



UNIVERSITÀ DEGLI STUDI DI MODENA E REGGIO EMILIA  
FACOLTÀ DI MEDICINA E CHIRURGIA



ATENEIO FONDATO NEL 1175

*“Il diabete nell’universo femminile”*  
**Il cuore e i vasi della  
donna diabetica**

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# **“Peculiarità” del diabete nel genere femminile**

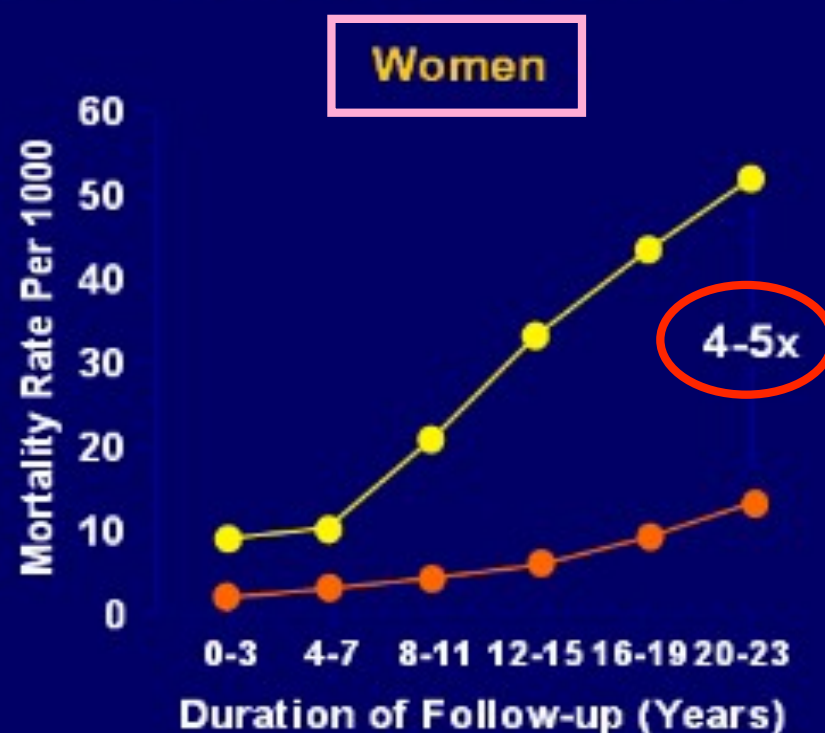
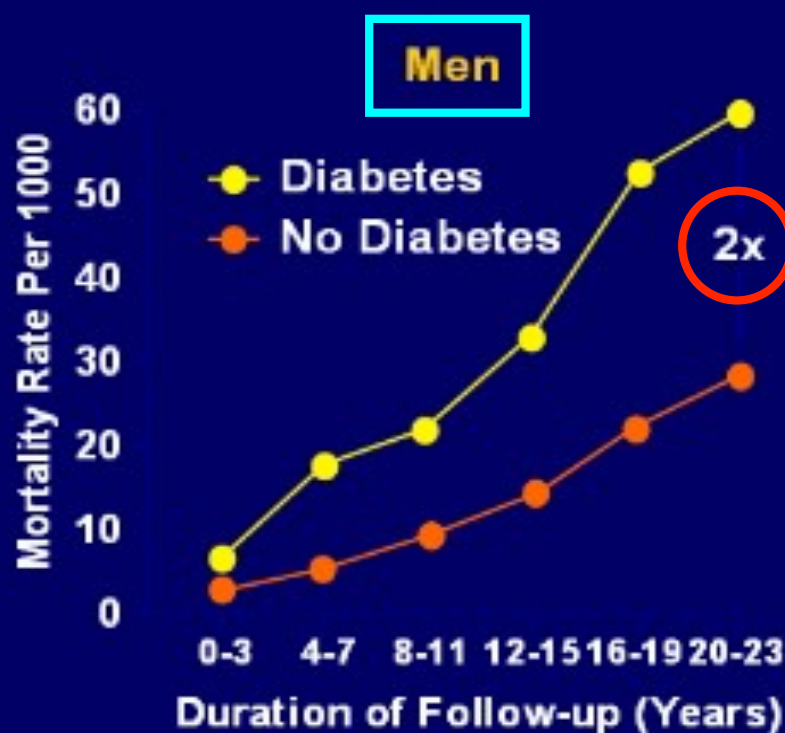
## Entità del Problema

- 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): 58S-81S.



ELSEVIER

# Atherosclerosis

[Atherosclerosis](#). 2008 Sep 17. [Epub ahead of print]

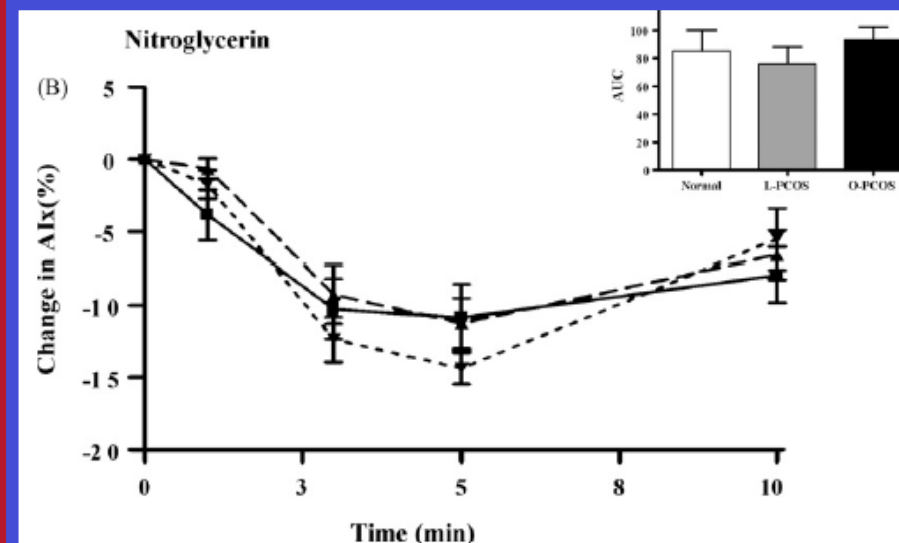
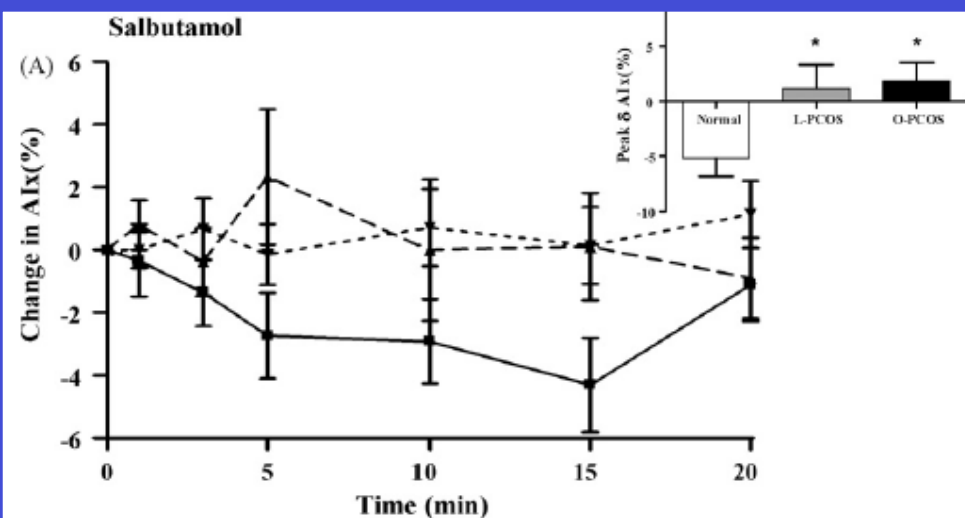
journal homepage: [www.elsevier.com/locate/atherosclerosis](http://www.elsevier.com/locate/atherosclerosis)

