Optimised medical therapy alone versus optimised medical therapy plus revascularisation for asymptomatic or low-to-intermediate risk symptomatic carotid stenosis (ECST-2): 2-year interim results of a multicentre randomised trial

Simone J A Donners, Twan J van Velzen, Suk Fun Cheng, John Gregson, Audinga-Dea Hazewinkel, Francesca B Pizzini, Bart J Emmer, Robert Simister, Toby Richards, Philippe A Lyrer, Marina Maurer, Gemma Smith, Gareth Tervit, Laurine van der Steen, Gwynedd E Pickett, Gordon Gubitz, Bob Roozenbeek, Maaike Scheele, John M Bamford, M Eline Kooi, Gert J de Borst, Hans Rolf Jäger*, Martin M Brown*, Paul J Nederkoorn*, Leo H Bonati*, on behalf of the ECST-2 investigators†

Summary

Background Carotid revascularisation, comprising either carotid endarterectomy or stenting, is offered to patients with carotid stenosis to prevent stroke based on the results of randomised trials conducted more than 30 years ago. Since then, medical therapy for stroke prevention has improved. We aimed to assess whether patients with asymptomatic and symptomatic carotid stenosis with a low or intermediate predicted risk of stroke, who received optimised medical therapy (OMT), would benefit from additional revascularisation.

Methods The Second European Carotid Surgery Trial (ECST-2) is a multicentre randomised trial with blinded outcome adjudication, which was conducted at 30 centres with stroke and carotid revascularisation expertise in Europe and Canada. Patients aged 18 years or older with asymptomatic or symptomatic carotid stenosis of 50% or greater, and a 5-year predicted risk of ipsilateral stroke of less than 20% (estimated using the Carotid Artery Risk [CAR] score), were recruited. Patients were randomly assigned to either OMT alone or OMT plus revascularisation (1:1) using a web-based system. The primary outcome for this 2-year, interim analysis was a hierarchical outcome composite of: (1) periprocedural death, fatal stroke, or fatal myocardial infarction; (2) non-fatal stroke; (3) non-fatal myocardial infarction; or (4) new silent cerebral infarction on imaging. Analysis was by intention-to-treat using the win ratio—ie, each patient in the OMT alone group was compared as a pair with each patient in the OMT plus revascularisation group, with a win declared for the patient with a better outcome within the pair (a tie was declared if neither patient in the pair had a better outcome). The win ratio was calculated as the number of wins in the OMT alone group divided by the number of wins in the OMT plus revascularisation group. This trial is registered with the ISRCTN Registry (ISRCTN97744893) and is ongoing.

Findings Between March 1, 2012, and Oct 31, 2019, 429 patients were randomly assigned to OMT alone (n=215) or OMT plus revascularisation (n=214). One patient allocated to OMT alone withdrew consent within 48 h and was not considered further. The median age of patients was 72 years (IQR 65–78); 296 (69%) were male and 133 (31%) female. No benefit was recorded in favour of either treatment group with respect to the primary hierarchical outcome assessed 2 years after randomisation, with 5228 (11·4%) wins for the OMT alone group, 5173 (11·3%) wins for the OMT plus revascularisation group, and 35395 (77·3%) ties between groups (win ratio 1·01 [95% CI 0·60–1·70]; p=0·97). For OMT alone versus OMT plus revascularisation, four versus three patients had periprocedural death, fatal stroke, or fatal myocardial infarction; 11 versus 16 had non-fatal stroke; seven versus five had non-fatal myocardial infarction; and 12 versus seven had new silent cerebral infarction on imaging. One periprocedural death occurred in the OMT plus revascularisation group, which was attributed to decompensated aortic stenosis 1 week after carotid endarterectomy.

Interpretation No evidence for a benefit of revascularisation in addition to OMT was found in the first 2 years following treatment for patients with asymptomatic or symptomatic carotid stenosis of 50% or greater with a low or intermediate predicted stroke risk (assessed by the CAR score). The results support treating patients with asymptomatic and low or intermediate risk symptomatic carotid stenosis with OMT alone until further data from the 5-year analysis of ECST-2 and other trials become available.

Funding National Institute for Health and Care Research; Stroke Association; Swiss National Science Foundation; Dutch Organisation for Knowledge and Innovation in Health, Healthcare and Well-Being; Leeds Neurology Foundation.

Department of Vascular Surgery, UMC Utrecht, Utrecht, Netherlands (S J A Donners MD, Prof G J de Borst PhD); **Department of Neurology, Amsterdam UMC, location AMC, Amsterdam, Netherlands** (T J van Velzen PhD, L van der Steen MSc, P J Nederkoorn PhD); **Stroke Research Centre, Department of Brain Repair and Rehabilitation, UCL Queen Square Institute of Neurology, University College London, London, UK** (S F Cheng PhD, R Simister PhD, Prof M M Brown FRCP); **Department of Medical Statistics, London School of Hygiene & Tropical Medicine, London, UK** (J Gregson PhD, A-D Hazewinkel PhD); **Department of Engineering for Innovation Medicine, University of Verona, Verona, Italy** (F B Pizzini PhD); **Department of Radiology and Nuclear Medicine, Amsterdam UMC, location AMC, Amsterdam, Netherlands** (B J Emmer PhD); **Comprehensive Stroke Service, University College London Hospitals NHS Foundation Trust, London, UK** (R Simister); **School of Health, Sport & Bioscience, University of East London, London, UK** (Prof T Richards FRCS); **Department of Neurology, University Hospital Basel, Basel, Switzerland** (P A Lyer MD, M Maurer, Prof L H Bonati MD); **Department of Clinical Research, Medical Faculty, University of Basel, Basel,**

Switzerland (P A Lyer, Prof L H Bonati); **Department of Neurology, County Durham and Darlington NHS Foundation Trust, Durham, UK** (G Smith MBBS); **Department of Vascular Surgery, South Tyneside and Sunderland Foundation Trust, Sunderland, UK** (G Tervit FRCSEd); **Division of Neurosurgery, Department of Surgery, Dalhousie University, Halifax, NS, Canada** (Prof G E Pickett MD); **Division of Neurology, Queen Elizabeth II Health Sciences Center, Dalhousie University, Halifax, NS, Canada** (Prof G Gubitz FRCPC); **Department of Neurology, Erasmus MC University Medical Center, Rotterdam, Netherlands** (Prof B Roozenbeek PhD, M Scheele); **Department of Neurology, Leeds Teaching Hospitals NHS Trust and University of Leeds, Leeds, UK** (J M Bamford MD); **Department of Radiology and Nuclear Medicine, CARIM Cardiovascular Research Institute Maastricht, Maastricht University Medical Centre (MUMC+), Maastricht University, Maastricht, Netherlands** (Prof M E Kooi PhD); **Neuroradiological Academic Unit, Department of Brain Repair and Rehabilitation, UCL Queen Square Institute of Neurology, University College London, London, UK** (Prof H R Jäger MD); **Lysholm Department of Neuroradiology, National Hospital for Neurology and Neurosurgery, University College London Hospitals NHS Foundation Trust, London, UK** (Prof H R Jäger); **Research Department, Reha Rheinfelden, Rheinfelden, Switzerland** (Prof L H Bonati)

Correspondence to:
Prof Martin M Brown, Stroke Research Centre, Department of Brain Repair and Rehabilitation, UCL Queen Square Institute of Neurology, University College London, London WC1B 5EH, UK
martin.brown@ucl.ac.uk

See **Online** for appendix

Research in context

Evidence before this study

We did a systematic search in PubMed and Embase (most recently on March 20, 2025, from database inception without any date or language restrictions) using the terms ("carotid stenosis" OR "carotid artery stenosis" OR "carotid artery disease") AND ("randomised trial" OR "randomised controlled trial" OR "clinical trial"). Our search identified several trials conducted in the 1980s and early 1990s showing that carotid endarterectomy reduced the risk of stroke in patients with symptomatic carotid stenosis of 50% or greater, and to a smaller extent in patients with asymptomatic stenosis, compared with what was then best medical treatment alone. Since the 1990s, medical treatment of vascular risk factors has improved considerably. Two more recent randomised controlled trials comparing the effect of contemporary medical therapy alone with additional revascularisation for carotid stenosis were identified. Both trials recruited only patients with asymptomatic carotid stenosis and did not find any convincing evidence that revascularisation was superior to best medical treatment, but the trials were terminated early. To date, no randomised studies have investigated the risks and benefits of carotid revascularisation in populations selected by criteria other than the degree of stenosis and symptom status.

