

Treatment of the Metabolic Syndrome

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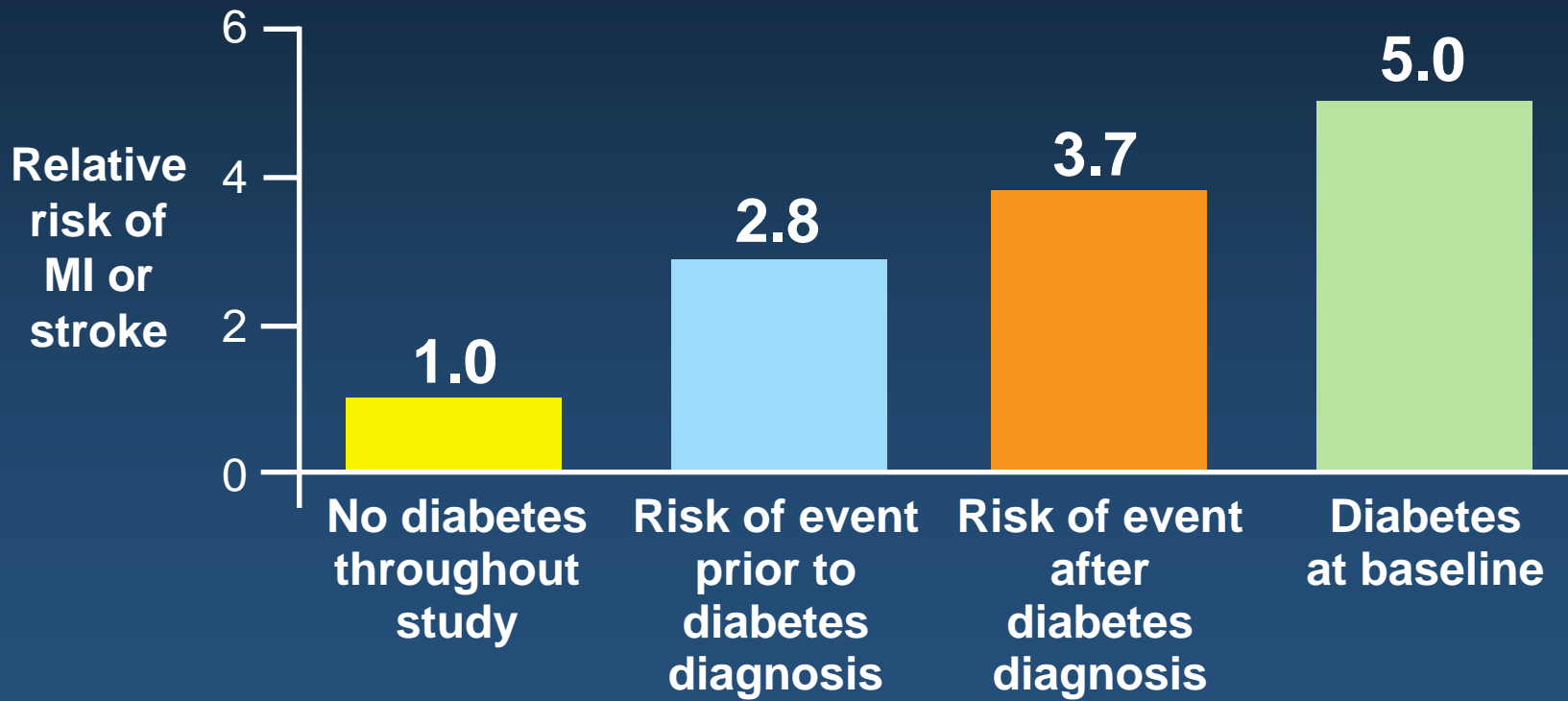
Management of Metabolic Syndrome

- Despite the ongoing controversy about the nomenclature, MS is associated with increased risk of DM & CVD.
- Treatment of MS is of paramount importance to prevent DM & CV events.
- There is no single therapy for MS, therefore individual components must be treated.



The Ticking Clock: ↑ CV Risk Before ↑ Glucose

Nurses' Health Study; 20-year follow-up of 117,629 women



Metabolic Syndrome Components

**Atherogenic
Dyslipidemia**

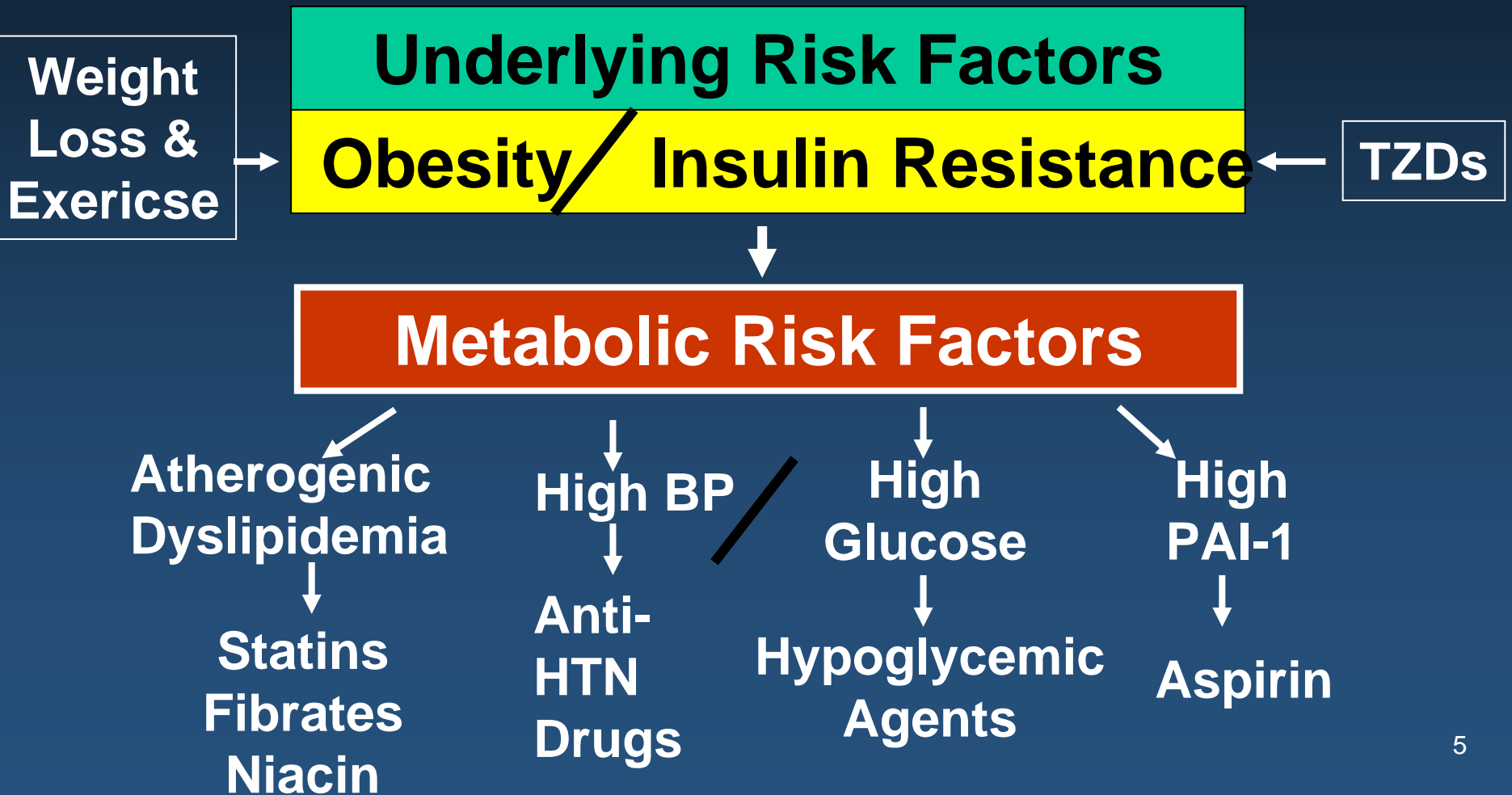
**Elevated
BP**

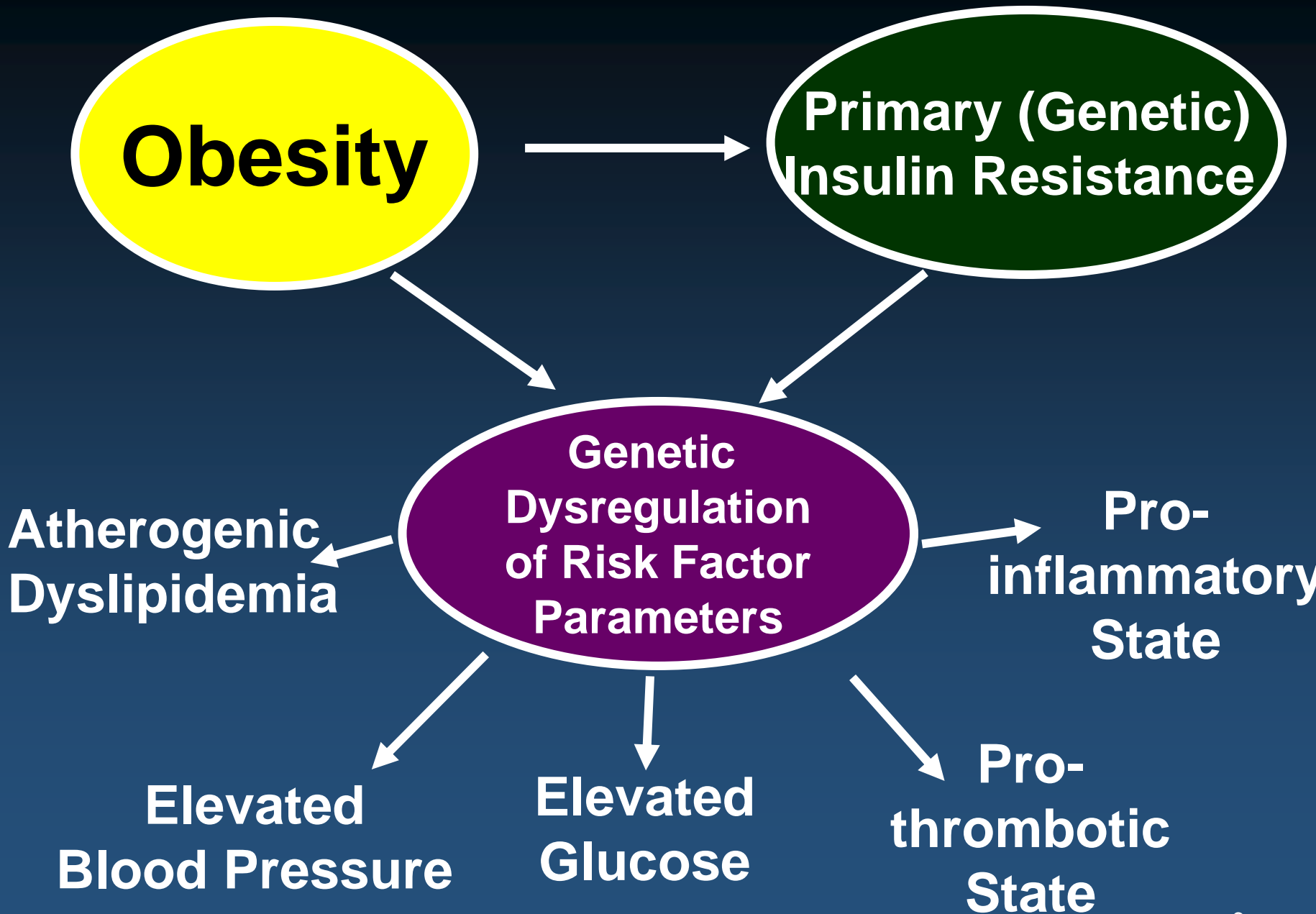
**Insulin
Resistance**
± Hyperglycemia

**Prothrombotic
State**

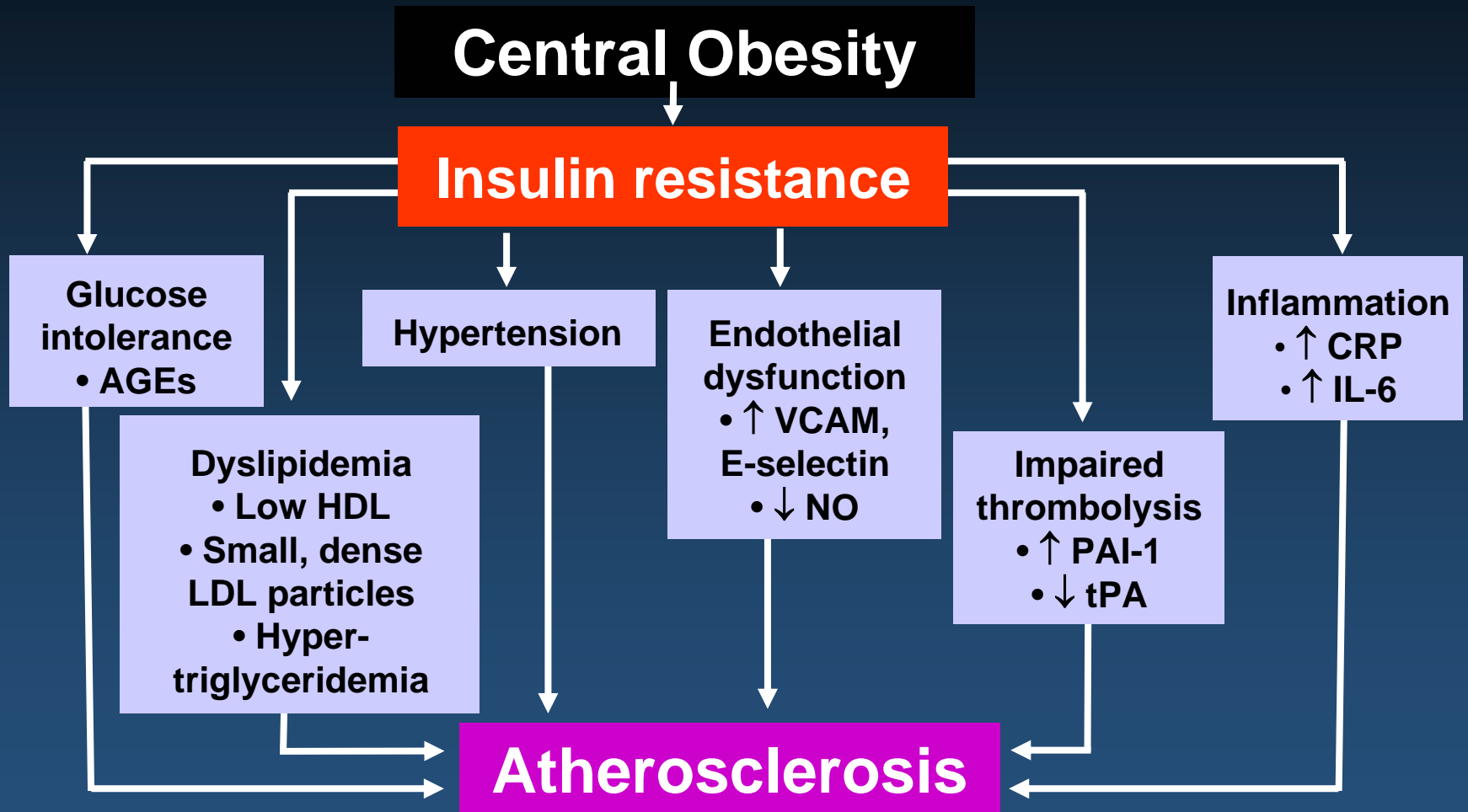
**Proinflammatory
State**

Management of Metabolic Syndrome





Association of Insulin Resistance With Cardiovascular Risk Factors and Atherosclerosis



