Role of Cardiologists in Stroke Prevention
Focusing on Hypertension
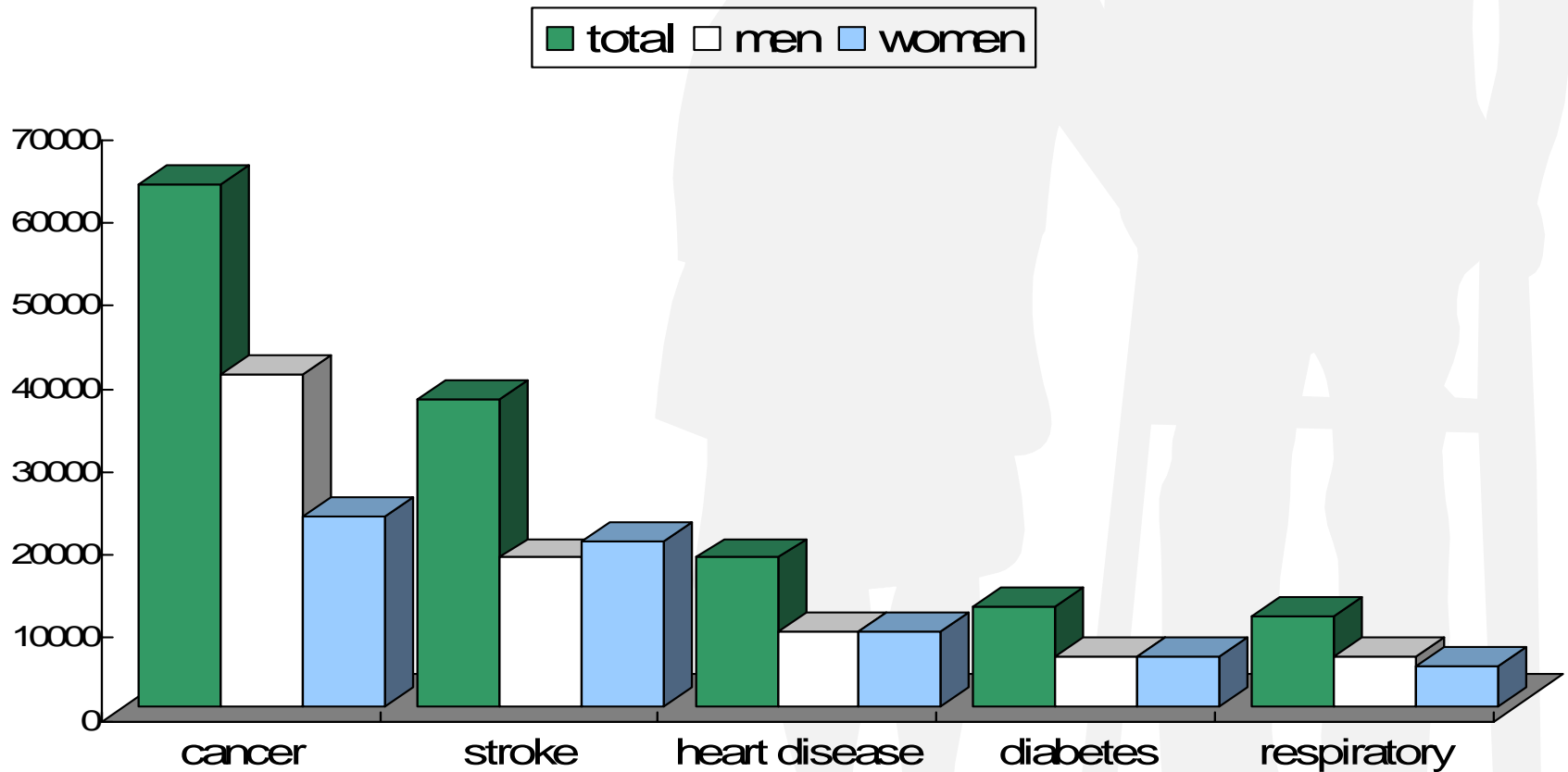
Se-Joong Rim, M.D.

Cardiology Division

Yongdong Severance Hospital

Yonsei University College of Medicine

Cause of Death in Korea

Korea National Statistical Office 2002

Stroke mortality by region

Country (Year)	Mortality rate (per 100,000)	
	Men	Women
Russian Federation (1998)	361	229
Romania (1999)	281	186
China, rural (1099)	243	152
Korea (1997)	182	114
Argentina (1996)	116	63
Japan (1997)	79	41
Mexico (1995)	61	52
England/Wales (1999)	52	41
United States (1999)	41	33
Australia (1996)	38	27

Aged 35 to 74 years

Burdens of Stroke

- Death
- Physical and mental disability (30%)
- Depression (18~50%)
- Economic burden

Type of Stroke

- Ischemic stroke 83%, hemorrhagic stroke 17% in US
  - Rosamond WD, et al. Stroke 1999;30:736-43

- Ischemic stroke 66%, hemorrhagic stroke 34% in Korea
  - The Korean National Health System Study (1986-2000)

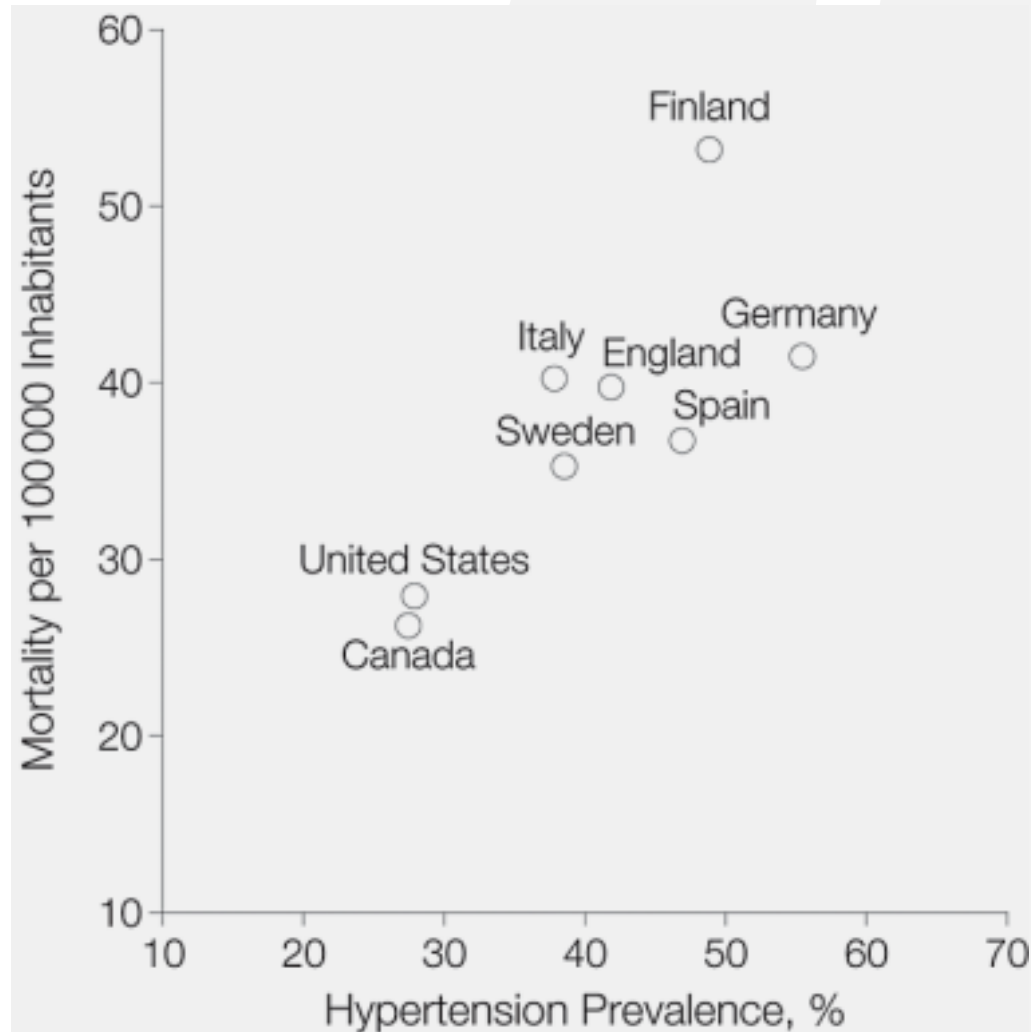   BMJ 2004;328:324-325

What Causes a Stroke?

Ischemic

- Hypertension
- Atherosclerosis
- Heart and/or blood conditions that contribute to clotting

Hemorrhagic

- Aneurysm
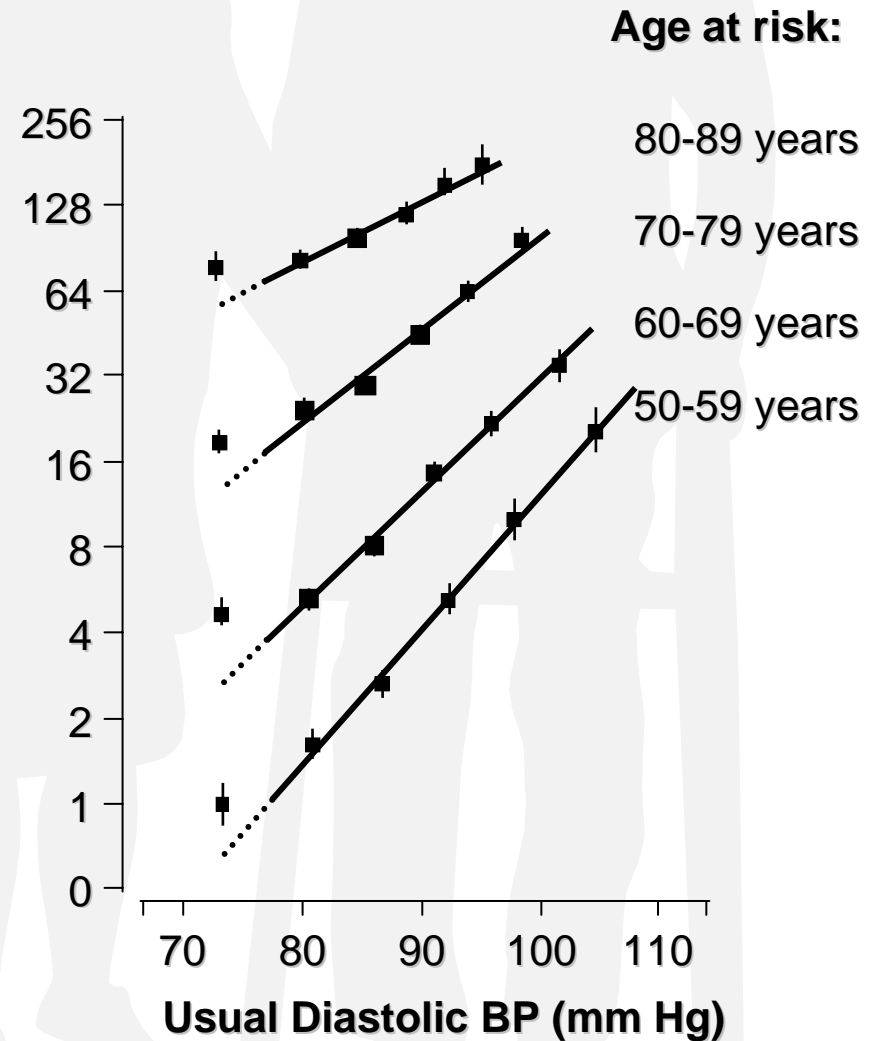- Arteriovenous Malformation

Hypertension Prevalences vs Stroke Mortality
6 European and 2 North American Countries

Wolf-Maier, K. et al. JAMA 2003;289:2363-2369.

Stroke Mortality and Usual BP by Age

Systolic Blood Pressure   Diastolic Blood Pressure

Age at risk: **Age at risk:**

Stroke Mortality (Floating Absolute Risk and 95% CI) vs **Usual Systolic BP (mm Hg)** and **Usual Diastolic BP (mm Hg)**, with curves for 80-89 years, 70-79 years, 60-69 years, and 50-59 years.

Prospective Studies Collaboration. *Lancet*. 2002;360:1903-1913.
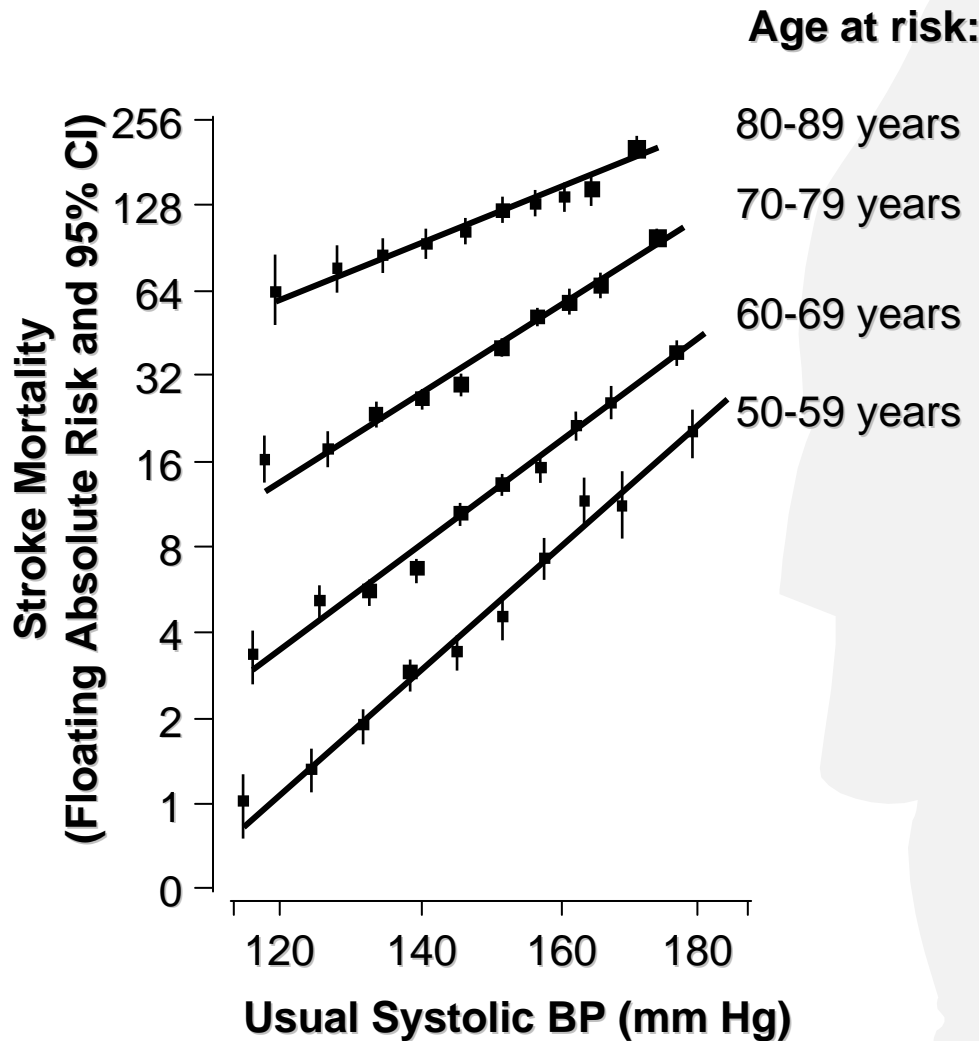
SBP and Stroke in Asia
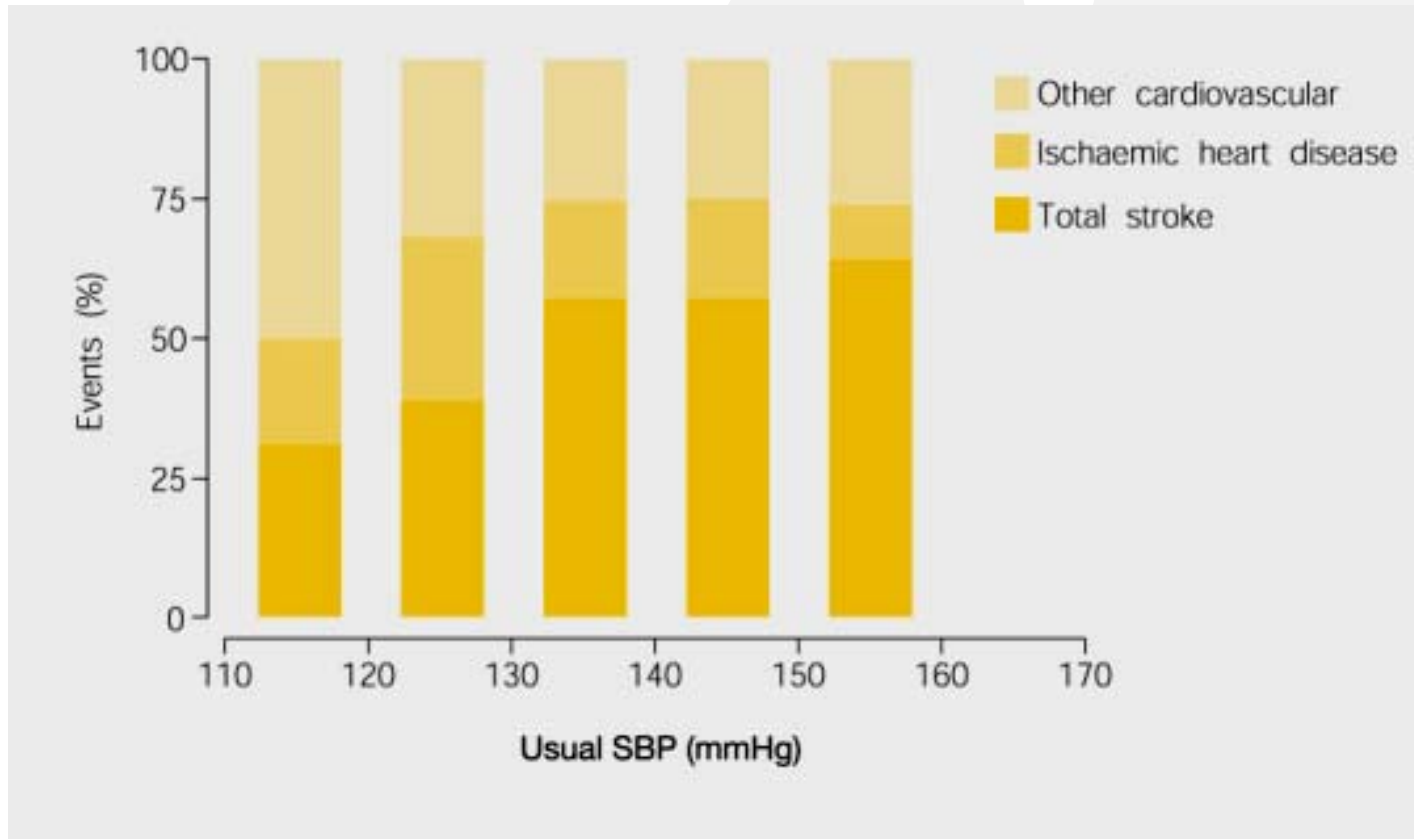
" **Increased blood pressure levels are directly responsible for the majority of stroke deaths (more than 50%)…in Eastern Asia.** "

