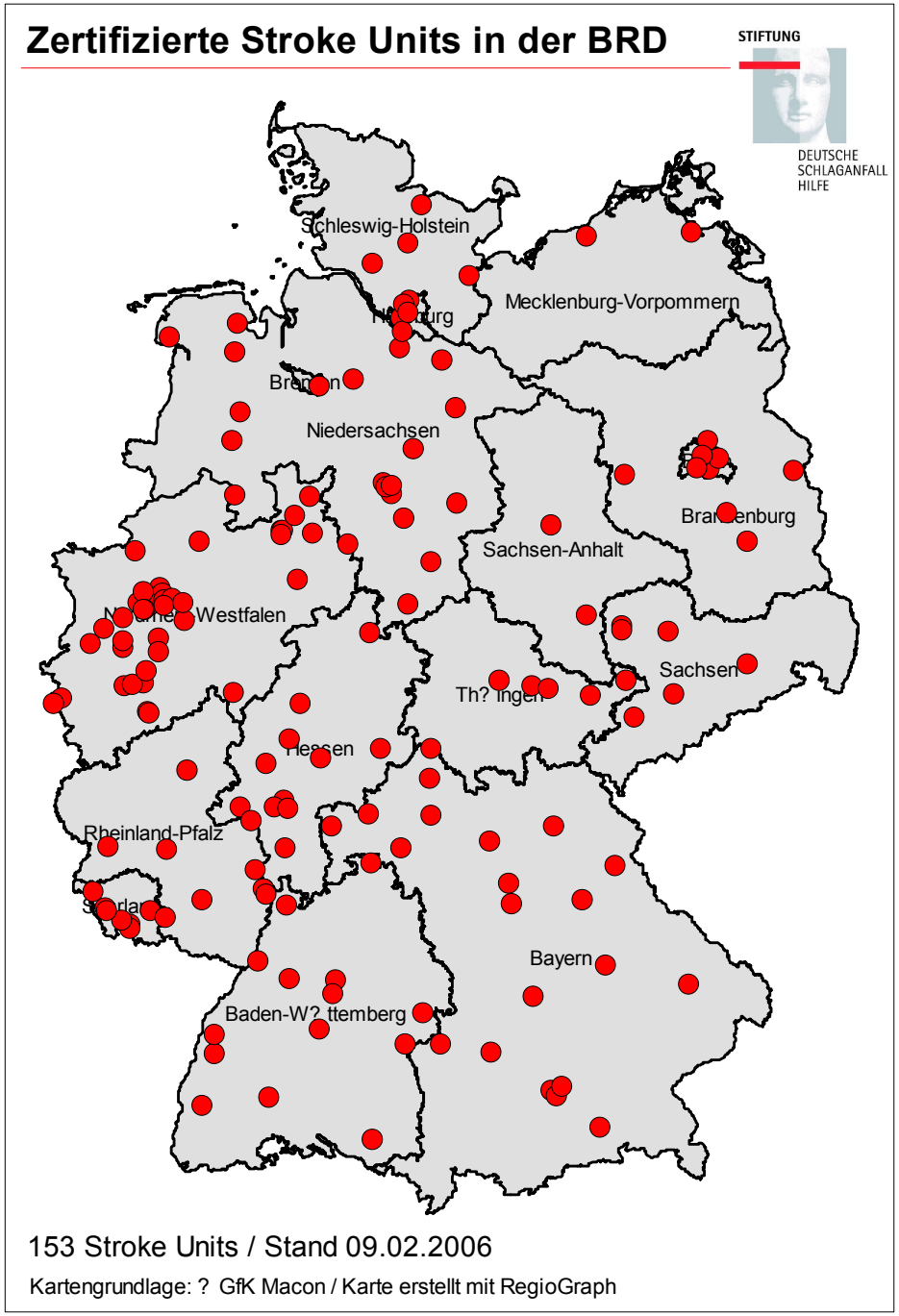


Germany

82.5 Mio. inhabitants

150.000 first ever strokes

Direct stroke costs
2006-2010
30 billion $
2006-2025
108 billion $

Population-based study of event-rate, incidence, case fatality, and mortality for all acute vascular events in all arterial territories (Oxford Vascular Study)

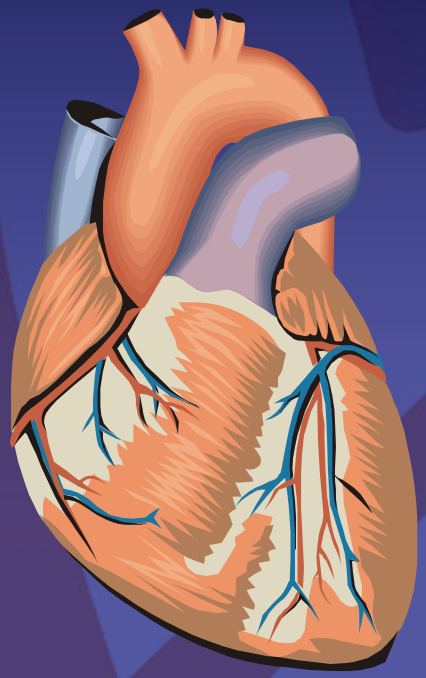
P M Rothwell, A J Coull, L E Silver, J F Fairhead, M F Giles, C E Lovelock, J N E Redgrave, L M Bull, S J V Welch, F C Cuthbertson, L E Binney, S A Gutnikov, P Anslow, A P Banning, D Mant, Z Mehta, for the Oxford Vascular Study

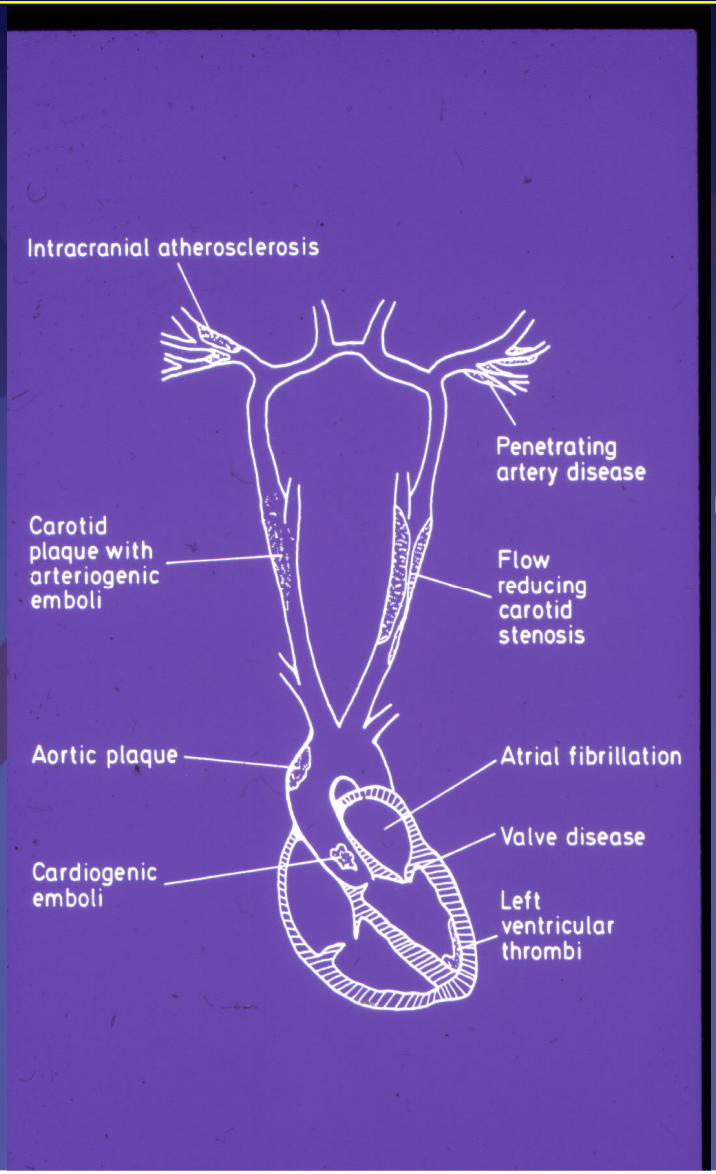
Lancet 2005; 366: 1773–83

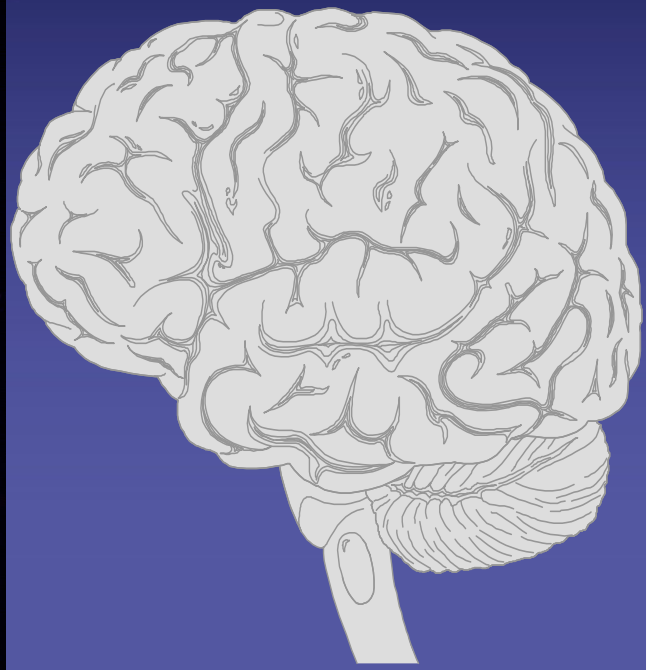
Methods We prospectively assessed all individuals presenting with an acute vascular event of any type in any arterial territory irrespective of age in a population of 91 106 in Oxfordshire, UK, in 2002–05.

Events	Total	first	second
Stroke	918	620	298
ACS	856	522	334
PAD	188	141	47
Total	1962	1283	679

