Tolerability of Long-Term Treatment With Lercanidipine Versus Amlodipine and Lacidipine in Elderly Hypertensives

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Background: Irrespective of their clinical relevance, side effects cannot be considered a negligible problem in antihypertensive therapy. The aim of this trial was to evaluate the tolerability profile of lercanidipine with that of two other calcium antagonists (amlodipine and lacidipine) in elderly hypertensives.

Methods: In a multicenter, double-blind, parallel study 828 elderly (aged ≥60 years) hypertensives were randomized to lercanidipine 10 mg/day (n = 420), amlodipine 5 mg/day (n = 200), or lacidipine 2 mg/day (n = 208) (ratio 2:1:1). If blood pressure (BP) control was unsatisfactory (systolic BP/diastolic BP ≥140/90 mm Hg), the dose of the double-blind medication was doubled and, as a further step, enalapril or atenolol (plus diuretic, if needed) was added. Patients were treated for an average of 12 months.

Results: Amlodipine patients had significantly (P < .001) higher rates of edema (19%) and of early study discontinuations due to edema (8.5%) compared with lercanidipine (9% and 2.1%) and lacidipine patients (4% and 1.4%). Similarly, edema-related symptoms (lower limb swelling and heaviness) occurred significantly (P < .01) more often with amlodipine (50% and 45%, respectively) than with lercanidipine (35% and 33%) and lacidipine (34% and 31%). Most edema cases occurred in the first 6 months, a between-treatment difference being evident since beginning of treatment. Other drug-related adverse events did not differ between treatments. Blood pressure was equally and effectively reduced in the three groups.

Conclusions: The two lipophilic dihydropyridine calcium antagonists, lercanidipine and lacidipine, have an antihypertensive effect comparable to that of amlodipine, but a better tolerability profile.

Key Words: Lercanidipine, amlodipine, lacidipine, essential hypertension, edema, elderly.

In spite of their antihypertensive efficacy and of their widespread use in the treatment of hypertension, dihydropyridine calcium antagonists are often reported to induce side effects responsible for treatment withdrawal or replacement with drugs of a different class.1–4 In the recent past, efforts were devoted to the development of new compounds or formulations capable of simultaneously displaying a good efficacy and tolerability. Lercanidipine is the newest of these compounds. Due to its high lipophilicity and high vascular selectivity,5 lercanidipine at daily doses ranging from 10 to 20 mg has been shown to ensure a gradual and prolonged antihypertensive effect, both in placebo-controlled studies7,8 and in comparative studies versus other antihypertensive drugs.9–12 In all these studies tolerability of lercanidipine was very good and, when compared with other dihydropyridine calcium antagonists,10–12 it appeared to be better. However, a reliable assessment of the comparative incidence of adverse drug reactions requires a study large enough and of sufficient duration to detect potential differences of clinical significance, and performed in conditions as close as possible to common clinical practice.

The aim of the present study was to evaluate the tolerability of lercanidipine with that of the most widely used...
dihydropyridine calcium antagonist, amlodipine, and with that of another lipophilic dihydropyridine, lacidipine. The drugs were given on a long-term basis (from 6 months up to 2 years) to elderly hypertensives in a randomized, double-blind, parallel study in which patients with concomitant diseases were also included and combination therapy with other antihypertensive agents was allowed, if necessary.

Methods
Study Population
The study included outpatients with essential hypertension. The main inclusion criteria were age ≥60 years and a diastolic blood pressure (DBP) of 96 to 115 mm Hg or a systolic blood pressure (SBP) of 161 to 210 mm Hg after a 2-week wash-out period. Patients with major cardiovascular diseases were excluded.

Written informed consent was obtained from all patients before their inclusion into the study. The study was approved by the local Ethics Committees of the centers involved and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice.

