



**ADVANCES IN CARDIAC
ARRHYTHMIAS**
and
**GREAT INNOVATIONS
IN CARDIOLOGY**

XXVI Giornate Cardiologiche Torinesi

Directors

Fiorenzo Gaita
Sebastiano Marra

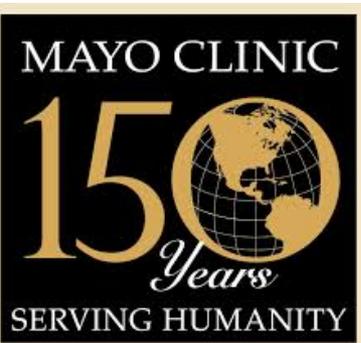
Turin

October 23-25, 2014

Galleria D'Arte Moderna
Centro Congressi Unione Industriale di Torino

Endothelial Function Assessment in Secondary Prevention

Amir Lerman, MD
Professor of Medicine
Chair for Research
Cardiovascular Division



Multiple Risk Factors

- 58-y.o. man with CV risk factors.
- History of HTN and hyperlipidemia
- Quit smoking 20 years ago
- Normal cardiac examination
- On Atrovostatin 80mg and baby ASA
- Mildly overweight BMI = 28.5 kg/m²

Laboratory

- TC = 127 mg/dL
- HDL-C = 39 mg/dL
- LDL-C = 62 mg/dL
- TG = 154 mg/dL
- eGFR= 45 ml/min/BSA
- CRP: Normal
- What is the risk of the patients for future CV events?
- How would you determine the risk

Multiple Novel Risk Factors

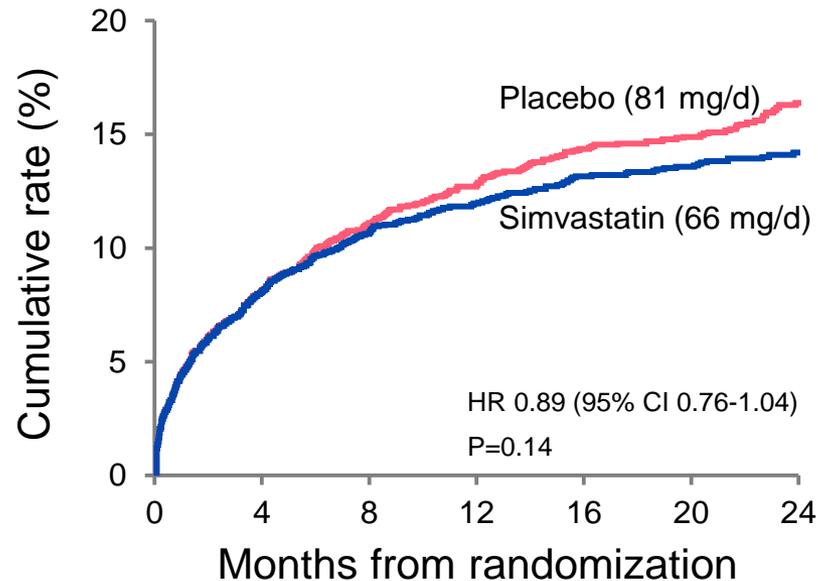
- 58-y.o. man with CV risk factors.
- History of HTN and hyperlipidemia
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- Mildly overweight BMI = 28.5 kg/m²
 - Recent NSTEMI with PCI with DES in the LAD

Early Intensive vs Delayed Conservative Simvastatin Strategy in Patients With Acute Coronary Syndromes

A to Z Trial

JAMA 292:1307, 2004

- Randomized double-blind trial of patients with ACS receiving 40 mg/d of simvastatin for 1 month followed by 80 mg/d thereafter compared with ACS patients receiving placebo for 4 months followed by 20 mg/d of simvastatin

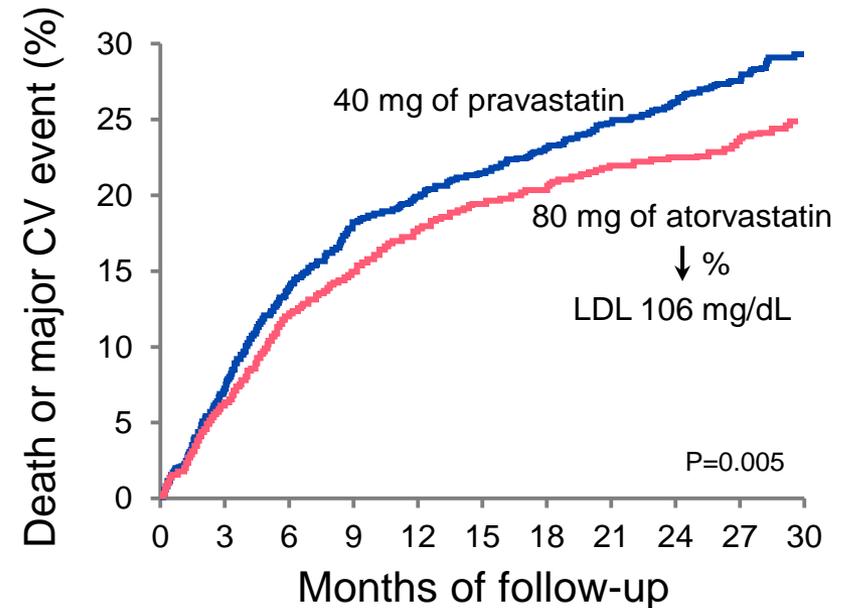


Intensive vs Moderate Lipid Lowering With Statins After Acute Coronary Syndromes

PROVE-IT

NEJM 350(15):1495, 2004

- 4,162 patients who had been hospitalized for an acute coronary syndrome within the preceding 10 days and compared 40 mg of pravastatin daily (standard therapy) with 80 mg of atorvastatin daily (intensive therapy)

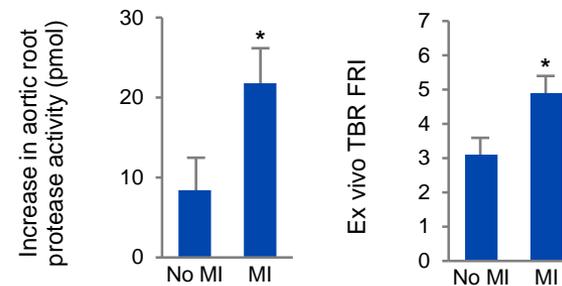
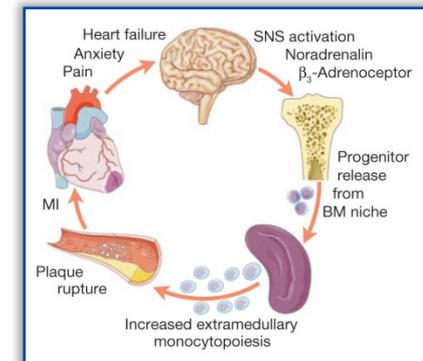
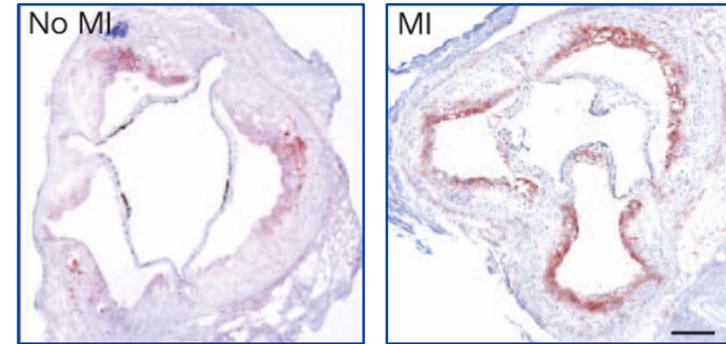


Myocardial infarction accelerates atherosclerosis

"New myocardial ischaemia occurred in 54% of patients within the first year after MI. The largest population study so far showed a 17.4% 1-year risk of re-infarction."

"To test the hypothesis that MI changes the course of atherosclerotic disease, imaged plaque activity in aortic plaques of Apoe ^{-/-} mice, before and 3 weeks after coronary ligation."

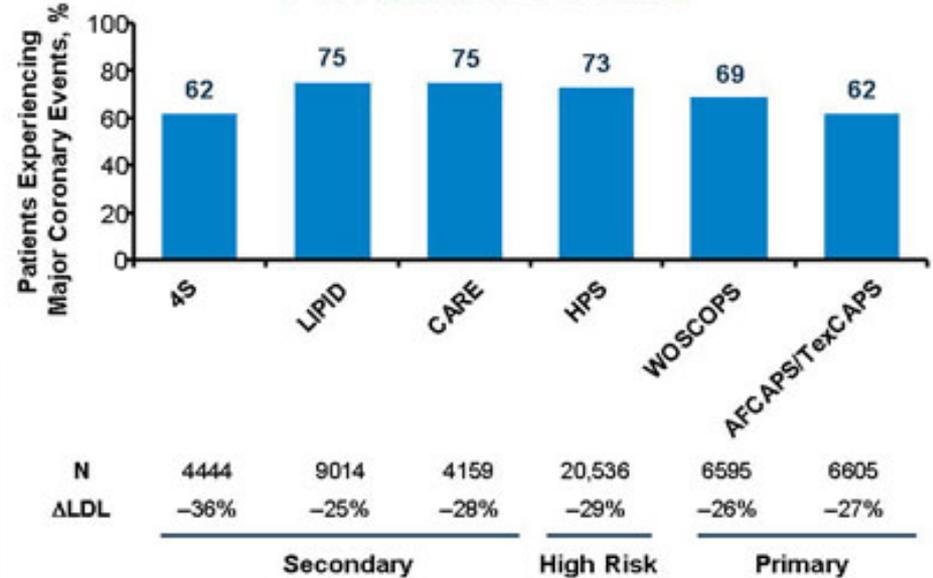
CD11b Staining and Lesion size



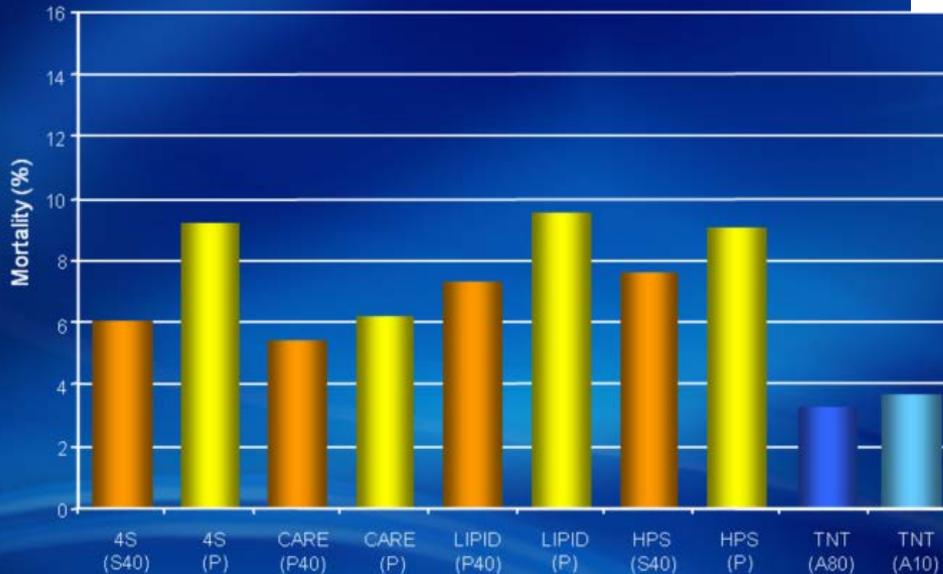
Dutta et al: Nature, 2012

Aggressive Treatment of Conventional risk factors and CV Events

Residual Cardiovascular Risk Despite Intervention in Primary and Secondary Prevention Trials



