My Latest Take on RCT Data: When is CEA or CAS the Best Option? The Interventional Position

Horst Sievert, Iris Grunwald
CardioVasculäres Centrum Frankfurt - CVC, Frankfurt
# Disclosures

<table>
<thead>
<tr>
<th>Physician name</th>
<th>Company</th>
<th>Relationship</th>
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<tbody>
<tr>
<td>Horst Sievert</td>
<td>Abbott, Aptus, Atrium, Biosense Webster,</td>
<td>Consulting fees,</td>
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<td>Boston Scientific, Carag, Cardiac Dimensions,</td>
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<td>CardioKinetix, CardioMEMS, Cardiox, Celonova,</td>
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<td>CSI, CVRx, ev3, FlowCardia, Gardia, Gore,</td>
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<td>Cardiokinetix, Access Closure, Coherex,</td>
<td>Stock options</td>
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My Latest Take on RCT Data: When is CEA or CAS the Best Option?


"CAS is the best option in patients with high grade carotid stenosis"

But I don't say that
The interventional position is rather comfortable!

- Initially, there was just medical treatment
- Surgeons had to prove that CEA is better than medical therapy
- Patients do not like surgery
- Therefore, we just have to show that CAS is at least as good as surgery
As you probably know, my general take on randomized clinical trial data is that CAS is as good as CEA!
The topic of this debate is whether we have sufficient data from randomized clinical trials to prefer one treatment modality over the other in specific patients.

The answer is NO
Randomised Trials

- CAVATAS
- SAPPHIRE
- EVA-3S
- SPACE
- ICSS (CAVATAS-2)
- CREST
- ACT-1
- ACST-2
CAVATAS

504 symptomatic patients, randomized to CEA or PTA (Stents only in 25 %!)

<table>
<thead>
<tr>
<th></th>
<th>PTA</th>
<th>CEA</th>
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<tbody>
<tr>
<td>Major stroke/death</td>
<td>6.4 %</td>
<td>5.9 %</td>
</tr>
<tr>
<td>stroke/death</td>
<td>10 %</td>
<td>10 %</td>
</tr>
<tr>
<td>Cranial nerve palsy</td>
<td>-</td>
<td>9 %</td>
</tr>
<tr>
<td>Hematoma</td>
<td>1.2 %</td>
<td>6.7 %</td>
</tr>
<tr>
<td>MI</td>
<td>0</td>
<td>0.8 %</td>
</tr>
</tbody>
</table>

* P < 0.05
Stent implantation was also superior to CEA regarding all secondary endpoints.
3 "negative" studies

- EVA 3S
- ICSS
- SPACE
EVA-3S Primary Endpoint 30 d

Mainly due to insufficient experience of CAS operators!

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Relative Risk ± 95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>2.7% 8.8% [0.3 (1.4-7.5)] 0.004</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>3.9% 9.6% [2.5 (1.2-5.1)] 0.01</td>
<td></td>
</tr>
<tr>
<td>Death/Stroke</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Stenting better, CEA better

International Carotid Stenting Study (ICSS)

- 1711 patients
- Symptomatic carotid stenosis
- Primary endpoint: major stroke within 3 yrs
- Interim analysis 2010:
  - Stroke or death within 4 months or periprocedural MI

Lancet 2010
ICSS
Interim analysis: stroke, death, or procedural myocardial infarction

"Negative trial!"

P < 0.01

Surgery

Stent

Lancet 2010
ICSS 4 yr Results
Lancet 2014

- Clinical status **not** different between CEA and stent at 1 year, 5 years, or final follow-up
- Slightly more re-stenoses after stent but stroke risk **not** increased
- Quality of life **not** different
- "CEA or stent" should be decided individually!

Bonati LH et al, Lancet 2015
ICSS: Predictors of Stroke, Myocardial Infarction or Death within 30 Days of Carotid Artery Stenting

Higher risk:
- Age (RR 1.17 per 5 years of age)
- Prior stroke
- Atrial fibrillation (RR 2.3)

Lower risk:
- Right-sided procedure (RR 0.54)
- Aspirin and clopidogrel in combination (RR 0.59)
- Smoker
- Experienced center

However, this analysis was done only in the stent group! Results were not compared with CEA results.

Table 4. Independent predictors of risk of stroke, MI or death within 30 days of carotid artery stenting in 748 ICSS per-protocol participants in whom the procedure was initiated and for whom complete predictor data are available. Results obtained from multivariable binomial regression.

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. events/ no. patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 5 years increase)</td>
<td>59/748</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>23/207</td>
</tr>
<tr>
<td>Former</td>
<td>31/359</td>
</tr>
<tr>
<td>Current</td>
<td>5/280</td>
</tr>
<tr>
<td>Nature of stroke</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
</tr>
<tr>
<td>Ret.</td>
<td></td>
</tr>
</tbody>
</table>

*Adjusted risk ratio (95% CI) * *Global p*
ICSS-MRI Substudy

- In contrast to other studies, no significant influence of anatomical parameters
  - degree of stenosis
  - ulceration
  - angle between the CCA and ICA
  - “pinhole” stenosis
  - length of stenosis
  - “diseased” CCA
  - contralateral stenosis

- Male gender is in contrast to other studies!