Asia Pacific Cohort Studies Collaboration. J Hypertens 2003; 21:707-16

Modifiable Risk Factors for Ischemic Stroke

Relative risk
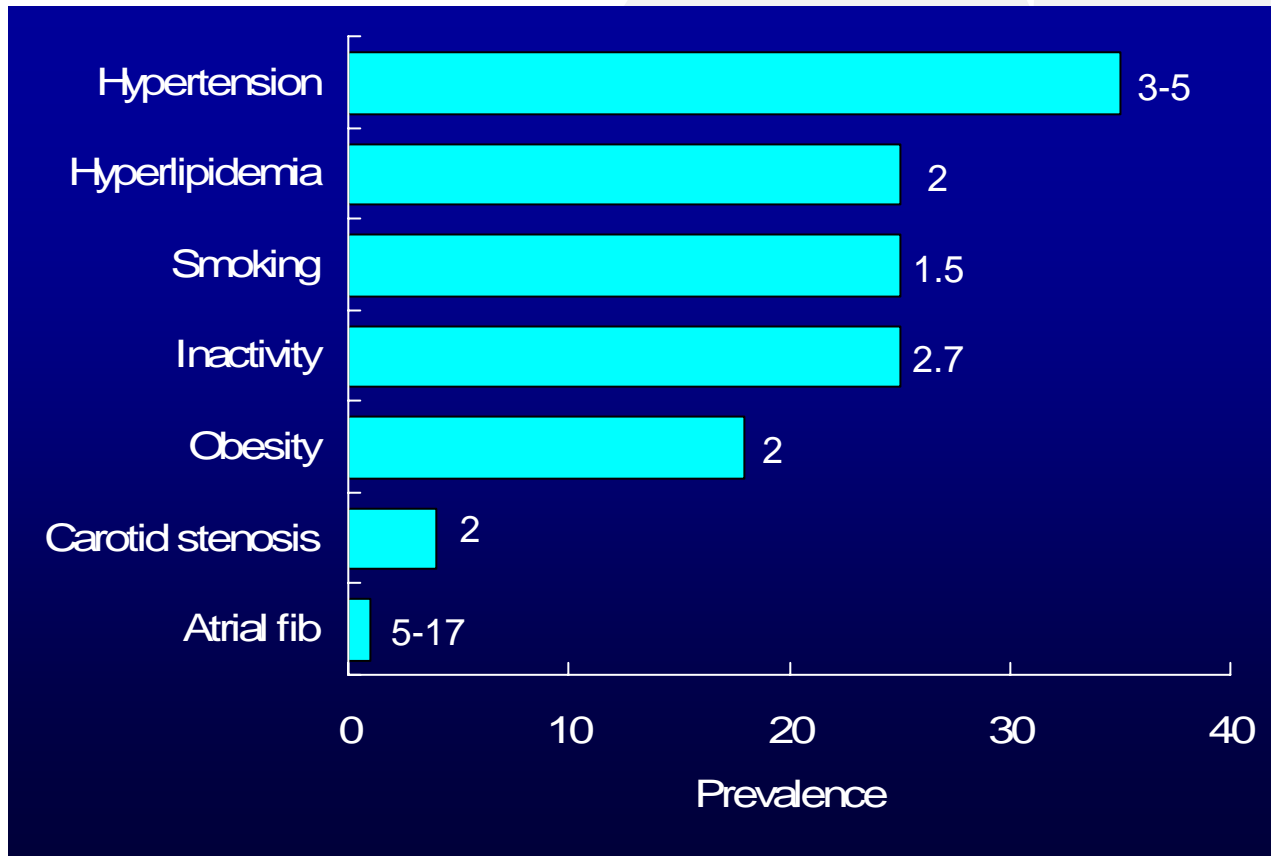
Guide to Primary Prevention of Strokes

- Smoking Cessation
- BP control
- Follow a Healthy Diet
- Aspirin
- Blood lipid management
- Exercise Regularly
- Weight management
- Diabetes management
- Treat chronic anticoagulation

Effectiveness of Primary Prevention Strategies

Strategy	Relative Risk Reduction, %	Number needed to prevent 1 stroke a year
Antihypertensive therapy	42	7937
Statins	25	13333
Aspirin	RR increase, 7	Not significant
Aspirin after myocardial infarction	36	400
ACE inhibitor	30	11111
Carotid endarterectomy	RR increase, 423	Not significant

Straus SE, et al. JAMA 2002;288:1388-1395

Effectiveness of Secondary Prevention Strategies

Strategy	Relative Risk Reduction, %	Number needed to prevent 1 stroke a year
Antihypertensive therapy	28	51
Statins	25	57
Warfarin for nonrheumatic Afib	62	13
Smoking cessation	33	43
Aspirin	28	77
Thienopyridines (vs aspirin)	13	64
Carotid endarterectomy	44	26

Annual recurrence rate 7% in patients with history of TIA or stroke

Straus SE, et al. JAMA 2002;288:1388-1395

Benefits of Lowering BP

	Average Percent Reduction
Stroke incidence	35–40%
Myocardial infarction	20–25%
Heart failure	50%

In stage 1 HTN and additional CVD risk factors, achieving a sustained 12 mmHg reduction in SBP over 10 years will prevent 1 death for every 11 patients treated.

JNC7

Prevention of Stroke by BP lowering drugs

- Is "Hypertension" needed for expecting a benefit from BP lowering drugs?
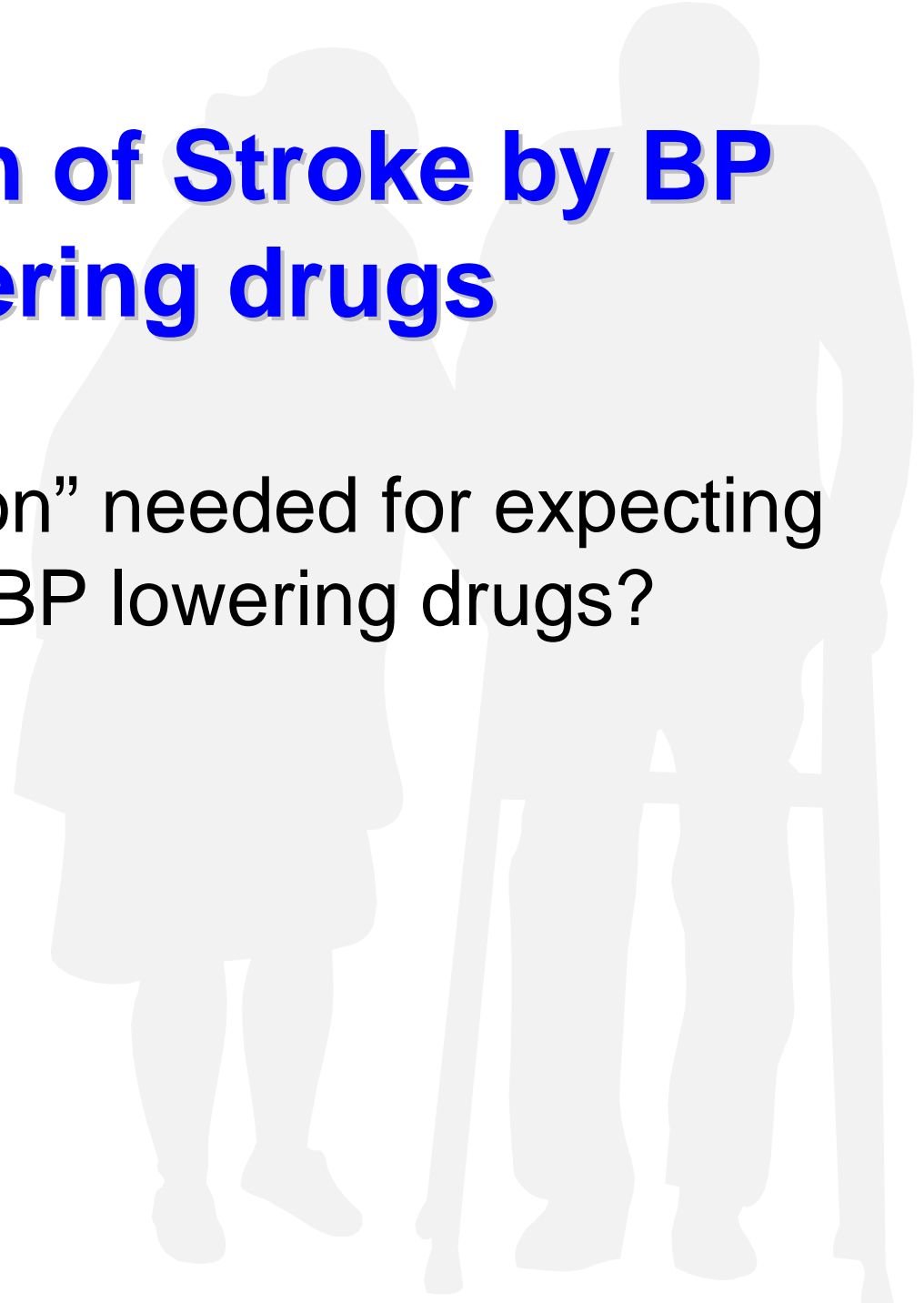
HOPE Study

- Design: multicenter, randomized, double-blind, placebo-controlled trial

- Patients: 9297 patients ≥55 years old with a history of CV disease or diabetes plus at least 1 other CV risk factor and without evidence of heart failure

- Treatment: ramipril 10 mg/day or placebo and vitamin E or placebo for an average of 5 years

- Primary end point: composite of MI, stroke, or CV death

Yusuf et al. *N Engl J Med*. 2000;342:145-153.

HOPE Study Outcomes: Events per Patient Group

Chart: Events per Patient Group (%), comparing Placebo (white bars) and Ramipril (green bars)

- **Combined Primary Outcome*** — RR=22%, *P*<.001 — Placebo 17.8, Ramipril 14
- **CV Death** — RR=26%, *P*<.001 — Placebo 8.1, Ramipril 6.1
- **MI** — RR=20%, *P*<.001 — Placebo 12.3, Ramipril 9.9
- **Stroke** — RR=32%, *P*<.001 — Placebo 4.9, Ramipril 3.4
- **Non-CV Death** — RR=0%, *P*=NS — Placebo 4.1, Ramipril 4.3
- **Total Mortality** — RR=16%, *P*=.005 — Placebo 12.2, Ramipril 10.4
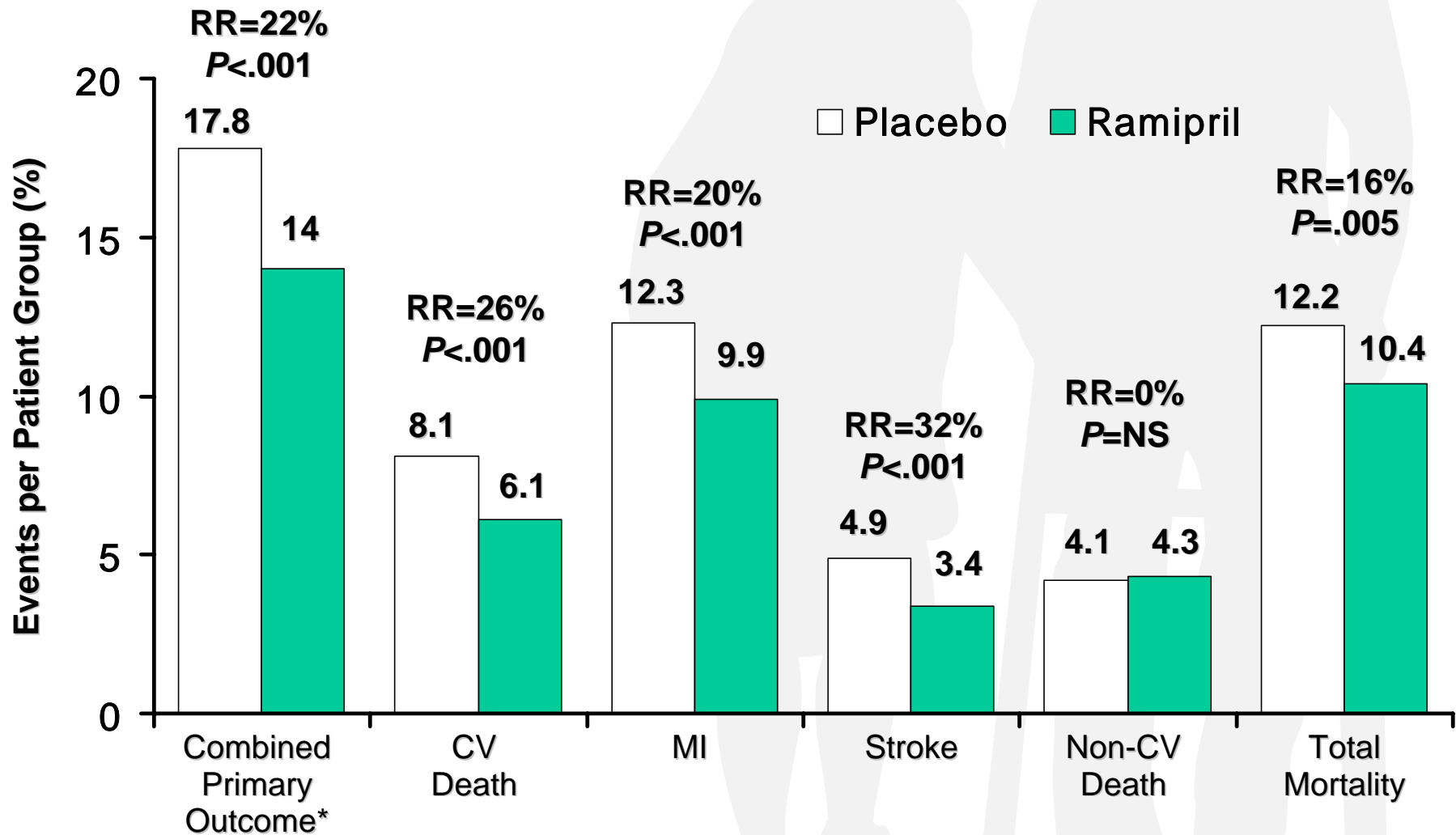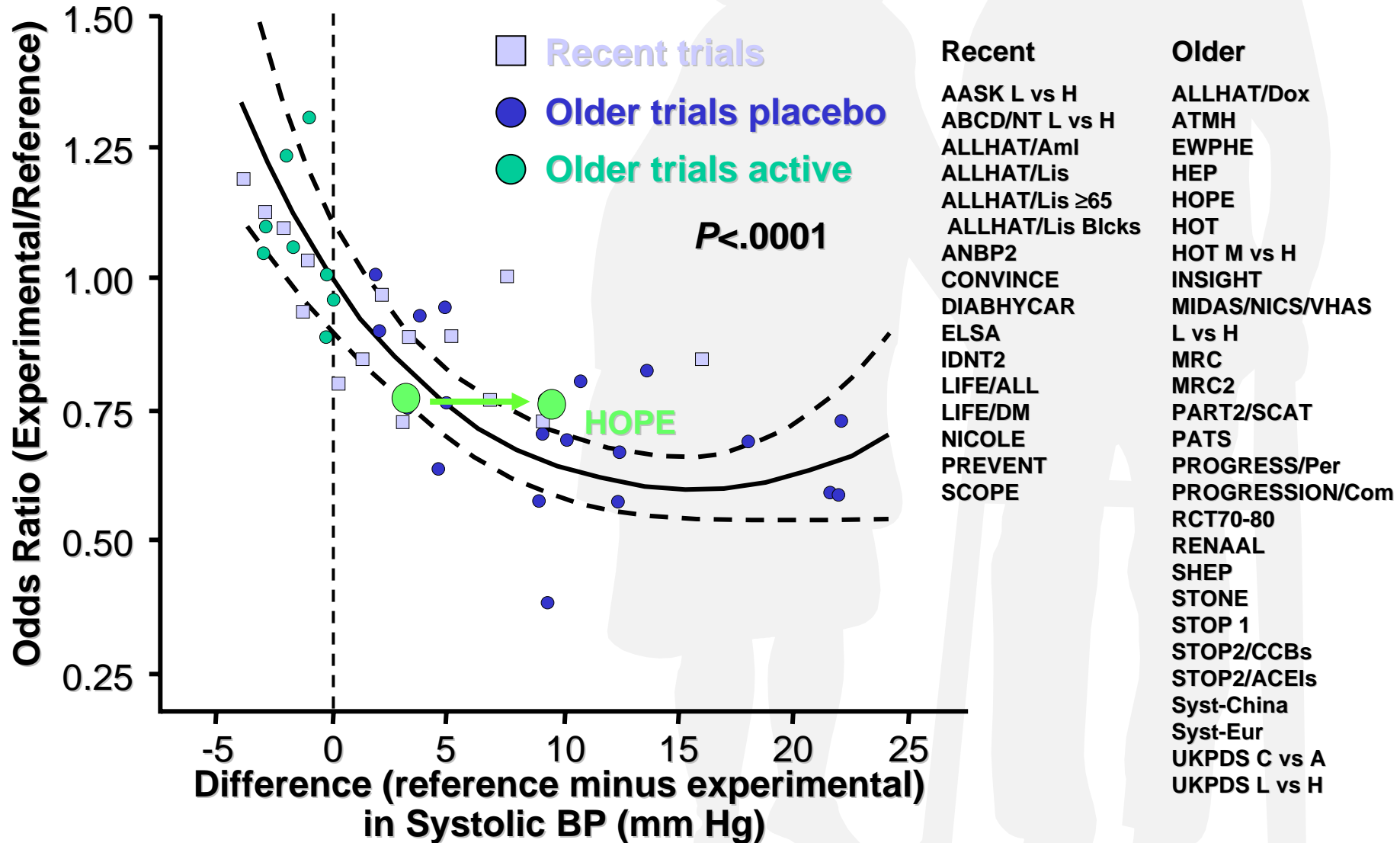
*MI, stroke, or CV death.
Yusuf et al. *N Engl J Med*. 2000;342:145-153.

