Morbidity and Mortality After Stroke, Eprosartan Compared With Nitrendipine for Secondary Prevention
Principal Results of a Prospective Randomized Controlled Study (MOSES)
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Background and Purpose—In hypertensive stroke patients, for the same level of blood pressure control, eprosartan will be more effective than nitrendipine in reducing cerebrovascular and cardiovascular morbidity and mortality.

Methods—A total of 1405 well-defined, high-risk hypertensives with cerebral event during the last 24 months (proven by cerebral computed tomography scan or nuclear magnetic resonance) were randomized to eprosartan or nitrendipine (mean follow-up 2.5 years). Primary end point was the composite of total mortality and all cardiovascular and cerebrovascular events, including all recurrent events.

Results—Randomization was successful without significant differences in the baseline characteristics. Blood pressure was reduced to a comparable extent without any significant differences between the 2 groups during the whole study period (150.7/84 mm Hg and 152.0/87.2 mm Hg with eprosartan and nitrendipine therapy to 137.5/80.8 mm Hg and 136.0/80.2 mm Hg, respectively, confirmed by ambulatory blood pressure monitoring). Moreover, already after 3 months, normotensive mean values were achieved, and 75.5% reached values <140/90 mm Hg with the eprosartan regimen and 77.7% with the nitrendipine regimen. During follow-up, in total, 461 primary events occurred: 206 eprosartan and 255 nitrendipine (incidence density ratio [IDR], 0.79; 95% CI, 0.66 to 0.96; P=0.014). Cardiovascular events were: 77 eprosartan and 101 nitrendipine (IDR, 0.75; 95% CI, 0.55 to 1.02; P=0.06); cerebrovascular events: 102 eprosartan and 134 nitrendipine (IDR, 0.75; 95% CI, 0.58 to 0.97; P=0.03).

Conclusions—The Morbidity and Mortality After Stroke, Eprosartan Compared With Nitrendipine for Secondary Prevention (MOSES) study was the first to compare an angiotensin II type 1 receptor antagonist with a calcium antagonist in secondary stroke prevention. In these high-risk hypertensive stroke patients, an early normotensive and comparable blood pressure was achieved. The combined primary end point was significantly lower in the eprosartan group. (Stroke. 2005;36:1218-1226.)

Key Words: eprosartan ■ hypertension ■ nitrendipine ■ stroke prevention

Hypertension is not only the major risk factor for primary stroke, but it also increases the risk of cardiovascular morbidity and mortality and recurrent strokes in patients after stroke. In spite of the importance of the secondary prevention, there are only a few studies in hypertensive stroke patients. The PROGRESS study was the first published large-scale prospective blood pressure study in secondary prophylaxis after stroke showing that a treatment regimen including an angiotensin-converting enzyme (ACE) inhibitor led to a 28% decrease in the rate of stroke when compared with placebo.1 But there are no further studies to compare the effect of various antihypertensive agents in secondary prevention of stroke. This was the reason to perform the Morbidity and Mortality After Stroke, Eprosartan Compared With Nitrendipine for Secondary Prevention (MOSES) study. The

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1218
study was created in 1997. The hypothesis was that in hypertensive stroke patients, for the same level of blood pressure control, eprosartan will be more effective than nitrendipine in reducing cerebrovascular and cardiovascular morbidity and mortality. The rationale to choose these drugs were cerebroprotective experimental effects of various sartans and the positive results of the Syst-Eur study in which nitrendipine reduced primary stroke and dementia.2

Methods

Study Organization

MOSES was a prospective, randomized, controlled multicenter study, and corresponded to the prospective, randomized, open, blinded end point (PROBE) design.3

MOSES was an investigator-initiated study involving patients from internal medicine and general medicine practices and hospitals in Germany and Austria. A blinded end point committee assessed all cerebrovascular and cardiovascular events. The data and safety monitoring board was blinded as well. The study protocol, amendments, and patients’ informed consent statements were submitted to and approved by the ethics committee of the Lower Saxony Regional Medical Association in Hannover and all involved local ethics committees in Germany and Austria. The trial was undertaken in accordance with the Declaration of Helsinki.