Results where not compared with CEA results

Table 3. Independent predictors of new DWI-MRI lesions following CAS in 115 patients.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>p</th>
<th>Incidence Risk Ratio (IRR)</th>
<th>95% Confidence interval for IRR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lower</td>
</tr>
<tr>
<td>Left-sided stenosis</td>
<td>.03</td>
<td>1.59</td>
<td>1.04</td>
</tr>
<tr>
<td>Age (per 10-year increase)</td>
<td>&lt; .01</td>
<td>2.10</td>
<td>1.61</td>
</tr>
<tr>
<td>Male</td>
<td>&lt; .01</td>
<td>2.83</td>
<td>1.72</td>
</tr>
<tr>
<td>Hypertension</td>
<td>&lt; .01</td>
<td>2.04</td>
<td>1.25</td>
</tr>
<tr>
<td>No diagnosis of cardiac failure</td>
<td>.03</td>
<td>6.58</td>
<td>1.23</td>
</tr>
</tbody>
</table>

Doig D et al, Eur J Vasc Endovasc Surg (2016) 51, 14e20
SPACE
Primary Endpoint: Ipsilateral Stroke and Death @ 30 Days

Also no differences in secondary endpoints and subgroup analyses.
SPACE
My Conclusions

- No difference in the primary endpoint
- No differences in secondary endpoints
- No differences in subgroups
- The study was "negative" just because it was underpowered
- But underpowered means we can not draw valid conclusions
  - not regarding the overall study results
  - and definitely not regarding subgroups
CREST

- 2502 patients
- Symptomatic and asymptomatic
- MI had been part of the primary endpoint
- Well trained interventionists
CREST Composite Primary Endpoint
(any stroke, MI, or death within peri-procedural period plus ipsilateral stroke thereafter)

<table>
<thead>
<tr>
<th></th>
<th>CAS</th>
<th>CEA</th>
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<tbody>
<tr>
<td>%</td>
<td>7.2</td>
<td>6.8</td>
</tr>
</tbody>
</table>

Brott et al. @ International Stroke Conference 2010
CREST
30 Day Results: Stroke

P<0.01 Driven by minor strokes, no difference regarding major stroke

Brott et al. @ International Stroke Conference 2010
CREST 30 Day Results: Myocardial Infarction

Brott et al. @ International Stroke Conference 2010
MIs and minor strokes do have a similar influence on quality of life!

Data from CREST
CREST secondary endpoints

• CEA patients had significantly more
  - Cranial nerve palsy
  - Access site hematoma
  - Wound infection
CREST:
"Surgery better in elderly patients, stenting better in younger patients"

Primary outcome – 4 year

P_{interaction} = 0.020
Hazard Ratio by age group: **no age trend**

Per protocol analysis

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Hazard Ratio</th>
<th>CAS</th>
<th>CEA</th>
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</thead>
<tbody>
<tr>
<td>Below 60</td>
<td>0.39</td>
<td>206</td>
<td>189</td>
</tr>
<tr>
<td>60 to 65</td>
<td>1.8</td>
<td>164</td>
<td>178</td>
</tr>
<tr>
<td>65 to 70</td>
<td>0.99</td>
<td>235</td>
<td>222</td>
</tr>
<tr>
<td>70 to 75</td>
<td>1.11</td>
<td>233</td>
<td>259</td>
</tr>
<tr>
<td>75 to 80</td>
<td>1.73</td>
<td>187</td>
<td>226</td>
</tr>
<tr>
<td>Above 80</td>
<td>1.01</td>
<td>106</td>
<td>102</td>
</tr>
</tbody>
</table>

analysis performed by FDA
Conclusion of the authors: "Additional data are needed to confirm whether this differential risk should be taken into account in decisions for treatment of carotid disease in women"
CREST
Lesion morphology

- Long lesions (>13mm)
  - OR stroke/death 3.4 vs 1.2
- Sequential / remote lesions
  - OR stroke/death 9 vs 1.4

Outdated data because today at least in these lesions we are using proximal protection devices …

... and even in complex lesions, stroke rate using prox protection is 50% lower than in CREST
ACT-1

- Asymptomatic stenosis
- < 80 yrs
- High risk surgery and high risk stenting excluded
- Endpoint: 30 day death, stroke, MI, ipsilateral stroke day 31-365
- 1453 patients randomized (2:1 stent: CEA)
- Primary endpoint 30 days
  - Stent 3.8%, CEA 3.4%
  - Non-inferior criteria met
- 5 yrs outcome similar in both groups

Not published yet but reported
ACST-2

- Asymptomatic stenosis
- 1949 pts randomized until Oct 2015
- Preliminary acute results:
  - 30 days disabling/fatal stroke or fatal MI in both groups: 1%
In all clinical trials, differences between operators have been huge and much more important than differences between treatment modalities!

Regression equation: $\log(y) = 4.71 - 0.85 \times \log(x)$

P-value of slope: $<0.0001$

R-square: 0.81

Data from CAPTURE 2

Gray et al: JACC Interv 2011
So when to do what?

• Randomized trials had not been powered for this question, but
  - CEA probably can or should be preferred
    • in difficult aortic arch anatomy and severely elongated CCA
    • in patients with allergy against aspirin or clopidogrel
    • in octogenarians??
    • if the surgeon is very experienced
  - CAS probably can or should be preferred
    • in all high surgical risk patients
    • in all other patients if the interventionist is very experienced
Thank you!
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