Pitfalls & Limitations of the Esteemed & Often Quoted CAS Versus CEA RCTs: Why They May Be Misleading

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Randomized CAS Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. of Pts.</th>
<th>CPD (%)</th>
<th>Asymptomatic (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAPPHIRE</td>
<td>334</td>
<td>96</td>
<td>71</td>
</tr>
<tr>
<td>EVA-3S</td>
<td>527</td>
<td>92</td>
<td>0</td>
</tr>
<tr>
<td>SPACE</td>
<td>1200</td>
<td>--</td>
<td>0</td>
</tr>
<tr>
<td>CREST</td>
<td>2502</td>
<td>96</td>
<td>47</td>
</tr>
<tr>
<td>ICSS</td>
<td>1703</td>
<td>72</td>
<td>0</td>
</tr>
</tbody>
</table>

SAPPHIRE Trial

- Stenting & Angioplasty with Protection in Patients at High Risk for Endarterectomy
- 70% were asymptomatic
- 30-day combined periop. MAE: 4.8% for CAS vs 9.8% for CEA (p=0.09)
- Combined MAE @ 1 yr.: 12.2% for CAS vs 20.1% for CEA (p=0.004 for noninferiority analysis)
- This trial showed noninferiority of CAS for pts. @ high-risk for CEA

Limitations:
- Sig. difference was mainly 2ry to non-Q-wave MI with CEA
- Risk of CEA pts. was felt to be too high, mainly ASX pts.

EVA-3S Trial

- CEA vs CAS in pts. with sx. severe carotid st.
- 527 standard risk pts. were randomized
- Stroke/death @ 30 days was sig. higher with CAS than CEA (9.6% vs 3.9%, RR 2.5)
- 5-yr cumulative prob. of stroke/death: 11% for CAS vs 6.3% for CEA (H.R.=1.9)

Main criticisms of EVA-3S trial:
- Surgeons performed @ least 25 CEAs within 1 yr. before trial, however interventionalists certified after doing 1/2 that number of CAS
  - However, subgroup analysis failed to show any difference based on level of experience
- CPDs were optional early: 30-day stroke/death was sig. L in pts. Rx with (n=277) than in those Rx without CPD (n=20) – 7.9% vs 25% (Mas JL, Stroke, 2014)
SPACE Trial

- Stent-Protected Angioplasty vs CEA
- Multicenter European: 1,183 sx. pts. were randomized
- 30-day stroke/death: 6.8% for CAS vs 6.3% for CEA (p=0.09)
- No sig. difference in stroke/death between CAS & CEA up to 2 yrs. (9.5% vs 8.8% in ITT & 9.4% vs 7.8% per protocol)
- >70% restenosis: sig. ↑ in CAS: 10.7% vs 4.6%
- Subset analysis: older age in CAS (not CEA) was associated with ↑ risk of stroke/death

SPACE Trial (cont.)

- Main criticisms of SPACE trial:
  - CPDs optional: no difference in outcome between pts. with & without CPDs
  - ≥ 25 CEA & ≥ 25 CAS before trial
  - In most endpoints: favorable trend towards surgical arm
  - Steering committee decided to terminate study after interim analysis on the basis of both futility & financial concern (2,500 pts. would be needed to adequately power the study)

ICSS Trial

- 1,713 sx. pts.: Excluded all high-risk pts.
- Stroke/MI/death: CAS 8.5% vs CEA 5.2% (H.R. 1.7, p=0.006) @ 120 days
- CAS had ↑ stroke rate (7.7% vs 4.1%), stroke/death (8.5% vs 4.7%), & all cause death (2.3% vs 0.8%)

ICSS Trial (cont.)

- Sub-analysis: new ischemic brain lesion on fusion-weighted MRI, sig. ↑ for CAS than CEA (50% vs 17%, OR = 5.2)
- At mean follow-up of 4 yrs: more strokes in CAS than CEA (119 vs 72):
- 5-yr risk of stroke 15% vs 9%, H.R.=1.7, p<0.001
- Main criticism: Operator was given authority to decide whether some of these pts. were unsuitable for CEA or CAS
- 50 CEAs were required & 50 stenting for interventionalists (10 of these were CAS (Bonati LH, Lancet, 2014)

CREST Trial

- NIH-sponsored trial: 30-day stroke/MI/death or ipsilateral stroke during 4 yrs.
- 2,502 sx. & asx.
- Rigorous credentialing:
  - surgeons should have @ least 12 CEA in previous yr. with stroke/death <3% & 5% for sx. & asx. pts.
  - interventionalists were certified after satisfactory evaluation of their CAS experience, participation in hands-on training & lead-in phase of up to 20 cases using ACCULINK & ACCUNET systems with excellent results: Best of the Best

