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Expert Opinion

Efficacy and tolerability of lercanidipine in patients with hypertension: results of a Phase IV study in general practice

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Introduction: Calcium antagonists are very effective drugs, recommended as first-line therapy in hypertension. However, their large use in clinical practice is often limited by a high incidence of peripheral oedema. Calcium antagonists of the third generation, such as lercanidipine, have been shown to be as effective as first- and second-generation calcium antagonists, while showing a better side-effect profile. *Objective and methods:* The purpose of the present Phase IV study was to investigate the efficacy and tolerability of lercanidipine in a large unselected population of hypertensive patients managed in private practice in Switzerland. A total of 504 physicians participated in this survey and 2199 patients were included. Treatment with lercanidipine was introduced at a dose of 10 mg and titration to 20 mg was optional according to the physician's decision. Evaluations of blood pressure control and tolerability were made after 4 and 8 weeks. *Results:* The results of the present study show that lercanidipine is an effective and well tolerated antihypertensive agent in newly treated hypertensive patients. In this group of patients, 63% reached the target blood pressure (≤ 140/90 mmHg) with lercanidipine alone. Lercanidipine is also an effective alternative in patients who are insufficiently controlled with another therapy, or in patients not tolerating other calcium channel blockers. Finally, lercanidipine is well-tolerated, with a very low rate of drop-out (1 – 2%) because of adverse events, and a low occurrence of peripheral oedema. *Conclusion:* Lercanidipine is an effective and well tolerated calcium channel blocker of the third generation. This new calcium antagonist represents a very useful tool to improve blood pressure control in the community.

Keywords: blood pressure control, calcium antagonists, diabetes, hypertension, side effects

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1. Introduction

Despite the wide choice of treatments available for the management of hypertensive patients, several surveys have repeatedly demonstrated that < 30% of hypertensives have a normalised blood pressure according to international guidelines (< 140/90 mmHg, and < 130/80 mmHg for hypertensive patients with diabetes or renal diseases with proteinuria) [1]. As morbidity and mortality derived from hypertension are strongly linked to the level of systolic (SBP) and diastolic blood pressure (DBP), as well as to the presence of other cardiovascular risk factors [2], the need to improve the quality of blood-pressure control in populations is crucial in order to reduce the persisting high risk of cardiovascular complications and target-organ damages.

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Table 1. Patient population and baseline demographics in subpopulations.

	Newly treated	Add-on therapy	Substitution therapy	
			Insufficient efficacy*	Adverse events*
Number of patients	683	844	343	320
% of total patient population	31	38	16	14
Females (%)	49	54	51	57
Age (mean ± standard deviation)	58 (13)	66 (12)	66 (13)	69 (12)
Patients ≥ 65 years old (%)	27	54	56	64
Patients with diabetes (%)	10	22	20	18
Reason for change at baseline‡				
Insufficient efficacy (%)	NA	93	100	18
Adverse events (%)	NA	0	16	100

*In some records the reason for substitution was "other".

‡In some cases no reason, other reasons or more than one reason for change was indicated.

NA: Not applicable.

Several factors have been identified that account for the relatively low percentage of patients achieving adequate blood-pressure control. These include the physicians' inertia and the patients' adherence to long-term therapy [3]. In fact, both of these factors are markedly influenced by the efficacy and tolerability of antihypertensive drugs used as first-line treatments. Indeed, physicians are more likely to initiate a treatment and maintain it if the drug is effective and well tolerated. Similarly, studies have demonstrated that the likelihood that a patient remains under the prescribed therapy depends on the tolerability profile of the drugs and on the ability of the drug to lower blood pressure effectively and rapidly [4]. In this respect, calcium channel blockers (CCBs) are recognised as very effective antihypertensive therapies, and recent, large, clinical trials have demonstrated their ability to reduce cardiovascular events [5-8]. However, the efficacy of calcium channel blockers is often limited by the occurrence of peripheral oedema, which can affect up to 30% of patients when the calcium antagonists is given alone, or ~ 20% when combined with a blocker of the rennin–angiotensin system [5,8].