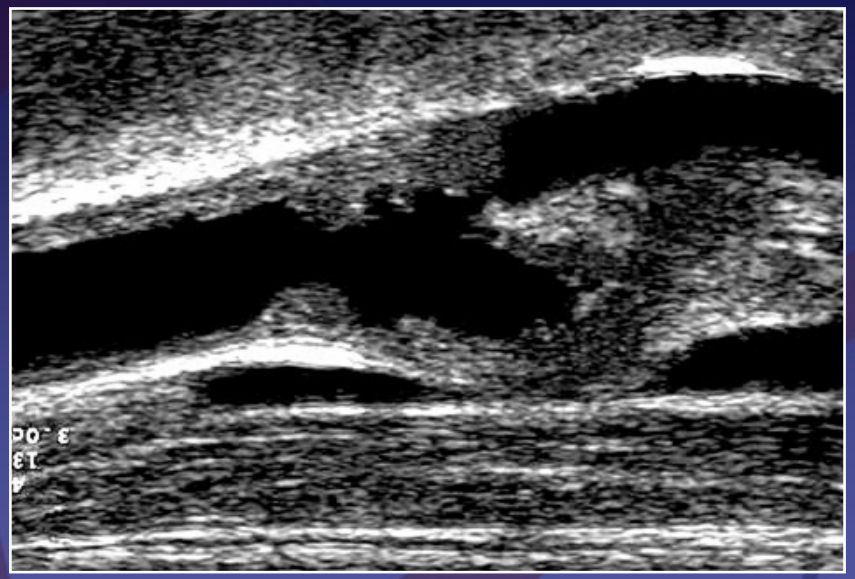
Hypertension and Stroke

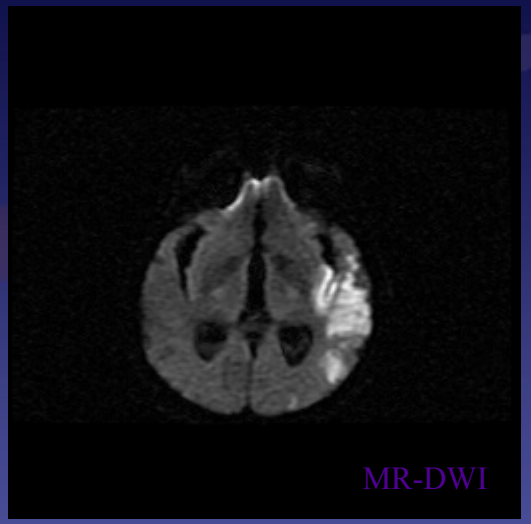


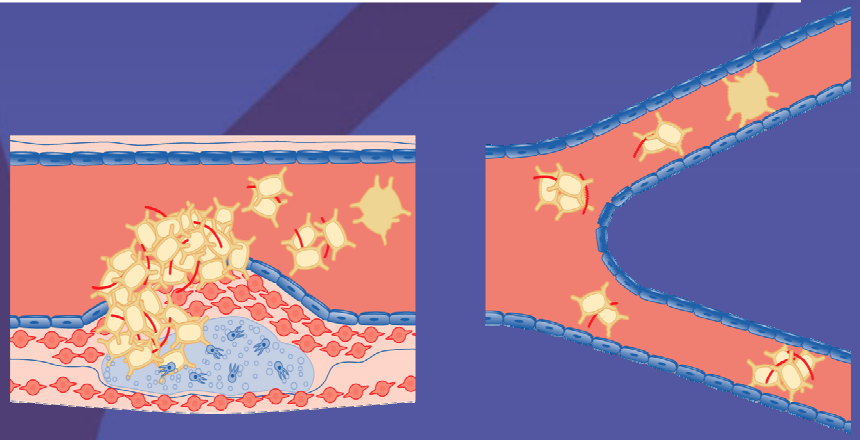


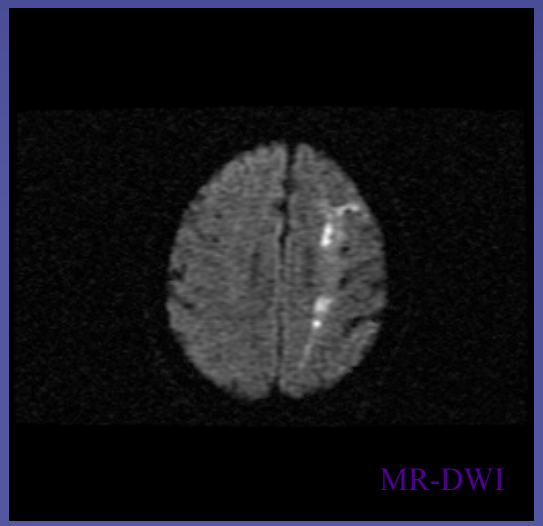


Large vessel disease

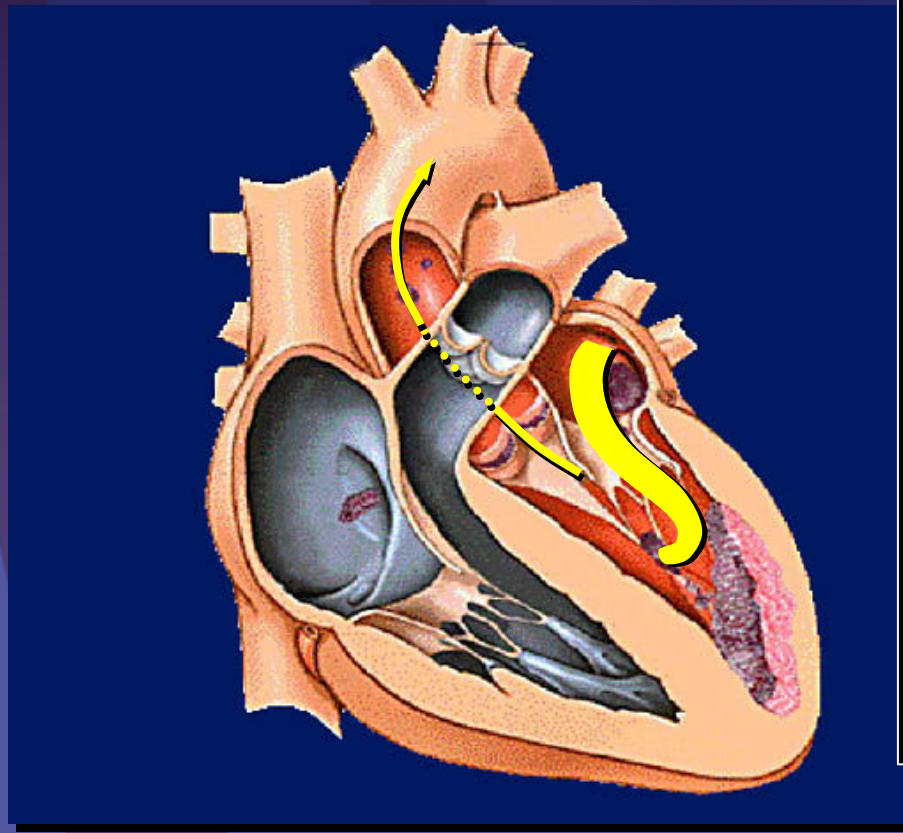


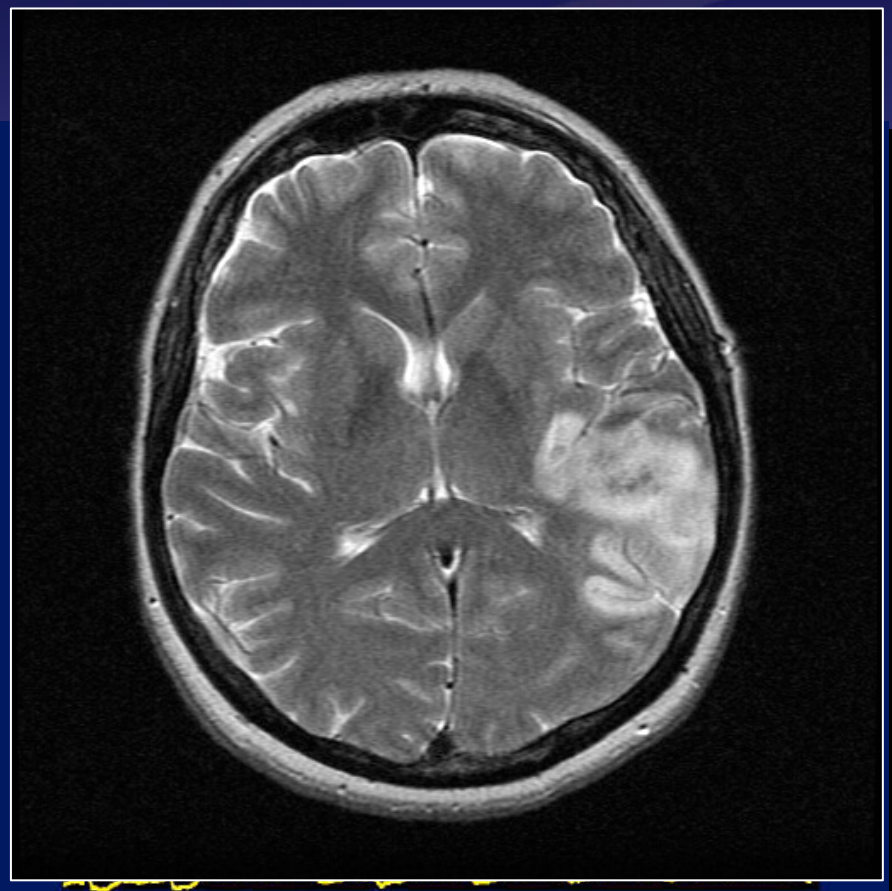




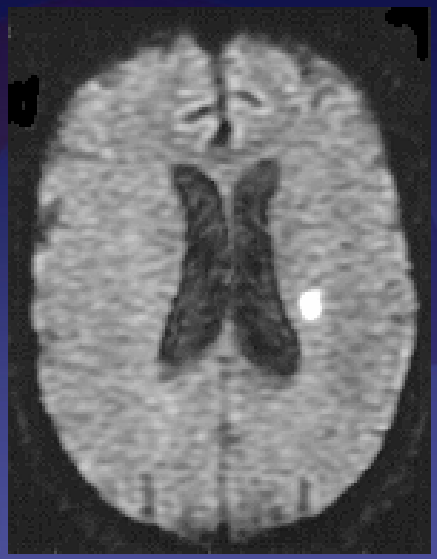


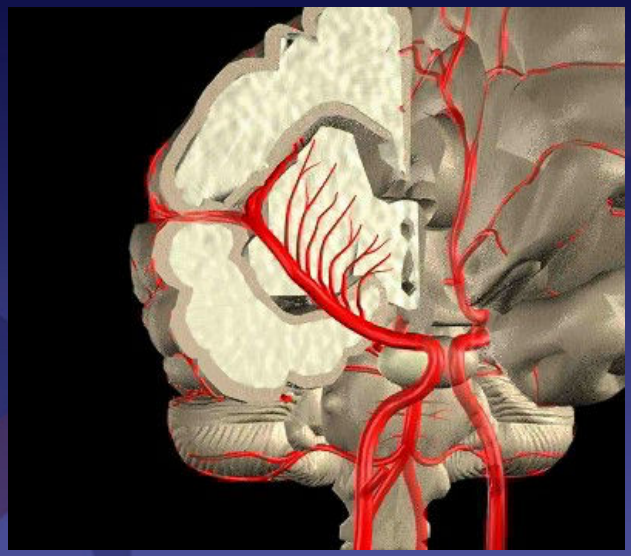
Cardioembolic stroke

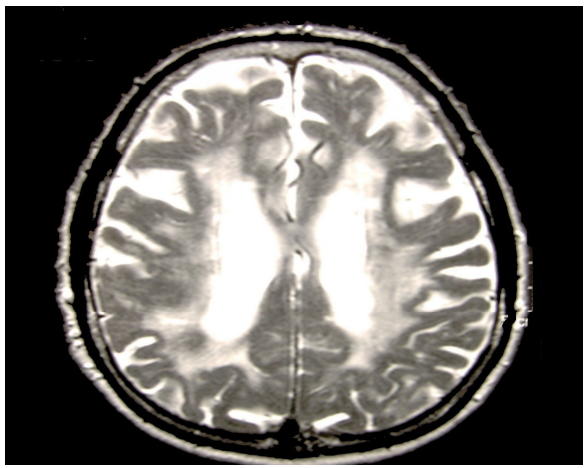




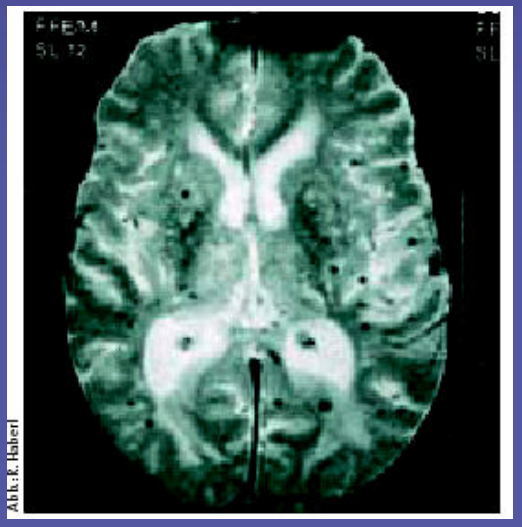
Small vessel disease





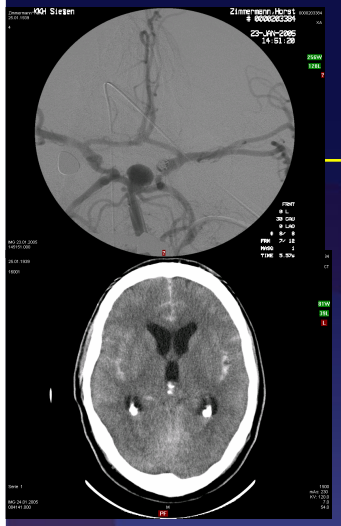


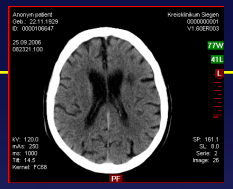
MR-T2



MR-FFE

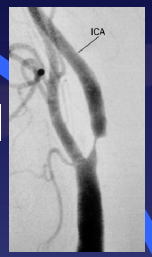
Stroke - Subtyps



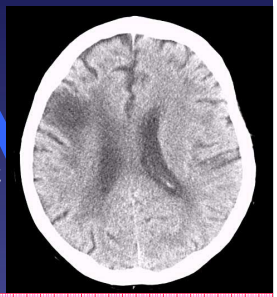


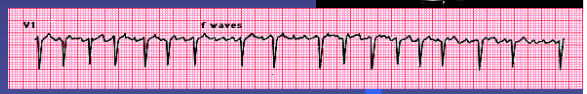
Small vessel
19%

Large vessel
6%



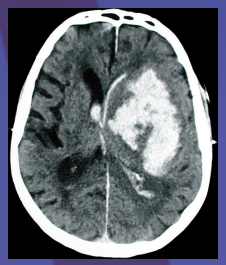
Cardioembolic
14%





SAH
13%

Hemorrhage
26%



ICH
13%

Other 3%

Undetermined
32%

Ischemic
71%

NINCDS Stroke Data Bank:
Foulkes, et al. *Stroke* 1988;19:547.

Costs of Stroke

	hospital	lifetime
Ischemia	9.882 $	90.981 $
ICH	21.535 $	123.565 $
SAH	39.994 $	228.030

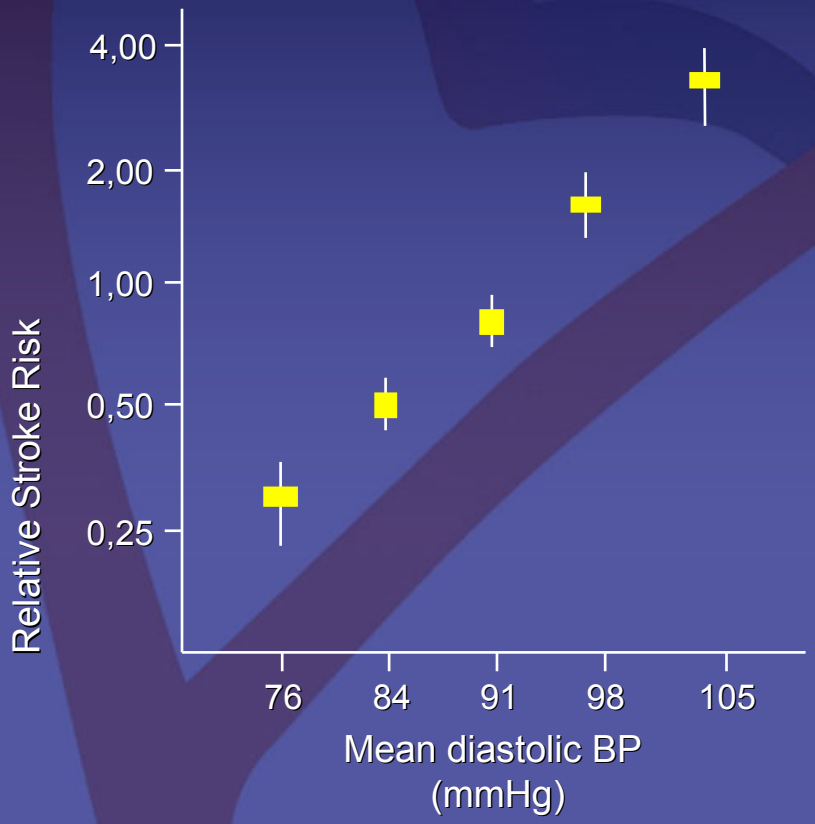
Stroke 1996;27:1459-1466

Blood Pressure (BP), Stroke und CAD

Stroke and diastolic BP

(5 categories of diastolic BP)

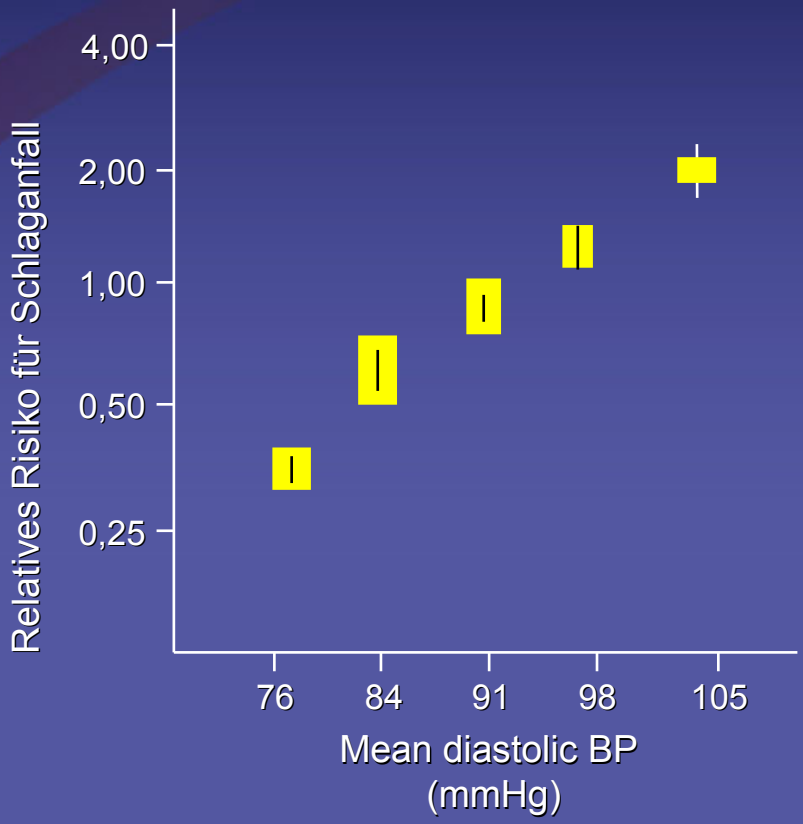
7 prospective cohort studies: 843 events



CAD and diastolic BP

(5 categories of diastolic BP)

9 prospective cohort studies: 4.856 events



MacMahon et al., Lancet 1990;335:766.

Blood Pressure - Treatment

1931

Publication of Hay, British Medical Journal:

“The greatest danger to a man with a high blood pressure lies in its discovery, because then some fool is certain to try to reduce it”

Prevention of stroke by antihypertensive treatment: SHEP[1]

Systolic Hypertension in the Elderly Programme (SHEP)

Objective: to assess the ability of antihypertensive treatment to reduce the risk of total stroke in isolated systolic hypertension

Patient population: n=4,736; chlorthalidone od (± atenolol; n=2,365), placebo od (n=2,371)

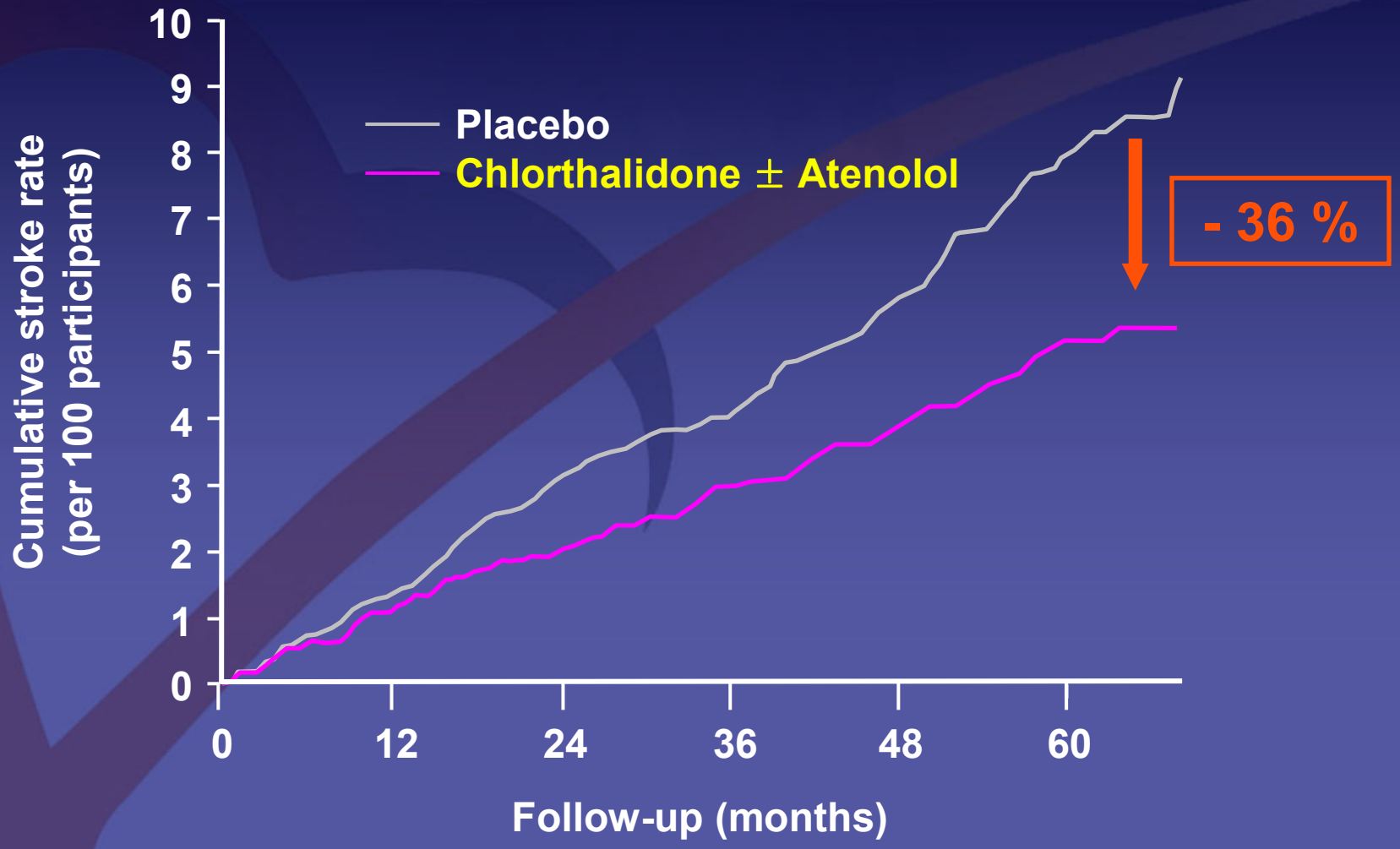
Primary outcome: non-fatal and fatal (total) stroke

Follow-up: 4.5 years

od = once daily

1. SHEP Cooperative Research Group. *JAMA* 1991;265:3255–3264.

SHEP results[1]



1. SHEP Cooperative Research Group. *JAMA* 1991;265:3255–3264.

Prevention of stroke by antihypertensive treatment: Syst-Eur

Systolic Hypertension in Europe (Syst-Eur)

Objective: to assess the effect of the antihypertensive nitrendipine on the risk of stroke

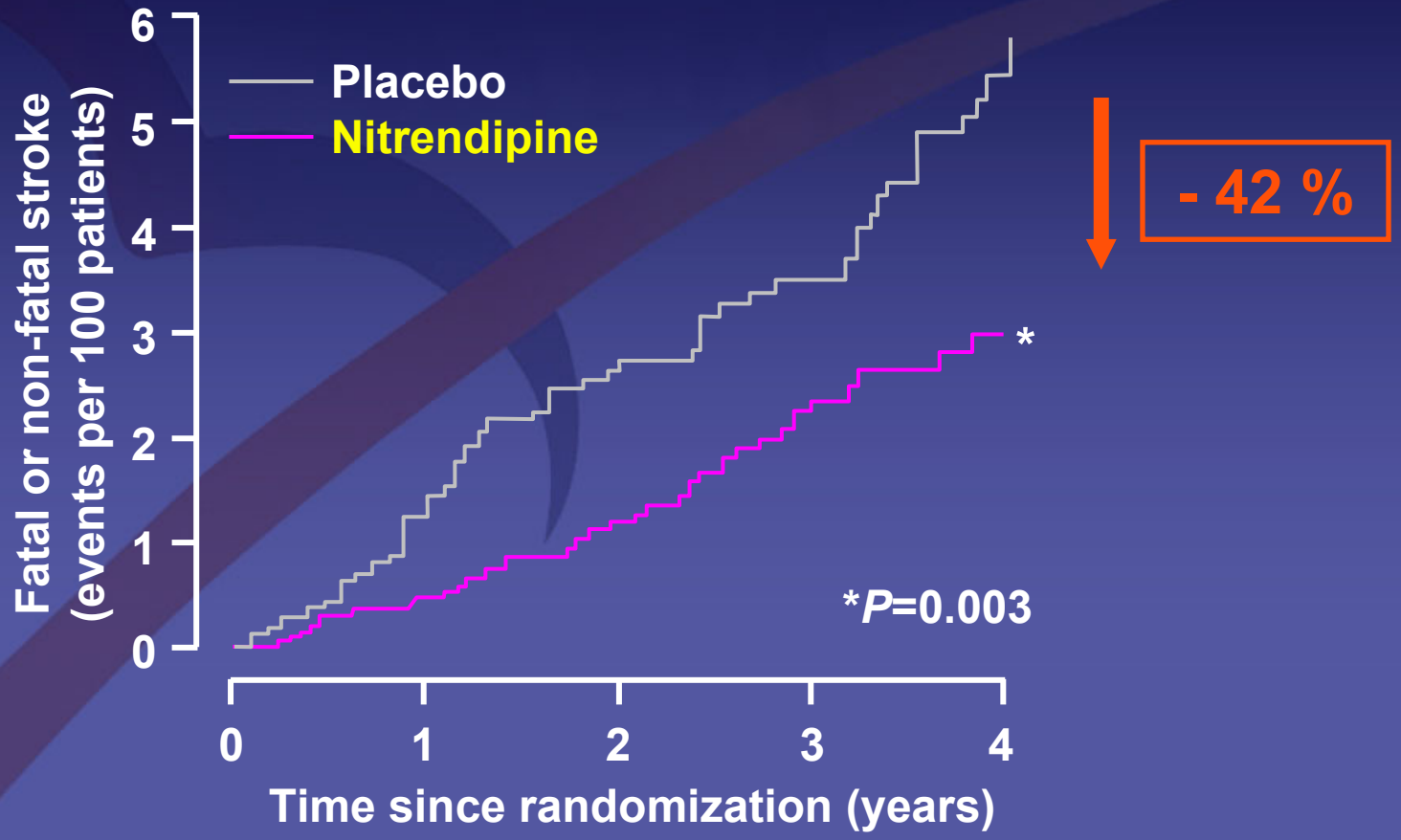
Patient population: n=4,695; nitrendipine (n=2,398), placebo (n=2,297)