Study Population

The study started in October 1998, and inclusion of patients ended in February 2002. Patients had to be followed up for ≥2 years, with a maximum of 4 years. There was some delay in recruiting while the eprosartan patent was transferred from SmithKline Beecham to Solvay Pharmaceuticals. A total of 1405 hypertensives with a history of cerebrovascular events were included. Inclusion criteria were treatment requiring hypertension and a history of a cerebrovascular event (transient ischemic attack [TIA], focal neurological deficit, ischemic stroke, cerebral hemorrhage), documented by either cranial computer tomography (CT) or magnetic resonance scan (within the past 24 months before inclusion).

Exclusion criteria included internal carotid artery occlusion or stenosis >70%, manifest heart failure (New York Heart Association grade III–IV), age ≥85 years at the time of the cerebrovascular event, patients treated with anticoagulants for a cardiac arrhythmia, high-grade aortic or mitral valve stenosis, or unstable angina pectoris. Attendance was voluntary, and each participant signed written informed consent before inclusion.

Interventions

Pretreatment was stopped and patients were directly rolled over from their previous treatment to the randomized study medication (eprosartan or nitrendipine). Allocation numbers were associated with their previous treatment to the randomized study medication (eprosartan). Allocation numbers were associated with their previous treatment to the randomized study medication (eprosartan). Allocation numbers were associated with their previous treatment to the randomized study medication (eprosartan). Allocation numbers were associated with their previous treatment to the randomized study medication (eprosartan). Allocation numbers were associated with their previous treatment to the randomized study medication (eprosartan). Allocation numbers were associated with their previous treatment to the randomized study medication (eprosartan).

From week 3 of treatment (earlier if required for medical reasons) the dose could be increased or combination therapy could be initiated. Target blood pressures for long-term therapy were sitting systolic blood pressure <140 mm Hg and diastolic blood pressure <90 mm Hg. It was intended to reach target blood pressure for two thirds of the patients within the first 3 months. It was recommended but not predefined to give diuretics as the first combination partner, followed by β-blockers and then α-blockers or centrally acting substances. Combination therapy with ACE inhibitors, angiotensin II type 1 receptor antagonists, or calcium antagonists had to be avoided and should only be given when clinically necessary. Flexibility with regard to the use of combination therapy for individual patients was an important clinical consideration to reach target blood pressure values as planned without unnecessary side effects.

Clinical Examinations

On inclusion the patient’s cardiovascular risk factors, family history, previous diseases, kind and date of the qualifying event, height, weight, blood pressure, resting pulse rate, and neurological symptoms were recorded. The disability level was determined using the modified Rankin Scale (score 0 to 5; best=0) and the Barthel Index (score 0 to 100; best=100), and cognitive function was assessed using the Mini Mental Status Exam (MMSE).4–7

Outpatient check-ups were scheduled for 3, 6, and 9 weeks and 3, 6, 12, 18, 24, 36, and 48 months; blood pressure was checked at each. Twenty-four-hour ambulatory blood pressure monitoring (ABPM), MMSE score, 12-, 24-, and 48-month; Rankin Scale, and Barthel Index were checked 24 and 48 months. Adverse events were assessed by the investigator at each examination.

End Points

Cardiovascular and cerebrovascular events, deaths, and severe adverse events were adjudicated by an independent blinded clinical event committee.

Primary end point was the composite of all-cause mortality and the number of cardiovascular and cerebrovascular events, including all recurrent events. Cerebral complications were defined as intracerebral hemorrhage, recurrence of stroke, or TIA/prolonged reversible ischemic neurological deficit. Cardiovascular complications were defined as any cardiovascular event (including myocardial infarction and new cardiac failure).

Secondary end points were all single components of the combined primary end point. Further prespecified secondary end points were assessment of the patients’ functional capacity and mental function.

