Plaque Characterization of Carotid Disease Predicting Outcome

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Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

<table>
<thead>
<tr>
<th>Affiliation/Financial Relationship</th>
<th>Company</th>
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<tbody>
<tr>
<td>Grant/Research Support</td>
<td>Abbott Vascular</td>
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<tr>
<td>Consulting Fees/Honoraria</td>
<td>Covidien</td>
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<td>Major Stock Shareholder/Equity</td>
<td>Setajon, North Wind</td>
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<td>Ownership/Founder</td>
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<td>Other Financial Benefit</td>
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AT THE PRESENT TIME, WE HAVE LIMITED KNOWLEDGE OF PLAQUE CHARACTERISTICS.
The goal is the search for the elusive plaque before it becomes symptomatic:

1. Identify vulnerable plaque and TCFA
2. Prevent Plaque rupture
3. Avoid stroke
The reality of severe carotid stenosis

The first symptom may be a sudden permanent stroke (25% of cases)
Histopathology of Carotid Plaques with different Clinical Presentation

A: Ruptured Carotid Plaque (Patient With Ipsilateral Major Stroke)
- Ruptured Fibrous Cap
- Thrombus

B: Carotid Plaque With Acute Thrombus (Patient With Transient Ischemic Attack)
- Thrombus

C: Carotid Plaque Without Associated Thrombus (Asymptomatic Patient)
- Lipid Core
- Fibrous Cap

D: Ruptured Carotid Plaque (Patient With Ipsilateral Major Stroke)
- F: Fibrous Cap
- NC: Nucleus
Whereas in terms of vulnerability the ranking, based on postmortem data, might be different with the CaTCFA being allegedly most high risk plaque and FCa more stable.
Significant Independent Predictors of Non-Cluprit Lesions

1. Plaque Burden
2. TCFA by IVUS
3. Minimum lumen area

Presence of 2 or 3 of these predictors in the coronary data have a 10-18% chance of an event within 3 years
IVUS Indicates Pt Best Suited for CEA
Results OCT

A. 

B. 

C. 

D. 

superficial erosion

TCFA
Essentially all trials were based on the Gold Standard

- Angiography
- Degree of Stenosis
The question is how do we find these Stroke indicators?

There are 14 to 20 factors that influence CAS outcomes.

Plaque morphology is only one, but it could be the one that will separate those patients best suited for surgery vs. stenting.
Ipsilateral Lesions after CAS

transient weakness of right hand: TIA
Stent erosion of Vulnerable Plaque with rupture ??

Is vulnerable plaque the culprit in procedural strokes?
The Problem

MZ, 74y, asymptomatic, LICA stenosis 85%

SZ, 68y, asymptomatic, LICA stenosis ~40% + ulcer

Which of the two plaques should be treated by (CAS) or (CEA)?
MZ, 74y, asymptomatic, LICA stenosis 85%

SZ, 68y, asymptomatic, LICA stenosis ~40% + ulcer

EBM: >90% probability stroke-free in 5–10 y

the pt declines intervention

Indication to CEA/CAS

NO indication to CEA/CAS

(in both – ‘full’ pharmacotherapy included ‘high-dose’ statin, ASA, ACEI)
MZ, 74y, asymptomatic, LICA stenosis 85%

Indication to CEA/CAS

SZ, 68y, asymptomatic, LICA stenosis ~40% + ulcer

NO indication to CEA/CAS

Motoric aphasia 4/5
Right hemiparesis 3/5
Patient selection

- 429 patients

- Male - 61.5% / Female - 38.5%

- Symptomatic (35%) and asymptomatic (65%)
  - Symptomatic
    - TIA, amaurosis fugax, or CVA with clinically, lateralizing symptoms ≤ 60 days preceding carotid intervention
Lesion Characteristics Based on Angiography

- Length of lesion
- Percent stenosis
- Location of lesion (ostial vs. non-ostial)
- Ulceration
- Calcification
- Contralateral internal carotid occlusion
Carotid Stent Case

