# Calcium Channel Blockers in Management of Hypertension

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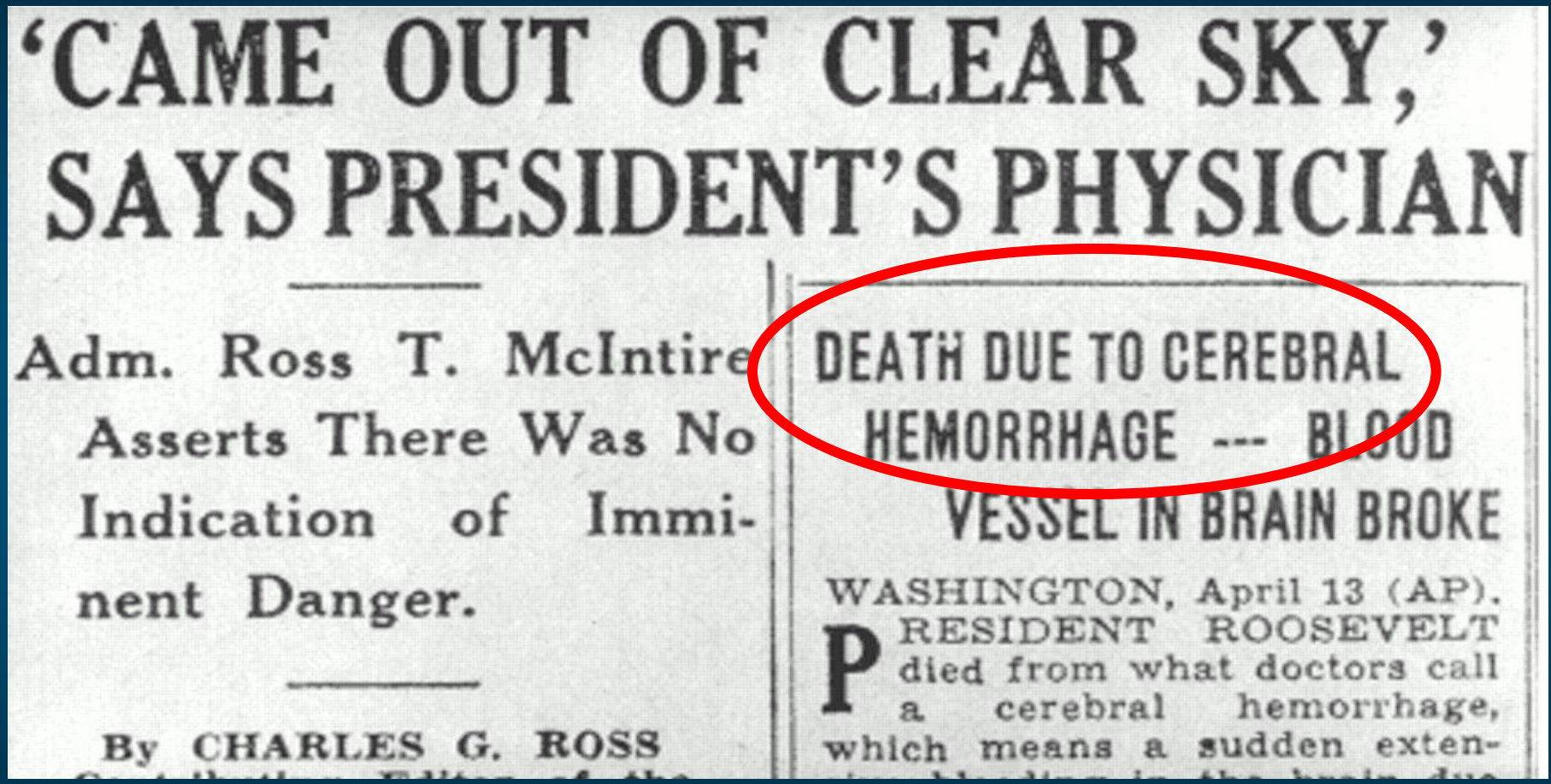
# Contents

- Clinical significance of hypertension
- CCB: Brief introduction
- Evidences of CCB's in HT and CAD
- Review on 'beyond BP lowering effect'
- Practical usefulness of CCB's



# ‘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

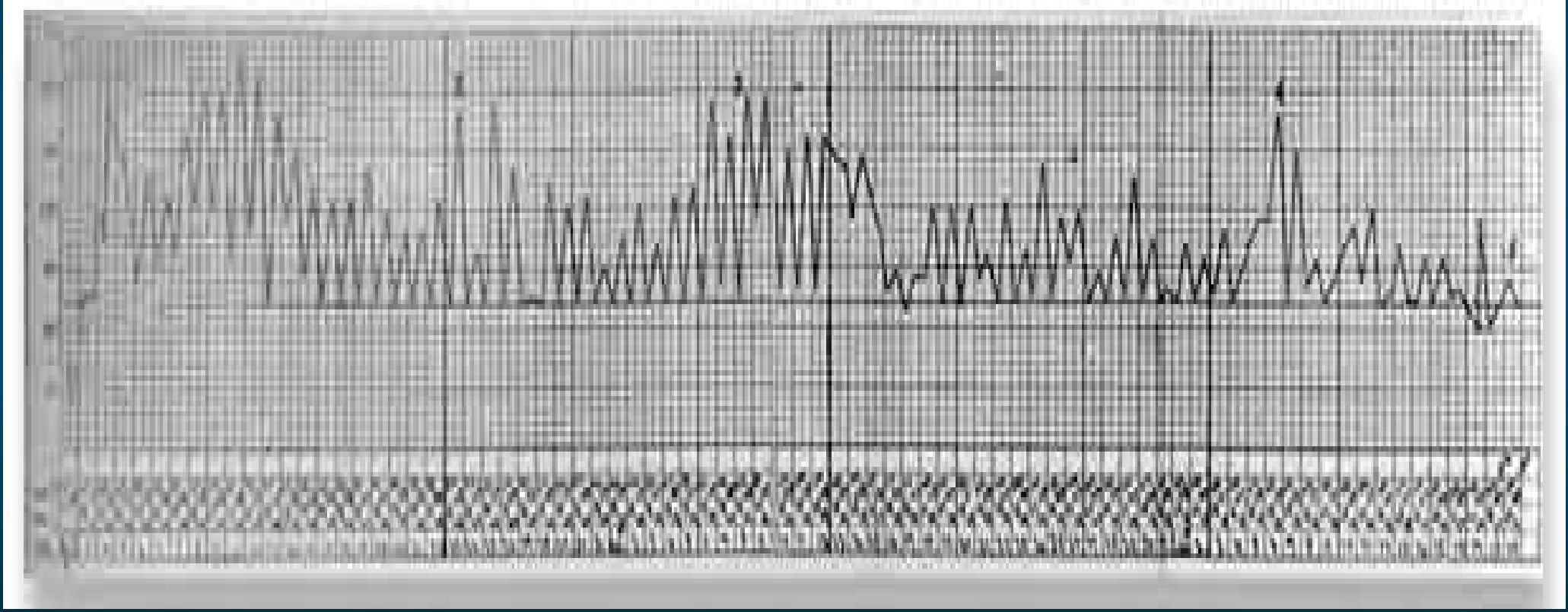
## DEATH DUE TO CEREBRAL HEMORRHAGE --- BLOOD VESSEL IN BRAIN BROKE

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)

# FDR's BP recorded April 1944



# Global Burden of CHD

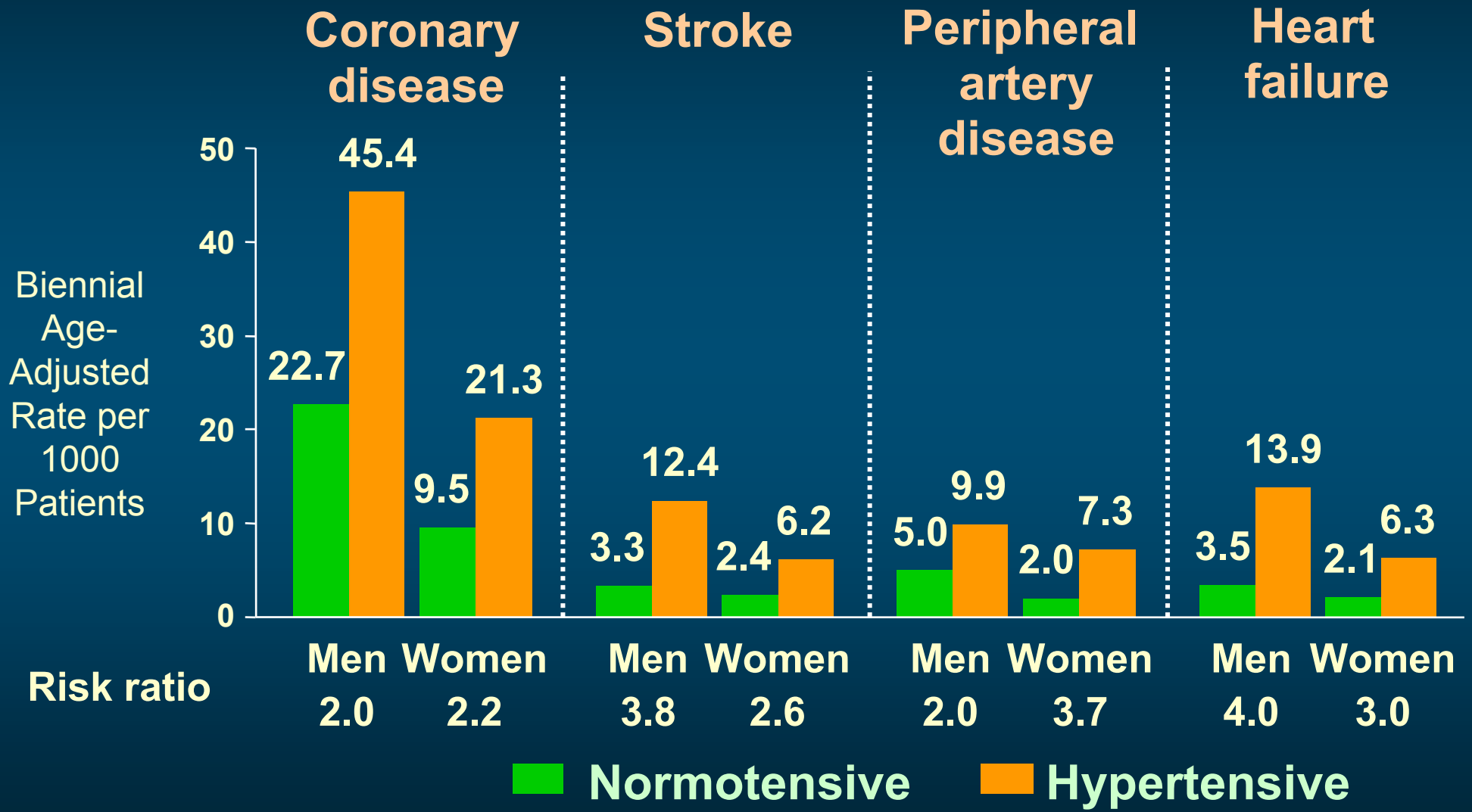
| Cause | 1990 Millions | 1990 (%) | 2020 Millions | 2020 (%) |
|---|---|---|---|---|
| CHD | 6.2 | 12.4 | 11.1 | 16.2 |
| Stroke | 4.3 | 8.5 | 7.7 | 11.3 |
| Other CVD | 2.6 | 5.1 | 6.0 | 8.8 |
| **TOTAL CVD** | **13.1** | **26.0** | **24.8** | **36.3** |
| All Cause Death | 50.4 | 100 | 68.3 | 100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

WHO:WHF

# Rank Order of Disability (DALYs)

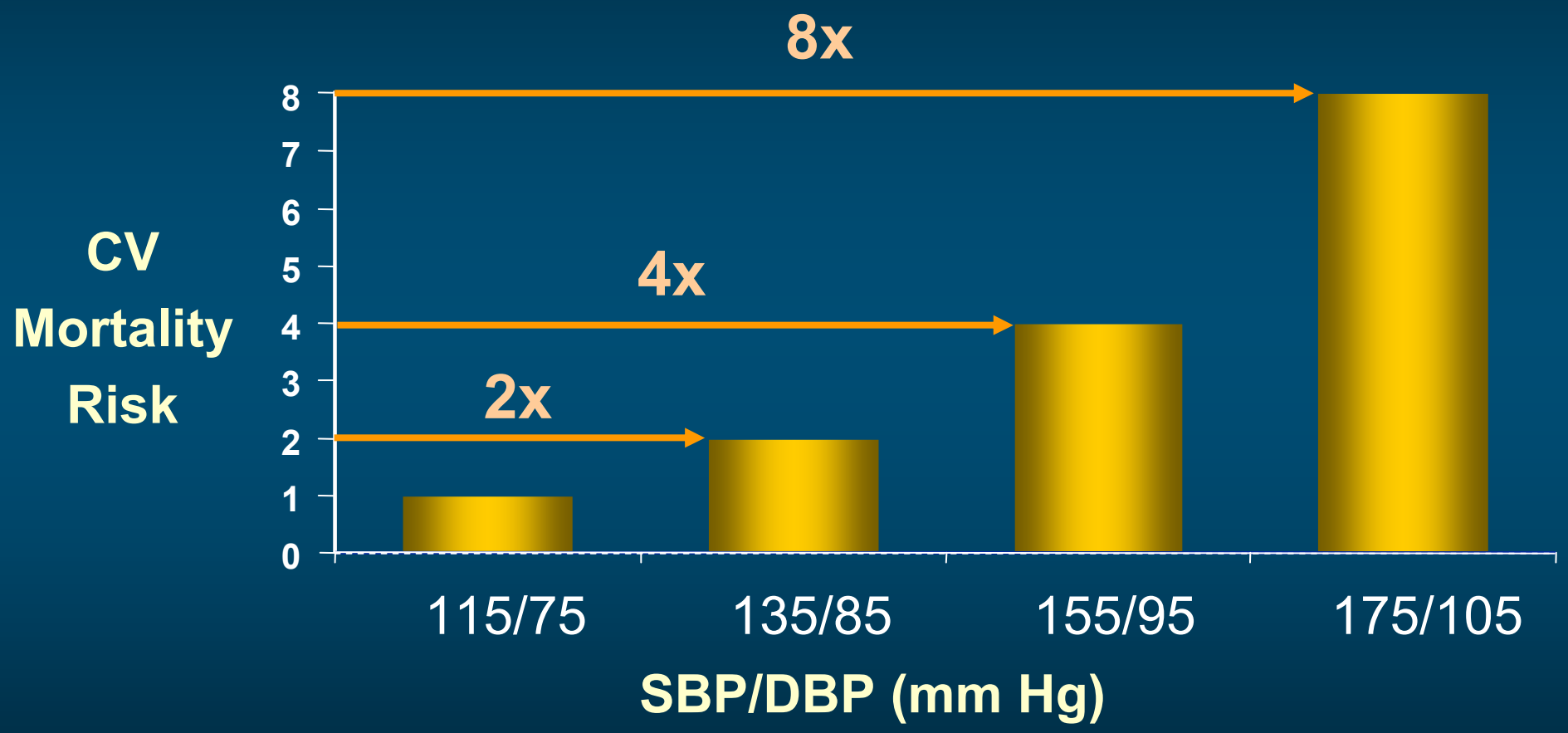
| *1999 Disease or Injury* | *2020 Disease or Injury* |
|---|---|
| 1. Acute lower respiratory infections | 1. **Coronary heart disease** |
| 2. HIV/AIDS | 2. Unipolar major depression |
| 3. Perinatal conditions | 3. Road traffic accidents |
| 4. Diarrhoeal diseases | 4. **Cerebrovascular disease**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

# HT: A Risk Factor for CV Disease




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

# CV Mortality Risk with BP Increment



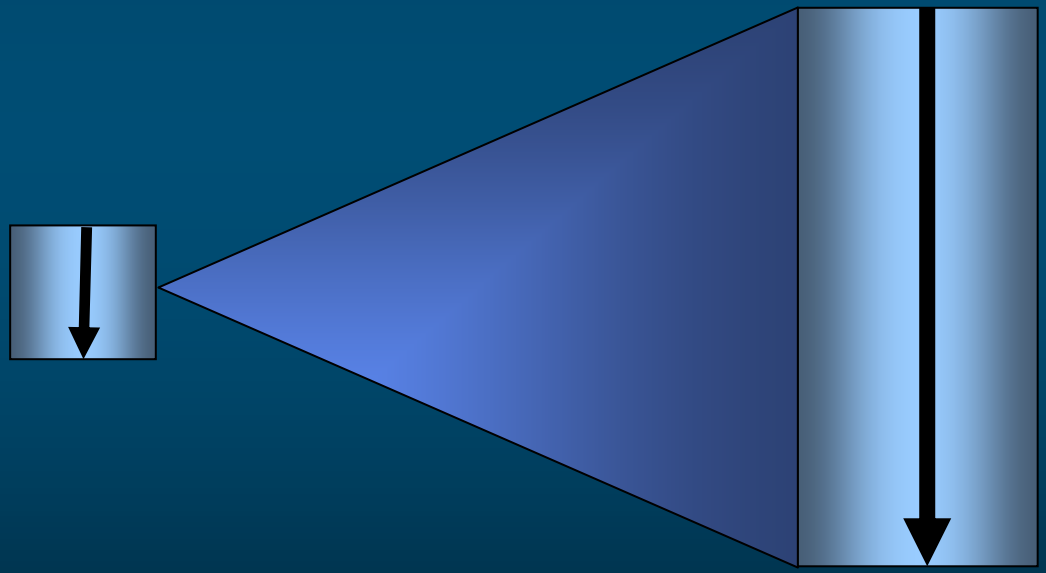

*Individuals aged 40 to 69 years, starting at blood pressure 115/75 mm Hg

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

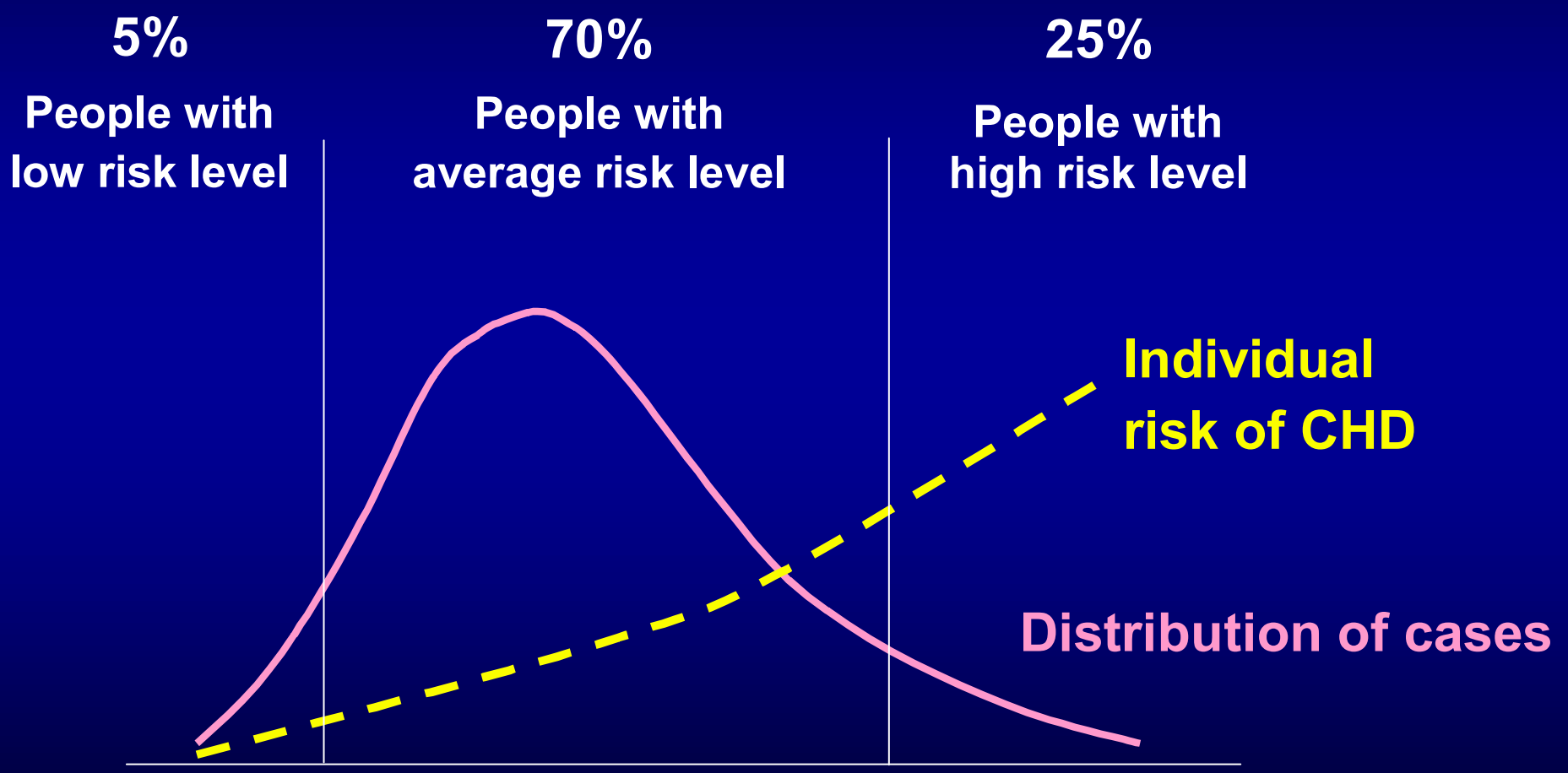
For every 2 mm Hg decrease in mean SBP



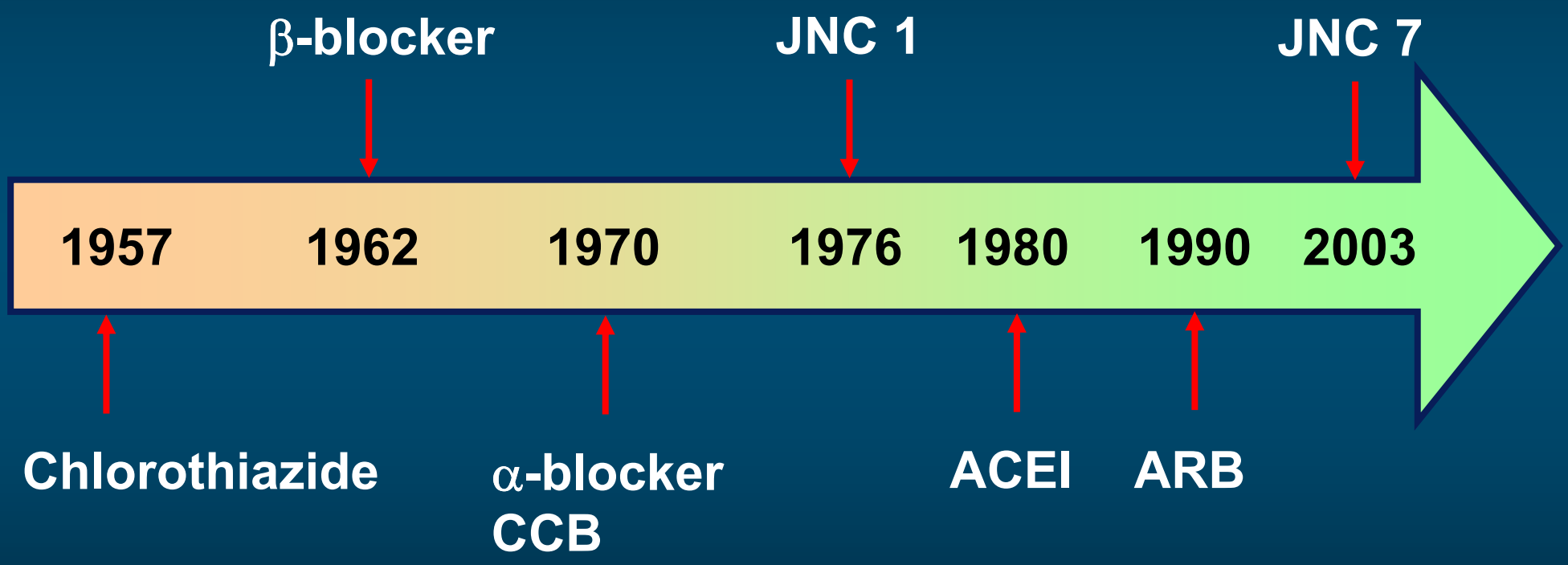
- 7% reduction in CHD mortality
- 10% reduction in stroke mortality

