**Istituto di medicina dello sport di Firenze**
**AMES**

# *Prevenzione cardiovascolare e cambiamenti negli stili di vita*

Firenze 22 settembre 2007

## Orientamenti attuali per un intervento farmacologico e non farmacologico nell'ipertensione arteriosa

**Maurizio Filice**

## 2007 Guidelines for the Management of Arterial Hypertension

**The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC)**

**Journal of Hypertension** 2007, **25**:1105–1187

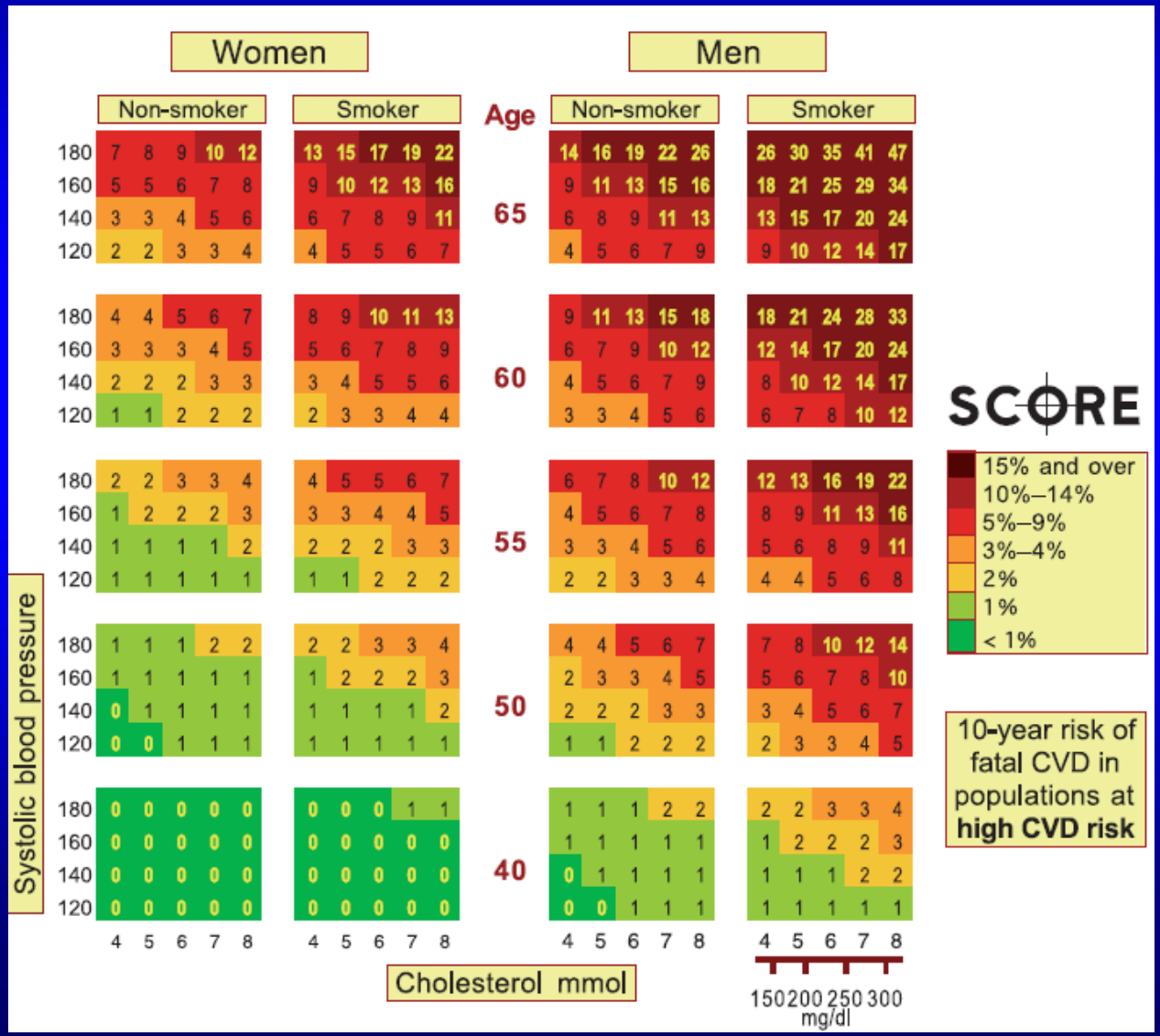
**Treatment of Hypertension in the Prevention and Management of Ischemic Heart Disease: A Scientific Statement From the American Heart Association Council for High Blood Pressure Research and the Councils on Clinical Cardiology and Epidemiology and Prevention**

(*Circulation.* 2007;115:2761-2788.)

# HYPERTENSION

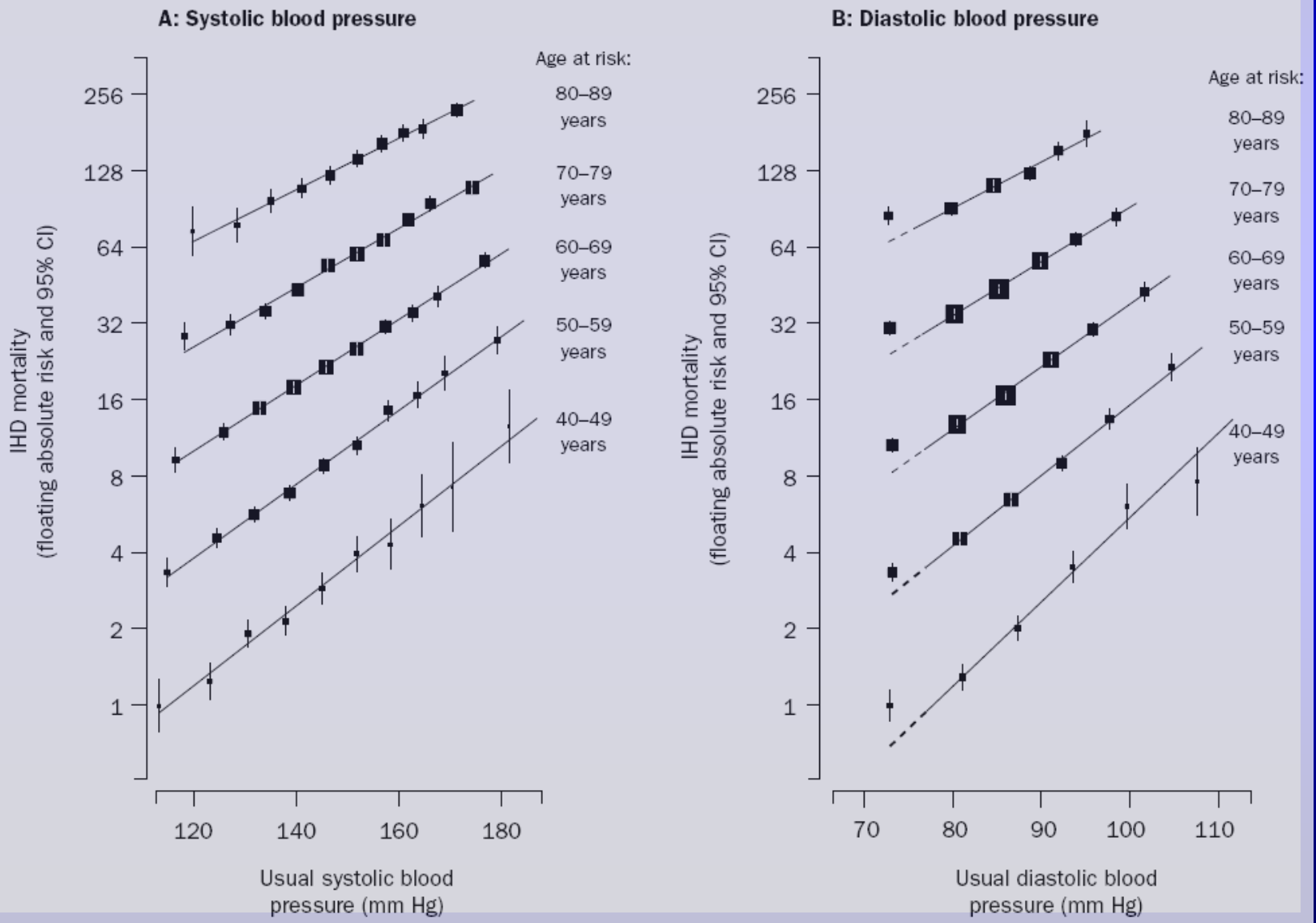
Management in adults in primary care: pharmacological update

