Articles

Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial

*MRC Asymptomatic Carotid Surgery Trial (ACST) Collaborative Group**

Summary

Background Among patients with substantial carotid artery narrowing but no recent neurological symptom (stroke or transient ischaemia), the balance of surgical risks and long-term benefits from carotid endarterectomy (CEA) was unclear.

Methods During 1993–2003, 3120 asymptomatic patients with substantial carotid narrowing were randomised equally between immediate CEA (half got CEA by 1 month, 88% by 1 year) and indefinite deferral of any CEA (only 4% per year got CEA) and were followed for up to 5 years (mean 3·4 years). Kaplan-Meier analyses of 5-year risks are by allocated treatment.

Findings The risk of stroke or death within 30 days of CEA was 3·1% (95% CI 2·3–4·1). Comparing all patients allocated immediate CEA versus all allocated deferral, but excluding such perioperative events, the 5-year stroke risks were 3·8% versus 11% (gain 7·2% [95% CI 5·0–9·4], p<0·0001). This gain chiefly involved carotid territory ischaemic strokes (2·7% *vs* 9·5%; gain 6·8% [4·8–8·8], p<0·0001), of which half were disabling or fatal (1·6% *vs* 5·3%; gain 3·7% [2·1–5·2], p<0·0001), as were half the perioperative strokes. Combining the perioperative events and the non-perioperative strokes, net 5-year risks were 6·4% versus 11·8% for all strokes (net gain 5·4% [3·0–7·8], p<0·0001), 3·5% versus 6·1% for fatal or disabling strokes (net gain 2·5% [0·8–4·3], p=0·004), and 2·1% versus 4·2% just for fatal strokes (net gain 2·1% [0·6–3·6], p=0·006). Subgroup-specific analyses found no significant heterogeneity in the perioperative hazards or (apart from the importance of cholesterol) in the long-term postoperative benefits. These benefits were separately significant for males and females; for those with about 70%, 80%, and 90% carotid artery narrowing on ultrasound; and for those younger than 65 and 65–74 years of age (though not for older patients, half of whom die within 5 years from unrelated causes). Full compliance with allocation to immediate CEA or deferral would, in expectation, have produced slightly bigger differences in the numbers operated on, and hence in the net 5-year benefits. The 10-year benefits are not yet known.

Interpretation In asymptomatic patients younger than 75 years of age with carotid diameter reduction about 70% or more on ultrasound (many of whom were on aspirin, antihypertensive, and, in recent years, statin therapy), immediate CEA halved the net 5-year stroke risk from about 12% to about 6% (including the 3% perioperative hazard). Half this 5-year benefit involved disabling or fatal strokes. But, outside trials, inappropriate selection of patients or poor surgery could obviate such benefits.

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Introduction

Patients with substantial (eg, 60–99%) carotid artery narrowing are at increased risk of suffering a disabling or fatal ischaemic stroke in the carotid territory of the brain. The hazard is greater if they are already symptomatic (ie, have recently suffered some relevant neurological symptom, such as stroke or transient cerebral or retinal ischaemia) in the parts of the brain supplied by the carotid arteries (the carotid territory). Carotid endarterectomy (CEA) can remove arterial narrowing, but the surgical procedure itself involves some immediate risk of perioperative death or stroke. Moreover, even successful CEA might not permanently eliminate all thromboembolic risk. Hence, the balance of risk and long-term benefit is uncertain, particularly for fatal and disabling strokes.

Several major randomised trials of CEA, some in symptomatic[1,2] and some in asymptomatic[3–5] (those who have had no relevant neurological symptoms) patients, have attempted to address the net effects of CEA on the risks of suffering a major stroke. In 1991, the European and North American carotid surgery trials (ECST[1] and NASCET[2]) demonstrated the net long-term benefits of CEA for symptomatic patients with severe carotid artery narrowing. There has remained, however, much uncertainty about the net benefits of CEA for asymptomatic patients, despite promising results in 1993 and 1995 from two US trials (VA[3] and ACAS[5]), which showed significant reductions in the incidence of transient cerebral ischaemia[3] or non-disabling stroke,[5] but not of fatal or disabling stroke.

The international Asymptomatic Carotid Surgery Trial (ACST)[4] was set up in 1993 with the aim of being large enough (and, eventually, having long enough follow-up) to assess the net long-term effects of CEA on overall stroke risk and on fatal or disabling stroke among patients with substantial carotid artery narrowing, but with no relevant neurological symptoms in the previous 6 months. Randomisation in ACST ended after 10 years, but long-term follow-up will continue for several more years. The present report of the ACST results describes the hazards and the medium-term benefits of CEA (analysed both separately and together) during just the first 5 years after randomisation.

*Collaborators listed at end of report

Correspondence to: Alison Halliday, Consultant Vascular Surgeon, ACST Office, St George's Hospital Medical School, London SW17 0RE, UK
(e-mail: acst@sghms.ac.uk)

Methods

ACST is a multicentre randomised trial among asymptomatic patients with substantial carotid artery narrowing, comparing immediate CEA versus deferral of any CEA until a definite indication was thought to have arisen. All other aspects of the management of the patients were left to the discretion of the clinician, and usually included antiplatelet therapy, antihypertensive treatment, and, in recent years, lipid-lowering therapy.

Selection of surgical and medical collaborators

126 hospitals in 30 countries took part in ACST. At every centre there was to be at least one vascular surgeon or neurosurgeon and one neurologist or stroke doctor collaborating in the trial. Potential surgical collaborators were first asked to submit a record of their last 50 carotid endarterectomies (most of which would have involved patients who had had relevant neurological symptoms). For the surgeon to be eligible, not more than three of these (6%) could have involved stroke or death within 30 days of surgery. If, during the trial itself, an individual surgeon had had an unacceptably high morbidity or mortality rate (as judged by the ACST endpoint review committee) then that surgeon would have been asked not to enter any further patients, but this situation never arose. Ethics approval was obtained at every collaborating centre and at the international coordinating centre.

Eligibility of patients

Patients from medical or surgical clinics were eligible for ACST if (1) they had unilateral or bilateral carotid artery stenosis that was considered to be severe (carotid artery diameter reduction of at least 60% on ultrasound), (2) this stenosis had not caused any stroke, transient cerebral ischaemia, or other relevant neurological symptoms in the past 6 months, (3) both doctor and patient were substantially uncertain[6,7] whether to choose immediate CEA, or deferral of any CEA until a more definite need for it was thought to have arisen, and (4) the patient had no known circumstance or condition likely to preclude long-term follow-up.

Exclusion criteria included previous ipsilateral CEA, an expectation of poor surgical risk (eg, because of recent acute myocardial infarction), some probable cardiac source of emboli (because the main stroke risk might then be from cardiac, not carotid, emboli), or any major life-threatening condition other than carotid stenosis. Thus, patients likely to require joint CEA and coronary artery bypass grafting were not randomised.

The local collaborating neurologist or stroke doctor was asked to confirm that every patient had no history of disabling stroke and had been neurologically asymptomatic for at least the past 6 months (although patients with minor neurological signs were still eligible provided there were no neurological symptoms in response to specific questioning). Informed consent was obtained before randomisation.

Assessment of carotid lesions

The degree of carotid artery stenosis recorded at randomisation was based on carotid duplex ultrasound. It was reported as the percentage luminal diameter reduction (assessed by locally validated criteria,[4] and generally rounded to 60%, 70%, 80%, or 90%). Although during the first few years of the study some patients also had angiography, this procedure was not an ACST requirement, and few did so in later years. In about half the patients, plaque echolucency was also estimated.

Randomisation, treatment, and follow-up

Entry was by telephone or fax to a service provided by the Clinical Trial Service Unit (CTSU) in Oxford, UK, that recorded age, sex, history of hypertension, diabetes, previous contralateral symptoms or CEA, previous ipsilateral symptoms more than 6 months before, percentage carotid stenosis on each side, an estimate of plaque echolucency (if available), and current drug treatment (antiplatelet, anticoagulant, antihypertensive, or lipid-lowering). The patient was then allocated by minimised randomisation[8] to immediate ipsilateral CEA or to deferral of any carotid surgery.

For those allocated immediate CEA, this procedure was to be carried out routinely as soon as possible, using the surgeon's normal operative techniques. Shunting during surgery to maintain perfusion of the carotid territory of the brain was optional. Anaesthetic technique was also left to individual centres. Patients allocated deferral of any CEA were not to be operated on unless they subsequently had carotid territory symptoms or unless some other definite indication for surgery was thought to have arisen. Patients in both groups were to receive appropriate medical care, which generally included antiplatelet therapy, antihypertensive treatment, and, increasingly in recent years, lipid-lowering therapy.