atherosclerosis



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

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



# Diabetes and Abnormal Glucose Tolerance in Women With Previous Gestational Diabetes

MERCE 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

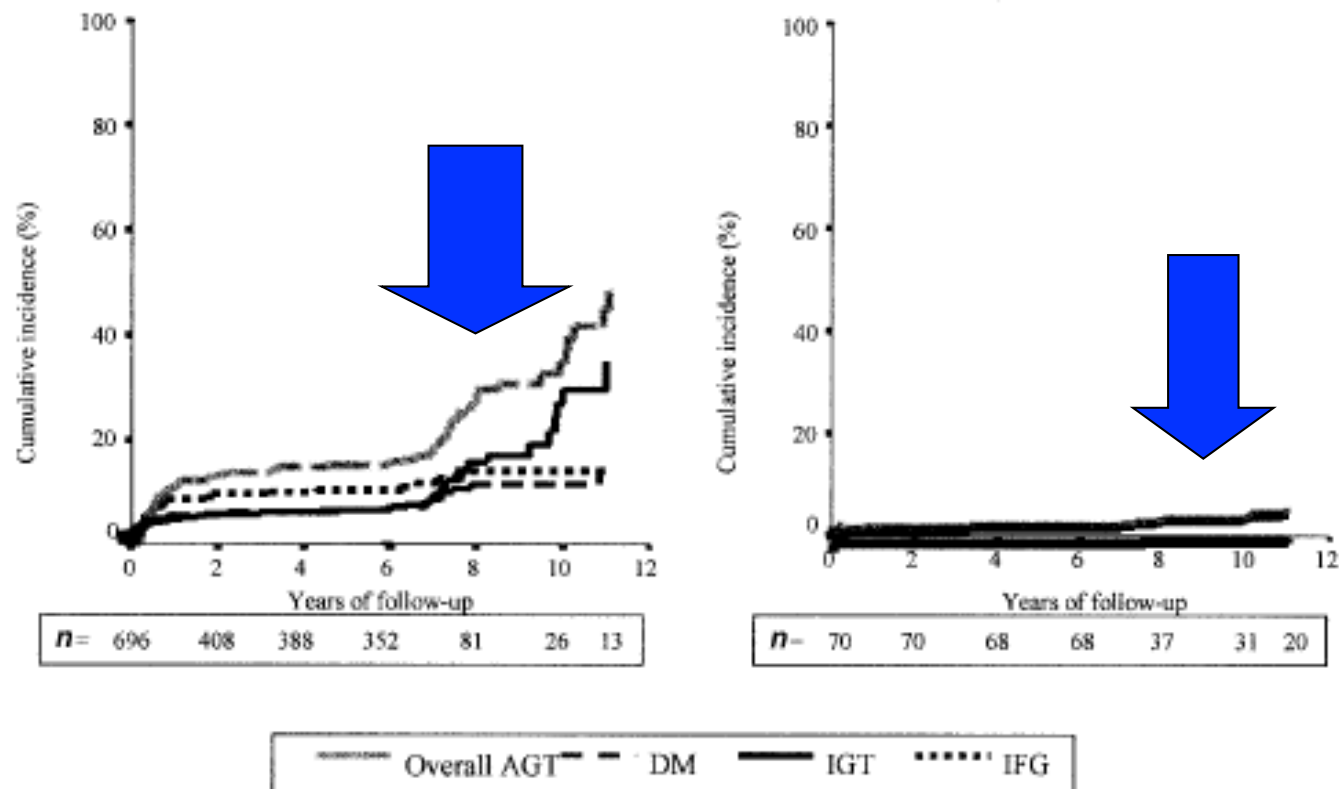


Figure 2—Cumulative incidence of diabetes and AGT (diabetes, IGT, IFG) in women with previous GDM (A) and control women (B) as determined by life table analysis. The cumulative rates of diabetes and overall AGT were 13.8 and 42.4% at 11 years of follow-up in women with GDM vs. 0 and 2.8% in control women.



# Transdermal 17- $\beta$ -Estradiol and Risk of Developing Type 2 Diabetes in a Population of Healthy, Nonobese Postmenopausal Women

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MARIA G. MODENA, MD<sup>1</sup>

*Diabetes Care* 27:645–649,  
2004

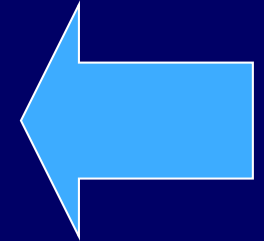
Table 2—Incidence rates of diabetes among the study population

	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.