Primary outcome: non-fatal and fatal (total) stroke

Follow-up: 4 years

1. Staessen JA, et al. *Lancet* 1997;350:757–764.

Syst-Eur results[1]



1. Staesson JA, et al. *Lancet* 1997;350:757–764.

SHEP and Syst-Eur: results and conclusions

SHEP

36% total stroke reduction in patients receiving antihypertensive treatment for isolated systolic hypertension[1]

Syst-Eur

42% total stroke reduction in patients receiving nitrendipine for isolated systolic hypertension[2]

Treatment of hypertension significantly reduces the rate of primary stroke

1. SHEP Cooperative Research Group. *JAMA* 1991;265:3255–3264;
2. Staesson JA, et al. *Lancet* 1997;350:757–764.

Secondary stroke prevention

- After a stroke, the risk of recurrent stroke is high:
  - 8% of patients suffer a further stroke within 1 year[1]
  - 17% of patients suffer a further stroke within 5 years[2]
- Therefore, there is a high medical need for a safe and effective treatment for secondary stroke prevention
- Hypertension is an important determinant of risk of stroke recurrence[3]
- Most published data relate to primary prevention; little is known about secondary prevention

1. Lees KR, et al. *BMJ* 2000;320:991–994; 2. Hankey GJ, Warlow CP. *Lancet* 1999;354:1457–1463;
3. Rogers A, et al. *BMJ* 1996;313:147.

Antihypertensive therapy in secondary stroke prevention: PROGRESS[1]

Perindopril pROtection aGainst REcurrent Stroke Study (PROGRESS)

Objective: to determine the effects of antihypertensive therapy with an ACE inhibitor on recurrent stroke in patients with a history of stroke or TIA, in both hypertensive and normotensive patients

Patient population: n=6,105; perindopril plus indapamide (n=3,051), placebo (n=3,054)

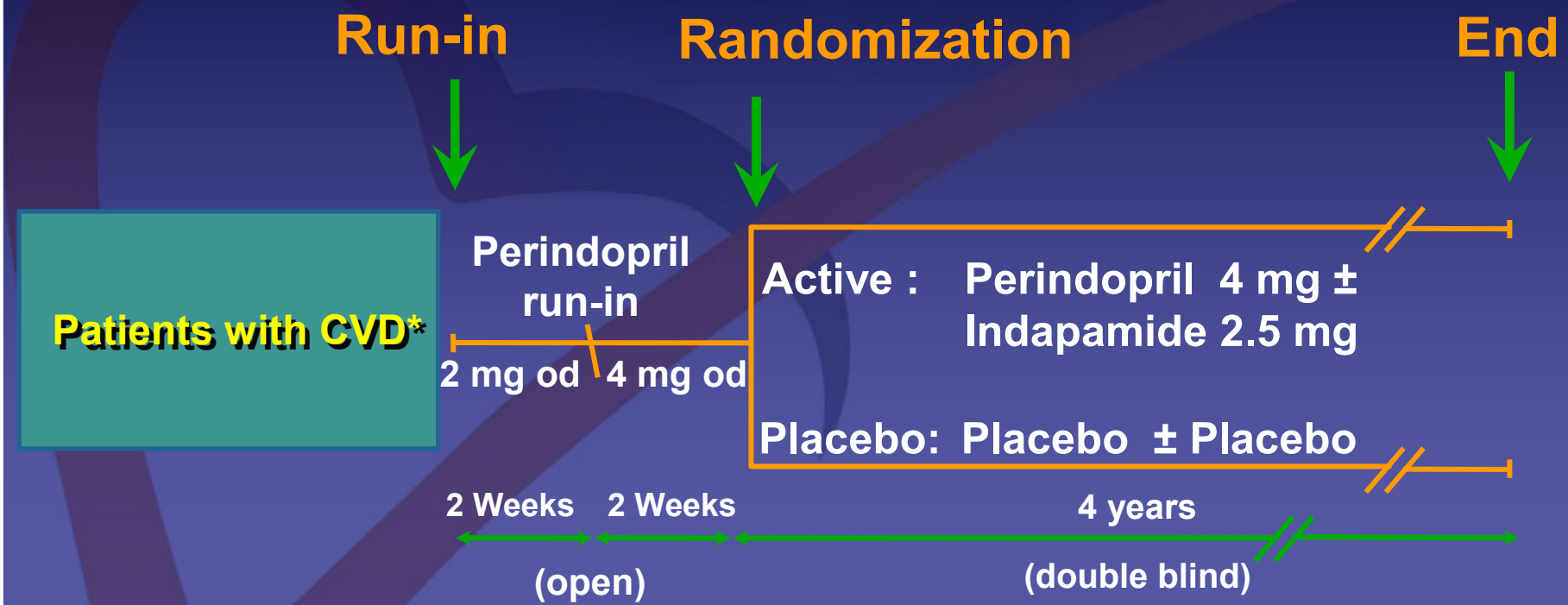
Primary outcome: total stroke (fatal or non-fatal)

Follow-up: 4 years

1. PROGRESS Collaborative Group. *Lancet* 2001;358:1033–1041.

PROGRESS - Design

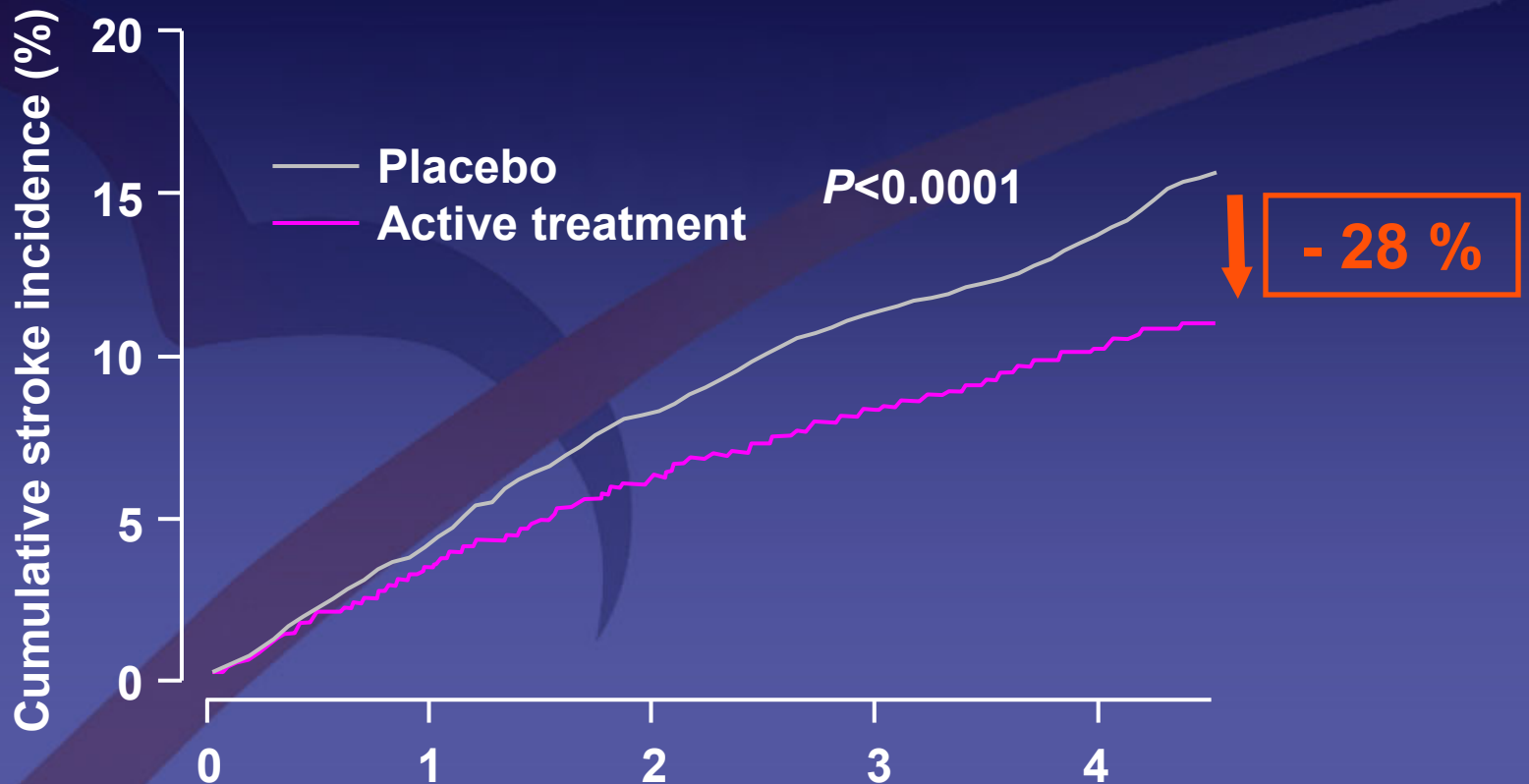
Perindopril Protection Against Recurrent Stroke Study



- ischemic or hemorrhagic stroke or TIA < 5 years
- hypertensiv if > 160/90 mmHg

PROGRESS Collaborative Group. Lancet 2001;358:1033

PROGRESS results[1]

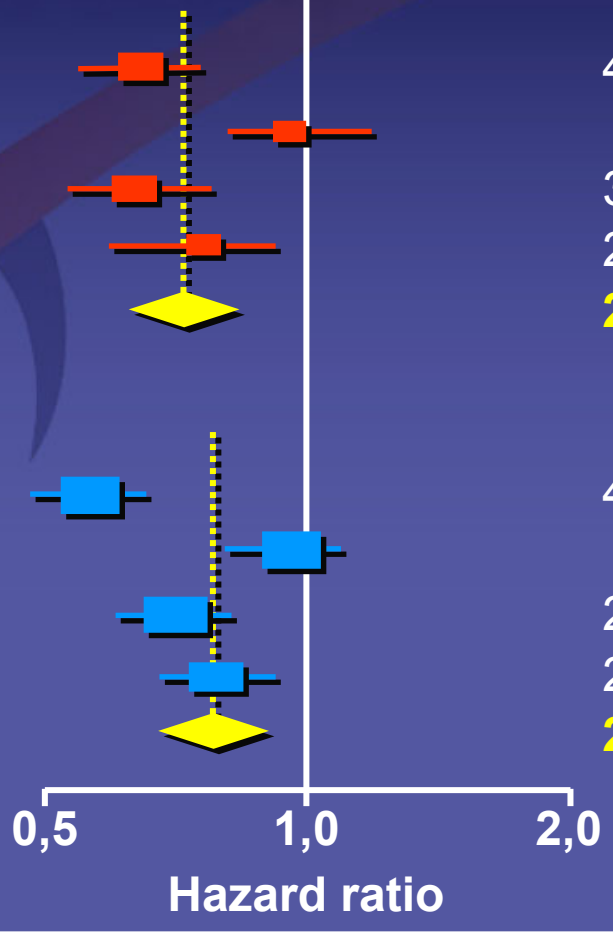


Numbers at risk					
Active	3051	2902	2765	2634	1595
Placebo	3054	2880	2707	2551	1533

1. PROGRESS Collaborative Group. *Lancet* 2001;358:1033–1041.

Subgroups (PROGRESS, Lancet 2001;358:1033)

	events/patients active	events/patients placebo	favors aktive	favors placebo	RRR (95% CI)
Stroke					
combination	150/1770	255/1774			43% (30 – 54)
monotherapy	157/1281	165/1280			5% (-19 – 23)
hypertensiv	163/1464	235/1452			32% (17 – 44)
non hypertens.	144/1587	185/1602			27% (8 – 42)
total	**307/3051**	**420/3054**			**28% (17 – 38)**
Major vascular events					
combination	231/1770	367/1774			40% (29 – 49)
monotherapy	227/1281	237/1280			4% (-15 – 20)
hypertensiv	240/1464	331/1452			29% (16 – 40)
non hypertens.	218/1587	273/1602			24% (9 – 37)
total	**458/3051**	**604/3054**			**26% (16 – 34)**



PROGRESS: conclusions[1]

Active treatment (perindopril and indapamide)

- Reduced blood pressure by 12.3/5.0 mm Hg
- 43% relative risk reduction in secondary stroke

Hypertensive vs normotensive

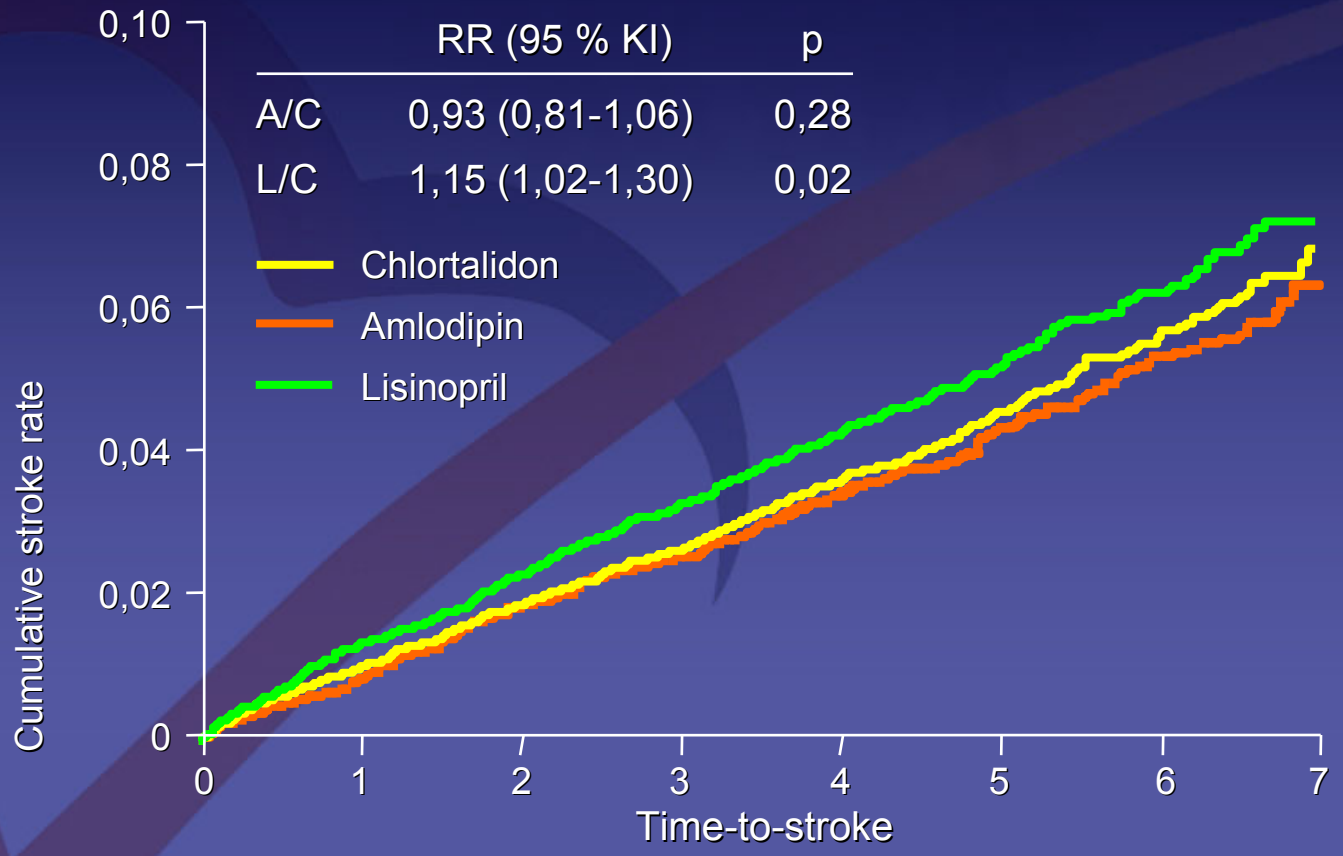
- Similar reduction in risk of stroke ($P<0.01$)
- No benefit from perindopril alone

Some antihypertensive treatments reduce the risk of recurrent stroke

1. PROGRESS Collaborative Group. *Lancet* 2001;358:1033–1041.

ALLHAT

Cumulative Stroke Rate



Patient number							
Chlortalidon	15,255	14,515	13,934	13,309	11,570	6,385	3,217	567
Amlodipin	9,048	8,617	8,271	7,949	6,937	3,845	1,813	506
Lisinopril	9,054	8,543	8,172	7,784	6,765	3,891	1,828	949

ALLHAT Coll Res Group, JAMA 2002;288:2981-2997.

