11 Cooper SA, Breen JF, Giuliani RL. The relative efficacy of indoprofen compared with opioid-analgesic combinations. *J Oral Surg* 1981;39:21-5.
12 Hopkinson JH, Bartlett FH, Steffens AO, McGlumphy TH, Macht EL, Smith M. Acetaminophen versus propoxyphene hydrochloride for relief of pain in episiotomy patients. *J Clin Pharmacol* 1973;13:251-63.
13 Hopkinson JH, Blatt G, Cooper M, Levin HM, Berry FN, Cohn H. Effective pain relief: comparative results with acetaminophen in a new dose formulation, propoxyphene napsylate-acetaminophen combination, and placebo. *Curr Ther Res Clin Exp* 1976;19:622-30.
14 Huskisson EC. Simple analgesics for arthritis. *BMJ* 1974;iv:196-200.
15 Liashek P Jr, Desjardins PJ, Triplett RG. Effect of pretreatment with acetaminophen-propoxyphene for oral surgery pain. *J Oral Maxillofac Surg* 1987;45:99-103.
16 Messick RT. Evaluation of acetaminophen, propoxyphene, and their combination in office practice. *J Clin Pharmacol* 1979;19:227-30.
17 Bloomfield SS, Barden TP, Mitchell J. A comparison of pirprofen, aspirin, acetaminophen and placebo in postpartum uterine cramp pain. *Curr Ther Res* 1981;30:139-51.
18 Cooper SA. The relative efficacy of ibuprofen in dental pain. *Compendium of Continuing Education in Dentistry* 1986;7:578-97.
19 Cooper SA, Kupperman A. The analgesic efficacy of flurbiprofen compared to acetaminophen with codeine. *J Clin Dent* 1991;2:70-4.
20 Dionne RA, Snyder J, Hargreaves KM. Analgesic efficacy of flurbiprofen in comparison with acetaminophen, acetaminophen plus codeine, and placebo after impacted 3rd molar removal. *J Oral Maxillofac Surg* 1994;52:919-24.
21 Forbes JA, Bakaszi BA, Ragland RN, Hankle JJ. Analgesic effect of acetaminophen, phenyltoloxamine and their combination in postoperative oral surgery pain. *Pharmacotherapy* 1984;4:221-6.
22 Forbes JA, Kolodny AI, Chachich BM, Beaver WT. Nalbuphine, acetaminophen, and their combination in postoperative pain. *Clin Pharmacol Ther* 1984;35:843-51.
23 Hopkinson JH, Smith MT, Bare WM, Levin HM, Postko RJ. Acetaminophen (500 mg) versus acetaminophen (325 mg) for the relief of pain in episiotomy patients. *Curr Ther Res* 1974;16:194-200.
24 Jain AK, Ryan JR, McMahon FG, Smith G. Comparison of oral nalbuphine, acetaminophen, and their combination in postoperative pain. *Clin Pharmacol Ther* 1986;39:295-9.
25 Melzack R, Jean ME, Kinch RA, Katz J. Diflunisal (1000 mg single dose) versus acetaminophen (650 mg) and placebo for the relief of post-episiotomy pain. *Curr Ther Res* 1983;34:929-39.
26 Sunshine A, Marrero I, Olson N, McCormick N, Laska EM. Comparative study of flurbiprofen, zomepirac sodium, acetaminophen plus codeine, and acetaminophen for the relief of postsurgical dental pain. *Am J Med* 1986;80(3A):50-4.
27 Sunshine A, Zighelboim I, De Castro A. Augmentation of acetaminophen analgesia by the antihistamine phenyltoloxamine. *J Clin Pharmacol* 1989;29:660-4.
28 Sunshine A, Olson NZ, Zighelboim I, Decastro A. Ketoprofen, acetaminophen plus oxycodone, and acetaminophen in the relief of postoperative pain. *Clin Pharmacol Ther* 1993;54:546-55.
29 Terrence CF, Potter DM, Fromm GH. Is baclofen an analgesic? *Clin Neuropharmacol* 1983;6:241-5.
30 Young RE, Quigley JJ, Arehambault Jr WAT, Gordon LL. Butorphanol/acetaminophen double-blind study in postoperative pain. *J Med* 1979;10:239-56.
31 Buck ME, Paintin DB. Diflunisal in post-episiotomy pain: a preliminary report of a double-blind comparative study. *Curr Med Res Opin* 1978;5:548-9.
32 Evans PJ, McQuay HJ, Rolfe M, O'Sullivan G, Bullingham RE, Moore RA. Zomepirac, placebo and paracetamol/dextropropoxyphene combination compared in orthopaedic postoperative pain. *Br J Anaesth* 1982;54:927-33.
33 Forbes JA, Foor VM, Bowser MW, Caderazzo JP, Shackleford RW, Beaver WT. A 12-hours evaluation of the analgesic efficacy of diflunisal, propoxyphene, a propoxyphene-acetaminophen combination, and placebo in postoperative oral surgery pain. *Pharmacotherapy* 1982;2:43-9.
34 Honig S, Murray KA. Postsurgical pain: zomepirac sodium, propoxyphene/acetaminophen combination, and placebo. *J Clin Pharmacol* 1981;21:443-8.
35 Petti A. Postoperative pain relief with pentazocine and acetaminophen: comparison with other analgesic combinations and placebo. *Clin Ther* 1985;8:126-33.
36 Sunshine A, Olson NZ, Zighelboim I, DeCastro A, Minn FL. Analgesic oral efficacy of tramadol hydrochloride in postoperative pain. *Clin Pharmacol Ther* 1992;51:740-6.
37 Beaver WT, Forbes JA, Barkaszi BA, Ragland RN, Hankle JJ. An evaluation of ibuprofen and paracetamol in postoperative oral surgery pain. *Clin Pharmacol Ther* 1987;41:180.
38 Beaver WT, Feise G. Comparison of the analgesic effect of acetaminophen and codeine and their combination in patients with postoperative pain. *Clin Pharmacol Ther* 1978;23:108.
39 Forbes JA, Beaver WT, Keller CK, Smith JW, Zeleznock JR, Ciccone PE. An evaluation of the analgesic efficacy of two dosage levels of acetaminophen (650 and 1000 mg) in postoperative oral surgery pain. *Clin Pharmacol Ther* 1983;33:196.
40 Seymour RA, Rawlins MD. Paracetamol, aspirin, dihydrocodeine tartrate and postoperative dental pain. *Pain* 1981;10:S248.
41 Gobel H, Fresenius J, Heinze A Dworschak M, Soyka D. [Effectiveness of peppermint oil and paracetamol in the treatment of tension headache.] *Nervenarzt* 1996;67:672-81. (In German.)
42 Weber B, Fontan JE, Scheller E, Debu E, Dufour B, Majorel P, et al. [Voluntary interruption of pregnancy induced by mifepristone associated with sulprostone: attempting analgesia with acetominophene or dipropyline.] *Contraception Fertilité Sexualité* 1990;18:1073-6. (In French.)
43 Wall R, Linford SMJ, Iftikhar Akhtar A. Addition to distalgesic (dextropropoxyphene). *BMJ* 1980;i:1213-4.
44 Begg C, Cho M, Eastwood S, Horton R, Moher D, Olkin I, et al. Improving the quality of reporting of randomised clinical trials—the CONSORT statement. *JAMA* 1996;276:637-9.
45 Perrier D, Gibaldi M. Influence of first-pass effect on the systemic availability of propoxyphene. *J Clin Pharmacol* 1973;12:449-52.
46 Miller RR, Feingold A, Paxinos J. Propoxyphene hydrochloride: a clinical review. *JAMA* 1970;213:996-1006.