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

# Individual Risk vs Proportional Attributable Risk



# Treatment of Hypertension



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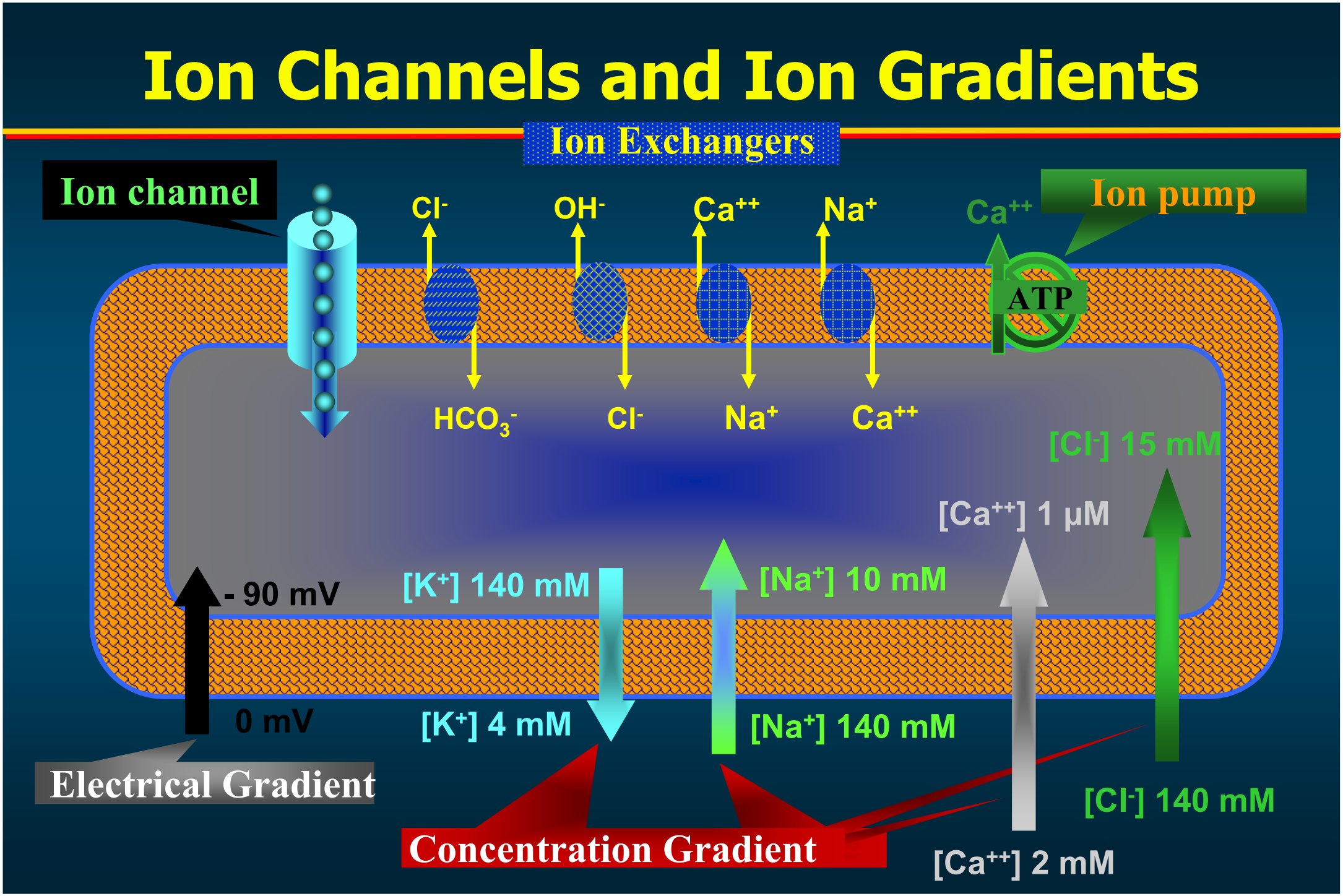
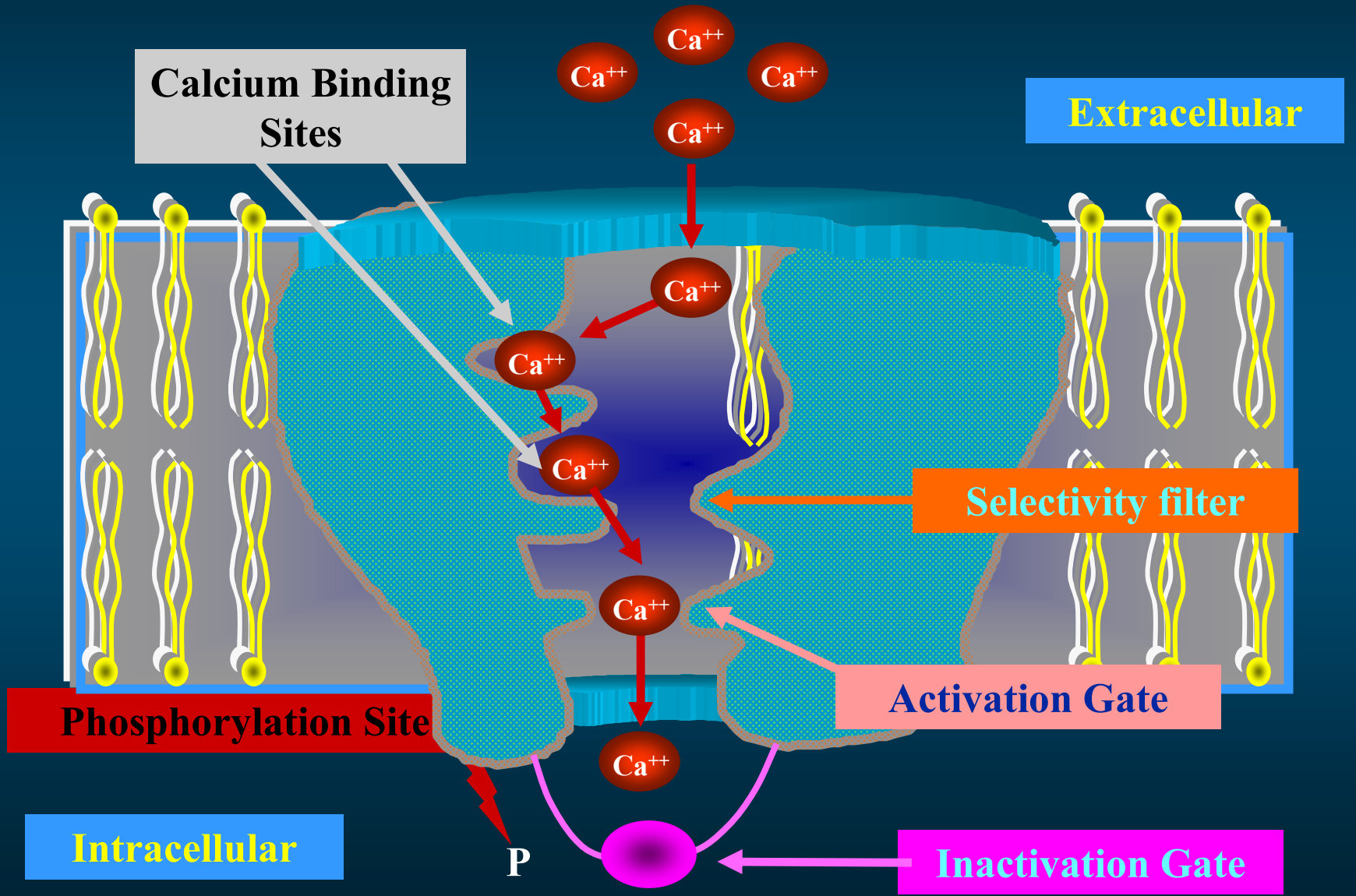
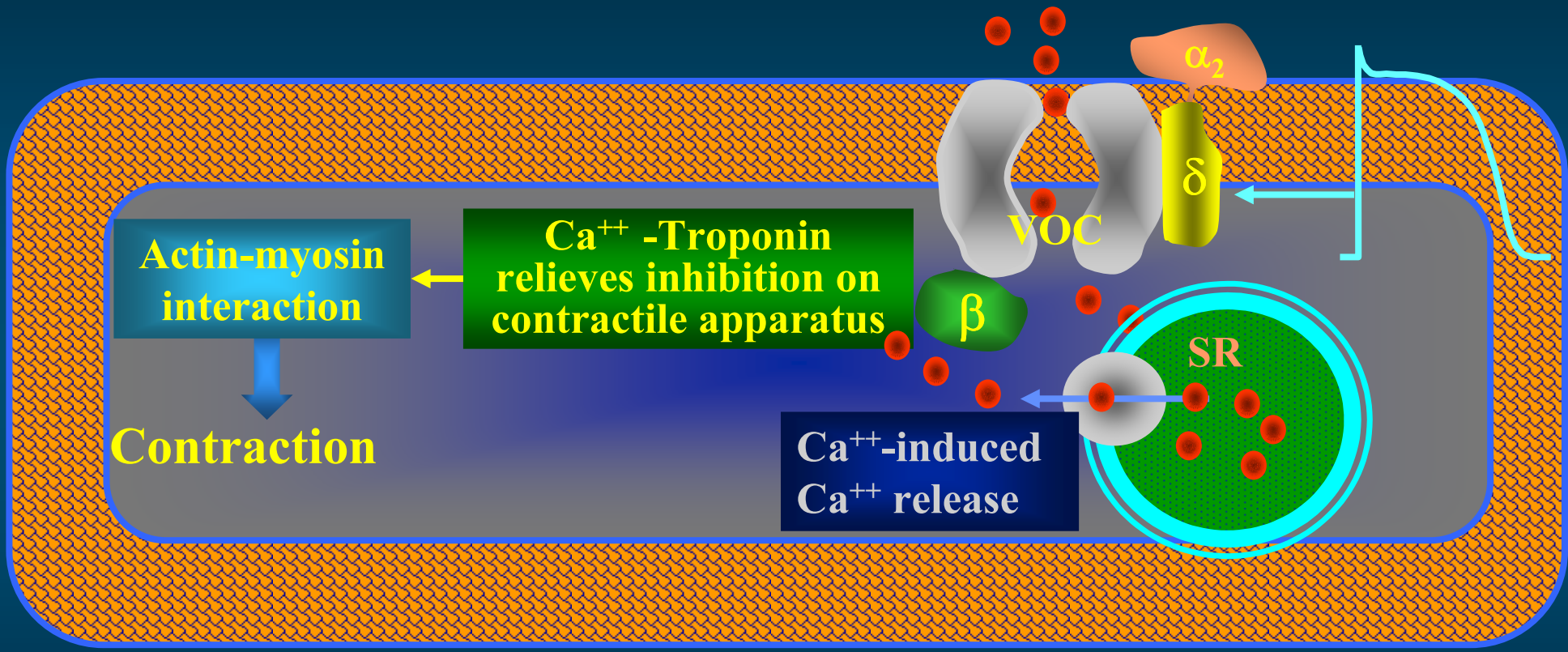
# Ion Channels and Ion Gradients



# Voltage-Dependent $Ca^{++}$ Channels

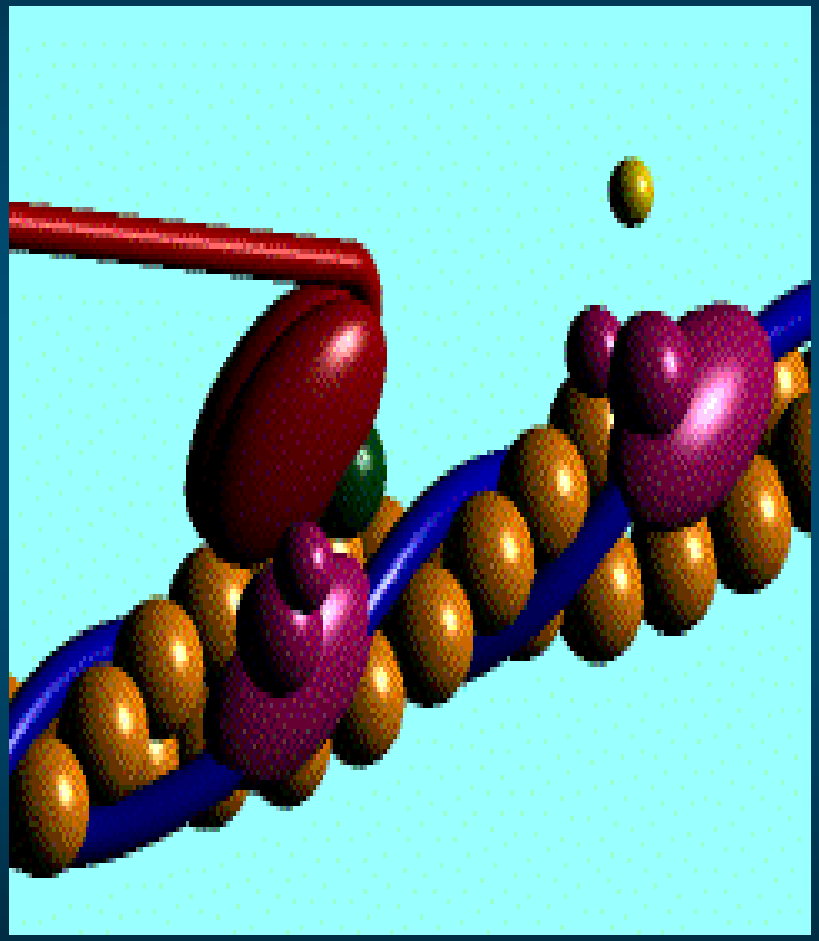


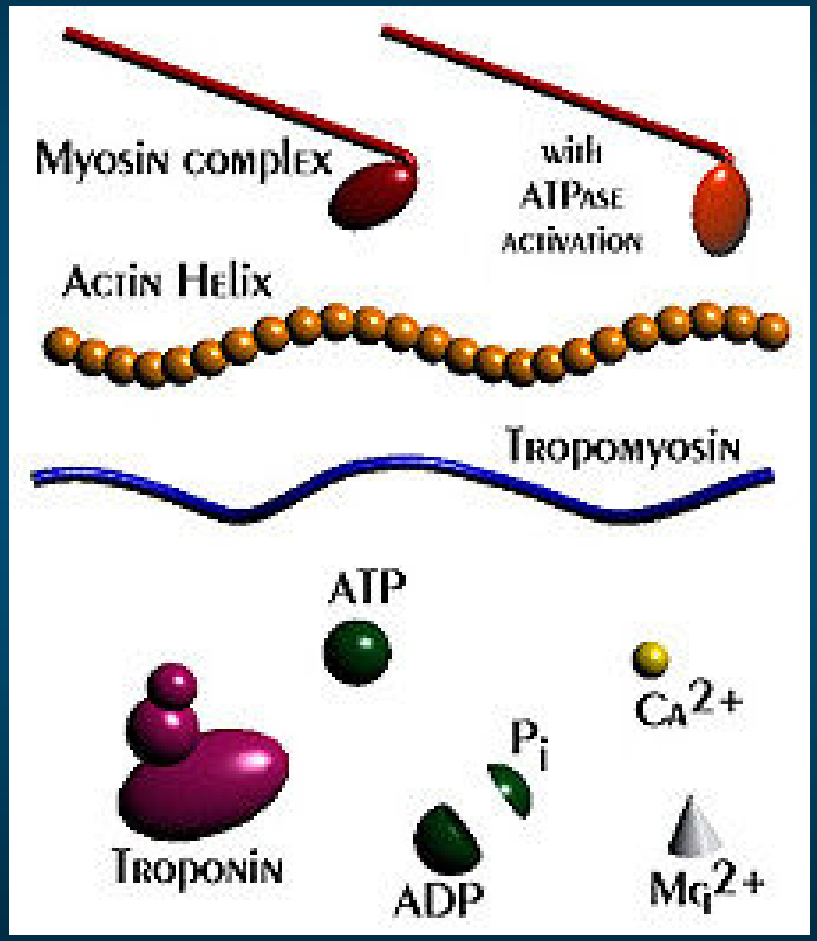
# Excitation-Contraction Coupling




- L-type $Ca^{++}$ channels open at a level of depol. of ~-60 mV.
- The entry of small $Ca^{++}$ triggers $Ca^{++}$ release from SR.

# Excitation-Contraction Coupling

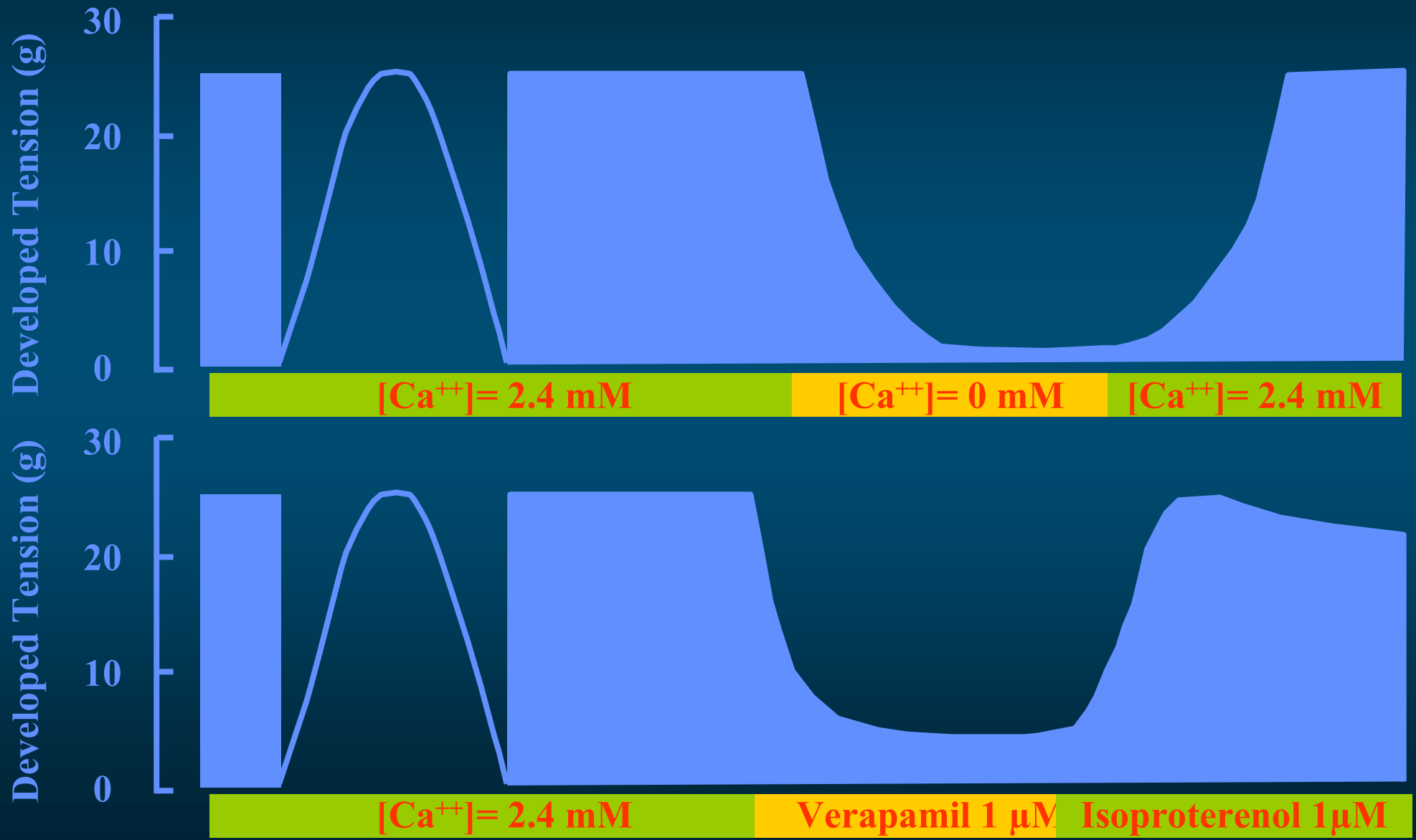




# Types of Calcium Channels

| Channel | Blockers | Properties | Location/Role |
|---|---|---|---|
| L type | Calcium antagonists | Large, long-lasting current with slow activation | Cardiac & smooth m. neurons; excitation-contraction, excitation-secretion coupling |
| T type | Amiloride | Tiny, transient current | SA & Purkinje cell; pacemaker activity |
| N type | Conotoxin | Neither L or T | Neurons; neurotransmitter release |

# First Observation about CCB in 1964



# Classes of L-Type CCB

| | | |
|---|---|---|
| Class I (diphenylalkylamine) | Verapamil | Isoptin™ |
| Class II (1,4-dihydropyridines) | Amlodipine | Norvasc™, Lotrel™ |
| | Felodipine | Plendil™, Lexxel™ |
| | Isradipine | Dynacirc™ |
| | Nicardipine | Cardene™ |
| | Nifedipine | Adalat™, Procardia™ |
| | Nimodipine | Nimotop ™ |
| | Nisoldipine | Sular™ |
| Class III (benzothiazepine) | Diltiazem | Angizem, Altiazem |
| Class IV (miscellaneous) | Bepridil | Vascor™ |
| Class V (T-type blocker) | Mibefradil (*withdrawn)* | |

# Pharmacodynamic Effects of CCBs

| | Phenylalkylamine (Verapamil) | Dihydropyridines (Nifedipine) | (Nimodipine) | Benzothiazepine (Diltiazem) |
|---|---|---|---|---|
| **Vasodilation** | | | | |
| peripheral | ++ | +++ | + | + |
| coronary | ++ | +++ | + | +++ |
| cerebral | + | + | +++ | + |
| **Heart rate** | ↓ | ↑ | -- | ↓ |
| **SA node** | ↓ | -- | -- | ↓↓ |
| **AV node** | ↓↓ | -- | -- | ↓ |
| **Contractility** | ↓↓ | ↑ | -- | ↓ |

# Classification of CCB's

| Group (specificity) | First generation | Second generation<br>New active principles and/or novel formulations | | Third generation |
|---|---|---|---|---|
| Dihydropyridine (artery > cardiac) | Nifedipine<br>Nicardipine | Nifedipine SR/GITS<br>Felodipine ER<br>Nicardipine SR | Benidipine<br>Isradipine<br>Manidipine<br>Nilvadipine<br>Nimodipine<br>Nisoldipine<br>Nitrendipine | Amlodipine<br>Lacidipine |
| Benzothiazepine (artery = cardiac) | Diltiazem | Diltiazem SR | | |
| Phenylalkylamine (artery < cardiac) | Verapamil | Verapamil SR<br>Gallopamil | | |

*Abbreviations: ER = extended release; GITS = gastrointestinal therapeutic system; SR = sustained release*

*Zanchetti, 1997*

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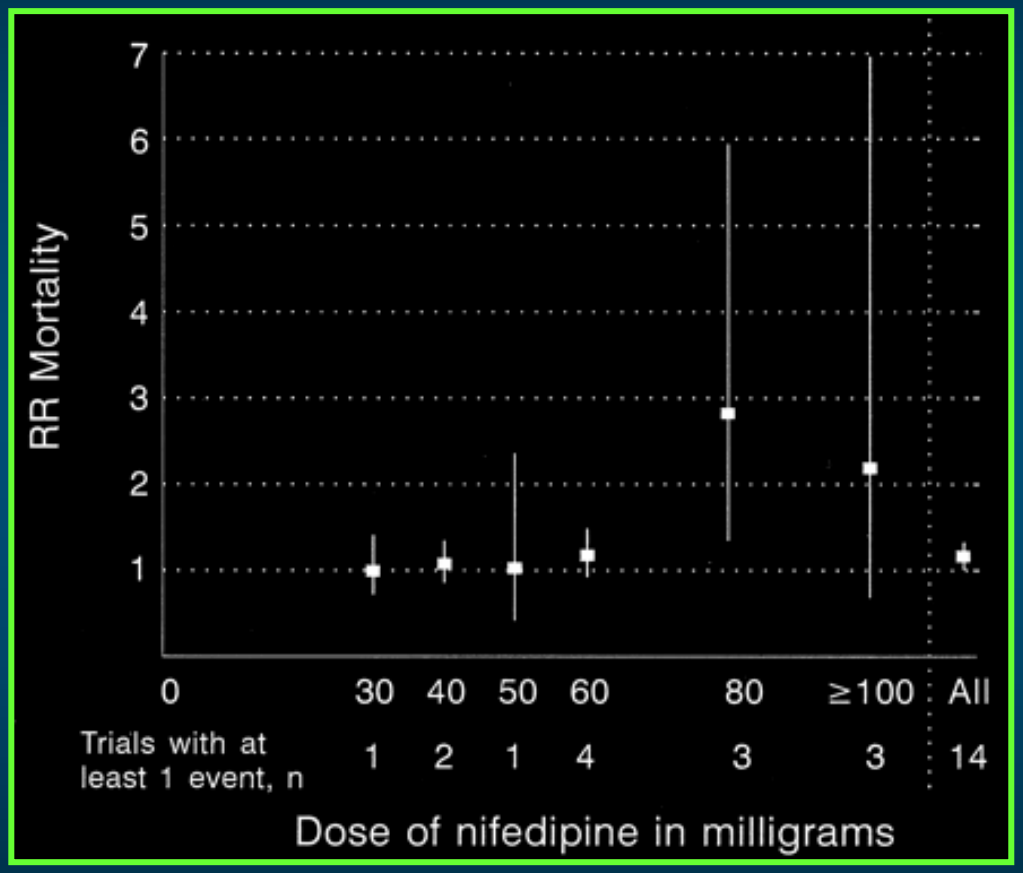
# CCB Controversy in 1990's



