



10-year stroke prevention after successful carotid endarterectomy for asymptomatic stenosis (ACST-1): a multicentre randomised trial

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Summary

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Background If carotid artery narrowing remains asymptomatic (ie, has caused no recent stroke or other neurological symptoms), successful carotid endarterectomy (CEA) reduces stroke incidence for some years. We assessed the long-term effects of successful CEA.

Methods Between 1993 and 2003, 3120 asymptomatic patients from 126 centres in 30 countries were allocated equally, by blinded minimised randomisation, to immediate CEA (median delay 1 month [IQR 0·3–2·5]) or to indefinite deferral of any carotid procedure, and were followed up for a median of 9 years (IQR 6–11). The primary outcomes were perioperative mortality and morbidity (death or stroke within 30 days) and non-perioperative stroke. Kaplan-Meier percentages and logrank p values are from intention-to-treat analyses. This study is registered, number ISRCTN26156392.

Findings 1560 patients were allocated immediate CEA versus 1560 allocated deferral of any carotid procedure. The proportions operated on while still asymptomatic were 89·7% versus 4·8% at 1 year (and 92·1% vs 16·5% at 5 years). Perioperative risk of stroke or death within 30 days was 3·0% (95% CI 2·4–3·9); 26 non-disabling strokes plus 34 other events in 1979 CEAs. Excluding perioperative events and non-stroke mortality, stroke risks (immediate vs deferred CEA) were 4·1% versus 10·0% at 5 years (gain 5·9%, 95% CI 4·0–7·8) and 10·8% versus 16·9% at 10 years (gain 6·1%, 2·7–9·4); ratio of stroke incidence rates 0·54, 95% CI 0·43–0·68, $p < 0·0001$. 62 versus 104 had a disabling or fatal stroke, and 37 versus 84 others had a non-disabling stroke. Combining perioperative events and strokes, net risks were 6·9% versus 10·9% at 5 years (gain 4·1%, 2·0–6·2) and 13·4% versus 17·9% at 10 years (gain 4·6%, 1·2–7·9). Medication was similar in both groups; throughout the study, most were on antithrombotic and antihypertensive therapy. Net benefits were significant both for those on lipid-lowering therapy and for those not, and both for men and for women up to 75 years of age at entry (although not for older patients).

Interpretation Successful CEA for asymptomatic patients younger than 75 years of age reduces 10-year stroke risks. Half this reduction is in disabling or fatal strokes. Net benefit in future patients will depend on their risks from unoperated carotid lesions (which will be reduced by medication), on future surgical risks (which might differ from those in trials), and on whether life expectancy exceeds 10 years.

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Introduction

Asymptomatic patients with substantial (eg, 60–90%) carotid artery narrowing but no recent neurological symptoms are at increased long-term risk of ischaemic stroke, especially in parts of the brain supplied by that artery (the ipsilateral carotid territory). Carotid endarterectomy (CEA) can remove the arterial narrowing, but the procedure itself causes some immediate risk of stroke or death.

The first Asymptomatic Carotid Surgery Trial 1 (ACST-1; study protocol on webappendix pp 12–35) randomly assigned patients during 1993–2003 to immediate CEA or deferral of any carotid artery procedure until a more definite indication was thought to have arisen, and followed them up until 2006–08.

In 2004, ACST-1 reported the medium-term benefits of CEA during the first few years after randomisation.¹ (Earlier trials^{2,3} had shorter follow-up.) This Article describes the immediate hazards and 10-year benefits of CEA, subdividing the benefits by participants' characteristics and medical treatment.

Methods

Study design and patients

In asymptomatic patients with substantial carotid artery narrowing, ACST-1 compared immediate CEA versus deferral. All other aspects of treatment were left to the clinician, but usually included long-term antithrombotic therapy, antihypertensive therapy, and, particularly in recent years, lipid-lowering therapy. Use of these

See Online for webappendix

medical treatments was recorded at randomisation and at yearly follow-up. 126 centres in 30 countries took part, each with a neurosurgeon or vascular surgeon (selected as previously described¹) and an independent neurologist or stroke doctor. Ethics approval was obtained both internationally and at each centre, and all patients provided written informed consent.

Patients were eligible if: (1) they had severe unilateral or bilateral carotid artery stenosis (generally carotid artery diameter reduction at least 60%, although there was no fixed minimum percentage); (2) this stenosis had not caused stroke, transient cerebral ischaemia, or any other relevant neurological symptoms in the past 6 months; (3) no circumstance or condition precluded long-term follow-up; and (4) doctor and patient were both substantially uncertain whether to choose immediate CEA or deferral of any CEA. The use of the uncertainty principle to define ACST eligibility is fully described in the study protocol (webappendix pp 18 and 36) and elsewhere.^{1,4}

Randomisation and masking

By use of minimised randomisation, the Clinical Trial Service Unit (CTSU; Oxford, UK) allocated patients equally to immediate CEA or deferral of any carotid surgery. Collaborating doctors telephoned or faxed the patients' identifiers and characteristics to the CTSU. Once these data were entered the patient was irrevocably in the trial, and the CTSU computer then generated a random allocation. This method minimised trial-wide imbalances within groups of age, sex, and percent stenosis, but was not affected by the collaborating doctor's location, so no foreknowledge of the treatment allocation was possible. When definite or probable strokes were reported, the London trial office sought medical records (or death records) through collaborating doctors for blinded review by the endpoints committee. There was no prespecified data analysis plan (except that the protocol-specified aim was to improve stroke-free survival time; webappendix p 14).

