Carotid Plaque Imaging in Acute Stroke (CAPIAS) Study

Clinical utility of carotid plaque hr-MRI

Martin Dichgans

Munich Carotid Conference 7.12. 2017
Agenda | Clinical Utility of Plaque MRI

- Correlation with histopathology
- Distinction **symptomatic vs asymptomatic** plaques
- **Non-stenosing vulnerable plaque** & stroke risk
- Vulnerable Plaque: **diagnostic utility**
  - risk prediction
- Influence **statin treatment** on plaque composition
Vulnerable Plaque | Histopathological criteria

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

**Secondary criteria**
- Superficial calcified nodule
- Intraplaque hemorrhage
- Endothelial dysfunction
- Outward remodeling

Naghavi et al. Circulation 2003
Plaque features that can be identified and quantified by plaque MRT

**Plaque Burden**

**Composition**
- Intraplaque hemorrh.
- Lipid core
- Calcification
- Fibrotic tissue

**Activity**
- Inflammation
- Neovascularization

**Morphology**
- Plaque surface
- Fibrous Cap
- AHA Lesion Type

*Courtesy Tobias Saam, Klinikum der Universität München*
MR validation studies (histology)

**Composition**
- Toussaint, Circulation 1996
- Trivedi, Neuroradiology 2004
- Yuan, Circulation 2001
- Cai, Circulation 2005
- Cappendijk Radiology 2005
- Saam ATVB 2005
- Takaya, JMRI 2006
- Cappendijk, JMRI 2008
- Kim, JMRI 2009
- Young, Neuroradiology 2010

**Activity**
- Kerwin, Circulation 2003
- Kerwin, Radiology 2006
- Kerwin, MRM 2008
- Chen, MRM 2010
- Kooi, Circulation 2003
- Trivedi, Stroke 2004
- Trivedi, ATVB 2006

**Plaque Burden**
- Yuan, Circulation 1998
- Zhang, MRI 2001
- Luo, MRM 2003
- Zhang, Radiology 2003
- Adams, MRI 2004
- Varghese, JMRI 2005
- Phan, JMRI 2006
- Mani, JCMR 2006
- Underhill, JMRI 2006

**Plaque morphology**
- Hatsukami, Circulation 2000
- Mitsumori, JMRI 2001
- Cai, Circulation 2002
- Chu, iJACC 2009

**Reproducibility**
- Saam, JCMR 2007 & 2009
- Takaya, JMRI 2006
- Kwee, Stroke 2008
Correlation hr-Plaque MRT and Histopathology

TABLE 2. Classification of Carotid Atherosclerotic Plaque by Multicontrast Weighted MRI and Histological Examination

<table>
<thead>
<tr>
<th>Classification by MRI</th>
<th>I-II</th>
<th>III</th>
<th>IV-V</th>
<th>VI</th>
<th>VII</th>
<th>VIII</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>I-II</td>
<td>8</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>8</td>
</tr>
<tr>
<td>III</td>
<td>4</td>
<td>30</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>34</td>
</tr>
<tr>
<td>IV-V</td>
<td>...</td>
<td>7</td>
<td>47</td>
<td>8</td>
<td>2</td>
<td>2</td>
<td>66</td>
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</table>

Cohen’s κ (95% CI)=0.74 (0.67 to 0.82); weighted κ=0.79.

sensitivity (AHA Typ VI): 82%
specificity (AHA Typ VI): 91%

black-blood MRI ideally suited for carotid vulnerable plaque detection
Differentiating characteristics of symptomatic vs. asymptomatic Carotid Plaques

### AHA Lesion Type Distribution

<table>
<thead>
<tr>
<th>AHA Lesion Type</th>
<th>Description</th>
<th>Symptomatic Arteries (%)</th>
<th>Asymptomatic Arteries (%)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Normal wall</td>
<td>4.3 ± 10.6</td>
<td>8.2 ± 18.4</td>
<td>.2</td>
</tr>
<tr>
<td>III</td>
<td>Eccentric plaque, no calcification</td>
<td>6.5 ± 10.8</td>
<td>4.5 ± 8.5</td>
<td>.5</td>
</tr>
<tr>
<td>Combined IV and V</td>
<td>Lesion with lipid-rich necrotic core</td>
<td>15.6 ± 16.7</td>
<td>34.5 ± 30.7</td>
<td>.005</td>
</tr>
<tr>
<td>VI</td>
<td>Complicated lesion</td>
<td>63.3 ± 25.2</td>
<td>40.7 ± 31.5</td>
<td>.004</td>
</tr>
<tr>
<td>VII</td>
<td>Calcified lesion</td>
<td>5.6 ± 10.7</td>
<td>7.6 ± 17.2</td>
<td>.5</td>
</tr>
<tr>
<td>VIII</td>
<td>Lesion with fibrosis</td>
<td>0.0 ± 0.0</td>
<td>0.7 ± 3.4</td>
<td>.3</td>
</tr>
</tbody>
</table>

