# 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?


**MO**rbidity and Mortality after

**S**troke –

**E**prosartan vs. Nitrendipine in

**S**econdary Prevention

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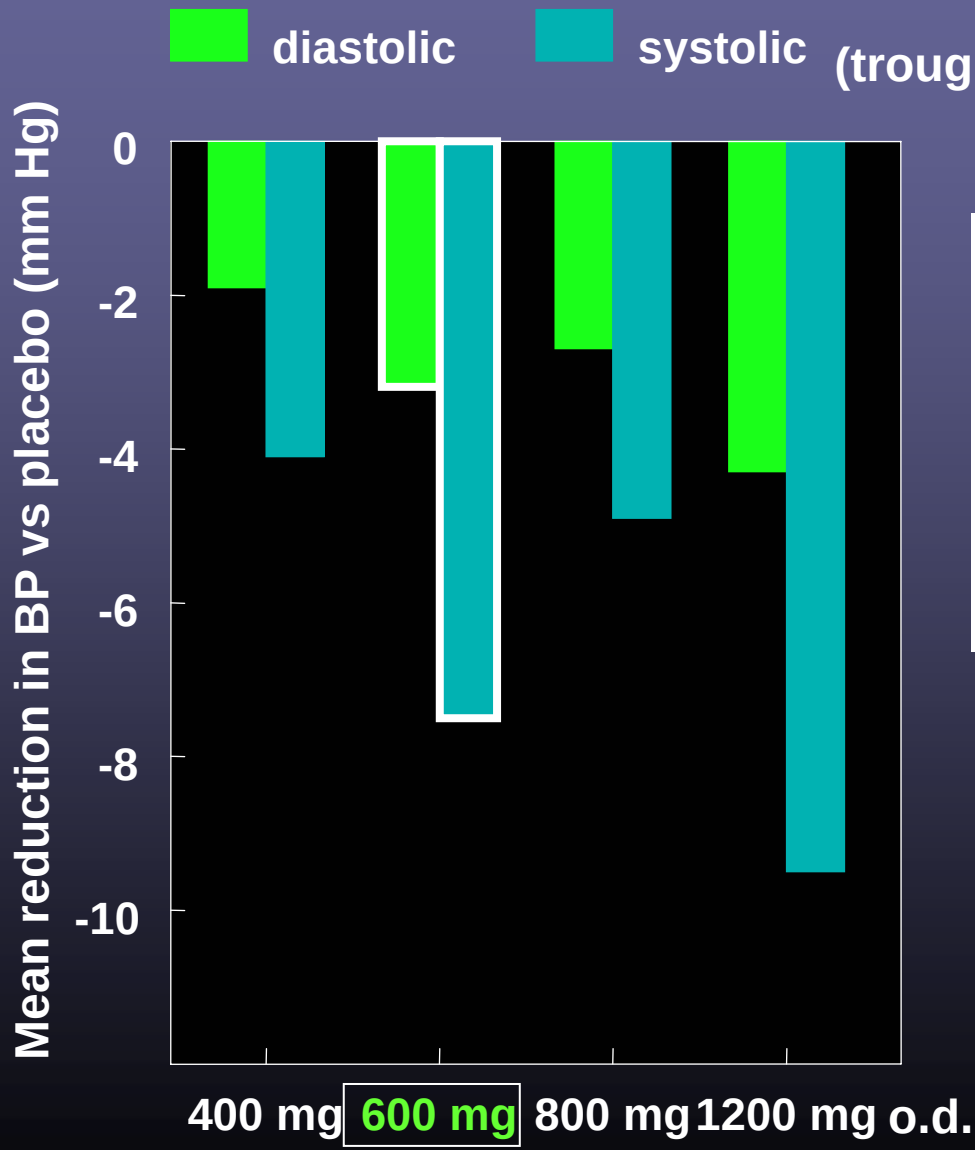
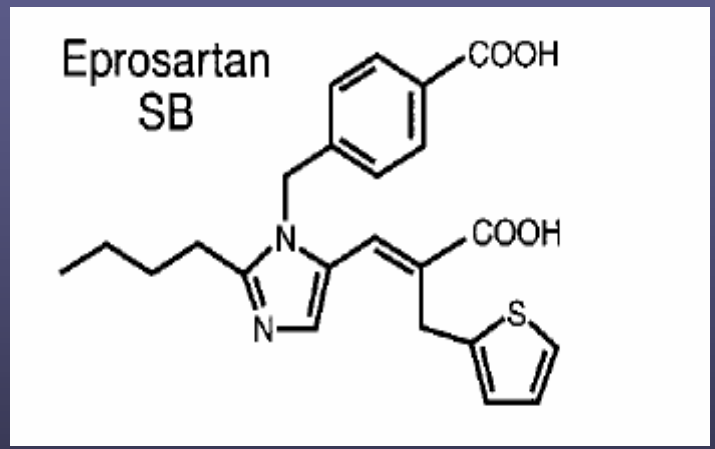
- **End Point Board**
  - Prof. Dr. U. Tebbe, Detmold (Chair)
  - Prof. Dr. M. Holzgreve, Seesen
  - Prof. Dr. R. Griebenow, Köln