Study Design
This was an Italian, multicenter (100 centers), randomized, double-blind, active controlled, flexible titration, three-parallel group trial. After a 2-week wash-out period, during which previous antihypertensive treatment was discontinued, eligible patients were randomized in a 2:1:1 ratio to double-blind administration of lercanidipine (10 mg), amlodipine (5 mg), or lacidipine (2 mg) given once daily (step 1). If at the end of the first 4 weeks of treatment DBP was not lowered to <90 mm Hg and SBP to <140 mm Hg the dose of the drugs was doubled to 20 mg for lercanidipine, to 10 mg for amlodipine, and to 4 mg for lacidipine (step 2). If after an additional 4 weeks of treatment patients had not satisfied response criteria, addition of open label atenolol (50 mg/day) or enalapril (10 mg/day) was prescribed (step 3), the choice of either drug being left to the investigator. If a BP <140/90 mm Hg was not reached, the dose of atenolol or enalapril was doubled to 100 and 20 mg/day, respectively (step 4), followed by addition of hydrochlorothiazide (12.5 mg/day [step 5] or 25 mg/day [step 6]). Treatment lasted a minimum of 6 months, with optional prolongation under double-blind conditions up to 2 years. Double-blind medications were taken once daily, in the morning, at least 1 h before breakfast.

Blood pressure, heart rate, adverse events, symptom checklist, well-being status, and compliance to treatment were assessed at each visit. A 12-lead standard electrocardiogram (ECG) was obtained, and hematology, clinical biochemistry, and urinalysis performed at the screening visit and after 8, 28, 52, 76, and 104 weeks of treatment. At screening and after 8, 16, 28, 40, 52, 64, 76, 92, and 104 weeks of treatment patients also underwent a physical examination.

Adverse Events
At each visit the type, duration, seriousness, intensity, expectedness, causality assessment, and actions taken were reported for all adverse events, as spontaneously reported by the patient or detected by the investigator. Peripheral edema was considered an adverse event if objectively detected by the investigator, and defined “mild” if not spontaneously reported by the patient, “moderate” if the volume increase was also spontaneously reported by the patient, and “severe” if a change of footwear was required or clearly evident prints of shoes or socks were present.

Symptom Checklist
At the end of each visit, after having reported adverse events, the investigator questioned the patient with a symptom checklist of 16 items. Lower limb swelling and lower limb heaviness/numbness/tingling were reported on the checklist as possible edema-related symptoms, independently of their association with objective edema detected by the investigator. Other symptoms were dizziness, tachycardia/palpitation, fatigue/weakness, chest pain, dyspnea, heartburn, constipation or diarrhea, itching/skin reddening, sexual dysfunction, painful breast swelling, gingival swelling, or bleeding.

Assessment of Well-Being Status
Well-being was evaluated by a visual analog scale (VAS), by asking the patient to indicate, on a scale ranging from 0 (worst) to 100 (best), the level of her or his perceived well-being status.

Data Analysis
The study sample size calculation was based on the assumption that the incidence of peripheral edema should have been lower in the lercanidipine (2%) than in the other groups (7.5%). On the basis of this assumption and on the 2:1:1 randomization ratio, the study had to include at least 360 patients in the lercanidipine, 180 in the amlodipine, and 180 in the lacidipine groups (power = 90%, α = 0.05, two-sided, expected percentage of drop-outs = 20%). Analysis of safety data was performed on all randomized patients who received at least one dose of treatment. In case of missing data the last observation carried forward.

BP and Heart Rate Measurement
Blood pressure was measured by a standard sphygmomanometer approximately 24 h after the last drug intake. Two measurements, taken at 3-min intervals in the sitting position, were averaged and used as the clinic BP reference value. Heart rate was measured from the radial pulse during 30 sec. Blood pressure and heart rate were also measured after 2 min of standing.
algorithm was applied for BP, heart rate, and VAS (intention-to-treat analysis). This algorithm was also applied to baseline values in case of missing measurements after baseline in the first 6 months of treatment. Accordingly, safety data are shown for all randomized patients; data on BP, heart rate, and VAS are presented for all patients in the first 6 months of treatment and then for groups of patients having completed more than 6, 12, and 18 months and therefore entering in the intention-to-treat analysis at 12, 18, and 24 months.