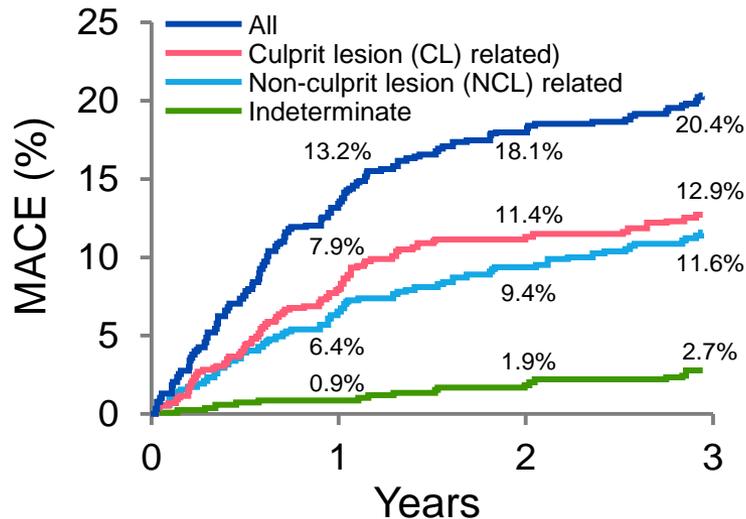
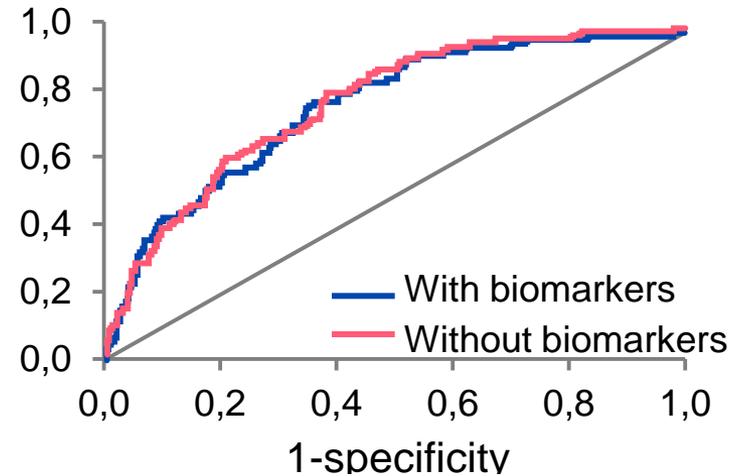
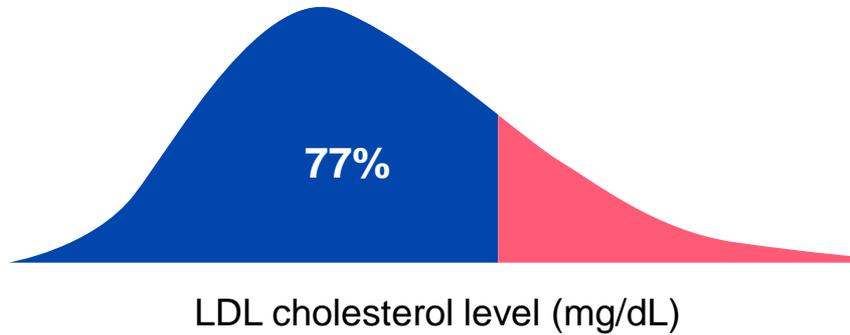
Cardiovascular Mortality in Secondary Prevention Studies



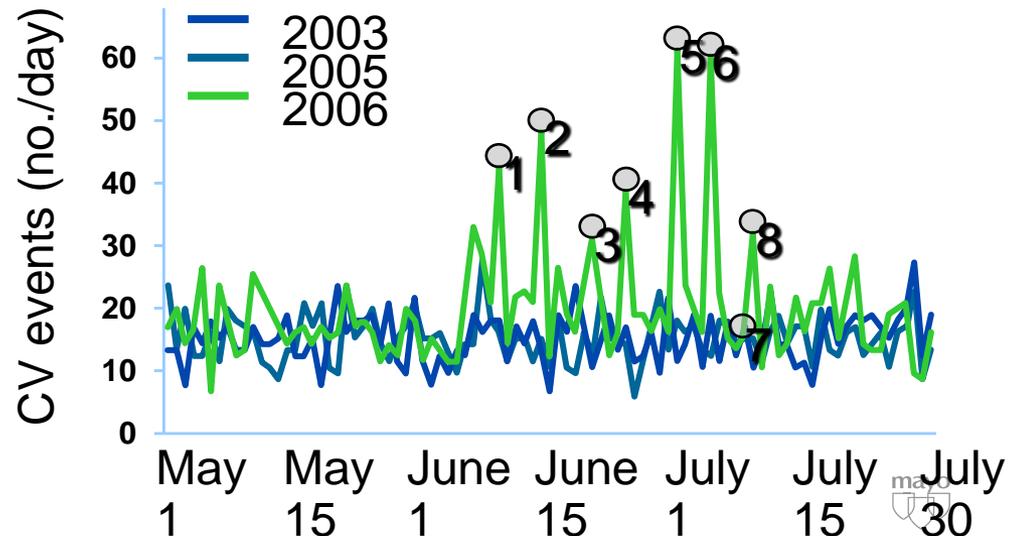
Traditional Risk Factors

Markers and Imaging Fail in Identifying Vulnerable Patient

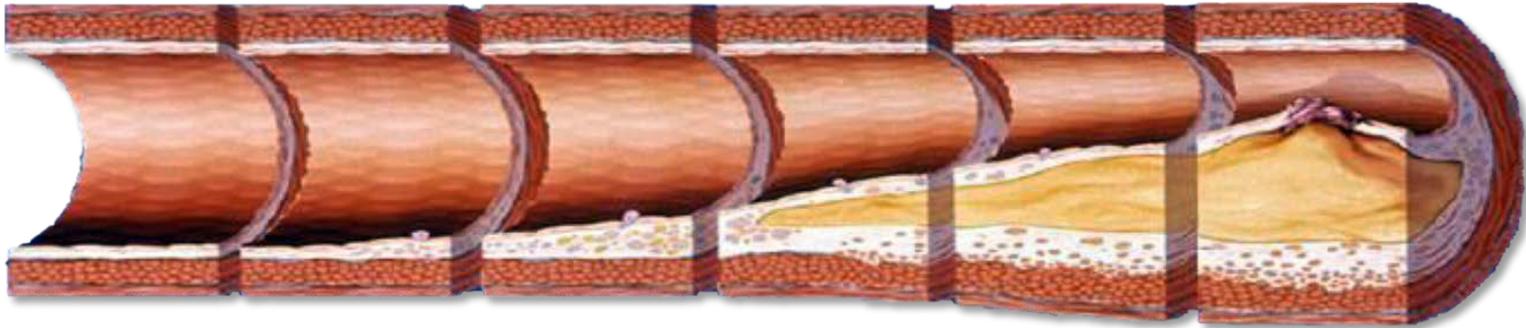
Of 136,905 patients hospitalized with CAD, 77% had normal LDL levels below 130 mg/dL



Cardiovascular Events during World Cup Soccer



How to Assess the Risk of the Patient



Surrogate risk markers

Hypercholesterolemia
Hypertension
Smoking
Diabetes
biomarkers

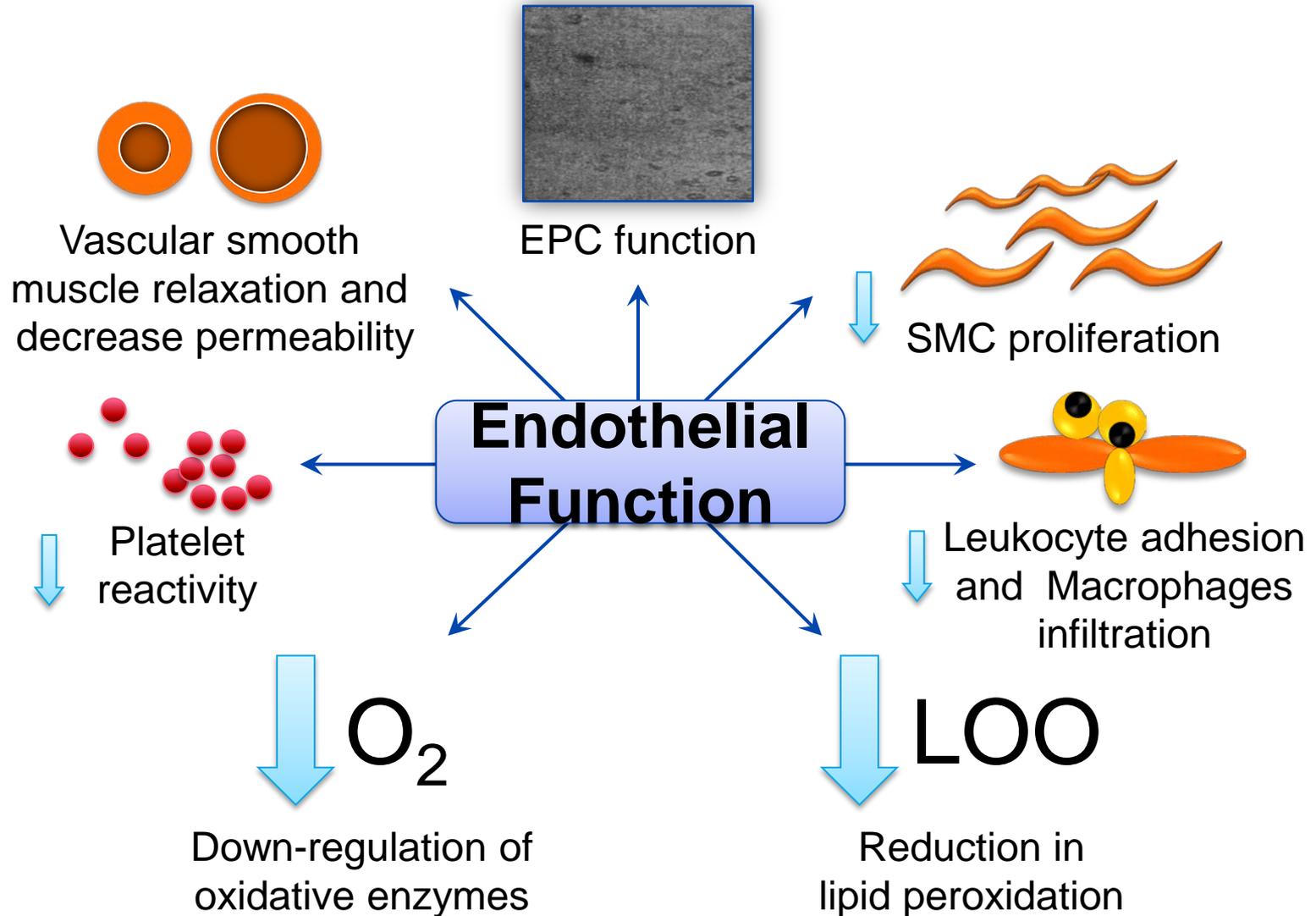


Direct Imaging of the disease

Carotid US
Coronary Calcium
Endothelial function

- The test should make a scientific sense
- Participate in the disease process
- A marker at different disease stages
- Reflects Reversibility
- Serves as a risk factor not only as a risk marker