Statistical Analysis

Sample size calculation assuming a power of 80% (2-sided test of α=5%) to prove a reduction of the 2-year event rate from 42% to 37.5% (relative reduction of 15%), assuming an accrual period of 2 years with 800 patients per year and study duration of 4 years shows that 716 events were needed. Because the number of patients per year was lower than expected, in an amendment to the protocol, it was decided to extend the observation period to receive the desired number of events. The time for the end of the study (February 2004) was predefined prospectively by study protocol amendment independently of any results.

All results are based on intention to treatment analyses. For nonfatal events, recurrent events were possible. The total person time under observation was computed and event rates per 100 person years were calculated. The sum of the events (including recurrent) was transformed in the incidence density. For the comparison of these incidence densities between the 2 treatments, the incidence density ratio (IDR) and their 95% CI were computed supposing a Poisson distribution.8

For descriptive purposes, additional analyses were performed for the first event in each category. These event rates were compared with the log-rank test. Treatment effects were measured by hazard ratios and their 95% CIs based on Cox regression model. Fisher’s exact test was applied to compare proportions between the treatment groups.

Results

Recruitment and Baseline Characteristics

Fifty-three patients withdrew consent before first intake of study drug. A total of 1352 patients (681 eprosartan group; 671 nitrendipine group) were eligible for analysis with mean follow-up of 2.5 years (SD 1.3; Figure 1). In eprosartan and nitrendipine groups at 12, 24, 36, and 48 months, patients at
risk for death were 655/653, 639/633, 631/626, and 624/619, respectively. Baseline characteristics are shown in Table 1.

Both treatment groups were similar in terms of demographic characteristics, with no significant differences in severity of hypertension (confirmed by ABPM), antihypertensive pretreatment, and prevalence of coexisting cardiovascular conditions. A total of 84% of all patients were pretreated with antihypertensive agents (Table 1).

**Effects on Blood Pressure**
The blood pressure reduction was similar in both groups at the same time and to a comparable extent without any significant differences during the study period (Figure 2). Already after 3 months, normotensive mean values were achieved and remained stable during the course of the study (3 months 136.7/80.8 versus 135/79.9).

At the end of the study or at the final visit, the mean office blood pressure was 137.5/80.8 mm Hg (SD 16.7/8.9), with eprosartan-based regimens and 136.0/80.2 mm Hg (SD 15.6/8.8) with nitrendipine-based regimens.

After 3 months, 75.5% in the eprosartan group and 77.7% in the nitrendipine group reached systolic and diastolic normotension (<140/90 mm Hg). Throughout the study period, an average of 76% of the patients had normalized blood pressure in the eprosartan group and of 78% in the nitrendipine group.