TEVETEN®
eprosartan mesylate

MOSES

Eprosartan in Secondary Stroke Prevention: The MOSES Study

MOSES

The MOSES study

MOrbidity and mortality after Stroke – Eprosartan compared with nitrendipine for Secondary prevention

(MOSES)

Hypothesis

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

Stroke, 2005;36:1218-1226

MOSES

Rationale

- High risk of recurrence after stroke
- Need for better management of stroke patients
- Few comparative trials focusing on the AIIAs vs other available antihypertensives
- Few recurrent stroke prevention trials
- Additional beneficial effects of AIIAs?
- Why eprosartan?
  - Effectively lowers systolic blood pressure[1,2]
  - Shown to reduce SNS activity[3]
  - Reduced secondary stroke in an experimental model[4]
- Why nitrendipine?
  - Significantly reduced the risk of a first stroke in the Syst-Eur trial[5,6]

1. Sega R. *Blood Press* 1999;8:114–121; 2. Gavras I, Gavras H. *Pharmacotherapy* 1999;19:102S–107S;
3. Ohlstein O, et al. *Pharmacology* 1997;55:244–251; 4. Barone FC, et al. *Cardiovasc Res* 2001;50:525–537;
5. Staesson JA, et al. *Lancet* 1997;350:757–764; 6. Forcette F, et al. *Arch Intern Med* 2002;162:2046–2052.

MOSES

Study design

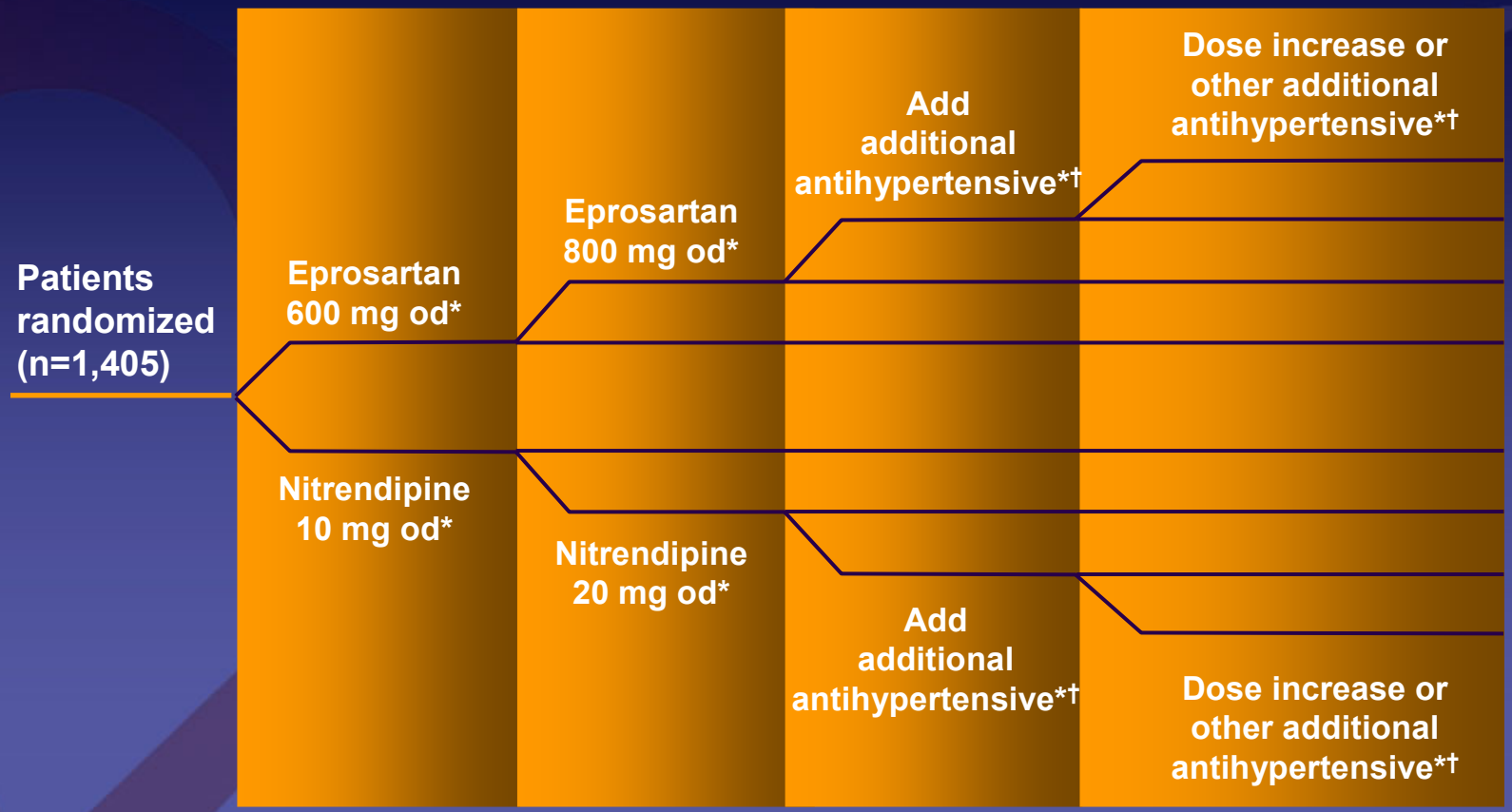
- PROBE design:
  - Prospective, Randomized, Open, Blinded Endpoint[1]
- Inclusion criteria:
  - Hypertension requiring treatment, plus one of the following within the 24 months prior to study enrolment:
    - Cerebral ischaemia (TIA, PRIND, complete stroke)
    - Cerebral haemorrhage
- Exclusion criteria:
  - Carotid artery stenosis >70%
  - Severe CHF, unstable angina, or valve disease
  - Age over 85 years
  - Contraindication for eprosartan or nitrendipine

PRIND=prolonged reversible ischaemic neurologic deficit; CHF=congestive heart failure

1. Hansson L, et al. *Blood Press* 1992;1:113–119.

MOSES

MOSES: treatment plan



*Titration upwards if target blood pressure (sitDBP <90 mm Hg/sitSBP <140 mm Hg) not reached.
†Combination therapy with antihypertensive agents, excluding ACE inhibitors, AIIAs and calcium channel blockers.

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Study endpoints

- Primary endpoint:
  - Total mortality plus total number of cardiovascular and cerebrovascular events
- Secondary endpoints:
  - Change in mental capacity and functional status (Barthel Index and Rankin Scale)
  - Individual elements of the combined primary endpoint
- Mean follow-up:
  - 2.5 years

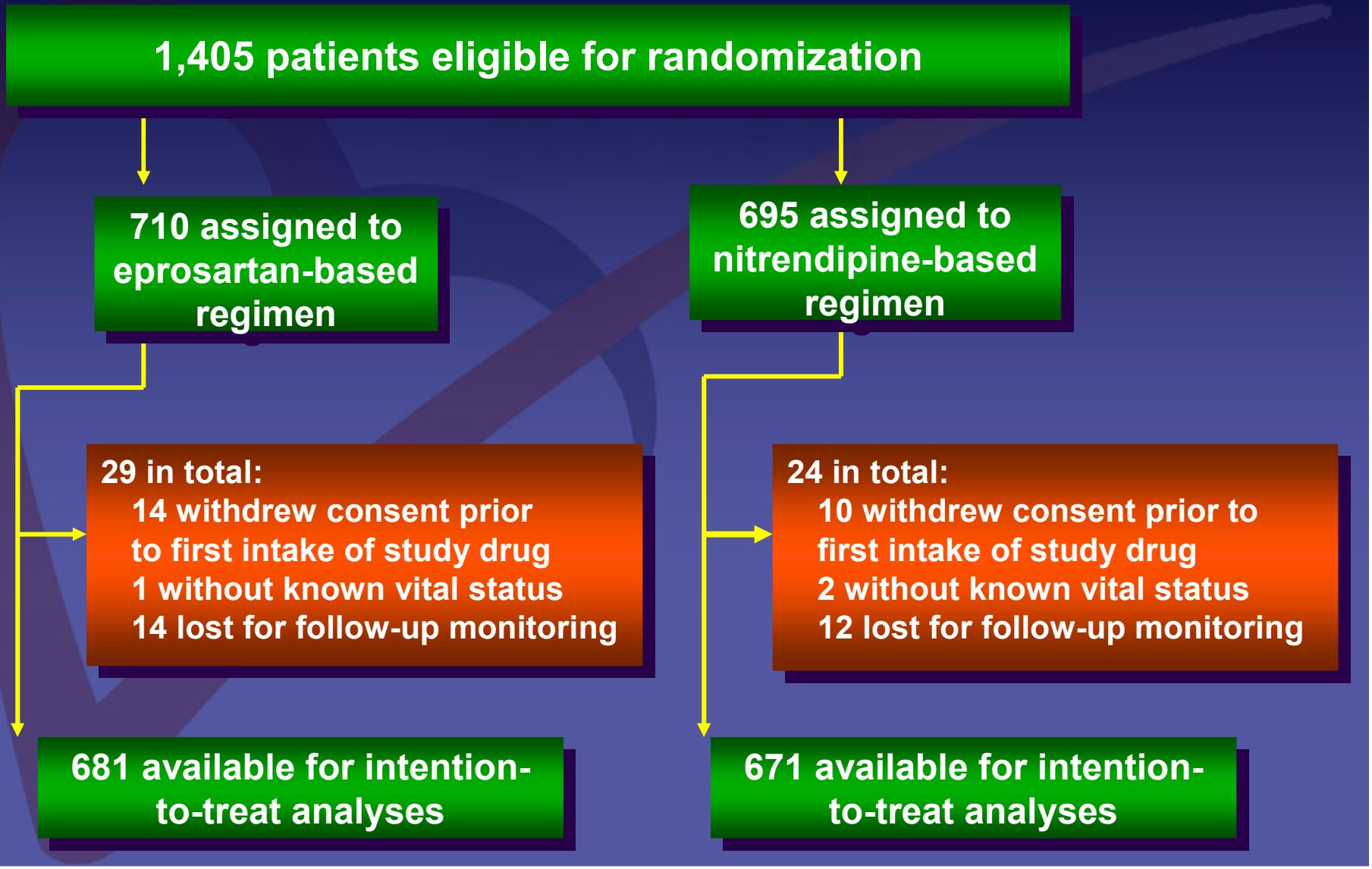
MOSES

Assessments

- Procedures regularly performed:
  - Sitting and ambulatory blood pressure measurements (ABPM)
  - Mini Mental State Examination (MMSE) score
  - Documentation of all drugs
  - Barthel Index and Rankin Scale
  - Electrocardiogram
  - Adverse event reporting

MOSES

Study profile



MOSES

Baseline characteristics

	Eprosartan	Nitrendipine
Patient number (n)	681	671
Sex (% male)	53.6	54.8
Age (years)	67.7	68.1
BMI (kg/m^2)	27.6	27.4
Mean 24 h SBP (mm Hg)	139.7	140.0
Mean 24 h DBP (mm Hg)	81.7	81.5
Time between qualifying event and allocation (days)	347.6	349.8

BMI=body mass index

MOSES

Baseline characteristics

	Eprosartan	Nitrendipine
Qualifying disease		
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)
MMSE score	25.8	25.8
Barthel Index (score)	90.6	90.2
Patients with Barthel index ≥90	75.6%	75.3%
Modified Rankin Scale (score)	1.5	1.5
None to slight disability (0–2)	70.4	71.4
Moderate disability (3)	17.9	15.9
Severe disability (4–5)	11.7	12.7

MOSES

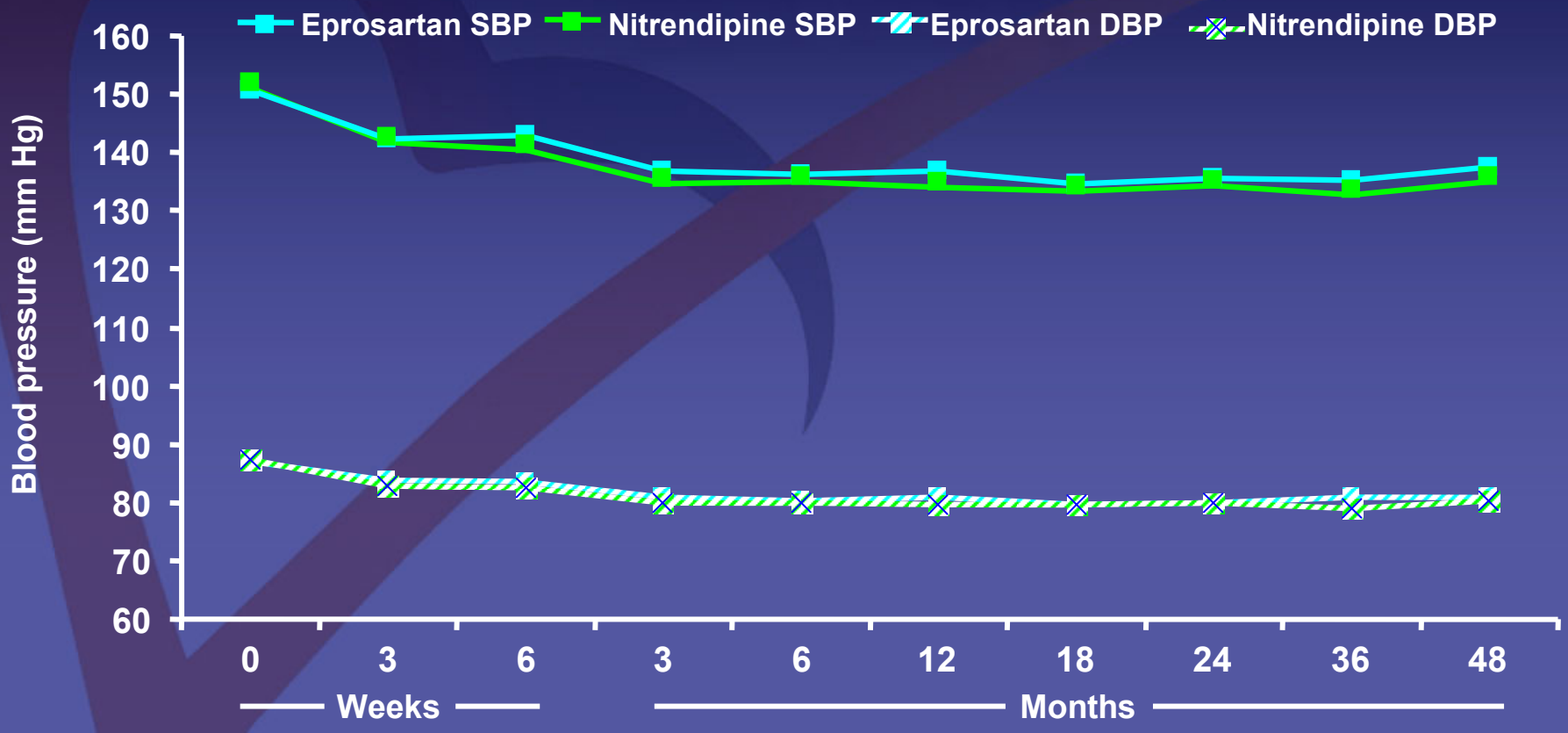
Baseline characteristics

	Eprosartan	Nitrendipine
Diabetes mellitus	36.0	37.7
Hyperlipidaemia	54.3	51.9
Hyperuricaemia	17.6	18.5
MI	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

