How to get the most out of your AWP– and what to do next!

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Disclosures

- Founder and CMO – Adventia, LLC
- Speaker – Quest/CHL

Learning objectives

- **Maximize utility of the AWP by:**
  - IDENTIFYING STAGES OF ASCVD USING BIOMARKERS
  - DISCOVERING ROOT CAUSES FOR
    - ENDOTHELIAL DYSFUNCTION
    - ARTERIAL INFLAMMATION
  - DEVELOPING NEXT STEPS USING NEW BIOMARKERS
    - FURTHER TESTING
    - TREATMENT


A380 AIRBUS


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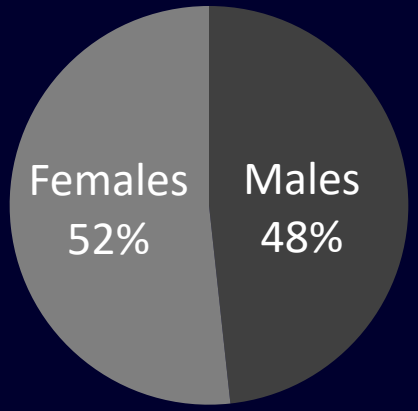
Annual Wellness Panel tests

- LIPOPROTEINS
  - NMR LipoProfile with Lipids
    OR
  - Advanced Lipid with ApoB
- ATHEROMA BURDEN
  - hsCRP
  - Cholesterol/HDL ratio
- ARTERIAL WELLNESS
  - MPO
  - ADMA/SDMA
- TMAO
- MISCELLANEOUS
  - TSH
  - CMP
  - CBC
- INSULIN RESISTANCE
  - Fasting Glucose
  - HgbA1C
  - Triglyceride/HDL ratio
  - Metabolic Syndrome
  - ALT/AST ratio
  - Uric Acid
  - Vitamin D

Risk identified using the AWP

6 months
Jan-June 2018

22,257
patients
tested

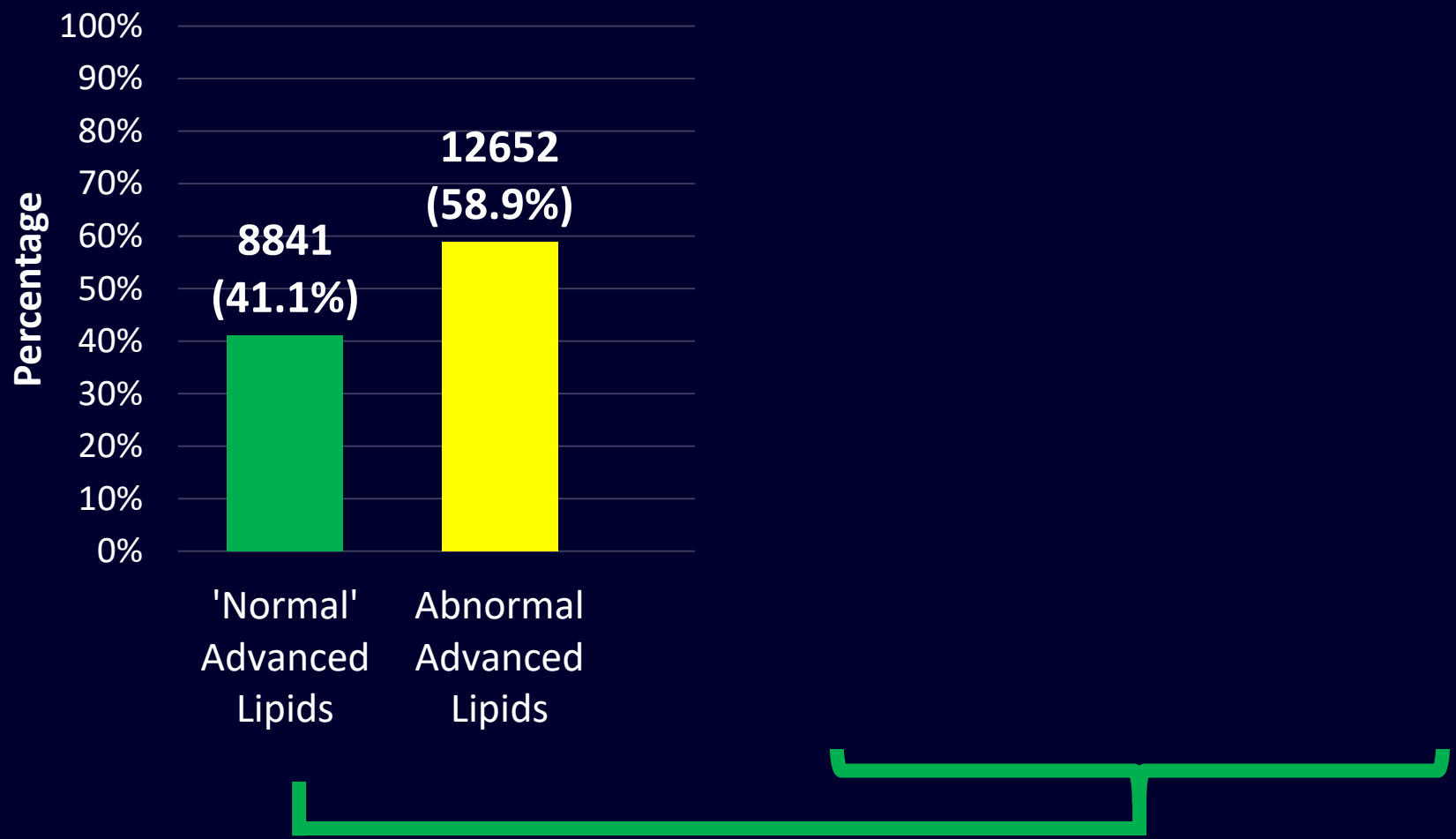


Average age: 66

Max age: 104

Min age: 18

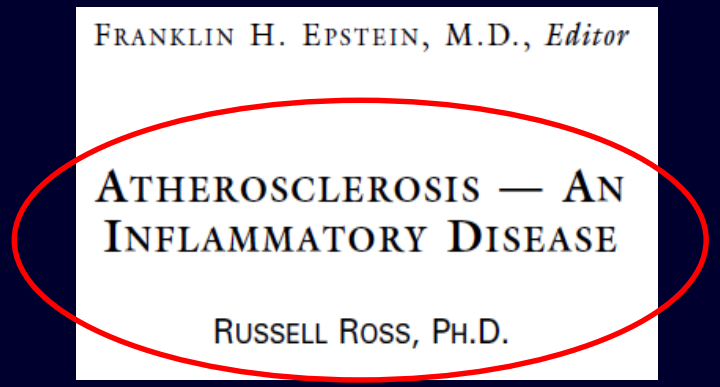
Risk identified using the AWP



'Normal' Advanced lipids:
ApoB <100
LDL-P <1000

Atherosclerosis is an inflammatory disease

Markers of inflammation help refine cardiovascular risk estimation


FRANKLIN H. EPSTEIN, M.D., *Editor*

ATHEROSCLEROSIS — AN INFLAMMATORY DISEASE

RUSSELL ROSS, PH.D.

