How to Achieve Better Cardiovascular Outcome in Hypertensive Patients

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Global Burden of CV Disease

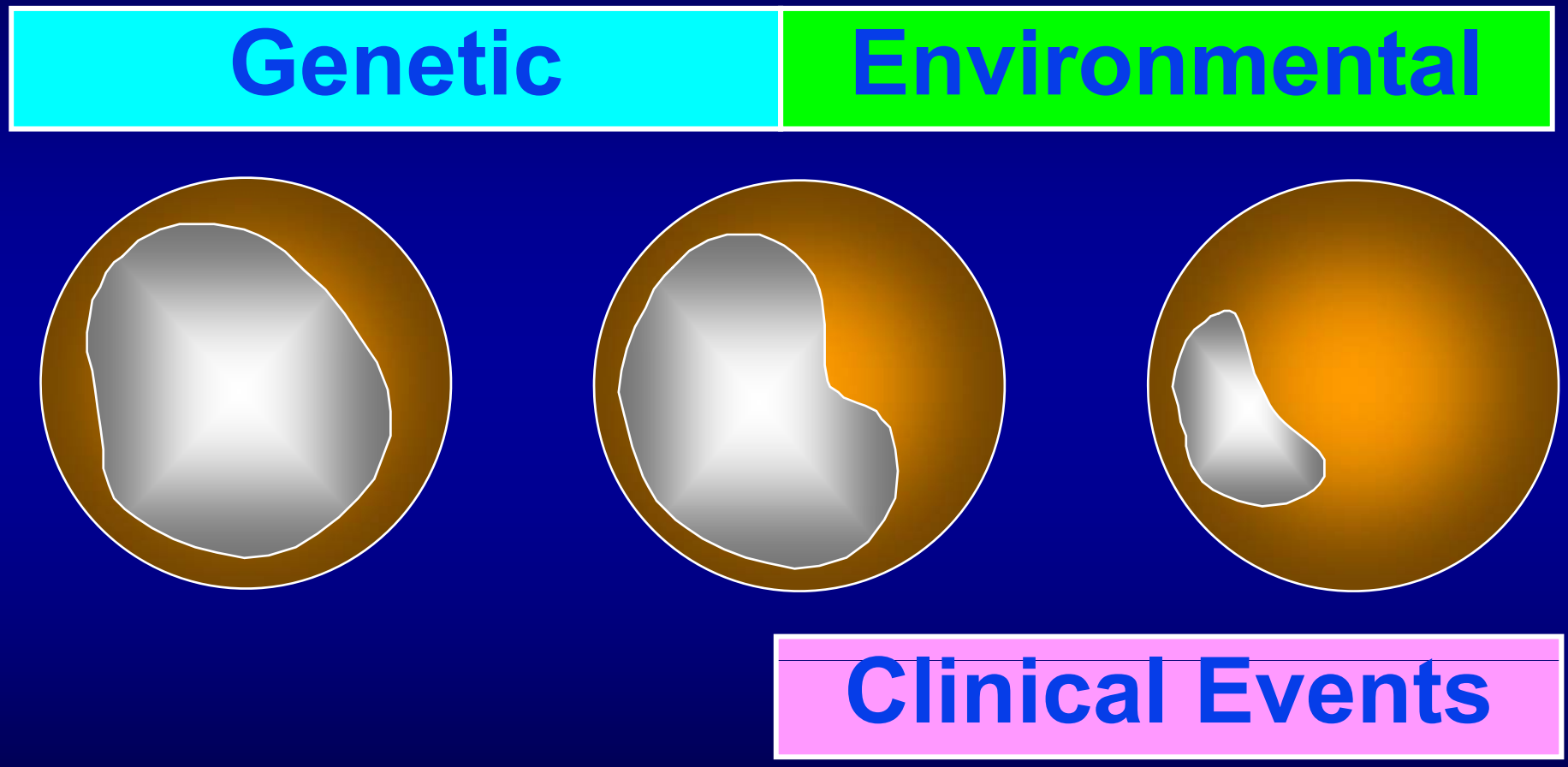
	1990		2020	
Cause	Millions	(%)	Millions	(%)
CHD	6.2	12.4	11.1	16.2
Stroke	4.3	8.5	7.7	11.3
Other CVD	2.6	5.1	6.0	8.8
TOTAL CVD	**13.1**	**26.0**	**24.8**	**36.3**
All Cause Death	50.4	100	68.3	100

WHO:WHF

Rank Order of Disability (DALYs)

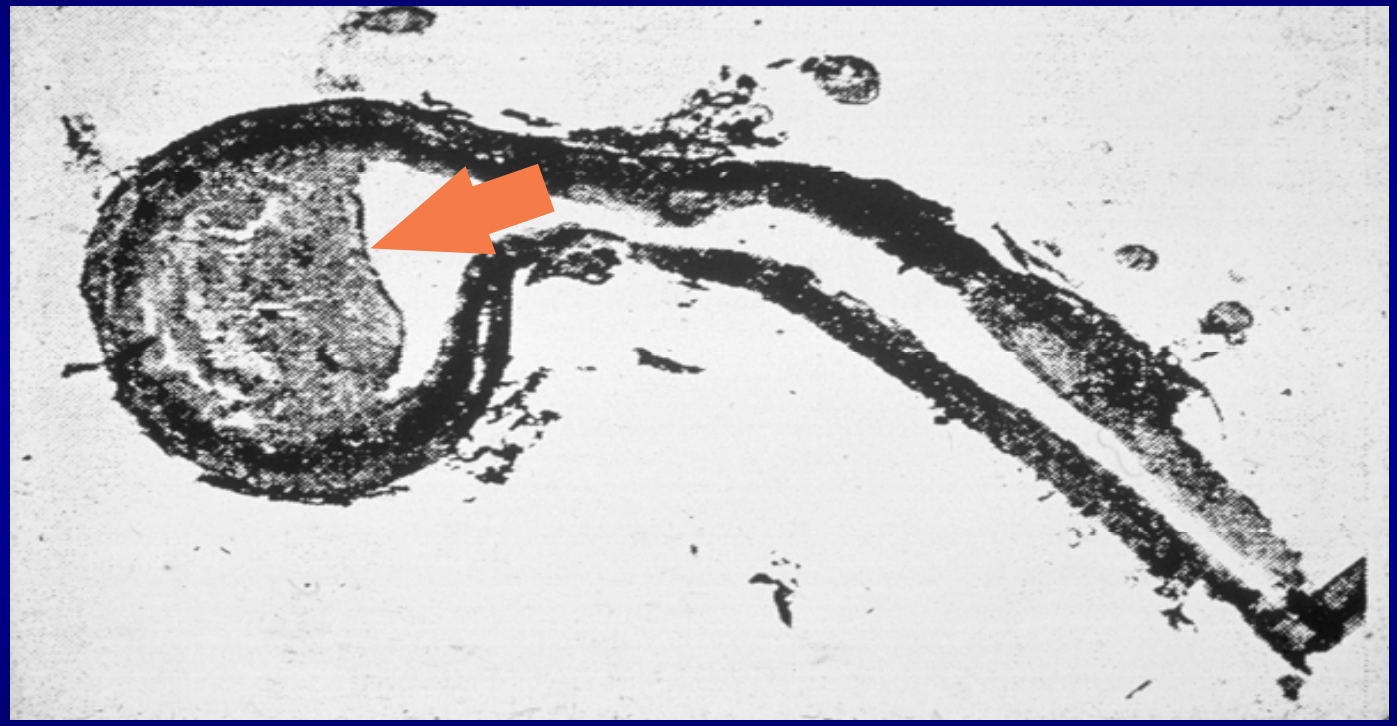
1999 Disease or Injury	*2020 Disease or Injury*
1. Acute lower respiratory infections	1. **Ischemic heart disease**
2. HIV/AIDS	2. Unipolar major depression
3. Perinatal conditions	3. Road traffic accidents
4. Diarrhoeal diseases	4. **Cerebrovascular disease**
5. Unipolar major depression	5. Chron obstruc pulmonary dis
6. **Ischemic heart disease**	6. Lower respiratory infections
7. **Cerebrovascular disease**	7. Tuberculosis
8. Malaria	8. War
9. Road traffic accidents	9. Diarrhoeal diseases
10. Chron obstruc pulmonary dis	10. HIV

Evolution of Atherosclerosis



Atherosclerosis in Korean War Casualties

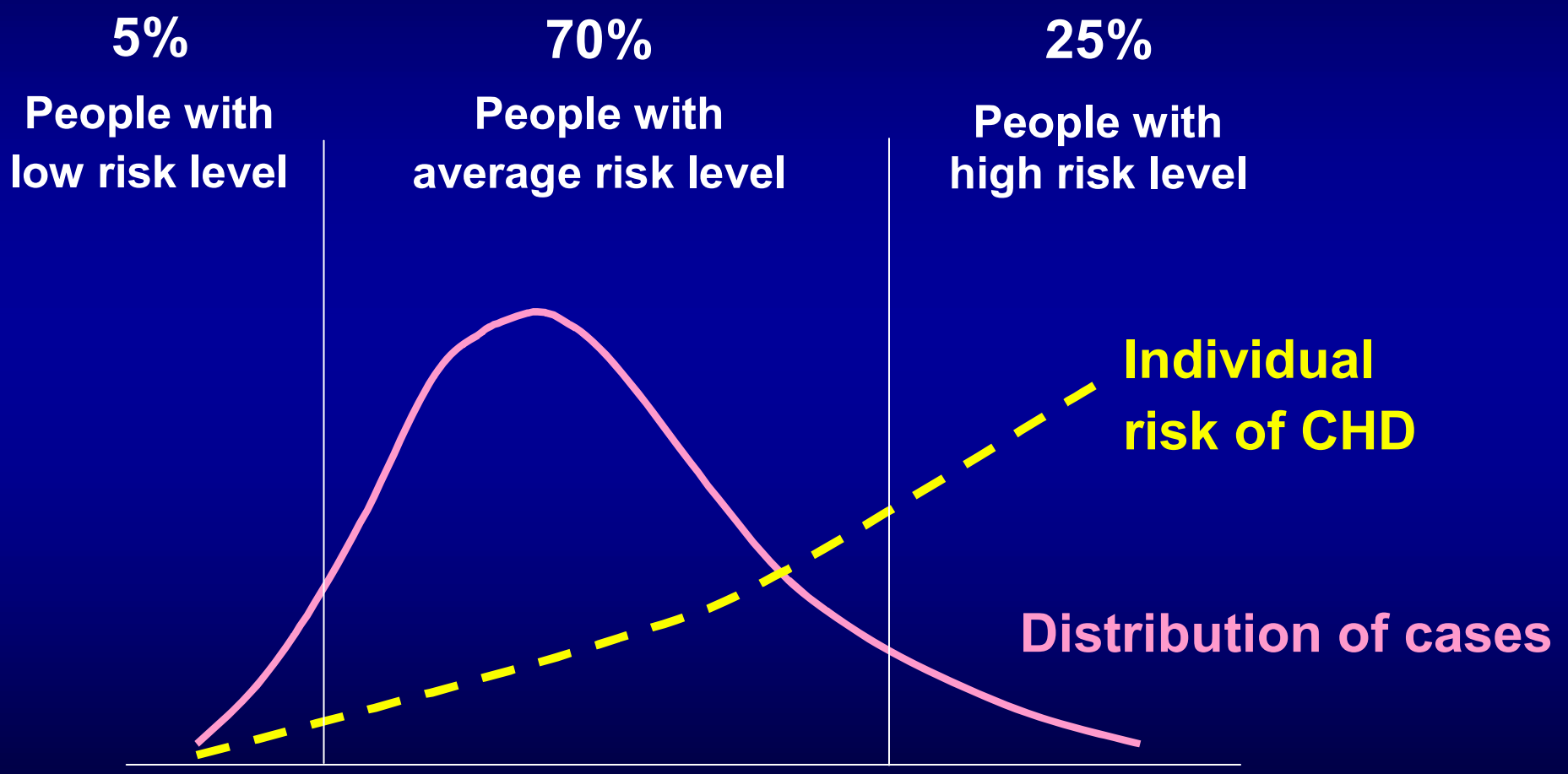
300 autopsies (mean 22.1 yrs)



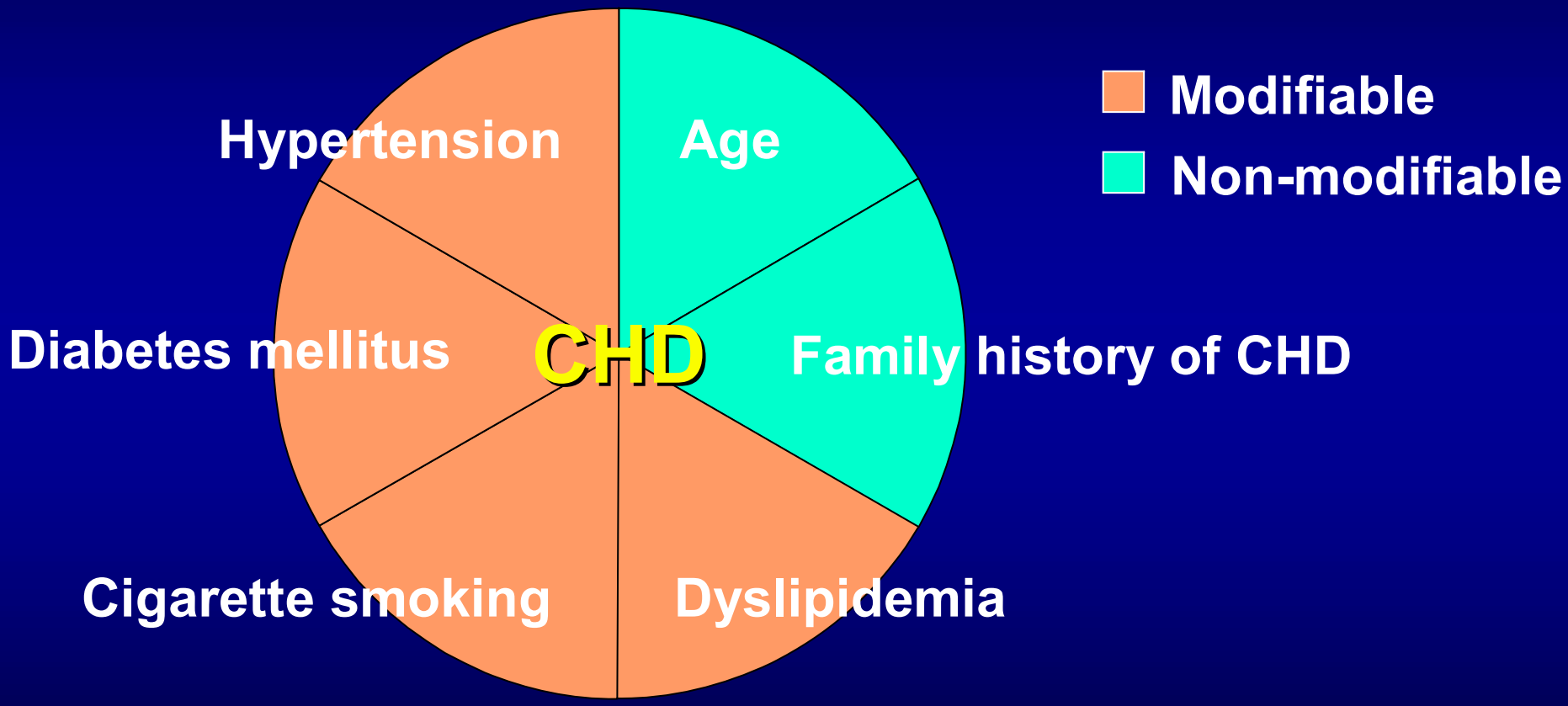
- 77 % Coronary atherosclerosis
- 39% Occlusive plaques

ENOS JAMA 1953

Individual Risk vs Proportional Attributable Risk

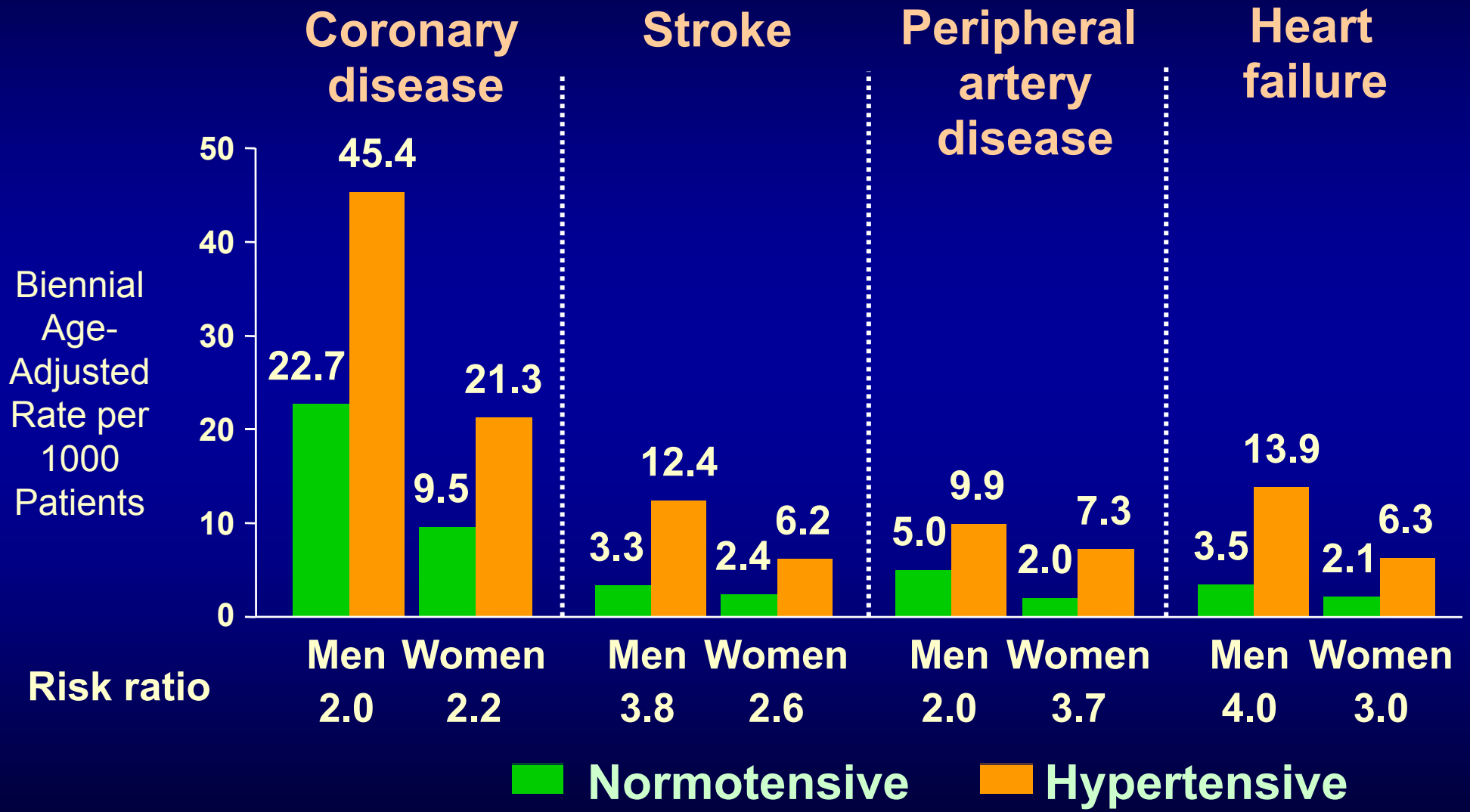


Primary Risk Factors for CVD



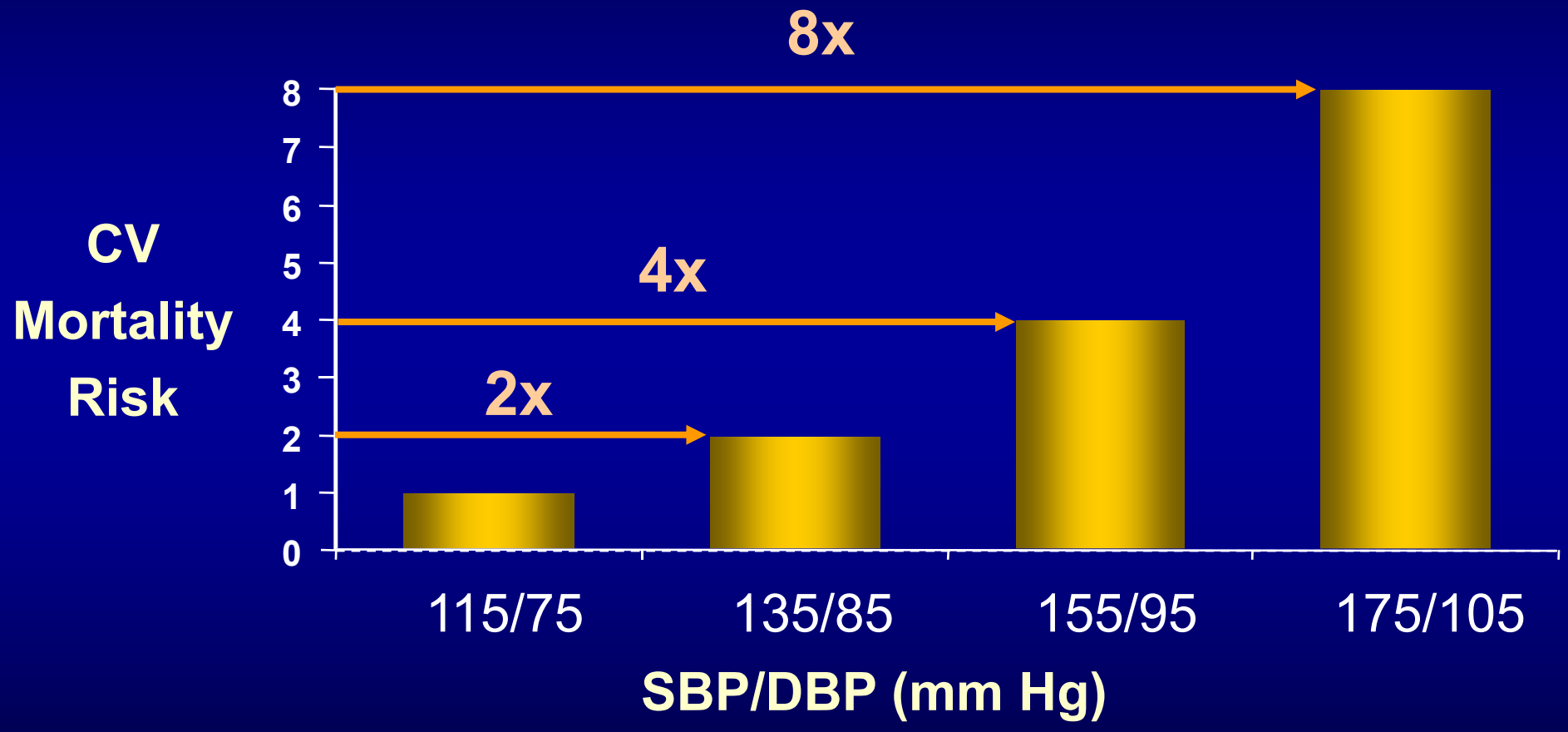
NCEP. *Circulation* 1994;**89**:1329–1445. *Eur Heart J* 1994;**15**:1300–1331.
Wood D *et al. Eur Heart J* 1998;**19**:1434–1503.

