High-risk vulnerable plaques.

Kostis Raisakis
“G.Gennimatas” General Hospital of Athens
Overview:

1. Definition-Pathology

2. Diagnostic Strategies
   - Invasive
   - Non Invasive

3. Prognostic Value of Detection

4. Treatment
   - General
   - Focused
Overview:

1 Definition-Pathology

2 Diagnostic Strategies
   • Invasive
   • Non Invasive

3 Prognostic Value of Detection

4 Treatment
   • General
   • Focused
CV Death

Necrotomic Examination

Culprit Lesions

Histological Similarities with Non-culprit Lesions

Vulnerable Plaques

Ex-vivo verification of Modalities

New Modalities
- Morphological
- Molecular
- Biochemical

Vulnerable Plaques

Ex-vivo verification of Modalities

- Introduction
  - Treatment Efficiency
    - Morphological
    - Molecular
    - Biochemical
  - Prognostic Value
    - Morphological
    - Molecular
    - Biochemical
  - Algorithms
    - Morphological
    - Molecular
    - Biochemical

- In-vivo comparison
Any thrombosis-prone plaque or plaque at a risk of rapid progression, with potential of becoming a culprit lesion and triggering an ACS, independent of its specific morphology.
1 Vulnerable Plaque Definition
Pathological Substrate of Thrombosis

1 Vulnerable Plaque Definition
Thin-cap Fibroatheroma (TCFA)

- Increased Plaque size
  Positive remodeling

- Increased Necrotic core
  ~34% of plaque area
  ~3.8 mm² & ~9 mm long

- Fibrous cap
  Reduced Thickness (<65 μm)
  Increased Macrophage Density, ~26% of cap
  Reduced Smooth Muscle Cells

- Increased Angiogenesis
  New Microvessels
  Intraplaque hemorrhage

- Perivascular inflammation

- Reduced Calcification & Spotty Calcification

Virmani R, et al. JACC 2006
Vulnerable Plaque Definition

Challenges to the VP concept

Multiple Vulnerable plaques co-exist in the coronaries

How many of them did rupture?

All ruptures all fatal?

All fatal events are caused by plaque rupture?

The vast majority of so called Vulnerable plaques do not exhibit clinical instability and seldom provokes ACS

From Vulnerable Plaque to Vulnerable Patient

Toutouzas et al, EHJ 2015
Overview:

1 Definition-Pathology

2 Diagnostic Strategies
   • Invasive
   • Non Invasive

3 Prognostic Value of Detection

4 Treatment
   • General
   • Focused
# Invasive Imaging

## Available Techniques for VP assessment

<table>
<thead>
<tr>
<th>Parameter</th>
<th>IVUS</th>
<th>IVUS VH</th>
<th>NIRS</th>
<th>OCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipid core</td>
<td>-/+</td>
<td>-</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td>Necrotic core</td>
<td>-/+</td>
<td>+++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Remodelling</td>
<td>+++</td>
<td>+++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Plaque burden</td>
<td>+++</td>
<td>+++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cap thickness</td>
<td>-</td>
<td>-</td>
<td>-/+</td>
<td>+++</td>
</tr>
<tr>
<td>Macrophages</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Calcific nodules</td>
<td>++</td>
<td>++</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>Microvessels</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>++</td>
</tr>
</tbody>
</table>
2a Invasive Imaging/IVUS

Grey Scale

- Stenosis Severity
- Plaque Burden
- Positive Remodeling
- Calcification
Tissue components of the plaque are correlated to specific colors.
Invasive Imaging/IVUS
Plaque Characterization with IVUS-VH

Intima thickness

thick-cap fibroatheroma

thin-cap fibroatheroma

Fibro-calcified Plaque
Invasive Imaging/OCT

Plaque Characteristics

- High resolution
- Cap thickness
- Lipid core
- Macrophages
- Microvessels
- Spotty Calcification
Invasive Imaging/OCT
Plaque Characterization with μOCT

Liu L et al, Nat Med. 2011
Invasive Imaging/NIRS
Chemical Characterization of the Arterial Wall