(Accepted 5 August 1997)

Clinical and angiographic predictors of stroke and death from carotid endarterectomy: systematic review

P M Rothwell, J Slattery, C P Warlow

Abstract

Objective: To identify risk factors for operative stroke and death from carotid endarterectomy.

Design: Systematic review of all studies published since 1980 which related risk of stroke and death to various preoperative clinical and angiographic characteristics, including unpublished data on 1729 patients from the European carotid surgery trial.

Main outcome measure: Operative risk of stroke and death.

Results: Thirty six published studies fulfilled our criteria. The effect of 14 potential risk factors was examined. The odds of stroke and death were decreased in patients with ocular ischaemia alone (amaurosis fugax or retinal artery occlusion) compared with those with cerebral transient ischaemic attack or stroke (seven studies; odds ratio 0.49; 95% confidence interval 0.37 to 0.66; $P < 0.00001$). The odds were increased in women (seven studies; 1.44; 1.14 to 1.83; $P < 0.005$), subjects aged ≥75 years (10 studies; 1.36; 1.09 to 1.71; $P < 0.01$), and with systolic blood pressure >180 mm Hg (four studies; 1.82; 1.37 to 2.41; $P < 0.0001$), peripheral vascular disease (one study; 2.19; 1.40 to 3.60; $P < 0.0005$), occlusion of the contralateral internal carotid artery (14 studies; 1.91; 1.35 to 2.69; $P < 0.0001$), stenosis of the ipsilateral internal carotid siphon (five studies; 1.56; 1.03 to 2.36; $P = 0.02$), and stenosis of the ipsilateral external carotid artery (one study; 1.61; 1.05 to 2.47; $P = 0.03$). Operative risk was not significantly related to presentation with cerebral transient ischaemic attack versus stroke, diabetes, angina, recent myocardial infarction, current cigarette smoking, or plaque surface irregularity at angiography. Multiple regression analysis of data from the European carotid surgery trial identified cerebral versus ocular events at

Department of Clinical Neurosciences, Western General Hospital, Edinburgh, EH4 2XU

P M Rothwell, *research fellow*

J Slattery, *statistician*

C P Warlow, *professor of neurology*

Correspondence to: Dr P M Rothwell, Department of Clinical Neurology, Radcliffe Infirmary, Woodstock Road, Oxford OX2 6HE
peter.rothwell@clneuro.ox.ac.uk

BMJ 1997;315:1571–7

presentation, female sex, systolic hypertension, and peripheral vascular disease as independent risk factors.

Conclusions: The risk of stroke and death from carotid endarterectomy is related to several clinical and angiographic characteristics. These observations may help clinicians to estimate operative risks for individual patients and will also facilitate more meaningful comparison of the operative risks of different surgeons or at different institutions by allowing some adjustment for differences in case mix.

Introduction

The absolute benefit derived from carotid endarterectomy is limited by the morbidity and mortality caused by the operation itself. The balance of risk and benefit is particularly fine in patients in whom the risk of stroke while they are receiving medical treatment is very low to begin with, such as those with asymptomatic stenosis.[1–3] To maximise the cost effectiveness of endarterectomy we need to identify subgroups of patients who are at high risk of stroke without surgery but who have a relatively low operative risk of stroke and death.[4] Much work has gone into prediction of the risk of major stroke on medical treatment alone,[5 6] but there has been less research into the factors which predict operative risk. Although there have been at least 126 reports of the morbidity and mortality of carotid endarterectomy published over the past 15 years,[7] many of which have made some attempt to identify possible risk factors, there has been no systematic review of risk factors for operative stroke and death. Such a review is required both to target endarterectomy more effectively and to help to correct for case mix in clinical research and audit. We performed a systematic review of all studies published since 1980 which related the risk of stroke and death from carotid endarterectomy to preoperative clinical and angiographic characteristics. The review also includes unpublished data from the European carotid surgery trial.[8 9] In addition, we performed a multiple regression analysis of the data from the European carotid surgery trial to identify which of the potential risk factors identified in the systematic review were independent predictors of operative outcome.

Methods

The methods of the systematic review have been published previously.[7] Briefly, studies were identified by a single observer from CD ROM (Cambridge Medline, 1980-6) by using the search strategies carotid endarterectomy and carotid surgery. The Cochrane Collaboration's stroke database was also searched,[10] but there was no systematic hand searching of journals. The reference lists of all papers identified electronically were searched.

