Results of a Meta-Analysis Comparing the Tolerability of Lercanidipine and Other Dihydropyridine Calcium Channel Blockers

Kelly Makarounas-Kirchmann, MEc[1,2]; Sophie Glover-Koudounas, PhD[3]; and Paolo Ferrari, MD, FRACP[4]

[1]KMC Health Care, Frankston, Victoria, Australia; [2]Department of Epidemiology and Preventative Medicine, Monash University, Melbourne, Victoria, Australia; [3]Medical and Scientific Affairs, Australia and New Zealand, Solvay Pharmaceuticals Australia, Pymble, New South Wales, Australia; and [4]Department of Nephrology, Fremantle Hospital and School of Medicine & Pharmacology, University of Western Australia, Perth, Western Australia, Australia

ABSTRACT

Background: Results from clinical studies suggest that the dihydropyridine calcium channel blocker (CCB) lercanidipine may be associated with a lower incidence of peripheral edema than are older dihydropyridine CCBs.

Objective: The objective of the present study was to conduct a meta-analysis of published data from randomized controlled trials (RCTs) to assess the relative risk (RR) of dihydropyridine CCB-specific adverse events with lercanidipine versus the older dihydropyridine CCBs (first generation: amlodipine, felodipine, and nifedipine), and versus the other lipophilic dihydropyridine CCBs (second generation: lacidipine and manidipine).

Methods: A systematic literature search (all years through August 11, 2008) of MEDLINE, EMBASE, and the Cochrane Library was conducted for English-language reports of single- or double-blind RCTs of ≥4 weeks' duration that compared the tolerability of lercanidipine with other dihydropyridine CCBs in participants with mild (140–159/90–99 mm Hg) to moderate (160–179/100–109 mm Hg) hypertension.

Results: Eight RCTs (6 used first-generation drugs, and 4 used second-generation drugs) met the criteria for inclusion. Efficacy outcomes for lowering blood pressure did not differ statistically between lercanidipine and either generation of medications. Compared with the first generation, lercanidipine was associated with a reduced risk of peripheral edema (52/742 with lercanidipine vs 88/627 with first generation; RR = 0.44 [95% CI, 0.31–0.62]), but not flushing or headache. The frequency of peripheral edema, flushing, and headache did not differ statistically between lercanidipine and the second-generation drugs. Study participants were less likely to withdraw from the RCTs because of peripheral edema (RR = 0.24 [95% CI, 0.12–0.47]) or any adverse event (RR = 0.51 [95% CI, 0.33–0.77]) when treated with lercanidipine rather than a drug from the first generation, but not when treated with lercanidipine rather than second-generation drugs.

Conclusion: In this meta-analysis, lercanidipine was associated with a lower risk of peripheral edema and a lower risk of treatment withdrawal because of peripheral edema than were the first-generation, but not the second-generation, dihydropyridine CCBs. (*Clin Ther.* 2009;31:1652–1663) © 2009 Excerpta Medica Inc.

Key words: calcium channel blocker, dihydropyridines, lercanidipine, edema, adverse events, tolerability.

INTRODUCTION

Dihydropyridine calcium channel blockers (CCBs) are used to treat mild to moderate hypertension and chronic stable angina pectoris.[1,2] These agents lower blood pressure by selectively preventing the influx of calcium into cardiac and vascular smooth muscle, thereby promoting vasodilation.[3] The vasodilatory effects of dihydropyridine CCBs may be associated with adverse events such as peripheral edema, headache,

Accepted for publication May 19, 2009.
doi:10.1016/j.clinthera.2009.08.010
0149-2918/$ - see front matter

and flushing.[4,5] Peripheral edema is often the most common adverse event reported, affecting 3% to 19% of patients treated with a dihydropyridine CCB-based regimen in randomized controlled trials (RCTs).[4,6,7] Although these adverse events are not life threatening, they can be distressing to many patients and, particularly in the case of peripheral edema, can contribute to poor persistence and adherence to therapy.[4,8,9]

Newer lipophilic, long-acting dihydropyridine CCBs (eg, lercanidipine, lacidipine) have been associated with an improved tolerability profile compared with older dihydropyridine CCBs, such as the short-acting agents that require multiple daily doses (eg, nifedipine, felodipine), delayed or modified-release formulations (eg, nifedipine), and the agents with longer plasma half-lives (eg, amlodipine).[4,10–13] Lercanidipine has significantly greater vasoselectivity, expressed as the ratio of the half maximal inhibitory concentration values obtained for cardiac and vascular tissue, compared with lacidipine, amlodipine, felodipine, and nitrendipine.[11] The vascular selectivity of lercanidipine implies that its therapeutically desirable vasodilator activity may be only minimally associated (or not at all associated) with a decrease in cardiac contractile force.

Results from clinical studies suggest that lercanidipine's efficacy is comparable with that of other dihydropyridine CCBs[14,15]; however, the incidence of adverse events associated with lercanidipine, which occur primarily within the first 4 weeks of treatment, appears to be lower than that of other dihydropyridine CCBs.[14,15] Findings from a large 12-week RCT (N = 828) specifically designed to assess differences in tolerability suggested that lercanidipine was associated with a significantly lower frequency of peripheral edema (9.3% vs 19%; $P < 0.001$) and greater persistence with therapy (97.9% vs 91.5%; $P < 0.001$) than was amlodipine.[4] Smaller RCTs comparing lercanidipine with other dihydropyridine CCBs have also reported tolerability data comparable with those found in larger studies; however, most of these trials were designed primarily to examine efficacy and were of insufficient sample size to assess statistically significant differences in tolerability.[6,16,17]

The benefits of meta-analysis of combined tolerability data from individual RCTs are an increased sample size and, potentially, a more valid appraisal of the differences in tolerability between drugs, particularly for events that occur at relatively low frequencies.[18] The objective of the present study was to conduct a meta-analysis of published data from RCTs to assess the relative risk (RR) of dihydropyridine CCB-specific adverse events with the newer second-generation dihydropyridine CCB lercanidipine versus the older dihydropyridine CCBs (first generation: amlodipine, felodipine, nifedipine), and versus the other lipophilic dihydropyridine CCBs (second generation: lacidipine, manidipine).

