Prevention of Stroke and Myocardial Infarction by CCB

성균관의대 삼성서울병원 순환기내과

박 승 우

성인에서의 고혈압 환자의 빈도

Year	Overall, % (95% CI)	Men, % (95% CI)	Women, % (95% CI)
2000	26.4 (26.0-26.8)	26.6 (26.0-27.2)	26.1 (25.5-26.6)
2025	29.2 (28.8-29.7)	29.0 (28.6-29.4)	29.5 (29.1-29.9)

Kearney PM et al. *Lancet* 2005; 365:217-223.

성인 고혈압 환자 수

Measure	n (95% CI)
Total number worldwide in 2000	972 million (957-987)
Total number in economically developed countries in 2000	333 million (329-336)
Total number in economically developing countries in 2000	639 million (625-654)
Total number worldwide in 2025	1.56 billion (1.54-1.58)

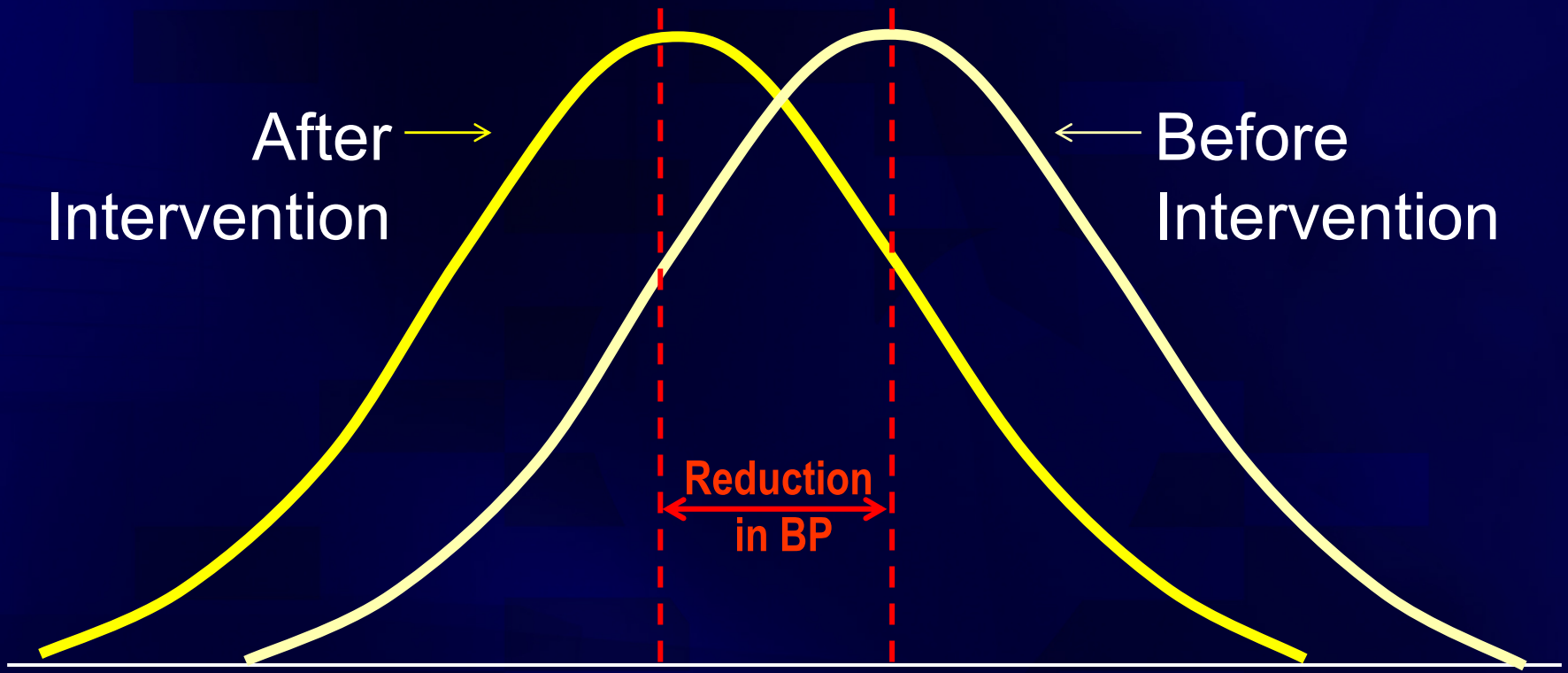
Kearney PM et al. *Lancet* 2005; 365:217-223.

임상적 통념

혈압 강하 자체가 고혈압에 의한 사망률과 유병율을 감소시키며 혈압강하의 방법에는 무관하다.

Population-Based Strategy

SBP Distributions



Reduction in SBP mmHg	% Reduction in Mortality		
	Stroke	CHD	Total
2	–6	–4	–3
3	–8	–5	–4
5	–14	–9	–7

고혈압 약제 비교 연구

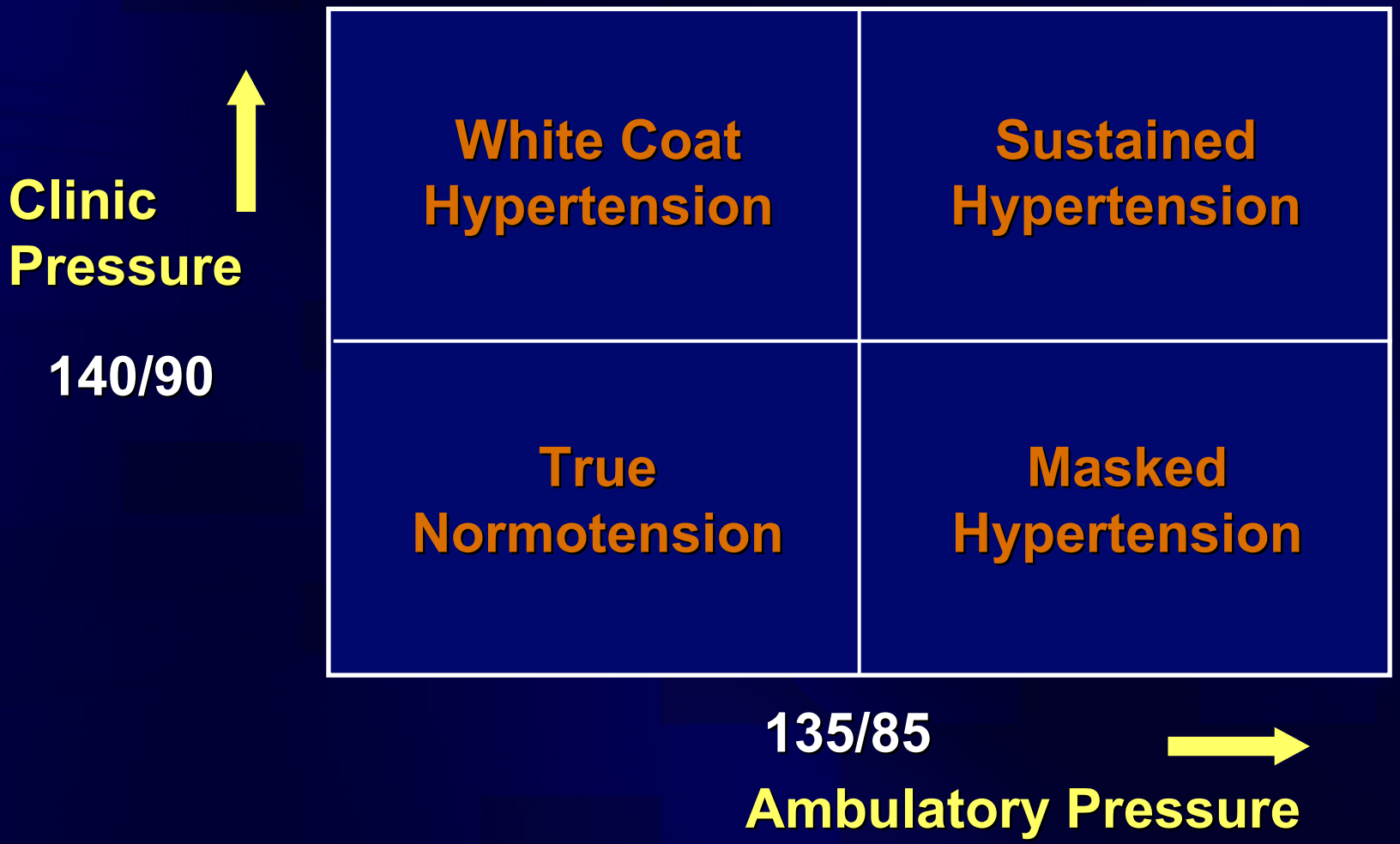
Different drug classes		N	추적기간 (년)
ACE inhibitor vs diuretic or β blocker[29]			
AASK[29]	Ramipril vs metoprolol	877	4·1
ALLHAT[32]	Lisinopril vs chlorthalidone	24328	4·9
ANBP2[33]	Enalapril vs hydrochlorothiazide	6083	4·1
CAPPP[34]	Captopril vs β blocker or diuretic	10985	6·1
STOP-2[35]	Enalapril or lisinopril vs atenolol or metoprolol or pindolol or hydrochlorothiazide+amiloride	4418	5·0
UKPDS-HDS[44]	Captopril vs atenolol	758	8·4
Calcium antagonist vs diuretic or β blocker			
AASK[29]	Amlodipine vs metoprolol	658	3·0
ALLHAT[32]	Amlodipine vs chlorthalidone	24321	4·9
CONVINCE[36]	COER-verapamil vs hydrochlorothiazide or atenolol	16476	3·0
ELSA[37]	Lacidipine vs atenolol	2334	4·0
INSIGHT[38]	Nifedipine GITS vs hydrochlorothiazide+amiloride	6321	4·0
NICS-EH[45]	Nicardipine vs trichlormethiazide	429	5·0
NORDIL[39]	Diltiazem vs β blocker or diuretic	10881	5·0
SHELL[40]	Lacidipine vs chlorthalidone	1882	3·6
STOP-2[35]	Felodipine or isradipine vs atenolol or metoprolol or pindolol or hydrochlorothiazide+amiloride	4409	5·0
VHAS[25]	Verapamil vs chlorthalidone	1414	2·0
ACE inhibitor vs calcium antagonist			
AASK[29]	Ramipril vs amlodipine	653	3·0
ABCD (H)[20]	Enalapril vs nisoldipine	470	5·3
ABCD (N)[21]	Enalapril vs nisoldipine	480	5·3
ALLHAT[32]	Lisinopril vs amlodopine	18113	4·9
JMIC-B[41]	ACE inhibitor vs nifedipine	1650	3·0
STOP-2[35]	Enalapril or lisinopril vs felodipine or isradipine	4401	5·0

혈압 측정의 어려움

- 진료실 혈압 **>** 가정 혈압
  - 수축기: **5–15 mmHg**, 이완기: **5-10 mmHg**
  - 진료실 혈압이 높을수록 차이도 크다
- **White coat HT, masked HT**
- **Dipper or Nondipper**

J Hypertens 2003, Eur Heart J 2002, Hypertension 2005, J Hypertens 2004, 22:2269–2272

ABPM을 이용한 정확한 혈압측정



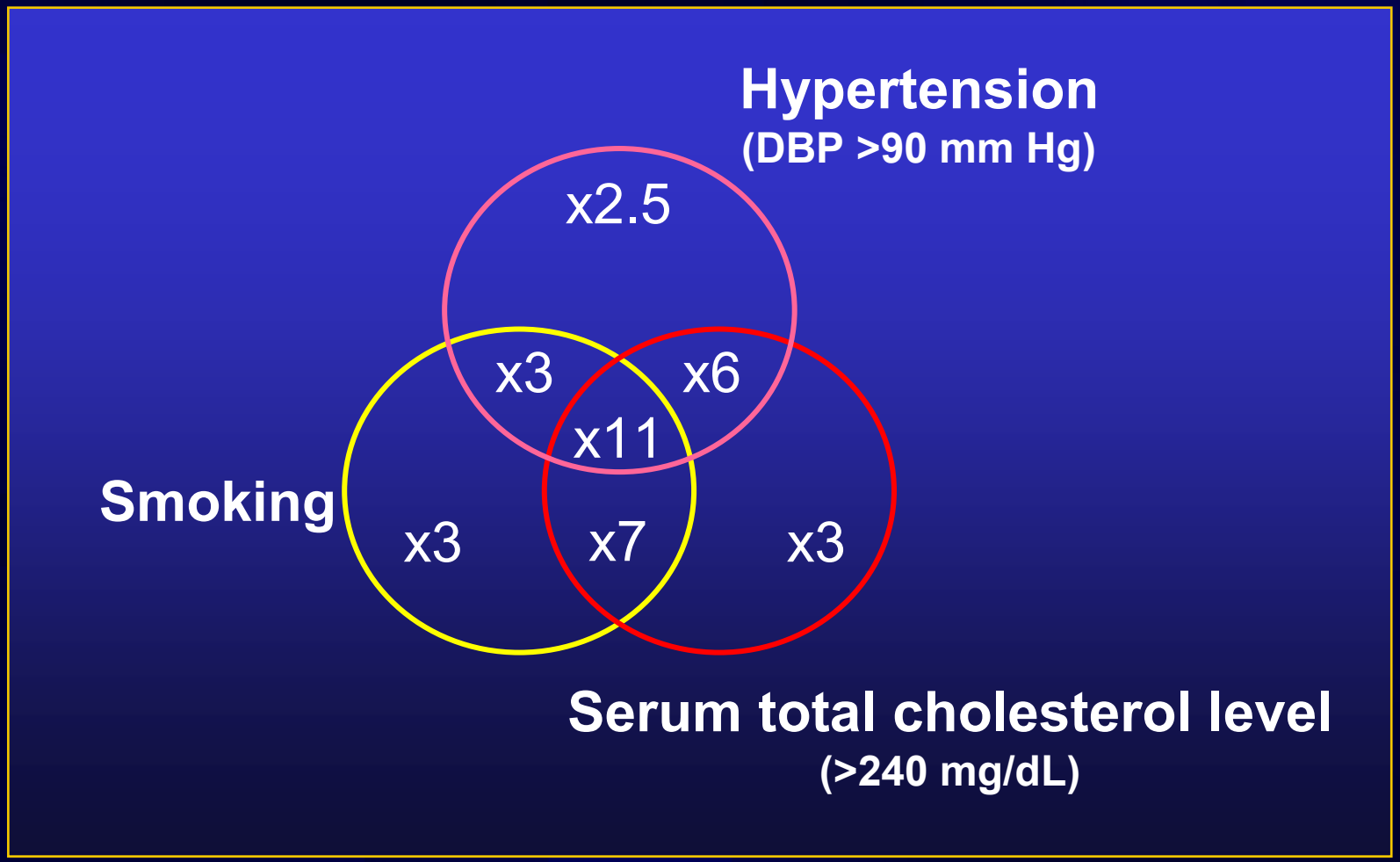
목표 혈압 설정의 문제

- 목표 혈압
  - **<140/90 mmHg**
  - 당뇨나 만성 신장질환의 경우 **<130/80 mmHg**

- 혈압과 심혈관질환의 위험은 연속적 관계
  - 혈압이 **115/75 mmHg** 이상인 경우,매 **20/10 mmHg** 증가마다 위험도가 **2**배씩 증가

JAMA 2003, 289:2560-2572

다른 위험인자와 고혈압이 함께 있는 경우



Kannel WB, et al. *Am Heart J.* 1986;12:825-836.

