Focus on Quality

heart.org/quality

GET WITH THE GUIDELINES.
STROKE

GET WITH THE GUIDELINES.
HEART FAILURE

GET WITH THE GUIDELINES.
RESUSCITATION

GET WITH THE GUIDELINES.
AFIB

ACTION Registry-GWTG™

THE GUIDELINE ADVANTAGE™

MISSION: LIFELINE

HOSPITAL Accreditation & Certification

TARGET: STROKE™

TARGET: HF

©2013, American Heart Association
The Main Message

Advanced biomarker testing in aggregate provides refined risk-stratification for cardiovascular disease, and individual biomarkers provide mechanistic explanation and individualized treatment targets, such that targeted therapies will improve overall cardiovascular outcomes.
Main Points

1. ApoB-containing lipoprotein particles are potentially atherogenic; the best clinical measure of overall atherogenic particle burden is a measure of all circulating apoB-containing particles.

2. A mal-adaptive inflammation is a response to the primary injury of atherogenic lipoprotein deposition; elevated serum inflammatory markers indicate that a systemic response has been mounted against atherogenic lipoprotein deposition.

3. Traditional risk-assessment only provides a population-based probability and no insight into individual abnormalities in individual patients.

4. A biology-based risk assessment provides mechanistic explanation for the patients’ atherosclerotic risk, and provides tangible treatment targets.
1. CV Disease Burden is High
2. We know the steps leading to CVD
3. We can assess cardiovascular risk
4. We can treat cardiovascular risk factors
5. Treating cardiovascular risk factors improves outcomes
6. CV Disease Burden is Reduced
Storyline

1. High burden of cardiovascular disease
2. Development of cardiovascular disease
3. Assessment of cardiovascular disease risk
4. Management of CVD risk factors
5. Improving patient outcomes by CVD risk factor management
High Burden of Cardiovascular Disease

Storyline

1. High burden of cardiovascular disease
2. Development of cardiovascular disease
3. Assessment of cardiovascular disease risk
4. Management of CVD risk factors
5. Improving patient outcomes by CVD risk factor management
Development of Cardiovascular Disease

- Genetic Factors
- Intermediate Phenotypes
- Ultimate Phenotype

- Environmental Factors
- DNA
- RNA
- Lipoproteins, Inflammation, BP
- Atherosclerosis

- Biomarkers
- Imaging
Atherosclerosis: Plaque

Genetic Predisposition
- DNA
- Environmental Factors

Gene Expression (RNA)

Atherogenic milieu
- Lipoproteins, IR, BP, shear

Plaque Rupture: ACS

- Thrombosis: ACS
  - Resting chest pain

Fixed Stenosis

Demand Ischemia

- Resting Ischemia
  - Rest Angina

Necrosis/Fibrosis

- Dyspnea

Myocardial Dysfunction

- Dyspnea

End-Organ Damage

- Renal, hepatic dysfunction

Exertional Angina

Dyspnea

Dyspnea

Myocardial Dysfunction

Dyspnea

Rest Angina

Renal, hepatic dysfunction

End-Organ Damage

Resting chest pain

Thrombosis: ACS

Plaque Rupture: ACS

Fixed Stenosis

Demand Ischemia

Resting Ischemia

Necrosis/Fibrosis

Myocardial Dysfunction
Atherosclerosis: Plaque

Fixed Stenosis

Demand Ischemia

Necrosis/Fibrosis

Resting Ischemia

Myocardial Dysfunction

End-Organ Damage

Genetic Predisposition

DNA

Environmental Factors

Gene Expression (RNA)

Atherogenic milieu
(Lipoproteins, IR, BP, shear)

Plaque Rupture: ACS

Resting chest pain

Thrombosis: ACS

Demand Ischemia

Fixed Stenosis

End-Organ Damage

NT-proBNP

hs-cTn, galectin 3

Lipoprotein testing
(FLP, apoB, LDL-P, sdLDL, Lp(a), apoA, HDL-P, HDL classes, sterols, FFA)
Insulin resistance, MS, DM
(insulin, glu, HbA1c, leptin, AN)
Inflammatory markers
(hs-CRP, LpPLA2, MPO, fibrinogen)

Genotyping:
ApoE, Factor II, V, CYP2C9

Creat, cystatin-C
Hepatic panel
VitD, PTH, Ca, Phos

Gene Expression (RNA)

