Symptomatic carotid ischaemic events: safest and most cost effective way of selecting patients for angiography, before carotid endarterectomy

Graeme J Hankey, Charles P Warlow

Abstract

Objective—To determine the safest, least costly, and most effective way to select patients with symptomatic carotid ischaemic events for carotid angiography before carotid endarterectomy.

Design—Prospective cohort study.

Setting—University departments of clinical neurosciences and clinical neurology.

Patients—485 Patients with carotid territory transient ischaemic attacks of the brain (n=224) or eye (n=162) or retinal infarction (n=99) were referred to a single neurologist between 1976 and 1986.

Interventions—Clinical examination by auscultation over the precordium, supraclavicular fossae, and neck vessels (all patients). Cerebral angiography of patients suitable for carotid endartarectomy.

Main outcome measures—Financial cost and number of disabling strokes after angiography.

Results—296 Patients were investigated by cerebral angiography. Ischaemic symptoms had occurred in the distribution of 298 internal carotid arteries (symptomatic) that were imaged, two patients having bilateral symptoms. The presence or absence of a carotid bruit and the maximum percentage diameter stenosis of the origin of the symptomatic internal carotid artery were correlated. The prevalence of mild disease (diameter stenosis ≥25%) of the symptomatic internal carotid artery was 57%, and if an ipsilateral carotid bruit was heard the probability of mild stenosis rose to 92%. The prevalence of moderate disease of the symptomatic internal carotid artery (stenosis ≥50%) was 39%, and if a bruit was heard the probability doubled to 78%. The prevalence of severe internal carotid disease (stenosis ≥75%) was 22%, and if a bruit was heard the probability was more than double, at 49%. The direct cost to both the NHS and the private health sector of investigating patients with symptomatic carotid ischaemia was estimated for several strategies of carotid artery imaging and expressed in terms of financial cost and number of strokes after angiography incurred in detecting all patients with diameter stenosis of the symptomatic internal carotid artery of ≥25%, 50%, or 75%. To detect diameter stenosis of the internal carotid artery of ≥25% it is most cost effective to proceed directly to cerebral angiography in patients with a carotid bruit over the symptomatic carotid bifurcation and to screen patients without a carotid bruit by duplex carotid ultrasonography; patients in whom duplex ultrasonography discloses stenosis of ≥25% are then referred for cerebral angiography. To detect only more severe internal carotid disease (stenosis of ≥50%) the same policy applies, unless the local duplex ultrasonographic service is particularly efficient and reliable, when it is probably most cost effective and safer to screen all patients by this method irrespective of the findings on cervical auscultation. To detect stenosis of 75% or greater it is most cost effective to screen all patients with duplex ultrasonography, whether a carotid bruit is present or not, because this approach reduces the number of angiograms required, is the least expensive, and results in the least number of strokes after angiography.

Conclusions—Patient selection for cerebral angiography before carotid endarterectomy needs to be appropriate and cost effective. Sound clinical evaluation and duplex carotid ultrasound are required. The findings of this study should not be applied to other medical centres without first considering possible differences in the prevalence of carotid artery disease, the efficiency and reliability of duplex ultrasonography, the local complication rates of cerebral angiography, and the local costs of the imaging procedures.

Department of Clinical Neurosciences, Western General Hospital, Edinburgh EH4 2XU
Graeme J Hankey, FRACP, *research fellow*
Charles P Warlow, MD, *professor of medical neurology*

Correspondence to:
Dr Hankey.

Br Med J 1990;300:1485-91

Introduction

Preventing stroke and other serious vascular events is the aim in managing patients who have had a transient ischaemic attack or mild ischaemic stroke. Preventive measures include management of vascular risk factors such as hypertension and smoking, long term antiplatelet treatment,[1] and, perhaps, carotid endarterectomy to remove atherothrombotic stenosis at the origin of the internal carotid artery.[2] The risk-benefit ratio of carotid endarterectomy is currently being evaluated in several large randomised trials in Europe and North America.

Before carotid surgery is considered the carotid bifurcation must be imaged to the surgeon's satisfaction. Although carotid endarterectomy is occasionally performed on the basis of duplex carotid ultrasonography[3] or intravenous digital subtraction angiography studies alone (which we believe are inadequate[4]), most surgeons require angiographic demonstration of the extracranial (and intracranial) carotid circulation by selective intra-arterial cerebral angiography.[5] As this procedure is uncomfortable, somewhat risky, costly, and requires hospital admission[6] it is important that it is not performed unnecessarily in patients who will not subsequently proceed to carotid endarterectomy, such as those who have normal or occluded internal carotid arteries. Identifying the groups of patients likely to benefit from carotid surgery is still controversial,[2] but they are probably patients who have recovered more or less completely from a carotid ischaemic event, who have some stenosis of the origin of the internal carotid artery, ipsilateral to the cerebral hemisphere or eye in which symptoms are manifest. Accurate selection of patients for carotid endarterectomy therefore requires

sound clinical assessment and safe, cost effective imaging of the relevant carotid circulation(s).

