

Can Biomarkers be Used to Assess Risk of Vascular Cardiotoxicity?

Kevin J. Croce, MD, PhD

**Director, Complex Coronary Artery Intervention Program
Director, Translational Discovery Program**

Interventional Cardiology

**Brigham and Women's Hospital
Harvard Medical School
Boston, MA**



Brigham and
Women's Hospital



Harvard Medical
School

Presenter Disclosure Information

Kevin J. Croce MD,PhD

FINANCIAL DISCLOSURE:

- St. Jude Medical: advisory board, speaker
- Ariad Pharmaceuticals: advisory board, research grant*
- Bristol Myer Squibb: advisory board
- Medicine Company: advisory board, speaker

UNLABELED/UNAPPROVED USE DISCLOSURE:

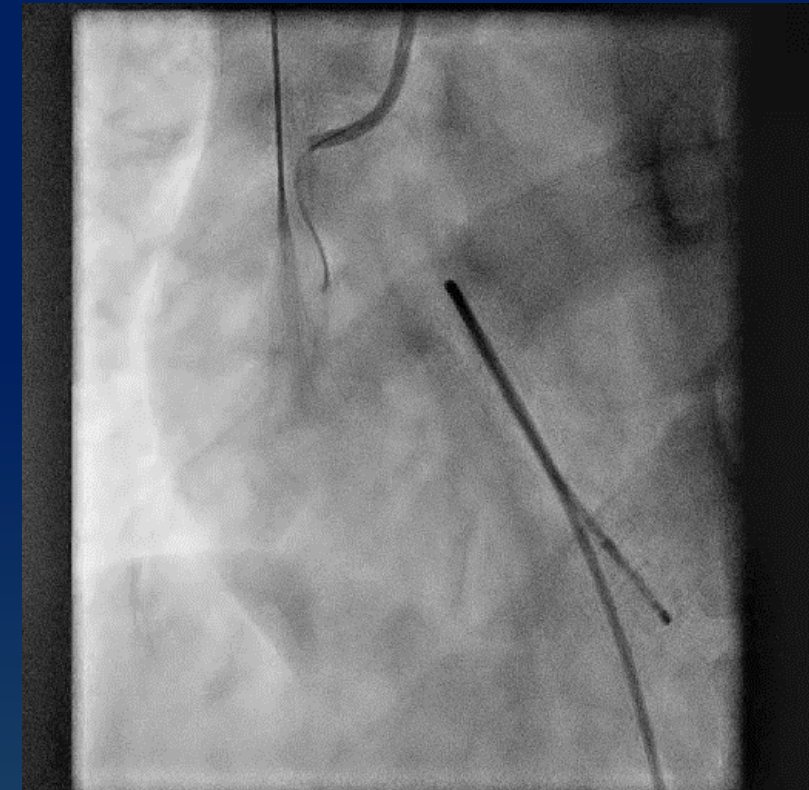
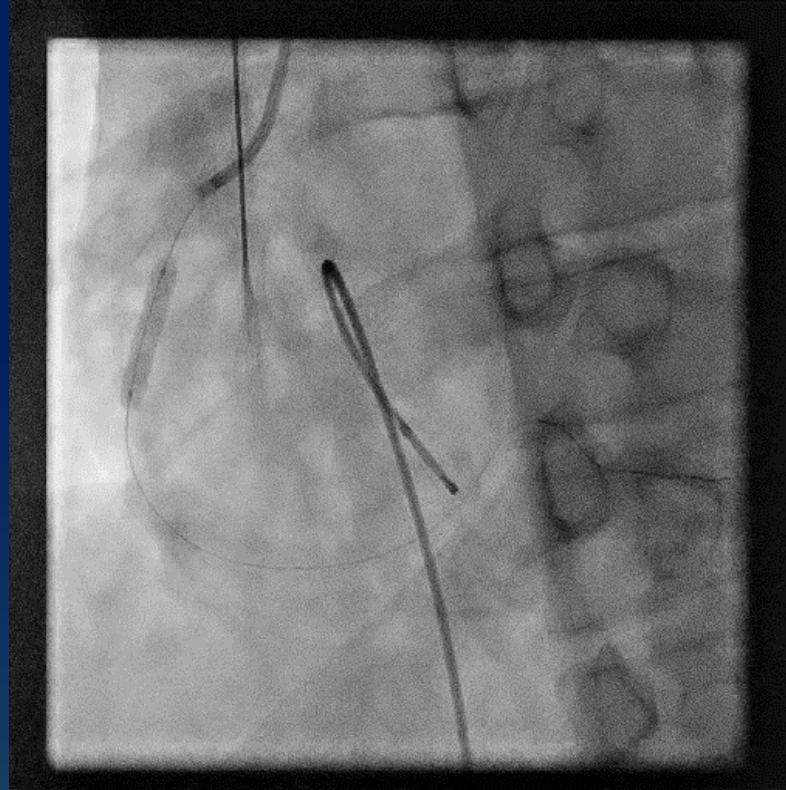
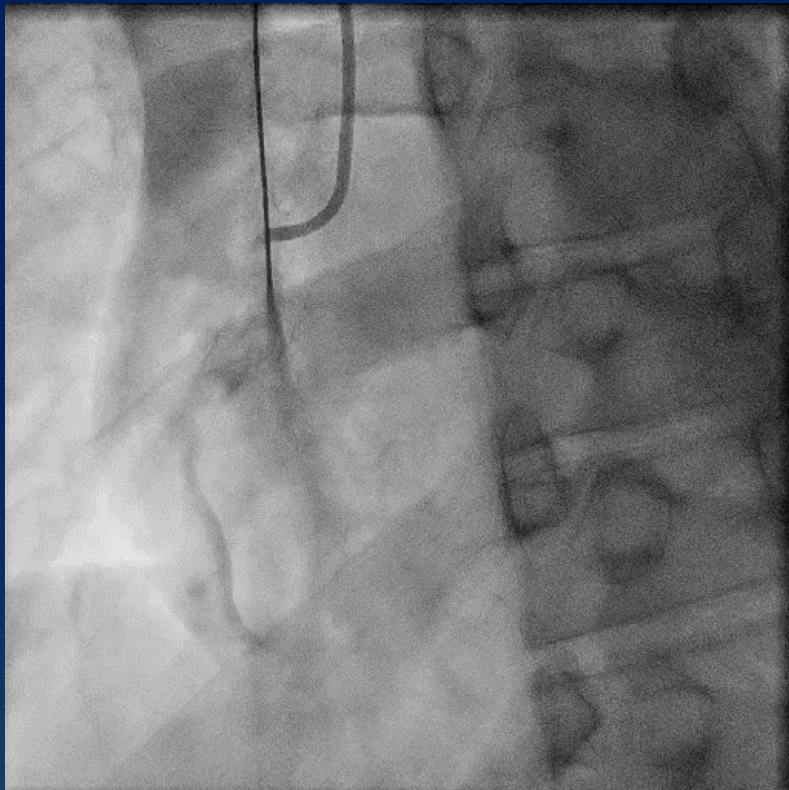
- None

Outline

- **Inflammatory pathobiology of vascular disease**
- **Endothelial dysfunction – cardiovascular pathology**
- **Mechanisms of ischemic vascular events**
- **Biomarkers of cardiovascular events**
 - biochemical biomarkers
 - imaging biomarkers
 - physiologic biomarkers
- **Monitoring for vascular toxicity and CV events in oncology trials**

Arterial Thrombosis: Not Unique to Targeted Novel Cancer Therapies

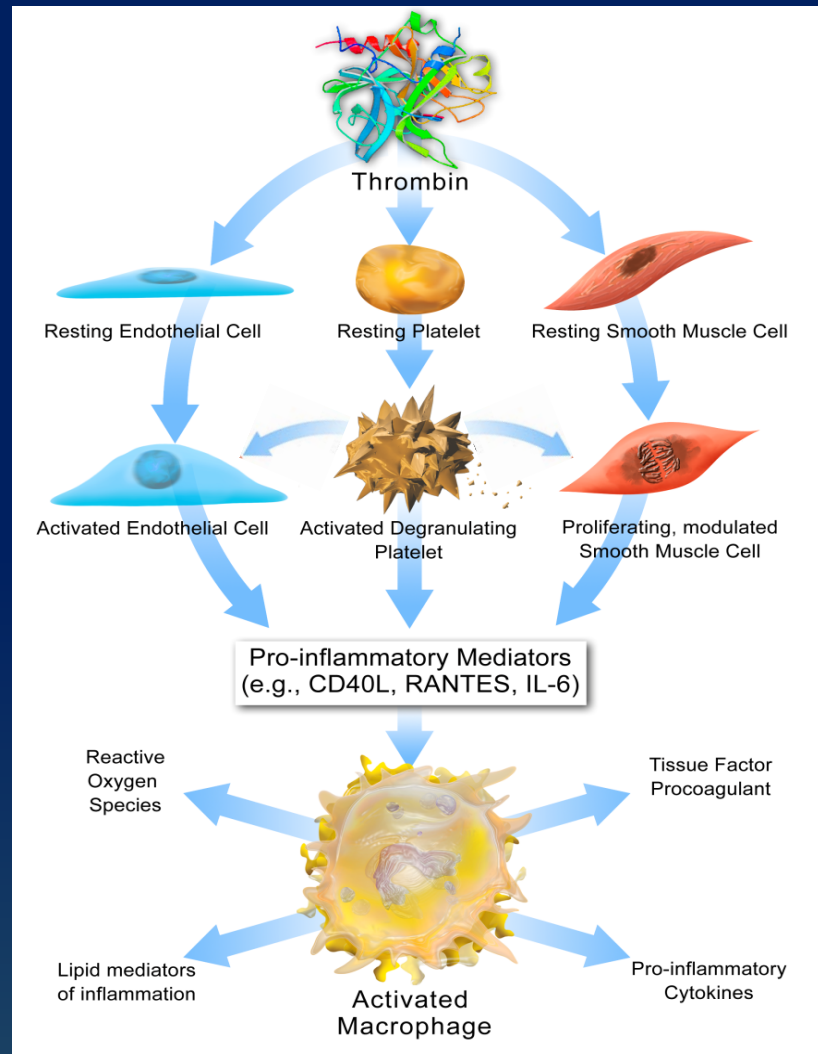
- 55 y.o female under treatment for pancreatic cancer
- On FOLFIRINOX- includes fluorouracil (5-FU), a pyrimidine analog antimetabolite (non targeted)
- Presented with chest pain and ST elevation MI
- Treated with coronary stenting, recovered, now starting alternate cancer therapy



Mechanism: possible 5-FU effect on endothelial function

Arterial Thrombosis is Complicated:

Inflammation and Thrombotic Pathways Intertwine in Vascular Pathobiology



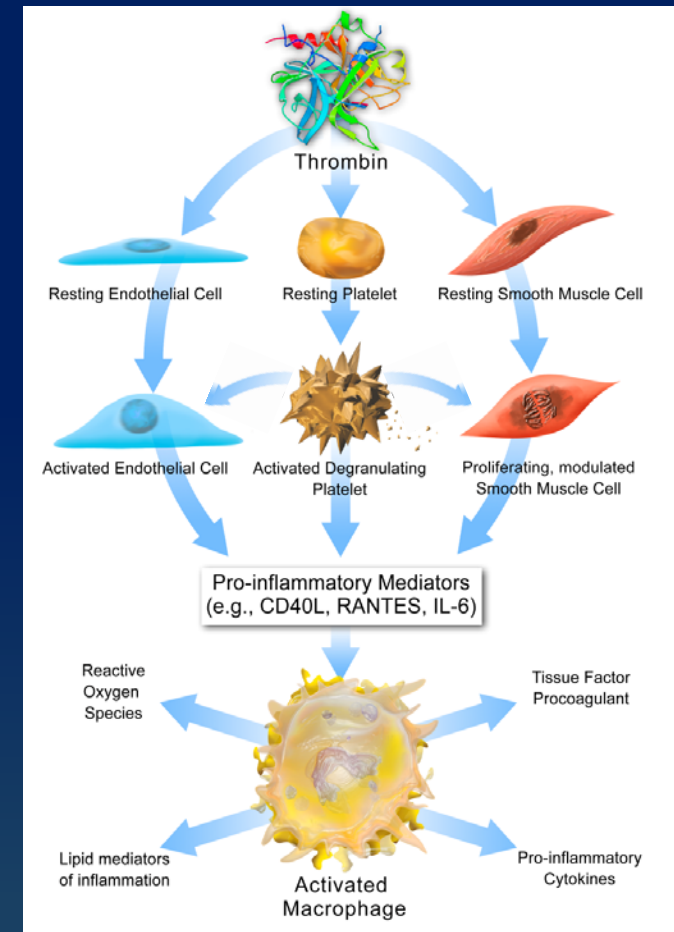
Molecular and cellular pathways link thrombotic and inflammatory processes.

- Atherogenesis
- Plaque stability
- Atherothrombosis
- Restenosis
- Vasculitis
- Vasospasm

Novel Cancer Therapies: Mechanisms of Vascular Toxicity

Unclear:

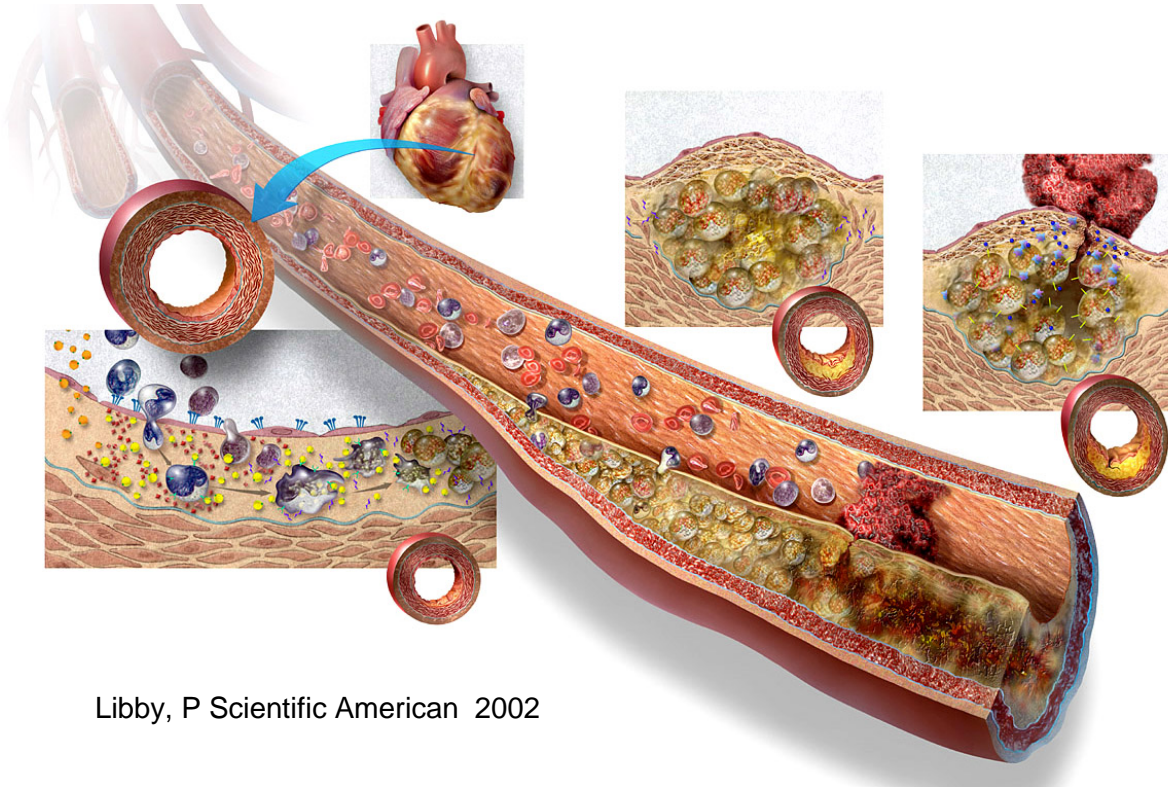
- On target vs. off target effects?
- Clinical vascular events can be triggered by effects on:
 - endothelial cells
 - smooth muscle cells
 - platelets
 - monocytes
 - clotting proteins



Novel Cancer Therapies: Mechanisms of Vascular Toxicity

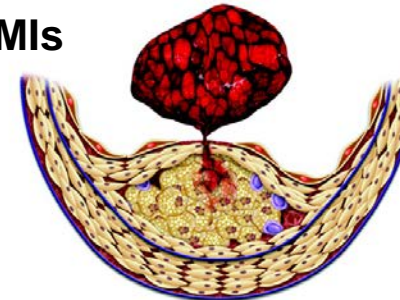
Heterogeneous Mechanisms:
atherogenic, plaque destabilizing, prothrombotic

Atherosclerotic Vasculopathy



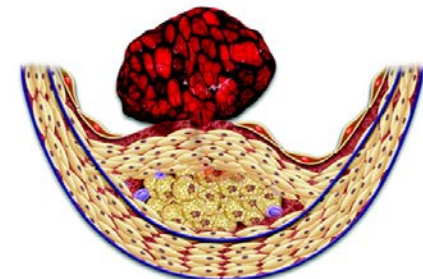
Atherothrombotic Vasculopathy

75% MIs

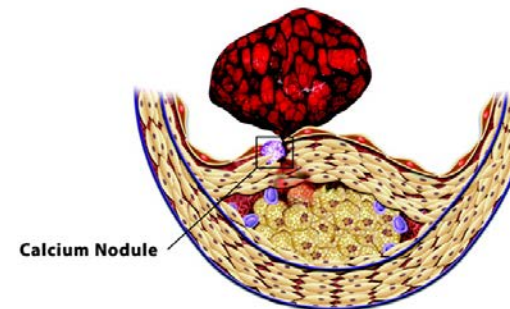


Rupture of Fibrous Cap

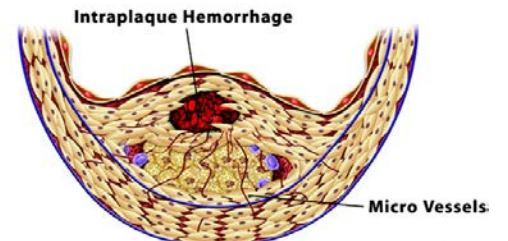
25% MIs
-DM
-Females



Superficial Erosion



Erosion of Calcium Nodule



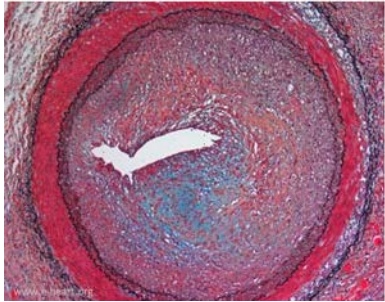
Intraplaque Hemorrhage

Novel Cancer Therapies: Mechanisms of Vascular Toxicity

Heterogeneous Mechanisms:
proliferative, vasospastic

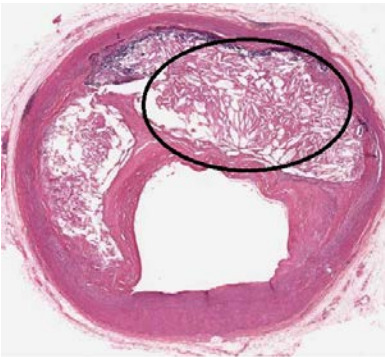
Proliferative Vasculopathy

Proliferative



Vs.

