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Accurate, practical and cost-effective assessment of carotid stenosis in the UK

JM Wardlaw, FM Chappell, M Stevenson, E De Nigris, S Thomas, J Gillard, E Berry, G Young, P Rothwell, G Roditi, M Gough, A Brennan, J Bamford and J Best

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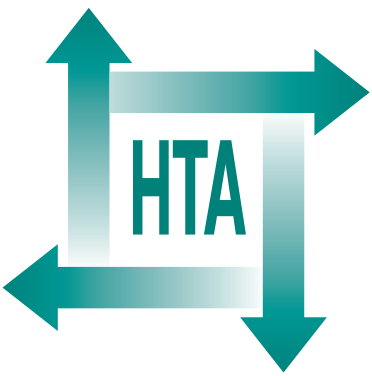

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Accurate, practical and cost-effective assessment of carotid stenosis in the UK

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Abstract

Accurate, practical and cost-effective assessment of carotid stenosis in the UK

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Objectives: To determine whether less invasive imaging tests [ultrasound (US), magnetic resonance angiography (MRA), computed tomographic angiography (CTA) and contrast-enhanced MRA (CEMRA)], alone or combined, could replace intra-arterial angiography (IAA), what effect this would have on strokes and deaths, endarterectomies performed and costs, and whether less invasive tests were cost-effective.

Data sources: Electronic databases covering the years 1980–2003 inclusive, updated to April 2004. Key journals from 1990 to the end of 2002.

Review methods: The authors constituted a panel of experts in stroke, imaging, vascular surgery, statistics and health economic modelling. The accuracy of less invasive carotid imaging was systematically reviewed using Standards for Reporting of Diagnostic Accuracy (STARD) methodology, supplemented by individual patient data from UK primary research and audit studies. A systematic review of the costs of less invasive tests, outpatient clinics, endarterectomy and stroke was performed, along with a microcosting exercise. A model of the process of care following a transient ischaemic attack (TIA)/minor stroke was developed, populated with data from stroke epidemiology studies in the UK, effects of medical and surgical interventions, outcomes, quality of life and costs. A survey of UK stroke prevention clinics provided typical timings. Twenty-two different carotid imaging strategies were evaluated for short- and long-term outcomes, quality-adjusted life-years (QALYs) and net benefit.

Results: In 41 included studies (2404 patients, median age 60–65 years), most data were available on 70–99% stenosis. CEMRA was the most accurate [sensitivity 0.94, 95% confidence interval (CI) 0.88 to 0.97; specificity 0.93, 95% CI 0.89 to 0.96], compared with US, MRA and CTA, which were all similar (e.g. for US: sensitivity 0.89, 95% CI 0.85 to 0.92; specificity 0.84, 95% CI 0.77 to 0.89). Data for 50–69% stenoses and on combinations of tests were too sparse to be reliable. There was heterogeneity between studies for all imaging modalities except for CTA. The individual patient data (2416 patients) showed that the literature overestimated test accuracy in routine practice and that, in general, tests perform with higher sensitivity and specificity in asymptomatic than in symptomatic arteries. In the cost-effectiveness model, on current UK timings, strategies allowed more patients to reach endarterectomy very quickly, and where those with 50–69% stenosis would be offered surgery in addition to those with 70–99%, prevented most strokes and produced greatest net benefit. This included most strategies with US as first or repeat test, and not those with IAA. However, the model was sensitive to less invasive test accuracy, cost and timing of endarterectomy. In patients investigated late after TIA, test accuracy is crucial and CEMRA should be used before surgery.

Conclusions: In the UK, less invasive tests can be used in place of IAA if radiologists trained in carotid imaging are available. Imaging should be carefully audited. Stroke prevention clinics should reduce waiting times at

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all stages to improve speed of access to endarterectomy. In patients presenting late after TIA, test accuracy is very important and US results should be confirmed by CEMRA, as patients with 50–69% stenosis are less likely to benefit. More data are required to define the accuracy of the less invasive tests, with improvements made in the data collection methods used and how data are presented. Consideration should also be given to the use of new technologies and randomised trials.

Contents

List of abbreviations vii

Executive summary ix

1 Background to the study of the accuracy, practicality and cost-effectiveness of less invasive imaging tests in the diagnosis of carotid stenosis in the UK 1
The burden of stroke 1
The problems with carotid imaging methods 1
Improving the assessment of diagnostic tests 3
Role of health economic modelling 3
The approach to the problem in the present study 5
Summary 5

2 Hypotheses tested in the review 7

3 Systematic review of less invasive imaging in carotid stenosis 9
Background 9
Methods 9
Results 12
Discussion 27
Conclusions 33

4 Individual patient data meta-analysis of studies of less invasive tests in the diagnosis of carotid stenosis 37
Background 37
Methods 38
Results 40
Discussion 56
Conclusions 58

5 Costing investigation of carotid artery disease, carotid endarterectomy and stroke, and determining the effect on quality of life of having a stroke 59
Background 59
Aim 59
Methods 60
Results 62
Discussion 68

6 Design and construction of a mathematical model to describe the investigation and treatment of patients with symptomatic carotid stenosis 73
Background 73
Objective 73
Methods 73
Discussion 85

7 Results of the cost-effectiveness analysis 87
Background 87
Results 88
Discussion 106

8 Discussion and conclusions 109
Strengths 109
Limitations 109
Questions raised 110
Implications for health care 114
Recommendations for future research 115

Acknowledgements 117

References 119

Appendix 1 Search strategy on accuracy of non-invasive imaging in the diagnosis of carotid stenosis: EMBASE 129

Appendix 2 Search strategy on accuracy of non-invasive imaging in the diagnosis of carotid stenosis: MEDLINE 133

Appendix 3 STARD initiative and related checklists 137

Appendix 4 HTA carotid stenosis checklists 1 and 2: mandatory and desirable requirements 141

