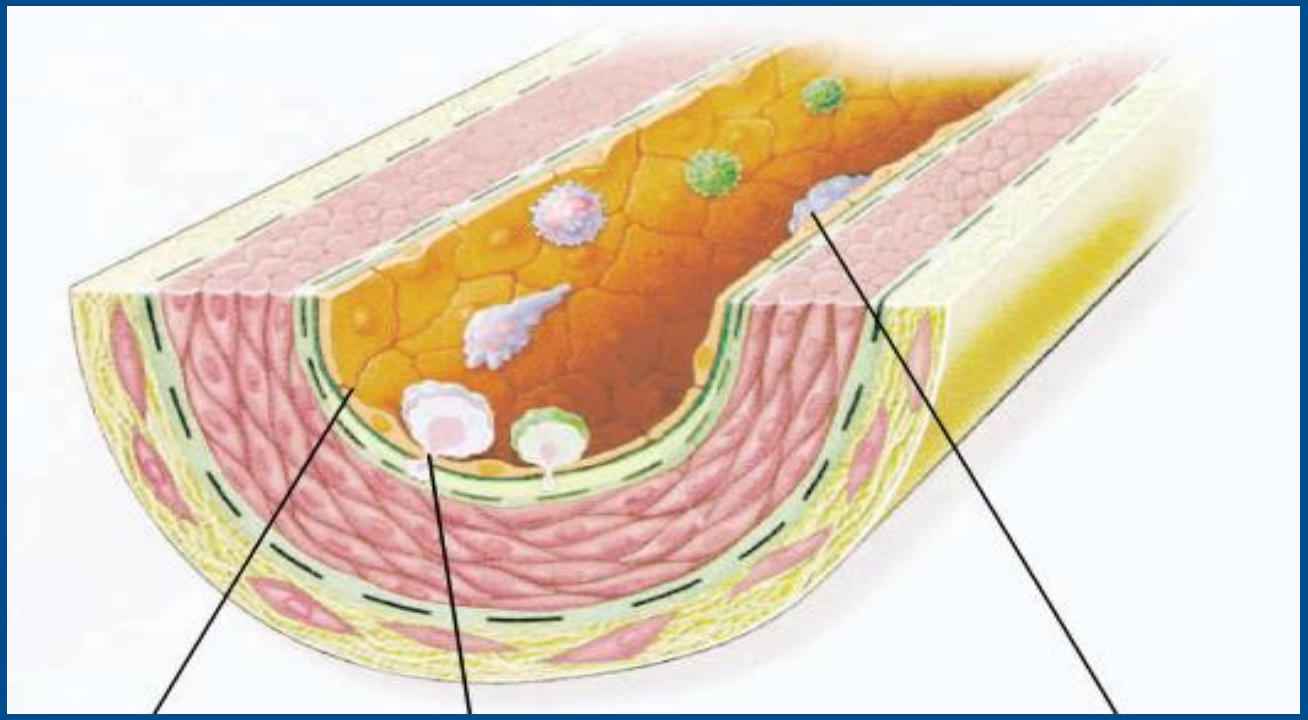
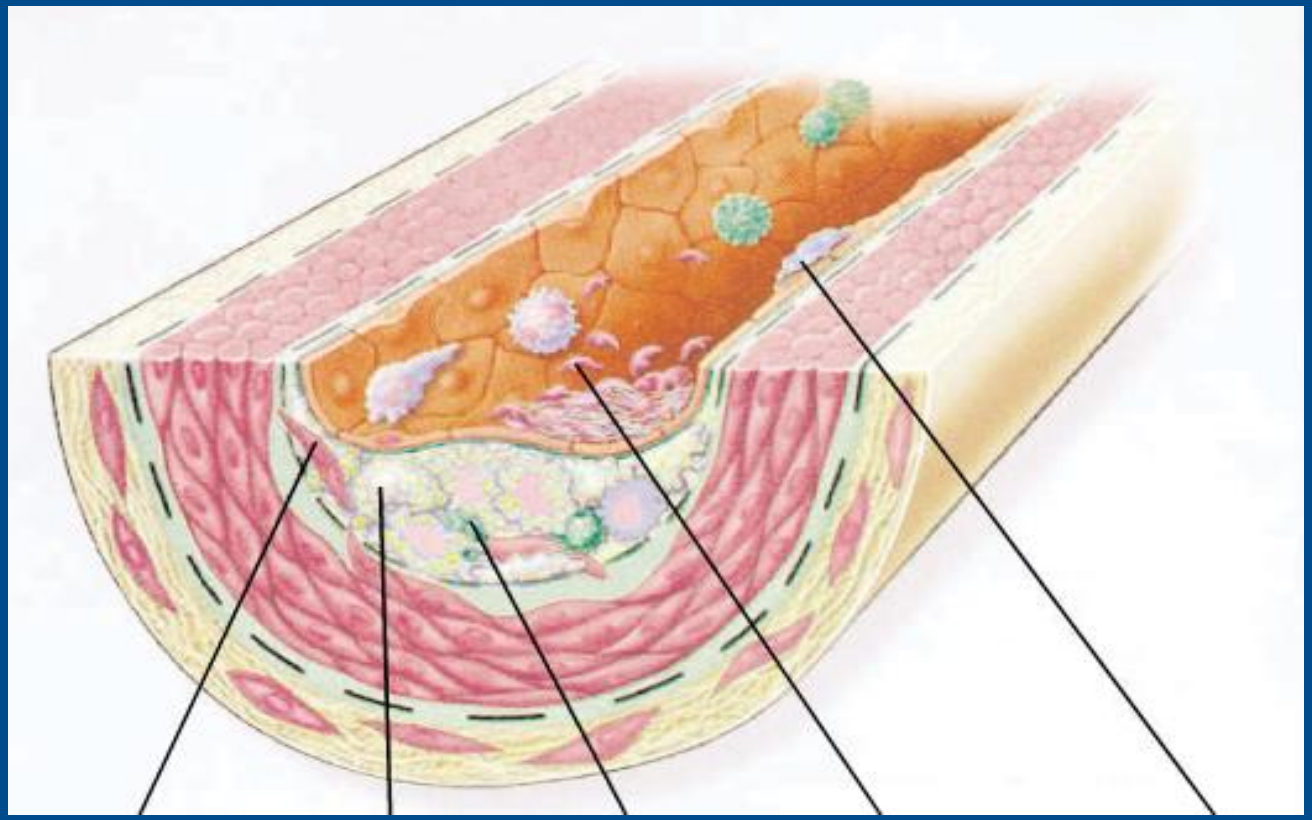
Vascular Dysfunction and Type 2 Diabetes: What is the Link?

Factors in Endothelial Dysfunction
Early-Stage Plaque



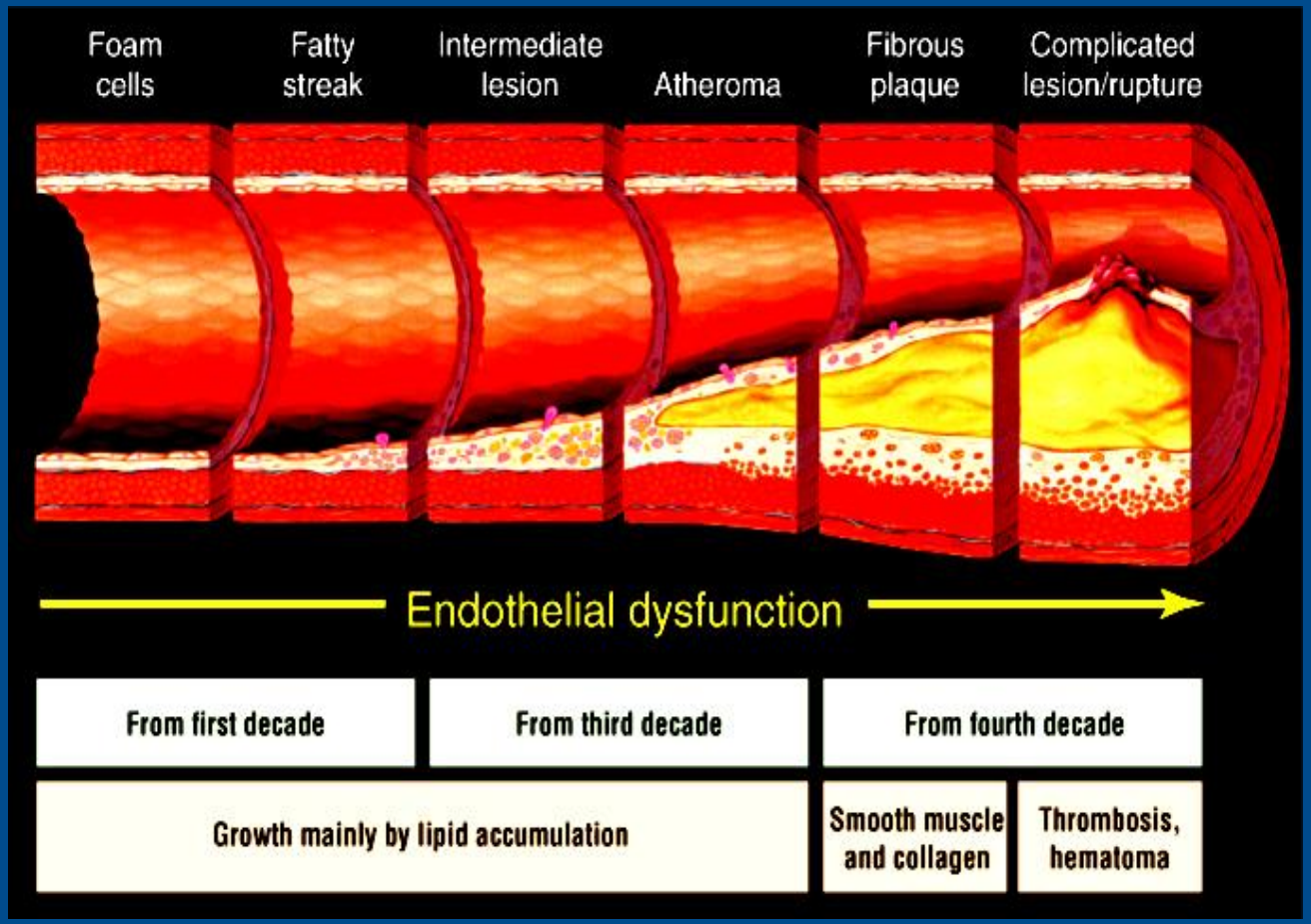
Adapted from Ross R. *N Engl J Med* 1999;340:115–126.

Factors in Endothelial Dysfunction
Late-Stage Plaque



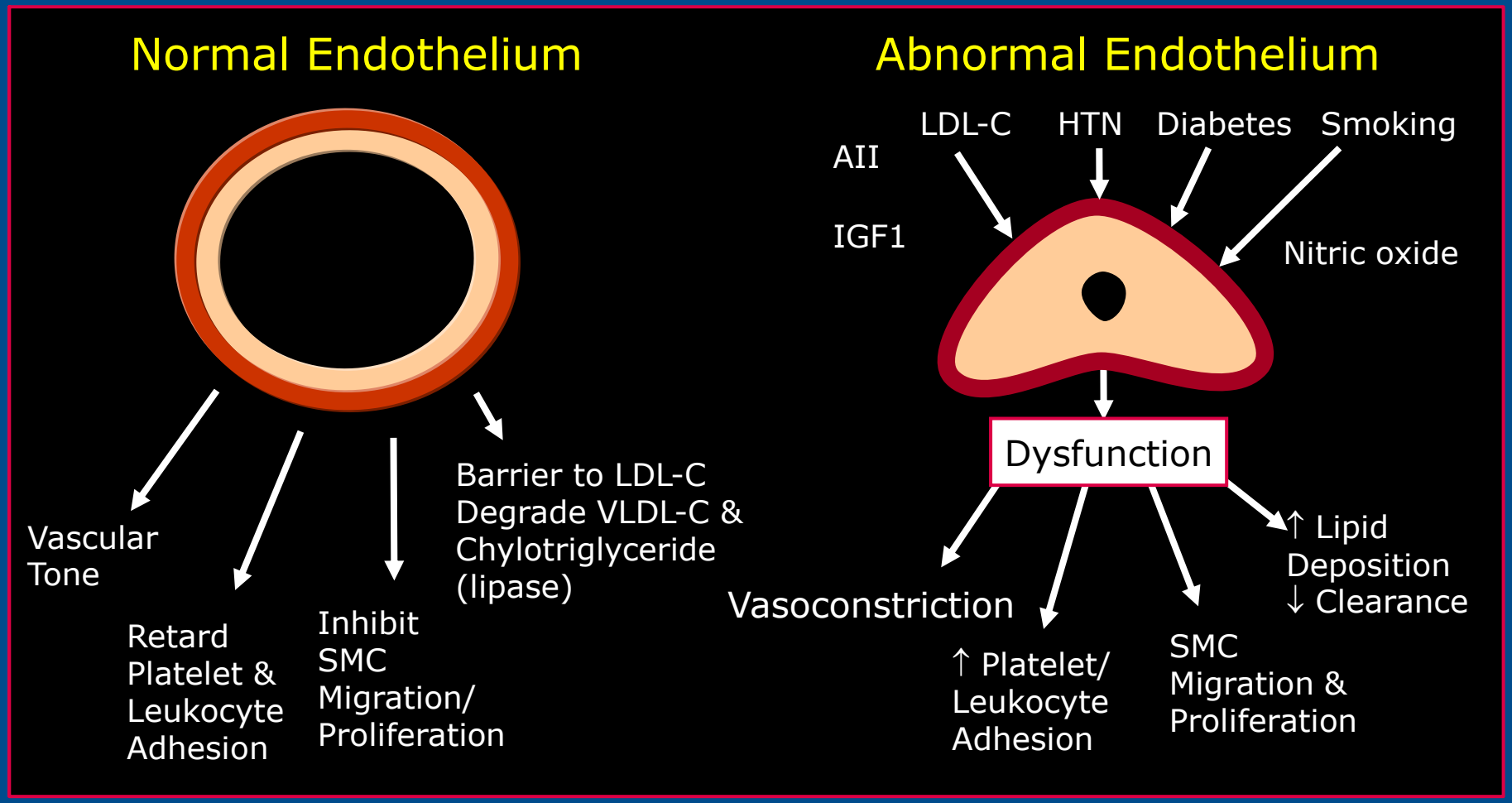
Adapted from Ross R. *N Engl J Med* 1999;340:115–126.