# Atherosclerosis in Diabetes

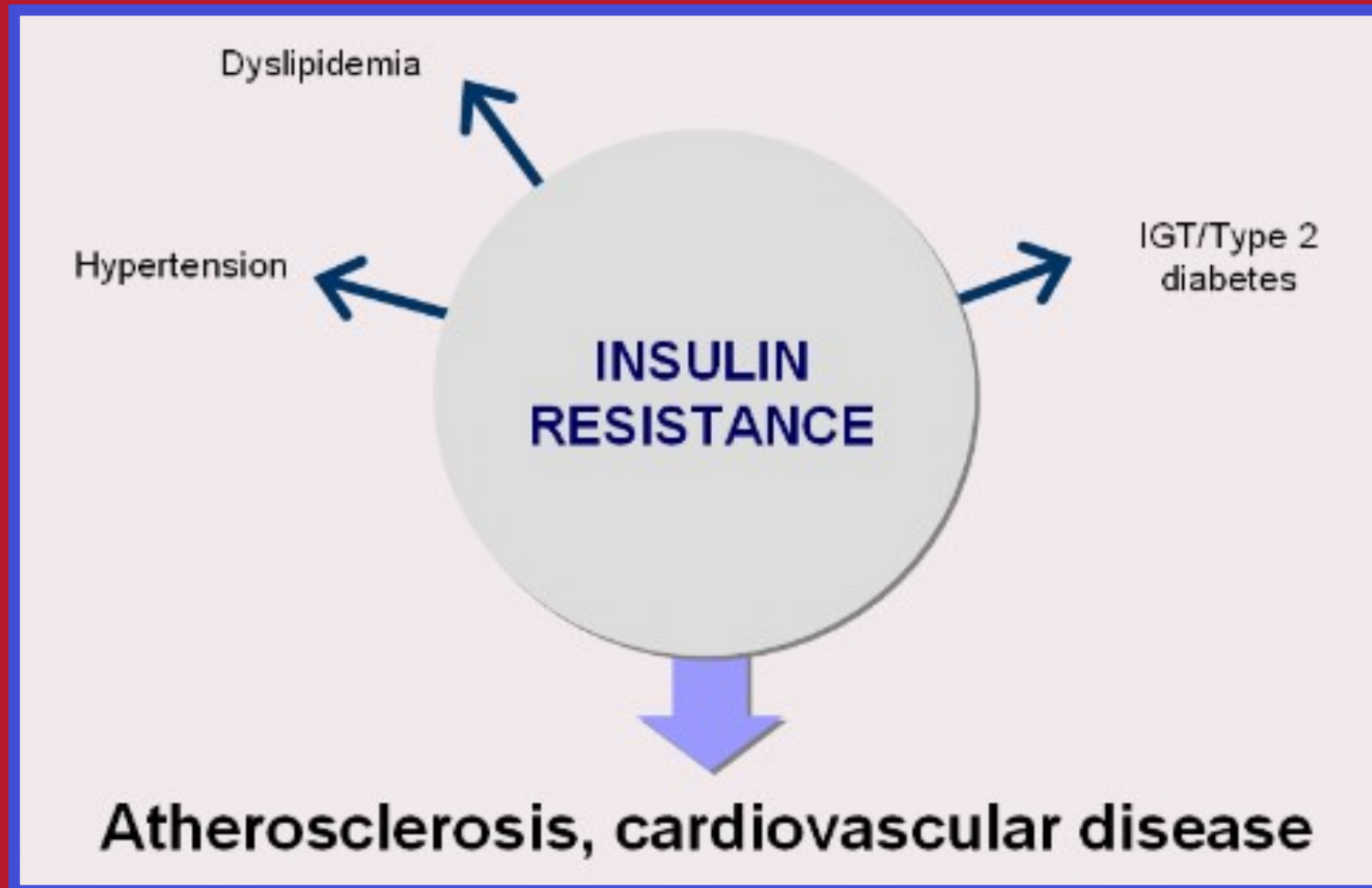
- Accelerated atherosclerosis is multifactorial and begins years/decades prior to diagnosis of type 2 diabetes
- **>50%** of patients with newly diagnosed type 2 diabetes have CHD
- Risk for atherosclerotic events is 2- to 4-fold greater in diabetics than in nondiabetics
- Atherosclerosis accounts for ~65% of all diabetic mortality
  - 40% due to ischemic heart disease
  - 15% due to other heart disease
  - 10% due to cerebrovascular disease



Garber AJ. *Clin Cornerstone*. 2003;5:22-37.  
Garber AJ. *Med Clin North Am*. 1998;82:931-948.  
National Diabetes Data Group. *Diabetes in America*.  
2nd ed. NIH;1995.







# Endothelial-Dependent Vasodilation and Incidence of Type 2 Diabetes in a Population of Healthy Postmenopausal Women

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ELENA CIONI, MD<sup>1</sup>  
ANNACHIARA NUZZO, MD<sup>1</sup>

GIORGIA ORIGLIANI, PHD<sup>2</sup>  
MARIA GRAZIA MODENA, MD<sup>1</sup>

**OBJECTIVE** — Both postmenopausal state and diabetes are associated with endothelial dysfunction and are well-known risk factors for atherosclerosis. However, the relationship of endothelium-dependent vasodilation and diabetes has never been prospectively evaluated. This study provided the opportunity to assess the association between endothelial vasodilation function and the incidence of diabetes in a cohort of apparently healthy postmenopausal women.

**RESEARCH DESIGN AND METHODS** — We conducted a prospective cohort study that began in 1997 with 840 apparently healthy, nonobese, postmenopausal women, aged  $53 \pm 6$  years, initially with normal glucose tolerance at the oral glucose tolerance test. All participants were followed up for a mean period of  $3.9 \pm 0.7$  years (range 0.5–6.9). Endothelial function was measured as flow-mediated dilation (FMD) of the brachial artery, using high-resolution ultrasound.

**RESULTS** — There were no significant differences in demographic, blood pressure, and biochemical profiles among each tertile group at baseline or at follow-up review. During follow-up, 102 women developed type 2 diabetes. The adjusted relative risk (RR) for women with FMD  $\leq 4.3$  (lowest tertile) was 5.87 (95% CI 4.34–8.10) versus women with FMD  $\geq 5.6$  (highest tertile reference). Each 1-unit decrease of FMD was associated with a significant 32% (22–48%) increase in the multiple-adjusted RR of incident diabetes.

**CONCLUSIONS** — These prospective data indicate a significant increase in the RR of diabetes with each unit decrease of FMD. This could suggest that an impaired endothelial function may play a fundamental role in diabetogenesis in postmenopausal women.

terms of mortality, morbidity, and financial resources (6). Endothelial dysfunction is a very frequent occurrence among diabetic patients (7–10).