Patients who had undergone CEA were to be assessed neurologically before discharge by the collaborating doctors, many of whom were neurologists. No tests for silent perioperative myocardial infarction were to be performed routinely. Any perioperative stroke, myocardial infarction, or death was to be reported promptly. Otherwise, follow-up reports were at 4 months after randomisation, at 12 months, and yearly thereafter (continuing irrespective of any non-fatal strokes). Follow-up data included any CEAs, their operative morbidity, any strokes or deaths, current drug treatment, and blood pressure. UK patients were flagged with the Office of National Statistics, so any death certificates were sent automatically to the ACST office: elsewhere, mortality follow-up was chiefly through the collaborating hospitals. Inquiries were made about patients who died to ensure any strokes were recorded. If patients were thought to have had a stroke, a neurological assessment (including CT or MRI scan) was to be carried out promptly. Collaborators were asked wherever possible to repeat the duplex doppler ultrasound examination of both carotid arteries at every follow-up visit up to 5 years.

Trial outcomes and stroke classification

The main trial outcomes were perioperative mortality and morbidity (stroke and myocardial infarction) and the incidence of non-perioperative stroke (particularly in the carotid territory of the brain). When patients died, or appeared to have suffered a stroke, copies of clinically relevant data such as post-mortem and brain scan reports were requested and a summary of the event, masked (even for perioperative events) to treatment allocation, was sent to the chair and one other member of the endpoint review committee. Any disagreements were resolved by discussion. Strokes were classified according to their probable location (ipsilateral, contralateral, vertebrobasilar), nature (haemorrhagic or ischaemic: a few of the latter were, based only on the cardiac risk factor criteria used by NASCET,[2] classified as probably cardioembolic), and eventual consequences (non-disabling, disabling, or fatal).

A non-disabling stroke was one that after 6 months would be associated with a modified Rankin score[9] of 0,

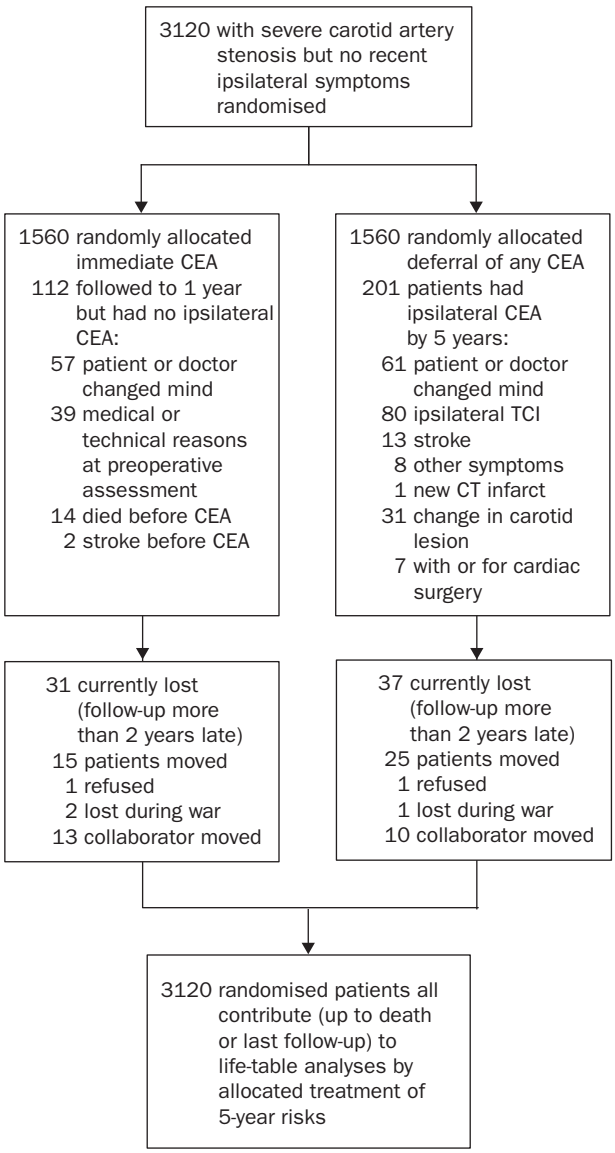

Figure 1: **Trial profile**

1, or 2 (ie, at most only slight disability from the index stroke, perhaps unable to carry out some previous activities, but no need for assistance in daily affairs). A disabling stroke was one that at 6 months had a score of 3, 4, or 5 (ie, at least moderate disability from the index stroke, with the need for some help in daily affairs). If the patient died of another cause within 6 months of the stroke, a clinical estimate of the probable future disability from the original stroke was made. A fatal stroke was one considered by the endpoint review committee to have eventually caused the death of the patient, either directly or by some non-neurological complication (eg, pulmonary embolism or pneumonia), irrespective of the delay between stroke and death. Perioperative events included all strokes and deaths that occurred within 30 days of CEA (but, although the perioperative strokes were all recognised soon after surgery, a few took more than 30 days to prove fatal).

Statistical methods

The main analyses involved Kaplan-Meier life-table methods[10] to assess the 5-year stroke risks among all those allocated immediate CEA (including the few who did not undergo it) and all those allocated deferral of any CEA (including the few who were eventually operated on). Information was included only up to year 5, or to the time of death from another cause (or, for survivors, the time of last follow-up).

In ACST, as in any trials of hazardous surgery, the early risk may be followed by later benefit. If so, the hazard ratio (treatment *vs* control) will undergo gross fluctuation, being very unfavourable during the first few months after randomisation, when most of the operations are being done, and favourable thereafter. Hence, for comparing two survival curves that include early risk and later benefit, standard proportional-hazard methods (which assume an approximately constant hazard ratio) or logrank tests are not appropriate.[10] The main statistical tests therefore involve comparisons between the 5-year probabilities of stroke (in the absence of other causes of death) in the two treatment groups. Some of these analyses included perioperative events (stroke or death within 30 days of CEA) and any other strokes within 5 years, but others were restricted to just the non-perioperative strokes (and excluded any perioperative events and the subsequent experience of those who had suffered them). For the latter analyses the logrank observed minus expected and its standard error, s, could have been used, but instead the absolute difference between the 5-year risks is cited, along with its own standard error, or its 95% CI (both calculated from the variances of the 5-year risks: the standard error of the log of the ratio of these risks was approximated by $1/s$).

During the study, unmasked interim analyses were supplied regularly to the data monitoring committee, as specified in the trial protocol.[4] The interim results did not justify premature disclosure, and recruitment continued until 2003, when the preliminary results were presented for discussion.

Role of the funding sources

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

3120 patients were randomised between April, 1993, and July, 2003, from 126 centres in 30 countries. 1560 were allocated to immediate CEA and 1560 to deferral

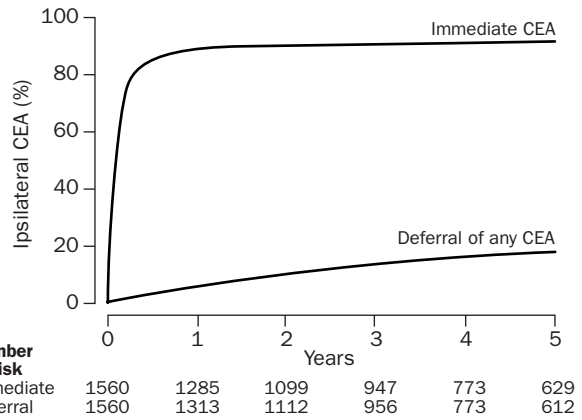

Figure 2: **Proportion with ipsilateral CEA by time from randomisation in ACST, with numbers alive and still under observation at various times**

	Allocated immediate CEA (n=1560)	Allocated deferral of any CEA (n=1560)
Surgical compliance		
Number of patients with any CEA	1348	229
Proportion (life-table) with CEA (%)		
Within 1 year	89·3%	6·9%
Within 5 years	91·8%	20·0%
Contralateral CEA	69	44
Proportion (life-table) with CEA (%)		
Within 1 year	2.9%	0.8%
Within 5 years	5.7%	3.9%
Ipsilateral CEA	1336	201
Proportion (life-table) with CEA (%)		
Within 1 year	88·5%	6.2%
Within 5 years	91·1%	17·7%
Number (%) with ipsilateral CEA preceded in trial by ipsilateral symptoms [stroke+TCI]*	7 [1+6] (0·5%)	93 [13+80] (46·3%)
Perioperative mortality and morbidity (ie, within 30 days of CEA)		
Stroke deaths†	10	2
Disabling strokes	9	3
Non-disabling strokes	16	6
Cardiac deaths	5	0
Non-fatal myocardial infarctions	10	0
Other deaths	0	0
Any perioperative stroke or death	40	11‡
% of number of CEAs	2·8%	4·5%
(95% CI)	(2·0–3·9)	(2·2–8·0)

TCI=transient cerebral ischaemia. *Of these 14 strokes, one versus 11 were ipsilateral. †Of these 12 strokes, none versus two caused death more than 30 days after CEA. ‡Seven had been operated on for ipsilateral symptoms (one stroke, six TCI), one in conjunction with cardiac surgery, and three because the doctor or patient changed their mind.

