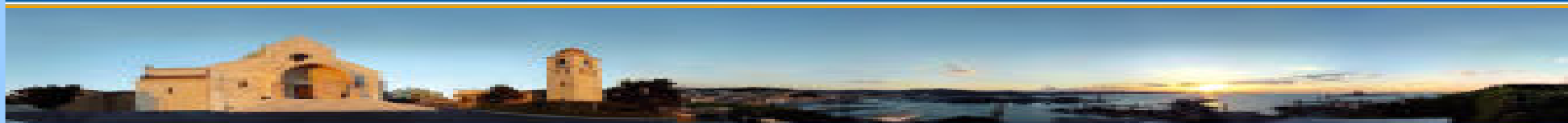


AMD

ASSOCIAZIONE MEDICI DIABETOLOGI

3° CONVEGNO NAZIONALE
Centro Studi e Ricerche



Ancona
12/14 Ottobre 2006

Possibili sviluppi nell'approccio al paziente iperteso con sindrome metabolica



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Sindrome Metabolica: *Le recenti polemiche*

- 1) Le evidenze sulla unitarietà etiopatogenetica sono insoddisfacenti (corretto il termine “sindrome” ?),**
- 2) I criteri diagnostici proposti sono diversi tra loro,**
- 3) La specificità con cui diversi criteri identificano il rischio vascolare individuale non è sempre ottimale,**
- 4) I singoli fattori sono profondamente diversi tra loro come “peso” nell’ambito del rischio vascolare,**
- 5) La rilevanza clinica è completamente diversa in base al tipo di combinazione di fattori di rischio presente,**
- 6) Nessuna evidenza ampia e controllata su riduzione degli eventi ed approccio globale alla sindrome.**

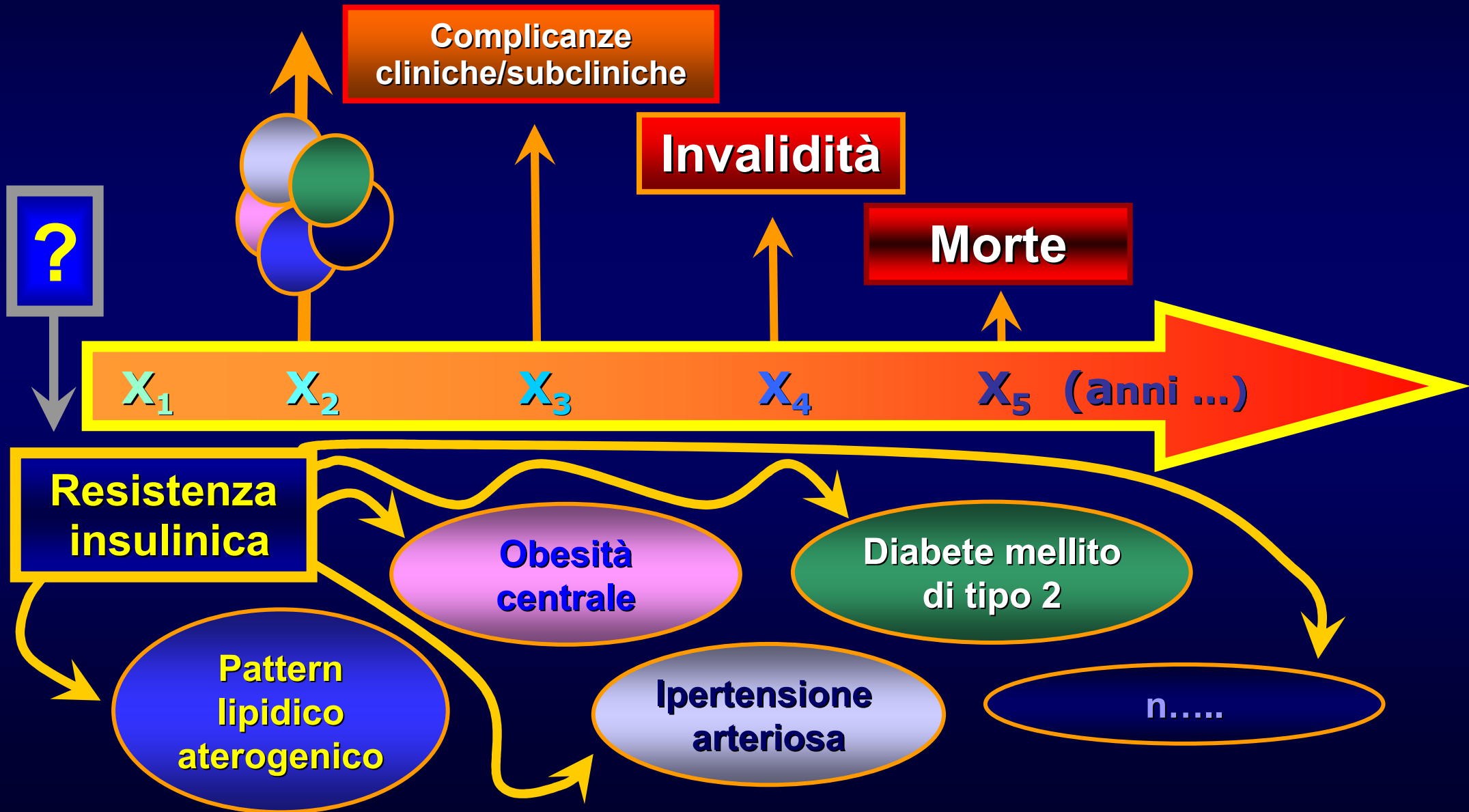
Sindrome (dal greco σύνδρομον) :

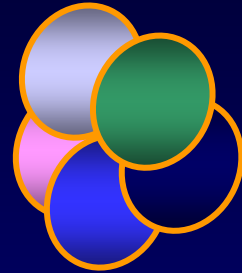
Letteralmente: "***che corrono insieme***".

Identifica un complesso di sintomi apparentemente disgiunti, aventi però – in tutto oppure in parte – una comune origine etiologica e/o patogenetica.

Non ha, per questo motivo, l'autonomia nosografica di una malattia.

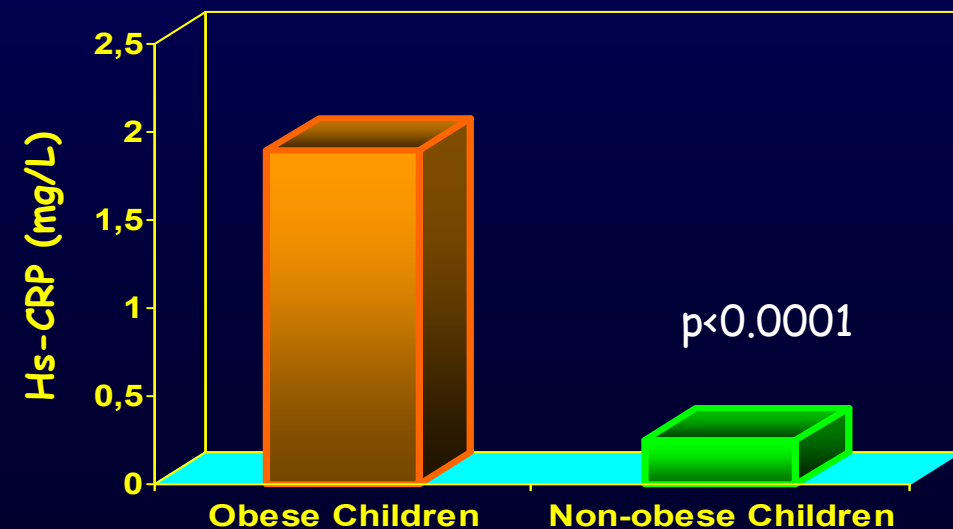
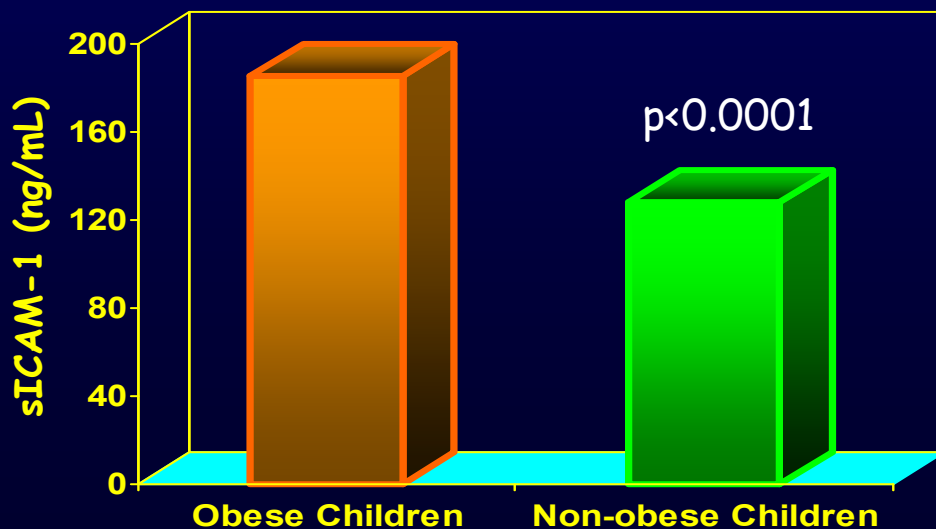
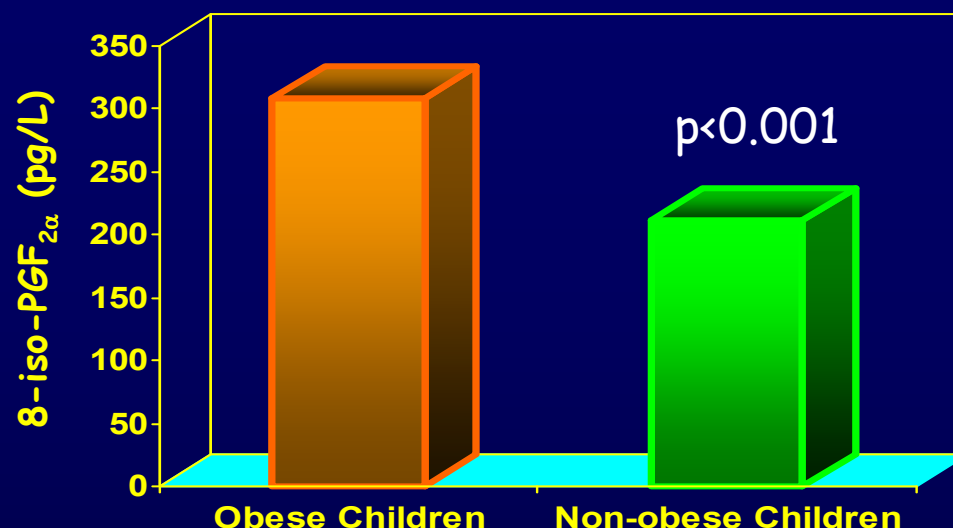
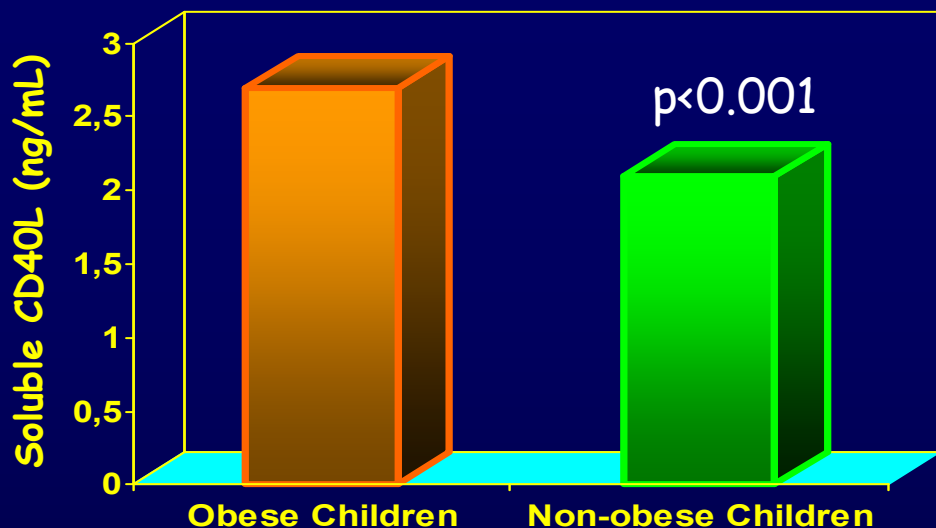
Costellazione di fattori di rischio



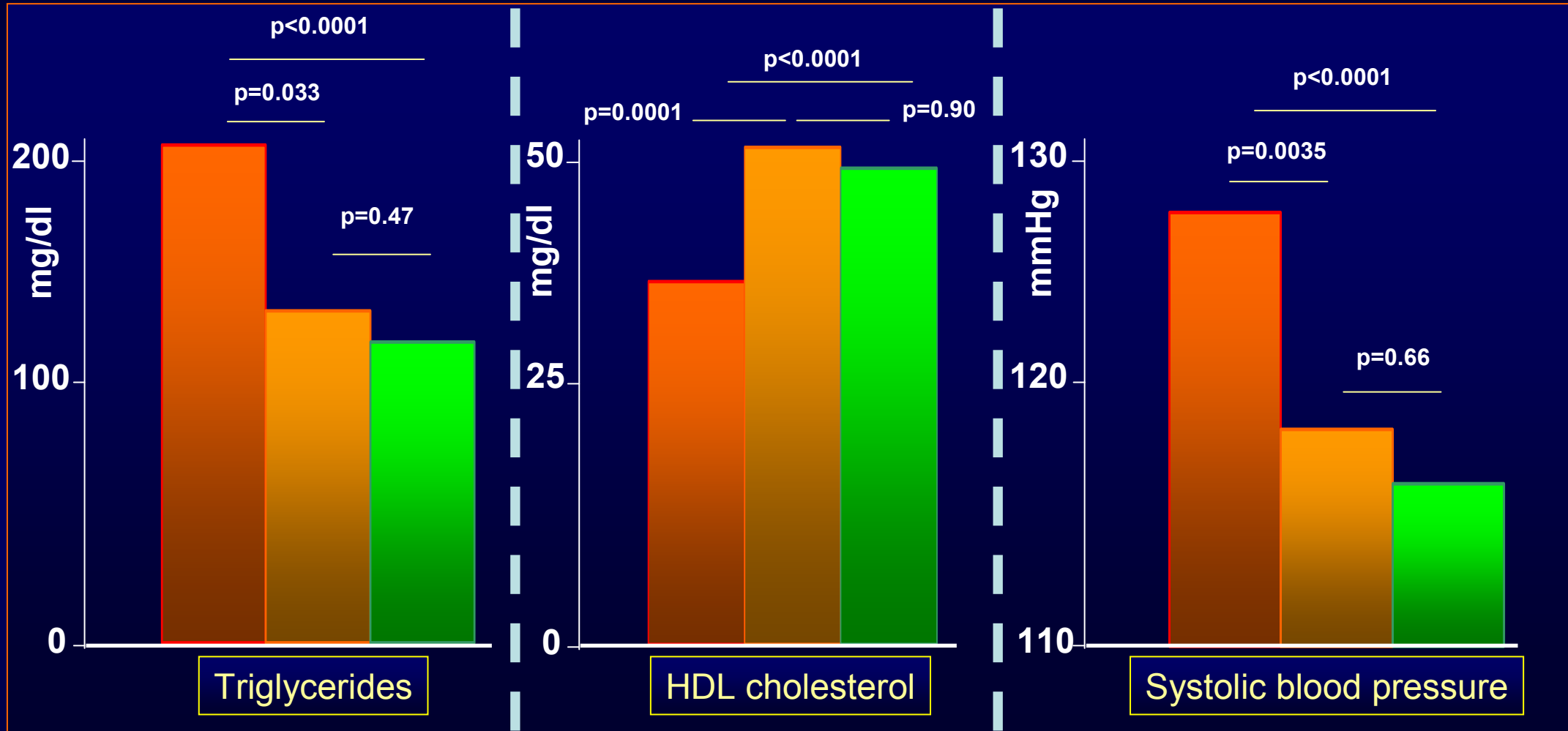


Evidenze a ***favore***
dell'unitarietà etiopatogenetica
della ***Sindrome metabolica***

Increased *Soluble CD40L*, *8-iso-PGF_{2α}*, *sICAM-1* and *Hs-CRP* Concentrations in Low Risk Obese Children.



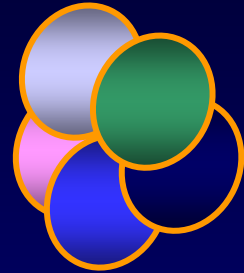
Levels of cardiovascular risk factors by HOMA IR (fasting insulin),
insulin secretion ($\Delta I_{30-0 \text{ min}}/\Delta G_{30-0 \text{ min}}$), and conversion status



- Converters to type-2 diabetes with high HOMA IR and High $\Delta I_{30-0 \text{ min}}/\Delta G_{30-0 \text{ min}}$
- Converters to type-2 diabetes with low HOMA IR and High $\Delta I_{30-0 \text{ min}}/\Delta G_{30-0 \text{ min}}$
- Non-converters

HOMA IR
HIGH **LOW**
BMI **32.3 \pm 0.7** **25.0 \pm 2.0**
p<0.0001

Haffner et al. *Circulation* 2000;101:975-980.



Evidenze **contro**
l'unitarietà etiopatogenetica
della **Sindrome metabolica**

N° of abnormalities

WHS

Ridker P et al, Circulation 2003, 107:391-397

NHANES III

Ford ES et al JAMA 2002;287(3):356-9

≥ 1

72.2 \pm 0.4%

70.9 \pm 1.2%

≥ 2

45.9 \pm 0.4%

42.7 \pm 1.3%

≥ 3

24.4 \pm 0.4%

23.4 \pm 0.9%

≥ 4

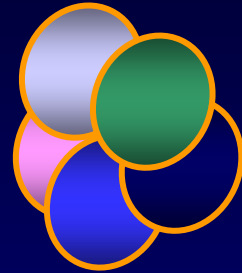
8.9 \pm 0.2%

9.6 \pm 0.5%

5

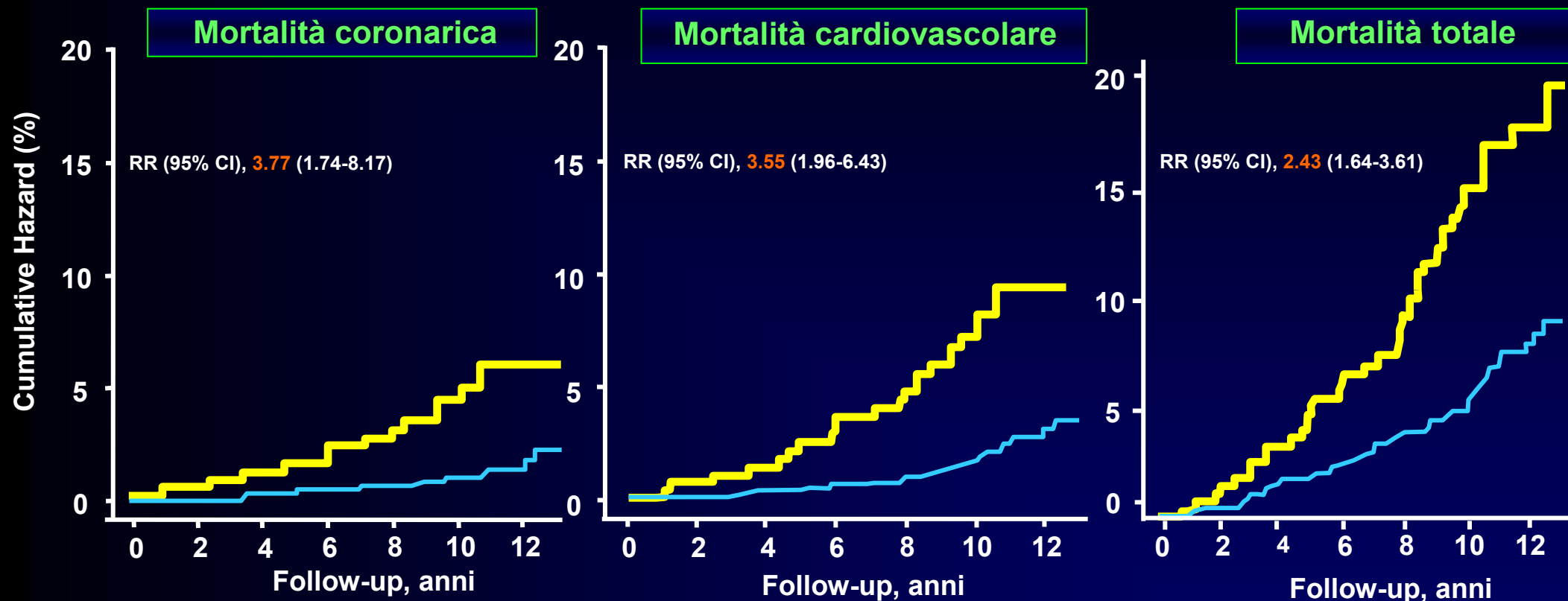
1.2 \pm 0.1%

2.9 \pm 0.3%



Evidenze a ***favore*** o ***contro***
l'unitarietà etiopatogenetica
della ***Sindrome metabolica***
(costellazione di fattori di rischio):
indubbio (pur con vari distinguo)
è il suo ruolo negativo per la salute

Mortalità coronarica, da cause cardiovascolari e totale in 1.209 uomini con sindrome metabolica, ma senza diabete mellito, malattie cardiovascolari o neoplasie all'inizio del follow-up



