

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 $BMI = 28.5 \text{ kg/m}^2$



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
- Quit smoking 20 years ago
- Normal cardiac examination
- On Atrovostatin 80mg and baby ASA
- 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

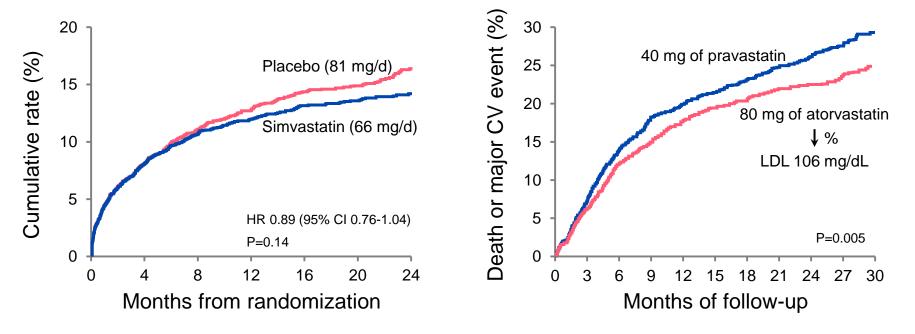
JAMA 292:1307, 2004

 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 preceeding 10 days and compared 40 mg of pravastatin daily (standard therapy) with 80 mg of atorvastatin daily (intensive therapy)





ARTICLE

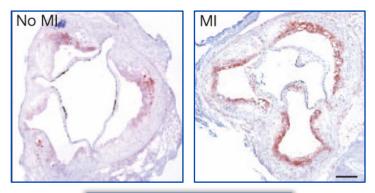
doi:10.1038/nature11260

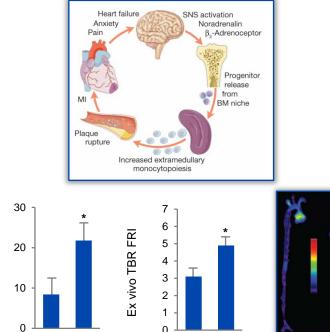
Myocardial infarction accelerates atherosclerosis

"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."

CD1 1b Staining and Lesion size





Increase in aortic root protease activity (pmol)

No MI MI

Dutta et al: Nature, 2012

No MI

MI

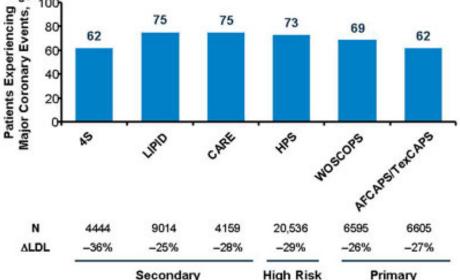


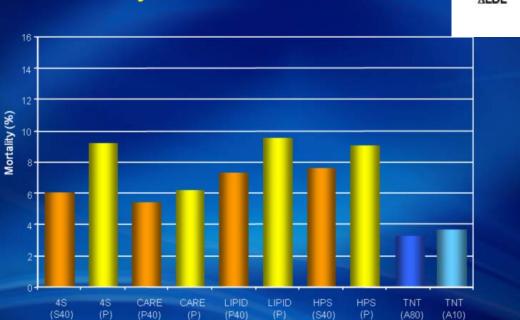
Aggressive Treatment of Conventional risk factors and CV Events

Cardiovascular Mortality in

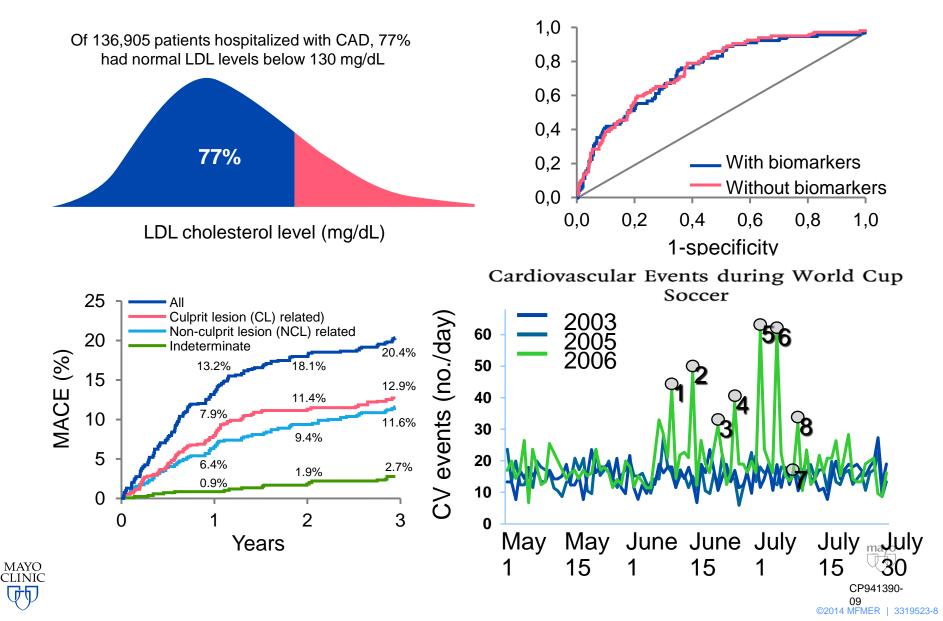
Secondary Prevention Studies

Residual Cardiovascular Risk Despite Intervention in Primary and Secondary Prevention Trials