Table 1: **Surgical compliance, mortality, and morbidity during first 5 years after randomisation**

of any CEA (figure 1). Because minimised randomisation[8] was used, there are no significant differences between the initial characteristics of the two groups (see below).

Compliance

Figure 2 and table 1 show time from recruitment to ipsilateral surgery (which is partly determined by non-compliance). Among those allocated immediate CEA, half had had ipsilateral surgery by 1 month after randomisation, 88% by 1 year, and 91% by 5 years. Among those allocated deferral of any CEA, about 4% per year underwent ipsilateral surgery (6% by 1 year and 18% by 5 years). From figure 2, it can be seen that by the middle of the 5-year period, about 90% of those allocated immediate CEA and about 10% of those allocated deferral would have undergone ipsilateral surgery. Hence, the intention-to-treat analyses that will be presented of the numbers of non-perioperative strokes during the whole 5-year period can be thought of as comparing the effects of operating on about 90% versus operating on only about 10% of such patients.

Among those allocated immediate CEA, the main reason for not undergoing surgery was that the patient eventually changed their mind, but in 39 cases the surgeon decided against surgery after the preoperative assessment. Another two had a disabling stroke and 14 died from unrelated causes within the first few months, forestalling their CEA.

Among those allocated deferral, 201 actually underwent ipsilateral CEA within 5 years, and the life-table estimate in table 1 suggests that 18% would eventually do so, if they survived. But, only 61 of these 201 operations were because the patient changed their mind, and life-table methods indicate that only about 5% would do this within 5 years if they survived, corresponding to 95% compliance. The remaining 140 were for medical reasons (figure 1), and those patients are therefore still compliant with their original allocation to deferral of any CEA.

Surgical hazards

Table 1 shows surgical mortality and morbidity. For those allocated immediate surgery, the median time from randomisation to surgery was only 1 month, so almost all were still neurologically asymptomatic when operated on. In this group, 1348 patients underwent a total of 1405 procedures, and the risk per CEA of perioperative stroke or death was 2·8%. Among those allocated deferral of any CEA, 229 patients underwent a total of 245 CEAs within 5 years of randomisation (half of which were because of the occurrence of neurological symptoms after randomisation), and the risk per CEA of perioperative stroke or death was 4·5%. These risks are not significantly different, and overall the risk per CEA of perioperative stroke or death was 3·1% (95% CI 2·3–4·1). This risk was not attributable to poor results at a few centres: the 51 perioperative events were distributed among 39 centres, none of which had risks significantly higher than 3%. Although perioperative strokes were defined to be those within 1 month of surgery, almost all were diagnosed at the time of surgery or within the first few days of surgery (although two of these caused death more than a month after they occurred). The webtable (http://image.thelancet.com/extras/04art3083webtable.pdf) shows analyses of the risks of perioperative stroke or death in various subgroups (sex, age, degree of stenosis, etc). In no case is there significant heterogeneity of risk, but since the total number of events is only 51, this apparent homogeneity is not particularly informative.

Hazards and benefits

Figure 3 shows the main 5-year results for all strokes (including perioperative events) and for non-perioperative strokes, subdivided by the severity of the stroke. In the results for all strokes (figure 3A), the early hazards of being allocated immediate surgery are clearly seen, as are the subsequent benefits of successful surgery. Most of these surgical hazards occur within the first few months (when most of the immediate surgery takes place), after which over the next 5 years the annual stroke rate is much lower among those allocated immediate CEA. At 2 years the lines in figure 3A cross over, and at 5 years the absolute difference between them is highly significant. Overall, including both the surgical hazards and the later benefits, there is a highly significant net reduction in the 5-year risk of stroke or perioperative death in those allocated immediate surgery. The difference in 5-year risk in figure 3A would probably have been slightly greater (eg, 6% *vs* 12%, instead of 6·4% *vs* 11·8%) if all those allocated immediate CEA had undergone it promptly, and if none of those allocated deferral of any CEA had undergone the procedure until after they had suffered an ipsilateral stroke or episode of transient cerebral ischaemia. The same is, of course, true for the other main analyses of 5-year risks.

About half the strokes involved death or disability and half did not (tables 1 and 2), so in figure 3B, which is restricted to fatal or disabling events, the absolute risks and benefits were only about half as big as in figure 3A.

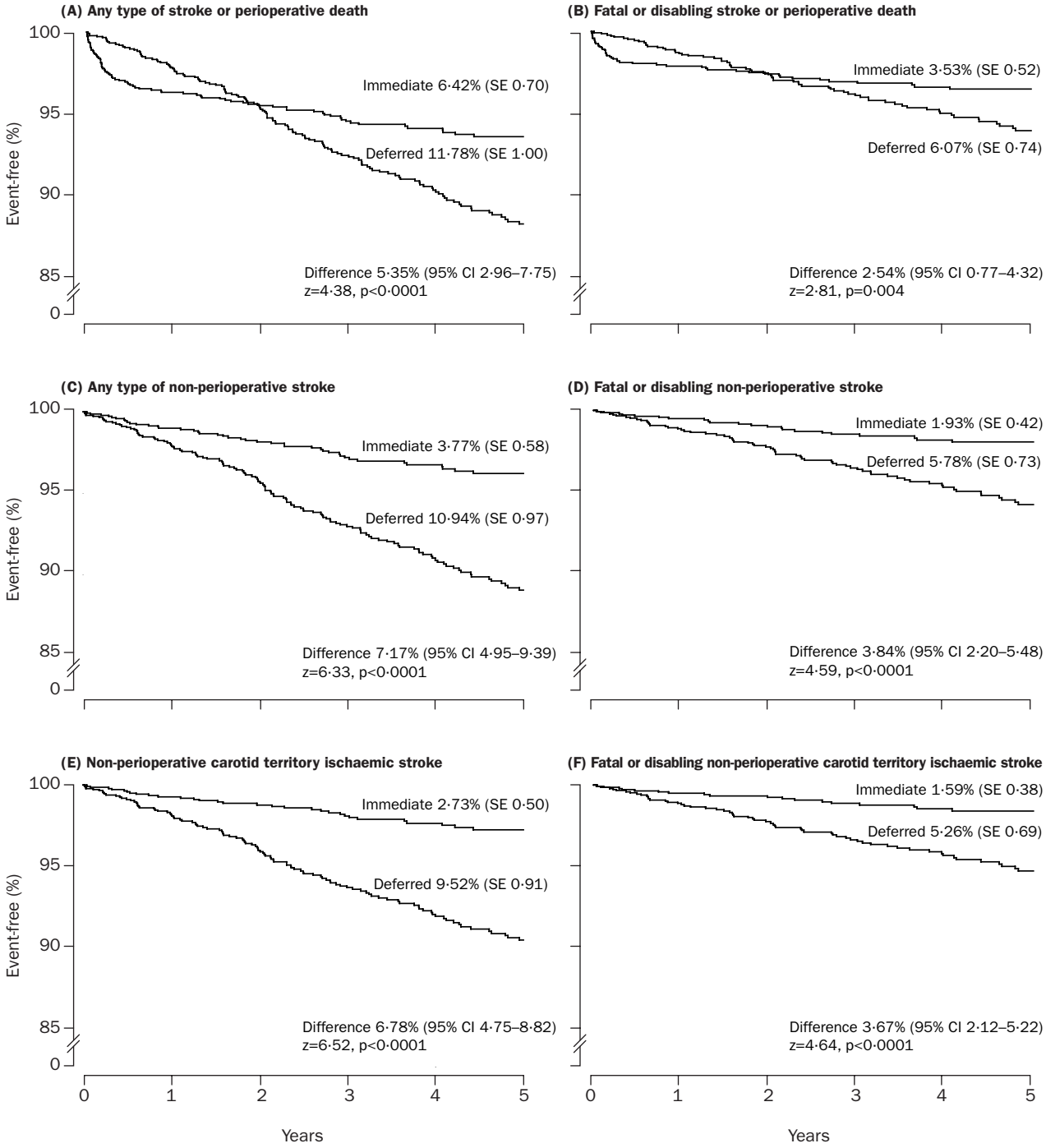

Figure 3: **5-year risks of various types of stroke**

A and B include perioperative morbidity and C–F do not. A, C, and E involve strokes of any severity; B, D, and F involve only those that were fatal or involved at least moderate long-term disability (requiring some help with daily affairs: modified Rankin score 3, 4 or 5). In E, five of the 30 strokes among those allocated immediate CEA were in patients who had not yet received it, and eight of the 105 strokes among those allocated deferral were in patients who had already undergone a CEA during the trial. z=difference/SE. p values are two-sided.