METHODS

Study Selection

RCTs comparing the efficacy and tolerability of lercanidipine with those of amlodipine, felodipine, lacidipine, manidipine, and nifedipine were identified using an electronic literature search of MEDLINE (all years through August 11, 2008), EMBASE (all years through August 11, 2008), and the Cochrane Database of Systematic Reviews, Central Register of Controlled Trials, and Database of Abstracts of Reviews of Effects (all years through August 11, 2008). (An updated MEDLINE search through July 2009 did not indicate any new published trials meeting the inclusion criteria for this meta-analysis.) The search terms were as follows: *lercanidipine, amlodipine, felodipine, nifedipine, isradipine, nicardipine, nimodipine, nisoldipine, nitrendipine, lacidipine, nilvadipine, manidipine, barnidipine, clinidipine, benidipine, hypertension, randomized controlled trial, random allocation, random, controlled clinical trial, clinical trial phase II, single or double blind method, meta-analysis,* and *systematic review*. Searches were limited to English-language reports about clinical trials. The title and abstract of potential trials were screened initially; full articles were assessed if the title and abstract were inconclusive. The literature search and data extraction were conducted by 3 reviewers who worked independently and who were familiar with the Cochrane review process. Trials were eligible for inclusion if they met the following criteria: (1) the study was an RCT; (2) the study design used a single- or double-blind method; (3) the study design compared the use of a dihydropyridine CCB with the use of lercanidipine; (4) participants were reported to have mild (140–159/90–99 mm Hg) to moderate (160–179/100–109 mm Hg) hypertension; (5) the duration of the RCT was ≥4 weeks; and (6) tolerability data were reported.

Outcome Measures

The tolerability outcome measures included in this meta-analysis were the incidence of adverse events possibly or probably associated with vasodilation (pe-

ripheral edema, flushing, and headache) and the proportion of participants that withdrew because of peripheral edema, other adverse events, or any reason.

Data Extraction and Management

Data were independently extracted by 3 independent reviewers using a data collection spreadsheet. The data collected were descriptive information, summary statistics of the outcome measures, quality scale ratings, and associated commentary. Reviewers attempted to obtain missing information by contacting investigators of the original trials by e-mail. The methodologic quality of each trial was assessed according to the following: (1) whether participants, investigators, or personnel assessing outcomes were blinded to treatment allocation; (2) the adequacy of concealment of treatment randomization; and (3) the proportion of participants who did not complete the trial (ie, were lost to follow-up or discontinued treatment).[19]

Statistical Methods

Outcome data were exported to Review Manager (RevMan) 4.2.9 and RevMan Analyses 1.0.5 software (The Cochrane Collaboration, Oxford, United Kingdom) for subsequent meta-analysis. Data for comparator dihydropyridine CCBs were combined and pooled into 2 data sets: the older first-generation CCBs (amlodipine, nifedipine, and felodipine); and the newer, lipophilic second-generation CCBs (lacidipine and manidipine). An inverse-variance method was used to calculate the pooled mean difference in efficacy measures (continuous data) between the 2 generations of CCBs. Tolerability measures included the incidence of vasodilatory adverse events (dichotomous data) and were analyzed using the random-effects model of Der Simonian and Kacker[20] to calculate the RR and 95% CI values. Given the lack of consistency in the way in which peripheral edema is defined and the lack of consistent methods of measurement of this parameter, peripheral edema was treated as a single dichotomous variable to reduce the effect of heterogeneity among the different outcome measures reported. Heterogeneity χ^2 and I^2 tests were conducted. Statistical significance for the hypothesis test (2-tailed z tests) for the overall meta-analysis estimate was set at $P < 0.05$.

RESULTS

Characteristics of Trials Identified for Meta-analysis

A total of 39 RCTs were identified; 8 RCTs met the selection criteria and were included in the present study (**Figure 1**, **Table**). Of these, 6 RCTs were included in the meta-analysis of lercanidipine versus the first-generation CCBs,[4,6,16,17,21,22] and 4 were included in the meta-analysis of lercanidipine versus the second-generation CCBs.[4,6,7,23] In terms of study design, 7 of the 8 studies were double-blind, parallel-group RCTs,[4,6,7,16,17,21,22] and 1 was a single-blind, parallel-group RCT.[23] The reasons for excluding the remaining 31 RCTs are listed in **Figure 1**.

The 8 RCTs analyzed a total of 2034 patients with mild to moderate hypertension, most of whom were white and were recruited from inpatient clinics. The RCT by Lund-Johansen et al[22] was conducted in postmenopausal women. For the remaining RCTs, there were slightly more women (>55%) in 2 trials,[6,7] slightly more men (>55%) in 2 trials,[21,23] and a relatively balanced mix of women and men in 3 trials[4,16,17] (**Table**). In the RCT conducted by Casiglia et al,[23] there was a statistically significant difference ($P < 0.05$) in the ratio of men to women between the 2 treatment groups. All trials were conducted in European countries for 8 weeks to 2 years (**Table**). All trials excluded participants with major cardiovascular disease, and most trials excluded participants with clinically significant renal or liver function impairment.

All trials used the intent-to-treat population for safety and tolerability analyses, and for efficacy analyses, 3 trials used the per-protocol population,[4,6,7] whereas the other 5 trials used the intent-to-treat population. No trials reported how blinding was achieved. Treatment randomization was adequately concealed in 1 trial,[16] but the method of randomization was not reported for the remaining trials. Loss to follow-up was low (0%–5%) in all trials.

Efficacy

No statistically significant differences in efficacy for lowering blood pressure were found between lercanidipine and the combined pooled data for either first- or second-generation CCBs. For lercanidipine versus the combined pooled data of the first-generation CCBs, the weighted mean difference in systolic blood pressure was 0.77 mm Hg (95% CI, –0.78 to 2.31) and the weighted mean difference in diastolic blood pressure was 0.42 mm Hg (95% CI, –0.45 to 1.28). For lercanidipine versus the combined pooled data of the second-generation CCBs, the weighted mean difference in SBP was –0.61 mm Hg (95% CI, –2.46 to 1.25) and the weighted mean difference in DBP was –0.66 mm Hg (95% CI, –1.77 to 0.45).

