Comprehensive Cardiovascular Risk Stratification

Role of Biomarkers

Szilard Voros, MD, FACC, FSCCT, FAHA
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.
Storyline

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

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

Environmental Factors

Genetic Factors

Intermediate Phenotypes

Ultimate Phenotype

DNA

RNA

Lipoproteins, Inflammation, BP

Atherosclerosis

Biomarkers

Imaging
Atherosclerosis: Plaque

- Plaque Rupture: ACS
  - Resting chest pain
  - Thrombosis: ACS
    - Resting chest pain
  - Fixed Stenosis
    - Fixed Stenosis
  - Demand Ischemia
    - Demand Ischemia
  - Necrosis/Fibrosis
    - Necrosis/Fibrosis
- End-Organ Damage
  - Renal, hepatic dysfunction
  - Dyspnea

- Myocardial Dysfunction
  - Dyspnea
  - Rest Angina
  - Exertional Angina

- Resting Ischemia
  - Rest Angina

Myocardial Dysfunction:

- Dyspnea

Necrosis/Fibrosis:

- Dyspnea

Atherogenic milieu:

- Lipoproteins, IR, BP, shear

Gene Expression (RNA):

- Genetic Predisposition DNA
  - Genetic Predisposition DNA
- Environmental Factors

Genetic Predisposition:

- DNA

Environmental Factors:

- Gene Expression (RNA)
Atherosclerosis: Plaque

Fixed Stenosis

Demand Ischemia

Necrosis/Fibrosis

Resting Ischemia

Myocardial Dysfunction

End-Organ Damage

Plaque Rupture: ACS

Resting chest pain

Thrombosis: ACS

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)

Gene Expression (RNA)

Atherogenic milieu (Lipoproteins, IR, BP, shear)

Genotyping: ApoE, Factor II, V CYP2C9

Genetic Predisposition DNA

Environmental Factors

creat, cystatin-C

Hepatic panel

VitD, PTH, Ca, Phos

NT-proBNP

hs-cTn, galectin 3

hs-cTn

hs-cTn
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

Lipoprotein Deposition

Maladaptive Inflammation

Apoptosis VSMC LRNC

Calcification

Fibrosis

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

Inflammatory Response
- CRP
- LpPLA2
- MPO
- Fibronigen

Ca-Metabolism
- Ca, Phos
- VitD
- PTH

Counteracted by apoA/HDL
- ApoA
- HDL
- Large HDL
Development of Cardiovascular Disease
Atherosclerosis: Major Steps

1. Atherogenic lipoprotein retention
2. Maladaptive inflammation
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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
- Apo A
  - Liver
    - Apo B100
  - HDL
    - Apo A1
  - LDL
    - Apo B100
  - IDL
    - Apo B100
  - VLDL
    - Apo B100
  - Chylomicrons
    - Apo B48
  - Lp(a)
    - Apo B100
Development of Cardiovascular Disease
Atherosclerosis: Lipoprotein Retention

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

Progression
LDL
Non-HDL

CRP, Lp-PLA2
Stabilization

Apo-A lipoproteins
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
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Atherosclerosis: Major Steps

1. Atherogenic lipoprotein retention
2. Maladaptive inflammation
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5. Fibrosis
Development of Cardiovascular Disease
Atherosclerosis: Mal-Adaptive Inflammation
Development of Cardiovascular Disease
Atherosclerosis: Mal-Adaptive Inflammation

- Lipoprotein Deposition
- Macrophage recruitment
- Cytokine release
- CRP
- Liver
- IL-6
- Plaque
- LpPLA-2
... 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

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

1. Atherogenic lipoprotein retention
2. Maladaptive inflammation
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5. Fibrosis
Development of Cardiovascular Disease
Atherosclerosis: Calcification

Ox-LDL, AngII, TNF-alpha

VSMC

Osteoblastic Transformation

Bone Formation: Osteoblasts (ALP)

ACP
Amorphous Calcium Phosphate

Nucleation

CHA
Calcium Hydroxyapatite

Bone Degradation (Osteoclasts: Acidic)

Development of Cardiovascular Disease
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- Fibrinogen

**Ca-Metabolism**
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- VitD
- PTH
Atherosclerosis: Plaque

Fixed Stenosis

Demand Ischemia

Resting Ischemia

Myocardial Dysfunction

Necrosis/Fibrosis

End-Organ Damage

Plaque Rupture: ACS

Resting chest pain

Thrombosis: ACS

Genetic Predisposition

Genotyping: ApoE, Factor II, V CYP2C9

DNA

Gene Expression (RNA)

Atherogenic milieu (Lipoproteins, IR, BP, shear)

