ASSOCIAZIONE MEDICI DIABETOLOGI

3° CONVEGNO NAZIONALE
Centro Studi e Ricerche

Diabete e Sindrome Metabolica
Stato dell'arte

Stefano Genovese
UO di Endocrinologia e Diabetologia

ISTITUTO CLINICO
HUMANITAS
Istituto di Ricovero e Cura
a Carattere Scientifico

The Metabolic Syndrome: Time for a Critical Appraisal

Joint statement from the American Diabetes Association and the European Association for the Study of Diabetes

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Diabetes Care 28:2289–2304, 2005

AHA/NHLBI Scientific Statement

Diagnosis and Management of the Metabolic Syndrome

An American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement

Scott M. Grundy, MD, PhD, Chair; James I. Cleeman, MD, Co-Chair; Stephen R. Daniels, MD, PhD; Karen A. Donato, MS, RD; Robert H. Eckel, MD; Barry A. Franklin, PhD; David J. Gordon, MD, PhD, MPH; Ronald M. Krauss, MD; Peter J. Savage, MD; Sidney C. Smith, Jr, MD; John A. Spertus, MD; Fernando Costa, MD

(*Circulation*. 2005;112:0000-0000.)

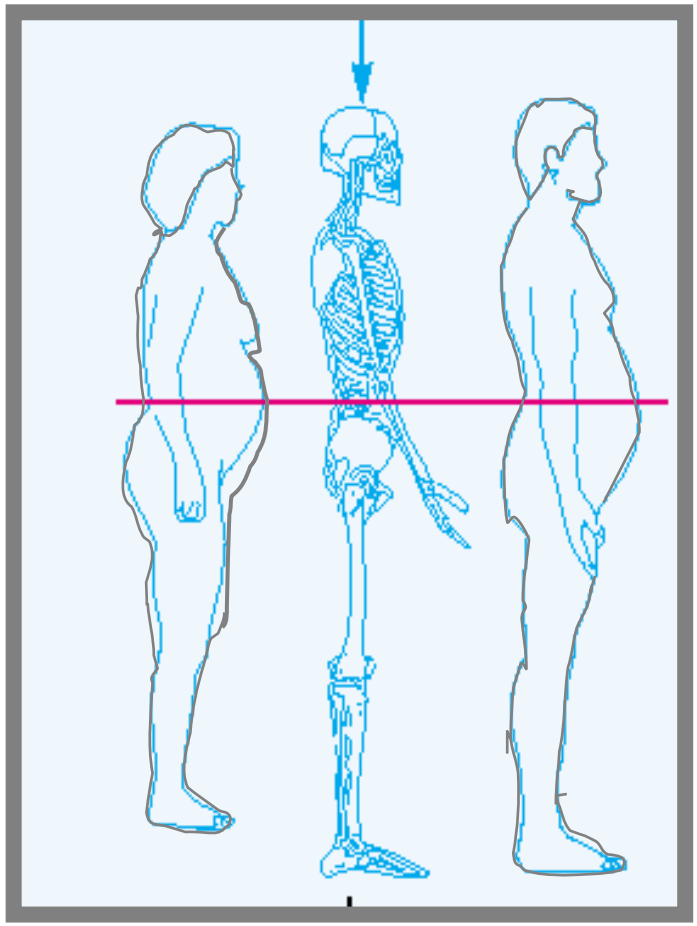
October 18, 2005

ADA & EASD Joint Statement

- Not enough information to define metabolic syndrome decisively
- Clinicians should evaluate and treat all CVD risk factors without regard to whether a patient meets the criteria for the diagnosis of metabolic syndrome
- Why is glucose intolerance (particularly diabetes) included in the definition of metabolic syndrome, since it appears to account for most, if not all, of the CVD predictive value?

The Metabolic Syndrome

- Constellation of major risk factors, life-habit risk factors and emerging risk factors
- Over-represented among populations with CHD
- Clue is distinctive body-type with increased abdominal circumference (although some leaner men and women with abdominal obesity without increased waist)



Caso Clinico

- A.M. maschio 52 anni
- Impiegato
- Sedentario
- Fumo (15 sigarette/giorno – ”light”)
- Dieta
  - Colazione: un caffè
  - Pranzo: un sandwich e una bibita, a volte ristorante
  - Cena: pasto completo con 2 bicchieri di vino e talvolta (una/due a settimana un superalcolico dopo cena)
- Familiarità di I grado per diabete mellito di tipo 2 e cardiopatia ischemica (padre)

Anamnesi

- Si presenta in ambulatorio di diabetologia per riscontro occasionale di iperglicemia (140 mg/dl), riferisce incremento ponderale di 12 kg in 10 anni da quando ha smesso di praticare attività fisica regolare.
- Riferisce riscontro di elevati valori di pressione arteriosa (150/95 mm Hg) nel corso di un check-up aziendale 5 anni prima; il MMG ha prescritto un β-bloccante che assume in modo discontinuo.

Esame Obiettivo

- Statura 1,78 m
- Peso 90 kg
- BMI 28,4 kg/m^2
- Circonferenza vita 103 cm
- Pressione arteriosa 158/92 mm Hg
- Frequenza cardiaca 66 r

ISTITUTO CLINICO HUMANITAS

Accertamenti

1. Esami ematochimici
   - glicemia, emoglobina glicata, colesterolo totale e HDL, trigliceridi, emocromo, creatinina, sodio, potassio
2. Microalbuminuria
3. Elettrocardiogramma

Risultati

- Glicemia basale 138 mg/dl
- Emoglobina glicata 7,5%
- Trigliceridi 220 mg/dl
- Colesterolo totale 270 mg/dl
- HDL 36 mg/dl
- LDL 190 mg/dl*
- Microalbuminuria (A/C ratio) 40 mg/g
- ECG: ipertrofia ventricolare sinistra (Sokolow-Lyon)

* Friedwald formula

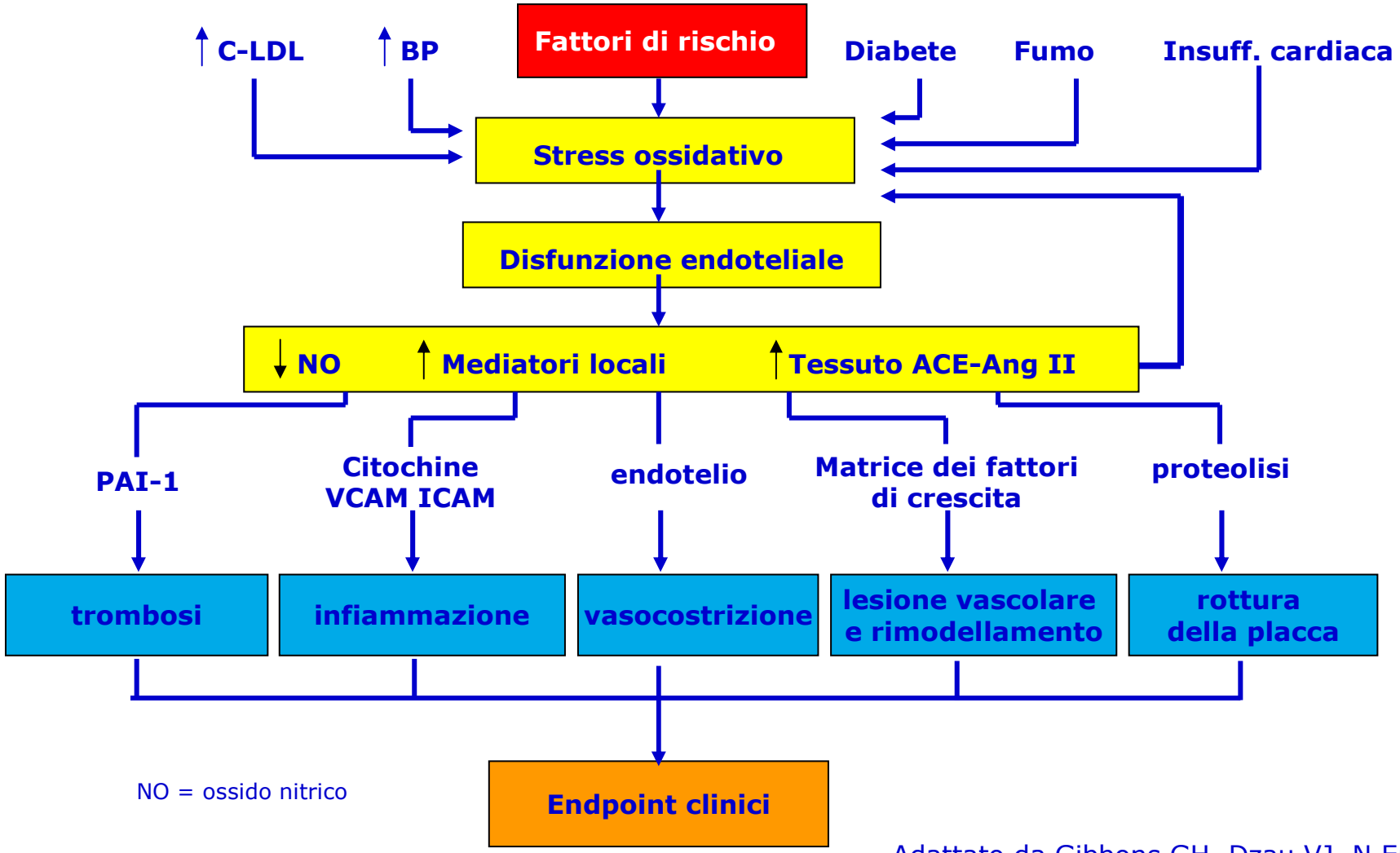
ISTITUTO CLINICO HUMANITAS

Fattori di rischio per la patologia cardiovascolare

- Modificabili
  - Fumo
  - Dislipidemia
    - Elevato C-LDL
    - Ridotto C-HDL
    - Elevati trigliceridi
  - Ipertensione
  - Diabete mellito
  - Obesità
  - Fattori dietetici
  - Fattori trombogenici
  - Scarso esercizio fisico
  - Eccessivo consumo di alcool
- Non modificabili
  - Anamnesi di CHD
  - Storia familiare di CHD
  - Età
  - Sesso

Adattato da: Pyörälä K et al. Eur Heart J 1994;15:1300–1331.