Traditional Risk Factors Markers and Imaging Fail in Identifying Vulnerable Patient



AHA/ACCF Secondary Prevention and Risk Reduction Therapy for Patients With Coronary and Other Atherosclerotic Vascular Disease: 2011 Update

A Guideline From the American Heart Association and American College of **Cardiology Foundation**

PRACTICE GUIDELINE

AHA/ACCF Secondary Prevention and Risk Reduction Therapy for Patients With Coronary and Other Atherosclerotic Vascular Disease: 2011 Update

A Guideline From the American Heart Association and American College of Cardiology Foundation

Endorsed by the World Heart Federation and the Preventive Cardiovascular Nurses Association Sidney C. Smith, JR, MD, FAHA, FACC, Chair; Emelia J. Benjamin, MD, ScM, FAHA, FACC; Robert O. Bonow, MD, FAHA, FACC; Lynne T. Braun, PhD, ANP, FAHA; Mark A. Creager, MD, FAHA, FACC; Barry A. Franklin, PhD, FAHA; Raymond J. Gibbons, MD, FAHA, FACC; Scott M. Grundy, MD, PhD, FAHA; Loren F. Hiratzka, MD, FAHA, FACC; Daniel W. Jones, MD, FAHA; Donald M. Lloyd-Jones, MD, ScM, FAHA, FACC; Margo Minissian, ACNP, AACC, FAHA; Lori Mosca, MD, PhD, MPH, FAHA; Eric D. Peterson, MD, MPH, FAHA, FACC; Ralph L. Sacco, MD, MS, FAHA; John Spertus, MD, MPH, FAHA, FACC; James H. Stein, MD, FAHA, FACC; Kathryn A. Taubert, PhD, FAHA

ince the 2006 update of the American Heart Association (AHA)/American College of Cardiology Founda-tion (ACCF) guidelines on secondary prevention (1), important evidence from clinical trials has emerged that further supports and broadens the merits of intensive riskreduction therapies for patients with established coronary and other atherosclerotic vascular disease, including peripheral artery disease, atherosclerotic aortic disease, and carotid artery disease. In reviewing this evidence and its clinical impact, the writing group believed it would be more appro-priate to expand the title of this guideline to "Secondary Prevention and Risk Reduction Therapy for Patients With Coronary and Other Atherosclerotic Vascular Disease." Indeed, the growing body of evidence confirms that in patients with atherosclerotic vascular disease, comprehensive risk factor management reduces risk as assessed by a variety of

MAYO CLINIC outcomes, including improved survival, reduced recurren events, the need for revascularization procedures, and improved quality of life. It is important not only that the healthcare provider implement these recommendations in appropriate patients but also that healthcare systems support this implementation to maximize the benefit to the patient.

Compelling evidence-based results from recent clinical trials and revised practice guidelines provide the impetus for this update of the 2006 recommendations with evidencebased results (2-165) (Table 1). Classification of recommendations and level of evidence are expressed in ACCF/AHA format, as detailed in Table 2. Recommendations made herein are largely based on major practice guidelines from the National Institutes of Health and updated ACCF/AHA practice guidelines, as well as on results from recent clinical trials.

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Applying Classification of Recommendation and Level of Evidence

