

Modelling the cost-effectiveness of asymptomatic carotid endarterectomy

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Abstract

Background

The aim of this study was to model the cost-effectiveness of asymptomatic carotid endarterectomy versus medical therapy based on the 10 year Asymptomatic Carotid Surgery Trial (ACST) data.

Methods

Cost-utility analysis based on clinical effectiveness data from ACST with UK specific costs and stroke outcomes. A Markov model was used to calculate the incremental cost-effectiveness ratio (ICER or cost per additional quality of life year) for a strategy of early endarterectomy versus medical therapy for the average patient and published subgroups. An exploratory analysis considered contemporary event rates.

Results

The ICER was £7584 per additional quality adjusted life year for the average patient in ACST. At a threshold of £20 000 to £30 000 there was a 74 to 84% chance of early endarterectomy being cost-effective. The ICERs for men above and below 75 years of age were £3254 and £71 699 respectively. For women under 75, endarterectomy was less costly and more effective than medical therapy. For women over 75, endarterectomy was less effective and more costly than medical therapy. At peri-operative event rates of 2.7% from the 2008 GALA trial and background any territory stroke rates of 1.6% from the last 5 years of the ACST, early endarterectomy remained cost-effective.

Conclusions

In ACST, early endarterectomy was predicted to be cost-effective in those below 75 years of age, using a threshold of £20 000 per quality adjusted life year. If background any territory stroke rates fell below 1% per annum, early endarterectomy would cease to be cost-effective.

Introduction

Stroke is the third leading cause of death and the leading cause of major disability in United Kingdom adults(1, 2). The economic cost of stroke in the United Kingdom has been estimated at £9 billion per year(3). Up to 15% percent of ischaemic stroke is thought to be a consequence of carotid atherosclerosis (4) which can be managed medically or in combination with revascularisation. However because severe carotid stenosis is prevalent in 1-3% of the European population over 70(5), prevention of subsequent stroke has considerable economic implications.

The Asymptomatic Carotid Surgery Trial (ACST) was a 3120 patient, European randomised controlled trial comparing early surgical endarterectomy with a medically treated control group. The 10 year results published in 2010, demonstrated a 4.6% absolute risk reduction in the incidence of any territory stroke in those randomised to early endarterectomy (6) . The ACST demonstrated that persons below 75 years of age were the main beneficiaries.

The aim of this study was to model the lifetime cost-utility of early endarterectomy in the United Kingdom, based on the effectiveness data reported by the ACST. The secondary aims were to model the effects of contemporary peri-operative and background stroke rates and the effects of eliminating crossovers for patient or physician preference.

Methods

Model overview

A Markov model was used to estimate the lifetime costs and quality adjusted life years (QALY) of early endarterectomy compared with medical therapy (more accurately termed deferral of endarterectomy, as 34.1% of patients eventually crossed over to endarterectomy). The model was adapted for the United Kingdom from an earlier published Swedish version(7). Patients entered the model after they had been randomised to early endarterectomy or deferral and started in the no event state. The model comprised of the following health states: no event, minor stroke, disabling stroke, and death (Figure 1). All patients faced a competing risk of intercurrent mortality (death from other causes) dependent on age and gender. The cycle length was one year. Those assigned to medical therapy were at a background risk of non-perioperative stroke (minor, major or fatal). Patients had reduced health related quality of life, higher costs and an increased mortality risk following stroke, which was assumed independent of previous treatment. Those assigned to surgery had a reduced long-term risk of non-perioperative stroke (the treatment effect), but had a short-term risk of perioperative stroke or death as per ACST (2.9% in the early endarterectomy arm and 3.6% for crossovers to surgery).

The outcome of the model was the cost per additional quality of life year (incremental cost-effectiveness ratio or ICER) for early endarterectomy versus medical therapy. The perspective of the analysis included the National Health Service and Personal Social Services (8) as recommended by the National Institute for Health and Clinical Excellence(8). This included the formal costs of supporting physically disabled persons (9).