Because endothelial dysfunction is also present in nondiabetic postmenopausal women (1,2), it is not clear whether endothelial dysfunction is a consequence or rather the cause of diabetes, thus preceding its onset. Although there are both references relating to the fact that endothelial dysfunction may precede insulin resistance (11,12) and unique recent work concerning the relationship between the spillover markers of endothelial dysfunction and incident diabetes (13), a clear relationship between endothelium-dependent vasodilation and diabetes has, to our knowledge, never been demonstrated. This study provided the opportunity to prospectively assess the association between endothelial vasodilation function, evaluated by ultrasound study of the brachial artery, and the incidence of diabetes among apparently healthy initially nondiabetic postmenopausal women.

*Diabetes Care* 28:702–707, 2005

**RESEARCH DESIGN AND METHODS**

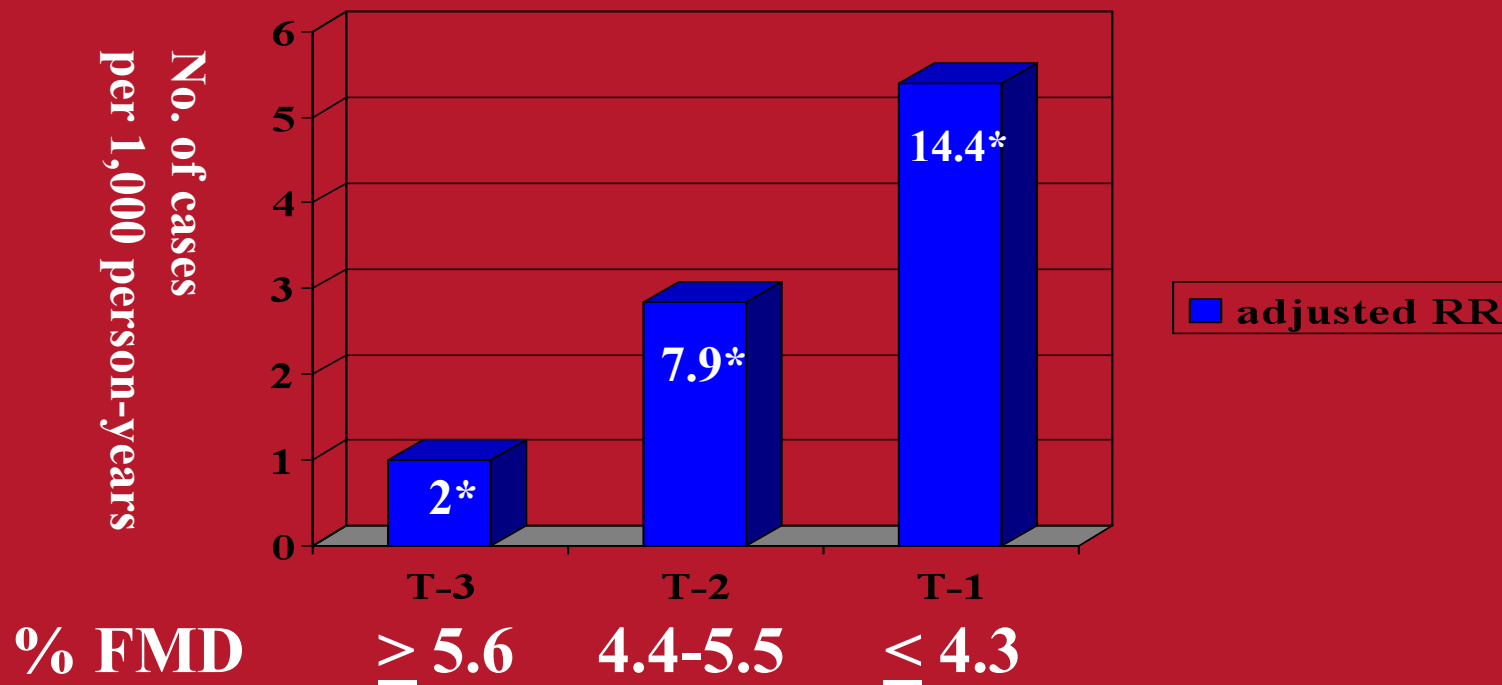
**Table 3—Crude and multiple-adjusted RR of incident diabetes by tertiles of endothelial-dependent FMD of the brachial artery**

	3rd tertile (referent)	2nd tertile	1st tertile
Levels of FMD (%)	≥5.6	4.4–5.5	≤4.3
Median FMD (%)	6.2	5.0	3.9
Incident diabetes (no. of cases)	9	35	58
Person-years	1,132	1,112	1,008
Incidence rate (no. of cases per 1,000 person-years)	2.0	7.9	14.4
Crude RR (95% CI)	1.00	3.95 (2.85–5.21)	7.20 (5.88–8.82)*
Multiple-adjusted RR (95% CI)†	1.00	2.85 (2.14–3.81)	5.40 (4.35–6.66)*

\*P < 0.0001. †Cox proportional hazards regression model adjusted for age (continuous), family history of diabetes (yes/no); level of plasma glucose (continuous); BMI (continuous); waist circumference (continuous); duration of postmenopausal period (continuous); alcohol consumption (never, 1–5 drinks/month, 2–6 drinks/week, ≥1 drink/day); physical activity (never, 1–2 times/week, ≥3 times/week); baseline systolic and diastolic blood pressure (continuous); BMI (continuous); waist circumference (continuous); and fasting plasma levels of glucose, total cholesterol, and triglycerides (continuous) and their changes from baseline to the last follow-up visit (continuous).

Rossi R. Diabetes Care, 2005

**Each 1-unit decrease in %FMD was associated with a significant 32% (95% CI: 22-48) increase in the multiple-adjusted relative risk of incident diabetes**



% FMD

≥ 5.6

4.4-5.5

≤ 4.3



# Flow-Mediated Vasodilation and the Risk of Developing Hypertension in Healthy Postmenopausal Women

Rosario Rossi, MD,\* Emilio Chiurlia, MD,\* Annachiara Nuzzo, MD,\* Elena Cioni, MD,\*  
Giorgia Origliani, PhD,† Maria Grazia Modena, MD, FESC, FACC\*  
Modena, Italy

**OBJECTIVES** This study provided the opportunity to assess the relationship between endothelial vasomotor function and incidence of hypertension in a cohort of postmenopausal women.

**BACKGROUND** Both menopause and hypertension are associated with endothelial dysfunction and are well-known risk factors for atherosclerotic-related disease.

