Verapamil treatment after coronary angioplasty in patients at high risk of recurrent stenosis

Eike Hoberg, Rainer Dietz, Udo Frees, Hugo A Katus, Bernhard Rauch, Albert Schömig, Gerhard Schuler, Franz Schwarz, Harald Tillmanns, Josef Niebauer, Wolfgang Kühbler

Abstract

Objective—To evaluate the efficacy of high-dose verapamil treatment (240 mg twice daily) in the prevention of angiographic restenosis after primary successful coronary angioplasty in patients at high risk of recurrent obstruction.

Design—A placebo controlled, double blind trial in which patients with stable angina pectoris and patients with unstable angina or non-Q wave infarction treated with 330 mg aspirin and 75 mg dipyridamole twice daily were randomised to a verapamil group or a control group. Follow up angiography was performed 6 months after angioplasty or sooner if signs of recurrent ischaemia developed.

Setting—University department of cardiology.

Patients—196 consecutive patients undergoing coronary angioplasty from the beginning of April 1987 to the end of March 1989 and meeting the selection criteria that included the presence of at least one of six predefined risk factors for restenosis. At the time of coronary angioplasty 113 patients had unstable angina or non-Q wave infarction and 83 had stable angina pectoris.

Results—In 89 (91%) patients in the verapamil group and in 83 (85%) control patients follow up angiograms were available. The restenosis rate was lower in the verapamil group (48.3%) than in the placebo group (62.7%) (odds ratio 0.56, 95% confidence interval (CI) 0.303 to 1.025 p = 0.059). Of the 172 patients in whom follow up angiograms were available, 24 (13 taking verapamil and 11 taking placebo) did not comply with the trial for more than 40 (34) days (mean (1 SD)). For the remaining 148 patients the restenosis rate was 47.4% in the verapamil group and 63.9% in the placebo group (odds ratio 0.52, 95% CI 0.271 to 0.993, p = 0.046). In the 97 patients with unstable angina or non-Q wave infarction the restenosis rate was not significantly influenced by verapamil (55.8% with verapamil v 62.2% with placebo, odds ratio 0.77, 95% CI 0.339 to 1.728, p = 0.520). In the 75 patients with stable angina pectoris the restenosis rate dropped from 63.2% with placebo to 37.8% with verapamil (odds ratio 0.36, 95% CI 0.137 to 0.917, p = 0.038).

Conclusion—The observed beneficial effect of high-dose verapamil treatment on the angiographic restenosis rate in patients with stable angina pectoris and at increased risk of recurrent obstruction requires confirmation in further prospective studies.

The primary success rate of coronary angioplasty has increased from 64% in the first series of Grünzig et al.1 to over 90% in experienced centres today.2 Serious complications of the procedure are rare and have declined during the past few years.3 Restenosis rates, however, remained constant, or even tended to increase as procedures were performed in patients with more complex lesions and in patients with multivessel disease.4 5 6 16 The recurrence of stenosis is the major limitation of coronary angioplasty, especially in patients at high risk of restenosis after initially successful coronary angioplasty.

Proliferation of smooth muscle cells in the media and their migration towards the intima of the vessel wall lead to the development of restenosis after coronary angioplasty.7 7 17 Experimental data indicate that verapamil inhibits this process.18 19 20 We have investigated the efficacy of verapamil in preventing restenosis in patients who are at increased risk for recurrent obstruction. Because chronic and acute ischaemic syndromes3 20 may respond differently to therapeutic interventions we studied the effect of verapamil on the development of restenosis in patients with stable angina pectoris and in patients with unstable angina or acute non-Q wave infarction.