Added value of this study

ECST-2 is unique in comparing the efficacy of optimised medical therapy (OMT) alone versus OMT plus carotid revascularisation in patients with both asymptomatic carotid stenosis and symptomatic carotid stenosis at low to intermediate predicted risk of future stroke, with 5-year follow-up. The risk of future stroke was calculated using the Carotid Artery Risk (CAR) scoring tool, which was recalibrated for use in this trial. ECST-2 is also the first stroke trial to use the win ratio method to analyse a primary hierarchical outcome. The ECST-2 trial included a 2-year interim analysis including silent infarction on imaging, which is reported here.

Implications of all the available evidence

The 2-year interim analysis of ECST-2 found no evidence for a benefit of revascularisation in addition to OMT for patients with symptomatic and asymptomatic carotid stenosis of 50% or greater, with a 5-year predicted stroke risk of less than 20% (as assessed by the CAR score), in the first 2 years following the procedure. The risk of stroke in patients treated with OMT alone was substantially lower than recorded with best medical treatment in previous carotid stenosis trials. Further follow-up of ECST-2 up to 5 years from randomisation, and data from other trials, will be needed to confirm these findings. In the meantime, our results support treating patients with asymptomatic and low or intermediate risk symptomatic carotid stenosis with OMT alone. Applying individualised risk assessment could result in a reduction in revascularisation procedures and substantial cost savings in the future. Identifying patients with carotid stenosis who are at high risk of future stroke, who might benefit from revascularisation, should also be a goal of future research.

Introduction

The current management of symptomatic carotid artery stenosis is based on results from trials conducted over three decades ago.[1–3] Guidelines based on these trials recommend carotid endarterectomy (CEA) in patients with recently symptomatic carotid stenosis of 70–99%, and in subgroups of patients with a symptomatic stenosis of 50–69%.[4,5] However, advances in medical therapy should prompt a re-evaluation of treatment paradigms.[6]

In the late 1990s, the first European Carotid Surgery Trial (ECST) and the North American Symptomatic Carotid Endarterectomy Trial (NASCET) established the benefit of CEA in preventing recurrent stroke in patients with symptomatic carotid stenosis.[1–3] CEA in these trials carried a perioperative risk of stroke and death of around 7%, and not all recurrent strokes were prevented, suggesting that surgery should be avoided in patients at low risk of stroke on medical treatment alone. Risk modelling was undertaken in ECST, with validation in NASCET, which showed that multiple factors in addition to the degree of stenosis—such as age, sex, time from index event, and carotid plaque morphology—could influence the risk of future stroke in patients treated with medical therapy alone.[7–9] These factors were each shown to have a clinically significant effect on the absolute benefit from intervention in a subgroup analysis of pooled individual patient data from the three initial trials of CEA for symptomatic carotid stenosis.[9]

Use of the ECST risk model suggested that patients with a predicted 5-year risk of ipsilateral stroke of more than 20% benefited substantially from CEA in the NASCET trial, whereas those with a lower predicted risk did not benefit.[7–9] However, the ability of the model to reliably identify low risk patients, for whom medical treatment alone might be appropriate, still needed to be tested prospectively in a contemporary randomised trial, particularly as both medical and surgical treatments have improved in the years since ECST and NASCET. Moreover, in the latest European guidelines on the management of carotid stenosis, the indication for carotid revascularisation is still mainly based on the degree of carotid stenosis and symptomatic status.[4,5]

Trials of CEA for asymptomatic carotid stenosis were also first conducted over 30 years ago, and the results are widely used to justify revascularisation in many parts of the world, despite the benefits being limited. In the Asymptomatic Carotid Atherosclerosis Study (ACAS), treatment with CEA reduced the 5-year risk of ipsilateral stroke and any perioperative stroke or death from 11·0% to 5·1%, and the first Asymptomatic Carotid Surgery Trial (ACST) subsequently confirmed that CEA conferred only an absolute benefit of 4·6% over 10 years.[10,11] Current

carotid stenosis guidelines, nevertheless, state that revascularisation should be considered in selected high risk asymptomatic patients with 60–99% stenosis.[4,5]

To reassess the balance of the benefits of treatment of carotid stenosis with OMT alone (prevention of stroke and myocardial infarction) with the risks of revascularisation (primarily stroke, myocardial infarction, and death caused by the procedure) in low or intermediate risk patients, and to test whether a recalibrated ECST risk model can reliably identify symptomatic patients who will not benefit from a revascularisation intervention, we conducted the Second European Carotid Surgery Trial (ECST-2). In this trial, we compared OMT alone with revascularisation plus OMT in patients with 50% or greater carotid stenosis predicted to be at low or intermediate risk of stroke. We included both patients with low or intermediate risk symptomatic stenosis and asymptomatic stenosis in ECST-2, because the ECST model suggested that the risk of stroke on medical treatment alone in both these groups was similar. Our hypothesis was that these patients would not benefit from additional carotid revascularisation when treated with OMT. Here, we report the 2-year interim results of ECST-2.

Methods

Study design

ECST-2 is an international, multicentre, open–label, non-inferiority, randomised controlled trial conducted at 30 centres in Europe and Canada (appendix pp 2–3) with stroke and carotid revascularisation expertise (appendix pp 4–5). The trial design was published in July, 2022.[12] ECST-2 was approved by the National Research Ethics Service in the UK (reference number 11/EE/0347) and participating centres had to obtain site-specific approval from their local ethics committees. The trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. This trial is registered with the ISRCTN Registry (ISRCTN97744893).

Participants

Patients were eligible for inclusion if they were aged 18 years or older and had atherosclerotic carotid stenosis of 50% or greater according to NASCET criteria.[13] Symptomatic patients were required to have a predicted 5-year risk of stroke of less than 20% based on the recalibrated original ECST risk model, which we named the Carotid Artery Risk (CAR) score.[12] Patients with stenosis that had been asymptomatic for at least 180 days were also eligible for inclusion and were assumed to have a low 5-year risk of ipsilateral stroke (≤5%) with OMT alone. Exclusion criteria included previous CEA or carotid artery stenting (CAS) in the randomised artery. Other inclusion and exclusion criteria, and details of the CAR score derivation, are in the appendix (p 4). All patients provided written informed consent.

Randomisation and masking

Participants were randomly assigned to a treatment group using a web-based randomisation system. Patients were allocated in a 1:1 ratio to either OMT alone or OMT plus revascularisation. The allocation was balanced by minimisation and random permuted blocks (appendix p 5). Patients and local investigators were not masked to treatment assignment. Stroke, transient ischaemic attack (TIA), myocardial infarction, and death outcome events were adjudicated by two independent neurologists or cardiologist as relevant masked to allocated treatment using as much relevant clinical data as could be obtained. MRI and CT brain scans were analysed by two expert neuroradiologists who were masked to allocated treatment; these assessors compared baseline and 2-year imaging and recorded the presence of new cerebral infarction. Disagreements were resolved by consensus or, if no consensus could be reached, a third assessor had the final decision. Sealed Envelope provided the internet-based randomisation service, online case report forms, and online database for the trial.

