Antihypertensive effectiveness of lercanidipine administered using an electronic pillbox compared with usual care in a cohort of mild-to-moderately hypertensive patients: the ELECTRA study

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Objective: It has been suggested that poor blood pressure (BP) control in the community is related to poor treatment tolerability and compliance. In the ELECTRA study we assessed whether the use of an electronic pillbox device (medical event monitoring system [MEMS]) could improve antihypertensive effectiveness of lercanidipine in a large group of hypertensive patients treated for 12 weeks. **Methods**: A total of 1523 outpatients with mild-to-moderate essential hypertension participated in this multicenter, randomized, open-label study. All patients received lercanidipine 10 mg once daily for 12 weeks. They were randomly allocated in a 1:2 design to use MEMS (n = 485) or usual care (actively monitored pill counts; n = 1038). If BP control was not achieved, additional therapy was allowed. Compliance was considered to be good if over 80% of tablets were taken by the patient. **Results**: Good compliance was observed in 92% of the MEMS group versus 91% of the usual-care group (p = not significant). At the study end, no differences were observed in BP reductions between the two arms. Systolic BP was reduced 21.6 ± 14.8 mmHg in the MEMS group versus 22.2 ± 13 mmHg in the usual-care group, and diastolic BP 12.8 ± 9.2 versus 13.8 ± 7.8 mmHg, respectively (p = not significant). Pulse pressure was also similarly reduced in both groups (8.8 ± 4.1 vs 8.4 ± 3.9 mmHg; p = not significant). At the study end, 24.2% of patients required add-on therapy to achieve BP goal (24% in the MEMS vs 24.3% in the usual-care group; p = not significant). A low incidence of adverse events (5.4%) was detected, edema being the most frequently reported (2.7%). As expected, in patients with poorer compliance, the antihypertensive effectiveness was worse. **Conclusion:** Lercanidipine produced effective and similar BP-lowering effects in the MEMS and usual-care groups over a 12-week period. Treatment compliance was high (>90%) with both regimens, which is most likely related to the good tolerability profile of lercanidipine, and also to active monitoring of compliance by physicians in the usual-care group. Further studies are warranted to confirm these data during longer follow-up.

Blood pressure (BP) is inadequately controlled in more than 70% of hypertensive patients and this is associated with a significant increase in cardiovascular risk [1,2]. Even small elevations of BP above normal values increase the likelihood of developing a cardiovascular event [3,4]. Therefore, lowering BP is critical to reduce the risk of cardiovascular disease and prevent major cardiovascular outcomes and end-organ damage. However, in hypertensive patients, treatment compliance is frequently low and is difficult to improve [5], and low compliance has been associated with lesser BP reductions and impairment of clinical prognosis [6]. This is partly related to the acceptability/tolerability of the medication; drugs with good tolerability profiles are usually associated with lower withdrawal rates and improved patient compliance rates.

Based on the above, any method of improving compliance should have a corresponding positive impact on BP control in patients with hypertension. Patient self-reports/pill counts are common methods to assess compliance in clinical trials and general practice. However, in recent years, different techniques have been developed to more accurately evaluate therapy compliance. Electronic devices for medication bottles that register the date and the time of each opening appear to be a useful method to assess compliance. It has been suggested that the use of electronic monitoring, such as medical event monitoring system (MEMS; Aprex Corporation, Fremont, CA, USA) in hypertension usually leads to improved medication compliance and, consequently, improved antihypertensive efficacy [5,7–9].

