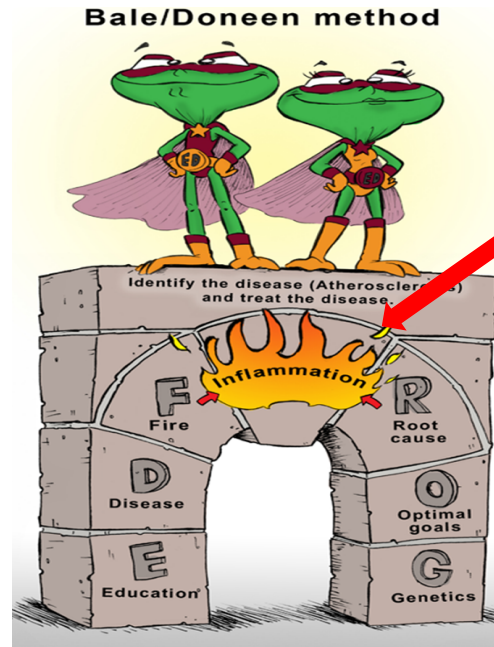


Arterial Inflammation: Permeating All Stages of Atherosclerosis

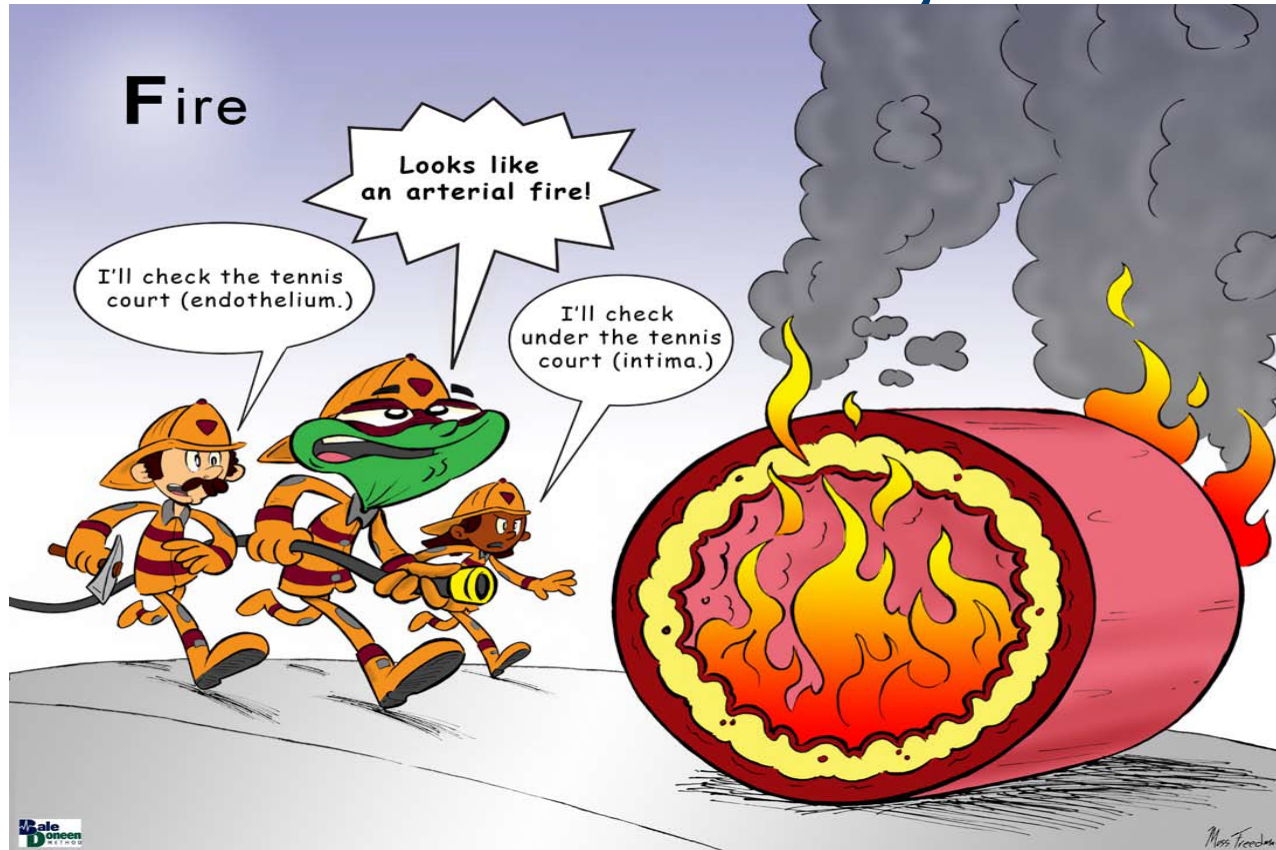


Bradley Bale, M.D.

Virtual BaleDoneen Method Course

02/19/2021

Fire-“From a little spark may burst a flame.” Dante Alighieri





Outline

Inflammation as causal
response to retention

Clinical Tests for Inflammation

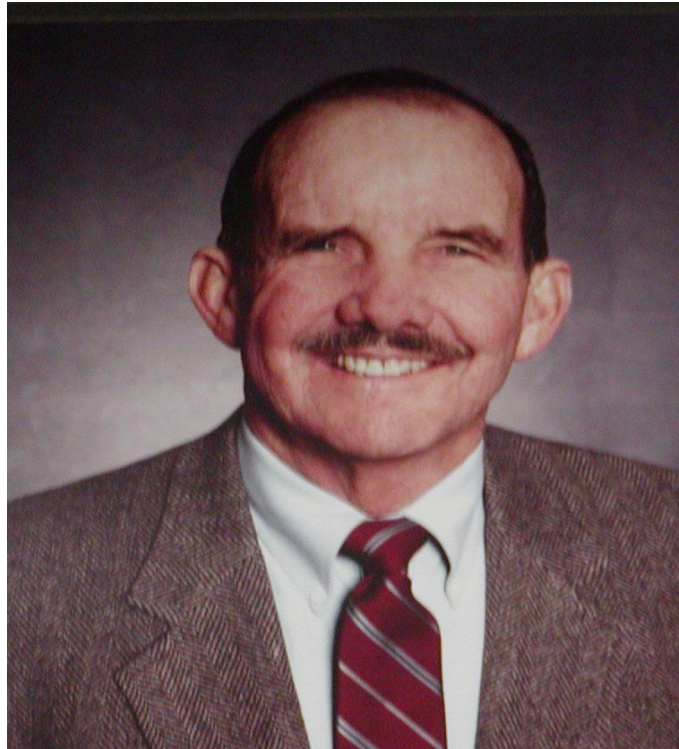
- a) oxidative stress
- b) endothelial tests
- c) intimal test
- d) wild card

Virchow 164 Years Ago Proposed Inflammation as Cause of Atherosclerosis



Virchow R: Phlogose und Thrombose im Gefasssystem, Gesammelte Abhandlungen zur Wissenschaftlichen Medicin, Frankfurt-am-Main, Meidinger Sohn and Company, 1856, p458

“Atherosclerosis is an inflammatory illness” – 1974



(picture 2001)

1961 J. Paul Shields, MD Arrived in Spokane First Adult Cardiologist in
Spokane Founder of Spokane Cardiology

Inflammation is Causal- 2012



Genome-wide Association Studies
(GWAS)



The interleukin-6 receptor as a target for prevention of coronary heart disease: a mendelian randomisation analysis.

