Università degli studi
di Modena e Reggio Emilia

EVENTI CARDIOVASCOLARI E DIFERENZE DI GENERE

Il Cuore delle donne: le differenze di genere nel diabete

Rosario Rossi

Il percorso di AMD per la medicina di genere:
1° Giornata Nazionale del Gruppo Donna.
- Dalle differenze di genere alle pari opportunità -
Olbia 16/17 marzo 2012

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero-Universitaria di Modena

Cattedra di Cardiologia

Global Prevalence of Diabetes

Estimates for the year 2000 and projections for 2030

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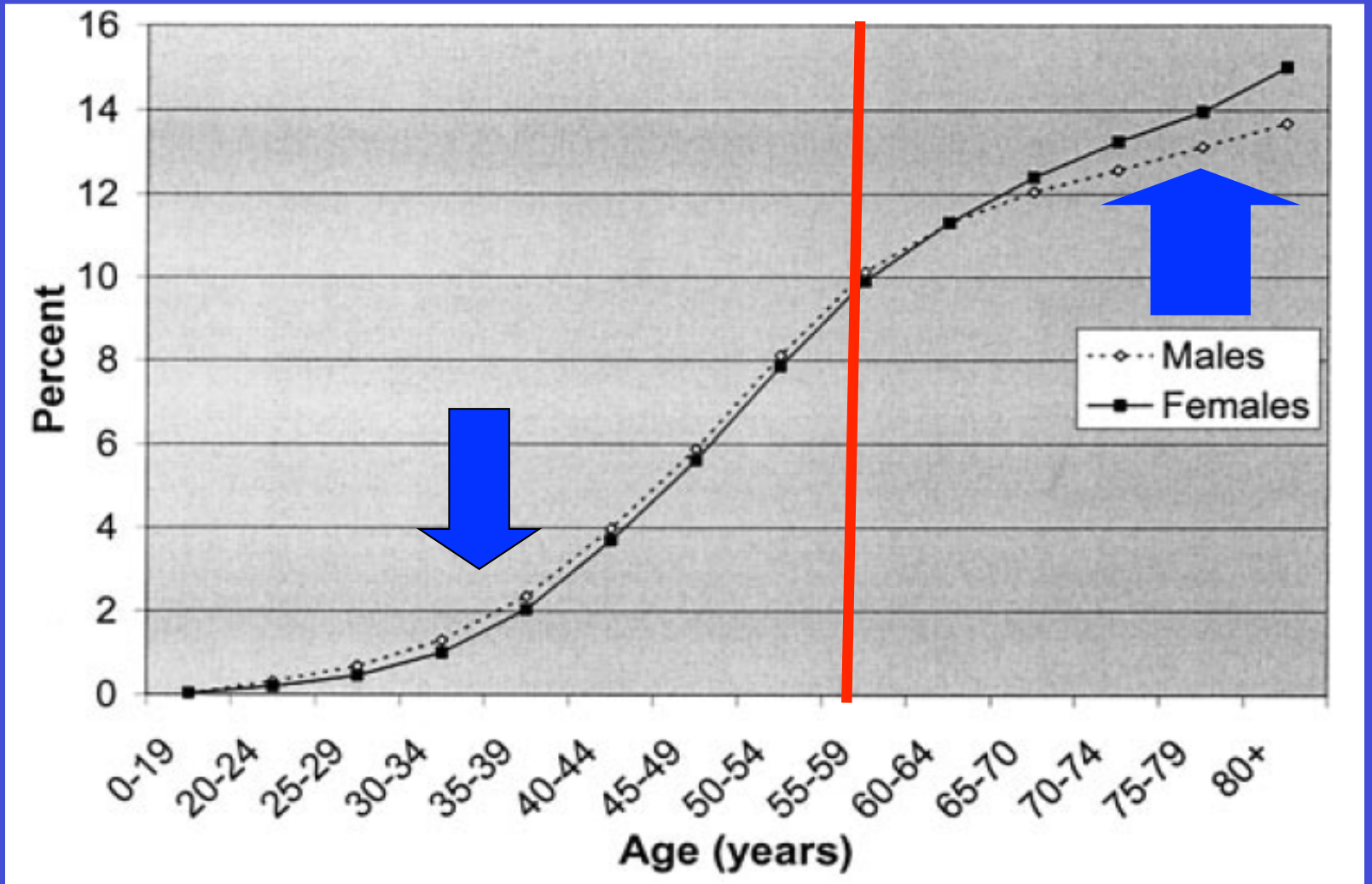
Gojka Roglic, MD[2]
Anders Green, MD, PHD, DR MED SCI[3]
Richard Sicree, MBBS, MPH[4]
Hilary King, MD, DSC[2]

Diabetes Care 27:1047–1053, 2004



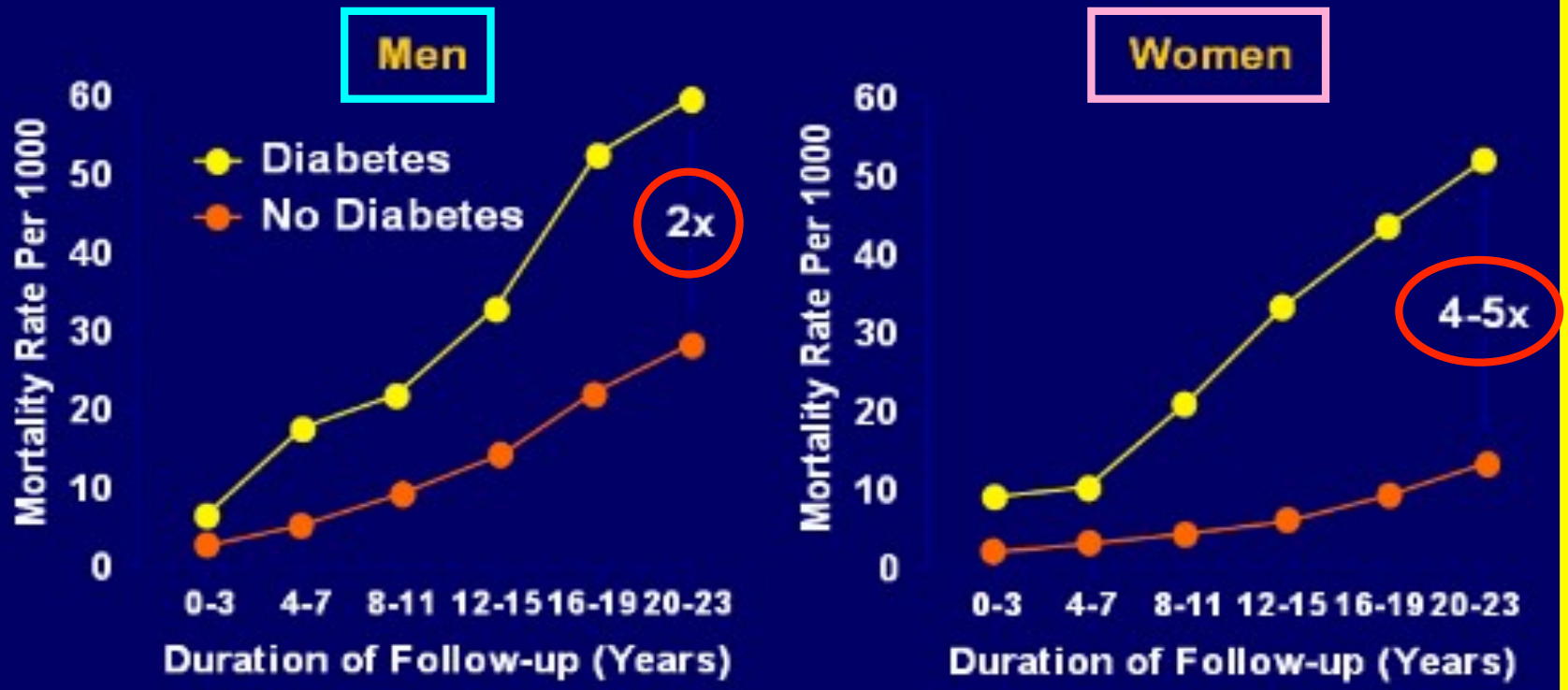
Entità del Problema

- Il DM rappresenta il maggiore tra i fattori di rischio per mortalità e invalidità cardiovascolare
- Il DM aumenta di oltre 4 volte il rischio di sviluppare malattia aterosclerotica ostruttiva (coronarica, cerebro-vascolare e periferica)
- Il beneficio legato al genere femminile (prima della menopausa) è eliminato dal DM

Luscher TF. Circulation 2003

FRAMINGHAM STUDY AND JOSLIN PATIENTS

Diabetes is a CV Risk Factor



Krolewski AS, et al. Evolving natural history of coronary disease in diabetes mellitus. *Am J Med* 1991;90(Supp 2A):56S-61S.

DIABETES FACTS

- The World Health Organization (WHO) estimates that more than 180 million people worldwide have diabetes. This number is likely to more than double by 2030.
- In 2005, an estimated 1.1 million people died from diabetes.[1]
- Almost 80% of diabetes deaths occur in low and middle-income countries.
- Almost half of diabetes deaths occur in people under the age of 70 years; 55% of diabetes deaths are in women.
- WHO projects that diabetes deaths will increase by more than 50% in the next 10 years without urgent action. Most notably, diabetes deaths are projected to increase by over 80% in upper-middle income countries between 2006 and 2015.

PECULIARITA' DEL DIABETE NEL GENERE FEMMINILE

ORIGINAL ARTICLE

Transdermal 17-β-Estradiol and Risk of Developing Type 2 Diabetes in a Population of Healthy, Nonobese Postmenopausal Women

ROSARIO ROSSI, MD[1]
GIORGIA ORIGLIANI, PHD[2]
MARIA G. MODENA, MD[1]

Diabetes Care 27:645–649, 2004

Table 2—*Incidence rates of diabetes among the study population*

	Cases of diabetes: *n/N* (%)	Incidence rate*	Incidence rate ratio† (crude)	*P*	Incidence rate ratio† (adjusted‡)	*P*
Total cohort	60/673 (8.91)	22.0	—	—	—	—
Hormone therapy nonusers	54/529 (10.20)	26.5	2.19§	0.006	1.97‖	0.004
Hormone therapy users	6/144 (4.16)	12.1	Referent	Referent	Referent	Referent

Our results suggest a **significant reduction in the incidence** of type 2 diabetes in our population of nonobese, healthy postmenopausal women **who used transdermal 17-B-estradiol**. This could suggest that, in some women, the **estrogen deficiency** that occurs after menopause could represent a fundamental step in the process of diabetogenesis.