Volume 340 Number 2

Ross R. Atherosclerosis--an inflammatory disease. N Engl J Med. 1999;340(2):115-26.

Clinical Conundrums

Why do many plaque-patients live for *years* without an event?

Why do some patients have stable angina for years, and others *present with* ACS, AMI, Sudden Death?

How can a patient pass a Stage IV Bruce ETT only to have a massive AWMI 6 weeks later?

Why do Ischemic Events happen even when I control BP, HgbA1C, and Lipids?

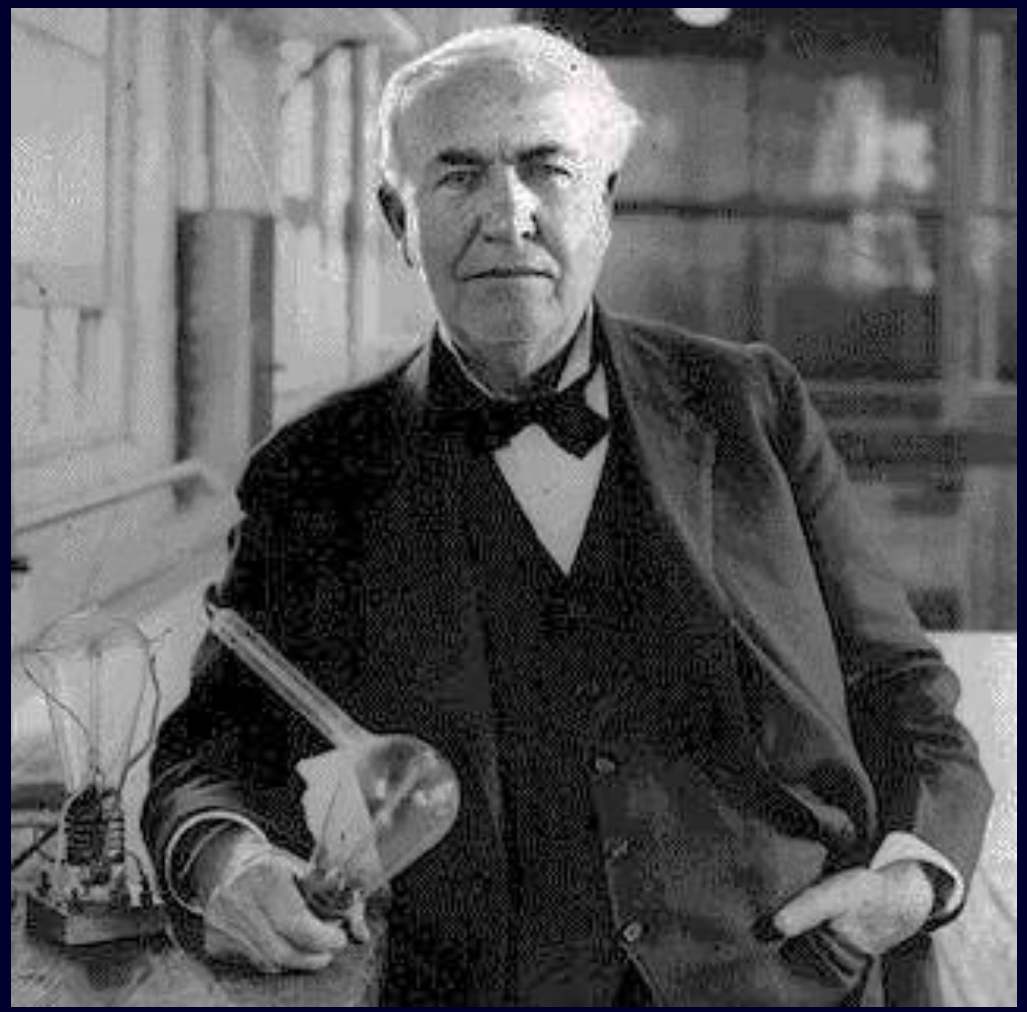
Why do 80% of T2DMs have an MI or CVA?

What is “Residual Risk”?

Would you like to do better?

If so,

HOW?



THE FUTURE IS NOW!!

~Thomas Edison, 1847-1931

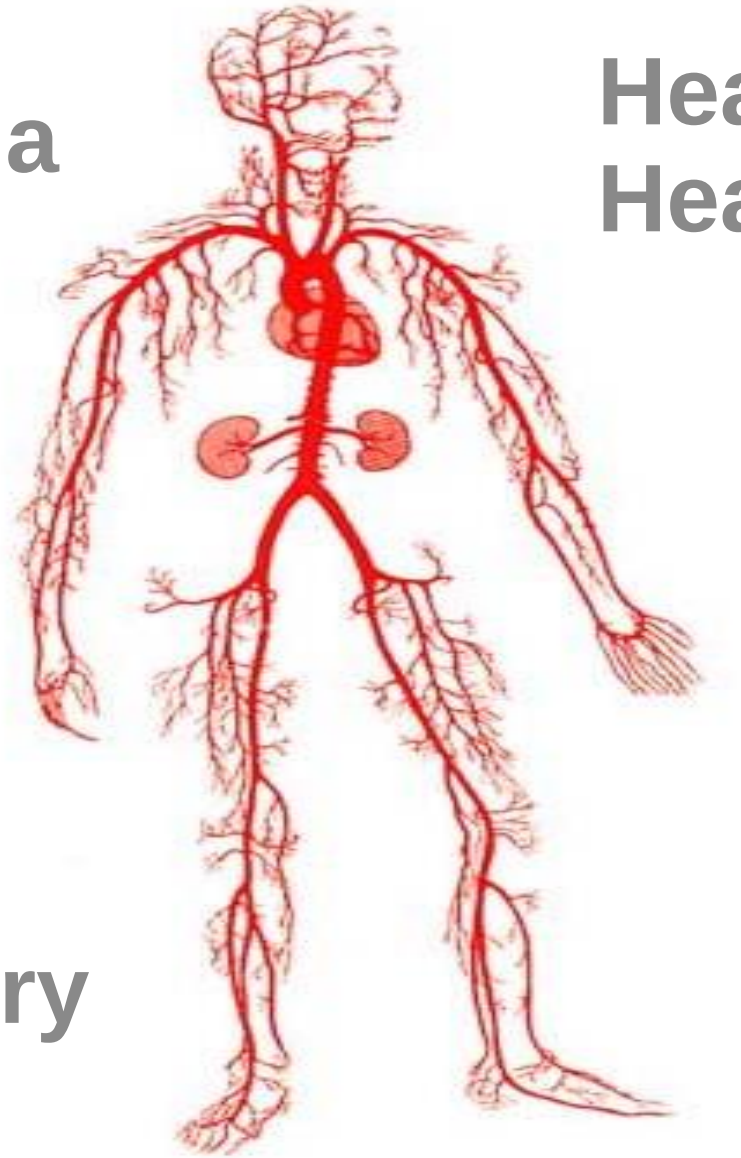
“A MAN IS AS OLD AS HIS ARTERIES”

