Use of VH-IVUS Findings as Surrogate Marker for Anti-Atherosclerotic Drug

Duk-Woo Park, MD, PhD

University of Ulsan College of Medicine
Asan Medical Center, Seoul, Korea
Virtual Histology -IVUS

In-vivo characterization of plaque composition via advanced spectral analysis

Fibrous; Fibrofatty; Necrotic core; Dense calcium
Potential VH-IVUS Applicability in Clinical Field

- Risk stratification
- PCI outcomes: acute and long-term
- Plaque Vulnerability
- Surrogate marker for Atherosclerotic Drug
Usefulness of VH-IVUS for risk stratification

“VH findings are well correlated with established risk factors predicting cardiovascular events”

• Known risk factors
  - each of established risk factors for CAD
  - established risk score system
    (Framingham and Score)
• Abnormal lipid profiles
• Multiple biomarkers (hs-CRP, tPA, etc)
Potential VH-IVUS Application improving PCI outcomes

- Find the origin of the problem (the culprit of the culprit) and large NC area
- Assess the risk of plaque protrusion
- Assess the risk of distal embolization or need for appropriate lesion preparation (dense calcified necrotic core and fibrofatty rich lesions)
Potential VH-IVUS Application to detect vulnerable plaques

- Plaque vulnerability assessed by VH-IVUS correlated well with clinical vulnerability (AMI>UA>SA)
- VH IVUS data correlates with known sites for plaque accumulation and ruptures.
- More data are needed to assess the relationship between current vulnerability by VH-findings and future coronary events.
Potential VH-IVUS Applicability in Clinical Field

- Risk stratification
- PCI outcomes: acute and long-term
- Plaque Vulnerability
- Surrogate marker for Atherosclerotic Drug
Cumulative non-target lesion event rate is higher than target lesion event rate after stenting

Optimal PCI
5-year outcomes after stenting: HCRI database

Serial Change in Plaque Type assessed VH-IVUS

Non-culprit lesion phenotype in 106 patients (201 lesions with plaque burden >40%) from the Global VH Registry with baseline and 8-month follow-up VH analysis

Kubo et al. AHA 2008
## Serial Change in Plaque Type assessed VH-IVUS

<table>
<thead>
<tr>
<th>Baseline (n=201)</th>
<th>Follow-up (n=201)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIT (n=64)</td>
<td>48 6 10 0 0</td>
</tr>
<tr>
<td>TCFA (n=21)</td>
<td>0 5 14 2 0</td>
</tr>
<tr>
<td>ThFA (n=94)</td>
<td>0 4 85 4 1</td>
</tr>
<tr>
<td>Fibrotic (n=22)</td>
<td>4 0 0 18 0</td>
</tr>
<tr>
<td>Fibrocalcific (n=20)</td>
<td>0 0 0 0 20</td>
</tr>
</tbody>
</table>
Serial Change in Plaque Type assessed VH-IVUS

Baseline

TCFA ➔ ThFA

Follow-up

TCFA ➔ Fibrocalcific
Serial Plaque Change Studies Using VH-IVUS Findings as Surrogate Marker for Anti-Atherosclerotic Drug
Effect of **Fluvastatin** on progression of coronary atherosclerotic plaque evaluated by VH-IVUS

Stable AP patients with informed consent

(One or two vessel disease)

VH-IVUS for non-target vessel(s)

Hyperlipidemia? (T-cho > 220 mg/dl, or TG > 160 mg/dl, or LDL-cho > 140 mg/dl)