고혈압 치료의 목적

고혈압으로 인한 심혈관계 및 신장질환의 사망률과 유병률을 감소시키는 것

JAMA 2003, 289:2560-2572

Calcium channel blocker (CCB)

- Available since the 1960s
- Common physiologic action: decreasing the intracellular availability of calcium ions in cardiac and vascular smooth muscle cells

Useful in…

- Hypertension
- Coronary heart disease
- Arrhythmias
- Cerebrovascular disease
- Raynaud's phenomenon
- Primary pulmonary hypertension

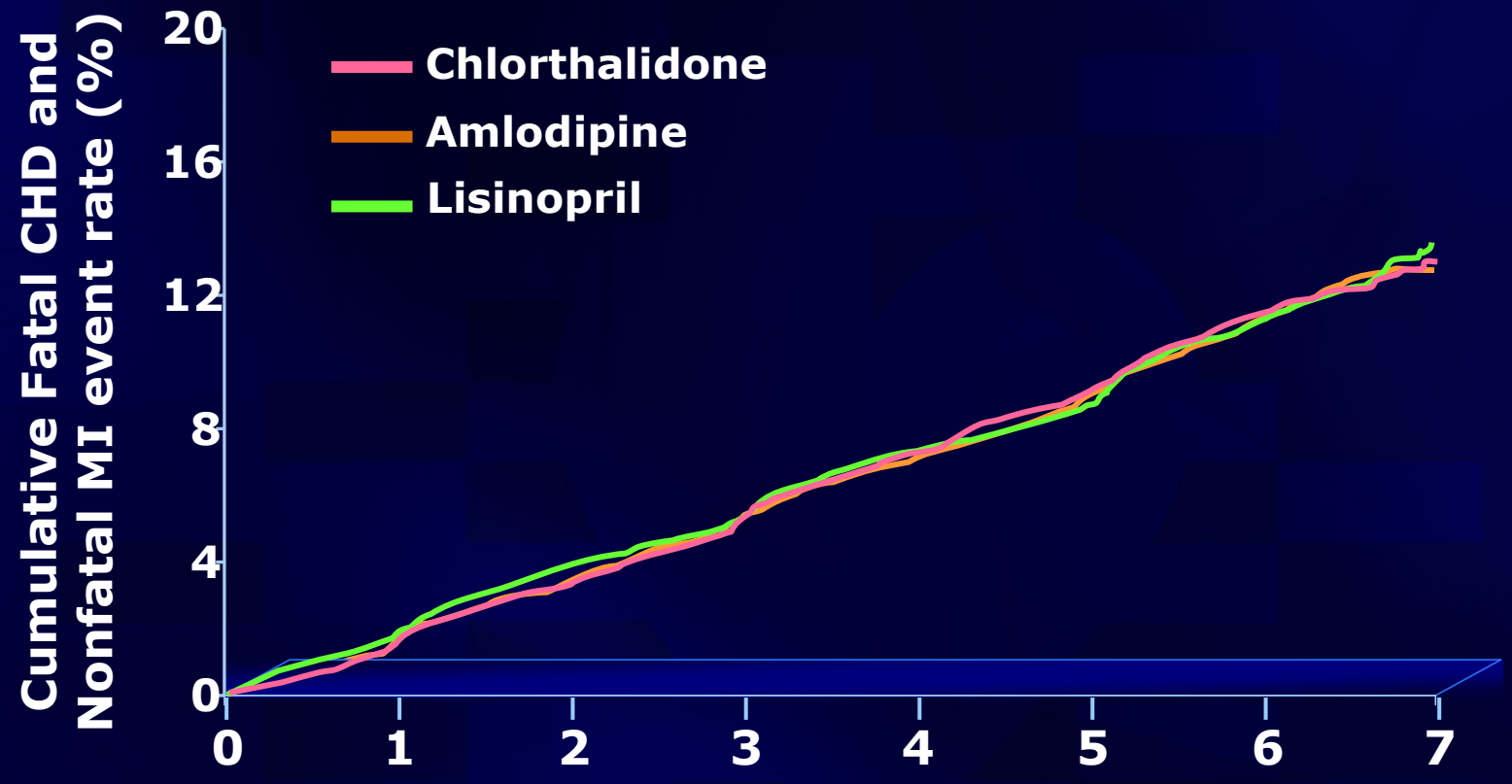
The Antihypertensive and Lipid-lowering Treatment to Prevent Heart Attack Trial (ALLHAT)

William C Cushman, MD, Charles E Ford, PhD, Jeffrey A Cutler, MD, Karen L Margolis, MD, MPH, Barry R Davis, MD, PhD, et al, for the ALLHAT Collaborative Research Group

ALLHAT: Trial design

- 33,357 patients age >55 with hypertension and 1 additional risk factor
- Randomized to:
  - chlorthalidone (12.5 mg to 25 mg/day, n=15,255)
  - amlodipine (2.5 mg to 10 mg/day, n=9,048)
  - lisinopril (10 mg to 40 mg/day, n=9,054)
- Primary end point: fatal CHD or nonfatal MI

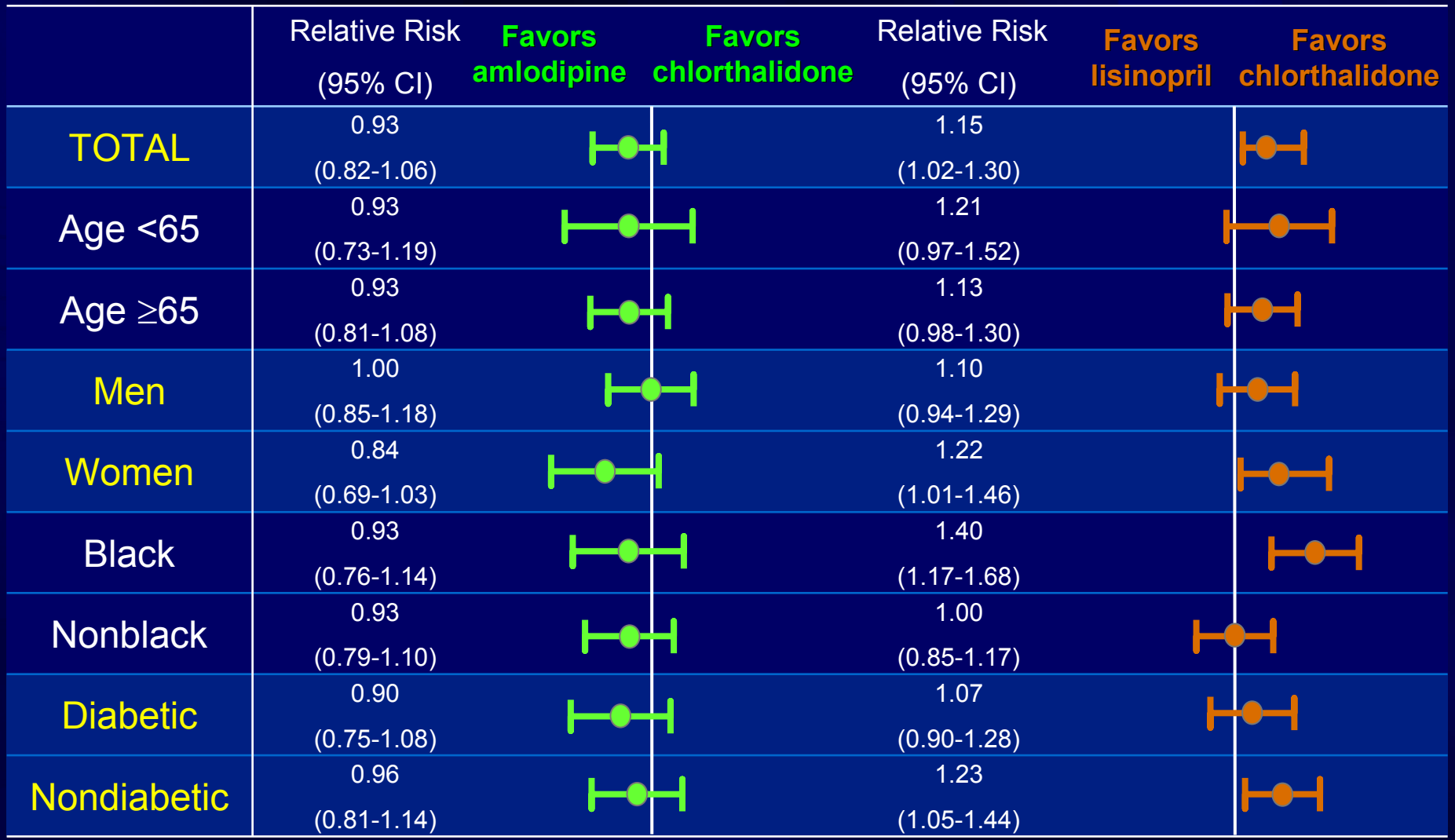
ALLHAT Primary Outcome by Treatment Group



No. at Risk								
Chlorthalidone	15255	14477	13820	13102	11362	6340	2956	209
Amlodipine	9048	8576	8218	7843	6824	3870	1878	215
Lisinopril	9054	8535	8123	7711	6662	3832	1770	195

ALLHAT Research Group. JAMA. 2002;288:2981-2997.

ALLHAT Stroke



ALLHAT Research Group. JAMA. 2002;288:2981-2997.

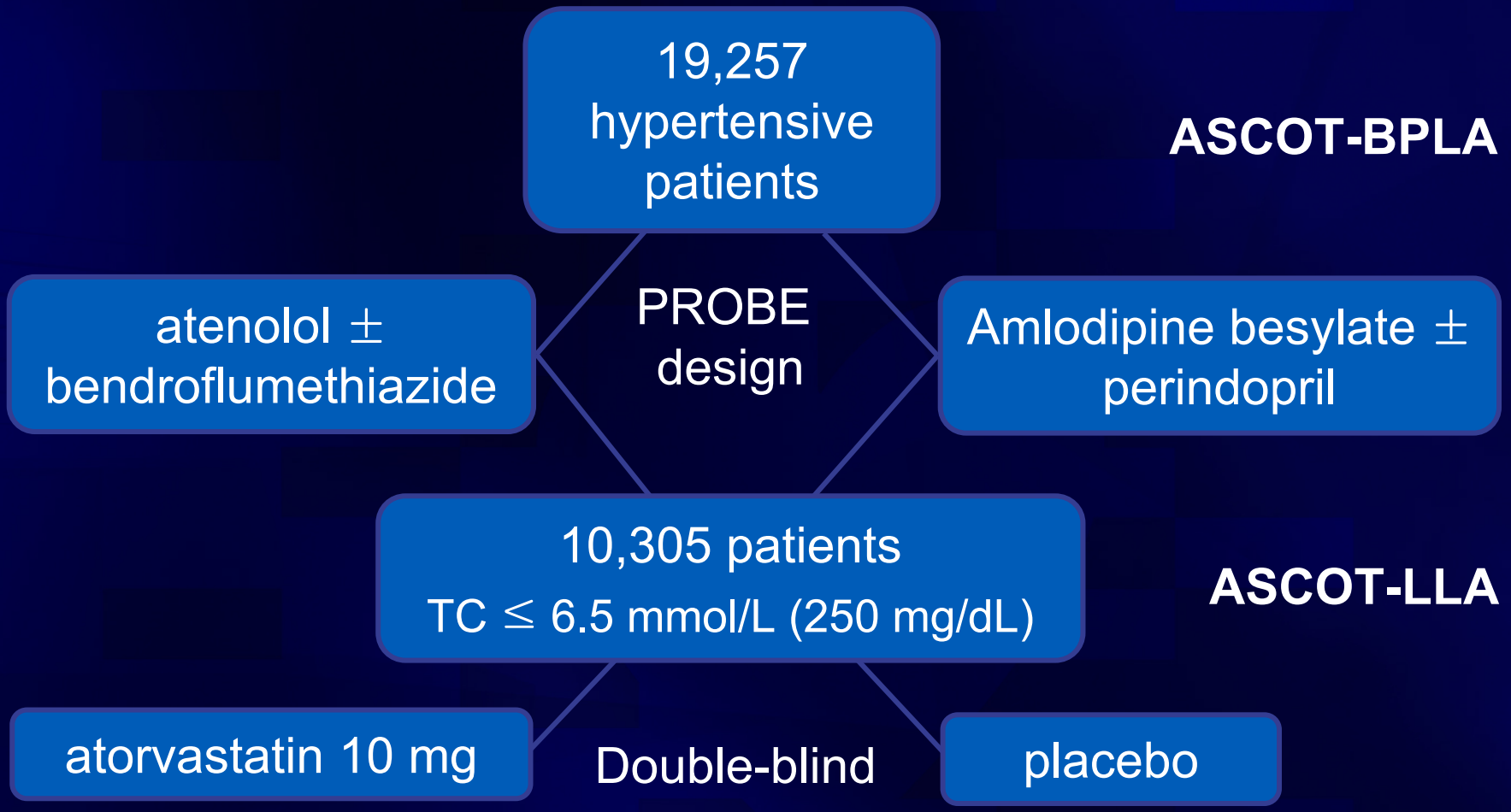
VBWG

Anglo-Scandinavian ascot Cardiac Outcomes Trial

A randomised controlled trial of the prevention of CHD and other vascular events by BP and cholesterol lowering in a factorial study design