~Thomas Sydenham, 1624-1689

Father of English Medicine

Stroke
Dementia

Heart Attack
Heart Failure



Kidney Failure
Erectile
Dysfunction

60,000 MILE ARTERIAL HIGHWAY!

Peripheral Artery
Disease

Injury + Response = Atherosclerotic Progression

The ‘Response to Injury’ Hypothesis

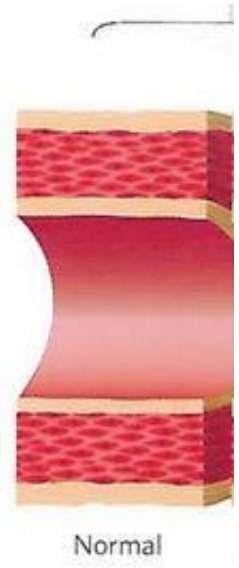
Injury

Lipids
Blood Pressure
Blood Glucose
Oxidation
Smoking
Age/Gender

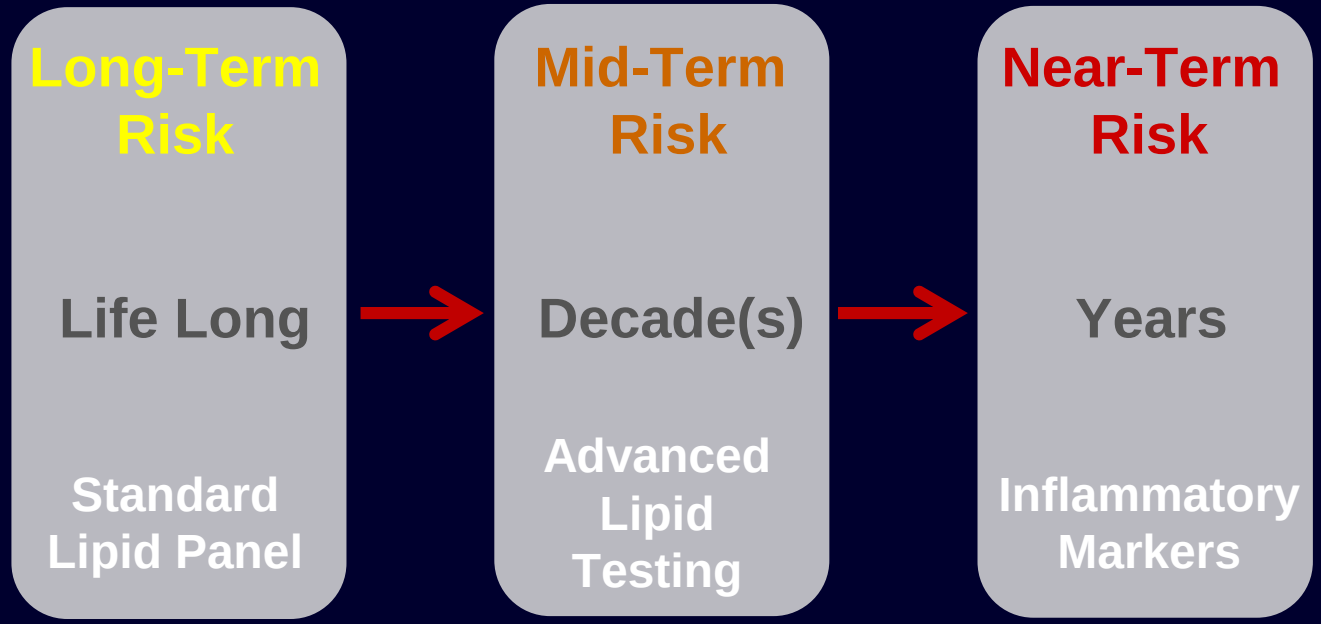
Inflammation

JUPITER and CANTOS:
Reducing inflammation, independent of lipids, provides added benefit

ARTERIAL AGING



Biomarkers to better define patients at risk



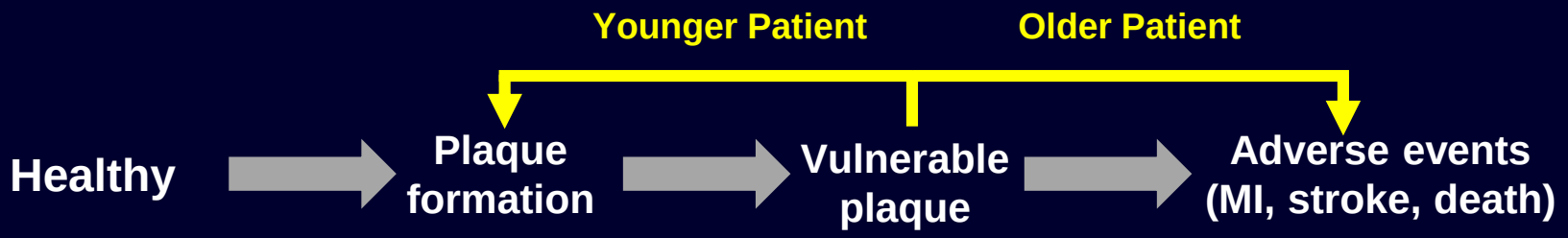
Cholesterol:HDL RATIO

Suggestive of:

Optimal plaque regression	< 2.8	
Suboptimal for plaque regression	≥ 2.8	< 3.0
Moderate risk for plaque progression	≥ 3.0	≤ 4.5
High risk for plaque progression	> 4.5	≤ 5.5
Very high risk for plaque progression	> 5.5	

Why monitor inflammation?

