Contemporary Outcome in Carotid Stenting (and CEA)
Predictive Variables and Risk Benefit Considerations

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Teaching Hospital of Dortmund - Germany

TCT 2006 Θ Washington DC
Statistics - the only science that enables different experts using the same figures to draw different conclusions

Evan Esar (1899-1995)
Evidence for treating ...

- symptomatic patients
- asymptomatic patients
- the ‘high-risk’ patient
## The International CEA Trials

<table>
<thead>
<tr>
<th>Risk (%)</th>
<th>ECST</th>
<th>Surgical</th>
<th>Medical</th>
<th>ARR (%)</th>
<th>NNT (%)</th>
<th>CVE Prevented per 1000 CEAs</th>
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<tbody>
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<td>&lt;30%</td>
<td>9.8  at 5y</td>
<td>3.9  at 5y</td>
<td>-5.9</td>
<td></td>
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</tr>
<tr>
<td>30-49%</td>
<td>10.2 at 5y</td>
<td>8.2  at 5y</td>
<td>-2.0</td>
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</tr>
<tr>
<td>50-69%</td>
<td>15.0 at 5y</td>
<td>12.1 at 5y</td>
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<tr>
<td>70-99%</td>
<td>10.5 at 5y</td>
<td>19.0 at 5y</td>
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<td>12</td>
<td>83 at 5y</td>
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</table>

<table>
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<tr>
<th>Risk (%)</th>
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<tr>
<td>30-49%</td>
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<td>50-69%</td>
<td>15.7 at 3y</td>
<td>22.2 at 3y</td>
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<td>15</td>
<td>67 at 3y</td>
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<td>70-99%</td>
<td>8.9 at 3y</td>
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<td>5</td>
<td>200 at 3y</td>
<td></td>
</tr>
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The International CEA Trials

2 different methods for measuring stenosis  
+  
2 different definitions for operative stroke  
+  
2 different methods of describing risk  
=  
many different interpretations of results!
CETC

Carotid Endarterectomy Trialists Collaboration

• combined ALL of the data from ECST, NASCET & VA
• 5,893 patients in database
• 33,000 patient years follow-up
• all angiograms reanalysed using NASCET method
ipsilateral stroke at 5 years
including operative risk

<table>
<thead>
<tr>
<th>stenosis</th>
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<td>32</td>
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<td>50-69%</td>
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<td>4.6%</td>
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<td>46</td>
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<tr>
<td>70-99%</td>
<td>10.36%</td>
<td>26.24%</td>
<td>15.9%</td>
<td>6</td>
<td>159</td>
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<tr>
<td>near occlusion</td>
<td>16.82%</td>
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PM Rothwell *Lancet* 2003
**Ipsilateral stroke at 5 years including operative risk**

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PM Rothwell *Lancet* 2003
For patients with TIA or ischemic stroke within the last six months and ipsilateral severe (70-99%) stenosis, CEA by a surgeon with a peri-operative morbidity/mortality of <6% is recommended.

(Class I, Evidence level A)

Circulation 2006;37:577-617
For patients with TIA or ischaemic stroke within the last six months and ipsilateral severe (70-99%) stenosis, CEA by a surgeon with a peri-operative morbidity/mortality of <6% is recommended. (Class I, Evidence Level A)

For patients with TIA or ischaemic stroke within the last six months and ipsilateral moderate (50-69%) stenosis, CEA is recommended, depending on patient specific factors such as age, gender, co-morbidity and severity of initial symptom. (Class I, Evidence Level A)
**Ipsilateral stroke at 5 years**

**including operative risk**

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954 unnecessary procedures

PM Rothwell *Lancet* 2003
Take-home Messages

The assumption that all patients have the same risk/benefit is flawed

achieving maximum benefit: - incremental
stenosis

-age
-rapid intervention
-gender
-plaque morphology
-contralateral occlusion
-operative risk
The assumption that all patients have the same risk/benefit is flawed.

achieving maximum benefit:
- incremental
stenosis
- age
- rapid intervention
- gender
- plaque morphology
- contralateral occlusion
- operative risk
Incremental Stenosis

Level I, grade A Evidence

ARR conferred by CEA (%)

- ARR at 3 years
- ARR at 5 years
- ARR at 8 years

 degree of stenosis

PM Rothwell Lancet 2003
Incremental Stenosis

ARR conferred by CEA (%)

ARR at 3 years
ARR at 5 years
ARR at 8 years

Level I, grade A Evidence

55 strokes prevented at 8 years by treating 1000 patients

PM Rothwell Lancet 2003
Incremental Stenosis

ARR conferred by CEA (%)