Visceral obesity

CT scans from men matched for BMI and total body fat
White = visceral fat area (VFA); black = subcutaneous fat

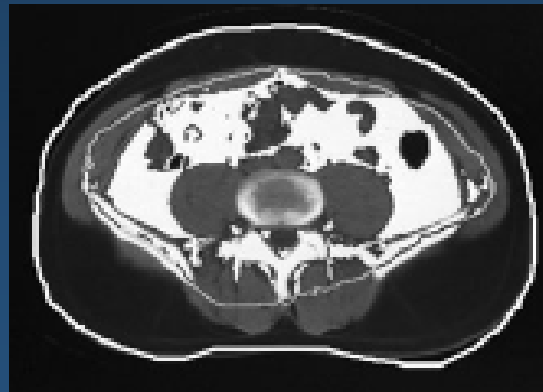
Visceral obesity

Fat mass: 19.8 kg
VFA: 155 cm²



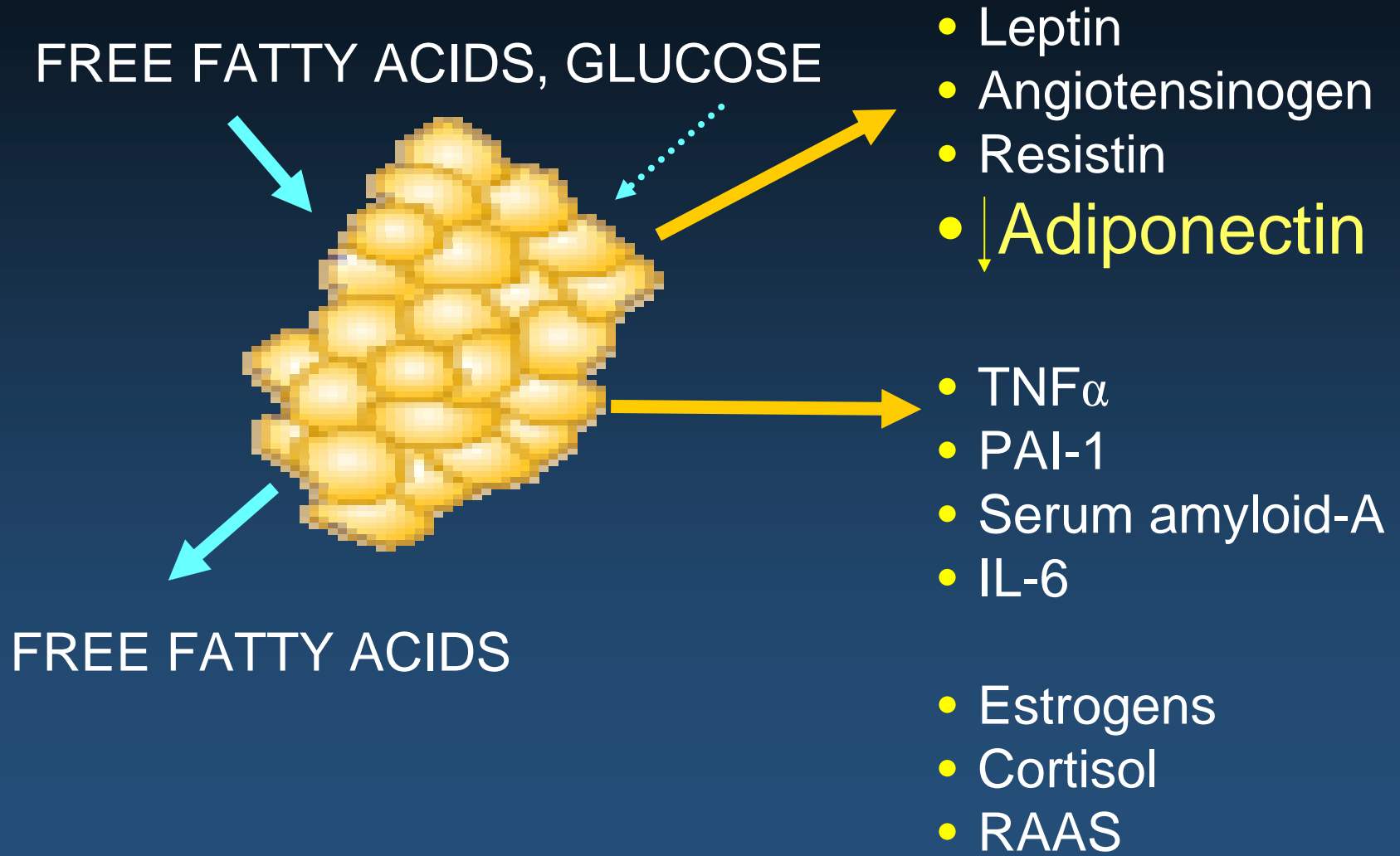
Subcutaneous obesity

Fat mass: 19.8 kg
VFA: 96 cm²

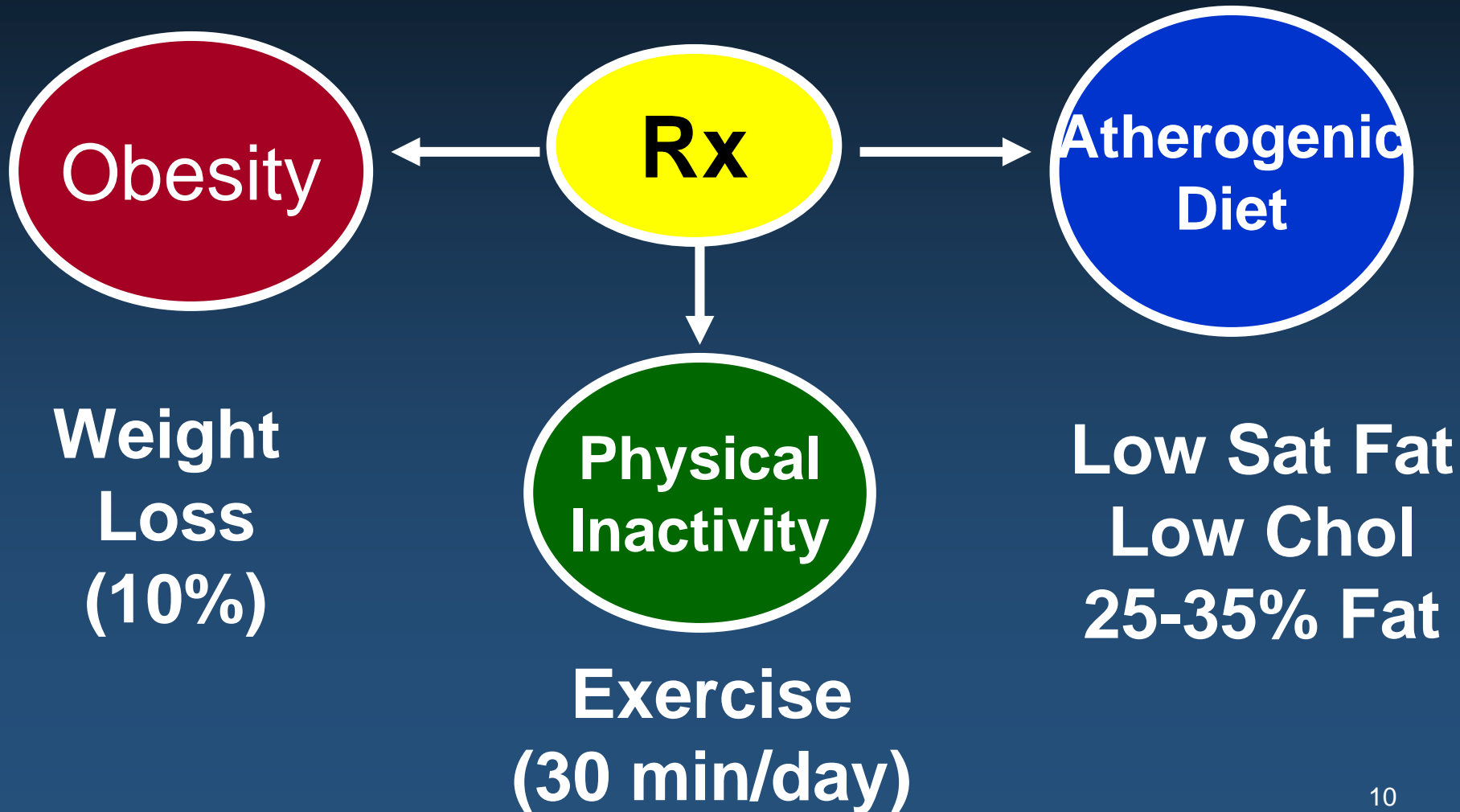


Visceral obesity
drives CV risk
progression
independent of BMI

Adipose Tissue: Secretory Organ



Treatment of Underlying Risk Factors



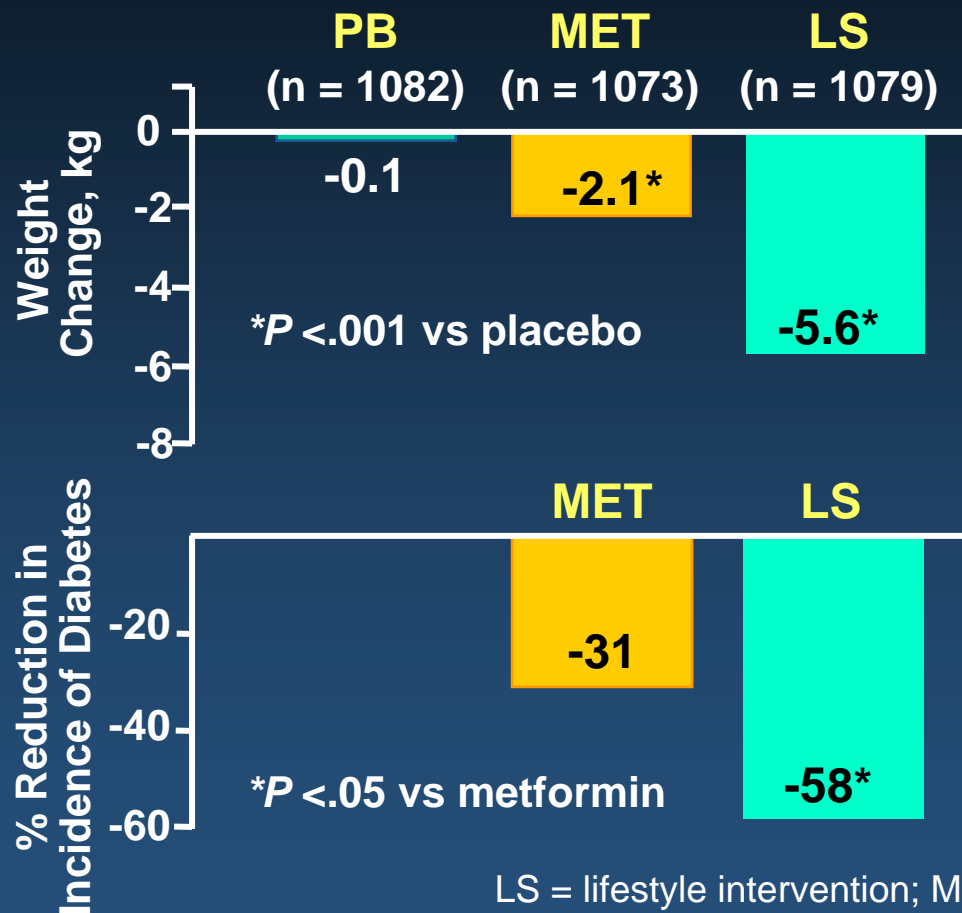
Hippocrates on Nutrition



“If we could give every individual the right amount of nourishment, we would have the safest way to health....”