Articles were included in this review if they fulfilled the following criteria: *(a)* prospective or retrospective (case note review) study; *(b)* reported numbers of strokes and deaths occurring within 30 days of carotid endarterectomy (or similar time period); *(c)* endarterectomy performed for symptomatic stenosis, asymptomatic stenosis, or a combination of the two, but not explicitly for acute stroke; *(d)* operative risks defined per operation rather than per patient in studies in which some patients underwent bilateral endarterectomy; *(e)* operative risk stratified according to one or more clinical or angiographic characteristics assessed before surgery; and *(f)* no evidence of a systematic policy for patients with different characteristics to be operated on by different surgeons or at different institutions. Unpublished data on the 1729 patients who underwent carotid endarterectomy as part of the European carotid surgery trial[8 9] were included. The North American symptomatic carotid endarterectomy trial continues to randomise patients and no data on surgical morbidity were available.[11]

The risk of stroke and death was defined per operation. The overall relative odds of stroke and death for one preoperative characteristic versus another were calculated by using the Mantel-Haenszel method.[12] Differences between studies in the relation between each

Table 1 Odds of stroke and deaths due to endarterectomy according to presence or absence of various preoperative clinical and angiographic characteristics

Characteristic	No of studies	Strokes and deaths/No of operations				Relative odds of stroke and death*		Heterogeneity	
		Cases	Controls	O-E	Variance	Odds ratio (95% CI)	P value	χ^2	P value
Clinical									
Presenting symptoms:									
Monocular *v* cerebral transient ischaemic attack	7	32/1262	304/4838	–34.6	49.3	0.49 (0.37 to 0.66)	< 0.00001	1.4	0.96
Cerebral transient ischaemic attack *v* stroke	7	115/1519	118/2718	0.5	59.1	1.01 (0.78 to 1.30)	0.70	14.0	0.04
Female *v* male sex	7	132/2520	195/4775	24.6	67.0	1.44 (1.14 to 1.83)	< 0.005	9.6	0.45
Age (>74 *v* <75)	10	125/2573	463/11453	23.2	75.0	1.36 (1.09 to 1.71)	< 0.01	13.9	0.15
Hypertension†	4	110/1842	141/2972	28.6	47.8	1.82 (1.37 to 2.41)	< 0.0001	0.6	0.9
Diabetes	2	32/647	156/3424	5.4	21.4	1.29 (0.84 to 1.97)	0.21	0.6	0.4
Angina	2	46/534	135/1892	5.1	28.4	1.20 (0.83 to 1.73)	0.16	0.1	0.7
Recent myocardial infarction	2	8/64	173/2362	3.3	4.3	2.14 (0.83 to 5.53)	0.15	0.6	0.4
Peripheral vascular disease	1	35/284	87/1445	N/A	N/A	2.19 (1.40 to 3.60)	0.0005	N/A	N/A
Current smoking	2	96/1818	87/2068	6.2	42.7	1.16 (0.86 to 1.56)	0.30	0.6	0.4
Angiographic									
Occlusion of contralateral internal carotid artery	14	60/935	347/7690	20.9	32.5	1.91 (1.35 to 2.69)	< 0.0001	21.6	0.08
Ipsilateral plaque surface irregularity	2	102/1273	79/1163	10.0	38.7	1.29 (0.95 to 1.77)	0.08	0	0.9
Stenosis of distal ipsilateral internal carotid artery	5	39/592	152/2906	9.8	22.1	1.56 (1.03 to 2.36)	0.02	4.6	0.3
Stenosis of ipsilateral external carotid artery	1	31/309	89/1373	N/A	N/A	1.61 (1.05 to 2.47)	0.03	N/A	N/A

O-E = observed minus expected. NA = not applicable.
*As overall odds ratios were calculated by combining individual study data with Mantel-Haenszel method they differ from odds which would be obtained simply by using totals shown in table.
†Systolic blood pressure >180 mm Hg.

clinical characteristic and operative risk were assessed by using the χ^2 test for heterogeneity. We used data on the 1729 patients in the European carotid surgery trial to perform multiple regression analysis to identify which of the potential risk factors identified in the review were independent predictors of operative stroke and death. A forward conditional stepwise logistic regression analysis (SPSS for windows, version 6.1) was used. Variables were entered at a significance level of $P = 0.05$ and removed at a level of $P = 0.1$.

Results

A total of 126 studies reporting the risk of stroke and death associated with carotid endarterectomy were identified from our literature search. Six studies contained no useful data and 84 did not stratify operative risk of stroke and death by baseline characteristics. In addition to the unpublished data from the European trial a total of 36 studies fulfilled our inclusion criteria.[3–47] One study[47] was excluded because the data reported overlapped with those of a subsequent study.[23] There were 122 major strokes or deaths within 30 days of endarterectomy in the 1729 patients in the European carotid surgery trial.

The clinical and angiographic characteristics for which the relation with operative risk was reported are summarised in table 1. Five clinical characteristics were associated with a significantly increased operative risk of stroke and death: surgery for cerebral symptoms (stroke or transient ischaemic attack) compared with monocular ischaemia (amaurosis fugax or retinal artery occlusion) (fig 1); female versus male sex (fig 2); age above or below 75 years (fig 3); and systolic blood pressure >180 mm Hg and peripheral vascular disease (fig 4). There was no significant heterogeneity between studies in the odds of stroke or death for any of these risk factors (table 1).

Three angiographic characteristics were associated with an increased risk of operative stroke or death: contralateral internal carotid artery occlusion (fig 5); stenosis of the intracranial portion of the ipsilateral internal carotid artery and of the ipsilateral external carotid artery (fig 6). None of these analyses showed significant heterogeneity between studies (table 1). There was no significant relation between operative risk and the presence of diabetes, angina, recent myocardial infarction, plaque surface irregularity, or a current history of smoking (table 1). There was no overall difference between the operative risk associated with cerebral transient ischaemic attack versus stroke (fig 7), although there was significant heterogeneity (χ^2 14.0; $df = 6$; $P = 0.04$; table 1). Meta-analysis of the six published studies suggested that stroke was associated with an increased risk (odds ratio 1.46; 95% confidence interval 1.04 to 2.04), whereas the data from the European carotid surgery trial suggested a significantly lower risk (0.62; 0.42 to 0.91).

Of the 14 risk factors in table 1 which were entered into a multiple logistic regression analysis of the data from the European carotid surgery trial, four were found to be significant independent predictors of operative stroke or death (table 2).

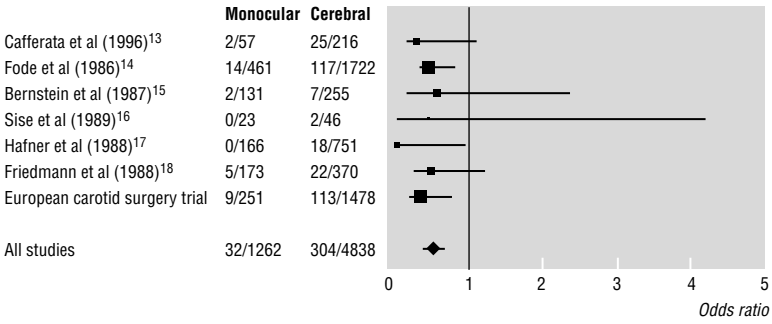

Fig 1 Odds of stroke and death from endarterectomy for monocular ischaemia (amaurosis fugax and retinal artery occlusion) compared with cerebral ischaemia (transient ischaemic attack or completed stroke). Odds ratio for each study represented by a square, the area of which is proportional to statistical power of estimate. Line represents 95% confidence interval of odds ratio. Diamond represents overall pooled estimate