Environmental Factors

Genetic Predisposition DNA
Development of Cardiovascular Disease

Development of Atherosclerosis
Development of Cardiovascular Disease
Atherosclerosis

1. Atherogenic lipoprotein retention
2. Maladaptive inflammation
3. Apoptosis/Necrosis
4. Calcification
5. Fibrosis
Development of Cardiovascular Disease
Atherosclerosis: Major Steps

1. Lipoprotein Deposition
   - Deposition of apoB particles
     • LDL
     • sdLDL
     • Lp(a)
     • Chylo-R
   - Counteracted by apoA/HDL
     • ApoA
     • HDL
     • Large HDL

2. Maladaptive Inflammation
   - Inflammatory Response
     • CRP
     • LpPLA2
     • MPO
     • Fibronigen

3. Apoptosis VSMC LRNC

4. Calcification

5. Fibrosis

Ca-Metabolism
- Ca, Phos
- VitD
- PTH
1. Atherogenic lipoprotein retention
2. Maladaptive inflammation
3. Apoptosis/Necrosis
4. Calcification
5. Fibrosis
Development of Cardiovascular Disease
Atherosclerosis: Lipoprotein Retention

Lipoproteins

Lipids

Proteins (Apoproteins)
Development of Cardiovascular Disease
Atherosclerosis: Lipoprotein Retention

Lipoproteins

Apo B
Intestines
Apo B48
Liver
Apo B100
Chylomicrons
ApoB48

Apo A

VLDL
Apo B100
IDL
Apo B100
LDL
Apo B100
Lp(a)
Apo B100
HDL
Apo Al
Development of Cardiovascular Disease
Atherosclerosis: Lipoprotein Retention

Apo-B lipoproteins
Chylomicrons
VLDL, IDL, LDL, Lp(a)

CRP, Lp-PLA2
Stabilization

Apo-A lipoproteins
HDL

Progression
LDL
Non-HDL

Regression
HDL
1. ApoB-containing lipoprotein particles are atherogenic

- LDL-particles
- Small-dense LDL particles
- Lp(a) particles
- Chylomicron remnants
Development of Cardiovascular Disease
Atherosclerosis: Lipoprotein Retention
Development of Cardiovascular Disease
Atherosclerosis: Lipoprotein Retention

Take Home Message #1:

…all apoB-containing lipoprotein particles are potentially atherogenic…

…the best clinical measure of overall atherogenic particle burden is a measure of all circulating apoB containing particles…

- ApoB, non-HDL-C, (LDL-P)
  - Specific apoB-containing atherogenic particle subtypes:
    - Lp(a)
    - sdLDL
Development of Cardiovascular Disease
Atherosclerosis: Major Steps

Lipoprotein Deposition → Maladaptive Inflammation → Apoptosis VSMC LRNC → Calcification → Fibrosis

Atherogenic LP: TC, ApoB, LDL-C, LDL-P, sdLDL, Lp(a), TG, FFA

Protective LP: ApoA, HDL-C, HDL subclasses

Inflammatory Response
• CRP
• LpPLA2
• Fibronigen

Ca-Metabolism
• Ca, Phos
• VitD
• PTH
2. ApoA-containing lipoprotein particles participate in reverse cholesterol transport, and their maturation by removing excess cholesterol is protective against atherosclerosis.

- ApoA
- HDL particles
Development of Cardiovascular Disease
Atherosclerosis: Major Steps

Lipoprotein Deposition → Maladaptive Inflammation → Apoptosis VSMC LRNC → Calcification → Fibrosis

Deposition of apoB particles
- LDL
- sdLDL
- Lp(a)
- Chylo-R

Inflammatory Response
- CRP
- LpPLA2
- Fibronigen

Counteracted by apoA/HDL
- ApoA
- HDL
- Large HDL

Ca-Metabolism
- Ca, Phos
- VitD
- PTH
Development of Cardiovascular Disease
Atherosclerosis: Major Steps

1. Atherogenic lipoprotein retention
2. Maladaptive inflammation
3. Apoptosis/Necrosis
4. Calcification
5. Fibrosis
Development of Cardiovascular Disease

Atherosclerosis: Mal-Adaptive Inflammation

[Image of a medical scan or tissue sample]
Lipoprotein Deposition

Macrophage recruitment

Cytokine release

CRP \[\xrightarrow{\text{Liver}}\] IL-6 \[\xrightarrow{\text{Plaque}}\] LpPLA-2

Development of Cardiovascular Disease
Atherosclerosis: Mal-Adaptive Inflammation
Development of Cardiovascular Disease
Atherosclerosis: Mal-Adaptive Inflammation

… There is no CRP found in atherosclerotic plaques…

(only in miniscule amounts)
Development of Cardiovascular Disease
Atherosclerosis: Mal-Adaptive Inflammation
Take Home Message #2:

...mal-adaptive inflammation is a response to the primary injury of atherogenic lipoprotein deposition...