- 80 year old male with two days of right arm weakness and brief expressive aphasia
- PMH quadrupresis secondary to remote cervical fracture, previous trach, PEG
- Transferred from OSH with CTA showing high grade left carotid stenosis
All flow from right side

RIGHT AP

RIGHT lateral
VH in lesion (PIF)
6mm straight stent 3 cm long Exact
The Challenge: Identify Unique Features Critical to Plaque Rupture

1. Plaque Burden
2. TCFA by IVUS, OCT, angioscopy, MRI-C
3. Lumen area (minimum)

**OCT**

*High resolution of fibrous cap thickness 10 x greater than IVUS.*

*Plaque characterization; Limitation – penetration lock 3mm.*
FibroAtheroma (FA)

Necrotic Core Without calcium

Fibrous Tissue
Acute Plaque rupture with thrombosis may occur in non-stenotic segment
What is optimal complete lesion coverage?

- Lack of clinical data comparing method

Impact on:
- Distal embolization
- Stent thrombosis
- Restenosis
- Plaque progression

Largest NC area

Angiography or IVUS-guided

VH-IVUS-guided
Stent may not expand
Carotid plaque
Proton Density Weighted Images of the Internal Carotid Artery at Baseline and after 12 months of Statin therapy
Outcomes of CAS Trials Over Time

Year 2000
ARCHeR 8.3%
SAPPHIRE 6.9%
SECURITY 7.5%
CAPTURE 6.1%
EXACT 4.1%
CAPTURE2 3.5%
CHOICE 3.9%
PROTECT 2.3%

Year 2008

30 day Composite of Death, Stroke & MI
- ARCHeR: 8.3%
- SAPPHIRE: 6.9%
- SECURITY: 7.5%
- CAPTURE: 6.1%
- EXACT: 4.1%
- CAPTURE2: 3.5%
- CHOICE: 3.9%
- PROTECT: 2.3%

30 day Composite of Death & Major Stroke
- ARCHeR: 2.9%
- SAPPHIRE: 3.3%
- SECURITY: 2.6%
- EXACT: 1.5%
- CAPTURE2: 1.4%
- PROTECT: 0.6%

(Enrollment: 2000-2008) CREST – 5.7%
(Enrollment: 2000-2008) CREST – 1.1%
Conclusion

The imaging modalities are impressive but have inherent limitations and no single one can produce the definitive information on vulnerability.
Shower Emboli

Diffusion weighted
Should we avoid the aortic arch puncture with 21g needle at C5 level?

Bergeron Technique for direct carotid access and vertebral

For the vertebral use radial or brachial access
Complex type 3 arch

May be indication for direct carotid access or radial for vertebral basilar stroke

Too difficult from femoral approach. 18% stroke incidence from the aortic arch

Archer Trial 2005
Remove wire, filter to internal carotid followed by pre dil and stent
SCAFFOLDING AND CONFOMABLE
Percutaneous cervical approach and closing for carotid artery stenting

N = 191

Markatis et al 2009
## TABLE IV. Neurological Complications and Deaths within 30 days after CAS

<table>
<thead>
<tr>
<th></th>
<th>In-hospital</th>
<th>0–30 days</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>1 (0.06)</td>
<td>3 (0.19)</td>
<td>4 (0.25)</td>
</tr>
<tr>
<td>Any stroke</td>
<td>8 (0.5)</td>
<td>11 (0.68)</td>
<td>19 (1.12)</td>
</tr>
<tr>
<td>Death + any stroke</td>
<td>9 (0.56)</td>
<td>13 (0.81)</td>
<td>22 (1.37)</td>
</tr>
<tr>
<td>Mayor stroke</td>
<td>6 (0.37)</td>
<td>3 (0.18)</td>
<td>9 (0.56)</td>
</tr>
<tr>
<td>Minor stroke</td>
<td>2 (0.12)</td>
<td>8 (0.50)</td>
<td>10 (0.62)</td>
</tr>
</tbody>
</table>