SIZE OF TREATMENT EFFECT

		CLASS I Benefit >>> Risk Procedure/Treatment SHOULD be performed/ administered	CLASS IIa Benefit >> Risk Additional studies with focused objectives needed IT IS REASONABLE to per- form procedure/administer treatment	CLASS IIb Benefit ≥ Risk Additional studies with broad objectives needed; additional registry data would be helpful Procedure/Treatment MAY BE CONSIDERED	CLASS III No Be or CLASS III Ha Proced Test COR III: Not No benefit Helpful COR III: Excess Harm w/o Ber or Harr	Irm ure/ Treatment No Proven Benefit Cost Harmful nefit to Patients
TREATMENT EFFECT	LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or mela-analyses	Recommendation that procedure or treatment is useful/effective Sufficient evidence from multiple randomized trials or meta-analyses	Recommendation in favor of treatment or procedure being useful/effective Some conflicting evidence from multiple randomized trials or meta-analyses	Recommendation's usefulness/efficacy less well established Greater conflicting evidence from multiple randomized trials or meta-analyses	Recommendation that procedure or treatment is not useful/effective and may be harmful Sufficient evidence from multiple randomized trials or meta-analyses	
CERTAINTY (PRECISION) OF	LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	Recommendation that procedure or treatment is useful/effective Evidence from single randomized trial or nonrandomized studies	Recommendation in favor of treatment or procedure being useful/effective Some conflicting evidence from single randomized trial or nonrandomized studies	Recommendation's usefulness/efficacy less well established Greater conflicting evidence from single randomized trial or nonrandomized studies	 Recommendation that procedure or treatment is not useful/effective and may be harmful Evidence from single randomized trial or nonrandomized studies 	
ESTIMATE OF CERTA	LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	 Recommendation that procedure or treatment is useful/effective Only expert opinion, case studies, or standard of care 	 Recommendation in favor of treatment or procedure being useful/effective Only diverging expert opinion, case studies, or standard of care 	Recommendation's usefulness/efficacy less well established Only diverging expert opinion, case studies, or standard of care	 Recommendation that procedure or treatment is not useful/effective and may be harmful Only expert opinion, case studies, or standard of care 	
	Suggested phrases for writing recommendations	should is recommended is indicated is useful/effective/beneficial	Is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	COR III: No Benefit is not recommended is not indicated should not be	COR III: Harm potentially harmful causes harm associated with
	Comparative effectiveness phrases*	treatment/strategy A is recommended/indicated in preference to treatment B treatment A should be chosen over treatment B	treatment/strategy A is probably recommended/indicated in preference to treatment B it is reasonable to choose treatment A over treatment B	should not be performed/ administered/ other is not useful/ beneficial/ effective		excess morbid- ity/mortality should not be performed/ administered/ other

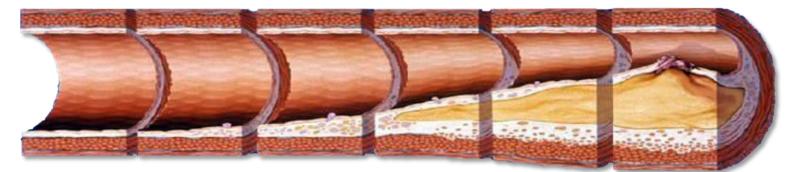
Areas for Intervention

- Class I •
- Smoking •
- Blood Pressure
- Lipid Management •
- **Physical Activity**

- Lipid Management
- Physical Activity
- Weight Management
- Type 2 Diabetes Management
- Antiplatlet Agent

Smith et al: JACC 58:2432, 2011

How to Assess the Risk of the Patient



Surrogate risk markers Hypercholesterolemia Hypertension Smoking Diabetes biomarkers