**Antihypertensive Drugs**
A total of 34.4% received monotherapy with eprosartan and 33.1% with nitrendipine. Combination therapy was necessary in 65.6% of the eprosartan patients and in 66.9% of the nitrendipine patients. Table 2 shows the distribution of study
<table>
<thead>
<tr>
<th></th>
<th>Eprosartan</th>
<th>Nitrendipine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total No. of eligible patients</strong></td>
<td>681</td>
<td>671</td>
</tr>
<tr>
<td><strong>Sex, No. (%), male</strong></td>
<td>365 (53.6)</td>
<td>368 (54.8)</td>
</tr>
<tr>
<td><strong>Age, y</strong></td>
<td>67.7±10.4</td>
<td>68.1±9.5</td>
</tr>
<tr>
<td><strong>Body mass index</strong></td>
<td>27.7±4.2</td>
<td>27.4±4.4</td>
</tr>
<tr>
<td><strong>Time between qualifying event and allocation, days</strong></td>
<td>347.6±322.5</td>
<td>349.8±325.7</td>
</tr>
<tr>
<td><strong>Patients enrolled within 1 week of qualifying event</strong></td>
<td>20 (2.9)</td>
<td>21 (3.1)</td>
</tr>
<tr>
<td><strong>Systolic office blood pressure, mm Hg</strong></td>
<td>150.7±18.5</td>
<td>152.0±18.2</td>
</tr>
<tr>
<td><strong>Diastolic office blood pressure, mm Hg</strong></td>
<td>87.0±10.8</td>
<td>87.2±9.6</td>
</tr>
<tr>
<td><strong>Heart rate, bpm</strong></td>
<td>74.7±10.2</td>
<td>75.7±10.5</td>
</tr>
<tr>
<td><strong>Mean systolic 24-hour blood pressure, mm Hg</strong></td>
<td>139.7±16.9</td>
<td>140.0±16.9</td>
</tr>
<tr>
<td><strong>Mean diastolic 24-hour blood pressure, mm Hg</strong></td>
<td>81.7±10.9</td>
<td>81.5±10.9</td>
</tr>
<tr>
<td><strong>Mean systolic daytime blood pressure, mm Hg</strong></td>
<td>143.1±17.6</td>
<td>143.9±19.0</td>
</tr>
<tr>
<td><strong>Mean diastolic daytime blood pressure, mm Hg</strong></td>
<td>84.0±12.0</td>
<td>84.3±12.6</td>
</tr>
<tr>
<td><strong>Mean systolic night blood pressure, mm Hg</strong></td>
<td>132.1±20.1</td>
<td>132.1±19.8</td>
</tr>
<tr>
<td><strong>Mean diastolic night blood pressure, mm Hg</strong></td>
<td>75.8±11.9</td>
<td>75.6±12.0</td>
</tr>
</tbody>
</table>

**Qualifying disease**

<table>
<thead>
<tr>
<th></th>
<th>Eprosartan</th>
<th>Nitrendipine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stroke</strong></td>
<td>418 (61.4)</td>
<td>407 (60.7)</td>
</tr>
<tr>
<td><strong>TIA</strong></td>
<td>186 (27.3)</td>
<td>184 (27.4)</td>
</tr>
<tr>
<td><strong>PRIND</strong></td>
<td>36 (5.3)</td>
<td>47 (7.0)</td>
</tr>
<tr>
<td><strong>Intracerebral hemorrhage</strong></td>
<td>41 (6.0)</td>
<td>33 (4.9)</td>
</tr>
<tr>
<td><strong>MMSE, score</strong></td>
<td>25.8±5.2</td>
<td>25.8±5.1</td>
</tr>
<tr>
<td><strong>Barthel Index, score</strong></td>
<td>90.6±18.1</td>
<td>90.2±18.6</td>
</tr>
<tr>
<td><strong>Patients with Barthel Index ≥90</strong></td>
<td>515 (75.6)</td>
<td>505 (75.3)</td>
</tr>
<tr>
<td><strong>Modified Rankin Scale, score</strong></td>
<td>1.5±1.5</td>
<td>1.5±1.5</td>
</tr>
<tr>
<td><strong>None to mild disability, 0–2</strong></td>
<td>475 (70.4)</td>
<td>476 (71.4)</td>
</tr>
<tr>
<td><strong>Moderate disability, 3</strong></td>
<td>121 (17.9)</td>
<td>106 (15.9)</td>
</tr>
<tr>
<td><strong>Severe disability, 4 and 5</strong></td>
<td>80 (11.7)</td>
<td>84 (12.7)</td>
</tr>
</tbody>
</table>

