Pharmacological Modification of Biomarkers and CV Risk

Jin-Ok Jeong
Cardiovascular Center
Chungnam National University Hospital
# The Ideal Biomarker

<table>
<thead>
<tr>
<th>2007</th>
<th>2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitive and specific</td>
<td>Either highly sensitive (diagnostic) or Highly specific (treatment effect)</td>
</tr>
<tr>
<td>Reflects disease severity</td>
<td>Reflects abnormal physiology/biochemistry</td>
</tr>
<tr>
<td>Correlates with prognosis</td>
<td>Prognosis is most meaningful if level is clinically actionable</td>
</tr>
<tr>
<td>Should aid in clinical decision making</td>
<td>Should be used as a basis for specific “biomarker guided-therapy”</td>
</tr>
<tr>
<td>Level should decrease following effective therapy</td>
<td>“Bio-monitoring” during treatment is an effective surrogate of improvement</td>
</tr>
</tbody>
</table>

Maisel, JACC 2011
Biomarkers

1. BNP
2. Arterial stiffness
3. LDL/ HDL
4. hs-CRP
5. Lp-PLA
6. Vascular calcification
Biomarkers

1. BNP
2. Arterial stiffness
3. LDL/ HDL
4. hs-CRP
5. Lp-PLA
6. Vascular calcification
BNP in Heart Failure

Mills RM. JACC 2008;51:2336
## Therapies with Effects on B-Type Natriuretic Peptide Levels

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Effect on BNP/NT-proBNP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuresis</td>
<td>↓</td>
</tr>
<tr>
<td>ACE-I</td>
<td>↓</td>
</tr>
<tr>
<td>ARB</td>
<td>↓</td>
</tr>
<tr>
<td>β-blockers</td>
<td>Some transiently ↑, most ↓</td>
</tr>
<tr>
<td>Aldosterone antagonists</td>
<td>↓</td>
</tr>
<tr>
<td>BiV pacing</td>
<td>↓</td>
</tr>
<tr>
<td>Exercise</td>
<td>↓</td>
</tr>
<tr>
<td>Rate control of AF</td>
<td>↓</td>
</tr>
<tr>
<td>BNP infusions</td>
<td>↓ N-BNP, ↑ BNP then ↓</td>
</tr>
</tbody>
</table>
Guided therapy combined analyses

Meta analysis of publication data

Pooled patient data from all available trials

HR=0.59 [0.41-0.84], p<0.001

Clinically-guided
BNP guided HF therapy: STARS

Outcomes as a function of response to guided therapy

- **High/High** group: Mean CV events = 1.57*
- **Low/High** group: Mean CV events = 0.71
- **High/Low** group: Mean CV events = 0.46
- **Low/Low** group: Mean CV events = 0.50

* p = 0.003 versus Low/Low group, p = 0.002 versus High/Low group
Summary of natriuretic peptide testing in ADHF

- Baseline measurement for diagnosis
- Most HF medication decrease BNP (ACEi/ARB, BB, MRA, Diuretics)

- Pre-discharge measurement to assess treatment response:
  - If rise >30%: discharge delayed, ↑Rx
  - If change <30%: possible discharge delay
  - If fall >30%: discharge authorized
Biomarkers

1. BNP
2. Arterial stiffness
3. LDL/ HDL
4. hs-CRP
5. Lp-PLA
6. Vascular calcification
Pulse Wave Velocity

- LV contraction $\rightarrow$ blood ejection into Asc aorta $\rightarrow$ generate pulse wave

- **Pulse wave velocity**
  - Propagation velocity of pulse wave
  - Index of arterial distensibility and stiffness
  - Higher velocity: higher arterial rigidity, lower distensibility
Raised PWV

- Established CV risk factors
  Age, hypercholesterolemia, type II diabetes, sedentary lifestyle