# Antihypertensive Action of Eprosartan
# Dose-dependent Effects

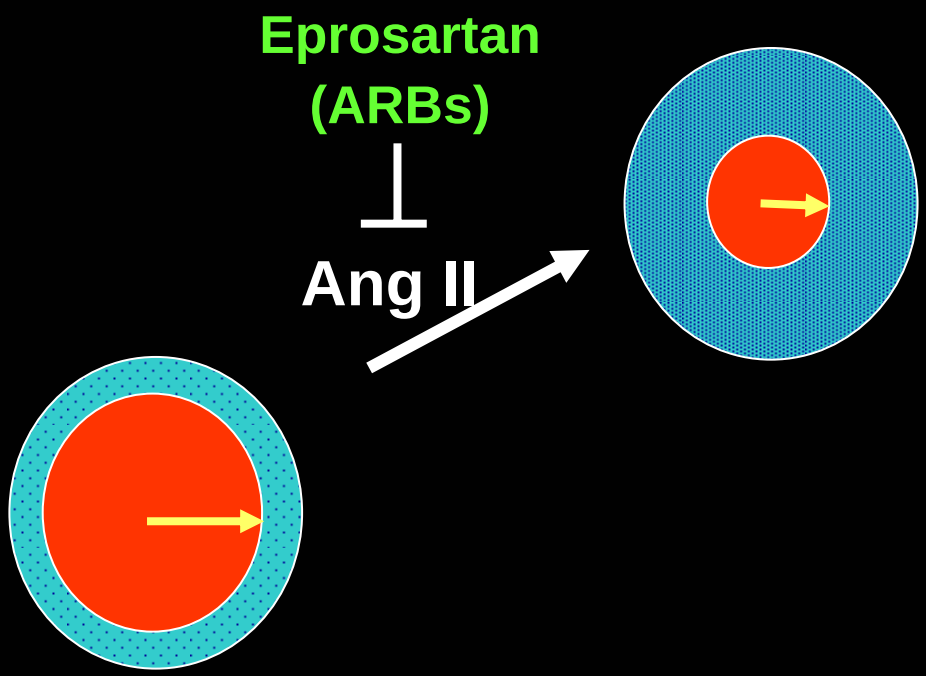



**Unique structure**
**Non-biphenyl**
**Non-tetrazole**

**Why plan a stroke prevention trial anticipating a specific benefit for angiotensin receptor blockers ?**

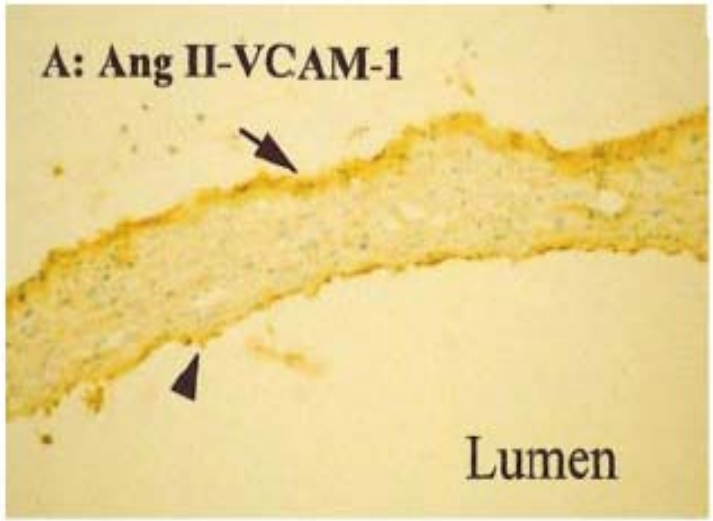
# Adverse Remodeling of the Vasculature From Systolic HT to Stroke