**Concomitant diseases**

<table>
<thead>
<tr>
<th></th>
<th>Eprosartan</th>
<th>Nitrendipine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diabetes mellitus</strong></td>
<td>245 (36.0)</td>
<td>253 (37.7)</td>
</tr>
<tr>
<td><strong>Hyperlipidemia</strong></td>
<td>370 (54.3)</td>
<td>348 (51.9)</td>
</tr>
<tr>
<td><strong>Coronary heart disease</strong></td>
<td>185 (27.2)</td>
<td>170 (25.3)</td>
</tr>
<tr>
<td><strong>Myocardial infarction</strong></td>
<td>58 (8.5)</td>
<td>52 (7.7)</td>
</tr>
<tr>
<td><strong>Renal insufficiency</strong></td>
<td>32 (4.7)</td>
<td>40 (6.0)</td>
</tr>
<tr>
<td><strong>Hyperuricemia</strong></td>
<td>120 (17.6)</td>
<td>124 (18.5)</td>
</tr>
<tr>
<td><strong>Chronic obstructive pulmonary disease</strong></td>
<td>30 (4.4)</td>
<td>24 (3.6)</td>
</tr>
<tr>
<td><strong>Patients without above-listed concomitant diseases</strong></td>
<td>146 (24.4)</td>
<td>155 (23.0)</td>
</tr>
</tbody>
</table>

**Antihypertensives at time of randomization**

<table>
<thead>
<tr>
<th></th>
<th>Eprosartan</th>
<th>Nitrendipine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Previously treated for hypertension</strong></td>
<td>564 (82.8)</td>
<td>571 (85.1)</td>
</tr>
<tr>
<td><strong>Angiotensin-converting enzyme inhibitor</strong></td>
<td>312 (55.3)</td>
<td>320 (66.0)</td>
</tr>
<tr>
<td><strong>β-Blocker</strong></td>
<td>209 (37.1)</td>
<td>191 (35.2)</td>
</tr>
<tr>
<td><strong>Calcium antagonist</strong></td>
<td>162 (28.7)</td>
<td>181 (31.7)</td>
</tr>
<tr>
<td><strong>Diuretics</strong></td>
<td>80 (14.2)</td>
<td>78 (13.7)</td>
</tr>
<tr>
<td><strong>Angiotensin receptor blocker</strong></td>
<td>78 (13.8)</td>
<td>81 (14.2)</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>47 (8.3)</td>
<td>49 (8.6)</td>
</tr>
</tbody>
</table>

Data are shown as No. of patients (%) or mean±SD.
In total, 236 cerebrovascular events occurred: 102 in the eprosartan group and 134 in the nitrendipine group (IDR, 0.75; 95% CI, 0.58 to 0.97; P=0.026). Ischemic strokes were 31 versus 39; TIA 66 versus 92; and intracerebral hemorrhage 5 versus 3.

Secondary End Points

In total, 236 cerebrovascular events occurred: 102 in the eprosartan group and 134 in the nitrendipine group (IDR, 0.75; 95% CI, 0.55 to 1.02; P=0.061). Acute coronary syndrome was 39 versus 48; heart failure 30 versus 46; fatal cardiac arrhythmia 7 versus 11; and pulmonary embolism 1 versus 3.

Total mortality was 109 patients without significant differences in the categories cardiovascular, cerebrovascular, and nonvascular death. The mean values before and at the end of the study showed no significant differences in the scores of MMSE, Barthel, and ranking.

### Analysis of First Occurrence of Cerebrovascular and Cardiovascular Events

In addition to fatal and nonfatal cerebrovascular and cardiovascular events, the first occurrence in each category was analyzed (Table 4). In total, 169 cerebrovascular events occurred: 80 in the eprosartan group and 89 in the nitrendipine group. The hazard ratio was not statistically significant (P=0.42).

Cardiovascular events were more frequent in the nitrendipine group. In total, 144 cardiovascular events occurred: 60 in the eprosartan group and 84 in the nitrendipine group. The hazard ratio was statistically significant (P=0.03).

### Adverse Events

The frequency of the relevant adverse events dizziness/hypotension (12.9% versus 10.6%), pneumonia (10.8% versus 11.4%), and metabolic disorder (5.5% versus 5.9%) was comparable in both treatment groups.

