Welcome!

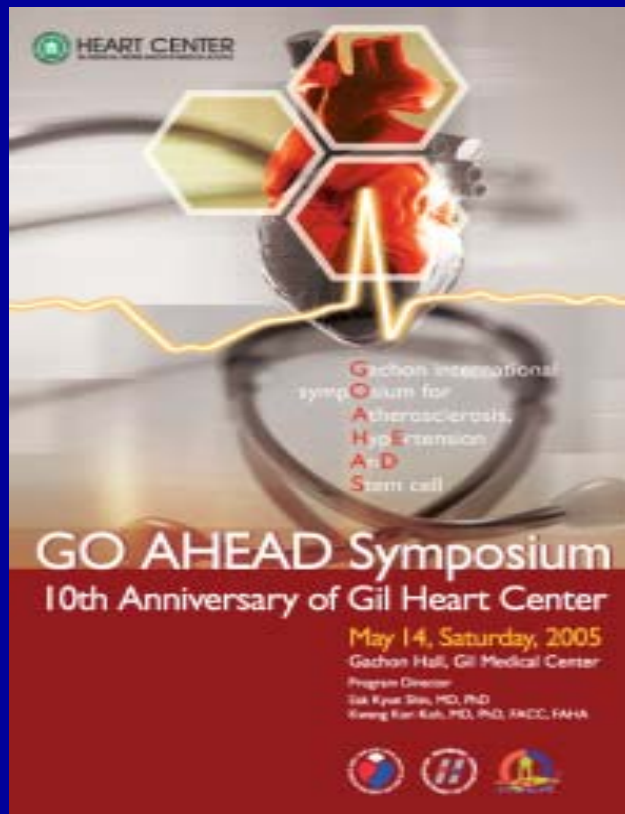
Mark
May 14, Sat!

춘계 순환기학회 심포지움, 4월 16일, 2005년, 대구

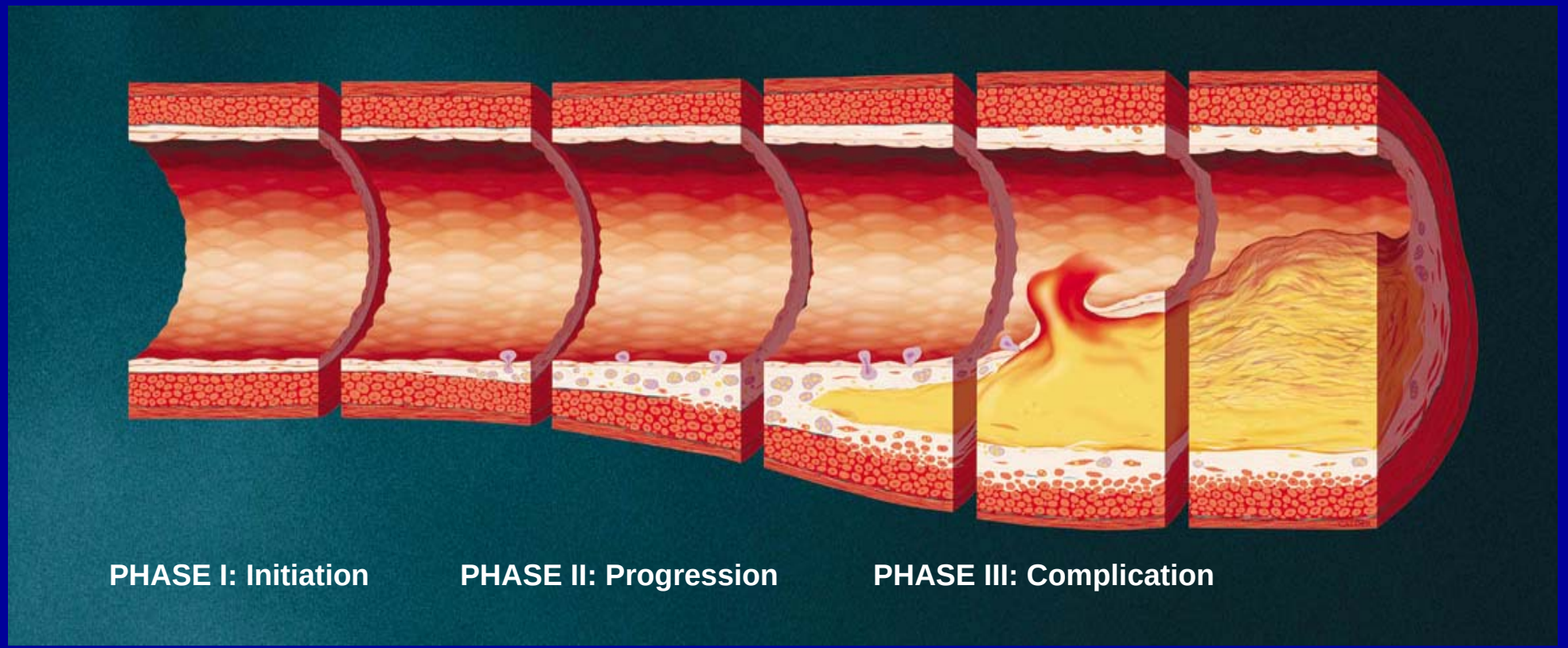
Endothelial Function Test as a Marker of Cardiovascular Disease

Seung Hwan Han, MD

Cardiology
Gachon Medical School
Incheon, Korea



Atherosclerosis: A progressive process

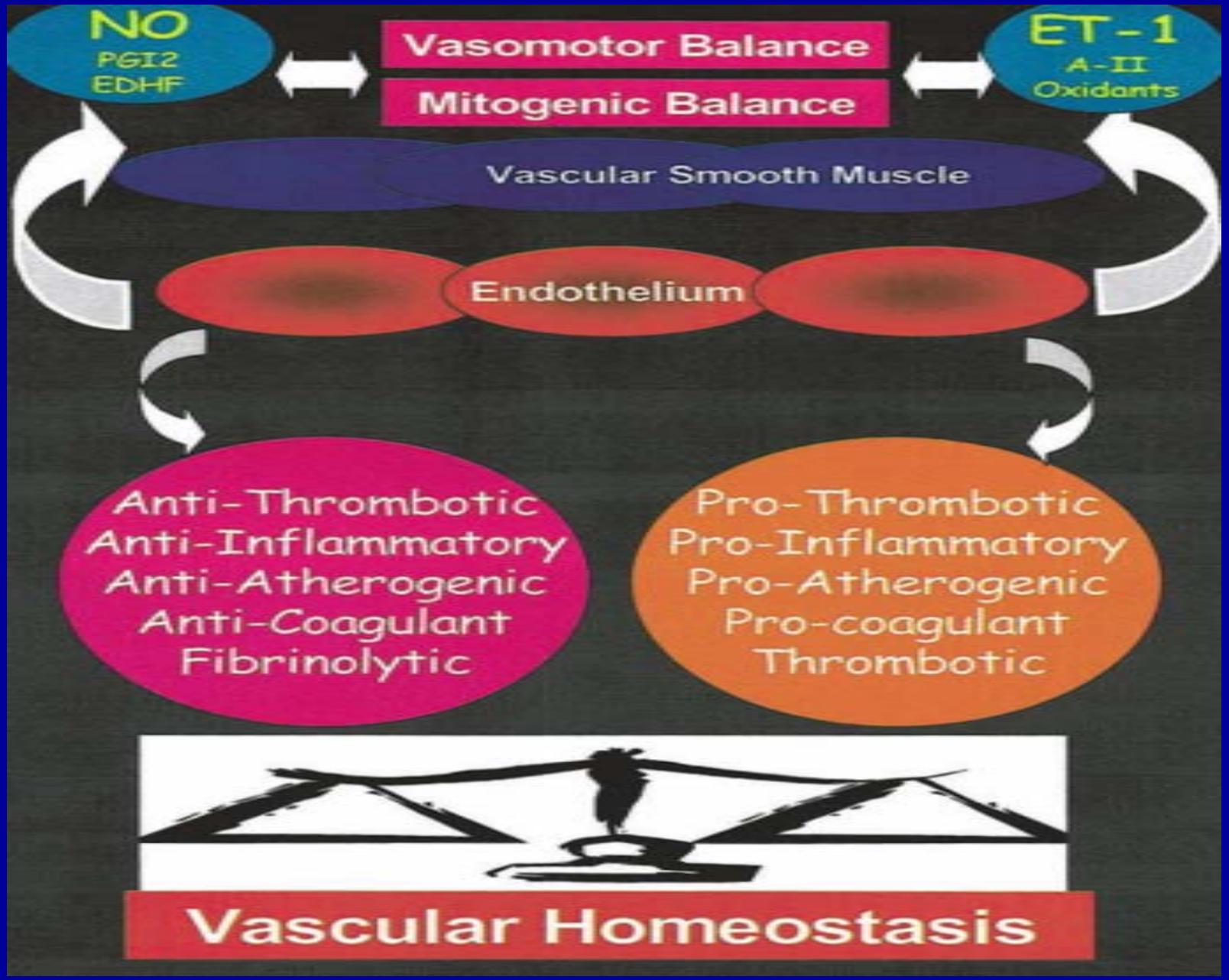


Disease progression

Regulatory Properties of Endothelium

- Vascular tone: Nitric oxide
- Inflammation
- Hemostasis
- Extracellular matrix
- Local cell growth
- Solute transport

Koh KK. Cardiovasc Res 2000;47:648 (Review)
Koh KK. Cardiovasc Res 2002;55:714 (Review)



Verma et al. Circulation 2002;105:546.

Endothelial Function Tests

1. Functional Change:

   Endothelial vasomotor function test

2. Anatomical Change: **Carotid IMT, plaque**

3. Mediators: Biomarkers

   (IL, **hs-CRP**, TNF-α, CAMs, MCP-1, MDA,

   MMP-9, **CD40L, adiponectin**, ..)

Endothelial Vasomotor Function Test

1. Coronary Endothelial Assessment

2. Peripheral Endothelial Assessment

   - Non-invasive: Flow-Mediated Dilation

   - Invasive: Plethysmography

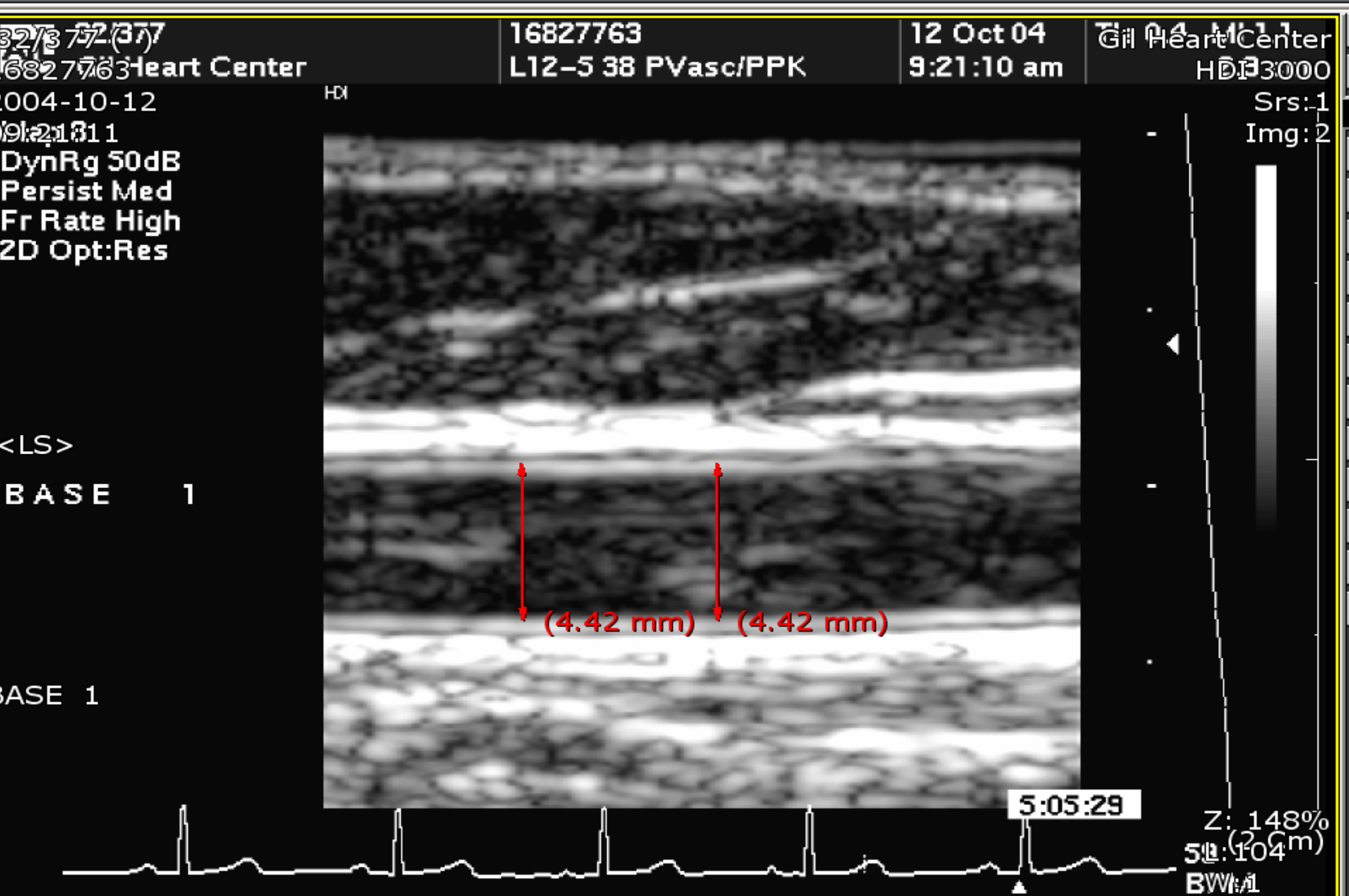
Nitric Oxide

- Regulates vasomotor tone
- Inhibits inflammatory cell attachment
- Inhibits platelet aggregation and attachment
- Inhibits release of procoagulant factors
- Inhibits release of growth factors