Multifunctional Nitric Oxide

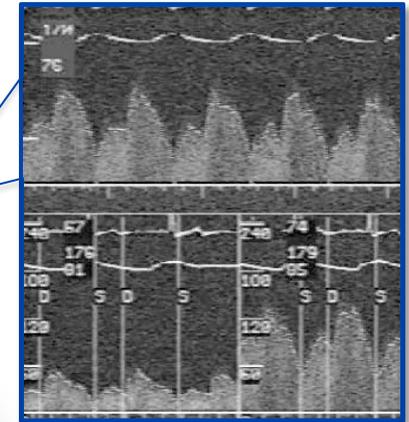


Functional Angiogram Protocol

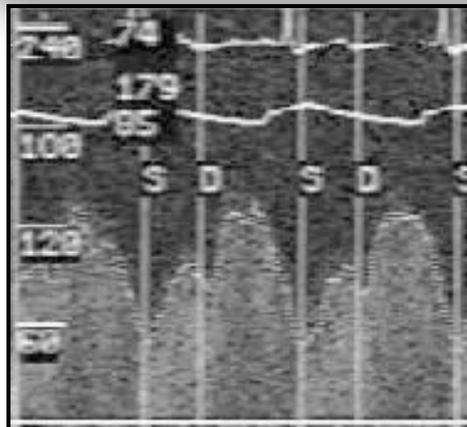
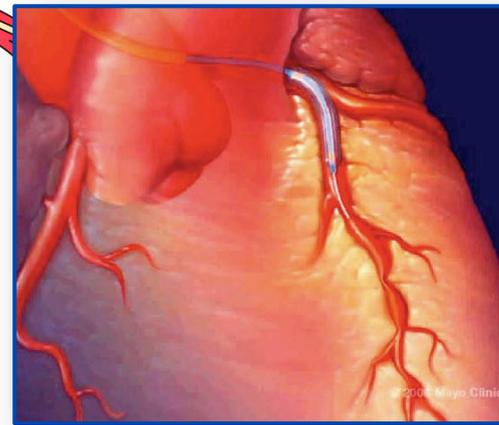
Diagnostic angiography

Adenosine IC
24-72 μg

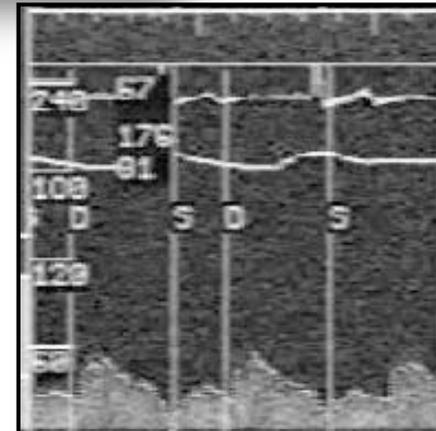
CFR: Non endothelium microcirculation



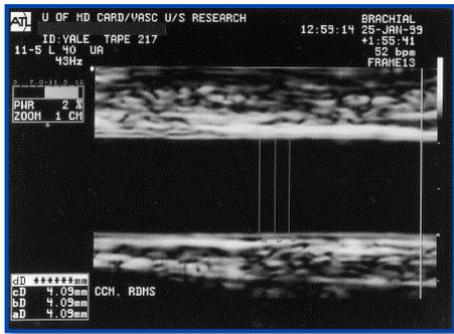
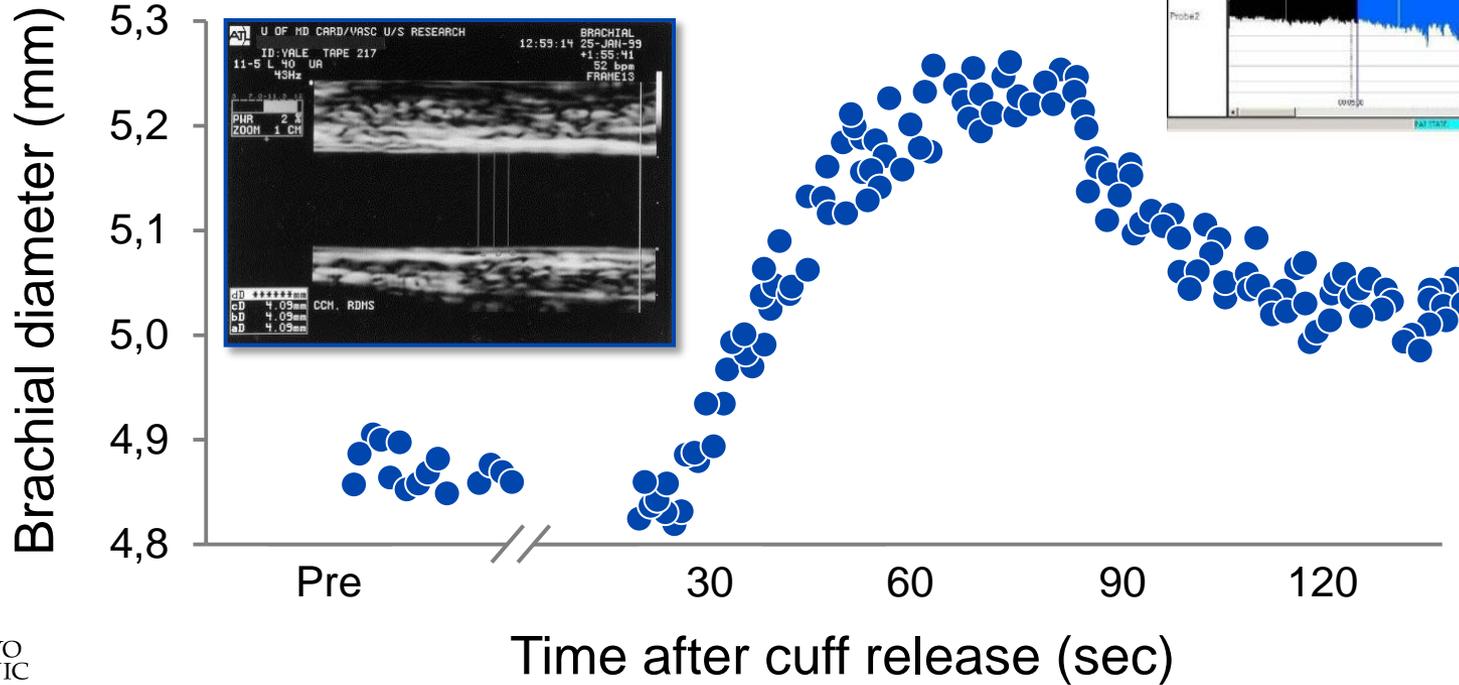
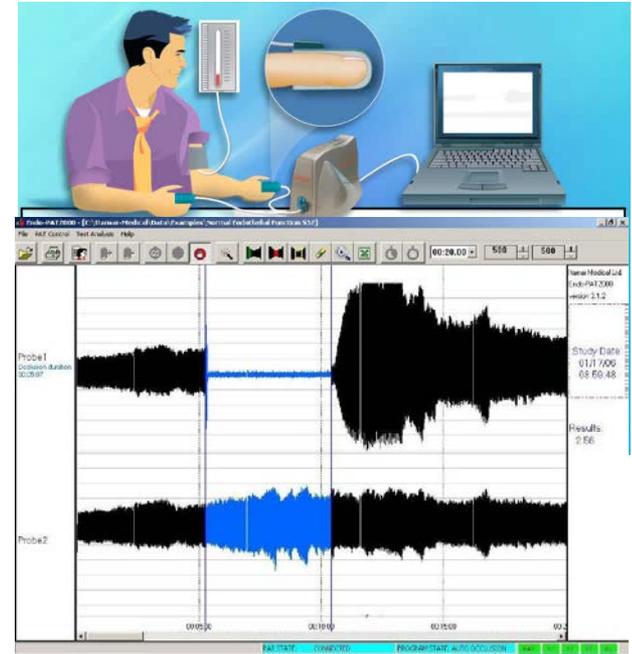
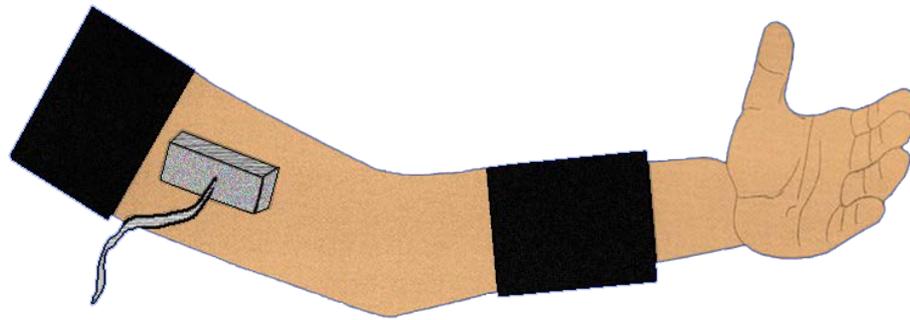
Acetylcholine
(endothelium dependent vasodilator)
Epicardial



Microcirculation



Reactive Hyperemia: Endothelium Dependent



How to Assess the Risk of the Patient

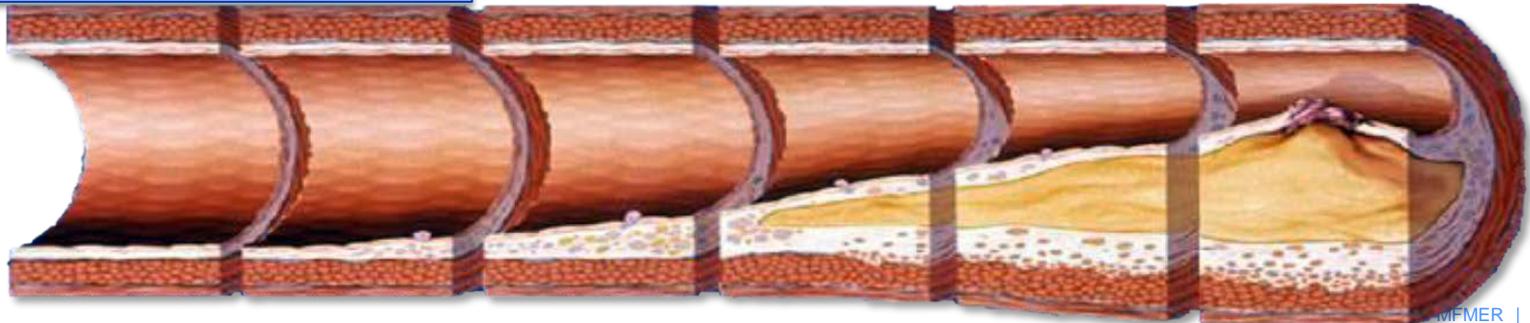


Endothelial dysfunction represent ingoing risk

Inadequate therapy



**On going CV risk
Unrecognized CV risk**



58-yo. man with CAD Recent NSTEMI with PCI with DES in the LAD

What is the residual risk of this patient?