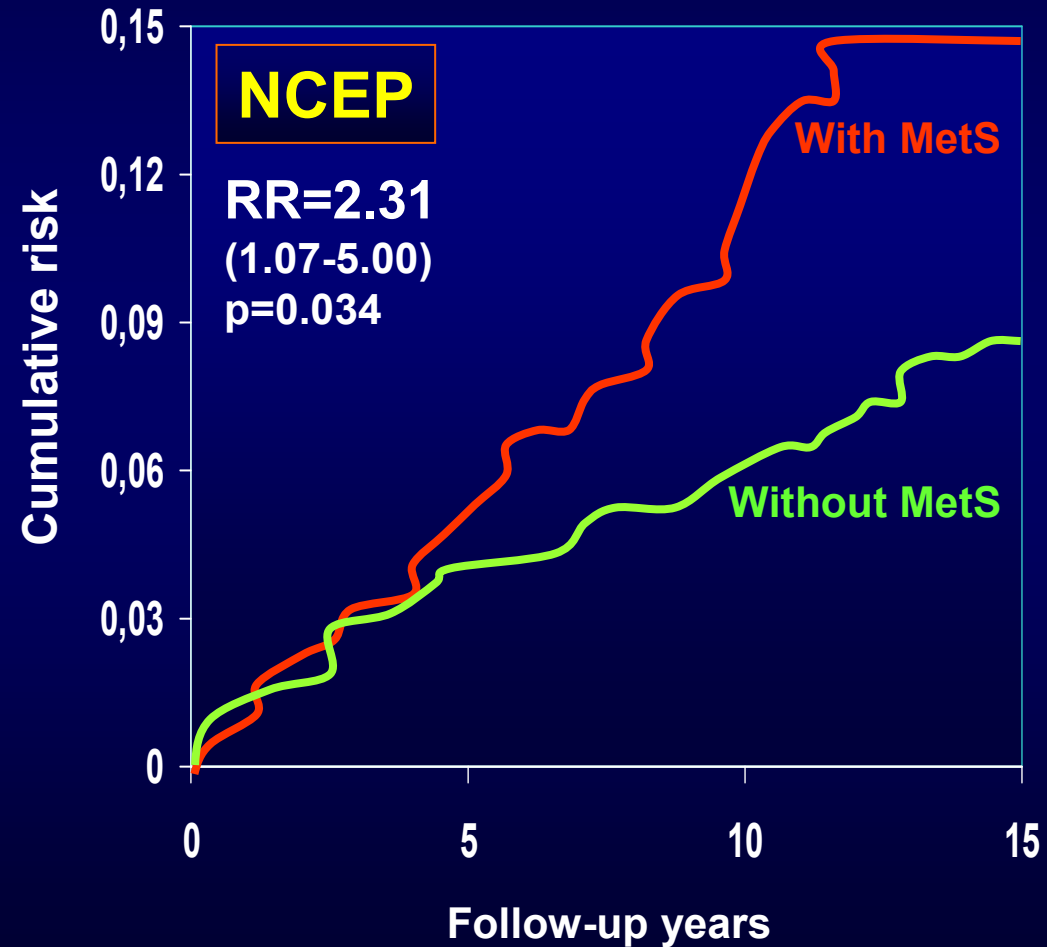
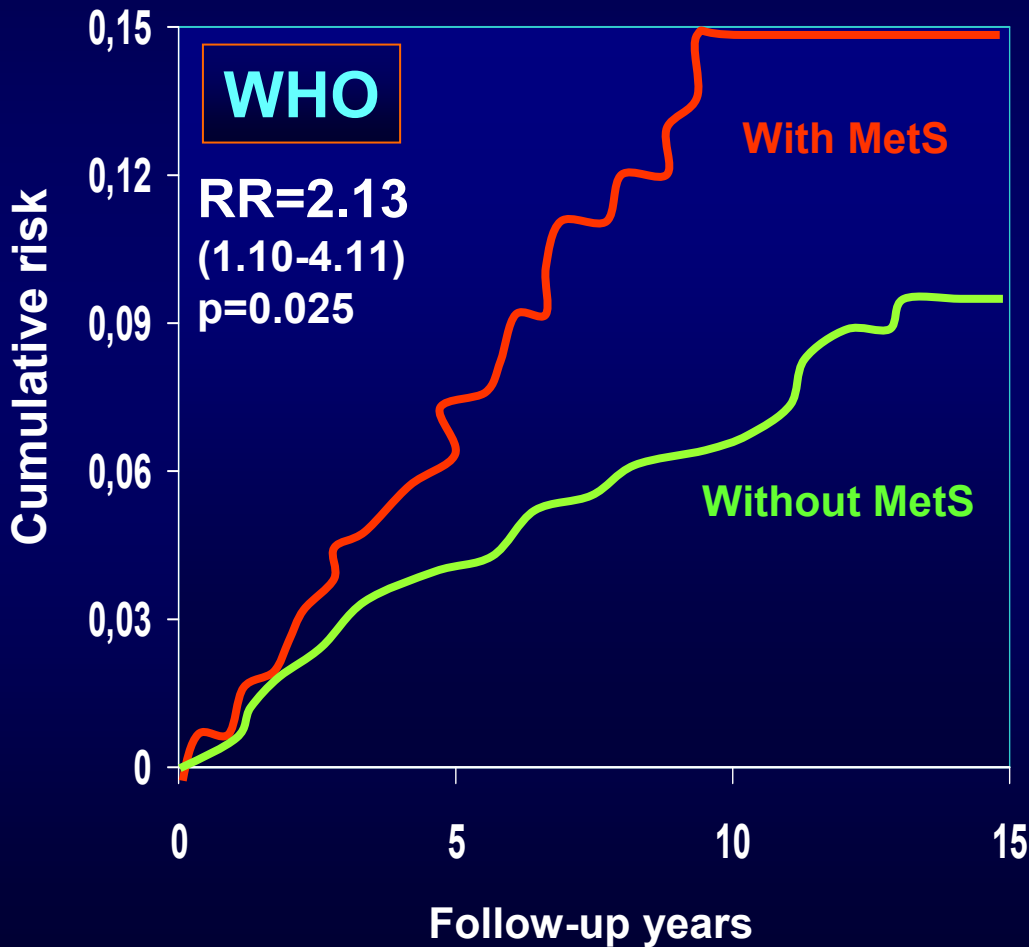
No. di soggetti a rischio
Sindrome metabolica

Si	866	852	834	292	866	852	834	292	866	852	834	292
No	288	279	234	100	288	279	234	100	288	279	234	100

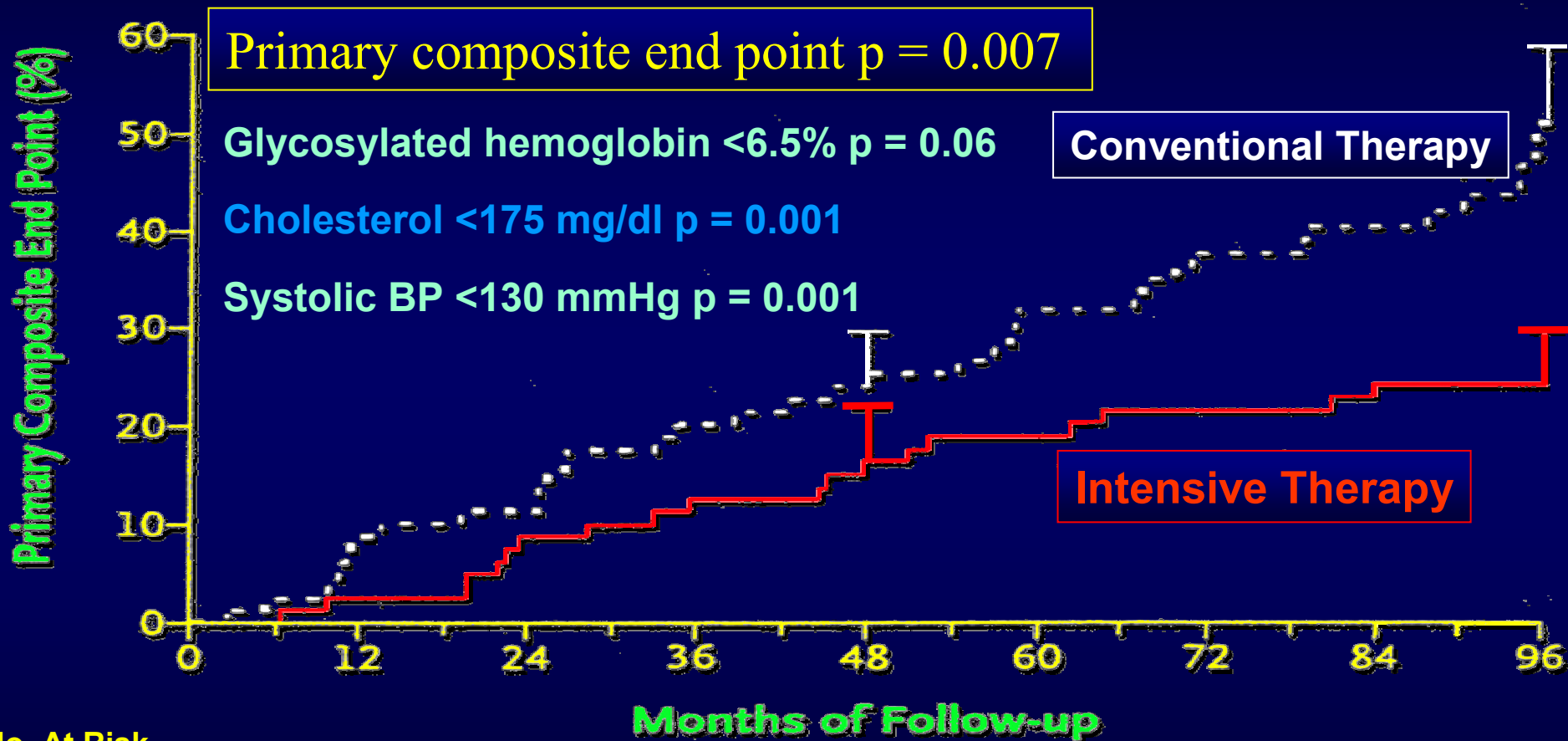
Sindrome metabolica — **Si** — — **No** —

Cumulative risk for **ischemic stroke** in men with metabolic syndrome (Met S) according to the definition of **WHO** and **NCEP** for an average follow-up of 14.3 years

N = 1.131 with no history of CV disease and diabetes at baseline

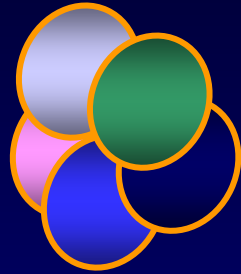


Steno-2: Composite end point of Death from Cardiovascular causes, Non Fatal Myocardial Infarction, Coronary-Artery Bypass Grafting, Percutaneous Coronary Intervention, Non Fatal Stroke, Amputation or Surgery for Peripheral Atherosclerotic Artery Disease in the Conventional Therapy Group and the Intensive Therapy Group



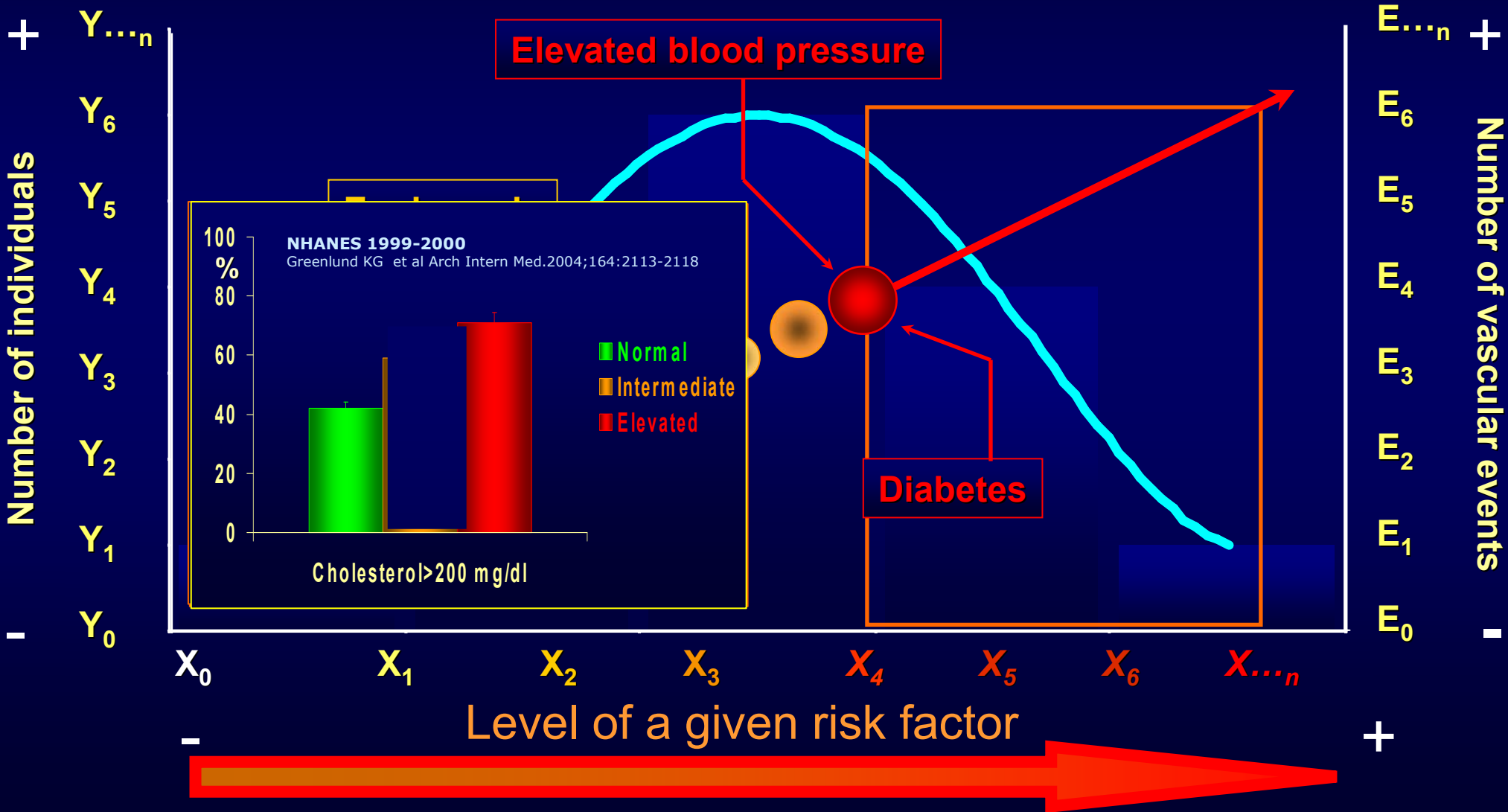
No. At Risk

Conventional	80	72	70	63	59	50	44	41	13
Intensive	80	78	74	71	66	63	61	59	19

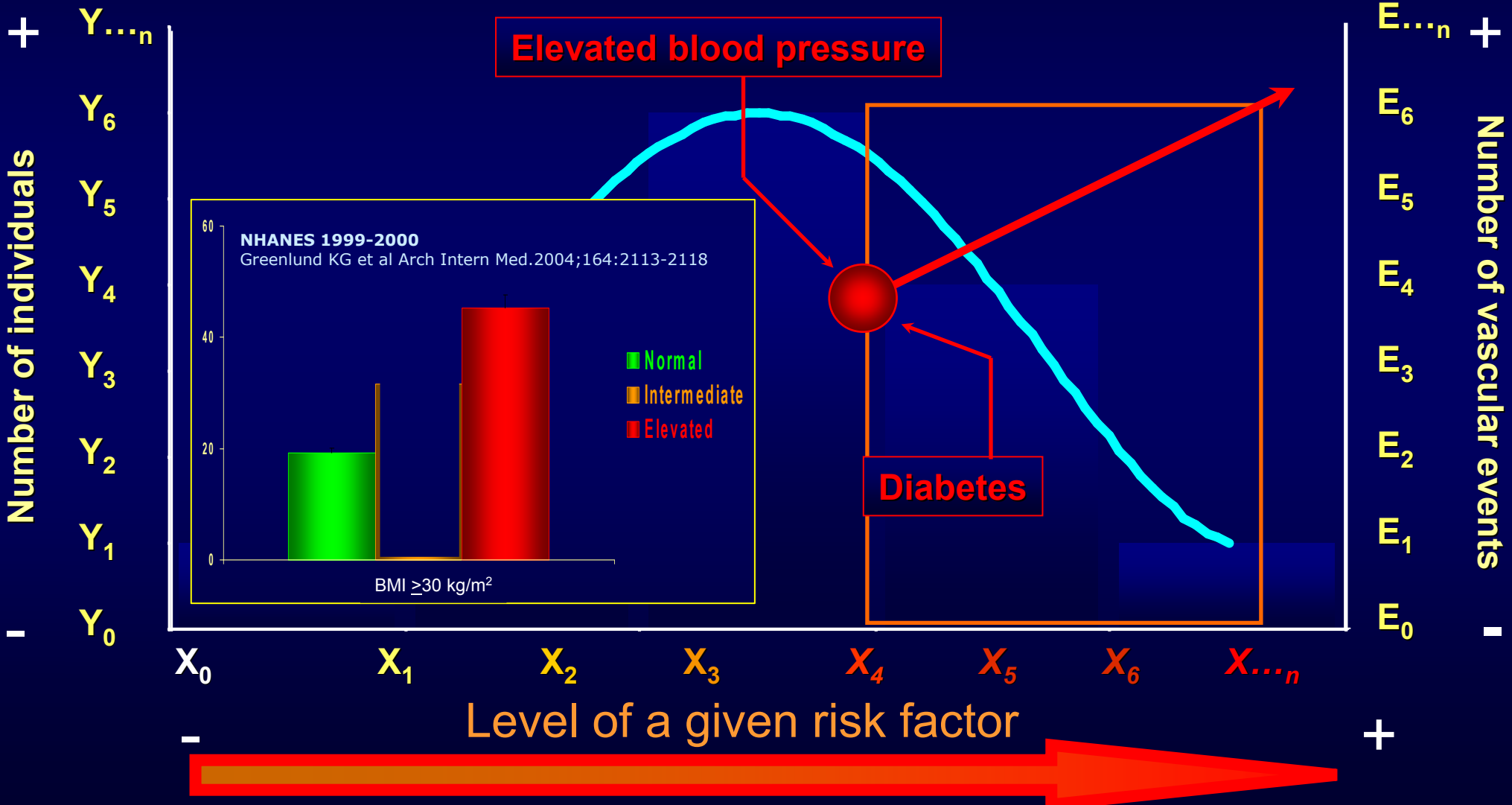


Prevenire è meglio che combattere.....

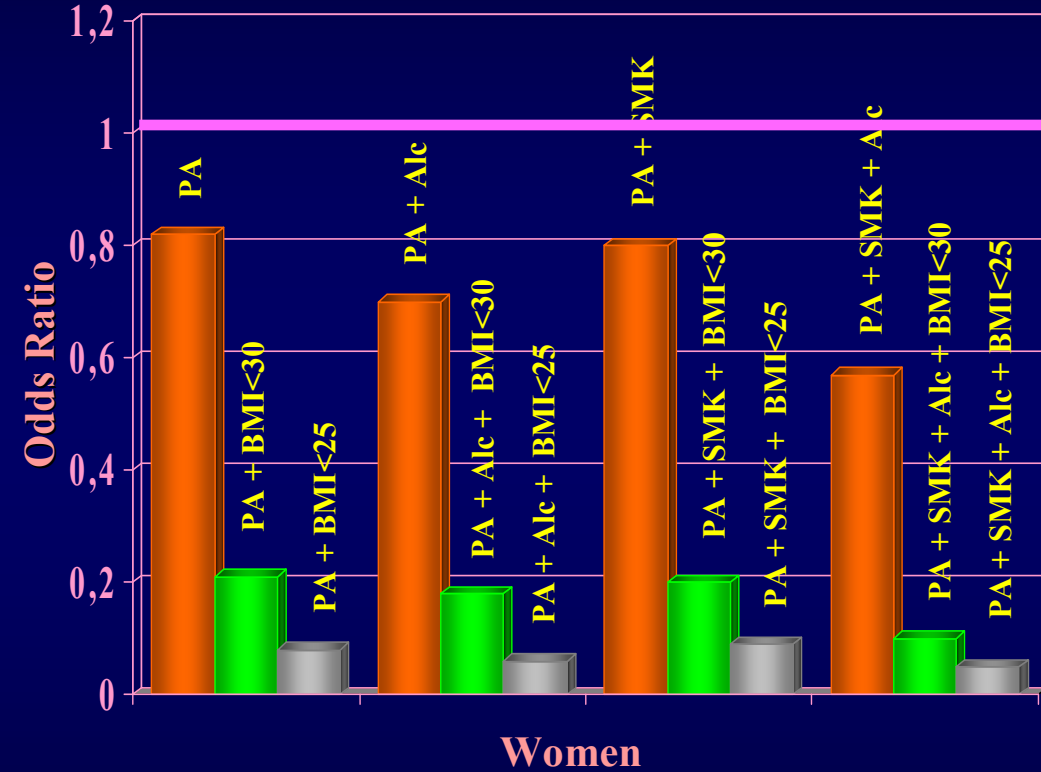
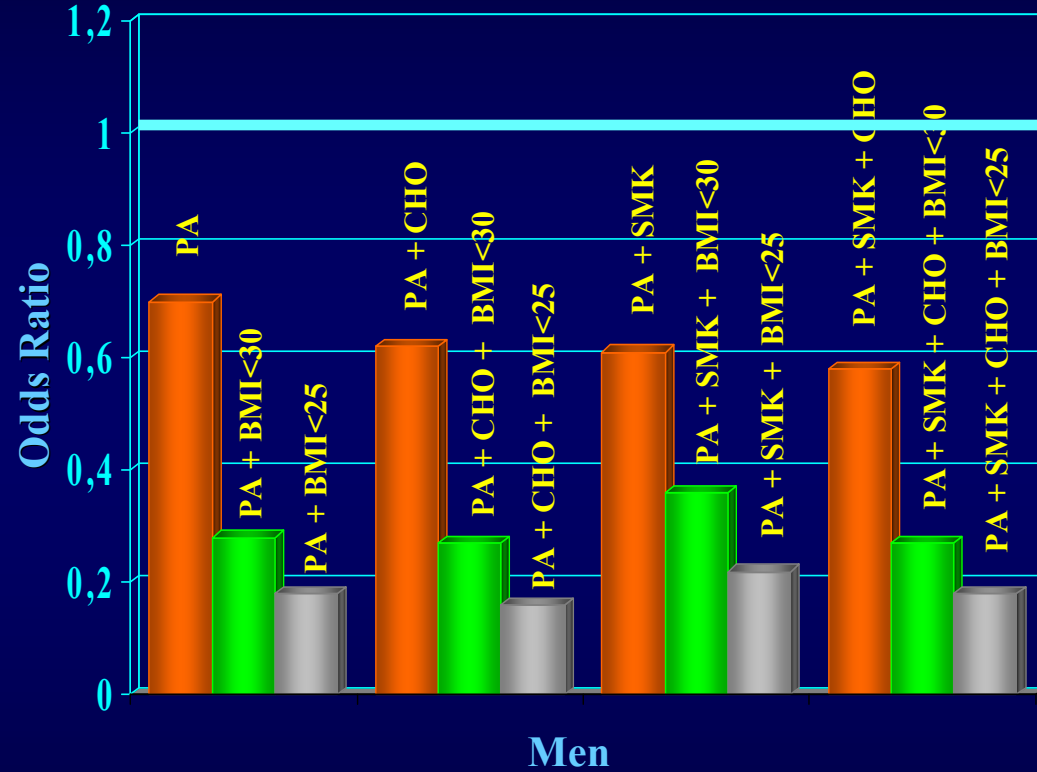
A given risk factor may precede diabetes