Appendix 5 HTA carotid stenosis checklist 3: quality assessment 143

Appendix 6 HTA carotid stenosis checklist 4: data extraction 145

Appendix 7 Flyer and letter asking for individual patient data sets 147

Appendix 8 Minimum data set requirements 149

Appendix 9 Sources of data for individual patient data meta-analysis 151

Appendix 10 Data in the individual patient data meta-analysis available for the analyses presented in Chapter 4 153

Appendix 11 Search strategy for the systematic review of costs of diagnostic tests, clinics, stroke patient care, carotid endarterectomy and quality of life after stroke 165

Appendix 12 Cost of investigations 167

Appendix 13 Questionnaire on organisation of stroke prevention clinics in the UK 171

Health Technology Assessment reports published to date 183

Health Technology Assessment Programme 197

List of abbreviations

ABC	activity-based costing
CCA	common carotid artery
CEA	carotid endarterectomy
CEMRA	contrast-enhanced magnetic resonance angiography
CI	confidence interval
CT	computed tomography
CTA	computed tomographic angiography
3D	three-dimensional
DOR	diagnostic odds ratio
DSA	digital subtraction angiography
DUS	Doppler ultrasound
ECA	external carotid artery
ECST	European Carotid Surgery Trial
Est	estimate
F	female
HRG	Health Resource Group
HSUVs	health state utility values
IAA	intra-arterial angiography
ICA	internal carotid artery
IPD	individual patient data
LOS	length of study
M	male
MI	myocardial infarction
MR	magnetic resonance
MRA	magnetic resonance angiography
MRI	magnetic resonance imaging
NA	not applicable
NASCET	North American Symptomatic Carotid Endarterectomy Trial
NB	net benefit
NS	not stated
OCSP	Oxfordshire Community Stroke Project
OXVASC	Oxford Vascular Study
PPP	purchasing power parity
QALY	quality-adjusted life-year
RCT	randomised controlled trial
ROC	receiver operating characteristic
SE	standard error
SG	standard gamble
STARD	Standards for Reporting of Diagnostic Accuracy
TIA	transient ischaemic attack
TTO	time trade-off
US	ultrasound
VIF	variance inflation factor

continued

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List of abbreviations (*continued*)

Initials of study participants

E De N	Enrico De Nigris	LB	Elizabeth Berry
FMC	Francesca Chappell	MS	Matt Stevenson
JJKB	Jonathan Best	PMR	Peter Rothwell
JMW	Joanna Marguerite Wardlaw	ST	Steve Thomas
KW	Karolina Wartolowska		

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Background

Carotid endarterectomy reduces the risk of stroke in patients with tight symptomatic carotid stenosis [70–99% on North American Symptomatic Carotid Surgery Trial (NASCET) criteria] and may also benefit patients with milder (50–69% NASCET) stenoses. The particularly high risk of stroke early after transient ischaemic attack (TIA) has recently been emphasised. Accurate carotid imaging is important to avoid operating on patients with less severe stenoses in whom the risk of surgery may outweigh the benefit. Carotid stenosis was measured originally on intra-arterial angiography (IAA), which is risky. Less invasive imaging tests [ultrasound (US), magnetic resonance angiography (MRA), computed tomographic angiography (CTA) and contrast-enhanced MRA (CEMRA)] have improved and could be accurate enough to replace IAA.

Objectives

The aim of the study was to determine whether less invasive imaging tests, alone or combined, could replace IAA, what effect this would have on strokes and deaths, endarterectomies performed and costs, and whether less invasive tests were cost-effective.

Methods

The authors constituted a panel of experts in stroke, imaging, vascular surgery, statistics and health economic modelling. The accuracy of less invasive carotid imaging was systematically reviewed using Standards for Reporting of Diagnostic Accuracy (STARD) methodology, supplemented by individual patient data from primary research and audit studies in the UK. A systematic review of the costs of less invasive tests, outpatient clinics, endarterectomy and stroke was performed, along with a microcosting exercise. A model of the process of care following a transient ischaemic attack (TIA)/minor stroke was developed, populated with data from stroke epidemiology studies in the UK, effects of medical and surgical interventions, outcomes, quality of life and costs. A survey of UK stroke prevention clinics provided typical timings. Twenty-two different carotid imaging strategies were evaluated for short- and long-term outcomes, quality-adjusted life-years and net benefit.

Results

In 41 included studies (2404 patients, median age 60–65 years), most data were available on 70–99% stenosis. CEMRA was the most accurate [sensitivity 0.94, 95% confidence interval (CI) 0.88 to 0.97; specificity 0.93, 95% CI 0.89 to 0.96], compared with US, MRA and CTA, which were all similar (e.g. for US: sensitivity 0.89, 95% CI 0.85 to 0.92; specificity 0.84, 95% CI 0.77 to 0.89). Data for 50–69% stenoses and on combinations of tests were too sparse to be reliable. There was heterogeneity between studies for all imaging modalities except for CTA. The individual patient data (2416 patients) showed that the literature overestimated test accuracy in routine practice and that, in general, tests perform with higher sensitivity and specificity in asymptomatic than in symptomatic arteries. In the cost-effectiveness model, on current UK timings, strategies allowed more patients to reach endarterectomy very quickly, and where those with 50–69% stenosis would be offered surgery in addition to those with 70–99%, prevented most strokes and produced greatest net benefit. This included most strategies with US as first or repeat test, and not those with IAA. However, the model was sensitive to less invasive test accuracy, cost and timing of endarterectomy. In patients investigated late after TIA, test accuracy is crucial and CEMRA should be used before surgery.

Conclusions

In the UK, less invasive tests can be used in place of IAA if radiologists trained in carotid imaging are available. Imaging should be carefully audited. Stroke prevention clinics should reduce waiting times at all stages to improve speed of access to endarterectomy. In patients presenting late after

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TIA, test accuracy is very important and US results should be confirmed by CEMRA, as patients with 50–69% stenosis are less likely to benefit.

