Can Biomarkers be Used to Assess Risk of Vascular Cardiotoxicity?

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Presenter Disclosure Information

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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
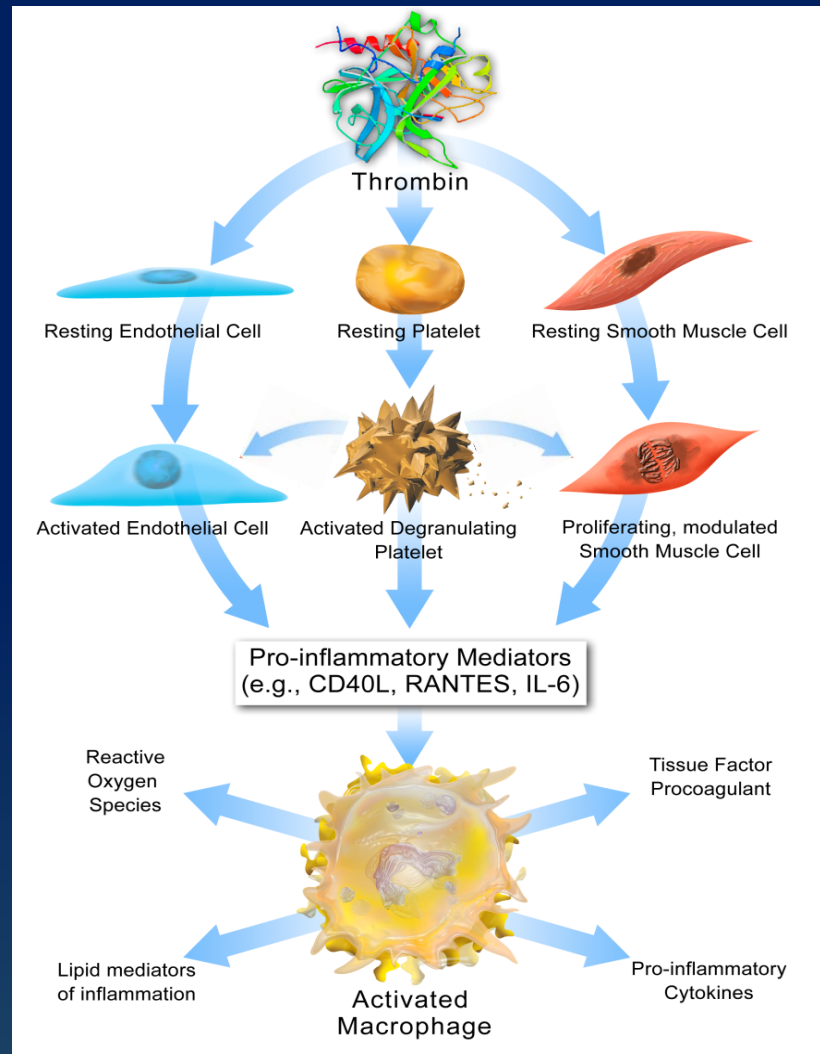
- 55 y.o female under treatment for pancreatic cancer
- On FOLFIRINOX- includes fluorouracil (5-FU), a pyrimidine analog antimetabolite (non targeted)

- Presented with chest pain and ST elevation MI
- Treated with coronary stenting, recovered, now starting alternate cancer therapy
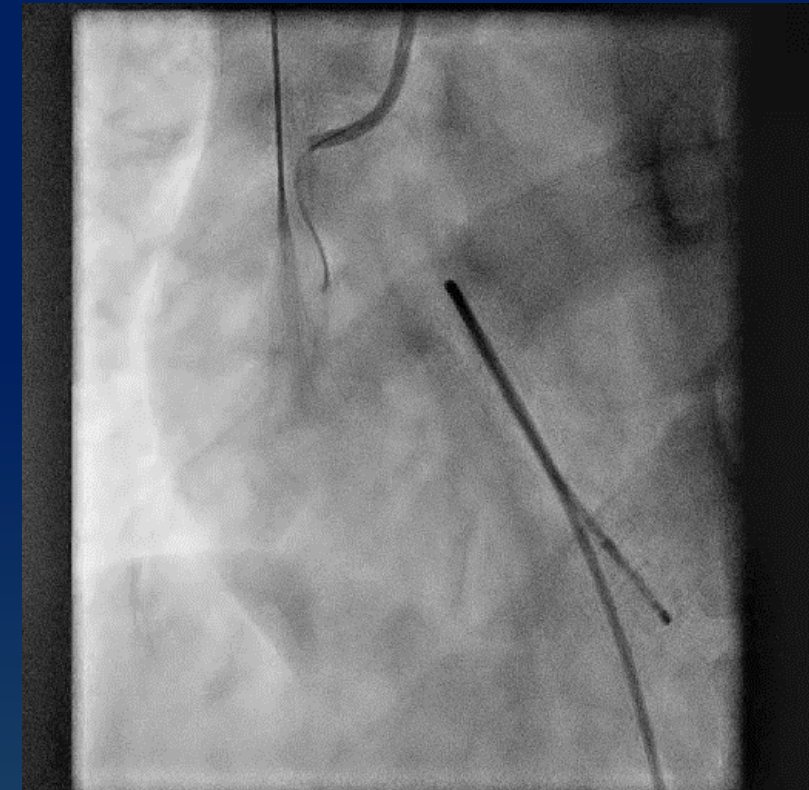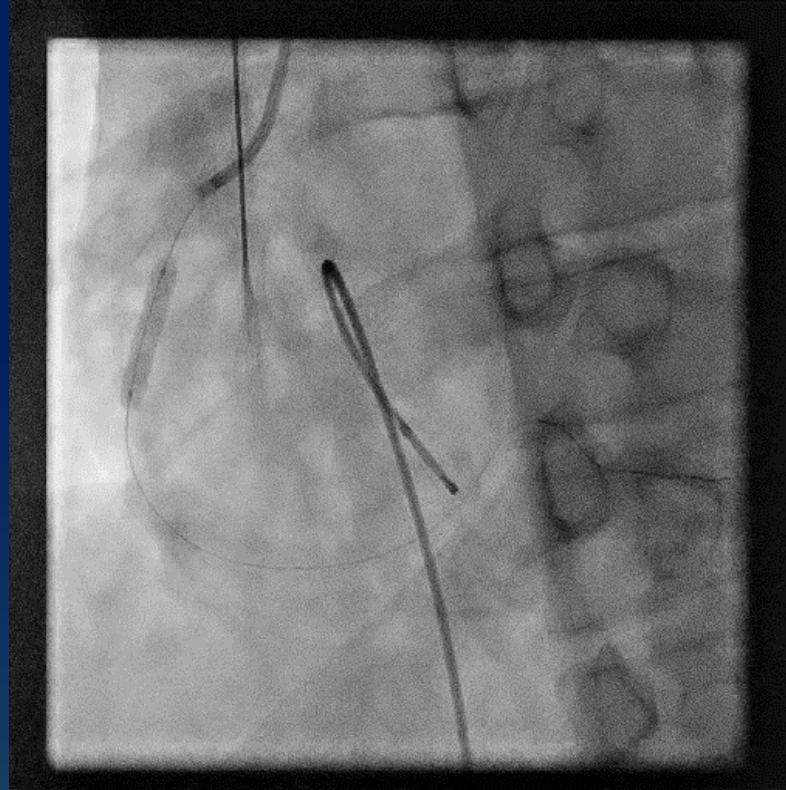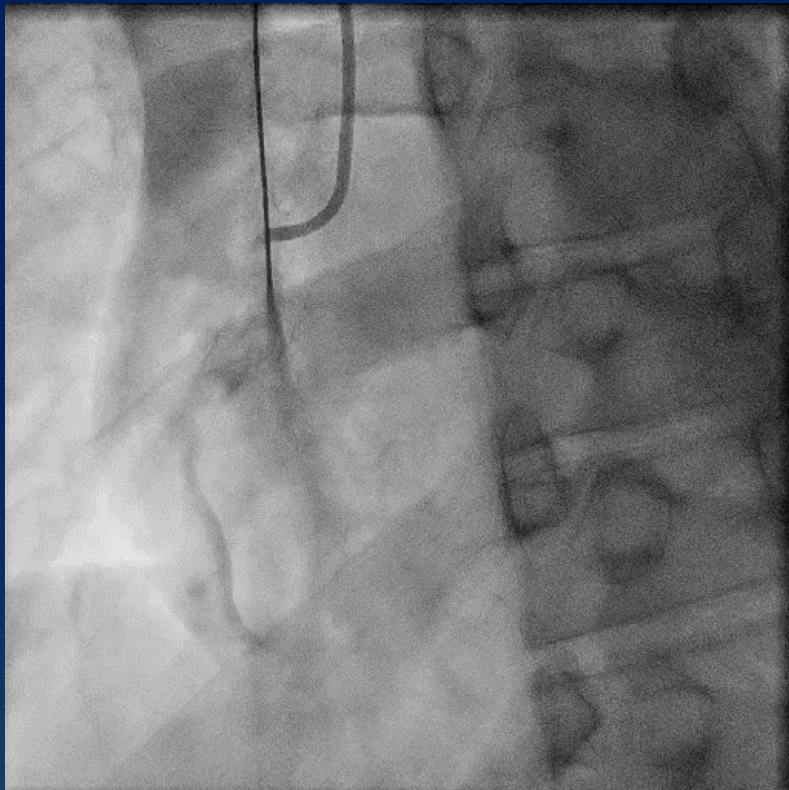
Mechanism: possible 5-FU effect on endothelial function

Arterial Thrombosis is Complicated:

## Inflammation and Thrombotic Pathways Intertwine in Vascular Pathobiology

Thrombin

Resting Endothelial Cell — Resting Platelet — Resting Smooth Muscle Cell

Activated Endothelial Cell — Activated Degranulating Platelet — Proliferating, modulated Smooth Muscle Cell

Pro-inflammatory Mediators (e.g., CD40L, RANTES, IL-6)

Reactive Oxygen Species — Tissue Factor Procoagulant

Lipid mediators of inflammation — Pro-inflammatory Cytokines

Activated Macrophage

Molecular and cellular pathways link thrombotic and inflammatory processes.