- **YES**
  - Randomization
  - Fluvastatin (60mg/day) group
  - Control group

- **NO**
  - Reject of Medication

Restudy of VH-IVUS after 12 months

Kenya Nasu, M.D., Toyohashi Heart Center, AHA 2007
### Serial VH IVUS FU

<table>
<thead>
<tr>
<th></th>
<th>Fluvastatin</th>
<th>Control</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ave. Fibrous CSA, mm²</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>3.18±1.50</td>
<td>2.46±1.20</td>
<td>0.04</td>
</tr>
<tr>
<td>Follow-up</td>
<td>2.38±1.30*</td>
<td>3.34±1.41*</td>
<td>0.008</td>
</tr>
<tr>
<td><strong>Ave. Fibro-fatty CSA, mm²</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>1.51±0.83</td>
<td>0.97±0.44</td>
<td>0.004</td>
</tr>
<tr>
<td>Follow-up</td>
<td>0.68±0.52*</td>
<td>1.32±0.84*</td>
<td>0.0008</td>
</tr>
<tr>
<td><strong>Ave. Necrotic CSA, mm²</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0.50±0.45</td>
<td>0.43±0.28</td>
<td>0.04</td>
</tr>
<tr>
<td>Follow-up</td>
<td>0.51±0.33</td>
<td>0.65±0.51*</td>
<td>0.24</td>
</tr>
<tr>
<td><strong>Ave. Dense calcium CSA, mm²</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0.18±0.16</td>
<td>0.24±0.20</td>
<td>0.24</td>
</tr>
<tr>
<td>Follow-up</td>
<td>0.24±0.20</td>
<td>0.37±0.31*</td>
<td>0.07</td>
</tr>
</tbody>
</table>

“**Fluvastatin may halt the progression of coronary atherosclerosis by the reduction of fibro-fatty.**”
**Multicenter, randomized, double-blind, parallel-group, placebo-controlled treatment trial in 330 patients with non-culprit CAD**

All patients on standard medical therapy !!!

IBIS-2: Effects of the direct Lp-PLA₂ inhibitor darapladib vs placebo on human coronary atherosclerotic plaque.

Plaque Composition by IVUS - VH
change from baseline in necrotic core volume

Entire region of interest
[mean 48 mm]

- mean change (mm$^3$)
  - $p=0.012$
  - $* p=0.009$
  - $p=0.71$

Placebo (plus standard of care) n=110
Darapladib 160 mg (plus standard of care) n=129

The worst 10 mm subsegment

- mean change (mm$^3$)
  - $p=0.003$
  - $p=0.162$
  - $* p=0.008$

“Despite standard-of-care medical Treatment, NC continued to expand in placebo group, but darapladib prevented NC expansion”
Effects of Statin Treatments on Coronary Plaque Stabilization Assessed by Volumetric VH-IVUS

Statin-naïve patients with angiographically mild to moderate coronary disease (N=100)

1:1 randomization (double-blinded)

- Simvastatin 20 mg (n=50)
- Rosuvastatin 10mg (n=50)

Serial VH-IVUS at baseline and 12 months

Hong et al. JACC Interv 2009, In press
Representative Case: Rosuvastatin group

Baseline

12 Mo FU

NC 2.3mm² (47%)

NC 1.1mm² (24%)

Hong et al. JACC Interv 2009, In press
## Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Simvastatin (N=50)</th>
<th>Rosuvastatin (N=50)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>58 ± 10</td>
<td>59 ± 9</td>
<td>0.7</td>
</tr>
<tr>
<td>Male gender</td>
<td>40 (80)</td>
<td>37 (74)</td>
<td>0.5</td>
</tr>
<tr>
<td>Hypertension</td>
<td>22 (44)</td>
<td>24 (48)</td>
<td>0.7</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>13 (26)</td>
<td>11 (22)</td>
<td>0.6</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>19 (38)</td>
<td>19 (38)</td>
<td>1.0</td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td>20 (40)</td>
<td>23 (46)</td>
<td>0.5</td>
</tr>
<tr>
<td>C-reactive protein (mg/dL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0.17 ± 0.22</td>
<td>0.21 ± 0.20</td>
<td>0.4</td>
</tr>
<tr>
<td>12-month follow-up</td>
<td>0.12 ± 0.12</td>
<td>0.09 ± 0.07</td>
<td>0.22</td>
</tr>
<tr>
<td>Changes</td>
<td>-0.05 ± 0.22</td>
<td>-0.12 ± 0.19</td>
<td>0.12</td>
</tr>
</tbody>
</table>

Hong et al. JACC Interv 2009, In press
## Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Simvastatin (N=50)</th>
<th>Rosuvastatin (N=50)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lipid profiles at baseline</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>191 ± 34</td>
<td>189 ± 27</td>
<td>0.7</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>119 ± 30</td>
<td>116 ± 28</td>
<td>0.6</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>43 ± 10</td>
<td>43 ± 11</td>
<td>0.8</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>149 ± 69</td>
<td>152 ± 75</td>
<td>0.9</td>
</tr>
<tr>
<td><strong>Lipid profiles at 12-month follow-up</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>142 ± 22</td>
<td>128 ± 20</td>
<td>0.002</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>78 ± 20</td>
<td>64 ± 21</td>
<td>0.002</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>48 ± 12</td>
<td>52 ± 14</td>
<td>0.127</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>115 ± 50</td>
<td>107 ± 96</td>
<td>0.6</td>
</tr>
</tbody>
</table>