HT: A Risk Factor for CV Disease



Kannel WB. *JAMA.* 1996;275:1571-1576.

CV Mortality Risk with BP Increment



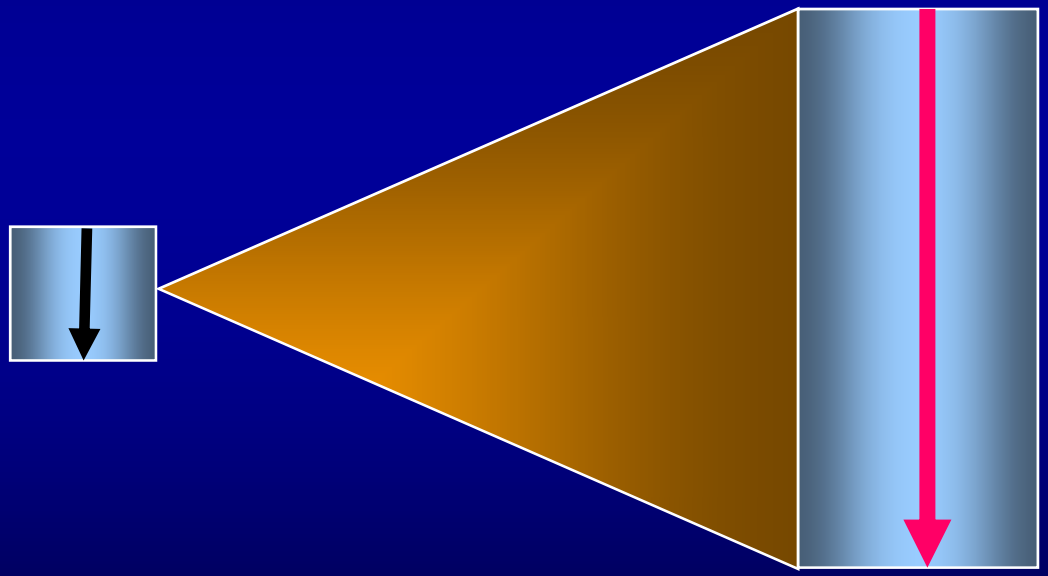
*Individuals aged 40 to 69 years, starting at blood pressure 115/75 mm Hg

Chobanian AV et al. *JAMA*. 2003;289:2560-2572. Lewington S et al. *Lancet*. 2002;360:1903-1913.

Small Difference Produces Big Impact

- Meta-analysis of 61 observational studies
- 1 million adults

For every 2 mm Hg decrease in mean SBP



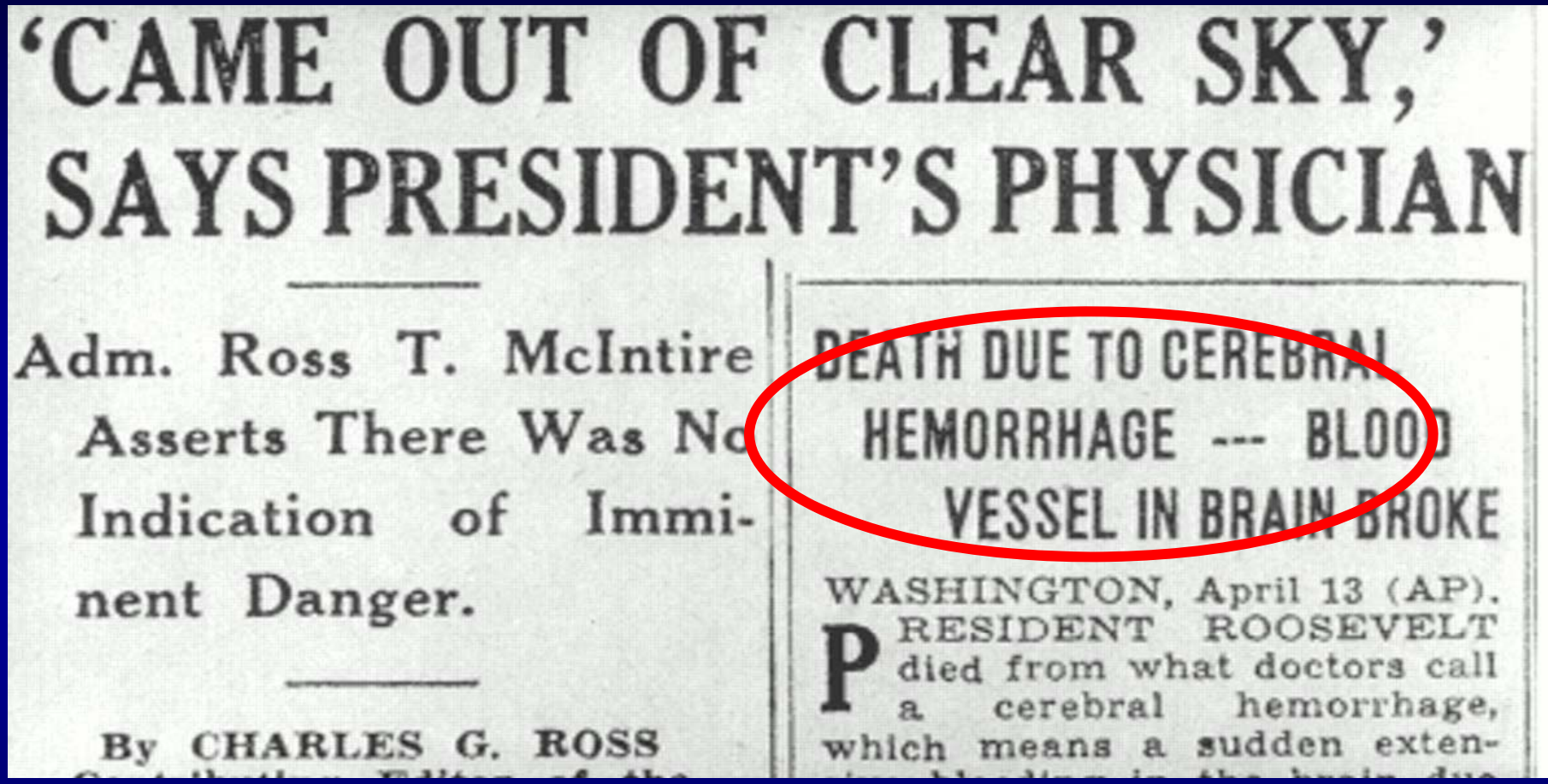
- 7% reduction in CHD mortality
- 10% reduction in stroke mortality

Lewington S et al. *Lancet.* 2002;360:1903-1913.

Evolution of Management of HT

" HT is an important compensatory mechanism and BP should not be tampered with "

Dr. White PD. Heart disease. 1937



‘CAME OUT OF CLEAR SKY,’ SAYS PRESIDENT’S PHYSICIAN

Adm. Ross T. McIntire Asserts There Was No Indication of Imminent Danger.

By CHARLES G. ROSS

DEATH DUE TO CEREBRAL HEMORRHAGE --- BLOOD VESSEL IN BRAIN BROKE

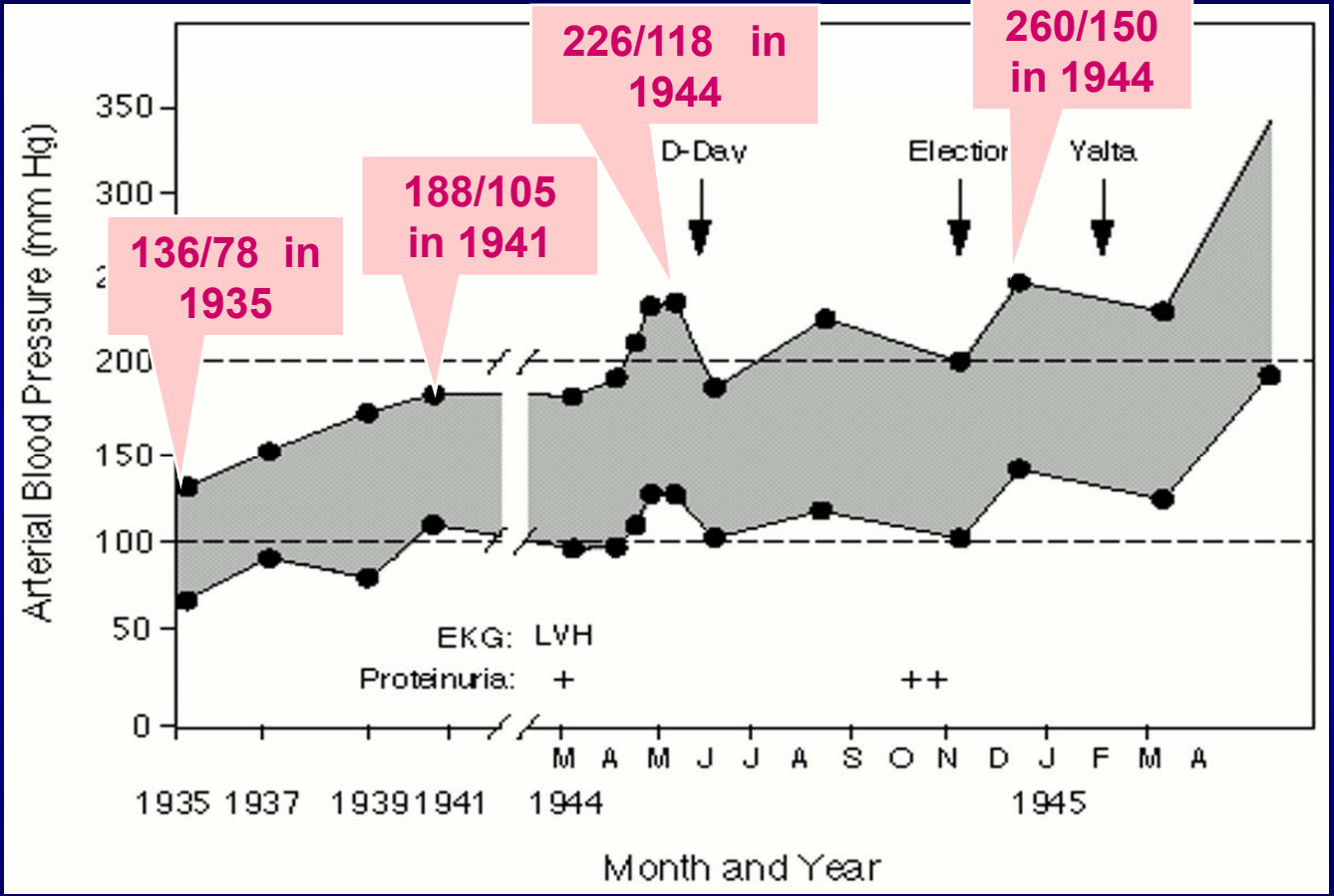
WASHINGTON, April 13 (AP). PRESIDENT ROOSEVELT died from what doctors call a cerebral hemorrhage, which means a sudden exten-

Headlines of the *St. Louis Post-Dispatch,* April 13, 1945

FDR's Final Picture (April 11, 1945)

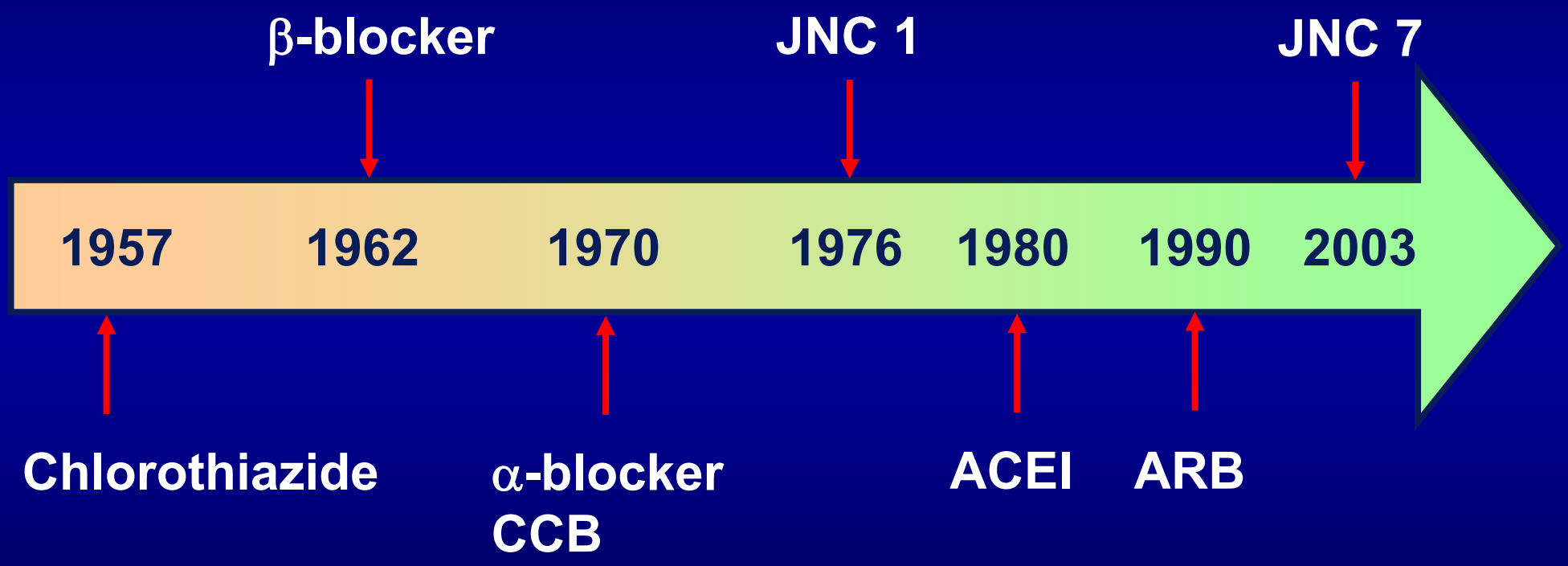
1882-1945
Thirty-Second President
(1933-1945)

Franklin D. Roosevelt



Messerli FH, *N Engl J Med.* 1995

Treatment of Hypertension



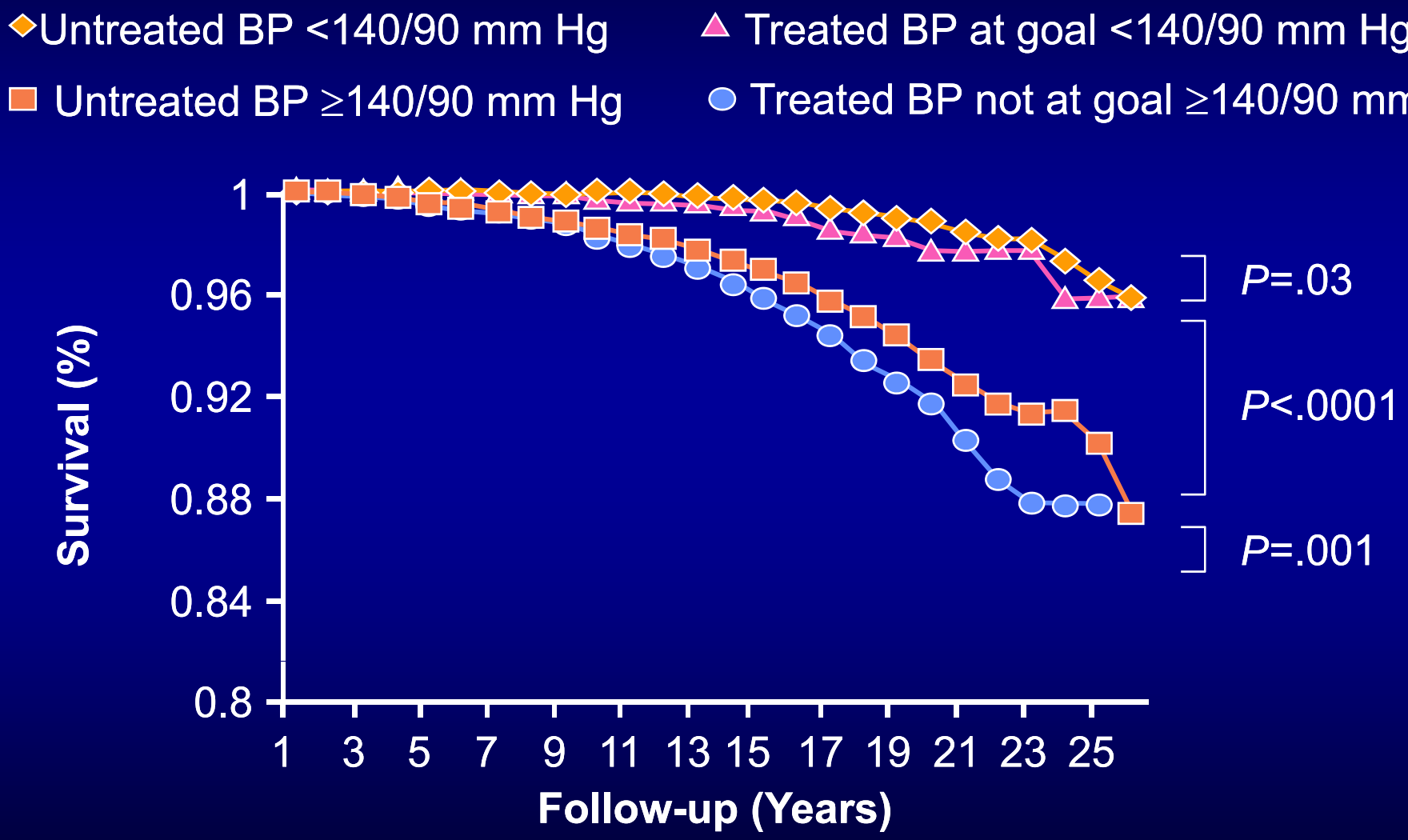
Outcome in Treated HT After >20 Yrs

	"Normotensive" (N = 6810)	Treated BP (N = 686)
Screening BP (mm Hg)	145/93	185/114
Final BP (mm Hg)	–	145/89
CHD (%)	10.3	20.1*
Stroke (%)	1.8	4.5*
Cancer (%)	10.8	8.9
All-cause death (%)	29.2	37.4*

*$P < .002$.

Andersson OK et al. *BMJ*. 1998;317:167-171.

CVD Survival in Treated HT

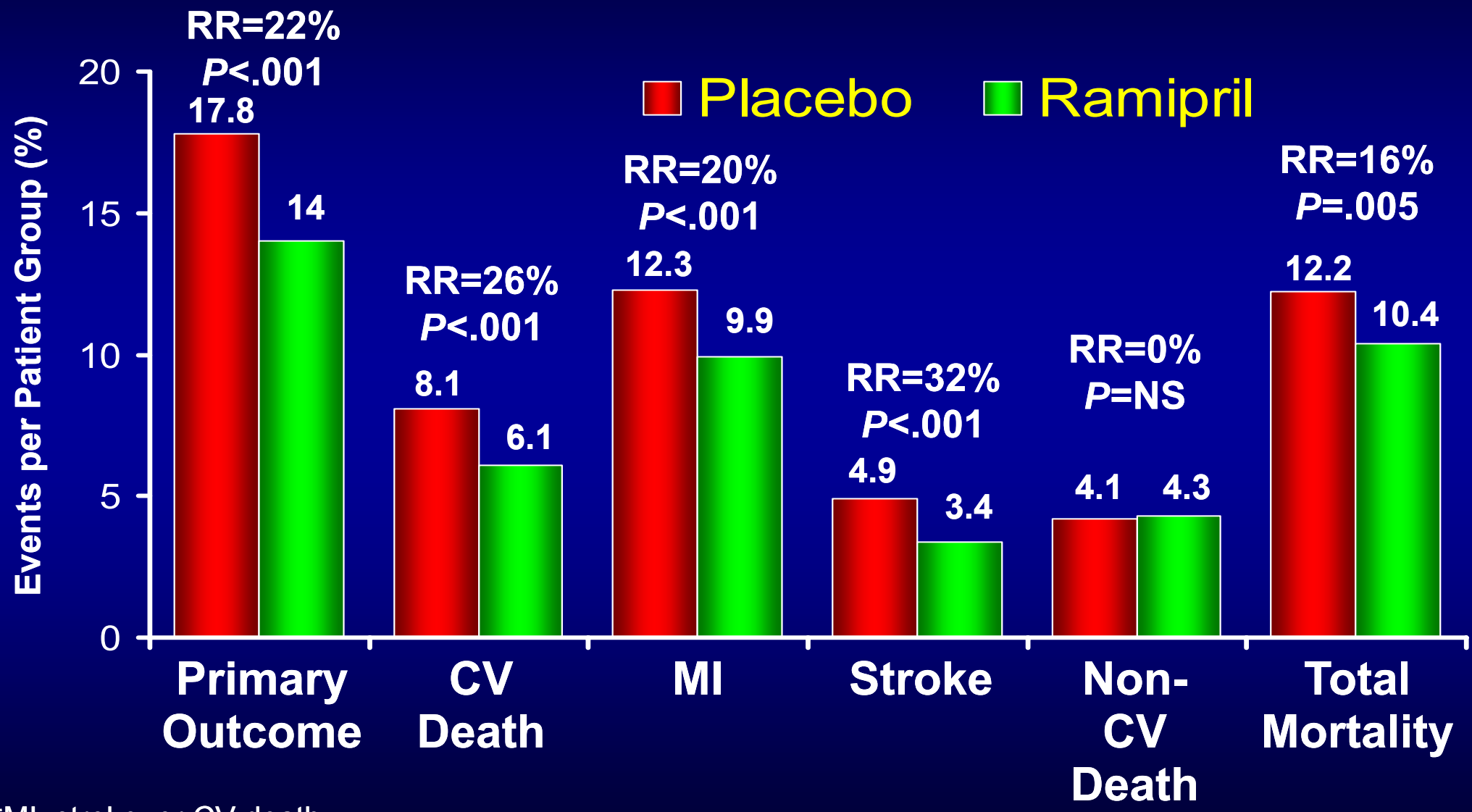


Benetos et al. *J Hypertens*. 2003;21:1635-1640.