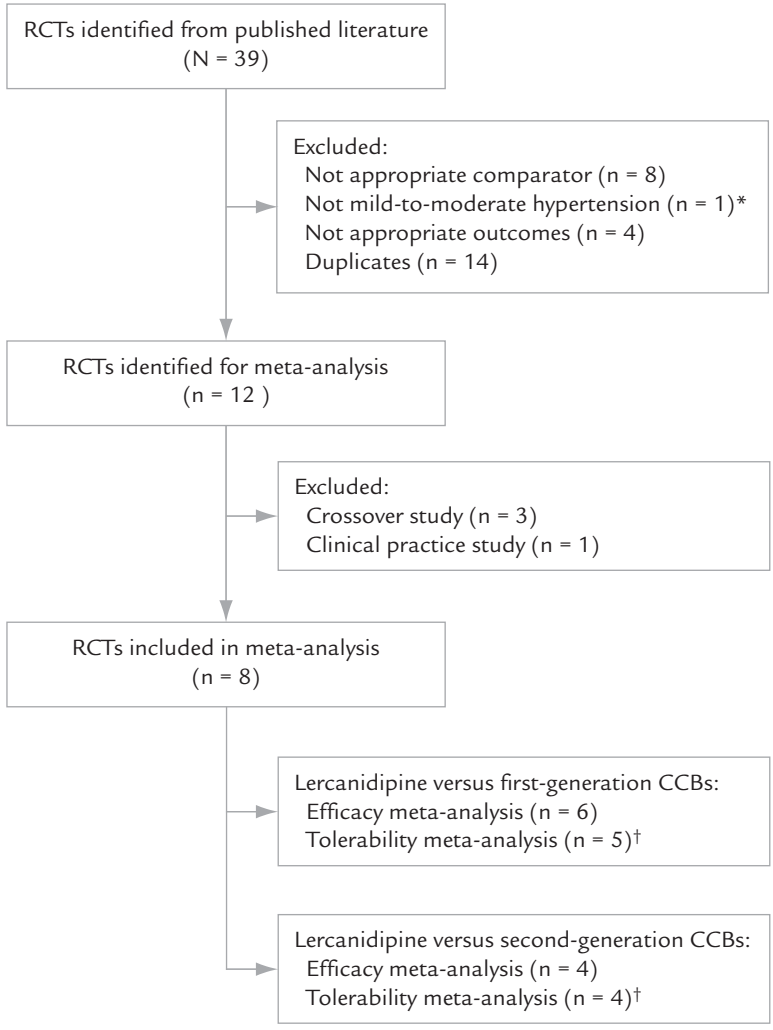

Figure 1. Flow of randomized controlled trials (RCTs) included in a meta-analysis to assess the relative risk of dihydropyridine calcium channel blocker (CCB)–specific adverse events with lercanidipine versus the combined pooled data from RCTs of older dihydropyridine CCBs (first generation: amlodipine, felodipine, nifedipine) and newer, lipophilic dihydropyridine CCBs (second generation: lacidipine, manidipine). *The indication for this study was chronic allograft nephropathy. †The number of studies included in each analysis varied because of the differences in the tolerability data reported in each study.

Tolerability

Differences in the tolerability profiles of lercanidipine and the combined pooled data of the first-generation CCBs were evident (**Figures 2** and **3**). However, differences in the tolerability profiles of lercanidipine and the combined pooled data of the second-generation CCBs were not statistically significant. The study by Leonetti et al[4] was weighted heavily, but exclusion of this RCT from the sensitivity analyses did not change the outcome of the analyses (data not shown).

Adverse Events Possibly Associated With Vasodilation

The overall incidence of vasodilatory adverse events in the combined pooled data of the first- and second-generation CCBs, but not lercanidipine, was 10.9% (118/1080) for peripheral edema, 2.6% (19/734) for flushing, and 4.6% (43/933) for headache. Lercanidi-

Table. Characteristics of 8 randomized controlled trials included in a meta-analysis comparing the tolerability of lercanidipine and other dihydropyridine calcium channel blockers for the treatment of hypertension.

Intervention	Total Daily Dose, mg	Treatment Duration	Patients, no.	Women, %	Age, Mean (SD), y	Blood Pressure, mm Hg		
						Inclusion Criteria	Baseline SBP, Mean (SD)	Baseline DBP, Mean (SD)
Policicchio et al[16]								
Lercanidipine	10–20	16 wks	64	53	57 (9)	DBP: 95–115	163 (13)	101 (5)
Nifedipine SR	40–80*	16 wks	66	51	58 (7)	DBP: 95–115	164 (13)	101 (5)
Fogari et al[21]								
Lercanidipine	10–20	12 wks	30	40	54 (10)	DBP: 90–109	163 (5)	98 (4)
Nifedipine GITS†	30–60	12 wks	30	47	54 (9)	DBP: 90–109	162 (6)	98 (4)
Leonetti et al[4]								
Lercanidipine	10–20	24–104 wks	420	51	70 (6)	SBP: 161–210; DBP: 96–115	170 (10)	97 (6)
Amlodipine	5–10	24–104 wks	200	58	70 (6)	SBP: 161–210; DBP: 96–115	171 (11)	97 (7)
Lacidipine	2–4	24–104 wks	208	46	69 (6)	SBP: 161–210; DBP: 96–115	170 (10)	97 (6)
Cherubini et al[6]								
Lercanidipine	5–10	24 wks	108	64	74 (8)	SBP: 140–180; DBP: 90–109	167 (11)	98 (5)
Lacidipine	2–4	24 wks	107	63	74 (7)	SBP: 140–180; DBP: 90–109	168 (12)	98 (4)
Nifedipine GITS	30–60	24 wks	109	75	72 (6)	SBP: 140–180; DBP: 90–109	167 (11)	97 (4)
Lund-Johansen et al[22]								
Lercanidipine	10–20	8 wks	48	100	59 (7)	SBP: 150–179; DBP: 95–109	166 (11)	95 (7)
Amlodipine	5–10	8 wks	44	100	61 (7)	SBP: 150–179; DBP: 95–109	163 (13)	96 (7)
Millar-Craig et al[7]								
Lercanidipine	10 or 20	16 wks	111	58	71	SBP: ≥160; DBP: <95	171.8 (9)	86.4 (6)
Lacidipine	2 or 4	16 wks	111	63	71	SBP: ≥160; DBP: <95	170.8 (9)	88.2 (7)
Romito et al[17]								
Lercanidipine	10–20	8 wks	109	54	58 (9)	DBP: 95–109	155 (11)	99 (3)
Nifedipine GITS†	30–60	8 wks	106	53	58 (9)	DBP: 95–109	155 (12)	99 (3)
Felodipine‡	10–20	8 wks	110	52	56 (8)	DBP: 95–109	155 (12)	99 (3)
Casiglia et al[23]								
Lercanidipine	10–20	3 mo	27	52§	68 (7)	SBP: <180; DBP: 90–109	159 (11)	96 (5)
Manidipine	10–20	3 mo	26	35§	66 (10)	SBP: <180; DBP: 90–109	156 (14)	94 (3)

SBP = systolic blood pressure; DBP = diastolic blood pressure; SR = slow release; GITS = gastrointestinal therapeutic system.

*Nifedipine SR 20 or 40 mg was administered twice daily for a total daily dose of 40 or 80 mg.

† Controlled-release formulation.

‡ Formulation of felodipine not stated.

§ The male-to-female ratio of the lercanidipine and manidipine treatment groups differed significantly ($P < 0.05$).