Hourly Means of Systolic and Diastolic Ambulatory BP in HOPE Substudy: Baseline and 1 Year
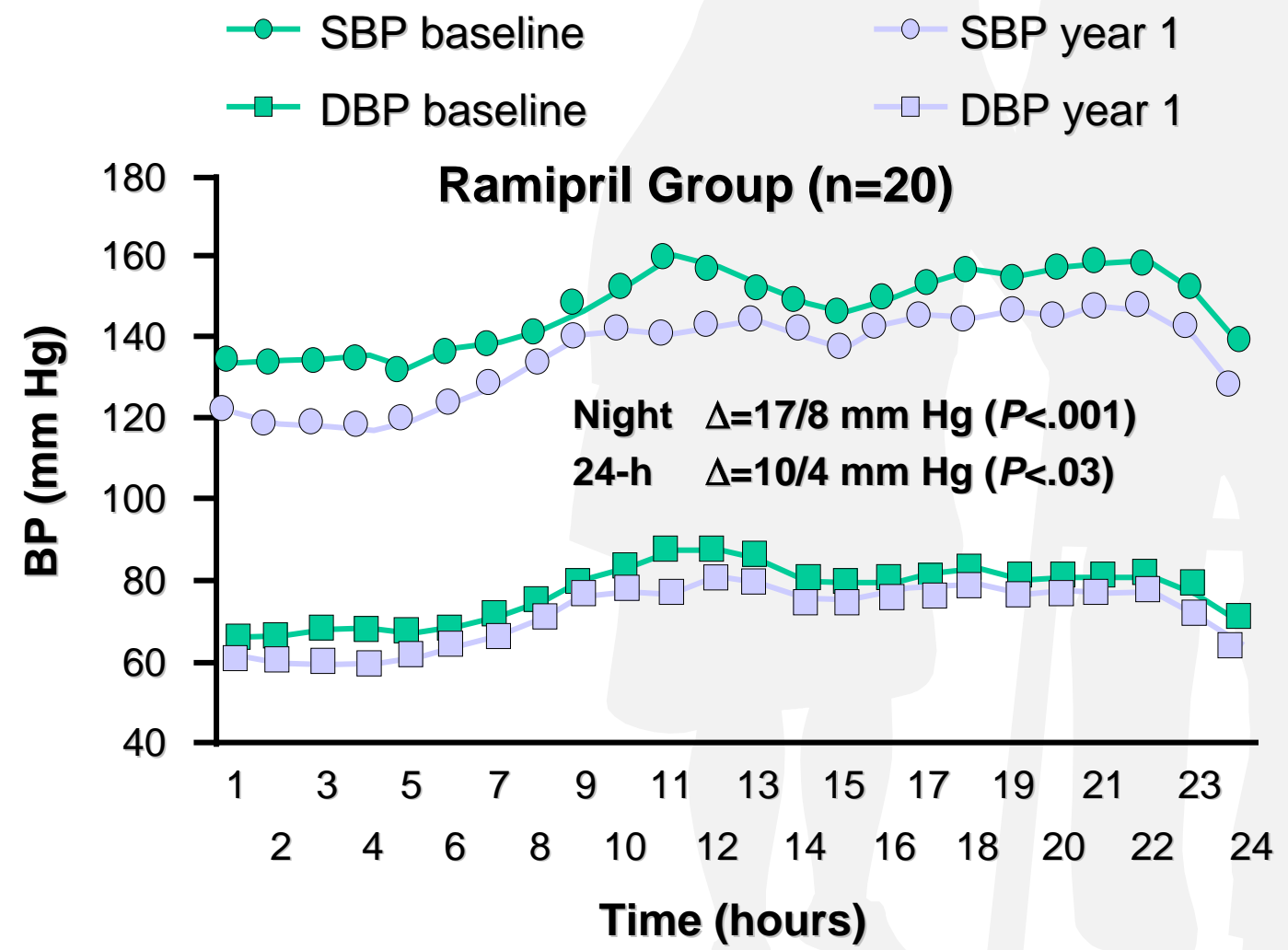
Svensson et al. *Hypertension*. 2001;38:e28-e32.

Odds Ratio for CV Events and Systolic BP Difference: Recent and Older Trials

■ Recent trials
● Older trials placebo
● Older trials active

P<.0001

HOPE

Odds Ratio (Experimental/Reference) vs **Difference (reference minus experimental) in Systolic BP (mm Hg)**

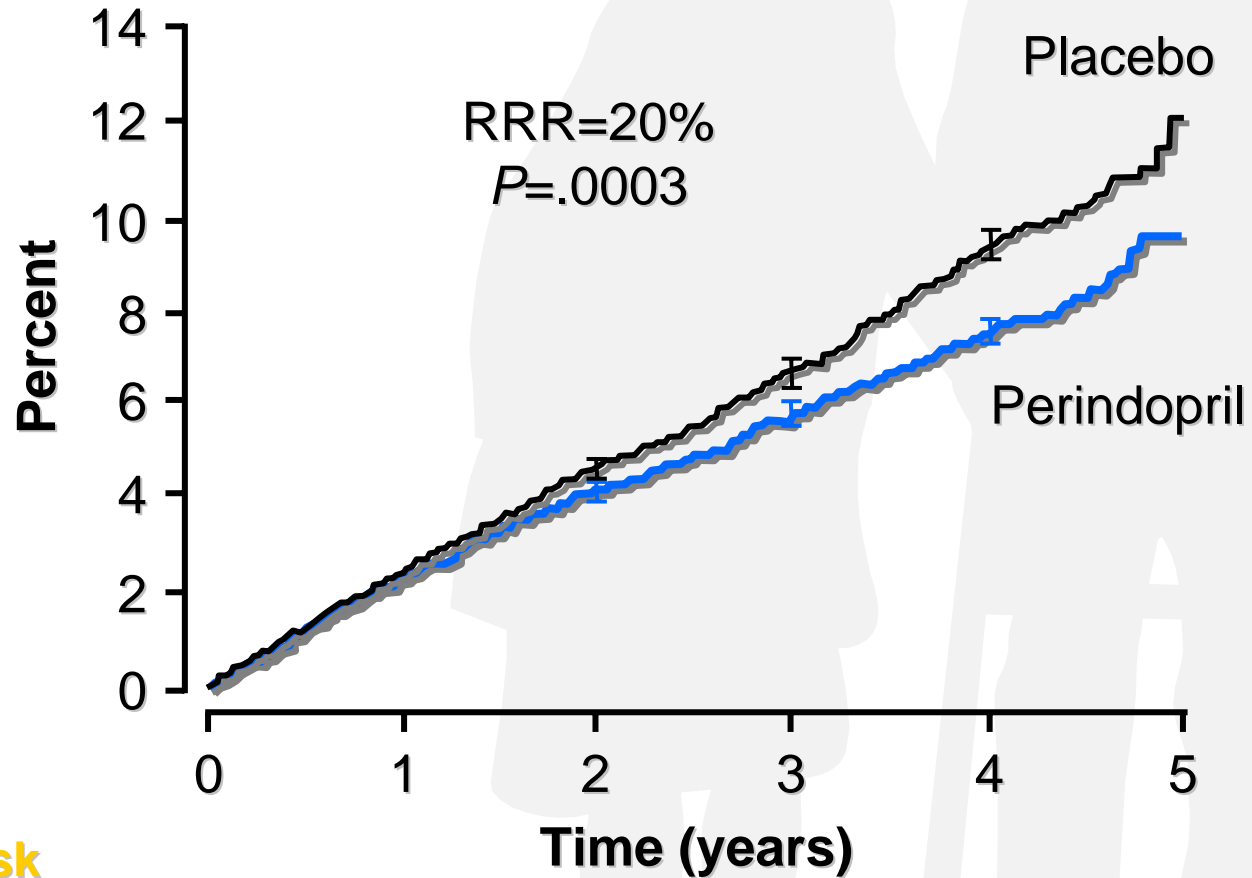| Recent	Older
AASK L vs H	ALLHAT/Dox
ABCD/NT L vs H	ATMH
ALLHAT/Aml	EWPHE
ALLHAT/Lis	HEP
ALLHAT/Lis ≥65	HOPE
ALLHAT/Lis Blcks	HOT
ANBP2	HOT M vs H
CONVINCE	INSIGHT
DIABHYCAR	MIDAS/NICS/VHAS
ELSA	L vs H
IDNT2	MRC
LIFE/ALL	MRC2
LIFE/DM	PART2/SCAT
NICOLE	PATS
PREVENT	PROGRESS/Per
SCOPE	PROGRESSION/Com
	RCT70-80
	RENAAL
	SHEP
	STONE
	STOP 1
	STOP2/CCBs
	STOP2/ACEIs
	Syst-China
	Syst-Eur
	UKPDS C vs A
	UKPDS L vs H

Staessen et al. *J Hypertens*. 2003;21:1055-1076.

EUROPA Study

- Design: multicenter, randomized, double-blind, placebo-controlled trial

- Patients: 12,238 patients ≥18 years old with previous MI, revascularization or angiographic evidence of ≥70% narrowing of ≥1 coronary arteries, and men with positive exercise test, stress echo or nuclear study;
no evidence of heart failure

- Treatment: perindopril 8 mg/day, or placebo for an average of 4.2 years

- Primary end point: composite of CV death, MI, or cardiac arrest

Fox. *Lancet*. 2003;362:782-788; Gomma et al. *Cardiovasc Drugs Ther*. 2001;15:169-179

EUROPA: Time to First Occurrence of Primary End Point (CV Death, MI, or Cardiac Arrest)

RRR=20%
P=.0003

Placebo

Perindopril

Percent (y-axis: 0, 2, 4, 6, 8, 10, 12, 14)

Time (years) (x-axis: 0, 1, 2, 3, 4, 5)

Patients at risk

Placebo	6108	5943	5781	5598	4450	71
Perindopril	6110	5957	5812	5653	4515	64

Fox. *Lancet*. 2003;362:782-788.

EUROPA: Frequency of Primary and Selected Secondary Outcomes

	Perindopril (n=6110)	Placebo (n=6108)	Relative Risk Reduction (95% CI)	*P*
CV mortality, MI, or cardiac arrest	**488 (8.0%)**	**603 (9.9%)**	**20% (9 to 29)**	**.0003**
CV mortality	**215 (3.5%)**	**249 (4.1%)**	**14% (-3 to 28)**	**.107**
Nonfatal MI	**295 (4.8%)**	**378 (6.2%)**	**22% (10 to 33)**	**.001**
Stoke	**98 (1.6%)**	**102 (1.7%)**	**1-2%**	**NS**
Total mortality, nonfatal MI, UA, cardiac arrest	**904 (14.8%)**	**1043 (17.1%)**	**14% (6 to 21)**	**.0009**
Total mortality	**375 (6.1%)**	**420 (6.9%)**	**11% (-2 to 23)**	**.1**

Fox. *Lancet*. 2003;362:782-788.

EUROPA Facts

- At baseline, 27% of patients were "hypertensive" (BP >160/95 mm Hg or receiving antihypertensive rx)

- Mean baseline BP: 137/82 mm Hg

- During run-in period, BP was reduced from 137/82 mm Hg to 128/78 mm Hg

- After randomization, systolic and diastolic BP among patients on perindopril were maintained

- During double-blind treatment, placebo group BP was 5/2 mm Hg higher than perindopril group BP
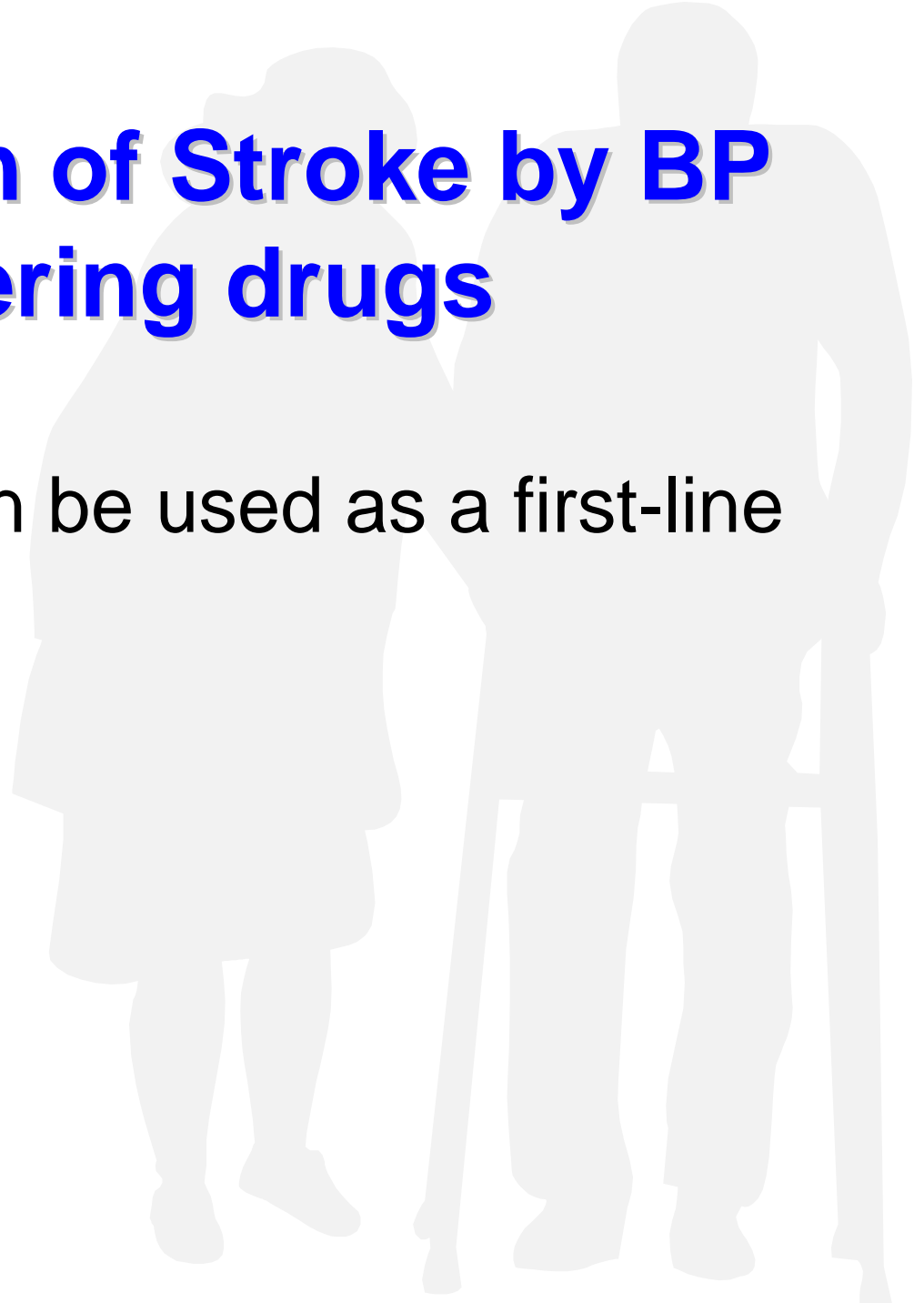
Fox. *Lancet*. 2003;362:782-788.

Odds Ratio for CV Events and Systolic BP Difference: Recent and Older Trials

Fox. *Lancet.* 2003;362:782-788; Staessen et al. *J Hypertens*. 2003;21:1055-1076.
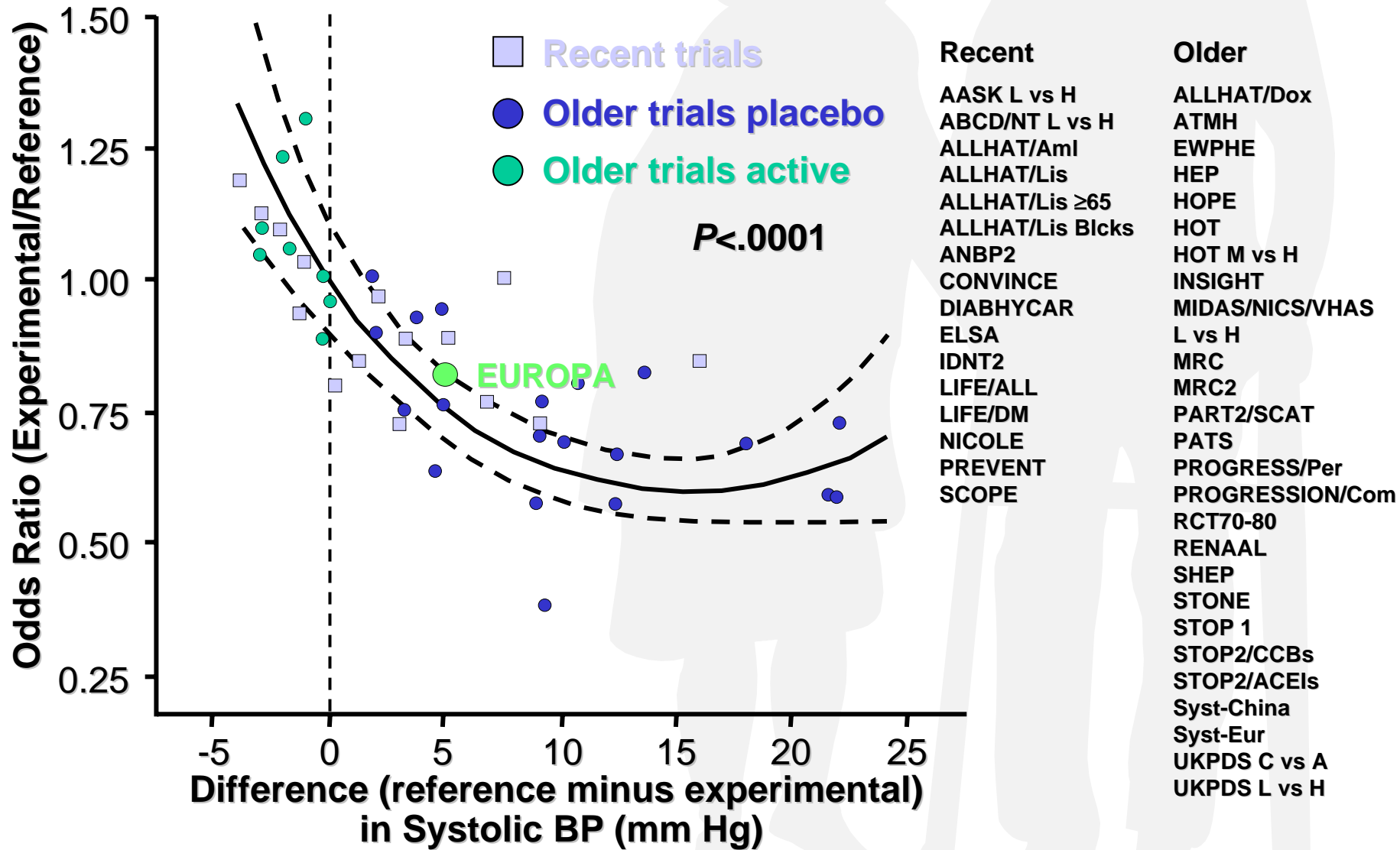
Prevention of Stroke by BP lowering drugs

- Which drug can be used as a first-line therapy?