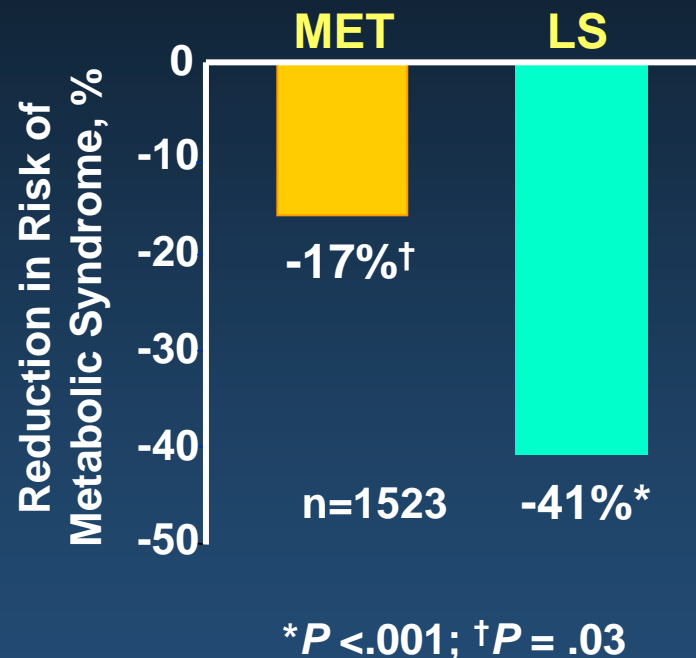
Effect of Interventions on Weight Change and Risk of Diabetes and Metabolic Syndrome

Diabetes Prevention Program

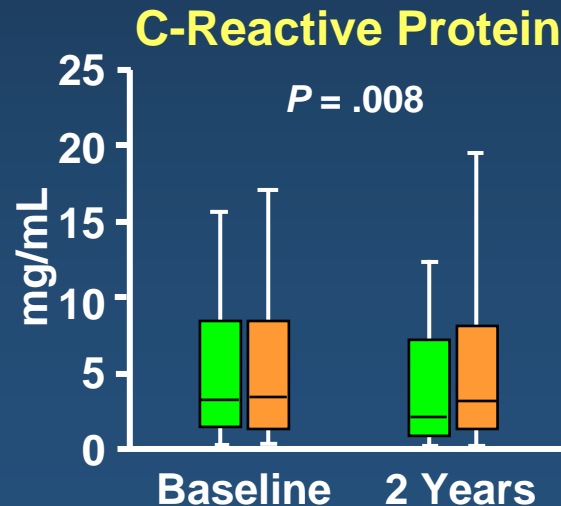
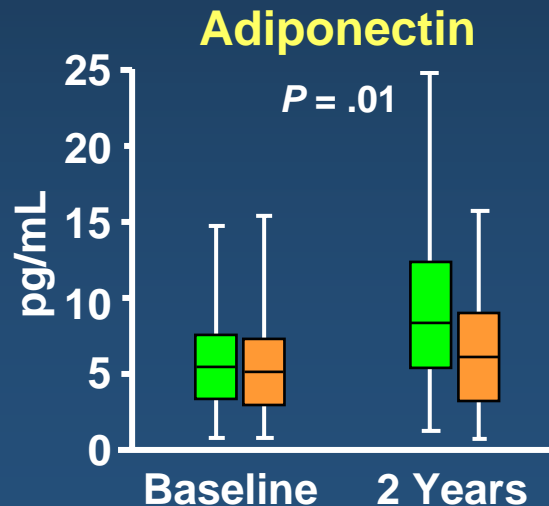
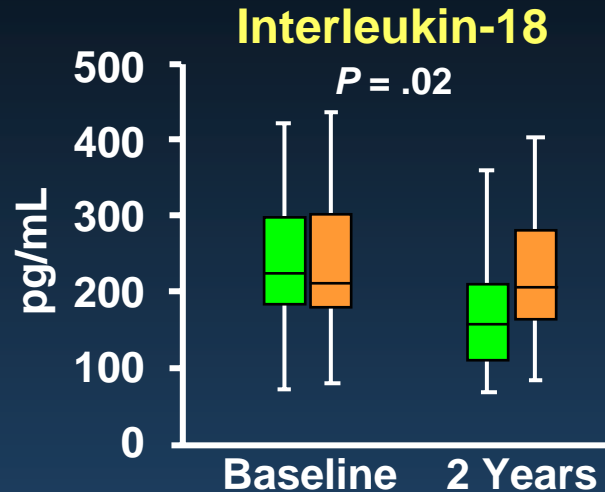
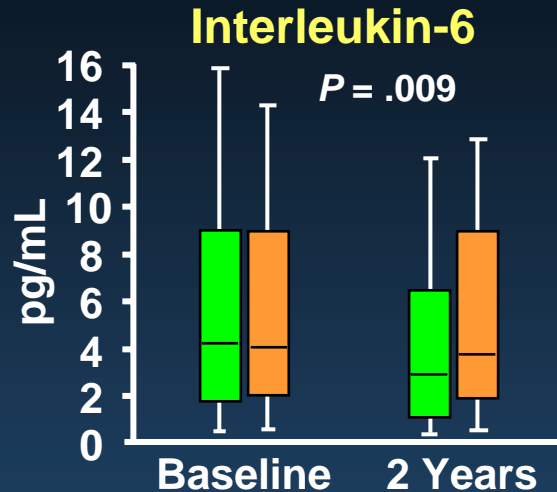


LS = lifestyle intervention; MET = metformin; PB = placebo.

Risk of developing metabolic syndrome



Obesity and Inflammation: Reversal Dietary Weight Loss

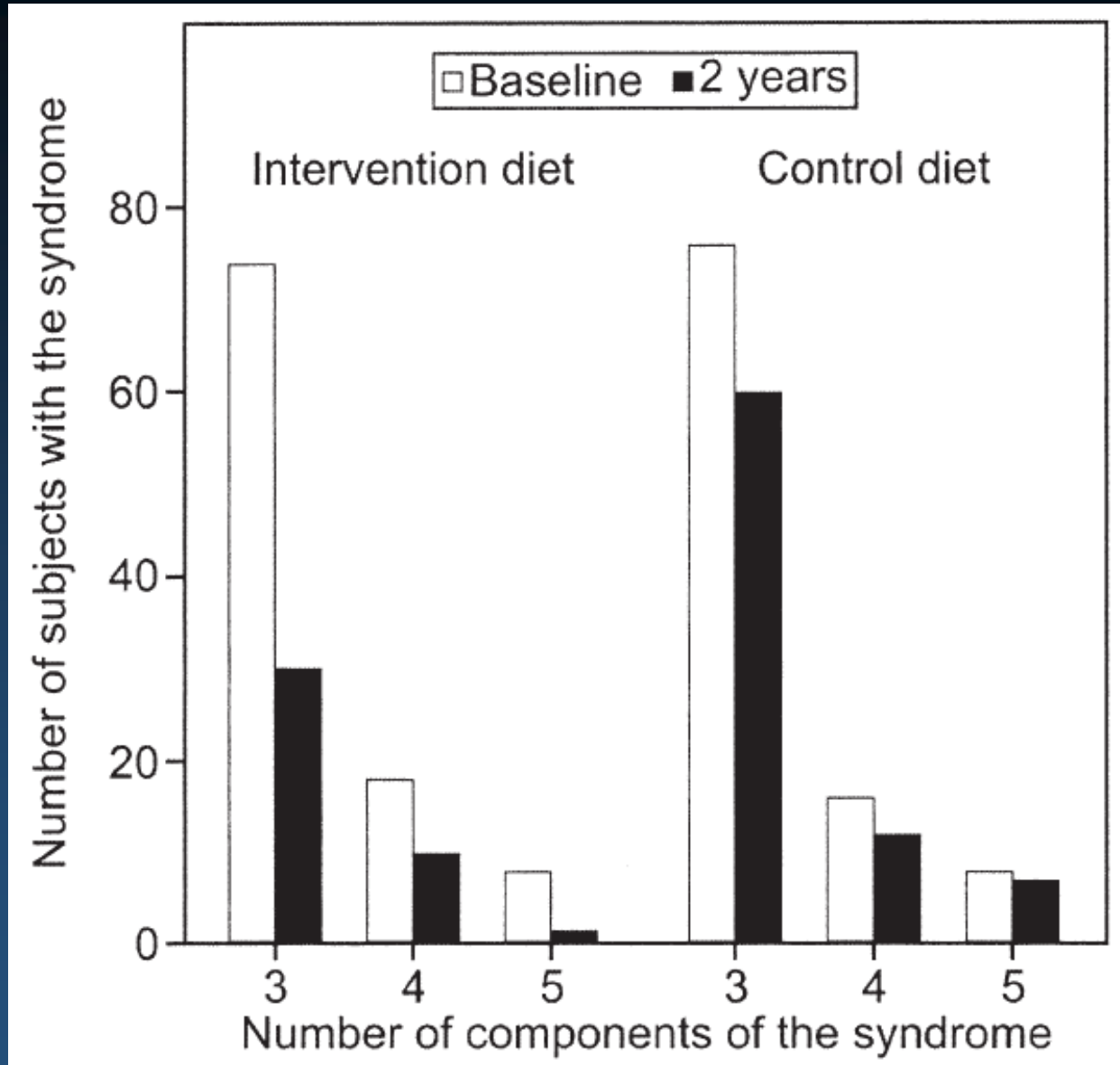


Randomized, single-blind, lifestyle-modification trial; Mediterranean diet w/increased activity

2-year follow-up;
4.2-fold decrease in BMI

Intervention
Control

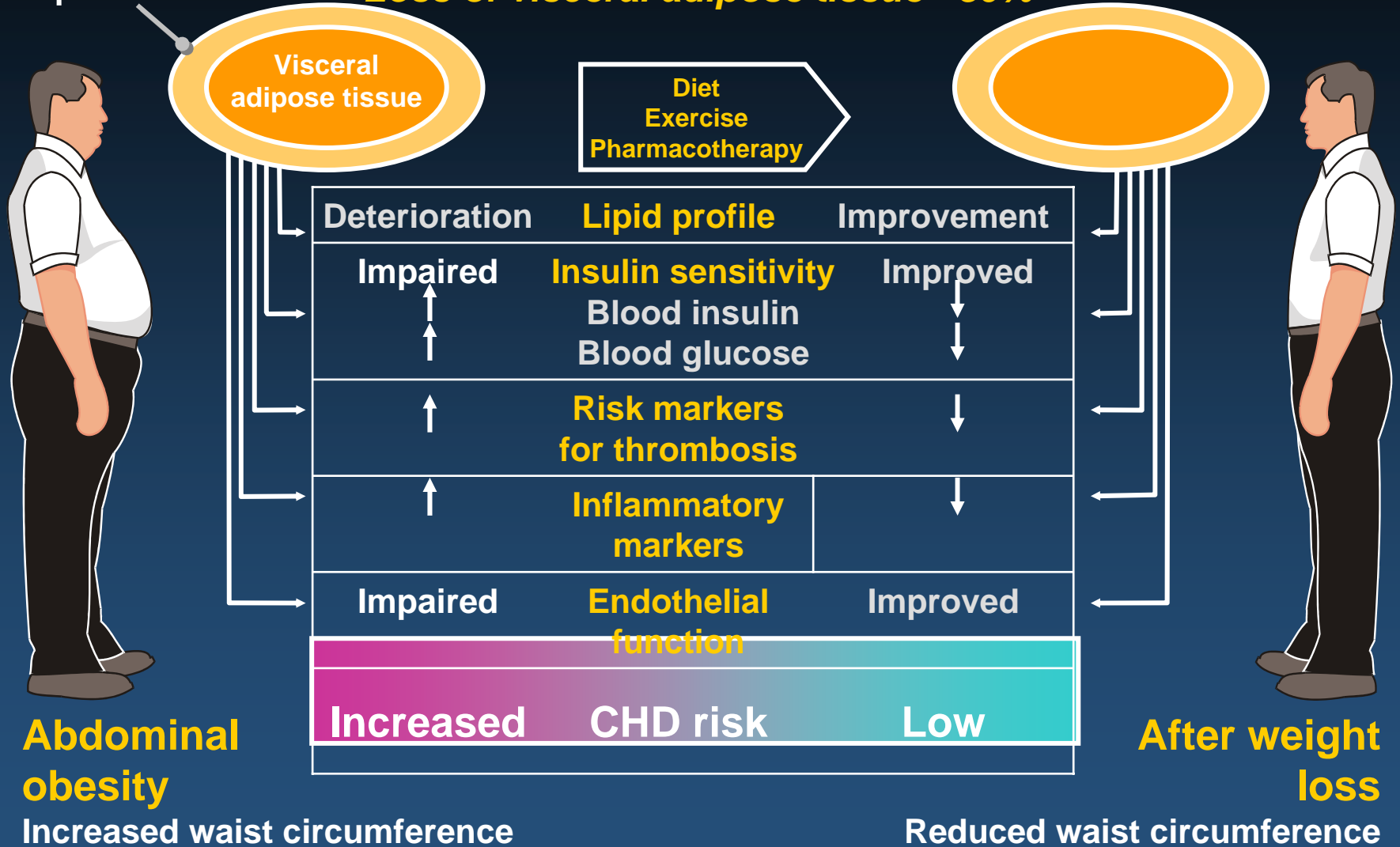
Effects of Mediterranean diet (ID) in patients with metabolic syndrome



