The Multisite Nature of Vulnerable Plaque: Insights from Clinical, Angiographic, and IVUS Studies
Criteria for defining vulnerable plaque

• **Major criteria**
  - Active inflammation
  - Thin cap with large lipid core
  - Endothelial denudation with superficial platelet aggregation
  - Fissured plaque
  - Stenosis >90%

• **Minor criteria**
  - Superficial calcified nodule
  - Glistening yellow
  - Intraplaque hemorrhage
  - Endothelial dysfunction
  - Outward (positive) remodeling

*Naghavi et al. Circulation 2003;108:1664-72*
<table>
<thead>
<tr>
<th><strong>Major criteria</strong></th>
<th>Angiography</th>
<th>IVUS</th>
<th>Angioscopy</th>
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<td>Active inflammation</td>
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<td>Thin cap with large lipid core</td>
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<td>Endothelial denudation</td>
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<tr>
<td>Fissured plaque</td>
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<td>±</td>
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<tr>
<td>Stenosis &gt;90%</td>
<td>+</td>
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<td>Endothelial dysfunction</td>
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<td>Positive remodeling</td>
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<td>Three vessel imaging</td>
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Almost everything that we know about vulnerable plaque has come either from histopathology or from in vivo detection of plaque rupture in patients who present with acute coronary syndromes - NOT from prospective correlative studies or prospective identification of vulnerable plaques before they rupture and/or thrombose
70% of ACS culprit lesions

30% of ACS culprit lesions

The IVUS diagnosis of erosion is probably one of exclusion: ACS without positive remodeling or plaque rupture.
Number of thin-cap atheromas in patients dying with MI, sudden death, or noncardiac causes and studied at necropsy

Burke et al. J Am Coll Cardiol 2003;41:1855-917
20 pts (58 arteries with 21 culprit lesions) underwent with angioscopy 1 month post-MI

- **Culprit lesions**
  - Yellow plaques in 90%
  - Thrombi in 81%
  - 3.7±1.6 yellow plaques/infarct related artery

- **Non-infarct related arteries**
  - Yellow plaques in 95%
  - 3.4±1.8 yellow plaques/non-infarct related artery
  - 91% of 185 yellow plaques were at angiographically normal sites

- The number of yellow plaques did not correlate with age, gender, HTN, hypercholesterolemia, DM, smoking, total cholesterol, HDL, or triglycerides

Asakura et al. J Am Coll Cardiol 2001;37:1284-8
Three Vessel IVUS Imaging in 24 Pts with ACS and Positive Tn

- 50 ruptured plaques
  - 9 culprit lesion
  - 41 nonculprit lesion
- 19 pts had at least 1 nonculprit plaque rupture (79%)
  - 17 pts had 1 plaque rupture in a second artery
  - 3 pts had plaque ruptures in all 3 arteries

Rioufol et al. Circulation 2002;106:804-808
Frequency of ruptured plaques in 122 patients with MI and 3-vessel IVUS

There was no significant difference in MI patients with ST elevation (primary versus delayed stenting) or non-ST elevation

Hong et al Circulation (in press)
Number of ruptured plaques in patients with MI versus stable angina

% of patients

Number of ruptured plaques per patient

AMI (n=122)  
SAP (n=113)

Hong et al Circulation (in press)
• In the entire cohort of 235 patients, the only independent predictor of plaque rupture was myocardial infarction ($p<0.01$, OR=4.867).

• In MI patients, the only independent predictor of plaque rupture was elevated CRP level ($p=0.035$, OR=2.139).

• In stable angina patients, the only independent predictor was diabetes mellitus ($p=0.034$, OR=2.553).

• The only independent predictor of multiple plaque ruptures was myocardial infarction ($p=0.003$, OR=3.752).
Frequency of multiple plaque ruptures in 46 patients with a first ACS (<4 weeks from onset)

- **Culprit lesion**: 20/41 (49%)
- **Non-culprit lesion**: 7/81 (15%)
  - 1 in the culprit artery
  - 6 in a non-culprit artery

Sumitsuji et al. ACC 2004
One year follow-up of MI patients depending on whether they presented with 1 or multiple complex angiographic plaques

However, not all multiple ruptures are evident angiographically

- 300 plaque ruptures in 257 arteries of 254 patients
- Sensitivity of angiographic complex lesion morphology in detecting IVUS plaque rupture was 90%
- However, in 40 patients with multiple plaque ruptures by IVUS, angiography showed only one lesion

<table>
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<th>Angiographic Findings</th>
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<tr>
<td>Complex lesions</td>
<td>91%</td>
</tr>
<tr>
<td>Ulceration</td>
<td>81%</td>
</tr>
<tr>
<td>Intimal flap</td>
<td>40%</td>
</tr>
<tr>
<td>Thrombus</td>
<td>7%</td>
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<tr>
<td>Aneurysm</td>
<td>7%</td>
</tr>
<tr>
<td>Lumen irregularity</td>
<td>4%</td>
</tr>
<tr>
<td>2° complex lesions not imaged by IVUS</td>
<td>24%</td>
</tr>
</tbody>
</table>
Association of positive remodeling and plaque rupture and ACS

