Virtual Histology: Multimodality Imaging of the Coronary Tree in Patients with Acute Coronary Syndromes: Baseline PROSPECT Results

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New York, NY
Virtual Histology (VH) - IVUS

Only the envelope amplitude (echo intensity) is used to form the greyscale IVUS image.

However, among reflected ultrasound signals of the same intensity, frequency can vary depending on the tissue.

VH-IVUS uses 8 parameters to classify plaque:

- maximum power
- corresponding frequency
- minimum power
- corresponding frequency
- Slope
- y-intercept
- mid-band fit
- integrated backscatter
Eagle Eye (20MHz Electronic Array Transducer)

VH IVUS vs histopathology from fresh 51 fresh, post mortem LADs (115 sections and 407 regions of interest)

<table>
<thead>
<tr>
<th>Tissue Type</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Predictive Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrous tissue (n=162)</td>
<td>84.0%</td>
<td>98.8%</td>
<td>92.8%</td>
</tr>
<tr>
<td>Fibrofatty (n=84)</td>
<td>86.9%</td>
<td>95.1%</td>
<td>93.4%</td>
</tr>
<tr>
<td>Necrotic core (n=69)</td>
<td>97.1%</td>
<td>93.8%</td>
<td>94.4%</td>
</tr>
<tr>
<td>Dense calcium (n=92)</td>
<td>97.8%</td>
<td>99.7%</td>
<td>99.3%</td>
</tr>
</tbody>
</table>
Thin Cap Fibroatheroma (TCFA)

“Thin Cap Fibro-Atheroma (TCFA)” or “Vulnerable Plaque” -- Confluent Necrotic Core >10% of total plaque, >33% of lesion circumference at the lumen surface, and present in 3 consecutive frames. Based on the presence or absence of Ca, the length of the NC, or signs of previous ruptures, TCFA can be further sub-classified.

- <10% calcium
- >10% calcium
- multiple layers

Still further sub-classification can be based on presence of luminal narrowing.

“Highest Risk TCFA”

- Confluent NC>20%
- No evidence of fibrotic cap
- Calcium >5%
- Remodeling index >1.05
- >50% plaque burden by IVUS

“TCFA without significant narrowing” - plaque burden <50% on IVUS and/or less than 25% narrowing on angiogram. (Pathologic data suggests that TCFA without significant plaque burden are less “vulnerable”)

(Pathologic data suggests that TCFA with significant plaque burden are the most vulnerable)
Healed ruptures are common in patients with acute events

- In 142 men with sudden cardiac death, the mechanism of death was presumed to be acute plaque rupture with acute thrombus in 44.
- Healed ruptures were present in 75% of hearts with acute plaque rupture: 9 showed 1 previous rupture site, 9 showed 2 previous rupture sites, 9 showed 3 previous rupture sites, and 6 showed 4 previous rupture sites.
- Acute ruptures at sites of ≥3 healed previous ruptures demonstrated greater underlying plaque burden (94±4%) than those without healed previous rupture (74±12%).

(Burke et al. Circulation 2001;103;934-40)
<table>
<thead>
<tr>
<th>Major criteria*</th>
<th>VH-IVUS</th>
</tr>
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<tbody>
<tr>
<td>Active inflammation</td>
<td></td>
</tr>
<tr>
<td>Thin cap</td>
<td>± (by inference)</td>
</tr>
<tr>
<td>Large lipid/necrotic core</td>
<td></td>
</tr>
<tr>
<td>Endothelial denudation</td>
<td></td>
</tr>
<tr>
<td>Fissured plaque</td>
<td></td>
</tr>
<tr>
<td>Plaque burden &gt;90%</td>
<td>+</td>
</tr>
<tr>
<td>Minor criteria*</td>
<td></td>
</tr>
<tr>
<td>Superficial calcific nodule</td>
<td>+</td>
</tr>
<tr>
<td>Glistening yellow</td>
<td></td>
</tr>
<tr>
<td>Intraplaque hemorrhage/neovascularization</td>
<td></td>
</tr>
<tr>
<td>Endothelial dysfunction</td>
<td></td>
</tr>
<tr>
<td>Positive remodeling</td>
<td>+</td>
</tr>
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</table>

The PROSPECT Trial

700 pts with ACS
UA (with ECG Δ) or NSTEMI or STEMI >24º
1-2 vessel CAD undergoing PCI
at up to 40 sites in U.S., Europe

Metabolic S.
• Waist circum
• Fast lipids
• Fast glu
• HgbA1C
• Fast insulin
• Creatinine