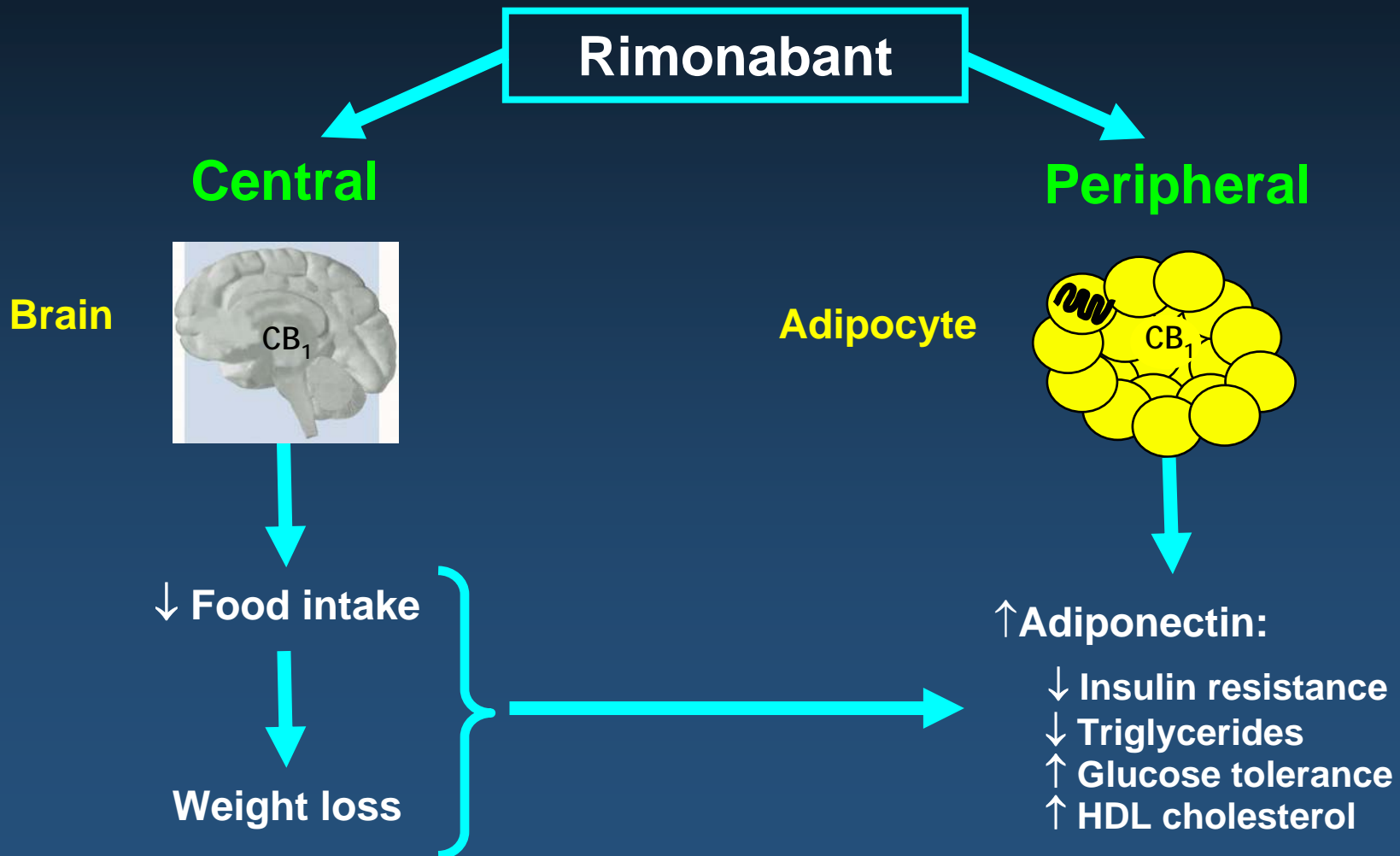
Weight loss ~10%

Loss of visceral adipose tissue ~30%

Subcutaneous
adipose tissue



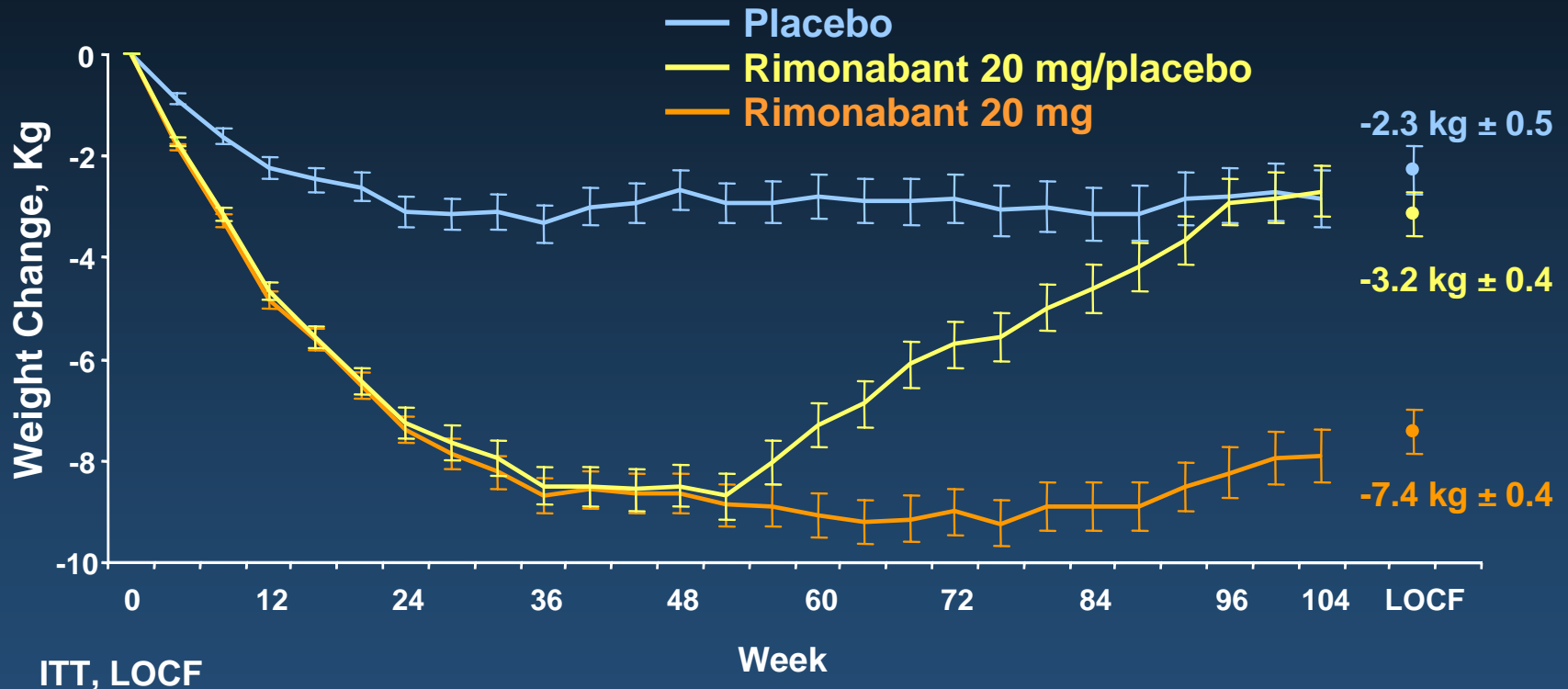
Rimonabant, the First CB₁ Blocker: A Multi-impact Medication



Rimonabant In Overweight/Obesity Trials

• Study	• Population	N	• Design
• RIO-North America	<ul style="list-style-type: none"> • Obese or overweight with/without comorbidities • (except diabetes) 	• 3045	<ul style="list-style-type: none"> • 1+1 year • Re-randomized
• RIO-Europe	<ul style="list-style-type: none"> • Obese or overweight with/without comorbidities • (except diabetes) 	• 1507	• 2 years
• RIO-Lipids	<ul style="list-style-type: none"> • Obese or overweight with untreated dyslipidemia • (diabetes excluded) 	• 1036	• 1 year
• RIO-Diabetes	<ul style="list-style-type: none"> • Obese or overweight with type 2 diabetes 	• 1045	• 1 year

RIO-North America: Weight Loss and Prevention of Weight Regain by Chronic Therapy



Weight (kg) Change From Baseline Over 2 Years (Mean ± SEM)

Adapted with permission from Pi-Sunyer XF, et al. *JAMA*. 2006;295:761-775.

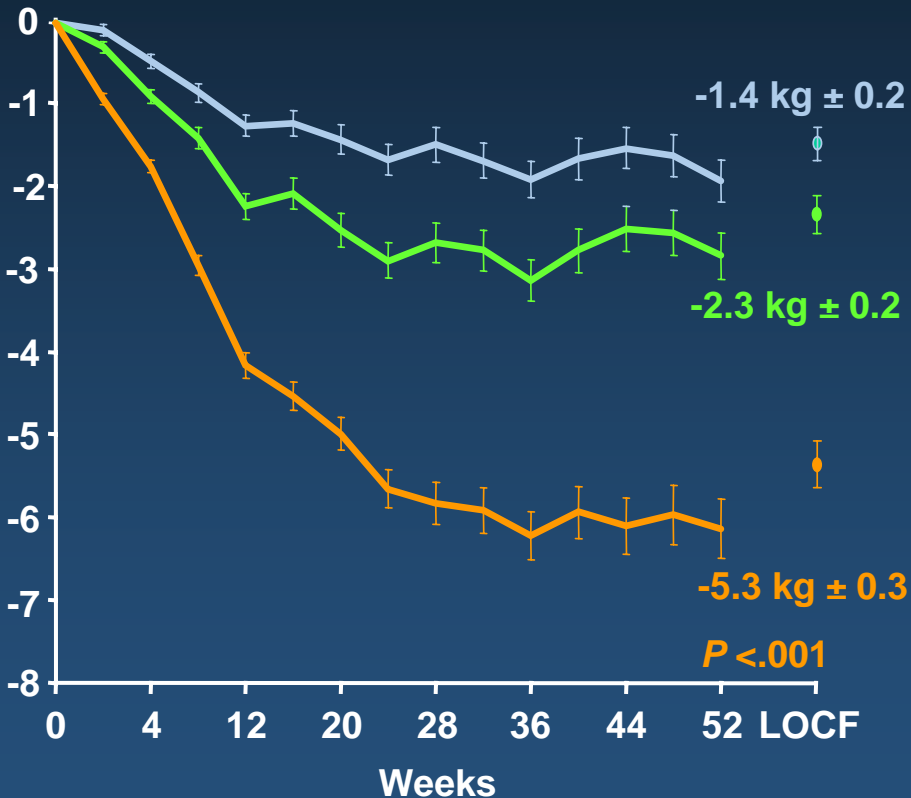
RIO-Diabetes: Change in Weight and Waist Circumference

- ITT, LOCF

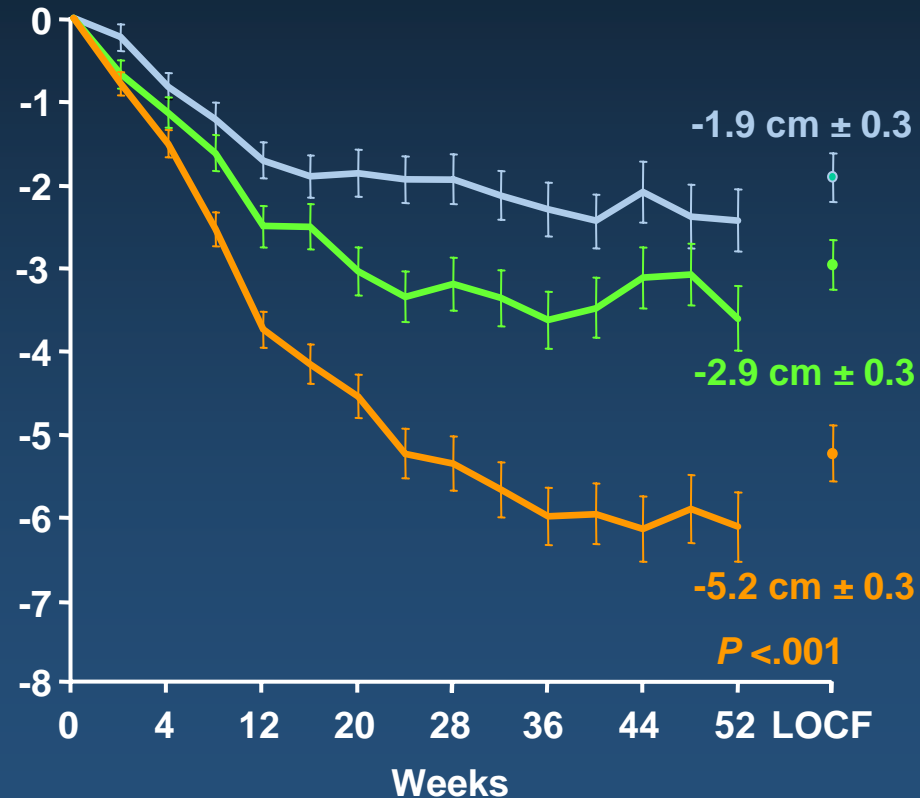
(mean change \pm SEM)

— Placebo
 — Rimonabant 5 mg
 — Rimonabant 20 mg

Body Weight (kg)

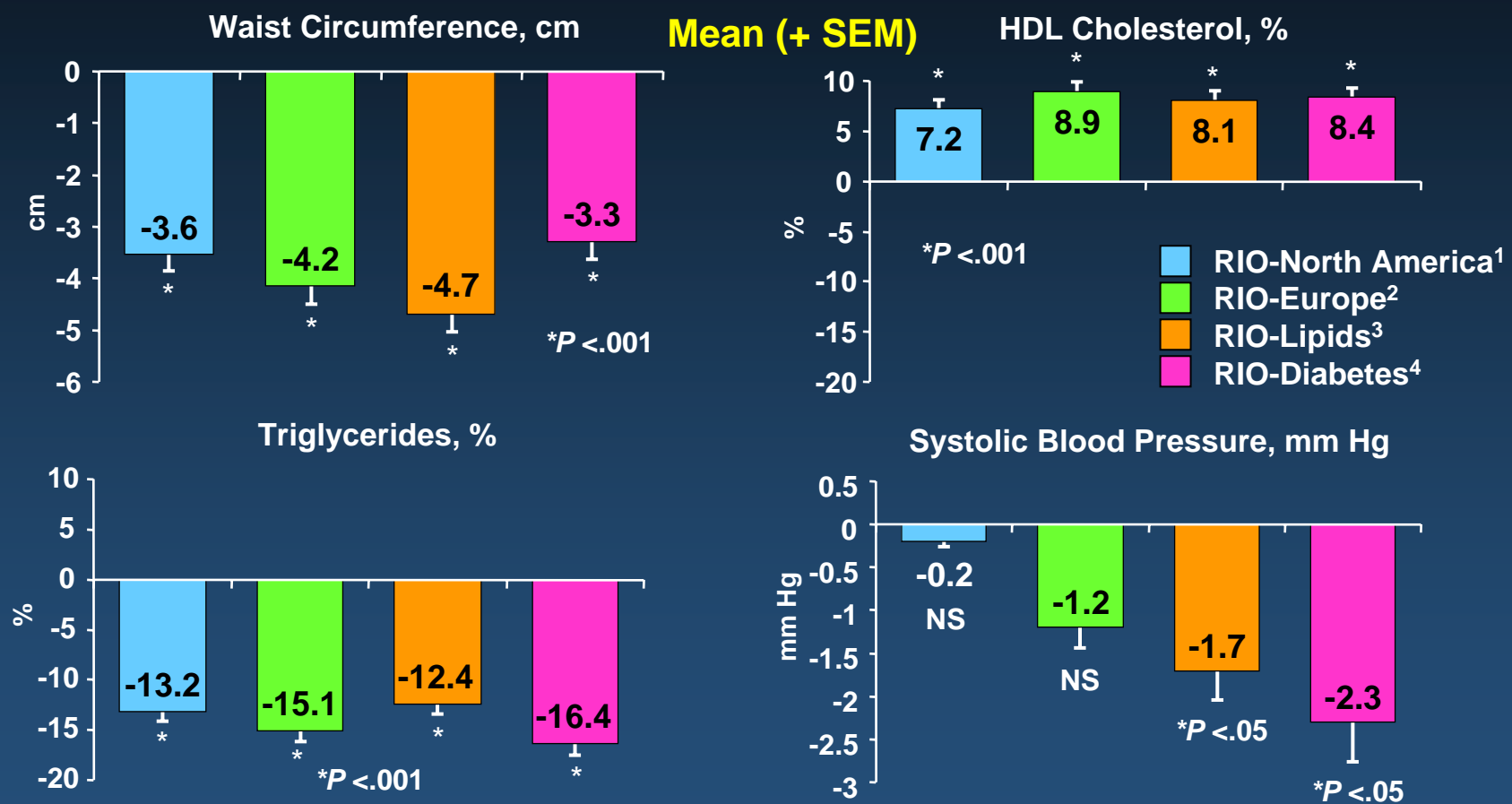


Waist Circumference (cm)



Andrè Scheen, MD, PhD. Presented at: American Diabetes Association 65th Annual Scientific Sessions; June 12, 2005; San Diego, Calif. Used with permission.