Patients and methods

PATIENTS

During the recruitment period, from the start of April 1987 to the end of March 1989, 1325 coronary angioplasty procedures were performed in 1076 patients at our laboratory. Primary success (>20% reduction in diameter stenosis without major procedure-related complications within 48 hours) was achieved in 1418 (91.4%) of the 1551 narrowings and occlusions attempted. All 981 patients with initially successful coronary angioplasty (patient-related primary success rate = 91.2%) were screened for entry into the trial. Because of their possible interaction with verapamil, the decision of the treating physician to
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Verapamil, calcium antagonist (example, for secondary prevention after myocardial infarction or for the treatment of arterial hypertension) excluded 215 patients. Further predefined criteria for exclusion were acute transmural myocardial infarction (n = 131), age >70 years (n = 51), an earlier revascularisation procedure (n = 45), severe concomitant disease (n = 18), congestive heart failure (n = 6), bradycardia <50 beats/min (n = 1), and other reasons (n = 25). Of the remaining 489 patients 308 agreed to participate in the trial, but only 196 patients presented with at least one of the following predictors for restenosis that were defined according to clinical studies reported before 1986: diabetes mellitus, multivessel coronary artery disease, total or subtotal occlusion of the dilated segment, eccentric narrowing, proximal lesion of the left anterior descending coronary artery, and residual stenosis of ≥30%. These patients were randomly assigned either to placebo (n = 98) or to treatment with verapamil (n = 98). To allow separate analysis of restenosis rates in chronic and acute ischaemic syndromes, patients with stable angina pectoris (n = 83) and patients with unstable angina or non-Q wave infarction (n = 113) were randomised as different subgroups. The unstable angina and non-Q wave infarction subgroup included 25 patients with recent onset angina, 45 patients with crescendo angina, eight patients with angina at rest, 31 patients with post-infarction angina, and four patients with non-transmural myocardial infarction within the last week.

STUDY PROTOCOL
Enrolled patients were randomly assigned in a double blind fashion to either the placebo group or the treatment group. The study drugs were provided for 7 months by the manufacturer as uniform tablets in numbered lots, beginning with sample No 1 for patients with stable angina pectoris and beginning with sample No 260 for patients with unstable angina or non-Q wave infarction. The patients received 2 months' supply of the study medication at hospital discharge. Two outpatient examinations were scheduled for 2 and 4 months after coronary angioplasty. On these occasions, the patient's history was taken and a 12 lead electrocardiogram was recorded. In addition, adherence to drug treatment was checked by pill counts, and the drug supply for the next 2 months was handed out to the patients. Six months after enrolment the patients were admitted to hospital for follow up angiography. Repeat angiography was performed early if symptoms of recurrent myocardial ischaemia suggested restenosis. The variables evaluated in the trial were presence or absence of angiographic restenosis, cardiac death, and myocardial infarction in the area supplied by the target coronary vessel if early follow up angiography did not confirm the clinical evidence of recurrence of obstruction, the patient continued to take the initially assigned medication, until final follow up angiography was performed at 6 months after enrolment. The study protocol was approved by the local ethics committee of the university of Heidelberg.

ANGIOPLASTY PROCEDURE
Before coronary angioplasty all patients were routinely premedicated with aspirin 330 mg plus dipyridamole 75 mg twice daily. Heparin (15,000 units) was injected intravenously just before the procedure. Dilatation was performed by a steerable technique with 8F guiding catheters. Angiograms were filmed in at least two orthogonal views before and after the angioplasty. Nitrates and calcium antagonists were not routinely given during the procedure.

POST-PROCEDURE MEDICATION
Heparin was infused intravenously at a rate of 1250 units per hour for 4–16 hours. After the groin sheath was removed 4–6 hours later, 7500 units heparin was given subcutaneously three times a day for the next 24 hours. Antiplatelet therapy with aspirin (330 mg) and dipyridamole (75 mg) was given twice a day for 6 months. Patients who entered the trial were given either verapamil 240 mg (Isopet RR, Knoll, Ludwigshafen, Germany) twice daily or placebo twice daily, starting on the first to third day after coronary angioplasty, and ending on the morning before follow up angiography. Concomitant treatment with β blockers or calcium antagonists for more than 3 days resulted in the exclusion of the patient. Other medication could be prescribed by the private physician.

MEASUREMENT OF CORONARY STENOSIS
Films were evaluated by two independent experts who were blinded to the identity and to the treatment of the patients. Measurements taken with computerised calipers at the smallest luminal diameter were compared with the closest normal segment and were averaged in two projections. The degree of stenosis expressed as the percentage reduction in luminal diameter was calculated as the mean of the measurements of both experts. We took great care to use the same projections for the analysis of all three angiograms for each patient. Restenosis was defined as ≥50% loss of the initial gain in stenosis reduction (National Heart, Lung and Blood Institute [NHLBI]) criterion IIb).