Clinical effectiveness data

The main source of data for the primary (base case) analysis was the ACST. The base case scenario was constructed to compare early endarterectomy versus medical therapy on average for patients in the ACST. Table 1 shows the rates of peri-operative stroke, non-peri-operative stroke and treatment effects at 10 years from this trial. The base case analysis used hazard ratios from 0-5 years and 5-10 years from the ACST. Treatments were defined on an intention to treat basis. It was assumed that after 10 years there was no further treatment effect, that is, the absolute difference in the rates of stroke between the treatments was maintained after 10 years but did not continue to diverge.

Quality of life after stroke

Health related quality of life after disabling and non-disabling stroke was taken from two published cohorts (10, 11) and for the purposes of economic evaluation is conventionally scored from 0 (death) to 1 (perfect health). The mean decrement in health related quality of life for stroke in comparison to the general population was assumed to be 0 for non-disabling stroke and 0.35 for disabling stroke.

Costs

The costs of preventative medical therapy were assumed to be identical in both arms. The reimbursement tariff that included endarterectomy (code QZ04Z, £3345) was obtained from the NHS 2010-2011 healthcare resource group (HRG). This tariff is calculated by the Department of Health as a national average unit cost for all admissions for this HRG in England over the previous year (12). As a sensitivity analysis, an alternative UK cost was used (£4978)(3), based on local costing from a small sample of UK patients. Post-stroke costs were obtained from published UK sources and included hospital, community, social services

and informal care (13) (14, 15). All costs were standardised to January 2010 prices by use of the National Health Service hospital and community health service inflation index(16) (Table 2). A discount rate of 3.5% per year was used for costs and QALYs(8).

Intercurrent and stroke related mortality

The rate of intercurrent mortality for men and women at each age in the general population was estimated from national sources, by deducting stroke related mortality from all-cause mortality rates(17). National rates of stroke related mortality were derived from ICD 10 codes I60 - I64 and I69(17, 18).

Intercurrent mortality was greater in the ACST than the general population. This was represented in the model by a mortality ratio, calibrated to match survival at 10 years in the ACST. The increase in the mortality rate post stroke (compared with asymptomatic patients) was estimated from the Oxfordshire Community Stroke Project (19) which was large, British and consistent with a more recent study from Perth, Australia(20).

Base case scenario

A base case scenario considered the average patient in the ACST: a person of age 68 years with a mean systolic blood pressure of 153mmHg and total cholesterol of 5.8mmol/L (Table 3, Figure 2). Published subgroups of men and women above and below 75 years of age in ACST were also considered (Table 4, Figure 2).

Sensitivity analyses

A series of deterministic sensitivity analyses were performed to test the robustness of the model predictions(21) (Table 5). Parameters varied included: using an average hazard ratio calculated over 10 years, assuming the rates of stroke in the two arms were the same after 5 years, a higher mortality rate post-stroke and increased hospital costs of surgery.

Probabilistic sensitivity analysis was performed using Monte Carlo simulation to reflect the sampling uncertainty in the model inputs(21) (Table 6). Rates of events were assigned gamma distributions, hazard ratios were assigned lognormal distributions, the probability of perioperative stroke was assigned a beta distribution, and the probabilities that a stroke event was non-disabling, disabling or fatal were assigned a multinomial (Dirichlet) distribution. The parameters for these distributions (for example, mean and standard error) were estimated from the ACST. HRG costs and other cause mortality rates were derived from population data and were therefore not subject to sampling uncertainty and not assigned probability distributions.

Exploratory analysis 1: Restriction of crossovers for patient or physician preference

In ACST 11.7% of patients allocated to medical therapy required endarterectomy for new symptoms. However an additional 22.4% chose endarterectomy for other reasons. Similarly 10.2% of patients allocated early endarterectomy did not receive it by one year. These crossovers might be expected to reduce the treatment effect. An exploratory analysis was performed in which crossovers for patient or physician preference were excluded, illustrating what could be termed a per-protocol (or endarterectomy only for new symptoms) scenario (Table 4, supplementary appendix).