# SCORE project



# IHD mortality rate in each decade of age versus usual blood pressure at the start of that decade

**Prospective study collaboration Lancet 2002**



# 2007 Guidelines for the Management of Arterial Hypertension (Terapia)

| 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 |

# Creatinina
## …ma …basta solo usare la Creatininemia?

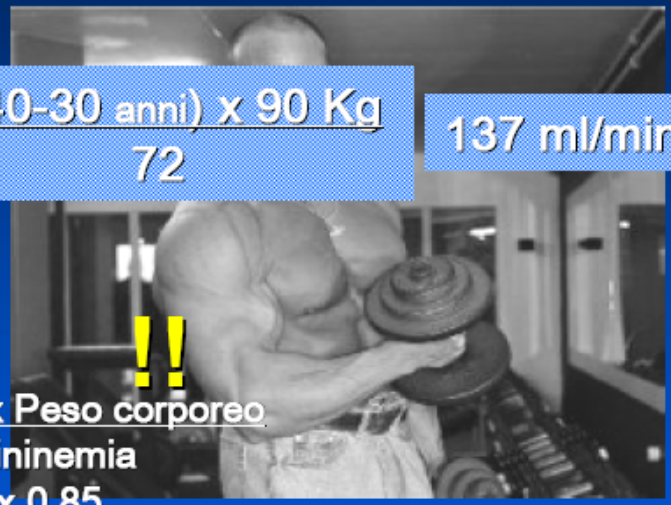
40 Kg 52 ml/min

1 mg/dl

30 anni

$$\frac{(140\text{-}30 \text{ anni}) \times 90 \text{ Kg}}{72}$$

137 ml/min



!!

Formula di Cocroft = $\frac{(140\text{- Età}) \times \text{Peso corporeo}}{72 \times \text{Creatininemia}}$

nelle donne moltiplicare x 0.85

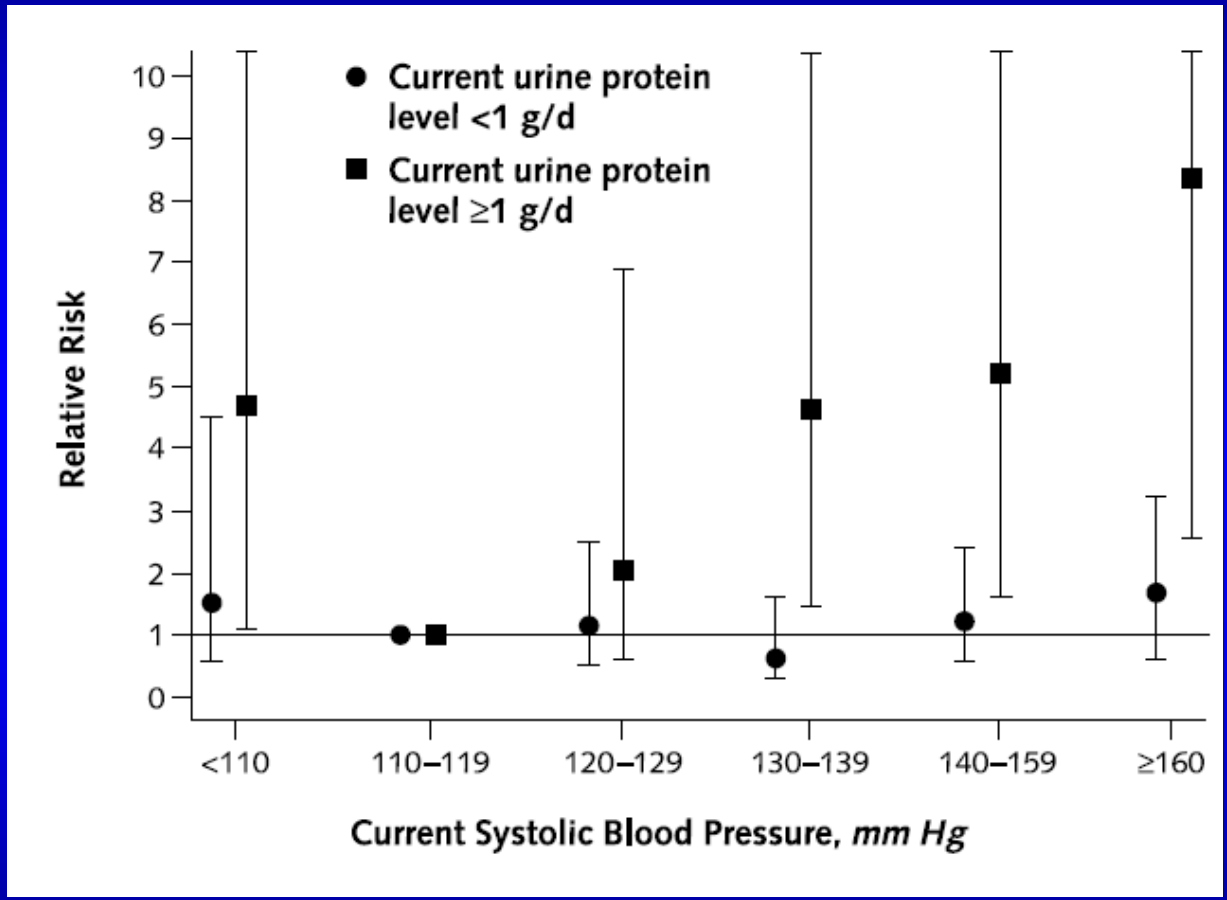
formula MDRD : Creatinina, età, sesso e razza

# HOPE TRIAL:
# Independent Predictive Variables for Combined Endpoints of CV Death, MI, and Stroke

| Variable | Hazard Ratio |
|---|---|
| **Microalbuminuria** | **1.59** |
| **Creatinine > 1.4 mg/dL** | **1.40** |
| **CAD** | **1.51** |
| **PVD** | **1.49** |
| **Diabetes Mellitus** | **1.42** |
| **Male** | **1.20** |
| **Age** | **1.03** |
| **Waist-Hip Ratio** | **1.13** |

Mann JFE, et al. Ann Intern Med. 2001;134(8):629-636.

# Relative risk for kidney progression based on level current systolic bood pressure and current urine protein excretion




*Ann Intern Med.* 2003;139:244-252.

# IRMA II Irbesartan vs Placebo Primary Endpoint at 2 Years

| | Total # of Patients | Progression to Nephropathy | | Unadjusted Risk Reduction | P Value† | Adjusted* Risk Reduction | P Value† |
|---|---|---|---|---|---|---|---|
| | | n | % | | | | |
| 300 mg Irbesartan | 194 | 10 | 5.2 | 70% | <0.001 | 68% | <0.001 |
| 150 mg Irbesartan | 195 | 19 | 9.7 | 39% | 0.08 | 44% | 0.05 |
| Placebo | 201 | 30 | 14.9 | - | - | - | - |

† For irbesartan vs placebo (the significance level for the primary endpoint was 0.025)

*Hazard ratios were adjusted for baseline level of microalbuminuria and blood pressure achieved during the study

Parving HH, et al. N Engl J Med. 2001;345(12):870-878.

# IRMA II Irbesartan vs Placebo Secondary Endpoints

- During the first 3 months, the decline in creatinine clearance (mL/min/$m^2$ body surface area per month) was greater than the decline between 3 and 24 months*
  - 0.9 vs 0.1 for the placebo group
  - 1.0 vs 0.2 for the 150 mg group
  - 1.9 vs 0.2 for the 300 mg group
- Irbesartan reduced the level of urine albumin excretion…
  - 24% in the 150 mg group (P=NS)†
  - 38% in the 300 mg group (P<0.001)†

***Neither the initial nor long-term decline differed significantly among the 3 groups**

**† Compared to placebo**

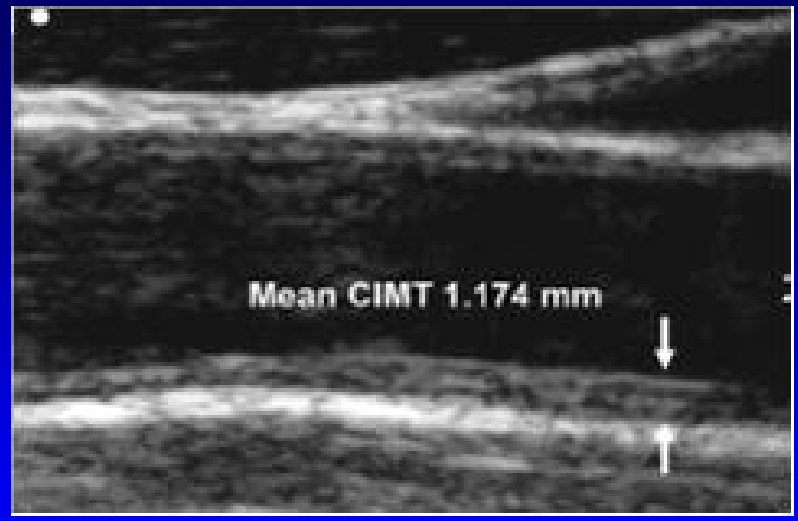
**Parving HH, et al. N Engl J Med. 2001;345(12):870-878.**

# IRMA II
# Summary of Important Findings

- Irbesartan significantly reduces the rate of progression from microalbuminuria to diabetic nephropathy
- Renoprotection from irbesartan in patients with type 2 diabetes and microalbuminuria is independent of its blood pressure lowering effect
- Antihypertensive treatment has a renoprotective effect in hypertensive patients with type 2 diabetes and microalbuminuria

Parving HH, et al. N Engl J Med. 2001;345(12):870-878.