Diabetes and Abnormal Glucose Tolerance in Women With Previous Gestational Diabetes

MERCÈ ALBAREDA, MD, PHD
AGUEDA CABALLERO, MD
GEMMA BADELL, MD
SANDRA PIQUER
ANGELS ORTIZ, PHD
ALBERTO DE LEIVA, MD, PHD
ROSA CORCOY, MD, PHD

Diabetes Care 26:1199–1205, 2003

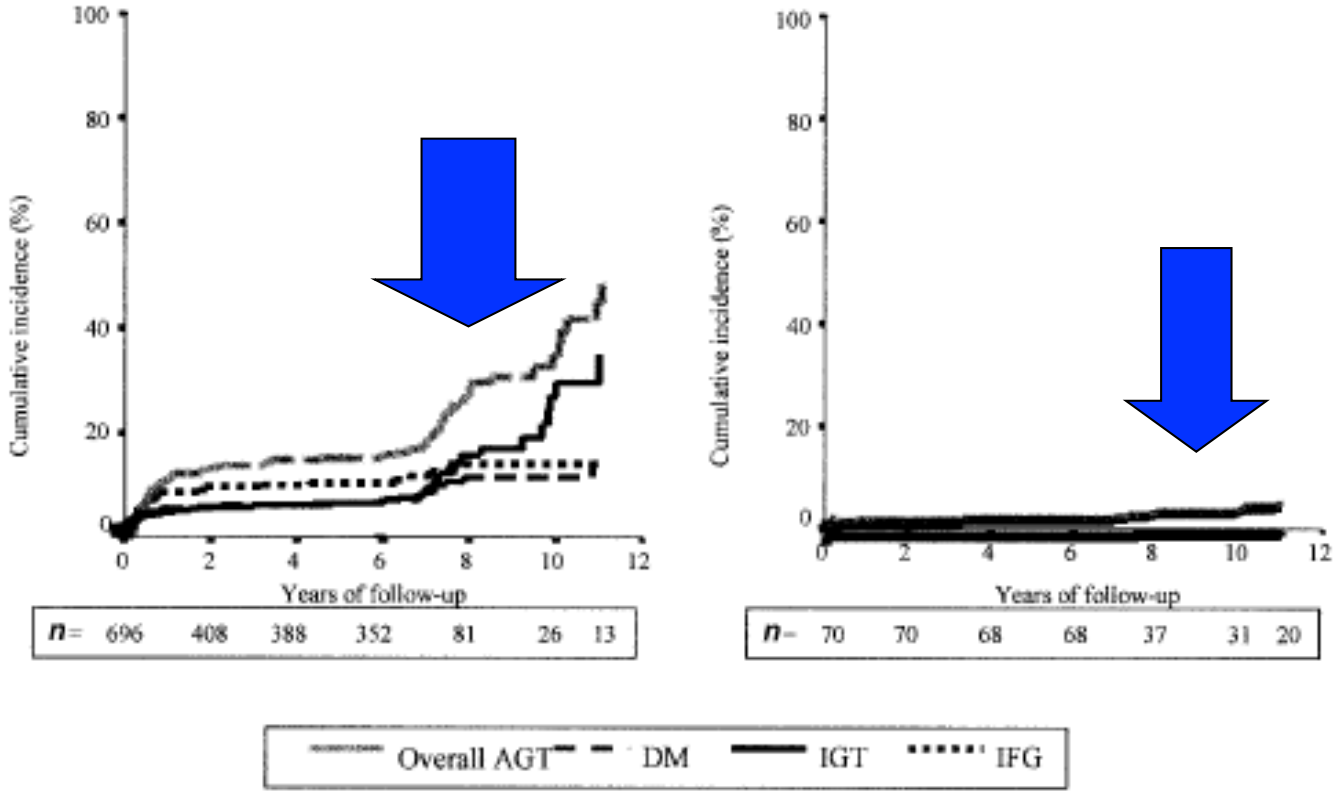


Figure 2—*Cumulative incidence of diabetes and AGT (diabetes, IGT, IFG) in women with previous GDM (A) and control women (B) as determined by life table analysis. The cumulative rates of diabetes and overall AGT were 13.8 and 42.4% at 11 years of follow-up in women with GDM vs. 0 and 2.8% in control women.*

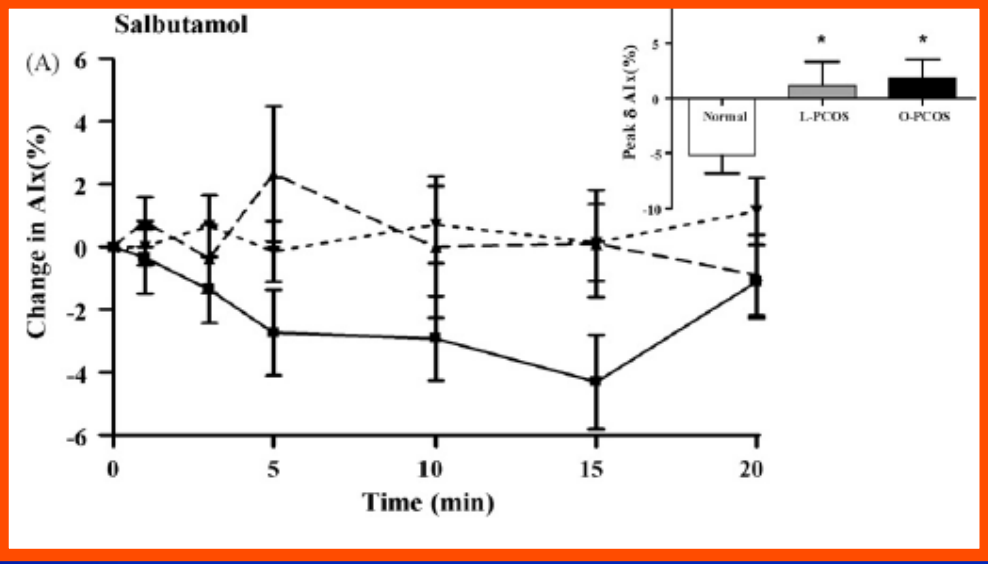
Atherosclerosis

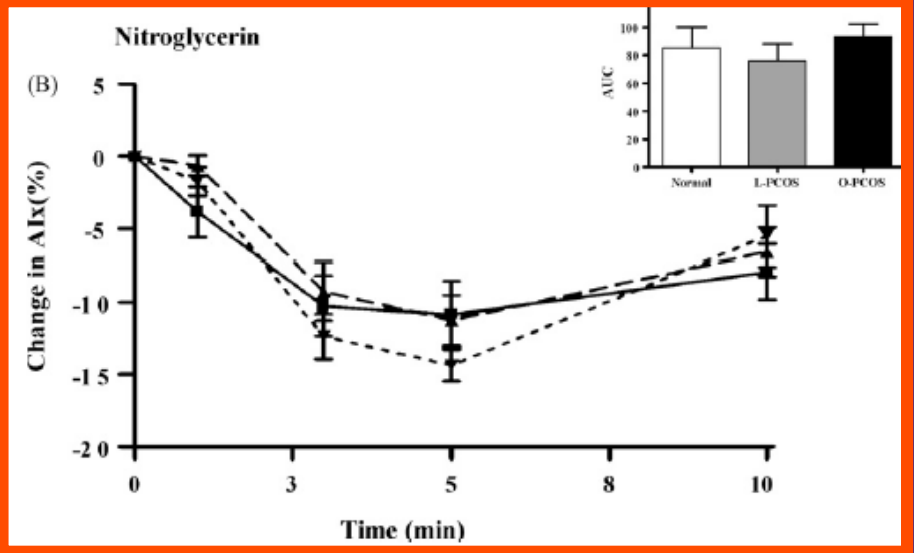
Atherosclerosis. 2008 Sep 17. [Epub ahead of print]

journal homepage: www.elsevier.com/locate/atherosclerosis

Polycystic ovary syndrome is associated with severe platelet and endothelial dysfunction in both obese and lean subjects

Sharmalar Rajendran[a], Scott R. Willoughby[a], Wai Ping A. Chan[a], Elizabeth A. Liberts[a], Tamila Heresztyn[a], Mrinal Saha[b], Michael S. Marber[b], Robert J. Norman[c], John D. Horowitz[a,*]





Cardiovascular disease risk in women with diabetes needs attention[1,2]