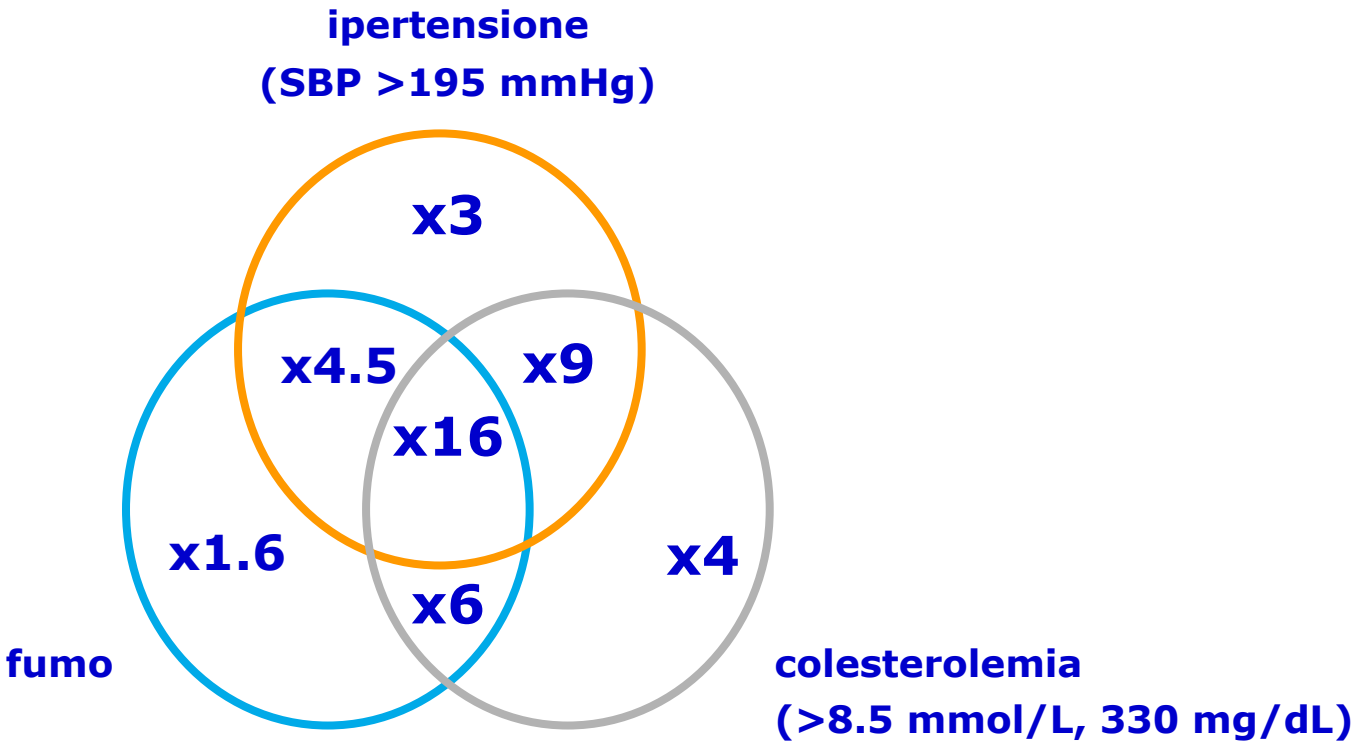
La progressione dai fattori di rischio cardiovascolare al danno endoteliale e agli eventi clinici



NO = ossido nitrico

Adattato da Gibbons GH, Dzau VJ. N Engl J Med 1994;330;1431–1438.

Livelli di rischio associati a fumo, ipertensione e ipercolesterolemia



Adattato da Poulter N *et al.*,1993

Diagnosi

- Diabete mellito di tipo 2
- Sovrappeso corporeo con distribuzione centrale dell'adipe
- Dislipidemia mista
- Ipertensione con microalbuminuria

(Sindrome Metabolica)

- Cardiopatia ipertensiva

Classificazione delle malattie, dei traumatismi, degli interventi chirurgici e delle procedure diagnostiche e terapeutiche

Versione Italiana della ICD-9-CM
International Classsification of Disease - 9th Revision - Clinical Modification - 2002

277.7 Sindrome X dismetabolica

Utilizzare un codice aggiuntivo per condizioni associate, come:

- malattie cardiovascolari (414.00 - 414.05)
- obesità (278.00 - 278.01)

The metabolic syndrome

WHO 1999*

Type 2 DM or IGT or insulin resistance with NGT

+

Two factors including:

Central obesity

Dyslipidemia

Hypertension

Microalbuminuria

ATP III 2001**

Three or more factors including:

Central obesity

M waist >102 cm

F waist >88 cm

Triglycerides $\geq$150 mg/dl

HDL cholesterol

M <40 mg/dl

F <50 mg/dl

BP $\geq$130/$\geq$85 mm Hg

FPG $\geq$110 mg/dl

*Report of WHO Consultation. Part 1. Department of Non communicable diasease Surveillance, Geneva 1999

**Expert Panel on Detection Evaluation and Treatment of High Blood Cholesterol in Adults JAMA 2001; 285: 2486-97

Definitions of the metabolic syndrome – IDF Consensus (2005)

- **Central obesity:** waist circumference ≥94 cm for Europid men ≥80 cm for Europid women, with ethnicity-specific values for other groups, **plus any two of the following four factors**:
  - **raised TG:** ≥1.7 mmol/L (150 mg/dL) or specific treatment for this lipid abnormality
  - **reduced HDL-C:** <1.0 mmol/L (40 mg/dL) in males and <1.3 mmol/L (50 mg/dL) in females or specific treatment for this lipid abnormality
  - **raised blood pressure:** ≥130/85 mmHg or treatment of previously diagnosed hypertension
  - **raised fasting plasma glucose:** ≥5.6 mmol/L (100 mg/dL) or previously diagnosed type 2 diabetes

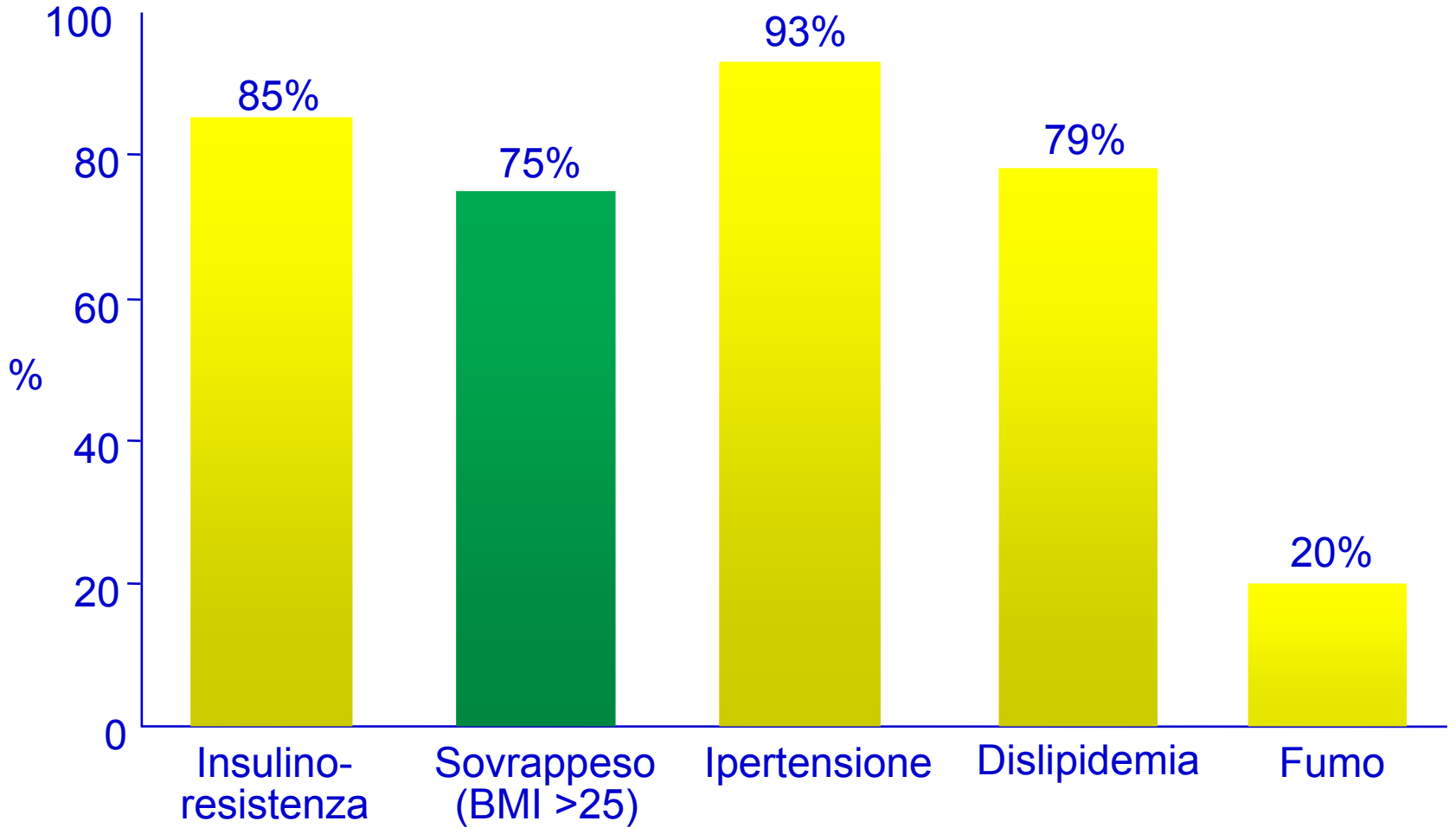
IDF Consensus Worldwide Definition of the Metabolic Syndrome. Available from: URL: www.idf.org/webdata/docs/IDF_Metasyndrome_definition.pdf

Metabolic Syndrome or "Central Obesity Syndrome?"

Gary TC Ko Diabetes Care 39: 752, 2006

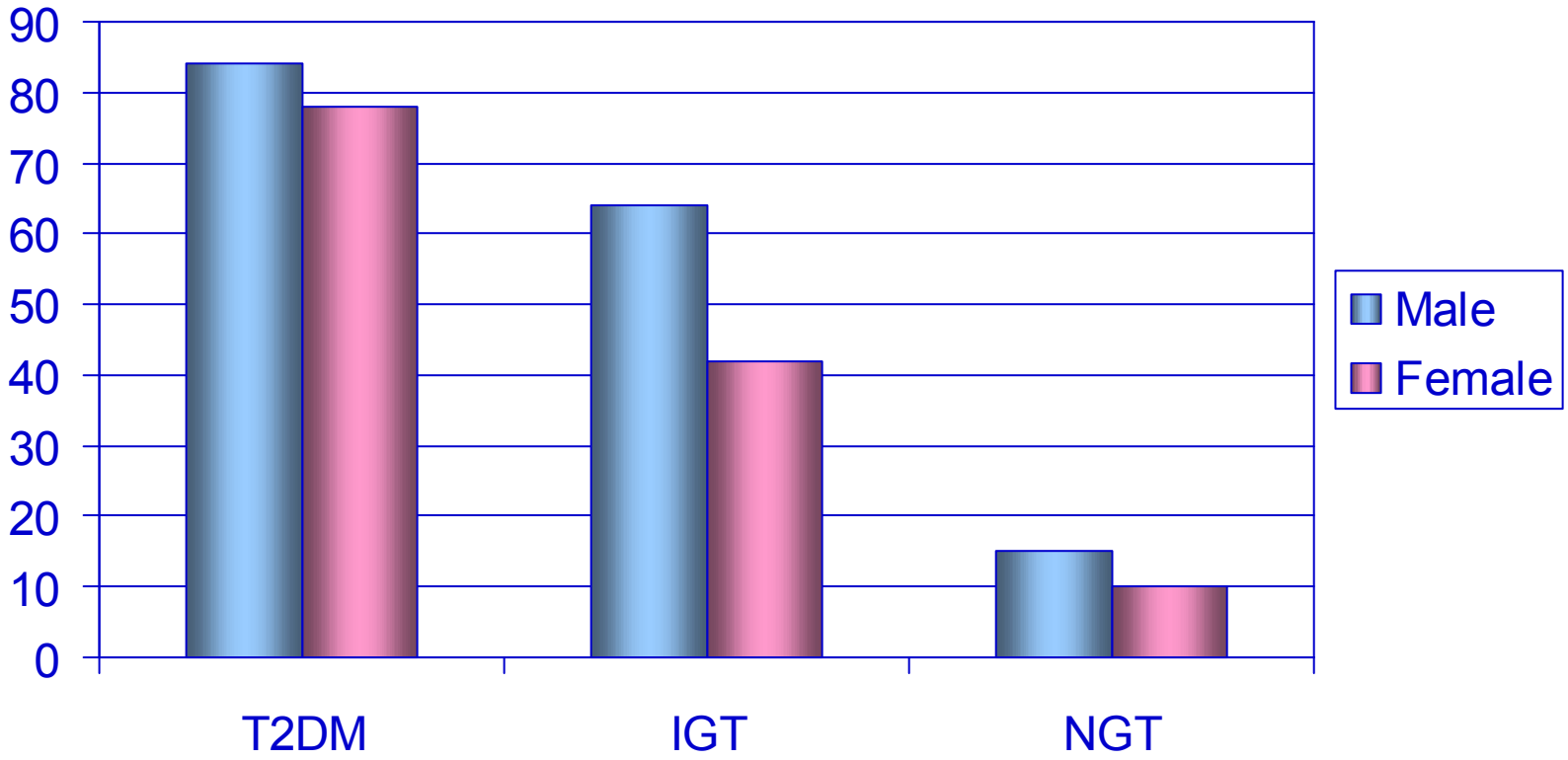
Prevalenza di fattori di rischio non glicemici nel diabete mellito di tipo 2