A given risk factor may precede diabetes



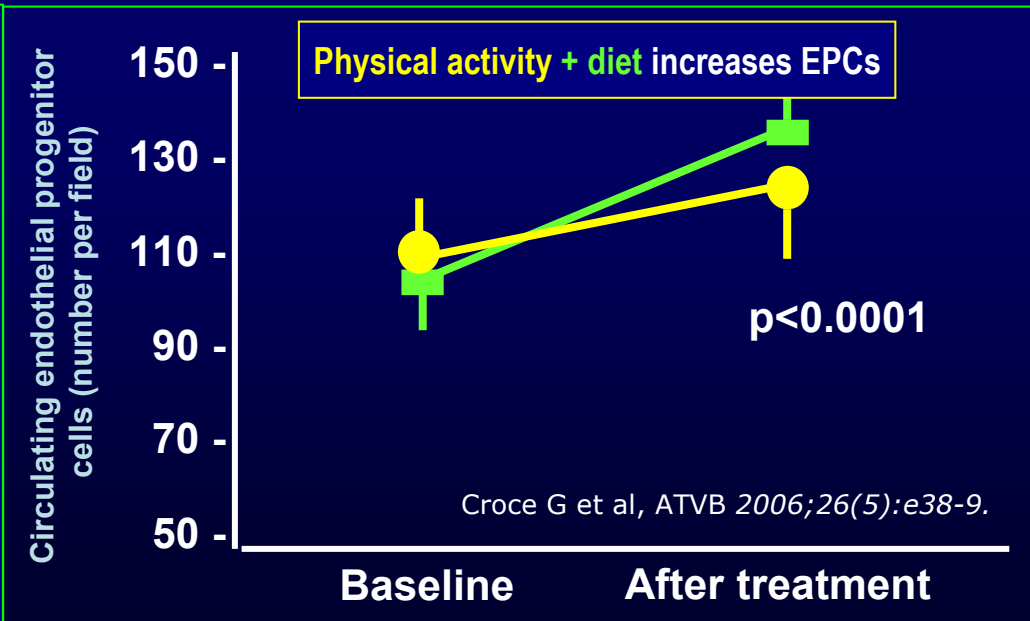
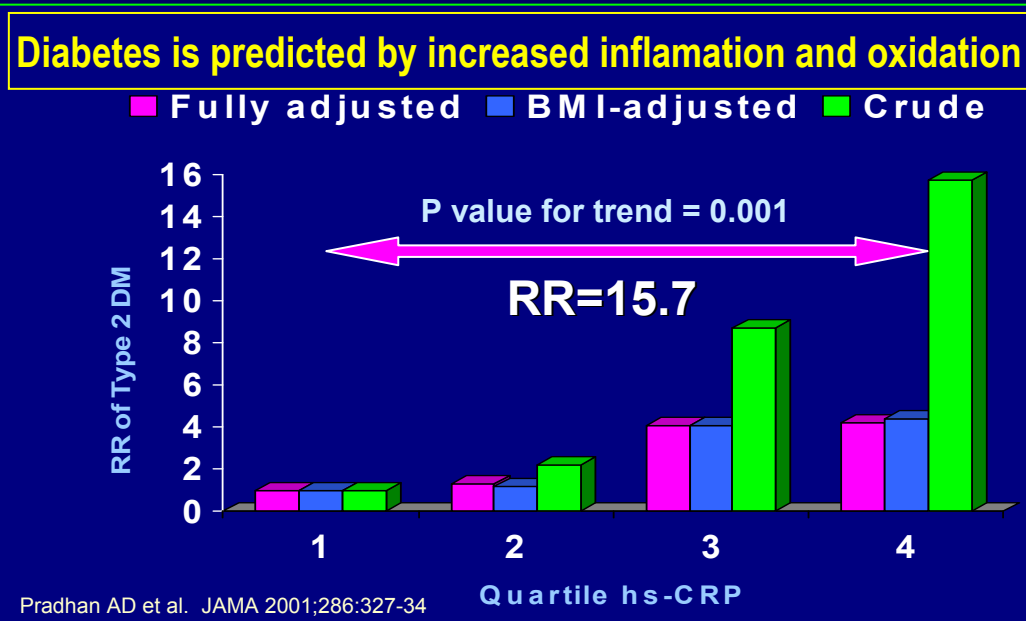
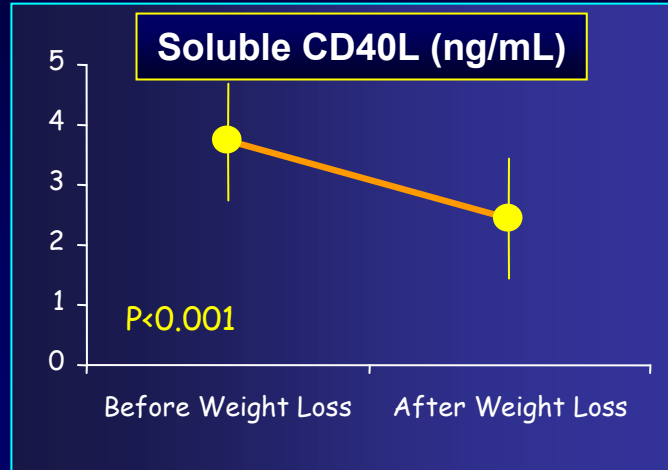
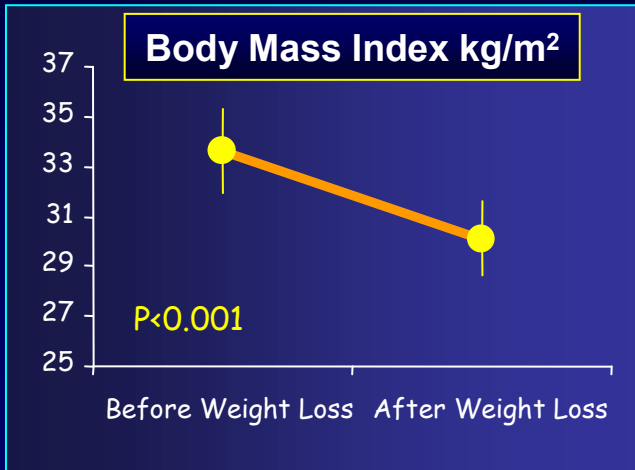
ORs of having the metabolic syndrome with low-risk behaviors or lifestyle (NHANES III)



PA: physically active
CHO: low and moderate carbohydrate intake (for men)
Alc: light to moderate alcohol consumption (for women)
SMK: Non smoking

Overall
Overweight
Normal weight

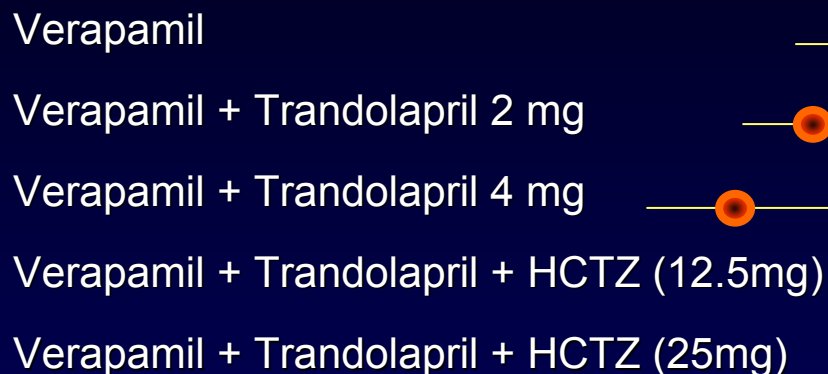
Effect of Weight Loss on Soluble CD40L and 8-iso-PGF_{2α} Levels in Obese Patients



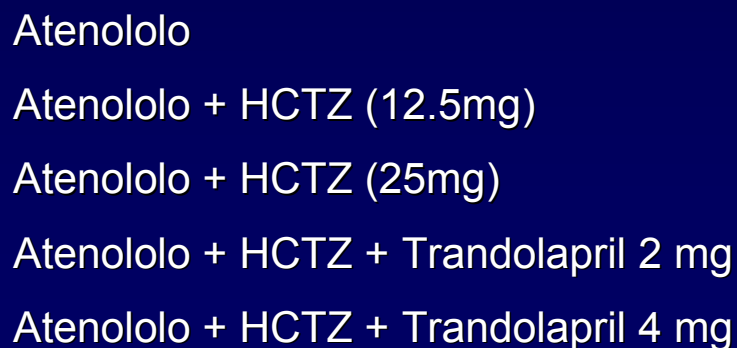
Prevenzione dei nuovi casi di diabete con diverse strategie di combinazione

Nuovi casi di diabete

Trandolapril+Verapamil



Atenololo+Idroclorotiazide (HCTZ)



0.5

1

1.5

2.0

Riduzione del rischio

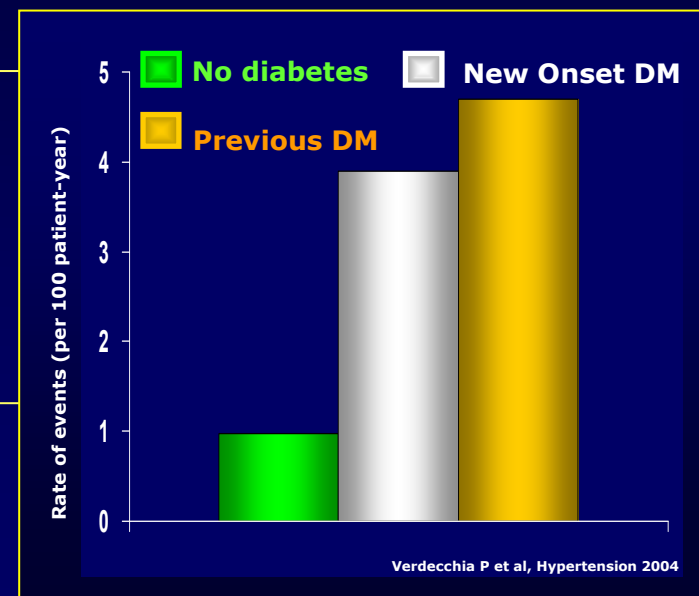
Aumento del rischio

Studio **INVEST**

Strategia trandolapril+verapamil
versus atenololo+idroclorotiazide

-15%

CV due to new onset DM

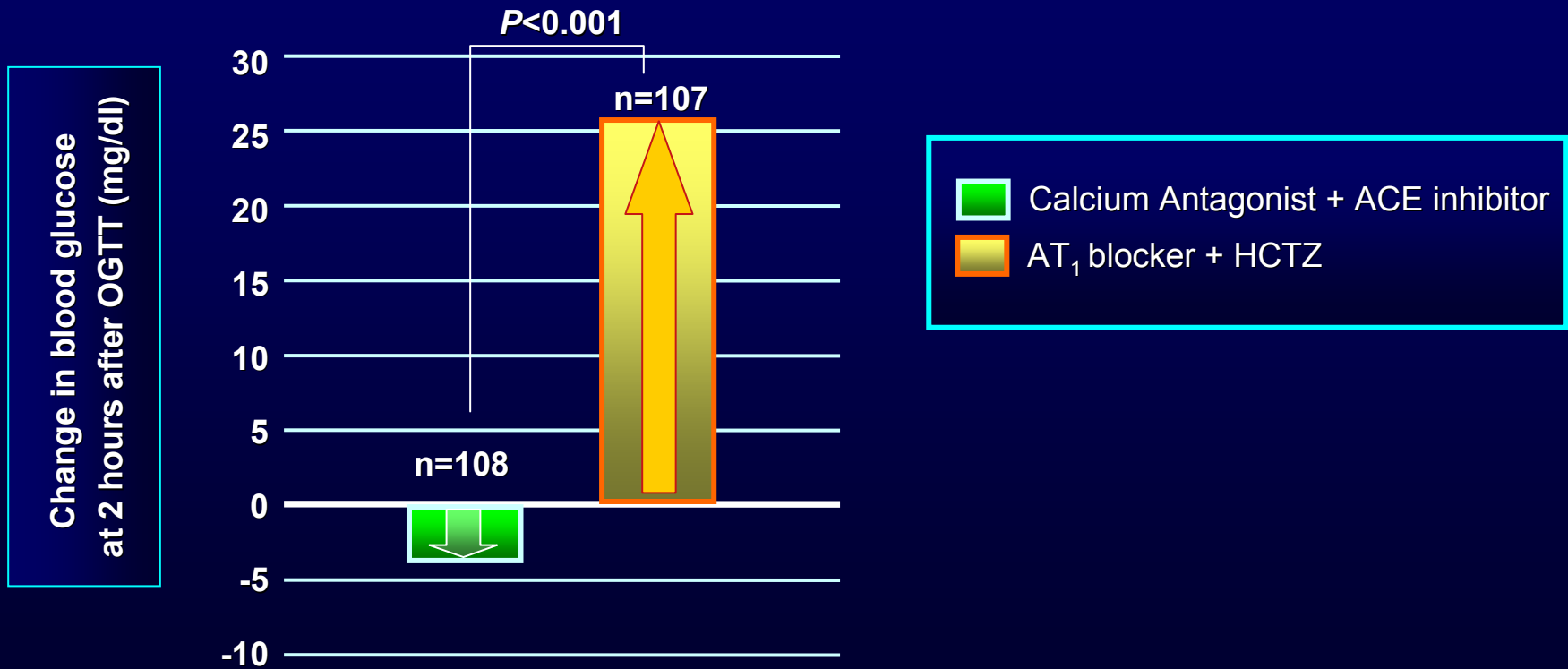


The Study of Trandolapril-verapamil And insulin Resistance



Primary end-point : Changes in plasma glucose levels

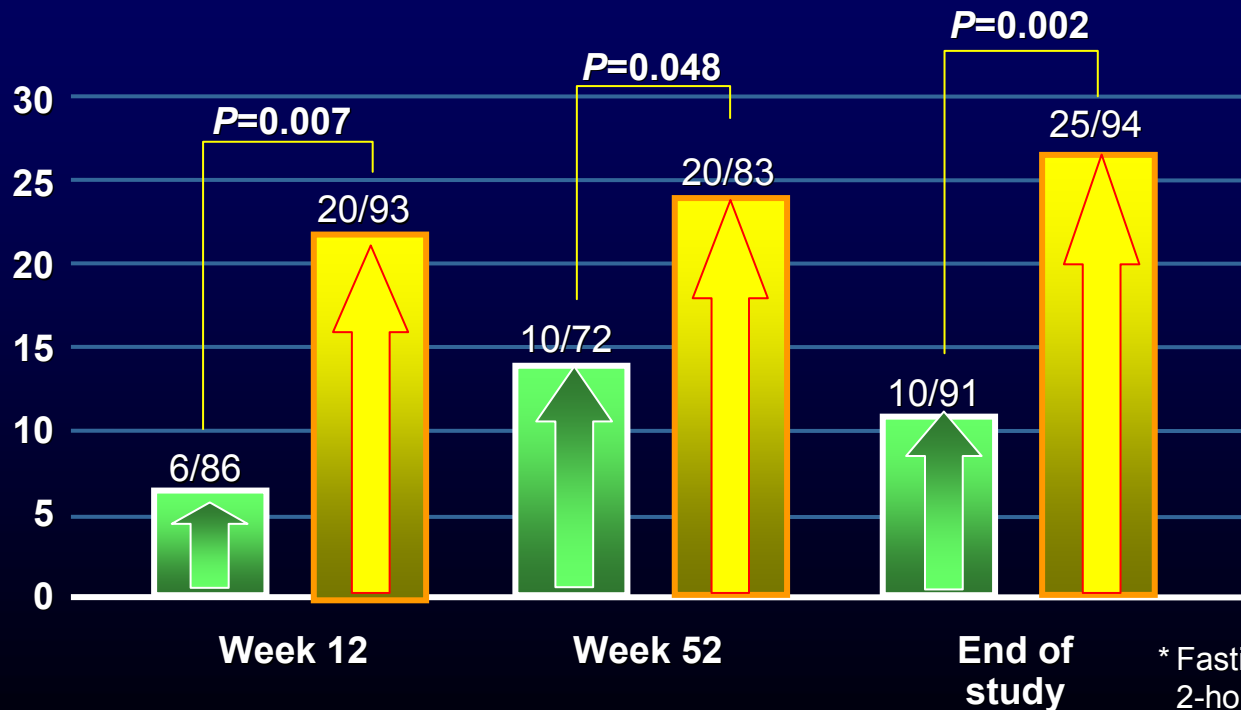
Losartan/HCTZ increased blood plasma glucose significantly more than verapamil SR/trandolapril following OGTT by study end*



Development of new-onset diabetes* **STAR**

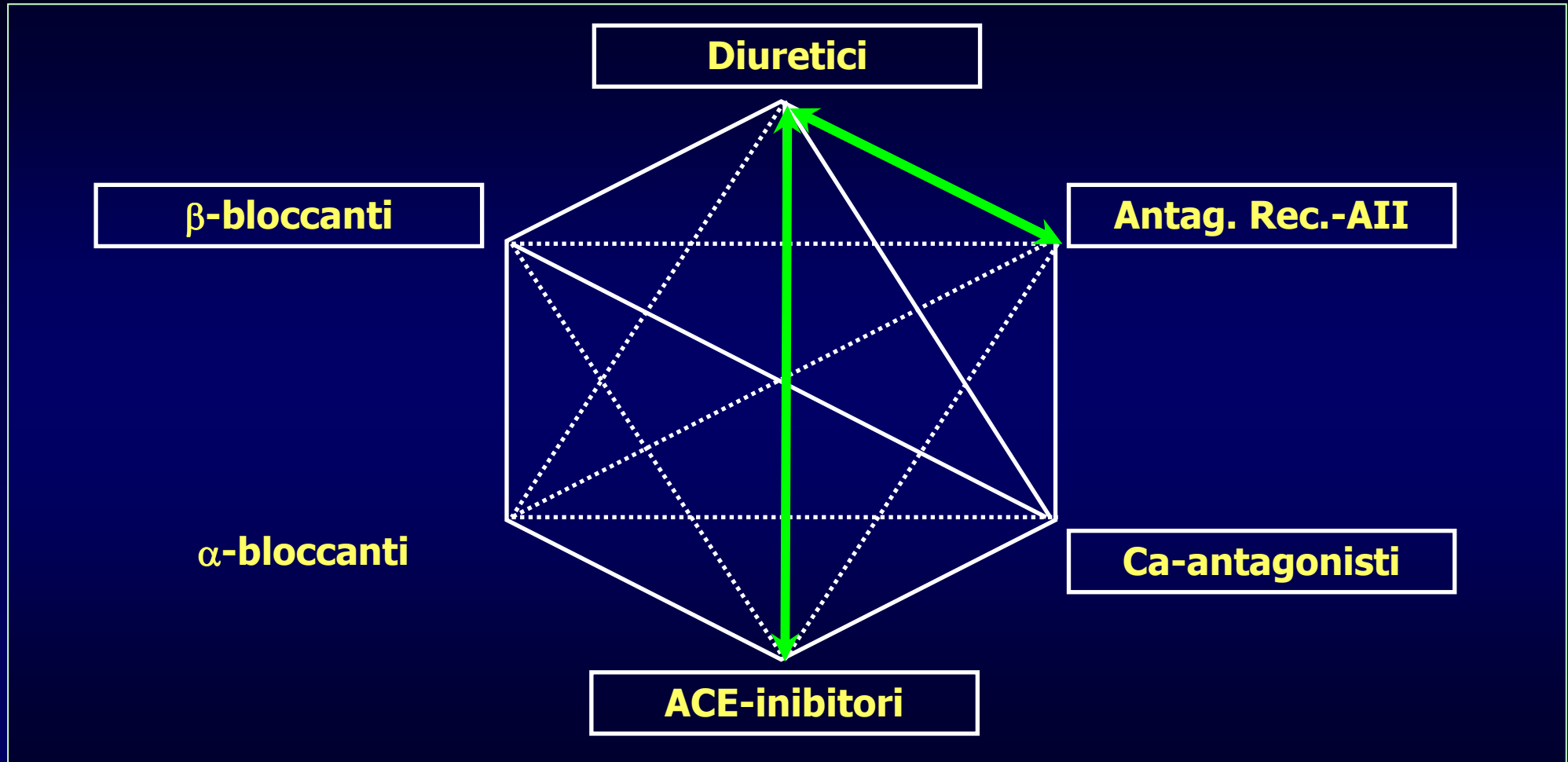
■ Calcium Antagonist + ACE inhibitor
■ AT₁ blocker + HCTZ

Percentage of Patients



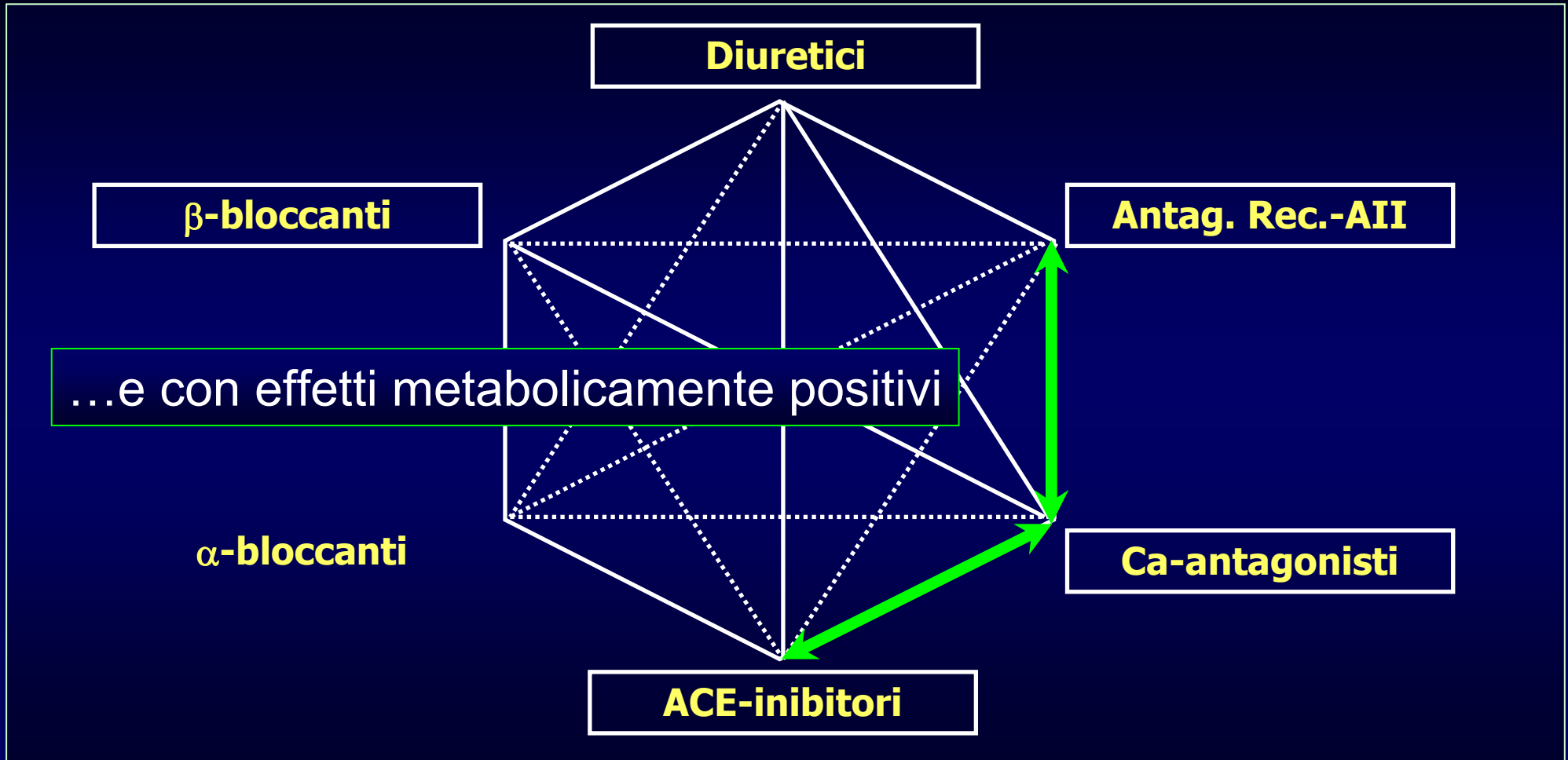
* Fasting blood glucose ≥ 126 mg/dl and/or 2-hour blood glucose levels after OGTT ≥ 200 mg/dl based on ADA definition

Associazione di farmaci dimostratesi efficaci e ben tollerate



- LE COMBINAZIONI PIU' RAZIONALI SONO ESPRESSE CON LINEE PIU' SPESSE
- I RIQUADRI SI RIFERISCONO ALLE CLASSI DI FARMACI ANTIPERTENSIVI I CUI BENEFICI SONO STATI DIMOSTRATI DA TRIAL CLINICI DI INTERVENTO

Associazione di farmaci dimostratesi efficaci e ben tollerate



- LE COMBINAZIONI PIU' RAZIONALI SONO ESPRESSE CON LINEE PIU' SPESSE
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Effetti principali di angiotensina II

Angiotensina II

Vasocostrizione

Flogosi vascolare

↓ Segnale
insulinico

↑ NADPH
Ossidasi

↑ LOX-1

↑ Aldosterone

n.....