B.Dahlof (Co-chair), P.Sever (Co-chair), N. Poulter (Secretary)
H. Wedel (Statistician), G. Beevers, M. Caulfield, R. Collins
S. Kjeldsen, A. Kristinsson, J. Mehlsen, G. McInnes, M. Nieminen
E. O'Brien, J. Östergren, on behalf of the ASCOT Investigators

Study design

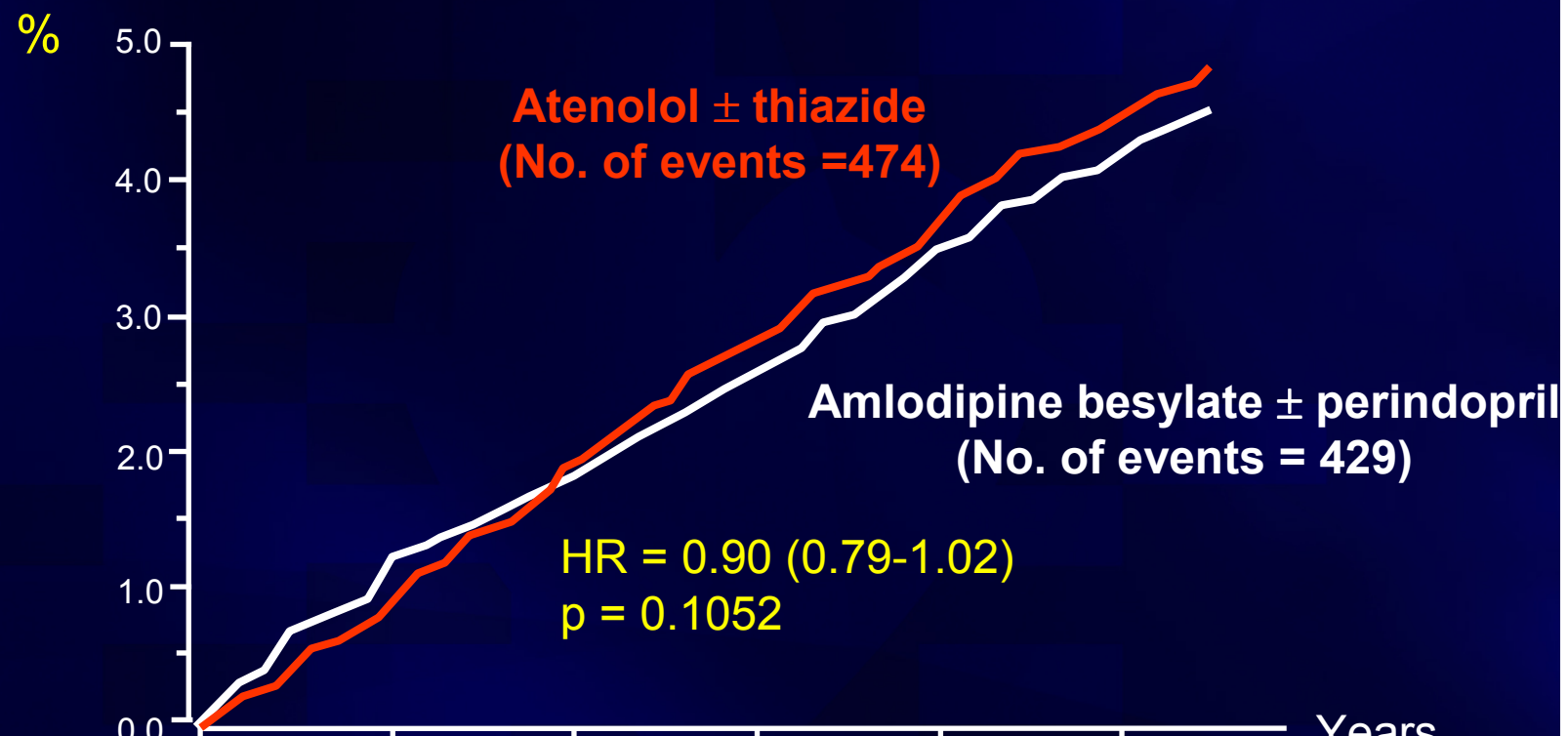


Investigator-led, multinational randomised controlled trial

ASCOT: Patient inclusion criteria

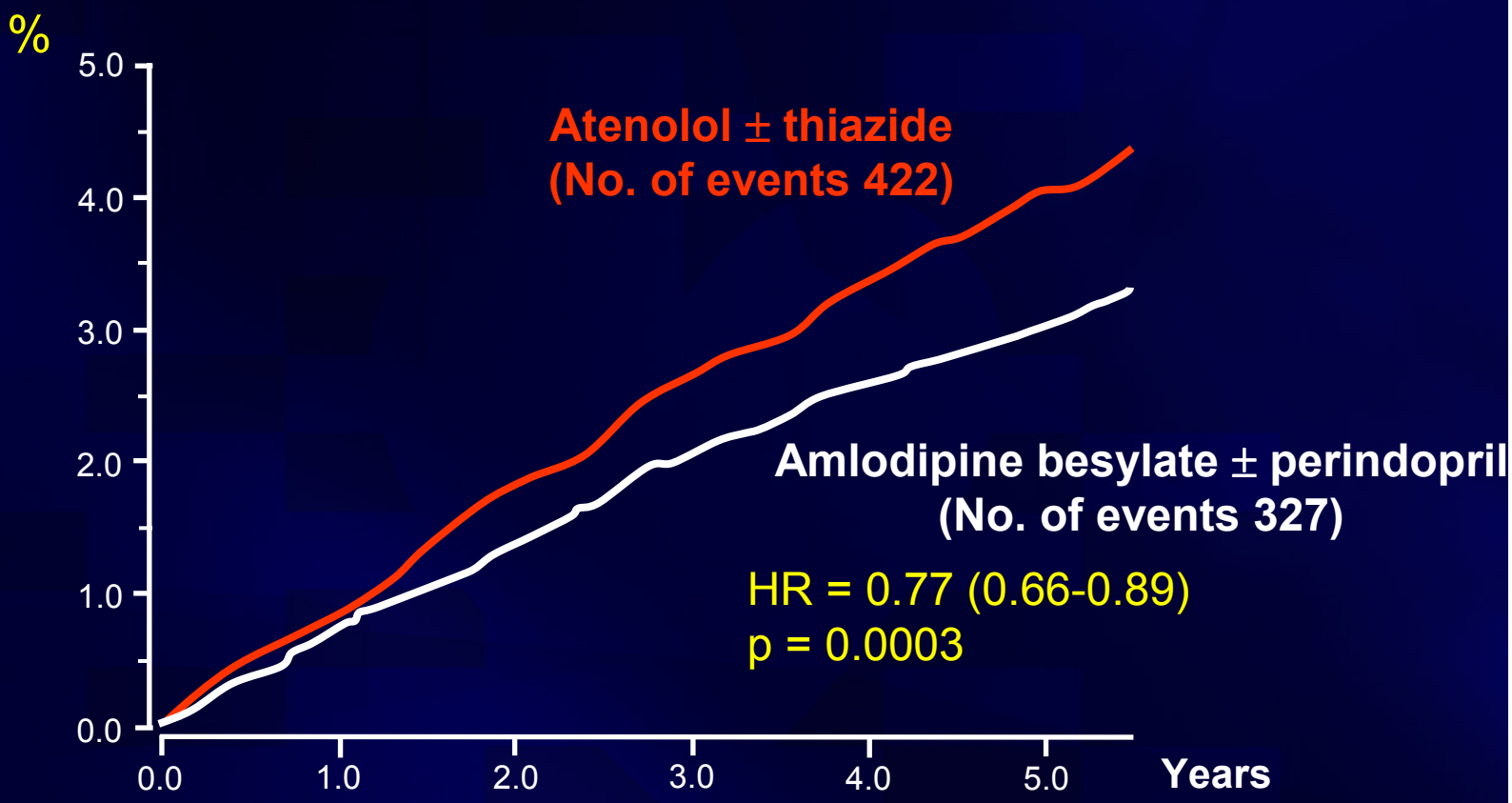
- Screening and baseline BP
  - ≥ 160/100 mm Hg untreated
  - ≥ 140/90 mm Hg following treatment with 1 or more drugs
- Age 40-79 years
- No previous MI or current clinical CHD
- 3 or more CV risk factors

Primary end point: Non-fatal MI, fatal CHD



Number at risk	0.0	1.0	2.0	3.0	4.0	5.0
Amlodipine besylate ± perindopril	9639	9475	9337	9168	8966	7863
Atenolol ± thiazide	9618	9470	9290	9083	8858	7743

Fatal and non-fatal stroke



Number at risk						
Amlodipine besylate ± perindopril	9639	9483	9331	9156	8972	7863
Atenolol ± thiazide	9618	9461	9274	9059	8843	7720

CAMELOT: Trial of BP reduction with ACEI or CCB in CAD patients without HF

Study design: Randomized, double-blind, multicenter, 24-month trial in patients with angiographically documented CAD, LVEF ≥40%, and no HF (N = 1991)

Treatment: Amlodipine (10 mg), enalapril (20 mg), or placebo added to background therapy with β-blockers and/or diuretics

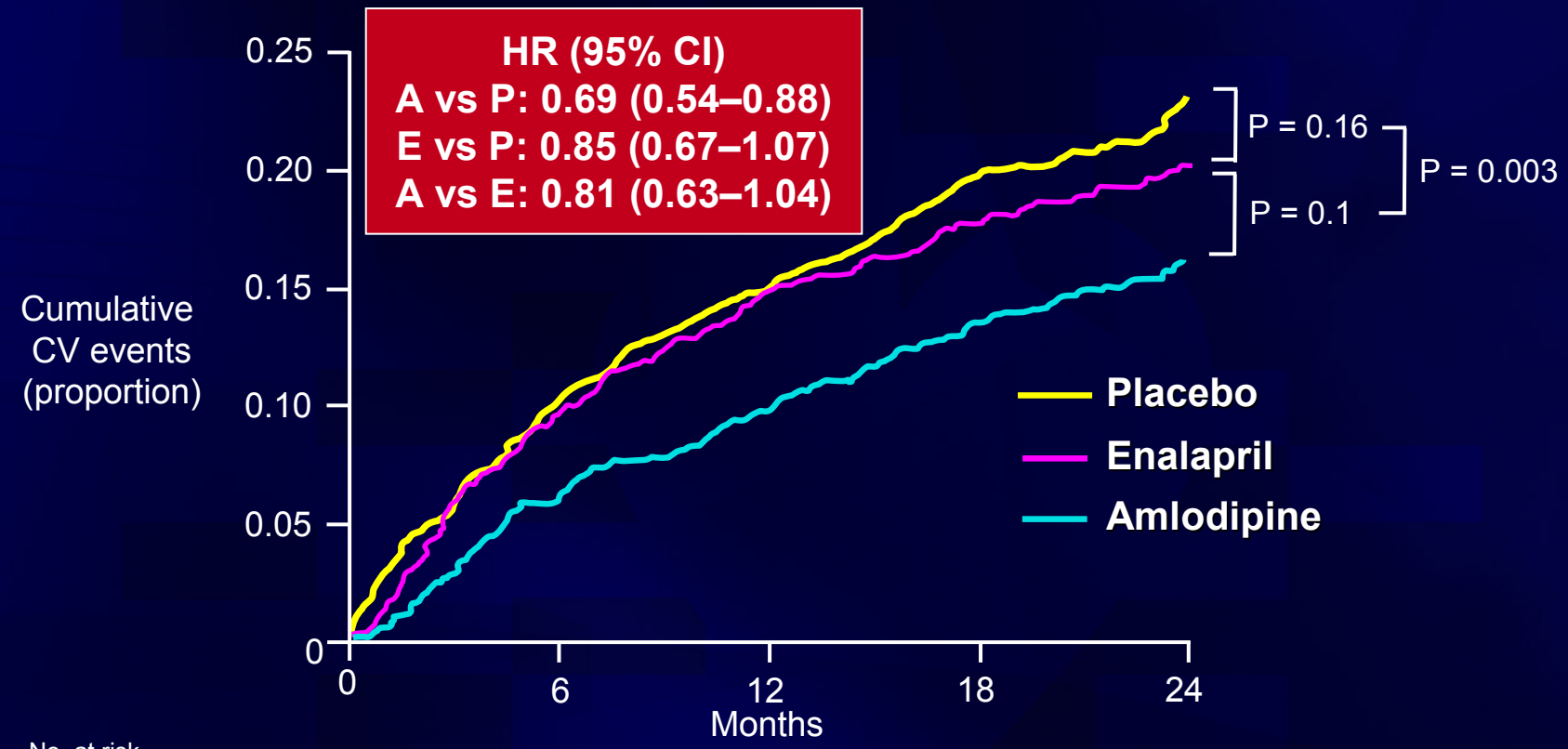
Primary outcome: Incidence of CV events for amlodipine vs placebo

IVUS substudy: Measurement of atherosclerosis progression using IVUS (n = 274)

Outcome: Change in percent atheroma volume

Nissen SE et al. *JAMA*. 2004;292:2217-26.

CAMELOT: Reduction in primary outcome with amlodipine and enalapril



No. at risk

Placebo	655	588	558	525	488
Enalapril	673	608	572	553	529
Amlodipine	663	623	599	574	535

Primary outcome = incidence of CV events

Nissen et al. *JAMA*. 2004;292:2217-26.