# Spessore intima media






JACC Vol. 41, No. 11, 2003
June 4, 2003:1855–917

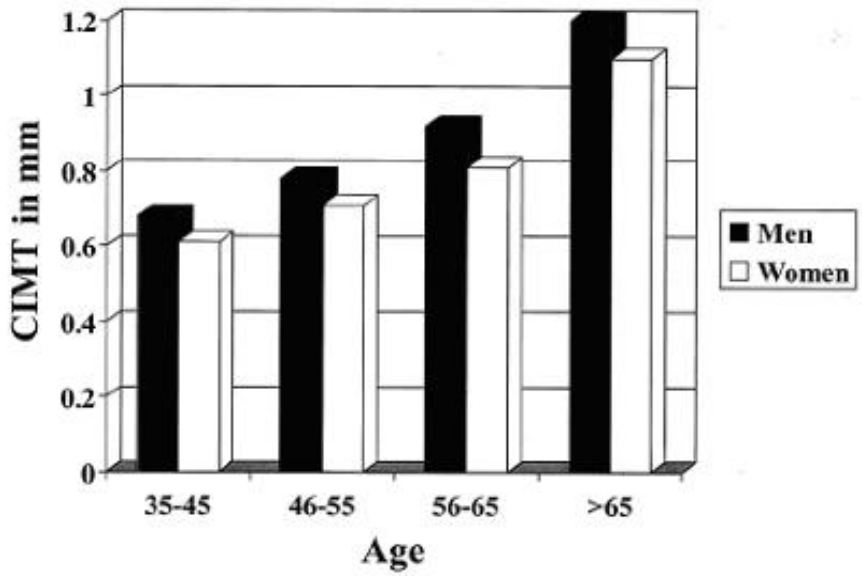
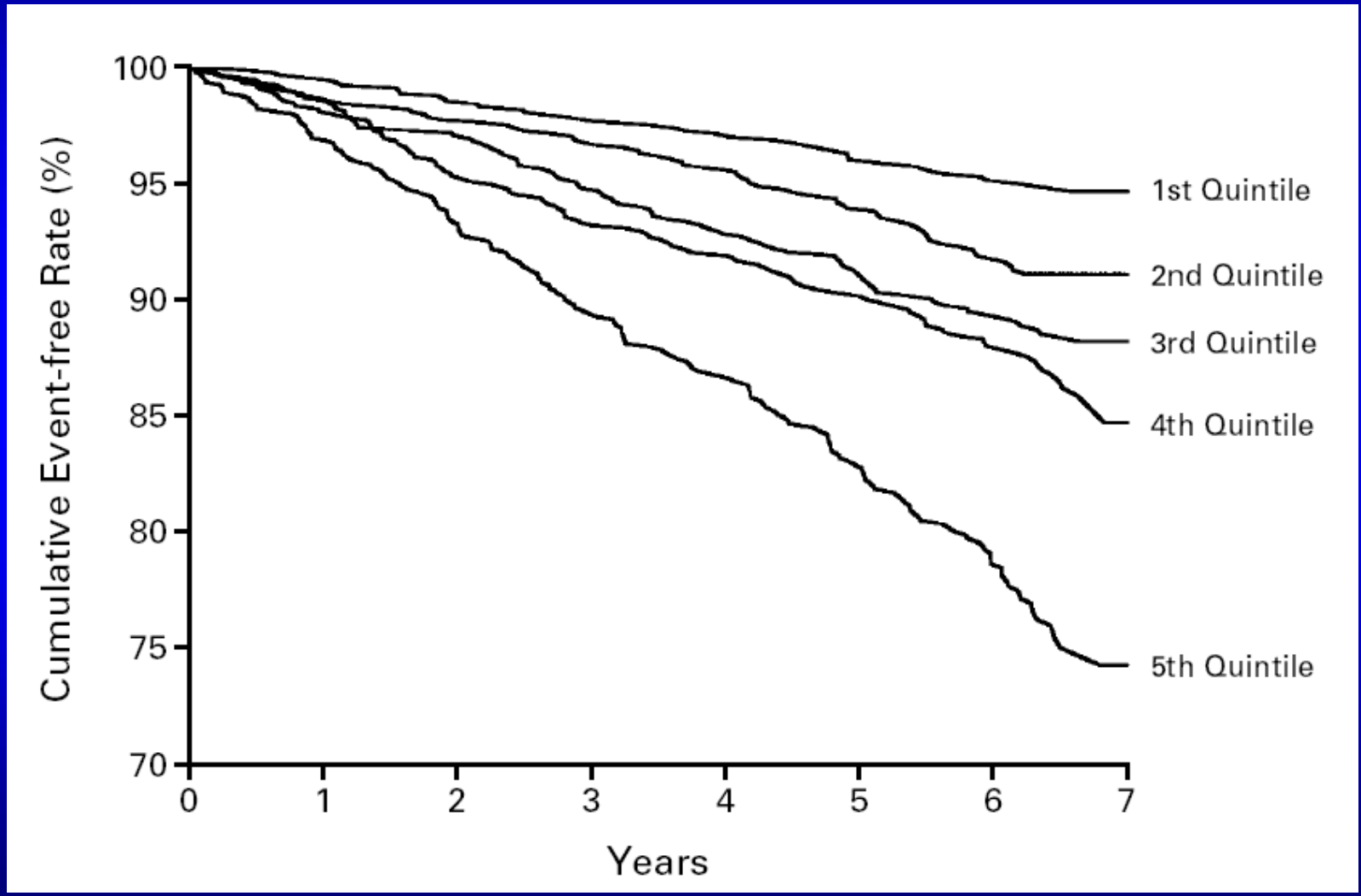



Figure 2. Approximate age and gender values for common carotid intima-media thickness (CIMT) representing the approximate 75th percentile value (4,12). Note that intima-media thickness increases with advancing age, and that the intima-media thickness of men is generally greater than that seen in women.

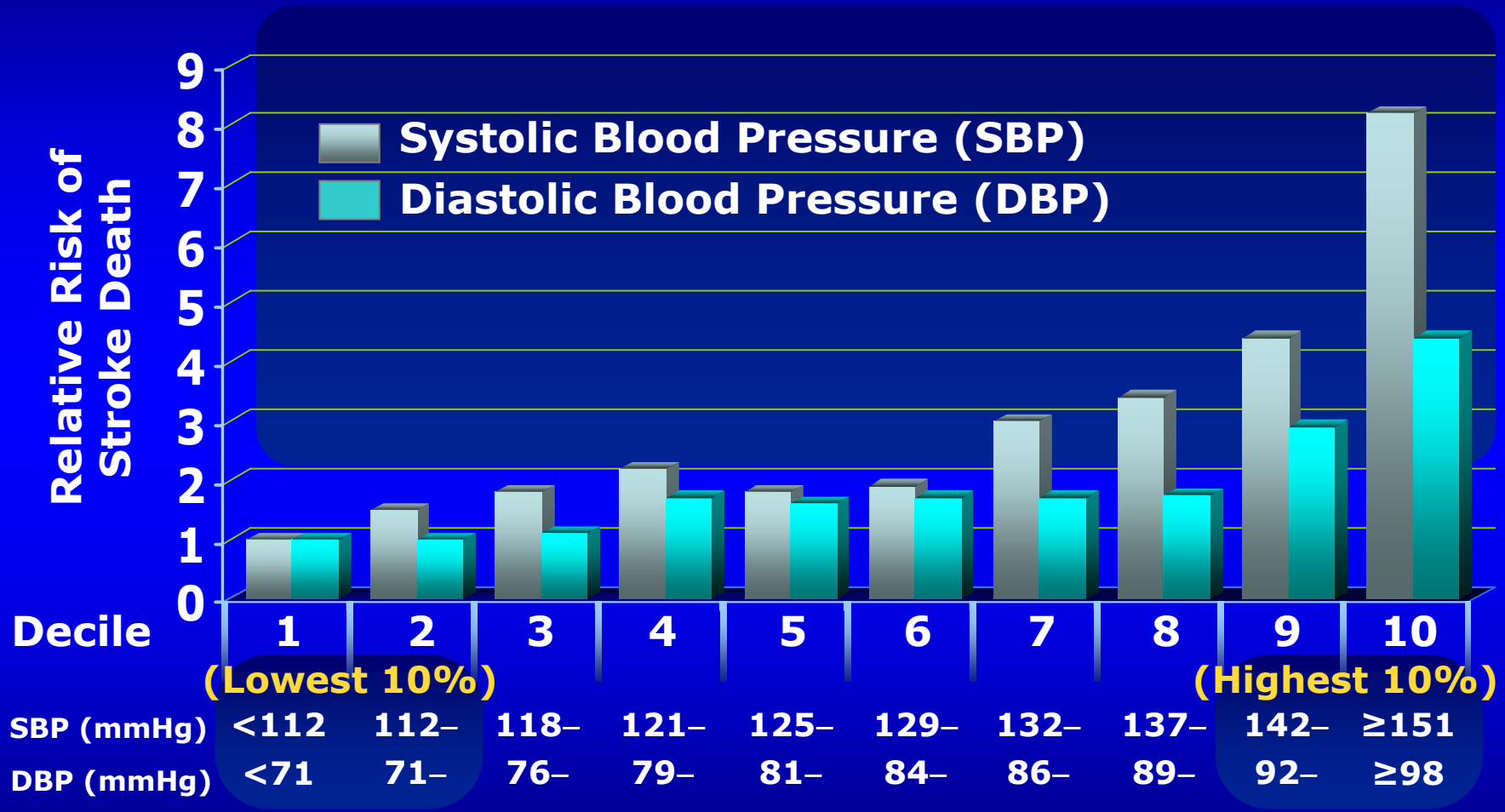
**Lo studio Kuopio Ischaemic Heart Disease Risk Factor Study ha dimostrato che il rischio di infarto miocardico aumenta dell'11% per ogni 0.1 mm di aumento di CIMT.**

