Efficacy and Safety of Nimodipine in Subcortical Vascular Dementia

A Randomized Placebo-Controlled Trial

Leonardo Pantoni, MD, PhD; Teodoro del Ser, MD; Andrea G. Soglian, MD; Silvia Amigoni, BSC, PhD; Giovanni Spadari, BSC; Daniela Binelli, BSC; Domenico Inzitari, MD

Background and Purpose—Evidence of drug efficacy in vascular dementia (VaD) is scanty. Therapeutic trials should address VaD subtypes. We studied the efficacy and safety of the calcium antagonist nimodipine in subcortical VaD.

Methods—242 patients defined as affected by subcortical VaD based on clinical (ICD-10) and computed tomography criteria were randomized to oral nimodipine 90 mg/d or placebo.

Results—230 patients (121 nimodipine, mean age 75.2±6.1; 109 placebo, 75.4±6.0) were valid for the intention-to-treat analysis. At 52 weeks, the Sandoz Clinical Assessment Geriatric scale 5-point variation (primary outcome measure) did not differ significantly between the 2 groups. However, patients on nimodipine performed better than placebo patients in lexical production (P<0.01) and less frequently showed deterioration (3 or more point-drop versus baseline) on a Mini-Mental State Examination (28.1% versus 50.5%; \( \chi^2 P<0.01 \)) and Global Deterioration Scale (\( P<0.05 \)). Dropouts and adverse events were all significantly more common among placebo than nimodipine patients, particularly cardiovascular (30 versus 13; RR, 2.26; 95% CI, 1.11 to 4.60) and cerebrovascular events (28 versus 10; RR, 2.48; 95% CI, 1.23 to 4.98), and behavioral disturbances requiring intervention (22 versus 5; RR, 3.88; 95% CI, 1.49 to 10.12). A worst-rank analysis, performed to correct for the effect of the high dropout rate in the placebo group, showed additional significant differences in favor of nimodipine in Set Test and MMSE total scores.

Conclusions—Nimodipine may be of some benefit in subcortical VaD. Confirming previous results, the safety analysis of this study shows that in this high-risk population, nimodipine might protect against cardiovascular comorbidities.

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Key Words: cognition ■ dementia ■ dementia, vascular ■ nimodipine

Vascular dementia (VaD) is a common type of dementia but current therapeutic options are scarce. Under the term VaD, various conditions with considerably different pathophysiological mechanisms are included, and therapeutic choices in VaD should focus on specific subtypes. Subcortical VaD is likely the most frequent VaD subtype and has a rather homogeneous clinical, radiological, and pathological picture.2,3 The dihydropyridinic calcium antagonist nimodipine has been proposed as a drug able to improve cognition in VaD because of vasoactive and neuroprotective actions.4 Its effect on age-related microangiopathy in experimental models8 makes nimodipine of potential interest for the treatment of small-vessel VaD subtypes. After the results of an open-label study6 and a post-hoc analysis of a randomized trial,7 both showing some beneficial effects of nimodipine in patients with subcortical VaD features, an ad hoc designed trial was conducted to further test the efficacy and safety of oral nimodipine in subcortical VaD.

Materials and Methods

Study Design

This was an explorative multicenter, randomized, double-blind, placebo-controlled trial conducted between December 1996 and February 2002. The aim was to investigate the efficacy and safety of oral nimodipine in patients defined as affected by subcortical VaD based on ICD-10 criteria corroborated by neuroimaging criteria.

The patients underwent a 4-week, single-blinded placebo run-in period before being randomized to receive either 3×30 mg nimodipine or matching placebo tablets per day for 52 weeks. The study was performed under the good clinical practice regulations and according to the Declaration of Helsinki. The protocol and the information for the patients and caregivers were approved by each center local ethic committee. A review committee formed by the principal investigators, independent clinicians, and biostatisticians performed preplanned blind reviews and monitored the study course.

