Angiotensin Receptor Blockers and Stroke Prevention: Results of the MOSES STUDY

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Angiotensin Receptor Blockers

Effectiveness

Low side effect rate (better than ACE inhibitors)

- - something extra in stroke prevention?
Morbidity and Mortality after Stroke – Eprosartan vs. Nitrendipine in Secondary Prevention
Commitees

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  Prof. Dr. W. Zidek, Berlin
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  Prof. Dr. H. Küppers, Hannover
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• **End Point Board**
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  Prof. Dr. M. Holzgreve, Seesen
  Prof. Dr. R. Griebenow, Köln
Antihypertensive Action of Eprosartan
Dose-dependent Effects

Mean reduction in BP vs placebo (mm Hg)

-10
-8
-6
-4
-2
0
2
4
6
8
10
400 mg 600 mg 800 mg 1200 mg o.d.

diastolic systolic (trough values)

Unique structure
Non-biphenyl
Non-tetrazole
Why plan a stroke prevention trial anticipating a specific benefit for angiotensin receptor blockers?
Adverse Remodeling of the Vasculature From Systolic HT to Stroke

Ang II → Vasoconstriction

Media hypertrophy
Collagen deposition

Eprosartan (ARBs)

Modified from Intengan & Schiffrin. Hypertension 2000; 36: 312-8
Ang II Infusion Induces Aortic VCAM-1 Expression

VCAM-1, vascular cell adhesion molecule, causes binding of inflammatory leukocytes to endothelium.

Tummala PE et al. *Circulation* 1999; 100: 1223-29
Chymase dependent Ang II Formation in Human Aorta

Arakawa K, Urata H. Hypertension 2000; 36: 638-41
Effects of Eprosartan versus Hydrochlorothiazide on Markers of Vascular Inflammation

Eprosartan reduced soluble vascular cell adhesion molecule in plasma.

Rahman ST et al. Am J Cardiol 2002; 89:686-90
A theoretical case, perhaps, for specific stroke prevention with ARBs - - - but I wish medical discovery was really that easy!!
In hypertensive stroke patients, for the same level of blood pressure control, the angiotensin receptor blocker, eprosartan will be more effective than the calcium channel blocker, nitrendipine in reducing cerebrovascular and cardiovascular morbidity and mortality.
• **Primary endpoints**
  - Total mortality + total number of cardiovascular and cerebrovascular events

• **Follow-up**
  - Mean: 2.5 years
**Inclusion criteria**

Hypertension (confirmed by ABPM), plus -

- cerebral ischaemia [TIA, PRIND, completed stroke]
  
or
- cerebral hemorrhagia

- - - during last 24 months prior to study
  (cerebral CT scan or MRI on all)
**Exclusion criteria**

- stenosis of carotid artery > 70%
- severe CHF
- unstable angina
- valve disease
- age over 85 years
- contra-indication for eprosartan or nitrendipine
Prior to randomisation: qualifying event documented by CCT or MRI and diagnosis of hypertension

Randomisation

At entry: Office-BP, ABPM, MMS, Rankin, Barthel
Pretreated patients: Rolled over directly to study medication

Dosage-increase or combination:
1. Diuretics
2. β-blockers
3. Alpha-blockers/other

Moses
1405 patients eligible for randomisation

710 assigned to eprosartan-based regimen
- 29 withdrew consent prior to first intake of study-drug
- 1 without known vital status
- 14 Lost for follow-up monitoring

695 assigned to nitrendipine-based regimen
- 24 withdrew consent prior to first intake of study-drug
- 2 without known vital status
- 12 Lost for follow-up monitoring

681 available for intention-to-treat analyses
671 available for intention-to-treat analyses
<table>
<thead>
<tr>
<th></th>
<th>Eprosartan</th>
<th>Nitrendipine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no. of eligible patients</td>
<td>681</td>
<td>671</td>
</tr>
<tr>
<td>Sex (number [%] male)</td>
<td>365 (53.6 %)</td>
<td>368 (54.8 %)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>67.7 (10.36)</td>
<td>68.1 (9.49)</td>
</tr>
<tr>
<td>BMI</td>
<td>27.7 (4.16)</td>
<td>27.4 (4.36 %)</td>
</tr>
<tr>
<td>Time between qualifying event and allocation (days)</td>
<td>347.6</td>
<td>349.8</td>
</tr>
</tbody>
</table>
Baseline characteristics of patients