Verona NIDDM Complication Study



Prevalence of the Metabolic Syndrome

Botnia Study: 4,483 subjects (aged 35-70 years)

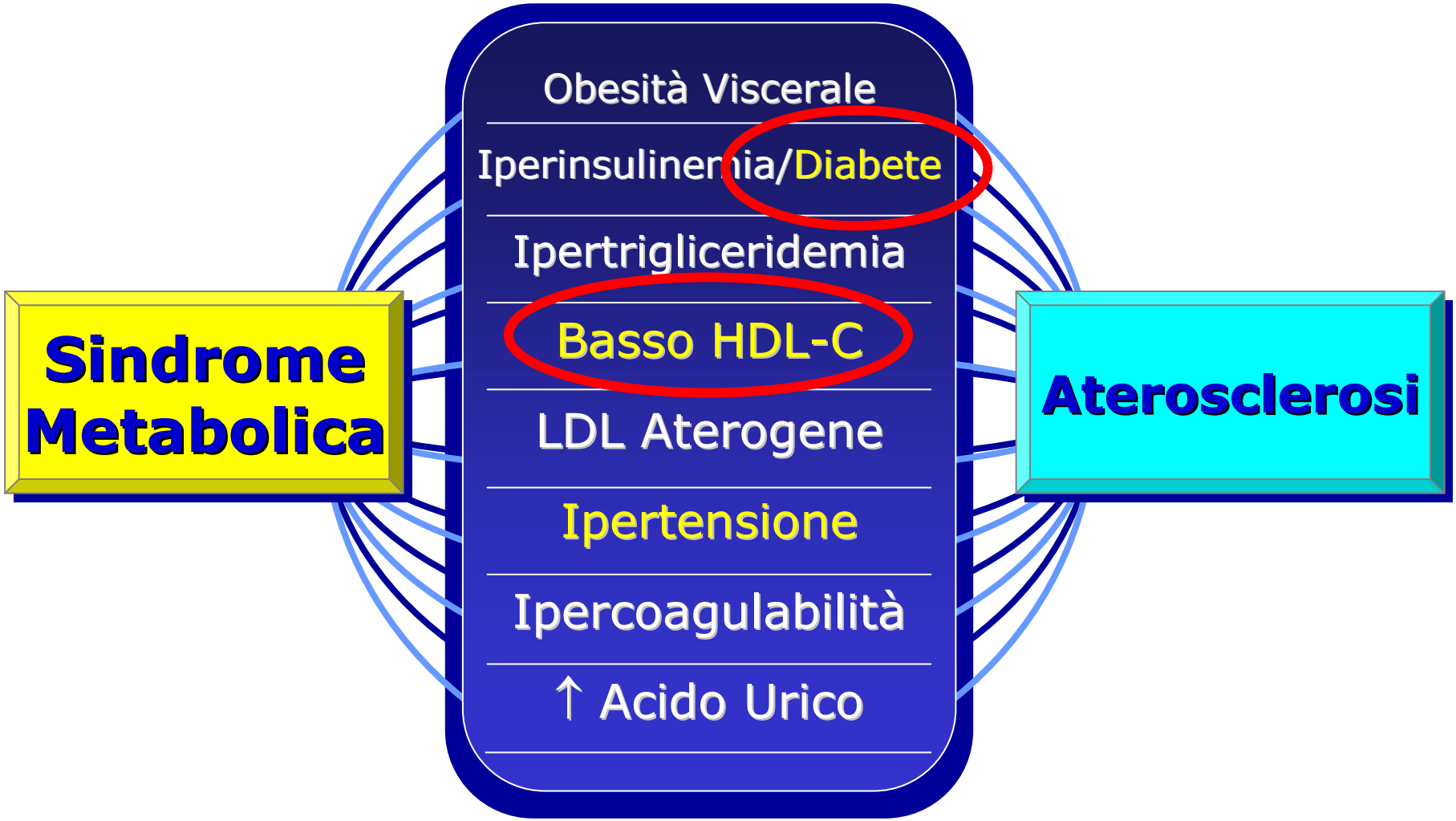


Isomaa B et al. Diabetes Care 2001; 24: 683-9

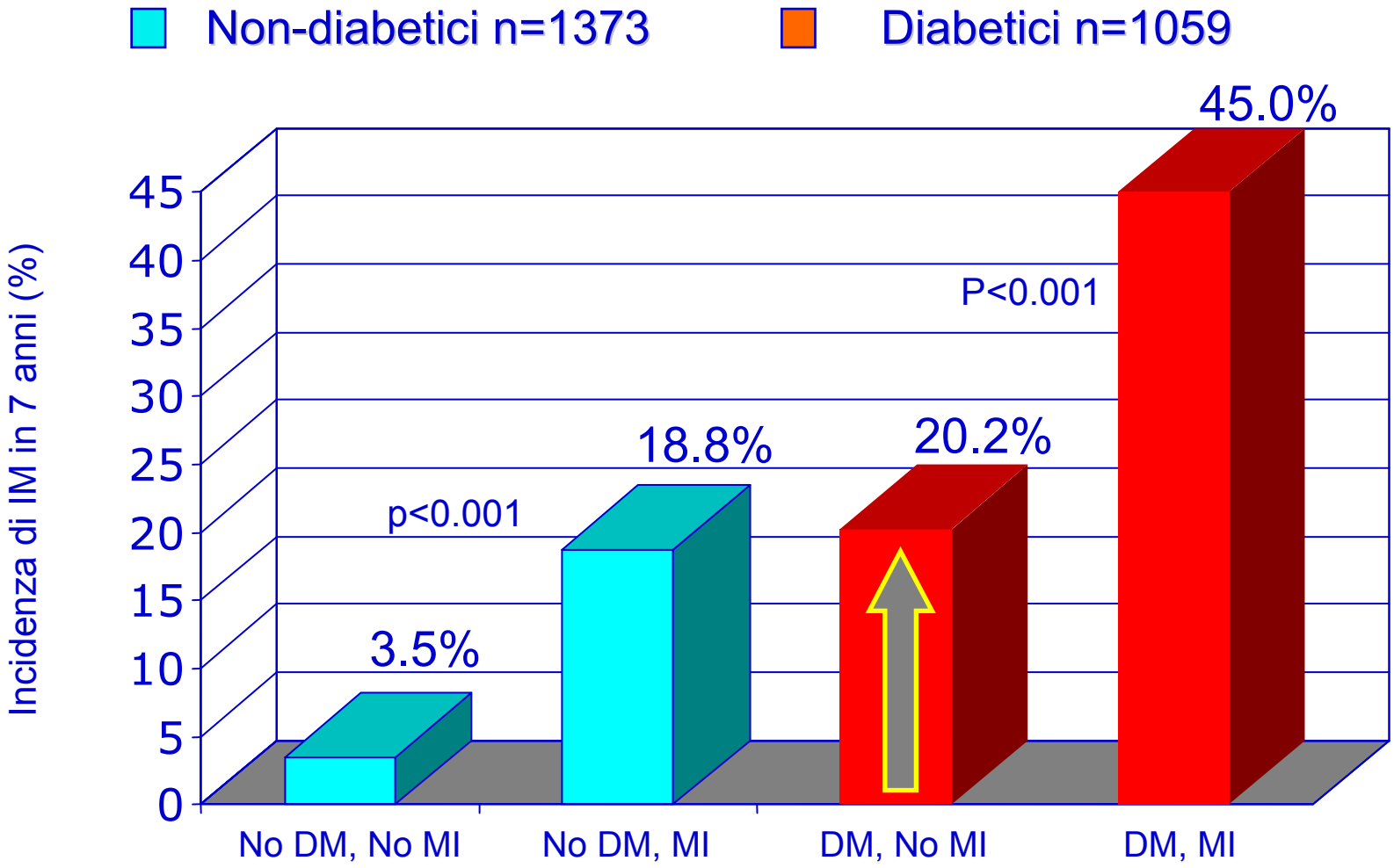
RISCHIO CARDIOVASCOLARE GLOBALE E SINDROME METABOLICA

- FATTORI DI RISCHIO MULTIPLI
  - TRADIZIONALI
  - NON TRADIZIONALI
- MORBIDITA' E MORTALITA' CARDIO-VASCOLARE
- SINDROME METABOLICA E TAVOLE DEL RISCHIO (Framingham e Progetto Cuore)

Sindrome Metabolica e Aterosclerosi



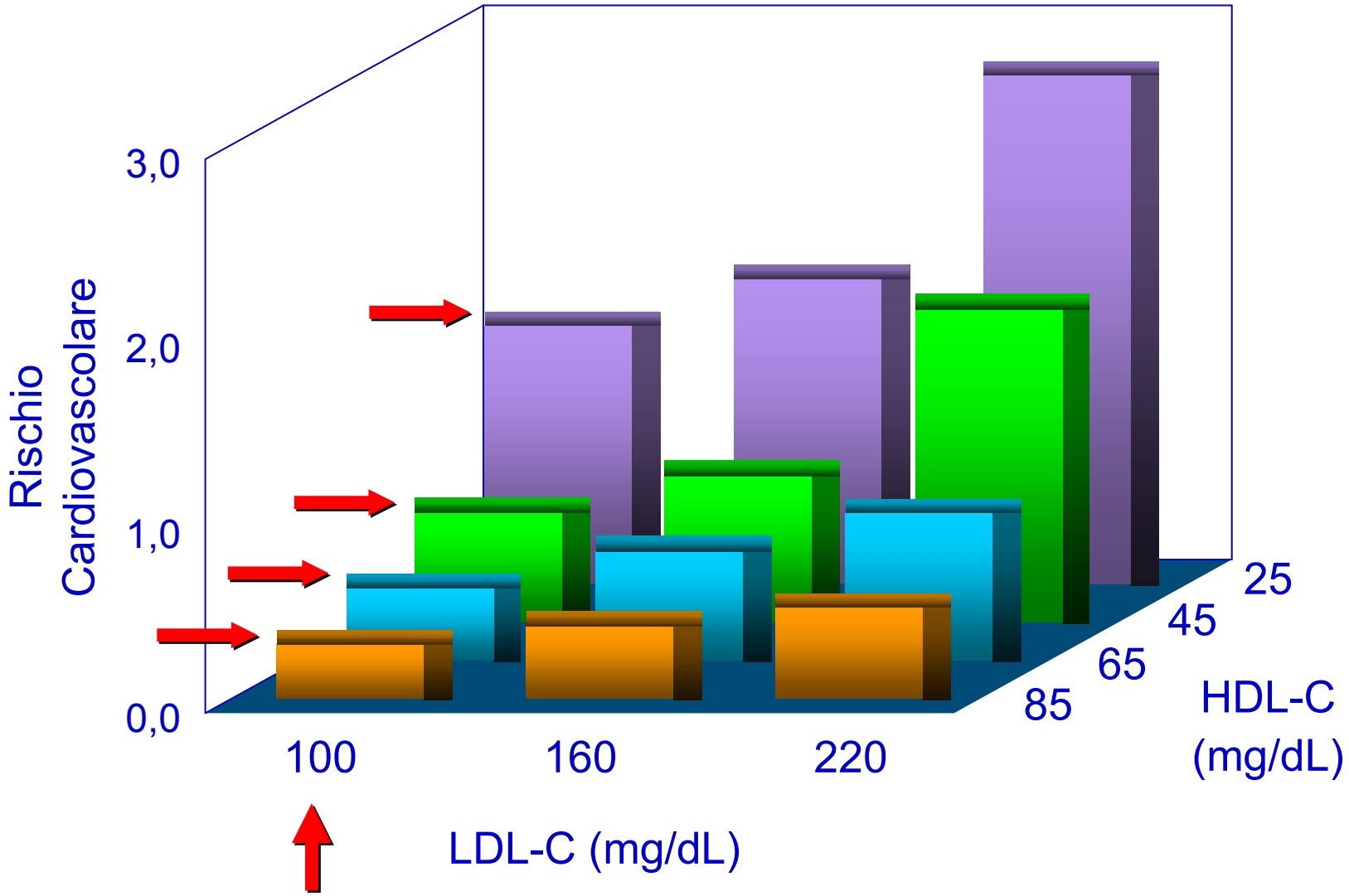
Diabete di Tipo 2 e Malattia Coronarica
Incidenza di IMA Fatale/Non fatale in 7 aa (East West Study)



