Coronary Heart Disease, CHD Risk Factors, CHF and Metabolic Cardiology Diagnosis, Prevention and Treatment Module II Cardiology 2019

MARK C. HOUSTON MD MS MSC FACP FAHA FASH FACN FAARM ABAARM DABC.

ASSOCIATE CLINICAL PROFESSOR OF MEDICINE

VANDERBILT UNIVERSITY MEDICAL SCHOOL

DIRECTOR, HYPERTENSION INSTITUTE AND VASCULAR BIOLOGY

MEDICAL DIRECTOR OF DIVISION OF HUMAN NUTRITION

SAINT THOMAS MEDICAL GROUP, SAINT THOMAS HOSPITAL, NASHVILLE, TENNESSEE

CLINICAL, INSTRUCTOR IN THE DEPARTMENT OF PHYSICAL THERAPY AND HEALTH CARE SCIENCES AT GEORGE WASHINGTON UNIVERSITY (GWU) SCHOOL OF MEDICINE AND HEALTH SCIENCE

New and Revolutionary Concepts in the Pathophysiology, Diagnosis and Treatment of Hypertension: Role of Nutrition, Supplements and Integrative Metabolic Medicine

- **Mark C. Houston MD MS MSc FACP FAHA FASH FACN FAARM ABAARM DABC**.
- Associate Clinical Professor of Medicine Vanderbilt University Medical School
- Director, Hypertension Institute and Vascular Biology
- Medical Director of Division of Human Nutrition
- Saint Thomas Medical Group, Saint Thomas Hospital, Nashville, Tennessee
- Clinical, Instructor in the Department of Physical Therapy and Health Care Sciences at George Washington University (GWU) School of Medicine and Health Science

Objectives

Learn how to apply global cardiovascular risk scoring using the new expanded COSEHC method and others.

Review Cardiovascular Genomics and SNP's, the top 5 CHD risk factors, the details of the correct analysis of each, the top 25 modifiable key CHD risk factors and the other 400 CHD risk factors, how to test and the interpretation

Clinical evaluation of chest pain

Review and understand CHD, MI, CHF and PAD.

Review metabolic cardiology treatment for CHD, angina and CHF.

Prioritize which laboratory and non invasive laboratory and cardiovascular tests should be evaluated in patients in the primary care setting and how to interpret and treat

Review integrative medical treatments with nutrition, nutritional supplements and drugs for cardiovascular disease.

Case Presentation

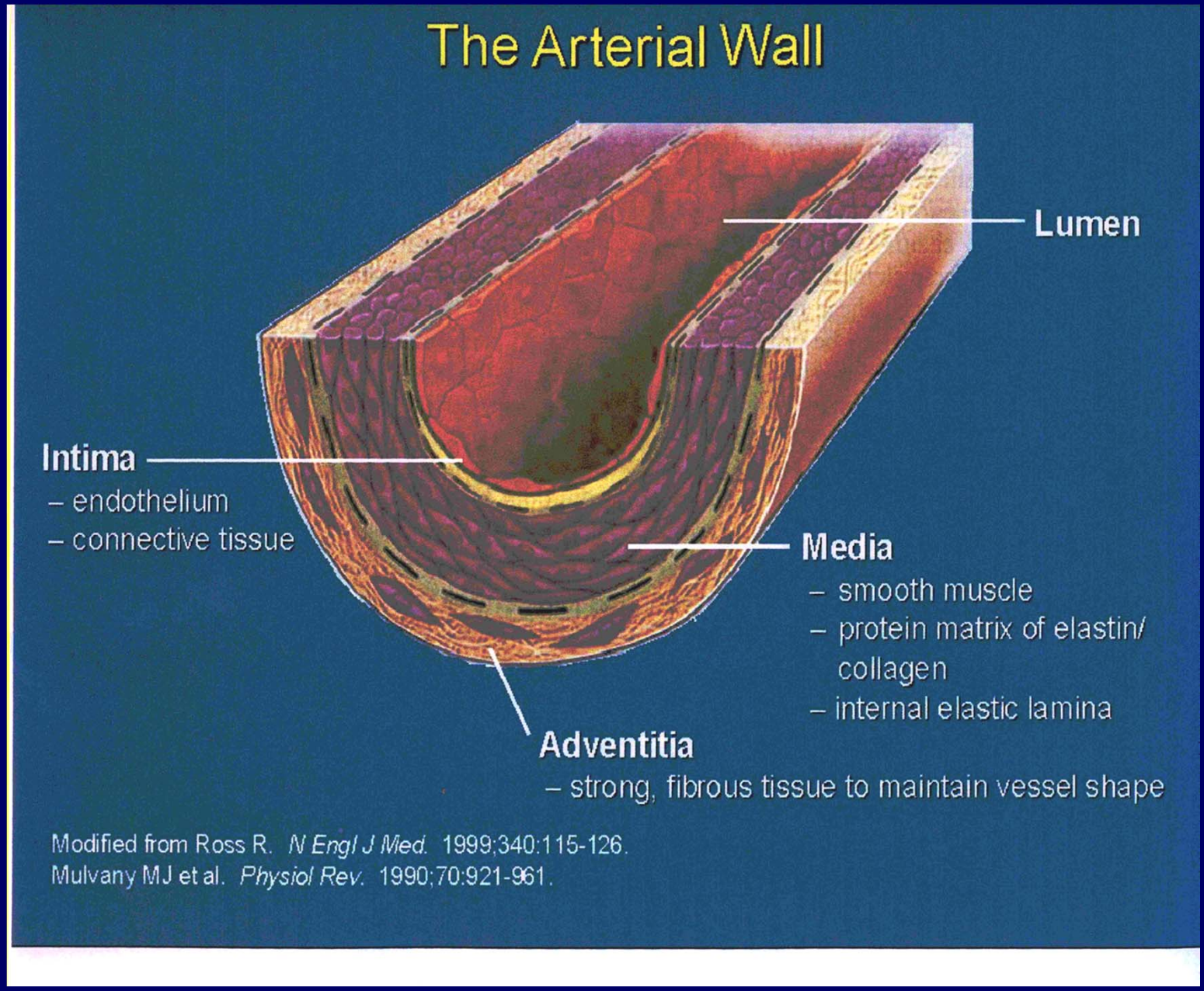
- 45 year old white male with strong FH in both parents of CHD and MI
- Presents with history of dyspnea for 3 months without chest pain
- No smoking, alcohol or caffeine.
- Normal weight and BMI
- BP 142/94 mm Hg. HR 76. Exam normal
- Advanced lipid testing: increased LDL-P of 1300 and low HDL of 35 with low HDL-P.
- Myeloperoxidase is elevated at 900 (normal < 495)
- FBS is 98 mg/dL
- ADMA (asymmetric dimethyl arginine) is elevated
- CV genetics show 9p21 homozygote (100% increase risk in CHD)
- Endopat shows endothelial dysfunction at 1.45 (normal is > 1.67)
- CORUS gene expression is elevated at 40 (68 % risk of obstructive CHD)

- What problems do this patient have and what is your next step?

Case Presentation

- CAC (coronary artery calcium score is 1243 mostly in LAD
- TMT is positive with 2 mm ST depression in inferior lateral leads

- Coronary arteriogram shows 96 % LAD obstruction and 88% LCX obstruction.
- 2 stents placed
- Start aggressive CHD prevention program



Vascular Biology in Clinical Practice, Oct. 2000; Mark C. Houston,MD

Preventing Heart Disease

American Heart Association Nutrition Committee. Diet and lifestyle recommendations revision 2006: a scientific statement from the American Heart Ass; *Circulation*. 2006 Jul 4;114(1):82-96 Implementing American Heart Association pediatric and adult nutrition guidelines: a scientific statement from the American Heart Association Nutrition Committee of the council on nutrition, physical activity and metabolism, council on cardiovascular disease in the young, council on arteriosclerosis, thrombosis and vascular biology, council on cardiovascular nursing, council on epidemiology and prevention, and council for high blood pressure research. *Circulation.* 2009 Mar 3;119(8):1161-75

- Heart Disease is the number one cause of death in the US
- Annual cost is 320 billion dollars
- About 80 percent of heart disease (heart attacks, angina, coronary heart disease and congestive heart failure) can by prevented by:

- Optimal nutrition
- Optimal exercise
- Optimal weight and body fat
- Mild alcohol intake
- Not smoking

Concept 1

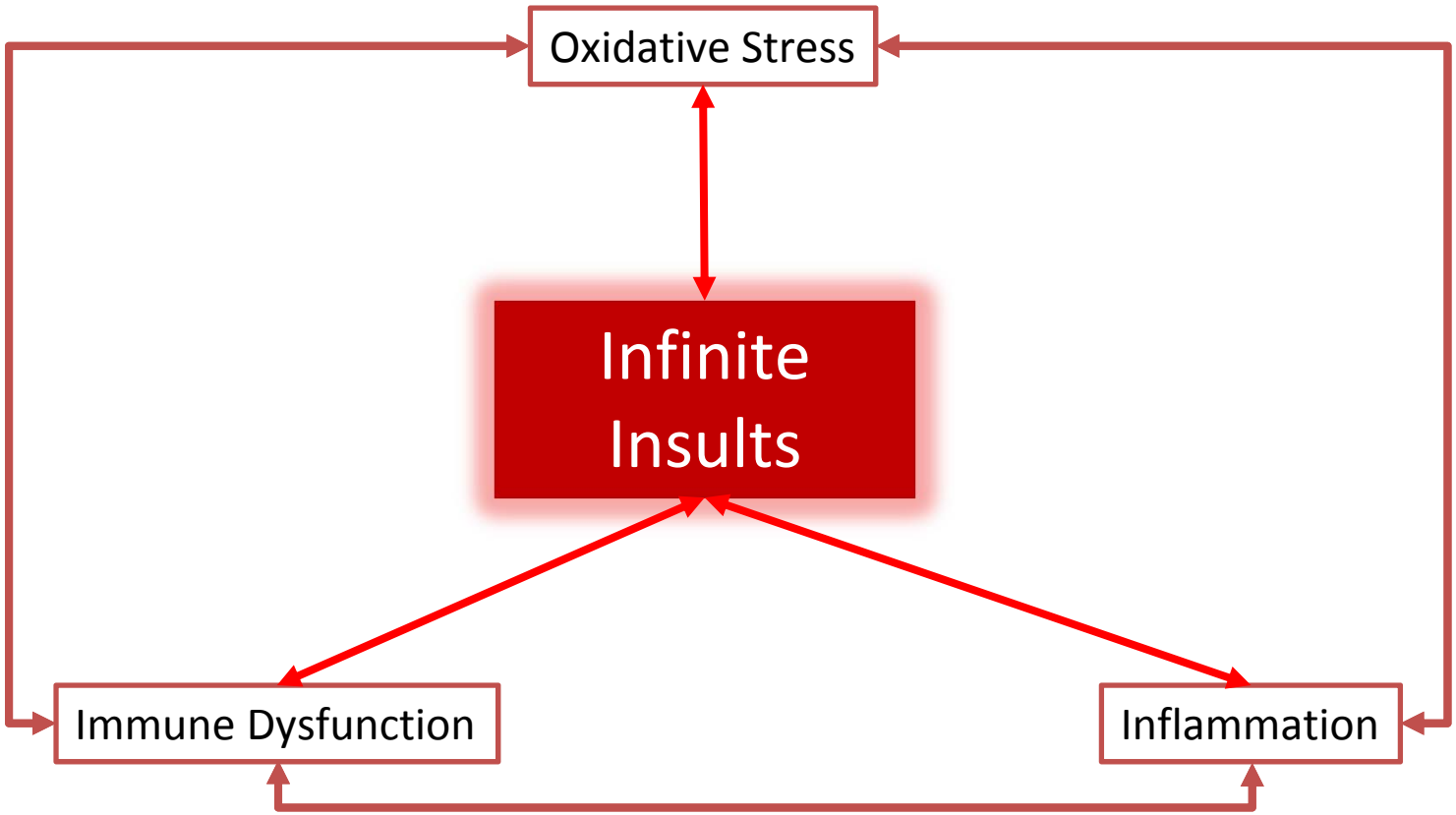
The blood vessel has only 3 finite responses to an infinite number of insults:

- **Inflammation**
- **Oxidative stress**
- **Immune vascular dysfunction and imbalance**

Houston 2011

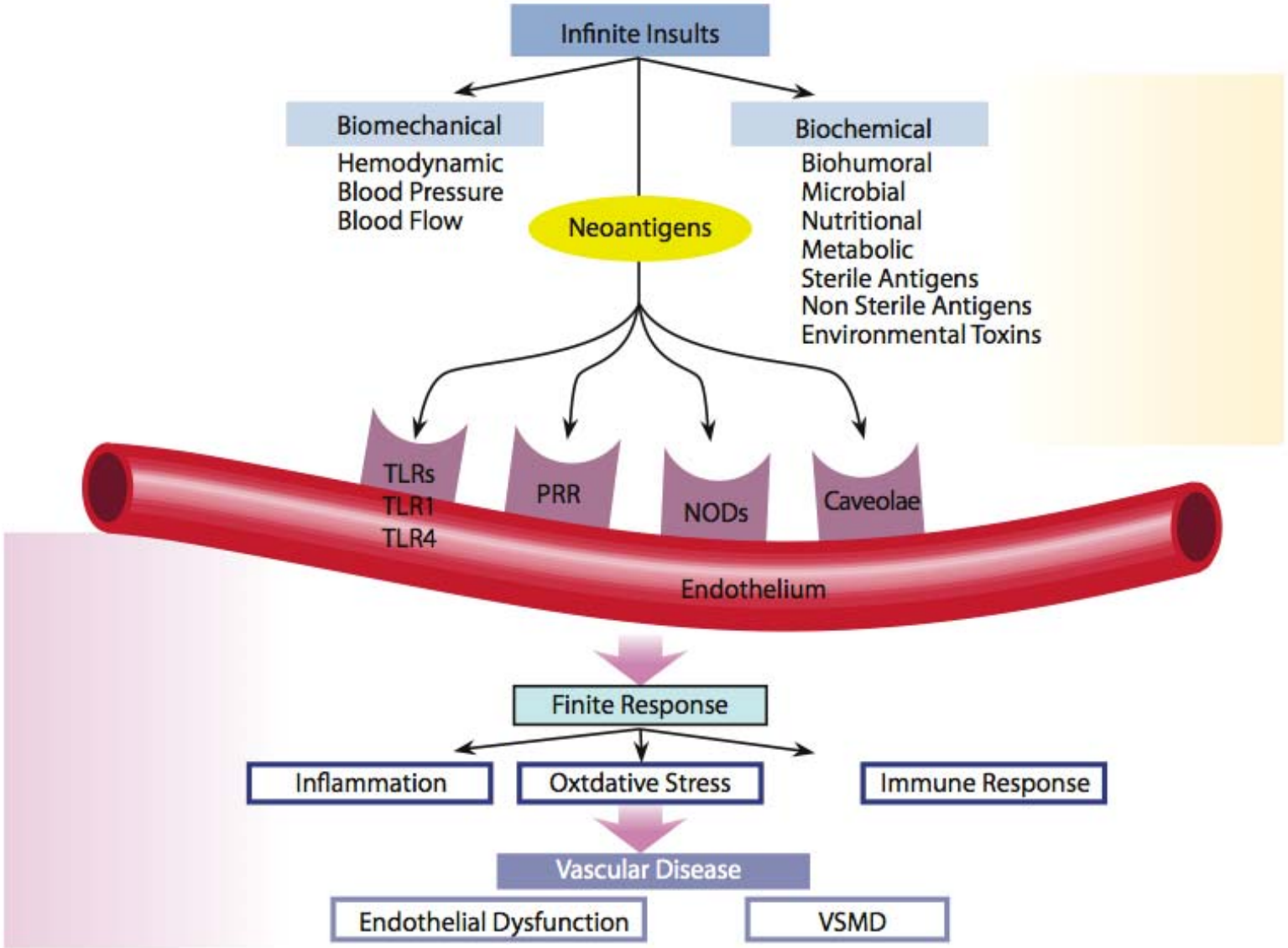
He, Feng. Int J Mol Sci 2015;16:1-12

Mechanism Of Model



Finite Responses

Infinite Insults



Concept 2: Blood Vessel is Innocent Bystander

J of the American Society of Hypertension 2010;4:272
Circulation 2007;115:1020 ,Expert Rev in CV Therapy 2010;8:821
Nephrol Dial Transplant 2006:21:850

- The blood vessel responds acutely as a defense mechanism to internal and external insults that are "correct and normal" but these chronic insults result in a chronic exaggerated and dysregulated cardiovascular dysfunction with preclinical then clinical CVD due to maladaptation.
- The subsequent environmental- gene expression patterns produce downstream mediators that damage the arteries.
- Proper assessment, comprehension, prevention and treatment of the top five and other 395 CHD risk factors and the downstream mediators is will reduce CHD.
- The cardiovascular system is the innocent bystander.

Concept 3: Endothelial Dysfunction and Membrane Dysfunction

Devlin,T.Textbook of Biochemistry Fifth Edition Wiley-Liss NY493-533

- Membrane Dysfunction: Body barriers and membranes protect cells and provide the initial interaction of the external infinite insults with the internal signaling mechanisms. Increased membrane permeability and dysfunction result in both abnormal intracellular and extracellular signaling mechanisms. This includes the endothelium, enterocyte, BBB and all other cell membranes.

  ED: endothelial dysfunction

  ED: enterocyte dysfunction

  BB: brain dysfunction

  MD: membrane dysfunction

Houston 2011

Concept 4: Continuum of Risk

Am J Medical Sciences 2005;329:276-291/ 292-305

There is a progressive continuum of risk within the CHD risk factors and mediators that effect the blood vessel leading initially to functional abnormalities (endothelial dysfunction), then to structural abnormalities (VSMH, arterial stiffness, LVH, carotid IMT) and eventually to preclinical and clinical cardiovascular disease.

The vascular system provides transport and integrative biological activity with cell dominance to deliver micronutrients, oxygen and engage in metabolism, communication and excretion.

Concept 5 :Translational Vascular Medicine
Risk Factors to Vascular Disease

Am J Cardiol 2014;113:1499

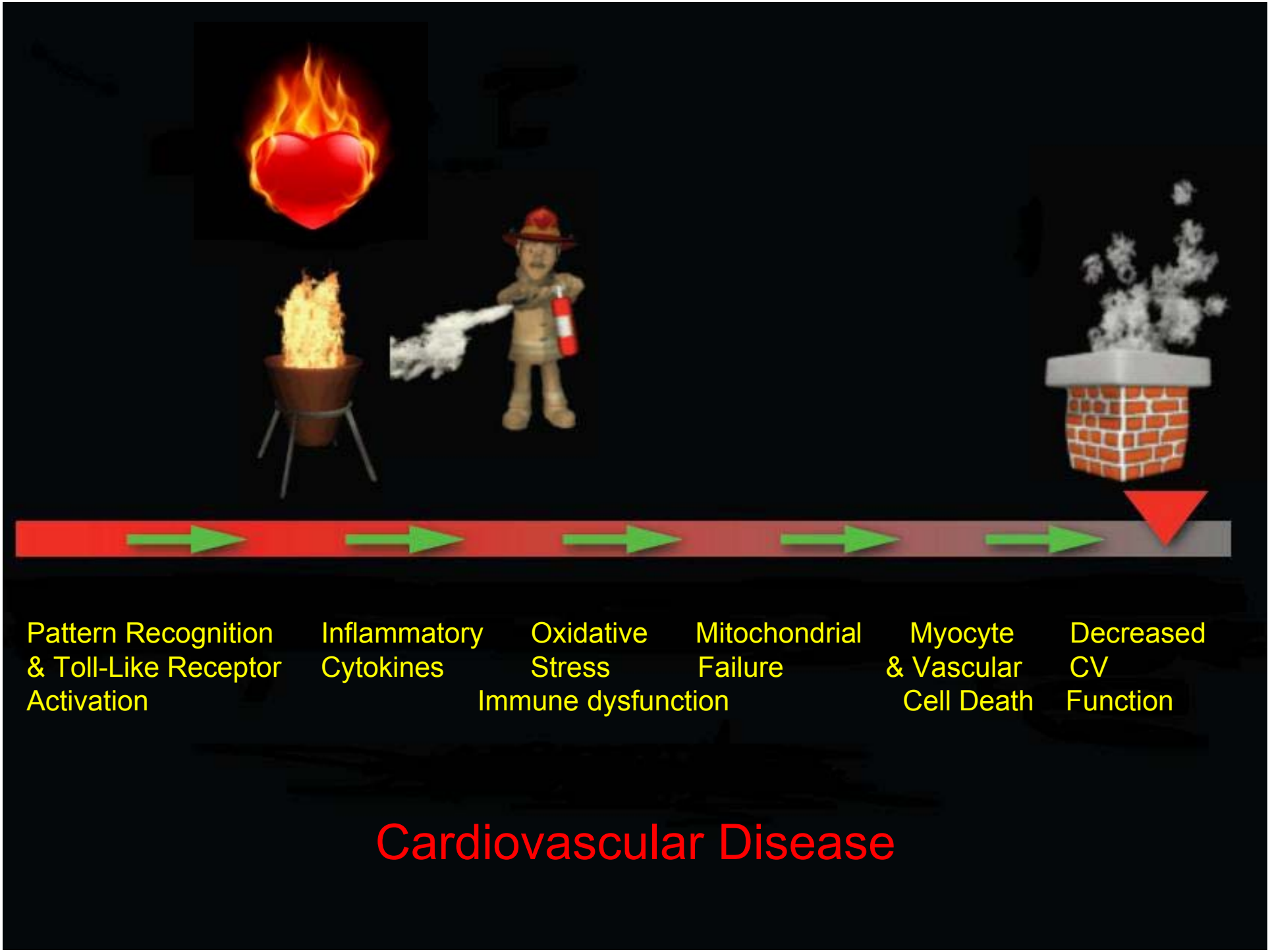
1. Do the risk factors translate into cardiovascular disease?
2. Does the absence of risk factors translate into cardiovascular health?
3. It is important to measure sensitive indicators of endothelial dysfunction and vascular disease to determine if the risk factors and insults induce vascular responses with functional and/or structural abnormalities.
4. Standard CHD risk factors do not adequately identify at-risk individuals. Need Endopat, CAPWA, CAC, carotid IMT and other noninvasive cardiovascular tests.
5. Early detection with aggressive treatment will reduce CVD, CHD and CHF.

Concept 6: Systems Biology and "Omics"

Nutrition 2007;137: 259S-268S

Global Advances in Health and Medicine 2012;1:36

- CVD needs to be approached with systems biology and evaluation of interconnections.
- CVD is part of the complex xenobiotic toxicity and hormetic response theory.
- Environmental-genetic interactions, nutragenomics, proteomics and metabolomics provide personalized CV medicine with distinguished individual responses.


Pattern Recognition & Toll-Like Receptor Activation
Inflammatory Cytokines
Oxidative Stress
Mitochondrial Failure
Immune dysfunction
Myocyte & Vascular Cell Death
Decreased CV Function
Cardiovascular Disease

Summary CVD Concept

- Metabolomic dominos lead to subtle preclinical pertubations then clinical CVD. Genetic CV profiles and gene expression interact with these infinite insults with an initial acute defensive correct finite 3 response that results in chronic dysregulation with the blood vessel as the “innocent bystander” resulting in cardiovascular damage, atherosclerosis, CHF, CHD and MI.

CVD and Chest Pain Evaluation

- Number one cause of death in US
- 60,000 miles of arteries in human body
- Symptoms of CHD

  Exertional precordial or substernal chest pressure, tightness or chest pain

  with or without radiation to arms, neck and shoulders or back and associated with:

  Dyspnea
  Diaphoresis
  Nausea
  Dizziness
  Sweating and pallor
  Weakness and fatigue
  Stomach and abdominal pain

Evaluate chest pain: History, PE, EKG, TMT, CPET, hs troponin, CPK MB, ABGs, CXR, chest CT scan. Rule out pulmonary emboli, lung disease, chest wall pain, aortic dissection, pneumothorax, pleurisy, pneumonia, medistanal disease, pericarditis, GERD, esophageal spasms etc.

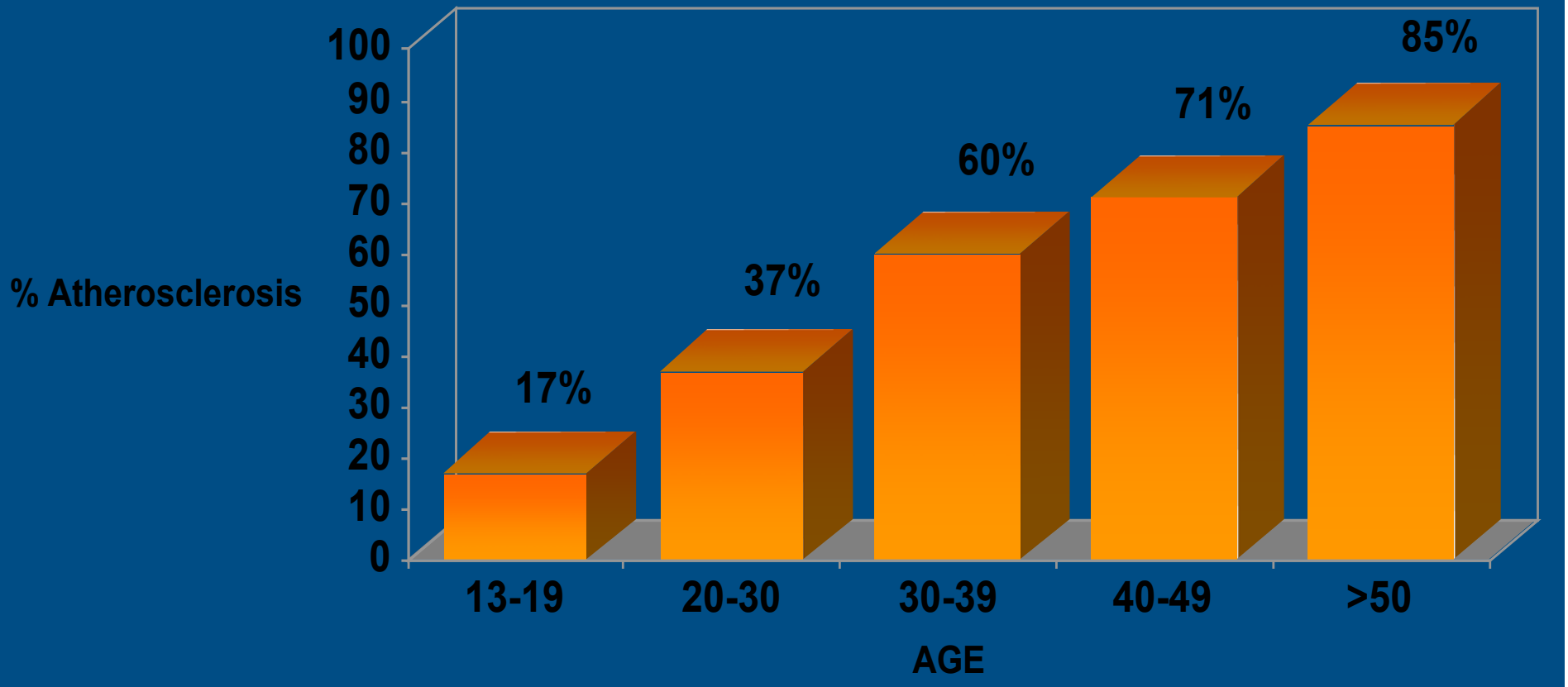
CVD begins at an early age

JAMA 1999;281:727-35
JAMA 1986;256:2859-62
Am J Path 1958;34:209

Atherosclerosis begins at an early age[42, 43, 45]

- PDAY study[42]: Ages 15-19 at autopsy
  - 60% with cholesterol deposits in abdominal aorta
  - 60% with fatty streaks in right coronary artery
- Korean War Soldiers at Autopsy[43]
  - Advanced CHD found at average age of 22
- Holman Study[45]
  - Fatty streaks in aorta : First Decade
  - Fatty streaks in coronary arteries : 2nd Decade
  - Fibrous Plaques / CHD : 2nd-3rd Decade

Prevalence of Atherosclerosis and CHD by IVUS



Nissen, S. ISH, August 2000

Key New Concepts in Hypertension, CHD Risk Factors, CHD and CVD

Lancet 2004;364:937

- The risk factor-induced development of target organ damage is only partially explained with the top five CHD risk factors.
- Recent results from clinical trails such as NAVIGATOR, ACCORD and ROADMAP suggest that we have reached a limit in terms of reducing CV events by solely controlling the top five CHD risk factors.
- ANCILLARY TREATMENTS will be necessary if we hope to reduce the sequelae of CHD and CVD in the future.
- Exercise, optimal nutrition, fruits and vegetables, moderate ETOH and smoking cessation reduce the risk of CHD and MI by up to 80%.

Endothelial Dysfunction (ED)

- Characterized by decreased release of nitric oxide and propensity to secrete vasoconstrictors. Reduced endothelial vasodilation (EDV)
- Key, initial and earliest event in vascular disease. Functional ED precedes structural disease.
- Present with only risk factors but no atherosclerosis.
- Precedes intimal thickening by a decade or more and clinical atherosclerosis.
- Correlation with future CV events (MI, CHD, PCTA, CABG, sudden death).
- Diverse pathophysiologic stimuli are capable of inducing similar nonadaptive dysfunction.
- Hypertension has reduced EDV in both peripheral and coronary arteries.

Vascular Disease

Clin 2010;33:746
Clin Cardiol 2010;33:730
He, Feng. Int J Mol Sci 2015;16:1-12

The pathophysiology of CHD/CVD is:

- Endothelial dysfunction (early) (functional)
- Abnormal vascular compliance with vascular smooth muscle and cardiac hypertrophy (late)(structural)
- Inflammation
- Oxidative stress
- Immune vascular dysfunction

Post Prandial Atherosclerosis

NaCl SFA Dispersed Fats

CHO TFA

ROS

Endotoxemia CD14 Inflammation

Bacterial products IL6 Autoimmune

ROS

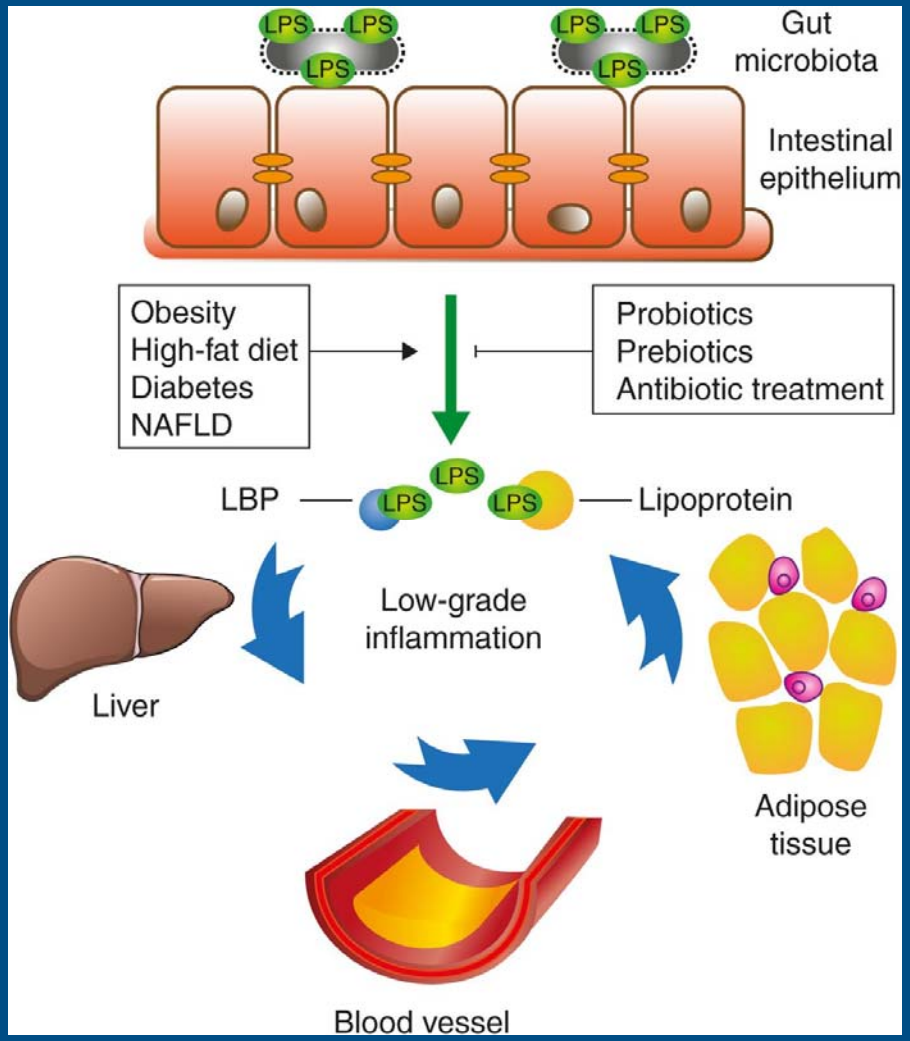
Blocked by
- Low glycemic foods
- MUFA
- PUFA
- OJ
- Antioxidants

ED

Low NO

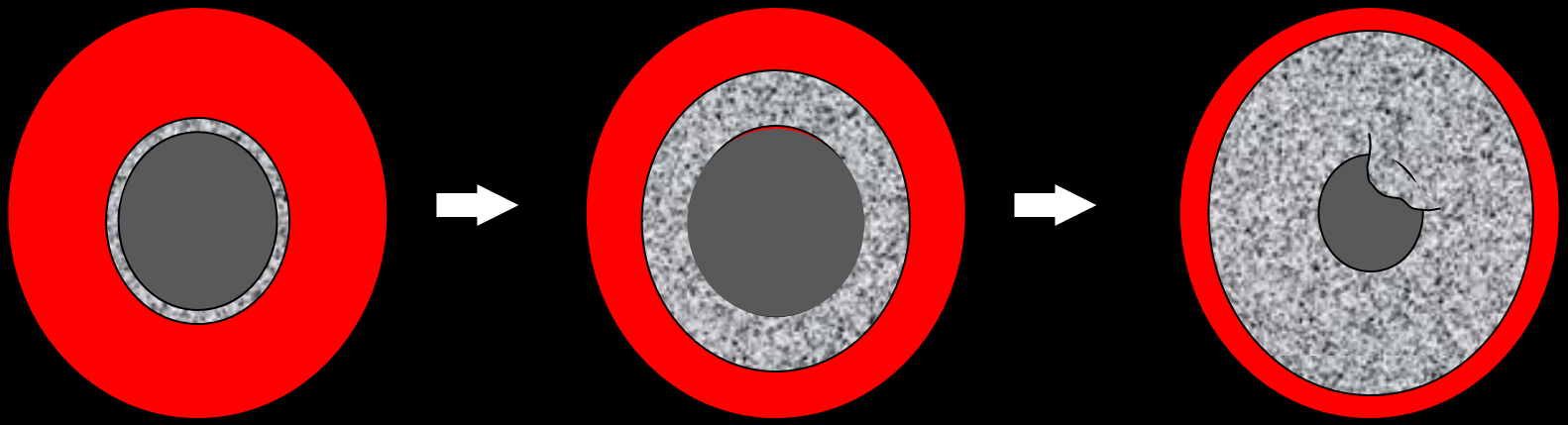
Increase ADMA

Figure 2 The gut epithelium is an efficient barrier that prevents absorption of LPS derived from Gram-negative gut microbiota. MICROBIOME and CVD



Neves A L et al. J Mol Endocrinol 2013;51:R51-R64

CHD: Extraluminal Disease:Begins as a disease of the subendothelium and the vessel wall



Minimal to mild CHD
Lumen Normal
Mild extraluminal atheroma

Moderate CHD
Lumen normal size
Mild extraluminal atheroma

Severe CHD
Lumen Stenosis
Severe extraluminal and intraluminal atheroma

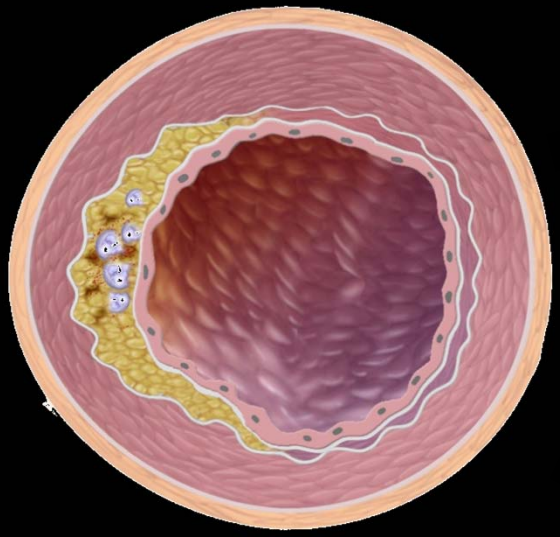
95 - 99%

1 -5%

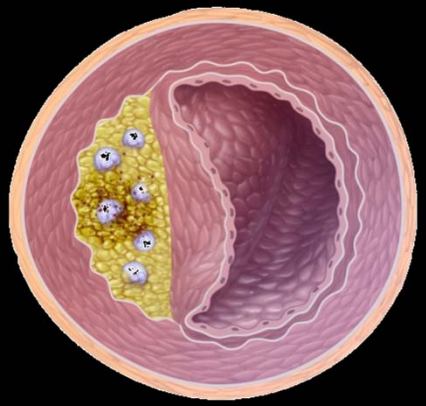
- 68% of MI: < 50% Stenosis
- 14% of MI: Significant Stenosis
- 62% men 1st **symptom** of CHD is MI
- 46% women 1st symptom of CHD is MI

Nissen, S. ISH, August 2000

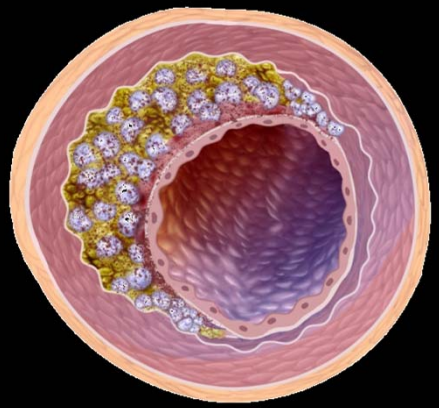
Stenotic Plaques May Be Stable. Plaques With Thin Fibrous Caps, Large Lipid Pools, & Inflammation Are Rupture-Prone



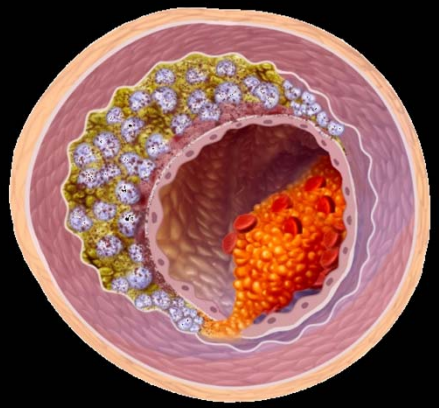
Early Plaque
with Lipid Pool



Thick Cap with Small
Necrotic Lipid Core
"Stable Plaque"



Thin Cap
"Rupture-Prone"
Plaque



Ruptured Plaque
with Thrombus
in Lumen

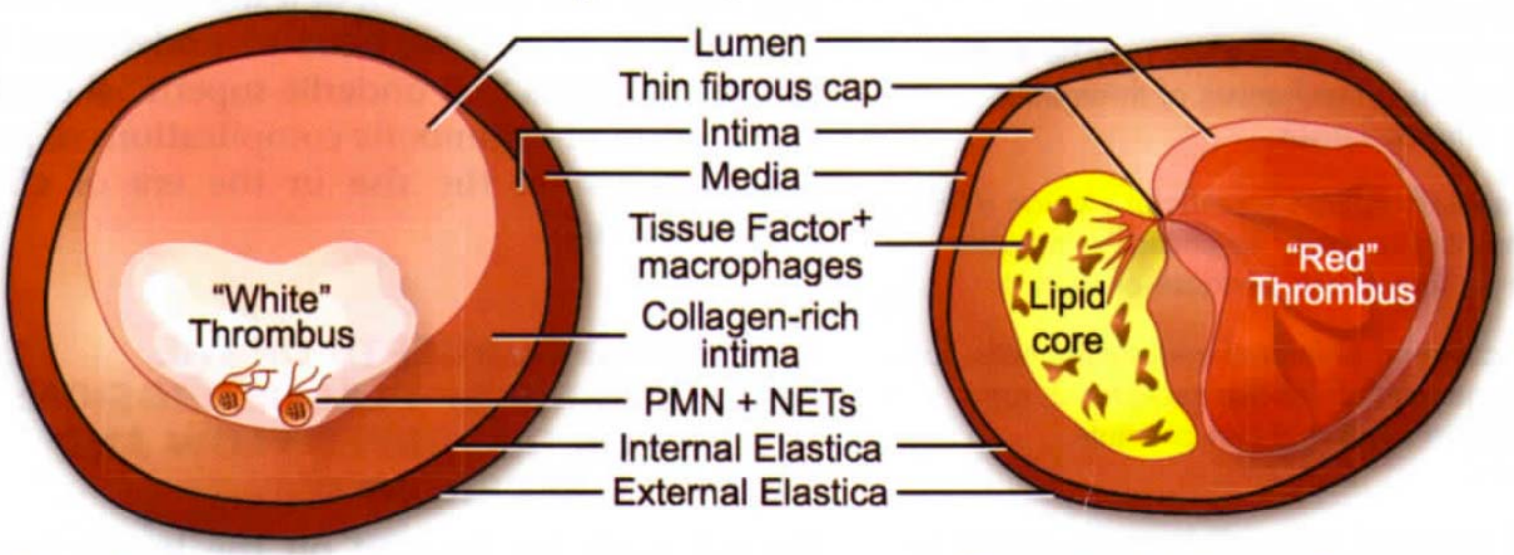
Adapted from Kolodgie F, et al. *Arterioscler Thromb Vasc Biol* 2006.