...elevated serum inflammatory markers indicate that a systemic response has been mounted against atherogenic lipoprotein deposition...

- CRP
- LpPLA2
- MPO
- (Fibrinogen, IL-6, SAA)
Development of Cardiovascular Disease
Atherosclerosis: Major Steps

Lipoprotein Deposition → Maladaptive Inflammation → Apoptosis VSMC LRNC → Calcification → Fibrosis

Atherogenic LP:
- TC, ApoB, LDL-C, LDL-P, sdLDL, Lp(a), TG, FFA

Protective LP:
- ApoA, HDL-C, HDL subclasses

Inflammatory Markers:
- CRP
- LpPLA2
- MPO
- Fibrinogen

Ca-Metabolism
- Ca, Phos
- VitD
- PTH
Development of Cardiovascular Disease
Atherosclerosis: Major Steps

1. Atherogenic lipoprotein retention
2. Maladaptive inflammation
3. Apoptosis/Necrosis
4. Calcification
5. Fibrosis
Development of Cardiovascular Disease
Atherosclerosis: Calcification

Ox-LDL, AngII, TNF-alpha

VSMC

Osteoblastic Transformation

ACP
Amorphous Calcium Phosphate

Nucleation

CHA
Calcium Hydroxyapatite

Bone Formation: Osteoblasts (ALP)

Bone Degradation (Osteoclasts: Acidic)

Development of Cardiovascular Disease
Atherosclerosis: Major Steps

Lipoprotein Deposition → Maladaptive Inflammation → Apoptosis VSMC LRNC → Calcification → Fibrosis

**Atherogenic LP:**
TC, ApoB, LDL-C, LDL-P, sdLDL, Lp(a), TG, FFA

**Ca-Metabolism**
Ca, Phos, VitD, PTH

**Protective LP:**
ApoA, HDL-C, HDL subclasses

**Inflammatory Markers:**
CRP, LpPLA2, Fibrinogen
Storyline

1. High burden of cardiovascular disease
2. Development of cardiovascular disease
3. Assessment of cardiovascular disease risk
4. Management of CVD risk factors
5. Improving patient outcomes by CVD risk factor management
Advanced biomarker testing in aggregate provides refined risk-stratification for cardiovascular disease, and individual biomarkers provide mechanistic explanation and individualized treatment targets, such that targeted therapies will improve overall cardiovascular outcomes.
Assessment of Cardiovascular Risk

1. Traditional paradigm
   - Population-based
   - Probabilistic

2. Biology-based paradigm
   - Individualized
   - Mechanistic and pragmatic
Assessment of Cardiovascular Risk

1. Traditional paradigm
   – Population-based
   – Probabilistic

2. Biology-based paradigm
   – Individualized
   – Mechanistic and pragmatic
Assessment of Cardiovascular Risk
Traditional Risk Assessment

1. Age
2. Gender
3. Tobacco
4. Blood pressure
5. Total cholesterol
6. HDL-cholesterol
7. (Diabetes)

Framingham, MA

http://hp2010.nhlbihin.net/atpiii/calculator.asp
...The FRS tells you that for example, the probability of a cardiovascular event in a given individual is 15% in the next 10 years...

“Probability Paradigm”
Assessment of Cardiovascular Risk
Traditional Risk Assessment

1. Low Risk: < 10% 10-Year Risk

2. Intermediate Risk: 10-20% 10-Year Risk

3. High Risk: > 10% 10-Year Risk
Assessment of Cardiovascular Risk
Traditional Risk Assessment

…This all sounds very nice, but…

…Almost not a single physician actually calculates the Framingham score…

…They “eyeball” the risk-factors; probably count them and come up with a “ballpark” estimate…

“I think this patient is probably low risk”
Assessment of Cardiovascular Risk
Traditional Risk Assessment
Assessment of Cardiovascular Risk
Traditional Risk Assessment

Lisa: Age 38; no heart disease

- Exercises
- Height: 5’3”
- Weight: 165
- No diabetes
- No tobacco
- Pre-menopausal
Assessment of Cardiovascular Risk

Traditional Risk Assessment

What is her 10-year risk?