- Stent thrombosis and restenosis
- CV events.
- Unrecognized risk factors
- Optimal medical therapy

What evidence do we have to support it?

Effects of Endothelial Dysfunction on Residual Platelet Aggregability After Dual Antiplatelet Therapy With Aspirin and Clopidogrel in Patients With Stable Coronary Artery Disease

Pharmacology

Effects of Endothelial Dysfunction on Residual Platelet Aggregability After Dual Antiplatelet Therapy With Aspirin and Clopidogrel in Patients With Stable Coronary Artery Disease

Koichiro Fujisue, MD; Seigo Sugiyama, MD, PhD; Takamichi Ono, MD, PhD; Yasushi Matsuzawa, MD, PhD; Eiichi Akiyama, MD; Koichi Sugamura, MD, PhD; Junichi Matsubara, MD, PhD; Hirofumi Kurokawa, MD; Koichi Kaikita, MD, PhD; Satomi Iwashita, MT; Hitoshi Sumida, MD, PhD; Seiji Hokimoto, MD, PhD; Kentaro Oniki, MS; Kazuko Nakagawa, MD, PhD; Kunihiko Matsui, MD, MPH;

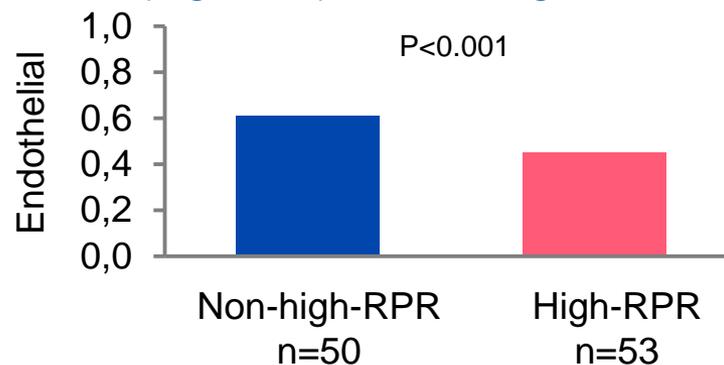
High residual platelet reactivity (high RPR) after dual antiplatelet therapy is associated with increased cardiovascular events

103 patients who lacked CYP2C19*2 or *3 loss-of-function allele to minimize the effect of this gene on high RPR were studied

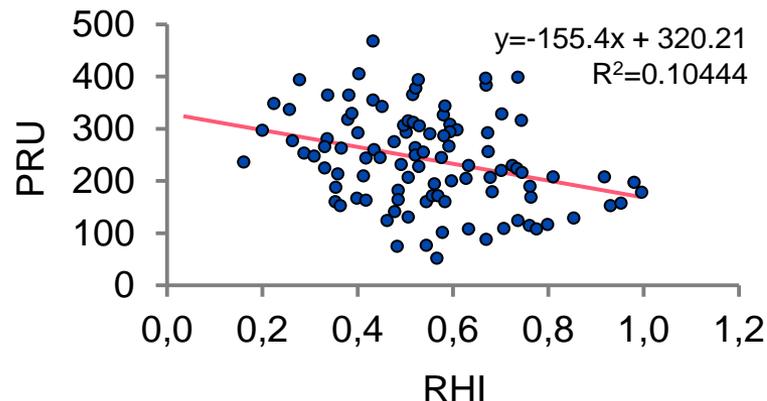
Reactive hyperemia index was significantly lower in high RPR patients compared with non-high RPR

In patients with stable coronary artery disease, endothelial function was significantly impaired in high RPR patients. Endothelial dysfunction is independently correlated with high RPR after dual antiplatelet therapy

Endothelial Function Index in Patients With High Residual Platelet Reactivity (High RPR) and Non-High RPR



Relationship Between Reactive Hyperemia Index and P2Y12 reaction unit



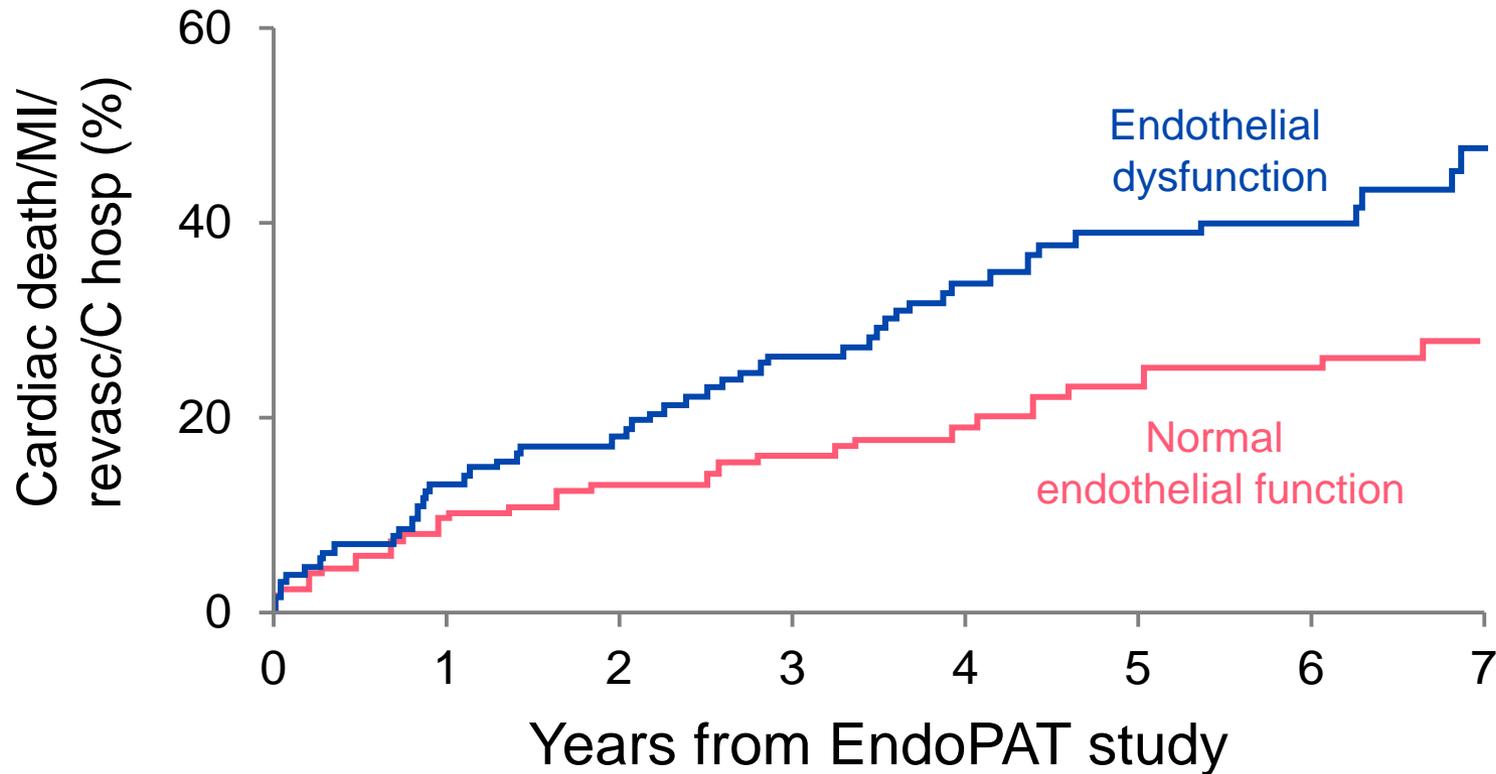
58-yo. man with CAD Recent NSTEMI with PCI with DES in the LAD

What is the residual risk of this patient?

- Stent thrombosis and restenosis
- CV events.
- Unrecognized risk factors
- Optimal medical therapy

What evidence do we have to support it?

Cardiac Events in Patients with Abnormal Endothelial Function with EndoPAT and Low FRS

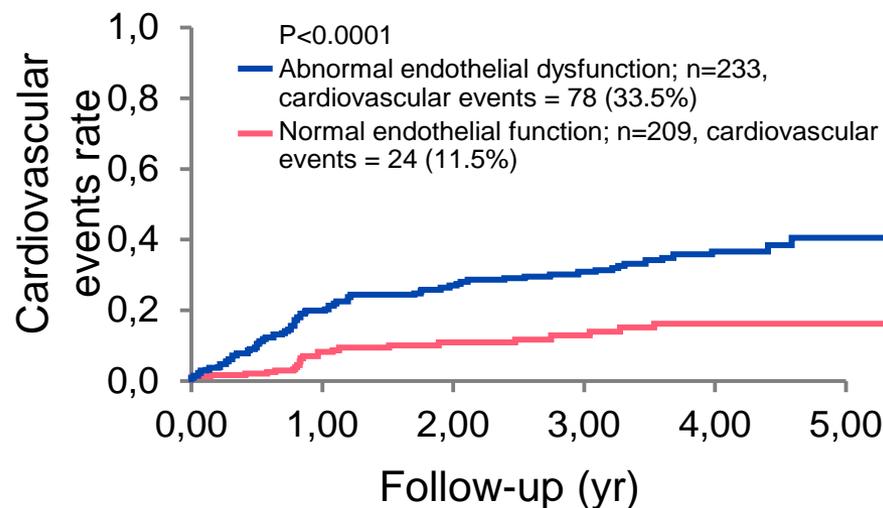
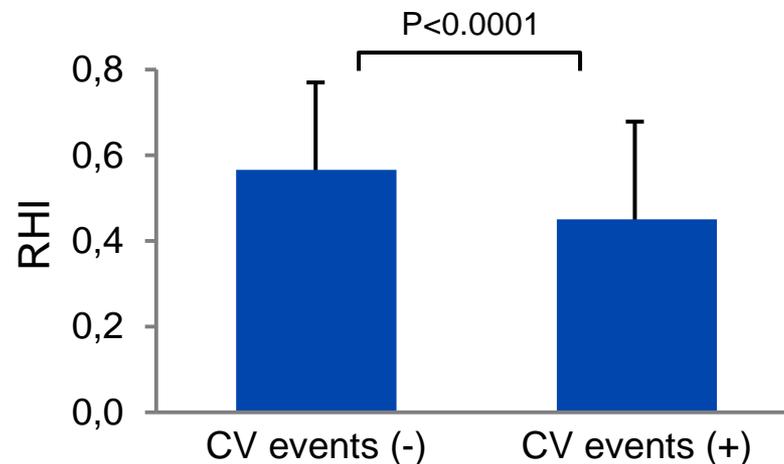
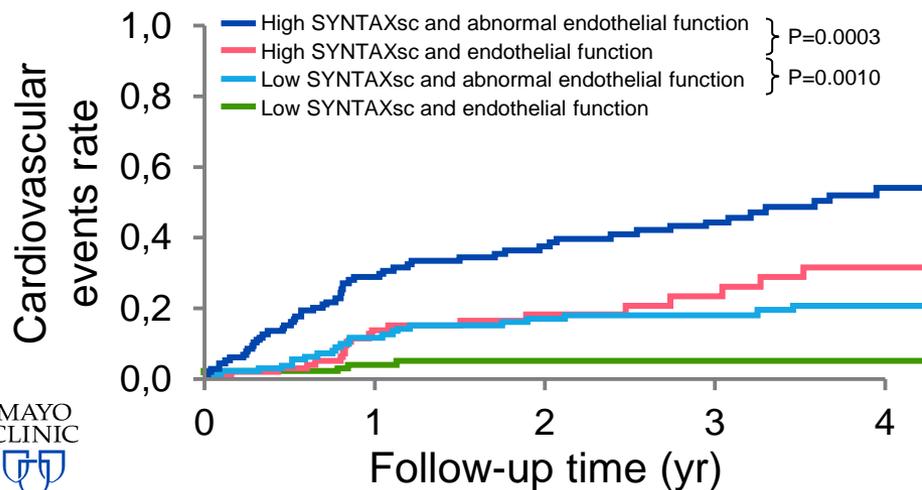


