Natural History of Vulnerable Plaque: Imaging Study

Angioplasty Summit – Seoul
April 29, 2010

James R. Margolis, M.D.
Marja Pauliina Margolis, M.D., Ph.D.
Miami, Florida USA
Virtual Histology
Clinical Uses Now and in the Future

Angioplasty Summit – Seoul
May 1, 2004

James R. Margolis, M.D.
Marja Pauliina Margolis, M.D., Ph.D.
Miami, Florida USA
Essence of 2004 Talk

• Plaque rupture is major cause of acute MI and sudden death.
• VH-IVUS could identify plaque components (fibrous, fibro-fatty, necrotic core and calcium) with 95% predictive accuracy.
• VH could possibly identify culprit lesions and even predict plaques that were likely to rupture in the future.
• Studies planned and in progress were designed to validate these bold claims.
Natural History of Vulnerable Plaque

• It all starts with endothelial dysfunction.
• Early lesion is positively remodeled without lumen compromise until plaque burden reaches ca. 40%.
• Expanding necrotic core eventually ruptures:
  • When rupture occurs into the lumen, thrombus forms – this may be partially or totally occlusive.
• Thrombus organizes, the rupture is covered, and the cycle repeats.
• All of these phenomena can be demonstrated by VH.
Progression of Atherosclerosis

Modified from Virmani et al Arterioslerosis Thromb Vasc Biol 2002:20;1262

Intimal Xanthoma, Lipid streaks

Fibrous Cap Atheroma

Intimal thickening

Pathologic intimal thickening

SUPERFICIAL EROSION

Healing

Thrombosis

SUDDEN DEATH

Calcification

Cl

Thrombosis

Healing

Fibrocalcific plaque

Healing

Thrombosis

SUDDEN DEATH

SUDDEN DEATH

SUDDEN DEATH

But that is not the end of the story ...
Culprit of the Culprit

- The site of plaque rupture is generally not the site of maximal arterial narrowing.
- When a plaque ruptures, thrombus forms not only at the rupture site but also proximally and distally.
- The greatest narrowing is usually at the site of the distal thrombotic tail, which may be a centimeter or more from the rupture site.
Rupture of an Eccentric TCFA

Fall Out of the problem Distal Thrombotic Tail (Red cell rich)

Site of MLD

Thrombotic patch (platelet rich)

Proximal thrombotic tail (Red cell rich)

Site of the problem

R Virmani, CVPath and P Margolis, Volcano Corp.

Miami International Cardiology Consultants
Clinical Presentation NSTEMI

Rupture of the Culprit (TCFA) proximal to MLA

Thrombus

MLA
Rupture site

Thick fibrous plaque with necrotic core

Pre DCA  Post DCA

Pre thrombectomy  Post thrombectomy

Red cell rich thrombotic tail

Thrombus Study In Japan

Courtesy: O. Katoh  P. Margolis
How often do we fail to see and miss treating the ruptured TCFA because the thrombus obscures our scenery?

- D. Dudek, et al.
  - n=40
    - n=20 STEMI
    - n=20 NSTEMI
  - Aspiration if feasible
  - VH IVUS
  - Stenting by angio guidance only
  - VH IVUS
Case 13 → Clinical Presentation STEMI

Angiographic findings
Rupture of the Culprit of the Culprit: 2 mm proximal to MLA, still at the angiographically significant lesion site, atheroma volume = 65%

MLA (thrombus) atheroma volume = 89%
Case 13, treatment / Stenting

Final angiogram

Just proximal to stent

BMS 4.5 x 13 mm
Plaque/thrombus protrusion within stent

Just distal to the stent
Distance of the Plaque Rupture Site from the Min Lumen Diameter

No statistical significant difference between STEMI and NSTEMI

STEMI (n=20)    NSTEMI (n=14)
The location of the Rupture Site with Reference to the Min Lumen Cross Sectional area (CSA)
Virtual Histology Can Differentiate Between Low and High Risk Lesions in These Patients?

