Carotid Artery Stenting: Current Randomized Evidence and Future Perspectives

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Disclosure

Speaker name:

.....Marco Roffi...........................................................

I have the following potential conflicts of interest to report:

☐ Consulting

☐ Employment in industry

☐ Stockholder of a healthcare company

☐ Owner of a healthcare company

☒ Other(s):

Unrestricted institutional research grants from Biotronik, Abbott Vascular, Medtronic, Boston Scientific, Terumo

Speaker fee: Terumo
CEA or CAS?

Instinctively → CAS! (less invasive)

Let’s be rational → Evidence-based medicine (RCTs)

Who in the room thinks that in the majority of RCT CAS was inferior to CEA?
Who in the room thinks that in the majority of RCT CAS was no different than CEA?
## Primary Endpoints in CEA vs CAS RCT

Enrolling >300 patients

<table>
<thead>
<tr>
<th>Trial</th>
<th>Begin of Enrollment</th>
<th>N</th>
<th>Symptomatic Patients</th>
<th>Primary Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAVATAS</td>
<td>1992</td>
<td>504</td>
<td>100%</td>
<td>No difference in 30-d death or stroke.</td>
</tr>
<tr>
<td>SAPPHIRE</td>
<td>2000</td>
<td>334</td>
<td>29%</td>
<td>No difference in death, stroke, MI within 30 d or death or ipsilateral stroke at 1 y</td>
</tr>
<tr>
<td>EVA-3S</td>
<td>2000</td>
<td>527</td>
<td>100%</td>
<td>CEA superior in any stroke or death at 30 d.</td>
</tr>
<tr>
<td>CREST</td>
<td>2000</td>
<td>2502</td>
<td>53%</td>
<td>No difference in periprocedural stroke, MI, or death or ipsilateral stroke within 4 y</td>
</tr>
<tr>
<td>SPACE</td>
<td>2001</td>
<td>1200</td>
<td>100%</td>
<td>No difference in ipsilateral stroke or death at 30 d.</td>
</tr>
<tr>
<td>ICSS</td>
<td>2001</td>
<td>1713</td>
<td>100%</td>
<td>No difference in fatal or disabling stroke at 5 y</td>
</tr>
<tr>
<td>ACT-1</td>
<td>2005 (3:1)</td>
<td>1453</td>
<td>0%</td>
<td>No difference in death, stroke, MI within 30 d or death or ipsilateral stroke at 1 y</td>
</tr>
</tbody>
</table>

Modified from Roffi M, Kulcsar Z, Carrera E, Cremonesi A. Heart 2016;102:1059-69
Meta-Analysis of RCT CEA vs. CAS: 30-Day Death or Stroke

LEICESTER (1998)
LEXINGTON I (2001)
WALLSTENT (2001)
LEXINGTON II (2004)
TESCAS–C (2006)
BACASS (2008)
EVA–3S (2008)
SAPPHIRE (2008)
SPACE (2008)
CAVATAS (2009)
ICSS (2010)
CREST (2010)

Overall (I–squared = 33.5%, p = 0.122)

1.54 (1.25, 1.89), p<0.001

Meta-Analysis of RCT CEA vs. CAS: 30-Day Stroke

Excess of minor strokes in the CAS arm

Meta-Analysis of RCT CEA vs. CAS: 30-Day Myocardial Infarction

Overall (I-squared = 0.0%, p = 0.994)

0.48 (0.29, 0.78), p=0.003
Meta-Analysis of RCT CEA vs. CAS: Cranial Nerve Injury

LEICESTER (1998)
LEXINGTON I (2001)
LEXINGTON II (2004)
TESCAS–C (2006)
BACASS (2008)
EVA–3S (2008)
SAPPHIRE (2008)
Steinbauer et al (2008)
CAVATAS (2009)
ICSS (2010)
CREST (2010)
Overall (I-squared = 0.0%, p = 0.599)

0.09 (0.05, 0.16), p<0.001

In the European trials (EVA-3S, SPACE, ICSS) 2/3 of the CAS patients were treated by operators with lifetime experience of 37 CAS or fewer at the time of the procedure.

