informed consent	X				
Inclusion/exclusion criteria	X	X			
Randomization		X			
Demographics	X				
Medical history	X				
Physical examination[a]	X	X	X	X	X
Blood pressure/heart rate	X	X	X	X	X
Biochemistry					
ALT	X		X		X
AST	X		X		X
Total bilirubin	X				X
Serum creatinine	X	X[b]	X	X	X
BUN	X	X[b]	X	X	X
Glucose	X				
Sodium	X	X[b]	X	X	X
Potassium	X	X[b]	X	X	X
Calcium	X	X[b]	X	X	X
Urinalysis					
β-hCG[c]	X				
Urine creatinine	X	X[b]		X	X
Spot urine albumin	X	X[b]		X	X
Antihypertensive therapy		X	X	X	X
Drug accountability			X	X	X
Prior/concomitant medication[d]	X	X	X	X	X
Adverse events		X	X	X	X

[a] Body height will be only measured at screening visit.
[b] Urine pregnancy test will only be conducted in female of childbearing potential.
[c] These tests could be omitted if the screening visit is conducted within 7 days.
[d] The record of concomitant medication should be traced back to 30 days before the commencement of observational prescription.
ALT = alanine aminotransferase; AST = aspartate aminotransferase; β-hCG = β-human chorionic gonadotropin; BUN = blood urea nitrogen; ET = earlier termination (the final visit could be conducted when subject discontinues from the study earlier).

decrease blood pressure but also be able to protect the patients' renal functions meanwhile.

From the abovementioned description, a more effective renoprotection in the third generation of CCBs prescribed to older generations could be found on hypertensive patients those who had received antihypertensive drugs before, and the renoprotection effects will be evaluated more quantitatively in this study. Thus, to approve that lercanidipine not only provided a high antihypertensive effect but also an additional improvement within renal function among elderly patients, this study will investigate both the antihypertensive and renoprotective efficacy of lercanidipine within hypertensive patients those who are at least 55 years old in Taiwan. Amlodipine, an antihypertensive drug in habitually treatment, will be prescribed to the other set of subjects as a compared group to figure out the effect of lercanidipine quantitatively.

The renoprotective effects of new generation of CCBs, such as lercanidipine, administered to patients with hypertension are not investigated well; yet, this trial will try to study this protective phenomenon on the elderly patients who are diagnosed with hypertension and administered lercanidipine as regimen. After all, this study will bring benefit to older patients who need drugs with both excellent antihypertensive and renoprotective efficacy. And the results will be provided for future treatment guideline of elderly population in Taiwan.

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