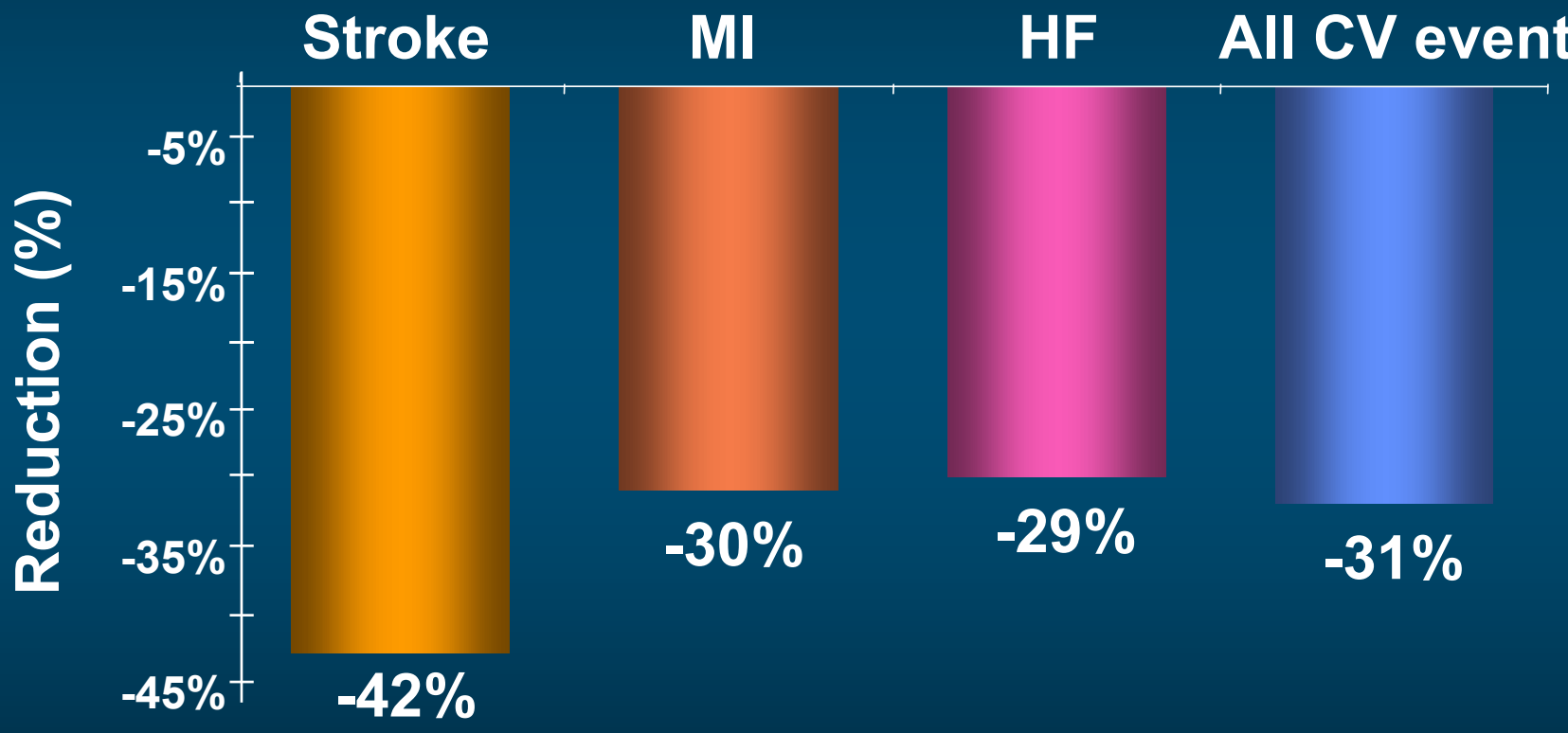

**Circulation 1995**

# Evidences of CCB's in HT, CAD

- CCB vs Placebo
  - Syst-EUR nitrendipine, *Lancet 1997*
  - PREVENT amlodipine, *Circulation 2000*
  - ACTION nifedipine GITS, *Lancet 2004*

# Syst-EUR

## *Nitrendipine reduces CV events*



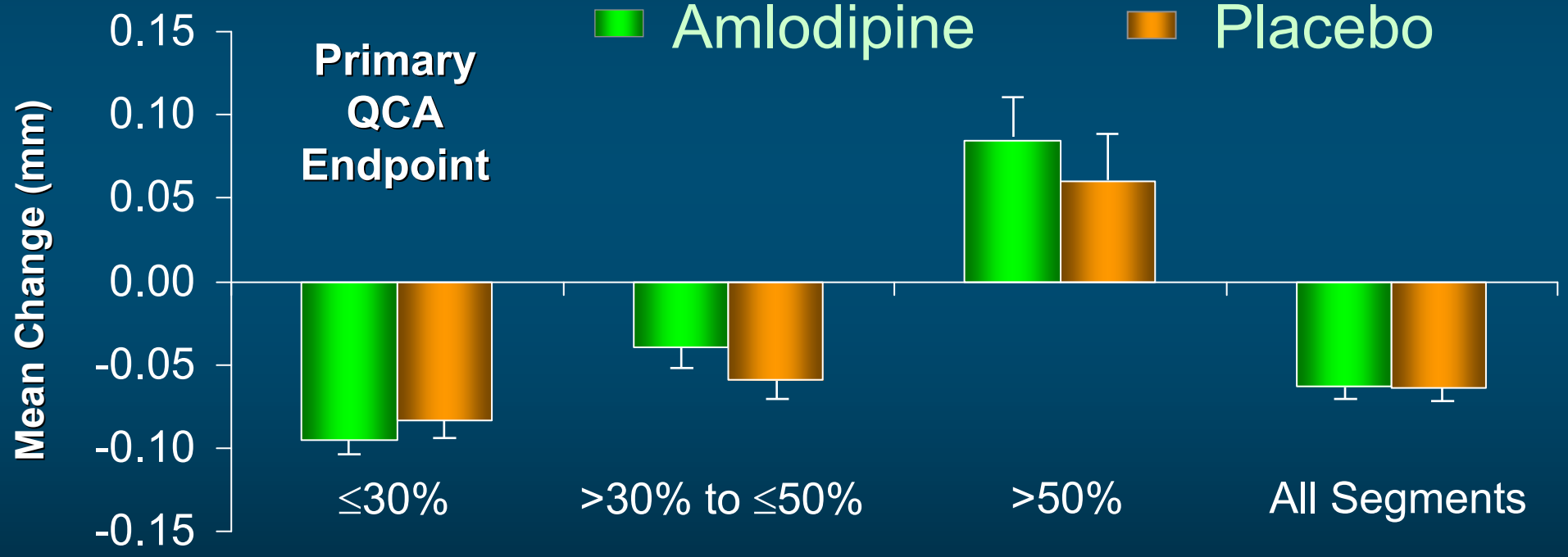

**4695 Elderly (> 60yr) pts with ISH: SBP>160, DBP<95)**

*Systolic Hypertension in Europe. Staessen et al, Lancet, 1997.*

# PREVENT: Primary QCA Endpoint

## 825 symptomatic CAD with 3yr f/u

## Change in Minimum Lumen Diameter (MLD)

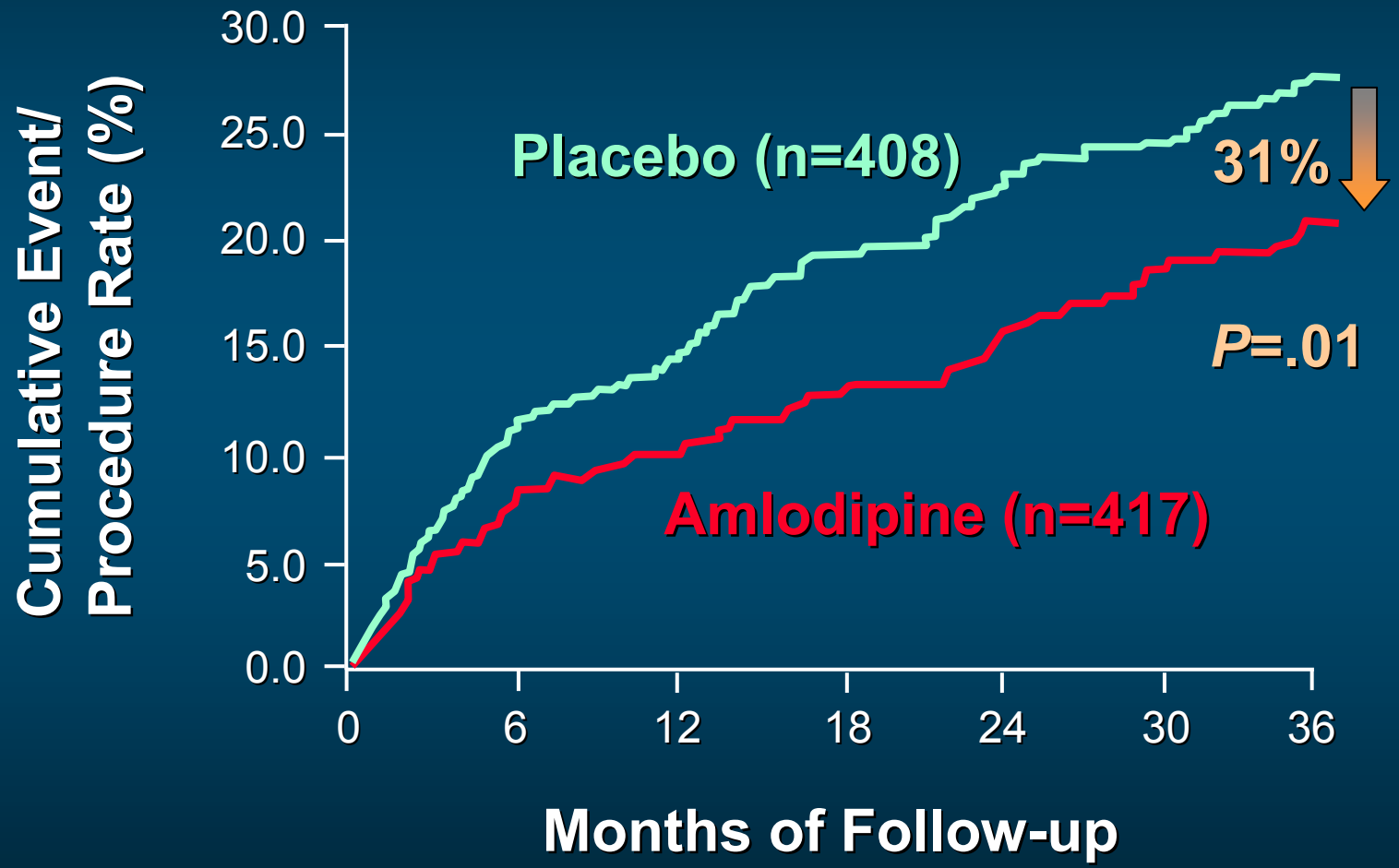



* Values are mean ± SE, adjusted for segment, clinic, and PTCA during baseline angiogram.

*P*=NS for all comparisons of amlodipine versus placebo.

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

# PREVENT: Vascular Event or Procedure

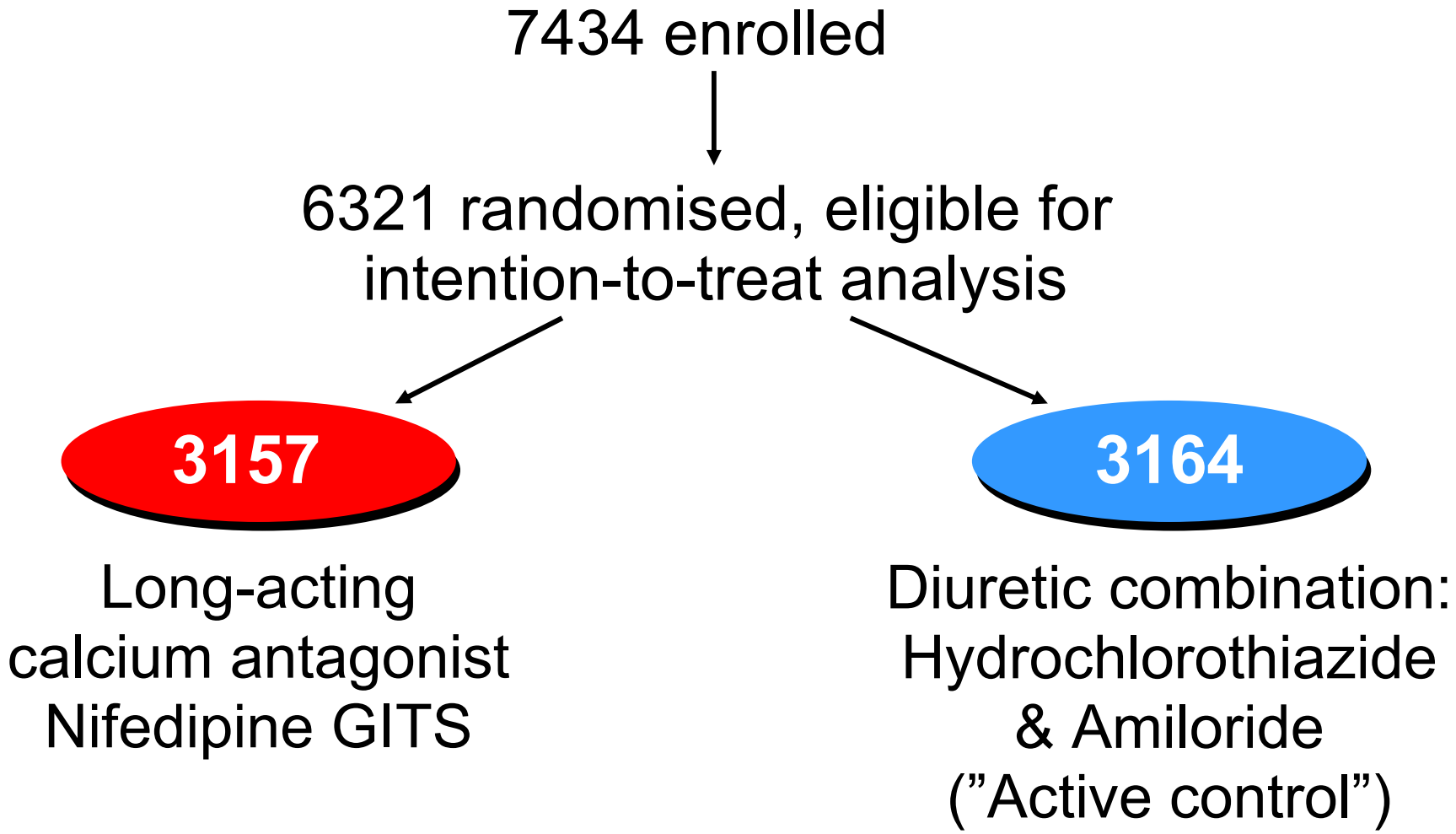



Pitt et al. *Circulation*. 2000;102:1503-1510.

# Evidences of CCB's in HT, CAD

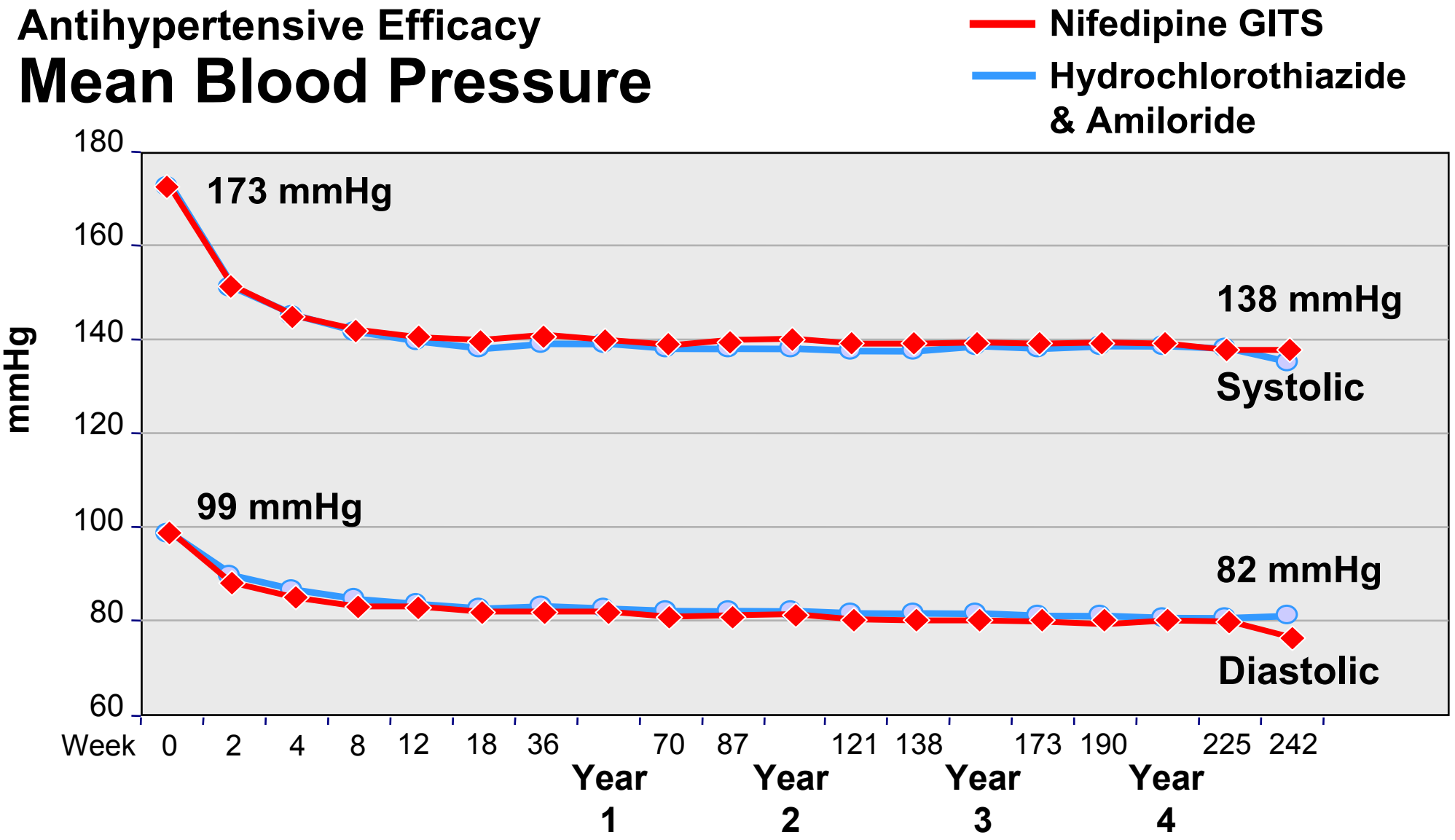
- CCB vs Active control
  - ABCD nisoldipine vs ACEI, *NEJM1998*
  - STOP-2 felodipine or isradipine vs ACEI or diuretic/BB, *Lancet 1999*
  - INSIGHT nifedipine GITS vs diuretics, *Lancet 2000*
  - ALLHAT amlodipine vs diuretics vs ACEI, *JAMA 2002*
  - AASK amlodipine vs BB vs ACEI, *JAMA 2002*
  - CONVINCE verapamil vs diuretic/BB, *JAMA 2003*
  - CAMELOT amlodipine vs ACEI, *JAMA 2004*
  - VALUE amlodipine vs ARB, *Lancet 2004*