1. < 1%
2. 1-10%
3. 10-20%
4. > 20%

Answer <1%
“Low Risk”

LOW RISK
Main Point #3

...the traditional evaluation only provides a population-based probability and no insight into individual abnormalities in individual patients...
Assessment of Cardiovascular Risk

1. Traditional paradigm
   - Population-based
   - Probabilistic

2. Biology-based paradigm
   - Individualized
   - Mechanistic and pragmatic
Atherosclerosis: Plaque

Fixed Stenosis

Demand Ischemia

Necrosis/Fibrosis

Resting Ischemia

Myocardial Dysfunction

End-Organ Damage

Genetic Predisposition

DNA

Gene Expression (RNA)

Atherogenic milieu

(Lipoproteins, IR, BP, shear)

Plaque Rupture: ACS

Thrombosis: ACS

Resting chest pain

Genotyping:
ApoE, Factor II, V CYP2C9

Lipoprotein testing
(FLP, apoB, LDL-P, sdLDL, Lp(a), apoA, HDL-P, HDL classes, sterols, FFA)

Insulin resistance, MS, DM
(insulin, glu, HbA1c, leptin, AN)

Inflammatory markers
(hs-CRP, LpPLA2, MPO, fibrinogen)

NT-proBNP

hs-cTn, galectin 3

hs-cTn

hs-cTn, galectin 3

NT-proBNP

creat, cystatin-C
Hepatic panel
VitD, PTH, Ca, Phos

Resting Ischemia

Fixed Stenosis

End-Organ Damage

Myocardial Dysfunction

Necrosis/Fibrosis

Resting chest pain

Thrombosis: ACS

Plaque Rupture: ACS

Atherosclerosis: Plaque

Lipoprotein testing
(FLP, apoB, LDL-P, sdLDL, Lp(a), apoA, HDL-P, HDL classes, sterols, FFA)

Insulin resistance, MS, DM
(insulin, glu, HbA1c, leptin, AN)

Inflammatory markers
(hs-CRP, LpPLA2, MPO, fibrinogen)

creat, cystatin-C
Hepatic panel
VitD, PTH, Ca, Phos

Resting chest pain

Thrombosis: ACS

Plaque Rupture: ACS

Atherosclerosis: Plaque

Lipoprotein testing
(FLP, apoB, LDL-P, sdLDL, Lp(a), apoA, HDL-P, HDL classes, sterols, FFA)

Insulin resistance, MS, DM
(insulin, glu, HbA1c, leptin, AN)

Inflammatory markers
(hs-CRP, LpPLA2, MPO, fibrinogen)

creat, cystatin-C
Hepatic panel
VitD, PTH, Ca, Phos
1. Evaluating genetic susceptibility
2. Evaluating the current atherogenic milieu
3. Evaluating myocardial ischemia, necrosis
4. Evaluating myocardial fibrosis
5. Evaluating myocardial dysfunction
6. Evaluating end-organ damage
Assessment of Cardiovascular Risk
Biology-Based Evaluation

1. Evaluating genetic susceptibility
   1. Family history
   2. Genotypes (DNA; SNP’s)
2. Evaluating the current atherogenic milieu
3. Evaluating myocardial ischemia, necrosis
4. Evaluating myocardial fibrosis
5. Evaluating myocardial dysfunction
6. Evaluating end-organ damage
1. Genotyping for risk-stratification
   - Genes identified in GWAS
2. Genotyping for intermediate phenotypes
   - ApoE: LDL vs. TG-related problems
     • Aids with dietary counseling
     • ?Aids with statin versus fibrate selection
   - CYP2C9 and VKORC1: Aids with warfarin dosing
   - CYP2C19: aids with clopidogrel resistance
1. Evaluating genetic susceptibility
2. Evaluating the current atherogenic milieu
   1. (Gene expression: RNA)
   2. Lipoproteins
      1. Atherogenic particle burden: apoB-particles
      2. Protective particles: apoA/HDL particles
   3. Inflammation: CRP, LpPLA2, MPO, fibrinogen
   4. Insulin-resistant states: Glu, HbA1c, insulin, leptin, adiponectin, etc.
3. Evaluating myocardial ischemia, necrosis
4. Evaluating myocardial fibrosis
5. Evaluating myocardial dysfunction
6. Evaluating end-organ damage
Development of Cardiovascular Disease
Atherosclerosis: Lipoprotein Retention