COPD=chronic obstructive pulmonary disease

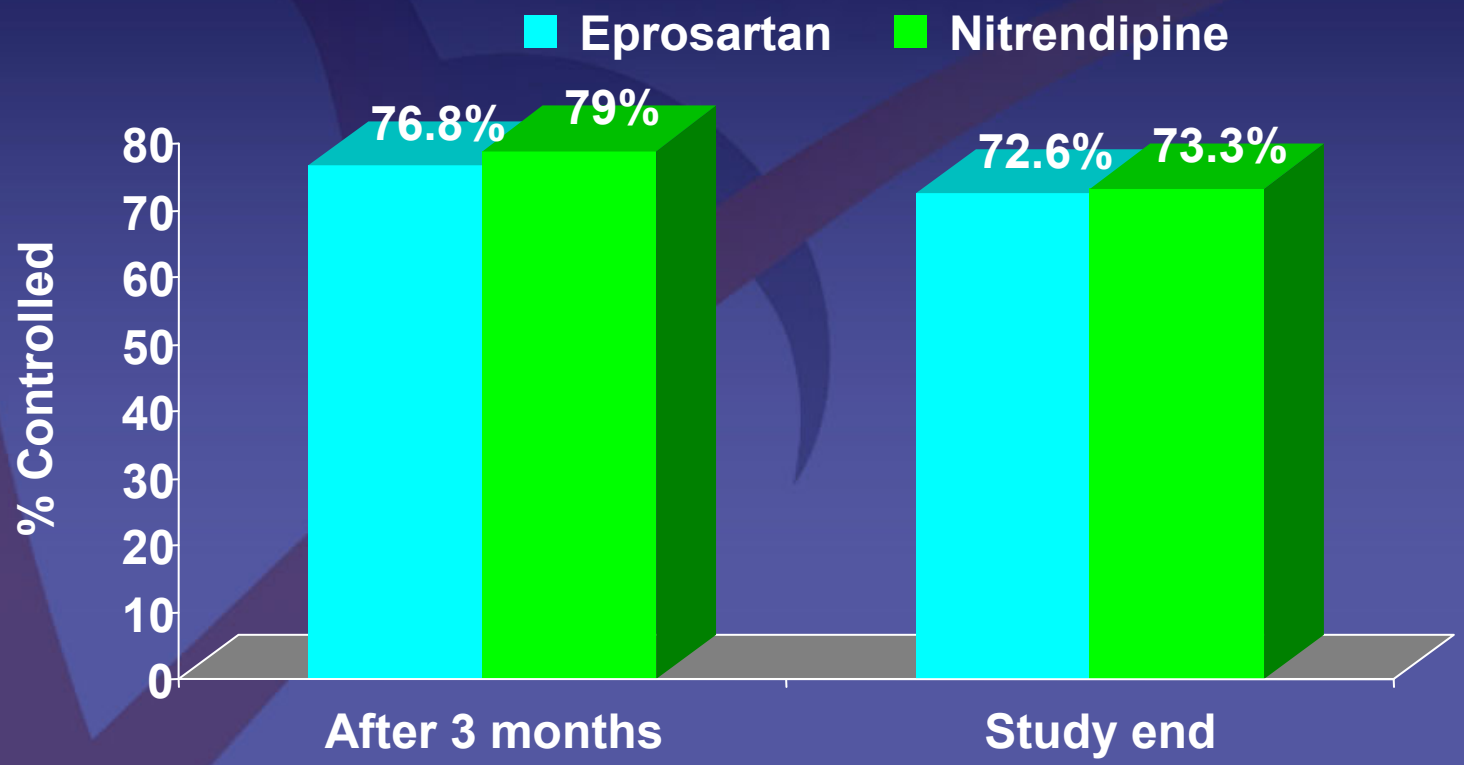
MOSES

SBP and DBP reduction



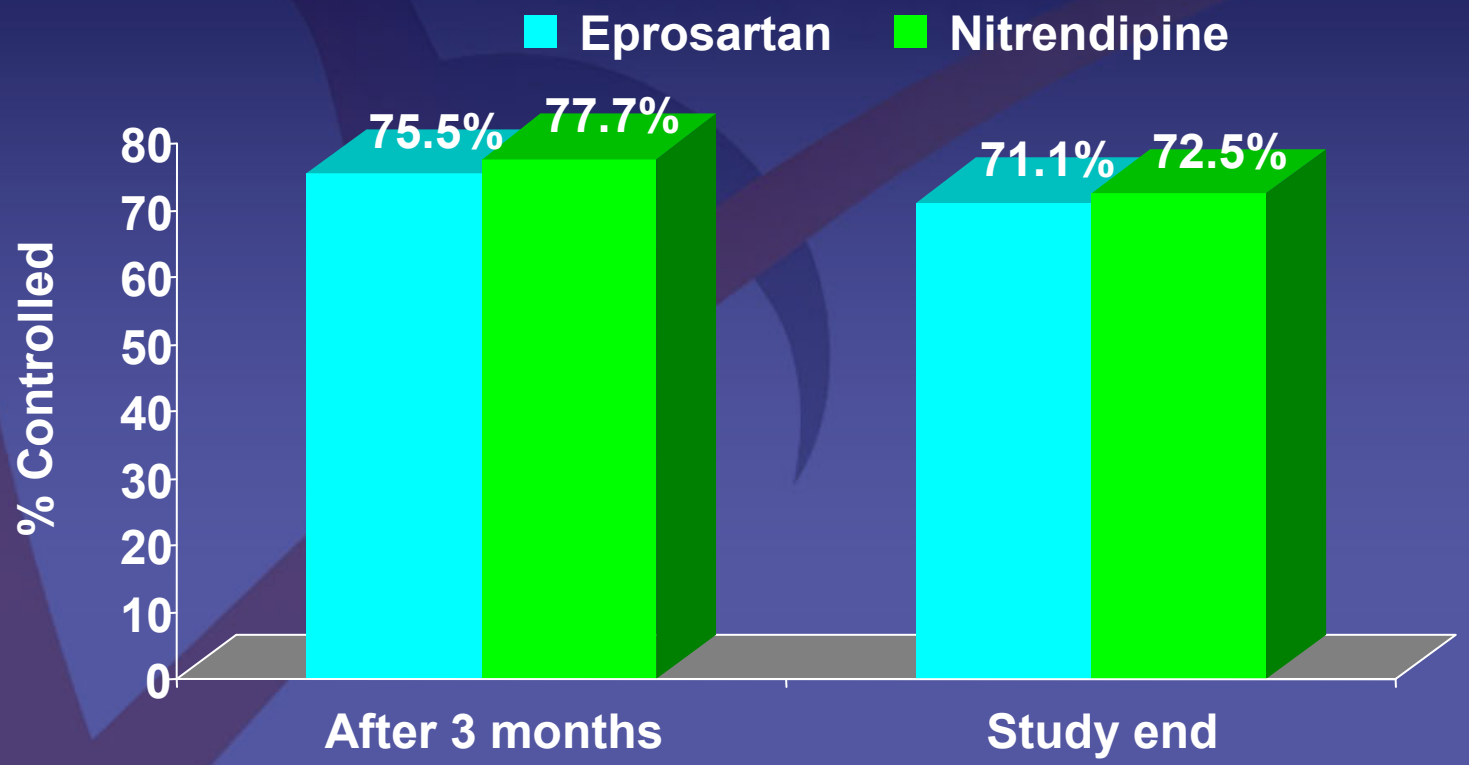
MOSES

SBP control <140 mm Hg



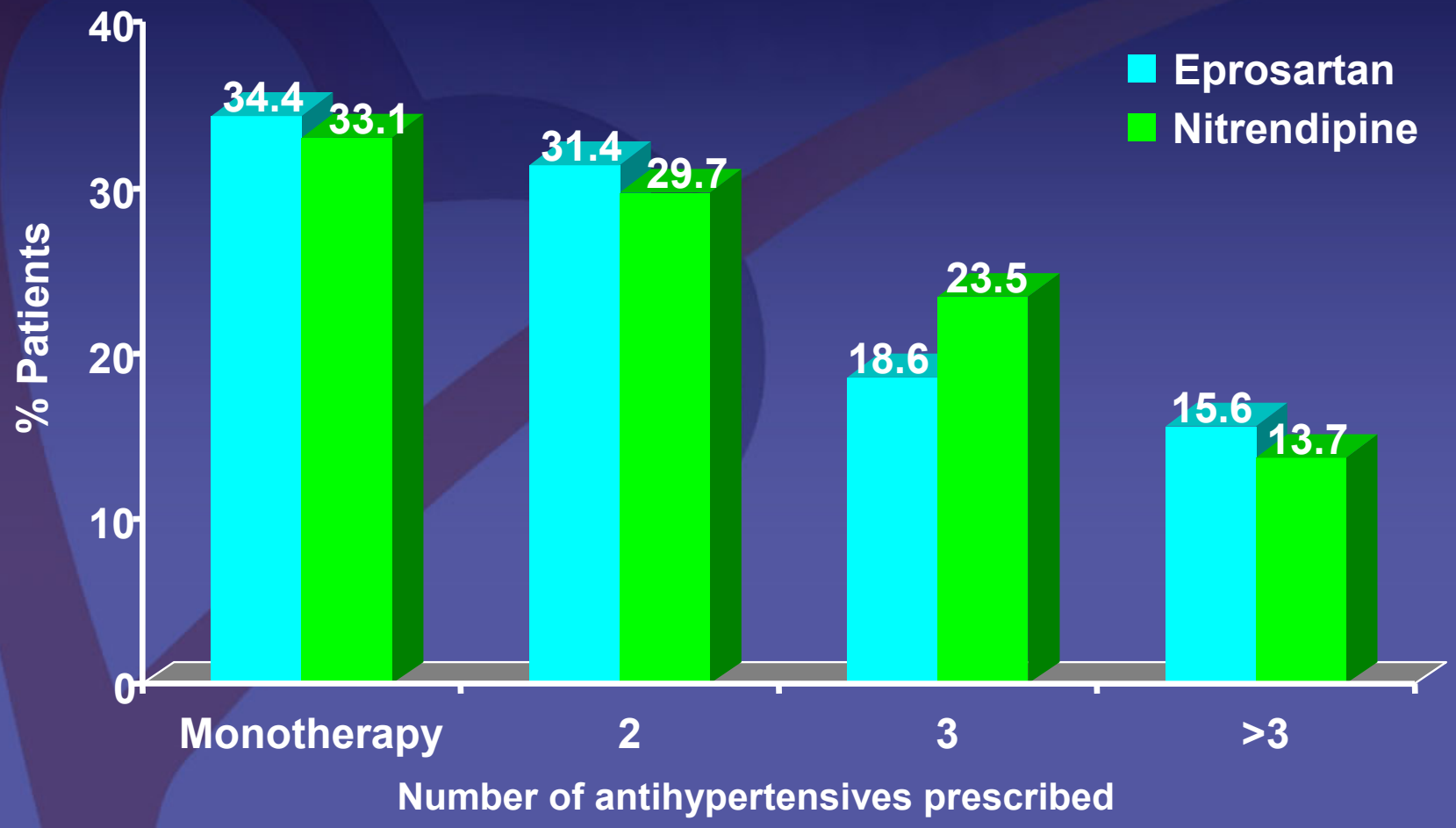
MOSES

SBP control <140 mm Hg and DBP <90 mm Hg



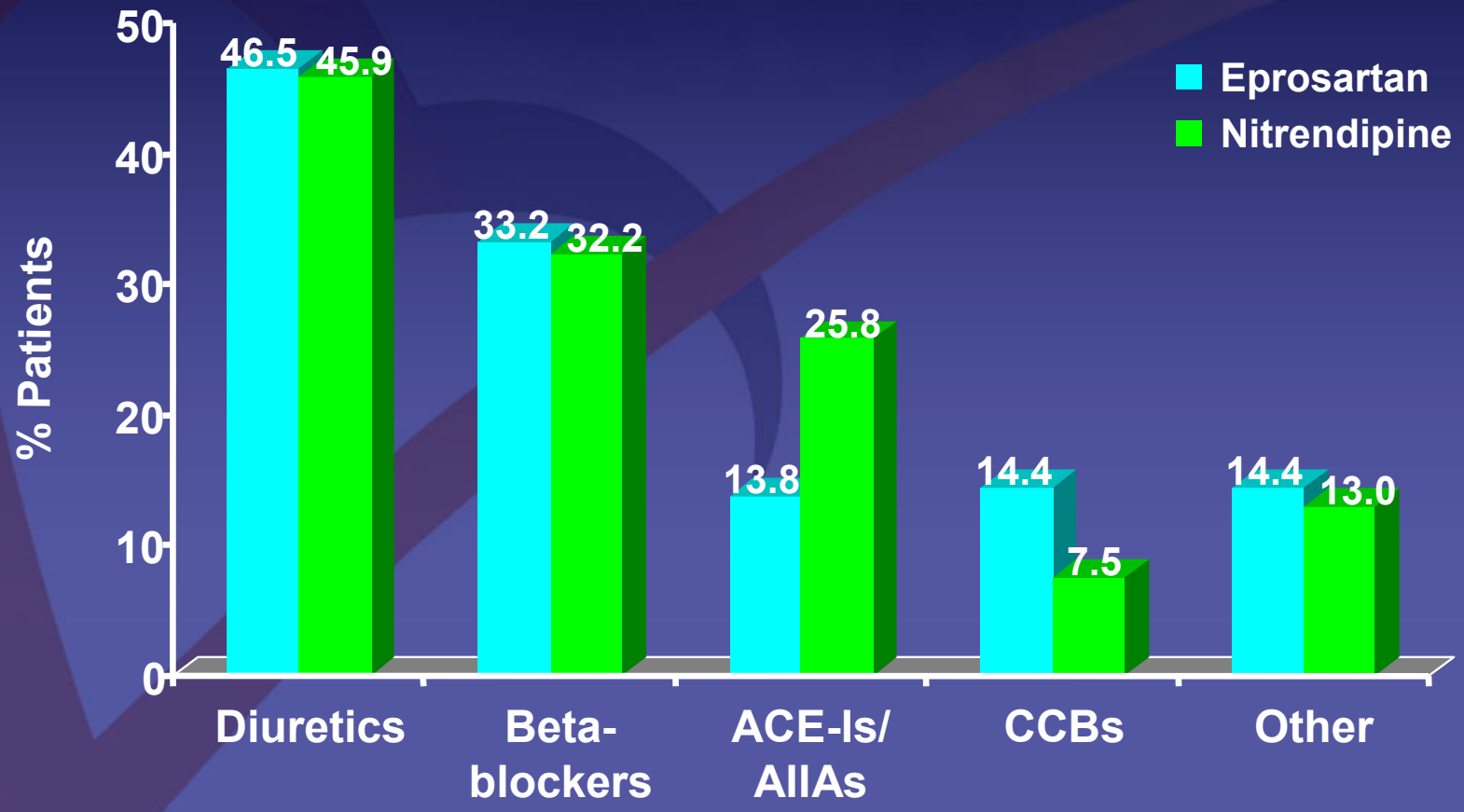
MOSES

Antihypertensive therapy



MOSES

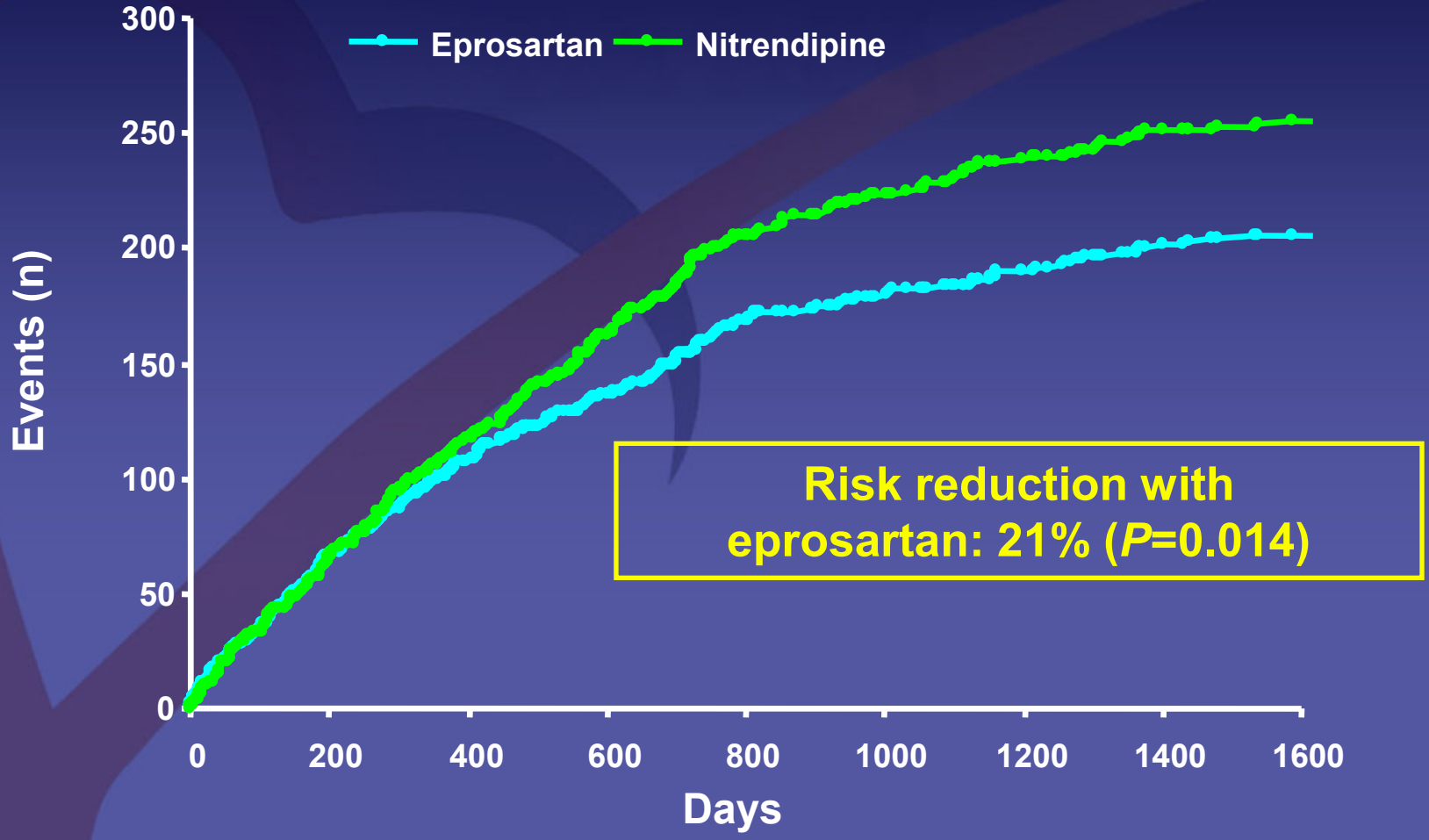
Antihypertensive medication (final visit)



ACE-Is=ACE inhibitors; CCBs=calcium channel blockers

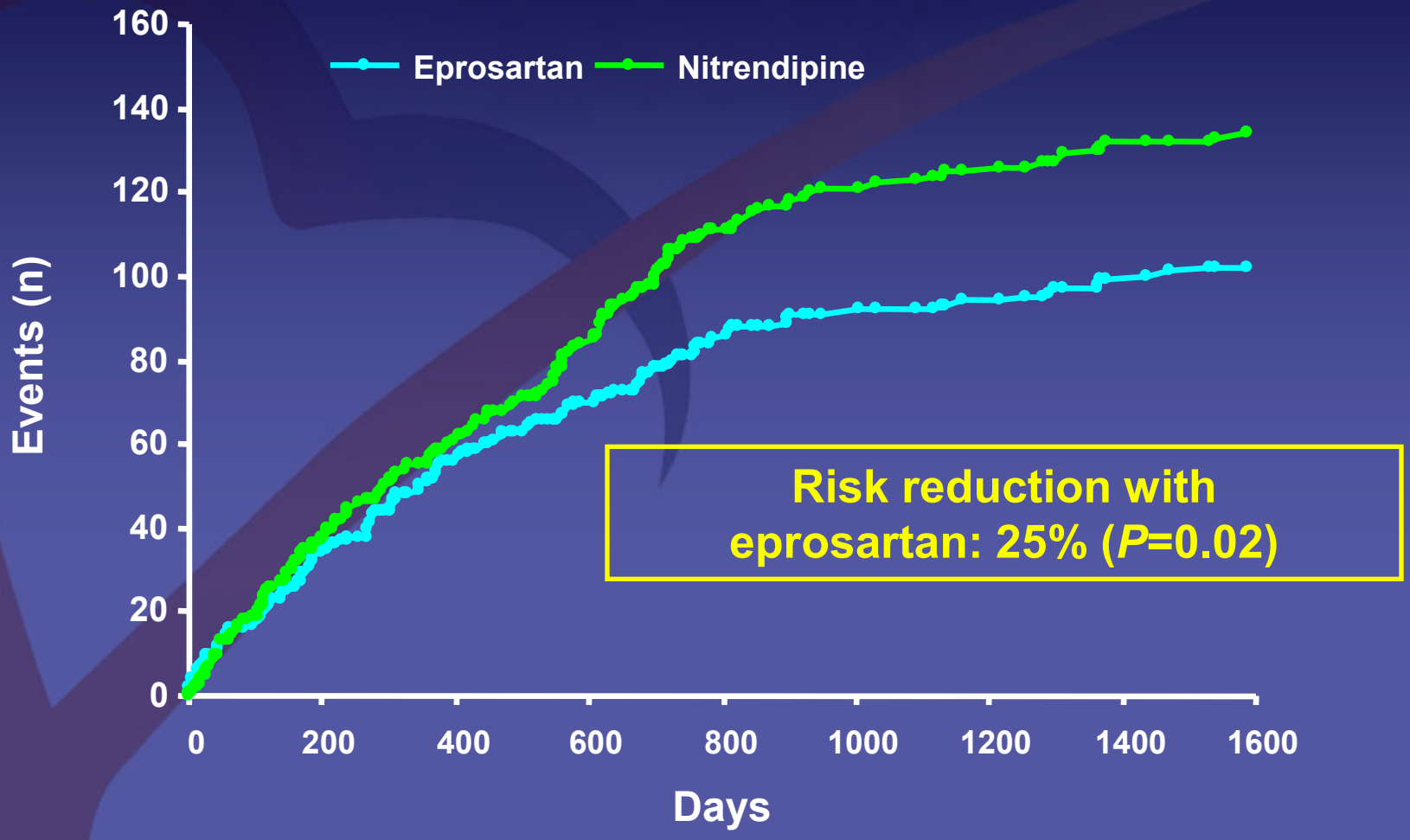
MOSES

Primary endpoint (morbidity and mortality)