Coronary Artery Plaque Erosion

Curr Opin Lipidol 2017;28:434

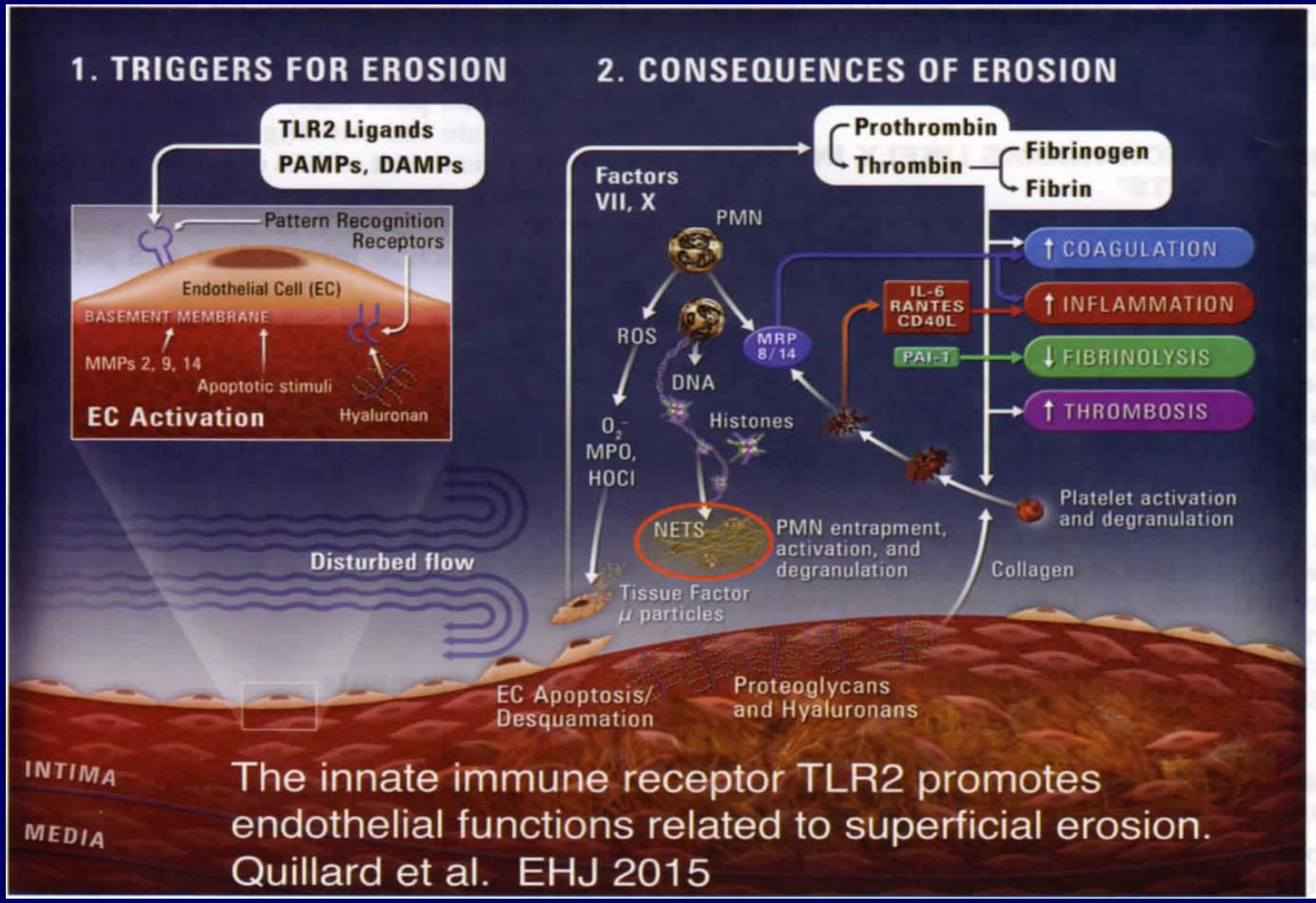
- One third of NSTEMI due to plaque erosion
- This is a “white thrombus” due to superficial intimal erosion
- Endothelial cell death and desquamation uncover basement membrane collagen (hyaluronic acid and glycosaminoglycans) which lead to TLR 2 expression
- PMN’s produce NETS (Netosis)(Necoptosis) which forms the scaffold for thrombus formation. NETS contain pathogen, proteases, histones, chromatin, proteins and ROS.
- Superficial erosions are different from other plaque (contain more VSMC, ECM and NETS but fewer lipids, macrophages, foam cells and inflammatory cells.
- Activation of superficial erosions by NADPH oxidase, high fat diet, cholesterol crystals and MPO

Coronary Artery Cross Sections



Thrombosis due to Erosion	Thrombosis due to Rupture
Fibrous cap thick & intact	Thin fibrous cap with fissure
"White" platelet-rich thrombus	"Red" fibrin-rich thrombus
Collagen trigger	Tissue Factor trigger
Smooth muscle cells prominent	Macrophages prominent
Often sessile, non-occlusive Thrombus	Often occlusive thrombus
Usually less remodelled outward	Usually expansively remodelled
Neutrophil extracellular traps (NETs) involved	Less NET involvement?
More frequent in Non-STEMI?	More frequently cause STEMI?

Current Opin Lipidol 2017, 28:434-441



Current Opin Lipidol 2017, 28:434-441

Coronary Artery Plaque Erosion

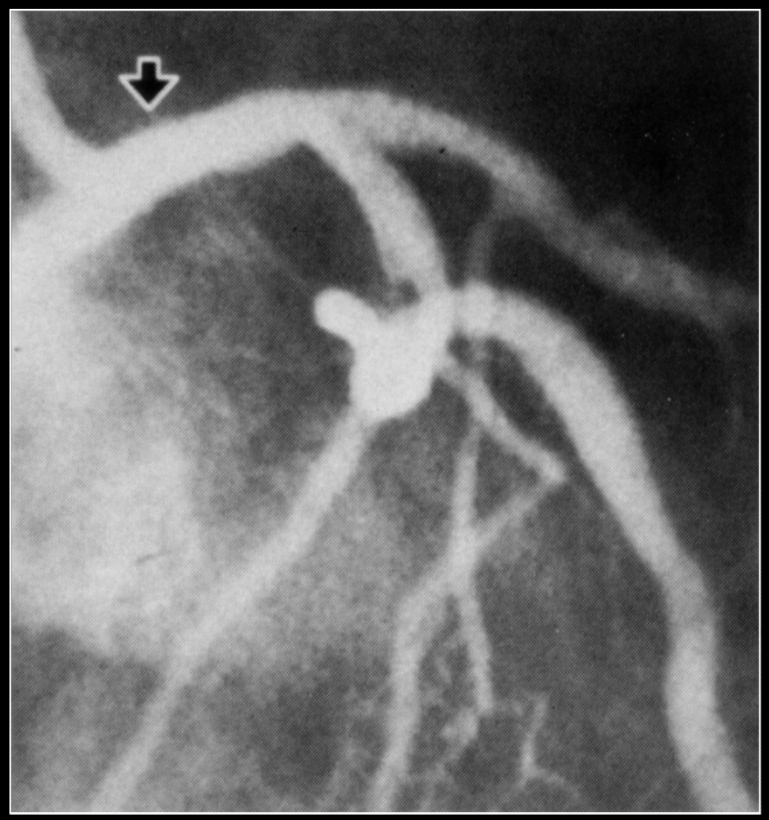
Curr Opin Lipidol 2017;28:434

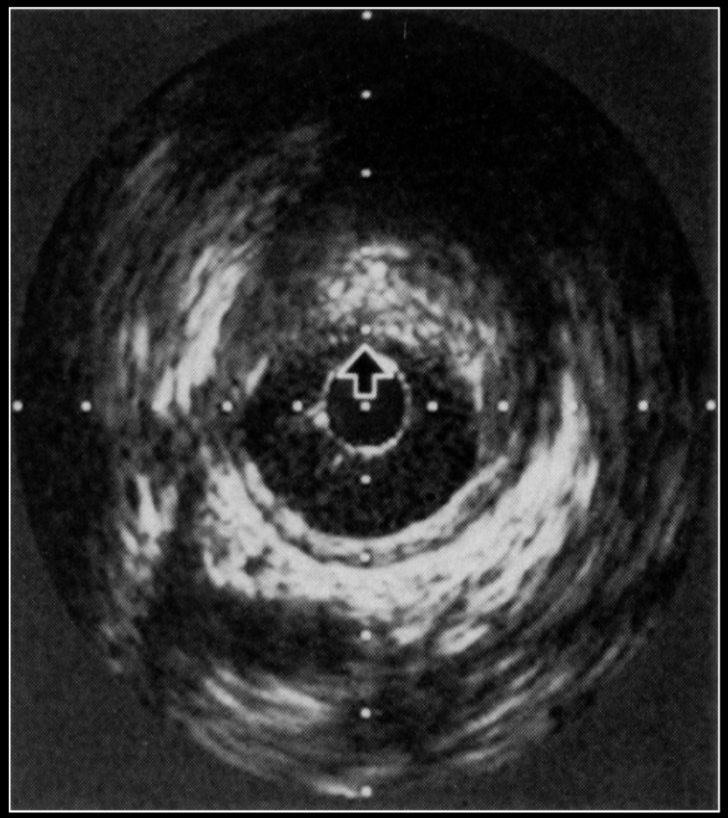
Treatment of superficial erosions

- **Reduce MPO with niacin, pomegranate and curcumin**
- **Low SFA and low TFA**
- **Decrease NADPH oxidase with RYR berberine, resveratrol, NAC and niacin**
- **TLR2 antagonists**
  - Curcurmin (Tumeric)
  - Cinnamaldehyde (Cinnamin)
  - Sulforaphane (Broccoli)
  - Resveratrol (nutritional supplement, red wine, grapes)
  - EGCG (Green Tea)
  - Luteolin (celery, green pepper, rosemary, carrots, oregano, oranges, olives)
  - Quercetin: (Tea, apples, onion, tomatoes, capers)

- **Anti-platelet drugs and ASA**
- **Statins?**

Angiographically Inapparent Atheroma





Nissen et al. In: Topol. *Interventional Cardiology Update.* 14;1995.

CHD Risk Factors and Mediators

NEJM 2011;365:2098-109

- Top Five CHD risk factors
- Top 25 key modifiable CHD risk factors
- Composite List : 400 or more CHD risk factors are known
- Discussion List
- Relative Predictive Risk

Conventional vs Emerging Risk Factors and CHD

Futterman, Am Critical Care 1998; 7:240-244) JAMA 2003; 290:898, JAMA 2003; 290:891)

- More than 50% of patients with CHD lack any of the five conventional risk factors. (Futterman, Am Critical Care 1998; 7:240-244)
- Only 10-15% of patients with CHD lack any of the five conventional risk factors of hypertension, hyperlipidemia, diabetes, smoking and obesity.
  (JAMA 2003; 290:898, JAMA 2003; 290:891)
- How do they define the top five risk factors??
- What are the details within each of the top five risk factors ?
- What risk factors/mediators are not even being evaluated and treated?

What is the REALITY???

Figure 1

Rohatgi, A . NEJM 2014; November 19 :1-10 EPUB

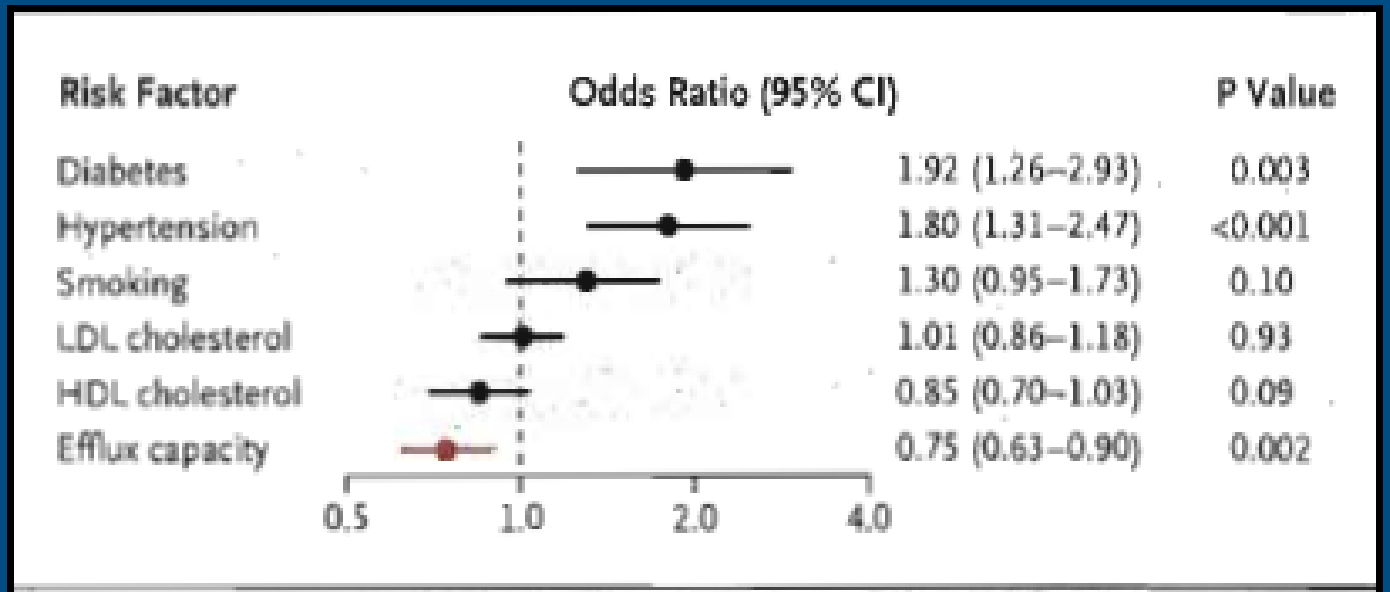
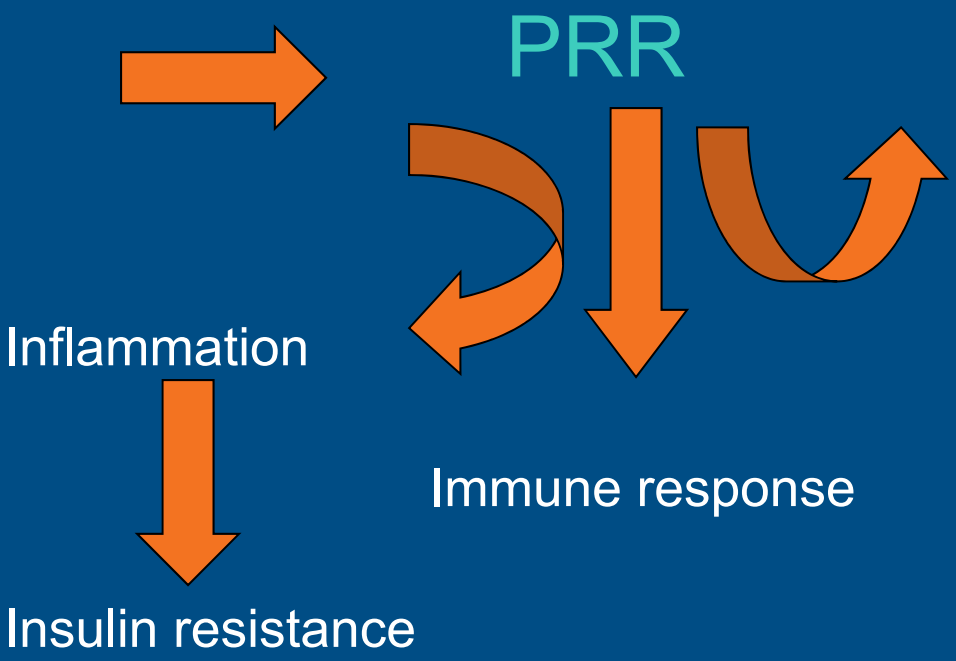


Figure 1. Odds Ratios for Coronary Artery Disease According to Efflux Capacity and Selected Risk Factors.

The logistic-regression model was also adjusted for age and sex. Odds ratios for continuous variables are per 1-SD increase.

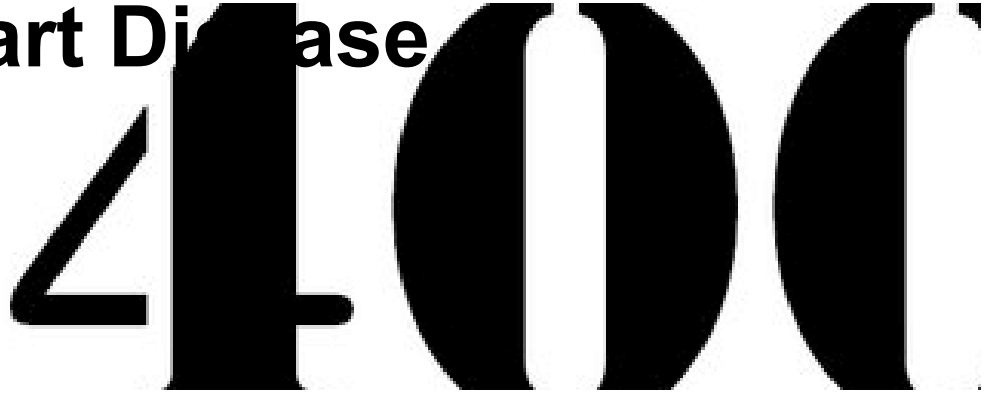
Activation of PRR leads to Vascular Disease

- Microbes
- Sterile Antigens
- Nutrients



Over 400 Coronary Heart Disease Risk Factors

Houston. What Your Doctor May Not Tell You About Heart Disease 2012.



- There exist over 400 CHD risk factors and mediators beyond the top 5 of hypertension, dyslipidemia, diabetes, smoking and obesity.
- The infinite insults and CHD risk factors and mediators induce only three finite responses of inflammation, oxidative stress and vascular immune dysfunction.
- Over 100 more genetic variants increase CHD

Coronary Heart Disease Risk Factors:General Classes

1. Genomics, SNP's and epigenetics
2. Gender and age
3. Inflammation
4. Oxidative stress
5. Vascular immune dysfunction
6. Infections
7. Metabolic and nutritional
8. Toxins
9. Psychological and neurological
10. Sleep disturbances
11. Lack of exercise
12. Structural and hemodynamic
13. Hormonal

Top 25 Modifiable CHD Risk Factors

Houston MC. What Your Doctor May Not Tell You About Heart Disease 2012

- Hypertension (24 hour ABM)
- Dyslipidemia (advanced lipid analysis)
- Hyperglycemia, metabolic syndrome, insulin resistance and diabetes mellitus
- Obesity
- Smoking
- Hyperuricemia
- Renal disease
- Elevated fibrinogen
- Elevated serum iron
- Trans fatty acids and refined carbohydrates
- Low dietary omega 3 fatty acids
- Low dietary potassium and magnesium with high sodium intake
- Inflammation: increased HSCRP, MPO, interleukins
- Increased oxidative stress and decreased defense
- Increased immune dysfunction
- Lack of sleep
- Lack of exercise
- Stress, anxiety and depression
- Homocysteinemia
- Subclinical hypothyroidism
- Hormonal imbalances in both genders
- Chronic clinical or subclinical infections
- Micronutrient deficiencies: numerous ones such as low vitamin D , K,E, CoQ10 etc.
- Heavy metals
- Environmental pollutants

Genomics of Cardiovascular Disease

NEJM 2011;365:2098-109

- Most are polygenic
- There are 30 loci associated with MI and CHD, but only a minority of loci mediate effects on CHD through known risk factors.
- 9p21 genetic variant is associated with MI and atherosclerosis. 33 gene enhancers are located in 9p21 region that are implicated in inflammatory pathways.
- Interactions of 9p21 increase genetic susceptibility to CHD and response to cardiovascular inflammatory signaling
- The best yield of genome wide association studies is the provision of insights into the biologic pathways that underlie causes of disease such as inflammation, vascular immune dysfunction and oxidative stress.

CARDIA X
Recommended Testing for Early Detection and Prevention of CHD
Genetic Testing

1. 9p21 (GG/CC): CHD, MI, ASCVD, DM, IR AAA, thrombosis, plaque rupture , inflammation and intracranial aneurysms.
2. 6p21.4: CHD,MI, DVT.
3. 4q25: atrial fibrillation, long QT and PR intervals.
4. ACE I/D (DD Allele): HBP,LVH,CRF, MAU , nephroangiogenesis, carotid IMT,MI and CHD.
5. COMT (catecholamines, CHD,MI, HBP, ASA and vitamin E responses
6. 1q25 (GLUL): CHD in DM, enterocytes and ED.
7. APO E : dyslipidemia, CHD, MI, nitric oxide, statin response.
8. MTHFR: methylation (1298C and 677T): hypertension, CHD, MI, CVA, thrombosis, homocysteine, ED.
9. CYP 1A2 : caffeine ,HBP,MI, aortic stiffness, PWV, AI, tachycardia, arrhythmias, vascular inflammation, catecholamines.
10. Corin : hypertension, CHF, volume overload, sodium sensitive, CVD, CRF, pre-clampsia), ANP and BNP.
11. CYP 11 B2 (TT allele): HBP, aldosterone and response to spironolactone.

CARDIA X
Recommended Testing for Early Detection and Prevention of CHD
Genetic Testing

1. GSHPx : CHD, MI, hypertension, LVH, CHF, Glutathione, ALA 6 alleles, selenium.
2. ADR B2: HBP, PRA, inflammation and DASH diet with ACEI, ARB or DRI.
3. APO A1 : lipids, HDL, CHD, MI obesity.
4. APO A2 : lipids, HDL, CHD, M I, obesity.
5. APC C 3 : dyslipidemia, CHD,MI, dysfunctional HDL, inflammation, DM.
6. CYP 4 A11: hypertension, ENaC and sodium, volume overload, CHD and amiloride.
7. CYP 4F 2 : hypertension, ENaC and sodium, volume overload, CHD and amiloride.
8. AGTR1 (ATR1AA): HBP, ARBs and potassium.
9. NOS 3: nitric oxide, hypertension, MI, CHD,CVA, thrombosis, ED, oxidative stress, inflammation.
10. SCARB1: lipids, dysfunctional HDL with high HDL, CHD, MI.

Gene Expression Testing: GES (Gene Expression Score) Corus CHD

Cath Lab Digest 2013;21:8 Circulation 2008;1:31
Critical Pathways in Cardiology 2013;12:37
Circulation: Cardiovascular Genetics 2013;6:154
J of Cardiovascular Translation Research 2012;3:366
Am Heart J 2012;164:320 ; Circ Cardiovas Genet 2008;1:31

- Gene expression test that measures changes in WBC RNA levels that sensitive to the presence of coronary plaque.
- Measures expression levels of 23 genes grouped into 6 categories.
- Highly correlated with QCA (quantitative coronary artery angiogram) and degree of stenosis.
- IMPACT, PREDICT, COMPASS trials

Gene Expression Testing: Gene Expression Score (GES) Corus CHD

Cath Lab Digest 2013;21:8 Circulation 2008;1:31
Critical Pathways in Cardiology 2013;12:37
Circulation: Cardiovascular Genetics 2013;6:154
J of Cardiovascular Translation Research 2012;3:366
Am Heart J 2012;164:320; Circ Cardiovas Genet 2008;1:31

Measures expression levels of 23 genes grouped into 6 categories.

- Cellular and neutrophil apoptosis and necrosis
- Neutrophil to lymphocyte ratio
- NKTc (Natural killer T cell)activation.
- Inflammatory cell biology and cell migration into atherosclerotic plaque
- Innate and adaptive immune response to LDL oxidation and other inflammatory processes

PREDICT TRIAL
Gene Expression Testing: GES (Gene Expression Score) Corus CHD

Ann Intern Med 2010;153:425
J of Cardiovascular Translation Research 2012;3(5):366
Am Heart Journal 2012;164:320

- Correlated QCA with Corus gene expression
- Higher the Corus score (0-40) the greater the chance of a 50% or greater stenosis in one major coronary artery and greater risk of future MACE (major adverse CV event).
- Score < 15 = Low risk for CHD
- Score 28 = 50% chance of major CHD
- Score 40 = 68% chance of major CHD

IMPACT Trial

J Am Board Fam Med 2014;27:258
Crit Pathways in Cardiol 2013;12:37

- Prospective study 251 non diabetic subjects with stable nonacute chest pain and related symptoms.
- GES done in all patients. Average score 16 (1-38)
- GES directed additional diagnostic CV testing and improved accuracy of diagnosis.

COMPASS TRIAL
Gene Expression Testing: (GES) Gene Expression Score: Corus CHD

Circ Cardiovasc Genet 2013;6:154

- Compared Corus gene expression to nuclear stress testing or myocardial perfusion imaging (MPI) in 537 patients.
- All patients had QCA or CTA
- Corus outperformed MPI in accuracy for predictive CHD. Corus 96% negative predictive value, 89% sensitive and 53% specificity and MPI was 88% negative predictive value
- Strong discrimination for CHD, proportional to QCA stenosis, better than MPI, good agreement with both CTA and QCA.

PULS(Protein Unstable Lesion Signature) Cardiac Test (CHL)

Curr Med Res Opin 2012;28:1819-30

Elevated score related to:

- **CHD development**
- **Presence of unstable or vulnerable arterial plaque**
- **Increased near-term risk of myocardial infarction**

Biomarkers:

- **MCP-3: immune cell direction and activity**
- **sFas: prevents apoptosis**
- **Fas Ligand: initiates cell recycling and death**
- **Eotaxin: activates immune cells at areas of injury**
- **CTACK: Helps to clean up damaged cells**
- **IL-16: recruits and activates immune cells, inflammation**
- **HGF: stimulates tissue repair.**

Normal less than 3.5. Borderline 3.5 -7.49. Elevated > 7.5

Mediterranean Diet and CV Risk

Am J Clin Nutr 2010;92:1189
NEJM 2013;368:1 PREDIMED)
. N Engl J Med.2013 ;368(14):1279-90.

In the 4.8 year primary prevention PREDIMED diet study of 7447 subjects

1. **The rate of major cardiovascular events from MI, CVA or CV death were reduced overall by 30 % with nuts and 30% with extra virgin olive oil (EVOO).**
2. **The reduction in CVA was 39 % overall ($p<0.003$) with a 33% reduction from EVOO and a 46% reduction from nuts.**
3. **The reduction in MI was 23 % overall ($p=0.25$) with a 20 % reduction for EVOO and a 26% reduction from nuts.**
4. **Total CV deaths were reduced overall by 17% ($p= 0.8$).**

Cancer mortality 6%

Neurodegenerative disease 13%

Dietary Patterns and Long-Term Survival: A Retrospective Study of Healthy Primary Care Patients

Am J Med.2018 Jan;131(1):48-55.

- In this observational cohort study at the Cooper Clinic preventive medicine center (Dallas, Tex), a volunteer sample of 11,376 men and women with no history of myocardial infarction or stroke completed a baseline dietary assessment between 1987 and 1999 and were observed for an average of 18 years. Proportional hazard regressions, including a tree-augmented model, were used to assess the association of the Dietary Approaches to Stop Hypertension (DASH) dietary pattern, Mediterranean dietary pattern, and individual dietary components with mortality. The primary outcome was all-cause mortality. The secondary outcome was cardiovascular mortality.

- RESULTS:
- Mean baseline age was 47 years. Each quintile increase in the DASH diet score was associated with a 6% lower adjusted risk for all-cause mortality ($P < .02$). The Mediterranean diet was not independently associated with all-cause or cardiovascular mortality. Solid fats and added sugars were the most predictive of mortality. Individuals who consumed >34% of their daily calories as solid fats had the highest risk for all-cause mortality.

- CONCLUSIONS:
- The DASH dietary pattern was associated with significantly lower all-cause mortality over approximately 2 decades of follow-up in a middle-aged, generally healthy population. Added solid fat and added sugar intake were the most predictive of all-cause mortality. These results suggest that promotion of a healthy dietary pattern should begin in middle age, before the development of comorbid risk factors

Nutrition, Dyslipidemia and CHD

Curr Opin Lipidol 2016;27: 323

SFA relationship to CHD is complex and depends on many factors

- Chemical and metabolic heterogeneity of the SFA.
- Type of replacement nutrient
- Inter-individual variability in dietary response and genetics (PPAR)
- Food and or dietary pattern context in which the SFAs are consumed.
- Presence of insulin resistance
- Obesity, BMI, body fat
- An emphasis on foods and dietary patterns to achieve cardiovascular health supersedes a focus on individual macronutrients.
- Sugars, refined carbohydrates, fructose, HFCS, starches and TFA confer more risk to dyslipidemia and CHD than SFA.
- Omega 3 FA, MUFA, fermented foods, fiber, F+V, dairy, TMD, DASH reduce CHD. Omega 6 FA consumption is now contested.

SFA, PUFA, MUFA, Lipids and CHD: Summary

Lipids 2010:45:893-905;Progress in CVD 2016;58:464;Am J Clin Nutrition 2016;104:1209; J of Nutritional Biochemistry 2016;36:1-20

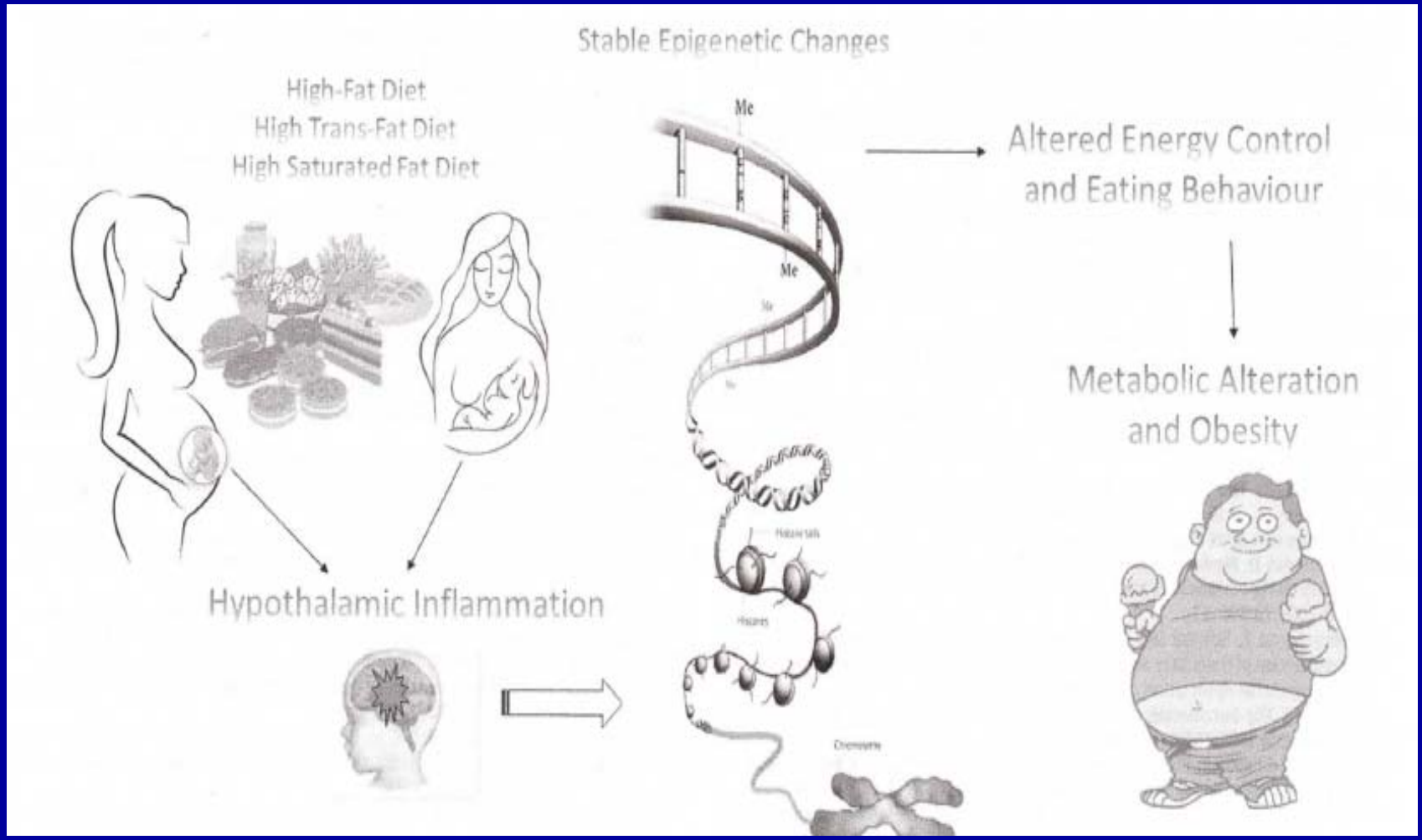
1. Dyslipidemia effects: increase LDL TC/HDL ratio
   - Increased LDL with lauric (12), myristic (14) and palmitic acid (16)
   - Decreased or neutral with stearic acid (18)
   - However, the increase in LDL is large type A, not small dense type B
2. Minimal to no association with CHD/CVD(2% increase)
   Mixed results with IR, DM, vascular function and stroke.
3. Replace SFA or dairy fat with PUFA reduces CHD/CVD 10%-24%
4. Replace dairy fat with other animal fat increases CHD/CVD risk 6%
5. Replace SFA with refined CHO, sugars, fructose, HFCS, or starches increase CVD/ CHD
6. Replace SFA or dairy fat with whole grains or non refined CHO reduce CHD/CVD by 28%
7. Replace SFA with MUFA lowers (1-2%) or minimal change in risk on CHD/CVD
8. Trans fat intake increased CHD 16%
9. Omega 6 FA increased CHD 1%

The relation of saturated fatty acids with low-grade inflammation and cardiovascular disease.

J Nutr Biochem.2016 Oct;36:1-20.

- The mantra that dietary (saturated) fat must be minimized to reduce cardiovascular disease (CVD) risk has dominated nutritional guidelines for decades.
- Parallel to decreasing intakes of fat and saturated fatty acids (SFA), there have been increases in carbohydrate and sugar intakes, overweight, obesity and type 2 diabetes mellitus.
- The "lipid hypothesis" coined the concept that fat, especially SFA, raises blood low-density lipoprotein-cholesterol and thereby CVD risk. In view of current controversies regarding their adequate intakes and effects.
- The intimate relationship between inflammation and metabolism, including glucose, fat and cholesterol metabolism, revealed that the dyslipidemia in Western societies, notably increased triglycerides, "small dense" low-density lipoprotein and "dysfunctional" high-density lipoprotein, is influenced by many unfavorable lifestyle factors. Dietary SFA is only one of these, not necessarily the most important, in healthy, insulin-sensitive people.
- The environment provides us not only with many other proinflammatory stimuli than SFA but also with many anti-inflammatory counterparts. Resolution of the conflict between our self-designed environment and ancient genome may rather rely on returning to the proinflammatory/ant-inflammatory balance of the Paleolithic era in consonance with the 21st century culture. Accordingly, dietary guidelines might reconsider recommendations for SFA replacement and investigate diet in a broader context, together with nondietary lifestyle factors.
- This should be a clear priority, opposed to the reductionist approach of studying the effects of single nutrients, such as SFA

Mechanism of Programming Induced by Dietary Fats



J Nutr Biochem 2017;42:1-6

Risk of T2D by the Updated Intake of SFAs

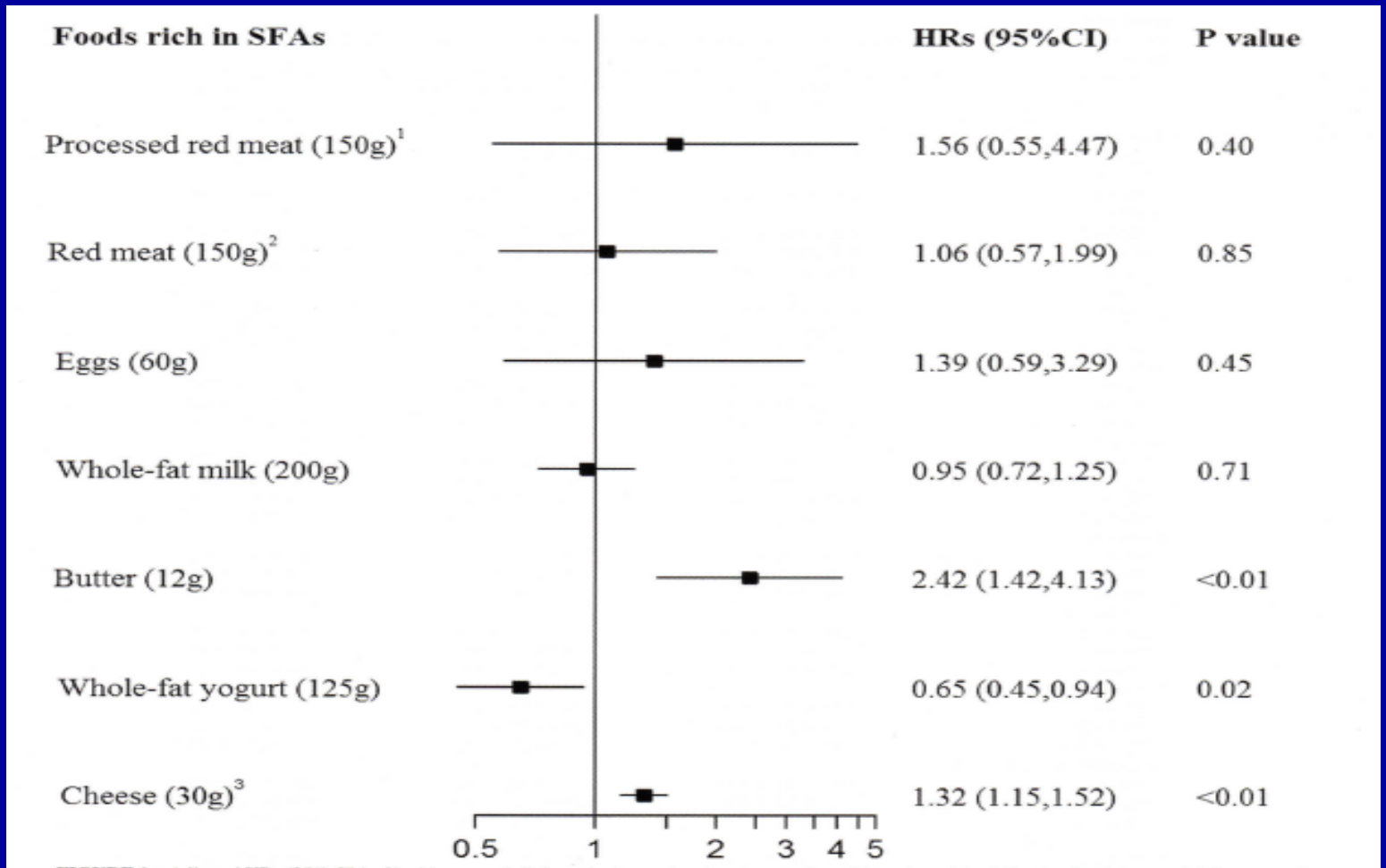


FIGURE 1 Adjusted HRs (95% CIs) of incident type 2 diabetes by increasing the consumption of 1 serving of the following food sources rich in saturated fat: processed red meat, red meat, eggs, whole-fat milk, butter, whole-fat yogurt, and cheese. The multivariable model was adjusted for age, sex, intervention group, BMI (in kg/m^2), smoking status, educational status, leisure-time physical activity, baseline hypertension or the use of antihypertensive medication, hypercholesterolemia or the use of lipid-lowering drugs, fasting plasma glucose, yearly updated total energy intake, alcohol intake, and the intake of vegetables, fruits, legumes, cereals, fish, meat, dairy, olive oil, nuts, and biscuits (except if the exposure was included in these food groups). The analyses were stratified by recruitment center. [1]Includes offal, ham, sausages, pâté, hamburgers, and bacon. [2]Includes pork, veal, beef, and lamb. [3]Includes petit Suisse, ricotta, cottage, spreadable, and semicured and cured cheeses.

Am J Clin Nutr 2017;105:723-35

SFA, Lipids and CHD: Summary

Lipids 2010:45:893-905;Am J Clin Nutr 2016:103:356
Am J Clin Nutr 2010;91:535;BMJ 2015;351:h3978
AmJ Clin Nutr 2009:89:1425;Am J Clin Nutr 1999;70:1001
Am J Clin Nutr 2003;77:1146; Am J Clin Nutr 2012;96:397
Int J Epidemiol 2010;39:1170;Ann Intern Med 2014;160:398

Meta-analysis showed on association between SFA intake and CHD risk with RRR of 1.07 to 1.03 (NS).