The mean difference in percentage reduction in luminal diameter before coronary angioplasty between both observers was 3.7 (2.7)% corresponding to an interobserver variability (difference of the two measurements divided by the mean value × 100) of 4.5 (3.6)%. Because computerised angiographic analysis with an automatic edge detection algorithm became available only after much of a the trial had been completed we retrospectively validated our mode of measurement in a random sample of 24 follow up angiograms (12 from the verapamil group and 12 from the placebo group). A third independent expert, who was blinded to the identity...
and the treatment of the patients, compared the results of the callipers method with the results of the Kontron Mipron image-processing system in combination with an automatic edge detection algorithm as described in detail earlier. The correlation for the two methods was $r = 0.92$ ($p < 0.0001$) with a slope of 0.88 and a $y$ intercept of 1.55%.

**Statistical Analysis**

We estimated that we needed to study at least 150 patients, assuming that a decrease of $>50\%$ in restenosis rate is clinically relevant. Because we selected patients at high risk, the restenosis rate in the placebo group was assumed to exceed 45%. With a presumed drop-out rate of 25%, 200 patients needed to enter the study to allow for a sufficient statistical power ($alpha = 0.05$, $beta = 0.2$) in a two-tailed test and for an efficacy analysis (compliant patients with available control angiography) in addition to a modified intention-to-treat analysis (all enrolled patients in whom follow up angiography was available). Based on experience in 1986 we decided on a recruitment period of two years.

We examined the homogeneity of the patient groups in terms of age, sex, demographic factors, history, and angiographic factors by appropriate parametric and non-parametric tests. The odds ratio and its 95% confidence interval were used to describe the relative risk for restenosis in the treatment group. Probabilities were regarded as statistically significant at the 0.05 level. Unless otherwise indicated, values are given as the mean (1 SD).

**Results**

**Baseline Characteristics**

Table 1 shows the clinical and angiographic characteristics of the treatment group and the placebo group. The incidence of diabetes mellitus was low and unbalanced (14% in the verapamil group vs 4% in the placebo group, $p < 0.05$). None of the other baseline patient characteristics or the characteristics of the dilated lesion in the two groups differed significantly. The mean number of risk factors for restenosis was 2.5 (1-0) in the verapamil group and 2.4 (0-9) in the placebo group (NS).

**Adherence to the Study Protocol**

Eighty-nine patients in the verapamil group (91%) and 83 patients in the placebo group (85%) had follow up angiography and were analysed on the modified intention-to-treat basis. Despite the availability of a follow up angiogram, 13 patients in the verapamil group and 11 patients in the placebo group were excluded from the efficacy analysis because they stopped taking the prescribed study medication after 40 (34) days and 41 (55) days respectively. Verapamil-related adverse side effects caused the withdrawal of three patients (constipation, dizziness, rise in circulating liver enzymes). Other reasons for dropping out were similar in patients on verapamil and in patients on placebo: in both groups four patients refused to participate in the trial after discharge from the hospital. In five patients in the verapamil group and in four patients in the placebo group $beta$ blockers or calcium antagonists were given by the private physician instead of the study medication. Tachycardia or high blood pressure or both were the reasons for stopping participation for three patients in the placebo and for one patient in the verapamil group, who had been on $beta$ blocker therapy before coronary angioplasty.

Death or myocardial infarction did not occur in either group during the study period. Twenty patients in the verapamil group and 25 patients in the placebo group developed signs of recurrent ischaemia and early repeat angiography confirmed restenosis after 83 (46 days) (verapamil group) and after 73 (28 days) (placebo group) after coronary angioplasty (NS). In one other patient who presented with recurrent angina, coronary angiography was performed 6 weeks after dilatation but it showed a sustained success of the procedure. According to the study protocol this patient continued to take the assigned study medication and underwent repeat angiography at 6 months after enrolment.