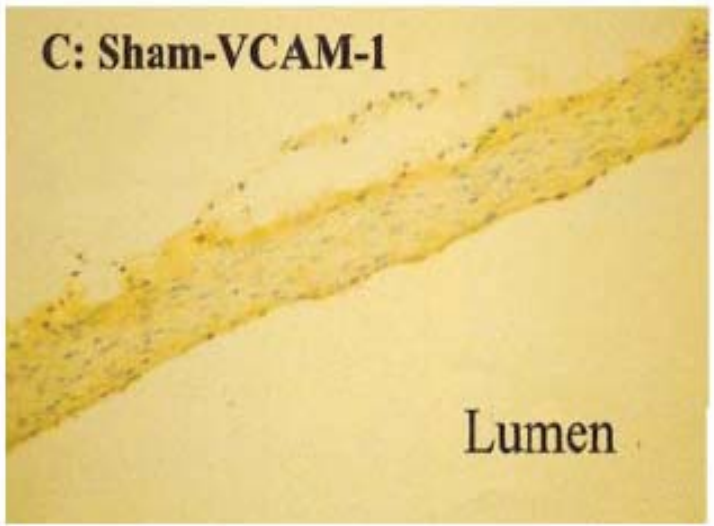



Vasoconstriction
Media hypertrophy
Collagen deposition

Modified from Intengan & Schiffrin. *Hypertension* 2000; 36: 312-8

# Ang II Infusion Induces Aortic VCAM-1 Expression



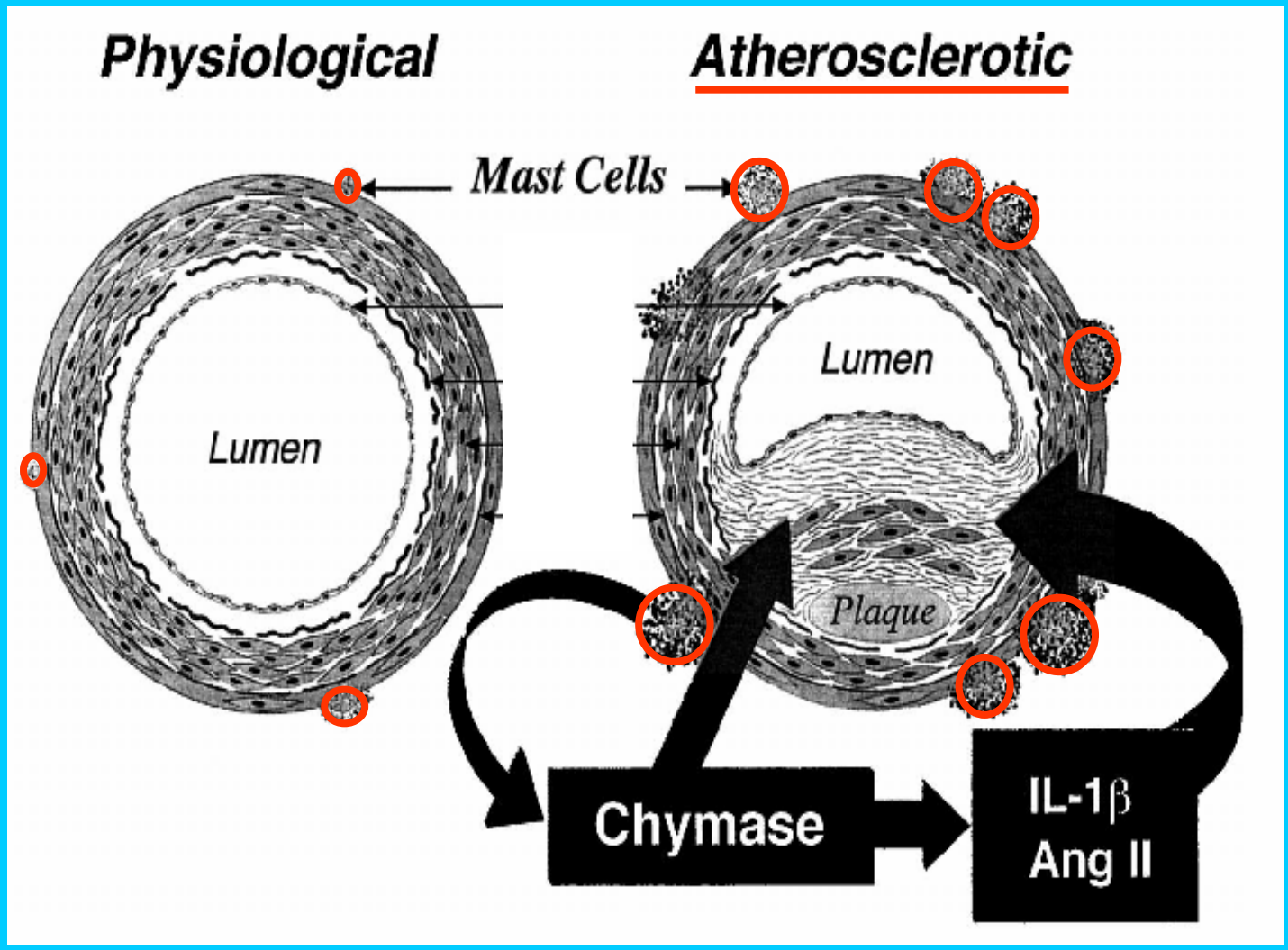

**VCAM-1**
**vascular cell adhesion molecule**

**causes binding of inflammatory leukocytes to endothelium**

**Tummala PE et al.**

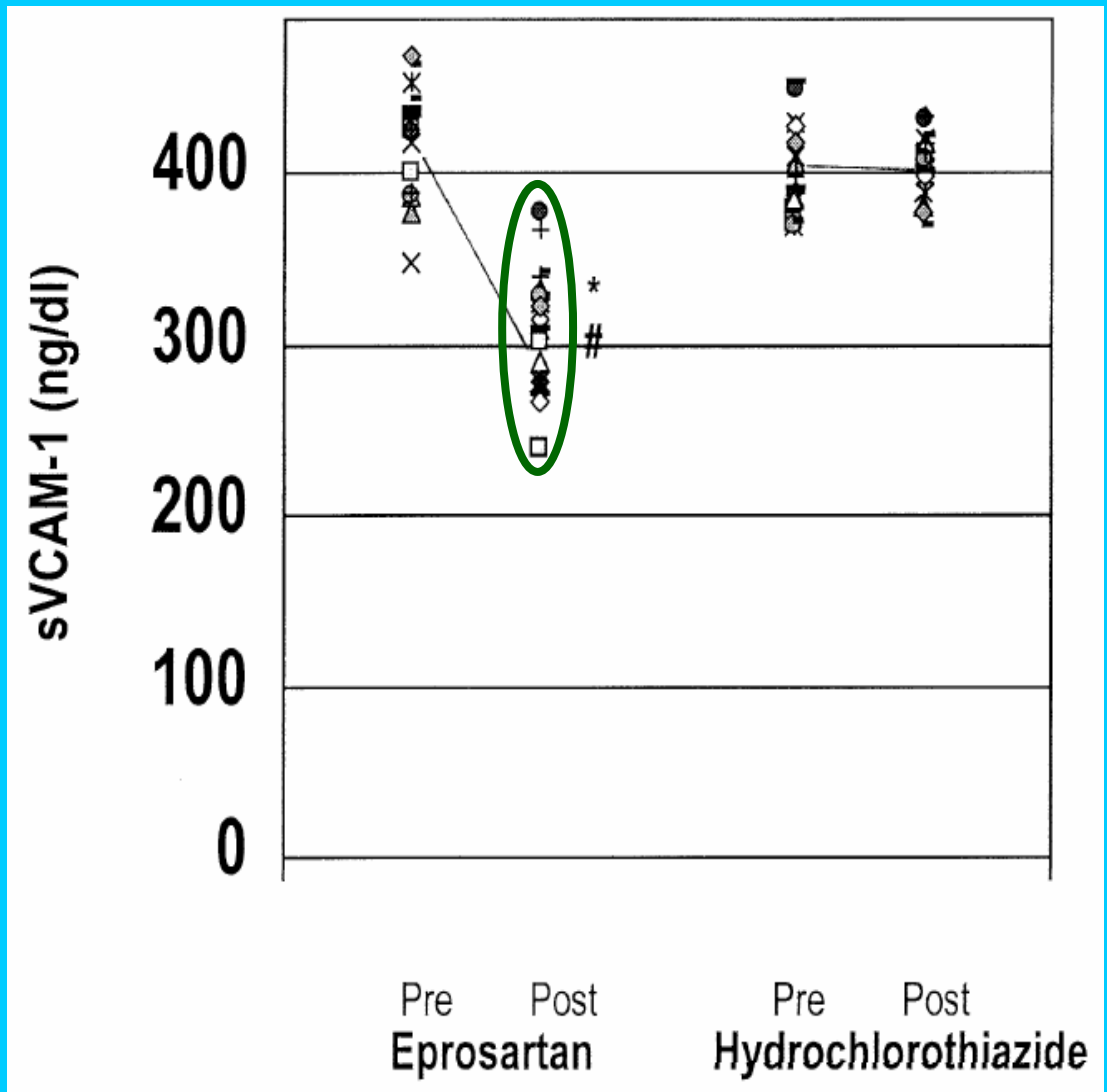
***Circulation* 1999; 100: 1223-29**

# 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!!**

# Hypothesis

**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.**

# MOSES study design

- ***Primary endpoints***
  - **Total mortality + total number of cardiovascular and cerebrovascular events**
- ***Follow-up***
  - **Mean: 2.5 years**

# MOSES

## MOrbidity and Mortality after Stroke – Eprosartan vs. Nitrendipine in Secondary Prevention

### *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)**

# MOSES

## MOrbidity and Mortality after Stroke – Eprosartan vs. Nitrendipine in Secondary Prevention

### *Exclusion criteria*

- stenosis of carotid artery > 70 %
- severe CHF
- unstable angina
- valve disease
- age over 85 years
- contra-indication for eprosartan or nitrendipine

# MOSES Study-Design

**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**

**Eprosartan 600 mg**

**Nitrendipine 10 mg**

3 weeks
↓
3 months
↓
6 months
↓
12 months
↓
18 months
↓
24 months
↓
36 months
↓
48 months