Lercanidipine is a long acting, lipophilic, dihydropyridine (CCB) of the third generation, with a high vascular selectivity [9,10]. The most prominent benefit of these pharmacological characteristics is a marked reduction in the incidence of peripheral oedema. This has been demonstrated by a drop-out rate (due to oedema) of 1.9% with lercanidipine as compared with a 7.5% drop-out rate with amlodipine in one randomised, double-blind comparative study [11]; as well as a likelihood to develop peripheral oedema which is reduced by 50% in patients who already experienced leg oedema with another dihydropyridine CCB [12]. Lercanidipine has a long-lasting effect with a uniform effect over 24 h [10]. The efficacy and safety of lercanidjpine have been, to a large extent, studied in mild and moderate hypertension at doses ranging between 10 and 20 mg once daily [10]. The results of these studies have shown that 10 mg is the initial effective antihypertensive dose. The overall findings of randomised controlled trials performed with this compound are that lercanidipine is as effective in lowering blood pressure as other dihydropyridine calcium antagonists, but with an improved tolerability profile when compared with the first and second generations of CCB.

The purpose of the present Phase IV study was to investigate the efficacy and tolerability of lercanidipine in a large unselected population of hypertensive patients managed in a private practice in Switzerland.

2. Patients and methods

The present investigation was a post-marketing surveillance conducted in general practices in Switzerland, as a prospective, non-interventional, observational study. General practitioners (GPs) from the three linguistic regions of Switzerland were asked to document their daily routine in the treatment of hypertensive patients with lercanidipine. GPs were asked to fill in a baseline visit form for every patient, and to document the efficacy and tolerability profile of the drug after 4 and 8 weeks of treatment. There was no specific financial incentive except for the reimbursement of the time needed to fill in the case report forms. The drug was prescribed as usual. No free samples of drugs were given. Physicians had to document two arterial blood pressure measurements at every visit, and to report concomitant antihypertensive medication and adverse events, as well as changes or discontinuation of treatment. BP could be assessed by two methods: either conventional methods or oscillometric measurements, using the Microlife Average Mode [13],

Table 2. Antihypertensive treatments in subgroups.

	Newly treated hypertensives	Add-on therapy	Substitution therapy	
			Due to insufficient efficacy	Due to adverse events
Baseline treatment				
Lercanidipine dose*				
10 mg	98	98	90	89
20 mg	2	2	10	11
Monotherapy with lercanidipine	98	–	56	38
Combination of lercanidipine with:				
1 AHT	2	40	20	25
2 AHT	0	45	17	25
3 AHT	–	15	6	11
4 AHT	–	0	1	1
Combination with*:				
AA	0	49	21	27
ACE	1	29	11	16
BB	1	34	17	25
D	1	60	23	42
Treatment at visit 3				
Lercanidipine dose*				
10 mg	61	64	47	60
20 mg	35	31	47	36
Monotherapy with lercanidipine	86	–	52	35
Combination of lercanidipine with:				
1 AHT	9	36	22	27
2 AHT	2	42	18	26
3 AHT	0	17	7	11
4 AHT	–	0	1	1
Combination with‡				
AA	4	49	25	27
ACE-I	2	28	10	17
BB	3	33	19	26
D	5	58	26	42

All figures are in % of patients who were on anti-hypertensive treatments (AHT), angiotensin-II-antagonists (AA), angiotensin converting enzyme inhibitors (ACE-I), β-blockers (BB) or diuretics (D).

*Some missing recordings.

‡Multiple combinations possible.

Table 3. Changes in blood pressure and heart rate from baseline according to sex, age and diabetes.