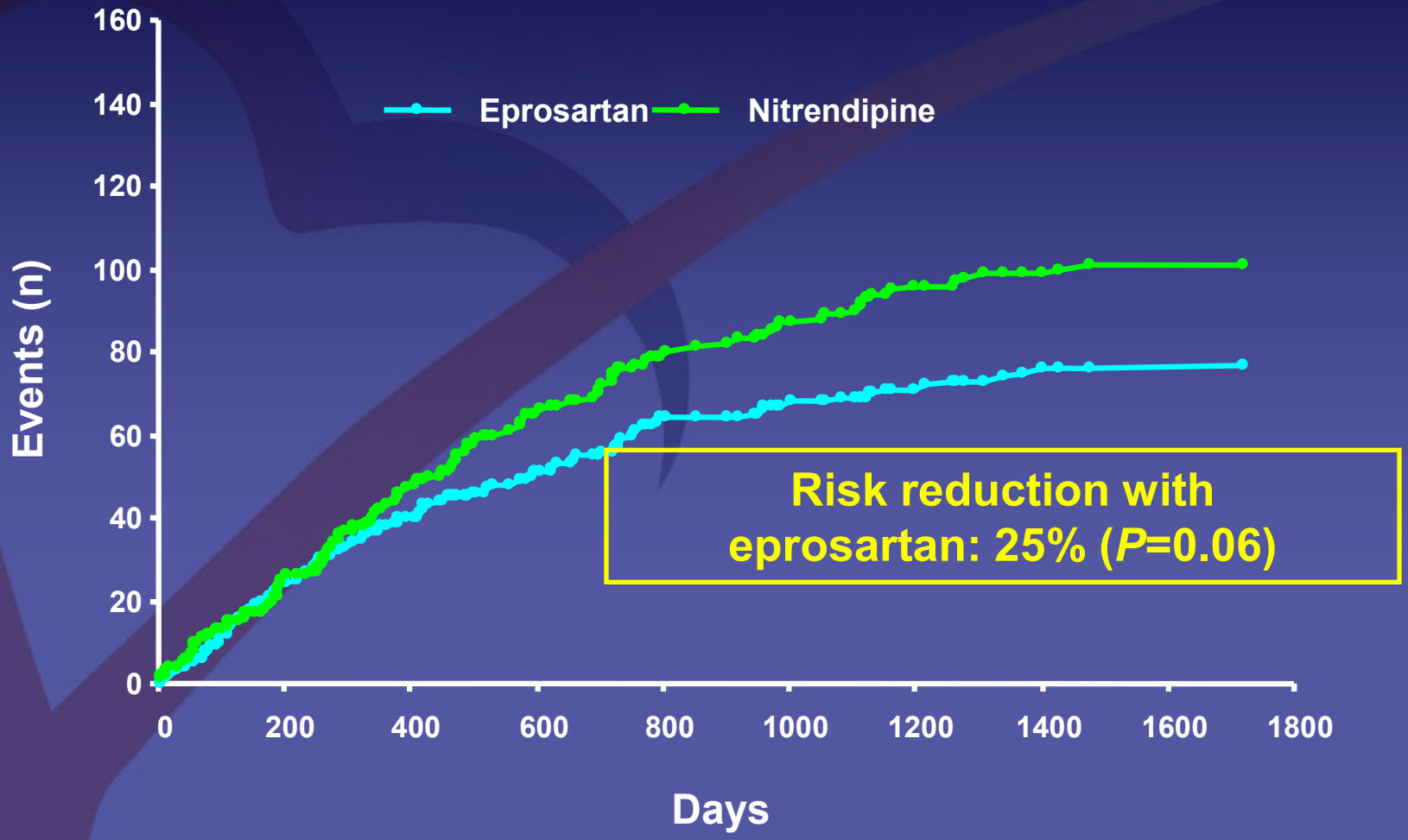
MOSES

Secondary endpoint (cerebrovascular events)



MOSES

Secondary endpoint (cardiovascular events)



MOSES

MMSE, Rankin Scale, Barthel Index

	Eprosartan	Nitrendipine
MMSE mean score	25.6	25.5
Modified Rankin Scale (score)	1.4	1.5
Barthel Index (score)	88.8	88.1

MOSES

Key results

- Blood pressure significantly and similarly reduced in both treatment groups
- Eprosartan reduced the incidence of the primary composite endpoint (mortality and total cerebrovascular and cardiovascular events) by 21%
- Total cerebrovascular events reduced by 25% with eprosartan

Additional benefits beyond blood pressure reduction: LIFE[1]

Losartan Intervention For Endpoint reduction in hypertension (LIFE) study

Objective: to establish whether the AIIA losartan provides additional cardiovascular benefits beyond blood pressure reduction

Patient population: 9,193 patients with systolic hypertension assigned either losartan (n=4,605) or atenolol (n=4,588)

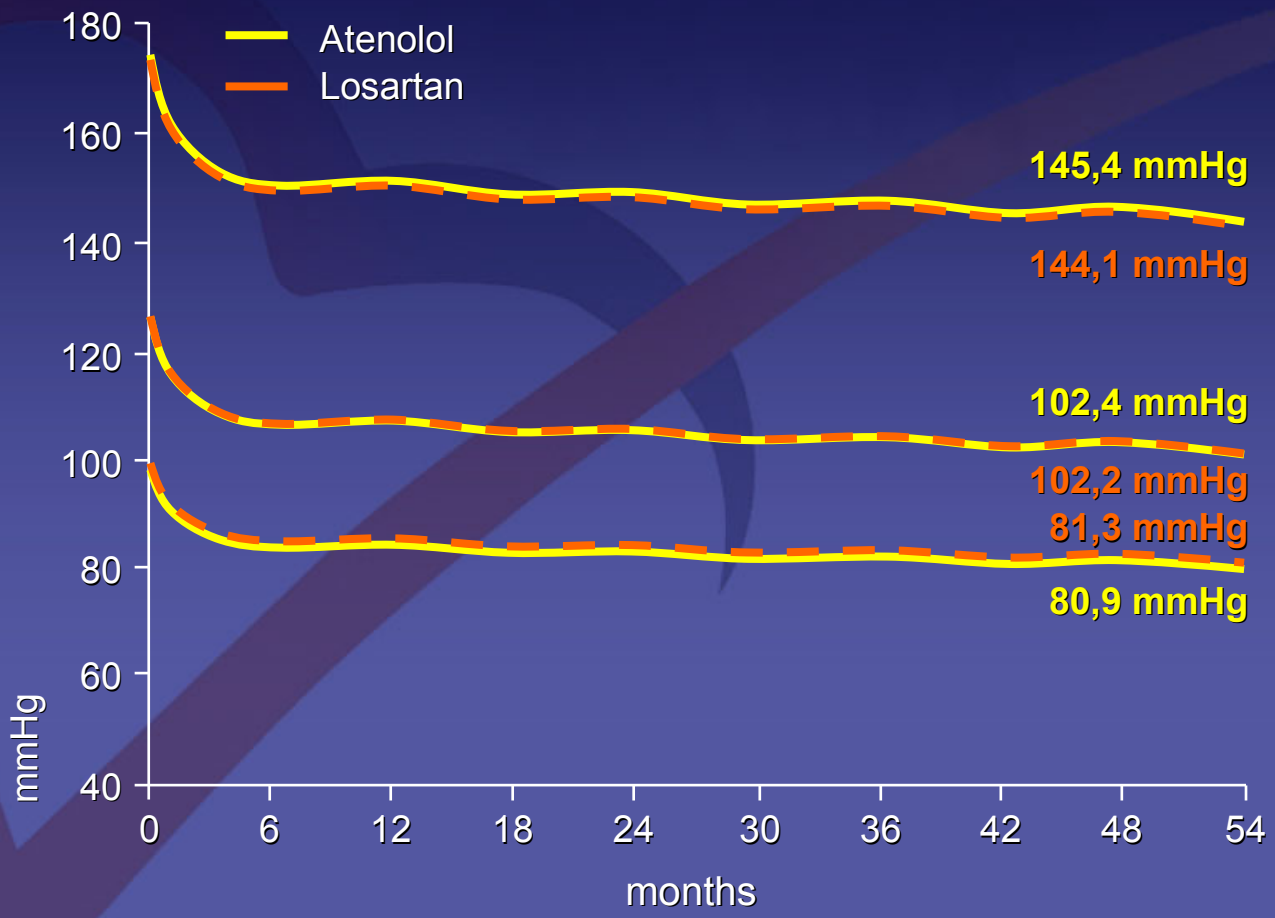
Primary outcome: death, MI, stroke

Mean follow-up: 4.8 years

1. Dahlöf B, et al. *Lancet* 2002;359:995–1003.

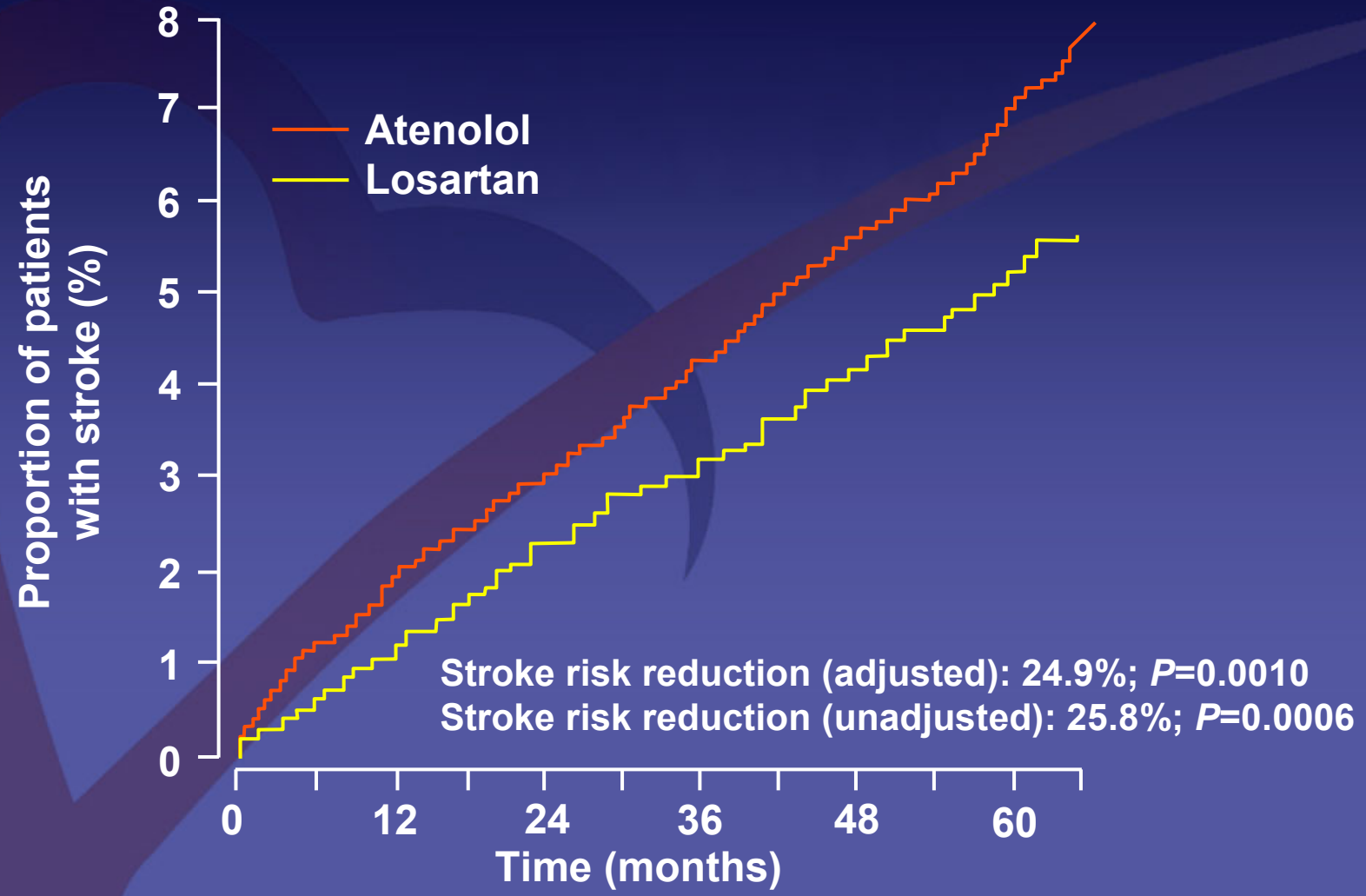
LIFE

Blood pressure reduction



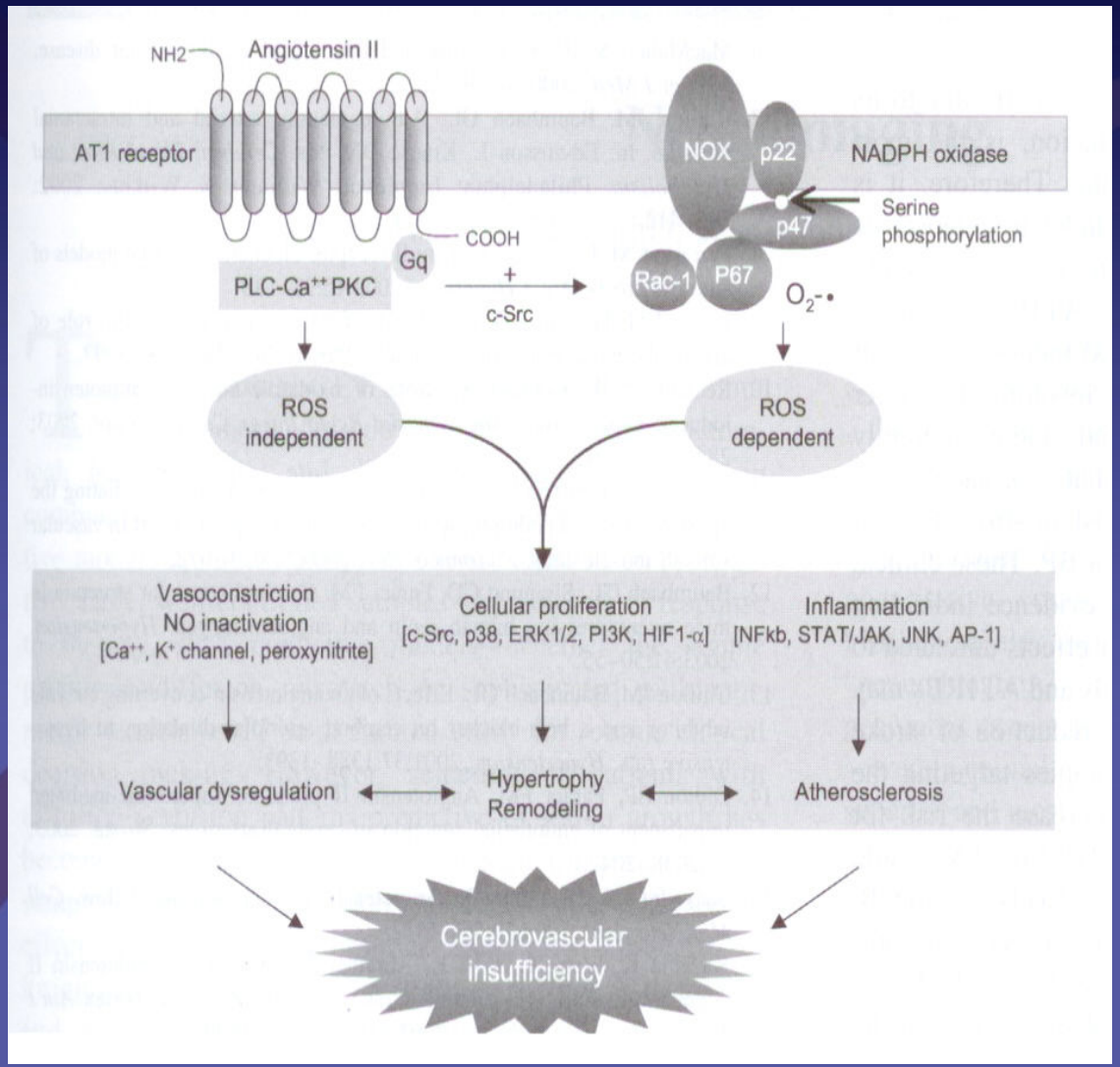
Dahlöf B, et al., Am J Hypertens 1997;10:705-713.