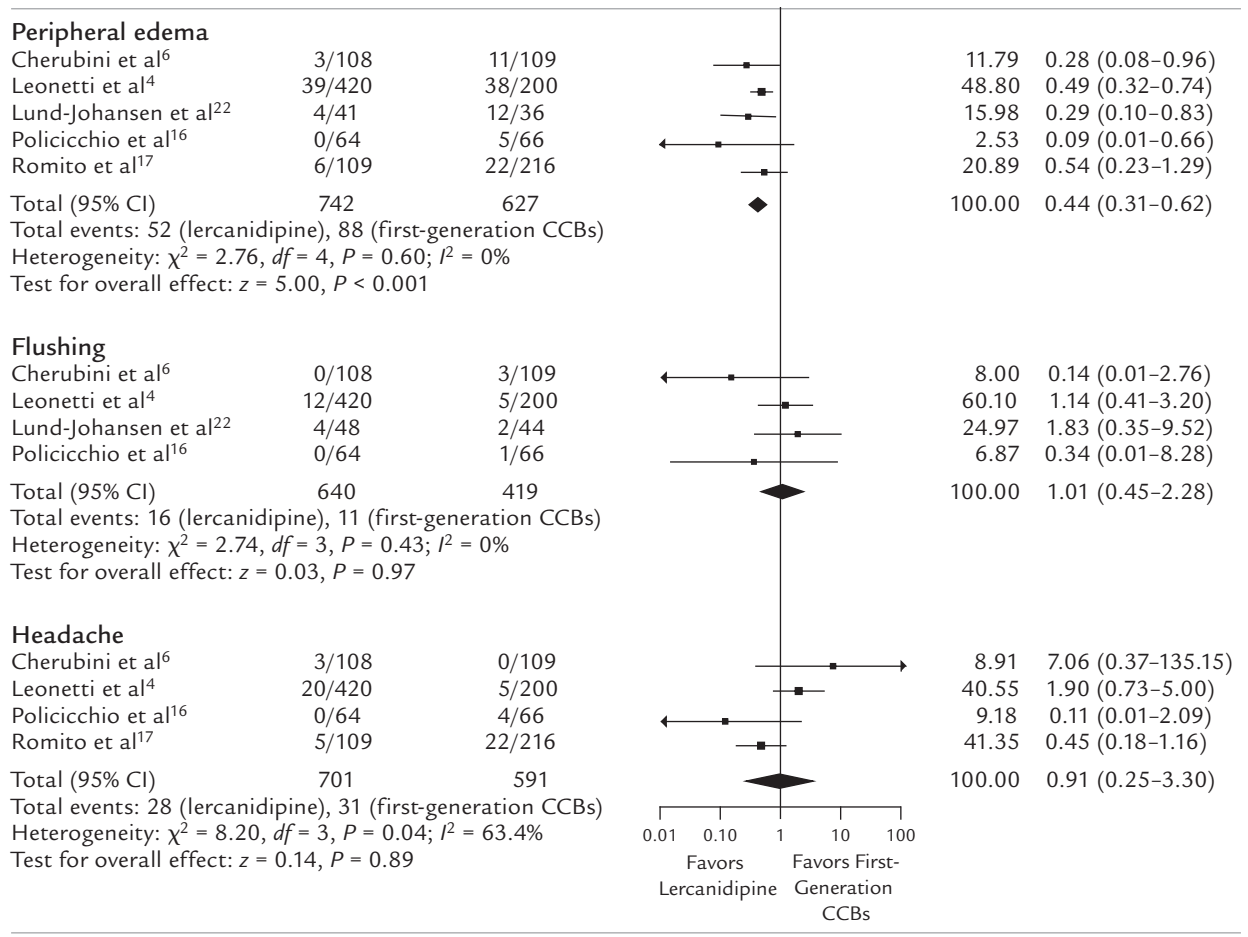

Figure 2A. Incidence of adverse events (random-effects model) in randomized controlled trials comparing lercanidipine versus first-generation dihydropyridine calcium channel blockers (CCBs): amlodipine, felodipine, and nifedipine. Data from the felodipine and nifedipine treatment arms of the Romito et al[17] trial were combined so that data from the lercanidipine treatment arm were only included once in this analysis. RR = relative risk.

pine was associated with a significant reduction in RR for peripheral edema by 56% compared with the combined pooled data of the first-generation CCBs (lercanidipine [52/742] vs first generation [88/627]: RR = 0.44 [95% CI, 0.31–0.62]; P < 0.001), but there were no significant differences in the RR of flushing (lercanidipine [16/640] vs first generation [11/419]: RR = 1.01 [95% CI, 0.45–2.28]; P = NS) or headache (lercanidipine [28/701] vs first generation [31/591]: RR = 0.91 [95% CI, 0.25–3.30]; P = NS) (**Figure 2A**). There were no significant differences in the risk of adverse events compared with the combined pooled data of the second-generation CCBs, such as peripheral edema (lercanidipine [57/666] vs second generation [30/453]: RR = 1.17 [95% CI, 0.62–2.19]; P = NS), flushing (lercanidipine [12/528] vs second generation [8/315]: RR = 0.85 [95% CI, 0.34–2.16]; P = NS), and headache (lercanidipine [26/555] vs second generation [12/342]: RR = 1.31 [95% CI, 0.67–2.56]; P = NS) (**Figure 2B**).

Seven of the 8 RCTs identified for meta-analysis reported the incidence of peripheral edema and were used to calculate the RR of peripheral edema (**Figures 2A** and **2B**).[4,6,7,16,17,22,23] Of these, peripheral edema