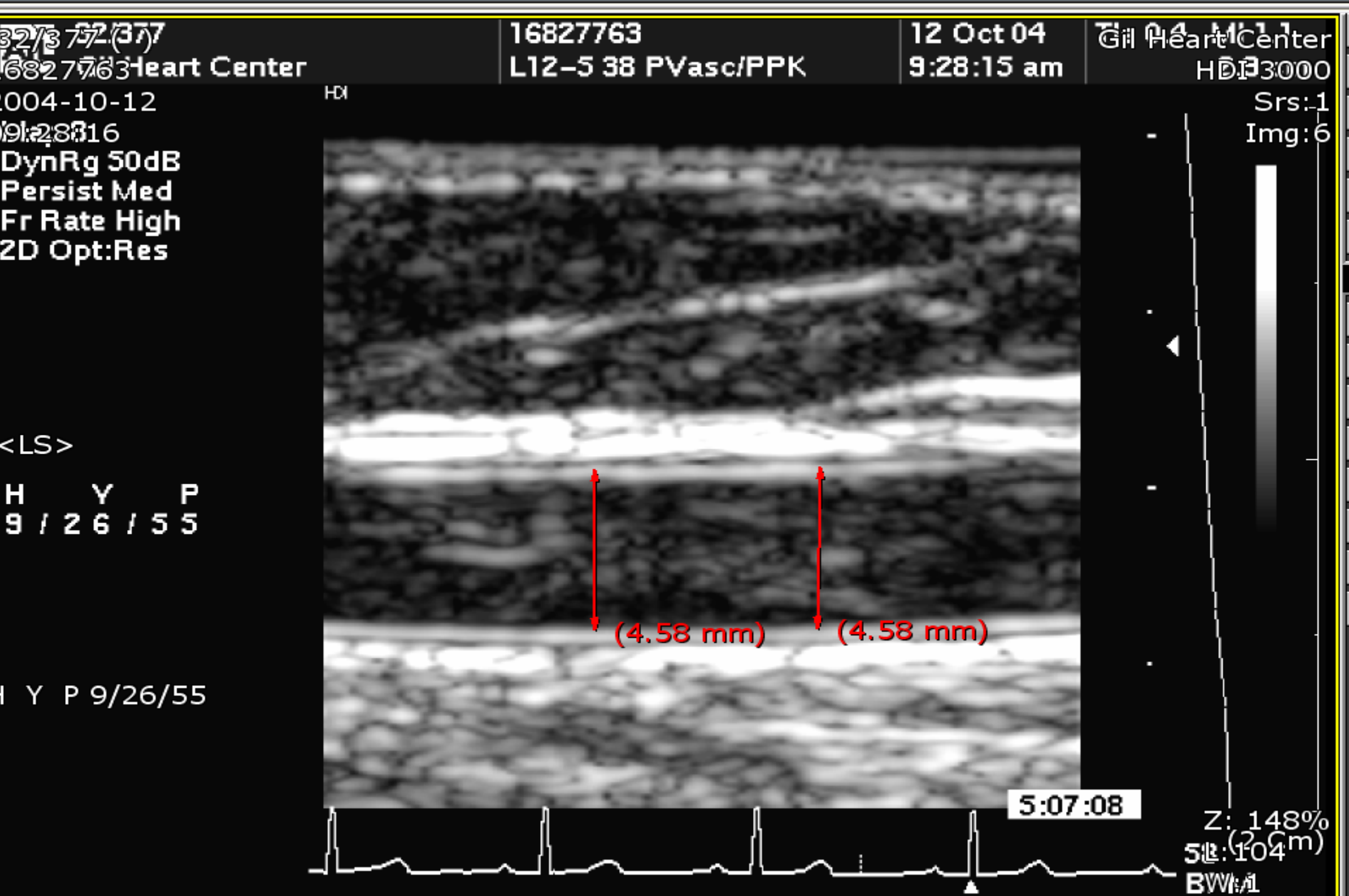
Koh KK. Cardiovasc Res 2000;47:648 (Review)
Koh KK. Cardiovasc Res 2002;55:714 (Review)

Flow-Mediated Dilation (FMD)

Baseline 1


16827763
L12-5 38 PVasc/PPK
12 Oct 04
9:21:10 am
Heart Center
HDI 3000
2004-10-12
DynRg 50dB
Persist Med
Fr Rate High
2D Opt:Res
Srs:1
Img:2
<LS>
BASE 1
(4.42 mm)
(4.42 mm)
5:05:29
Z: 148%
(2.6cm)

Reactive Hyperemia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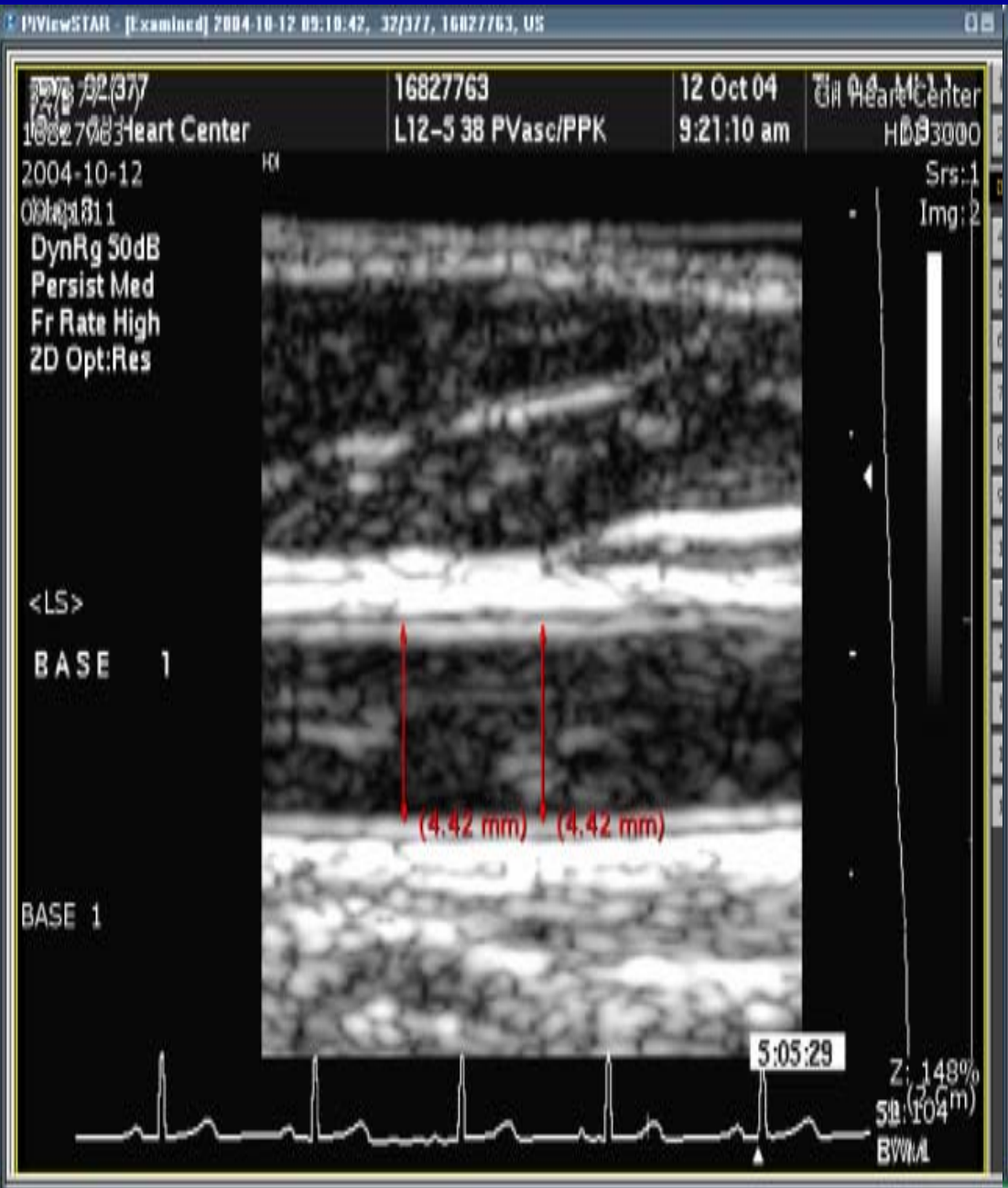
Heart Center
HDI 3000
2004-10-12
DynRg 50dB
Persist Med
Fr Rate High
2D Opt:Res
<LS>
H Y P
9 / 2 6 / 5 5
Srs:1
Img:6
(4.58 mm)
(4.58 mm)
5:07:08
Z: 148%
(2 Cm)

Baseline 1



Reactive Hyperemia

Sensitivity and Specificity of FMD Tests in Predicting CAD

Test	Sensitivity (95% CI)	Specificity (95% CI)
Angina Pectoris (n = 112)	96/101; 95.1% (88.8-98.4)	5/21; 23.8% (8.2-47.2)
Exercise ECG testing (n = 112)	75/91; 82.4% (73.0-89.6)	12/21; 57.1% (34.0-78.2)
Myocardial Perfusion Imaging (n = 34)	30/30; 100.0% (88.4-100.0)	0/4; 0.0% (0-60.2)
FMD% (n = 122)	**72/101; 71.3% (61.4-79.6)**	**17/21; 81% (58.1-94.6)**

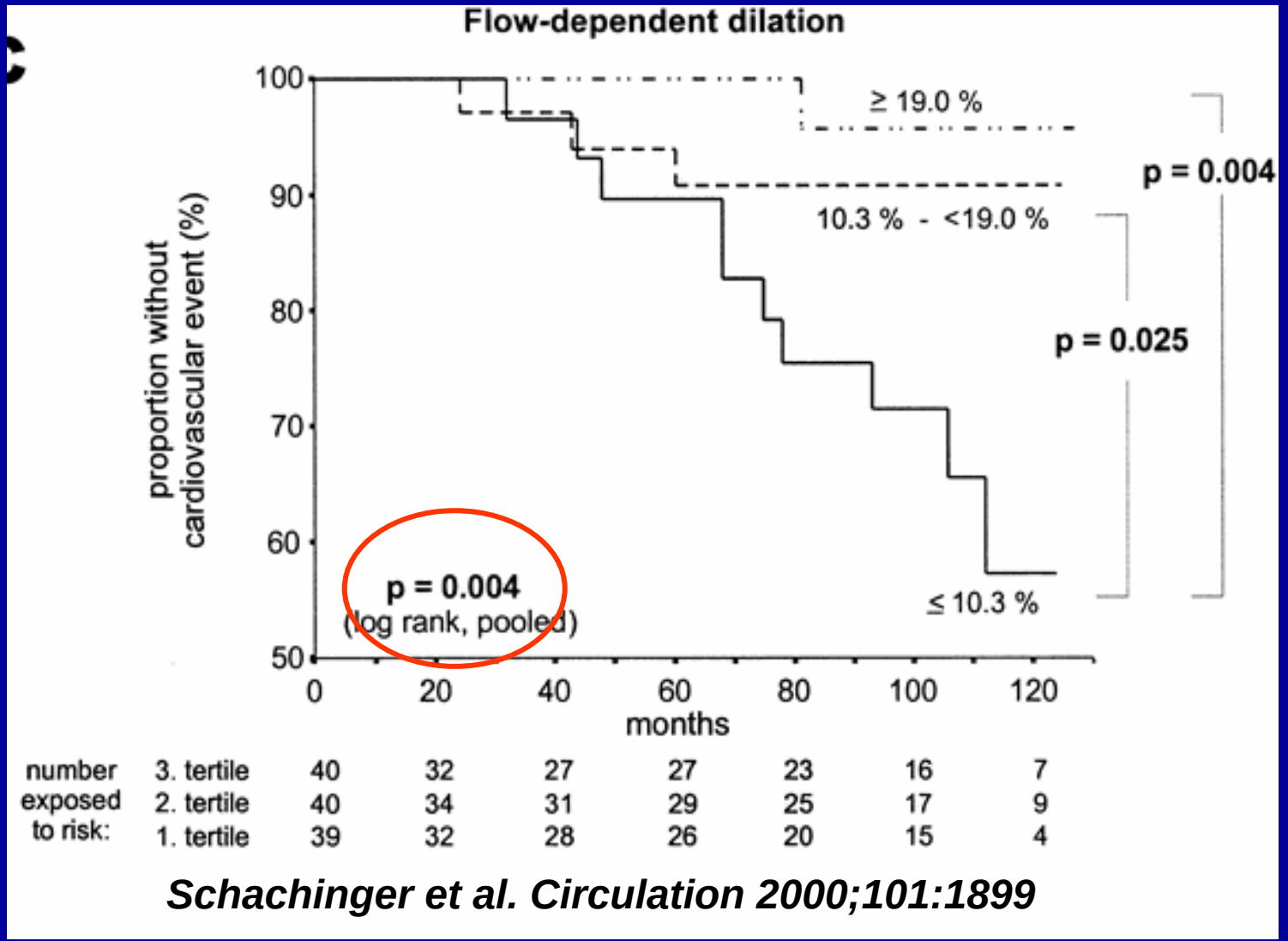
Schroeder et al. Am Heart J 1999;138:731

Prognostic Value of Endothelial Vasomotor Function

Study	Population	Vascular Bed	Test of Endothelial Function	No. of Patients	Follow-Up, mo	Clinical Events
Al Suwaidi et al[38]	CAD	Coronary resistance vessels	Acetylcholine	157	28	MI, cardiovascular death, revascularization, CHF
Schächinger et al[37]	CAD	Epicardial coronary arteries	Acetylcholine and flow-mediated dilation	147	92	MI, cardiovascular death, revascularization, unstable angina, ischemic stroke
Halcox et al[38]	CAD	Epicardial coronary arteries and resistance vessels	Acetylcholine	308	46	MI, cardiovascular death, unstable angina, stroke
Perticone et al[39]	Hypertension	Forearm resistance vessels	Acetylcholine	225	32	Cardiac, cerebrovascular, peripheral vascular
Heitzer et al[40]	CAD	Forearm resistance vessels	Acetylcholine	281	54	MI, cardiovascular deaths, ischemic stroke, revascularization
Neunteufl et al[41]	CAD	Brachial arteries	Flow-mediated dilation	73	60	MI, revascularization
Gokce et al[42]	PAD	Brachial arteries	Flow-mediated dilation	187	1	Cardiovascular death, MI, unstable angina, stroke
Modena et al[32]	Hypertension, postmenopausal	Brachial arteries	Flow-mediated dilation	400	67	Cardiovascular events
Gokce et al[43]	PAD	Brachial arteries	Flow-mediated dilation	199	14	Cardiovascular death, MI, unstable angina, stroke
Targonski et al[44]	Risk factors, but normal coronary arteries	Coronary resistance vessels	Acetylcholine	503	16	Cerebrovascular events

Ganz et al. Circulation 2003;108:2049

Endothelial Vasomotor Function Test had a Long-Term Prognostic Value for CV Events