DM - diabete mellito
IM - infarto del miocardio

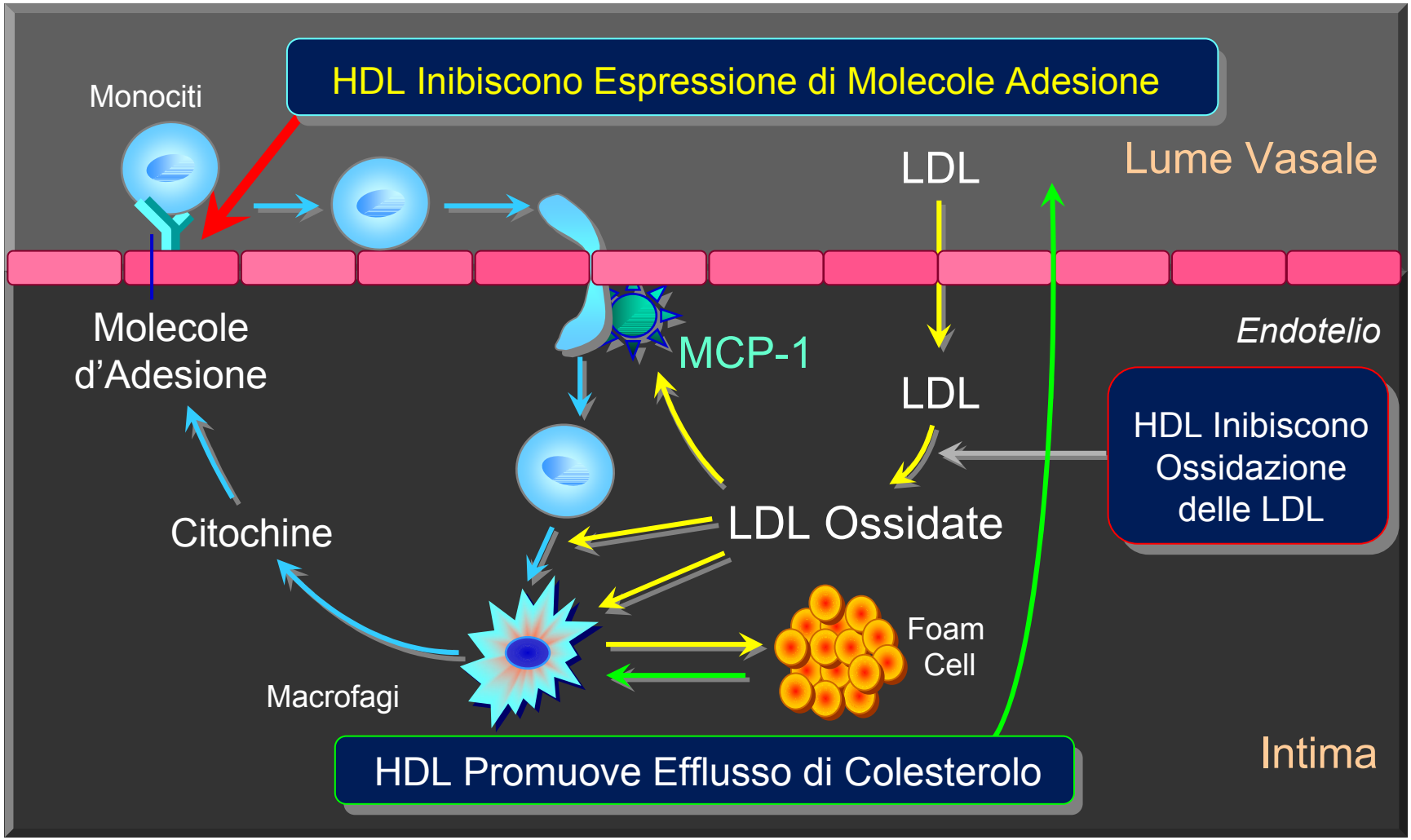
Haffner, et al. *N Engl J Med* 1998;339:229-234

Basso HDL-C è un fattore predittivo indipendente di rischio cardiovascolare anche a bassi livelli di LDL-C



Gordon T et al. Am J Med 1997;62:707-714.

HDL: Effetti Antiaterogeni



Cockerill GW et al. Arterioscler Thromb Vasc Biol 1995;15:1987-1994.

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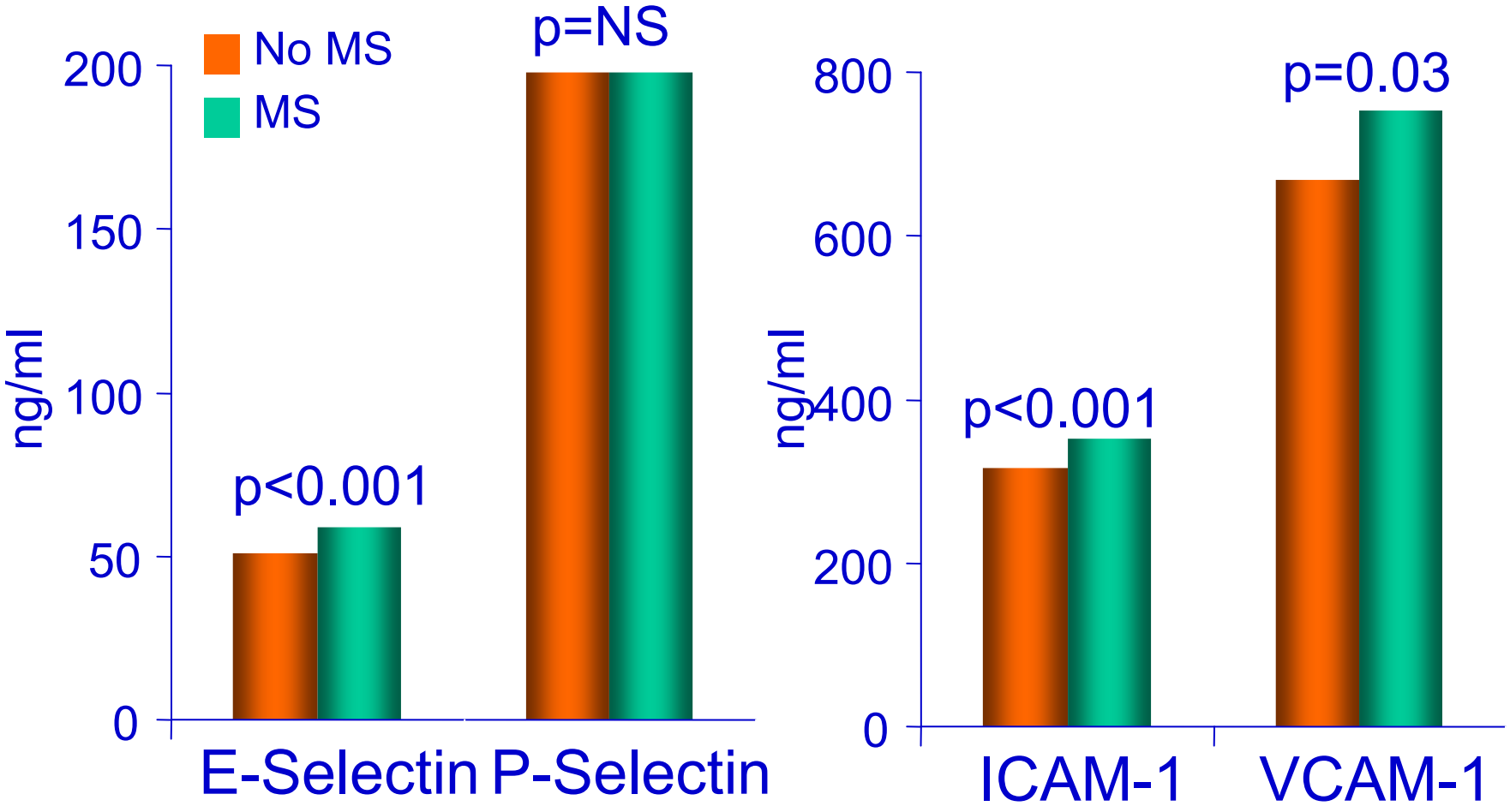
Ancillary Features of the Metabolic Syndrome
ENDOTHELIAL ADHESION MOLECULES
(Bruneck Study; Bonora et al; Int J Obes 27:1283, 2003)