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

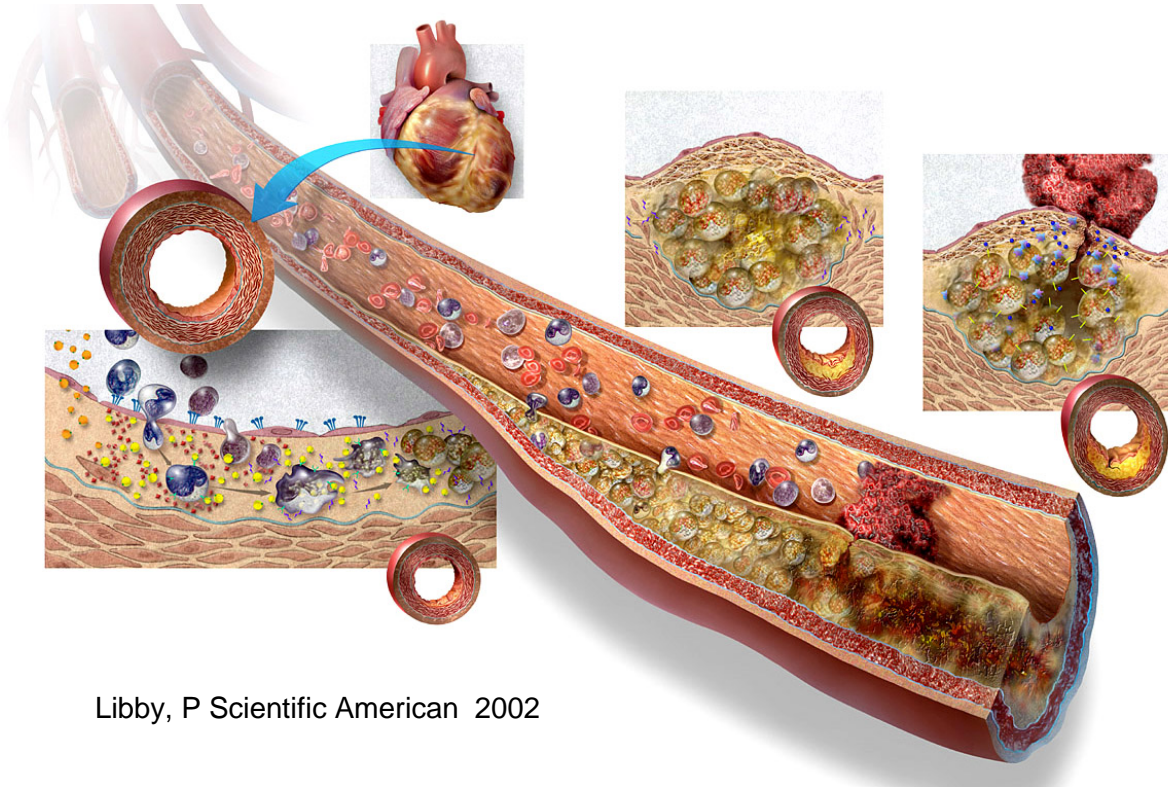# Novel Cancer Therapies: Mechanisms of Vascular Toxicity

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**
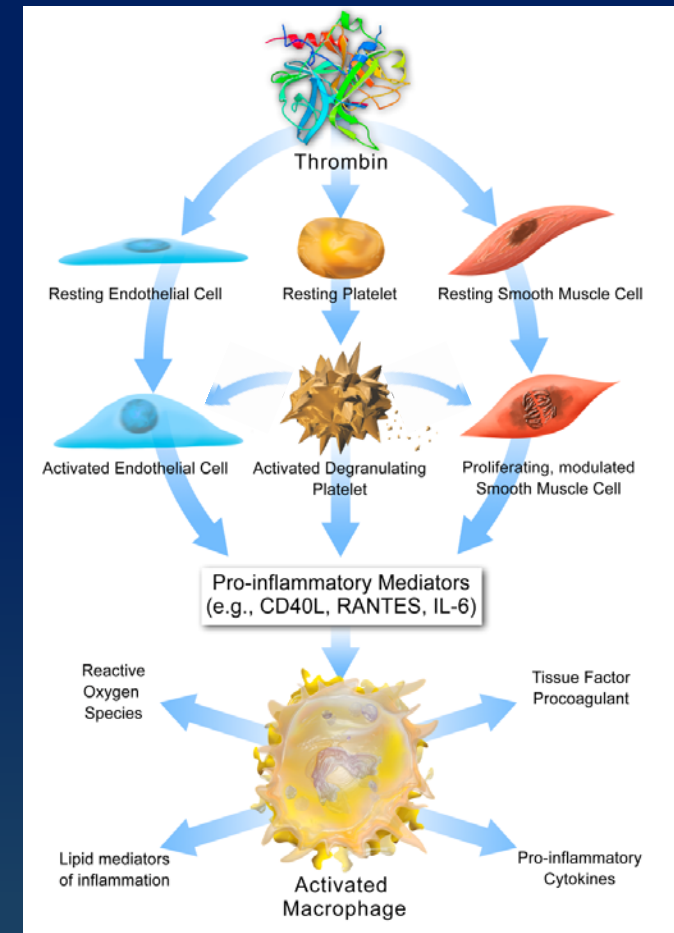
Novel Cancer Therapies: Mechanisms of Vascular Toxicity

Heterogeneous Mechanisms:
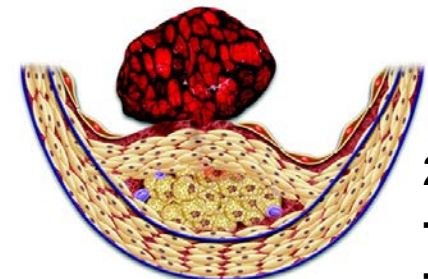**atherogenic, plaque destabilizing, prothrombotic**

Atherosclerotic Vasculopathy

Libby, P Scientific American 2002

Atherothrombotic Vasculopathy

75% MIs
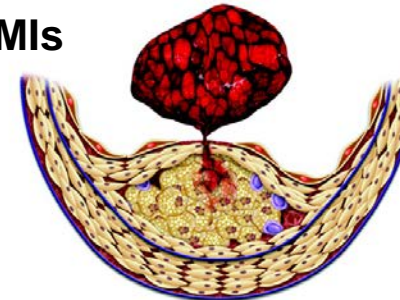
25% MIs
-DM
-Females

Rupture of Fibrous Cap

Superficial Erosion
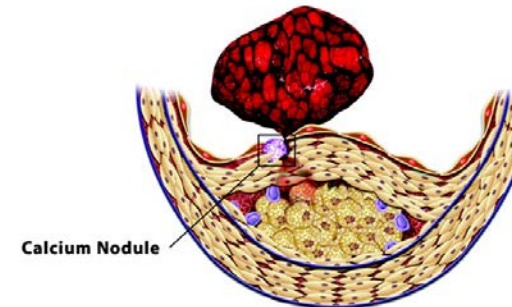
Erosion of Calcium Nodule
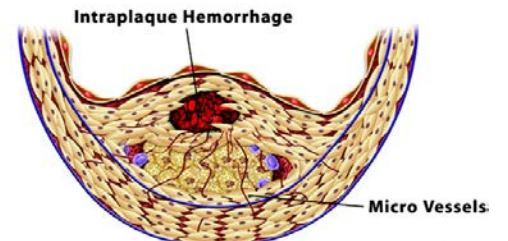
Intraplaque Hemorrhage

Calcium Nodule

Intraplaque Hemorrhage

Micro Vessels

Novel Cancer Therapies: Mechanisms of Vascular Toxicity
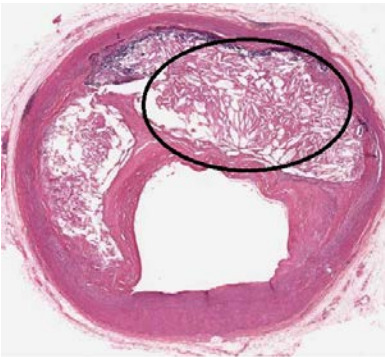
Heterogeneous Mechanisms: proliferative, vasospastic
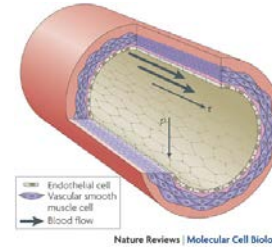
Proliferative Vasculopathy
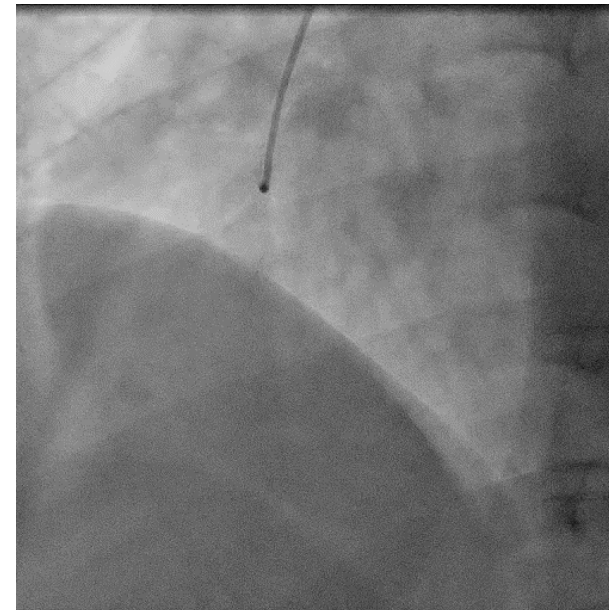
Proliferative
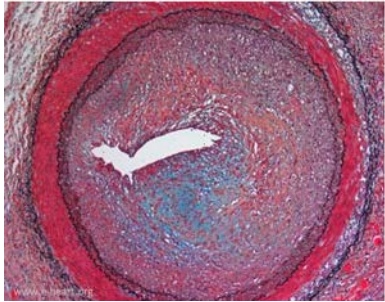
Vs.

Atherosclerotic

Nilotinib PAOD

Am. J. Hematol. 86:533–539, 2011

Vasospastic Vasculopathy

Endothelial cell
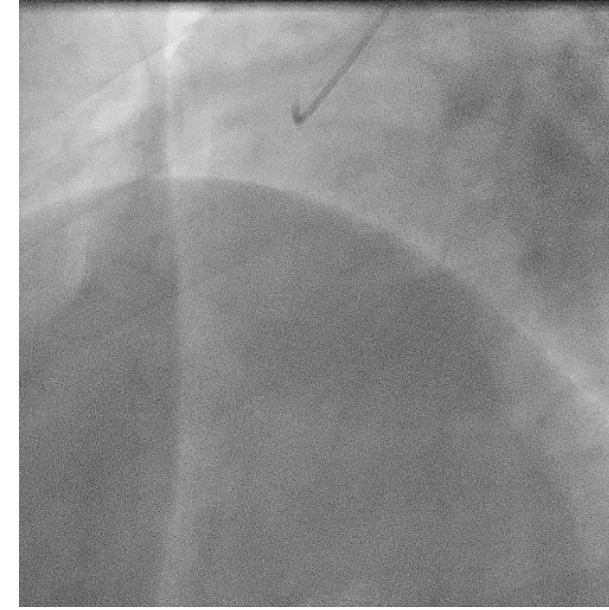Vascular smooth muscle cell
Blood flow
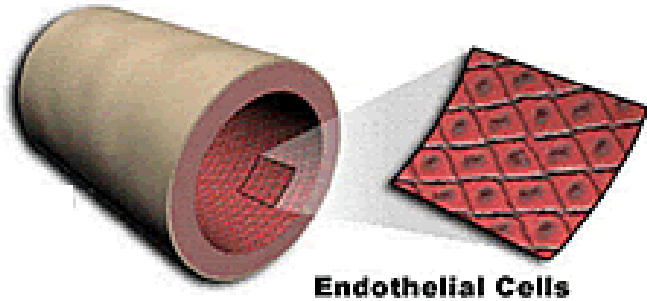
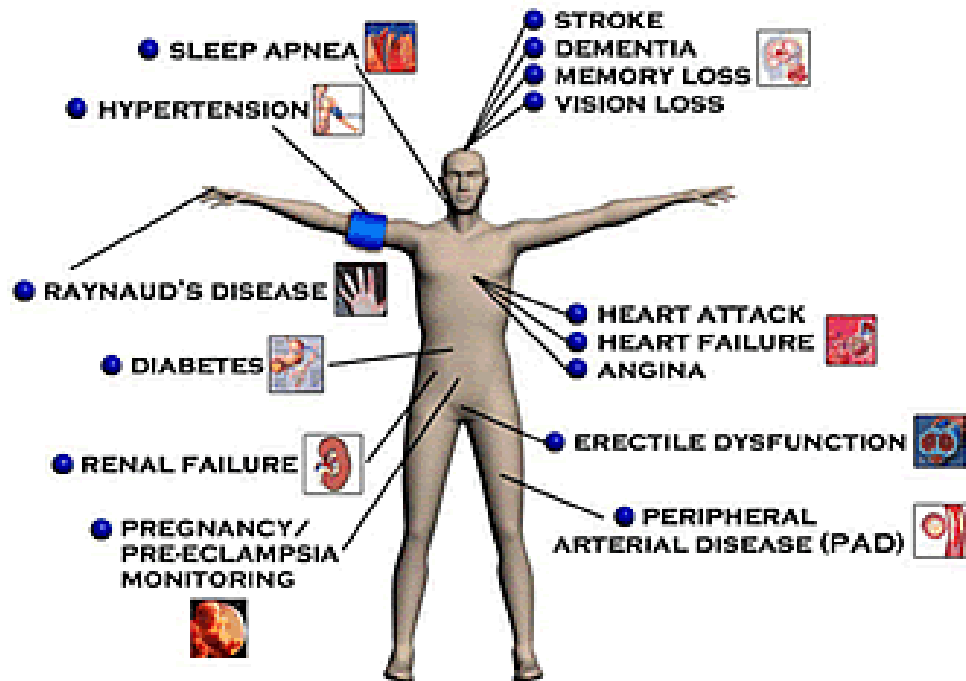Nature Reviews | Molecular Cell Biology