	Gender		Age		Co-morbidity	
	Females	Males	< 65 y	≥ 65 y	Non-diabetic	Diabetic
ΔSBP (mmHg)	-26 ± 15	-24 ± 14	-24 ± 15	-29 ± 15	-25 ± 15	-21 ± 11
ΔDBP (mmHg)	-14 ± 9	-14 ± 9	-14 ± 9	-13 ± 9	-13 ± 11	-11 ± 7
Normalised BP (≤140/90 mmHg)	66%	61%	65%	60%	63% (≤ 140/≤ 90)	11% (≤ 130/≤ 80)
HR (beats/min)	-2 ± 10	-2 ± 10	-2 ± 10	-1 ± 10	-2 ± 10	-3 ± 8

DBP: Diastolic blood pressure; HR: Heart rate; SBP: Systolic blood pressure.

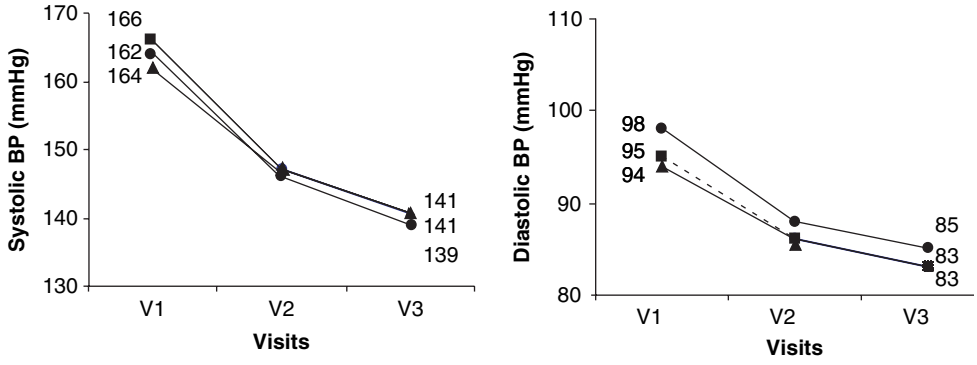

Figure 1. Systolic and diastolic blood pressure levels in the three sub-populations of the study: i) treatment initiation patients (circles: n = 683); ii) patients with lercanidipine as add-on therapy (squares: n = 844); iii) patients taking lercanidipine as substitution due to insufficient efficacy on previous treatment (triangles: n = 343).

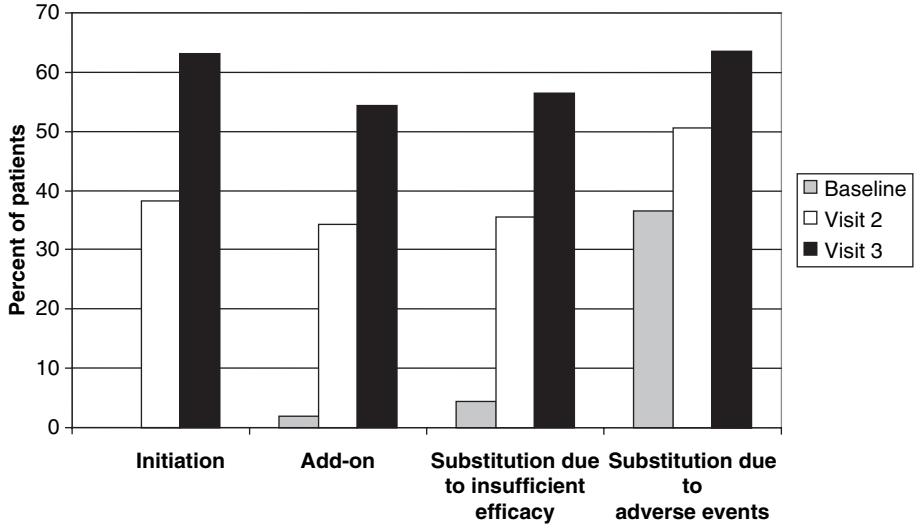

Figure 2. Proportion of patients with blood pressure ≤ 140/90 mmHg in the four patient groups at baseline, and during treatment (results shown for non-diabetic patients only).

which was validated according to standards of the European Society of Hypertension. Physicians could use one or the other method, but had to keep the same method throughout the observation period.