For **Sealed Envelope** see https://www.sealedenvelope.com/

Procedures

We coined the term OMT to describe the medical therapy we specified for recruited patients; this terminology contrasted with older terminology (best medical treatment), because it was planned that OMT should be applied at the time of randomisation to the individual patient and then checked for compliance and modified as necessary at each trial follow-up visit. OMT was delivered according to a manual of advice and recommendations provided to our investigators. These recommendations included a low cholesterol diet, target-adjusted cholesterol-lowering medication, antihypertensive medication according to blood pressure readings, and guideline-based antithrombotic therapy. The targets included a maximum target total cholesterol of less than 4·0 mmol/L (<155 mg/dL) and LDL cholesterol of less than 2·0 mmol/L (<77 mg/dL), and treatment to lower blood pressure to an ambulatory recording or home measurement target of 135/85 mm Hg or a clinic measurement of 140/90 mm Hg. In patients older than 80 years, higher targets of 145/85 mm Hg or 150/90 mm Hg, respectively, were suggested. Combination antiplatelet therapy with aspirin and clopidogrel was recommended for 3 months after TIA and minor stroke, before CEA or CAS, and for up to 6 weeks after CAS, unless the patient required full-dose anticoagulation. Patients underwent targeted risk factor modification, including smoking cessation and reduction of bodyweight, if relevant. Separate guidelines were given for management of diabetes.

In patients allocated to revascularisation, CEA (or CAS, if considered preferable by local investigators) was to be performed as soon as possible and not more than 2 weeks after randomisation for patients with symptomatic carotid stenosis, and not more than 4 weeks after randomisation for patients with asymptomatic carotid

stenosis. Revascularisation procedures were done according to the standards of the individual centre.

Patients were invited for follow-up visits at 4–6 weeks, 6 months, and then annually after randomisation. At each visit, patients were evaluated using a structured questionnaire for clinical events and for the modified Rankin Scale (mRS) score. Follow-up between annual visits, and any follow-up that could not be done in the clinic, was done by telephone.

Brain MRI was done at the time of randomisation, before any revascularisation procedure, using recommended sequences (appendix p 5). Brain CT was to be done in patients with contraindications to MRI, or if MRI was unavailable. Follow-up brain imaging was done at 2 years after randomisation, using the same method (MRI or CT) and preferably the same machine as used at baseline, unless contraindicated.

Outcomes

The primary outcome for this interim analysis was a hierarchical outcome composite within 2 years after randomisation of: (1) periprocedural death, fatal stroke, or fatal myocardial infarction; (2) non-fatal stroke; (3) non-fatal myocardial infarction; or (4) new silent cerebral infarction on MRI (or CT) within 2 years of follow-up.[14] The hierarchy of these components was determined by consensus among members of the trial steering committee. Periprocedural death was defined as death within 90 days after randomisation. Silent cerebral infarction was defined as new infarction on brain imaging without a clinical history of a new stroke. Definitions of other outcome events are outlined in the appendix (p 5).

Secondary outcomes within 2 years included individual components of the hierarchical outcome composite; all-cause death and cardiovascular death; subtypes of stroke (eg, ipsilateral, ischaemic, and haemorrhagic); TIA; all-cause hospitalisation; subtypes of new cerebral infarction on imaging (eg, ipsilateral with respect to the randomised artery, contralateral, subcortical, and silent or proceeded by symptoms); and decline in functional status, determined by an increase in the mRS score from baseline. In addition, other procedural complications occurring within 30 days after revascularisation (eg, cranial nerve palsy and haematoma) were assessed. Safety aspects of the trial were overseen by an Independent Data Monitoring Committee with expertise in neurology, clinical trials, medical statistics, vascular surgery, and clinical pharmacology, who met regularly and confidentially reviewed ongoing data during recruitment.

Statistical analysis

Our initial sample size calculations suggested that 2000 participants would be required to show non-inferiority of a primary outcome event, limited to any stroke plus periprocedural death. However, to enable us to perform the planned interim analysis using a much smaller sample size, we decided to include the additional outcome events of myocardial infarction and silent infarction seen on brain imaging at 2 years after randomisation in the primary outcome measure.[12] The sample size for the 2-year interim analysis including these additions was originally based on a non-inferiority analysis of the composite of periprocedural death, stroke, myocardial infarction, or new silent cerebral infarction on imaging at 2 years (protocol version 3.1, appendix p 13). We expected a combined rate of 11% in the OMT alone group (comprised of 3% stroke, 2% myocardial infarction, and 6% new silent infarction on imaging) and 18% in the revascularisation group (comprised of 5% stroke, 3% myocardial infarction, and 10% new infarction on imaging). Assuming these outcome event rates, 314 patients (157 in each group) were required. However, monitoring of the ongoing trial showed that the number of patients with both baseline and 2-year MRI was less than expected; therefore, we increased the sample size of the interim analysis to 429 patients.

The COVID-19 pandemic had no effect on recruitment of patients, because this aspect of the trial was completed in 2019. However, the pandemic affected follow-up, which often had to be conducted by telephone rather than in person, or follow-up was missed altogether until after the pandemic, reducing the availability of data requiring in-person contact and the number of patients with follow-up imaging. The steering committee increased the time window allowed for follow-up and imaging to 6 months after the expected follow-up date, but this change had little effect given the length of the pandemic, especially in the UK, where COVID-19 research was prioritised over all other topics. The important consequence was that the power of the MRI analysis was less than anticipated. A lesser consequence was that some planned analyses (eg, analysis of ultrasound examinations and cognitive scores) were postponed to the 5-year follow-up. Secondary outcomes and imaging findings not presented in the current report, and 5-year follow-up results, will be available in later publications.

The primary analysis was performed based on a hierarchical outcome analysed using the Finkelstein–Schoenfeld method and win ratio. We chose to use the win ratio method to analyse data after the protocol was written but before any analyses were done and before we finalised the statistical analysis plan (appendix p 38). We used the win ratio method because we considered that the win ratio would provide a more powerful and clinically relevant hierarchical method of analysing the various primary outcome events, compared with conventional non-inferiority comparisons, and allowed us to incorporate silent infarction (detected on brain imaging) with clinically evident events to increase the power of the analysis.[14] For this method, sample size calculations are complex and were not done. Details of the win ratio calculation are given in the appendix (p 6). In brief, each patient in the OMT group was compared as a pair with each patient in the OMT plus revascularisation group, with a win declared for the patient with a better outcome within the pair,

considering the time to event if both patients within a pair had the same event (a tie was declared if neither patient in the pair had a better outcome). Given that each patient in one group is compared with each patient in the other group, the total number of paired comparisons was the product of multiplying together the number of patients in each group. The total number of wins within all the paired comparisons were counted for each treatment group. The win ratio was then calculated as the total number of wins in the OMT alone group divided by the total number of wins in the OMT plus revascularisation group. A 95% CI for the win ratio was calculated using the method of Pocock and colleagues.[15] An exploratory subgroup analysis of the primary hierarchical outcome was also performed using the win ratio to examine the influence of various prespecified baseline characteristics. A post-hoc sensitivity analysis, in which the order of non-fatal stroke and non-fatal myocardial infarction was switched in the order of the hierarchical outcome composite, was performed at the request of a reviewer.