JNC 7: Compelling Indications for Individual Drug Classes

Compelling Indication	Initial Therapy Options	Clinical Trial Basis
Diabetes	**Diuretic, BB, ACE inhibitor, ARB, CCB**	**NKF-ADA Guideline, UKPDS, ALLHAT**
Chronic kidney disease	**ACE inhibitor, ARB**	**NKF Guideline, Captopril Trial, RENAAL, IDNT, REIN, AASK**
Recurrent stroke prevention	**Diuretic, ACE inhibitor**	**PROGRESS**

Chobanian et al, and the National High Blood Pressure Education Program Coordinating Committee. *Hypertension*. 2003;42:1206-1252.

WHO/ISH: Compelling Indications for Specific Antihypertensive Drugs

| Compelling Indications	Preferred Drug	Primary End Point
Elderly with isolated systolic hypertension	Diuretic DHP CCB	Stroke Stroke
Renal disease		
Diabetic nephropathy type 1	ACE inhibitor	Progression of renal failure
Diabetic nephropathy type 2	ARB	Progression of renal failure
Nondiabetic nephropathy	ACE inhibitor	Progression of renal failure
Cardiac disease		
Post-MI	ACE inhibitor β-blocker	Mortality Mortality
LV dysfunction	ACE inhibitor ACE inhibitor	Heart failure Mortality
CHF (diuretics almost always included)	β-blocker Spironolactone	Mortality Mortality
LV hypertrophy	ARB	CV morbidity and mortality
Cerebrovascular disease	ACE inhibitor + diurectic Diuretic	Recurrent stroke Recurrent Stroke

WHO/ISH Writing Group. *J Hypertens*. 2003;21:1983-1992.

PROGRESS Study

- Design: multicenter, randomized, placebo-controlled trial

- Patients: 6105 patients with a history of stroke or transient ischaemic attack

- Treatment: active treatment (perindopril (4 mg daily), with the addition of indapamide) or placebo for 4 years

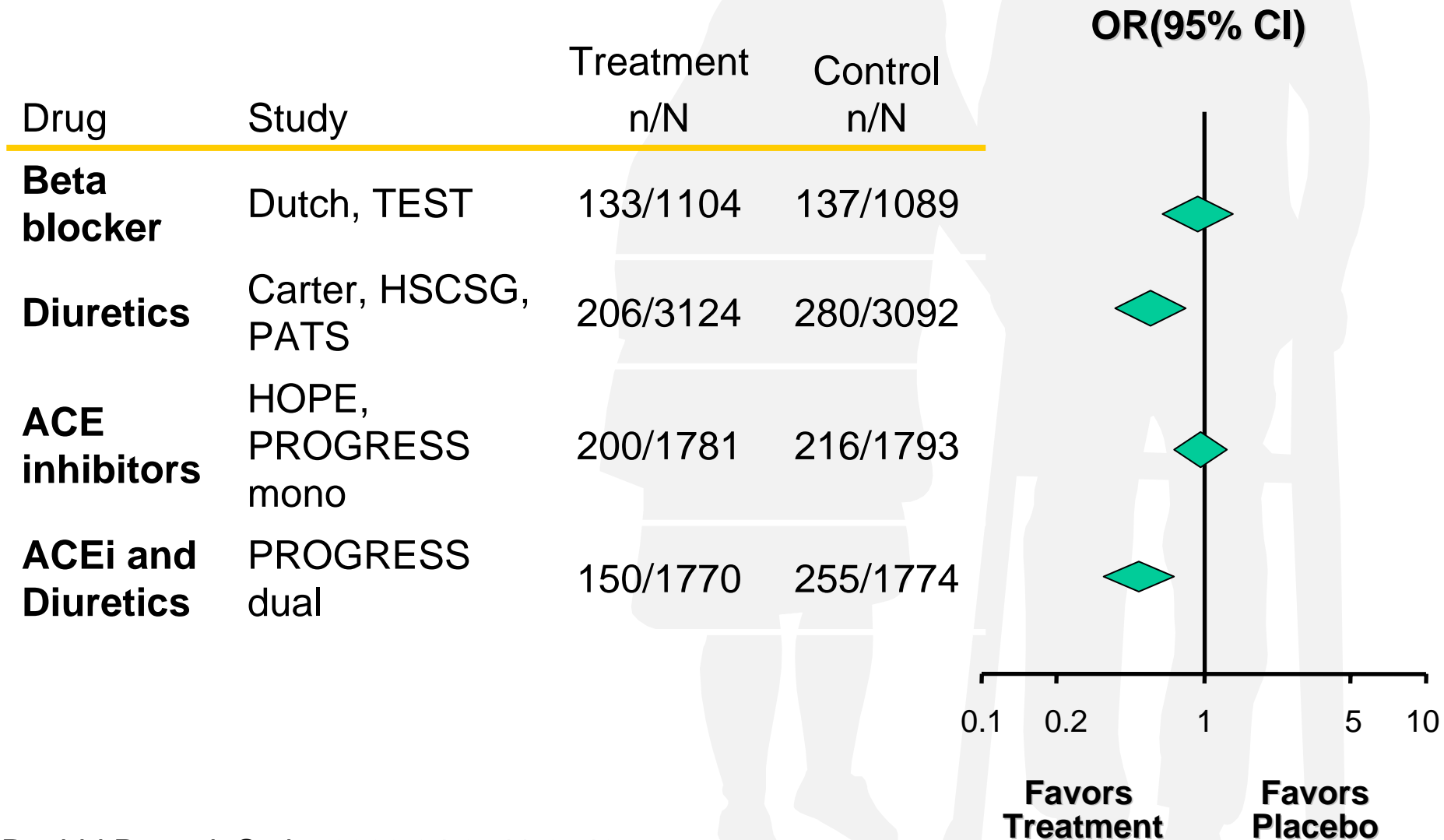- Primary end point: total stroke (fatal or non-fatal)

PROGRESS Collaborative Group. Lancet. 2001;358:1033- 1041

Progress
Cumulative incidence of stroke
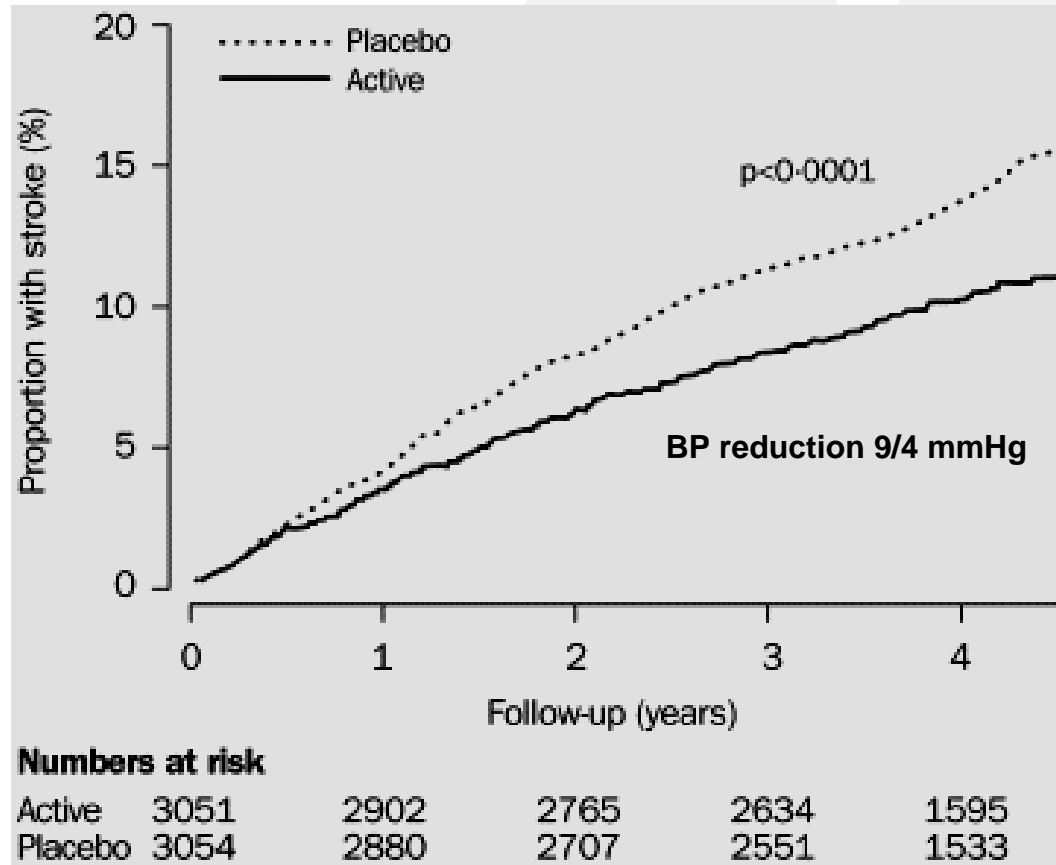
Perindopril alone : 5/3 mmHg difference with no benefit (5% RR, 95% CI -19% to 23%)
Perindopril / indapamide : 12/5 mmHg difference with 43% RR (30% to 54%)

PROGRESS Collaborative Group. Lancet. 2001;358:1033-1041

Effect of antihypertensive therapy on recurrent stroke

Drug	Study	Treatment n/N	Control n/N	OR(95% CI)
Beta blocker	Dutch, TEST	133/1104	137/1089	
Diuretics	Carter, HSCSG, PATS	206/3124	280/3092	
ACE inhibitors	HOPE, PROGRESS mono	200/1781	216/1793	
ACEi and Diuretics	PROGRESS dual	150/1770	255/1774	

0.1　0.2　1　5　10

Favors Treatment　　　**Favors Placebo**

Rachid P, et al. Stoke 2003;34:2741-2749

Prevention of Stroke by BP lowering drugs

- Which drug can be used as a first-line therapy for **primary prevention**?
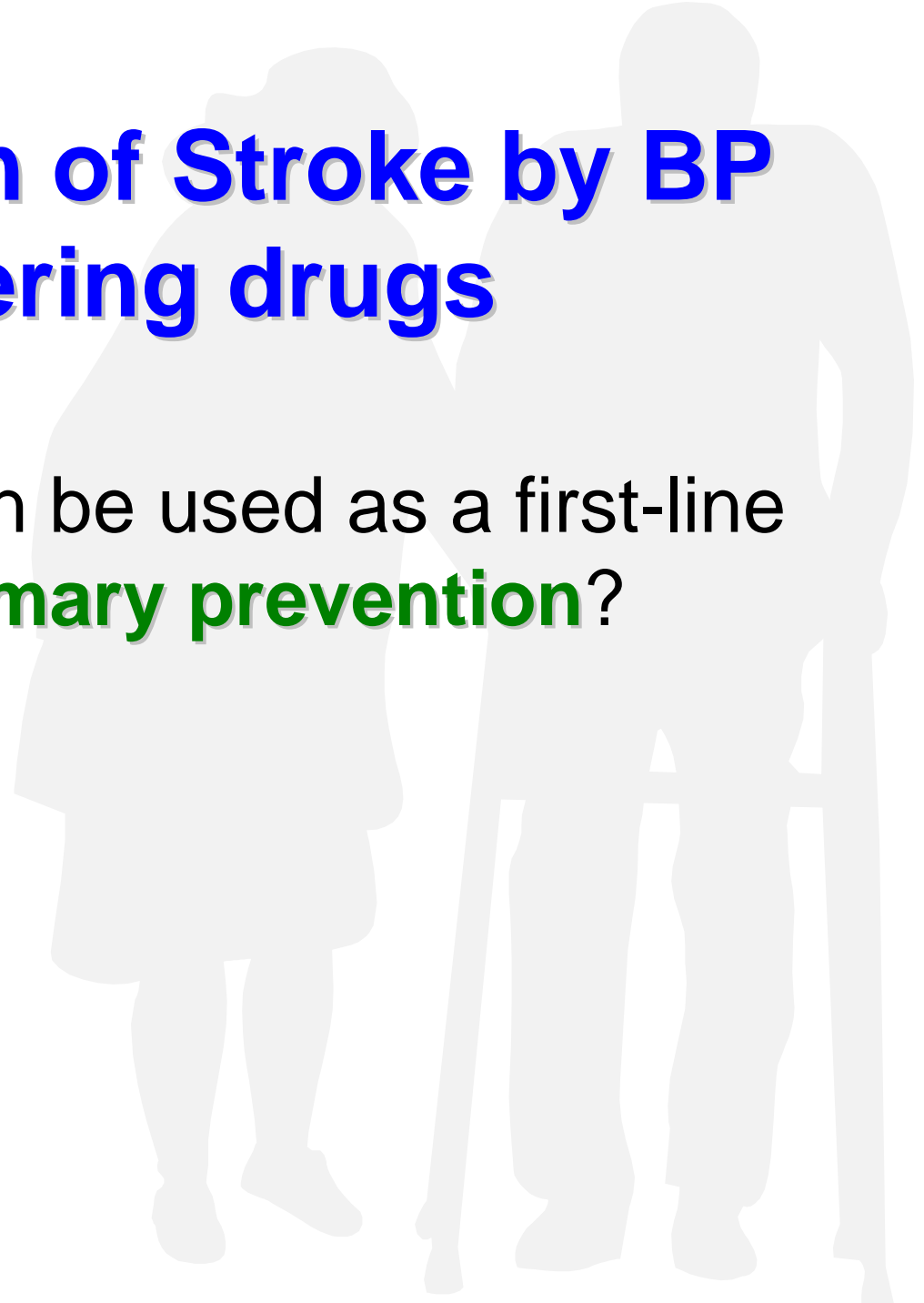
MRC Trial: Design

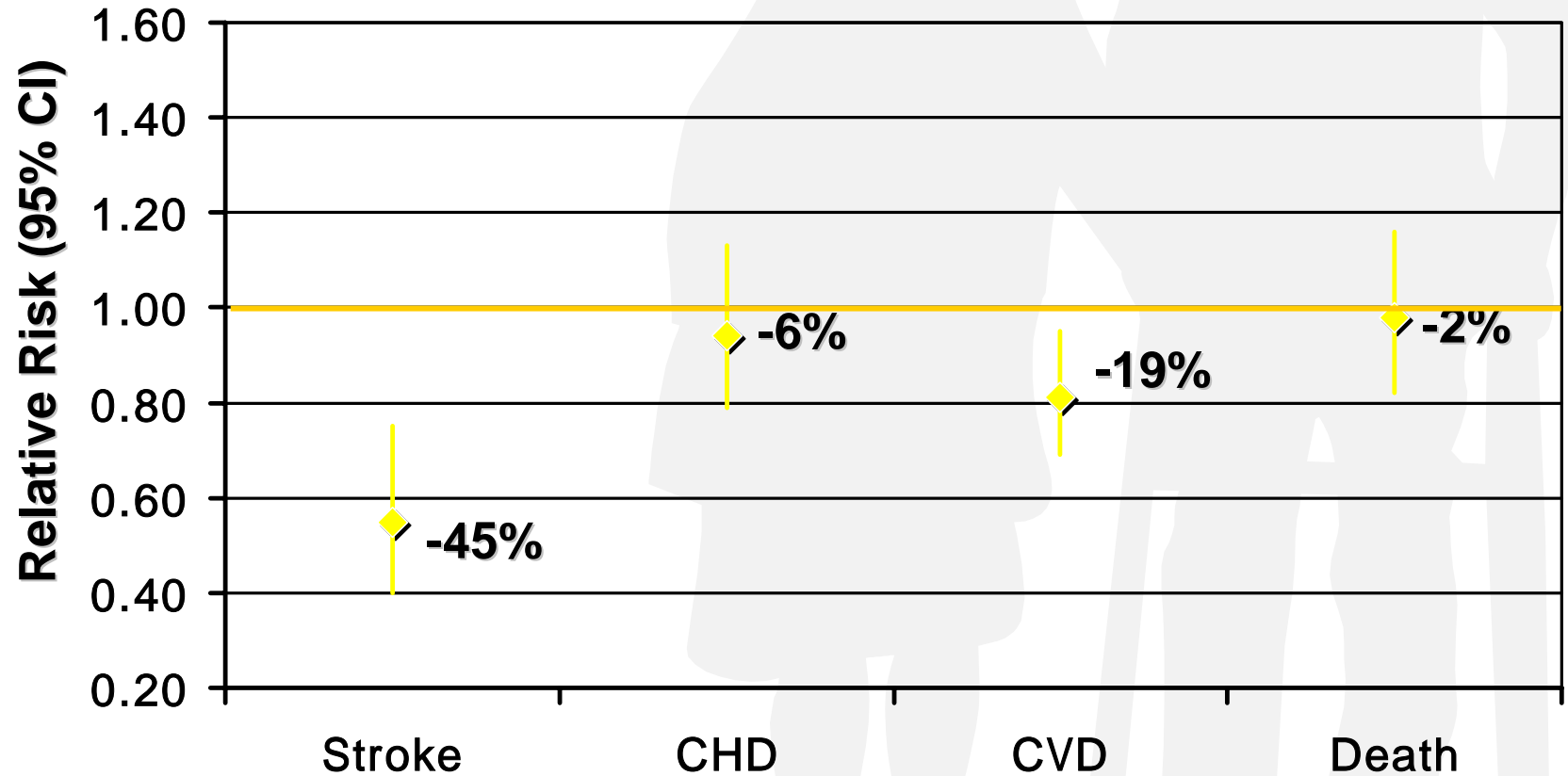- N: 17,354; 52% men
- Age: 35-64 years
- BP: diastolic BP 90 to 109 mm Hg
- Design: 3 treatment groups
- Treatment: bendrofluazide vs propranolol vs placebo
- Diastolic BP difference: 6 mm Hg
- Duration: 5.5 years

MRC Working Party. *BMJ*. 1985;291:97-104.