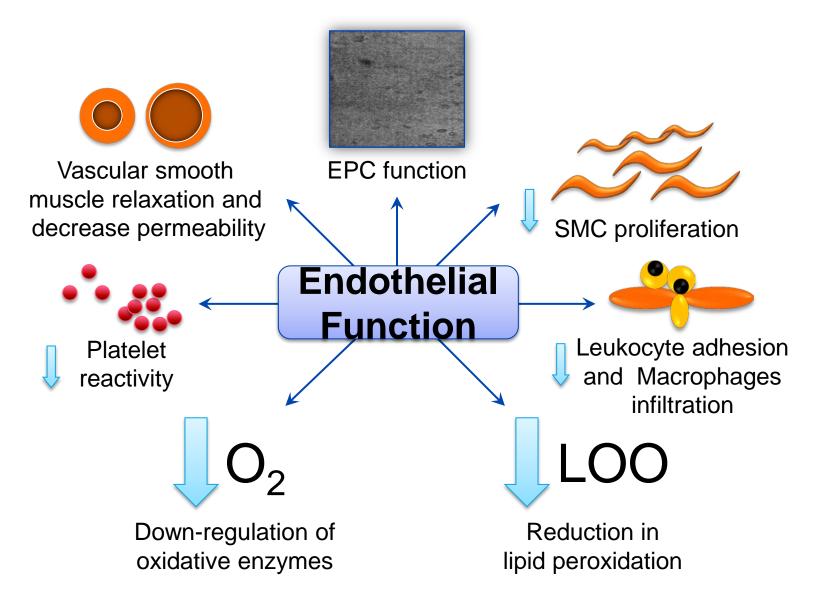


Direct Imaging of the disease Carotid US Coronary Calcium Endothelial function

- 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



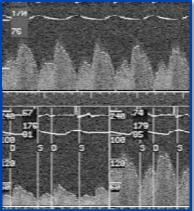


Functional Angioram Protocol

Diagnostic angiography



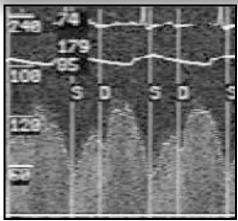
CFR: Non endothelium



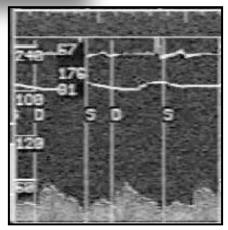




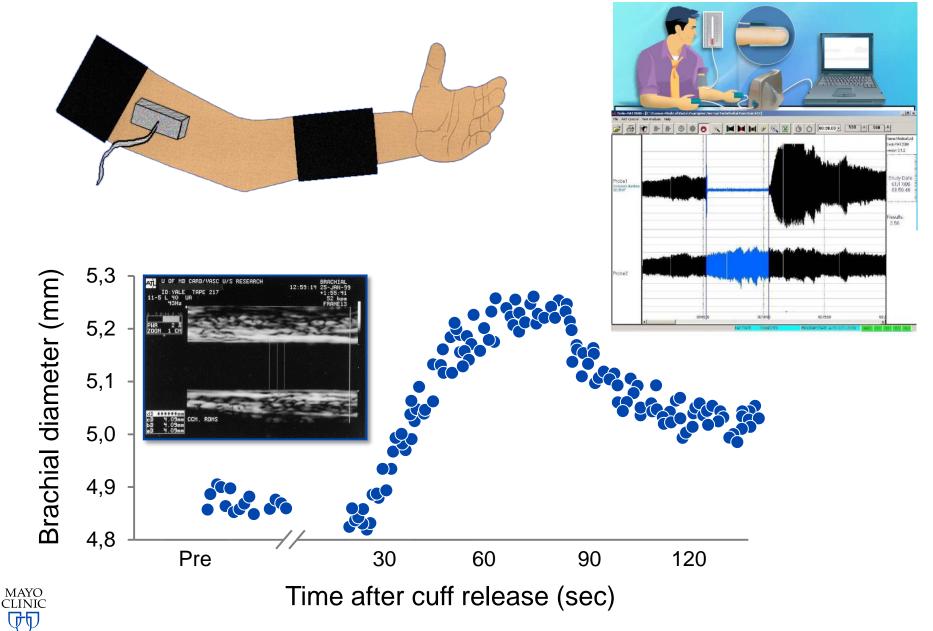
Acetylcholine (endothelium dependent vasodilator) Epicardial



Microcirculation



Reactive Hyperemia: Endothelium Dependent



How to Assess the Risk of the Patient



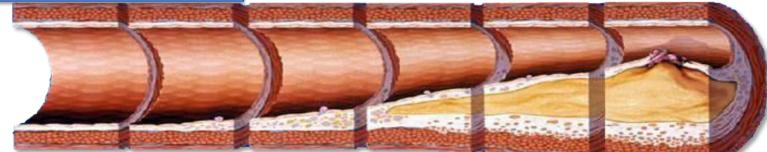
Endothelial dysfunction represent ingoing risk

Inadequate therapy

MAYO CLINIC



On going CV risk Unrecognized CV risk



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

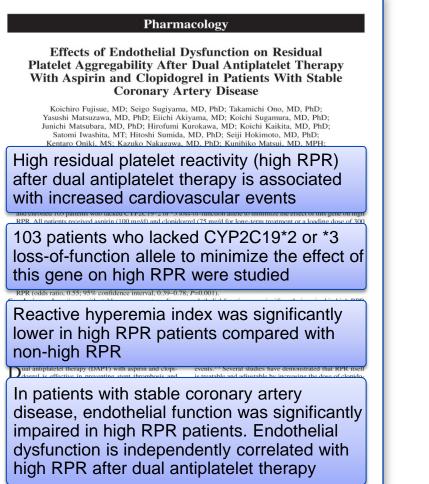
What is the residual risk of this patient?

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

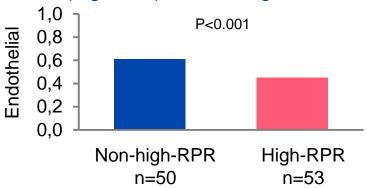
What evidence do we have to support it?



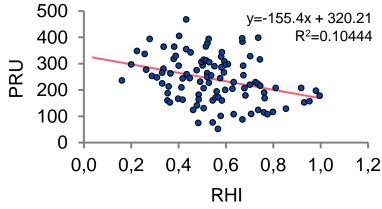
Effects of Endothelial Dysfunction on Residual Platelet Aggregability After Dual Antiplatelet Therapy With Aspirin and Clopidogrel in Patients With Stable Coronary Artery Disease



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

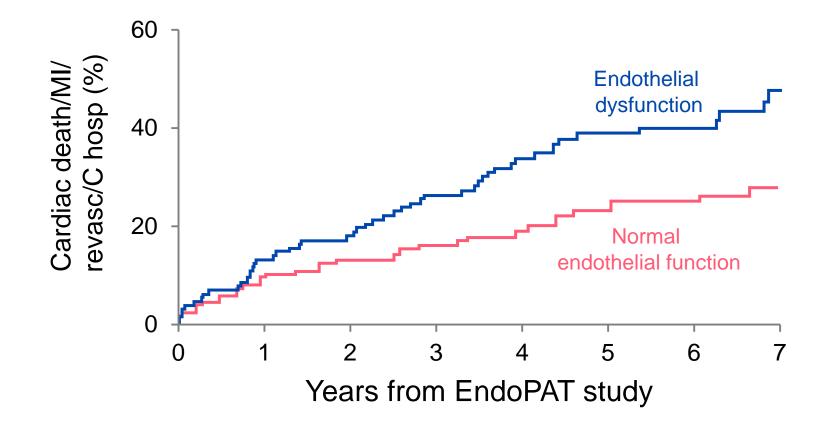
What is the residual risk of this patient?

