

# Efficacy and tolerability of lercanidipine in mild to moderate hypertension among Asians of different ethnic groups

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## ABSTRACT

**Introduction:** Calcium channel blockers are well established modalities for the treatment of hypertension. However, in spite of the availability of many efficacious agents, hypertension control continues to be poor. One reason is poor tolerability due to adverse events. Racial differences also exist. Lercanidipine, a third-generation calcium channel blocker, is associated with better tolerability. However, it has not been studied in the Asian population. This study examines its efficacy and tolerability in Asian subjects of different ethnicities.

**Methods:** This was an eight-week open label study of adults with mild to moderate hypertension. Blood pressure (BP), pulse rate, self-administered symptom check and laboratory evaluations were done at baseline. Patients were prescribed 10 mg lercanidipine, with up-titration to 20 mg if BP was not controlled at Week 4. Baseline evaluations were repeated at Week 8. Adverse events were also enumerated.

**Results:** 27 patients (mean age 53.4 +/- 12.1 years) completed the study. The baseline systolic BP (SBP), diastolic BP (DBP) and heart rate was 159 +/- 12.2, 96.6 +/- 7.7 mmHg and 71 +/- 13/min, respectively. Three racial groups were represented. SBP and DBP decreased significantly after four weeks of therapy. A further reduction to 139 +/- 14.3 and 88 +/- 9.8 (p-value is less than 0.0001) was seen in Week 8. The absolute SBP and DBP reduction was 20.5 mmHg (95 percent confidence interval [CI] 16.5–24.5, p-value is less than 0.0001) and 9.3 mmHg (95 percent CI 6.2–12.5, p-value is less than 0.0001), respectively. All adverse symptoms, except for palpitations, were reduced at the end of the study.

**Conclusion:** Lercanidipine is efficacious and well

tolerated in Asians of different ethnicities. Its BP lowering effects and tolerability in Asians appear to be similar to other studies on Caucasians and other calcium channel blockers.

**Keywords:** blood pressure, calcium channel blockers, hypertension, lercanidipine

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## INTRODUCTION

A lowering of just 12 mmHg systolic blood pressure (SBP) in hypertensive patients reduces heart failure by 50%, stroke by 48% and coronary heart disease by a more modest 16%.<sup>(1,2)</sup> Calcium channel blockers (CCBs) have been widely used for the treatment of systemic arterial hypertension for more than 20 years.<sup>(3)</sup> All the drugs in this class have been shown to be effective in lowering BP and cardiovascular events in hypertensive patients, either as monotherapy or in combination with other drug classes.<sup>(4-8)</sup> In particular, dihydropyridine (DHP) CCBs have been shown to reduce cardiovascular events in older patients with isolated systolic hypertension.<sup>(4,9)</sup> Furthermore, DHP CCBs have been shown in a randomised, placebo-controlled, crossover study to be more effective than angiotensin-converting enzyme (ACE) inhibitors or  $\beta$ -blockers in lowering SBP in 65- to 86-year-old patients with hypertension.<sup>(10)</sup> With the availability of so many classes of antihypertensives that are effective in lowering BP as well as in reducing cardiovascular events,<sup>(5-8,11)</sup> it might well be asked why hypertension is not better controlled. The cause of this is complex and multifactorial, but the two most likely reasons are using too few drugs to achieve the goal BP and poor drug tolerability. Poor drug tolerability in turn promotes poor adherence to therapy and it is well documented that one in four patients discontinue antihypertensive treatment within the first year of therapy because of adverse events.<sup>(12-14)</sup>

Many antihypertensive medications display characteristic class-wide adverse events but even within a class, the DHP CCBs included, there are fundamental differences between them.<sup>(15)</sup> The development of newer generations of DHP CCBs from the prototype (nifedipine)