The primary end point of the study was the incidence of peripheral edema in the three treatment groups. Safety evaluation was also based on other types of adverse events, symptoms, changes in patient’s well-being, heart rate, laboratory tests, and ECG. Efficacy was evaluated by computing 1) absolute values and changes in BP from baseline; 2) percentage of responders (SBP and DBP <140/90 mm Hg or reduction in SBP and DBP of at least 20 and 10 mm Hg, respectively); 3) percentage of normalized patients (SBP and DBP <140/90 mm Hg); and 4) percentage of patients requiring additional antihypertensive drugs.

Baseline data were compared by one-way analysis of variance (continuous variables) and $\chi^2$ or Fisher’s exact test (categoric variables). The incidence of peripheral edema in the treatment groups was compared by the $\chi^2$ test and odds ratio, with 95% confidence intervals for lercanidipine versus amlodipine and lercanidipine versus lacidipine. Frequencies of patients with adverse events, drop-outs for adverse events, and of patients with symptoms were similarly evaluated. The SBP and DBP changes were assessed by covariance analysis, using baseline values as covariate. Rates of BP normalization, response, or combination therapy were compared by the $\chi^2$ test. Changes in well-being from baseline (VAS scale) was assessed by repeated measures analysis of variance and between treatment difference by covariance analysis.

A secondary per protocol analysis was carried out on efficacy parameters in patients who were treated for more than 150 days without major protocol violations to evaluate the consistency with the primary intention-to-treat analysis.

In addition, to evaluate whether the antihypertensive effect was linked to the occurrence of peripheral edema, an additional (not previously planned) statistical analysis was performed for DBP taking into account also this term (analysis of covariance).

Data are shown as means $\pm$ SD (or $\pm$ SE for adjusted mean values when required by protocol). A $P < .05$ was used as the level of statistical significance.

Results

Demographic and Clinical Data

A total of 859 patients were randomized to treatment, but 31 patients were excluded from analysis before breaking the code because of inadequate documentation. Therefore, 828 patients (420 lercanidipine, 200 amlodipine, and 208 lacidipine) were analyzed. The average duration of treatment was similar between the three treatment groups (lercanidipine, 357 ± 214 days [median, 352 days]; amlodipine, 329 ± 217 days [median, 298 days]; lacidipine, 372 ± 223 days [median, 355 days]). Patients continuing the study for more than 6, 12, and 18 months of treatment were, respectively, 528 (276 lercanidipine, 118 amlodipine, and 134 lacidipine), 323 (169 lercanidipine, 70 amlodipine, and 84 lacidipine), and 153 (78 lercanidipine, 30 amlodipine, and 45 lacidipine). In the three treatment groups patients on low-dose monotherapy were 52%, 56%, and 47%, on high-dose monotherapy 22%, 23%, and 24%, with two-drug combinations 19%, 16%, and 21%, and with multiple drug combinations 7%, 6%, and 8%.

A total of 226 patients (26% in the lercanidipine, 31% in the amlodipine, and 26% in the lacidipine treatment group) discontinued the study within the first 6-month period because of consent withdrawal ($n = 85$), adverse events ($n = 74$), poor compliance to treatment ($n = 5$), poor compliance with study procedures ($n = 17$), lack of efficacy ($n = 7$), protocol violation ($n = 17$), or other minor reasons ($n = 21$). Another 20 patients discontinued treatment because of adverse events during the optional prolongation of the study up to 2 years. On the whole, treatment withdrawal due to adverse events occurred in the treatment groups with different incidence: 11% lercanidipine, 16% amlodipine, and 8% lacidipine ($x^2 = 7.1282; P < .05$). Only a few patients ($n = 13$) interrupted the study for lack of efficacy.

General characteristics of the study population at the time of randomization are shown in Table 1. No between-group difference was observed for any of the characteristics considered. More than 50% of the patients in all groups had concomitant diseases (52% lercanidipine, 54% amlodipine, and 55% lacidipine) and concomitant treatments were present in approximately half of the patients in all groups.