**Restenosis**

The mean diameter stenosis in the 172 patients for whom follow up angiograms were available decreased from 86.4 (8.5%) before coronary angioplasty to 34.8 (14.5%) immediately after. There were no significant differences between the two groups. At follow up angiography the mean coronary obstruction had increased by 26.9 (24.6%) in the verapamil group and by 31.9 (29.0%) in the placebo group ($p = 0.11$). In the 172 patients with a follow up angiogram restenosis occurred in 48.3% in the verapamil group and 62.7% in the placebo group (odds ratio 0.56, 95% CI 0.303 to 1.025, $p = 0.059$). In the 148 patients, who actually received the treatment, the difference in restenosis rate between the two groups was statistically significant (odds ratio 0.52, 95% CI 0.271 to 0.993, $p = 0.046$). The cumulative distribution curves of the lesions before dilatation and
immediately after coronary angioplasty were similar in the two groups (fig 1). At follow up angiography the lesion distribution curve of the verapamil group showed a shift to the left indicating a higher incidence of low degree lesions compared with the placebo group (fig 1).

STABLE ANGINA PECTORIS COMPARED WITH UNSTABLE ANGINA OR NON-Q WAVE INFARCTION

Baseline demographic data and lesion-related characteristics were similar in the verapamil groups and the placebo groups with stable angina (n = 83) and unstable angina or non-Q wave infarction (n = 113) (table 2). In the 97 patients with unstable angina or non-Q wave infarction in whom follow angiography was available high-dose verapamil treatment did not significantly influence the development of restenosis after coronary angioplasty (restenosis rates 55-8% with verapamil and 62-2% with placebo, p > 0-15) (table 3). The cumulative distribution curve of the lesions at follow up angiography showed a slight shift to the left in the verapamil group compared with the placebo group (fig 2). Efficacy analysis of the 81 compliant patients gave similar results (table 3).

In contrast to the group with unstable angina, in the 75 patients with stable angina pectoris and a follow up angiogram the restenosis rate decreased significantly from 63-2% with placebo to 37-8% with verapamil (odds ratio 0-36, 95% CI 0-137-0-917, p = 0-038) (table 3). The cumulative distribution curve of the lesions at follow up was shifted to

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**Table 2** Characteristics related to the patient and lesion in 113 patients with unstable angina or non-Q wave infarction and in 83 patients with stable angina pectoris

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Unstable angina</th>
<th>Stable angina</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient related</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>54-0 (7-8)</td>
<td>54-8 (6-5)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>77</td>
<td>82</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>18</td>
<td>7</td>
</tr>
<tr>
<td>Arterial hypertension by history (%)</td>
<td>47</td>
<td>54</td>
</tr>
<tr>
<td>Hyperlipidaemia by history (%)</td>
<td>54</td>
<td>54</td>
</tr>
<tr>
<td>Peripheral arterial disease (%)</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>Previous myocardial infarction (%)</td>
<td>44</td>
<td>48</td>
</tr>
<tr>
<td>Multivessel coronary artery disease (%)</td>
<td>37</td>
<td>41</td>
</tr>
<tr>
<td><strong>Lesion related</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proximal lesion of the left anterior</td>
<td>70</td>
<td>70</td>
</tr>
<tr>
<td>Descending coronary artery (%)</td>
<td>60</td>
<td>41</td>
</tr>
<tr>
<td>Eccentric narrowing (%)</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>Subtotal/total occlusion (%)</td>
<td>85-3 (8-6)</td>
<td>86-9 (8-6)</td>
</tr>
<tr>
<td>% Stenosis before angioplasty (mean)</td>
<td>55-1 (12-4)</td>
<td>56-0 (17-5)</td>
</tr>
<tr>
<td>% Residual lesion ≥30% (%)</td>
<td>72</td>
<td>64</td>
</tr>
</tbody>
</table>

**Table 3** Results of the modified intention-to-treat analysis (all patients with available control angiography) and of the efficacy analysis (compliant patients for whom follow up angiograms were available in the prospectively stratified subgroups of stable angina pectoris and unstable angina or non-Q wave infarction.