Atherosclerosis Timeline



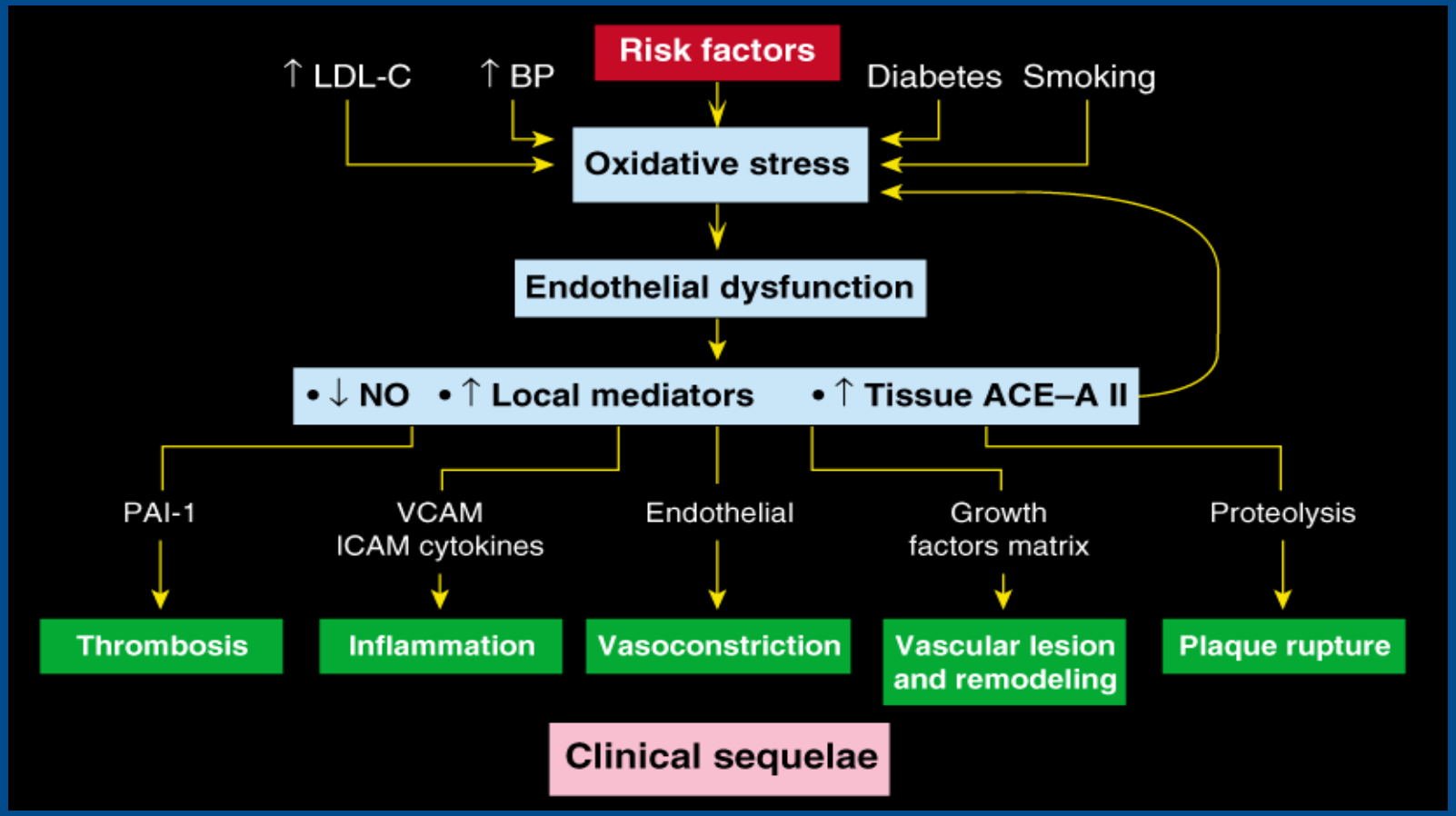
Adapted from Pepine CJ. *Am J Cardiol* 1998;82(suppl 10A):23S–27S.

Endothelial Dysfunction Leads to Imbalance of Factors, Resulting in Vascular Disease



Adapted from Vogel RA. *Am J Med* 1999;107:479-487.

Causes and Consequences of Endothelial Dysfunction: A Unifying Model

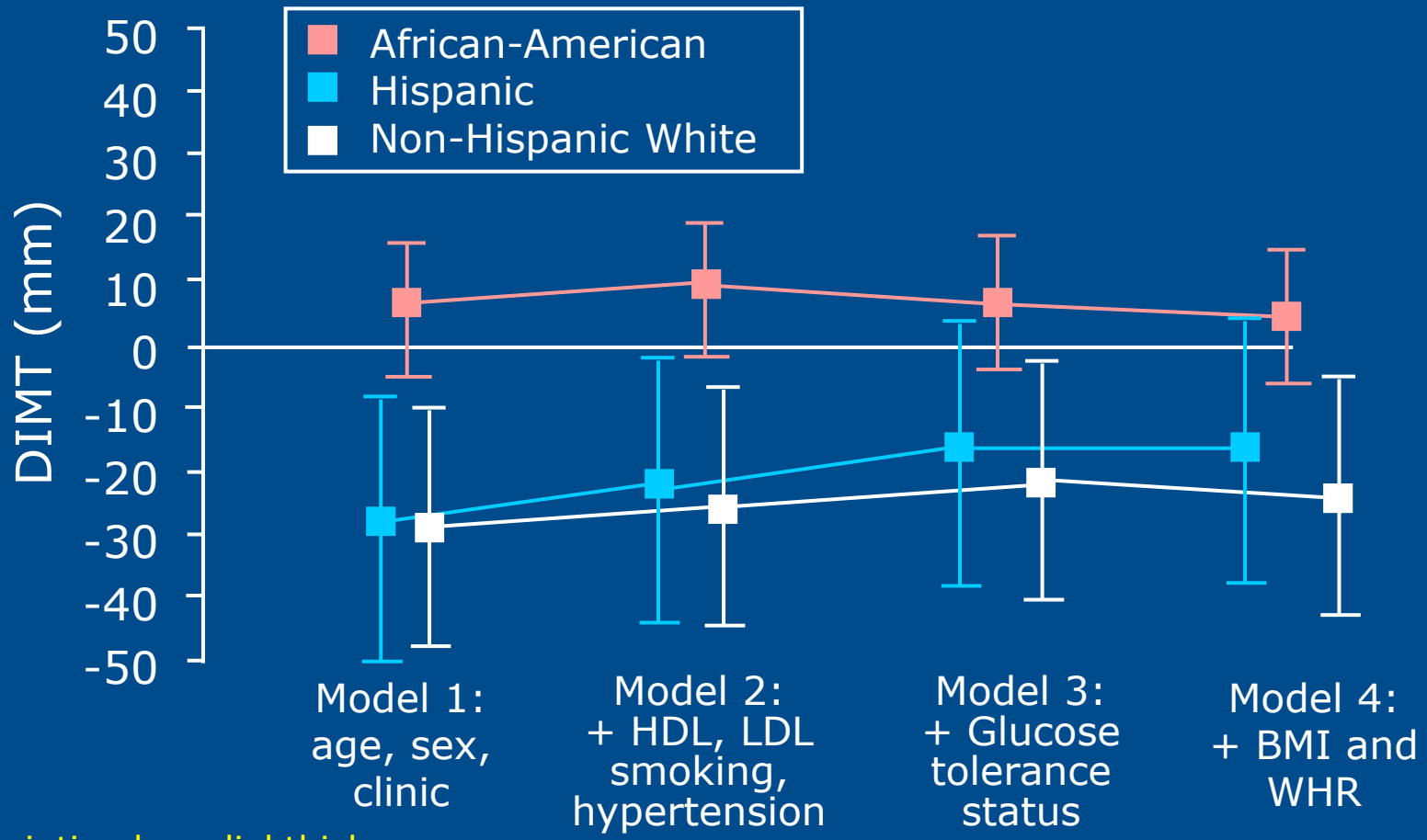


NO=nitric oxide; A II=angiotensin II;
PAI-1=plasminogen activator inhibitor-1.

Adapted from Gibbons and Dzau. *N Engl J Med* 1994;330:1431–1438.

Insulin Resistance Atherosclerosis Study

Difference (95% of CI) in Mean IMT of Internal Carotid Artery/Unit Difference in S_I



IMT=intimal-medial thickness
S_I=insulin sensitivity
WHR=waist-to-hip ratio

Adapted from Howard et al. *Circulation* 1996;93:1809–1817.

Vascular Risk Factors by Degree of Insulin Sensitivity in Type 2 Diabetic Subjects

	Insulin-sensitive	Insulin-resistant	*P* value
Blood Pressure (mm Hg)			
Systolic	128.7	129.1	0.749
Diastolic	77.6	78.5	0.595
Coagulation			
Fibrinogen (mg/dL)	270	293	0.029
PAI-1	17.7	27.3	<0.001
Glucose, Insulin			
Fasting glucose (mg/dL)	153.5	173.7	0.045
AIR ($pmol \cdot mL^{-1} \cdot min^{-1}$)	2.88	7.05	0.270
S_I ($x10^{-4}\ min^{-1} \cdot mU^{-1} \cdot mL^{-1}$)	2.62	0.38	<0.001

PAI-1= plasminogen activator inhibitor-1
AIR= acute insulin response
S_I= insulin sensitivity

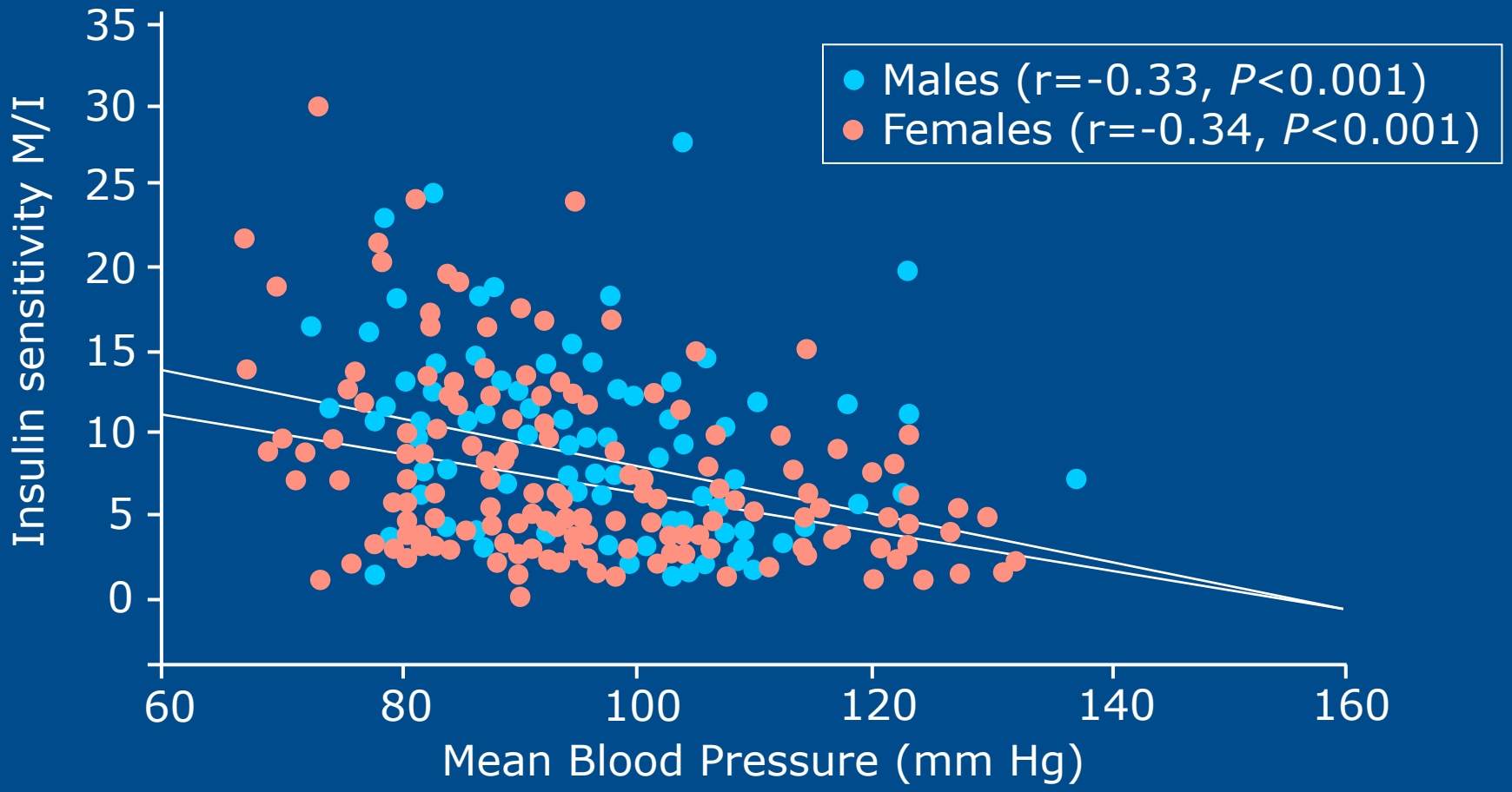
Haffner SM et al. *Diabetes Care* 1999;22:562–568.

Vascular Risk Factors by Degree of Insulin Sensitivity in Type 2 Diabetic Subjects

Lipids (mg/dL)	Insulin-sensitive	Insulin-resistant	*P* value
Total cholesterol	220.2	215.2	0.507
LDL cholesterol	145.7	140.4	0.403
HDL cholesterol	45.3	39.5	0.001
VLDL cholesterol	20.5	26.5	0.033
Total triglyceride	133	166	0.019
VLDL triglyceride	87.2	122.4	0.004
LDL size (Å)	260.5	256.9	0.032

Haffner SM et al. *Diabetes Care* 1999;22:562–568.