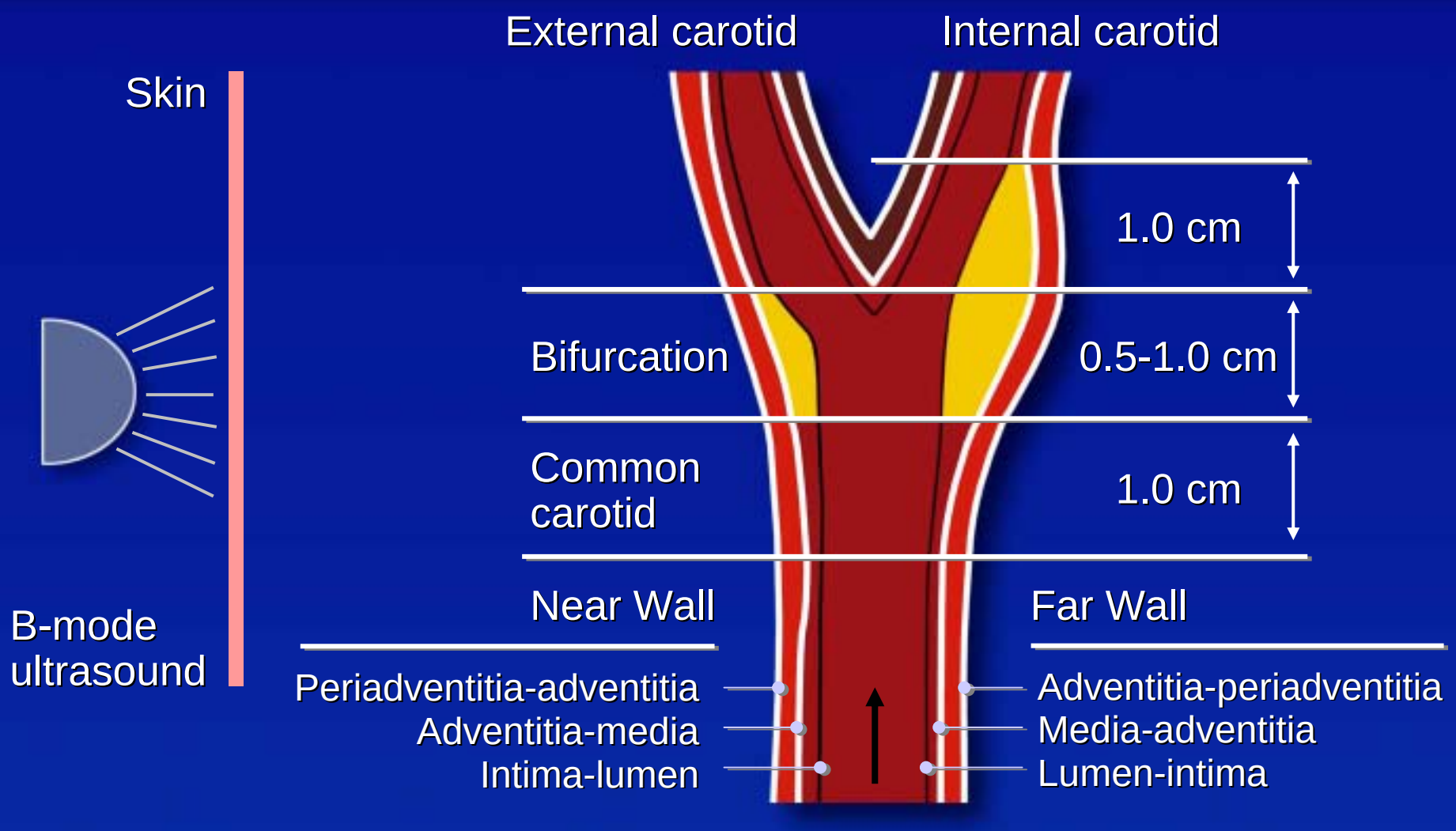


Schachinger et al. Circulation 2000;101:1899

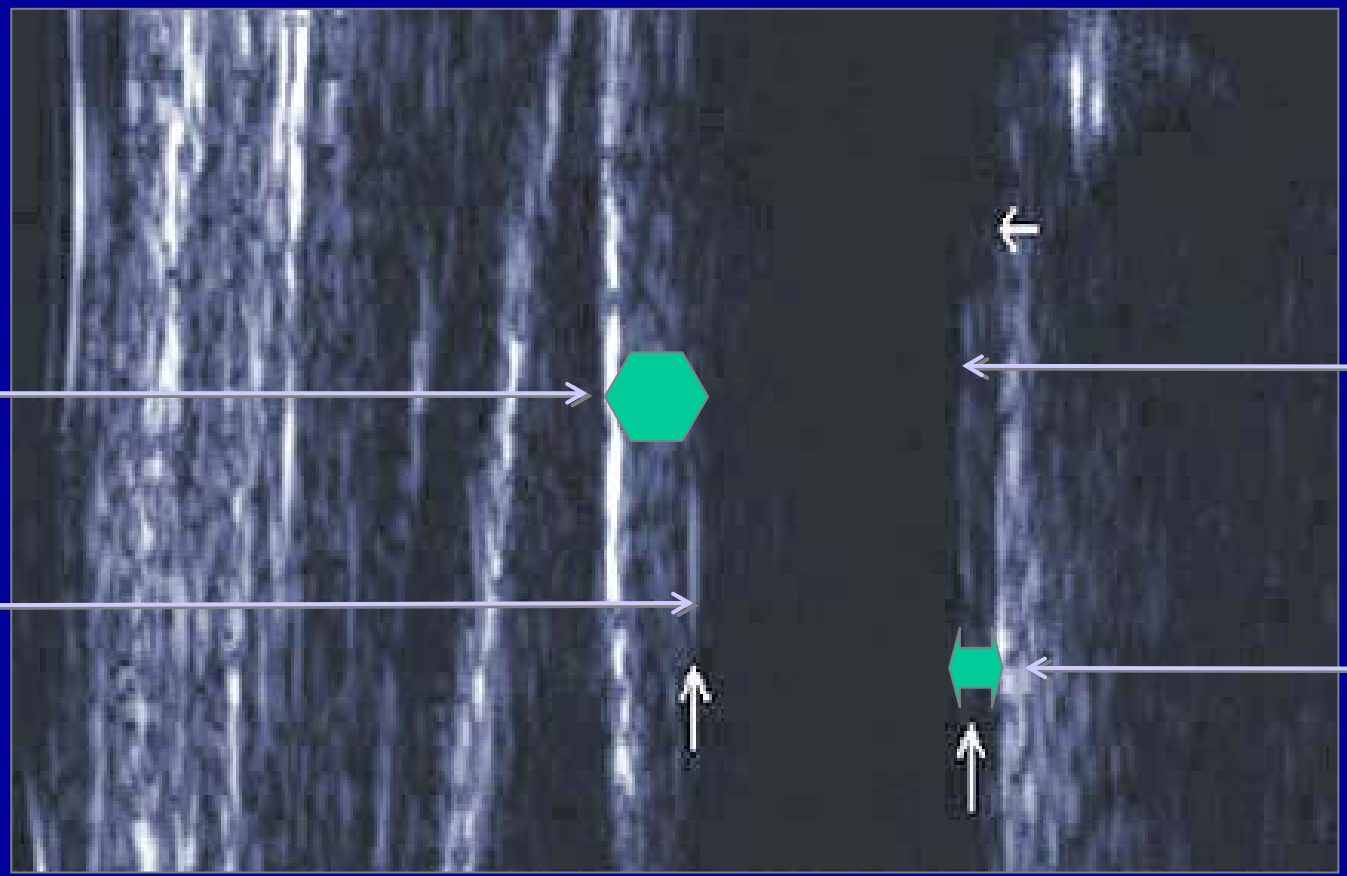
(10 yrs Follow-up)

Carotid Intima-Media Thickness (IMT)

B-Mode Ultrasound Examination of the Carotid Artery



Example of B-Mode Ultrasound Imaging



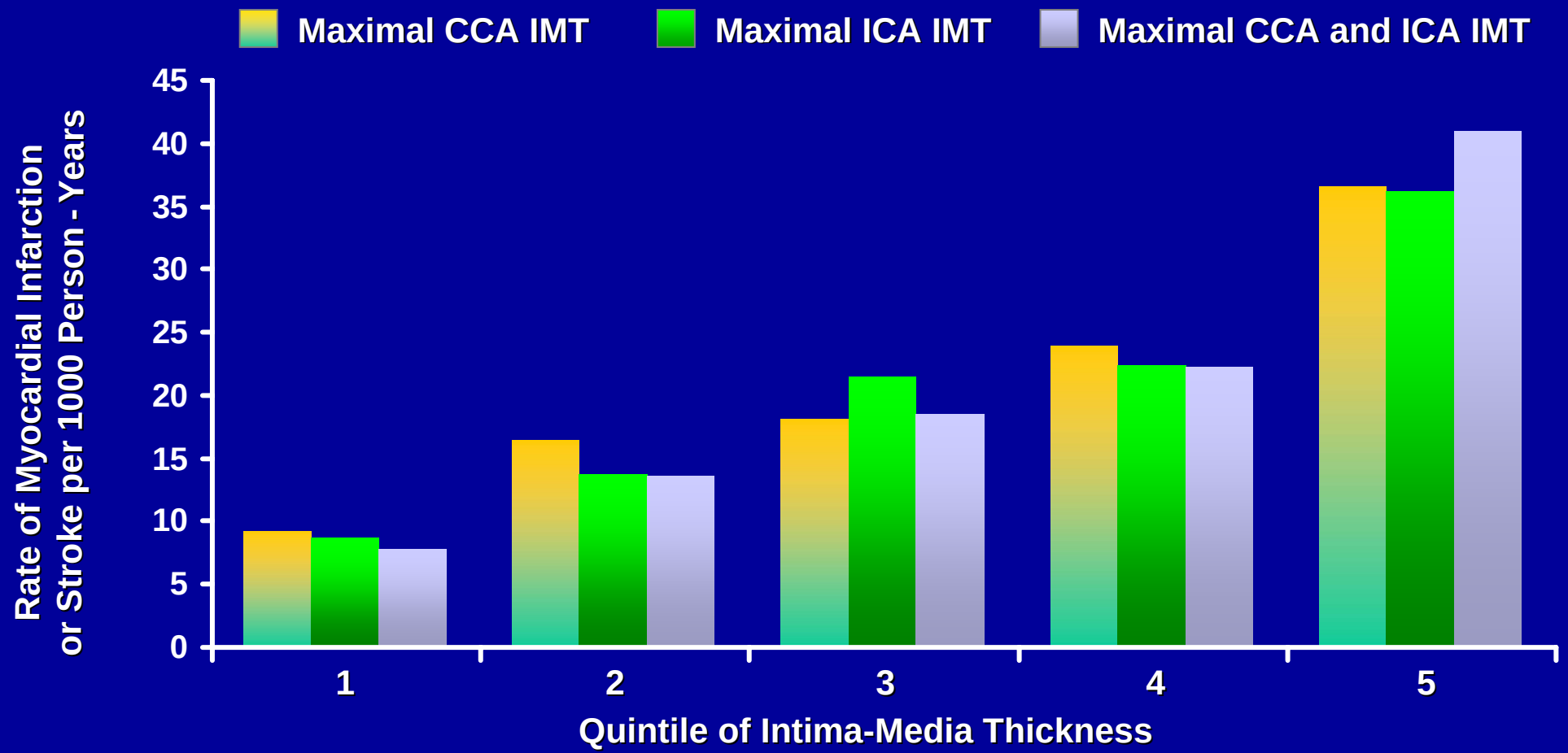
Intima media thickness (near wall)

Intima (near wall)

Intima (far wall)

Normal intima media thickness (far wall)

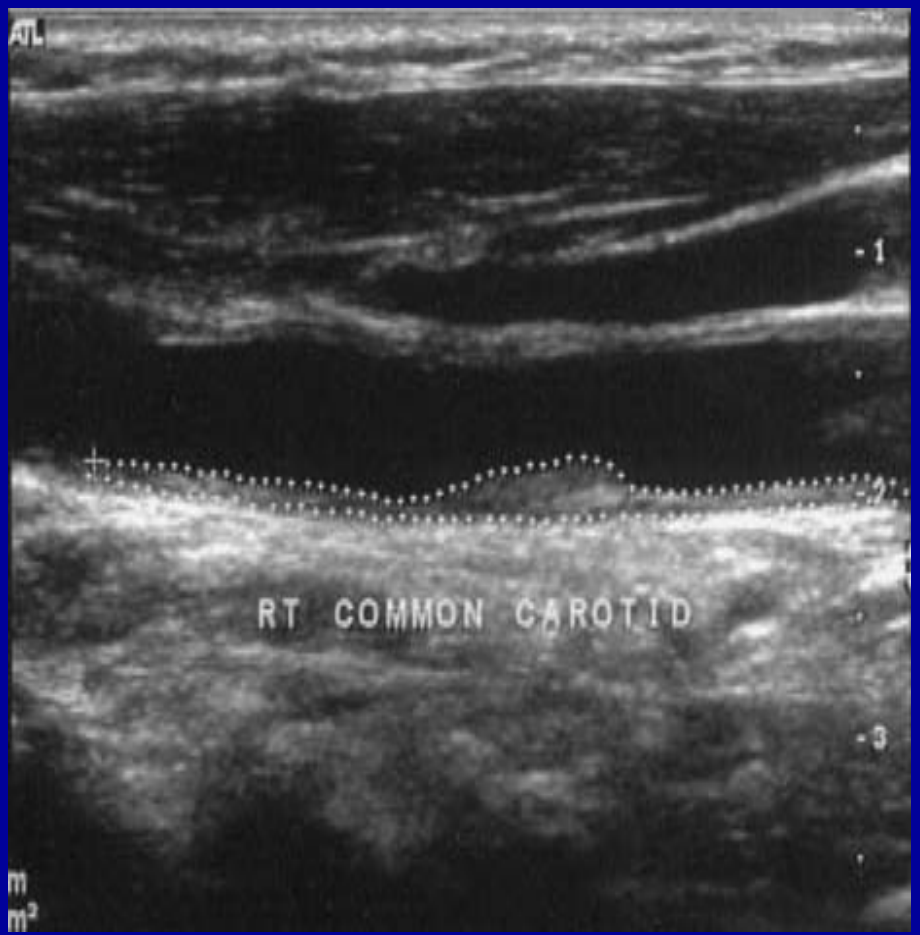
Increased IMT is an Independent Predictor of Future Cardiovascular Events

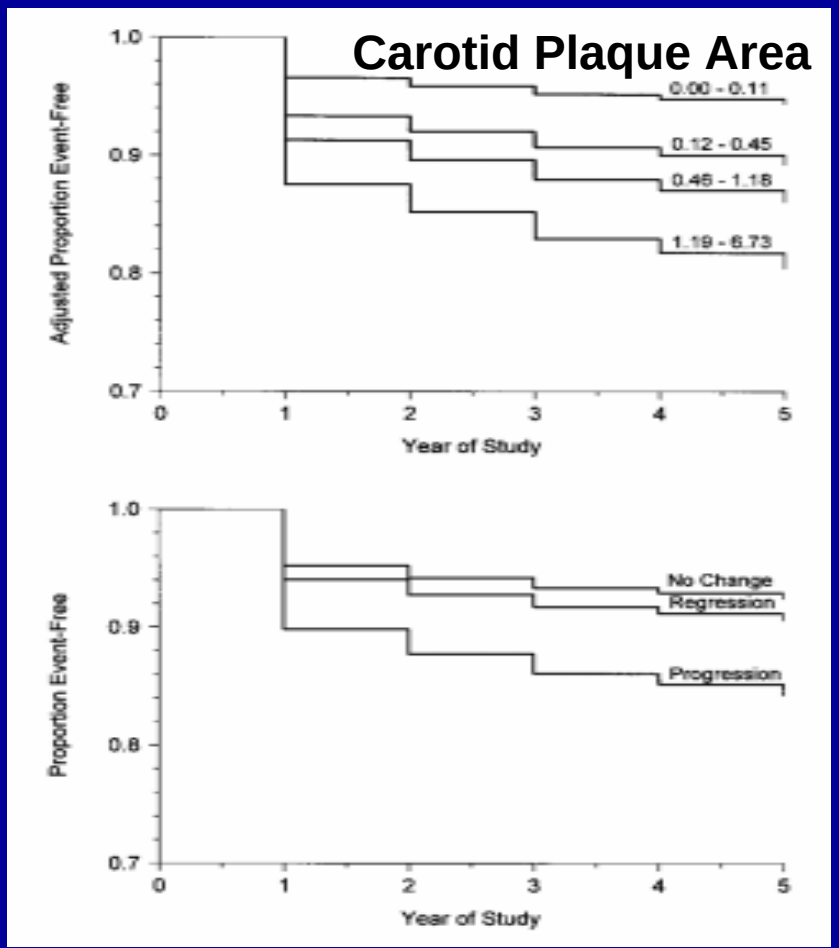


High-resolution ultrasound measurements of the intima and media of the common and internal carotid artery made in **5858 subjects ≥65 years of age**. New MI or stroke served as outcome variables in subjects without clinical CVD (n=4476) over a median follow-up of **6.2 years.**

O'Leary DH et al. *N Engl J Med.* 1999;340:14-22.