1637 patients European high volume experienced operator trial
OCT
Reflected Infrared Light

**Advantages**
- Spatial resolution 10X > than US

**Disadvantages**
- Displace blood with saline
- Limited penetration
- Cannot do entire vessel wall
<table>
<thead>
<tr>
<th>Institution</th>
<th>Enrolled Patients</th>
<th>Operators</th>
<th>Patients/operator per year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dendermonde</td>
<td>176</td>
<td>2</td>
<td>88</td>
</tr>
<tr>
<td>Cotignola</td>
<td>257</td>
<td>3</td>
<td>85.7</td>
</tr>
<tr>
<td>Frankfurt</td>
<td>80</td>
<td>1</td>
<td>80</td>
</tr>
<tr>
<td>Liepzig</td>
<td>188</td>
<td>3</td>
<td>62.7</td>
</tr>
<tr>
<td>Mercogliano</td>
<td>309</td>
<td>3</td>
<td>103</td>
</tr>
<tr>
<td>Mirano</td>
<td>143</td>
<td>3</td>
<td>47.7</td>
</tr>
<tr>
<td>Perugia</td>
<td>254</td>
<td>3</td>
<td>84.7</td>
</tr>
<tr>
<td>Siena</td>
<td>204</td>
<td>4</td>
<td>51</td>
</tr>
<tr>
<td>Type of embolic protection used</td>
<td>N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>----------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proximal</td>
<td>525 (32.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distal</td>
<td>1,082 (67.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>4 (0.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Embolic protection device</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distal filter device only</td>
<td>1,076 (66.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proximal occlusion only</td>
<td>517 (32.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distal occlusion balloon only</td>
<td>6 (0.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proximal occlusion and distal filter both used</td>
<td>8 (0.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>4 (0.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postdilation</td>
<td>1,579 (98.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stent design</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Closed</td>
<td>104 (6.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hybrid</td>
<td>456 (28.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1 (0.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Open + closed</td>
<td>1 (0.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Open + hybrid</td>
<td>1 (0.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Open</td>
<td>437 (27.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stainless steel</td>
<td>611 (37.9)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Patient selection

- 429 patients
- Male - 61.5% / Female - 38.5%
- Symptomatic (35%) and asymptomatic (65%)
  - Symptomatic
    - TIA, amaurosis fugax, or CVA with clinically, lateralizing symptoms ≤ 60 days preceding carotid intervention
Conversely the 3 year event rate in 1650 IVUS patients was only .3% and no events in the coronary artery segment when plaque volume less than 40% (Prospect)
THIS IS THE PROBLEM

IA (IVUS Defined) TCFAs
Major limitations in relying on angiography for lesion severity and plaque composition
<table>
<thead>
<tr>
<th>Lesion Length (mm)</th>
<th>Peri-operative CVA (%)</th>
<th>30 day CVA (%)</th>
<th>30 day Adverse Event (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 – 4.9</td>
<td>2.1</td>
<td>3.2</td>
<td>3.2</td>
</tr>
<tr>
<td>5 – 9.9</td>
<td>2.2</td>
<td>2.7</td>
<td>3.3</td>
</tr>
<tr>
<td>10 – 14.9</td>
<td>1.9</td>
<td>2.9</td>
<td>3.8</td>
</tr>
<tr>
<td>≥ 15</td>
<td>17.0</td>
<td>17.0</td>
<td>19.1</td>
</tr>
</tbody>
</table>
Anatomic and Lesion characteristics are not always accurate predictors of Stroke for CAS.

