Update of the European Carotid Surgery Trial (ECST-2)

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ECST-2 farewell address ...

recruitment stopped on 31st Oct 2019
From the TSC (1):

“Since randomisation in ECST–2 commenced, it has been shown very clearly in prospective studies that patients with a “vulnerable” or “unstable” plaque at the time of the index event (found in approximately 50% of patients with Sx carotid stenosis) have a far higher recurrent stroke risk (HR > 10) than patients with a stable plaque.”

“The TSC met on 13.09.19 and concluded that, in view of the accumulating evidence regarding the importance of plaque imaging, it would not be appropriate to continue randomisation according to the current ECST-2 protocol.”
429 pts randomised from >30 active sites across Europe
60% Asymptomatic; 40% Lower-risk Symptomatic

• Pilot safety study now completed:
  – 320 pts with baseline brain MRI and MRI at 2 yrs
• Plaque sub-study:
  – 200 pts with plaque & brain MRI at baseline & at 2 yrs

**Intensive Medical Therapy versus CEA**
  – *Goal directed lipid-lowering: TC <4mmol/L*
  – *BP<135/85mmHg*
  – “Optimal” anti-platelet therapy
Intensive medical therapy versus CEA

Primary outcome (composite):
- Ipsilateral stroke
- TIA
- New Silent Brain Infarcts
  *(Either on MRI at 2 years or during coincidental brain imaging in interim)*

Expect these 2 year results in 2021/2022
All 429 patients will be followed up for up to 5 years
ECST-2 Hypothesis 1

Optimised medical therapie (OMT) is as effective in the prevention of stroke in patients with a relative low CAR-score as carotid revascularisation plus this medication in patients with ACI stenosis ≥50%
Risk reduction by medication

Figure 1: Risk of recurrent stroke after first seeking medical attention in all patients with TIA or stroke in the whole study population (A) and in all patients with TIA (B)

Rothwell et al. Lancet 2007
• 5 yr risk ipsilateral cerebral infarction/TIA
• Based on ECST and NASCET
• Risk by adequate secondary profylaxe

Rothwell et al. Lancet 2005
No clear benefit for CEA with CAR score <20%

Rothwell et al. Lancet 2005
Orwellian dilemma

Low risk symptomatic patients may actually hold the very same risk for stroke as high risk asymptomatic patients
Management of Atherosclerotic Carotid and Vertebral Artery Disease: 2017 Clinical Practice Guidelines of the European Society for Vascular Surgery (ESVS)


Keywords: Carotid, Vertebral, Stroke, Transient ischaemic attack, Endarterectomy, Stenting, Medical therapy, Screening, Dementia, Asymptomatic, Symptomatic, Thrombolysis, Imaging, Bypass, Surgical techniques, Complications, Patch infection, Restenosis
(continued)

**Asymptomatic**
- Carotid stenosis 60-99%
- Carotid stenosis <60%
- Occlusion or near occlusion
- Carotid stenosis <50%
- Carotid stenosis 50-69%
- Carotid stenosis 70-99%

**Symptomatic**

**Life expectancy >5 yrs?**
- Favourable anatomy?
- ≥1 feature suggesting higher stroke risk on BMT?

**No**
- BMT
  - Class I A

**Yes**
- CEA + BMT should be considered
  - Class IIa B
- CAS + BMT may be considered
  - Class IIb B

**CAS + BMT should be considered if high-risk for CEA**
  - Class IIa B
  - otherwise may be considered
    - Class IIb B

clinical/imaging features that may be associated with an increased risk of stroke on BMT