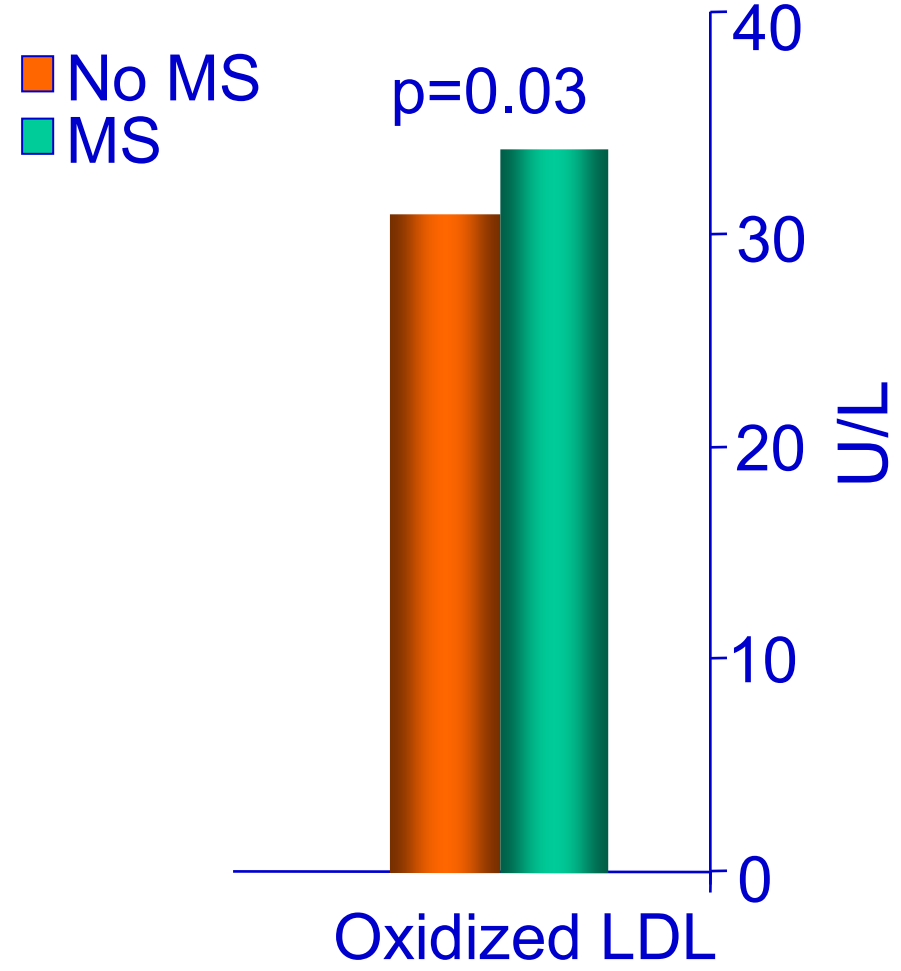


Adjusted for sex, age, smoking, alcohol, physical activity, social status

Ancillary Features of the Metabolic Syndrome

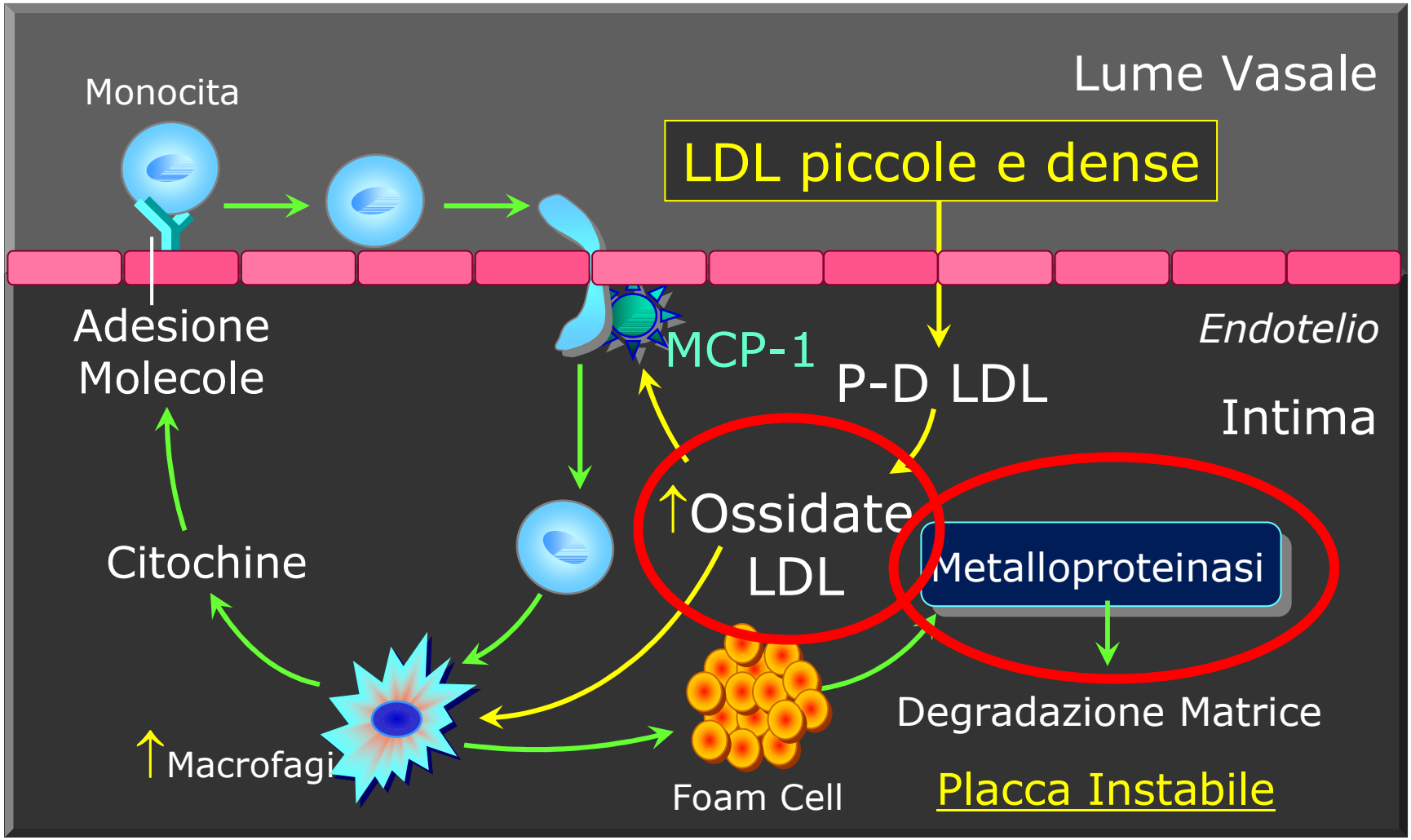
OXIDIZED LDL

(Bruneck Study; Bonora et al; Int J Obes 27:1283, 2003)



Adjusted for sex, age, smoking, alcohol, physical activity, social status

LDL piccole e dense e Placca Aterosclerotica Instabile

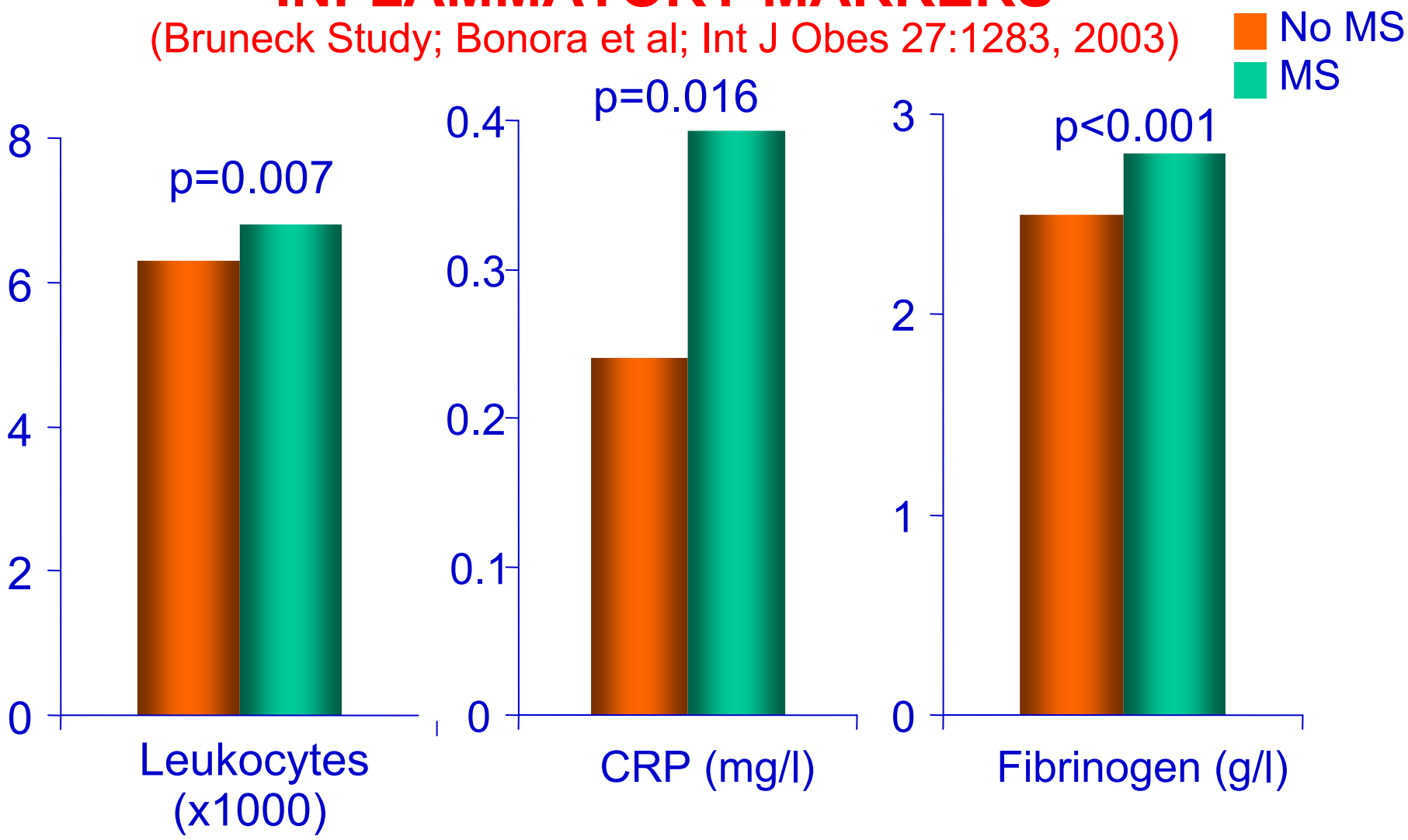


Ross R. *N Engl J Med* 1999;340:115-126.

Ancillary Features of the Metabolic Syndrome

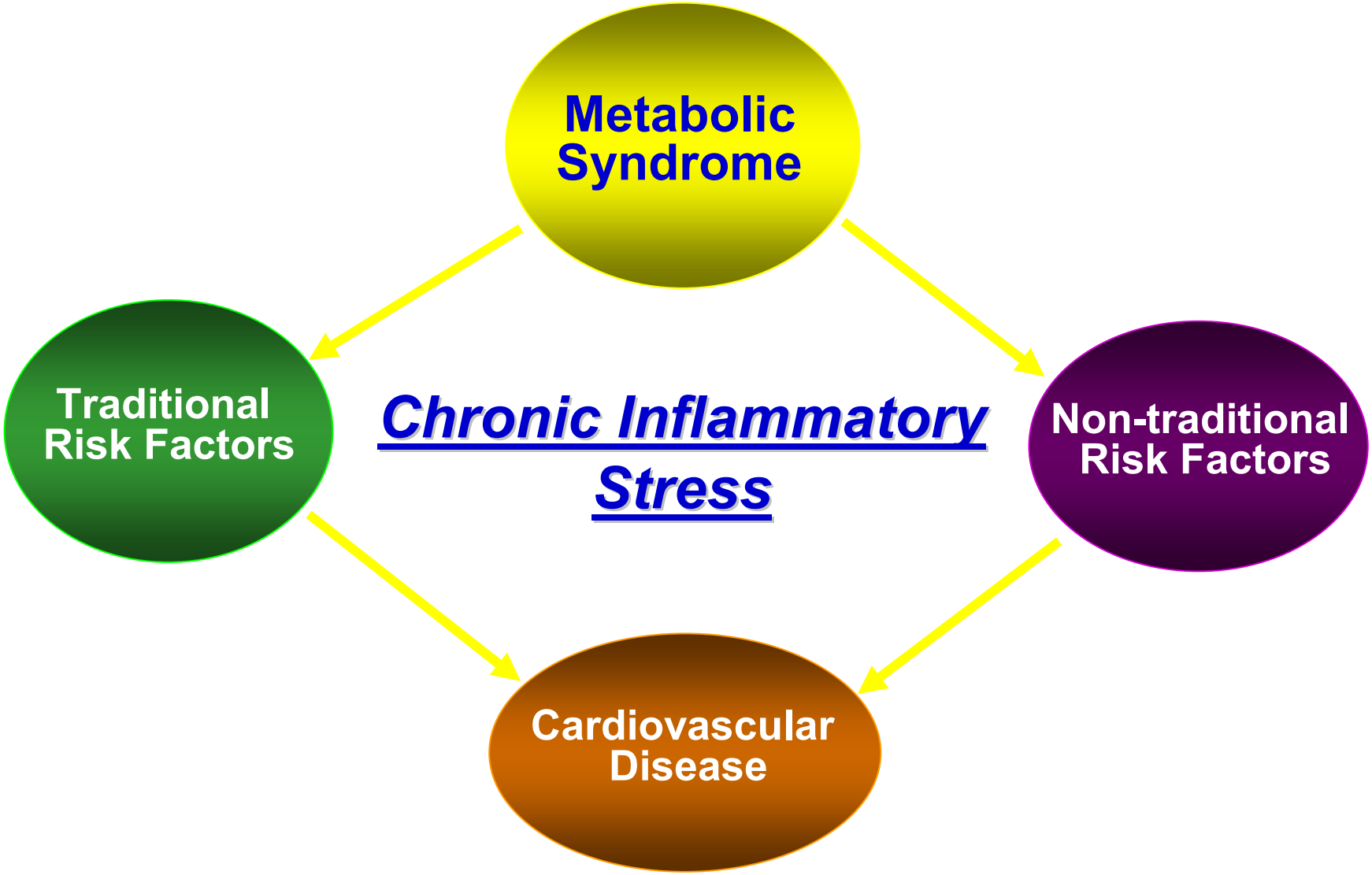
INFLAMMATORY MARKERS

(Bruneck Study; Bonora et al; Int J Obes 27:1283, 2003)