For secondary outcomes looking at the time to an event, we calculated Kaplan–Meier estimates of cumulative risk at 2 years by treatment group. We calculated the absolute risk difference as the difference in Kaplan–Meier estimates of 2-year risk between treatment groups. We used Greenwood's standard errors from these estimates to estimate 95% CIs for the risk difference. We divided the absolute risk difference by its standard error to calculate Z-statistics which were used to generate p values for the difference in rates at 2 years. Hazard ratios and 95% CIs were calculated using unadjusted Cox proportional hazards models. Supplementary analyses considered the restricted mean survival time spend event-free. For binary outcomes (eg, new silent cerebral infarction on imaging), we estimated the proportions of patients with an event per group (among patients with relevant outcome data) and calculated p values using the χ^2 test or Fisher's exact test (if any expected cell count was <5). Decline in functional status determined by an increase in the mRS score was compared between groups using the Mann–Whitney U test.

The primary analysis was by intention-to-treat. Supportive analyses were done in the per-protocol population, which excluded patients assigned to OMT alone who underwent revascularisation within 6 weeks of randomisation without relevant symptoms and patients assigned to revascularisation who were not revascularised within 6 weeks. Patients assigned to OMT alone who received carotid revascularisation more than 6 weeks after randomisation were censored at the time of onset of the revascularisation procedure. Analyses were done using R statistical software (version 4.2.3) and Stata version 18.

Role of the funding source
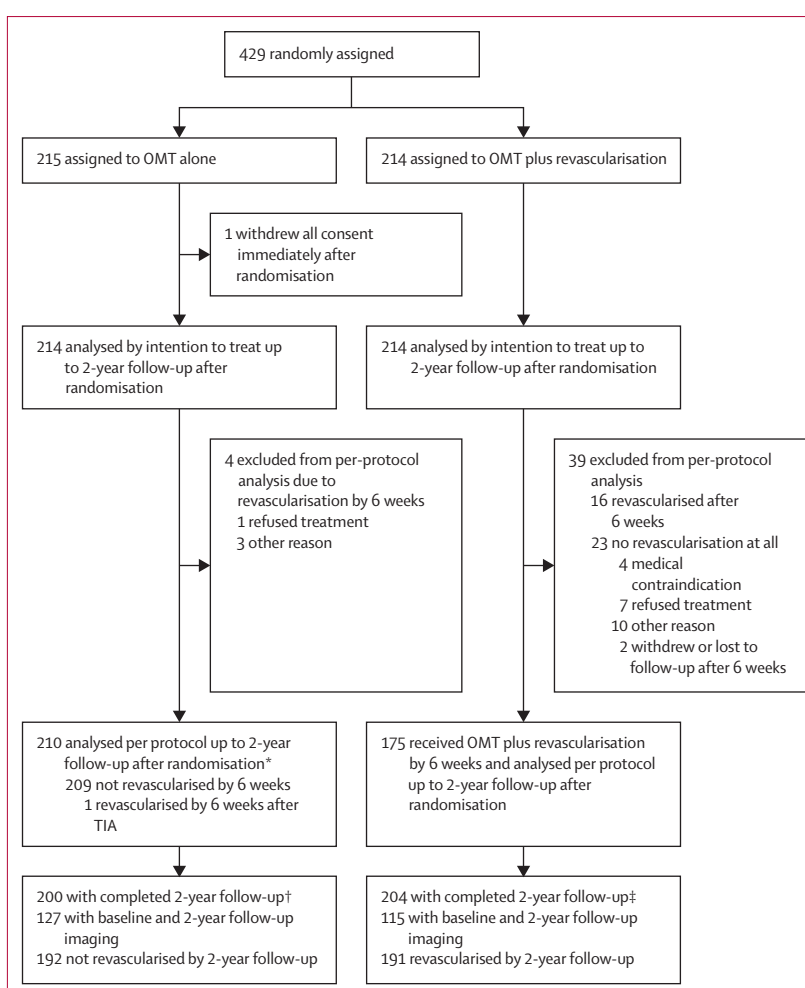
Figure 1: Trial profile
OMT=optimised medical therapy. TIA=transient ischaemic attack. *Patients allocated to OMT alone who received carotid revascularisation more than 6 weeks after randomisation were included in the per-protocol analysis but censored at the time of onset of the revascularisation procedure. †Of the 214 patients in the OMT alone intention-to-treat population, nine withdrew during the study and five were lost to follow-up. ‡Of the 214 patients in the OMT plus revascularisation intention-to-treat population, seven withdrew during the study and three were lost to follow-up.

Results

Between March 1, 2012, and Oct 31, 2019, 429 patients were randomly assigned to OMT alone (n=215) or OMT plus revascularisation (n=214). One patient allocated to OMT alone withdrew consent within 48 h and is not considered further (figure 1). Among the remaining 214 patients allocated to OMT alone, 22 (10%) underwent an ipsilateral revascularisation procedure during follow-up, of whom four had the procedure without previous symptoms within 6 weeks of randomisation (the predefined criteria for crossover). Among 214 patients allocated to OMT plus revascularisation, 181 (84%) underwent CEA, ten (4%) underwent CAS, and 23 (10%) did not undergo an ipsilateral revascularisation procedure. Of the 191 patients who received ipsilateral revascularisation, 74 had symptomatic carotid stenosis and 117 had asymptomatic carotid stenosis; 58 (78%) symptomatic patients received

the procedure within 2 weeks of randomisation, and 82 (70%) asymptomatic patients received the procedure within 4 weeks. The median time from randomisation to first ipsilateral revascularisation procedure was 7 days (IQR 5–12) in symptomatic patients and 20 days (12–31) in asymptomatic patients. For symptomatic patients, this period was 23 days (14–74) from their most recent symptoms. Considering both treatment groups, complete 2-year follow-up data were available in 404 patients (94%). The median age of patients was 72 years (IQR 65–78), more patients were male (296 [69%]) than female

(133 [31%]), and baseline characteristics were generally well balanced between groups (table 1). New cerebral infarction on imaging was assessed in 242 patients, of whom 234 had MRI at both baseline and 2-year follow-up, 14 had CT at both timepoints, and four had MRI at baseline and CT at 2-year follow-up. Adherence to medical therapy was high and similar in both groups—eg, at 2-year follow-up, 97–98% were treated with lipid-lowering medication and 86–87% were taking antihypertensive medication (appendix p 7).

Figure 2 shows the primary analysis after 2 years of follow-up, which was hierarchically assessed in the order: (1) time to periprocedural death, fatal stroke, or fatal myocardial infarction; (2) time to non-fatal stroke; (3) time to non-fatal myocardial infarction; and (4) new silent cerebral infarction on imaging. No difference in outcomes was noted between treatment groups after 2 years of follow-up. Based on 5228 (11·4%) wins for the OMT alone

	OMT alone (n=214)	OMT plus revascularisation (n=214)
Age, years	72 (65–78)	71 (65–77)
Sex		
Female	66 (31%)	67 (31%)
Male	148 (69%)	147 (69%)
Carotid stenosis		
Symptomatic	85 (40%)	85 (40%)
Asymptomatic	129 (60%)	129 (60%)
Risk group		
Asymptomatic stenosis ≤69%	47 (22%)	48 (22%)
Asymptomatic stenosis ≥70%	82 (38%)	81 (38%)
Symptomatic, CAR score <15%	35 (16%)	35 (16%)
Symptomatic, CAR score 15–19%	50 (23%)	50 (23%)
Smoking status		
Never smoked	36 (17%)	44 (21%)
Ex smoker	131 (61%)	132 (62%)
Currently smoking	47 (22%)	38 (18%)
Diabetes	63 (30%)	54 (25%)
BMI, kg/m²	27·4 (24·8–30·1)	27·7 (24·5–30·4)
Hypertension	162 (76%)	164 (77%)
Blood pressure		
Systolic, mm Hg	142 (128–156)	141 (131–154)
Diastolic, mm Hg	75 (69–83)	75 (68–83)
Total cholesterol, mmol/L	4·0 (3·4–4·7)	4·0 (3·5–4·6)
Modified Rankin scale score		
0	95 (45%)	114 (54%)
1	81 (38%)	51 (24%)
2	37 (17%)	48 (22%)
History of angina, coronary stenting, or CABG	43 (20%)	45 (21%)
History of atrial fibrillation	21 (10%)	18 (8%)
Other cardioembolic source	5 (2%)	10 (5%)
Medication at baseline		
Anticoagulant	24 (11%)	24 (11%)
Antihypertensive	169 (79%)	174 (82%)
Antiplatelets	198 (93%)	190 (89%)
Statin	207 (97%)	205 (96%)

Data are median (IQR) or n (%). Ethnicity was not recorded. CABG=coronary artery bypass graft. CAR=Carotid Artery Risk. OMT=optimised medical therapy.

