Inflammation and Carotid Artery Risk for Atherosclerosis Study

ICA R A S

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Department Angiology

TCT 2005; October 2005, Washington
Presenter Disclosure Information

Name: Minar Erich

Nothing to disclose
Background

Stroke is the third-leading cause of death and the most common cause of permanent disability.

Large-artery thromboembolism originating from atherosclerosis in the carotid arteries accounts for 30% of these events.

Recently, a substantially increased risk for neurological events was noted in patients with rapid progression of atherosclerotic lesions in the carotid arteries, with 2-year stroke rates exceeding 10% (Bertges et al; Arch Intern Med 2003;163:2285).

Prediction of the risk for progression of carotid atherosclerosis, however, remains a major unresolved issue.
Atherosclerosis is an inflammatory disease.

The extent of vascular inflammation reflects the activity of the disease and the likelihood for plaque progression.

Acute phase parameters – quantifying the extent of inflammation – may predict progression of carotid stenosis.
To determine whether the extent of inflammation measured by acute phase parameters shows a temporal association with morphological progression of carotid atherosclerosis.

To determine whether inflammation and progression of carotid disease predict cerebrovascular events.
Study Endpoints

Morphological endpoint.
• Progression of atherosclerosis by ultrasound
  - increase >20%
  - change of PSV baseline – follow-up

Clinical endpoints.
• Ipsilateral neurological events (TIA, any stroke)
Database

- Prospective cohort study 03/2002 – 03/2003
- 1268 consecutive patients undergoing DUS for suspected ICA atherosclerosis
  - carotid bruit
  - atherosclerotic disease in other vessel areas (coronary, peripheral)
  - scheduled for major cardiac surgery
- Cardiovascular risk factors / comorbidities
- Follow-up at 6-9 months:
  - repeated carotid ultrasound
  - evaluation of neurological events
Agreement DUS vs. Angiography

Angiographic Degree of Stenosis (NASCET) vs. Duplex Degree of Stenosis

- Angiographic Degree of Stenosis:
  - 0 to 29%: 205
  - 30 to 49%: 112
  - 50 to 69%: 111
  - 70 to 99%: 525
  - 100%: 53

- Duplex Degree of Stenosis:
  - 0 to 29%
  - 30 to 49%
  - 50 to 69%
  - 70 to 99%
  - 100%

$r^2 = 0.66$
$p < 0.001$

Radiology 2004; 232: 431-439
Excellent agreement between Duplex ultrasound (study endpoint) and angiography (gold standard) has been demonstrated previously in our laboratory in 1006 carotid arteries.

Duplex ultrasound. Excellent agreement between Duplex ultrasound (study endpoint) and angiography (gold standard) has been demonstrated previously in our laboratory in 1006 carotid arteries.

Duplex Degree of Stenosis

ICARAS

Agreement DUS vs. Angiography

Radiology 2004; 232: 431-439
## Events

### Follow up
(x 7.5 [6-9] months)

<table>
<thead>
<tr>
<th>Event</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stenosis progression</td>
<td>103 (8.1%)</td>
</tr>
<tr>
<td>De-novo occlusion</td>
<td>8 (0.6%)</td>
</tr>
<tr>
<td>Neuro-events</td>
<td>15 (1.2%)</td>
</tr>
</tbody>
</table>
Inflammation and Disease Progression

hs C-reactive Protein at baseline

Log Rank p<0.001

Circulation 2005;111: 2203-09
ICARAS

Inflammation and Disease Progression

Serum Amyloid A at Baseline

Follow-up Time (Months)

Freedom from Disease Progression (%)

Log Rank p<0.001

n=1268

Circulation 2005;111: 2203-09
Inflammation is associated with Progression of Carotid Stenosis.
Fibrinogen plays a pivotal role in the initial phase and the advanced stages of atherosclerosis.

Large population-based studies such as the Copenhagen city study (N=8755) and the Gothenburg Study (N=792) unequivocally demonstrated an increasing risk for future stroke with increasing levels of fibrinogen.

Plaque composition of patients with elevated fibrinogen levels is characterized by the presence of a high number of inflammatory cells localized mainly in the shoulder and in the cap of the plaque.