Rubinshtein and Lerman: Euro Heart J, 2010

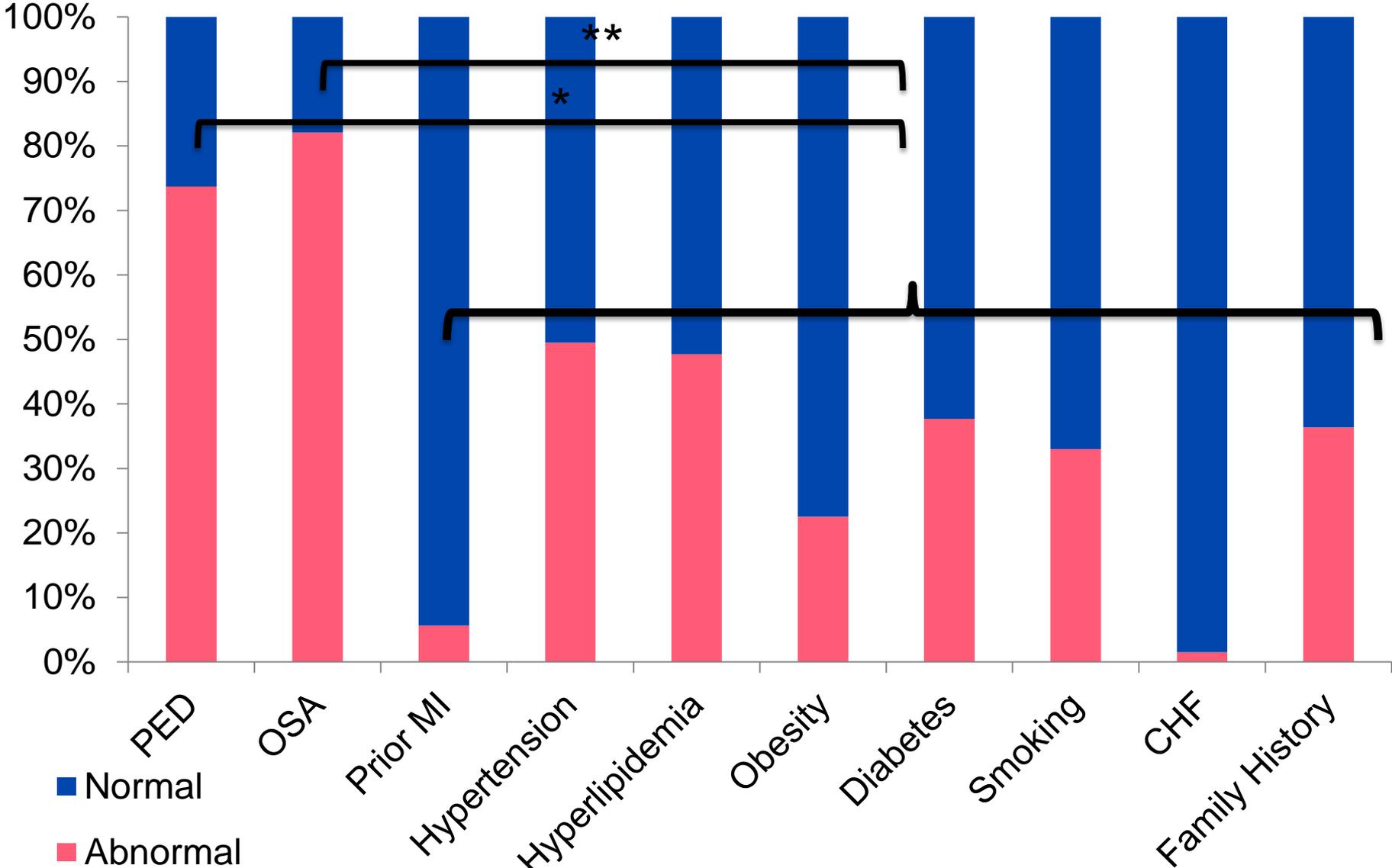
Peripheral Endothelial Function and Cardiovascular Events in High-Risk Patients

- a) Prospective study in 528 stable patients at high risk for cardiovascular events. Endothelial function (RHI) was measured before coronary angiography, and coronary complexity was assessed by SYNTAXsc. After optimal therapies including coronary revascularization, there was follow-up with patients
- b) Advanced endothelial dysfunction significantly correlated with near-future cardiovascular events in high-risk patients. This physiological vascular measurement improved risk determination when added to the FRS, BNP, and SYNTAXsc

RHI and Cardiovascular Events in 442 CAD Patients



Risk Factors in Patients Post PCI for ACS



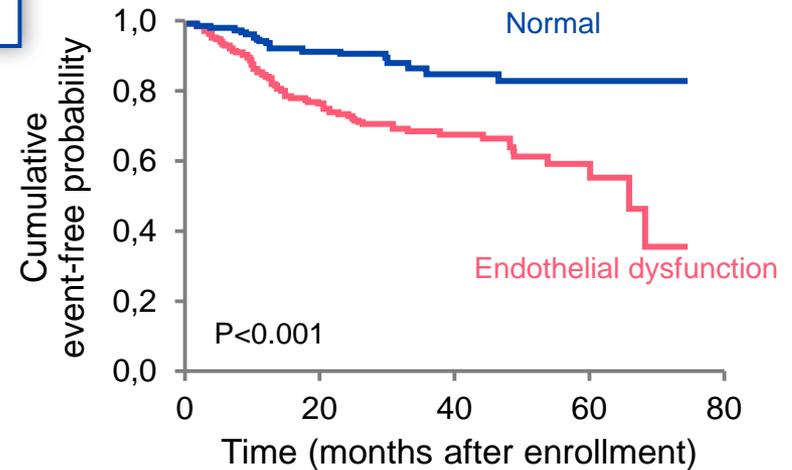
Endothelial function and Cardiovascular Events in Chronic Kidney Disease

Yoshihiro Hirata, MD^a, Seigo Sugiyama, MD, PhD^{a,b,*}, Eiichiro Yamamoto, MD, PhD^a,

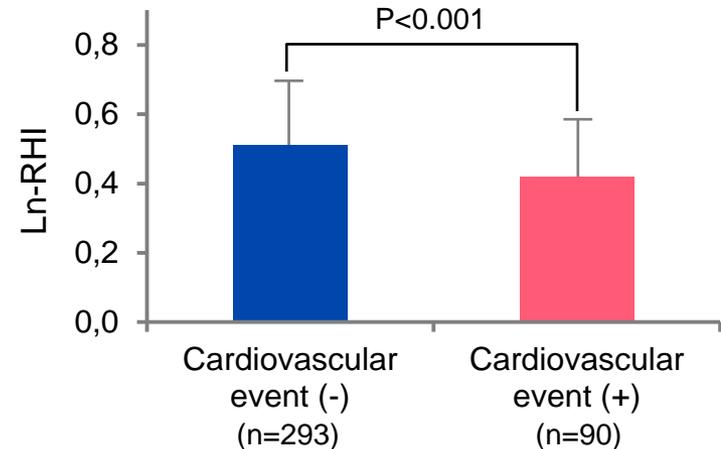
- 383 CKD patients with at least one coronary risk factor. Peripheral endothelial function was assessed by reactive hyperemia peripheral arterial tonometry index (RHI).
- Endothelial function was significantly impaired in CKD patients and correlated with the presence of CAD.
- Severe endothelial dysfunction was an independent and incremental predictor of cardiovascular events in CKD

	All CKD patients (n=383)	High-Ln-RHI patients (n=167)	Low-Ln-RHI patients (n=216)
Age (years)	72.0	72.2	71.8
Sex (male, %)	64.2	62.3	65.7
BMI (kg/m ²)	24.3	24.3	24.2
Hypertension (yes, %)	90.6	93.4	88.4
DM (yes, %)	44.9	44.3	45.4
Dyslipidemia (yes, %)	83.0	82.6	83.3
LVEF (%)	62.1 (7.4)	62.2 (7.1)	61.9 (7.6)
Hs-CRP (mg/dL)	0.08	0.07	0.08
eGFR (mL/min/1.73 m ²)	49.4 (12.9)	50.1 (12.1)	48.9 (13.5)

Kaplan-Meier Analysis Demonstrated a Significantly Higher Probability of Cardiovascular Events in patients with endothelial dysfunction



