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ORIGINAL ARTICLE

Lercanidipine *vs* lacidipine in isolated systolic hypertension

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This randomised, double-blind, double-dummy, parallel group, multicentre study compared the efficacy and tolerability of lercanidipine with lacidipine. Elderly patients with isolated systolic hypertension (supine blood pressure ⩾160/<95 mmHg) were enrolled and underwent a placebo run-in period of 14–27 days before random allocation to lercanidipine tablets 10 mg once daily ($n=111$) or lacidipine tablets 2 mg once daily ($n=111$) for the assessment period (112–160 days). Titration to lercanidipine 20 mg once daily (two 10 mg tablets) or lacidipine 4 mg once daily (two 2 mg tablets) was allowed after 8 weeks, if required. Both treatments decreased supine and standing systolic and diastolic blood pressure between the end of the run-in period and the end of the assessment period ($P<0.0001$). At the end of the assessment period, the estimated mean treatment difference (95% confidence intervals) in supine systolic blood pressure was −0.81 (−4.45, 2.84) mmHg. These confidence intervals were within the limits specified for equivalence, that is, (−5, 5) mmHg. Ambulatory blood pressure monitoring showed that the antihypertensive effects of both drugs lasted for the full 24-h dosing period and followed a circadian pattern. Both treatments were well tolerated with a low incidence of adverse drug reactions and a low withdrawal rate. Significantly fewer patients withdrew from treatment with lercanidipine ($P=0.015$). Neither treatment had any clinically significant effect on pulse rate or cardiac conduction. In conclusion, both treatments were equally effective in controlling supine systolic blood pressure in patients with isolated systolic hypertension.
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Introduction

The British Hypertension Society defines isolated systolic hypertension (ISH) as a systolic blood pressure (SBP) ⩾160 mmHg and a diastolic BP (DBP) <90 mmHg.[1] SBP increases with age, therefore ISH is a particular problem in the elderly. Treatment of ISH has been shown to reduce stroke, coronary events, and major cardiovascular events.[2,3]

Lercanidipine is a dihydropyridine calcium channel blocker. It has an unusual pharmacokinetic profile resulting from its high lipophilicity. It binds strongly to the lipid bilayer of cell membranes close to the calcium channel from where it is slowly released over subsequent hours. This slow release from cell membranes gives a gradual onset and 24-h duration of action despite the drug's short plasma half-life of 2–5 h.[4–6] Studies have shown that lercanidipine tablets are more effective than placebo in lowering BP and are as effective as other antihypertensive agents such as atenolol, hydrochlorothiazide, captopril, and slow release nifedipine.[7–11] There is also evidence that lercanidipine tablets are effective in the treatment of ISH.[12]

Like lercanidipine, lacidipine is a dihydropyridine calcium channel blocker with a slow onset and long duration of action. The efficacy of lacidipine in mild to moderate hypertension has been shown in studies comparing it with hydrochlorothiazide, atenolol, and nifedipine.[13–15] The efficacy of lacidipine in the treatment of ISH is currently being assessed in the Systolic Hypertension in the Elderly Long-term Lacidipine (SHELL) trial.[16]

Studies have shown that there is a role for long-acting dihydropyridine calcium channel blockers in the treatment of ISH,[2,17] so we designed this study to compare the efficacy, tolerability, and 24-h BP control profile of lercanidipine tablets with lacidipine tablets in patients with ISH. We wanted to show equivalence between the two treatments in terms of supine SBP.

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Materials and methods

Patients

We carried out this study in general practices and hospital outpatient hypertension clinics in the UK. Patients were of either sex, aged 60–85 years, inclusive, with ISH. Patients with secondary hypertension, angina, or any other significant cardiac condition were excluded, as were patients whose BP was not adequately controlled with antihypertensive monotherapy, and patients who had an SBP >200 mmHg. Other exclusion criteria included: signs of postural hypotension; hypovolaemia; myocardial infarction, stroke, or a transient ischaemic attack in the last 3 months; clinically significant hepatic or renal dysfunction; diabetes mellitus.