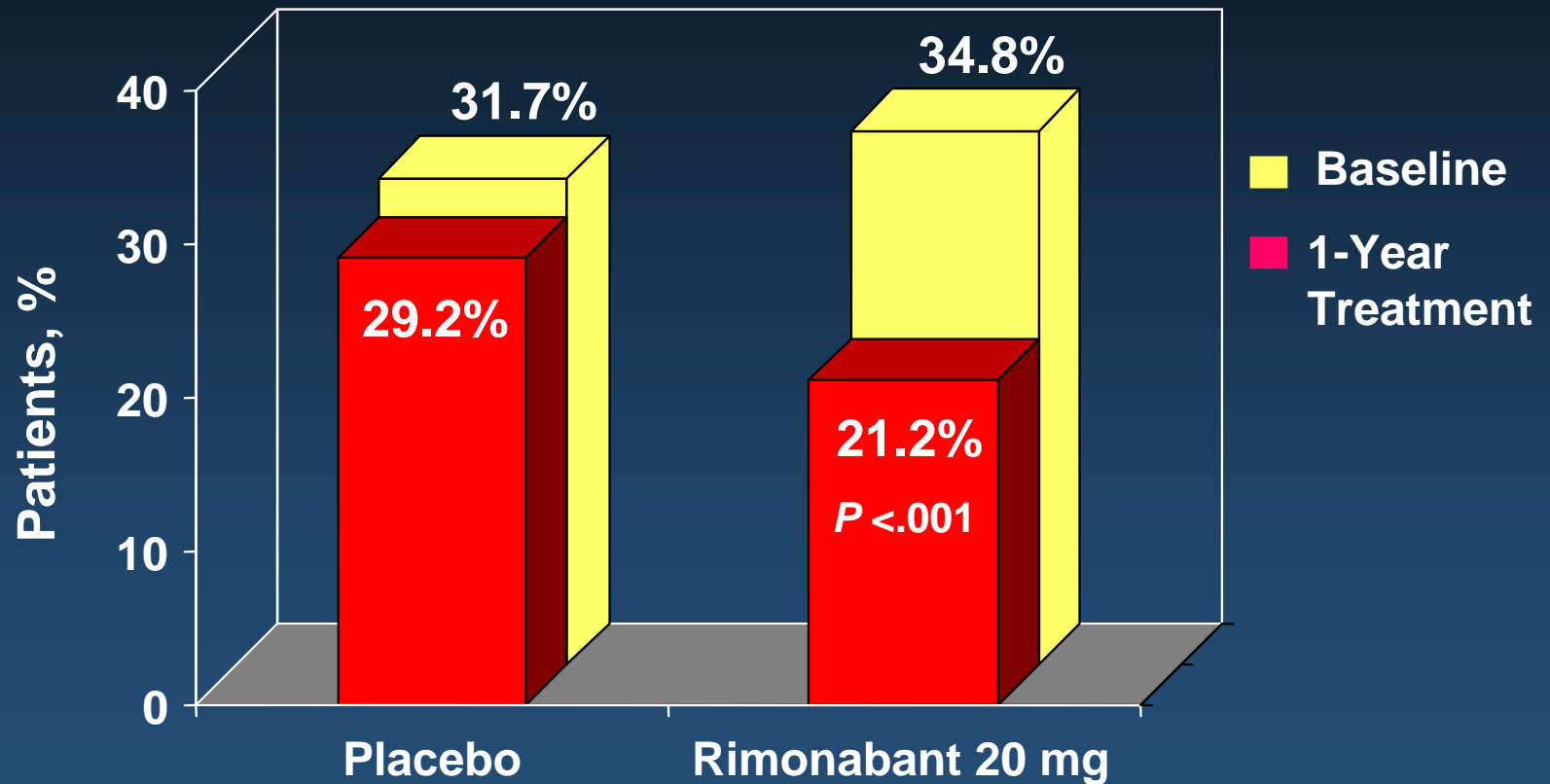
Placebo-subtracted Change in MS Parameters in 4 Rimonabant Trials



1. Pi-Sunyer FX, et al. *JAMA*. 2006;295:761-775.
 2. Van Gaal LF, et al. *Lancet*. 2005;365:1389-1397.
 3. Després JP, et al. *N Engl J Med*. 2005;353:2121-2134.
 4. Scheen AF. Presented at: 65th Annual Scientific Sessions of the ADA; June 12, 2005; San Diego, Calif.

N = >6600; ITT, LOCF

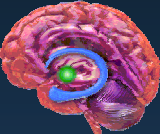
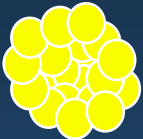



RIO-North America: Change in Metabolic Syndrome Status



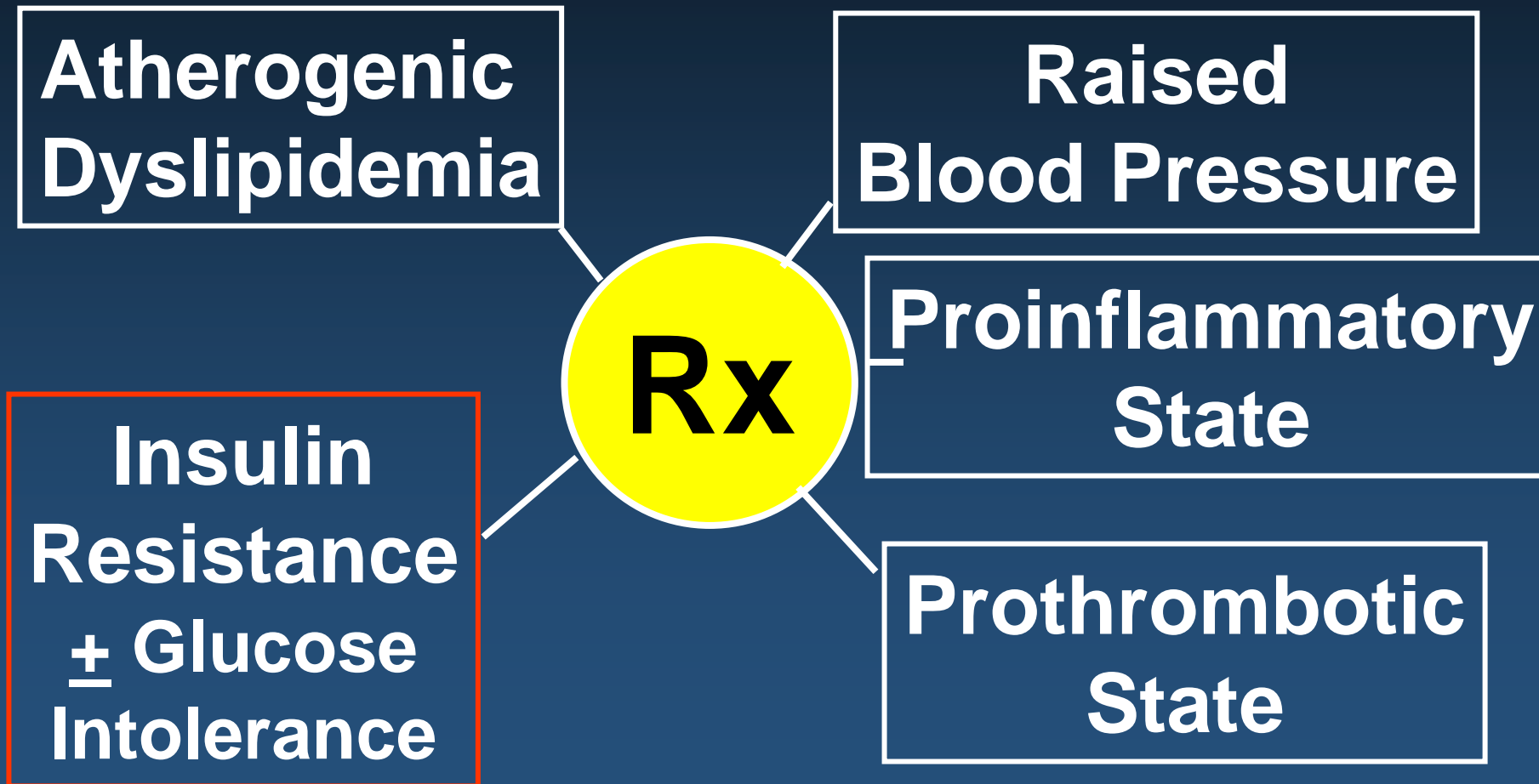
ITT, LOCF

Pi-Sunyer FX, et al. *JAMA*. 2006;295:761-775.

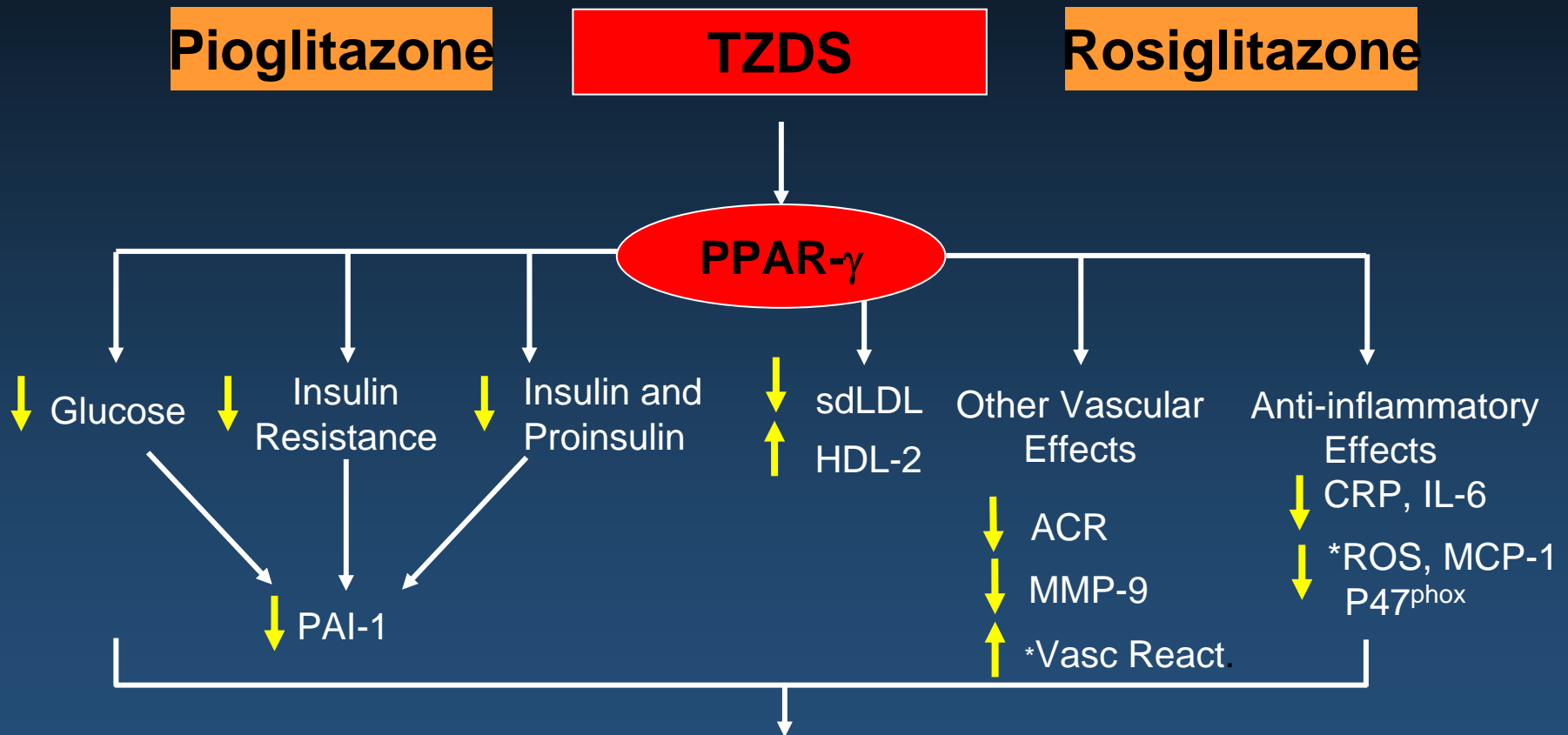
Multisite Impact of a CB₁ Antagonist on Metabolism

Site of Action	Mechanism(s)	Clinical Implications
 Hypothalamus/ Nucleus accumbens	↓ Food intake	Weight loss, reduced waist circumference
 Adipose tissue	↑ Adiponectin ↓ Lipogenesis	Reduced visceral fat Improved lipidemia Insulin sensitivity
 Muscle	↑ Glucose uptake ↑ O ₂ consumption	Glucose homeostasis
 Liver	↓ Lipogenesis	Improved lipidemia Insulin sensitivity
 GI tract	↑ Satiety	Weight loss