Adverse Events

A total of 109 patients in the lercanidipine (26%), 56 patients in the amlodipine (28%), and 45 in the lacidipine group (22%) reported adverse events considered certainly, probably, possibly, or remotely related to study treatment ($x^2 = 2.3392; P = not significant$). The adverse event most frequently reported was peripheral edema, the primary end point of the study (Fig. 1, top). The incidence of peripheral edema was greater for the amlodipine (19%) than for the lercanidipine (9.3%) and lacidipine (4.3%) groups ($x^2 = 24.6945; P < .001$; odds ratio [OR]: amlodipine versus lercanidipine 2.29 [1.41–3.71], lacidipine versus lercanidipine 0.44 [0.21–0.93]). Most cases occurred in the first 6 months of treatment (amlodipine 18.5%, lercanidipine 8.3%, and lacidipine 4.3%, $x^2 = 25.2354; P < .001$; OR: amlodipine versus lercanidipine...
The percentage of patients who withdrew because of peripheral edema was significantly ($\chi^2 = 19.6886; P < .001$) greater in the amlodipine (8.5%) than in the lercanidipine (2.1%) and lacidipine (1.4%) groups; OR: amlodipine versus lercanidipine 4.24 [1.86–9.70], lercanidipine versus lacidipine 0.67 [0.18–2.50]. Again most cases of drop-out occurred in the first 6 months of treatment: amlodipine (7.5%), lercanidipine (1.9%), and lacidipine (1.0%) ($\chi^2 = 18.5024; P < .001$; OR: amlodipine versus lercanidipine 2.38, lacidipine versus lercanidipine 0.50 [0.11–2.38]). Edema was observed more frequently in women (14.3%) than in men (6.2%) ($P < .05$) and was equally distributed in patients with (10.2%) or without (10.4%) lower limb varicose veins. Significant differences among treatments were found both in female and male groups and in patients with and without varicose veins. The incidence of other adverse events spontaneously reported by the patients among those frequently occurring during therapy with calcium antagonists (flushing, headache, dizziness, vertigo, asthenia, palpitation, and tachycardia) did not differ among groups (Table 2, upper part).

Cardiovascular events (stroke, transient ischemic attack, myocardial infarction, angina pectoris, arrhythmia, heart failure, and syncope) were infrequent and occurred in 2.6% of patients treated with lercanidipine, 2.5% of patients treated with amlodipine, and 1.9% of patients treated with lacidipine. Three patients died: 1 patient in the lercanidipine group (suicide) and 2 in the lacidipine group (strokes).

### Symptom Checklist

A symptom checklist was filled in by 402 of 420, 191 of 200, and 200 of 208 patients on lercanidipine, amlodipine, and lacidipine; 72%, 73%, and 69% of whom reported at least one symptom during the study ($\chi^2 = 1.2671; P = \text{not significant}$). Edema-related symptoms (ie, lower limb swelling and heaviness) were the most frequent complaints (Fig. 1, middle and bottom). In all treatment groups their incidence was higher than that of edema. More than 95% and 76% of the patients with peripheral edema complained of swelling and heaviness, respectively, at the symptom checklist, but these symptoms were not necessarily associated with report of overt edema detected by the investigator, suggesting that they were also indicators of subclinical edema.

Lower limb swelling occurred significantly ($P < .001$) more often in the amlodipine (50% of patients) as compared to the lercanidipine (35%) and lacidipine treatment groups (34%) ($\chi^2 = 14.8671, P < .001$; OR: amlodipine versus lercanidipine 1.87 [1.32–2.65], lacidipine versus lercanidipine 0.95 [0.67–1.36]). Similarly, lower limb heaviness occurred significantly more with amlodipine (45% of patients) than with lercanidipine (33%) and lacidipine (31%) ($\chi^2 = 10.1803, P < .01$; OR: amlodipine versus lercanidipine 1.64 [1.15–2.34], lacidipine versus lercanidipine 0.90 [0.62–1.29]). Again most of the patients had already complained of these symptoms in the first 6 months of treatment. On the contrary, the incidence of