MRC Trial: Endpoints
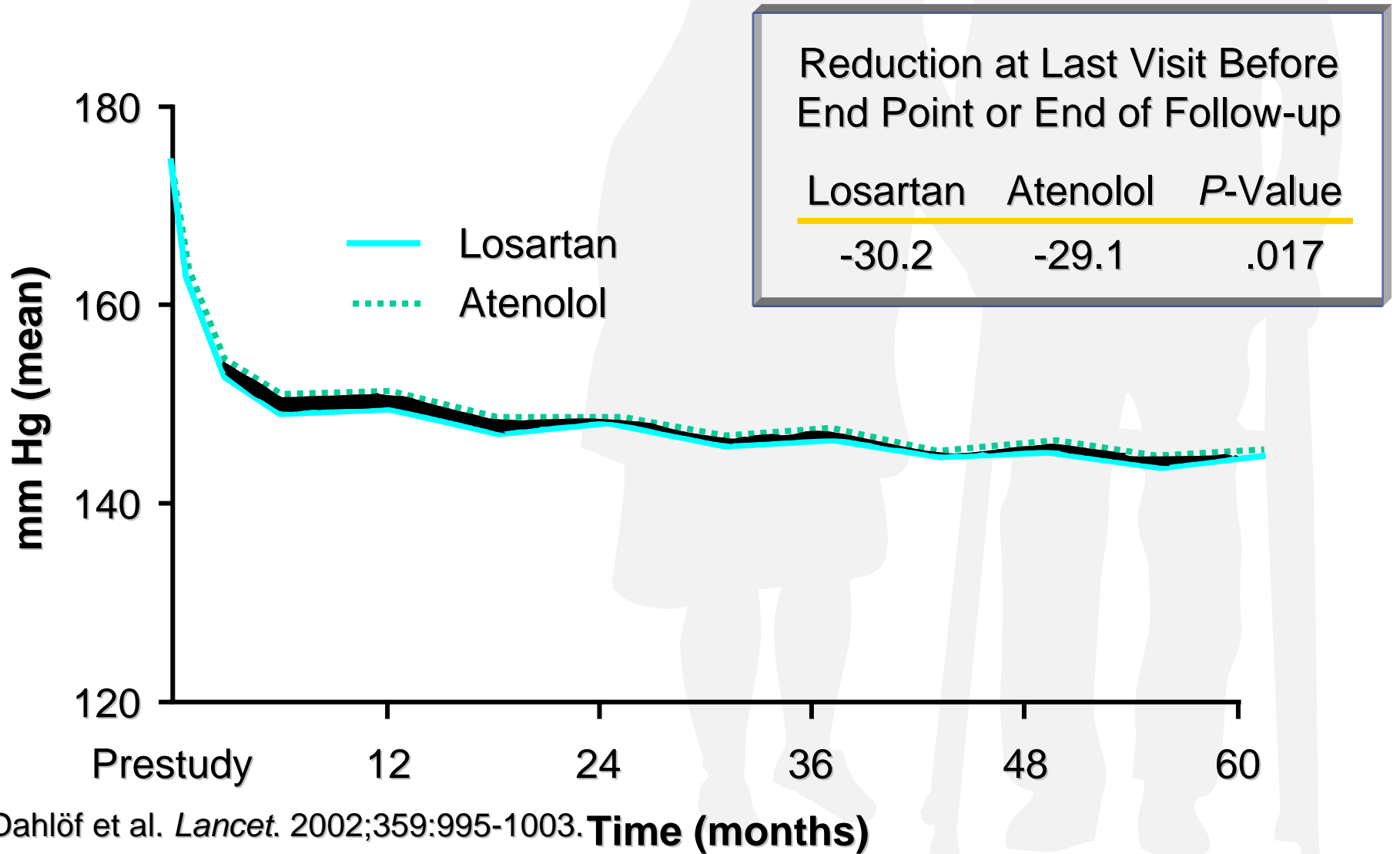
Active Therapy vs Placebo

The reduction in stroke rate on bendrofluazide was greater than that on propranolol (p = 0.002).

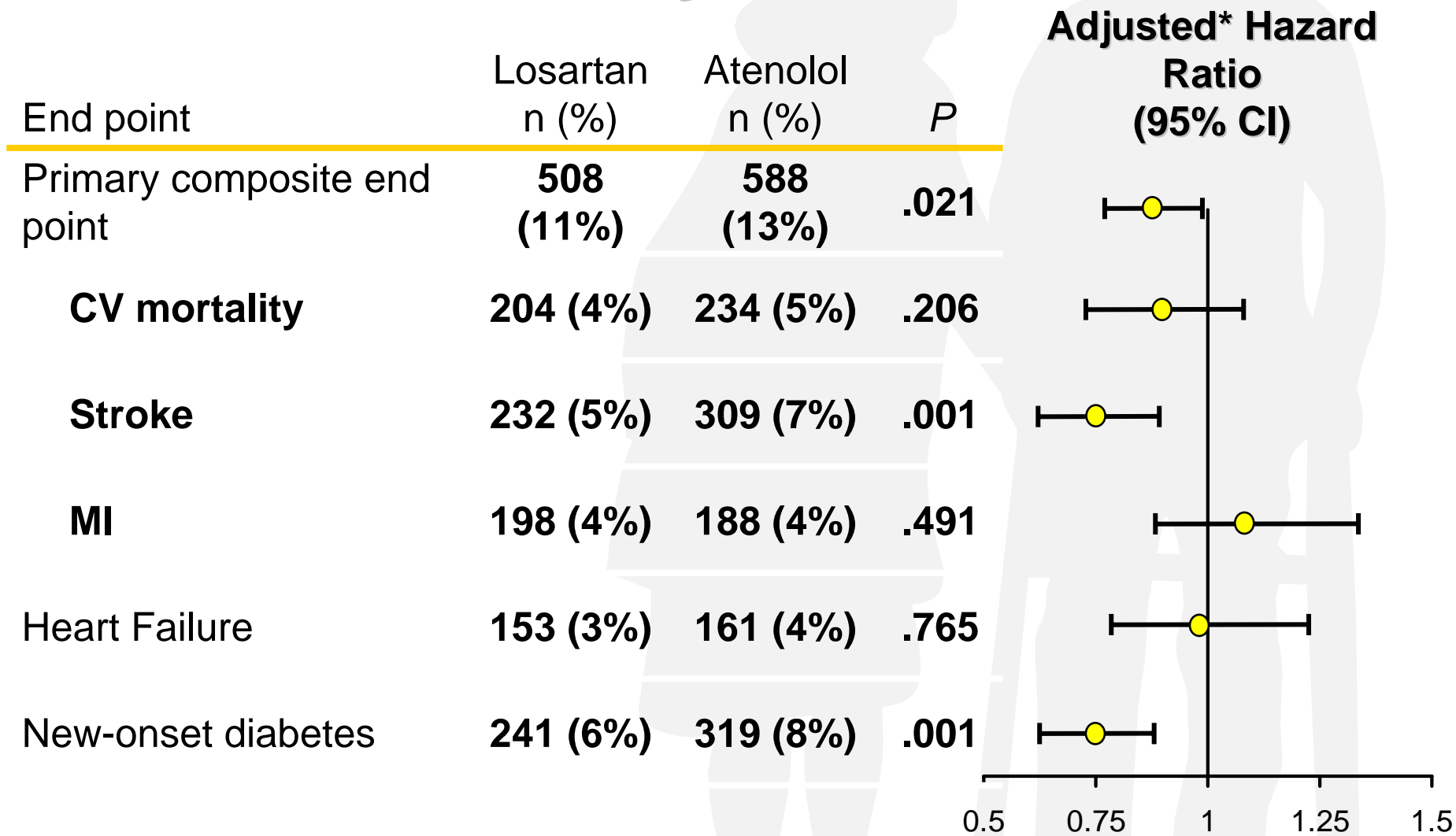MRC Working Party. *BMJ*. 1985;291:97-104.

LIFE Study

- Design: multicenter, double-blind, randomized trial

- Patients: 9193 patients 55-80 years old with previously treated or untreated essential hypertension (systolic BP 160-200 mm Hg and/or diastolic BP 95-115 mm Hg) and LVH determined by ECG

- Treatment: losartan 50 to 100 mg/day with additional drugs as needed vs atenolol 50 to 100 mg/day with additional drugs as needed to achieve goal BP of <140/90 mm Hg for an average of 4.8 years

- Primary end point: composite of CV mortality, fatal and nonfatal MI, and fatal and nonfatal stroke

Dahlöf et al. *Lancet*. 2002;359:995-1003.

LIFE: Systolic Blood Pressure

Reduction at Last Visit Before End Point or End of Follow-up

Losartan	Atenolol	*P*-Value
-30.2	-29.1	.017

Losartan
Atenolol

mm Hg (mean)
180
160
140
120

Prestudy   12   24   36   48   60

Time (months)

Dahlöf et al. *Lancet*. 2002;359:995-1003.

LIFE: Study End Points

End point	Losartan n (%)	Atenolol n (%)	P	Adjusted* Hazard Ratio (95% CI)
Primary composite end point	**508 (11%)**	**588 (13%)**	**.021**	
CV mortality	**204 (4%)**	**234 (5%)**	**.206**	
Stroke	**232 (5%)**	**309 (7%)**	**.001**	
MI	**198 (4%)**	**188 (4%)**	**.491**	
Heart Failure	153 (3%)	161 (4%)	.765	
New-onset diabetes	**241 (6%)**	**319 (8%)**	**.001**	

0.5   0.75   1   1.25   1.5

Favors Losartan   **Favors Atenolol**

*For degree of LVH and Framingham risk score at randomization.
Dahlöf et al. *Lancet*. 2002;359:995-1003.

ANBP2 Study

- Design: prospective, randomized, open-label trial with blind end point assessment (PROBE)

- Patients: 6083 patients 65 to 84 years of age with hypertension (≥160/90 mm Hg) who received health care at 1594 family practices

- Treatment: initial therapy recommended with either enalapril or hydrochlorothiazide to reduce systolic BP by ≥20 mm Hg or to under 140 mm Hg, and diastolic BP by ≥10 mm Hg or to under 80 mm Hg. Choice of specific agent or dose made by family practitioner

- Primary end point: all CV events or deaths from any cause

Wing et al. *N Engl J Med*. 2003;348:583-592.

ANBP2 End Points

	ACE Inhibitor (n=3044)	Diuretic (n=3039)	Hazard Ratio	*P* value
All CV events or death	695	736	0.89	.05
First CV event or death	490	529	0.89	.06
All-cause mortality	195	210	0.90	.27
First CV event	394	429	0.88	.07
Coronary event	173	195	0.86	.16
MI	58	82	0.68	.04
Other CV event	134	144	0.90	.36
Heart failure	69	78	0.85	.33
Cerebrovascular event	152	163	0.90	.35
Stroke	112	107	1.02	.91

Wing et al. *N Engl J Med*. 2003;348:583-592.

ALLHAT: BP Results by Treatment Group
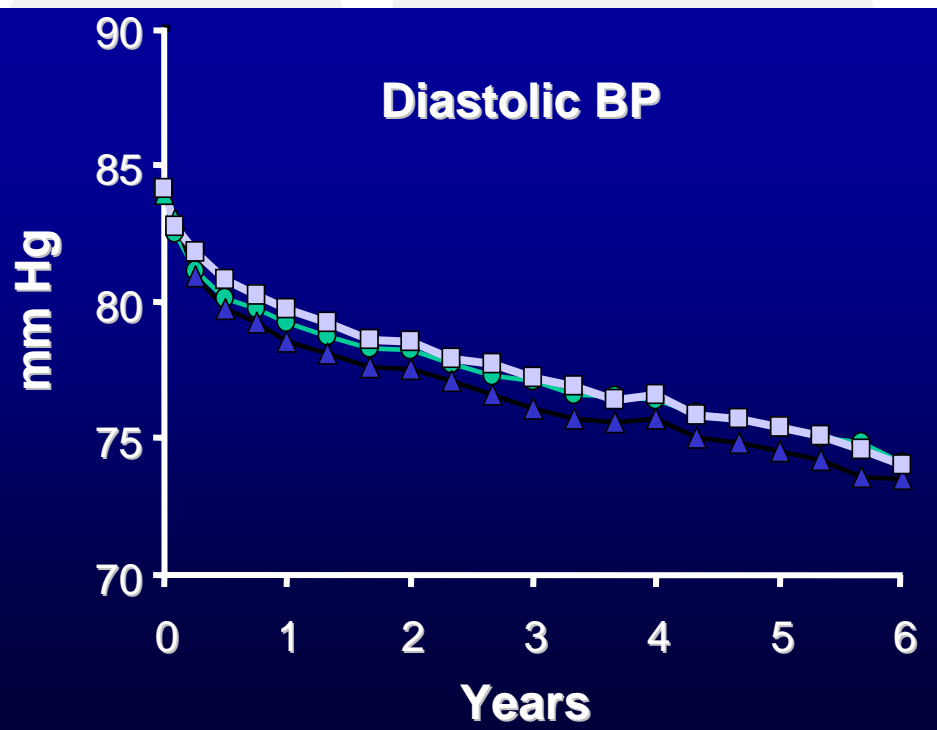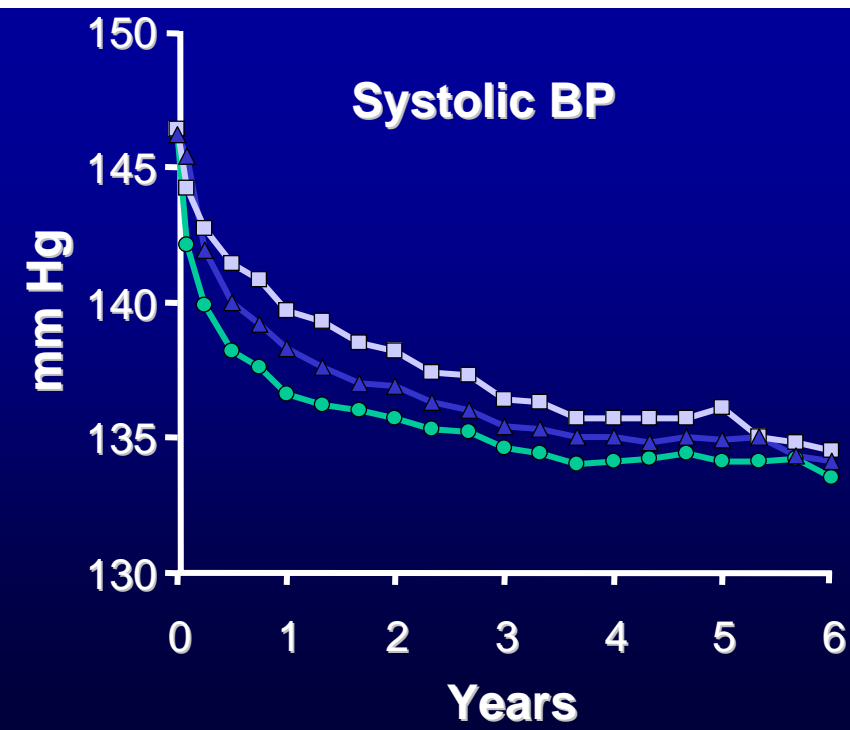
Compared with chlorthalidone:
SBP significantly higher in the amlodipine group (0.8 mm Hg) and the lisinopril group (2 mm Hg) at 5 years

Compared with chlorthalidone:
DBP significantly lower in the amlodipine group (0.8 mm Hg) at 5 years

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

ALLHAT: Primary Outcome (CHD Death and Nonfatal MI)

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

ALLHAT: Secondary End Points

Relative Risk (95% CI)

Total mortality

Amlodipine	0.96 (0.89-1.02)
Lisinopril	1.00 (0.94-1.08)

Stroke

Amlodipine	0.93 (0.82-1.06)
Lisinopril	1.15 (1.02-1.30)

Combined CVD

Amlodipine	1.04 (0.99-1.09)
Lisinopril	1.10 (1.05-1.16)

Heart failure

Amlodipine	1.38 (1.25-1.52)
Lisinopril	1.19 (1.07-1.31)