# Number of Patients



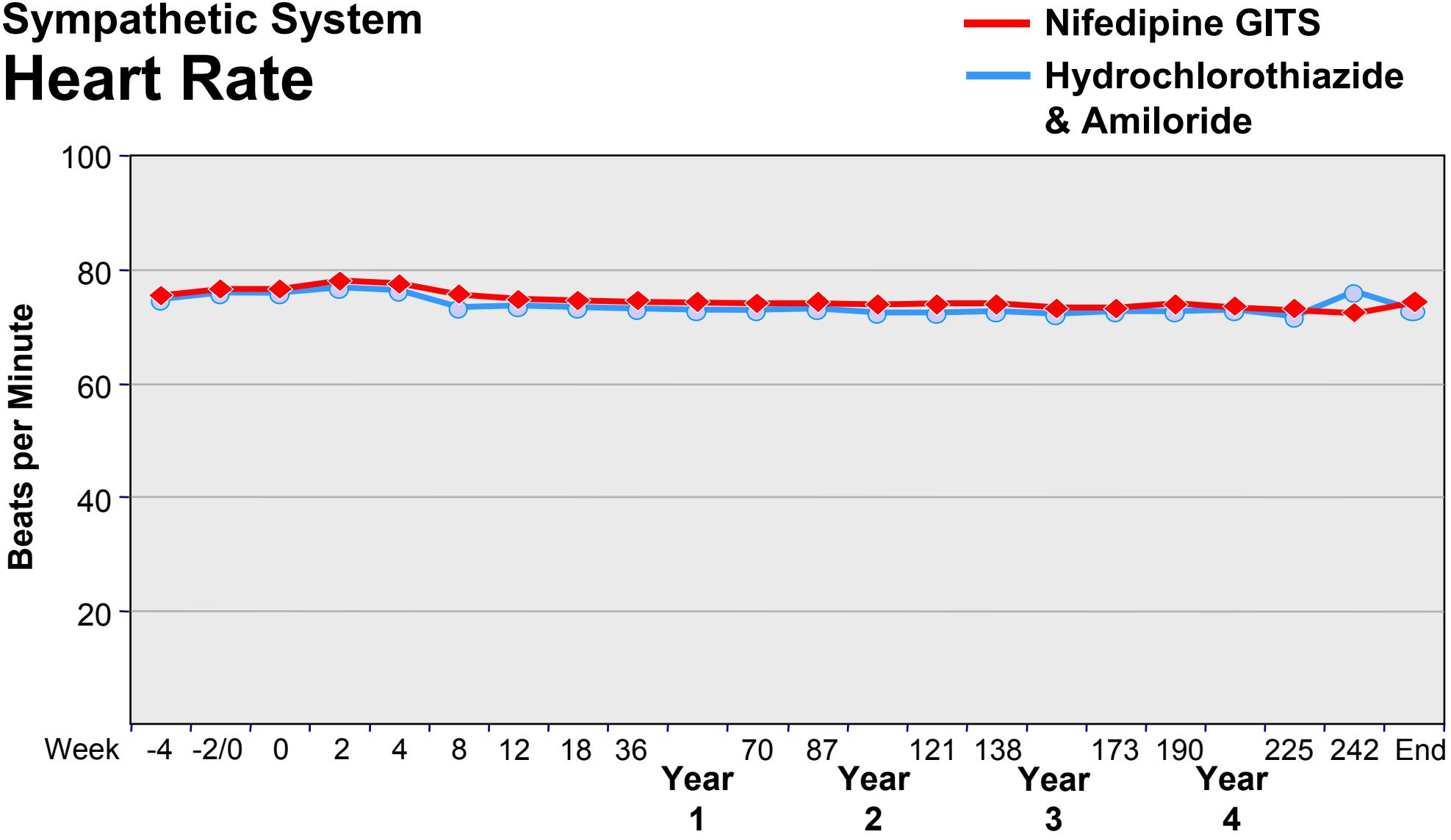
## Antihypertensive Efficacy

# Mean Blood Pressure



## Sympathetic System

# Heart Rate

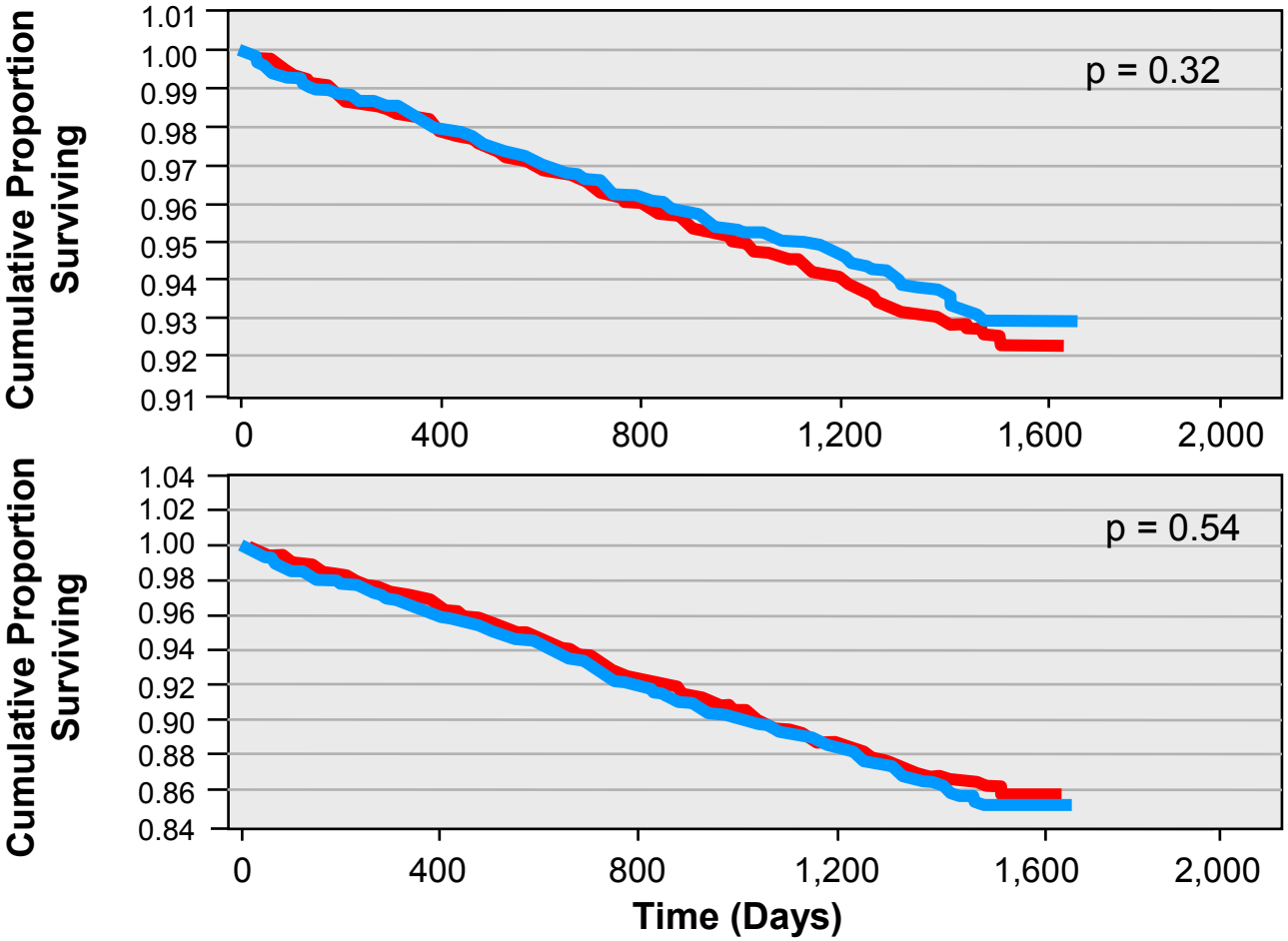


# Main Clinical Outcome

## Kaplan Meier Curves

Nifedipine GITS

Hydrochlorothiazide & Amiloride

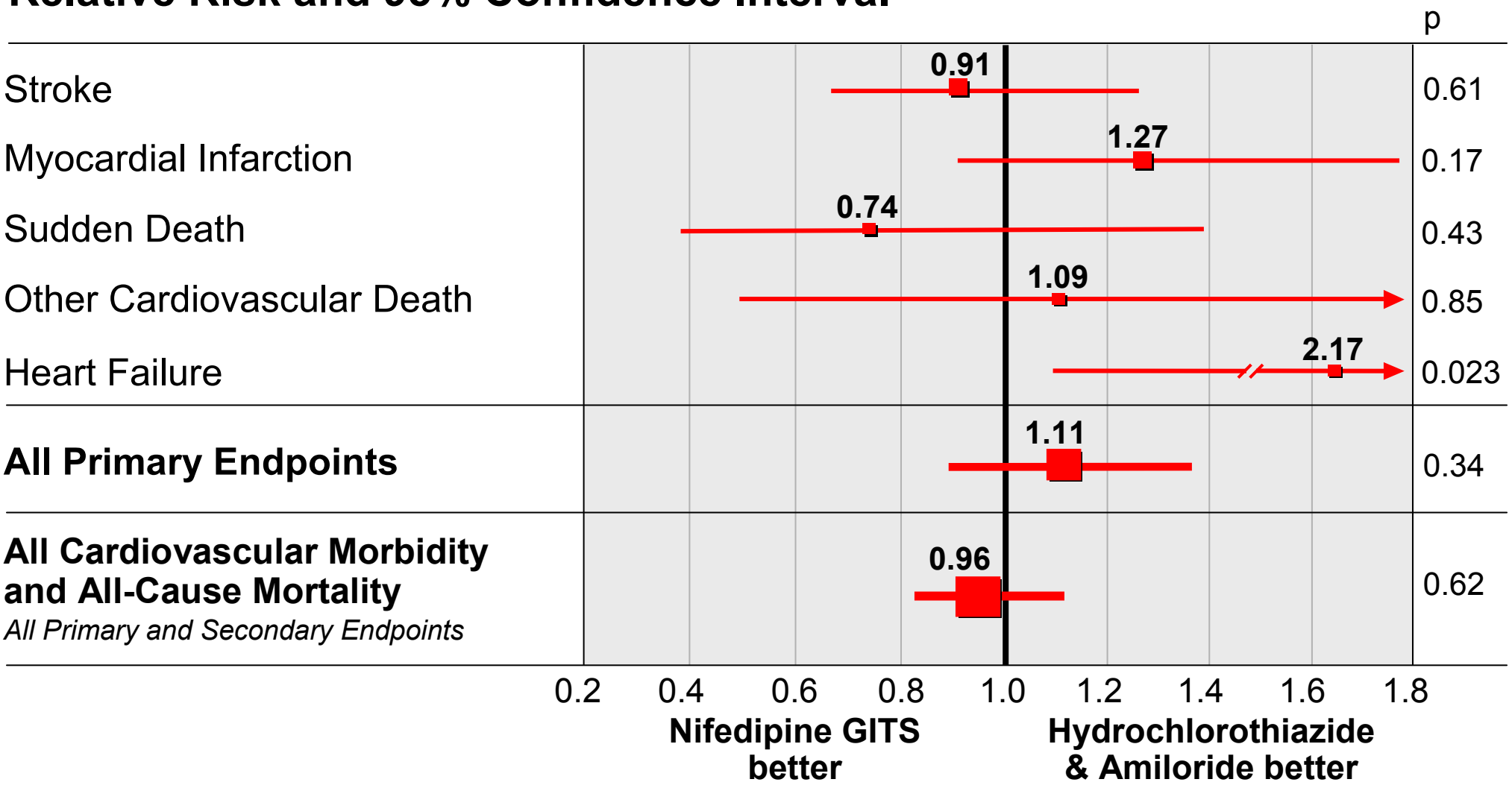



**Myocardial Infarction, Sudden Death, Stroke, Heart Failure, Other Cardiovascular Death**
*(Primary Endpoints)*

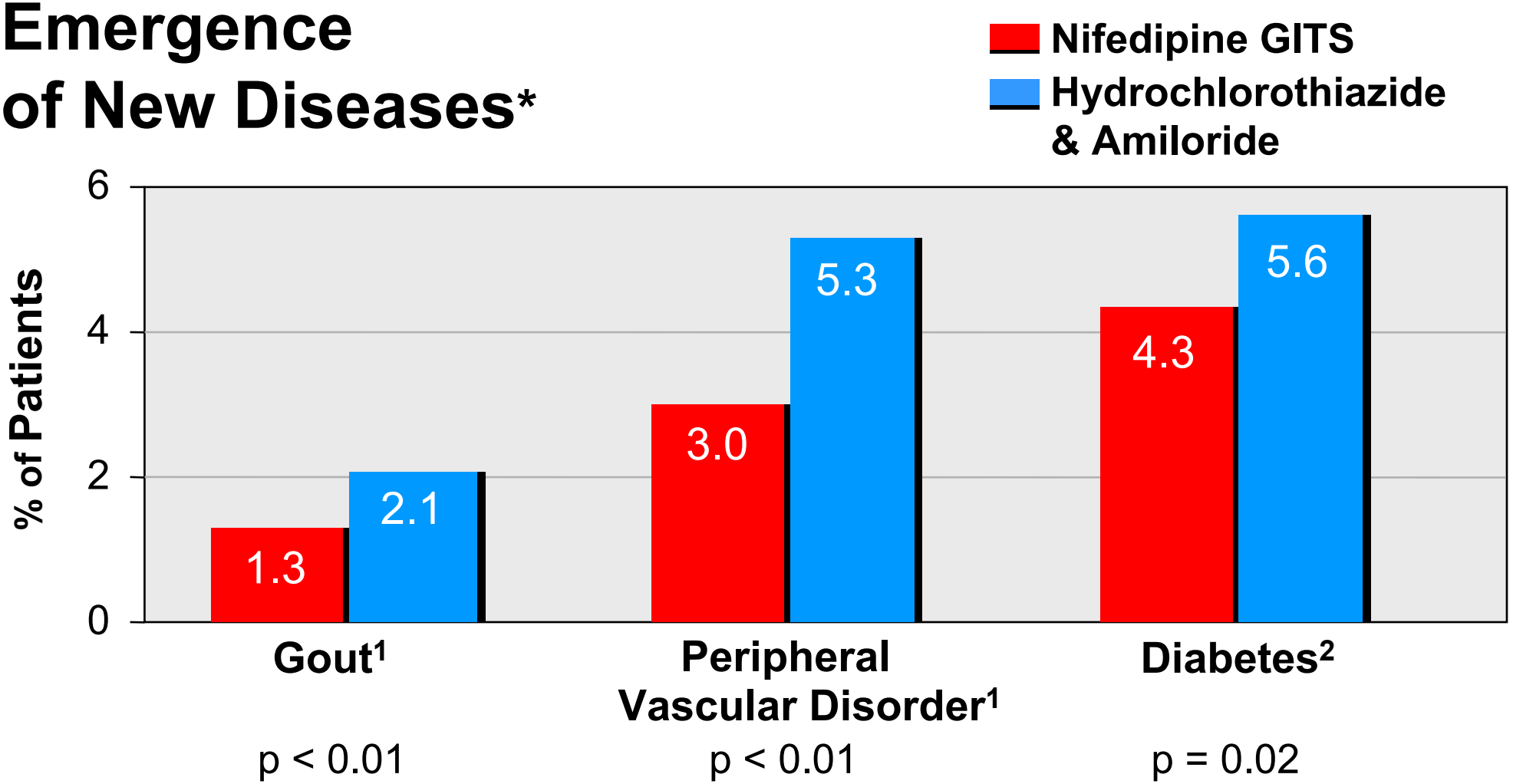
**All Cardiovascular Morbidity and All-Cause Mortality**
*(Sum of Primary and Secondary Endpoints)*

# Overview: Individual and Combined Endpoints

## Relative Risk and 95% Confidence Interval

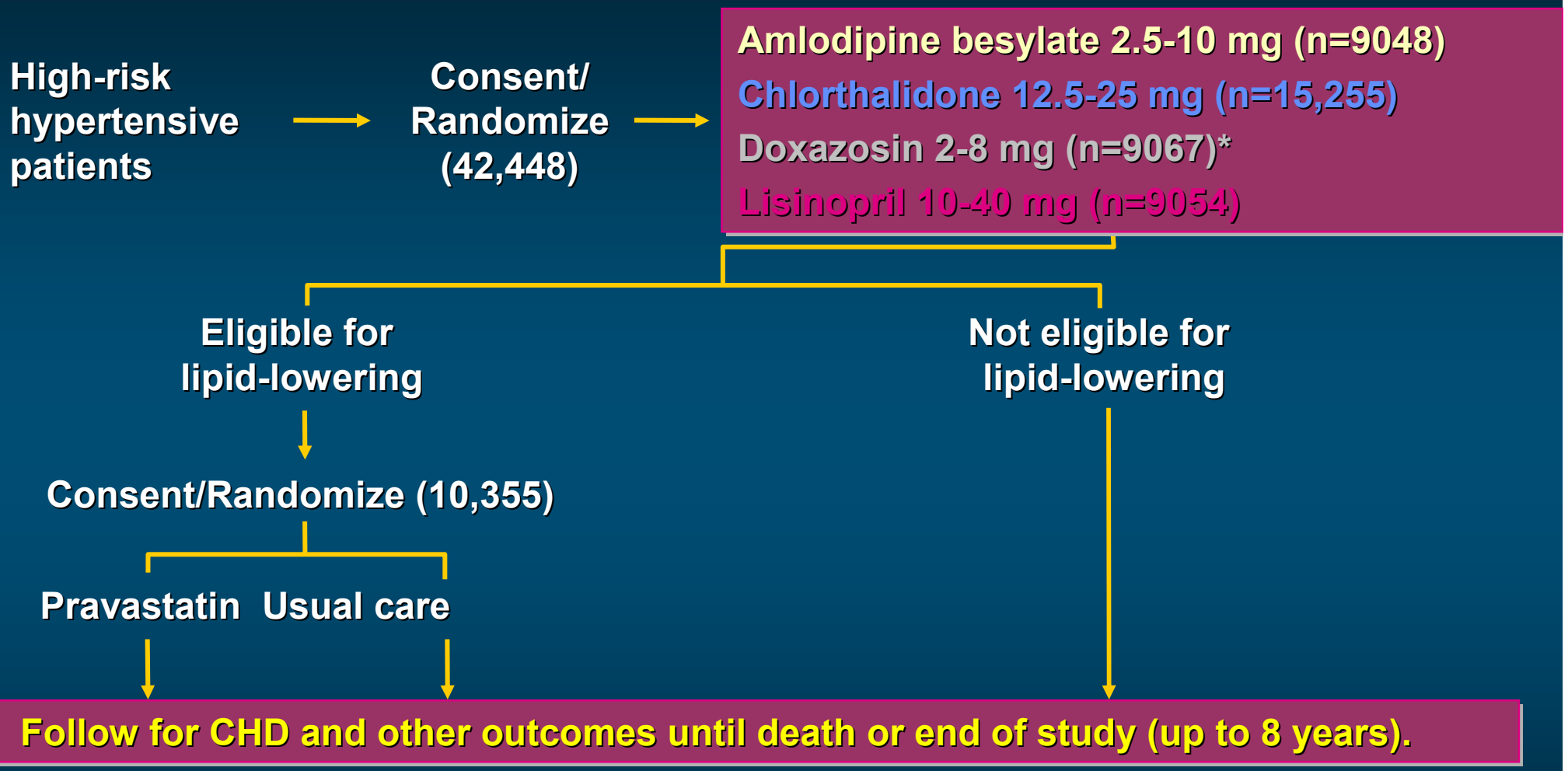


# Emergence of New Diseases*




*or Recurrence; [1] Reported by investigator; [2] WHO definition of random glucose measurement >11.0 mmol/l or use of anti-diabetic drugs

# Randomized Design of ALLHAT

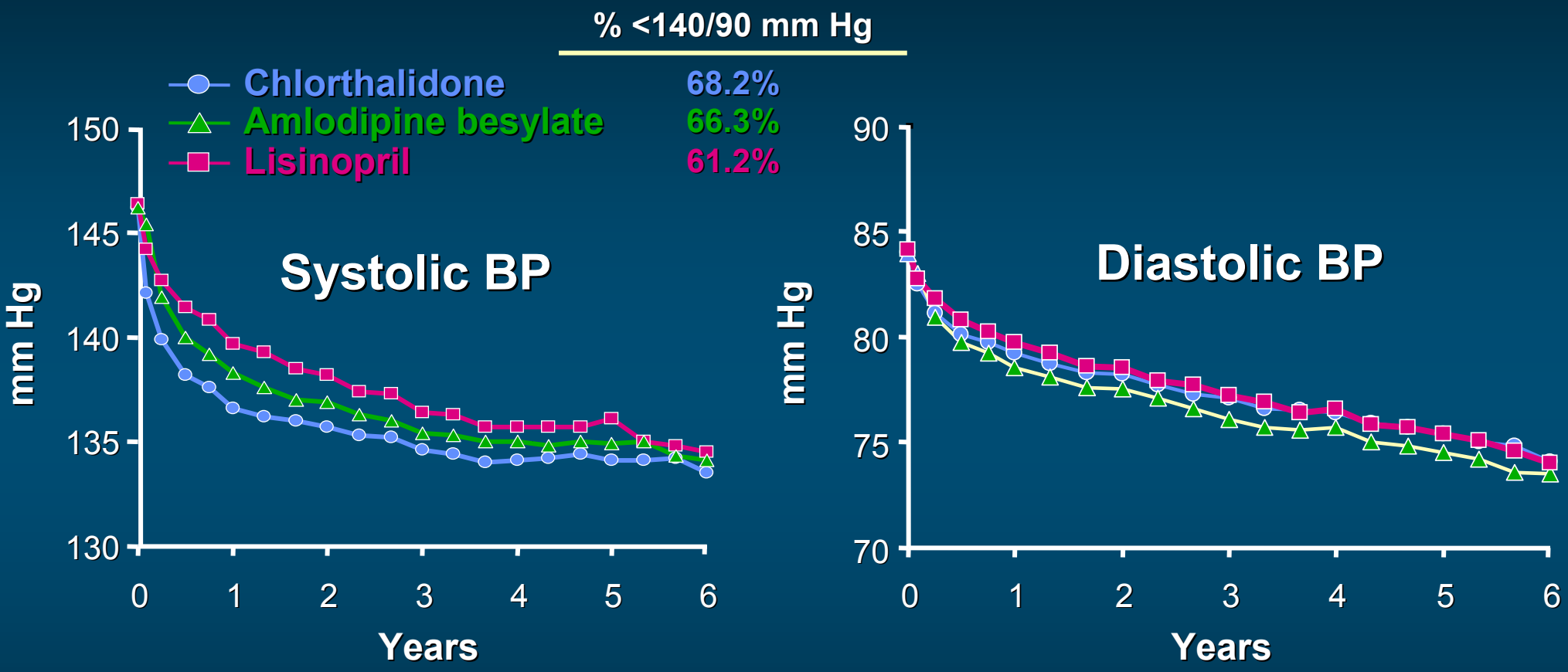



*In January 2000, the National Heart, Lung, and Blood Institute decided to discontinue the doxazosin arm of the antihypertensive trial and report results.

ALLHAT Collaborative Research Group. *JAMA*. 2000;283:1967-1975.

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

# ALLHAT: BP by Treatment Group




**Compared with chlorthalidone:**

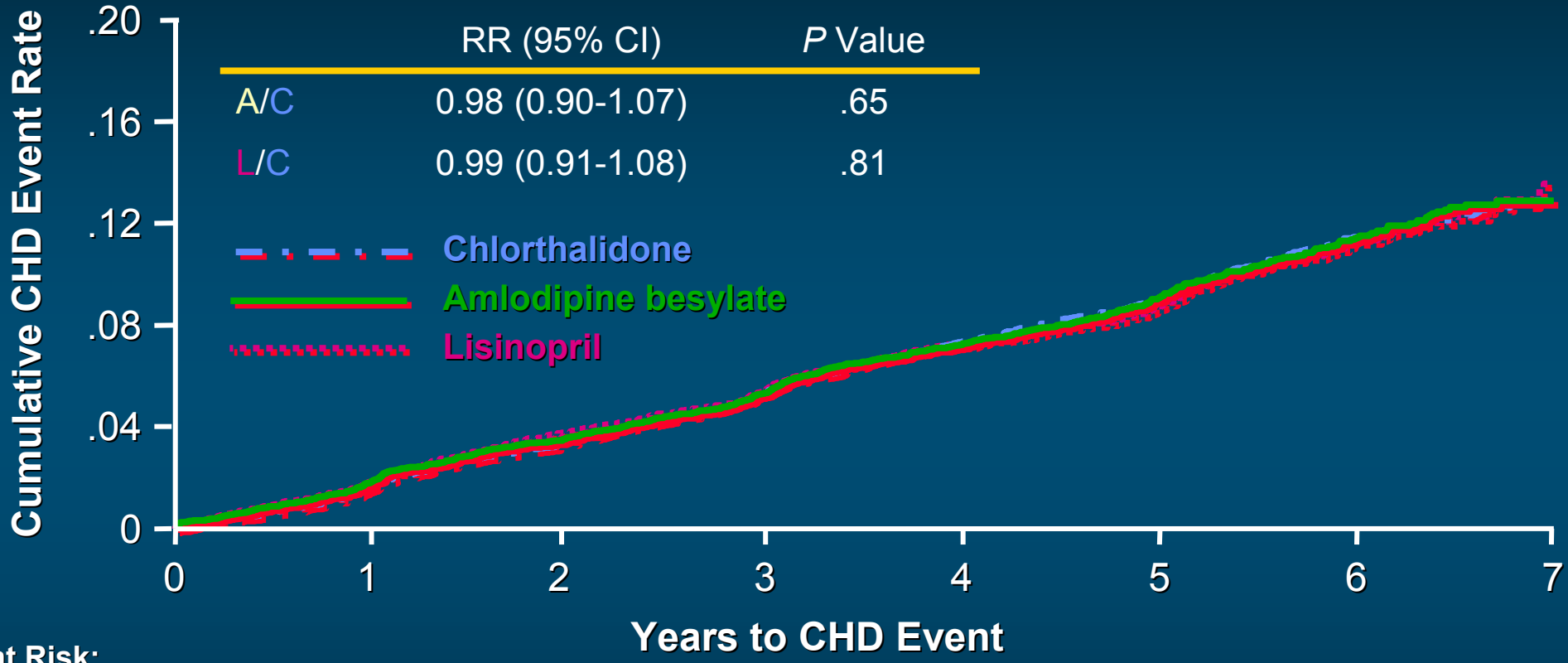
**SBP significantly higher in the amlodipine group (0.8 mm Hg) and the lisinopril group (2 mm Hg) at 5 years**

**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: Fatal CHD or Nonfatal MI



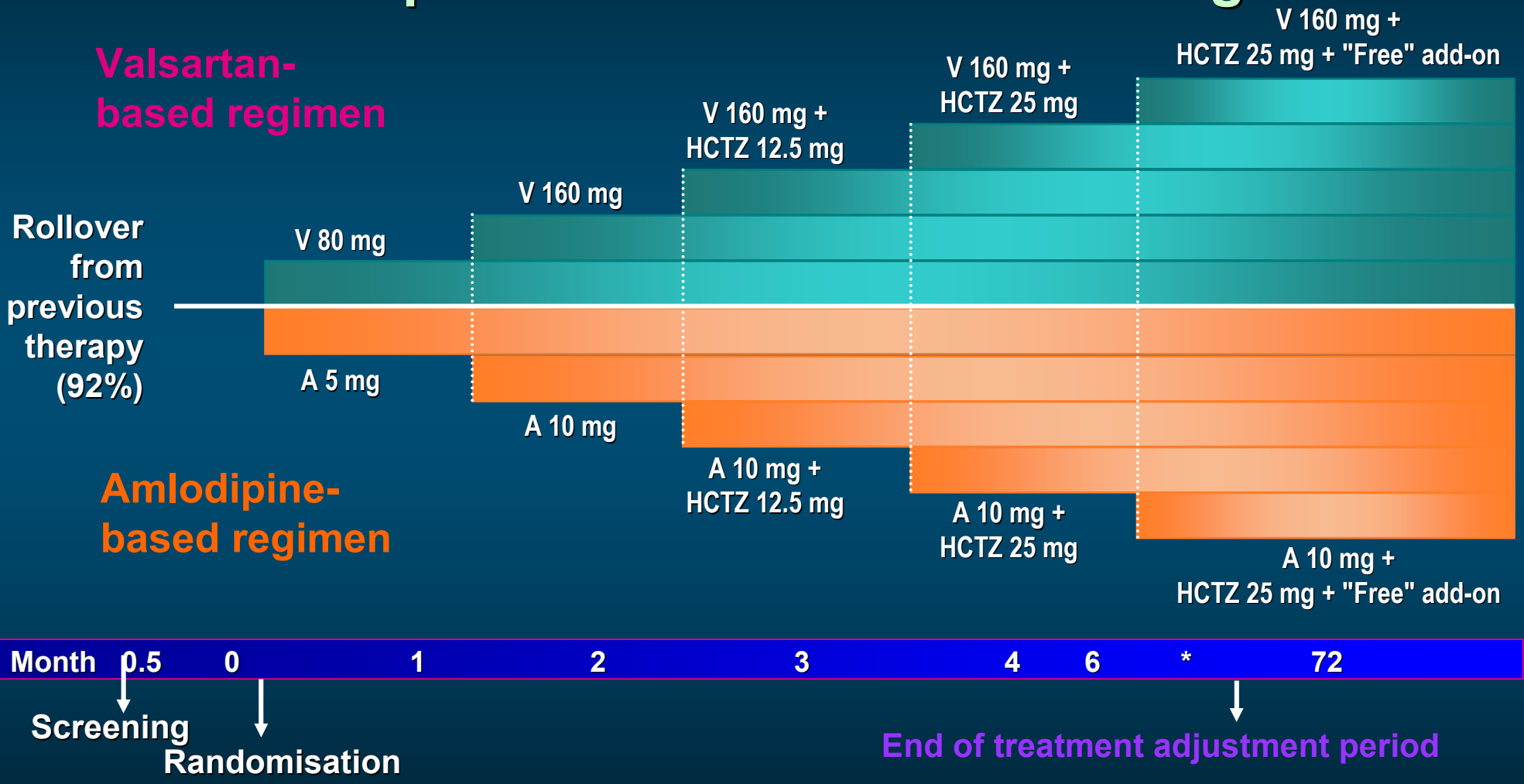

**Number at Risk:**

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Chlorthalidone | 15,255 | 14,477 | 13,820 | 13,102 | 11,362 | 6340 | 2956 | 209 |
| Amlodipine | 9048 | 8576 | 8218 | 7843 | 6824 | 3870 | 1878 | 215 |
| Lisinopril | 9054 | 8535 | 8123 | 7711 | 6662 | 3832 | 1770 | 195 |

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

# VALUE: Design

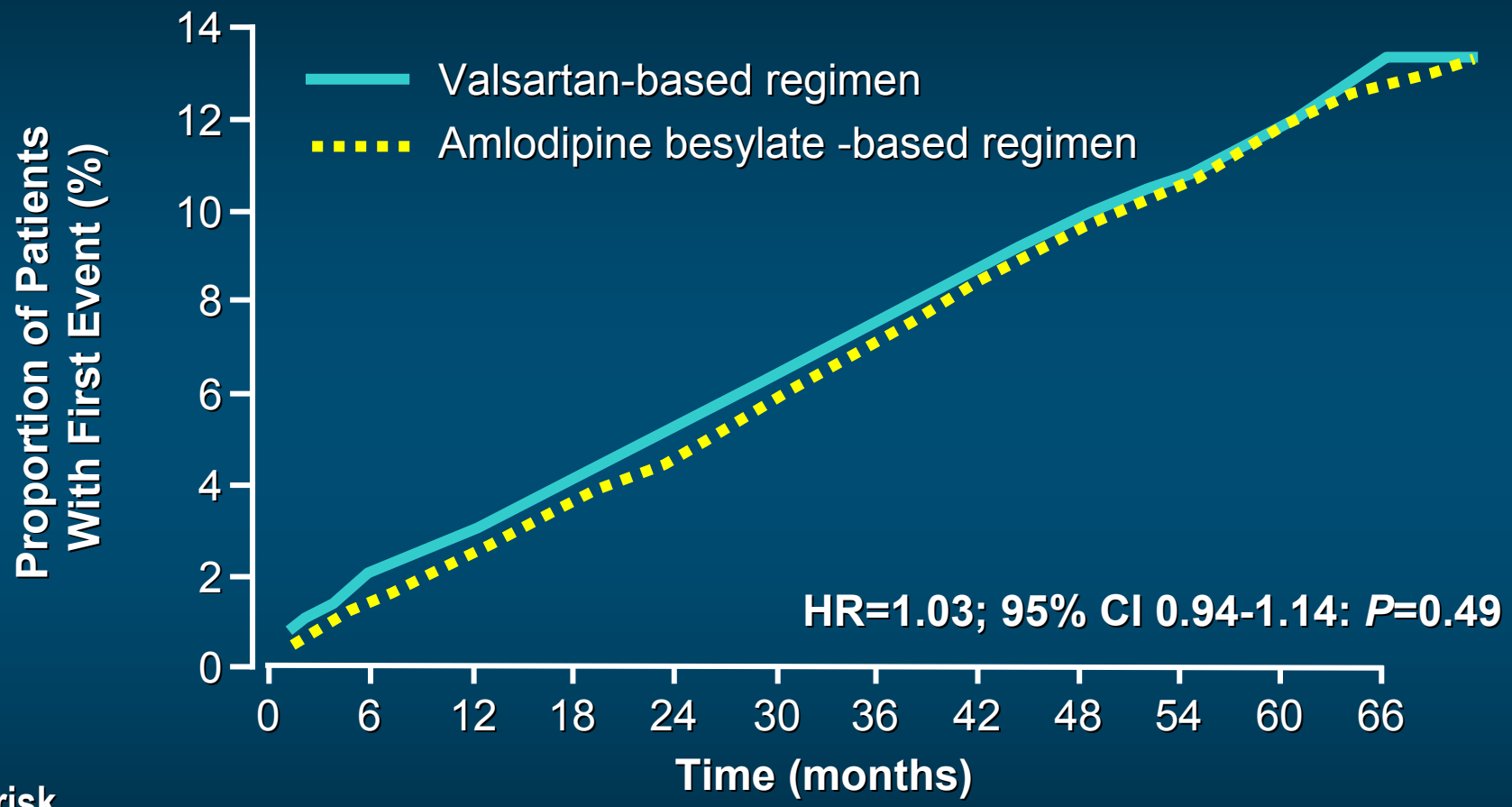
## 15245 HT pt with elective titration to target BP




*Patient visits every 6 months for months 6-72.