Studies continue to show the value of assessing the *degree* of inflammation in a patient

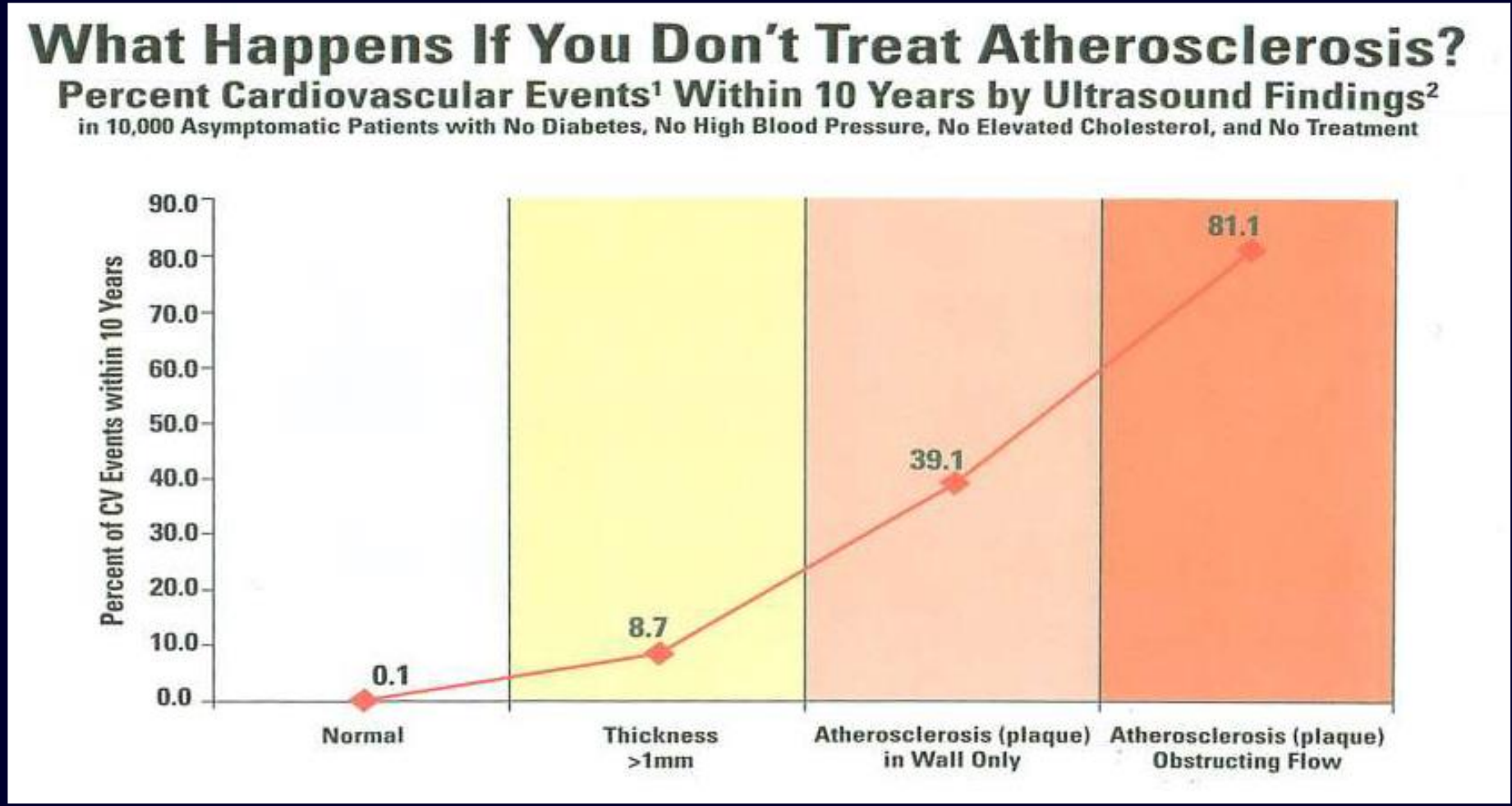


STRATEGY

- PLAQUE PRESENT?
- INFLAMMATION PRESENT?
- ROOT CAUSES?—the Jumbo Jets!
- TREATMENT OPTIONS BASED ON PATHOPHYSIOLOGY

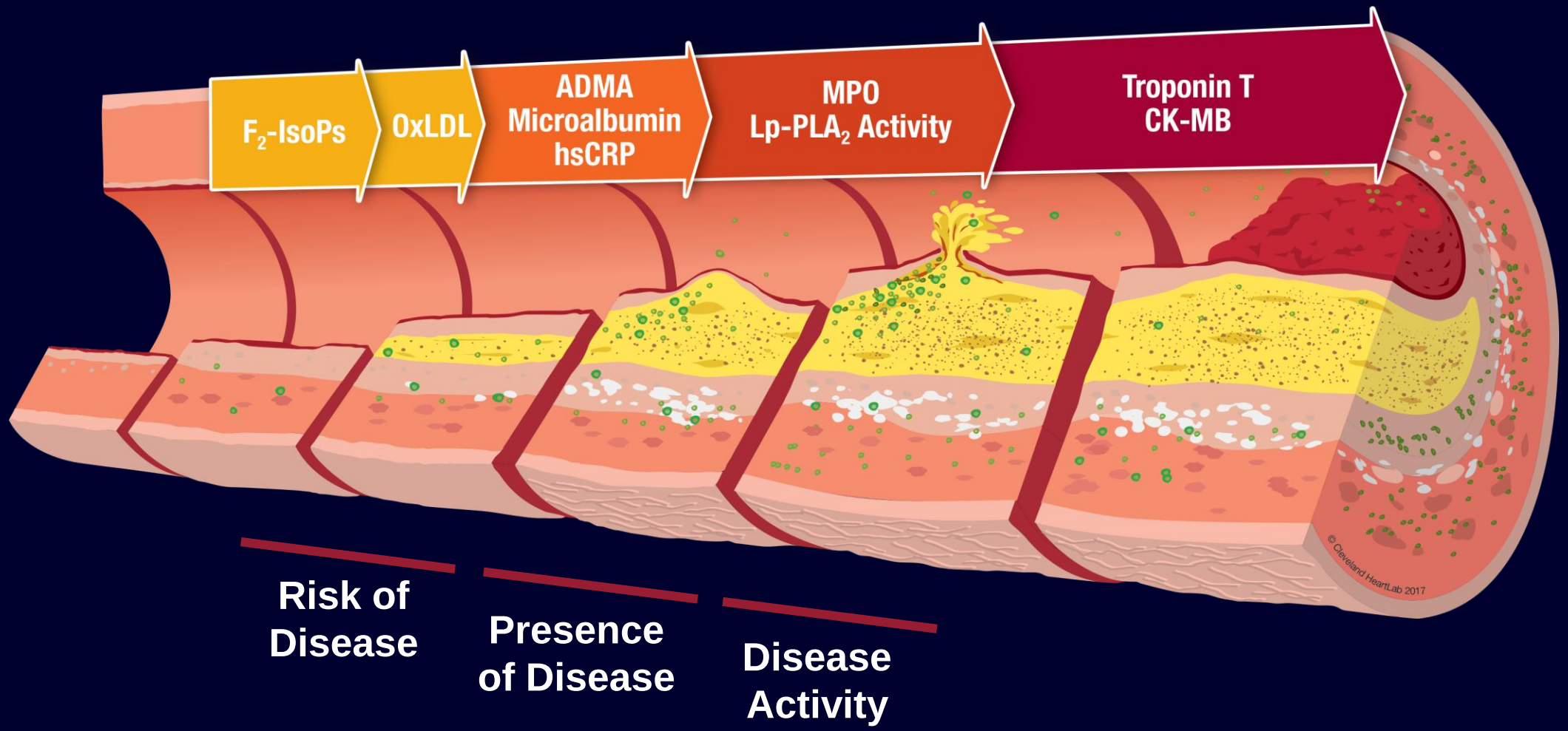
Bale BF, Doneen AL *J Clin Exp Cardiology*. 201;5:298
Bale B and Doneen A. *Beat The Heart Attack Gene.* New York, NY: Wiley; 2014

