Struggles to Stabilize Vulnerable Plaques

Angioplasty Summit
Introduction
Normal Coronary Artery and Its Histology
Coronary Arteries in Each Stages

- Normal coronary artery
- Fatty streak (FS)
- Ruptured plaque
## Risk Factors

<table>
<thead>
<tr>
<th>Major</th>
<th>Predisposing</th>
<th>Conditional</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cigarette smoking</td>
<td>Family history of premature CHD</td>
<td>Elevated serum triglycerides</td>
</tr>
<tr>
<td>Elevated blood pressure</td>
<td>Ethnic characteristics</td>
<td>Small LDL particles</td>
</tr>
<tr>
<td>Elevated total cholesterol (and LDL-C)</td>
<td>Psychological factors</td>
<td>Elevated serum homocysteine</td>
</tr>
<tr>
<td>Low serum HDL-C</td>
<td></td>
<td>Elevated serum lipoprotein(a)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Advancing age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical inactivity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>?</td>
<td></td>
<td>Prothrombotic factors (eg, fibrinogen, TF)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inflammatory markers (eg, CRP)</td>
</tr>
</tbody>
</table>

Fuster V, Gotto A. *Circulation* 2000; 102:IV-94 (Framingham, AHA)
<table>
<thead>
<tr>
<th>Functions of the Normal Endothelium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Permeability barrier</td>
</tr>
<tr>
<td>Production of thrombogenic and nonthrombogenic products</td>
</tr>
<tr>
<td>Metabolism of vasoactive substances</td>
</tr>
<tr>
<td>Production of cytokines and growth factor</td>
</tr>
<tr>
<td>Synthesis of leukocyte adhesion molecules</td>
</tr>
<tr>
<td>Synthesis of basement membrane constituents</td>
</tr>
<tr>
<td>Lipid metabolism</td>
</tr>
</tbody>
</table>

**Vascular Endothelial Cell**

- **Anticoagulant Mechanisms**
  - PGI₂ (Prostaglandin I₂)
  - Thrombomodulin
  - Heparan Sulfates
  - t-PA (Tissue Plasminogen Activator)

- **Procoagulant Mechanisms**
  - PA₄ (Plasminogen Activator Inhibitor)
  - vWF (von Willebrand factor)
Thrombotic and antithrombotic properties of the endothelium
Development of Atherosclerotic Plaque

Berlin et al, Circulation 1995;91:2488-2496
Sequence of Leukocytic Events in Inflammation

Rolling → Activation → Adhesion → Transmigration

Selectins
(P, E, L)

Integrins / Immunoglobulins
(LFA 1, MAC 1 / ICAM 1)
(VLA-4 / VCAM-1)

PECAM-1 others

Chemoattractants

Stimulus

Activation

Chemotaxis
Atherosclerotic Plaque Progression and Disruption

Blood Flow

Coagulation
TF + VIIa
TF:VIIa
Prothrombin
Xa
Thrombin
Fibrinogen
Fibrin

Fibrinolysis

Lumen

Endothelium

Media
Smooth Muscle Cells (SMC)

Platelets Aggregation

Dysfunctional Endothelium

SMC Contraction

TxA2
ET-1

TF
MMPs
**Proposed Histopathological and Clinical Criteria for Definition of Vulnerable Plaques**

**Major Criteria:**

1. Active inflammation (monocyte/macrophage infiltration)
2. Thin cap (<65μm) with Large Lipid Core (>40%)
3. Endothelial Denudation with Superficial Platelet Aggregation
4. Fissured / Wounded Plaque
Characteristics of Plaque Prone to Rupture

Phase and Lesion Morphology of Progression of Coronary Atherosclerosis

- Fatty Streak
- Pre-atheroma
- Atheroma
- Fibro-atheroma
- Rapid Progression
- Rupture - Erosion
- Stabilization
- Regression

Acute Syndromes:
- Myocardial infarction
- Unstable angina
- Ischemic sudden death

No Symptoms

Phase 1

Phase 2

Phase 3

Phase 4

Phase 5

Angina Pectoris
High-Risk, Disrupted and Fibro-Calcific Plaques

Percent Lipid Core Area

Elastic Trichrome Stain

High-Risk, Disrupted and Fibro-Calcific Plaques

Fibrous Cap Thickness (microns)