Ann M Coulston

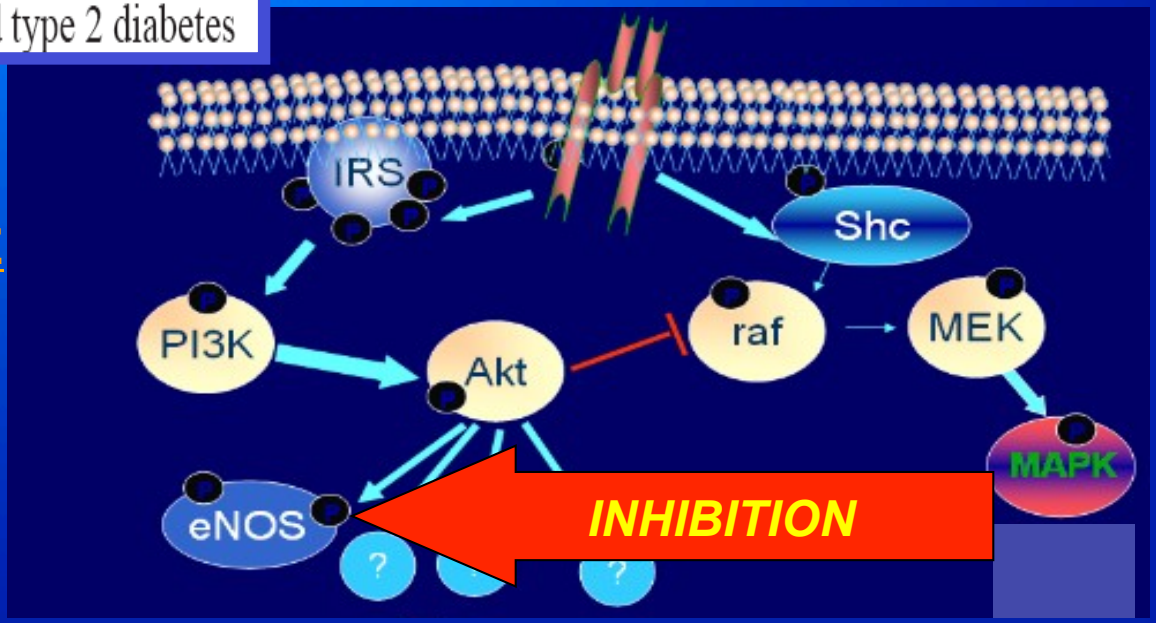
Am J Clin Nutr 2004;79:931–2

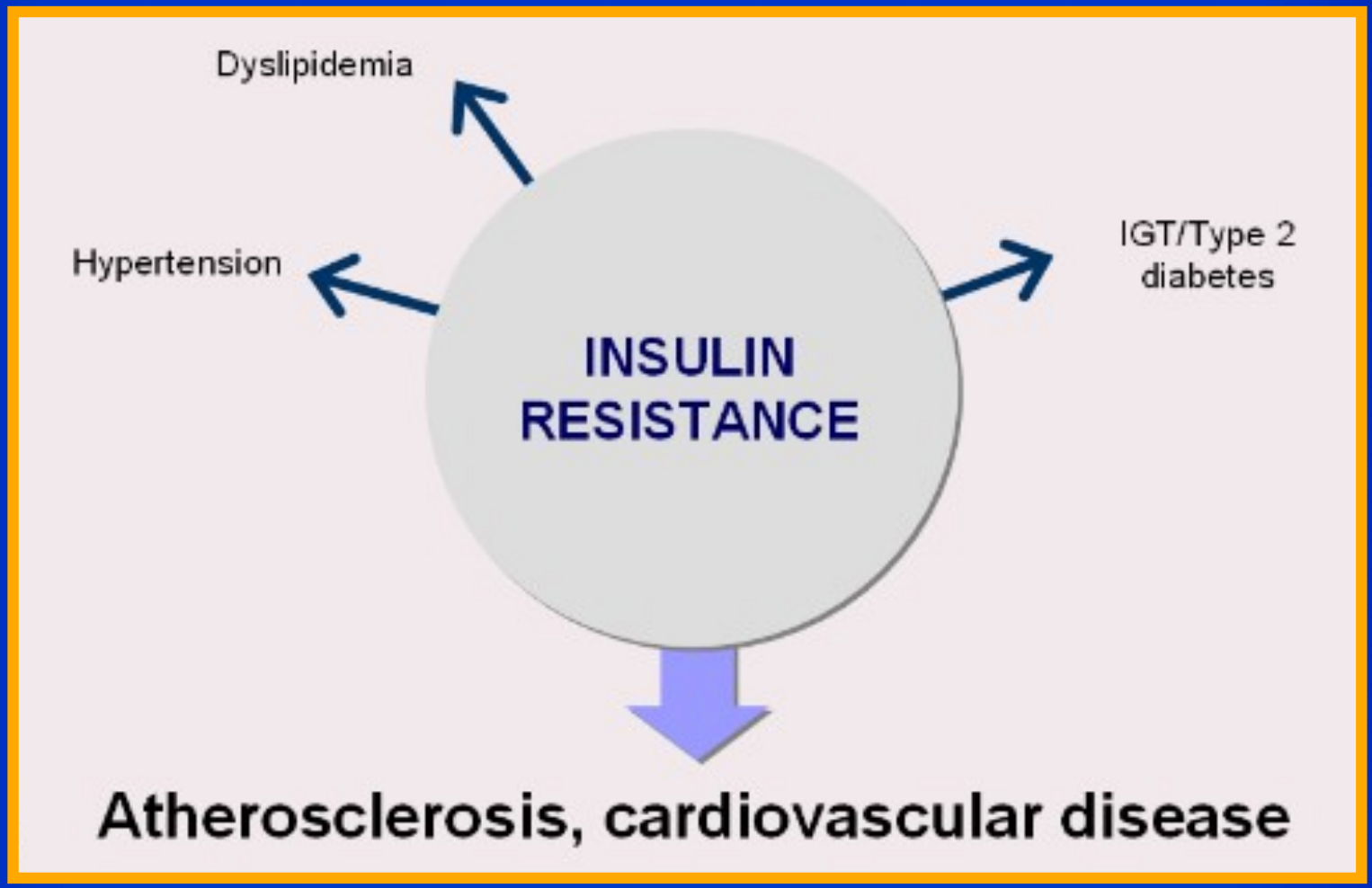
Insulin resistance is a key factor in the pathogenesis of type 2 diabetes, and it predates the development of frank hyperglycemia by many years. Characteristic features of the insulin resistance syndrome include dyslipidemia, glucose intolerance, central obesity, hypertension, and specific abnormalities of endothelial and vascular function. The interplay between these signs of insulin resistance and their vascular, metabolic, and clinical consequences points to increased risks of CVD and type 2 diabetes

1) Il T2DM è una malattia principalmente da insulino-resistenza

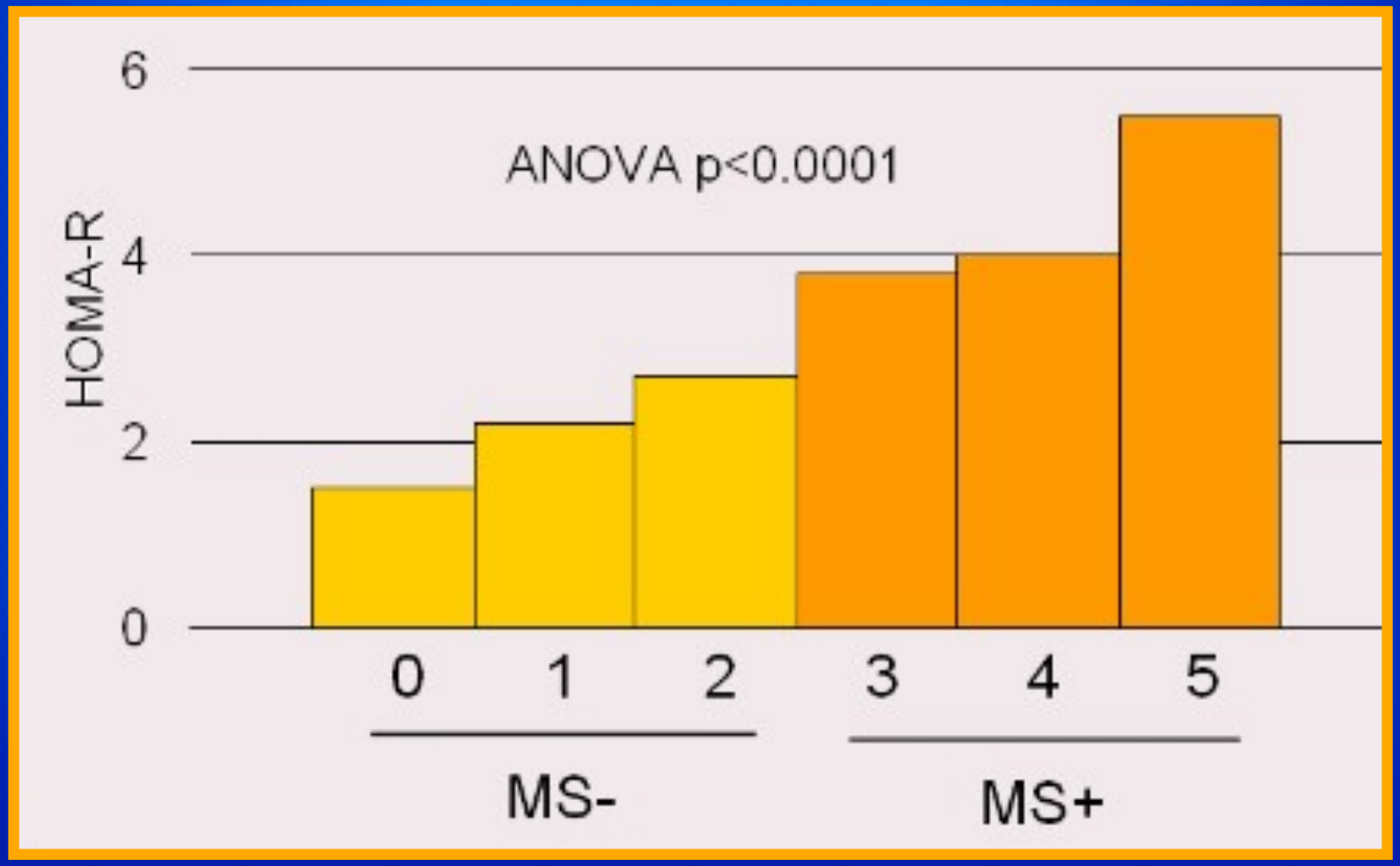
2) L'insulino-resistenza è spesso associata a SINDROME METABOLICA

3) La SINDROME METABOLICA è associata a DISFUNZIONE ENDOTELIALE e RIMODELLAMENTO VASCOLARE, che rappresentano il tramite che conduce all'aumento del rischio cardiovascolare