Stenosis of the extracranial internal carotid artery may be detected clinically (by cervical auscultation for an arterial bruit) and with non-invasive imaging (ultrasonography, computed tomography, and magnetic resonance angiography) and invasive imaging (intra-arterial or intravenous digital subtraction angiography or conventional cerebral angiography).

Although a high anterolateral cervical bruit usually indicates diameter stenosis of the origin of the internal carotid artery of ≥25%,[7,8] its predictive value for carotid bifurcation disease is uncertain.[9-21] In some patients, particularly those with tight carotid stenosis or occlusion, there may be no bruit. In patients without carotid stenosis a bruit may result from disorders that will not be treated by carotid endarterectomy (for example, stenosis of the external carotid artery, vessel kinking, venous hums, and states of high arterial or venous flow that may accompany anaemia, pregnancy, or intracranial arteriovenous malformations[22]), and these do not therefore usually require cerebral angiography.

It seems that presently, the most effective non-invasive, and therefore safe, method of detecting carotid bifurcation disease is by duplex ultrasonography, utilising both Doppler flow studies and B mode imaging (although magnetic resonance angiography seems promising).[6,23] In recent studies the sensitivity of duplex ultrasonography for detecting mild atherosclerotic disease in the common carotid artery and proximal internal carotid artery was 91-99% and the specificity was 84-96%.[23] For detecting stenosis of more than 50% the sensitivity increased to 94-100%. Duplex ultrasonography can suggest occlusion of the internal carotid artery with a sensitivity of 80-96% and a specificity of 95%.[23] It does, however, require skill, it is costly, and (in the United Kingdom at least) it is not widely available.

Selective intra-arterial angiography is still regarded by many as the reference standard for imaging the carotid bifurcation, but it is associated with an inherent risk. We recently concluded that the total neurological complication rate of conventional cerebral angiography (mostly due to transient ischaemic attack or stroke) was about 4% and that the permanent neurological complication rate (due to disabling stroke) was about 1%.[24]

To ascertain the safest and most cost effective way to identify carotid bifurcation disease in patients with symptomatic carotid ischaemic events we examined the clinical and angiographic findings of a prospectively studied cohort of 296 patients and applied estimates of the cost of duplex carotid ultrasonography and cerebral angiography to the NHS and private health sector. We concentrated on the symptomatic rather than the asymptomatic internal carotid artery (see below) because there is currently little evidence to advocate prophylactic carotid endarterectomy for the asymptomatic condition.[25-27]

Patients and methods

From 1977 to 1986, 485 consecutive patients with carotid territory transient ischaemic attacks of the brain or eye, or both, or retinal infarction were referred to one of us (CPW) and evaluated. Clinical examination included auscultation over the precordium, supraclavicular fossae, and neck vessels (proximally and distally) in all patients. Bruits were classified as being carotid, supraclavicular, or transmitted from the chest. A carotid bruit was heard only in the high anterolateral cervical region over the carotid bifurcation or, alternatively, more proximally but with clear accentuation over the carotid bifurcation. Venous hums were ignored. The presence or absence of a carotid bruit was recorded as a simple dichotomous variable before cerebral angiography was considered.

The decision to proceed to cerebral angiography was made irrespective of the presence or absence of a carotid bruit. Non-invasive ultrasonography of the carotid circulation was not available for screening and selecting patients for angiography, and angiography was performed only if the patient was a potential candidate for carotid endarterectomy on clinical grounds (that is, had symptoms of carotid ischaemia and was fit for surgery) and had agreed to consider surgery if the angiogram were to show a potentially operable lesion of the symptomatic internal carotid artery.

Conventional cerebral angiography was performed under local anaesthesia with selective catheterisation (either by direct puncture or indirectly through the femoral route) of the symptomatic carotid artery and, in several patients, both carotid arteries. The carotid bifurcation was imaged in at least two planes in all patients, and triplanar imaging was obtained in some. Maximum percentage diameter stenosis (or the presence of occlusion) was calculated for the subclavian, vertebral, common carotid, extracranial internal carotid artery origin, external carotid artery origin, intracranial internal carotid artery siphon, and anterior and middle cerebral arteries for each side and also for the innominate artery. It was calculated by subtracting the diameter of the residual lumen from that of the vessel at the same site, dividing the difference by the diameter of the vessel at that site, and multiplying by 100. At the carotid bulb, just distal to the carotid bifurcation, this required an imaginary line to be extrapolated between the proximal and distal margins of the stenotic lesion, taking into account the natural convex curvature of the carotid bulb. The diameter of the vessel was not determined by measuring its diameter distal to the carotid bulb as this is commonly narrower than the normal diameter of the carotid bulb and would have led to an underestimate of the stenosis.

The maximum percentage diameter stenosis of each vessel was expressed on a clinically applicable interval scale (normal, 1-24%, 25-49%, 50-74%, 75-99%, occluded) and subsequently transformed into nominal (dichotomous) data for further analysis (< or ≥25%; < or ≥50%; < or ≥75%; occluded).