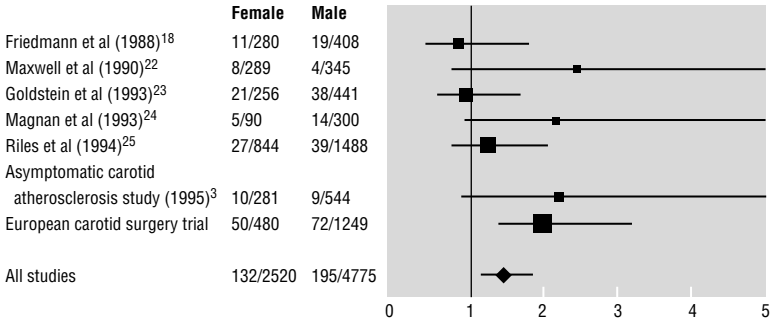

Fig 2 Odds of stroke and death from carotid endarterectomy in women compared with men

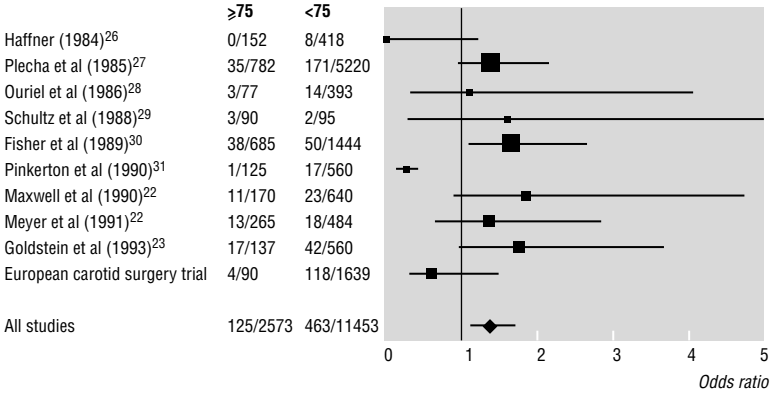

Fig 3 Odds of stroke and death from endarterectomy in patients aged 75 years and older compared with patients aged less than 75 years

Discussion

This is the first systematic review of the clinical and angiographic factors associated with an increased risk of stroke and death from carotid endarterectomy. The analysis was restricted to defining the overall relative odds of stroke and death according to the presence or absence of each potential risk factor in those studies in which the information was available. In view of the clear variation between different studies in the reported risks[7] we did not determine absolute risks. Restriction of the analysis to relative odds allowed us to include, when appropriate, data from reports of surgery for asymptomatic stenosis as well as symptomatic stenosis. Even though the reported absolute risks of surgery for asymptomatic stenosis are consistently

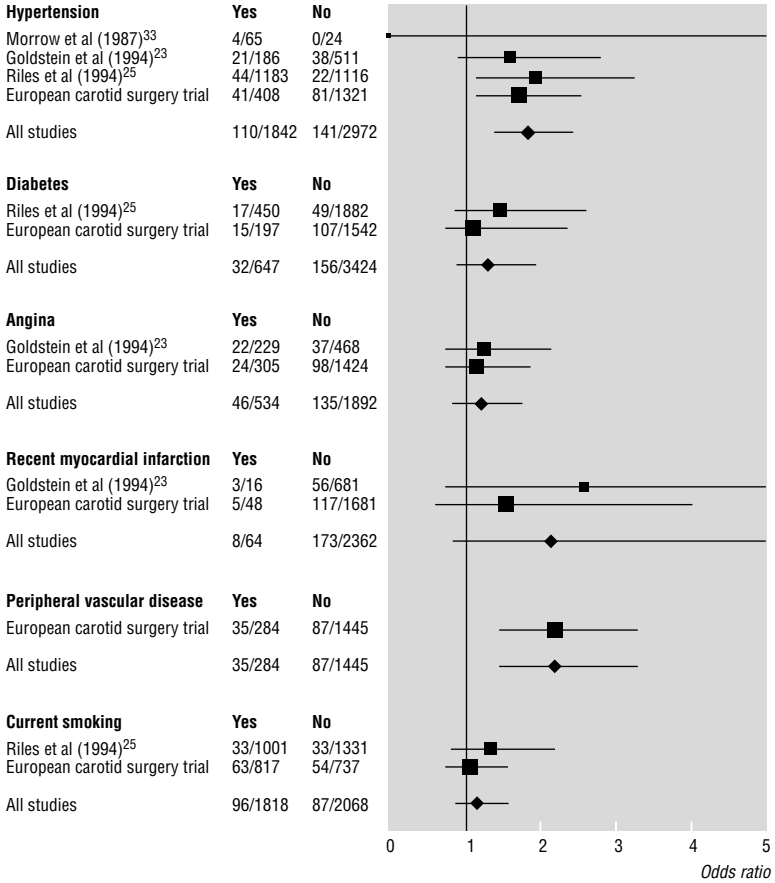

Fig 4 Odds of stroke and death from carotid endarterectomy associated with presence of hypertension (systolic blood pressure >180 mm Hg), diabetes mellitus, angina, recent myocardial infarction (within previous year), peripheral vascular disease, and current cigarette smoking

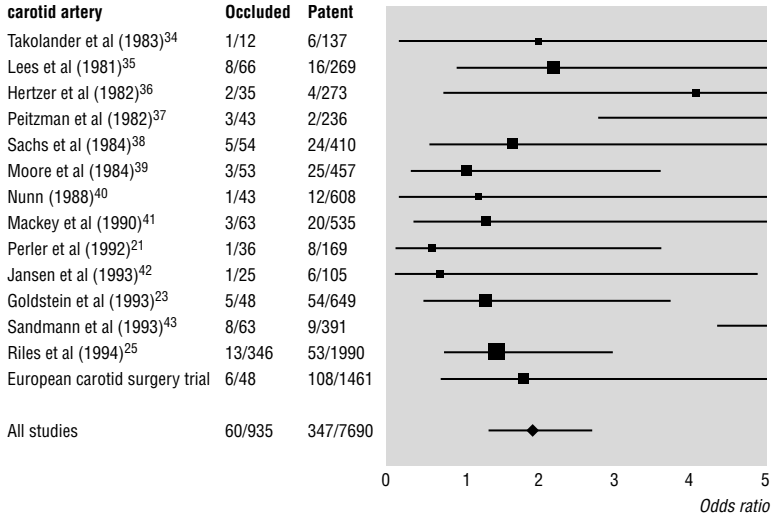

Fig 5 Odds of stroke and death from carotid endarterectomy in patients with occlusion of contralateral carotid artery compared with those with patent artery

lower than in patients with symptomatic stenosis,[48] there is no evidence that the relative effect of clinical characteristics such as age or sex on the operative risk of stroke and death will differ. This is supported by the lack of significant heterogeneity between studies for any of the risk factors for which data from studies of symptomatic patients were combined with data from studies of asymptomatic patients.