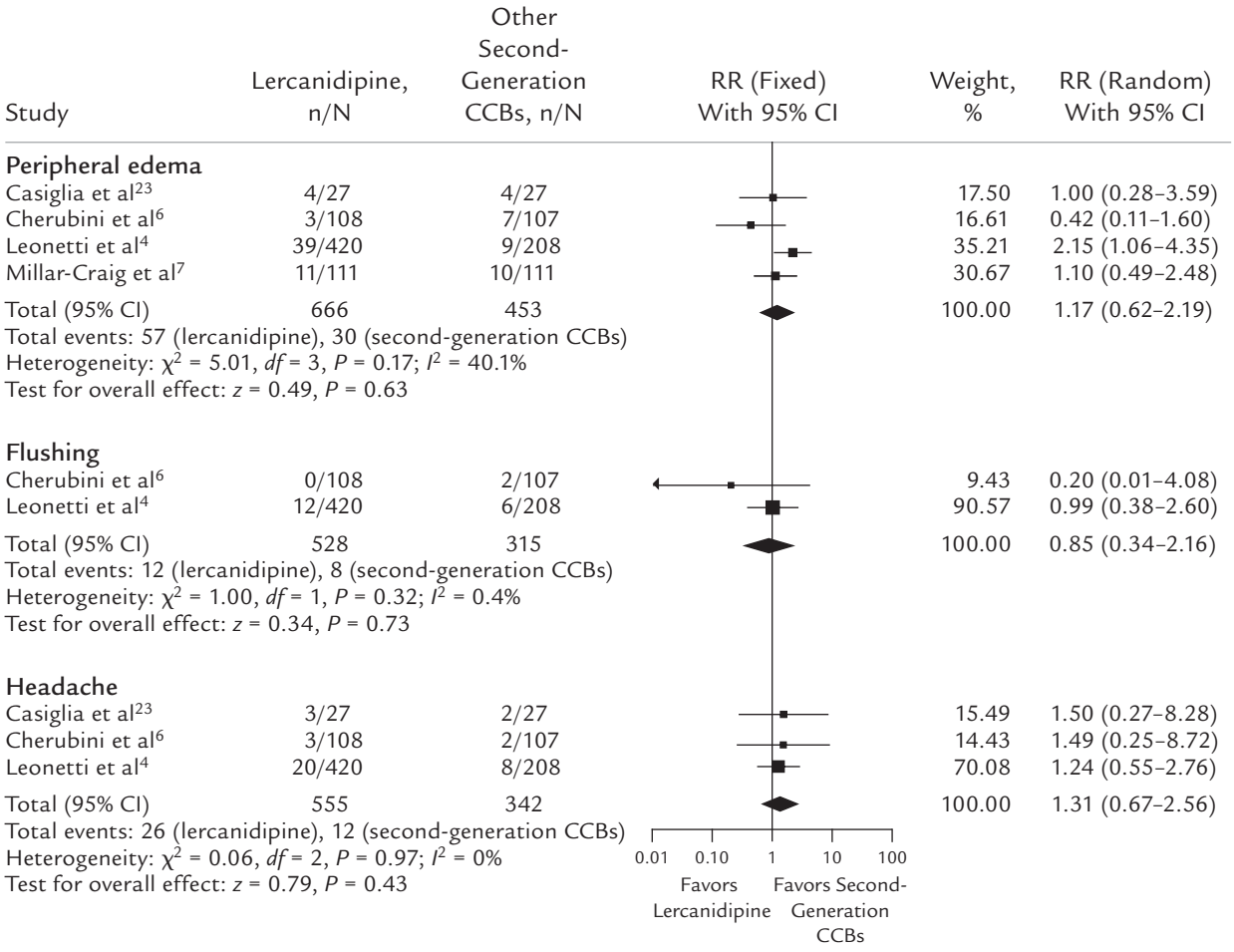

Figure 2B. Incidence of adverse events (random-effects model) in randomized controlled trials comparing lercanidipine with other second-generation dihydropyridine calcium channel blockers (CCBs): lacidipine and manidipine. RR = relative risk.

was defined quantitatively or objectively using a 4-point scale in 3 RCTs[4,22,23]; the remaining 4 RCTs reported the incidence of peripheral edema but did not report how peripheral edema was defined.[6,7,16,17] Although peripheral edema was defined quantitatively in the RCT conducted by Fogari et al,[21] this study did not report the incidence of peripheral edema and was not included in the analysis.

Six of the 8 RCTs identified for meta-analysis reported the incidence of flushing and headache (**Figures 2A** and **2B**) and were used to calculate the RR for these events,[4,6,16,17,22,23] but it was not reported how these adverse events were defined. For the comparison of lercanidipine with the combined pooled data of the first-generation CCBs, there was a statistically significant heterogeneity among the RCTs for the effect of headache (χ^2 = 8.20; P = 0.04; I^2 = 63.4%).

Withdrawal From Treatment

Six of the 8 trials reported the rates of total withdrawal (adverse events and other reasons) from treatment (**Figure 3**). The proportion of all participants who discontinued from the treatment arms was 0% to 15% in 4 trials,[6,16,22,23] 16% to 26% in 1 trial,[4] and not reported in 1 trial.[17] In the remaining trials, the proportion of participants who discontinued because of adverse events from the lercanidipine treatment arm was 0% to 15%, whereas the proportion who