However this depends on the following:

- **Macronutrients that replace the SFA in the diet**
- **Specific types of SFA that differ in carbon chain length. LCFA (C12-C18, lauric, myristic, palmitic and stearic) will have varied effects on both serum lipids and risk of CHD. LCFA increased risk of CHD but SCFA (C4-C10, butyric-capric) did not increase CHD risk.**
- **Different food sources and inherent nutrients in those food sources of SFA will alter lipids and CHD risk. In MESA, dairy SFA at 5 grams per day had 16% lower risk and meat at 5 grams per day had 29% higher risk of CHD.**

Caffeine, Coffee, Hypertension, CHD and MI.

J of Hypertension 2009;27:1594;Am J Clin Nutr 2007;86:457
European J Clinical Nutrition 2007;61:796; Am J Clin Nutr 2011;94:1113
Current Opinion in Lipidology 2007;18:13;JAMA 2006;295:1135.

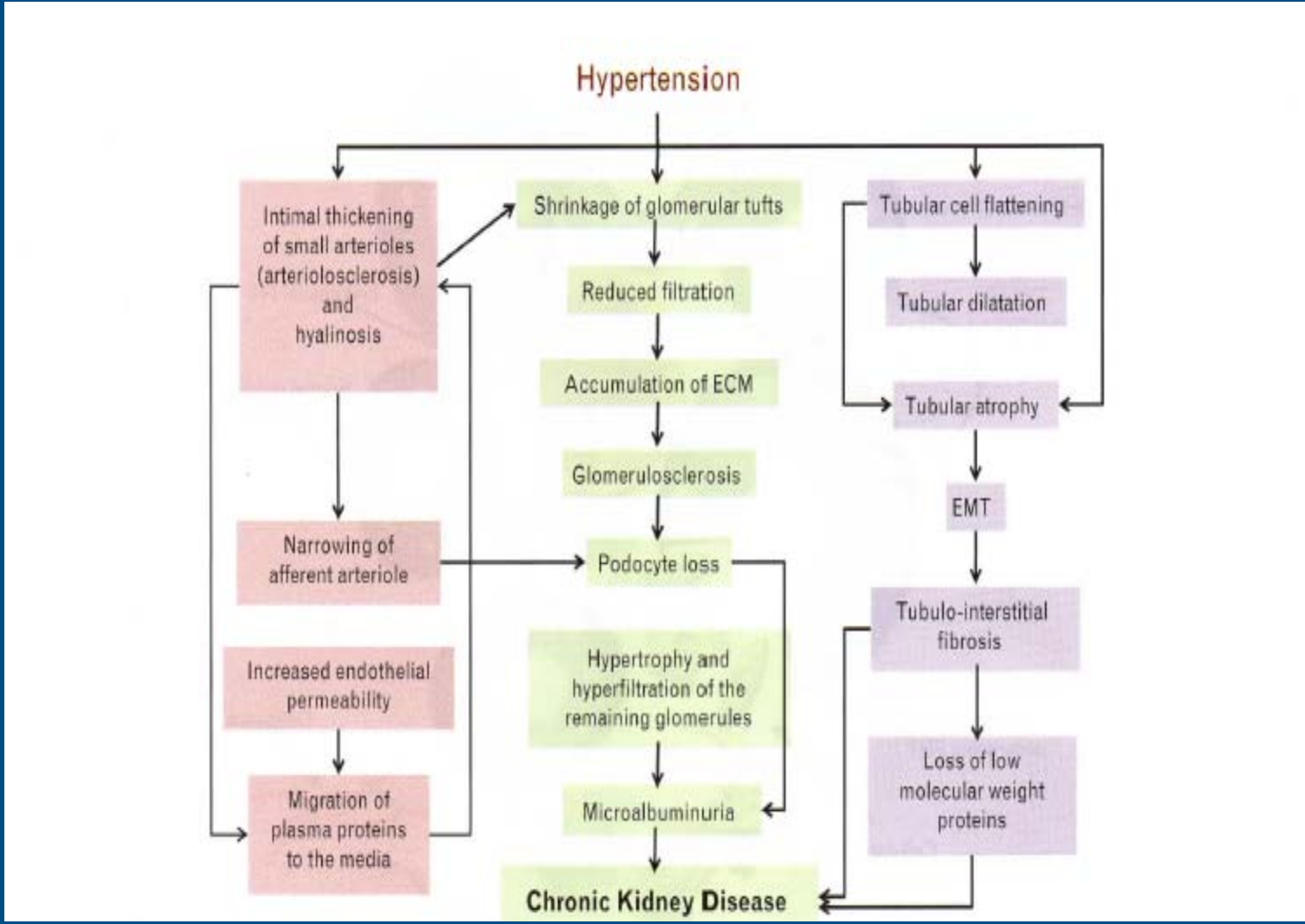
- Cytochrome P-450 - CYP1A2 genotype modifies the association between caffeinated coffee intake and the risk of hypertension, CVD, CHD and MI in a linear relationship. Caffeine is exclusively metabolized by CYP1A2 to paraxanthine, theobromine and theophylline.
- Chromosome 15q24.1. SNP is rs7762551 A to C. C SNP decreases enzymatic activity. Caffeine also blocks vasodilating adenosine receptors.
- Rapid metabolizers of caffeinated coffee IA/IA allele have lower BP and lower risk of MI. Hypertension .36 to .80 RR. SBP decrease 10/7 mm Hg. MI is 17%-52% reduction. About 40-45% of the population.
- Slow metabolizers of caffeine IF/IF or IA/IF allele have higher BP 8.1/5.7 mm Hg lasting > 3 hours after consumption. Have tachycardia, increased aortic stiffness and increased catecholamines. Increased hypertension 1.72 to 3.00 RR. Over age 59: MI 36% increase (2-3 cups/d) ; 64 % increase 4 cups or more/d. Under age 59: MI 24% (1 cup/d), 67%(2-cups/d) and 233%(4 or more cups/d) About 55-60% of population
- Increased aortic stiffness , increased arterial pulse wave velocity and wave reflections and vascular inflammation. Augments SBP and PP.
- Polyphenols, chlorogenic acid and dihydro-caffeic acid increase eNOS, NO, improve ED and lower BP 10/7 mm Hg at 140 mg / day (cocoa in coffee). Diterpenes in unfiltered coffee and caffeine increase risk of CHD.

Heart rate predicts cardiac events in treated hypertensive patients

Am J Cardiol 2012;109:68;Am J Cardiol. 2012;109:699-704
J Clin Hypertens 2013;15:579 ;JASH 2014;8:699; Am J Med 2015;128:219

- 15,193 patients(VALUE trial) : 5 years
- Each 10 bpm increase starting at 62 b/min in resting HR increased risk for cardiovascular events (CHD, CHF, MI) by 16% or more.
- BP control did not modify the effect but RAAS drugs did. Unknown if reduction in HR will improve CV outcomes.
- HRRT also predicts CVD: Should drop 16 beats at one minute post exercise.
- Also HRV (heart rate variability) if abnormal increases CVD and inflammation.(SNS/vagal tone)

Changes Associated With



J Hypertens 2017;35:205-212

Microalbuminuria (MAU)

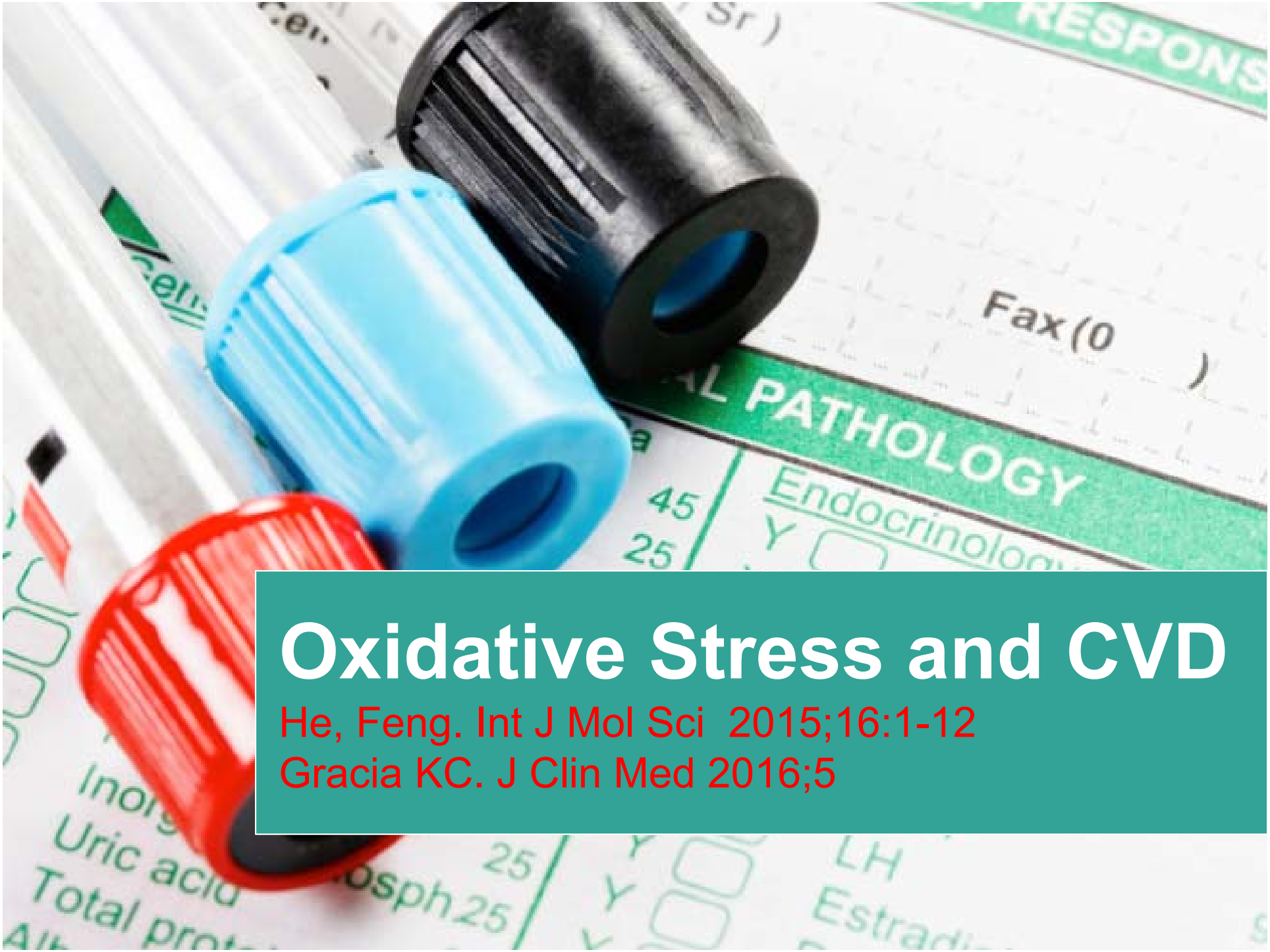
Clin J Am Soc Nephrol 2010;5:1099
Am J Cardiol 2010;106:976
J of Hypertension 2011;29:1411
Crnt Opin in Nephr and HTN 2010;19:513
J of Hypertension 2010;28:1983
J Hypertension2010;28:2357

- Microalbuminuria is one of the earliest abnormalities in vascular system and kidney that reflects endothelial dysfunction and increased vascular permeability.
- High correlation with progression to proteinuria, renal disease, LVH and future CVD, CHD, MI, CHF, and CVA.
- Linear relationship of albumin /creatinine ratio: ACR starting below 5 mg/gm (previous cutoff for normal of 30 mg/gm is too high). Spot urine sample is required not 24 hour urine..
- MAU triggers tubular RAAS activation via megalin/cubilin receptors and inflammatory/oxidative stress reaction with NFkB/AP-1.
- Reduced best with excellent BP control with RAAS drugs and also with omega 3 fatty acids and lipoic acid.

Lipoprotein-associated phospholipase A2 (Lp-PLA2)

J of Clinical Lipidology 2009;3:85
Curr Treatment Options CardiovascMed 2013;15:313
Nutr Metabl Cardiovasc Dis 2013; Nov 1 EPUB
J of Clinical Lipidology 2016;10:512

- Expressed in atherosclerotic plaques, foam cells and macrophages in fibrous cap
- Attached to LDL and is only enzyme responsible for hydrolysis of oxidized phospholipids to produce lysophosphatidylcholine and other lysophospholipids (proinflammatory and atherogenic) FA hydroperoxides and oxidized FA and stimulates IL-1B and IL-6
- Distribution between LDL and HDL determined by glycosylation.
- High levels mean unstable plaque and rupture vulnerability.
- Predicts MI and CVA and carotid IMT. Independent risk factor
- One gram Omega 3 FA in stable angina decrease LpPLA2 by 9.4% and oxLDL by 12.3%. No change in MPO or IL6. Expressed in atherosclerotic plaques, foam cells, and macrophages in fibrous cap
- Reduced by omega 3 FA (11%-20%), niacin (20-32%), fibrates (13%-30%) and statins (25%-41%)
- Rosuvastatin alone 41%, R +F=38% , R +O = 30%
- Also high protein, ETOH, MUFA, weight loss lowers LpPLA 2

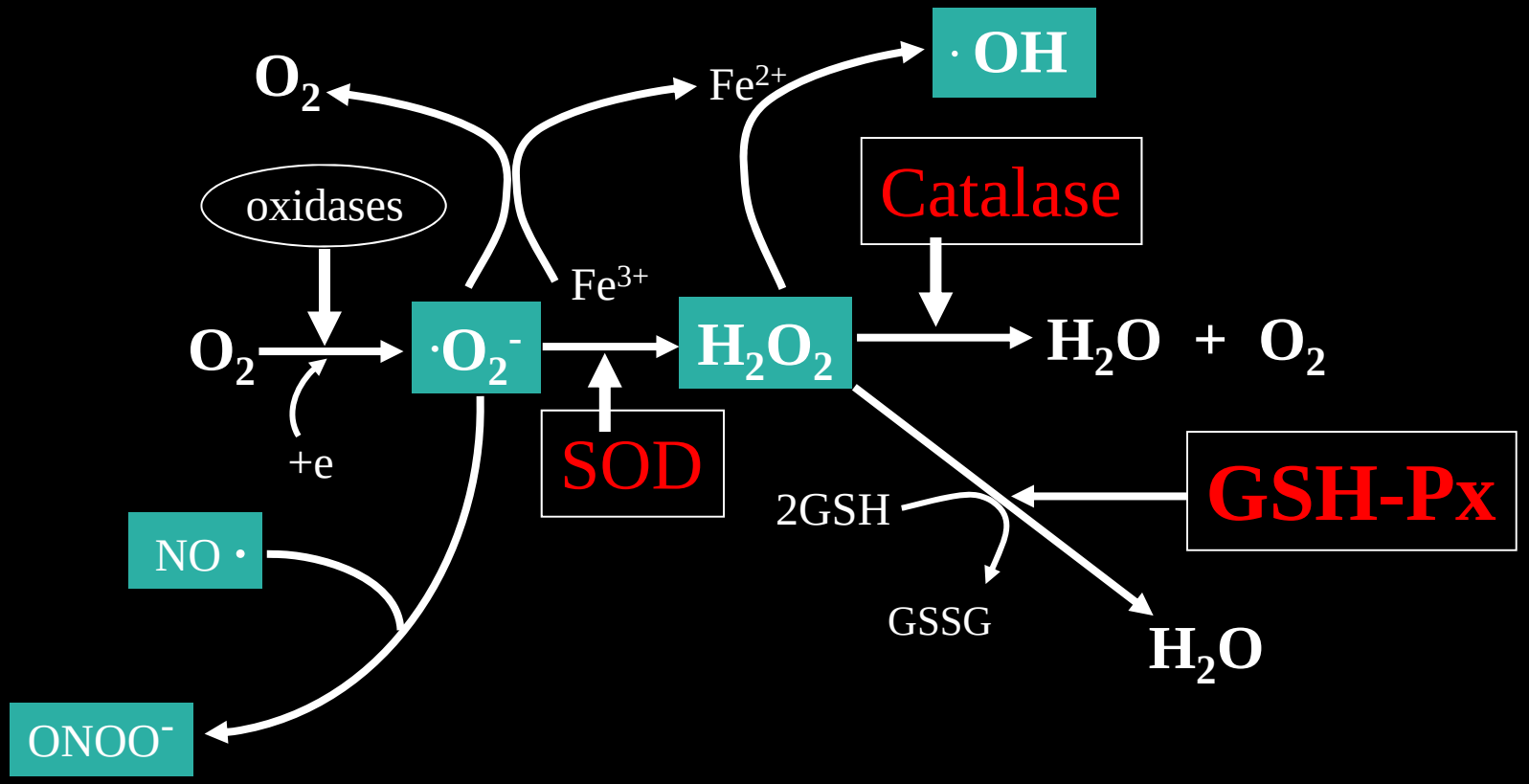


Oxidative Stress and CVD

He, Feng. Int J Mol Sci 2015;16:1-12

Gracia KC. J Clin Med 2016;5

Reactive Oxygen Species [1,11] Formation and Defenses



Vascular ROS. Highlighted in gray are some of the most important ROS in vascular cells. Oxidases convert oxygen to $O_2^{\cdot -}$, which is then dismutated to H_2O_2 by superoxide dismutase (SOD). H_2O_2 can be converted to H_2O by catalase or glutathione peroxidase (GSH-Px) or to hydroxyl radical (OH^-) after reaction with Fe^{2+}. In addition, $O_2^{\cdot -}$ reacts rapidly with nitric oxide ($NO^{\cdot}$) to form peroxynitrite ($OONO^-$).

Oxidative Stress, Glutathione, Glutathione Peroxidase, HTN, and CHD (Level A)

Circulation 2004; 109:544-549

- Increased glutathione peroxidase (GSH-Px) lowers BP, reduces MI, LVH and CHF.
- GSH-Px confers more cell, tissue and organ protection than SOD or catalase, or the combination of both.
- 5 GSH-Px (#1-#4 are selenium-dependent, #5 is not) is located in mitochondria and cytosol, which neutralize lipid peroxides and hydrogen peroxide, preventing formation of hydroxyl radical and other ROS. GSH-Px has greater affinity for hydrogen peroxide than catalase.
- Peroxiredoxins (Prx) (#1-6) scavenge hydrogen peroxide as well. Prx #3 is in the mitochondria and protects cardiac muscle.
- Highest quartile of RBC GSH-Px had 71% lower risk of MI compared to lowest quartile ($p<.001$). GSH-Px is major CHD risk factor (NEJM 2003; 349:1605-13). Abnormal genotypes also exist which increase risk (Coronary Artery Disease 2003; 14:149-153).

Iron and Ferritin

Atherosclerosis 2001;154:739 (ARIC study)
Klin Med (Mosk) 2005;83:25
Diabetes Care 2007;30:101

- Enhanced iron-mediated oxidative stress and LDL peroxidation contribute to dyslipidemia-related and non-lipid ROS-mediated endothelial dysfunction, atherosclerosis, CHD.
- Increased risk of CHD, MI, and carotid artery disease with increased iron levels is genetic and not universal (HFE C282Y mutation) (ARIC Study).
- Genetic predisposition, men, diabetes, postmenopausal women at greatest risk.

Iron and Ferritin

Atherosclerosis 2001;154:739 (ARIC study)
Klin Med (Mosk) 2005;83:25
Diabetes Care 2007;30:101

- Related to severity of perfusion and functional abnormalities of coronary arteries, but not always anatomic angiographic obstruction. Microvascular angina and endothelial dysfunction of the coronary arteries.
- Compounds CHD with dyslipidemia and other CHD risk factors. Iron supplementation directly increases LDL cholesterol levels.
- Ferritin = Iron Stores (and CHD risk)
  Ferritin > 200 ug/L = 2 x risk (Finnish)
  Ferritin x 10 = Iron Stores

Controlled Reduction of Body Iron Stores Reduces PAD, MI, and CVA

Am Heart J 2011;162:949

- Lower iron burden and controlled phlebotomy improved CV outcomes of PAD, MI and CVA and life expectancy.
- Ferritin levels of 76.5 ng/ml had lowest event rate for CVD.

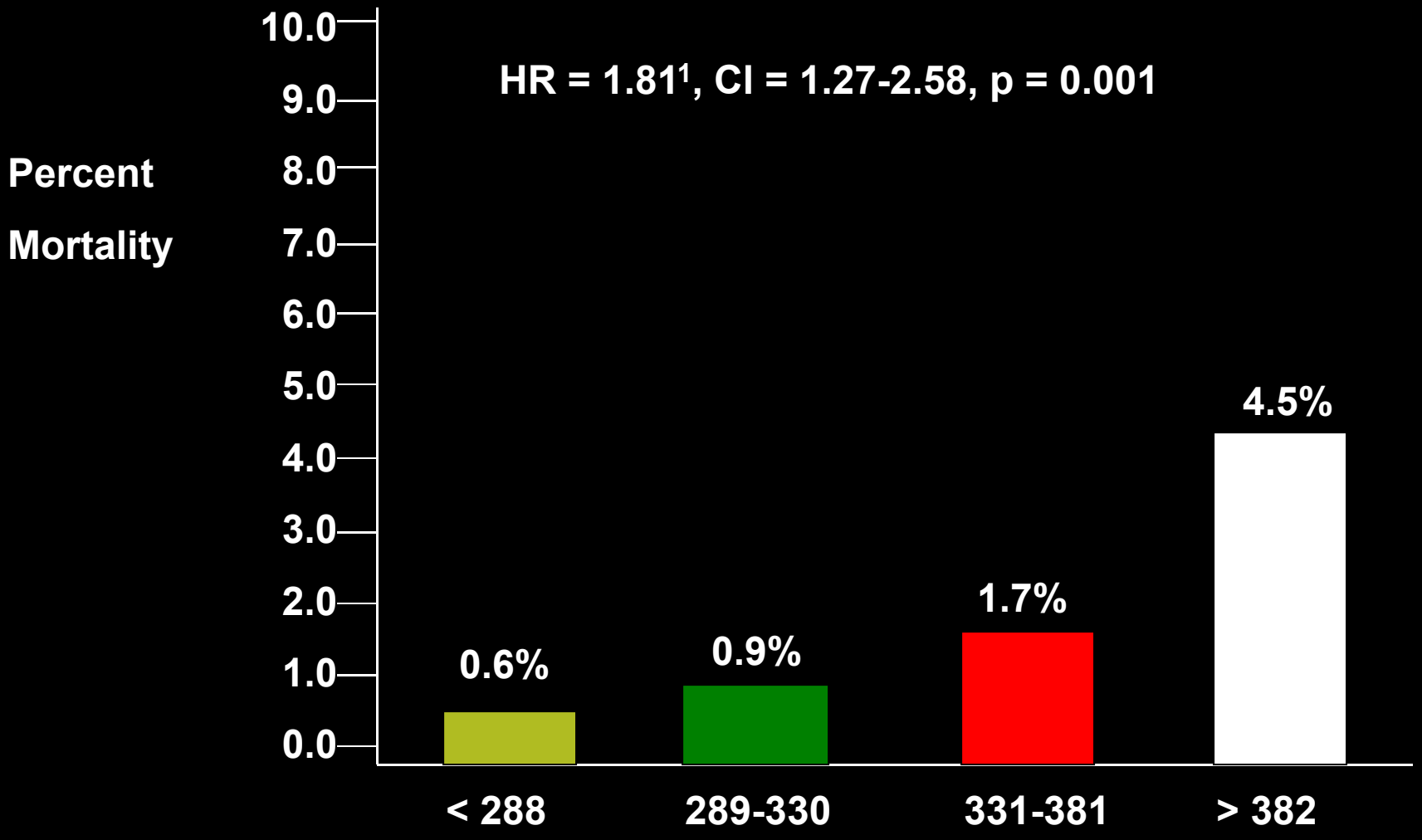
Fibrinogen

- Directly associated with increased thrombotic rate:
  - CHD / MI
  - Independent short-term predictor of mortality
  - ASCVD
  - CVA / TIA

Fibrinogen

- Meta-Analysis: (Arterioscler Thromb Vasc Biol 1999; 19:368)
  CV risk in highest tertile of fibrinogen was 2 x risk in lowest tertile (OR = 1.99) ($p < .05$)
- Each 50 mg/dL increase = 30% increase CHD
- Keep level below 380 mg/dL
- Plasma viscosity correlates with fibrinogen and is independent risk factor. Compounds risk with fibrinogen.
- 2,126 patients (Am Heart J 2002; 143:277-282)
  - Highest quartile (OR = 1.22) ($p < .001$) for CHD
  - Presence of CHD or H/O MI (OR = 1.25) ($p < .001$)
  - Total mortality increased (HR = 1.81)($p < .001$)

FIBRINOGEN



Mortality rate by fibrinogen quartile

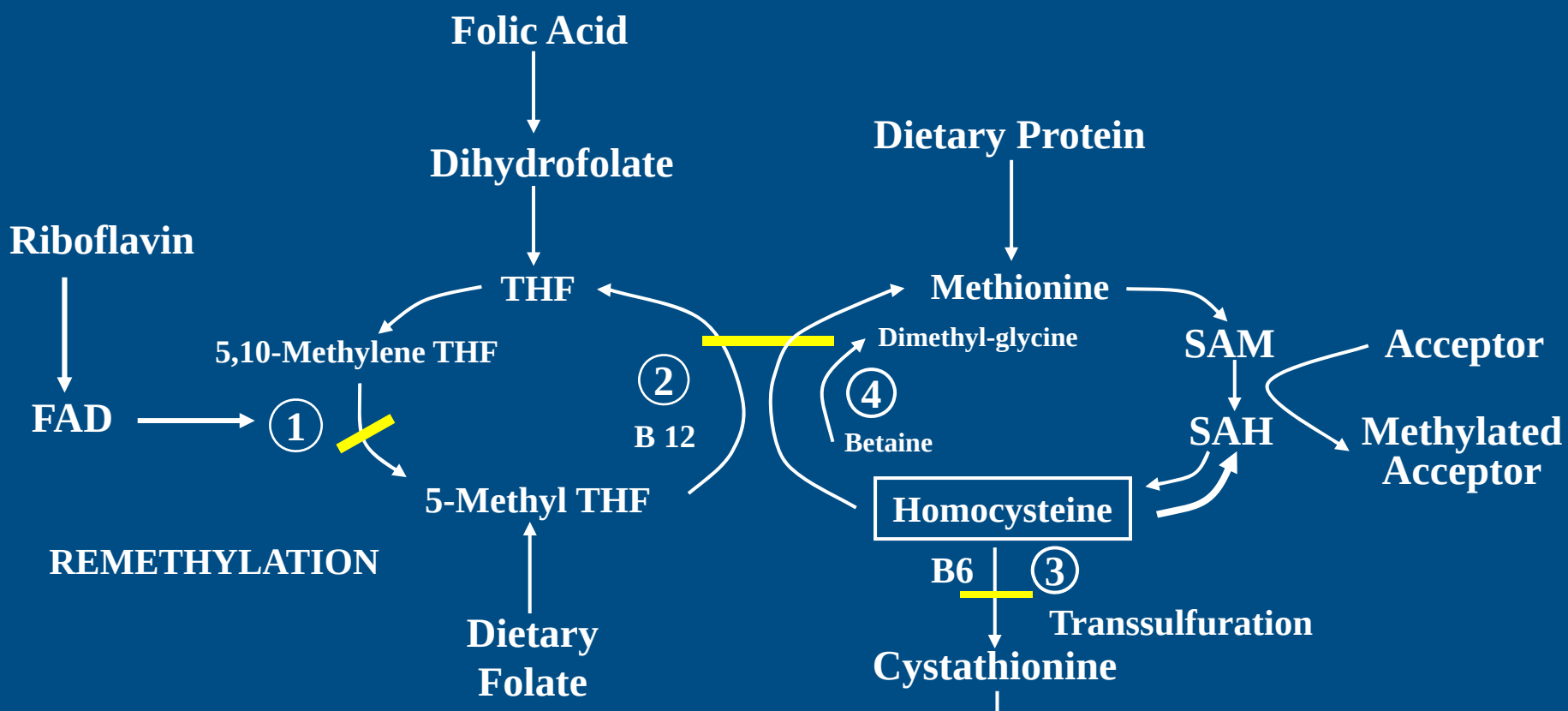
[1] Adjusted for Framingham risk score

Plasma Viscosity

Therapeutic Advances in Cardiovascular Disease 2015;9:19-25

- Resistance to blood flow in a blood vessel
- Blood viscosity decreases as shear rate increases (non-Newtonian fluid due to RBC deformability and deaggregation).
- Worse at outer wall of vascular branches and inner wall of curves.
- Fibrinogen can bind RBC and induce aggregation.
- Seen in atherosclerosis, hypertension, dyslipidemia, DM, metabolic syndrome, tobacco use, obesity, aging, hyperfibrinogenemia, polycythemia, thrombocytosis, elevated globulins, cryoglobulinemia and male gender.
- LDL is large enough to bind RBC. HDL is smaller and cannot.
- Normal viscosity is 32.6 millipoise at shear rate of 100/s

Homocysteine and Folate Metabolism



1. Methylenetetrahydofolate reductase
2. Methionine synthase
3. Cystathionine β-synthase
4. Betaine-homocysteine methyltransferase

THF = Tetrahydrofolate
SAM = S-adenosylmethionine
SAH = S-adenosylhomocysteine
= possible enzyme deficiency

Hyperuricemia

J of Hypertension 2015;33:1729-41

- Increases risk of hypertension, endothelial dysfunction, metabolic syndrome, CVD,CHD,MI,ACS,CVA,CHF and CKD.
- Humans lack uricase to convert UA to soluble allantoin.
- Keep UA level below 6 mg/dl
- Both anti-oxidant and pro-oxidant depending on level in localization.
- Increase oxidative stress, RAAS activation, inflammation, immune dysfunction of blood vessels, VSMH, lowers NO, sodium sensitivity and hypertension, arterial stiffness.
- Genetics, ETOH, drugs (diuretics, BB, ASA), obesity, diet increase UA..
- Allopurinol lowers BP 3.3/1.3 mm Hg, improves ED, PWV,CHD/ angina exercise time, LVH and perhaps CHF.

Relation of Lipid Content of Coronary Plaque to Level of Serum Uric Acid.

Am J Cardiol. 2015 .116(9):1346-50.

- Elevated serum uric acid (SUA) level is a prognostic factor in patients with acute coronary syndrome (ACS).
- A total of 81 patients with ACS underwent intravascular ultrasound (IVUS)
- Classified into 3 groups according to tertiles of SUA level.
- Tissue components were classified into 4 categories: calcium deposits, dense fibrosis, fibrosis, and lipid.
- Tertiles of SUA level : low tertile <5.0 mg/dl; intermediate tertile 5.0 to 6.4 mg/dl; and high tertile >6.4 mg/dl.
- There was a trend toward greater vessel volume in the high tertile group than in the low and intermediate tertile groups (p = 0.05).
- There was no significant difference in lumen volume between the 3 groups.
- Plaque volume was significantly greater in the high than in the low tertile group (, p = 0.01).
- IB-IVUS analysis demonstrated greater lipid (, p = 0.001) and less fibrous components (, p <0.001) in the high than in the low and intermediate tertile groups. Multivariate analysis shows high SUA as an independent predictor of increasing lipid volume.
- Elevated SUA level is associated with greater lipid content with less fibrous components of coronary plaque and plaque volume in patients with ACS than in patients with normal levels.

ADMA (Asymmetric Di-methyl Arginine)

- Autocrine regulator of eNOS
- Inhibits eNOS and reduces NO (competitive substrate)
- Elevated in hypertensive children and young adults
- Elevated in DM, CRI, Smokers, HBP, HLP, homocysteine, Elderly, Atherosclerosis
- VCAM and VWF positively correlate with ↑ ADMA
- Levels of ADMA (Endothelial > Plasma levels)

Normal	1.0 ± 0.1 μmol/ L
HLP	2.2 ± 0.2 μmol/ L
HBP	2.2 ± 0.2 μmol/ L
Elderly *with* AS	2.5 ± 3.5 μmol/ L

- oxLDL → ↑ ADMA → Citrullene
- Methionine (Homocysteine) → DDAH

- eNOS + ADMA → O_2^- → NFκB activation → ↑ MCP-1

- DDAH = Dimethyl Dihydroxy Arginine Hydrolase
- Inhibited by : oxLDL, PPAR, Cytokines (TNF-α) , homocysteine and insulin
- Stimulate by : retinoic acid

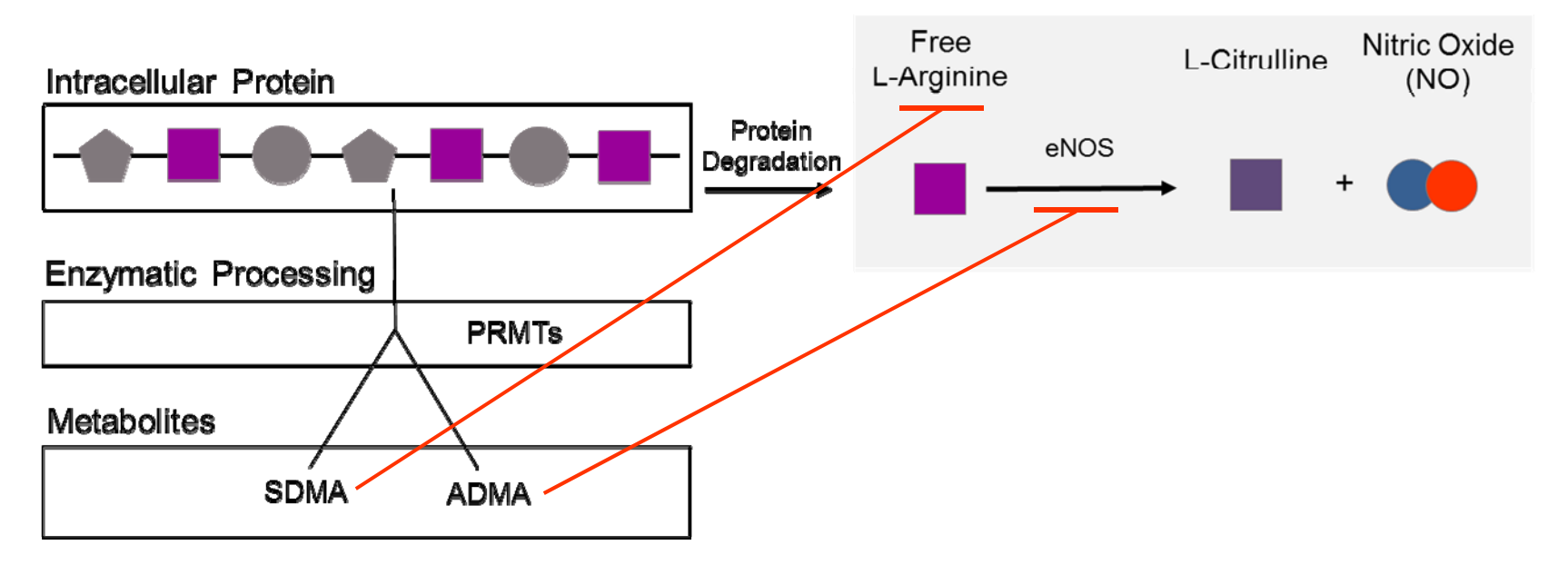
Vascular Biology in Clinical Practice, Oct. 2000; M C. Houston,

ADMA: Asymmetric Dimethlyarginine

Circulation 2004;109:1813-1818

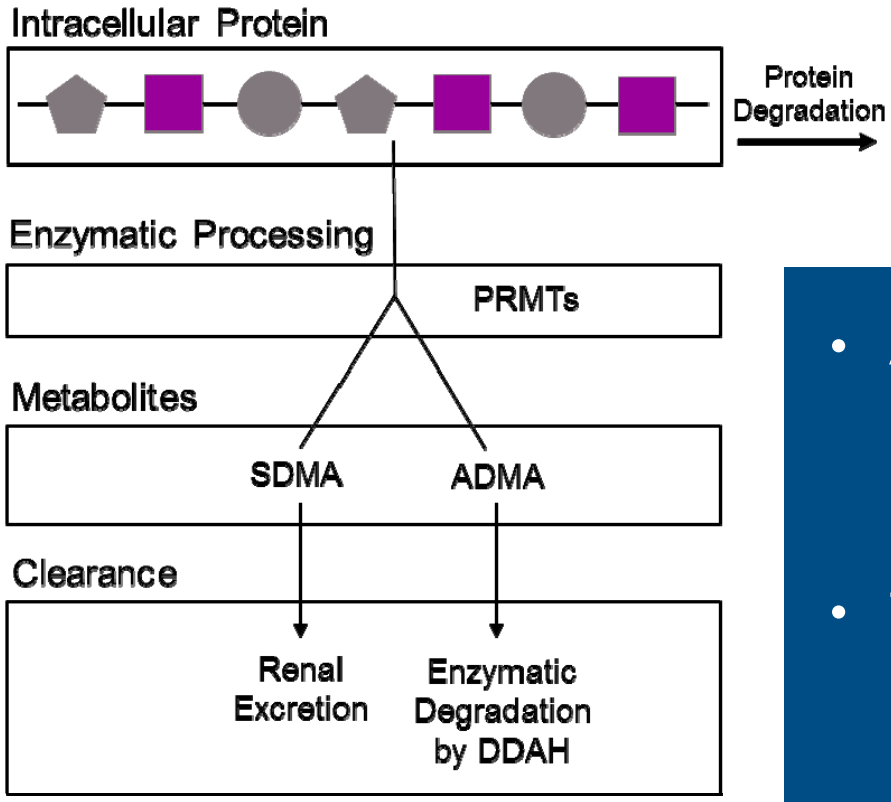
- Most traditional risk factors mediate vascular and endothelial dysfunction by reductions in bioavailable nitric oxide(NO)
- The mechanism is by ADMA accumulation, in part, that is a competitive inhibitor of eNOS . This reduces the production of NO.
- activity of DDAH II (dimethylarginine dimethylhydrolase), the endothelial enzyme that breaks down ADMA.
- DDAH II is inhibited by oxidative stress, oxLDL, inflammation, cytokines, hyperglycemia, hyperlipidemia, homocysteinemia, infectious agents. (oxidize sulfhydryl group in the enzyme)
- If ADMA levels are high and eNOS is not working, then statins will only reduce LDL but will not increase NO or improve ED.

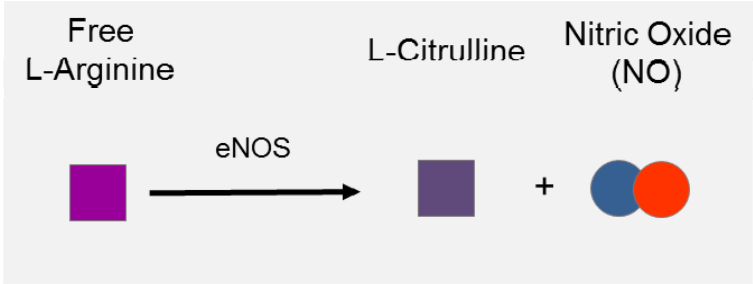
Regulation of NO production by ADMA and SDMA



- ADMA directly blocks eNOS to inhibit NO production
- SDMA indirectly blocks NO production by inhibiting the availability of free L-Arginine.

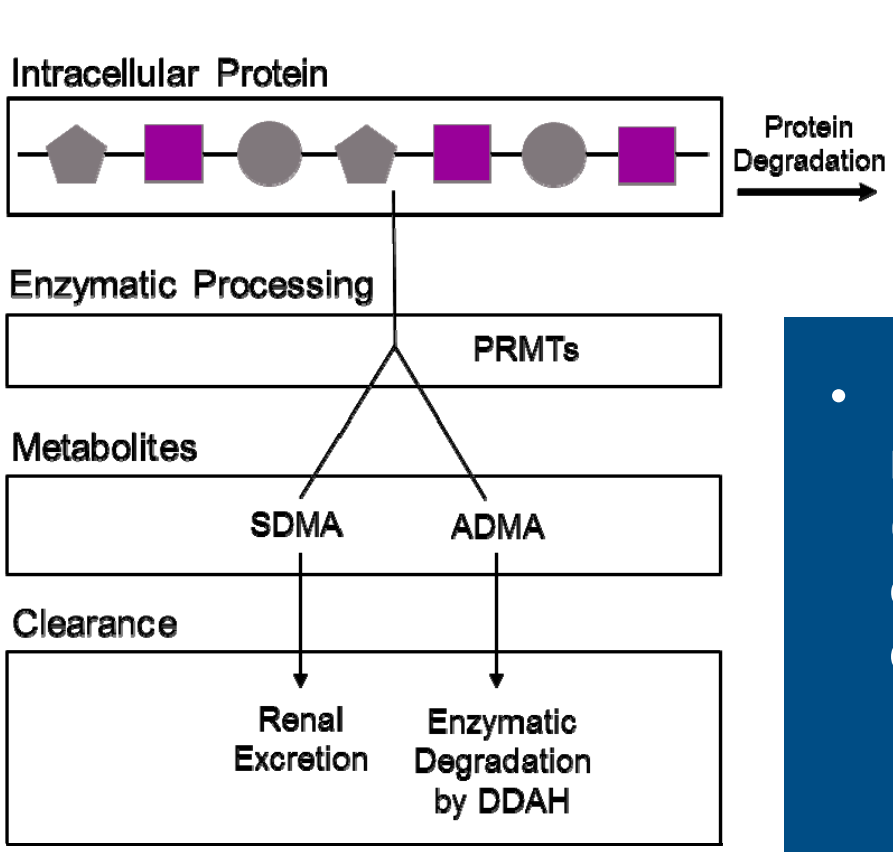
ADMA and SDMA are excreted/degraded by distinct mechanisms, and therefore manifest differently

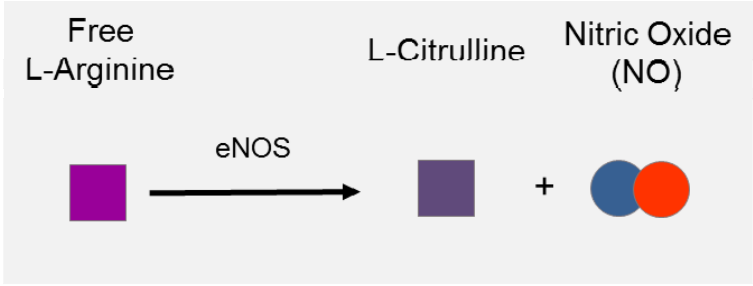




- ADMA is cleared gradually by degradation while SDMA is cleared rapidly through the urine
- Therefore, ADMA identifies endothelial dysfunction and CV risk whereas SDMA identifies renal insufficiency and subsequent renal failure

Uncontrolled risk factors modulate the production of ADMA and SDMA





- Uncontrolled risk factors[1-4] modulate ADMA and SDMA (through regulation of key enzymes) resulting in endothelial damage
  - Promote formation through PRMTs
  - Inhibit degradation of ADMA by DDAH

[1]Lin KY et al. *Circulation*. 2002; 106: 987-92.
[2]Böger RH et al. *Circ Res*. 2000; 87: 99-105.
[3]Osanai, T et al. *Hypertension*. 2003; 42: 985-90.
[4]Mah E and Bruno RS. *Nutrition Research*. 2012; 32: 727-740.