# CAROTID-ARTERY INTIMA AND MEDIA THICKNESS AS A RISK FACTOR FOR MYOCARDIAL INFARCTION AND STROKE IN OLDER ADULTS




N Engl J Med 1999;340:14-22

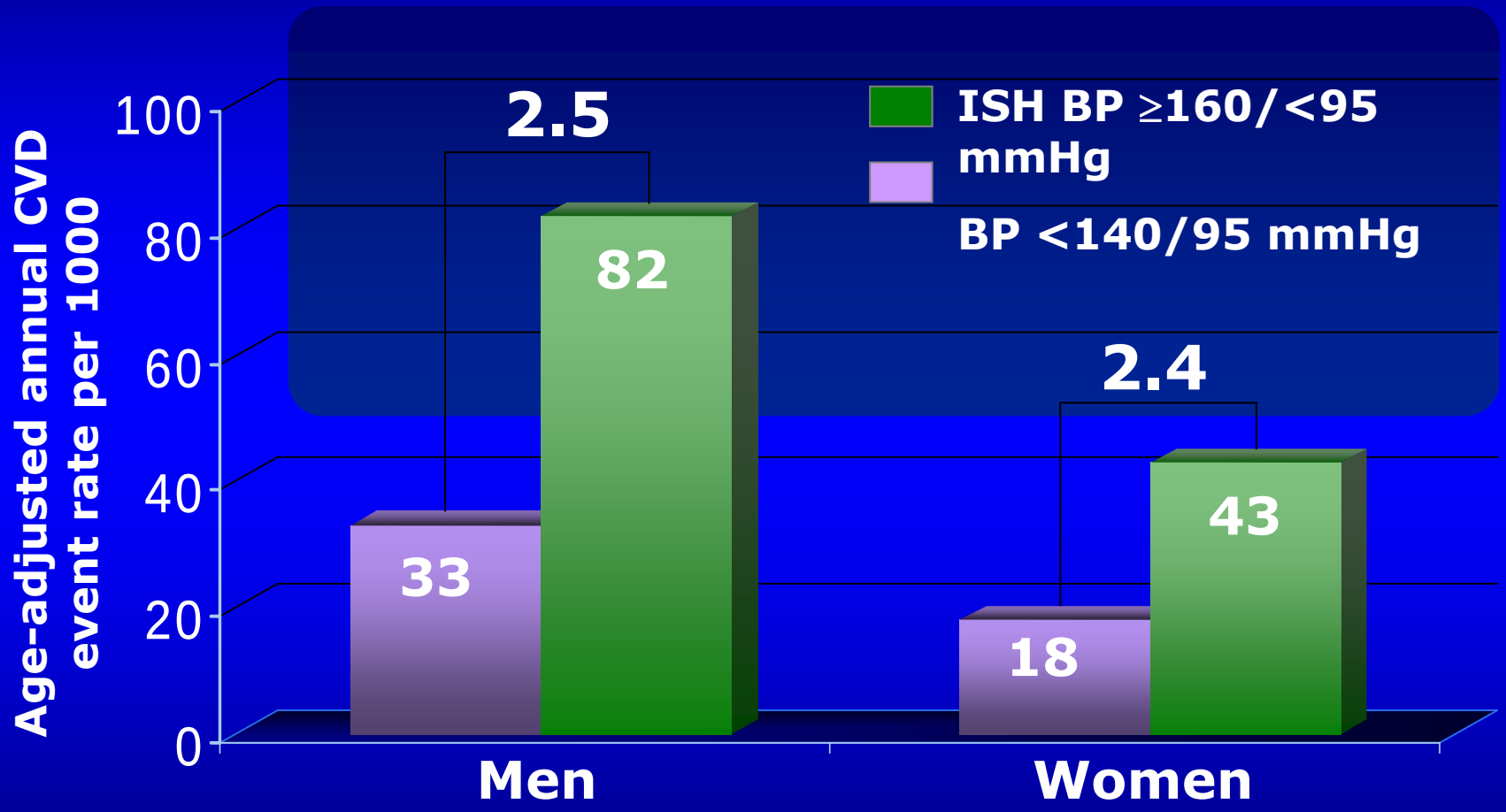
# Risk of Stroke Death According to Blood Pressure: MRFIT




MRFIT, Multiple Risk Factor Intervention Trial.

Stamler J, et al. *Arch Intern Med*. 1993;153:598-615;
He J, Whelton PK. *Am Heart J*. 1999;138(Pt 2):211-219.

# Isolated Systolic Hypertension and CVD Risk in Framingham Heart Study




CVD=cardiovascular disease ISH=isolated systolic hypertension
P<0.001 for difference between both men and women with ISH and blood pressure (BP) <140/95 mmHg

Wilking SV et al. JAMA. 1988;260:3451-3455.

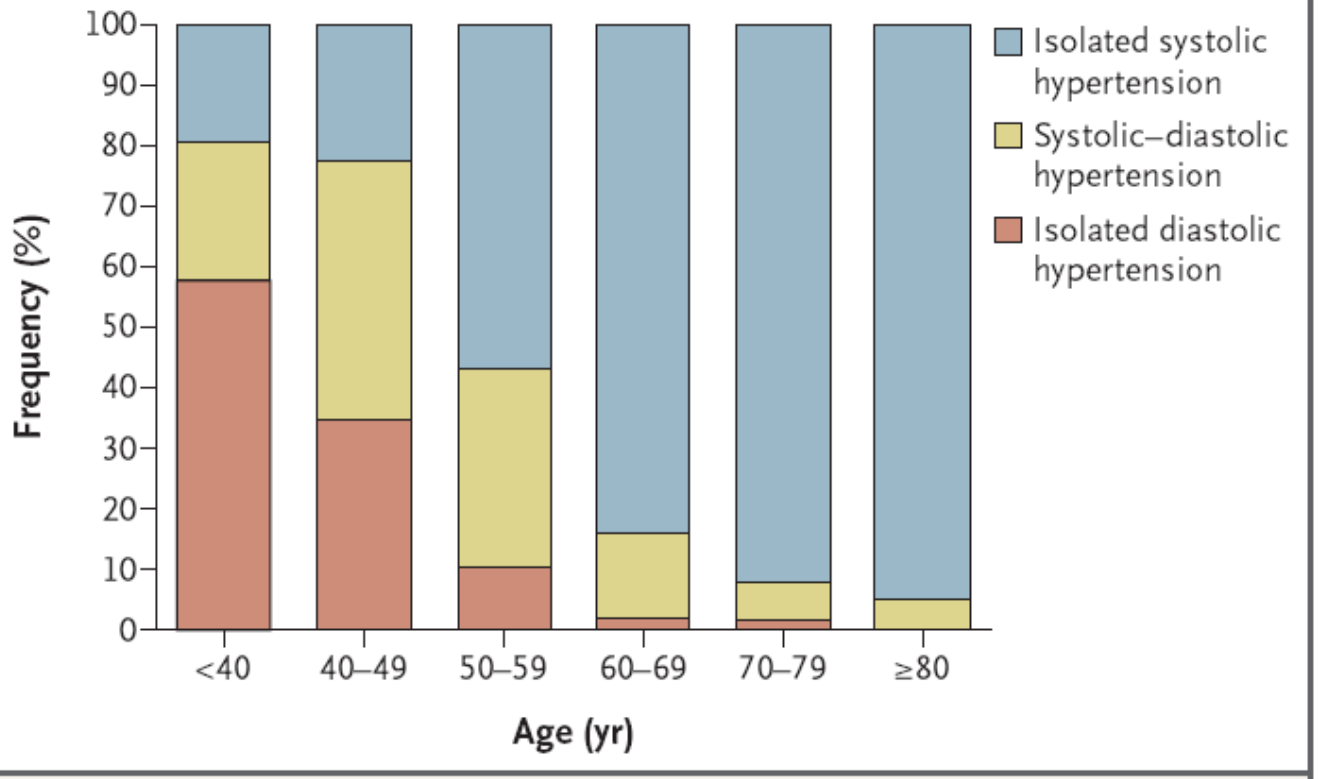



**Figure 2. Frequency of Untreated Hypertension According to Subtype and Age.**

Data are from Franklin et al.[5]