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- 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

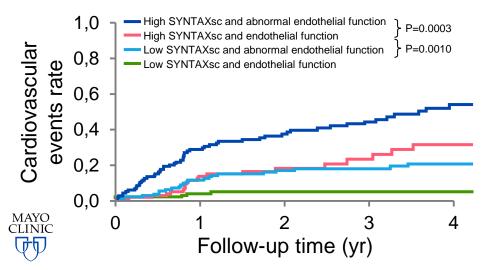


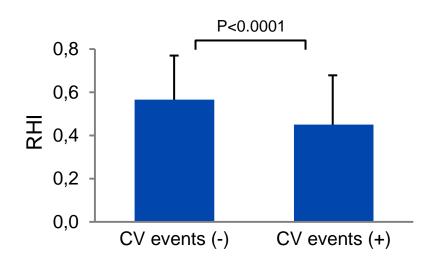
MAYO CLINIC Rubinshtein and Lerman: Euro Heart J, 2010

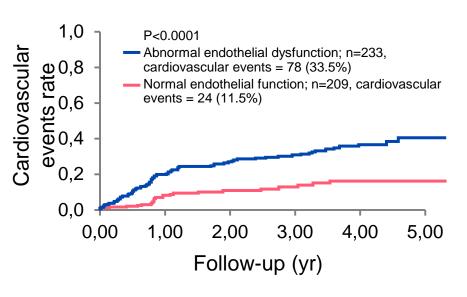


- a) Prospective study in 528 stable patients at high risk for cardiovascular events. Endothelial function (RHI) was measured before coronary angiography, and coronary complexity was assessed by SYNTAXsc. After optimal therapies including coronary revascularization, there was follow-up with patients
- 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

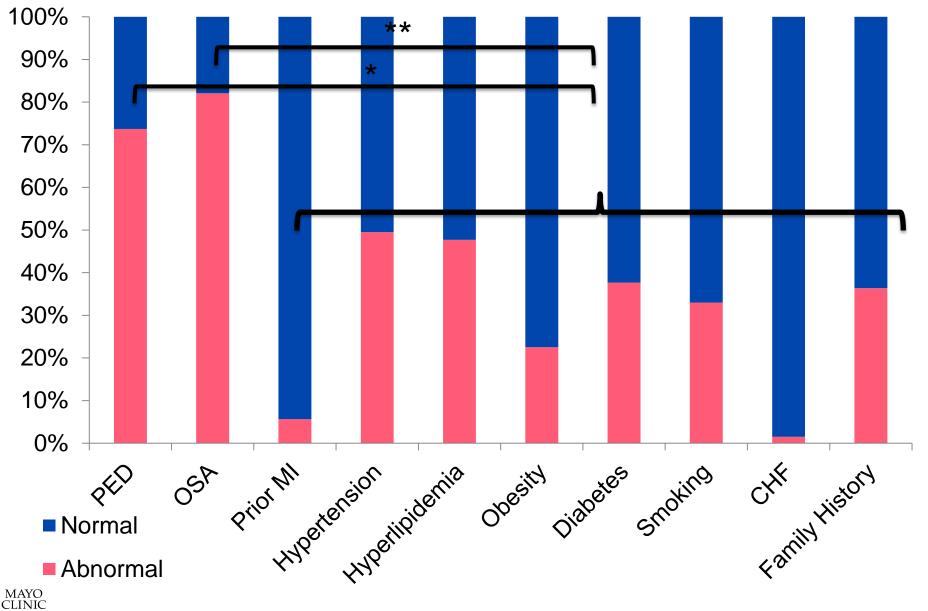






Matsuzawa et al: J Am Heart Assoc, 2013 ©2014 MFMER | 3319523-20

Risk Factors in Patients Post PCI for ACS



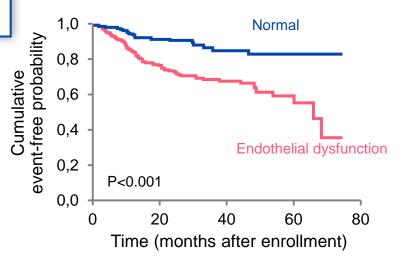
Endothelial function and Cardiovascular Events in Chronic Kidney Disease