Keywords: antihypertensive drugs, compliance, hypertension, lercanidipine

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Calcium channel blockers (CCBs) are well-established first-line treatments in arterial hypertension. Early CCBs, while being very effective for lowering BP, were often associated with side effects that could negatively affect patient compliance. Therefore, while initial research focused on increasing potency and selectivity, recent pharmacological investigation has aimed to develop new CCBs with better tolerability profiles [10]. One of these is lercanidipine, a third-generation vasoselective dihydropyridine, which acts by inhibiting the L-type calcium channels in cell membranes [11–13]. This drug has high lipophilicity, which enables a slower and smoother onset and longer duration of action compared with other dihydropyridines [14]. In clinical trials, lercanidipine has been well tolerated, with a low incidence of adverse effects, as a result of its long-lasting and vasoselective calcium entry-blocking activity, with no sympathetic activation or reflex tachycardia [11,12]. The overall incidence of side effects for lercanidipine is lower than that observed for older dihydropyridines [15,16]. Efficacy has been evaluated in non-comparative [17–19] and comparative studies with other CCBs and different antihypertensive drugs [20–23]; results show that lercanidipine is at least as effective as other drugs. Lercanidipine has also proved useful in patients with severe or resistant hypertension, elderly subjects and patients with diabetes mellitus [23,24].

It has been suggested that electronic monitoring may result in better compliance and increase overall efficacy. Thus, the aim of the ELECTRA (Estudio Sobre la Eficacia de Lercanidipino y el Cumplimiento del Tratamiento) study was to assess whether the use of an electronic pillbox device (MEMS) improved the BP-lowering effect of lercanidipine in a large group of mild-to-moderately hypertensive patients.

Patients & methods

The ELECTRA study was a multicenter, randomized, open-label study comparing the antihypertensive effectiveness of lercanidipine administered using an electronic pillbox (MEMS) with identical therapy given by usual care (physician-monitored pill counts) in patients with hypertension. Patients aged 18 years and older, of both genders, with mild-to-moderate, newly diagnosed or previously treated and uncontrolled essential hypertension, defined as systolic BP (SBP) of at least 140 mmHg (≥130 mmHg in diabetics) and less than 180 mmHg, and diastolic BP (DBP) of at least 90 mmHg (≥80 mmHg in diabetics) and less than 110 mmHg, or with side effects due to previous antihypertensive medication, were elegible. Exclusion criteria were: severe hypertension (SBP ≥180 mmHg or DBP ≥110 mmHg) [25,26], known hypersensitivity or history of severe adverse events to any dihydropyridine, evidence of unstable angina or decompensated congestive heart failure, myocardial infarction within the previous 30 days, left ventricular outflow obstruction, severe rhythm disturbances with no pacemaker, liver dysfunction (with a greater than twofold increase in serum aminotransferases, or greater than 1.5-fold increase above upper limit of normality for serum bilirubin), or serum creatinine concentrations greater than 2.0 mg/dl. An additional exclusion criterion was any contraindication to lercanidipine, as included in the product labeling information or as stipulated by the investigator. Pregnant women, nursing mothers, women of childbearing potential and not using adequate contraception were also excluded. Informed consent was obtained from all participants.

The patients were randomly allocated in a 1:2 design to MEMS (n = 485) or usual-care (n = 1038) groups. In the first group, electronic monitoring (MEMS) was used to assess compliance patterns. Lercanidipine was packed in pill bottles fitted with a specialized cap containing an electronic microprocessor, which registered date, time and duration of each opening of the cap. Patients were given instructions on how to use the specialized cap on their medication bottles. For each patient, all calculations were derived from the date and the time of each opening. Each opening recorded by the pillbox was considered a single-dose intake, and MEMS-group compliance was defined by the number of pillbox openings. Missed doses were defined by the absence of recorded openings during the defined dosing periods. Thus, medication compliance was evaluated at the end of the study. In the usual-care (no-MEMS) group, standard pill count was used to assess compliance. In this group, compliance was evaluated at each visit. The number of handed-in pills in the containers was counted. Compliance was defined by the number of pills taken (dispensed pills minus returned pills) in relation to the theoretical number of prescribed doses, and was expressed as a percentage. Good compliance was considered to be greater than 80%.

All patients were treated with lercanidipine 10 mg once daily, taken immediately upon awakening, and followed for a 12-week period.