### Table 1. Baseline characteristics of the 828 patients before randomization to treatment (means ± SD)

<table>
<thead>
<tr>
<th></th>
<th>Lercanidipine ($n = 420$)</th>
<th>Aamlodipine ($n = 200$)</th>
<th>Lacidipine ($n = 208$)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (y)</strong></td>
<td>70 ± 6</td>
<td>70 ± 6</td>
<td>69 ± 6</td>
</tr>
<tr>
<td><strong>Gender — m/f (%)</strong></td>
<td>49/51</td>
<td>42/58</td>
<td>54/46</td>
</tr>
<tr>
<td><strong>Height (cm)</strong></td>
<td>164 ± 8</td>
<td>163 ± 8</td>
<td>164 ± 8</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>73 ± 12</td>
<td>72 ± 11</td>
<td>73 ± 13</td>
</tr>
<tr>
<td><strong>Clinic SBP (mm Hg)</strong></td>
<td>170 ± 10</td>
<td>171 ± 11</td>
<td>170 ± 10</td>
</tr>
<tr>
<td><strong>Clinic DBP (mm Hg)</strong></td>
<td>97 ± 6</td>
<td>97 ± 7</td>
<td>97 ± 6</td>
</tr>
<tr>
<td><strong>Clinic HR (beats/min)</strong></td>
<td>74 ± 10</td>
<td>73 ± 9</td>
<td>74 ± 9</td>
</tr>
<tr>
<td><strong>History of hypertension (%)</strong></td>
<td>90</td>
<td>93</td>
<td>91</td>
</tr>
<tr>
<td><strong>Duration of hypertension (y)</strong></td>
<td>8 ± 7</td>
<td>9 ± 8</td>
<td>8 ± 8</td>
</tr>
<tr>
<td><strong>Treatment of hypertension (%)</strong></td>
<td>71</td>
<td>74</td>
<td>72</td>
</tr>
<tr>
<td><strong>Family history of hypertension (%)</strong></td>
<td>47</td>
<td>46</td>
<td>49</td>
</tr>
<tr>
<td><strong>Smoking (%)</strong></td>
<td>17</td>
<td>12</td>
<td>16</td>
</tr>
<tr>
<td><strong>BMI &gt;30 (%)</strong></td>
<td>21</td>
<td>21</td>
<td>23</td>
</tr>
<tr>
<td><em><em>Hypercholesterolemia</em> (%)</em>*</td>
<td>32</td>
<td>40</td>
<td>36</td>
</tr>
<tr>
<td><strong>Diabetes mellitus (%)</strong></td>
<td>11</td>
<td>15</td>
<td>13</td>
</tr>
<tr>
<td><strong>History of cardiovascular disease (%)</strong></td>
<td>4</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td><strong>Varicose veins (%)</strong></td>
<td>15</td>
<td>17</td>
<td>16</td>
</tr>
</tbody>
</table>

SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate; BMI = body mass index.* Total cholesterol >220 mg/dL.
other symptoms did not differ between groups (Table 2, lower part).

**Well-Being Status**

A significant \( P = .0001 \) improvement in the general well-being status as compared to baseline was seen for all the three treatment groups and time period (Fig. 3), without any difference between groups. As expected, smaller positive changes in well-being were observed in the first 6 months of treatment when most of the adverse events occurred.

**Laboratory Tests**

Treatment with the three drugs was accompanied by either no change or by small and not significant increases or reductions in the various hematology and blood chemistry values considered in the study. No increase in the number of patients with abnormal findings, as assessed by the investigator, was seen during treatment as compared to pretreatment values.

**Blood Pressure**

After 6 months of treatment sitting SBP and DBP were significantly \( P < .01 \) reduced by lercanidipine (adjusted mean reduction from baseline \( \pm SE \): 29.6 \( \pm \) 0.7/14.3 \( \pm \) 0.4 mm Hg), amlodipine (29.7 \( \pm \) 1.1/14.5 \( \pm \) 0.6 mm Hg), and lacidipine (29.4 \( \pm \) 1.0/14.0 \( \pm \) 0.6 mm Hg). No significant differences were observed in SBP and DBP reductions obtained by the three treatment regimens (Fig. 4, top and middle). Similar changes were observed for values collected in the smaller groups of patients continuing the study for more than 6 months and therefore entering in the analysis at 12, 18, or 24 months.