IV-Va

P=0.0001

177 ± 162

183

337

17

High-

Risk

(n=89)

Disrupted

(n=55)

Fibro-Ca++

(n=18)

Elastic Trichrome Stain

High-Risk, Disrupted and Fibro-Calcific Plaques

Inflammation: Tunica Intima

Relationship of Fibrous Cap Thickness to Macrophage Infiltration

Cell Mean for % Kp-1

- less than 65 mm
- 66 to 200 mm
- 201 – 300 mm
- more than 300 mm

P = 0.03
P = 0.06
Proposed Histopathological and Clinical Criteria for Definition of Vulnerable Plaques

Minor Criteria:

1. Superficial Calcified nodule
2. Glistening Yellow
3. Intraplaque Hemorrhage
4. Critical Stenosis
5. Positive Remodeling?
## VP in Acute Coronary Syndromes

<table>
<thead>
<tr>
<th>Coronary Syndromes</th>
<th>No.</th>
<th>Thrombus Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute Myocardial Infarction</strong></td>
<td>n=15</td>
<td></td>
</tr>
<tr>
<td>Plaque Rupture</td>
<td>9 (60%)</td>
<td>80%</td>
</tr>
<tr>
<td>Plaque Erosion</td>
<td>3 (20%)</td>
<td></td>
</tr>
<tr>
<td>Stable Plaque</td>
<td>3 (20%)</td>
<td></td>
</tr>
<tr>
<td><strong>Sudden Death</strong></td>
<td>n=126</td>
<td></td>
</tr>
<tr>
<td>Plaque Rupture</td>
<td>38 (30%)</td>
<td></td>
</tr>
<tr>
<td>Plaque Erosion</td>
<td>21 (17%)</td>
<td></td>
</tr>
<tr>
<td>Calcified Nodule</td>
<td>3 (2%)</td>
<td></td>
</tr>
<tr>
<td>Stable Plaque</td>
<td>64 (51%)</td>
<td></td>
</tr>
</tbody>
</table>
Detection of Vulnerable plaque
Diagnosis and Screening – Plaque Level

- Plaque inflammation (macrophage density or rate of monocyte infiltration)
- Matrix digesting enzyme activity in the cap (MMP 2, 3, 9, etc)
- Endothelial denudation or dysfunction (local NO production, anti/pro-coagulation properties of the endothelium)
- Superficial platelet aggregation and fibrin deposition (residual mural thrombus)
- Plaque cap thickness with a resolution of <65~100 micron
- Collagen content, lipid core size, mechanical stability (stiffness and elasticity)
Diagnosis and Screening – Plaque Level

- Calcification burden and pattern (nodule, scattered, intimal, deep)
- Angiogenesis, leaking vasa vasorum, and intraplaque hemorrhage
- Presence of certain microbial antigens
- Rate of apoptosis (apoptosis protein markers, coronary microsatellite, etc)
- Shear stress imaging (flow pattern throughout coronary artery)
Diagnosis and Screening–Systemic Level

• Markers of blood fibrinolysis

• Markers of lipid-peroxidation

• PAPP-A, pregnancy associated plasma protein-A

• Plaque specific markers of immune activation (anti-LDL ab)
Diagnosis and Screening–Systemic Level

- CRP, CD 40L, ICAM-1, VCAM, and other serological markers of inflammation

- MMPs and acidic digesting proteinases and their inhibitors such as TIMMPs and cystatin

- Circulating apoptosis markers

- Markers of blood hypercoagulability
Immunolocalization of CRP in Coronary Artery Section

Burke A, et al. 
*Circulation.* 2002;105:2019
### Serum hs-CRP Correlated with Immunohistochemical Staining Intensity

<table>
<thead>
<tr>
<th>CRP</th>
<th>CRP staining intensity of plaques*</th>
<th>Mean number of thin cap atheroma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low CRP group (&lt;1.0mg/mL)</td>
<td>2.9 ±0.5</td>
<td>0.95 ±0.22</td>
</tr>
<tr>
<td>High hs-CRP group (&gt;3.2mg/mL)</td>
<td>6.2±0.6</td>
<td>3.0 ±0.3</td>
</tr>
</tbody>
</table>