Clinical presentation and operative risk

We have shown that the risk of stroke and death from carotid endarterectomy depends on the type of presenting symptoms. The odds of stroke and death in patients with only ocular symptoms (amaurosis fugax or retinal artery occlusion) are less than half those in patients with cerebral transient ischaemic attacks. Although not strictly comparable, the 2.5% (95% confidence interval 1.8 to 3.5) risk of stroke and death in the eight reports of endarterectomy for ocular symptoms alone is similar to the 3.4% (2.4 to 4.3) overall risk derived from 25 studies of endarterectomy for asymptomatic stenosis.[48] It is interesting to note that the risk of stroke on medical treatment is also lower in patients with amaurosis fugax than in patients with cerebral transient ischaemic attack.[4 5 49]

Contrary to expert guidelines on carotid endarterectomy[50 51] we found no overall difference in the operative risk of stroke and death in patients operated on for stroke compared with those operated on for transient cerebral ischaemia, although there was significant heterogeneity between studies. We suspect that the increased risk in patients operated on for stroke in the published studies may well have been due to the inclusion in some of these studies of patients with stroke in evolution or very recently completed stroke. In the European carotid surgery trial, in which patients operated on for stroke had a significantly lower operative risk than patients operated on for transient cerebral ischaemia, surgeons were advised not to operate until at least one month after the occurrence of a stroke. The suggestion that surgery for transient ischaemic attacks has a lower operative risk than surgery for stroke may also be due to a failure to distinguish between ocular and cerebral transient ischaemic attacks. The real dichotomy is not between transient ischaemic attack and stroke but between ocular and cerebral ischaemia. This should be reflected in future guidelines. The expected operative risks for endarterectomy for asymptomatic stenosis and ocular ischaemia are in the region of 2-4%, whereas the risk of endarterectomy for cerebral ischaemia is about double this.

Sex and operative risk

Operative morbidity and mortality in coronary artery surgery is higher in women than in men.[52] We therefore examined the effect of sex on the risk of stroke and death from carotid endarterectomy. In the seven studies which reported data, the overall odds of stroke and death were increased by 44% in women. A significantly increased operative risk in women was mentioned in two further studies, but insufficient data were given to allow inclusion in the review.[53 54] The increased risk reported in women might be due to publication bias—authors reporting data only if there is an interesting trend. No studies, however, reported a significantly increased operative risk in men. The higher operative risk observed in women compared with men might be accounted for by differences in other factors, such as age, presenting symptoms, or coexisting illness. Multiple regression analysis of the data from the European carotid surgery trial, with correction for the other variables listed in table 1, however,

failed to reduce the association between female sex and operative risk (table 2). It is unclear why women should be at greater operative risk than men. Possibly the fact that the carotid arteries in women are, on average, about 40% smaller than in men makes the operation technically more difficult.

Other clinical and angiographic characteristics and operative risk

The risk of stroke and death due to endarterectomy was increased in patients aged 75 and over, those with systolic hypertension, and those with peripheral vascular disease. The association of peripheral vascular disease with increased operative risk was reported in another study,[55] but no data were given. With regard to hypertension, it is unclear whether treatment before surgery would be beneficial. The increased risk of surgery in patients aged 75 years and over is not large, and age should not be regarded as a contraindication to surgery. There was no evidence that angina, recent myocardial infarction, diabetes, or smoking are associated with an increased risk of stroke or death due to endarterectomy, although more data are required before any useful conclusions can be drawn. They may, of course, be associated with other postoperative morbidity, such as myocardial infarction or chest infection.

Given that patients with irregular stenoses are at increased risk of ipsilateral ischaemic stroke on medical treatment,[56 57] the observation that angiographic irregularity of the plaque surface is not clearly associated with an increased risk of stroke with surgical treatment is important. Patients with irregular or ulcerated plaques are probably, therefore, particularly likely to benefit from endarterectomy, although more data on the relation between plaque surface morphology and operative risk are required.

There was a trend towards an increased operative risk with occlusion of the contralateral internal carotid artery in 12 of the 14 studies (see fig 5). Because of the relatively low prevalence of contralateral occlusion in the studies reviewed (407/8626; 4.7%), however, this reached significance in only two. This is also likely to account for the lack of a significant association between contralateral occlusion and operative risk in the multiple regression analysis of the data from the European carotid surgery trial.

Limitations of this study

The studies included in the systematic review were of varying methodological quality. Some were retrospective and only a minority of the remainder had independent assessment of outcome by a neurologist. Although this may have led to an underestimation of the absolute operative risk in some studies,[58] we have assumed that this will not bias the relative odds of stroke and death due to surgery with respect to particular risk factors. We have also assumed that the "effect" of the risk factor on operative risk is relatively independent of other treatments—such as anticoagulation, patching, or shunting—the use of which may have varied between studies. Our previous experience of similar analyses suggests that these assumptions are reasonable. In a systematic comparison of the operative risk of carotid endarterectomy for asymptomatic compared with symptomatic stenosis we identified 25 studies in which the operations had been carried out by the same surgeon or in the same institution.[48] Even though there were major differences between the studies in terms of methodology and other treatments given, a trend towards a reduced operative risk associated with asymptomatic stenosis was found in 24 (96%) of the studies, and there was virtually no quantitive heterogeneity of effect between studies (χ^2 13.6; df = 24; P = 0.96). In the present study, one of the meta-analyses showed borderline significant heterogeneity (see table 1). Given that this study includes 12 meta-analyses, however, one significantly heterogeneous result would reasonably be expected by