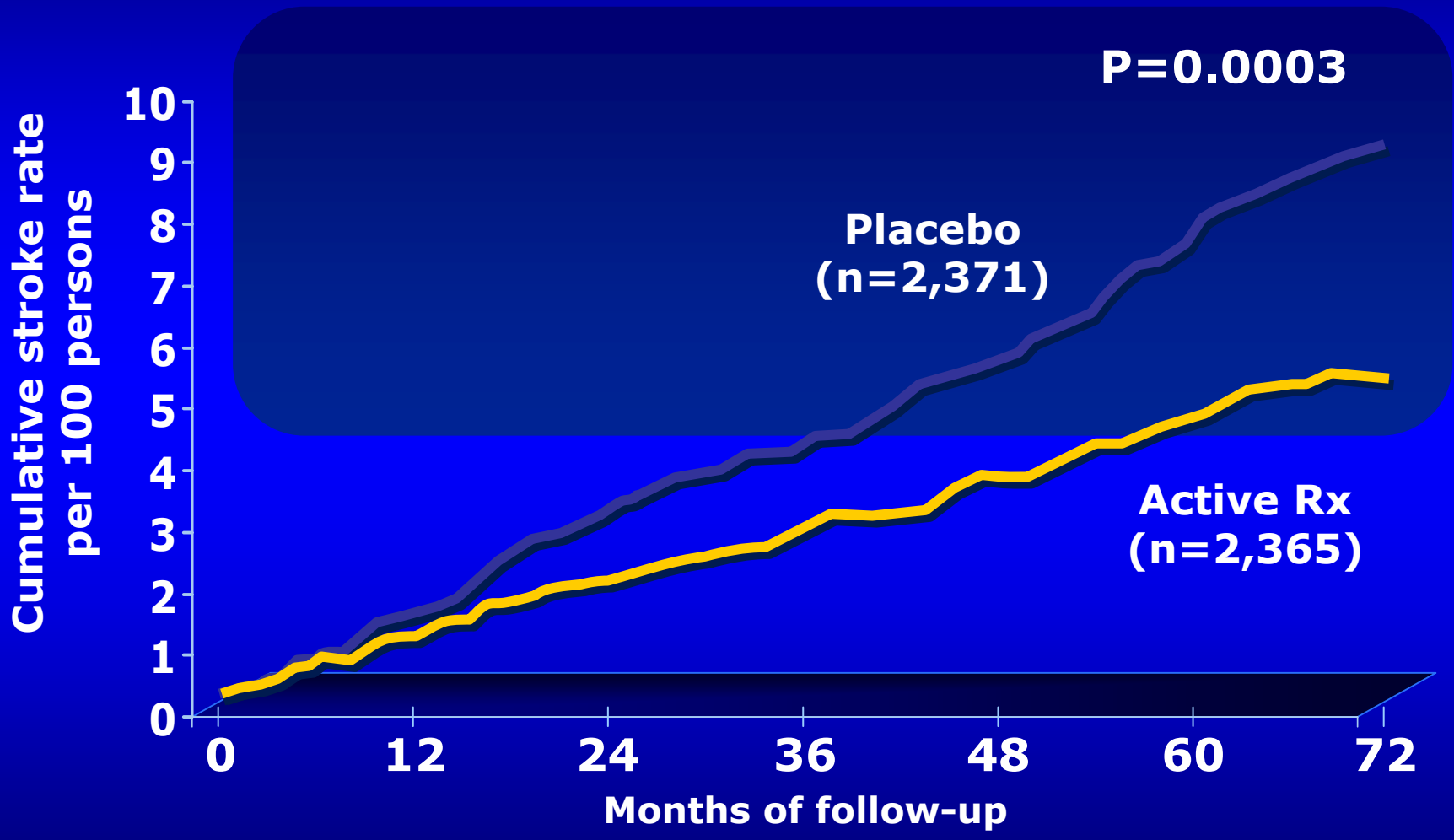
Circulation 1997

# Ipertensione sistolica

On the basis of wealth of current available evidence, the committee now recommends a major paradigm shift in urging that **systolic BP became the major criterion for diagnosis, staging, and therapeutic management** of hypertension in particularly in middle age and older Americans.

Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI). *Arch Intern Med*. 1997;157:2413–2446.