- ARR at 3 years
- ARR at 5 years
- ARR at 8 years

380 strokes prevented at 8 years by treating 1000 patients

PM Rothwell *Lancet* 2003
Incremental Stenosis

ARR conferred by CEA (%)

0 strokes prevented at 8 years by treating 1000 patients

PM Rothwell Lancet 2003
You cannot treat symptomatic patients with ‘50-99% stenoses’ as being a homogenous group of equal risk.
The assumption that all patients have the same risk/benefit is flawed

achieving maximum benefit: 
- incremental
stenosis

-age
-rapid intervention
-gender
-plaque morphology
-contralateral occlusion
-operative risk
Effect of Age on Benefit from CEA

- <65
- 65-74
- >75

strokes prevented/1000 CEAs at 2 years

adapted from NASCET 2001
Effect of Age on Benefit from CEA

- <65
- 65-74
- >75

Strokes prevented/1000 CEAs at 2 years

- <50% stenosis
- 50-69%
- >70% stenosis

Adapted from NASCET 2001
Effect of Age on Benefit from CEA

 adapted from NASCET 2001

strokes prevented/1000 CEAs at 2 years

<50% stenosis  50-69%  >70% stenosis

<65  65-74  >75

adapted from NASCET 2001
Effect of Age on Benefit from CAS

Stroke rates increase with age

adapted from ProCAS, Lennox Hill etc.
The general feeling that elderly patients do not gain significant benefit because of an increased procedural risk is unsustainable. They have the most to gain! But CAS must keep the 6% limit!!!
The assumption that all patients have the same risk/benefit is flawed

**achieving maximum benefit:**
- incremental
- stenosis
- age
- rapid intervention
- gender
- plaque morphology
- contralateral occlusion
- operative risk
Rapid Tx of Symptomatic Patients

Time from last event to randomisation

No of strokes prevented per 1000 CEAs at 3 years

- 0-2 wks
- 2-4 wks
- 4-12 wks
- 12+ wks

Adapted from Rothwell 2004
Every third stroke is a second stroke!
ICA stenosis should be treated as early as reasonably possible, regardless of the invasive method used.
The assumption that all patients have the same risk/benefit is flawed

achieving maximum benefit: - incremental
stenosis
-age
-rapid intervention
-gender
-plaque morphology
-contralateral occlusion
-operative risk
Gender, Delay & Stenosis Severity

Strokes prevented/1000 CEAs at 5 years

- 70-99% stenosis
- 50-69% stenosis

MALES

CETC Lancet 2005
Gender, Delay & Stenosis Severity

Strokes prevented/1000 CEAs at 5 years

- **0-2 weeks**
  - 70-99% stenosis
  - 50-69% stenosis

- **2-4 weeks**
  - 70-99% stenosis
  - 50-69% stenosis

- **4-12 weeks**
  - 70-99% stenosis
  - 50-69% stenosis

- **>12 weeks**
  - 70-99% stenosis
  - 50-69% stenosis

CETC Lancet 2005
Conclusion

It is an uncomfortable observation that unless women with moderate stenoses receive treatment within a month of symptoms, they gain little benefit but face all the risks. They should not be considered ‘high-risk’
The assumption that all patients have the same risk/benefit is flawed

**achieving maximum benefit:**  
- incremental
  - stenosis
  - age
  - rapid intervention
  - gender
  - plaque morphology
  - contralateral occlusion
  - operative risk
Influence of Plaque Morphology

- smooth stenosis
- ulcerated stenosis
CEA confers benefit in ulcerated stenoses

ipsilateral strokes prevented/1000 CEAs at 2 years

adapted from NASCET 1994
There has been much debate about the merits of studying plaque morphology. A simple assessment of whether the surface is irregular or smooth could have immense predictive benefit.
The assumption that all patients have the same risk/benefit is flawed

**achieving maximum benefit:**
- incremental
- stenosis
- age
- rapid intervention
- gender
- plaque morphology
- contralateral ICA occlusion
- operative risk
Stenosis & Contralateral Occlusion
Effect of Contralateral Disease

No of ipsilateral strokes prevented per 1000 CEAs at 2 years

extent of contralateral disease

NASCET 1995
Effect of Contralateral Disease

No of ipsilateral strokes prevented per 1000 CEAs at 2 years

extent of contralateral disease

NASCET 1995
In parallel with plaque irregularity, the presence of contralateral occlusion is the single biggest predictor of benefit from intervention. NASCET stroke risk of 14.7% much higher than with CAS (~5%)!
The assumption that all patients have the same risk/benefit is flawed

achieving maximum benefit:  -incremental
stenosis

- age
- rapid intervention
- gender
- plaque morphology
- contralateral occlusion
- operative risk
Effect of 30-d Risk on Outcome