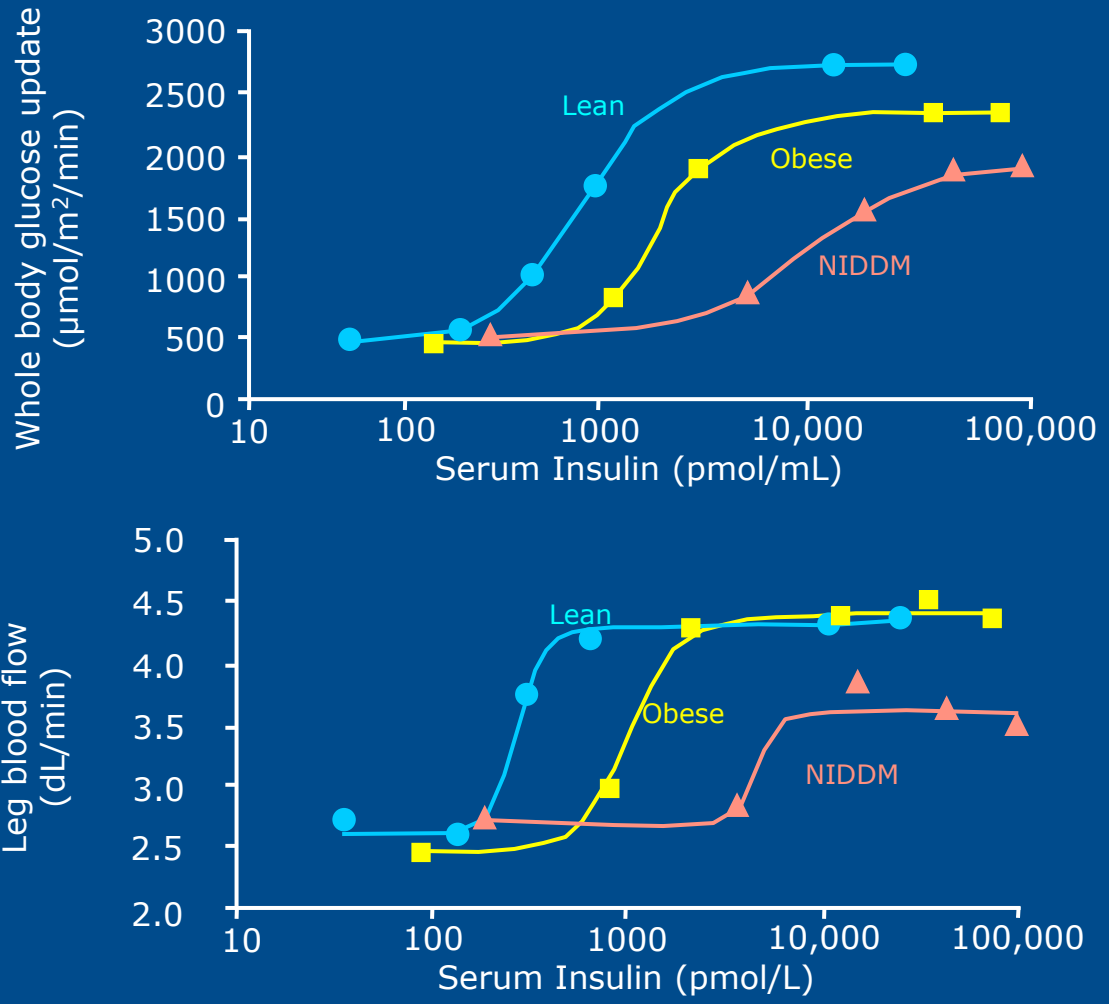
Insulin Resistance Impairs Endothelial Function



Study of 304 nondiabetic black men (n=108) and women (n=196).

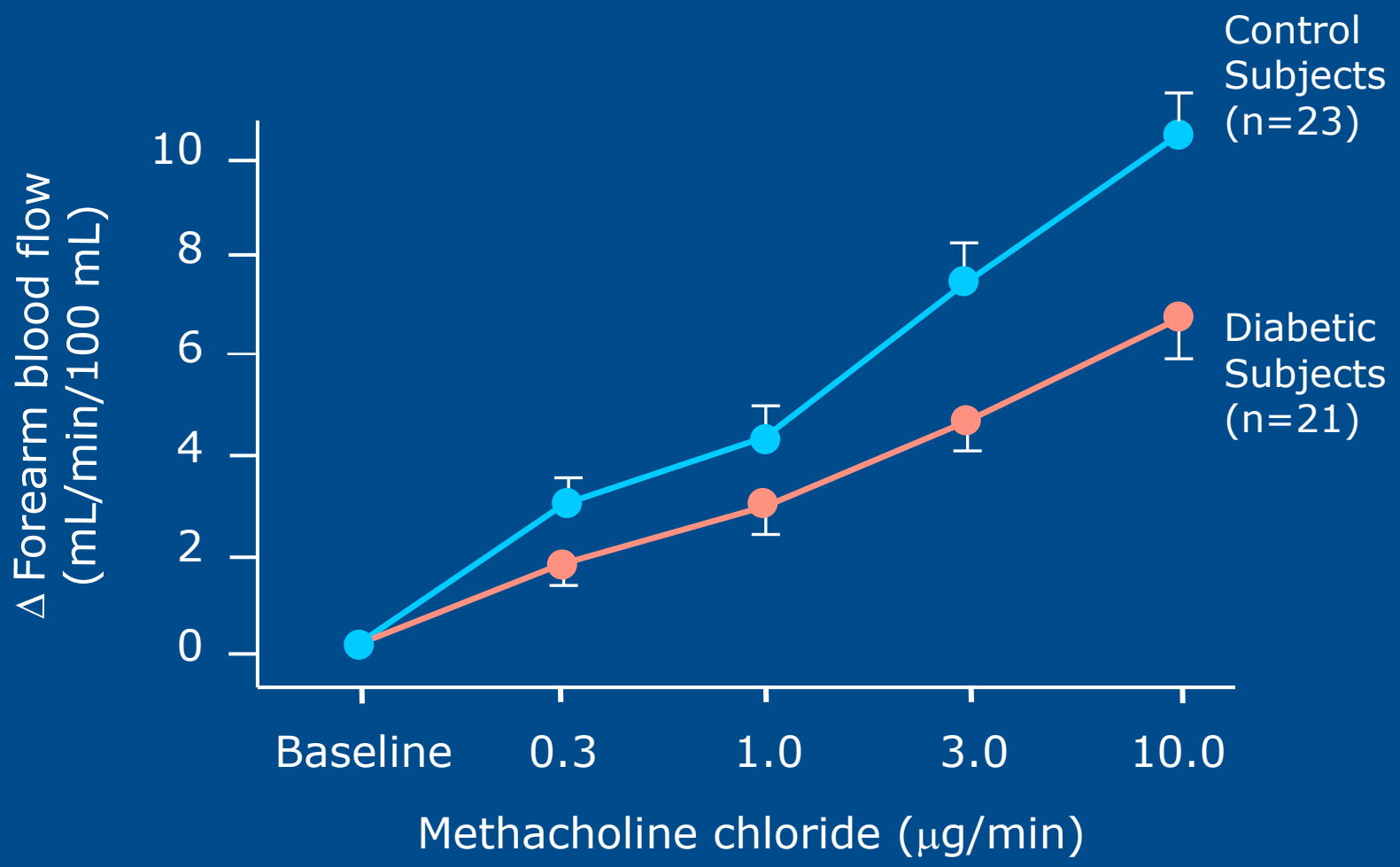
Falkner B et al. *Hypertension* 1999;34:1086–1090.

Diabetes Mellitus Impairs Endothelial Function



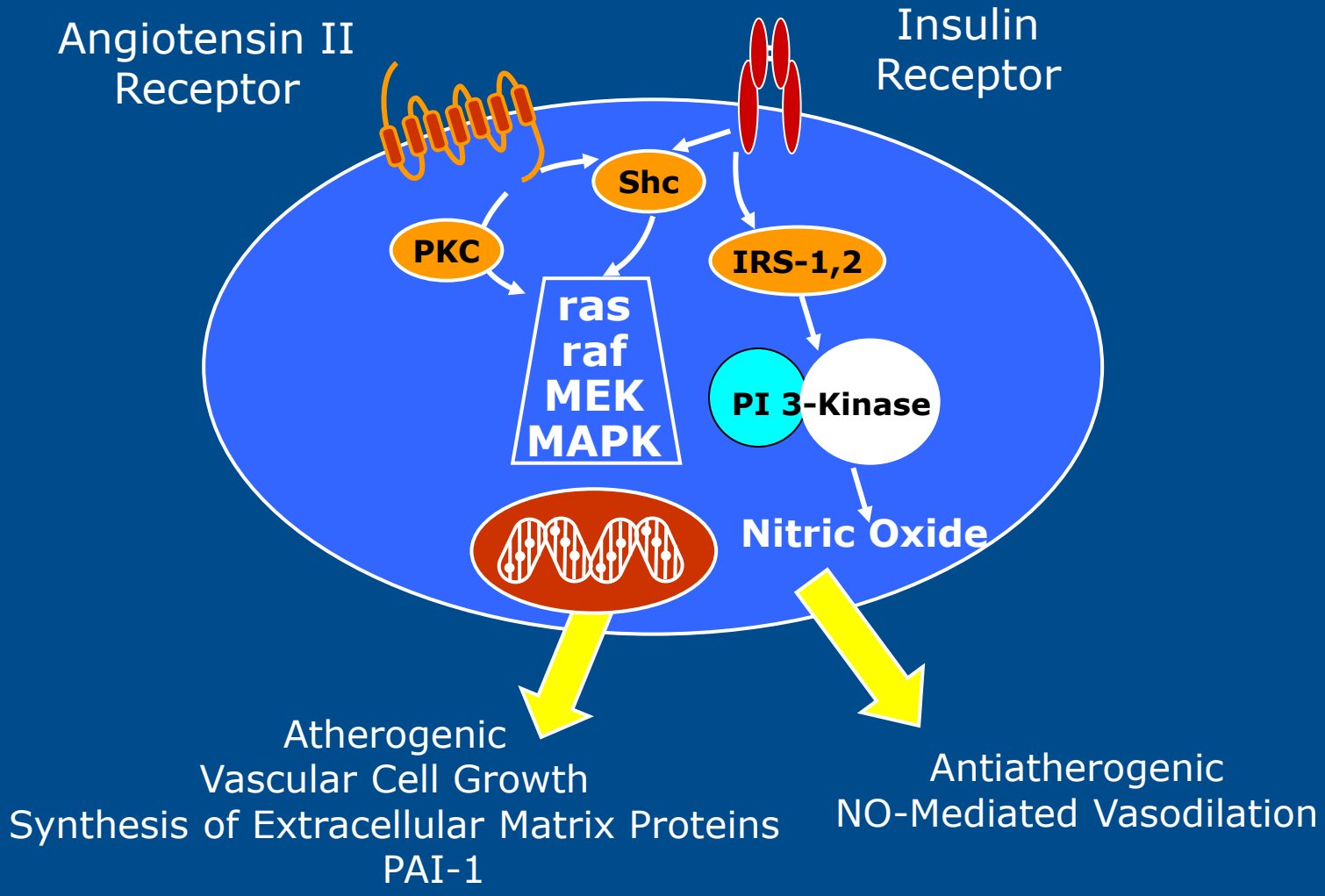
Laakso M et al. *Diabetes* 1992;41:1076–1083.

Decreased Vascular Responsiveness in People with Diabetes



Williams SB et al. *J Am Coll Cardiol* 1996;27:567–574.

Insulin
Potential Atherogenic & Antiatherogenic Actions in Vascular Cells



Feener EP, King GL. *Lancet* 1997;350(suppl 1):SI9–SI13.

Insulin Receptor Signaling Through the PI 3-Kinase Pathway

	Lean controls (n=8)		Obese nondiabetics (n=9)		Type 2 diabetics (n=10)	
	Basal	Insulin	Basal	Insulin	Basal	Insulin
Insulin receptor phosphorylation	0.415	0.624*	0.433	0.416†	0.529	0.514†
IRS-1 phosphorylation	0.485	0.875*	0.691	1.015	0.819†	0.879
p85 association with IRS-1	0.384	0.623*	0.383	0.665*	0.312	0.315†‡
IRS-1-associated PI 3-kinase activity	0.105	0.218*	0.096	0.151*	0.094	0.121†
Total (p110-associated) PI 3-kinase activity	0.845	1.83*	0.591	0.802†	0.385	0.539†

*P<0.05 verse basal values. †P<0.05 versus values in lean control subjects. ‡P<0.05 versus values in obese nondiabetics. Data are given as means. Insulin receptor and IRS-1 phosphorylation and p85 association with IRS-1 were determined by scanning densitometry following immunoprecipitation and immunoblot analysis, and the units are arbitrary density units. PI 3-kinase activity was determined as described in the text and expressedas arbitrary units relative to a pooled positive Jurkat cell control.

Cusi K et al. *J Clin Invest* 2000;105:311–320.