CREST Trial Results: Endpoints According to Treatment with CAS or CEA

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>CAS (n = 1240)</th>
<th>CEA (n = 1238)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any peri/procedure stroke or postprocedure ipsilateral stroke (%)</td>
<td>4.1 ± 0.8</td>
<td>2.3 ± 0.4</td>
<td>0.01</td>
</tr>
<tr>
<td>Major stroke (%)</td>
<td>0.9 ± 0.3</td>
<td>0.6 ± 0.2</td>
<td>0.52</td>
</tr>
<tr>
<td>Minor stroke (%)</td>
<td>3.2 ± 0.5</td>
<td>1.7 ± 0.4</td>
<td>0.01</td>
</tr>
<tr>
<td>Myocardial infarction (%)</td>
<td>1.1 ± 0.3</td>
<td>2.3 ± 0.4</td>
<td>0.01</td>
</tr>
<tr>
<td>Death (%)</td>
<td>0.7 ± 0.2</td>
<td>0.3 ± 0.2</td>
<td>0.18</td>
</tr>
<tr>
<td>Primary study endpoint: perioperative (%)</td>
<td>5.2 ± 0.6</td>
<td>4.5 ± 0.6</td>
<td>0.38</td>
</tr>
<tr>
<td>Primary endpoint to 4 years (%)</td>
<td>7.2 ± 0.8</td>
<td>6.0 ± 0.8</td>
<td>0.51</td>
</tr>
<tr>
<td>Cranial nerve palsy</td>
<td>0</td>
<td>9%</td>
<td>—</td>
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</tbody>
</table>
CREST Results

- 2 yr. analysis for sx. pts., the periop stroke & death was sig. higher in CAS vs CEA: 6% vs 3.2%, H.R.=1.9
- Sub-study showed that @ 1 yr. stroke had a large sig. effect on quality of life, while MI & cranial nerve palsy had a smaller impact (SF-36Q)
- Periprocedural strokes/death plus ipsilateral strokes during 10 yr. f/u was 8% for CEA & 11% for CAS

Limitations of CREST Design Analysis

- Major criticism of study, trial only allowed use of ACCULINK & ACCUNET
- Originally designed for sx. pts.
- Appropriate to consider all 3 primary endpoints, but not as equal in importance
- Rigid credentialing
- Primary objective of carotid intervention: stroke prevention

Other CAS Trials Design Flaws

- Inclusion/exclusion: up to ⅓ of eligible pts. were excluded
- Sx. status
- Sx. onset/intervention
- No. of CAS/Provider: in real world registry of >21,000 CEA or CAS, between 2010-2012 median annual volume of 1.5 for CAS vs 3 for CEA

Inclusion Criteria in RCTs: CEA vs CAS

- SAPPHIRE: only 30% of CAS & 27% of CEA were sx.
- EVA3-S: neuro. sx. <120 days b/f randomization
- ICSS: neuro. sx. <12 mos. b/f randomization
- SPACE: neuro. sx. <6 mos. b/f randomization
- CREST: neuro sx. <6 mos. b/f randomization (47% of CAS & 47% of CEA pts. were asx.)

CAS Results in the Real World

- Periop. death: >2 rate in CREST & SAPPHIRE
- 1.7% for mortality, 3.3% for stroke, 2.5% MI
- Mean follow-up 2 yrs.: mortality risk 42% for pts >80 yrs. & 28% for asx. pts.
- More than 90% of physicians didn’t meet requirements of CREST trial (>1/2 were cardiology)
- A major concern must be raised about generalizing results of RCT


- Cross-sectional study for CAS (n=124,265) & CEA (n=1,260,647) during 10-yr. in U.S. hospitals
- M.V. propensity score-matched analysis:
  - CAS assoc. with ↑ risk of death (O.R. = 1.7) & stroke (O.R. = 1.4), & MAE (death, stroke, MI, O.R.=1.3, p<0.001)
  - In asx. pts.: sig. ↑ in stroke &/or death (p<0.001) & no sig. difference in MAE (OR = 1.1), but sig. differences for sx. pts. in all endpoints (p<0.001)

(Choi, Stroke, 2015)

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(Kim, et al, Circ Cardiovasc Interv, 2014)
Stroke/Death Rates Following CAS & CEA in Contemporary Administrative Dataset Registries: A Systematic Review

- Systematic review of more than 1,500,000 CAS/CEA
- CAS was performed on Asx pts. with stroke/death rate that exceeded 3% risk threshold recommended by AHA
- 9/21 registries (43%) reported death & stroke rates >3% risk threshold (AHA) in asx. pts. after CAS
- Compared to 1/21 (5%) after CEA

(KI Paraskevas, et al, Eur JvascEndovasc Surg, 2016)

Overview of Primary & Secondary Analyses From 20 RCTs Comparing CAS vs CEA

- 30 day death/stroke rate sig. ↑ after CAS vs CEA in 7 RCTs (3,467 asx. pts.) OR 1.64
- 10 RCTs (5,797 sx. pts.) OR 1.71
- Excluding procedural risk, late ips. stroke was 4% @ 9 yrs. for both CEA & CAS
- New white matter lesions were sig. more common after CAS (52% vs 17%) & assoc. w/↑ late stroke/TIA rates (23% vs 9%)

(Batchelder & Naylor, EJVES, 2019)

Conclusions

- Pending RCTs in progress: CREST2, ACST II
- Use of CAS should be selective at this stage
- Must be done by experienced operators/centers
- CAS is better Rx for sx. pts. who are high-surg. risk (anatomical/physiological) for CEA
- The value of CAS in high surg. risk asx. pts. is ? @ this stage
- Flow reversal system may change these rules in the future

THANK YOU!!!