Procedures

Carotid artery stenosis was recorded as percentage luminal diameter reduction (assessed with duplex Doppler ultrasound by local criteria, which were generally as defined by the North American Symptomatic Carotid Endarterectomy Trial [NASCET⁵]), and was usually rounded to 60%, 70%, 80%, or 90%. Plaque echolucency was recorded in some patients. During the first few years some also had angiography, but this procedure was not a requirement.

CEA was to be done as soon as routinely possible. Surgeons' normal operative techniques were used; shunting during surgery to maintain perfusion was optional, and anaesthetic technique was decided locally. Patients allocated deferral were not to be treated unless they later developed carotid territory symptoms or some

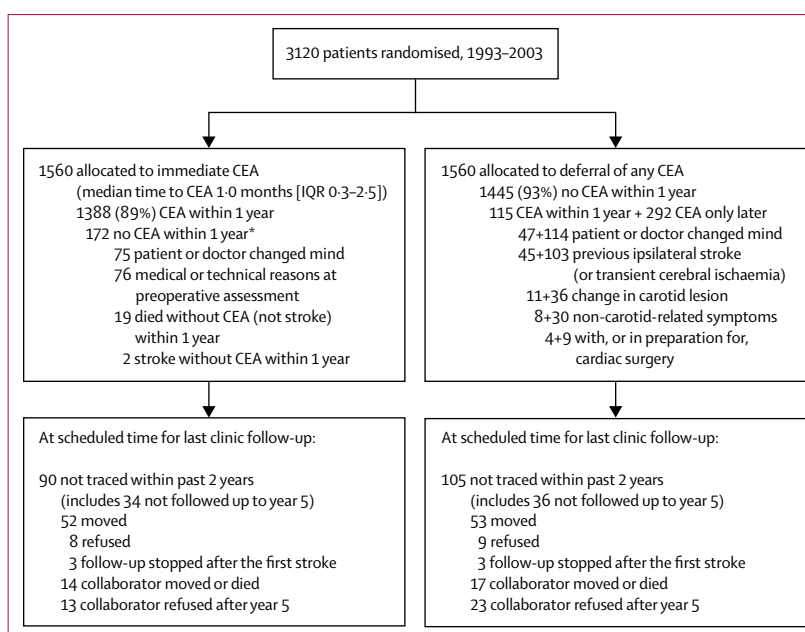


Figure 1: Trial profile

CEA=carotid endarterectomy. *Not 112, as was reported in 2004.

other indication for surgery (or unless the doctor or patient changed their mind). Both groups were to receive appropriate medical care. Postoperatively, patients were assessed before discharge by the independent neurologist or stroke doctor. Tests for silent myocardial infarction were not routinely done. Follow-up was scheduled at 4 months and 12 months, and then yearly until 2006–08, irrespective of any non-fatal strokes. It used forms completed by local doctors for the first 5 years after randomisation, then forms completed centrally from telephone contact with them. Both forms recorded any CEAs, their perioperative morbidity, any strokes or deaths, blood pressure, and current drug treatment (drug type, but not drug name or dose). Yearly carotid ultrasound was requested for only the first 5 years after randomisation. UK patients were flagged with the Office of National Statistics, so death certificates came automatically; elsewhere, mortality reporting was mainly through collaborating hospitals. Enquiries were made about all patients who died to ensure that no strokes had been missed.

Outcome classification

The primary outcomes were perioperative mortality and morbidity (death or stroke within 30 days) and non-perioperative stroke. Copies of post-mortems and brain scan reports were requested centrally from collaborators. The event summary, masked to treatment allocation (even for perioperative events), was sent to the endpoint review committee chair and one other member; disagreements were resolved by discussion. Strokes were classified according to location (ipsilateral, contralateral, vertebrobasilar), cause (haemorrhagic,

probably cardioembolic, other ischaemic [not only large artery but also lacunar, as defined in NASCET³]), and outcome after 6 months (non-disabling, disabling, fatal). Disability was Rankin score 3 or greater (at least moderate disability, needing help in daily affairs); if a patient died of another cause within 6 months, the endpoint committee estimated previous stroke disability from clinical records. Most analyses were of first strokes; analyses of worst strokes counted patients only once, and fatal strokes were those that caused death directly or indirectly (eg, via pulmonary embolism or pneumonia), irrespective of the delay between stroke and death.

Statistical analysis

Information is reported up to year 10, or previous loss to follow-up or death. Kaplan-Meier life-table methods⁵ describe 5-year and 10-year stroke risks in all patients allocated immediate CEA (including the few who did not undergo it) and all allocated deferral (including those eventually operated on). Additionally, analyses are given of procedural risks in patients who actually underwent CEA, plus details of which strokes within the first year were in patients who had not undergone CEA. In ACST, as in other trials of hazardous surgery, early risk may be followed by later benefit, so the overall hazard ratio (immediate CEA *vs* deferral) will undergo gross fluctuation, being unfavourable during the first few months after entry (when most operations are being done) and favourable thereafter. Hence, when comparing life-tables that include early risk and later benefit, standard proportional-hazard methods (which assume no gross fluctuations in hazard ratios) are inappropriate. Some analyses, however, are restricted to non-perioperative strokes, so log-rank *p* values and event rate ratios are appropriate.⁵ If the log-rank observed minus expected (O-E) has variance *V*, the stroke incidence rate ratio is calculated as $\exp([O-E]/V)$. 95% CIs are used for rate ratios and for binomial proportions.⁶

This study is registered, number ISRCTN26156392.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. AH, EH, HP, and RP had full access to all the data in the study, and had final responsibility for the decision to submit for publication.