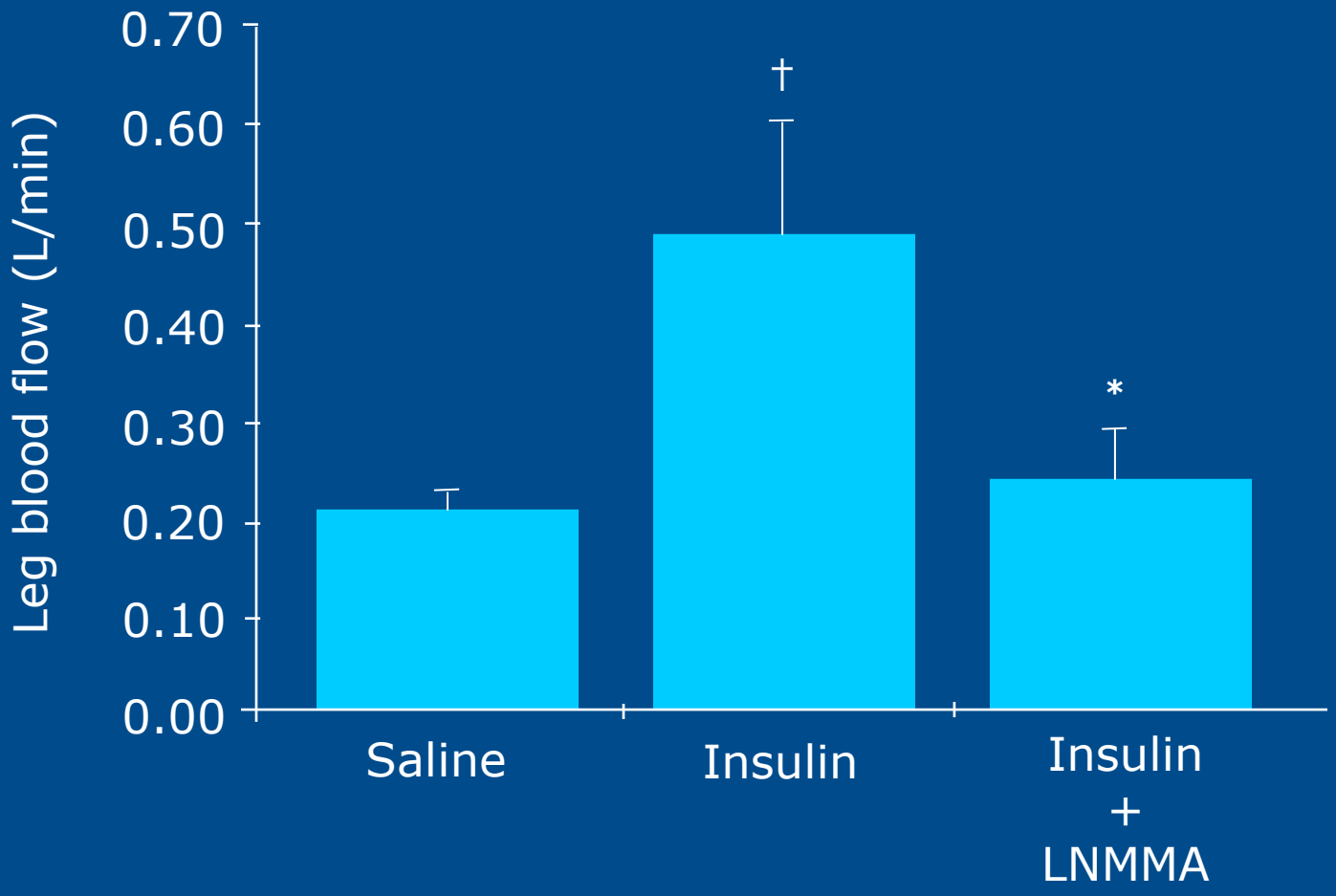
Insulin Receptor Signaling Through the MAP Kinase Pathway

	Lean controls (n=8)		Obese nondiabetics (n=9)		Type 2 diabetics (n=10)	
	Basal	Insulin	Basal	Insulin	Basal	Insulin
ERK phosphorylation	0.659	0.918*	0.652	0.936*	0.720	0.980*
ERK activity	1.384	2.420*	1.110	1.832*	1.425	2.408*
MEK1 activity	0.716	1.213*	0.801	1.294*	0.685	1.268*

*$P<0.05$ versus basal values. Data are given as means. ERK phosphorylation was determined by scanning densitometry after immunoblot analysis, and data are expressed in arbitrary density units. ERK and MEK1 activity are expressed as disintegrations per minute relative to ERK or MEK1 protein content determined by scanning densitometry following immunoblot analysis.

Cusi K et al. *J Clin Invest* 2000;105:311–320.

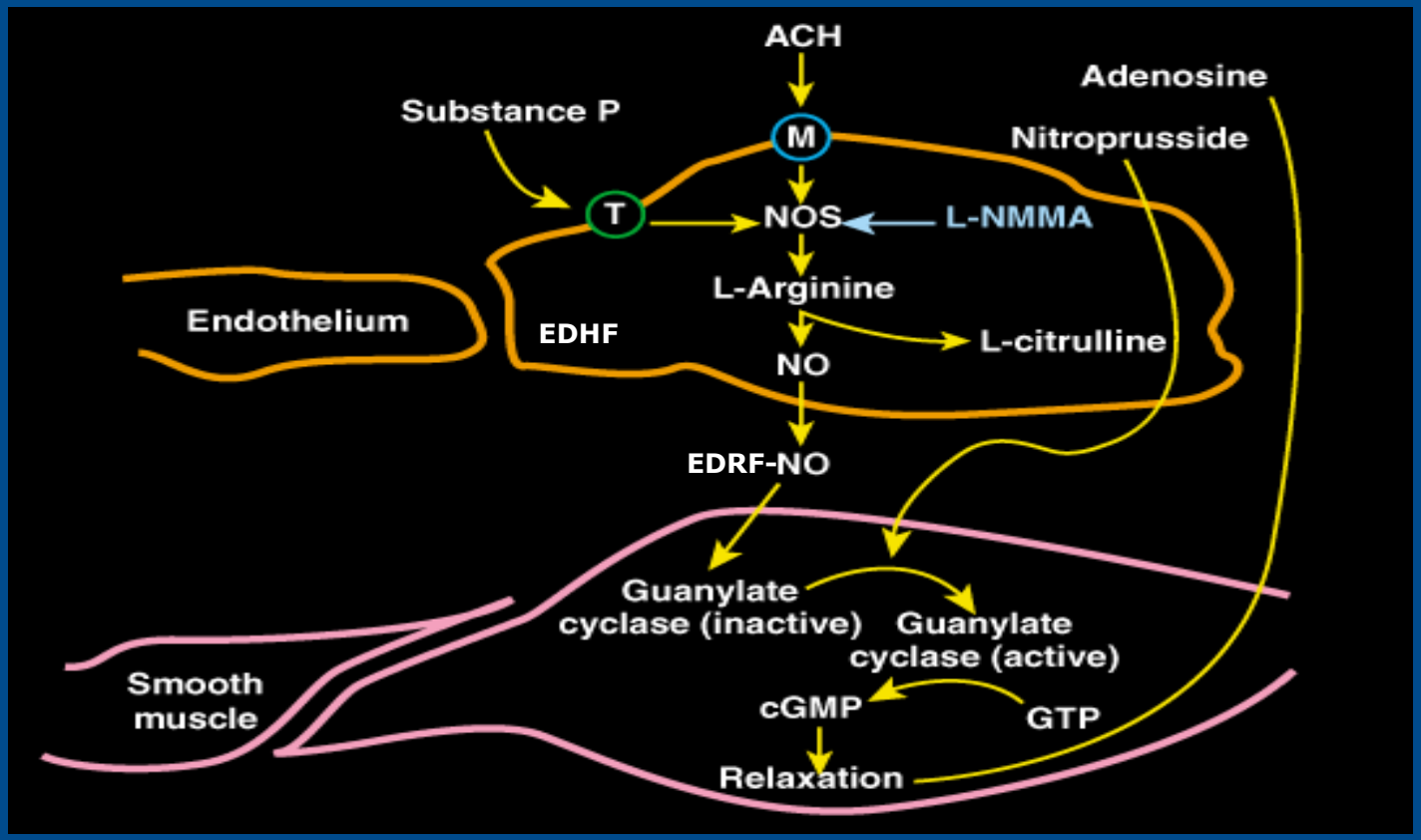
Nitric Oxide Mediates Insulin Vasodilation



*P<0.05; †P<0.01; LNMMA=N-monomethyl-L-arginine.

Steinberg HO. *J Clin Invest* 1994;94:1172–1179.

Physiology of NO in the Human Coronary and Peripheral Vasculature

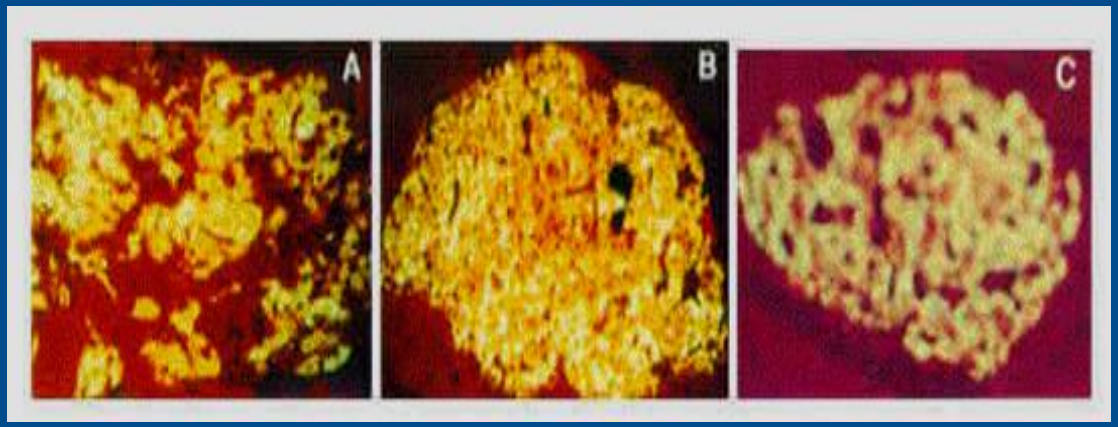


L-NMMA= N-monomethyl-L-arginine; NO=nitric oxide; NOS=nitric oxide synthase.

Adapted from Quyyumi AA. *Am J Med* 1998;105(1A):32S–39S.

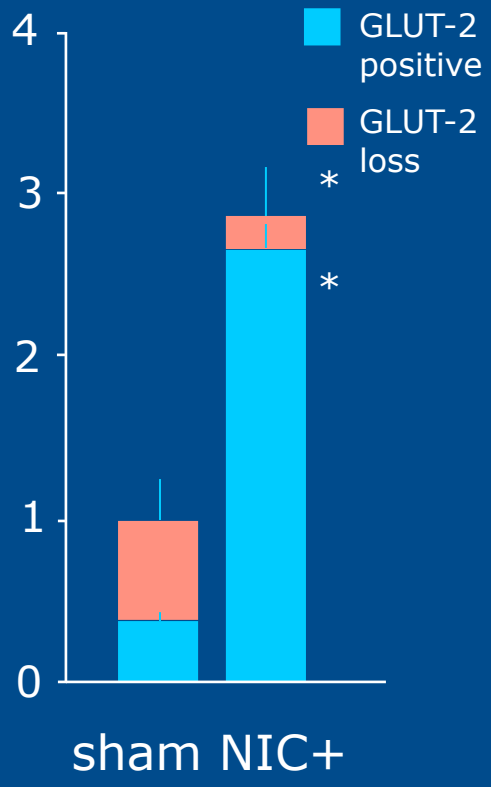
Nitric Oxide–Induced Islet Apoptosis

A. Islet of 12-week-old obese *fa/fa* ZDF rats stained for insulin



sham NIC+ AG+

B. β-Cell volume fraction (%)

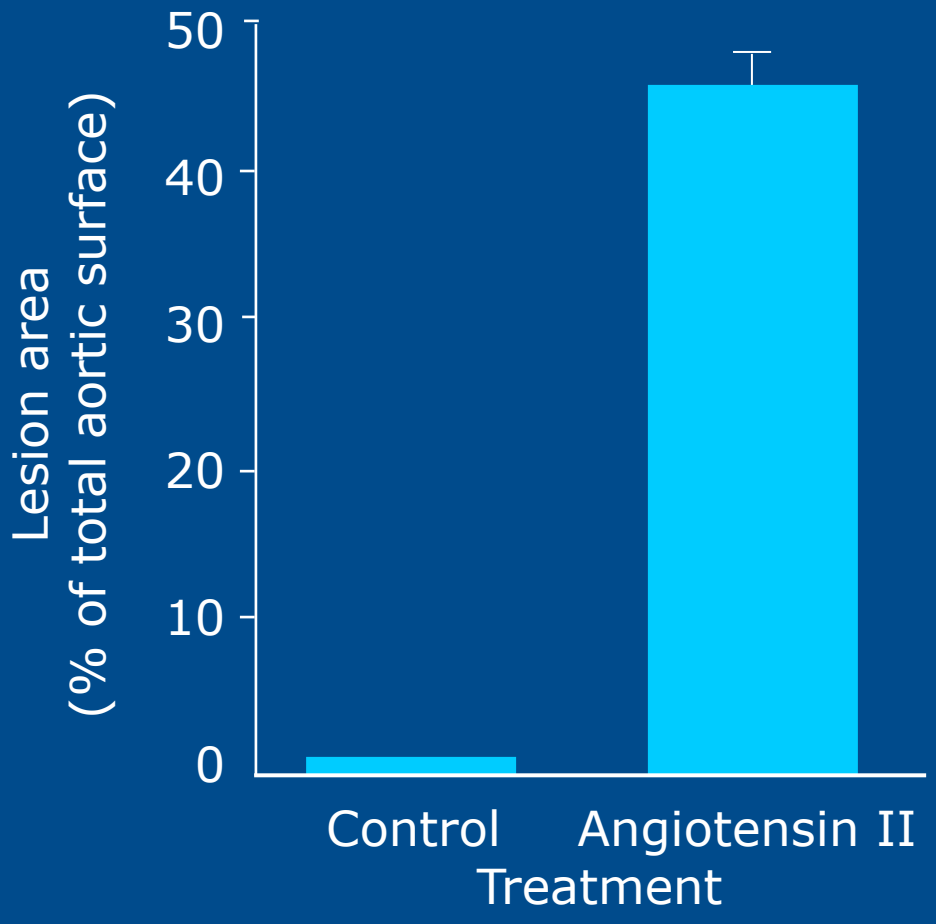


AG=aminoguanidine; NIC=nicotinamide.