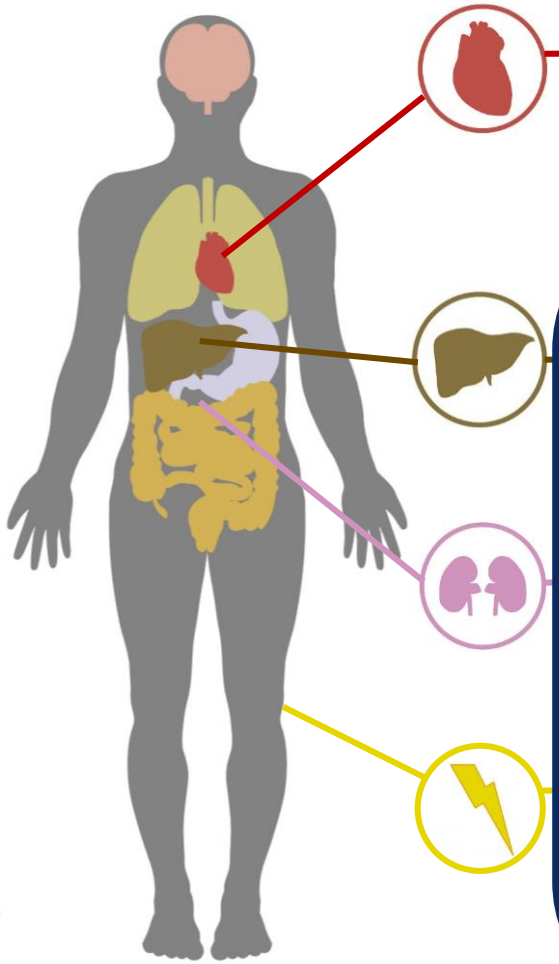
FIND DISEASE!



Belcaro, G., et. al. *Atherosclerosis*. 2001;156:379-387.

Inflammatory biomarkers across a spectrum of risk





Vascular Inflammation

Myeloperoxidase (MPO)

$Lp\text{-}PLA_2$ Activity

General Inflammation

hsCRP

Endothelial Damage

Urinary Microalbumin

ADMA/SDMA

Oxidation/Lifestyle

Oxidized LDL (OxLDL)

F_2-Isoprostanes

FIRE ALARMS!!

SMOKE DETECTORS

hsCRP EVALUATION

- < 1 mg/dL normal, but < 0.38 mg/dL is lowest risk
- 1-3 mg/dL think about cardiac risk
  - Visceral fat cytokines drive hepatic CRP production!
  - Indicative of atheroma burden
- 3-10 mg/dL can be cardiac or other
- > 10 mg/dL think about systemic problems

hsCRP

- **Trials showing benefit of Rx when hsCRP ≥ 2 mg/dL**
  - **JUPITER Trial even when LDL < 130 mg/dL[1]**
  - **CANTOS Trial when blocking IL-1Beta (which drives hsCRP)[2] $$$$**

(1.) Libby P, Ridker PM, Hansson GK. Inflammation in atherosclerosis: from pathophysiology to practice. J Am Coll Cardiol. 2009;54(23):2129-38. (2.)Ridker PM, Everett BM, Thuren T, et al. Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. N Engl J Med. 2017.

ADMA/SDMA

- Both inhibit production of NO, indicates
  - Endothelial Dysfunction
  - Arterial disease
- SDMA renally cleared, indicates renal dysfunction
- ADMA predicts presence of plaque and 2x risk of MACE
- LOOK FOR PLAQUE!

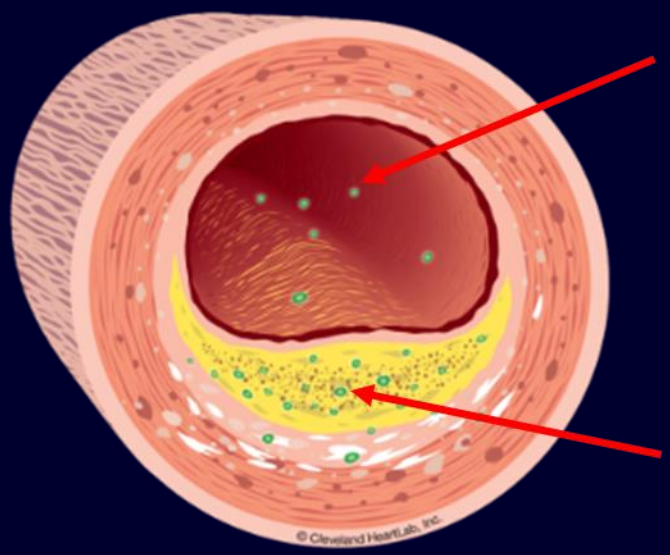
1. Maas R, Xanthakis V, Polak JF, et al. Association of the endogenous nitric oxide synthase inhibitor ADMA with carotid artery intimal media thickness in the Framingham Heart Study offspring cohort. Stroke. 2009;40(8):2715-9. 2. Hsu CP, Hsu PF, Chung MY, Lin SJ, Lu TM. Asymmetric dimethylarginine and long-term adverse cardiovascular events in patients with type 2 diabetes: relation with the glycemic control. Cardiovasc Diabetol. 2014;13:156..

