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Morbidity and Mortality After Stroke in Patients with Diabetes – Subgroup Analysis from the MOSES Study

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Background: The MOSES study was the first one to show significant advantages in the treatment with eprosartan in contrast to nitrendipine in the secondary prevention of hypertensive stroke patients. In prespecified analyses, we compared the effects of antihypertensive treatment with eprosartan and nitrendipine on cerebro- and cardiovascular morbidity and mortality.

Methods: As part of the MOSES study carried out in accordance with the PROBE design (prospective, randomised, open-label, blinded endpoint) we assigned a group of 498 hypertensive stroke patients with diabetes on eprosartan or nitrendipine based treatment with regard to cerebro- and cardiovascular events. Primary endpoint included all deaths and all recurrent cerebro- and cardiovascular events.

Results: There were no relevant differences in the basic demographic data between eprosartan and nitrendipine based therapy. Initial similar blood pressure values (150.7/85.2 mmHg versus 152.3/86.1 mmHg) turned into higher systolic and diastolic ones in the eprosartan group after 3 months and even reached statistical significance after 12 months (140.3/80.4 mmHg versus 135.9/78.3 mmHg) and 36 months (140.1/82.4 mmHg versus 134.9/78.8 mmHg). While primary endpoints, cerebro- and cardiovascular events showed no significant difference between eprosartan and nitrendipine based therapy groups, in contrast they were all significantly more frequent (p = 0.001) in the diabetic patients compared to the non-diabetic group.

Conclusion: There was no difference in the event rate between both groups, although blood pressure reduction was significantly higher in nitrendipine than eprosartan based therapy. This lacking difference is due to different blood pressure reduction. This underlies the outstanding importance of blood pressure reduction in high-risk patients towards beyond blood pressure lowering effects of antihypertensive drugs. J Clin Basic Cardiol 2006; 9 (Suppl 1): 2–5.

Key words: eprosartan, hypertension, diabetes mellitus, nitrendipine, stroke prevention

A rtial hypertension is not only one of the main risk factors for an initial stroke, but in patients who have already suffered a stroke it can also lead to an increase in cerebrovascular morbidity and mortality. The PROGRESS study [1] was able to demonstrate a significant benefit of antihypertensive treatment to reduce blood pressure in the secondary prevention by detecting a 28 % reduction in the rate of strokes. For the first time the MOSES study [2] gives evidence of a difference between two antihypertensive drugs in hypertensive stroke patients.

In this high-risk group, which included a total of 1,352 stroke patients, the AT1 receptor antagonist eprosartan proved to be superior to the calcium antagonist nitrendipine at achieving the same reduction in blood pressure in terms of the incidence of primary endpoints, defined as the total of all deaths plus fatal and non-fatal cerebral and cardiovascular incidents. Thus a significant 21 % reduction in the number of primary endpoints occurred in the group treated with eprosartan compared with the nitrendipine group (206 vs. 255; p = 0.014). The cardiovascular incidents were 30 % lower (p = 0.061) and the cerebrovascular incidents 25 % lower (p = 0.026) in the eprosartan group than in the nitrendipine group.

The risk of recurrent stroke seems to be higher in diabetic patients. As part of a subgroup analysis, we therefore investigated all patients who had diabetes mellitus at the start of the MOSES study with regard to the incidence rate pertaining to their study medication (eprosartan as opposed to nitrendipine). The question arises as to whether the results of the MOSES study should be carried over in the same way to the subpopulation of diabetics or whether, on the basis of the LIFE study [3, 4], diabetics would benefit even more strongly from anti-hypertensive therapy with an AT1 blocker or nitrendipine.