- Independent predictor of CV and all cause mortality in hypertensives
  5m/s $\uparrow \rightarrow 1.34$ all cause mortality, 1.51 CV mortality
  Aortic PWV $>13$m/s, strong predictor of CV mortality

- Stroke (relative risk = 1.39 for each 4 m/sec increase) independently of classical CV risk factors
Aortic stiffness is reduced beyond BP lowering

Short term (0-8 days)

Long term (1-6 months)

# Anti-hypertensives & Increased Aortic Stiffness

## Meta-analysis of RCTs: ACEi vs Placebo

### PWV

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean Difference</th>
<th>SE</th>
<th>Weight</th>
<th>IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ahimastos 2007</td>
<td>-2.1</td>
<td>0.31</td>
<td>35.3%</td>
<td>-2.10 [-2.71, -1.49]</td>
</tr>
<tr>
<td>Ahimastos 2008</td>
<td>-2.1</td>
<td>0.36</td>
<td>26.2%</td>
<td>-2.10 [-2.81, -1.39]</td>
</tr>
<tr>
<td>Mitchell 2007</td>
<td>-0.9</td>
<td>0.35</td>
<td>27.7%</td>
<td>-0.90 [-1.59, -0.21]</td>
</tr>
<tr>
<td>Rahman 2007 A</td>
<td>-1.2</td>
<td>1.27</td>
<td>2.1%</td>
<td>-1.20 [-3.69, 1.29]</td>
</tr>
<tr>
<td>Rahman 2007 B</td>
<td>-2.1</td>
<td>0.8</td>
<td>5.3%</td>
<td>-2.10 [-3.87, -0.33]</td>
</tr>
<tr>
<td>Yu 2006</td>
<td>-0.3</td>
<td>1</td>
<td>3.4%</td>
<td>-0.30 [-2.26, 1.66]</td>
</tr>
</tbody>
</table>

Total (95% CI): 100.0% -1.69 [-2.05, -1.33]

Heterogeneity: Chi² = 10.48, df = 5 (P = 0.06); I² = 52%

Test for overall effect: Z = 9.16 (P < 0.00001)

### AIx

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean Difference</th>
<th>SE</th>
<th>Weight</th>
<th>IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ahimastos 2008</td>
<td>-4.4</td>
<td>0.36</td>
<td>25.2%</td>
<td>-4.40 [-5.11, -3.69]</td>
</tr>
<tr>
<td>Dart 2001</td>
<td>-4.7</td>
<td>0.68</td>
<td>23.6%</td>
<td>-4.70 [-6.03, -3.37]</td>
</tr>
<tr>
<td>Deary 2002 (F)</td>
<td>-1</td>
<td>5.55</td>
<td>3.4%</td>
<td>-1.00 [-11.88, 9.88]</td>
</tr>
<tr>
<td>Deary 2002 (M)</td>
<td>-5</td>
<td>3.48</td>
<td>7.3%</td>
<td>-5.00 [-11.82, 1.82]</td>
</tr>
<tr>
<td>Mitchell 2007</td>
<td>-0.9</td>
<td>0.36</td>
<td>25.2%</td>
<td>-0.90 [-1.61, -0.19]</td>
</tr>
<tr>
<td>Rahman 2007 A</td>
<td>-9.1</td>
<td>7.41</td>
<td>2.0%</td>
<td>-9.10 [-23.82, 5.42]</td>
</tr>
<tr>
<td>Rahman 2007 B</td>
<td>-16.2</td>
<td>7.68</td>
<td>1.9%</td>
<td>-16.20 [-31.25, -1.15]</td>
</tr>
<tr>
<td>Tsang 2006</td>
<td>-4</td>
<td>2.75</td>
<td>9.9%</td>
<td>-4.00 [-9.39, 1.39]</td>
</tr>
<tr>
<td>Yu 2006</td>
<td>-4</td>
<td>9.39</td>
<td>1.3%</td>
<td>-4.00 [-22.40, 14.40]</td>
</tr>
</tbody>
</table>

Total (95% CI): 100.0% -3.79 [-5.96, -1.63]

Heterogeneity: Tau² = 4.70; Chi² = 59.56, df = 8 (P < 0.00001); I² = 87%

Test for overall effect: Z = 3.43 (P = 0.0006)

---

*Shahin et al. Atherosclerosis 221 (2012) 18–33*
**ARB improves baPWV independent of BP in type 2 diabetic patients with hypertension.**

Candesartan significantly improves baPWV independent of BP.  