Table 1: Baseline characteristics
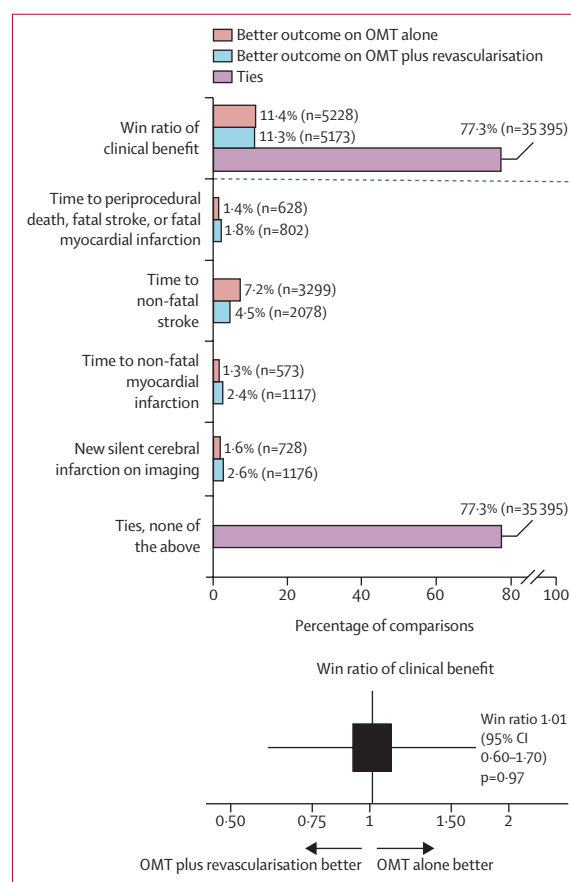
Figure 2: Win ratio results for the primary outcome

Win ratio results of 2-year primary outcome and components among patients randomly allocated to OMT (n=214) versus OMT plus revascularisation (n=214). The total number of comparisons between the two groups made to calculate the win ratio was 45 796. The left-hand side of the figure gives the percentages (and numbers) of these comparisons which favoured one group or the other, or were tied. Details of the win ratio calculation, and further information about the primary analysis, are in the appendix (pp 6, 8). The win ratio can be interpreted as follows: for a random pair of patients, the odds that the better outcome occurs in the patient receiving OMT alone is 1·01. OMT=optimised medical therapy.

group, 5173 (11·3%) wins for the OMT plus revascularisation group, and 35 395 (77·3%) ties between the groups, the win ratio for the primary outcome was 1·01 (95% CI 0·60–1·70; p=0·97). Further details of this win ratio primary analysis are given in the appendix (p 8). Considering components of the primary outcome, four instances of periprocedural death, fatal stroke, or fatal myocardial infarction occurred in the OMT alone group versus three in the OMT plus revascularisation group; non-fatal strokes occurred in 11 versus 16; non-fatal myocardial infarction in seven versus five; and new silent cerebral infarction on imaging in 12 versus seven.

Prespecified subgroup analyses of the primary hierarchical composite outcome (by symptomatic status, age, sex, risk group, CAR score [<15% and 15–19%], diabetes, hypertension, stenosis severity [<70% and ≥70%], contralateral stenosis or occlusion, and centre size [recruiting ≤20 patients and ≥21 patients]) yielded no

significant evidence of heterogeneity of the treatment effect (appendix p 9), although the statistical power to detect any potential differences in subgroups was low. The prespecified sensitivity analysis in the per-protocol group did not show any differences (appendix p 8). A post-hoc sensitivity analysis, in which the order of non-fatal stroke and non-fatal myocardial infarction was switched in the order of the hierarchical outcome composite, did not show any differences (not shown).

There was little difference between the two groups in relation to secondary outcomes. The number of patients experiencing any of periprocedural death, stroke, or myocardial infarction was similar between groups (21 [10·2%] for OMT alone vs 22 [10·5%] for OMT plus revascularisation; 2-year risk difference –0·3% [95% CI –6·1 to 5·6], p=0·46; table 2, figure 3A). Stroke in any territory occurred in 12 (5·9%) patients in the OMT alone group and 18 (8·6%) patients in the OMT plus

	Events (%)		Hazard ratio (95% CI)*	2-year risk difference (95% CI)†	p value
	OMT alone (n=214)	OMT plus revascularisation (n=214)			
Composite of periprocedural death, stroke, or myocardial infarction	21 (10·2%)	22 (10·5%)	0·92 (0·51 to 1·67)	–0·3% (–6·1 to 5·6)	0·46
Composite of periprocedural death, fatal stroke, or fatal myocardial infarction	4 (2·0%)	3 (1·5%)	1·31 (0·29 to 5·88)	0·5% (–2·0 to 3·0)	0·34
All-cause death	13 (6·4%)	13 (6·3%)	1·00 (0·46 to 2·16)	0·2% (–4·6 to 4·9)	0·47
Periprocedural death (within 90 days of randomisation)	0	1 (0·5%)	NA*	0·5%*	0·50
Cardiovascular death	5 (2·5%)	7 (3·4%)	0·71 (0·23 to 2·24)	–0·9% (–4·2 to 2·3)	0·29
Stroke	12 (5·9%)	18 (8·6%)	0·64 (0·31 to 1·33)	–2·7% (–7·7 to 2·3)	0·14
Fatal stroke	1 (0·5%)	2 (1·0%)	0·50 (0·04 to 5·47)	–0·5% (–2·1 to 1·2)	0·29
Ipsilateral stroke	6 (2·9%)	13 (6·2%)	0·45 (0·17 to 1·17)	–3·3% (–7·3 to 0·7)	0·052
Ischaemic stroke	11 (5·4%)	16 (7·7%)	0·66 (0·31 to 1·43)	–2·3% (–7·0 to 2·5)	0·18
Intracerebral haemorrhage	1 (0·5%)	2 (1·0%)	0·50 (0·04 to 5·47)	–0·4% (–2·1 to 1·2)	0·30
Transient ischaemic attack‡	14 (6·8%)	8 (3·9%)	1·75 (0·74 to 4·18)	3% (–1·4 to 7·3)	0·091
Myocardial infarction	10 (4·9%)	5 (2·5%)	2·00 (0·68 to 5·85)	2·4% (–1·3 to 6·0)	0·10
Fatal myocardial infarction	3 (1·5%)	0	NA*	1·5%*	0·13
All-cause hospitalisation§	56 (27·2%)	72 (35·1%)	0·73 (0·52 to 1·04)	–7·9% (–16·8 to 1·6)	0·043
New cerebral infarction on imaging¶	12 (9·4%)	9 (7·8%)	NA‖	1·6% (–6·3 to 9·5)	0·82
Ipsilateral	8 (6·3%)	7 (6·1%)	..	0·2% (–6·1 to 6·5)	1
Contralateral	4 (3·1%)	3 (2·6%)	..	0·5% (–4·2 to 5·)	1
Cortical	3 (2·4%)	3 (2·6%)	..	–0·2% (–4·4 to 3·9)	1
Subcortical	10 (7·9%)	6 (5·2%)	..	2·7% (–4·4 to 9·7)	0·45
Silent**	12 (9·4%)	7 (6·1%)	..	3·4% (–4·2 to 10·9)	0·35
Preceded by transient ischaemic attack	2 (1·6%)	1 (0·9%)	..	0·7% (–2·8 to 4·2)	1
Preceded by non-fatal stroke	0	2 (1·7%)	..	–1·7% (–5·0 to 1·5)	0·23