Plaque Size had the Greatest Prognostic Value Among all Ultrasound Parameters

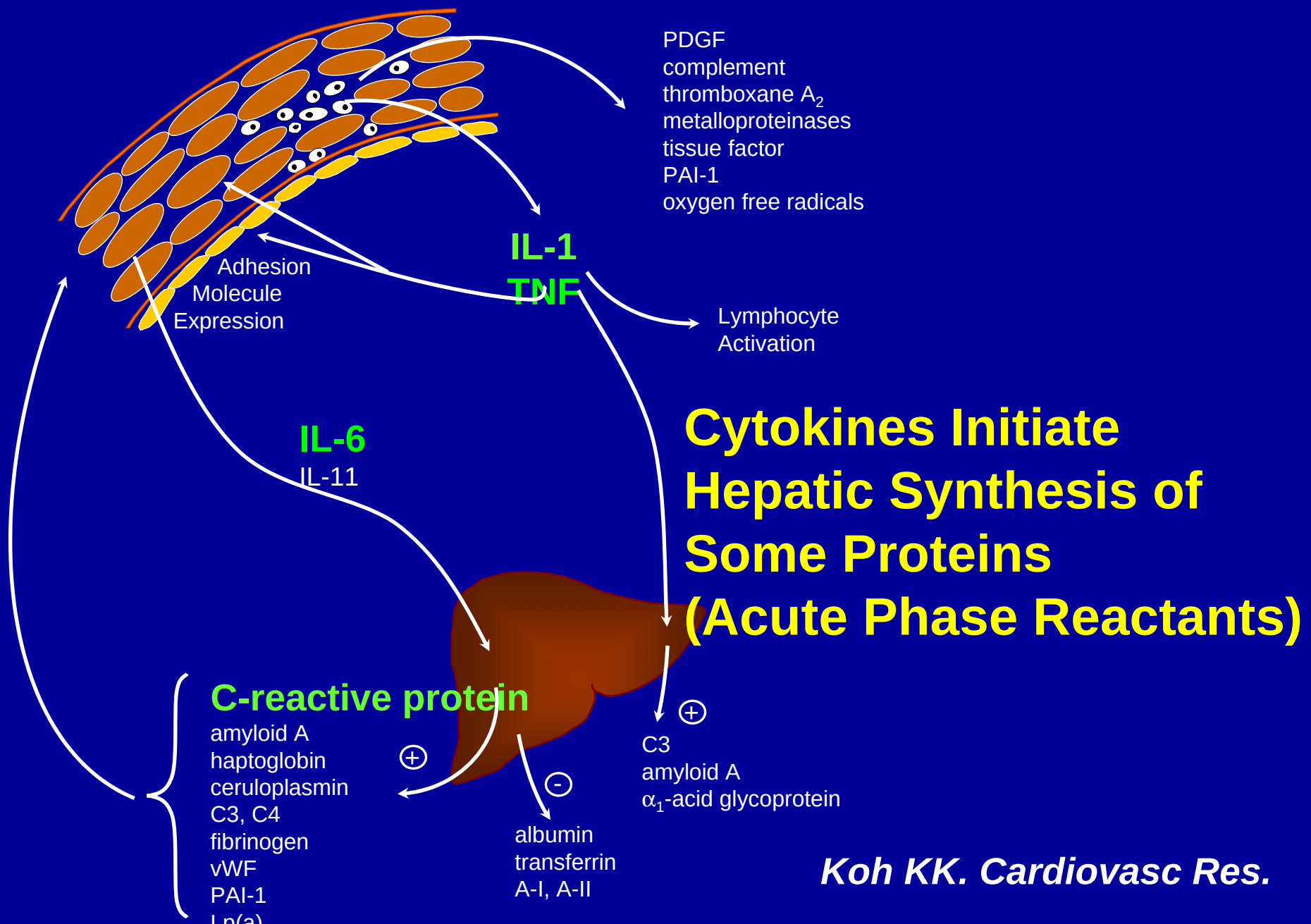




1686 patients, CV events: Stroke, MI.

Spence JD, et al. Stroke 2002;33:2916

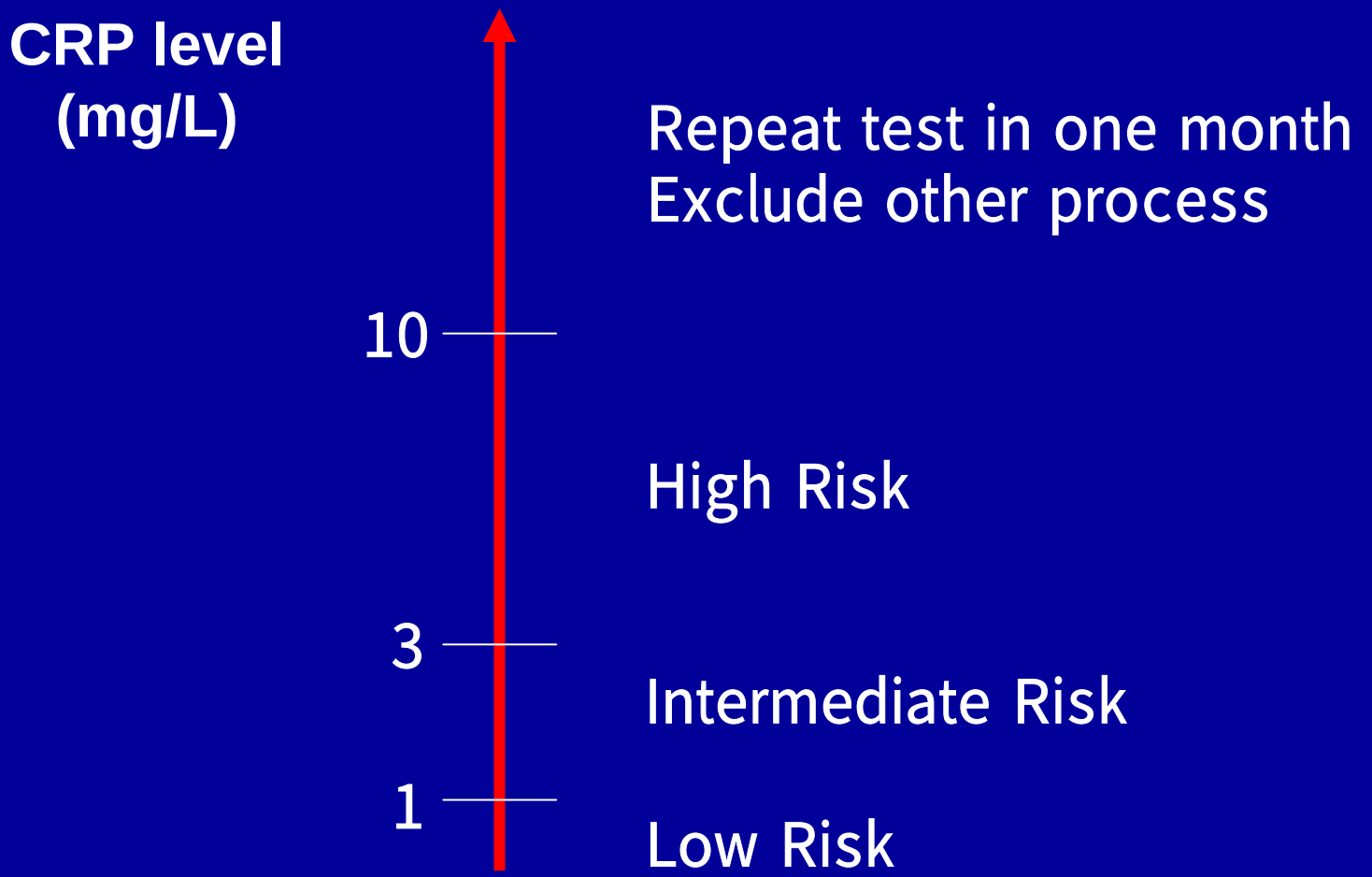
High-sensitivity CRP (hs-CRP)



Cytokines Initiate Hepatic Synthesis of Some Proteins (Acute Phase Reactants)

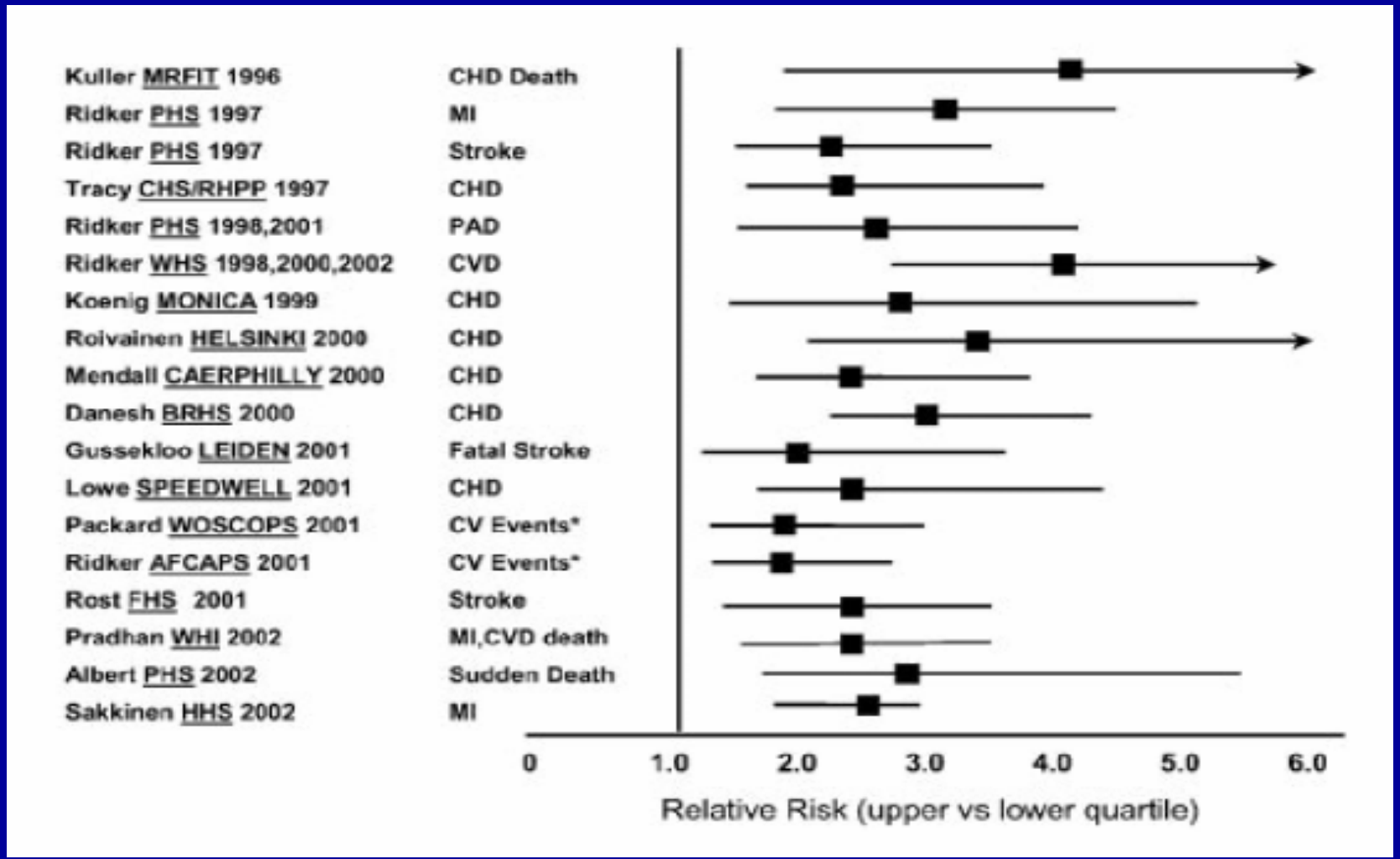
Koh KK. Cardiovasc Res. 2002;55:714. (Review)

CRP Level and Cardiovascular Risk



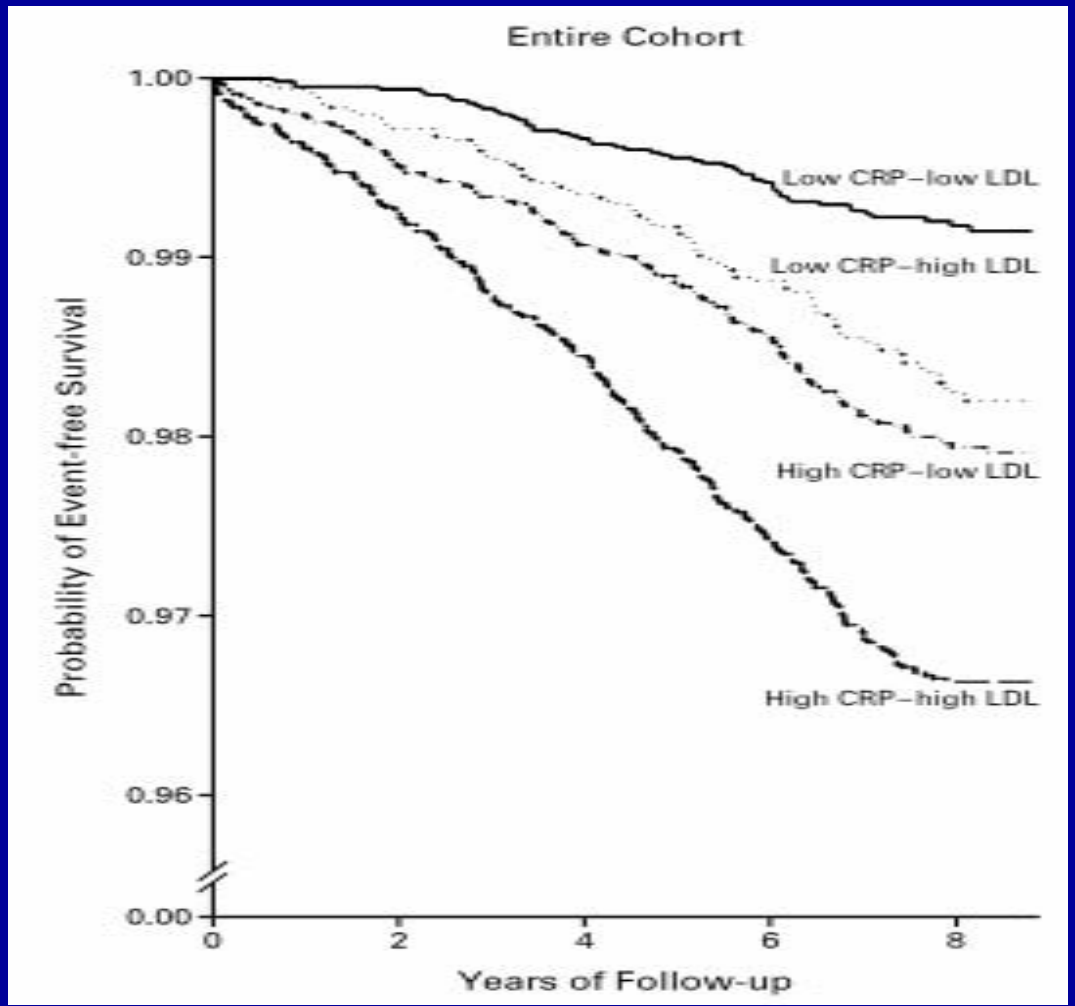
Circulation 2003;107:499.

Prospective Studies Relating Baseline CRP Levels to the Risk of First CV Events



Ridker et al. Circulation 2003;107:363.