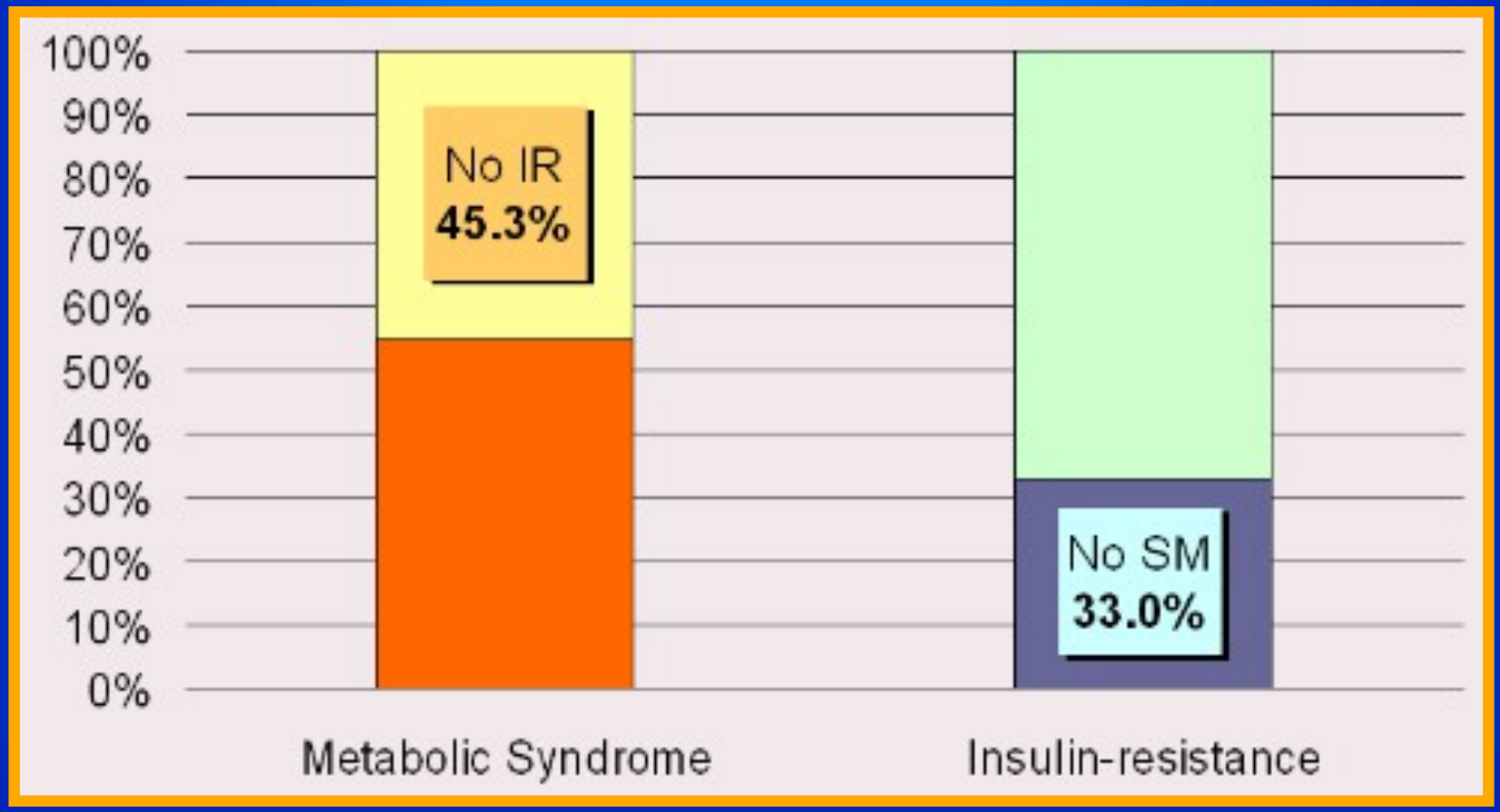



Dyslipidemia
Hypertension
IGT/Type 2 diabetes
INSULIN RESISTANCE
Atherosclerosis, cardiovascular disease

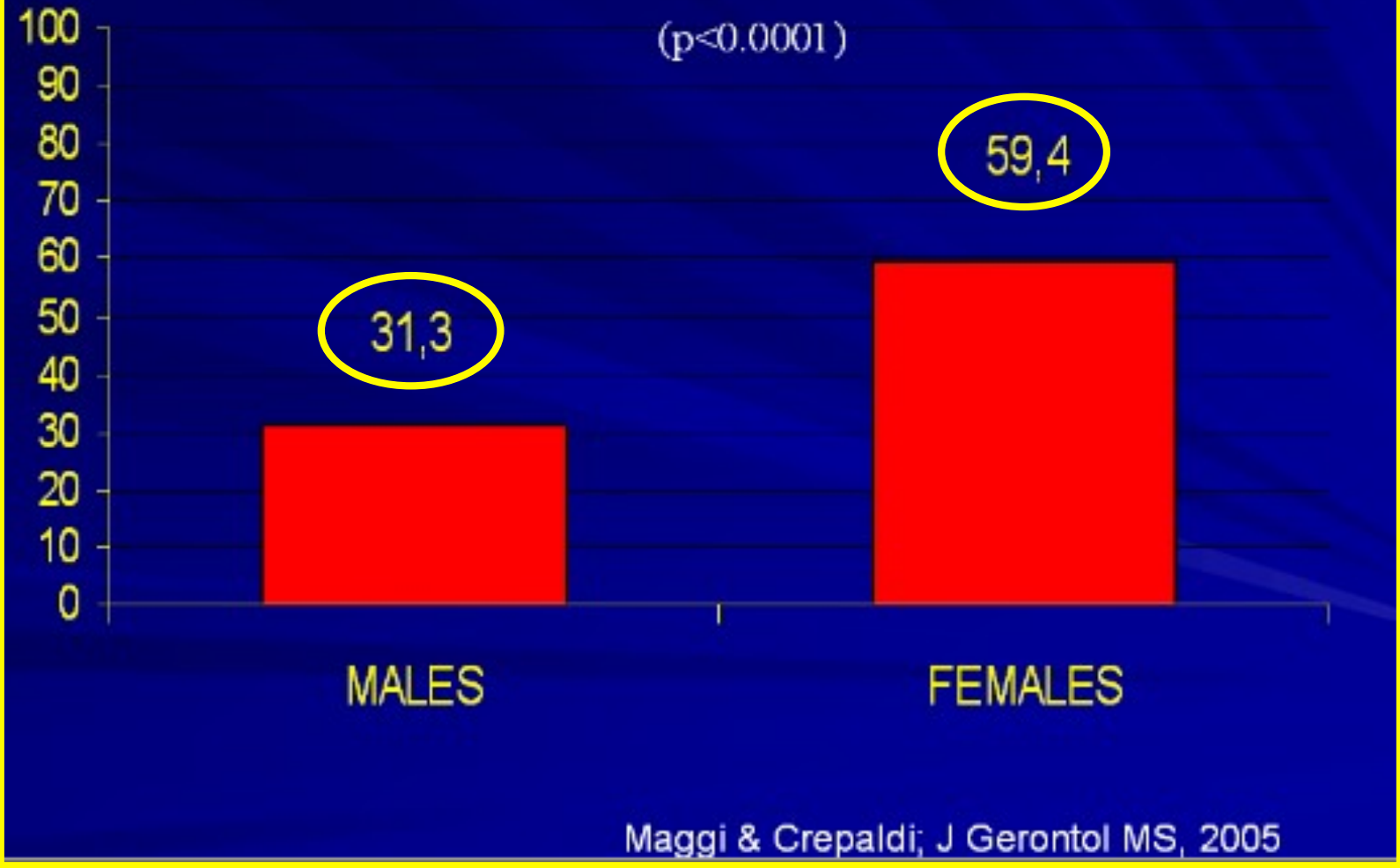
Relazione tra Insulino Resistenza e Sindrome Metabolica. Lo studio GENFIEV



Relazione tra insulino resistenza e Sindrome Metabolica. Lo studio GENFIEV



PREVALENCE (%) OF METABOLIC SYNDROME



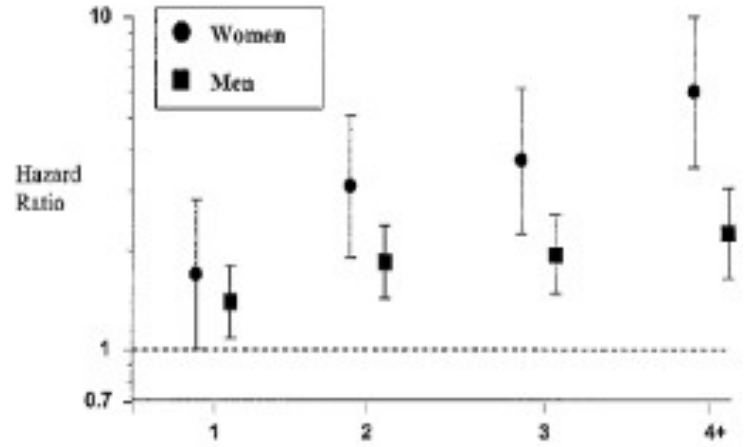
Maggi & Crepaldi; J Gerontol MS, 2005

The Metabolic Syndrome and 11-Year Risk of Incident Cardiovascular Disease in the Atherosclerosis Risk in Communities Study

Ann Marie McNeill, phd[1]
Wayne D. Rosamond, phd[1]
Cynthia J. Girman, drph[2]
Sherita Hill Golden, md, mhs[3]
Maria I. Schmidt, md[4]
Honey E. East, md[5]
Christie M. Ballantyne, md[6]
Gerardo Heiss, md, phd[1]

The metabolic syndrome has l
identified as a constellation of
abolic and nonmetabolic disor
related to defects in insulin sensitivity

Diabetes Care 28:385–390, 2005



Components of the ATP III Metabolic Syndrome

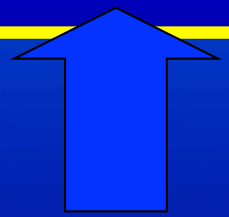
In the current study, we found that among a population free of prevalent CHD, stroke, and diabetes, men and women with the metabolic syndrome were 1.5 and 2 times more likely to develop CHD after adjustment for established risk factors.

National Cholesterol Education Program Versus World Health Organization Metabolic Syndrome in Relation to All-Cause and Cardiovascular Mortality in the San Antonio Heart Study

Kelly J. Hunt, PhD; Roy G. Resendez, MA; Ken Williams, MS;
Steve M. Haffner, MD; Michael P. Stern, MD

(*Circulation*. 2004;110:1251-1257.)

	General Population		
Adjusted for Age and Ethnic Group	Women	Men	P
Model 1: NCEP–MetS	4.65 (2.35–9.21)	1.82 (1.14–2.91)	0.03
Model 2: WHO–MetS	2.83 (1.55–5.17)	1.15 (0.72–1.86)	0.02



Hypertension
JOURNAL OF THE AMERICAN HEART ASSOCIATION
American Heart Association
Learn and Live

Different Impact of the Metabolic Syndrome on Left Ventricular Structure and Function in Hypertensive Men and Women

Giuseppe Schillaci, Matteo Pirro, Giacomo Pucci, Massimo R. Mannarino, Fabio Gemelli, Donatella Siepi, Gaetano Vaudo and Elmo Mannarino

Hypertension 2006;47:881-886; originally published online Apr 3, 2006;

	women			men		
	NoMS	MS		NoMS	MS	
LV mass index, g×m$^{-2.7}$	40.0 (10)	49.5 (12)	<0.001	46.1 (10)	50.3 (12)	0.003
LV hypertrophy, ≥51 g×m$^{-2.7}$	14	37	<0.001	29	39	0.09
LV mass, % from predicted	103.6 (18)	122.4 (20)	<0.001	112.2 (21)	119.5 (26)	0.02
Inappropriately high LV mass, %	5	28	<0.001	16	26	0.08
Relative wall thickness	0.39 (0.07)	0.42 (0.07)	0.004	0.41 (0.07)	0.42 (0.07)	0.20

Variable	B	β	Multiple R	P
Women (n=253)				
Body mass index, kg/m^2	0.85	0.35	0.44	<0.001
Age, y	0.27	0.28	0.53	<0.001
24-h systolic BP, mm Hg	0.16	0.22	0.59	<0.001
MS, yes/no	4.80	0.19	0.61	<0.001
Men (n=365)				
Body mass index, kg/m^2	0.97	0.36	0.40	<0.001
24-h systolic BP, mm Hg	0.29	0.33	0.52	<0.001
Age, y	0.20	0.20	0.60	<0.001
Smoking, yes/no	2.12	0.09	0.61	0.048
MS, yes/no	...	...	...	0.20

Hypertension

JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association. Learn and Live.