(Mauriello et al; Circulation 2000;101:744 –750)
## Risk for Progression of Carotid Atherosclerosis

### Univariate Model

<table>
<thead>
<tr>
<th>Fibrinogen Level</th>
<th>Adjusted HR (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>Below 333 mg/dL</td>
<td>1.0</td>
</tr>
<tr>
<td>333 to &lt;376 mg/dL</td>
<td>1.97 (1.13 to 3.44)</td>
</tr>
<tr>
<td>376 to &lt;432 mg/dL</td>
<td>2.34 (1.38 to 3.97)</td>
</tr>
<tr>
<td>Above 432 mg/dL</td>
<td>2.71 (1.57 to 4.66)</td>
</tr>
</tbody>
</table>

### Multivariate Model

Adjusting for age, sex, body mass index, HbA1c, smoking, arterial hypertension, total cholesterol, family history of atherosclerotic disease, peripheral artery disease, history of myocardial infarction, history of stroke, serum creatinine, statin treatment, degree of stenosis and clustering by patient for the side of the lesion.

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<tr>
<td>333 to &lt;376 mg/dL</td>
<td>1.83 (1.04 to 3.23)</td>
</tr>
<tr>
<td>376 to &lt;432 mg/dL</td>
<td>2.09 (1.21 to 3.61)</td>
</tr>
<tr>
<td>Above 432 mg/dL</td>
<td>2.45 (1.40 to 4.28)</td>
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### Multivariate Model

Additionally adjusting for hs-CRP

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<td>1.05 (0.56 to 1.95)</td>
</tr>
<tr>
<td>376 to &lt;432 mg/dL</td>
<td>1.47 (0.81 to 2.69)</td>
</tr>
<tr>
<td>Above 432 mg/dL</td>
<td>1.50 (0.83 to 2.71)</td>
</tr>
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**Adjusted Hazards Ratio (95% CI)**

*Stroke 2005;36:1400-1404*
Inflammation, Degree of Stenosis and Disease Progression

Log Rank p<0.001

ICA<50%
low CRP
ICA<50%
high CRP
ICA>50%
low CRP
ICA>50%
high CRP

ICA<50%
low SAA
ICA<50%
high SAA
ICA>50%
low SAA
ICA>50%
high SAA

Circulation 2005;111: 2203-09
Inflammation, Degree of Stenosis and Disease Progression

**Risk for Progression of Atherosclerosis**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Adjusted Hazard Ratio (95% CI)</th>
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<tbody>
<tr>
<td>baseline</td>
<td>1.0</td>
</tr>
<tr>
<td>ICA&lt;50% + low hs-CRP (n=478)</td>
<td>1.0</td>
</tr>
<tr>
<td>ICA&lt;50% + high hs-CRP (n=281)</td>
<td>3.13 (1.70 to 5.75)</td>
</tr>
<tr>
<td>ICA&gt;50% + low hs-CRP (n=302)</td>
<td>4.05 (1.60 to 6.89)</td>
</tr>
<tr>
<td>ICA&gt;50% + high hs-CRP (n=207)</td>
<td>6.07 (2.21 to 10.21)</td>
</tr>
<tr>
<td>ICA&lt;50% + low SAA (n=349)</td>
<td>1.0</td>
</tr>
<tr>
<td>ICA&lt;50% + high SAA (n=411)</td>
<td>1.96 (1.06 to 3.62)</td>
</tr>
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<td>ICA&gt;50% + low SAA (n=321)</td>
<td>3.13 (1.09 to 5.19)</td>
</tr>
<tr>
<td>ICA&gt;50% + high SAA (n=187)</td>
<td>4.04 (1.74 to 6.69)</td>
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*ICA* refers to the internal carotid artery.

*Circulation 2005;111: 2203-09*
Neurological Events

Follow-up Time (Months)

Freedom from ischemic neurological events (%)

Log Rank $p=0.011$

n=1268

Patients without progressive carotid disease

Patients with progressive carotid disease

95%
98%
91%
96%
91%
Progression of ICA Stenosis is a Risk Factor for Stroke.
Inflammation, Degree of Stenosis and Neurological Events

Circulation 2005;111: 2203-09
# Inflammation, Degree of Stenosis and Neurological Events

**RISK FOR NEUROLOGICAL EVENTS**

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<td>8.27 (0.90 to 75.99)</td>
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<td>7.30 (0.87 to 61.08)</td>
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Circulation 2005;111: 2203-09
**Inflammation, Degree of Stenosis and Neurological Events**

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Inflammation adds to Clinical Risk Prediction.
Conclusions

✓ Inflammation is associated with disease progression in atherosclerotic carotid arteries.

✓ Inflammation adds to clinical risk prediction for neurological events.