The Lancet, 379(9822), 1214-1224.

IL6R Genetics Consortium and Emerging Risk Factors Collaboration, Dr Nadeem Sarwar, Dr Adam S Butterworth, et. al.

Lancet 3/31/2012; 379: 1205–13

Inflammatory Imaging Is Confirmational - 2014

In vivo imaging :

FDG-PET/CT¹-MI
Radioactively Labeled Monocytes²-ASVD
Microwave Radiometry³-Stroke

¹Kim, E. J., et. al. (2014). Metabolic Activity of the Spleen and Bone Marrow in Patients With Acute Myocardial Infarction Evaluated by 18F-Fluorodeoxyglucose Positron Emission Tomographic Imaging. *Circulation: Cardiovascular Imaging*, 7(3), 454-460.

²van der Valk, F. M., et al. (2014). In Vivo Imaging of Enhanced Leukocyte Accumulation in Atherosclerotic Lesions in Humans. *J Am Coll Cardiol*, 64(10), 1019-1029.

³Toutouzas, K., et. al. (2015). Incremental Predictive Value of Carotid Inflammation in Acute Ischemic Stroke. *Stroke*, 46(1), 272-274.

However! July 2017



I still think
cholesterol causes
arterial disease.



CANTOS- Anti-inflammatory Therapy Reduces CV Risk

10,061 post MI pts; 74% male; mean age 61;
vast majority on optimal medical therapy;
CRP \geq 2 (mean 4.2).

Randomized to monoclonal antibody to IL-1 beta or
placebo; followed 3.7 yrs for CV outcomes.

Ridker, P., Thuren, E., MacFadyen, T., et al. (2017). Antiinflammatory therapy with canakinumab for atherosclerotic disease. The New Eng J of Med.
DOI:10.1056/NEJMoa1707914



CANTOS- Anti-inflammatory Therapy Reduces CV Risk

Higher dose of medication significantly reduced incidence of non-fatal MI & stroke and CV death 14% without any change in cholesterol.

Ridker, P., Thuren, E., MacFadyen, T., et al. (2017). Antiinflammatory therapy with canakinumab for atherosclerotic disease. *The New Eng J of Med.*
DOI:10.1056/NEJMoa1707914

Acceptance At Last!!

“For the first time we have this new target – inflammation, it is sort of the dawning of a new era. I really think it’s big.”



08/30/2017- Steve Nissan



Inflammation and Atherosclerosis - The End of a Controversy

The CANTOS trial establishes beyond doubt that inflammation is a treatable pathogenic mechanism in atherosclerosis.

Hansson, G. K. (2017). Inflammation and Atherosclerosis - The End of a Controversy. *Circulation*. doi:10.1161/circulationaha. Published online 09/15/2017

Reducing Inflammation to Reduce Atherothrombotic Risk

Because of Cantos, the term to describe the high rate of recidivism for CV events is “residual inflammatory risk”.



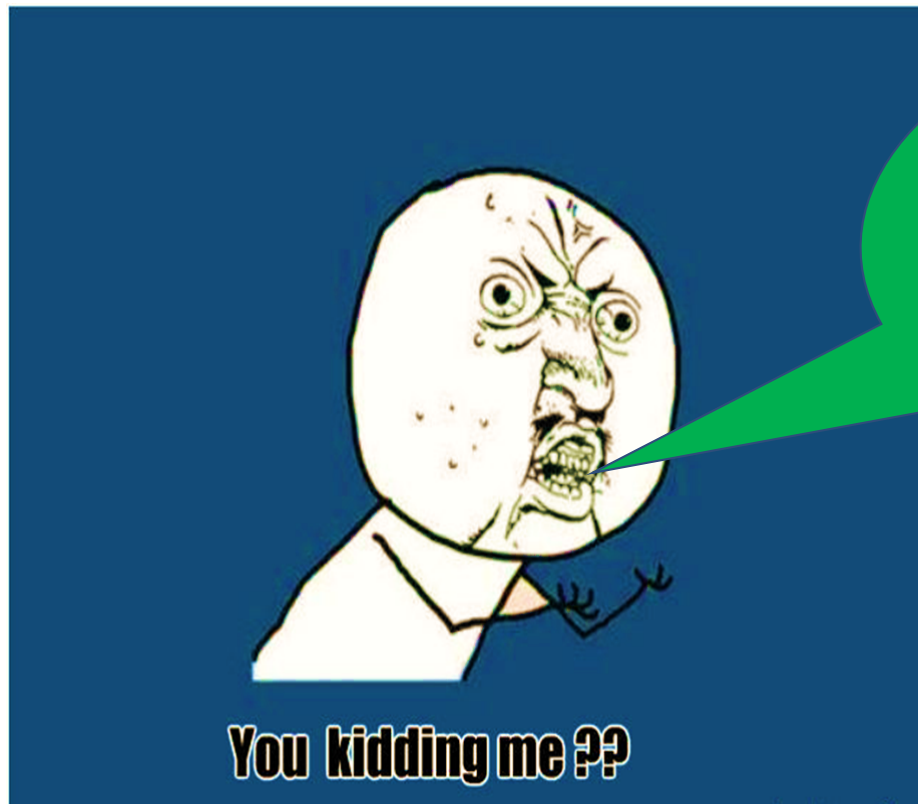
Ridker, P. Guide to reducing inflammation to reduce atherothrombotic risk:
JACC Review. J Am Coll Cardiol 12/25/2018;72:3320–31.

Pathogenesis of Atherosclerosis: 1st Step Intimal Binding of Lipoproteins

Every journey begins
with the first step.



Lipoprotein Binding in the Intima: The First Step in Atherogenesis



I thought it would be endothelial dysfunction allowing the cholesterol through!



All Cholesterol Particles Except Chylomicrons Pass Through a Healthy Endothelium

Lipoproteins up to 70 nm (1/100 th of a RBC) in diameter can cross an intact endothelium through transcytosis.

HDL- ~9 nm, LDL-18to 25 nm, IDL-25 to 35 nm, lipo (a)- <70nm are easily taken up by transcytosis.

VLDL – 30-80 nm; chylomicrons- 100-350 nm

Fogelstrand, P., & Borén, J. (2012). Retention of atherogenic lipoproteins in the artery wall and its role in atherogenesis. *Nutrition, Metabolism and Cardiovascular Diseases*, 22(1), 1-7.

Lipoproteins Flow Through the Arterial Wall



What!!

Most lipoproteins that enter the vessel wall diffuse through and efflux on the adventitial side.

The # of retained lipoproteins is several orders of magnitude less than the # diffusing through.

Fogelstrand, P., & Borén, J. (2012). Retention of atherogenic lipoproteins in the artery wall and its role in atherogenesis. *Nutrition, Metabolism and Cardiovascular Diseases*, 22(1), 1-7.