*Which test is best for this?*
This Is The Problem

ID (IVUS Defined) TCFAs
The reality of severe carotid stenosis

The first symptom may be a sudden permanent stroke (25% of cases)

Hallett, J., Veith
All imaging modalities have inherent limitations
Carotid plaques
Representative Lesion Morphologies f  (A) The earliest atherosclerotic lesion, pathological intimal thickening, highlighted by lipid pools (LP) in the deep intima (Movat pentachrome stain) with CD68+ ...
VH IVUS Produces a color-coded map of 4 Histological Types

- dark green: fibrous
- yellow/green: fibrofatty
- white: calcified
- red: necrotic lipid core plaque
Follow-up data were available on 56 (84%) of 67 patients in the CAS population.

(2) major adverse events

- Two immediate periprocedural strokes.
  - One patient (A) experienced a stroke in the distribution of the PCA as shown on CT, likely related to arch manipulation
- One stent thrombosis occurred, likely due to discontinuation of anticoagulation

No strokes were reported in 2 of the 4 patients referred for CEA who were available at follow-up.
Conclusions

- Understanding plaque morphology is a crucial aspect in managing carotid occlusive disease.

- However, in this small sample population, stroke rates were not different than those reported elsewhere for carotid stenting. In these cases, VH IVUS did not offer insight into the possible causes of the events.

- Future studies are needed with prospective trials to evaluate CAS and patient outcomes correlated with VH IVUS findings.
## Results

CAS was performed in 65 of 71 patients

- Four patients were excluded and referred for CEA due to unfavorable VH IVUS plaque characteristics
- One patient was excluded due to lack of significant stenosis
- One patient underwent PTA of a restenosed stent

### Population

<table>
<thead>
<tr>
<th>Population</th>
<th>CAS</th>
<th>CEA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>41 (61%)</td>
<td>2</td>
</tr>
<tr>
<td>Female</td>
<td>36 (39%)</td>
<td>2</td>
</tr>
<tr>
<td>Age (years)</td>
<td>73 ± 9.7</td>
<td>84</td>
</tr>
<tr>
<td>Side of ICA Lesion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>31 (46%)</td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>36 (54%)</td>
<td></td>
</tr>
<tr>
<td>Percent Stenosis</td>
<td>89% ± 7.8</td>
<td></td>
</tr>
<tr>
<td>Clinical Indication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIA</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Amrous Fagux</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Stroke</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>24</td>
<td>1</td>
</tr>
<tr>
<td>Prior CEA/Stent</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>Unknown</td>
<td>8</td>
<td>1</td>
</tr>
</tbody>
</table>

### CAS Predominate Plaque Characteristics
- 1 Necrotic Core
- 1 Dystrophic Calcification

### CEA Predominate Plaque Characteristics
- 24 Necrotic Core
- 76 Dystrophic Calcification
Two (3%) of the 59 patients undergoing CAS experienced adverse events.

- One patient (A) suffered a minor stroke in the perioperative period due to stent occlusion related to thrombosis due to discontinued anticoagulation.

- One minor stroke (B) in the perioperative period in the left posterior cerebral artery (PCA) distribution likely related to arch manipulation. Returned to baseline at 3 month follow-up.
Patient selection

- 429 patients
- Male - 61.5% / Female - 38.5%
- Symptomatic (35%) and asymptomatic (65%)
  - Symptomatic
    - TIA, amaurosis fugax, or CVA with clinically, lateralizing symptoms ≤ 60 days preceding carotid intervention
Lesion Characteristics

- Length of lesion highly significant
- Percent stenosis
- Location of lesion (ostial vs. non-ostial)
- Ulceration
- Calcification
- Contralateral internal carotid occlusion
Plaque Surface Irregularity


Hazard Ratio 3.1
Computer assisted analysis suggested that increased echolucency of plaque was a risk factor during and immediately post stenting.

Biasi, Circulation 2004
Acute Plaque rupture with thrombosis may occur in non-stenotic segment
Patient Selection

- 429 patients
- **Male** - 61.5% / **Female** - 38.5%
- Symptomatic (35%) and asymptomatic (65%)
  - Symptomatic
    - TIA, amaurosis fugax, or CVA with clinically, lateralizing symptoms ≤ 60 days preceding carotid intervention
What is Optimal Complete Lesion Coverage?

