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
Annual Wellness Panel tests

- **LIPOPROTEINS**
  - NMR LipoProfile with Lipids
  - 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

Females 52%
Males 48%
Individuals with 'normal' ApoB or LDL-P risk identified using the AWP.

Risk identified using the AWP:

- 8841 (41.1%)
- 12652 (58.9%)

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

Abnormal Advanced Lipids:
- HsCRP
- MPO

27% of patients with 'normal' advanced lipids have hidden CV risk.
Atherosclerosis is an inflammatory disease

Markers of inflammation help refine cardiovascular risk estimation

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
60,000 MILE ARTERIAL HIGHWAY!

- Stroke
- Dementia
- Heart Attack
- Heart Failure
- Kidney Failure
- Erectile Dysfunction
- 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

- **Long-Term Risk**
  - Life Long
  - Standard Lipid Panel

- **Mid-Term Risk**
  - Decade(s)
  - Advanced Lipid Testing

- **Near-Term Risk**
  - Years
  - Inflammatory Markers
<table>
<thead>
<tr>
<th>Cholesterol:HDL Ratio</th>
<th>Suggestive of</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 2.8</td>
<td>Optimal plaque regression</td>
</tr>
<tr>
<td>2.8 ≤ X &lt; 3.0</td>
<td>Suboptimal for plaque regression</td>
</tr>
<tr>
<td>3.0 ≤ X ≤ 4.5</td>
<td>Moderate risk for plaque progression</td>
</tr>
<tr>
<td>X &gt; 4.5</td>
<td>High risk for plaque progression</td>
</tr>
<tr>
<td>X &gt; 5.5</td>
<td>Very high risk for plaque progression</td>
</tr>
</tbody>
</table>
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
FIND DISEASE!

What Happens If You Don’t Treat Atherosclerosis?
Percent Cardiovascular Events\(^1\) Within 10 Years by Ultrasound Findings\(^2\)
in 10,000 Asymptomatic Patients with No Diabetes, No High Blood Pressure, No Elevated Cholesterol, and No Treatment

Inflammatory biomarkers across a spectrum of risk

- **F₂-IsoPs**
- **OxLDL**
- **ADMA Microalbumin hsCRP**
- **MPO Lp-PLA₂ Activity**
- **Troponin T CK-MB**

Risk of Disease
Presence of Disease
Disease Activity
Vascular Inflammation
- Myeloperoxidase (MPO)
- Lp-PLA₂ Activity

General Inflammation
- hsCRP
- Endothelial Damage
- Urinary Microalbumin
- ADMA/SDMA

Oxidation/Lifestyle
- Oxidized LDL (OxLDL)
- F₂-Isoprostanates

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 \( \geq 2\) mg/dL
  - JUPITER Trial even when LDL < 130 mg/dL\(^1\)
  - CANTOS Trial when blocking IL-1Beta (which drives hsCRP)\(^2\) $$$$$

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!

ADMA/SDMA DRIVERS

• Insulin Resistance!!!

• Hypertension

• Dyslipidemia

• Presence of Atherosclerosis!

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

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.

Log-rank test: p<0.001 for trend.

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?

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

Evaluation of MPO Levels

MPO

<470
Monitor every 3-6 mo.

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

470-539 or ≥539 in the absence of chest pain

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/titrated 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

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:

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>MEN</th>
<th>WOMEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waist Circumference</td>
<td>&gt;40”</td>
<td>&gt;35”</td>
</tr>
<tr>
<td>HDL Cholesterol*</td>
<td>&lt;40mg/dL</td>
<td>&lt;50mg/dL</td>
</tr>
<tr>
<td>Triglycerides*</td>
<td>&gt;150mg/dL</td>
<td>&gt;150mg/dL</td>
</tr>
<tr>
<td>Blood Pressure*</td>
<td>&gt;130 systolic OR &gt;85 diastolic</td>
<td></td>
</tr>
<tr>
<td>Fasting Plasma Glucose*</td>
<td>≥ 100mg/dL</td>
<td>≥ 100mg/dL</td>
</tr>
</tbody>
</table>

* 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\(^2\)

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 1/3\textsuperscript{rd} 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
  - 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

Lp-PLA₂ Activity

- < 75
  - Monitor every 3-6 mo.
  - Assess diet/lifestyle
  - Assess blood pressure
  - Assess insulin sensitivity
  - Assess dental health

- ≥ 75
  - 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 levels
    - Initiate/titrate statin therapy, if medically necessary
NEXT STEPS TO CONSIDER

INSULIN RESISTANCE

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

NEXT STEPS TO CONSIDER

MYOCARDIAL FUNCTION

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