The 2nd European Carotid Surgery Trial interim results

Gert J. de Borst on behalf of the ECST-2 investigators

Trial funding

- National Institute for Health and Care Research
- Swiss National Science Foundation
- The Netherlands Organisation of Scientific Research
- Leeds Neurology Foundation

- No personal conflicts of interest

Background

- Current guidelines for carotid endarterectomy (CEA) based on robust but old evidence (trials 20-30 years ago)*
- Medical treatment has improved significantly, risk of stroke roughly halved
- Decision on CEA still largely based on degree of stenosis and symptom-status
- Plaque ulceration, patient characteristics and comorbidities might influence risk-benefit ratio of revascularisation

*NASCET, ECST, ACST, ACAS, pooled analyses

Hypothesis

Patients with carotid stenosis ≥50% with a low to intermediate risk of stroke will not benefit from additional carotid revascularisation when treated with optimised medical therapy (OMT)

Methods

- Multicentre, randomised, controlled, prospective, open clinical trial with blinded outcome adjudication
- Randomisation (1:1 ratio): revascularisation plus OMT vs OMT alone
- Suitable patients:
  - Atherosclerotic carotid stenosis ≥50%
  - Low to intermediate 5-year risk of stroke: Carotid Artery Risk (CAR)-score < 20%
  - Both symptomatic and asymptomatic

Protocol paper: Cheng et al, Trials 2022

Carotid Artery Risk (CAR) score

- Prediction score to estimate 5-year risk of ipsilateral stroke
- Data originally derived from ECST and NASCET
- Risk under OMT has strongly declined since trials
- Score was recalibrated for likely benefit OMT to date
- Asymptomatic stenosis = CAR ≤ 5%

- Sex
- Age
- Stenosis %
- Type of event
- Time since event
- DM
- MI
- PVD
- HT
- Ulcerated plaque

Rothwell et al, Stroke 2003, Cheng et al, Trials 2022

Interventions

- Optimised Medical Therapy (OMT)
  - Applied to both groups
  - Includes antihypertensive medication, cholesterol lowering medication and diet, antiplatelet agents, anticoagulation if indicated
  - Predefined targets & guidelines
    - Total cholesterol <4.0mmol/L
    - LDL cholesterol <2.0mmol/L
    - BP ≤ 135/85 mmHg (<80 years)
    - BP ≤ 150/90 mmHg (≥80 years)
- Revascularisation
  - CEA
  - CAS in selected patients
  - Recommended within 2 weeks in symptomatic and 4 weeks in asymptomatic patients after randomisation
- All patients brain MRI at baseline and at 2 years

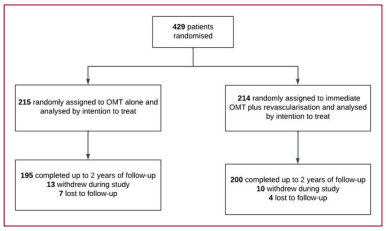
Trial history

- Trial originally designed for 2000 patients
- Interim analysis planned after enrolment of 320 patients
- Recruitment started 2012
- Recruitment suspended by TSC end of 2019 (n=429) to allow planned interim analysis and plan future study design
- Clear that recruitment of 2000 patients was not practical without change in trial design and further funding

Current interim analysis

- Composite primary outcome within 2 years:
  - peri-procedural death (within 90 days of randomisation)
  - clinically manifest stroke
  - myocardial infarction
- Analyses based on ITT

Results N=429



Baseline characteristics

		OMT	REVASC + OMT
N Patients		215	214
Symptomatic		86/215 (40.0%)	85/214 (39.7%)
Age (years)		72 (64 to 78), n=215	71 (65 to 77), n=214
Sex	Female	66/215 (30.7%)	67/214 (31.3%)
	Male	149/215 (69.3%)	147/214 (68.7%)
Smoking			
	Never Smoked	36/214 (16.8%)	44/214 (20.6%)
	Ex smoker	131/214 (61.2%)	132/214 (61.7%)
	Currently Smoking	47/214 (22.0%)	38/214 (17.8%)
Diabetes			
	No	151/215 (70.2%)	160/214 (74.8%)
	Yes - type I	2/215 (0.9%)	2/214 (0.9%)
	Yes - type II	62/215 (28.8%)	52/214 (24.3%)
Hypertension		163/215 (75.8%)	164/214 (76.6%)