Inexperience

→ two-fold increased risk for the patient
   - insufficient operator skills
   - inappropriate patient selection

Virtually no information on supra-aortic anatomy (THE most important risk factor for CAS-related events!) available from the trials, as the degree of stenosis per carotid ultrasound was sufficient to enrol patients.
Asymptomatic Stenosis
CEA vs. CAS in Asymptomatic Patients: SAPPHIRE-1 Year Major Adverse Events

N=334, 72% asymptomatic

CEA vs. CAS in Asymptomatic Patients: CREST: Periprocedural Events

D=death; S=stroke; MI=myocardial infarction

N=1181

CAS

CEA

No difference in the primary endpoint up to 4 years

Brott et al. NEJM 2010
ACT-1: Primary Endpoint of Death, Stroke, or MI within 30 days or ipsilateral stroke within 1 year

- 1453 asymptomatic patients
- Randomized 3:1 CAS:CEA

Rosenfield K et al. NEJM 2016
### ACT-1: 30-Day Events

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Stenting (N = 1089)</th>
<th>Endarterectomy (N = 364)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Death, stroke, or myocardial infarction</em></td>
<td>35/1072 (3.3)</td>
<td>9/348 (2.6)</td>
<td>0.60</td>
</tr>
<tr>
<td><em>Death or stroke</em></td>
<td>31/1072 (2.9)</td>
<td>6/348 (1.7)</td>
<td>0.33</td>
</tr>
<tr>
<td><em>Death or major stroke</em></td>
<td>6/1072 (0.6)</td>
<td>2/348 (0.6)</td>
<td>1.00</td>
</tr>
<tr>
<td><em>Death</em></td>
<td>1/1072 (0.1)</td>
<td>1/348 (0.3)</td>
<td>0.43</td>
</tr>
<tr>
<td><em>All stroke</em></td>
<td>30/1072 (2.8)</td>
<td>5/348 (1.4)</td>
<td>0.23</td>
</tr>
<tr>
<td>Major stroke</td>
<td>5/1072 (0.5)</td>
<td>1/348 (0.3)</td>
<td>1.00</td>
</tr>
<tr>
<td>Ipsilateral</td>
<td>4/1072 (0.4)</td>
<td>1/348 (0.3)</td>
<td>1.00</td>
</tr>
<tr>
<td>Nonipsilateral</td>
<td>1/1072 (0.1)</td>
<td>0/348</td>
<td>1.00</td>
</tr>
<tr>
<td>Minor stroke</td>
<td>26/1072 (2.4)</td>
<td>4/348 (1.1)</td>
<td>0.20</td>
</tr>
<tr>
<td>Ipsilateral</td>
<td>22/1072 (2.1)</td>
<td>4/348 (1.1)</td>
<td>0.36</td>
</tr>
<tr>
<td>Nonipsilateral</td>
<td>4/1072 (0.4)</td>
<td>0/348</td>
<td>0.58</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>5/1072 (0.5)</td>
<td>3/348 (0.9)</td>
<td>0.41</td>
</tr>
<tr>
<td>Composite measure of complications</td>
<td>31/1089 (2.8)</td>
<td>17/364 (4.7)</td>
<td>0.13</td>
</tr>
<tr>
<td><em>Cranial-nerve injury</em></td>
<td>1/1089 (0.1)†‡</td>
<td>4/364 (1.1)</td>
<td>0.02</td>
</tr>
</tbody>
</table>
# SPACE-2: A Missed Opportunity to Compare Carotid Endarterectomy, Carotid Stenting, and Best Medical Treatment in Patients with Asymptomatic Carotid Stenoses


<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>30-day death</th>
<th>30 death or stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEA, N=203</td>
<td></td>
<td>0%</td>
<td>4/203 =2.0%</td>
</tr>
<tr>
<td>CAS, N=197</td>
<td></td>
<td>0%</td>
<td>5/197 =2.5%</td>
</tr>
</tbody>
</table>
Symptomatic Stenosis
Primary endpoints

Montorsi P, Galli S, Ravagnani PM, Roffi M. Prog Cardiovas Dis 2017, in print.
Montorsi P, Galli S, Ravagnani PM, Roffi M. Prog Cardiovas Dis 2017, in print.
Long-Term Restenosis

No difference in repeat revascularization

Conclusions (1)

- **Asymptomatic stenosis**: SAPPHIRE, CREST-asympt, ACT-1
  - No difference in the primary endpoint
  - No difference in the composite or individual endpoints at 30 days

- **Symptomatic stenosis**: despite equivalence in the primary endpoint in all but one trial (EVA-3S), RCT (with all their limitations) showed an increase in (minor) strokes and this has primed the community of neurologists.

- In all the trials: comparable long term efficacy in terms of ipsilateral stroke prevention, restenosis or repeat revascularization.
Conclusions (2)

• CAS has to further reduce embolic events (surgery is also getting better!) through improved skills, appropriate patient selection, and innovations such as proximal occlusion and double layer mesh stents.

• Unfortunately, no trials directly comparing CEA and CAS in symptomatic patients are ongoing, while in asymptomatic patients ACST-2 trial results should be available only in 2019.

• Therefore, little new data will be available to convince our neurological colleagues that CAS is efficacious and, in appropriately selected patients treated by experienced operators, equivalent to CEA.
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