Current Status and Perspectives of ACST-2, CREST-2, ECST-2 and ACTRIS

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Two BIG questions in carotid research
Question #1
Should we consider any intervention (CEA / CAS) for asymptomatic carotid patients?
An Overview of Carotid RCTs

Asymptomatic Carotid Patients

Revascularisation uncertain

Revasc vs. BMT
ECST-2 / ACTRIS
CREST-2
Two Concurrent Two-arm Trials

CREST-2

Screened → Randomized

CAS n=620
Med n=620

Screened → Randomized

CEA n=620
Med n=620

Endpoint

4 years

Lal BK, Meschia J, Brott TG et al. Semin Vasc Surg 2017
Medical Management

Primary Risk Factor Targets
- Systolic BP <130 mm Hg
- LDL cholesterol <70 mg/dl

Secondary Risk Factor Targets
- Non-HDL cholesterol <100 mg/dl
- Hemoglobin A1c <7.0%
- Smoking cessation
- Targeted weight management
- >30 minutes of moderate exercise 3 times a week

CEA Trial: aspirin 325mg/d
CAS Trial: dual antiplatelet therapy for ≥1 month post-procedure; then aspirin
Both Trials: statin (PCSK9 inhibitors as needed)
Projected vs. Actual Enrollment

As of November 21, 2018

As of November 21, 2018

Actual: 1221
Mandated Milestone: 1392

vs

as of November 30, 2018
Goal: To determine whether carotid plaque disruption may be influenced by biomechanical forces acting in combination with morphological changes occurring within the plaque

Enrollment goal: 500 patients across all CREST-2 sites

Additional testing: Carotid MRA, Carotid ultrasound, carotid ultrasound cine-loop, Brain MRI

Huston J et al, AJNR 2016
Lal BK et al, J Vasc Surg 2017
Lower risk symptomatic and asymptomatic pts

- 371 patients randomised from >30 active sites across Europe
- 310 baseline brain MRI & 170 baseline plaque MRI

- Pilot safety study target:
  - 320 patients with baseline brain MRI and MRI at 2 years
- Plaque sub-study target:
  - 244 patients with plaque & brain MRI at baseline & at 2 yrs

- **Intensive Medical Therapy**
  - Goal directed lipid-lowering and BP regimens
    - TC<4mmol/L and BP<135/85mmHg
    - “Optimal” anti-platelet therapy
Any patient with carotid stenosis ≥50%

Clinical screening
CAR Score (to assess 5-year stroke risk)

≥20% risk:
Carotid surgery recommended

<20% risk:
Eligible for ECST-2

MRI brain ± plaque
Ultrasound plaque

Randomisation in ECST-2

OMT

OMT plus CEA

1m, 6m, annual FU
Clinical assessment

2-year FU
Clinical assessment
MRI brain

Clinical follow-up continues for a minimum of 2 years, maximum 5 years after randomisation

ECST-2 Design
ACTRIS: CEA & OMT v OMT Alone
Inclusion Criteria

- Tight asymptomatic stenosis PLUS at least one marker of ipsilateral stroke risk:
  - TCD-detected microembolic signals
  - Impairment of TCD-measured cerebral vasomotor reserve
  - Intra-plaque haemorrhage on MRI
  - Rapid and severe stenosis progression

Target = 700 patients
All previous studies of CEA v MT alone have shown a **halving** of long-term stroke risk following successful surgery.

New trials may confirm these results...

Also, >1M asymptomatic carotid procedures will be done whilst waiting for trial results.
Question #2
CEA vs CAS in asymptomatic patients?