Standing BP was also reduced to the same extent by the
three treatments. During the first 6 months of treatment, standing SBP and DBP were reduced from 168.8 ± 11.0/98.3 ± 6.9 to 140.3 ± 15.4/84.1 ± 8.9 mm Hg with lercanidipine, from 169.7 ± 10.3/97.3 ± 7.8 to 140.6 ± 14.8/83.3 ± 9.4 mm Hg with amlodipine, and from 168.7 ± 10.2/97.5 ± 6.9 to 141.4 ± 16.7/84.4 ± 9.3 mm Hg with lacidipine, respectively (P < .001 for all), with no differences between the three treatment groups. No evidence of hypotension upon standing was observed.

Responder Rates and Combination Therapy

After 6 months of treatment the percentage of responder patients, normalized patients, and patients who needed

Table 2. Relative distribution (%) of adverse events spontaneously reported by patients or detected by the investigator and of elicited symptoms, as indicated by patients in the symptom checklist

<table>
<thead>
<tr>
<th></th>
<th>Lercanidipine (n = 420)</th>
<th>Amlodipine (n = 200)</th>
<th>Lacidipine (n = 208)</th>
<th>χ² (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse events</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edema</td>
<td>9.3</td>
<td>19</td>
<td>4.3</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Headache</td>
<td>4.8</td>
<td>2.5</td>
<td>3.9</td>
<td>NS</td>
</tr>
<tr>
<td>Astenia</td>
<td>3.8</td>
<td>3.0</td>
<td>2.9</td>
<td>NS</td>
</tr>
<tr>
<td>Vertigo</td>
<td>2.9</td>
<td>4.5</td>
<td>1.4</td>
<td>NS</td>
</tr>
<tr>
<td>Palpitation</td>
<td>2.6</td>
<td>1.5</td>
<td>4.3</td>
<td>NS</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1.9</td>
<td>3.5</td>
<td>1.9</td>
<td>NS</td>
</tr>
<tr>
<td>Flushing</td>
<td>2.9</td>
<td>2.5</td>
<td>2.9</td>
<td>NS</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>1.7</td>
<td>0.5</td>
<td>0.5</td>
<td>NS</td>
</tr>
<tr>
<td>Symptoms*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower limb swelling</td>
<td>35</td>
<td>50</td>
<td>34</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Lower limb heaviness</td>
<td>33</td>
<td>45</td>
<td>31</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Fatigue</td>
<td>37</td>
<td>34</td>
<td>32</td>
<td>NS</td>
</tr>
<tr>
<td>Dizziness</td>
<td>30</td>
<td>35</td>
<td>30</td>
<td>NS</td>
</tr>
<tr>
<td>Headache</td>
<td>28</td>
<td>27</td>
<td>33</td>
<td>NS</td>
</tr>
<tr>
<td>Flushing</td>
<td>24</td>
<td>26</td>
<td>24</td>
<td>NS</td>
</tr>
<tr>
<td>Tachycardia or palpitation</td>
<td>24</td>
<td>18</td>
<td>20</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS = not significant.

* A symptom checklist was filled in by 402 of 420, 191 of 200, 200 of 208 patients on lercanidipine, amlodipine, and lacidipine, respectively.

FIG. 3. Average changes (%) in well-being status assessed by visual analog scale (VAS) in the intention-to-treat population at 6 months (n = 828) and in groups of patients continuing treatment and entering in the analysis at 12, 18, and 24 months. Data are separately shown for the lercanidipine (open bar), amlodipine (striped bar), and lacidipine (solid bar) treatment groups.

FIG. 4. Sitting systolic (SBP, top) and diastolic (DBP, middle) blood pressure and heart rate (HR, bottom) in the intention-to-treat population at 6 months (n = 828) and in groups of patients continuing treatment and entering in the analysis at 12 (n = 528), 18 (n = 323), and 24 (n = 153) months. Data are separately shown for the lercanidipine (open circles and dashed lines), amlodipine (open square and dashed line), and lacidipine (closed circles and solid line) treatment groups (means ± SD). B = baseline.
combination therapy with atenolol or enalapril, plus eventually hydrochlorothiazide, was similar between the three treatment groups (Fig. 5). The same percentage was displayed by the groups of patients entering in the analysis at 12, 18, and 24 months of treatment.