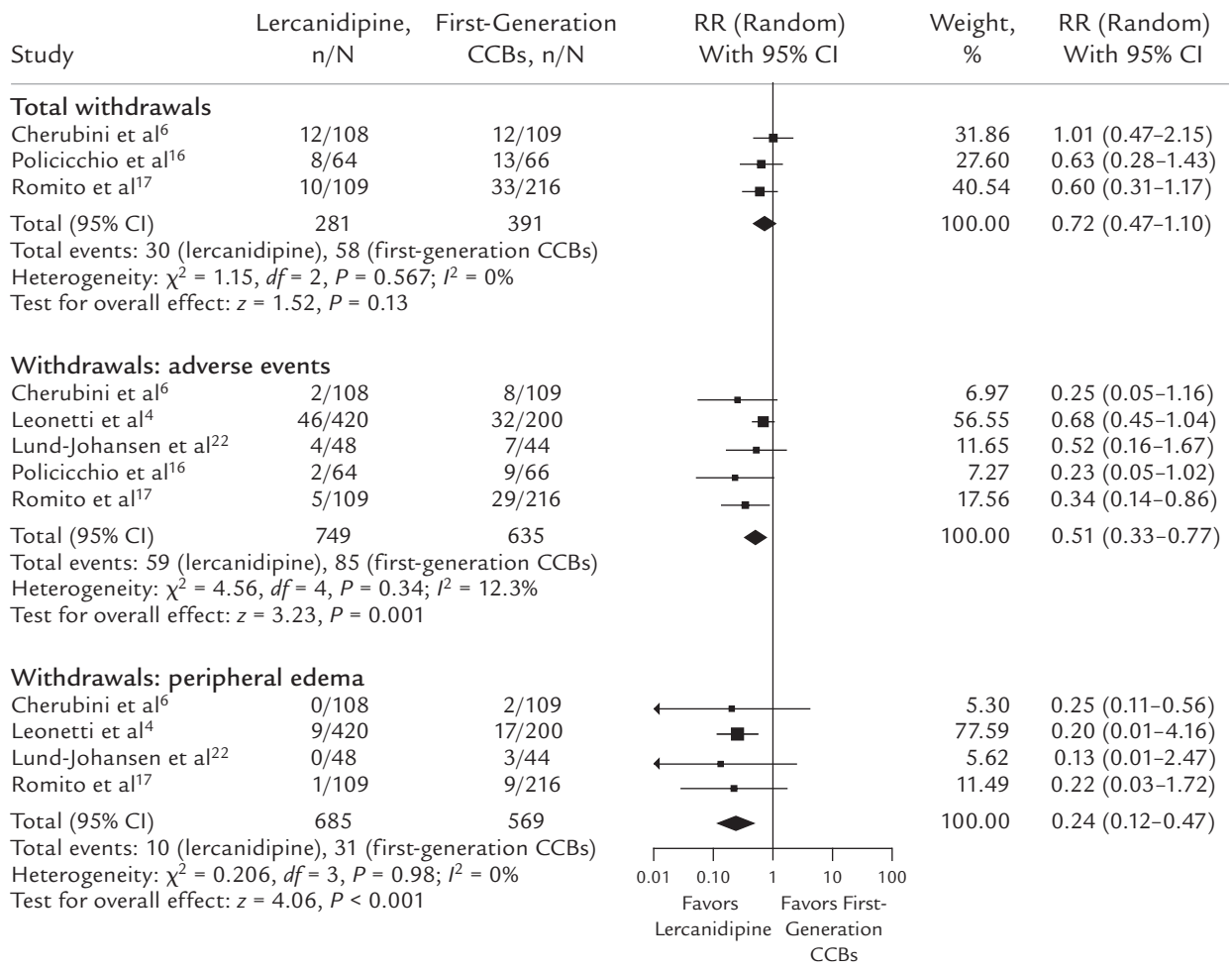

Figure 3A. Proportion (random-effects model) of participants who withdrew for any reason or because of adverse events in randomized controlled trials comparing lercanidipine versus first-generation dihydropyridine calcium channel blockers (CCBs): amlodipine, felodipine, and nifedipine. Data from the felodipine and nifedipine treatment arms of the Romito et al[17] trial were combined so that data from the lercanidipine treatment arm were only included once in this analysis. RR = relative risk.

discontinued from the comparator treatment arms was 16% to 26%.[7,22] For the comparison of lercanidipine with the combined pooled data of the first-generation CCBs, there was no significant difference in the risk of withdrawal when all reasons, including lack of efficacy, were considered (RR = 0.72 [95% CI, 0.47–1.10]; P = NS); however, lercanidipine was associated with a significant reduction in risk of participants withdrawing from an RCT because of any adverse event (RR = 0.51 [95% CI, 0.33–0.77]; P = 0.001) or peripheral edema (RR = 0.24 [95% CI, 0.12–0.47]; P < 0.001) (**Figure 3A**). For the comparison of lercanidipine with the combined data of the second-generation CCBs, there were no significant differences in the risk of withdrawal when all reasons were considered (RR = 0.70 [95% CI, 0.24–2.07]; P = NS), when all adverse events were considered (RR = 0.77 [95% CI, 0.28–2.15]; P = NS), and when just peripheral edema was considered (RR = 2.23 [95% CI, 0.49–10.22]; P = NS) (**Figure 3B**).

Five of the 8 RCTs identified for meta-analysis reported withdrawal for any reason,[6,7,16,17,23] 4 reported

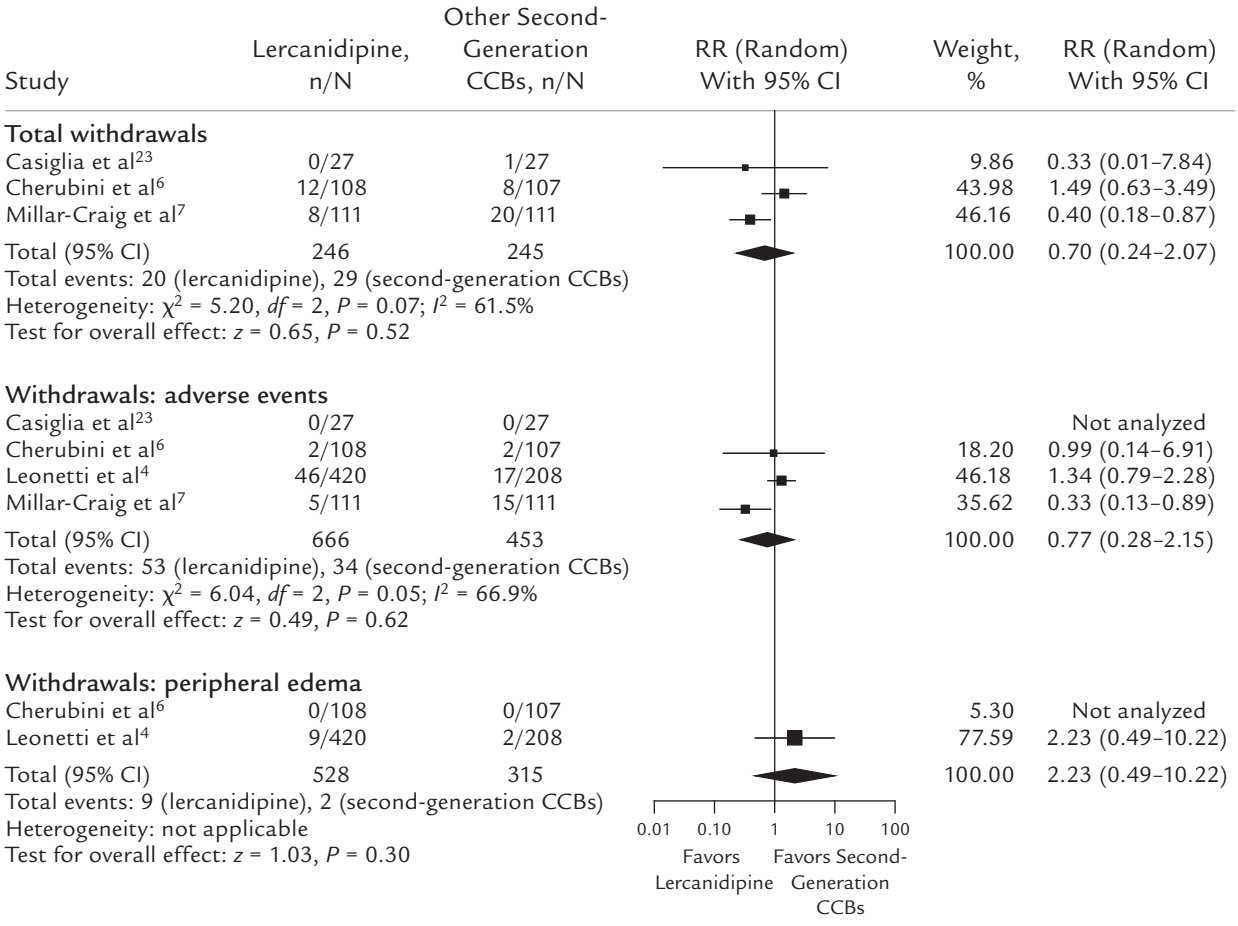

Figure 3B. Proportion (random-effects model) of participants who withdrew for any reason or because of adverse events in randomized controlled trials comparing lercanidipine versus other second-generation dihydropyridine calcium channel blockers (CCBs): lacidipine and manidipine. RR = relative risk.

withdrawal because of peripheral edema,[4,6,17,22] and 7 reported withdrawal because of adverse events[4,6,7,16,17,22,23]; these RCTs were used to calculate the RR of these withdrawal events (**Figures 3A** and **3B**). For the comparison of lercanidipine with the combined pooled data of the second-generation CCBs, there was statistically significant heterogeneity among the RCTs for withdrawal because of adverse events (χ^2 = 6.04; P = 0.05; I^2 = 66.9).