CVEs prevented at 5 years per 1000 patients

- 70-99% (Red line)
- 50-69% (Teal line)

30-day death/stroke (%) vs. CVEs prevented at 5 years per 1000 patients

- At 0% 30-day death/stroke: 168 CVEs are prevented
- At 9% 30-day death/stroke: 138 CVEs are prevented
- At 10% 30-day death/stroke: 50 CVEs are prevented

Effect of 30-d Risk on Outcome

 CVEs prevented at 5 years per 1000 patients

30-day death/stroke (%)
Effect of 30-d Risk on Outcome

CVEs prevented at 5 years per 1000 patients

30-day death/stroke (%)

CAVATAS
EVA-3S
CREST
SPACE

Effect of 30-d Risk on Outcome

CVEs prevented at 5 years per 1000 patients

70-99%
50-69%
No surgeon or interventionist can justify offering treatment on the basis of the International Trials if his procedural risks are out of accepted guidelines.

Personal audit is mandatory.
Evidence for treating ...

- symptomatic patients
- asymptomatic patients
- the ‘high-risk’ patient
<table>
<thead>
<tr>
<th>5 year stroke risk</th>
<th>surgery</th>
<th>BMT</th>
<th>ARR</th>
<th>RRR</th>
<th>NNT</th>
<th>CVE/1000</th>
</tr>
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<tr>
<td>ACAS (n=1662)</td>
<td>5.1%</td>
<td>11.0%</td>
<td>5.9%</td>
<td>54%</td>
<td>17</td>
<td>59</td>
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</table>

ACAS, 1995
Criticisms of ACAS

- disabling/fatal stroke not reduced
- ACAS observed no significant benefit in women
- patients had to live 5 years to gain benefit
- stroke reduction only achieved in year five
- concerns over surgeon selection
- no association between stenosis severity & stroke risk
- no association between bilateral disease & stroke risk

ACAS, 1995
### ACAS & ACST Findings

<table>
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<tr>
<td><strong>ACST</strong> (n=3120)</td>
<td>6.4%</td>
<td>11.8%</td>
<td>5.4%</td>
<td>46%</td>
<td>19</td>
<td>53</td>
</tr>
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ACAS, 1995   ACST, 2004
Principle Messages from ACST

- maximum benefit in patients aged <75 years
- no evidence of benefit in patients aged >75 yrs
- ‘apparent’ benefit for men and women
- 50% reduction in disabling/fatal stroke

ACAS, 1995   ACST, 2004
Benefit in Women?

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Events/Patients</th>
<th>Surgical</th>
<th>Medical</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
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<tr>
<td><strong>MALES</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACST</td>
<td>51 /1021 97 /1023</td>
<td>0.50</td>
<td>0.35-0.72</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACAS</td>
<td>18 /544 38 /547</td>
<td>0.46</td>
<td>0.26-0.81</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOTAL</td>
<td>69 /1565 135 /1570</td>
<td>0.49</td>
<td>0.36-0.66</td>
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<td></td>
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<tr>
<td><strong>FEMALES</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACST</td>
<td>31 /539 34 /537</td>
<td>0.90</td>
<td>0.55-1.49</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACAS</td>
<td>15 /281 14 /287</td>
<td>1.10</td>
<td>0.52-1.82</td>
<td></td>
<td></td>
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<tr>
<td>TOTAL</td>
<td>46 /820 48 /824</td>
<td>0.96</td>
<td>0.63-1.45</td>
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ACAS, 1995   ACST, 2004

P.M. Rothwell  Lancet 2004
You cannot ignore the obvious fact that women gained less benefit from intervention than men. Treatment should probably be reserved for women aged <70 years with no significant co-morbidity. Asymptomatic females could never be considered ‘high-risk’
Evidence for treating …

- symptomatic patients
- asymptomatic patients
- the ‘high-risk’ patient
“When carotid endarterectomy is not feasible in high-risk patients and carotid stenting is, patients should undergo stenting regardless of the medical risk”

Alhaddad
Among patients with a severe (>70%) symptomatic stenosis in whom the stenosis is difficult to access surgically, major medical conditions are present, or other specific circumstances exist (e.g. radiation arteritis, recurrent stenosis), CAS is not inferior to CEA and may be considered, provided CAS is performed with established peri-procedural risks of 4-6%.