To determine the accuracy of a carotid bruit in predicting stenosis of the ipsilateral extracranial internal carotid artery the presence or absence of a bruit was correlated with the angiographic findings of the maximum percentage diameter stenosis at the origin of the ipsilateral internal carotid artery. The sensitivities, specificities, predictive values, likelihood ratios, odds (before and after the test (cervical auscultation)), and 95% confidence intervals of the findings on cervical auscultation compared with those on angiography were calculated by standard methods.[28,29] The confidence intervals for the likelihood ratios were calculated with the same methods as those used for calculating the confidence intervals for relative risks and odds ratios.[29]

FINANCIAL COSTS

The financial costs of duplex ultrasonography and cerebral angiography were defined in terms of "imaging cost units" (that is, the direct cost of one procedure on one patient (ignoring indirect costs such as the amount of patient time lost from paid employment)). The actual cost to the NHS is not known. We obtained an estimate of cost, however, by adding the semivariable costs of (*a*) admission to hospital for two days in a bed for patients having cerebral angiography (£160/day), (*b*) materials, power, non-medical staff (£110 for cerebral angiography, £25 for duplex ultra-

sonography (Lothian Health Board), and (c) a consultant ultrasonographer or angiographer. Although the schedule of fees for private consultant work prepared by the BMA's fees working party in 1989 recommends a consultants' fee of £25-45 for duplex ultrasonography and £150-200 for cerebral angiography,[30] the British United Provident Association will reimburse patients up to £270 for the ultrasonographer's fee and up to £335 for the angiographer's fee. In view of the considerable range of fees that a consultant may charge while still ensuring full reimbursement for the patient, we considered that a more accurate measure of the real cost to the NHS of these procedures would be given by a calculation including the consultant's salary per unit time paid by the NHS and the time taken to perform the procedure. The cost to the NHS of a consultant radiologist employed by the service is about £50 000 per year (annual salary and superannuation). In theory most radiologists work for 40 weeks each year (allowing six weeks' annual leave and six weeks' study leave) and 40 hours per week. About half the week is taken up with performing radiological procedures and half with administration, teaching, meetings, etc. Therefore, the cost of the radiologist per "procedure hour" is about £60 (50 000/(40×20). Duplex ultrasonography takes up to one hour and cerebral angiography one hour, with an additional half an hour needed to read the films and discuss the findings with the referring clinicians. The calculated costs of duplex ultrasonography and cerebral angiography to the NHS are therefore about £85 and £520 respectively and to the private sector about £295 and £765 respectively (table I). The risk of a major disabling stroke after angiography was estimated at 1%.[24]

TABLE I—*Costs (£) of duplex ultrasonography of carotid arteries and cerebral angiography to the NHS and private health sector*

	Duplex ultrasonography	Cerebral angiography
NHS		
Hospital bed (£160/day)	0	320
Materials	25	110
Consultant (£60/h)	60	90
Total	85	520
Private		
Hospital bed (£160/day)	0	320
Materials	25	110
Consultant (£60/h)	270	335
Total	295	765

TABLE II—*Number (percentage) of patients with symptomatic internal carotid artery disease and ipsilateral carotid bruit according to degree of diameter stenosis of symptomatic internal carotid artery*

	Diameter stenosis of symptomatic internal carotid artery (%)						
	0	1-24	25-49	50-74	75-99	100	Total
Symptomatic internal carotid artery disease	50 (17)	79 (27)	54 (18)	49 (16)	46 (15)	20 (7)	298
Ipsilateral carotid bruit	2 (4)	6 (8)	13 (24)	27 (55)	35 (76)	12 (60)	95

TABLE III—*Detection of bruit according to degree of diameter stenosis of symptomatic internal carotid artery and occlusion*

	Diameter stenosis (%)						Occluded	
	≥25	<25	≥50	<50	≥75	<75	Yes	No
Bruit:								
Present	87	8	74	21	47	48	12	83
Absent	82	121	41	162	19	184	8	195
Total	169	129	115	183	66	232	20	278

TABLE IV—*Association of ipsilateral carotid bruit with diameter stenosis of symptomatic internal carotid artery according to degree of stenosis and to occlusion (95% confidence intervals)*

	Diameter stenosis			
	≥25%	≥50%	≥75%	Occluded
Pretest probability (prevalence)	57% (51 to 63)	39% (33 to 45)	22% (17 to 27)	7% (4 to 10)
Sensitivity	51% (43 to 59)	64% (55 to 73)	71% (60 to 82)	60% (39 to 81)
Specificity	94% (90 to 98)	89% (84 to 94)	79% (74 to 84)	70% (65 to 75)
Positive predictive value/Post-test probability	92% (87 to 97)	78% (70 to 86)	49% (39 to 59)	13% (6 to 20)
Negative predictive value	60% (53 to 67)	80% (74 to 86)	91% (87 to 95)	96% (93 to 99)
Positive likelihood ratio	8·3 (4·2 to 16·4)	5·6 (3·6 to 8·6)	3·4 (2·6 to 4·6)	2·0 (1·4 to 3·0)
Negative likelihood ratio	0·5 (0·4 to 0·7)	0·4 (0·3 to 0·5)	0·4 (0·2 to 0·5)	0·6 (0·3 to 1·0)
Pretest odds	1·3 (1·0 to 1·7)	0·6 (0·5 to 0·8)	0·3 (0·2 to 0·4)	0·1 (0·04 to 0·1)
Post-test odds	10·9 (4·3 to 50)	3·6 (1·7 to 9·8)	1·0 (0·5 to 2·0)	0·2 (0·04 to 0·3)