CRP is a Stronger Predictor of Risk Than LDL Cholesterol Among Apparently Healthy Women



Women's Health Study

27939 women,

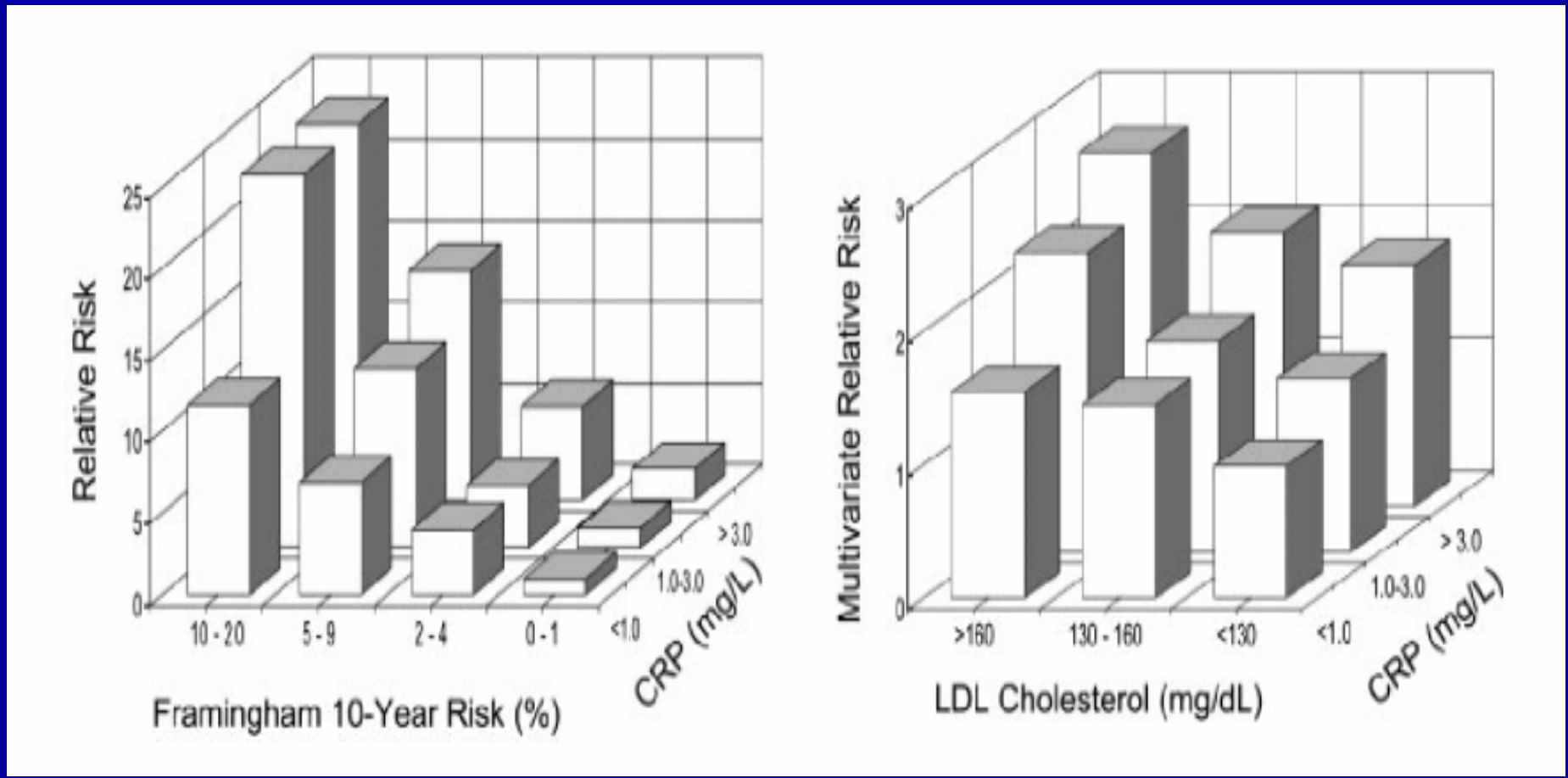
The median values:

CRP 1.52mg/L,

LDL cholesterol 123.7mg/dl

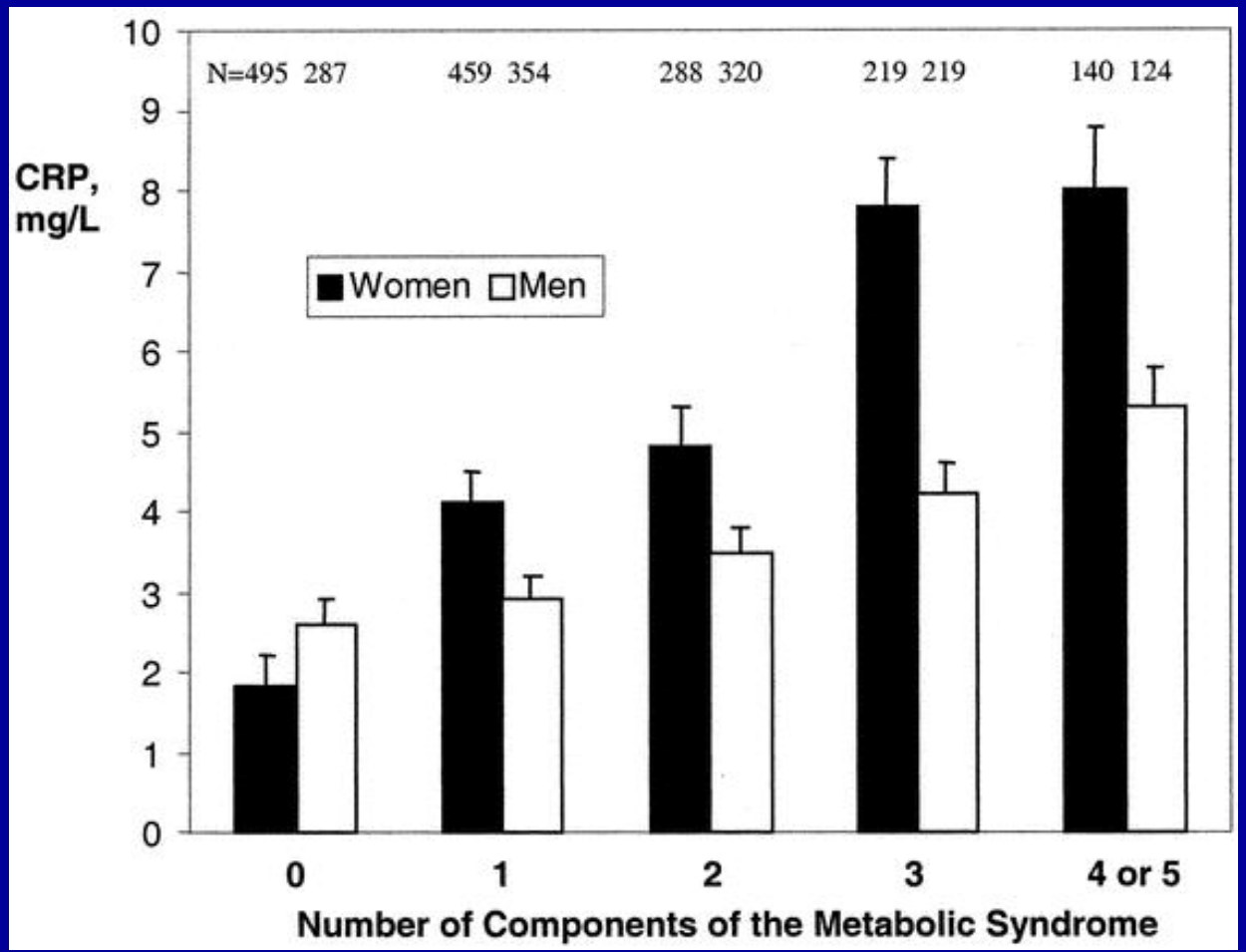
Ridker PM, et al. N Engl J Med 2002;347:1557.

hsCRP Provides Prognostic Information at all Levels of Framingham Risk Score and LDL cholesterol



Ridker PM, et al. Women's Health Study. N Engl J Med 2002;347:1557.

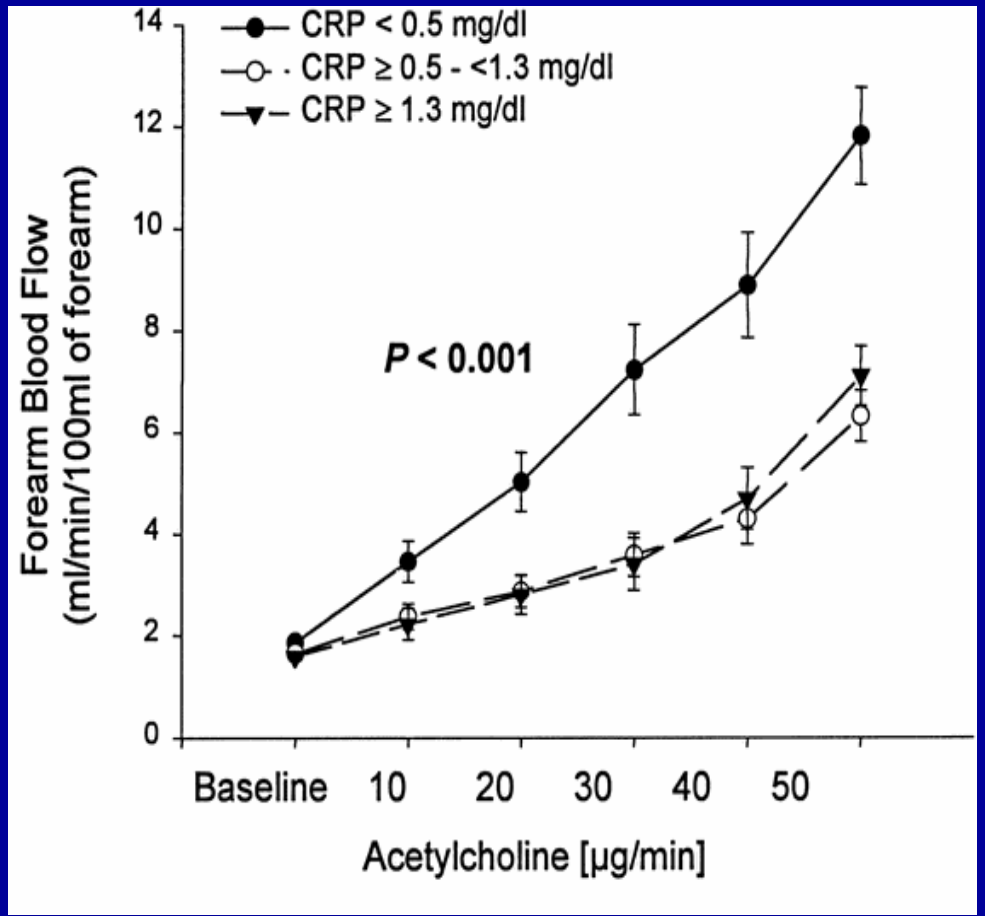
CRP, Metabolic Syndrome, and Prediction of CV Events in the Framingham Offspring Study

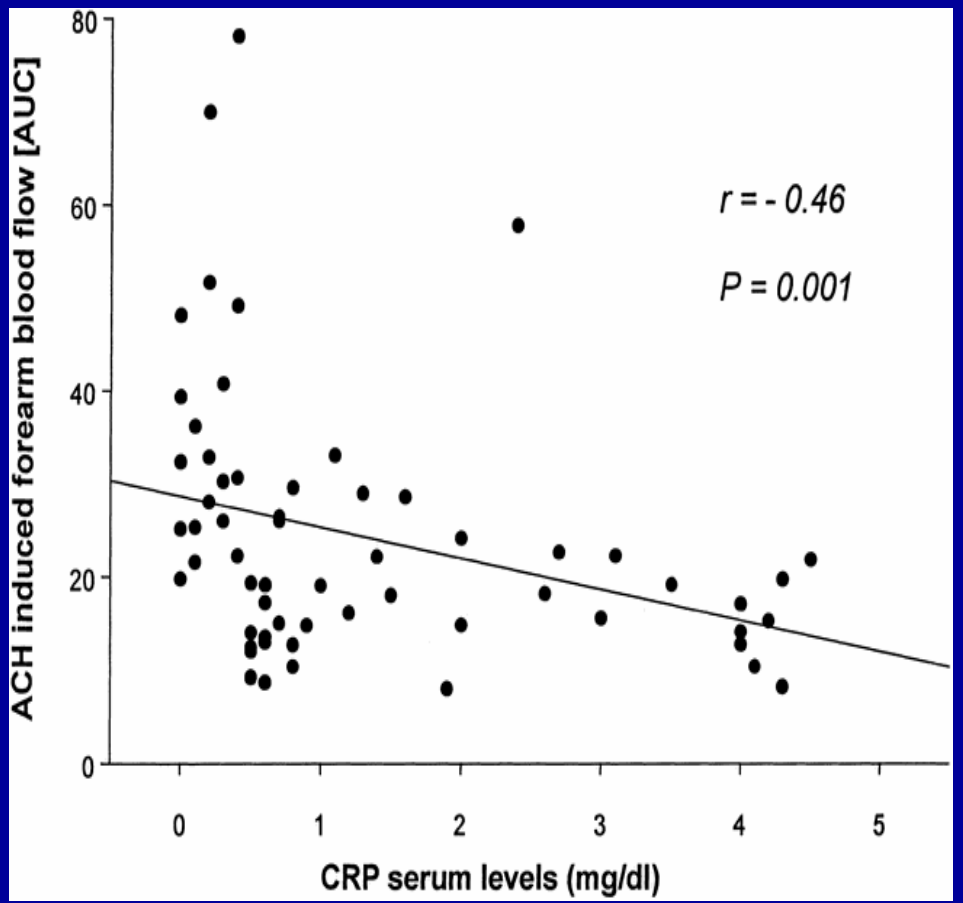


Both CRP and MetS are independent predictors of new CVD events over 7 years

Circulation. 2004;110:380.

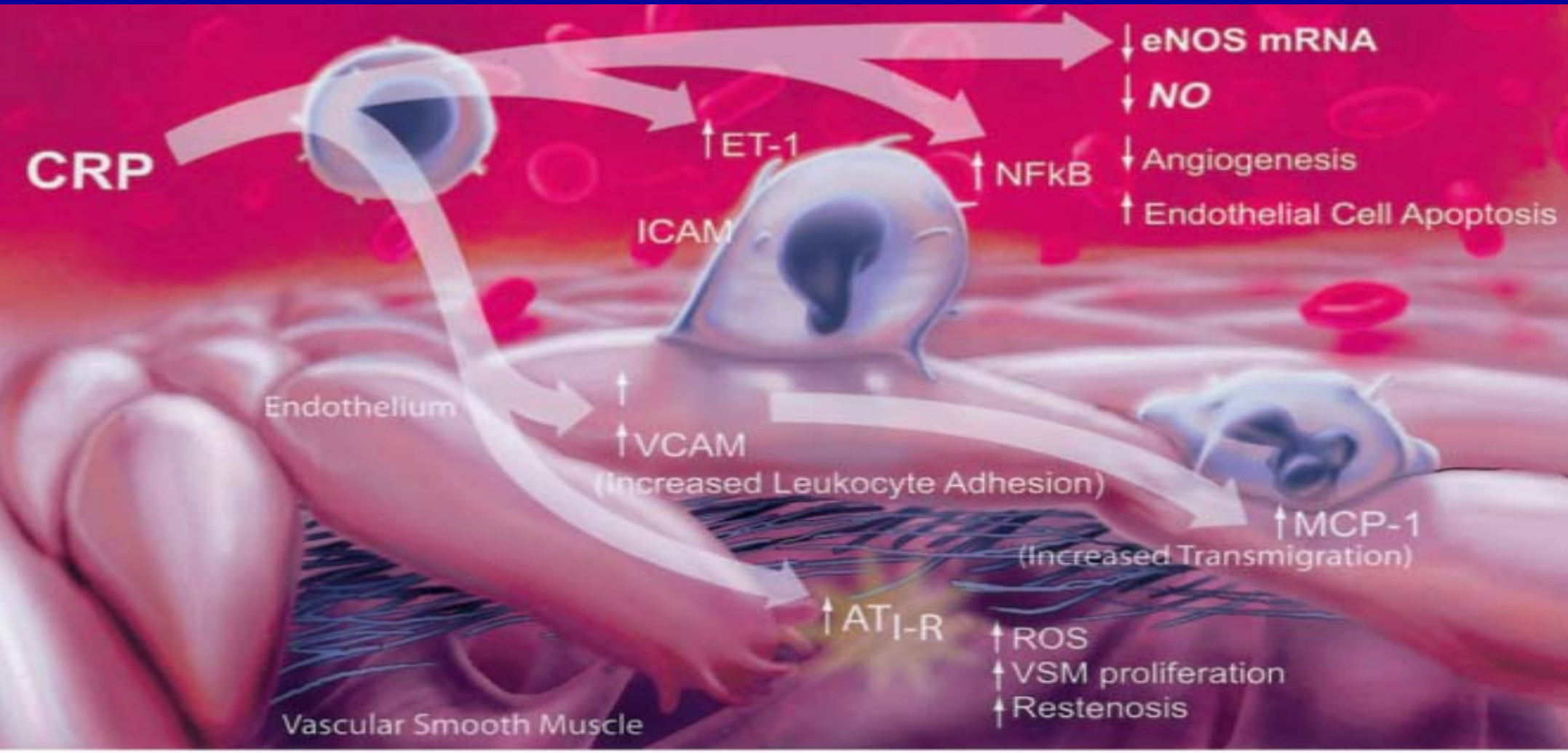
Elevated CRP Levels and Impaired Endothelial Vasoreactivity in Patients with CAD