Better Outcome in HT

- **Agents with beyond BP lowering ?**

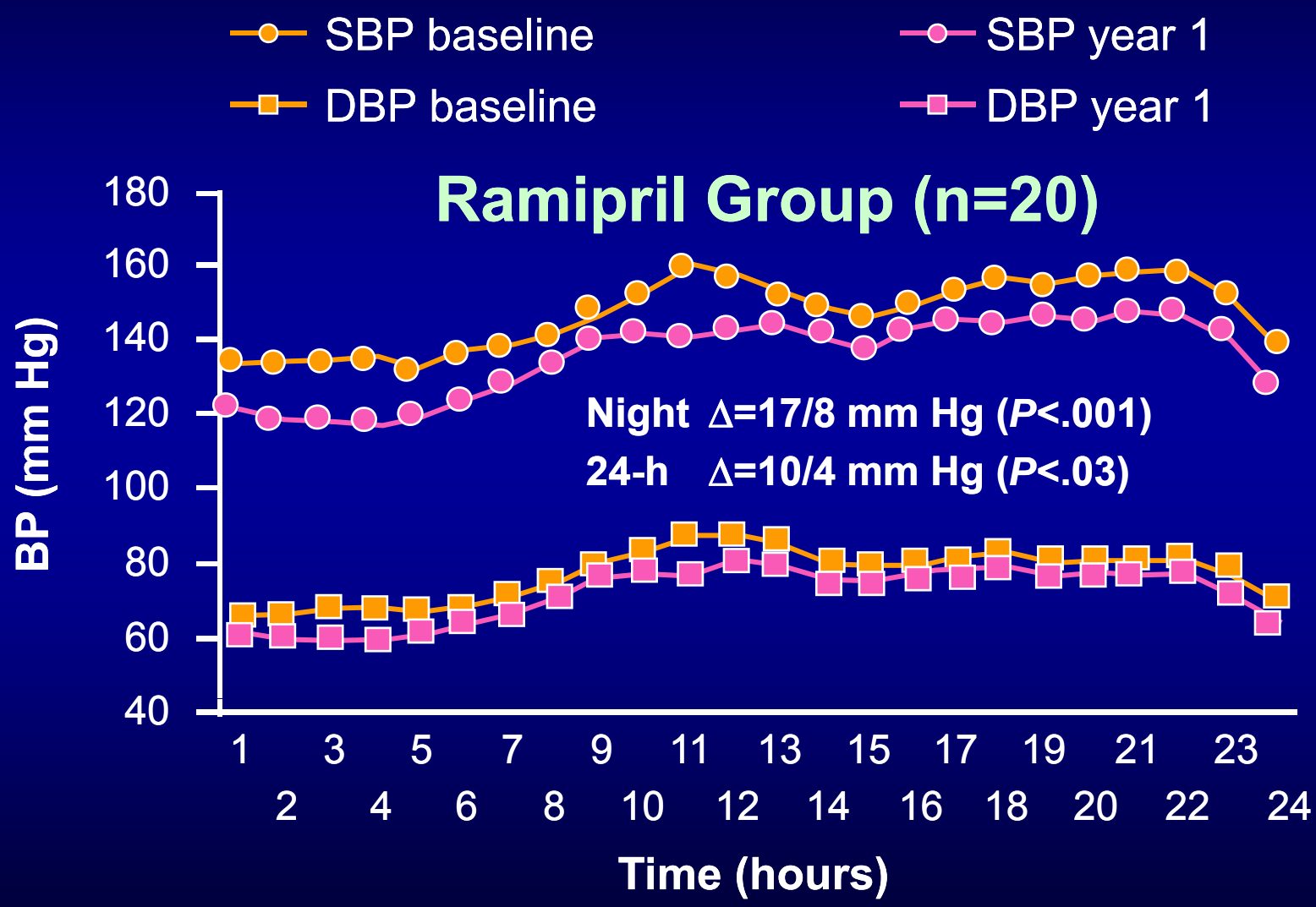
HOPE: Events per Patient Group



*MI, stroke, or CV death.

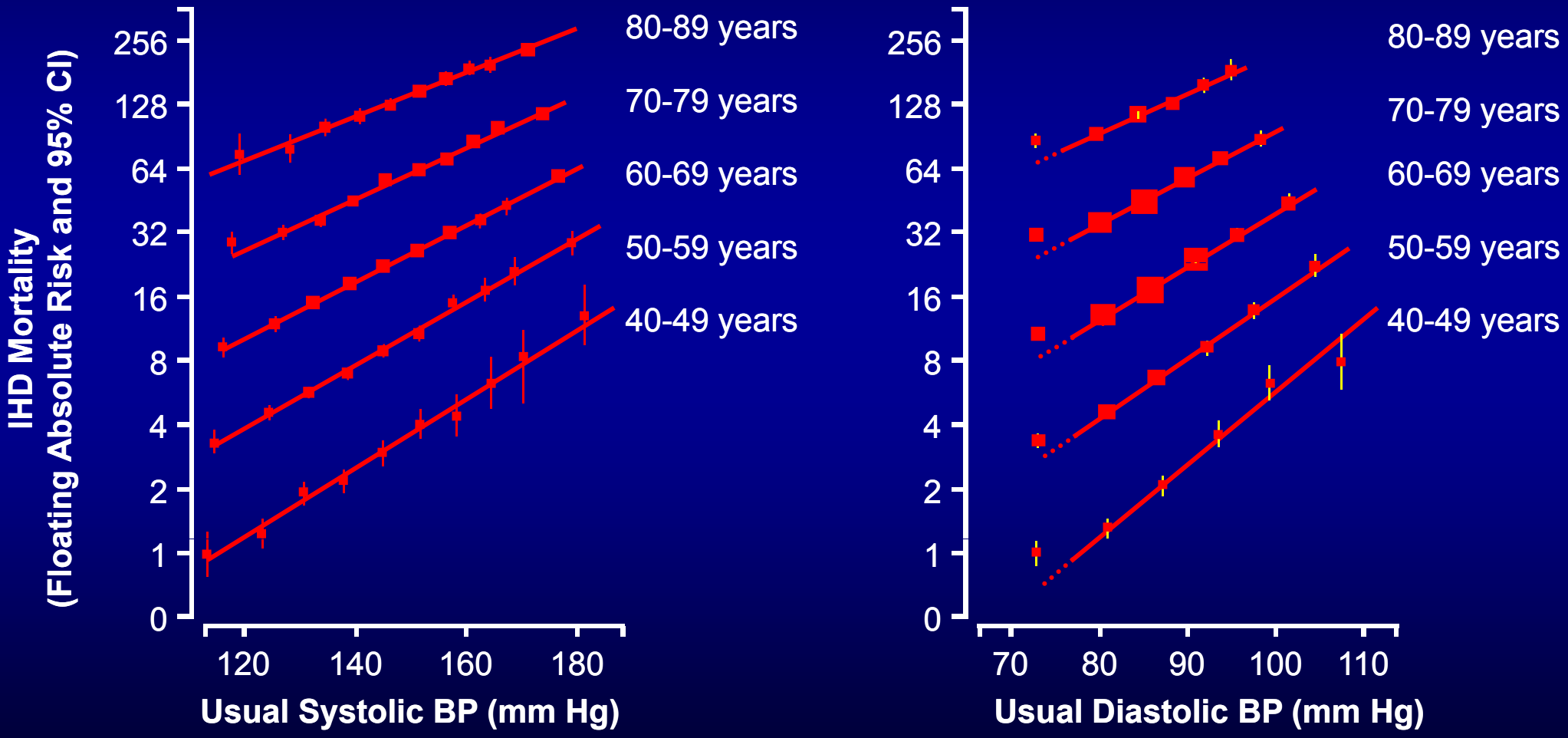
Yusuf et al. *N Engl J Med*. 2000;342:145-153.

Ambulatory BP in HOPE Trial



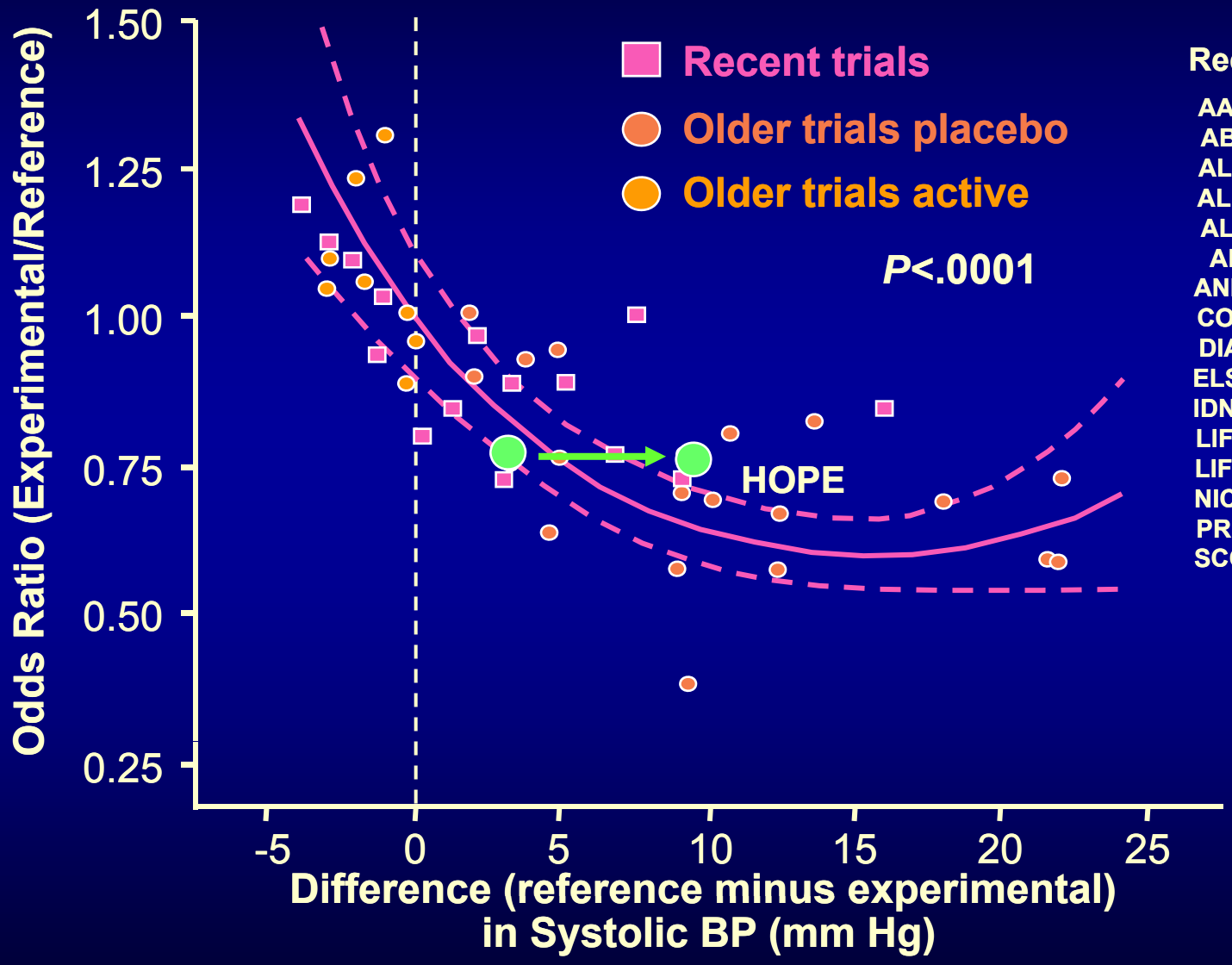
Svensson et al. *Hypertension.* 2001;38:e28-e32.

CAD Mortality and Usual BP by Age



Prospective Studies Collaboration. *Lancet*. 2002;360:1903-1913.

Odds Ratio for CV Events & SBP



Recent

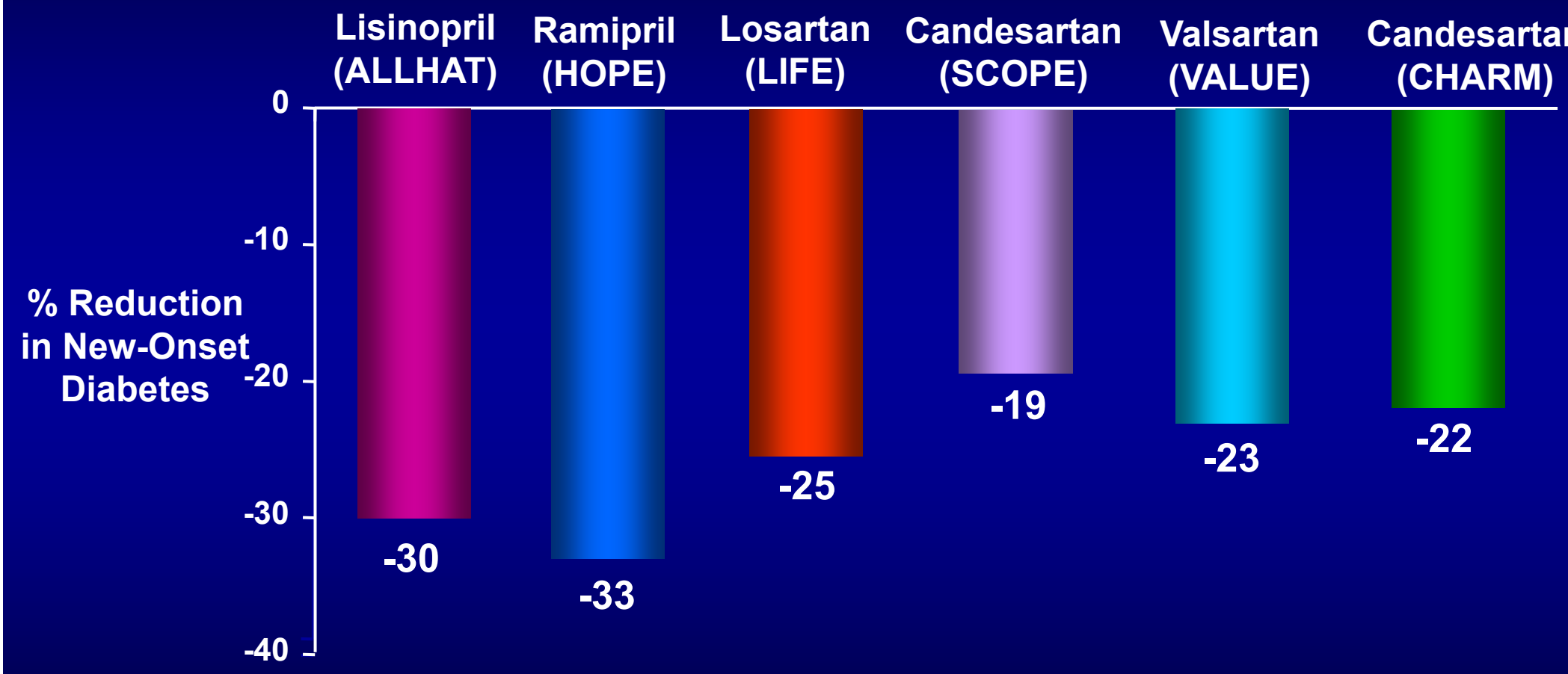
AASK L vs H
ABCD/NT L vs H
ALLHAT/Aml
ALLHAT/Lis
ALLHAT/Lis ≥65
ALLHAT/Lis Blcks
ANBP2
CONVINCE
DIABHYCAR
ELSA
IDNT2
LIFE/ALL
LIFE/DM
NICOLE
PREVENT
SCOPE

Older

ALLHAT/Dox
ATMH
EWPHE
HEP
HOPE
HOT
HOT M vs H
INSIGHT
MIDAS/NICS/VHAS
L vs H
MRC
MRC2
PART2/SCAT
PATS
PROGRESS/Per
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.

New-Onset DM With RAS Blockade

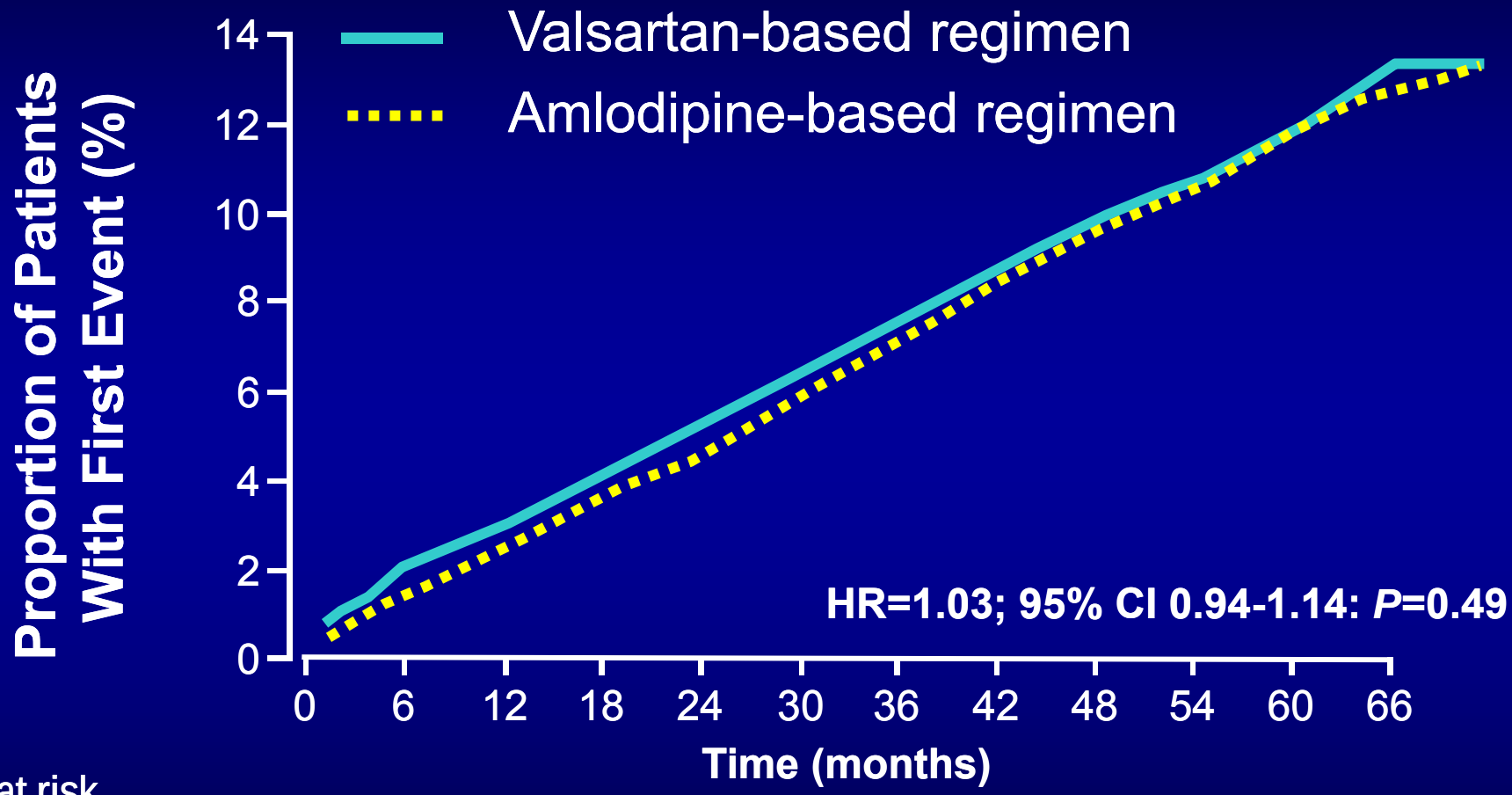


ALLHAT Officers and Collaborators. *JAMA*. 2002;288:2981-2997. Yusuf S et al. *JAMA*. 2001;286:1882-1885. Dähloff B et al. *Lancet*. 2002;359:995-1003. Lithell H et al. *J Hypertens*. 2003;21:875-886. Julius S et al. *Lancet*. 2004;363:2022-2031. Pfeffer MA et al. *Lancet.* 2003;362:759-766.