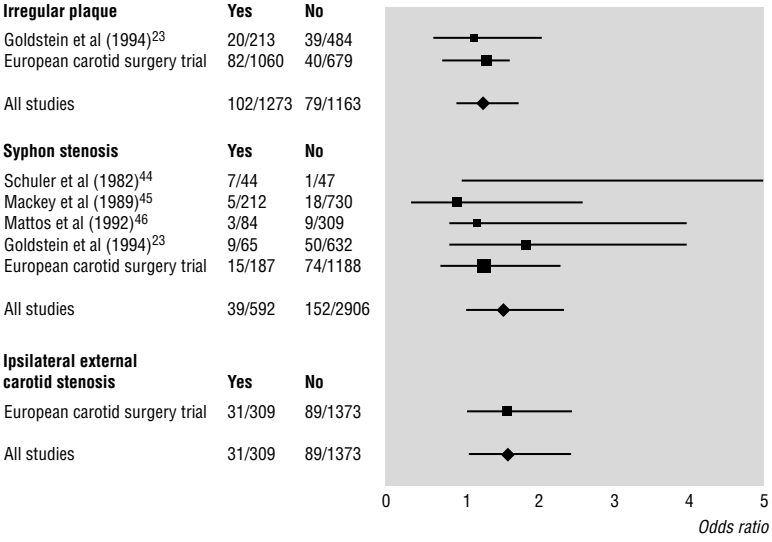

Fig 6 Odds of stroke and death from carotid endarterectomy associated with following angiographic characteristics: ipsilateral plaque surface irregularity; stenosis of the ipsilateral carotid syphon; >50% stenosis of ipsilateral external carotid artery

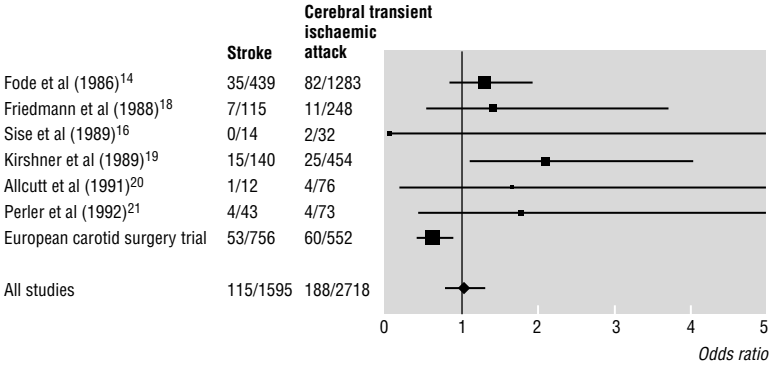

Fig 7 Odds of stroke and death from endarterectomy for cerebral transient ischaemic attack compared with completed stroke

Table 2 Multiple regression analysis of operative risk of stroke and death in 1729 patients who underwent carotid endarterectomy in European carotid surgery trial in relation to potential clinical and angiographic risk factors identified in systematic review

Risk factor*	Hazard ratio (95% CI)	P value
Ocular *v* cerebral symptoms	0.46 (0.24 to 0.91)	0.02
Female sex	1.41 (1.16 to 1.70)	0.0005
Systolic hypertension (>180 mm Hg)	1.93 (1.22 to 3.04)	0.005
Peripheral vascular disease	1.44 (1.17 to 1.79)	0.0007

*Variables not included in model: age >75 years (P=0.36); angina (P=0.99); recent myocardial infarction (P=0.30); diabetes mellitus (P=0.84); current smoking (P=0.86); occlusion of contralateral internal carotid artery (P=0.82); 50-100% stenosis of ipsilateral external carotid artery (P=0.23); ipsilateral carotid plaque surface irregularity (P=0.12); stenosis of distal ipsilateral internal carotid artery (P=0.62).

Key messages

- Although carotid endarterectomy has been shown to reduce the risk of stroke in selected patients, there is about a 5% operative risk of stroke and death
- The cost effectiveness of the operation is limited by the associated morbidity and mortality
- The risk of stroke and death from carotid endarterectomy is higher in women than in men
- Other clinical characteristics associated with an increased risk include cerebral as opposed to ocular transient ischaemic attack, age over 75 years, systolic hypertension, and peripheral vascular disease
- Angiographic characteristics associated with an increased operative risk include occlusion of the contralateral internal carotid artery and stenosis of the ipsilateral carotid siphon or external carotid artery

chance. The remainder of the analyses showed relatively little heterogeneity, suggesting that our assumptions were reasonable.

As discussed above with reference to the increased operative risk reported in women, publication bias is a further potential problem with the study. It is quite possible that some of the studies we included looked at the interaction of several risk factors with operative risk but published only those which were "interesting" or significant. This should, however, introduce bias in both directions—that is, analyses are probably equally likely to be published whether or not a particular risk factor indicates an abnormally high or an abnormally low operative risk. Funnel plots of the analyses reported in our paper do not show any obvious skewing suggestive of publication bias.

The associations between clinical and angiographic characteristics and the risk of stroke and death from endarterectomy in the systematic review cannot, of course, be corrected for the possible confounding effect of other variables. The risk factors identified in the multiple regression analysis of the European data, however, are independent to the extent that the association with operative risk has been corrected for the other potential risk factors in table 1. This does not, of course, mean that the associations are necessarily causal. For example, the association between peripheral vascular disease and an increased operative risk is probably due to some confounding factor which has not been measured in this study. In terms of identifying patients at high risk of operative stroke and death, however, it is association rather than causation that is important.

To improve the cost effectiveness of carotid endarterectomy patients should be selected on the basis of their likely risk of stroke without surgery as well as their risk of stroke and death from endarterectomy. Although we have identified risk factors for increased surgical risk, it does not follow that the presence of these risk factors will necessarily reduce the possible absolute benefit of endarterectomy. Certain characteristics may be associated with an increased risk of stroke on medical treatment as well as surgical treatment and will not therefore be associated with reduced absolute benefit from surgery. Other characteristics, such as female sex, seem to indicate an increased surgical risk but are not related to the risk of stroke on medical treatment alone and may therefore be useful in identifying patients with less to gain from endarterectomy.

Conclusions

We have defined several clinical and angiographic characteristics that are associated with an increased risk of stroke and death from carotid endarterectomy. These observations may help clinicians to estimate the possible operative risks for individual patients and will also facilitate more meaningful comparison of the operative risks of different surgeons or different institutions by allowing some adjustment for differences in case mix. The risk factors derived from the systematic review and those derived from analysis of the data from the European carotid surgery trial, however, need to be validated on a large independent dataset before they can be used routinely in clinical practice.

We acknowledge the European Carotid Surgery Trial Collaborative Group for the collection of the data from the European carotid surgery trial used in this study.

Funding: PMR and JS were funded by the Medical Research Council.

Conflict of interest: None.