Exploratory analysis 2: Contemporary peri-operative stroke rates

Improved peri-operative safety has been reported since ACST. The peri-operative stroke or death rate was 2.9% in ACST, 2.7% in the 2008 GALA trial (32 strokes and 5 deaths in 1361 asymptomatic patients, Dr Stephanie Lewis, personal communication), 1.6% from 2005-2009 US registry data(22) and 1.4% in the 2010 US CREST trial(23). The 2011 UK carotid audit reported a 30 day stroke or death rate of 3%, however this data is hard to interpret as it was not stratified by symptom status(24). The range of 1.4-2.7% could thus be considered to reflect contemporary peri-operative stroke or death rates from randomised studies. The effects of lower peri-operative stroke or death rates and their implications for cost-effectiveness are illustrated in Figure 3 and Table 4.

Statistical analysis

Data was analysed using Excel 2007 (Microsoft, California, USA). WinBUGS v1.4 (Medical Research Council, Cambridge, UK) was used to simulate per protocol event rates (Appendix 1) and figures created using Prism v5 (GraphPad, California, USA).

Results

Base case analysis

Results are shown as model predictions of the difference in stroke-related outcomes at ten years, lifetime discounted costs and quality adjusted life years (Table 3). For the base-case scenario, the additional lifetime cost of a strategy of early endarterectomy compared with deferral of endarterectomy was £641 and the difference in lifetime QALYs was 0.085 (equivalent to 1 additional month of healthy life). The predicted ICER was £7584 per QALY.

Sensitivity analyses

Deterministic sensitivity analysis was used to predict the effect on the base case ICER using an alternative, cost of £4978 for endarterectomy (Table 5), increasing the ICER to £18 677.

Probabilistic sensitivity analysis was used to take account of the sampling uncertainty in the model inputs. Results differed from the deterministic analysis because the random distributions assigned to the inputs were asymmetrical. The mean difference in costs was £942 (95% CI -73 to 1936) and the mean difference in QALYs was 0.081 (95% CI -0.004 to 0.160) (Table 6). At threshold of £20 000 per QALY there was a 74% chance of early endarterectomy being cost-effective, which rose to 84% at a threshold of £30 000 per QALY (Table 4).

Subgroup and exploratory analyses

For men under 75 years of age in ACST, the ICER for early endarterectomy was £3254 per QALY, and for women under 75 early endarterectomy was less costly and more effective. For men over 75 the ICER was £71 699 per QALY. For women over 75, early endarterectomy was more costly and less effective than medical therapy. These results are shown in Table 4.

Restricting crossovers for patient or physician preference increased the ICER to £10 149 per QALY for early endarterectomy versus per-protocol medical therapy (Table 5).

Using the peri-operative stroke or death rate of 2.7% from GALA, the ICER for early endarterectomy crossed the £20 000 per QALY threshold at any territory stroke rates below 1.5% per annum. Using the peri-operative stroke or death rate of 1.4%, from CREST, the

ICER for early endarterectomy crossed the £20 000 per QALY threshold at any territory stroke rates below 1% per annum (Figure 3).

Discussion

The principal finding of this study was that early endarterectomy for the average in the ACST was predicted to be cost-effective based on the £20-30 000 threshold set by the UK National Institute for Health and Clinical Excellence(8). This was clear for individuals under 75 years of age, who had a larger, more certain treatment effect and lived longer. Interestingly, it was no less cost-effective to offer early endarterectomy to women compared with men less than 75 years, a new finding based on the 10 year data. The model predictions appeared robust if the cost of procedure rose by 50% or if a per-protocol scenario was simulated but were sensitive to background stroke rates and operative hazards.

Simulating a policy of allowing crossovers to surgery only for new symptoms resulted in no improvement in the ICER in comparison with the base case scenario. This was the result of two opposing effects. Firstly, because early surgery was cost-effective, disallowing crossovers in patients assigned to medical therapy improved the relative cost-effectiveness of surgery. However, the benefits of surgery declined with age, making late crossovers to surgery less effective than early surgery and more expensive than medical treatment, i.e. represented a cost-ineffective treatment strategy.