LIFE results[1]

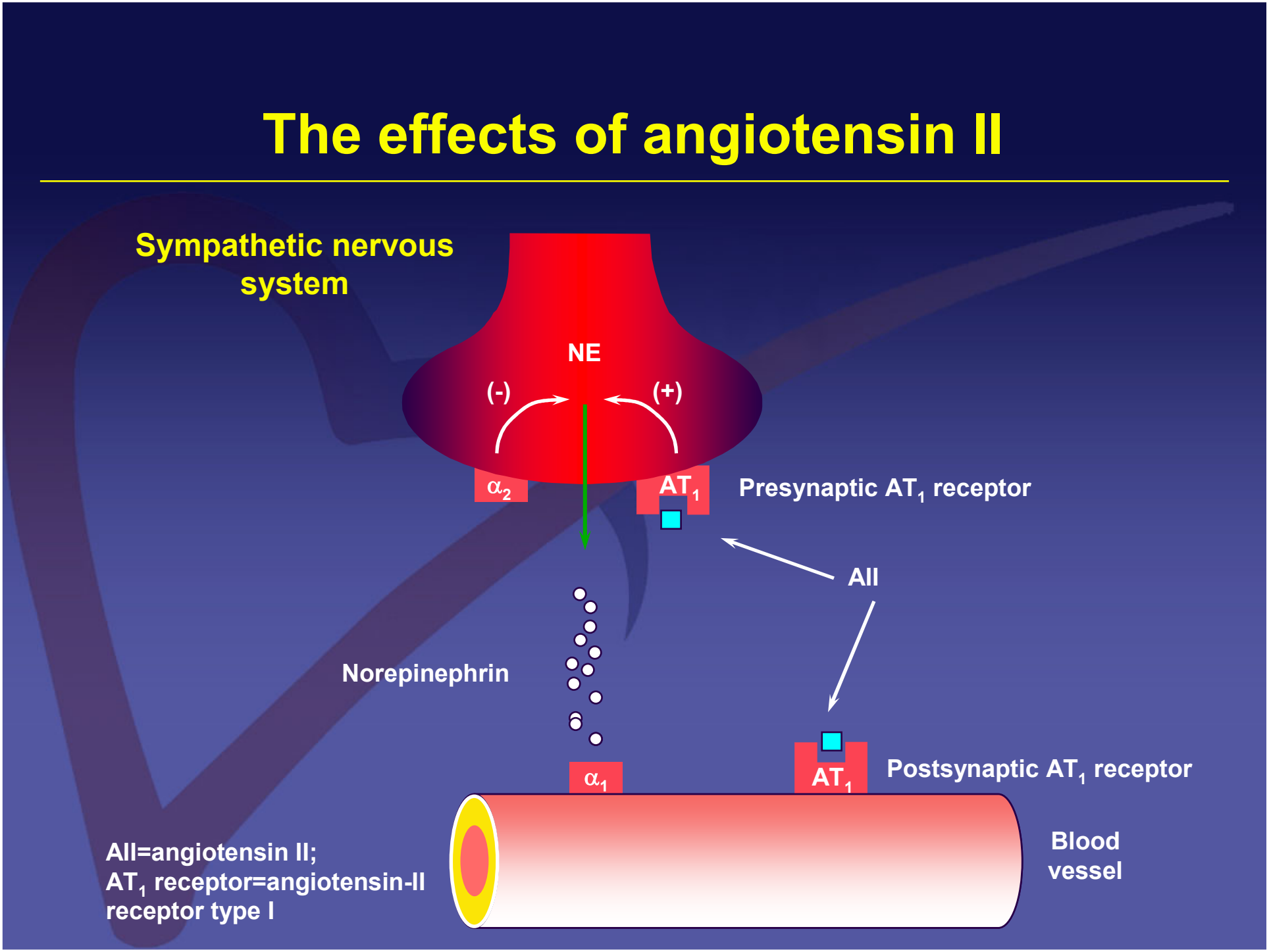


1. Dahlöf B, et al. *Lancet* 2002;359:995–1003.

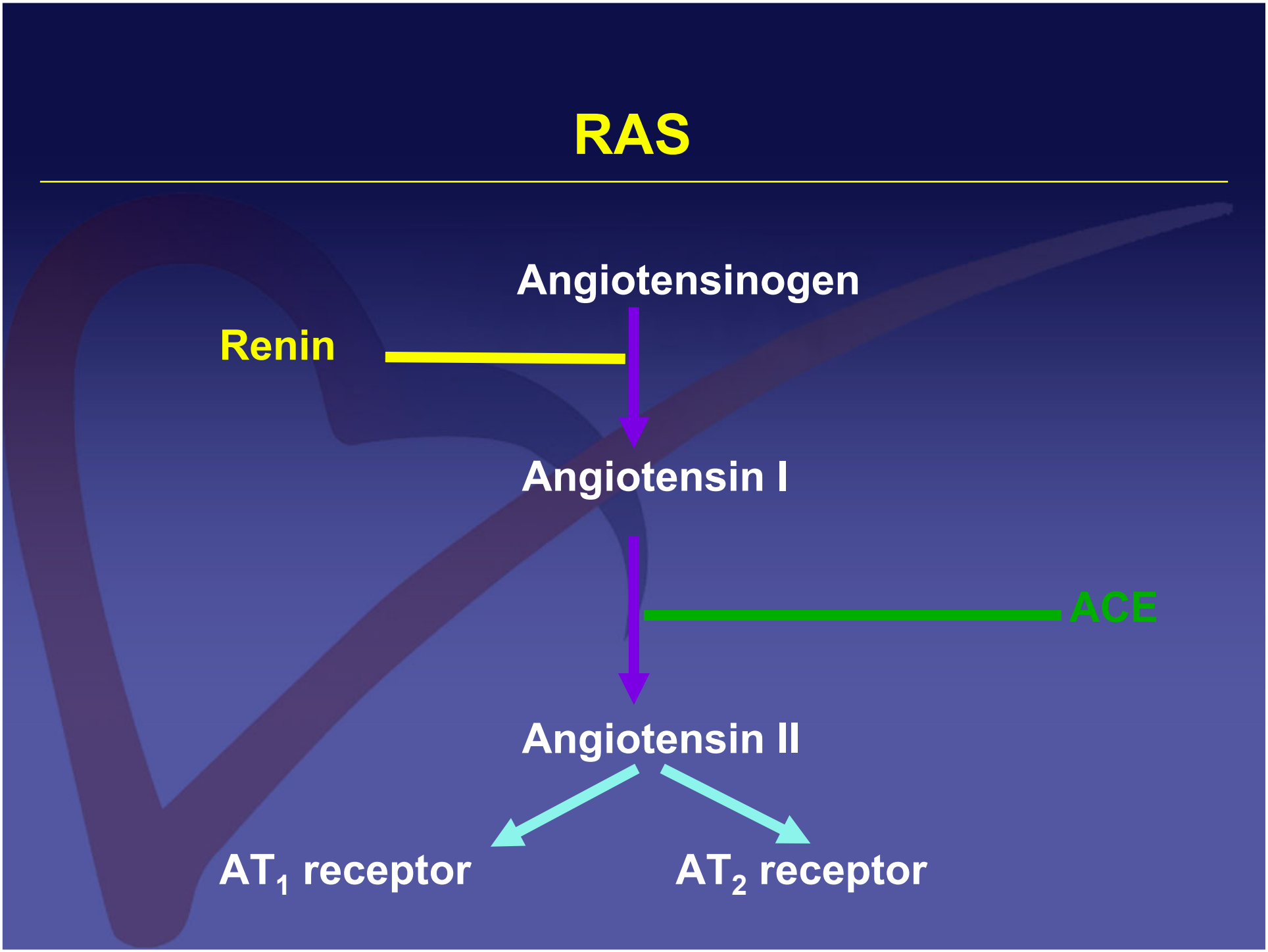
Effect of AIIAs on cerebral arteries

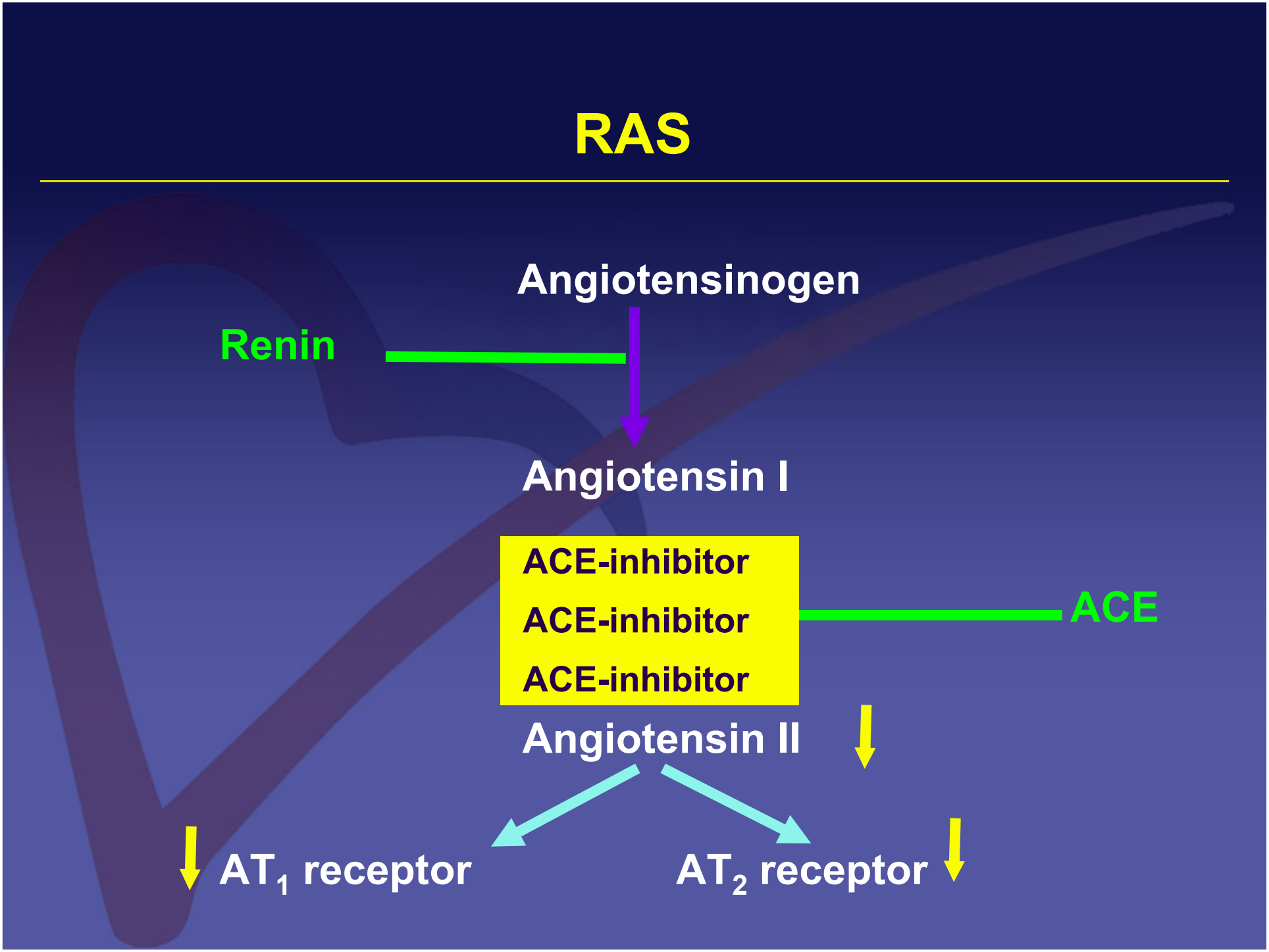


The effects of angiotensin II

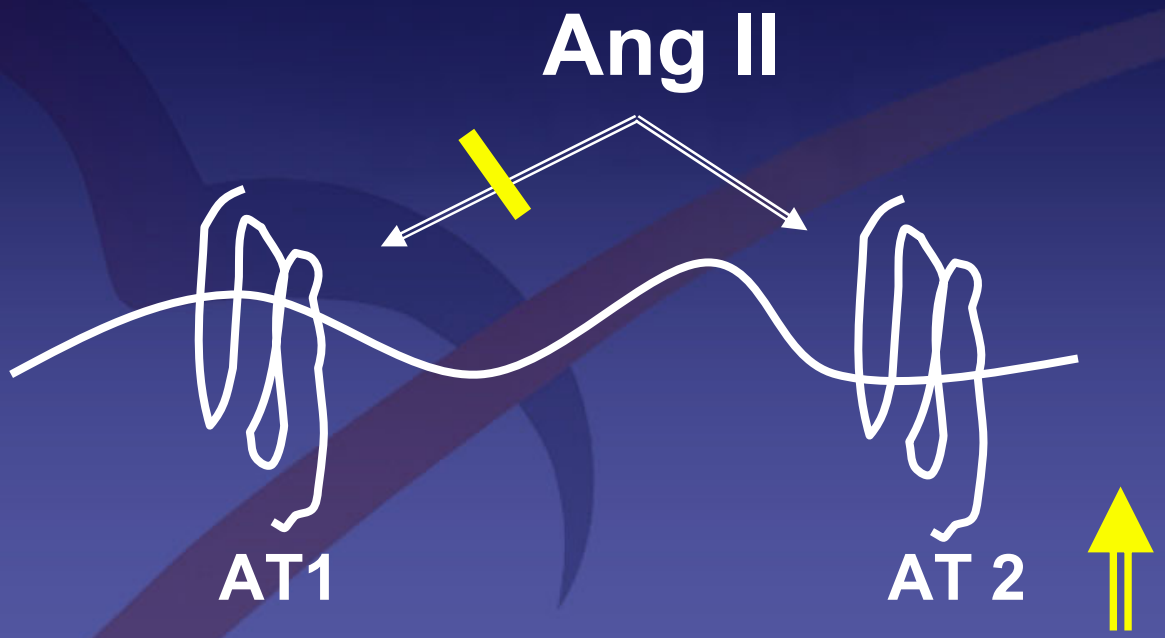


RAS


Angiotensinogen
Renin
Angiotensin I
ACE
Angiotensin II
AT1 receptor
AT2 receptor


RAS
Angiotensinogen
Renin
Angiotensin I
ACE-inhibitor
ACE-inhibitor
ACE-inhibitor
ACE
Angiotensin II
AT1 receptor
AT2 receptor

Cerebral RAAS



Vasoconstriction

Aldosteron/vasopressin release

Cell proliferation, ITF induction

Natriuresis, drinking response

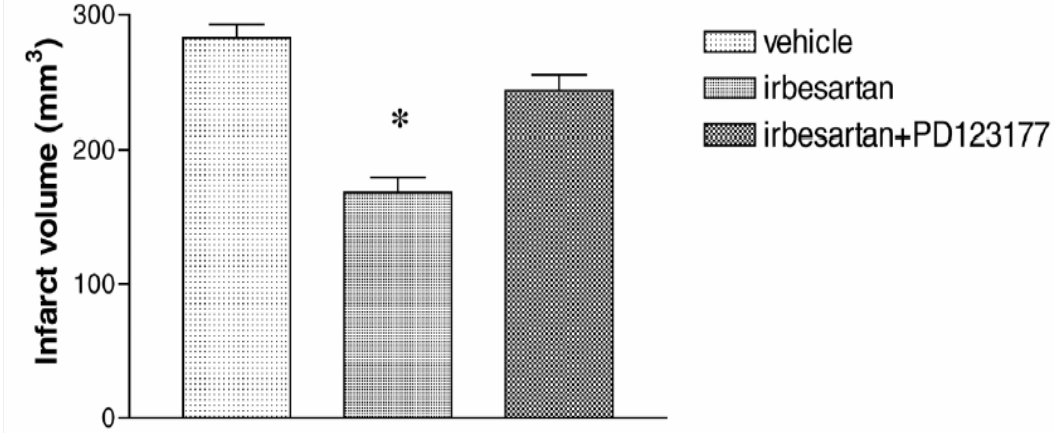
Regeneration

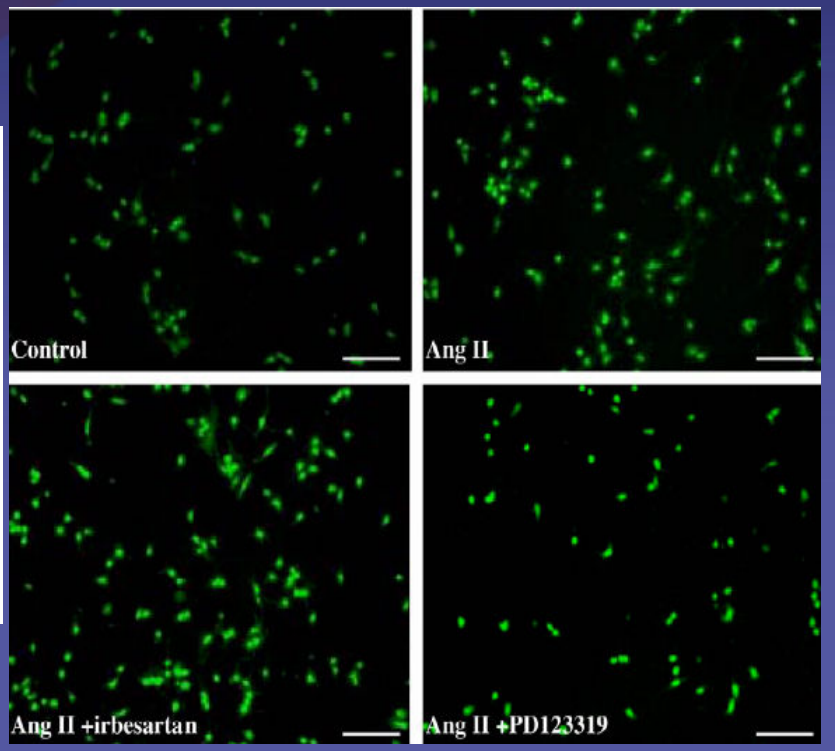
Differentiation/antiproliferation

The FASEB Journal express article 10.1096/fj.04-2960fje. Published online January 21, 2005.