Study Patients

Inclusion criteria included ICD-10 criteria for subcortical VaD (dementia, hypertension, and evidence of vascular disease in the...
cerebral hemispheric deep white matter with cortical preservation); dementia syndrome for >6 months and <3 years, mild-to-moderate severity as defined by a Mini-Mental State Examination (MMSE) score ≥12 and ≤24, and a Global Deterioration Score ≥3 and ≤5; computed tomography scan performed not >3 months before baseline showing white matter changes of severe degree, ie, extending to the centrum semiovale (corresponding to grade 2 of van Swieten et al’s scale) and at least 1 definite image consistent with a lacunar infarct. These criteria were checked centrally before randomization by a single observer who, examining the scan of each candidate patient, adjudicated cases for enrollment. No new cerebrovascular event had to occur between computed tomography scanning and the baseline visit. Inclusion criteria also included age between 55 and 87 years; Hachinski ischemic score >4;6,12 expected good compliance to study medication and protocol; and informed written consent.

Exclusion criteria were: (1) past diagnosis of major depression, schizophrenia, major anxiety syndrome, or manic–depressive illness; (2) Alzheimer disease as defined using the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer’s Disease and Related Disorders Association criteria;14 Parkinson disease, Huntington disease, and fronto-temporal dementia; (3) other diseases known to cause dementia (eg, central nervous system trauma, tumor or infections, normal pressure hydrocephalus, metabolic disorders, folic acid, vitamin B12, or thyroid hormone deficiency; (4) contraindications to dibhydropropyridine derivatives; (5) medical conditions expected to progress, recur, or change to such a degree that interfere with the assessment of the clinical and mental status; (6) clinically relevant cardiac or pulmonary insufficiency; (7) relevant electrocardiograph abnormalities; (8) Bradycardia (<50 bpm) or tachycardia (>120 bpm) under resting conditions; (9) myocardial infarction within the past 6 months; (10) stroke still requiring neurological rehabilitation; (11) severe/uncontrolled blood pressure (systolic >180 mm Hg, diastolic >95 mm Hg); clinically relevant hepatic function impairment; (13) insulin-dependent diabetes mellitus; (14) idiopathic epilepsy and anti-epileptic treatment; (15) severe anemia (Hb <10 mg/dL); (16) severe gastrointestinal disease; and (17) cancer.

The intake of cerebral vasodilators, nootropic agents, and pentoxifyllin was not allowed. Other psychotropic drugs were allowed if started ≥3 or more months before the inclusion in the study and the dose was expected to be stable during the whole double-blind phase. Angiotensin-converting enzyme inhibitors, diuretics, β-blockers, verapamil, or diltiazem were allowed if the treatment had been initiated at least 6 weeks before inclusion. Permitted were also short-acting benzodiazepines, anti-arrhythmics, or antithrombotics.

Before the inclusion, all patient data were reviewed under blind conditions by the review committee to verify inclusion/exclusion criteria, concomitant diseases, and medications.

Efficacy Assessment

The effect of nimodipine compared with that of placebo was assessed using the following instruments: (1) Sandoz Clinical Assessment Geriatric (SCAG) scale,14 an inventory of 18 target symptoms (severity of each is rated by a 7-point scale) covering 4 areas: global cognition, mood and behavior, ability to cope with activities of daily living, and somatic symptoms; (2) Global Deterioration Score;10 (3) Set test13 and lexical production,16 exploring semantic and phonemic verbal fluency, respectively; (4) Digit Span17; (5) MMSE; (6) Zahlen-Verbindungs Test (ZVT-G);18 (7) gait performance test;19 (8) Nurses Observation Scale for Geriatric patients;20 an index of activities of daily living; (9) the Clinical Global Impression scale expressed in 7 classes (marked, moderate, or slight improvement; no effect; slight, moderate, or severe deterioration); and (10) Hamilton Depression scale.22

The main efficacy measure was the SCAG 5-point variation chosen on the results of the aforementioned pilot study. Here, in a pilot open design, similarly defined patients were administered nimodipine and were followed-up using similar assessment procedures. After 52 weeks, treatment patients showed a 5-point change compared with the baseline, a variation that was considered clinically meaningful based on investigators’, patients’, and relatives’ judgment. All the remaining test results served as secondary measures. Safety measures included recording of adverse events, blood pressure, cardiovascular vital signs, and laboratory data. To be classified as severe, adverse events had to be life-threatening or cause death, hospitalization, or prolongation of hospital stay. Other adverse events and the introduction of new drug treatments recorded in the case report form were checked by the monitoring agency and finally reviewed and classified blind to the treatment group by the review committee using the Coding Symbols for Thesaurus of Adverse Reaction Terms terminology.