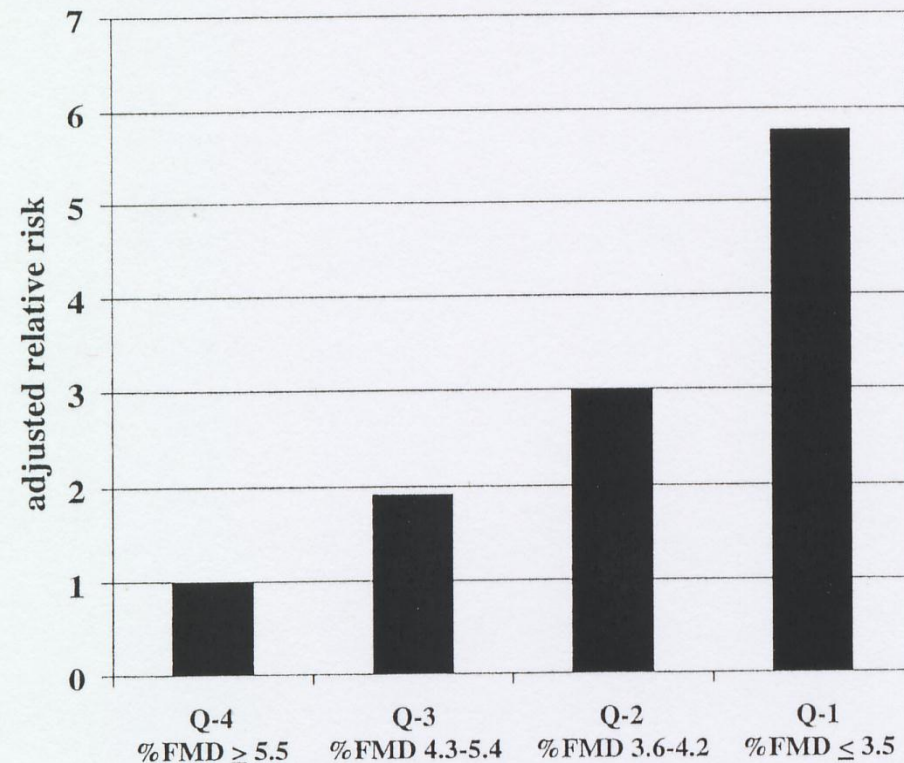
**METHODS** We conducted a prospective cohort study that began in 1996 on 952 apparently healthy postmenopausal women, age  $53 \pm 5$  years (range 44 to 60 years), with initially normal levels of blood pressure and no history of hypertension. All participants were followed up for a mean period of  $3.6 \pm 0.7$  years (range 0.5 to 6.9 years). Endothelial function was measured as flow-mediated dilation of the brachial artery using high-resolution ultrasound.

**RESULTS** During follow-up 112 women developed hypertension. Those with flow-mediated dilation of 3.5 or less (lowest quartile) 4.34 to 8.10) versus women with flow-mediated dilation (referent). Each one-unit decrease of flow-mediated dilation was associated with a 16% (95% confidence interval 12% to 33%) increase in the incidence of hypertension.

**CONCLUSIONS** These prospective data indicate a significant increase in the incidence of hypertension with each unit decrease of flow-mediated dilation that is independent of age, body mass index, and diastolic blood pressure values. This could suggest that endothelial dysfunction precedes and predicts the future development of hypertension in healthy postmenopausal women. (J Am Coll Cardiol 2004;44:1636-40) © 2004 American College of Cardiology Foundation

952 healthy postmenopausal women, mean age: 53 years, were followed-up for a mean period of 3.6 years.

112 women developed hypertension: 10, 20, 40, 61 cases/1000 women/years in the 4 quartiles of %FMD





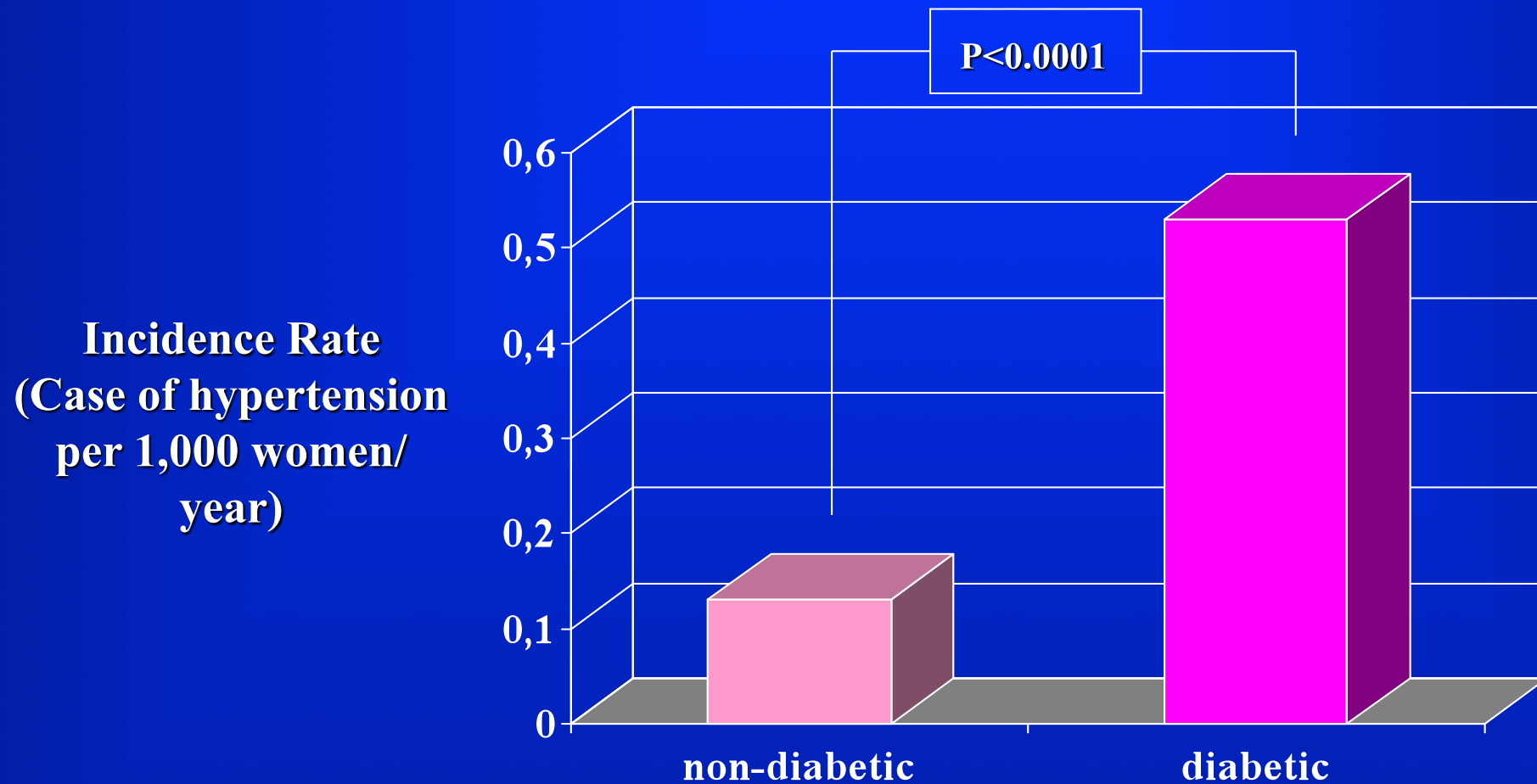
**Type 2 diabetes mellitus is a risk factor for the development of hypertension in postmenopausal women**