Recommendations for research

The first six recommendations are as follows:

- More data are required to define the accuracy of less invasive tests used at 50–69% stenoses, and in combination (e.g. US plus CEMRA).
- The methodology for primary studies of the accuracy of less invasive imaging tests needs to improve.
- Clearer presentation of data in reports of primary studies of diagnostic test accuracy would enable more key sensitivity analyses to be performed in future meta-analyses.
- Methods of evaluating new technologies as they emerge are required.
- Consideration should be given to new randomised trials to evaluate different less invasive imaging strategies before endarterectomy.
- Streamlined methods of collecting data to audit less invasive tests when used in routine clinical practice are required to monitor test accuracy.

Chapter 1

Background to the study of the accuracy, practicality and cost-effectiveness of less invasive imaging tests in the diagnosis of carotid stenosis in the UK

The burden of stroke

Stroke consumes about 10% of NHS resources.[1] It remains the most common cause of disability in adults. Effective acute treatments are proving elusive, and so prevention of stroke is crucial. Secondary prevention with carotid endarterectomy (CEA) in patients with 80–99% symptomatic carotid stenosis prevents about one stroke per ten operations.[2] However, this fine balance of risk and benefit appears to depend on accurate measurement of stenosis. In other words, operating on patients with less than 80% stenosis [or 70% if measured by the North American Symptomatic Carotid Endarterectomy Trial (NASCET) method][3] appears to be less effective as the patients' risk of stroke is less but they are still exposed to the risk of surgery, so the net benefit is less or they may actually be harmed. More recent analyses of combined endarterectomy trial data suggest that at least some patients with a symptomatic 50–69% stenosis may benefit from endarterectomy, particularly younger males if they can be operated on quickly.[4,5] Data from several observational stroke incidence studies also emphasise that following a transient ischaemic attack (TIA) or minor stroke, the highest risk of disabling stroke is within the first few days, the risk declining progressively thereafter.[6–9] This means that stroke prevention needs to be implemented rapidly if we are to prevent most strokes.

In the CEA trials, the stenosis was measured on intra-arterial angiography (IAA), the imaging test that was in routine use at the time, and which is therefore the reference standard for assessment of stroke risk against which any other diagnostic test must be calibrated, otherwise the estimate of stroke risk (and hence decision on whether CEA is required) may be wrong. *Figure 1* shows the different ways of measuring carotid stenosis on IAA. Note that IAA provides a good outline of the degree of stenosis, but little information about the composition of the atheroma causing the stenosis (e.g. fibrous cap, lipid core, amount of internal or surface thrombus) which might be important in determining thromboembolic potential, although more recent analyses suggest that there may be a relationship between plaque surface irregularity and disease activity.[12]

The problems with carotid imaging methods

What is wrong with angiography?

IAA is invasive and in patients with symptomatic ischaemic cerebrovascular disease, causes one death and four disabling strokes for every 100 patients, even in expert hands.[13,14] It may delay endarterectomy while patients wait to be admitted to hospital to have the angiogram.[15] The highest risk of disabling stroke is in the few weeks following a TIA,[16] so rapid investigation and treatment is important for maximum reduction in stroke risk. Although some investigators favour day-case IAA with narrow-gauge catheters to reduce the risk of bleeding at the arterial puncture site, this is not universally accepted. As stroke is a disease of the elderly, the patients who need CEA are often frail and live alone, and so require overnight hospital observation after the IAA for safety. Hence the impetus to substitute newer, less invasive, imaging tests, such as Doppler ultrasound (DUS), computed tomographic angiography (CTA) and magnetic resonance angiography (MRA) in place of IAA,[17–20] as these can be done more quickly, on outpatients, with little risk or discomfort. Furthermore, some experts believe that IAA may be a rather imperfect reference standard for measurement of stenosis, as the standard three views (two 45-degree obliques and a straight lateral view centred on the common carotid bifurcation) may not provide the optimal view of the stenosis, compared with ultrasound (US), CTA and both MRA techniques, which can provide views in many different axial and longitudinal planes.[20,21]

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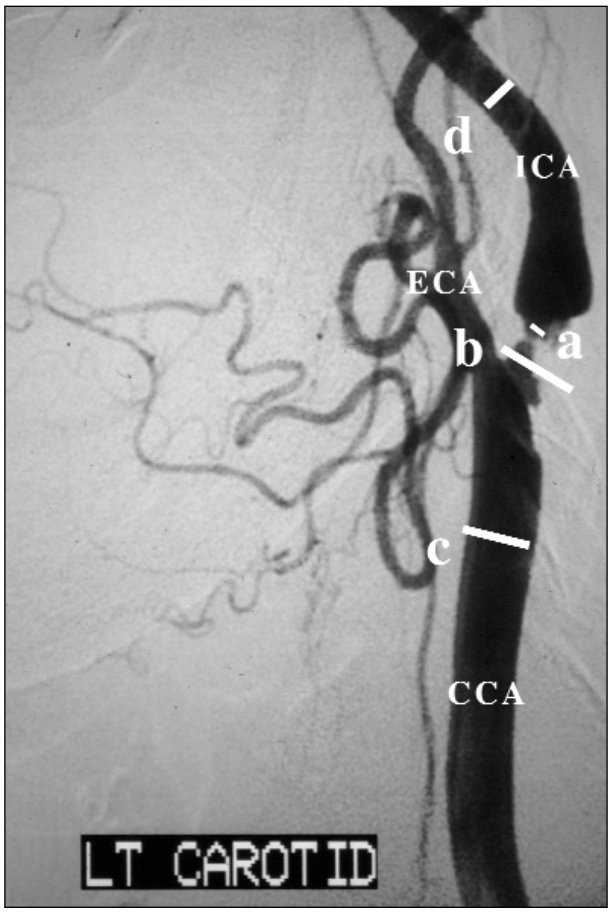

FIGURE 1 *Intra-arterial angiogram of the common carotid artery (CCA) bifurcation showing a tight stenosis at the origin of the internal carotid artery (ICA). ECA, external carotid artery. Different measurements required to calculate the degree of stenosis are indicated by the white bars. In the European Carotid Surgery Trial (ECST),*[10] *stenosis was calculated as (b – a) × 100/b, in NASCET*[3] *by (d – a) × 100/*d*, and a third method, the common carotid method, is (c – a) × 100/c. A 70–99% NASCET stenosis is equivalent to a 80–99% ECST stenosis, and a 50–69% NASCET stenosis is equivalent to a 70–79% ECST stenosis.*[11]

Why not just use the less invasive tests?