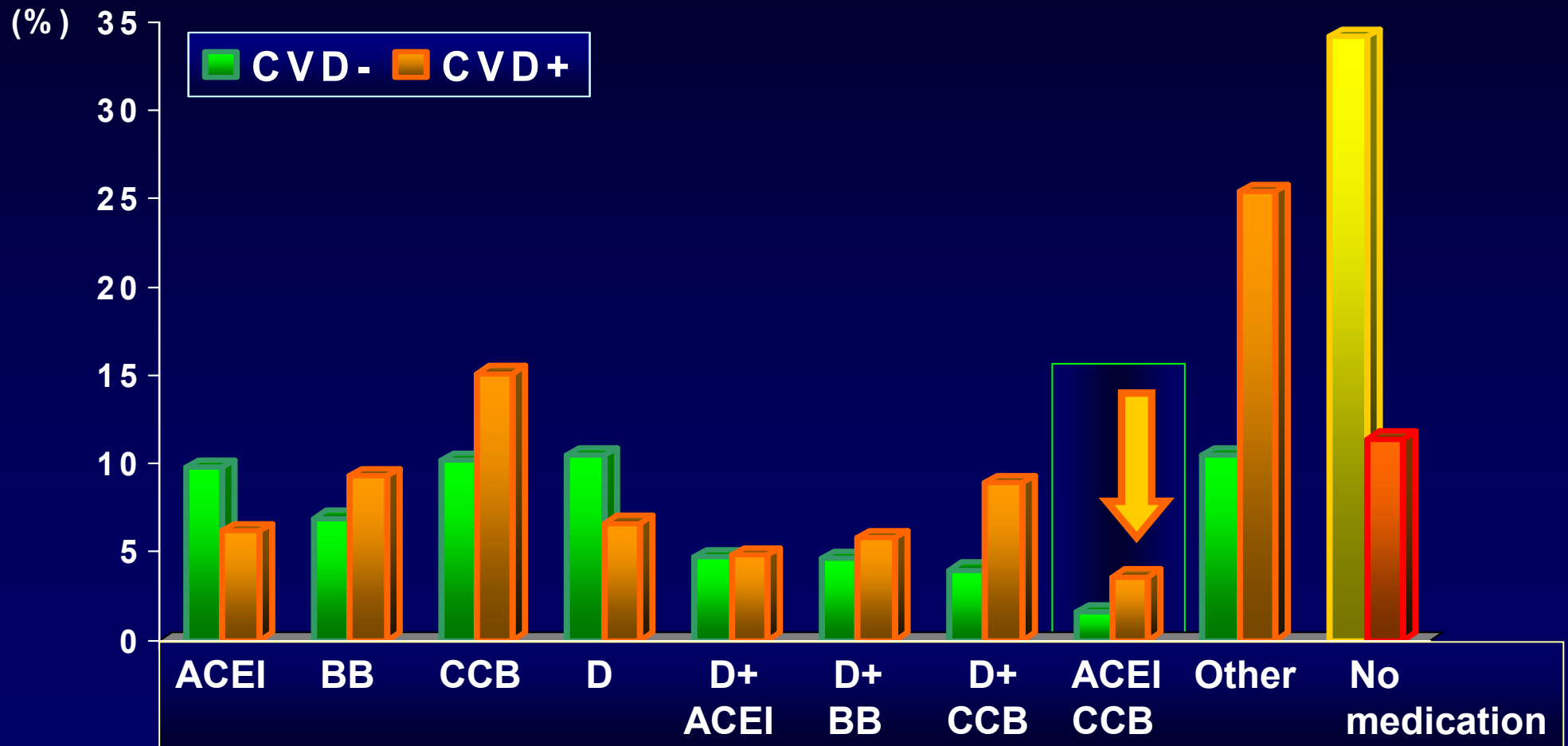
Ca^{++}

**sinergismo antiipertensivo
tra inibitori del RAAS e Ca^{++} antagonisti**

Danno Vascolare

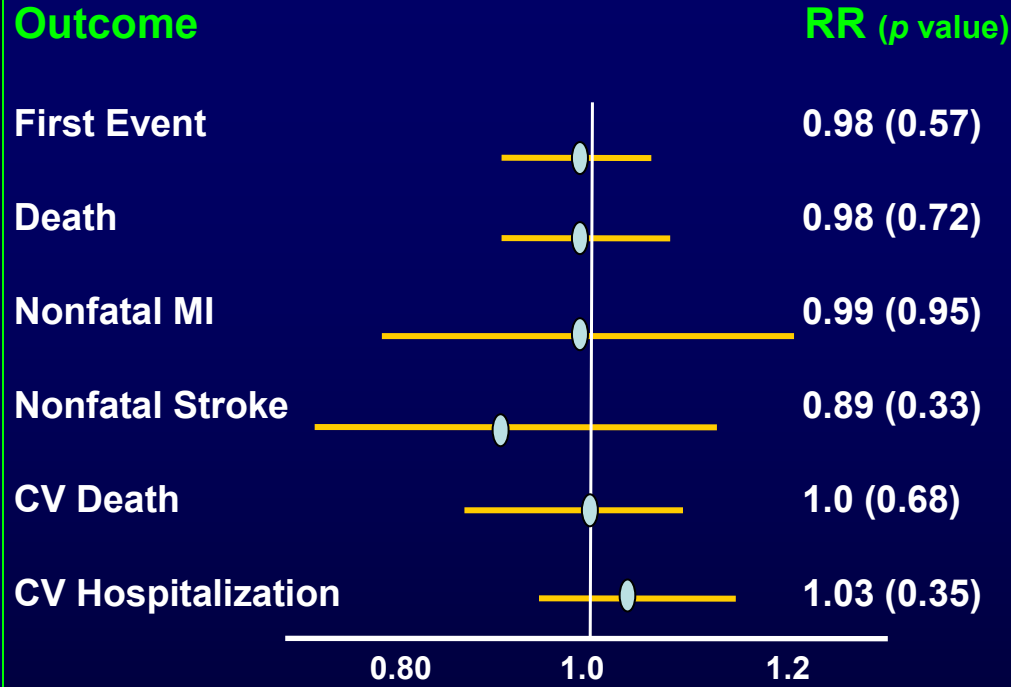
Antihypertensive Drug Treatment in Older Women

Women with hypertension enrolled in the Women's Health Initiative Observational Study, a longitudinal multicenter cohort study of 93,676 women aged 50 to 79 years at baseline (1994-1998), assessed for a mean of 5.9 years.



CCB+ACE-inhibitor antyhypertensive strategy - Outcomes

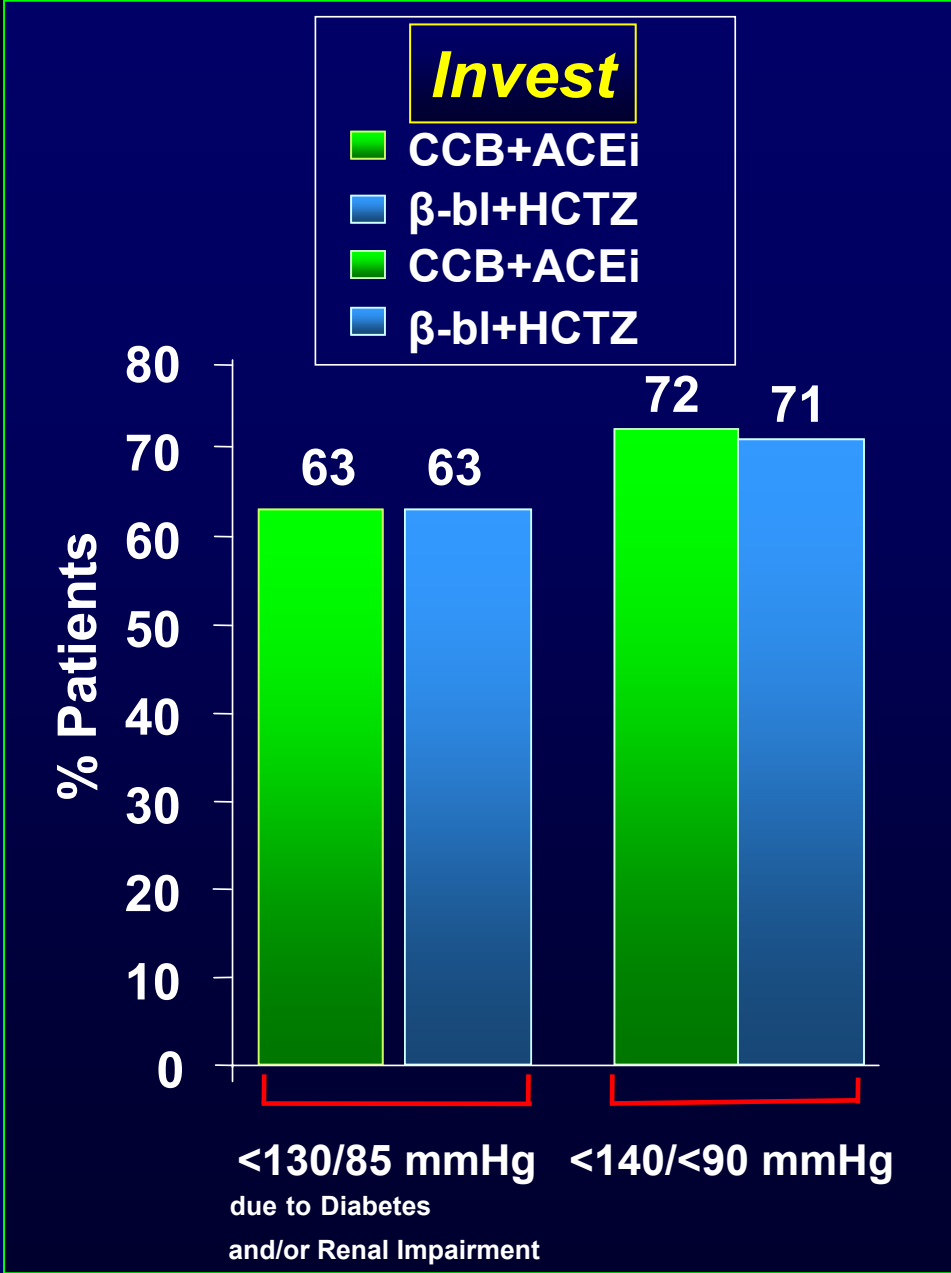
INVEST



CCB+ACEi Better beta-bl+HCTZ Better

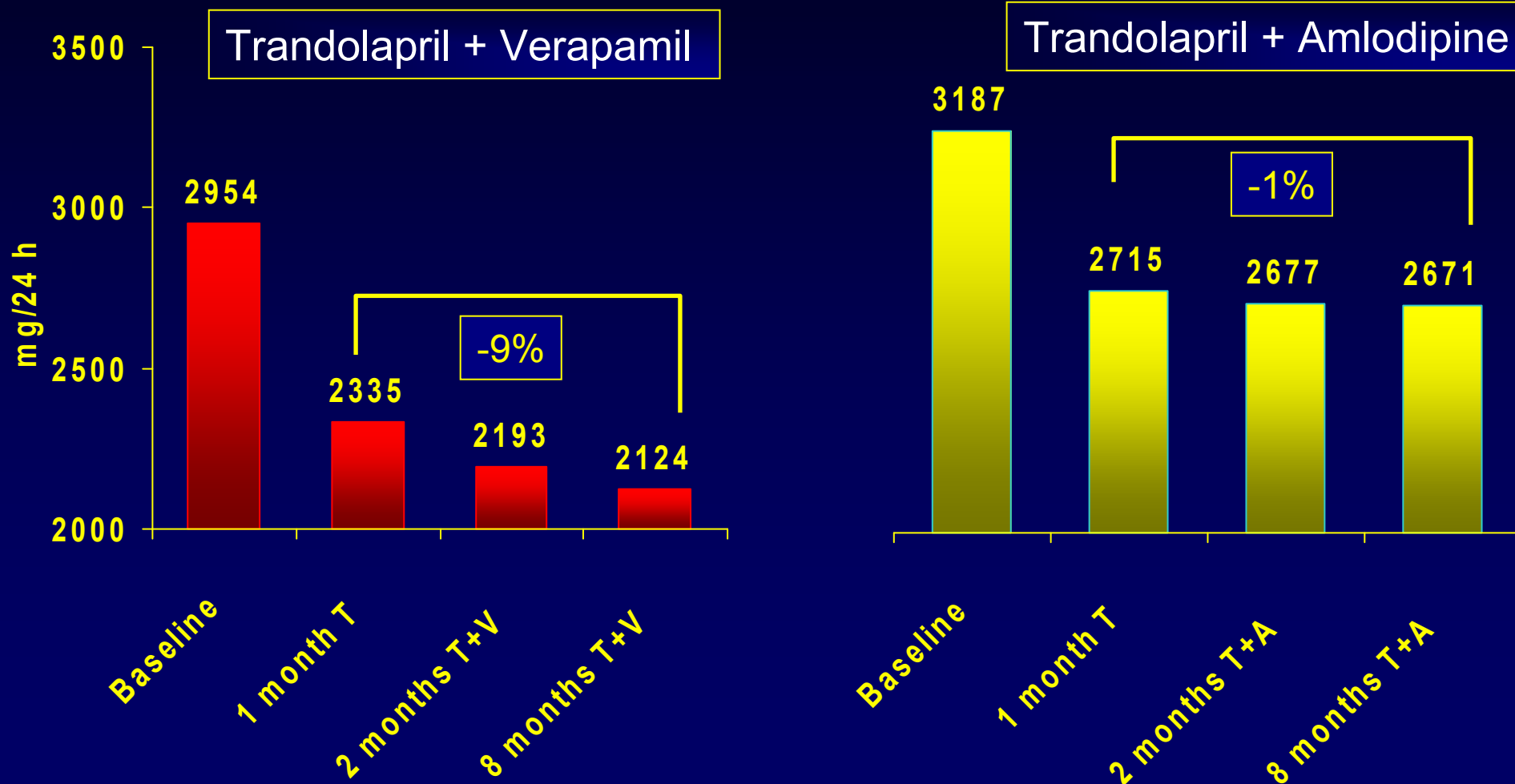
Number of angina attacks x week
 CCB+ACEi: 0.77±1.31 beta-bl+HCTZ: 0.88±1.62 p=0.02

Overall BP Control at 24 Months

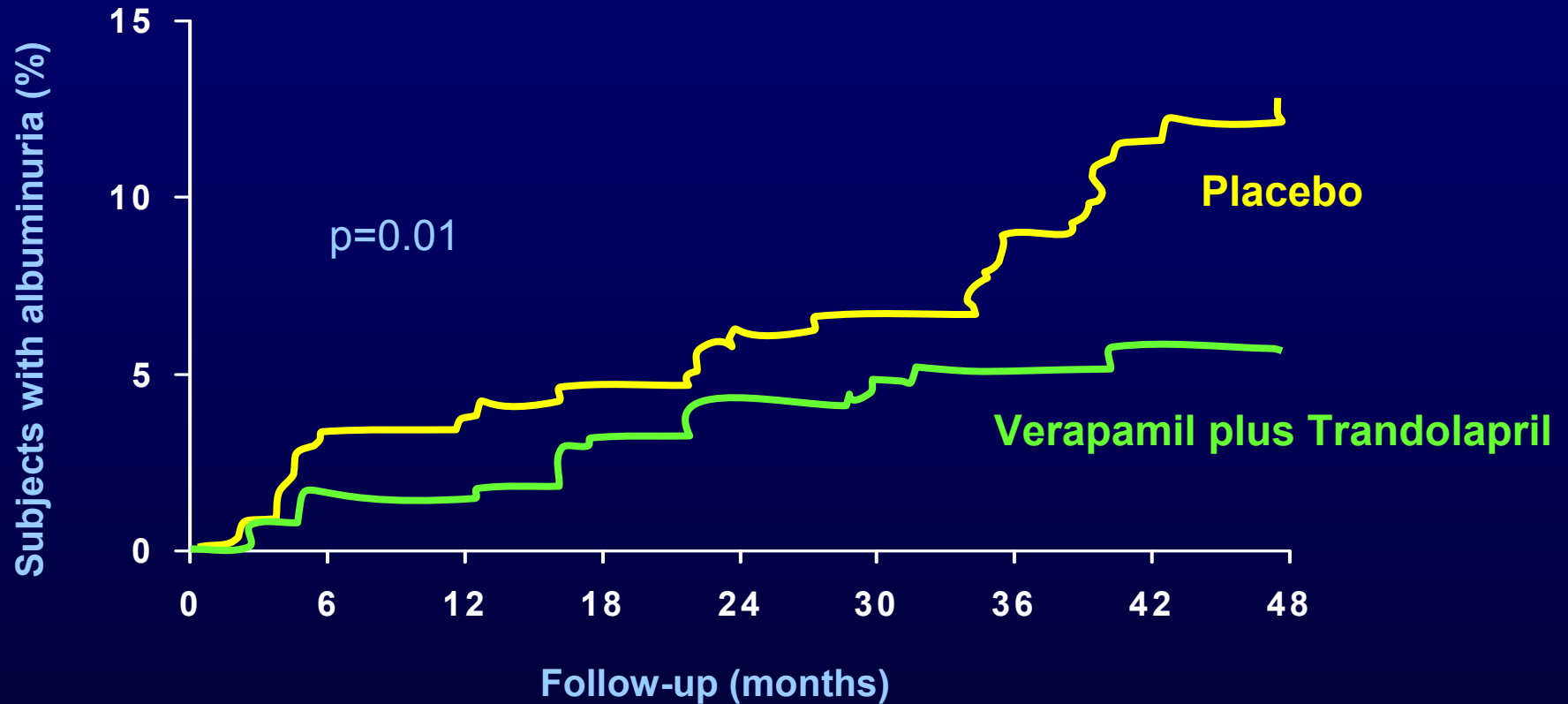


Renal endpoints

Urinary Protein Excretion



The **BENEDICT** trial: Kaplan-Meier Curves for the Percentages of Subjects with Microalbuminuria during treatment with Trandolapril plus Verapamil or Placebo



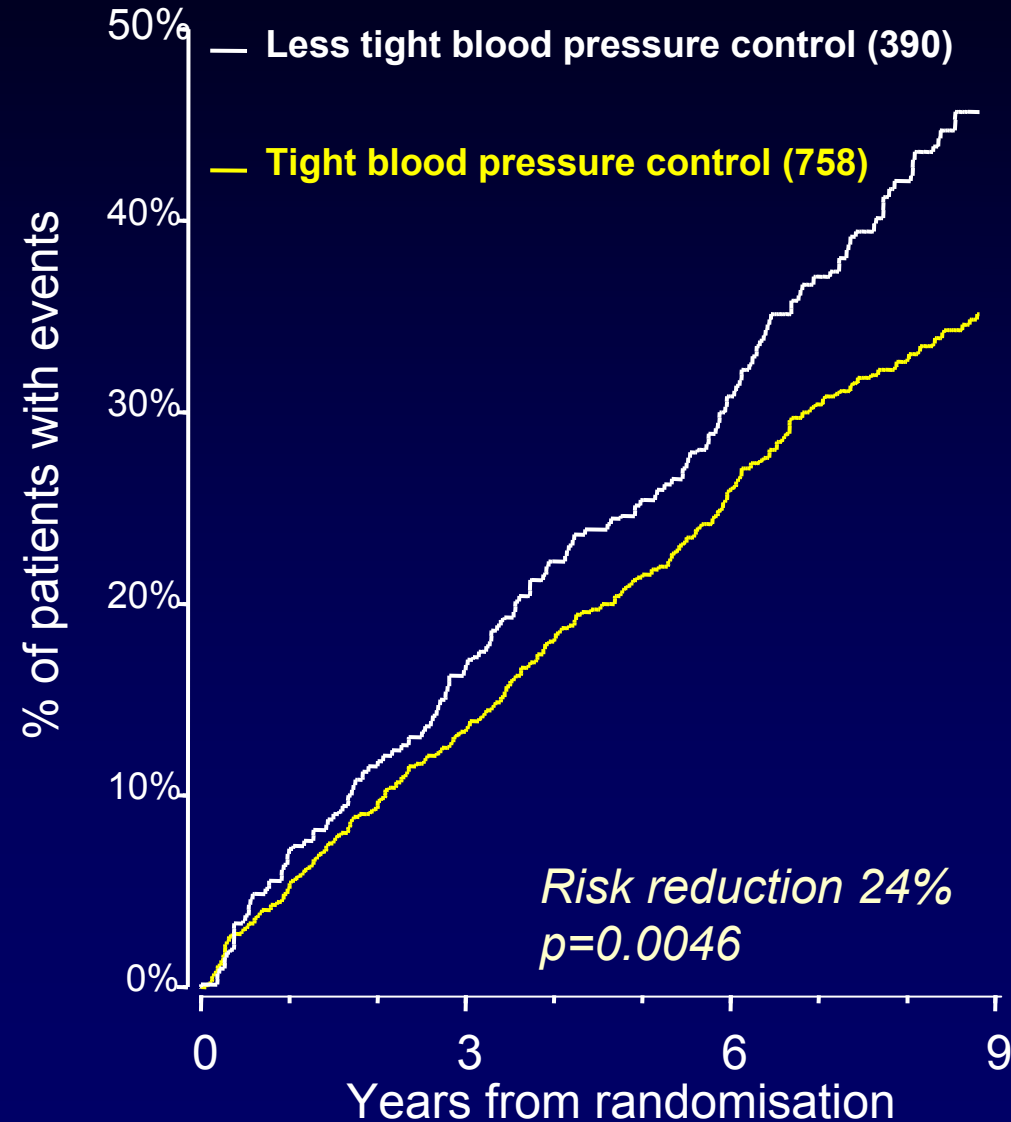
No. At Risk

Verapamil plus trandolapril	300	249	232	217	210	201	192	162	115
Placebo	300	229	214	203	187	176	164	136	89

