Why CREST-2 & ACST-2 May Have Little Definitive Value: Although they May Provide Useful Information

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1st Burning Question:
Who, if anyone, with ACS is likely to benefit from a carotid procedure (CEA) in addition to current optimal medical intervention?

Advances in Medical Revascularisation ≥50-75% ACS

At Most 4% of Persons ACS Will Have Stroke Caused by the Lesion!
- Average annual ipsilateral stroke rate is 0.8%.
- Average age of diagnosing 50%-99% ACS: 70 yrs
- Average survival is 10 years (0.8 x 10 = 8%)
- About half the strokes occurring in the distribution of a 50%-99% ACS not are due to the stenosis.
- Assumes 30-day procedural stroke/death rate = 0
- Overall harmful & wasteful to procedure them all!

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BUT
Stroke risk stratification cannot identify those who now benefit from CEA …& CAS is overall more harmful than CEA

Many Proposed Markers of High Risk
Including from the 2017/18 ESVS Guideline
CEA (Class IIa) or CAS (Class IIb) recommendations for average CEA risk 60-99% ACS if >1 of these or other features:

1. Silent Infarct on CT
2. Asymptomatic stenosis progression
3. Relative large plaque area on U/S
4. Juxtaluminal black areas on U/S
5. Intra-plaque haemorrhage on MRI
6. Impaired CVR
7. Plaque echolucency on US
8. Transcranial embolic signals +/- echolucency
9. Contralateral TIA/stroke
10. Others- undefined
11. 80-99% stenosis
12. ACSR model plaque, stenosis + prior symptoms: ips stroke risk 0-10%/yr

2nd Burning Question:
Will prevailing carotid trials find a current procedural indication in STROKE prevention?

- ACST-2
- CREST-2
- ECST-2
- ACTRIS

**ACST-2**

[Link](https://acst-2.org/onewebmedia/ACST-2%20protocol%20v4.2_Dec%202007.pdf)
CEA vs CAS, US ‘stenosis’, Asymptomatic > ‘some’ months, ‘Average’ CEA risk, 5000 pts

- No
- No medical-only-arm (not testing efficacy)
- Will help measure harm of CAS vs CEA
- Little value without a procedural indication
- May over / under estimate procedural harm:
  - Relatively open inclusion criteria
  - Medical intervention is out-sourced & not standardised- no targets
  - Postal follow-up after the first 30 days

**CREST-2**

Howard et al, US 2017:12(70);770-778
CEA or CAS + Medical vs Medical, >70%, asymptomatic >3 mos,
Sample sizes: 1240+ 1240

- No
- Randomising average risk persons, like in ACAS
- No stroke risk stratification before recruitment
- Not pre-powered for high stroke risk markers
- Cognition is a secondary outcome

**CREST-2 Sample Size:**
Approximately 85% power to detect differences in peri-procedural stroke or death or later (4 year) ipsilateral stroke with CEA or CAS vs medical intervention if

The average annual event rate in the medical intervention arm is  > 2.1% or < 0.2%

Compared to 0.9% in a procedural arm*

CREST-2: Stroke: Likely to show CAS harm & CEA- ‘No statistically significant difference’ compared to medical intervention alone...

ie, no procedural indication

*Howard et al, Int J Stroke, 2017

**ECST-2**

[Link](http://s489637516.websitehome.co.uk/ECST2/index1.htm)
CEA or CAS vs Medical, >50%, Asymptomatic > 3months/ CAR score <20%, 2000 total pts

- No
- Randomising average risk persons, like in ACAS
- No stroke risk stratification before recruitment
- Not pre-powered for high stroke risk markers
- Cognition is a secondary outcome
**ACTRIS**

https://clinicaltrials.gov/ct2/show/NCT02841098
CEA vs medical in high stroke risk, asymptomatic $\geq 3$ months, 700 pts

- Possibly
- Inclusion:
  - TCD-detected microembolic signals
  - Impairment of TCD-measured CVR
  - Intraplaque haemorrhage on MRI
  - Rapid & severe stenosis progression
- Separate vs combined subgroup analyses?
- Appears under-powered

**Meanwhile: Trans-Carotid Arterial Revascularisation: TCAR**

- Assessed only in registries +/- CREST-2
- Absent / underpowered comparisons with current medical intervention
- Clinical indication unlikely to be established

**Procedural Trials are Premature**

**What We Need to Do…**

- Define current optimal medical intervention
- Measure its impact
- Risk stratify
- Use procedural trials only if ipsilateral stroke risk is high enough
- Who would like to help?