**Study Data:**  
22 Type 2 diabetic patients with hypertension received either ARB (candesartan, n = 11) or a calcium channel blocker (amlodipine or nifedipine, n = 11) for 12 weeks.

Angiotensin II type-I receptor blocker, candesartan, improves brachial-ankle pulse wave velocity independent of its blood pressure lowering effects in type 2 diabetes patients.
Effect of high-dose ARB and ARB plus low-dose diuretic on baPWV

High-dose ARB: valsartan improves baPWV.

Subjects and methods:
Subjects: 43 patients with morning hypertension despite treatment with 80mg valsartan were randomly assigned to receive 160 mg valsartan (n = 22) or 80mg valsartan plus low-dose trichlormethiazide (1mg) (n = 21) for 6 months. Japanese.
Fluvastatin prevents development of arterial stiffness in hemodialysis patients with type 2 diabetes mellitus.

Fluvastatin significantly reduces baPWV and decreases serum concentrations of CRP.

**Study Data:**
Subjects: 22 hemodialysis patients with type 2 diabetes received fluvastatin (20mg/day) or a placebo for 6 months.

Fluvastatin prevents development of arterial stiffness in hemodialysis patients with type 2 diabetes mellitus.
Effects of Pharmacologic Intervention

- All antihypertensive drugs reduce arterial stiffness (passive decrease of PWV)
- The ability of RAS blockers to reduce arterial stiffness as assessed by PWV seems to be independent to be of their ability to reduce BP
- ACEi and ARBs reduce PWV in the recent meta-analysis
- Statins decrease arterial stiffness
Biomarkers

1. BNP
2. Arterial stiffness
3. LDL/ HDL
4. hs-CRP
5. Lp-PLA
6. Vascular calcification
CAD risk as a function of LDL-C and HDL-C

Framingham Heart Study

CASTELLI WP. Am J Cardiol 1998; 82:60-65
# Distribution of LDL-C and HDL-C in men with CHD

N=8,500 men with CHD in the U.S. in 1990–92

<table>
<thead>
<tr>
<th>LDL-C mg/dL</th>
<th>Number</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100</td>
<td>1,003</td>
<td>13</td>
</tr>
<tr>
<td>100–130</td>
<td>2,234</td>
<td>28</td>
</tr>
<tr>
<td>131–160</td>
<td>2,711</td>
<td>33</td>
</tr>
<tr>
<td>&gt;160</td>
<td>2,139</td>
<td>26</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HDL-C mg/dL</th>
<th>Number</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;35</td>
<td>3,286</td>
<td>38</td>
</tr>
<tr>
<td>35–40</td>
<td>2,166</td>
<td>25</td>
</tr>
<tr>
<td>&gt;40</td>
<td>3,126</td>
<td>36</td>
</tr>
</tbody>
</table>

Veterans Affairs HDL Intervention Trial

- About 40% of CAD patients: LDL cholesterol level below 130 mg/dL.
- 20 to 30% of CAD patients: low HDL cholesterol without high LDL.