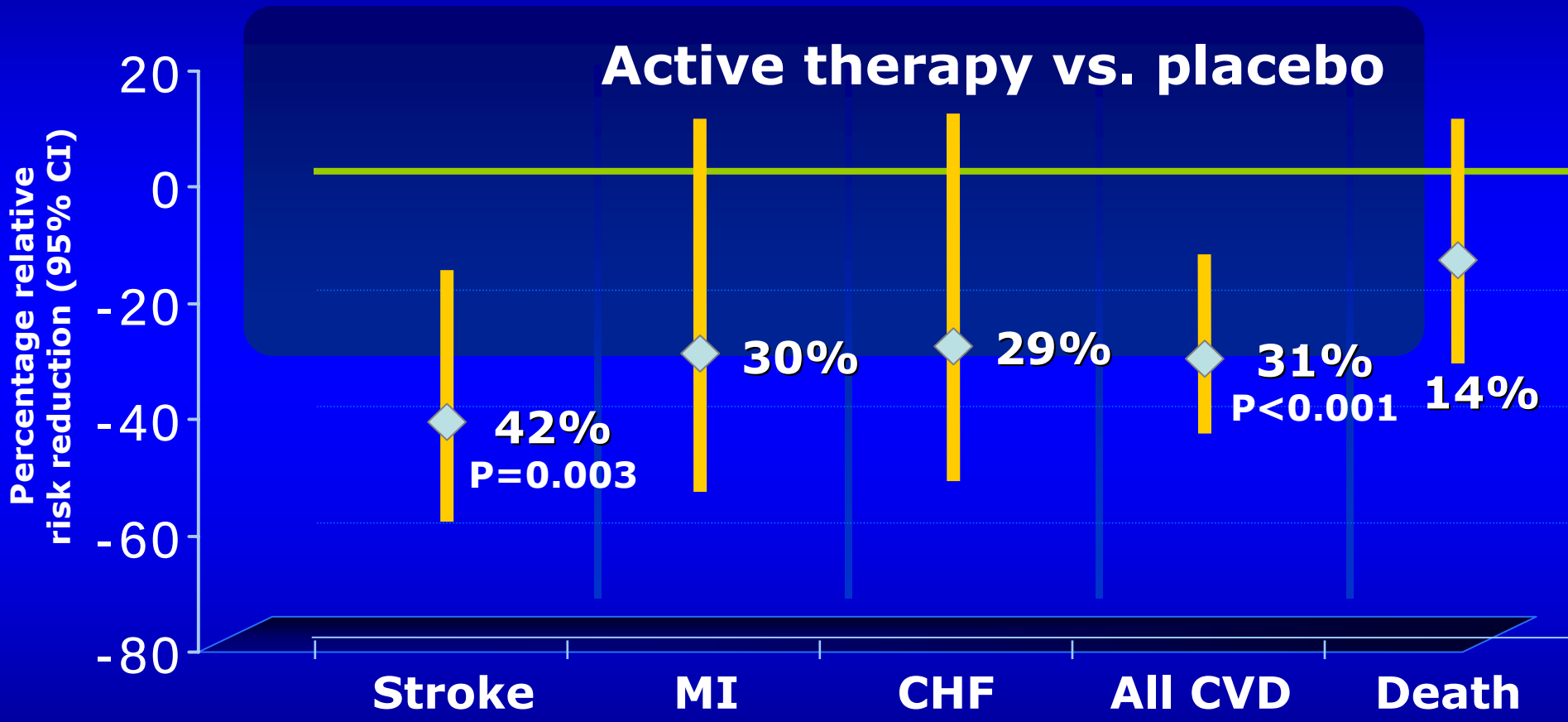
# SHEP
# Cumulative Stroke Rate




SHEP=Systolic Hypertension in the Elderly Program

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

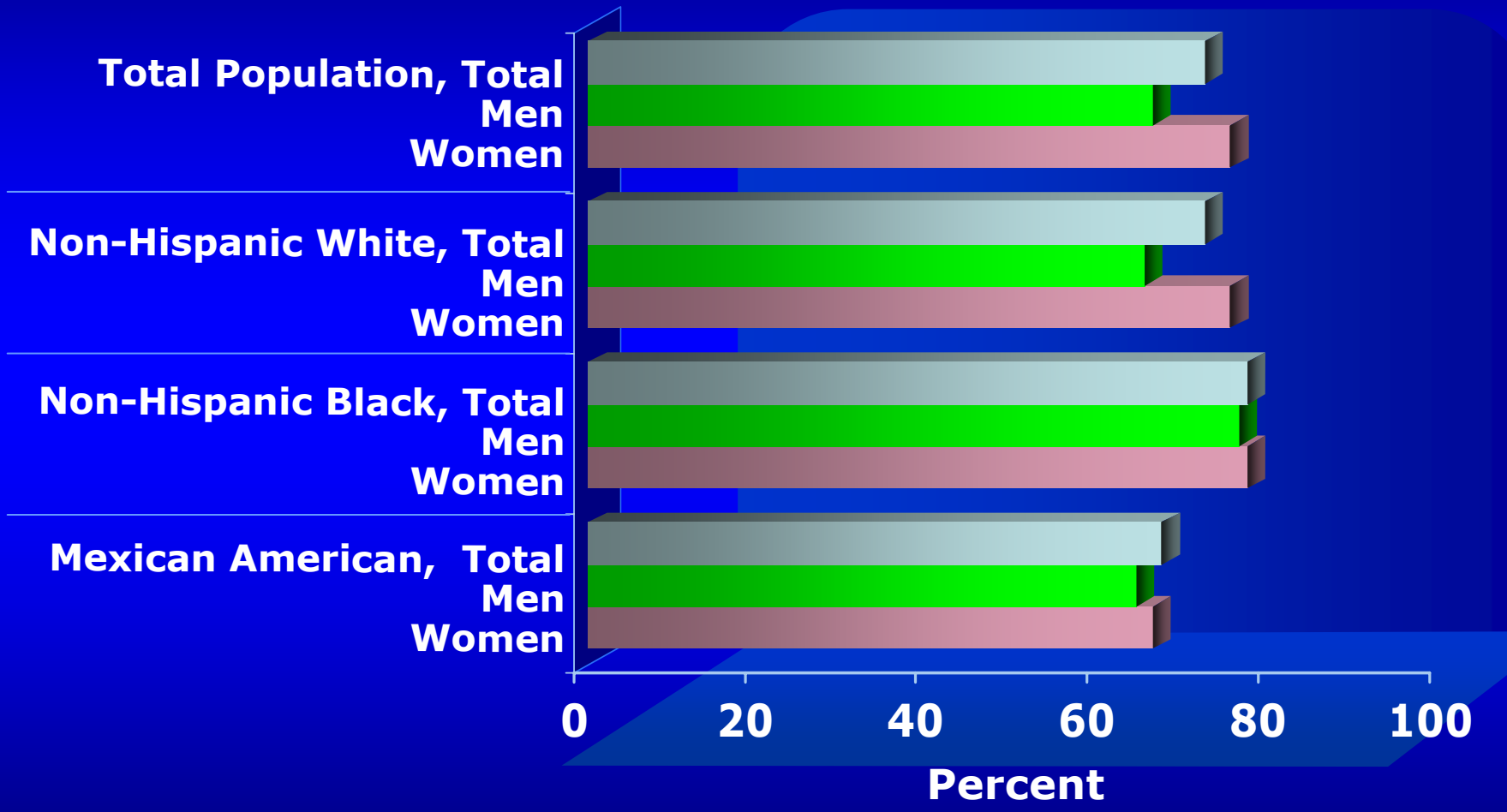
# Syst-Eur
# Cardiovascular Disease Endpoints




Syst-Eur=Systolic Hypertension in Europe Trial

Staessen JA, et al. Lancet. 1997;350:757-764.

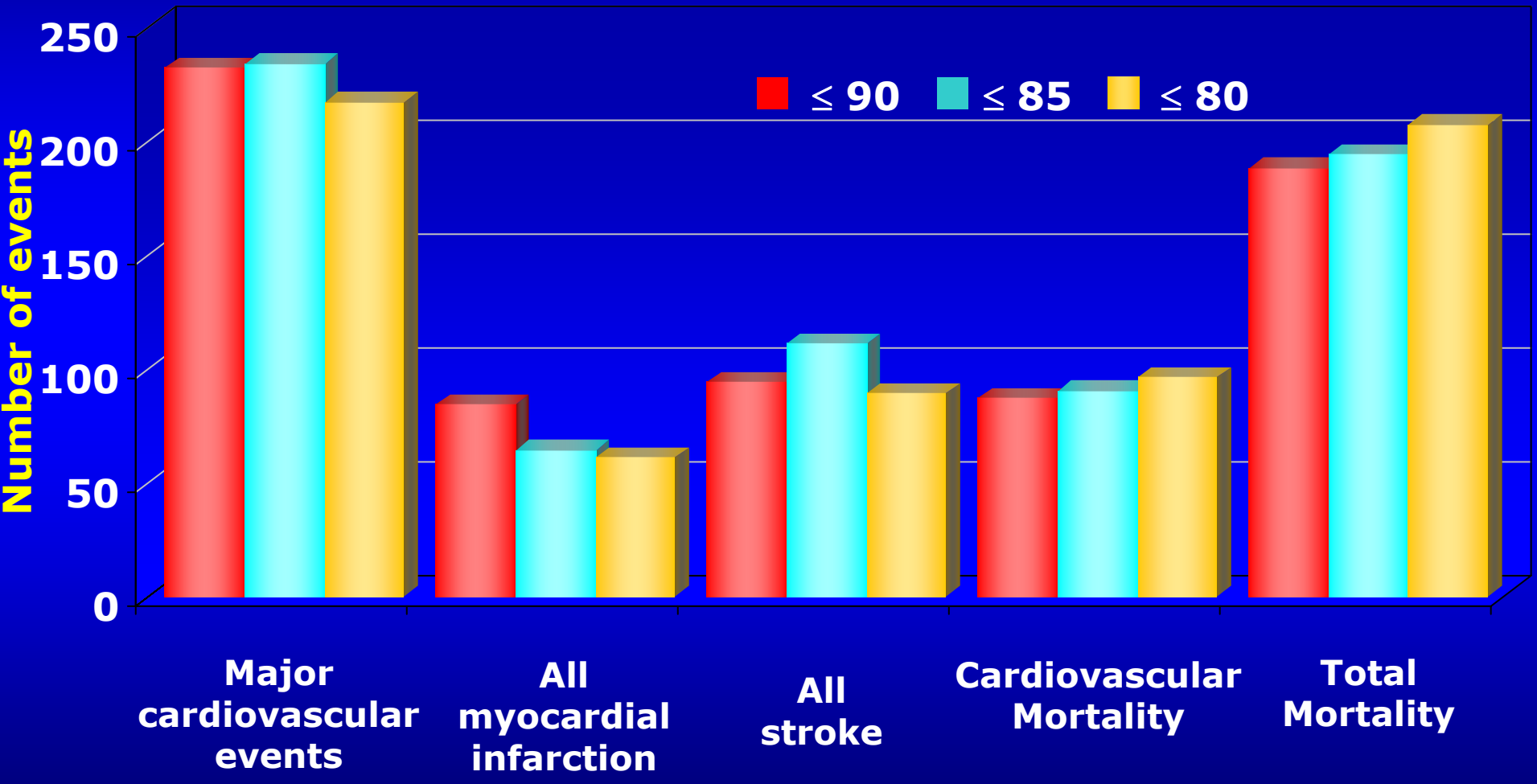
# NHANES III 1988-1994 Prevalence of Elevated Blood Pressure* in Diabetic Adults




NHANES III=Third US National Health and Nutrition Examination Survey (1988-1994)
*≥130/85 mmHg or current use of prescription medication for hypertension

Geiss LS, et al. Am J Prev Med. 2002;22:42-48.