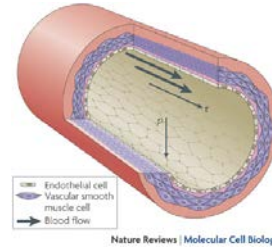
Atherosclerotic



Nilotinib PAOD

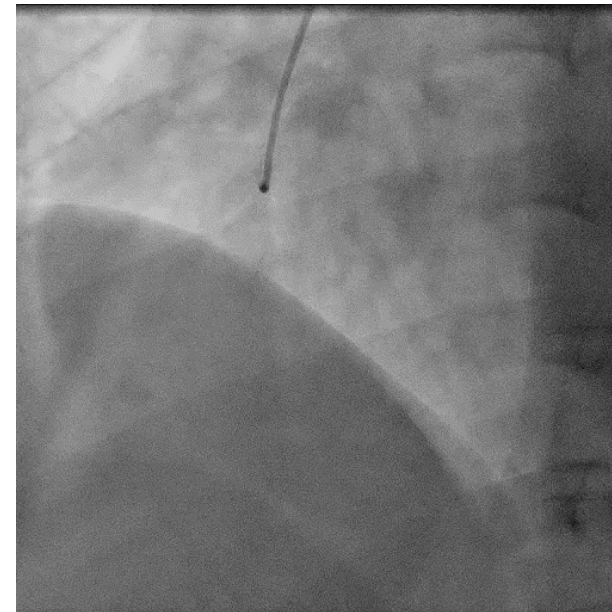


Am. J. Hematol. 86:533–539, 2011

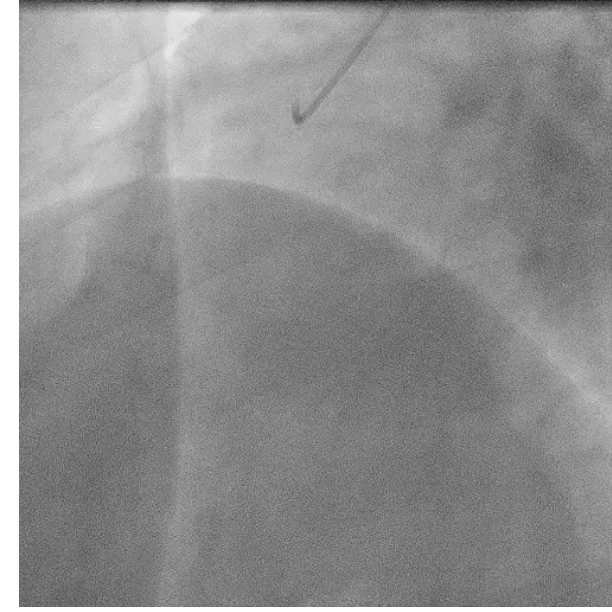


Vasospastic Vasculopathy

Initial Angio

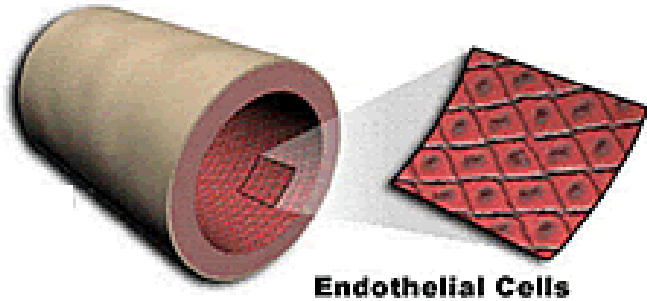


After IC Nitro



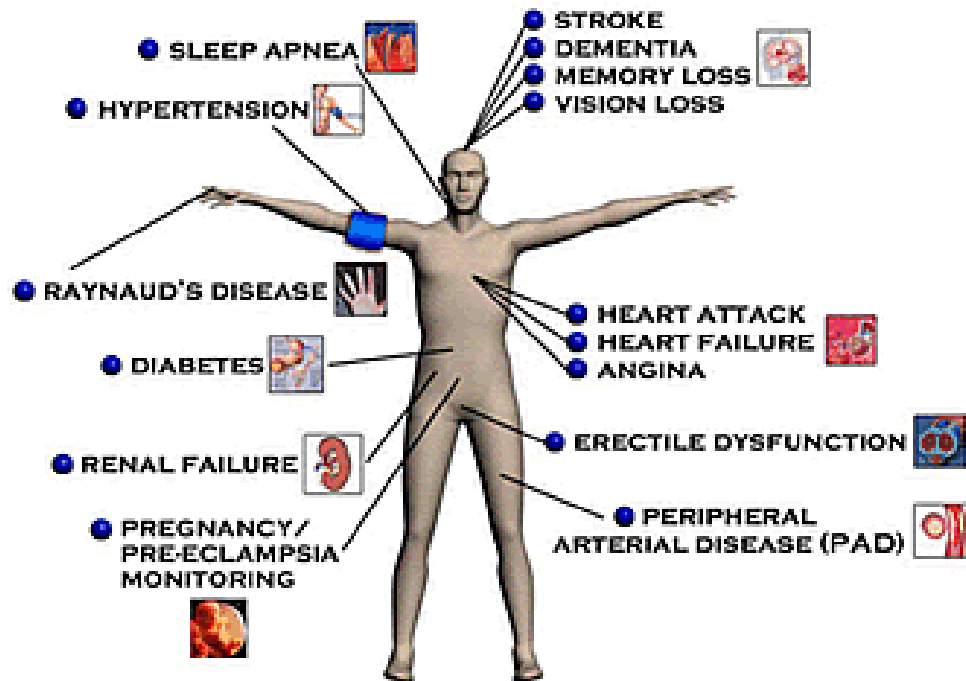
Endothelial Dysfunction: Central in the Pathobiology of Vascular Disease

ENDOTHELIAL DYSFUNCTION

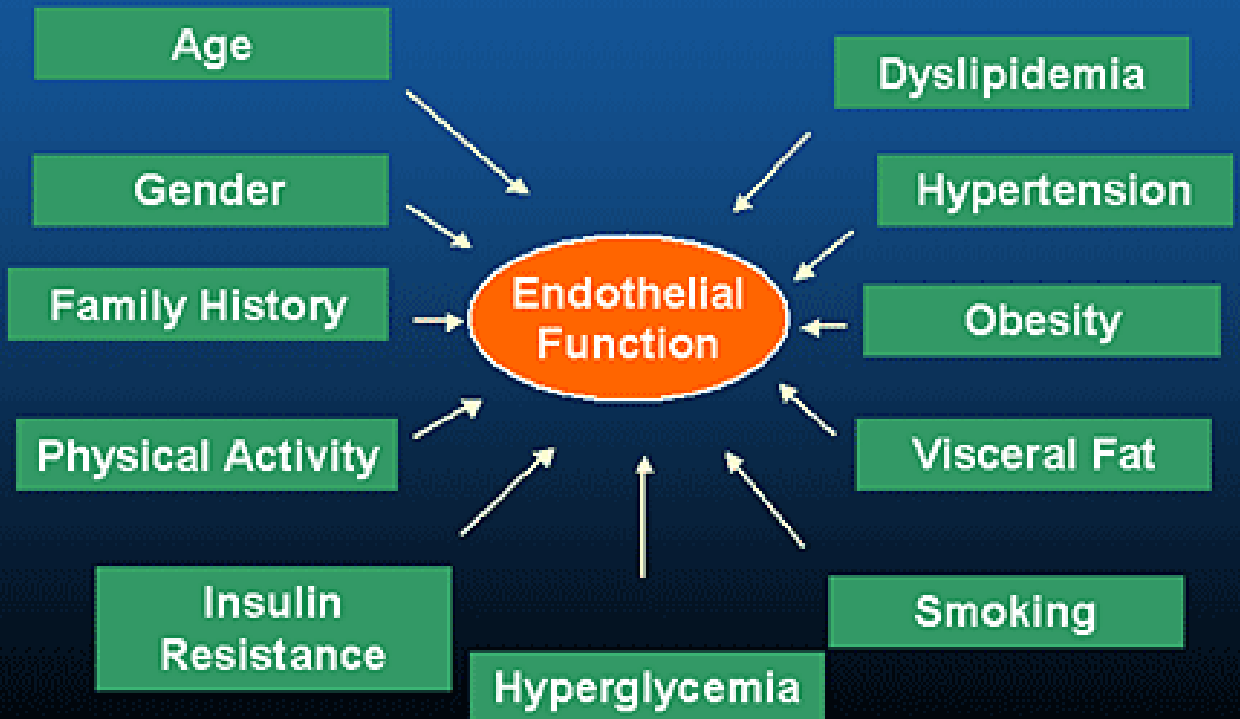


Endothelial Cells

IS THE PRECURSOR OF:



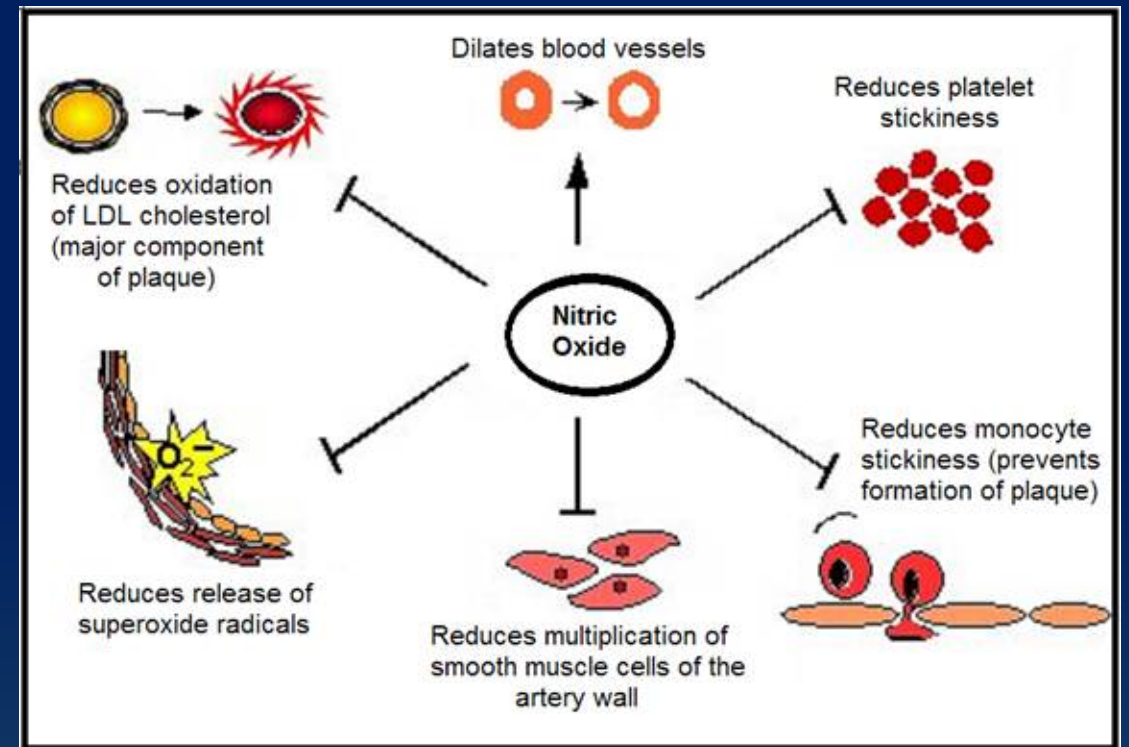
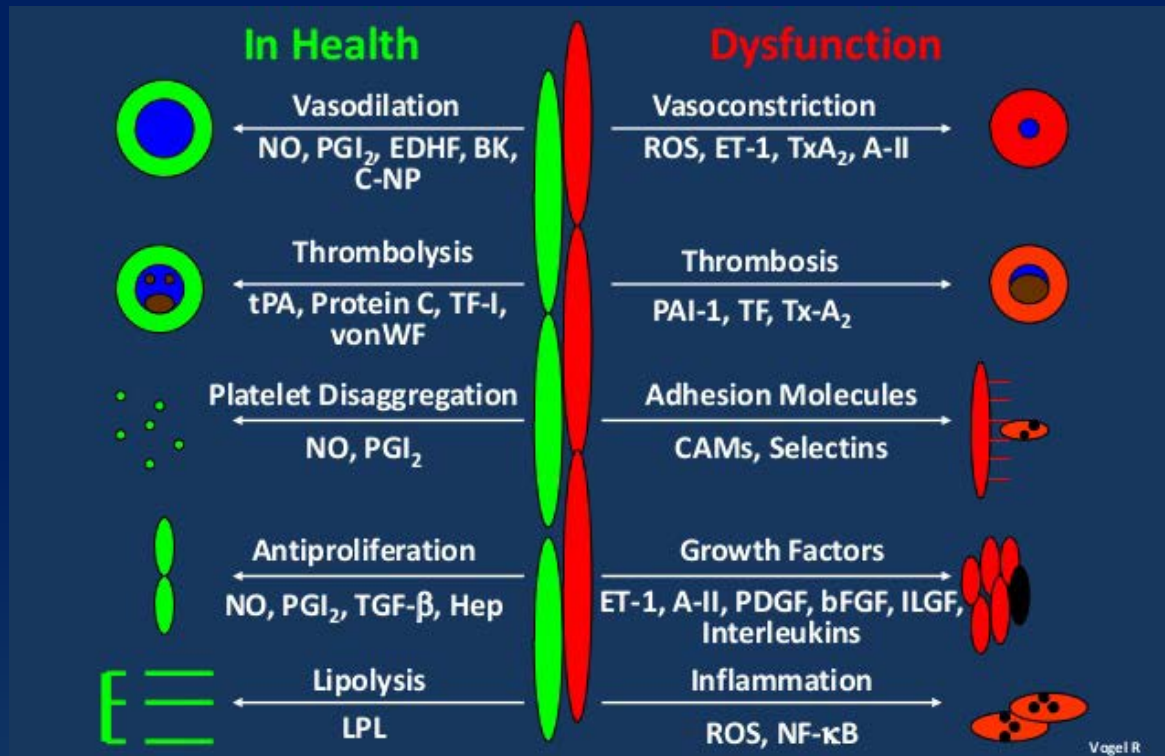
Main Factors That Affect Endothelial Function