ADMA/SDMA DRIVERS

- **Insulin Resistance!!!**
- **Hypertension**
- **Dyslipidemia**
- **Presence of Atherosclerosis!**

Stühlinger MC, Abbasi F, Chu JW, et al. *JAMA*. 2002; 287: 1420-1426. Böger RH, Bode-Boger Sm, Szuba A, et al. *Circulation*. 1998; 98: 1842-1847. (3.) Sibal L, et al. *Curr Cardiol Rev*. 2010; 6 (2): 82-90.

The two sides of vulnerable plaque



Outside the vessel wall

MPO can be used to identify circulating white blood cells activating in response to fissures, erosions, or warming plaque increasing the risk of vulnerable plaque rupture.

Inside the vessel wall

Lp-PLA$_2$ Activity can be used to identify active inflammation within the vessel wall contributing to vulnerable plaque formation.

MPO VALUE

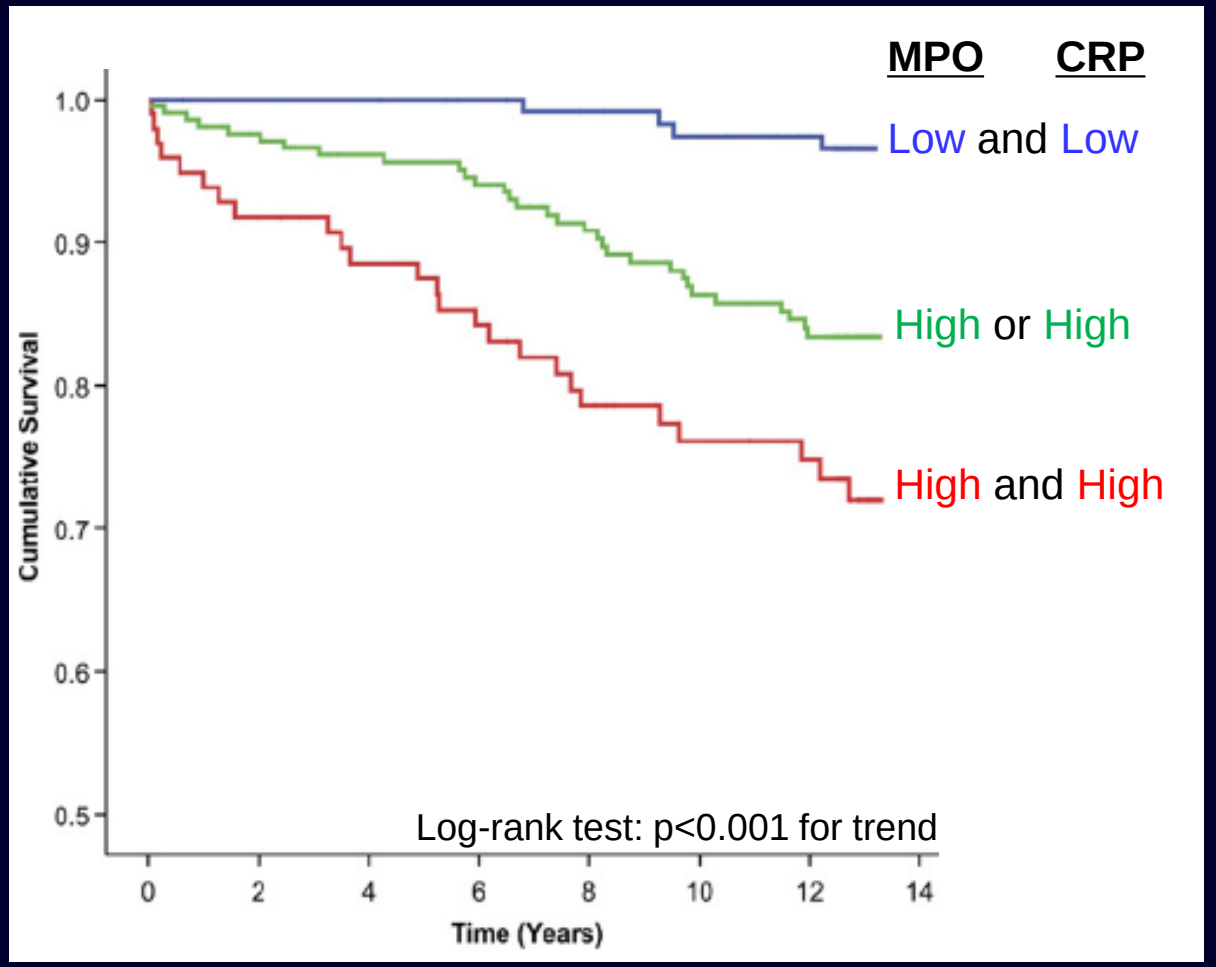
- Predictive of ASCVD Event Risk up to 13 years in advance
  - 2x CV mortality
- Luminal interface risk for plaque rupture or erosion
  - Younger women more likely to have plaque erosions
- Additive to hsCRP for Risk Prediction
- Signals Endothelial Damage

Heslop CL et al. *J Am Coll Cardiol.* 2010; 55 (11): 1102-9.

Myeloperoxidase (MPO)

- MPO and CRP have combined utility in predicting cardiovascular mortality risk in patients with angiographic evidence of CAD

- Patients with either a high MPO or high CRP had 5.3-fold higher mortality risk
- Patients with high levels of both MPO and CRP had a 4.3-fold risk vs. patients with only one elevated marker



Modified from: Heslop CL, et al. *J Am Coll Cardiol.* 2010;55(11):1102-9.

MPO DRIVERS

Always consider In vitro processing error during separation of plasma!

Drivers of Arterial Injury

- **Dyslipidemia**
- **Insulin Resistance**
- **Hypertension**
- **Obstructive Sleep Apnea**
- **Lifestyle**
  - **Extreme Athletes!! ?reason for some of their MACE?**

Hazen SL and Heinecke JW *J Clin Invest.* 1997; 99: 2075-2081. Weirsma JJ, et al. *Med Sci Monit*. 2008;14(8):CR406-410. Van der Zwan LP, et al. *Hypertension*. 2010;55:1366-1372. Richter B et al. *Thromb Haemost*. 2005;94(06):1306-1311. Melanson SE, et al. *Am J Clin Pathol*. 2006;126:888-893.