Nevertheless, the difference in the net 5-year risk of fatal or disabling stroke or perioperative death in figure 3B was still significant. As before, the absolute difference in the 5-year risk of death or disability would probably have been slightly greater than in figure 3B if there had been full compliance with the random allocation. For perioperative death or fatal stroke, the 5-year risk was 2·1% versus 4·2% (net gain 2·1% [95% CI 0·6–3·6]; p=0·006).

Non-perioperative strokes

Figure 3C shows the effects of treatment allocation on all non-perioperative strokes (ignoring any perioperative events in either group). In both groups, half the non-perioperative strokes were disabling or fatal and half were not, so in figure 3D the absolute reduction in the 5-year risk of fatal or disabling stroke was only half as great as in figure 3C. Table 2 provides further details of the non-perioperative strokes: in the immediate versus

	Allocated immediate CEA (n=1560)	Allocated deferral of any CEA (n=1560)
Mean follow-up (years) during first 5 years	3·4	3·4
Carotid strokes*		
Ipsilateral	13 (3+4+6)	62 (24+11+27)
Contralateral	11 (3+3+5)	35 (9+8+18)
Unknown laterality	6 (5+0+1)	8 (6+0+2)
Subtotal†	30 (11+7+12)	105 (39+19+47)
Other strokes		
Ischaemic vertebrobasilar	8 (1+1+6)	8 (1+0+7)
Haemorrhagic	4 (0+2+2)	7 (4+0+3)
Subtotal	12 (1+3+8)	15 (5+0+10)
Total‡	42 (12+10+20)	120 (44+19+57)
5-year risk of stroke	3·8%	11·0%

*Probable or definite carotid territory ischaemic strokes (fatal+disabling +non-disabling). †6 (1+1+4) versus 5 (1+0+4) were probably cardioembolic, of which 4(1+1+2) versus 4(1+0+3) were ipsilateral. The strokes of unknown laterality are also of unknown cause and territory, but are included in this subtotal. ‡If patients are classified by the first neurological outcome they suffered within 5 years (and the fatal strokes only include strokes that caused death less than 30 days later), these totals would become 42 (6+15+21) versus 120 (30+29+61). No patient had a perioperative stroke followed by another stroke.

Table 2: **Probable type and severity of worst non-perioperative stroke within 5 years of randomisation**

deferral comparison, exclusion of the 12 versus 15 strokes that were definitely vertebrobasilar or haemorrhagic, and hence unlikely to be affected by CEA, left the category of probable or definite carotid territory ischaemic strokes. These carotid strokes should include all the real beneficial effect of allocation to immediate CEA, so most subsequent analyses are restricted to them. Among them, six versus five were classified as probably cardioembolic (based only on cardiac risk factors), and another six versus eight were of unknown laterality, nature, and territory—so, some might not actually have been carotid territory ischaemic strokes. But, irrespective of whether these strokes were included or excluded, the magnitude of the effect of the allocated treatment on the aggregate of all carotid strokes (30 *vs* 105; table 2 and figure 3E) was so extreme that most of those that occurred in the deferred CEA group must have originated from the carotid artery.

Among strokes of known laterality, there was a highly significant effect not just on ipsilateral (13 *vs* 62, p<0·0001) but also on contralateral (11 *vs* 35, p=0·0004) carotid strokes (see Discussion). The latter difference was not attributable to any substantial difference in the use of contralateral CEA (table 1). Figure 3F shows the corresponding analysis just for fatal or disabling carotid strokes: the difference remained highly significant (18 *vs* 58 disabling or fatal carotid strokes, p<0·0001).

Effects of non-compliance

Of the 30 carotid strokes among patients allocated immediate CEA, five occurred among the few who did not get operated on, and some of these might well have been avoidable by surgery. Conversely, among those allocated deferral, 61 eventually had an ipsilateral CEA just because the doctor or patient eventually changed their mind (figure 1), and some risk of carotid stroke must have been prevented by the deferred surgery among these patients (although two suffered such a stroke). These numbers suggest that with stricter compliance the relative risk would have been about 0·2 rather than 0·3, and that the absolute difference in 5-year risk produced by actual use of CEA could well be about 8%, rather than the difference of 7% that is suggested by figures 3C and 3E. (Exclusion from both groups of any cardioembolic strokes, lacunar strokes attributable just to small-vessel disease, and misdiagnosed vertebrobasilar or haemorrhagic strokes might make the relative risk more extreme, but would not be expected to have any material effect on the absolute benefit.)

Subgroup analyses

Although the overall results of this trial are statistically very definite, subgroup analyses might still yield false-negative results, especially if they were based on the combined endpoint of hazard plus benefit (figure 3A), for which the results are less extreme than for carotid stroke alone (figure 3E). Indeed, even for carotid strokes, subgroup analyses that involve fewer than 1000 individuals might yield inconclusive findings, and should be interpreted cautiously. Figure 4 displays the findings for non-perioperative carotid stroke in six particular subgroups, and figure 5 shows statistical analyses of the findings for non-perioperative carotid stroke in those and several other subgroups. The study included 2044 men and 1076 women. For men (figure 4A), the results involved a total of 95 non-perioperative carotid territory strokes (18 immediate *vs* 77 deferred, p<0·0001), and the reduction in risk is definite. For women (figure 4B), the results involved a total of only 40 non-perioperative carotid territory strokes (12 *vs* 28, p=0·02), so the results are not as definite. Among these 40 strokes, however, four (all in women allocated immediate CEA) were classified as probably cardioembolic, leaving eight versus 28 (p=0·001) that probably originated from the carotid artery.

The study involved 912 patients younger than 65 years of age, 1558 aged 65–74 years, and only 650 who were older than this when randomised (mean ages at entry about 60, 70, and 80 years, respectively). The results were statistically definite both for those younger than 65 years of age (six *vs* 33 carotid strokes; figure 4C) and for those aged 65–74 years (12 *vs* 54; figure 4D), but are currently still uncertain for those older than this at entry (12 *vs* 18).

At the time of randomisation, the ipsilateral carotid diameter reduction on ultrasound was generally recorded as 70%, 80%, or 90%. Among the 1284 patients with less than 80% diameter reduction at entry (mean diameter reduction 69%), the 5-year risks of carotid stroke were 2·1% versus 9·5% (figure 4E). Among those with tighter stenosis at entry (mean diameter reduction 87%), the 5-year risks were 3·2% versus 9·6% (figure 4F). Thus, the 5-year probability of a carotid stroke (and hence the 5-year benefit of successful CEA) appeared to be about as great for those with about 70% diameter reduction on ultrasound as for those with 80% or 90% reduction.