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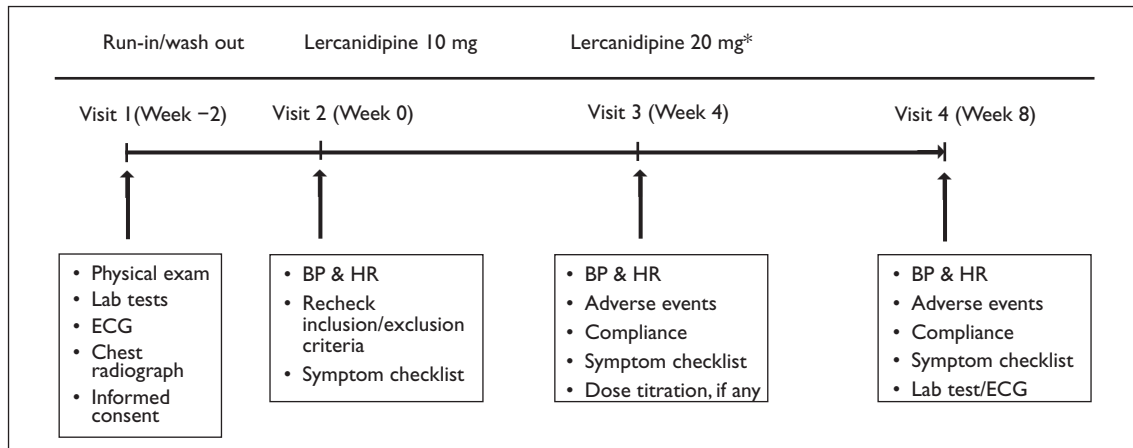
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**Fig. 1** Flow chart of the study design.

\*Titration was encouraged if SBP  $\geq$  140 mmHg or DBP  $\geq$  90 mmHg.

usually endows them with different pharmacokinetics and consequently perhaps a better safety and tolerability profile. However, most of the studies on the efficacy and tolerability of antihypertensives, including CCBs, have been done on a mainly western population. Most adverse events are dose-related, but even for those classes of antihypertensive agents whose adverse events are not dose-related, e.g. the ACE inhibitors, the frequency of cough associated with ACE inhibitors varies among different populations and is much higher than expected in Asians compared to the Caucasian population.<sup>(16-18)</sup>

Lercanidipine is a third-generation DHP CCB that is lipophilic. It is characterised by a gradual onset and long duration of action, as well as vascular selectivity and a lack of inotropic effects. It is effective in different types of arterial hypertension and its therapeutic efficacy is similar to other DHP CCBs. Lercanidipine has been shown to be well-tolerated and its adverse events lower than other commonly-used DHP CCBs in Caucasian hypertensive patients.<sup>(19-21)</sup> As efficacy and tolerability to antihypertensives may vary between populations, this study was done to examine the efficacy and tolerability of lercanidipine in Asians.

## METHODS

This was an investigator-initiated study. At the time this study was conducted, lercanidipine was not yet registered for use in the country. It was a prospective, open-label trial in patients with mild to moderate hypertension. The study protocol design and data handling were all done by the investigators themselves. Informed consent was obtained from the patients and ethics approval from the institution was granted for this study.

Adults with newly-diagnosed hypertension (140  $\leq$  SBP  $\leq$  179 mmHg and/or 90  $\leq$  diastolic BP [DBP]  $\leq$  109

mmHg) or whose BP was not controlled on their current medication, were eligible to enter the study. Patients were excluded if there was evidence of recent (i.e. within the past six months) myocardial infarction, angioplasty, cardiac bypass surgery, unstable angina, cerebrovascular events, congestive heart failure (New York Heart Association Classes III and IV), clinically significant arrhythmia, liver or renal impairment, pregnancy, secondary hypertension or a known allergy to CCBs. As the predicted efficacy of lercanidipine is a SBP lowering of at least 10 mmHg with a 10-mg dose, to show a significant ( $p < 0.05$ ) BP lowering between baseline and at the end of four and eight weeks and with a 80% power to detect this difference, only 30 patients were required for this study. The data was analysed with an intention-to-treat basis using the Statistical Package for Social Sciences version 11.5 (SPSS Inc, Chicago, IL, USA) and the two-tailed paired sample *t*-test for the baseline and treatment period BP changes.