Initial Angio

After IC Nitro

Endothelial Dysfunction:
Central in the Pathobiology of Vascular Disease
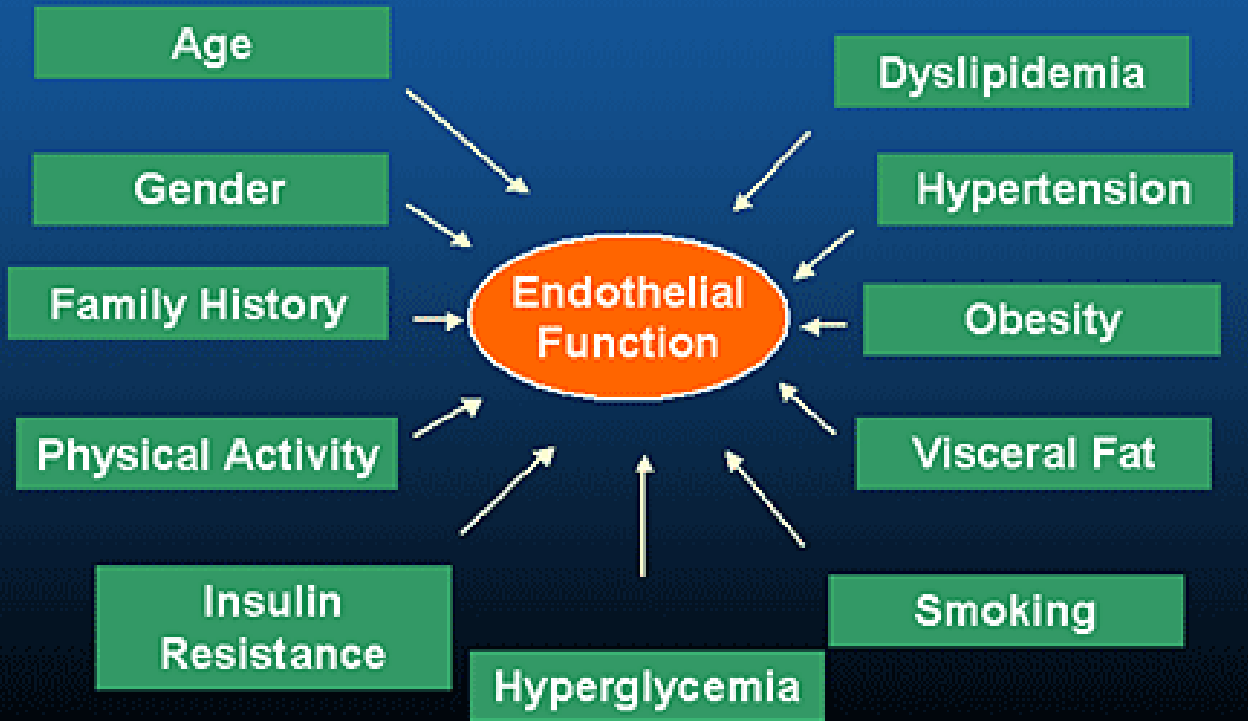
Endothelial Dysfunction: Central in the Pathobiology of Vascular Disease

Endothelial injury -inciting event predisposes to atherosclerosis and thrombosis

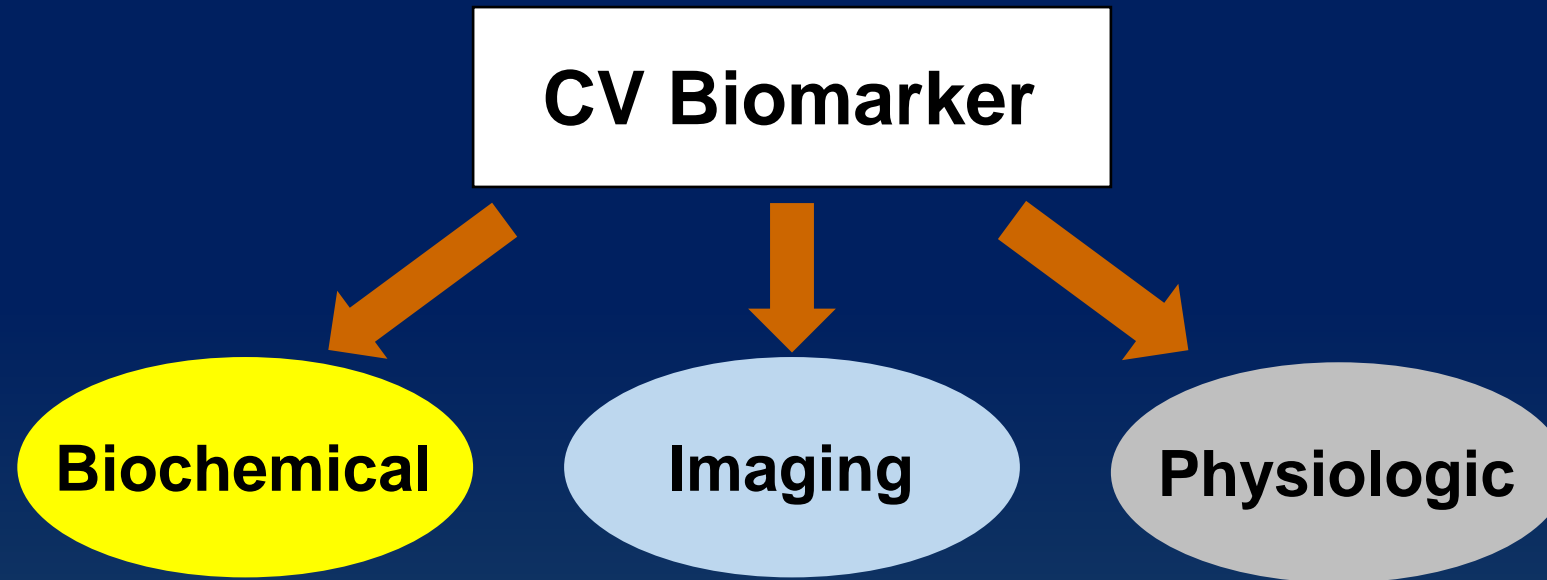**Endothelial nitric oxide (NO) critically regulates vascular Health**
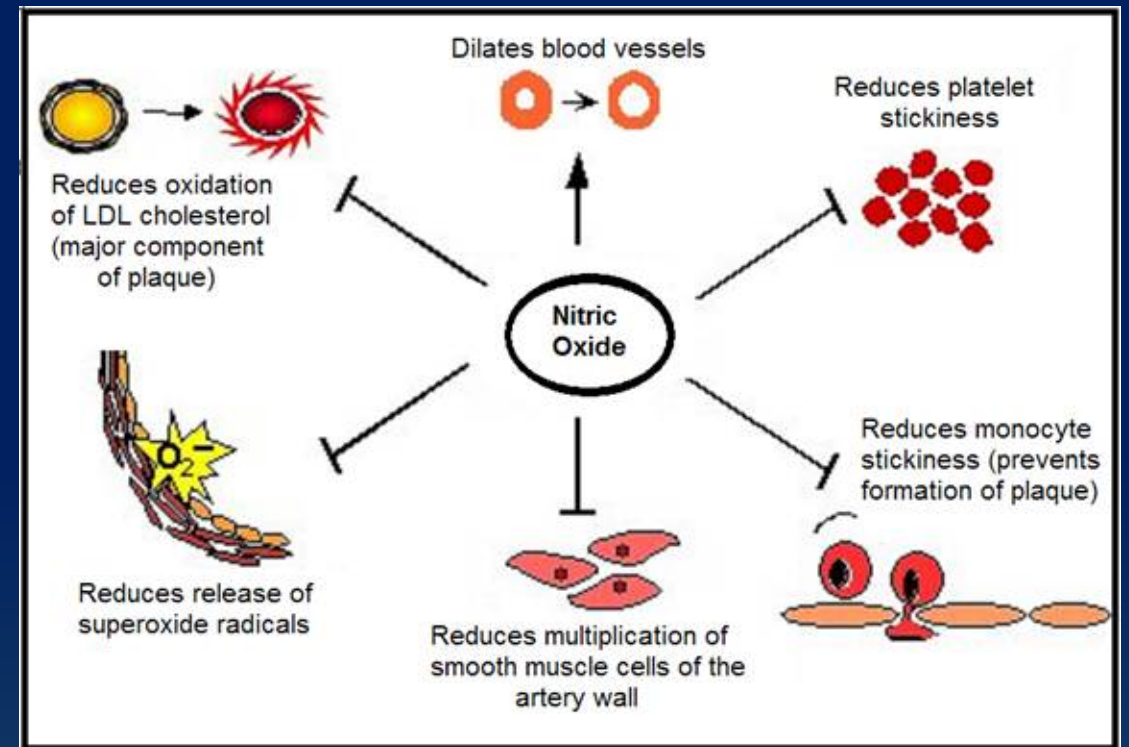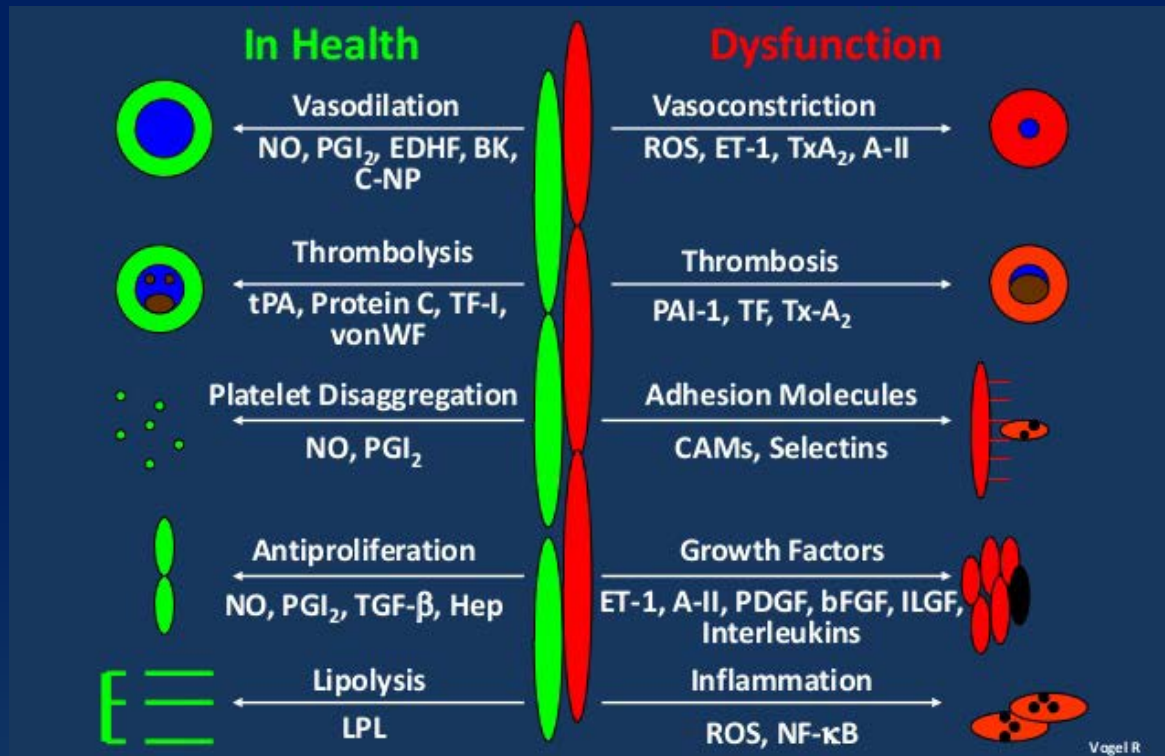
- Decreased NO bioavailability indicative of endothelial dysfunction and damage.
- NO dysregulation one of the earliest events in all types of vascular pathology.