*$P<0.05$ vs. untreated obese *fa/fa* ZDF rats. Mean±SE.

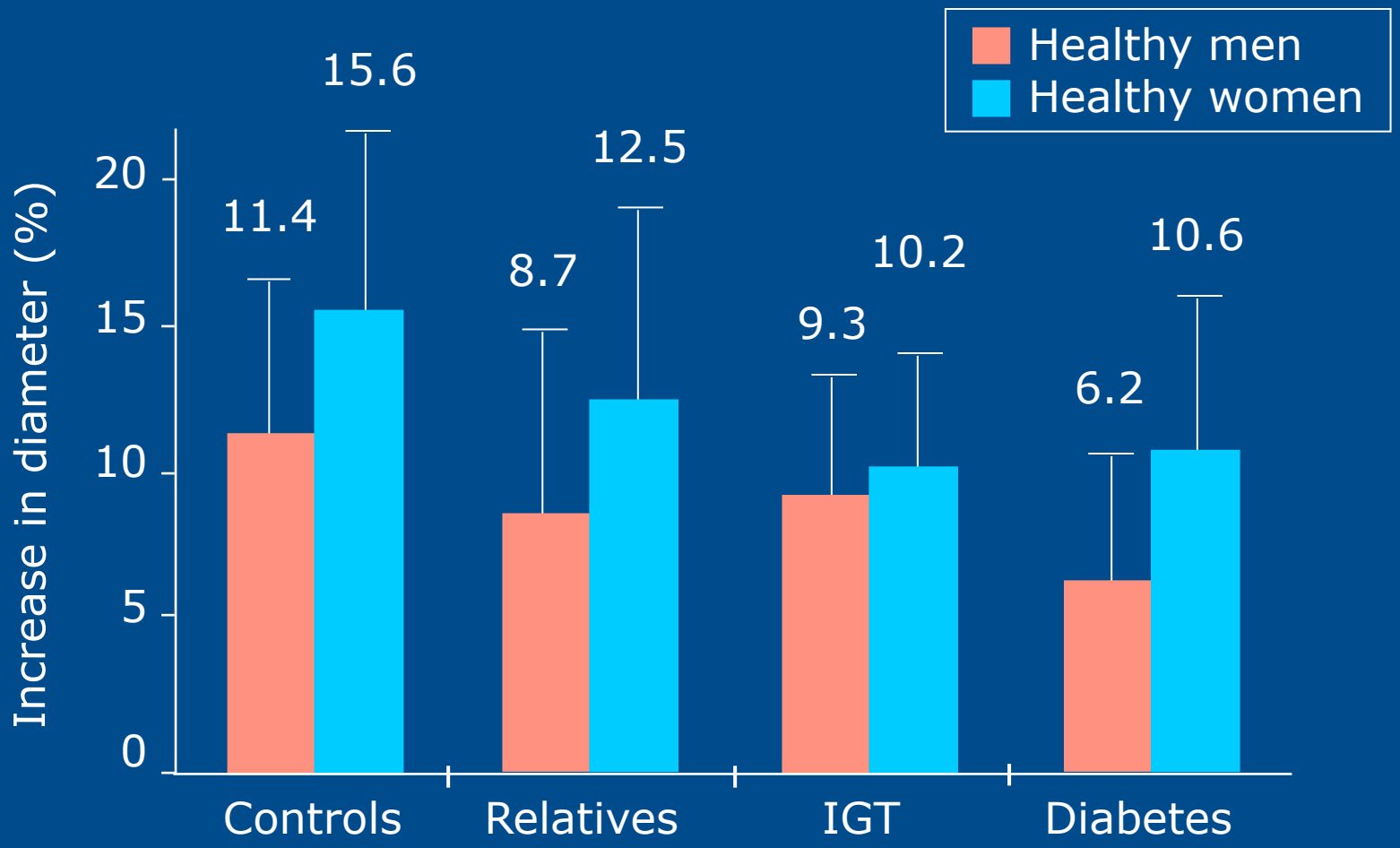
Shimabukuro M et al. *J Clin Invest* 1997;100:290–295.

Angiotensin II Increases the Rate of Atherosclerosis



Collins AR et al. *Diabetes* 2001;50(suppl 2):A72 (abstract 292PP).

Brachial Artery Reactivity in Controls, Relatives, IGT & Diabetes



Caballero AE et al. *Diabetes* 1999;48:1856–1862.

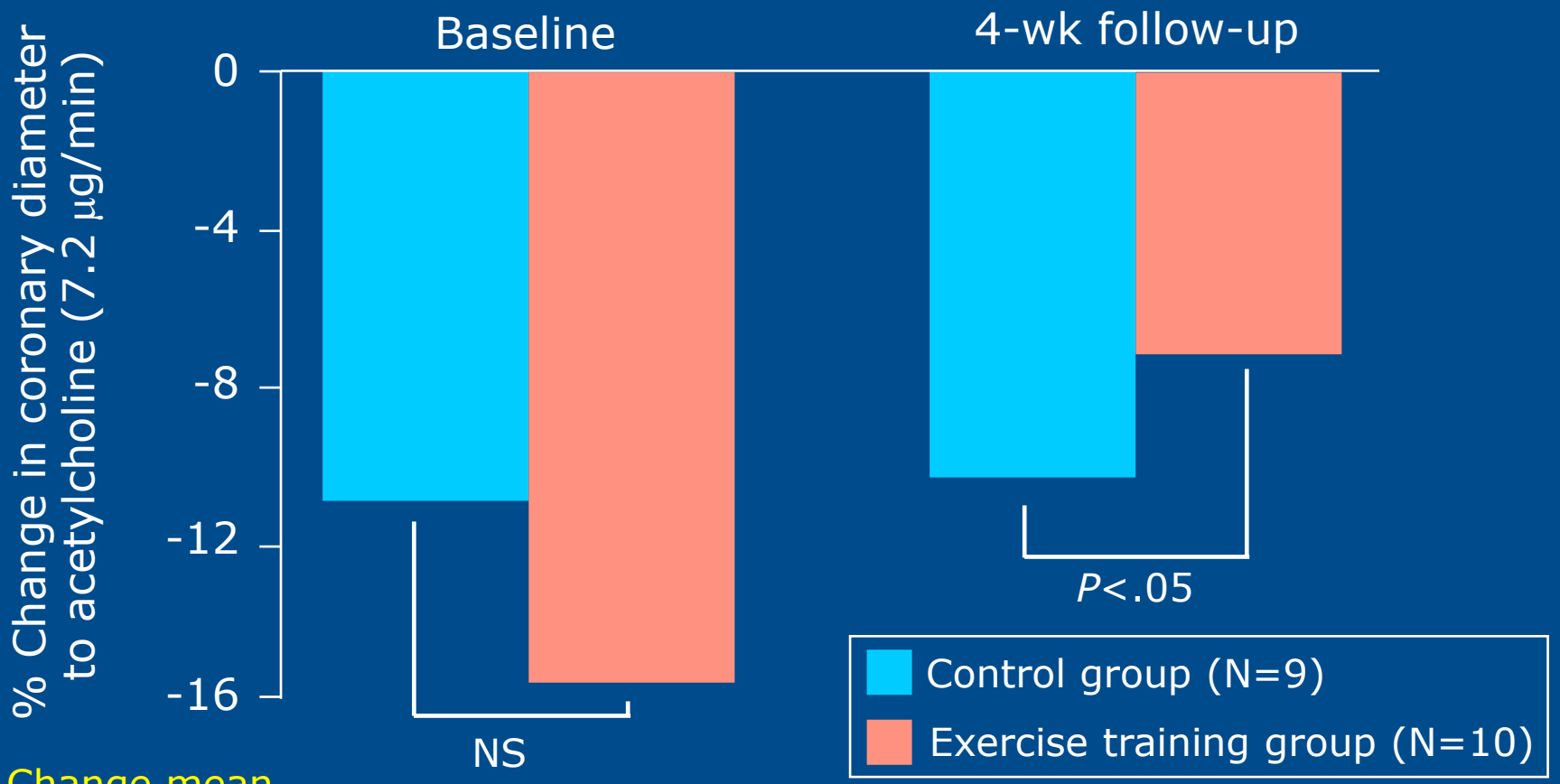
Markers of Endothelial Dysfunction in Controls, Relatives, IGT, and Diabetes

	Controls (C)	Relatives (R)	IGT	Diabetes (D)
v-WF (%)*	110±49	103±41	121±45	135±51
ET-1 (pg/mL)†	3.8 (1.4–12.3)	5.3 (1.2–33.4)	6.8 (1.3–43.1)	5.4 (1.5–39.1)
sICAM (ng/mL)‡	222±57	251±89	264±56	301±106
SVCAM (ng/mL)§	661±176	747±171	759±254	831±257

ET-1=endothelin-1; SiCAM=soluble intercellular adhesion molecule; SVCAM=soluble vascular cell adhesion molecule; v-WF=vonWillebrand factor.
*C and R vs D, $P<0.05$; †C vs R, IGT, and D, $P<0.05$;
‡C vs IGT and D and R vs D, $P<0.01$; §C vs R and D, $P<0.05$.

Caballero AE et al. *Diabetes* 1999;48:1856–1862.

Exercise Improves Coronary Endothelial Function in CAD

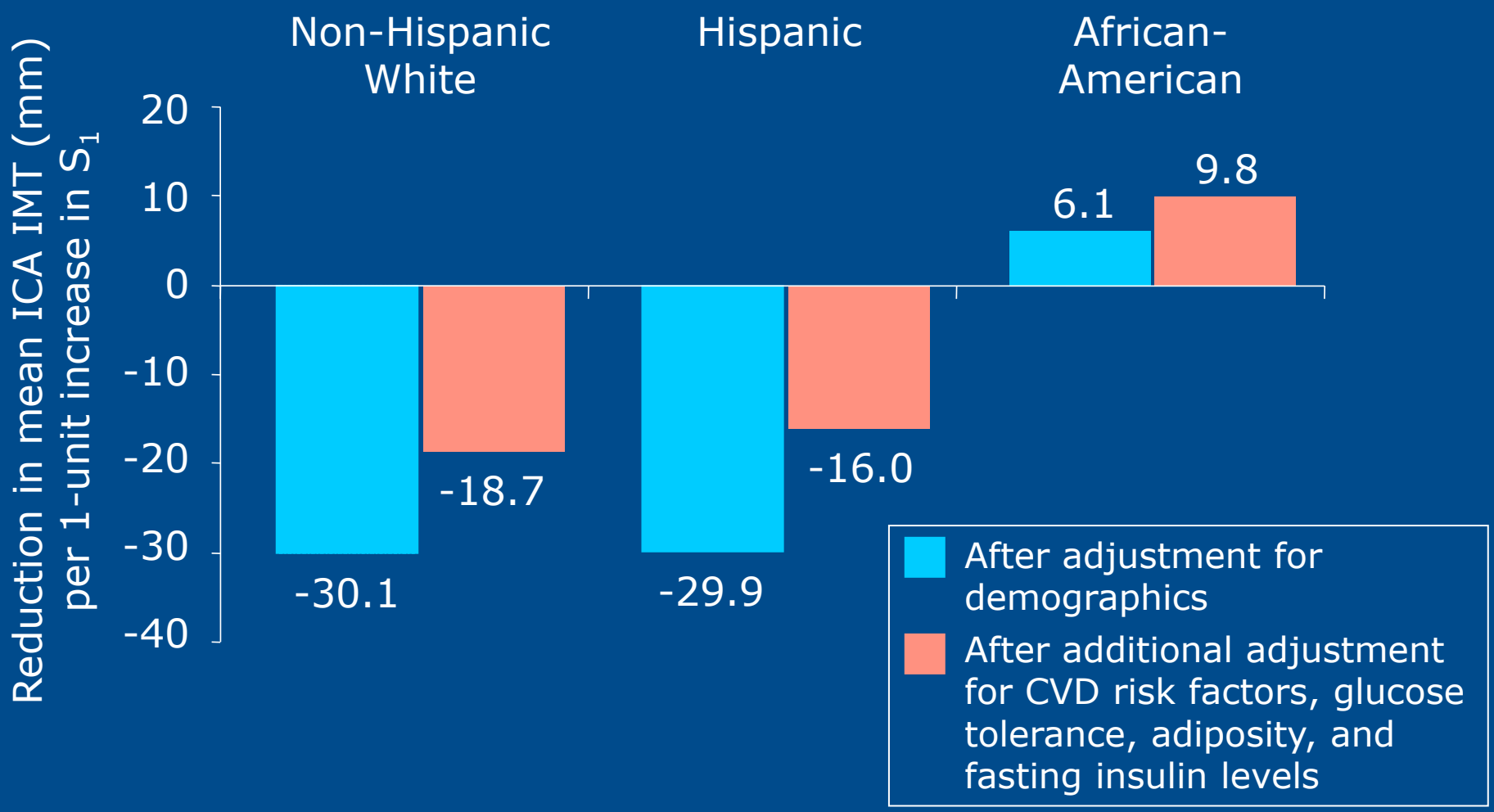


% Change mean peak coronary blood flow velocity: 65±14 78±16 57±17 142±28*

*$P<0.01$ vs control group.