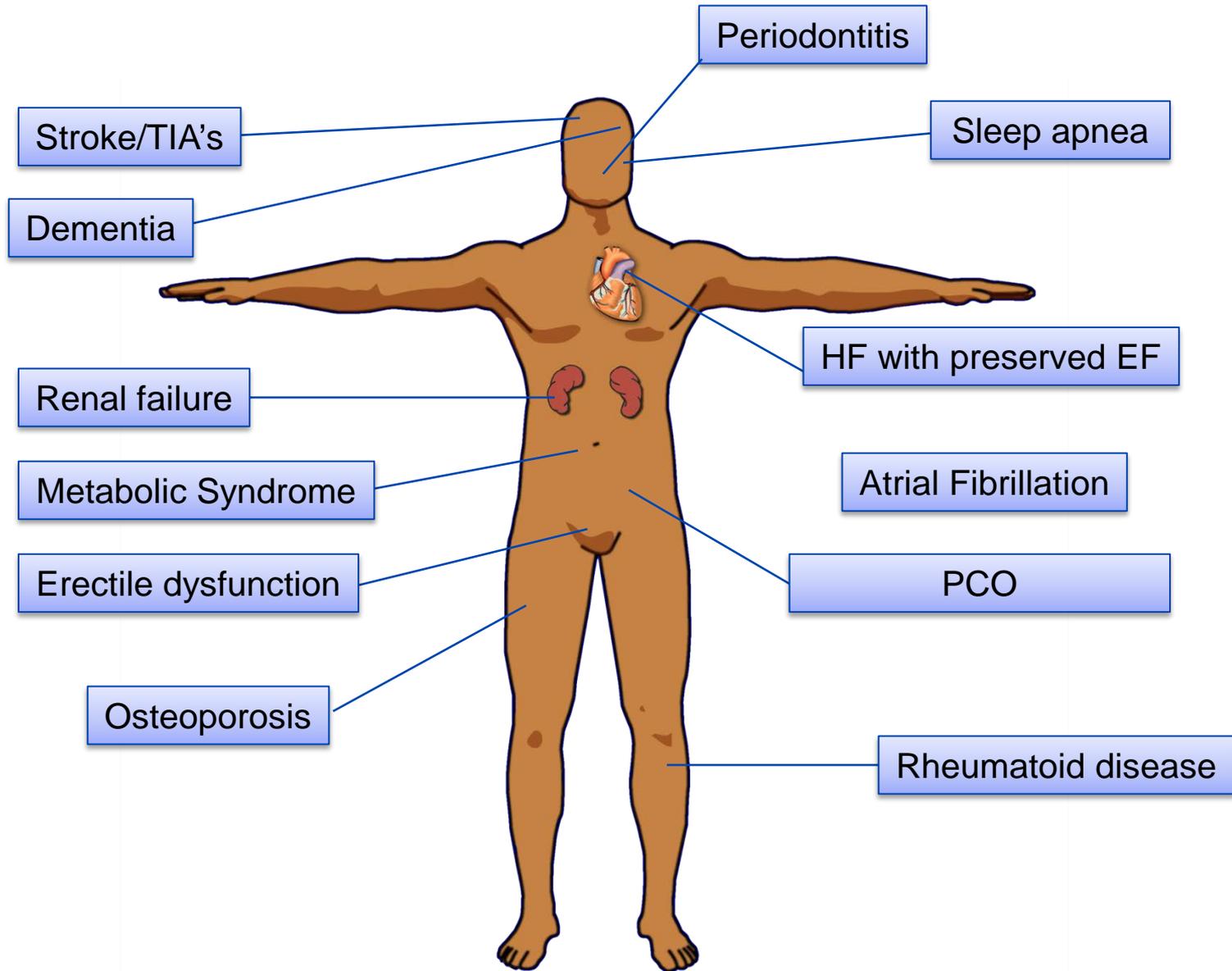
Endothelial function was Significantly Lower in Patients With Cardiovascular Events Than Without Cardiovascular Events



Hirata et al: Int J of Card, 2014

Systemic Manifestation of Endothelial Dysfunction

The Vulnerable Patient

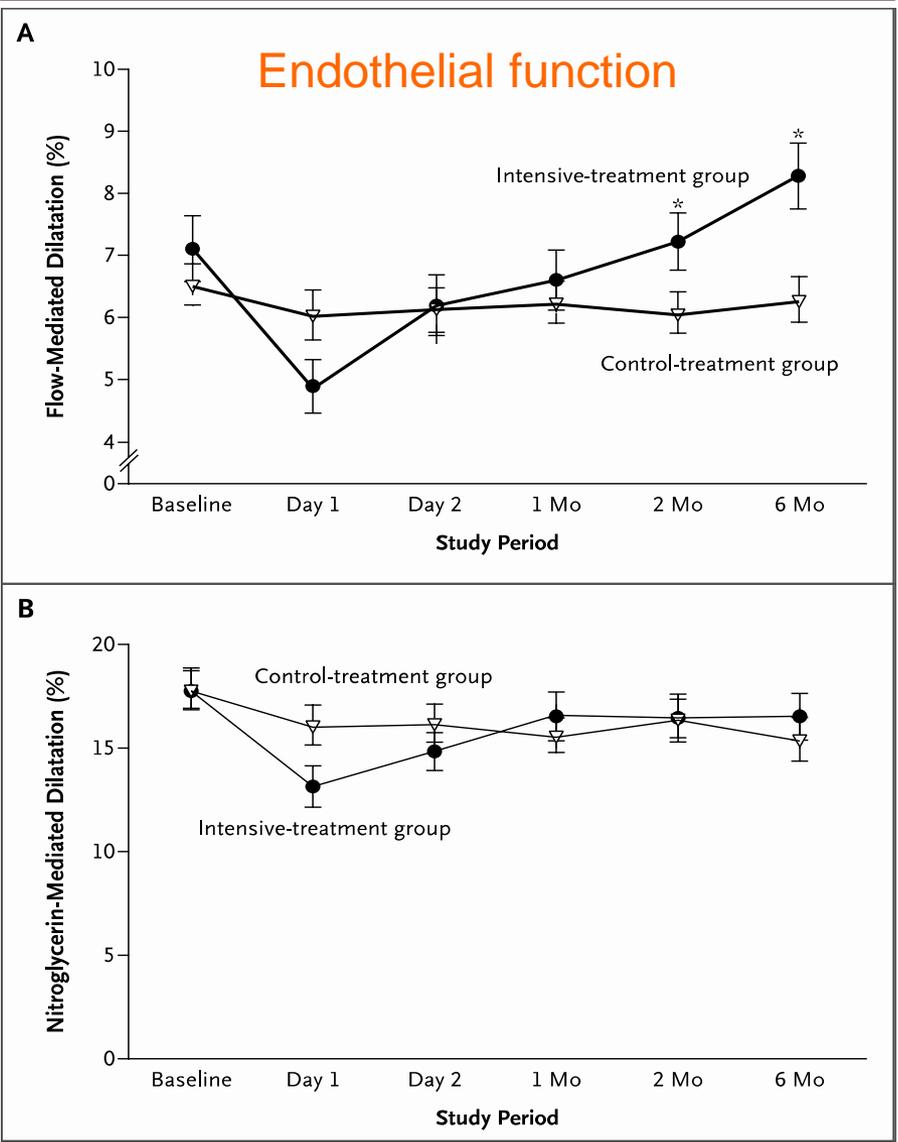


Treatment of Periodontitis and Endothelial Function

Maurizio S. Tonetti, D.M.D., Ph.D., Francesco D'Aiuto, D.M.D., Ph.D., Luigi Nibali, D.M.D., Ph.D., Ann Donald, Clare Storry, B.Sc., Mohamed Parkar, M.Phil., Jean Suvan, M.Sc., Aroon D. Hingorani, Ph.D., Patrick Vallance, M.D., and John Deanfield, M.B., B.Chir.

120 patients randomly assigned with severe periodontitis to community-based periodontal care or intensive periodontal treatment.

Endothelial function, as assessed by measurement of the diameter of the brachial artery during flow (flow-mediated dilatation), and inflammatory biomarkers and markers of coagulation and endothelial activation were evaluated before treatment and follow up.



58-yo. man with CAD Recent NSTEMI with PCI with DES in the LAD

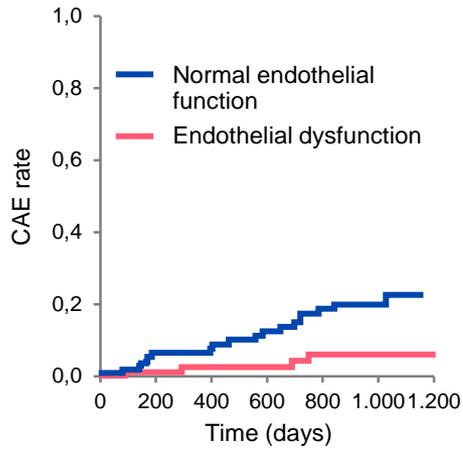
What is the residual risk of this patient?

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- CV events.
- Unrecognized risk factors
- Optimal medical therapy

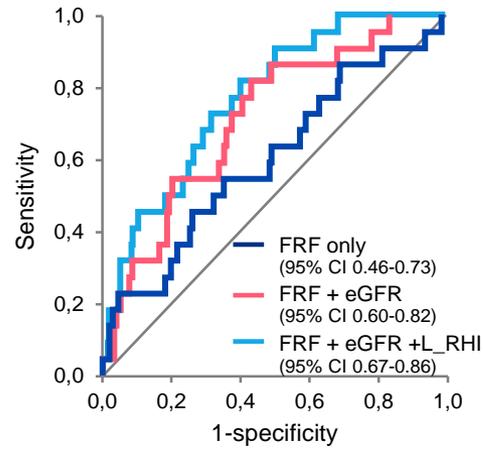
What evidence do we have to support it?

a) Endothelial function was assessed in 213 CAD patients who had already achieved LDL-C <100 by statin therapy. Patients were followed for secondary CAE for a median of 2.7 years

Kaplan-Meier Survival Curves of CAD Patients with endothelial dysfunction



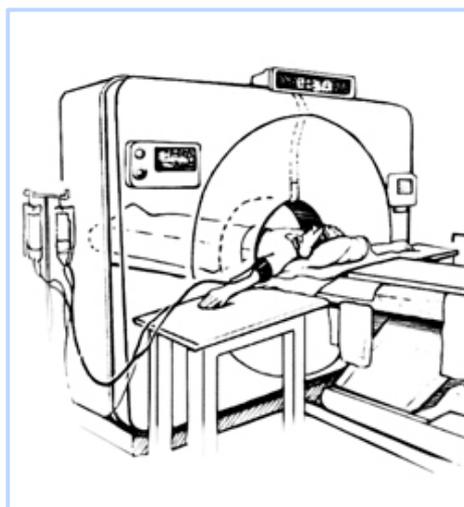
Receiver-Operating Characteristic Curves of Framingham Traditional Risk Factors Only



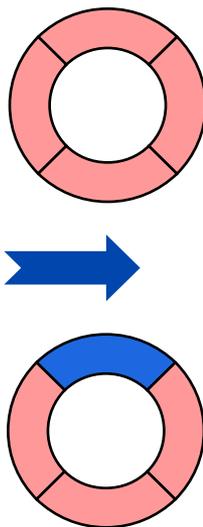
b) FRF alone failed to predict future secondary CAE in patients with CAD treated with statin. However, adding endothelial function measurement to FRF in the logistic regression model significantly improved the predictive ability for future CAE