### Luminal Surface Status and Hemorrhage by Type and Location

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Symptomatic Plaques</th>
<th>Asymptomatic Plaques</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrous cap status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thick</td>
<td>0 (0)</td>
<td>5 (22)</td>
<td>.06</td>
</tr>
<tr>
<td>Thin</td>
<td>3 (13)</td>
<td>9 (39)</td>
<td>.1</td>
</tr>
<tr>
<td>Ruptured</td>
<td>18 (78)</td>
<td>7 (30)</td>
<td>.007</td>
</tr>
<tr>
<td>Other (no fibrous cap or image quality &lt; 3 on TOF images)</td>
<td>2 (9)</td>
<td>2 (9)</td>
<td>&gt;.999</td>
</tr>
<tr>
<td>Hemorrhage of any type present at any location</td>
<td>23 (100)</td>
<td>20 (87)</td>
<td>.3</td>
</tr>
<tr>
<td>Hemorrhage type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I (fresh)</td>
<td>20 (87)</td>
<td>12 (52)</td>
<td>.021</td>
</tr>
<tr>
<td>II (recent)</td>
<td>22 (96)</td>
<td>18 (78)</td>
<td>.2</td>
</tr>
<tr>
<td>Hemorrhage location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intraplaque</td>
<td>21 (91)</td>
<td>19 (83)</td>
<td>.5</td>
</tr>
<tr>
<td>Juxtaluminal or thrombus</td>
<td>14 (61)</td>
<td>6 (26)</td>
<td>.039</td>
</tr>
<tr>
<td>Luminal calcification and adjacent hemorrhage</td>
<td>13 (57)</td>
<td>9 (39)</td>
<td>.2</td>
</tr>
</tbody>
</table>

Saam et al. Radiology 2006
66-year-old male patient

Ischemic stroke in the right cerebral hemisphere

Ultrasound: 50% stenosis right ICA

T1w right T1w left CE T1w right CE T1w left DWI


Typical for symptomatic carotid artery stenosis: Vulnerable AHA Typ VI plaque!
Non-stenosing carotid artery plaque and stroke

“stroke while squeezing a pimple“

Non-stenosis carotid artery plaques are a potential source of stroke!

Freilinger, ..., Dichgans, Saam, Neurology 2011
Vulnerable carotid artery plaque & cryptogenic stroke pilot study (N=32 patients, non-stenosing plaque)

Prevalence of complicated AHA Typ VI plaques in cryptogenic stroke

Ipsilateral (n=32)
- Type VI: 37%
- Type VII: 13%
- Type VIII: 9%
- Type I/II: 28%
- Type III: 0%

Contralateral (n=31)
- Type VI: 0%
- Type VII: 10%
- Type VIII: 13%
- Type I/II: 29%
- Type III: 48%

(p=0.001 McNemar)

Freilinger, ... Dichgans, Saam. JACC Cardiovascular Imaging 2012
Vulnerable carotid artery plaque & cryptogenic stroke pilot study (N=32 patients, non-stenosing plaque)

Prevalence of complicated AHA Typ VI plaques in cryptogenic stroke

complicated AHA Typ VI Plaques

- hemorrhage
- mural thrombus
- rupture fibrous cap

non-stenosing vulnerable plaques as a source of cryptogenic stroke

(p=0.001 McNemar)

Freilinger, …, Dichgans, Saam. JACC Cardiovascular Imaging 2012
Intraplaque hemorrhage & stroke risk

Meta-Analysis: 8 publications; 689 patients with symptomatic or asymptomatic CAS
median follow-up: 20 mths | rate of CV events: 9.6%/year; hemorrhage: 49%

plaque-MRI for stroke risk prediction in carotid artery stenosis

Saam T, Hetterich H, …, Dichgans M, et al. JACC 2013,
CAPIAS (Carotid Plaque Imaging in Acute Stroke)

Aim

Frequency, characteristics, and outcome of AHA Typ VI plaques

Primary endpoint

Frequency ipsilateral AHA Typ VI plaques
In patients with cryptogenic stroke compared to:
- contralateral
- other defined stroke ethiologies

Secondary endpoints

recurrent ischemic events
incident ischemic lesions (cMRT;12 months)
CAPIAS | Inclusion – Exclusion criteria

**Inclusion criteria**

**Plaques** in ipsilateralen ICA (ultrasound)*

≥1 unilateral **DWI** lesion ICA territory

age > 49 years

Neurological symptoms of AIS in anterior circulation

symptom start last 7 days

**Exclusion criteria**

DWI lesion **other vascular territory**

Ipsilateral **carotid artery stenosis > 69%** (NASCET)