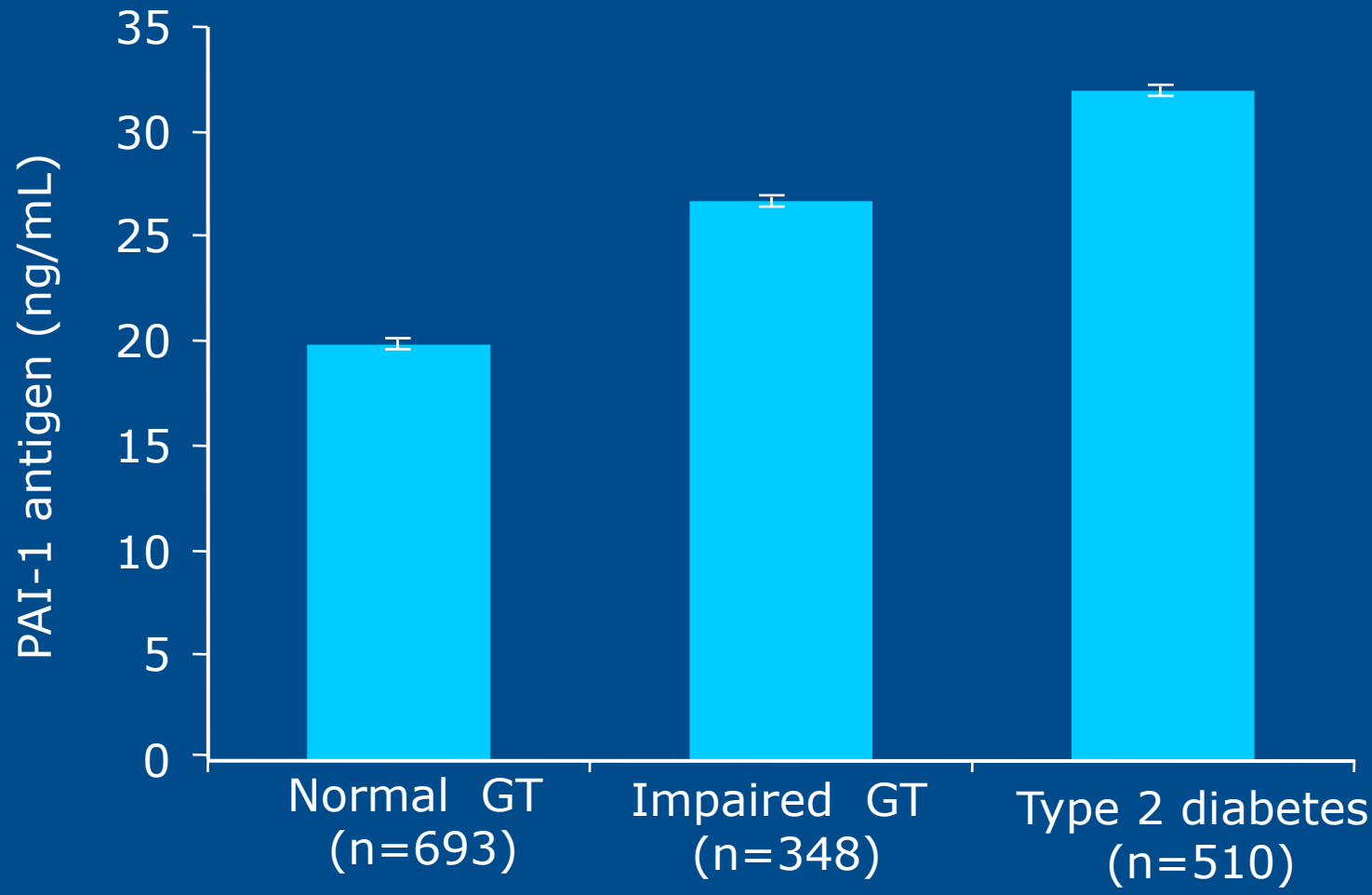
Hambrecht R et al. *N Engl J Med* 2000;342:454–460.

Negative Association Between Insulin Sensitivity and Atherosclerosis: IRAS



Howard G et al. *Circulation* 1996;93:1809–1817.

IRAS: Plasma Concentration of PAI-1 in Normal Subjects, IGT, and Type 2 Diabetes



Adjusted for age, gender, and ethnic group. IRAS=Insulin Resistance Atherosclerosis Study.

Festa A et al. *Arterioscler Thromb Vasc Biol* 1999;19:562–568.

Correlation Analysis (Unadjusted) in the Overall IRAS Population (N=1551)

	BMI	Fasting Insulin	S_I
PAI-1	0.38 (0.0001)	0.47 (0.0001)	-0.43 (0.0001)
Fibrinogen	0.28 (0.0001)	0.20 (0.0001)	-0.24 (0.0001)

IRAS= Insulin Resistance Atherosclerosis Study
BMI= body mass index
S_I= insulin sensitivity
PAI-1= plasminogen activator inhibitor-1

Festa et al. *Arterioscler Thromb Vasc Biol* 1999;19:562–568.

Effect of PPARγ Ligands on Monocytes/Macrophages in Atherosclerosis

Attachment

Variable effects (↓ to no change VCAM), no effects on ICAM

Migration

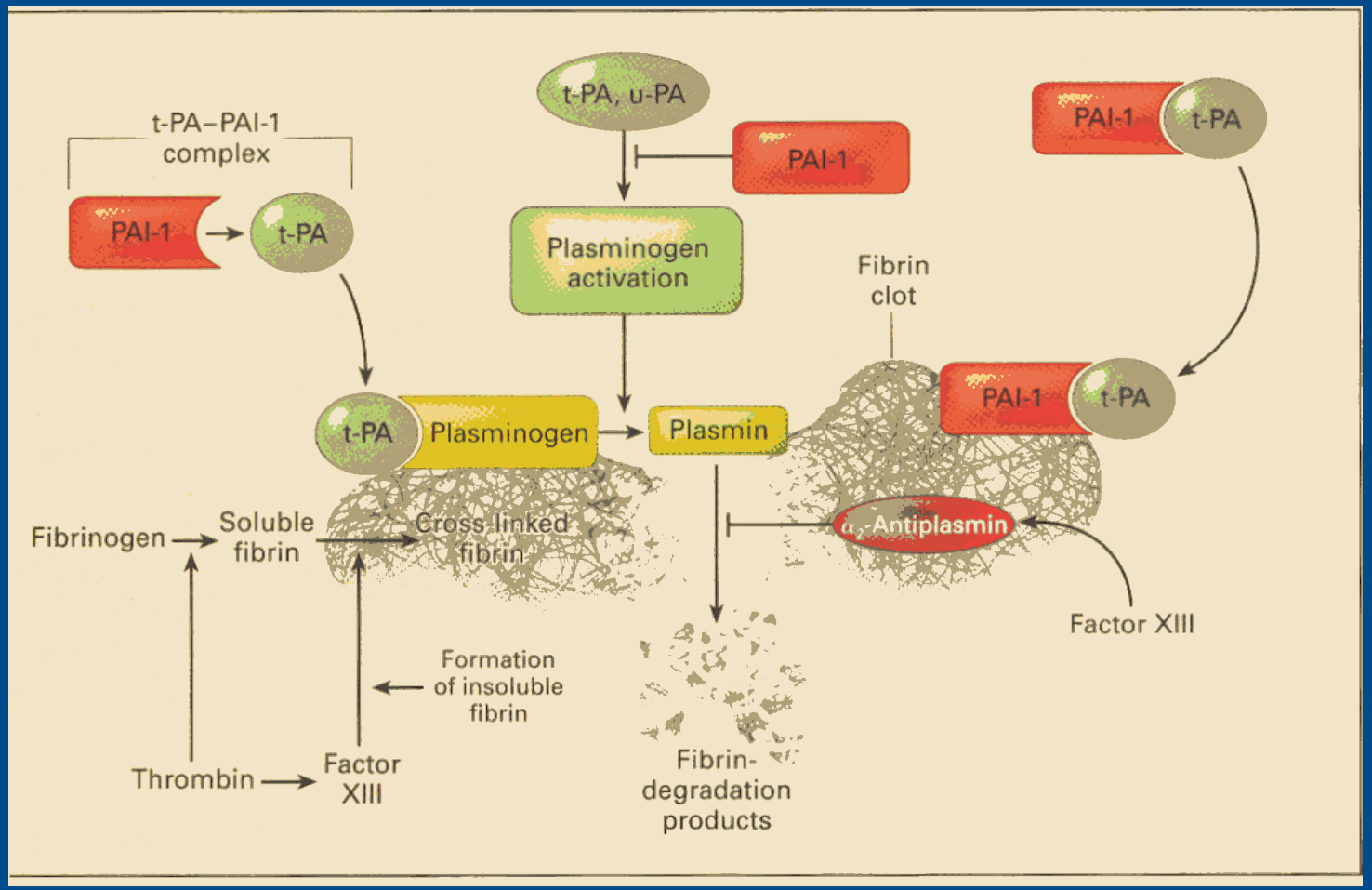
All ligands inhibit

Foam cell formation

1) Do not affect differentiation monocytes→macrophages
2) CD36 but tends to ↓SRA
3) ABCA1 to increase cholesterol efflux
4) ↓IL-6, MMP, NO - ? PPARγ mediated

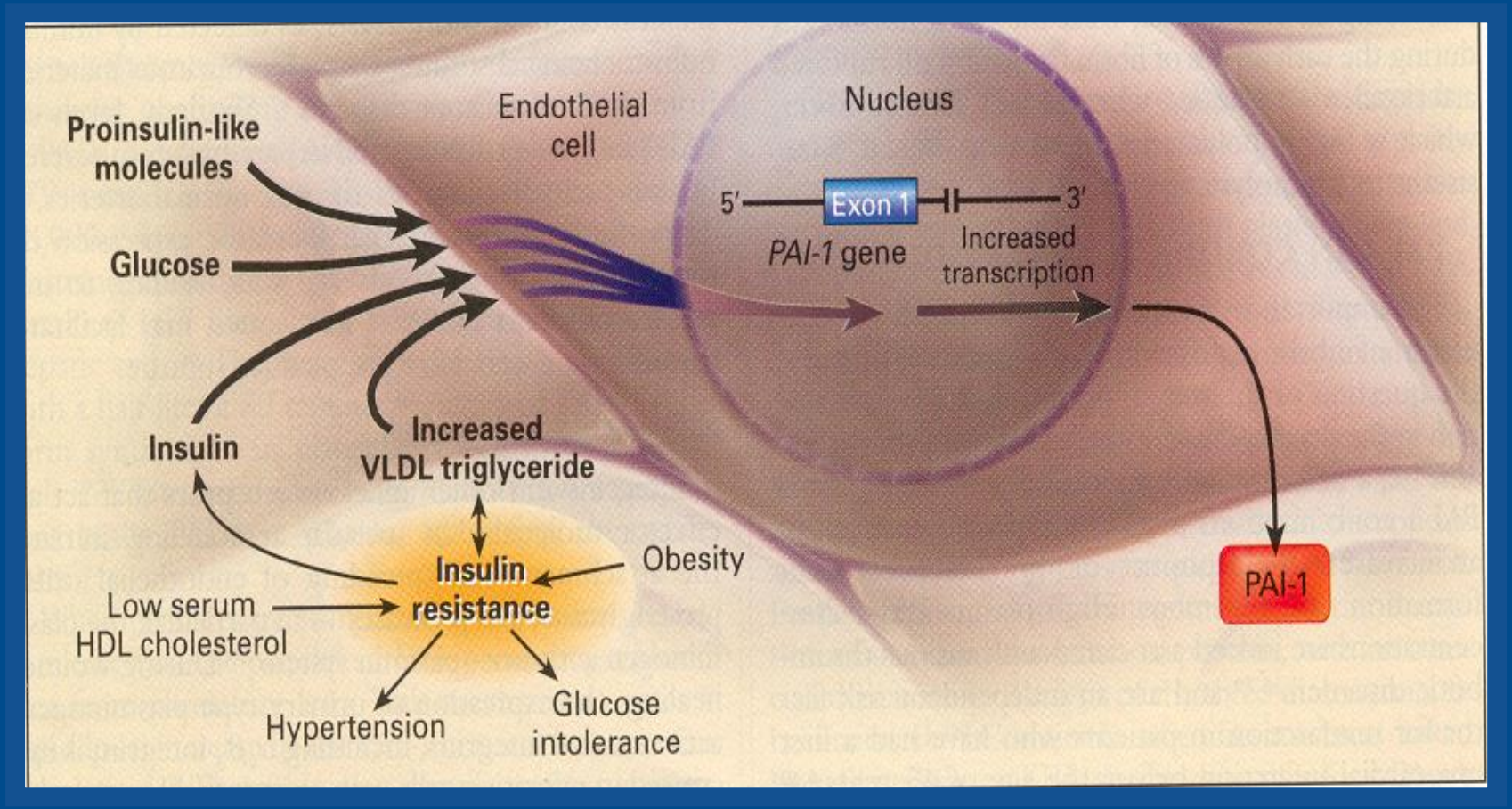
Chinetti G et al. *Nature Medicine* 2001;7:53–58.
Parulkar AA et al. *Ann Intern Med* 2001:134:61–71.
Sarraf P et al. *Nat Med* 1998;4:1046–1052.
Vamecq J, Latruffe N. *Lancet* 1999:354:141–148.