Variables	Normal Endothelial Function	Endothelial Dysfunction
Blood pressure (mm Hg)		
Systolic	134.0±19.5	130.5±16.2
Diastolic	75.1±10.3	74.6±10.3
Risk factors (%)		
Medications (%)		
ACE-I/ARB	73 (73.7)	80 (70.2)
Beta blocker	65 (65.7)	67 (59.8)
Calcium channel blocker	42 (42.4)	46 (40.4)
Aspirin	99 (100)	114 (100)
Thienopyridine	22 (22.2)	34 (29.8)
High-sensitive CRP (ng/mL)	381 (221.0-621.5)	376 (245.5-708.0)
T-C (mg/dL)	145.1±17.7	144.7±18.8
TG (mg/dL)	119.0±45.6	118.9±39.9
HDL-C (mg/dL)	50.3±11.4	52.0±11.7
LDL-C (mg/dL)	70.9±13.8	69.0±12.9
LDL-C <70 mg/dL (%)	44 (44.4)	60 (52.6)

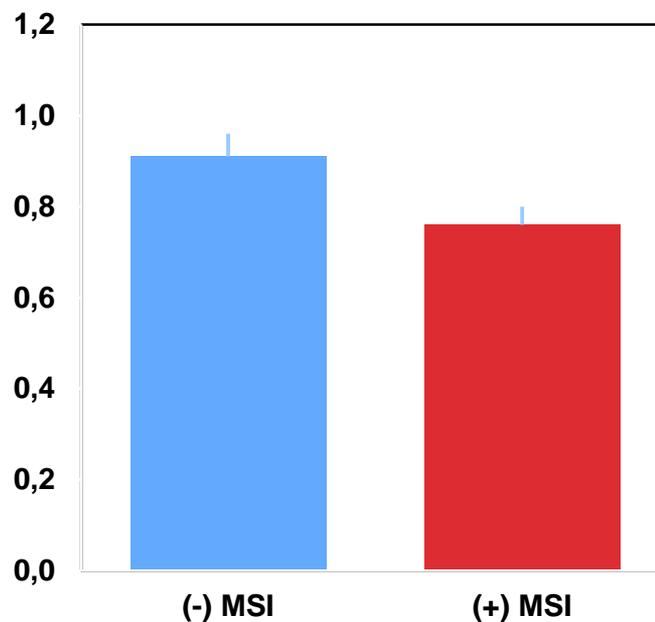
Non-Invasive Detection of Risk for Emotion Provoked Myocardial Ischemia



↓
Mental stress



Endothelial Function: EndoPAT



Can We use Endothelial Function to Individualize Therapy?

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Women and Cardiovascular Disease

Prognostic Role of Reversible Endothelial Dysfunction in Hypertensive Postmenopausal Women

Maria G. Modena, MD, FESC, FACC, Lorenzo Bonetti, MD, Francesca Coppi, MD, Francesca Bursi, MD, Rosario Rossi, MD

Modena, Italy

Journal of the American College of Cardiology
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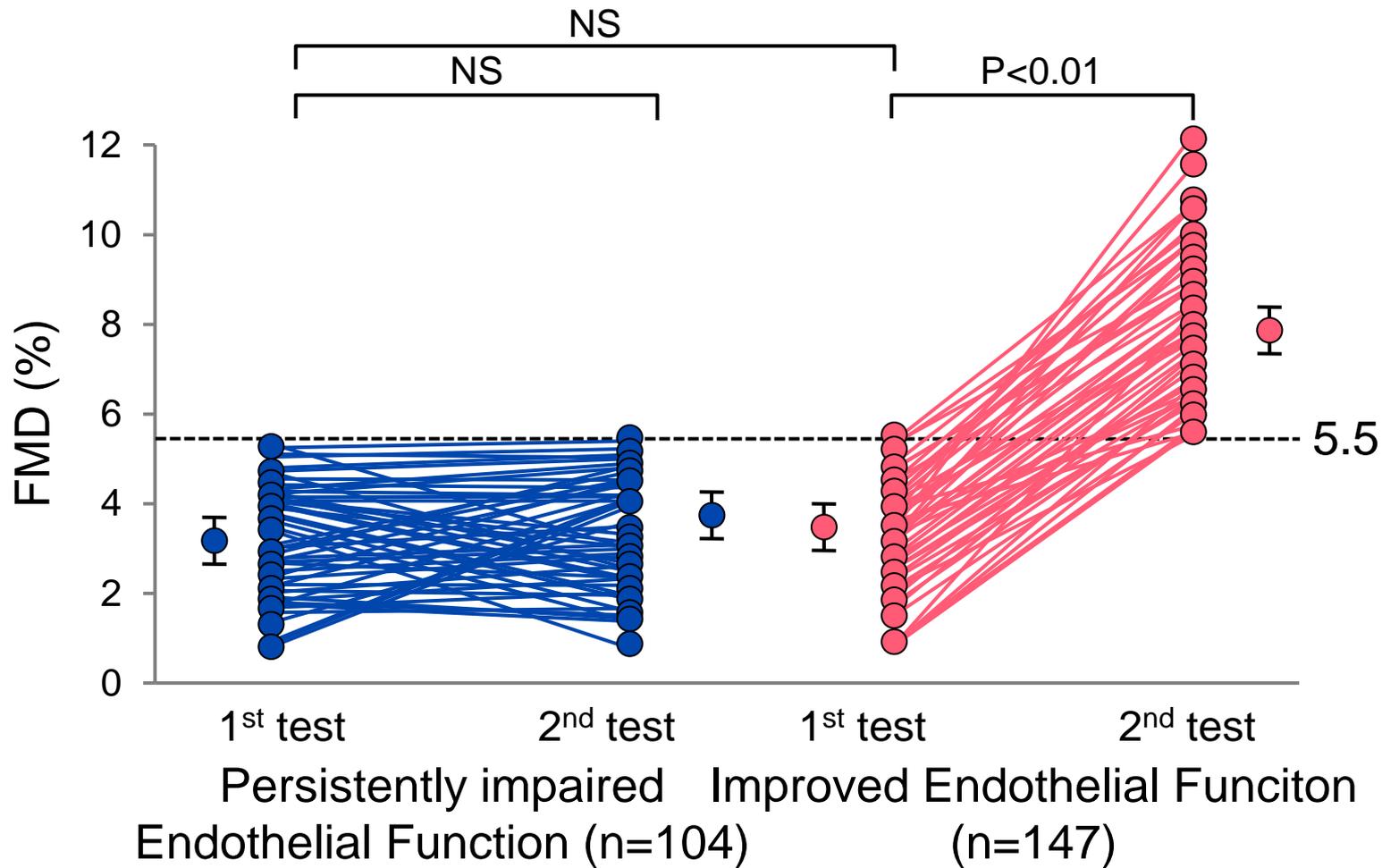
Vol. 53, No. 4, 2009
ISSN 0735-1097/09/\$36.00
doi:10.1016/j.jacc.2008.08.074

Persistent Impairment of Endothelial Vasomotor Function Has a Negative Impact on Outcome in Patients With Coronary Artery Disease

Yoshinobu Kitta, MD, PHD, Jyun-ei Obata, MD, PHD, Takamitsu Nakamura, MD, Mitsumasa Hirano, MD, Yasushi Kodama, MD, Daisuke Fujioka, MD, PHD, Yukio Saito, MD, Ken-ichi Kawabata, MD, PHD, Keita Sano, MD, Tsuyoshi Kobayashi, MD, Toshiaki Yano, MD, Kazuto Nakamura, MD, PHD, Kiyotaka Kugiyama, MD, PHD

Yamanashi, Japan

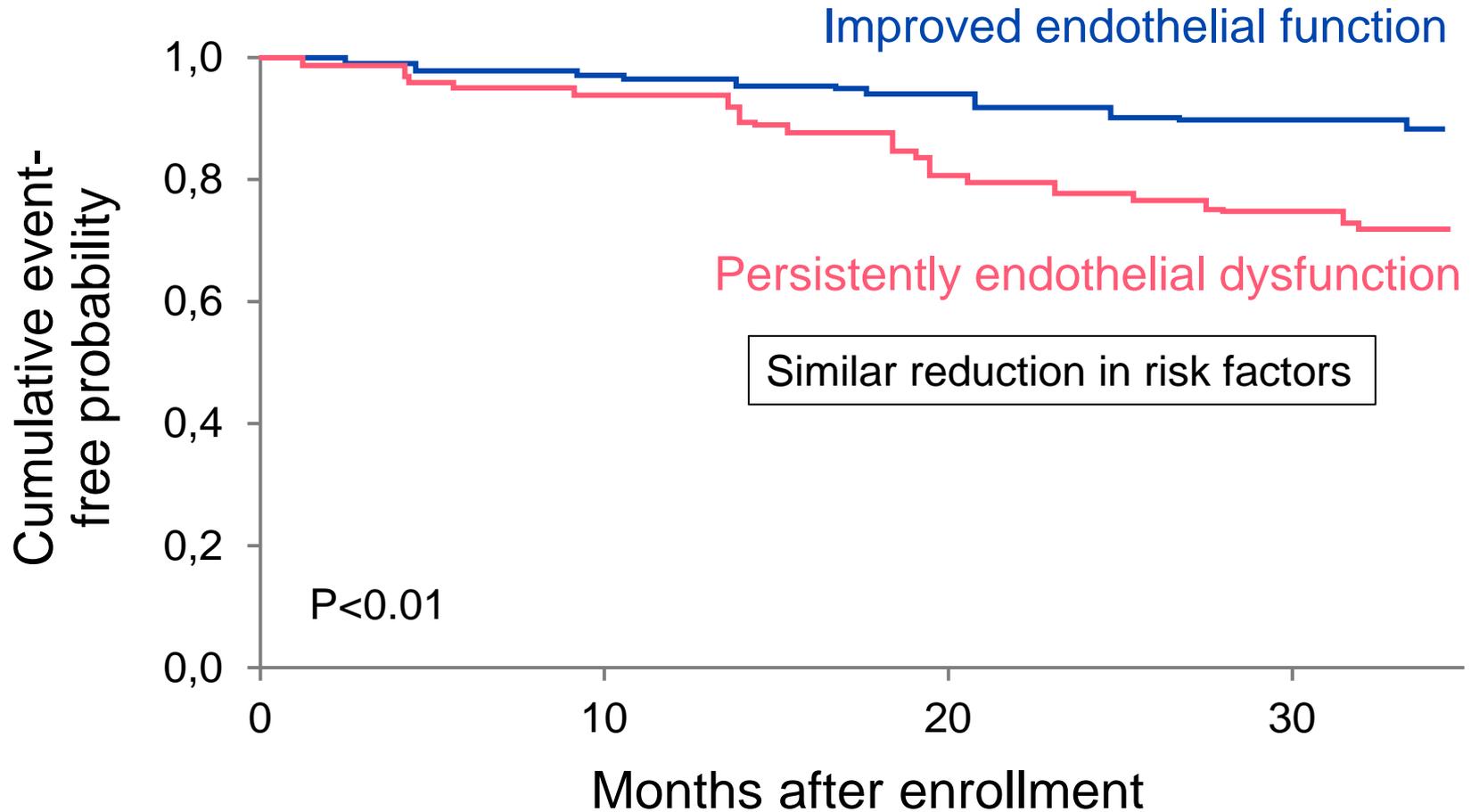
Endothelial Function Comparison Between First and Second Test in CAD Patients on OMT



Kitta Y et al: J Am Coll Cardiol 53:323, 2009



Event-Free Survival and Endothelial Function



Kitta Y et al: J Am Coll Cardiol 53:323, 2009

Endothelial Function can Reclassify Risk of Patients

Endothelial Function in Resistance and Conduit Arteries and 5-Year Risk of Cardiovascular Disease

Lars Lind, MD, PhD; Lars Berglund, PhD; Anders Larsson, MD, PhD; Johan Sundström, MD, PhD

Background—Impaired endothelial function has been implicated as a cause of cardiovascular disease. Little is known of the relations of measures of endothelial function in resistance and conduit arteries to incident cardiovascular disease in the general population, and available techniques have not been compared.