Lipoproteins Must Be Retained in the Intima to Start Forming an Atheroma

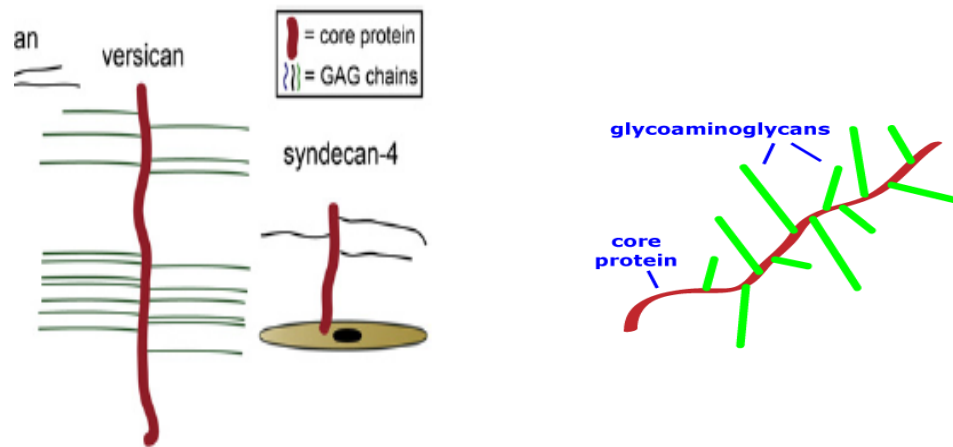
The first step in the pathogenesis of atherosclerosis is the trapping and retention of cholesterol in the intima followed by infiltration and accumulation of macrophages.

Nakashima, Y., et. al. (2008). Early atherosclerosis in humans: role of diffuse intimal thickening and extracellular matrix proteoglycans. *Cardiovasc Res*, 79(1), 14-23.

How do they get stuck in the intima??



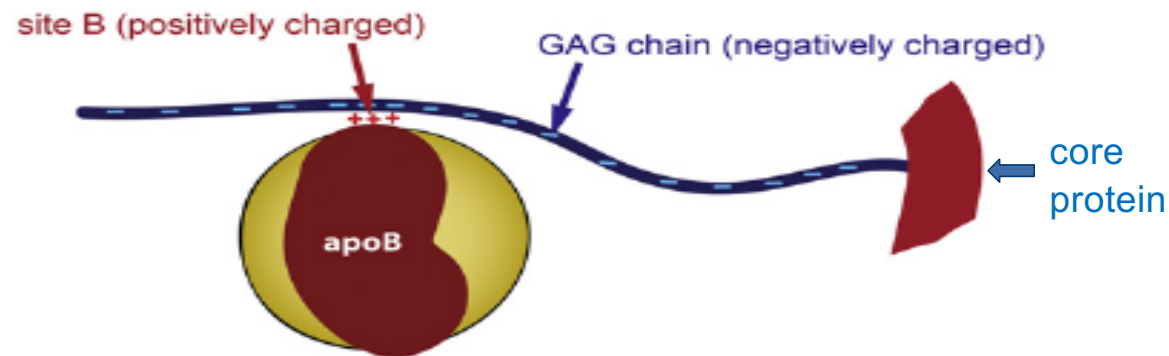
Proteoglycans Grab the Lipoproteins



Proteoglycans are composed of a protein core with attached linear polysaccharides with a negative charge.

Fogelstrand, P., & Borén, J. (2012). Nutrition, Metabolism and Cardiovascular Diseases, 22(1), 1-7.

Apo B Binds to the Proteoglycans Via Electrostatic Force



clusters of positively charged amino acids on apoB attach to negatively charged glycosaminoglycan (GAG) chains on proteoglycans

Fogelstrand, P., & Borén, J. (2012). *Nutrition, Metabolism and Cardiovascular Diseases*, 22(1), 1-7.



There Are At Least Three Sites for Binding of Apo B

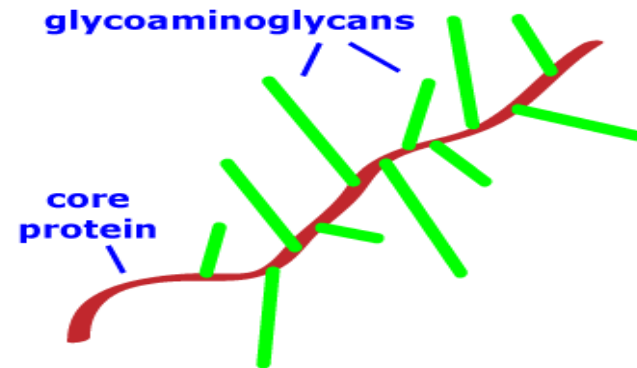
Site 'B' is the main site and is only found in apoB100.

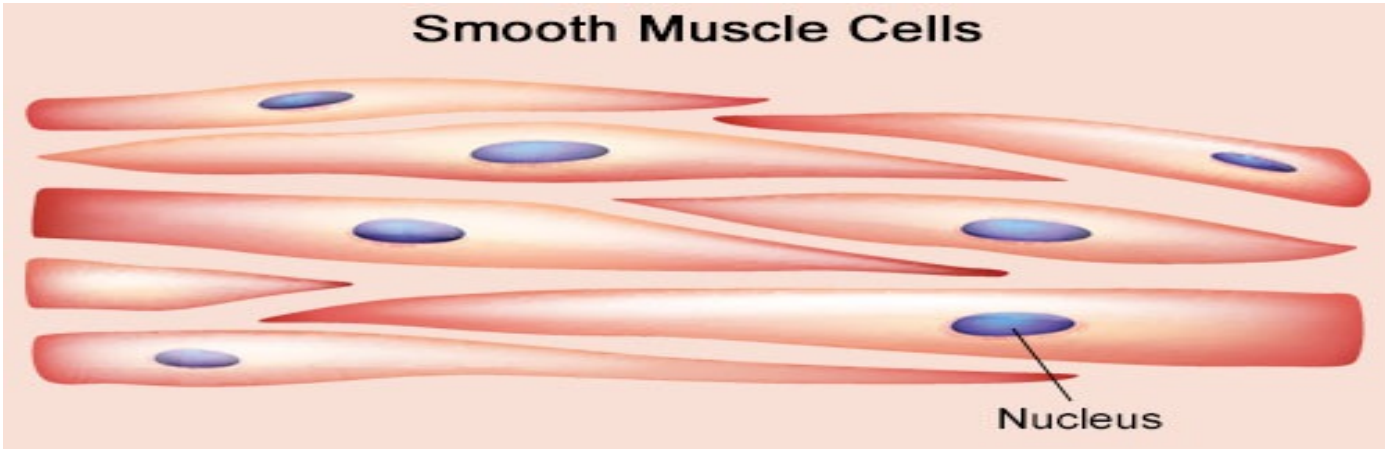
Site 'B-1b' is *only exposed in apoB48 (chylomicrons)*.

Site 'A' is in apoB100; but is *only exposed* when LDL is modified by secretory phospholipase A2 (sPLA2) which creates *small dense LDL*.

Fogelstrand, P., & Borén, J. (2012). *Nutrition, Metabolism and Cardiovascular Diseases*, 22(1), 1-7.