Overview

Clinical Study	Cohort	ADMA is associated with:
Framingham Offspring Study	'Asymptomatic'	Individuals who have an abnormal CIMT and disease burden
		Individuals who are at risk of all-cause mortality
Athero*Gene*	With known CAD	Individuals with known disease at risk of events
LURIC	With and without known CAD	Individuals with known disease at risk of CV-related mortality

Clinical Study	Cohort	SDMA is associated with:
LURIC	With and without known CAD	Reduced renal function and CV-related mortality

Clinical Interpretation

Test			Interpretation
ADMA		SDMA	
Low		Low	• Normal endothelial function
Med	High	Low	• Endothelial dysfunction and possible presence of pre-diabetes/diabetes or CVD
Low		High	• Reduced renal function
Med	High	High	• Endothelial dysfunction and possible presence of pre-diabetes/diabetes or CVD • Possible renal failure

DDAH

- Increase activity: retinoic acid, arginine
- Decrease activity: oxLDL, HLP, HBP, DM, AGE, insulin, PPAR, HC, TNF alpha, cytokine and ROS

PPI increase CHD Risk

MPR July 16,2013, Circulation Research, May 10, 2016
AHA May 10, 2016
PLOS One June 10,2015 1-16

- PPIs elevate ADMA and decrease NO and induce ED. ADMA elevated 20-30%.
- Inhibit DDAH (dimethylarginine dimethylaminohydrolase enzyme) that degrades ADMA. DDAH clears 80% of ADMA
- Impairs acid production in endothelial cell lysosomes that prevent waste removal and accelerate endothelial cell aging
- Increases risk for CHD
- Also increase risk for CKD

Diet Soft Drink Consumption is Associated with Increased Risk of Vascular Events in Northern Manhattan Study

J Gen Intern Med 2012;Jan 27 EPUB
Am J Clin Nutr 2012;95:1190
Am J Clin Nutr 2012;96:1390

- Daily diet soft drinks consumption increases the risk of all vascular events by 43%.
- Includes stroke (83% for ischemic CVA in highest vs lowest intake),, CHD, MI and vascular death.
- Population-based cohort study of 2564 subjects over 10 years
- Another study showed both sugar-sweetened and low calorie sodas significantly increased the risk of stroke by 16 % per one serving per day

Artificial Sweeteners

Trends Endocrinol Metab 2013;July 3 Epub
Nutrition 2013;29:1293

- **Sugar substitutes increase the risk for**

- **Obesity and weight gain**
- **Metabolic Syndrome**
- **Type 2 DM**
- **CVD**

- **Interfere with learned responses that normal contribute to glucose and energy homeostasis.**
- **Kills microbiome and probiotics**
- **Alters leptin levels and decreases satiety**

Microbiome and CVD

Circulation 2017;135:1008-10

- The human gastrointestinal tract is predominantly a bacterial ecosystem (microbiome) that harbors >100 trillion microbial cells, with the highest microbe densities found in the colon. Gut microbes are for the most part codependent, both on one another and on their host, requiring metabolic support from additional members of the community for survival and a symbiotic relationship with the host. For example, gut microbes help with the digestion of nutrients, prevent significant colonization of pathogens, and promote gut immunity, while the host provides a favorable environment for microbial survival.
- Gut microbiome changes (dysbiosis) leading to increased long-term susceptibility to disease can originate early in life, similar to traditional risk factors. There is a growing awareness that microbial inhabitants within the host often contribute to global metabolism within the host, and dysbiosis can fuel enhanced susceptibility for metabolic and immunological diseases, sometimes emerging decades later. Indeed, alterations in the composition of the human gut-associated microbiome and accompanying functional changes in metabolism have been implicated in the pathogenesis of several chronic conditions ranging from atherosclerosis and thrombosis to obesity and insulin resistance

Human Microbiome and CVD

Curr Opin Lipidology 2016;27:615

- Endotoxemia: LPS
- TMAO : from choline, phosphatidyl choline and carnitine
- SCFA : butyrate, propionate, acetate. Relates to conic health, IR, DM, lipids, gluconeogenesis, lipogenesis, intestinal epithelial health and gluconeogenesis, energy and glucose homeostasis, signaling molecules for GPR 41 and 43, GLP-1, PYY,
- Bile acid metabolism: primary to secondary bile acids. Metabolic switches for FXR, FPR TGR5, glucose metabolism, lipid metabolism, GLP-1, thermogenesis in BAT, role in obesity and alterations with antibiotics.
- Other microbiome products

- Relate to obesity, insulin resistance, DM, hypertension, dyslipidemia, CHD, MI, CHF.
- Treatment with diet (plant based), fiber, FMT (encapsulated), prebiotics, probiotics, EVOO, DMB (dimethylbutanol).

Metabolic Endotoxemia Treatment

Alternative Therapeutics 2017;23(4):42

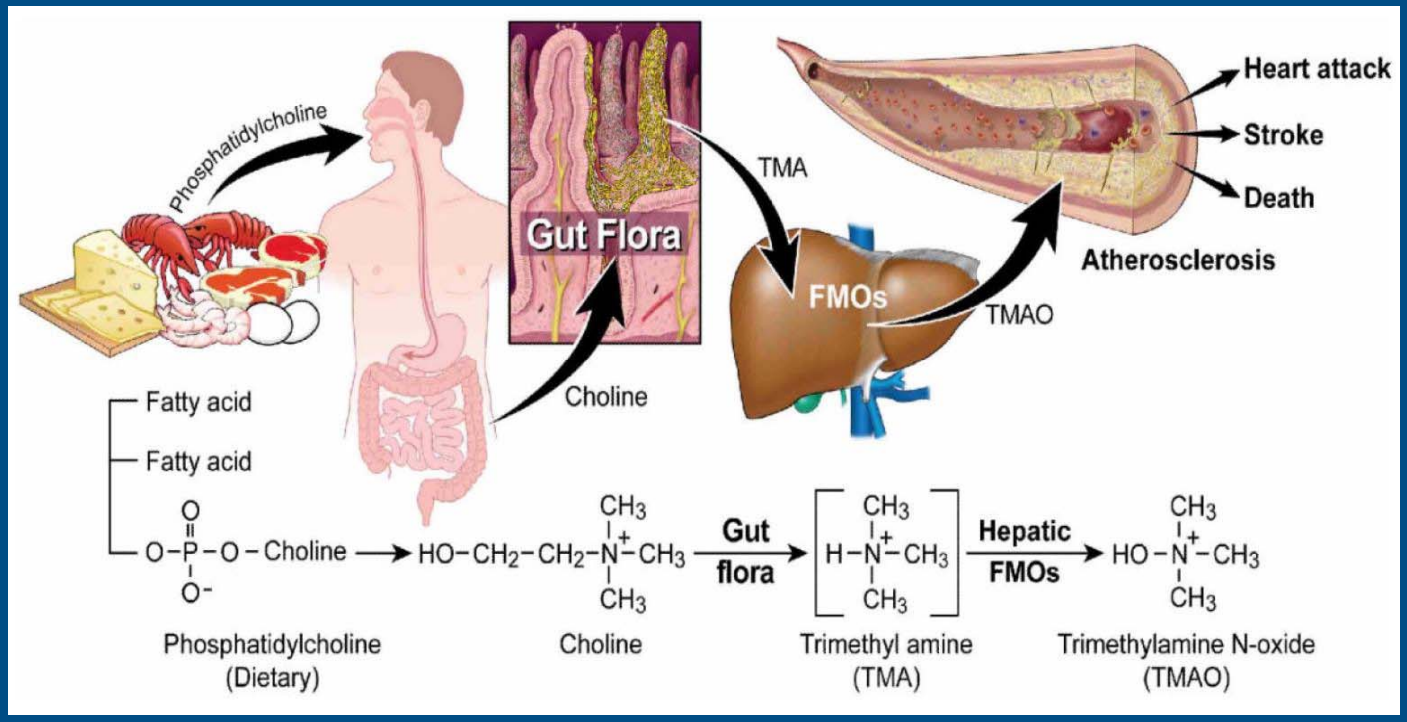
- Reduce SFA and TFA. Increase PUFA and MUFA
- Reduce refined carbohydrates and sugars
- Increase fruits and vegetables, legumes and whole grains
- Reduce alcohol intake. Red wine at 272 ml per day
- Multivitamin and minerals with zinc, Vit A, D, C and magnesium
- Prebiotics
- Probiotics
- Polyphenol rich plants and plant extracts
- Glutamine
- Lactoferrin from whey protein
- Berberine
- Fermented foods

TMAO is gut-derived metabolite formed from dietary nutrients

1
Ingestion of dietary nutrients

2
Gut bacteria metabolize nutrients to TMA

3
TMA converted to TMAO by the liver



Wang Z et al. *Nature.* 2011; 472: 57-63.

TMAO, Hypertension and CVD

Nature Medicine 2013 April 7 Epub
NEJM 2013;368:1575;Cell Metabolism 2013;17:49
Mayo Clin Proc 2013;88(8):786; Am J Clin Nutr 2016;103:703
Atherosclerosis 2013;231:456; Cell 2015;16 3: 1585-95; Nutrition 2018;46:7-12

- Elevated TMAO is associated with CVD, MI,DM, hypertension,PAD and CRI. Seen also with low HDL and PL and hypomethylation.
- TMAO is produced by certain gut microbes in the cecum to make TMA (gas) then metabolized in liver by FMO3 . Various foods (meat, chicken, turkey , fish and eggs) have high concentrations of carnitine and choline that are used as food by the bacteria to form the TMAO.
- Antibiotic administration decreases TMAO
- DMB (3,3 dimethyl-1butanol inhibits TMA production and atherosclerosis in mice
- TMAO reduces RCT and increases modified LDL uptake into macrophages by SRA and CD 36.
- TMAO prolongs the effect of A-II and hypertension

TMAO and CVD

Nature Medicine 2013 April 7 Epub
Cell Metabolism 2013;17:49
Cell 2015;16 3: 1585-95
J Nutritional Biochemistry 2016;33:145; Nutrition 2018;46:7-12

- FMO3 is increased by estrogens and bile acids
- FMO3 is increased by dioxin- like pollutants and PCBs which increase TMAO and CVD. PCBs also modulate gut microbiome.
- FMO3 is decreased by arginine, nitric oxide and androgens.
- TMAO explains 11 % of the variation in CHD

Test Report Example

METABOLIC

	In Range	Out of Range	Flag**	Relative Risk	Reference/ Optimal Range	Units
TMAO (Trimethylamine N-oxide) (1)		7.1		MOD	<6.2	uM

Based on a population (N=4007) defined as ambulatory stable patients without acute coronary syndrome who underwent elective diagnostic coronary angiography (1) and a reference range study of apparently healthy donors (N=180), we've defined the following cut-offs for TMAO to assess relative risk of a cardiovascular event: A cut-off of <6.2 uM defines an "apparently healthy" population at low risk, 6.2-9.9 uM defines a population at intermediate risk, and >=10.0 uM defines a population at high risk for a cardiovascular event (2-fold increased risk of MACE at 3 years). (Reference: 1-Tang et al. N Engl J Med. 2013; 368:1575-1584).

METABOLIC

	In Range	Out of Range	Flag**	Relative Risk	Reference/ Optimal Range	Units
TMAO (Trimethylamine N-oxide) (1)		11.3		HIGH	<6.2	uM

Based on a population (N=4007) defined as ambulatory stable patients without acute coronary syndrome who underwent elective diagnostic coronary angiography (1) and a reference range study of apparently healthy donors (N=180), we've defined the following cut-offs for TMAO to assess relative risk of a cardiovascular event: A cut-off of <6.2 uM defines an "apparently healthy" population at low risk, 6.2-9.9 uM defines a population at intermediate risk, and >=10.0 uM defines a population at high risk for a cardiovascular event (2-fold increased risk of MACE at 3 years). (Reference: 1-Tang et al. N Engl J Med. 2013; 368:1575-1584).

Carnitine reduces CVD Meta-analysis

Mayo Clin Proc 2013;88:544-551
Atherosclerosis 2013;231:456

- L carnitine reduced all cause mortality 27%, ventricular arrhythmias 65% and angina 40% in the setting of acute MI compared to placebo in 13 controlled trials of 3629 subjects.
- No change in CHF or recurrent MI

TMAO Conclusions

Cell. 2015 Dec 17;163(7):1585-95.

- Gut microbes populate the human digestive tract and play a role in human metabolism
- TMAO is a byproduct of gut bacteria metabolism and is associated with CVD risk
- Phosphatidylcholine, choline, and L-carnitine provide the dietary material for TMAO production
- Dietary composition influences gut microbiota and consequently TMAO production
- Other than avoidance of eggs and meat, specific therapies of elevated TMAO include TMD, Low fat diet, vegetarian diet, probiotics, Di-methyl Butanol (DMB) inhibits microbial TMA Lyase and EVOO at 50-80 grams per day.

Cytokines and Cell Adhesion Molecules

Cytokines

Vascular Biology in Clinical Practice, Oct. 2000; Mark C. Houston

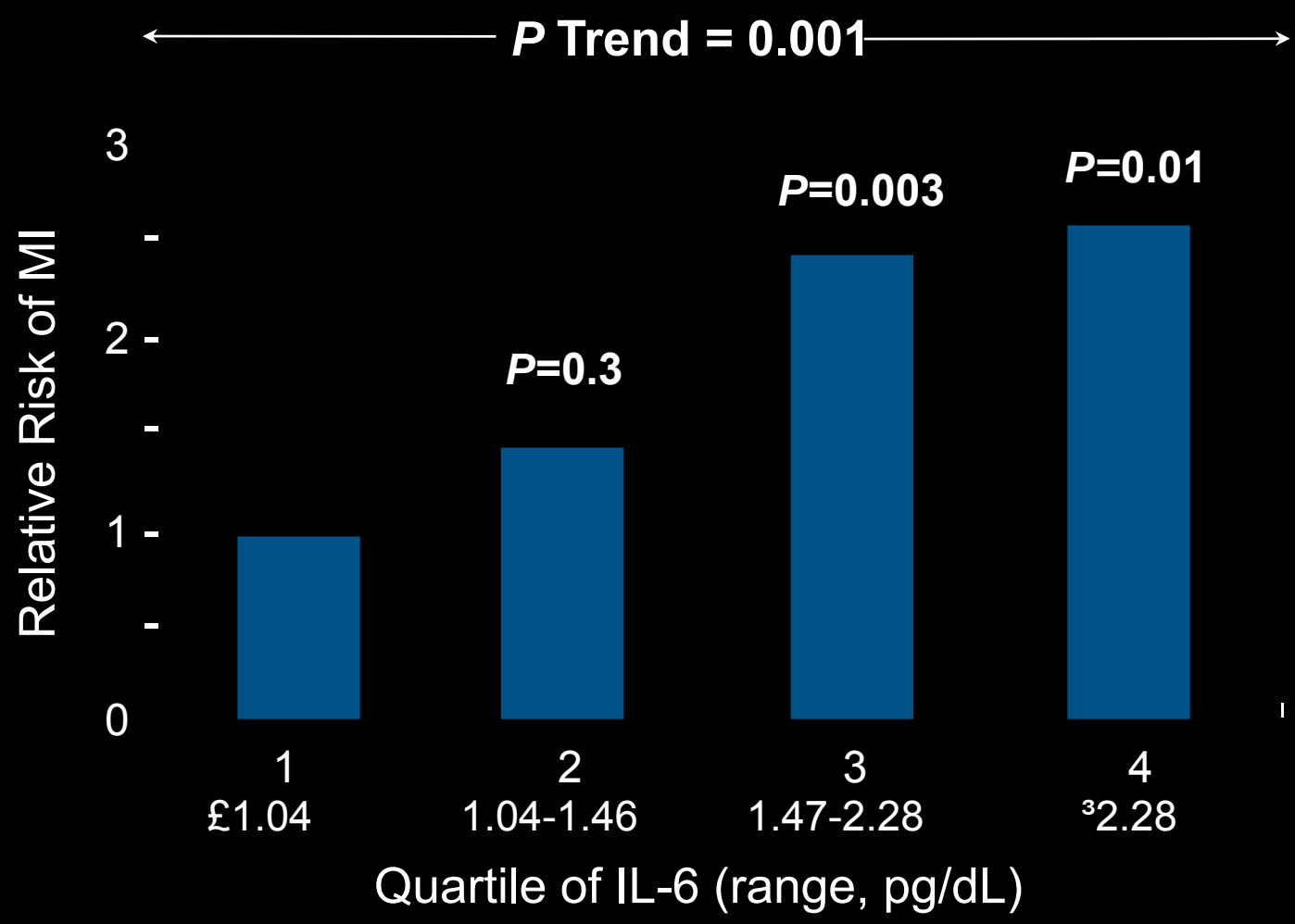
- Pro-Inflammatory Cytokines
  - Interleukin 1 (IL-1)
  - Interleukin 6 (IL-6)
  - Interleukin 8 (IL-8)
  - Tumor Necrosis Factor (TNF-α)
- Colony-Stimulating Factors
  - Granulocyte Colony Stimulating Factor (G-CSF)
  - Monocyte-Colony Stimulating Factor (M-CSF)
  - Granulocyte-Monocyte Colony Stimulating Factor (GM-CSF)

Cytokines Classification

Vascular Biology in Clinical Practice, Oct. 2000; Mark C. Houston

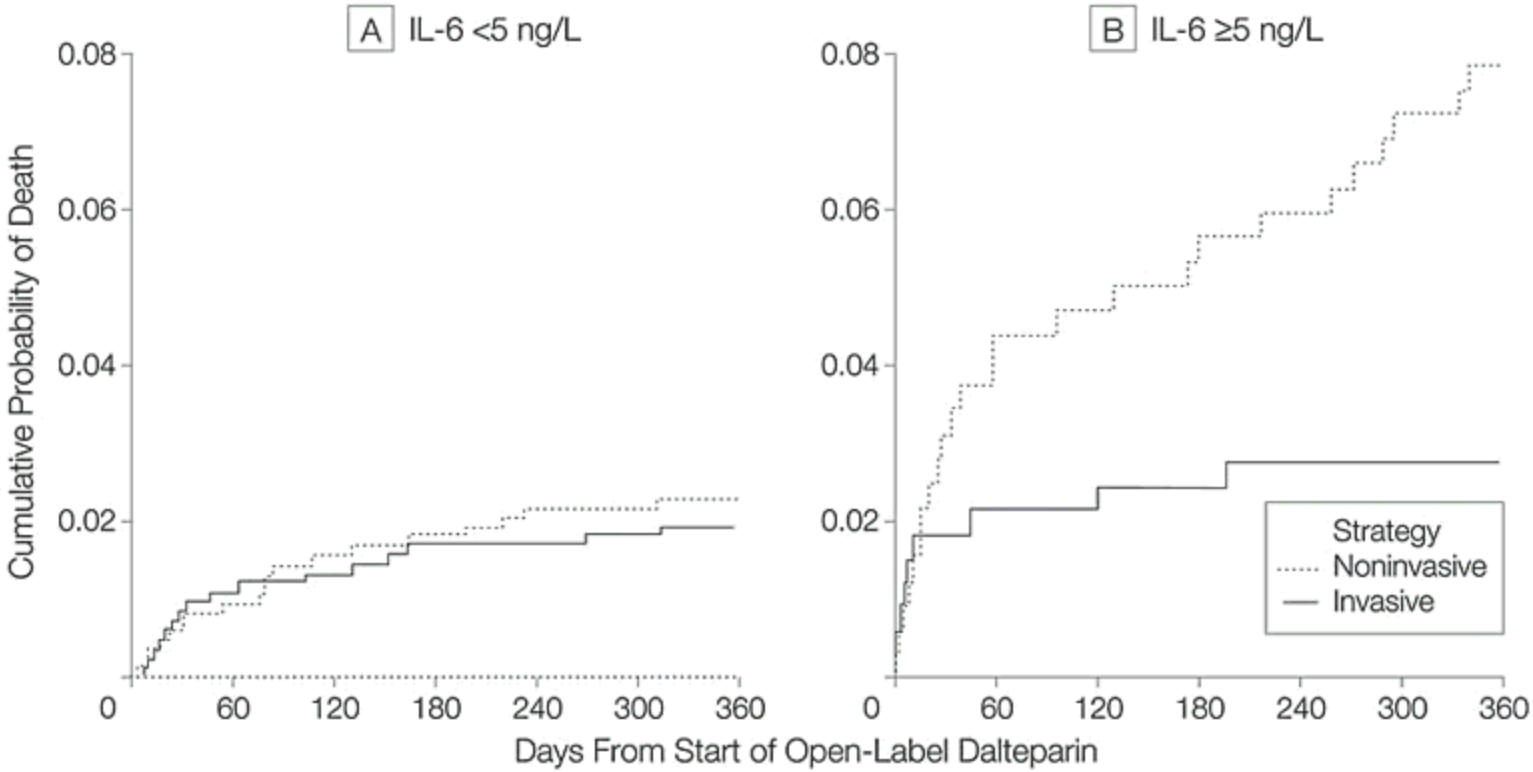
- Chemotactic Factors (Chemoattractants)
    1. Monocyte Chemoattractant Protein – 1 (MCP-1)
    2. Macrophage Inhibitory Protein – 1B (MIP-1B)
    3. Platelet Activating Factor (PAF)
    4. Leukotriene B4 (L-B4)
    5. Complement Components
    6. N-Formyl Peptides
    7. GRO - α

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



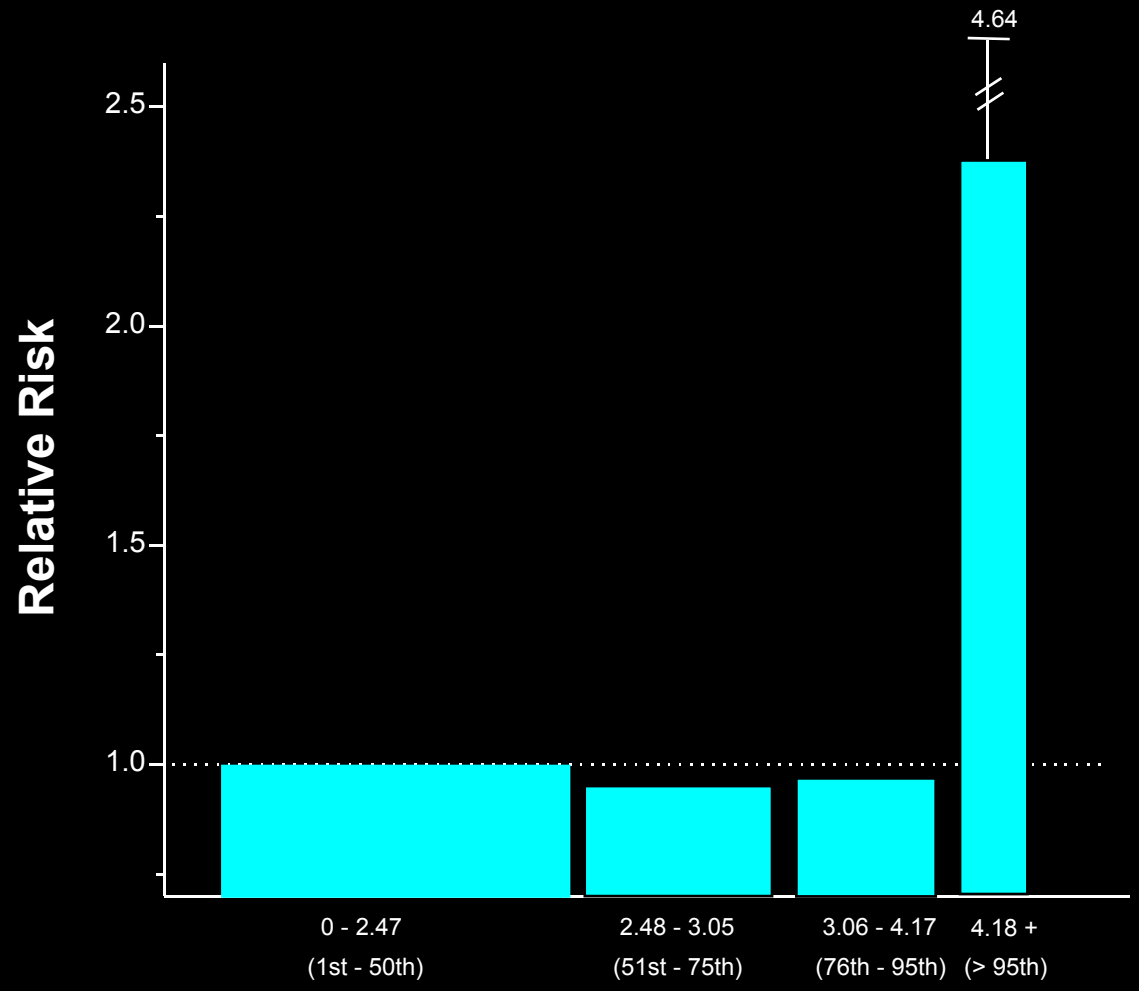
Ridker et al, Circulation 2000;101:1767-1772

IL-6 to Target Invasive Strategy in ACS Patients



Lindmark et al, JAMA 2001

Plasma Concentration of TNF-alpha and Risk of Recurrent Coronary Events



Ridker et al, Circulation 2000;101:2149-53

Cell Adhesion Molecules (CAM'S)

Houston MC Vascular Biology in Clinical Practice . Hanley and Belfus. 2002 Philadelphia.

- High levels correlate with vascular diseases and conditions
  - Atherosclerosis (VCAM-1, ICAM-1)
  - DM
  - HLP
  - HBP
  - CHD
  - PCTA/Restenosis

CELL ADHESION MOLECULES

Houston MC Vascular Biology in Clinical Practice . Hanley and Belfus. 2002 Philadelphia.

- **Selectins**
- **Immunoglobulin Superfamily**
- **Cadherins**
- **Integrins**

Multiple Protein Families on Endothelial Surface Cell-Adhesion Molecules (CAM'S)

Houston MC Vascular Biology in Clinical Practice . Hanley and Belfus. 2002 Philadelphia.

- **Selectins**
  (Slowing and Rolling of Leukocyte on Endothelium)
  1. P-Selectin (Platelet/Endothelium Selectin)
  2. E-Selectin (Endothelial Selectin)
  3. L-Selectin (Leukocyte-Selectin)
  4. CD-34 (Cluster of Differentiation 34)

- **Immunoglobulin Superfamily**
  (Adhesion, Immune Response, Inflammation, Atherosclerosis)
  1. ICAM-1, ICAM-2, ICAM-3, ICAM-4, ICAM-5 (Intracellular Adhesion Molecule)
  2. VCAM (Vascular Cell Adhesion Molecule)
  3. MADCAM-1 (Mucosal-Adhesion Cell Adhesion Molecule)
  4. PECAM-1 (Platelet-Endothelial Cell Adhesion Molecule)

Multiple Protein Families on Endothelial Surface Cell-Adhesion Molecules (CAM'S)

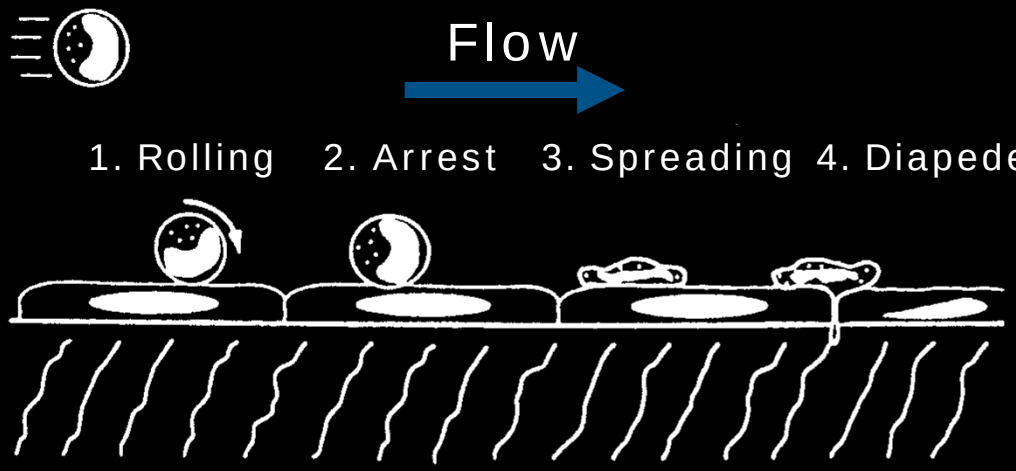
Houston MC Vascular Biology in Clinical Practice . Hanley and Belfus. 2002 Philadelphia.

- **Cadherins**
  (Epithelial Integrity and Correct Architecture)
  1. N, P, R, B, E Cadherins
  2. Desmogleins 1 and 3
  3. Desmocollins

- **Integrins**
  (External Cell Membrane to Internal Signal Proteins)
  1. B-1 (Leukocyte - ECM) VLA
  2. B-2 (Leukocyte - ICAM)
  3. B-3 (Platelets)
  4. B-4 - B-8
  5. Subunits Attached to All B Subunits (> 20 Types)

Endothelial Activation

Adhesive Interactions During Leukocyte (Monocyte) Emigration



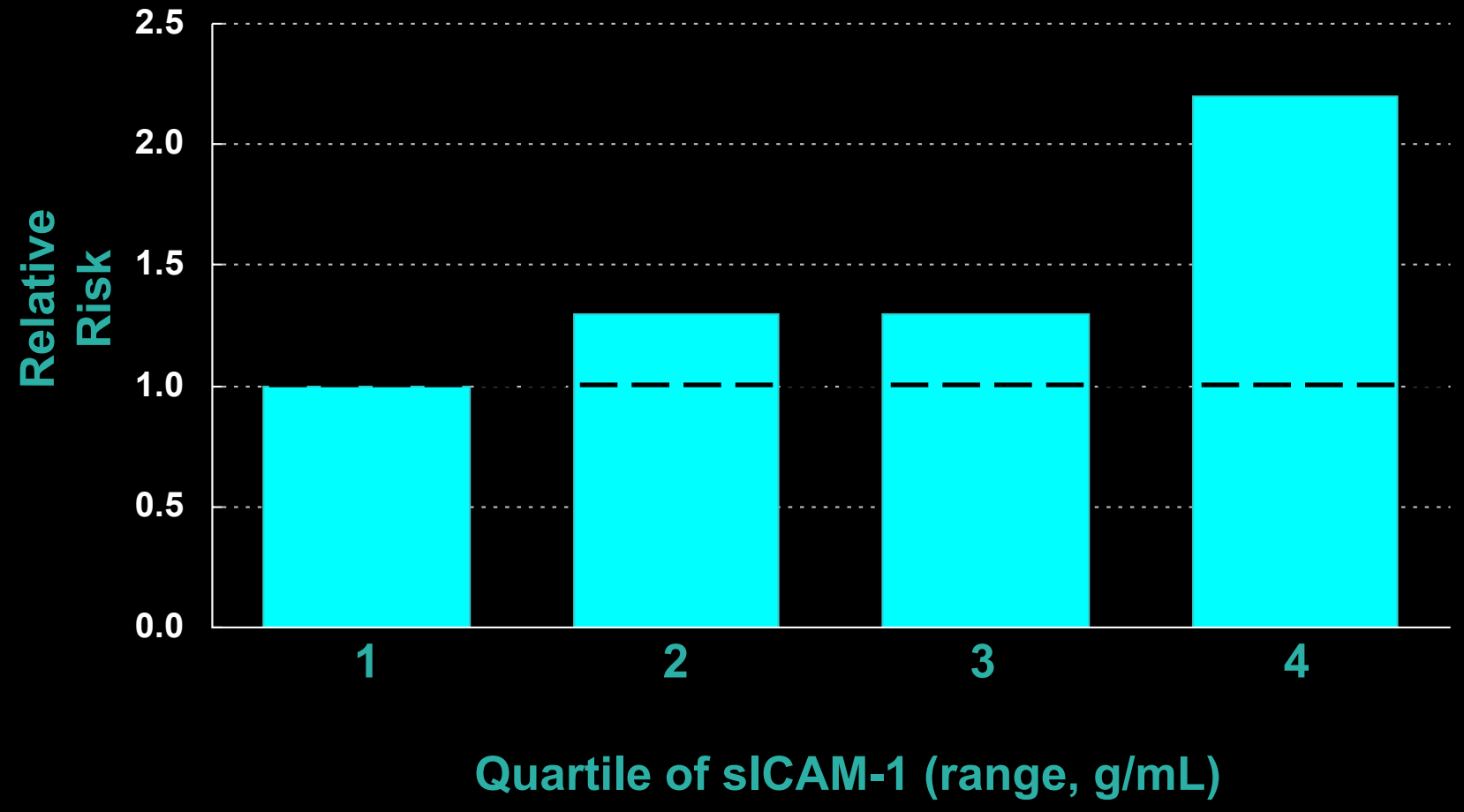
Series of events as identified by intravital microscopic studies under flow. The adhesive interactions involved in leukocyte emigration involve several distinct phases: 1) initial transient adhesion (rolling), 2) activation, 3) firm adhesion (arrest and spreading), and 4) transendothelial migration (diapedesis).

Molecules Involved:

	Rolling	Activation	Firm Adhesion	Transendothelial Migration
Leukocyte	^{s}Lex and other sialylated, fucosylated structures L-selectin	Cytokine, chemokine, and chemoattractant receptors	β-1, β-2, and β-3 integrins	PECAM-1 and β-1 and β-2 integrins
Endothelial	P-selectin L-selectin ligand E-selectin CD34 MAdCAM-1	Chemokines (eg, IL-8, MCP-1, MIP-1β) PAF PECAM-1 E-selectin	ICAM-1, ICAM-2, VCAM-1, MAdCAM-1	PECAM-1 ICAM-1 VCAM-1

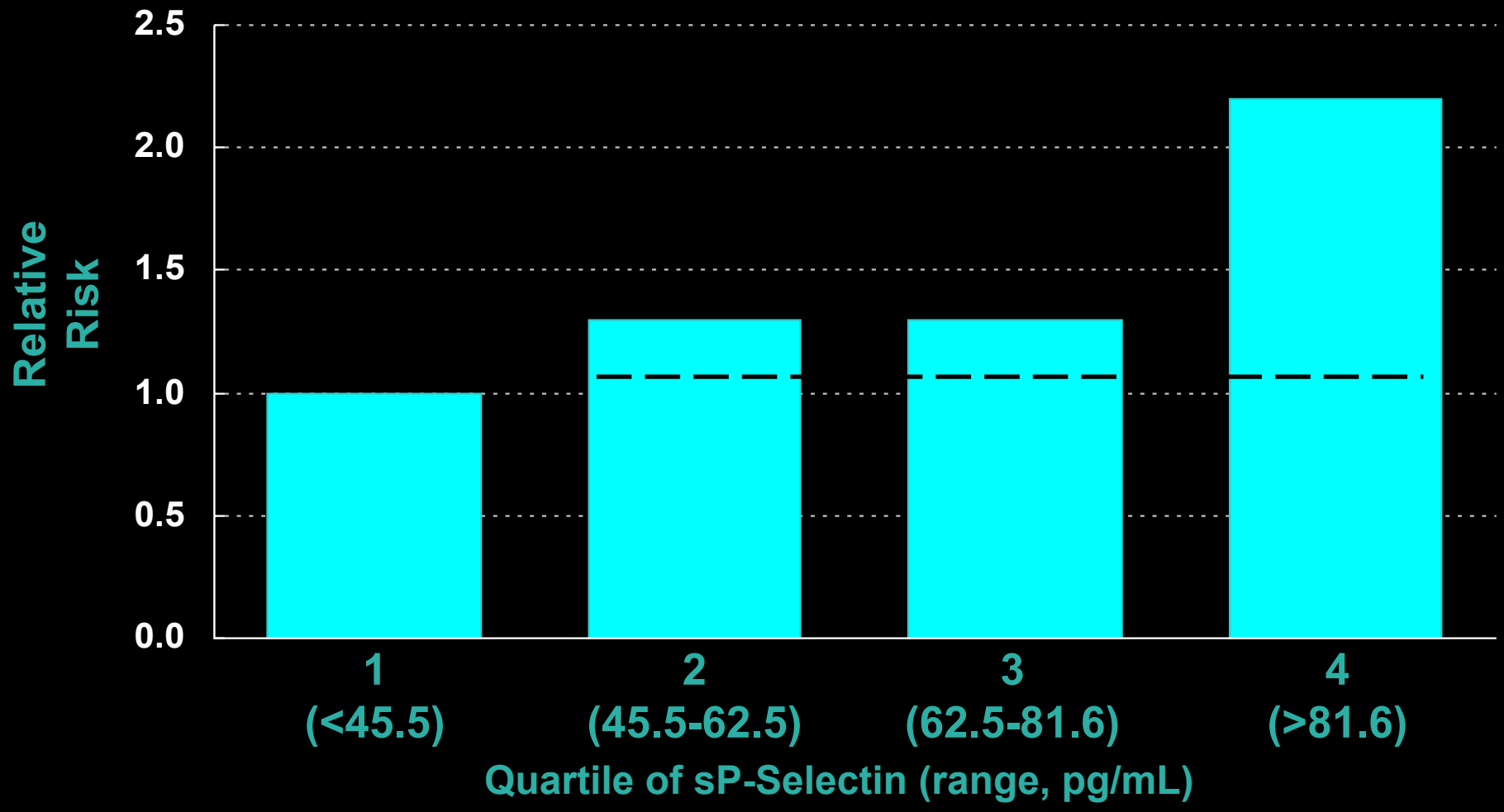
Recent in vitro and in vivo studies indicate that rolling is mediated by multiple low-affinity interactions between selectin receptors and their cognate carbohydrate ligands. Firm adhesion and diapedesis are largely dependent on integrin and immunoglobulin-like proteins. CD34, cluster of differentiation 34; PECAM, platelet-endothelial cell adhesion molecule; ICAM, intercellular adhesion molecule; IL, interleukin; MAdCAM, mucosal adhesion cell adhesion molecule 1; MCP, monocyte chemoattractant protein; MIP, macrophage inhibitory protein; PAF, platelet activity factor; sLe^{x}, sialyl Lewis: VCAM, vascular cell adhesion molecule.