All PROSPECT slides courtesy of Gregg Stone, M.D.
The PROSPECT Trial

700 pts with ACS
UA (with ECGΔ) or NSTEMI or STEMI >24°
undergoing PCI of 1 or 2 major coronary arteries
at up to 40 sites in the U.S. and Europe

PCI of culprit lesion(s)
Successful and uncomplicated

Formally enrolled

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

Biomarkers
- Hs CRP
- IL-6
- sCD40L
- MPO
- TNFα
- MMP9
- Lp-PLA2
- others

PI: Gregg W. Stone
Sponsor: Abbott Vascular; Partner: Volcano
The PROSPECT Trial

3-vessel imaging post PCI

Culprit artery, followed by non-culprit arteries

Angiography (QCA of entire coronary tree)

- IVUS
- Virtual histology
- Palpography (n=~350)

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

MSCT Substudy
- N=50-100

F/U: 1 mo, 6 mo, 1 yr, 2 yr, ±3-5 yrs

Repeat imaging in pts with events

Proximal 6-8 cm of each coronary artery
MACE attributable to non-culprit lesions*

- Cardiac death
- Cardiac arrest
- Myocardial infarction
- Rehospitalization due to
  - Unstable angina
  - Progressive angina

MACE during FU were adjudicated by the CEC as attributable to culprit lesions (those treated during or before the index hospitalization) or non culprit lesions (untreated areas of the coronary tree) based on angiography (+ECGs, etc.) at the time of the event; events occurring in pts without angiographic follow-up were considered indeterminate in origin.
Lesions are classified into 5 main types:

1. Fibrotic
2. Fibrocalcific
3. Pathological intimal thickening (PIT)
4. Thick cap fibroatheroma (ThCFA)
5. VH-thin cap fibroatheroma (VH-TCFA) (presumed high risk)

**PROSPECT: Methodology**

Virtual histology lesion classification

Lesions are classified into 5 main types.
PROSPECT: Baseline Features

N = 697*

*3 patients who were never consented were de-registered
### Imaging Summary

**Length of coronary arteries analyzed (core lab)**

<table>
<thead>
<tr>
<th>Mean (mm)</th>
<th>Angiography (N=697)</th>
<th>IVUS (N=673)</th>
<th>VH data* (N=623)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LM</td>
<td>9.3 ± 4.3</td>
<td>12.8 ± 9.8</td>
<td>12.8 ± 9.7</td>
</tr>
<tr>
<td>LAD</td>
<td>153.5 ± 41.1</td>
<td>73.3 ± 34.1</td>
<td>73.8 ± 33.7</td>
</tr>
<tr>
<td>LCX</td>
<td>132.7 ± 49.9</td>
<td>63.3 ± 36.1</td>
<td>63.6 ± 36.0</td>
</tr>
<tr>
<td>RCA</td>
<td>148.3 ± 45.1</td>
<td>85.2 ± 39.6</td>
<td>85.5 ± 39.4</td>
</tr>
<tr>
<td><strong>Total per pt</strong></td>
<td><strong>437.9 ± 86.4</strong></td>
<td><strong>192.0 ± 97.7</strong></td>
<td><strong>206.7 ± 85.4</strong></td>
</tr>
<tr>
<td><strong>Total all pts</strong></td>
<td><strong>305,228.3</strong></td>
<td><strong>129,216.8</strong></td>
<td><strong>128,757.9</strong></td>
</tr>
</tbody>
</table>

*Note: VH data doesn’t register if there is no plaque*
Virtual histology
(N=2811 lesions in 611 pts)
- Mean plaque composition-

<table>
<thead>
<tr>
<th>Plaque subtype</th>
<th>N=2811</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrotic</td>
<td>2.5%</td>
</tr>
<tr>
<td>Fibrocalcific</td>
<td>1.2%</td>
</tr>
<tr>
<td>PIT</td>
<td>35.9%</td>
</tr>
<tr>
<td>Fibroatheroma</td>
<td>57.4%</td>
</tr>
<tr>
<td>- Thick cap</td>
<td>36.2%</td>
</tr>
<tr>
<td>- VH-TCFA</td>
<td>18.9%</td>
</tr>
<tr>
<td>- Single, - Ca</td>
<td>5.2%</td>
</tr>
<tr>
<td>- Single, + Ca</td>
<td>0.5%</td>
</tr>
<tr>
<td>- Multiple, - Ca</td>
<td>9.5%</td>
</tr>
<tr>
<td>- Multiple, + Ca</td>
<td>6.1%</td>
</tr>
</tbody>
</table>

- Dense calcium 13.0%
- Fibrotic 6.5%
- Fibrofatty 21.1%
- Necrotic core 59.4%
PROSPECT: MACE

- **MACE (%):**
  - **Time in Years:** 0, 1, 2, 3
  - **All:** 12.9%, 20.4%
  - **Culprit lesion (CL) related:** 11.6%, 12.9%
  - **Non culprit lesion (NCL) related:** 2.7%
  - **Indeterminate:** 2.7%

**Number at risk**
- **ALL:** 697, 557, 506, 480
- **CL related:** 697, 590, 543, 518
- **NCL related:** 697, 595, 553, 521
- **Indeterminate:** 697, 634, 604, 583
### PROSPECT: MACE