Statistical Analyses

The needed sample size was calculated taking into account the following assumptions and hypotheses from the previously quoted pilot study.6–7 Considering the difference between groups by SCAG=5 points, standard deviation=11 points, an overall level of 5% for a 2-sided test with a 90% power (1–β), the required minimum number of valid patients was 100 per treatment group. Given an expected dropout of 20%, the total number of patients to be randomized was increased to 240.

The review committee included 3 samples of patients: (1) valid for efficacy (or per protocol); all randomized patients with evaluation made while on study drug at week 52; (2) intention-to-treat (ITT): patients receiving at least 1 dose of treatment and followed-up at least once; and (3) safety population: patients with a baseline evaluation and at least 1 dose of the tested drug. The baseline homogeneity of the treatment groups for demographic and baseline scores was evaluated with ANOVA for continuous variables and χ² test or Fisher exact test for categorical ones. Efficacy analysis was planned on the per-protocol sample using the 5-point cutoff variation. The SCAG total score was also analyzed by groups at the end of treatment period with an ANCOVA model, adjusting the final scores for the baseline ones. For patients not completing the 52-week treatment, the last observation carried forward approach was planned for the final evaluation in the ITT analysis.

Figure 1 accounts for the disposition of all the patients. A larger than expected number of patients discontinued, and discontinuations occurred mostly in the placebo group. Given the significantly unbalanced dropout rate, the results based on both the per-protocol and the ITT samples could be too conservative relating to nimodipine treatment and the last observation carried forward approach inadequate for a 1-year study of a progressive disease. Thus, besides the conventional analyses, a nonplanned worst-rank analysis23 was performed. In this approach, missing observations are considered informative when they have a suspected causal association with the patient’s underlying disease,24 a common fact in progressive diseases. Each missing informative observation is replaced with a rank score corresponding to a measurement value worse than any actually observed score and a rank analysis is subsequently performed. ANCOVA was used in this analysis.

Safety Analysis

The frequency of adverse events and the mean baseline and final blood pressure values were compared by treatment group. Absolute incidence rate of major events at 52 weeks was counted and relative risks (RRs) were calculated between nimodipine and placebo together with 95% confidence intervals (CIs).

Results

The total number of randomized patients was 242, 124 in the nimodipine and 118 in the placebo group. One hundred seven patients (86.3%) in the nimodipine and 77 (65.2%) in the placebo group completed the study (Fisher exact test P=0.0001). One hundred forty-nine patients, 94 in the nimodipine and 55 in the placebo group, were valid for the per-protocol analysis. Reasons for exclusion were: adverse events (4 nimodipine, 16 placebo); not allowed medication (7 nimodipine, 15 placebo); poor compliance (5 nimodipine, 3
placebo); consent withdrawn (7 nimodipine, 10 placebo); protocol violation (2 nimodipine, 4 placebo); lost to follow-up (2 nimodipine, 5 placebo); death (3 nimodipine, 7 placebo); and concomitant disease (3 placebo). Figure 1 shows timing of dropouts. A description of demographic and baseline characteristics of the ITT population is provided in Table 1. Physical examination alterations, history of smoking or drug allergy, and education level were all balanced between the groups. Use of concomitant medications at baseline was present in almost all patients in both groups.

**Efficacy Analyses**

When considering the primary end point effect, ie, a SCAG total score variation of >5 points comparing baseline versus end of study in the per-protocol population (Table 2), worsening was recorded in 13 of the 94 (13.8%) nimodipine-treated and in 13 (23.6%) of the 55 placebo-treated patients, a difference that was not statistically significant. Very similar results were obtained using the ITT population. Evaluating secondary outcome measures (Tables 3 and 4 show the results from per protocol and ITT analyses, respectively), patients on nimodipine performed significantly better on lexical production than placebo patients. A similar trend, although not statistically significant, was apparent for the Set Test.