Four visits were scheduled, at baseline and after 4, 8 and 12 weeks of treatment. At each visit, BP and heart rate (HR) were measured, compliance was checked in the usual-care group, and adverse events were recorded. If BP was uncontrolled with lercanidipine 10 mg at any visit, additional therapy was allowed. All adverse events were designated by the investigator as either potentially drug related or not drug related. Blood tests measuring serum fasting glucose, creatinine, uric acid, ions, standard biochemical variables, hepatic enzymes and a complete lipid profile were performed at baseline and at study end. Seated SBP and DBP were measured after 10 min resting. Both mercury sphygmomanometer and automatic devices were used depending on their availability at the healthcare center, and the same method was always used for each patient throughout the study. The patients were advised to quit smoking or drinking coffee within 30 min prior to BP assessment. The recorded BP was the average of two separate measurements (a third measurement was obtained when there was a difference of 5 mmHg between the two readings). Adequate BP control was defined as SBP less than 140 mmHg and DBP less than 90 mmHg for nondiabetic patients, and SBP less than 130 mmHg and DBP less than 80 mmHg for diabetic patients [25,26]. The flow chart of the study protocol is shown in **Table 1**.

Statistical analysis

The sample size was calculated considering an α-level of 0.05, a test power of 0.80 and a risk of loss of patients to follow-up of 10–15%. To observe a different efficacy between both groups of at least 10%, it was considered necessary to include 400 patients in the MEMS group and 800 patients in the usual-care group.

Categorical data are expressed as numbers and percentages and continuous data as mean (± standard deviation). The Student's t-test for paired and unpaired data was used to assess the effects of treatment on continuous variables. Categorical variables were analyzed with the χ^2 test. In order to study differences in the quantitative variables over time as well as progression, or between-group differences, the analysis of variance (ANOVA) for repeated or independent measurements was used. The analysis of covariance (ANCOVA) was used to assess the effect of lercanidipine in subsets of the study population divided according to presence or absence of vascular diseases. Statistical significance was set at a p-value of less than 0.05. The SPSS statistical software package for Windows (version 9.1) was used to analyze the data.

Results

A total of 1523 patients with mild-to-moderate essential hypertension (52% men), with a mean age of 63.2 ± 11.3 years (61% aged >60 years), were included in the study. The most prevalent additional cardiovascular risk factors were current smoking (33%) and hypercholesterolemia (29%). The most frequent concomitant diseases were ischemic heart disease (14%) and peripheral artery disease (6%). Grade I (mild) hypertension was diagnosed in 40% of patients and grade II (moderate) in 60%. Overall, BP at baseline was 159.1 ± 10.3/95.3 ± 6.8 mmHg and pulse pressure was 63.8 ± 6.3 mmHg. BP was

Table 1. Flow chart of the study protocol.

Procedure	Visit 0 (baseline)	Visit 1 (4 weeks)	Visit 2 (8 weeks)	Visit 3 (12 weeks)
SBP, DBP, HR	X	X	X	X
Eligibility criteria	X			
Demographic data	X			
Patient history and physical examination	X			
Study medication (lercanidipine) supplied	X			
Lifestyle changes recommendations	X	X	X	X
Adverse events report		X	X	X
Compliance with treatment in MEMS group				X
Compliance with treatment in usual-care group		X	X	X

DPB: Diastolic blood pressure; HR: Heart rate; MEMS: Medical Event Monitoring System; SBP: Systolic blood pressure.

158.7 ± 10.6/94.6 ± 7.1 mmHg and pulse pressure (PP) 64.1 ± 6.5 mmHg in the MEMS group, and in the usual-care group, BP was 159.3 ± 10.1/95.6 ± 6.6 mmHg and PP was 63.7 ± 6.1 mmHg (p = not significant [NS] for both). HR was 76.3 ± 8.4 beats/min, with no significant differences between the two groups. Baseline characteristics of the study population are shown in **Table 2**. A total of 37% of patients were newly diagnosed essential hypertensives. In previously treated patients (63%), lercanidipine was prescribed owing to uncontrolled hypertension in 73% and drug-related adverse events with other agents in 27% (**Table 3**).