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**

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              ┌─────────────────┐
              │  CV Biomarker   │
              └─────────────────┘
           ↙          ↓          ↘
    Biochemical    Imaging    Physiologic
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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**
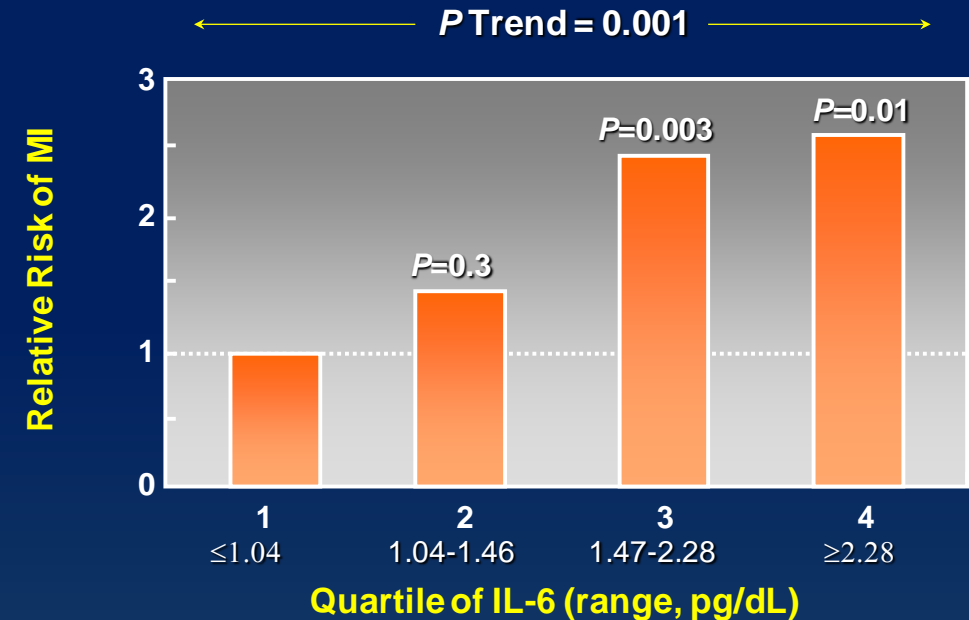
- **Epigenetic markers**

- **Multimarker strategies**

Inflammatory Biomarkers Predict Risk of Cardiovascular Events
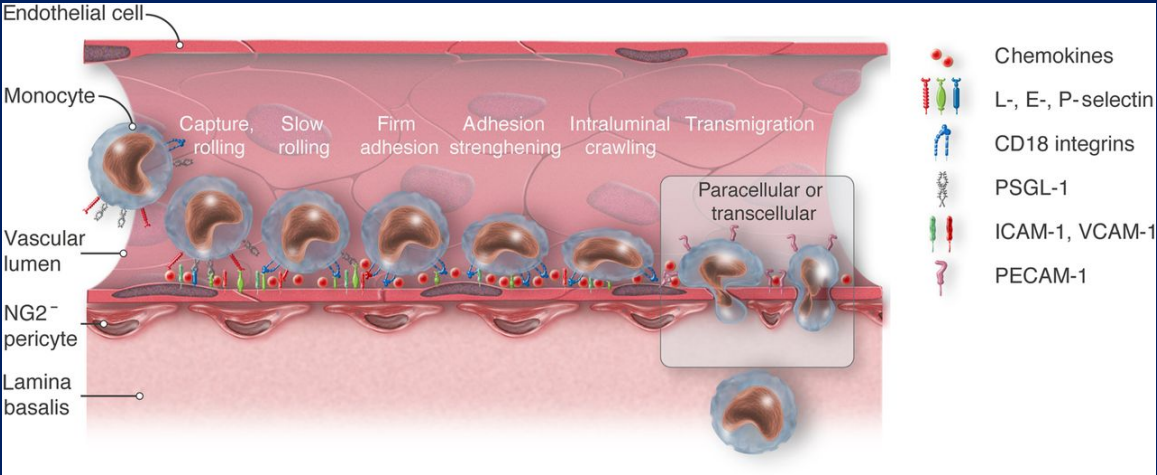

hs-CRP is Specific for Cardiovascular Events

Risk of Cardiovascular Death — Quartile of hs-CRP

Risk of Non-Cardiovascular Death — Quartile of hs-CRP
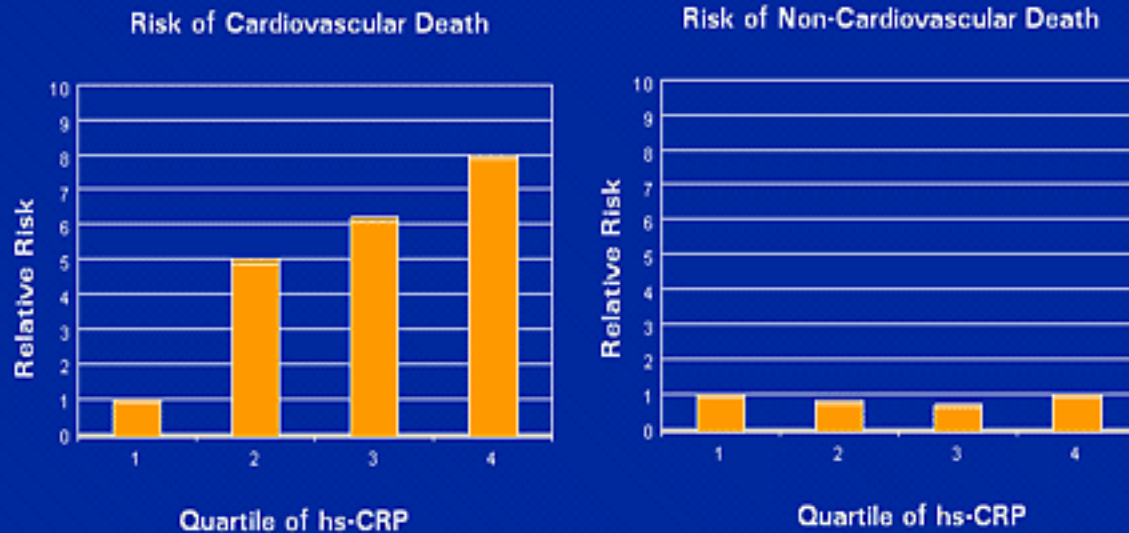
Tice A et al, Am J Med 2003;114;199-205

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

P Trend = 0.001

Relative Risk of MI

P=0.3 P=0.003 P=0.01

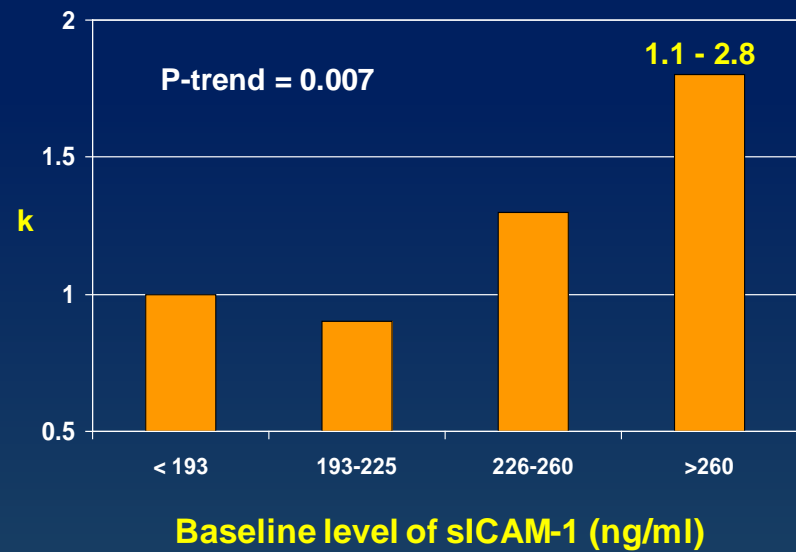| 1	2	3	4
≤1.04	1.04-1.46	1.47-2.28	≥2.28