The cost of each of the various possible carotid imaging strategies was derived by extrapolating the results of the prevalence and predictive value of a carotid bruit for each degree of carotid stenosis in our patients with symptoms (tables II, III, and IV) together with the estimated costs of duplex ultrasonography and angiography to a hypothetical sample of 1000 patients (appendix, table V). The cost was expressed in terms of the number of pounds and the number of strokes after angiography that may be incurred in order to detect all patients with internal carotid stenosis of various degrees.

DEFINITIONS

Transient ischaemic attack—Acute loss of focal cerebral or ocular function with symptoms lasting <24 hours, which after adequate investigation was presumed to be due to embolic or thrombotic vascular disease.[31]

Retinal infarction—Acute, painless, and persistent (>24 hours) monocular loss of visual acuity or visual field with ophthalmoscopic findings of pallor of all or a section of the posterior pole of the retina. Additional findings included the presence of an afferent pupillary defect, embolic material in retinal arteries or arterioles, and a cherry red spot over the fovea in cases of central retinal artery occlusion.

Symptomatic internal carotid artery—The internal carotid artery supplying the territory of the brain or eye that manifested dysfunction due to ischaemia. The internal carotid artery may not necessarily have been the actual cause of the ischaemic syndrome (that is, it may have been the ipsilateral middle cerebral artery) but it was considered to be responsible in most cases.

Asymptomatic internal carotid artery—The internal carotid artery supplying the territory of the brain or eye that did now show ischaemia.

Results

Of the 485 patients with carotid territory ischaemic events cerebral angiography was not performed in 189 (39%); 113 patients (60%) were men and the median age was 70 years, range 20-83 years. The presenting disorder was transient ischaemia of the brain (82, 43%) or of the eye (64, 34%) or retinal infarction (43, 23%). A carotid bruit was audible over 90 carotid arteries in 60 of the 189 patients (32%).

Carotid angiography was performed in 296 patients (61%) after presentation (median 16 days, mean 24 days); 207 patients (70%) were men and the median age was 61 years, range 21 to 75 years. The presenting disorder was transient ischaemia of the brain (142, 48%) or of the eye (98, 33%) or retinal infarction (56, 19%). Angiography adequately imaged 422 carotid arteries in the 296 patients; a bruit was heard over 136 carotid arteries (32%) in 95 patients (32%). The patients' symptoms reflected cerebral or retinal dysfunction in the distribution of 298 internal carotid arteries (71%) that were examined radiologically, which were therefore classified as symptomatic, but not in 124 arteries examined, which were asymptomatic. Two patients had bilateral symptomatic carotid ischaemia, hence there were 298 symptomatic carotid

arteries. A carotid bruit was heard over 95 of the 298 symptomatic internal carotid arteries (32%) and over 41 of the 124 asymptomatic internal carotid arteries (33%). Tables II-IV and figures 1 and 2 show the results concerning the symptomatic carotid arteries.

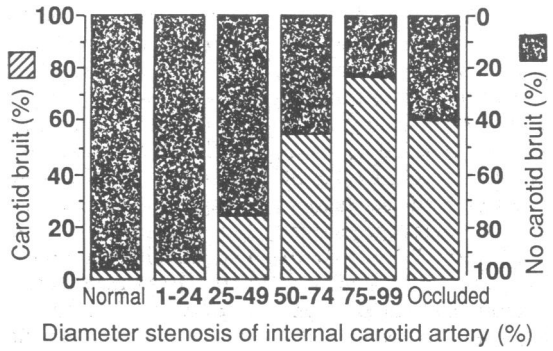

FIG 1—*Relative proportion of ipsilateral carotid bruit or no bruit by degree of diameter stenosis of symptomatic internal carotid arteries (n=298)*

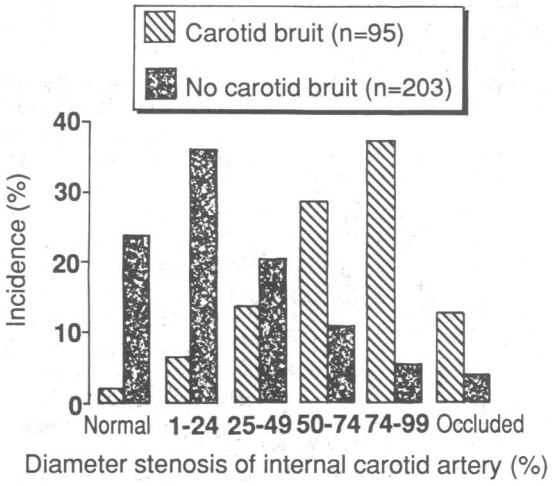

FIG 2—*Range of diameter stenosis in symptomatic internal carotid arteries with and without a carotid bruit*