#### 3-year follow-up, hierarchical

<table>
<thead>
<tr>
<th>Event</th>
<th>All</th>
<th>Culprit lesion related</th>
<th>Non culprit lesion related</th>
<th>Indeterminate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac death</td>
<td>1.9% (12)</td>
<td>0.2% (1)</td>
<td>0% (0)</td>
<td>1.7% (11)</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>0.3% (2)</td>
<td>0.3% (2)</td>
<td>0% (0)</td>
<td>0% (0)</td>
</tr>
<tr>
<td>MI (STEMI or NSTEMI)</td>
<td>2.7% (17)</td>
<td>1.7% (11)</td>
<td>1.0% (6)</td>
<td>0.2% (1)</td>
</tr>
<tr>
<td>Rehospitalization for unstable or progressive angina</td>
<td>15.4% (101)</td>
<td>10.4% (69)</td>
<td>10.7% (68)</td>
<td>0.8% (5)</td>
</tr>
<tr>
<td>Composite MACE</td>
<td>20.4% (132)</td>
<td>12.9% (83)</td>
<td>11.6% (74)</td>
<td>2.7% (17)</td>
</tr>
</tbody>
</table>

Rates are 3-yr Kaplan-Meier estimates (n of events)
Baseline variables examined (n=152)

Demographic, history and PE (n=19)
Labs (n=7; including CrCl, lipids, hgbA1C, CRP)
Angio non core lab (n=1; visible lesions >30% DS)

QCA measures (n=12)
IVUS area and volumetric measures (n=22)
Virtual histology measures (n=74)

Treatment related (n=1; # vessels stented)
Medications in-hosp. and at discharge (n=16)
PROSPECT: Multivariable Correlates of Non Culprit Lesion Related Events

Independent predictors of patient level events by Cox Proportional Hazards regression

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR [95% CI]</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin dependent diabetes</td>
<td>3.32 [1.43, 7.72]</td>
<td>0.005</td>
</tr>
<tr>
<td>Prior PCI</td>
<td>2.03 [1.15, 3.59]</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Variables entered into the model: age, gender, hypertension, insulin dependent diabetes, prior PCI, CRP at baseline, family history
PROSPECT: Multivariable Correlates of Non Culprit Lesion Related Events

Independent predictors of lesion level events by Cox Proportional Hazards regression

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR [95% CI]</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{PB}_{\text{MLA}} \geq 70%$</td>
<td>$5.03 [2.51, 10.11]$</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>VH-TCFA</td>
<td>$3.35 [1.77, 6.36]$</td>
<td>0.0002</td>
</tr>
<tr>
<td>MLA $\leq 4.0 \text{ mm}^2$</td>
<td>$3.21 [1.61, 6.42]$</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Variables entered into the model: minimal luminal area (MLA) $\leq 4.0 \text{ mm}^2$; plaque burden at the MLA ($\text{PB}_{\text{MLA}}$) $\geq 70\%$; external elastic membrane at the MLA ($\text{EEM}_{\text{MLA}}$) $<$median (14.1 mm$^2$); lesion length $\geq$median (11.2 mm); distance from ostium to MLA $\geq$median (30.4 mm); remodeling index $\geq$median (0.94); VH-TCFA.
Number of factors present: $\text{PB}_{\text{MLA}} \geq 70\%$, MLA $\leq 4.0\text{mm}^2$ or TCFA

PB = plaque burden at the MLA
PROSPECT: VH-TCFA and Non Culprit Lesion Related Events

Lesion HR 3.90 (2.25, 6.76) 6.55 (3.43, 12.51) 10.83 (5.55, 21.10) 11.05 (4.39, 27.82)
P value <0.0001 <0.0001 <0.0001 <0.0001
Prevalence* 46.7% 15.9% 10.1% 4.2%

*Likelihood of one or more such lesions being present per patient. PB = plaque burden at the MLA
**PROSPECT: Thick CFA and Non Culprit Lesion Related Events**

- **Thick CFA** and **Non Culprit Lesion**
  - **Lesion HR**
    - **ThCFA**: 0.92 (0.52, 1.63) *P value*: 0.77
    - **ThCFA + MLA ≤4.0mm²**: 3.41 (1.75, 6.65) *P value*: 0.0003
    - **ThCFA + PB ≥70%**: 8.7 *P value*: <0.0001
    - **ThCFA + PB ≥70% + MLA ≤4mm²**: 5.02 (1.99, 12.63) *P value*: <0.0001
  - **Prevalence***
    - ThCFA: 2.0 %
    - ThCFA + MLA ≤4.0mm²: 1.8 %
    - ThCFA + PB ≥70%: 1.7 %
    - ThCFA + PB ≥70% + MLA ≤4mm²: 1.9 %