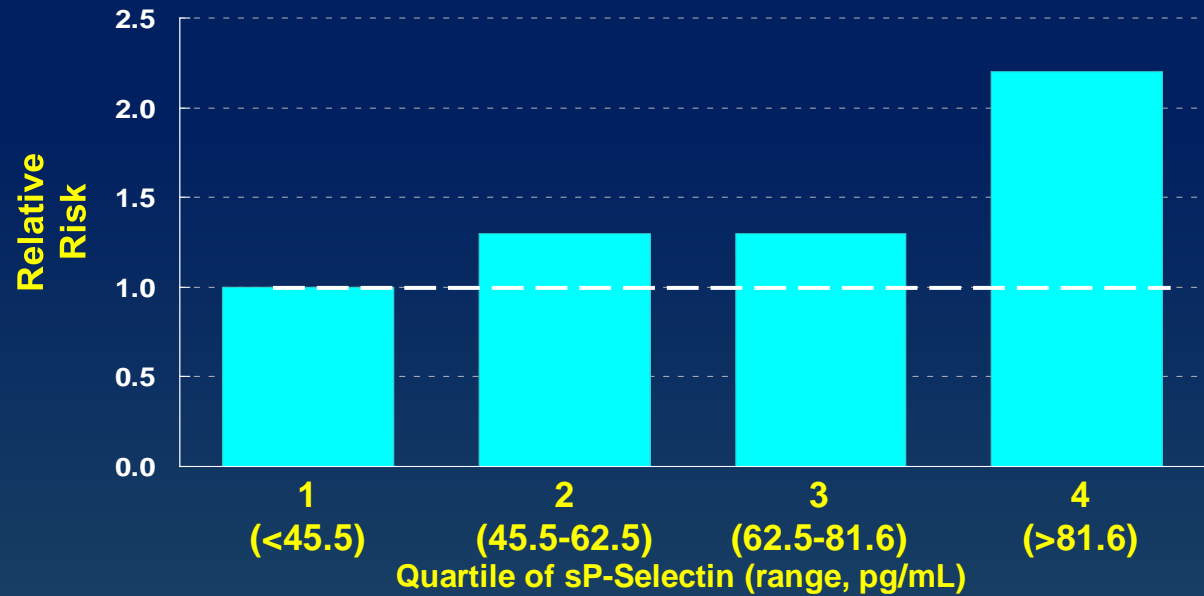Quartile of IL-6 (range, pg/dL)

Ridker PM. Circulation, 2000

Inflammatory Biomarkers Predict Risk of Cardiovascular Events

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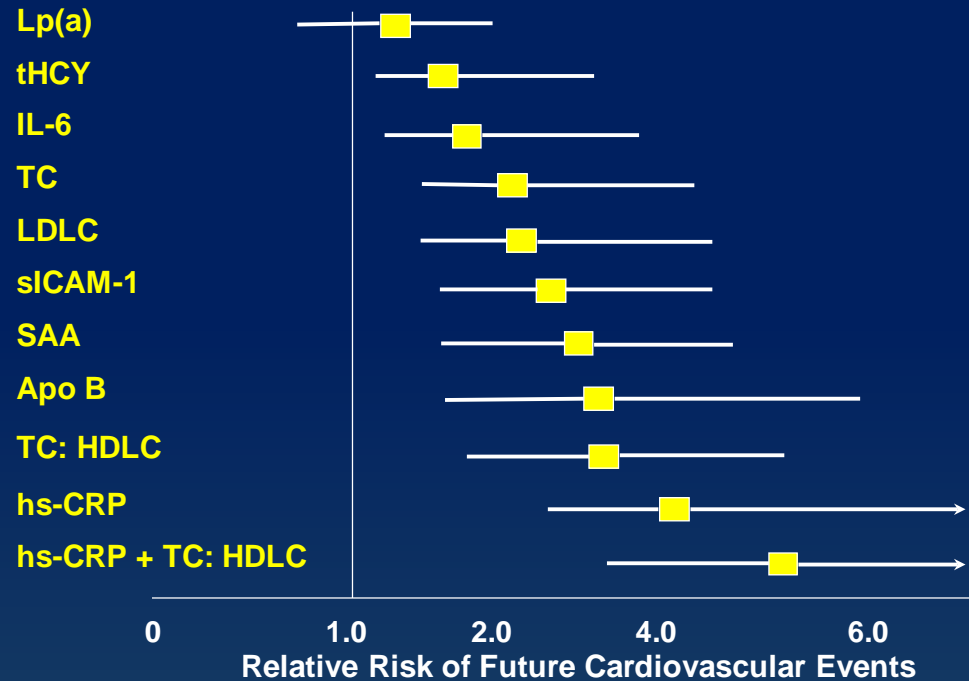

P-trend = 0.007

1.1 - 2.8

k

Baseline level of sICAM-1 (ng/ml)

(< 193, 193-225, 226-260, >260)

51:88-92

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

Relative Risk

Quartile of sP-Selectin (range, pg/mL)

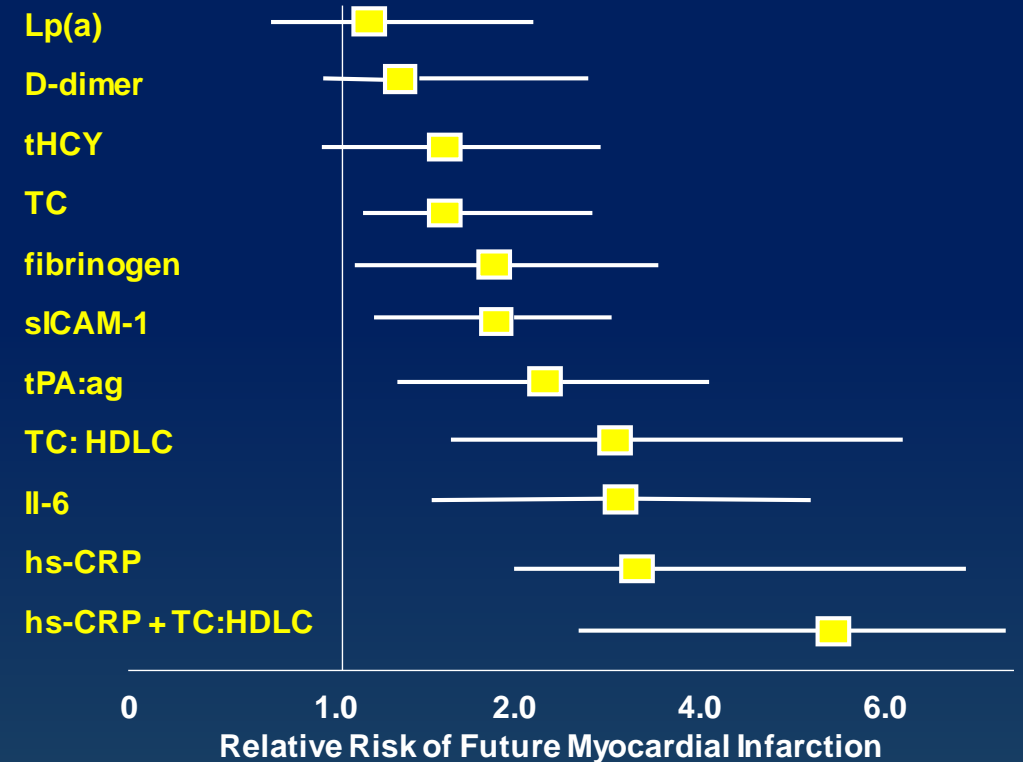| 1 (<45.5) | 2 (45.5-62.5) | 3 (62.5-81.6) | 4 (>81.6) |

Ridker, Buring, Rifai. Circulation 2001

Inflammatory Biomarkers Predict Risk of Cardiovascular Events

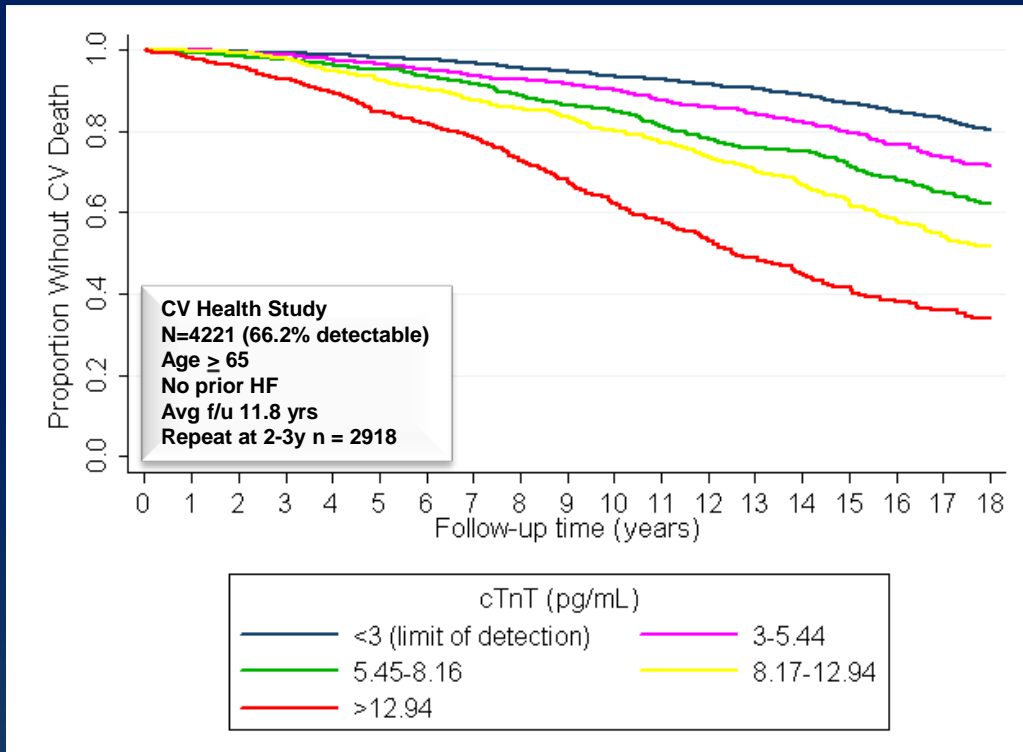**Novel Risk Markers for Cardiovascular Events in Apparently Healthy Middle Aged Women**

Lp(a)
tHCY
IL-6
TC
LDLC
sICAM-1
SAA
Apo B
TC: HDLC
hs-CRP
hs-CRP + TC: HDLC

Relative Risk of Future Cardiovascular Events

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

Lp(a)
D-dimer
tHCY
TC
fibrinogen
sICAM-1
tPA:ag
TC: HDLC
Il-6
hs-CRP
hs-CRP + TC:HDLC

Relative Risk of Future Myocardial Infarction

Ridker PM et al, NEJM 2000

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

Myocardial Necrosis Biomarker: cTroponin in Cancer Chemotherapy

Risk of CV death, by cTnT

Risk of LV dysfunction by cTnT
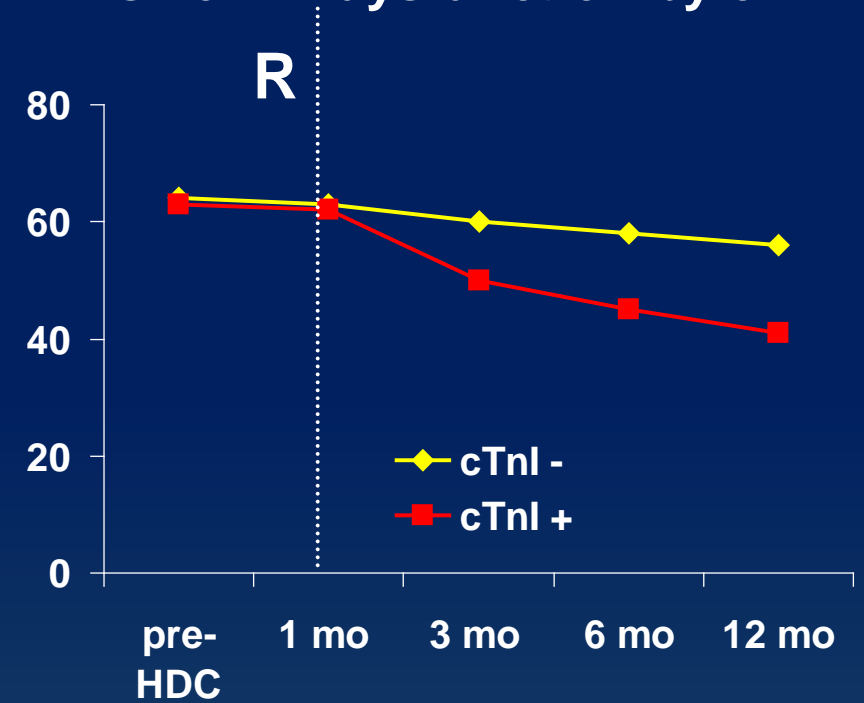
cTnl increased in 114/473 pts receiving high dose chemo