1 The European Carotid Surgery Trialists' Collaborative Group. Risk of stroke in the distribution of an asymptomatic carotid artery. *Lancet* 1995;345:209-12.
2 Hobson RW, Weiss DG, Fields WS, Goldstone J, Moore WS, Towne JB, et al. Efficacy of carotid endarterectomy for asymptomatic carotid stenosis. *N Engl J Med* 1993;328:221-7.
3 Asymptomatic Carotid Atherosclerosis Study Group. Carotid endarterectomy for patients with asymptomatic internal carotid artery stenosis. *JAMA* 1995;273:1421-8.
4 Rothwell PM, Slattery J, Warlow CP on behalf of the European Carotid Surgery Trial. Can we identify the patients with most to gain and least to lose from endarterectomy? *Cerebrovasc Dis* 1994;suppl 1:260.
5 Hankey GJ, Slattery JM, Warlow CP. Transient ischaemic attacks: which patients are at high (and low) risk of serious vascular events? *J Neurol Neurosurg Psychiatry* 1992;55:640-52.
6 Dutch TIA Trial Study Group. Predictors of major vascular events in patients with a transient ischemic attack or nondisabling stroke. *Stroke* 1993;24:527-31.
7 Rothwell PM, Slattery J, Warlow CP. A systematic review of the risks of stroke and death due to carotid endarterectomy for symptomatic stenosis. *Stroke* 1996;27:260-5.
8 European Carotid Surgery Trialists' Collaborative Group. MRC European carotid surgery trial: interim results for symptomatic patients with severe (70-99%) or with mild (0-29%) carotid stenosis. *Lancet* 1991;337:1235-43.
9 European Carotid Surgery Trialists' Collaborative Group. MRC European carotid surgery trial. The effectiveness of carotid endarterectomy in patients with 30-69% symptomatic carotid stenosis. *Lancet* 1996;347:1591-3.
10 *Cochrane database of systematic reviews*. London: BMJ Publishing Group, 1995.
11 North American Symptomatic Carotid Endarterectomy Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. *N Engl J Med* 1991;325:445-53.
12 Yusuf S, Peto R, Lewis J, Collins R, Sleight P. Beta-blockade during and after myocardial infarction: an overview of the randomised trials. *Prog Cardiovasc Dis* 1985;27:335-71.
13 Cafferata HT, Gainey MD. Carotid endarterectomy in the community hospital: a continuing controversy. *J Cardiovasc Surg* 1986;27:557-60.
14 Fode NC, Sundt TM, Robertson JT, Peerless SJ, Shields CB. Multicenter retrospective review of results and complications of carotid endarterectomy in 1981. *Stroke* 1986;17:370-6.
15 Bernstein EF, Dilley RB. Late results after carotid endarterectomy for amaurosis fugax. *J Vasc Surg* 1987;6:333-40.
16 Sise MJ, Sedwitz MM, Rowley WR, Shackford SR. Prospective analysis of carotid endarterectomy and silent cerebral infarction in 97 patients. *Stroke* 1989;20:329-32.
17 Hafner CD, Evans WE. Carotid endarterectomy with local anesthesia: results and advantages. *J Vasc Surg* 1988; 7:232-9.
18 Friedmann P, Garb JL, Berman J, Sullivan C, Celoria G, Rhee SW. Carotid endarterectomy. Clinical results in a community-based teaching hospital. *Stroke* 1988;19:1323-7.
19 Kirshner DL, O'Brien MS, Ricotta JJ. Risk factors in a community experience with carotid endarterectomy. *J Vasc Surg* 1989;10:178-86.
20 Allcutt DA, Chakraborty M, Sengupta RP. Neurosurgical experience with carotid endarterectomy: a 12 year study. *Br J Neurosurg* 1991;5:257-64.