Progression
- Apo-B lipoproteins
  - Chylomicrons
  - VLDL, IDL, LDL, Lp(a)
- LDL
- Non-HDL

CRP, Lp-PLA2
Stabilization

Regression
- Apo-A lipoproteins
  - HDL
- HDL

Non-HDL
Assessment of Cardiovascular Risk
Biology-Based Evaluation: Lipoproteins

- **Apo B**
  - Intestines: Apo B48
  - Liver: Apo B100

- **Apo A**
  - Chylomicrons: Apo B48
  - VLDL: Apo B100
  - IDL: Apo B100
  - LDL: Apo B100
  - Lp(a): Apo B100
  - HDL: Apo AI
Assessment of Cardiovascular Risk
Biology-Based Evaluation: Lipoproteins

- **Total Cholesterol**
  - Apo B
  - Apo A

- **Intestines**
  - Apo B48

- **Liver**
  - Apo B100

- **Chylomicrons**
  - Apo B48

- **VLDL**
  - Apo B100

- **IDL**
  - Apo B100

- **LDL**
  - Apo B100

- **HDL**
  - Apo A1

- **Lp(a)**
  - Apo B100
Assessment of Cardiovascular Risk
Biology-Based Evaluation: Lipoproteins

ApoB or Non-HDL-C

Apo B

Apo B48
Intestines
Apo B100
Liver

Apo B100

Chylomicrons
ApoB48
VLDL
Apo B100
IDL
Apo B100
LDL
Apo B100
Lp(a)
Apo B100

Apo A
HDL
Apo Al
Assessment of Cardiovascular Risk
Biology-Based Evaluation: Lipoproteins
Assessment of Cardiovascular Risk
Biology-Based Evaluation: Lipoproteins

Apo B
- Intestines
  - Apo B48
- Liver
  - Apo B100

Apo A

Chylomicrons
- Apo B48

VLDL
- Apo B100

IDL
- Apo B100

LDL
- Apo B100

Lp(a)
- Apo B100

HDL
- Apo AI

sdLDL
Assessment of Cardiovascular Risk
Biology-Based Evaluation: Lipoproteins

- Apo B
  - Intestines: Apo B48
  - Liver: Apo B100
- Apo A
- Chylomicrons: ApoB48
- VLDL: Apo B100
- IDL: Apo B100
- LDL: Apo B100
- Lp(a): Apo B100
- HDL: Apo AI

Lp(a)-C or Lp(a)-mass

Lp(a): Apo B100
• Overall atherogenic particle burden
  – ApoB and non-HDL-C
  – LDL-P (captures about 90%)
• Specific atherogenic lipoprotein subtypes
  – sdLDL
  – Lp(a)-C and Lp(a) mass
Assessment of Cardiovascular Risk
Biology-Based Evaluation: Lipoproteins

- ApoB versus LDL-C
  - In most studies, apoB better than LDL-C
- ApoB versus LDL-P
  - Mixed data
- sdLDL provides incremental information over LDL-C
- Lp(a) provides independent, incremental information
Assessment of Cardiovascular Risk
Biology-Based Evaluation: Lipoproteins

Relative Risk

… in 18 primary and secondary prevention studies…

14 studies: apoB superior to LDL-C

2 studies: apoB and LDL-C are equivalent

2 studies: LDL-C was superior to apoB
Net Proportion of Subjects Correctly Reclassified Using Model including sdLDL-C in Females: 6%

Females:
AUC = 0.81
AUC = 0.72
p = 0.05

All Patients:
AUC = 0.807
AUC = 0.802
p = 0.76

Males:
AUC = 0.81
AUC = 0.79
p = 0.43

Females:
AUC = 0.81
AUC = 0.72
p = 0.05

Assessment of Cardiovascular Risk
Biology-Based Evaluation: Lipoproteins

Joshi, Voros et al. Manuscript in review.
Assessment of Cardiovascular Risk
Biology-Based Evaluation: Lipoproteins