2.1 Patient selection

All patients with newly diagnosed, mild-to-moderate hypertension, or with treated hypertension requiring a change of medication according to the GP, and who were administered lercanidipine, were considered for the survey. There were neither demographic nor clinical exclusion criteria. The only condition to participate was that patients should not have been pretreated with lercanidipine. Treatment with lercanidipine was introduced at a dosage of 10 mg and titration to 20 mg was optional according to the physician's discretion.

2.2 Statistics

After collection of anonymous data by fax transmission, routine data quality-checks were performed. Clinical data were entered on an SAS database and analyses were performed using descriptive statistics (analysis of variance for repeated measurements and Student t-tests). All included patients were analysed for safety. Clinical efficacy was evaluated in patients who had a baseline measurement and an end of treatment documentation (visit 3 or premature termination).

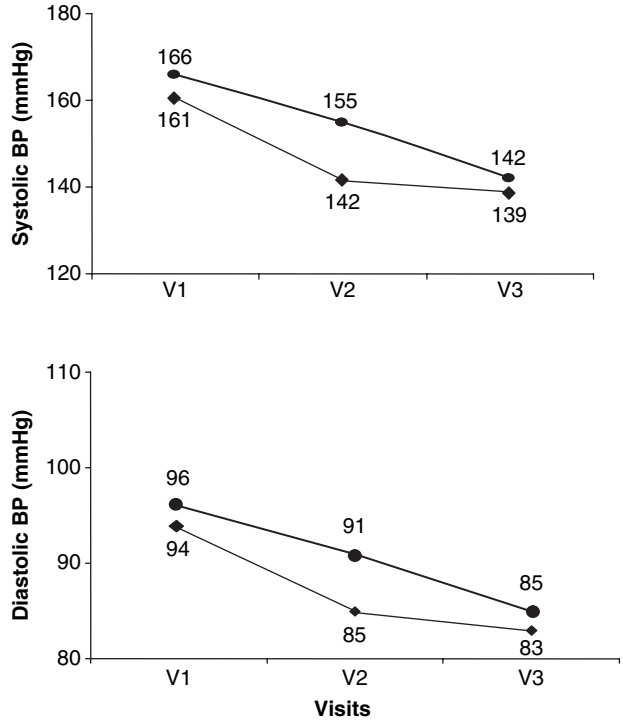

Figure 3. Changes in systolic and diastolic blood pressure in patients with: i) 'stable dose' of 10 mg lercanidipine at visit 3 (diamonds; n = 1405); and ii) 'titration' to 20 mg lercanidipine at visit 2 (circles; n = 509).

Table 4. Premature termination of treatment due to adverse events in the three patient groups.

	Initiation (n = 683)	Add-on (n = 844)	Substitution (n = 672)
Premature termination of treatment due to adverse events	4.4	7.8	8.8
Ankle oedema	0.6	1.9	3.0
Headache	0.6	1.1	1.1
Flush	0.4	1.3	0.6
Others	2.8	3.8	4.3

All figures in % of patients.

2.3 Definition of therapeutic targets

Response to treatment was defined as reaching a SBP ≤ 140 mmHg and/or a DBP ≤ 90 mmHg, or a reduction of SBP by ≥ 10 mmHg and DBP ≥ 5 mmHg. In real-life practice, however, the objective should be the normalisation of systolic (< 140 mmHg) and diastolic BP (< 90 mmHg). Therefore, how often these targets were achieved was also investigated (< 140 mmHg SBP and < 90 mmHg DBP or both). Physicians were informed of the target BP in non-diabetics and diabetics.