Results

3120 patients entered the study between April, 1993, and July, 2003, with no significant differences in baseline characteristics between those randomly allocated immediate CEA and deferral.¹ Patients allocated immediate CEA underwent ipsilateral surgery within a median of 1 month (IQR 0.3–2.5; figure 1) of randomisation. Of those allocated deferral, an average of about 4% per year underwent CEA over the next decade

	Immediate CEA (n=1560)	Deferral of any CEA (n=1560)
Surgical compliance		
Number of patients with any CEA	1425 (91.3%)	407 (26.1%)
Proportion with any CEA (%)*		
Within 1 year	89.8%	7.5%
Within 5 years	92.4%	23.5%
Within 10 years	92.5%	34.1%
Proportion with non-symptomatic CEA (%)*		
Within 1 year	89.7%	4.8%
Within 5 years	92.1%	16.5%
Within 10 years	92.2%	23.5%
Proportion with ipsilateral CEA (%)*		
Within 1 year	88.9%	6.9%
Within 5 years	91.5%	21.3%
Within 10 years	91.6%	29.8%
Proportion with contralateral CEA (%)*		
Within 1 year	2.9%	0.8%
Within 5 years	5.5%	4.0%
Within 10 years	7.7%	7.5%
Perioperative mortality and morbidity		
Total number of CEAs†	1532	447
Stroke death	11	2
Cardiac death	5	0
Other death	1	1
Disabling stroke	9	5
Non-disabling stroke	18	8
Non-fatal myocardial infarction	10	1
Any perioperative stroke or death	44	16
% of total number of CEAs (95% CI)	2.9% (2.1–3.8)	3.6% (2.2–5.7)
This table includes only CEAs done within 10 years of randomisation. CEA=carotid endarterectomy *Kaplan-Meier time-dependent percentages; denominators at these times are shown in figure 2. †Ipsilateral or contralateral (bilateral=two CEAs) first or subsequent CEAs.		
Table: Surgical compliance, mortality, and morbidity		

(figure 2). Only about a third (148/407) of these operations were in patients who had had a new ipsilateral stroke or episode of transient cerebral ischaemia; the main other reason was that patients or doctors changed their minds, not that lesions changed (figure 1). Follow-up to death or at least year 3 is now 98% complete (3062/3120), and median follow-up in survivors is 9 years (IQR 6–11).

Of patients allocated deferral, 26% (407/1560) underwent CEA within 10 years (table). The life-table estimate suggests that about a third would eventually have done so, had they survived; by 5 years after randomisation, about 92% versus 16% of those still without symptoms would have undergone CEA (figure 2 and table). Hence, the Kaplan-Meier estimates of the differences in 10-year outcome between those allocated immediate CEA and those allocated deferral

indicate the differences in 10-year outcome that could be expected from operating before symptom onset on only about three-quarters (92% minus 16%) of patients allocated immediate CEA and on none of those allocated deferral.

The perioperative hazards of CEA in patients allocated immediate CEA and in those allocated deferral did not differ significantly (overall risk 3.0% [60/1979], 95% CI 2.4–3.9; table). There was no significant heterogeneity between perioperative hazards in subgroups of age, sex, or extent of stenosis (data not shown), but this apparent homogeneity is not particularly informative since there were only 60 such events. National audits based on much larger numbers would yield more stable estimates of how perioperative hazards depend on patient (and operator) characteristics.

Figure 3 shows 10-year results for all strokes, including perioperative events, and for non-perioperative strokes, excluding mortality from causes other than CEA or stroke. In figure 3A the hazards of surgery are clearly seen, as are the subsequent benefits of successful surgery, and the absolute net benefits that are apparent by year 5 are maintained to year 10. If all patients allocated immediate CEA had undergone it promptly and none of those allocated deferral had undergone CEA unless they had had a stroke or an episode of transient cerebral ischaemia, the overall differences would, in expectation, have been slightly greater. Of the 99 patients allocated immediate CEA who had a non-perioperative stroke, 11 had not yet been operated on when their first stroke occurred; some of these 11 strokes might have been avoided by immediate CEA.

Figure 3B ignores perioperative events, assessing the effects of treatment allocation only on non-perioperative strokes. The non-perioperative stroke incidence rate during the first 5 years was approximately halved in patients allocated immediate CEA, and the absolute difference in risk at year 5 was still apparent at year 10.

The ratio of non-perioperative stroke rates in patients allocated immediate CEA versus those allocated deferral was 0.54 (95% CI 0.43–0.68, $p < 0.0001$), corresponding, on average, to a 46% reduction in the stroke incidence rate. In webappendix p 7 the result is subdivided by the outcome of the worst stroke, and by the territory and cause of the first stroke. More than half of the patients with stroke (166/287) died of or were disabled by stroke, and the proportional reduction in disabling or fatal stroke seemed to be similar to that for any stroke. For strokes of known laterality, the greatest absolute reduction was in ipsilateral strokes (38 vs 92 events, RR 0.43 [0.28–0.68], $p < 0.0001$), but there was also a significant reduction in other strokes (39 vs 64 contralateral and 11 vs 23 vertebrobasilar). The reduction in contralateral strokes was separately significant ($p = 0.01$), was not attributable to any substantial difference in the use of contralateral CEA, and was largely independent of previous contralateral carotid symptoms or patency.

The small numbers of haemorrhagic and of probably cardioembolic strokes did not seem to be affected by CEA (webappendix p 7). The main effect, as expected, was on ischaemic stroke (43 vs 104, including seven vs 24 classified as definitely lacunar).