UK Prospective Diabetes Study - Any Diabetes Related Endpoint

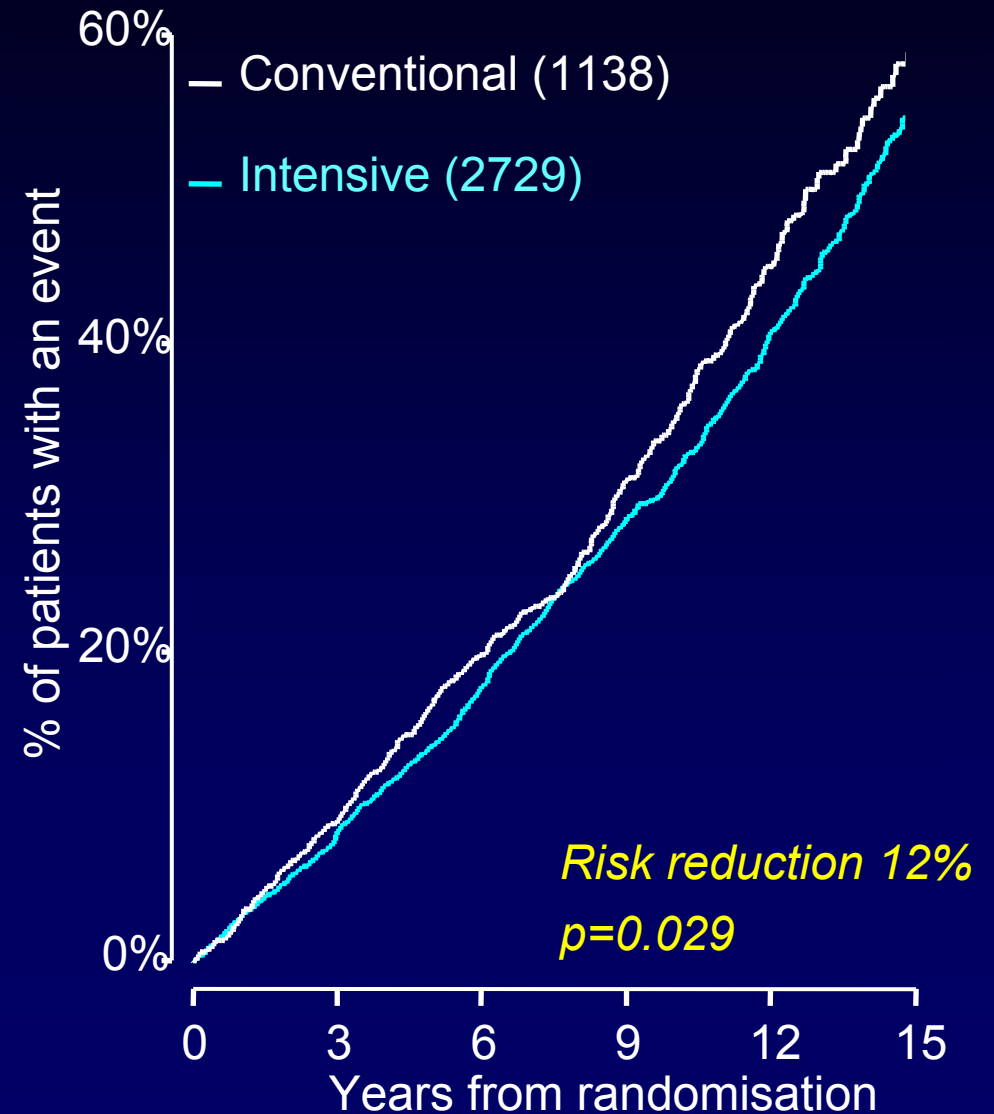
Blood Pressure Control Study

UKPDS 38 BMJ 1998;317:703-713



Glucose Control Study

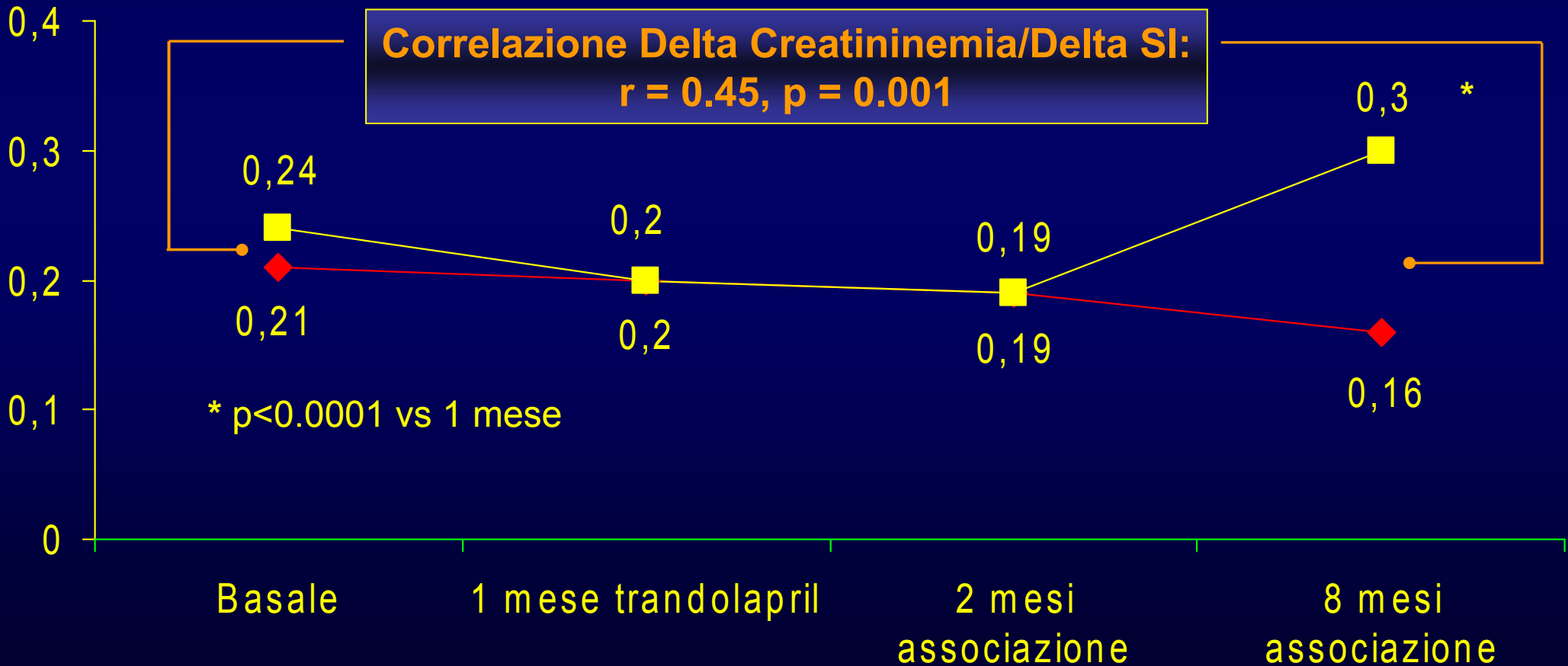
UKPDS 33 BMJ 1998;352:837-853



Risultati

Indice di selettività

◆ Verapamil 180 + Trandolapril ■ Amlodipina + Trandolapril

Correlazione Delta Creatininemia/Delta SI:
 $r = 0.45, p = 0.001$ 

Linee guida American Diabetes Association

Diabete

≥ 126 mg/dl

< 126 mg/dl

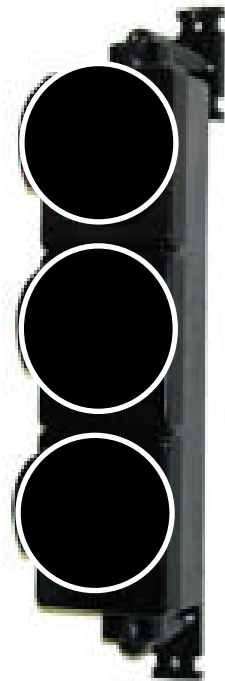
≥ 100 mg/dl

< 100 mg/dl

Normale

Pre-
Diabete

**Glicemia a
digiuno**



Diabete

≥ 200 mg/dl

< 200 mg/dl

≥ 140 mg/dl

< 140 mg/dl

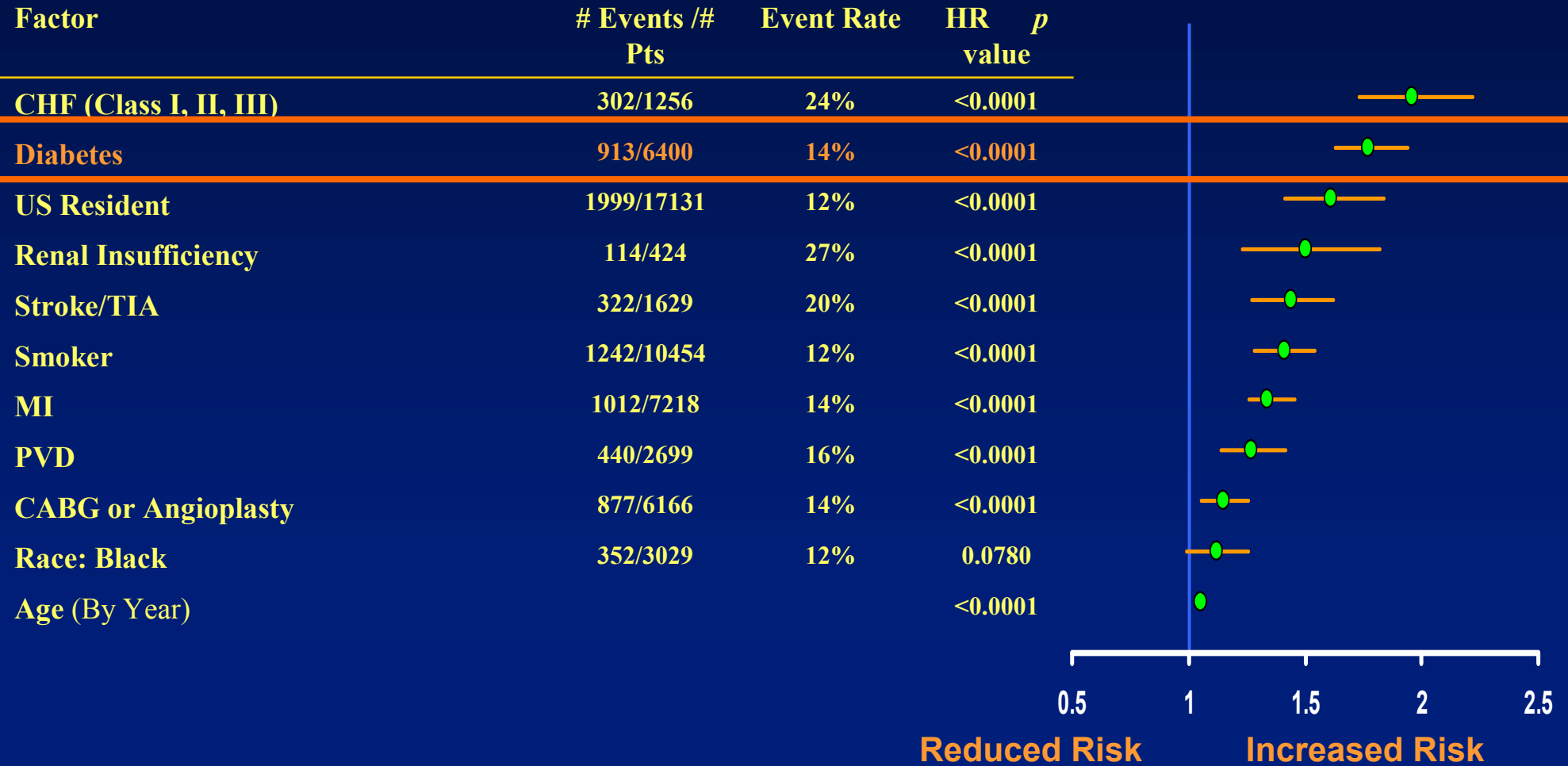
Normale

Pre-
Diabete

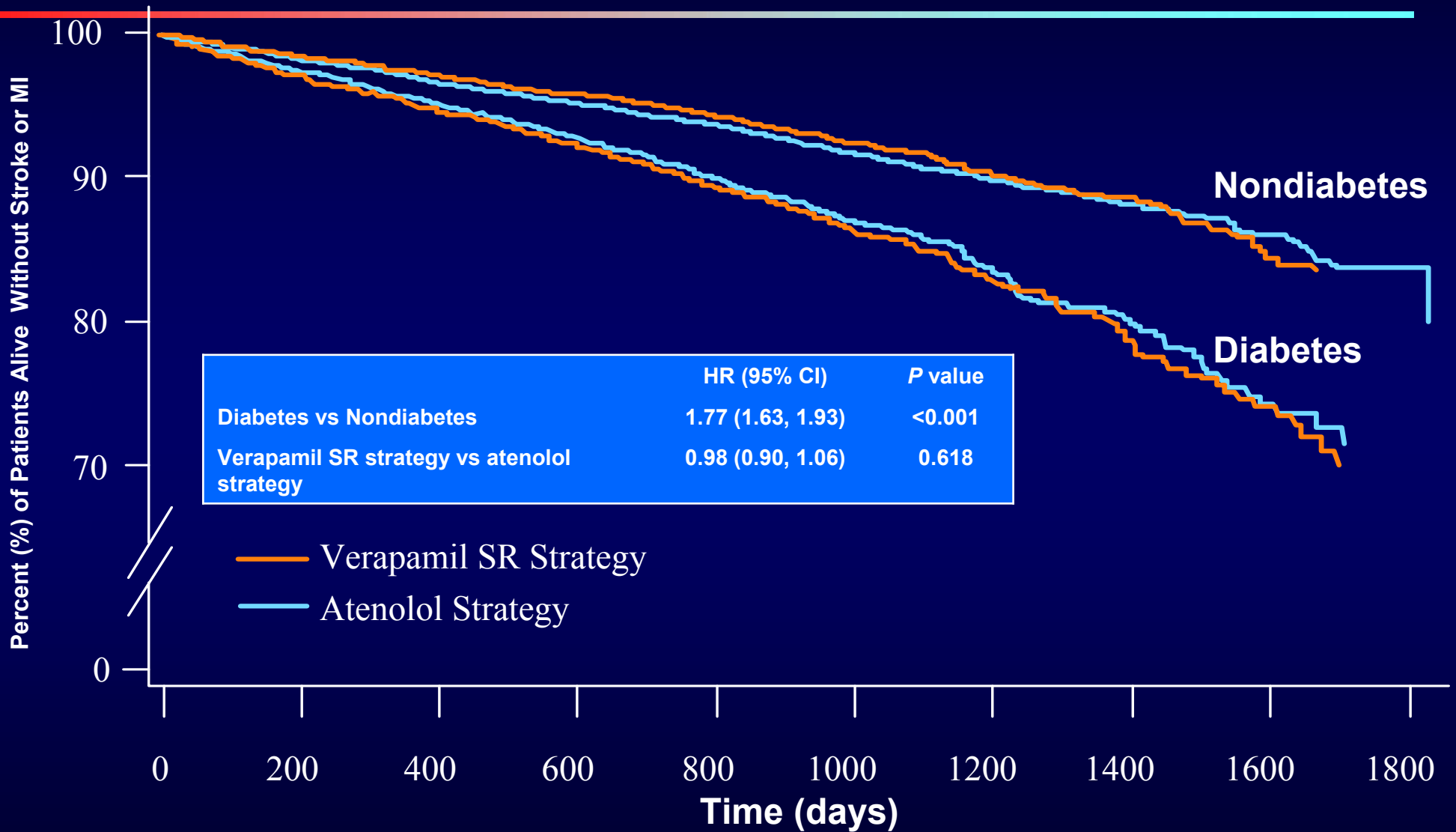
**Glicemia dopo carico orale
di glucosio**

Factors Associated With Increased Risk For The Primary Outcome

Hazard Ratio Estimates From Multivariate Stepwise Model



Kaplan-Meier Survival Curve: Primary Outcome



HR = hazard ratio

CCB+ACE-inhibitor antyhypertensive strategy

ASCOT-BPLA

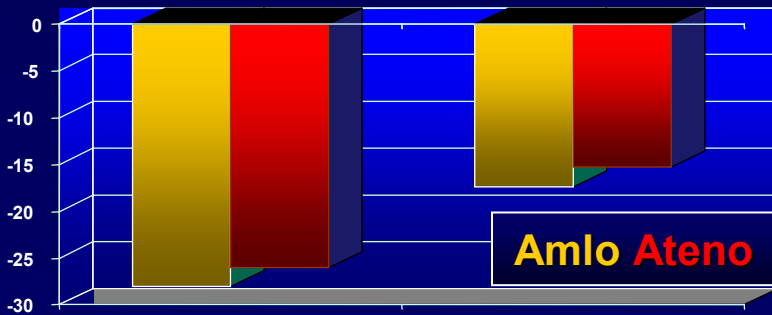
Dahlöf B et al Lancet 2005;366:895-906

SBP 137.7 vs 136.1 mmHg

Mean difference=2.7, $p<0.0001$

DBP 79.2 vs 77.4 mmHg

Mean difference=1.9 $p<0.0001$



Amlodipine-based

SBP

DBP

Primary endpoints

Non-fatal MI (including silent) +fatal CHD

0.90(0.79-1.02)
 $p=0.1052$

Secondary endpoints

Non-fatal MI (excluding silent) +fatal CHD

0.87(0.76-1.00)
 $p=0.0458$

Total coronary endpoint

0.87(0.79-0.96)
 $p=0.0070$

Total CV events and procedures

0.84(0.78-0.90)
 $p<0.0001$

All-cause mortality

0.89(0.81-0.99)
 $p=0.0247$

CV mortality

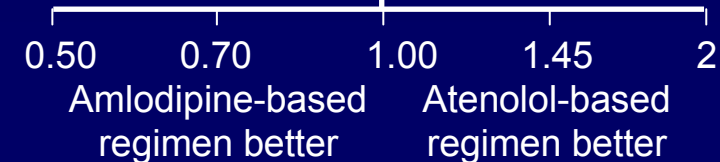
0.76(0.65-0.90)
 $p=0.0010$

Fatal and non-fatal stroke

0.77(0.66-0.89)
 $p=0.0003$

Fatal and non-fatal heart failure

0.84(0.66-1.05)
 $P=0.1257$



Dahlöf B et al
Lancet 2005;366:895-906

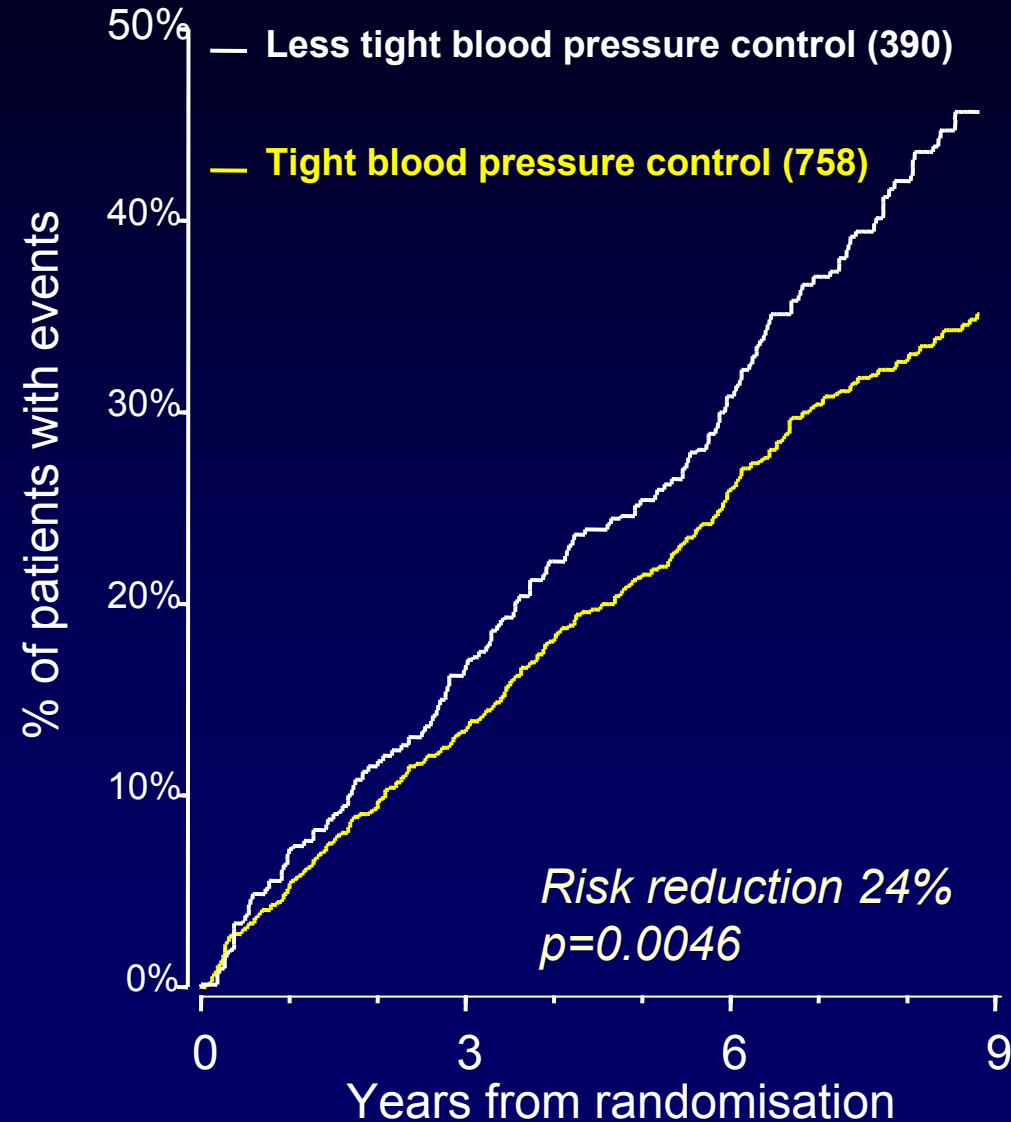
0.50 0.70 1.00 1.45 2
Amlodipine-based regimen better

Atenolol-based regimen better

UK Prospective Diabetes Study - Any Diabetes Related Endpoint

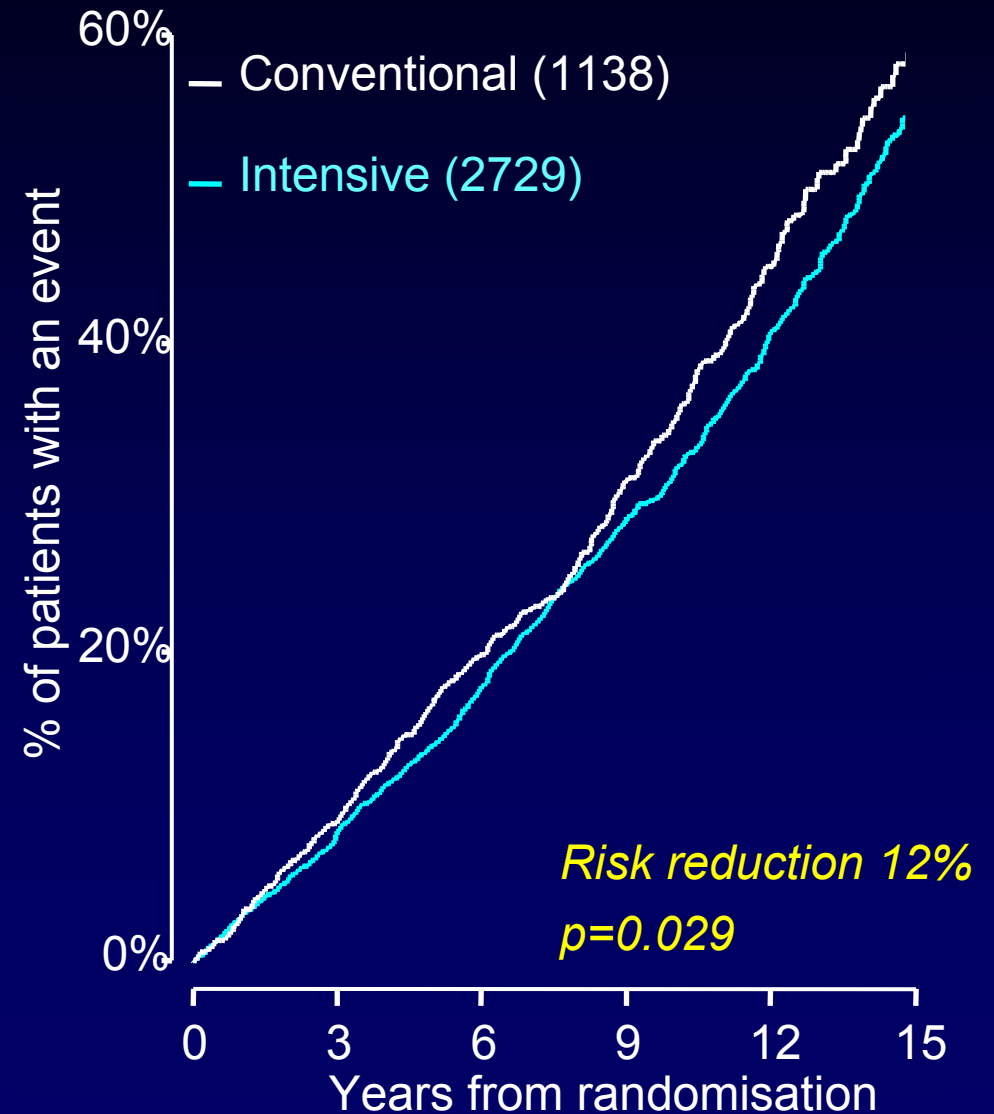
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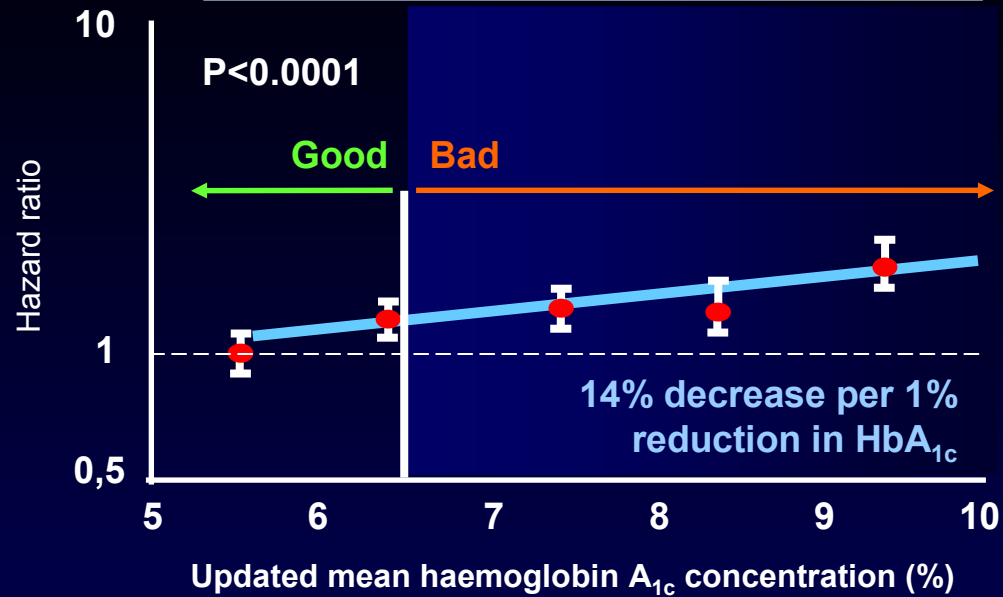