In contemporary practice there is evidence for improved operative safety and reduced background stroke rates(22, 23, 25) . With a safety profile similar to the 2008 GALA trial which was UK based and included trainee operators, early endarterectomy crossed the £20 000 per QALY threshold at background, any territory stroke rates of 1.5% per annum, similar to the 1.6% seen in the final years of ACST (Table 4). However, if background, any territory stroke rates fell below 1% per year, endarterectomy would cease to become cost-effective,

even if operative safety improved to the levels seen in CREST (Figure 2). Recent any territory stroke rates from cohort studies of non-surgical populations vary between 0.8-2.3% per annum(26) (27). It will be interesting to see whether these very low stroke rates are replicated in the on-going randomised interventional trial SPACE-2, which is due to report shortly(28).

This is the first UK cost-utility analysis for asymptomatic carotid surgery based on long-term, European, randomised controlled trial data. Data from the more recent, European ACST rather ACAS was modelled for specific reasons (29). Firstly, in the earlier ACAS the incidence of stroke on medical therapy alone was substantially higher (ACAS medical arm 5 year any stroke or peri-operative death rate 17.5% versus 10.9% in ACST). Secondly the follow up period for the ACST was a median of 9 years in comparison with 2.7 years in ACAS, which is important because the long-term benefit of endarterectomy was examined in the ACST. Thirdly, the ACST was a larger trial of 3120 patients, with a large British contribution(30) and therefore more relevant to the UK. Finally the ACST used the primary endpoint of all stroke or peri-operative death, which accounted for the effects on other stroke subtypes following carotid revascularisation, which are sometimes ignored.

This study has limitations. First, resource use for individual patients was not reported in ACST and costs for endarterectomy were based on average national costings. Second, the subgroup of patients above 75 years of age was small in ACST and further research is required before firm conclusions can be drawn regarding patients in this age range. Third, ACST did not include transient ischaemia attack (TIA) as an endpoint, which is associated with cost of £1339 (HRG code AA29Z), but no lasting change in quality of life (10, 11). ACAS demonstrated a reduction in TIA after endarterectomy(31) and excluding TIA is thus a conservative assumption. Fourth, loss of earnings were not considered, as they are not

reimbursed by PSS. The mean age of patients in ACST was 68 years, thus only a minority of patients were working. In these patients there would be additional productivity savings in the surgical arm. Fifth, this analysis looked at cost-per-QALY over a lifetime, but did not estimate the affordability of offering surgery to the population at risk. Considering the number needed to treat(6) and the prevalence of significant asymptomatic carotid stenosis, the upfront costs of endarterectomy may simply be unaffordable on a large scale to a publicly funded national health service, a finding which has been echoed in a recent Australian analysis(32). Sixth, carotid stenting was not considered in this analysis, following interim guidance from NICE(33) pending the completion of ACST-2 in which detailed resource use data are being collected. Finally, this analysis focussed on the cost-effectiveness of surgery over medical therapy, not the cost-effectiveness of case finding using ultrasound. Earlier analyses have demonstrated that case finding is cost-effective if the prevalence of haemodynamically significant asymptomatic carotid stenosis is $\geq 20\%$ (34), for example patients with symptomatic peripheral arterial disease(35). The costs of case finding were pre-requisite in both arms of the ACST, however because both arms were equal in size, the costs of case finding were also likely to be equal and unlikely to affect the question of whether surgery or medical therapy was more cost-effective. Without case finding, the long-term prognosis for patients with asymptomatic carotid disease cannot be established on any therapy.

