Stenosis and stenosis-progression

- ACAS and ACST found **no evidence** of increased rate of stroke with
  - Increasing degrees of stenosis
  - Bilateral stenosis
  - Stenosis with contralateral occlusion

- **Progression** of stenosis by 2 ultrasound velocity categories
  - Doubled the stroke rate from 1% to 2% per year (OR~2)
  - 100 plaques that progressed → 2 strokes

ACAS, JAMA 1995
Halliday et al, Lancet 2004
Sabaté et al, Stroke 2007

2D Ultrasound plaque morphology

- CHS found that hypoechoic plaques had an
  - Increased rate of strokes on follow up (OR 2.8)

- Objective quantification of plaque image brightness on B-mode imaging
  - Low GSM predicted stroke; though the threshold value varied in studies (OR ~3)

Sabaté et al, J Vasc Surg 2003

2D ultrasound plaque histology

- ACSRS found that
  - Juxtaluminal black area or quantifying the hypoechoic region in a plaque >10 mm² → annual stroke rate of 5%

- ACSRS
  - Combination of clinical characteristics with plaque area, stenosis and JBA measurements → annual stroke rate of 4% (n=84 patients)

Kakkos et al, JVS 2013
Nicolaides et al, JVS 2010

2D ultrasound plaque histology

- ACSRS
  - Combination of clinical characteristics with plaque area, stenosis and JBA measurements → annual stroke rate of 4% (n=84 patients)

Lal BK et al, Stroke 2003
AlMuhanna et al, J Vasc Surg 2014
2D imaging is convenient, but only provides a "snapshot" sample of the plaque. 3D imaging is now commercially available.

3D imaging results are anticipated to enroll ~1400 patients in the "medical" arms of the trial. Development of thresholds for 2D plaque imaging biomarkers using "un-blinded" imaging of ~700 patients. Prospective validation of the thresholds on "blinded" imaging of ~700 patients. Endpoints measured: Stroke and cognitive function.

Combinations of 3D-TOF, MP-RAGE, CE-MRA. Initially using dedicated cervical coils. More recently, using clinical neurovascular coils. Fibrous cap rupture, intraplaque hemorrhage, large lipid core size → stroke rates consistent with OR 3 to 8.

Plaque disruption may be influenced by biomechanical forces and morphology. The first multicenter clinical study to evaluate plaque morphological and biomechanical markers that render it vulnerable to rupture. Combination of MRI and dynamic ultrasonography. Develop thresholds based on ~220 patients. Prospectively validate the thresholds on ~100 patients.

Summary
We are not there yet; but getting closer to a reliable composite biomarker for high-risk patient/plaque.

<table>
<thead>
<tr>
<th>Imaging marker</th>
<th>Modality</th>
<th>~ Number of patients</th>
<th>~ Event risk</th>
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</thead>
<tbody>
<tr>
<td>Hypoechoic region quantification</td>
<td>2D B-mode ultrasound</td>
<td>2000</td>
<td>OR 3</td>
</tr>
<tr>
<td>Embolic signals</td>
<td>TCD</td>
<td>1000</td>
<td>OR 6</td>
</tr>
<tr>
<td>Intraplaque hemorrhage</td>
<td>MRI</td>
<td>400</td>
<td>OR 3-8</td>
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<tr>
<td>Large lipid-rich necrotic core</td>
<td>MRI</td>
<td>300</td>
<td>OR 5</td>
</tr>
<tr>
<td>Thin/ruptured fibrous cap</td>
<td>MRI</td>
<td>200</td>
<td>OR 4</td>
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