ACST-2
An Overview of Carotid RCTs

Asymptomatic Carotid Patients

Revascularisation needed

Uncertain if CAS or CEA

CAS vs. CEA
ACST-2

Revascularisation uncertain

Revasc vs. BMT
ECST-2 / ACTRIS
CREST-2
ACST-2

RCT of CEA vs CAS

Asymptomatic patients

3600 randomised by 2020

Large streamlined trial

ACST-2 Flow Chart

Eligible Patients
- Tight carotid stenosis
- No (recent) ipsilateral symptoms
- Intervention considered necessary
- Both CEA and CAS feasible and anatomically practicable

Randomise (phone or web)

CEA

30 day follow-up visit (in person)
- Procedural details & neurological assessment
- (with any strokes reviewed 6 months later)

CAS

Annual follow-up (by postal questionnaire)
- Stroke, death & current drug therapy
- (with any suspected strokes reviewed medically)
ACST-2: An International Trial
ACST-2 Cumulative Recruitment

Number of centres ever recruited a patient

Cumulative centres

Cumulative recruited patients

Number of patients recruited

3129
Recruitment by country November 2018

- Italy: 700 patients
- United Kingdom: 400 patients
- Serbia: 300 patients
- Sweden: 200 patients
- Germany: 200 patients
- Russia: 100 patients
- Hungary: 100 patients
- Greece: 100 patients
- Belgium: 100 patients
- Poland: 100 patients
- Brazil: 100 patients
- The Netherlands: 100 patients
- Switzerland: 100 patients
- Spain: 100 patients
- France: 100 patients
- Austria: 100 patients
- Slovenia: 100 patients
- Canada: 100 patients
- Estonia: 100 patients
- Israel: 100 patients
- Bulgaria: 100 patients
- China: 100 patients
- Croatia: 100 patients
- Japan: 100 patients
- Slovak Republic: 100 patients
- Norway: 100 patients
- Other Countries: 100 patients

DE (202)
CH (58)
AT (43)
ACST-2: CEA vs CAS

Sex, Age, Co-morbidities:
Men 70%
Median age 70 years
Coronary artery disease 37%
Diabetic 29%
Renal impairment 8%

Medical Treatments at entry:
BP drugs 87%
Lipid-lowering 85%
Anti-thrombotic 96%
### Stent use

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<tr>
<th>Stent Type</th>
<th>Quantity</th>
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<tr>
<td>Wallstent <em>(Closed)</em> (44%)</td>
<td>345</td>
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<tr>
<td>Xact</td>
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<tr>
<td>Adapt</td>
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<tr>
<td>Precise <em>(Open)</em> (33%)</td>
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<td>Zilver</td>
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<td>Cristallo Ideale <em>(Hybrid)</em> (14%)</td>
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<tr>
<td>Sinus Carotid Conical RX</td>
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<tr>
<td>Mer</td>
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<tr>
<td>Roadsaver <em>(Membrane)</em> (9%)</td>
<td>73 (36)</td>
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### CPD use

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<td>AngioGuard</td>
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<td>FiberNet</td>
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<td>Wirion System</td>
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<td>Proximal occlusion (17%)</td>
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<td>Moma</td>
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<tr>
<td>Flow Reversal</td>
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<td>T CAR</td>
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<tr>
<td>Distal balloon (1%)</td>
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<td>Twin One</td>
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<tr>
<td>Viatrac</td>
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<tr>
<td>None (15%)</td>
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ACST-2 procedural hazards much lower than in symptomatic trials (CEA+CAS) and lower than in ACST-1

Disabling and fatal Stroke ≤ 30 days:
1.0% in ACST-2 (blinded)

Lower than in previous trial of CEA 1.7% (ACST-1)
Time Line

Sept 2018  >3000 ACST-2 patients randomised

End 2019  Randomise 3600 patients
           Median follow-up of 5 years

2020 - 2021  ACST-2 report initial results
              Procedural risks and early (ie, 4 year) benefits

              *IPD: CREST-1, ACT-1 and SPACE-2 (n=6000)*

Mid 2025  ACST-2 10-year results
           Reliably compare durability of CEA vs CAS

           CREST-2, ECST-2 & ACTRIS (?) report long-term results
           Compare intervention vs medical therapy