This was an eight-week active treatment study. Fig. 1 shows the flow chart of the study design. At the screening visit (Visit 1, Week -2), sitting BP, physical examination, standard laboratory evaluations (complete blood count, urinalysis, fasting plasma glucose, serum lipids, blood urea nitrogen, serum creatinine, serum electrolytes, liver function tests), a 12-lead electrocardiogram (ECG) and chest radiography were done. After a two week run-in or washout period (Visit 2, Week 0), the sitting BP was rechecked. At every visit, BP was recorded using a standardised mercury sphygmomanometer and the values were recorded as a mean of two measurements taken five minutes apart after a ten-minute rest. The patient was instructed to omit the medication dose on the morning of each study visit and SBP, DBP and heart rate (HR) were measured in the morning between 8 am and 12 pm. A review was done to ensure eligibility for the study. A

**Table I. Baseline characteristics of patients.**

Demographics	No. (%) of patients (n = 27) or mean $\pm$ SD of values
<b>Gender</b>	
Male	12 (42.3)
Female	15 (57.7)
<b>Race</b>	
Chinese	12 (44.4)
Malays	6 (22.2)
Indians	9 (33.3)
<b>Hypertension category</b>	
Stage 1	13 (43.3)
Stage 2	17 (56.7)
Age (years)	53.4 $\pm$ 12.1
<b>Blood pressure (mmHg)</b>	
Systolic	159.0 $\pm$ 12.2
Diastolic	96.6 $\pm$ 7.7
<b>Baseline readings (mmol/L)</b>	
Glucose	5.8 $\pm$ 1.2
Cholesterol	5.4 $\pm$ 1.1
Triglycerides	1.7 $\pm$ 0.8
Uric acid	330.8 $\pm$ 95.2

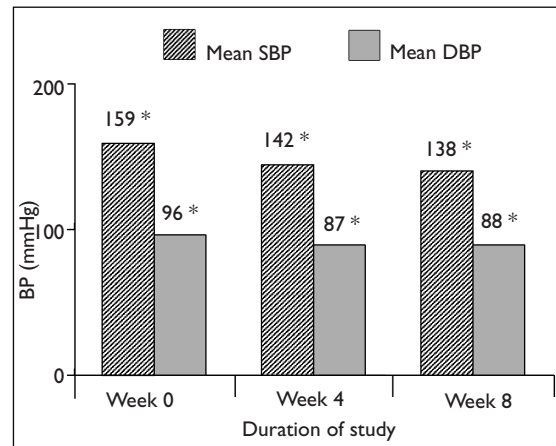
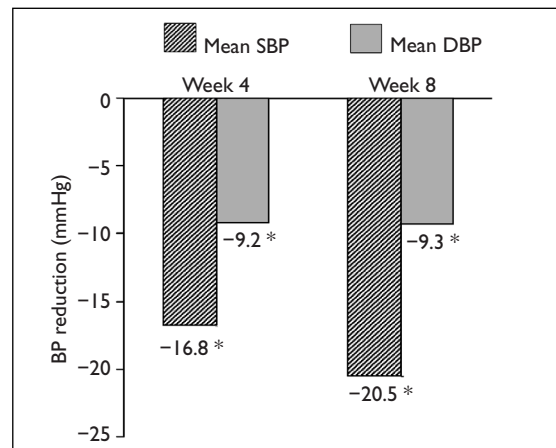
SD: standard deviation

self-administered symptom checklist was given to the patient at this point. The symptom checklist included all the documented adverse events associated with CCB usage and was applied at every subsequent visit. The patient was then started on 10 mg of lercanidipine and was seen four weeks later.

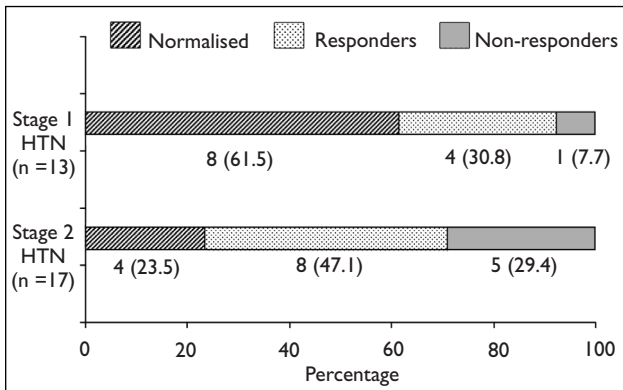
At the third visit (Week 4), BP and HR were re-measured. Besides applying the symptom checklist again, adverse events were also looked for by the investigators. Compliance was checked by a pill count. If the BP was not controlled, i.e. SBP  $\geq$  140 and/or DBP  $\geq$  90 mmHg, the dose of lercanidipine was titrated to 20 mg and the patient was seen another four weeks later. At the last visit (Visit 4, Week 8), BP, HR, adverse events, pill count and the symptom checklist were done again. The laboratory test and ECG were repeated during this last visit. Efficacy is defined as a BP-lowering effect of at least 10/5 mmHg and tolerability as not needing to go off treatment because of adverse events related to the drug.