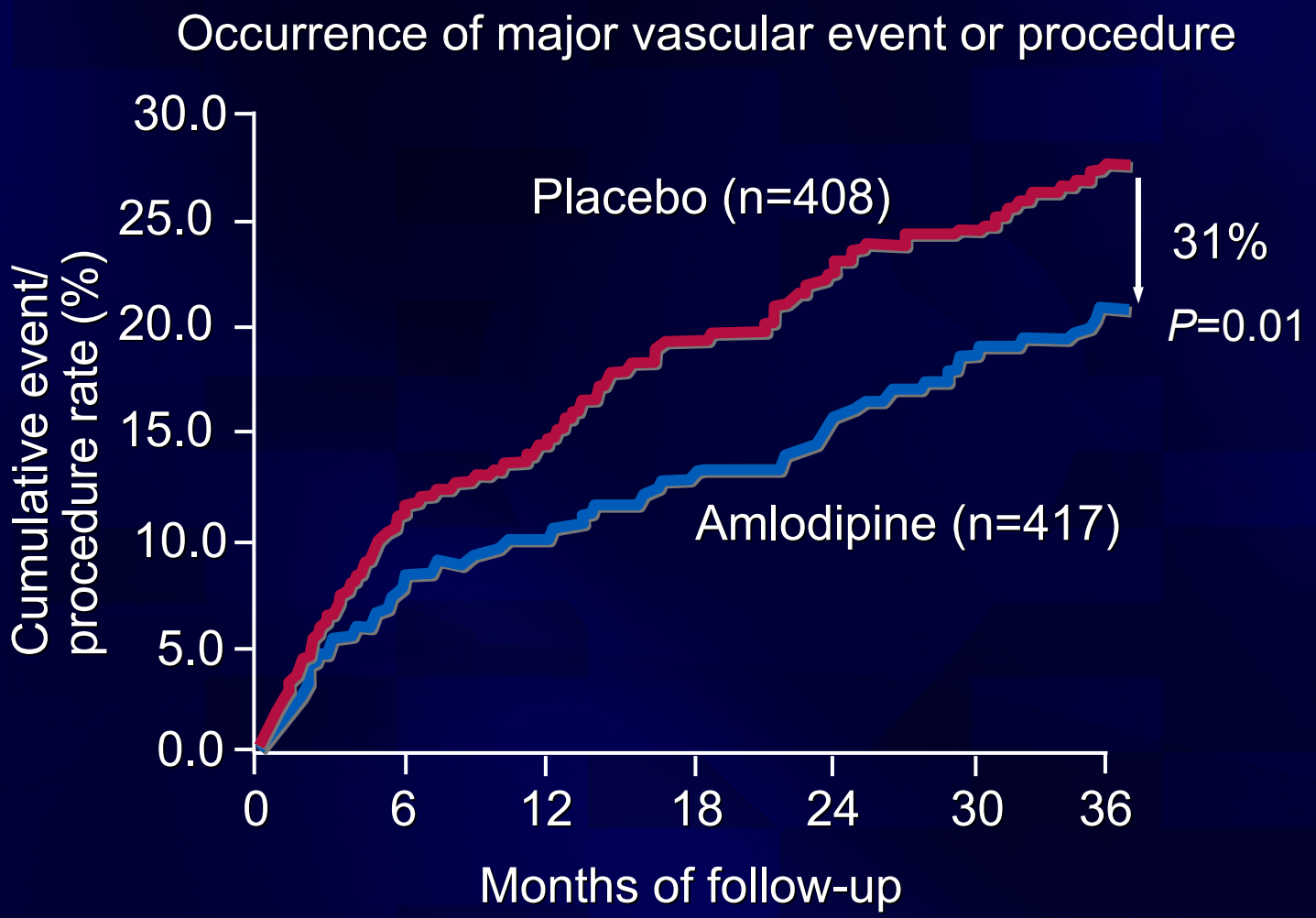
PREVENT: Study Design

Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial

Patients	825 patients with angiographically documented CAD Carotid IMT measured in 377 patients
Baseline BP	129.4/78.8 mm Hg
Treatment	Long-acting DHP CCB (amlodipine 10 mg/d) or placebo
Follow-up	3 year
Primary endpoint	Average change in mean minimal diameters of segments with 30% stenosis at baseline

Pitt et al *Circulation* 2000;102:1503-10

PREVENT: Amlodipine Reduced Occurrence of Major Vascular Event or Procedure



Pitt et al. *Circulation*. 2000;102:1503-1510.

The Irbesartan in Diabetic Nephropathy Trial

IDNT overview

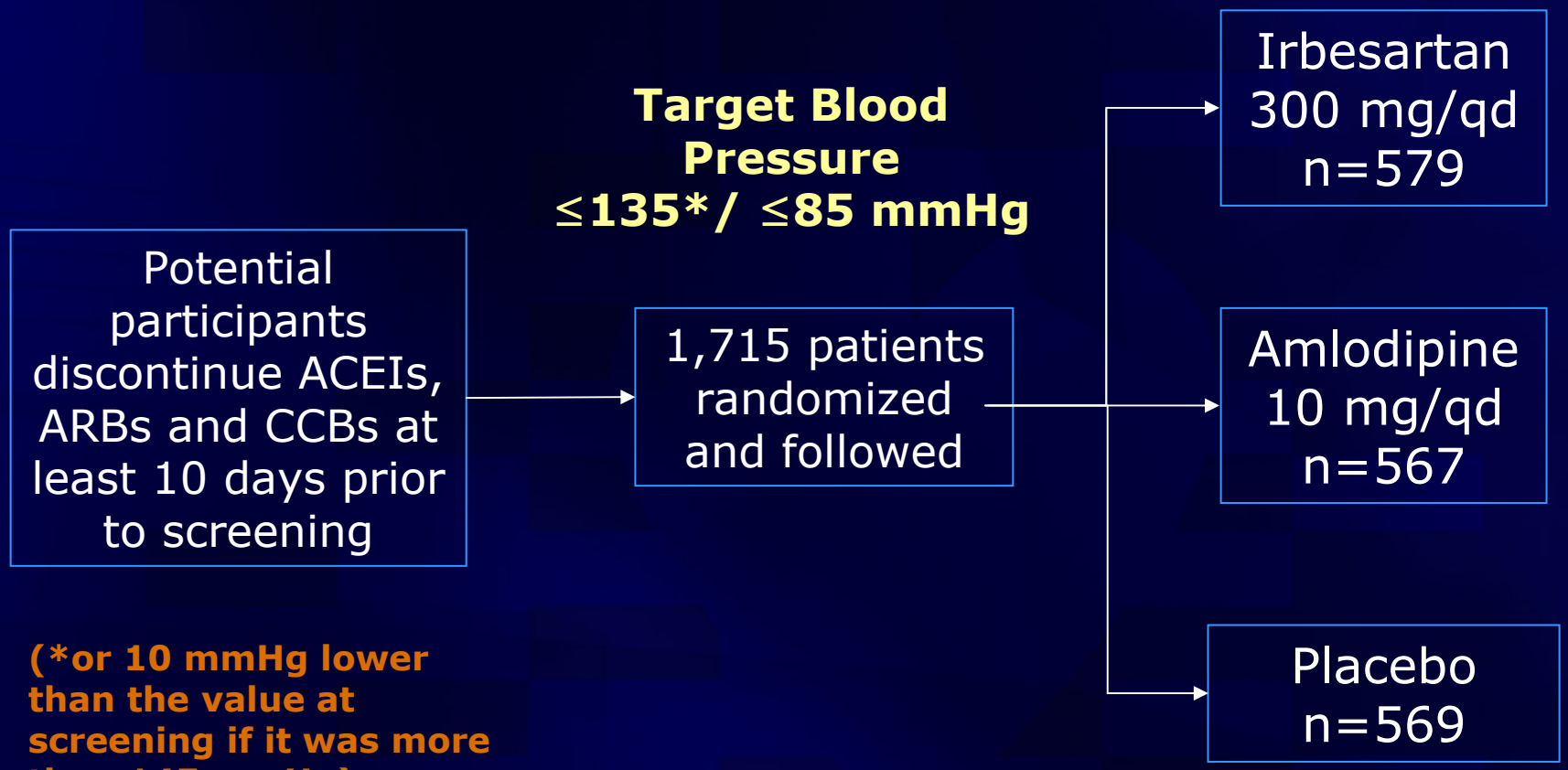
- Randomized, double-blind trial to determine if irbesartan, an angiotensin II receptor blocker, and amlodipine, a calcium channel blocker, slow the progression of nephropathy in type 2 diabetics

Population

- 1,715 patients (30 to 70 years old)
  - Diagnosed type 2 diabetes
  - Hypertension (systolic BP>135, diastolic BP >85 mmHg or treatment w/ antihypertensive agents)
  - Nephropathy (urinary protein excretion of at least 900 mg/24hrs and serum creatinine between 1.0–3.0 mg/dL in women, and 1.2–3.0 mg/dL in men)

Lewis EJ, et al. N Engl J Med. 2001;345(12):851-860.

IDNT Study Design



Lewis EJ, et al. N Engl J Med. 2001;345(12):851-860.

IDNT Endpoints

Primary Endpoint

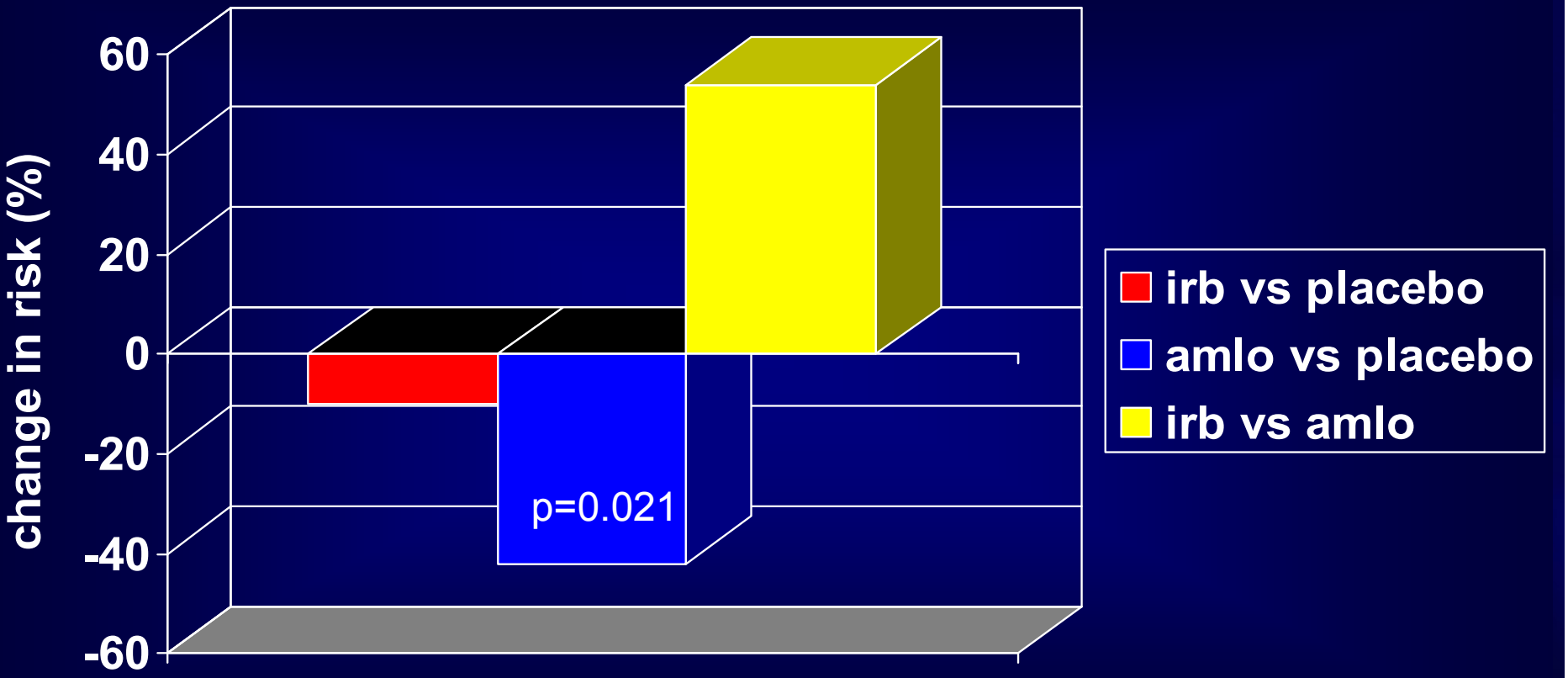
- Composite of a doubling of serum creatinine, end stage renal disease (as indicated by starting dialysis, serum creatinine ≥ 6 mg/dl, or transplantation), or death

Secondary Cardiovascular Endpoint

- Composite of death from cardiovascular causes, nonfatal myocardial infarction, heart failure resulting in hospitalization, a permanent neurologic deficit caused by a cerebrovascular event, or lower limb amputation above the ankle