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

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

MRP-14 and Risk of CV Disease

Relative Risk of CVD (y-axis: 0.0, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5)

C-Reactive Protein Tertile (x-axis: <1.48, 1.48 - 3.33, >3.33)

MRP-8/14 Tertile (depth axis: <1.43, 1.43 - 2.66, >2.66)
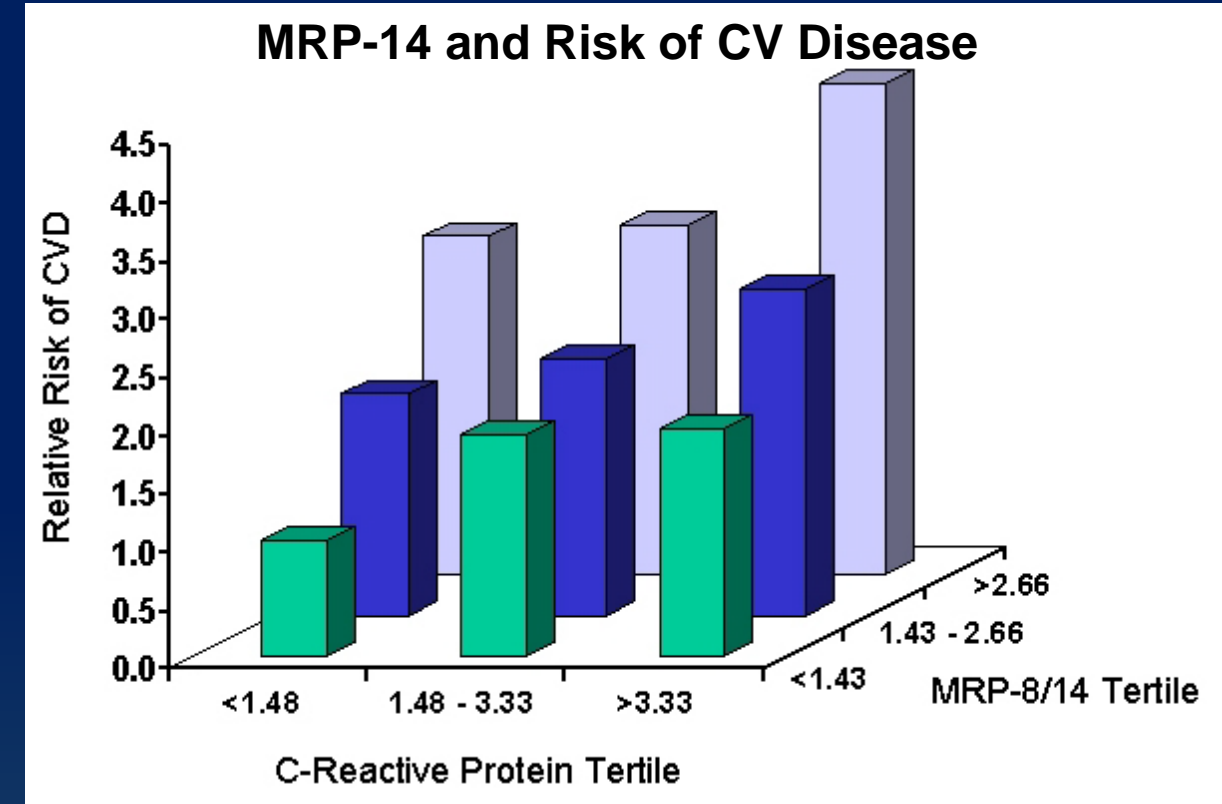
Healy, A. Circulation 2006
Croce, K. Circulation 2009
Schmizu, K. Circulation 2011
Maiseyeu A . ATVB 2012
Wang, Y. J Clin Invest 2014

# Micro RNAs: Novel Circulating Biomarkers of Cardiovascular Disease

- miR-181b novel inhibitor of atherosclerosis, regulates EC inflammation

- inhibited the expression of importin-α3 which supports NF-κB inflammatory function
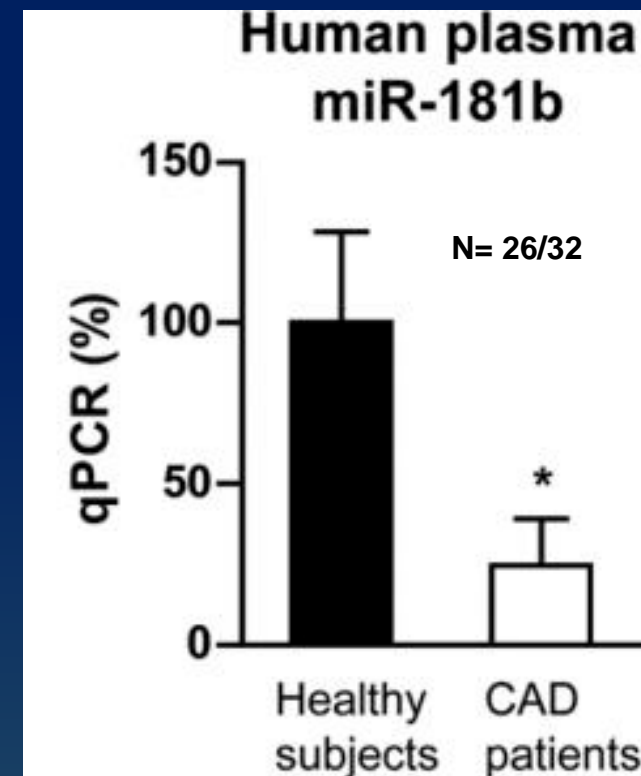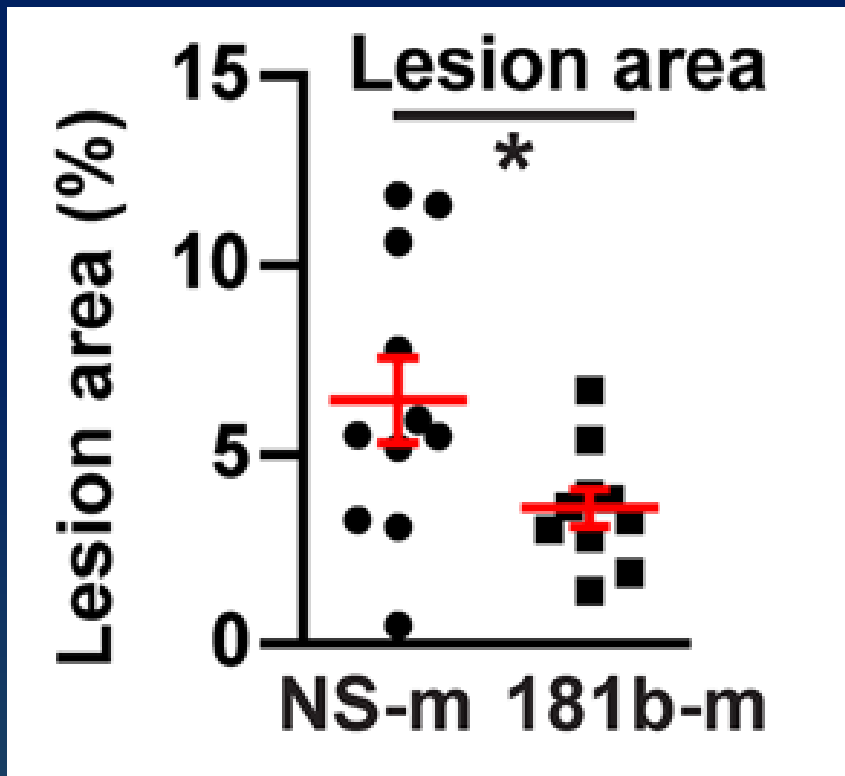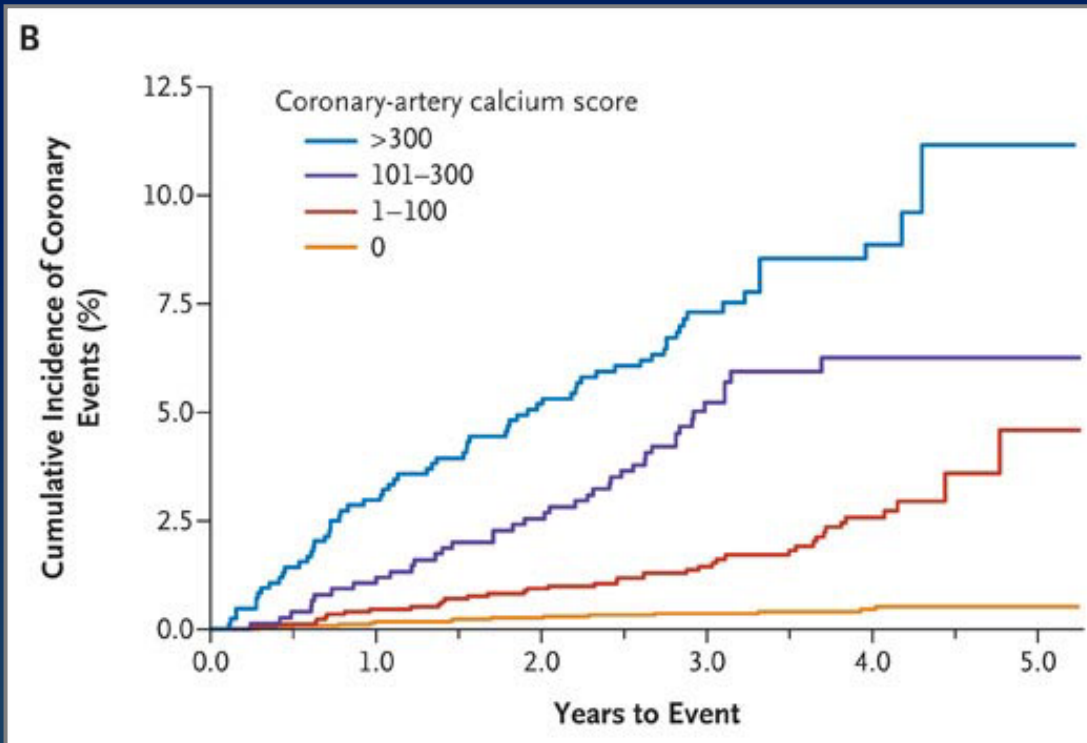
Imaging Biomarkers:

- **Structural**

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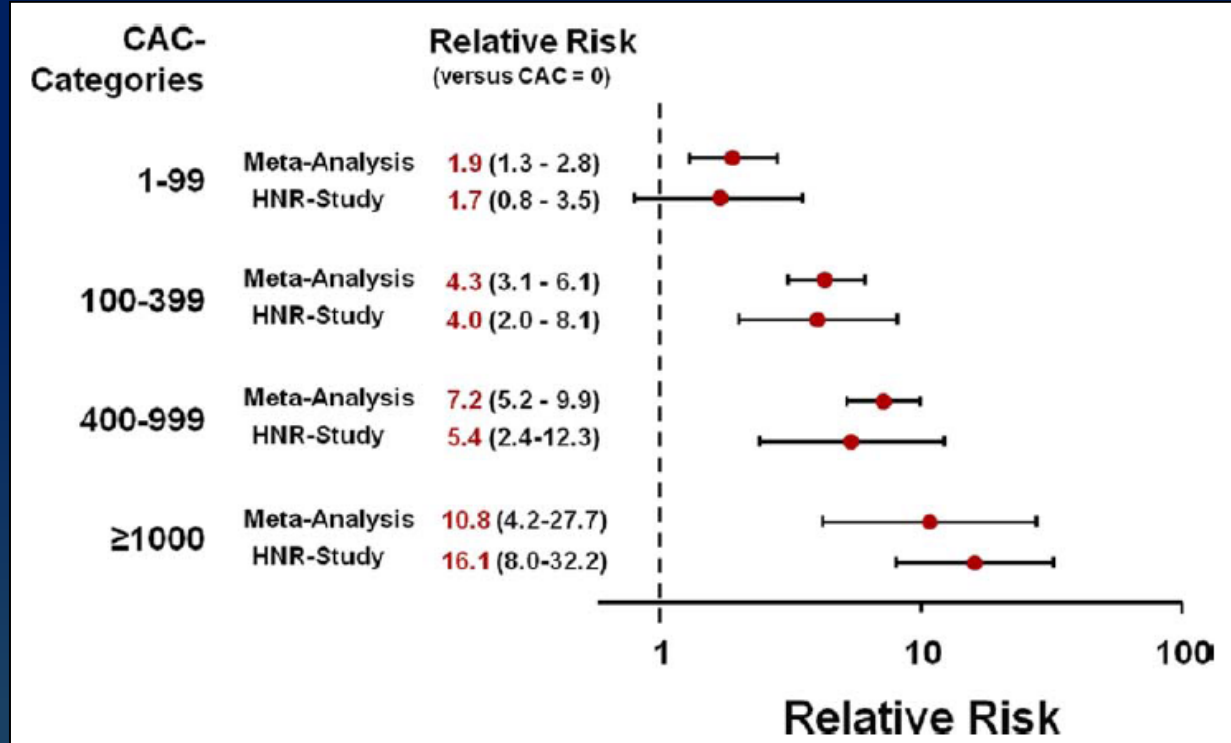   - **Ischemia / perfusion imaging**

Coronary Artery Calcium Score:
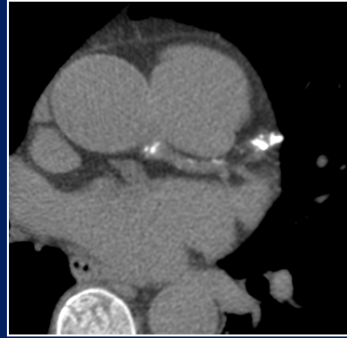
Report: Agatston calcium score

Multi-Ethnic Study of Atherosclerosis

Heinz Nixdorf Recall Study

CT Angiography of Coronary Arteries:
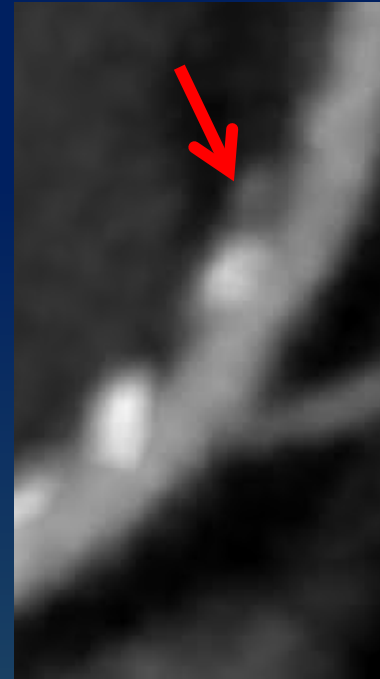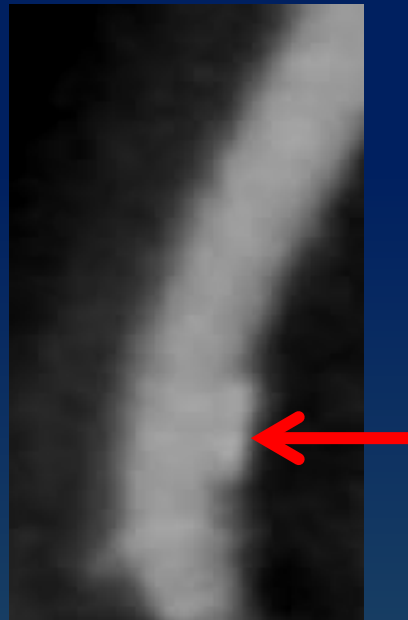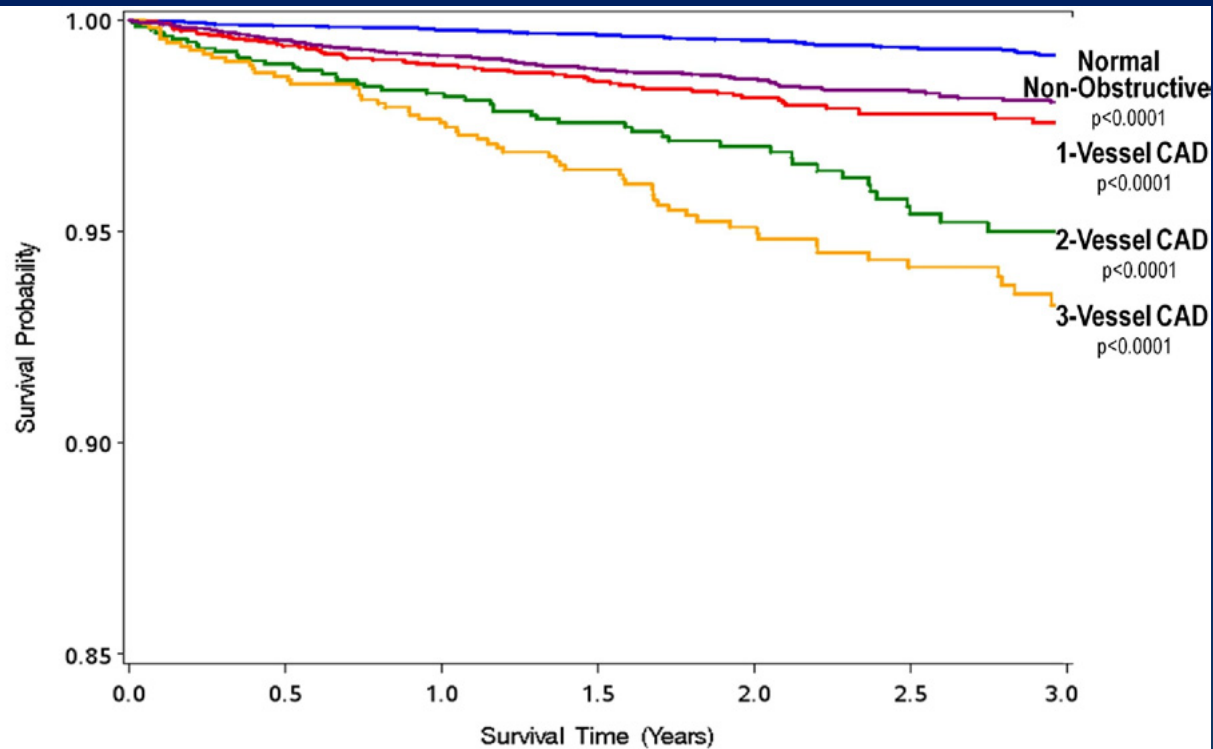
Extent of disease

Minimal (0-25%)

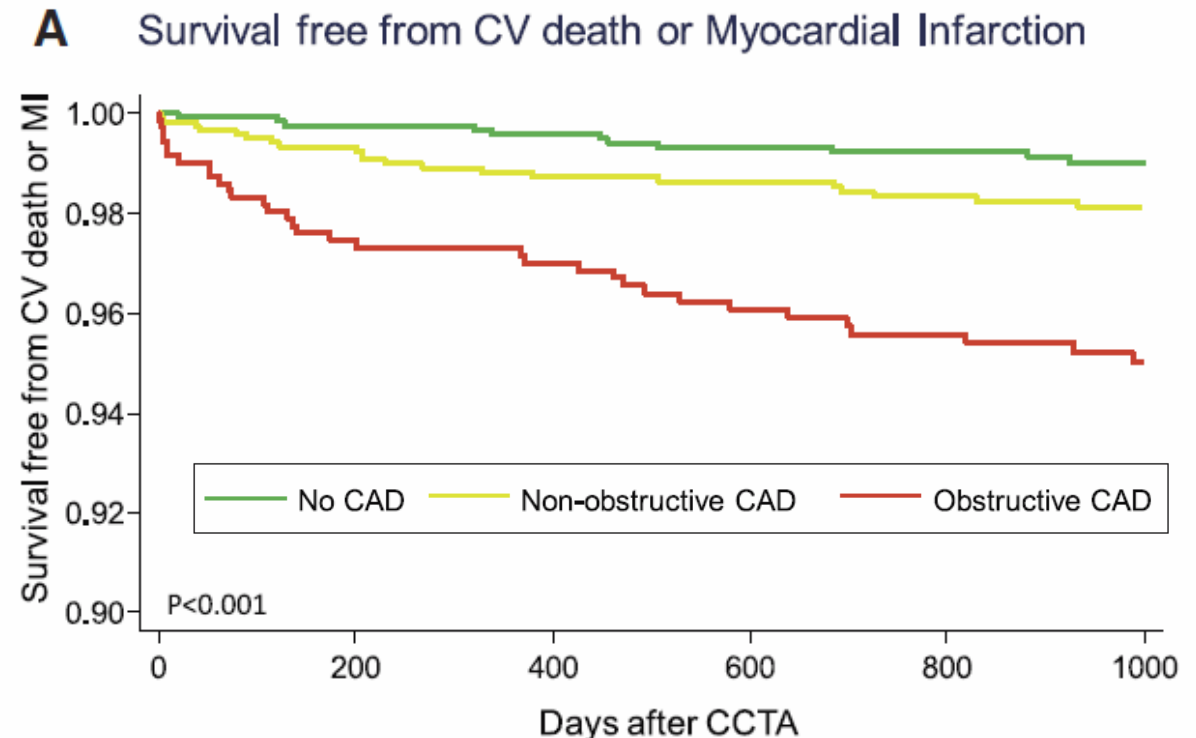**Mild (25-49%)**

Moderate (50-69%)

Severe (>70%)