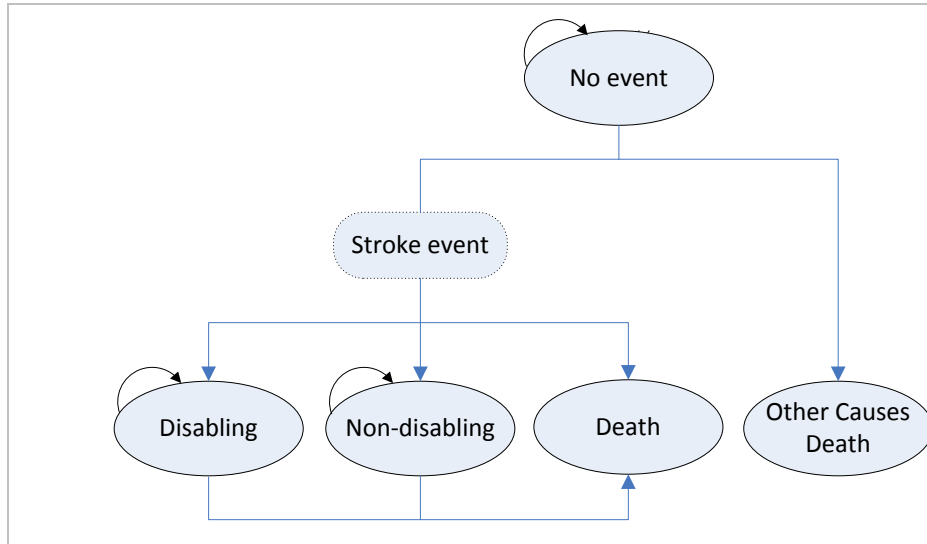
These findings are in line with an earlier intention to treat analysis from ACAS which calculated the average ICER for early endarterectomy to be \$8000 (approximately £5000)(29). The present study estimated lower ICERs for men and women under 75 years of age than a Swedish cost-utility analysis(7). The main differences between the studies relate to the choice of inputs. The Swedish study used the 5 year ACST data which showed

less benefit for women, assumed no treatment effect for CEA beyond 5 years, used higher costs for surgery, and excluded the extra costs and perioperative deaths in the crossovers from medical therapy to surgery.

The results of this study suggest that at the end of ACST, in individuals under 75 years of age it was likely that a strategy of early endarterectomy was cost-effective in comparison to a strategy of medical therapy alone in the UK. This finding was conditional on background stroke rates and hazards of operation, factors which change with time. If any territory stroke rates on contemporary medical therapy fall substantially below that seen in the ACST (<1%), surgery would cease to be cost-effective. For this reason development of low-cost, practical risk stratification tools and improvements in operative safety are now required.