Local research ethics committees approved the study and patients gave written informed consent. All staff involved in the study followed the sponsor's standard operating procedures.

Study design

This was a randomised, double-blind, double-dummy, parallel group study. Patients who were currently receiving antihypertensives had to undergo a washout period of 14–20 days before entering the single-blind, placebo run-in period. Patients who were not receiving any antihypertensive therapy proceeded straight to the run-in period, which lasted for 14–27 days (one run-in week lasted for 7–9 days). To enter the run-in period, patients had to have a mean supine SBP/DBP of $\geqslant 160/<95$ mmHg. During this period, they received placebo lercanidipine tablets and placebo lacidipine tablets and their BP was assessed at each study visit (every 7–9 days). To enter the assessment period, patients had to have a SBP/DBP of $\geqslant 160/<95$ mmHg at the start of the run-in period and at two visits during the run-in period.

The double-blind assessment period lasted for 112–160 days (one assessment week lasted for 7–10 days). Patients received either active lercanidipine and placebo lacidipine tablets, or placebo lercanidipine and active lacidipine tablets. They attended study visits every 28–40 days. There were two dose levels of study medication. Level 1 was 10 mg lercanidipine tablets or 2 mg lacidipine tablets. Level 2 was 20 mg lercanidipine tablets (two 10 mg tablets) or 4 mg lacidipine tablets (two 2 mg tablets). These are the recommended doses according to the Summary of Product Characteristics for each product. All patients started treatment on Dose Level 1.