DISCUSSION

Findings from this meta-analysis of data from RCTs indicate that there are differences in tolerability among these dihydropyridine CCBs when used for the treatment of hypertension. Overall, the analysis suggests that compared with combined pooled data for the first-generation CCBs, lercanidipine did not differ with regard to blood pressure–lowering efficacy, was associated with a reduced RR (0.44) of peripheral edema, and was associated with a reduced RR (0.24) of patients withdrawing from treatment because of peripheral edema. In addition, compared with combined pooled data for the second-generation CCBs, lercanidipine did not differ with regard to blood pressure–lowering efficacy, the incidence of peripheral edema, or the risk of withdrawal from treatment because of peripheral edema.

Despite the broad range of antihypertensive agents available, uncontrolled blood pressure remains a problem for 50% to 65% of patients treated for

hypertension.[24,25] Part of the reason for the high prevalence of uncontrolled blood pressure is poor persistence with therapy,[9,26,27] primarily because of inadequate effectiveness and patient intolerance for adverse events.[28,29] Thus, dihydropyridine CCBs with improved tolerability profiles may improve persistence with antihypertensive therapy.[30] Peripheral edema is one of the more common adverse events arising from the use of dihydropyridine CCBs and can result in patients withdrawing from therapy. In a large RCT that enrolled 828 patients with mild to moderate hypertension,[4] peripheral edema was reported to affect up to 19% of patients and was responsible for treatment withdrawal in 8.5% (17/200) of patients who received amlodipine compared with 3.8% (9/240) of those who received lercanidipine. Results from our meta-analysis suggest that patients treated with lercanidipine were less likely to experience peripheral edema than were those treated with older CCBs such as amlodipine, felodipine, or nifedipine, and, therefore, they may be more likely to persist with therapy. In a prospective evaluation of persistence with antihypertensive agents in clinical practice, the rate of persistence was significantly higher in patients treated with lercanidipine than with other CCBs (59.3% vs 46.6%; $P < 0.05$).[31] The similarity of the incidence of peripheral edema between lercanidipine and the second-generation CCBs (lacidipine and manidipine) is predictable, given that lacidipine and manidipine share pharmacologic characteristics similar to lercanidipine, such as a long-receptor half-life.[11] These results are clinically important because patients who persist with treatment and achieve controlled blood pressure can considerably reduce their risk of cardiovascular events, kidney failure, and stroke.[25,32]

Of the 7 trials included in the tolerability meta-analysis, 4 did not provide details of any standard methods for assessment of peripheral edema,[6,7,16,17] 2 trials used various quantitative measures of peripheral edema,[22,23] and 1 trial used an objective 4-point scale of severity.[4] Because the different measures of peripheral edema in these trials may have introduced some statistical heterogeneity to the analysis, only data describing the incidence of peripheral edema were included. Although the RCT conducted by Fogari et al[21] quantitatively assessed peripheral edema, this study did not report the incidence of peripheral edema and could not be pooled for tolerability meta-analysis. However, findings from this trial indicate that lercanidipine was associated with statistically significant decreases in ankle–foot volume and pretibial subcutaneous tissue pressure compared with nifedipine gastrointestinal therapeutic systems.[21] Overall, these data support the findings from our meta-analysis that lercanidipine was associated with a reduced risk of peripheral edema compared with the older dihydropyridine CCBs.

As with all meta-analyses, there are a number of limitations that must be addressed. Limiting the literature search to RCTs written in English may have introduced bias, although findings from 1 study suggest that the use of language restrictions in systematic reviews does not appear to bias the estimates of a drug's effectiveness.[33] By only including RCTs, we reduced the potential effects of inadequate treatment randomization. Although the cumulative number of patients from the available RCTs included in our study was small, the frequency of the adverse events, particularly peripheral edema, in the comparator arms was sufficient to allow an adequate comparison of tolerability. In our meta-analysis, fewer patients withdrew because of peripheral edema and adverse events when treated with lercanidipine than with the first-generation CCBs; however, no statistical difference was evident for total withdrawals. This finding is difficult to interpret because 2 of the 5 RCTs were excluded from the analysis of total withdrawals owing to differences in the way data were reported,[4,22] thus reducing the data set available. Moreover, although there was a possibility that the relatively large weighting of the study by Leonetti et al[4] may have unduly influenced our meta-analysis, sensitivity analyses indicated that inclusion of this single trial did not influence the combined pool of data for the first- and second-generation CCBs. Some statistical heterogeneity was observed in the analyses that were conducted that may have influenced the study outcomes; however, no heterogeneity was observed among trials for the effect of peripheral edema, which was the main focus of the analysis.

CONCLUSIONS

In this meta-analysis of 8 RCTs, lercanidipine was associated with a lower risk of peripheral edema and a lower risk of treatment withdrawal because of peripheral edema than were the first-generation dihydropyridine CCBs (amlodipine, felodipine, and nifedipine), but not the second-generation lipophilic dihydropyridine CCBs (lacidipine and manidipine). These findings

may have implications for patient persistence and adherence to therapy in clinical practice when CCBs are prescribed for the treatment of hypertension.

ACKNOWLEDGMENTS

This analysis was sponsored by Solvay Pharmaceuticals Australia. Ms. Makarounas-Kirchmann has previously received consultancy fees from Solvay Pharmaceuticals, and Dr. Ferrari has received speaker fees from Solvay Pharmaceuticals.

The authors acknowledge the independent medical writing assistance provided by ProScribe Medical Communications (Queensland, Australia), funded from an unrestricted financial grant from Solvay Pharmaceuticals.