Rosario Rossi<sup>a</sup>, Vincenzo Turco<sup>a</sup>, Giorgia Origliani<sup>b</sup> and M. Grazia Modena<sup>a,b</sup>

**J Hypertens. 2006 Oct; 24(10): 2017-22**

- We assessed the risk of developing hypertension in **102** diabetic (type 2 diabetes mellitus) postmenopausal women, compared with **538** diabetic-free women.
- The mean follow-up was **38 ± 8** months (range 6 - 66 months).

# Type 2 diabetes mellitus is a risk factor for the development of hypertension in postmenopausal women

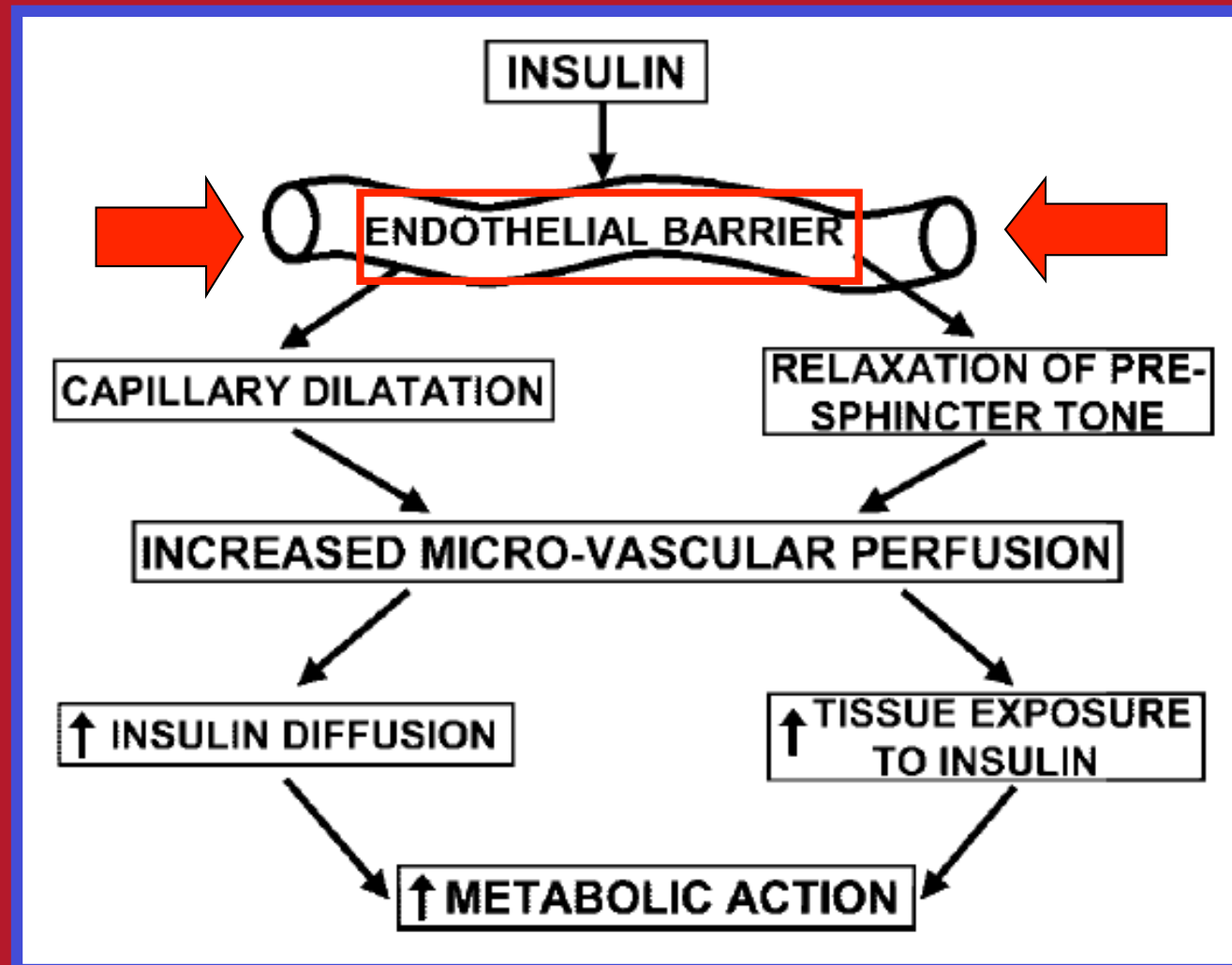




# Insulin resistance and endothelial dysfunction: the road map to cardiovascular diseases

Eugenio Cersosimo  
Ralph A. DeFronzo

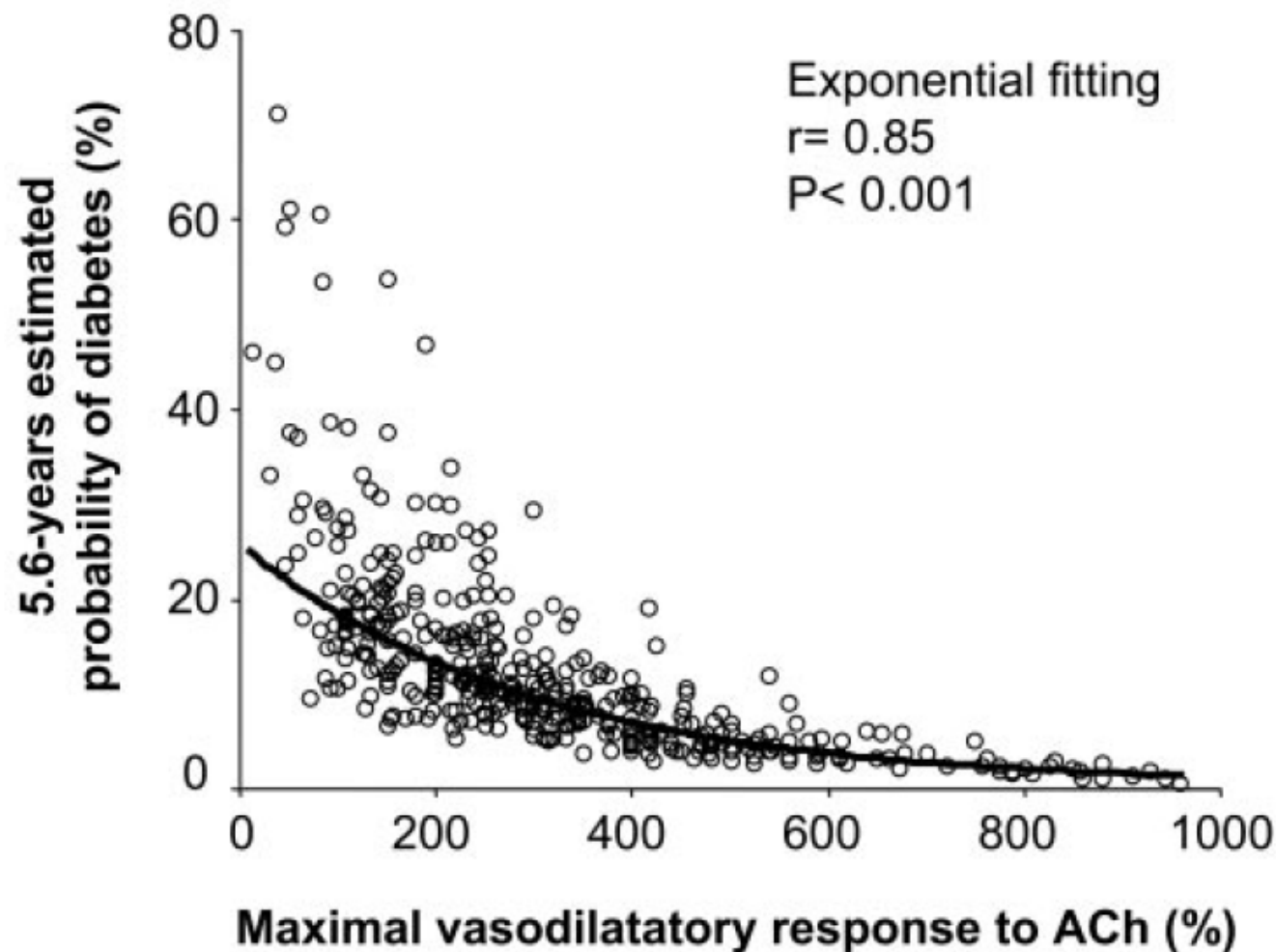
DIABETES/METABOLISM RESEARCH AND REVIEWS  
*Diabetes Metab Res Rev* 2006; 22: 423-436.



# Endothelial Dysfunction and C-Reactive Protein Are Risk Factors for Diabetes in Essential Hypertension

Francesco Perticone,<sup>1</sup> Raffele Maio,<sup>1</sup> Angela Sciacqua,<sup>1</sup> Francesco Andreozzi,<sup>1</sup> Giuseppina Iemma,<sup>1</sup> Maria Perticone,<sup>1</sup> Carmine Zoccali,<sup>2</sup> and Giorgio Sesti<sup>1</sup>