*Grading of staining intensity was assessed on macrophages and Lipid core. A quantitative score of 0 to 4 was applied to each. A sum of the 2 scores resulted in overall grading system of 0 to 8
**Imaging the Vulnerable Plaque**

- **Two Important Features**;
  - degree of luminal obstruction
  - composition of the plaque

- **Invasive Techniques**
  - angiography
  - intravascular ultrasound
  - angioscopy
  - optical coherence tomography

- **Noninvasive Techniques**
  - B-mode ultrasound
  - MDCT, MRI, Scintigraphy
Morphology vs. Activity Imaging

Thermography, Spectroscopy, MRI with targeted CM

Activity

Active and inflamed plaque

Inactive and non-inflamed plaque

Morphology

IVUS

OCT

MRI w/o CM
Angiography

Thrombus, Ulceration, Plaque Irregularity, Impaired Flow

Angiography

Multiple Atherosclerotic Plaque Ruptures Detected by IVUS

Rioufol et al. Circulation 2002; 106:804-808
Vulnerable Plaques in ACS

79% of ACS patients have > 1 ruptured plaque

Rioufol et al. Circulation 2002; 106:804-808

# Ruptured plaques in addition to culprit lesion
IVUS Imaging of VP

Ruptured plaque
Angioscopy

- Characterize plaque morphology directly
  - Yellow plaque: presence of lipid-laden atheroma
  - Gray-yellow plaque: degenerated or fibrous plaque
  - Gray-white plaque: fibrous plaque without degeneration

- Considered the gold standard for the detection of thrombus and luminal dissection \textit{in vivo}

- \textit{But, Invasive and Subjective}
Angioscopy

• Biological tissues have unique absorbance in the NIR wavelength range
• NIR light has enough penetration that may obtain spectra through blood
Tissue Evaluation by Near-IR Spectroscopy

Absorbance peaks are caused by:
- Combinations of fundamental bonds (C-H, C=C, C=O)
- Electron transitions in the heaviest atoms
Advantages of Near-IR Spectroscopy For Vulnerable Plaque Research

- Analysis under 1 second
- Simultaneous, multi-component, non-destructive analysis
- Chemical, biological and molecular information
- Automated predictions using computer algorithms
- Detection limits can be very low (from picograms to planets)
- Cost per analysis is minimal (no reagents used)

**Coronary Composition by NIR Spectroscopy**

**147 Human Coronary Sections**

**Hypothesis**
- Lipid pool in coronary plaques

**Methods**
- Spectrometer: Foss/NIRSystems
- H & E and Trichrome staining

**Identification Algorithm Model**
- Training Set (76 sections)
- Validation set (70 sections)

Moreno PR, et al. JACC 2001;37:356A
Coronary Plaque Lipid Pool Detection by Near-IR Spectroscopy

Validation set (70 sections)

<table>
<thead>
<tr>
<th>NEAR-INFRARED SPECTROSCOPY</th>
<th>HISTOLOGY</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+</td>
</tr>
<tr>
<td>+</td>
<td>21</td>
</tr>
<tr>
<td>-</td>
<td>1</td>
</tr>
</tbody>
</table>

- Sensitivity (%) 95
- Specificity (%) 96
- PPV (%) 91
- NPV (%) 98

Moreno PR, et al. JACC 2001;37:356A
Optical Coherence Tomography

- Analogous to ultrasonography, measuring the intensity of back-reflected infrared light rather than sound.

- Characteristics
  
  First, its resolution, at 4 to 20μm, is higher than that of any currently available imaging technology.

  Second, acquisition rates are near video speed.

  Third, OCT catheters consist of simple fiber optics and contain no transducers within their frame (catheters are slim and inexpensive).

  Fourth, OCT systems are compact and portable.
**MGH OCT System**

**Technical Data**

- Optical wavelength: 1300 nm
- Image acquisition rate: 4-8 images/sec
- Catheter: 3.0 F
- Axial Resolution: 10 μm
- Transverse Resolution: 25 μm
- Data storage: Digital
OCT vs IVUS: Fibrous Plaque
OCT vs IVUS: Lipid Rich Plaque
Optical Coherence Tomography

- But, Light scattering occurs from RBCs, saline flushes were required during imaging at 2~3mL/s
Thermography
Thermography

**In Vivo Coronary Sinus Thermography**

![Graph showing temperature changes over time](image)