## RESULTS

30 patients were entered into the trial. 27 completed the study. One patient voluntarily withdrew from the study before the end of four weeks as she wanted to get her own medication from a clinic near her home. Another patient developed diarrhoea and while the clinical decision was made that she could continue with the study, the patient decided to withdraw from it. The third patient went for an unscheduled (but not emergency) herniorrhaphy. While he could not continue with the study, he was continued

**Fig. 2** Bar chart shows the systolic and diastolic blood pressures at baseline, Week 4 and Week 8.\* $p < 0.0001$ **Fig. 3** Bar chart shows the mean systolic and diastolic blood pressure reductions at Week 4 and Week 8.\* $p < 0.0001$ 

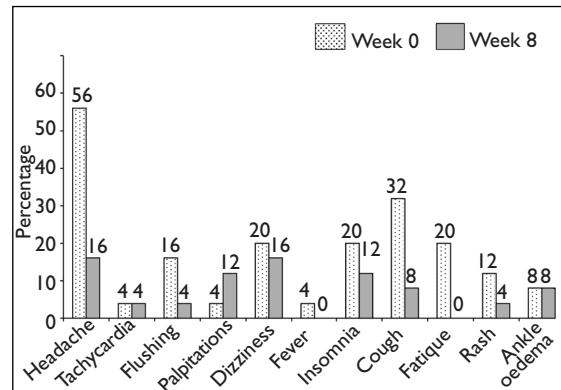
on the medication as the anaesthetist deemed the BP to be very well controlled, and was hence a very good and low surgical risk patient. The baseline characteristics are shown in Table I. The baseline mean of the SBP, DBP and HR was, respectively, 159  $\pm$  12.2 mmHg, 96.6  $\pm$  7.7 mmHg and 71  $\pm$  13  $\text{min}^{-1}$ . 43.3% (13 out of 30) of the subjects had stage 1 hypertension and 56.7% (17 out of 30) had stage 2 hypertension. Both genders and the three main racial groups were represented. The baseline biochemical parameters were unremarkable. Fig. 2 shows the BP changes at Week 4 and Week 8. The SBP and DBP values decreased significantly to 142  $\pm$  15.1 and 87  $\pm$  8.3 mmHg, respectively, after four weeks of therapy. A further reduction was seen at the end of the study and actually achieved the goal of BP treatment, being 139  $\pm$  14.3 and 88  $\pm$  9.8 mmHg, respectively. Fig. 3 shows the absolute reduction in the mean SBP and DBP at the end of Week 4 and Week 8. The mean SBP reduction was, respectively,



**Fig. 4** Bar chart shows the response after eight weeks of therapy.  
HTN: hypertension

16.8 (95% CI 12.8–20.8,  $p < 0.0001$ ) and 20.5 (95% CI 16.5–24.5,  $p < 0.0001$ ) mmHg at Week 4 and Week 8 compared to the baseline, and the mean DBP reduction was, respectively, 9.2 (95% CI 5.6–12.9,  $p < 0.0001$ ) and 9.3 mmHg (95% CI 6.2–12.5,  $p < 0.0001$ ) at Week 4 and Week 8 compared to the baseline. Hence, it can be seen that lercanidipine is efficacious as it lowered the BP by more than 10/5 mmHg. Fig. 4 shows the response of the patients at the end of the study. The number of normalised patients (defined as BP < 140/90 mmHg) at the end of the study was 61.5% and 23.5% for those with stage 1 and stage 2 hypertension, respectively. Responders (defined as patients with DBP < 90 mmHg or with a reduction of DBP > 10 mmHg compared to the baseline) was 30.8% and 47.1% for stage 1 and stage 2 hypertension, respectively. The remaining 7.7% and 29.4% with stage 1 and stage 2 hypertension, respectively, did not normalise or respond. The three subjects who did not complete the study were included as non-responders as this was an intention-to-treat analysis. There was no significant difference between the findings of the per-protocol and intention-to-treat analysis. Compliance done by pill count was very good, with all patients who completed the study achieving more than 80%. No deaths or other serious adverse events were encountered in this study. One patient voluntarily withdrew from the study because of diarrhoea although the clinical assessment was that she could have continued with the study at no increased risk.