Adjusted for sex, age, smoking, alcohol, physical activity, social status

The Several Routes from the Metabolic Syndrome to Cardiovascular Disease



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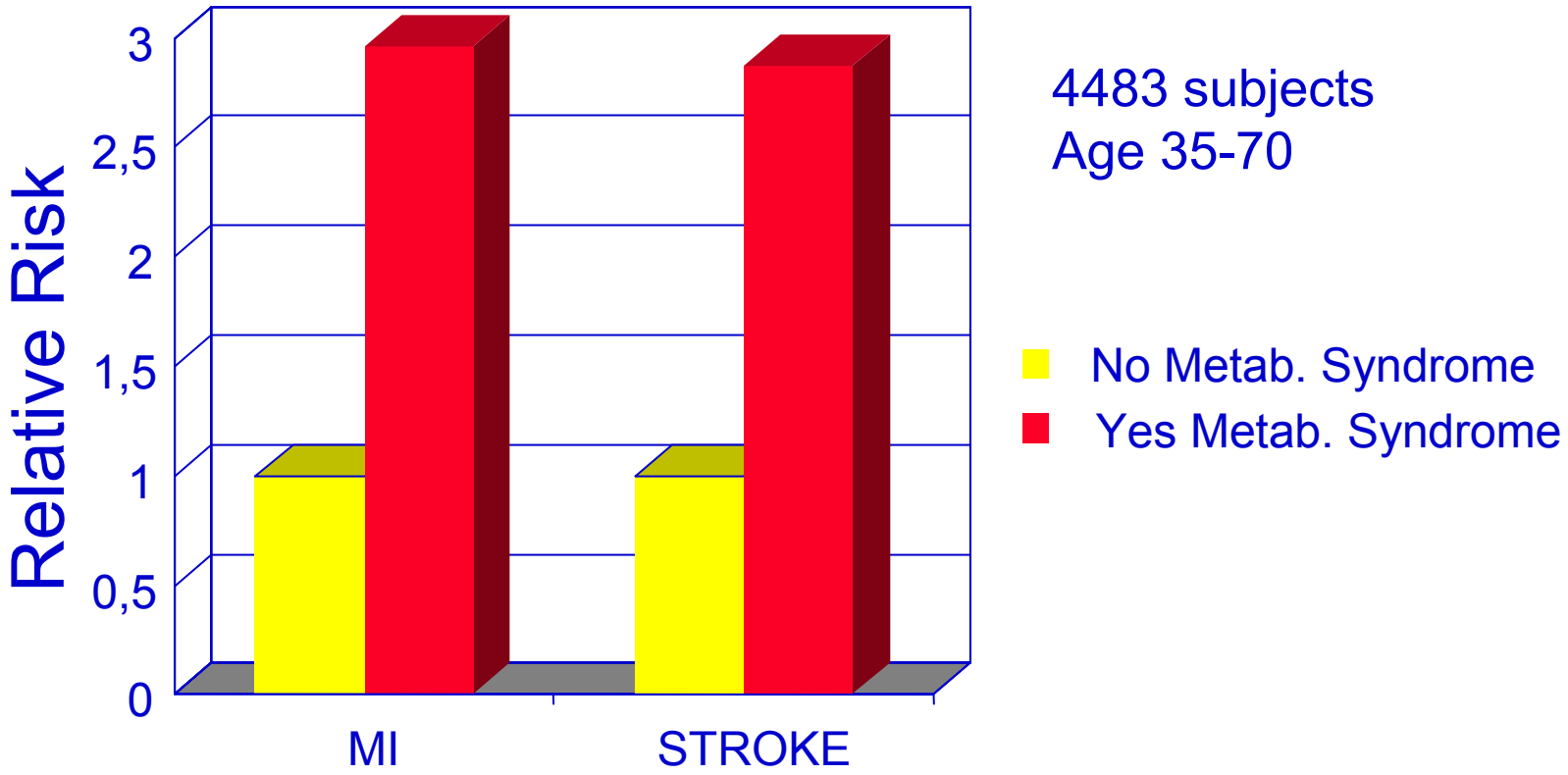
Relative Risk of MI and Ischemic Stroke in Relation to the Plurimetabolic Syndrome

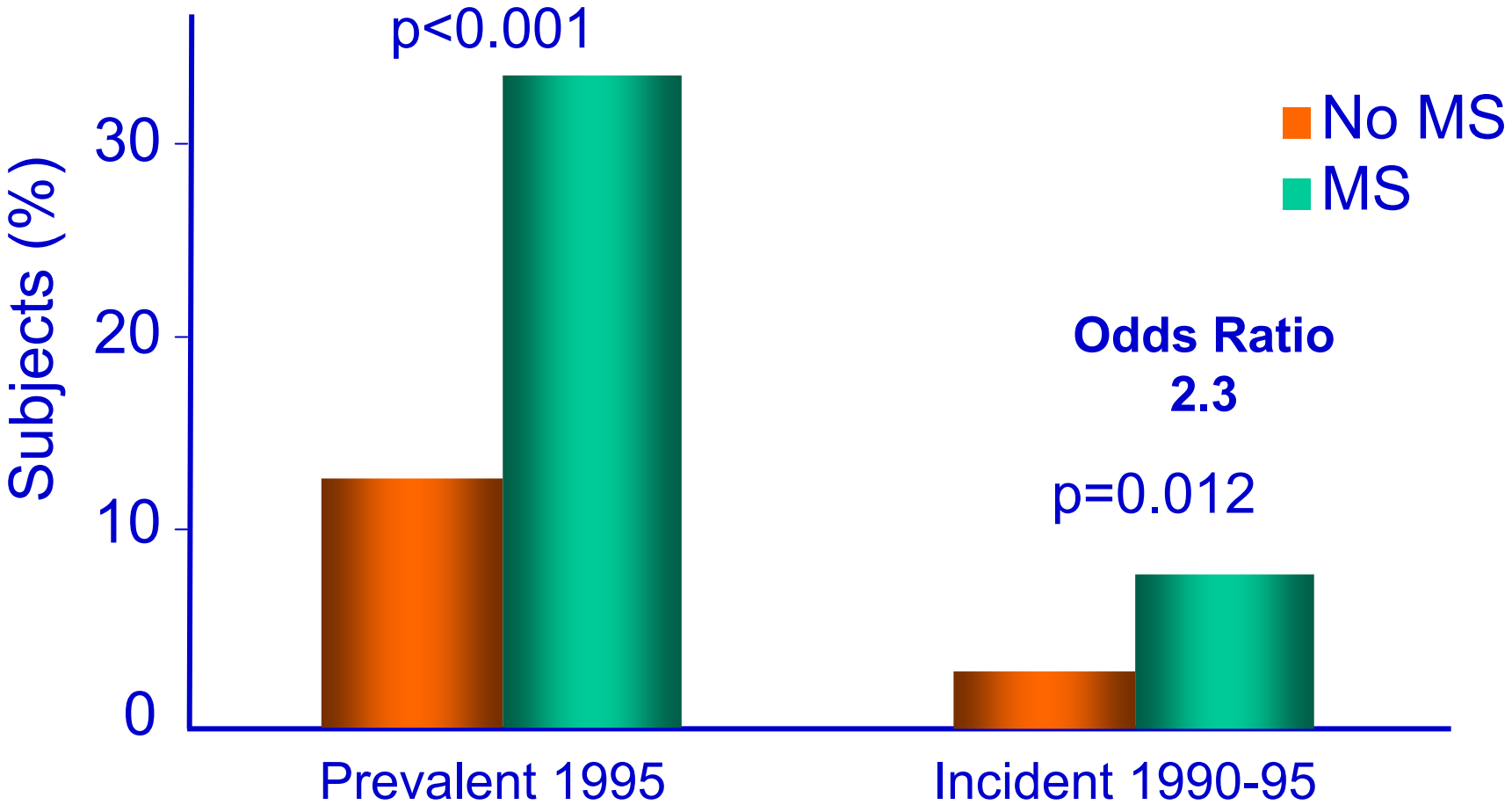
(The Botnia Study)



(Groop, Taskinen et al. Diabetes Care 2001)

Coronary Heart Disease in the Metabolic Syndrome

(Bruneck Study; Bonora et al, Diabetes Care 26:1251, 2003)



Adjusted for sex, age, smoking, alcohol, physical activity, social status, LDL cholesterol, baseline CHD

Cardiovascular Mortality Associated with the Metabolic Syndrome

- Cardiovascular mortality was markedly increased in subjects with the metabolic syndrome (12.0 vs 2.2% $p<0.001$)
- Microalbuminuria conferred the strongest risk of cardiovascular death (RR 2.80; $p=0.002$)

Isomaa B et al. Diabetes Care 2001; 24: 683-9

- The Metabolic Syndrome is extremely common among subjects of mature-advanced age.

- The clinical phenotype of the Syndrome is very complex and includes a constellation of non-metabolic abnormalities documenting a mild chronic inflammatory state, an increased oxidative stress, a pro-coagulant state, an endothelial dysfunction, and a steato-hepatitis.

- Obesity and insulin resistance are common denominators of most of classic and non-classic clinical features of the Syndrome.

- Subjects with the Syndrome have an increased risk of atherosclerosis and clinical cardiovascular disease.

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Estimated Cardiovascular Risk
(Framingham)

54,8% in 10 years

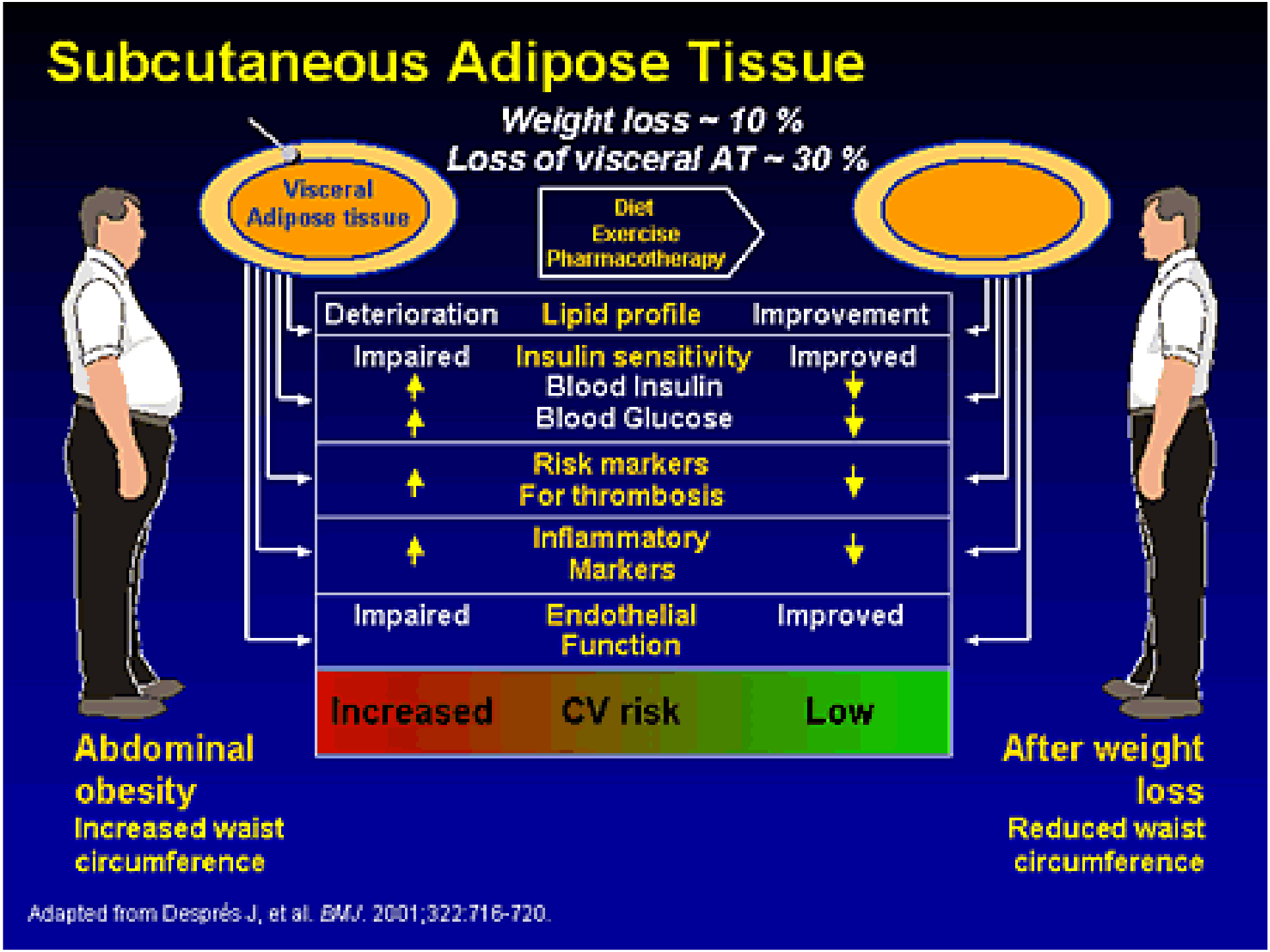
ISTITUTO CLINICO HUMANITAS

Estimated Cardiovascular Risk
(Progetto Cuore)