- **Coronary Sinus**
- **Right Atrium**
Results of Thermography

Temperature difference (°C)

Control  CAD

P=0.02
Electron beam tomography permits the sensitive detection and quantification of coronary artery calcification.
Coronary calcium vs Overall Plaque burden

The amount of calcium correlates to overall plaque burden

However, no close relationship between calcium in a vessel segment and degree of luminal stenosis.
EBCT

Even though calcium does not permit to specifically detect vulnerable plaque, it is wrong to assume that calcified plaques are stable or more frequently stable than non-calcified plaques.
EBCT

632 asymptomatic patients
32 +/- 7 months follow-up
myocardial infarction and death

**Annual event rate:**

- 0.1% for calcium score of 0
- 2.1% for calcium score 1-99
- 4.1% for calcium score 100-400
- 4.8% for calcium score > 400

70% of events in 25% of patients with highest calcium score

Raggi et al, Circulation 2000;101:850-855
What is the potential clinical role of coronary calcium detection?

In clinical practice, clearly low-risk and clearly high-risk individuals probably do not need further testing for risk stratification.

Intermediate risk patients, however, might profit:

**ACC/AHA:** selected use of coronary calcium scores when a physician is faced with the patient with intermediate coronary artery disease risk may be appropriate.
Role of EBCT in risk stratification?

Coronary calcium, even though it does not permit to detect the „vulnerable plaque““, permits to identify the patient with high plaque burden.

The detection of coronary calcium therefore permits identification of patients at increased risk for coronary artery events.

It may be beneficially applied in patients who seem to be at „intermediate“ risk.
**MSCT**

- **Detection of stenoses**
  - Calcium
  - Small vessels

- **Characterization of plaques**
  - Identify atheromas
  - Follow up under therapy

- **Acute coronary event**
  - Intracoronary thrombus
  - Myocardial infarction
Non-calcified Plaque in MSCT:
Left Coronary Artery (RAO)

Coronary Angiography

MDCT & VRT
Right Coronary Artery (LAO)

Coronary Angiography

MDCT & VRT
## Coronary Stenoses
### CT Angio & Angiography

<table>
<thead>
<tr>
<th>Author</th>
<th>Journal</th>
<th>PPV</th>
<th>NPV</th>
<th>n.a.</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Niemann</td>
<td>Lancet 2001</td>
<td>81%</td>
<td>97%</td>
<td>30%</td>
<td>35</td>
</tr>
<tr>
<td>Achenbach</td>
<td>Circulation 2001</td>
<td>59%</td>
<td>98%</td>
<td>32%</td>
<td>64</td>
</tr>
<tr>
<td>Mean/sum</td>
<td></td>
<td>70%</td>
<td>98%</td>
<td>31%</td>
<td>99</td>
</tr>
</tbody>
</table>

Niemann, Lancet, 2001
Achenbach, Circulation, 2001
Mean/sum

Coronary Plaque Imaging

MDCT

Coronary Angiography
Atheroma

Risk Factors
- Cholesterol
- Smoker
- No calcium
Calcified Nodule

- 62 /M
- Suspicion of CAD
Fibrocalcified Plaque

100 HU
Thrombus

Risk Factors

Hypertension
Smoker

No calcium
Acute Posterior Wall Infarction
Limitations of CT Angio

- **Artifacts**
  - Cardiac motion
  - Breathing
  - Blooming

- **Poor opacification**

- **Small vessel**
Black-Blood Coronary Plaque MR

Eccentric ("lipid-rich")  Concentric ("fibrotic")  Ectatic ("remodeled")

Integration of CT and MRI

High Risk Asymptomatic Patient

High CT Coronary Calcium Score

Contrast Enhanced CTA/MRA

No Plaque/Stenosis

Plaque Burden/Stenosis

MR Plaque Characterization

Fibrotic (Vc)

Thrombus (VI)

Atheroma (IV/Va)

Ca Plaque* (Vb)

Identified by CT

Fayad ZA, Fuster V, Nikolaou K, Becker C *Circulation*. 2002;106:2026
Characterization of Human Coronary Lesions by Magnetic Resonance Microscopy

Fibrous plaque
Ruptured plaque / thrombus
Inner wall surface

3D images isotropic voxel 39 microns
Stabilization of Vulnerable Plaques
Short-Term Stabilization of Destabilized Plaques