Glucose Control Study

UKPDS 33 BMJ 1998;352:837-853

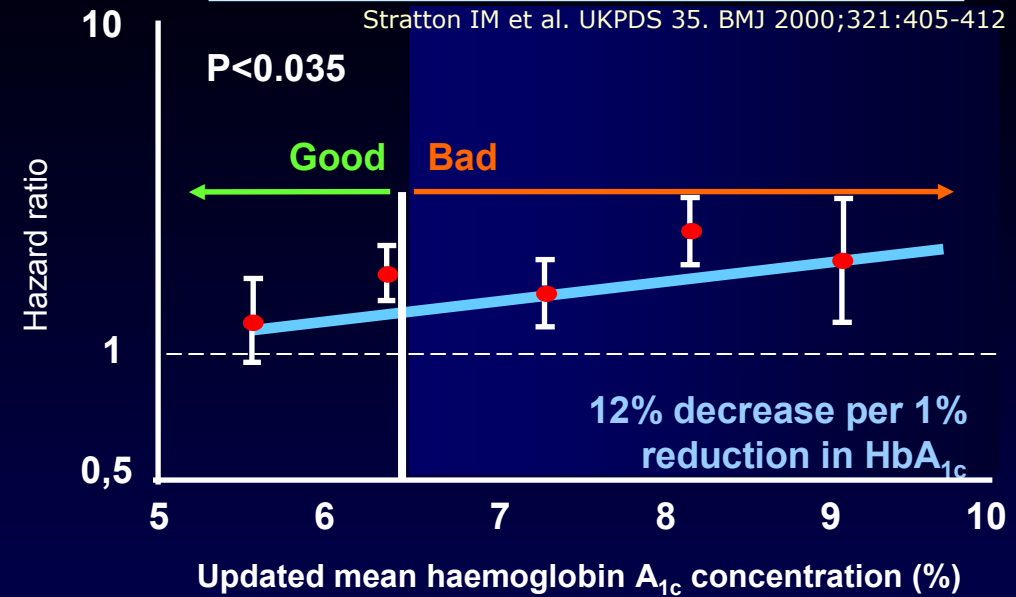


Fatal and non-fatal myocardial infarction

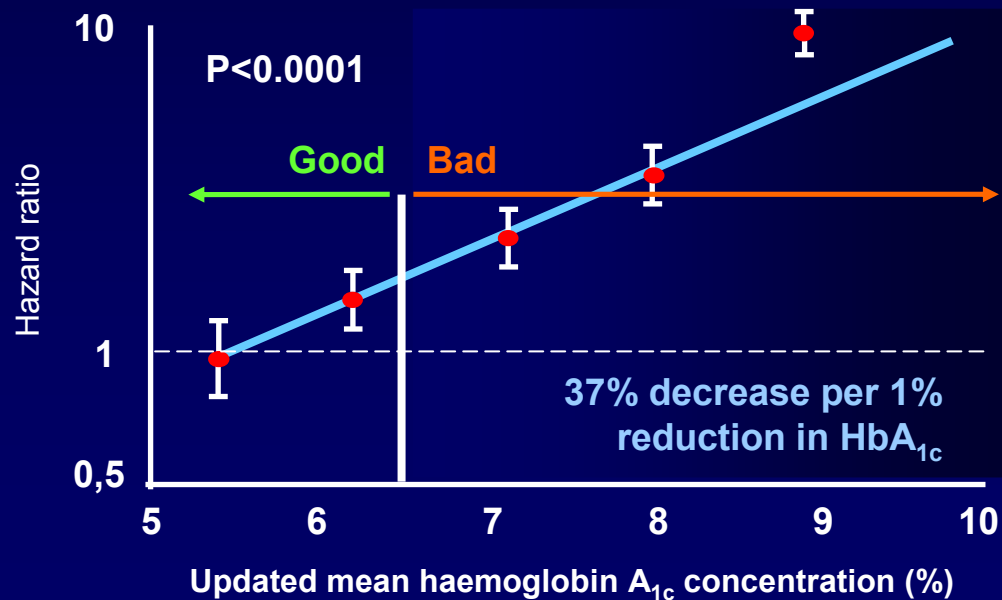


Fatal and non-fatal stroke

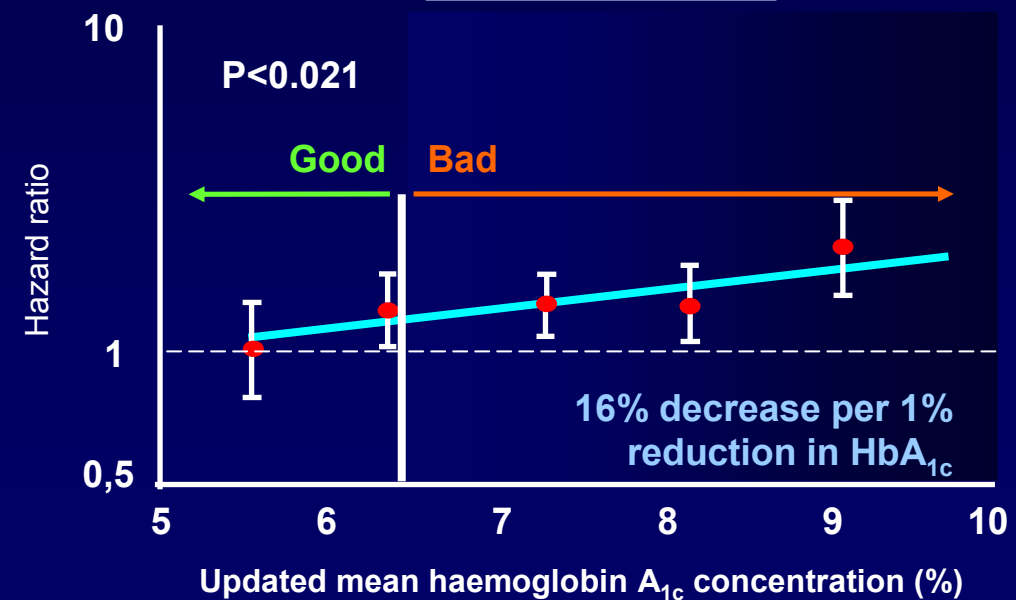
Stratton IM et al. UKPDS 35. BMJ 2000;321:405-412



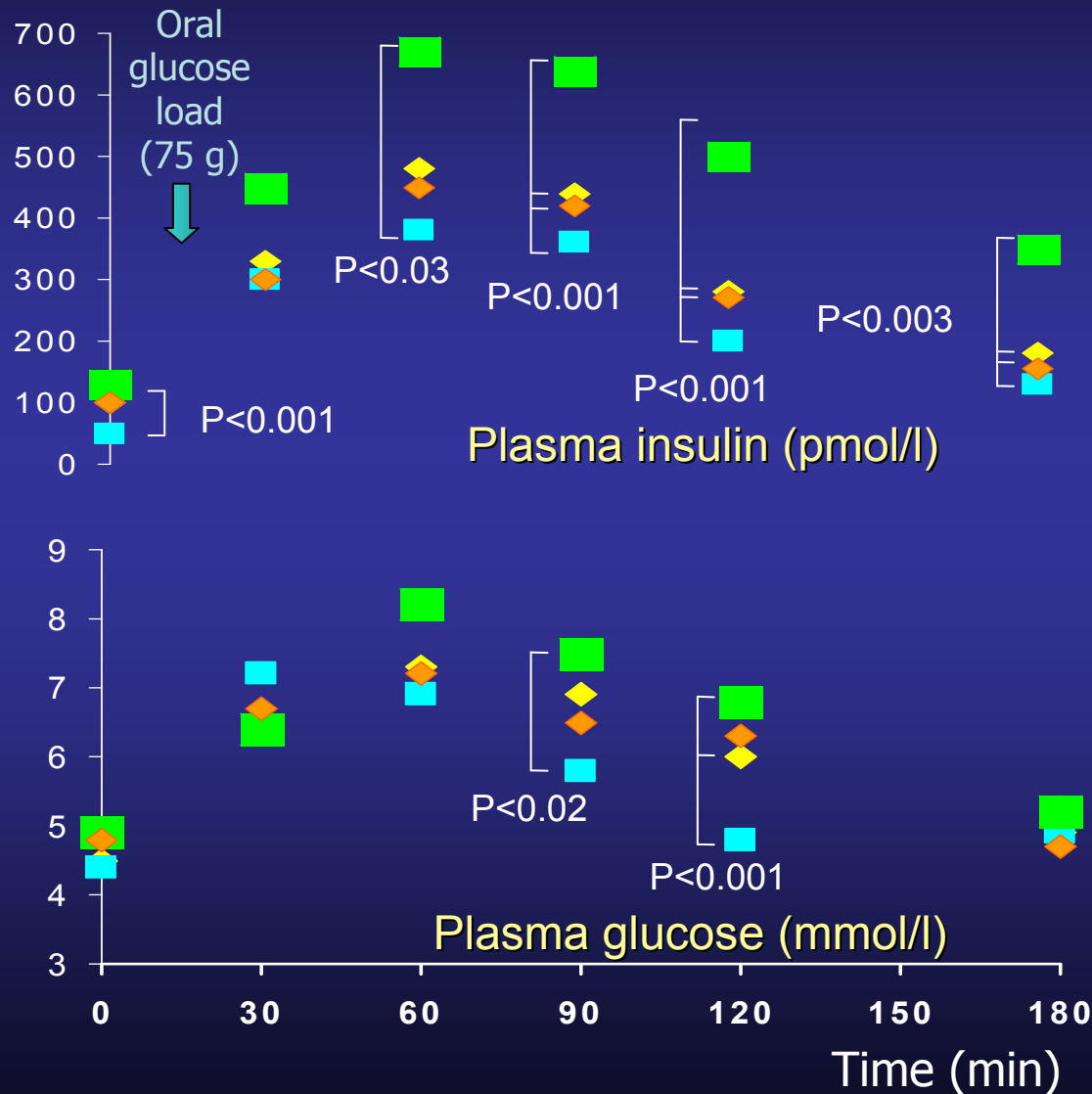
Microvascular end points



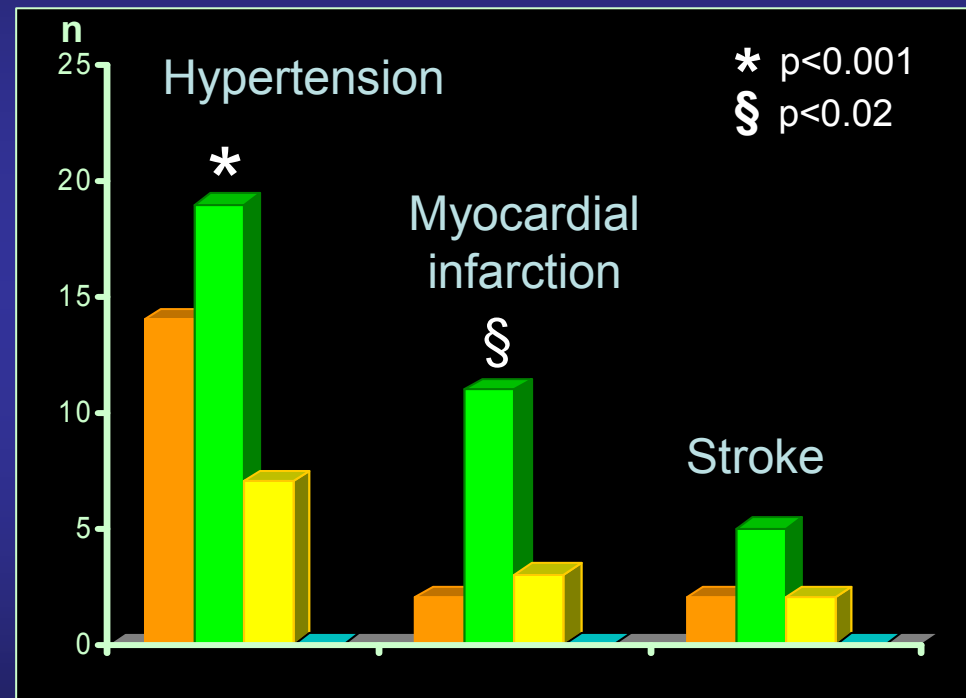
Heart failure



Relationship between insulin resistance and Nonmodulating Hypertension

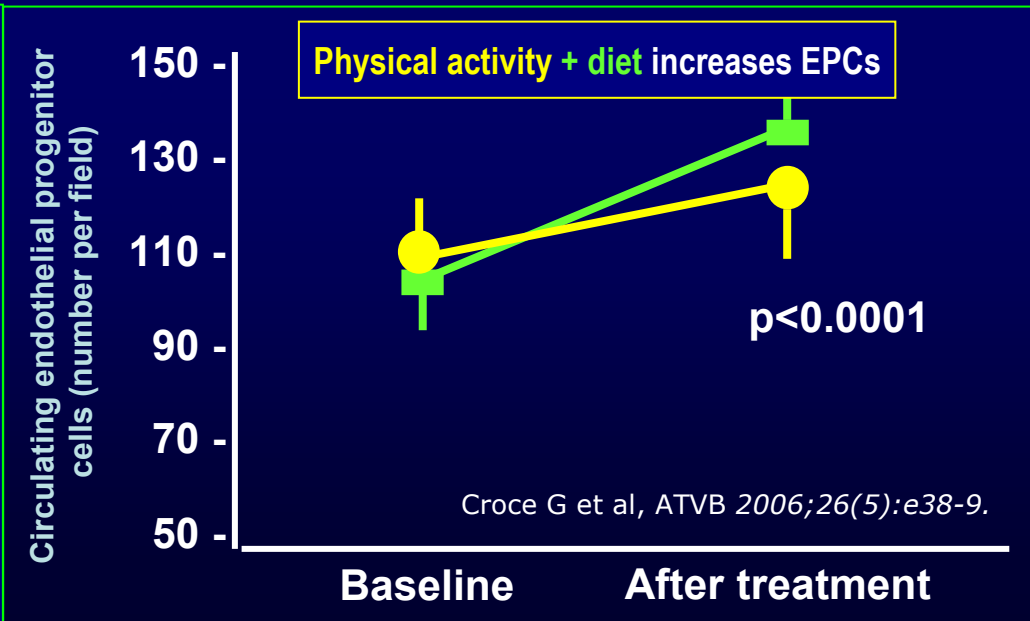
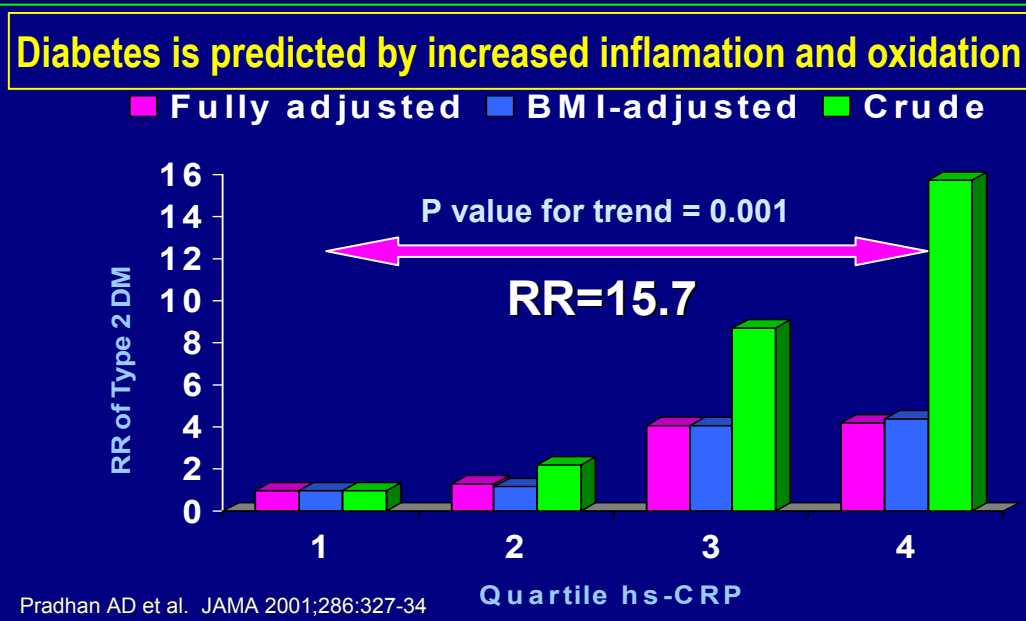
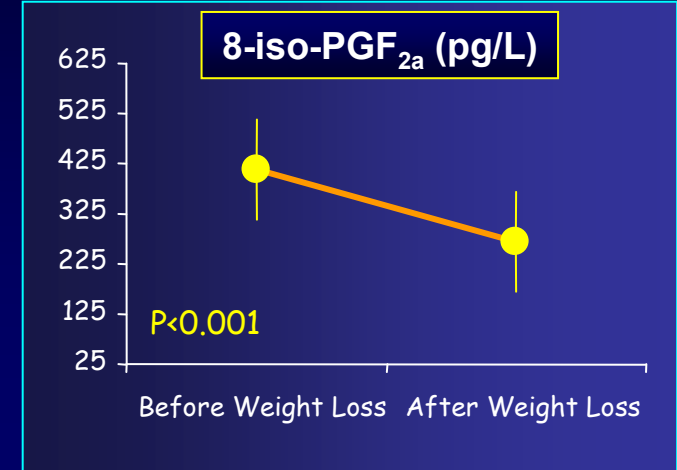
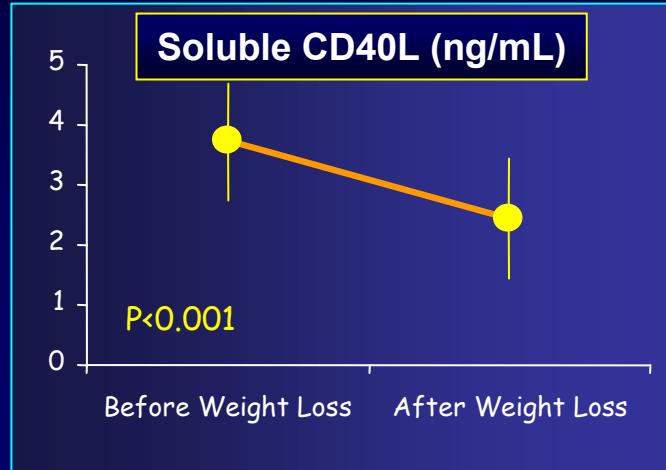
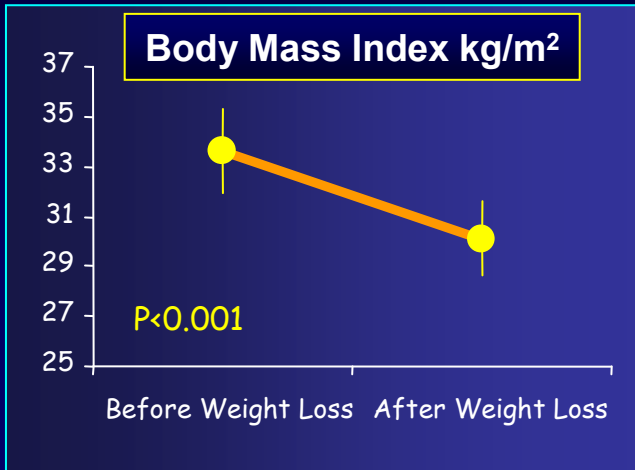


Familial occurrence in the three hypertensive subgroups



Low-renin subjects
Nonmodulators
Modulators
Normotensive Controls

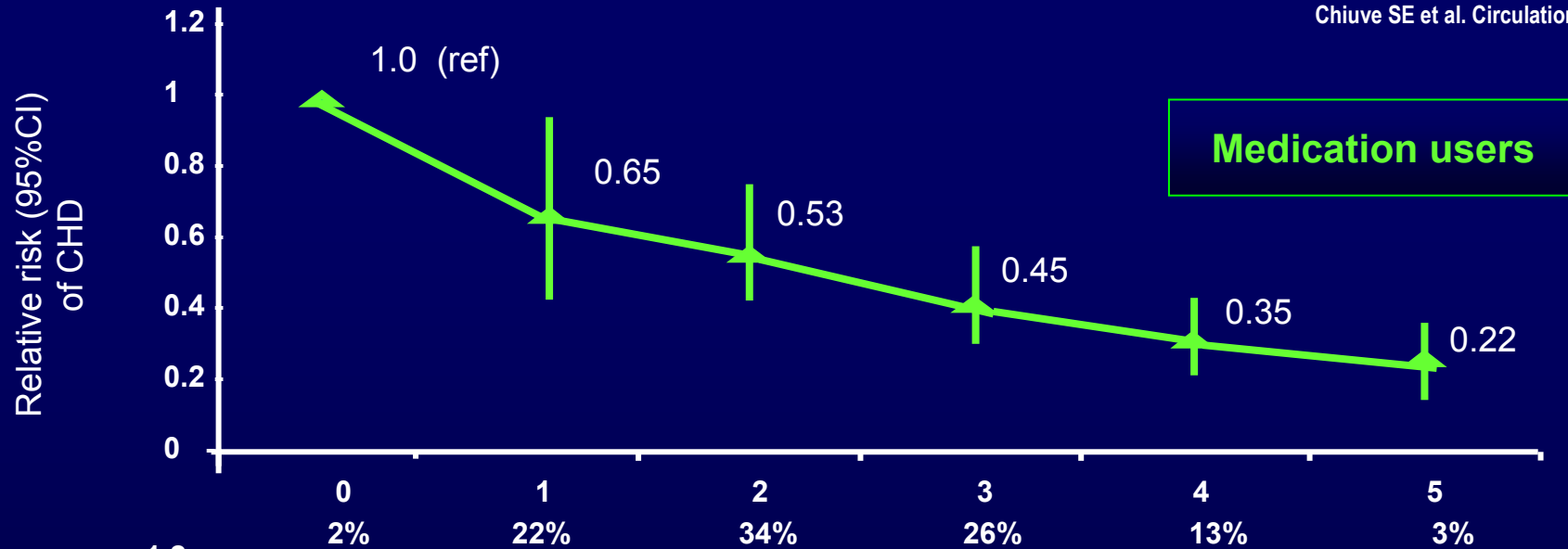
Effect of Weight Loss on Soluble CD40L and 8-iso-PGF_{2α} Levels in Obese Patients