The techniques of US, CTA and MRA have been available for some years (for US since the early 1980s) and have undergone major technological improvements over that time. However, the accuracy of individual tests, or combinations of tests,[22] and the circumstances in which they could replace angiography are still debated.[23] A recent 'paper exercise' to assess what results of which less invasive tests would be accepted by clinicians in making the decision of whether or not to proceed to endarterectomy indicated little confidence in using single, less invasive tests except where there was a severe symptomatic stenosis.[21] This uncertainty results in wide variation in practice in the UK.[24,25] Some rely on one US alone, or on US plus CTA or MRA, or on two independent USs, and others on US plus IAA[25] (also personal communications). Some favour the newest technique of contrast-enhanced MRA (CEMRA).[26] Some of this variation may be due to differences in available technology or operator expertise, but whatever the reason, where there is such wide variation, it is very unlikely to be compatible with the delivery of the best evidence-based care.

Why the confusion about the less invasive diagnostic tests?

Radiologists and clinicians have probably not been convinced by, or have been confused by, the available data from studies of US,[27] CTA and MRA accuracy.[28–30] A recent literature search identified over 2500 primary papers on MRA alone.[31] Small, very positive studies, with detailed descriptions of the imaging technique but woefully inadequate information on the patients or proportion of severe stenoses, which omit to mention whether the imaging assessment was blinded to the reference standard, rarely give details of how many images were excluded because they were 'suboptimal', give no information on observer reliability and fail to seek patients' opinions, are all too common.[28,29,32] Some of this is due to genuine difficulty in conducting such studies (e.g. sample size), but some is just lack of awareness of good methodology. There is even confusion over how to measure the stenosis from the angiogram: some use the ECST and some the NASCET method, yet in the former an 80% or more stenosis is operable, and in the latter a 70%. From their own studies,[33,34] the present authors know the difficulty of achieving an adequate sample size (patient throughput is slow, even by joining up with another hospital),[34] and dropout rates are high (machines are not always available; patients refuse additional tests or suffer complications of angiography).[34] The results are often presented in a way that is difficult to translate into clinical practice. Sensitivities, specificities and receiver operating characteristic (ROC) curves are important, but it would be easier for radiologists and clinicians to understand as the proportion of patients misdiagnosed and the effect that that has on outcome after treatment (e.g. life-years gained or lost as a result of inaccurate assessment of the degree of stenosis and stroke risk).[34] Studies of diagnostic test accuracy are given lower priority than treatments, so are difficult to fund. Yet treatments delivered to the wrong patient group because of inaccurate diagnosis could be disastrous to the patient and costly to the health service, so this perception is misguided.

Improving the assessment of diagnostic tests

Is it possible at present to conduct a randomised trial of carotid imaging?

The ideal method for evaluating the less invasive carotid imaging tests would be a randomised trial of carotid imaging before endarterectomy; that is, either (1) randomise to a less invasive technique or IAA and operate and see which patient group had the better outcome, or (2) repeat the endarterectomy trials replacing IAA with the less invasive test and see whether the benefit of endarterectomy still occurs at the same stenosis level. However, this would be extremely expensive, difficult to do and possibly unethical at present. In addition, the individual less invasive tests or combinations of tests to be evaluated would be quite broad and therefore need a large sample size. So at the time of starting the present project, a trial of imaging was not appropriate.

A systematic review would summarise all the available evidence from non-invasive tests.[35] This would provide a more robust estimate of accuracy than is available in individual studies by increasing the effective sample size, be educational by highlighting methodological errors in previous studies[35,36] and identify gaps in existing knowledge for which new studies are required. Although the methodology for diagnostic test systematic reviews[37] was less developed than treatment reviews, nonetheless it was important to combine all the available evidence to determine the accuracy of these less invasive imaging tests. In addition, there have been significant developments in the awareness of methodological points for diagnostic test systematic reviews in the past few years. For example, for literature searching the UK Royal College of Radiologists has developed a validated search methodology (J Grimshaw, F Gilbert), and there is increased awareness of the importance of specialist knowledge in undertaking the review,[38] the assessment and influence of primary study quality,[39–41] the influence of the disease population,[42–45] the inclusion of English-language only or all publications,[46–47] and methods of presenting the results (the Cochrane Collaboration Methods Working Group produced guidelines but left many questions unanswered: http://som.flinders.edu.au/cochrane). Previous systematic reviews of non-invasive carotid imaging did not address methodological issues, or test all modalities, or the combination of modalities.[32,48–53] As the technology and literature change rapidly, so previous work needs to be updated. Cumulative meta-analysis could be used to examine trends over time as new tests emerge or old tests are refined, and complement a 'tracker trial'[54] of carotid stenosis assessment as technology continues to change.

Can we add to the information available from a systematic literature review?

Recognising that the general quality of the imaging literature is poor (http://www.jr2.ox.ac.uk/bandolier/booth/diagnos/Diagessy.html), it is unlikely that a robust estimate will be obtained of how to assess carotid stenosis from a systematic review of published data. To address this likely deficiency in quality data, individual patient data from recent or ongoing studies of less invasive tests will be added. This would fill the gap between the last publication (inevitably already out of date as technology changes rapidly) and the present, help to plan future services and improve quality. It may also give a better estimate of the accuracy of less invasive tests in routine clinical use rather than in dedicated research studies, which unfortunately are what most of the published literature refer to. Individual patient data (IPD) meta-analyses of diagnostic data are virtually unheard of, but the group of investigators in the present study have been responsible for six completed or ongoing studies of DUS, MRA, CTA or CEMRA[21,33,34,55,56] and have data in addition to those published so far (for those studies that have been published) that will supplement the review evidence.