# HOT Outcomes by Target Blood Pressure Group*




*The outcomes for different blood pressure groups were not statistically significant

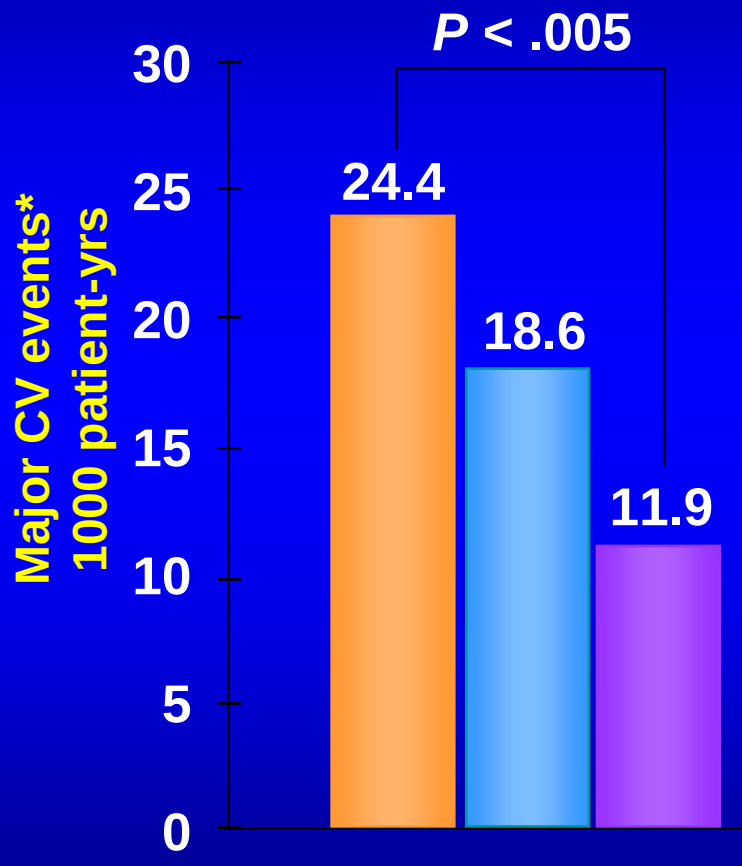
Hansson L, et al. Lancet. 1998;351:1755–1762.

# HOT Trial: BP Control Reduces Cardiovascular Events in Diabetics

## Diabetes Subgroup

| Target Diastolic BP (mmHg) | Number of Patients | Achieved* Systolic BP (mmHg) | Achieved* Diastolic BP (mmHg) |
|---|---|---|---|
| ≤ 90 | 501 | 143.7 | 85.2 |
| ≤ 85 | 501 | 141.4 | 83.2 |
| ≤ 80 | 499 | 139.7 | 81.1 |

*Achieved = Mean of all BPs from 6 months of follow-up to end of study




*includes all myocardial infarction, all strokes, and all other CV deaths

Hansson L, et al. Lancet. 1998;351:1755–1762.

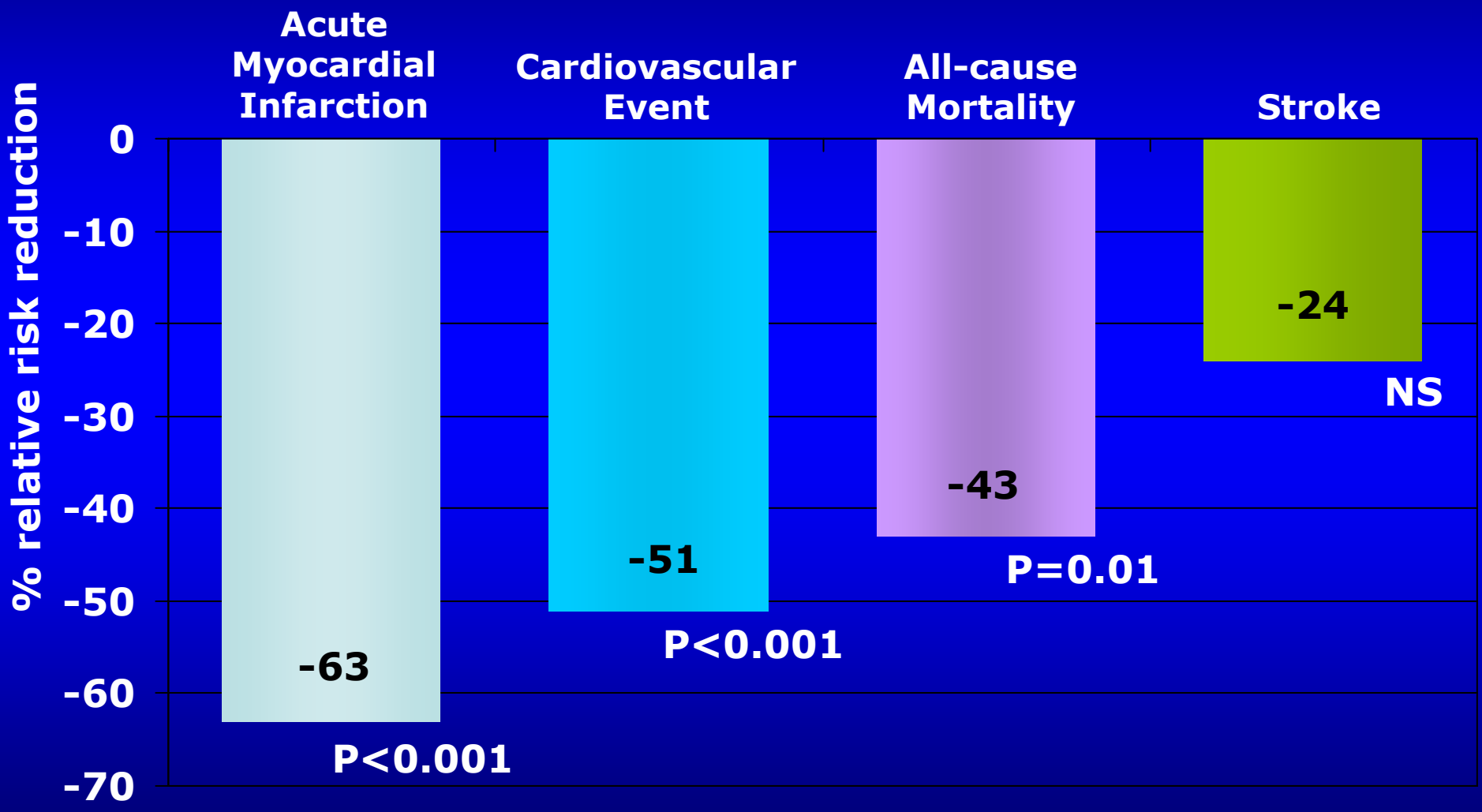
# Impact of Blood Pressure Reduction on Mortality in Diabetes

| Trial | Conventional care | Intensive care | Risk reduction | P-value |
|---|---|---|---|---|
| UKPDS | 154/87 | 144/82 | 32% | 0.019 |
| HOT | 144/85 | 140/81 | 66% | 0.016 |

**Mortality endpoints are:**
**UK Prospective Diabetes Study (UKPDS) – "diabetes related deaths"**
**Hypertension Optimal Treatment (HOT) Study – "cardiovascular deaths" in diabetics**