The absolute effect of halving the background stroke rate depends on what that background rate would have been without surgery, which depends on what long-term medical treatments are used. Figure 4 shows, by year, the proportions on various types of medical treatment (irrespective of whether patients were receiving those treatments when they entered the study). Long-term medical therapy did not differ significantly between the two groups (figure 4). Use of antihypertensive drugs increased during the study, whereas diastolic blood pressure decreased (from 84.0 mm Hg [SD 10] in 1995 to 77.5 mm Hg [SD 11] in 2005). Antithrombotic drug use (mainly aspirin) was common throughout the study, but use of lipid-lowering drugs increased from less than 10% to more than 80% (figure 4). Webappendix p 8 subdivides non-perioperative strokes not only by the randomly allocated surgical treatment but also by what long-term medical treatment the patient was receiving at the time of the stroke (ie, what treatment the patient was receiving at the last follow-up before the stroke). The stroke rate ratio (CEA vs not) seemed to be similar for patients on lipid-

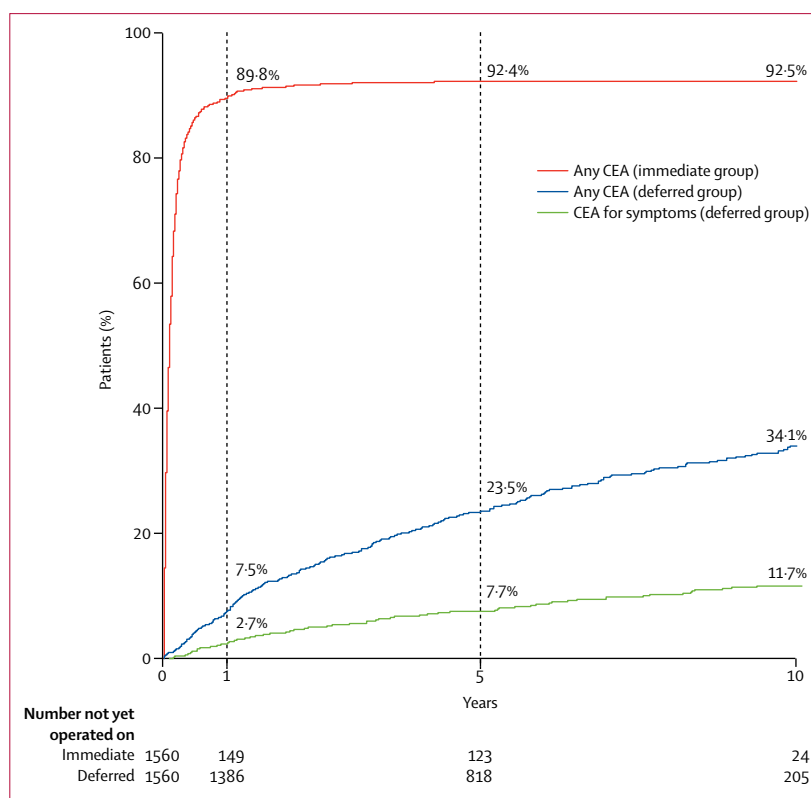


Figure 2: Allocated and actual use of CEA
CEA=carotid endarterectomy.

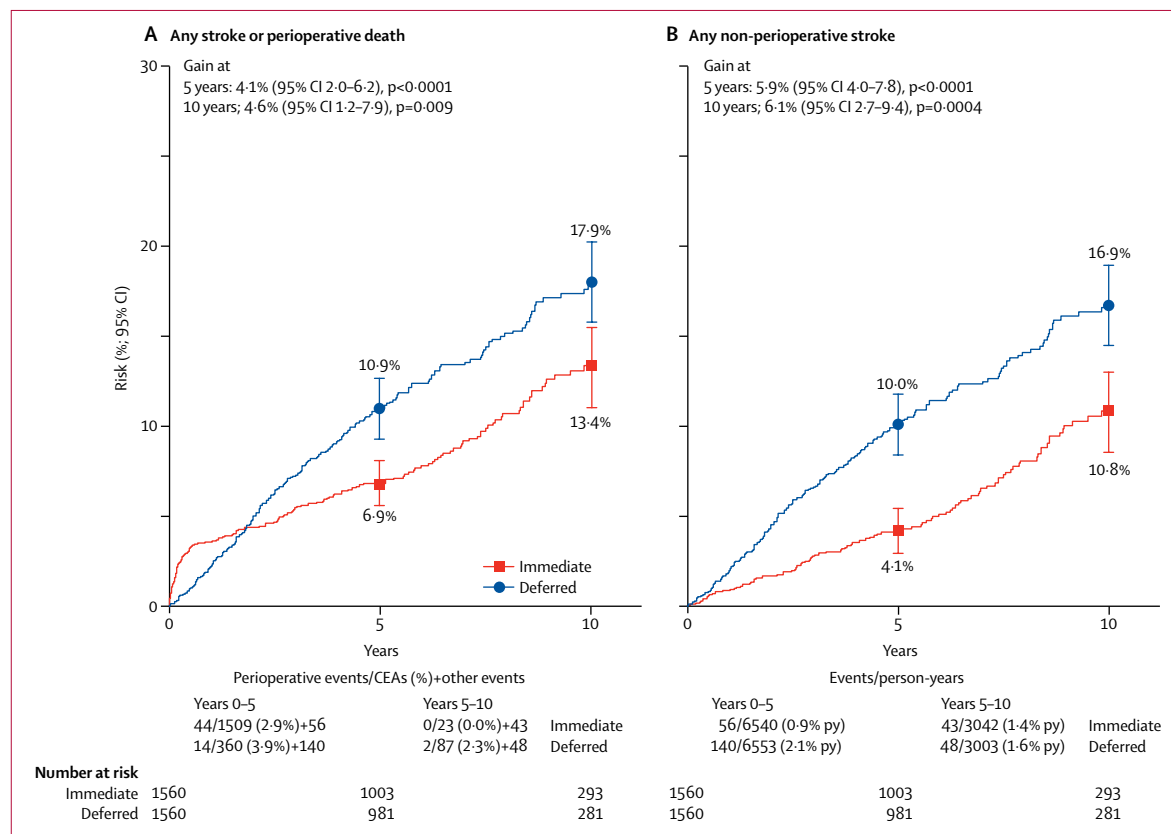
lowering therapy and those not, but because the absolute stroke rates were lower in those on lipid-lowering therapy, the absolute difference in the stroke incidence rate produced by allocation to immediate CEA was not as great (0.7 vs 1.3% per year [$p<0.0001$] for those currently on lipid-lowering therapy, and 1.8 vs 3.3% per year [$p<0.0001$] for those not; webappendix p 8). Figure 5 shows the estimated effects on 10-year outcome (in patients who do not die from other causes within the first 10 years), analysing stroke rates according to both the allocated surgical treatment and current lipid-lowering therapy. The event rates in patients on lipid-lowering therapy suggest somewhat lower perioperative risks and lower absolute benefits, but still with a significant reduction in net risk at year 10 (figure 5A).