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)

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hs-cTn, galectin 3

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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
Assessment of Cardiovascular Risk
Traditional Risk Assessment

...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"
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

PR Consent on File at PHI
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

- Plaque Rupture: ACS
  - Resting chest pain
  - Myocardial Dysfunction
    - End-Organ Damage
  - Necrosis/Fibrosis
    - Necrosis/Fibrosis
  - Resting Ischemia
  - Demand Ischemia
  - Fixed Stenosis

Atherogenic milieu
- Lipoproteins, IR, BP, shear

Gene Expression (RNA)

Genotyping:
- ApoE, Factor II, V, CYP2C9

Genetic Predisposition
- DNA

Environmental Factors
- Creat, cystatin-C
- Hepatic panel
  - VitD, PTH, Ca, Phos
- NT-proBNP
- hs-cTn, galectin 3
- hs-cTn

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
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. 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
Assessment of Cardiovascular Risk
Evaluation of Genetic Susceptibility: Genotyping

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
Assessment of Cardiovascular Risk
Biology-Based Evaluation

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

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

Progression
LDL
Non-HDL

CRP, Lp-PLA2
Stabilization

Apo-A lipoproteins
HDL

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

- **Intestines**: Apo B48
- **Liver**: Apo B100
- **Chylomicrons**: ApoB48
- **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
- Intestines: Apo B48
- Liver: Apo B100
- Chylomicrons: Apo B48
- 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

ApoB or Non-HDL-C

Apo B

Apo A

Intestines
Apo B48

Liver
Apo B100

Chylomicrons
Apo B48

VLDL
Apo B100

IDL
Apo B100

LDL
Apo B100

HDL
Apo Al

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

- **Intestines**: Apo B48
- **Liver**: Apo B100
- **Chylomicrons**: Apo B48
- **VLDL**: Apo B100
- **IDL**: Apo B100
- **LDL**: Apo B100
- **Lp(a)**: Apo B100
- **HDL**: Apo A1

**LDL-C or LDL-P**
Assessment of Cardiovascular Risk
Biology-Based Evaluation: Lipoproteins

Apo B

Intestines
Apo B48

Liver
Apo B100

VLDL
Apo B100

IDL
Apo B100

LDL
Apo B100

Lp(a)
Apo B100

HDL
Apo Al

Apo A

Chylomicrons
ApoB48

sdLDL
Assessment of Cardiovascular Risk
Biology-Based Evaluation: Lipoproteins

Apo B
Intestines
Apo B48

Liver
Apo B100

Apo B

Chylomicrons
Apo B48

VLDL
Apo B100

IDL
Apo B100

LDL
Apo B100

Lp(a)
Apo B100

HDL
Apo AI

Apo A

Lp(a)-C or Lp(a)-mass
Assessment of Cardiovascular Risk
Biology-Based Evaluation: Lipoproteins

- Overall atherogenic particle burden
  - ApoB and non-HDL-C
  - LDL-P (captures about 90%)

- Specific atherogenic lipoprotein sub-types
  - sdLDL
  - Lp(a)-C and Lp(a) mass
• 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
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>
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<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

<table>
<thead>
<tr>
<th>Study</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>MONICA</td>
<td>1.37</td>
<td>(1.16, 1.62)</td>
</tr>
<tr>
<td>WOSCOPS</td>
<td>1.19</td>
<td>(1.06, 1.33)</td>
</tr>
<tr>
<td>WHS</td>
<td>1.73</td>
<td>(0.87, 3.44)</td>
</tr>
<tr>
<td>ARIC</td>
<td>1.78</td>
<td>(1.33, 2.38)</td>
</tr>
<tr>
<td>Brilakis</td>
<td>1.28</td>
<td>(1.06, 1.54)</td>
</tr>
<tr>
<td>HELICOR</td>
<td>1.61</td>
<td>(1.06, 2.44)</td>
</tr>
<tr>
<td>ROTTERDAM</td>
<td>2.36</td>
<td>(1.58, 3.52)</td>
</tr>
</tbody>
</table>

Random effects pooled estimates (95% CI)

1.47 (1.25, 1.72)

Favors no CVD  Favors CVD
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

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.
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

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

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
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

- Vytorin
- Norvasc
- Folic acid
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
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- Fixed Stenosis
- Demand Ischemia
- Necrosis/Fibrosis
- Resting Ischemia
- Myocardial Dysfunction
- End-Organ Damage

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- DNA
- Gene Expression (RNA)

Atherogenic milieu
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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

Environmental Factors

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

hscTn, galectin 3

hs-cTn

NT-proBNP
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

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