Metabolic Syndrome Affects Cardiovascular Risk Profile and Response to Treatment in Hypertensive Postmenopausal Women

Rosario Rossi, Annachiara Nuzzo, Giorgia Origliani, and Maria Grazia Modena

Hypertension. 2008 Nov;52(5):865-72.

Table 1. Baseline Characteristics of the Study Patients Divided in two Groups According with the Presence of Metabolic Syndrome

parameter	*MS yes*	*MS no*	*p*
n. of patients	180	170	
Caucasian, %	100 (n = 180)	100 (n = 170)	ns
Age, y	54 ± 8	53 ± 10	ns
Time from menopause, months	37 ± 14	38 ± 12	ns
Family history of hypertension, %	52.8 (n = 95)	53.5 (n = 91)	ns
Family history of diabetes, %	56.1 (n = 101)	36.4.(n = 62)	0.003
History of gestational diabetes, %	12.2 (n = 22)	3.5 (n = 6)	0.01
Insulin-resistance indexes			
Fasting plasma Insulin, U/L	6.6 ± 4.9	3.5 ± 2.9	< 0.0001
HOMA-IR	7.9 ± 4.9	3.5 ± 3.4	< 0.0001

Sub-clinical inflammation			
hs-CRP, ng/L	2.2 ± 0.6	1.7 ± 0.7	< 0.01
Endothelial function-related parameters			
FMD, %	2.4 ± 2.2	4.4 ± 2.5	0.01
Echocardiographic parameters			
LAD, mm	42 ± 13	43 ± 12	ns
EDLVD, mm	47 ± 14	49 ± 14	ns
Left ventricular FS, %	29 ± 7	31 ± 8	ns
Left ventricular mass, $g/m^{2.7}$	44 ± 15	41 ± 16	0.03
Left ventricular hypertrophy, %	30.5 (n = 55)	24.1 (n = 41)	0.04

Table 2. Blood Pressure Values at Baseline and After One Year of Treatment and the Antihypertensive Regimen: A Comparison Between Groups.

	MS yes ***(n = 180)***	***MS no*** ***(n = 170)***	***p***
Blood pressure measurements			
Baseline blood pressure values (systolic/diastolic), mmHg	154 ± 14 / 94 ± 7	155 ± 13 / 94 ± 8	ns
Blood pressure values after 1 year of treatment (systolic/diastolic), mmHg	131 ± 15 / 83 ± 8 *	130 ± 16 / 84 ± 7 *	ns
Regimen			
Nonpharmachologic treatment, %	2.9 (n = 5)	2.4 (n = 4)	ns
Single-drug therapy, %	7.7 (n = 14)	9.4 (n = 16)	ns
Two antihypertensive drugs, %	15.5 (n = 28)	30.6 (n = 52)	0.001
Three or plus antihypertensive drugs, %	73.9 (n = 133)	57.6 (n = 98)	0.01

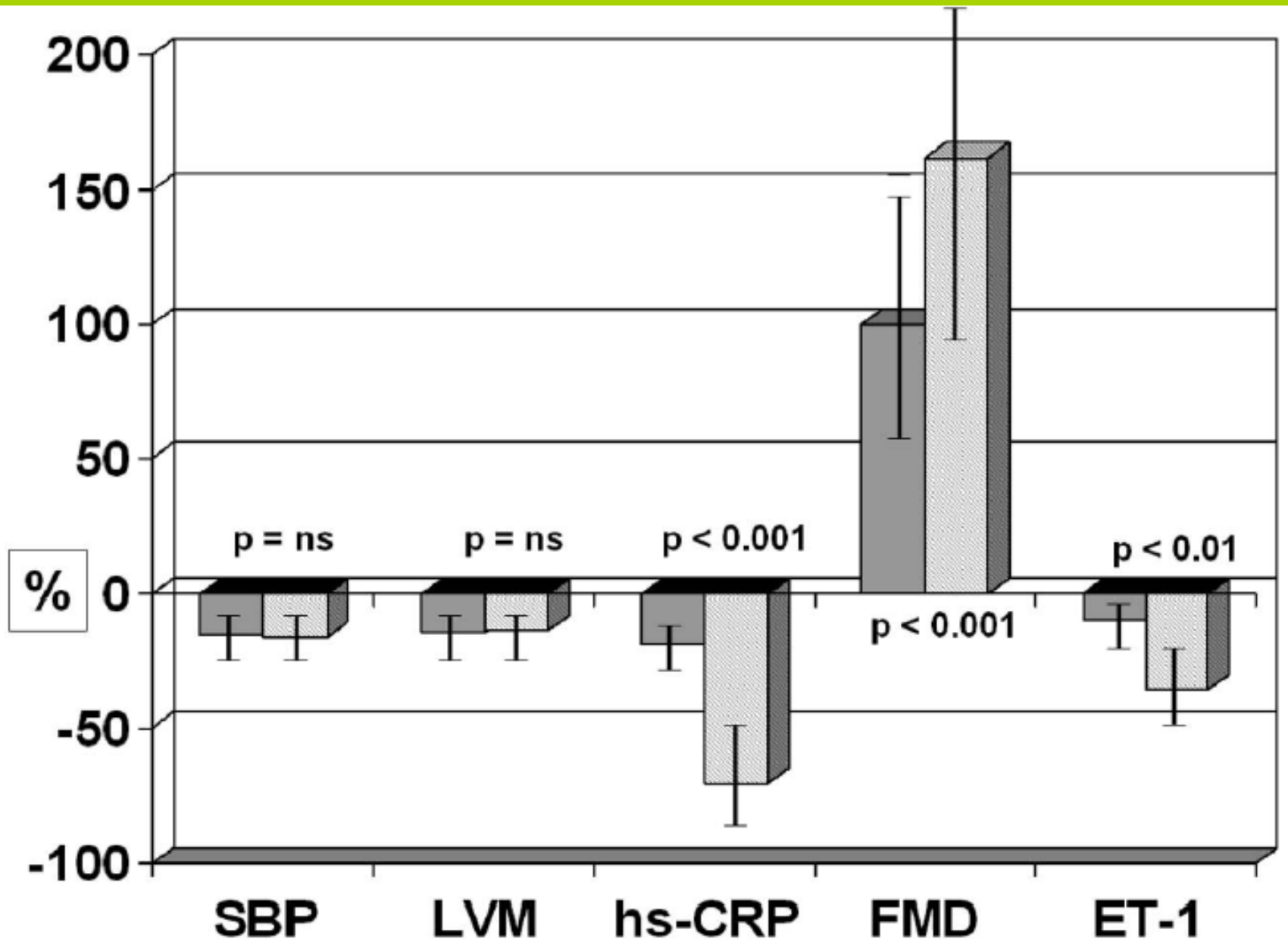
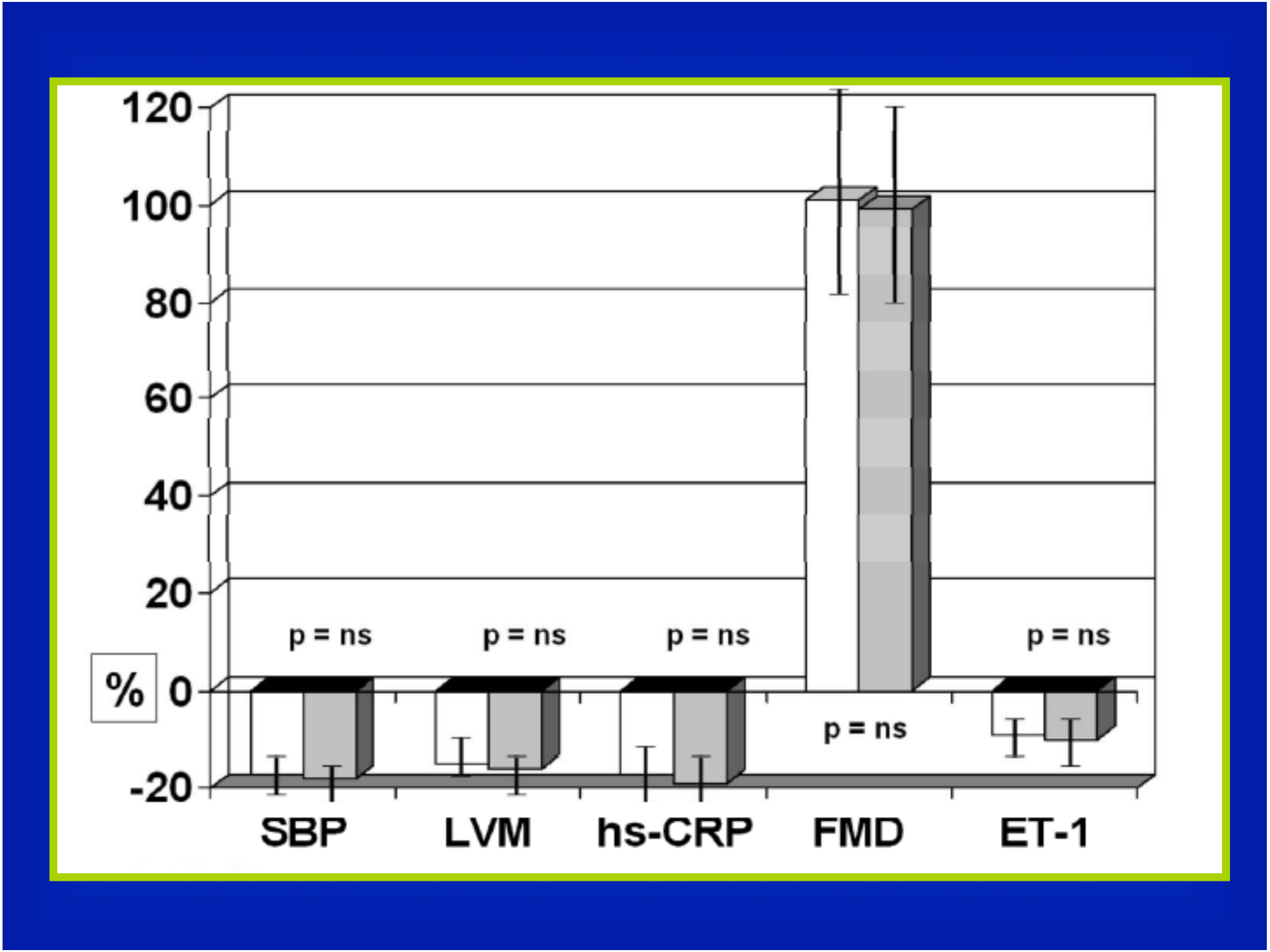

200
150
100
50
%
0
-50
-100
p = ns
p = ns
p < 0.001
p < 0.001
p < 0.01
SBP
LVM
hs-CRP
FMD
ET-1