Endothelial Dysfunction: Central in the Pathobiology of Vascular Disease

Endothelial injury -inciting event predisposes to atherosclerosis and thrombosis

Endothelial nitric oxide (NO) critically regulates vascular Health

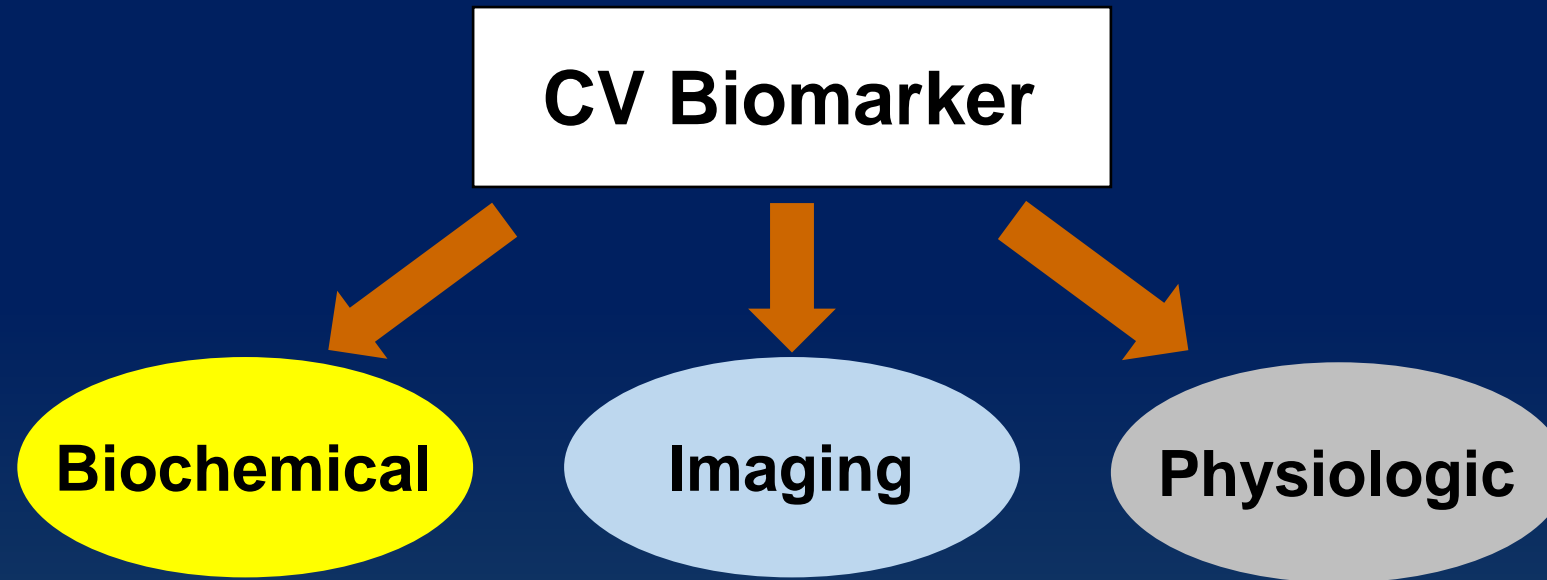


- Decreased NO bioavailability indicative of endothelial dysfunction and damage.
- NO dysregulation one of the earliest events in all types of vascular pathology.

Biomarkers and Vascular Cardiotoxicity

Biomarker (WHO):

- Substance, structure, or process that can be measured in the body or its products and influence or predict the incidence of outcome or disease*
- Measurement reflecting an interaction between a biological system and a potential hazard - not just incidence and outcome of disease, but also the effects of treatments, interventions, and exposure**



Assess underlying mechanisms of CV disease

*Clin Pharmacol Therapeutics. 2001;69:89–95

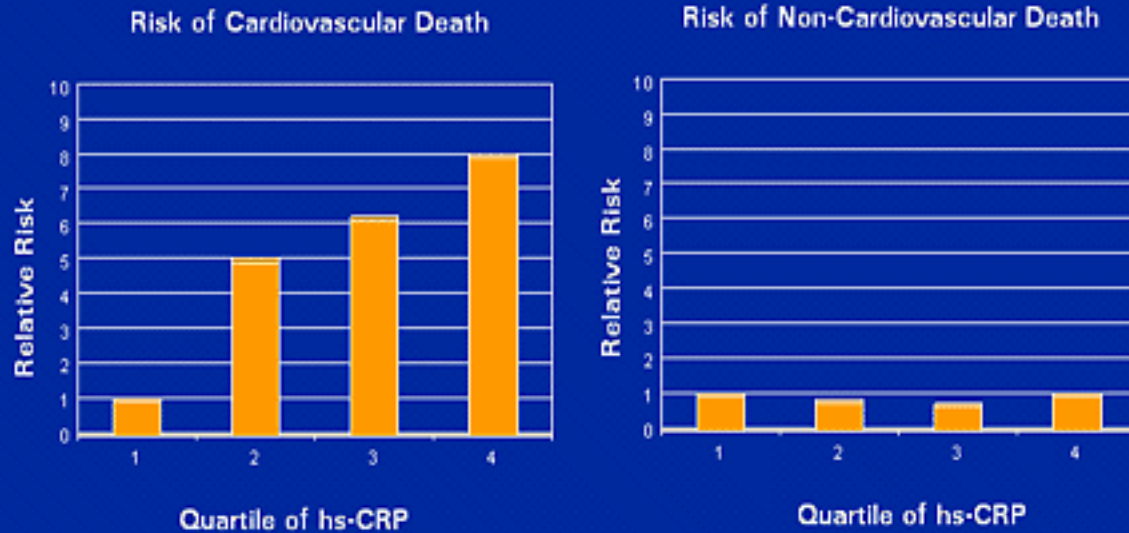
**WHO International Programme on Chemical Safety Biomarkers in Risk Assessment: Validity and Validation. 2001

Biochemical Biomarkers:

- Proteomic markers
- Phosphoprotein markers
- Epigenetic markers
- Multimarker strategies

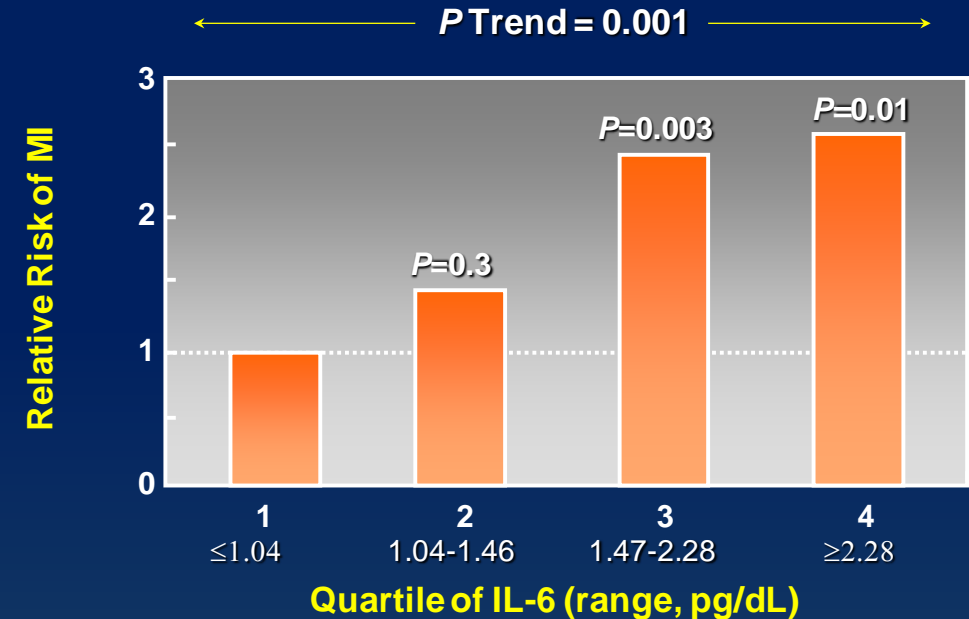
Inflammatory Biomarkers Predict Risk of Cardiovascular Events