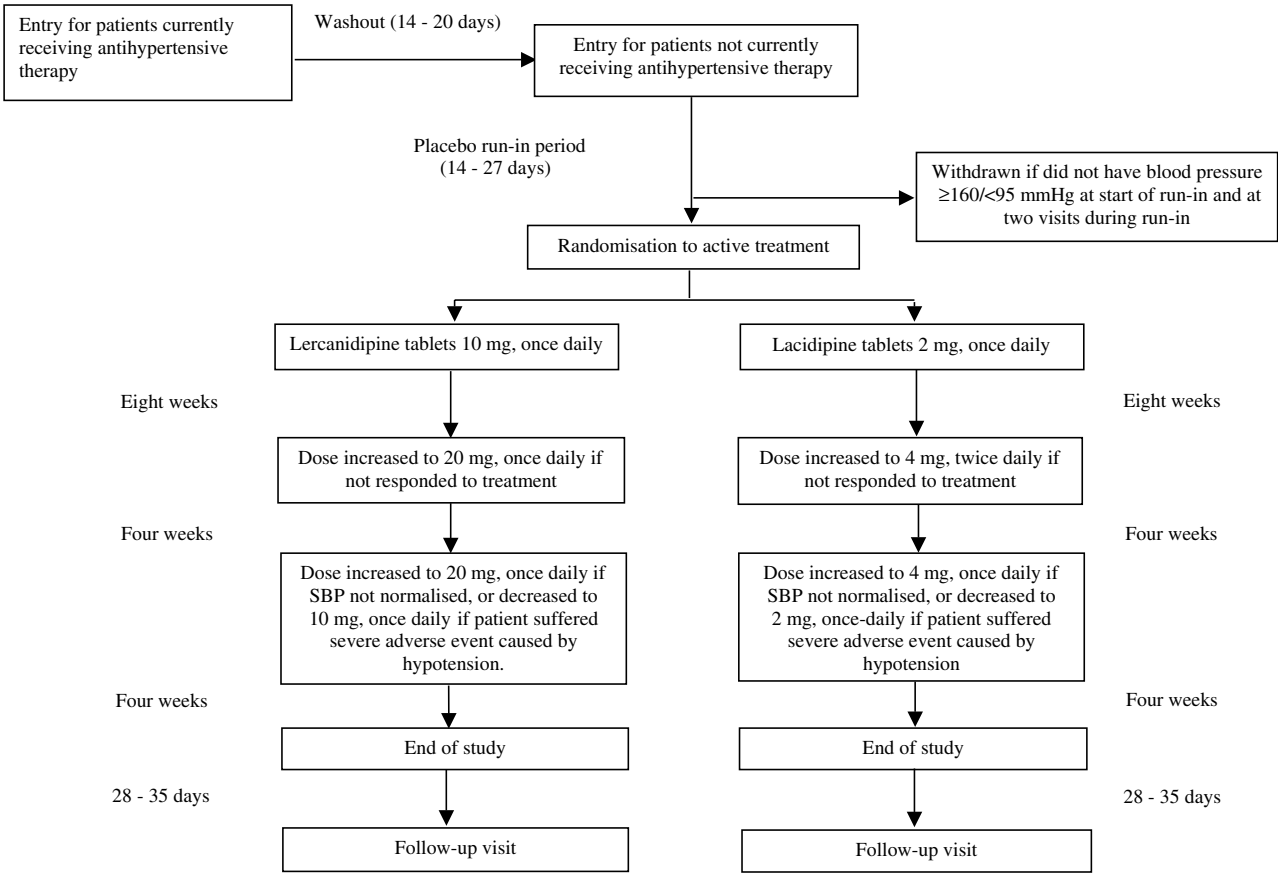

Figure 1 Study design.

Patients took their study medication once daily. Dose titration was allowed as follows:

- After approximately 8 weeks in the assessment period, the investigator could increase the patient's dose from Level 1 to Level 2 if he/she had not responded to treatment (i.e. if he/she had not achieved an SBP of $\leqslant 140$ mmHg or a decrease in SBP of $\geqslant 20$ mmHg).
- After approximately 12 weeks in the assessment period, the investigator could increase the patient's dose from Level 1 to Level 2 if he/she had not achieved normalised SBP ($\leqslant 140$ mmHg), or decrease the patient's dose from Level 2 to Level 1 if he/she had experienced a severe adverse event caused by hypotension. If the patient was already receiving Level 2, no further increase in dose was allowed, but the investigator could withdraw the patient if he/she felt that the patient's BP was not adequately controlled.

The study design is shown in Figure 1.

Investigators measured patients' supine and standing SBP/DBP at each study visit. All the investigators used a standard mercury sphygmomanometer that had been calibrated in the last 12 months and the measurements had to be taken under standardised conditions, that is, at approximately the same time of day at each visit, by the investigator or co-investigator, and using the same sphygmomanometer. The investigator measured the patient's BP in the supine position (after the patient had been supine for at least 5 min) and standing (after the patient had been standing for 2 min). The investigator took two readings in each position and recorded both of these readings, together with the mean. If the two systolic readings in the supine position differed from each other by more than 10 mmHg, two further readings were taken. At the first visit, the investigator measured the patient's BP in both arms and the arm with the highest reading was used for the rest of the study.

A subgroup of 62 patients also underwent 24-h ambulatory BP monitoring at the end of the run-in and assessment periods. All investigators used a Spacelab ambulatory BP system (Spacelabs Medical Data, Redmond, Washington, USA). Between 0600 and 2200 hours, readings were taken every 15 min. Between 2200 and 0600 hours, readings were taken every 30 min.

From the ambulatory data, we calculated diurnal variation (mean night-time BP subtracted from mean daytime BP), BP load (the percentage of SBP readings that were >140 mmHg during the day and >120 mmHg during the night), and the smoothness index. The smoothness index was determined for each patient by calculating the mean difference in SBP between the run-in and assessment periods over 24 h and dividing the result by its s.d. Data for individual patients were averaged to obtain mean (s.d.) values for each treatment group as a whole. We used the smoothness index to assess the homogeneity of 24-h BP reduction.[18]

Investigators measured patients' pulse rate (radial pulse) at each study visit, and recorded a standard 12-lead electrocardiogram at the start of the run-in period and at the end of the assessment period. They also took a 10 ml blood sample from each patient at the start of the run-in period and at the end of the assessment period for biochemical and haematological screening, and recorded any volunteered adverse events at each study visit.