SBP decreased from 159.1 ± 10.3 mmHg at baseline to 137.3 ± 9.9 mmHg at study end, and DBP from 95.3 ± 6.8 to 81.9 ± 6.7 mmHg (p < 0.001 for both). HR decreased from 74 ± 8 to 72 ± 11 beats/min (p = NS). **Figure 1** shows SBP and DBP changes in the two study groups. At week 12, SBP was reduced 21.6 ± 14.8 mmHg in the MEMS group versus 22.2 ± 13 mmHg in the usual-care group and DBP was reduced by 12.8 ± 9.2 and 13.8 ± 7.8 mmHg, respectively (p = NS for both). PP was also similarly reduced in the two groups, 8.8 ± 4.1 mmHg in teh MEMS group versus 8.4 ± 3.9 mmHg in the usual-care group (p = NS). No changes in baseline or final HR were detected between the two groups. No significant changes were observed with lercanidipine in fasting glucose, serum creatinine, uric acid, ions, standard biochemical variables or hepatic or lipid profile in either group.

At the study end, 24.2% of patients required more antihypertensive medication to achieve BP goal (24% in the MEMS group vs 24.3% in the usual-care group; p = NS). Overall, a mean of 1.2 ± 0.4 drugs were added to achieve BP control, with no difference in the number or type of drugs between the MEMS and usual-care patients. The most prescribed add-on medication was an angiotensin-converting enzyme (ACE) inhibitor in both study groups (78% in the MEMS group and 76.3% in the usual-care group; p = NS). Overall, 92% of patients completed the 12-week treatment period with lercanidipine. There was a low incidence of adverse events (5.4%), edema being the most frequent (2.7%), followed by headache (1.4%), flush (0.7%), dizziness (0.5%), asthenia (0.4%), skin rash (0.2%) and palpitations (0.2%). No significant differences were observed between the groups. **Figure 2** shows the percentage of patients with a compliance over 80%; compliance was similar in the MEMS and usual-care groups. Overall, the subgroup of patients who experienced adverse events exhibited a worse rate of compliance (67 vs 87%; p < 0.05). BP lowering was greater when compliance was higher (**Figure 3**). The incidence of adverse events and BP reductions were similar in hypertensive patients with and without vascular disease (**Figure 4**).

Table 2. Baseline characteristics of the study population.

Data	Baseline characteristics	
	Percent (%)	*Mean ± SD*
Total patients (n = 1523)		
Age (years)		63.2 ± 11.3
Patients > 60 years	61	
Sex (% male)	52	
SBP (mmHg)		159.1 ± 10.3
DBP (mmHg)		95.3 ± 6.8
HR (beats/min)		74.3 ± 8.4
Grade I hypertension	40	
Grade II hypertension	60	
Cardiovascular risk factors		
Smoking	33	
Hypercholesterolemia	29	
Excessive alcohol intake	10	
Diabetes mellitus	4	
Family history of cardiovascular disease	2	
Concomitant diseases		
Ischemic heart disease	14	
Peripheral artery disease	6	
Renal insufficiency	5	
Cerebrovascular disease	4	
Congestive heart failure	2	

DPB: Diastolic blood pressure; HR: Heart rate; SBP: Systolic blood pressure; SD: Standard deviation.