*Am J Cardiol 1995;75:1196–1201*
Human CETP deficiency
  - ↑ in HDL-C (codominant)

Reducing CETP activity ⇒ ↓ atherosclerosis in animal models

ILLUMINATE study: Changes of HDL-C and LDL-C

Kastelein JJP et al. NEJM. 2007;356(16):1620-1630
ILLUMINATE study:
Kaplan–Meier Curves for Death from Any Cause and for the Primary Composite Outcome

A
Death from any Cause

No. at Risk
Atorvastatin only
Torcetrapib plus atorvastatin

0 90 180 270 360 450 540 630 720 810
Days after Randomization

Patients without Event (%)

100
99
98
97
96
95
90

B
Major Cardiovascular Events

No. at Risk
Atorvastatin only
Torcetrapib plus atorvastatin

0 90 180 270 360 450 540 630 720 810
Days after Randomization

Patients without Event (%)

100
99
98
97
96
95
90
The Failure of Torcetrapib: Was it the Molecule or the Mechanism?

↑ Cholesterol efflux via ABCG1
↓ Macrophage foam cells
↓ Coronary Atherosclerosis

↑ Blood pressure
  (↑ Aldosterone, ↓ Potassium)

↑ Death from sepsis? Other effects?

Further clinical trials with CETP inhibitors that do not increase BP or aldosterone are ongoing
DAL-OUTCOMES: HDL-C and LDL-C by treatment group

HDL cholesterol (mg/dl)

LDL cholesterol (mg/dl)

Placebo
Dalcetrapib

Months

0 1 3 6 12 24 36

40 45 50 55 60

60 65 70 75 80 85 90

0 1 3 6 12 24 36
DAL-OUTCOMES: Primary outcome* by treatment group

Cumulative % of Patients with Primary Outcome

- Placebo
- Dalcetrapib

Hazard ratio 1.04
(95% CI 0.93-1.16)
P=0.52 by log rank test

No. at Risk
- Placebo: 7933, 7386, 6551, 1743
- Dalcetrapib: 7938, 7372, 6495, 1736

* Coronary heart disease death, non-fatal MI, ischemic stroke, hospitalization for unstable angina, resuscitated cardiac arrest
DEFINE study: Safety of anacetrapib in patients with or at high risk for CHD

Cardiovascular Center, Chungnam National University Hospital
Clinical Trials with CETP Inhibitors

**Drug and lipoprotein effects**

**Torcetrapib:**
- 60% increase in HDL-C
- 20% decrease in LDL-C

**Dalcetrapib:**
- 30% increase in HDL-C
- no effect on LDL-C

**Anacetrapib:**
- 120% increase in HDL-C
- 30% decrease in LDL-C

**Evacetrapib:**
- similar Lp profile to anacetrapib

**Clinical Status**

**ILLUMINATE**
- excess CVD and death
- ↑ BP

**DAL-OUTCOMES**
- stopped for futility
- Slight ↑ in BP, CRP

**DEFINE**
- safety study excluded
- torcetrapib-like CVD toxicity

**REVEAL**
- study ongoing

**ACCELERATE**
- study ongoing
Summary of CETP inhibitor

- The failure of torcetrapib was likely related to off target adverse cardiovascular effects

- Lowering of LDL, Lp(a) and VLDL cholesterol levels with potent CETP inhibitors has strong anti-atherogenic potential pending outcome trials with Anacetrapib and Evacetrapib
Biomarkers

1. BNP
2. Arterial stiffness
3. LDL/ HDL
4. hs-CRP
5. Lp-PLA
6. Vascular calcification
### CRP and Coronary Disease

<table>
<thead>
<tr>
<th>Study</th>
<th>Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRFIT Kuller 1996</td>
<td>CHD Death</td>
</tr>
<tr>
<td>PHS Ridker 1997</td>
<td>MI</td>
</tr>
<tr>
<td>PHS Ridker 1997</td>
<td>Stroke</td>
</tr>
<tr>
<td>CHS/RHPP Tracy 1997</td>
<td>CHD</td>
</tr>
<tr>
<td>PHS Ridker 1998</td>
<td>PVD</td>
</tr>
<tr>
<td>WHS Ridker 1998,2000</td>
<td>CVD</td>
</tr>
<tr>
<td>MONICA Koenig 1999</td>
<td>CHD</td>
</tr>
<tr>
<td>HELSINKI Rovaiinen 2000</td>
<td>CHD</td>
</tr>
<tr>
<td>CAERPHILLY Mendall 2000</td>
<td>CHD</td>
</tr>
<tr>
<td>BRITAIN Danesh 2000</td>
<td>CHD</td>
</tr>
</tbody>
</table>