Soluble Intercellular Adhesion Molecule Type 1 (sICAM-1) and the Risk of Future Myocardial Infarction



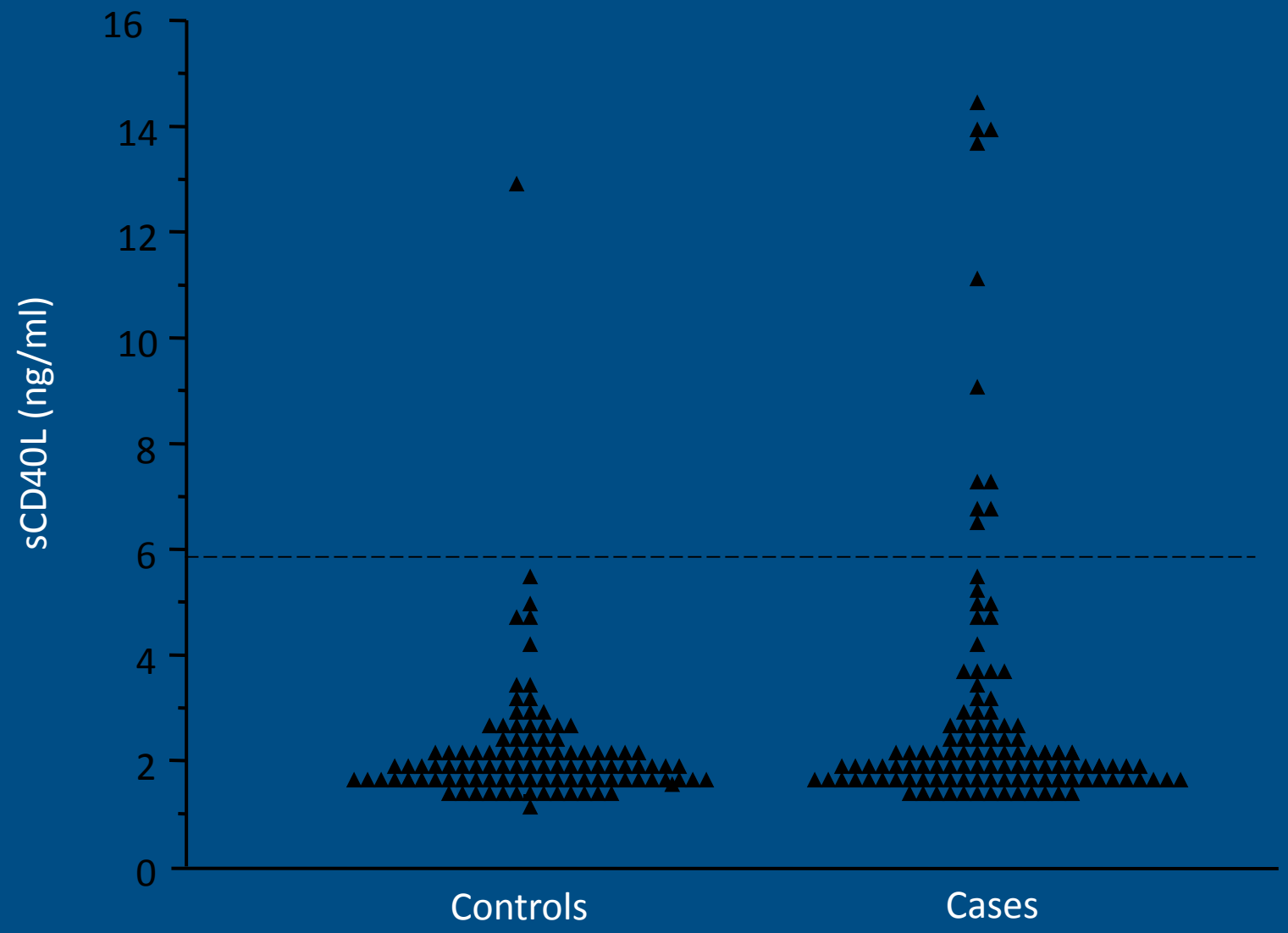
Ridker et al, Lancet 1998

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



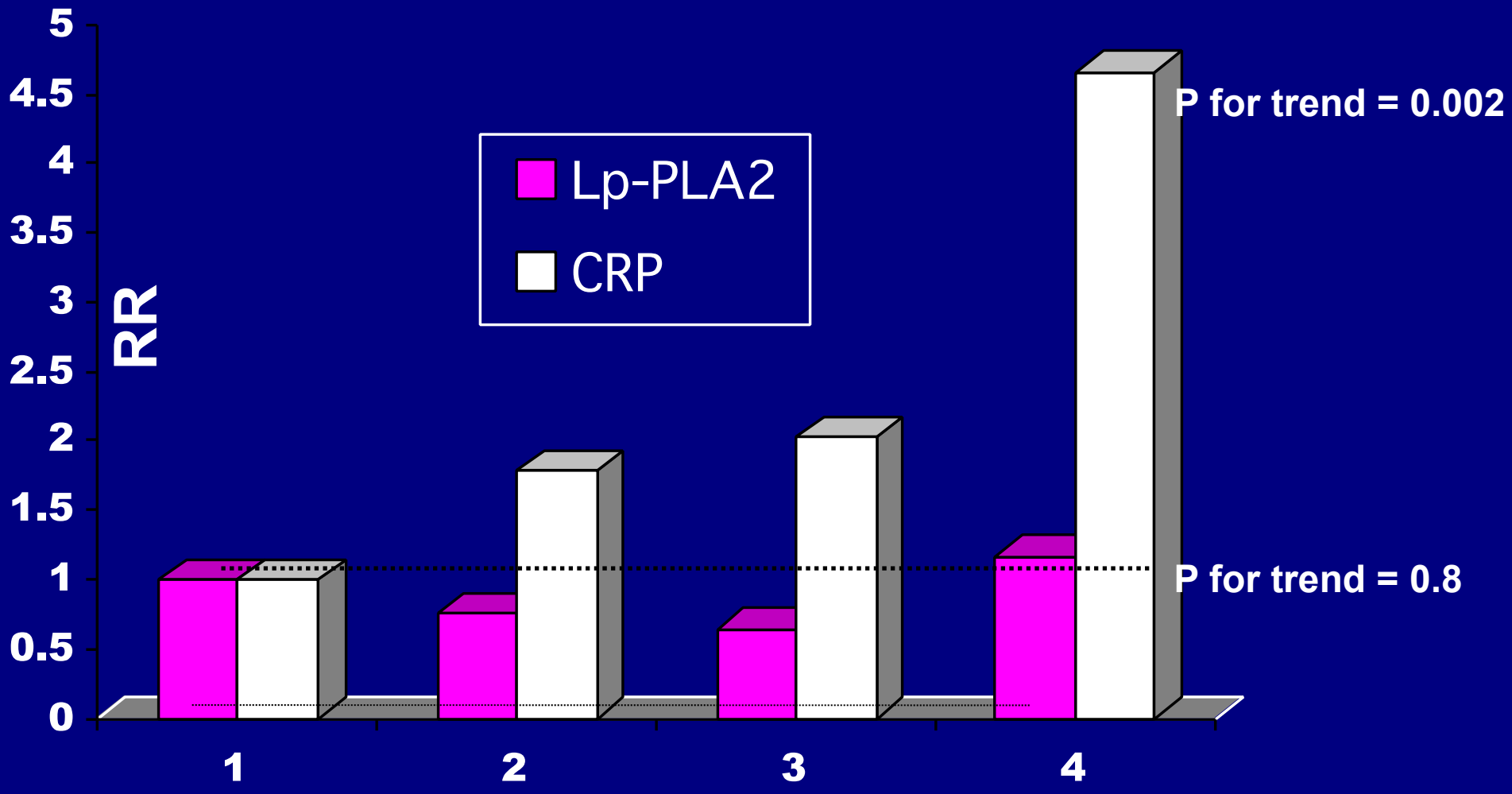
Ridker, Buring, Rifai. Circulation 2001

Soluble CD40 Ligand and Risk of Future Vascular Events



Schoenbeck et al, 2001

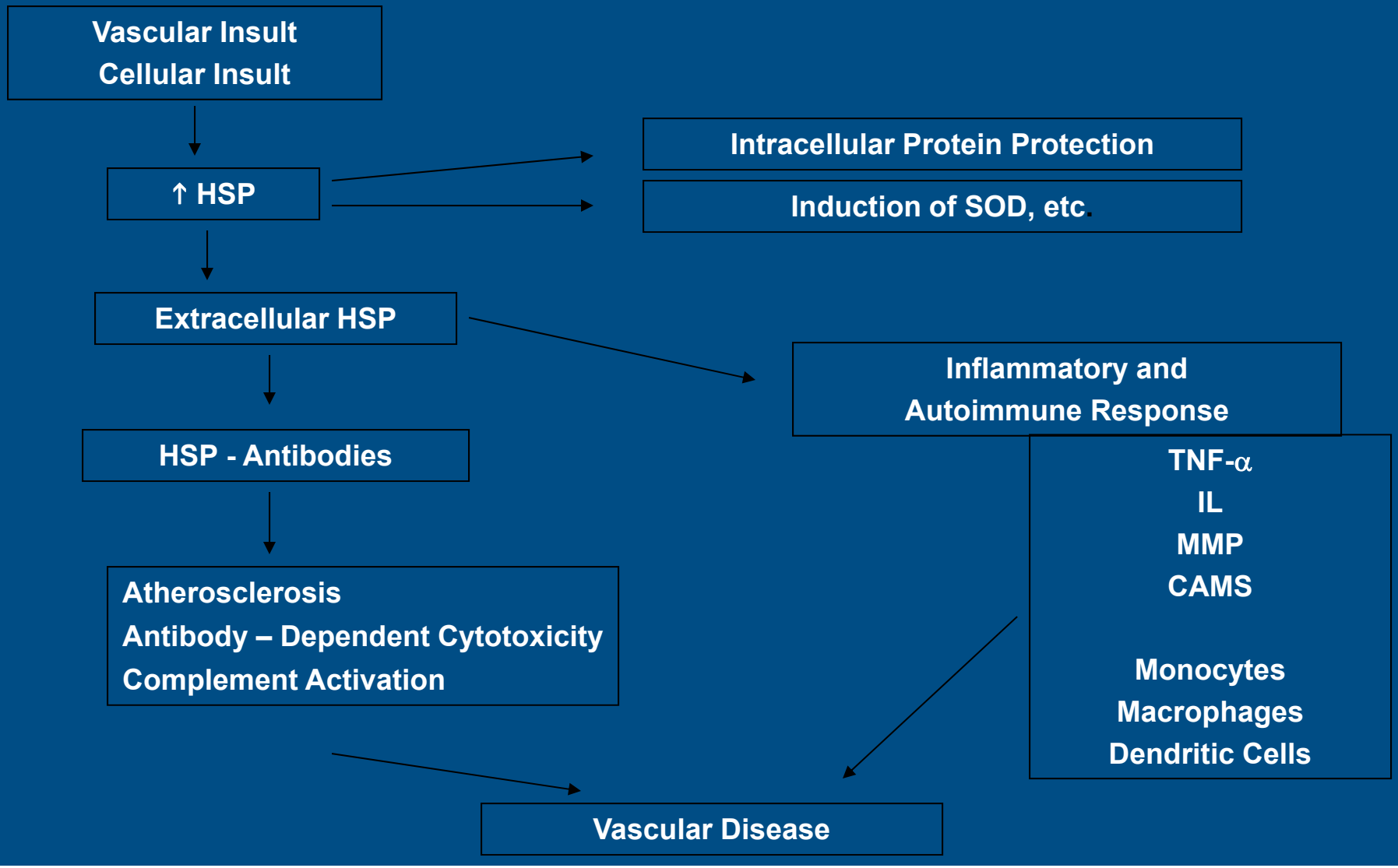
Adjusted Relative Risks of cardiovascular events according to Quartile of plasma level of Lp-PLA_2 and CRP



Blake et al, JACC 2001

Heat Shock Proteins: HSP
Vascular Inflammation and Autoimmune Reaction

Vascular Biology in Clinical Practice, Oct. 2000; . Houston



Pathogenic Burden and CHD
The Microbial Connection

Pak J Pharm Sci 2012;25:89
In Vivo 2005;19:351
Circulation 2003;108:678
Circulation 2002;106:184

- The pathogenic burden of various microorganisms has a significant correlation with endothelial dysfunction with impaired responses to nitric oxide and acetyl choline in coronary arteries and both the presence and severity of CHD defined by coronary calcification and coronary arteriograms (p =0.001).
- Individual micro-organisms also have significant correlations with CHD including HSV, CMV, *H. Pylori*, Chlamydia Pneumoniae, Hepatitis A, B, C, and EBV as defined by IgG, IgA and IgM antibodies.
- HSV DNA is detected in CHD arteries and plaque at autopsy.

Endothelial Dysfunction is Reversible in *H. Pylori*-positive subjects

Am J of Med 2011;124:1171

- 31 *H. Pylori* positive patients with endothelial dysfunction had resolution of the ED after treatment and eradication of the H Pylori infection. IL-6 levels were not altered.
- Other studies show *H. Pylori* patients have increased HSCRP, positive HP antibodies, ICAM, decrease PON -1, increased carotid IMT, increased apo B, decreased HDL, increased cytotoxin A, increased ADMA.

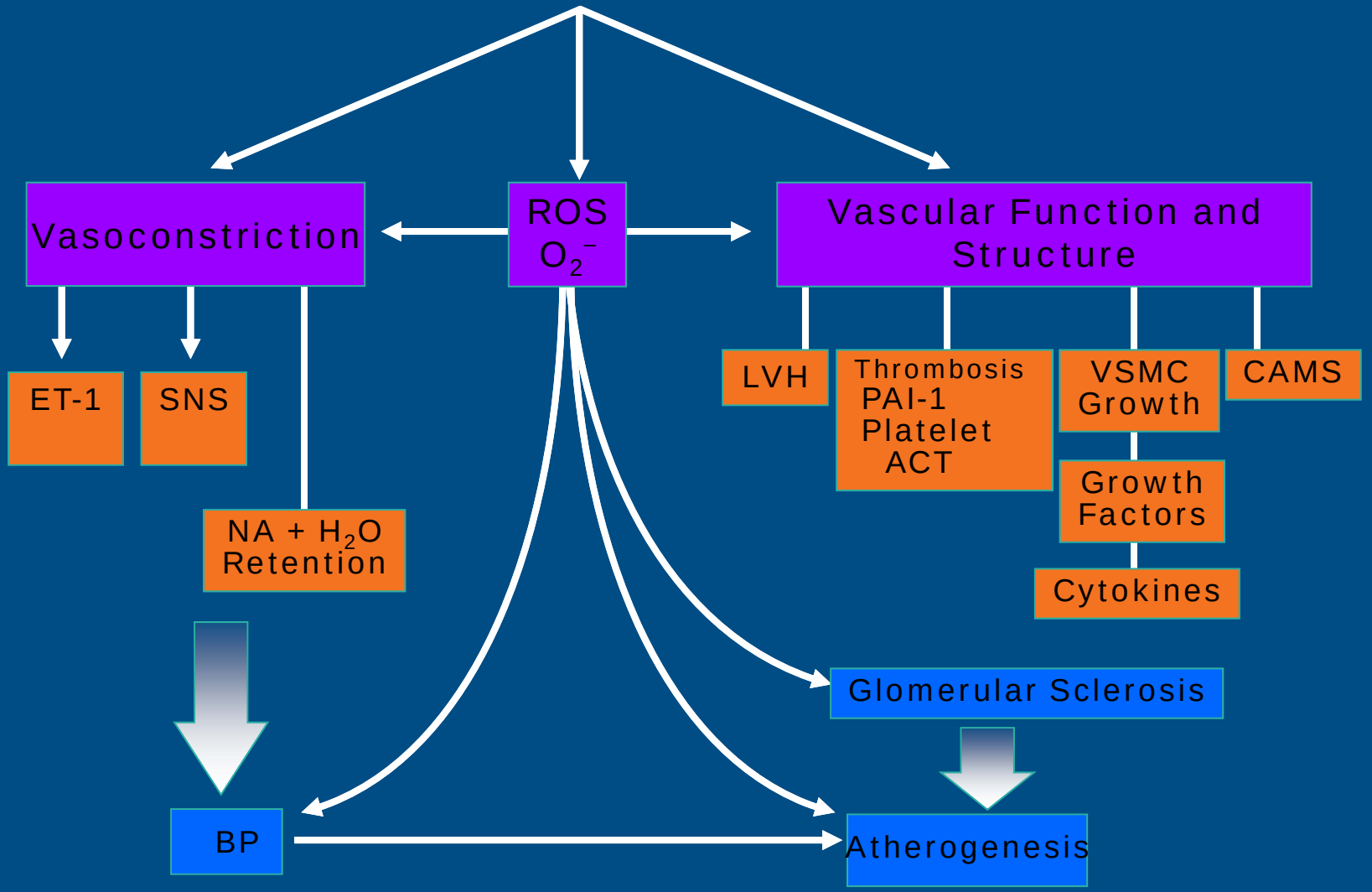
Impact of hepatitis C seropositivity on the risk of coronary heart disease events.

Am J Cardiol.2014 Dec 15;114(12):1841-5.

- Chronic infections have been shown to enhance atherogenicity.
- However, the association between chronic hepatitis C (HCV) and coronary heart disease (CHD) remains controversial.
- A total of 8,251 HCV antibody positive, 1,434 HCV RNA positive, and 14,799 HCV negative patients were identified. Patients with HCV antibody and RNA positivity had a higher incidence of hypertension, diabetes mellitus, obesity, and chronic lung disease, but lower serum cholesterol levels compared with patients who were HCV negative ($p < 0.001$).
- HCV seropositive patients had a higher incidence of CHD events compared with controls (4.9% vs 3.2%, $p < 0.001$). In the HCV cohort, patients with detectable HCV RNA had a significantly higher incidence of CHD events compared with patients who were only HCV antibody positive with no detectable RNA (5.9% vs 4.7%, $p = 0.04$). In multivariate logistic regression analyses, both HCV antibody positivity (odds ratio 1.32, 95% confidence interval 1.09 to 1.60, $p < 0.001$) and HCV RNA positivity (odds ratio 1.59, 95% confidence interval 1.13 to 2.26, $p < 0.001$) were independent risk factors for incident CHD events.
- In conclusion, there is an increased incidence of CHD events in patients with HCV seropositivity and the incidence is much higher in patients with detectable HCV RNA compared with patients with remote infection who are only antibody positive. Lipid profile does not appear to be a good cardiovascular risk stratification tool in patients with HVC

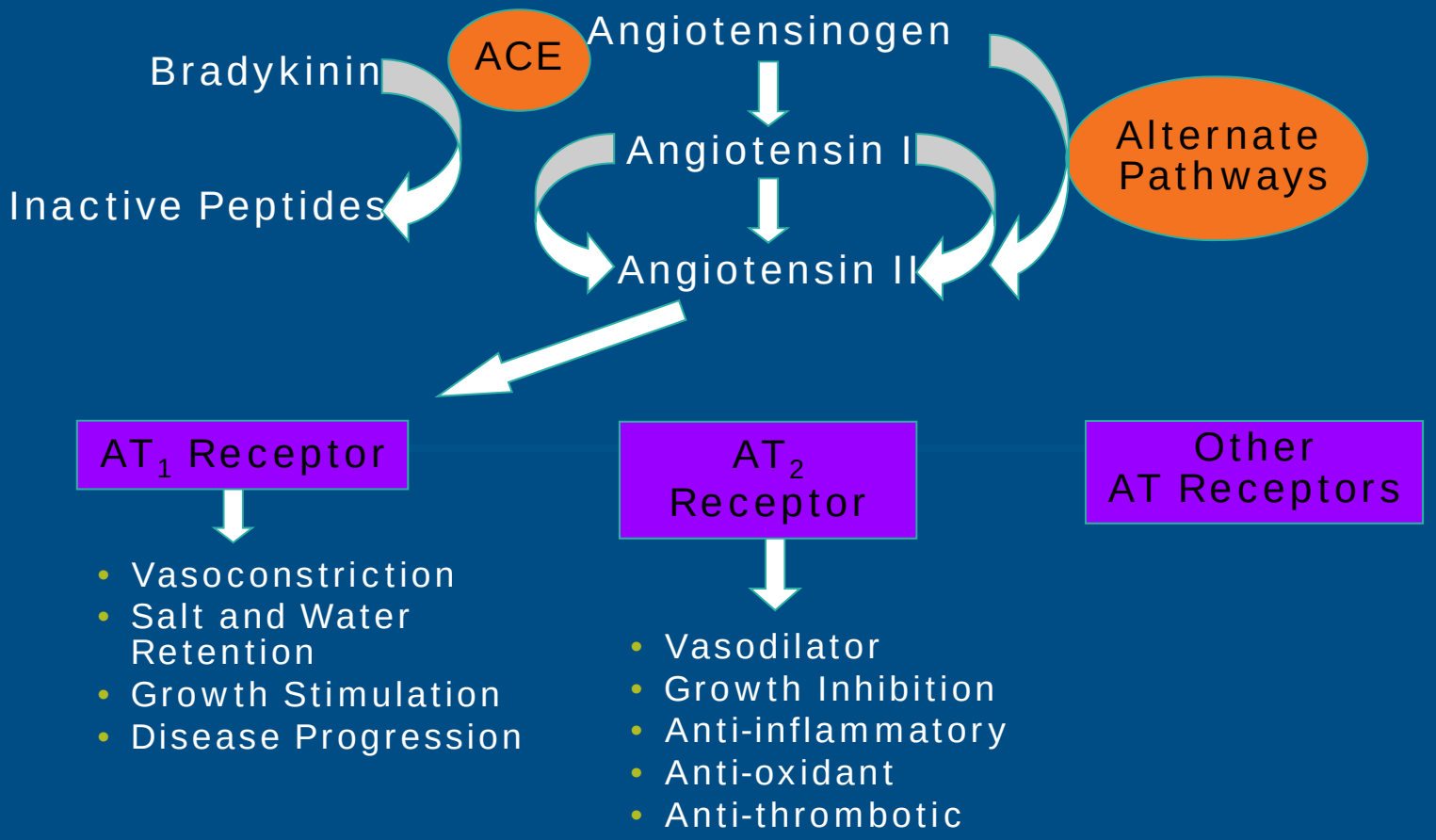
Angiotensin II (A-II)

Vascular Biology in Clinical Practice, Oct. 2000; Mark C. Houston

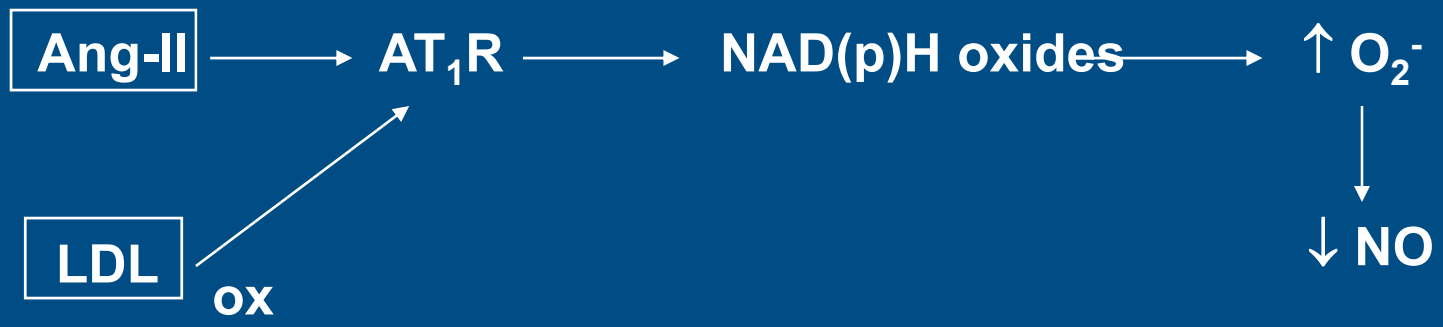


Postulated Role of Angiotensin II

Vascular Biology in Clinical Practice, Oct. 2000; Mark C. Houston



Hypertension and Hyperlipidemia Role of Ang-II, LDL, and AT_1R

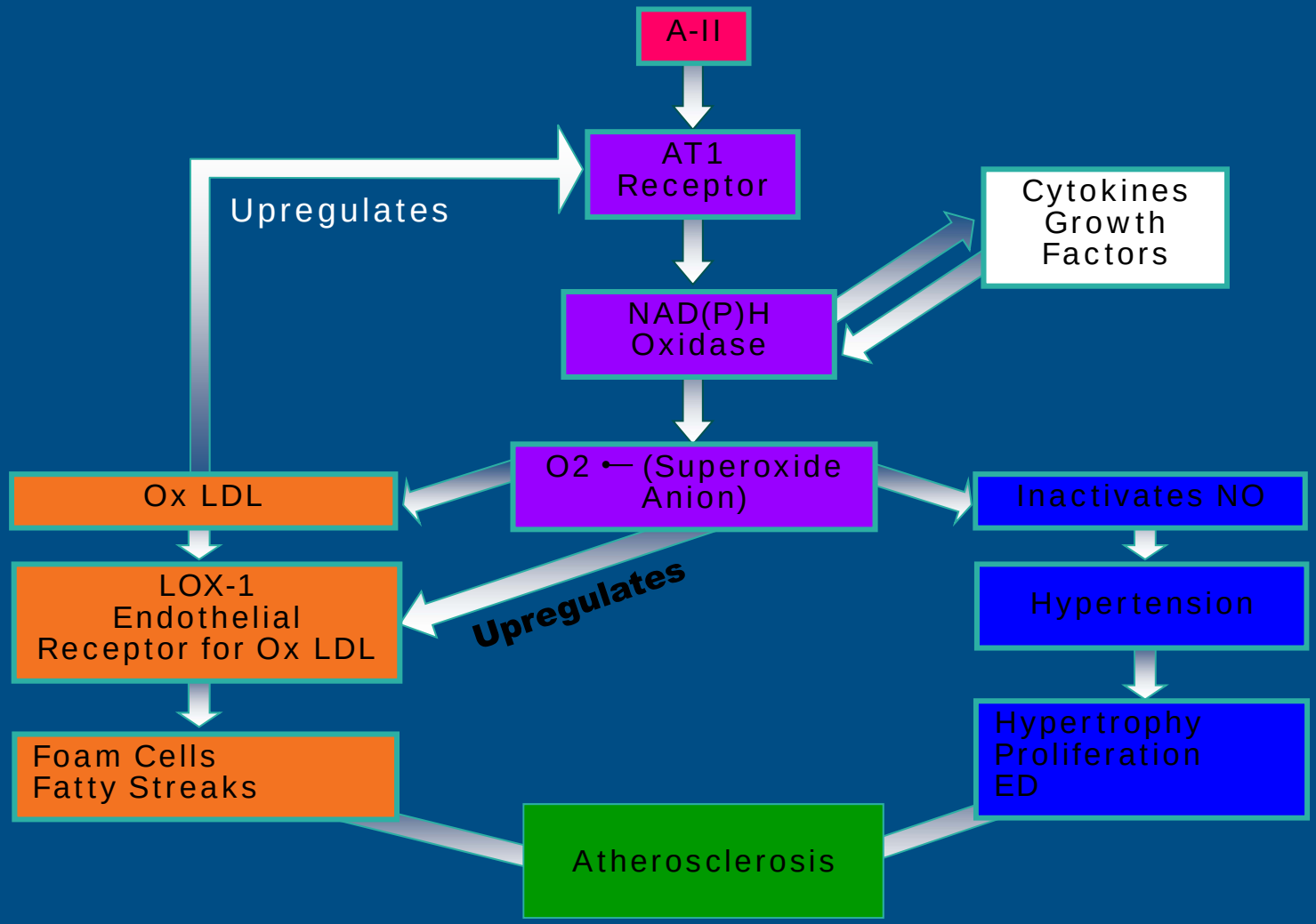


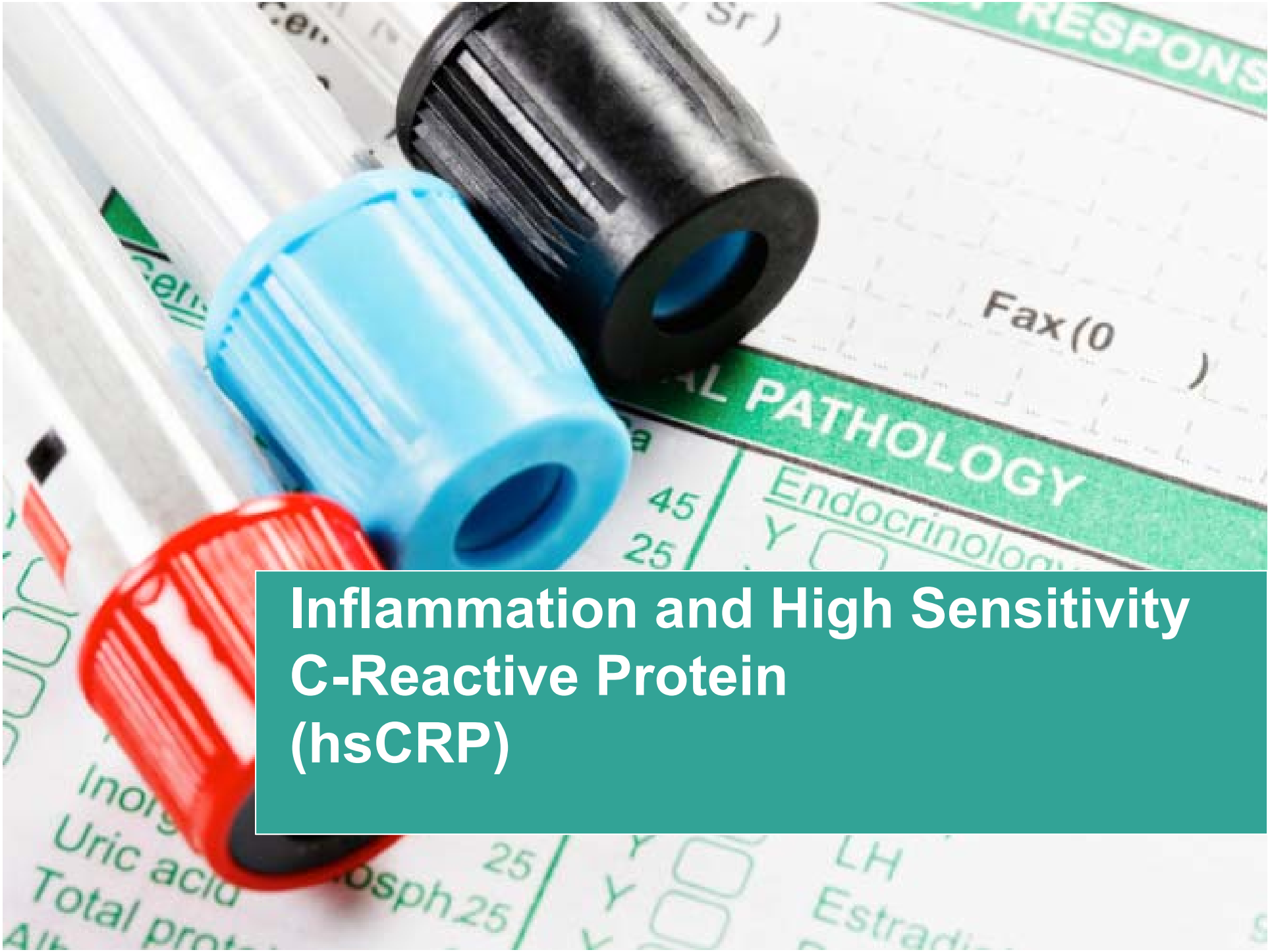
Relationship between hypertension and hyperlipidemia and why statins decrease BP

Vascular Biology in Clinical Practice, Oct. 2000; Mark C. Houston, MD

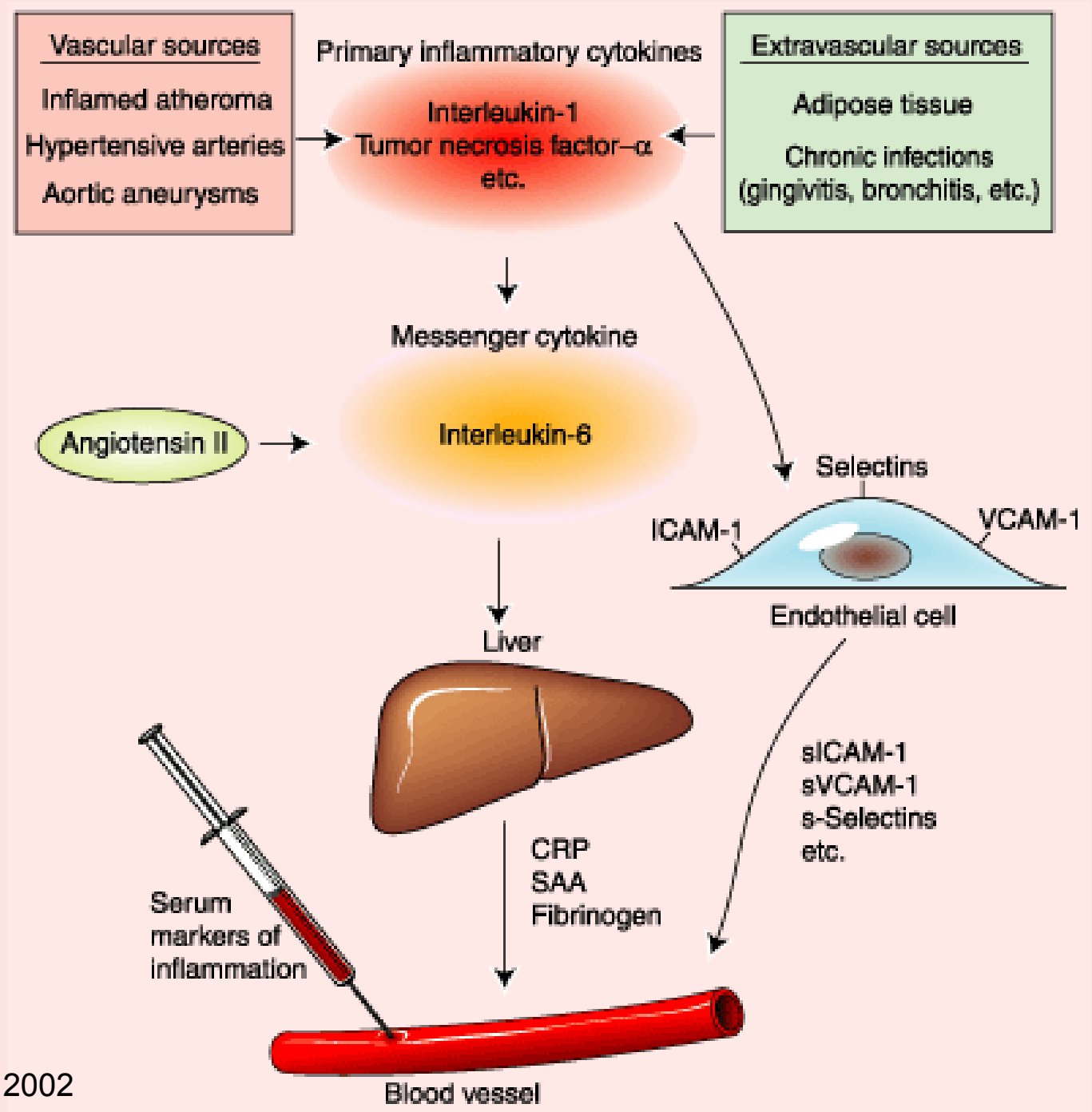
Angiotensin II:Role of ROS on Hypertension and Hyperlipidemia and Atherosclerosis

Vascular Biology in Clinical Practice, Oct. 2000; Mark C. Houston

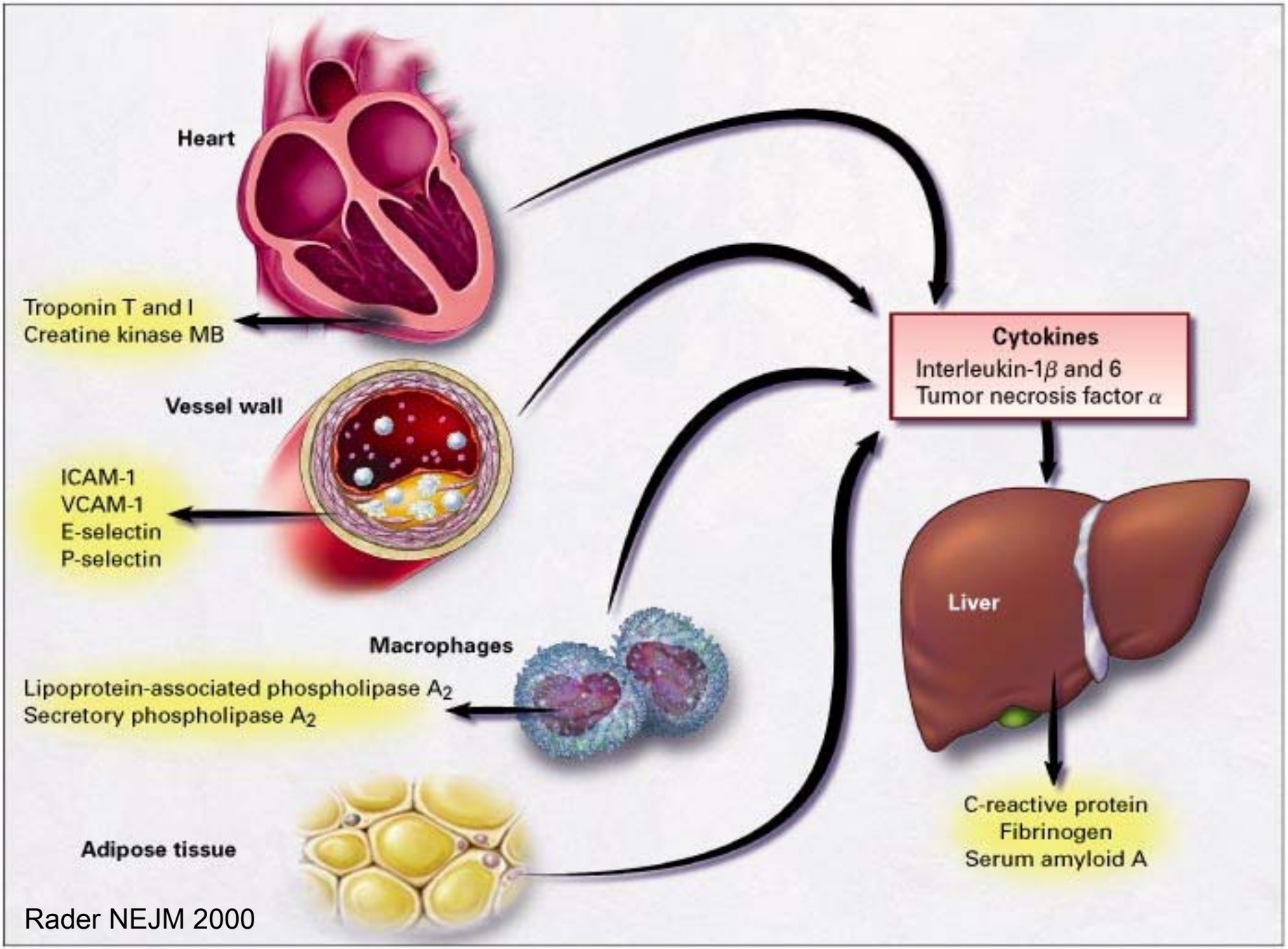




Inflammation and High Sensitivity C-Reactive Protein (hsCRP)