Treatment of Components of Metabolic Syndrome



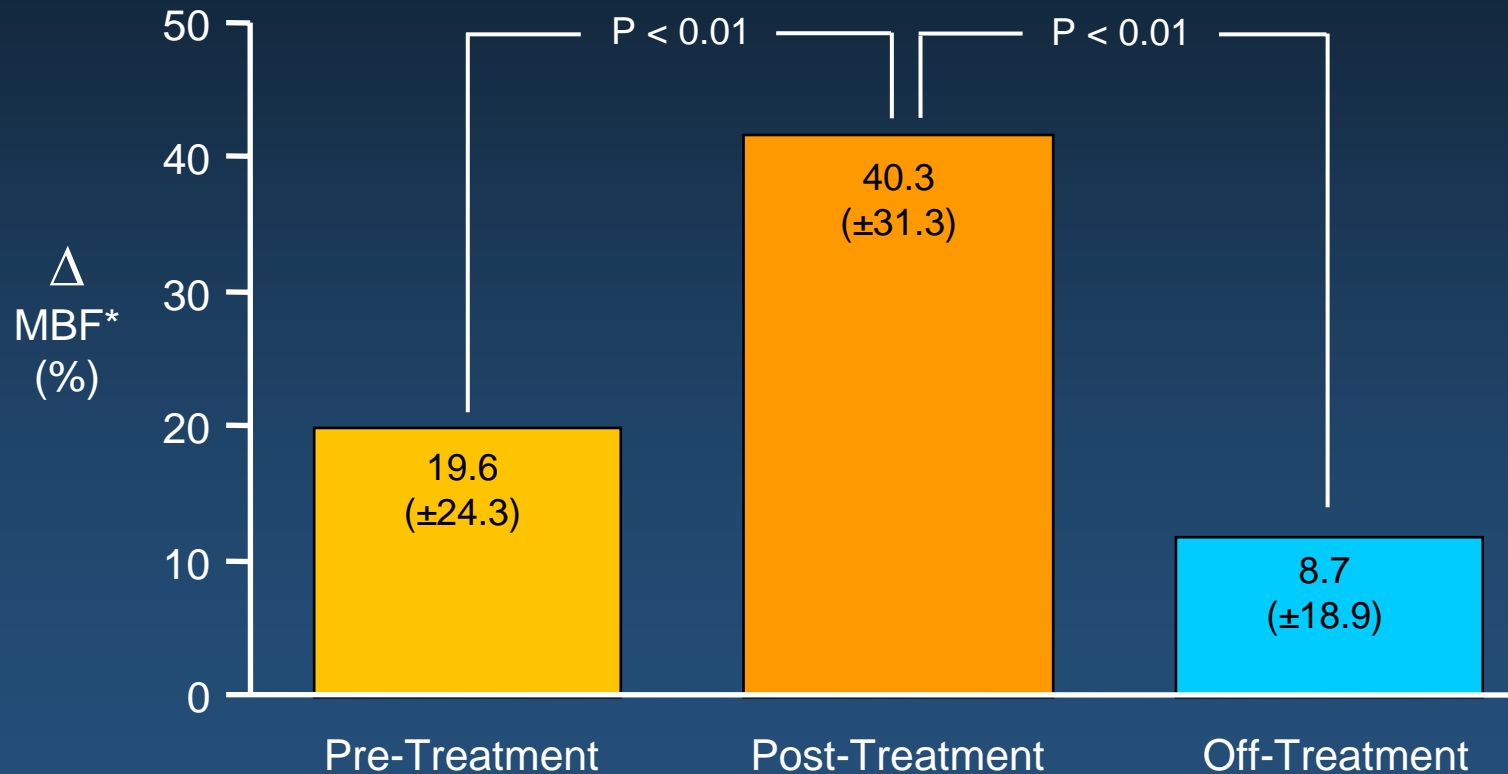
Pleiotropic Effects of Thiazolidinediones on Cardiovascular Risk



Reduced Potential Cardiovascular Implications

PPAR γ agonist normalizes coronary vasomotor abnormalities in IR

N = 16 with insulin resistance; rosiglitazone 8 mg for 3 months

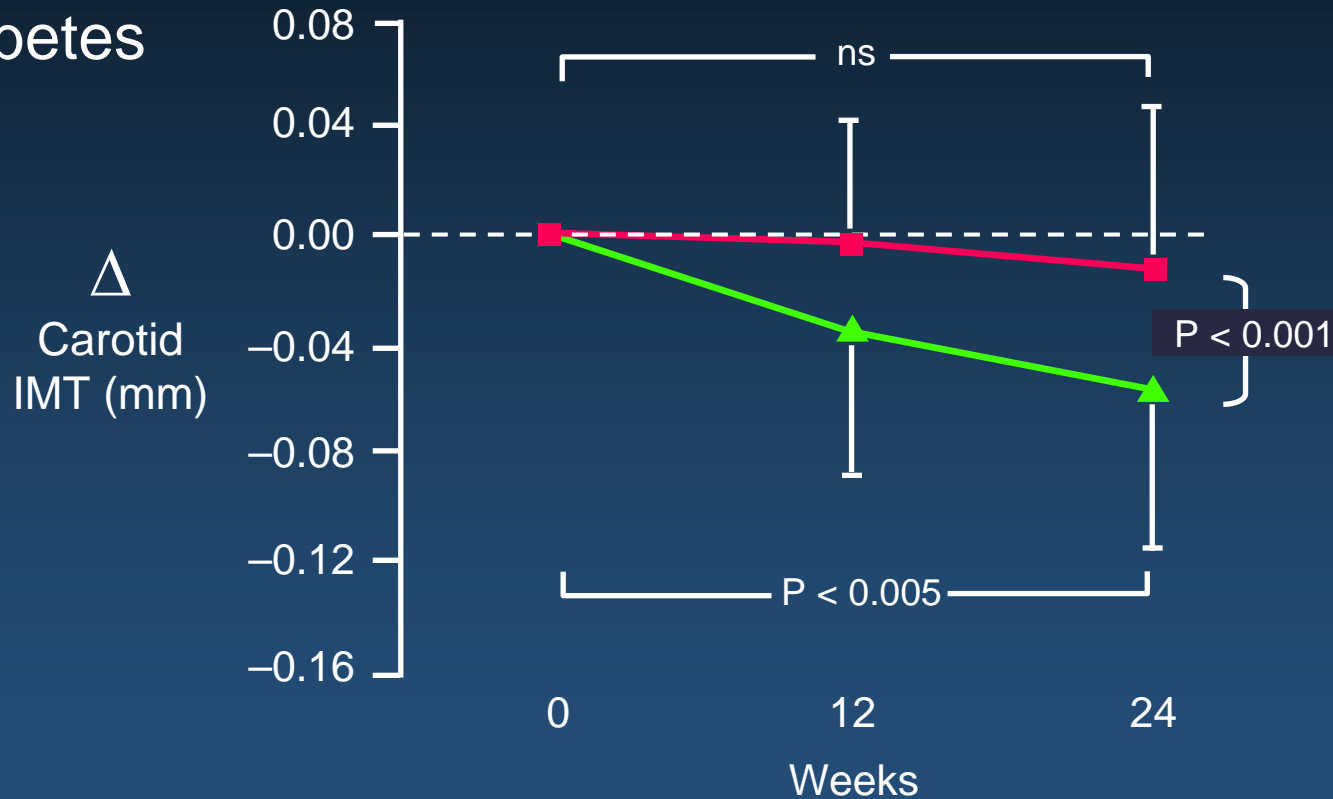


* from rest

Quiñones MJ et al. *Ann Intern Med.* 2004;140:700-8.

PPAR γ agonist blunts progression of carotid atherosclerosis

- N = 173 with type 2 diabetes



▲ Pioglitazone 45 mg ■ Glimepiride 2.7 mg

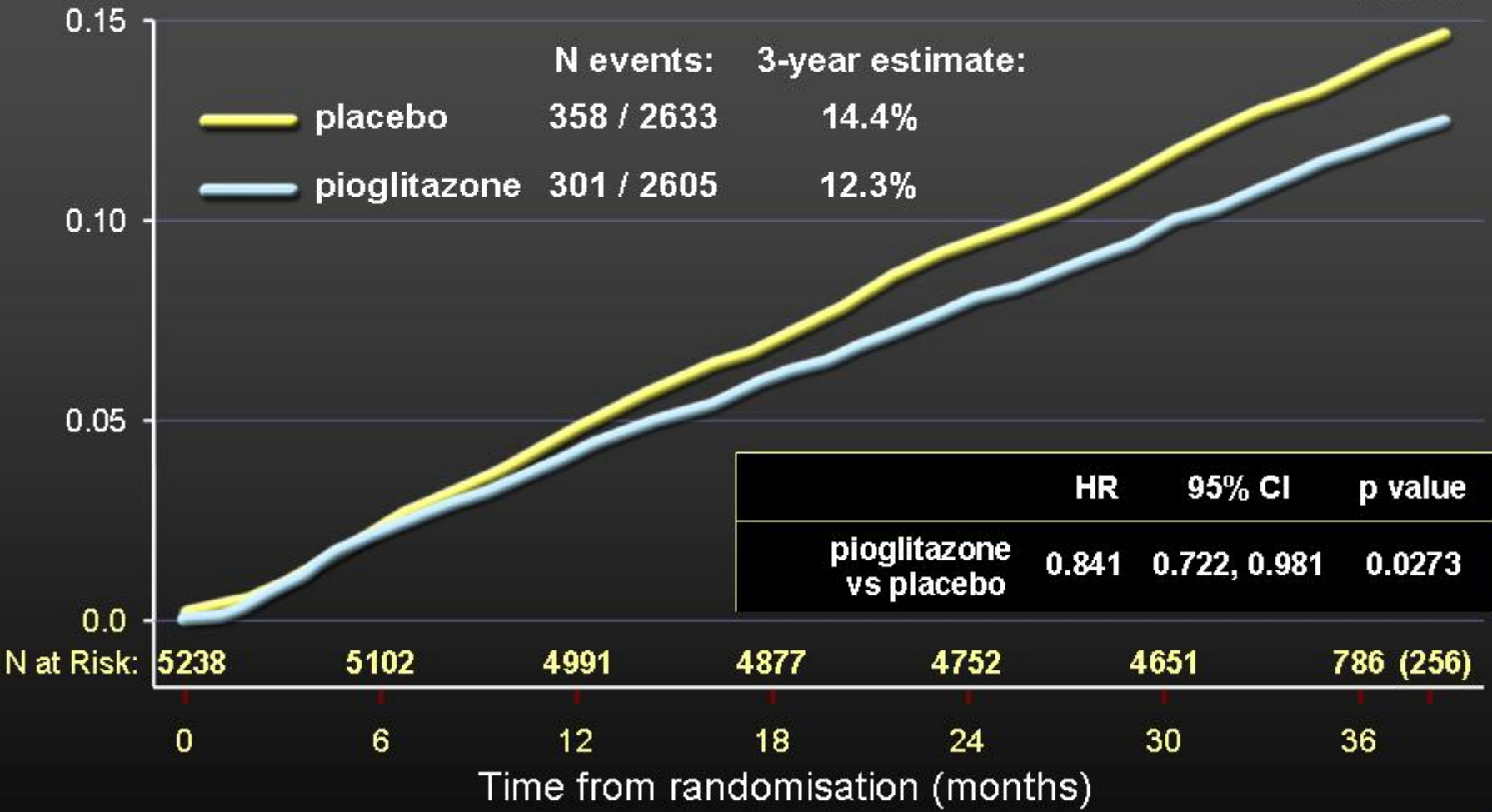
Cardiovascular Benefits of Thiazolidinediones

- Reduction in insulin resistance
- Effects on cardiovascular risk factors
 - Improve dyslipidemia (\uparrow HDL, \downarrow LDL density, \downarrow or \leftrightarrow TG)
 - \downarrow Renal microalbumin excretion
 - \downarrow Blood pressure
 - \downarrow VSMC proliferation/migration in arterial wall
 - Enhance thrombolytic mechanisms
 - \downarrow Plasminogen activator inhibitor-1 levels
 - \downarrow C-reactive protein levels
- Significantly reduce rate of restenosis
- Outcomes studies underway

Time to Death, MI (Excluding Silent) or Stroke

Kaplan-Meier event rate

2.1% ARR
NNT-48



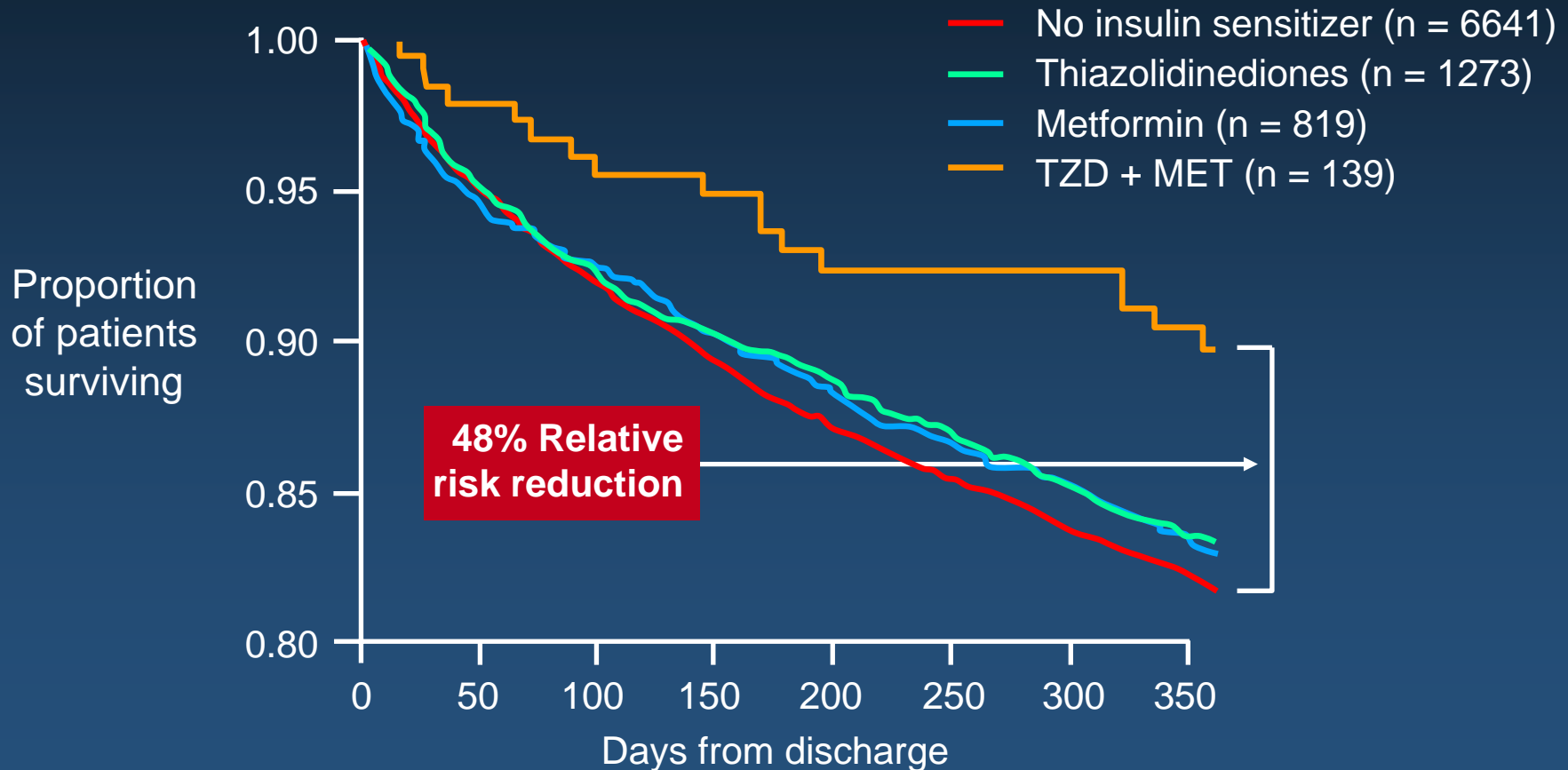
Predefined: Principal Secondary Endpoint