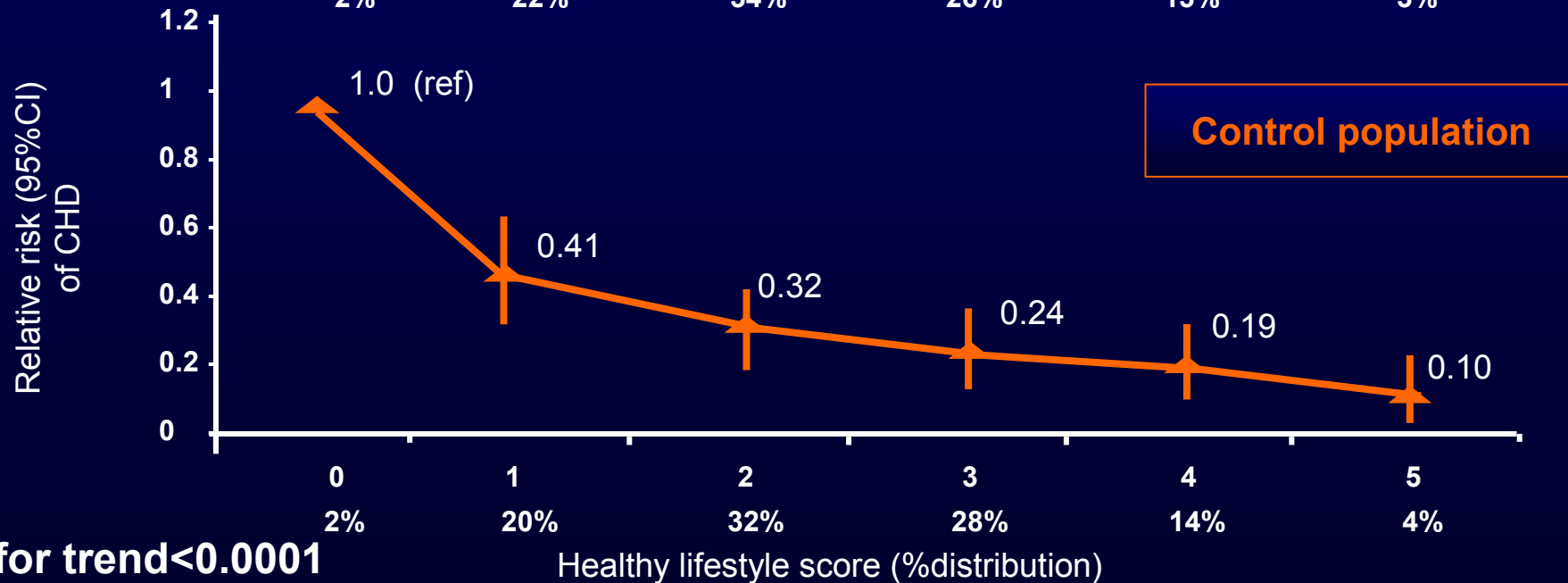
Relative risk of CHD among reported antihypertensive and lipid-lowering medication users (A) and nonusers (B) by healthy lifestyle score. Pts: 42.847 men 40 to 75 years of age

Chiuve SE et al. Circulation 2006;114:160-167

A

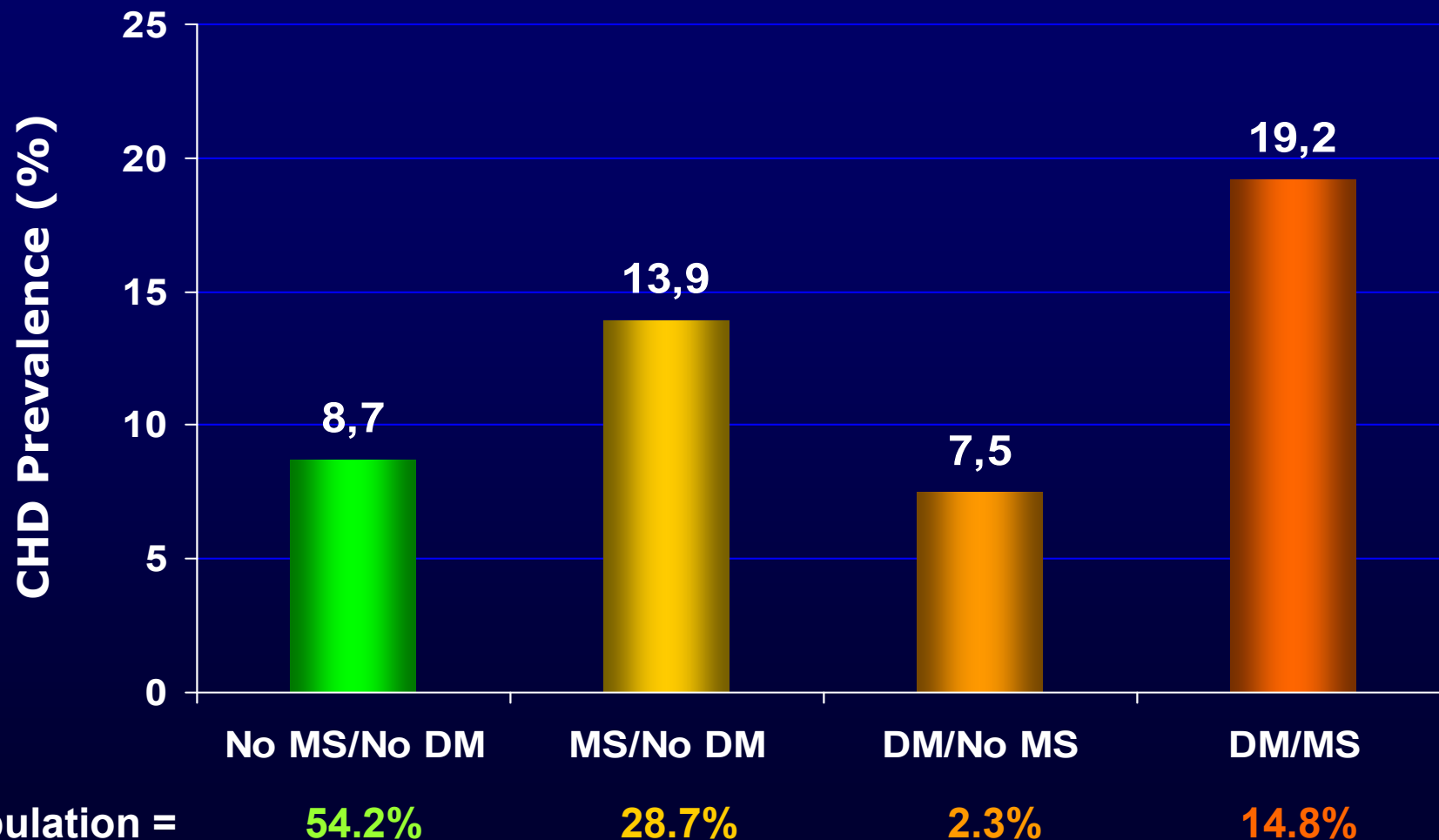


B



P for trend < 0.0001

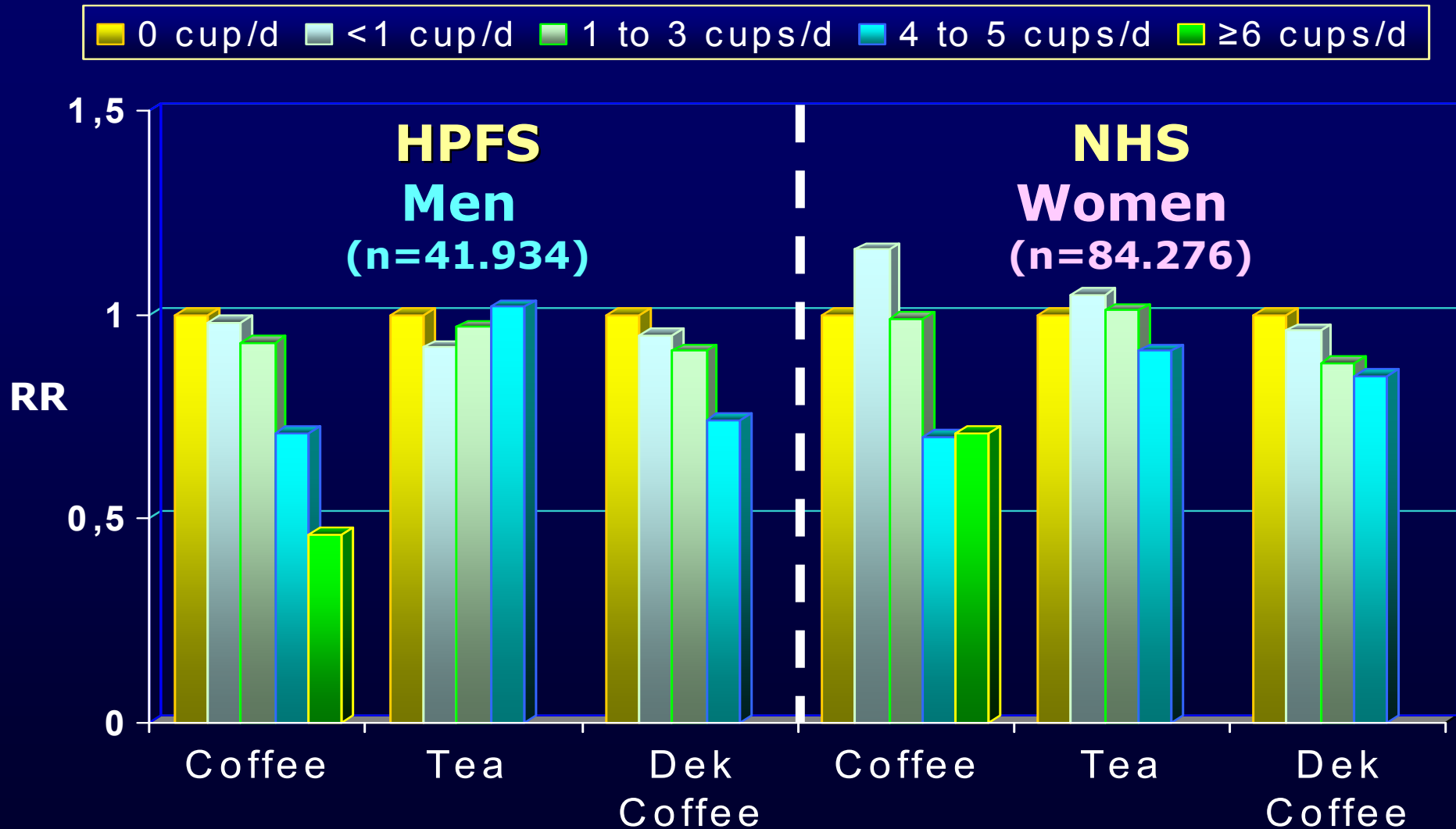
Age-adjusted prevalence of CHD in the U.S. population over 50 years of age categorized by presence of metabolic syndrome and diabetes. Combinations of metabolic syndrome (MS) and diabetes mellitus (DM) status are shown



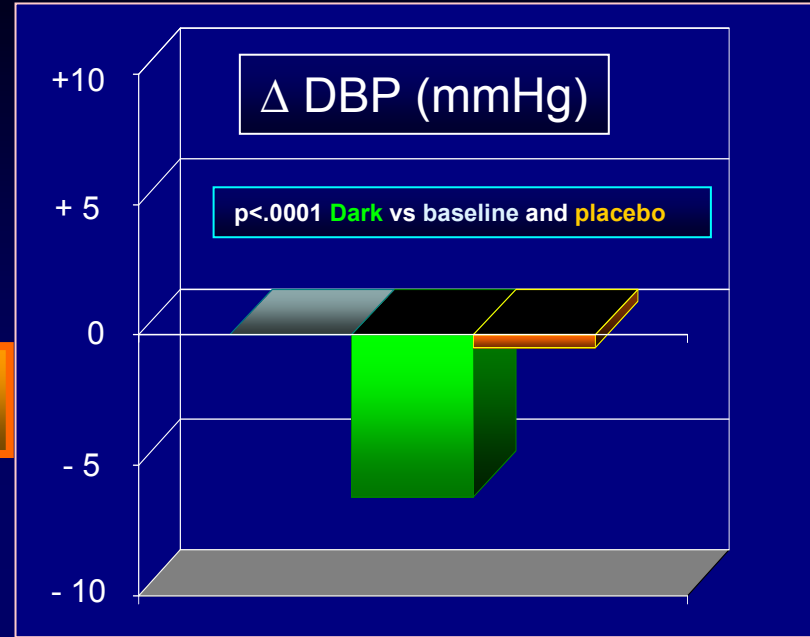
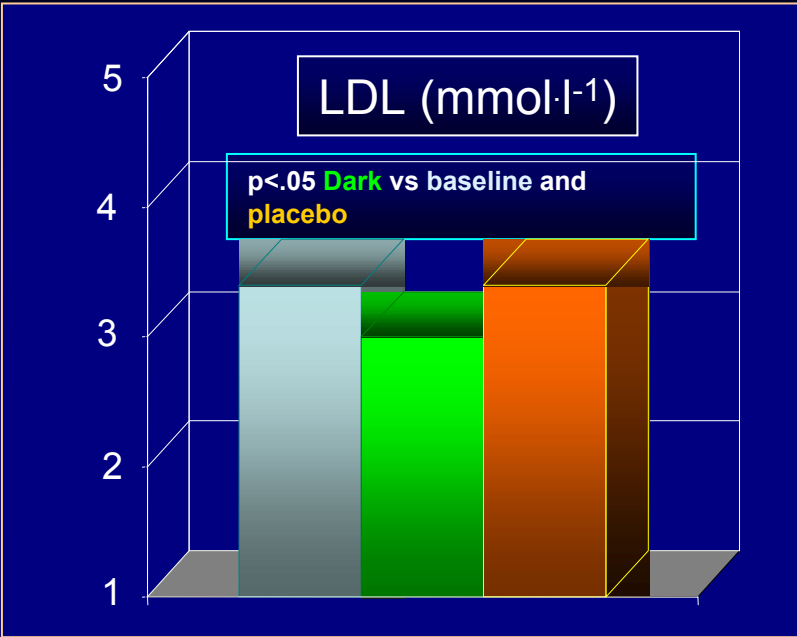
Adjusted Multivariate Relative Risk for Type 2 Diabetes Mellitus according to Coffee, Tea, and Decaffeinated (Dek) Coffee Consumption

The Health Professionals Follow-up Study (HPFS) from 1986 to 1998 - 40 to 75 years of age

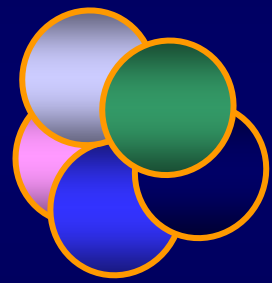
The Nurses' Health Study (NHS) 1980 to 1998 - 30 to 55 years of age



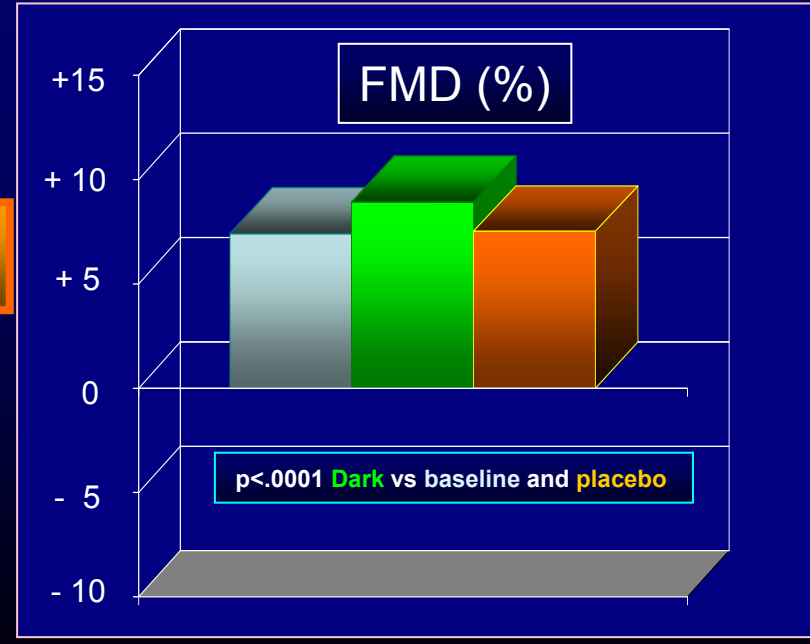
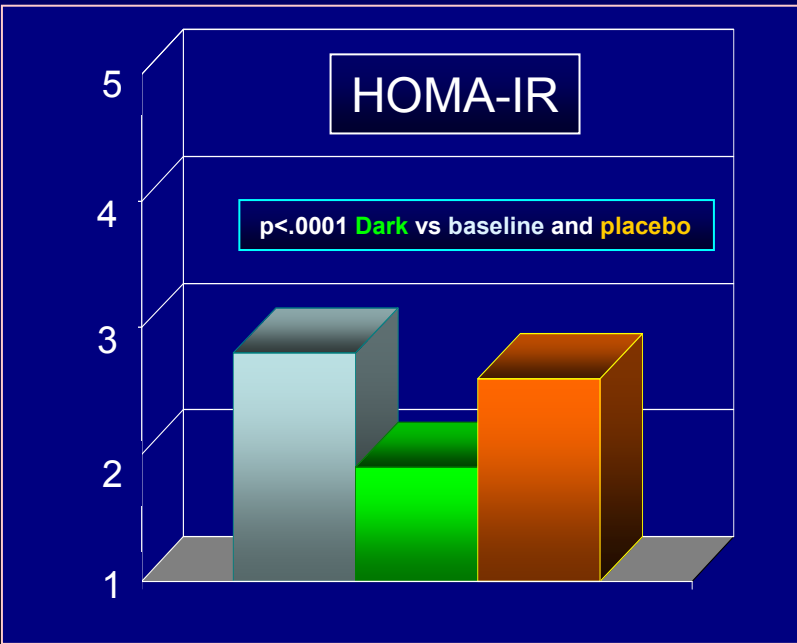
Effects of 15 Days of either **Dark Chocolate** or **Placebo Chocolate** in hypertensive patients



Risk factor constellation

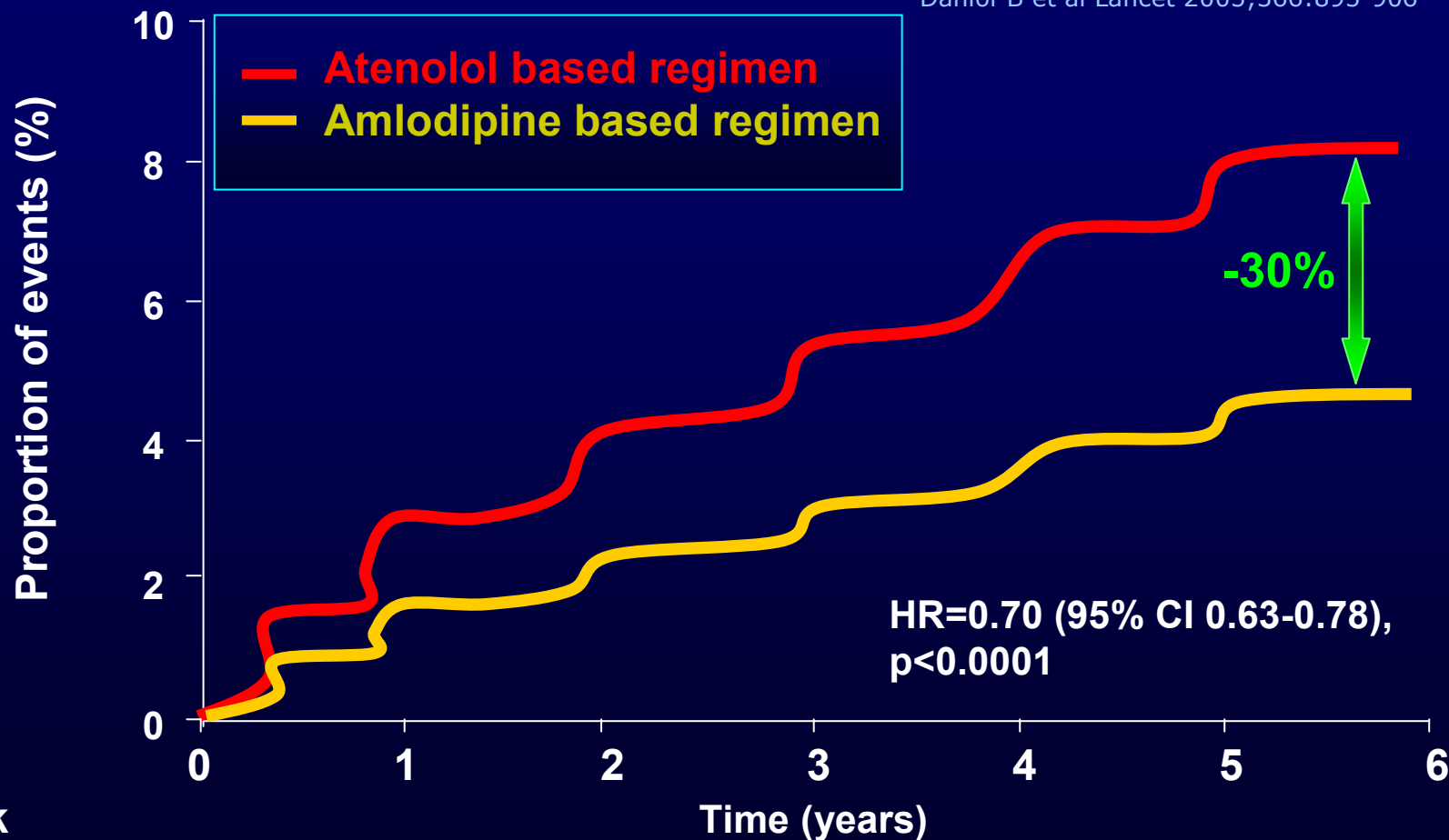


Risk factor constellation



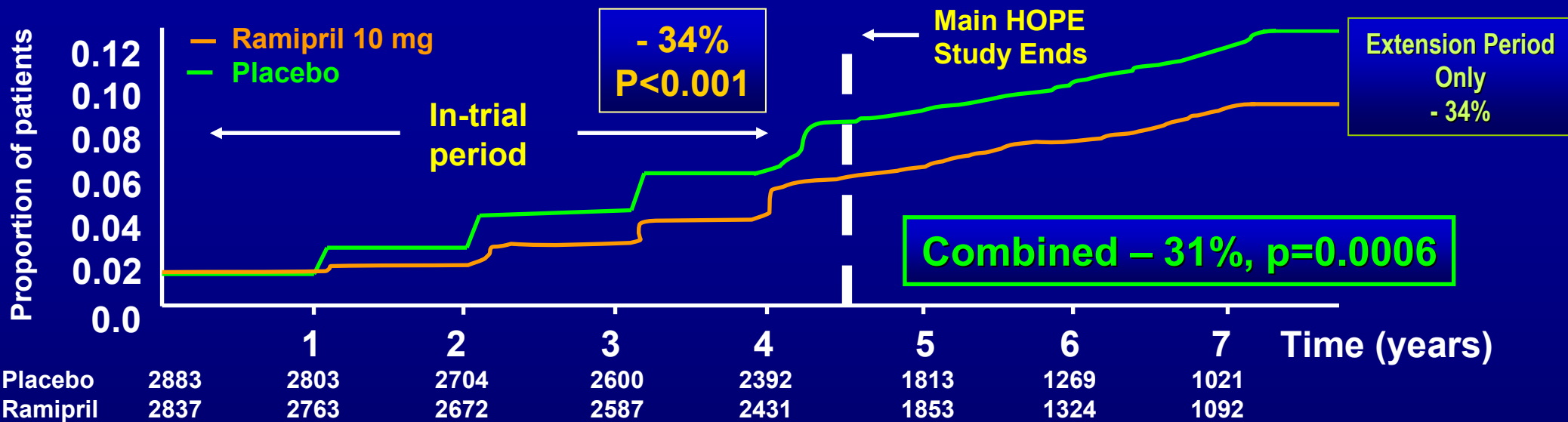
Kaplan-Meier curves of cumulative incidence of *new-onset diabetes mellitus*