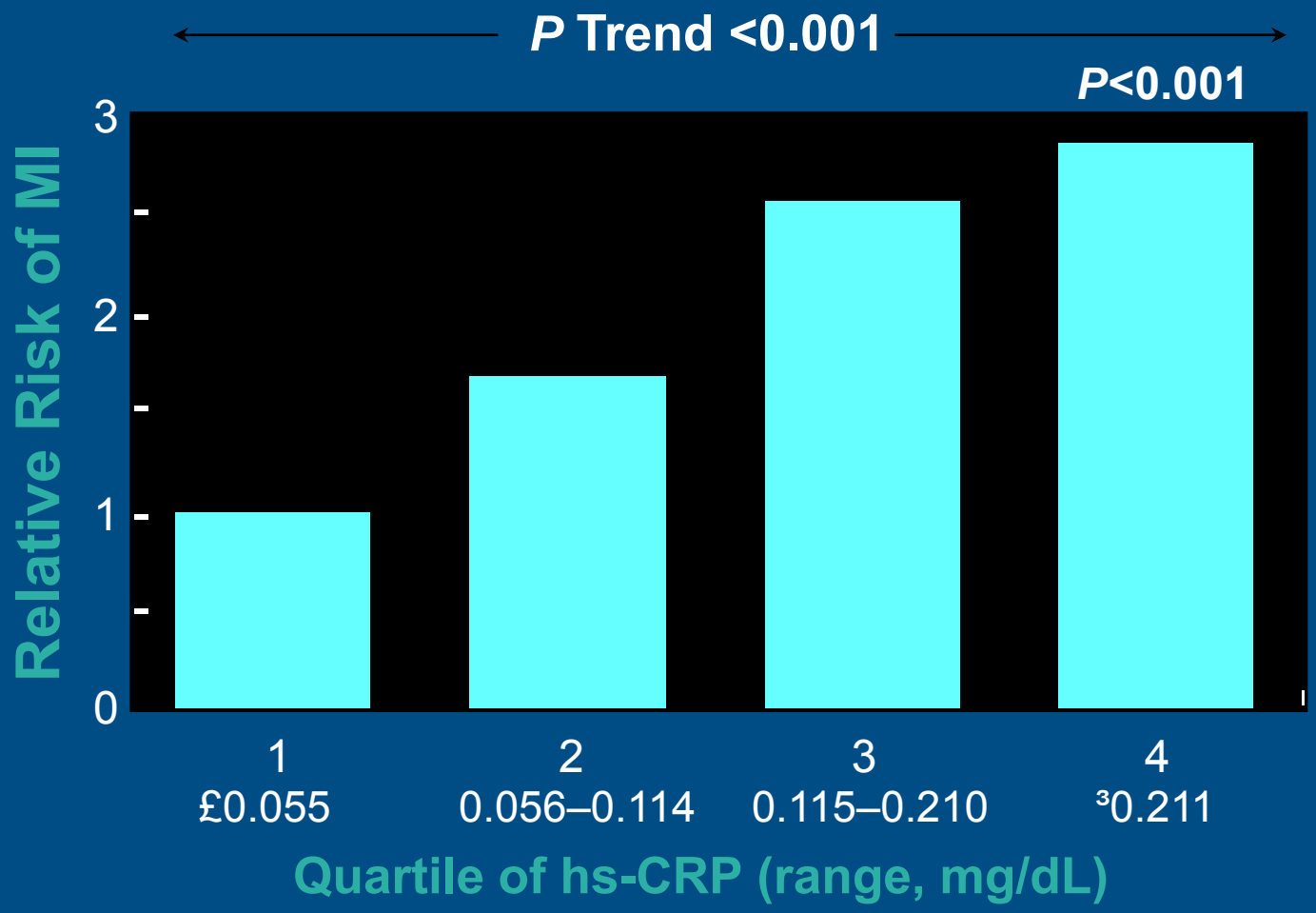


Libby, Science 2002



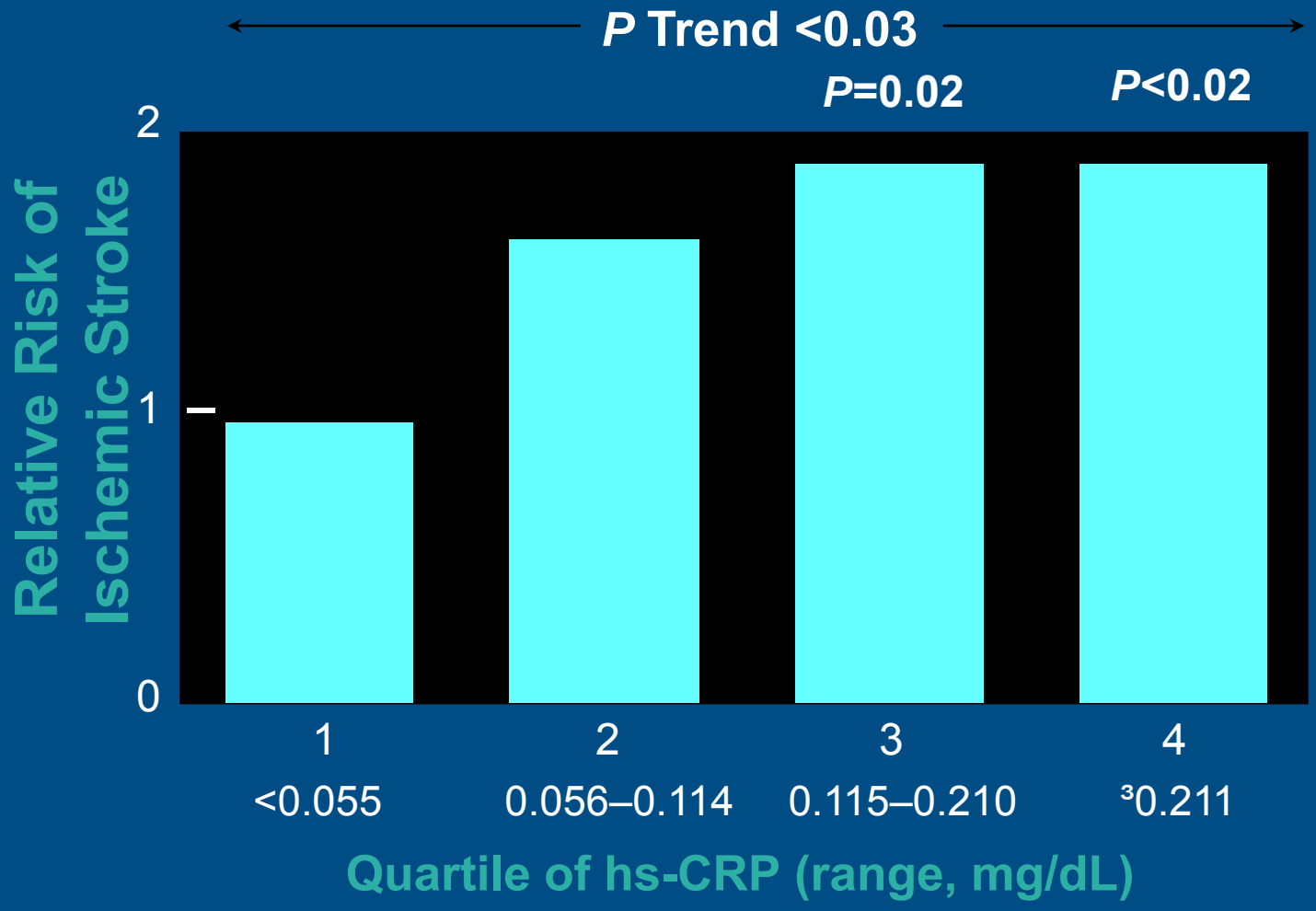
Rader NEJM 2000

hs-CRP and Risk of Future MI in Apparently Healthy Men



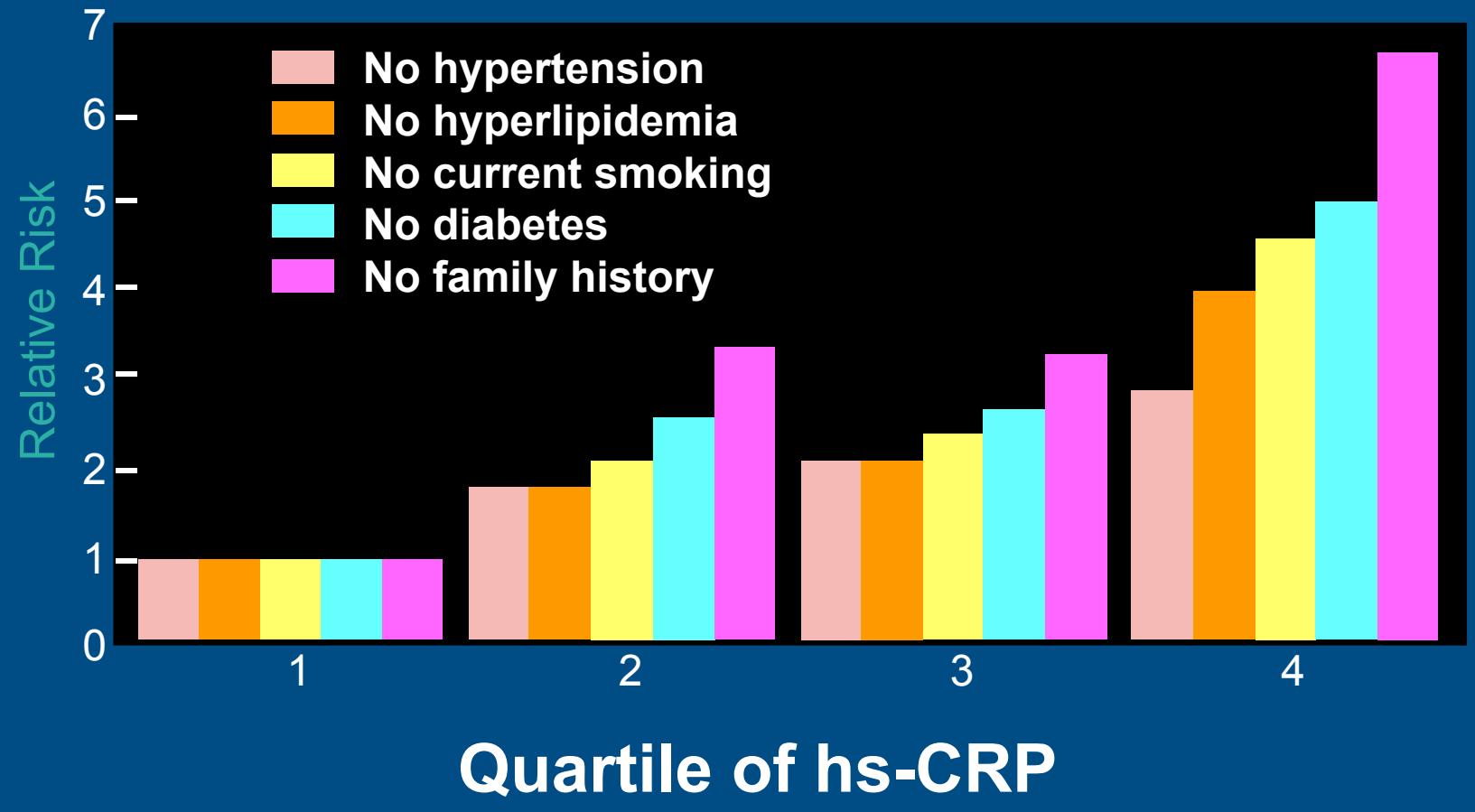
Ridker PM et al. *N Engl J Med.* 1997;336:973–979.

hs-CRP and Risk of Future Stroke in Apparently Healthy Men



Ridker PM et al. *N Engl J Med.* 1997;336:973–979.

hs-CRP and Risk of Future Cardiovascular Events in Apparently Healthy Women: Low-Risk Subgroups

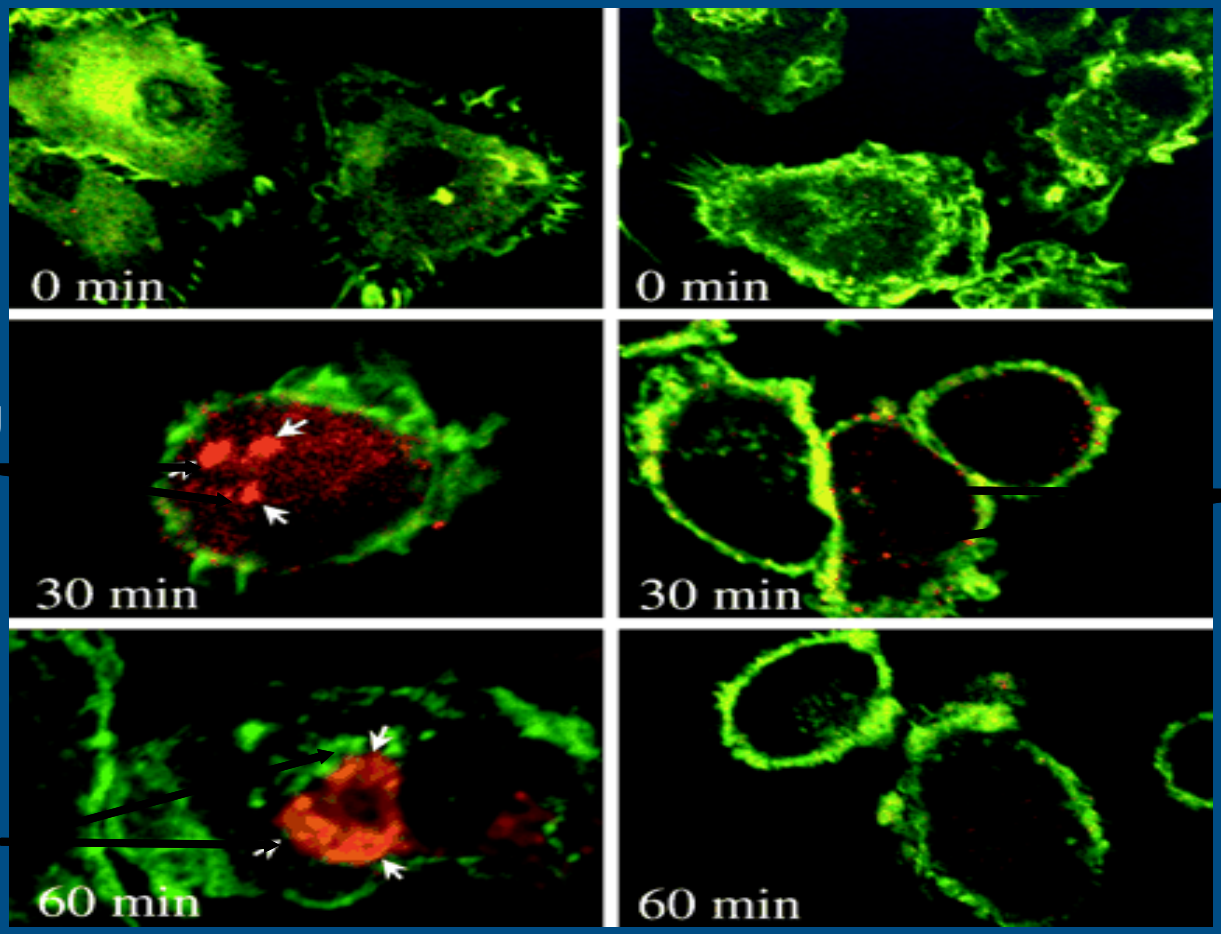


Ridker. *Circulation.* 1998;98:731–733.

CRP Mediated Uptake of LDL by Macrophages

Macrophages incubated with CRP/LDL

Macrophages incubated with LDL alone



LDL Containing Vesicles

LDL vesicles - deeper and disseminated within the cytoplasm

Slight dissemination of LDL

No LDL Containing Vesicles

Adapted from Zwaka TP, et al. *Circulation.* 2001;103:1194-1197.

Inflammation Increases BP and CVD - CRP and Leukocytosis and Autoimmune Dysfunction

J of Am Society of Hypertension 2010;4:272

- Hs CRP causes hypertension and elevated BP increases hs CRP. Bidirectional risk.
- CRP is both risk factor and risk marker for hypertension and CVD.
- Best vascular inflammation marker. Composite of vascular and nonvascular sources of TNF alpha, IL 6, and IL 1b
- Leukocytosis especially increased neutrophils and decreased lymphocyte count increases BP especially in blacks. SBP 6 mm Hg higher and DBP 2 mmHg higher from highest to lowest quartiles.
- Dysregulation of CD4+ and CD8+ T lymphocytes.

Reduction in CRP

Houston. What Your Doctor May Not Tell You About Heart Disease

- Mediterranean Diet
- High fruit and vegetable diet
- Omega 3 FA and MUFA
- Curcumin
- Quercetin
- Plant Sterols
- Weight and fat (visceral) Loss
- Stop Smoking
- Vitamins E, A, D, C and B
- R-lipoic acid
- Grape seed extract
- Ginger
- Nettles
- EGCG
- Rosemary
- Magnesium
- Fiber

Reduction in CRP

Houston. What Your Doctor May Not Tell You About Heart Disease

- Resveratrol
- Boswellia
- Nattokinase
- Dark Chocolate
- Bromelin
- Reduce Insulin resistance
- Exercise and Sleep and Stress reduction
- Cold water fish
- Flavonoids
- CoQ10
- Selenium
- Aspirin
- ACEI
- ARB
- Statins

JUPITER Trial : Inflammation

NEJM 2008;359:2195
Lancet 2009;373:1175

- 17,802 patients with mean LDL of 100 mg/dl, Framingham scores of <10 and HSCRP >2.0mg/L
- Rosuvastatin 20 mg per day
- 54% decrease in MI
- 51% decrease in ischemic CVA
- 46% decrease in PCTA and CABG
- 43% decrease in thromboembolic disease
- 20% decrease in all cause mortality

Microparticles (MPs) – “Cell Dust”

J of HTN 2010;28:1611-13,673-75 & 1655-1665
J Am Soc Nephrol 2005;16:3381
Cell Tissue Res 2009;335:143
Current Opin Nephrol HTN 2010;19:177
Eur J Heart Failure 2010;12: 1223
Cir Res 2011;109:593

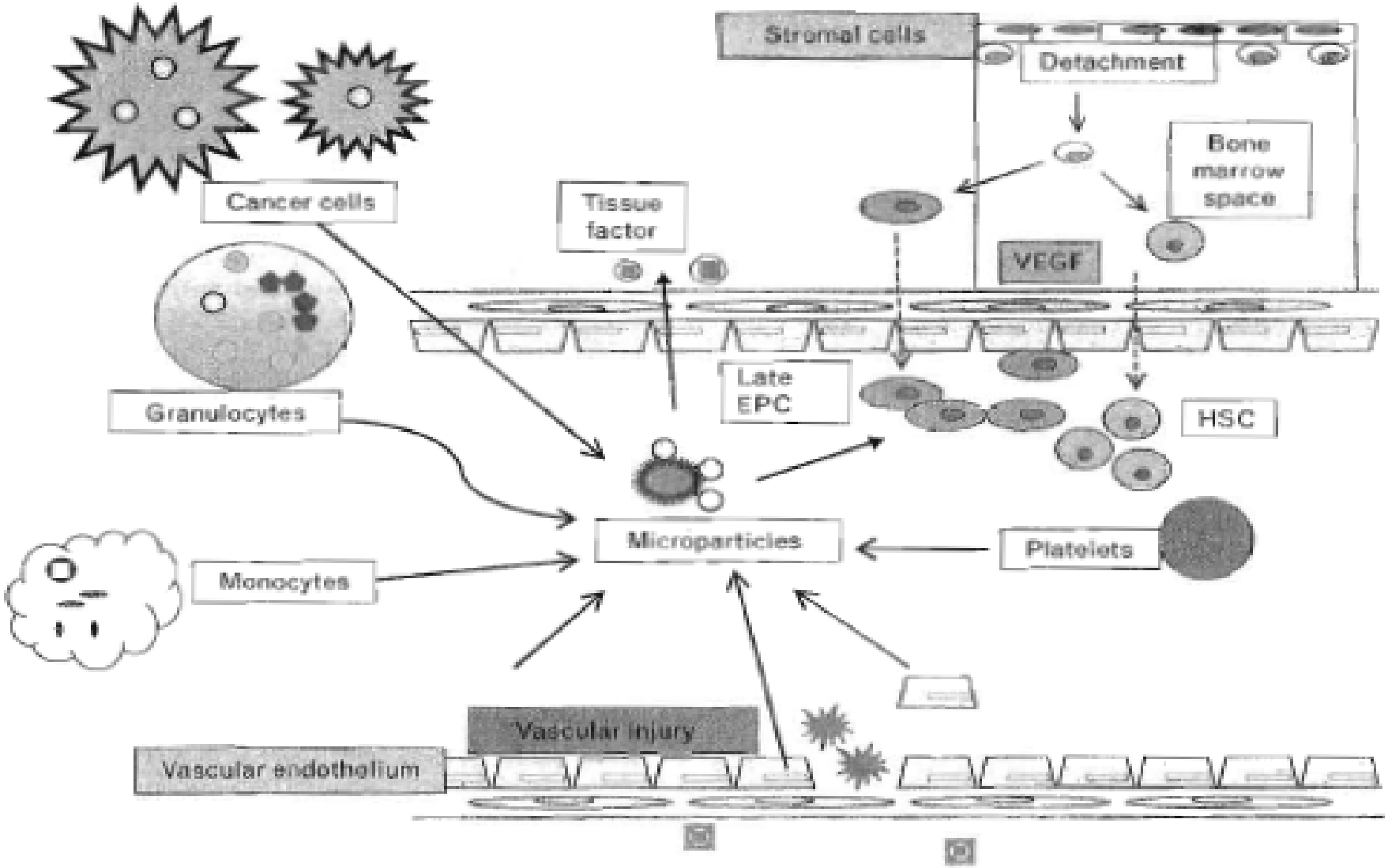
- Damaged fragments of protein and lipids from endothelial cells, leukocytes, erythrocytes and platelets, mast cells and vascular smooth muscle cells and cancer cells that circulate in the blood. Platelet derived particles are 70-90%
- Relate to asymmetric phospholipid distribution in cell membranes that break off during cell activation of apoptosis. Exosomes and ectosomes. Membrane shed MPs released after cell activation or apoptosis.
- Procoagulants by binding to coagulation factors

Microparticles

J of HTN 2010;28:1611-13 and 1655-1665
J Am Soc Nephrol 2005;16:3381
Cell Tissue Res 2009;335:143

Current Opin Nephrol HTN 2010;19:177
Eur J Heart Failure 2010;12: 1223
Circ Res 2011;109:593

- Inflammatory cytokines and chemokines: proinflammatory
- Reduce NO and damage endothelium
- CAMs and CD3 and monocyte recruitment
- Annexin V apoptosis
- ROS
- Stimulate angiogenesis to make unstable plaque
- PAI-I and tissue factor: procoagulant
- Associated with altered vascular function, vascular remodeling, autoimmunity, CRF, MAU, HBP, DM, CHD, MI, CHF, ACS, preeclampsia, and cancer.



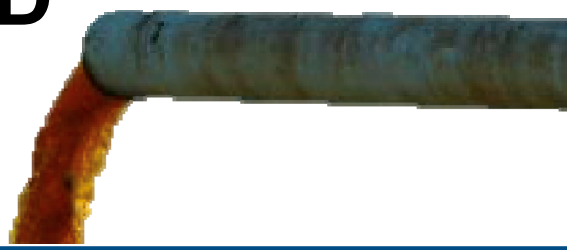
f microparticles and endothelial progenitor cells.

dothelial progenitor cells; HSC, hematopoietic stem cell; VEGF, vascular endothelial growth factor.

Microparticles Summary

Environmental Pollutants are CHD Risk Factors

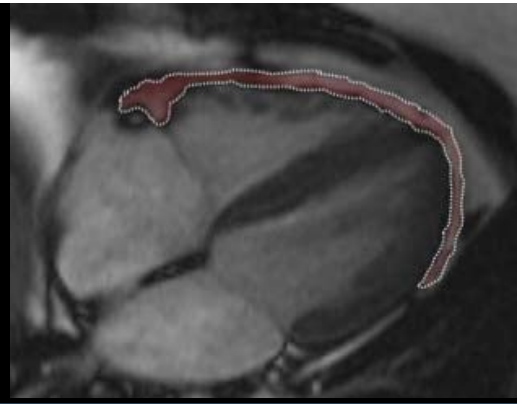
JAMA 2011;306:2081
Environ Health Perspect October 11, 2011 EPUB



- POPs (persistent organic pollutants) are CHD risk factors, independent of other risk factors.
- Included PCB's, dioxin, pesticides, BDE47, etc.
- Higher levels are associated with hypertension, obesity, metabolic syndrome, dyslipidemia, and DM.
- Associated with MI and carotid artery plaque.
- Impair DNA repair and cell cycling in vascular smooth muscle leading to oxidative stress, inflammation, immune dysfunction with atherosclerosis and plaque formation.

Epicardial fat is associated with an increased risk for CHD

Clin Cardiol 2011;34:166



- Epicardial Fat (EF) is the visceral fat of the heart deposited under the visceral layer of the pericardium and has same embryonic origin as abdominal visceral fat.
- EF is the direct source of FFA and inflammatory cytokines to the coronary arteries by epicardial arteries.
- EF is associated with CHD and CAC by 64 slice CT.
- Increases myocardial insulin resistance
- Inflammation, oxidative stress and immune dysfunction of cardiac muscle and coronary arteries.

Epicardial Adipose Tissue (EAT)

Curr Opin Nephrol Hypterten 2015;24:517

- EAT is a metabolically active visceral fat that covers 80% of the cardiac surface and 20% of total cardiac weight.
- Endocrine functions: secretes hormones and inflammatory cytokines. Higher concentration of IL-6, IL-1B, MCP and TNF alpha in patients with CHD.
- Regulates local fatty acid homestasis
- Provides immediate local energy source
- Assists in coronary artery remodeling
- Supports coronary arteries against torsions from cardiac contraction and arterial pulse wave
- Higher correlation with CHD than VAT, BMI, body weight, DM etc.
- Evaluate by ECHO, CT or MRI.

Epicardial Fat (EAT) is associated with an increased risk for CHD

Clin Cardiol 2011;34:166 J Cardiol 2012;109:1295
Am J Cardiol;2012;110; Am J Cardiol 2012;110:1793
Am J Cardiol 2013;111:73;Am J Cardiol 2013;112:943
J Clin Hypertension 2013;15:893;Am J Cardiol 2014;113:1505
J Clinical Lipidology 2015;9:305; Curr Opin Neprhol Hypertens 2015;24:517

- Epicardial Fat (EF) is the visceral fat of the heart deposited under the visceral layer of the pericardium. Same origin as abdominal visceral fat
- EF is source of FFA and inflammatory cytokines to the coronary arteries by epicardial arterial supply. (paracrine effect)
- EF is associated with CAD and CAC by 64 slice CT but showed NS trend by ECHO in Mayo clinic trial. EAT thickness at left AV groove (AVG) shows highest correlation with CHD. Location may be more important than amount of total thickness of EAT. AVG location may dump pro-inflammatory mediators directly into the coronary sinus and thus impact LCX and LAD blockage.
- ECHO, cardiac MRI and CT have high correlation of EAT and CVD.
- Increased myocardial insulin resistance
- Inflammation, oxidative stress and immune dysfunction and elevated HSCRP and lower catalase levels.
- Predicts risk for hypertension , ED metabolic syndrome, diastolic dysfunction , CHD, MI, CAC,LVH, myocardial inflammation, oxidative stress and atrial fibrillation

Perivascular Adipose Tissue (PAT) and CHD

Atherosclerosis 2013;230:177

- PAT as well as EAT exert important roles in the pathogenesis of CVD beyond the contribution of VAT due to their close anatomic relationships with vascular structures and the myocardium
- Paracrine effects in obese or metabolic disease patients by direct diffusion of various adipokines like IL 6, TNF alpha, leptin, visfatin that induce vasoconstriction, ED, VSM proliferation, plaque rupture, CHD and hypertension.
- Exert vasodilatory protective effect in non obese by releasing adiponectin, adrenomedulin , IL-10 and ADRF.

SLEEP and Obstructive Sleep Apnea (OSA): Short Sleep Duration, Hypertension CHD, CVD, CVA

J of Am Soc of Hypertension. 2010;4:255 J of Hypertension 2012;30:13354 Clin. Cardiol 36: 11:671

- Short sleep duration is an independent risk factor for silent cerebral infarcts and of future stroke events (OR 2.01)in hypertensive patients. Less than 6 hrs
- Also increases risk for CVD, CHF (1.6), hypertension, diabetes, obesity, metabolic syndrome, CHD, MI (2.04)
- Prolonged sleep increases CVA risk also: over 10 hours
- 8 hours appears to be the perfect sleep duration to prevent CVA and CVD events etc.
- OSA is most common cause of secondary hypertension, increases CHD, MI. CVA, CHF, sudden death, arrhythmias, obesity, IR,DM, MS, inflammation, cortisol and catecholamines. Do out patient or inpatient sleep studies (watchPAT). Treatment, ENT consult, weight reduction, surgery and CPAP.

Sleep and LVH

Am J Cardiol 2013;112:599

- Too short or too long sleep duration are associated with hypertension, poor CV health, LV mass and mortality.
- U shaped curve
- Sleep over 1 hours had increased nocturnal SBP and higher diurnal SBP

Hormones and CVD

Thyroid and the Heart

Circulation 2003;107:708 J Cardiol 1993;23:205
Am J Med 2001;111:699 Eur J Cardiothorac Surg 2003;24:487
Ann Int Med 2000;132:270 Thyroid 1996;6:527, Am J Card 1998;81:443
J of Hypertension 2012;30:592;Arch Int Med 2012;172:811
Am J of Medicine 2014;127:691

- CVD,CHD/MI, PAD and general atherosclerosis
- V Tach and V fib
- A Fib post CABG
- Sudden death
- Predictor of death post MI in 12 months, especially in younger patients
- CHF, low EF, diastolic dysfunction
- Hypertension and dyslipidemia
- Homocysteinemia
- Endothelial dysfunction
- Obesity
- Metabolic syndrome, IR, DM
- Future risk for hypothyroidism
- Increased carotid IMT, PWV, AI and markers of ED and arterial stiffness
- Starts at TSH over 2.5 mIU /ml
- If TSH is below .10 mIU/ml in hyperthyroidism then CHD and AF increase.

Steroidogenic Pathways Insulin Resistance, Inflammation, BP and CVD

Inflammation from any cause such as visceral obesity, insulin resistance, hyperglycemia, metabolic syndrome, poor nutrition, dyslipidemia, hypertension will alter regulation of steroid pathway enzymes and thus hormone level

CORTISONE AND CORTISOL

- Inflammation, adiposity, insulin resistance, metabolic syndrome, hyperglycemia, smoking and dioxin upregulate **11B HSD** and downregulate **17,20 lyase.**
- Upregulated 11 HSD converts inactive cortisone to active cortisol
- Downregulated 17,20 lyase increases 17 OH pregenolone and decreases DHEA and increases 17 OH progesterone which decreases androstendione and also increases cortisol ,catabolic pathways and 17 OH CS and reduces anabolic steroid pathways and 17OH KS.
- Pregenolone and progesterone are decreased due to upregulation of 17 hydrolase by similar conditions.
- This leads to increases in BP and vascular disease due to increased cortisol and lower DHEA, testosterone and estrogen levels.

Aldosterone is a modulator of immunity, hypertension and CVD

J of Hypertension 2011;29:1684
J of Hypertension 2013;31:3-15

- Aldosterone is an independent risk factor for CVD.
- Mineralocorticoid receptors exist in heart, blood vessels, brain and immune cells.
- Blockade of aldosterone even with persistance of hypertension and in normotensive patients reduces CV risk .
- Aldosterone mediated non-hemodynamic effects increase CVD.
- Aldosterone is associated with increased adaptive immunity and autoimmune responses with CD4+T cell activation and Th 17 polarization increased IL-17, TGF-B and TNF alpha which modulate over 30 inflammatory genes

Aldosterone is a modulator of immunity, hypertension and CVD

J of Hypertension 2011;29:1684
J of Hypertension 2013;31:3-15
Mol Cell Pharmacol. 2010 Jan 1;2(1):7-14

- To cell is converted to Th17 rapidly in presence of high NaCl with aldosterone, insulin, steroids in the presence of SGK1 (serum glucocorticoid kinase 1), IL1B and IL 4.
- Due to Na+ not Cl and not due to hypertonic state. NaCL concentration in interstitial fluid is higher (156-192mmol/L)
- If inhibit SGK1 or NFATS then decrease immune response and lower BP.
- Nuclear factor of activated T cells (NFAT) is a transcription factor that translocates from cytosol to nucleus following dephosphorylation by the Ca(2+)/calmodulin dependent protein phosphatase calcineurin (CN) and increases CNS disease
- NFAT also increases VEGF-C
- NaCL also increases multiple sclerosis by SGK1.
- Dysregulation of the immune system induces autoimmune vascular disease and hypertension.

Aldosterone and Mineralocorticoids in Hypertension, CHF and CKD. Feed Forward Loops and Hypertension, CHF, CVD and CKD

JASH 2015;9:586

- Intracrine properties of Aldosterone, AII, A 1-7 have feed forward regulatory loops leading to upregulation of themselves or of their signaling pathways.
- This loop can be self perpetuated even after removal of the original stimulus both within the cell and adjacent cells.
- Progressive hypertension with A-II and CKD with hyperglycemia despite normalization of BP and glucose.
- Non genomic actions of aldosterone. Increased by AII, low K and hyperglycemia.
- Aldosterone upregulates ACE in endothelium and cardiomyocytes and renin in JGA of kidney.
- Aldosterone blockade alone or with RAS inhibition with ACEI or ARB would add more protection for CHF and CKD.

Th 17, SGK1, NaCL, Hypertension and CVD

Nature 2013: 496::513–517
Am J of Pathology 2012;181:8

- T_H17 cells (interleukin-17 (IL-17)-producing helper T cells) are highly proinflammatory cells that are critical for clearing extracellular pathogens and for inducing multiple autoimmune diseases such as RA, SLE, MS, psoriasis , IBD, allergy, asthma and other inflammatory vascular diseases such as hypertension.
- IL-23 stabilizes and reinforces the T_H17 phenotype by increasing expression of IL-23 receptor (IL-23R)
- Serum glucocorticoid kinase 1 (SGK1) regulates IL-23R expression and stabilizes the T_H17 cell phenotype
- SGK1 has been shown to govern Na^+ transport and salt (NaCl) homeostasis in other cells
- A modest increase in salt concentration induces SGK1 expression, promotes IL-23R expression and enhances T_H17 cell differentiation accelerating the development of autoimmunity and inflammation . Loss of SGK1 abrogated Na^+-mediated T_H17 differentiation in an IL-23-dependent manner.
- SGK1 has a critical role in the induction of pathogenic T_H17 cells and provide a molecular insight into a mechanism by which an environmental factor such as a high salt diet triggers T_H17 development and promotes tissue inflammation related to hypertension, CVD and neurodegenerative diseases.

Aldosterone in vascular and metabolic dysfunction

Curr Opin Nephrol Hypertens 2016;25:16

- The mineralocorticoid receptor (MR) is expressed in vascular smooth muscle and vascular endothelium
- Adipocyte-derived leptin stimulates aldosterone secretion
- Overexpression of the MR induces metabolic syndrome.
- Aldosterone stimulates adipocyte expansion, leptin expression, decreases adiponectin and increases IR, obesity and ED.

Proanthocyandins block aldosterone –dependent up regulation of cardiac gamma ENaC via SGK1

J of Nutritional Biochemistry 2016;27:13-19

- The up regulated aldosterone mediator SGK1, ENaC and Nedd are blocked by proanthcyandins in cardiac muscle that protect the heart from fibrosis, oxidative stress and aldosterone mediated cardiovascular damage.

Autoimmune dysfunction and hypertension and CVD : Summary

Curr Opin Lipidol 2018;29:411

- Activation of the immune system plays a casual role in the pathogenesis of hypertension and hypertension-induced target organ damage and CVD.
- The antigen involved in the immune activation is infinite
- APC activate T cells which enter the target organs and promote damage
- Different macrophage subtypes can either amplify the inflammatory response, help in the repair process or counter-regulate the disease process.
- Both A-II and Aldosterone increase immune responses and increase IL-17 levels.

Continuity of Risk Concept and Vascular Disease

- There is a direct correlation of CHD, vascular disease, and atherosclerosis with the level of the risk factor starting at very low or “normal levels” for:

• Blood Pressure	MRFIT, Framingham	110/70 mmHg
• Lancet Meta-analysis on BP		115/75 mmHg
• LDL Cholesterol	HPS, ASCOT, PROVE IT	60 mg/dl
• Serum FBS	AAA, Whitehall, Hamilton	75 mg/dl
• Homocysteine	Observational Studies	5

Global Cardiovascular Risk

Houston MC et al Am J Medical Sciences 2005;329:276-291 and 292-305

- Absolute Risk: probability of an adverse event occurring in an individual within a defined period of time
- Relative Risk: probability of an adverse event happening in an individual compared to average or normal individuals sharing similar demographics other than the risk factor

COSEHC Global Cardiovascular Risk Calculation Definitions

Houston MC et al Am J Medical Sciences 2005;329:276-291 and 292-305

- HIGH CARDIOVASCULAR RISK with expanded CHD risk factors beyond Framingham
- Relative Risk > 60th percentile
- Absolute Risk: Risk score > 40
  > 2.3% risk of CV death / 5 years

CHD RISK SCORING: COSHEC
(*Merged Framingham, PROCAM and INDANA Data Tables)

Houston MC et al Am J Medical Sciences 2005;329:276-291 and 292-305

Risk Factors: Men = 17, Women = 12

- Being male
- Age (years)
  Extra for cigarette smoking
- Systolic blood pressure (mm Hg)
- Total cholesterol conc. (mg / dL)
- LDL cholesterol (mg / dL)
- HDL cholesterol (mg / dL)
- Triglyceride (mg / dL)
- Height (inches)
- Creatinine conc. (mg / dL)
- Homocysteine (µmol / L)
- Prior MI
- Family history of MI pre- 60
- Prior Stroke
- LVH
- Diabetes
- Non-Diabetic, FBS (mg / dL)

COSHEC ABSOLUTE RISK ANALYSIS FOR DEATH FROM CHD IN 5 YEARS

Risk Score	% dying from cardiovascular disease in 5 years
0	0.04
5	0.07
10	0.11
15	0.19
20	0.31
25	0.51
30	0.84
35	1.4
40	2.3
45	3.7
50	6.1
55	9.8
60	15.6
65	24.5
70	37.0

COSHEC ABSOLUTE RISK CALCULATION

Houston MC et al Am J Medical Sciences 2005;329:276-291 and 292-305

- VERY LOW RISK: SCORE 0-10
- LOW RISK: SCORE 10-20
- MODERATE RISK SCORE 20-30
- MODERATE/HIGH SCORE 30-40
- HIGH RISK SCORE 40-50
- VERY HIGH RISK SCORE > 50
- NOTE TRIPLE RISK WITHIN EACH 10 POINT RISK SCORE

COSHEC RISK SCORE FOR MEN

Risk factor	Addition to risk score	Risk Score
Being Male	Add 12 points	+12
Age (years)	35-39: 0; 40-44: +4; 45-49: +7; 50-54: +11; 55-59: +14; 60-64: +18; 65-69: +22; 70-74: +25	
Extra for cigarette smoking	+9; +7; +7; +6; +6; +5; +4; +4	
Systolic Blood pressure (mm Hg)	110-119: 0; 120-129: +1; 130-139: +2; 140-149: +3; 150-159: +4; 160-169: +5; 170-179: +6; 180-189: +8; 190-199: +9; 200-209: +10; ≥210: +11	
Total cholesterol conc. mg/dL	≤193: 0; 194-231: +2; 232-269: +4; 270-308: +5; 309-347: +7; ≥348: +9 Only if total ≤193 see below	
LDL cholesterol mg/dL	If total cholesterol ≤ 193; LDL: <100: 0; 100-129: +1; 130-159: + 3; 160-189: + 4	
HDL cholesterol mg/dL	If total cholesterol ≤ 193; HDL: <35: + 4; 35-44: + 2; 45-54: + 1; ≥55: 0	
Triglyceride mg/dL	If total cholesterol ≤ 193; TG: < 100: 0; 100-149: +0; 150-199: +1; ≥200: + 1	
Height (inches)	<63: +6; 63 - <67: +4; 67- <71: +3; 71 - < 75: +2; ≥75: 0	
Creatinine conc. (mg/dL)	≤0.8: 0; 0.9: +1; 1.0: +1; 1.1: +2; 1.2: +2; 1.3: +3; 1.4: +3; >1.4: +4	
Homo-cysteine (µmol/L)	≤5: -6; 5 – 5.9: -5; 6 – 6.9: -4; 7 – 7.9: -3; 8 – 8.9: -2; 9 - 9.9: -1; 10 – 11.8: 0; 11.9-12.9: +1; 13-13.9: +2; 14-14.9: +4; 15-15.9: +5; ≥16: +6	
Prior MI	No 0; Yes +8	
Family History of MI pre- 60	No 0; Yes +1	
Prior Stroke	No 0; Yes +8	
LVH	No 0; Yes +3	
Diabetes	No 0; Yes +2 If not diabetic, see below	
Non-diabetic, FBS (mg/dL)	≤75: -1.5; 76-81: -1; 82-88: -0.5; 89-99: 0; 100-105: +0.5; 106-111: +1; 112-117: +1.5; 118-125: +2; ≥126: Diabetic (above)	
	Total Risk Score =	

Absolute Risk Score	% dying from cardiovascular disease in 5 years
0	0.04
5	0.07
10	0.11
15	0.19
20	0.31
25	0.51
30	0.84
35	1.4
40	2.3
45	3.7
50	6.1
55	9.8
60	15.6
65	24.5
70	37.0

Rasmussen Center CV scoring

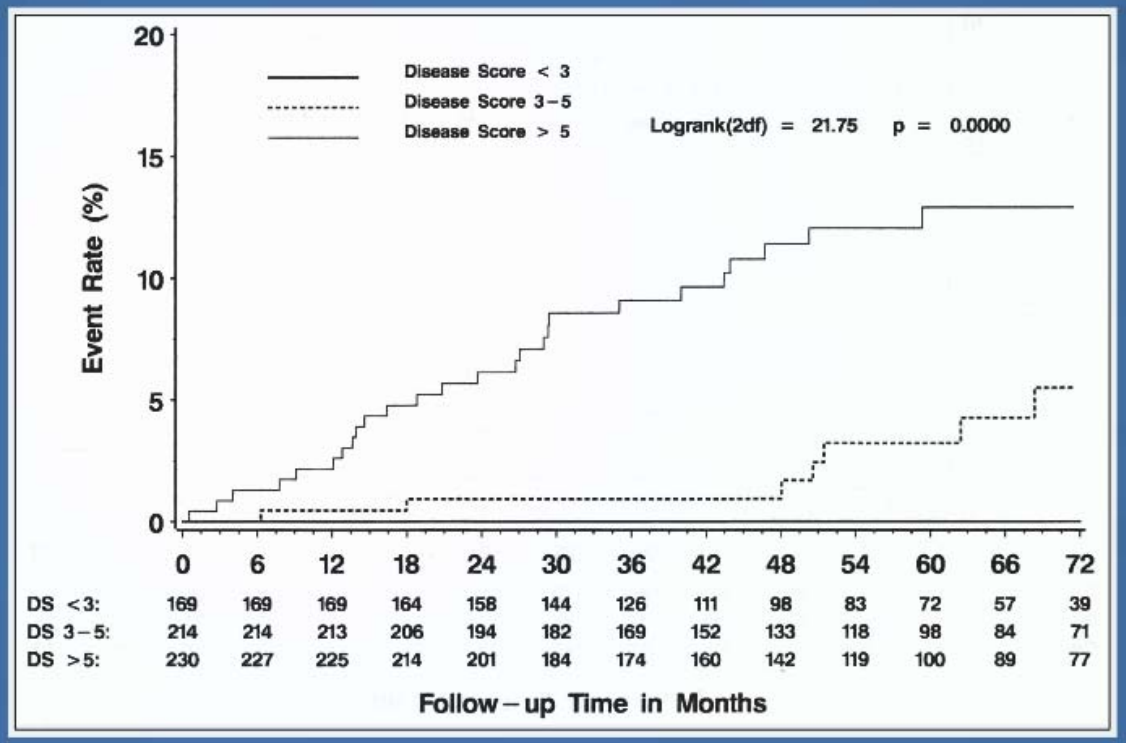
J Am Society of Hypertension 2011;5:2011

- Disease score 0-2: no CV events in 6 yrs
- Disease score 3-5: 5%CV events in 6 yrs
- Disease score over 6: 15 % CV events in 6 yrs
- Superior to Framingham risk score
- Variables measured: CAPWA, BP at rest and exercise, LV mass by ECHO, microalbuminuria, BNP, retinal score, Carotid IMT and US, EKG

Rasmussen Center CV Scoring

J Am Society of Hypertension 2011;5:401

Test	Normal	Borderline	Abnormal
Score for each test	0	1	2
Large artery elasticity		(age- and gender-dependent)	
Small artery elasticity		(age- and gender-dependent)	
Resting BP (mm Hg)	SBP <130 and DBP <85	SBP 130–139 or DBP 85–89	SBP ≥140 or DBP ≥90
Treadmill exercise BP (mm Hg)	SBP increase <30 and SBP ≤169	SBP increase 30–39 or SBP 170–179	SBP increase ≥40 or SBP ≥180
Optic fundus photography retinal vasculature	A/V ratio >3:5	A/V ratio ≤3:5 or mild A/V crossing changes	A/V ratio ≤1.2 or A/V nicking
Carotid IMT		(age- and gender-dependent)	
Microalbuminuria (mg/mmol)	≤0.6	0.61–0.99	≥1.00
Electrocardiogram	No abnormalities	Nonspecific abnormality	Diagnostic abnormality
LV ultrasound LVMI (g/m^2)	<120	120–129	≥130



Kaplan-Meier curves of time morbid events during 6 years of follow-up in the three Rasmussen Disease Score (DS) Groups.
The difference among the curves (P = .0000) is highly significant.
Two events after 72 months are not depicted.