There were no significant changes in the HR at the end of the study compared to the baseline, 72.2 vs. 72.9  $\text{min}^{-1}$  ( $p = 0.8$ ), respectively. There were also no significant changes in the relevant metabolic parameters. No other clinically meaningful changes were noted at the end of the study. Furthermore, no clinically-significant abnormalities were seen in the ECG. Fig. 5 shows the frequency of symptoms at the baseline and at the end of the study. It can be seen



**Fig. 5** Bar chart shows the comparison of adverse events at baseline and at the end of the study.

that all symptoms were lessened at the end of the study compared to at baseline, except for palpitations, which occurred in two patients whose dose of lercanidipine was titrated to 20 mg for better BP control.

## DISCUSSION

The results of this study confirm that lercanidipine is effective in lowering BP in the Asian population, and is similar to findings in other studies involving Caucasians.<sup>(21,22)</sup> Furthermore, the amount of BP lowering seen in this study is similar to that seen in other studies done in western countries and is also comparable to other commonly-used CCBs.<sup>(23–25)</sup> That more than half of the patients with stage 1 hypertension had their BP normalised and achieved the target BP goals suggests that lercanidipine plays a big role as monotherapy in patients with stage 1 hypertension.<sup>(21)</sup> It is also known that some patients do not respond to certain classes of antihypertensive agents. Again, as seen here, of those who did not normalise their BP, 30.8% and 47.1% with stage 1 and stage 2 hypertension, respectively, responded to lercanidipine. This suggests that a second drug could be added in combination with lercanidipine to try to achieve the target BP.

It is acknowledged that because this was not a blinded, randomised, controlled study (RCT) with a comparator or a placebo (placebo trials in hypertension are no longer allowed by ethics committees), the magnitude of BP lowering achieved in this study may be exaggerated. In earlier studies where placebo-controlled trials with active agents were allowed, the BP lowering achieved with placebo was SBP 10–15 mmHg and DBP 2–5 mmHg.<sup>(2,4,9,26,27)</sup> On the other hand, the active agents achieved an SBP and DBP lowering of 20–27 mmHg and 5–8 mmHg, respectively. So while this study does not have a comparator nor is it compared against a placebo, the BP lowering achieved is well within these ranges. Discounting for the placebo effect, the “true” BP

lowering of lercanidipine in this study can be estimated to be around 10/5 mmHg. This “true” BP lowering of around 10/5 mmHg is also comparable to the magnitude of BP lowering in other studies where lercanidipine was compared in RCT to other agents.<sup>(21,23,25)</sup>

In terms of safety and tolerability, the symptoms and adverse events, except for palpitations, were low. In fact, the incidence of symptoms and adverse events was actually lower when patients were on lercanidipine. The incidence of these adverse symptoms is also similar to that seen in the western population,<sup>(24)</sup> again suggesting, unlike what was seen with ACE inhibitors, that lercanidipine is well tolerated by Asian patients. While this study has no comparator, in other studies that compared lercanidipine against other CCBs, the incidence of adverse events was lower in the lercanidipine group.<sup>(13,25,28)</sup> Common adverse events like ankle oedema,<sup>(29,30)</sup> headache and flushing appear to be much less common with lercanidipine than with the use of other DHP CCBs.<sup>(23,25,28)</sup> This better profile of tolerability seen with lercanidipine can potentially enhance hypertension treatment by promoting better adherence to drug therapy.

While there are currently no outcome studies to demonstrate a cardiovascular benefit through the use of lercanidipine in the treatment of hypertension, the very fact is that lercanidipine, just by its ability to lower BP effectively, may be translated into a potential benefit. Some CCBs that have been widely used in hypertensive patients for a good number of years did not initially have outcome studies either, but they also demonstrated BP lowering, and were subsequently shown to reduce cardiovascular morbidity and mortality.<sup>(5,6,8)</sup> Because it is of no advantage if a drug is efficacious but not well tolerated, lercanidipine, with its good safety and tolerability profile and its effectiveness in lowering BP, has a useful and important role to play in the treatment of mild to moderate hypertension<sup>(31,32)</sup> in Asians.

## ACKNOWLEDGEMENT

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