Relative Risk

JUPITER;
Justification for the Use of statins in Primary prevention: an Intervention Trial Evaluating Rosuvastatin

No history of CAD
men ≥50 yrs
women ≥60 yrs
LDL-C <130 mg/dL
CRP ≥2.0 mg/L

Placebo run-in

Rosuvastatin 20 mg (n=8901)

Placebo (n=8901)

Visit: 1 2 3 4
Week: -6 -4 0 13

Median follow-up 1.9 years

CAD=coronary artery disease; LDL-C=low-density lipoprotein cholesterol; CRP=C-reactive protein; HbA$_{1C}$=glycated haemoglobin

JUPITER

Effects on LDL-C, HDL-C, TG and hsCRP at 12 months; Percentage change between rosvuastatin and placebo

Percentage change from baseline (%)

-60 -50 -40 -30 -20 -10 0 10

LDL-C HDL-C TG hsCRP

50% 4% 17% 37%
p<0.001 p<0.001 p<0.001

*P-value at study completion (48 months) = 0.34

**JUPITER - Primary Endpoint**

(Time to first occurrence of a CV death, non-fatal stroke, non-fatal MI, unstable angina or arterial revascularization)

**Hazard Ratio 0.56**

(95% CI 0.46-0.69)

\[ P<0.00001 \]

---

**Cumulative Incidence**

**Follow-up (years)**

<table>
<thead>
<tr>
<th>Number at Risk</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosuvastatin</td>
<td>8,901</td>
<td>8,631</td>
<td>8,412</td>
<td>6,540</td>
<td>3,893</td>
</tr>
<tr>
<td>Placebo</td>
<td>8,901</td>
<td>8,621</td>
<td>8,353</td>
<td>6,508</td>
<td>3,872</td>
</tr>
</tbody>
</table>

**NNT for 2y = 95**

**5y* = 25**

*Extrapolated figure based on Altman and Andersen method*

---

**JUPITER ; Total Mortality**
(Death from any cause ; Secondary outcome )

*Hazard Ratio 0.80 (95% CI 0.67-0.97) p=0.02*

![Graph showing cumulative incidence over follow-up years for Placebo and Rosuvastatin 20mg]

**Number at Risk**
- Rosuvastatin: 8,901, 8,847, 8,787, 6,999, 4,312, 2,268, 1,602, 1,192, 683, 227
- Placebo: 8,901, 8,852, 8,775, 6,987, 4,319, 2,295, 1,614, 1,196, 684, 246

The JUPITER study included patients with low to normal LDL-C who were at increased CV risk as identified by elevated CRP levels and who did not require statin treatment based on current treatment guidelines.

A 44% reduction in the primary endpoint of major cardiovascular events (composite of: CV death, MI, stroke, unstable angina, arterial revascularisation) was observed in patients who received rosuvastatin 20 mg compared with placebo (p< 0.0001).