Credit: D. A. Duprez et al. / Journal of the American Society of Hypertension 5(5) (2011) 401 - 409

CHAN2T3 CHD Risk Score

Am Heart J 2017;193:95

Risk Factors

- HS-CRP > 3.4 mg/L
- Homocysteine >8.9 umol/L
- Albuminuria > 30 mg/g
- N terminal prohormone of BNP >117 picograms/mL
- Troponin-T detected

Ten year risk of CHD event per risk factor above

0 = 2.09 %

1 = 4.16 %

2 = 6.09 %

3 = 6.95 %

4= 10.22 %

5= 25 %

Comparison of Novel Risk Markers to Improve CV Risk Assessment

JAMA 2012;308:788

- 6814 participants in MESA study evaluating CAC, Carotid IMT, ABI, BFMD, HS-CRP and FH of CHD compared to the FRS.

Results in multivariable analysis:

- CAC: HR 2.60 (p<0.001) : BEST (also best in Rotterdam study, Kavousi study and others)
- FH: HR 2.18 (p<0.001)
- HS –CRP: HR 1.28 (p< 0.05)
- Carotid IMT: HR 1.17 (p=.13)
- BFMD: HR .93 (p=.52)
- ABI: HR .79 (p= .01)

Incremental Risk Reduction

Basile, Houston, Ferrario. J of Clinical Hypertension 2006;8:688-696

- There is a continuous and graded increase in CV risk proportional to the severity of each primary CVD risk factor.
- Incremental reduction in each risk factor proportionally reduces the CVD risk depending on one's absolute global risk.
- It may be better to reduce multiple risk factors to "goals" rather than reduce one risk factor to a "normal" level.
- "Silo" thinking vs "Global" thinking

Non-invasive Vascular Testing

Non Invasive Vascular Testing

Functional Tests

Endopat (endothelial dysfunction, AI and HRV)
CAPWA (computerized arterial pulse wave analysis)
HRV:Heart rate variability and HRRT(heart rate recovery time)
EKG and TMT and CPET
MCG (magnetocardiography)

Structural Tests

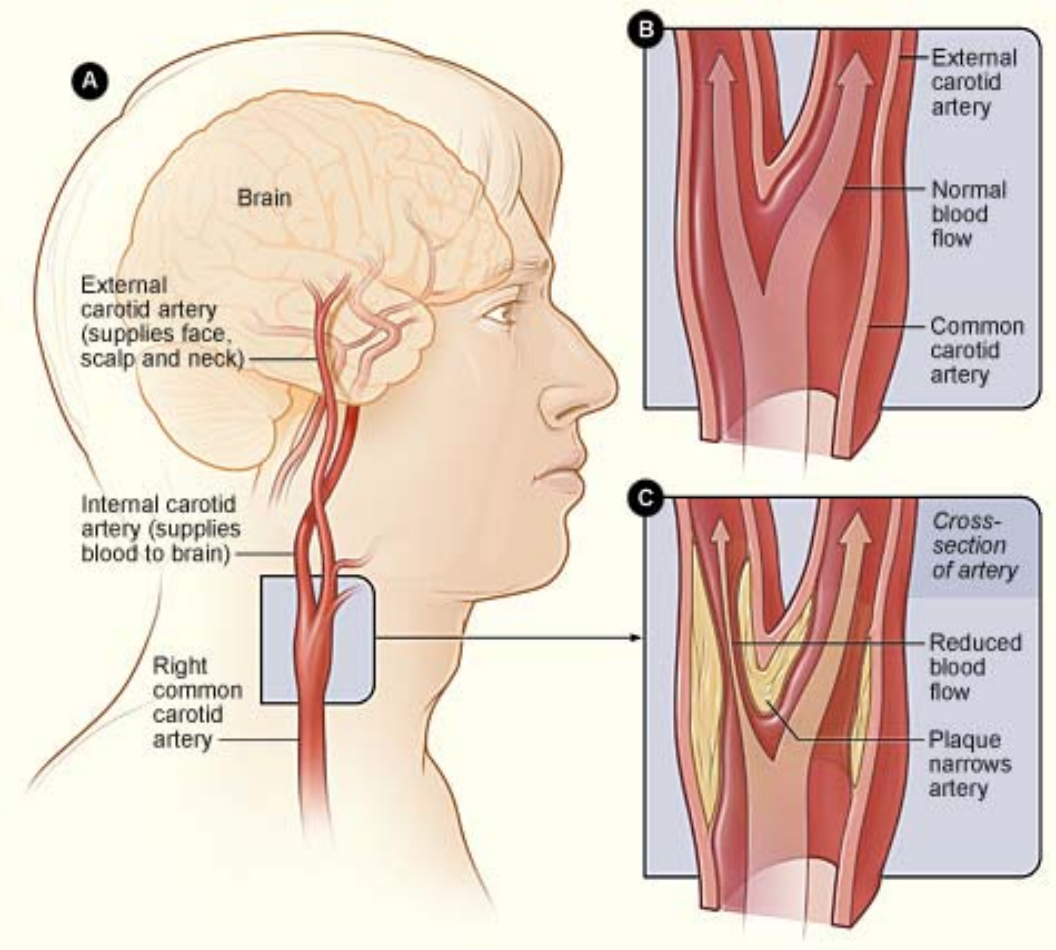
Carotid IMT/Duplex
EBT and CT angiogram (CTA) with CAC scoring
Cardiac MRI (CMR)
ECHO: Rest and exercise
ABI: Rest and exercise
Retinal scan and OPA (Ocular Pulse Amplitude)

Other

Cardiac PET, SPECT
FDG-PET/CT: vascular inflammation/plaque/biologic activity
PET/CT/F-NaF for coronary plaque/inflammation/morphology
PET/MRI for coronary plaque morphology and inflammation
IVUS: Intravascular ultrasound
Coronary angiogram

Carotid Intimal Medial Thickness (IMT) and Carotid Atherosclerosis

Carotid Artery Structure



This illustrates the structure of the carotid artery tree that is scanned in the IMT test. The measurement is taken in the common carotid artery which provides the best look at the degree of atherosclerosis.

Plaque Assessment

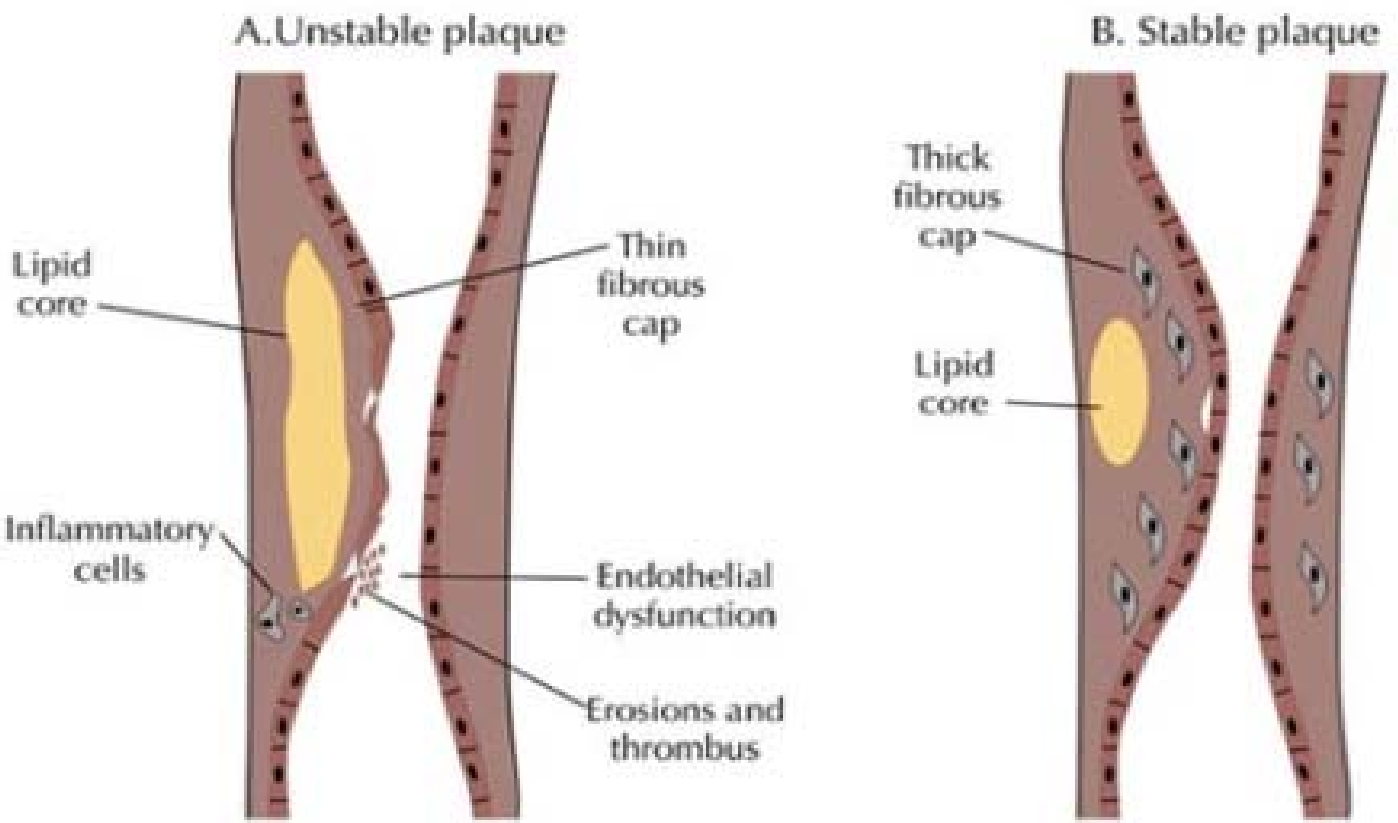
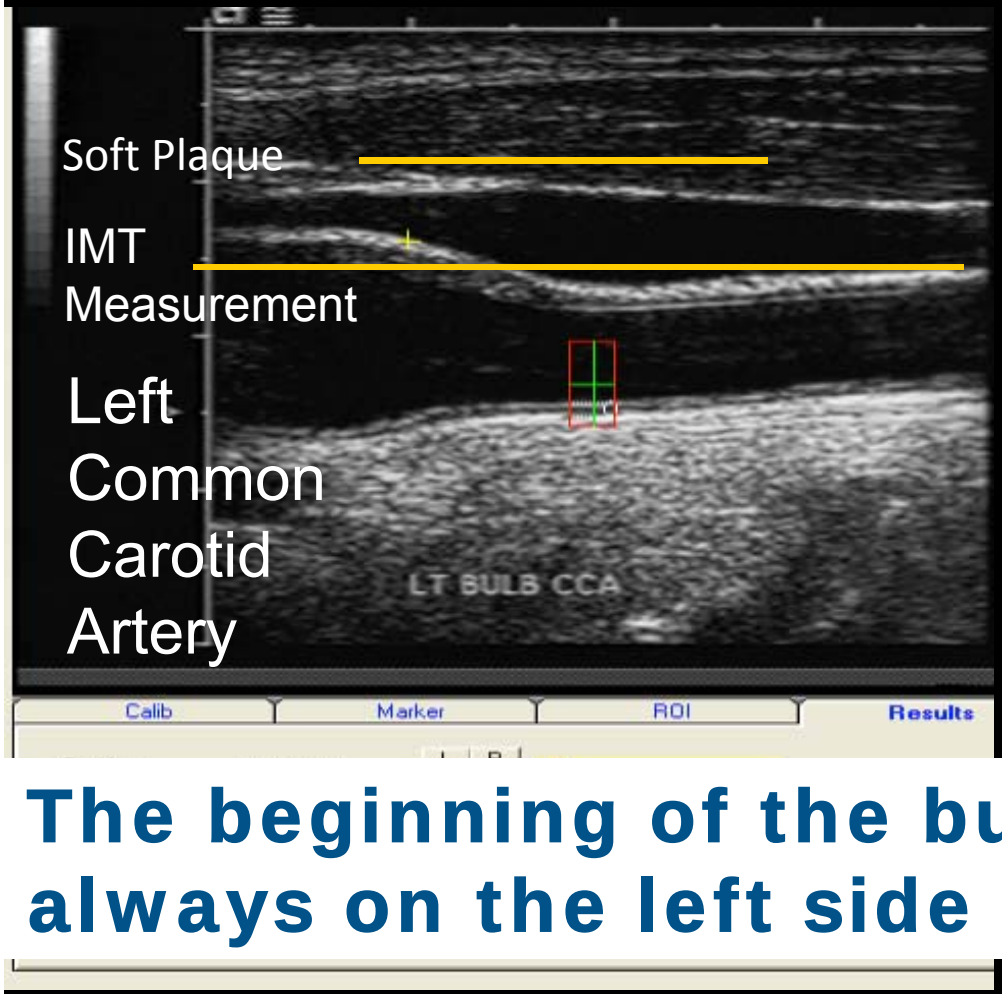


Image Measurement and Analysis



This shows the ideal view of the area used for analysis.

Note: The double-line seen at both the top and bottom show scan is “on-axis.”

The beginning of the bulb is always on the left side

Carotid IMT

Cerbrovasc Dis 2007;23:75

- Carotid IMT measures the intima-media thickness of the common carotid artery. It reflects early atherosclerosis and non-atherosclerotic medial hypertrophy from smooth muscle cell hyperplasia and fibrocellular hypertrophy.
- Normal values without any plaque present:
- Less than 0.6 mm: Normal low risk
- 0.6 to 0.7mm: Moderate risk
- 0.7 to 0.95 mm: High risk
- The normal IMT accretion rate (CIMTAR) is 0.016 mm / year.

Carotid IMT and Relationship to Risk Factors Predicts CV Events Independently from Framingham Risk Score

Ann Med 2008;40:21
Nutr Metab Cardiovasc Dis 2006 ;16: 22 ,
Atherosclerosis 2008;199:3

Circulation 2007;115:459
Eur Heart J 2010 May 25,
JAMA 2003;290: 2271,
NEJM 2011;366:213

- Hypertension
- Dyslipidemia
- Diabetes Mellitus, insulin resistance and hyperinsulinemia
- Smoking
- Obesity and increased BMI
- Lack of exercise
- Nutrition: low intake of fruits and vegetables
- hsCRP, fibrinogen and ICAM, Apo E, ACE D
- MI, CVA, CVD, atherosclerosis.

Carotid IMT Correlates with Future CV Events – Metaanalysis

Circulation 2007;115:459

- **Myocardial Infarction**
- 1.26 (95% CI 1.21-1.30) per one SD common carotid artery IMT difference and 1.15 (95% CI 1.12-1.17) per 0.10 mm common carotid artery IMT difference over 5 years. ICA IMT is best predictor.

- **Stroke**
- 1.32 (95% CI 1.27-1.38) per one SD common carotid artery IMT difference and 1.18 (95% CI 1.16-1.21) per 0.10 mm common carotid artery IMT difference over 5 years.

Carotid IMT vs Carotid Plaque

Curr Cardiol Rep 2009;11:21.

- Carotid IMT is most closely correlated with hypertension and ischemic CVA.
- Carotid plaque is most closely correlated with hyperlipidemia and smoking.
- Total plaque area is the most strongly predictive of CV risk of the ultrasound phenotypes.

Carotid IMT and Plaque Predict Stroke

Acta Neurol Scand Suppl 209;189:68
J Stroke Cerebrovasc Dis 2007;16:14
Int Angiol;2010;3:216
Atherosclerosis 2009;205:486

- Stroke predictors include:
  - IMT especially CCA IMT
  - Total plaque area: strongest predictor of stroke and CVD
  - Plaque number
  - Plaque echogenicity: vulnerable soft plaque and lipid content
  - Silent brain infarcts associated with carotid plaque

Trans Fats and Carotid Plaque

J of Nutritional Biochemistry 2016;38:81-85

- For each 0.1 % increase in RBC total c-18:1 TFA isomer, carotid plaque prevalence increased by 53%. This predicts future CV events.
- In contrast, for each 0.1% increase in RBC alpha linolenic acid ,omega 3 FA, the carotid plaque prevalence decreased by 43 %.

Echo

- Left ventricular hypertrophy
- Left atrial hypertrophy
- Diastolic dysfunction
- Valve function
- Ejection fraction
- Wall motion abnormalities

Coronary Artery Calcification and Cartoid IMT (MESA)

Arch Intern Med 2008;168:1333
Am J Cardiology 2015;116:520.

- Coronary artery calcification was associated more strongly than carotid IMT with risk of incident CVD (n=6698) over 5.3 years.
- CAC: CVD risk increased 2.1 fold per one SD
- Carotid IMT: CVD risk increased 1.3 fold per one SD
- CAC highly associated with glycemic load and index.

Vascular Calcification: Pathogenesis

Circulation1995;92: 2029-32;JCI 1994;93:2106-13
Arch Int Med 2007;167:879-85;Free Radic Biol Med 2001;31:509-19
Curr Opin Nephrol Hypertens 2013;22:405-412.
European Heart J 2014;35:1515

- Active process by calcifying vascular cells in vascular smooth muscle
- Mediated by signaling molecules
  1. Osteocalcin
  2. Osteopontin
  3. Bone morphogenic protein BMP-2
  4. Matrix Gla protein
  5. Fibroblast growth factor (FGF 23)

  Associated with all cause mortality and CVD events (CHF and CVA). Alters Vitamin D metabolism and RAAS.

. Signals are induced by inflammatory and lipid mediators such as TGF beta and oxLDL which lead to transformation of vascular smooth muscle cells into osteoblast-type cells, PTH, vitamin D, calcium and phosphate are all key elements.

Vascular Calcification: Pathogenesis

Circulation1995;92: 2029-32;JCI 1994;93:2106-13
Arch Int Med 2007;167:879-85;Free Radic Biol Med 2001;31:509-19
Curr Opin Nephrol Hypertens 2013;22:405-412.

- Imbalance between inducers and inhibitors
- Various stimuli lead to dedifferentiation of VSMC into osteoblast/chondroblast-like cells
- Multipotent vascular stem cells
- Micro-RNA involved
- FGF 23/Klotho axis
- Vitamin D and K
- BMP 2
- Serum phosphorous and calcium
- CKD

Vascular Calcification: Pathogenesis Inhibitors of Calcification

Ann Intern Med 2010;152:640-8
Heart and Soul Study 833 patients 6 yrs.

- Fibroblast Growth Factor 23 (FGF 23)

  Associated with all cause mortality and CVD events (CHF and CVA). Alters Vitamin D metabolism and RAAS.
- Matrix Gla protein (MGP): carboxylated

  Associated with reduction in all cause mortality and CHD and MI.
- Fetuin A
- Osteoprogerin(OPG)
- Inorganic pyrophosphate

CT Angiogram (CTA) and CAC

Am J Cardiol 2010;106:1574; Am J Cardiology 2011;107:799;Am J Cardiol 2012;109:1449; Mayo Clinic Proc 2014;89(10): 1350-59
Am J Card 2104;114:1707; Am Heart J 2016;177:17
Am J of Cardiology 2017;120:2154

- The risk of major CV events or death increased in a graded manner with the degree of coronary atherosclerosis as defined by CTA even in the absence of high grade coronary artery stenosis
- Both the CAC score and the number of calcified plaques improve risk strategication
- In the absence of high grade stenosis there is not a superior prognostic value of CTA compared to EBT CAC
- CAC is superior to predict future CHD events compared to the Framingham risk score and other biomarkers for CHD. Predicts increase risk A. Fib.
- CAC imparts increased CHD risk in younger and elderly individuals, across all age groups.
- Sugar –sweetened beverages have the highest correlation with CAC of food groups.

CHD Progression by EBT on Phytonutrient Concentrate Powder

Houston MC,. Juice Powder Concentrate and Systemic Blood Pressure, Progression of Coronary Artery Calcium and Antioxidant Status in Hypertensive Subjects: A Pilot Study. Evidence-Based Complementary and Alternative Medicine 4:455-462, 2007.

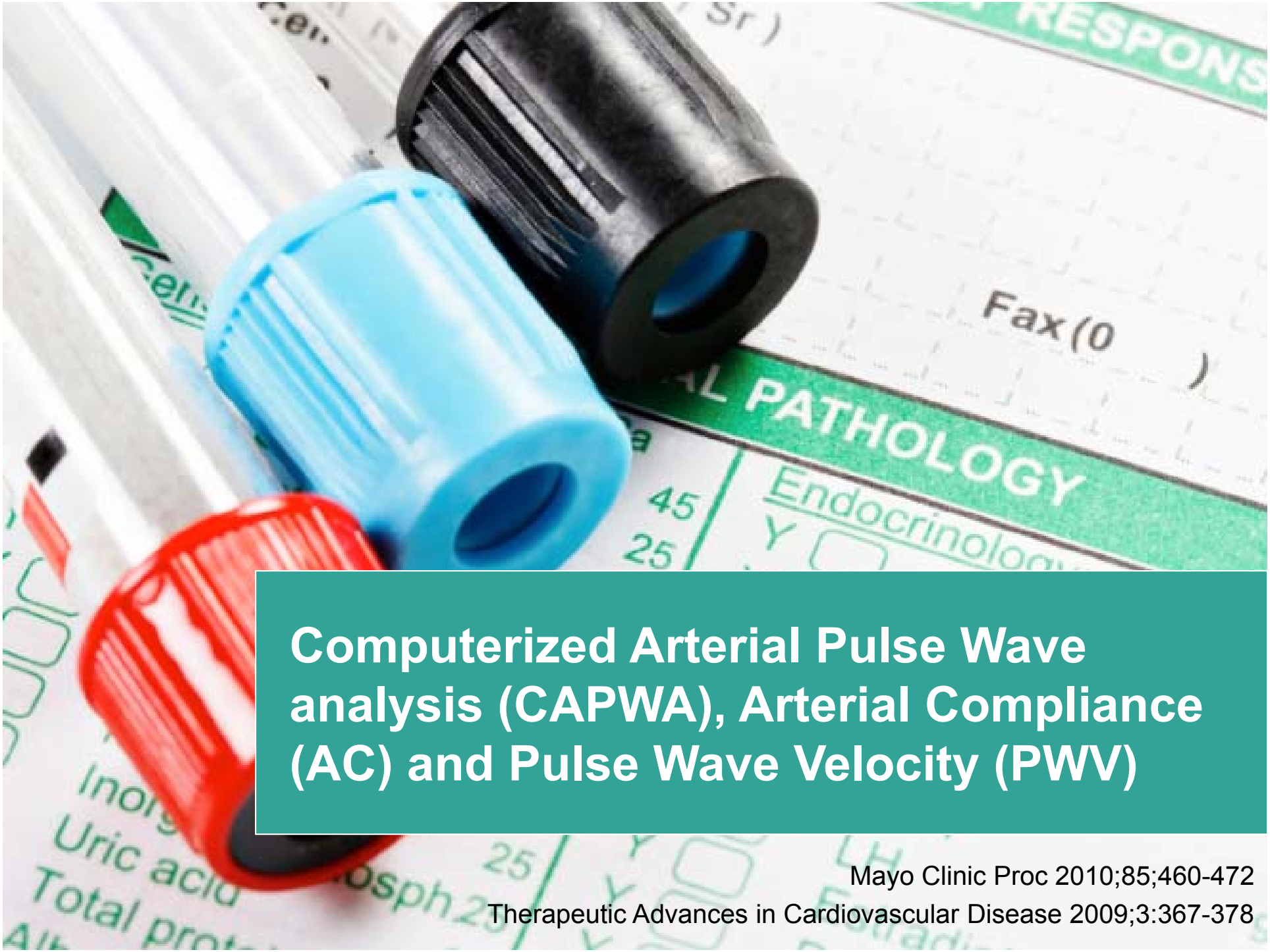
- 42 patients studied over 2 years showed a significant reduction in progression of CHD as assessed by EBT compared to historical controls using phytonutrient concentrate.
- Coronary artery calcium score increased by 19.6 % in treated patients vs. 34.7 % in controls ($p < 0.009$).

CTA vs Angiogram

Am J Cardiology 2016:117:1863

- Coronary CTA detects approximately twice as many coronary segments with plaque compared to coronary angiograms.

- This results in 52% of patients being assigned to a greater risk category.



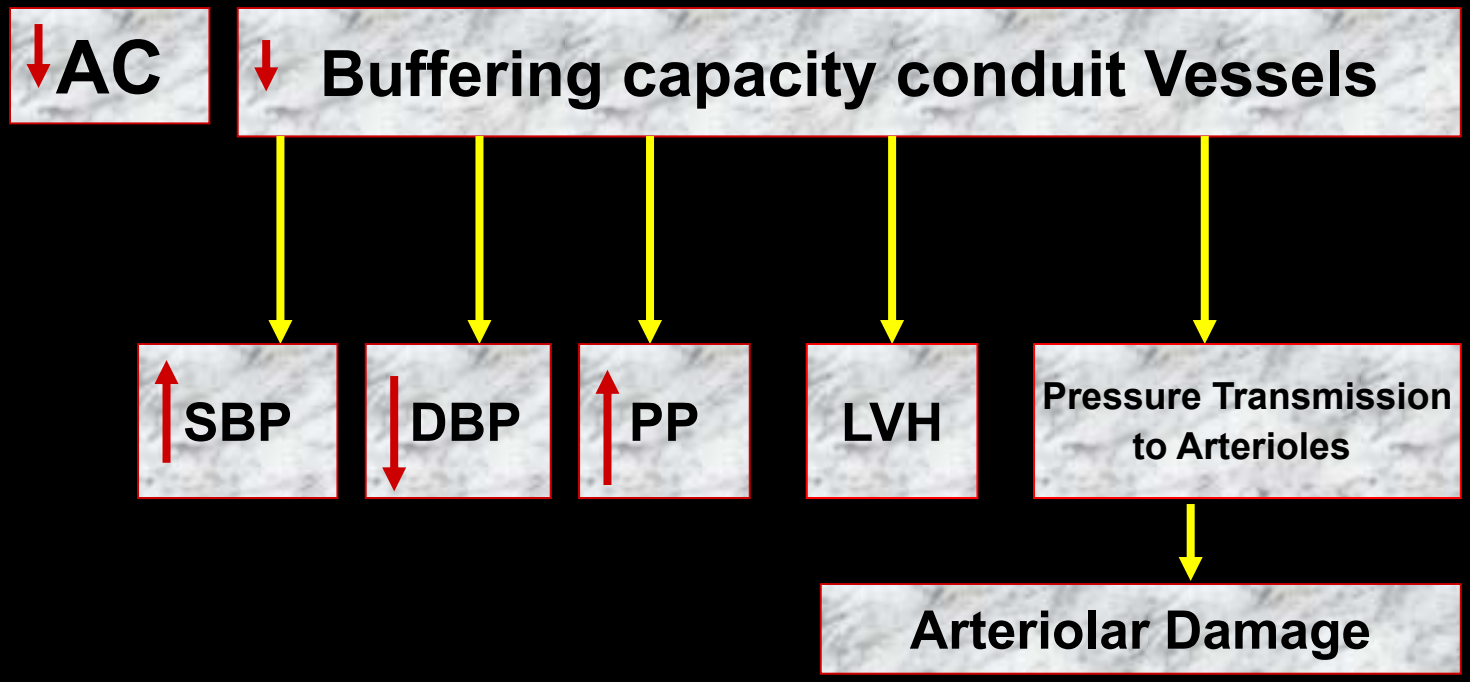
Computerized Arterial Pulse Wave analysis (CAPWA), Arterial Compliance (AC) and Pulse Wave Velocity (PWV)

Mayo Clinic Proc 2010;85;460-472

Therapeutic Advances in Cardiovascular Disease 2009;3:367-378

Vascular Compliance: Introduction and Overview

Vascular Biology in Clinical Medicine 2002. Houston MC. Hanley and Belfus. Philadelphia, Pennsylvania.



Vascular Compliance – Artery Types

Vascular Biology in Clinical Medicine 2002. Houston MC. Hanley and Belfus. Philadelphia, Pennsylvania.

- Conduit (Capacitive): C1 (store blood in systole) (buffer) (thin endothelium with thick elastin and collagen) ↓VSM
- Branch (Oscillatory): C2 (pressure oscillations/reflected waves) (intermediate structure)
- Arterioles (Resistance): C2 (control blood flow) VSM + endothelium primarily with minimal elastin or collagen) NO dependent. Early marker vascular disease (HBP, HLP, DM)
- Endothelium role is greatest in thin wall vessels – (oscillatory and resistance). ED earlier and greatest in C-2 vessels.

Buffering System of Vasculature

Vascular Biology in Clinical Medicine 2002. Houston MC. Hanley and Belfus.

Philadelphia, Pennsylvania.

- In systole there is rapid infusion of SV
- 20 – 30% is forward flow
- 70 – 80% is stored in large conduit (capacitive) arteries, then released to periphery during diastole
- Converts pulsatile flow in aorta to continuous flow in capillaries (Windkessel effect)
- Loss of buffering with ↓ AC causes reduced continuous flow but increased pulsatile flow to precapillary and capillary vasculature inducing small vessel damage, end organ dysfunction and damage (↑↑ PWV)
- Reflected wave
- Augmentation index (systole)

Arterial Compliance – Measurement

Noninvasive Applanation Tonometry (CAPWA)

- (Computerized Arterial Pulse Waveform Analysis)
- Synthesize central pressure waveform from the brachial or radial waveform
- Central hemodynamics improves: Diagnosis, monitoring, prognosis
- Index of wave augmentation
- + Arterial stiffness + Wave reflection
- + Vascular load + Coronary perfusion
- Evaluate therapy - Central vs peripheral pressure discrepancies
- PWV is independent risk factor for CVD in HBP

Pulse Wave Velocity and Arterial Compliance And Elasticity

J Am Coll Cardiol 2002;39 abstract 3523
Blood Pressure Monitoring. 2002.7: 231
Am Heart J 2003;146:679
J Hypertens 2010;28:1935

- C2 compliance identifies the presence of endothelial dysfunction in the microvascular circulation, the very small arterioles and arteries (range 4-9).
- C1 compliance is a measure of the elastic behavior of the aorta and larger arteries (range 8-17).
- Lower numbers indicate diseased arteries and are age and gender adjusted. .
- Low C2 and increased PWV predict CVD/CHD.

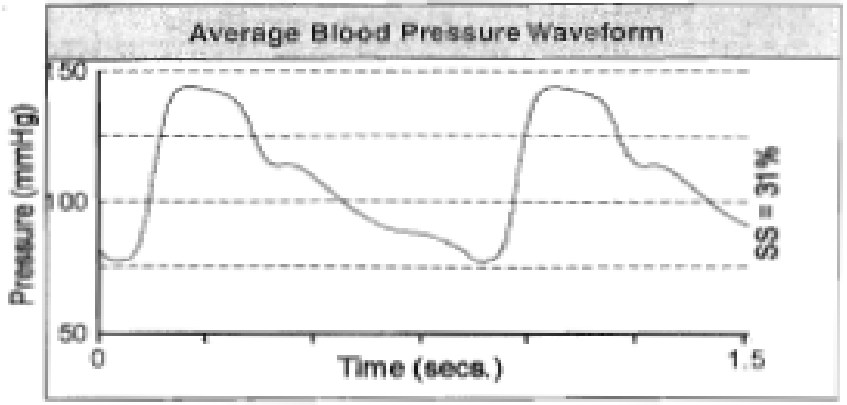
CV Report Patient

Profile by: ST THOMAS MEDICAL GROUP

~~ID#: 4442221~~

Name: [redacted]

SSN:
Date: Jan 01, 1997
Time: 00:17
Age: 47 years
Gender: Female
Height: 5 ft 7 in
Weight: 160 lbs
BSArea: 1.93 meters²
Body Mass Index: 28.2



PARAMETER		VALUE
Systolic Blood Pressure	(mmHg)	144
Diastolic Blood Pressure	(mmHg)	78
Mean Arterial Blood Pressure	(mmHg)	104
Pulse Pressure	(mmHg)	66
Pulse Rate	(beats/min)	71
C1 – Large Artery Elasticity Index (Capacitive Arterial Compliance)	(ml/mmHg x 10)	10.2
C2 – Small Artery Elasticity Index (Oscillatory or Reflective Arterial Compliance)	(ml/mmHg x 100)	3.5

MEDICAL HISTORY

CV Disease:	N
CV Medications:	?
Diabetes:	?
Relatives CV Disease:	?
Tobacco:	?
Race:	?

CLINICAL COMMENTS:

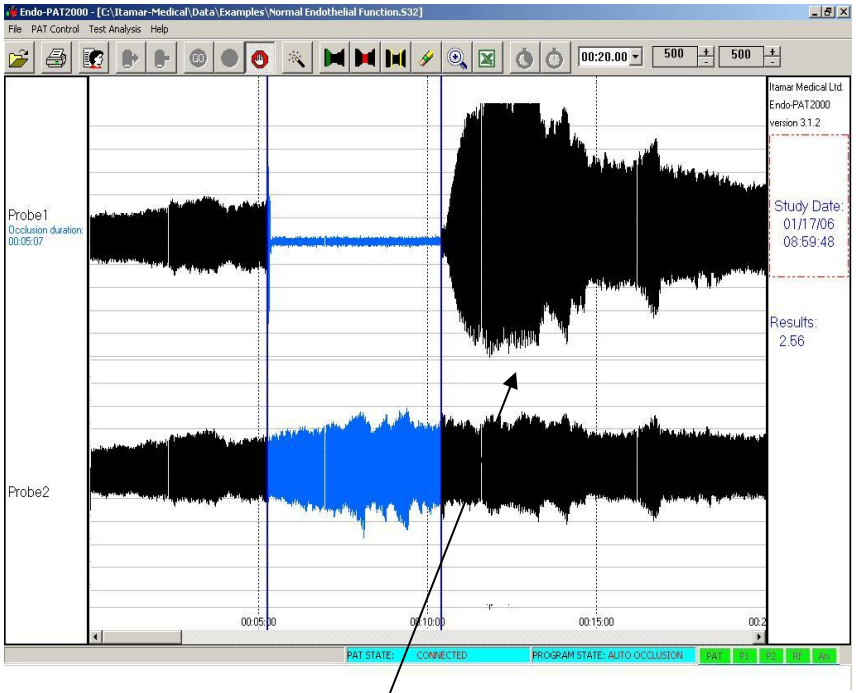
Abnl C2
ED
NORMAL > 7.6

ENDO-PAT – ED and CVD

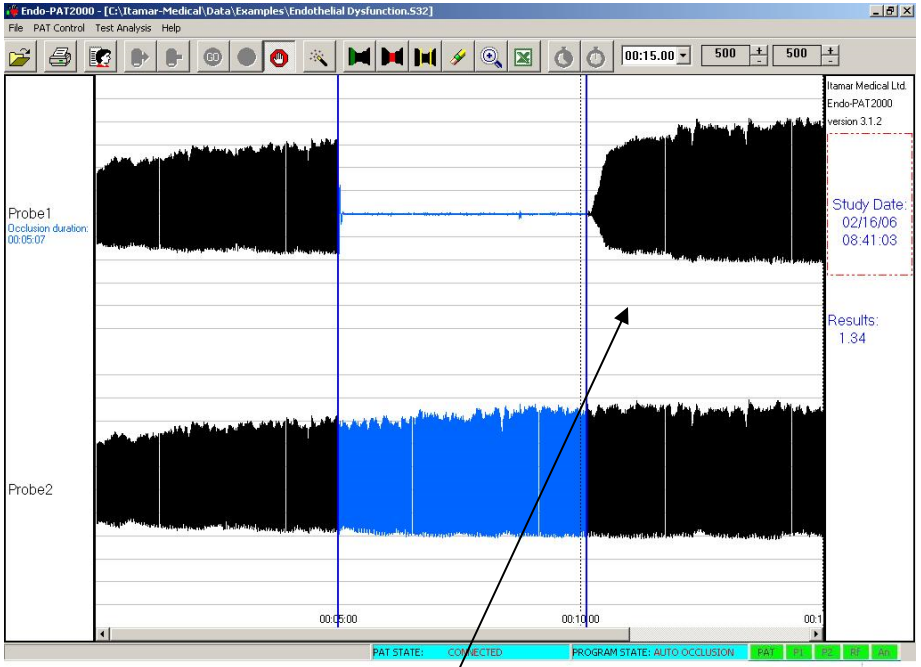
JACC 2010;55:1688 Circulation 2008;117:2467
JACC 2004;44:2137

- Measures reactive hyperemia and ED. FDA approved. About $25,000.
- 5 minute occlusion of brachial artery with BP cuff.
- Digital measurement for ED-FMD as increase in signal amplitude.
- Measure pre and post occlusion ratio index.
- Index of 1.67 has sensitivity of 82% and specificity of 77% to diagnose coronary ED and highly correlates to brachial artery FMD (r=.0.33 to 0.55).

Good and Poor Results



Normal EF



Poor EDF

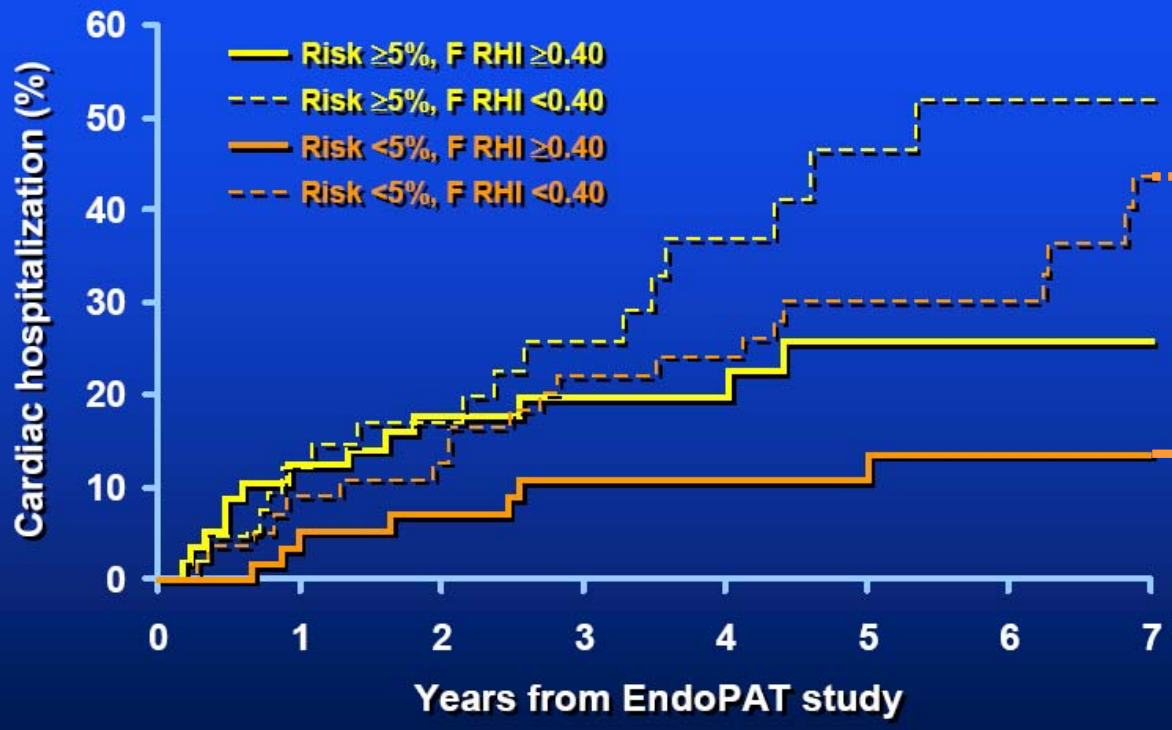
J Am Coll Cardiol 2004;44:2137-41

- Study designed to assess EndoPAT RHI v. Coronary Endothelial Function.
- 94 Patients without angiographic CAD
- All underwent Coronary endothelial function testing with Acetylcholine.
- 39 were normal (CBF increased by 50% or more after ACh infusion).
- 55 were abnormal.
- EndoPAT RHI Measured in all Patients. Average RHI was 1.27 in patients with coronary endothelial dysfunction and 1.78 in those without coronary ED.
- Conclusion: EndoPAT RHI score correlated well with coronary endothelial function testing and is therefore a valid predictive model for subsequent CVD events.