Webappendix p 9 further subdivides non-perioperative stroke rates by time since entry (white squares) and by patient characteristics at entry (black squares). As already noted, the main gains were during the first 5 years after entry, but there was no evidence that these early gains were lost in later years. The other subgroup analyses do not provide good evidence that the proportional risk reductions depend on initial patient characteristics (webappendix p 9). That does not mean the proportional risk reductions really are all identical, only that there is no trustworthy evidence of heterogeneity.

Consider, for example, the age-specific effects of treatment allocation. The protective effects were significant both for men and for women younger than 75 years of age at entry (figure 6), but not for older patients (webappendix p 9). This apparent heterogeneity of effect could, however, have been due mainly to chance. If it was, then the overall results (figures 3 and 5) might provide the best guide as to what to expect in men or women of any age, if mortality from causes other than stroke is ignored. At entry, however, the older patients were, on average, 78 years of age, so within 10 years most of them would have died from causes other than stroke (webappendix p 11, which also shows that about 90% of all deaths in this study were not from stroke—indeed, there were almost five times as many deaths from other vascular diseases as from stroke). Thus, expected 10-year gains would be greatly curtailed by intercurrent mortality in older patients, and somewhat curtailed even in younger ones.

Combining perioperative or stroke mortality and other mortality, the total number of deaths within 10 years was not significantly lower in patients allocated immediate CEA than in those allocated deferral of any CEA (17 vs three perioperative deaths [including 11 vs two from stroke], 39 vs 68 other stroke deaths [$p=0.006$], 298 vs 267 other vascular deaths [$p=0.15$], 111 vs 101 cancer deaths [$p=0.44$], and 145 vs 131 other deaths [$p=0.33$]; webappendix p 11). After year 10, there were a

Figure 3: 10-year risk of any stroke or perioperative death (A) and any non-perioperative stroke (B)
After year 10 there were no perioperative strokes and four immediate versus seven deferred first strokes.
CEA=carotid endarterectomy.
py=per year.



further three stroke deaths in each group and 48 versus 54 other deaths.

An apparently greater proportional risk reduction was recorded in patients with high cholesterol, mainly because prerandomisation cholesterol seemed (perhaps by chance) to be inversely related to the stroke rate in those allocated immediate CEA (webappendix p 9), but this finding was

based on fairly small numbers of strokes. Among those allocated deferral, the patient characteristics recorded at entry (including age, sex, cholesterol, blood pressure, plaque echolucency, and extent of stenosis) seemed to be of remarkably little relevance to subsequent stroke rates (webappendix p 9), which depended only on whether they were currently on lipid-lowering therapy (figure 5).