Fichtlscherer et al. Circulation 2000;102:1000

CRP as a Mediator of Atherosclerosis

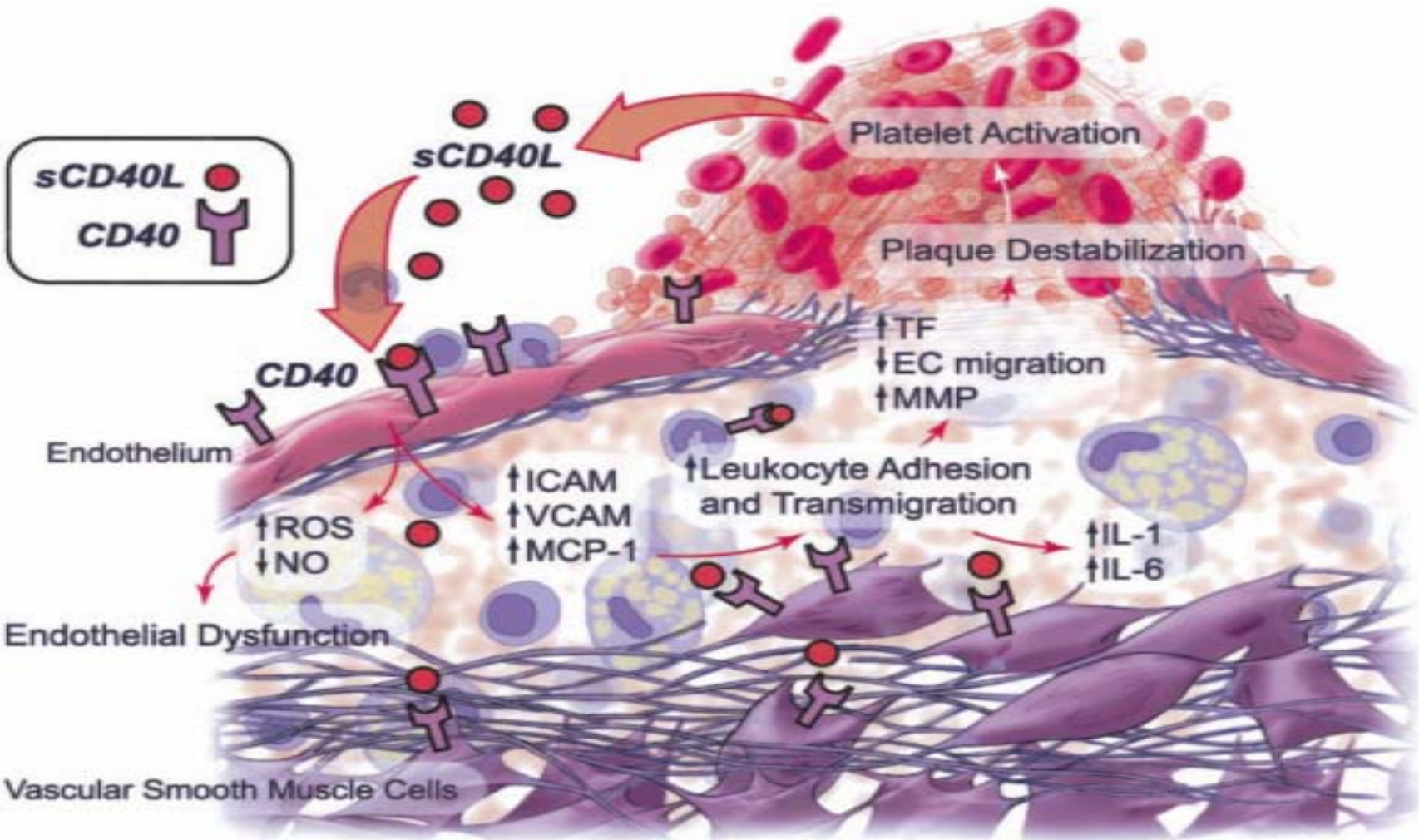


CRP inhibits BM-derived endothelial progenitor cell survival and differentiation.

Szmitko et al.Circulation 2003;108:1917

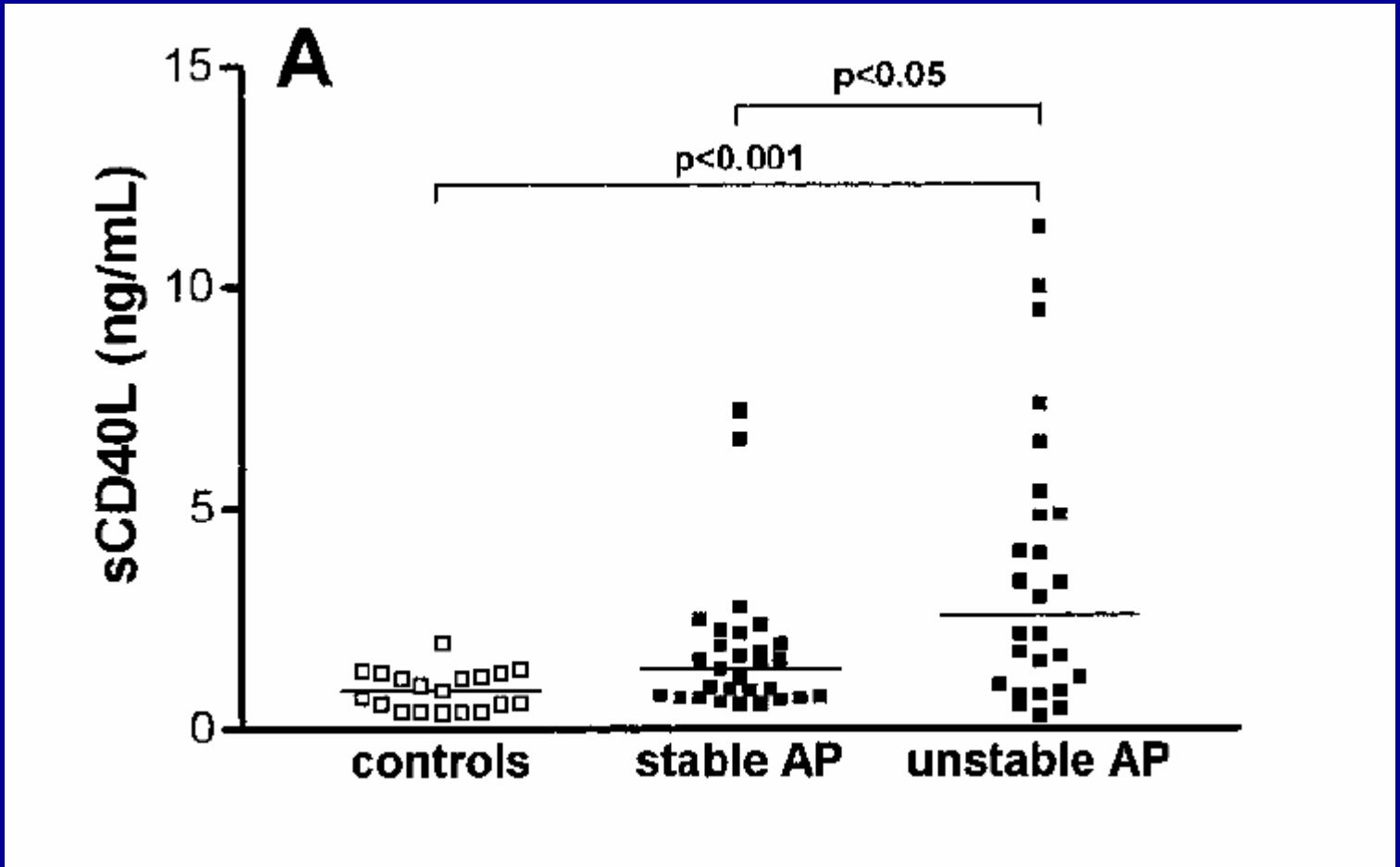
CD40L

CD40L on vascular endothelial, SMCs, and Mononuclear phagocytes, mediates a broad Gamut of proatherothrombotic functions



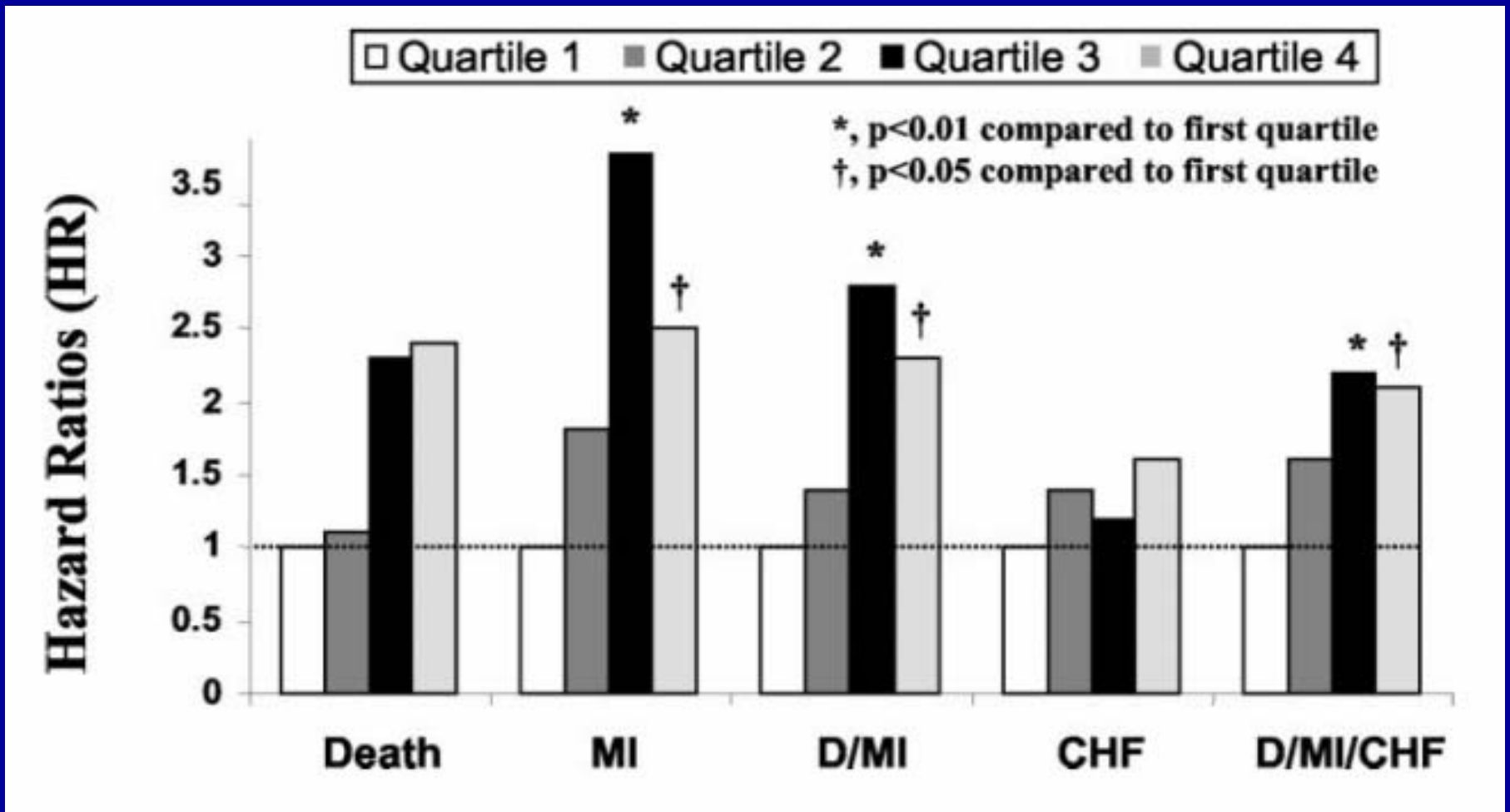
Szmitko et al
Circulation
2003;108:1917

Patients with unstable angina have Elevated Plasma Levels of sCD40L



Aukrust P, et al. Circulation 1999;100:614.

sCD40L is an Important Prognostic Indicator in Acute Coronary Syndromes



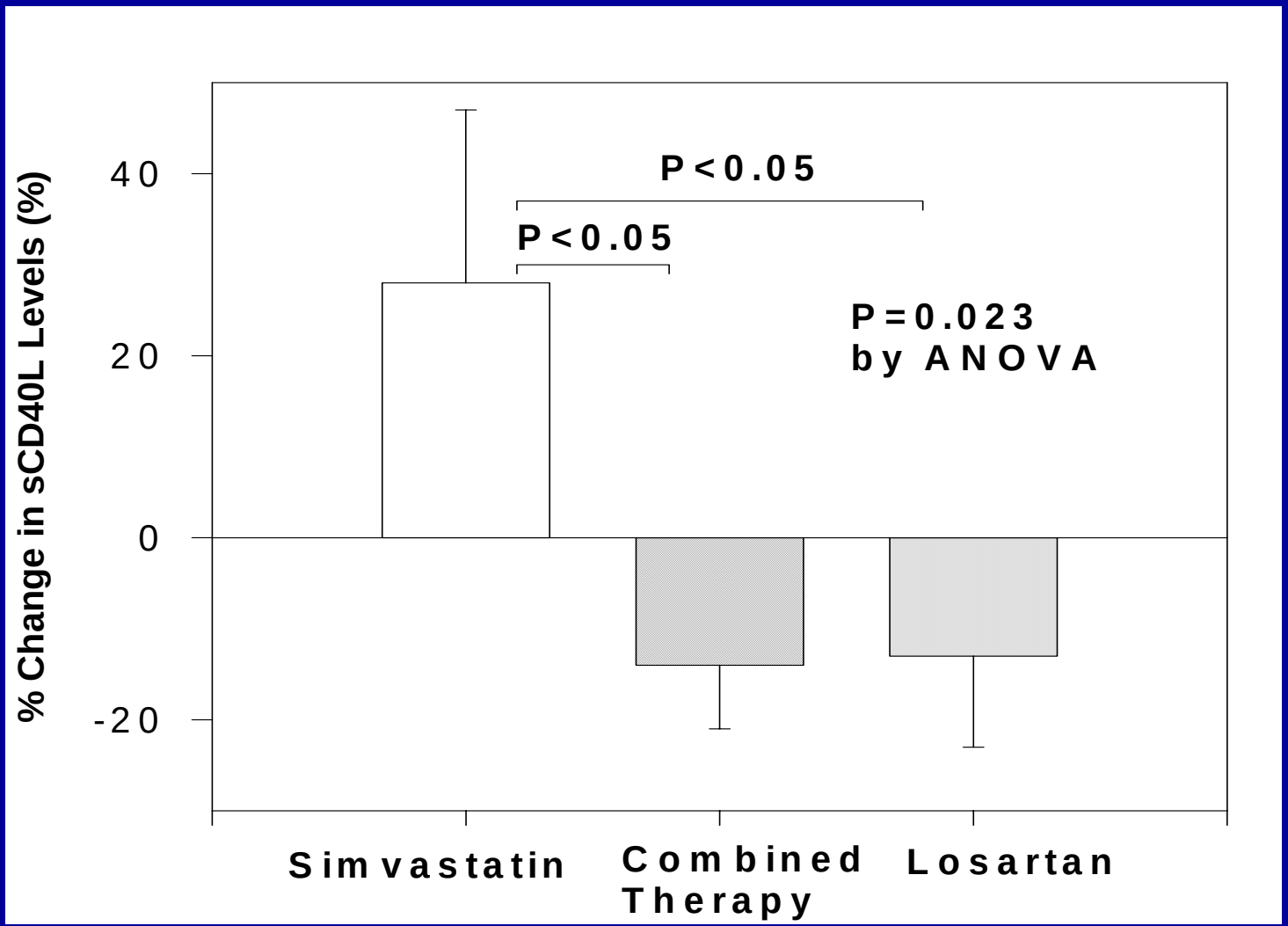
Varo N, et al. OPUS-TIMI 16 Trial. Circulation 2003;108:1049.