3. Results

3.1 Patient population

A total of 504 physicians participated in this survey and 2199 patients were included: 1963 of them completed the observational study (89.3%). A total of 186 patients (8.4%) prematurely terminated the study: 31 patients (1.4%) due to insufficient blood pressure control, 80 patients (3.6%) due to CCB-specific adverse events (ankle oedema, flush and headache) and 75 patients (3.4%) due other adverse events (AE). A total of 50 patients (2.3%) were classified by physicians as 'lost to follow-up'. Lercanidipine was administered to hypertensive patients as first-line treatment, as 'add-on' or as 'substitution' in respectively 31.1, 38.4 and 30.6% of the patients (p = non-significant).

3.2 Demographics

The patient population consisted of 54% females and 46% males, with a mean age of 64.2 (median: 64.0, a range of 18 to 99, standard deviation [SD] = 13.0) including a total of 18% of patients with diabetes. In the group of newly diagnosed patients, the average age of patients (58.4 ± 12.7 years), the proportion of patients older than 65 years (27.4%) and the proportion of patients with diabetes (10.0%) were lower than in the 'add-on' and 'substitution' groups, as shown in **Table 1**. The previous antihypertensive drugs were substituted, to an equal proportion, due to insufficient treatment (15.4%) and due to AEs (14.1%). BP was measured in 39% of the patients using the Microlife Average Mode.

3.3 Treatments

In newly treated patients, initiation of therapy was generally performed using lercanidipine mono-therapy (98%) at the dose of 10 mg (98%) as shown in **Table 2**. At visit 3 (8 weeks later), 39% of these patients were on 20-mg lercanidipine and 13.5% needed a combination with another antihypertensive drug. Lercanidipine was introduced as 'add-on' at a dose of 10 mg in 98% of the patients. The proportion of patients with a combination of 2 – 5 antihypertensive drugs, and the proportion of the various antihypertensive classes are shown in **Table 3**. At visit 3, the number and types of combinations were comparable to baseline, but the proportion of patients with a 20-mg dose of lercanidipine increased to 36%. Substitution of an antihypertensive drug by lercanidipine, either due to insufficient efficacy or AEs, was performed in the majority of patients using 10 mg of lercanidipine. The proportion of patients with a 20-mg dose at visit 3 was 47% among patients with so-called insufficient efficacy and 36% in patients who switched therapy because of AEs. The proportion of patients with a mono-therapy or a combination of 2 – 5 antihypertensive drugs, and the proportion of the various antihypertensive classes were similar at visit 3, and at baseline (**Table 2**). The average duration of lercanidipine administration (baseline to visit 3) was 63 days and was similar in all 3 subpopulations.

3.4 Efficacy

The changes in blood pressure induced by lercanidipine in the three subgroups ('treatment initiation', 'add-on' and 'substitution' groups) are presented in **Figure 1**. Mean systolic and diastolic BP and heart rate for all included patients (n = 2199) were 162 ± 18 mmHg, 94 ± 10 mmHg and 75 ± 10 b/min, respectively. Significant and comparable decreases in BP were observed in all three groups, resulting in an overall reduction of 22 ± 18 and 11 ± 10 mmHg. At visit 3, mean BP reductions compared with baseline were similar in all 3 subpopulations for SBP (25 ± 15, 25 ± 18 and 21 ± 18 mmHg) and DBP (13 ± 9, 12 ± 10 and 11 ± 10 mmHg), respectively. No difference in heart rate was observed in the population of included patients, nor in one of the subpopulations. The overall response rate (defined as a decrease in SBP by ≥ 10 mmHg and DBP by ≥ 5 mmHg) was 71.8%, and the proportion of patients with a normalised BP (SBP ≤ 140 and DBP ≤ 90 mmHg) was 58.9% in all patients without diabetes (n = 1811). The baseline SBP and DBP in the group 'substitution due to AE' were lower compared with the other 3 treatment groups (150 ± 17 and 87 ± 11 mmHg, respectively). However, the mean SBP and DBP at visit 3 were similar (138 ± 12 and 87 ± 11 mmHg, respectively) compared to the other treatment groups.