0.5   1   1.5   2

Favors Amlodipine
Favors Lisinopril

Favors Chlorthalidone

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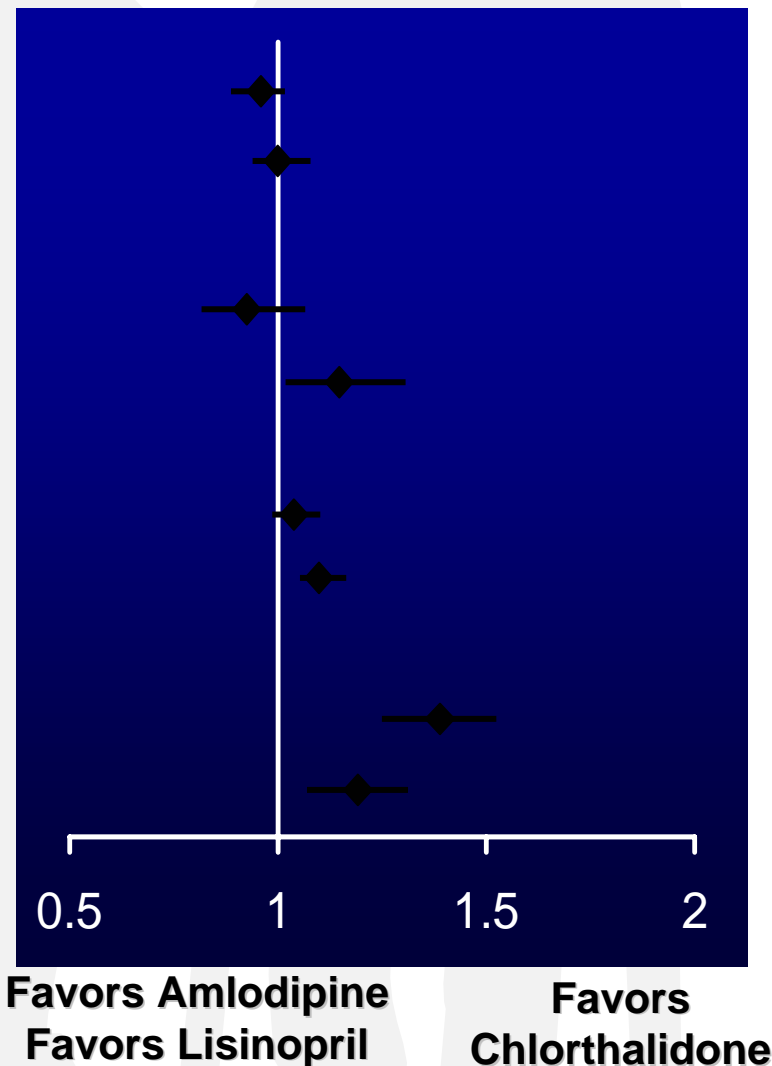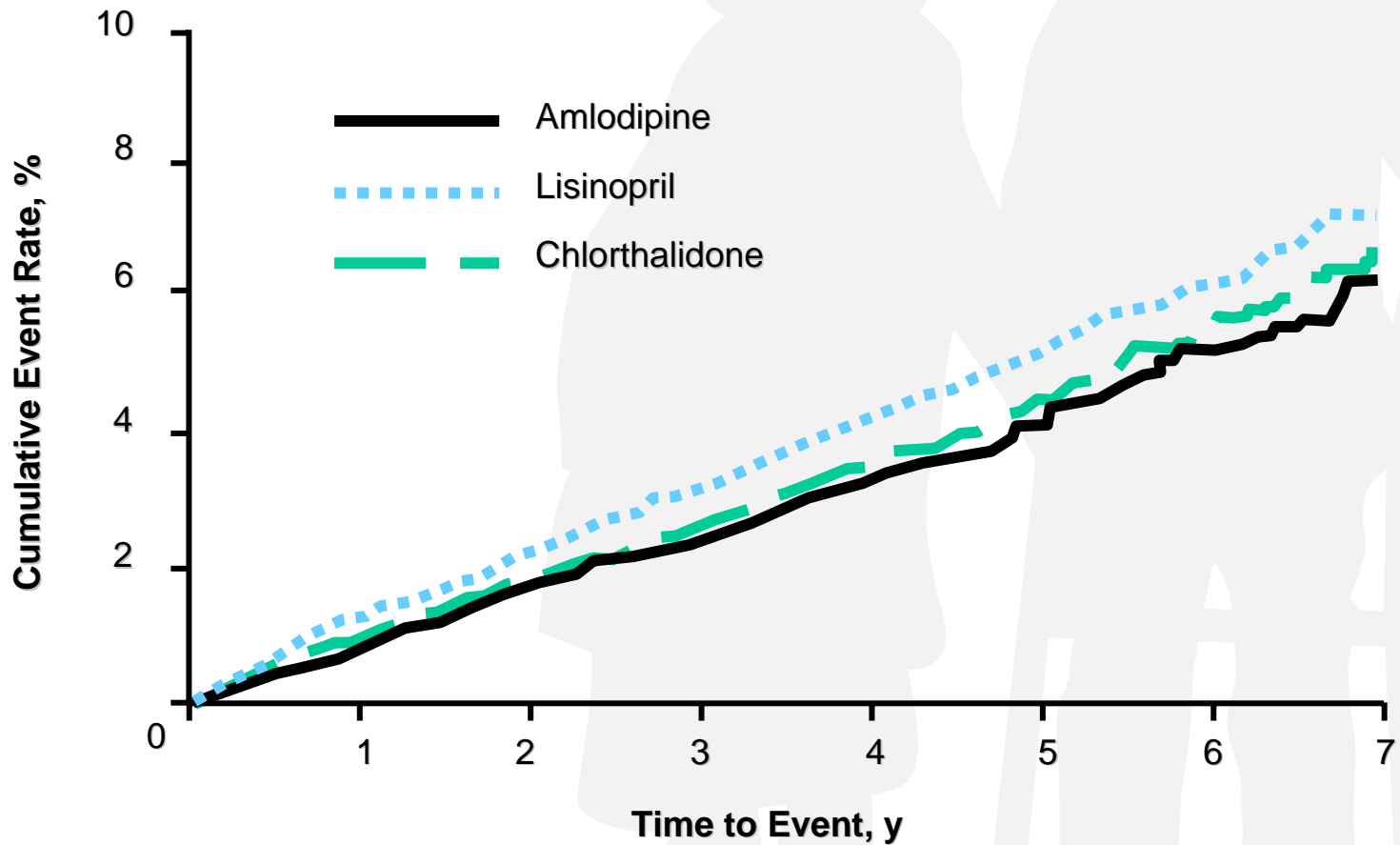
ALLHAT: Stroke

No. at Risk							
Chlorthalidone	15,255	14,515	13,934	13,309	11,570	6385	3217	567
Amlodipine	9048	8617	8271	7949	6937	3845	1813	506
Lisinopril	9054	8543	8172	7784	6765	3891	1828	949

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

ALLHAT: Stroke (Amlodipine vs Chlorthalidone) Subgroups

Relative Risk (95% CI)

	Relative Risk (95% CI)
Total	0.93 (0.82-1.06)
Age <65	0.93 (0.73-1.19)
Age ≥65	0.93 (0.81-1.08)
Men	1.00 (0.85-1.18)
Women	0.84 (0.69-1.03)
Black	0.93 (0.76-1.14)
Nonblack	0.93 (0.79-1.10)
Diabetic	0.90 (0.75-1.08)
Nondiabetic	0.96 (0.81-1.14)

0.5 1 1.5

Amlodipine Better   **Chlorthalidone Better**
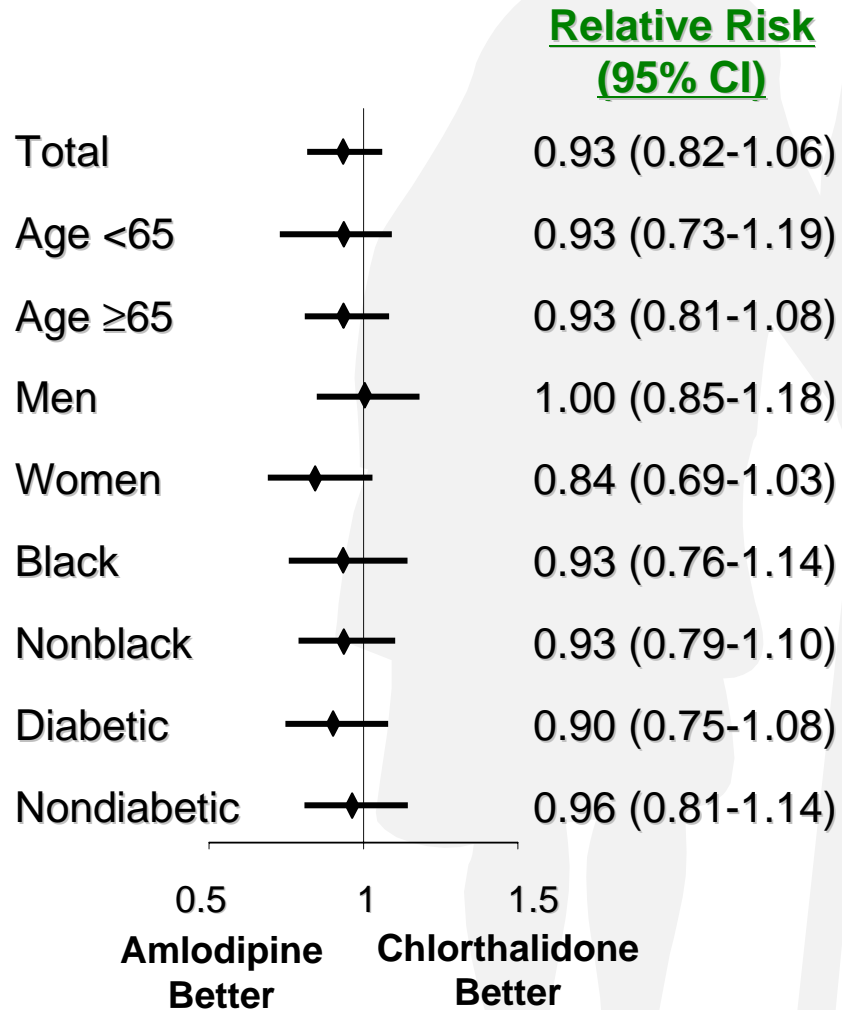
ALLHAT: Stroke (Lisinopril vs Chlorthalidone) Subgroups

Relative Risk (95% CI)

Total	1.15 (1.02-1.30)
Age <65	1.21 (0.97-1.52)
Age ≥65	1.13 (0.98-1.30)
Men	1.10 (0.94-1.29)
Women	1.22 (1.01-1.46)
Black	1.40 (1.17-1.68)
Nonblack	1.00 (0.85-1.17)
Diabetic	1.07 (0.90-1.28)
Nondiabetic	1.23 (1.05-1.44)

0.5   1   2

Lisinopril Better   **Chlorthalidone Better**

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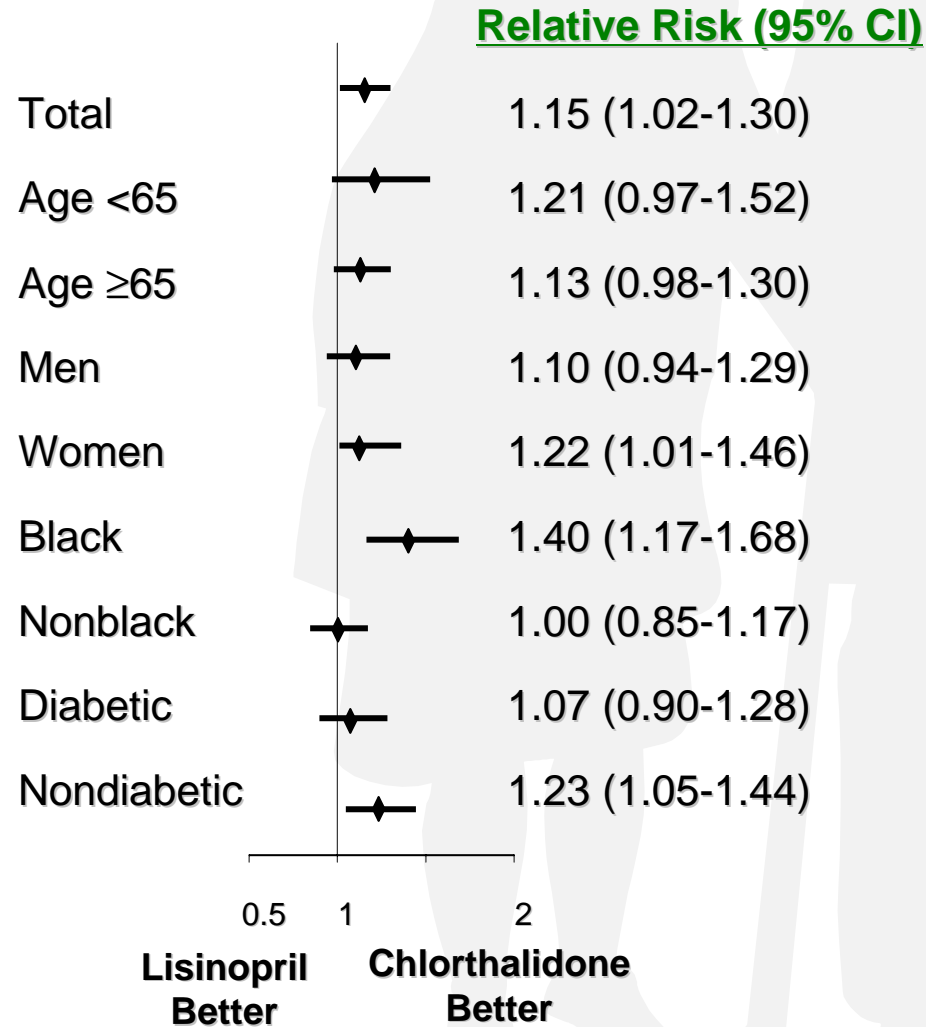
ALLHAT Summary

- Study confirmed importance of systolic BP
- No difference between study medications in primary endpoint of fatal/nonfatal CHD
- Nonsignificant reduction in stroke with amlodipine compared with diuretic
- Significantly higher incidence of stroke with lisinopril than with chlorthalidone
  - Difference particularly pronounced in black subpopulation
  - Systolic BP not as well controlled in lisinopril group, especially in black subpopulation
- CHF, a component of the secondary endpoint, lower in diuretic group than in amlodipine or chlorthalidone group
- ALLHAT showed that multiple medications often are required to get to BP goal

ALLHAT Collaborative Research Group. *JAMA*. 2002;288:2981-2997;
Cushman et al. *J Clin Hypertens*. 2002;4:393-404..

BP-Lowering Treatment Trialists
Comparisons of Active Treatments and Control

	BP Difference (mm Hg)	Relative Risk	RR (95% CI)
Stroke			
ACEI vs placebo	-5/-2		0.72 (0.64, 0.81)
CA vs placebo	-8/-4		0.62 (0.47, 0.82)
Coronary heart disease			
ACEI vs placebo	-5/-2		0.80 (0.73, 0.88)
CA vs placebo	-8/-4		0.78 (0.62, 0.99)
Heart failure			
ACEI vs placebo	-5/-2		0.82 (0.69, 0.98)
CA vs placebo	-8/-4		1.21 (0.93, 1.58)
Major CV events			
ACEI vs placebo	-5/-2		0.78 (0.73, 0.83)
CA vs placebo	-8/-4		0.82 (0.71, 0.95)
CV mortality			
ACEI vs placebo	-5/-2		0.80 (0.71, 0.89)
CA vs placebo	-8/-4		0.78 (0.61, 1.00)
Total mortality			
ACEI vs placebo	-5/-2		0.88 (0.81, 0.96)
CA vs placebo	-8/-4		0.89 (0.75, 1.05)
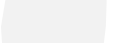
0.5   1.0   2.0

Favors Active   Favors Control

Blood Pressure Lowering Treatment Trialists' Collaboration. *Lancet*. 2003;362:1527-1535.

BP-Lowering Treatment Trialists
Comparisons of Different Active Treatments

	BP Difference (mm Hg)	Relative Risk	RR (95% CI)
Stroke			
ACE Inhibitor vs D/BB	**2/0**		**1.09 (1.00, 1.18)**
CA vs D/BB	**1/0**		**0.93 (0.86, 1.01)**
ACE Inhibitor vs CA	**1/1**		**1.12 (1.01, 1.25)**
CHD			
ACE Inhibitor vs D/BB	**2/0**		**0.98 (0.91, 1.05)**
CA vs D/BB	**1/0**		**1.01 (0.94, 1.08)**
ACE Inhibitor vs CA	**1/1**		**0.96 (0.88, 1.05)**
HF			
ACE Inhibitor vs D/BB	**2/0**		**1.07 (0.96, 1.19)**
CA vs D/BB	**1/0**		**1.33 (1.21, 1.47)**
ACE Inhibitor vs CA	**1/1**		**0.82 (0.73, 0.92)**

0.5 **Favors** 1.0 **Favors** 2.0
First Listed **Second Listed**

Blood Pressure Lowering Treatment Trialists' Collaboration. *Lancet.* 2003;362:1527-1535.

BP-Lowering Treatment Trialists
Comparisons of Different Active Treatments

	BP Difference (mm Hg)	Relative Risk	RR (95% CI)
Major CV events			
ACEI vs D/BB	2/0		1.02 (0.98, 1.07)
CA vs D/BB	1/0		1.04 (0.99, 1.08)
ACEI vs CA	1/1		0.97 (0.92, 1.03)
CV mortality			
ACEI vs D/BB	2/0		1.03 (0.95, 1.11)
CA vs D/BB	1/0		1.05 (0.97, 1.13)
ACEI vs CA	1/1		1.03 (0.94, 1.13)
Total mortality			
ACEI vs D/BB	2/0		1.00 (0.95, 1.05)
CA vs D/BB	1/0		0.99 (0.95, 1.04)
ACEI vs CA	1/1		1.04 (0.98, 1.10)

0.5   **Favors First Listed**   1.0   **Favors Second Listed**   2.0

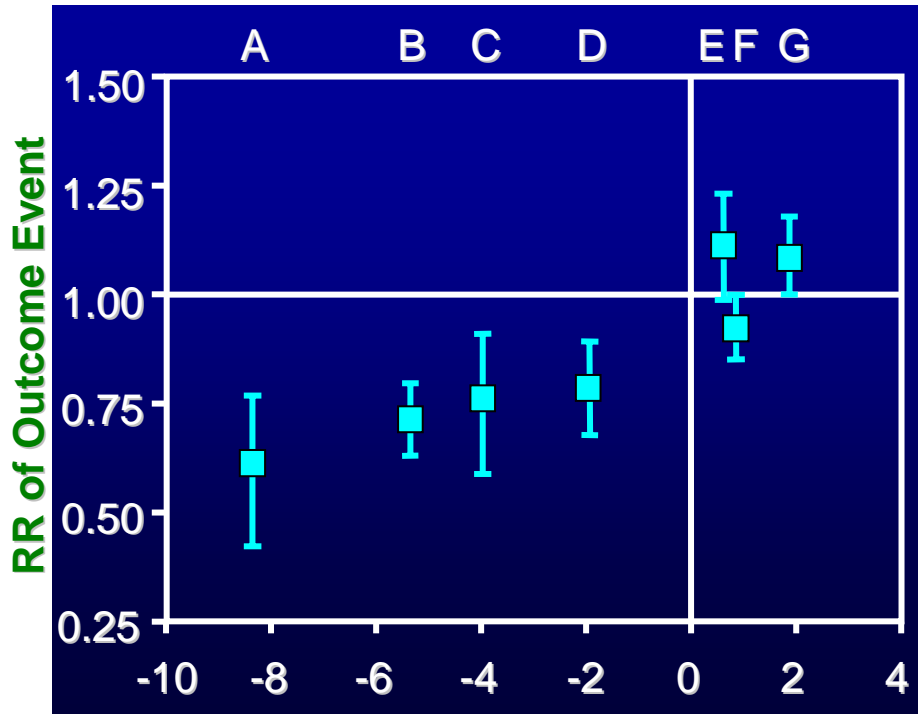Blood Pressure Lowering Treatment Trialists' Collaboration. *Lancet*. 2003;362:1527-1535.