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

# VALUE: Primary Composite Endpoint

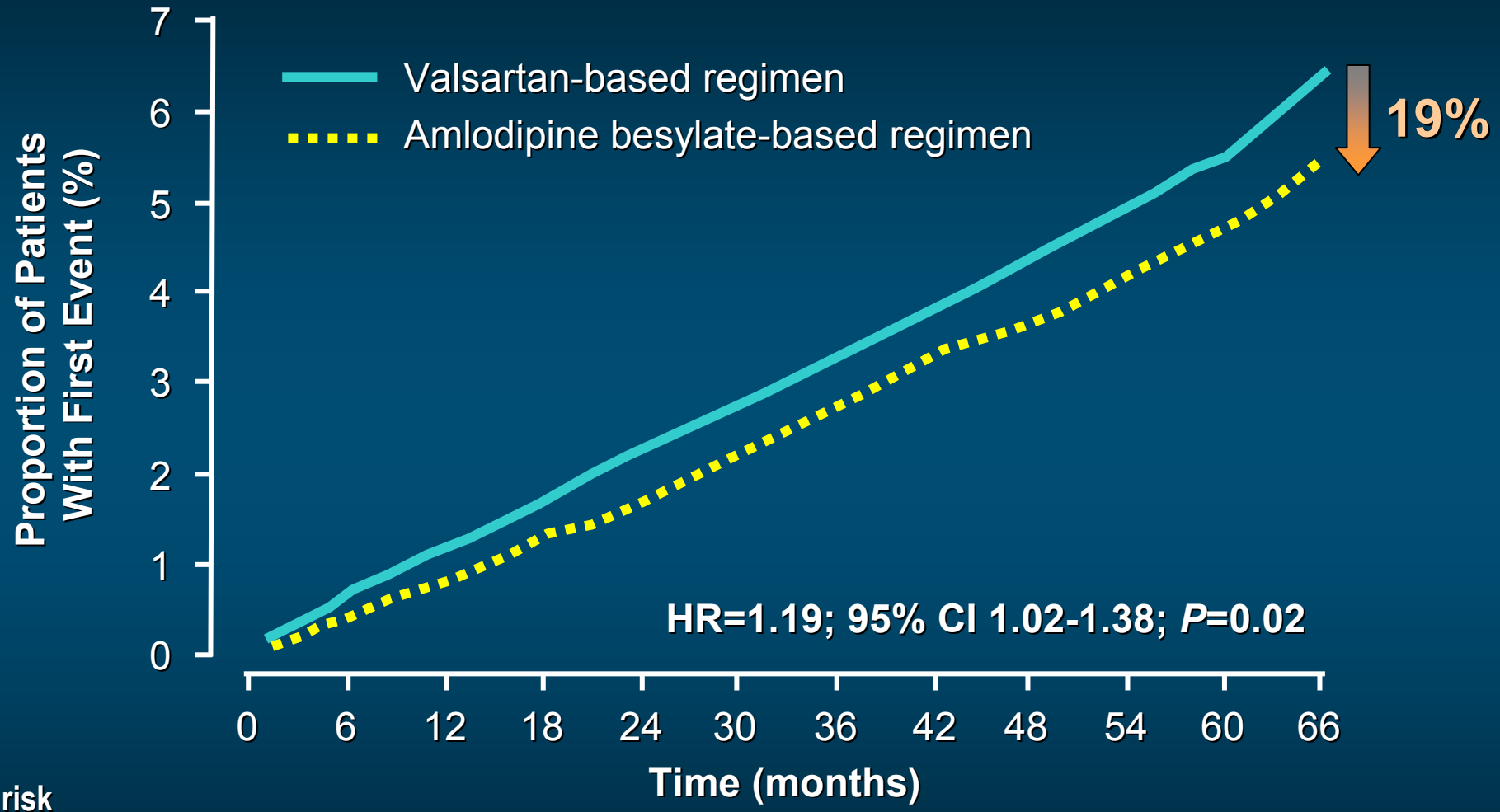



**Number at risk**

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 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

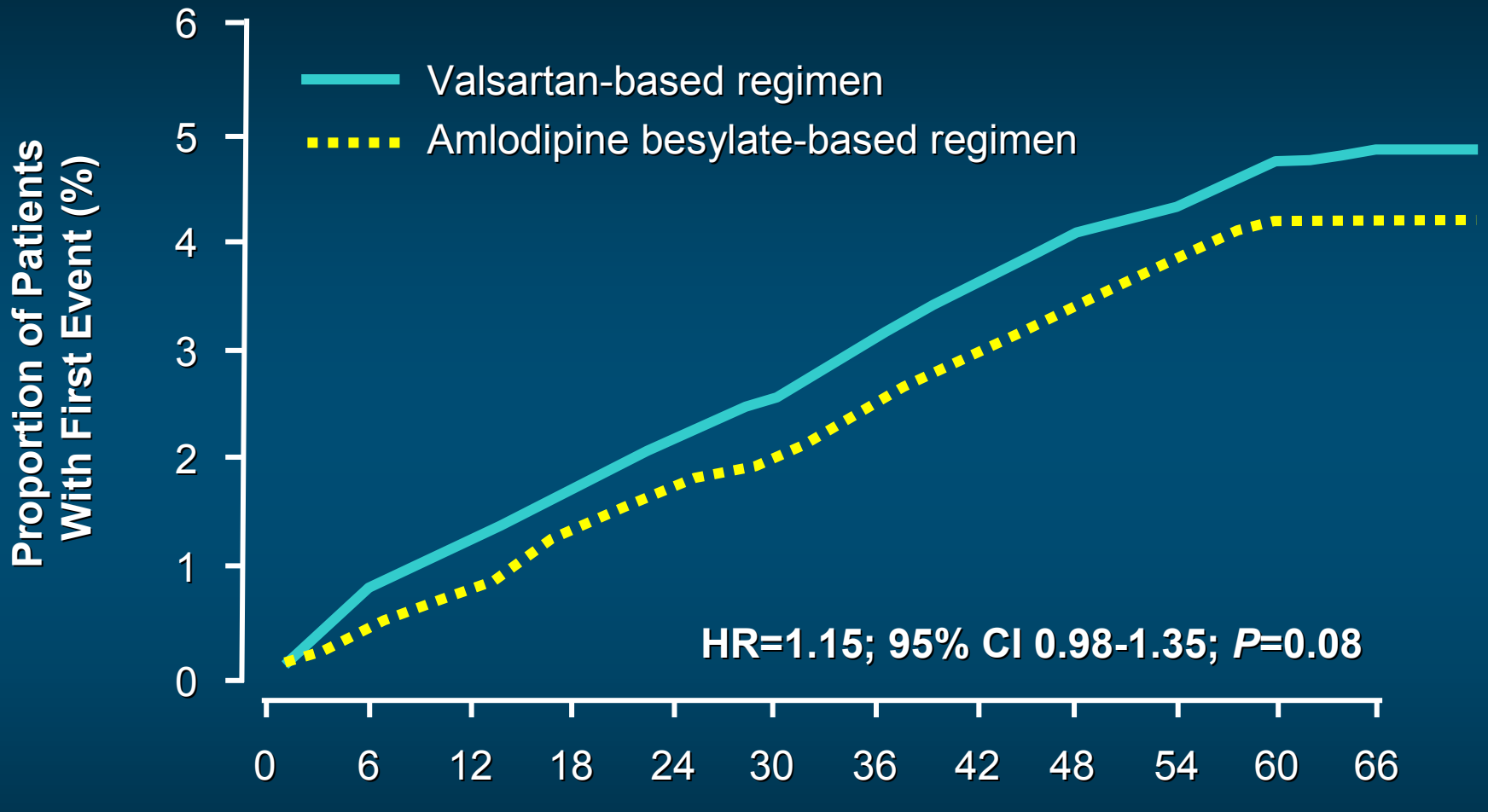



**Number at risk**

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 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: Fatal and Non-fatal Stroke

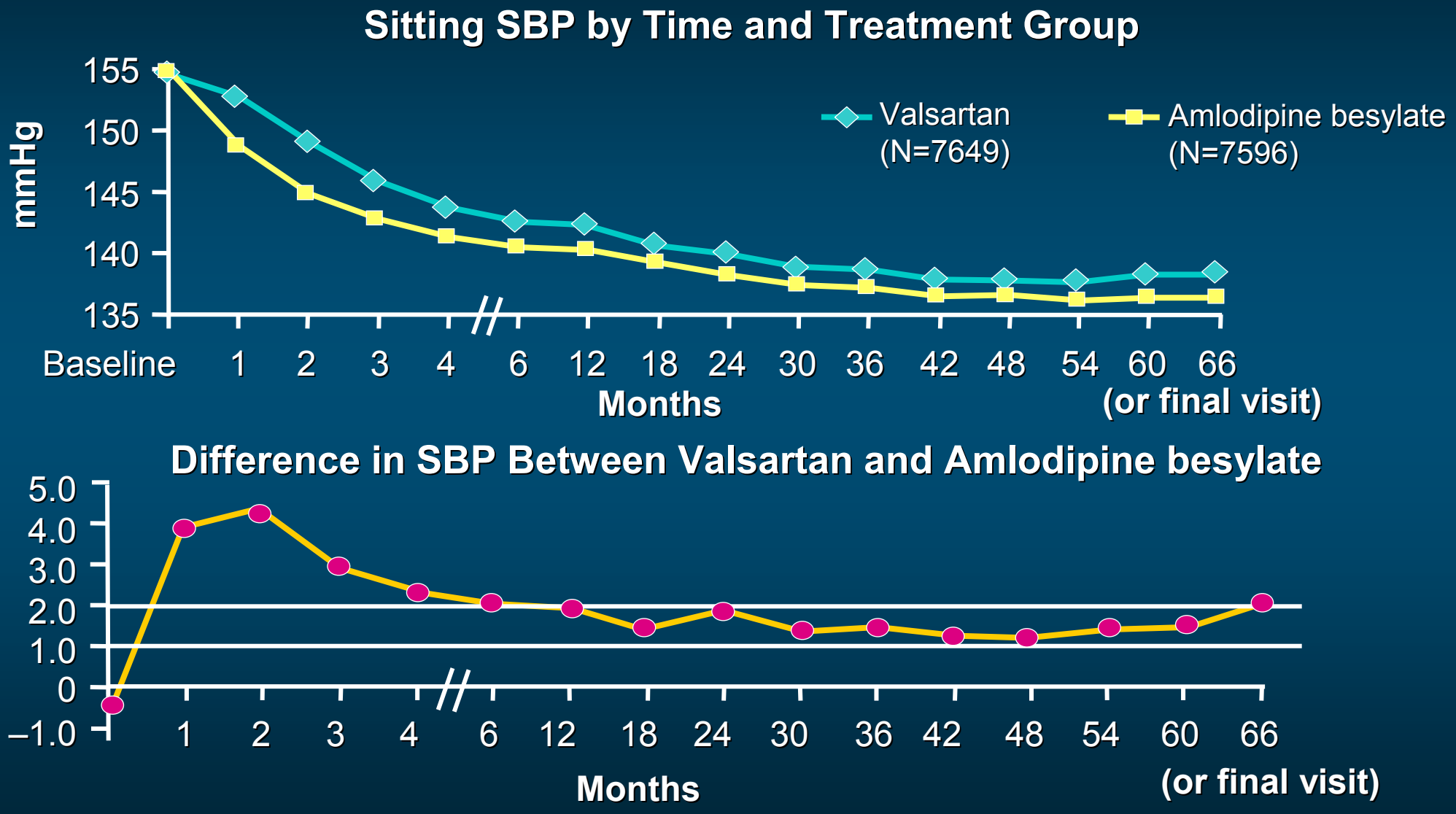



**Number at risk**

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

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

# VALUE: Systolic BP in Study

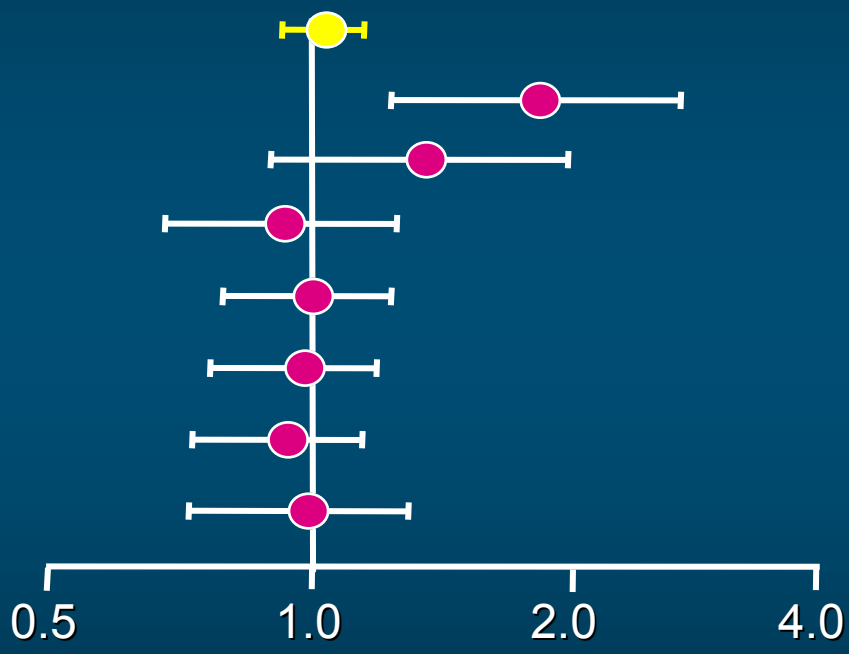



Julius S et al. *Lancet*. June 2004;363.

# VALUE: Outcome and SBP Differences

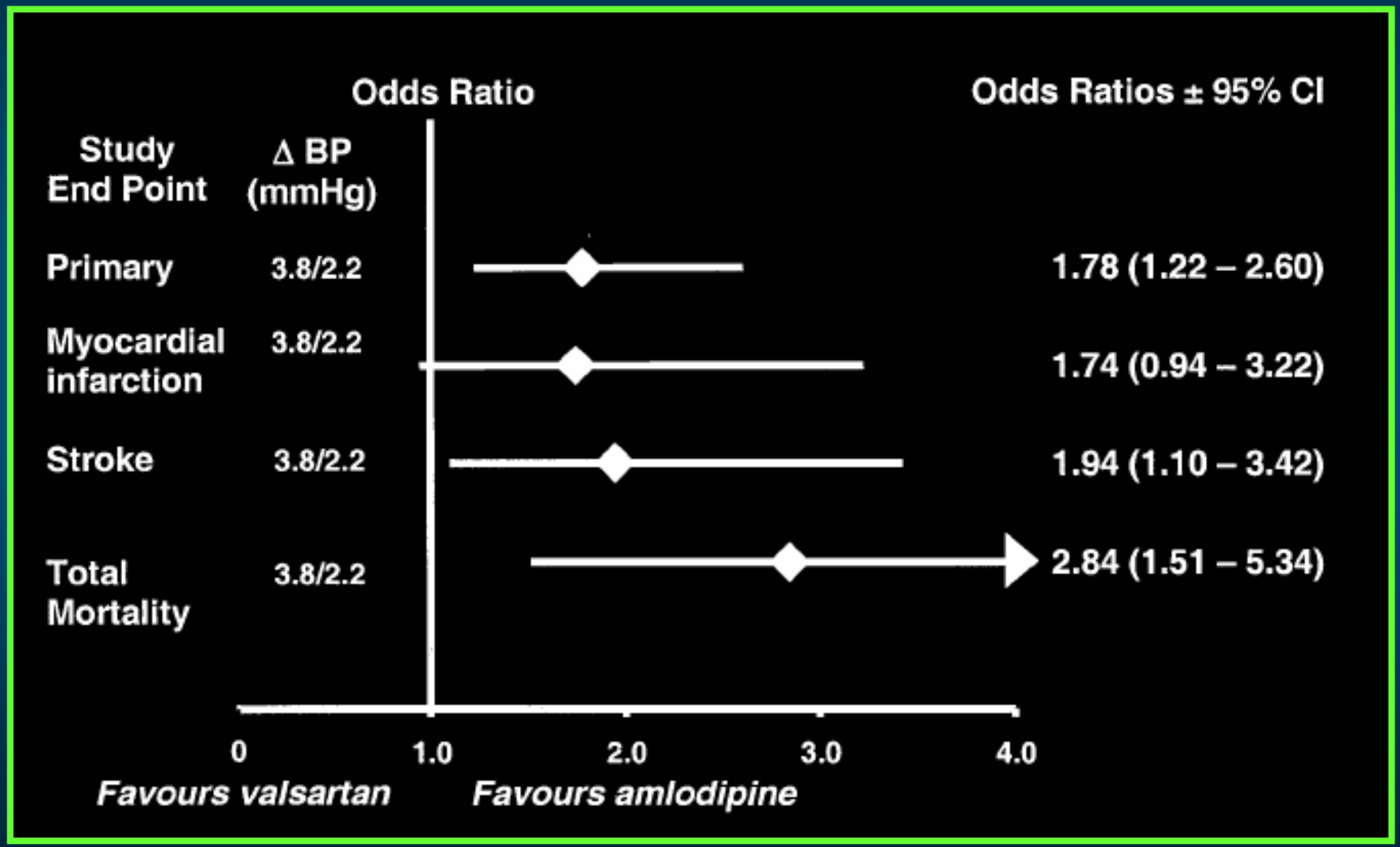
| Time Interval (months) | ΔSBP mm Hg |
|---|---|
| **Overall study** | **2.2** |
| 0–3 | 3.8 |
| 3–6 | 2.3 |
| 6–12 | 2.0 |
| 12–24 | 1.8 |
| 24–36 | 1.6 |
| 36–48 | 1.4 |
| Study end | 1.7 |

**PRIMARY ENDPOINT**
**Odds Ratios and 95% CIs**




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

# VALUE: Outcome and SBP Differences

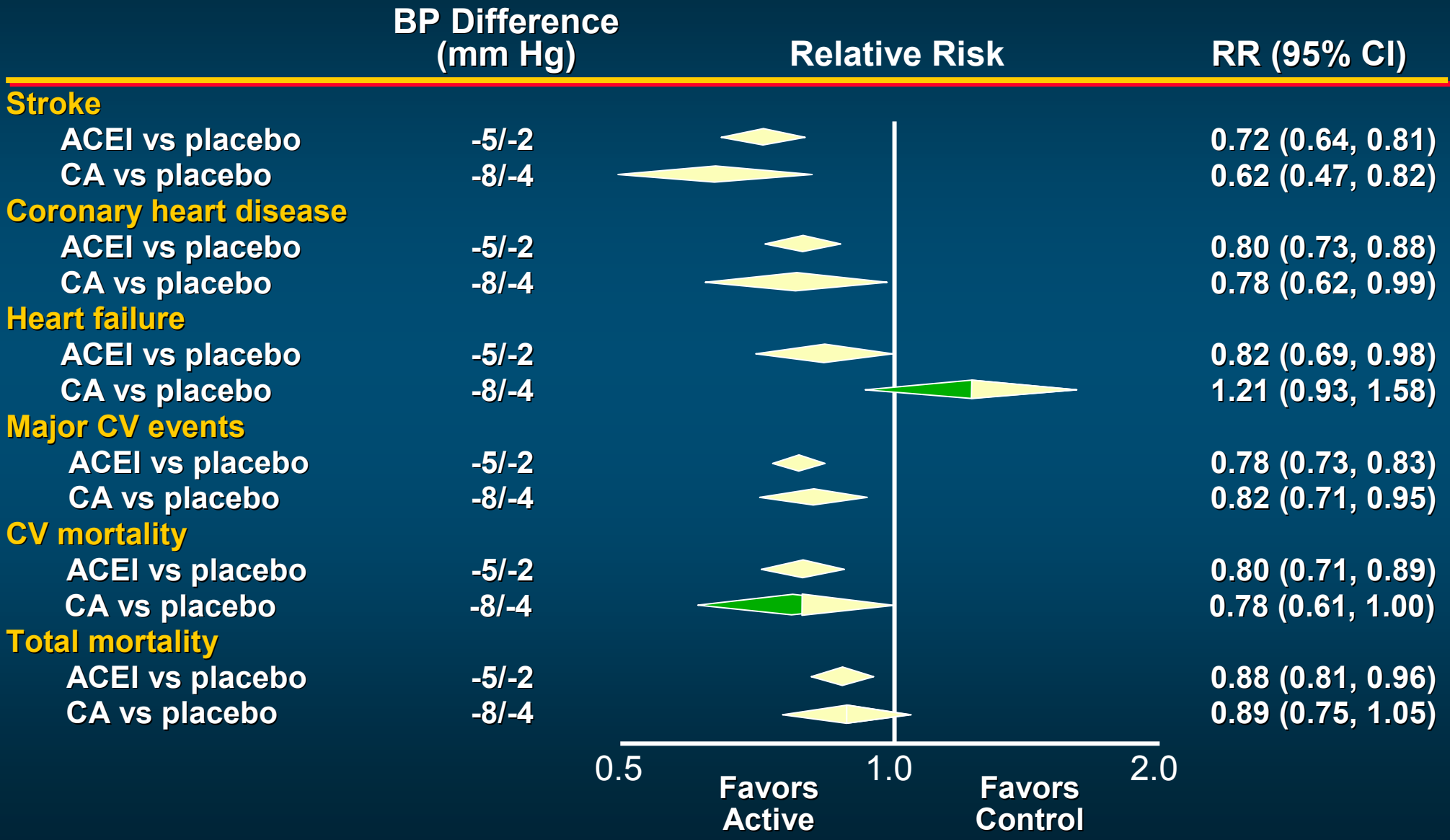


# New ESC Guideline: Early Treatment

| 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 |

# BP-Lowering Treatment Trialists

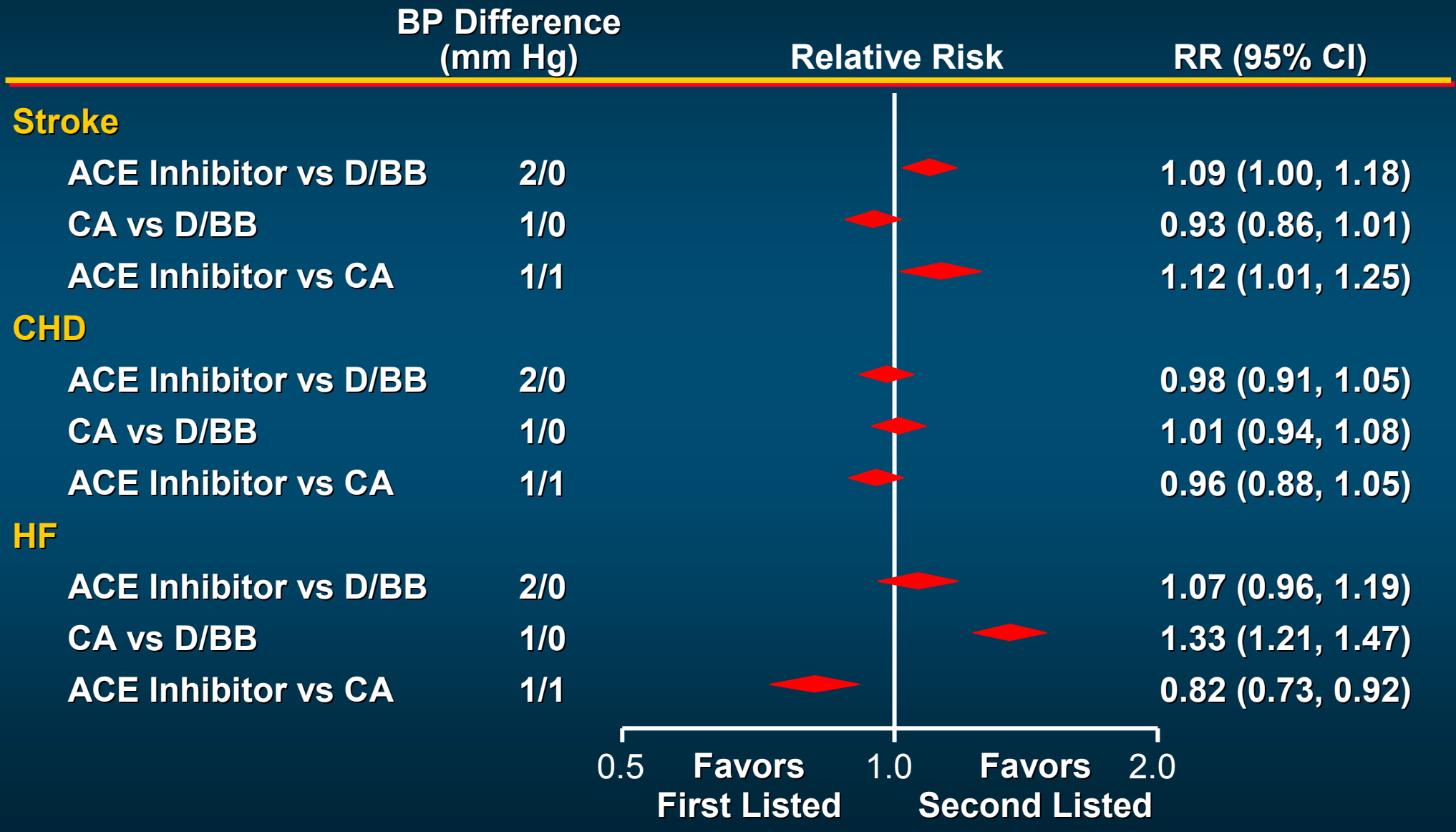
## *Comparisons of Active Treatments and Control*