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

# MOSES Trial profile

1405 patients eligible for randomisation

710 assigned to eprosartan-based regimen

695 assigned to nitrendipine-based regimen

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

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

# Baseline characteristics of patients

| | Eprosartan | Nitrendipine |
|---|---|---|
| Total no. of eligible patients | 681 | 671 |
| Sex (number [%] male) | 365 (53.6 %) | 368 (54.8 %) |
| Age (years) | 67.7 (10.36) | 68.1 (9.49) |
| BMI | 27.7 (4.16) | 27.4 (4.36 %) |
| Time between qualifying event and allocation (days) | 347.6 | 349.8 |

# Baseline characteristics of patients

Patients with Prior Antihypertensive Pretreatment: 84%

| | Eprosartan | Nitrendipine |
|---|---|---|
| Systolic office blood pressure (mmHg) | 150.7 | 152.0 |
| Diastolic office blood pressure (mmHg) | 87.0 | 87.2 |
| Heart rate (beats per min) | 74.7 | 75.7 |

# Baseline characteristics of patients

## Qualifying disease

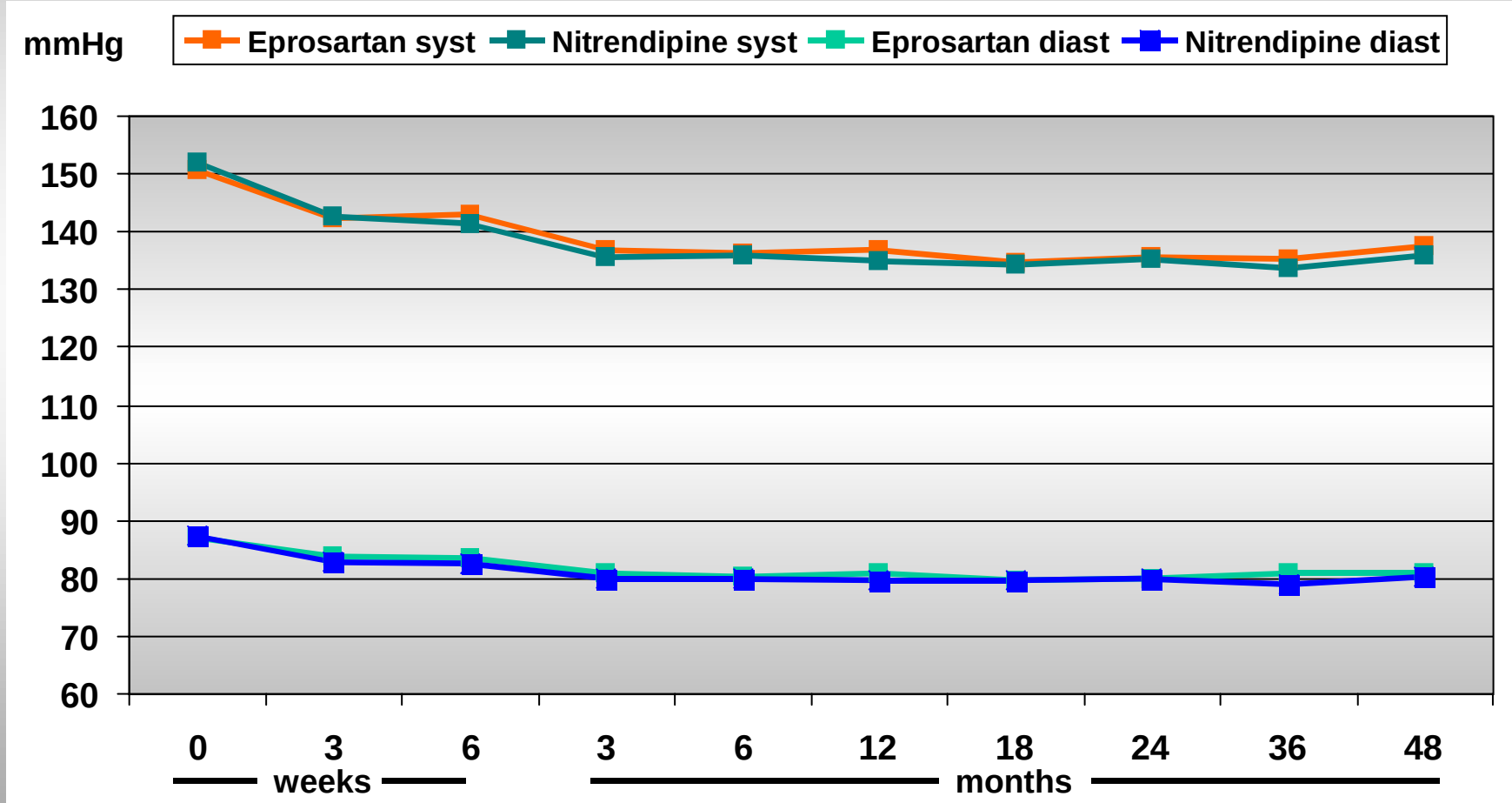
| | Eprosartan | Nitrendipine |
|---|---|---|
| **Stroke** | **418** (61.4 %) | **407** (60.7 %) |
| **TIA** | **186** (27.3 %) | **184** (27.4 %) |
| **PRIND** | **36** (5.3 %) | **47** (7.0 %) |
| **Intracerebral haemorrhage** | **41** (6.0 %) | **33** (4.9 %) |

