A simple long-term stroke risk model for asymptomatic carotid stenosis – will it help us select patients for intervention in the future?

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University of Oxford

MAC, 09.00 7th December 2017
Age-standardised stroke mortality declining, but total number rising

GBD 2015 Mortality and Causes of Death Collaborators, DALYs and HALE Collaborators (2016), Lancet
Carotid Artery Disease

• Important cause of ischaemic stroke (15-20%)

• Most (80%) carotid strokes have no warning symptoms

• Asymptomatic stenosis: important long-term stroke risk

• RCTs confirm net benefit of CEA among asymptomatic patients

• Successful CEA ~halves long-term stroke risk
## Trial Characteristics – CEA vs not

<table>
<thead>
<tr>
<th></th>
<th>VA</th>
<th>ACAS</th>
<th>ACST-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recruitment</td>
<td>1983 -</td>
<td>1987 -</td>
<td>1993 -</td>
</tr>
<tr>
<td></td>
<td>1987</td>
<td>1993</td>
<td>2003</td>
</tr>
<tr>
<td>Participants</td>
<td>444</td>
<td>1 662</td>
<td>3 120</td>
</tr>
<tr>
<td>Region</td>
<td>USA</td>
<td>USA</td>
<td>Europe</td>
</tr>
<tr>
<td>Follow-up, Median</td>
<td>5.7 [4.5-7.0]</td>
<td>4.8 [3.7-5.0]</td>
<td>9.0 [6.1-11.1]</td>
</tr>
</tbody>
</table>
VA, ACAS, ACST-1 Trials

2291 Patients on **triple therapy** (ie, including statin) before stroke

A. Any stroke or perioperative death

- CEA + TMT
- TMT alone

B. Any non–perioperative stroke

- CEA + TMT
- TMT alone

Event Risk %, (SE)

2291 Patients on triple therapy (ie, including statin) before stroke
Purpose of this Study

*There is uncertainty as to which asymptomatic patients benefit most from carotid intervention*

**AIM:** to develop a simple clinical risk score to identify patients with *high risk* asymptomatic carotid stenosis
Methods

• IPD of ‘medically treatment’ patients from all 3 asymptomatic trials
  
  • VA
  
  • ACAS
  
  • ACST-1

• Restricted to those with no CEA prior to stroke (ie, medically managed)

• Stroke risk ratios (RR) from Cox regression

• Most important factors included in risk score (RR >1.3)
Association of CV Risk Factors with Stroke (among medically managed)

<table>
<thead>
<tr>
<th>Association</th>
<th>Events / Person-years</th>
<th>Stroke RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of Diabetes</td>
<td>87/2433 278/10751</td>
<td>1.32 (1.03-1.68)</td>
</tr>
<tr>
<td>Male Sex</td>
<td>260/8631 105/4553</td>
<td>1.23 (0.97-1.55)</td>
</tr>
<tr>
<td>Total Cholesterol (per 2 mmol/L)</td>
<td>* 316/11665</td>
<td>1.16 (0.95-1.40)</td>
</tr>
<tr>
<td>Older Age (per 10 years)</td>
<td>* 365/13184</td>
<td>1.15 (1.00-1.33)</td>
</tr>
<tr>
<td>Systolic Blood Pressure (per 20 mmHg)</td>
<td>* 364/13147</td>
<td>1.09 (0.98-1.21)</td>
</tr>
<tr>
<td>History of Ischaemic Heart Disease</td>
<td>137/4625 228/8559</td>
<td>1.03 (0.83-1.27)</td>
</tr>
</tbody>
</table>

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Association of Cerebrovascular Events with Stroke (among medically managed)

<table>
<thead>
<tr>
<th>Events / Person-years</th>
<th>Stroke RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>At Risk</td>
</tr>
<tr>
<td>Brain Infarct on Imaging</td>
<td>93/2435</td>
</tr>
<tr>
<td>Prior Contralateral Event</td>
<td>133/3497</td>
</tr>
<tr>
<td>Prior CEA</td>
<td>91/2821</td>
</tr>
<tr>
<td>Prior Ipsilateral Event</td>
<td>28/1084</td>
</tr>
<tr>
<td>Contralateral Stenosis &gt;80%</td>
<td>51/1624</td>
</tr>
<tr>
<td>Ipsilateral Stenosis &gt;80%</td>
<td>123/4596</td>
</tr>
</tbody>
</table>
# 3 Important Stroke Risk Factors

<table>
<thead>
<tr>
<th>Event</th>
<th>At Risk</th>
<th>Reference</th>
<th>Stroke RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain Infarct on Imaging</td>
<td>93/2435</td>
<td>158/6301</td>
<td>1.57 (1.21-2.03)</td>
</tr>
<tr>
<td>Prior Contralateral Event</td>
<td>133/3497</td>
<td>232/9687</td>
<td>1.57 (1.26-1.94)</td>
</tr>
<tr>
<td>History of Diabetes</td>
<td>87/2433</td>
<td>278/10751</td>
<td>1.32 (1.03-1.68)</td>
</tr>
</tbody>
</table>