Prevention of Stroke by BP lowering drugs

- Is more reduction of BP related with greater prevention of stroke?
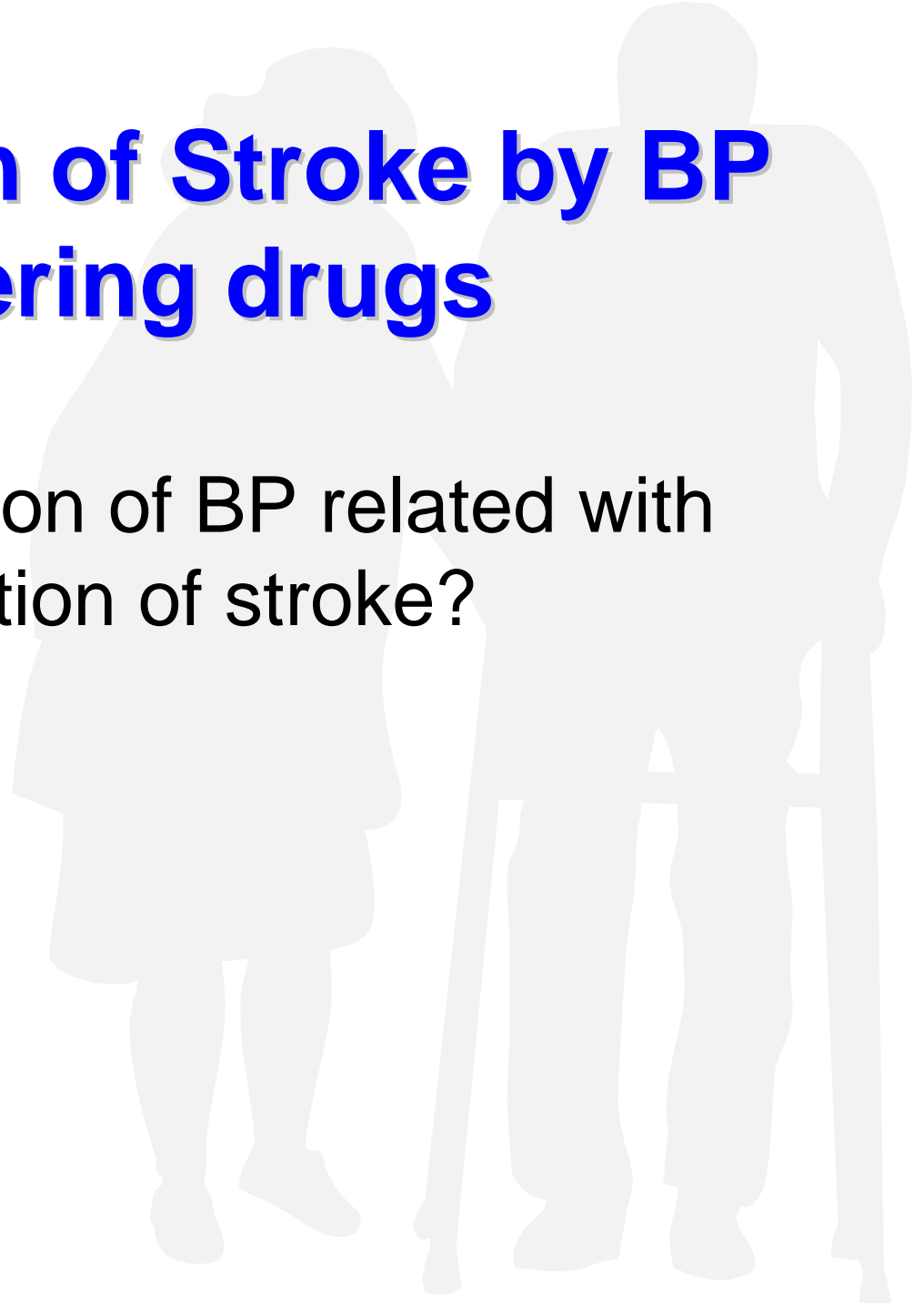
BP-Lowering Treatment Trialists
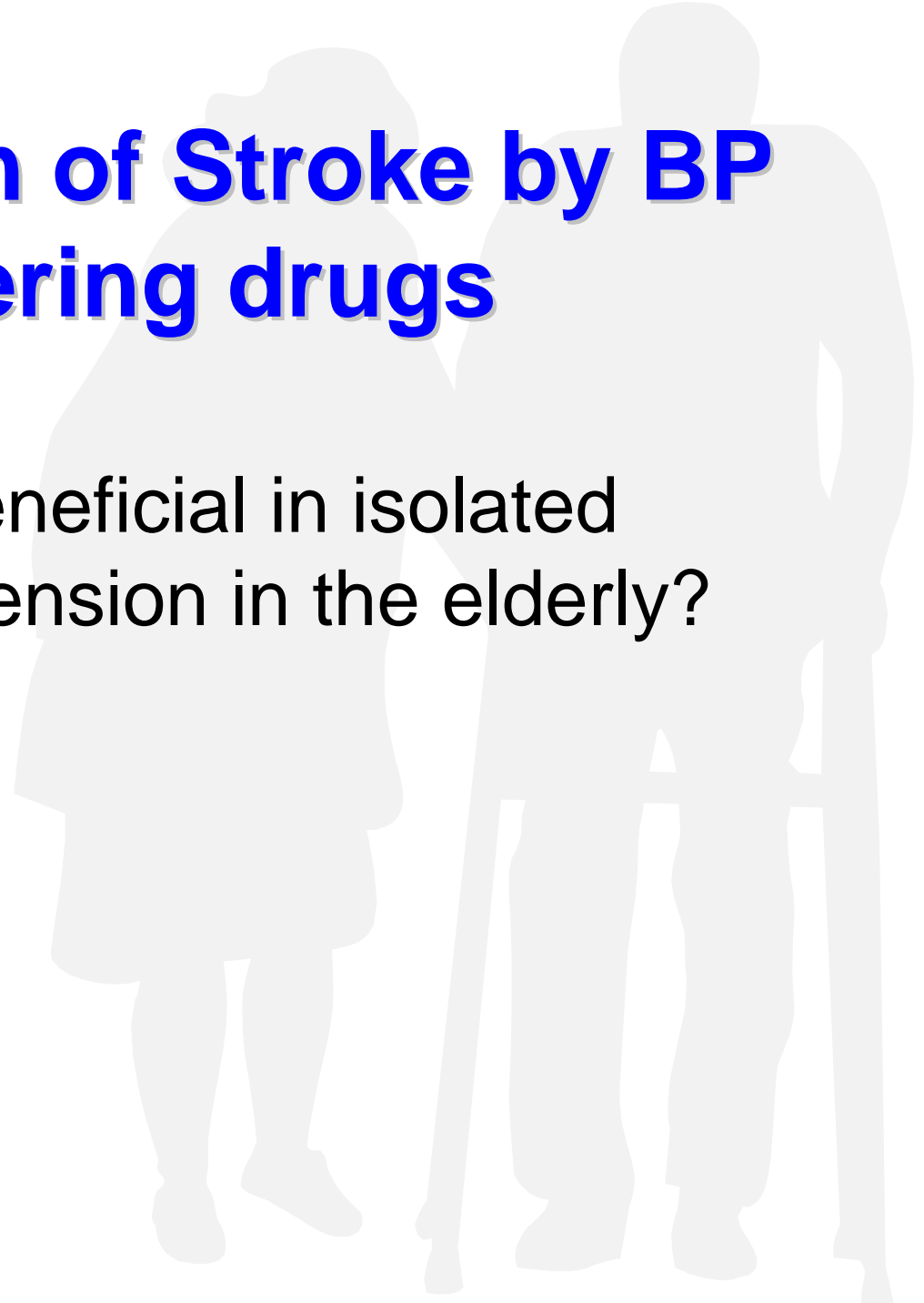
Stroke

CHD

RR of Outcome Event

Systolic BP Difference Between Randomized Groups (mm Hg)

A = CA *vs* placebo; B = ACE inhibitor vs placebo; C = more intensive vs less intensive blood-pressure-lowering; D = ARB vs control; E = ACE inihibitor vs CA; F = CA vs diuretic or -blocker; G = ACE inhibitor vs diuretic and -blocker.

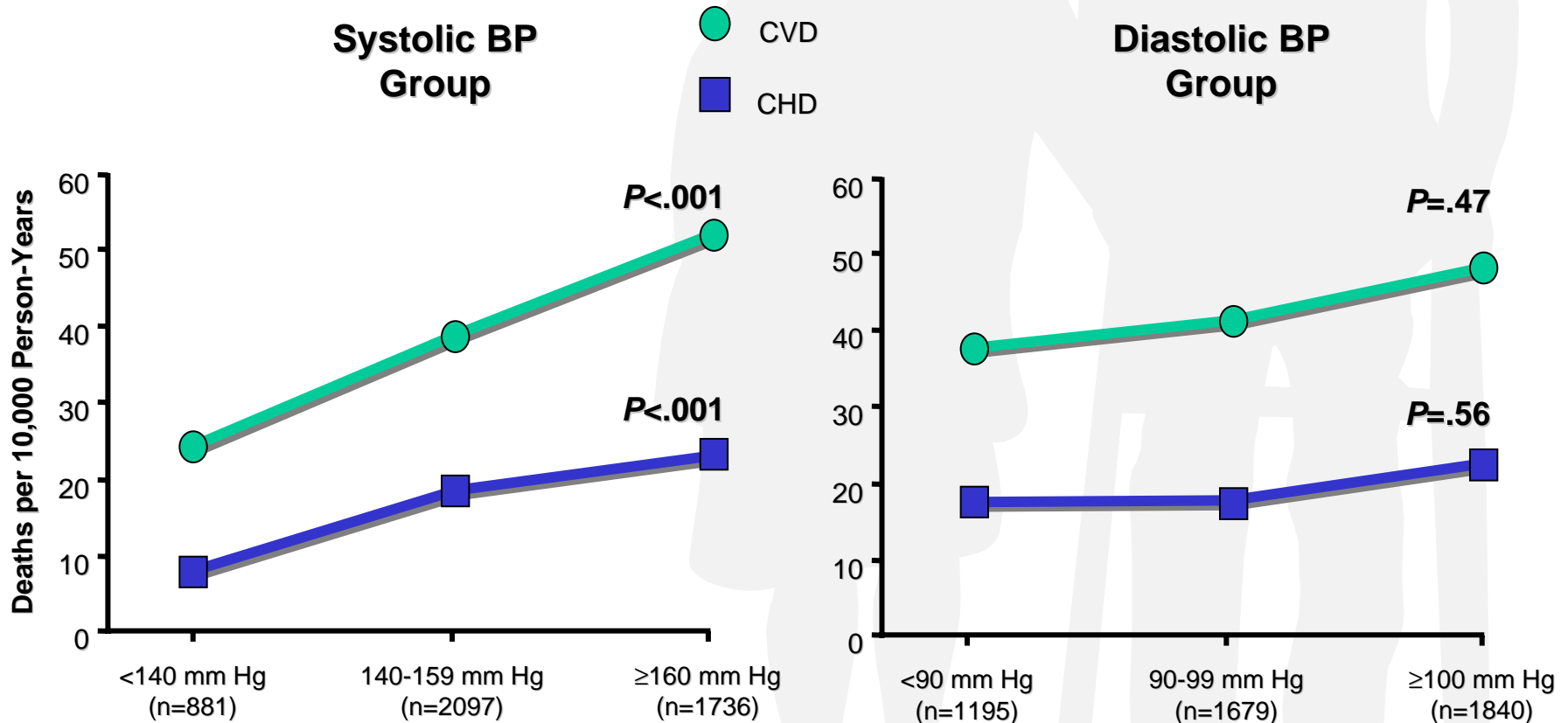Blood Pressure Lowering Treatment Trialists' Collaboration. *Lancet*. 2003;362:1527-1535.

Prevention of Stroke by BP lowering drugs

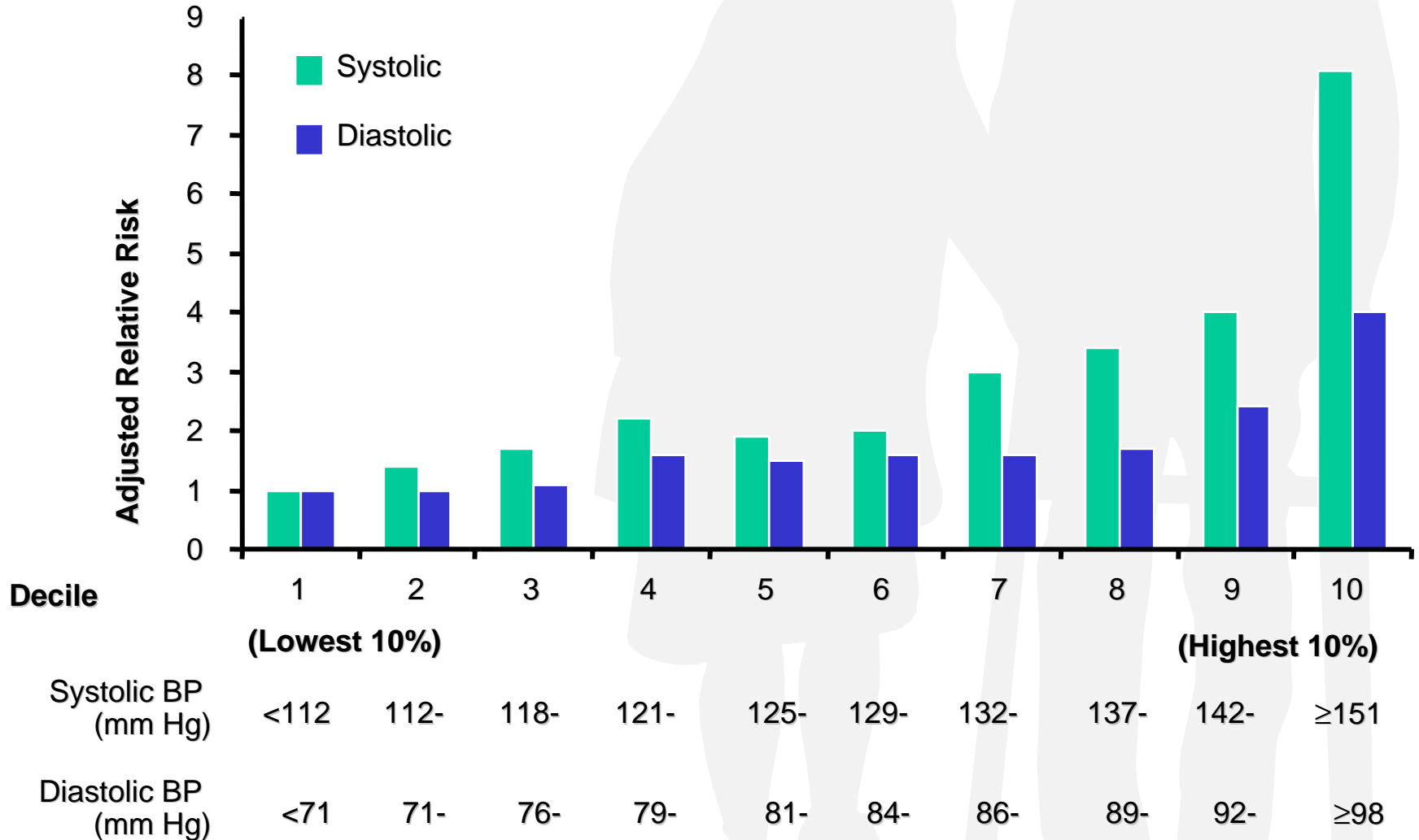- Is treatment beneficial in isolated systolic hypertension in the elderly?

Systolic BP, Not Diastolic BP, Predicts CVD and CHD Mortality

Observational Study of 4714 Middle-Aged Hypertensive Men

Benetos et al. *Arch Intern Med*. 2002;162:577-581.