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ECST-2

Baseline characteristics

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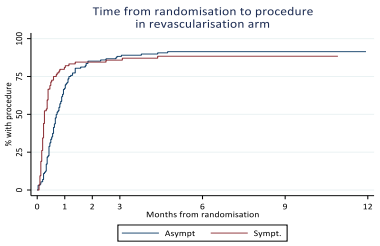
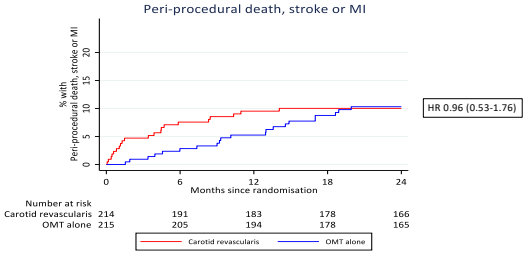
ECST-2



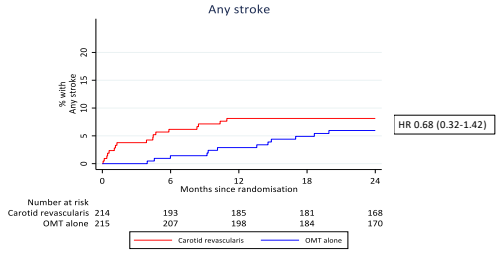
ECST-2

Primary outcome interim analysis

ECST-2



ECST-2



ECST-2

Outcome	No. of events (%) at 2 years		Difference at 2 years (95% CI)	Hazard ratio (95% CI)	P-value
	OMT	Revasc + OMT			
Composite	21 (10.3%)	21 (10.0%)	0.3% (-5.5%, 6.1%)	0.96 (0.53, 1.76)	0.90
Procedural death	0 (0%)	1 (0.5%)	-	-	-
Stroke	12 (6.0%)	17 (8.1%)	-2.2% (-7.1%, 2.8%)	0.68 (0.32, 1.42)	0.30
Myocardial infarction	10 (4.9%)	5 (2.5%)	2.4% (-1.3%, 6.0%)	2.00 (0.68, 5.84)	0.21

Subgroups

- Numbers very small, precluding valid conclusions
- No differences in any of the predefined subgroups
- No difference between symptomatic and asymptomatic stenosis
- If any, trend towards more effect in higher CAR score group (>10%), OMT only

Conclusions interim results

- In patients with carotid stenosis ≥50% and a low to intermediate predicted risk of stroke treated with optimised medical therapy, **there was no evidence of benefit at 2 years** from additional carotid revascularisation
- Complete 2-year results will include analysis of silent infarcts on MRI
- Longer clinical follow-up needed (and planned up-to 5-years)

Future work

- Design and validate novel stroke risk prediction rule including MRI plaque imaging
  - Individualised (high risk) patient-selection for revascularisation
- Cost-effectiveness analysis

Local investigators of participating centres

- Albert Schweitzer Hospital Dordrecht
- AMC/Flevo Amsterdam
- Ashford and St Peter's Hospitals NHS Foundation Trust
- Bradford Teaching Hospitals NHS Trust
- Calderdale &Huddersfield NHS Foundation Trust
- Dalhousie University, Halifax
- East Kent Hospitals University NHS Foundation Trust
- Erasmus University Medical Centre, Rotterdam
- Frimley Park Hospital
- Hospices Civiles de Lyon
- Kantonsspital St. Gallen
- Leeds General Infirmary
- Maastricht University Medical Centre
- Manchester Royal Infirmary
- NHS Ayrshire and Arran
- Nottingham University Hospitals
- NSI-Lugano
- Pennine Acute Hospitals NHS Trust
- Radboud University Nijmegen Medical Centre
- Royal Devon and Exeter Hospital
- Sheffield Teaching Hospitals
- St George's Healthcare NHS Trust
- Stroke Centre, University Hospital Basel
- Universitätsklinikum Magdeburg
- Otto-von-Guericke-Universität
- University Hospital North Durham
- University Hospital South Manchester
- University of Leipzig
- University Medical Center Utrecht
- Verona University Hospital
- UCLH London

Pre-specified complete 2-year analysis ECST-2

- Composite outcome within 2 years:
  - peri-procedural death (within 90 days of randomisation)
  - clinically manifest stroke
  - myocardial infarction
  - **silent cerebral infarct on MRI**
- Win-ratio analysis
- 360 patients needed (180 in each arm) with
  - 11% rate in OMT alone arm
  - 18% in revascularisation arm
  - **non-inferiority** margin of 4%
  - 5 % drop out and 15% missing 2-year MRI

Acknowledgements

- Participants and caregivers
- ECST-2 investigators, trial nurses, TMC, TSC, DSMB
- Funders
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  - Swiss National Science Foundation
  - The Netherlands Organisation of Scientific Research
  - Leeds Neurology Foundation

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Thank you!

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