Figure 5 shows these and other subgroup analyses for carotid stroke. The webfigure (http://image.thelancet.com/extras/04art3083webfigure.pdf) shows those for any non-perioperative stroke, and the webtable those for perioperative events. No clear evidence of heterogeneity of benefit is apparent, except perhaps with respect to blood lipids. But, although the benefit appeared to be larger for the quarter of all patients whose initial cholesterol was 6·5 mmol/L or above (absolute gain 11·8% [95% CI 9·8–13·8]) than for the three-quarters for whom it was lower (absolute gain 4·6% [2·2–7·0]), the benefit in both cases was substantial. There was no significant heterogeneity of

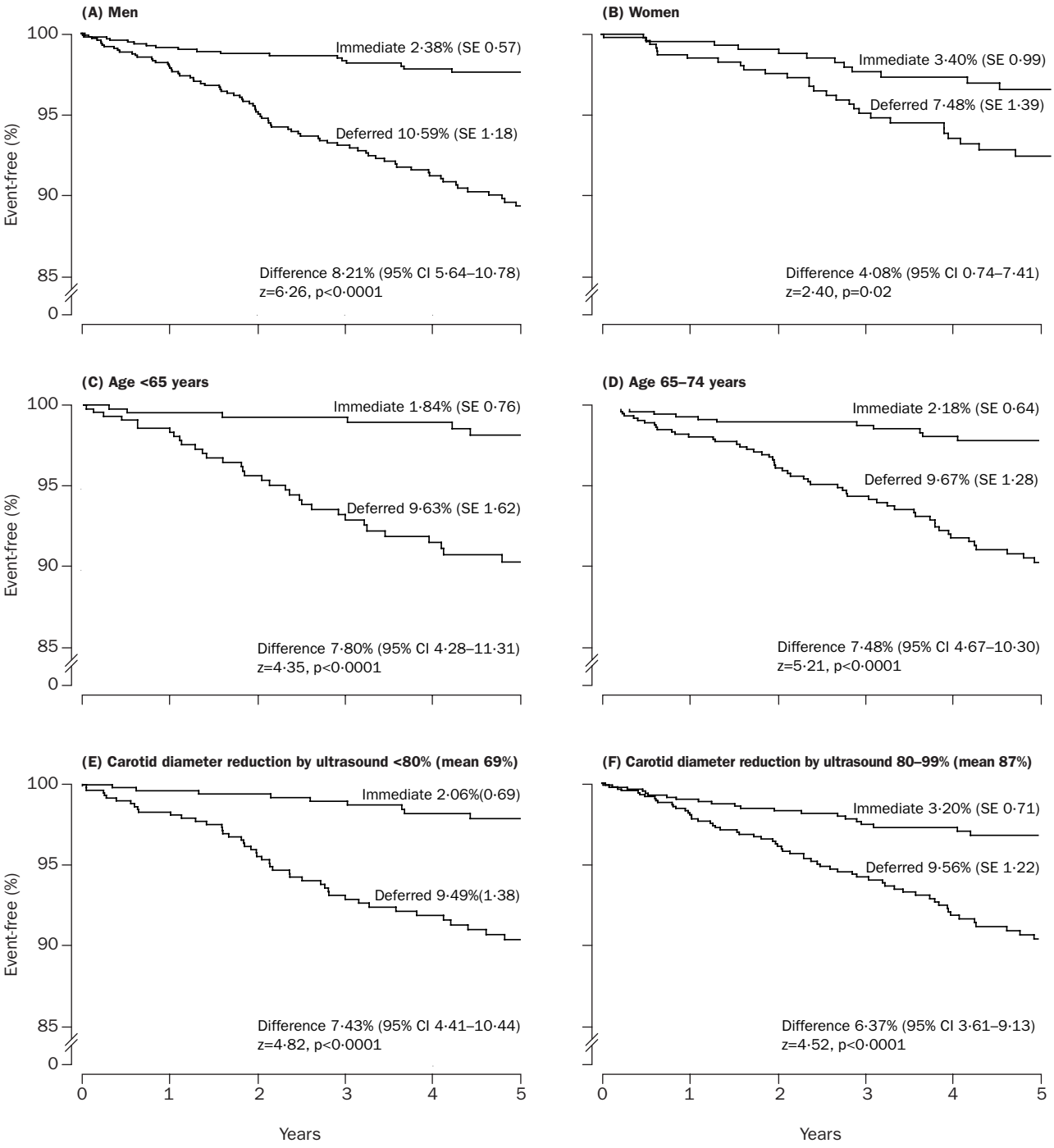

Figure 4: **5-year risks of non-perioperative carotid territory ischaemic stroke in selected subgroups**
z=difference/SE. p values are two-sided.

benefit according to whether the systolic blood pressure at entry was above or below 160 mm Hg, whether plaque echolucency was above or below 25%, whether there had been previous ipsilateral symptoms more than 6 months ago, whether there had been contralateral occlusion, surgery or symptoms, or whether patients had diabetes or ischaemic heart disease.

Overall mortality

Combining perioperative mortality, stroke mortality, and other mortality, the total number of deaths among those allocated to immediate CEA was non-significantly greater than among those allocated deferral of any CEA (15 *vs* two perioperative deaths, 12 *vs* 44 other stroke deaths, 144 *vs* 127 cardiac or other vascular deaths, 64 *vs* 47 cancer deaths and 29 *vs* 30 other deaths). The perioperative deaths and stroke deaths cannot simply be added, because for many patients the 5-year follow-up is not yet complete. Combining them properly, a significant reduction is seen in the 5-year risk of perioperative death or stroke death (2·1% *vs* 4·2%, net gain 2·1% [95% CI 0·6–3·6]; p=0·006). The excesses of cancer deaths and of non-perioperative, non-stroke vascular deaths are, by contrast, not conventionally

Category of stroke (□) or patient (■)	Number with stroke/patients and 5-year risk (%[SE]) Immediate CEA	Deferral	Absolute 5-year gain (95% CI)
Severity of worst stroke after randomisation			
Non-disabling	12/1560 (1·1% [0·3])	47/1560 (4·3% [0·6])	3·1% (1·8:4·4)
Disabling or fatal	18/1560 (1·6% [0·4])	58/1560 (5·3% [0·7])	3·7% (2·1:5·2)
Sex			
Men	18/1021 (2·4% [0·6])	77/1023 (10·6% [1·2])	8·2% (5·6:10·8)
Women	12/539 (3·4% [1·0])	28/537 (7·5% [1·4])	4·1% (0·7:7·4)
Age at entry (years)			
<65	6/456 (1·8% [0·8])	33/456 (9·6% [1·6])	7·8% (4·3:11·3)
65–74	12/775 (2·2% [0·6])	54/783 (9·7% [1·3])	7·5% (4·7:10·3)
⩾75	12/329 (5·5% [1·6])	18/321 (8·8% [2·1])	3·3% (−1·9:8·4)
Prerandomisation cholesterol (mmol/L)			
<6·5 (250 mg/dL)	24/1146 (3·3% [0·7])	61/1146 (7·9% [1·0])	4·6% (2·2:7·0)
⩾6·5	6/414 (1·6% [0·7])	44/414 (13·4% [1·9])	11·7% (7·8:15·7)
Prerandomisation systolic blood pressure (mm Hg)			
<160	16/877 (2·5% [0·6])	55/909 (8·9% [1·2])	6·3% (3·7:9·0)
⩾160	14/683 (3·0% [0·8])	50/651 (10·4% [1·4])	7·4% (4·1:10·6)
Ipsilateral carotid diameter reduction (% by ultrasound)			
<80 (mean 69)	9/641 (2·1% [0·7])	45/643 (9·5% [1·4])	7·4% (4·4:10·5)
80–89 (mean 81)	7/421 (2·8% [1·1])	35/455 (11·0% [1·8])	8·1% (4·0:12·3)
90–99 (mean 92)	14/498 (3·4% [0·9])	25/462 (8·1% [1·6])	4·6% (1·0:8·2)
Ipsilateral plaque echolucency (% soft material)			
<25	5/390 (1·7% [0·8])	26/411 (8·5% [1·6])	6·8% (3·3:10·3)
⩾25	10/371 (3·6% [1·2])	33/403 (11·1% [1·9])	7·4% (3·1:11·7)
Not estimated	15/799 (2·8% [0·7])	46/746 (9·1% [1·3])	6·3% (3·3:9·3)
Ipsilateral carotid territory status at entry: previous symptoms			
None before entry	22/1372 (2·3% [0·5])	91/1375 (9·4% [1·0])	7·1% (4·9:9·2)
>6 months previous	8/188 (6·1% [2·1])	14/185 (10·7% [2·8])	4·6% (−2·2:11·5)
Contralateral status at entry: previous symptoms, resultant CEA history, and patency			
No symptoms, patent	19/1023 (2·7% [0·6])	56/1057 (7·6% [1·0])	4·9% (2·6:7·2)
Previous symptoms, CEA, patent	4/242 (1·9% [1·0])	24/233 (14·7% [2·9])	12·7% (6·8:18·7)
Previous symptoms, no CEA, patent	6/148 (5·9% [2·4])	15/142 (15·2% [3·7])	9·4% (0·7:18·1)
Occluded	1/147 (1·5% [1·5])	10/128 (10·1% [3·1])	8·6% (1·9:15·4)
Diabetes or ischaemic heart disease recorded at entry			
Diabetes	9/316 (4·5% [1·5])	22/306 (11·7% [2·5])	7·2% (1·5:12·8)
Ischaemic heart disease (non-diabetic)	8/411 (3·0% [1·1])	31/419 (10·7% [1·9])	7·7% (3·5:12·0)
Neither	13/833 (2·1% [0·6])	52/835 (8·3% [1·1])	6·2% (3·7:8·7)
All patients	**30/1560 (2·7% [0·5])**	**105/1560 (9·5% [0·9])**	**6·8% (4·8:8·8)**