Data are n (%) unless otherwise indicated. The percentages given for each group are the 2-year Kaplan–Meier estimates, with the exception of new cerebral infarction on imaging, where the values are the actual percentages (number of events/number of scans). NA=not applicable. OMT=optimised medical therapy. *Hazard ratio and 95% CI for 2-year risk difference not calculable when events occur exclusively in one treatment group. †Risk in OMT alone group minus risk in OMT plus revascularisation group. ‡Transient episodes associated with new cerebral infarction were classified as ischaemic stroke. §Excluding hospitalisation for carotid revascularisation procedures. ¶The numbers of patients with imaging available for analysis at 2 years was 127 in the OMT alone group and 115 in the OMT plus revascularisation group. ‖The time at which the new infarcts seen on imaging occurred is unknown, and therefore a hazard ratio cannot be calculated. **Silent infarction was defined as new infarction on brain imaging without a clinical history of a new stroke.

Table 2: Secondary and exploratory outcomes within 2 years follow-up of OMT versus OMT plus revascularisation
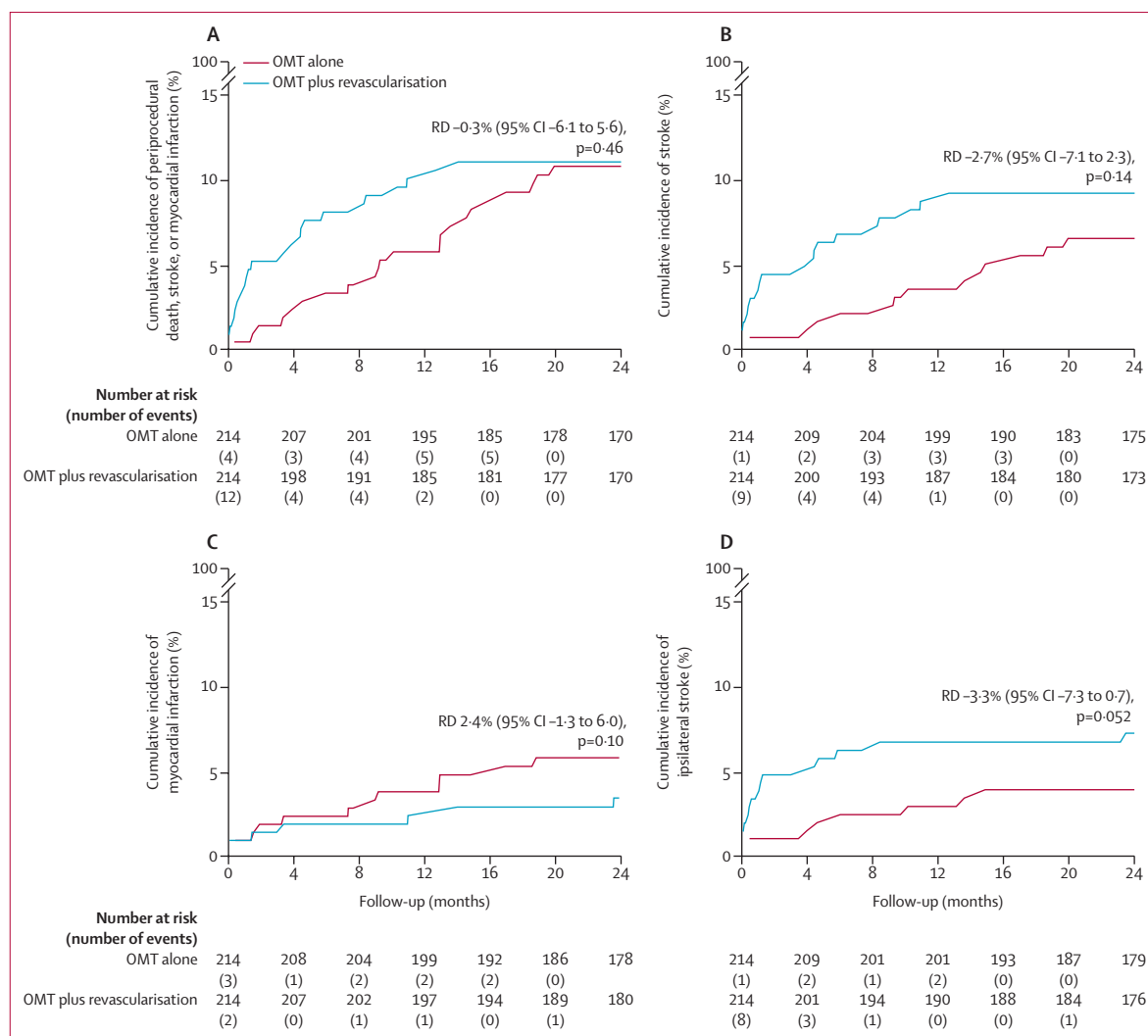
Figure 3: **Kaplan–Meier estimates for 2-year cumulative incidence of secondary outcomes**
(A) Composite of periprocedural death, stroke, or myocardial infarction. (B) Stroke. (C) Myocardial infarction. (D) Ipsilateral stroke. The percentage of events (cumulative incidence) is shown plotted against months since randomisation. The numbers in each graph below each tick mark refer to the numbers of patients followed up at each timepoint. The numbers in parentheses refer to the number of events that occurred in the 4-month period between that timepoint and the next timepoint. OMT=optimised medical therapy. RD=risk difference at 2-year follow-up.

revascularisation group (2-year risk difference −2·7% [−7·7 to 2·3], p=0·14; figure 3B). Of these, 27 patients had an ischaemic stroke (11 [5·4%] with OMT alone *vs* 16 [7·7%] with OMT plus revascularisation, 2-year risk difference −2·3% [−7·0 to 2·5], p=0·18) while three patients had intracerebral haemorrhage (one [0·5%] with OMT alone *vs* two [1·0%] with OMT plus revascularisation, 2-year risk difference −0·4% [−2·1 to 1·2], p=0·30). Ipsilateral stroke occurred in six (2·9%) patients in the OMT alone group and 13 (6·2%) with OMT plus revascularisation (2-year risk difference −3·3% [−7·3 to 0·7], p=0·052; figure 3D). Myocardial infarction occurred in ten (4·9%) patients in the OMT alone group and five (2·5%) patients in the OMT plus revascularisation group (2-year risk difference 2·4% [−1·3 to 6·0], p=0·10; figure 3C). Only

one patient had a stroke before planned revascularisation, which occurred 2 days after randomisation (13 days after symptoms). There was one periprocedural death in the OMT plus revascularisation group, attributed to decompensated aortic stenosis 1 week after CEA. Additional exploratory analyses considering the average event-free survival time are shown in the appendix (p 10). The secondary analysis of functional outcome as measured by mRS scores at 2 years is displayed in figure 4, with no significant difference between the two groups (p=0·53).