Garg et al, Eurointervention 2013
Madder et al, JACC Cardiovasc Interv. 2013
Invasive Imaging/NIRS
Chemical Characterization of the Arterial Wall

Toutouzas et al, JACC 2007
2a Novel Intravascular Imaging

Bourantas et al, EHJ. 2016
Hybrid Intravascular Imaging

IVUS-OCT

Bourantas et al, EHJ. 2016

Li et al, J Biomed Opt 2013
Non Invasive Imaging/MDCT

- Detection of Calcium/Calcium score
- Spatial resolution (240-600μm) does not permit the direct visualization of thin fibrous cap
- Dimensions of the large necrotic core reach the detection threshold of CTA
- Napkin-Ring Sign
Non Invasive Imaging/CTA
Plaque Characterization

Motoyama et al, JACC 2007
Non Invasive Imaging/MDCT

Plaque Characterization

ACS

positive remodeling
NCP plaque (areas of 30 HU)

spotty calcification

Stable Angina Pectoris

Motoyama et al, JACC 2007
plaque core with low CT attenuation surrounded by a rim-like area of higher CT attenuation as napkin ring like

- large central lipid core surrounded by fibrous plaque tissue.
- deep micro-calcifications
- intramural thrombus
- neovascularization,
Non Invasive Imaging/MDCT
Plaque Characterization/ Semi-automated software tool.

Quantitative plaque characteristics of the worst coronary segment for each of the high-risk plaque features stratified by diagnosis of acute coronary syndrome.

<table>
<thead>
<tr>
<th></th>
<th>ACS (N = 37)</th>
<th>No ACS (N = 223)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume of plaque with &lt;60 HU (mm³)</td>
<td>11.9 (6.1–25.1)</td>
<td>2.0 (0.4–5.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Volume of plaque with &lt;30 HU (mm³)</td>
<td>3.8 (1.7–7.3)</td>
<td>0.7 (0.1–2.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Spotty calcium, n (%)</td>
<td>37 (100.0)</td>
<td>194 (87.0)</td>
<td>0.020</td>
</tr>
<tr>
<td>Remodeling index</td>
<td>1.36 (1.14–1.52)</td>
<td>1.12 (1.01–1.24)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Positive remodeling, n (%)</td>
<td>31 (83.8)</td>
<td>126 (56.5)</td>
<td>0.002</td>
</tr>
<tr>
<td>Plaque length (mm)</td>
<td>22.2 (15.6–31.4)</td>
<td>7.9 (4.2–12.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diameter stenosis (%)</td>
<td>66.5 (44.5–83.3)</td>
<td>14.7 (7.6–23.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ROMICAT score, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Score = 0</td>
<td>0 (0.0)</td>
<td>18 (8.1)</td>
<td></td>
</tr>
<tr>
<td>Score = 1</td>
<td>1 (2.7)</td>
<td>81 (36.3)</td>
<td></td>
</tr>
<tr>
<td>Score = 2</td>
<td>11 (29.7)</td>
<td>87 (39.0)</td>
<td></td>
</tr>
<tr>
<td>Score = 3</td>
<td>23 (62.2)</td>
<td>36 (16.1)</td>
<td></td>
</tr>
<tr>
<td>Score = 4</td>
<td>2 (5.4)</td>
<td>1 (0.5)</td>
<td></td>
</tr>
</tbody>
</table>

ACS = Acute Coronary Syndrome, HU = Hounsfield Units; IQR = Interquartile Range.

Ferencik et al, J Cardiovasc Comput Tomogr. 2015
Non Invasive Imaging/PET-CT
fluorodeoxyglucose F^{18} (^{18}F- FDG)

Naghavi et al, Circulation 2003
Non Invasive Imaging/PET-CT

$^{18}$F- FDG versus $^8$F-sodium fluoride ($^{18}$F-NaF)

Joshi et al, Lancet 2014
Overview:

1. Definition-Pathology

2. Diagnostic Strategies
   - Invasive
   - Non Invasive

3. Prognostic Value of Detection

4. Treatment
   - General
   - Focused

5. Future Perspectives
3 Prognostic Value of Imaging VP
IVUS-VH/PROSPECT Study

<table>
<thead>
<tr>
<th>Lesion Hazard Ratio (95% CI)</th>
<th>P value</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCFA (all)</td>
<td>3.90 (2.25–6.76)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TCFA + MLA ≤4 mm²</td>
<td>6.55 (3.43–12.51)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TCFA + PB ≥70%</td>
<td>10.83 (5.55–21.10)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TCFA + PB ≥70% + MLA ≤4 mm²</td>
<td>11.05 (4.39–27.82)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

3 Prognostic Value of Imaging VP

IVUS-ESS/ PREDICTION Study

Prognostic Value of Imaging VP

ATHEROREMO-NIRS Study

LCBI=Lipid Core Burden Index

Oemrawsingh et al, JACC 2014
3 Prognostic Value of Imaging VP
CTA-Napkin ring sign

PR=Positive Remodeling
LAP=Low Attenuation Plaque

Otsuka et al. JACC Caridiovasc Imaging 2013
3 Prognostic Value of Imaging VP CTA

HRP=High Risk Plaque (positive remodeling and low attenuation plaques)
SS=Significant stenosis

Motoyama et al. JACC 2015
Prognostic Value of Imaging VP PET/CT $^{18}$F-FDG

TBR=Target to Background Ratio

Figueora et al, JACC Cardiovasc Imaging. 2013
Prognostic Value of Imaging VP

PET/18F-NaF

Patients with myocardial infarction and multi-vessel disease (n=700)

In Vivo Plaque Characterisation Sub-study (n=80)

Invasive plaque assessment during index coronary angiogram

Baseline 18F-Fluoride PET and CTCA (<21 days from ACS)

Short-term Reproducibility Sub-study (n=20)

Repeat PET-CTCA (2±1 week)

Natural History Sub-study (n=80)

Repeat PET-CTCA at:
- 6±1 week (n=20)
- 12±2 weeks (n=20)
- 26±2 weeks (n=20)
- 52±2 weeks (n=20)

Telephone interview at 1 year

Follow-up CTCA at 2 years

Ongoing periodic review of Electronic Health Records and Telephone Interview as necessary
Overview:

1. Definition-Pathology

2. Diagnostic Strategies
   • Invasive
   • Non Invasive

3. Prognostic Value of Detection

4. Treatment
   • General
   • Focused
Medical Treatment for VP/Statins
Plaque regression

\[ y = 0.055x - 4.477 \]
\[ r^2 = 0.926 \]

Tsujita et al. J Am Coll Cardiol. 2015
Medical Treatment for VP/Statins
Atheroma Calcification promotion

PAV=percent atheroma volume

Puri et al. J Am Coll Cardiol. 2015
Medical Treatment for VP/Statins
NIRS/Plaque lipid depletion

LRNC=Lipid-Rich Necrotic Core

Zhao et al. JACC Cardiovasc Imaging. 2011
Medical Treatment for VP/Statins
PET/CT, Vessel Inflammation

Tawakol et al. J Am Coll Cardiol. 2013
Medical Treatment/Statins

Metanalysis for major events

Baigent et al. Lancet. 2010
Medical Treatment for VP/Olmesartan

Plaque burden regression/IVUS

Hirohata et al. J Am Coll Cardiol. 2010
Medical Treatment for VP/Evolocumab
GLAGOV study/IVUS

Screening and placebo run-in period
1. Clinically indicated coronary angiogram
2. IVUS based on coronary angiogram results
3. Subcutaneous injection of 3 mL placebo

Up to 4 week lipid stabilization period
Assigned to background statin therapy

Randomization 1:1 to study drug

Placebo SC every month

Evolocumab 420 mg SC every month

2-4 weeks

Max. 6 weeks

Study visits:

Study drug was administered monthly, at home or in the clinic.