Statistical analyses

We designed this as an equivalence study, so the per protocol population was used in the primary analysis. Unless otherwise stated, data are presented for the per protocol population. We used analysis of variance (ANOVA) to compare patients' age and the χ^2 test to compare patients' sex between treatment groups. We compared patients' BP and electrocardiogram results between treatment groups using analysis of covariance (ANCOVA) with baseline values as covariates. For supine SBP, we included centre as a factor in the analysis. We analysed the change in BP between the end of the run-in period and the end of the assessment period using the paired *t*-test, and the smoothness index using the unpaired *t*-test. We used the χ^2 test to analyse the percentage of patients who responded to treatment and the percentage of patients who achieved normalised SBP. We analysed the percentage of patients on each dose level who responded to treatment using the loglinear model. We also used the χ^2 test to analyse withdrawals and ANCOVA to analyse patients' pulse rates, with the values at the end of the run-in period as covariates. We estimated mean treatment differences and 95% confidence intervals (CIs) for supine and ambulatory SBP, diurnal variation, and heart rate. Equivalence was assumed if the 95% CI for the estimated mean treatment difference in supine SBP fell within the range $(-5, 5)$ mmHg.

We estimated that we needed to recruit a maximum of 250 patients to achieve 94 completing patients in each group. With 94 completing patients per group, the study would have 90% power at the 5% significance level to show that the 95% CI for the estimated mean treatment difference in supine SBP at the end of the study was within the limits of $(-5, 5)$ mmHg (assuming an s.d. of 10.5 mmHg).

Results

Patients

A total of 14 centres took part in the study (one hospital and 13 GP surgeries). A total of 290 patients were enrolled, 284 entered the run-in period, and 222 entered the assessment period. Of the 68

patients who withdrew before the assessment period, 34 failed the continuation criteria (i.e. did not have an SBP/DBP of $\geqslant 160/<95$ mmHg at the start of the run-in period and at two other visits during the run-in period), eight withdrew because of adverse events with/without 'other reasons', and 26 withdrew for 'other reasons' alone.

Baseline characteristics (Table 1) were analysed for the intent to treat population. In all, 64 patients (58%) in the lercanidipine group and 70 patients (63%) in the lacidipine group were female. The two groups were comparable for sex ($P=0.410$), mean age ($P=0.900$), height, and weight. All of the patients were Caucasian.

During the assessment period, eight of the 111 patients (7%) receiving lercanidipine and 20 of the 111 patients (18%) receiving lacidipine withdrew. This treatment difference was statistically significant ($P=0.015$). Five patients (5%) receiving lercanidipine and 15 (14%) receiving lacidipine withdrew because of adverse events and/or lack of efficacy. Three patients (3%) receiving lercanidipine and five (5%) receiving lacidipine withdrew for 'other reasons'.

Table 1 Baseline characteristics

Parameter		*Lercanidipine tablets* (n=*111*)	*Lacidipine tablets* (n=*111*)
Sex	number (%):		
Male		47 (42)	41 (37)
Female		64 (58)	70 (63)
Age (years)			
Mean (range)		70.7 (60–85)	70.8 (60–83)
Weight (kg)			
Mean (range)		72.6 (44–133)	74.4 (40–127)
Height (cm)			
Mean (range)		164.0 (108–187)	164.8 (141–190)
Smoking history	number (%):		
Never smoked		50 (45)	43 (39)
Smoker		23 (21)	18 (16)
Ex-smoker		38 (34)	50 (45)
Disease duration	number (%):		
1–3 months		32 (29)	32 (29)
3 months–1 year		18 (16)	13 (12)
1–5 years		32 (29)	35 (32)
>5 years		28 (26)	31 (28)

Blood pressure

Both treatments gave decreases in supine and standing SBP and DBP between the end of the run-in period and the end of the assessment period (Table 2). All of these decreases were statistically significant ($P<0.0001$). Analysis of supine and standing measurements showed no evidence of postural hypotension. At the end of the assessment period, the estimated mean treatment difference (95% CI) in supine SBP was −0.81 (−4.45, 2.84) mmHg (lercanidipine−lacidipine). This CI was within the predefined limits for equivalence, that is, (−5, 5) mmHg.