Better Outcome in HT

- **Agents with beyond BP lowering ?**
- **Rapid BP lowering in high-risk patients**

VALUE: Primary Composite Endpoint

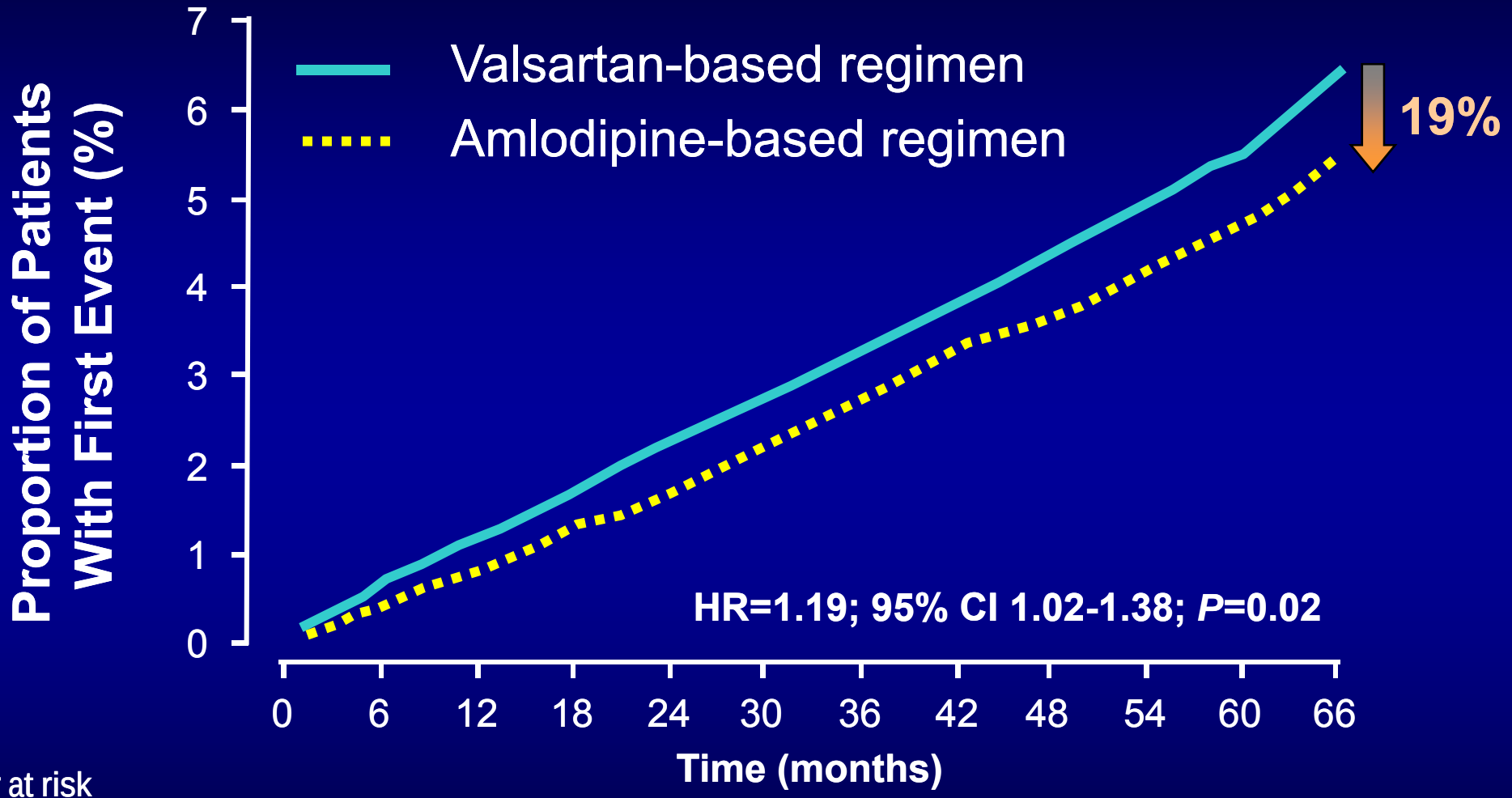


Number at risk

Valsartan	7649	7459	7407	7250	7085	6906	6732	6536	6349	5911	3764	1474
Amlodipine besylate	7596	7469	7424	7267	7117	6955	6772	6576	6391	5959	3725	1474

Julius et al. *Lancet*. June 2004;363.

VALUE: Fatal and Non-Fatal MI



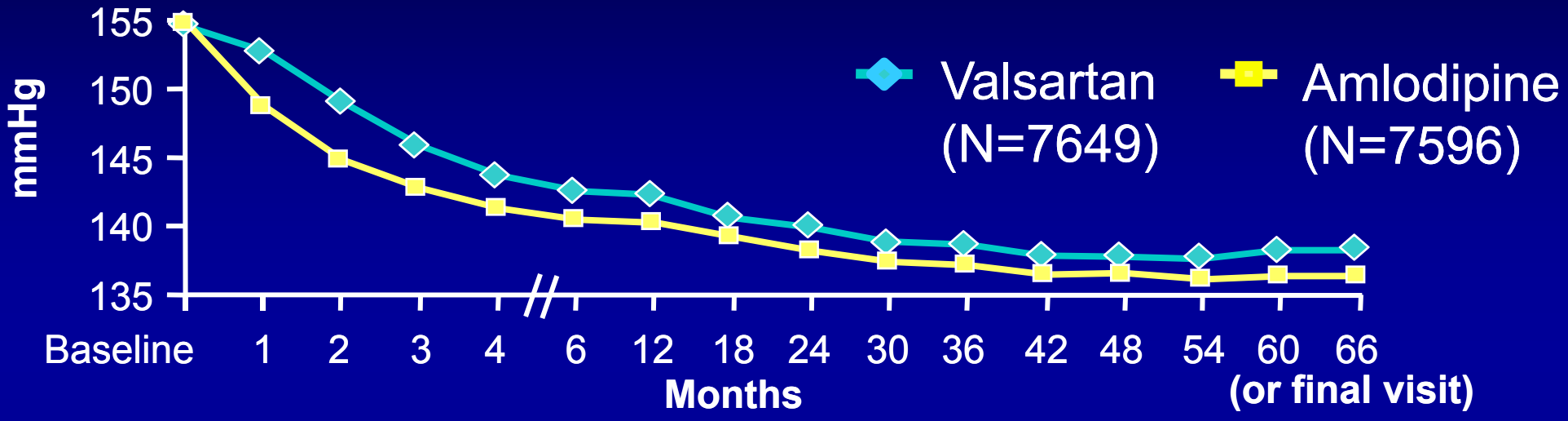
Number at risk

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

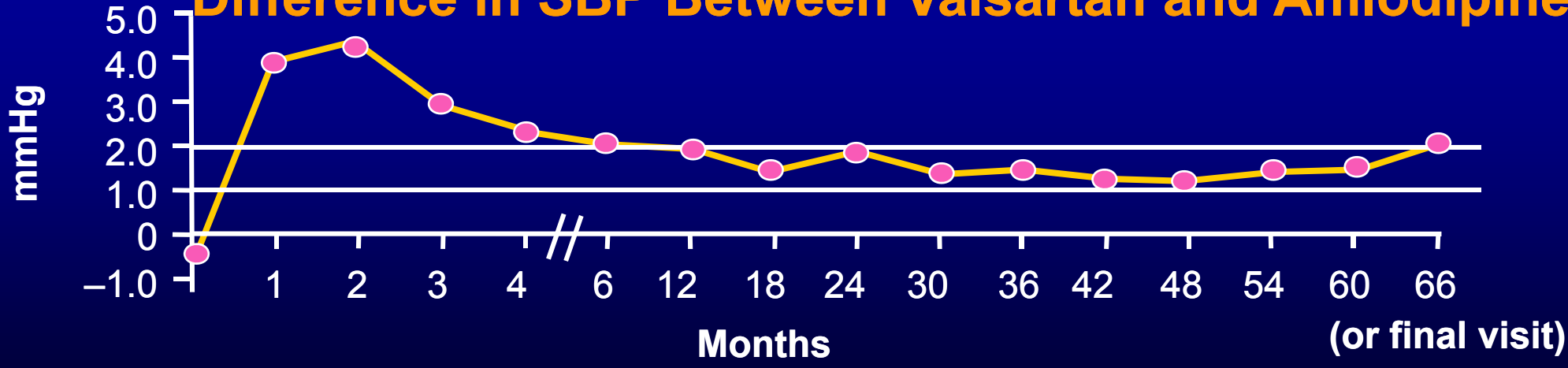
Julius S et al. *Lancet*. June 2004;363.

VALUE: Systolic BP in Study

Sitting SBP by Time and Treatment Group

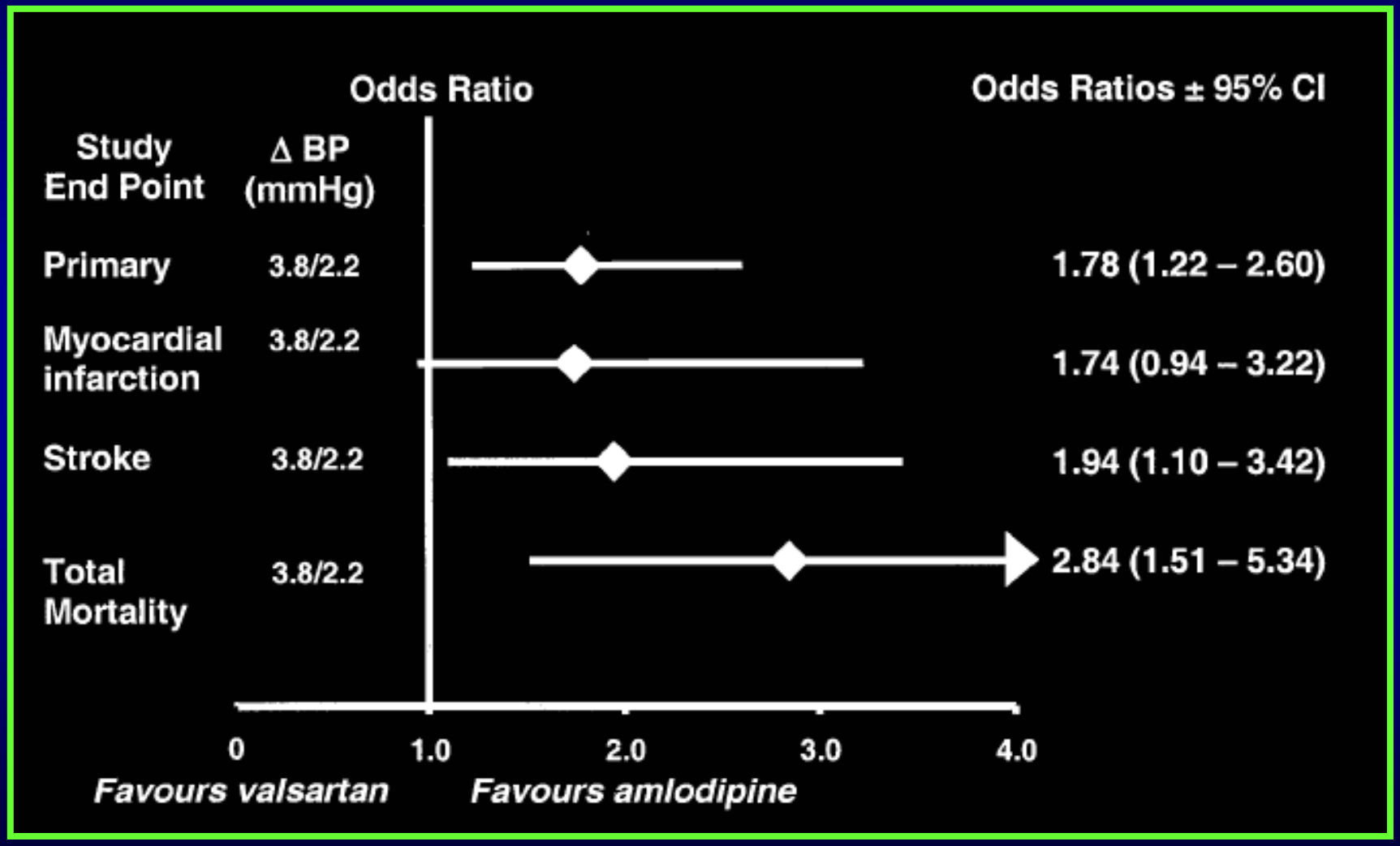


Difference in SBP Between Valsartan and Amlodipine



Julius S et al. *Lancet*. June 2004;363.

VALUE: Outcome and SBP Differences



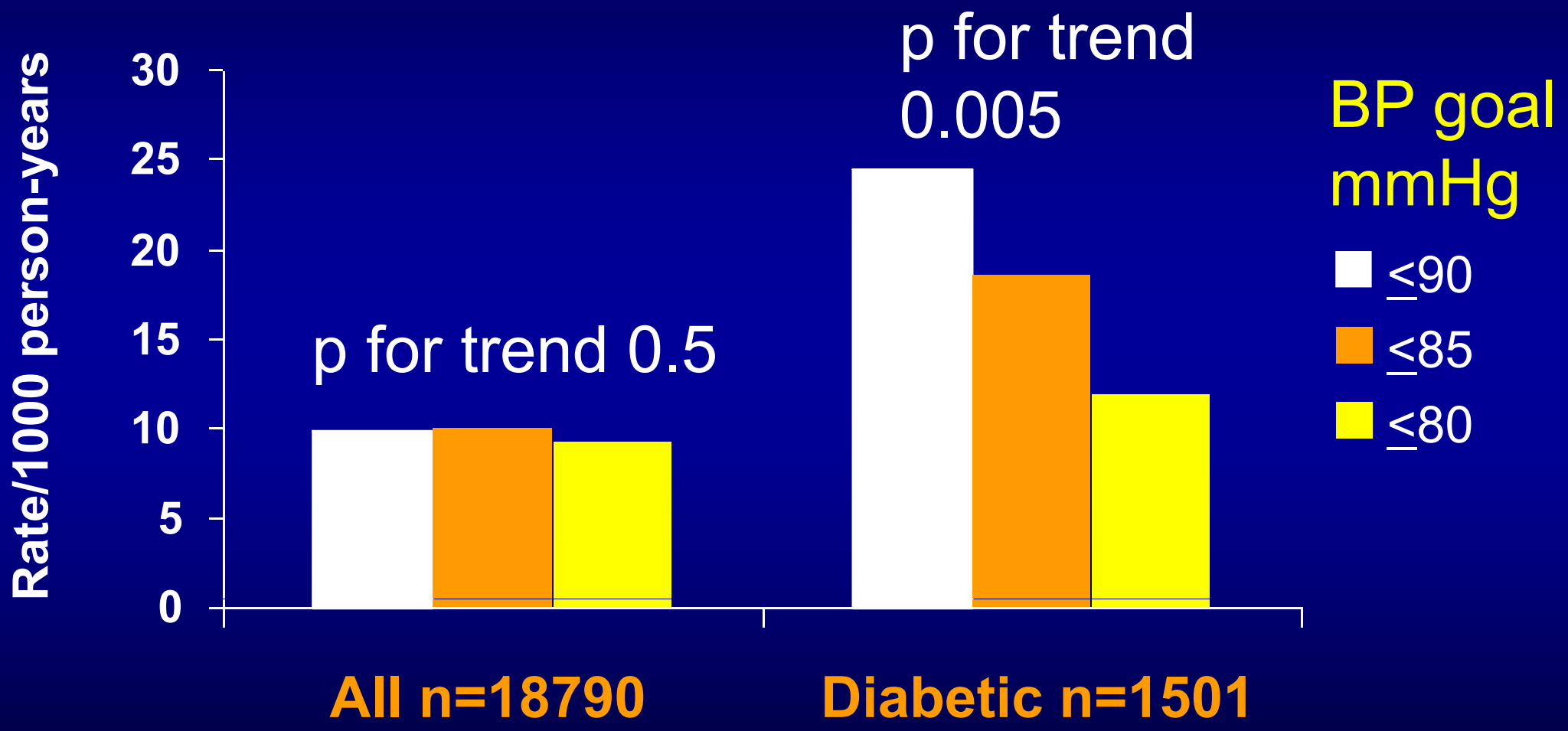
New ESC Guideline: Early Treatment

Blood pressure (mmHg)					
Other risk factors OD or disease	Normal SBP 120–129 or DBP 80–84	High normal SBP 130–139 or DBP 85–89	Grade 1 HT SBP 140–159 or DBP 90–99	Grade 2 HT SBP 160–179 or DBP 100–109	Grade 3 HT SBP ≥180 or DBP ≥110
No other risk factors	No BP intervention	No BP intervention	Lifestyle changes for several months then drug treatment if BP uncontrolled	Lifestyle changes for several weeks then drug treatment if BP uncontrolled	Lifestyle changes + Immediate drug treatment
1–2 risk factors	Lifestyle changes	Lifestyle changes	Lifestyle changes for several weeks then drug treatment if BP uncontrolled	Lifestyle changes for several weeks then drug treatment if BP uncontrolled	Lifestyle changes + Immediate drug treatment
≥3 risk factors, MS or OD	Lifestyle changes	Lifestyle changes and consider drug treatment	Lifestyle changes + Drug treatment	Lifestyle changes + Drug treatment	Lifestyle changes + Immediate drug treatment
Diabetes	Lifestyle changes	Lifestyle changes + Drug treatment			
Established CV or renal disease	Lifestyle changes + Immediate drug treatment	Lifestyle changes + Immediate drug treatment	Lifestyle changes + Immediate drug treatment	Lifestyle changes + Immediate drug treatment	Lifestyle changes + Immediate drug treatment

Better Outcome in HT

- **Agents with beyond BP lowering ?**
- **Rapid BP lowering in high-risk patients**
- **Lower BP target in high-risk patients**

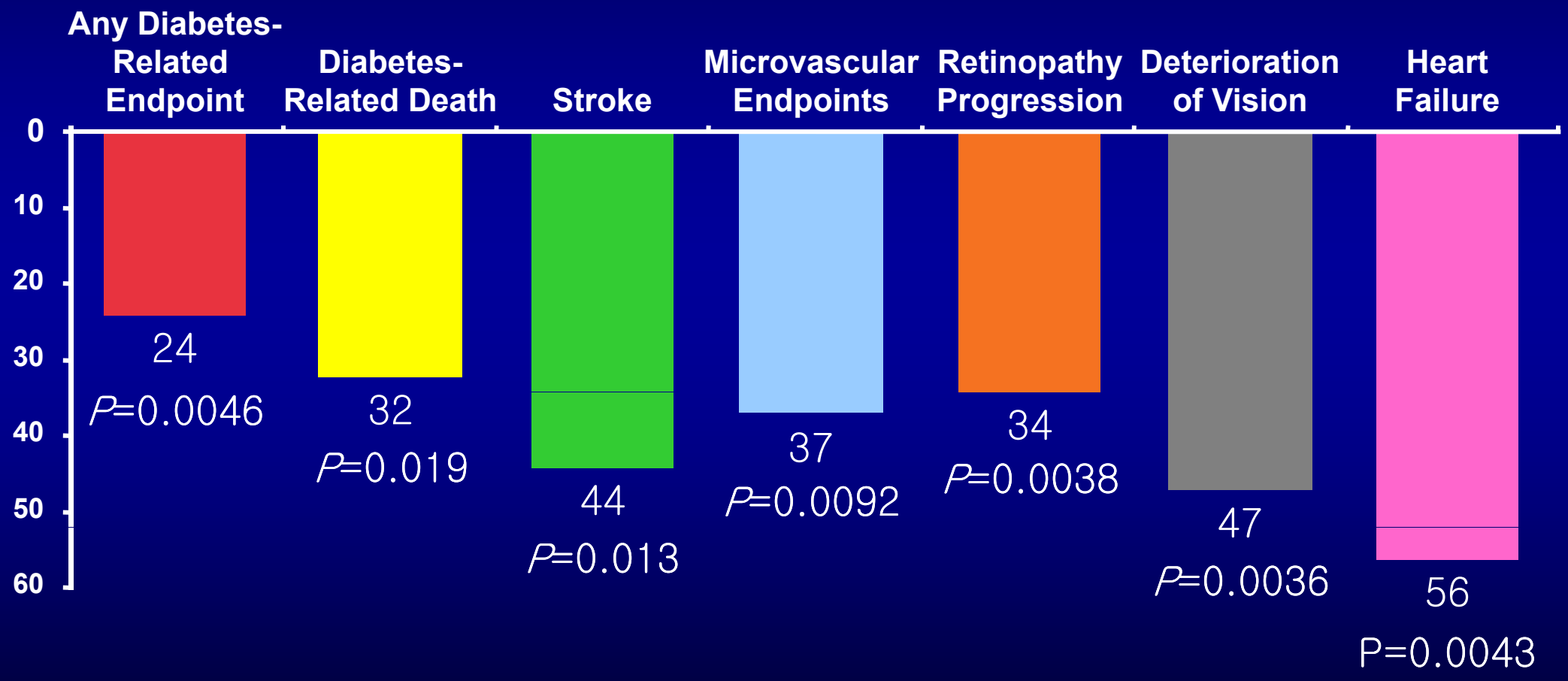
HOT – Rate of Major CV Events



Hansson et al., Lancet 1998

UKPDS: Tight BP Control

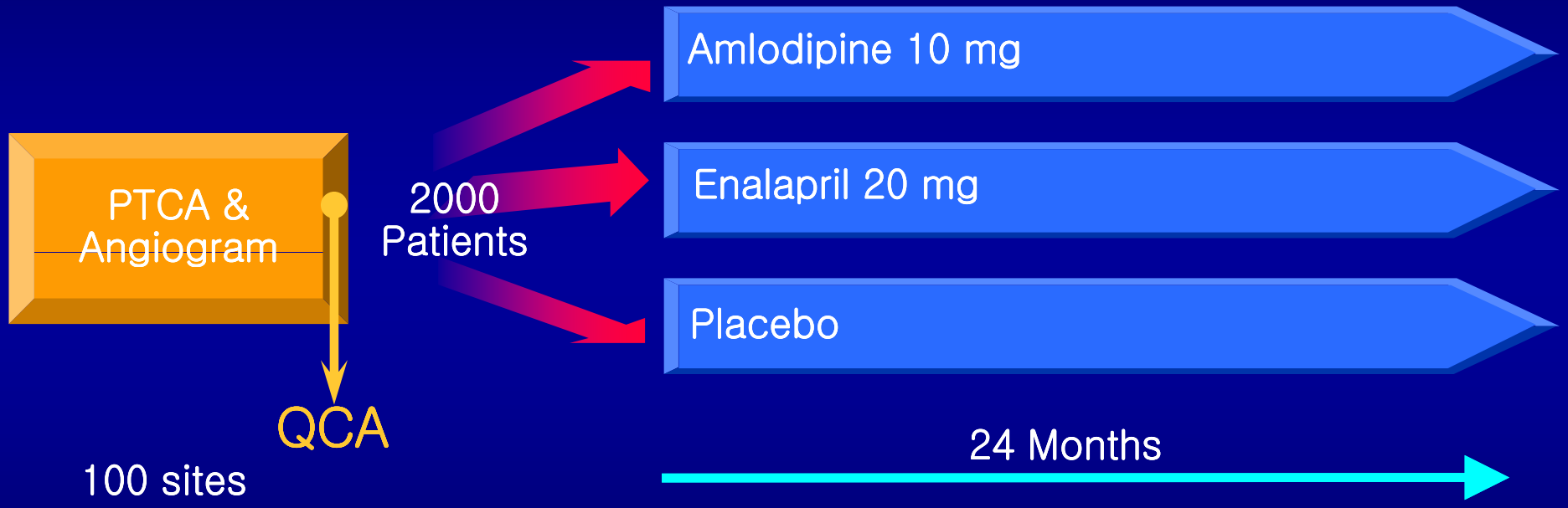
Tight group 144/82 mmHG vs less tight 154/87 mmHG



*Compared with less tight control. Captopril and atenolol were equally effective in reducing risk and were equally safe in patients with diabetes.
UKPDS Group. *BMJ*. 1998;317:703-713.