Biomarkers
• Hs CRP
• IL-6
• sCD40L
• MPO
• TNF α
• MMP9
• Lp-PLA2
• others

PCI of culprit lesion(s)
Successful and uncomplicated
Formally enrolled

PI: Gregg W. Stone
Sponsor: Abbott Vascular (Partner: Volcano)
3-vessel imaging post PCI

Angiography (QCA of entire coronary tree)

IVUS

Virtual histology

Palpography (n=\sim350)

Proximal 6-8 cm of each coronary artery

Meds rec
Aspirin
Plavix 1yr
Statin
Repeat biomarkers
@ 30 days, 6 months

F/U: 1 mo, 6 mo, 1 yr, 2 yr, \pm 3-5 yrs
Until 100 VP events occur

MSCT Substudy N=50-100

Repeat imaging in pts with events

Repeat imaging in pts with events

F/U: 1 mo, 6 mo, 1 yr, 2 yr, \pm 3-5 yrs
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CARDIOVASCULAR RESEARCH FOUNDATION

COLUMBIA UNIVERSITY MEDICAL CENTER
PROSPECT: Baseline Features

N = 697

- STEMI >24 hrs: 30.3%
- NSTEMI: 65.4%
- Unstable angina with ST changes: 4.3%
### PROSPECT: Imaging Summary

#### Data acquisition (N=697)

<table>
<thead>
<tr>
<th>N vessels</th>
<th>Angiography</th>
<th>IVUS / VH</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Imaged</strong></td>
<td>N=697</td>
<td>N=697</td>
</tr>
<tr>
<td>1, 2, 3</td>
<td>0%, 0%, 100%</td>
<td>1%, 10%, 88%</td>
</tr>
<tr>
<td><strong>Mean</strong></td>
<td>3.0 ± 0</td>
<td>2.84 ± 0.5</td>
</tr>
<tr>
<td><strong>Core lab analyzable</strong></td>
<td>N=697</td>
<td>N=616 (88.4%)</td>
</tr>
<tr>
<td>1, 2, 3</td>
<td>0.1%, 0.4%, 99.4%</td>
<td>14%, 32%, 55%</td>
</tr>
<tr>
<td><strong>Mean</strong></td>
<td>3.0 ± 0</td>
<td>2.42 ± 0.70*</td>
</tr>
<tr>
<td><strong>Length (mm)</strong></td>
<td>446±84</td>
<td>183±76 / 166±70</td>
</tr>
</tbody>
</table>
Navigating the Depth of the PROSPECT Baseline Data

- Angiography
- IVUS
- VH
- QC-IVUS
- QCA
PROSPECT: Imaging Summary

QCA DS% in 1798 angiographically visible lesions

Mean DS 38.5 ± 15.5%

DS% by QCA:
- <10%: 5.7%
- 10-20%: 4.6%
- 20-30%: 5.7%
- 30-40%: 44.1%
- 40-50%: 21.8%
- >50%: 18.2%
### PROSPECT: Imaging Summary

**IVUS of angiographic non-culprit lesions**

By IVUS (in 786 of the 1798 total angiographic lesions)

<table>
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<th>Parameter</th>
<th>Value</th>
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<td>EEM area, mm²</td>
<td>16.72 ± 6.36</td>
</tr>
<tr>
<td>MLD, mm</td>
<td>2.82 ± 0.64</td>
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<tr>
<td>Lumen area, mm²</td>
<td>8.89 ± 4.12</td>
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<tr>
<td>Mean LD, mm</td>
<td>3.26 ± 0.72</td>
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<td>Plaque area, mm²</td>
<td>11.29 ± 4.15</td>
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<tr>
<td>MVD, mm</td>
<td>4.04 ± 0.88</td>
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<td>Plaque burden %</td>
<td>47 ± 11</td>
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<tr>
<td>Mean VD, mm</td>
<td>4.45 ± 0.87</td>
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<tr>
<td>MLA, mm²</td>
<td>6.36 ± 3.75</td>
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<tr>
<td>Max VD, mm</td>
<td>4.90 ± 1.02</td>
</tr>
<tr>
<td>Remodeling index</td>
<td>0.94 ± 0.16</td>
</tr>
<tr>
<td>Lumen ecc.</td>
<td>0.93 ± 0.70</td>
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**PROSPECT: Imaging Summary**

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210 (26.7%) angiographically mild lesions had an MLA <4.0 mm²
PROSPECT: Imaging Summary
IVUS of angiographic non-culprit lesions