During the assessment period, the percentage of patients who had responded to treatment (i.e. achieved an SBP of $\leqslant 140$ mmHg or a decrease in SBP of $\geqslant 20$ mmHg) was higher in the lercanidipine group. After 8 weeks' treatment, this difference was statistically significant (65% compared with 50% in the lacidipine group; $P=0.044$). At the end of the assessment period, the difference was not statistically significant (67 *vs* 58%; $P=0.196$). In all, 32% of the patients receiving lercanidipine and 27% receiving lacidipine achieved normalised supine SBP ($\leqslant 140$ mmHg) after 8 weeks of treatment ($P=0.408$). At the end of the assessment period, the corresponding values were 31% and 38%, respectively ($P=0.343$).

In total, 60 patients (61%) receiving lercanidipine were titrated from 10 mg to 20 mg during the assessment period. In the lacidipine group, 58 patients (67%) were titrated from 2 mg to 4 mg. The difference between treatment groups in the number of patients receiving each dose level was not statistically significant. The number of responding patients in each treatment group was summarised by

Table 2 Supine and standing SBP and DBP

	Mean (s.d.) BP (mmHg)			
	Lercanidipine tablets (n=*99*)		*Lacidipine tablets* (n=*87*)	
	End of run-in	*End of assessment*	*End of run-in*	*End of assessment*
Systolic				
Supine	171.8 (9.2)	148.0 (12.7)	170.8 (9.4)	149.2 (13.0)
Standing	167.6 (10.8)	146.8 (13.5)	167.9 (9.9)	147.8 (13.8)
Diastolic				
Supine	86.4 (6.3)	80.7 (8.0)	86.1 (7.0)	80.9 (8.4)
Standing	88.7 (6.3)	82.8 (8.3)	88.2 (7.2)	83.3 (8.3)

the dose level. At Level 1, the percentage of responding patients was similar in both groups (74% in the lercanidipine group and 76% in the lacidipine group), but at Level 2, the percentage of responding patients was greater in the lercanidipine group (62%) than in the lacidipine group (48%). There was no evidence to suggest that these treatment differences were statistically significant.

Ambulatory blood pressure

Figure 2 shows the hourly mean ambulatory SBP at the end of the run-in and assessment periods. Both treatments gave decreases in BP that were sustained over the 24-h dosing interval and followed a circadian pattern. In both treatment groups, the mean ambulatory SBP and DBP were lower at the end of the assessment period compared with the end of the run-in period (Table 3). The estimated mean treatment differences (95% CIs) in daytime (0600–2200 hours) and night-time (2200–0600 hours) ambulatory SBP at the end of the assessment period were 2.89 (−3.63, 9.42) mmHg and 1.35 (−4.42, 7.12) mmHg, respectively, (lercanidipine−lacidipine). These treatment differences were not statistically significant.

In both treatment groups, diurnal variation was lower at the end of the assessment period compared with the end of the run-in period. At the end of the assessment period, the mean (s.d.) diurnal variation in SBP was 10.5 (14.1) mmHg in the lercanidipine group and 11.7 (10.7) mmHg in the lacidipine group. The estimated mean treatment difference (95% CI) was −0.71 (−7.93, 6.52) mmHg (lercanidipine–lacidipine). The corresponding values for the diurnal variation in DBP were 8.6 (9.0) mmHg and 10.9 (7.3) mmHg, respectively, and the estimated mean treatment difference (95% CI) was −2.18 (−7.00, 2.63) mmHg (lercanidipine−lacidipine). These treatment differences were not statistically significant.

The mean (s.d.) values for the smoothness index were 0.51 (0.69) for lercanidipine and 0.51 (0.65) for lacidipine ($P = 0.762$).

BP load was lower at the end of the assessment period compared with the end of the run-in period in both treatment groups.