TABLE V—*Relative costs (£) of investigating 1000 patients with carotid ischaemia*

Strategy/disabling stroke	Diameter stenosis of internal carotid artery (%) ≥25%	≥50%	≥75%
NHS (angiography £520, duplex ultrasonography £85)			
Angiography in all patients	520 000	520 000	520 000
No duplex examination			
No of disabling strokes	10	10	10
Angiography in patients with bruit	365 000	295 000	260 000
Duplex examination in patients without bruit			
Angiography in patients with abnormalities in duplex examination			
No of disabling strokes	5·9	4·6	3·8
Duplex examination in all patients	380 000	285 000	200 000
Angiography in patients with abnormalities on duplex examination			
No of disabling strokes	5·7	3·9	2·2
Angiography in patients with bruit	165 000	165 000	165 000
No duplex examination			
No of disabling strokes	3·2	3·2	3·2
% Of patients excluded*	40%	20%	9%
Private sector (angiography £750, duplex ultrasonography £300)			
Angiography in all patients	750 000	750 000	750 000
No duplex examination			
No of disabling strokes	10	10	10
Angiography in patients with bruit	650 000	550 000	490 000
Duplex examination in patients without bruit			
Angiography in patients with abnormalities in duplex examination			
No of disabling strokes	5·9	4·6	3·8
Duplex examination in all patients	725 000	590 000	465 000
Angiography in patients with abnormalities on duplex examination			
No of disabling strokes	5·7	3·9	2·2
Angiography in patients with bruit	240 000	240 000	240 000
No duplex examination			
No of disabling strokes	3·2	3·2	3·2
% Of patients excluded*	40%	20%	9%

*A considerable proportion (100%−negative predictive value) of patients with no carotid bruit have ipsilateral proximal internal carotid artery stenosis and are not detected with this strategy.

Table V shows the costs to the NHS and private sector of the various possible duplex or angiographic imaging strategies, or both, in relation to the findings of cervical auscultation.

Discussion

SELECTION OF PATIENTS

This paper describes a cohort of 485 patients with symptomatic carotid ischaemic events, of whom 296 were investigated by cerebral angiography. The prevalence of carotid bruits was equal (32%) in patients who had and did not have cerebral angiography so it was unlikely that selection of patients for the procedure was inadvertently contingent on the findings of cervical auscultation, even though the patients not having cerebral angiography were older.

Carotid bruits were also detected with equal incidence over the symptomatic and asymptomatic carotid arteries that were examined angiographically. The result was probably explained by our tendency to study angiographically both carotid systems if a potentially operable lesion of the symptomatic internal carotid artery was found on angiography. If a patient had a bruit over the symptomatic carotid bifurcation he or she was usually referred for selective angiography of the symptomatic carotid system. If a potentially operable lesion was disclosed the radiologist then usually studied the contralateral carotid system because this information was required for the surgeon. If no lesion was found on the symptomatic side the contralateral side was not studied angiographically.

CAROTID BRUIT

The first part of this study aimed at determining the validity of a clinical sign (carotid bruit) in predicting stenosis of the symptomatic extracranial internal carotid artery origin, as measured by cerebral angiography, in a representative sample of patients referred to a neurologist with symptomatically mild ischaemic events in the carotid distribution. Previously, results varied widely,[9-21] the type of bruit or degree of arterial stenosis was not characterised in some studies, little distinction was made between the symptomatic and asymptomatic internal carotid artery, and the cost effectiveness of the various methods of determining internal carotid artery disease was not considered.

The positive predictive value of a carotid bruit for diameter stenosis of the internal carotid artery of ≥50% ranges from 51% to 90%,[9-21] the conditions possibly contributing to the variation including (*a*) the variable definitions of a carotid bruit (focal *v* diffuse *v* not specified),[14 19] (*b*) interobserver variation in assessing a carotid bruit,[20] (*c*) intraobserver variation, and (*d*) differences in selection of patients and in the prevalence and extent of carotid disease.[9-21] The criteria for angiographic abnormality also vary. Carotid angiograms may be classified as abnormal if they are unusual or representative of lesions that are associated with disease or are treatable, or both. As there is no definite cut off point whereby a particular degree of diameter stenosis becomes abnormal we arbitrarily chose degrees of disease which are referred to commonly in clinical practice: ≥25%, ≥50%, ≥75%, and occluded; exactly which category may be helped by carotid endarterectomy remains to be seen when the current trials in Europe and North America are completed.

The advantages of this study are that symptomatic and asymptomatic carotid bruits were analysed separately and that the greatest potential sources of variation (*a* and *b* above) were avoided; bruits were assessed by a single observer with a predetermined and standardised definition. The limitations of this study for the general population are that the study popu-

lation included only patients with symptomatic carotid ischaemia, and therefore, the prevalence of carotid disease in this population was fairly high and the results may be applied only to patients with a similar prevalence of carotid stenosis. Nevertheless, Ingall *et al* found that the predictive value of carotid bruit for ≥50% diameter stenosis of the internal carotid artery was similar among patients with and without atherosclerotic cerebrovascular disease (and also among those with localised or diffuse bruits).[21]

Stenosis of the symptomatic internal carotid artery of ≥25% was present in 57% of our study population, and if a carotid bruit was heard the probability of the patient having ≥25% diameter stenosis of the internal carotid rose to 92%. The probability of stenosis ≥50% doubled from 39% to 78% if a bruit was present and the probability of stenosis ≥75% more than doubled from 22% to 49% if an overlying bruit was heard.