EOS, end of study. IVUS, intravascular ultrasound; SC, subcutaneously
*Last dose of study drug
*Last IVUS procedure

# Medical Treatment for VP

## Phase III Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Design</th>
<th>Aim</th>
<th>Drug tested</th>
<th>Primary endpoint</th>
<th>Secondary endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>CANTOS (Canakinumab Anti-inflammatory Thrombosis Outcomes Study)</td>
<td>Phase III, randomised, double-blind, placebo-controlled, multi-centre, event-driven trial</td>
<td>Tests if reducing inflammation can reduce rates of recurrent cardiovascular events among stable post-myocardial infarction patients who remain at elevated vascular risk (hsCRP ≥ 2 mg/l) despite usual care, including statin therapy</td>
<td>Canakinumab, a human monoclonal antibody that neutralises IL-1β</td>
<td>Composite of non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death</td>
<td>Total mortality, hospitalisation for unstable angina requiring revascularisation, new onset diabetes</td>
</tr>
<tr>
<td>CIRT (Cardiovascular Inflammation Reduction Trial)</td>
<td>Phase III, randomised, double-blind, placebo-controlled, multi-centre, event-driven trial</td>
<td>Tests if reducing inflammation among stable coronary artery disease patients (prior myocardial infarction or angiographically demonstrated multi-vessel coronary artery disease) with type 2 diabetes or metabolic syndrome can reduce rates of cardiovascular events</td>
<td>Low-dose methotrexate</td>
<td>Composite of cardiovascular death, non-fatal myocardial infarction and stroke</td>
<td>All-cause mortality, percutaneous or surgical coronary revascularisation, hospitalisation for congestive heart failure, incident venous thromboembolism, incident atrial fibrillation, incident diabetes, Incident peripheral artery disease, clinically worsening aortic stenosis</td>
</tr>
<tr>
<td>ENTRACTE (A Clinical Outcomes Study to Evaluate the Effects of IL-6 Receptor Blockade With Tocilizumab in Comparison With Etanercept on the Rate of Cardiovascular Events in Patients With Moderate to Severe Rheumatoid Arthritis)</td>
<td>Phase IV, randomised, open-label, parallel-group, multi-centre study</td>
<td>Evaluates the frequency of cardiovascular events on tocilizumab in comparison with etanercept in participants with rheumatoid arthritis.</td>
<td>Tocilizumab, a humanised monoclonal antibody against the IL-6 receptor and etanercept, a soluble TNF receptor</td>
<td>Composite of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke</td>
<td>A composite endpoint of major cardiovascular events plus non-fatal coronary revascularisation procedures and hospitalisation for unstable angina; as well as investigating the frequency of adverse events and serious adverse events</td>
</tr>
</tbody>
</table>

*De Caterina et al. Thromb Haemost 2016*
Invasive Sealing of VP

PROSPECT II Study
PROSPECT ABSORB RCT

900 pts with ACS after successful PCI
3 vessel IVUS + NIRS (blinded)

≥1 IVUS lesion with ≥65% plaque burden present?

Yes (N=300)

No (n=600)

R 1:1

ABSORB BVS + GDMT (N~150)
GDMDT (N=150)

Routine angio/3V IVUS-NIRS FU at 2 years

Clinical FU for up to 15 years
Invasive Sealing of VP

PREVENT Trial (n=1600)
Any Significant Epicardial Coronary Stenosis (DS>50%) (ACS and non-ACS) with FFR >0.80 and with Two of the following

1. MLA <4.0 mm²
2. Plaque Burden at MLA site >70%
3. Lipid-Rich Plaque on NIRS (max LCBI₄₄₄₄mm>500)
4. TCFA defined by OCT or VH-IVUS

BVS+OMT N=800

OMT N=800

Primary endpoint at 2 years:
CV death, MI, hospitalization for unstable angina

TCFA
- OCT definition: fibrous cap thickness<65 µm and arc>90°
- VH-IVUS definition: ≥10% confluent NC with >30° abutting to the lumen in 3 consecutive slices
PI: SJ Park
Summary

- Accurate detection of VP is a “battle” and not “war” winning.
- Novel imaging techniques provided new morphological information regarding VP.
- Available Imaging is unable to completely assess plaque’s pathology and function.
- Prognostic implications of the presence of VPs is questionable.
- More accurate multi-modality techniques needed for stratification and identification of patients at risk for future events.
- Novel treatment targeting both the vulnerable plaque and vulnerable patient needed.
Thank you for your attention