<table>
<thead>
<tr>
<th>Clinical</th>
<th>history of contralateral TIA/stroke</th>
<th>RCT, multicentre</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT/MRI</td>
<td>ipsilateral silent infarction</td>
<td>RCT, multicentre</td>
</tr>
<tr>
<td>Ultrasound imaging</td>
<td>stenosis progression (&gt;20%)</td>
<td>RCT, multicentre</td>
</tr>
<tr>
<td></td>
<td>spontaneous embolisation on TCD</td>
<td>multicentre</td>
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<tr>
<td></td>
<td>impaired cerebral vascular reserve</td>
<td>meta-analysis</td>
</tr>
<tr>
<td></td>
<td>large volume plaques (&gt;80mm²)</td>
<td>multicentre</td>
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<tr>
<td></td>
<td>echolucent plaques</td>
<td>multicentre</td>
</tr>
<tr>
<td></td>
<td>large juxta-luminal black area (&gt;8mm²)</td>
<td>multicentre</td>
</tr>
<tr>
<td>MRA</td>
<td>intra-plaque haemorrhage</td>
<td>meta-analysis</td>
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<tr>
<td></td>
<td>lipid rich necrotic core</td>
<td>meta-analysis</td>
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</tbody>
</table>
ECST2 Hypothesis 2

Plaque MRI combined with clinical outcome will enhance individual prediction for the risk on cerebral infarction/TIA and thus decision making on the identification for carotid revascularization.

Protocol ECST-2 versie 3.2, januari 2018
Table 2. Summary of Results* of 3 Meta-Analyses for the Risk of Stroke Associated With the Presence of Plaque Components: Intraplaque Hemorrhage, Lipid-Rich Necrotic Core and Thin Fibrous Cap24–26

<table>
<thead>
<tr>
<th>Plaque Component</th>
<th>No. of studies</th>
<th>Total population</th>
<th>Follow-up period (mean)</th>
<th>HR/OR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intraplaque hemorrhage</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Saam et al 2013 (HR)23</td>
<td>8</td>
<td>689</td>
<td>1–38 (20) months</td>
<td>5.7 [3.0–10.9]</td>
</tr>
<tr>
<td>Gupta et al 2013 (HR)21</td>
<td>7</td>
<td>678</td>
<td>9–38 (20) months</td>
<td>4.6 [2.9–7.2]</td>
</tr>
<tr>
<td>Hosseini et al 2013 (OR)22</td>
<td>7</td>
<td>667</td>
<td>9–38 months</td>
<td>10.0 [5.5–18.4]</td>
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<tr>
<td><strong>Lipid-rich necrotic core</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gupta et al 2013 (HR)21</td>
<td>4</td>
<td>403</td>
<td>12–38 (24) months</td>
<td>3.0 [1.5–5.9]</td>
</tr>
<tr>
<td><strong>Thin or ruptured fibrous cap</strong></td>
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<td></td>
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<tr>
<td>Gupta et al 2013 (HR)21</td>
<td>4</td>
<td>363</td>
<td>12–38 (22) months</td>
<td>5.9 [2.7–13.2]</td>
</tr>
</tbody>
</table>

*Combined data on symptomatic and asymptomatic stenosis. NB: the studies included in the 3 meta-analyses largely overlap. CI, confidence interval; HR, hazard ratio; OR, odds ratio.
“Rather, given the unique dataset with regard to carotid plaque imaging, there would be greater scientific and ethical validity if randomisation was halted, and whilst planned follow-up would continue, preparations could be made for the early analysis of baseline and early follow-up data.”

“The TSC considered that this was very likely to result in a modified design for a future trial (i.e. ECST-3) in which MRI plaque imaging would be central to any risk stratification model.”
Revascularisation

v

Good Medical Tx

is a valid question
An Overview of Carotid RCTs

(A)symptomatic Carotid Patients

Revascularisation ‘needed’

Uncertain if CAS or CEA

CAS vs. CEA
  CREST; ACT-1; SPACE-2; ACST-2

Revascularisation Uncertain

Revasc vs. BMT
  ECST-2; CREST-2; ACTRIS
CEA / CAS v Good Medical Tx

> 3000 patients

Follow-up of ~ 5 years

Pool with 5000 patients from older trials

Focus on relative risks

Identify those in whom intervention appropriate
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