Activation and Inhibition of the Fibrinolytic Pathway



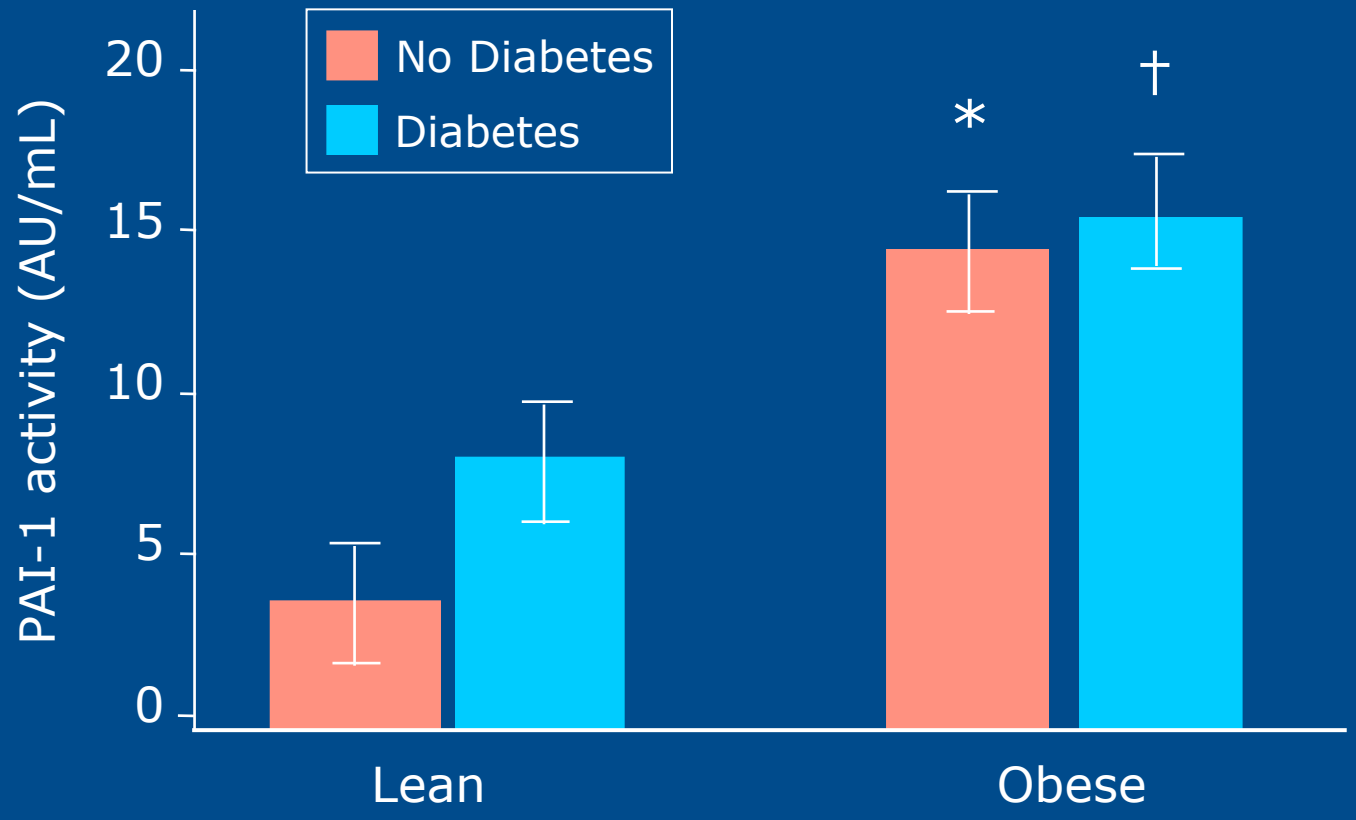
Kohler HP. *N Engl J Med* 2000;342:1792–1801.

Insulin Resistance Syndrome and Activation of the PAI-1 Gene



Kohler HP. *N Engl J Med* 2000;342:1792–1801.

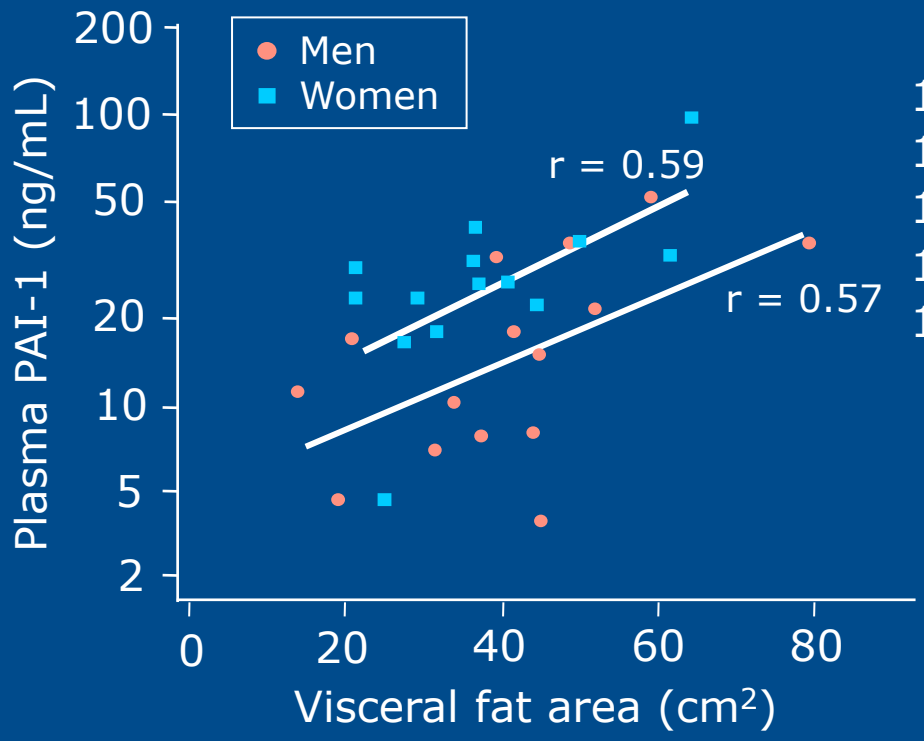
Changes in Plasminogen Activator Inhibitor-1 Activity in Diabetes

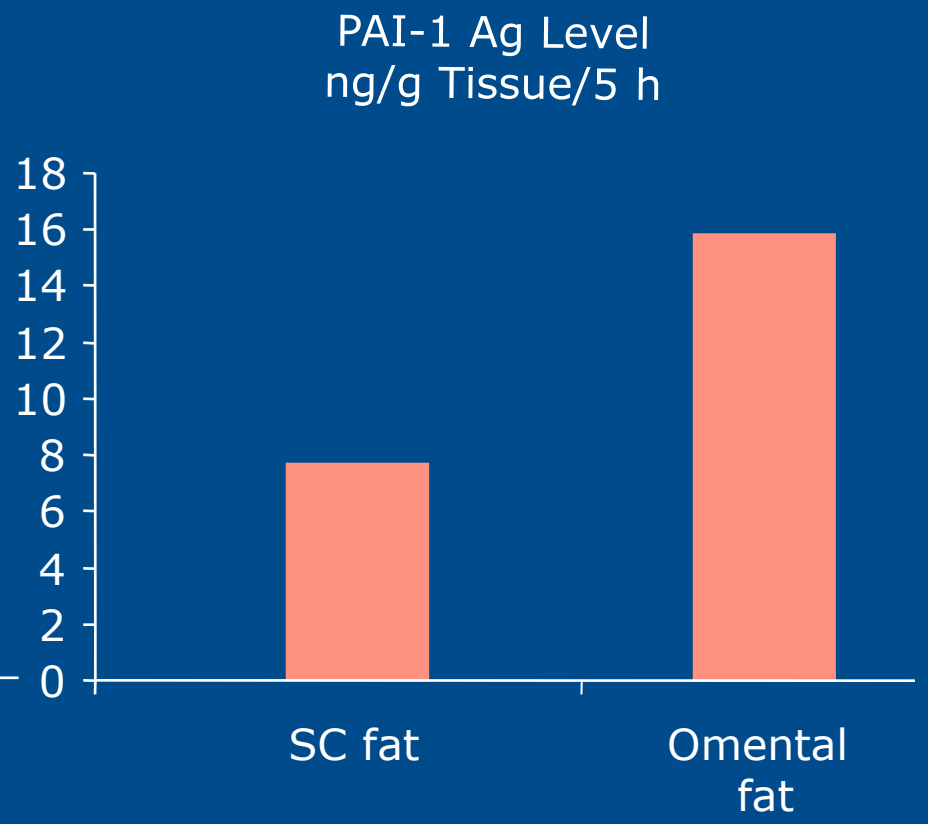


*P<0.001 vs lean subjects of the same type.
†P<0.01 vs lean subjects of the same type.

Adapted from McGill JB et al. *Diabetes* 1994;43:104–109.

PAI-1 and Visceral Fat

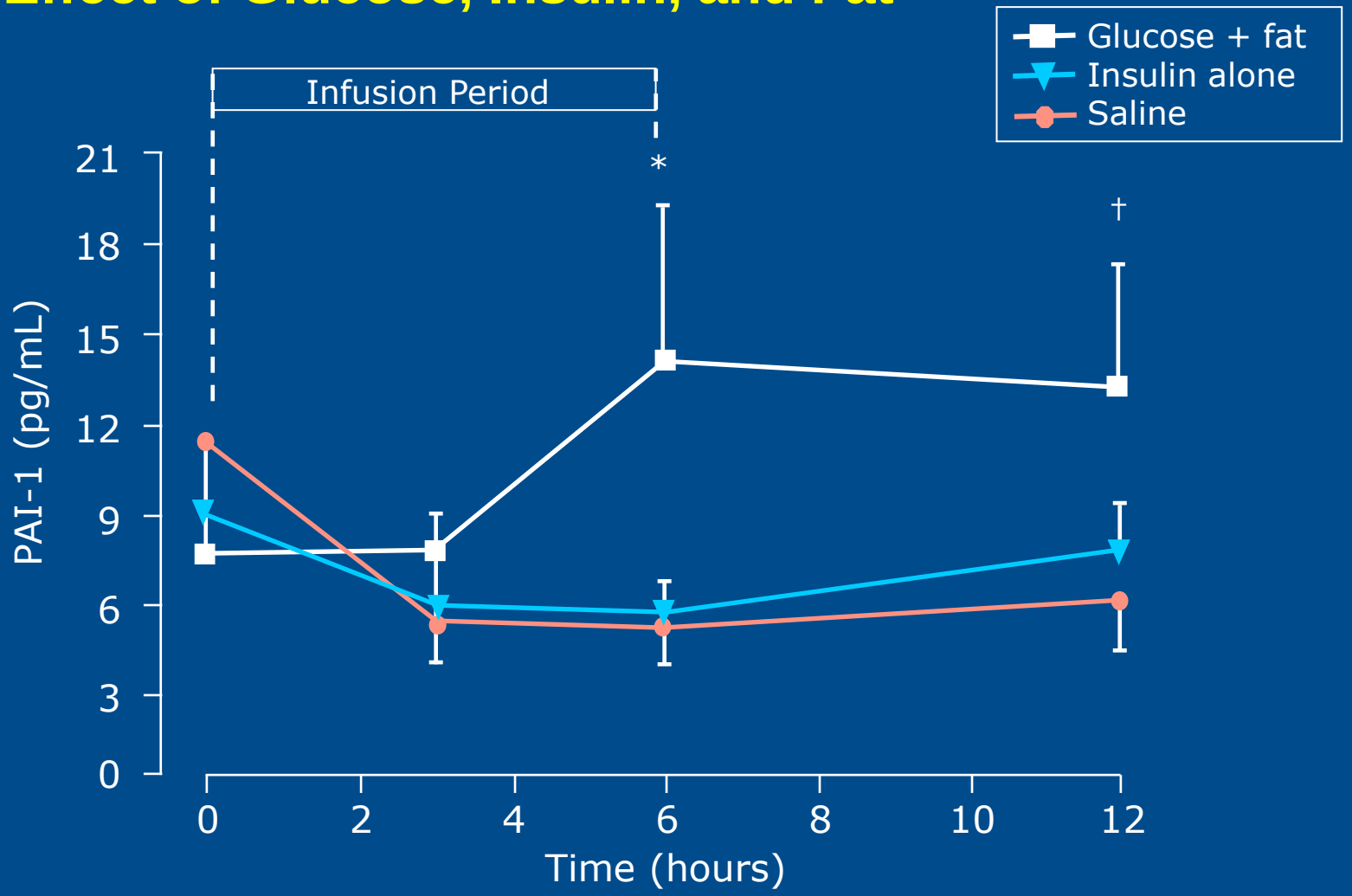




Alessi. *Diabetes* 1997;46:860–867.
Giltay EJ et al. *Arterioscler Thromb Vasc Biol* 1998;18:1716–1722.

PAI-1 in Blood

Effect of Glucose, Insulin, and Fat



*P=0.017; †P=0.06.

Calles-Escandon J et al. *Diabetes* 1998;47:290–293.

Partial Spearman Correlation Analysis of Inflammation Markers With Variables of IRS

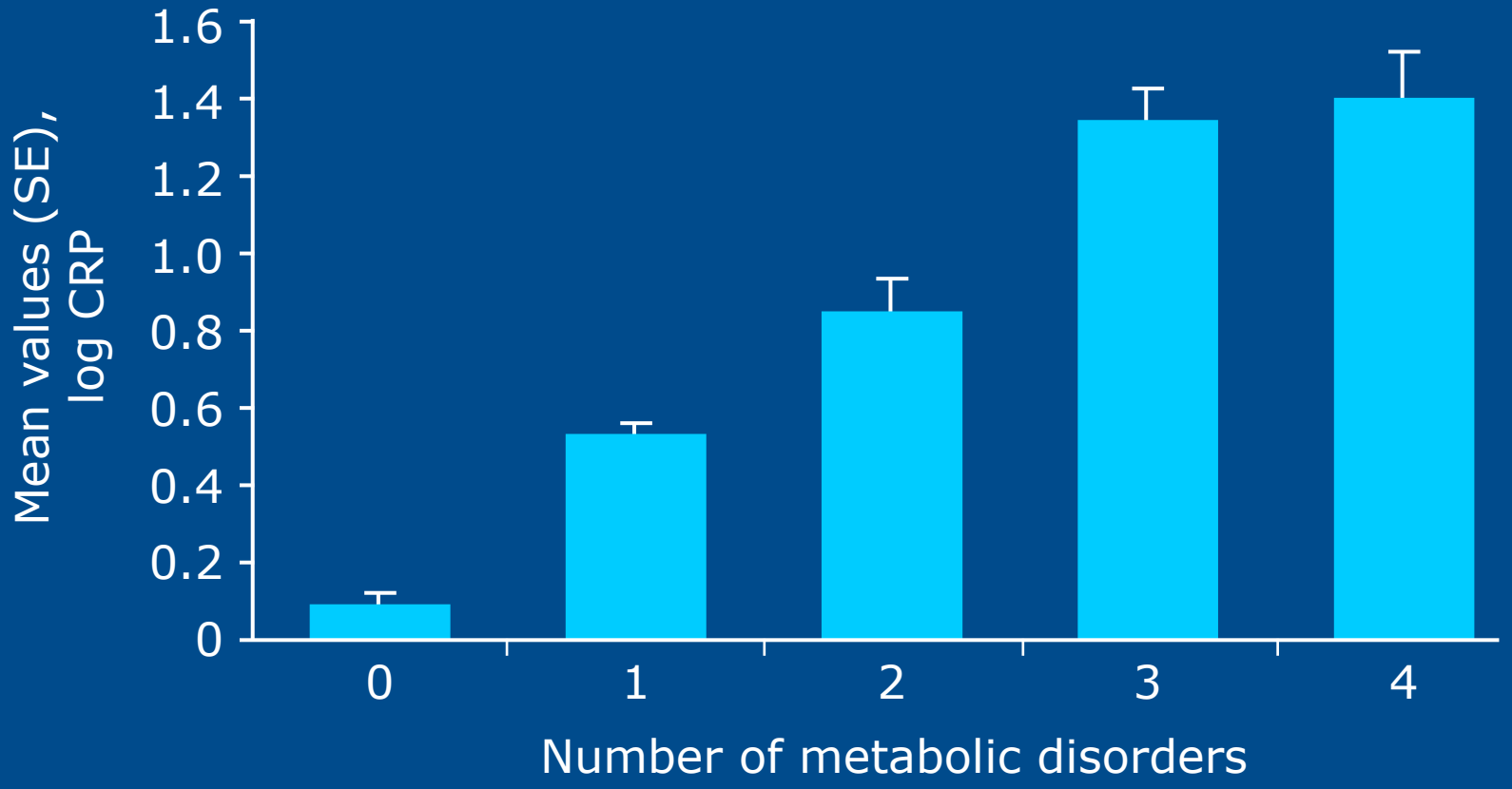
Adjusted for Age, Sex, Clinic, Ethnicity, and Smoking Status

	CRP	WBC	Fibrinogen
BMI	0.40‡	0.17‡	0.22‡
Waist	0.43‡	0.18‡	0.27‡
SBP	0.20‡	0.08*	0.11†
Fasting glucose	0.18‡	0.13‡	0.07*
Fasting insulin	0.33‡	0.24‡	0.18‡
S_I	-0.37‡	-0.24‡	-0.18‡

*P<0.05, †P<0.005, ‡P<0.0001
CRP=C-reactive protein
IRS=insulin resistance syndrome
WBC=white blood cell count

Adapted from Festa et al. *Circulation* 2000;102:42–47.