Using IPD, it was hoped to be able to include data on patient characteristics (age, symptoms, concomitant disease), imaging method and technology, the method of calculating the stenosis, the actual stenosis, whether the artery was symptomatic or not, the accuracy of tests used in combination, the effect of reader's experience, any complications, patient preferences, and inter- and intra-observer reliability. The plan was to calculate the overall sensitivity, specificity, and positive and negative predictive values for each modality, and to perform sensitivity analyses to assess the effect of patient characteristics, degree of stenosis and other factors as above, where data were available.

Role of health economic modelling

The need for modelling in this topic

The questions being addressed by this project were concerned with the relative cost-effectiveness of

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alternative diagnostic strategies for patients with carotid stenosis. Cost-effectiveness analyses require a single unit of outcome against which alternative strategies can be compared in terms of cost per unit gain of this outcome (e.g. cost per life-year saved).[57] The treatment of carotid stenosis has multiple outcomes for mortality and morbidity, such as strokes prevented or caused, death or myocardial infarction (MI). One solution to this problem was to select the most important outcome and use this to calculate the cost-effectiveness ratio. This seemed to be oversimplistic and unwise in the context of stroke prevention, given the importance and frequency of the other outcomes. It was therefore proposed to use two approaches to assess cost-effectiveness:

- cost per unit of effect measured in 'natural' units, including life saved, life-years saved (using life tables for the expected survivors) and strokes avoided
- cost per quality-adjusted life-year (QALY) based on available data on the consequences for quality of life of the different outcomes (see below).

Furthermore, it was clear at the outset that the evidence base on less invasive diagnostic strategies versus conventional IAA would not yet provide a definitive answer on cost-effectiveness. In particular:

- Currently available primary studies report sensitivity and specificity of tests but, with one exception,[34] have not included an estimate of effect on subsequent treatments and final health outcomes.
- Existing studies differed in terms of subgroups of patients identified (symptomatic, asymptomatic, etc.).
- Studies varied in the sequence and combination of tests used, and in definitions (e.g. in the method used to measure stenosis).

There were virtually no studies that had attempted to cost the process of running stroke prevention clinics or factor in the effect of using different less invasive imaging strategies. Hankey and Warlow[58] published in 1992 an assessment of the impact of different investigations (e.g. echocardiogram, various blood tests) in the evaluation of patients with TIA and minor stroke for secondary stroke prevention, using local Edinburgh estimates of cost, but this only considered US and IAA, as at that time CTA and MRA were really only experimental. Their recommendations were that the most cost-effective strategy for selecting patients for IAA before endarterectomy, was to (1) ensure that the patient has carotid territory TIAs/minor stroke, (2) ensure that the patient was medically fit and willing to consider carotid IAA and endarterectomy, and (3) perform carotid US before considering IAA. If the US suggested more than about 50% diameter symptomatic internal carotid artery stenosis, then the patient should be considered for IAA. This essentially avoided the extra cost and risk of performing IAA on patients who were unlikely to proceed to endarterectomy, and is in essence the way that most stroke prevention services seem to have operated since, except that there has been a gradual drift towards not using the IAA and substituting MRA, CTA or CEMRA, or a second US instead.

A systematic review of cost-effectiveness research in stroke published in 1999[59] identified 12 studies of radiological procedures, but only seven were on the investigation of carotid stenosis: five were about the cost-effectiveness of screening for asymptomatic carotid stenosis, one was about routine use of US for postendarterectomy surveillance, and only one (from 1995)[60] concerned morbidity and cost-effectiveness of imaging strategies in symptomatic carotid stenosis. Kent and colleagues[60] evaluated four diagnostic strategies for selecting symptomatic patients for endarterectomy (US alone, MRA alone, IAA alone, or US and MRA with IAA for disagreements). The most cost-effective strategy was US and MRA together with IAA to sort out disagreements between the two: this increased quality-adjusted life expectancy and cost more ($22,400 per quality-adjusted life-year gained), but was more effective than US alone. Three other studies in the Kent study[60] which evaluated the cost-effectiveness of CEA did not include the screening or stenosis evaluation strategies but started with an already defined operable lesion (see Holloway and colleagues[59] for details). Thus, existing economic evaluations were very out of date, and would not have included the developments in stroke prevention that occurred in the late 1990s and early 2000s.

Thus, at the start of the present study, there was a considerable evidence base on the various disparate elements of the stroke prevention service. In addition, the authors were aware that new relevant information would become available through members of the study group in the course of the project or that they would be able to conduct new research to obtain the data. A rigorous and systematically constructed health

economic model was therefore feasible and would be informative for policy and determining what further research is required.

The approach to economic modelling

Diagnostic services for stroke prevention were particularly amenable to a decision-tree modelling approach, partly because the key decision points and consequences follow each other in time in a relatively clear way and because there is little feedback to earlier parts of the process from later ones. Thus, it would be fairly straightforward for the health economics modellers in the project group to build a decision model reflecting the process of referral and care in a stroke prevention service applicable to individual patients, with guidance from the clinical and radiological incorporating the data on the effectiveness of carotid surgery in different patient groups,[61] the accuracy of non-invasive tests and their combination (obtained from the systematic review and individual patient data meta-analysis), costings (obtained from the literature and data from participating departments), timings (obtained from participating departments and a survey of practice in specific UK centres) to model speed of investigation as well as accuracy (i.e. one-stop clinics versus traditional management pathways). The basic structure of the model would incorporate the incidence/prevalence of the disease, the presentation rate to the service, the alternative diagnostic strategies (including the probabilities of true-positive, false-positive, true-negative and false-negative results for clinically significant carotid artery disease) and the probabilities of complications arising from investigations (e.g. stroke, haematoma). The model would use conventional IAA as the reference standard and assume 0% false positives (as a starting point), with sensitivity analyses to address the effect of timings, stenosis levels and other factors. Health outcomes of each treatment profile (mortality, life-years gained, QALYs and net benefit) would be derived.[62]