A 20% reduction in total mortality was observed in patients who received rosuvastatin 20 mg compared with placebo (p=0.02), a unique finding for statins in a population without established CHD.
Serum inflammatory biomarkers and plaque inflammation assessed by [18F] - fluorodeoxyglucose positron emission tomography in the dal-PLAQUE study: a post-hoc analysis by baseline features

Raphael Duivenvoorden¹, Venkatesh Mani², Mark Woodward³, David Kallend⁴, Gabriela Suchankova⁴, Valentin Fuster⁵, James H.F. Rudd⁶, Ahmed Tawakol⁷, Michael E. Farkouh²,⁸, Zahi A. Fayad²

¹Translational and Molecular Imaging Institute, Mount Sinai School of Medicine, New York, United States of America; ²Mount Sinai School of Medicine, New York, United States of America; ³George Institute, University of Sydney, Sydney, Australia; ⁴F. Hoffmann-La Roche Ltd, Basel, Switzerland; ⁵Cardiovascular Institute, Mount Sinai School of Medicine, New York, United States of America; ⁶Division of Cardiovascular Medicine, University of Cambridge, Cambridge, United Kingdom; ⁷Massachusetts General Hospital and Harvard Medical School, Boston, United States of America; ⁸Peter Munk Cardiac Centre and Li Ka Shing Knowledge Institute, Toronto, Canada

European Society of Cardiology Congress, Munich, Germany, 25-29 Aug 2012
Example of High Versus Low Vascular Inflammation
### Results – Difference in $\text{MDS}_{\text{max}}$ for Highest Versus Lowest Biomarker Tertile

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Difference highest versus lowest tertile</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>hsCRP</td>
<td>0.04</td>
<td>0.82</td>
</tr>
<tr>
<td>IL-6</td>
<td>-0.10</td>
<td>0.52</td>
</tr>
<tr>
<td>Lp-PLA$_2$ mass</td>
<td>0.34</td>
<td>0.03*</td>
</tr>
<tr>
<td>MMP-3</td>
<td>-0.10</td>
<td>0.53</td>
</tr>
<tr>
<td>MMP-9</td>
<td>0.20</td>
<td>0.20</td>
</tr>
<tr>
<td>MPO</td>
<td>0.17</td>
<td>0.28</td>
</tr>
<tr>
<td>sE-Selectin</td>
<td>-0.04</td>
<td>0.80</td>
</tr>
<tr>
<td>sVCAM-1</td>
<td>0.03</td>
<td>0.84</td>
</tr>
<tr>
<td>sICAM-1</td>
<td>-0.09</td>
<td>0.57</td>
</tr>
</tbody>
</table>

$\text{MDS}_{\text{max}}$, most diseased segment; hsCRP, high-sensitivity C-reactive protein; IL-6, interleukin-6; Lp-PLA$_2$, lipoprotein phospholipase A$_2$; MMP-3, matrix metalloproteinase-3; MMP-9 matrix metalloproteinase-9; MPO, myeloperoxidase; sE-Selectin, soluble E-Selectin; sVCAM-1, soluble vascular cell adhesion molecule; sICAM-1, soluble intracellular adhesion molecule
Biomarkers

1. BNP
2. LDL/ HDL
3. Arterial stiffness
4. hs-CRP
5. Lp-PLA
6. Vascular calcification
Lipoprotein-associated Phospholipase A$_2$ (Lp-PLA$_2$) activity: Background

Lumen

native LDL carrier of Lp-PLA$_2$

Lp-PLA$_2$

Intima

Oxidized LDL substrate for Lp-PLA$_2$

Leukocyte

Lp-PLA$_2$

Atheroma

Sustained Inflammation

Necrotic Core Expansion

Contrasting histopathological characteristics of a stable versus a vulnerable or ruptured plaque

**Stable Plaque**
- Low Lp-PLA$_2$ content (dark staining)
- May have significant stenosis
- Thick fibrous cap / high collagen content
- Modest lipid pool
- Few inflammatory cells

**Vulnerable or ruptured Plaque**
- High Lp-PLA$_2$ content (dark staining)
- May have minimal stenosis
- Thin fibrous cap / low collagen content
- Large lipid pool
- Many inflammatory cells

Lp-PLA$_2$ and CHD risk: The Lp-PLA$_2$ Studies Collaboration; compared with conventional risk factors