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

# BP-Lowering Treatment Trialists

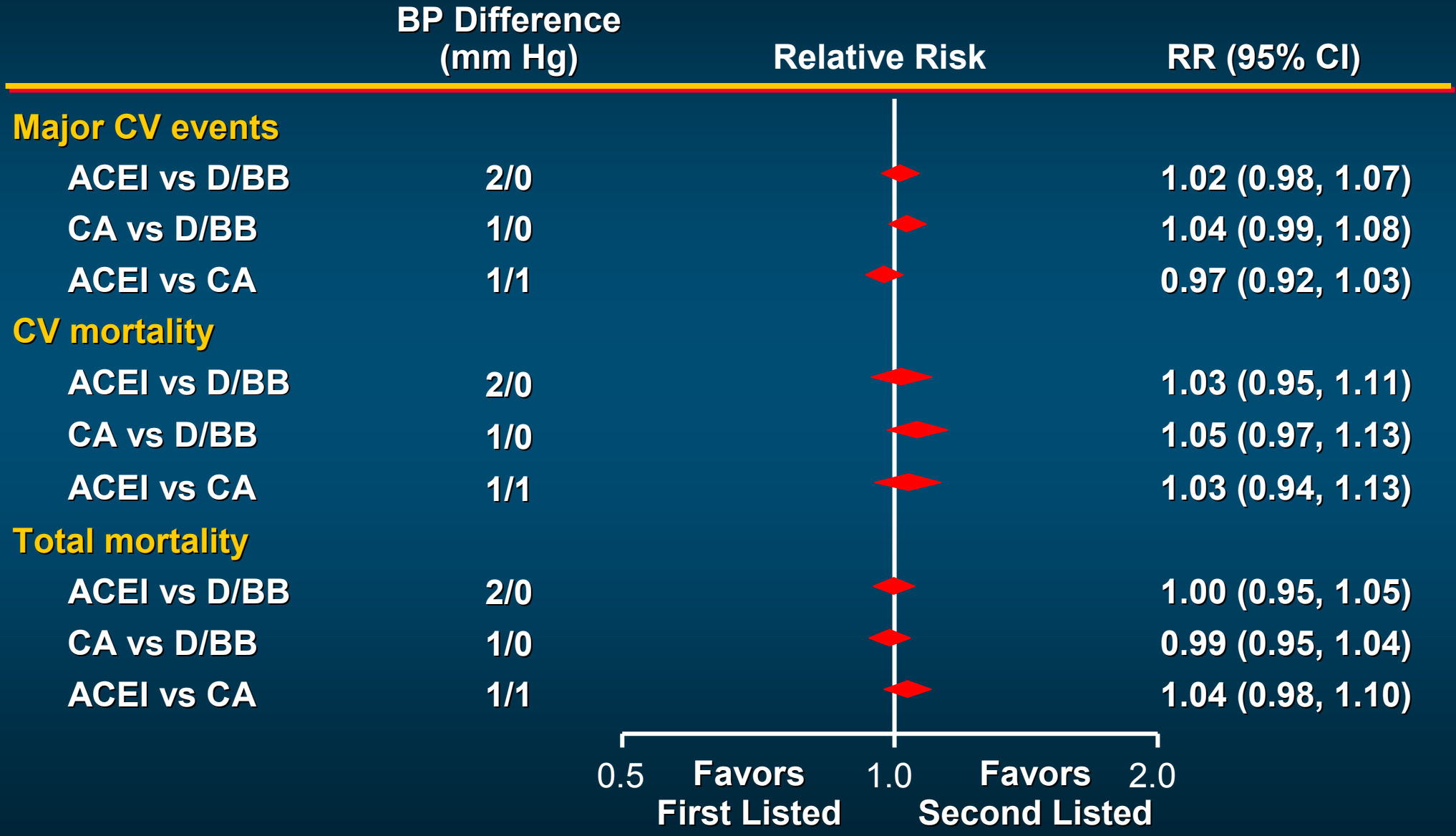
## *Comparisons of Different Active Treatments*




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

# BP-Lowering Treatment Trialists

## *Comparisons of Different Active Treatments*




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

# Contents

- Clinical significance of hypertension
- CCB: Brief introduction
- Evidences of CCB's in HT and CAD
- Review on 'beyond BP lowering effect'
- Practical usefulness of CCB's

# HOPE Trial

**9,297 pt with CAD or DM plus 1 RF (no CHF, LV dysfxn)**

**75% Aspirin, 40% beta-blocker, 30% statin**

**Ramipril 10mg/day**
**n=4,645**

**Placebo**
**n=4,652**

**Primary Endpoint**

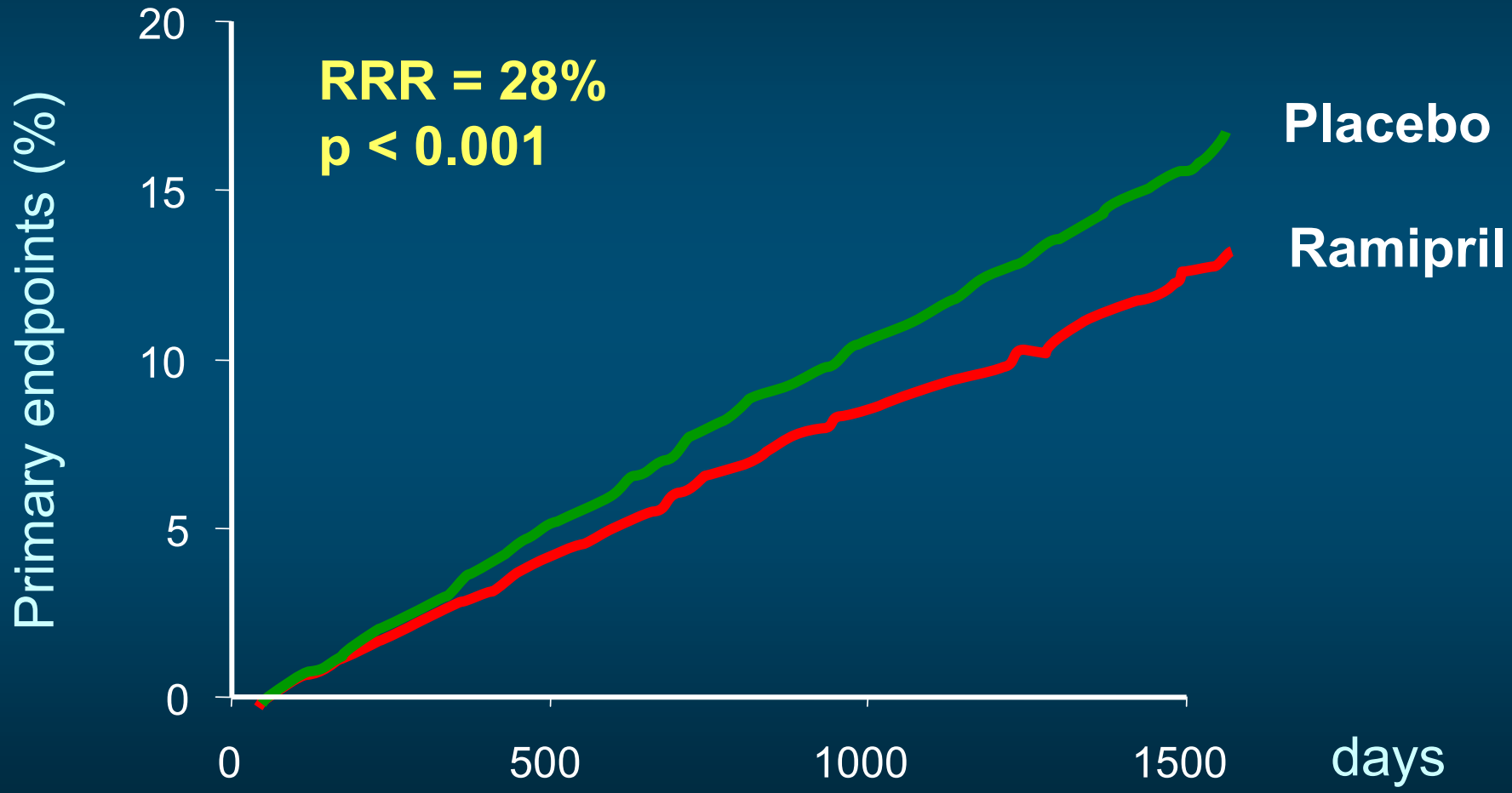
**Composite of cardiac death, MI, or stroke**

**follow-up: 5 years**

The HOPE investigators. N Engl J Med 2000 ; 342 : 145-53

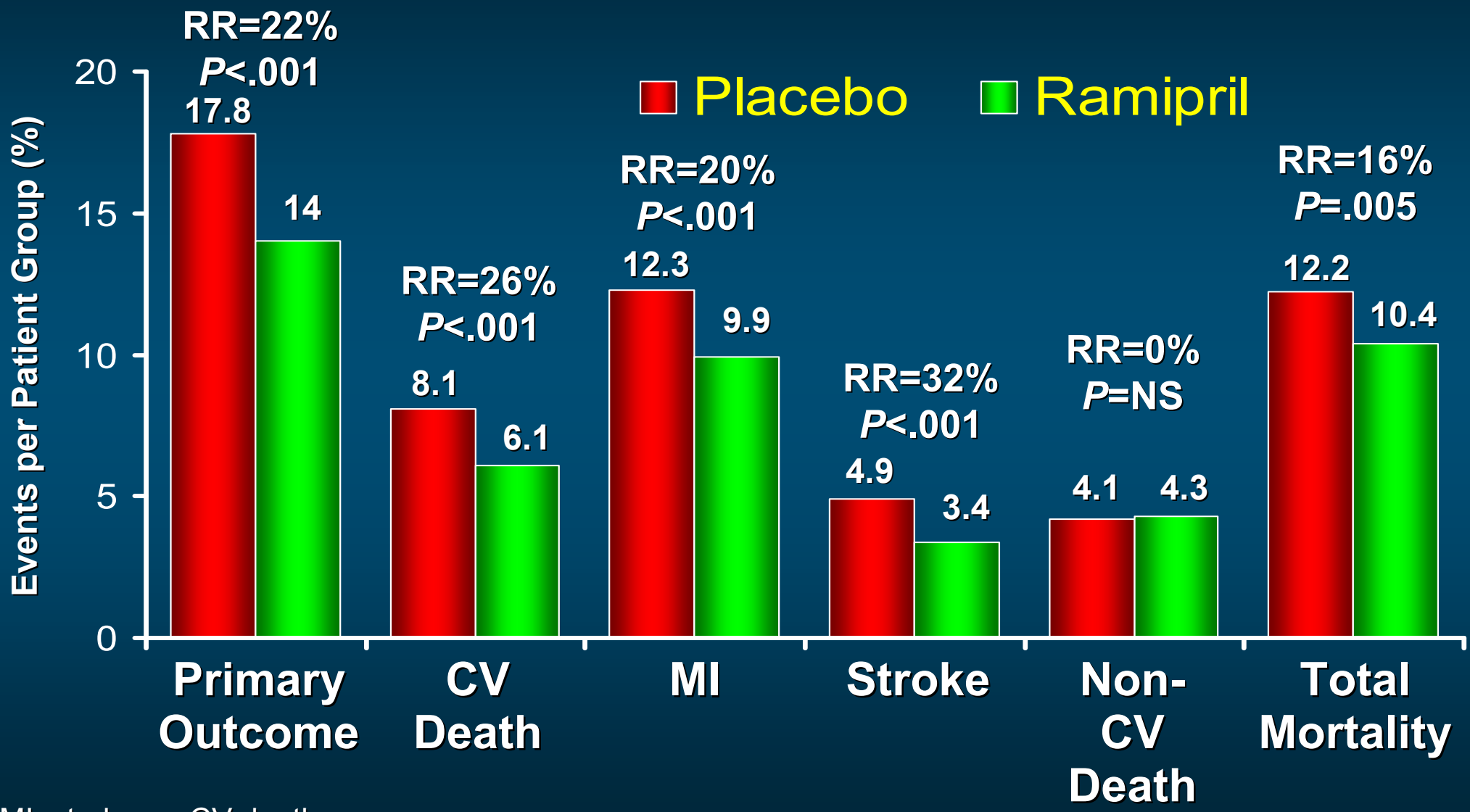
# HOPE: Primary Endpoint

## cardiac death, MI, or stroke




The HOPE investigators. N Engl J Med 2000 ; 342 : 145-53

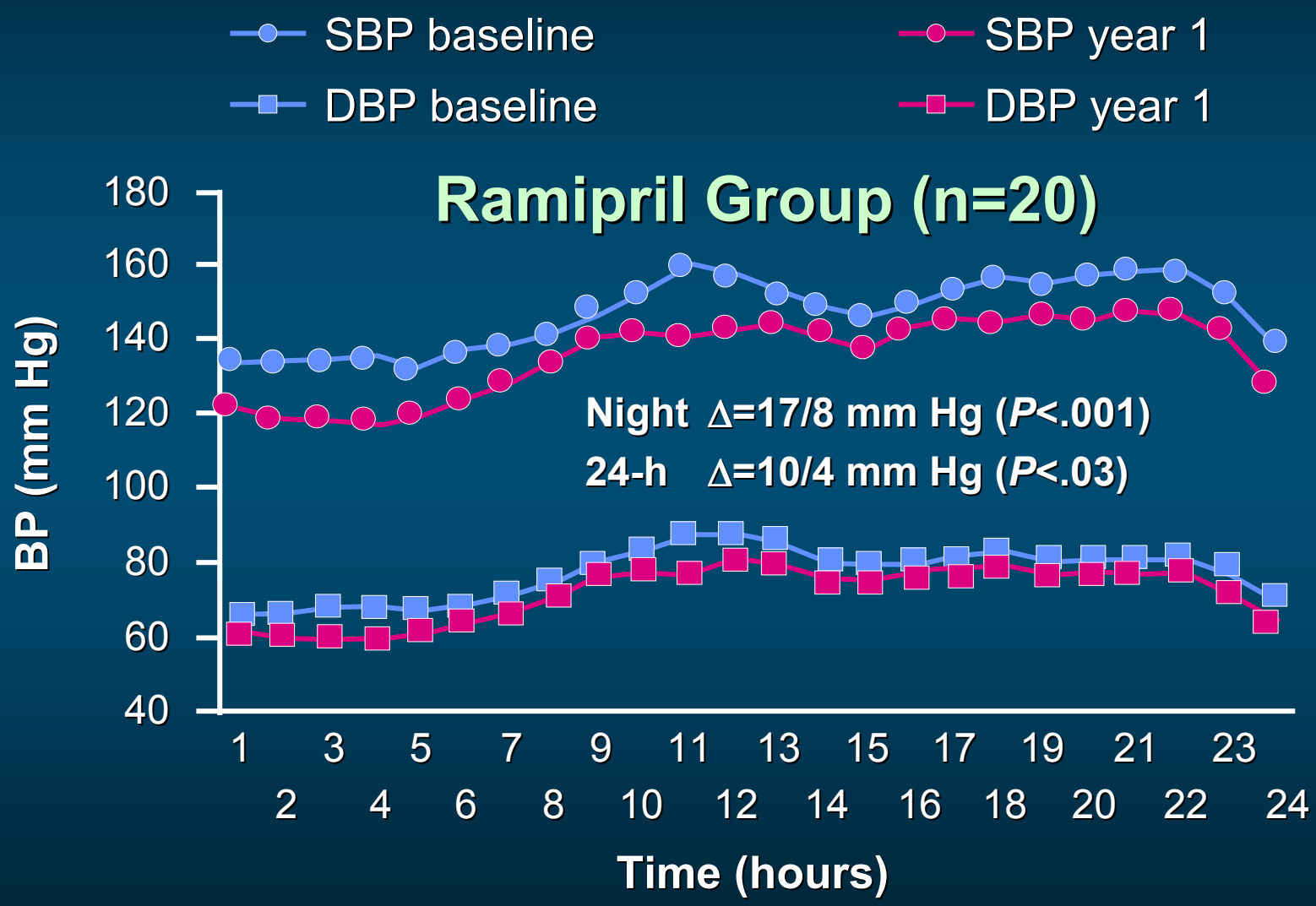
# HOPE: Events per Patient Group




*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.

# EUROPA Trial

**12,218 patients with stable angina without CHF**

**90% Aspirin, 60% beta-blocker, 60% statin**

**Perindopril 8mg/day**
**n=6,110**

**Placebo**
**n=6,108**

**Primary Endpoint**

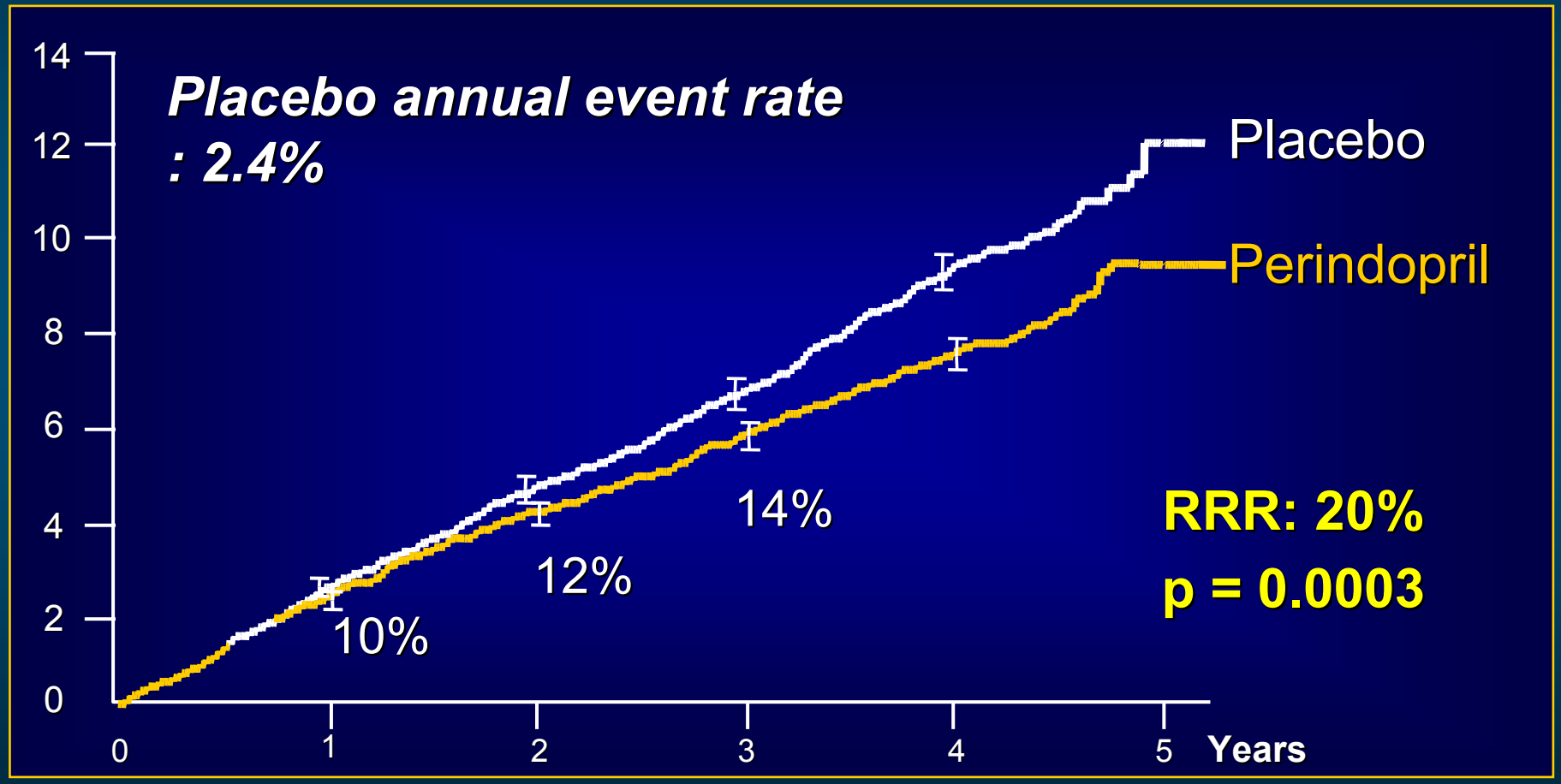
**Composite of cardiac death, MI, or cardiac arrest**