hs-CRP is Specific for Cardiovascular Events



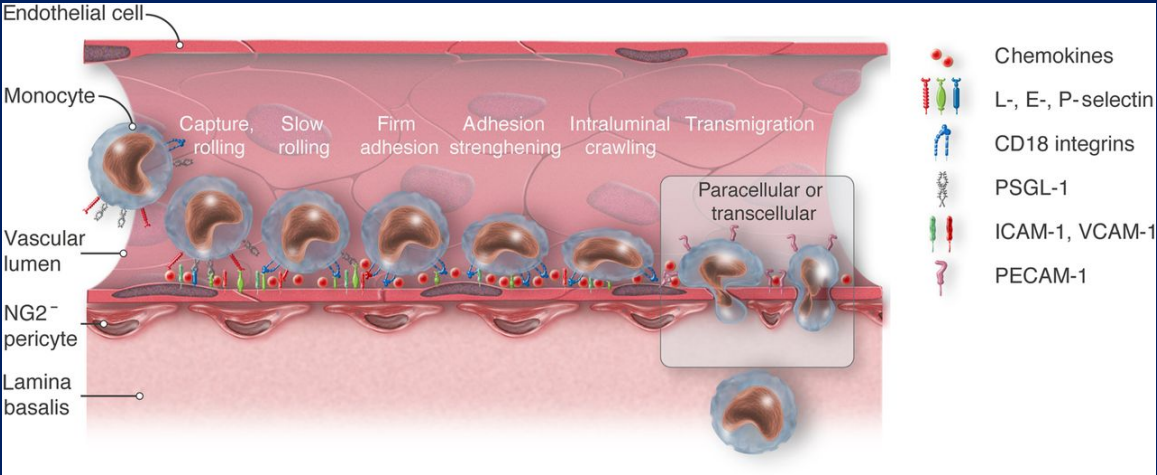
Tice A et al, Am J Med 2003;114:199-205

IL-6 and Risk of Future MI in Apparently Healthy Men

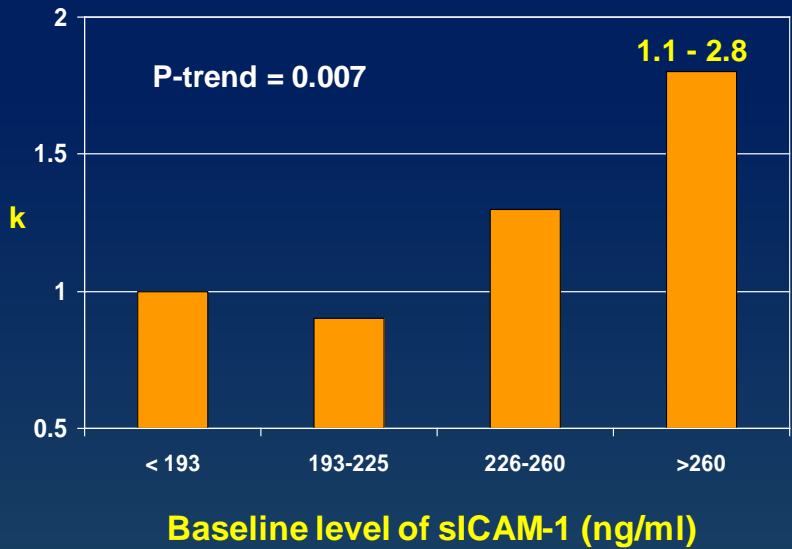


Ridker PM. Circulation, 2000

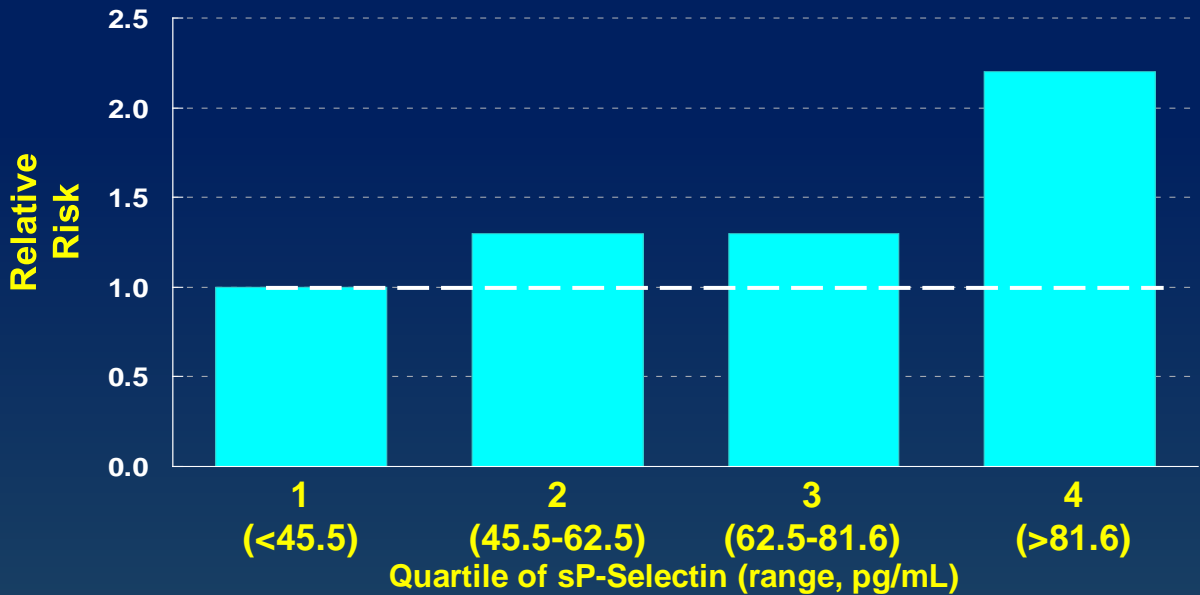
Inflammatory Biomarkers Predict Risk of Cardiovascular Events



Plasma Concentration of Soluble ICAM-1 and Risks of Future Myocardial Infarction

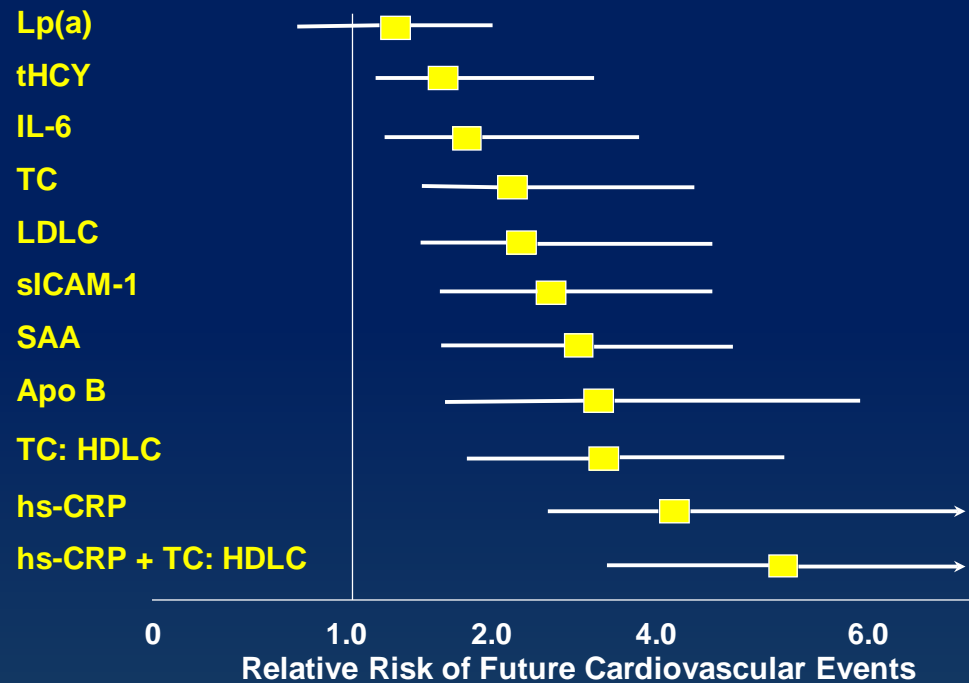


Soluble P-Selectin and the Risk of Future Cardiovascular Events: The Women’s Health Study



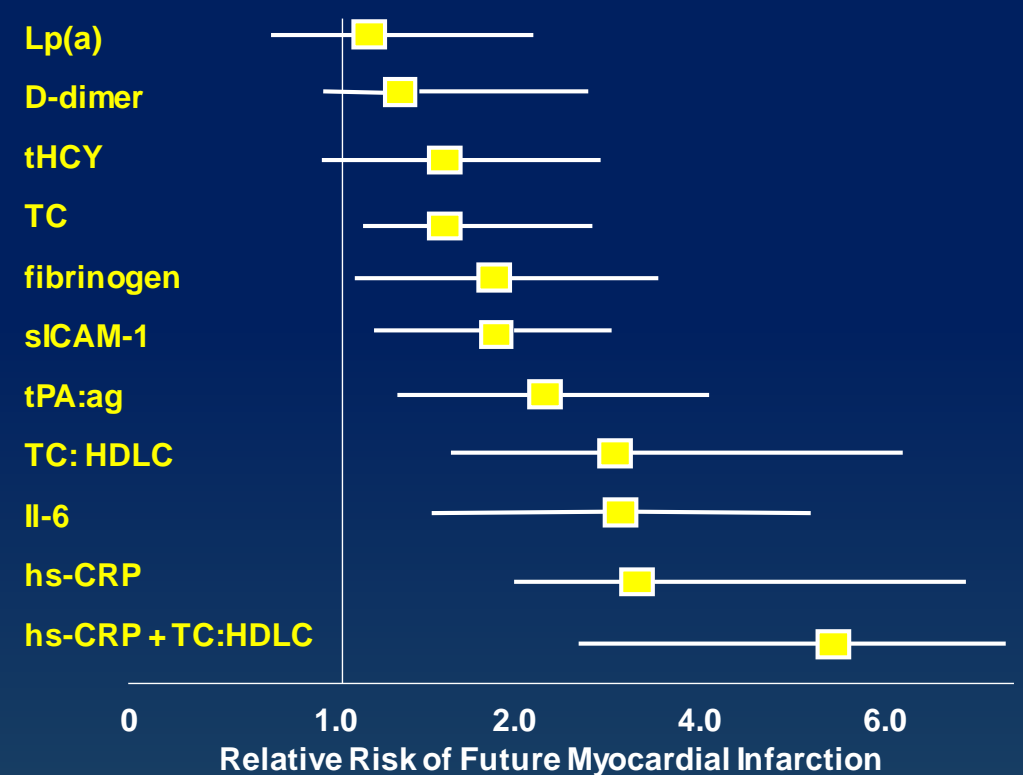
Inflammatory Biomarkers Predict Risk of Cardiovascular Events

Novel Risk Markers for Cardiovascular Events in Apparently Healthy Middle Aged Women



Ridker PM et al, NEJM 2000

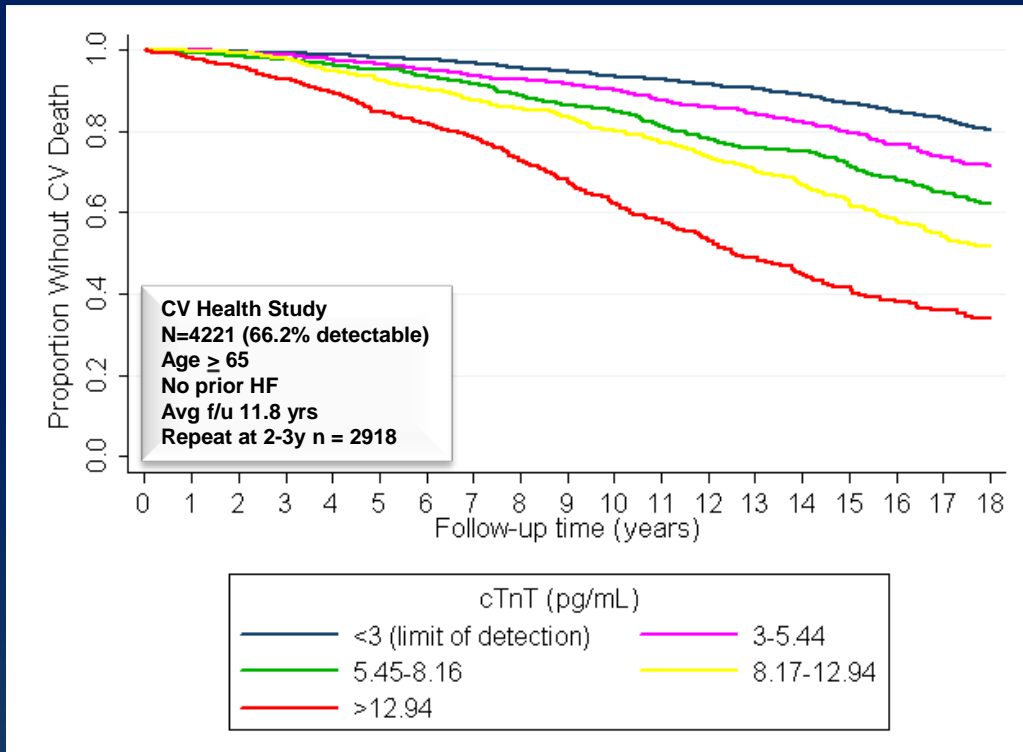
Novel Risk Markers for Myocardial Infarction in Apparently Healthy Middle Aged Men