Risk of Stroke Death According to Systolic BP and Diastolic BP in MRFIT

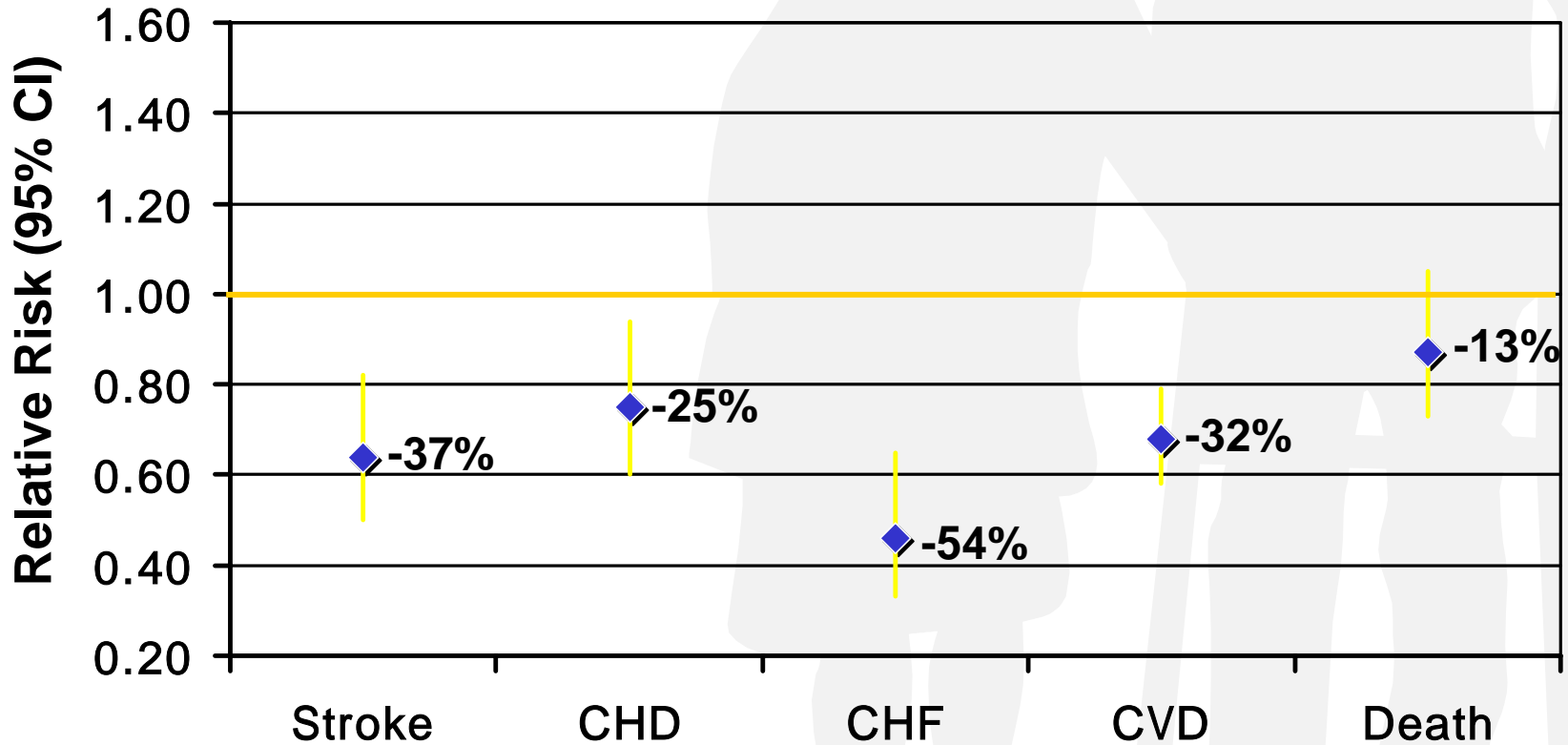| Decile	1	2	3	4	5	6	7	8	9	10
	(Lowest 10%)									(Highest 10%)
Systolic BP (mm Hg)	<112	112-	118-	121-	125-	129-	132-	137-	142-	≥151
Diastolic BP (mm Hg)	<71	71-	76-	79-	81-	84-	86-	89-	92-	≥98

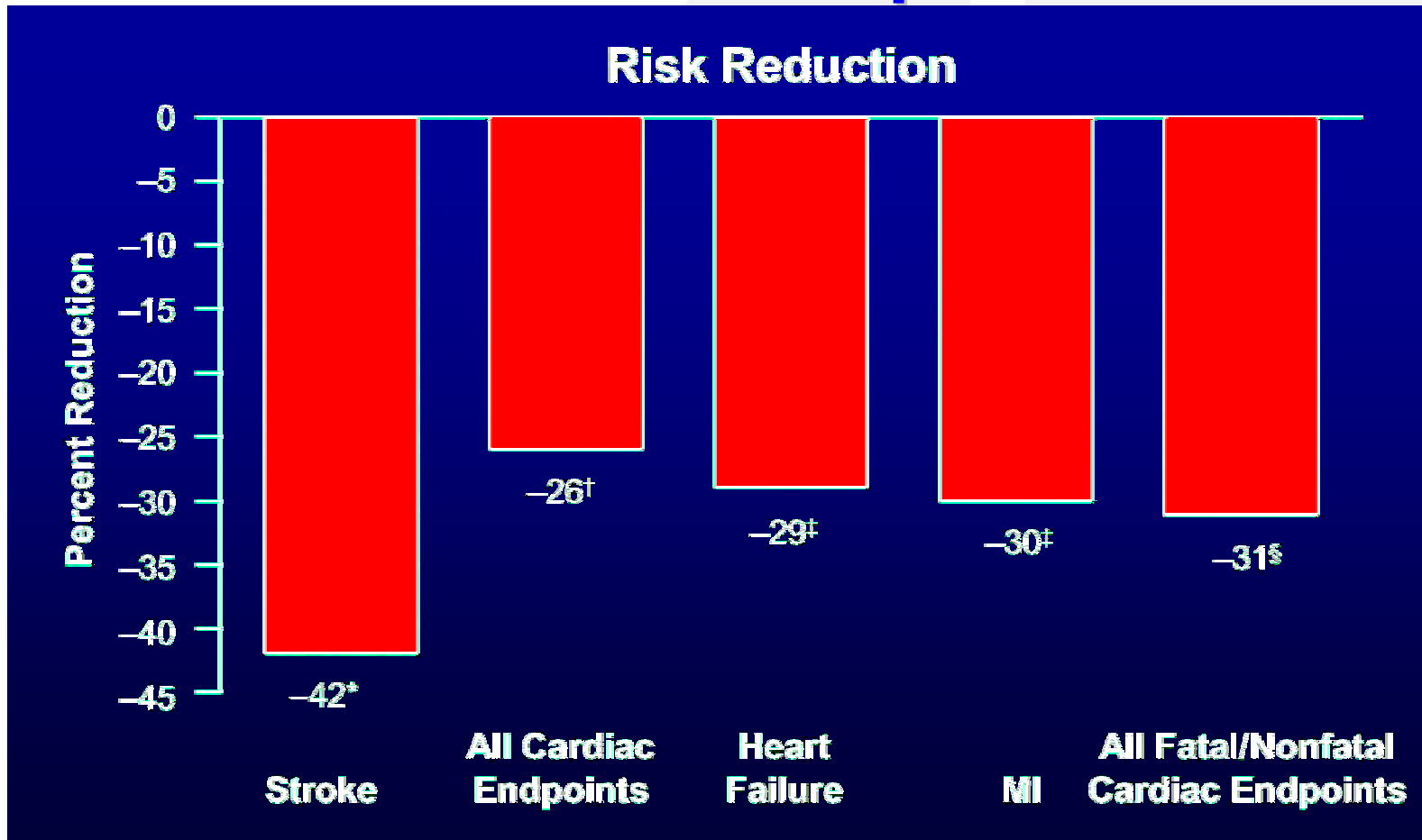Stamler et al. *Arch Intern Med*. 1993;153:598-615.

SHEP Trial: Design

- N: 4736; 43% male
- Age: ≥60 years
- BP: systolic BP 160-219 mm Hg and diastolic BP <90 mm Hg
- Design: placebo-controlled, double-blind
- Active treatment: chlorthalidone (atenolol as step 2)
- Systolic BP difference: 12 mm Hg
- Duration: 4.5 years

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

SHEP Trial: Endpoints

Active Therapy vs Placebo

SHEP Cooperative Research Group. *JAMA*. 1991;265:3255; Kostis et al. *JAMA*. 1997;278:212-216.

Systolic Hypertension in Europe (Syst-Eur) – with Nitrendipine

Risk Reduction

Percent Reduction

Stroke: −42*
All Cardiac Endpoints: −26†
Heart Failure: −29‡
MI: −30‡
All Fatal/Nonfatal Cardiac Endpoints: −31§
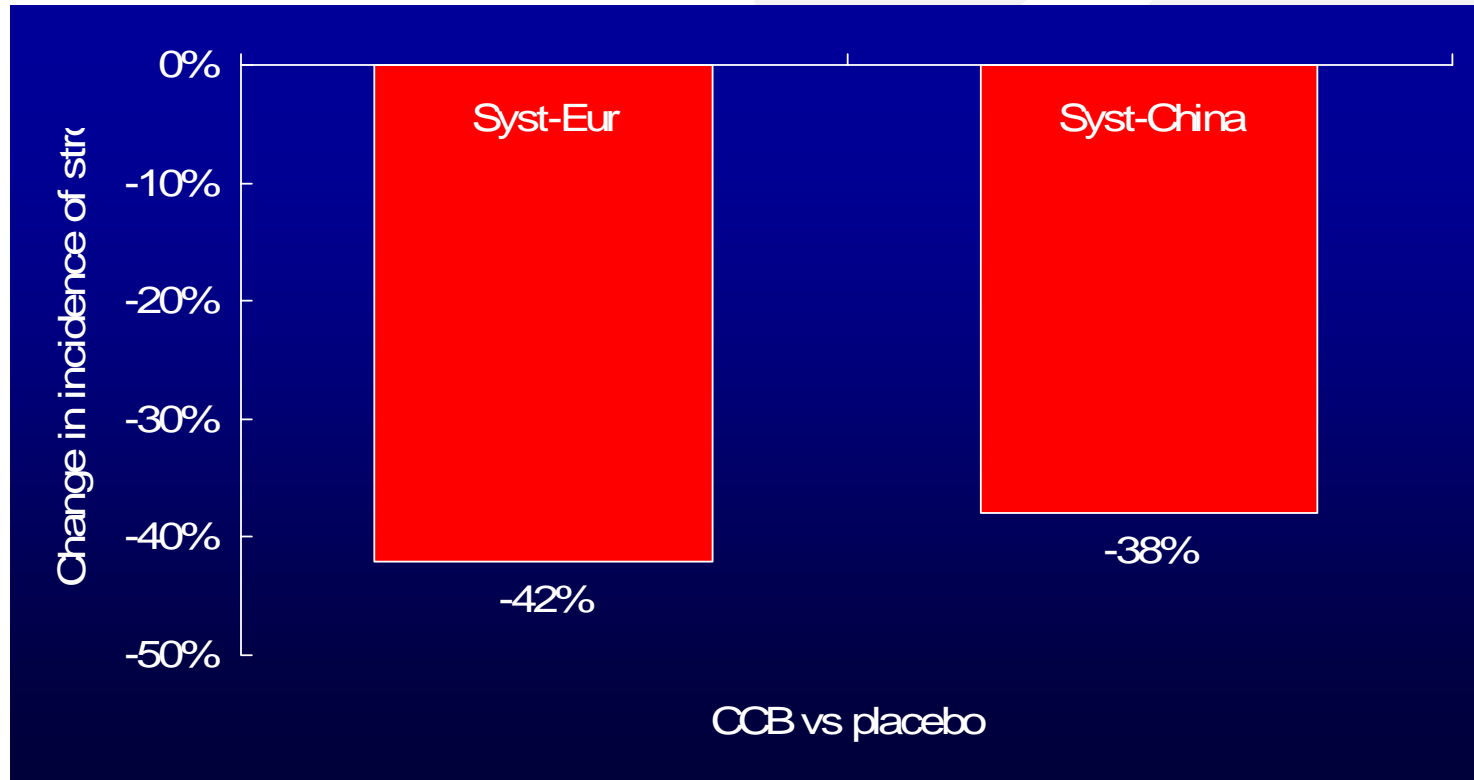
nitrendipine 2398, placebo 2297, SBP160-219, DBP <95, >60 years-old follow for 2 years
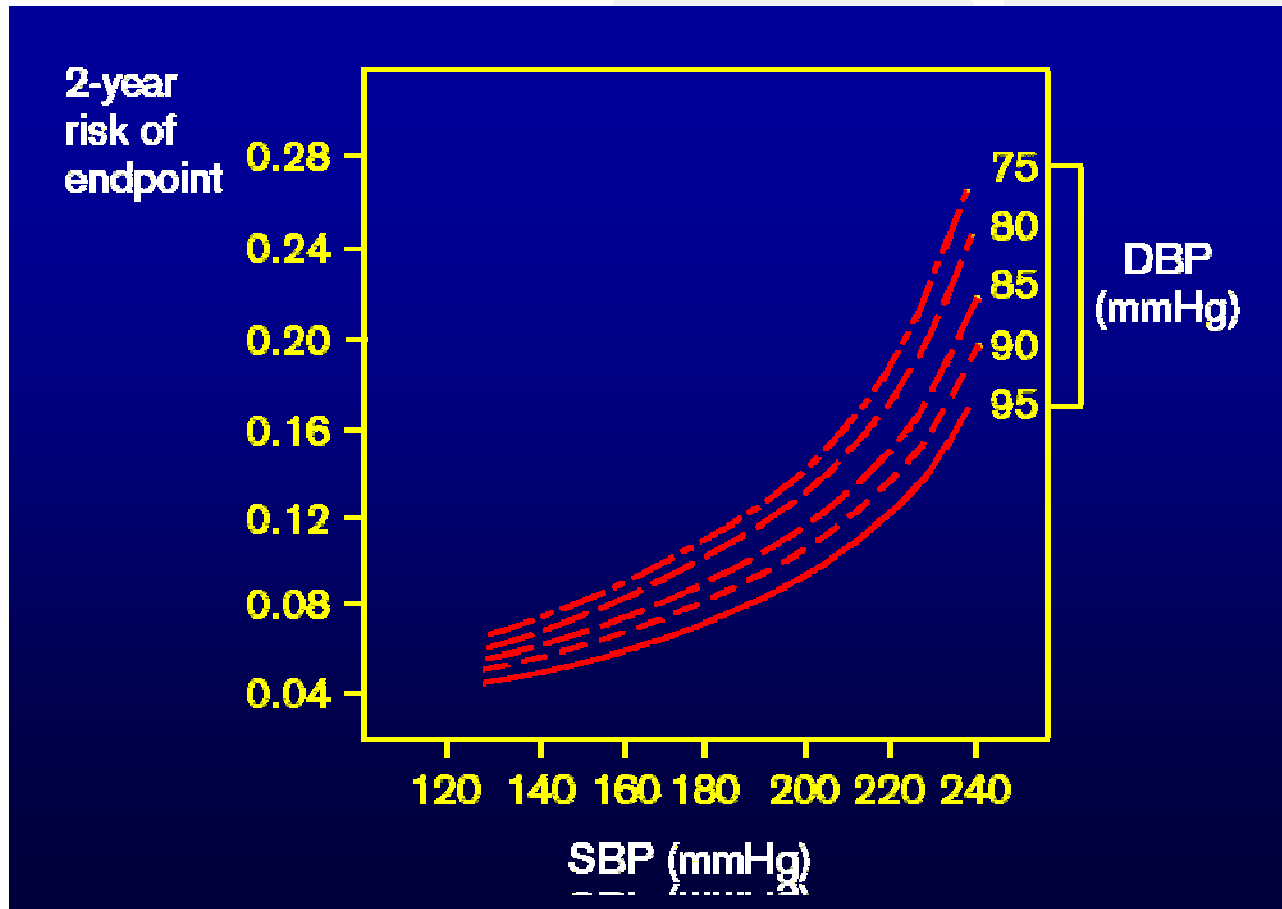Staessen JA et al. Lancet. 1997

SHEP and Syst-Eur: Key Results

	SHEP	Syst-Eur
Reduction in SBP (mmHg)	27	23
Risk Reduction, %		
All-cause mortality	13	14
All cardiovascular endpoints	32	31
Fatal and nonfatal stroke	36	42
Cardiac endpoints	25	26

Benefit of CCB in stroke

- The benefit of antihypertensive therapy in preventing stroke is well-recognized.
- In the randomized, placebo-controlled Syst-Eur and Syst-China trials, CCB-based therapy **reduced the incidence of stroke** by **42%** (p=0.003) and **38%** (p=0.01) respectively, compared with placebo.

Staessen JA et al. Lancet 1997; 350:757-64.
Liu L et al. J Hypertens 1998; 16:1823-829.

Cardiovascular risk and Pulse pressure in elderly

Blacher J et al. Arch Med 2000

# Risk of Causing Widened PP When Treating SH

- In treatment group of SHEP, and increase of 10 mmHg in PP on therapy was independently predictive of significant increases in the risks of stroke (24% increased risk) and heart failure (32%)

Viola Vaccarino, et al. Am J Cardiol 2001;88:980-986

Relative Risk of Stroke Death According to PWV: Multivariate Models

Parameters	Relative Risk	95% CI	*P*
Model including PWV			
$\chi^2 = 39.0$			
PWV (4 m/s)	1.39	1.08–1.72	0.022
Age (10 y)	1.80	1.37–2.35	0.001
Smoking	3.34	1.06–10.50	0.03
Model including pulse pressure			
$\chi^2 = 30.3$			
PP (10 mm Hg)	1.19	0.96–1.47	0.10
Age (10 y)	2.39	1.54–3.71	0.001

Laurent et al. Stoke 2003;34:1203-1206

DBP and Risk of Stroke
J shaped relation in treated ISH
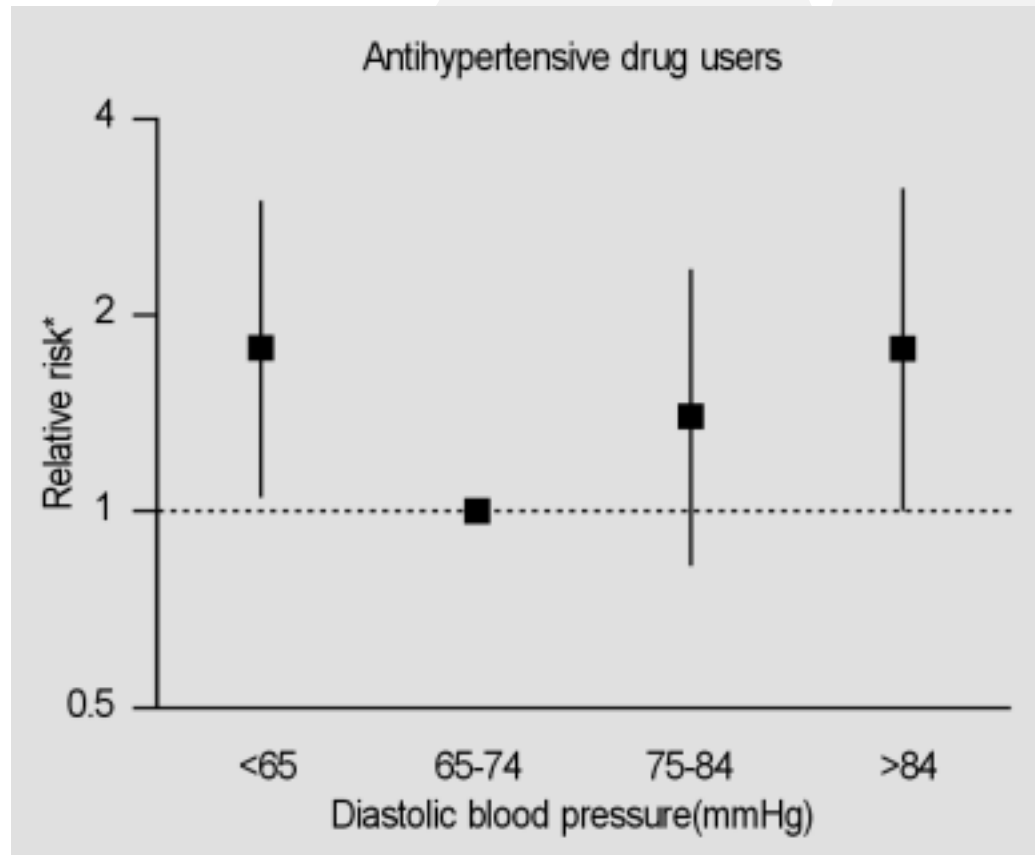
Voko Z et al. Hypertension 1999

Conclusions

- BP lowering in hypertensives is effective in the primary and secondary prevention of stoke.

- For primary prevention, whether any antihypertensive class is superior to the others is uncertain.

- For secondary prevention, diuretics alone or its combination with ACEi can achieve reduction in risk of stroke.

- Controlling isolated systolic hypertension in the elderly is important.