The approach to the problem in the present study

An expert group was established including stroke physicians and neurologists, radiologists, epidemiologists and trialists, statisticians, health economists and modellers at the start of the project. The whole group met formally three times during the project. The first meeting was to discuss the criteria for the systematic reviews, the process of obtaining IPD, obtaining data on TIA clinics and costs, and the key elements for the formal modelling approach. The second meeting was to review the interim results of the systematic reviews and the initial structure of the model, and identified that a formal microcosting exercise was required (for the cost of diagnostic imaging), that a survey of UK stroke prevention clinics was needed, and key items of missing information needed for the economic model. The third meeting reviewed the final results of the systematic review and the interim results of the IPD meta-analysis, refined the model information input and identified the final missing information needed, and determined the sensitivity analyses required. In between the meetings, there was continuous and considerable exchange of information and opinion seeking within the project group. In addition, the principal investigator (PI), statistician (in Edinburgh) and health economist, modeller, and ST (in Sheffield) had monthly teleconferences to discuss details of the model, the information sources and their reliability, and both the principal investigator and modeller had regular discussions with PMR in Oxford about CEA and new stroke/TIA epidemiology data emerging from ongoing analyses of the combined CEA database and the Oxford Vascular Study (OXVASC), which is a repeat of the Oxfordshire Community Stroke Project (OCSP), a study of stroke epidemiology in the UK.

Thus, it was ensured that the information in the model was as up to date and accurate as it could possibly be, and that the model was validated by expert concurrence. In other words, the model and the data emerging from it made sense to experts in the field of secondary stroke prevention (the right factors were included, the mathematical relationships were intuitive and the data sources were reasonable), it had internal validity (it matched the results of the source data used to construct it) and the predictions agreed with non-source data (e.g. the risk of a stroke over time predicted by the model was consistent with other existing results).

Summary

Although a randomised trial of carotid imaging would be the optimum way to obtain a definitive answer to the current question, the authors accepted the difficulty and cost of designing and undertaking such a trial: it would need a large sample size, so require participation of many centres, and would be very expensive, difficult to coordinate and possibly unethical. Thus, a

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combination of systematic review, individual patient data, and decision analysis modelling was adopted as the only practical alternative at this stage. Fortunately, the radiological community is awakening to the need for better evidence.[63,64]

The use of IPD by the collaborative group ensured the participation of clinicians and radiologists who were dealing on a daily basis with the problem of how best to assess carotid stenosis, as well as having an academic interest in the subject. The interested investigators brought together for this project were well placed to provide a clear statement on best practice at present. The plan is to retain the group as a discussion forum, to continue to refine strategies for carotid stenosis assessment as technology, treatment and health service resources change.[54,65] The group was also well placed to provide information on costings and typical patterns of radiological and neurovascular clinic practice, to inform the decision modelling process, and to ensure that the results of this project are disseminated widely as quickly as possible.

The study personnel were based in the Department of Clinical Neurosciences in the Interdisciplinary Research Group in Brain Imaging in the University of Edinburgh, and at the School of Health and Related Research (ScHARR) at the University of Sheffield.

The full study collaborative group met three times, at the beginning, middle and end of the project, to plan the details of the project design, sources of information and key points in the performance of the systematic reviews, to develop the economic model, and to discuss and interpret the results.

There were four components to the study: (1) a systematic review of less invasive diagnostic tests accuracy (Chapter 3); (2) analysis of the present authors' and others' IPD (Chapter 4); (3) an economic evaluation of the costs of imaging, stroke prevention clinics, carotid endarterectomy and caring for patients with stroke (Chapter 5); and (4) the construction of a model (Chapter 6) to reflect the process of running stroke prevention services and decision analysis modelling (Chapter 7). Conclusions and an assessment of the implications for current practice and future research are presented in Chapter 8. Supporting information is provided in the appendices.

Chapter 2

Hypotheses tested in the review

In this work, it was hypothesised that less invasive carotid imaging tests would have lower sensitivity and specificity than IAA in the diagnosis of carotid stenosis, but in spite of that, that less invasive tests would be more cost-effective because:

- patients could reach CEA more quickly after less invasive tests than after IAA: faster imaging assessment would avoid strokes occurring during the wait for IAA and treatment
- avoidance of the risk of IAA (which can cause stroke) would also improve stroke prevention.

Furthermore, it was hypothesised that US would be the most cost-effective test as it would be the least expensive and would be no less accurate than the other commonly available less invasive imaging tests.

The primary research objectives were:
- to define the accuracy of imaging (DUS, MRA, CTA), individually and in combination, in the diagnosis of carotid stenosis, using systematic reviews and IPD in a meta-analysis
- to perform an economic evaluation of the costs and benefits of less invasive imaging strategies in the diagnosis of carotid stenosis
- to use decision modelling to establish the effect on life expectancy of substituting less invasive tests for angiography, or retaining the use of angiography in conjunction with the less invasive tests, to test uncertainty and to assess the effects of changes in service provision
- to perform subgroup analyses to determine the effect on test accuracy of degree of stenosis; patient symptoms, other patient characteristics (e.g. age and gender), generation of imaging technology, different US, CTA or MRA techniques (e.g. non-contrast and contrast enhanced), observer reliability and effect of observer experience.

The secondary research objectives were:
- to consolidate a group of UK investigators to provide an informed network for future studies and 'tracker trials' as the imaging technology and knowledge of stroke prevention continue to evolve
- to determine how best to audit the accuracy of less invasive imaging tests when used routinely in clinical practice to maintain a high degree of accuracy in the absence of IAA, using systematic reviews, IPD and reviews of practice in UK centres.

There will be four components to the work: a systematic review, analysis of the present group's and others' IPD, an economic evaluation, and decision analysis modelling.