### Discussion

The study was designed to test the hypothesis that in hypertensive stroke patients, for the same level of blood pressure control, an eprosartan-based regimen is more effective than a nitrendipine-based regimen in reducing cerebrovascular and cardiovascular morbidity and mortality. The importance of not only comparable but also of normalized blood pressure values was convincingly demonstrated in the last hypertension studies. It was clearly shown, namely in the VALUE trial, that small differences in blood pressure lead to significant differences in vascular events, especially in the rate of stroke and heart failure. Furthermore, VALUE demonstrated that an early normalization of blood pressure is of great importance in lowering cardiovascular and cerebrovascular events.

Therefore, the most important goal in MOSES was to achieve a comparable normalization of blood pressure; this goal was reached. Blood pressure was reduced to a comparable extent without significant differences between the 2 groups during the whole study period. At the end of the study,

### Table 2. Medication in the Study

<table>
<thead>
<tr>
<th>Patients on Study Drug and Antihypertensive Combination Therapy</th>
<th>Eprosartan (%)</th>
<th>Nitrendipine (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monotherapy</td>
<td>234 (34.4)</td>
<td>222 (33.1)</td>
</tr>
<tr>
<td>2 drugs</td>
<td>214 (31.4)</td>
<td>199 (29.7)</td>
</tr>
<tr>
<td>3 drugs</td>
<td>127 (18.6)</td>
<td>158 (23.5)</td>
</tr>
<tr>
<td>&gt;3 drugs</td>
<td>106 (15.6)</td>
<td>92 (13.7)</td>
</tr>
<tr>
<td>Patients on concomitant therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretics</td>
<td>317 (46.5)</td>
<td>308 (45.9)</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>226 (33.2)</td>
<td>216 (32.2)</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitor</td>
<td>77 (11.3%)</td>
<td>141 (21.0)</td>
</tr>
<tr>
<td>Angiotensin receptor blocker</td>
<td>17 (2.5)</td>
<td>32 (4.8)</td>
</tr>
<tr>
<td>Calcium antagonist</td>
<td>98 (14.4)</td>
<td>50 (7.5)</td>
</tr>
<tr>
<td>Other antihypertensives</td>
<td>98 (14.4)</td>
<td>87 (13.0)</td>
</tr>
<tr>
<td>Antiplatelet therapy</td>
<td>518 (76.1)</td>
<td>537 (80.0)</td>
</tr>
<tr>
<td>Statin treatment</td>
<td>119 (32.2)</td>
<td>106 (30.5)</td>
</tr>
</tbody>
</table>
or at the final visit, the mean values of systolic and diastolic blood pressure were normalized (eprosartan group 133.2/80.4 mm Hg; nitrendipine group 132.7/80.2 mm Hg). Additionally, these results were confirmed by ABPM. This excludes differences in blood pressure during special time intervals during 24 hours.

Moreover, early normalization of the blood pressure was achieved. It was intended to achieve normal blood pressure in two thirds of the patients after 3 months. A total of 75.5% reached values <140/90 mm Hg with the eprosartan regimen and 77.7% with the nitrendipine regimen. Throughout the study period, an average of 76% or 78%, respectively, showed normalized blood pressure. The fact that the number of events actually recorded was lower than that estimated a priori might be because of the strong effect of blood pressure lowering in both treatment arms.

Mean values and number of normalized patients in MOSES are superior when compared with other studies (Losartan Intervention for Endpoint reduction in hypertension [LIFE] study, 49% and 46%; VALUE, 58% and 64%).

What was the reason for the high number of controlled patients in the MOSES study? We tried to design a study protocol that was very near to normal clinical practice. The PROBE design might have been helpful in this regard. Second, it was recommended but not predefined to give diuretics as the first combination partner, followed by β-blockers and then α-blockers or centrally acting substances. This flexibility with regard to the use of combination therapy for individual patients was an important clinical consideration to reach target blood pressure values as planned without unnecessary side effects.

Additionally, it can be speculated that it is easier to have very tight clinical control in patients who already experienced TIA or stroke, which might lead to better compliance of patients and their families.