In newly treated patients, the percentage of patients who normalised their BP was 63.1% (**Figure 2**). In the 'add-on', this percentage was 1.8% at baseline (before administration of lercanidipine) and increased to 54.3% with the addition of this calcium antagonist. In the 'substitution due to insufficient efficacy' group, the percentage of patients achieving a normalised BP increased from 4.4 to 56.6%, and in the 'substitution due adverse events', group the same percentage raised from 36.5 to 63.6%. Thus, the percentage of non-diabetic patients reaching the target blood level (SBP ≤ 140 and DBP ≤ 90 mmHg) in newly treated, add-on therapy and substitution therapy groups was 63.1, 54.3 and 56.6%, respectively. With the cutoff BP set at < 140 and < 90 mmHg, the overall response percentage was 35%. Some physicians used an automated device to monitor BP, whereas others used the conventional ausculatory method of a sphygmomanometer. The percentage of patients achieving the target of SBP ≤ 140 mmHg and/or a DBP ≤ 90 mmHg was slightly greater among physicians using the conventional sphygmomanometer, suggesting a clear digit preference with this method. When targets were defined as < 140 and < 90 mmHg, no difference was found between the two methods.

Table 3 shows that lercanidipine induced comparable changes in BP and heart rate in young and elderly hypertensives, in males and females and diabetics and non-diabetics, although in diabetics, the percentage of patients achieving the target BP is lower than in non-diabetics.

Figure 3 illustrates the changes in BP of all patients with a titration of lercanidipine from 10 to 20 mg at visit 2, and the results are compared with the changes in BP among patients with a stable dose of 10 mg lercanidipine. Mean baseline BP of these two subpopulations were similar, but the reduction at visit 2 was less marked in the subpopulation 'titration' (-11 ± 16/-5 ± 10 mmHg) compared with the subpopulation 'stable dose' (-19 ± 16/-9 ± 9 mmHg).

3.5 Tolerability

Premature termination of treatment due to insufficient efficacy was very low in all 3 subpopulations, and was in the range of 1 to 2%. An overview of premature terminations is shown in **Table 4**. Premature terminations due to AEs for CCB-specific AEs, such as ankle oedema, headache or flush and 'others', were lowest in the group of newly treated patients, and slightly higher in the 'add-on' and 'substitution' population.

In 320 out of the 2199 included patients (14.1%), lercanidipine was administered as substitution of another antihypertensive drug because of intolerable AEs with the previous treatment (**Figure 4**). The most prominent antihypertensive classes responsible for the switch were the CCBs (66%) and the most prominent AE responsible for the change in therapy was ankle oedema (182 out of 211 AEs: 82.4%). The majority of the recorded AEs with drugs of the other classes were also class-specific, such as sleepiness, bradycardia and sexual dysfunction with β-blockers, cough with angiotensin-converting enzyme inhibitors (ACE-I) and sodium/potassium-imbalance with diuretics. After substitution with lercanidipine, 90% of these patients continued their antihypertensive treatment with a good tolerability, whereas only 10% experienced an AE leading to termination of lercanidipine treatment. Of the 10 patients with ankle oedema on lercanidipine, 8 patients had exhibited ankle oedema with their previous CCB treatment.

4. Discussion and conclusion

This non-interventional, observational study that enrolled 2199 hypertensive patients and managed by > 500 participating physicians in Switzerland is the second largest study conducted in the real world using the third generation calcium antagonist lecarnidipine. The results demonstrate:

- That lercanidipine is an effective and well tolerated antihypertensive agent in newly treated hypertensive patients. In this group of patients, 63% of patients reached the target blood pressure (≤ 140/90 mmHg) with lercanidipine alone.
- That lercanidipine is also an effective alternative in patients who are insufficiently controlled with another therapy or in patients who cannot tolerate other CCBs.
- That lercanidipine is well-tolerated, with a very low rate of drop-out (1 – 2%) because of AEs.