CAMELOT Study Design

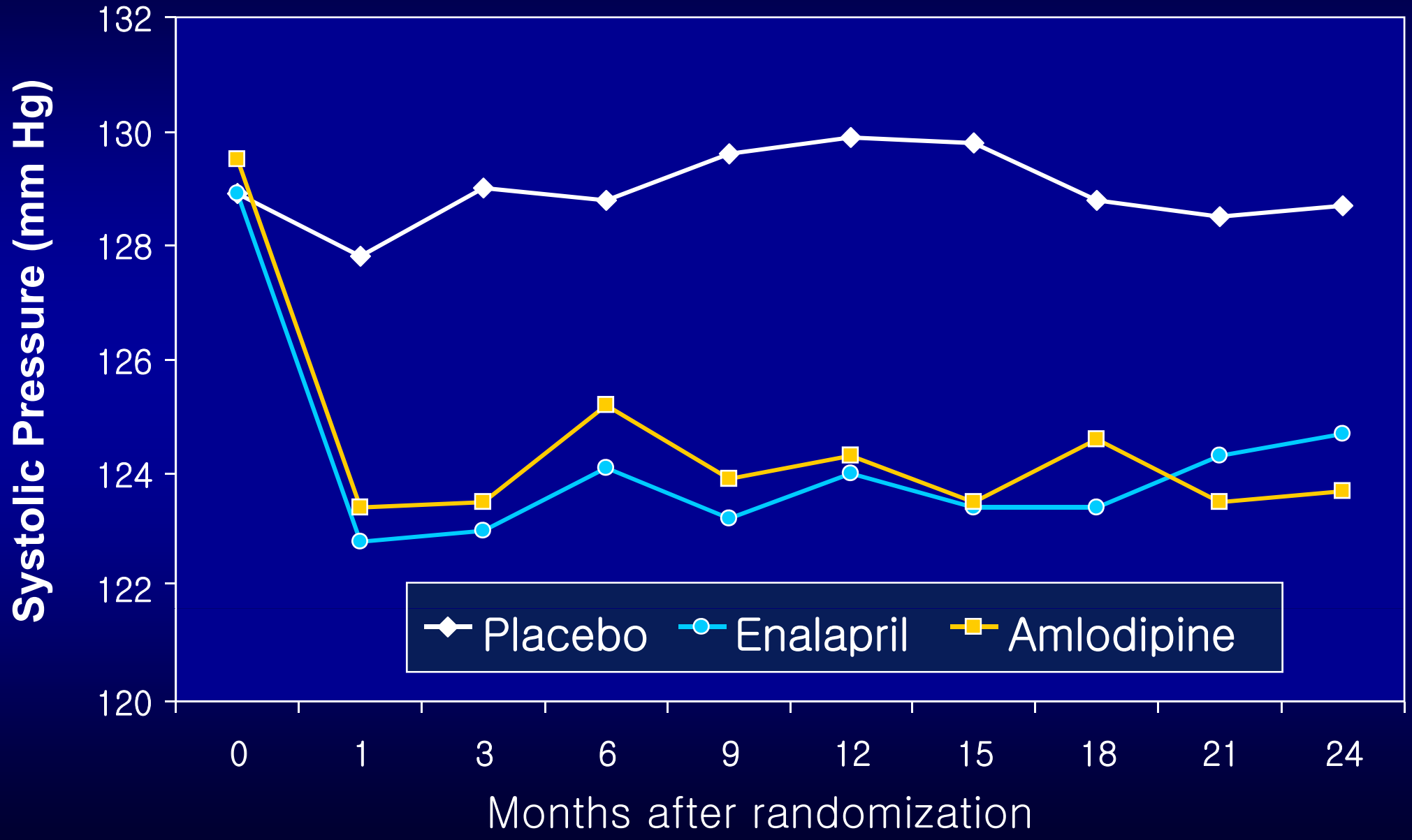
Comparison of Amlodipine versus Enalapril to Limit Ischemic Occurrences of Thrombosis



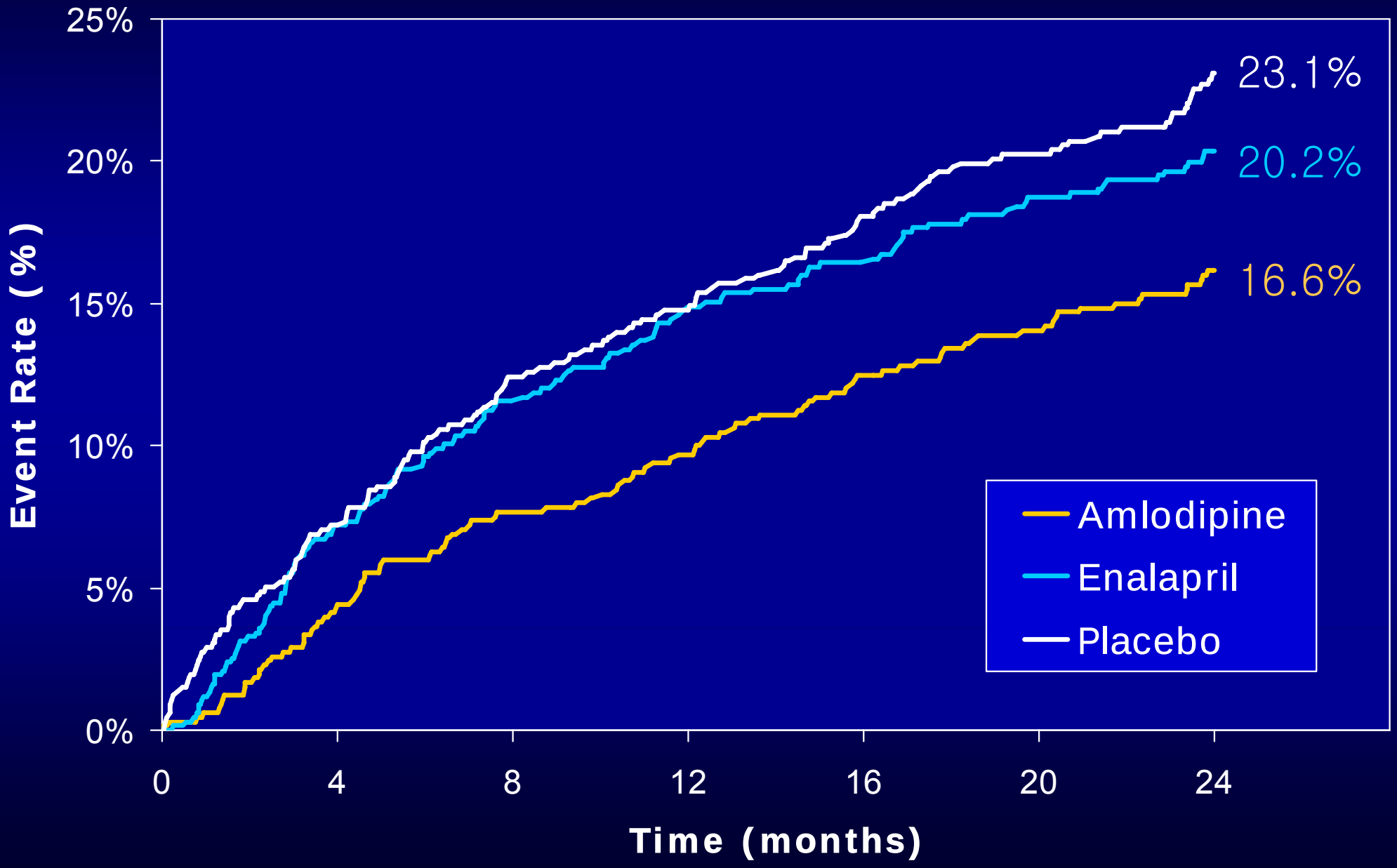
Prospective, Randomized, Double Blind, Multicenter

Endpoints: CHD Death, Resuscitated Arrest, Nonfatal MI, Stroke, TIA, CABG, Revascularization, Unstable Angina, Hospitalized CHF

CAMELOT: Systolic BP



CAMELOT: Time to Major CV Event



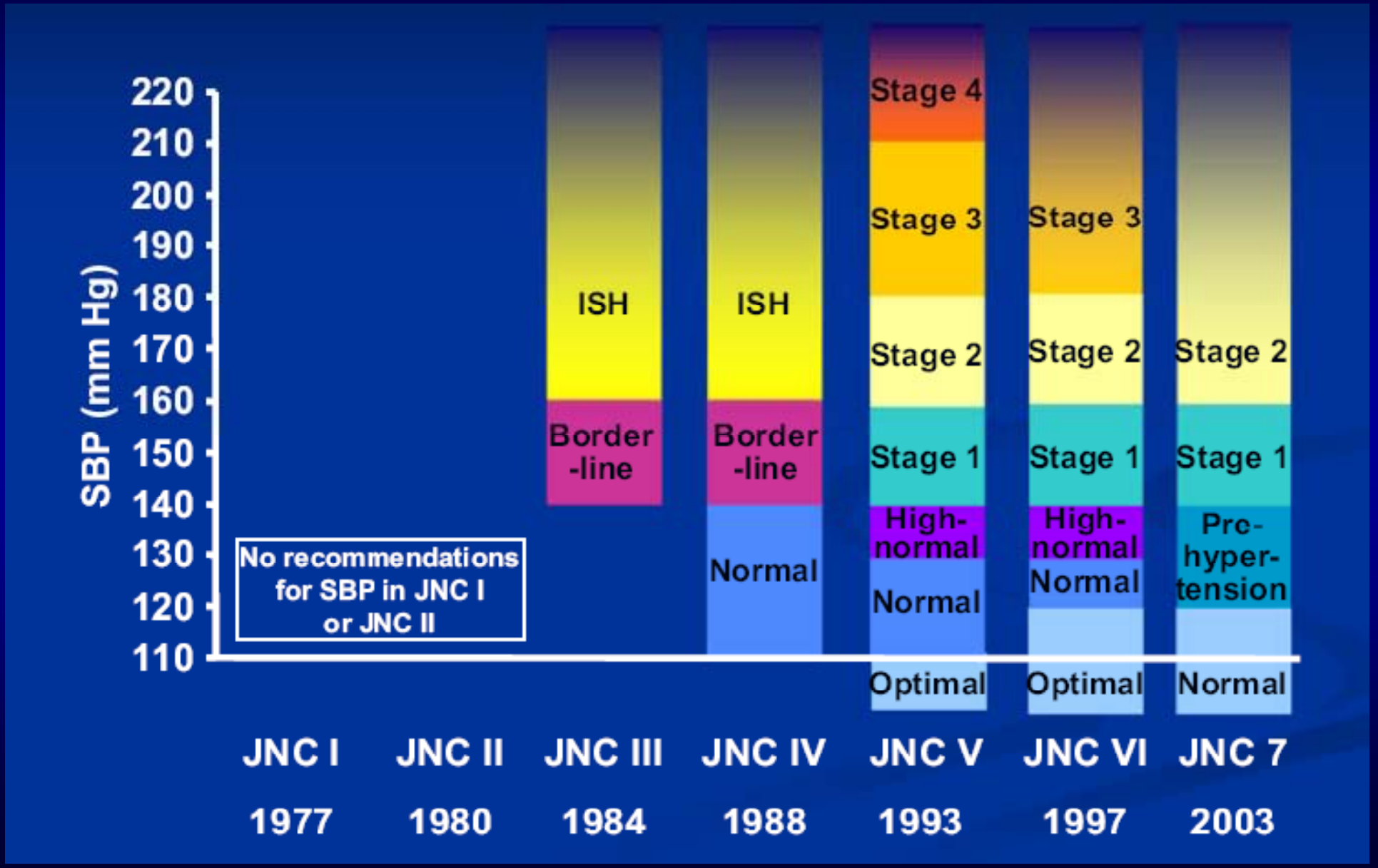
ESC Guidelines for Target BP

- In hypertensive patients, the primary goal of treatment is to achieve maximum reduction in the long-term total risk of cardiovascular disease.
- This requires treatment of the raised BP per se as well

Target BP should be at least <130/80 mmHg in diabetics and in high or very high risk patients, such as those with associated clinical conditions (stroke, myocardial infarction, renal dysfunction, proteinuria).

betics and in high or very high risk patients, such as those with associated clinical conditions (stroke, myocardial infarction, renal dysfunction, proteinuria).

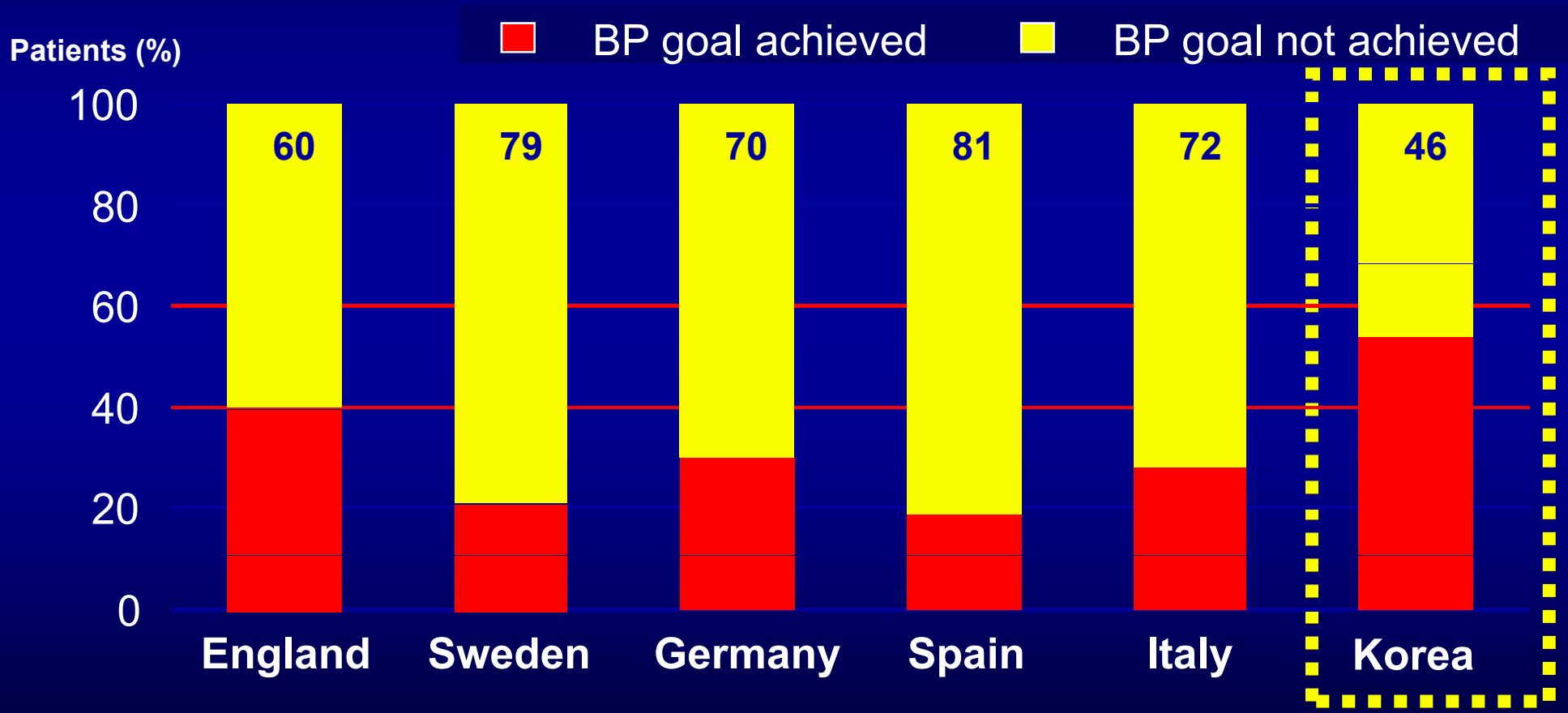
Evolution of JNC Guidelines



Better Outcome in HT

- **Agents with beyond BP lowering ?**
- **Rapid BP lowering in high-risk patients**
- **Lower BP target in high-risk patients**
- **Improve target BP lowering: adherence**

Target BP Lowering

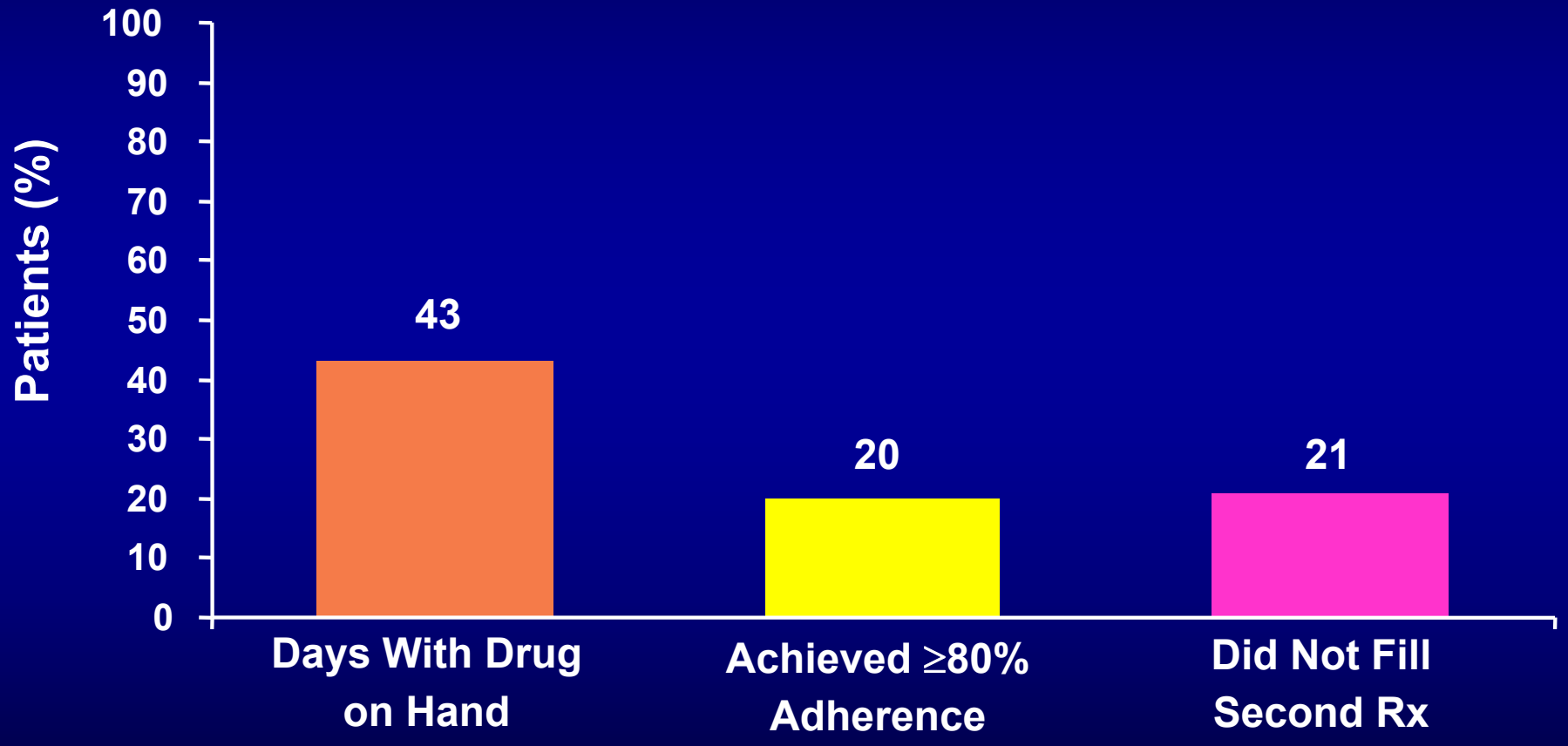


*Treated for hypertension
BP goal is <140/90 mmHg

Source: Wolf-Maier et al. Hypertension 2004;43:10–17;
Korea National Health and Nutrition Survey 2005

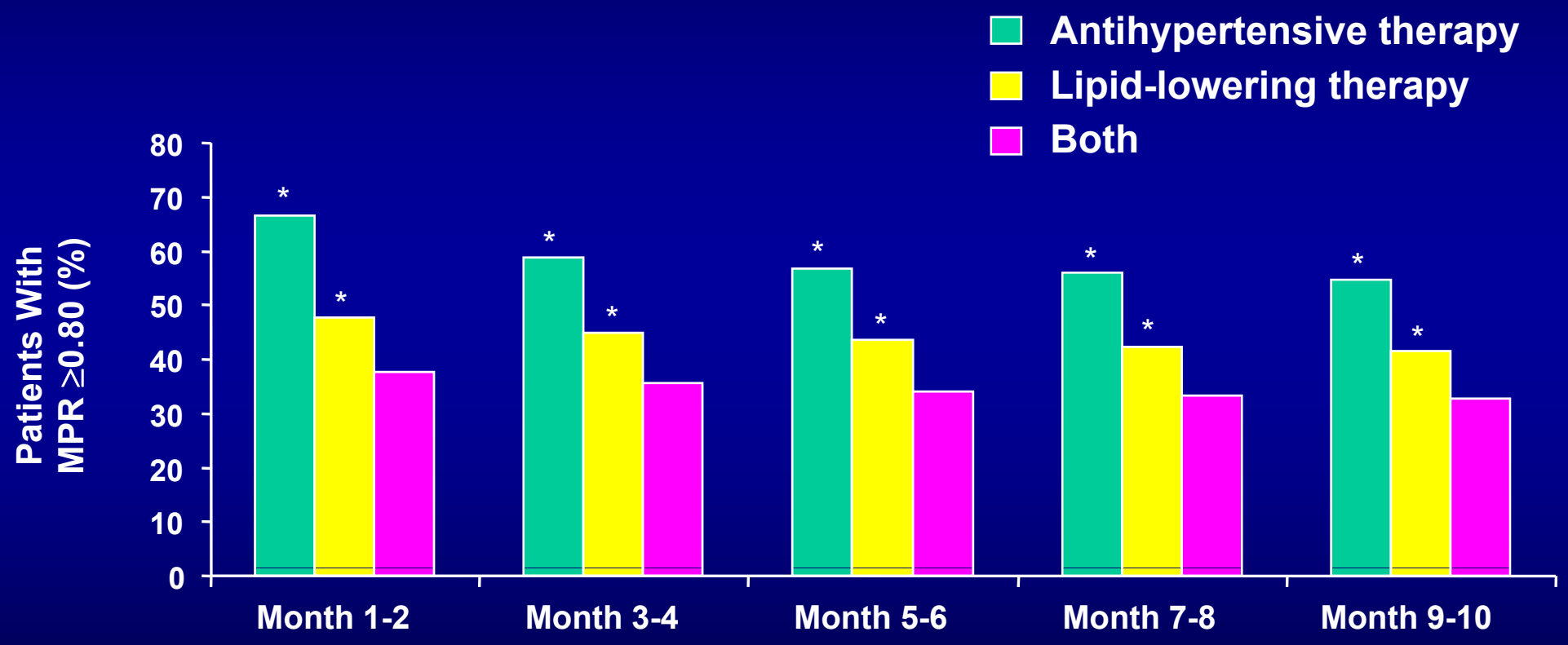
Nonadherence With Antihypertensive Medication

1-year retrospective study in new starters (N = 8643)



Monane M et al. *Am J Hypertens.* 1997;10:697-704.