**Turner RC, et al. BMJ. 1998;317:703-713.**
**Hansson L, et al. Lancet. 1998;351:1755–1762.**

# Relative Risk Reduction With ACEIs in ABCD, CAPPP and FACET

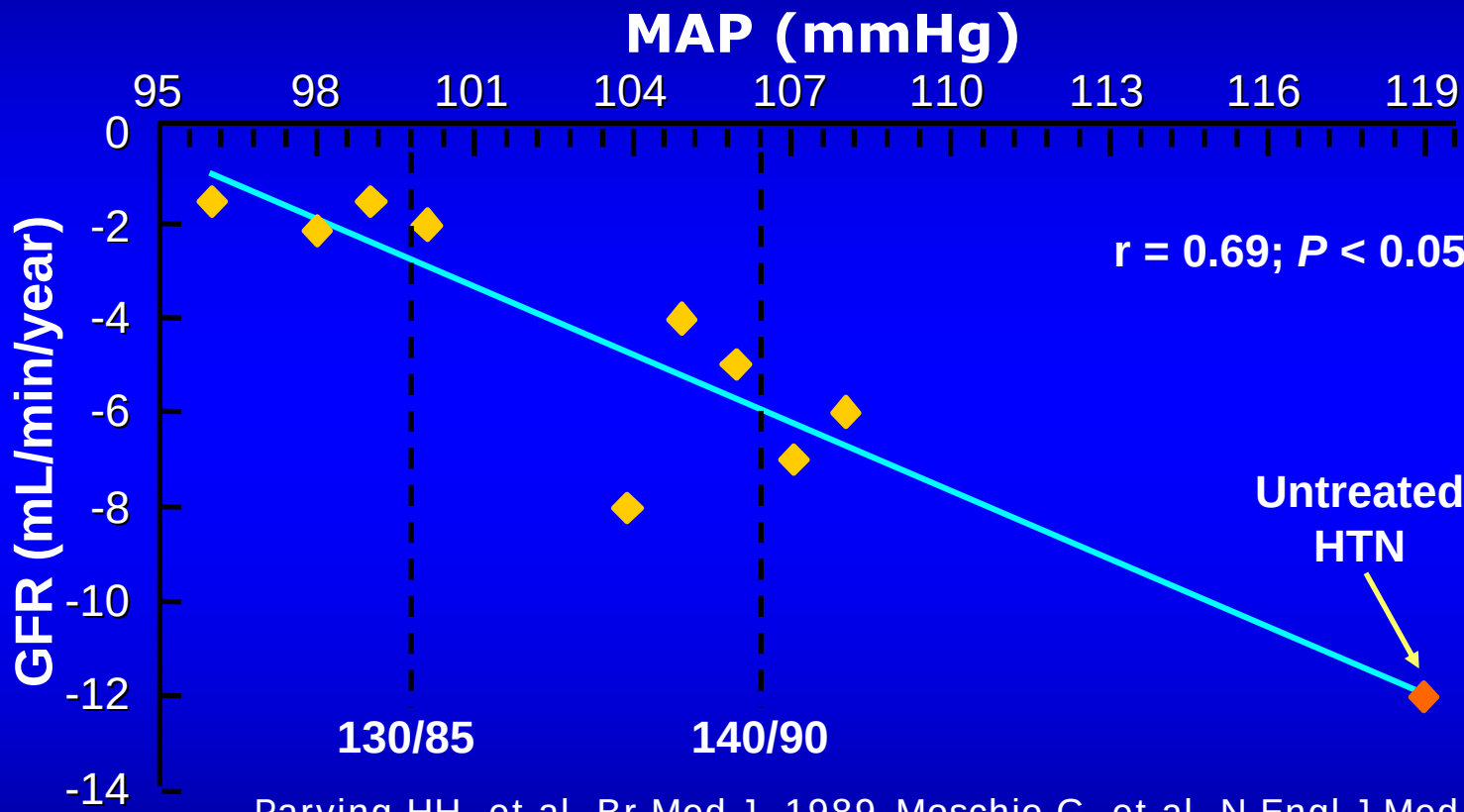



Pahor M, et al. Diabetes Care. 2000;23:888-892.

# Renal Disease and Hypertension Core Concepts of Treatment

- Hypertension and proteinuria (albuminuria) are both independent variables that predict long-term decline in renal function
- Renal disease is both a cause and consequence of hypertension;
- Reduction of blood pressure reduces cardiovascular risk and renal risk
- Reduction of proteinuria (albuminuria) may lower both cardiovascular risk and renal risk

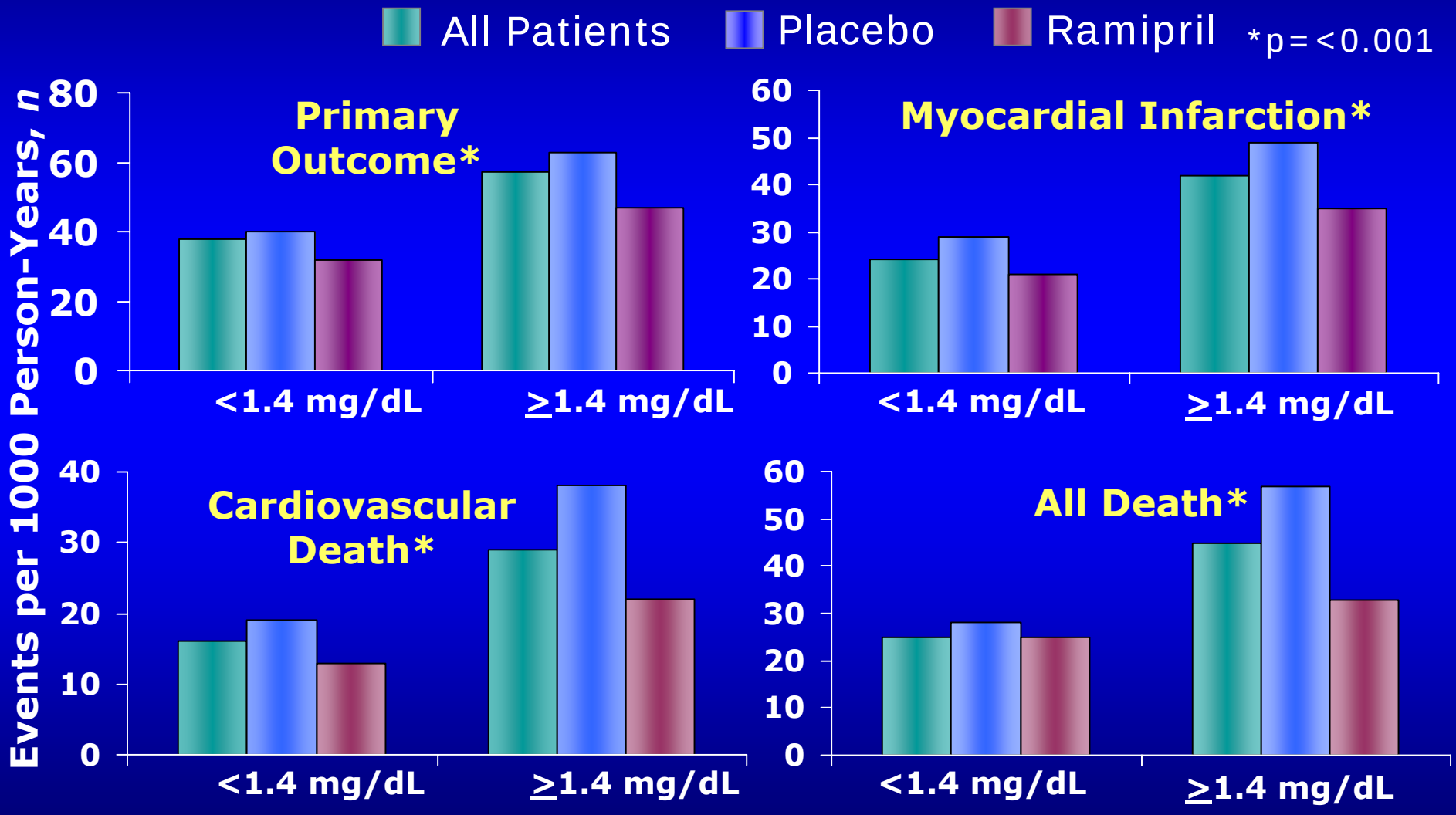
# Meta Analysis: Lower Mean BP Results in Slower Rates of Decline in GFR in Diabetics and Non-Diabetics




Parving HH, et al. Br Med J. 1989.
Viberti GC, et al. JAMA. 1993.
Klahr S, et al. N Eng J. Med 1994.
Hebert L, et al. Kidney Int. 1994.
Lebovitz H, et al. Kidney Int. 1994.
Moschio G, et al. N Engl J Med. 1996.
Bakris GL, et al. Kidney Int. 1996.
Bakris GL. Hypertension. 1997.
The GISEN Group. Lancet. 1997.

**Bakris GL, et al. Am J Kidney Dis. 2000;36(3):646-661.**

# HOPE Trial: Main Outcomes and Serum Creatinine




Mann JFE, et al. Ann Intern Med. 2001;134(8):629-636.
Reprinted by permission, ACP-ASIM.

# IDNT
# Summary of Important Findings

In hypertensive, type 2 diabetics with nephropathy:

- Irbesartan reduced the incidence of the primary composite endpoint of a doubling of serum creatinine, end stage renal disease, or death by 23% vs amlodipine (P=0.006) and 20% vs placebo (P=0.02)
- Proteinuria was reduced 33% in the irbesartan group compared to 10% with placebo
- These benefits were above and beyond those attributable to blood pressure reduction alone

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

# ALLHAT Implications

- Unless contraindicated, or unless specific indications are present that would favor use of another drug class, diuretics should be the initial drug of choice in antihypertensive regimens

- Only 30 percent of patients achieve both systolic BP <140 mmHg and diastolic BP <90 mmHg on monotherapy

- Many high-risk hypertensive patients will require 2 or more drugs for BP control

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

# Conclusioni

- L’orientamento attuale per il management del paziente con ipertensione arteriosa prevede:
  - una valutazione globale del rischio cardiovascolare, utilizzando un approccio multiparametrico (non ancora del tutto standardizzato);
  - la definizione dei marker di rischio;
  - la definizione del target terapeutico in base al profilo complessivo del rischio cardiovascolare e renale.