28.3% in 10 years

ISTITUTO CLINICO HUMANITAS

Subcutaneous Adipose Tissue



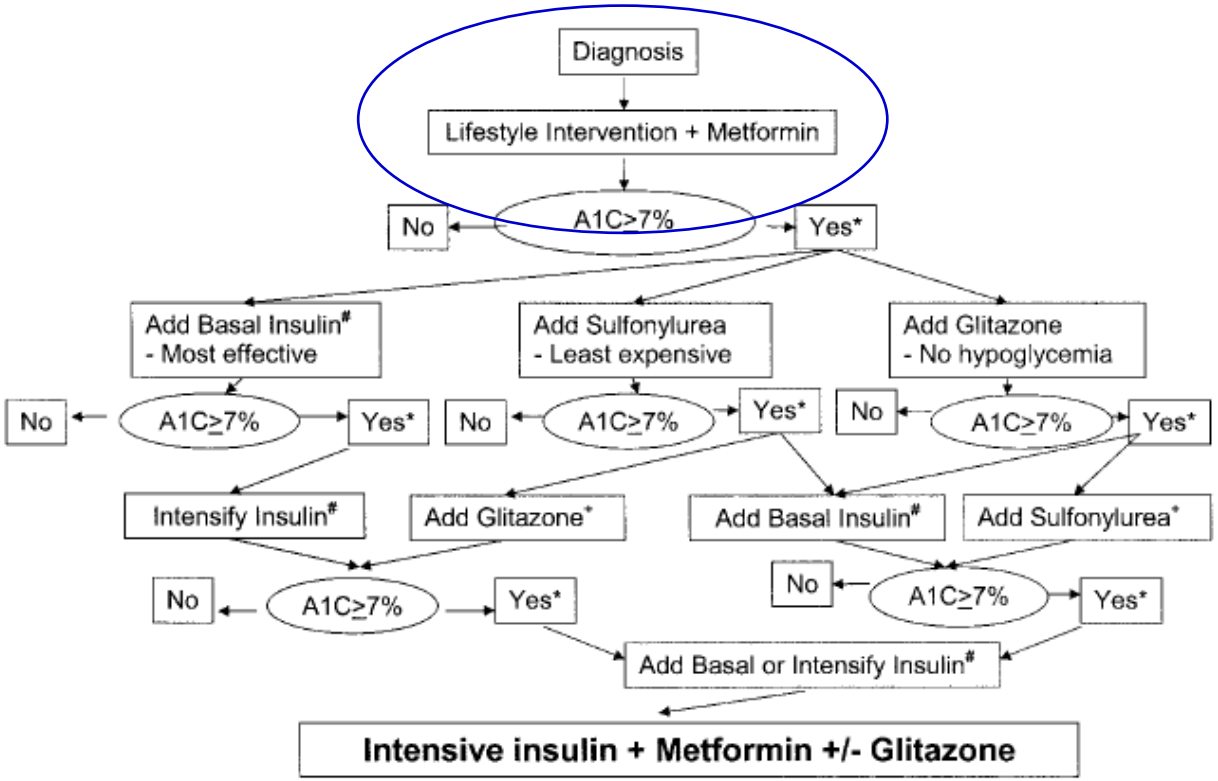
Adapted from Després J, et al. *BMJ*. 2001;322:716-720.

Therapy

- TLC (Therapeutic Lifestyle Changes)
  - *Stop smoking*
  - *Diet*
  - *Physical activity*
- Metformin + TZD
- ACE-inhibitors / ARBs
- Statin

Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy

A consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes



Diabetes Care 2006, 29: 1963

Metabolic Benefits of Weight Loss

- Reverse changes of insulin resistance and metabolic syndrome
- Raise HDL-C (can see increase of 1.6 mg/dl from a 10-lb weight loss)

Dattilo AM et al. *Am J Clin Nutr* 1992;56:320-328.

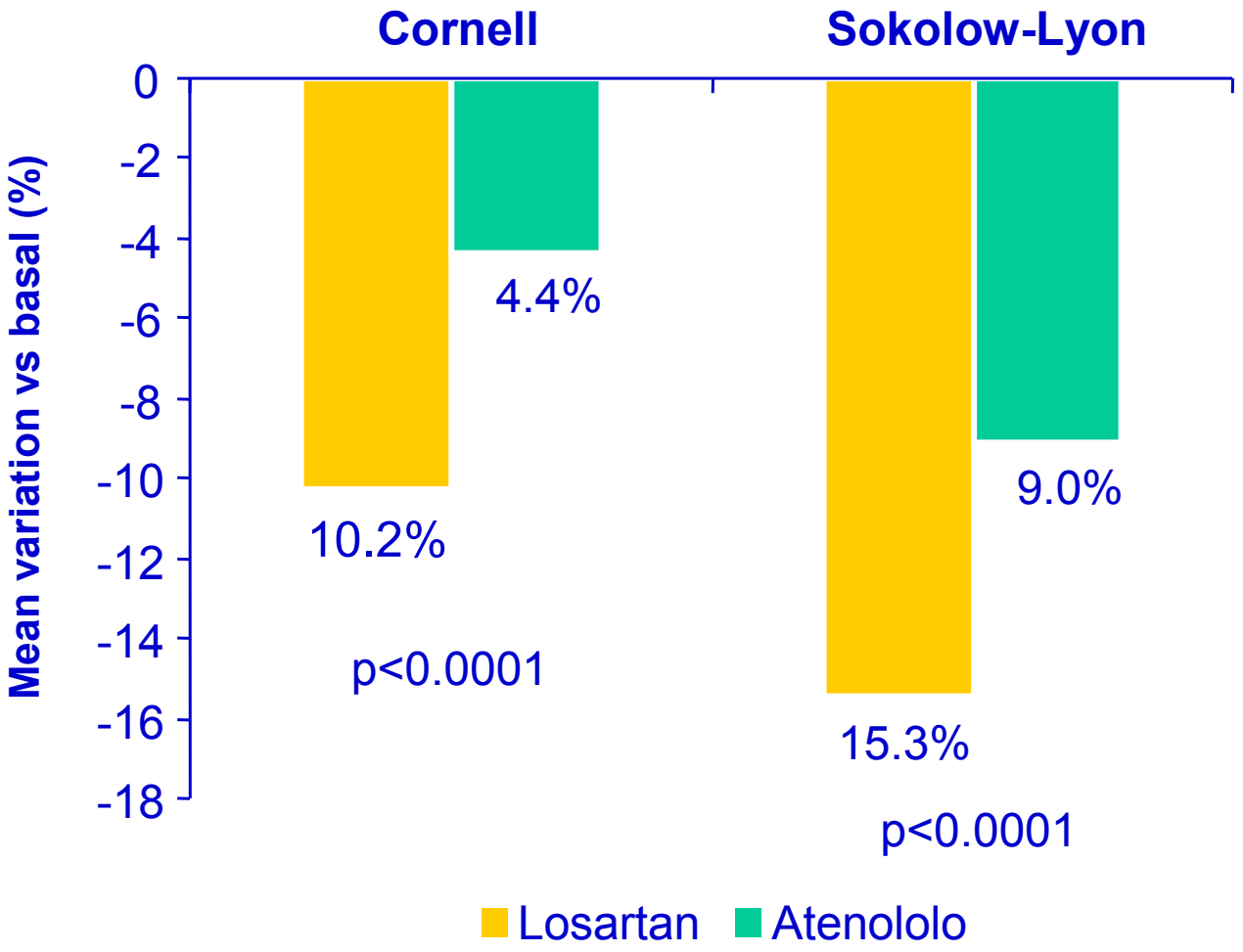
Metformin in Overweight Patients UKPDS

- compared with conventional policy
  - 32% risk reduction in any diabetes-related endpoints p=0.0023
  - 42% risk reduction in diabetes-related deaths p=0.017
  - 36% risk reduction in all cause mortality p=0.011
  - 39% risk reduction in myocardial infarction p=0.01

I Tiazolidinedioni

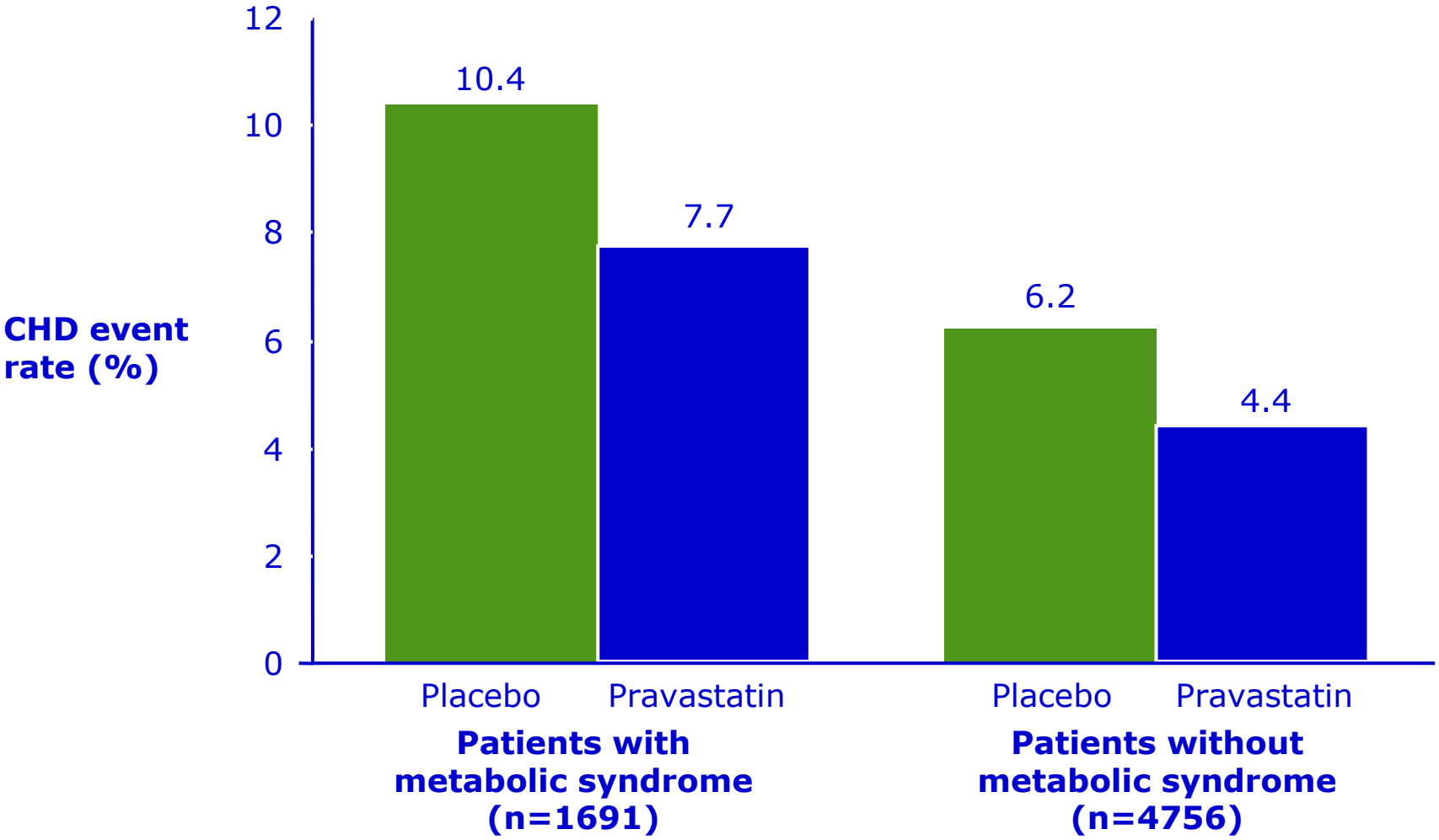
- Aumentano i piccoli adipociti nel tessuto sottocutaneo
  - Riducono FFA circolanti
  - Riducono la lipotossicità
  - Riducono l'insulino-resistenza
- Agiscono sull'endotelio
  - Riducono l'adesione dei monociti
  - Riducono l'infiammazione
  - Riducono la formazione di placche
- … abbassano la glicemia!