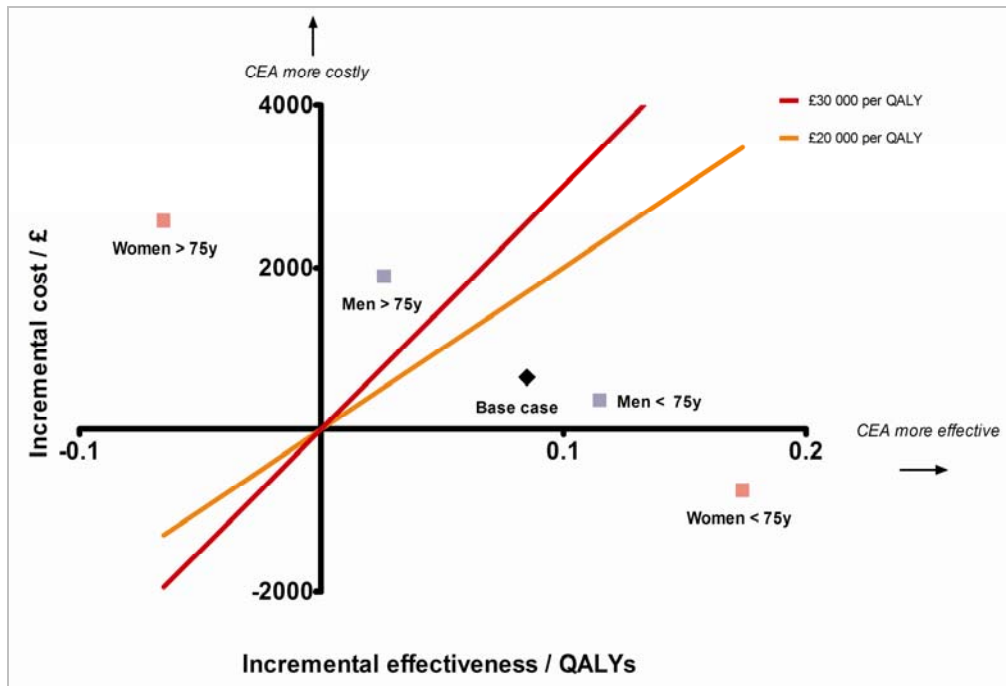
Figure Legends

Figure 1: Long-term Markov model structure



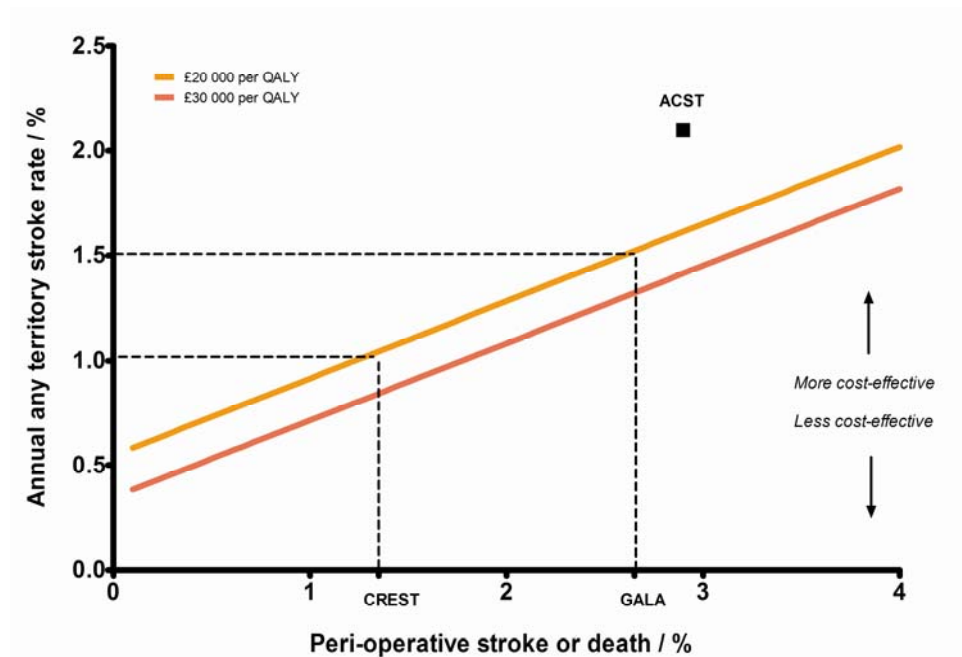
Patients enter the model in the no event state and transitions may occur into the either the stroke or death state in yearly cycles at event rates taken from ACST. Those undergoing endarterectomy incur an additional short-term peri-operative risk of stroke or death (not shown).

Figure 2: Cost-utility grid



Cost-effectiveness plane for a strategy of early endarterectomy versus medical therapy. To be considered effective, an intervention should lie to the right of the y-axis. To be considered less costly an intervention should lie beneath the x-axis. The NICE £20-£30 000 thresholds are represented by orange and red lines respectively. To be considered cost-effective, an intervention should lie beneath the respective threshold line. QALYS = quality adjusted life years.

Figure 3: Effect of contemporary event rates



Cost per additional quality adjusted life year for early endarterectomy is dependent on peri-operative safety and background any territory stroke rates. The peri-operative stroke or death rates from ACST (2.9%), GALA (2.7%) and CREST (1.4%) are indicated. The dotted lines indicate the any territory stroke rates below which a strategy of early endarterectomy would cross the £20 000 NICE threshold (orange line).

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Table 1. Clinical inputs to the model. Rates of stroke related events and size of treatment effect. Source: ACST-10 Year Data Supplement(6). HR = hazard ratio, CI = confidence interval. (a) Inputs used in base case analysis (b) inputs used in sensitivity analysis

Non peri-operative stroke or death (intention to treat)	Early endarterectomy			Deferral of endarterectomy			HR (95% CI)
	Events (n)	Patient years at risk	Rate per person-year	Events (n)	Patient years at risk	Rate per person-year	
0-5 year (a)	56	6540	0.009	140	6553	0.0214	0.43 (0.29 to 0.62)
5-10 year(a)	43	3042	0.014	48	3003	0.0159	0.89 (0.52 to 1.52)
Average 0-10 year (b)	99	9582	0.0103	188	9556	0.0197	0.54 (0.43 to 0.68).

Table 2. Unit costs for stroke related procedures and events with data sources.