Global heterogeneity between risk ratios: χ^2_{16}**=20·04; p=0·4**

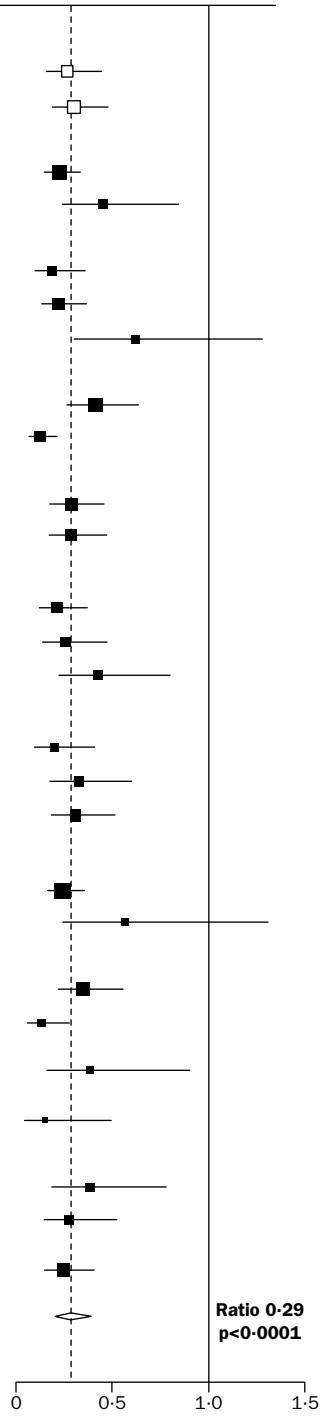

Figure 5: **5-year risks of non-perioperative carotid territory ischaemic stroke in various subcategories**

significant, and could well be largely or wholly attributable to the play of chance (see Discussion).

Changes in medical treatment

At randomisation, there was widespread use of antiplatelet and antihypertensive drugs (but little use of anticoagulants), and increasing use of lipid-lowering drugs (17% among those randomised in 1993–1996, 58% in 2000–2003; figure 6). After randomisation, the use of all three types of drug increased still further; at the last follow-up in 2002–2003, more than 90% of the survivors were on antiplatelet therapy, 81% were on antihypertensives, and 70% were on lipid-lowering treatment. The use of these drugs (and the mean blood pressure) was similar in both treatment groups not only at randomisation but also during follow-up, so the trial is one of surgery against a background of fairly intensive medical management for most patients. Without this, the incidence of stroke could well have been substantially greater, particularly among those allocated

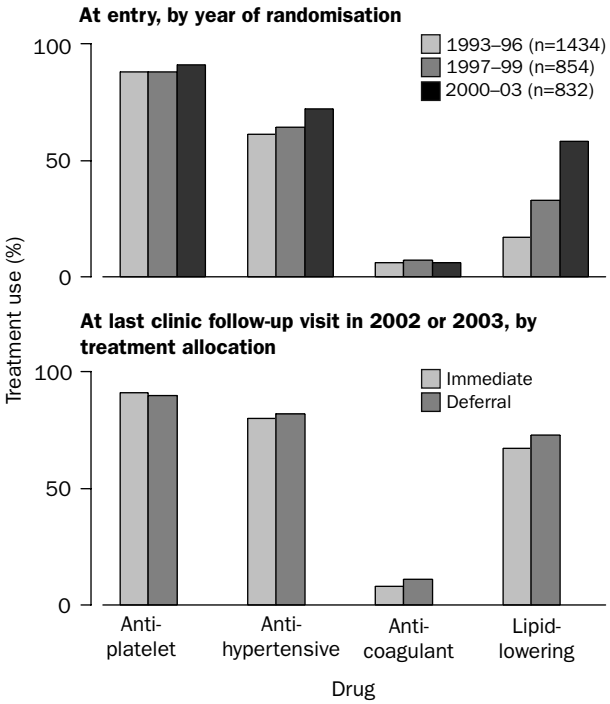

Figure 6: **Use of medical treatments**
At follow-up in 2002 or 2003, mean blood pressure was 148/79 in both groups.

deferral. A March, 2004, survey of ACST collaborators indicated that routine lipid-lowering therapy use in ACST patients will now (appropriately[11]) rise from 70% to at least 90%. But, since such drugs are already so widely used in ACST, it is unlikely that still wider use over the next few years would reduce the incidence of stroke among those allocated deferral of any CEA much below the current rate of about 2% per year (figure 3), especially since randomisation has ceased and the survivors are getting older.

Discussion

Because ACST involves large numbers of patients, its 5-year overall findings for stroke prevention are clear. Among patients up to 75 years of age with severe carotid stenosis on ultrasound but no relevant neurological symptoms, CEA approximately halved the net 5-year risk of stroke. These results include the 3% perioperative hazard. Almost all the gain involved carotid territory ischaemic strokes, of which half were disabling or fatal.

The only other large trial, ACAS, involved similar patients in North America (table 3) and had generally similar findings for stroke prevention to the largely European ACST (table 4). Although the overall ACAS results[5] were less clear, particularly for fatal or disabling stroke, this probably relates to the smaller numbers of patients in ACAS and the somewhat shorter duration of follow-up.

In ACST, there was no significant heterogeneity in the surgical risk of about 3% perioperative stroke or death between different types of patient or between different hospitals, but because they involve fairly small numbers of perioperative events, such subgroup analyses are of limited reliability: much larger numbers of cases would, for example, need to be studied to compare reliably the surgical hazards for men and women.

The reduction in carotid stroke was separately significant for men and for women, for those aged 65–74 years and for those younger than 65 years of age at entry, and for those with only about 70% carotid artery diameter reduction on ultrasound as well as for those with more severe stenosis. Indeed, in this and the other main trial[5] among asymptomatic patients, those with about 70% stenosis appear to benefit about as much as those with 80% or 90% stenosis, by contrast with the apparent findings in the two main trials[1,2] in symptomatic patients.[12–14] Although echolucent plaque might be more unstable, our measures of plaque echolucency did not identify a lower or higher risk group.

Different angiographic techniques might have assessed carotid stenosis somewhat more reliably,[15] and other technologies are likely to emerge that help to determine which arterial lesions are particularly risky. But, despite the increasing availability of newer ultrasound, magnetic resonance, and CT methods, the range of duplex ultrasound techniques that were actually used in this trial is still reasonably representative of much current practice.

The absolute benefit gained was significantly greater than average for the few with high cholesterol, but was separately significant for those with and without high cholesterol, with or without high blood pressure, and with or without previous myocardial infarction or diabetes. Benefit was definite among the 88% who had never had any ipsilateral symptom (figure 5), and appeared to be largely independent of contralateral carotid symptoms or patency. Although the main reduction was in the risk of ipsilateral carotid stroke, contralateral carotid stroke was also highly significantly reduced, presumably through mechanisms involving collateral arterial flow within the brain (via the circle of Willis). Because the reduction in contralateral carotid stroke was so definite (11 *vs* 35 events), exclusion of such strokes from the main analyses of carotid stroke would have underestimated the net benefits of successful CEA.

Age, reduced life expectancy, and intercurrent mortality

For those younger than 75 years of age, the 5-year probability of dying from unrelated causes is about one-sixth (so, their 5-year differences in stroke-free survival would be only about five-sixths of the 5-year benefits in

	Asymptomatic Carotid Surgery Trial (ACST)	Asymptomatic Carotid Atherosclerosis Study (ACAS)
Baseline characteristics		
Period of entry	1993–2003	1987–1993
Region	Mainly Europe	North America
Number randomised	3120	1662
Follow-up (years)	3·4*	2·7
Age-range (years)	40–91	40–79
Mean age (years)	68	67
Men (%)	66	66
Treated hypertension (%)†	65	64
Mean systolic blood pressure (mm Hg)	153	146
Diabetes (%)	20	23
Previous contralateral CEA (%)	24	20
Ipsilateral CT infarct (%)	8	8
Contralateral occlusion (%)	9	9
Mean cholesterol (mmol/L)	5·8	5·9

*To 2003, but follow-up continues in ACST. †ACAS: "Has your doctor ever told you you had high blood pressure or were hypertensive?"