MPO DRIVERS

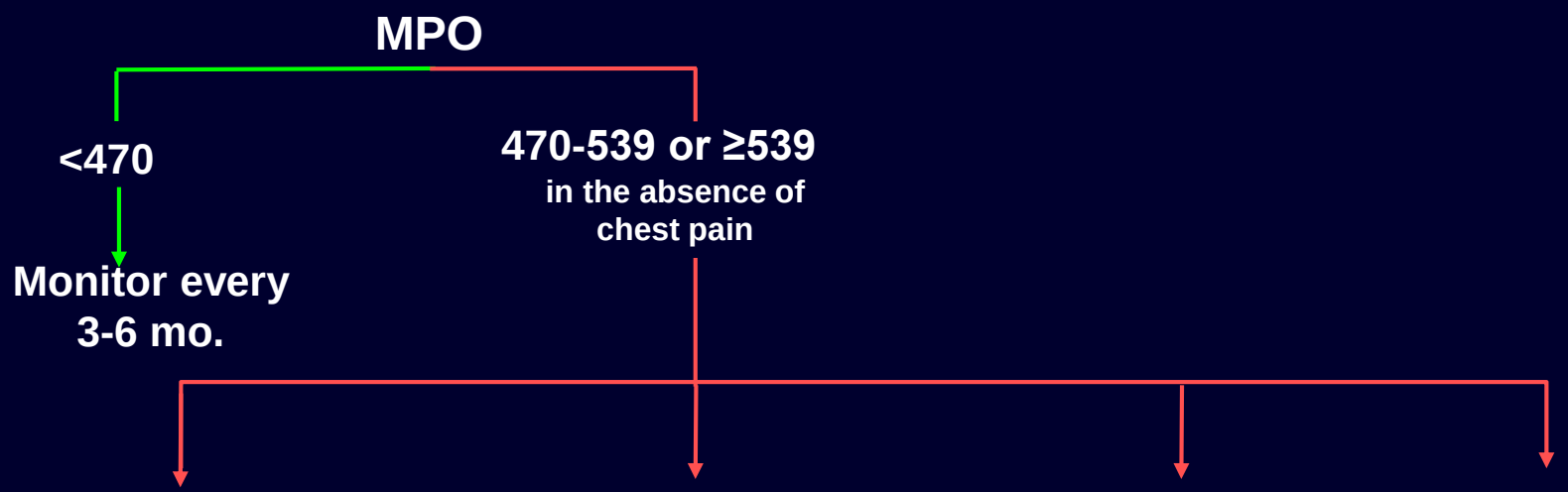
- Vasculitis
- Autoimmune Inflammatory—known risk factors for MACE!
- Gut Microbiome?
- Oral Microbiome?
  - Periodontal Disease—drives ASCVD
  - Endodontic Disease—anecdotal evidence is suggestive

Other Drivers

- Diastolic CHF—HFpEF
- Myeloproliferative Disorders

Melikoglu MA, et al. *J Enzyme Inhib Med Chem*. 2012;27(1):12-17. Ramirez JH, et al. *Aust Dent J*. 2014;59:29-36.

Evaluation of MPO Levels



Assess diet/lifestyle
Assess blood pressure
Assess insulin sensitivity
Assess dental health

Assess presence of CAD w/ imaging (CIMT/CACS)

- If clinically appropriate, consider dual platelet inhibition

Assess risk for pre-diabetes/ diabetes

- If pre-diabetic/ diabetic, consider insulin sensitizing therapy

Assess LDL-C

- Initiate/titrate statin therapy, if medically necessary

INSULIN RESISTANCE FAQ'S

- 70% of patients with plaque
- 90% specificity in patients with Metabolic Syndrome
  - But only 50% sensitivity
- 20+ years to progress from normal to Type 2 Diabetes
- Waistline is the simplest indicator and metric to discover/follow
  - > 40 inches men BUT optimal is < 36 inches
  - > 35 inches women BUT optimal is < 32 inches
  - Ethnicity cut points can vary

Okosieme OE, Peter R, Usman M, et al. *Diabetes Care*. 2008;31(10):1955-9.

INSULIN RESISTANCE IMPACT

- **FAT FERTILIZER—makes people grow, around the waistline!**
- **PLAQUE FERTILIZER—faster and thicker!**
- **INFLAMMATION TRIGGER!!**

Diagnosis of Metabolic Syndrome

Presence of 3 of 5 following risk factors:

Risk Factor	MEN	WOMEN
Waist Circumference	>40”	>35”
HDL Cholesterol*	<40mg/dL	<50mg/dL
Triglycerides*	>150mg/dL	>150mg/dL
Blood Pressure*	>130 systolic OR	>85 diastolic
Fasting Plasma Glucose*	≥ 100mg/dL	≥ 100mg/dL

*** OR ON DRUG THERAPY**

INSULIN RESISTANCE
GENERAL LAB CLUES

GLUCOSE

- Fasting glucose > 88 mg/dL
- A1C > 5.6%
  - (1% ~ 30 mg/dL avg glucose)

LIVER

- ALT ≥ 20 U/L in women
  ≥ 34 U/L in men
- GGTP ≥ 21 U/L in women
  ≥ 47 U/L in men

RENAL

- Uric Acid > 6 mg/dL

NUTRITIONAL

- 25-OH Vitamin D < 20-30 ng/mL

INSULIN RESISTANCE
LIPID CLUES

- Cholesterol:HDL > 4.5
- Triglycerides > 130 mg/dL
- HDL
  - < 40 mg/dL in men
  - < 50 mg/dL in women
- Triglyceride/HDL ratio
  - Caucasians > 3.5
  - Mexican-American > 3
  - Non-Hispanic Black > 2

- NMR Profile
  - Small LDL-P > 528 nmol/L
  - LDL size < 20.5 nm
  - sdLDL > 40 mg/dL
  - Large VLDL-P > 2.7 nmol/L
  - VLDL size > 46.6 nm
  - Large HDL-P < 4.8 umol/L
  - HDL2B < 28% in women,
    < 26% in men
- OxLDL > 60 U/L

INSULIN RESISTANCE
ENDOTHELIAL & ARTERIAL WALL CLUES

ENDOTHELIAL

- hsCRP > 1 mg/dL
- MACR ≥ 3.9 mg/g in men, ≥ 7.5 mg/g in women
- ADMA > 100 ng/mL

ARTERIAL WALL

- LpPLA2 Activity > 75 nmol/min/mL
- MPO > 470 pmol/L

INSULIN RESISTANCE INTERVENTION

- **Diabetes Prevention Program[1]**
  - **Lifestyle intervention can reverse in 58%**
    - **5-7% Weight Loss and Exercise**
  - **Metformin can reverse in 31%**
    - **Ages 25-44 and BMI over 35 respond best**

- **Pioglitazone can reduce risk of diabetes over 2.4 years in 72% of pre-diabetics[2]**

(1.) Knowler WC, et al. *N Engl J Med.* 2002;346(6):393-403. (2.) Defronzo RA et al. *N Engl J Med*. 2011;364(12):1104-15.