*Diabetes* 57:167–171, 2008

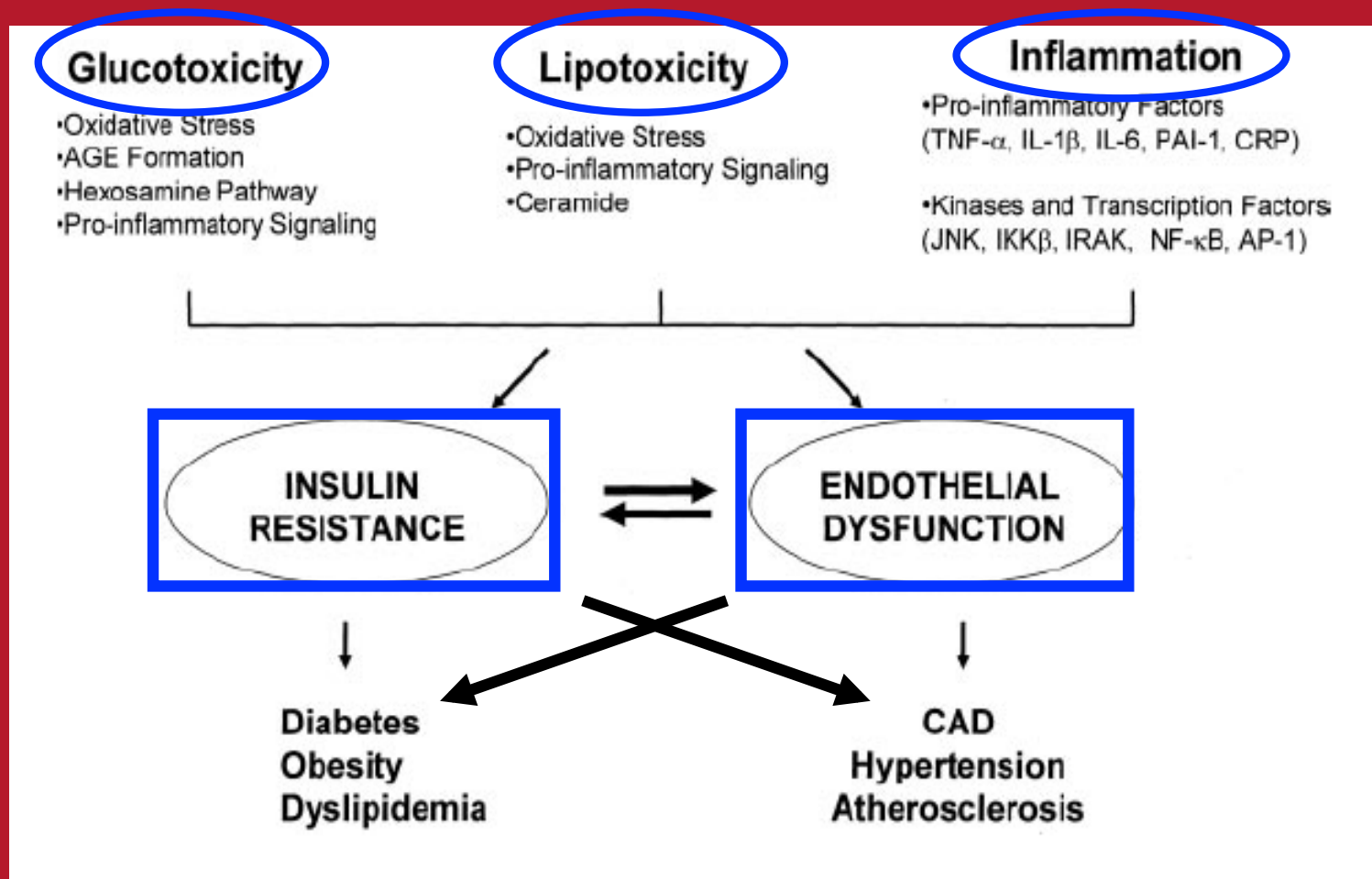


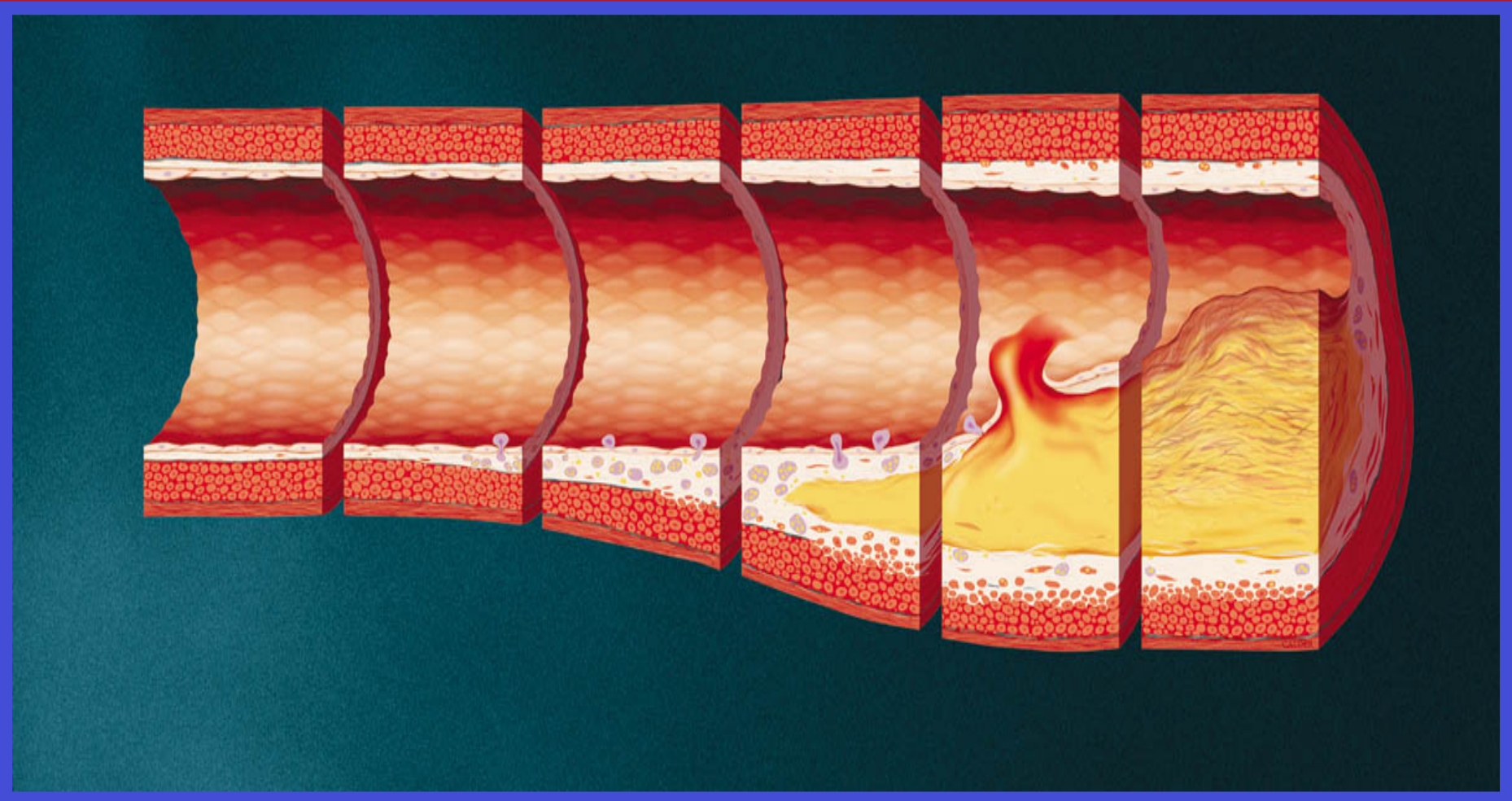
# Reciprocal Relationships Between Insulin Resistance and Endothelial Dysfunction

## 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.)





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

# Insulin-resistance affects remodeling of the systemic 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
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

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

## Risultati

Estensione della Coronaropatia	0 vasi	1 vaso	2 vasi	3 + vasi	p
	(n=38)	(n=34)	(n=30)	(n=22)	trend
WC,cm	86±10	89±11	93±11	97±12	.001
HbA1c,%	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

# Determinanti “indipendenti” di Coronaropatia

- **MASCHIO**
- Ipercolesterolemia
- Abitudine Tabagica
  
- **FEMMINA**
- **HOMA-IR**

# Insulin Resistance and the Endothelium

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

There is increasing evidence of a parallel progression between insulin resistance and endothelial dysfunction, suggesting a close association between insulin action and the endothelium. Numerous studies have demonstrated that endothelial dysfunction occurs early in the insulin-resistant state and is predictive of future cardiovascular events. Similarly, insulin resistance has been associated with the metabolic syndrome, which also increases the risk of adverse cardiovascular outcomes. Approaches that improve endothelial dysfunction, such as treat-

ment with statins, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or peroxisome proliferator-activated receptor  $\gamma$  ligands, have been shown to prevent both diabetes and cardiovascular disease. This article reviews the relation between endothelial dysfunction and cardiovascular disease, assesses the endothelium in the spectrum of insulin resistance, and examines the effect of the thiazolidinediones on endothelial function. *Am J Med.* 2004;117:109–117. ©2004 by Elsevier Inc.

	Improve Endothelial Function	Reduce Incidence of New-Onset Diabetes	Prevent Cardiovascular Disease
Exercise and diet	+	+	+
Statins	+	+	+
ACE inhibitor	+	+	+
AT <sub>1</sub> receptor blocker	+	+	+