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Chapter 3

Systematic review of less invasive imaging in carotid stenosis

Background

Patients with symptomatic tight carotid stenosis are at a high risk of stroke.[4] Removal of the stenosis by the operation of CEA reduces the risk of stroke.[3,10] For patients with 'tight' symptomatic carotid stenosis (80–99% by ECST and 70–99% by NASCET), operating on ten patients prevents two disabling strokes but one stroke will occur as a complication of surgery,[66,67] so the net gain is one stroke prevented.[4]

These major CEA trials for symptomatic carotid stenosis used IAA to determine precisely the degree of stenosis. A recent reanalysis of combined data from both trials found that some patients with 50% or more stenosis by the NASCET method also benefit from CEA.[4] However, IAA is an invasive procedure (see the section 'The problems with carotid imaging methods', p. 1) with a small risk of stroke or death,[13,14] is expensive and often requires an overnight stay in hospital. The wait for a hospital bed and limited availability of IAA may introduce delays to surgery.

The technology for other less invasive (and less risky) carotid imaging techniques has gradually improved, so radiologists and clinicians have investigated whether other less invasive modalities (e.g. US, CTA, MRA and CEMRA) could replace IAA as the definitive diagnostic test before CEA. The finely balanced risk/benefit ratio of CEA means that it is essential to know how accurate the less invasive modalities are compared to IAA. A randomised controlled trial (RCT) comparing outcomes associated with IAA, US, CTA, MRA and CEMRA would be logistically difficult, extremely expensive, and perhaps ethically questionable, and so a systematic review of published literature was undertaken to answer the following questions:

- What is the accuracy of US, CTA, MRA or CEMRA, alone or in combination, in comparison to IAA in diagnosing 0–49% occluded, 50–69% and 70–99% stenosis by the NASCET method in symptomatic patients?
- Could this estimate be biased by the design of individual studies and if so by how much (e.g. source of patients, inclusion criteria, use of blinding, expertise of radiologists, specialist or non-specialist centre)?
- Is there evidence that the accuracy of less invasive tests has improved with newer generations of technology?

Methods

Papers were sought that described the accuracy of less invasive imaging tests in patients with symptoms of carotid territory ischaemia, that is, TIA or minor stroke. To avoid bias and ensure that the review results were as relevant as possible to day-to-day practice in stroke prevention clinics, prospective studies were sought, including 20 or more subjects, with good descriptions of methods of patient recruitment and selection, in which one or a combination of less invasive tests had been compared blindly with the reference standard of IAA, in patients who would be candidates for CEA for symptomatic tight carotid stenosis. Studies published only in abstract form were not included as there were insufficient data in the abstracts to perform a critical appraisal or extract for the meta-analysis, and an individual patient data meta-analysis was planned to overcome any consequent bias in the literature meta-analysis.[46,47]

Identification of the literature

Extensive search strategies were created in MEDLINE and EMBASE (Appendices 1 and 2). The search strategy was created by starting with prior knowledge of commonly-used terms in the literature on non-invasive carotid imaging tests (JMW), and by looking at how a few relevant references were indexed with MeSH or Emtree search terms for MEDLINE or EMBASE, respectively (FMC).[68] These search terms were then added to the search strategy to see whether they produced additional useful material. This process continued iteratively until the search strategies stopped finding new, relevant material. The initial search strategies were a few lines long, the final versions are over 200 lines each. Draft strategies were discussed with the Trials Search Coordinator for the Cochrane Stroke Group, an

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experienced professional literature searcher with more than 10 years' experience of literature searching. The full search strategies are in Appendix 1 (EMBASE) and 2 (MEDLINE). An obvious omission from the search strategies was the use of 'diagnosis' as a free text search term. This was deliberate, as "diagnosis" was not found to be useful in previous research into the utility of various search terms.[69]

The search covered the years 1980–2003 inclusive, and was updated to April 2004. The search was started in 1980 because that was when DUS became available in clinical use. US was the first of the less invasive strategies to be developed and applied to carotid imaging. CTA and MRA were not really used to image arteries until the late 1980s and early 1990s, and CEMRA was not developed until the late 1990s.

The electronic search strategies were tested against handsearching of key journals to validate the search strategy. The key journals searched were *Radiology*, *Neuroradiology*, *American Journal of Neuroradiology*, *American Journal of Roentgenology*, *Stroke* and *European Journal of Vascular and Endovascular Surgery*, from 1990 to the end of 2002. The electronic searches identified 88% of the references found in the handsearch. Of those not found, 83% had been published before 1995, reflecting changes in indexing practice by MEDLINE and EMBASE.

The reference lists cited in review articles on carotid stenosis imaging were also searched. Over 100 extra papers were found by this method. In addition, the authors reviewed the literature to see whether they were aware of any missing literature. Taking into account the extra papers found by using reference lists, only one extra reference was found by handsearching.

The abstracts identified by the electronic search were independently assessed by a neuroradiologist (JMW) or a radiologist (JJKB) and a statistician (FMC) according to predetermined inclusion and exclusion criteria for their relevance to the review. The electronic searches were rerun in April 2004 to capture recently published studies. The predetermined criteria for the inclusion or exclusion of abstracts were:

- include all studies published in 1980 or subsequently
- include if comparing IAA with US, CTA, MRA or CEMRA
- exclude studies of trauma or cancer patients
- exclude studies performed on healthy volunteers only
- exclude paediatric or foetal patients
- exclude non-humans
- exclude studies only describing a technical development rather than assessing accuracy
- exclude unless measuring carotid stenosis.

Owing to the size of the literature and limitations on study resources, the exclusion criteria were later widened to cover studies published in 1985 or before and non-English-language studies. This was because it became clear that the less invasive imaging technologies described in the literature before 1986 were too primitive to be relevant to modern imaging practice, and the group did not have access to translators who could provide translations of all non-English publications within the time-frame of the study. However, the exclusion of the non-English-language literature may bias the result of the systematic literature review.[70,71]

The statistician (FMC) reviewed reference lists of review articles looking for relevant studies. References were included if not already identified by the electronic searches and the article title suggested that they were relevant.