A post-hoc analysis was also performed using different cutoffs for the MMSE score variations. Considering subgroups of patients with 1-, 2-, 3-, or 4-point differences from baseline MMSE score, the analyses gave significant results for both 2 and 3 cutoff points, not for 1 or 4. We decided to report the results achieved using the 3-point cutoff because they were considered to be clinically more sound. The proportion of patients worsening at least 3 points on MMSE total score after treatment was significantly lower among nimodipine (n=34; 28.1%) than placebo patients (n=55; 50.5%) (χ² P<0.01). A significant trend was also observed for the Global Deterioration Score scale with less patients using nimodipine (n=22, 18.2%) than placebo (37, 33.9%) being in the severe category at 52 weeks (P<0.05). When the whole data set was re-analyzed with the worst-rank approach, some differences emerged with statistical significance: MMSE, lexical production, and Set test scores after the 1-year duration of the study were significantly better among patients who were treated with nimodipine (Table 4).

**Safety**

A total of 239 patients were valid for the safety analysis, 124 in nimodipine and 115 in placebo group. Adverse events of any type were reported more frequently in the placebo than in the nimodipine group (180 versus 135; RR, 1.29; 95% CI, 1.15, 1.44; P=0.01). A significant trend was also observed for the Global Deterioration Score scale with less patients using nimodipine (n=22, 18.2%) than placebo (37, 33.9%) being in the severe category at 52 weeks (P<0.05). When the whole data set was re-analyzed with the worst-rank approach, some differences emerged with statistical significance: MMSE, lexical production, and Set test scores after the 1-year duration of the study were significantly better among patients who were treated with nimodipine (Table 4).

**TABLE 1. Demographic Characteristics of the Intention-to-Treat Population**

<table>
<thead>
<tr>
<th></th>
<th>Nimodipine (n=121)</th>
<th>Placebo (n=109)</th>
<th>Total Sample (n=230)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, no. %</td>
<td>70 (58)</td>
<td>67 (61)</td>
<td>137 (60)</td>
<td>0.59</td>
</tr>
<tr>
<td>Age, mean±SD</td>
<td>75.2±6.1</td>
<td>75.4±6.0</td>
<td>75.3±6.0</td>
<td>0.84</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>21.4±3.1</td>
<td>20.7±2.8</td>
<td>21.1±3.0</td>
<td>0.07</td>
</tr>
<tr>
<td>HIS</td>
<td>8.45±2.6</td>
<td>8.85±2.9</td>
<td>8.64±2.7</td>
<td>0.19</td>
</tr>
<tr>
<td>Disease duration, y</td>
<td>1.31±0.9</td>
<td>1.39±0.8</td>
<td>1.35±0.9</td>
<td>0.31</td>
</tr>
</tbody>
</table>

*Fisher exact test or ANOVA.

BMI indicates body mass index; HIS, Hachinski ischemic score.

**TABLE 2. Proportion of Patients Showing >5-Point Change on Sandoz Clinical Assessment Geriatric Scale**

<table>
<thead>
<tr>
<th></th>
<th>Improvement No. (%)</th>
<th>No Change No. (%)</th>
<th>Worsening No. (%)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nimodipine</td>
<td>34 (36.2)</td>
<td>47 (50.0)</td>
<td>13 (13.8)</td>
<td>94</td>
</tr>
<tr>
<td>Placebo</td>
<td>16 (29.1)</td>
<td>26 (47.3)</td>
<td>13 (23.6)</td>
<td>55</td>
</tr>
<tr>
<td>Total</td>
<td>50 (33.5)</td>
<td>73 (49.0)</td>
<td>26 (17.4)</td>
<td>149</td>
</tr>
</tbody>
</table>

χ² P=0.29.