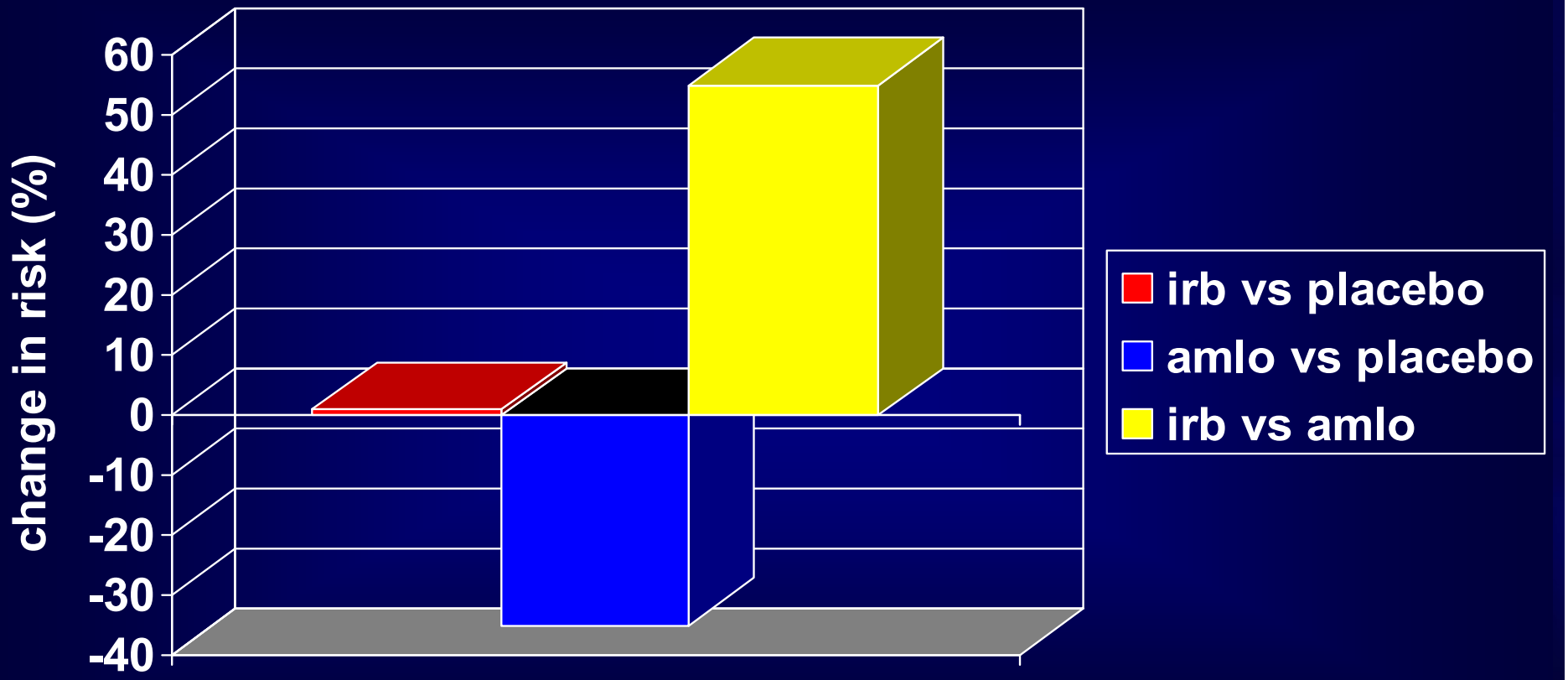
Lewis EJ, et al. N Engl J Med. 2001;345(12):851-860.

IDNT : MI Rate



Berl et al for the Collaborative study group, Ann Intern Med 138:542, 2003

IDNT : Stroke Rate



Berl et al for the Collaborative study group, Ann Intern Med 138:542, 2003

VALUE: Valsartan Anti-hypertensive Long-term Use Evaluation

Purpose

To test the hypothesis that, for the same blood pressure control, valsartan would reduce cardiac morbidity and mortality more than amlodipine in hypertensive patients at high cardiovascular risk

Lancet 2004;363:2022–2031

VALUE: Trial Design

Design

Multicenter, multinational, randomized, double-blind

Patients

15,245 patients ≥ 50 yrs with treated or untreated hypertension and high risk of cardiovascular events

Follow up and primary endpoint

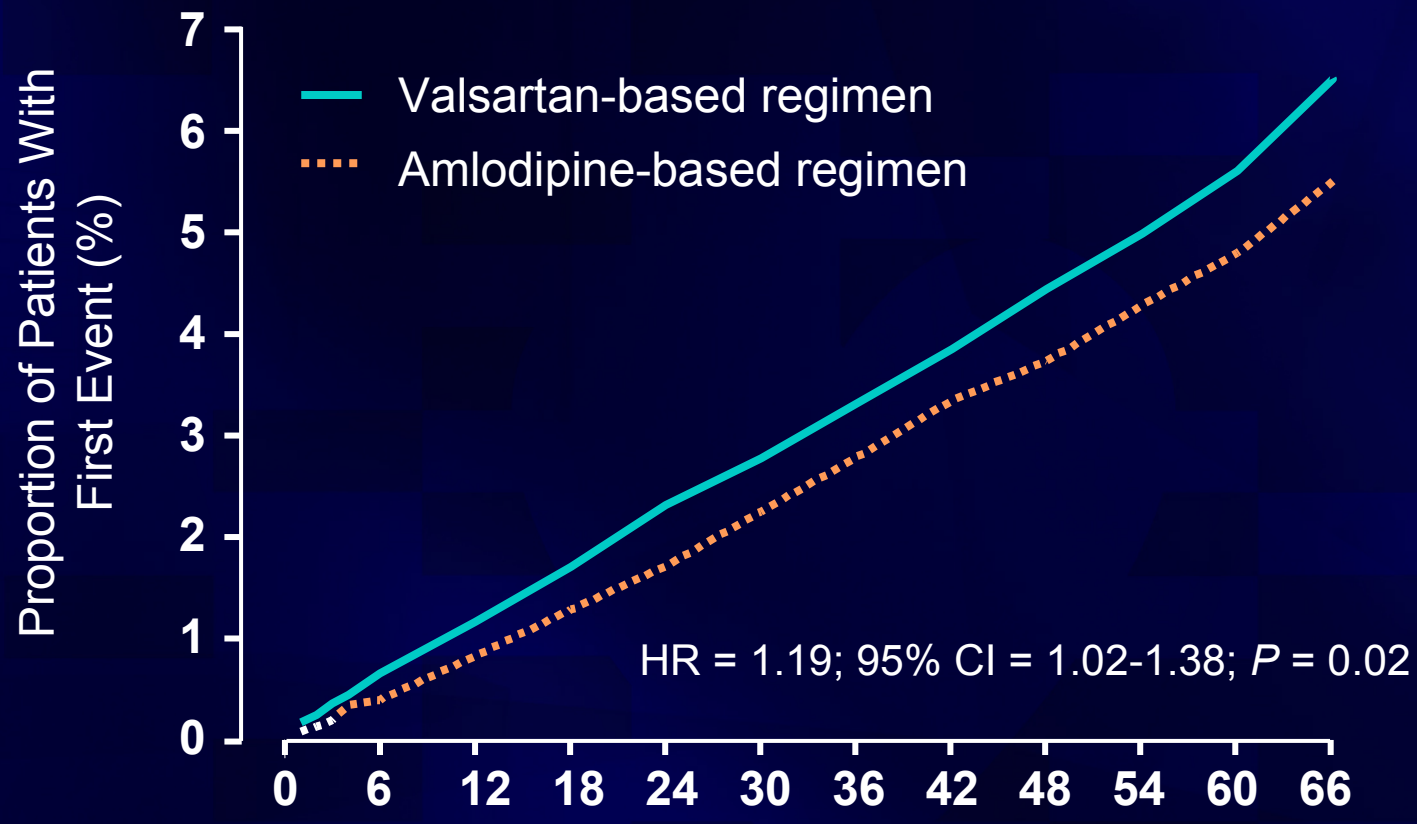
First event: a composite of cardiac morbidity and mortality

Treatment

Treatment initiated with valsartan (80 mg), or amlodipine (5 mg) and titrated upwards until a BP < 140/90 mmHg was achieved; other antihypertensive drugs other than ACE inhibitors or calcium antagonists, could be added if necessary

Lancet 2004;363:2022–2031

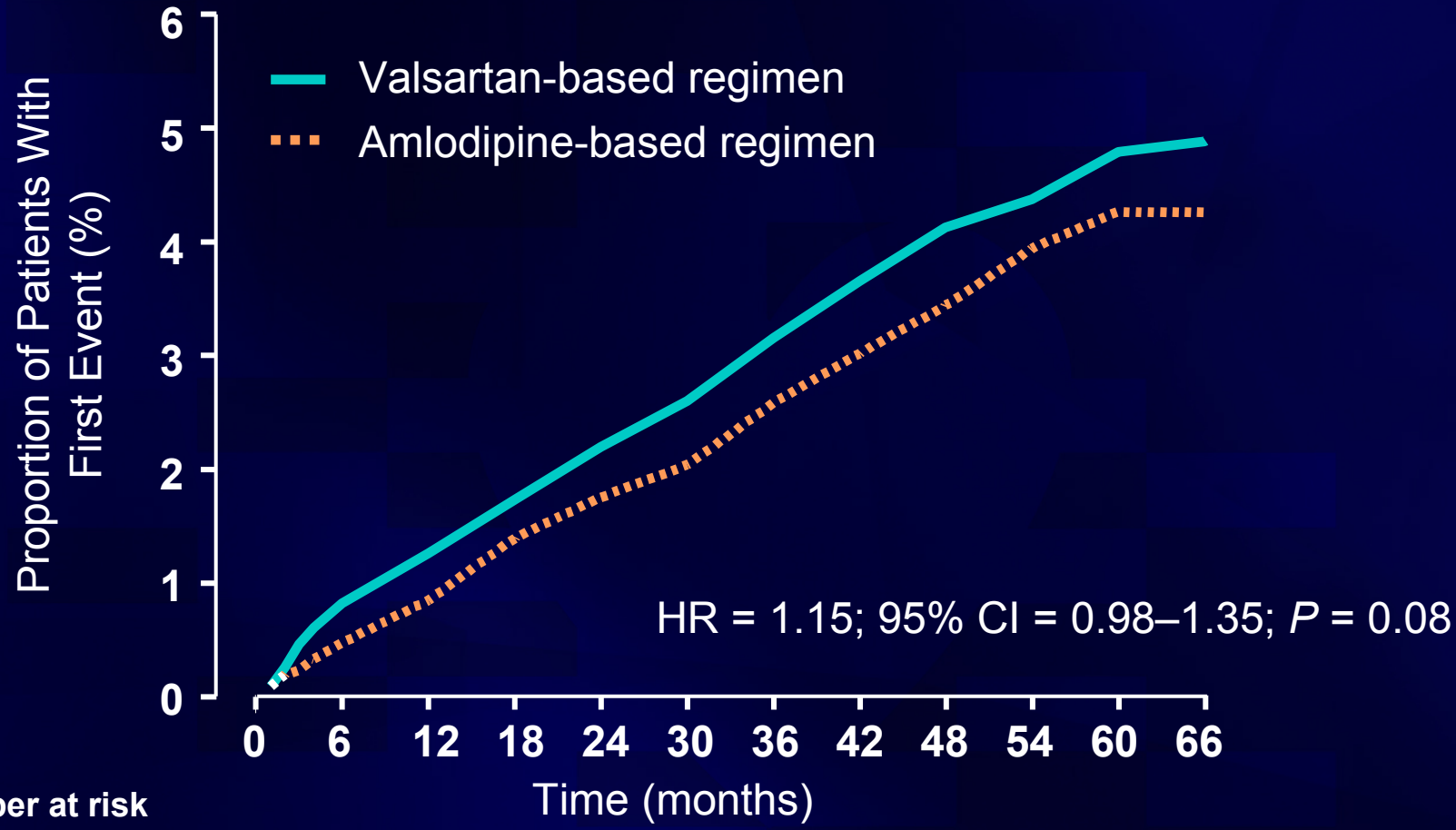
VALUE: Fatal and non-fatal MI



Number at risk												
Valsartan	7649	7499	7458	7319	7177	7016	6853	6680	6504	6078	3864	1520
Amlodipine	7596	7497	7458	7332	7205	7065	6905	6727	6562	6141	3840	1532

Lancet 2004;363:2022–2031

VALUE: Fatal and non-fatal stroke



Number at risk												
Valsartan	7649	7494	7448	7312	7170	7022	6877	6692	6515	6093	3859	1516
Amlodipine	7596	7499	7455	7334	7195	7055	6918	6744	6587	6163	3846	1532

Lancet 2004;363:2022–2031

International Verapamil-Trandolapril Study (INVEST)

Treatment strategies

- Calcium antagonist strategy (CAS) using verapamil-SR
- Non-calcium antagonist strategy (NCAS) using atenolol
- Addition of trandolapril to the regimen of patients with concomitant diabetes, renal failure, or heart failure was recommended
- Additional antihypertensive therapy was allowed to achieve and maintain goal blood pressure

Pepine CJ, et al. JAMA. 2003;290:2805-2816.

INVEST: Primary and Secondary Endpoints

Primary composite endpoint

First occurrence of

- **Death (all-cause), or**
- **Nonfatal myocardial infarction, or**
- **Nonfatal stroke**

Secondary endpoints

- **Each of the above as individual endpoints**
- **Cardiovascular death**
- **Time to most serious event (death, then MI, then stroke)**
- **Angina**
- **Cardiovascular hospitalizations**
- **Blood pressure control**
- **Cancer, Alzheimer's disease, Parkinson's disease, and gastrointestinal bleeding**
- **New diagnosis of diabetes mellitus**

Pepine CJ, et al. JAMA. 2003;290:2805-2816.