The largest uncontrolled study conducted with lercanidipine was the ELLYPSE study (*Eficacia de Lercanidipino y su Perfil de Seguridad*: a study of antihypertensive efficacy and

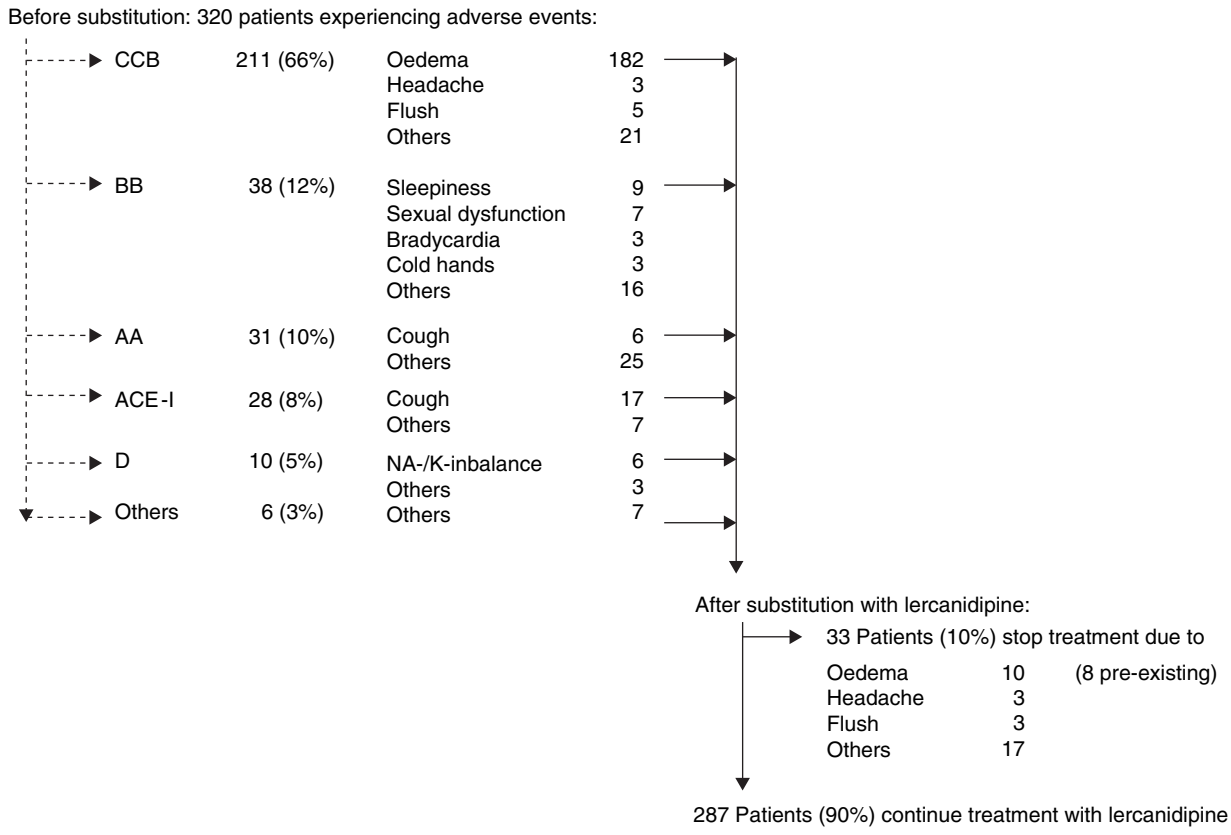

Figure 4. Termination of previous anti-hypertensive treatment due to adverse events, switch to lercanidipine and tolerability profile on treatment with lercanidipine (10 mg or 20 mg).