Brain imaging at both baseline and 2-year follow-up was available for analysis in 242 patients (table 2). The numbers of patients with new cerebral infarction on imaging at 2-year follow-up were similar between treatment groups, with 12 (9·4%) of 127 patients in the OMT alone group versus nine (7·8%) of 115 in the OMT plus revascularisation
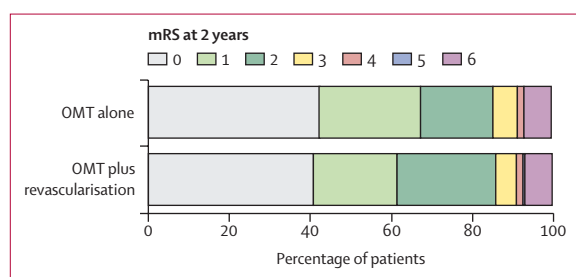
Figure 4: **Functional outcome at 2 years**
Functional outcome was assessed by mRS scores using the Rankin Focused Assessment. Individual scores can be described as: 0, no disability; 1, no significant disability despite symptoms; 2, slight disability; 3, moderate disability; 4, moderately severe disability; 5, severe disability; 6, death. OMT=optimised medical therapy. mRS=modified Rankin Scale.

group having new cerebral infarction (2-year risk difference 1·6% [95% CI –6·3 to 9·5]; p=0·82). Of the 21 patients with new cerebral infarction on imaging, 19 were silent (12 in the OMT alone group *vs* seven in the OMT plus revascularisation group), whereas two were preceded by non-fatal stroke in the OMT plus revascularisation group. Sensitivity analyses of secondary and exploratory outcomes in the per-protocol group did not differ from the intention-to-treat analyses (appendix p 12).

Procedural complications are described in the appendix (p 11). No strokes within 30 days occurred in the 22 patients who underwent deferred revascularisation in the OMT alone group. In the OMT plus revascularisation group, among 191 patients who received ipsilateral revascularisation by 2 years, eight strokes (4%) occurred within the first 30 days after any revascularisation, of which all but one were ipsilateral to the randomised artery; five (7%) occurred in the 74 symptomatic versus three (3%) in the 117 asymptomatic patients. One of the strokes, a cerebral haemorrhage that occurred 2 days after CEA, was fatal, which is in addition to the aforementioned periprocedural death within 90 days of randomisation. However, the CEA procedure leading to the cerebral haemorrhage was delayed by more than 90 days after randomisation and therefore was not classified as a periprocedural death according to our definition. One non-fatal myocardial infarction occurred in the 30-day period after the procedure. Of the 181 CEA procedures performed as first intervention in the OMT plus revascularisation group, 12 (7%) had cranial nerve palsy described within 1 month.

Discussion

ECST-2 is the first randomised trial of the management of carotid artery disease in which patients were selected for the trial using a calculated measure of the risk of stroke. Among patients with carotid stenosis of 50% or greater, with a low to intermediate predicted 5-year risk of ipsilateral stroke of less than 20% (based on the CAR score), no evidence was found for a benefit of carotid revascularisation in addition to OMT in a 2-year interim analysis. We cannot rule out the possibility that revascularisation will provide a small to moderate benefit in our patients beyond 2 years. We are, therefore, continuing follow-up to 5 years after randomisation. Nevertheless, the Kaplan–Meier risk curves appear to plateau within the first 2 years of follow-up, suggesting that further follow-up might not favour revascularisation. However, much larger trials or long-term follow-up would be required to show this result definitively. In the meantime, these 2-year interim results support treating asymptomatic and low or intermediate risk symptomatic carotid stenosis with OMT alone until further data become available.

The pooled analysis from the NASCET, ECST, and Veterans Affairs trials conducted more than 30 years ago,[1] which showed a substantial benefit of CEA in preventing stroke, seems obsolete now because the risks of stroke after CEA have declined. For example, in NASCET, the risk of any stroke for symptomatic patients with 70% or greater stenosis after CEA was 29·4% over 8 years,[3] whereas in a later trial, CREST, that rate was 15·7% over 10 years.[16] However, the recurrent stroke risk of symptomatic patients treated with modern OMT alone was largely unknown. ECST-2 is the first contemporary randomised controlled trial presenting results of symptomatic patients treated by OMT alone.

We selected patients based on a CAR score predicting a 5-year risk on OMT alone of less than 20%. Our results indicate that this CAR score reliably predicted patients at low risk of stroke, with a 2-year risk of ipsilateral stroke in the OMT alone group of only 2·9%, compared with 6·2% in the OMT plus revascularisation group. Our trial is also unusual in including patients with asymptomatic and low or intermediate risk symptomatic carotid stenosis because we hypothesised that they would both have a similar low risk of stroke when treated with OMT and would not benefit from additional revascularisation. There was no evidence in the subgroup analysis (appendix p 9) of a difference in outcomes between asymptomatic and our selected patients with symptomatic stenosis, in keeping with our hypothesis. It is notable that more than half had severe carotid stenosis (≥70%), a characteristic that might be considered an indication for revascularisation, but there was no evidence in subgroup analysis that these patients benefitted from revascularisation. We excluded recently symptomatic patients with carotid stenosis who had a predicted 5-year ipsilateral risk of stroke of 20% or higher, and it remains uncertain whether such patients still require revascularisation.

MRI has been shown to be more sensitive to brain infarction than clinical assessment. In ECST-2, 9·4% of patients in the OMT alone group and 7·8% of patients in the OMT plus revascularisation group had new ischaemic brain lesions on imaging at 2-year follow-up, of which 90% were silent. It is known that silent infarcts are associated with stroke recurrence and cognitive decline.[17]

Therefore, we recommend that future studies in patients with carotid stenosis include silent brain infarcts as an outcome measure given their clinical significance in predicting future events.

To our knowledge, ECST-2 is the first stroke trial to use the win ratio for its primary analysis. The statistical power to demonstrate a difference between treatment groups depends on the event rate. The recent decline in stroke rates attributable to advances in medical therapy and lifestyle modification means that very large study populations are required to show significant treatment effects if outcome measures are limited to symptomatic events. Several studies did not include the target number of patients due to slow inclusion rates such as SPACE-2 and the AMTEC study.[18,19] To conduct randomised trials with sufficient power in such populations, a modified statistical method is necessary. Using brain imaging follow-up to detect silent infarction allows a smaller sample size to reach conclusions about treatment effects.[20,21] A standard time-to-event analysis cannot be used because the exact timing of silent infarction cannot be determined. We therefore used the win ratio method to allow the inclusion of MRI-detected infarction as an outcome event.[14] The win ratio enables different events to be analysed in a combined hierarchical manner based on severity of each event. This enables greater emphasis on more severe events. It can also handle a composite outcome where components are of different outcome types (ie, a mixture of time-to-event, continuous, and categorical outcomes). A limitation of the win ratio method is that it is not currently possible to adjust for covariates used in stratified randomisation or minimisation, as is usually recommended.

We provided our investigators with recommendations for applying OMT in both groups. During the trial, there was a remarkably high compliance with OMT with nearly all patients on lipid-lowering and antithrombotic therapy up to the 2-year follow-up (appendix p 7). Patients who take part in trials are more closely monitored for lifestyle modification and risk factor control, which potentially motivates patients to stay compliant, and therefore our findings might not reflect clinical practice. Nevertheless, our results demonstrate the benefit of target-led cardiovascular risk management.

Limitations of the interim analysis include the fact that the number of patients included in the analysis was relatively small. Nevertheless, the results should inform the design and sample size of future trials. For example, the results of ECST-2 will contribute to the design of trials of carotid revascularisation based on selection of patients with intra-plaque haemorrhage shown by dedicated carotid artery MRI, which appears to be a powerful predictor of stroke outcome in lower risk patients treated medically.[22,23] We introduced MRI follow-up for silent infarction and analysis using the win ratio to increase the power of our sample size, but it is a limitation of ECST-2 that although most patients had clinical data available for analysis, the numbers of patients with brain imaging at 2-years follow-up was limited by the COVID-19 pandemic. However, it is unlikely that our findings would have been altered substantially if more patients had had 2-year imaging. The present analysis only considers events occurring within 2 years of randomisation and we cannot completely exclude the possibility of moderate benefit or harm that might appear within one group with further follow-up. We will therefore continue to follow up patients. Another limitation is that ECST-2 is the first study to use the recalibrated CAR score and, although event rates in ECST-2 were well within that predicted by the score, its accuracy has not been independently tested.