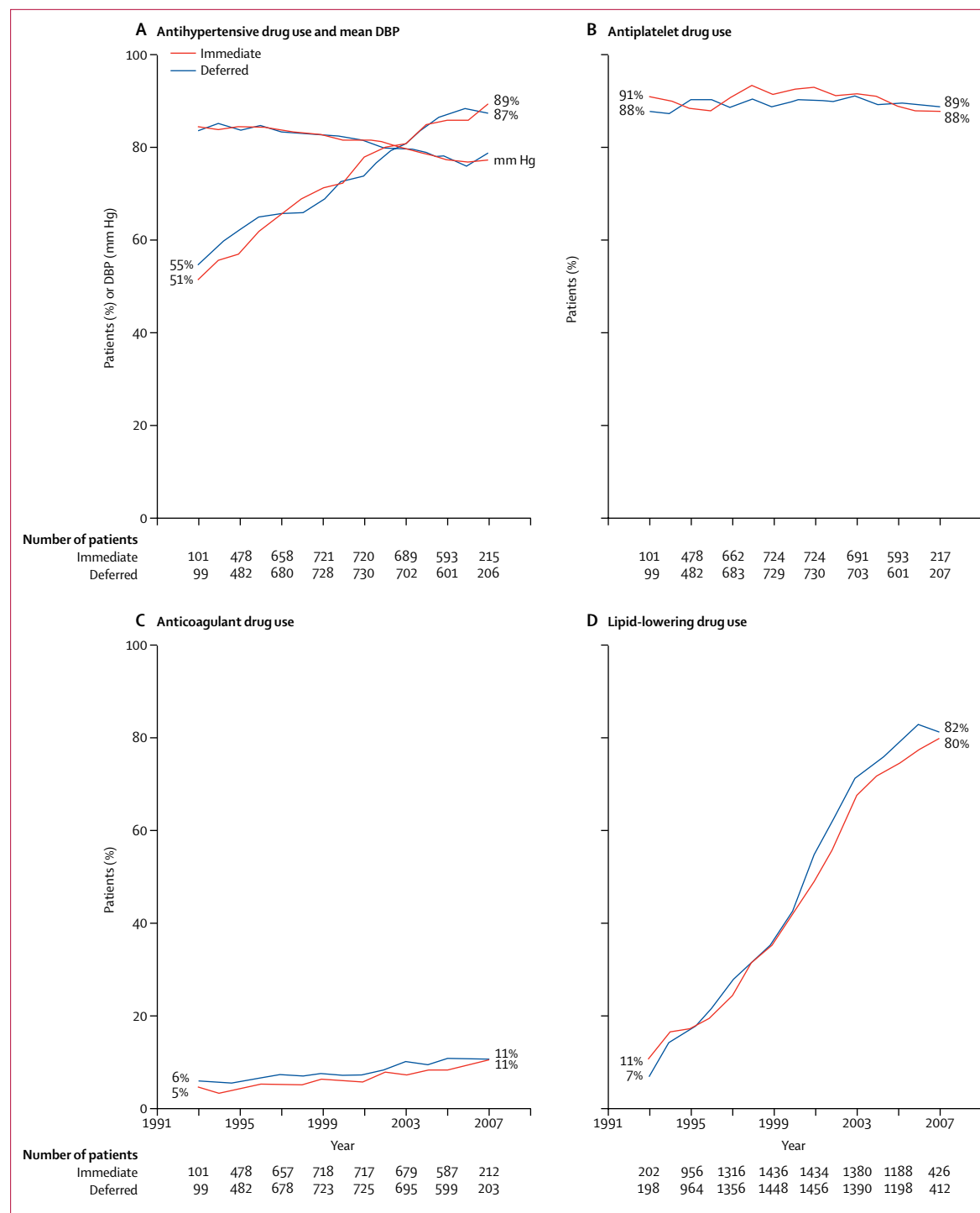


Figure 4: Current use (at or after randomisation) of various medical treatments by year of follow-up and by original treatment allocation (to immediate or deferred CEA)
CEA=carotid endarterectomy.
DBP=diastolic blood pressure.