What Creates This Velcro??





They can morph quickly!





Smooth Muscle Cell Transformation and Migration Critical Step in ASVD

SMC transition to a 'migratory synthetic' phenotype initiates and propagates ASVD.

These cells move into the intima and produce proteoglycans which trap lipoproteins.

Rudijanto, A. (2007). The role of vascular smooth muscle cells on the pathogenesis of atherosclerosis. *Acta Med Indones*, 39(2), 86-93.

*Doran, A. C., Meller, N., & McNamara, C. A. (2008). Role of Smooth Muscle Cells in the Initiation and Early Progression of Atherosclerosis.

Arteriosclerosis, Thrombosis, and Vascular Biology, 28(5), 812-819.



Smooth Muscle Cell Migration Critical Step in ASVD

SMCs are the first intimal cells present in locations destined to develop ASVD.

Deposition of apoB in the deep layer of the intima is the initial phase of an atheroma.

*Doran, A. C., Meller, N., & McNamara, C. A. (2008). Role of Smooth Muscle Cells in the Initiation and Early Progression of Atherosclerosis. *Arteriosclerosis, Thrombosis, and Vascular Biology*, 28(5), 812-819.

How Can SMCs Get Genetically Change!!???



We can do it!



SMC Transformation is Complex & Related to Inflammatory Issues

Platelet derived growth factor (PDGF) is a key factor driving SMC transformation.

Angiopoietin 2 (Angpt2) also significantly induces the transformation. *

(our course will address issues that can increase or decrease SMC transformation.)

Owens, G. K., et. al. (2004). Molecular regulation of vascular smooth muscle cell differentiation in development and disease. *Physiol Rev*, 84(3), 767-801.

*Zhang, B., et. al. (2015). *Infect Immun*. doi:10.1128/iai.00498-15



Binding of Lipoproteins Generates Additional Inflammation

These trapped lipoproteins become oxidized generating inflammatory signals.

turns on the immune system

Subsequently, macrophages enter the intima, infiltrate deeper toward the deposited lipids, and phagocytize the deposited lipids to become foam cells.

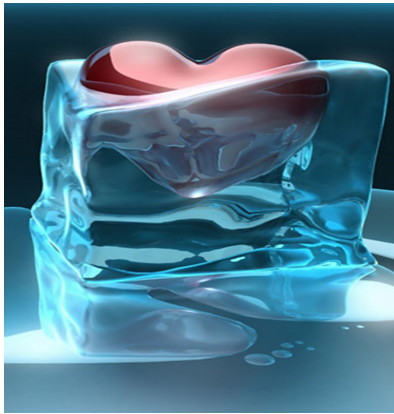
Nakashima, Y., et. al. (2008). Early atherosclerosis in humans: role of diffuse intimal thickening and extracellular matrix proteoglycans. *Cardiovasc Res*, 79(1), 14-23.

If This Process is not Quelled, Dangerous Atheroma Will Ensue

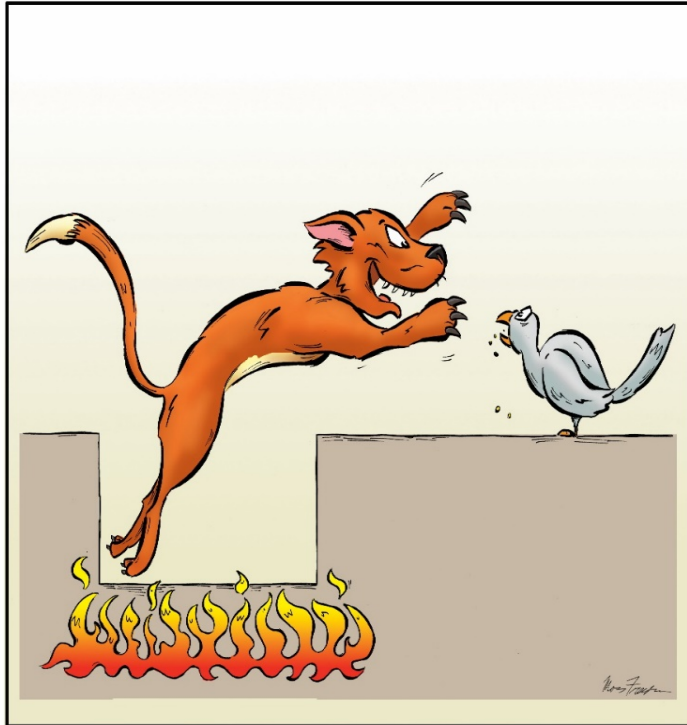


Keeping your arteries cold is critical for maintaining health throughout your life!

I know, hot arteries can kill me plus silently lead to chronic diseases of aging!



How Hot is It??!!



F2 isoprostane; microalbumin/creatinine ratio; hsCRP;
fibrinogen; Lp-PLA2; myeloperoxidase

Is This Happening to You??!





Oxidative Stress

Oxidative stress: imbalance between the formation of ROS or free radicals and antioxidant protective mechanism

Oxidation can initiate the atherogenic process.

Griffiths HR et. al. Mol Aspects Med 2002; 23:101-208

Montuschi P et. al. FASEB J 2004; 18:1791-800

Basu S. Free Radic Res 2004; 38:105-22



Oxidation Activates Platelets



Platelet Activation Increases Platelet Derived Growth Factor (PDGF)*

PDGF causes genetic transformation of contractile SMCs to secretory SMCs.

These cells migrate to the intima and enhance lipoprotein binding in the intima.^

*Rossi, E., et. al. (1998). Increased Plasma Levels of Platelet-Derived Growth Factor (PDGF-BB + PDGF-AB) in Patients with Never-Treated Mild Essential Hypertension.

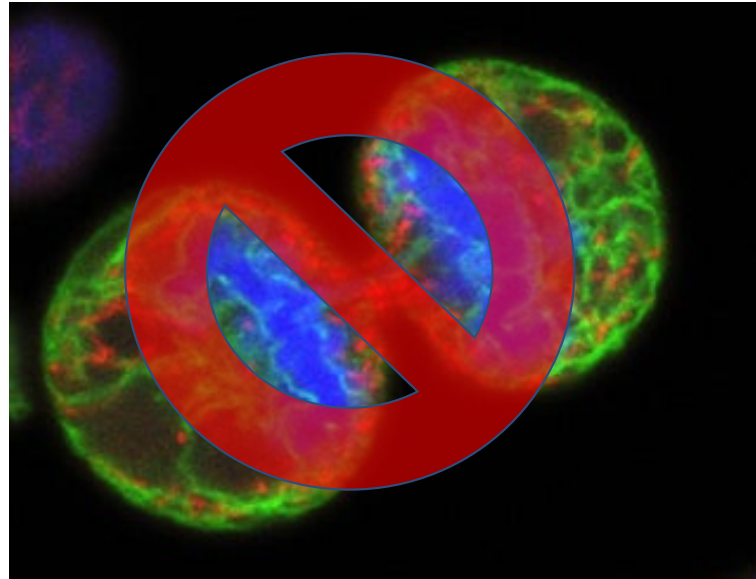
American Journal of Hypertension, 11(10), 1239-1243.