Baseline vs end of study, per protocol population.
1.03–1.61). Significantly different was also the number of serious adverse events: 43 in the nimodipine and 66 in the placebo group (RR, 1.58; 95% CI, 1.03–2.42). No serious adverse event or study discontinuation was imputed to the study drug. No clinically meaningful abnormality in blood chemistry, urinalysis, and laboratory examinations was considered to be related to nimodipine. Mean blood pressure values did not change throughout the study, remaining consistent in the 2 groups (baseline: nimodipine 144/83 mm Hg; placebo 145/82; 26 weeks: nimodipine 142/81, placebo 142/82; 52 weeks: nimodipine 143/82, placebo 144/82). The most frequent adverse events were cardiovascular and cerebrovascular acute events. Eleven strokes occurred, 2 in the nimodipine group (1.6%) and 9 in the placebo group (7.8%); 10 transient ischemic attacks, 4 in the nimodipine group (3.2%) and 6 in the placebo group (5.2%); 7 hypertensive crises, all in the placebo group (6.1%); 9 myocardial infarctions, 3 in the nimodipine group (2.4%) and 6 in the placebo group (5.2%). Adverse events were further grouped into cardiac, cerebrovascular, psychiatric, neurological, and residual events (classification available on request). Compared with placebo, significantly less nimodipine-treated patients experienced cardiac, cerebrovascular, or psychiatric events, all events, and serious events (Figure 2).

**Discussion**

Being the first randomized, double-blind, controlled trial focusing on subcortical VaD, this study has to be considered exploratory. An unblinded controlled study and 2 open trials have been reported in similar patients. Although the primary outcome measure was not significantly altered by the active treatment, some secondary measures showed differences in favor of nimodipine, namely lexical production and the MMSE when a substantial 3-point change cutoff to assess improvement or worsening was used as an outcome measure. The first of these 2 results may indicate a positive effect in the executive function domain known to be selectively compromised in subcortical VaD. The worst-rank analysis we performed post-hoc to take into account the large dropout rate observed in the placebo group improved the results of some

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**TABLE 3. Scores of Neuropsychological, Functional, Motor, and Depression Scales**

<table>
<thead>
<tr>
<th></th>
<th>Nimodipine (n=94) Mean (±SD)</th>
<th>Placebo (n=55) Mean (±SD)</th>
<th>P* (vs baseline)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline 52 Weeks Baseline 52 Weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCAG</td>
<td>43.7 (13.0) 48.6 (16.4) 45.0 (12.6) 47.9 (16.1)</td>
<td>0.27</td>
<td></td>
</tr>
<tr>
<td>MMSE</td>
<td>20.0 (3.0) 19.2 (4.6) 20.5 (3.2) 19.1 (5.5)</td>
<td>0.60</td>
<td></td>
</tr>
<tr>
<td>Set Test</td>
<td>26.9 (10.5) 25.6 (11.2) 29.3 (11.8) 24.9 (11.7)</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td>Digit Span</td>
<td>2.4 (1.2) 2.2 (1.3) 2.6 (1.3) 2.6 (1.4)</td>
<td>0.15</td>
<td></td>
</tr>
<tr>
<td>Lexical Production</td>
<td>8.6 (5.9) 8.3 (5.6) 10.5 (6.2) 8.1 (6.9)</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>ZVT-G (seconds)</td>
<td>148.0 (86.6) 139.5 (82.8) 120.1 (80.0) 121.2 (87.3)</td>
<td>0.75</td>
<td></td>
</tr>
<tr>
<td>NOSGER</td>
<td>68.1 (17.7) 74.8 (19.7) 68.0 (13.7) 75.6 (17.3)</td>
<td>0.71</td>
<td></td>
</tr>
<tr>
<td>Hamilton</td>
<td>7.9 (5.1) 8.5 (6.3) 8.3 (5.2) 8.0 (5.0)</td>
<td>0.38</td>
<td></td>
</tr>
<tr>
<td>Motor performance</td>
<td>10.3 (3.2) 10.1 (3.1) 10.8 (3.2) 10.5 (3.4)</td>
<td>0.83</td>
<td></td>
</tr>
</tbody>
</table>

*ANOVA.