Table 4. Baseline Characteristics of the 180 Women with Hypertension and Metabolic Syndrome Divided in two Groups According with the Presence of Overweight/Obesity

parameter	*Normal weight* ($20<BMI<25\ Kg/m^2$)	*Overweight/Obesity* ($BMI > 25\ Kg/m^2$)	*p*
n. of patients	54 of 180 (30%)	126 of 180 (70%)	
Caucasian, %	100 (n = 54)	100 (n = 126)	ns
Age, y	53 ± 9	55 ± 8	ns
Time from menopause, months	37 ± 13	38 ± 12	ns
Family history of hypertension, %	55.5 (n = 30)	51.6 (n = 65)	ns
Family history of diabetes, %	94.4 (n = 51)	39.7 (n = 50)	< 0.0001
History of gestational diabetes, %	35.2 (n = 19)	2.3 (n = 3)	< 0.0001


120
100
80
60
40
20
0
-20
%
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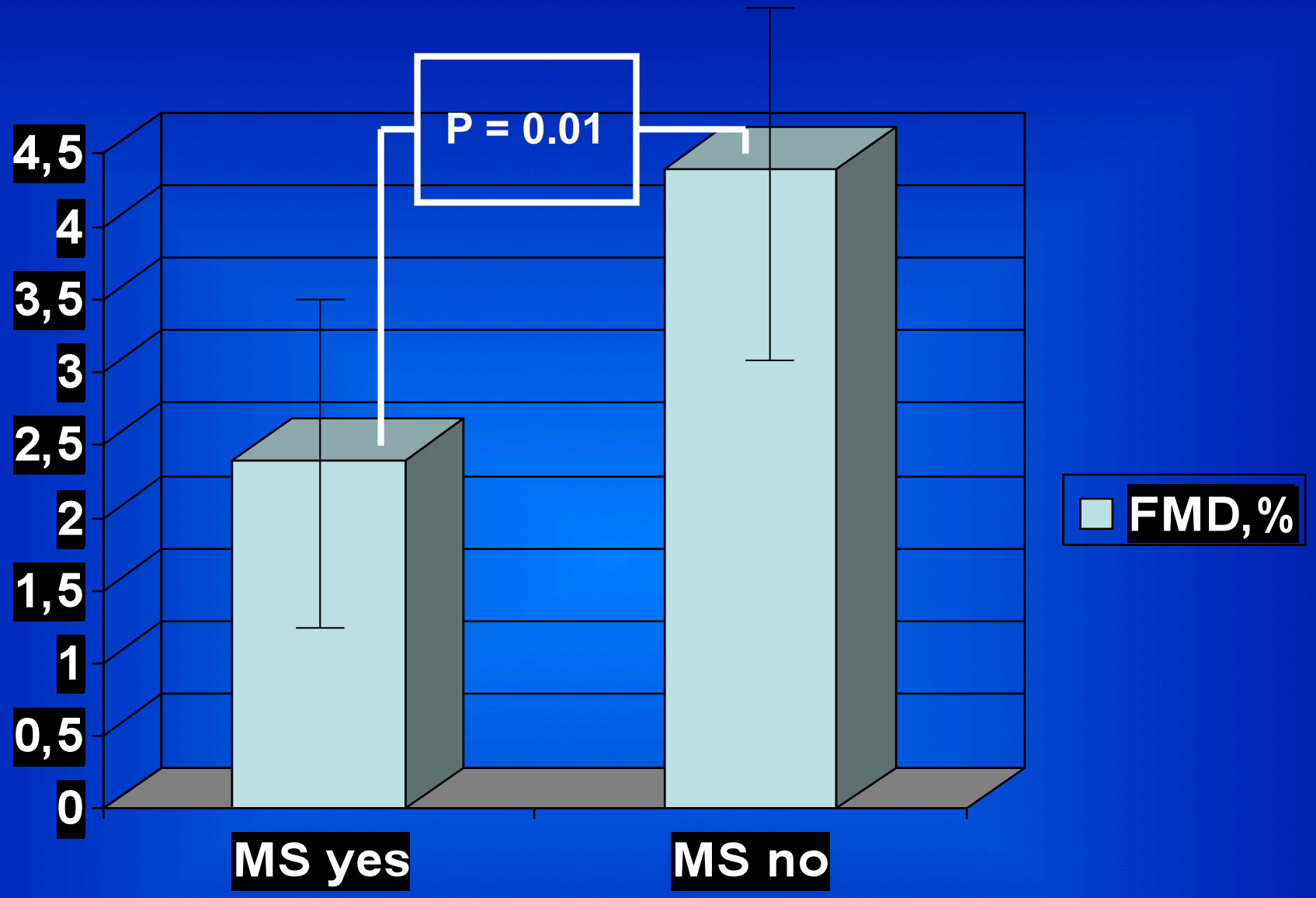
p = ns
p = ns
p = ns
p = ns
SBP
LVM
hs-CRP
FMD
ET-1



Funzione endoteliale in 350 pazienti ipertese

Effects of insulin resistance on endothelial function: possible mechanisms and clinical implications

D. Tousoulis,[1] K. Tsarpalis,[2] D. Cokkinos[2] and C. Stefanadis[1]

[1]Cardiology Unit, Hippokration Hospital, Athens University Medical School, Athens, Greece
[2]1st Cardiology Department, Onassis Cardiac Surgery Center, Athens, Greece

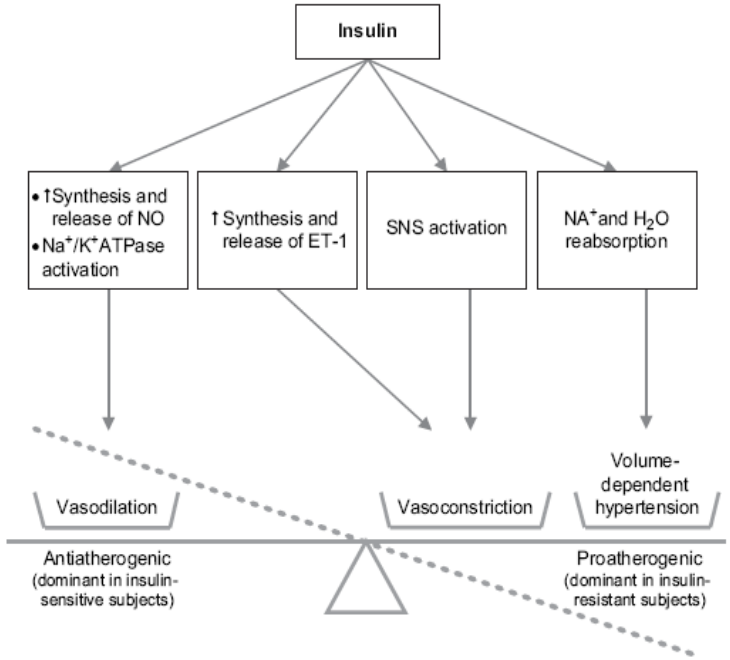


Fig. 1 Haemodynamic effects of insulin. In states of health, a fine balance is kept between the opposing effects of insulin with a net anti-atherogenic effect. In states of insulin resistance, selective impairment of the vasculoprotective actions of insulin occurs (left side of the figure), while the unopposed detrimental actions are actually exaggerated further by the ensuing hyperinsulinaemia (right side of the figure). As a result, in insulin-resistant subjects, the balance is tipped towards a state promoting atherogenesis. ET-1, endothelin-1; SNS, sympathetic nervous system.

Reciprocal Relationships Between Insulin Resistance and Endothelial Dysfunction

Molecular and Pathophysiological Mechanisms

Jeong-a Kim, PhD; Monica Montagnani, MD, PhD; Kwang Kon Koh, MD; Michael J. Quon, MD, PhD

(*Circulation*. 2006;113:1888-1904.)

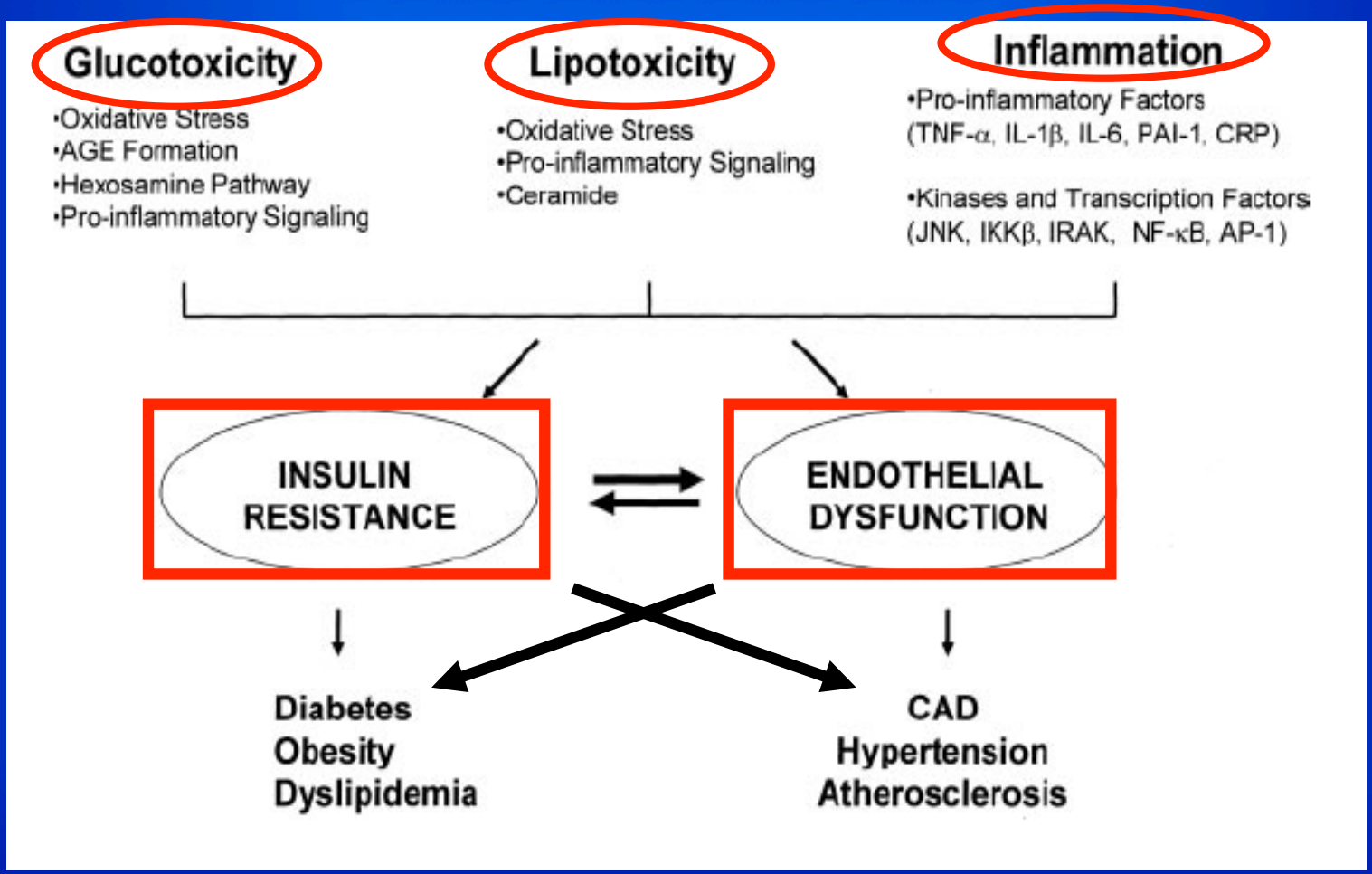


Table 3 Cardiovascular Event Rates and Association Between FMD Tertiles and Cardiovascular Events in Our Population