Table 3: **Comparison of ACST and ACAS baseline characteristics of randomised patients**

	ACST		ACAS		Total	
	Immediate	Deferral	Immediate	Deferral	Immediate	Deferral
Number of patients	1560	1560	825	834	2385	2394
Follow-up (years)	3·4	3·4	2·7	2·7	3·1	3·1
CEA undertaken	1348	..	724	..	2072	..
Procedural morbidity*						
Death†	15	2	3	1	18	3
Non-fatal stroke	25	9	16	2	41	11
Non-procedural stroke						
Fatal (within 5 years)†	12	44‡	6	9	18	53‡
Non-fatal	30	76‡	35	74‡	65	150‡
5-year risk (%) of stroke or procedural morbidity§	6·4	11·7‡	5·1	11·0	6·0	11·5‡
Other deaths						
Other vascular	144	127	37	50	181	177
Neoplastic	64	47	15	13	79	60
Respiratory	9	11	10	9	19	20
Other/unknown	20	19	12	9	32	28

*Perioperative events in ACST, angiographic or perioperative events in ACAS. (One patient in the deferral arm of ACST had a procedural stroke after having another stroke.) Note that absolute numbers suffering procedural morbidity and non-procedural stroke cannot simply be added to assess net benefit: instead, life-table methods must be used, as in figure 3. †Net 5-year risk of procedural death or stroke death in ACST is 2·1% versus 4·2%, p=0·006. ‡p<0·0001. §Procedural morbidity or ipsilateral stroke in ACAS.

Table 4: **Combined analysis of results from ACST and ACAS**

figures 3–5). Among those aged under 65, 65–74, and 75 or more years of age, the mean ages at entry were about 60, 70, and 80 years, respectively, and the 10-year probabilities of dying from unrelated causes (in the absence of any stroke deaths) would be about a quarter, a half, and three-quarters.

Only 650 patients were older than 75 years of age when randomised, so the lack of significant net benefit of successful CEA among them might well be a false-negative subgroup result. However, because their normal life expectancy is short, any net benefits would probably be of limited duration. Figures 3 and 4 suggest that CEA in asymptomatic patients should be considered a long-term investment, whereas in symptomatic carotid disease there is a substantial early risk (which might lessen thereafter) within 2 or 3 years of the first neurological event. (Hence, even those older than 75 years of age might benefit if they have recently had relevant neurological symptoms.[16])

The aggregated findings from ACST and ACAS for mortality from causes other than CEA or stroke (lower part of table 4) indicate a non-significant excess of cancer mortality that should probably, on biological grounds, be dismissed as being largely or wholly an artifact of chance. There were no material differences in the numbers dying from the remaining three groups of other causes (table 4). There were about ten times as many deaths from other causes as from stroke in ACST, so the real effects of CEA on overall mortality cannot be reliably estimated by a crude comparison of overall mortality in the two treatment groups. If, however, it is assumed that successful CEA affects only stroke mortality, then a useful estimate of the long-term effects of CEA on overall mortality (in the circumstances of the present trial) can be made by combining the average mortality from other causes with an estimate of the perioperative mortality from CEA and an estimate of the long-term effects of CEA just on stroke mortality. This combination cannot yet be done, because the findings are, as yet, statistically stable only to about year 5 after randomisation, at which point the reduction in the net 5-year risk of fatal stroke or perioperative death is about 2% (2·1% *vs* 4·2%, p=0·006).

Applicability of findings

The reduction of about four-fifths in carotid ischaemic stroke is so extreme that it can reasonably be generalised to patients with severe carotid artery stenosis in a whole range of future circumstances: for example, although wider use of statins will somewhat reduce the risk of carotid stroke,[11] still about 80% of whatever risk remains from the carotid lesion should be avoidable by successful surgery.

Unsuccessful surgery, however, can do much harm and some of the commentary on previous CEA trial results has emphasised that, in non-trial settings, poor surgery, inadequate audits, or inappropriate selection of patients could result in widespread misuse of CEA.[17] The balance of risk and benefit depends on surgical morbidity rates (which could be significantly greater,[17] but could eventually be lower,[5] than in the present study) and on the risk of carotid stroke in the absence of surgery. These stroke risks could be lowered somewhat further by even better medical treatment,[18] although antiplatelet, anti-hypertensive, and lipid-lowering therapy were already widely used in ACST, and strokes are continuing to occur at about 2% per year among controls. The balance of risk and benefit also depends, however, on what happens after the 5th year of follow-up, and the continued divergence between the carotid stroke risks in the two treatment groups throughout the first 5 years of follow-up (figure 3E) suggests that longer observation could reveal some further gain. Until the 10-year stroke rates have been monitored by several more years of follow-up, direct estimates of the numbers needed to treat to avoid one stroke, and of the expected years of life gained, are premature (as are health economic evaluations), and might undervalue immediate surgery.

MRC ACST collaborative group
Writing committee—A Halliday (principal investigator), A Mansfield, J Marro, C Peto, R Peto, J Potter, D Thomas (principal neurological investigator).
Steering committee—M Brown, B Farrell, A Halliday, A Mansfield, R Peto, J Potter (chair), A Rau, D Thomas, C Wolfe.
Data monitoring committee—R Collins, R Gray, J-M Orgogozo, C Warlow (chair).
Endpoint review committee—R Foale, M Harrison (chair), C Jamieson, V Ruckley.