Ridker PM. *Advances in Int Med* 2000;45:391-418

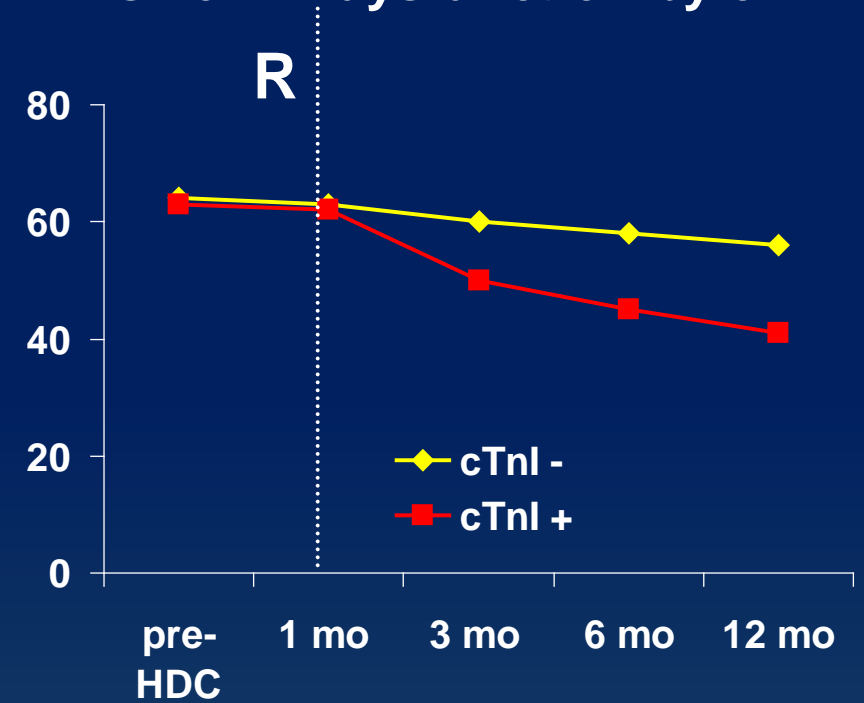
Myocardial Necrosis Biomarker: cTroponin in Cancer Chemotherapy

Risk of CV death, by cTnT



deFilippi C et al. JAMA 2010;304:2494-2502.

Risk of LV dysfunction by cTnT

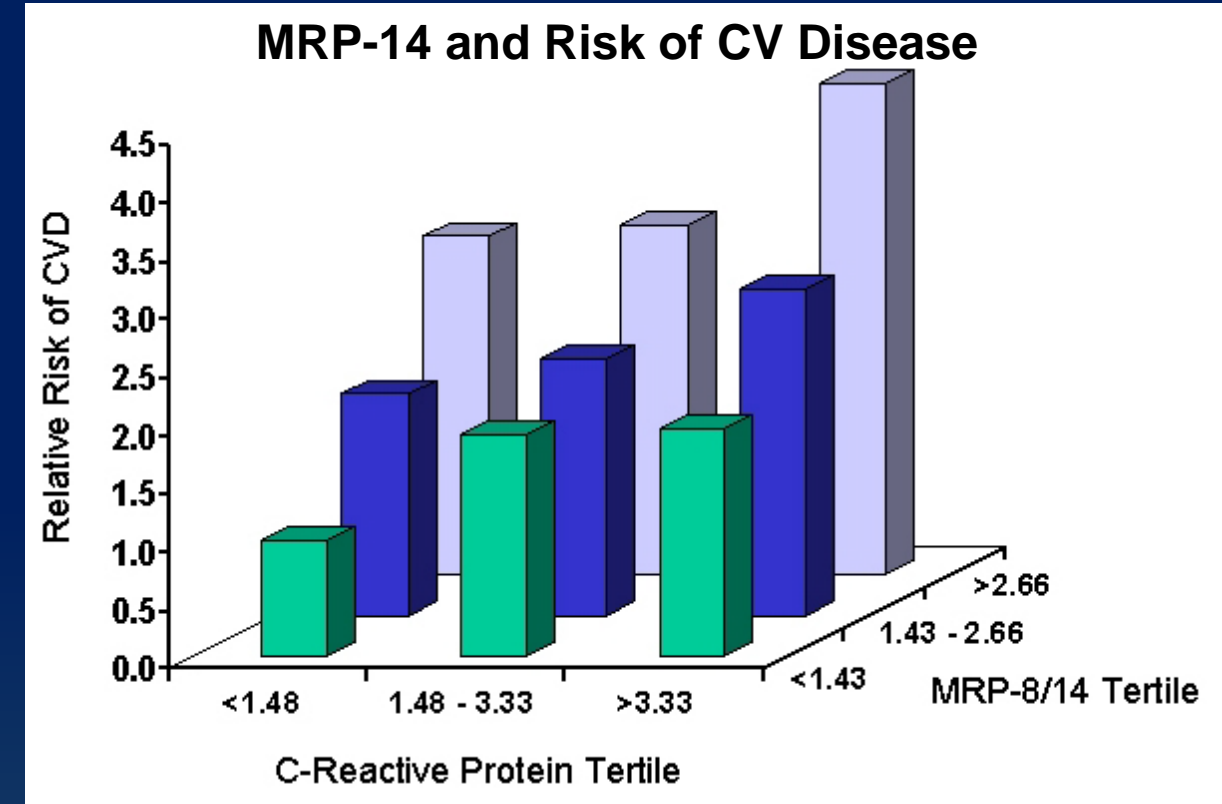


*cTnI increased in 114/473 pts receiving high dose chemo

Cardinale et al. Circulation 2006;114:2474-81

Clinical Phenotyping to Identify Novel CV Biomarkers

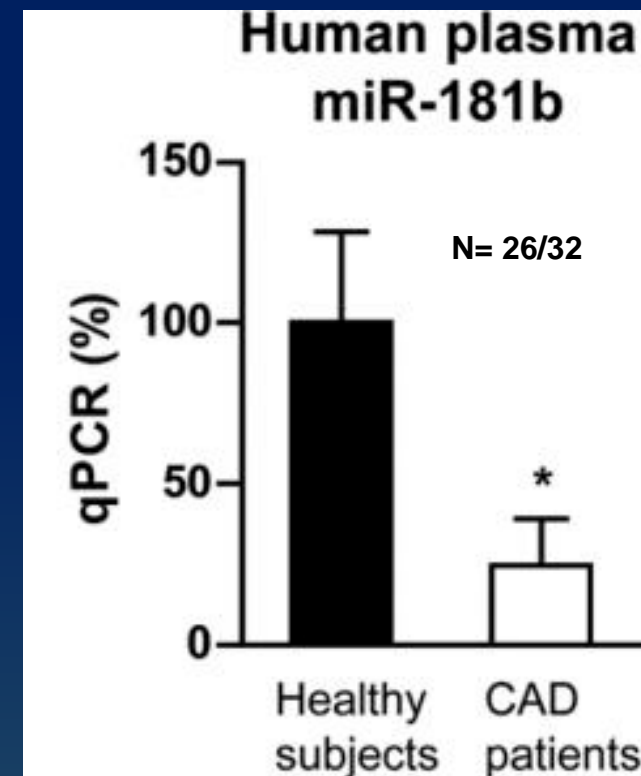
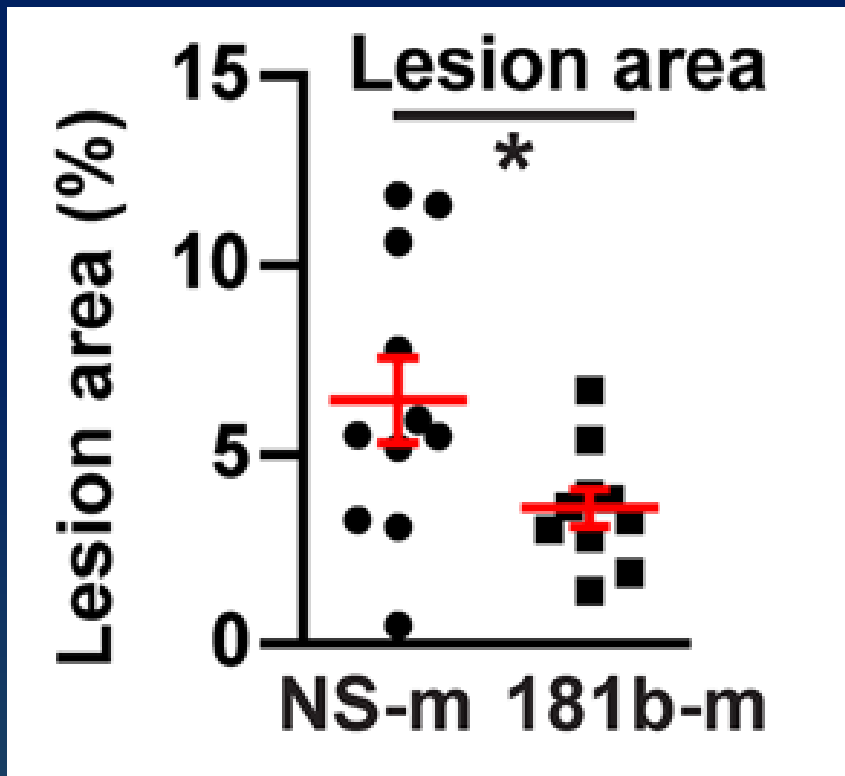
- Platelet mRNA Profiling
- Acute MI patients vs stable CAD patients
- Find :genes responsible for plaque rupture/MI
- 24 differentially regulated genes
- Lead candidate = MRP-14 (elevated in MI)
 - CVD biomarker (preclinical and humans)
 - regulates atherosclerosis
 - activates platelets through CD36



Healy, A. *Circulation* 2006
Croce, K. *Circulation* 2009
Schmizu, K. *Circulation* 2011
Maiseyeu A. *ATVB* 2012
Wang, Y. *J Clin Invest* 2014

Micro RNAs: Novel Circulating Biomarkers of Cardiovascular Disease

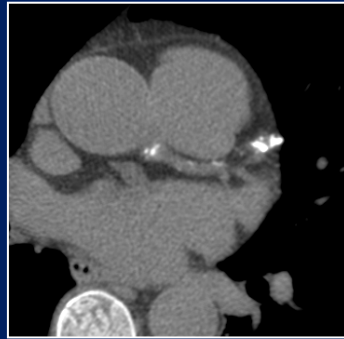
- miR-181b novel inhibitor of atherosclerosis, regulates EC inflammation
- inhibited the expression of importin- α 3 which supports NF- κ B inflammatory function



Imaging Biomarkers:

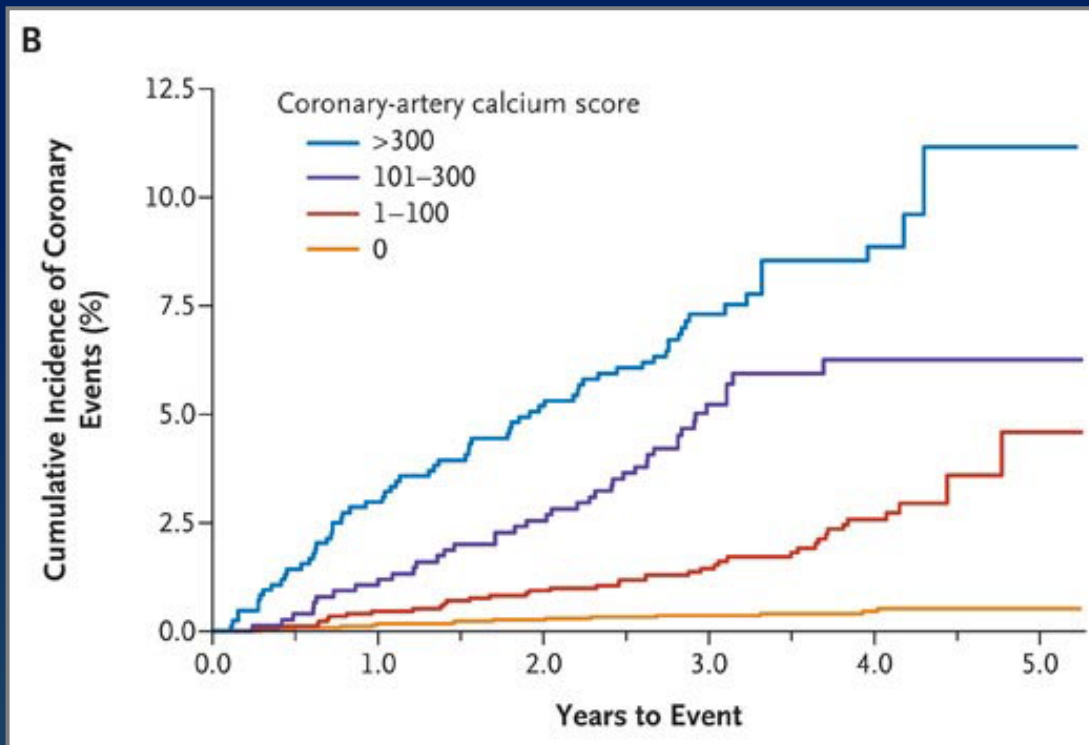
- **Structural**
- **Structural / functional**
 - **Inflammation imaging**
 - **Ischemia / perfusion imaging**

Coronary Artery Calcium Score:

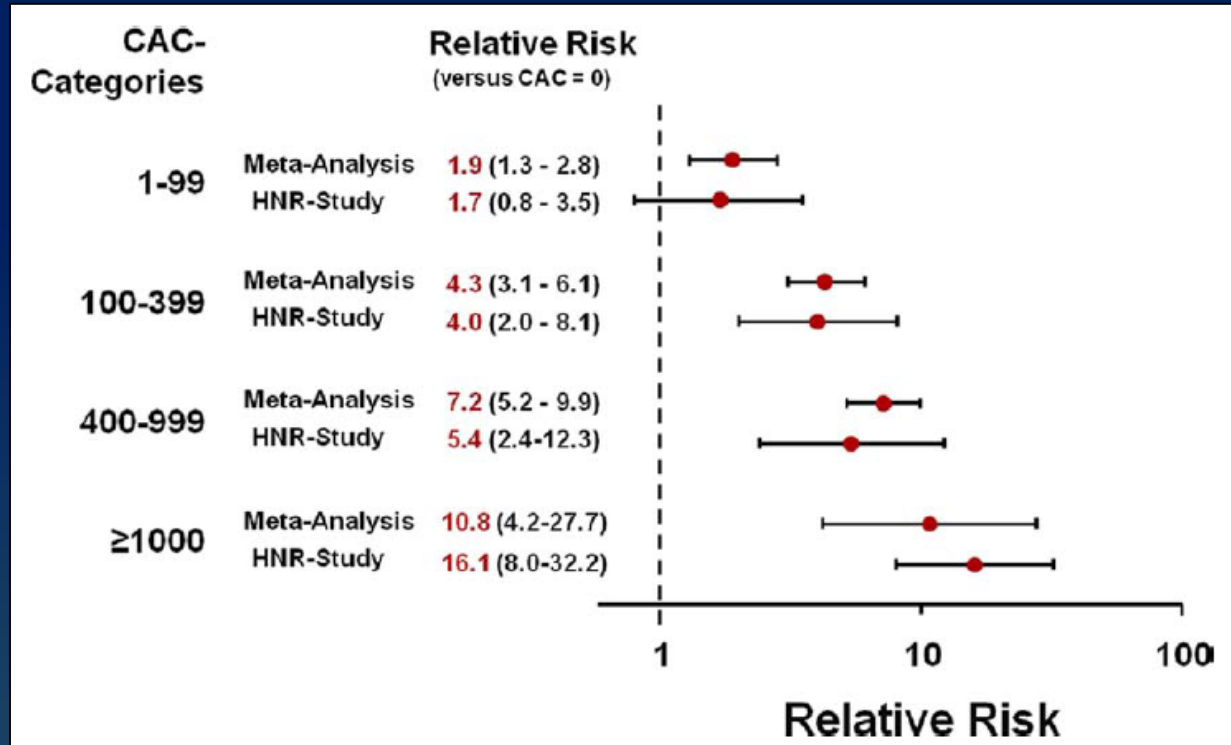


Report: Agatston calcium score

Multi-Ethnic Study of Atherosclerosis



Heinz Nixdorf Recall Study



CT Angiography of Coronary Arteries:



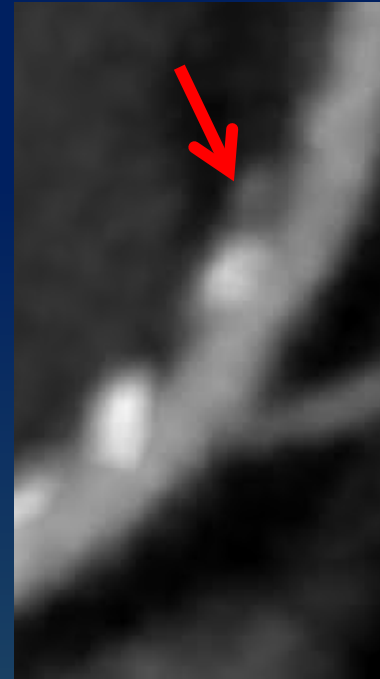
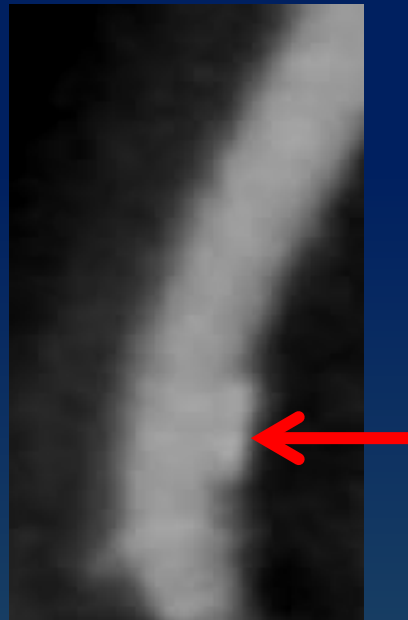
Extent of disease