<table>
<thead>
<tr>
<th>Restenosis rate (%)</th>
<th>Verapamil</th>
<th>Placebo</th>
<th>Odds ratio (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intention-to-treat:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unstable angina (n = 97)</td>
<td>55-8</td>
<td>62-2</td>
<td>0-77 (0-339 to 1-728)</td>
<td>0-52</td>
</tr>
<tr>
<td>Stable angina (n = 75)</td>
<td>37-8</td>
<td>63-2</td>
<td>0-36 (0-137 to 0-917)</td>
<td>0-038</td>
</tr>
</tbody>
</table>

At treated:  
| Unstable angina (n = 81) | 60-5 | 65-8 | 0-80 (0-316 to 1-992) | 0-62 |
| Stable angina (n = 67)   | 30-3 | 61-8 | 0-27 (0-096 to 0-754) | 0-03 |
Discussion
We found that high dose verapamil treatment reduced the restenosis rate in patients with stable angina pectoris but not in patients with unstable angina or non-Q wave infarction. We studied only patients at increased risk for restenosis so it may be that the beneficial effect of verapamil is limited to this group.

Comparison with other clinical studies
Three earlier trials have not shown that calcium channel blockers have a beneficial effect on restenosis rate after coronary angioplasty. Corcos et al investigated the influence of 90 mg diltiazem three times daily in a prospective randomised trial including 92 patients without variant angina or previous coronary bypass surgery.15 Although the restenosis rate (defined as \( \geq 70% \) coronary obstruction at follow up angiography) was lower in the diltiazem group (15%) than in the control group (22%), this difference was not statistically significant. More recently O'Keefe and colleagues reported on a randomised trial evaluating the effect of a higher dose of diltiazem (mean 329 mg/day) in 201 patients without evolving myocardial infarction.13 Follow up angiography at one year was obtained in 60% of the patients. It showed no significant difference between the restenosis rates in the diltiazem (36%) and placebo groups (32%).

Whitworth et al investigated the influence of nifedipine on the development of restenosis in 241 patients without documented coronary artery spasm.11 At a dose of 40 mg daily this calcium antagonist did not reduce the restenosis rate after coronary dilatation (28% in the nifedipine group v 29-5% in the placebo group). Differences in study design may account for conflicting results of these previous studies and the present trial.

Because we selected patients in whom the risk of restenosis was high the subsequent event rate was high too. This increased the statistical power of the study for detecting a possible beneficial effect of the treatment. In the diltiazem trial of Corcos et al,12 the small sample size combined with a low event rate, based on \( \geq 70% \) stenosis at follow up angiography as the definition of restenosis, may account for the result not being statistically significant despite of a reduction of one third in restenosis.

We used a high dose of verapamil because experimental data suggested that calcium blockers had an anti proliferative effect only at high plasma concentrations. The fact that verapamil treatment was stopped because of drug-specific side effects in only three patients indicates that treatment with 240 mg verapamil in slow release form twice daily is practicable and safe. The results of cell culture experiments indicated that the choice of calcium antagonist may be relevant. Verapamil was a more potent inhibitor of the proliferation of smooth muscle cells than nifedipine or diltiazem.16

The prospective stratification of patients into groups with stable angina and unstable angina or non-Q wave infarction allowed us to detect the selective inhibitory effect of verapamil treatment on the restenosis rate in patients with stable angina pectoris only. Earlier studies were not designed to detect any selective effects in stable and unstable angina.

Possible mechanism of action
Proliferation and migration of medial smooth muscle cells into the intima of the vessel wall are assumed to play major parts in the pathogenesis of restenosis after coronary angioplasty.1728 This process is mediated by platelet-derived growth factor and other proteins with similar or supplementary mitogenic effects.29 According to recent experiments with vascular smooth muscle cells in culture, calcium antagonists show a concentration-dependent inhibitory effect on several actions mediated by platelet-derived growth factor, including cell proliferation and an increase in the cytoplasmic concentration of free calcium.30 These findings accord with animal studies that showed inhibition of smooth muscle cell proliferation by calcium antagonists after localised arterial injury.31 Most smooth muscle cell proliferation seems to be completed within 10 days after injury of the vessel wall.32 The beneficial effect of verapamil on the restenosis rate after coronary angioplasty that we saw may therefore be caused by an inhibitory effect at this early stage of restenosis development.