The results of ECST-2 provide an important step towards more individualised treatment in patients with carotid stenosis enabled by the CAR score. However, our findings only apply in general to the group of patients with low or intermediate risk symptomatic stenosis selected using the CAR score, and to asymptomatic patients. Identifying individual patients with carotid stenosis within these groups and those excluded from our selection criteria who are most likely to benefit from or be harmed by revascularisation should be a goal of future research. We expect that patients who might still benefit from revascularisation would be those with specific high risk markers for future stroke, low periprocedural risk of stroke or death, and sufficient life expectancy to derive benefit from revascularisation. The use of dedicated plaque imaging could play a key role in identifying such patients and has potential to optimise the CAR score.[24] The effect of intraplaque haemorrhage on the risk of future stroke and the benefit of revascularisation has been investigated in a substudy of ECST-2 and will be the subject of a separate report. Future models with implementation of clinical characteristics and plaque imaging have great potential to optimise the individualised treatment strategy in patients with carotid artery disease. In the meantime, the CAR score calculator can be used to identify symptomatic patients with a risk of less than 20% that might be managed by OMT alone and also symptomatic patients with a risk of more than 20% to consider for revascularisation.

In conclusion, ECST-2 has shown at 2 years of follow-up no evidence of benefit from additional carotid revascularisation compared with OMT alone among patients with 50% or greater carotid stenosis with 5-year risk of ipsilateral stroke of less than 20% as predicted by the CAR score. The results demonstrate that symptomatic patients at low risk of stroke treated with OMT alone can be reliably identified using the CAR score. The risks of stroke associated with carotid stenosis treated with OMT in ECST-2 were substantially lower than recorded in similar patients during previous carotid stenosis trials.

For the **CAR score calculator** see www.sealedenvelope.com/car/

References
1 Rothwell PM, Eliasziw M, Gutnikov SA, et al. Analysis of pooled data from the randomised controlled trials of endarterectomy for symptomatic carotid stenosis. *Lancet* 2003; **361:** 107–16.
2 European Carotid Surgery Trialists' Collaborative Group. Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). *Lancet* 1998; **351:** 1379–87.
3 Barnett HJM, Taylor DW, Eliasziw M, et al. Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. *N Engl J Med* 1998; **339:** 1415–25.
4 Naylor R, Rantner B, Ancetti S, et al. European Society for Vascular Surgery (ESVS) 2023 clinical practice guidelines on the management of atherosclerotic carotid and vertebral artery disease. *Eur J Vasc Endovasc Surg* 2023; **65:** 7–111.
5 Bonati LH, Kakkos S, Berkefeld J, et al. European Stroke Organisation guideline on endarterectomy and stenting for carotid artery stenosis. *Eur Stroke J* 2021; **6:** I–XLVII.
6 Bonati LH, Jansen O, de Borst GJ, Brown MM. Management of atherosclerotic extracranial carotid artery stenosis. *Lancet Neurol* 2022; **21:** 273–83.
7 Rothwell PM, Warlow CP. Prediction of benefit from carotid endarterectomy in individual patients: a risk-modelling study. *Lancet* 1999; **353:** 2105–10.
8 Rothwell PM, Mehta Z, Howard SC, Gutnikov SA, Warlow CP. Treating individuals 3: from subgroups to individuals: general principles and the example of carotid endarterectomy. *Lancet* 2005; **365:** 256–65.
9 Rothwell PM, Eliasziw M, Gutnikov SA, Warlow CP, Barnett HJM. Endarterectomy for symptomatic carotid stenosis in relation to clinical subgroups and timing of surgery. *Lancet* 2004; **363:** 915–24.
10 Walker MD, Marler JR, Goldstein M, Grady PA, Toole JF, Baker WH. Endarterectomy for asymptomatic carotid artery stenosis. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. *JAMA* 1995; **273:** 1421–28.
11 Halliday A, Harrison M, Hayter E, et al. 10-year stroke prevention after successful carotid endarterectomy for asymptomatic stenosis (ACST-1): a multicentre randomised trial. *Lancet* 2010; **376:** 1074–84.
12 Cheng SF, van Velzen TJ, Gregson J, et al. The 2nd European Carotid Surgery Trial (ECST-2): rationale and protocol for a randomised clinical trial comparing immediate revascularisation versus optimised medical therapy alone in patients with symptomatic and asymptomatic carotid stenosis at low to intermediate risk of stroke. *Trials* 2022; **23:** 606.
13 Rothwell PM, Gibson RJ, Slattery J, Sellar RJ, Warlow CP. Equivalence of measurements of carotid stenosis a comparison of three methods on 1001 angiograms. *Stroke* 1994; **25:** 2435–39.
14 Gregson J, Donners SJA, Dippel D, et al. Use of the win ratio for analysis of stroke trials: description, illustration and planned use in the second European Carotid Surgery Trial (ECST-2). *Stroke* 2025; **56:** 230–38.
15 Pocock SJ, Ariti CA, Collier TJ, Wang D. The win ratio: a new approach to the analysis of composite endpoints in clinical trials based on clinical priorities. *Eur Heart J* 2012; **33:** 176–82.
16 Brott TG, Howard G, Roubin GS, et al. Long-term results of stenting versus endarterectomy for carotid-artery stenosis. *N Engl J Med* 2016; **374:** 1021–31.
17 Vermeer SE, Longstreth WT Jr, Koudstaal PJ. Silent brain infarcts: a systematic review. *Lancet Neurol* 2007; **6:** 611–19.
18 Reiff T, Eckstein HH, Mansmann U, et al. Carotid endarterectomy or stenting or best medical treatment alone for moderate-to-severe asymptomatic carotid artery stenosis: 5-year results of a multicentre, randomised controlled trial. *Lancet Neurol* 2022; **21:** 877–88.
19 Kolos I, Troitskiy A, Balakhonova T, et al. Modern medical treatment with or without carotid endarterectomy for severe asymptomatic carotid atherosclerosis. *J Vasc Surg* 2015; **62:** 914–22.
20 Streifler JY, den Hartog AG, Pan S, et al. Ten-year risk of stroke in patients with previous cerebral infarction and the impact of carotid surgery in the Asymptomatic Carotid Surgery Trial. *Int J Stroke* 2016; **11:** 1020–27.
21 Traenka C, Engelter ST, Brown MM, Dobson J, Frost C, Bonati LH. Silent brain infarcts on diffusion-weighted imaging after carotid revascularisation: A surrogate outcome measure for procedural stroke? A systematic review and meta-analysis. *Eur Stroke J* 2019; **4:** 127–43.
22 van Dam-Nolen DHK, Truijman MTB, van der Kolk AG, et al. Carotid plaque characteristics predict recurrent ischemic stroke and TIA: the PARISK (Plaque At RISK) study. *JACC Cardiovasc Imaging* 2022; **15:** 1715–26.
23 Schindler A, Schinner R, Altaf N, et al. Prediction of stroke risk by detection of hemorrhage in carotid plaques: meta-analysis of individual patient data. *JACC Cardiovasc Imaging* 2020; **13:** 395–406.
24 Saba L, Cau R, Murgia A, et al. Carotid Plaque-RADS: a novel stroke risk classification system. *JACC Cardiovasc Imaging* 2024; **17:** 62–75.