	3° (Higher) Tertile (FMD ≥8.1%)	2° (Intermediate) Tertile (FMD From 4.6% to 8.0%)	1° (Lower) Tertile (FMD ≤4.5%)	p Value*
TIA, %	0.26 (2 of 754)	1.72 (13 of 755)	4.23 (32 of 755)	<0.0001
Ischemic stroke, %	0.39 (3 of 754)	1.05 (8 of 755)	1.32 (10 of 755)	<0.01
Nonfatal myocardial infarction, %	0.26 (2 of 754)	3.97 (3 of 755)	5.29 (4 of 755)	<0.05
Hospitalization for coronary revascularization, %	0.13 (1 of 754)	0.92 (7 of 755)	0.26 (2 of 755)	NS
Cardiac-related death, %	0	0	0.39 (3 of 755)	NS
Cardiovascular events (total), %	1.06 (8 of 754)	4.10 (31 of 755)	6.75 (51 of 755)	<0.0001
Relative risk (crude)	1.0	3.87	6.36	<0.0001
95% CI	Referent	2.05–8.55	4.26–11.50	—
Relative risk (adjusted for age and other conventional risk factors)	1.0	1.33	4.42	<0.0001
95% CI	Referent	1.09–4.09	2.97–8.01	—

*p is the overall significance between groups, calculated by chi-square test, linear-by-linear association.

TIA = transient ischemic attack; other abbreviations as in Table 2.

Rossi R & Modena MG. JACC 2008

REVIEW

Insulin Resistance and the Endothelium

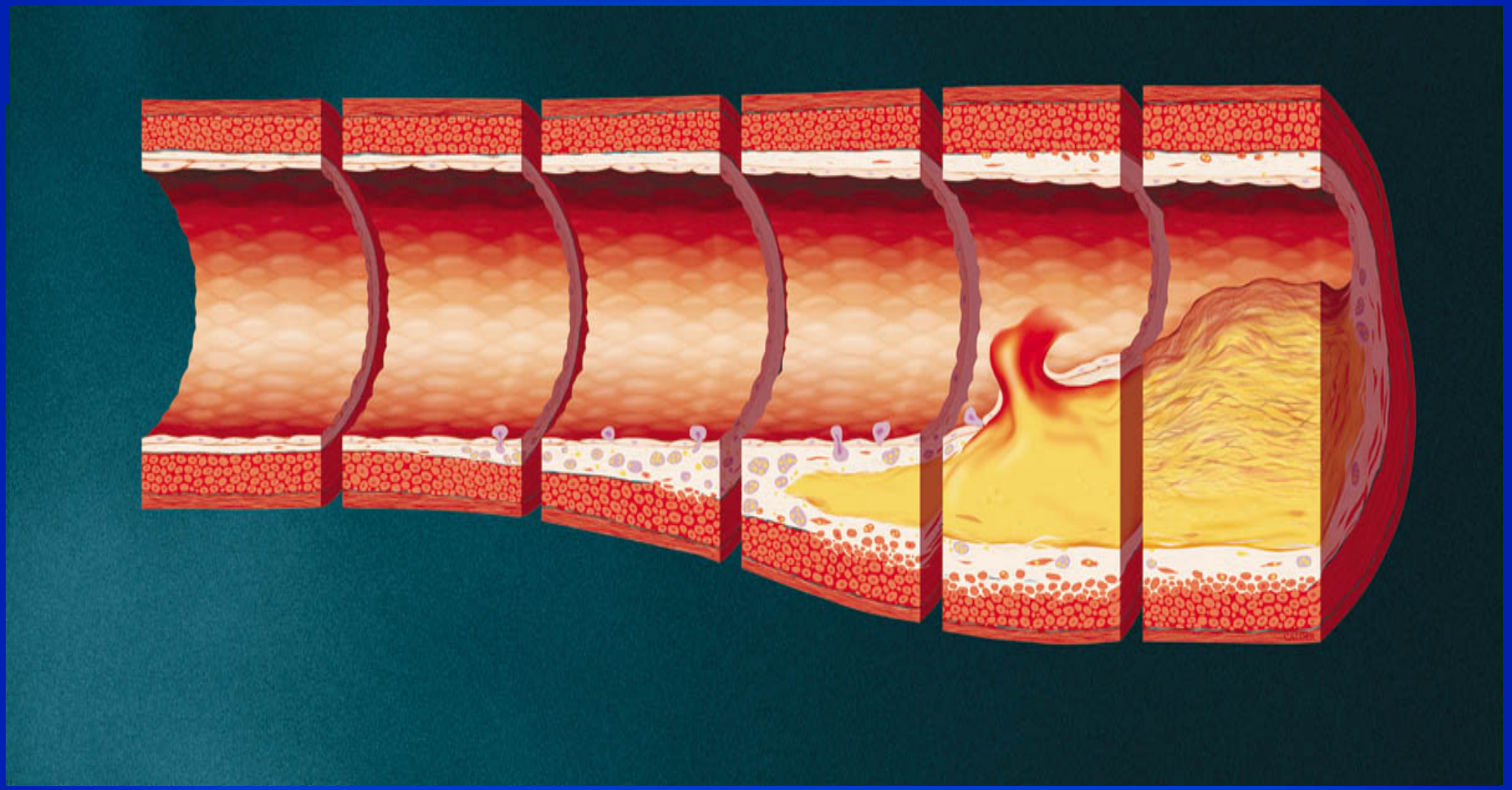
Willa A. Hsueh, MD, Christopher J. Lyon, PhD, Manuel J. Quiñones, MD

s increasing evidence of a parallel progression between resistance and endothelial dysfunction, suggesting a ssociation between insulin action and the endothelium. ous studies have demonstrated that endothelial dysfunc- curs early in the insulin-resistant state and is predictive re cardiovascular events. Similarly, insulin resistance has ssociated with the metabolic syndrome, which also in- the risk of adverse cardiovascular outcomes. Ap-

ment with statins, angiotensin-converting enzyme i angiotensin receptor blockers, or peroxisome prolife vated receptor γ ligands, have been shown to prevent betes and cardiovascular disease. This article review tion between endothelial dysfunction and card disease, assesses the endothelium in the spectrum resistance, and examines the effect of the thiazolidine endothelial functi n. Am J Med. 2004;117:109–117.

TREATMENT	IMPROVE ENDOTHELIAL FUNCTION	REDUCE THE INCIDENCE OF T2 DIABETES
Exercise and Diet	Yes	Yes
ACE inhibitors and ARBs	Yes	Yes
PPAR-γ ligands	Yes	Yes
Estrogen replacement	Yes	Yes
Statins	Yes	Yes
Metformin	Yes	Yes

IL RIMODELLAMENTO VASCOLARE



Adapted from Libby P. *Circulation* 2001; 104: 365-372

Il modello HIV

- Il paziente con HIV trattato con politerapia anti-retrovirale sviluppa spesso SM, insulino-resistenza e diabete mellito tipo 2; ed aumenta, di conseguenza, il rischio CV.
- Abbiamo studiato, in uno studio cross-sectional, 570 pazienti con infezione da HIV, tutti trattati con terapia anti-retrovirale (età media = 46 ± 7 anni)
- MS- = 466; MS+ = 104; prev. = 18.2%

ELSEVIER

Metabolism Clinical and Experimental xx (2009) xxx – xxx

www.metabolismjournal.com

Metabolic disorders induced by highly active antiretroviral therapy and their relationship with vascular remodeling of the brachial artery in a population of HIV-infected patients

Rosario Rossi[a,*], Annachiara Nuzzo[a], Giovanni Guaraldi[b], Nicola Squillace[b], Gabriella Orlando[b], Roberto Esposito[b], Antonella Lattanzi[a], Maria G. Modena[a]

[a]*Institute of Cardiology, University of Modena and Reggio Emilia. Policlinico Hospital, 41100 Modena, Italy*