Assessment of Cardiovascular Risk
Biology-Based Evaluation: Lipoproteins

Figure 1. Risk of Myocardial Infarction by Extreme Levels of Lipoprotein(a) in the General Population

<table>
<thead>
<tr>
<th>Lipoprotein(a)</th>
<th>Participants, No.</th>
<th>Events, No.</th>
<th>Multivariable Adjusted</th>
<th>Multivariable Adjusted and KIV-2 Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentile</td>
<td>mg/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;95th</td>
<td>&gt;117</td>
<td>376</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>90th-95th</td>
<td>77-117</td>
<td>450</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>67th-89th</td>
<td>30-76</td>
<td>1731</td>
<td>155</td>
<td></td>
</tr>
<tr>
<td>22nd-66th</td>
<td>5-29</td>
<td>3385</td>
<td>241</td>
<td></td>
</tr>
<tr>
<td>&lt;22nd [Reference]</td>
<td>&lt;5</td>
<td>1582</td>
<td>104</td>
<td></td>
</tr>
</tbody>
</table>

Hazard ratios (HRs) were multivariable adjusted for age, sex, total cholesterol (corrected for the lipoprotein[a] contribution), triglycerides, body mass index, hypertension, diabetes mellitus, smoking, and use of lipid-lowering therapy and for women also for menopause and hormone therapy or for all of these variables as well as kringle IV type 2 (KIV-2) genotype. P values are test for trend of hazard ratios where lipoprotein(a) groups with increasing levels were coded 1, 2, 3, 4, and 5. Values are from the 1991-1994 examination of the Copenhagen City Heart Study with up to 16 years of follow-up (n=7524). Controls used in the Copenhagen Ischemic Heart Disease Study (n=1200) were excluded from analysis. CI indicates confidence interval.
Assessment of Cardiovascular Risk
Biology-Based Evaluation: Inflammation-CRP

Ridker et al. NEJM-JUPITER Trial.
Assessment of Cardiovascular Risk
Biology-Based Evaluation: LpPLA2

Assessment of Cardiovascular Risk
Biology-Based Evaluation: LpPLA2

Assessment of Cardiovascular Risk
Biology-Based Evaluation

1. Evaluating genetic susceptibility
2. Evaluating the current atherogenic milieu
3. Evaluating myocardial ischemia, necrosis
   1. High-sensitivity cardiac troponin
4. Evaluating myocardial fibrosis
5. Evaluating myocardial dysfunction
6. Evaluating end-organ damage
Assessment of Cardiovascular Risk
Biology-Based Evaluation: hs-cTn

Assessment of Cardiovascular Risk
Biology-Based Evaluation

1. Evaluating genetic susceptibility
2. Evaluating the current atherogenic milieu
3. Evaluating myocardial ischemia, necrosis
4. Evaluating myocardial fibrosis
   1. Galectin-3
5. Evaluating myocardial dysfunction
6. Evaluating end-organ damage
Assessment of Cardiovascular Risk
Biology-Based Evaluation

Gullestad et al. ESC 2011.
Assessment of Cardiovascular Risk
Biology-Based Evaluation

1. Evaluating genetic susceptibility
2. Evaluating the current atherogenic milieu
3. Evaluating myocardial ischemia, necrosis
4. Evaluating myocardial fibrosis
5. Evaluating myocardial dysfunction
   1. NT-proBNP
6. Evaluating end-organ damage
Assessment of Cardiovascular Risk
Biology-Based Evaluation: pro-NT-BNP

Log rank P = .03

### Event-free survival

- **NT-proBNP (N=75)**
- **Standard-of-care (N=76)**

<table>
<thead>
<tr>
<th>Treatment arm</th>
<th>Number at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>NT-proBNP</td>
<td>74 68 67 65 62 57 47 46 42 40 39</td>
</tr>
<tr>
<td>SOC</td>
<td>75 69 62 56 53 48 37 35 34 32 30</td>
</tr>
</tbody>
</table>