^Owens, G. K., et. al. (2004). Molecular regulation of vascular smooth muscle cell differentiation in development and disease.

Physiol Rev, 84(3), 767-801.

Oxidative Stress

Oxidation is pro-inflammatory in another manner.



cellular division

Montuschi, P., Barnes, P. J., & Roberts, L. J., 2nd. (2004). Isoprostanes: markers and mediators of oxidative stress. *FASEB J*, 18(15), 1791-1800.

Basu, S. (2004). Isoprostanes: novel bioactive products of lipid peroxidation. *Free Radic Res*, 38(2), 105-122.

Senescence

Cell senescence = irreversible loss of the ability of cells to divide.
Two types.

- 1)- replicative senescence; 'aging'; shortened telomeres
- 2) stress-induced premature senescence (SIPS); triggered by oxidative stress; not usually characterized by telomere shortening

Wang, J. C., & Bennett, M. (2012). Aging and atherosclerosis: mechanisms, functional consequences, and potential therapeutics for cellular senescence. *Circ Res*, 111(2), 245-259.



Atherosclerosis and Senescence

Endothelial senescence is associated with loss of function and a shift toward a proinflammatory and proapoptotic state.

VSMCs senescence generate a proinflammatory environment and have diminished ability to repair plaque.

Monocyte senescence generates a greater proinflammatory environment

Wang J C , Bennett M Circulation Research 7/2012;111:245-259



Extra 'Event' Risk with Oxidation

Prothrombotic state!!



Oxidative Stress Increases Risk of Thrombosis

Oxidative stress significantly increases platelet aggregation via activation of the glycoprotein IIb/IIIa.

(??? over-ride protection of clopidogrel type medication?
keep in mind with aspirin 'non-responder')

Pignatelli, P., et. Al. (2012). Immediate antioxidant and antiplatelet effect of atorvastatin via inhibition of Nox2. *Circulation*, 126(1), 92-103.



Oxidative Stress: How can we measure it?

Isoprostane is the “gold standard” to measure oxidative stress.

Morrow, J. D. (2005). Quantification of Isoprostanes as Indices of Oxidant Stress and the Risk of Atherosclerosis in Humans. *Arteriosclerosis, Thrombosis, and Vascular Biology*, 25(2), 279-286.

Isoprostanes Reduced With Healthy Lifestyle

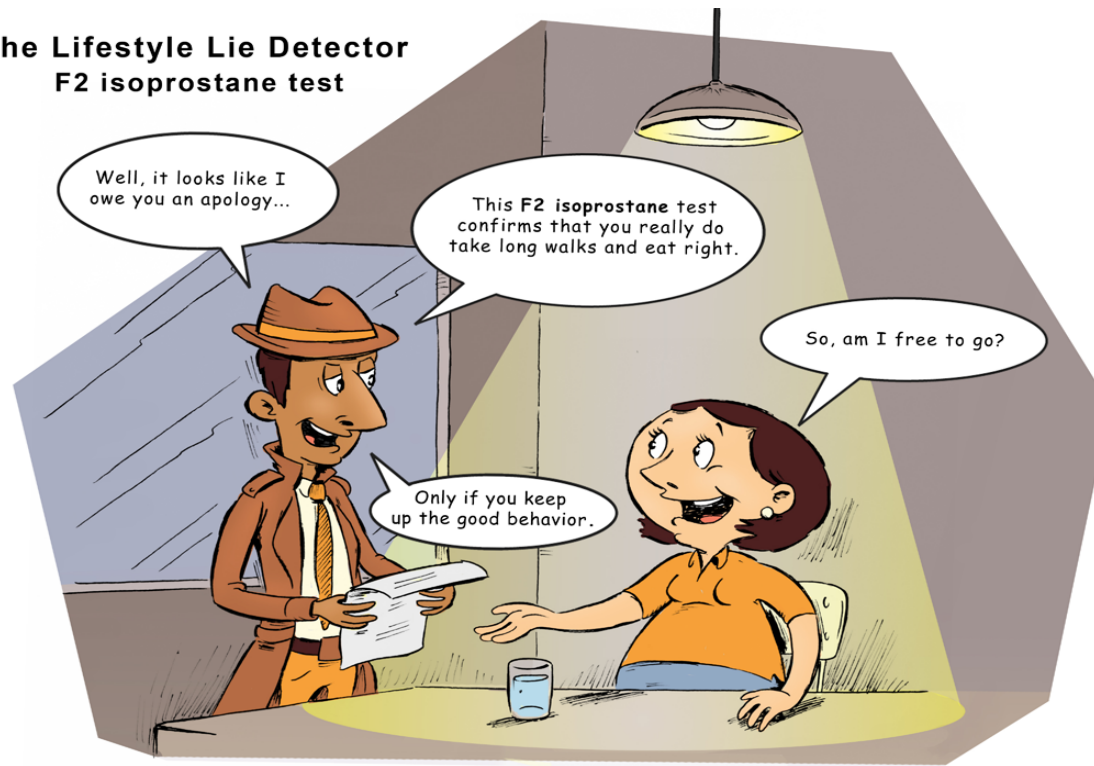
A+

F



Lifestyle Lie Detector

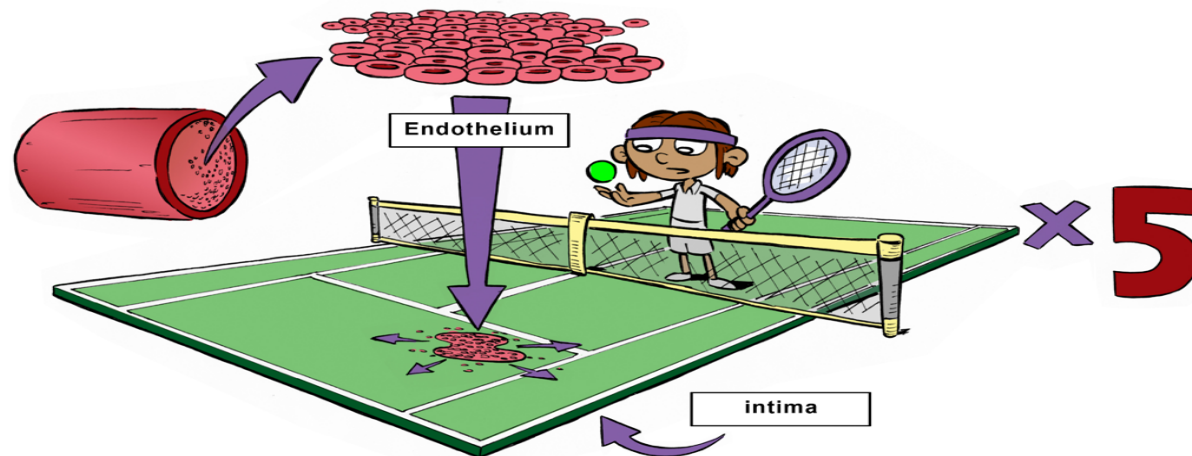
The Lifestyle Lie Detector F2 isoprostane test



The **F2 isoprostane** is a urine test which assesses our overall oxidative state. This is directly related to how fast we age and is driven by lifestyle. So if a patient says they are eating right and exercising and their oxidative levels come back normal - they're probably telling the truth!