The response to verapamil treatment depends on the clinical manifestation of coronary artery disease at the time of angioplasty: in unstable angina pectoris, the rupture of atherosclerotic plaques may initiate a cascade of events resulting in proliferative lesion properties that differ from those of fixed lesions in stable angina when the vessel wall is injured during coronary angioplasty. Treatment after dilatation will not affect the early stages of proliferation in most patients with unstable angina pectoris whereas it will in patients with stable angina.

Limitations of the study
We used computerised callipers to measure the percentage diameter reduction. This method is more precise than visual estimation, and in the present trial the interobserver variability was <5%. In recent studies, however, computerised angiographic analysis was preferred, because despite some limitations it may give more a reproducible and objective measure of lumen diameter narrowing.33 It
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seems unlikely that the result of the present study depends on the mode of measurement: the retrospective analysis of a subset of 24 follow up angiograms by a third independent expert showed a correlation at r = 0.92 between the computerised calipers method used throughout the present study and the Kontron Mipron image-processing system with an automatic edge detection algorithm. Because our study was a prospective, randomised and double-blinded trial with the measurement of each lesion performed blind by two experts, the number and extent of measurement errors are likely to be similar in the treatment and placebo groups. Furthermore, cumulative distribution curves of the lesions confirmed the results obtained by the calculation of restenosis rates (figs 1–3). Nevertheless, our data need to be confirmed in a prospective trial using computerised angiographic measurement of absolute luminal diameter.

A limitation of the study design is the time at which the measurement started. Because patients were enrolled only after successful coronary angioplasty, treatment started on the first to third day after the procedure. Experimental studies, however, indicate that restenosis begins to develop within the first days after injury to the vessel wall.12 Earlier treatment with verapamil might have had a more pronounced effect on the restenosis rate.

To increase the number of events (recurrent obstructions) only patients at high risk for restenosis were enrolled into the present trial and the results only apply to this subgroup of coronary angioplasty patients. The restenosis rate in the placebo group was much higher than the rate of 45%, which was assumed for the estimation of the minimum sample size. This high restenosis rate is not typical of the catheter laboratory at the University of Heidelberg: the restenosis rate in unselected patients was 28% in those with stable angina and 38% in those with unstable angina in a previous series of 328 patients in the same laboratory.34 The selection of patients at high risk for recurrent obstruction may not only explain the high restenosis rate in the present trial but also the similar recurrence rates in patients with stable angina and those with unstable angina in the placebo group. The calculated rate of restenosis depends on the definition applied. According to a comparative study of Serruys et al35 the use of NHLBI criterion IV, which was prospectively selected for the present trial, results in higher restenosis rates than other criteria such as >50% stenosis at follow up angiography or NHLBI criteria I, II, or III. The cumulative distribution curves at follow up showed a similar treatment effect on restenosis rates. In the present study the difference between the placebo group and the verapamil group in patients with stable angina pectoris was most pronounced for coronary obstructions of about 50%. The treatment effect would have been missed by the use of NHLBI criterion II (>70% stenosis at follow up), which was applied by Corcos and colleagues to the evaluation of diltiazem treatment12 (see figs 1 and 2).

IMPLICATIONS OF THE TRIAL

Aspirin has been shown to reduce the incidence of myocardial infarction early after successful coronary angioplasty, when the risk of thrombus formation at the site of the injured vessel is high.36 The restenosis rate at 6 months after the procedure, which seems to depend largely on the proliferation and migration of medial smooth cells, obviously cannot be influenced by aspirin.37,38 The observed beneficial effect of verapamil on the angiographic restenosis rate in patients with stable angina may be due to the inhibition of this process which is mediated by growth factor. Hence combined medication with aspirin and verapamil in the early stage and the medication with verapamil alone thereafter may be effective during the first 4 months after coronary angioplasty in patients with stable anginapectoris. But before such an approach can be recommended the decrease in angiographic restenosis rate that we found was associated with treatment with a calcium antagonist needs to be confirmed in other studies.

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