Contraindications for MRI or contrast agent

Renal insufficiency

*(Plaque Dicke ≥ 2mm; innerhalb 1cm proximal oder distal der Karotisbifurkation)
## CAPIAS | Schedule of Assessment

<table>
<thead>
<tr>
<th>Assessment</th>
<th>0</th>
<th>3</th>
<th>12</th>
<th>24</th>
<th>36</th>
</tr>
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<tbody>
<tr>
<td>Informed consent</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Interview / clinical endpoints</strong></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Neuropsychological testing</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Clinical examination</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>blood draws for biobanking, laboratory investigations</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Screening ultrasound of the carotid arteries</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>24-hour ECG</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transoesophageal and transthoracic ultrasound</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>High resolution black blood carotid MRI</strong></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cerebral MRI (T1, T2/PDW, DWI/ADC, TOF)</strong></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contrast enhanced ultrasound</td>
<td>(X)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

www.clinicaltrials.gov NCT01284933
CAPIAS | Study Profile

487 patients with acute ischemic stroke or TIA and plaques > 2mm

- Patients not undergoing plaque MRI: n=276
  - No DWI positive lesion on brain MRI: n=48
  - Bilateral ischemic infarcts: n=113
  - Ischemic infarcts in the posterior circulation: n=63
  - Ipsilateral carotid artery stenosis ≥ 70% (NASCET): n=52

211 patients receiving plaque MRI

- Patients excluded from analysis: n=13 (6%)
  - Plaque MRI not passing QC: 10
  - Incomplete MRI exam: 3

198 patients with complete MRI scans
<table>
<thead>
<tr>
<th>Demographic Characteristics</th>
<th>Patients receiving plaque MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years (±SD)</td>
<td>73±10.0</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>63 (30)</td>
</tr>
<tr>
<td><strong>Vascular risk factors</strong></td>
<td></td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>146 (69)</td>
</tr>
<tr>
<td>Hypercholesterinemia, n (%)</td>
<td>70 (33)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>46 (22)</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>37 (18)</td>
</tr>
<tr>
<td>Ever smoked, n (%)</td>
<td>121 (58)</td>
</tr>
<tr>
<td><strong>Clinical examination</strong></td>
<td></td>
</tr>
<tr>
<td>NIHSS Score, median [Q1-Q3]</td>
<td>3 [1-6]</td>
</tr>
<tr>
<td><strong>Stroke subtype by TOAST</strong></td>
<td></td>
</tr>
<tr>
<td>Large artery atherosclerosis, n (%)</td>
<td>35 (17)</td>
</tr>
<tr>
<td>Cardioembolism, n (%)</td>
<td>45 (21)</td>
</tr>
<tr>
<td>Small artery occlusion, n (%)</td>
<td>18 (9)</td>
</tr>
<tr>
<td>Other, n (%)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Competing etiology, n (%)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Undefined, n (%)</td>
<td>101 (48)</td>
</tr>
<tr>
<td>Incomplete diagnostic, n (%)</td>
<td>4 (2)</td>
</tr>
</tbody>
</table>
Results | Primary Endpoint

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Number of Patients</th>
<th>Ipsi</th>
<th>Contra</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRYPT</td>
<td>101</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAS</td>
<td>35</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CES</td>
<td>45</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SVD</td>
<td>18</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

McNemar: p=5.104e-05
Cond. log. regr: p=0.0015

p=0.007
p=0.0029
p=0.75
p=0.59
p=0.074
p=n.a.
Results | Primary Endpoint – IAS as a separate category

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>n</th>
<th>ipsi</th>
<th>contra</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRYPT</td>
<td>101</td>
<td></td>
<td></td>
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<tr>
<td>LAS</td>
<td>24</td>
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<tr>
<td>CES</td>
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<td>SVD</td>
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<tr>
<td>IAS</td>
<td>11</td>
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<td></td>
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</tbody>
</table>

McNemar: p=5.104e-05, p=0.007, p=0.75, p=0.074, p=n.a.
Condition log. regr: p=0.0015, p=0.0029, p=0.59, p=n.a., p=n.a.
Plaque progression | Recurrent events in CAPIAS

66j. m, cryptogenic stroke, multiple DWI lesions > inclusion into CAPIAS

baseline (after cryptogenic stroke)

follow-up (11 months) (following transient visual loss)
Effects of Rosuvastatin on plaque composition

ORION study
33 patients
LDL 100-250mg/dl
ICA Stenosis
5mg or 40mg Rosuvastatin

Carotid plaque MRI enables detection of treatment-associated changes in plaque composition
Carotid plaque MRI might assist in treatment decisions
Complex Plaques | proximal descending aorta
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