- Lack of clinical data comparing
  - VH-IVUS guided vs. angiography/conventional IVUS guided PCI

- Impact on:
  - Distal embolization
  - Stent thrombosis
  - Restenosis
  - Plaque progression
TYPE A Lesion

TYPE 4 ARCH
Procedure completed

FILTER REMOVED
Shower Emboli

Diffusion weighted
Presence of 2 or 3 of these predictors have a 10-18% chance of an event within 3 years.
Acute Plaque rupture with thrombosis may occur in non-stenotic segment
TIP 5 - Continued
67 Female with TIA's referred for CEA; Path reports soft, atheromatous lesion

Both Patients referred for CEA instead of CAS

Dangerous: Soft Plaque

Plaque Analysis: Are These Necrotic Cores?
Arterial wall assessment of morphology is less impressive than degrees of stenosis.

Calcification is the only histologic content using CTA.
- MRI with plaque rupture and intra plaque bleed

Gao et al., *Cerebrovasc Dis*, 2009
TYPE A Lesion

TYPE 4 ARCH
Procedure completed

FILTER REMOVED
Shower Emboli

Diffusion weighted
Shower Emboli

Diffusion weighted
ADVANTAGES

- Procedure time
- Less contrast media
- No aortic arch manipulation
- No contralateral or vertebral embolisation
What have we overlooked in the neurovascular evaluation?

The aortic arch as a source of vulnerable plaque whether diagnostic or interventional procedures are being done.
21 g needle at C5
Conclusions

Administration of lipid modulating agents appears to have initial paradoxical effects on lumen size:

- A decrease in vessel wall area and lipid area is accompanied by a decrease in lumen area
- An increase in vessel wall area and lipid area is accompanied by an increase in lumen area
Conclusion

- Percent stenosis provides relatively little information about vulnerability of *de novo*, statin-naive carotid plaques.

- As most current imaging studies concentrate on plaque stenosis, a more appropriate focus on plaque composition provides a more robust quantifiable volumetric metric and may be more indicative of the underlying pathology by high-resolution 3D CMR.
Carotid Plaque Analysis

- Images were acquired in axial projection in a 2D and 3D manner via QPlaque (Medis, The Netherlands). Plaque morphology determined by T1, T2/PD CMR.
- Windows and level settings were set to constant levels to standardize signal intensities for each analyzed image.
- Manual contours identified:
  1. Fibrous cap
  2. Lipid pool
  3. Outer and inner wall contours
  4. T2 images were reviewed to determine/confirm lipid core determination with the T2 image used to confirm lumen contour.

- Fasting lipid profiles drawn on day of MR imaging
Currently all trials were based on the Gold Standard.

- Angiography
- Degree of Stenosis
CAN IVUS FINDINGS DURING CAS PREDICT OUTCOME?
Carotid plaques
Proton Density Weighted Images of the Internal Carotid Artery at Baseline and after 12 months of Statin therapy
Plaque Morphology by DSA cannot determine which plaque is stable or vulnerable.

The implication of ulceration and degree of stenosis as a stroke marker has conflicting results.

Wallace De Vries, JVS, 2008
AT THE PRESENT TIME, WE HAVE LIMITED KNOWLEDGE OF PLAQUE CHARACTERISTICS
Outcomes of CAS Trials Over Time

- CAS results have vastly improved over time due to: (1) more experienced operators; (2) better patient selection and; (3) a wider spectrum of technology

- CAS outcomes have evolved over time similarly to CEA
PROBLEMS of the aortic arch
Complexities of the aortic arc are responsible for almost all technical failures
MINIMAL PLAQUE WITH THIN CAP: RUPTURE-CLOT
Major limitations in relying on angiography alone for lesion severity and plaque composition
All imaging modalities have inherent limitations