When comparing carotid bruits over symptomatic and asymptomatic carotid arteries the sensitivities of a bruit for detecting carotid stenosis were similar but the specificity, positive predictive value, and likelihood ratio were consistently greater for the symptomatic artery with all degrees of stenosis. Although the positive predictive value of a bruit for stenosis of the symptomatic carotid artery was favourably influenced by the greater prevalence of symptomatic carotid disease, the likelihood ratio was less vulnerable to the effects of prevalence. Therefore, distinguishing between the symptomatic and asymptomatic carotid artery does not seem to be important when considering the sensitivity of a carotid bruit but may be relevant to the specificity, positive predictive value, and likelihood ratio and therefore to post-test odds and probability.

SELECTION OF PATIENTS FOR CEREBRAL ANGIOGRAPHY

If clinicians wish to select patients for cerebral angiography by clinical methods alone and to aim at detecting patients with diameter stenosis of the symptomatic internal carotid artery ≥25% then the presence of a bruit over the symptomatic carotid artery should predict the target disease in about 92% of cases. In other words, if all patients with symptoms and a bruit are referred for angiography diameter stenosis of <25% will be disclosed in only 8% (in whom angiography will have therefore been performed unnecessarily). Cerebral angiography will, however, also disclose occlusion of the internal carotid artery (which is inoperable) in 13% of cases. The true rate of unnecessary cerebral angiography will therefore be 21% (8% plus 13%)—that is, 21% of patients with bruits will not be appropriate candidates for carotid endarterectomy. Prior screening of all such patients with duplex ultrasonography would not substantially reduce the number of unnecessary angiograms because occlusion and tight stenosis cannot always be differentiated reliably, and this distinction is important because management is clearly different. Many investigators therefore recommend cerebral angiography even if duplex ultrasonography shows features of occlusion.

If money is not a consideration and the clinician's policy is to recommend carotid endarterectomy in patients with diameter stenosis of the symptomatic internal carotid artery ≥25% it seems sensible to proceed directly to cerebral angiography in those patients with a bruit over the symptomatic internal carotid artery, thus avoiding the delay of prior duplex ultrasonography, and to screen those patients who do not have a bruit with duplex ultrasonography. If the policy, however, is to operate only for greater degrees of stenosis the rate of unnecessary angiography would be unacceptable (35% (22% plus 13%) for ≥50% stenosis and 64% (51% plus 13%) for ≥75% stenosis (table IV). It would therefore be more appropriate to screen all patients with symptoms, whether they have a carotid bruit or not, with duplex ultrasonography to optimise selection for cerebral angiography.

Costs

With rising health care costs, however, money is of major concern. The costs of duplex ultrasonography and cerebral angiography to the NHS are not known or widely available; our assessment of costs is only an estimate. It is not sufficient to accept the model fee recommended by the BMA or the standard reimbursement from the private health insurance companies because these reflect the charge for the procedure and not necessarily the cost. A charge is not an accurate reflection of cost because a proportion of the fee charged may be used otherwise, such as for profit or to subsidise research or another form of health care.[32] A more accurate assessment of cost is to classify costs into variable (materials, contrast media, and x ray films), semivariable (staff, materials, and maintenance of equipment), and fixed (district and capital) costs and to derive these costs from known expenditure, if available. It is also necessary to consider the principle of overhead absorption for expenditure (depreciation).[33] In the financial year 1984-5 Bretland considered the average cost of ultrasonography and cerebral angiography as £20 and £540 respectively for the NHS.[33] We believe the estimate of £20 for carotid ultrasonography is unrealistic in 1990.

The analysis was less complicated and our conclusions were not altered if several assumptions were made: (*a*) the sensitivity of duplex ultrasonography for diagnosing all degrees of stenosis of the internal carotid artery was assumed to be 100%; (*b*) the angiographic complication rate was assumed to be equal for all degrees of stenosis; and (*c*) capital costs such as domestic (hospital building) rates, building maintenance costs, and the costs of purchase and depreciation of duplex ultrasonographic and angiographic equipment were not included. We also assumed that referral of patients for duplex studies was sensible; only those patients with carotid ischaemic symptoms who were likely to proceed to carotid angiography and endarterectomy were referred.

Sensitivity analysis using published sensitivities of duplex examination and complication rates of cerebral angiography for different degrees of stenosis of the internal carotid artery[24 34] did not significantly affect the results. Although only three studies correlated the severity of stenosis with the complication rate after cerebral angiography, a pooled estimate of the odds of any neurological complication after angiography in patients with more than about 90% stenosis of the symptomatic internal carotid artery was 2·2 times greater than in those with less severe carotid disease (95% confidence interval of odds ratio 1·1 to 4·5).[34] The capital costs of duplex ultrasonography and cerebral angiography are difficult to ascertain because both are usually performed in the same site and the equipment is not used exclusively for such examinations. Although the purchase cost of angiographic equipment may be greater, ultrasound equipment probably has a higher rate of turnover.