Clinical Trial Service Unit, Oxford, UK—A Baxter, J Burrett, R Collins, J Godwin, S Knight, R Peto, A Radley, S Richards.
Trial Office—A Baxter, S Byrd, A Clarke, M Emson, S Hamilton, E Hayter, D Kamugasha, J Marro, P Neave, C Peto, A Rau, P Robless, R Steele, J Wilcox.
Collaborating clinicians
Austria (30 patients): Innsbruck (G Fraedrich, C Schmidauer); Vienna (T H Hölzenbein, G Kretschmer, V Metz, P Polterauer).
Belgium (1 patient): Antwerp (P Cras, P Van Schil).
Brazil (2 patients): Natal (G Gurgel).
Bulgaria (6 patients): Sofia (V Petrov, G Slabakov [deceased]).
Canada (30 patients): Halifax (G Gubitz, R Holness, W Howes, R Langille, G MacKean, S J Phillips, J Sullivan, J Wood).
Croatia (2 patients): Zagreb (T Sosa).
Cyprus (13 patients): Nicosia (N S Angelides, A Malikidou).
Czech Republic (18 patients): Pilzen (Z Ambler, J Polivka, J Simaná); Prague (V Beneš, F Kramár).
Finland (18 patients): Helsinki (M Kaste, M Lepäntalo, L Soinne).
France (2 patients): Nimes (J-M Cardon, A Legallou).
Germany (98 patients): Augsburg (B Gengenbach, K Pfadenhauer, K D Wölfle); Berlin (I Flessenkämper, B F Klumpp, J Marsch); Düsseldorf (R Kolvenbach, T Pfeiffer, W Sandmann); Freiburg (F Beyersdorf, A Hetzel, G Spillner); Giessen (H J Lutz); Heidelberg (D Böckler, N Maeder); Minden (O Busse, J Grönniger, F Haukamp); Mülheim an der Ruhr (K Balzer, H G Knoob, G Roedig, L Virreira); Würzburg (S Franke, R Moll, J Schneider).
Greece (10 patients): Athens (J Dayantas, M N Sechas, S Tsiaza); Thessaloniki (D Kiskinis).
Hungary (59 patients): Budapest (A Apor, L Entz, K Hüttl, Z Jàrànyi, I Mogan, Z Nagy, A Szabo, D Varga); Miskolc (G Juhász, L Mátyás).
Ireland (7 patients): Dublin (M Hutchinson, D Mehigan).
Israel (245 patients): Ashkelon (Z Aladjem, S Elmakias, B Yoffe); Haifa (H Ben-Meir, L Dagan, R Karmeli, G Keren, A Shimony, B Weller); Petach Tikva (R Avrahami, A Koren, J Streifler, S Tabachnik, A Zelikovski).
Italy (328 patients): Bari (F Federico, L Pascazio, G Regina); Bologna (E Pozzati); Brescia (S Bonardelli, S M Giulini, B Guarneri); Caserta (P Caiazzo); Ferrara (F Mascoli); Genova (G Becchi, R Masini, E Santoro, G Simoni); L'Aquila (L Cucciolillo, C Spartera, P Scarpelli, M Ventura); Milano (O Arena, M Collice, M Puttini, F Romani, V Segramora); Padova (G Deriu, F Verlato); Perugia (P G Cao, E Cieri, P De Rango, L Moggi); Pescara (A Antico, F Spigonardo); Reggio Emilia (G Malferrari, N Tusini, E Vecchiati); Rome (A Cavallaro); Savona (N Zinicola); Torrette di Ancona (F P Alò, G Pagliariccio); Torino (D Palombo, F Peinetti); Trieste (R Adovasio, G Mase); Udine (V Fregonese, L Mozzon).
Netherlands (132 patients): Beverwijk (J De Nie, J Doelman, N Yilmaz); Eindhoven (J Buth, G Stultiens); Geldrop (J Boiten, A Boon, F van der Linden); Leeuwarden (D C Busman, A Engström); Rotterdam (H A W Sinnige, T I Yo); Utrecht (B C Eikelboom, L J Kappelle, R W H van Reedt Dortland, T E Westra).
New Zealand (10 patients): Hamilton (R Blair, J Chuen, C Holdaway, F Shakibaie).
Norway (47 patients): Oslo (A Kroese, C E Slagsvold); Trondheim (T Dahl, H J Johnsen, H O Myhre).
Poland (88 patients): Katowice (J Gniadek); Warsaw (P Andziak, M Elwertowski, A K Malek, J Mieszkowski, W Noszczyk, M Szostek).
Portugal (13 patients): Porto (C Correia, M C Pereira).
Russia (10 patients): Moscow (R S Akchurin).
Slovenia (44 patients): Maribor (V Flis, K Miksic, B Stirn, E Tetickovic).
Spain (196 patients): Barcelona (M Cairols, J M Capdevila, E Iborra-Ortega, V Obach, V Riambau, F Vidal-Barraquer, R Vila-Coll); Coruna (E Diaz-Vidal, J I Iglesias-Negreia, A Tovar-Pardo, R J Segura Iglesias); Galdakao (A F Alfageme, A Barba, J C Garcia-Monco); Palma (C Corominas, J Julia, P Lozano); San Sebastian (J F Marti-Masso, R M Porta); Vigo (A Rosendo Carrera, J Gomez).
Sweden (532 patients): Göteborg (C Blomstrand, J Gelin, J Holm, L Karlström, E Mattsson); Helsingborg (S Bornhov, J Dahlstrom, G De Pedis, S M Jensen, H Pärsson, G Plate, P Qvarfordt); Kalmar (B Arvidsson, L Brattström, C Forssell, A Potemkowski, C Skiöldebrand, P Stoor); Linköping (M Blomqvist, M Callander, C Forssell, F Lundgren); Lund (H Almqvist, L Norgren, B Norrving, E Ribbe, J Thörne); Malmö (A Gottsäter, T Mätzsch, M E Nilsson); Norrkoping (C Forssell, M Lonsson, F Lundgren, B Stahre); Örebro (L Norgren, B Stenberg); Stockholm (P Konrad, L Lundqvist, P Olofsson, S Rosfors, C Skiöldebrand, J Swedenborg, R Takolander, N Wahlgren); Uppsala (D Bergqvist, C Ljungman, H Pärsson).
Switzerland (6 patients): Bern (H W Kniemeyer, M K Widmer); St Gallen (W Nagel, D Sege, B Weder).
Tunisia (11 patients): Montfleury (H Jaber, J Manaa, R B Meftah, B R Nabil, T Sraieb).
UK (1069 patients): Bath (D Bateman, J Budd, M Horrocks, M Kivela, L Shaw, R Walker); Belfast (A A B Barros D'Sa, K Fullerton, R Hannon, J M Hood, B Lee, K McGuigan, J Morrow, J Reid, C V Soong); Birmingham (M Simms); Bristol (R Baird, M Campbell, S Cole, I T Ferguson, P Lamont, D Mitchell, A Sassano, F C T Smith); Cambridge (P J Kirkpatrick, P Martin, C Turner); Cheshire (J F Clegg, M Crosley, J Hall); Chester (L De Cossart, P Edwards, D Fletcher, S Rosser); Dundee (P T McCollum, D Davidson, R Levison); Edinburgh (A W Bradbury, R T A Chalmers, M Dennis, J Murie, C V Ruckley, P Sandercock); Exeter (W B Campbell, T Frankel, C Gardner-Thorpe, N Gutowski, R Hardie, W Honan, P Niblett, A Peters, B Ridler, J F Thompson); Glasgow (I Bone, G Welch); Hereford (E C Grocott, P Overstall); Huddersfield (M I Aldoori, B E A Dafalla); Hull (J Bryce, C Clarke, P T McCollum, A Ming, A R Wilkinson); Leeds (J Bamford, D Berridge, J Scott); Leicester (R J Abbott, R Naylor); Liverpool (P Harris, P Humphrey); London (M Adiseshiah, M Aukett, D Baker, C C R Bishop, A Boutin, M Brown, P Burke, K G Burnand, A Colchester, L Coward, A H Davies, M Espasandin, A E B Giddings, G Hamilton, M Harrison, C Judge, S Kakkos, A Mansfield, C McGuiness, A Nicolaides, T S Padayachee, H Riordan, E Sullivan, P Taylor, D Thomas, M Thompson, J H N Wolfe); Manchester (C N McCollum, P A O'Neill, S Welsh); Newcastle (J Barnes, M Davis, A D Mendelow, J E O'Connell, M S S Siddique, G Stansby, R Vivar); Plymouth (S Ashley, C Cosgrove, J Gibson, D C Wilkins,); Southampton (A D B Chant, J Frankel, C P Shearman, J Williams); Stirling (G Hall, R Holdsworth); Truro (J N Davies, B McLean, K R Woodburn); Wakefield (G Brown, P Curley, L Loizou).
USA (16 patients): Detroit (S Chaturvedi, F Diaz).
Yugoslavia (77 patients): Belgrade (D Radak, P R Todorovic).

Conflict of interest statement

A Mansfield is Chair of The Stroke Association.

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Uses of error

I never did become a cardiologist

Kenneth D Bagshawe

The admission card from casualty read "Hysterical hyperventilation! Good teaching case." She was 19 and was so dyspnoeic that she crawled into the hospital. As a hopeful would-be cardiologist, I found a thrusting right ventricle and normal breath sounds. A radiograph and electrocardiogram were consistent with right ventricular strain and the lung fields were clear. It was concluded she had pulmonary hypertension. She died a few days later.

Autopsy was on a Saturday morning by the professor of pathology who pronounced "She has been a naughty girl. She had pelvic sepsis and it spread to her lungs." Also present at the autopsy was another physician who said "That is not sepsis! That's choriocarcinoma. I saw a similar case 10 years ago. It was described briefly in a cardiology text book." A subsequent search confirmed that it was the only such recorded case. Histology in both cases showed the pelvic vessels and pulmonary arteries were occluded by choriocarcinoma and secondary thrombus and there was no extravascular tumour.

Some months later, as duty registrar, I was called to the gynaecology ward where a 34-year-old woman had signs of pulmonary embolism 10 days after hysterectomy for menorrhagia. She was started on anticoagulants. Later, she complained to her general practitioner of shortness of breath and came to the hospital for breathing exercises. While at the hospital, she had chest pain and was admitted to our ward. Chest radiograph showed a few linear streaks. Re-examination of her uterus confirmed there was no malignant disease. Despite anticoagulants and the oxygen tent she continued to deteriorate with increasing evidence of pulmonary hypertension.

I had read of a case of metastatic choriocarcinoma with no tumour in the uterus, so we decided to test for human chorionic gonadotropin (hCG). I took a urine specimen to the laboratory and foolishly fumbled my reasons for the request to the laboratory head. He went through his ritual response to a fatuous request from a junior doctor, which was to remove his glass eye and polish it on a red and white handkerchief before replacing it to deliver a paralysing stare. He said he refused to sacrifice a rabbit (the Friedman test) for a woman who could not be pregnant and whose uterus showed no malignant disease. A colleague alleged he was fond of hospital scandal and sent the urine to the laboratory with a request to confirm pregnancy for a carefully selected pseudonym.

The following Friday afternoon a consultant examined her and said "She will not last the weekend." That evening, I received her laboratory report: "Friedman test: strongly positive."

Choriocarcinoma was reputedly the most rapidly growing of all solid carcinomas so it seemed possible that the newly introduced antimetabolites, which were beginning to show responses in childhood leukaemia, might do something useful. In the pharmacy I found 6-mercaptopurine tablets which she started taking that night. During the weekend she seemed ever closer to death, but on the Monday morning she was out of the oxygen tent, having breakfast. Later that week, methotrexate was added, and after 7 months of toxic treatment she went home. She is still in touch 45 years later.

Department of Medical Oncology, Imperial College School of Medicine, Charing Cross Campus, London W6 8RF, UK (K D Bagshawe FRS)