# Baseline characteristics of patients

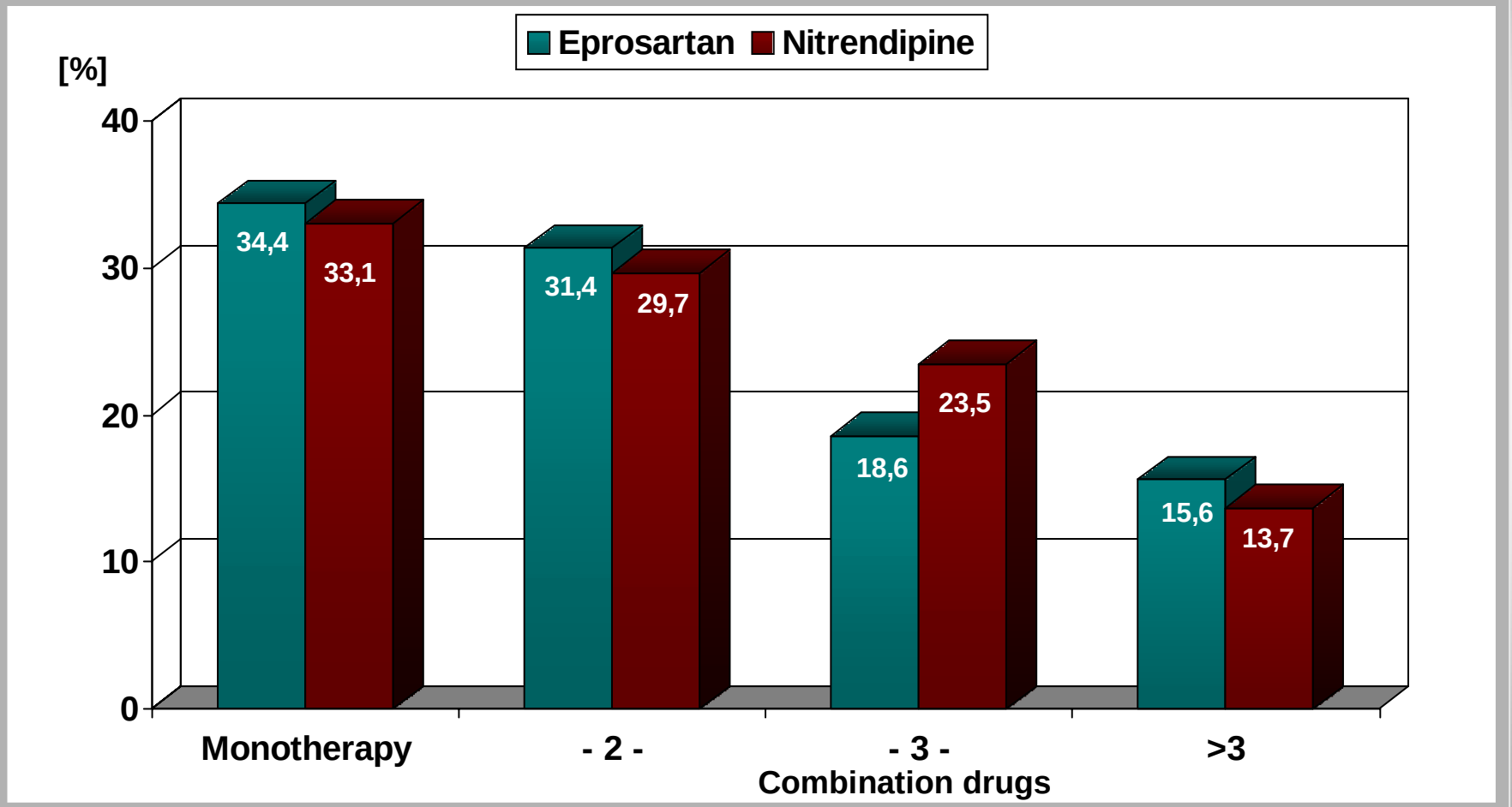
## Concomitant diseases

| | Eprosartan | Nitrendipine |
|---|---|---|
| Diabetes mellitus | 36.0 % | 37.7 % |
| Hyperlipidemia | 54.3 % | 51.9 % |
| Hyperuricemia | 17.6 % | 18.5 % |
| Myocardial infarction | 8.5 % | 7.7 % |
| Renal insufficiency | 4.7 % | 6.0 % |
| Coronary heart disease | 27.2 % | 25.3 % |
| COPD | 4.4 % | 3.6 % |
| No concomitant diseases | 24.4 % | 23.0 % |