**Minimal
(0-25%)**

**Mild
(25-49%)**

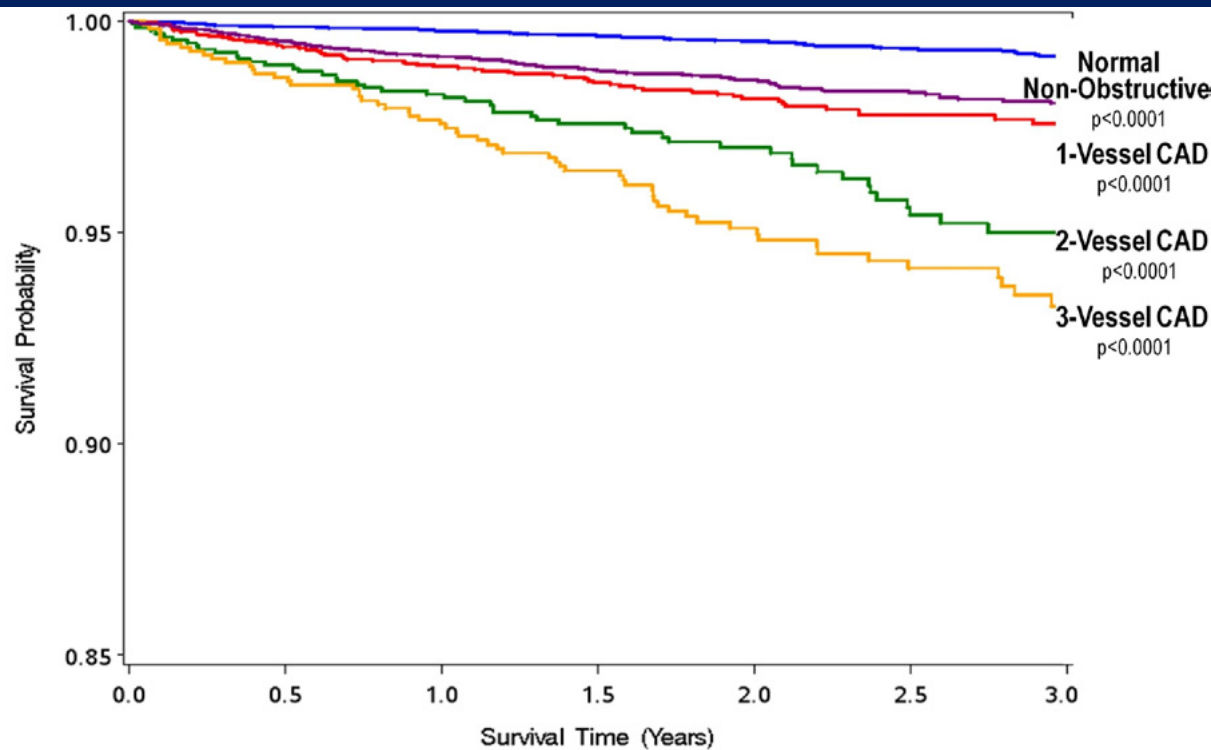
**Moderate
(50-69%)**

**Severe
(>70%)**



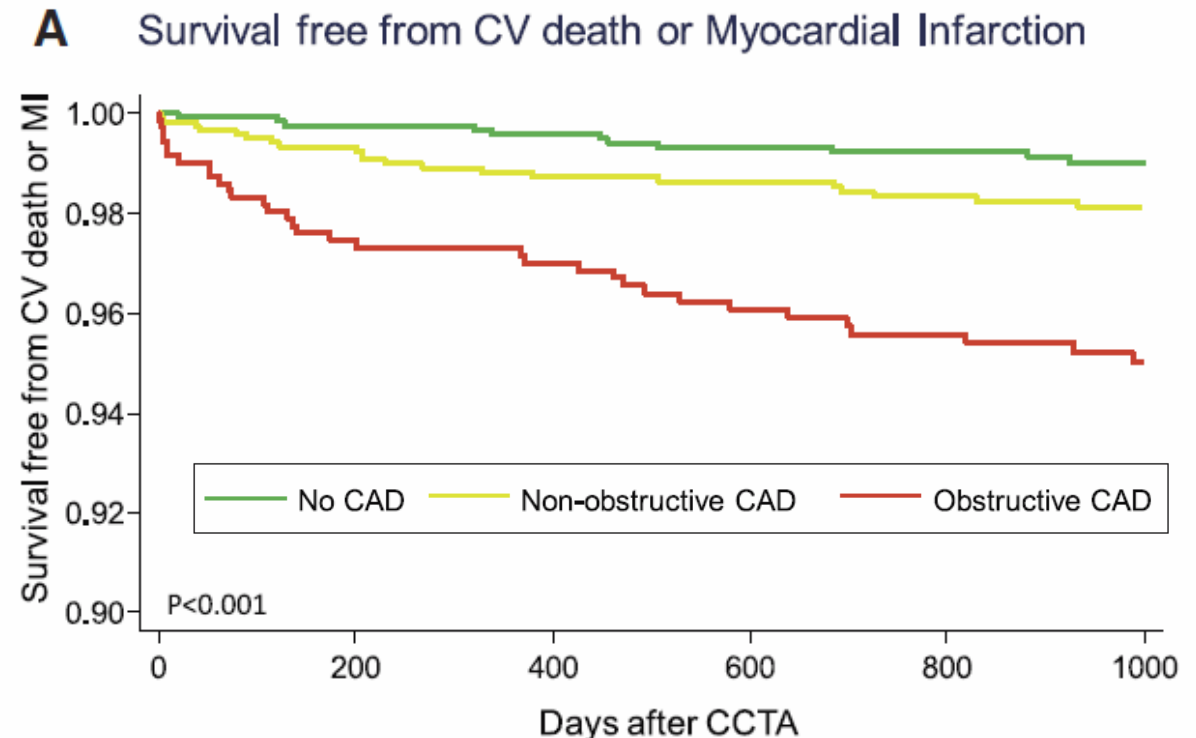
Coronary CT Angiography: Disease Burden Predicts Outcomes

CONFIRM Registry 23,854 patients



Min JACC 2011

MGH/BWH Registry N=3242 patients
mean f/u 3.6 years
1^o outcome: CV death / MI



Bittencourt, Circulation CV Imaging 2014

Non-obstructive plaque → increased risk of CV death / MI

Myocardial Perfusion and FDG PET: Functional and Structural Imaging

Normal Study

Normal myocardial perfusion
and no FDG uptake

Perfusion



F18-FDG



Perfusion



F18-FDG



Perfusion



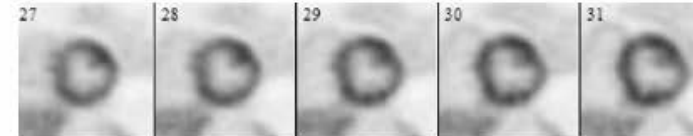
F18-FDG



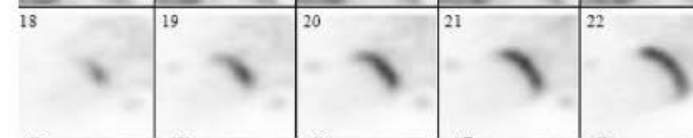
Cardiac Sarcoidosis

Abnormal myocardial perfusion
and focal FDG uptake

Perfusion



F18-FDG



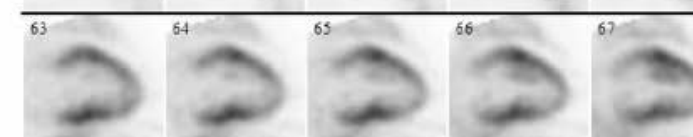
Perfusion



F18-FDG



Perfusion



F18-FDG



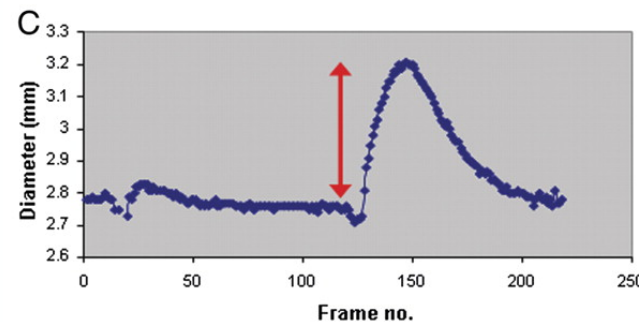
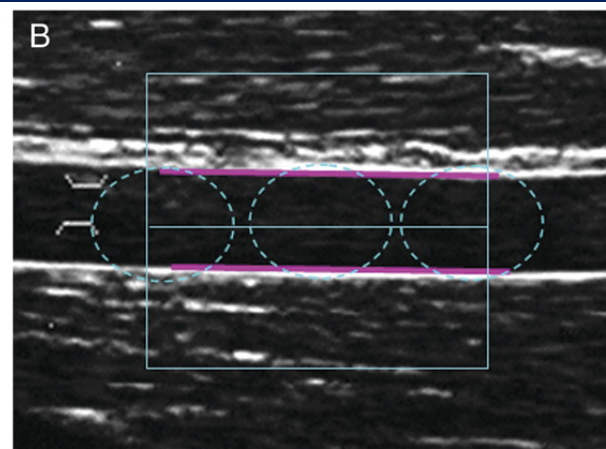
Physiologic Cardiovascular Biomarkers:

- Blood pressure / heart rate
- Heart rate recovery after exercise
- Endothelial function

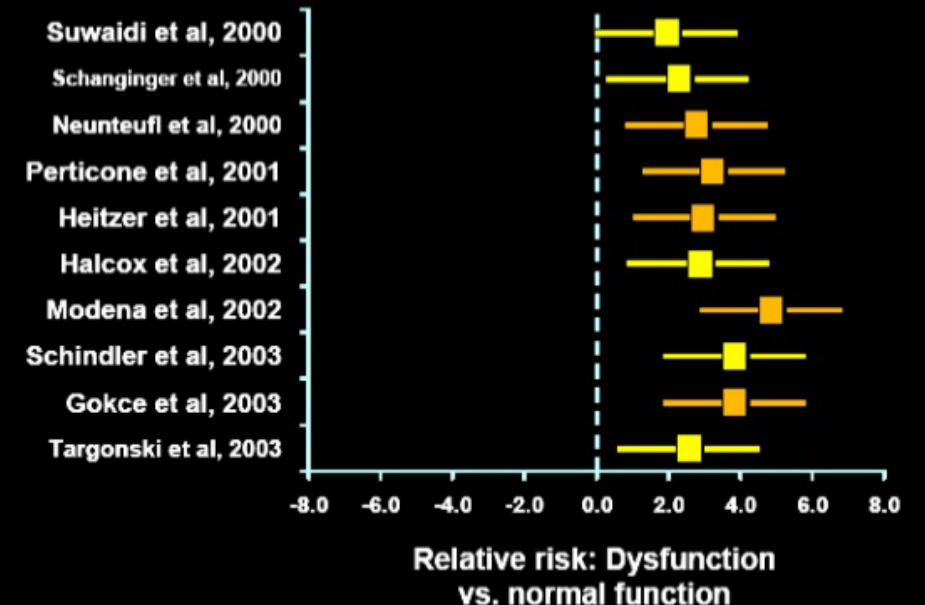
Quantifying Endothelial Function in Humans

Brachial artery flow-mediated dilation

- Metric of endothelial dysfunction.
- Correlates with coronary flow-mediated dilation.
- Predicts long-term CV events.

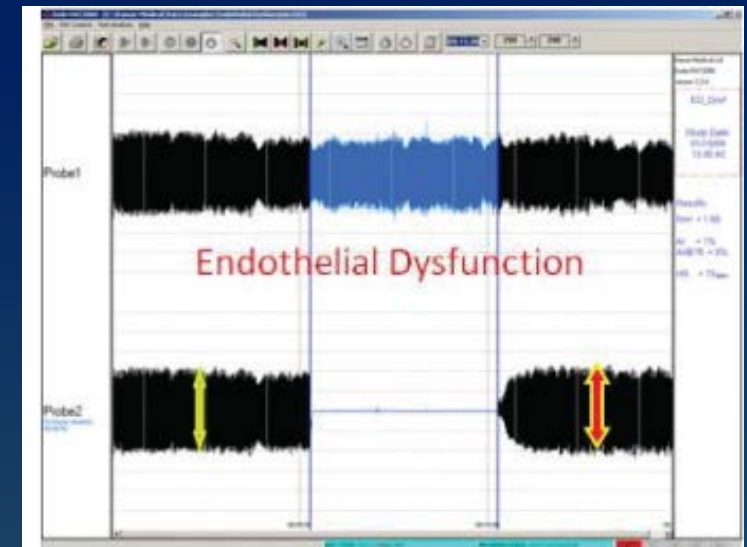
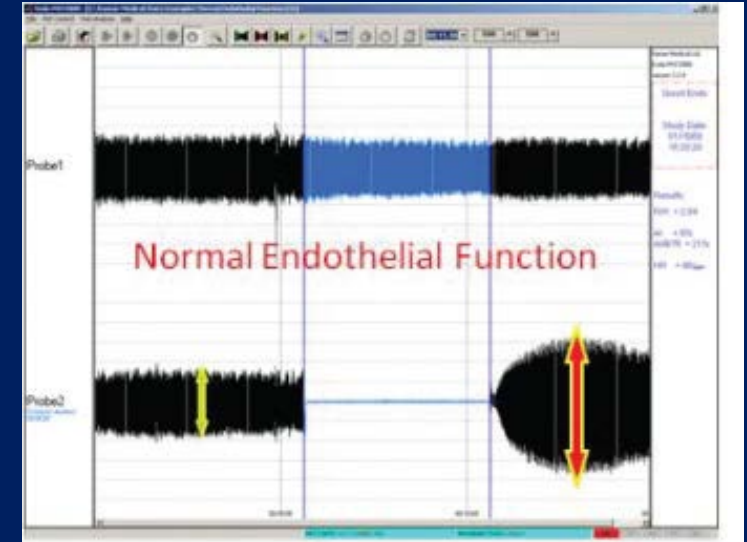


Prediction of future cardiovascular events by measurement of endothelial function



Quantifying Endothelial Function in Humans

- Endo-PAT
 - endothelial mediated vasodilation
 - reactive hyperemia index



Summary

- The pathobiology of vascular disease is complex process that involves multiple cell types.
- Inflammation and endothelial dysfunction are common to all vascular pathologies.
- Vascular events can arise from dysregulation any of a several homeostatic processes (athero, spasm, intimal obliteration).
- The complex pathobiology of vascular disease creates challenges in predicting whether a targeted cancer therapy will have adverse cardiovascular effects.
- Cardiovascular biomarkers track the molecular and structural processes that underlie the pathobiology of vascular disease.
- Biomarkers predict risk of vascular events and can in some cases inform about vascular disease mechanism.
- Biomarker limitations include poor ability to identify individual patients who will experience a vascular event.