Coronary CT Angiography:
Disease Burden Predicts Outcomes

CONFIRM Registry 23,854 patients

**MGH/BWH Registry N=3242 patients
mean f/u 3.6 years
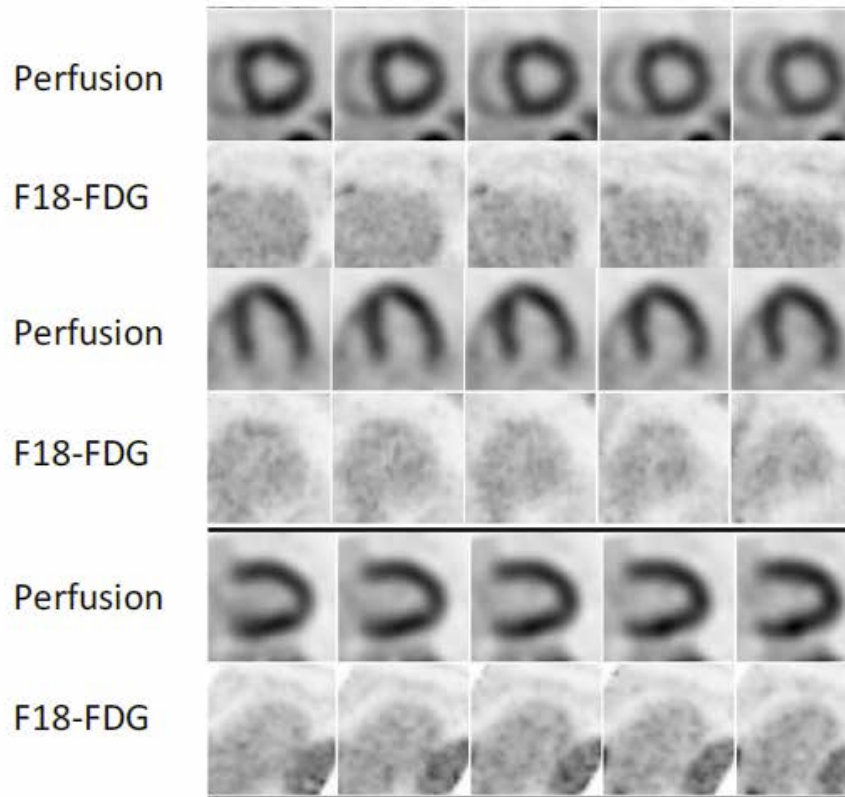1⁰ outcome: CV death / MI**

Min JACC 2011

Bittencourt, Circulation CV Imaging 2014

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

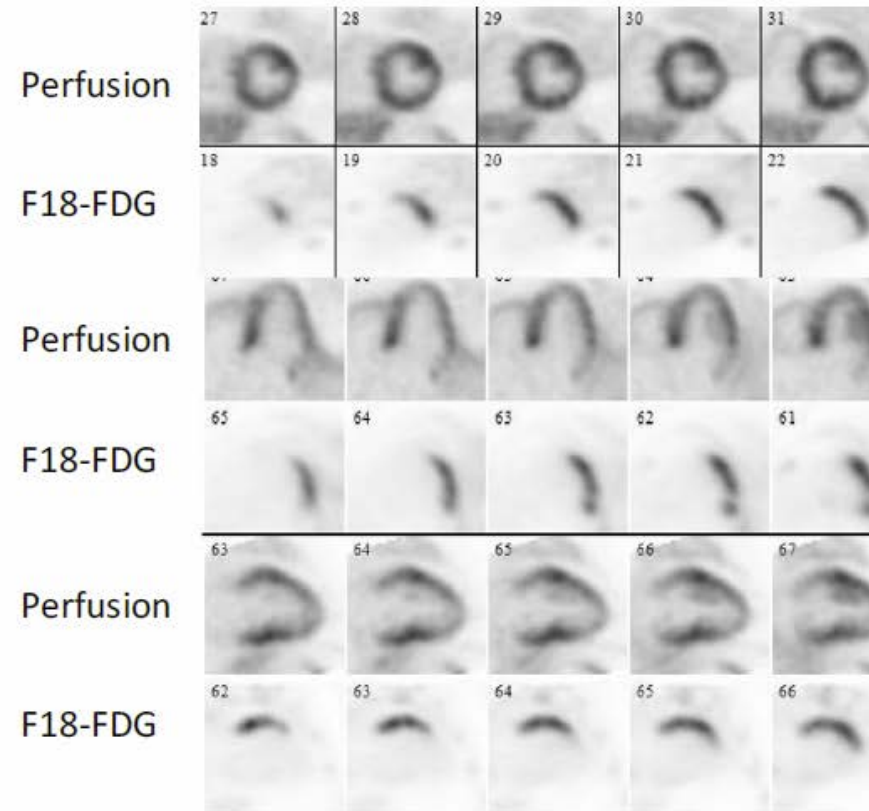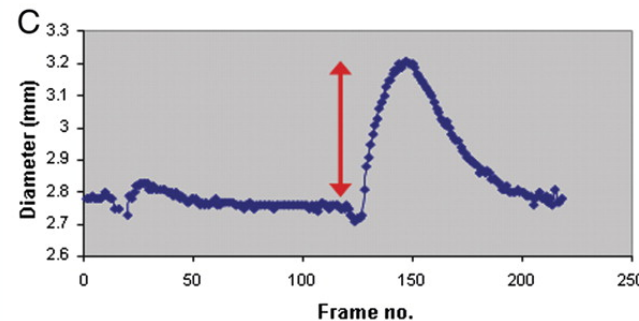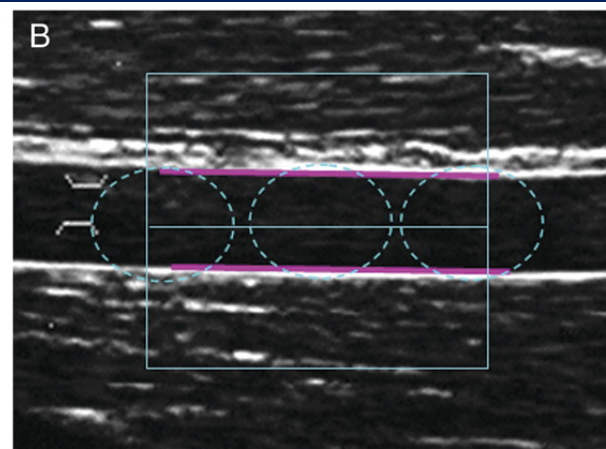# Myocardial Perfusion and FDG PET: Functional and Structural Imaging

Physiologic Cardiovascular Biomarkers:

- **Blood pressure / heart rate**

- **Heart rate recovery after exercise**
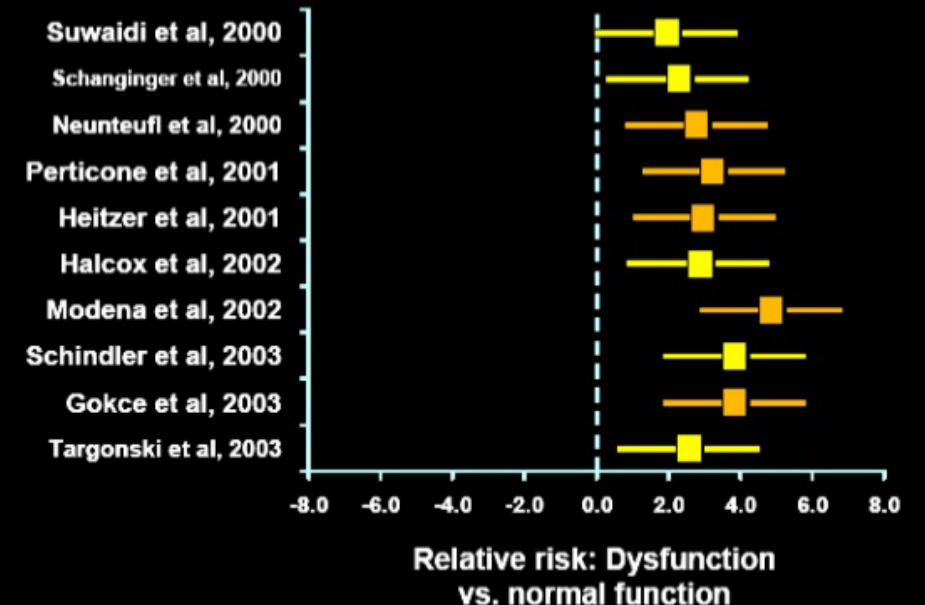
- **Endothelial function**

Quantifying Endothelial Function in Humans

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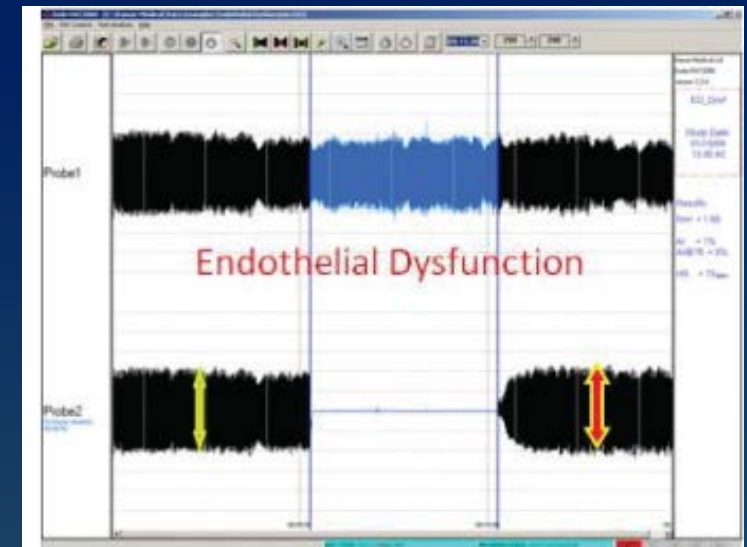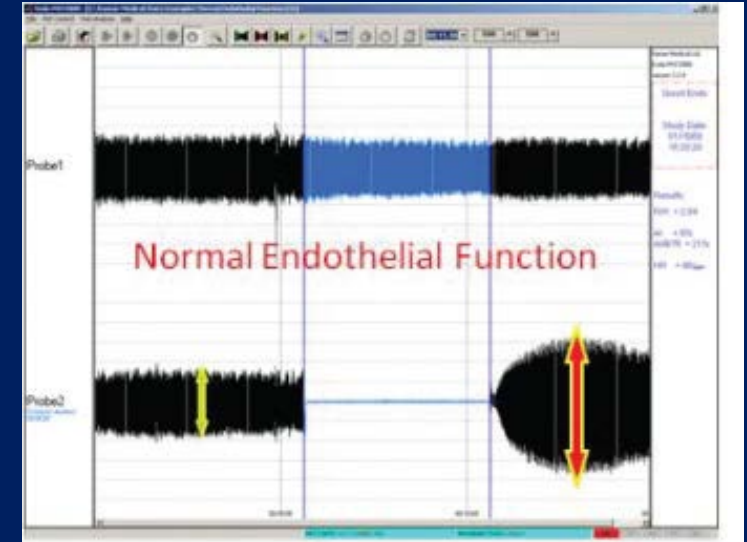- Predicts long-term CV events.

Quantifying Endothelial Function in Humans

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

Normal Endothelial Function

Endothelial Dysfunction

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.