Discussion

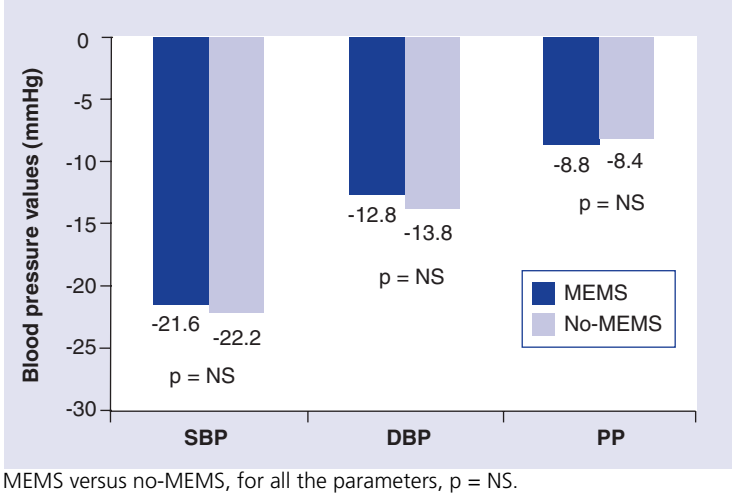
Globally, the control of hypertension in the community is poor, and many patients continue to have elevated BP and are at a high risk of secondary cardiovascular complications [1]. Many factors contribute to inadequate BP control, such as therapeutic inertia and unsatisfactory tolerability or treatment compliance. Therefore, the search for newer (and better tolerated) antihypertensive agents and improved methods for ensuring treatment compliance has been an important focus in this therapeutic setting. Despite the best efforts, medication adherence remains poor [27,28]. The present study was designed to examine whether,

Table 3. Previous antihypertensive medication and reasons for the prescription of lercanidipine.

Data	Patients (%)
Total patients (n = 1523)	
Naive patients, newly treated (n = 564)	37
Previously treated with antihypertensive drugs (n = 959)	63
Previous antihypertensive medication (in previously treated population; n = 959)	
Diuretics	26
Angiotensin-converting enzyme inhibitors	26
β-blockers	16
Calcium channel antagonists	9
Angiotensin-receptor blockers	8
Other medications	15
Reasons to prescribe lercanidipine (in previously treated population; n = 959)	
Uncontrolled blood pressure	73
Adverse events with other drugs	27

using an electronic pillbox-monitoring system, the compliance and subsequently effectiveness of an antihypertensive agent could be improved compared with usual care. The use of an electronic monitoring system should facilitate better adherence to therapy and, consequently, improve overall efficacy. However, in the present study, this was not the case because of the high compliance rate in the usual-care group (>90%), similar to the MEMS group. This was somewhat unexpected in the no-MEMS group and presumably relates to the excellent tolerability of lercanidipine and to the increased medical care provided as part of the clinical trial design (monthly assessments, tablet counts and additional therapy as part of routine patient care). This is indicative of high acceptance by patients in this clinical setting, and it corresponds with the good clinical profile of lercanidipine, which was reported in earlier studies [15,17,19,20].

Figure 1. Reductions in blood pressure values at study end in both groups (MEMS vs no-MEMS).

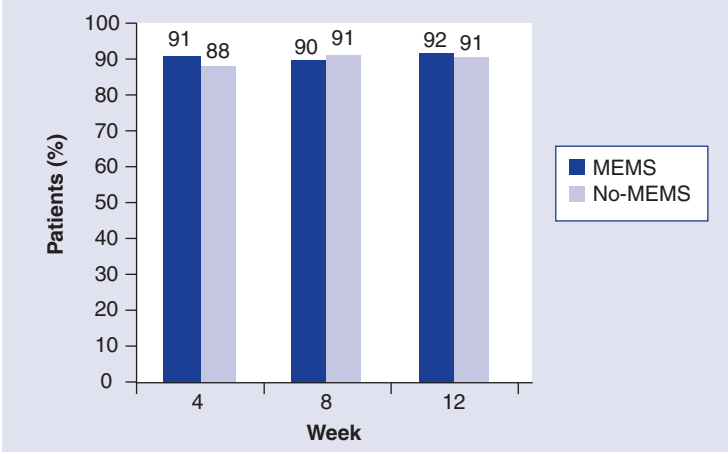


MEMS versus no-MEMS, for all the parameters, p = NS.
DBP: Diastolic blood pressure; NS: Not significant; PP: Pulse pressure; SBP: Systolic blood pressure.