Heart Rate and ECG

Sitting heart rate was similar before and during treatment (Fig. 4, bottom). As expected, heart rate was slightly increased by standing up, but still no differences were observed during treatment with lercanidipine, amlodipine, or lacidipine (data not shown). No increase in the number of patients with abnormal findings on ECG was seen during treatment as compared to pretreatment values.

Additional Analysis

To evaluate whether the antihypertensive effect was linked to the occurrence of peripheral edema as an adverse event, an additional statistical analysis was performed for sitting DBP in the first 6 months. No difference in the magnitude of the antihypertensive effect was observed in patients with and without peripheral edema (ANCOVA: treatment $P = .4452$, edema $P = .1011$, treatment by edema $P = .5452$). In addition, as concomitant treatments may have an influence on the occurrence of peripheral edema during calcium antagonist therapy, the same analysis was performed at week 4 (ie, at a time when all patients were on low-dose monotherapy with 10 mg of lercanidipine, 5 mg of amlodipine, or 2 mg of lacidipine). Again no difference in the magnitude of the antihypertensive effect was observed in patients with and without edema (ANCOVA: treatment $P = .2233$, edema $P = .4555$, treatment by edema $P = .4939$).

Per Protocol Analysis

Five hundred sixty-four patients (289, 129, and 146 patients in the lercanidipine, amlodipine, and lacidipine group, respectively) entered in this analysis. The results were consistent with the intention-to-treat analysis for all efficacy parameters.

Discussion

Irrespective of their clinical relevance, the occurrence of side effects per se cannot be considered a negligible problem. A limited compliance with the prescribed treatment is one of the main causes of therapeutic failures, in particular concerning chronic therapies for diseases like hypertension, which are silent.$^{4,16-18}$ To evaluate the efficacy of antihypertensive therapy tolerability is, therefore, at least equally important as effectiveness, because the practical value of any therapy depends on a combination of effectiveness and the extent to which the patients comply with the proper administration. Often different classes of agents are compared,$^{4}$ but different tolerability is also found between compounds of the same class.$^{12}$

This study was focused on the evaluation of the incidence of peripheral edema, which is frequently associated with treatment based on dihydropyridine calcium antagonists,$^{19-21}$ but all adverse events were taken into consideration. In addition, as there is often a gap between the physicians’ perception of tolerability and the real experi-
ence of the patients, the possible occurrence of symptoms was also evaluated by means of a symptom checklist.

As expected, peripheral edema was the most common adverse event recorded in the patients of the study and was the most common reason for patient’s withdrawal. Peripheral edema, edema-related symptoms, and withdrawal due to edema occurred much more frequently in the amlodipine than in the lercanidipine and lacidipine treatment groups. On the contrary, the incidence of other adverse events or symptoms typical of calcium antagonists (such as flushing, headache, dizziness, asthenia, palpitation) did not differ significantly among treatments.

There are some other points to be discussed with regard to occurrence of peripheral edema in this study. First, the different incidence of edema in the three treatment groups was not related to a greater BP lowering effect exerted by amlodipine. The magnitude of the BP decrease was similar for the three treatment regimens and no difference in the magnitude of the antihypertensive effect was observed in patients with and without ankle edema. Second, combined treatment did not influence the different occurrence of peripheral edema in the three groups, even if angiotensin converting enzyme inhibitors have known to alleviate lower extremity edema induced by dihydropyridine calcium antagonists. In fact, the proportion of patients requiring additional antihypertensive therapy was not significantly different among groups and, in addition, the greater incidence of edema with amlodipine was already evident since the first visits when the patients were still treated only with dihydropyridines.