Cost effectiveness was analysed by using the estimated cost to the NHS and to the private sector of several imaging strategies that may be used to investigate a hypothetical sample of 1000 patients with symptomatic carotid ischaemia to detect all patients with ≥25%, ≥50%, or ≥75% diameter stenosis of internal carotid stenosis.

If clinicians wish to operate on diameter stenosis of internal carotid arteries ≥25% it is probably most cost effective to proceed directly to cerebral angiography in patients with a carotid bruit over the symptomatic

carotid bifurcation and to screen only those patients with no bruit by duplex ultrasonography. If the duplex study suggests ≥25% stenosis then cerebral angiography should be considered. This approach will cost the NHS about £365 per patient and result in six strokes after angiography for every 1000 patients evaluated.

If clinicians wish to operate only on diameter stenosis of ≥50% it is probably more cost effective (£285 per person and about four strokes per 1000 patients) to investigate all patients with symptomatic carotid ischaemia by duplex ultrasonography first, irrespective of the findings on cervical auscultation, and then by angiography for patients with findings of duplex ultrasonography suggesting ≥50% stenosis of the symptomatic internal carotid artery. It is slightly less cost effective to investigate patients with a carotid bruit by angiography and to screen for angiography those with no bruit by duplex ultrasonography (£295 per person and four to five strokes per 1000). These conclusions apply only if duplex in ultrasonography is performed efficiently and fairly accurately. Ordering a duplex examination ultimately delays the appropriate patient having cerebral angiography and treatment with carotid endarterectomy. This delay may represent one or two days of additional time in hospital; this therefore greatly increases the actual cost of the procedure and may allow a stroke to occur, which might have been prevented by earlier carotid endarterectomy. Therefore, if duplex ultrasonography is likely to precipitate or to prolong a stay in hospital a policy of screening all patients by this method will probably be less cost effective.

If clinicians aim at detecting only stenosis ≥75% it is clearly most cost effective (less expensive, with associated occurrence of fewer strokes) to investigate all patients with symptomatic carotid ischaemia by duplex ultrasonography first and then those with an abnormal result, suggesting ≥75% stenosis, by angiography. This strategy will cost about £200 per patient and result in about two disabling strokes after angiography for every 1000 patients investigated.

If only patients with a carotid bruit are investigated by cerebral angiography the immediate cost would be much lower (£165 000 for NHS and £240 000 for the private sector; about three strokes), but 40% of the patients denied investigation will have ≥25% stenosis, 20% will have ≥50% stenosis, and 9% will have ≥75% stenosis. Such a policy clearly misses much potentially treatable disease and is therefore not acceptable if carotid endarterectomy is an effective treatment.

It is clearly much more expensive and dangerous to investigate all clinically suitable patients (with or without carotid bruit) by angiography without first doing a duplex examination on some of them (the proportion depending on the degree of stenosis to be detected). Although all patients with treatable disease will be detected by this strategy, the cost and risk are unacceptably high. It is, therefore, both unnecessarily costly and dangerous if hospitals investigating these patients do not have duplex equipment, which was the case in Oxford at the time of this study, and we suspect is still the case in most hospitals in the United Kingdom.

We emphasise that our conclusions are based on our study population; in generalising them to other institutions it is important to consider any differences in disease prevalence, the efficiency and diagnostic accuracy of the local duplex ultrasonography service, the local complication rate of cerebral angiography, and the local cost of hospital admission and materials for duplex ultrasonography and cerebral angiography. For example, a fairly small difference in the ratio of costs of duplex ultrasonography and cerebral angiography might easily alter the policy for imaging for detecting stenosis ≥25% or ≥50%, but differences would have to be very large to alter the recommended policy for stenosis ≥75%. Major differences will require recalculation of the figures collected locally from which conclusions can be drawn that are relevant to the institution under consideration. Also the future measurements of percentage diameter stenosis may need to be complemented by physiological measurements (that is, cerebral perfusion reserve[15] in selecting patients for carotid endarterectomy). The considerably greater charge for carotid artery imaging in the private sector compared with the calculated costs to the NHS may be worth consideration by health authorities tempted to contract out these services that they currently provide themselves.

We thank Drs Peter Sandercock and John Forbes for reviewing the manuscript. Dr Hankey was supported by the Chest, Heart and Stroke Association of Scotland.