*Likelihood of one or more such lesions being present per patient. PB = plaque burden at the MLA.*
PROSPECT: Non Fibroatheromas and Non Culprit Lesion Events

- **Likelihood of one or more such lesions being present per patient.**
- **PB = plaque burden at the MLA**

### Median 3.4 year MACE rate per lesion (%)

<table>
<thead>
<tr>
<th>Lesion Type</th>
<th>Present</th>
<th>Absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non FA (all)</td>
<td>0.7%</td>
<td>3.0%</td>
</tr>
<tr>
<td>Non FA + MLA ≤4.0mm²</td>
<td>2.5%</td>
<td>2.0%</td>
</tr>
<tr>
<td>Non FA + PB ≥70% + MLA ≤4mm²</td>
<td>2.6%</td>
<td>2.1%</td>
</tr>
<tr>
<td>Non FA + PB ≥70%</td>
<td>5.6%</td>
<td>2.0%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lesion Characteristics</th>
<th>Present</th>
<th>Absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathological Intimal thickening</td>
<td>0.7%</td>
<td>3.0%</td>
</tr>
<tr>
<td>Fibrotic</td>
<td>2.5%</td>
<td>2.0%</td>
</tr>
<tr>
<td>Fibrocalcific</td>
<td>2.6%</td>
<td>2.1%</td>
</tr>
<tr>
<td>Pathological Intimal thickening</td>
<td>Present</td>
<td>Absent</td>
</tr>
</tbody>
</table>

- **Lesion HR**
  - Non FA (all): 0.22 (0.10, 0.49), *P* value = 0.0002, Prevalence* = 67.9%
  - Non FA + MLA ≤4.0mm²: 1.22 (0.44, 3.39), *P* value = 0.70, Prevalence* = 19.7%
  - Non FA + PB ≥70%: 1.25 (0.17, 9.01), *P* value = 0.83, Prevalence* = 5.6%
  - Non FA + PB ≥70% + MLA ≤4mm²: 2.60 (0.36, 18.84), *P* value = 0.34, Prevalence* = 2.7%

*Likelihood of one or more such lesions being present per patient. PB = plaque burden at the MLA*
PROSPECT 82910-012: 52 yo♂

2/13/06: NSTEMI, PCI of MLAD

2/6/07 (51 weeks later): NSTEMI attributed to LCX

Index 2/13/06

QCA PLCX DS 28.6%

Event 2/6/07

QCA PLCX DS 71.3%
Baseline PLCX
QCA: RVD 2.82 mm, DS 28.6%, length 6.8 mm
IVUS: MLA 5.3 mm$^2$
VH: ThCFA
Lesion: TCFA
Culprit sub-lesion: TCFA

Index: 4/15/05
Event: 6/25/07

* distal
* branch

Lesion: TCFA
1. TCFA
2. 4.3
3. 36%
Lesion: TCFA
Culprit sub-lesion: TCFA
Lesion: CaThCFA/ Echolucent Plaque
PROSPECT: Conclusions

Approximately 20% of pts with ACS successfully treated with stents and contemporary medical Rx develop MACE within 3 years, with adverse events equally attributable to recurrence at originally treated culprit lesions (treatment failure) and to previously untreated non culprit coronary segments.

Approximately 12% of pts develop MACE from non culprit lesions during 3 years of follow-up.

Patients treated with contemporary medical therapy who develop non culprit lesion events present most commonly with progressive or unstable angina, and rarely with cardiac death, cardiac arrest or MI.
• While plaques which are responsible for unanticipated future MACE are frequently angiographically mild, most untreated plaques which become symptomatic have a large plaque burden and a small lumen area (which are detectable by IVUS but not by angiography)

• The prospective identification of non culprit lesions prone to develop MACE within 3 years can be enhanced by characterization of underlying plaque morphology with virtual histology, with VH-TCFAs representing the highest risk lesion type

• The combination of large plaque burden (IVUS) and a large necrotic core without a visible cap (VH-TCFA) identifies lesions which are at especially high risk for future adverse cardiovascular events
Summary

• Six years and >150 publications later, the predictions we made here are proving to be accurate.
• VH can identify culprit lesions and even predict plaques that are likely to rupture in the future.
• Suppositions regarding the natural history of vulnerable plaque, that had been formed on the basis of postmortem data have now been demonstrated in vivo.
• With our new understanding of in vivo histology, we are able to plan and perform PCI in a more intelligent way with the hope of significantly reducing MACE events in the future.