The Effects of Simvastatin, Losartan, and Combined Therapy on sCD40L in Hypercholesterolemic, Hypertensive Patients

Seung Hwan Han, Kwang Kon Koh,
Eak Kyun Shin, ……. Michael J. Quon

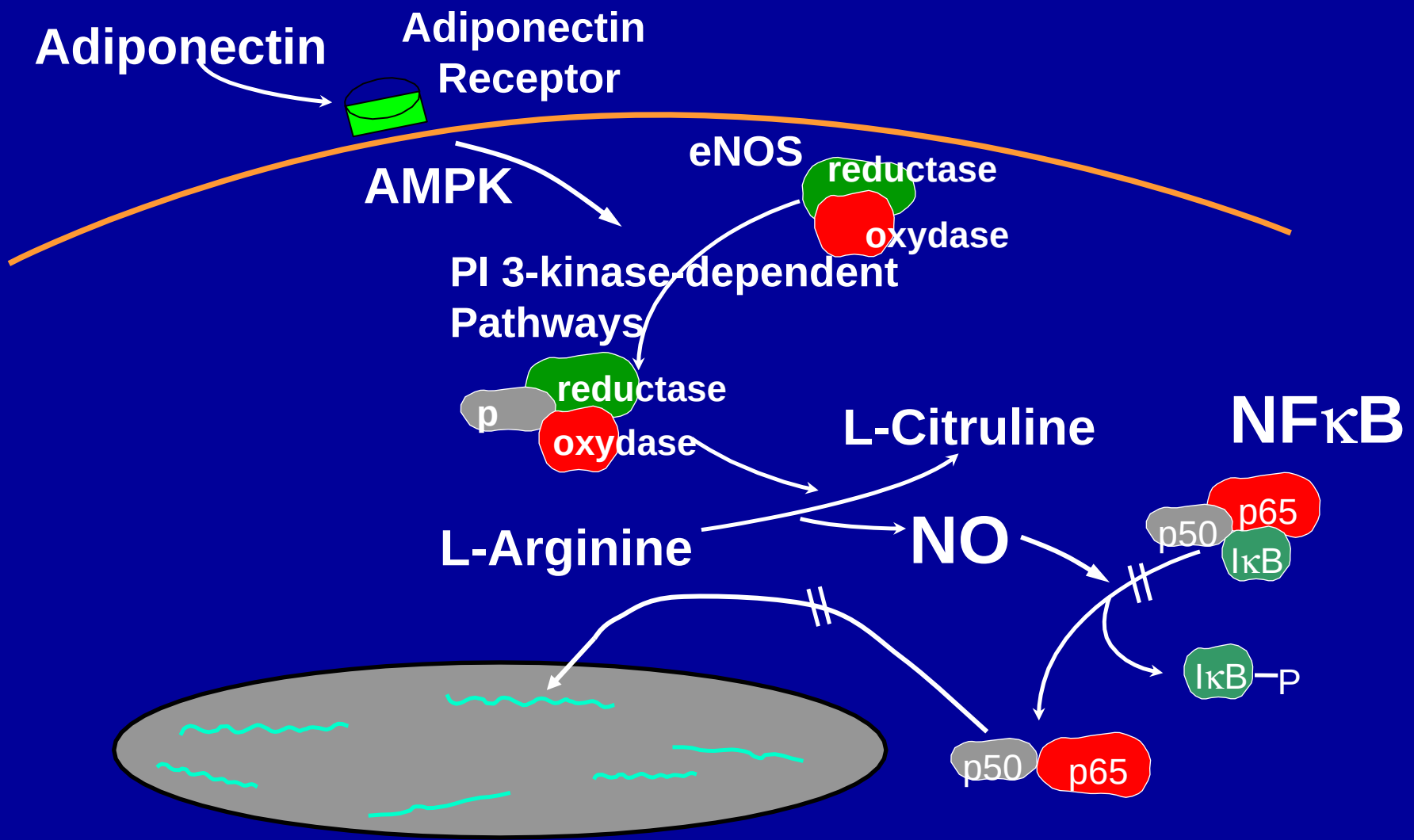
J Am Coll Cardiol (submitted)

Combined Therapy and Losartan Reduces Plasma Levels of sCD40L



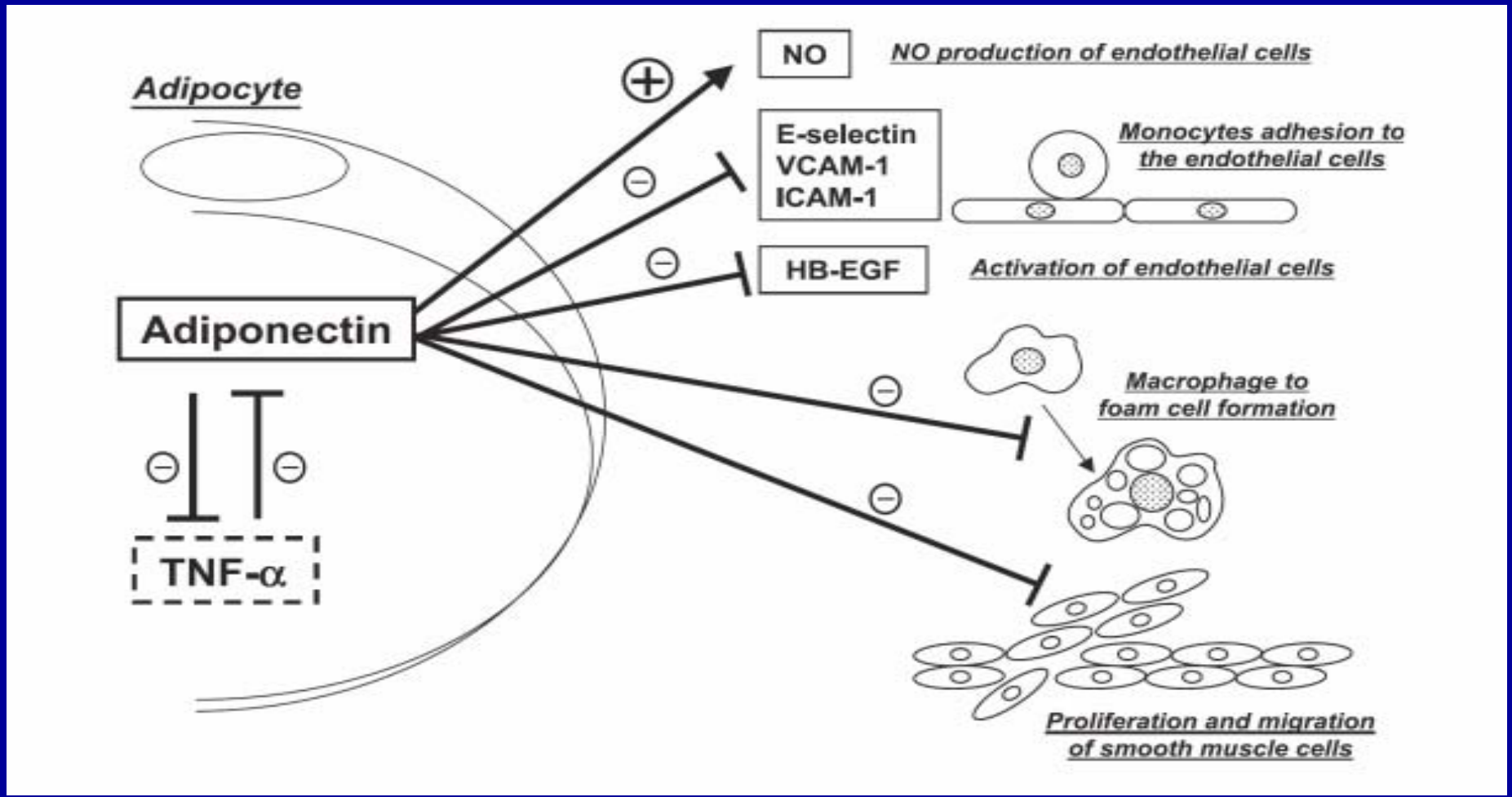
Adiponectin

Adiponectin can directly stimulate NO production from endothelium via activation of AMP-activated protein kinase



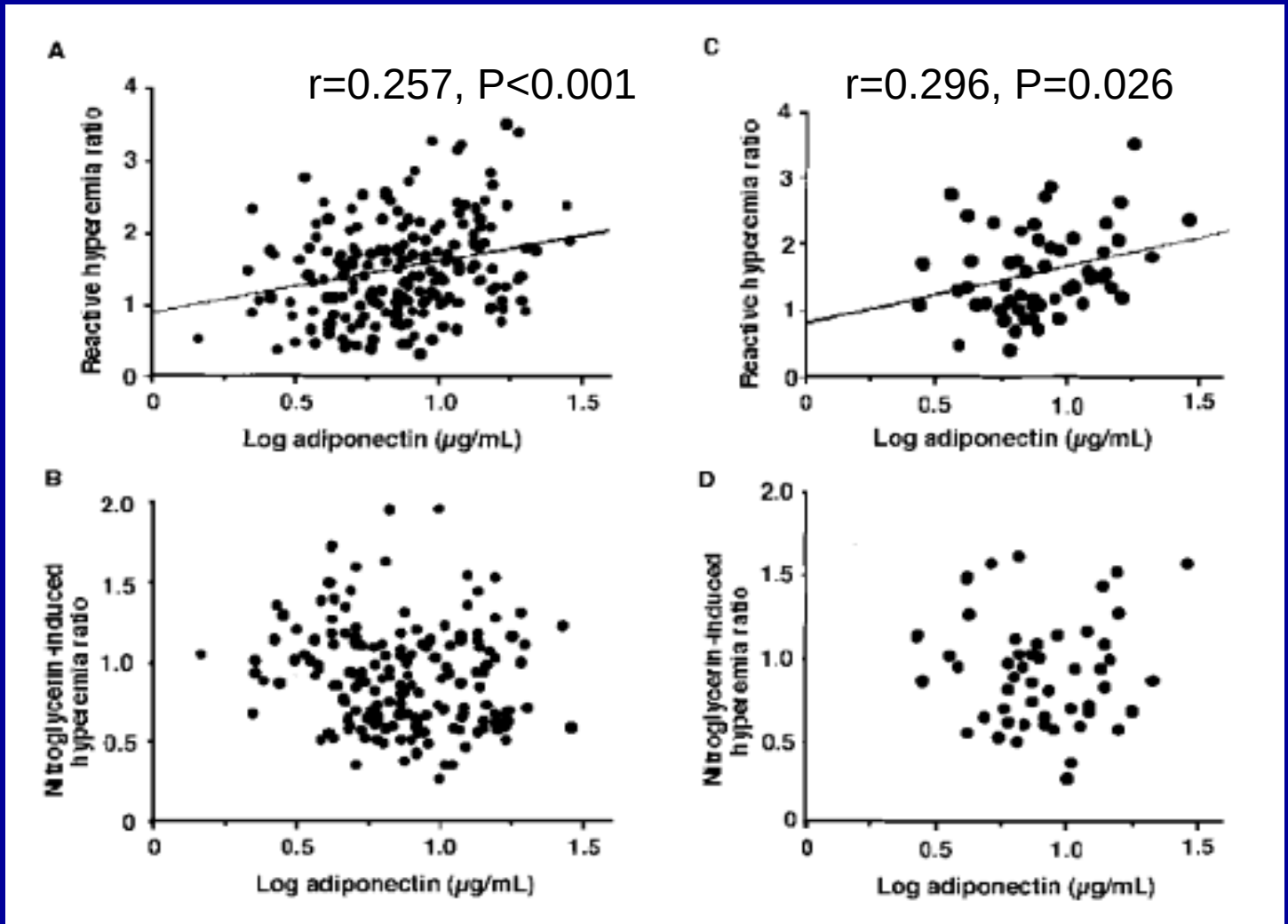
Han SH, Koh KK, et al. Circulation (Review, submitted)

Adiponectin has Anti-inflammatory and Anti-atherogenic effects



Shimada K et al. Clinica chimica Acta 2004;344:1.

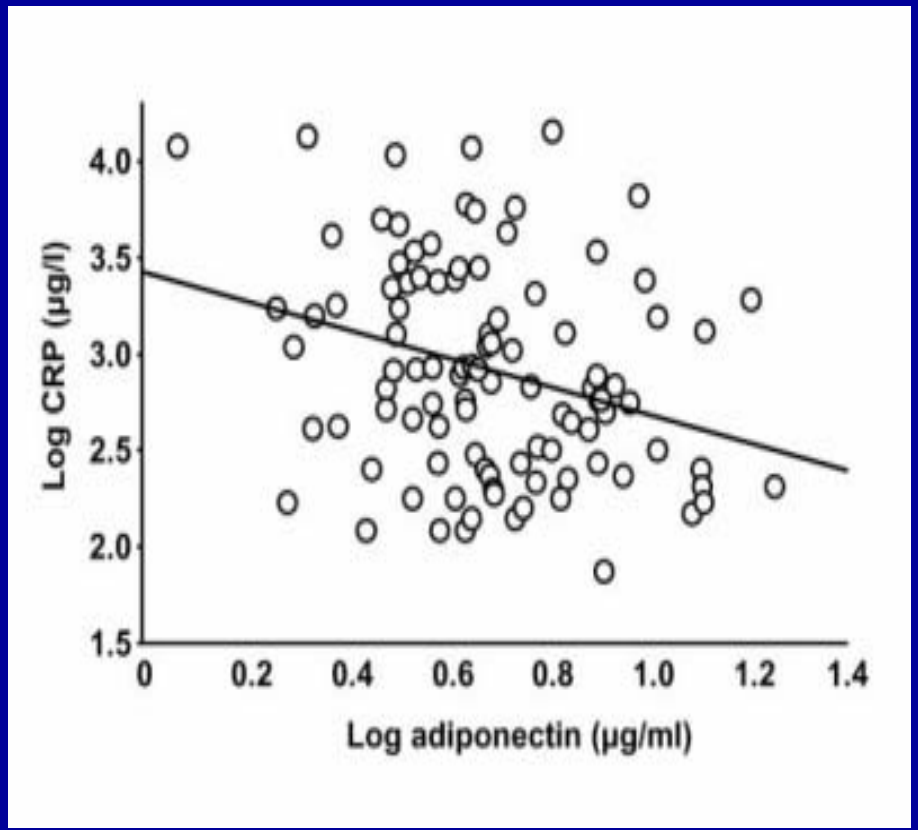
Adiponectin and Endothelial Function



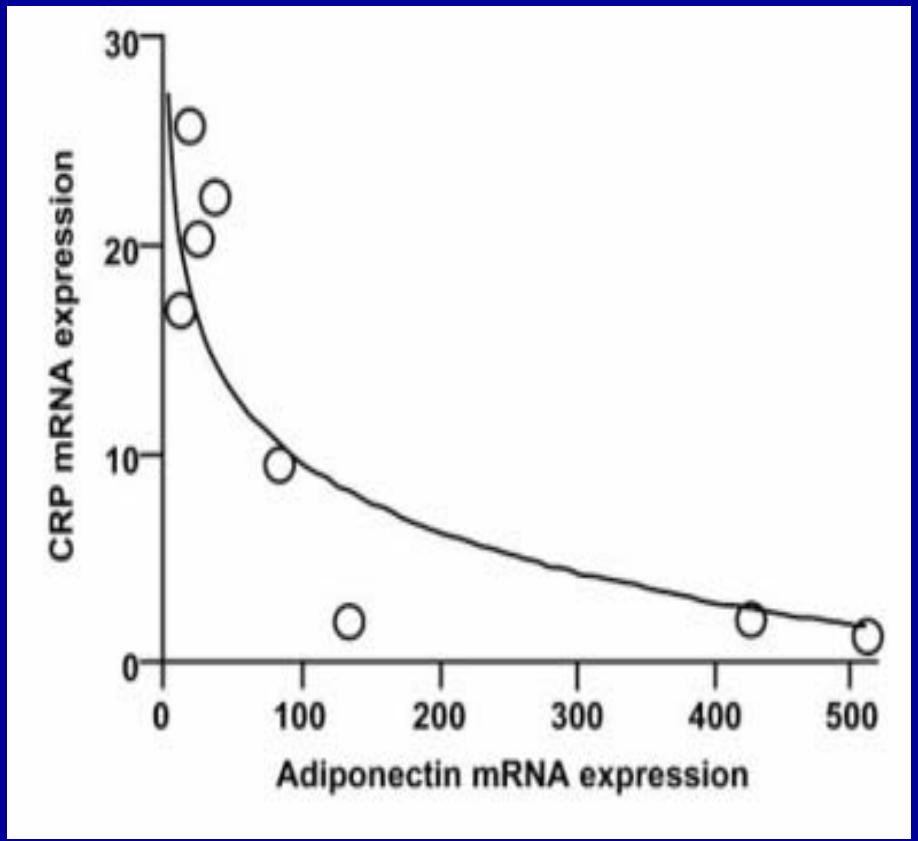
Strain-gauge phethysmography

Ouchi N, et al. Hypertension 2003;42:231.