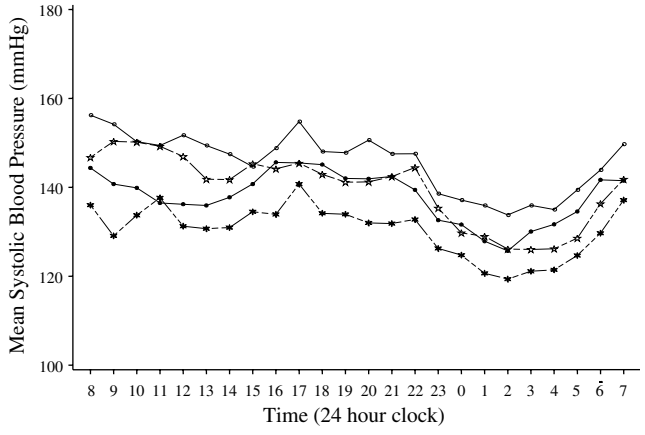

Figure 2 Mean ambulatory SBP recorded at the end of the run-in and assessment periods. End of run-in: ○ lercanidipine tablets; ☆ lacidipine tablets. End of assessment: ● lercanidipine tablets; ★ lacidipine tablets.

Pulse rate and electrocardiogram

Neither treatment had any clinically significant effects on pulse rate or PR interval; mean values were within clinically acceptable limits (i.e. 70–80 beats per minute (bpm) for pulse rate and 120–200 ms for PR interval). Electrocardiogram results showed evidence of an increase in heart rate recorded as part of the electrocardiogram between the start of the run-in period and the end of the assessment period in both treatment groups. At the start of the run-in period, the mean (s.d.) heart rate was 70.6 (11.9) bpm in the lercanidipine group and

Table 3 Ambulatory SBP and DBP

	Mean (s.d.) BP (mmHg)			
	Lercanidipine tablets		*Lacidipine tablets*	
	Run-in[a]	*Assessment*[b]	*Run-in*[c]	*Assessment*[d]
Daytime				
Systolic	149.1 (19.0)	140.7 (15.5)	145.9 (18.0)	132.6 (12.7)
Diastolic	106.0 (15.1)	99.6 (11.0)	103.9 (12.6)	96.3 (8.6)
Night-time				
Systolic	135.6 (21.0)	130.3 (17.8)	127.6 (14.8)	122.2 (13.3)
Diastolic	94.0 (16.4)	91.0 (13.3)	88.7 (10.9)	86.1 (8.9)

[a] $n=30$ for daytime readings and $n=29$ for night-time readings.
[b] $n=26$ for daytime and night-time readings.
[c] $n=31$ for daytime readings and $n=29$ for night-time readings.
[d] $n=21$ for daytime readings and $n=22$ for night-time readings.

70.9 (11.6) bpm in the lacidipine group. At the end of the assessment period, the corresponding values were 76.9 (12.7) bpm and 73.3 (11.8) bpm, respectively. At the end of the assessment period, the estimated mean treatment difference (95% CI) in heart rate was 3.49 (0.54, 6.44) bpm (lercanidipine−lacidipine). Although this treatment difference was statistically significant ($P=0.021$), it was not considered to be clinically relevant, as the mean values were within clinically acceptable limits (between 70 and 80 bpm).

Biochemical and haematological screens

Some patients had abnormal values for blood biochemistry and haematology parameters, but in most cases the investigator considered that these were not clinically significant. One patient receiving lacidipine tablets had abnormal results for random glucose, alanine aminotransferase, and gamma-glutamyl transpeptidase that the investigator considered to be clinically significant. A further two patients receiving lacidipine had abnormal results that the investigator considered to need further investigation. Neither treatment had any obvious effect on random glucose values.

Adverse drug reactions

Tolerability data were analysed for the intent to treat population. During the assessment period, 32 patients (29%) receiving lercanidipine and 38 patients (34%) receiving lacidipine reported at least one adverse drug reaction (ADR; i.e. an adverse event that the investigator considered to be related to treatment). Peripheral oedema and dizziness were the most commonly reported ADRs. In all, 11 patients (10%) receiving lercanidipine and 10 (9%) receiving lacidipine reported peripheral oedema. A total of 10 patients (9%) receiving lercanidipine and eight (7%) receiving lacidipine reported dizziness. All other ADRs were reported by less than 5% of patients.