# Systolic and diastolic blood pressure among patients assigned eprosartan or nitrendipine



# Antihypertensive Therapy



# MOSES MOrbidity and Mortality after Stroke – Eprosartan vs. Nitrendipine in Secondary Prevention

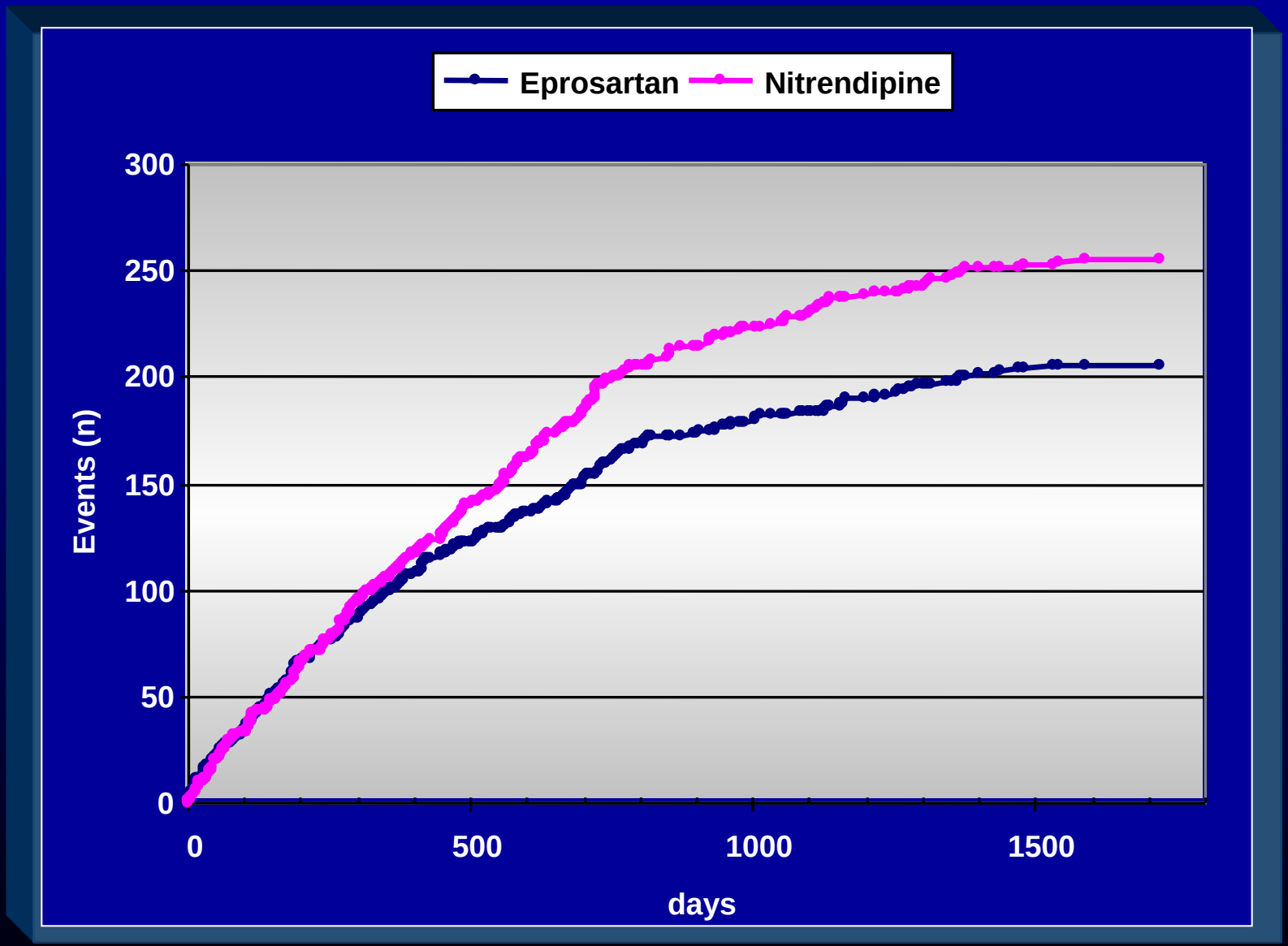
- first comparison of 2 antihypertensive drugs in secondary stroke prevention
- investigator-created, -initiated and –performed study
- blinded end point committee
- well defined hypertensive stroke patients (CT or NMR, ABPM in all)
- very tight clinical control of BP (av. 136/81 mm Hg)
- comparable blood pressure control in the treatment groups