Negative Relationship between Adiponectin and CRP



r=-0.29, P<0.01

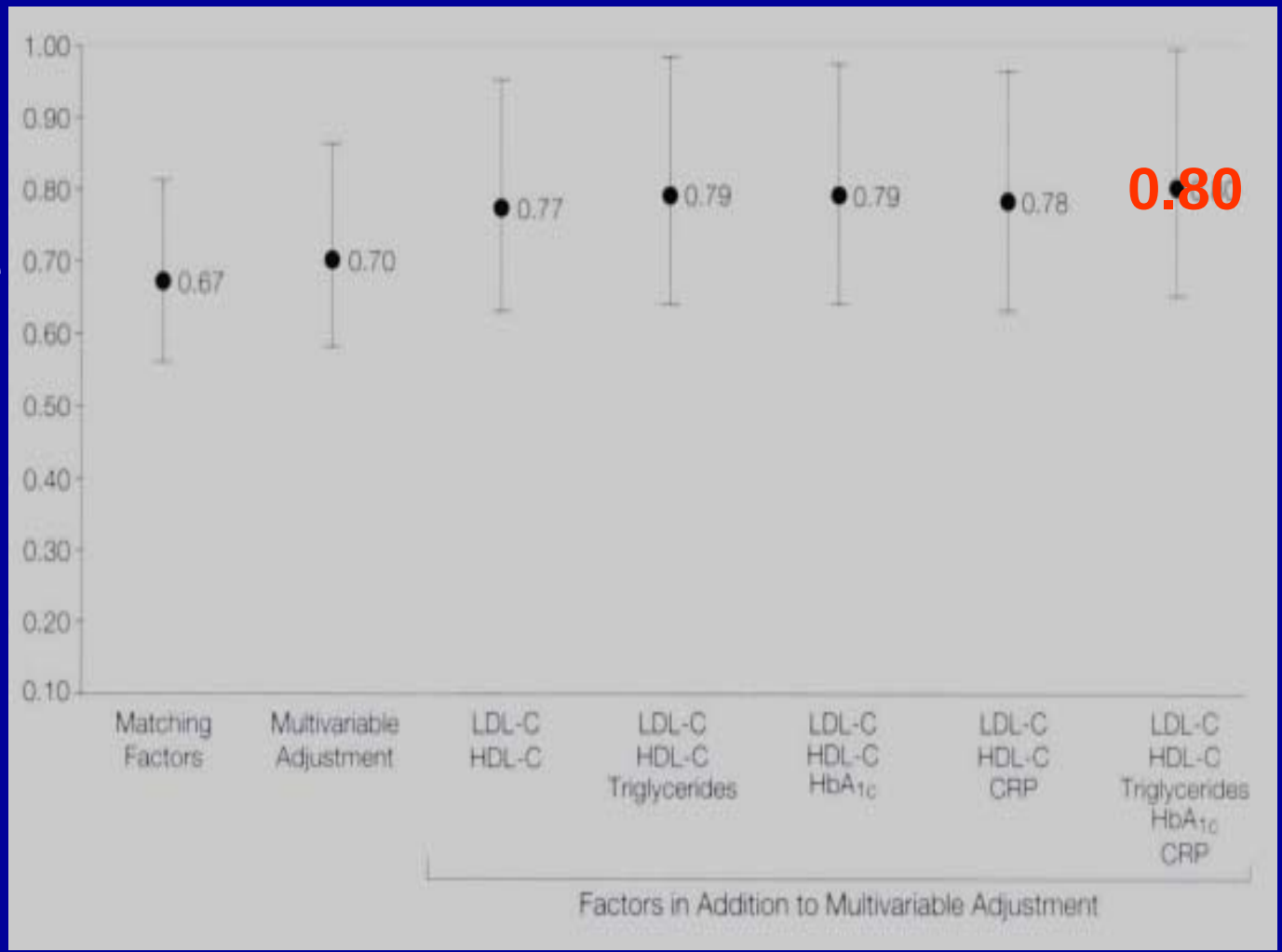


r=-0.89, P<0.01

Ouchi N, et al. Circulation 2003;107:671.

High Plasma Adiponectin Concentrations are Associated with Lower Risk of MI in Men

Relative Risk



6 yrs follow-up

Health Professionals Follow-up Study
Pischon T, et al. JAMA 2004;291:1730.

Additive Beneficial Effects of Losartan Combined with Simvastatin in Treatment of Hypercholesterolemic, Hypertensive Patients

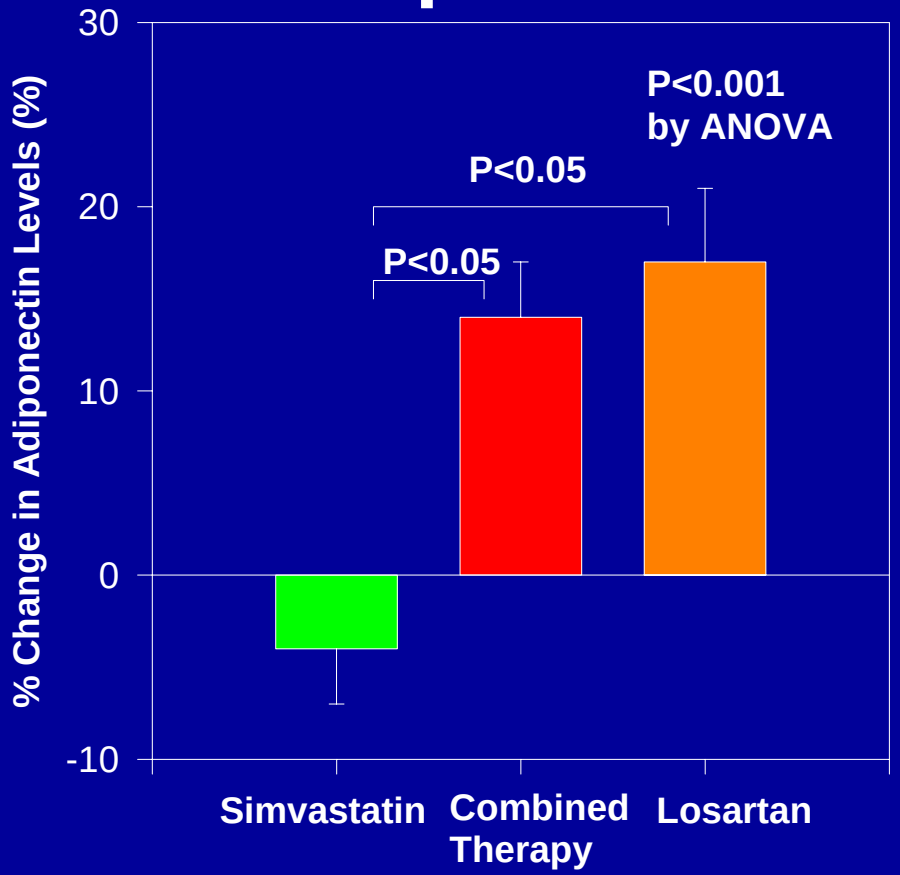
Kwang Kon Koh, Seung Hwan Han
Eak Kyun Shin, .. Michael J. Quon*

Cardiology, Gachon Medical School, Incheon, Korea
Diabetes Unit, NIH, USA*

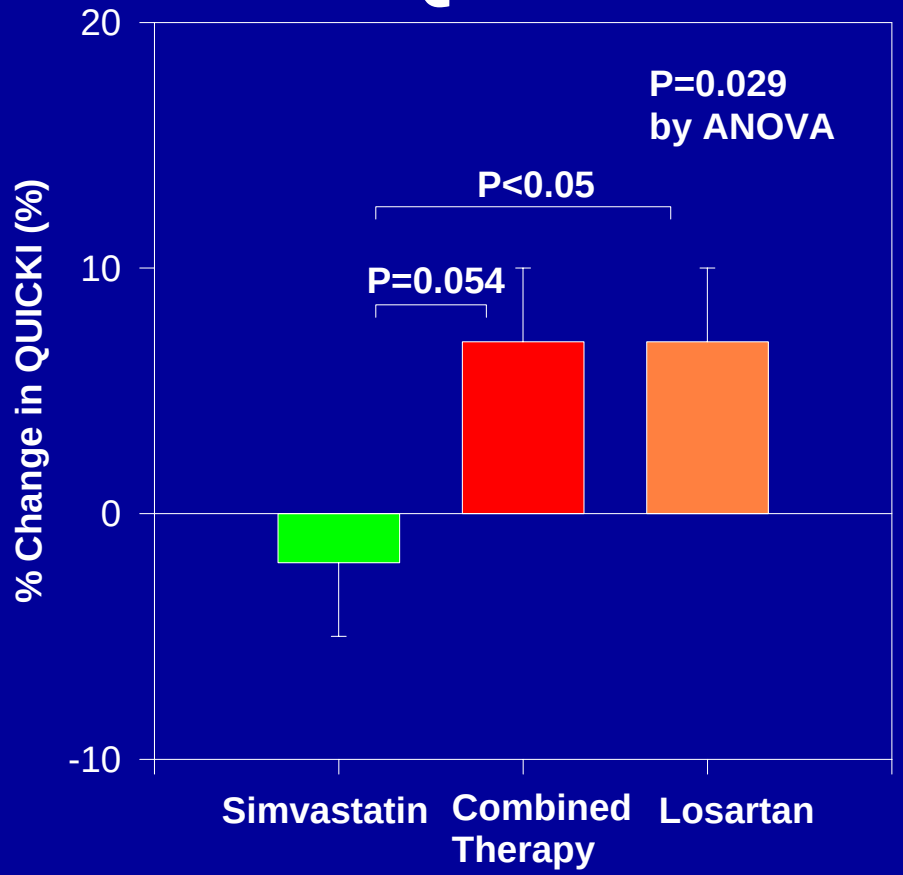
Circulation 2004:110:3687.

Combined Therapy or Losartan Alone Significantly Increases Insulin Sensitivity

Adiponectin



QUICKI



*QUICKI=Quantitative Insulin-Sensitivity Check Index, a surrogate index of insulin sensitivity, QUICKI = 1/[log(insulin)+log(glucose)]

Koh KK, et al. Circulation 2004;110:3687.

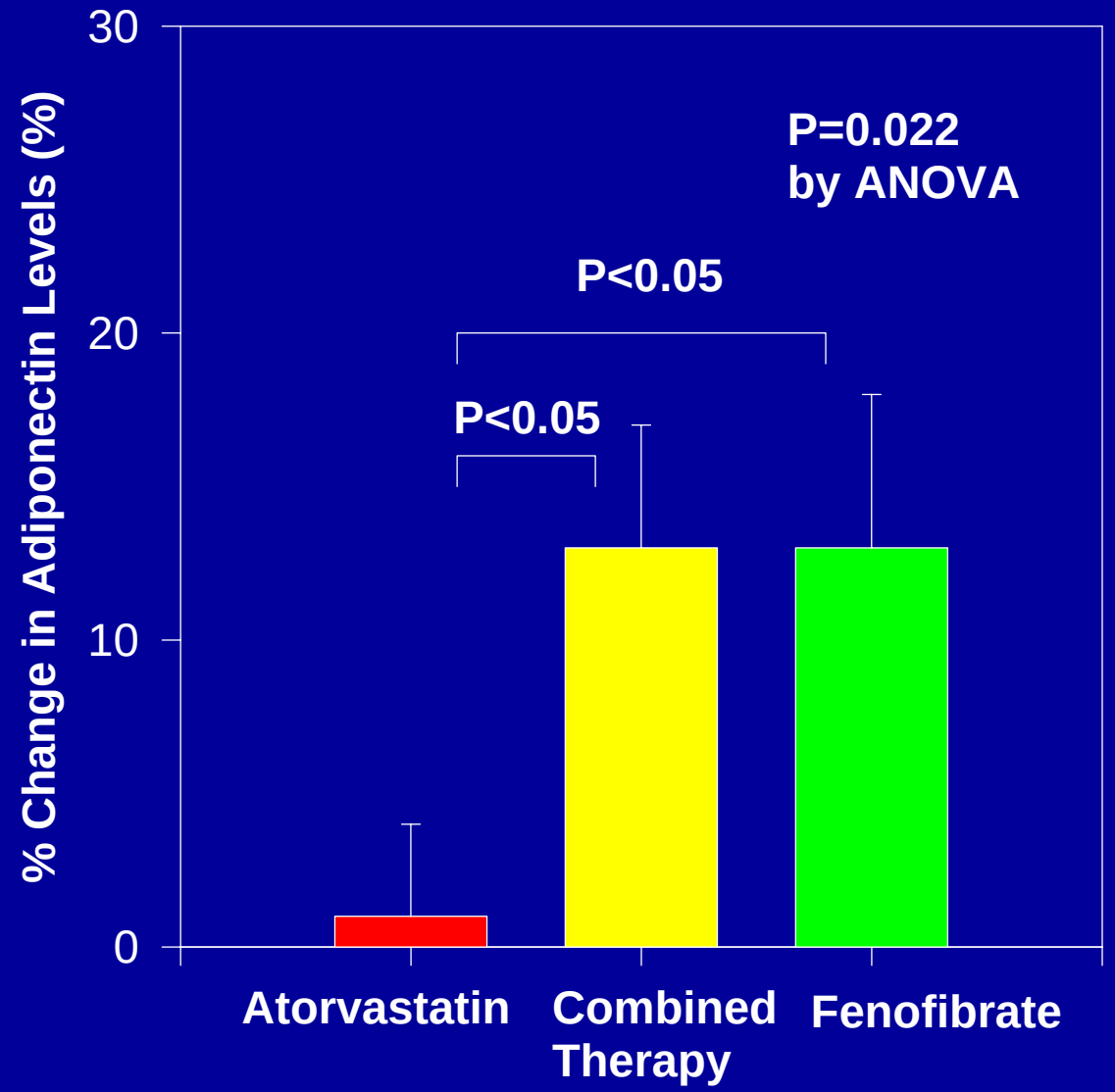
Additive Beneficial Effects of Fenofibrate Combined with Atorvastatin In Treatment of Combined Hyperlipidemia

Kwang Kon Koh, Seung Hwan Han
Eak Kyun Shin, ……. Michael J. Quon*

Diabetes Unit, NIH, USA*

ACC 2005, Orlando, USA
JACC 2005 (May)

Combined Therapy or Fenofibrate Alone Significantly Increases Adiponectin Levels



Conclusions (I)

- The endothelial dysfunction plays an important role in the pathogenesis of atherosclerosis.

- Endothelial function tests such as endothelial vasomotor function test, carotid artery IMT, biomarkers (hs-CRP, CD40L, adiponectin, etc..) are **useful predictors of CV events.**

Conclusions (II)

- The endothelial function tests are **useful research tools** to evaluate mechanisms of atherosclerosis and the effects of cardiovascular drugs.

- Further investigations for the development of **more simple, reliable, cost-effective endothelial function tests** are warranted.

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