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

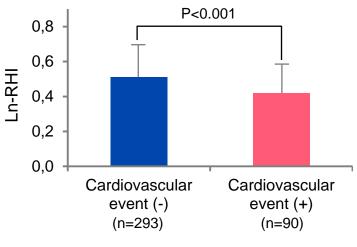
- 383 CKD patients with at least one coronary risk factor. Peripheral endothelial function was assessed by reactive hyperemia peripheral arterial tonometry index (RHI).
- Endothelial function was significantly impaired in CKD patients and correlated with the presence of CAD.
- Severe endothelial dysfunction 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)
Ag	ge (years)	72.0	72.2	71.8
Se	ex (male, %)	64.2	62.3	65.7
BN	VII (kg/m²)	24.3	24.3	24.2
Hy	ypertension (yes, %)	90.6	93.4	88.4
D	M (yes, %)	44.9	44.3	45.4
Dy	yslipidemia (yes, %)	83.0	82.6	83.3
L٧	/EF (%)	62.1 (7.4)	62.2 (7.1)	61.9 (7.6)
Hs	s-CRP (mg/dL)	0.08	0.07	0.08
	GFR (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

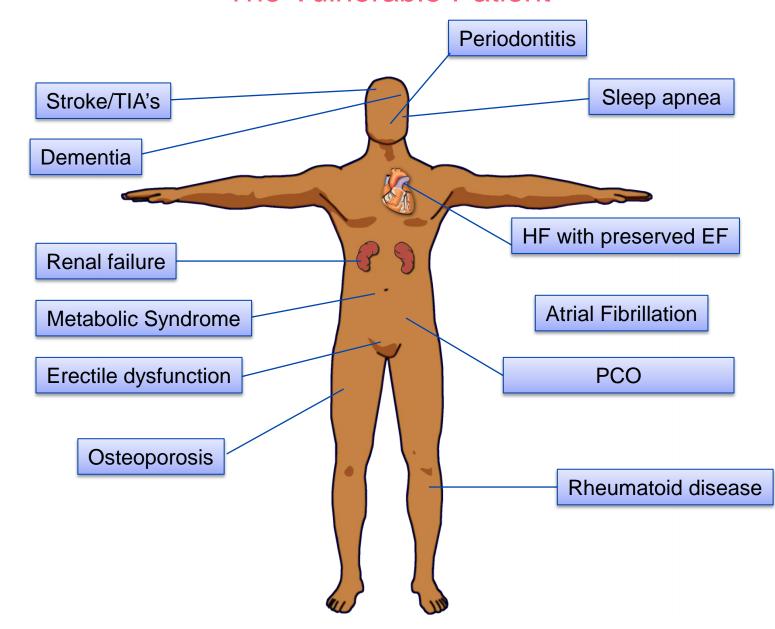


Endothelial function was Significantly Lower in Patients With Cardiovascular Events Than Without Cardiovascular Events



Hirata et al: Int J of Card, 2014

Systemic Manifestation of Endothelial Dysfunction The Vulnerable Patient



The NEW ENGLAND JOURNAL of MEDICINE

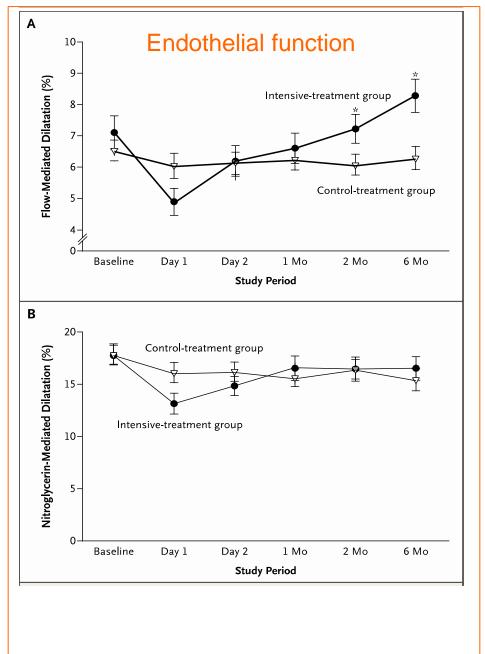
ORIGINAL ARTICLE

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 communitybased 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?

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

What evidence do we have to support it?

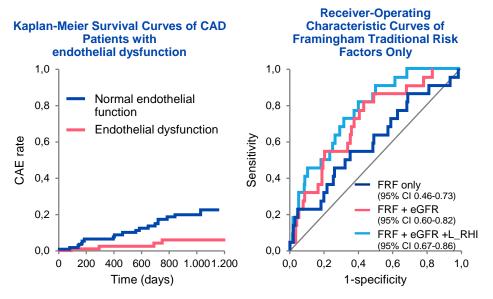




Peripheral microvascular dysfunction predicts residual risk in coronary artery disease patients on statin therapy