Bio-markers for Endothelial ('Tennis Court') Inflammation

“Tennis court”



The endothelial cells which line our arteries are so numerous that, if taken out of your body, they would cover the surface of five tennis courts. These endothelial cells “tennis court” create a vital protective wall against heart attacks and strokes.



Fibrinogen

Meta-analysis 31 prospective trials; 154,211 pts.

HR for CHD & stroke per 100mg /dL increase in fibrinogen above 250 mg/dL: 1.82 (95% CI 1.54-2.16) adjusted for: age, gender, smoking, TC, BP, BMI, alcohol, sub-particles, DM.

Reliable demonstration that fibrinogen is associated with CHD and stroke risk.

Fibrinogen Studies, C. (2005). Plasma fibrinogen level and the risk of major cardiovascular diseases and nonvascular mortality: An individual participant meta-analysis.
JAMA, 294(14), 1799-1809.

Risk of CV Death/MI or Stroke Increase with hs-CRP levels of ≥ 1 mg/L

hs-CRP level	Hazard ratio of CV death/MI/stroke (95% CI)	p
1–3 mg/L	1.39 (1.06–1.81)	0.016
>3 mg/L	1.52 (1.152.02)	0.003

Adjusted for baseline characteristics and treatments

3771 stable CAD pts. followed 4.8 yrs.; 400 major events

Sabatine, M. S., et. al. (2007). Prognostic Significance of the Centers for Disease Control/American Heart Association High-Sensitivity C-Reactive Protein Cut Points for Cardiovascular and Other Outcomes in Patients With Stable Coronary Artery Disease. *Circulation*, 115(12), 1528-1536.

Fibrinogen & hs-CRP are Just Predictors: they are not causal ☹️

SO, how strong are they???





C-Reactive Protein & Fibrinogen Are as Predictive First Cardiovascular Events as Total Cholesterol and HDL

Pooled analysis of data from ~250,000 people without CVD

Adding CRP and or fibrinogen significantly improved risk assessment for a first event.

As predictable as TC and HDL.

The Emerging Risk Factors Collaboration. N Engl J Med. October 4, 2012
Volume 367(14):1310-1320

I am the Best for the
Endothelium!





Microalbuminuria

Is a marker of endothelial inflammation with increased permeability and dysfunction.

Bakris, G. L. (2001). Microalbuminuria: what is it? Why is it important?
What should be done about it?
J Clin Hypertens (Greenwich), 3(2), 99-102.

Microalbumin/Creatinine Ratio (MACR) Independently Predicts Risk of CV Events

Biomarker	Adjusted hazard ratio per 1 SD increment in the log value
------------------	--

MACR	1.20
-------------	-------------

Framingham data; 3209 pts.; followed 7.4 yrs.; 207 deaths

Eight markers not predictive: CRP, N-terminal proatrial NP, aldosterone, fibrinogen, D-dimer, PAI-1, renin, homocysteine

Bottom line: MACR trumps hsCRP and fibrinogen

Wang, T. J., et. al. (2006). Multiple Biomarkers for the Prediction of First Major Cardiovascular Events and Death.
New England Journal of Medicine, 355(25), 2631-2639.

MACR Cut Points for Marking Increased CV Risk

Risk when MACR > 7.5 ug/mg in women
and > 4.0 ug/mg in men

End point	Hazard ratio	p
CV event	2.92	<0.001

1,568 Fram. Offspring healthy pts. ; mean age 55; 58% women Followed 6 yrs.

Ärnlov, J., et. al. (2005). Low-Grade Albuminuria and Incidence of Cardiovascular Disease Events in Nonhypertensive and Nondiabetic Individuals: The Framingham Heart Study. *Circulation*, 112(7), 969-975.



Microalbumin Changes are Prognostic of CV Events

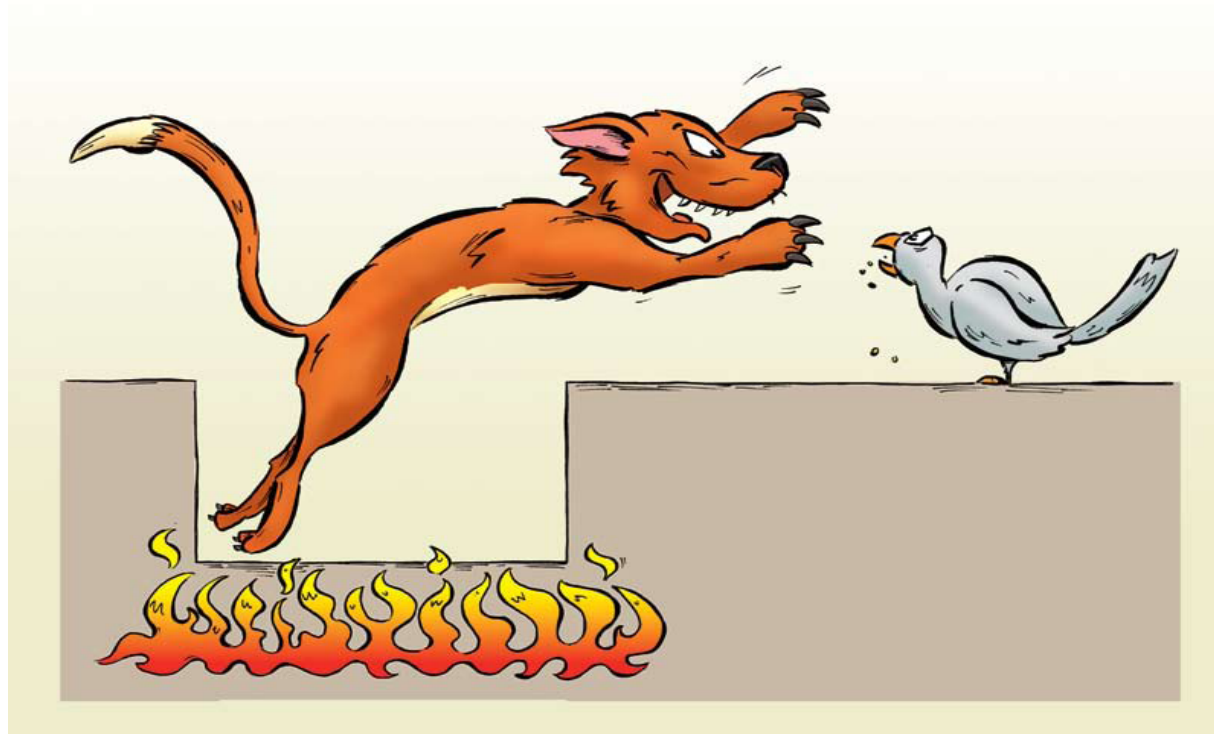
MACR represents a measurement of organ (endothelium) damage.

MACR predicts risk for CV events independent of other CV risk factors including coronary risk estimation.

It is reasonable to take information from changes in MACR to assess whether treatment is successful.