Using the MEMS system did not improve the high treatment-compliance rate observed in usual care and, as might be anticipated, the BP-lowering effect was also similar in the two groups. The study also confirms that the efficacy of an antihypertensive drug not only depends on its capacity for reducing BP, but also on its tolerability. This is clearly demonstrated in the subgroup of patients who reported adverse events, in whom compliance was lower and was associated with reduced antihypertensive efficacy. Our data are consistent with the established view that the use of well-tolerated drugs, which are associated with a low incidence of adverse effects, concord with high patient acceptance and good compliance, and help promote better BP control [29–31]. These data confirm the effectiveness and favorable tolerability profile of lercanidipine in a large cohort of patients with mild-to-moderate essential hypertension recruited in general practice, and are consistent with data previously reported in randomized trials [10,24] and in surveillance studies such as ELYPSE and LAURA [17,19].

In the elderly population, lowering elevated SBP and PP is an important clinical objective, since these pressures correlate with cardiovascular

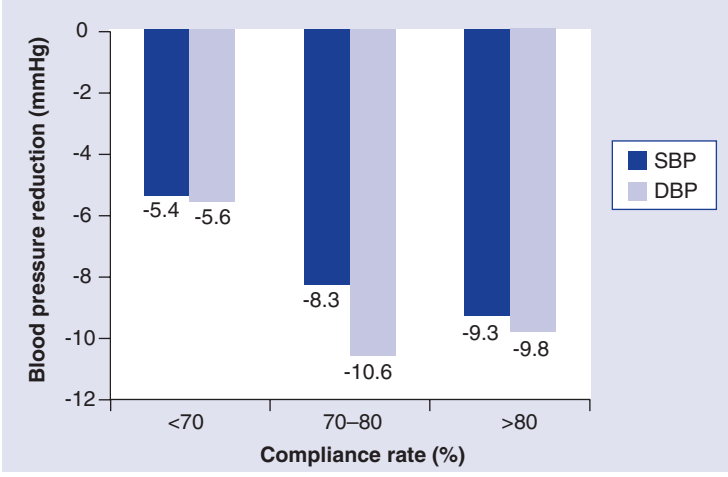
Figure 2. Percentage of patients with a treatment compliance of greater than 80%.



p = Not significant for all comparisons.
MEMS: Medical event monitoring system.

risk and are more difficult to control. Analysis of data from two prospective cardiovascular risk/disease studies indicate that BP control remains poor in the elderly population, with less than a third of older hypertensive women and a fifth of men receiving adequate treatment to control SBP and PP [32]. In this regard, CCBs have shown to be effective drugs for reducing both SBP and PP [33]. Notably, older patients are generally at higher cardiovascular risk and frequently receive multiple treatments for comorbid conditions; this increases the likelihood of developing an adverse event. Thus, in patients aged over 60 years, the use of well-tolerated drugs may be particularly important. Interestingly, more than 60% of patients included in the present study were aged over 60 years, and treatment with lercanipidine was effective in reducing SBP and PP and was well-tolerated. As such, lercanidipine appears to be a very useful antihypertensive medication for elderly hypertensive patients.

Figure 3. Compliance rate and blood pressure reduction.