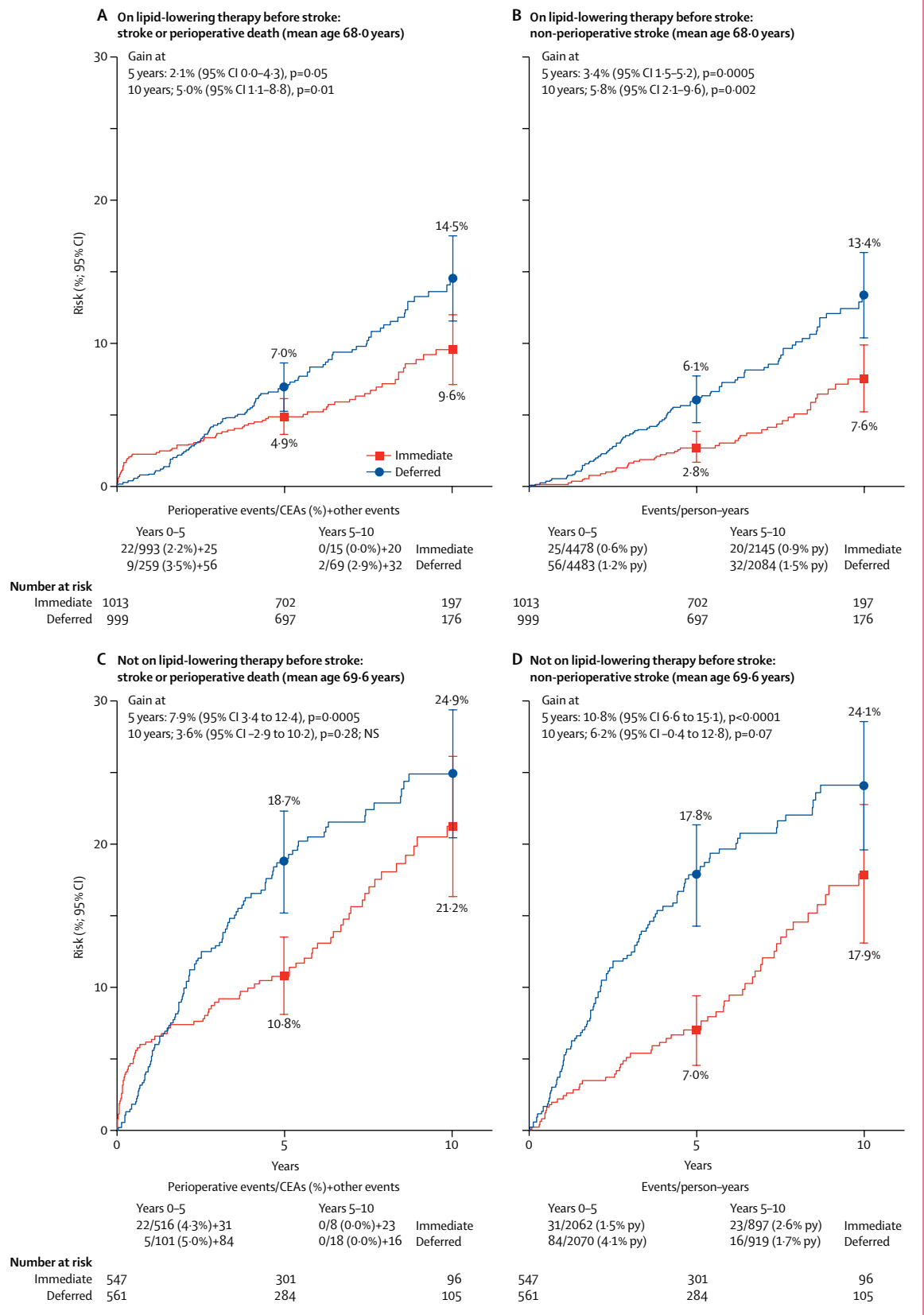


Figure 5: 10-year risks, by current lipid lowering therapy (at or after randomisation)
CEA=carotid endarterectomy.
py=per year.

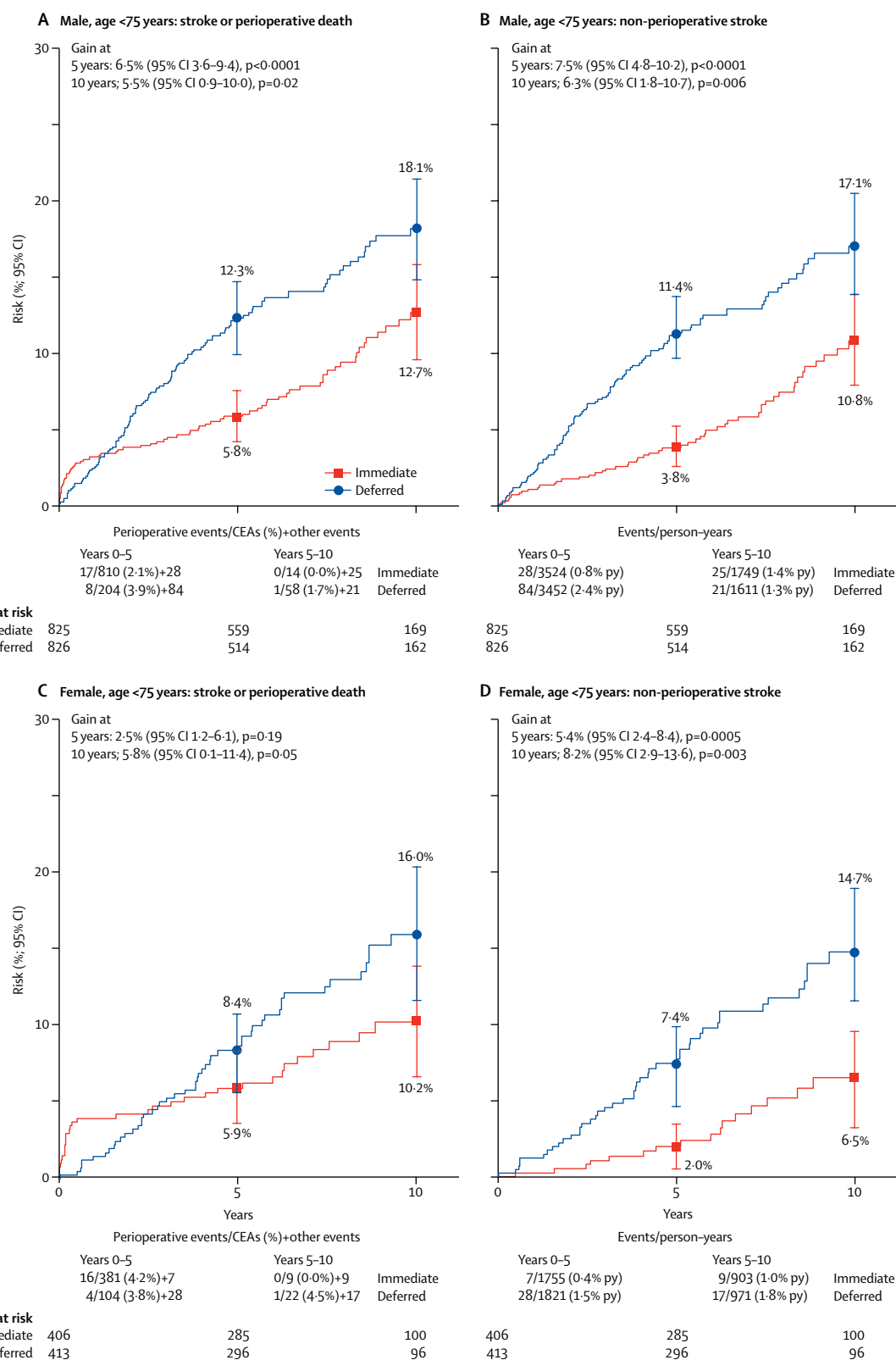


Figure 6: 10-year risks for men and women younger than 75 years of age (mean 66) at entry
CEA=carotid endarterectomy.
py=per year.

Discussion

ACST-1 recruited more than 3000 patients with severe carotid artery stenosis that had not yet caused symptoms, randomly allocated them to immediate CEA or to deferral of any carotid procedure, and followed them up for a median of 9 years, which is much longer than in any previous trial reports.¹⁻³ CEA caused some risk of perioperative stroke or death, but allocation to immediate CEA almost halved the non-perioperative stroke rate over the next 10 years. The characteristics recorded at entry of the patients and their carotid lesions were of little relevance to subsequent stroke rates, or to the effect of CEA. The effect of CEA was only on ischaemic strokes (including lacunar strokes, but not cardioembolic strokes); although the main effect was on ipsilateral stroke, contralateral stroke was also reduced, presumably through mechanisms involving the circle of Willis.