Despite blood pressure control being achieved in a similar time and to a similar degree in both treatment arms, the eprosartan-based regimen lowered primary end points significantly more than the nitrendipine group. The primary end point was the composite of total mortality plus the total number of cardiovascular and cerebrovascular events, including multiple recurrences in 1 patient. This protocol appears to be appropriate for secondary prevention studies in which the aim is to prevent all following events in contrast to primary prevention studies because multiple recurrent events are an important practical and clinical problem, especially in stroke patients, and have a major impact on the development of vascular dementia.

Meanwhile, data from LIFE and the Acute Candesartan Cilexetil Therapy in Stroke Survivors (ACCESS) study also suggest that angiotensin II type 1 receptor antagonists might be beneficial in patients with cerebrovascular diseases.

The MOSES data support this view, showing a reduced number of first cardiovascular events and a reduced total number of cerebrovascular events. However, first cerebrovascular events were not significantly different. A similar trend was also found in VALUE, in which valsartan-treated patients showed a lower incidence of heart failure compared with amlodipine-treated patients. In conclusion, eprosartan offers more effective protection from heart failure in stroke patients than nitrendipine.

The MOSES study differs in several other aspects from the recent hypertension trials. MOSES is a trial on secondary prevention. The patients studied in MOSES all had a high risk of cardiovascular disease because all of them had had ≥1 cerebrovascular event. The data show that compared with LIFE and VALUE, in MOSES, more patients with a much higher cardiovascular risk were studied than in both other primary prevention trials. MOSES differs from other recent trials also in that the qualifying cerebrovascular event was documented by an appropriate imaging procedure (ie, either by CT or magnetic resonance scan).

The percentage of patients treated with a monotherapy consisting of the drugs to be compared was comparably high in MOSES: 34.4% and 33.1% were treated exclusively with eprosartan and nitrendipine, respectively (LIFE 11% and 12%, and VALUE 27% and 25%). This is a further point that is crucial to the interpretation of comparative hypertension trials.

Conclusions

The MOSES trial thus fulfills the most important prerequisites of comparative hypertension trials. (1) In MOSES, a high percentage of patients reached target blood pressure with the study drugs; (2) A comparatively high percentage of patients only received the drugs to be compared; and (3) Nearly equal levels of blood pressure control were achieved in both treatment arms. Thus, in MOSES, underestimation and overestimation of potential angiotensin receptor blocker effects can largely be excluded. Truly, blood pressure–independent effects of an angiotensin receptor blocker compared with a calcium antagonist could be delineated more clearly. With these prerequisites given, MOSES does reveal protective effects of eprosartan over nitrendipine in high-risk patients.
Appendix

MOSES Investigators

Germany

Austria

MOSES Committees

Contributors and Writing Committee

J.S. had the idea for study design. S.L. and J.S. wrote the first draft of this manuscript.
A.K., F.H., K.P., J.B., W.Z., P.D., and H.C.D. contributed toward analysis or interpretation of data and revision of this manuscript.

Steering Committee


End Point Committee


Statistical Analysis


Data and Safety Monitoring Board

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References

Secondary Prevention of Stroke Is Important
But All Hypertensive Drugs Are Not Created Equal?

The Morbidity and Mortality After Stroke—Eprosartan Compared With Nitrendipine for Secondary Prevention (MOSES) study\(^1\) has 2 important messages. First, it consolidates the evidence that is beneficial to treat hypertension even after a cerebrovascular disorder (stroke or transient ischemic attack) has occurred. Second, and more intriguing, it supports the idea that antihypertensive drugs (specifically angiotensin receptor blocker [ARB] therapy) may have benefits beyond blood pressure lowering.

