What Are The Ongoing Carotid Trials (CREST-2, SPACE-2, ACST-2, ACT-1, ECST-2) Telling Us And Going To Tell Us

1.18-1.23
VEITH Friday, Session 81

Alison Halliday
Professor of Vascular Surgery
University of Oxford

Why RCTs need to be larger....

Take a simple question, like treatment for acute MI
What level of improvement will change practice?

Long ago...30 years...

**COMMIT: Effect of adding clopidogrel during MI on death/re-MI/stroke (45,000 patients)**

<table>
<thead>
<tr>
<th></th>
<th>Placebo + ASA:</th>
<th>Clopidogrel + ASA:</th>
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<tbody>
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<td>2310 with event (10.1%)</td>
<td>2121 with event (9.2%)</td>
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9% (SE3) relative risk reduction (2P=0.002)

**ISIS-2: 2 x 2 “factorial” study of iv streptokinase and of oral aspirin in acute MI (17,000 patients)**

ISIS-2: Placebo 14%

ASA 10%

Aspirin + clopidogrel vs nil: ~50 per 1000 treated

**COMMIT:**

ASA 10%

ASA + Clop. 9%

Aspirin & Clopidogrel:
Effects on death, further MI, Stroke
Not just large numbers... but long term results
the symptomatic ICSS trial (1710 patients):
Lancet 2014

CEA vs CAS; mean follow up 4 years

• ‘equivalent long-term disability’
• ‘quality of life is similar’ despite differences in rates of non-disabling outcome events

Falling risks from CEA and CAS

• Reduced procedural risk for CEA (Statins)
• Reduced procedural risks for CAS...

Techniques, devices, experience have all changed since the symptomatic trials...

Now - FLOW-reversal systems, direct puncture, membrane stents.....

Carotid RCTs

Asymptomatic

Revascularisation needed; CAS or CEA?

Need for revascularisation uncertain

| CAS vs. CEA |
| ACT-1 |
| ACST-2 |

Revasc vs. BMT
SPACE-2, CREST-2 (ECST-2)

The SPACE network and recruitment 2009-12

Recruitment insufficient
(10-15% of all pts in 3 yrs)

SPACCE-2

Stent-protected Angioplasty
in Asymptomatic Carotid Artery Stenosis vs. Endarterectomy

A three-arm Clinical Trial

a three-armed interventional RCT is not feasible!

SPACE-2: New design

Despite new design SPACE 2 has stopped

Possible reasons:
• Reimbursement - good for procedure, poor for medical treatment alone
• Difficulties when patients want a procedure
• Concept of being in a trial (“randomisation, uncertainty” not popular with patients

Future solutions....?  
• Where evidence is needed, patients should recognise that they are safer in a trial (cf AIDS)

The Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis Study
Health and Hope for Patients at Risk for Stroke

The ACST-2/ACT-1 research question..

For asymptomatic patients with tight stenosis requiring intervention:

Which procedure is generally better (in addition to good medical treatment)?
- carotid surgery (CEA)
- carotid stenting (CAS)

ACT-1 results at last!

1453/1658 enrolled (88%; stopped because slow), Abbott-funded (Xact + Emboshield), 3 CAS :1 CEA

Age limit <80 years (43-79, mean 71yrs)
Men 61%, mean ipsilateral stenosis 74% (34-98%)

30 day outcomes
- Stroke, MI, Death 3.3% CAS vs 2.6% CEA
- Stroke or Death 2.9% CAS vs 1.7%
- Minor stroke 2.4% CAS vs 1.1%
- Major stroke/death 0.6% CAS vs 0.6%
- Other complications 2.8% CAS vs 4.7%
ACT-1 results at last!

5 year outcomes (survival 88%)
Any stroke 6% CAS vs 5% CEA
Ipsi- stroke (non-procedural) 2.2% CAS vs 2.7%
Any clinical re-intervention 1.6% CAS vs 3.3% (p=0.05)

Conclusions: Lower enrollment reduced power
but CAS is non-inferior to CEA up to 1 year, with similar
5-year results, and lower re-intervention rates

ACST-2: Experienced collaborators
207 centre/operators’ experience to 2014:
(73 do both procedures)

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<tr>
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<th>CEA</th>
<th>CAS</th>
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<tbody>
<tr>
<td>Total procedures</td>
<td>118,287</td>
<td>45,693</td>
</tr>
<tr>
<td>Median Experience</td>
<td>17</td>
<td>11</td>
</tr>
<tr>
<td>[Years]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median Procedures</td>
<td>346</td>
<td>150</td>
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<tr>
<td>/operator</td>
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We still need to know (>8000 patients)

- Long term results (5-10 years)
- Better CAS experience – is it important?
- Men and women, are results similar?
- Are there now newer and better devices?
  open vs closed cell stents, flow-reversal CPDs,
  direct intervention (eg Roadsaver)
- Medical treatment alone (will patients comply in real life?)

CREST 2 (2480) and SPACE-2 (500+) = 3000 patients
ACST-2 (3600) and ACT-1 (1480) patients = 5000 patients