Assessment of Cardiovascular Risk
Biology-Based Evaluation

1. Evaluating genetic susceptibility
2. Evaluating the current atherogenic milieu
3. Evaluating myocardial ischemia, necrosis
4. Evaluating myocardial fibrosis
5. Evaluating myocardial dysfunction
6. Evaluating end-organ damage
   1. Renal dysfunction
      1. Abnormal calcium/phosphorus metabolism
         1. Ca, Phos, PTH, VitD
   2. Hepatic dysfunction
   3. Cerebral ischemia
      1. NR2 antibody
Main Point #4

...a biology-based risk assessment provides mechanistic explanation for the patients’ atherosclerotic risk, and provides tangible treatment targets...
Assessment of Cardiovascular Risk
Biology-Based Risk Assessment

Traditional Risk Assessment

1. Age: 38
2. Gender: Female
3. Total cholesterol: 165
4. HDL cholesterol: 48
5. Tobacco: Never
6. High BP: Yes

Rx
✓ Exercise
✓ Diet
✓ Flu shot
✓ Pap-Smear
✓ Seatbelt

LOW RISK

PR Consent on File at PHI
Assessment of Cardiovascular Risk
Biology-Based Risk Assessment

Comprehensive Assessment

Genetic Predisposition

1. **Family History:**
   - Father had CABG

2. **Genotyping:**
   - Apo E3 (E3/E3)
   - E-selectin: -/-
   - AGT: +/-

PR Consent on File at PHI
Assessment of Cardiovascular Risk
Biology-Based Risk Assessment

Comprehensive Assessment

Phenotyping

1. Lipoproteins
   • ApoB: 74 mg/dL
   • LDL-C: 111 mg/dL
     • LDL size: 21.54 nm
   • Lp(a): 9 mg/dL
   • ApoA: 121 mg/dL
   • HDL: 58 mg/dL
   • TG: 79 mg/dL

2. Inflammation
   • CRP: 0.3 mg/dL
   • Lp-PLA2: 160 ng/mL

3. Blood Pressure:
   • 143/89
Assessment of Cardiovascular Risk

Biology-Based Risk Assessment

Comprehensive Assessment

Phenotyping

Imaging: Coronary Calcium

Has calcified plaque:

- Calcium score: 13
- Percentile: 98%

98% of women her age should have less calcium!

High Risk

- Exercise
- Diet
- Flu shot
- Pap-Smear
- Seatbelt

Rx

- Exercise
- Diet
- Vytorin
- Norvasc
- Folic acid

HIGH RISK
Main Points

1. ApoB-containing lipoprotein particles are potentially atherogenic; the best clinical measure of overall atherogenic particle burden is a measure of all circulating apoB-containing particles

2. A mal-adaptive inflammation is a response to the primary injury of atherogenic lipoprotein deposition; elevated serum inflammatory markers indicate that a systemic response has been mounted against atherogenic lipoprotein deposition

3. Traditional risk-assessment only provides a population-based probability and no insight into individual abnormalities in individual patients

4. A biology-based risk assessment provides mechanistic explanation for the patients’ atherosclerotic risk, and provides tangible treatment targets
Atherosclerosis: Plaque

Fixed Stenosis

Demand Ischemia

Necrosis/Fibrosis

Resting Ischemia

Myocardial Dysfunction

End-Organ Damage

Genetic Predisposition

DNA

Environmental Factors

Gene Expression (RNA)

Atherogenic milieu

(Lipoproteins, IR, BP, shear)

Plaque Rupture: ACS

Resting chest pain

Thrombosis: ACS

Demand Ischemia

Fixed Stenosis

Lipoprotein testing
(FLP, apoB, LDL-P, sdLDL, Lp(a), apoA, HDL-P, HDL classes, sterols, FFA)

Insulin resistance, MS, DM
(insulin, glu, HbA1c, leptin, AN)

Inflammatory markers
(hs-CRP, LpPLA2, MPO, fibrinogen)

NT-proBNP

hs-cTn, galectin 3

hs-cTn

creat, cystatin-C
Hepatic panel
VitD, PTH, Ca, Phos

Genotyping:
ApoE, Factor II, V CYP2C9

Genetic Predisposition
DNA
Advanced biomarker testing in aggregate provides refined risk-stratification for cardiovascular disease, and individual biomarkers provide mechanistic explanation and individualized treatment targets, such that targeted therapies will improve overall cardiovascular outcomes.
Comprehensive Cardiovascular Risk Stratification

Role of Biomarkers

Szilard Voros, MD, FACC, FSCCT, FAHA