Patients with Prior Antihypertensive Pretreatment: 84%

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Systolic office blood pressure (mmHg)</td>
<td>150.7</td>
<td>152.0</td>
</tr>
<tr>
<td>Diastolic office blood pressure (mmHg)</td>
<td>87.0</td>
<td>87.2</td>
</tr>
<tr>
<td>Heart rate (beats per min)</td>
<td>74.7</td>
<td>75.7</td>
</tr>
</tbody>
</table>
## Baseline characteristics of patients

### Qualifying disease

<table>
<thead>
<tr>
<th>Disease</th>
<th>Eprosartan</th>
<th>Nitrendipine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>418 (61.4 %)</td>
<td>407 (60.7 %)</td>
</tr>
<tr>
<td>TIA</td>
<td>186 (27.3 %)</td>
<td>184 (27.4 %)</td>
</tr>
<tr>
<td>PRIND</td>
<td>36 (5.3 %)</td>
<td>47 (7.0 %)</td>
</tr>
<tr>
<td>Intracerebral haemorrhage</td>
<td>41 (6.0 %)</td>
<td>33 (4.9 %)</td>
</tr>
</tbody>
</table>
## Baseline characteristics of patients

### Concomitant diseases

<table>
<thead>
<tr>
<th>Condition</th>
<th>Eprosartan</th>
<th>Nitrendipine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>36.0 %</td>
<td>37.7 %</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>54.3 %</td>
<td>51.9 %</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>17.6 %</td>
<td>18.5 %</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>8.5 %</td>
<td>7.7 %</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>4.7 %</td>
<td>6.0 %</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>27.2 %</td>
<td>25.3 %</td>
</tr>
<tr>
<td>COPD</td>
<td>4.4 %</td>
<td>3.6 %</td>
</tr>
<tr>
<td>No concomitant diseases</td>
<td>24.4 %</td>
<td>23.0 %</td>
</tr>
</tbody>
</table>
Systolic and diastolic blood pressure among patients assigned eprosartan or nitrendipine
Antihypertensive Therapy

- Monotherapy
- Combination drugs
- >3

Eprosartan Nitrendipine

34.4 33.1 31.4 29.7 18.6 23.5 15.6 13.7

[%]
• first comparison of 2 antihypertensive drugs in secondary stroke prevention
• investigator-created, -initiated and -performed study
• blinded end point committee
• well defined hypertensive stroke patients (CT or NMR, ABPM in all)
• very tight clinical control of BP (av. 136/81 mm Hg)
• comparable blood pressure control in the treatment groups
### Primary endpoints
*(total occurrence including recurrent events)*

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Eprosartan</th>
<th>Nitrendipine</th>
<th>IDR</th>
<th>95%CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary endpoints</strong></td>
<td>461</td>
<td>206</td>
<td>255</td>
<td>0.79</td>
<td>0.66</td>
<td>0.96</td>
</tr>
</tbody>
</table>

ID: Incidence per 100 person-years; IDR: Incidence density ratio; 95%CI: 95 % confidence limits of IDR
Primary Endpoints
(Total occurrence including recurrent events)

![Graph showing the comparison of events over days between Eprosartan and Nitrendipine.](image)
## Cerebrovascular events
*(total occurrence including recurrent events)*

<table>
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<th>IDR</th>
<th>95%CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cerebrovascular events</strong></td>
<td>236</td>
<td>102</td>
<td>134</td>
<td>0.75</td>
<td>0.58</td>
<td>0.97</td>
</tr>
</tbody>
</table>

**ID:** Incidence per 100 person-years; **IDR:** Incidence density ratio; **95%CI:** 95% confidence limits of IDR
Cerebrovascular Events
(Total occurrence including recurrent events)

- Eprosartan
- Nitrendipine
Recent conceptual advances in hypertension treatment:

1. Lowered goal blood pressures
   (special groups needing BP lowering may even have “normal” blood pressure)

2. ARBs as “specifics” in stroke prevention?