79,036 participants from 32 prospective studies

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>RR (95% CI) per 1-SD higher</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lp-PLA$_2$ activity</td>
<td>1.11 (1.05-1.16)</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>1.10 (1.00-1.21)</td>
</tr>
<tr>
<td>Smoking status</td>
<td>1.34 (1.19-1.51)</td>
</tr>
<tr>
<td>Non HDL cholesterol</td>
<td>1.10 (1.02-1.18)</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>1.15 (1.06-1.24)</td>
</tr>
</tbody>
</table>

Adjusted for non-lipid and lipid conventional risk factors

LSC Lancet 2010; 375:1536
Rationale for targeting Lp-PLA$_2$

Native LDL carrier of Lp-PLA$_2$

Lumen

Lp-PLA$_2$

Intima

Oxidized LDL substrate for Lp-PLA$_2$

Leukocyte

Sustained Inflammation

Necrotic Core Expansion

Atheroma

Darapladib (Lp-PLA$_2$ inhibitor)

STABILITY Trial
Stabilization of Atherosclerotic plaque By Initiation of darapLadlb TherapY

Patients with chronic CHD
(prior MI >1 mth, prior coronary revascularization, multivessel CAD)

Enrichment criteria: ≥60 years of age, diabetes mellitus, low HDL, current smoking, significant renal dysfunction, polyvascular disease

15,828 patients randomized

Darapladib 160mg  Placebo

Optimized guideline-mandated treatment

median follow-up 3.7 years , 1588 events

Primary endpoint: composite of CV death, MI, stroke
Secondary endpoints: major coronary events, total coronary events
Primary Endpoint:
Time to First Occurrence CV Death, MI, Stroke

HR (95% CI) = 0.94 (0.85, 1.03)
P-value = 0.20
Placebo events = 819
Darapladib 160mg events = 769
Time to First Occurrence Major Coronary Events (CHD Death, MI, Urgent Coronary Revascularization)

HR (95% CI) = 0.90 (0.82, 1.00)

P-value = 0.045

Placebo events = 814
Darapladib 160mg events = 737
Time to First Occurrence Total Coronary Events (CHD Death, MI, Any Coronary Revascularization, Hospitalization for Unstable Angina)

HR (95% CI) = 0.91 (0.84, 0.98)
P-value = 0.02
Placebo events = 1269
Darapladib events = 1159
Summary of STABILITY

- Did not significantly reduce the incidence of the primary composite endpoint of CV death, MI or stroke
- There was no effect on stroke or total mortality
- Reduced the prespecified coronary-specific secondary endpoints of major coronary events (1% absolute) and total coronary events (1.5% absolute) with nominal significance (p<0.05)
- Further analyses of the trial results in subgroups based on biomarkers, including Lp-PLA$_2$ levels, and genetics will explore if darapladib might be useful in specific patient subsets

- SOLID trial (ACS); coming soon
Biomarkers

1. BNP
2. LDL/ HDL
3. hs-CRP
4. Arterial stiffness
5. Lp-PLA
6. Vascular calcification
Vascular calcification as a marker of increased cardiovascular risk: a meta-analysis

Coronary artery calcium is a better predictor of cardiovascular events than the Framingham risk score and can help to reclassify asymptomatic individuals into high-risk or low-risk categories

Rennenberg et al. Vascular health and risk management 2009

Alexopoulos et al. Nature Reviews Cardiology 2009
Warfarin causes rapid calcification of the elastic lamellae in rat arteries

*Warfarin induced artery calcification is promoted by increases in serum calcium or phosphate. Strong upregulation of MGP at sites of calcification, though in the inactive uncarboxylated form*