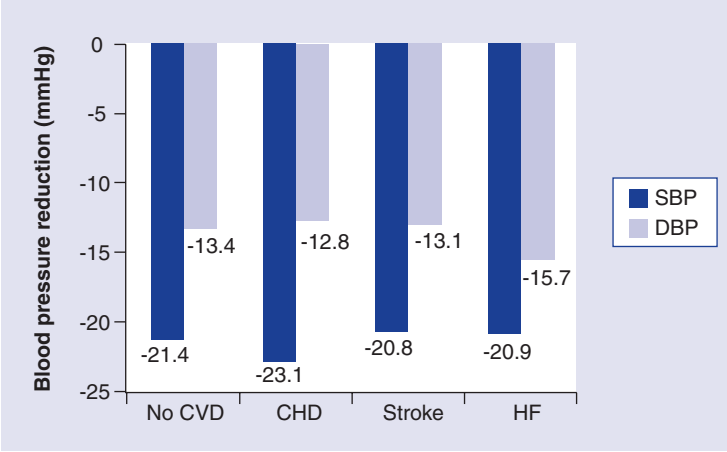


p < 0.05.
DPB: Diastolic blood pressure; SBP: Systolic blood pressure.

In a separate subanalysis, lercanidipine demonstrated good antihypertensive efficacy and tolerability in hypertensive patients with associated vascular diseases (coronary heart disease, heart failure and stroke). These data indicate good compliance and a low withdrawal rate regardless of cardiovascular risk, and they are consistent with the findings of the LAURA study, which showed that lercanidipine is effective and well-tolerated in high-risk hypertensive patients [19]. Since the majority of hypertensive patients attending daily in primary care belong to higher-risk groups, these findings are clinically relevant [34,35]. It must be remembered that these results are limited to a relatively short-term (12-week) observation period. Potentially, compliance could deteriorate with time and this is when an electronic pill counter might provide more clinical advantages. Further studies are required to assess longer-term compliance rates with the MEMS system and the overall impact on BP control.

Some limitations must be recognized in this study. The main one is that treatment compliance may somehow be increased in this kind of study, because the study design may create a certain environment that could, in some cases, artificially improve compliance. However, the two treatment arms experience the same environment and so would be affected equally, therefore will not bias the comparison between both therapy strategies. On the other hand, since this study was performed in daily clinical practice and, as usual in this setting, no placebo run-in period was designed, regression to the mean could partly explain the observed drug antihypertensive effect. However, although the BP-lowering effect may be partly overestimated, this should not specifically modify the main study results, which are that similar BP reductions are observed with the use of MEMS versus usual care. It should also be born in mind that these results are limited to a relatively short-term (12-week) observation period. Potentially, compliance could deteriorate with time and this is when an electronic pill counter might provide more clinical advantages.

Figure 4. Systolic blood pressure and diastolic blood pressure reductions in patients with and without vascular diseases.



p = not significant for all comparisons.
CHD: Coronary heart disease; CVD: Cardiovascular disease; DPB: Diastolic blood pressure; HF: Heart failure; SBP: Systolic blood pressure.

Further studies are required to assess longer-term compliance rates with the MEMS system and the overall impact on BP control.

In conclusion, similar antihypertensive effectiveness was documented in hypertensive patients treated with lercanidipine for 12 weeks whose adherence was monitored using an electronic pill counter (MEMS) or by the more usual physician monthly pill counts. These results provide convincing evidence that, in this large general practice population, the good tolerability of lercanidipine is associated with excellent compliance to treatment (>90%) and, when combined with routine clinical follow-up and management (including additional therapy whenever necessary), is associated with an effective BP-lowering effect. Reaffirming findings from previous randomized, controlled trials and surveillance studies, lercanidipine appears to be a useful choice for treating hypertensive patients in daily clinical practice, including the elderly.

Executive summary

- Blood pressure (BP) is inadequately controlled in over 70% of hypertensive patients, and this is associated with a significant increase in cardiovascular risk.
- Two of the main reasons contributing to inadequate BP control are unsatisfactory tolerability/safety and poor treatment compliance.
- In this large general practice population, the good tolerability of lercanidipine was associated with excellent compliance to treatment (>90%).
- Using the medical event monitoring system did not improve the high treatment-compliance rate observed with usual care.
- Reaffirming findings from previous controlled studies, lercanidipine is a useful choice for treating hypertensive patients in daily clinical practice, including the elderly.

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