Medication Adherence Declines When a Second Drug Is Prescribed

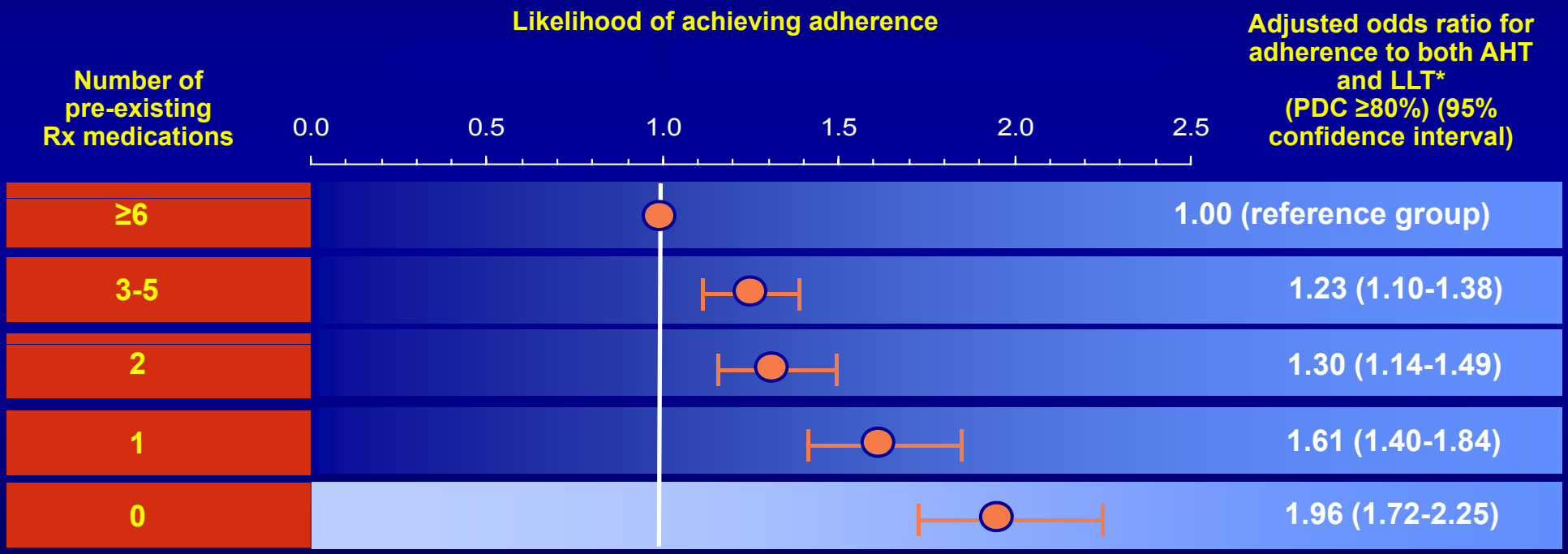


*$P < .05$ vs both.

Schwartz JS et al. *J Am Coll Cardiol*. 2003;41(6 suppl A):526A. Abstract 1095-57.

Lower Pill Burden
better adherence to AHT and LLT

As the number of pre-existing Rx meds increased, the likelihood of adequately refilling AHT and LLT decreased



*P<0.001 for all groups versus reference group.

Retrospective cohort study of a managed care population. N=8406 patients with hypertension who added AHT and LLT to existing Rx meds within a 90-day period. Adherence to concomitant therapy: sufficient AHT and LLT Rx meds to cover ≥80% of days per 91-day period.

Chapman RH, et al. *Arch Intern Med*. 2005;165:1147-1152.

ESC Guidelines on Combination Therapy

- **More than one agent is necessary to achieve target BP in the majority of patients**
- **Fixed combinations of two drugs simplify treatment/favor compliance**

Task Force of ESH/ESC. J Hypertens 2007;25:1105–87

Adherence is fundamental to better cardiovascular (CV) health

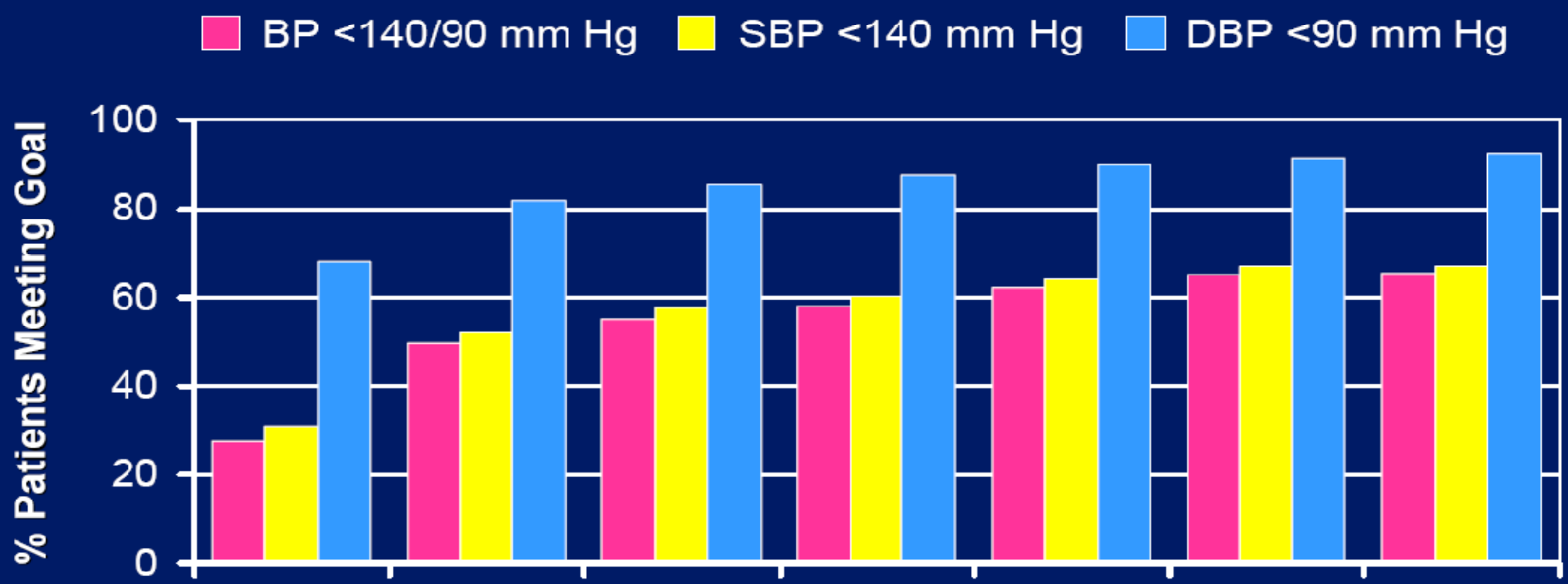
"Drugs don't work in patients who don't take them."

— C. Everett Koop, (Former US Surgeon General)

Better Outcome in HT

- **Agents with beyond BP lowering ?**
- **Rapid BP lowering in high-risk patients**
- **Lower BP target in high-risk patients**
- **Improve target BP lowering: adherence**
- **Global risk management: “Add statin”**

Target BP lowering in ALLHAT

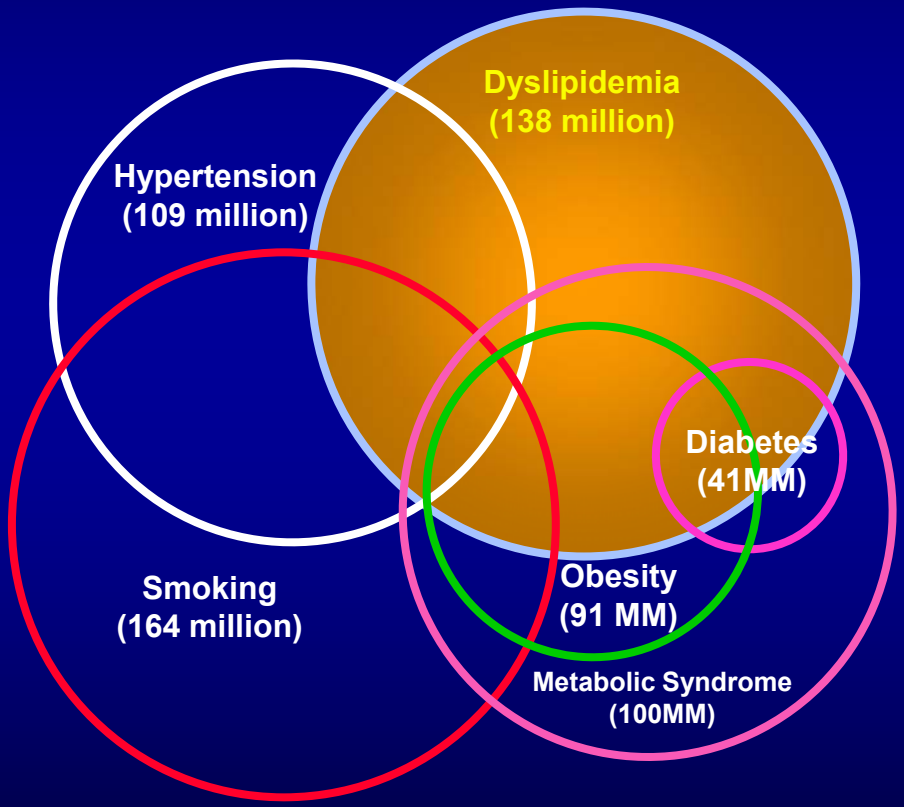


	Baseline	6 mo	1 y	2 y	3 y	4 y	5 y
Mean BP	145/83	140/81	138/79	137/78	136/77	135/76	135/75
No drugs	–	1.3	1.4	1.6	1.7	1.8	2.0

Cushman et al. *J Clin Hypertens*. 2002;4:393-404.

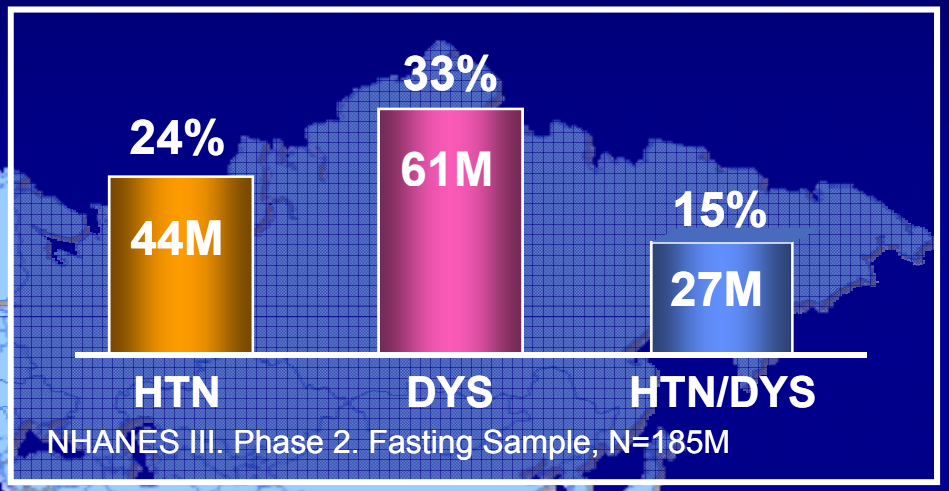
Global Risk Management

Millions of people, WW*, 2000



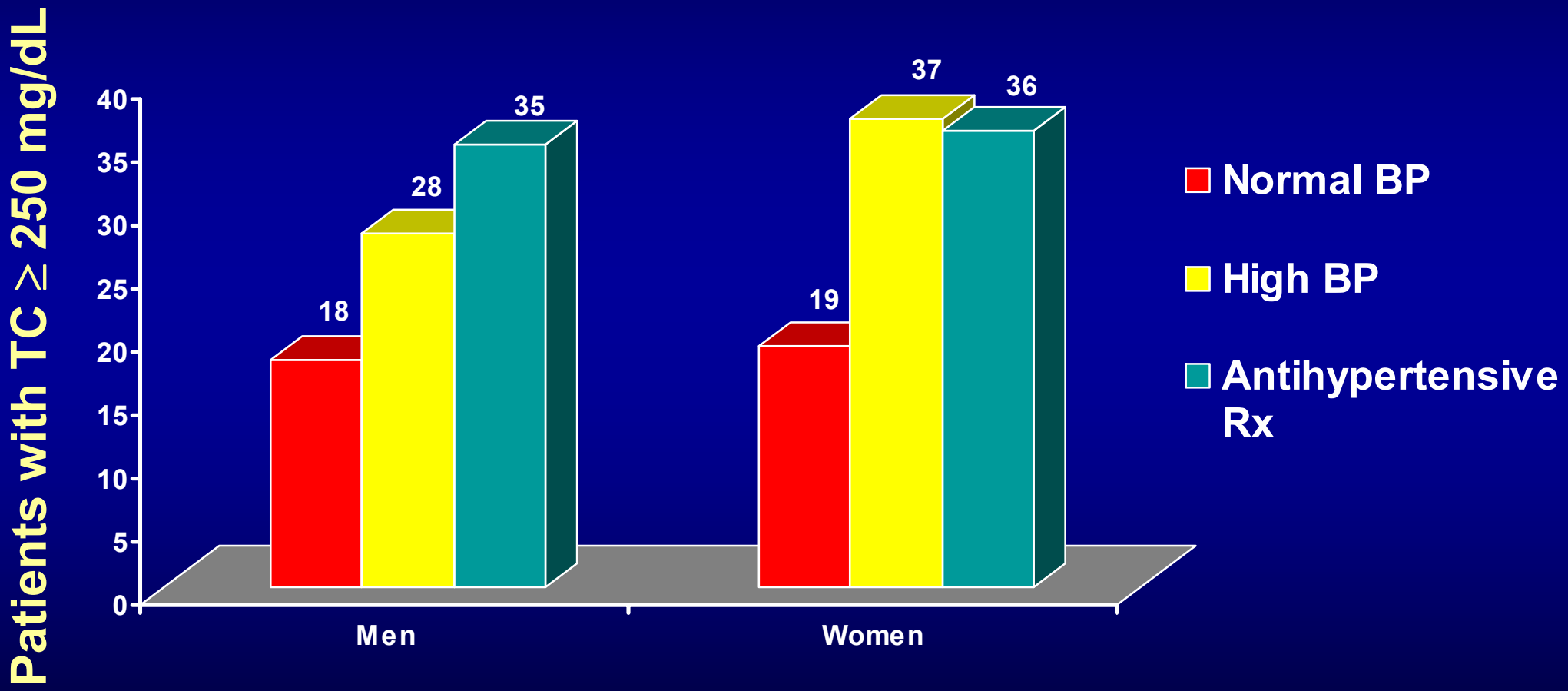
*7 countries: U.S., U.K., Italy, Germany, France, Spain, and Japan; population 706 million
Source:Decision Resources; Cardiovascular Outlook; DataMonitor

Concurrent Hypertension and Dyslipidemia Is Very Prevalent



15%
27 Million Patients

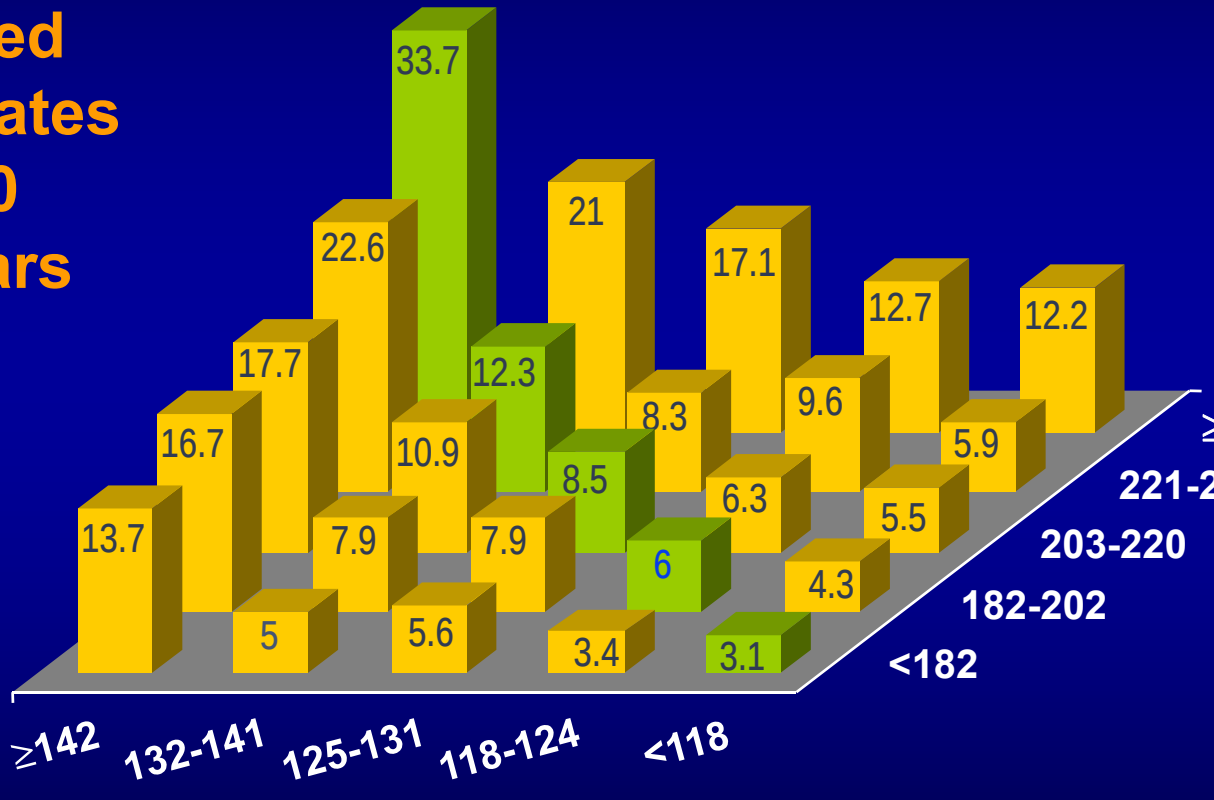
Hypercholesterolemia Is Common in Patients With Hypertension*



MacMahon SW, et al. *Arteriosclerosis*. 1985;5:391–396.

SBP and Cholesterol on CHD Death Rate

Age-adjusted CHD death rates per 10,000 person-years

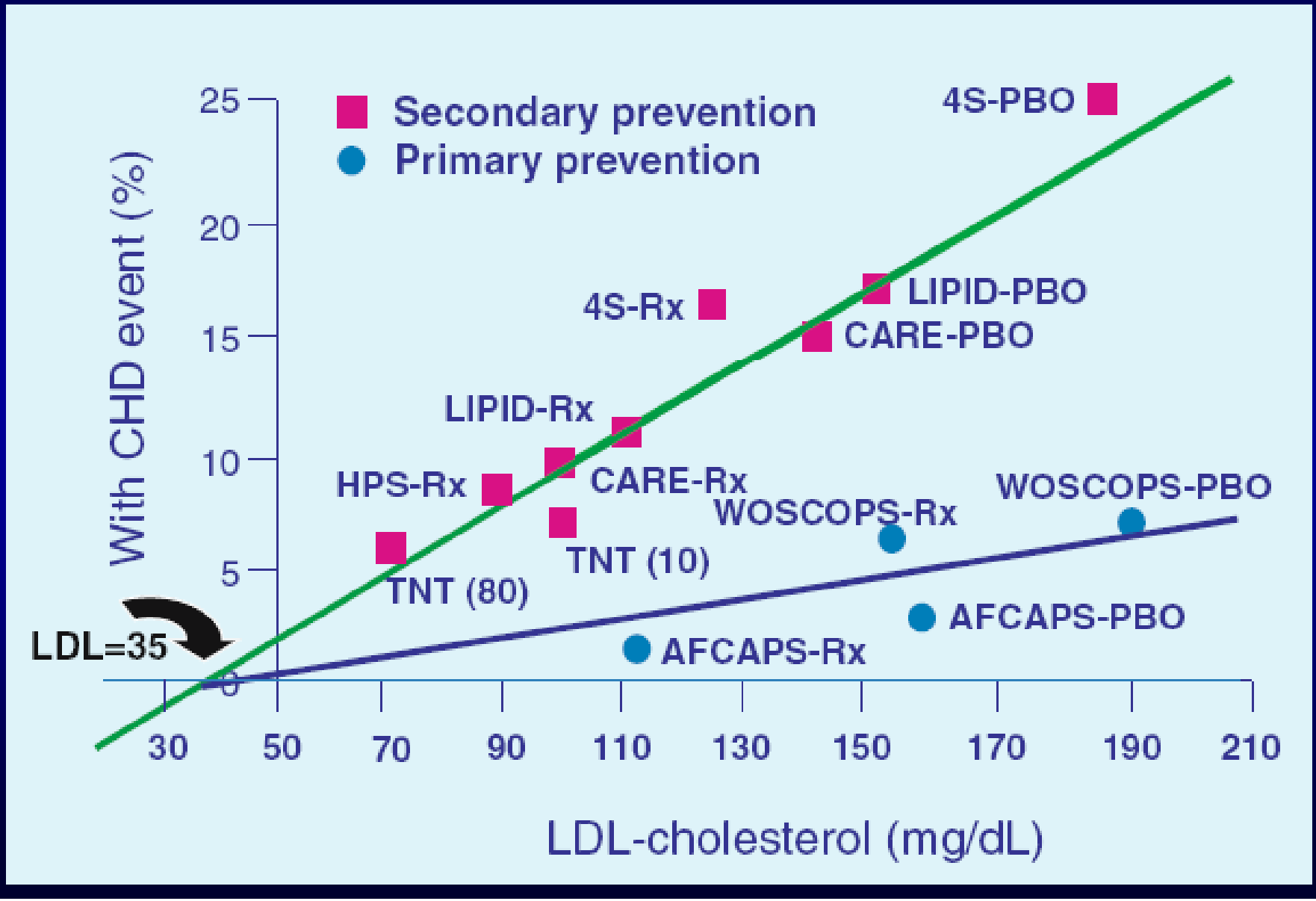


Neaton JD et al. *Arch Intern Med* 1992;152:56-63.