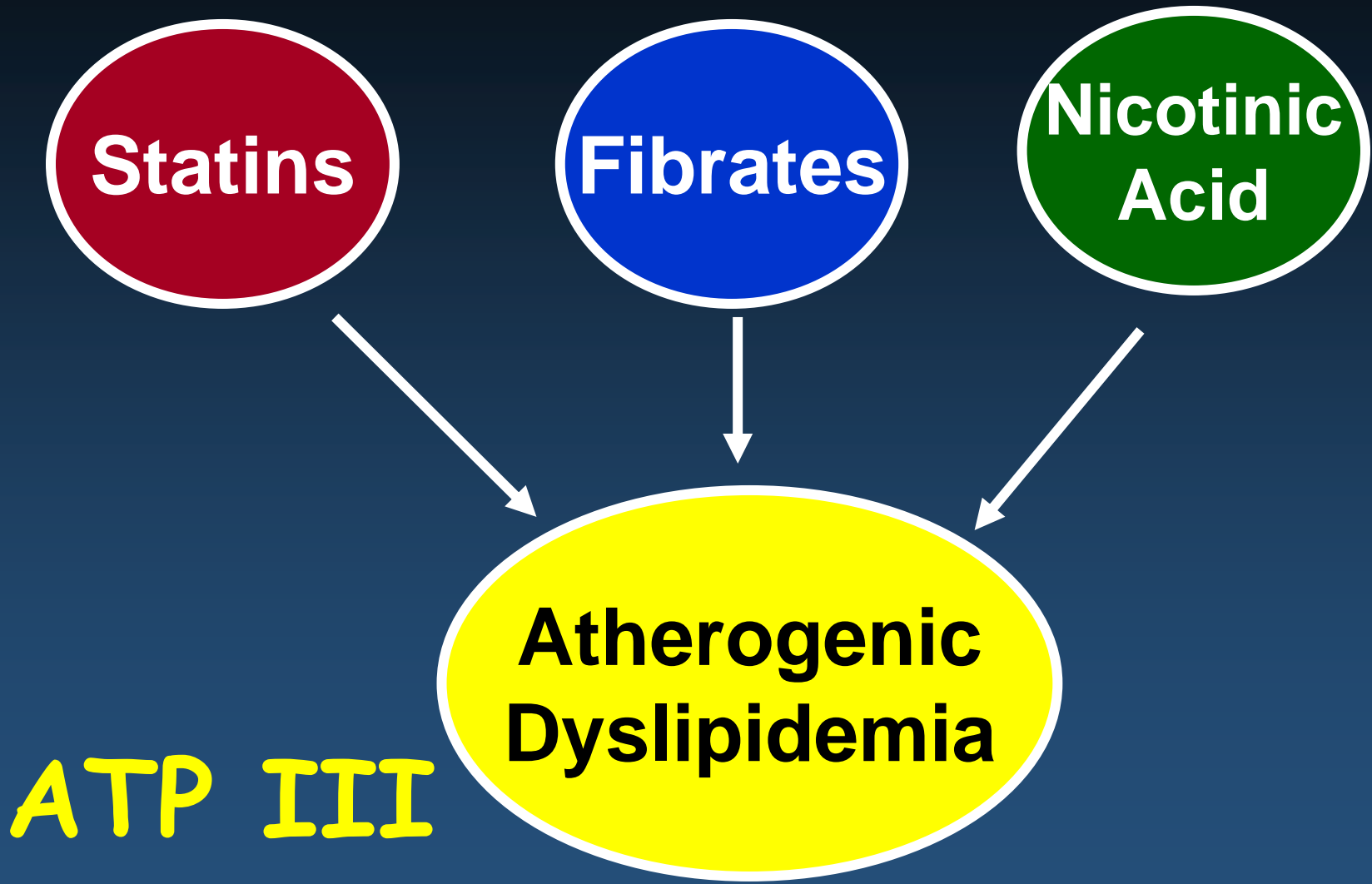
www.proactive-results.com



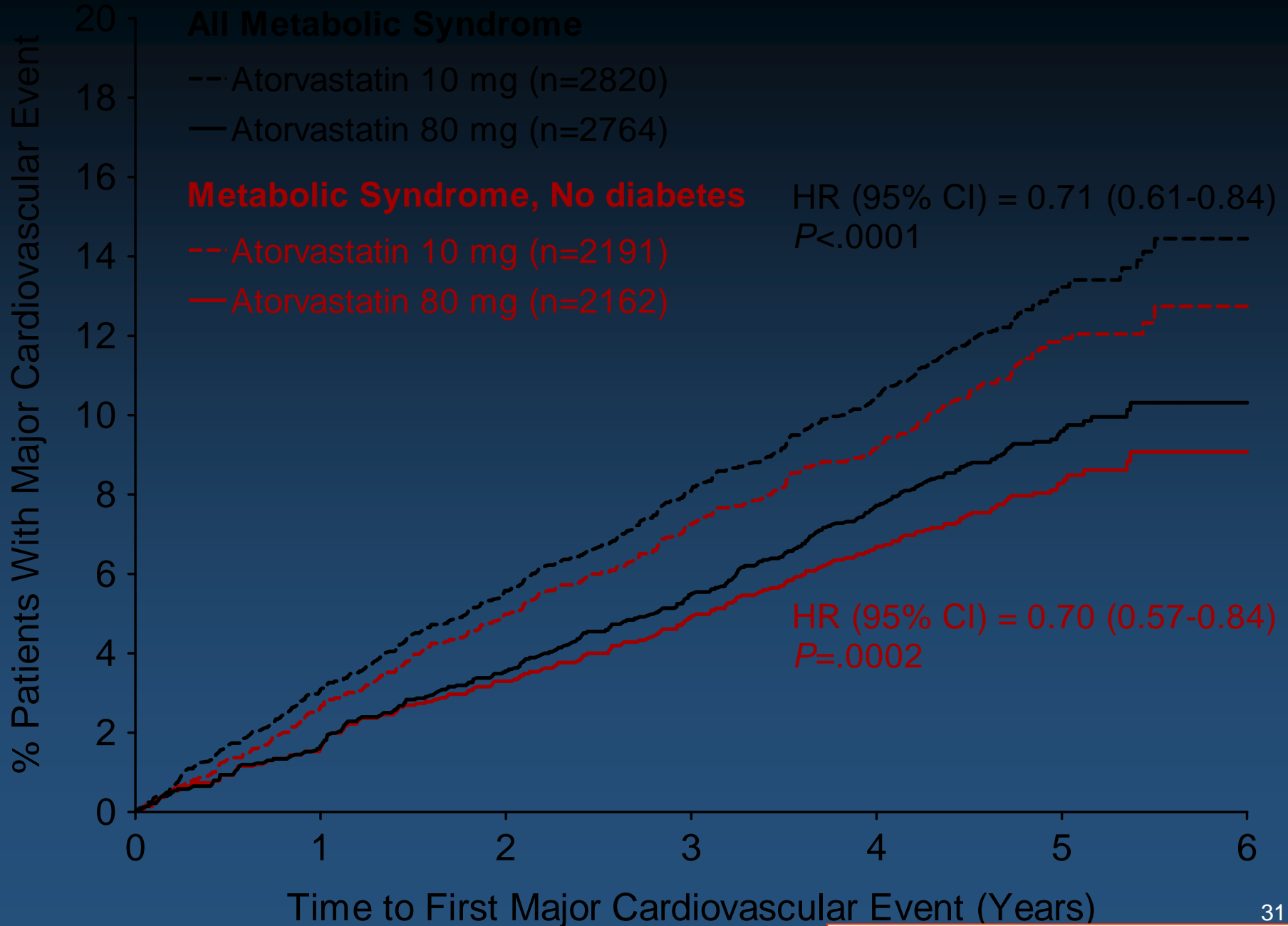
Mortality benefit with combined insulin-sensitizing therapy

8872 acute MI patients, mean age 76.4 years, discharged on glucose-lowering medication