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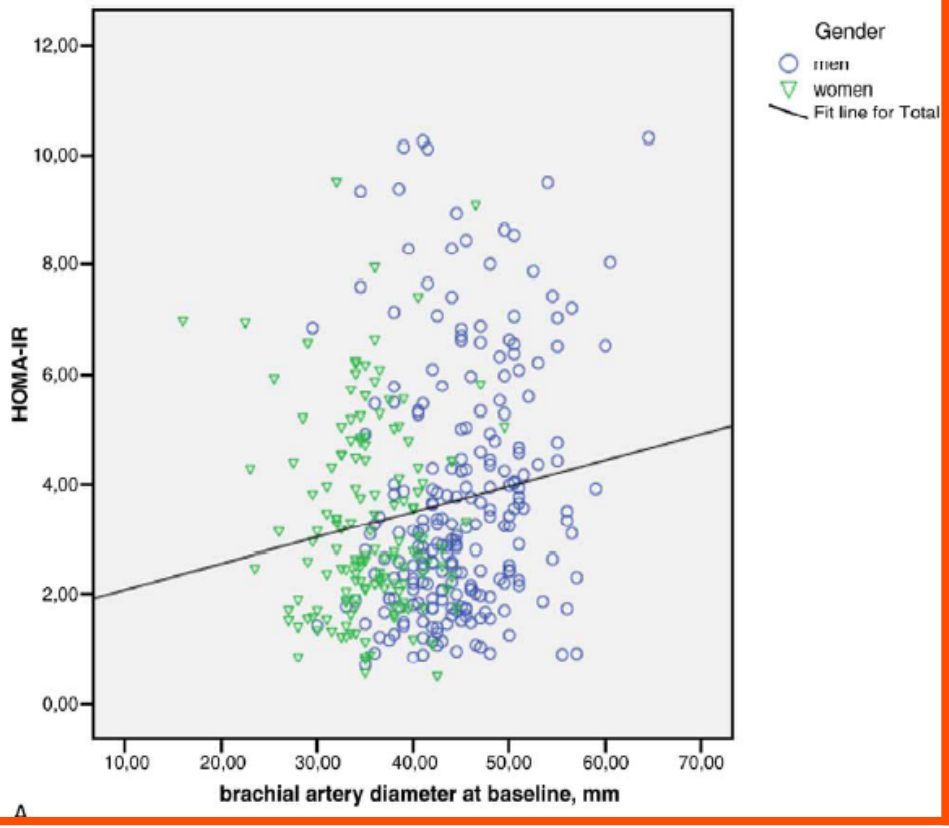
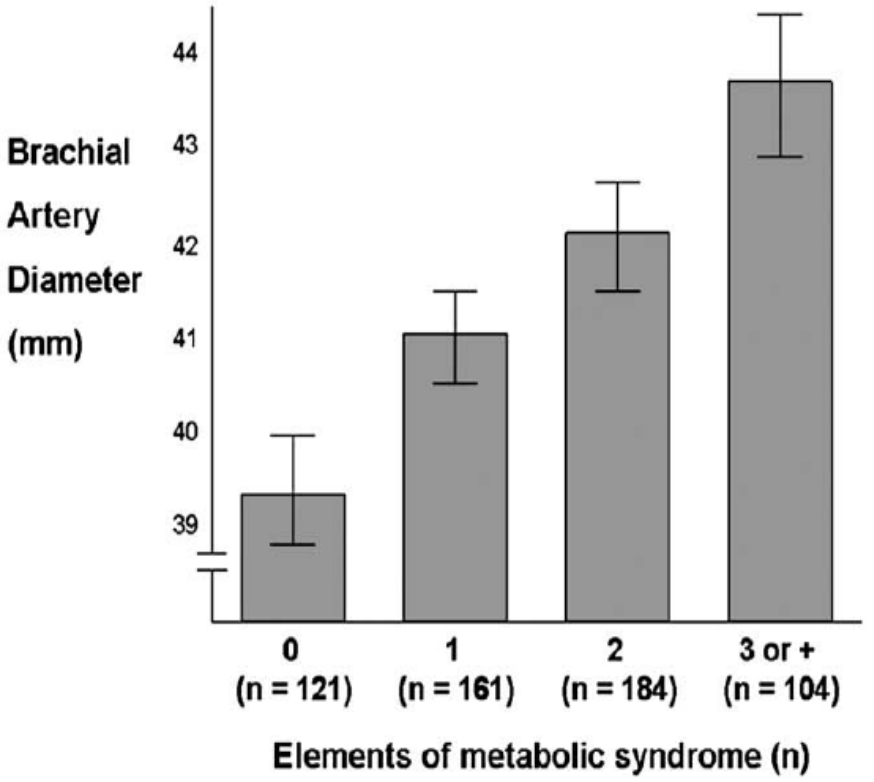
Received 25 August 2008; accepted 17 February 2009





Insulin-resistance affects remodeling of the systemic conductance arteries in postmenopausal women

Abbiamo studiato 124 donne in postmenopausa (diabetiche escluse), che effettuavano coronarografia nel sospetto di coronaropatia. In tutte abbiamo misurato il diametro del tronco comune, della discendente anteriore, della circonflessa e della coronaria destra prossimale. Inoltre, abbiamo misurato il diametro dell'arteria brachiale e delle carotidi interne, ed abbiamo effettuato lo studio della funzione endoteliale tramite il calcolo della vasodilatazione flusso-mediata.

In corso di valutazione su Diabetes Care

Insulin-resistance affects remodeling of the systemic conductance arteries in postmenopausal women

- Le nostre pazienti sono state suddivise, in relazione alla presenza di malattia coronarica, in 4 gruppi: coronarie indenni (0 vasi); 1 vaso coronarico epicardico malato; 2 vasi; 3 o più vasi malati
- 38 pazienti (30.6%) presentavano coronarie indenni (gruppo di riferimento); 34 (27.4%) una malattia di 1 vaso; 30 (24.2%) di 2 vasi; e 22 (17.8%) una malattia di 3 o più vasi.

In corso di valutazione su Diabetes Care

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Risultati

Estensione della Coronaropatia	0 vasi (n=38)	1 vaso (n=34)	2 vasi (n=30)	3 + vasi (n=22)	p trend
TC, mm	36±7	38±7	39±8	41±8	.0001
IVA prox, mm	32±6	34±8	37±9	38±7	.001
Cx prox, mm	28±6	29±5	31±7	33±7	.001
CDx prox, mm	34±6	36±7	38±7	40±9	.001

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Risultati

Estensione della Coronaropatia	0 vasi (n=38)	1 vaso (n=34)	2 vasi (n=30)	3 + vasi (n=22)	p trend
BAD, mm	34±8	37±9	40±9	43±7	.0001
ICA Sx, mm	66±6	69±7	71±7	74±9	.0001
ICA Dx, mm	64±8	67±7	69±8	73±9	.0001

Insulin-resistance affects remodeling of the systemic conductance arteries in postmenopausal women

Risultati

Estensione della Coronaropatia	0 vasi (n=38)	1 vaso (n=34)	2 vasi (n=30)	3 + vasi (n=22)	p trend
BMI,Kg/m^2	26±4	27±5	27±7	28±8	0.2
SC,m^2	1.8±0.2	1.8±0.2	1.9±0.2	1.9±0.3	0.7

In corso di valutazione su Diabetes Care

Insulin-resistance affects remodeling of the systemic conductance arteries in postmenopausal women

Risultati

Estensione della Coronaropatia	0 vasi (n=38)	1 vaso (n=34)	2 vasi (n=30)	3 + vasi (n=22)	p trend
WC,cm	86±10	89±11	93±11	97±12	.001
HbA_1c,%	4.7±0.9	5.1±1.0	5.5±0.9	6.0±0.8	.001
HOMA-IR	3.8±3.0	4.8±3.2	5.7±4.1	6.9±3.5	.0001

In corso di valutazione su Diabetes Care

Insulin-resistance affects remodeling of the systemic conductance arteries in postmenopausal women

Risultati

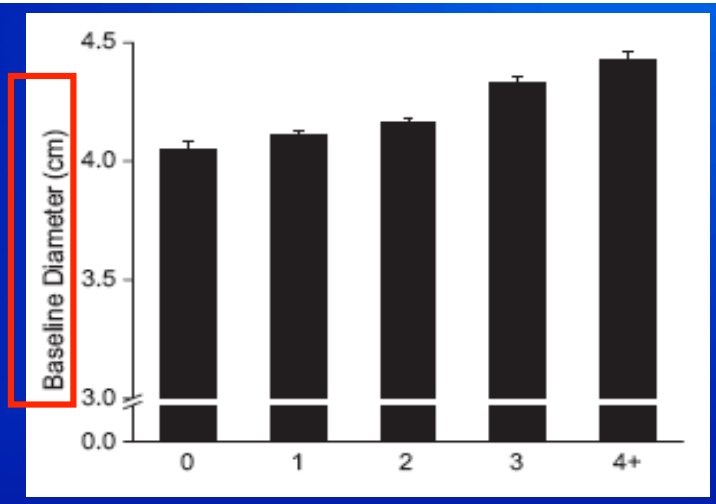
Estensione della Coronaropatia	0 vasi (n=38)	1 vaso (n=34)	2 vasi (n=30)	3 + vasi (n=22)	p trend
BAD, mm	34±8	37±9	40±9	43±7	.0001
FMD,%	14±10	10±12	8±11	4±9	.001
NTGMD,%	24±10	22±11	18±10	18±11	.05

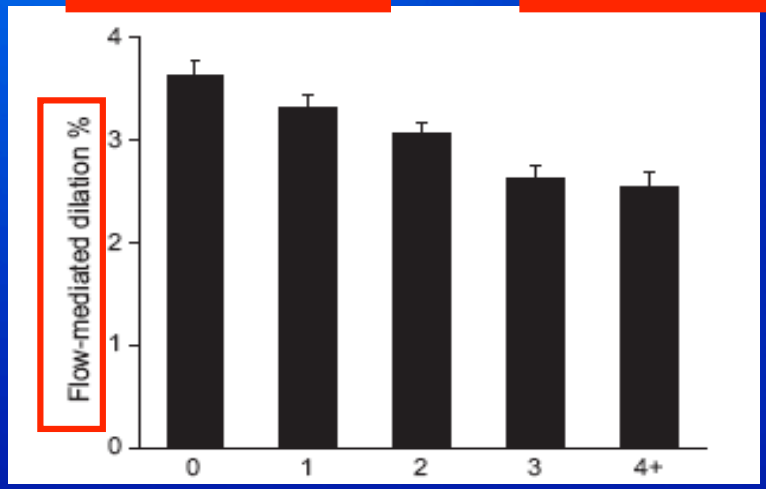
Metabolic Syndrome, Insulin Resistance, and Brachial Artery Vasodilator Function in Framingham Offspring Participants Without Clinical Evidence of Cardiovascular Disease

Naomi M. Hamburg, MD[a], Martin G. Larson, ScD[b,c], Joseph A. Vita, MD[a], Ramachandran S. Vasan, MD[a,b], Michelle J. Keyes, PhD[b,c], Michael E. Widlansky, MD, MPH[a], Caroline S. Fox, MD, MPH[b,d], Gary F. Mitchell, MD[e], Daniel Levy, MD[b], James B. Meigs, MD, MPH[f], and Emelia J. Benjamin, MD, ScM[a,b,*]

(Am J Cardiol 2008;101:82–88)

	MS yes	MS no
HOMA-IR*	5.3 ± 3.0	2.9 ± 1.5
Insulin resistance*†	51%	10%





CONCLUSIONI

- Il diabete mellito tipo 2 è il fattore di rischio maggiormente significativo nella donna per malattie cardiovascolari. Incide così tanto che merita l'appellativo di "tallone d'Achille".

- Così come il T2DM, anche l'insulino-resistenza, e la sua forma clinicamente evidente: la Sindrome Metabolica, incrementano significativamente il rischio cardiovascolare, specificamente nella donna.

CONCLUSIONI 2

I meccanismi tramite cui questo si verifica sono 2:

- **la Disfunzione Endoteliale**
- **il Rimodellamento Vascolare**

Conclusioni 3

- Il rimodellamento vascolare correla ampiamente con il rischio di eventi cardiovascolari.
- Dovrebbe essere compreso meglio, al fine di classificare il livello individuale di rischio.
- L'effetto negativo sul rimodellamento delle arterie di conduttanza sembra per lo più mediato dall'insulino-resistenza (componente metabolica).
- La dimensione dell'arteria e lo studio del flusso danno indicazioni "complementari".