Method

The MOSES study was a multicentre study carried out in accordance with the PROBE [5] design (prospective, randomised, open-label, blinded endpoint). Hypertensive patients requiring treatment who had a previous history of a cerebrovascular incident within the past 2 years (transient ischaemic attacks, cerebral ischaemia or intracerebral haemorrhage) and had undergone a CT or MRT diagnosis were randomised and then treated for over 2 years either with the study medication eprosartan or with nitrendipine whilst undergoing observation. Where blood pressure was insufficiently lowered by the monotherapy, a combination treatment with additional antihypertensives was permitted. High-grade carotid stenosis (> 70 %) and existing oral anticoagulation therapy were significant criteria for exclusion. During the observation period – which continued for a maximum of 4 years – in addition to the blood pressure readings determined by means of measurements taken by at the surgery and by ambulant blood pressure measurements, the primary and secondary endpoints were recorded and evaluated by the Endpoint Committee in blinded form. The primary endpoints included all deaths and all recurrent cerebrovascular events, defined as intracerebral haemorrhage, recurrence of stroke, TIA (transitoric ischaemic attack) or PRIND (prolonged ischaemic neurological deficit), and cardiovascular incidents including myocardial infarction and new occurrences of cardiac insufficiency. The secondary endpoints consisted of the corresponding individual components of the combined primary endpoint.
Results

Patients

245 patients were treated on an eprosartan based regimen, 253 patients on a nitrendipine based regimen. The basic demographic data and concomitant diseases (Tab. 1) were comparable in both groups. Furthermore, at the time of the patients' acceptance there was no significant difference in the severity of the hypertension and the proportion of patients who had previously been treated for hypertension in both groups.

Compared with the patients who showed no symptoms of diabetes at the start of the MOSES study (Tab. 2), the diabetics on average had a higher age (+1.9 years), a higher BMI (+1.3 kg/m²), a higher diastolic blood pressure on acceptance (+4.1 mmHg) and lower MMS score (–1.0) and Barthel score (–5.2). Overall there was not only a higher percentage of concomitant cardiovascular diseases in this patient collective but also a higher proportion of patients with manifest apoplexy (68.7% vs. 56.6%).

Blood Pressure (Fig. 1)

Initially, blood pressure was not significantly different in the two groups (150.7±16.8 mmHg vs. 152.3±18.4 mmHg). Despite adequate reduction in blood pressure in each case, after 12 months there was a significant mean difference in both systolic and diastolic blood pressure to the disadvantage of the eprosartan group (140.3 mmHg vs. 135.9 mmHg; p = 0.011 and 80.4 mmHg vs. 78.5 mmHg; p = 0.028, respectively), which in due course tended to show a further increase after 36 months (140.1 mmHg vs. 134.9 mmHg; p = 0.024 and 82.4 mmHg vs. 78.8 mmHg; p = 0.007, respectively).

Primary Endpoints

The relative frequency of primary endpoints (Tab. 3) in the group of diabetics compared to the non-diabetic group had risen significantly (p = 0.001).

During the observation period, a total of 214 primary endpoints occurred among the diabetics: 102 in the eprosartan group, 112 in the nitrendipine group (Tab. 4). The difference was not significant (p = 0.83).
Secondary Endpoints

In the comparison of the diabetic group with the non-diabetic group, there was a significant (p = 0.001) increase in the relative frequency of both cardiovascular and cerebrovascular events in the diabetic group (Tab. 3).

Fewer cerebrovascular events occurred in the eprosartan group than in the nitrendipine group (49 vs. 61), but the difference was not significant (p = 0.42). With cardiovascular incidents, the results were to the contrary: these were detected in fewer numbers in the nitrendipine group (44 vs. 40; p = 0.46) without reaching significance (Tab. 4).