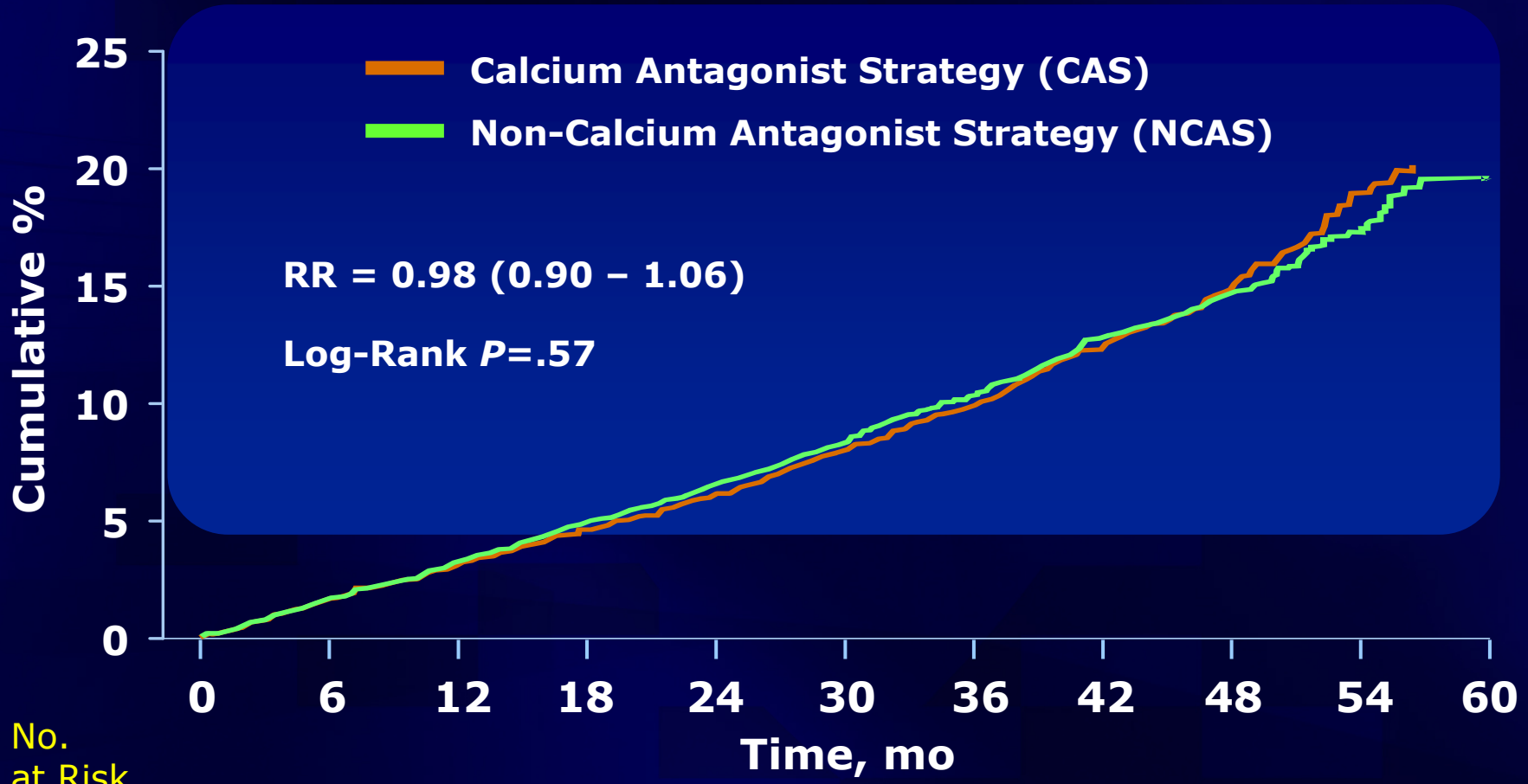
INVEST: Baseline Demographics

	Calcium Antagonist Strategy (n=11,267)	Non-Calcium Antagonist Strategy (n=11,309)
Mean age (yrs)	66.0	66.1
Women (%)	51.9	52.3
Race/ethnicity (%)		
White	48.5	48.3
Hispanic	35.7	35.6
Black	13.4	13.5
Asian	0.6	0.8
Other	1.9	1.9
Mean BMI (kg/m^2)	29.1	29.2

BMI = Body Mass Index

Pepine CJ, et al. JAMA. 2003;290:2805-2816.

INVEST: Primary Composite Endpoint



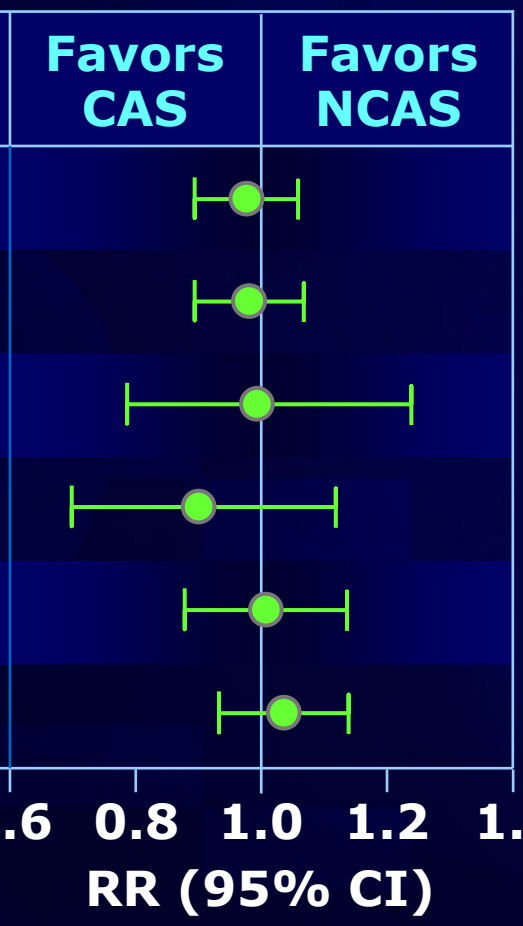
No. at Risk

CAS	11267	10921	10716	10512	10008	6612	3738	1568	974	393	35
NCAS	11309	10991	10785	10536	10048	6604	3706	1563	960	390	33

Pepine CJ, et al. JAMA. 2003;290:2805-2816.

INVEST: Relative Risk of Primary and Secondary Outcomes

	RR (95% CI)
First event*	0.98 (0.90 – 1.06)
Death	0.98 (0.90 – 1.07)
Nonfatal MI	0.99 (0.79 – 1.24)
Nonfatal stroke	0.89 (0.70 – 1.12)
Cardiovascular death	1.00 (0.88 – 1.14)
Cardiovascular hospitalization	1.03 (0.93 – 1.14)



CAS = Calcium Antagonist Strategy
NCAS = Non-Calcium Antagonist Strategy

*** Primary Outcome = first occurrence of death, nonfatal MI, or nonfatal stroke**

Pepine CJ, et al. JAMA. 2003;290:2805-2816.

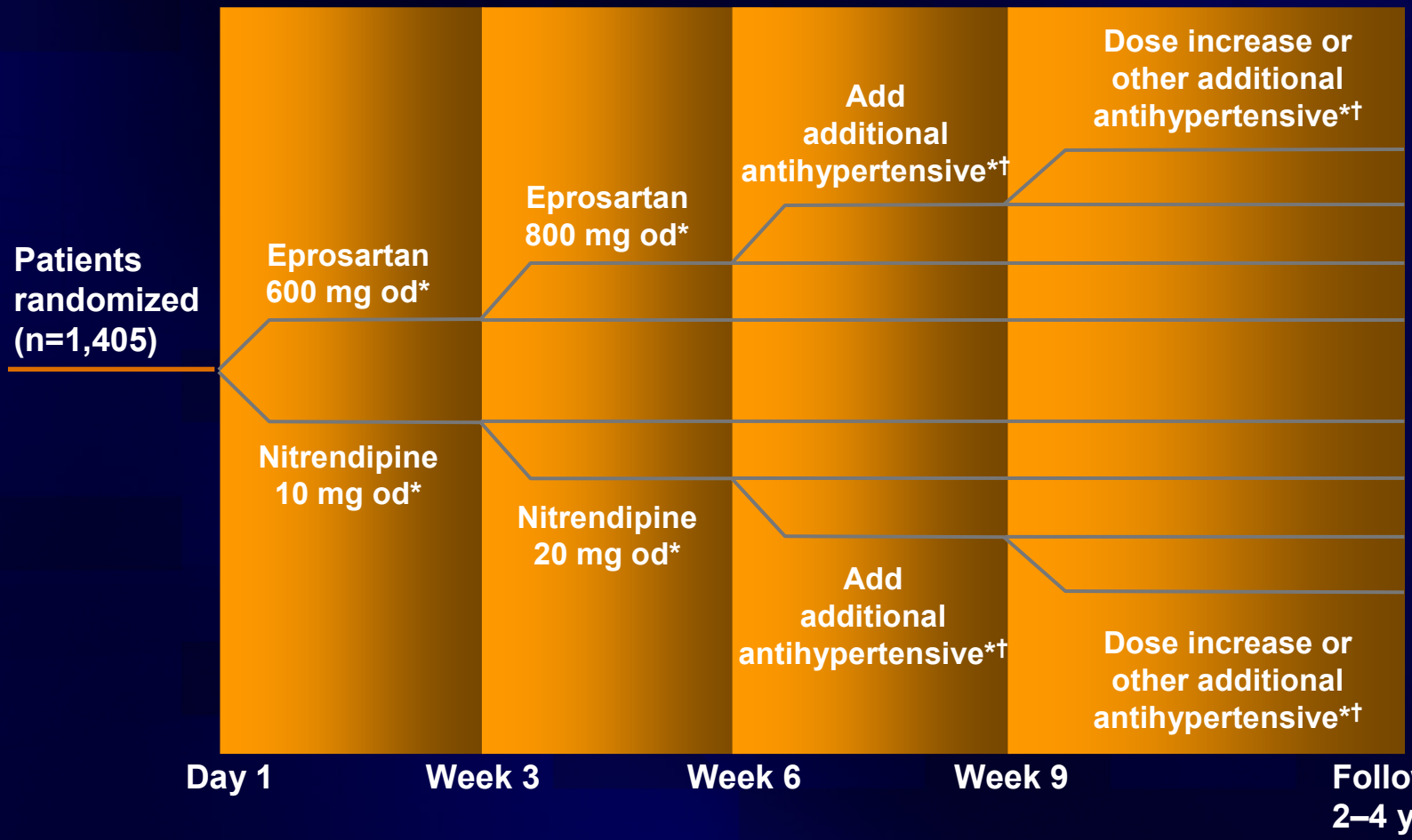
MOSES Study: design

- 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

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

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 ACEIs, ARBs and CCBs.

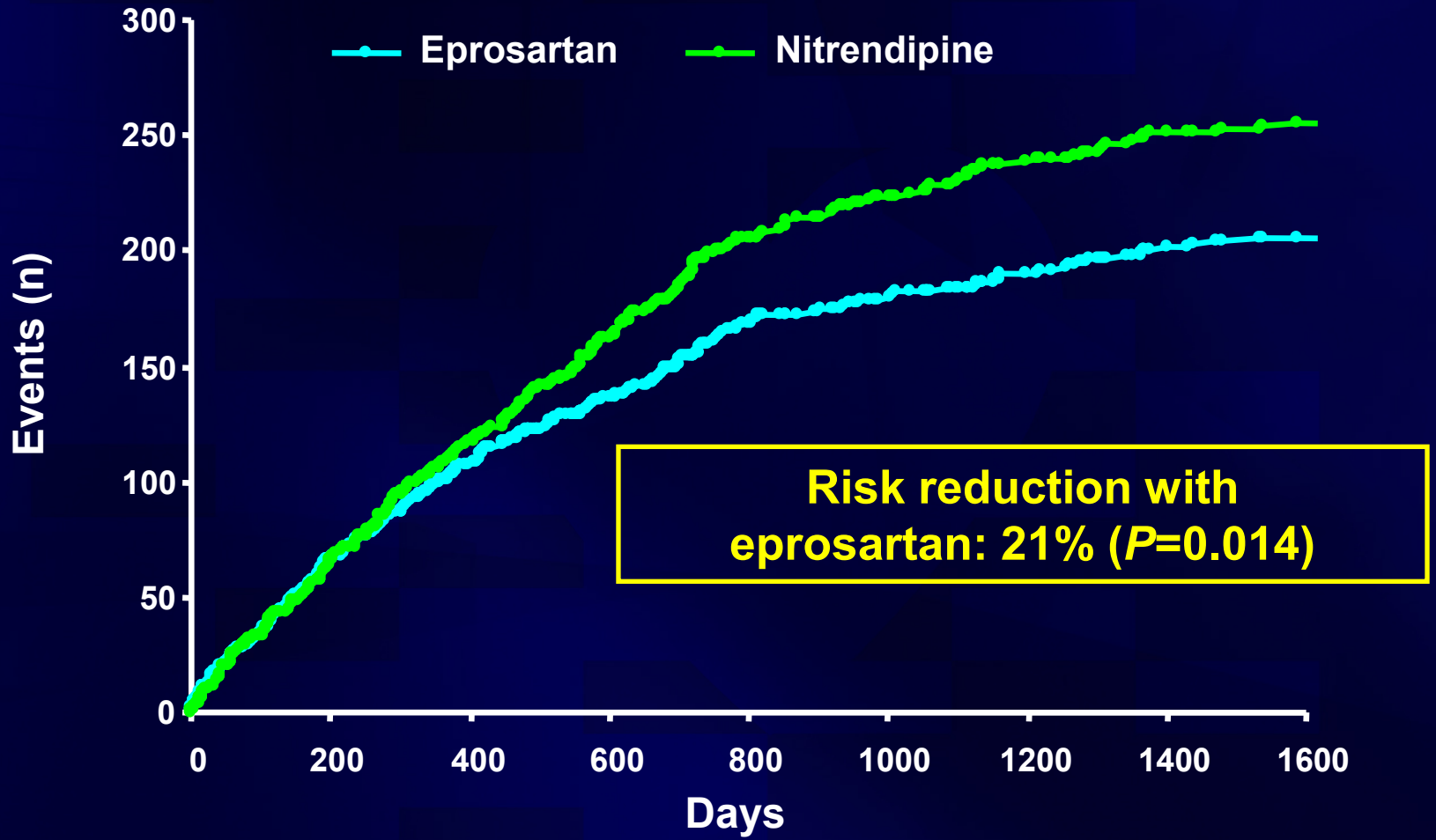
Hansson L, et al. *Blood Press* 1992;1:113–119.