Appendix

Calculation of the costs of the various imaging strategies for 1000 patients with symptomatic carotid ischaemia, using the calculated NHS costs (cost of each angiogram £520, cost of each duplex examination £85, rate of disabling stroke after angiography 1%) and aiming at detecting diameter stenosis of internal carotid artery ≥25%:

Angiography in all patients, no duplex examination

1000 patients × £520/angiogram	£520 000
1000 patients × 1% rate of disabling strokes after angiography	10 strokes

Angiography in patients with bruit, duplex examination in patients without bruit, angiography in patients with abnormalities on duplex examination

Bruit present in 32% (95/298):	
1000 × 32% = 320 patients with carotid bruit	
320 × £520/angiogram	£166 400
320 × 1% rate of disabling stroke after angiography	3·2 strokes
No bruit heard in 68% (203/298):	
1000 × 68% = 680 patients with no bruit	
680 × £85/duplex examination	£57 800
Abnormal results on duplex examination (≥25% stenosis) in 40% (82/203) of 680:272	
272 patients × £520/angiogram	£141 440
272 × 1% rate of disabling stroke	2·7 strokes
Total cost (£166 400 + £57 800 + £141 440)	£365 640
= 3·2 + 2·7 disabling strokes	5·9 strokes

Duplex examination in all patients, angiography in patients with abnormalities on duplex examination

1000 × £85/duplex examination	£85 000
Abnormal results on duplex examination (≥25% stenosis) in 57% (169/298) of 1000:570	
570 × £520/angiogram =	£296 400
570 × 1% rate of disabling stroke	5·7 strokes
Total cost (£85 000 + £296 400)	£381 400
	5·7 strokes

Angiography in patients with bruit, no duplex examination

Bruit present in 32% (95/298) of 1000:320	
320 × £520/angiogram	£166 400
320 × 1% rate of disabling stroke	3·2 strokes

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(*Accepted 6 March 1990*)

Human papillomaviruses in anogenital warts in children: typing by in situ hybridisation

A F Padel, V A Venning, M F Evans, A M Quantrill, K A Fleming

Abstract

***Objective*—To identify the types of human papillomaviruses found in anogenital warts in children and to relate these to clinical and social information.**

***Design*—In situ hybridisation using biotin labelled DNA probes to 11 types of human papillomavirus was performed on biopsy specimens from 17 children with anogenital warts.**

***Setting*—Nuffield department of pathology and the department of dermatology, Oxford.**

***Patients*—Children in one group were referred by general practitioners or paediatricians to the dermatology department, where biopsies were performed. The other children were seen in four different hospitals, and biopsy specimens were submitted to the laboratory at the physician's or pathologist's request.**

***Results*—Of the 17 biopsy specimens, 10 contained cells positive with a probe to a genital human papillomavirus type (types 6 or 11), while six were positive with a skin virus type (types 2 or 3). One was negative. The virus type present bore no relation to the site or appearance of the warts. The virus type did, however, appear to correlate with groups of children. Skin types were commoner in older children (over 4 years), in those with a relative who had skin warts, and in children with warts elsewhere; there was no relation with the child's sex and no suspicion of sexual abuse in these children. These circumstances suggested non-sexual transmission, such as autoinoculation. In contrast, genital types were commoner in girls, in children under 3 years, in children with relatives with genital warts, and in those with no warts elsewhere. Nevertheless, there was suspicion or evidence of sexual abuse in only half these children, suggesting that other routes of transmission—for example, perinatal—might have been implicated.**

***Conclusion*—Anogenital warts in children may contain either skin or genital wart virus type. Although the type of human papillomavirus present may give some indication of the likely mode of transmission, this can be interpreted only in conjunction with all available clinical and social information. The type of virus does not provide proof of the presence or absence of sexual transmission.**

Nuffield Department of Pathology, John Radcliffe Hospital, Oxford OX3 9DU
A F Padel, MB, *senior registrar*
M F Evans, BSC, *research assistant*
A M Quantrill, AIMLS, *medical laboratory scientific officer*
K A Fleming, FRCPATH, *clinical reader*

Department of Dermatology, Slade Hospital, Oxford OX3 7JH
V A Venning, MRCP, *senior registrar*

Correspondence to:
Dr Fleming.

Br Med J 1990;300:1491-4

Introduction

There has recently been a massive increase in the number of human papillomavirus types characterised by DNA technology, but some specific types are repeatedly found in certain sites and lesions. Thus in adults types 6 and 11 are found almost exclusively in anogenital warts,[1-5] whereas types 1, 2, 3, and 4 are found in skin warts.[6,7] This finding, in conjunction with epidemiological evidence, indicates that human papillomavirus types 6 and 11 are venereally—that is, sexually—transmitted. By extrapolation, it has been suggested that anogenital warts in a child may also be sexually transmitted and thus provide grounds for suspecting sexual abuse.

In the United States there is therefore a tendency to start social and criminal investigations for possible sexual abuse in all children with anogenital warts,[8-10] although this has not been advocated in Britain.[11] Some have, however, proposed that the identification of a genital human papillomavirus type in anogenital warts in a child would support the possibility of sexual transmission.[11,12] This assumes that the tissue distribution of human papillomavirus types in children is the same as in adults. Very little data exist to support this assumption and those data conflict. Three studies have reported a total of 23 patients under 13 years old.[13-15] In 18 the anogenital warts contained one or more of the genital human papillomavirus types. In contrast, Fleming *et al* reported a boy of 5 years with human papillomavirus type 2 in both hand and perianal warts,[16] and Androphy recently reported unpublished observations in which 25% of childhood anogenital warts contained type 2.[17] Thus, the correlation of human papillomavirus type with anatomical site may