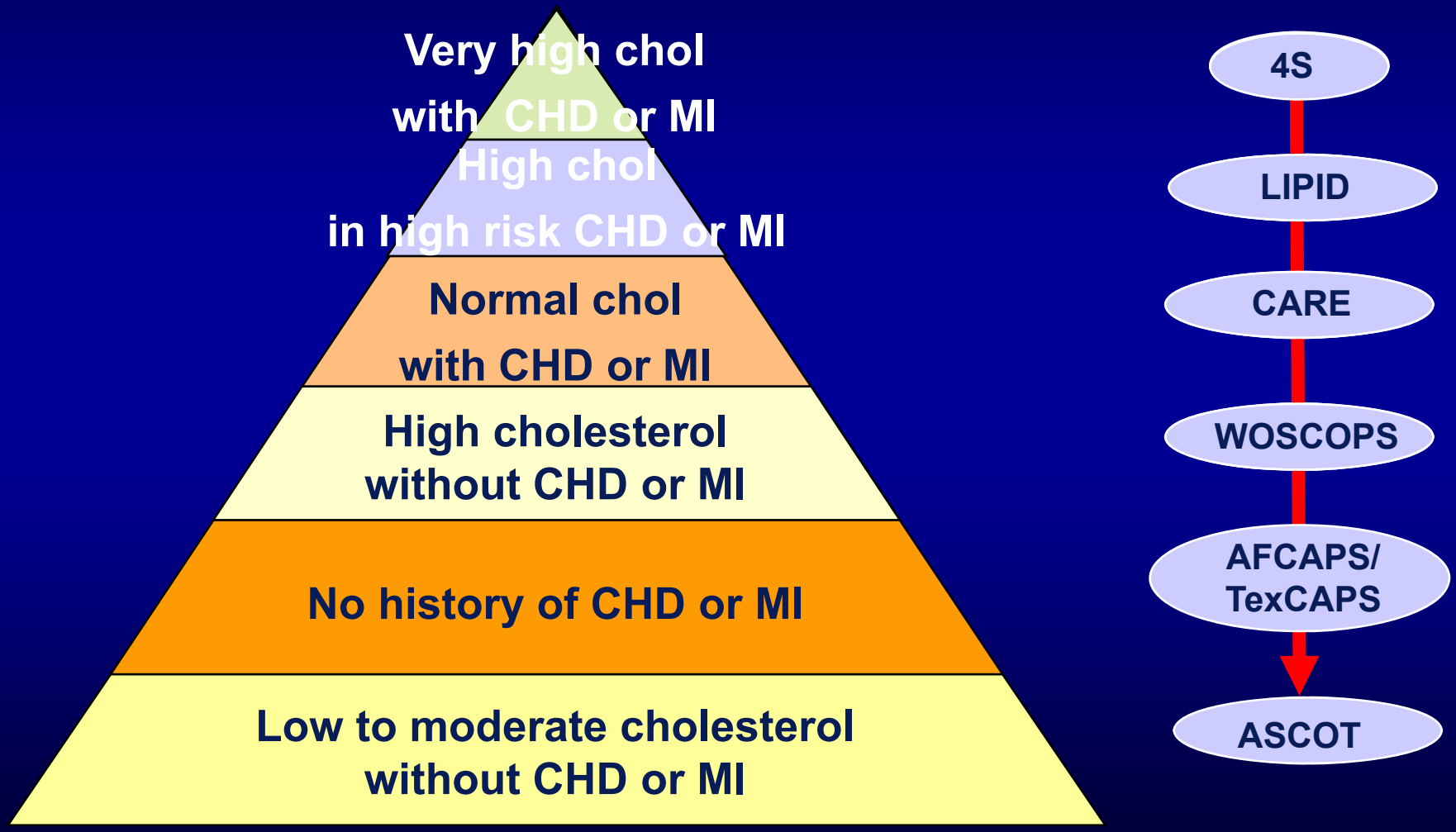
Evolution of Management of Hypercholesterolemia

Guideline (reference)	Year	High risk (CHD or CHD risk equivalent; 10-year risk >20%)	Moderately high risk (2+ risk factors; 10-year risk 10% to 20%)	Moderate risk (2+ risk factors; 10-year risk <10%)	Low risk (0–1 risk factor)
NCEP ATP I [86]	1988	←	<130 mg/dL	→	<160 mg/dL
NCEP ATP II [87]	1994	≤100 mg/dL	←	<130 mg/dL →	<160 mg/dL
NCEP ATP III [8]	2002	<100 mg/dL	←	<130 mg/dL* →	<160 mg/dL
NCEP ATP III update [88]	2004	<100 mg/dL or <70 mg/dL[b]	<130 mg/dL or <100 mg/dL[‡]	<130 mg/dL	<160 mg/dL

Evolution of Management of Hypercholesterolemia



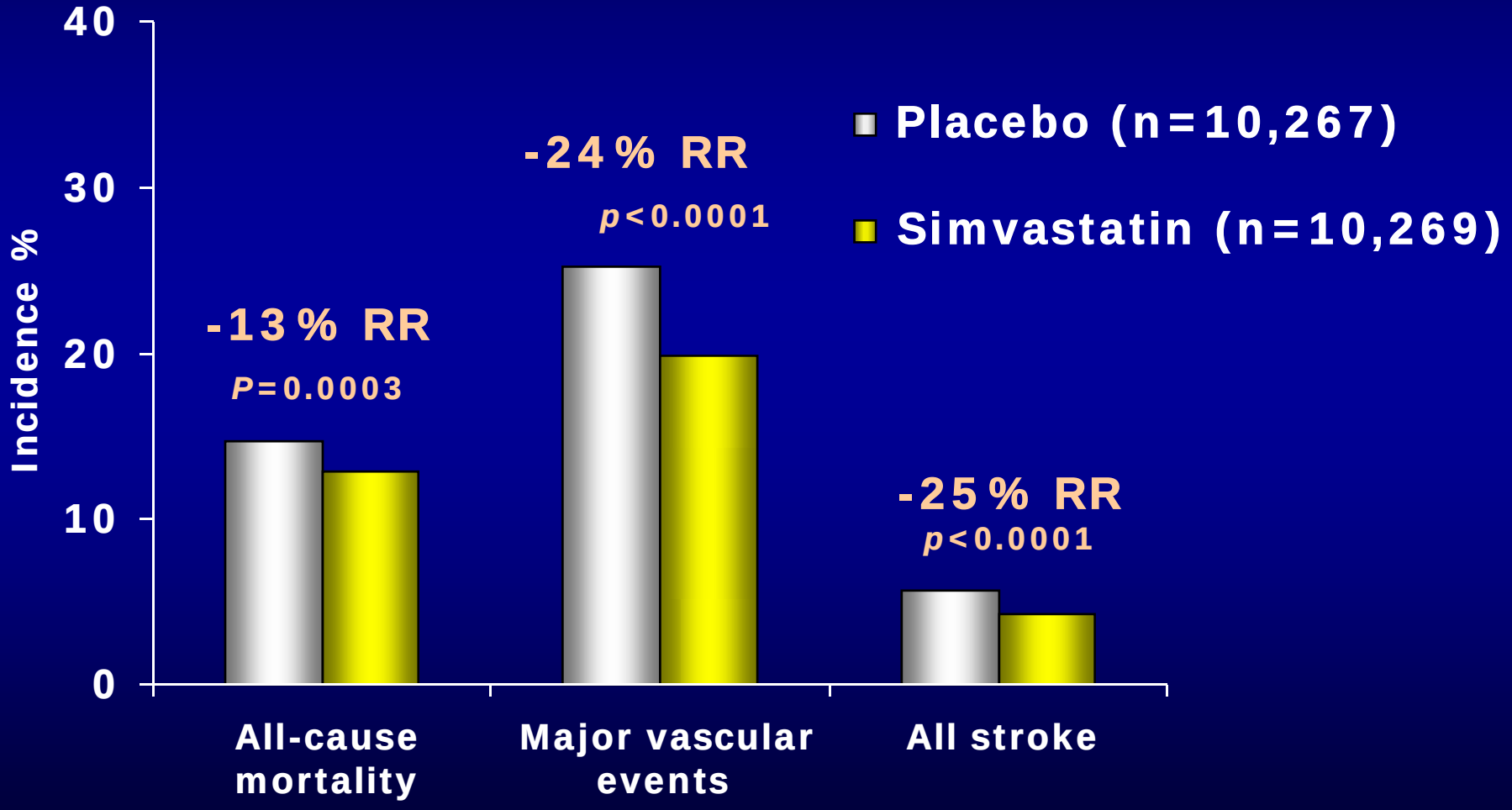
The Pyramid of Recent Trials



How About in Patients with Normal Cholesterol ?

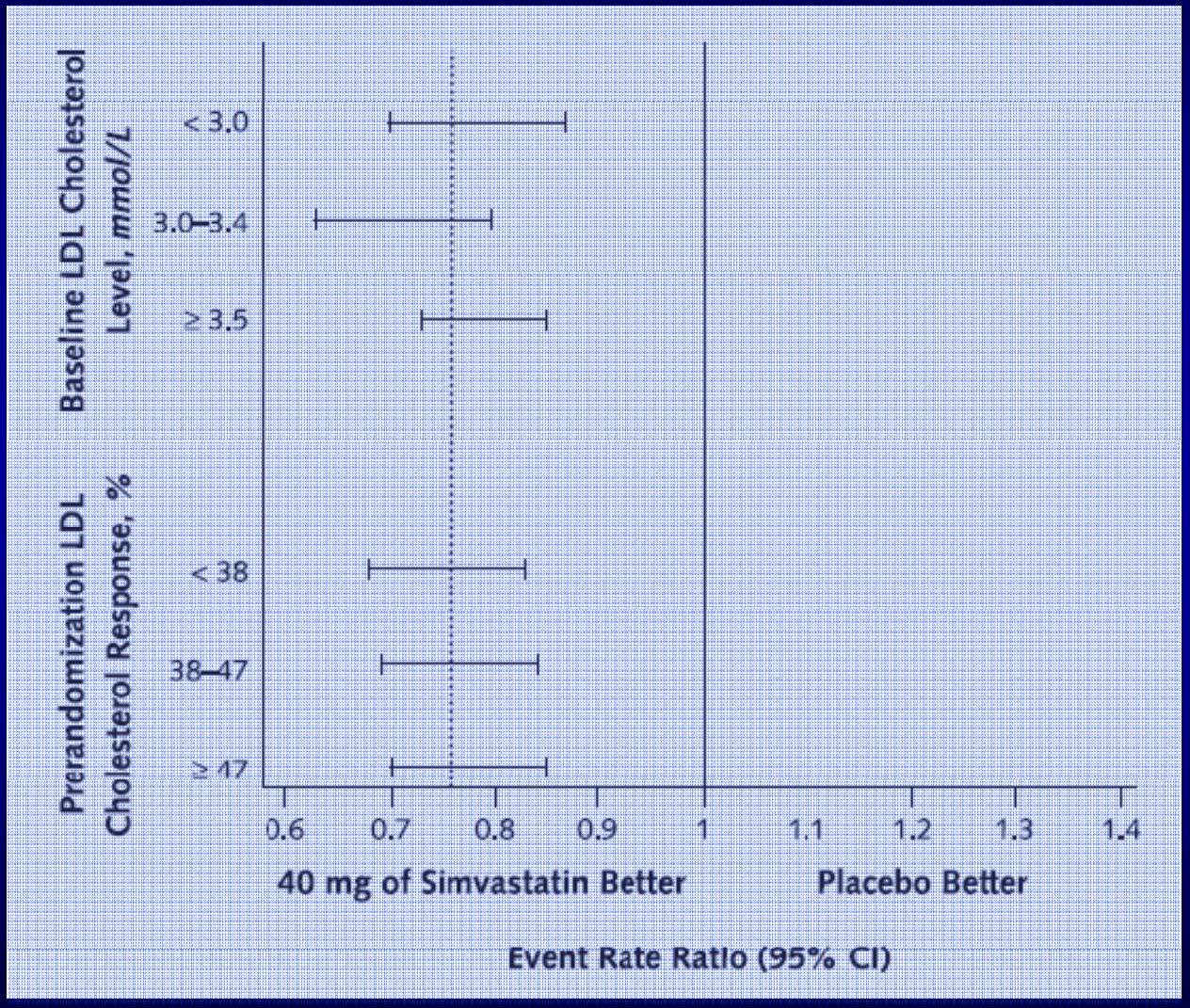
Heart Protection Study

20,000 pt with CHD or at high risk (TC >135 mg/dl)

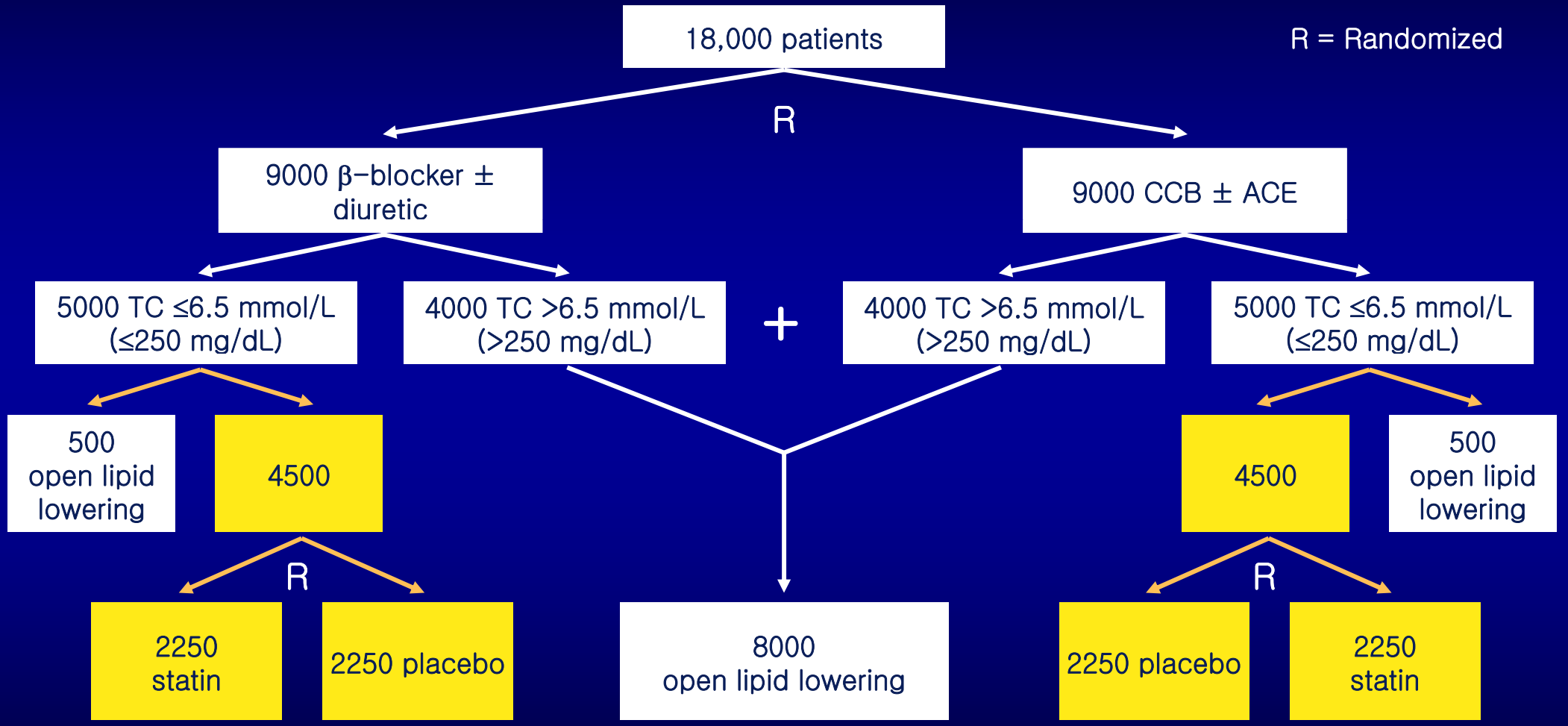


Adapted from HPS Collaborative Group, *Lancet* 2002;**360**:7–22

Heart Protection Study



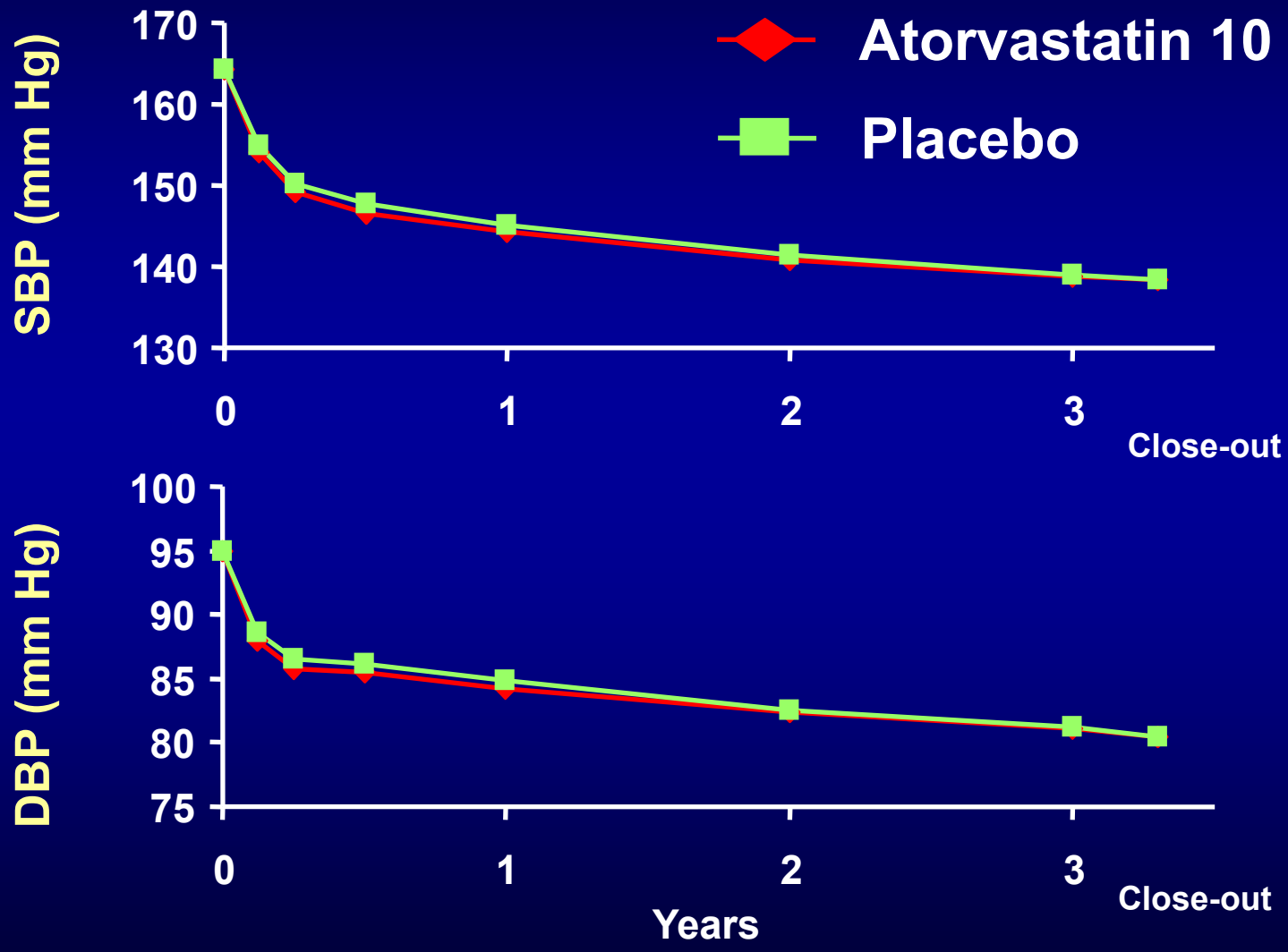
ASCOT Study Design



These are the target numbers of patients.