By IVUS (in 786 of the 1798 total angiographic lesions)

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<th>Standard Deviation</th>
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<td></td>
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210 (26.7%) angiographically mild lesions had an MLA < 4.0 mm²

259 (33.0%) of angiographically visible lesions were NOT considered IVUS lesions (<40% plaque burden or present for <3 frames)
PROSPECT: Baseline features

Presence of $\geq 1$ VH lesion subtypes (2381 lesions in 616 pts)

- Fibrotic: 16.5%
- Fibro-calcific: 33.1%
- PIT: 73.5%
- Fibro-atheroma: 67.2%
- Thick cap FA: 58.5%
- VH TCFA: 28.4%
28.4% of patients have ≥1 VH-TCFA

0.42 ± 0.78 VH-TCFAs per patient
(range 0 – 5 per patient)

Total 266 VH-TCFAs in 616 patients
PROSPECT: Imaging Summary

IVUS MLA in 263 VH-TCFA lesions

Only 24.3% of VH-TCFAs have an MLA ≤ 4.0 mm²
### PROSPECT: Baseline Features

% imaged lesions with TCFAs

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<tr>
<th>Area</th>
<th># IVUS lesions</th>
<th># imaged</th>
</tr>
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<tbody>
<tr>
<td>LM 0–10 mm</td>
<td>62</td>
<td>464</td>
</tr>
<tr>
<td>LM 10–20 mm</td>
<td>19</td>
<td>137</td>
</tr>
<tr>
<td>LAD 0–10 mm</td>
<td>52</td>
<td>277</td>
</tr>
<tr>
<td>LAD 10–20 mm</td>
<td>162</td>
<td>454</td>
</tr>
<tr>
<td>LAD 20–30 mm</td>
<td>158</td>
<td>467</td>
</tr>
<tr>
<td>LAD 30–40 mm</td>
<td>128</td>
<td>463</td>
</tr>
<tr>
<td>LAD 40–50 mm</td>
<td>102</td>
<td>439</td>
</tr>
<tr>
<td>LAD 50–60 mm</td>
<td>74</td>
<td>410</td>
</tr>
<tr>
<td>LAD 60–70 mm</td>
<td>57</td>
<td>355</td>
</tr>
<tr>
<td>LAD 70–80 mm</td>
<td>38</td>
<td>271</td>
</tr>
<tr>
<td>LAD 80–90 mm</td>
<td>18</td>
<td>162</td>
</tr>
<tr>
<td>LAD 90–100 mm</td>
<td>9</td>
<td>101</td>
</tr>
<tr>
<td>LAD &gt;100 mm</td>
<td>8</td>
<td>65</td>
</tr>
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Mean LAD 156 mm by QCA
PROSPECT: IVUS Summary

2381 IVUS lesions (plaque burden >40%)

- 946 Fibroatheromas (40.5%)
- 263 VH-TCFAs (11.0%)
- 683 Thick cap FAs (29.5%)
- 64 MLA <4.0 mm² (2.7%)
- 199 MLA ≥4.0 mm² (8.3%)
- 165 Single NC (6.9%)
- 98 Multiple NC (4.1%)

476 IVUS lesions had MLA <4.0 mm² (20%)
At least one secondary lesion with an IVUS MLA <4.0mm$^2$ was identified in ~42% of patients.

VH-TCFAs were identified in the coronary tree in ~28% of patients (mean 0.42 ± 0.78, range 0-5 per patients) which was less common than expected.

Follow-up will continue until there are 100 documented VP events – ACS+documented lesion progression – at which time we will determine whether baseline demographics, biomarkers angiography, IVUS, and VH predicted patients and lesions at risk for future adverse cardiovascular events.

Conclusions
PROSPECT: Acute MI

Pre PCI

Post PCI
Mid RCA fibroatheroma

Angiographically near normal

Stent

IVUS MLA: 6.4 mm²

VH-TCFA
Multiple NC
Length 3.7 mm
F 35%
FF 1%
NC 52%
DC 12%
Prox RCA fibroatheroma

Angiographically mild lesion

Stent

2nd VH-TCFA
Single NC
Length 11 mm
F 39%
FF 1%
NC 53%
DC 7%

MLA: 6.1 mm²
Mid LAD fibroatheroma

Angiographically mild lesion

VH-TCFA
Single NC
Length 11 mm
F 40%
FF 7%
NC 42%
DC 11%

MLA: 11.1 mm²