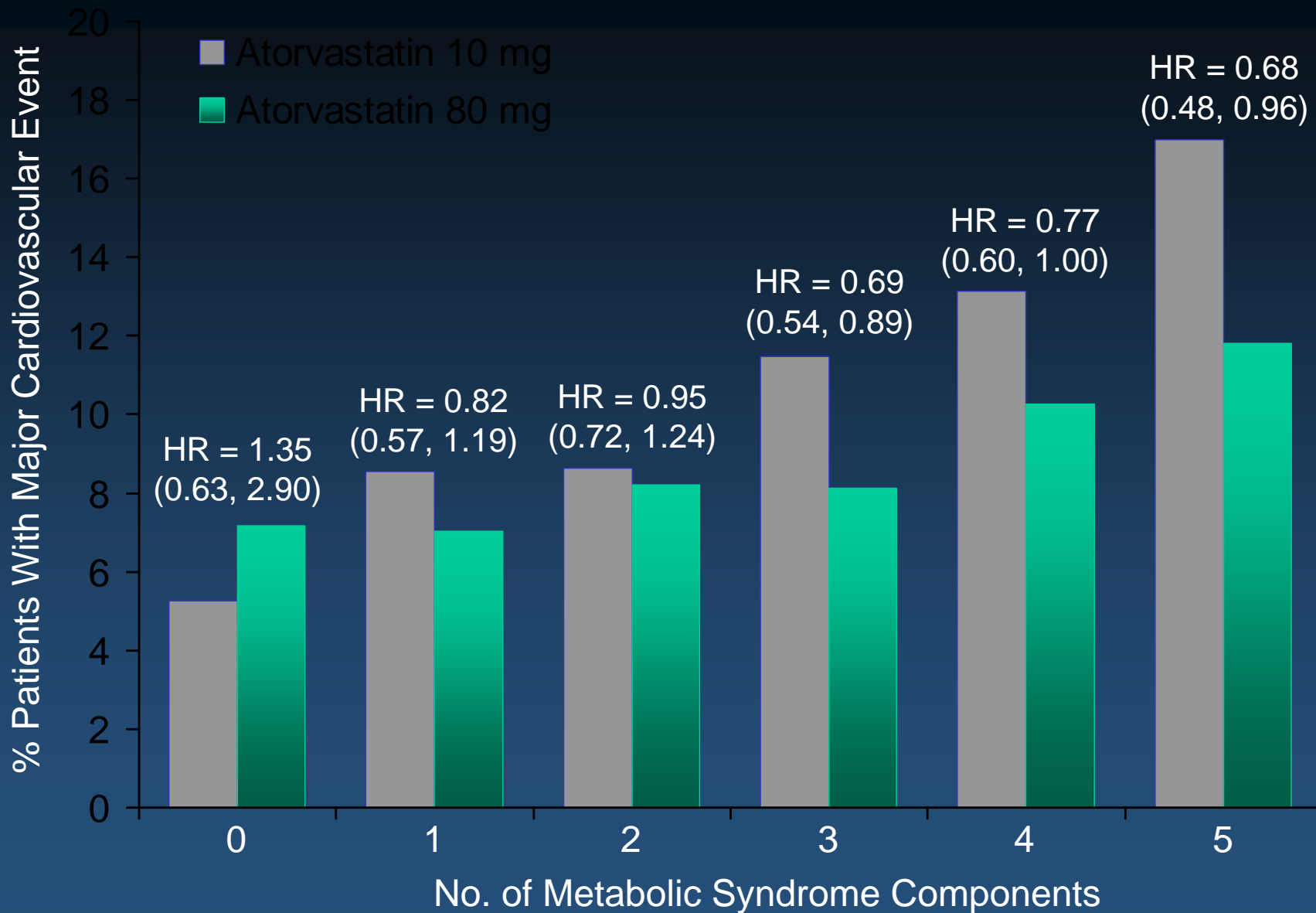




TNT Metabolic Syndrome Subanalysis



TNT Metabolic Syndrome Subanalysis



Atorva 10: 11/209

65/761

105/1216

147/1282

141/1073

79/465

Atorva 80: 16/223

52/739

104/1269

109/1342

99/965

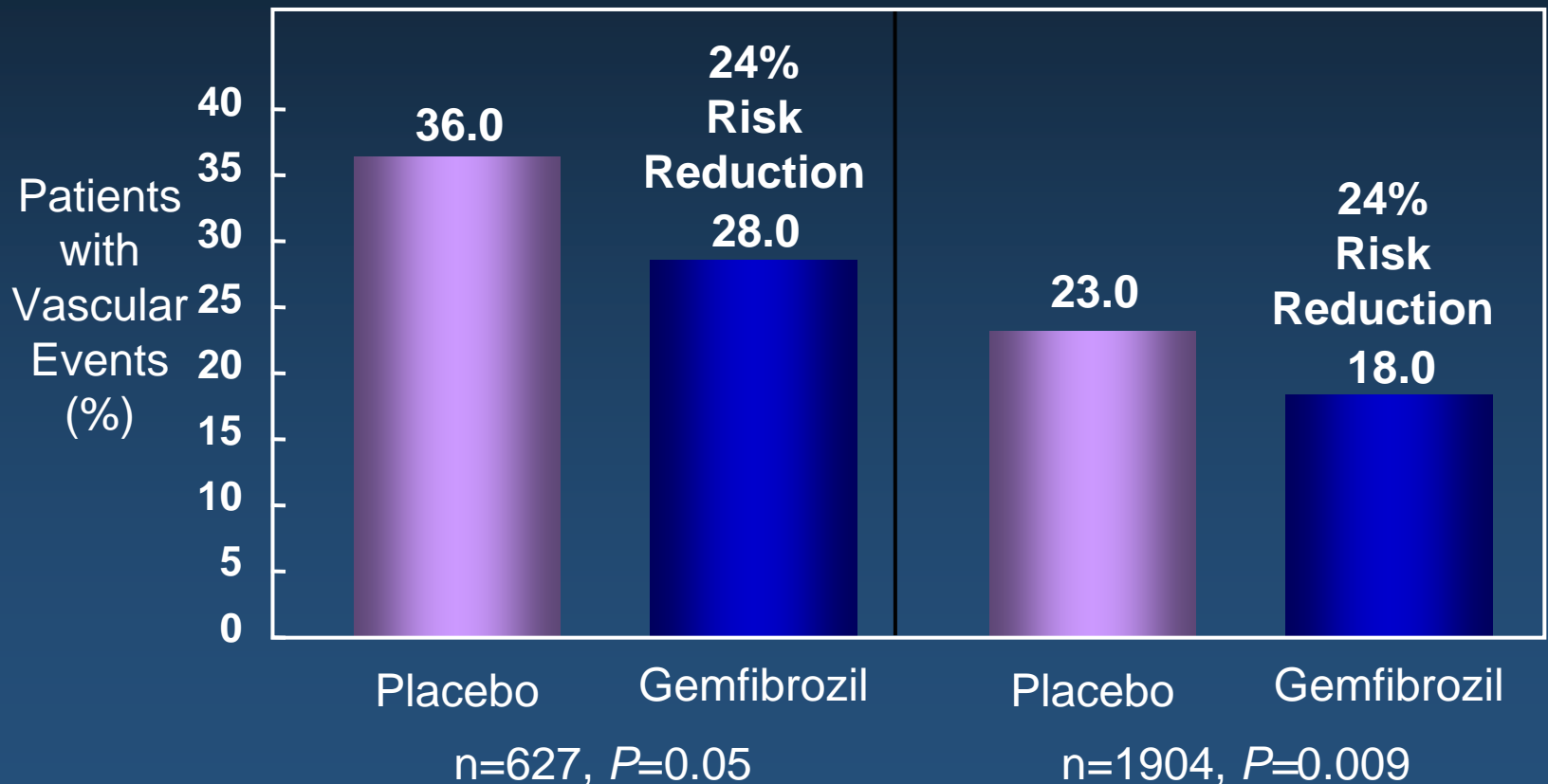
54/457

Increasing HDL-C Reduces Vascular Events in Patients with Diabetes

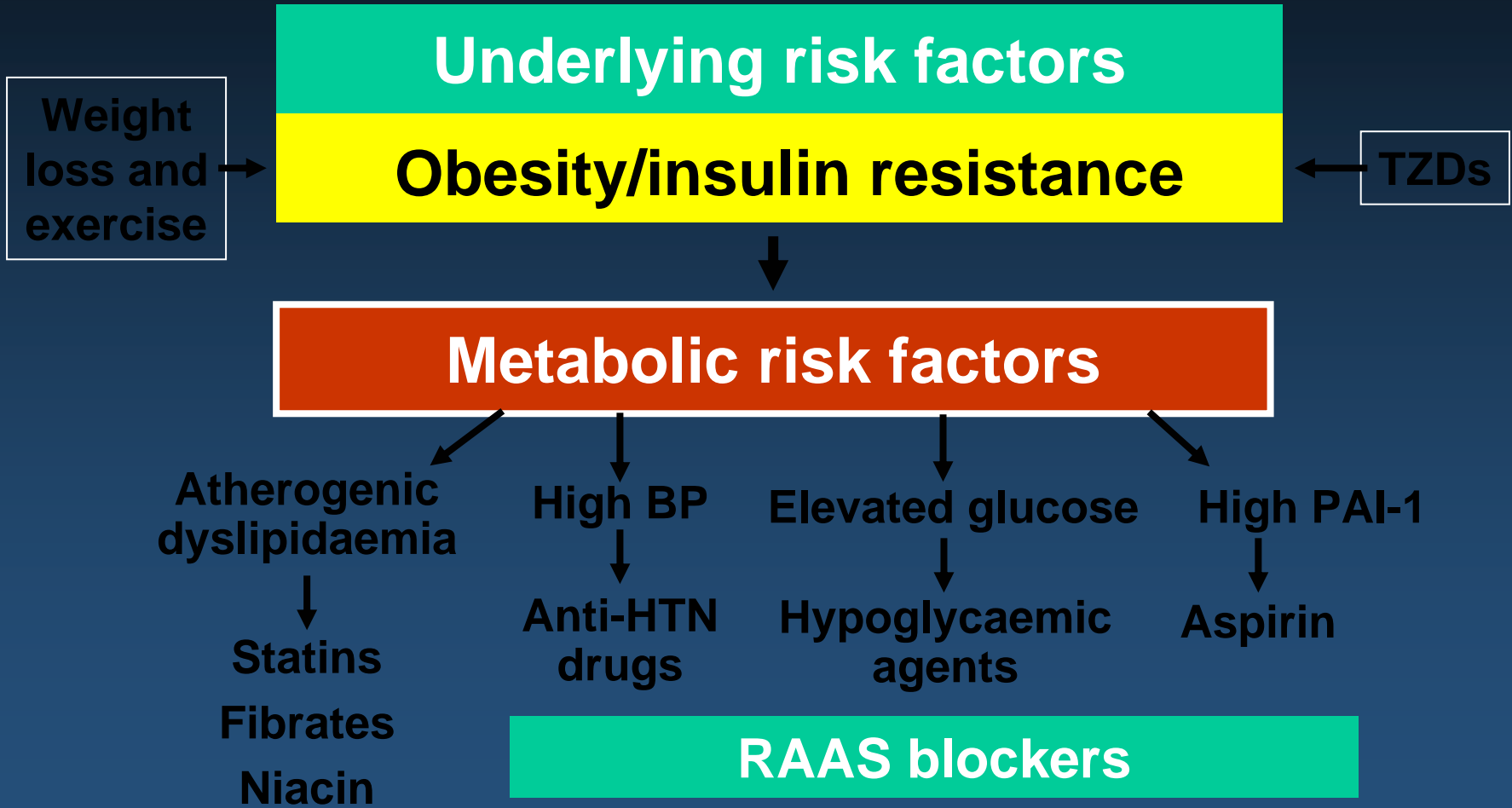
VA-HIT (HDL-C Intervention Trial)

Diabetic Patients

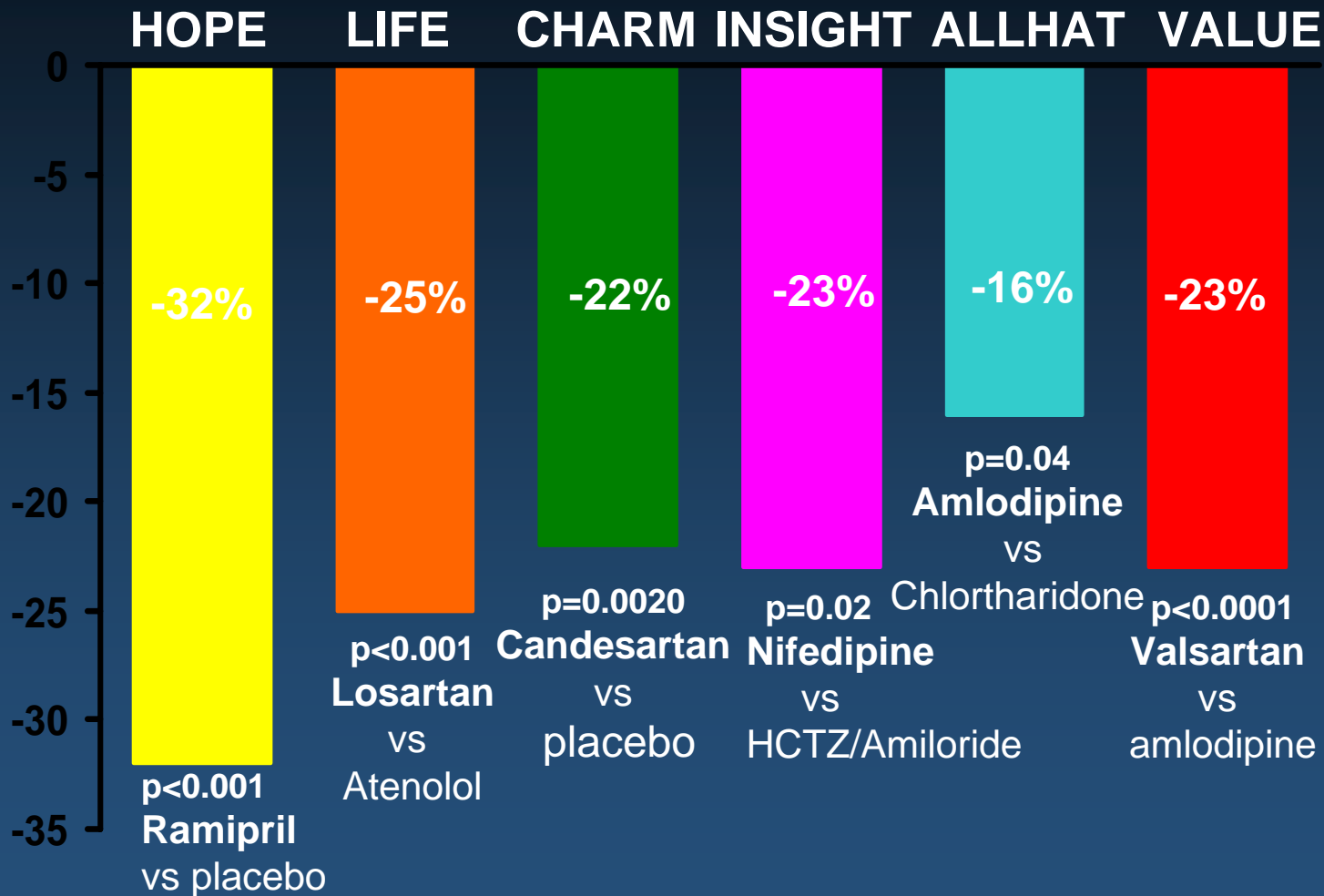
Non-diabetic Patients



Management of Metabolic Syndrome



Impact on New Onset Diabetes by Various Anti-hypertensives: Benefits of RAAS Inhibition in preventing DM

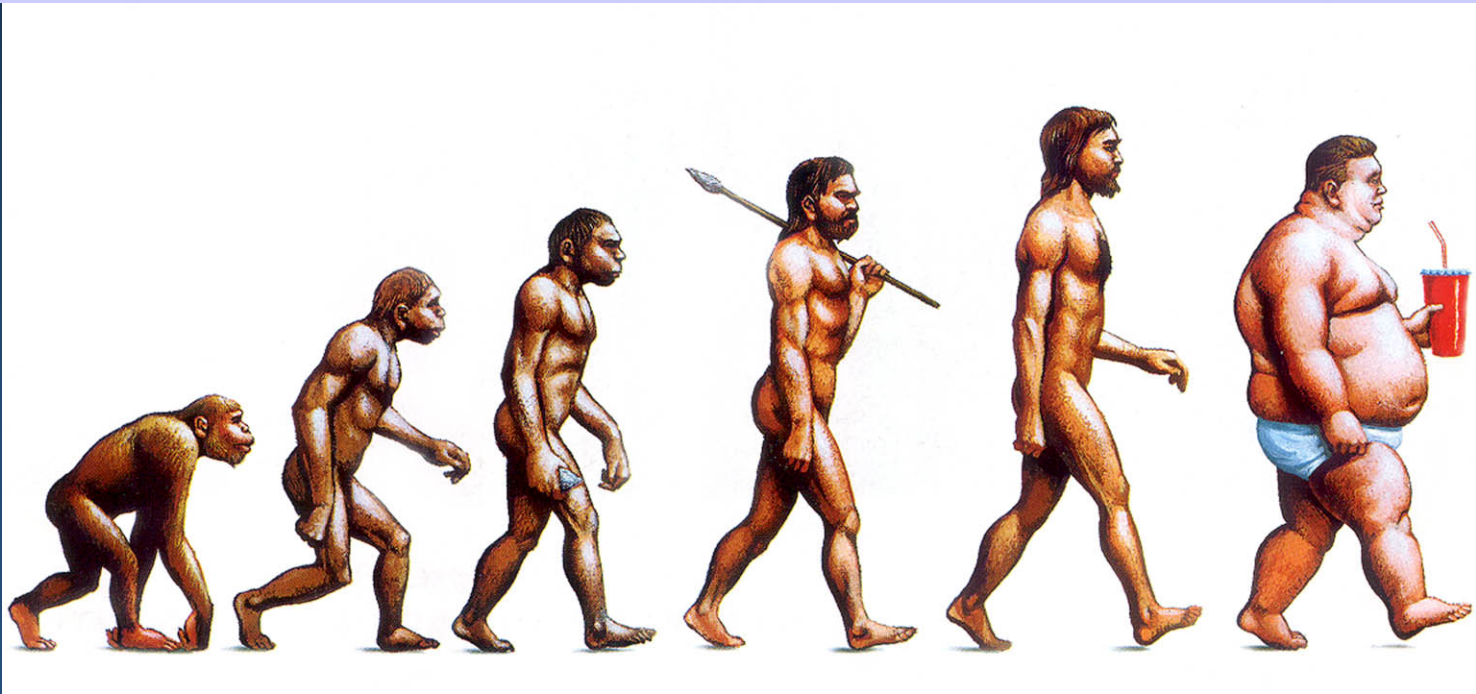


HOPE: N Eng J Med 2000;342:145-53 LIFE: Lancet 2002;359:995-1003 CHARM: Lancet 2003;362:759-66
 INSIGHT: Lancet 2000;356:366-72 ALLHAT: JAMA 2002;288:2998-3007 VALUE: Lancet 2004 ;362:2022-31
 Vijayaraghavan & Deedwania. Cardiol Clin 2005;23:165-83

Large multicenter trials in diabetes and prediabetes



The Future is Already Here!



上医医未病之病

中医医将病之病

下医医已病之病

~黄帝内经~

Superior doctors prevent the disease.

Mediocre doctors treat the disease before evident.

Inferior doctors treat the full blown disease.

-Huang Dee: Nai-Ching (2600 B.C. 1st Chinese Medical Text.)