AA: Angiotensin-II-antagonists; ACE-I: Angiotensin converting enzyme inhibitors; BB: β-blockers; CCB: Calcium channel blockers; D: Diuretics.

tolerability of lercanidipine in daily clinical practice), which included ~ 9000 hypertensive patients followed in clinical practice [14]. In this study, lercanidipine induced a significant decrease in BP of ~ 19/13 mmHg after 12 weeks of treatment. In our study, which lasted 8 – 9 weeks, a similar overall change in BP was observed (-22/11 mmHg). Interestingly, the lercanidipine-induced reduction in BP was comparable in never-treated hypertensive patients and in patients who switched to lercanidipine either because of an insufficient BP control or because of side effects with the previous treatment. In newly treated patients, two thirds of the patients were on lercanidipine 10 mg, 86% of the patients were on monotherapy and 63% of patients had a BP ≤ 140/90 mmHg. Importantly, lercanidipine was effective in all categories of hypertensive patients (i.e., young and elderly, men and women and diabetics and non-diabetics). This latter observation confirms the results obtained in two previous studies involving elderly patients, the COHORT and the ELLE (Elderly and Lercanidipine) study [15,16]. However, in diabetic patients, although the absolute change in BP induced by lercanidipine was comparable to that observed in non-diabetics, it was often not sufficient to achieve the recommended target BP of < 130/80 mmHg. These data confirm the difficulty to reach these targets in diabetic patients, and further emphasise the need for combination therapies in this clinical situation. Of note, in diabetic patients, lercanidipine 20 mg has been reported to be as effective as 10 mg ramipril in lowering BP and microalbuminuria [17].

It is now well recognised that many hypertensive patients need more than 2 drugs to reach the target BP, particularly when this target is set at a lower level, such as in diabetics or renal-failure patients [18]. In our survey, almost 50% of the patients received lercanidipine because BP was insufficiently controlled with a previous treatment. In this subgroup, lercanidipine was also very effective and enabled the improvement of the percentage of well-controlled patients. It is noteworthy that these patients were generally older, with a mean age of 69 years, and the proportion of diabetics was higher than among newly-treated patients (20 – 22% versus 10%). Nonetheless, lercanidipine was found to be effective in lowering BP in these patients.

One advantage of the third generation of CCBs is their improved tolerability profile. Thus, in a challenge/rechallenge study, lercanidipine was found to reduce the likelihood of developing peripheral oedema by 50% in patients who had

peripheral oedema with another CCB [12]. In accordance with these observations, few patients developed peripheral oedema in our study. Thus, in pretreated patients, 182 patients were switched to lercanidipine because they had peripheral oedema with another CCB. Among these patients, only 10 experienced oedema when on lercanidipine during the 2 months follow-up. Overall, the incidence of premature termination of treatment due to AEs and insufficient efficacy was very low in the group 'treatment initiation' with an incidence of < 1% for ankle oedema, headache and flush. Although slightly higher in the other two subpopulations, the proportion of drop-outs due to AEs remained low. The low rate of patients who were lost to follow-up probably reflects the good patient guidance of the primary care physicians, good compliance and a good tolerability profile of lercanidipine. Patients who experienced an AE, either specific or non-specific for one of the 5 antihypertensive classes, were switched to lercanidipine. The relatively high proportion of patients (90%) who continued treatment with lercanidipine after substitution also confirms the good tolerability profile of lercanidipine.

This study has some limitations linked to its design. The most important ones are, obviously, the lack of a control group and the absence of randomisation. Thus, a placebo effect could account for the significant reduction of BP, particularly in newly treated patients; and so, an overestimation of the efficacy of lercanidipine cannot be excluded. Moreover, the improved BP control observed during the 3-month observation period could have been linked to a non-specific improvement in general management of BP. There was also no standardisation of the methods used to measure BP, and this could have increased the variability of the results. However, this was intended to be a real-life study evaluating the effect of lercanidipine in less stringent conditions of use. In this respect, we do find a clear end-digit preference (~ 15%) particularly among physicians using a conventional sphygmomanometer.

In conclusion, the results of the present survey conducted in the Swiss community show that lercanidipine is an effective and well-tolerated antihypertensive agent that enables control of BP in a large proportion of patients who were either never-treated or previously treated. Lercanidipine is effective in all subgroups of patients, and may be a very useful therapeutic choice to improve BP control in the real world.

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