Class IIa, Evidence Level B

Circulation 2006
Registries of carotid stenting in patients at high risk for CEA are consistent with the SAPPHIRE trial. Patients who have serious co-morbid medical or anatomical conditions that increase the risk from an open surgical approach or general anaesthesia should be primary candidates for carotid stenting.”

G. Roubin Circulation 2006
Do we have enough data to make this recommendation?

Make sure you're Comparing Apples to Apples
SAPPHIRE

723 ‘high risk’ patients considered for inclusion

general criteria: symptomatic + stenosis >50%
   asymptomatic + stenosis >80%

‘high-risk’ criteria
   - significant cardiac disease
   - severe pulmonary disease
   - contralateral occlusion
   - contralateral RLN palsy
   - previous neck surgery
   - radiation arteritis
   - recurrent stenosis
   - age >80 years

NEJM 2004;351:1493
Some Interventions are Obviously High-risk!
‘High-risk’ for what, exactly?

<table>
<thead>
<tr>
<th>high risk plaque</th>
<th>high risk patient</th>
<th>high risk procedure</th>
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<tr>
<td>symptomatic</td>
<td>cardiac disease</td>
<td>contralateral occlusion</td>
</tr>
<tr>
<td></td>
<td>pulmonary disease</td>
<td>rec laryngeal N palsy</td>
</tr>
<tr>
<td></td>
<td>&gt;80 years</td>
<td>PMH neck surgery</td>
</tr>
<tr>
<td></td>
<td></td>
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</tr>
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<td></td>
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<td>recurrent stenosis</td>
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‘High-risk’ for what, exactly?

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<td></td>
<td>recurrent stenosis</td>
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It is difficult, based on evidence, to place ‘asymptomatic’ patients within any of these categories.
Based on evidence, will CAS prevent stroke?

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<th>Condition</th>
<th>Symptomatic</th>
<th>Asymptomatic</th>
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<tbody>
<tr>
<td>aged &gt;75 years</td>
<td>+++</td>
<td>0</td>
</tr>
<tr>
<td>with plaque irregularity</td>
<td>+++</td>
<td>0</td>
</tr>
<tr>
<td>incremental stenosis</td>
<td>+++</td>
<td>0</td>
</tr>
<tr>
<td>with contralateral occlusion</td>
<td>+++</td>
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Based on data from ECST, NASCET, ACAS, ACST, SPACE, and SAPPHIRE
71% of the randomised patients were asymptomatic in whom:

30 day death/stroke following angioplasty = 5.8%
following surgery = 6.1%
Conclusions from SAPPHIRE

So, a trial where 70%+ were asymptomatic and in whom there was a 6% procedural risk and in whom you will never confer any long term benefit in stroke prevention has been used to develop guidelines for all high-risk patients i.e. including all the symptomatic ones!
Strokes Prevented per 1000 CEAs

SAPPHIRE asymp with 6% risk 22/1000 at 5 years

source: ACAS, ACST, ECST & NASCET
## “high relative risk/benefit group”

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<thead>
<tr>
<th>Patient Subgroup</th>
<th>CVE Prevented per 1000 CEAs</th>
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<td>SAPPHIRE asymptomatic with 6% risk</td>
<td>22 at 5y</td>
</tr>
<tr>
<td>sympt, 70-99% aged &gt;75 years</td>
<td>333 at 2y</td>
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<td>sympt, 70-99% with high co-morbidity</td>
<td>333 at 2y</td>
</tr>
<tr>
<td>sympt, 70-99% recurrent TIAs for &gt;6 mths</td>
<td>333 at 2y</td>
</tr>
<tr>
<td>sympt, 70-99% with operations &lt;2 weeks</td>
<td>333 at 3y</td>
</tr>
<tr>
<td>sympt, 80-99% with intracranial disease</td>
<td>333 at 3y</td>
</tr>
<tr>
<td>sympt, 90-99% with no string sign</td>
<td>370 at 3y</td>
</tr>
<tr>
<td>sympt, 70-99%, with contralateral occlusion</td>
<td>500 at 2y</td>
</tr>
<tr>
<td>sympt, 90-99% with plaque ulceration</td>
<td>500 at 2y</td>
</tr>
</tbody>
</table>
What in whom?

We have still a lot of unanswered questions
Irrespective of any debate about which asymptomatic patient should be treated, whether CEA or CAS is safer, how and by whom CAS should be performed, ALL pale into insignificance compared with the effect of delay in treating symptomatic patients with severe carotid artery disease.