*Hong et al. JACC Interv 2009, In press*
**Plaque Composition by IVUS - VH**

**change from baseline in necrotic core volume**

**The worst 10 mm Segment**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean Change (mm$^3$)</th>
<th>Percent Change (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simvastatin (n=50)</td>
<td>$-1.4\pm8.1$</td>
<td>$-3\pm13$</td>
</tr>
<tr>
<td>Rosuvastatin (n=50)</td>
<td>$-2.5\pm7.0$</td>
<td>$-5\pm12$</td>
</tr>
</tbody>
</table>

- $p=0.22$ for Simvastatin vs baseline
- $p=0.015$ for Rosuvastatin vs baseline
- $p=0.3$ for Simvastatin vs Rosuvastatin
- $p=0.16$ for baseline vs Simvastatin
- $p=0.003$ for baseline vs Rosuvastatin

There was no significant treatment effect among statin groups. However, by intra-group serial analysis, there was significant reduction of NC in the rosuvastatin group.

Hong et al. JACC Interv 2009, In press
SPECIAL
: clinically silent plaque progression

• PIs: Dr Tadanori Aizawa and Dr Etsuo Tsuchikane
• Multicenter study on the safety of 3-vessel VH-IVUS interrogation, clinical event rate and silent plaque progression of angiographically intermediate lesions in ACS patients
• Angiographic and IVUS follow-up at 1 year
• All sites: Japan
• n=300
ATLANTA
Assessment of Tissue characteristics, Lesion morphology and hemodynamics by Angiography with fractional flow reserve, intravascular ultrasound and virtual histology and Non-invasive computed Tomography in Atherosclerotic plaques

the correlation with VH IVUS and FFR with a non-invasive MSCT

- PI Dr S Voros
- Single center registry with one year clinical outcome (MACE) of intermediate lesions by angiogram and diagnostic correlation with further assessment by FFR, MSCT and grayscale and VH IVUS
- N=300
Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein


“Suggested Plausible Mechanism of Statin to Reduce Major Cardiovascular Events was Plaque Stabilization”
The STABLE trial

(STatin and Atheroma VulneraBiLity Evaluation)

: Double-blinded, Prospective, Randomized, Controlled Trial

Statin-naïve patients with angiographically documented mild to moderate coronary disease
(Total 312 patients needed)

2:1 randomization (double-blinded)

Rosuvastatin 40mg
(n=208)

Rosuvastatin 10mg
(n=104)

VH-IVUS, Conventional IVUS, and OCT follow-up at 12 months
Clinical follow-up at 12 months

**Primary end point:** % compositional change of coronary plaque from baseline to 12-months follow-up.
1. Perform IVUS with VH of “index” vessel - at least prox 50 mm
2. Perform on-site VH IVUS analysis of “index” vessel
3. Identify all FibroAtheromas

No FA
→ Image 2nd vessel

Only one FA
→ This becomes the index lesion

Multiple FAs
→ TCFA-yes
   → This becomes the index lesion
   
   → TCFA-no
   → FA with Largest NC
   → Becomes Index lesion

4. VH IVUS study sent to core lab to see if index lesion meets enrollment criteria (FA)
   a. If yes, patient is followed for 12 mos and imaging repeated
   b. if no, patient is de-enrolled and a replacement patient sought

   Additional secondary end-points:
   ▪ Delta % NC volume of entire pullback length
   ▪ Analysis of all other lesions (plaque burden >40% in 3 consecutive frames)
Overall Summary

Current Clinical Study Results and Future Study Perspective

• VH Findings showed good correlation with known risk factors, blood biomarker, clinical presentation, and pathologic plaque composition suggested in previous literatures.

• Ongoing clinical study will provide the information regarding the impact of VH-findings on future clinical outcomes (PROSPECT, SPECIAL, ATLANTA)

• VH-IVUS plaque vulnerability can also be used as good surrogate marker for plaque stabilization or regression (IBIS-1, IBIS-2, STABLE trial)