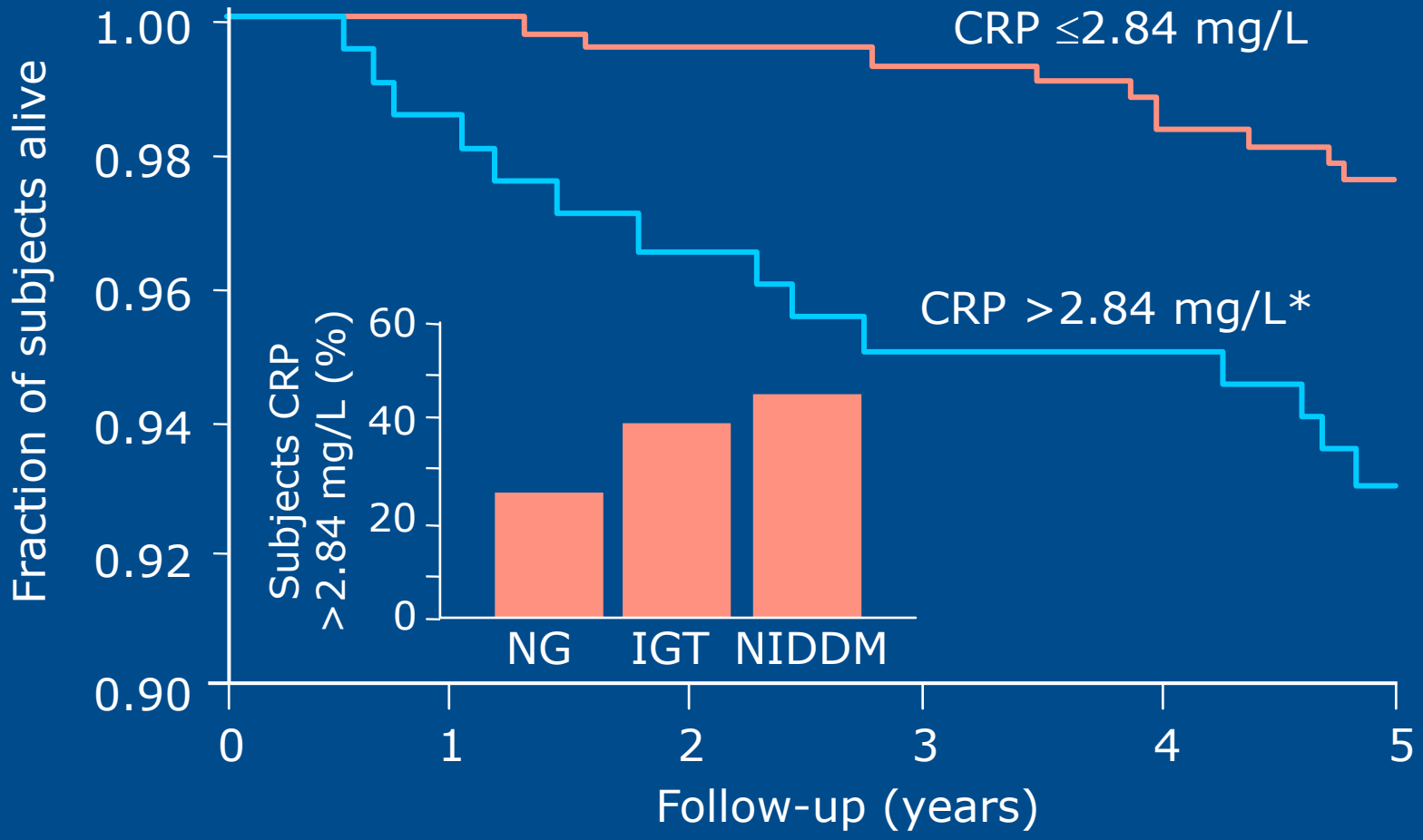
Chronic Subclinical Inflammation
Part of the Insulin-Resistance Syndrome



All comparisons P=0.0001, except for 2 vs 4, in which P<0.005, and 3 vs 4, in which P=NS.

Festa A et al. *Circulation* 2000;102:42–47.

Hoorn Study: Cardiovascular Survival According to Plasma CRP Levels



* *P*<0.006

Jager A et al. *Arterioscler Thromb Vasc Biol* 1999;19:3071–3078.

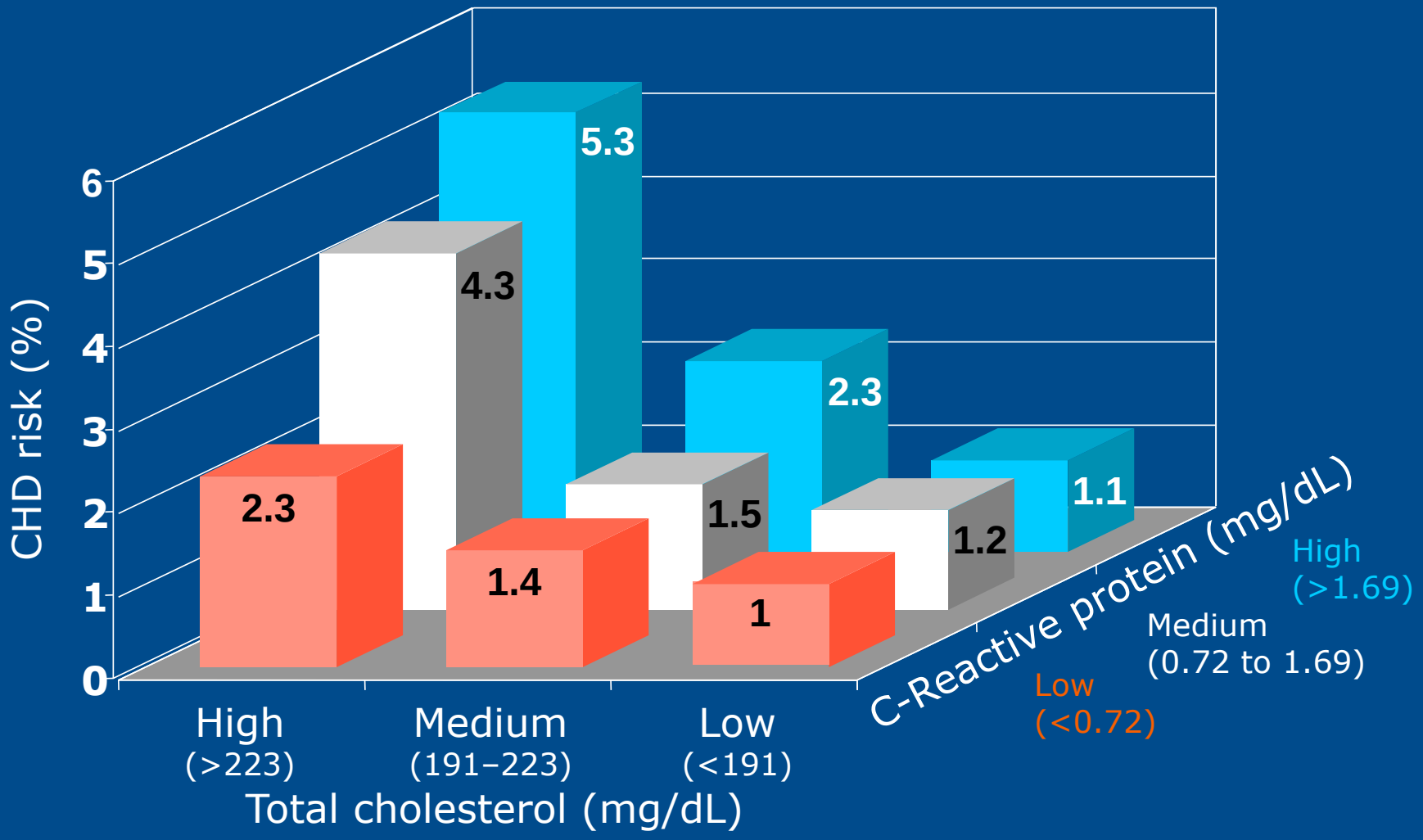
ARIC: Markers of Inflammation and Development of Diabetes Over 7 Years

	Risk Reduction*	Adjusted Risk Reduction†
WBC	1.9	1.5
Low Albumin	1.3	0.98
High Fibrinogen	1.2	0.93

*Adjusted for age, sex, center, ethnic origin, baseline glucose, family history of diabetes, physical activity, and pack-years of cigarette smoking.
†Additionally adjusted for BMI and WHR.

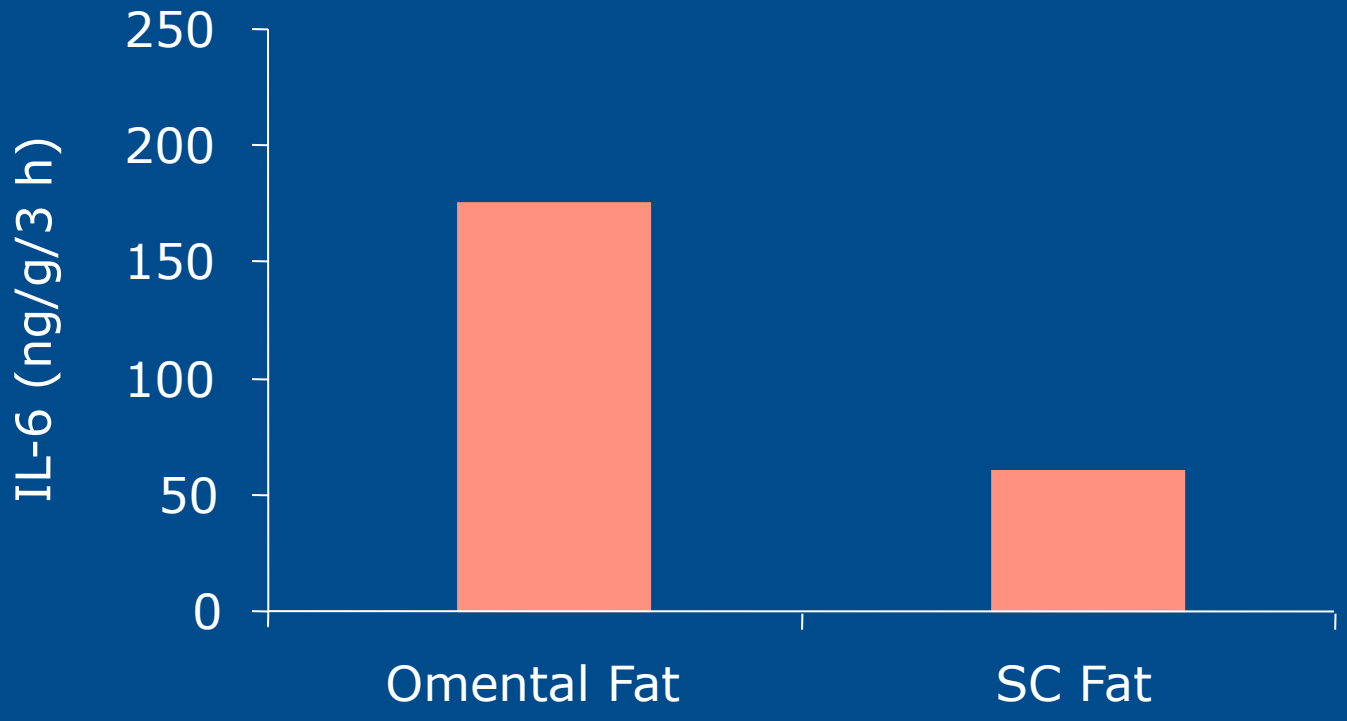
Adapted from Schmidt MI et al. *Lancet* 1999;353:1649–1652.

C-Reactive Protein Adds to the Predictive Value of Total Cholesterol in Determining the Risk of First MI



Adapted from Ridker PM et al. *Circulation* 1998;97:2007–2011.

Human Omental & SC Fat Release Interleukin 6: Depot Differences



N=6; *P*<0.05.

Fried SK et al. *J Clin Endocrinol Metab* 1998;83:847–850.