# Primary endpoints
## (total occurrence including recurrent events)

| | Total | Eprosartan | | Nitrendipine | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | n | ID | n | ID | IDR | 95%CI | | p |
| Primary endpoints | 461 | 206 | 13,25 | 255 | 16,71 | 0,79 | 0,66 | 0,96 | 0.014 |

ID: Incidence per 100 person-years; IDR: Incidence density ratio; 95%CI: 95 % confidence limits of IDR

# Primary Endpoints
## (Total occurrence including recurrent events)



# Cerebrovascular events
## (total occurrence including recurrent events)

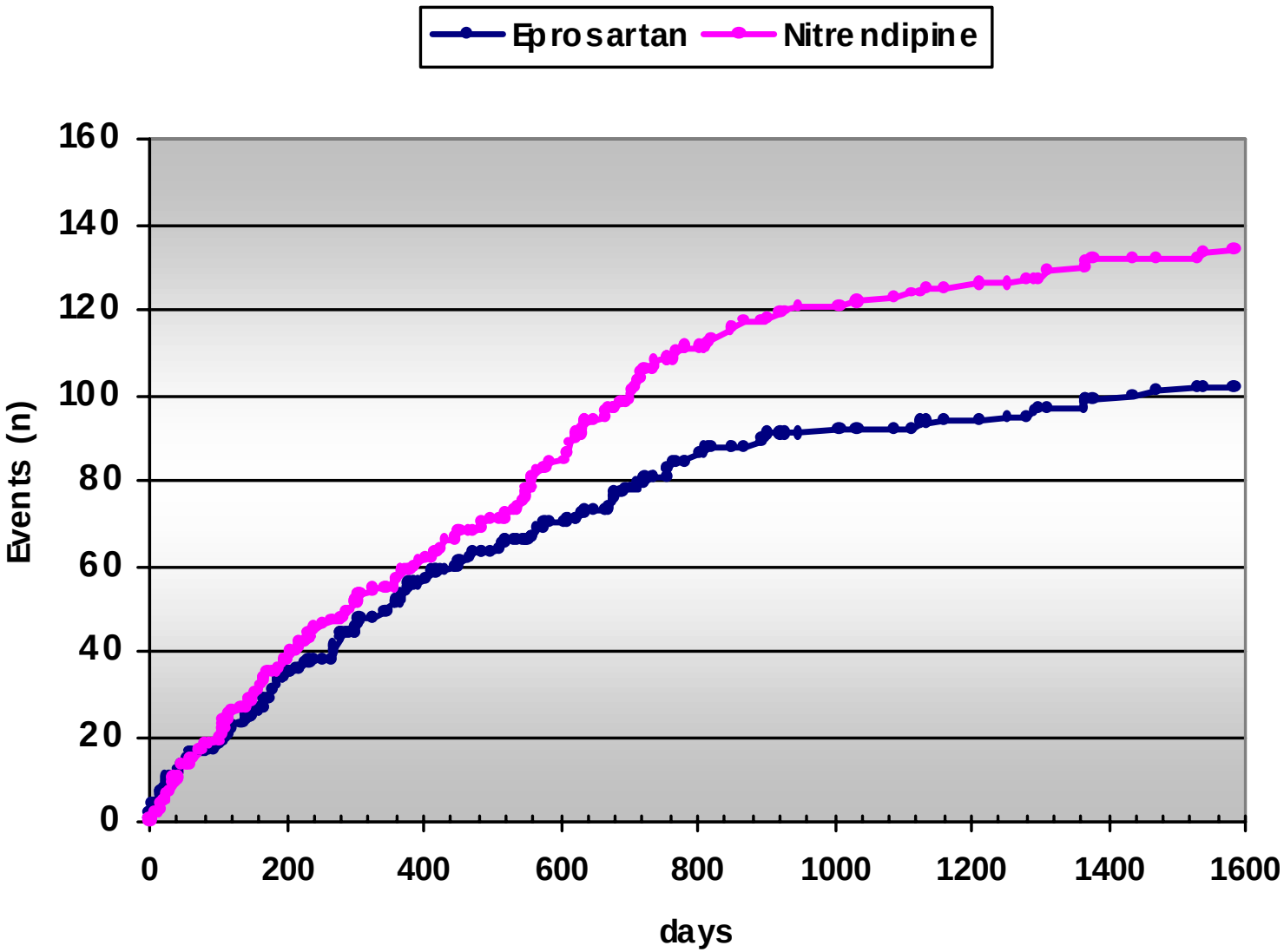
| | Total | Eprosartan | | Nitrendipine | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | n | ID | n | ID | IDR | 95%CI | | p |
| Cerebrovas-cular events | 236 | 102 | 6,56 | 134 | 8,78 | 0.75 | 0.58 | 0,97 | 0.02 |

ID: Incidence per 100 person-years; IDR: Incidence density ratio; 95%CI: 95 % confidence limits of IDR

MOSES

# Cerebrovascular Events

## (Total occurrence including recurrent events)



# 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 ?**