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# Summative Risk Score

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>Diabetes only</td>
<td>1</td>
</tr>
<tr>
<td>Prior cerebral ischaemia* only</td>
<td>2</td>
</tr>
<tr>
<td>Both</td>
<td>3</td>
</tr>
</tbody>
</table>

*Prior contralateral symptoms or brain infarct on imaging*
# Risk Prediction

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Participants</th>
<th>Events / Person-years</th>
<th>Stroke RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None (Score 0)</td>
<td>1597</td>
<td>78/4230</td>
<td>1.00 (0.80-1.25)</td>
</tr>
<tr>
<td>Diabetes Only (Score 1)</td>
<td>438</td>
<td>28/929</td>
<td>1.54 (1.06-2.24)</td>
</tr>
<tr>
<td>Prior Cerebral Ischaemia only* (Score 2)</td>
<td>1145</td>
<td>113/2881</td>
<td>2.15 (1.79-2.59)</td>
</tr>
<tr>
<td>Both (Score 3)</td>
<td>328</td>
<td>32/697</td>
<td>2.39 (1.69-3.39)</td>
</tr>
</tbody>
</table>

*Prior contralateral symptoms or brain infarct on imaging

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Risk Prediction

If the 10-year stroke risk is:

- 9% (no risk factors)  10y Absolute gain from CEA ~5%
- 13%* (diabetes)    10y Absolute gain from CEA ~7%
- 20% (prior ischaemia)  10y Absolute gain from CEA ~10%  
  (1/3 of trial participants)

*Stroke risk in medically treated ACST-1 participants taking statins
Implications

- **Statins work:** With CEA or without CEA, modern statin
  ~halves stroke risk

- **And CEA works:** With a statin or without a statin, successful CEA ~halves stroke risk

- Risk of stroke ~**double with prior cerebral ischaemia**

- **Those with higher risk scores** should **derive greater absolute benefit** from CEA
Conclusion

Simple characteristics (diabetes, prior ischaemia) can be used to identify high stroke risk patients who might benefit most from CEA.
ACST-2
Surgery vs Stenting

Asymptomatic patients with tight stenosis requiring intervention:

Which procedure is generally better (in addition to good medical treatment)?

- carotid surgery (CEA)
- or
- carotid stenting (CAS)?
ACST-2 progress – High Stroke Risk patients

>2731/3600 now recruited, 869 still needed, by end of 2019

30% diabetic
35% previous symptoms or cerebral infarcts

Follow up to date - 3.5 years
Statin treatment is good
2017 ESVS and ESC Guidelines

ACST-2 Go with the Guidelines!

"10-15% of all strokes follow thromboembolism from an asymptomatic ICA stenosis > 50%"  
ESVS Guidelines, 2017

Consider for Intervention

IIa B

Asymptomatic 60-90% stenosis at increased risk of late stroke, provided perioperative risk of stroke/death is <3% and life expectancy > 5 yrs

Patients at higher risk of stroke

- History of contralateral TIA/Stroke
- Silent ipsilateral infarction
- Diabetes
- Specific plaque markers/TCD emboli
- Impaired cerebral reserve

"ACST-2 has been randomising asymptomatic patients to CEA or CAS – it is hoped that all surgeons and interventionalists will support these RCTs"  
ESVS Guidelines, 2017

Medical Treatment for all

- Longterm single APT (usually aspirin)
- Clopidogrel if aspirin intolerant
- Statin therapy
- BP lowering treatment to maintain BP < 140/90
- APT periprocedure and longterm
- Continue statins
- Caution in reducing BP, but avoid uncontrolled hypertension > 180/90 mmHg

CEA & CAS

- Consider EPDs
- DAPT (aspirin/clopidogrel) for at least 1 month after

CAS only

- I B

Post procedure

- Independent assessment is recommended

ESC/ESVS

Algorithm for Treatment of Asymptomatic Carotid Stenosis

60-99% stenosis  
No recent TIA/stroke  
Symptoms ipsilaterally

- Life expectancy >5 yrs?
- Favourable anatomy?
- Higher stroke risk on BMT?

Yes  
Yes  
No

Within ACST-2

Consider CEA + BMT  
Consider CAS + BMT

BMT I A
ACST-2: Long-term statin use >80%
ACST-2: >75% on good (or very good) statin regimens

- Simva 40
- Atorva 20
- Rosuva 10
- Combined
Acknowledgements

ACST, ACAS, VA Trialists and to the participants who took part

ACST-2 information website acst-2.org