During the trial, no differences in medical management were recorded between the two treatment groups. Most patients were on long-term antihypertensive and antithrombotic therapy. The population not on such therapy was too small to study separately, but that is not an important limitation because these treatments are effective and continue to be used widely. Nowadays, lipid-lowering therapy is also used widely, but it was not in 1993, when ACST-1 began. In ACST, the proportion of patients on lipid-lowering therapy rose from less than 10% in 1993 to more than 80% when follow-up ended in 2006–08. Both for patients on lipid-lowering therapy and for those not, allocation to immediate CEA roughly halved the non-perioperative stroke rate (webappendix pp 8 and 9). These two results are separately significant, and reinforce each other. However, because those on lipid-lowering therapy had lower stroke incidence rates, the absolute benefit from successful CEA is correspondingly smaller for them than for others (figure 5).

Appropriate generalisation of results from surgical trials to future practice is indirect, because trial results do not directly assess risks or benefits for future patients. The procedural hazards in this trial (or in other particular case series) might well differ from the hazards of CEA in future non-trial circumstances. Assessment of CEA risks in routine surgical practice will need large-scale, long-term audits that continue to monitor perioperative morbidity in many hospitals in many countries. Audits can, if large enough, relate the hazards to the characteristics of the patient or lesion. The present report of 60 perioperative events in fewer than 2000 individuals makes only a small contribution to this monitoring of hazards, and cannot assess reliably the dependence of risk on patient characteristics. We note, however, that the 3% morbidity rate in this series is similar to that for both men and women in some audits.^{7,8} The suggestion that procedural risks might be lower for patients on lipid-lowering therapy also needs to be confirmed in series much larger than ours.⁹⁻¹¹

Expected benefits depend on the likelihood that an unoperated asymptomatic lesion will eventually cause a serious stroke, and this risk can be substantially reduced by long-term medication, thereby reducing the expected benefits of surgery. These expected benefits also depend on the likelihood of death from unrelated causes over the next 10 years (which, considered separately, do not depend significantly on treatment allocation but do depend strongly on age; webappendix p 11). For men and for women on moderately good long-term antihypertensive, antithrombotic, and lipid-lowering drugs, the 10-year stroke rates in the absence of other causes of death might be about as in figures 5A and 5B. If, however, there was more than a 50% chance of dying from other causes within 10 years (as for those who were older than 75 years at entry to the study), this absolute 10-year benefit would be reduced by more than half, while leaving the surgical risk unchanged. Although good antihypertensive therapy would have further improved blood pressure control (figure 4) and modern statin regimens can reduce occlusive vascular event rates by more than a third,¹²⁻¹⁴ patients with tight carotid stenosis cannot have the risk from it completely abolished by medical treatment alone. Hence, successful surgery could still usefully add to the effects of good medical therapy, especially in patients who would otherwise have more than 10 years of reasonable life expectancy.

Despite the increasing availability of newer methods, the duplex ultrasound techniques used in this trial are still representative of much current practice. The extent of stenosis indicated by them was, somewhat surprisingly, of little relevance to long-term stroke risk, either in this study or in the largest other such trial.² Stenosis was recorded with strong digit preference, generally as 60%, 70%, 80% or 90% (with few values less than 60% and none greater than 99%). Although more moderate degrees of stenosis might, if untreated, also be associated with substantial hazard, ACST-1 did not study them. Factors associated with plaque rupture are incompletely understood; although moderately stenotic asymptomatic plaques can rupture, causing symptoms, they may remain unchanged for many years.^{15,16} Our measures of plaque echolucency were of little predictive value. Future non-invasive techniques might, however, establish more reliably which asymptomatic lesions are particularly risky, which could greatly improve patient selection for CEA (or for carotid stenting; CREST,¹⁷ SPACE-2,¹⁸ and ACST-2^{19,20} are now comparing carotid stenting *vs* carotid surgery; see webappendix p 36).

Calculations of the cost-effectiveness of CEA and of the number of patients that need to be treated to avoid one stroke should consider separately patients with short life expectancy and those with more than 10 years of reasonable life expectancy, because the potential long-term benefits of CEA are sharply curtailed in those who have less than 10 years of life expectancy.

Conversely, figure 5A (reinforced by the results in other subgroups) suggests that, in patients with effective antihypertensive, antithrombotic, and lipid-lowering therapy and with little likelihood of death from other causes within 10 years, the absolute 10-year stroke reduction would be about 5%. If so, the number needed to treat to avoid one stroke would be about 20. Allowance for non-compliance might reduce this number to about 15 (because 92% rather than 100% underwent early CEA, and by year 5 about 16% of those allocated deferral had undergone elective CEA). Conversely, appropriate allowance for intercurrent mortality from unrelated causes would increase the number needed to treat, so in patients older than 75 years little net benefit might be expected. For otherwise healthy men and women younger than 75 years, however, the results from this trial suggest net benefit from CEA, as long as perioperative risks remain low.

Contributors

AH (principal investigator), MH, AM, RP, and DT designed the study. All authors participated in study conduct or long-term follow-up of patients. AH, EH, HP, and RP did the analysis and drafted the report, which all authors revised.

ACST collaborative group

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Conflicts of interest

We declare that we have no conflicts of interest.

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