An overview of hypertension trials including stroke survivors suggested that antihypertensive treatment decreased recurrence of stroke by 28%.\(^2\) The preliminary result of the Post-Stroke Antihypertensive Treatment Study (PATS) corroborated this finding by showing that indapamide monotherapy with a 5 mm Hg systolic blood pressure reduction lowered the risk of recurrent stroke by 29% compared with placebo.\(^3\) The large PROGRESS study further showed that compared with placebo, angiotensin convertase enzyme (ACE) inhibitor–based therapy decreased recurrent cardiovascular complications in stroke survivors.\(^4\) Interestingly, this effect was not seen in those patients on ACE inhibitor alone, only in those with indapamide and ACE inhibitor combined. This result again strengthened the view that thiazide diuretics may have special effects in stroke prevention.\(^5\) Now the MOSES study shows that ARB (eprosartan)-based therapy decreased recurrent events compared with calcium channel blocker (nitrendipine)–based therapy among patients with previous cerebrovascular disorders. Because MOSES did not include a placebo group, it is essential that nitrendipine has been tested previously against placebo in the Syst-Eur trial,\(^6\) and there it reduced stroke by 38% and coronary events by 26%.\(^6\) Consequently, MOSES suggests that with eprosartan, a substantial further decrease of vascular events can be achieved.

With all this evidence, it is clear that hypertensive patients with a history of cerebrovascular disorder (transient ischemic attack, PRIND, or stroke) must be treated effectively with antihypertensive drugs; they are high-risk patients. Also, other risk factors including dyslipidemia must be taken into account. It should be remembered that stroke survivors are at increased risk of other vascular diseases, such as coronary heart disease, as well. Studies with statins in the treatment of dyslipidemia have shown that high-risk patients benefit from the treatment irrespective of the baseline low-density lipoprotein cholesterol value.\(^7\) Similarly, in the PROGRESS study, stroke survivors actually benefited from the treatment whether they did or did not have hypertension at baseline.\(^4\)

MOSES differs from PROGRESS because recruited participants had to have treatment-requiring hypertension. Despite identical blood pressure lowering, eprosartan reduced vascular events more than nitrendipine. Actually, the latter even lowered blood pressure somewhat better. In previous studies, ARBs have been shown to especially reduce strokes and heart failure.\(^8\) Furthermore, in the Losartan Intervention for Endpoint (LIFE) study, ARB losartan–based therapy reduced strokes better than β-blocker–based therapy.\(^9\) However, in the VALUE study, valsartan was nonsignificantly worse than amlodipine in stroke prevention, but post hoc analyses\(^10\) suggested that this may have been attributable to less effective blood pressure control by valsartan during the first 6 months of the trial (4.0/2.1 mm Hg difference in favor of amlodipine).

If ARBs were truly better than other antihypertensive drugs in stroke prevention, what could be the mechanism? According to the Fournier hypothesis, the reason may lie in the selective blocking by ARBs of the deleterious effects mediated through the angiotensin II type 1 (AT1) receptor, whereas the effects through the AT2 receptor are unaffected or even enhanced.\(^11\) AT2 receptor seem to mediate beneficial effects on the endothelium through decreased coagulation and inflammation and altered vessel structure, and AT2 receptor also protects brain tissue from ischemia in experimental models.\(^12,13\) However, direct proof of this in humans lacking. Also, other mechanisms may be operating. ARBs have been shown to prevent diabetes,\(^14\) and losartan prevented new-onset atrial fibrillation in the LIFE study.\(^15\) Diabetes and atrial fibrillation are important risk factors of stroke, but their possible role in the MOSES study has not been analyzed further.

Finally, the MOSES results do not corroborate the recent suspicions of increased myocardial infarction risk with ARBs.\(^16\) In these high-risk patients, cardiovascular events (including myocardial infarction) tended to be less frequent in the eprosartan group, even though nitrendipine, compared with placebo, prevented coronary events in the Syst-Eur trial.\(^6\)

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References


Morbidity and Mortality After Stroke, Eprosartan Compared With Nitrendipine for Secondary Prevention: Principal Results of a Prospective Randomized Controlled Study (MOSES)

Joachim Schrader, Stephan Lüders, Anke Kulschewski, Frank Hammersen, Kerstin Plate, Jürgen Berger, Walter Zidek, Peter Dominiak, Hans Christoph Diener and the MOSES Study Group

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