21 Perler BA, Burdick JF, Williams GM. Does contralateral internal carotid artery occlusion increase the risk of carotid endarterectomy? *J Vasc Surg* 1992;16:347-53.
22 Maxwell JG, Rutherford EJ, Covington DL, Churchill P, Patrick RD, Scott C, et al. Community hospital carotid endarterectomy in patients over age 75. *Am J Surg* 1990;160:598-603.
23 Goldstein LB, McCrory C, Landsman PB, Samsa GP, Ancukiewicz M, Oddone EZ, et al. Multicenter review of preoperative risk factors for carotid endarterectomy in patients with ipsilateral symptoms. *Stroke* 1994;25:1116-21.
24 Magnan P-E, Caus T, Branchereau A, Rosset E, Prima F. Internal carotid artery surgery: ten-year results. *Ann Vasc Surg* 1993;7:521-9.
25 Riles TS, Imparato AM, Jacobwitz GR, Lamparello PJ, Giangola G, Adelman MA, et al. The cause of perioperative stroke after carotid endarterectomy. *J Vasc Surg* 1994;19:206-16.
26 Haffner CD. Minimising the risks of carotid endarterectomy. *J Vasc Surg* 1984;1:392-7.
27 Plecha FR, Bertin VJ, Plecha EJ, Avellone JC, Farrell CJ, Hertzer NR, et al. The early results of vascular surgery in patients 75 years of age and older: an analysis of 3259 cases. *J Vasc Surg* 1985;2:769-74.
28 Ouriel K, Penn TE, Ricotta JJ, May AG, Green RM, DeWeese JA. Carotid endarterectomy in the elderly patient. *Surg Gynecol Obstet* 1986; 162:334-6.
29 Schultz RD, Sterpetti AV, Feldhaus RJ. Carotid endarterectomy in octogenarians and nonagenarians. *Surg Gynecol Obstet* 1988;166:245-51.
30 Fisher ES, Malenka DJ, Solomon NA, Bubolz TA, Whaley FS, Wennberg JE. Risk of carotid endarterectomy in the elderly. *Am J Public Health* 1989;79:1617-20.
31 Pinkerton JA, Gholkar VR. Should patient age be a consideration in carotid endarterectomy? *J Vasc Surg* 1990;11:650-8.
32 Meyer FB, Meissner I, Fode NC, Losasso TJ. Carotid endarterectomy in elderly patients. *Mayo Clin Proc* 1991;66:464-9.
33 Morrow CE, Espada R, Howell JF. Operative and long-term results of staged contralateral carotid endarterectomy: a personal series. *Surgery* 1988;103:242-6.
34 Takolander RJ, Bergentz SE, Ericsson BF. Carotid artery surgery in patients with minor stroke. *Br J Surg* 1983;70:13-6.
35 Lees CD, Hertzer NR. Postoperative stroke and late neurologic complications after carotid endarterectomy. *Arch Surg* 1981;116:1561-8.
36 Hertzer NR, Beven EG, Modic MT, O'Hara PJ, Vogt DP, Weinstein MA. Early patency of the carotid artery after endarterectomy: digital subtraction angiography after two hundred and sixty-two operations. *Surgery* 1982;92:1049-56.
37 Peitzman AB, Webster MW, Loubeau J-M, Grundy BL, Bahnson HT. Carotid endarterectomy under regional (conductive) anesthesia. *Ann Surg* 1982;196:59-64.
38 Sachs SM, Fulenwider JT, Smith RB, Darden WA, Salam AA, Perdue GD. Does contralateral carotid occlusion influence neurologic fate of carotid endarterectomy? *Surgery* 1984;96:839-44.
39 Moore DJ, Modi JR, Finch WT, Sumner DS. Influence of the contralateral carotid artery on neurologic complications following carotid endarterectomy. *J Vasc Surg* 1984;1:409-14.
40 Nunn DB. Carotid endarterectomy in patients with territorial transient ischemic attacks. *J Vasc Surg* 1988;8:447-52.
41 Mackey WC, O'Donnell TF, Callow AD. Carotid endarterectomy contralateral to an occluded carotid artery: perioperative risk and late results. *J Vasc Surg* 1990;11:778-85.
42 Jansen C, Vriens EM, Eikelboom BC, Vermeulen FEE, van Gijn J, Ackerstaff RGA. Carotid endarterectomy with transcranial Doppler and electroencephalographic monitoring: a prospective study in 130 operations. *Stroke* 1993;24:665-9.
43 Sandmann W, Kolvenbach R, Willeke F. Risks and benefits of shunting in carotid endarterectomy. *Stroke* 1993;24:1098-9.
44 Schuler JJ, Flanigan P, Lim LT, Keifer T, Williams LR, Behrennd AJ. The effect of carotid siphon stenosis on stroke rate, death, and relief of symptoms following elective carotid endarterectomy. *Surgery* 1982;92:1058-66.
45 Mackey WC, O'Donnell TF, Callow AD. Carotid endarterectomy in patients with intracranial vascular disease: short-term risk and long-term outcome. *J Vasc Surg* 1989;10:432-8.
46 Mattos MA, van Bemmelen PS, Hodgson KJ, Barkmeier LD, Ramsey DE, Sumner DS. The influence of siphon stenosis on short- and long-term outcome after carotid endarterectomy. *J Cardiovasc Surg* 1992;33:387-400.
47 McCrory DC, Goldstein LB, Samsa GP, Oddone EZ, Landsman PB, Moore WS, et al. Predicting complications of carotid endarterectomy. *Stroke* 1993;24:1285-91.
48 Rothwell PM, Slattery J, Warlow CP. A systematic comparison of the risks of stroke and death due to carotid endarterectomy for symptomatic and asymptomatic stenosis. *Stroke* 1996;27:266-9.
49 Streifler JY, Eliasziw M, Benavente OR, Harbison JW, Hachinski VC, Barnett HJM, et al, for the North American Symptomatic Carotid Endarterectomy Trial. The risk of stroke in patients with first-ever retinal vs hemispheric transient ischemic attack and high-grade carotid stenosis. *Arch Neurol* 1995;52:246-9.
50 Beebe HG, Clagett GP, DeWeese JA, Moore WS, Robertson JT, Sandok B, et al. Assessing risk associated with carotid endarterectomy. A statement for health professionals by an ad hoc committee on carotid surgery standards of the Stroke Council, American Heart Association. *Stroke* 1989;20:314-5.
51 Ad Hoc Committee, American Heart Association. Guidelines for carotid endarterectomy. *Stroke* 1995;26:188-201.
52 Weintraub WS, Wenger NK, Jones EL, Craver JM. Changing clinical characteristics of coronary surgery patients. Differences between men and women. *Circulation* 1993;88:1179-86.
53 Kirshner DL, O'Brien MS, Ricotta JJ. Risk factors in a community experience with carotid endarterectomy. *J Vasc Surg* 1989;10:178-86.
54 Hertzer NR, Flanagan RA, O'Hara PJ, Beven EG. Surgical vs nonoperative treatment of asymptomatic carotid stenosis. *Ann Surg* 1986;204:163-71.
55 Bass A, Meisel S, Walden R. Intermittent claudication as a prognostic marker in carotid surgery. *J Vasc Surg* 1986;4:893.
56 Eliasziw M, Streifler JY, Fox AJ, Hachinski VC, Ferguson GG, Barnett HJM for the North American Symptomatic Carotid Endarterectomy Trial. Significance of plaque ulceration in symptomatic patients with high grade carotid stenosis. *Stroke* 1994;25:304-8.
57 Rothwell PM, Villagra R, Donders R, Warlow CP. The role of carotid atherosclerosis in the aetiology of ischaemic stroke. *Cerebrovasc Dis* 1996;6(suppl 2);1.
58 Rothwell PM, Warlow CP. Is self-audit reliable? *Lancet* 1995;346:1623.

(Accepted 9 July 1997)

The West of Scotland coronary prevention study: economic benefit analysis of primary prevention with pravastatin

J Caro, W Klittich, A McGuire, I Ford, J Norrie, D Pettitt, J McMurray, J Shepherd for the West of Scotland Coronary Prevention Study Group

See editorial by Muldoon

The members of the executive committee are listed at the end of the article.

Caro Research, 336 Baker Avenue, Concord, MA 01742, USA
J Caro, *scientific director*
W Klittich, *director of informatics*

continued over

BMJ 1997;315:1577–82

Abstract

Objective: To estimate the economic efficiency of using pravastatin to prevent the transition from health to cardiovascular disease in men with hypercholesterolaemia.

Design: Economic benefit analysis based on data from the West of Scotland coronary prevention study. Treatment specific hazards of developing cardiovascular disease according to various definitions were estimated. Scottish record linkage data provided disease specific survival. Cost estimates were based on extracontractual tariffs and event specific average lengths of stay calculated from the West of Scotland coronary prevention study.

Subjects: Men with hypercholesterolaemia similar to the subjects in the West of Scotland coronary prevention study.

Main outcome: Cost consequences, the number of transitions from health to cardiovascular disease prevented, the number needed to start treatment, and cost per life year gained.

Results: If 10 000 of these men started taking pravastatin, 318 of them would not make the transition from health to cardiovascular disease (number needed to treat, 31.4), at a net discounted