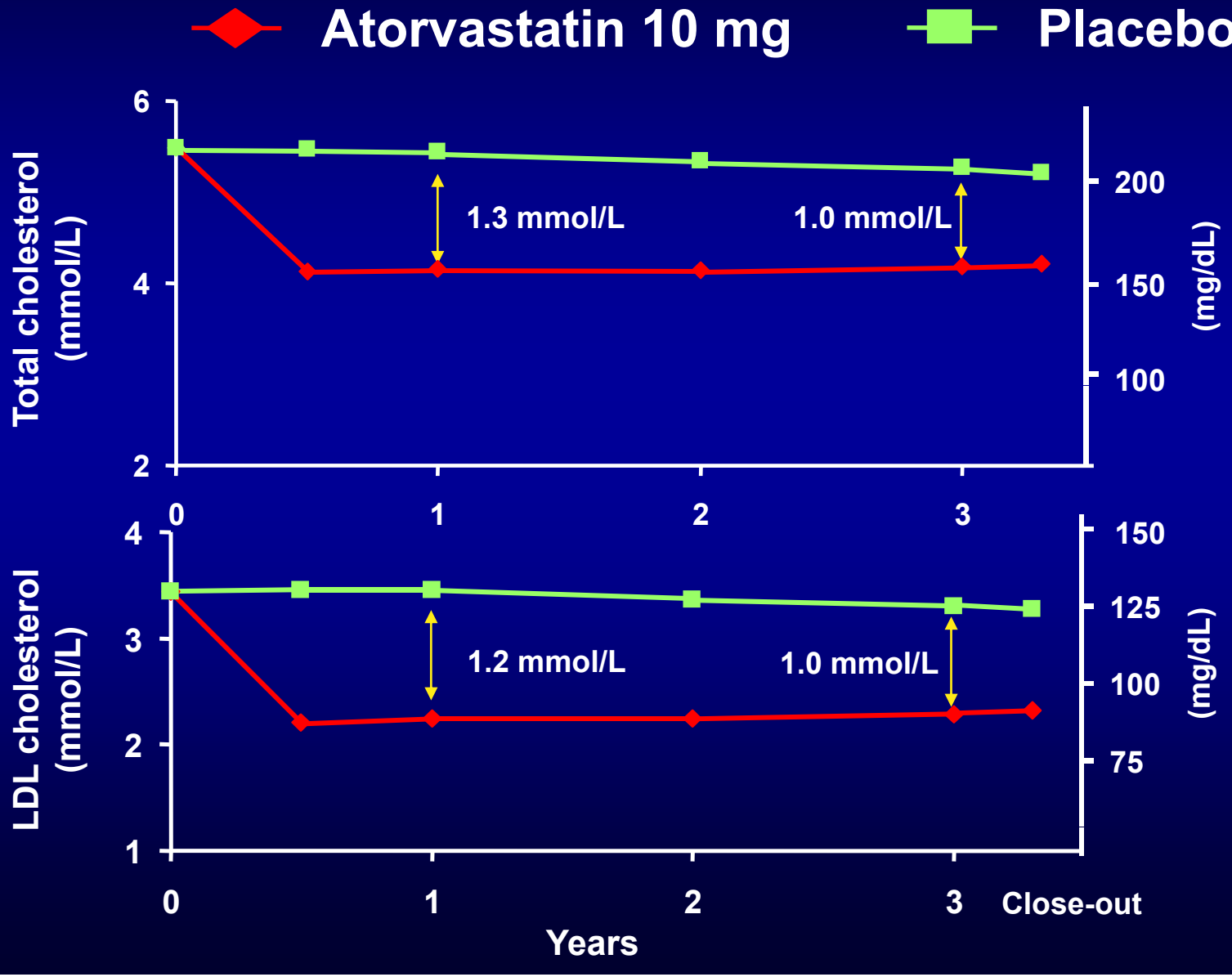
Sever PS, et al, for the ASCOT investigators. *J Hypertens*. 2001;19:1139–1147.

ASCOT–LLA: BP changes

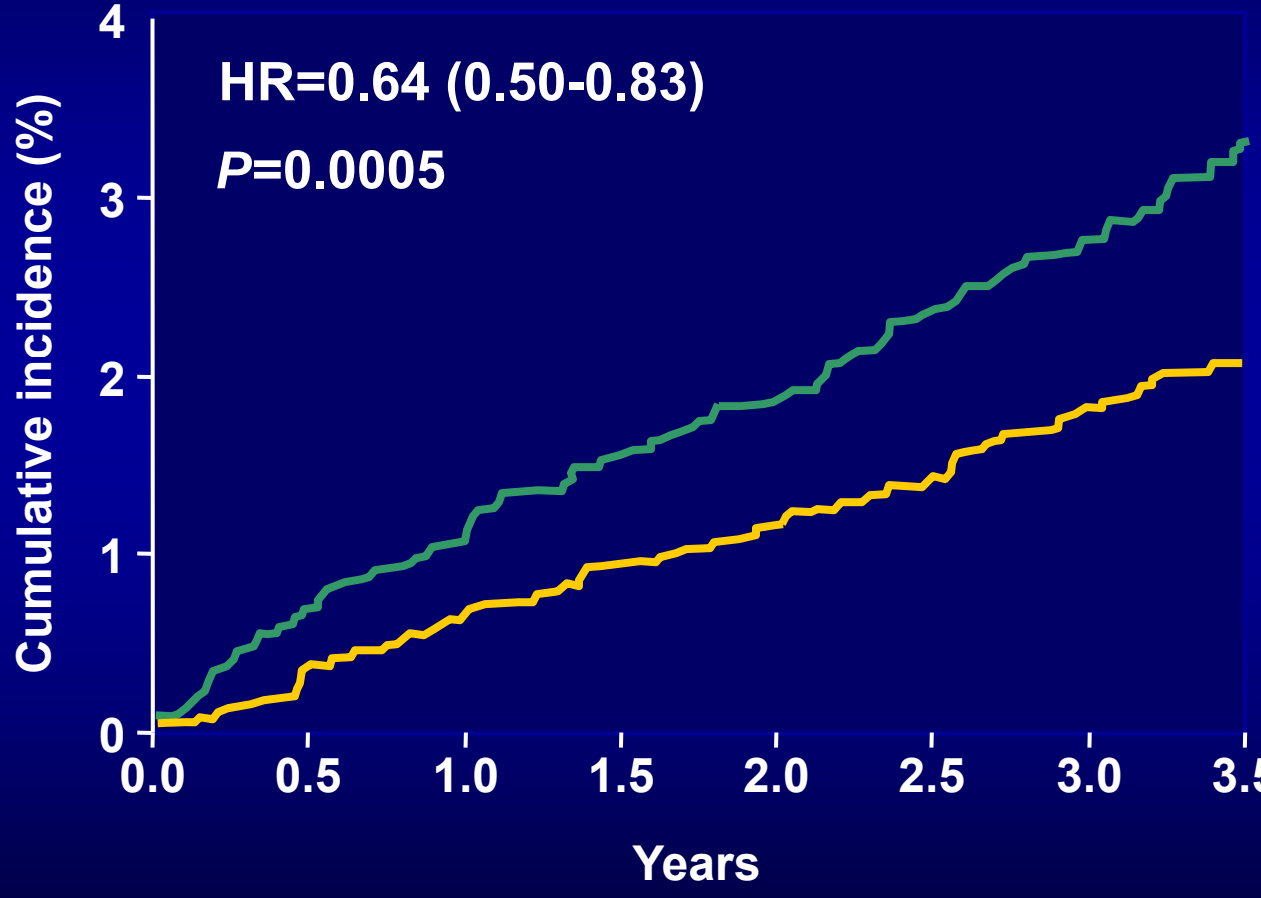


Sever PS, Dahlöf B, Poulter N, Wedel H, et al, for the ASCOT Investigators. Lancet. 2003;361:1149-58

ASCOT–LLA: cholesterol changes



ASCOT–LLA: nonfatal MI & fatal CHD



36% reduction

Atorvastatin 10mg

Placebo

Sever PS et al. Lancet 2003;361:1149-1158

ASCOT–LLA

"Benefits are Independent of Baseline Cholesterol"

Baseline TC (mg/dl)	RR	p
< 5,0 (193)	0.63	0.098
5,0 – 5,99 (193-231)	0.62	0.011
> 6,0 (231)	0.69	0.084

ASCOT BPLA and LLA Combined

Rates/1000 Patient-Years

End Point	Amlodipine ± Perindopril + Atorvastatin	Atenolol ± Thiazide + Placebo	Relative Risk Reduction
Nonfatal MI and fatal CHD	**4.6**	**9.0**	**48%**
Fatal and nonfatal stroke	**4.2**	**8.6**	**44%**

Sever P et al. *Eur Heart J*. 2006;27:2982-2988;
http://www.ascotstudy.org/healthcare_professionals/slides_and_resources.htm.

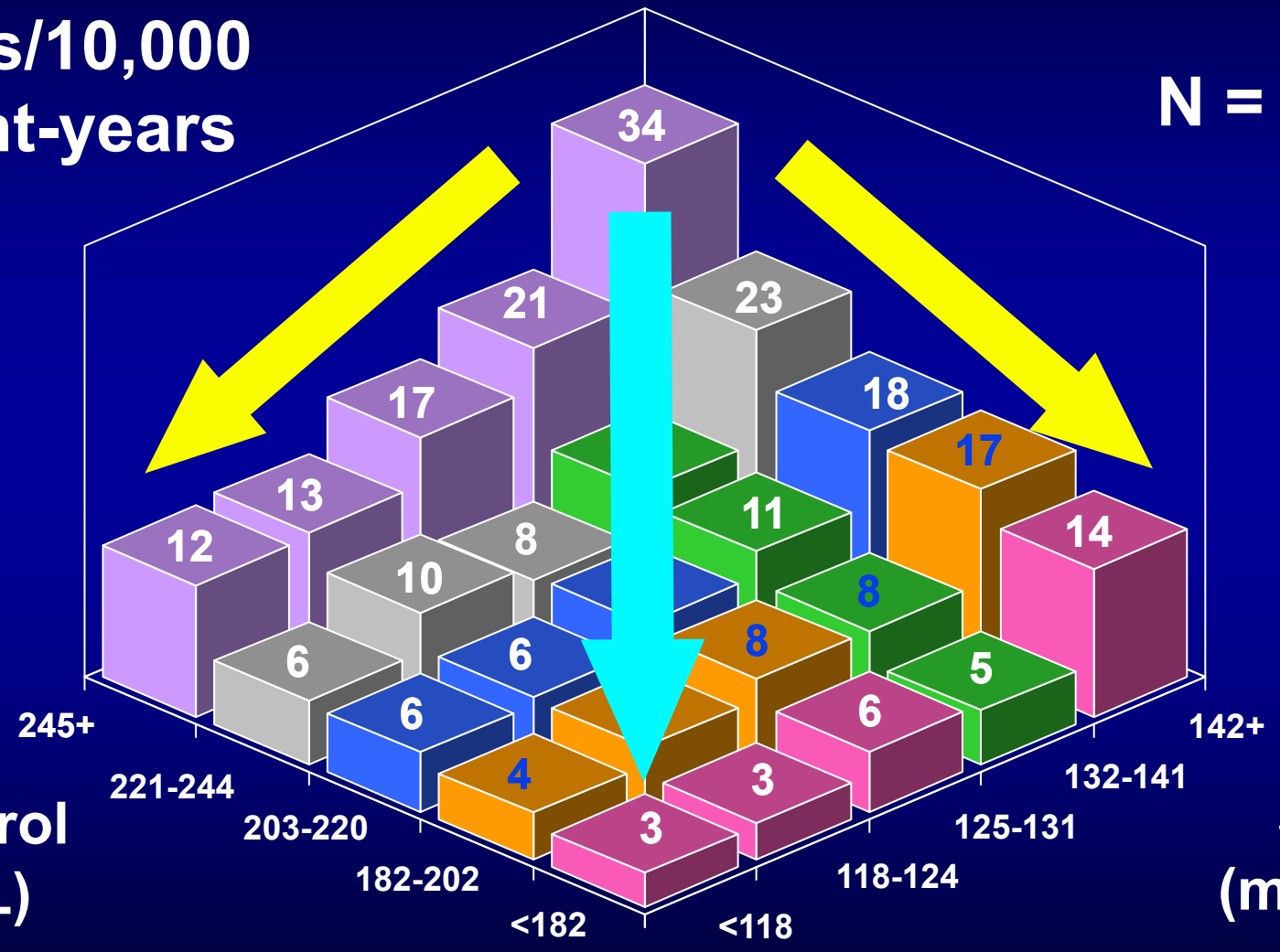
Global Risk Management: "Add statin"

- If perfect control of a risk factor is difficult (eg, blood pressure control in the elderly), total risk can still be reduced by reducing other risk factors such as smoking or blood cholesterol

Emberson J et al. *Eur Heart J*. 2004;25:484-491.

Graham et al. *Eur Heart J*. 2007. Advance Access Published Online August 28, 2007 Accessed at http://eurheartj.oxfordjournals.org/cgi/content/full/ehm316v1

Effect of Cholesterol and BP on CHD Risk



BP = blood pressure; CHD = coronary heart disease.

Neaton JD et al. *Arch Intern Med*. 1992;152:56-64.

Box 21 Position statement: Treatment of associated risk factors

Lipid lowering agents

- All hypertensive patients with established cardiovascular disease or with type 2 diabetes should be considered for statin therapy aiming at serum total and LDL cholesterol levels of, respectively, <4.5 mmol/l (175 mg/dl) and <2.5 mmol/l (100 mg/dl), and

- Hypertensive patients without overt cardiovascular disease but with high cardiovascular risk (≥20% risk of events in 10 years) should also be considered for statin treatment even if their baseline total and LDL serum cholesterol levels are not elevated.

ESH Guidelines. *Eur Heart J.* 2007. http://eurheartj.oxfordjournals.org/cgi/content/full/ehm236v1#SEC10

Circulation

(*Circulation*. 2001;104:e9051.)

American Heart Association 2001 Scientific Sessions

Late-Breaking Science

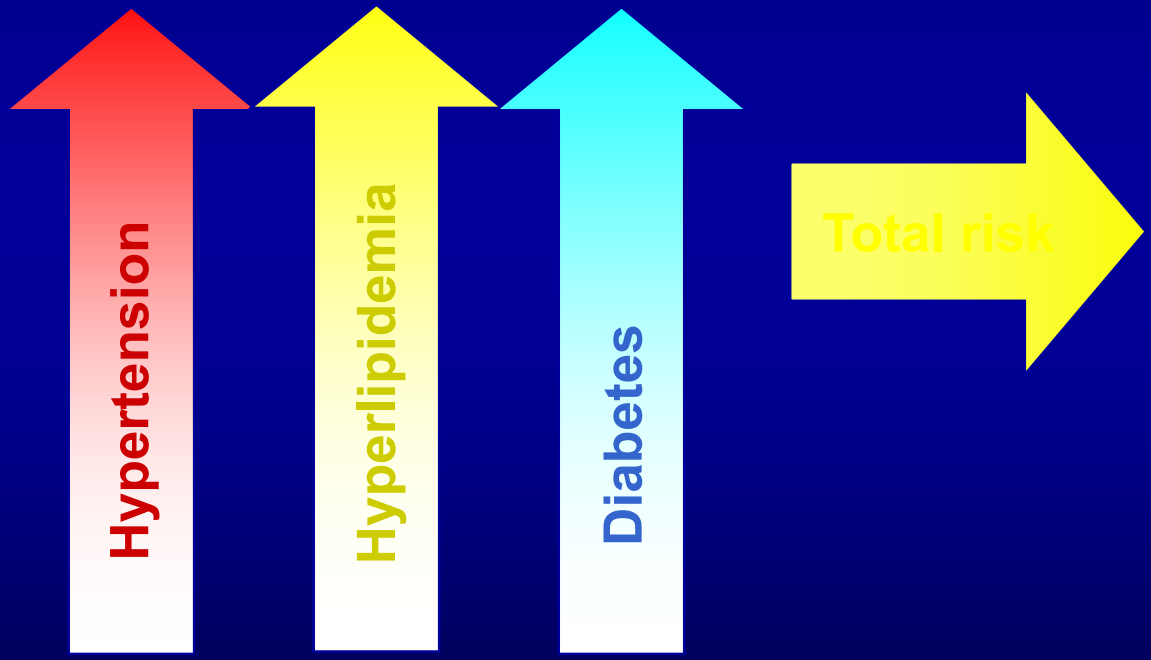
Robin Fox, FRCP

Statins: The New Aspirin?

No work presented at American Heart Association's 2001 Scientific Sessions is likely to have greater clinical impact than the Medical Research Council/British Heart Foundation Heart Protection Study, reported by Dr Rory Collins (Clinical Trial Service Unit of Oxford University, Oxford, UK). The latest guidelines from the National Cholesterol Education Program probably will have to be modified. Patients (n=20 536) were recruited in 69 UK hospitals, the entry criterion being high risk of coronary heart disease without a clear indication for cholesterol-lowering therapy. Specifically targeted were women, people >70 years of age, people with diabetes, those with noncoronary vascular disease, and those with average or below-average cholesterol levels. Patients were 40 to 80 years old (28% age $\geq$70 years) and one fourth were women. Two regimens were under investigation: simvastatin (40 mg daily), and a cocktail of antioxidant vitamins (vitamin E [600 mg], vitamin C [250 mg], ß-carotene [20 mg daily]). Patients were randomized to 4 groups of $\approx$5000 each, receiving simvastatin alone, simvastatin plus vitamins, vitamins alone, or placebo. Average follow-up period was 5.5 years. In the vitamin part of the study, the results were entirely negative. No benefit or harm

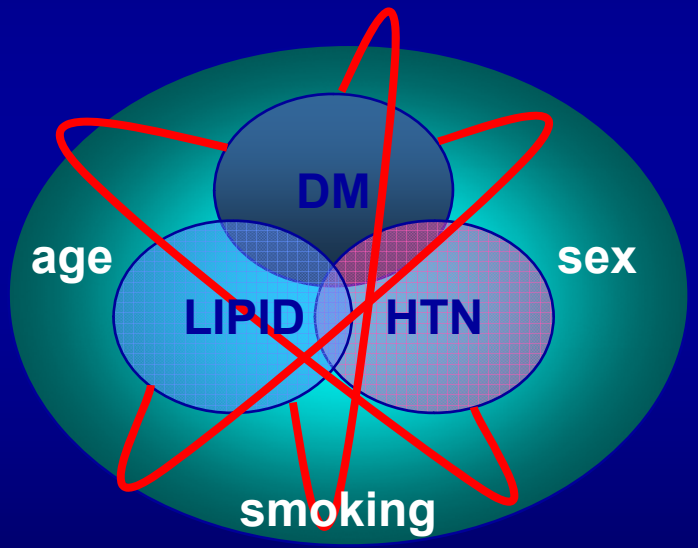
Evolution in Understanding CVD

Traditional CVD Perspective



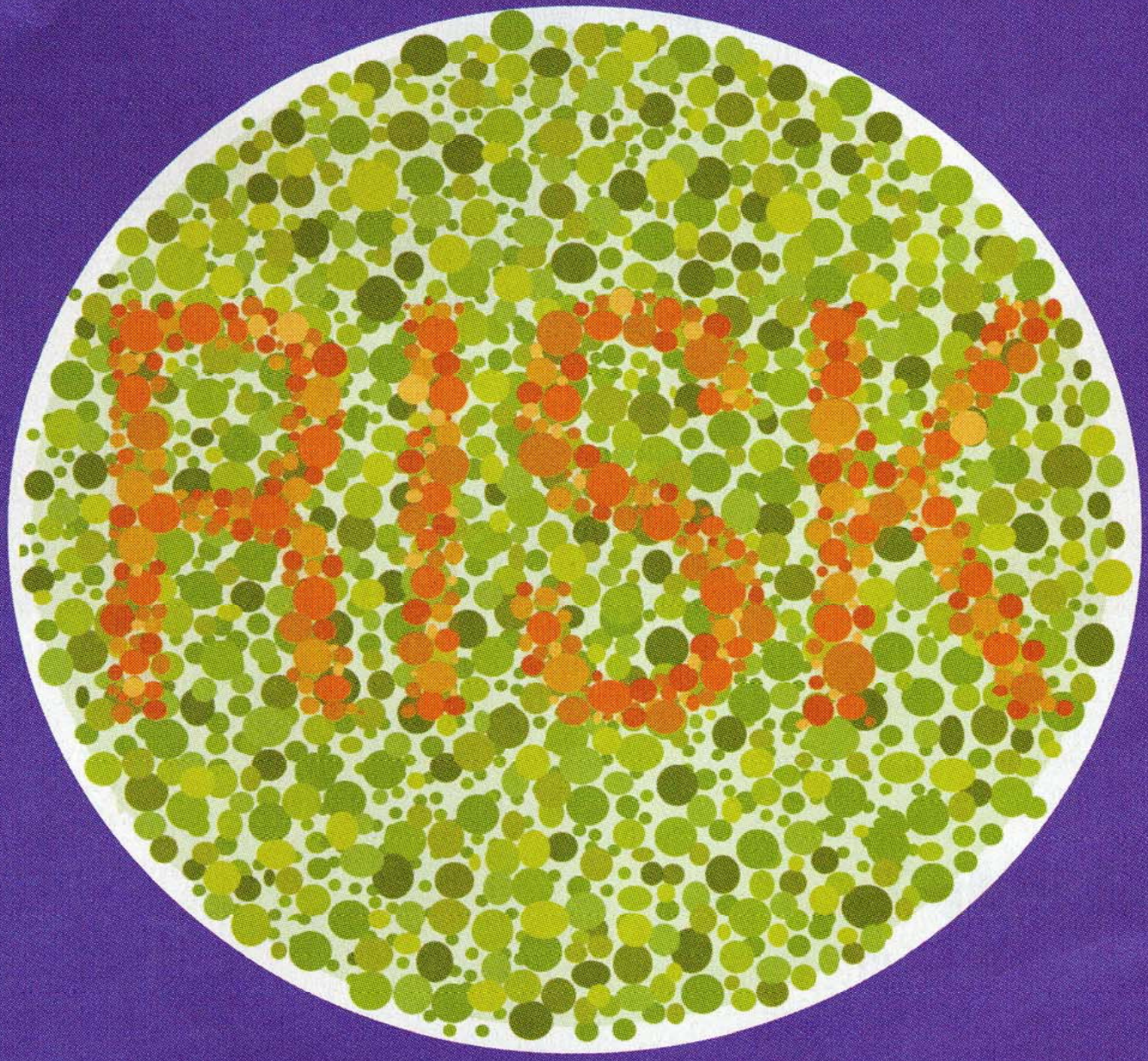
Independent risk-factors treated individually

Global CV Risk Perspective



Vascular Disease Is an Interplay of risk-factors

THANK YOU!



CAN YOU SEE THE RISK?