**mean follow-up: 4.2 years**

Lancet 2003; 362: 782-88

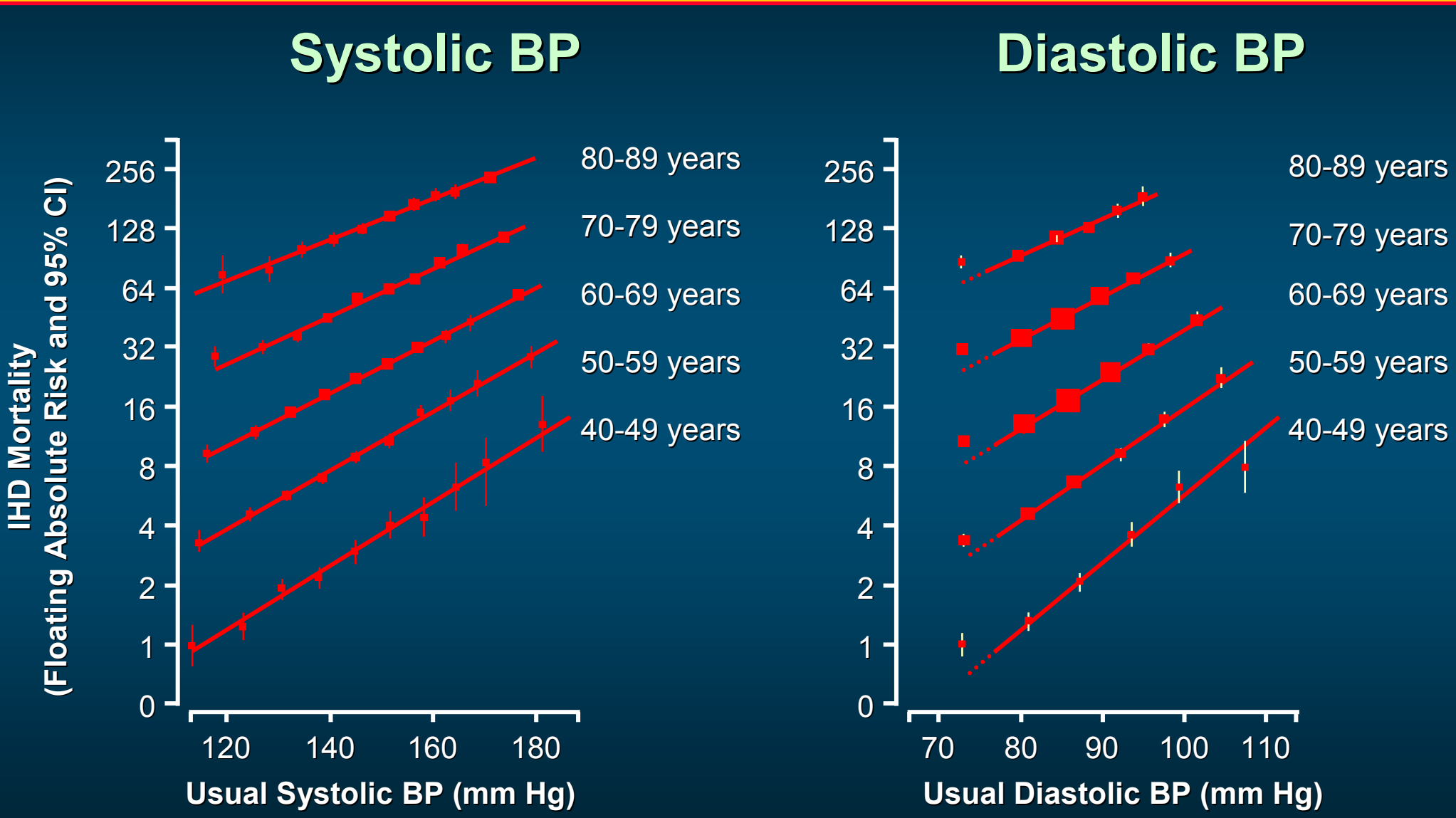
# EUROPA: Primary Endpoint

## % CV death, MI or cardiac arrest



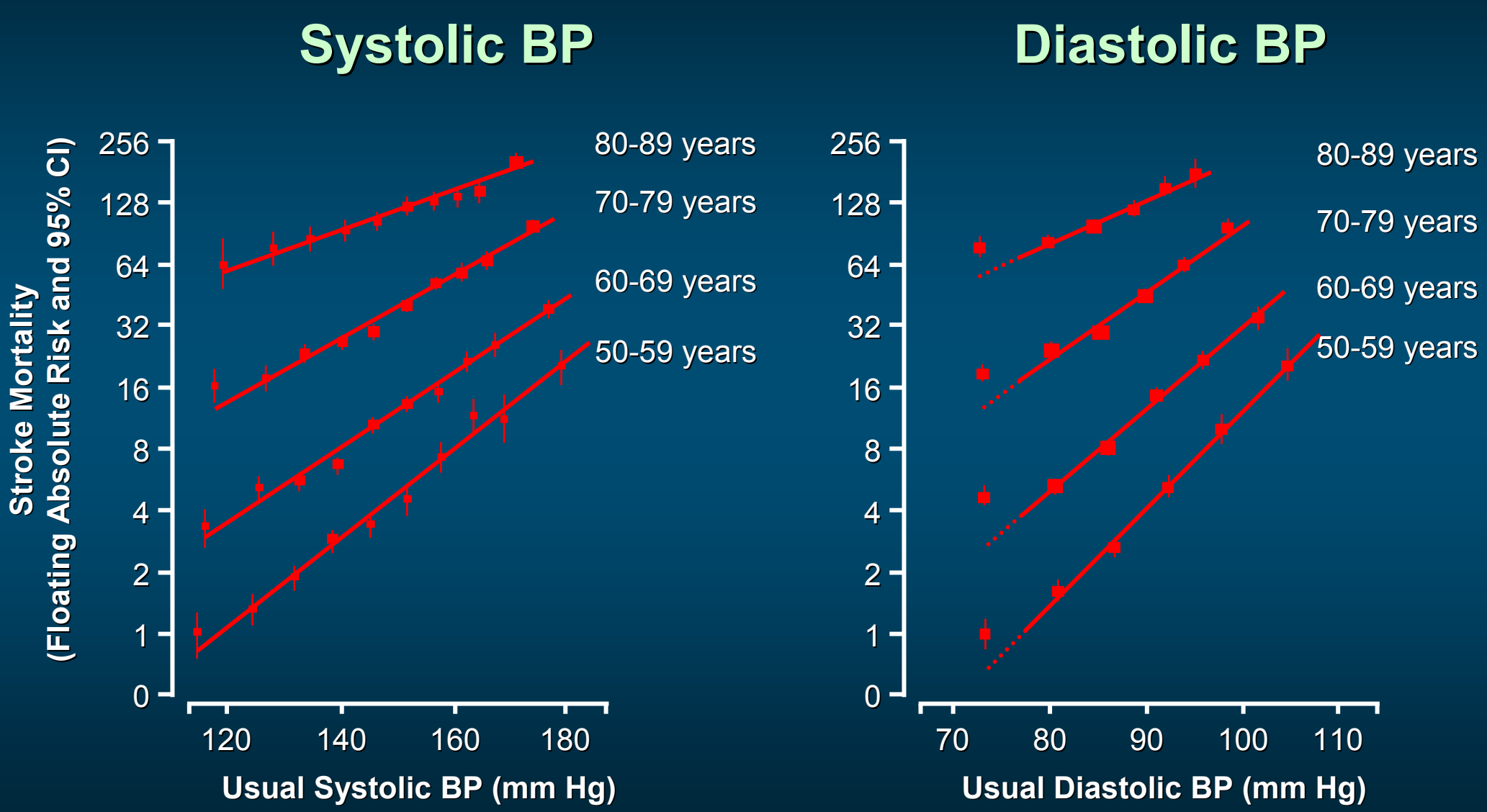

Lancet 2003; 362: 782-88

# CAD Mortality and Usual BP by Age



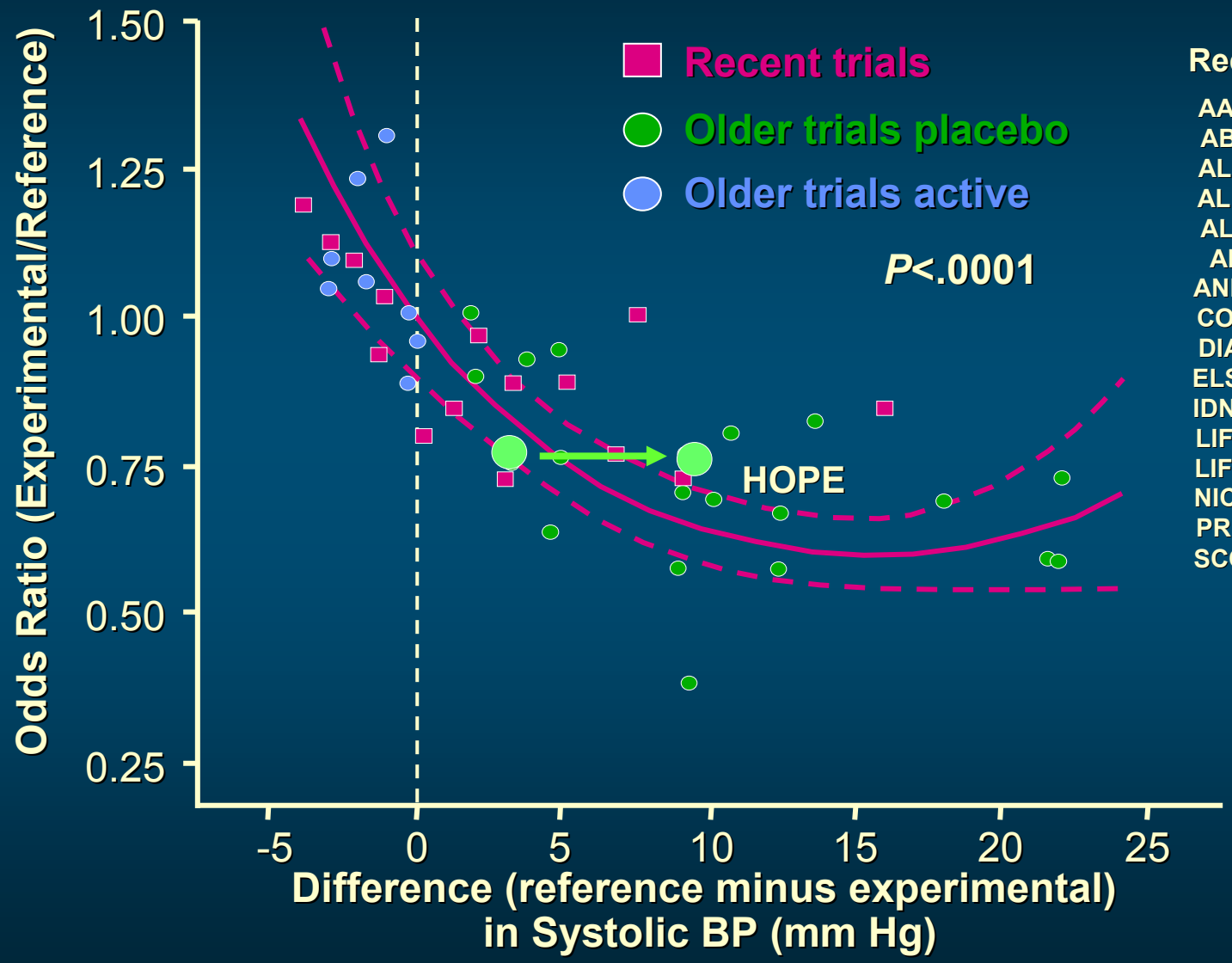

Prospective Studies Collaboration. *Lancet*. 2002;360:1903-1913.

# Stroke Mortality and Usual BP by Age




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

# Odds Ratio for CV Events & SBP Difference




**Recent**

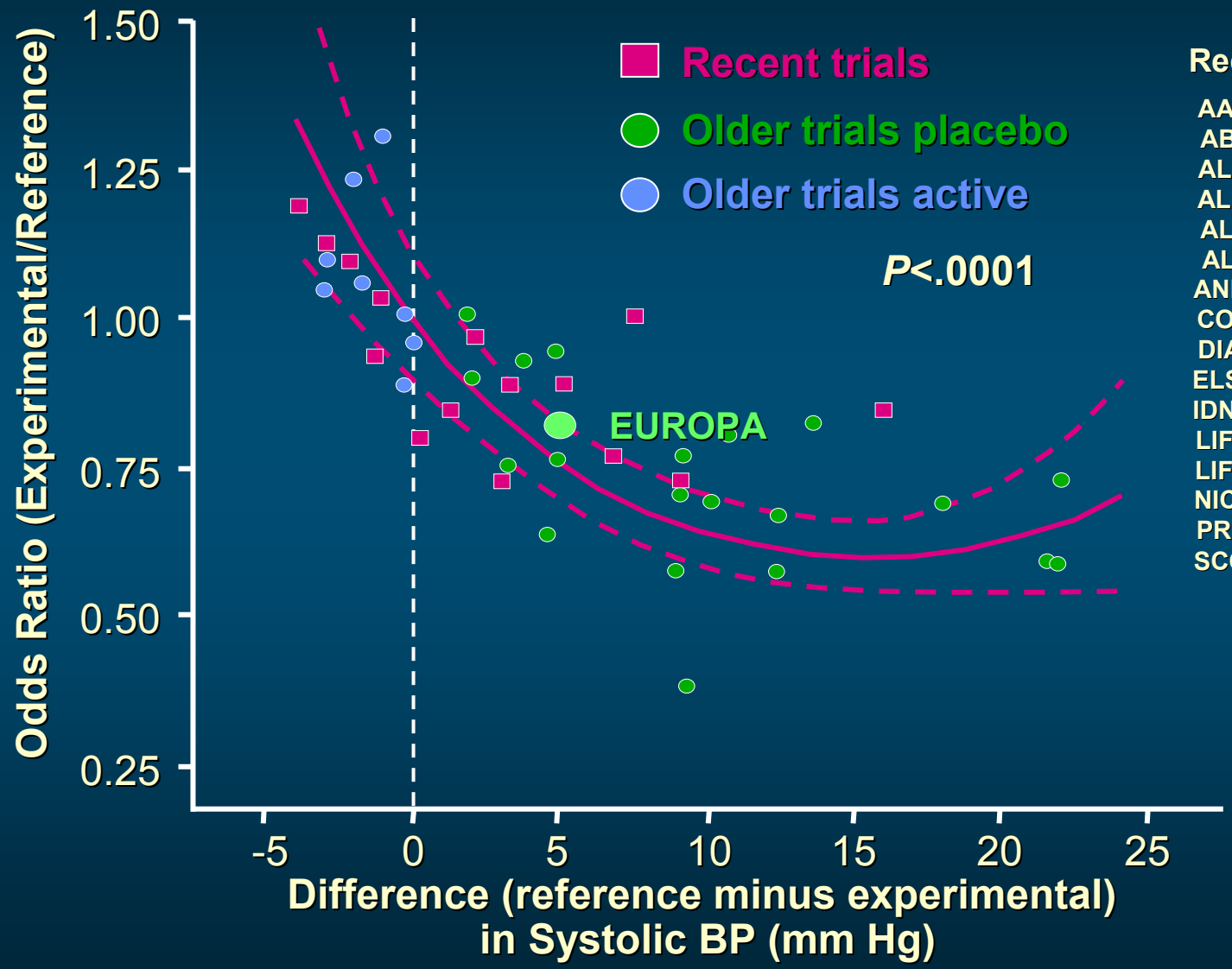
AASK L vs H
ABCD/NT L vs H
ALLHAT/Aml
ALLHAT/Lis
ALLHAT/Lis ≥65
ALLHAT/Lis Blcks
ANBP2
CONVINCE
DIABHYCAR
ELSA
IDNT2
LIFE/ALL
LIFE/DM
NICOLE
PREVENT
SCOPE

**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.

# Odds Ratio for CV Events & SBP Difference




**Recent**

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

**Older**

- ALLHAT/Dox
- ATMH
- EWPHE
- HEP
- HOPE
- HOT
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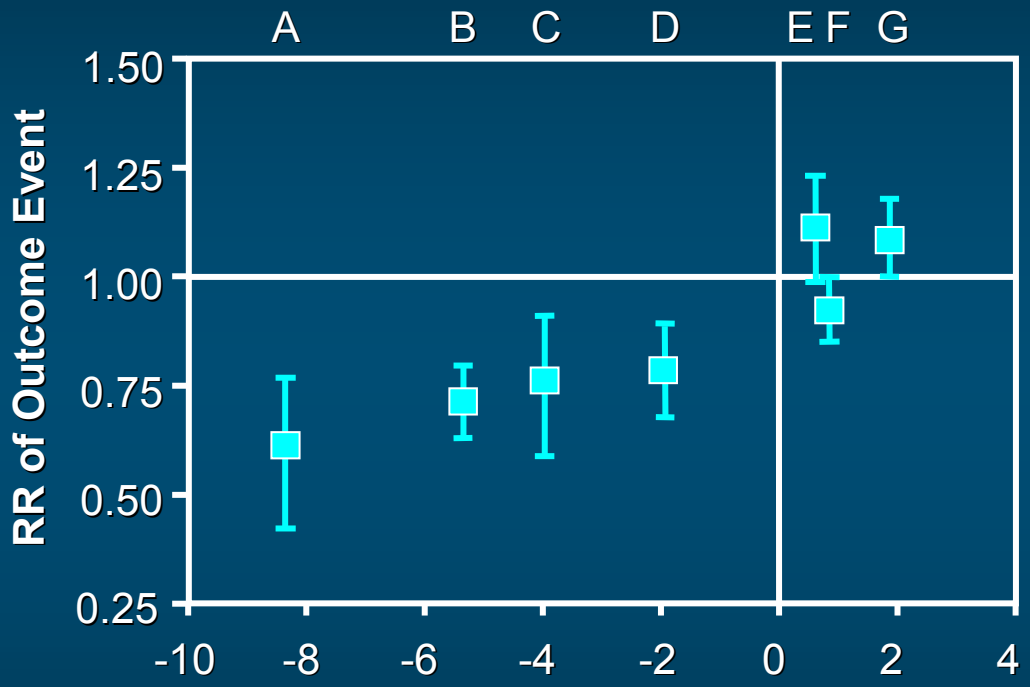
Fox. *Lancet.* 2003;362:782-788; Staessen et al. *J Hypertens*. 2003;21:1055-1076.

# Target BP in HT

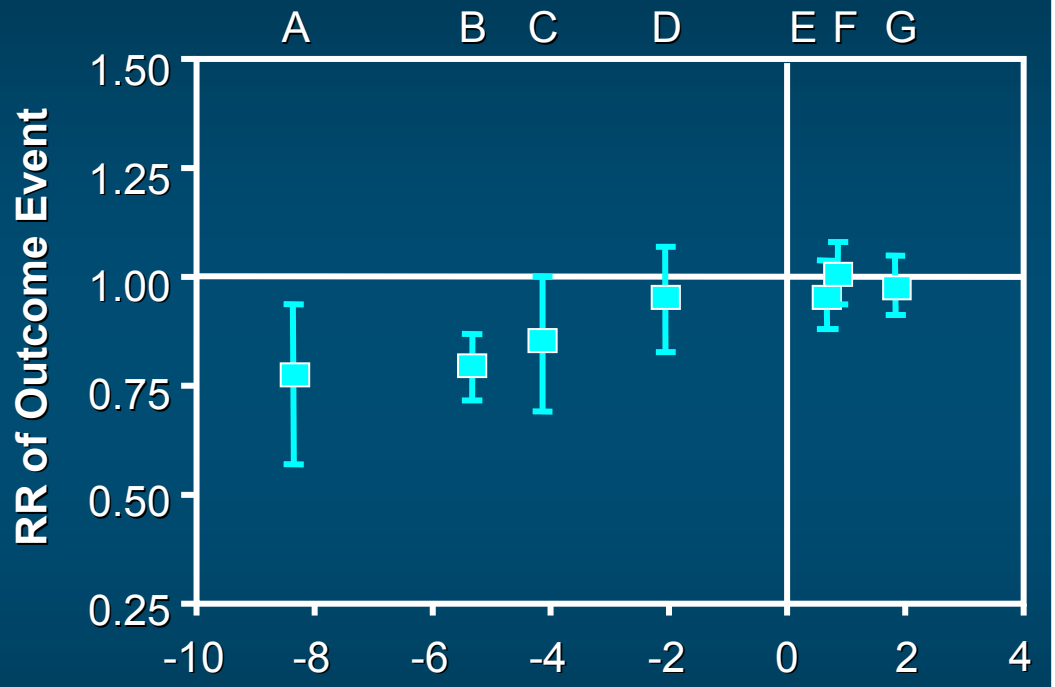
- JNC 7, 2004
  - 140/90
  - 130/80: DM, renal disease
- ESC guideline, 2007
  - 140/90
  - 130/80: DM,
    established CV ds ( stroke, MI, renal ds)

# BP-Lowering Treatment Trialists

## Stroke




## CHD

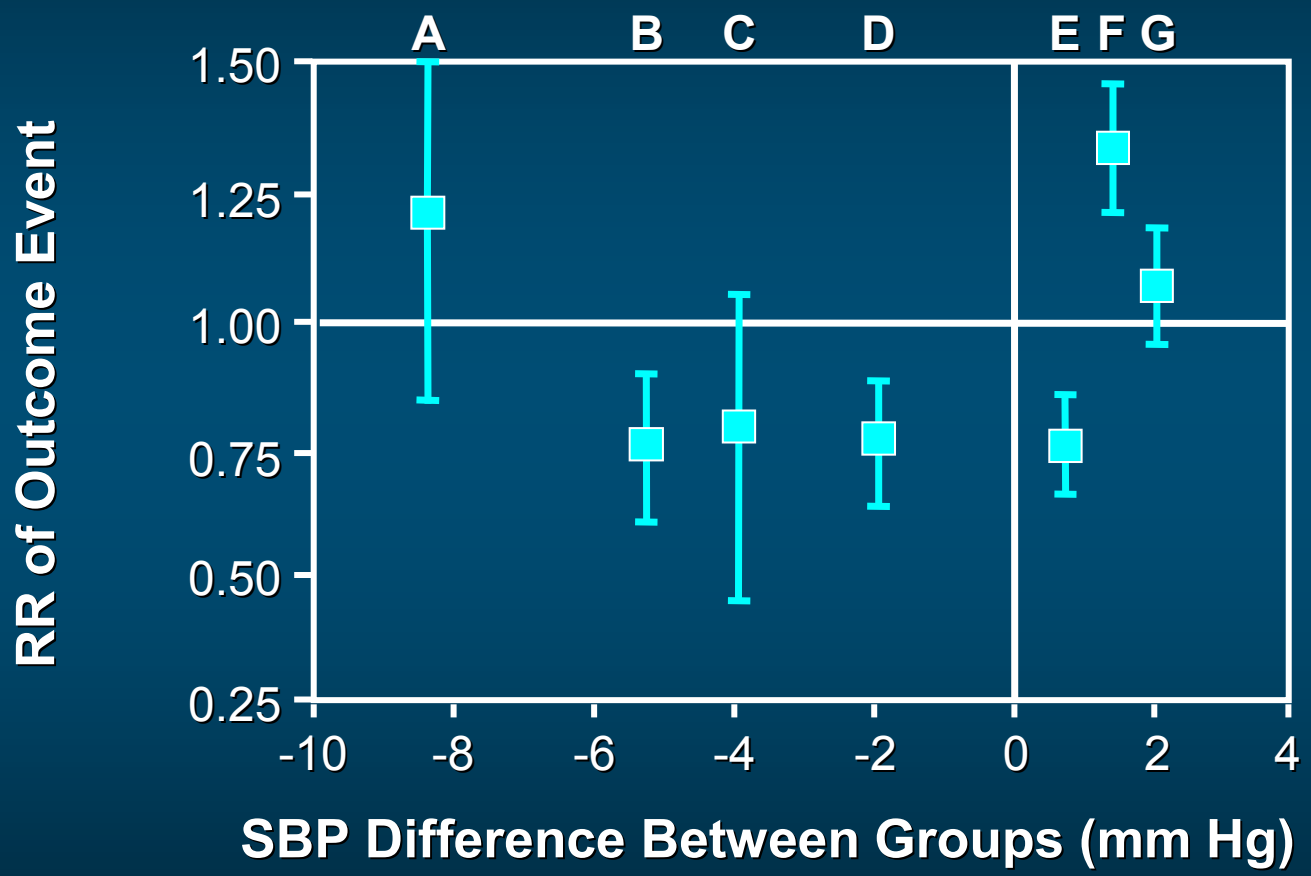



A = CA *vs* placebo; B = ACE inhibitor vs placebo; C = more intensive vs less intensive blood- pressure-lowering; D = ARB vs control; E = ACE inihibitor vs CA; F = CA vs diuretic or β-blocker; G = ACE inhibitor vs diuretic and β-blocker.

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

# BP-Lowering Treatment Trialists

## Heart Failure



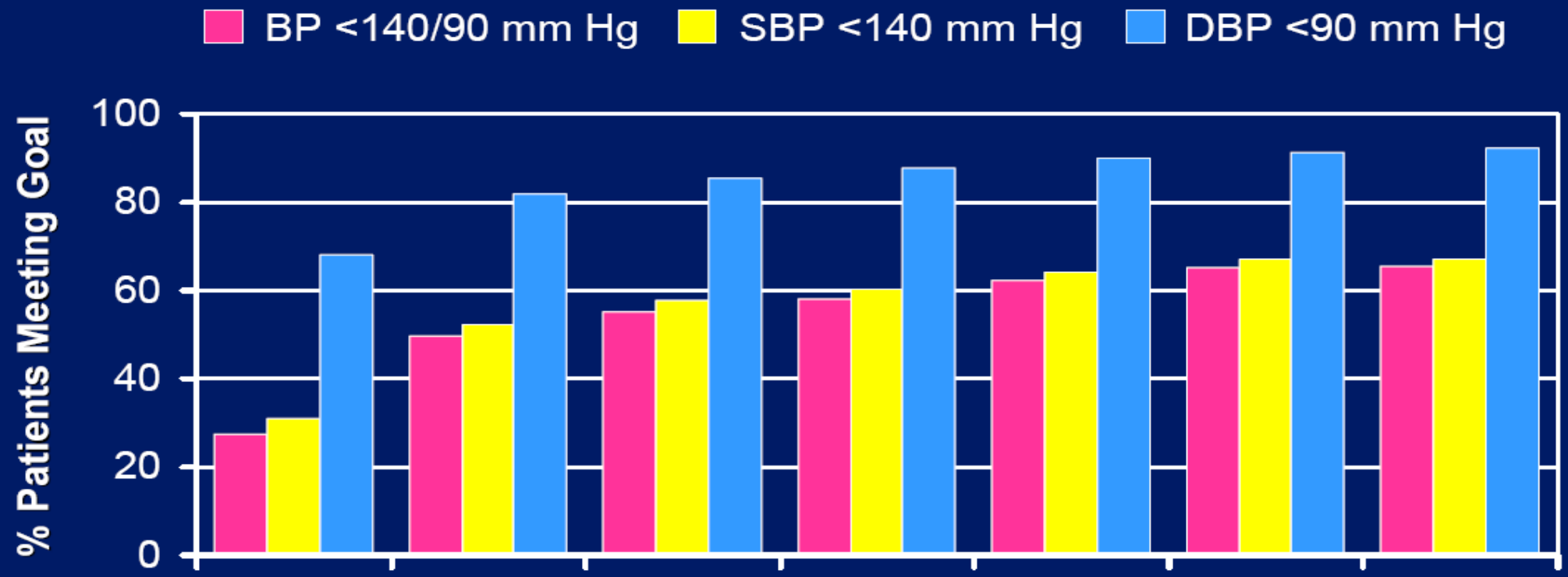

A = CA *vs* placebo; B = ACE inhibitor vs placebo; C = more intensive vs less intensive blood- pressure-lowering; D = ARB vs control; E = ACE inihibitor vs CA; F = CA vs diuretic or β-blocker; G = ACE inhibitor vs diuretic and β-blocker.

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

"Regimens based on each of the most commonly used drug classes produce reductions in the risk of major cardiovascular events that appear to be roughly proportional to the size of the blood pressure reductions achieved **With the exception of heart failure, the intensity of blood pressure lowering appears to be a more important determinant of outcome** than the choice of drug class."