There were no deaths during the study. One patient receiving lacidipine tablets had a serious ADR (a transient ischaemic attack). The study medication was stopped and the patient fully recovered.

Discussion

Both treatments were effective in reducing SBP in patients with ISH and the response to treatment was good. Equivalence was shown for the two treatments in terms of supine SBP.

After 8 weeks, significantly more patients receiving lercanidipine had responded to treatment. However, at the end of the assessment period, this treatment difference was no longer statistically significant. This may suggest that patients responded earlier to lercanidipine than they did to lacidipine.

Over 60% of patients in each treatment group had their dose titrated up to Level 2. Most of these patients had their dose changed after 8 weeks of treatment. However, it has been shown that patients' BP continues to fall for up to 4–5 months after starting treatment with lercanidipine,[19] so it is possible that some patients had their dose increased unnecessarily. There was some evidence to suggest that there was a better response in the lercanidipine group in those patients who required titration to the higher dose, but the treatment difference was not statistically significant.

Active management of ISH has been clearly shown to reduce cardiovascular and cerebrovascular events in three randomised, controlled trials. The Systolic Hypertension in the Elderly Program (SHEP),[3] Systolic Hypertension in Europe (Syst-Eur),[2] and Systolic Hypertension in China (Syst-China)[17] trials demonstrated that mean reductions in SBP of around 26 mmHg, 23 mmHg, and 20 mmHg, respectively, significantly reduced the incidence of fatal and non-fatal stroke, cardiovascular morbidity, and cardiovascular mortality. In the present study, both lercanidipine and lacidipine gave similar reductions in SBP to those seen in SHEP, Syst-Eur, and Syst-China.

In previous studies, ambulatory BP monitoring showed that the antihypertensive effect of a once daily dose of lercanidipine lasted for 24 h and that lercanidipine did not alter the circadian BP profile.[5,20] This present study confirms these results.

The smoothness index is a novel method for assessing the homogeneity of 24-h BP reduction by antihypertensives.[18] It has an advantage over the trough:peak ratio because it takes into account all BP changes induced by treatment over the 24-h period, whereas the trough:peak ratio refers only to two short segments of the 24-h BP profile. The values for the smoothness index obtained for lercanidipine and lacidipine suggest that both treatments have similar BP lowering effects and provide efficacy over the full 24-h dosing interval. They are comparable with that previously calculated for the angiotensin-converting enzyme inhibitor, lisinopril.[18]

The lack of a placebo arm is a drawback for the analyses of the results of this study, but it was not considered ethical to treat patients with placebo for the duration of the study. In addition, the efficacy of both lercanidipine and lacidipine in lowering blood pressure is well established.[7–15]

The withdrawal rate was low in both treatment groups, although significantly fewer patients withdrew from treatment with lercanidipine. The overall incidence of ADRs was low with both treatments and only peripheral oedema and dizziness were reported by more than 5% of patients during the assessment period. Peripheral oedema is a common problem with some dihydropyridines; for example,

in one study, 28% of patients treated with long-acting nifedipine reported peripheral oedema.[21] However, when patients who experienced typical dihydropyridine-related adverse events when treated with dihydropyridines such as nifedipine and amlodipine were switched to lercanidipine, there was a statistically significant reduction in these adverse events.[22] In a long-term study of elderly patients (aged $\geqslant$60 years), both lercanidipine and lacidipine gave significantly lower rates of oedema and resultant withdrawals than amlodipine.[23]

Neither treatment had any clinically significant effect on pulse rate or PR interval. Patients in the lercanidipine group had a statistically significantly higher heart rate recorded on the electrocardiogram at the end of the assessment period, but the mean values were within clinically acceptable limits (between 70 and 80 bpm).

In conclusion, lercanidipine and lacidipine were equally effective in controlling supine SBP in patients with ISH. Both treatments were effective in reducing patients' SBP and DBP and were effective over the 24-h dosing period. Both treatments were well tolerated with a low incidence of ADRs. The withdrawal rate was low in both groups; however, significantly fewer patients withdrew from treatment with lercanidipine. Neither treatment had any clinically significant effect on pulse rate or cardiac conduction.

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