MOSES: 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

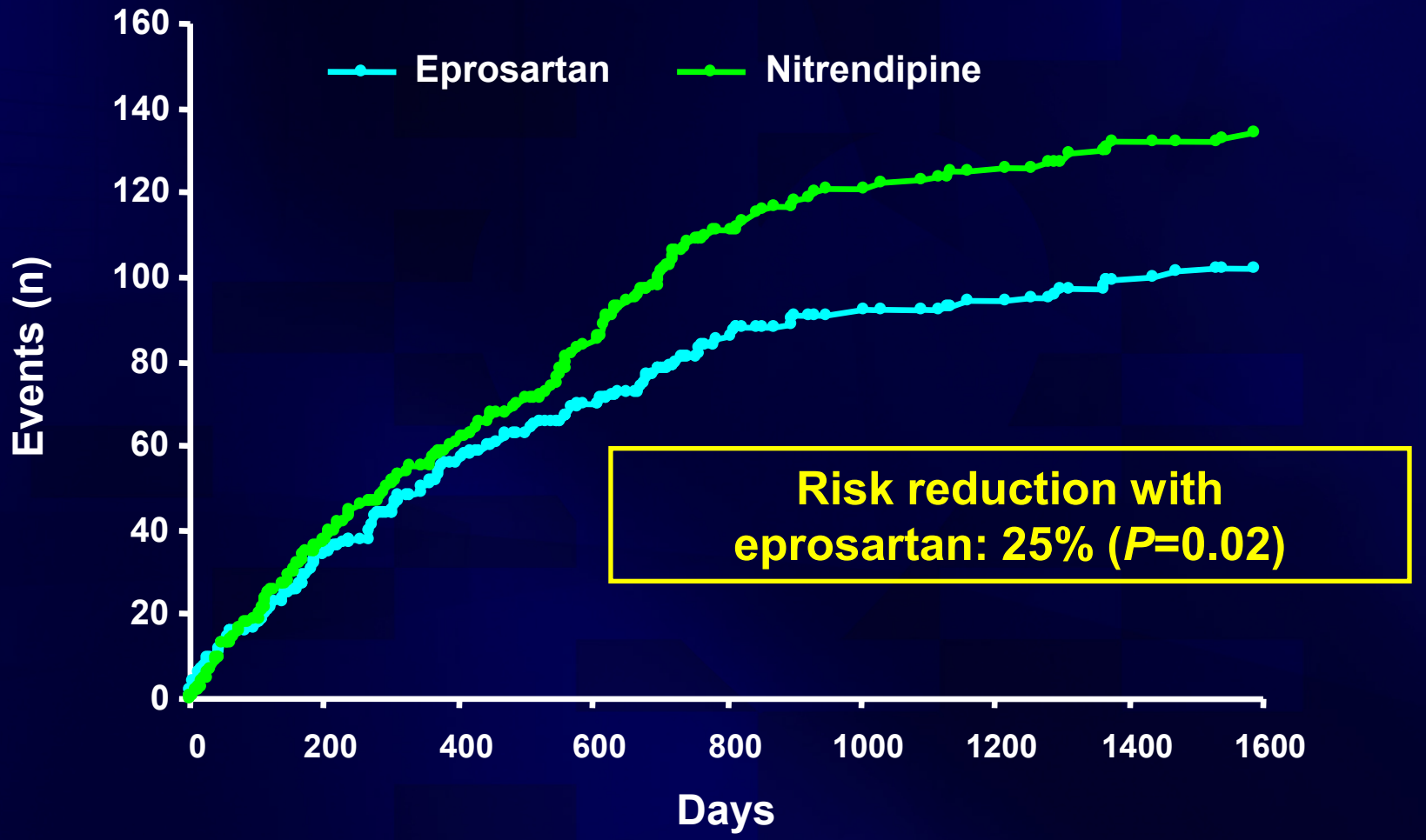
Hansson L, et al. *Blood Press* 1992;1:113–119.

Primary endpoint (morbidity and mortality)



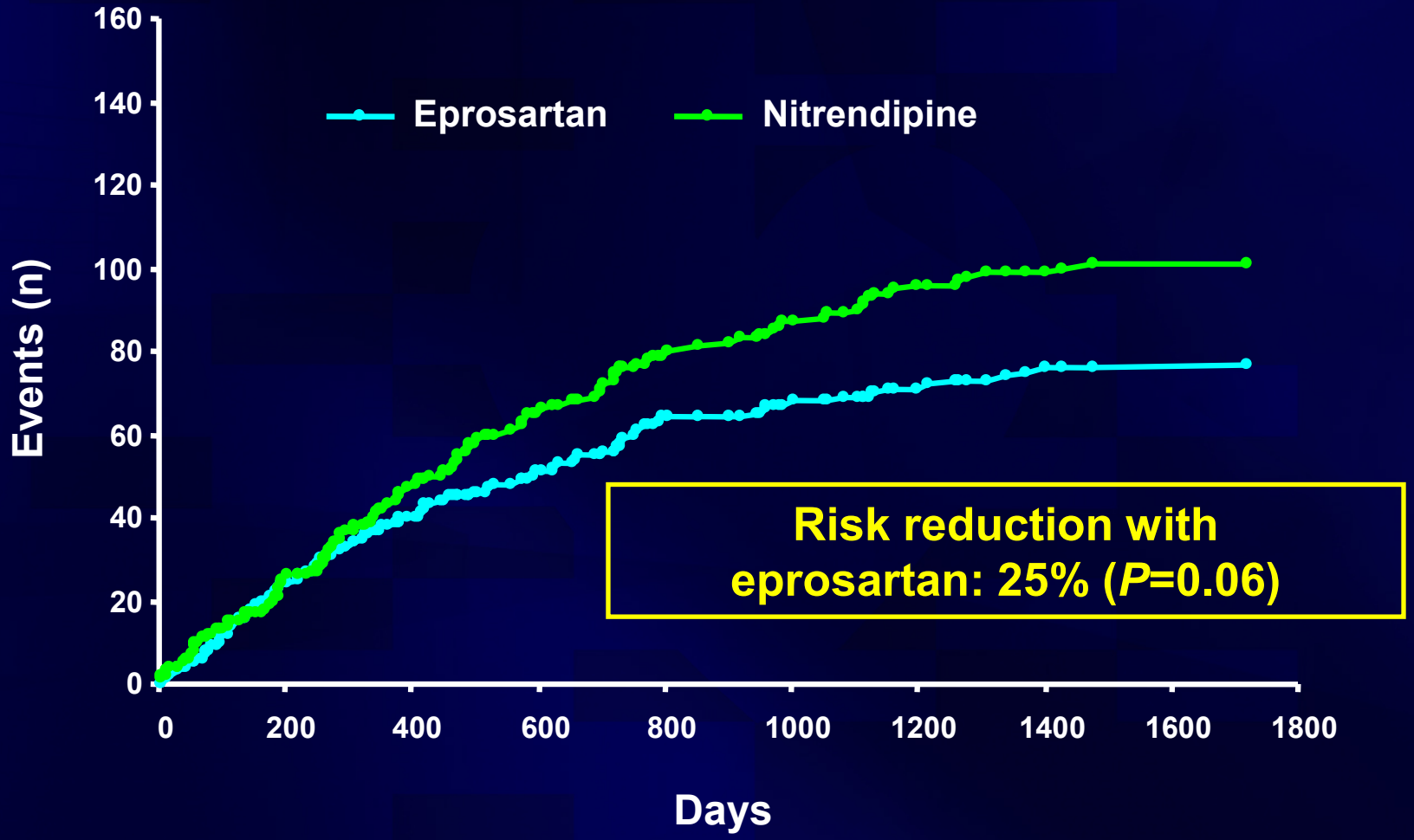
Hansson L, et al. *Blood Press* 1992;1:113–119.

Secondary endpoint (cerebrovascular events)



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

Secondary endpoint (cardiovascular events)



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

Prevention of Stroke and Myocardial Infarction by Amlodipine and Angitensin Receptor Blockers

A Quantitative Overview

Ji-Guang Wang, Yan Li, Stanley S. Franklin, Michel Safar

Hypertension 2007;50:1-8

Design

- 12 trials of 94,338 patients
- Patients : with hypertension, coronary artery disease or diabetic nephropathy
- Amlodipine vs. other anti-hypertensive agents
- ARBs vs. other anti-hypertensives agents

Characteristics of Trials

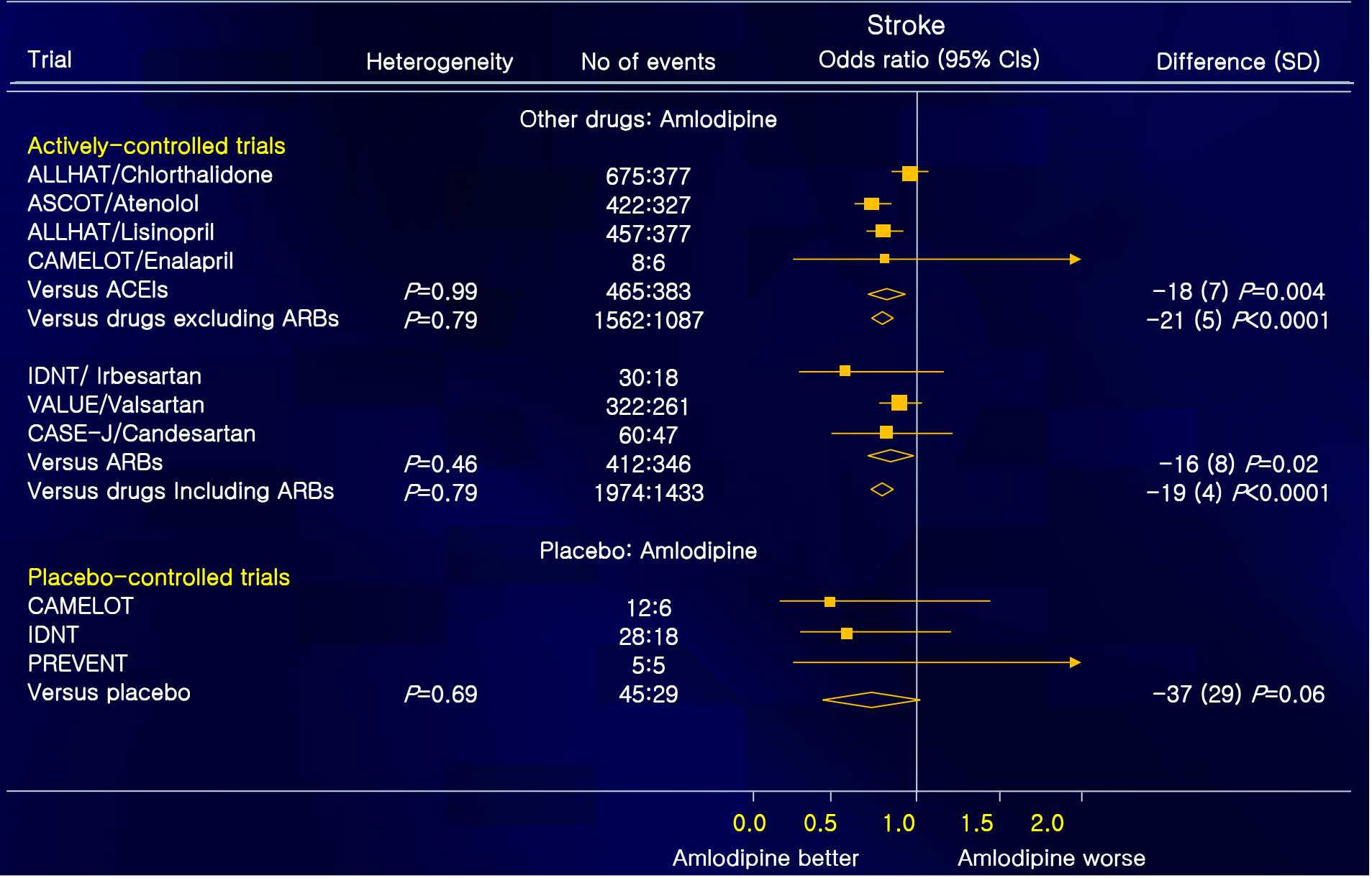
Trial	Masking	Total No. of Patients	Main Selection Criteria			Primary Outcome	Antihypertensive Treatment	
			Age, y	SBP/DBP, mmHg	Disease or Risk Factors		Control, mg	Experimental, mg
Trials involving amlodipine								
ALLHAT[19,20]	Double	33 357*	≥55	140 to 180/90 to 110 or treated ≤ 160/100	1 risk factor	Coronary death + MI	Chlorthalidone (12.5 to 25)	Amlodipine (2.5 to 10) or Lisinopril (10 to 40)
ASCOT [21]	Open	19 257	40 to 79	≥160/100 or treated ≥ 140/90	3 risk factor	Coronary death + MI	Atenolol (50 to 100)	Amlodipine (5 to 10)
CAMELOT[12]	Double	1991	30 to 70	Untreated or treated/≤ 100	CAD (>20% stenosis)	CV death + MI + RCA + AP + CR + HF + stroke + PAD	Placebo	Amlodipine (5 to 10) or Enalapril (10 to 20)
PREVENT[23]	Double	825	30 to 80	Untreated or Treated/<95	CAD (>20% stenosis)	Rate of coronary atherosclerosis	Placebo	Amlodipine (5 to 10)
Trials involving an ARB								
LIFE[8]	Double	9193	55 to 80	160 to 200/ 95 to 115	ECG LVH	CV death + MI + stroke	Atenolol (50 to 100)	Losartan (50 to 100)
DETAIL[11]	Double	250	35 to 80	Treated < 180/ 95 on ACEI	2DM + nephropathy+	Change in GFR	Enalapril (10 to 20)	Telmisartan (40 to 80)
MOSES[13]	Open	1352	any§	≥140/90 or treated	CBV	All cause death + MI + HF + CBV	Nitrendipine (10)	Eprosartan (600)
SCOPE[9]	Double	4937	70 to 89	Untreated or treated	No	CV death + M I+ stroke	Placebo	Candesartan (8 to 16)
RENAAL[7]	Double	1513	31 to 70	160 to 179/90 to 99 Any	2DM + nephropathy#	All-cause death + ESRD + DBSC	Placebo	Losartan (50 to 100)
Trials involving amlodipine and an ARB								
IDNT[6]	Double	1715	30 to 70	≥ 135/85 or treated	2DM + nephropathy¶	All cause death + ESRD + DBSC	Placebo	Irbesartan (75 to 300) or Amlodipine(2.5 to 10)
VALUE[10]	Double	15 245	≥ 50	160 To 210/≥115 or treated ≤ 210/115	CV diseases or risk factors§	MI + HF	Amlodipine (5 to 10)	Valsartan (80 to160)
CASE-J[18]	Open	4703	20 to 85	<70 y ≥140/90 or ≥70 y ≥ 160/90	1 disease or risk factor	CV death + MI + AP + CR + HF + CBV + VE + ESRD	Amlodipine (2.5 to 10)	Candesartan (4 to 12)