Pascual, J. M., et. al.(2014). Prognostic Value of Microalbuminuria During Antihypertensive Treatment in Essential Hypertension. Hypertension. doi: 10.1161/HYPERTENSIONAHA.114.04273

'Fire In The Hole' Can Make the Cat Jump





How hot is it under your
tennis court ??!!

Lipoprotein associated
phospholipase A2
(Lp-PLA2 or PLAC2 test)



Lp-PLA2 is not an Acute Phase Reactant as Opposed to CRP

32 healthy subjects; 50% female; mean age 26 ± 4 yrs.; infused with
3 ng/kg endotoxin

Endotoxin produced an acute febrile illness

Resulted in 100 fold increase in CRP at 24 hours

No significant change in Lp-PLA2

Ferguson, J. F., et al. (2012). "Translational studies of lipoprotein-associated phospholipase A(2) in inflammation and atherosclerosis."
J Am Coll Cardiol **59**(8): 764-772.



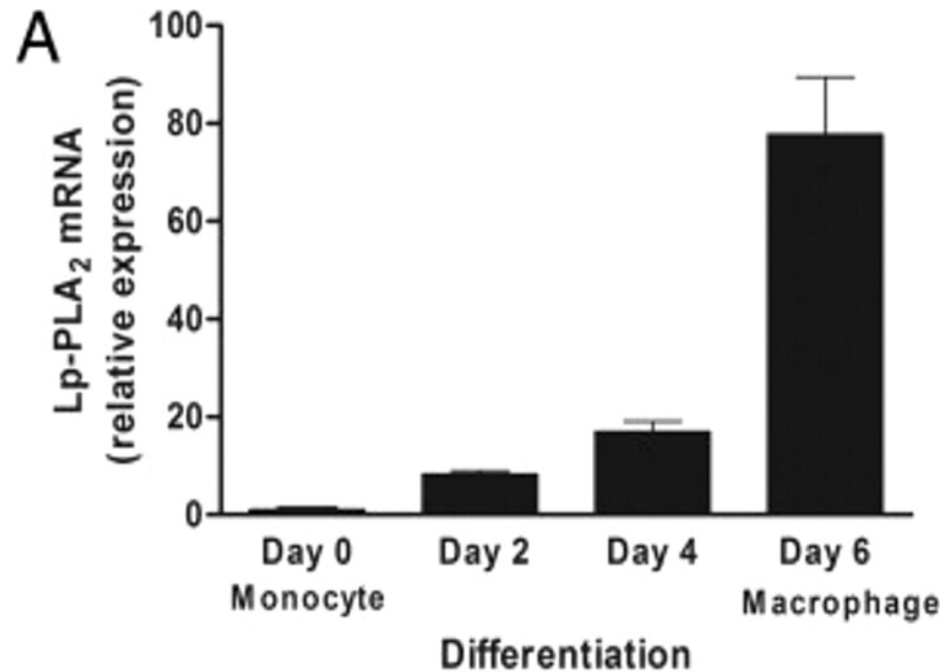
Lp-PLA2 Increases Inflammatory Macrophages in Vitro

Monocytes were isolated and transitioned into macrophages over six days (using LPS).

Lp-PLA2 levels measured during this transition.

Ferguson, J. F. et al. J Am Coll Cardiol 2/2012;59:764-772

Lp-PLA₂ Increases During Differentiation of Human Monocytes to Macrophages



Ferguson, J. F. et al. *J Am Coll Cardiol* 2/2012;59:764-772



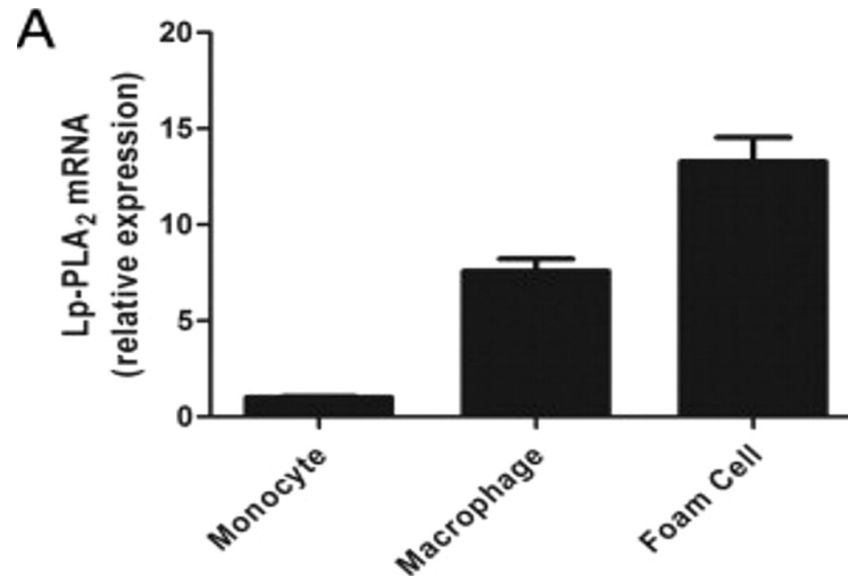
Lp-PLA2 Increases When 'Foam Cells' Form

Macrophages exposed to oxidized LDL-C for 48 hrs inducing foam cell production.

Lp-PLA2 levels measured during this process.

Ferguson, J. F. et al. J Am Coll Cardiol 2/2012;59:764-772

Lp-PLA2 Levels Rise Sharply With Foam Cell Production



It appears Lp-PLA₂ is generated by macrophages and foam cells rather than by circulating leukocytes. This would mean it is marking an active atherosclerotic disease process.

Ferguson, J. F. et al. *J Am Coll Cardiol* 2/2012;59:764-772

Markers vs Players





Players are direct targets for therapy.

Miss Freedman





Periodontal Disease (PD) Associated with Elevated Lp-PLA2

421 healthy adults screened for Lp-PLA2 & hx of PD.

Pts with PD were 1.8 times more likely to have elevated Lp-PLA2 levels.

37% of pts with no CV risk factors except PD had elevated Lp-PLA2.

Mochari, H., et. al. (2008). Usefulness of self-reported periodontal disease to identify individuals with elevated inflammatory markers at risk of cardiovascular disease.

Am J Cardiol, 102(11), 1509-1513.



Lp-PLA2 Reduced with Treatment of Periodontitis

32 pts. with moderate to severe periodontal disease; age 43 \pm 11 years; 3 mos. local rx.

Rx improved PD with reduced pocket size and BOP

Lp-PLA2 serum activity reduced 10% with a $p < 0.001$

Lösche, W., et. al. (2005). Lipoprotein-associated phospholipase A2 and plasma lipids in patients with destructive periodontal disease.
J Clin Periodontol, 32(6), 640-644.



Lp-PLA2 Change Predicts CV Events

7,863 CAD pts. ~ 16% female; randomized to pravastatin or placebo; 6 yr. follow-up for CHD (events & death); evaluate Lp-PLA2 as a predictor at baseline and with change at one yr.

Lp-PLA2 was categorized in quartiles

White, H. D., et. al. (2013). Changes in Lipoprotein-Associated Phospholipase A2 Activity Predict Coronary Events and Partly Account for the Treatment Effect of Pravastatin: Results From the Long-term Intervention with Pravastatin in Ischemic Disease Study. *J Am Heart Assoc*, 2(5), e000360.