Methods and Results—In 1016 participants (70 years of age) of the population-based Prospective Study of the Vasculature in Uppsala Seniors (PIVUS) study (52% women), we measured endothelium-dependent vasodilation using the invasive forearm technique with acetylcholine given in the brachial artery, the brachial artery ultrasound technique with measurement of flow-mediated dilatation, and the pulse-wave analysis–based method with β -2-agonist terbutaline provocation. During 5 years of follow-up, 101 participants experienced a composite end point of myocardial infarction, stroke, or death, excluding the 85 persons with a history of myocardial infarction or stroke at baseline. In logistic regression models adjusted for several established and novel cardiovascular disease risk factors and medications, endothelium-dependent vasodilation by the invasive forearm technique with acetylcholine was associated with risk of the end point (odds ratio, 0.72 per SD; 95% confidence interval, 0.56 to 0.93; $P=0.01$). Endothelial function by the other 2 methods was not related to risk of the end point. Addition of endothelium-dependent vasodilation to the Framingham risk score improved discrimination of risk of the end point.

1,016 subjects, the overall net correct reclassification 31%

Epidemiology and Prevention

Predictive Value of Brachial Flow-Mediated Dilation for Incident Cardiovascular Events in a Population-Based Study

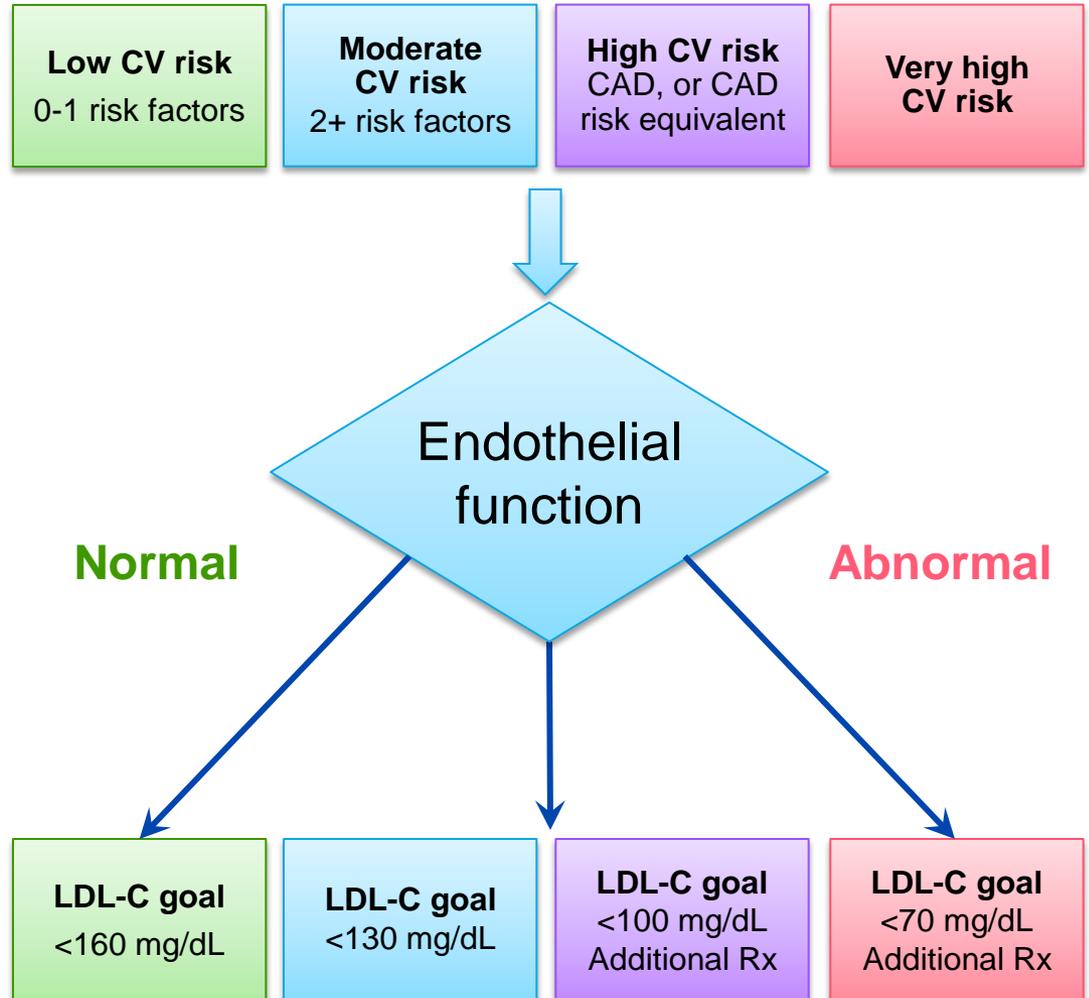
The Multi-Ethnic Study of Atherosclerosis

Joseph Yeboah, MD, MS; Aaron R. Folsom, MD; Gregory L. Burke, MD, MS; Craig Johnson, MS; Joseph F. Polak, MD, MPH; Wendy Post, MD, MS; Joao A. Lima, MD; John R. Crouse, MD; David M. Herrington, MD, MHS

Background—Although brachial artery flow-mediated dilation (FMD) predicts recurrent cardiovascular events, its predictive value for incident cardiovascular disease (CVD) events in adults free of CVD is not well established. We assessed the predictive value of FMD for incident CVD events in the Multi-Ethnic Study of Atherosclerosis (MESA).

Methods and Results—Brachial artery FMD was measured in a nested case-cohort sample of 3026 of 6814 subjects (mean \pm SD age, 61.2 \pm 9.9 years) in MESA, a population-based cohort study of adults free of clinical CVD at baseline recruited at 6 clinic sites in the United States. The sample included 50.2% female, 34.3% white, 19.7% Chinese, 20.8% black, and 25.1% Hispanic subjects. Probability-weighted Cox proportional hazards analysis was used to examine the association between FMD and 5 years of adjudicated incident CVD events, including incident myocardial infarction, definite angina, coronary revascularization (coronary artery bypass grafting, percutaneous transluminal coronary

3,026 of 6,814 subjects in MESA, The overall net correct reclassification 29%



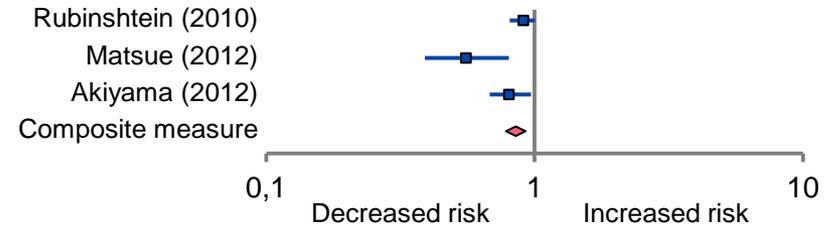


Non-invasive endothelial function testing and the risk of adverse outcomes: a systematic review and meta-analysis

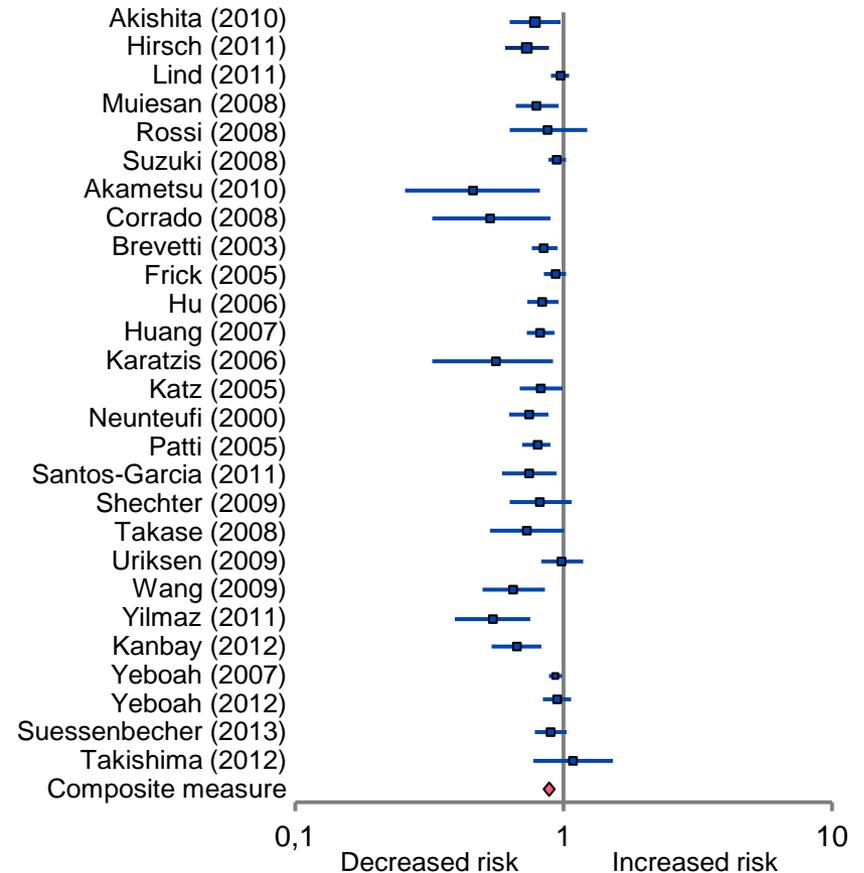
Yang Xu¹, Rakesh C. Arora², Brett M. Hiebert², Blake Lerner¹, Andrea Szwajcer³, Kerry McDonald¹, Claudio Rigatto¹, Paul Komenda¹, Manish M. Sood³, and Navdeep Tangri^{1*}

- FMD of the BA and PAT are noninvasive measures of endothelial function
- **Conclusion:** Brachial FMD and PAT are independent predictors of CV events and all-cause mortality.

Forest Plot of Multivariable Relative Risk – PAT



Forest Plot of Multivariable Relative Risk – FMD



Xu et al: Eur Heart J, 2013

Endothelial Dysfunction in Secondary Prevention

Smoking

Hypertension

Hypercholesterolemia

Age

Diabetes

Normal endothelial Function



Endothelial Dysfunction

Continue current management

Ongoing CV risk and Events

PLT reactivity

Sleep Apnea

Metabolic syndrome

Ongoing Vascular injury

Inflammation

Mental stress

Modify current management



YOU ARE ONLY AS OLD AS YOUR BLOOD VESSELS

Sir William Osler, Father of Modern Medicine