CrossMark

 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

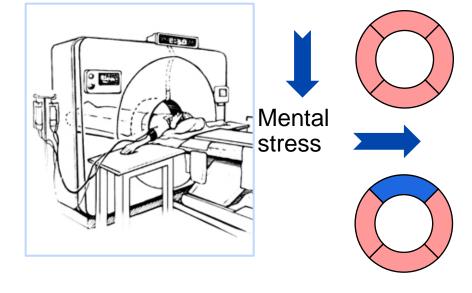


 b) FRF alone failed to predict future secondary CAE in patients with CAD treated with statin. However, adding endothelial function measurement to FRF in the logistic regression model significantly improved MAYO

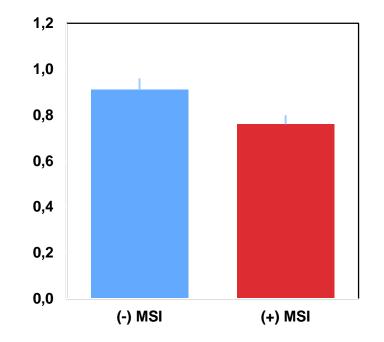
CLINIC

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



Endothelial Function: EndoPAT





Can We use Endothelial Function to Individualize Therapy?

Journal of the American College of Cardiology © 2002 by the American College of Cardiology Foundation Published by Elsevier Science Inc. Vol. 40, No. 3, 2002 ISSN 0735-1097/02/\$22.00 PII \$0735-1097(02)01976-9

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 © 2009 by the American College of Cardiology Foundation Published by Elsevier Inc. Vol. 53, No. 4, 2009 ISSN 0735-1097/09/\$36.00 doi:10.1016/j.jacc.2008.08.074

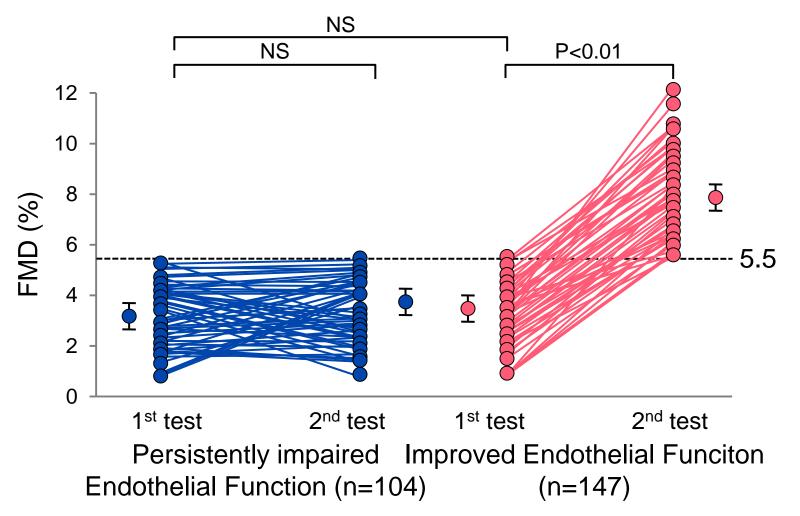
Persistent Impairment of Endothelial Vasomotor Function Has a Negative Impact on Outcome in Patients With Coronary Artery Disease

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

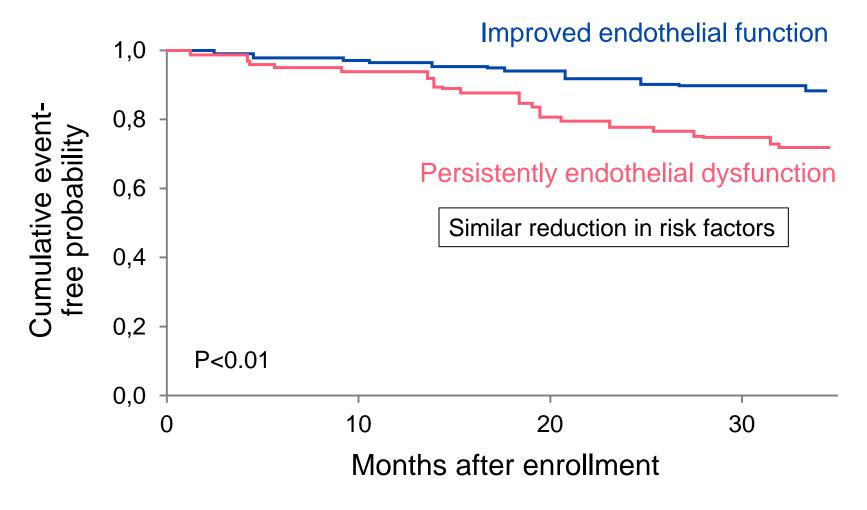


Endothelial Function Comparison Between First and Second Test in CAD Patients on OMT



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

Event-Free Survival and Endothelial Function



MAYO CLINIC 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 modubelium-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 agoinst 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 vascullation 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%