Lp-PLA2 Change Predicts CV Events

Change in Lp-PLA2 was a significant independent predictor of CHD events after adjustment for these 23 risk factors, including LDL-C and LDL-C changes. $P < 0.001$

The reduction in Lp-PLA2 accounted for 59% of the risk reduction;

LDL reduction accounted for 0%!!!

White, H. D., et. al. (2013). *J Am Heart Assoc*, 2(5), e000360.



FDA Approves Lp-PLA-2 for Heart Attack Risk Assessment in All Adults

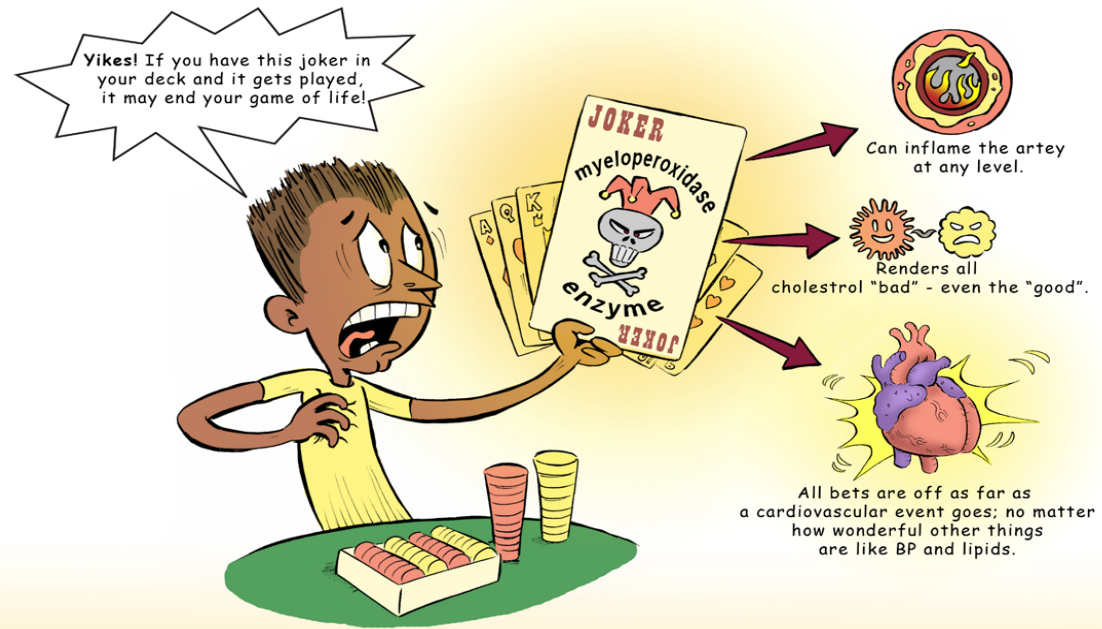
The FDA- December 15, 2014- cleared Lp-PLA2 as a screening test that predicts a pt's risk of future coronary heart disease (CHD) events.

FDA cleared the test for use in all adults regardless of history of heart disease.

<http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm426799.htm>

Yikes!

THE JOKER



The Joker (Myeloperoxidase enzyme), is elevated in approximately 2 out of every 50 patients. We need to test to see if he is in your deck and if he is - we want to take him out!



Miss Freedman



Myeloperoxidase (MPO)

Member of the heme peroxidase family

Stored in azurophilic crystals in leukocytes

Secreted during leukocyte activation

Important in innate infectious disease host defenses

Nicholls, S. J., & Hazen, S. L. (2005). Myeloperoxidase and Cardiovascular Disease. *Arteriosclerosis, Thrombosis, and Vascular Biology*, 25(6), 1102-1111.

MPO Activity

MPO co-substrate is hydrogen peroxide

MPO generates numerous reactive oxidants

Chlorinates hydrogen peroxide into hypochlorous acid (HOCl) – active ingredient in bleach

Halogenating oxidants – create chlorotyrosine

Creates nitrogen species = nitrotyrosine

Nicholls, S.J.; Hazen, S.L., *Arterioscler. Thromb. Vasc. Biol.*
2005;25;1102-1111



MPO is Detrimental to the Lipids

HOCl oxidizes apo B-100

Reactive nitrogen species oxidize LDL (NO₂LDL)

Nitrotyrosine and chlorotyrosine bind to apo A-1 and HDL
impairing reverse cholesterol transport

Nicholls, S.J.; Hazen, S.L.,
Arterioscler. Thromb. Vasc. Biol. 2005;25;1102-1111



MPO Impairs Endothelial Function

Consumes NO as a co-substrate

Reduces production of NO by crippling NOS

- a) reactive nitrogen species uncouple NOS
- b) oxidized HDL inhibits NOS activity
- c) HOCl chlorinates arginine which reduces the activity of NOS

Nicholls, S.J.; Hazen, S.L.,
Arterioscler. Thromb. Vasc. Biol. 2005;25;1102-1111



MPO Creates Vulnerable Plaques

HOCl promotes activation of MMP-7 –
fibrous cap rupture

HOCl promotes endothelial apoptosis and detachment-
erosive events

Nicholls, S.J.; Hazen, S.L.,
Arterioscler. Thromb. Vasc. Biol. 2005;25;1102-1111



Plaque Erosion

The thrombus overlying plaque erosion has higher concentrations of MPO than that observed in ruptured plaques.

Pts with erosive thrombi have higher serum levels of MPO.

Partida, R. A., Libby, P., et. al. (2018). Plaque erosion: a new in vivo diagnosis and a potential major shift in the management of patients with acute coronary syndromes. *Eur Heart J*, 39(22), 2070-2076.



Serum Levels of MPO Rise With Infection

Serum levels of MPO are raised in infections.

The levels are much higher with bacteria than viral infections.

Lena Kulander, K. P. P. V. (2001). Soluble Adhesion Molecules, Cytokines and Cellular Markers in Serum in Patients with Acute Infections. *Scandinavian Journal of Infectious Diseases* 33(4): 290-300..



Myeloperoxidase (MPO) Predicts Future Risk of Coronary Artery Disease in Healthy People

Regardless of other known risk factors !

Meuwese, M. C., et. al. (2007). Serum myeloperoxidase levels are associated with the future risk of coronary artery disease in apparently healthy individuals: the EPIC-Norfolk Prospective Population Study.

J Am Coll Cardiol, 50(2), 159-165.



Take to the Trenches

Inflammation is causal of atherosclerosis; it all starts with SMC transformation. 'Fire' triggers atherothrombotic events. Remember the 'sound of silence'!

Tests to monitor routinely:

F2 isoprostane –urine

MACR –urine

LpPLA2 – serum

MPO - serum

Tests that may also be useful

hs-CRP -serum

fibrinogen - serum

Routinely Monitor for Fire; When You Spot Some Heat Extinguish It Quickly!



"WE LOOK FOR FIRE IN THE ARTERIES ROUTINELY AND WHEN WE SEE SOME HEAT, WE EXTINGUISH QUICKLY."



*Moss
FREEDMAN*



Cat In The Gutter