REFERENCES

1. Materson BJ, Reda DJ, Cushman WC, et al. Single-drug therapy for hypertension in men. A comparison of six antihypertensive agents with placebo. The Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents [published correction appears in *N Engl J Med*. 1994;330:1689]. *N Engl J Med*. 1993;328:914–921.
2. Eisenberg MJ, Brox A, Bestawros AN. Calcium channel blockers: An update. *Am J Med*. 2004;116:35–43.
3. Braunwald E. Mechanism of action of calcium-channel-blocking agents. *N Engl J Med*. 1982;307:1618–1627.
4. Leonetti G, Magnani B, Pessina AC, et al, for the COHORT Study Group. Tolerability of long-term treatment with lercanidipine versus amlodipine and lacidipine in elderly hypertensives. *Am J Hypertens*. 2002;15:932–940.
5. Messerli FH, Oparil S, Feng Z. Comparison of efficacy and side effects of combination therapy of angiotensin-converting enzyme inhibitor (benazepril) with calcium antagonist (either nifedipine or amlodipine) versus high-dose calcium antagonist monotherapy for systemic hypertension. *Am J Cardiol*. 2000;86:1182–1187.
6. Cherubini A, Fabris F, Ferrari E, et al. Comparative effects of lercanidipine, lacidipine, and nifedipine gastrointestinal therapeutic system on blood pressure and heart rate in elderly hypertensive patients: The ELderly and LErcanidipine (ELLE) study. *Arch Gerontol Geriatr*. 2003;37:203–212.
7. Millar-Craig M, Shaffu B, Greenough A, et al. Lercanidipine vs lacidipine in isolated systolic hypertension. *J Hum Hypertens*. 2003;17:799–806
8. Anderson RB, Hollenberg NK, Williams GH. Physical Symptoms Distress Index: A sensitive tool to evaluate the impact of pharmacological agents on quality of life. *Arch Intern Med*. 1999;159:693–700.
9. Simons LA, Ortiz M, Calcino G. Persistence with antihypertensive medication: Australia-wide experience, 2004–2006. *Med J Aust*. 2008;188:224–227.
10. Borghi C, Prandin MG, Dormi A, Ambrosioni E, for the Study Group of the Regional Unit of the Italian Society of Hypertension. Improved tolerability of the dihydropyridine calcium-channel antagonist lercanidipine: The lercanidipine challenge trial. *Blood Press Suppl*. 2003;1:14-21.
11. Angelico P, Guarneri L, Leonardi A, Testa R. Vascular–selective effect of lercanidipine and other 1,4-dihydropyridines in isolated rabbit tissues. *J Pharm Pharmacol*. 1999; 51:709–714.
12. Epstein M. Lercanidipine: A novel dihydropyridine calcium-channel blocker. *Heart Dis*. 2001;3:398–407.
13. Herbette LG, Vecchiarelli M, Sartani A, Leonardi A. Lercanidipine: Short plasma half-life, long duration of action and high cholesterol tolerance. Updated molecular model to rationalize its pharmacokinetic properties. *Blood Press Suppl*. 1998;2:10–17.
14. Borghi C. Lercanidipine in hypertension. *Vasc Health Risk Manag*. 2005;1:173–182.
15. Beckey C, Lundy A, Lutfi N. Lercanidipine in the treatment of hypertension. *Ann Pharmacother*. 2007;41:465–473.
16. Policicchio D, Magliocca R, Malliani A. Efficacy and tolerability of lercanidipine in patients with mild to moderate essential hypertension: A comparative study with slow-release nifedipine. *J Cardiovasc Pharmacol*. 1997;29 (Suppl):S31–S35.
17. Romito R, Pansini MI, Perticone F, et al. Comparative effect of lercanidipine, felodipine, and nifedipine GITS on blood pressure and heart rate in patients with mild to moderate arterial hypertension: The Lercanidipine in Adults (LEAD) Study. *J Clin Hypertens* (*Greenwich*). 2003; 5:249–253.
18. Mulrow CD. Rationale for systematic reviews. *BMJ*. 1994;309:597–599.
19. Higgins JP, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions*. Chichester, UK: Wiley; 2008.
20. Der Simonian R, Kacker R. Random-effects model for meta-analysis of clinical trials: An update. *Contemp Clin Trials.* 2007;8:105–114.
21. Fogari R, Malamani GD, Zoppi A, et al. Comparative effect of lercanidipine and nifedipine gastrointestinal therapeutic system on ankle volume and subcutaneous interstitial pressure in hypertensive patients: A double-blind, randomized, parallel-group study. *Curr Ther Res Clin Exp*. 2000;61:850–862.
22. Lund-Johansen P, Stranden E, Helberg S, et al. Quantification of leg oedema in postmenopausal hypertensive patients treated with lercanidipine or amlodipine. *J Hypertens*. 2003;21:1003–1010.
23. Casiglia E, Mazza A, Tikhonoff V, et al. Therapeutic profile of manidipine and lercanidipine in hypertensive patients. *Adv Ther*. 2004;21:357–369.
24. Briganti EM, Shaw JE, Chadban SJ, et al, for the Australian Diabetes, Obesity and Lifestyle Study (AusDiab).

Untreated hypertension among Australian adults: The 1999–2000 Australian Diabetes, Obesity and Lifestyle Study (AusDiab). *Med J Aust*. 2003;179:135–139.
25. Chobanian AV, Bakris GL, Black HR, et al, for the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National Heart, Lung, and Blood Institute; National High Blood Pressure Education Program Coordinating Committee. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension*. 2003;42:1206–1252.
26. Jones JK, Gorkin L, Lian JF, et al. Discontinuation of and changes in treatment after start of new courses of antihypertensive drugs: A study of a United Kingdom population. *BMJ*. 1995;311:293–295.
27. Van Wijk BL, Klungel OH, Heerdink ER, de Boer A. Rate and determinants of 10-year persistence with antihypertensive drugs. *J Hypertens*. 2005;23:2101–2107.
28. Aranda P, Tamargo J, Aranda FJ, et al. Use and adverse reactions of antihypertensive drugs in Spain. Part I of the RAAE Study. *Blood Press Suppl*. 1997;1:11–16.
29. Düsing R, Weisser B, Mengden T, Vetter H. Changes in antihypertensive therapy—the role of adverse effects and compliance. *Blood Press*. 1998;7:313–315.
30. Pruijm MT, Maillard MP, Burnier M. Patient adherence and the choice of antihypertensive drugs: Focus on lercanidipine. *Vasc Health Risk Manag*. 2008;4:1159–1166.
31. Veronesi M, Cicero AF, Prandin MG, et al. A prospective evaluation of persistence on antihypertensive treatment with different antihypertensive drugs in clinical practice. *Vasc Health Risk Manag*. 2007;3:999–1005.
32. He J, Whelton PK. Elevated systolic blood pressure and risk of cardiovascular and renal disease: Overview of evidence from observational epidemiologic studies and randomized controlled trials. *Am Heart J*. 1999;138:211–219.
33. Moher D, Pham B, Lawson ML, Klassen TP. The inclusion of reports of randomised trials published in languages other than English in systematic reviews. *Health Technol Assess*. 2003;7:1–90.

Address correspondence to: Paolo Ferrari, MD, FRACP, Department of Nephrology, Fremantle Hospital, Fremantle, WA 6160, Australia. E-mail: paolo.ferrari@health.wa.gov.au