MISCELLANEOUS CLUES

TSH

- Dyslipidemia
- Atrial Fibrillation risk
- Insulin Resistance

CMP

- Gilbert's Syndrome—Indirect bilirubin is a natural anti-oxidant!
- Hepatic Enzymes—Fatty liver, NASH➔Insulin Resistance!

CBC

- MCV—possible B12/Folate deficiency with hyperhomocysteinemia
  - VTE
  - Cerebral Sinus Thrombosis
  - CV Risk

HOW TO GO BEYOND THE AWP

- **LIPOPROTEINS**
  - Lp(a)
  - sdLDL
  - ApoB & A1
- **ARTERIAL WELLNESS**
  - MACR
  - LpPLA2 Activity
- **INSULIN RESISTANCE**
  - OxLDL
- **MYOCARDIAL STATUS**
  - NT-ProBNP
- **GENETIC TESTING**
  - ApoE

NEXT STEP TESTS TO CONSIDER

LIPOPROTEINS

- Lp(a)—invisible to standard lipid testing
  - present in 1/3rd of Americans
  - Case-finding within families
  - Predicts early event risk
- sdLDL—correlates with small particles
  - easier to follow
  - Lower cost
- ApoB & A1—direct measurement
  - ApoB/ApoA1 single most predictive for Acute MI risk over next 5 years

    Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet. 2004;364(9438):937-52.
  - ApoB easier to follow/lower cost

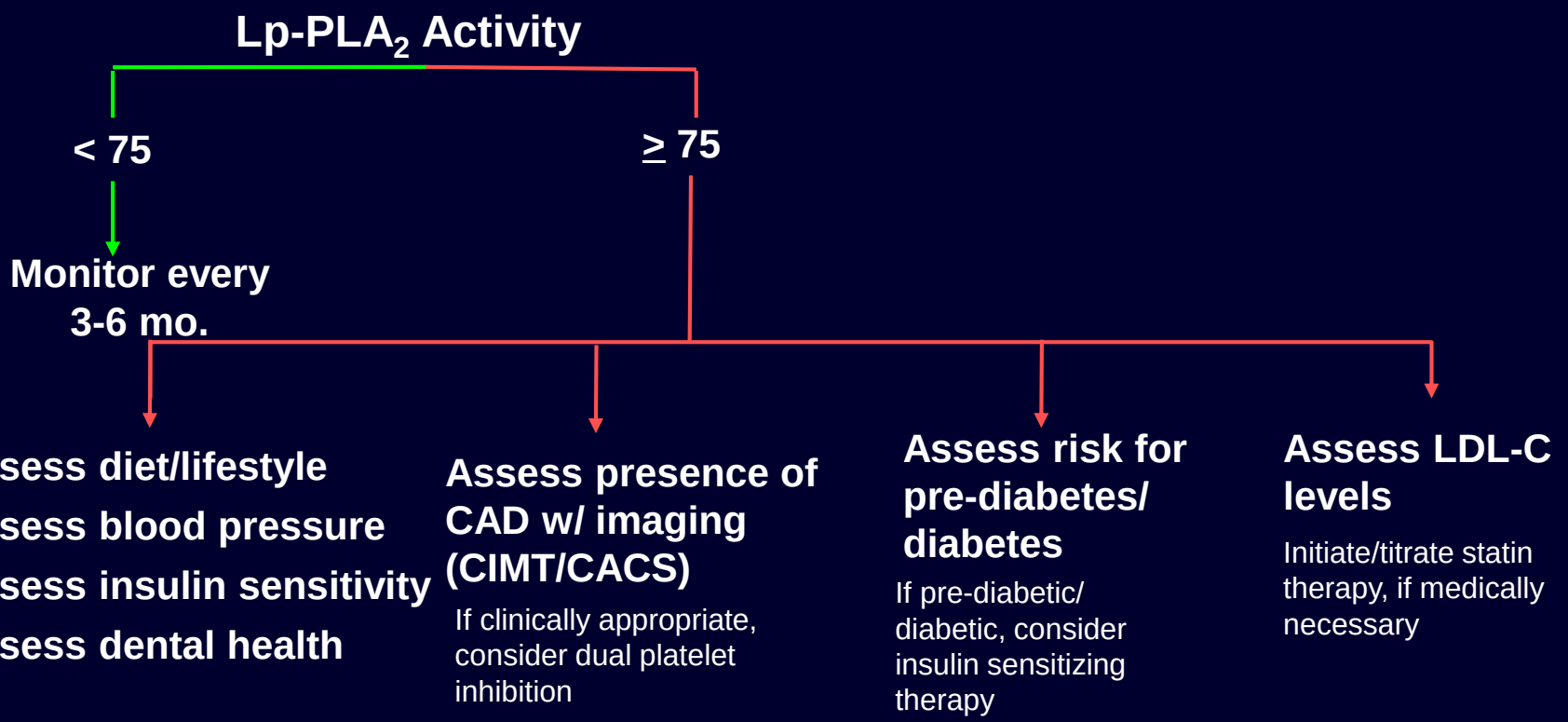
NEXT STEP TESTS TO CONSIDER

ARTERIAL WELLNESS

- MACR—"CANARY IN THE COAL MINE"
  - Great "How is your endothelium doing" test!
  - Cut Point of 3.9 mg/g men, 7.5 mg/g women

- LpPLA2—Arterial Wall specific
  - Localizes with oxLDL
  - Causes ASCVD
  - Increases risk for plaque rupture
  - Uncovers risk missed by MPO and others
  - FDA-cleared 2014 as a screening test to predict future risk of MACE

Evaluation of Lp-PLA2 Levels



NEXT STEPS TO CONSIDER

INSULIN RESISTANCE

- oxLDL—"Macrophage Food"
  - Predictive 5 years in advance of Metabolic Syndrome
  - Associated with LpPLA2 accumulation within vessel wall

Holvoet P, et al. *Future Lipidol*. 2008;3(6):637-649.

NEXT STEPS TO CONSIDER

MYOCARDIAL FUNCTION

- NT-proBNP—”Unhappy Heart Hormone”
  - LV Dysfunction
    - Valvular
    - Hypertension
    - Ischemia
    - Intrinsic
  - Predictive of HF MACE