Item	Unit	NHS Tariff 2010/2011	Source
Carotid endarterectomy (base case)	Per procedure	£3345	HRG tariff 2010 - 2011
Carotid endarterectomy (sensitivity analysis)	Per procedure	£4978	Saka 2009(3)
Disabling stroke (first year)	Per event, first year	£29,312	Wardlaw 2006(36)
Disabling stroke (subsequent years)	Per year	£14,846	Sandercock 2002(37)
Non-disabling stroke (first year)	Per event, first year	£4,938	Wardlaw 2006(36)
Non disabling stroke (subsequent years)	Per year	£1,152	Sandercock 2002(37)
Social services, community care and informal care	Per year after disabling stroke	£3,500	Patel 2004(15)

Table 3. Base case analysis of a 68 year old hypertensive, hypercholesterolaemic individual. Cost effectiveness of endarterectomy in all asymptomatic patients following intention to treat analysis. ICER = incremental cost-effectiveness ratio, QALY=quality adjusted life year.

Outcome estimated by the model	Immediate endarterectomy	Delayed endarterectomy	Difference
10- year probability of any stroke or peri-operative death	0.142	0.196	0.054
10- year probability of any non-peri-operative stroke	0.116	0.185	0.069
Life time cost (£)	8496	7855	641
Life years	9.627	9.547	0.090
Quality adjusted life years (QALY)	7.250	7.165	0.085
ICER (incremental cost per QALY ratio)			7584

Table 4. Results of subgroup and exploratory analyses. NC: Not calculated (a negative incremental cost-effectiveness ratio).

Alternative scenario	Cost difference (£)	Difference in quality adjusted life years	Incremental cost-effectiveness ratio (£/QALY)	Interpretation of results
Base case (intention to treat analysis in a population with the same characteristics as ACST)	641	0.085	7584	Early endarterectomy is cost effective compared with deferral
Men younger than 75 years (HR 0.50; 95% CI 0.33 to 0.75)	360	0.115	3254	Early endarterectomy is cost effective compared with deferral
Women younger than 75 years (HR 0.41; 95% CI 0.21 to 0.79)	-746	0.174	NC	Early endarterectomy is less costly and more effective than deferral.
Men older than 75 years (HR 0.63; 95% CI 0.26 to 1.50)	1894	0.026	71 699	Early endarterectomy is not cost effective compared with deferral
Women older than 75 years (HR 1.03; 95% CI 0.42 to 2.53)	2574	-0.065	NC	Early endarterectomy is more costly and less effective than deferral.
Restriction of crossovers	1326	0.131	10149	Early endarterectomy is cost-effective compared with deferral
Peri-operative stroke or death rate of 2.7% and 1.6% any territory background stroke rate	962	0.055	17 384	Early endarterectomy is cost effective compared with deferral

Table 5. Results of deterministic sensitivity analyses

Sensitivity analyses	Cost difference (£)	Difference in quality adjusted life years	Incremental cost-effectiveness ratio (£/QALY)	Interpretation of results
Base case	641	0.085	7584	Early endarterectomy is cost effective compared with deferral
Using average rates of stroke estimated over 0-10 years	582	0.089	6501	Results are similar to the base case
Lower mortality rate post-stroke (as in the Swedish model)	114	0.074	1554	Endarterectomy appears more cost-effective than the base case.
Increased in-hospital cost of surgery	1579	0.085	18677	Endarterectomy appears more costly and less cost-effective than the base case, though still within a threshold of £20,000 per QALY
No treatment effect for CEA after 5 years	763	0.074	10276	Endarterectomy appears less effective and less cost-effective than the base case though still within a threshold of £20,000 per QALY.

Table 6. Probabilistic sensitivity analyses. The inputs in the base-case model are assigned probability distributions to reflect the sampling uncertainty in their estimated values. ICER=incremental cost per QALY.

<u>Outcome estimated by the model</u>	<u>Immediate endarterectomy</u>	<u>Delayed endarterectomy</u>	<u>Difference (95% CI)</u>
Lifetime Cost (£)	8547	7605	942 (-73 to 1936)
Quality adjusted life years	7.244	7.163	0.081 (-0.004 to 0.160)
ICER			11671