BP Lowering Treatment Trialists' Collaboration,
*The Lancet* (2003)

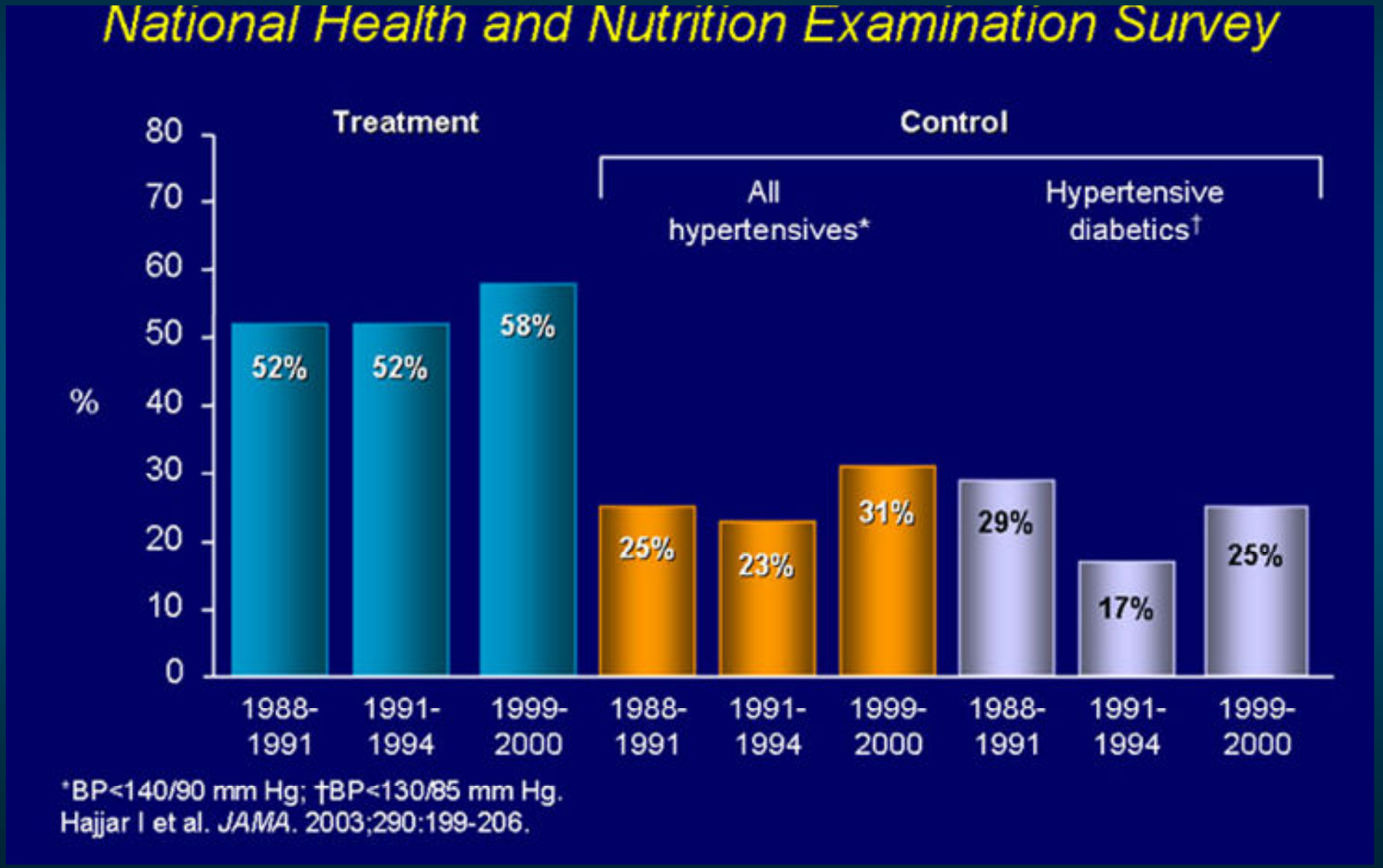
# Target BP lowering in ALLHAT




| | 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.

# Adequate BP Control First !



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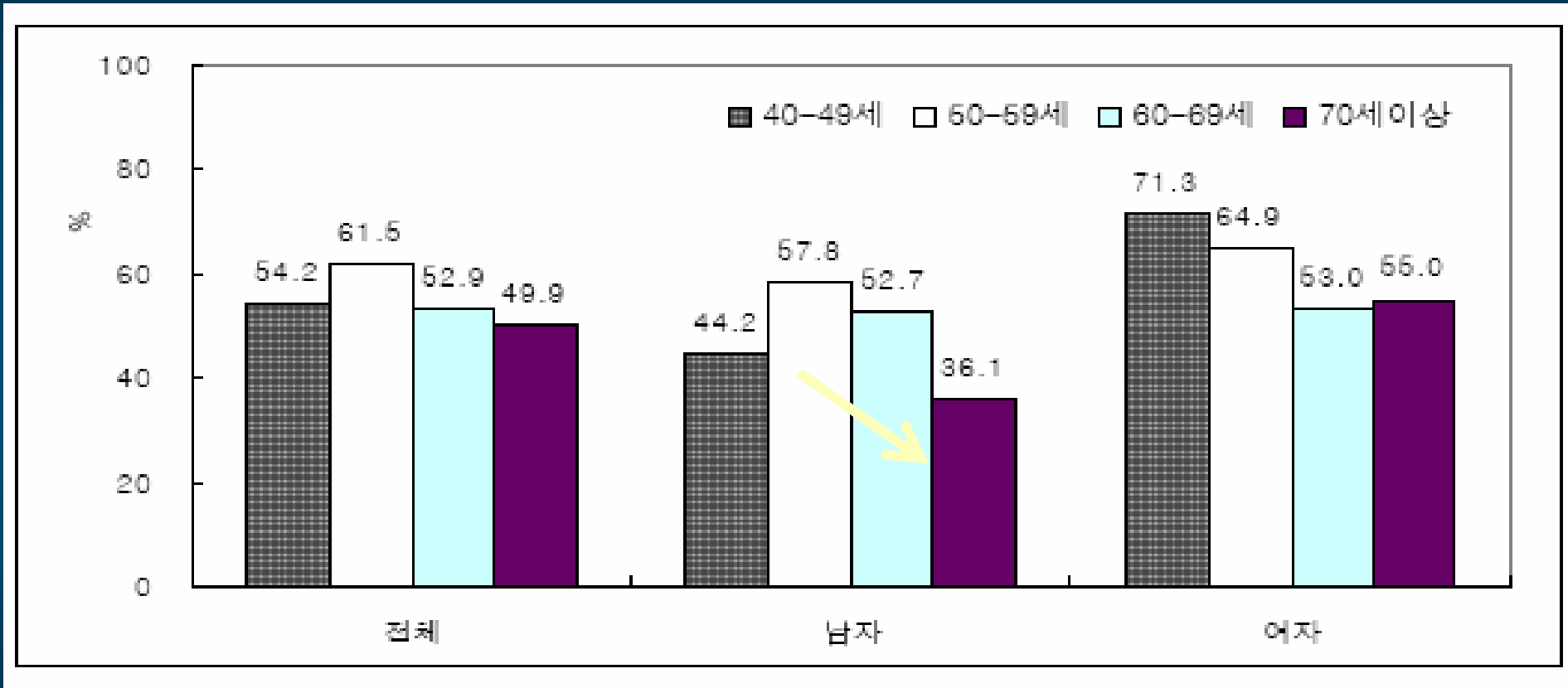
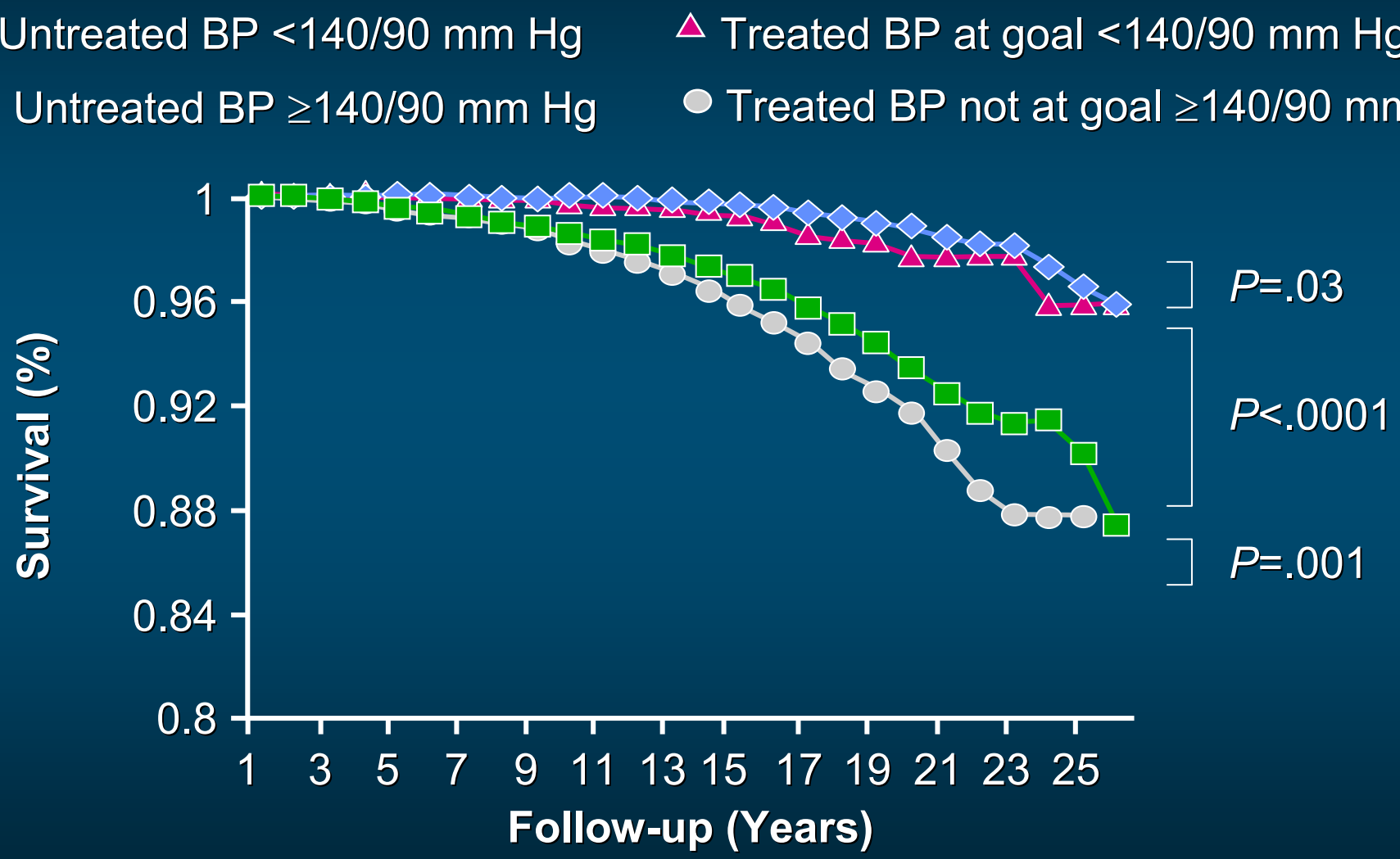



source: National health and nutrition examination survey, 2005

# CVD Survival in Treated HT




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

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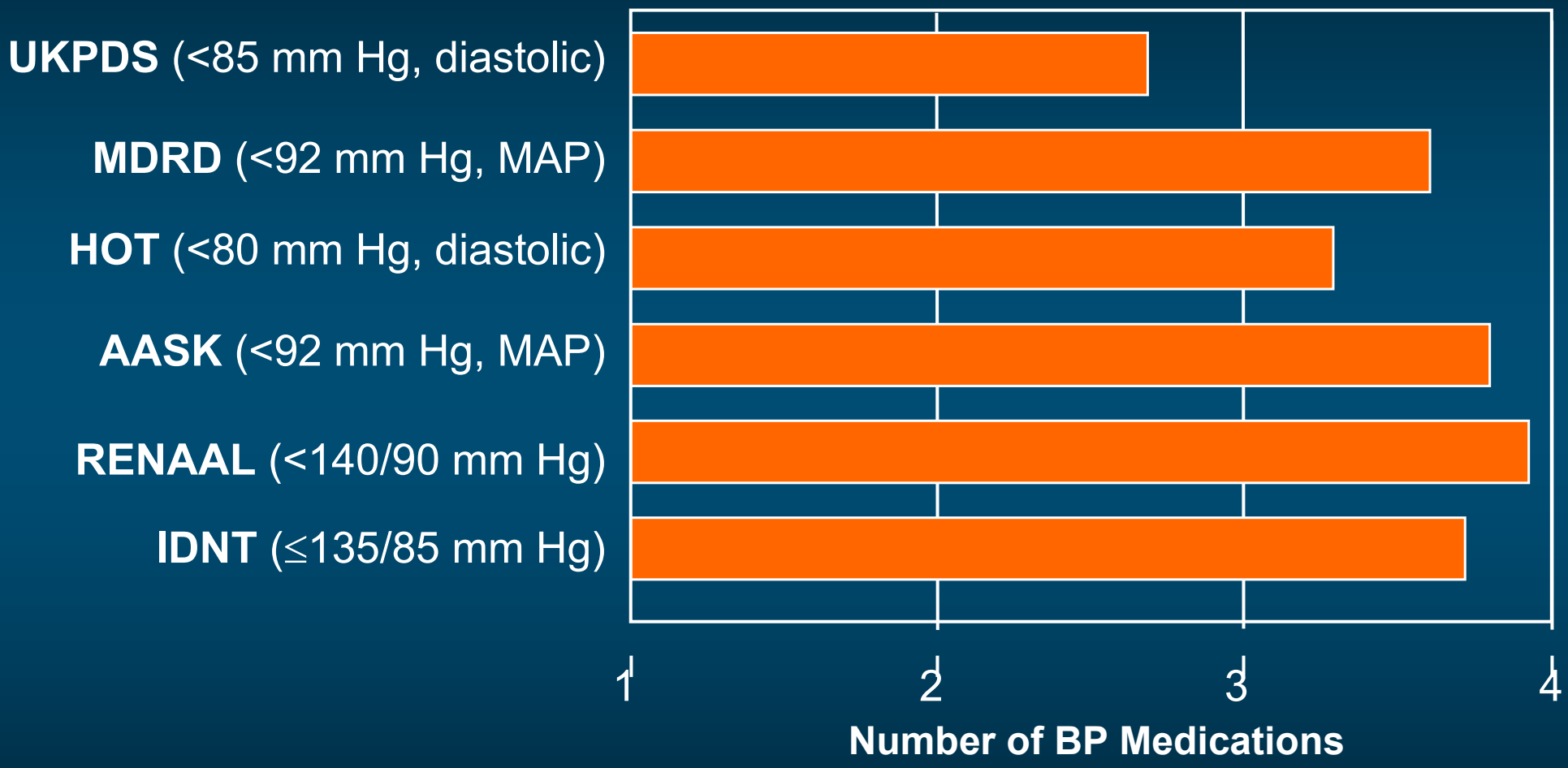
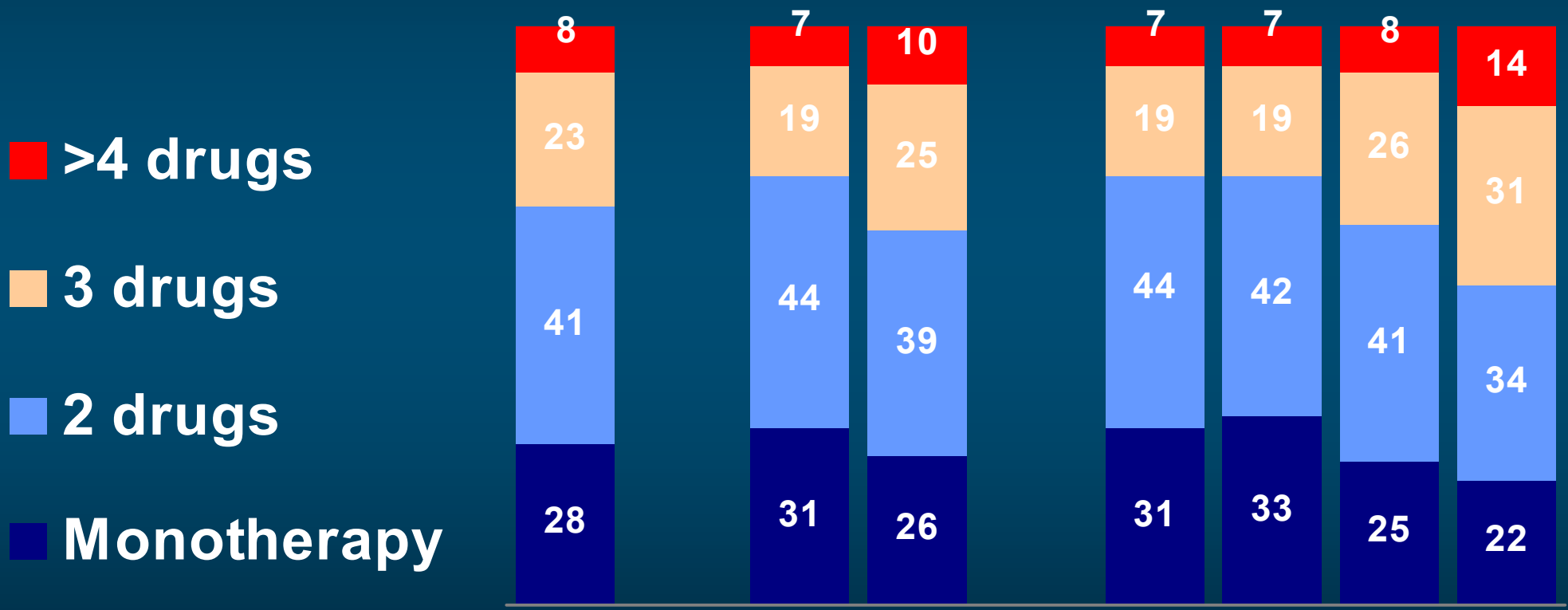
# No. of agents to Achieve BP Goal



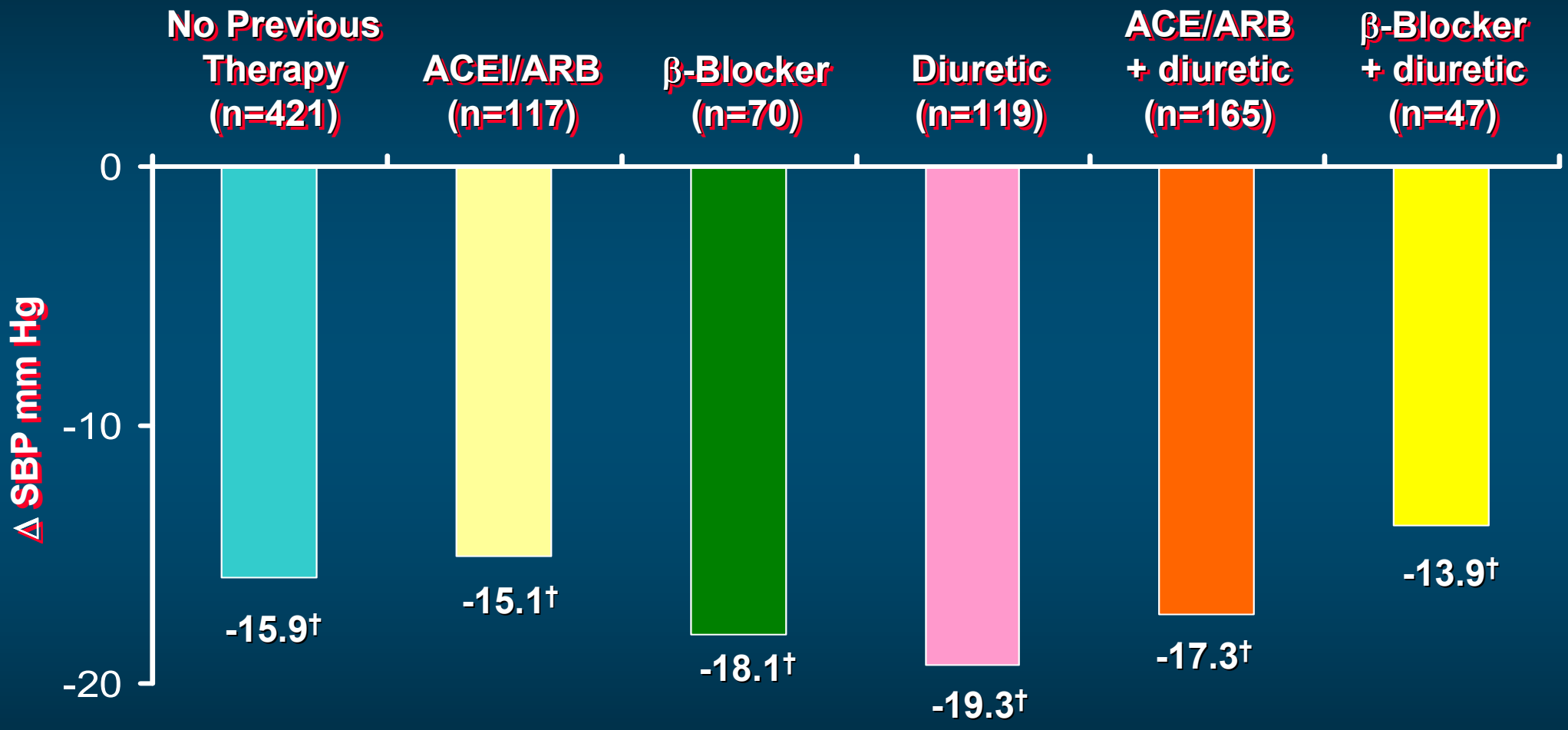

Bakris et al. *Am J Kidney Dis*. 2000;36:646-661; Bakris et al. *Arch Intern Med*. 2003;163:1555-1565; Lewis et al. *N Engl J Med*. 2001;345:851-860.

# Combination Therapy in Korea




Note: * Consider small base number for implementation especially when n<30

# Effect of CCB for Add-on Therapy

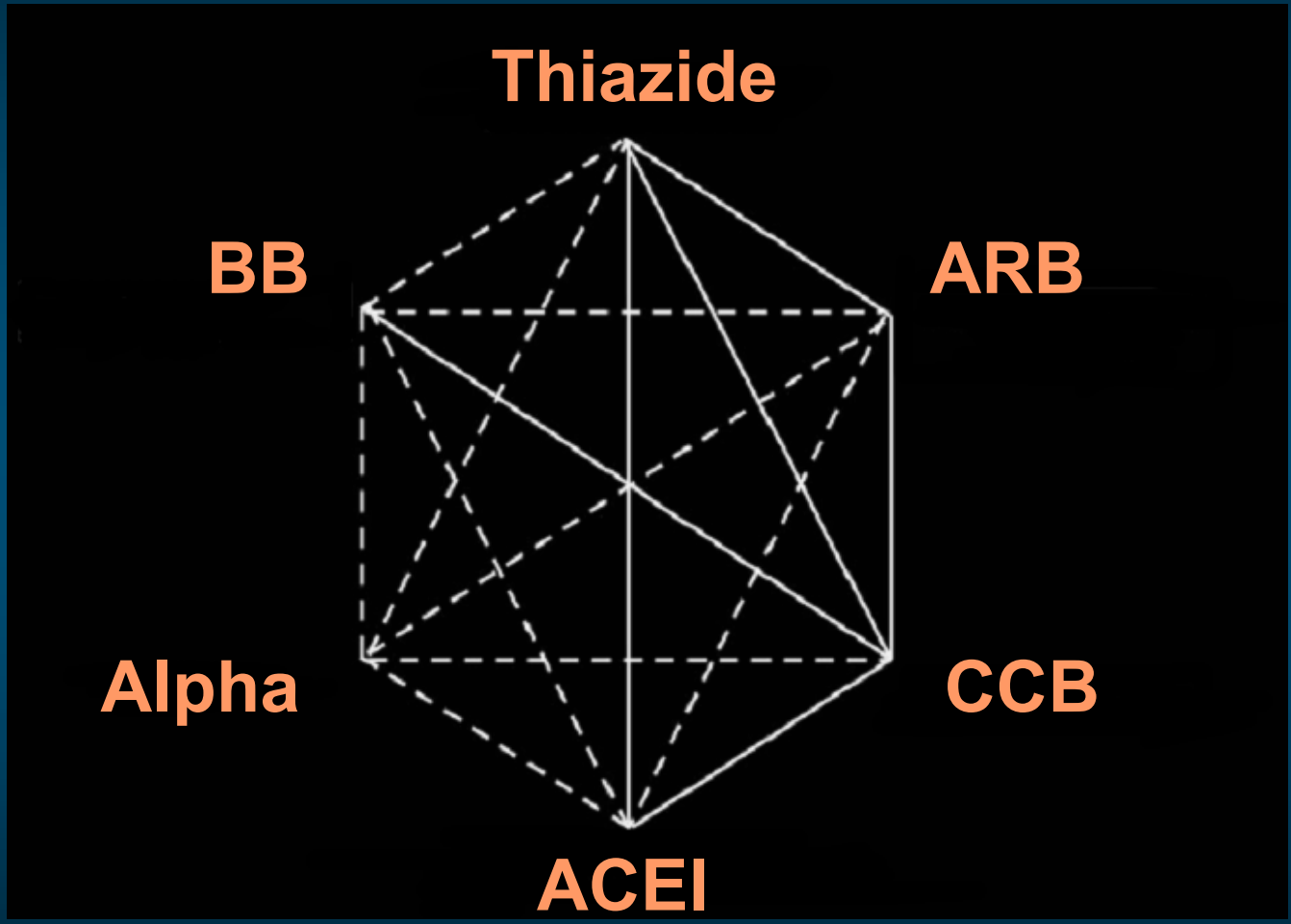



*The DHP CCB was Norvasc® (amlodipine besylate).

†*P*<.001 vs baseline.

McLaughlin et al. *Am J Hypertens*. 2003;16:123A. Abstract P-237.

# Guideline on Combination Therapy




ESC guideline 2007

# Summary

- CCB: strong evidences in management in HT
- Benefit of HT drugs: mainly from BP lowering effect
- Early initiation of HT drug: high risk patients
- Importance of BP lowering at goal

# Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C S Smith, Jill P Pell

## Results

Our search strategy did not find any randomised controlled trials of the parachute.

aircraft. The perception that parachutes are a successful intervention is based largely on anecdotal evidence. Observational data have shown that their use is associated with morbidity and mortality, due to both failure of the intervention[1 2] and iatrogenic complications.[3] In addition, "natural history" studies of free fall indicate that failure to take or deploy a parachute does not inevitably result in an adverse outcome.[4] We therefore undertook a systematic review of randomised controlled trials of parachutes.

### Methods

**Literature search**

We conducted the review in accordance with the QUOROM (quality of reporting of meta-analyses) guidelines.[5] We searched for randomised controlled trials of parachute use on Medline, Web of Science, Embase, the Cochrane Library, appropriate internet sites, and citation lists. Search words employed were "parachute" and "trial." We imposed no language restriction and included any studies that entailed jumping from a height greater than 100 metres. The

Parachutes reduce the risk of injury after gravitational challenge, but their effectiveness has not been proved with randomised controlled trials

# Thank You for Your Attention!