ENDO-PAT and Framingham Risk Score and CHD Risk

EndoPAT vs. Framingham Risk Score

Mayo Clinic, 2010



~300%

Low risk but <u>with</u> endothelial dysfunction

Low risk & <u>normal</u> endothelial function

n=270, Intermediate risk patients
Mayo Clinic & Tufts Medical Center

All CV Deaths were in Patients with Endothelial Dysfunction

MAYO CLINIC

ENDO-PAT and CVD outcomes

Eur Heart J 2010 ;31:1142

- 270 patients over 7 years: ED and Framingham risk score
- Abnormal Index predicted cardiac events such as cardiac death, MI cardiac hospitalization, and CABG: 48% vs 28% (p=0.03). This was independent of Framingham risk score.
- Also correlates with risk factors
- The more severe the CVD, the worse the index

Associations of Endopat and IVUS assessed coronary plaque morphology in CHD

Am J Cardiology 2012;109:1711

- An abnormal reactive hyperemia (ED) by Endopat is associated with plaque structure that is more prone to rupture as measured by IVUS.
- More necrotic core
- More dense calcium
- Less fibrous tissue

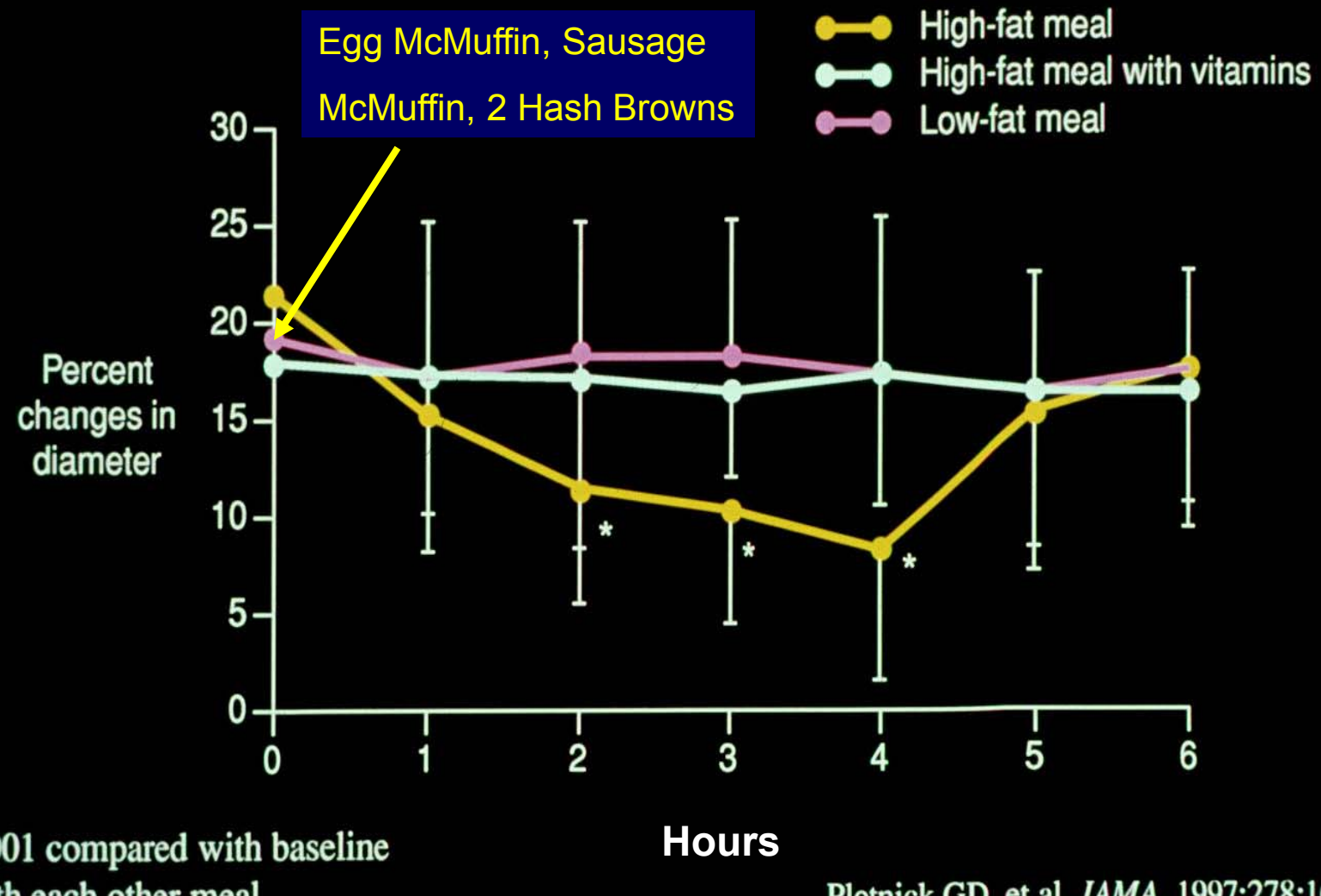
Peripheral Endothelial Function and Cardiovascular Events in High Risk Patients

J of American Heart Assoc 2013;2. Nov 2 2013 Epub

- 528 patients with high risk for CV events over 5 years.
- EndoPat RHI was measure before and after coronary angiogram
- RHI, BNP and CV score by SYNTAX were all independent risk predictors for all future CV events such as MI, CV death, unstable angina, ischemic CVA, CABG, CHF and PAD.
- When RHI was added to FRS, BNP and SYNTAX the net reclassification index was significantly improved by 27.5 % with a significant increase in in C-statistic from .728 to .766.

VBWG

Effect of Fast-Food High-Fat Meal on Brachial Artery Flow-Mediated Vasodilation

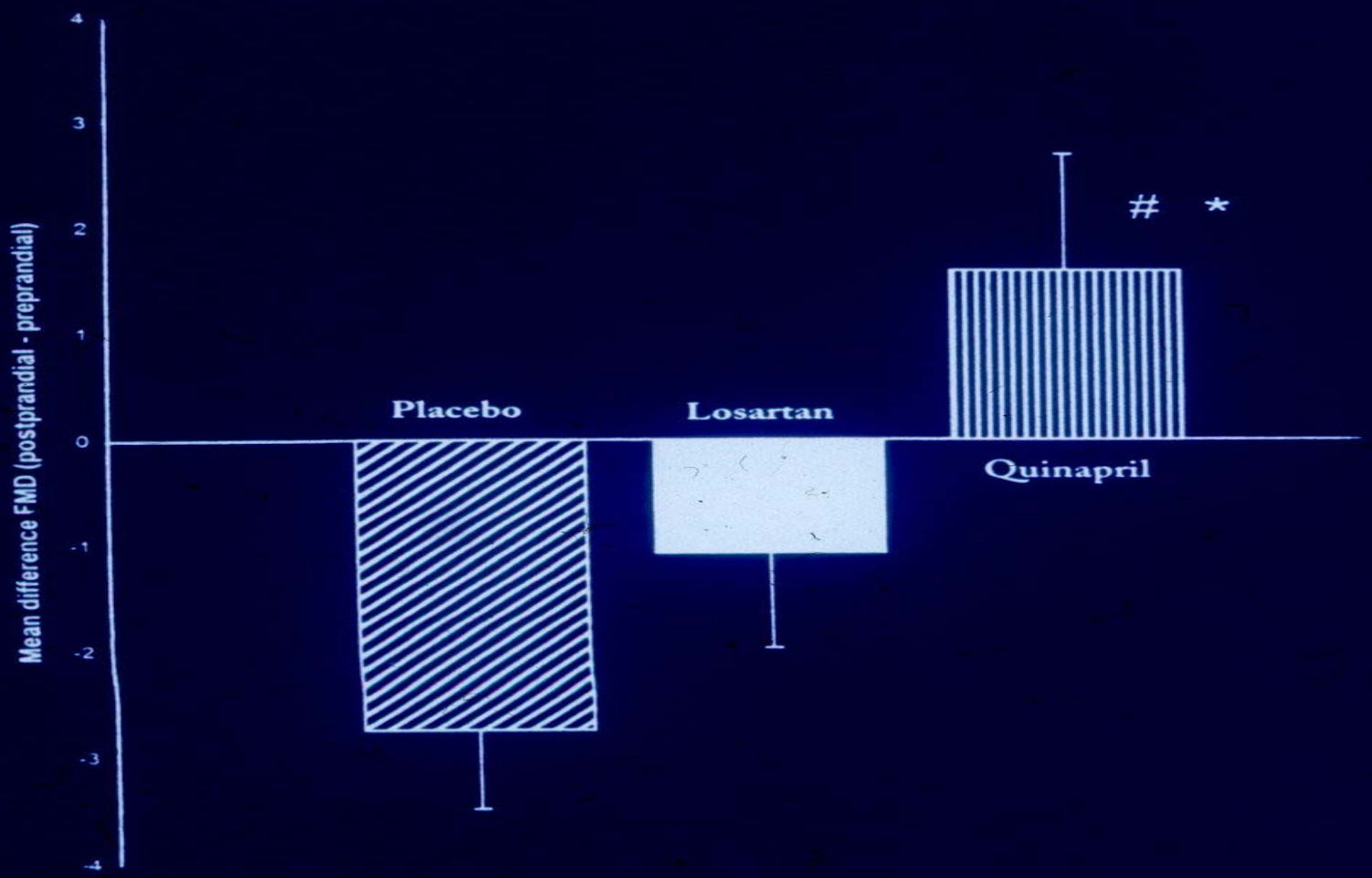


*$P < 0.001$ compared with baseline and with each other meal

Plotnick GD, et al. *JAMA*. 1997;278:1682-1686.

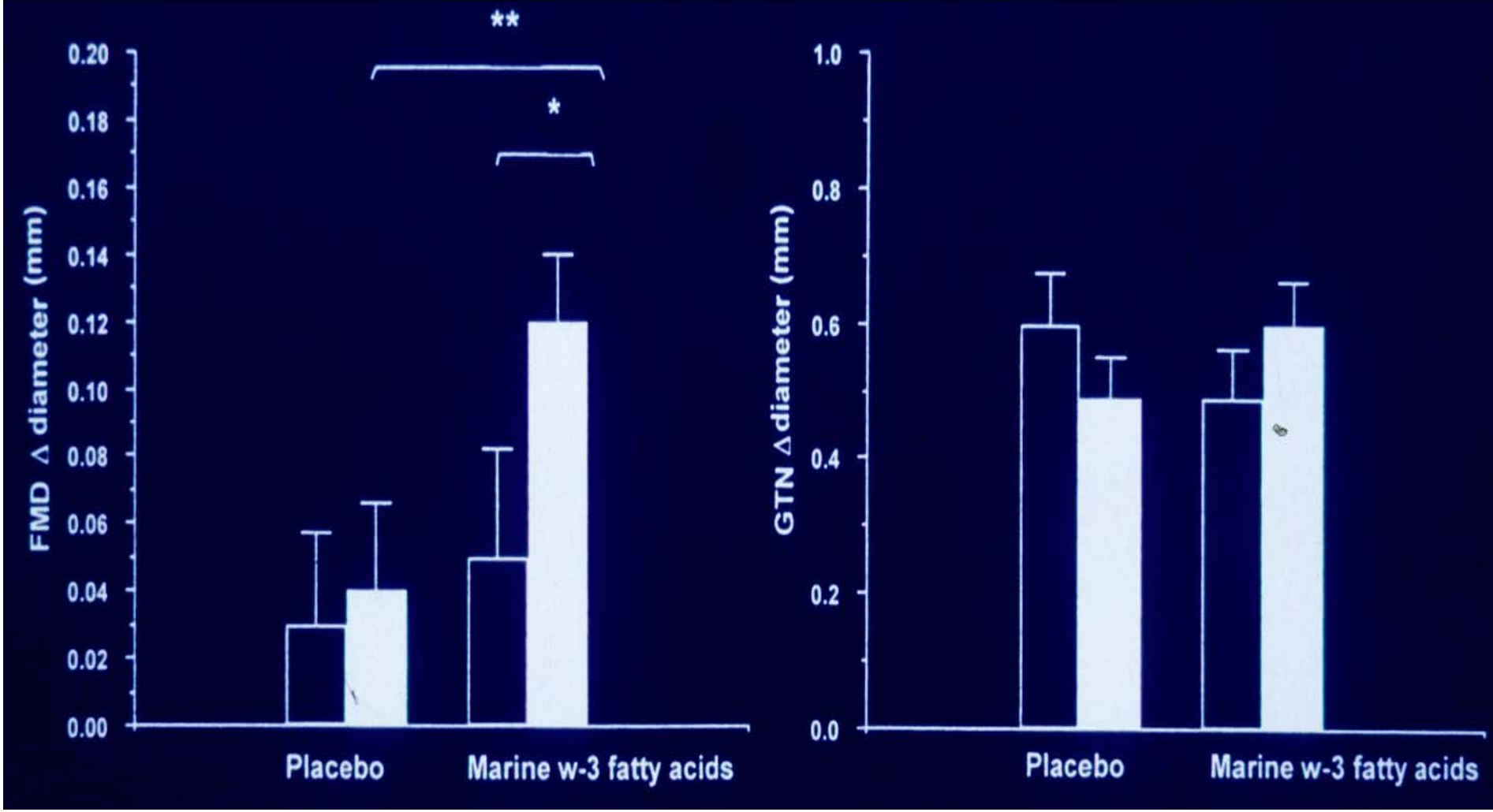
Effect of ACE-I and ARB on High-Fat Meal Induced Decline in Flow-Mediated Vasodilation

Wilmink et al, J Am Coll Cardiol 1999;34:140



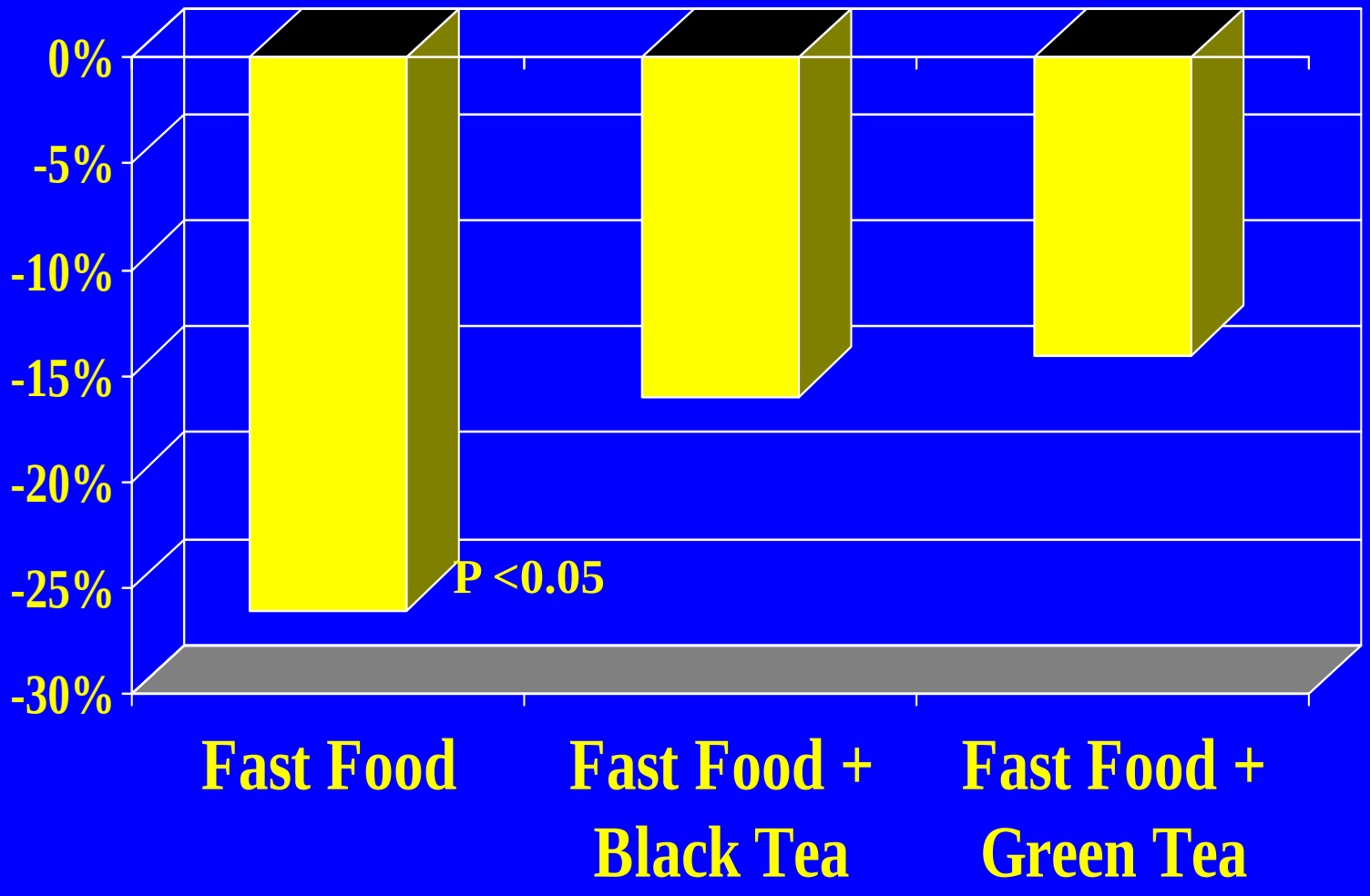
Effect of Ω-3 Fatty Acid Intake (4 gm/d) on Brachial Artery Flow-Mediated Vasodilation in Hypercholesterolemic Subjects at 4 Months

Goodfellow et al, JACC 2000;35:265



Effect of Fast Food Meal with/without 8 Oz Black or Green Tea on Brachial Artery FMD

Corretti M et al, J Am Coll Cardiol 2002;39:218A



Ankle Brachial Index

Diabetes Care. 2006;29:637-42
J Am Coll Cardiol 2008;52;1736
Ren Fail 2004;26: 433
Korean Circ J 2010;40:224
JAMA 2008;300:197

- Low ABI < 0.9 and PAD are associated with increased risk of CVD and CHD independent of the metabolic syndrome and other major CVD risk factors and predicts CKD.
- 10 year CV mortality with ABI < 0.9 is 4 x greater than normal ABI.
- Improves CV risk prediction beyond Framingham Risk Score (FRS)

Ankle Brachial Index

Atherosclerosis, Thrombosis and Vascular Biology. 2005;25:1463
Blood Pressure 2010;19:308

- Meta-analysis of 22 studies 28,000 patients with low ABI outcomes
- CHD: 16.5% sensitive, 92.7% specific
- Stroke: 16% sensitive, 92.2% specific
- Cardiovascular mortality: 41% sensitive and 87.9% specific
- Incidence of PAD in patients with previous CHD or CVA is 35%.

Post-exercise ABI Predicts All-cause Mortality

Am J Cardiol 2011;107:778

- Post exercise ABI is a powerful independent predictor for all-cause mortality and provides additional risk stratification beyond the ABI at rest.
- HR 1.67 with p <0.0001.
- Defined as ABI < 0.85.

Lab Testing

- CBC with diff
- UA
- CMP 12
- Advanced lipid profile
- APO B , APO AI and AII
- Free T4,T3, TSH, RT3, thyroid antibodies
- Magnesium
- Iron, TIBC and Ferritin
- Fibrinogen
- HSCRP
- Homocysteine
- Uric acid
- Microalbuminuria
- GGTP and hepatic profile
- Myeloperoxidase (MPO)
- Cardiovascular SNP's
- Toxicology and heavy metal screen: Spot or 24hr urine or blood

Lab Testing

- Vitamin D 3
- Fasting C peptide, AIC, insulin, proinsulin, 2hr GTT
- PRA and aldosterone
- Free testosterone, SHBG, estradiol, estriol. Progesterone, DHEA and DHEAS
- EKG and TMT
- Chest X Ray
- CAPWA
- ENDOPAT
- ABI at rest and with exercise
- MNT, LPP, Omega 3 index, APO E, telomere test
- Body impedance analysis, waist circumference, WHR
- ECHO
- Carotid duplex and IMT
- EBT and CT angio (CTA), CAC or cardiac MRI
- Retinal scan
- Rest and exercise BP and 24 hour ABM
- CORUS gene expression testing
- PULS cardiac testing

Plaque Reversal and Reduction in Coronary Artery Calcification

- Vitamin K2 MK 7: Menaquinone 100-200 ug/d
- Omega 3 Fatty acids: 5 gms/d
- Aged Garlic (with or without statins) *Life Sci 2009;85:2011`*
- *Prev Med 2004;39:985;Prev Med 2009;49:101 ;Am J Cardiol2010;105:459*
- Curcumin 500 to 1000 mg bid: Am J Cardiology 2012;110;40 J Pharmacol Exp Ther 2009;329(3):959-66;J Cardiovasc Med 2010;11(1): 1-6
- Trans resveratrol 100 mg : Nutrition 2013;29;178
- B complex, arginine 2000 mg with citrullene 1000 mg *Life Sci 2009;85:2011`;Prev Med 2004;39:985; Prev Med 2009;49:101; Am J Cardiol2010;105:459*
- Beet root extract 500 mg Nutrition Research 2012;32:160-168
- Pomegranate seeds (1 cup) and 500 mg Vitamin C Atherosclerosis 2001;158:195 Clin Nutr 2004;23:423;Nitric Oxide 2007;17:50 Nutr Rev 2009;67:49;Phytother Res 2010;24: S 196;Complement Ther Clin Pract 2011;17:113;Am J Health Syst Pharm 2011;68:1302
- Magnesium: J of Clinical Hypertension 2017;35: 523
- Pycnogenol with Kotu Kola
- Statins and ACEI and possibly ARBs

Curcuminoids and CHD, MI and CABG

Am J Cardiology 2012;110;40
J Pharmacol Exp Ther 2009;329(3):959-66
J Cardiovasc Med 2010;11(1): 1-6
Sci China Life Sci 2012; 55:527

- Decrease proinflammatory cytokines during CABG procedure
- Decrease occurrence of cardiomyocytic apoptosis after cardiac ischemic-reperfusion injury
- Reduce MI post CABG from 30 to 13 % ($p<0.038$) at 4 grams per day given 3 days before and 5 days after CABG.
- Decrease HS CRP, MDA and NtBNP
- Lower NFkB, COX 2, LOX, MMP 2, MMP 9 and iNOS.
- Membrane stabilizing effect on cardiac myocytes and modulates signaling in dose dependent manner to both bilayers
- Inhibit platelet activation.
- Inhibits VSMC proliferation /arterial stenosis : upregulate PTEN (phosphatase and tensin homolog, a tumor suppressor gene)

Curcumin improves mitochondrial function

Int J Mol Med 2012;30:643

- Improves mitochondrial biogenesis and cell survival, decreases dysfunction
- Increases mt DNA
- Increases PGC1 alpha
- Increases NRF 1
- Increases Tfam
- Improves MMP (mito membrane potential)
- Increased cell survival
- Down regulates NF-kB.

Curcumin reduces atherosclerosis in type 2 DM

J of Nutritional Biochemistry 2014;25:144

- Curcumin 250 mg bid for 6 months
- Decreased PWV
- Increased adiponectin
- Decreased leptin
- Improved IR
- Lowered TG, LDL and increase HDL
- Lowered UA
- Decreased visceral and total body fat
- Reduced inflammation and oxidative stress

Quercetin

Nutrition 2013;29:219;J Am Coll Nutr 2013;32:160;Planta Med 2013;79:465;Mol Med Rep 2014;9:435
Med Sci Sports Exerc. 2010;42:338; Nutr Res 2013;33:136

- Quercetin (25 mg/kg) administered to rabbits on high cholesterol diet had reduced progression and increased regression of atherosclerosis
- Decreased inflammation , 5-LOX ,12- LOX and COX
- Reduced MPO
- Increases RCT
- Increase PON 2
- Improved ED and NO . Reduce iNOS
- Reduces TNG tolerance
- Reduces arrhythmias and AAA in animals.
- Reduced hs CRP
- Decrease platelet aggregation and thrombosis.
- Also reduces ox LDL and ROS in other studies
- Also decrease TLR-NFkB pathway .
- Increases exercise endurance
- Increased muscle mitochondria in humans.

Sulforaphane reduces vascular inflammation and prevents TNF-α-induced monocyte adhesion to primary endothelial cells through interfering with the NF-κB pathway

J Nutr Biochem. 2014 Aug;25(8):824-33.

- Sulforaphane (cruciferous vegetables) at concentrations that are achieved in the diet of 0.5-2 uM reduce endothelial inflammation, decrease eruption of the endothelial lining of the aorta and preserve elastin fibers in VSM.
- Decrease TNF alpha, MCP-1, VCAM, E- selectin
- Reduce activation of NFkB.
- Decrease endothelial lipase
- Induces Nrf2.

PhosphatidylSerine in Atherosclerosis and CHD

Curr Opin Lipidol 2016;27:414

- Anti-inflammatory
- Anti-coagulation
- HDL functionality
- Apoptosis
- Cell membrane physiology
- RCT and CEC (LXR, ABCA1 transporter, PS membrane receptor with apoptotic cells,BSAI-1, Rac 1)
- Dose: 300-600 mg bid

Carotid plaque stabilization induced by the supplement association Pycnogenol® and centella asiatica (Centellicum®).

Minerva Cardioangiol.2016 Dec;64(6):603-9.

- Evaluation of the stability of carotid plaques by ultrasound in asymptomatic subjects with high oxidative stress given a combination of the extract from bark of Pinus pinaster, and Centella asiatica leaf extract.
- 50 patients, mean age 61.5 years, with carotid plaques (<50% stenosis) and high oxidative stress. 26 patients received the combination of Pinus pinaster and Centella asiatica and standard management, a control group received standard management only.
- **RESULTS:**
- Pinus pinaster and Centell asiatica leaf extract reduced significantly ($p<0.05$) plaque height and length as well as the number of plaques relative to controls.
- The plaque stability index, based on the echogenicity in the ultrasound picture of the "white" components of the plaque, increased significantly ($p<0.01$) in the treated group vs controls
- Plasma free radicals were significantly ($p<0.05$) decreased in treated vs controls
- **CONCLUSIONS:** There was a significant increase in stability of plaques, indicated by an enhanced density of the plaques, following supplementation with the combination of Pinus pinaster and Centella asiatica leaf extract. As size and number of plaques was simultaneously reduced,

Sauna Treatment improves Endothelial Dysfunction and CHF

Am J Cardiol 2012;109:100

- Improves CHF and exercise tolerance
- Improves LVEF
- Decrease NE
- Decrease BNP
- Improve FMD and ED
- Increase V02
- Increases CD34+ and EPC's
- 5 times /week for 15 min at 60 degrees C then blanket for 30 min to increase body temp 1.0-1.2 degrees C

Melatonin in CVD

Curr Opin Lipidol 2016:27:408

- Reduces myocardial ischemia-reperfusion injury, myocardial hypoxia-reoxygenation injury, pulmonary hypertension, atherosclerosis, valvular heart disease, MI, CHF and hypertension.
- Anti-oxidant, anti-inflammatory, regulates lipids and glucose metabolism, activates SIRT-1, reduces apoptotic protiens (Ac FOX O1, Ac-p53, Ac NF-kB, BCL2 and BAX), increases BCL-2, increase Cu/ZN SOD, FGF, ILGF-1, protects MSC, lowers capase, preserves mitochondria, improves ATP synthesis, lowers insulin levels, increases adiponectin, increase NO, reduces TNF alpha
- Dose 2-10 mg per day

Melatonin Reduces MI size

Am J Cardiol 2017;120:522

- Melatonin IV and intracoronary reduces myocardial infarct size (MIS) post STEMI post PCI as measures by cardiac magnetic resonance
- Must treat early < 136 minutes
- Reduces lipid peroxidation and mitochondrial DNA damage

Effect of l-arginine, asymmetric dimethylarginine, and symmetric dimethylarginine on ischemic heart disease risk: A Mendelian randomization study

Am Heart J.2016 Dec;182:54-61.

- l-arginine is a commonly consumed dietary conditional essential amino acid found in food items and supplements, which is closely related to asymmetric dimethylarginine (ADMA) and symmetric dimethylarginine (SDMA). l-arginine is thought to increase nitric oxide and be cardioprotective, whereas ADMA and SDMA may inhibit nitric oxide synthesis and increase cardiovascular disease risk. Unexpectedly, l-arginine increased mortality in a small trial. To clarify the effects of these potential targets of intervention, we assessed the risk of ischemic heart disease (IHD) by genetically determined l-arginine, ADMA, and SDMA.

- Single nucleotide polymorphisms (SNPs) contributing to l-arginine, ADMA, and SDMA, at genome-wide significance, were applied to the CARDIoGRAMplusC4D 1000 Genomes-based genome-wide association study IHD case (n=60,801, ~70% myocardial infarction)-control (n=123,504) study. We obtained unconfounded estimates using instrumental variable analysis by combining the Wald estimators for each SNP, taking into account any correlation between SNPs using weighted generalized linear regression.

- Higher l-arginine was associated with higher risk of IHD (odds ratio [OR] 1.18 per SD increase, 95% CI 1.03-1.36) and of myocardial infarction (OR 1.29, 95% CI 1.10-1.51), based on 2 SNPs from MED23. Symmetric dimethylarginine had an OR of 1.07 per SD (95% CI 0.99-1.17) for IHD based on 5 SNPs from AGXT2. Asymmetric dimethylarginine had and OR of 1.08 per SD (95% CI 0.99-1.19) for IHD based on 4 SNPs from DDAH1.
- CONCLUSION: l-arginine could possibly cause IHD. Given that l-arginine occurs in many common dietary items, investigation of its health effect is required.

Other Considerations for CHF

- Pentoxifylline (Trental): (Th1-Th2)
- Famotidine
- Colchicine
- Methotrexate
- Berberine (AMPK)

Effect of Renin-Angiotensin System Inhibitors on Long-Term Survival in Patients Treated With Beta Blockers and Antiplatelet Agents After Acute Myocardial Infarction (from the MONICA/KORA Myocardial Infarction Registry

Am J Cardiol.2014 Aug 1;114(3):329-3

- Median follow up of 5 years after acute MI
- Use of ACEI or ARB reduced morality by 26% already on other guideline CV drugs post MI.

Low dose colchicine for secondary prevention of CVD

J Am Coll Cardiol 2013;61:404
J Rheumatology 2012;39:1458

- Colchicine at .5 mg per day in 532 patients with stable CHD on maximal medical treatment reduced ACS, cardiac arrest and CVA by 71 % over 3 years
- In VA study colchicine decreased MI by 54%
- Another VA study showed MI reduction of 57-67%
- Anti-inflammatory and neutrophil effect.
- Suppresses TNF alpha, ILB, and other cytokines in neutrophils, macrophages and endothelial cells.
- Interferes with assembly of inflammasome complex
- Decreases IL-1 Beta in neutrophils and monocytes
- Reduces SAA

Colchicine and CV Events

JAMA 2016;316:1106

- No reduction in all cause mortality
- Lower risk for MI by 80% (p=0.003)
- No reduction in CV mortality
- More GI effects

- Treatment of 1000 persons with colchicine for 3 years is associated with 46 fewer MI.

Metformin

Current Opinion in Lipidology 2011;22:445;Current Opinion in Lipidology 2014;25:446 Annals Internal Medicine 2017;166:191;Diabetes Obes Metab 2014;16:1165. Cardiovasc Drugs Ther 2015;29:265;Cardiovasc Diabetol 2104;13:152; J Hypertension 2017;35:18 Current Opin Lipidology 2018;29:346

- Cardioprotective and anti-atherosclerotic: 39% reduction in MI and all cause mortality in UKPDS. Reduces infarct size and reduces CHF. Other studies show 68-75% reduction in death post MI at one and 12 months.
- In CKD reduces all cause mortality, CHF, CHD
- Inhibits gluconeogenesis 36% and reduces body weight and fat.
- Increases skeletal muscle/ adipocyte insulin sensitivity and glucose uptake, lowers insulin 25%.
- Changes mitochondrial complex I AMP/ATP ratio to stimulate AMPK, increase PCG-1 alpha. Blocks TOR
- Reduces DNA damage and facilitates DNA repair
- Improves mitochondrial function especially in endothelial cells.
- Reduces FFA, lowers TG, LDL and increases HDL. Blocks LDL oxidation, improves RCT and reduces macrophage lipid accumulation.
- Improves ED and increases NO
- Reduces coagulation
- Reduces carotid IMT
- Limits myocardial ischemic reperfusion injury, ischemic preconditioning by closing of MPTP (mitochondrial permeability transition pore) via RISK and PI3K/Akt pathways, increased adenosine receptor stimulation and AMPK. Statins and adenosine also close MPTP.
- Lowers blood pressure
- Slows aging in both DM and non DM by up to 15 % or more (Diabetes Obes Metab 2014;16:1165.

Treatment Summary for Prevention and Treatment of CHD and CVD

Prevention and Treatment of CVD 1

1. **Diet/ and dietary nitrate : 0.1 mmol/kg of body weight /day. 10 servings of fruits (4)(berries) and vegetables (6) with dark green leafy vegetables. DASH 2 and Mediterranean diets. Caloric restriction (12.5/12.5 EE with overnight fast. 30 % protein, 30 % MUFA and omega 3 FA with limited SFA and no trans fat, minimal refined CHO(50 grams), more complex CHO (40%). Consume smaller meals more frequently with antioxidants/meal Minimal caffeine depending on CYP 1A2 status.**
2. **Vitamin C sustained release : 250-500 mg bid.**
3. **Vitamin K 2 MK 7 200-1000 mcg per day**
4. **Polyphenols: 20 grams dark chocolate (>70%), EGCG 500 mg bid or green tea 32 oz/day (decaffeinated), 6 ounces red wine.**
5. **Quercetin 500-1000 mg/day.**
6. **Curcumin 500 mg-1000 mg bid.**
7. **2 gram sodium, 10 gram potassium, 1000 mg magnesium /day**
8. **500 mg beetroot juice: 45 mmol/L or 2.79 g/L inorganic nitrate/day.**
9. **Pomegranate seeds: 1/2 cup per day or juice 6 ounces/day.**

Prevention and Treatment of CVD 2

9. **BH4** 2mg/kg/day with 5 methyl folate 1000 -5000ug per day with B complex vitamins.
10. **R-lipoic acid (RLA)** 100 mg per day with biotin 5000 ug/day for GSH (glutathione) and acetyl –L-carnitine 1000 mg/d (mitochondrial function)
11. **NAC(n-acetyl cysteine)** 500 mg bid for GSH (glutathione) etc.
12. **Whey protein** 30-40 grams per day for GSH (glutathione)
13. **Niacinamide** 500-1000 mg bid for GSH (glutathione) etc.
14. **MSM** 500 mg bid
15. **Branched chain amino acids** (leucine , valine, isoleucine 4:1:1 ratio) 5000 mg/d
16. **D-Ribose** 5 grams tid and nicotinomide riboside one per day
17. **Phosphatidyl Serine** 300-600 mg bid
17. **Trans-resveratrol** 250 mg per day with grape seed extract 500 mg bid
18. **Balanced omega 3 FA** (DHA, EPA, GLA with gamma delta tocopherols: 2- 5 grams per day
19. **Exercise** 60 min /day 6 days per wk. (aerobic/ resistance)(ABCT)
20. **8 hours of sleep.** Circadian rhythm. Early to bed and early to rise.
21. **Stress Reduction and IBW and composition (M 16%, F 22%)**

Prevention and Treatment of CVD 3

1. **Plant sterols** 2.5 grams per day and sterolins.
2. **Reishi and Shiitake mushrooms**: one serving per day.
3. **Vitamin D3** to level of 60 ng/ml.
4. **AGED garlic (Kyolic)** CV formulation: 600 mg bid.
5. **Co enzyme Q 10** :100 mg per day to level of 3 ug/dl and PPQ 20 mg/d
6. **Lycopene**: 20 mg per day (supplement, tomato, pink grapefruit, watermelon etc.).
7. **Carnosine** 500 mg bid
8. **Berberine** 500-1000 mg per day
9. **High quality varied multivitamin and fruit and vegetable extracts**
10. **Probiotics:** 50 billion CFU per day.

Pharmacologic treatments

ARB (telmisartan 80mg qd) or ACEI (perindopril 16 mg qd).

Amlodipine 5mg qd

Rosuvastatin 5mg qd or intermittent therapy

Metformin 500 mg qd

Colchicine 0.5 mg qd

Bezafibrate 200 mg per day

ASA and BIHRT

Reduce inflammation, oxidative stress, immune dysfunction and CHD risk factors and insults.

Association of dietary nitrate with atherosclerotic vascular disease mortality: a prospective cohort study of older adult women.

Am J Clin Nutr.2017 Jul;106(1):207-216.

- **Nitrate-rich vegetables lower blood pressure and improve endothelial function in humans.**
- **However does an increased consumption of nitrate-rich vegetables translates to a lower risk of atherosclerotic vascular disease (ASVD) mortality.**
- **Objective: investigate the association of nitrate intake from vegetables with ASVD mortality.**
- **Design: 1226 Australian women aged 70-85 y without prevalent ASVD and/or diabetes were r were studied for 15 y. Demographic and ASVD risk factors were determined at baseline and a validated food-frequency questionnaire was used to evaluate dietary intake.**
- **The primary outcome was any death attributed to ASVD**
- **Results: Follow-up period of 15,947 person-years, (19.4%) women died of ASVD-related causes. The mean ± SD vegetable nitrate intake was 67.0 ± 29.2 mg/d. Each SD higher vegetable nitrate intake was associated with a lower risk of ASVD mortality in both unadjusted [HR: 0.80 (95% CI: 0.70, 0.92), *P* = 0.002] and multivariable-adjusted [HR: 0.79 (95% CI: 0.68, 0.93), *P* = 0.004] analyses. Higher vegetable nitrate intake (per SD) also was associated with a lower risk of all-cause mortality [multivariable-adjusted HR: 0.87 (95% CI: 0.78, 0.97), *P* = 0.011]**
- **Conclusions: Nitrate intake from vegetables was inversely associated with ASVD mortality independent of lifestyle and cardiovascular disease risk factors in this population of older adult women without prevalent ASVD or diabetes. 20% reduction in ASVD mortality per SD if nitrate intake and 23 % reduction in all cause mortality per SD of nitrate intake.**

Therapeutic Implications Phytochemicals and PRR, TLR (Toll Like Receptors and NLRs (NOD like Receptors)

J of Nutritional Biochemistry 2012;23:39-50

Inhibit PRR vascular receptors

- Curcurmin (Tumeric): TLR 4, NOD 1 and NOD 2
- Cinnamaldehyde: Cinnamon : TLR 4
- Sulforaphane: Broccoli : TLR 4
- Resveratrol: nutritional supplement, red wine, grapes and grape seed extract: TLR 1
- EGCG (green tea):TLR 1
- Luteolin: celery, green pepper, rosemary, carrots, oregano, oranges, olives : TLR 1
- Quercetin: Tea, apples, onion, tomatoes, capers :TLR 1.
- Chrysin: TLR 1

Nutrition and Supplements to improve endothelial function, nitric oxide and vascular elasticity

Curr Opin Lipidol 2012;23:147-156 Nutrition 2013;29:71-75
Nutrition 2015;31:28

- DASH diet
- Mediterranean diet with EVOO
- Nut consumption: 20 % reduction death with 7 servings per wk
- Vitamin D 4000IU per day
- Vitamin C 500 mg per day
- Beet Root extract with arginine, citrullene and hawthorne in the form of NEO 40
- Dietary nitrate at 0.1 mmol/kg of body weight per day (high intake of F and V) reduces DBP 3.5 mm Hg.
- Effect is potentiated by Vitamin C and polyphenols.
- 500 mg beetroot juice with 45 mmol/L of 2.79 g/L of inorganic nitrate lowers BP 10.4/8.1 mm Hg, inhibits platelet aggregation by 20% and increased FMD 30%.
- Lycopene 20 mg per day
- Omega 3 fatty acids 5 grams per day EFA Sirt Supreme
- Polyphenols, Flavonoids and Flavonoid-rich foods. Best data with flavones and flavonols. Pomegranate seeds and juice. ½ cup per day of seeds or 6 oz of juice per day.

Nutrition and Supplements to improve endothelial function, nitric oxide and vascular elasticity

Curr Opin Lipidol 2012;23:147-156 Nutrition 2013;29:71-75
Nutrition 2015;31:28

- Resveratrol 250mg trans form per day
- Grape seed extract 500 mg twice per day
- EGCG 500 to 1000mg twice per day
- Co Enzyme Q 10 100 mg twice per day
- Cacao and dark chocolate 30 grams per day
- Tea and catechins: EGCG 500 mg bid
- Curcumin 1000 to 2000 mg twice per day
- Quercetin 500 mg bid
- Berry anthocyanins and pomegranate seeds
- Orange juice and hesperidin
- Wine polyphenols: Pinot Noir is the best 4- 6 ounces per day
- Rhodiola extract: 200 to 500 mg /day
- Kyolic Aged Garlic extract- KYOLIC GARLIC (AGE): 600 mg twice per day
- Arginine 2 grams bid
- Citrullene 2 grams bid
- Methyl folate 400 micrograms bid
- Superoxide dismutase one bid
- VasculoSIRT