Maehara et al. J Am Coll Cardiol 2002;40:904-10
Schoenhagen et al. Circulation 2000;101:598-603
244 Patients with Stable Angina and Single Vessel Intervention

- Positive Pre-PCI Remodeling (n=70)
- Intermediate Pre-PCI Remodeling (n=110)
- Negative Pre-PCI Remodeling (n=64)

MACE (%): p=0.024
Target Lesion Restenosis (%): p=0.036
New Stenosis Formation (%): p=0.007

The likelihood of developing acute coronary syndromes correlates with the severity of coronary plaque burden. Measures of plaque burden may, therefore, be indirect indices of the number of vulnerable plaques.
Volumetric IVUS analysis of 19 RCA's with 1 or 2 focal de novo stenoses

<table>
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<tr>
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<th>Lesion</th>
<th>Non-Stenotic Segment</th>
<th>p</th>
</tr>
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<tbody>
<tr>
<td>EEM vol (mm³)</td>
<td>119 ± 111</td>
<td>459 ± 283</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Lumen vol (mm³)</td>
<td>29 ± 30</td>
<td>228 ± 156</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>P&amp;M vol (mm³)</td>
<td>90 ± 86</td>
<td>231 ± 140</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Length (mm)</td>
<td>9.4 ± 7.6</td>
<td>33.4 ± 13.5</td>
<td>&lt;0.0001</td>
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Therefore, 72±12% of the plaque volume (range 46-86%) was in nonstenotic segments.

Tinana et al. Am J Cardiol 2002;89:757-60
Calcium is an indirect measure of plaque

IVUS arc of calcium (°)

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<tr>
<th>Percentage</th>
<th>Total</th>
<th>Calcified</th>
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<tbody>
<tr>
<td>50%</td>
<td></td>
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<tr>
<td>51-75%</td>
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<td>40%</td>
</tr>
<tr>
<td>75-90%</td>
<td></td>
<td>70%</td>
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<tr>
<td>91-100%</td>
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<td>73%</td>
</tr>
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IVUS plaque burden

Volumetric index of total calcium

Total plaque volume (mm³)

r=0.57, p=0.011

Mintz et al. J Am Coll Cardiol 1997;29:268-74
Tinana et al. Am J Cardiol 2002;89:757-60
Multiple studies have shown that EBCT calcium score predicts acute coronary events at 1 year follow-up.


Arad et al. J Am Coll Cardiol 2000;36:1253-60
Calcium Does Not Increase the Biomechanical Instability of Atherosclerotic Plaques

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<thead>
<tr>
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<th>Stable (n=10)</th>
<th>Ruptured (n=10)</th>
<th>p</th>
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<tr>
<td>Ca++ CSA (%)</td>
<td>4.1</td>
<td>5.4</td>
<td>0.4</td>
</tr>
<tr>
<td>Lipid CSA (%)</td>
<td>14.1</td>
<td>2.8</td>
<td>0.3</td>
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<tr>
<td>Maximal stress (kPa)</td>
<td>286</td>
<td>458</td>
<td>0.038</td>
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When fibrous plaque was replaced with calcium, stress changed insignificantly (p=0.85). In contrast, stress decreased by 26% (p=0.02) when lipid was replaced with fibrous plaque.

Huang. Circulation 2001;103:1051-6
Relationship between left main plaque progression and cardiac events

What separates lesions with asymptomatic plaque rupture from plaque ruptures that cause acute symptoms?
42 Consecutive Pts with Angiography Both Before and After MI

- 29 patients had a newly occluded artery
  - In 19 pts, the artery previously had a <50% DS
  - In only 10 pts the occlusion was at the site of the most severe stenosis

"Because the aggregate risk of rupture associated with many non-significant lesions (each with an admittedly lower individual risk potential) exceeds that of the fewer significant lesions, an MI will more likely originate from a nonsignificant lesion."

Kern and Meier. Circulation 2001;103:3142-9

Comparison of Culprit and Non-Culprit Rupture Sites in ACS Patients with Rupture Sites in Non-ACS Patients

Independent predictors of ACS were MLA and thrombus (both p=0.01)

Fuji et al. Circulation 2003;108:2473-8
Conclusions

- We do not have a technique to detect vulnerable plaques in vivo; we can only detect ruptured (complicated) plaques ± thrombus formation. Histology shows an average of three unruptured thin-capped atheromas in men dying from acute myocardial infarction.

- Multiple plaque ruptures are common in ACS patients, but the exact frequency is still debatable
  - More common with IVUS than angiography (specific, but not sensitive)
  - Multiple complex angiographic plaques and positive IVUS culprit lesion remodeling are associated with worse outcomes

- Most atherosclerosis (approximately 75%) is in non-stenotic segments where vulnerable plaques appear to arise.
  - Calcium is a marker for total plaque burden from which a vulnerable plaque arises

- Some plaque ruptures lead to acute coronary syndromes, but others are asymptomatic. Determinants include
  - Pre-event lumen dimensions
  - Whether or not rupture leads to thrombus formation and lumen compromise