Dihydropyridine-associated edema is ascribed to an increase of fluid filtration from the vascular to the interstitial compartment due to an increase in intracapillary hydrostatic pressure, caused by a more pronounced inhibition of vascular tone in precapillary than in postcapillary resistance vessels. Different hypotheses can be made on the possible mechanisms responsible for the lower incidence of edema in patients treated with lercanidipine or lacidipine. One mechanism may be a smaller discrepancy between arteriolar and venular vasodilation with these two drugs, possibly caused by a lower sympathetic activation and consequently, a smaller vеноconstriction than with amlodipine. This lesser activation has been shown when lercanidipine was compared to felodipine and no comparison with amlodipine has yet been made, but amlodipine is known to induce a more marked sympathetic activation than other dihydropyridines despite an unchanged heart rate. Different actions on vascular permeability and consequent fluid extravasation, however, cannot be excluded.

Another important observation, which is provided by this study, is that the three drugs did not cause any increase in heart rate at rest, in the sitting or upright position, confirming that chronic treatment with a long-acting calcium antagonist does not significantly change the heart rate. This is clinically relevant, because heart rate has been shown to be an important cardiovascular risk factor in the general population, its increase being potentially more unfavorable when an additional risk factor such as arterial hypertension is already present.

This study also showed an improvement in general well-being status in all the treatment groups, in line with what was observed in some previous studies with dihydropyridine calcium antagonists, although other studies have reported no change in quality of life or worsened symptoms.

A secondary end point of this study was a comparison of lercanidipine efficacy with that of the other two dihydropyridine calcium antagonists. The antihypertensive efficacy of the three drugs was superimposable both in terms of average BP changes from baseline and in terms of responder rates and percent of patients requiring combination treatment. All three treatment regimens did not induce postural hypotension, which should be avoided in elderly patients.

In conclusion, with the same BP-lowering efficacy, the two lipophilic dihydropyridine calcium antagonists, lercanidipine and lacidipine, show a significantly better tolerability profile than amlodipine, and consequently a better compliance to a long-term antihypertensive therapy with these drugs can be reasonably expected.

**Appendix: List of Participants in the Study**

**Steering Committee:** A. Zanchetti (chairman), G. Leonetti, B. Magnani, A. Pessina, A. Rappelli, B. Trimarco.

**Participating centers:** A. Achilli (Viterbo), A. Albano (Taranto), F. Alabisini (Roma), B. Aloisi (Enna); G.B. Ambrosio (Venezia), A. Antonelli (Lucca), M. Aquilina (Forli), A. Barabino (La Spezia), G. Battistini (Cesena), C. Bellet (Brescia), G. Bolli (Perugia), A. Bordin (Venezia), P. Boscolo, M. Della Loggia (Chioggia), F. Bux (Bari), G. Calcare (Catania), V. Calcaterra (Catanzaro), C. Calvelli, G. Bisignani (Cosenza), P. Candia (Cosenza), A. Capucci (Piacenza), F. Carmignani (Trieste), G. Carrara (Piacenza), U.G. Cereda (Varese), S. Cicogna (L’Aquila), M. Cigolini (Cosenza), M. Cigolini, R. Corrocher (Verona), V. Conti (Iesi), F. Corbara (Padova), S. Cozzari (Perugia), E. Dal Monte (Ravenna), L.A. De Giorgio (La Spezia), I. De Luca (Bari), U. De Martino (Salerno), G. De Rinaldis (Lecce), G. Di Biase (Bologna), G. Di Marco (Chieti), A. Di Taranto (Foggia), V. Donadon (Pordenone), R. Fanelli (Foggia), G. Fantini (Modena), G. Faticanti (Frosinone); A. Ferrara (Napoli), F. Ferri (Roma), R. Fogari (Pavia), O. Garognoli (Perugia), E. Giovannini, G. Minardi (Roma), G. Granato Corigliano (Napoli), S. Guerrisi (Catania), A. Iacono (Napoli), N. Lanni (Benevento), R. Liberati (Perugia), G. Licata (Palermo), A. Lopizzo (Potenza), P. Maiolino (Padova), G. Maioranò (Bari), R. Maira (Catanzaritetta), C. Mancone (Frosinone), S. Mangiameli (Catania), G. Mannini (Arezzo), S. Mansueto (Palermo), F. Marchettà (Bologna), F. Marchi (Firenze), F. Mariello (Lecce), D.F. Martinò (Avellino), C. Mattiauda (Savona), F. Mirri

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References