LIFE: Regression of LVH



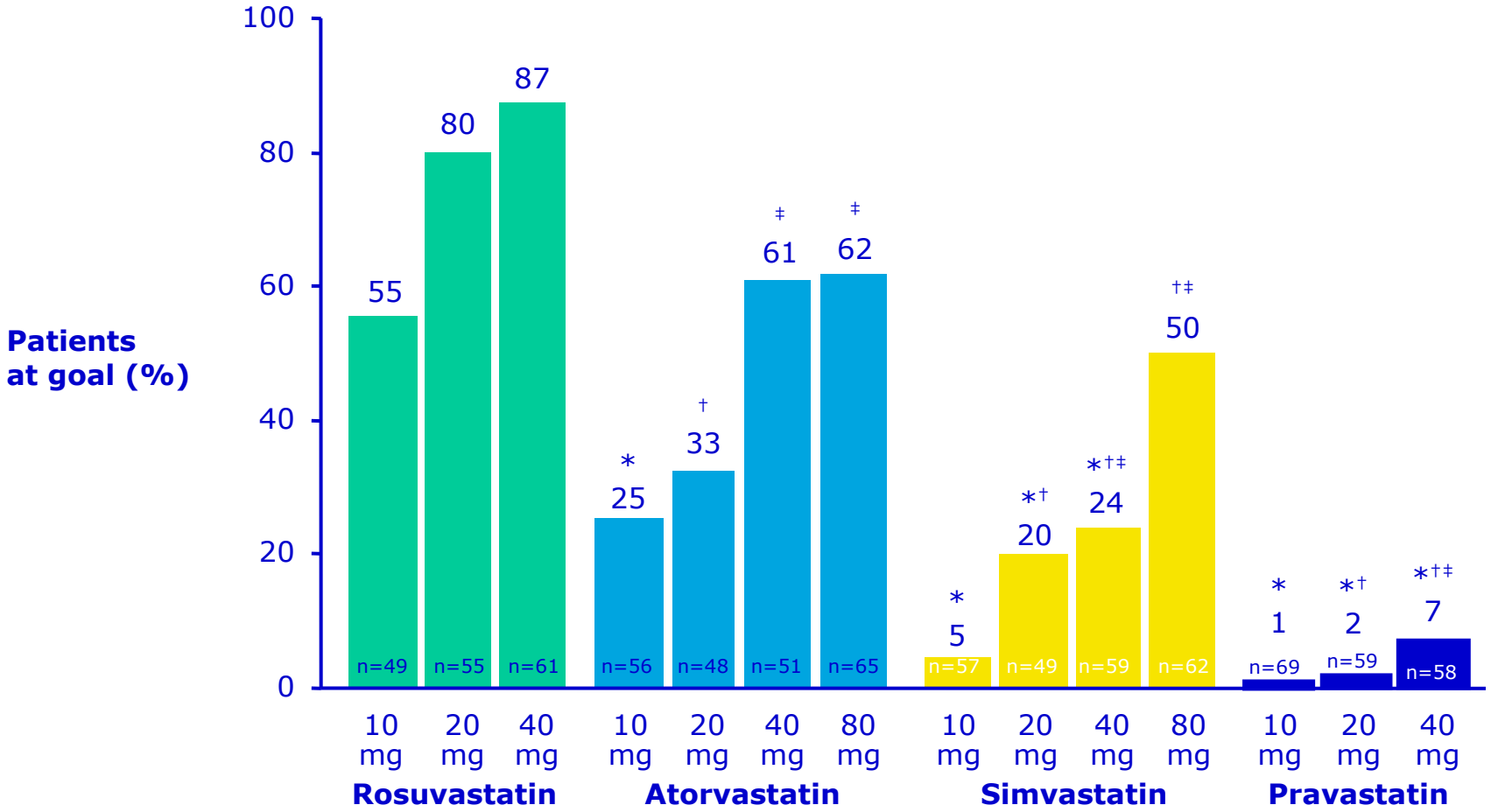
Dahlöf B et al *Lancet* 2002;359:995-1003.

Reduction in CHD event rates with statin treatment (WOSCOPS)



CHD=coronary heart disease; WOSCOPS=West of Scotland Coronary Prevention Study
Sattar N et al. *Circulation* 2003; 108: 414–419

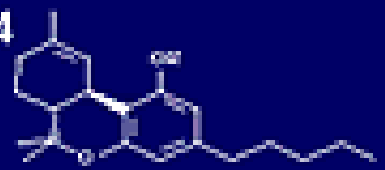
STELLAR – achievement of LDL-C goal <2.6 mmol/L (100 mg/dL) by patients with the metabolic syndrome



STELLAR=**S**tatin **T**herapies for **E**levated **L**ipid **L**evels compared **A**cross doses to **R**osuvastatin;
LDL-C=low-density lipoprotein cholesterol
*p<0.002 vs rosuvastatin 10 mg; †p<0.002 vs rosuvastatin 20 mg; ‡p<0.002 vs rosuvastatin 40 mg
Deedwania P et al. *Am J Cardiol* 2005; 95: 360–366

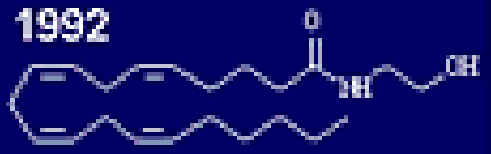
Cannabinoid Receptors

1964

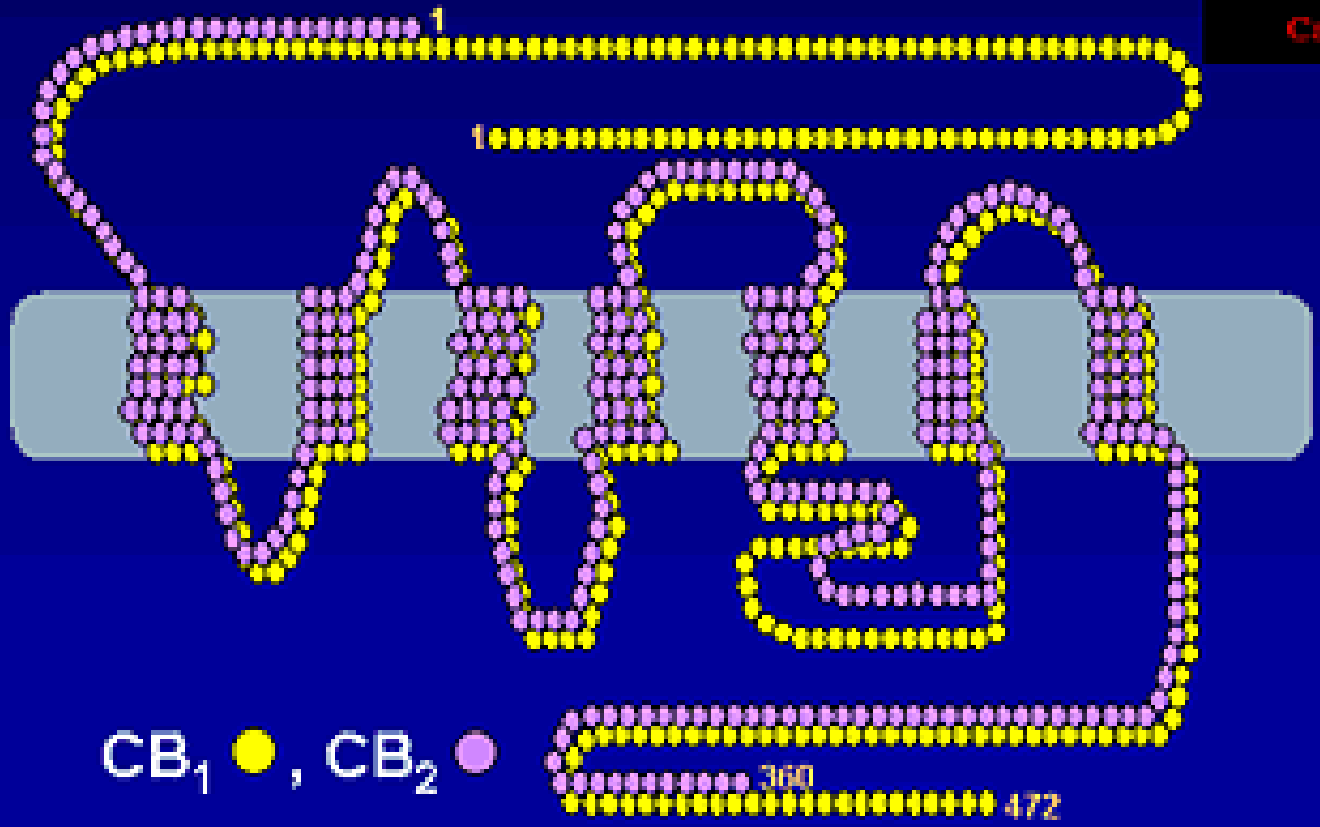


Δ^9-Tetrahydrocannabinol

1992



Anandamide



CB_1 ●, CB_2 ●

- Hippocampus
- Basal ganglia
- Cortex
- Cerebellum
- Hypothalamus
- Limbic structures
- Brainstem
- Adipocytes
- GI Tract
- Immune cells and tissues

Treat to Target

- Glycosylated hemoglobin below *7%*
- Blood pressure below *130/80 mm Hg*
- Triglycerides below *150 mg/dl*
- High-density lipoprotein cholesterol above *40 mg/dl*
- Low-density lipoprotein cholesterol below *100 mg/dl*

Estimated Cardiovascular Risk
(Framingham)

11.3% in 10 years

ISTITUTO CLINICO HUMANITAS

Estimated Cardiovascular Risk
(Progetto Cuore)

8.0% in 10 years

ISTITUTO CLINICO HUMANITAS

European Diabetes Policy Group Advise

"Failure to attempt to reach agreed targets is inadequate care"

From European Diabetes Policy Group. A desktop guide to type 2 diabetes. Diabet Med 1999; 16: 716-730.