Angiotensin AT2 receptor protects against cerebral ischemia-induced neuronal injury

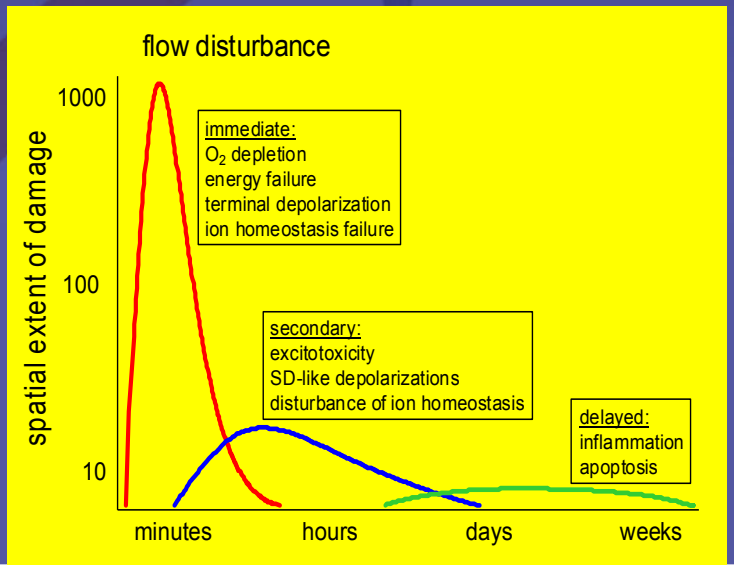
Jun Li,* Juraj Culman,‡ Heide Hörtnagl,* Yi Zhao,‡ Nadezhda Gerova,* Melanie Timm,* Annegret Blume,‡ Mathias Zimmermann,* Kerstin Seidel,* Ulrich Dirnagl,† and Thomas Unger*





Neuroprotection by AIIAs

- Improvement of autoregulation (Penumbra perfusion ⇑)
- Modulation of the biochemestry of „Ischemic cascade“
- AT2-stimulation ⇒ axonal regeneration ⇑



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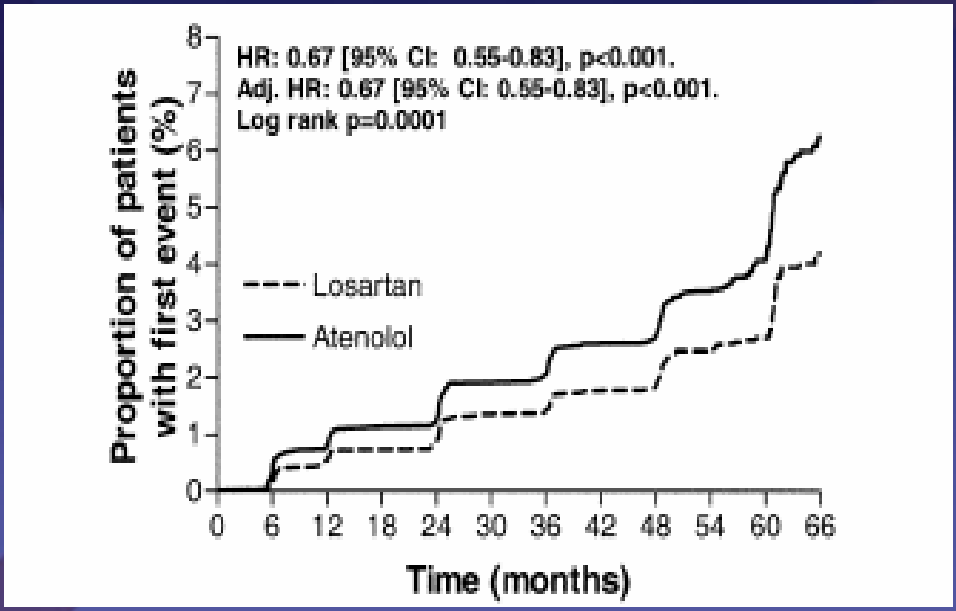
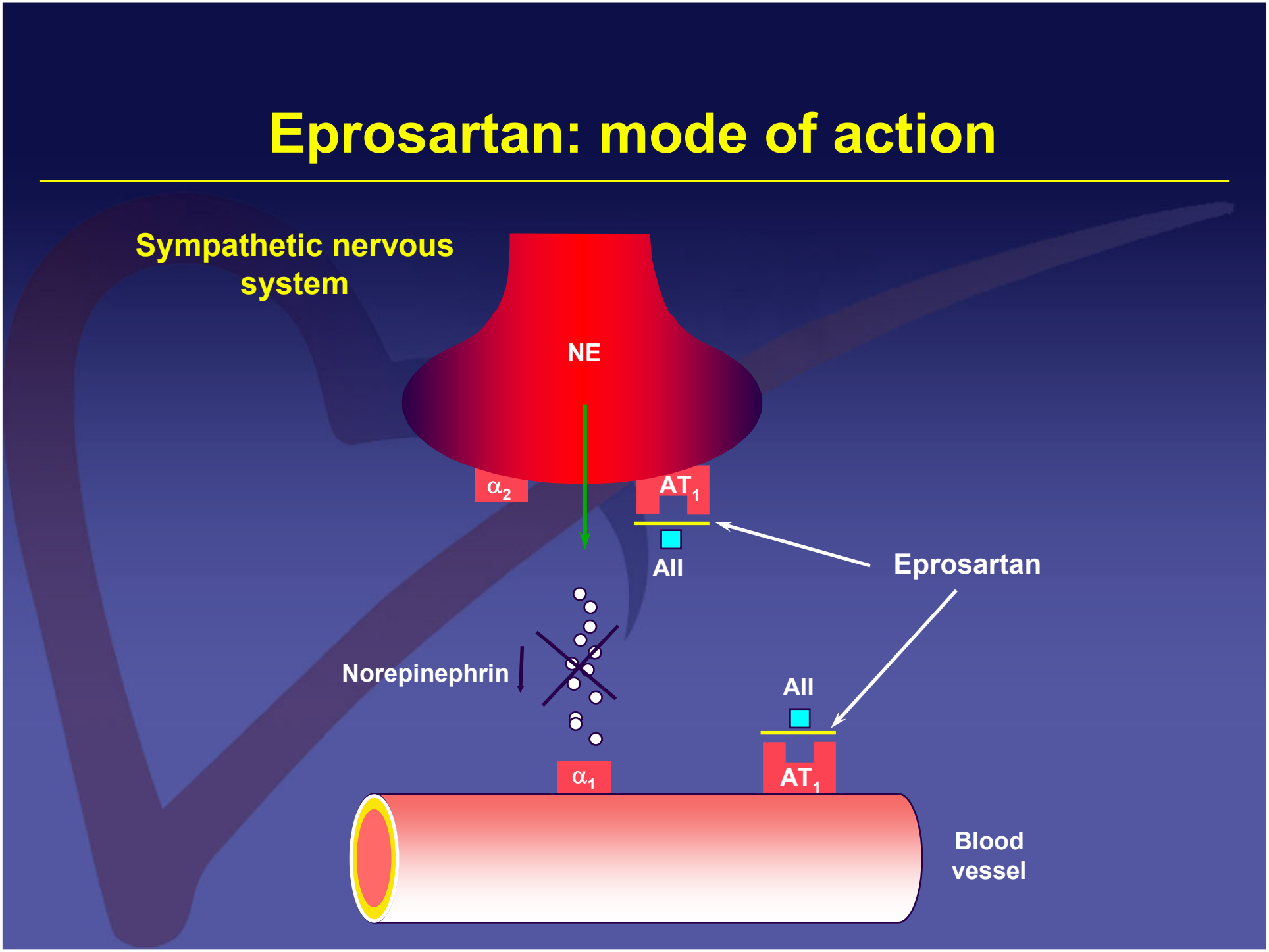
Angiotensin II Receptor Blockade Reduces New-Onset Atrial Fibrillation and Subsequent Stroke Compared to Atenolol

The Losartan Intervention for End Point Reduction in Hypertension (LIFE) Study

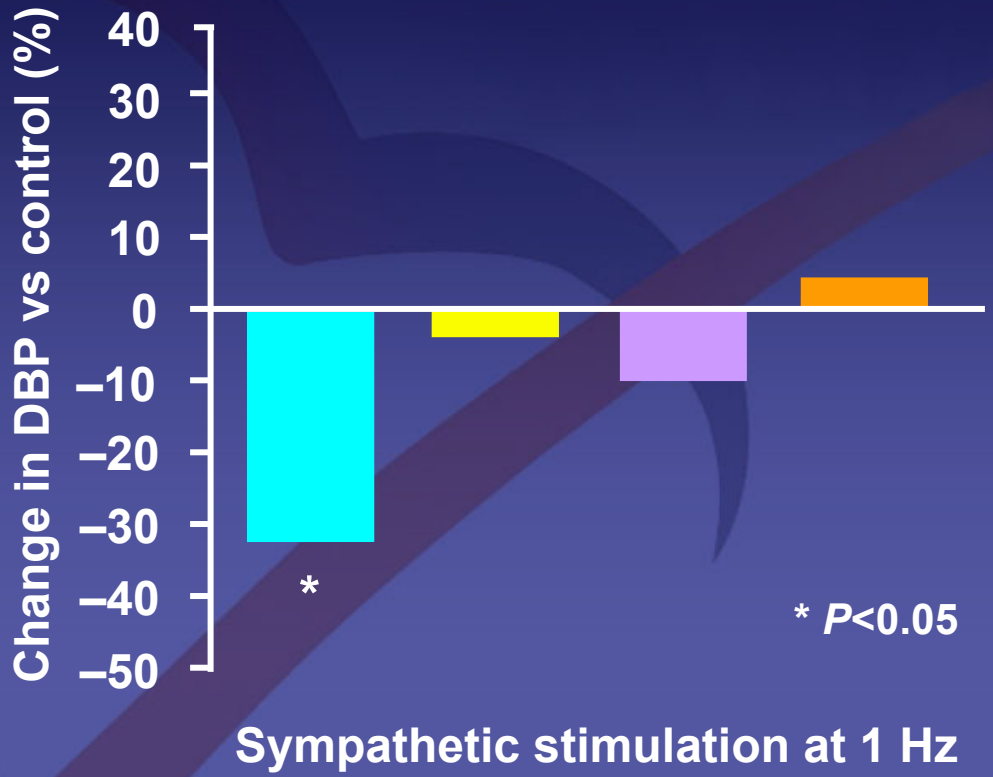


End Point	New-Onset Atrial Fibrillation* (n = 371) Rate†	n	(%)	Sinus Rhythm (n = 8,480) Rate‡	n	(%)	Adjusted Hazard Ratio* (95% CI)	p Value	Unadjusted Hazard Ratio (95% CI)	p Value
Primary composite end point	47.4	82	22.1	22.5	911	10.7	1.88 (1.50–2.36)	<0.001	2.12 (1.70–2.66)	<0.001
Components										
Cardiovascular mortality	15.2	28	7.5	8.4	352	4.2	1.57 (1.07–2.31)	0.021	1.80 (1.22–2.64)	0.003
Stroke	32.0	57	15.4	10.3	428	5.0	2.82 (2.14–3.72)	0.000	3.12 (2.37–4.12)	<0.001
Myocardial infarction	13.5	25	6.7	8.2	342	4.0	1.49 (0.99–2.24)	0.055	1.65 (1.10–2.47)	0.016

Eprosartan: mode of action



Eprosartan reduces SNS activity

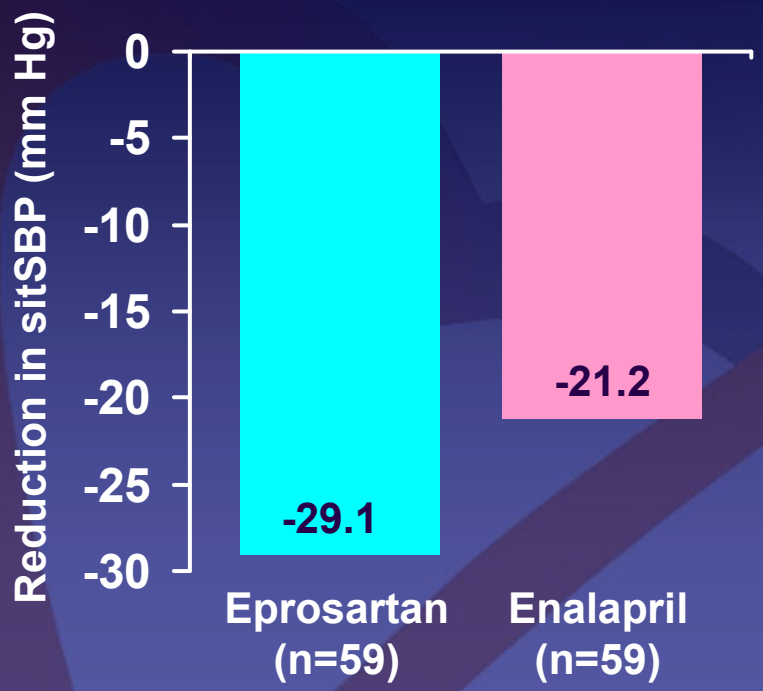


- Eprosartan (0.3 mg/kg)
- Losartan (0.3 mg/kg)
- Valsartan (0.3 mg/kg)
- Irbesartan (0.3 mg/kg)

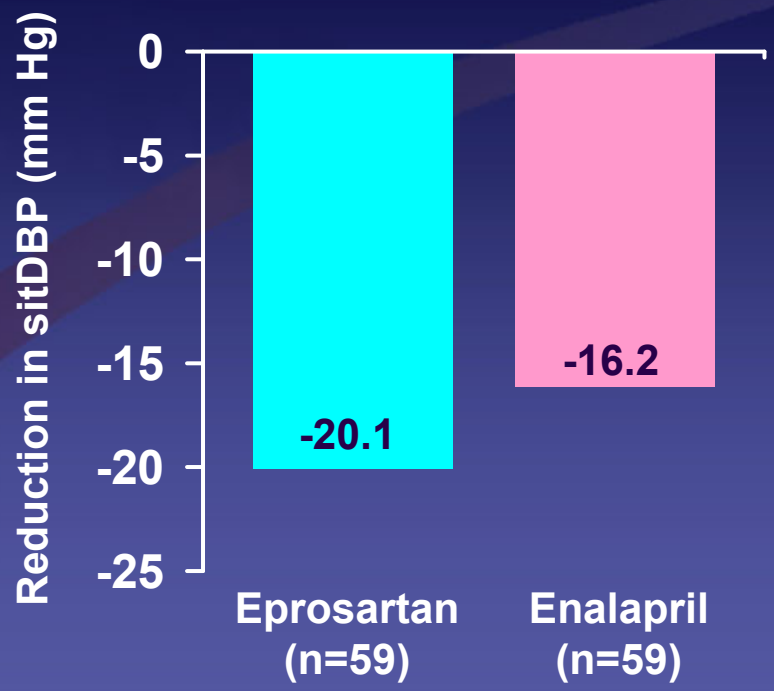
Intravenously 10 min before stimulation (acute effect)

Adapted from Ohlstein O, et al. *Pharmacology*, 1997;55:244–251.

Eprosartan effectively reduces blood pressure[1] and is well tolerated[2]



P=0.025



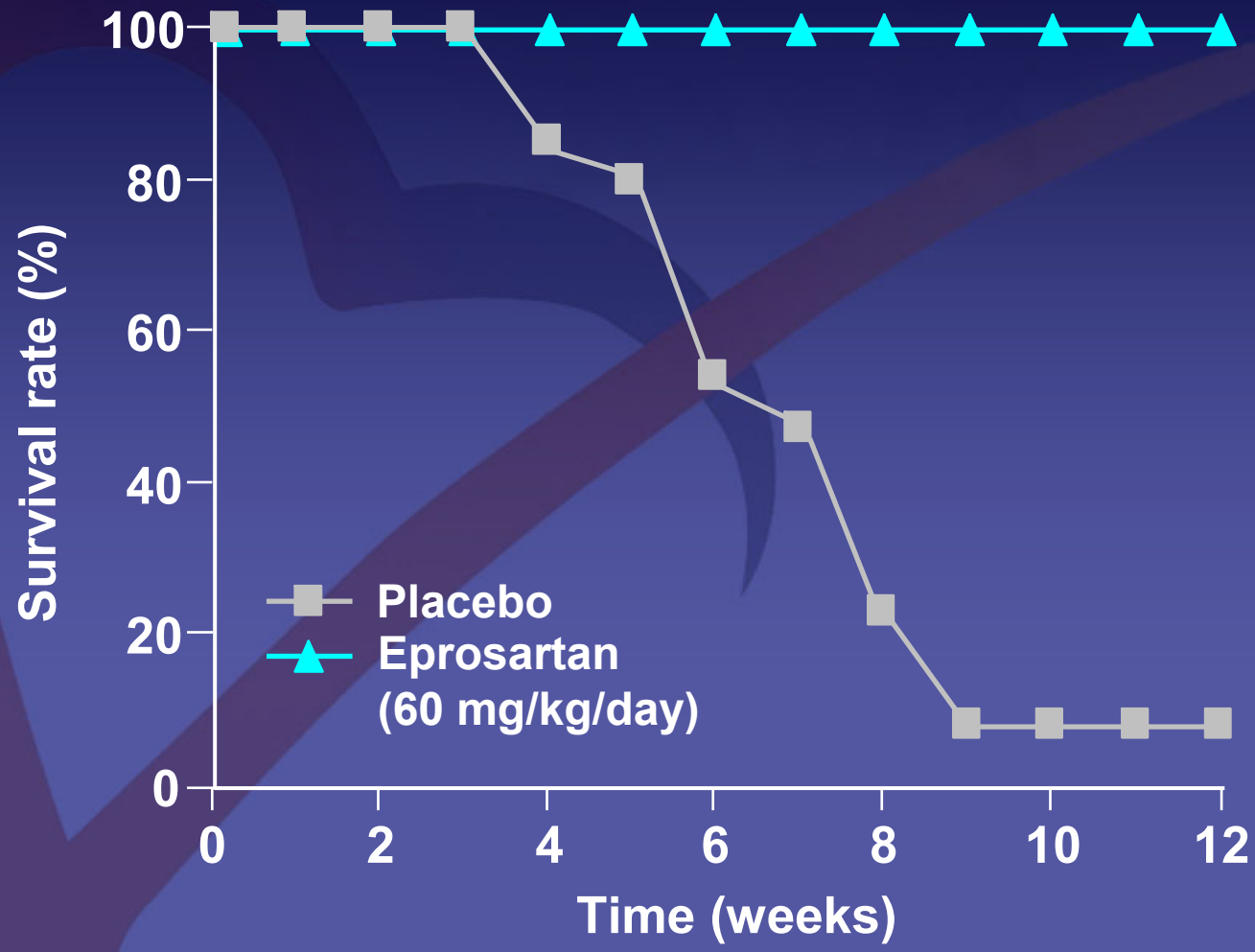
P=0.136

Eprosartan has a placebo-like side-effect profile[2]

sitDBP=sitting DBP; sitSBP=sitting SBP

1. Sega R. *Blood Press* 1999;8:114–121; 2. Gavras I, Gavras H. *Pharmacotherapy* 1999;19:102S–107S.

Eprosartan increases post-stroke survival in animal models



1. Barone FC, et al. *Cardiovasc Res* 2001;50:525–537.

MOSES

Summary

- Eprosartan significantly and similarly lowers and maintains blood pressure over time in a high-risk patient population
- Compared with the calcium channel blocker nitrendipine, eprosartan affords additional benefits in terms of cerebrovascular and cardiovascular outcome
- These benefits are achieved above and beyond that of lowering blood pressure