Outcome trials : randomized, controlled designed : publication in a peer-reviewed journal : assessment of BP and CVD : follow up for ≥ 2 years : sample size of ≥ 100

Characteristics of Patients

Trial	No. of Patients*		Mean Age, y	Mean SBP/DBP, mm Hg		Percentage of Patients					Follow-Up yr
	Control	Experimental*		Mean At entry	Difference During Follow-Up+	Women	Treated Hypertension	CAD(MI)	Stroke	Diabetes Mellitus	
Vs amlodipine											
ALLHAT chlorthalidone[19]	15 255	9048	67	146/84	−1.1/+0.6§	47	90	25	21	36	4.9
ASCOT atenolol[21]	9618	9639	63	164/95	+2.7/+1.9§	23	91	0	11#	27	5.5
ALLHAT lisinopril[19,20]	9054	9048	67	146/84	+1.5/+1.1§	47	90	25	21	36	4.9
CAMELOT enalapril[12]	673	663	58	129/77	−0.1/+0.1	26	39	100 (39)	4	17	2.0
CAMELOT placebo[12]	655	663	57	129/78	+4.1/+1.9§	25	61	100 (38)	4	19	2.0
PREVENT placebo[23]	408	417	57	129/79	+6.8/+3.7§	20	…	100 (45)	3	0¶	3.0
IDNT placebo[6]	569	567	59	159/87	+4/+3§	33	100	…	…	100	2.6
Vs ARBs											
LIFE atenolol[8]	4588	4605	67	174/98	+1.1§/+0.2	54	100	16	7.9#	13	4.8
DETAIL enalapril[11]	130	120	61	152/86	+4.0 §/−	27	100	…	…	100	5.0
MOSES nitrendipine[13]	671	681	68	151/87	−2.8/−0.8§	46	84	26 (8)	100#	37	2.5
SCOPE placebo[9]	2460	2477	76	166/90	+3.2/+1.6§	65	53	8.4	…	12	3.7
IDNT placebo[6]	569	679	59	159/87	+6/+3§	32	100	…	…	100	2.6
RENAAL placebo[7]	762	751	60	153/82	+1§/0	37	93	21 (11)	0	100	3.4
Amlodipine vs ARBs											
IDNT[6]	567	579	59	160/87	+2§/0	36	100	…	…	100	2.6
VALUE[10]	7649	7596	67	155/88	−2.2/−1.6§	42	92	46	20#	32	4.2
CASE-J[18]	2349	2354	64	163/92	−1.9§/0	45	67	14	19#	43	3.2

Effect of Amlodipine on Stroke



Result of Amlodipine on Stroke

- Amlodipine besylate vs. drug including ARBs

  : 19% reduction (p<0.0001)

- Amlodipine besylate vs. drug excluding ARBs

  : 21% reduction (p<0.0001)

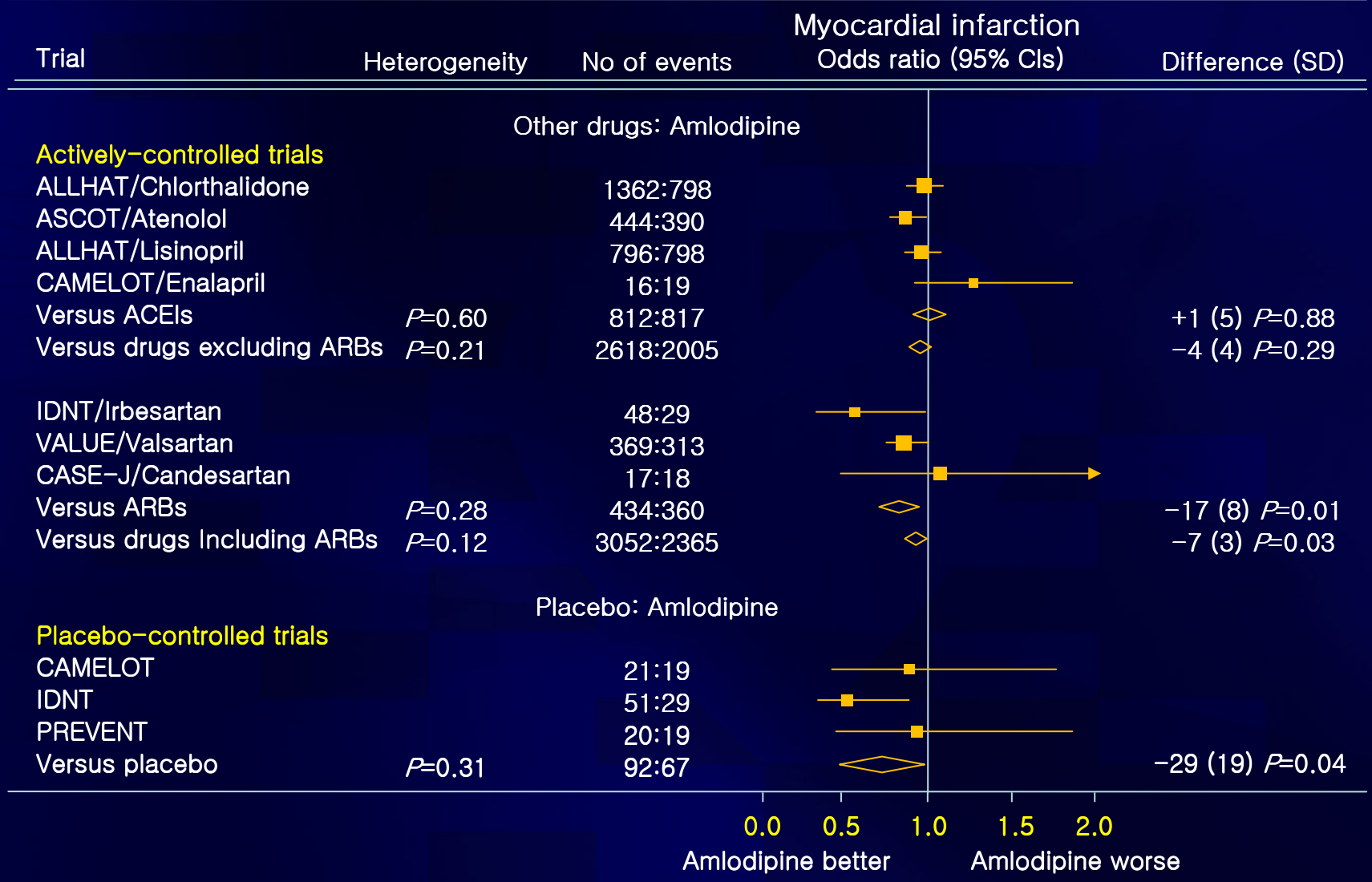
- Amlodipine besylate vs. ARBs

  : 16% reduction (p<0.02)

- Amlodipine besyalte vs. Placebo

  : 32% reduction (p=0.06), due to the small number of event (74 strokes) only reached borderline statistical significance for stroke

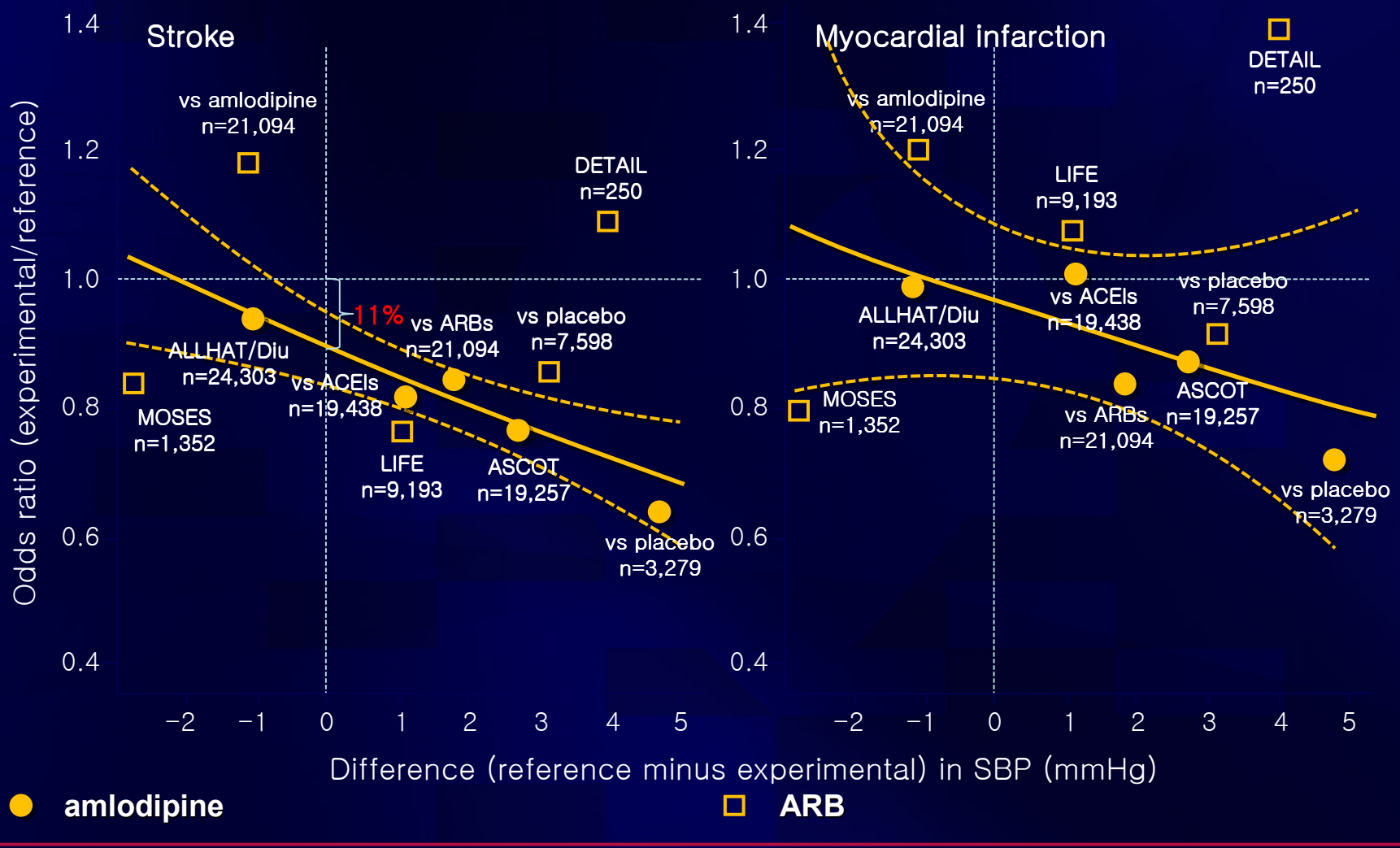
Effect of Amlodipine on MI



Result of Amlodipine on MI

- Amlodipine besylate vs. drug including ARBs
  : 7% reduction (p<0.03)
- Amlodipine besylate vs. drug excluding ARBs
  : 4% reduction (p=0.29)
- Amlodipine besylate vs. ARBs
  : 17% reduction (p=0.01)
- Amlodipine besyalte vs. Placebo
  : 29% reduction (p=0.04)

Odds Ratio for Stroke & MI in relation to the difference in SBP *



Summary

- The ability to reduce the cardiovascular risk was different among CCBs.
- Amlodipine besylate substantially reduced the risk of stroke & MI.
- The benefit of initial treatment with amlodipine besylate vs other antihypertensive could not be entirely explained by BP difference.

"Antihypertensive agents produce no obvious benefit in patients over 65"

Fry J, Lancet 1974

"Hypertensive drugs should probably not be given (in the elderly) unless the blood pressure is more than 200/110 mm Hg."

Editorial, Br Med J, 1978

He hasn't been trained in the latest technology. He isn't aware of the latest treatment. The tests he relies on will miss eight out of 10 cases. Yet the enemy he's fighting is heart disease, the leading killer of men. Who is he? He's your doctor

Lie

BY JOE KITA

DAVID RUBINSON HAD A HEART attack at age 39. But he blames himself for that. As a record producer and manager of such acts as Santana and the Pointer Sisters, he thought he was Superman. And eventually the late nights in the studio, the rich foods, and the extreme stress caught up with him. A poor lifestyle, combined with a family history of heart disease, became his kryptonite.

But he considers himself blameless for what happened next. In the ensuing decade, he transformed his life. He downsized his business, became a vegetarian, stopped smoking, started exercising, lost weight, and took up yoga. His total cholesterol plummeted from 380 to 210, he qualified for $2 million worth of new life insurance, he passed his treadmill stress tests, and his doctors gave him nothing but back pats. Then one night at dinner, almost 10 years to the day after his heart attack and just 12 hours after running 9½ miles across the Golden Gate Bridge, he felt a familiar dread.

"It wasn't real pain," he recalls. "It was more a sense of depletion, like somebody had pulled the plug and all the water was running out of the tub. Later, after I put everyone to bed, I went into my office at home and took a nitroglycerin tablet. And when it made me feel better, I knew I was in trouble. I woke my wife and told her we had to go to the hospital."

When doctors did an angiogram to assess the situation, Rubinson couldn't believe what he saw. "The grafts from my original bypass were completely dried up," he says. "They looked like black strings. I'd been running across that bridge on nothing. It's hard to describe what I felt. Rage, betrayal, terror. My son asked the doctors, 'How could this happen? My God, look

Men's Health, June 2001

Men's Health, June 2001

- "He hasn't been trained in the latest technology."
- "He isn't aware of the latest treatment."
- "The test that he relies on will miss 8 out of 10 cases."
- "Yet the enemy he is fighting is heart disease, the leading killer of men."
- "Who is he?"
- "He's your doctor."