Endpoint Analysis (Tab. 3, 4)

Table 3. Comparing diabetics with non-diabetics

<table>
<thead>
<tr>
<th></th>
<th>Eprosartan</th>
<th>Nitrendipine</th>
<th>Rate ratio IDR</th>
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<tbody>
<tr>
<td></td>
<td>Number</td>
<td>Rate (ID)</td>
<td></td>
</tr>
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<td></td>
<td>(n = 245)</td>
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<tr>
<td>All</td>
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<td>12.39</td>
<td>1.217</td>
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<tr>
<td>Cerebral</td>
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<td>6.32</td>
<td>1.173</td>
</tr>
<tr>
<td>Cardial</td>
<td>94</td>
<td>4.72</td>
<td>1.173</td>
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</tbody>
</table>

Table 4. Comparing eprosartan with nitrendipine in diabetics

<table>
<thead>
<tr>
<th></th>
<th>Eprosartan</th>
<th>Nitrendipine</th>
<th>Rate ratio IDR</th>
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<td></td>
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<td></td>
<td>(n = 245)</td>
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<tr>
<td>All</td>
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<td>Cardial</td>
<td>44</td>
<td>8.41</td>
<td>1.464</td>
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</table>

Discussion

Among the hypertensive stroke patients there was a higher incidence of cerebrovascular events in those patients who had diabetes mellitus at the start of the study. Within this study of secondary prophylaxis in patients following a stroke, the diabetics had, overall, an incidence rate approximately one-third higher than non-diabetics. The patients with diabetes mellitus were older, had a higher BMI and had already, at the start of the MOSES study, a higher cardio- and cerebrovascular risk profile than the non-diabetics. However, the higher rate of pre-existing conditions might also have been brought about essentially by the combination of hypertension and diabetes mellitus. But all in all this data also confirms other studies on primary prophylaxis (VALUE, LIFE; [3, 7]) which likewise showed a higher incidence rate in diabetics.

However, the results of the subgroup analysis showed no significant difference with regard to the frequency of primary and secondary endpoints between the stroke patients with diabetes mellitus who were treated with eprosartan or nitrendipine. In contrast to the whole study, in which a significant advantage was found with the primary endpoints in the eprosartan-based therapy as opposed to the nitrendipine therapy, here it was not possible to detect any advantage. This lack of difference compared with the whole study group might, however, be fundamentally caused by the different reductions in blood pressure. Other than in the entire study group in the MOSES study, among the diabetics higher levels of systolic and diastolic blood pressure were found in the eprosartan group during the comparison of blood pressure values between the eprosartan-based and the nitrendipine-based treatment groups from the third month onward. At this time this difference in blood pressure amounted to 3 mmHg systolic and to 3–4 mmHg diastolic in favour of nitrendipine.

However, despite the significantly higher blood pressure in the eprosartan group, there was no difference in the primary endpoints. Since it has become clear from studies carried out over the past few years that a difference in blood pressure of even a few mmHg can lead to a difference in the incidence rate of strokes in particular, the differences in blood pressure found here must have led to a significant reduction in the primary endpoints in the nitrendipine-based group. On the contrary, the blood pressure values were comparable in patients in the study as a whole and it was possible to discern a significant difference in the primary endpoints. Consequently, any possible protective effect of eprosartan compared with nitrendipine was offset by a detrimental reduction in blood pressure. All in all, these results clearly show that a reduction in blood pressure is of paramount importance compared with other protective effects. In order to prove the advantages irrespective of blood pressure, blood pressure values must be exactly equal in the groups being compared.

In contrast to these results, in the LIFE study the incidence rate in patients being treated with losartan was lower among the diabetics compared to atenolol, whereas a greater reduction in blood pressure occurred among the diabetes patients in the losartan group compared to the atenolol group. Using losartan, systolic blood pressure was around 2 mmHg lower, which may explain at least in part, but not exclusively, the positive effect of losartan. Despite the differences in blood pressure to the disadvantage of eprosartan, it was possible to detect an insignificant trend in the reduction of the total number of cerebrovascular incidents in favour of eprosartan, whilst cardiovascular incidents differed only very slightly. It is speculative whether this trend would have led to a significant advantage in the reduction of cerebrovascular events in case of equal blood pressure reduction in both groups or in sufficiently large numbers of patients despite the blood pressure results being worse.

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