Dahlöf B et al Lancet 2005;366:895-906

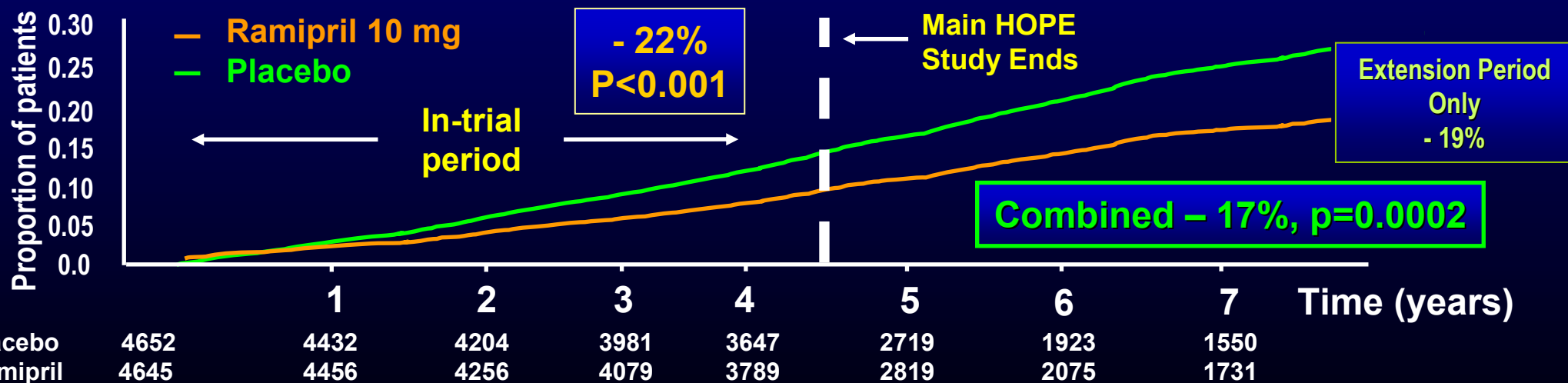


	0	1	2	3	4	5	6
Amlodipine based regimen (567 events)	9639	9383	9165	8966	8726	7618	
Atenolol based regimen (799 events)	9618	9295	9014	8735	8455	7319	

Kaplan-Meier estimates for the outcome of the **development of diabetes** in the ramipril and placebo groups

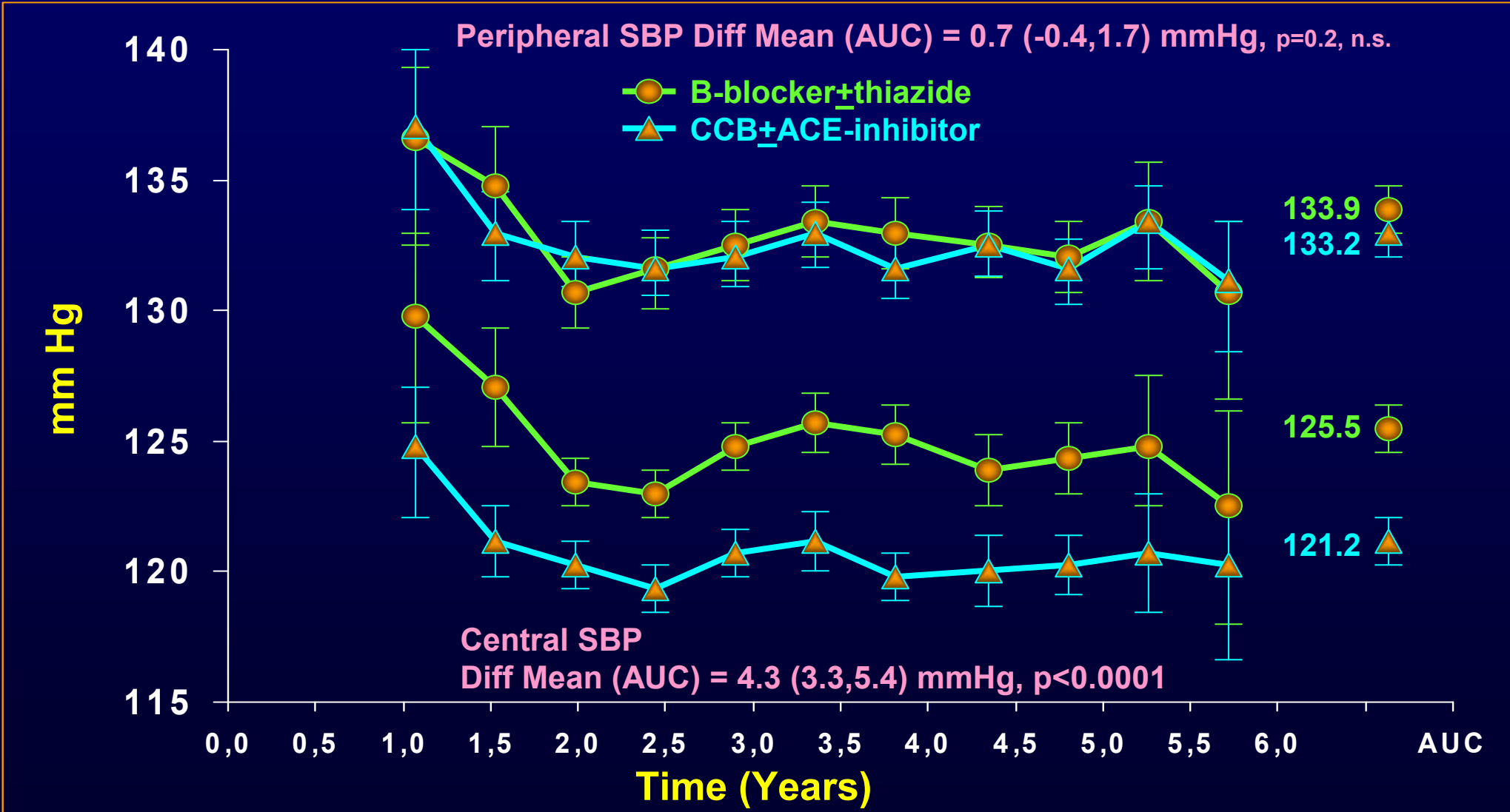


Kaplan-Meier estimates for the outcome of the **composite outcome** of myocardial infarction, stroke or CV death



Brachial And Derived Central Aortic SBP With Time for Patients Randomized to Receive B-blocker+thiazide- or CCB+ACE-inhibitor -Based Therapy

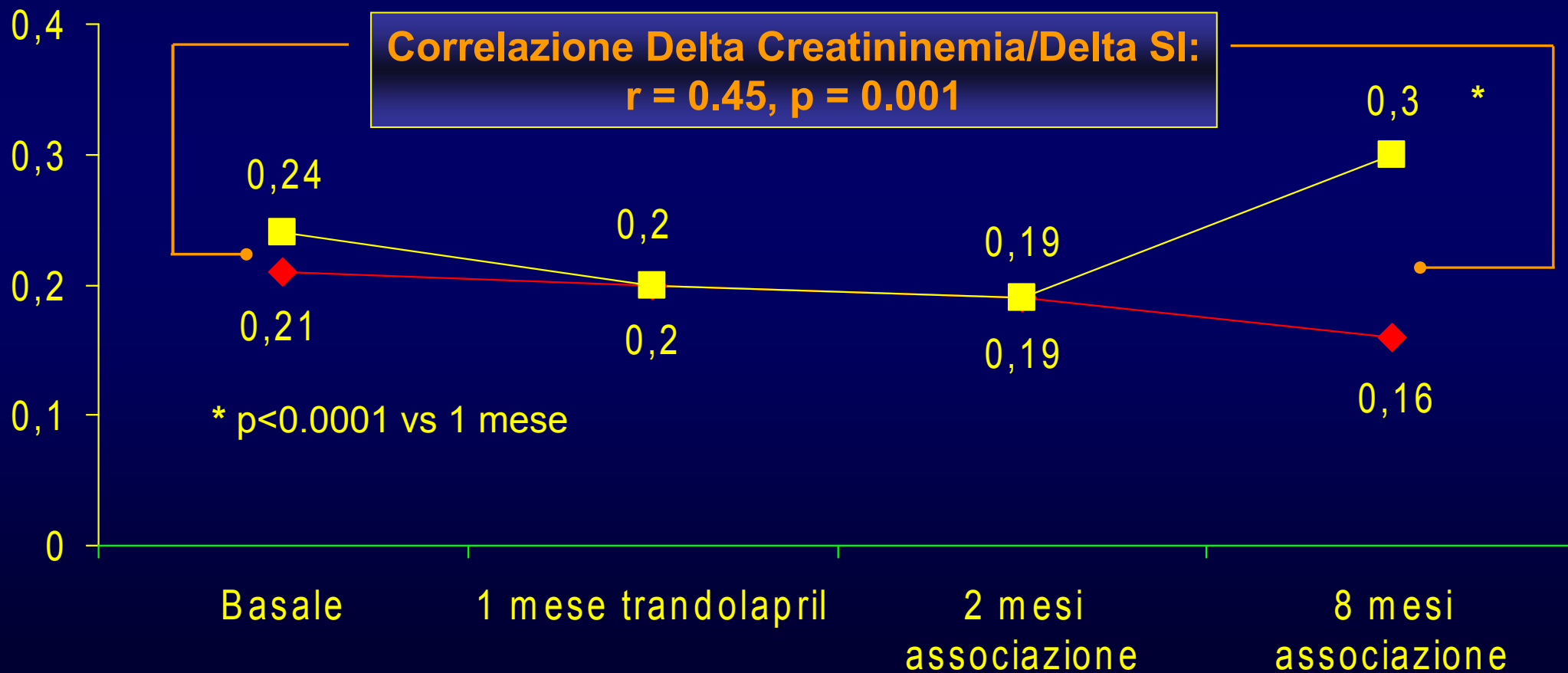
Conduit Artery Function Evaluation (CAFE) Study



Risultati

Indice di selettività

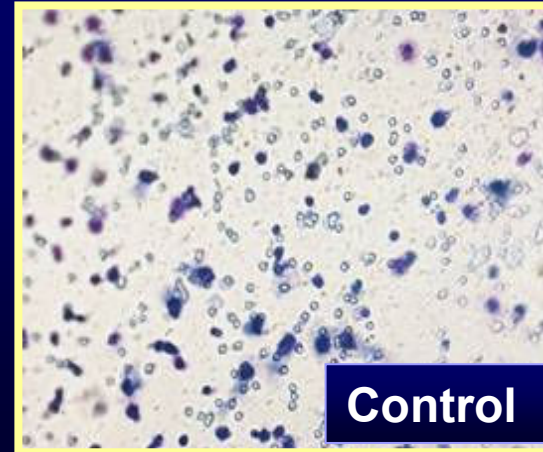
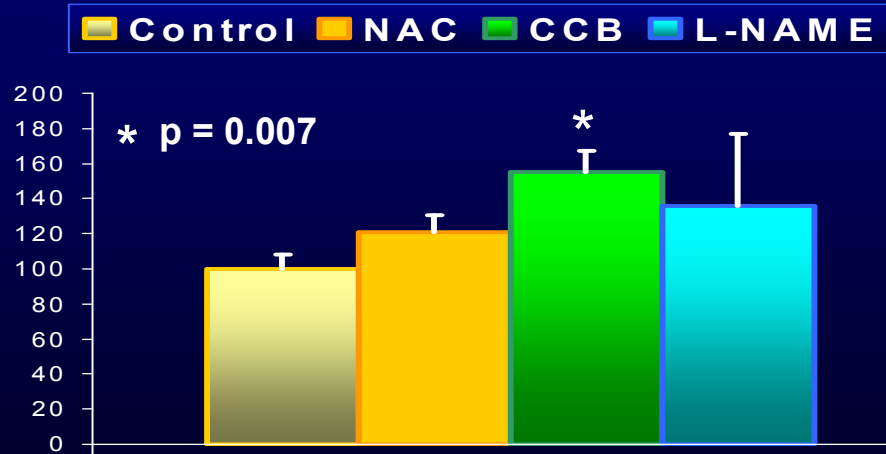
◆ Verapamil 180 + Trandolapril ■ Amlodipina + Trandolapril

Correlazione Delta Creatininemia/Delta SI:
 $r = 0.45, p = 0.001$ 

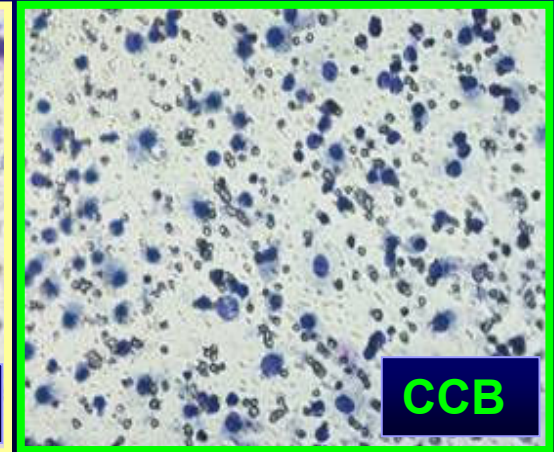
CCBs and vascular repairing abilities: Effects of CCB on migratory (A) and adhesive (B) abilities in EPCs

A

Migrated EPCs (% of control)



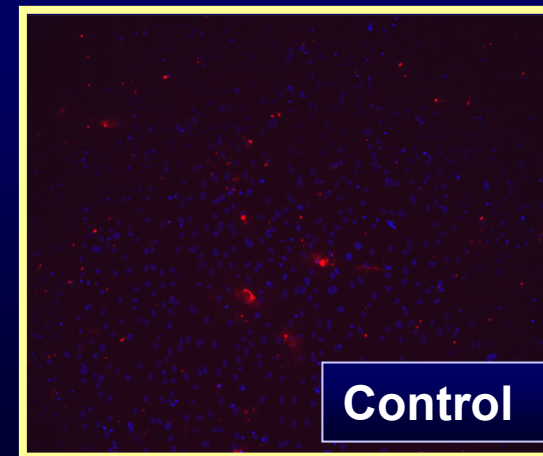
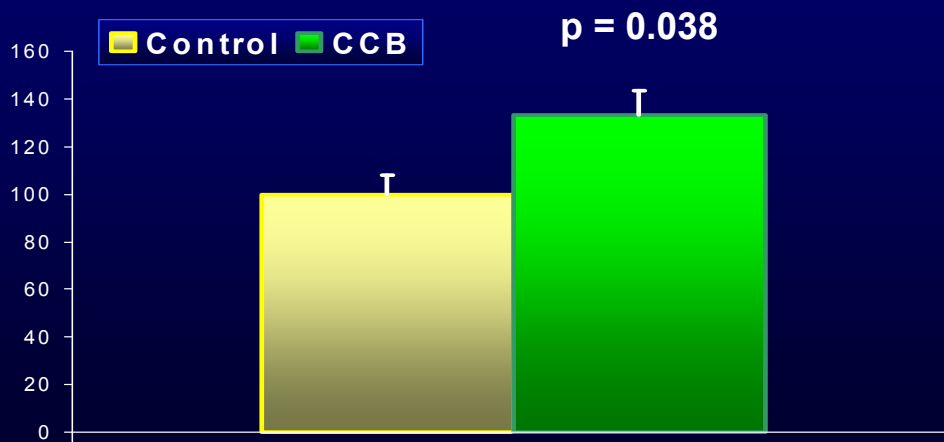
Control



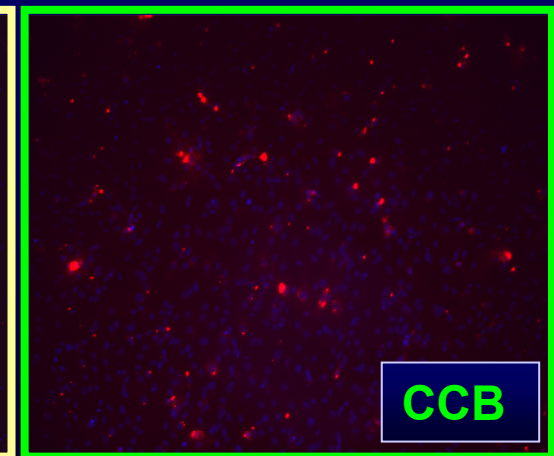
CCB

B

EPC adhesion (% of control)

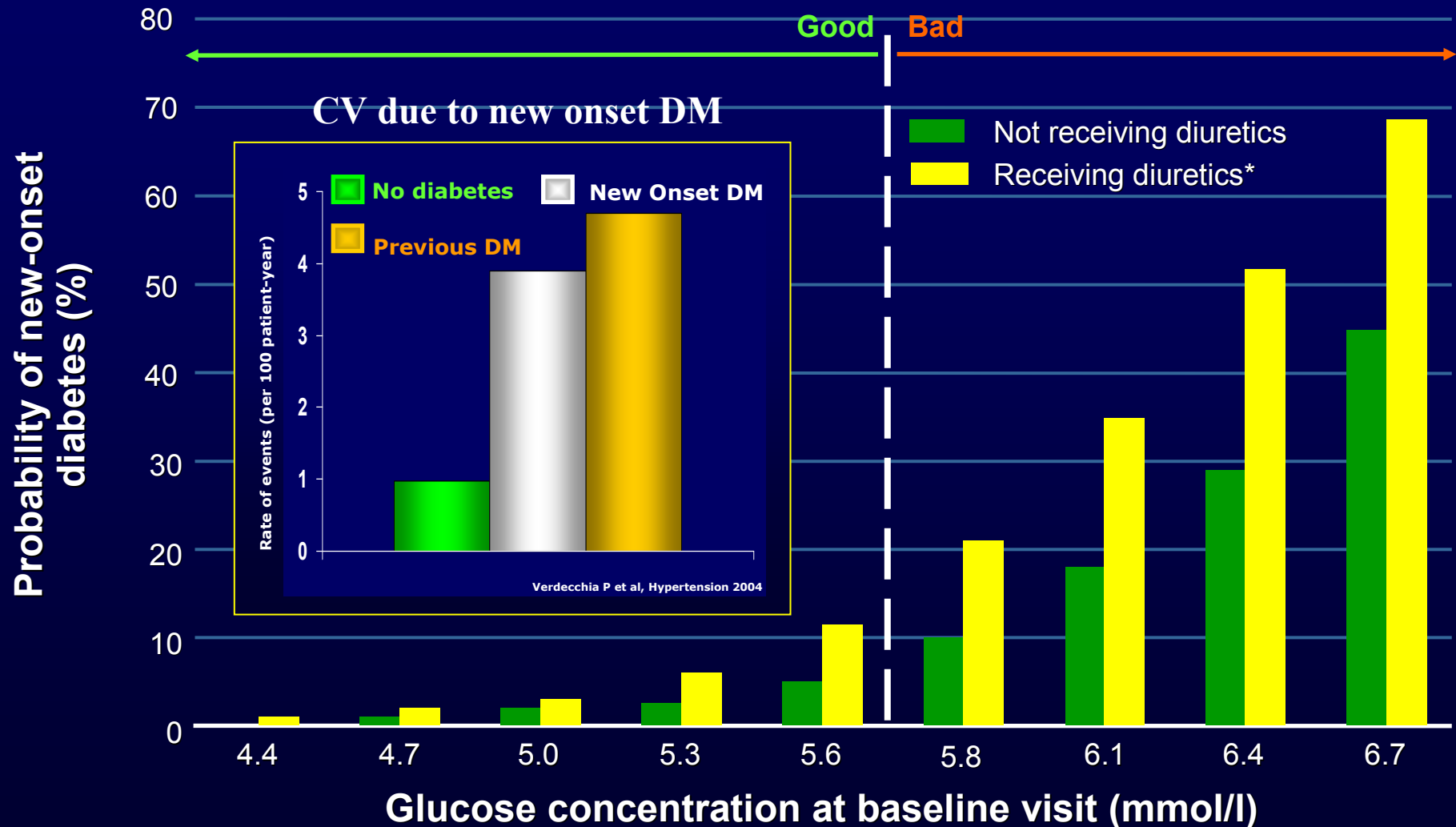


Control



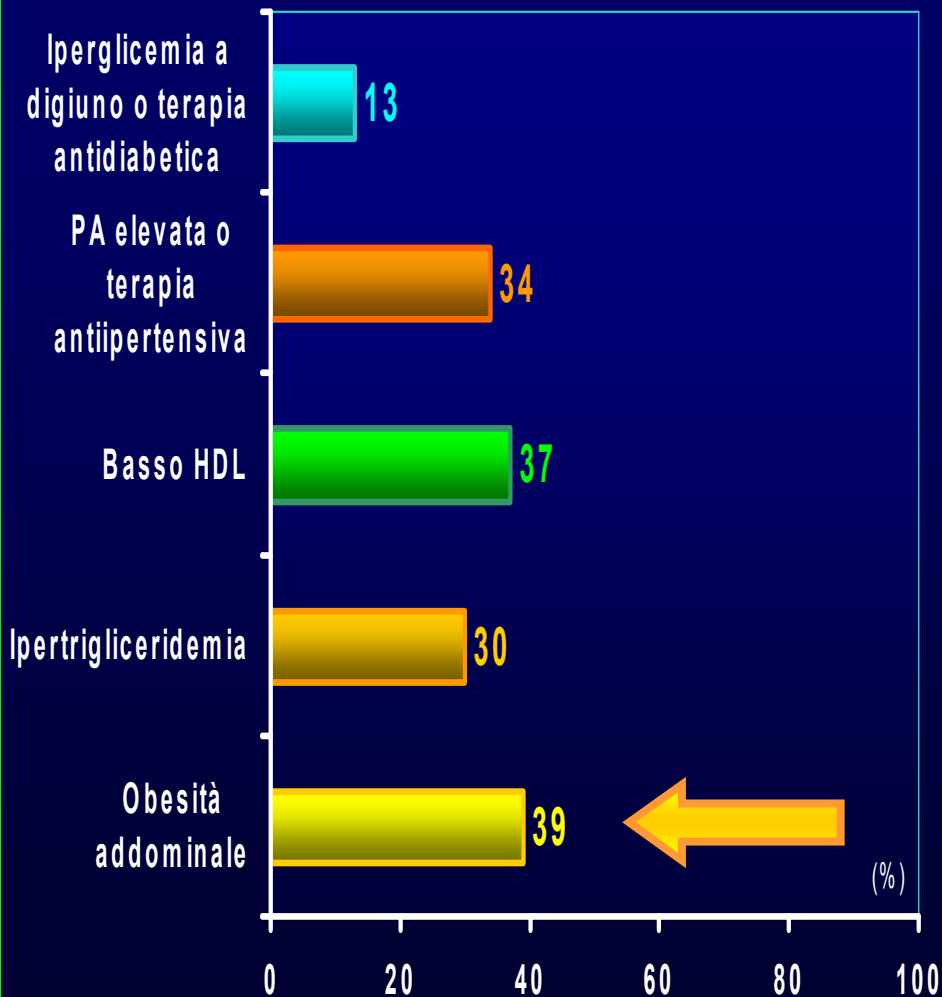
CCB

Antihypertensive treatment with diuretics increased the probability of new-onset diabetes



Prevalenza delle componenti della sindrome metabolica * NHANES III

*Adulti statunitensi di età ≥20 anni (1988-1994)



Ford ES, et al. *JAMA*. 2002;287:356-359.

Different Components of the NCEP Metabolic Syndrome Predict CHD NHANES III

Pts 50 years and older

Variable	Odds Ratio	Lower 95% Limit	Upper 95% Limit
Waist circumference	1.13	0.85	1.51
Triglycerides	1.12	0.71	1.77
HDL cholesterol*	1.74	1.18	2.58
Blood pressure*	1.87	1.37	2.56
Impaired fasting glucose	0.96	0.60	1.54
Diabetes*	1.55	1.07	2.25
Metabolic syndrome	0.94	0.54	1.68

Alexander CM et al *Diabetes* 2003; 52 :1210-1214

Antihypertensive Drug Treatment in Older Women

Women with hypertension enrolled in the Women's Health Initiative Observational Study, a longitudinal multicenter cohort study of 93,676 women aged 50 to 79 years at baseline (1994-1998), assessed for a mean of 5.9 years.