*Price et al. ATVB 1998*
Warfarin induced calcifications

Before coumarin Tx

9 months after start of coumarin Tx

Schurgers et al. Blood, Nov 2004
Low-risk AF patients on VKA treatment

Age < 65 years

- No VKA
- VKA 6-60 months
- VKA >60 months

<table>
<thead>
<tr>
<th>Agatston score 0-10</th>
<th>Agatston score 101-400</th>
<th>Agatston score 11-100</th>
<th>Agatston score &gt; 400</th>
</tr>
</thead>
</table>

Age > 65 years

- No VKA
- VKA 6-60 months
- VKA >60 months

<table>
<thead>
<tr>
<th>Agatston score 0-10</th>
<th>Agatston score 101-400</th>
<th>Agatston score 11-100</th>
<th>Agatston score &gt; 400</th>
</tr>
</thead>
</table>

Weijts et al. Eur Heart J 2011
Vitamin K supplementation reduces progression of VC

**Design:**
n = 388, mean age 68 years, 500µg K1 supplementation daily
Endpoint: Coronary artery calcification (CAC) progression over 3 y.

**Results:**
Significant differences were only apparent after secondary analysis, restricted to patients >85% adherent to supplementation (n = 367).

K1 supplementation slows the progression of CAC in healthy older adults with preexisting CAC, independent of its effect on total MGP concentrations. No difference in CV morbidity / mortality between the groups.

Shea et al. AJCN 2009
VitaK-CAC Study
- Design -

Population
- CAC-patients (n = 200)
- Not on VKA
- CAC score >100; < 400

Standard therapy + placebo (n = 100)
randomised (1:1) follow-up = 2.0 years

Standard therapy + Vitamin K2 (360) (n = 100)

Week 0, Week 52, Week 104

End points: primary = progress of coronary calcification
secondary = vascular stiffness and biomarkers
Aortic stenosis - Study
- Design -

Population

- AS-patients (n = 200)
- Not on VKA
- AVC score > 50

Standard therapy + placebo (n = 100)

randomised (1:1) follow-up = 1.0 years

Standard therapy + Vitamin K1 (2mg) (n = 100)

- End points:
  primary = progress of aortic valve calcification and CAC
  secondary = Echocardiography and biomarkers
ASCVD Risk Calculator
Search “ACC/AHA Prevention Guidelines risk calculator”

2013 Prevention Guidelines Tools
CV Risk Calculator

The American Heart Association and the American College of Cardiology provide a series of new cardiovascular prevention guidelines for the assessment of cardiovascular risk, lifestyle modifications that reduce risk, management of blood cholesterol, and management of increased body weight in adults. To facilitate the implementation of these guidelines, the new Pooled Cohort Equations CV Risk Calculator and additional Prevention Guideline Tools are available below. Others may be added and available in the near future.

Figure 1. Implementation of Risk Assessment Work Group Recommendations

Does the patient have existing clinical ASCVD? 
Yes
No

Is the patient <20 y or >79 y of age? 
No
Yes

Assess traditional risk factors every 1-3 y in patients 20-79 y of age: estimate 10-y risk in those 40-79 y of age using Pooled Cohort Equations

Low 10-y risk (<7.5%)

Assess 30-y or lifetime risk in those 20-59 y of age: Communicate risk data and refer to 2013 Adult Preventive Guidelines: Blood Cholesterol, Obesity, Lifestyle Management


See 2012 NHLBI Pediatric CV Risk Reduction Guidelines and 2013 Adult Prevention Guidelines: Blood Cholesterol, Obesity

Elevated 10-y risk (≥7.5%)
10-year ASCVD risk

Gender(M/F);
Age(20~79);
Race(White/African American/Other);
Total cholesterol(mg/dl, 130-320);
HDL cholesterol(mg/dl, 20-100);
Systolic BP(90~200);
Treatment for HT(Y/N);
Diabetes(Y/N);
Smoker(Y/N);
Conclusions

➢ The use of some biomarker (esp. natriuretic peptides) to objectively guide HF therapy is a promising approach.

➢ Direct modification of biomarker still need development and proof through more large RCTs.
감사합니다