MMSE indicates mini-mental state examination; SCAG, Sandoz Clinical Assessment Geriatric Scale.

Per-protocol population.

**TABLE 4. Scores of Neuropsychological, Functional, Motor, and Depression Scales**

<table>
<thead>
<tr>
<th></th>
<th>Nimodipine (n=121) Mean (±SD)</th>
<th>Placebo (n=109) Mean (±SD)</th>
<th>P* (vs baseline)</th>
<th>ITT†</th>
<th>Worst Rank†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline 52 Weeks Baseline 52 Weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCAG</td>
<td>44.0 (12.8) 49.0 (16.1) 46.2 (12.7) 50.3 (16.1)</td>
<td>0.36 0.15</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMSE</td>
<td>20.1 (3.1) 19.2 (4.6) 20.0 (3.1) 18.4 (5.5)</td>
<td>0.10 &lt;0.01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Set Test</td>
<td>27.2 (10.7) 26.0 (12.4) 28.1 (12.1) 25.4 (12.8)</td>
<td>0.13 &lt;0.01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digit Span</td>
<td>2.5 (1.3) 2.2 (1.3) 2.6 (1.5) 2.5 (1.4)</td>
<td>0.43 0.27</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lexical Production</td>
<td>8.9 (6.2) 8.7 (5.9) 9.5 (6.7) 8.1 (7.0)</td>
<td>&lt;0.01 &lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ZVT-G (seconds)</td>
<td>142.4 (92.4) 133.6 (81.1) 131.2 (85.8) 128.9 (84.8)</td>
<td>0.38 n.a.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NOSGER</td>
<td>68.6 (18.1) 75.0 (19.8) 72.5 (16.8) 78.6 (19.4)</td>
<td>0.71 0.24</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hamilton</td>
<td>7.9 (5.3) 8.5 (6.5) 8.6 (5.5) 8.3 (5.0)</td>
<td>0.62 0.06</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor performance</td>
<td>10.3 (3.1) 10.1 (3.2) 10.3 (3.3) 10.1 (3.5)</td>
<td>0.82 n.a.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*ANOVA.† ANCOVA.† ANCOVA.

ITT and worst rank analyses.

ITT indicates intention-to-treat analysis (last observation carried forward).
efficacy measures in favor of treatment with nimodipine. This approach is based on the assumption that all the dropout patients deteriorated, which may be not necessarily true. However, more than half of the dropouts that occurred in the placebo group appeared somehow related to the underlying disease progression, eg, acute cardiovascular and cerebrovascular events, acute psychiatric episodes, or death. Another cause of dropout, ie, the introduction of not allowed medications, major sedatives necessary to control episodes of agitation in most cases, can also be considered an epiphenomenon of the underlying disease worsening.

Our study major limitation rests on the large dropout rate. Interestingly, dropouts and adverse events occurred much more frequently in the placebo group given the randomized and double-blind design of the study. The significantly fewer cardiovascular and cerebrovascular events observed in the nimodipine group, a finding already observed in another randomized double-blind study, could suggest a protective effect of nimodipine against vascular disease progression in this high-risk population. This effect does not seem to depend on an antihypertensive action because blood pressure values remained stable during the study period. Because the aim of the study was not to test the efficacy of nimodipine in the secondary prevention of vascular diseases, this observation has to be taken as hypothesis-generating.

A strength of our study may be the rigorous selection of patients. The computed tomography diagnosis of subcortical VaD, required to complement the clinical one, was based on strict criteria applied before randomization by 1 observer blind to the patient clinical data. The requirement of clinical criteria combined with neuroimaging findings of extensive leukoaraiosis associated with lacunar infarcts is consistent with the recently proposed criteria for subcortical VaD. Another study strength is the rather long duration of follow-up under blind conditions, which was double compared with other recent trials performed in VaD. It is worth noting that in our study, the placebo group outcome was less favorable than that shown by other recent trials in VaD, pointing toward a more severe progression in this VaD subtype of patients.

In conclusion, patients with subcortical VaD may benefit from treatment with oral nimodipine, although the observations of our study need to be corroborated by a larger controlled study.

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References


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