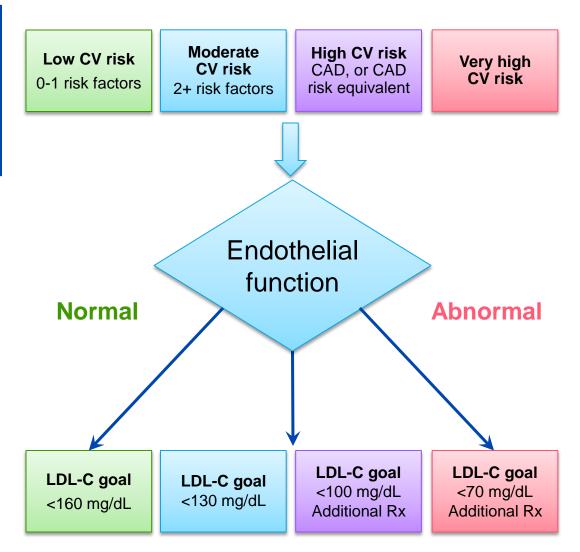
Epidemiology and Prevention

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 2SD age, 61.2:9.9 years) in MESA, a population-based cohort study of adults free of clinicial CVD at baseline recruited at 6 clinic sites in the United States. The sample included 50.2% female, 34.3% white, 19.7% Crinese, 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 aming, cornary revascularization (cornary artery bypass graftine, percutaneous transluminal coronary

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





European Heart Journal - Cardiovascular Imaging Advance Access published January 7, 2014



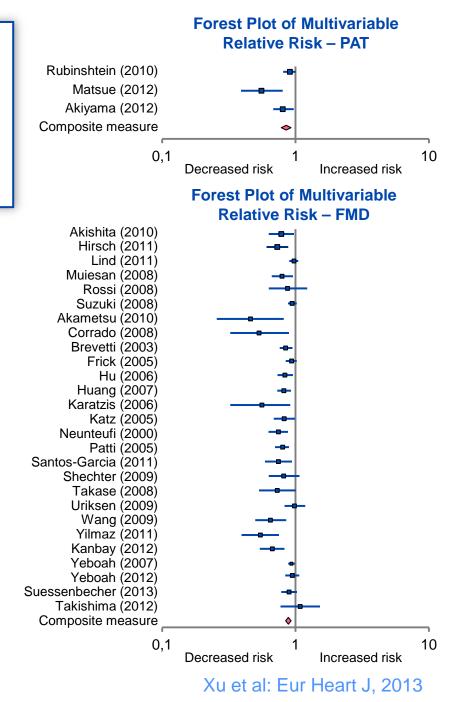
European Heart Journal – Cardiovascular Imaging doi:10.1093/ehjci/jet256

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*}

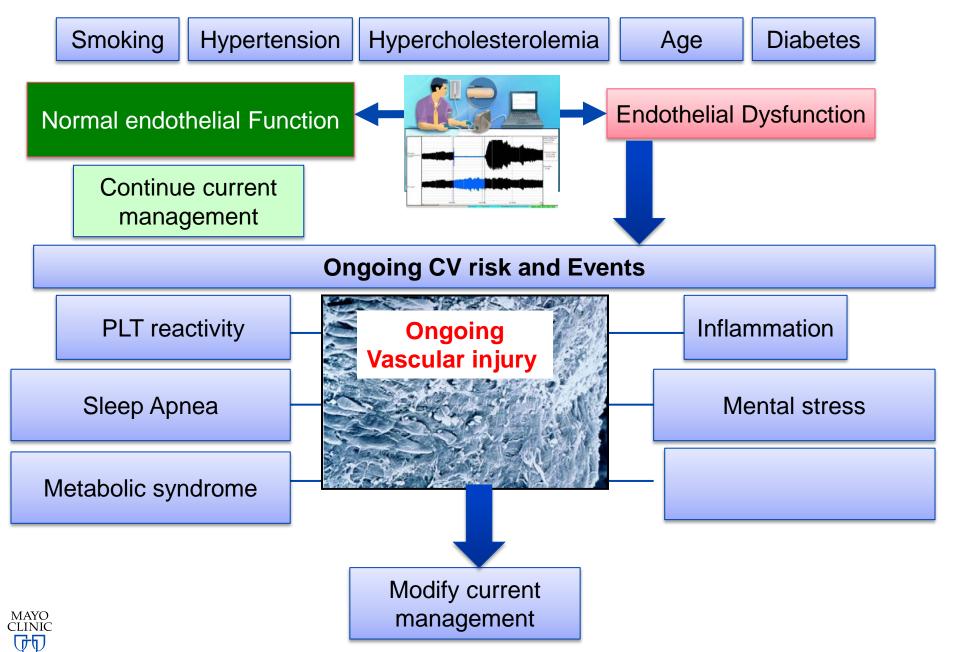
 FMD of the BA and PAT are noninvasive measures of endothelial function

 Conclusion: Brachial FMD and PAT are independent predictors of CV events and all-cause mortality.





Endothelial Dysfunction in Secondary Prevention





YOU ARE ONLY AS OLD AS YOUR BLOOD VESSELS Sir William Osler, Father of Modern Medicine