Percutaneous intervention with stenting and GP IIb/IIIa inhibitors

Long-term antithrombotic + anticoagulant therapy (ASA+Coumadin)
- APRICOT-2, ASPECT-2, WARIS-2

Long-term combined antithrombotic therapy (ASA+Clopidogrel)
- CURE

High dose lipid lowering therapy
- MIRACL

Long-Term Stabilization of Destabilized Plaques

Culprit lesion undergoing PCI:
Reducing restenosis
- Drug-eluting stents
- Brachytherapy
- Stents + GP IIb/IIIa inhibitors in diabetics

Non-PCI lesion
Reducing future acute events
- Antithrombotics
- Lipid lowering agents
- ACE inhibitors
- β-blockers

Potential Mechanisms of Action of Statin therapy
Effect of Statins on CHD Event Reduction

CHD event reduction (%)

Rosenson et al JAMA 1998;279:1643-50
Summary of the Results of the 15 Published Angiographic Lipid Lowering Trials

In control population
- <10% of patients showed lesion regression
- >50% of patients showed lesion progression
- Average estimates of disease severity per patient progressed by ~ 3%

In treated population
- ~25% of patients regressed
- ~25% of patients progressed
- Average estimates of disease severity per patient regressed by ~1%
### Lipid Lowering Angiographic Trials—Reduction in CV Events

NHLBI, CLAS, POSCH, FATS, SCOR, STARS, SCRIPT, HARP, MARS, CCAIT, MAAS, REGRESS, HEIDELBERG, PLACI

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Reference</th>
<th>Treated</th>
<th>Relative Risk</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Cardiac Events</td>
<td>602/2106</td>
<td>417/2173</td>
<td>0.69</td>
<td>0.62-0.76</td>
</tr>
<tr>
<td></td>
<td>(28.1%)</td>
<td>(19.2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac Mort/Non-fatal MI</td>
<td>231/1982</td>
<td>151/2049</td>
<td>0.64</td>
<td>0.53-0.78</td>
</tr>
<tr>
<td></td>
<td>(11.7%)</td>
<td>(7.4%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Peroxisomal Proliferator-Activated Receptors (PPARs) Agonists

Pleitropic effects of PPAR-γ agonist

- Reduced Thrombosis
- Reduced ET-1, PAI-1
- Reduced MCP-1, VCAM, chemokines
- Reduced Recruitment, adherence and homing of macrophages

Blood

- Increased Scavenger receptor CLA-1
- Increased APO A-1
- Increased HDL
- Increased Reverse cholesterol transport

Hepatic cell

- ABC-1 receptor

Vessel wall

- Reduced MMPs
- Reduced SMC migration
- Reduced ET-1
- Reduced Vasoconstriction
Potential Antiatherosclerotic Mechanisms of Action for Amlodipine

Future Pharmacologic Stabilization of Vulnerable Plaque?

- Antioxidants
- Antibiotics
- Angiogenesis inhibitors
- MMP inhibitors
- Apo A1 Milano, HDL
- TF inhibitors
- Cytokines antagonists (selectins, ICAM, VCAM, NFkB, MCP-1, PDGF)
- Antibodies to CD40 ligand
- Cap strengthening (TGF-beta, antibody to IFN-gamma)
- Anti-inflammatory agents
Conclusion

(1) The concept of plaque stabilization should be expanded to include treatment for plaques that have already destabilized as well as preventing future destabilization in quiescent plaques.

(2) For the destabilized plaque, percutaneous intervention is an effective method of short-term stabilization in selected cases. As an alternative, new randomized trials with either long-term aspirin therapy in combination with coumadin, the combination of aspirin and clopidogrel, or high-dose lipid-lowering therapy will reduce subsequent coronary events potentially through plaque-stabilizing effects. Short-term powerful antithrombotic agents alone such as GP IIb/IIIa inhibitors in this setting do not appear effective in reducing events on follow-up.
Conclusion

(3) ACE inhibitors and β-blockers in addition to lipid-lowering agents potentially possess plaque-stabilizing properties that contribute to their beneficial effects on reducing subsequent events. Aspirin reduces future events by its antiplatelet effects and possibly through an antiinflammatory mechanism.
The End