Critical appraisal of primary studies

The full papers of studies not excluded at the abstract stage, or identified from review paper reference lists and which appeared relevant, were examined in detail according to prespecified criteria. Further exclusions were based on features identified in the full text. These criteria, determined a priori at the beginning of the study, were as follows. Exclude unless the study included:

- patients with symptoms consistent with TIA, minor stroke, amaurosis fugax, or retinal artery occlusion
- a comparison of IAA, US, CTA, MRA or CEMRA
- information to fill a 2×2 table of true positives and negatives and false positives and negatives
- a statement that the index (i.e. less invasive) test had been assessed blind to the results of the reference test
- explicit description of the method used for defining the degree of stenosis (e.g. NASCET or ECST[72]
- sufficient description of the imaging techniques to allow repetition of the procedure
- patients, at least 70% of whom were symptomatic
- prospective data collection
- data from 20 or more patients.

The checklists used to appraise the papers were based on the statement standards for Reporting of Diagnostic Accuracy (STARD) as advised by the HTA panel (see Appendix 3, http://www.consort-statement.org/stardstatement.htm).[39] The checklists were also partly based on those developed for a previous HTA-funded review of MRA in carotid stenosis.[73] Although the STARD statement is not an instrument for the critical appraisal of diagnostic studies, it does identify study features that may create bias. It would have been preferable to use the QUADAS instrument,[74] but this was not published until after critical appraisal process had begun. However, the QUADAS instrument is very similar to the checklists developed for this HTA project (Appendix 4). These initial checklists were piloted (by FMC, JMW and KW) and refined. The final critical appraisal checklists for assessing studies for inclusion in the review are given in Appendices 4–6.

Data extraction

Two types of data were needed from each study:

- Information on design features that could be sources of bias or heterogeneity. These design features included (see Appendices 5 and 6):
  - method of patient recruitment (e.g. consecutive series or random sample)
  - spectrum of disease: the proportion of patients in the study with carotid stenosis (in effect, whether the patients had been screened by US or not before entering the study, and the catchment population)
  - whether IAA had been performed and interpreted blind to the results of the less invasive (index) procedure (studies where the IAA results could have been known to the reader of the less invasive procedure were excluded).
- The numbers of true positives, true negatives, false positives and false negatives in stenosis bands reflecting definitely not operable (0–49% or occluded), possibly operable (50–69%), and definitely operable (70–99%) according to the NASCET stenosis measurement method.[3] Stenosis data given as ECST or common carotid (CCA) diameter methods[11,72] were converted to a NASCET stenosis using the equation: NASCET = (ECST – 40)/0.6.[72] Note that the same equation also converts a CCA stenosis to NASCET. The NASCET method was chosen as the common standard, as this is a common method for calculating the percentage stenosis.

The data extraction for both the critical appraisal and numbers required for accuracy analysis were checked by at least two reviewers. In the case of disagreements, the paper was referred to a third reviewer for a final decision. Checklists 3 and 4 (Appendices 5 and 6) give full details of the critical appraisal data sought.

Care was taken to avoid the possibility of including data from the same data set twice, so if two papers appeared to report data from the same patients (or were felt to have very probably used the same patients), only one paper's results were used in the meta-analysis.

Data synthesis

Indeterminate index tests were counted as negative test results as the patient would not be referred for endarterectomy with such a test outcome, provided the result of IAA was known. If a study reported that a number of arteries was not included owing to indeterminate index test results, and the result of the IAA was also not reported, then these arteries could not be included in the analysis, as their true disease state was not known. The number of arteries or patients excluded from the analysis for this reason was noted for each study if possible.

Adjusting for differences in number of image readers, arteries and patients

Studies reported their results in different ways. For example, some papers described the number of patients correctly diagnosed as normal or abnormal by the index imaging test; some papers described the number of arteries correctly diagnosed (but there were two arteries per patient); and in some, the interpretations of several readers were described, falsely increasing the number of patients. Therefore, the raw values of true positive, true negative, false positive and false negative were adjusted so that the number of true positives, true negatives, false positives and false negatives added up to the number of patients in the study. In many cases it was not possible to ascertain the exact number of patients who contributed data as only the number of arteries was given. The number of arteries could have been derived from patients who had given just one measurement, or from patients who had given measurements from both arteries. Most papers made no statement on how many (or why) patients had only one artery measured. A conservative way around this was to divide the data by two, and thus not overestimate the precision of the meta-analysis results. If a study had reported the stenosis measurements from more than one reader, and so inflated the numbers in the 2×2 table, the results were

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divided by the number of readers to reflect the number of patients. More sophisticated methods of analysis are possible where the individual patient/reader data are given, but this was not possible. A final adjustment was to make a continuity correction by adding 0.5 to each value to avoid the mathematical difficulty of dividing by zero[35] in the sensitivity analyses.

Meta-analysis and obtaining data required for the cost-effectiveness modelling

The primary meta-analysis of included studies was undertaken by determining a summary estimate for sensitivity and specificity of each less invasive imaging technique compared with IAA, and the 95% confidence intervals (CIs) of the sensitivity or specificity, for each of the three stenosis bands. A random effects meta-analysis model was chosen to combine the individual estimates from the included studies; in this way, the model could allow for heterogeneity between the studies. Also, for the purposes of the cost-effectiveness model, meta-analytic methods often used for diagnostic studies, such as summary ROC curves, were not suitable as they do not provide the required point estimates of sensitivity and specificity or 95% CIs, or an estimate of heterogeneity, important for sensitivity analyses.

Sensitivity analyses and assessment of heterogeneity

Testing for heterogeneity

There were a priori reasons to expect heterogeneity: differences in technology, different readers and differences in the patient groups. Another important source of heterogeneity in diagnostic studies is due to different diagnostic thresholds being used. Although all the studies used ostensibly the same diagnostic thresholds, it is still possible for the diagnostic threshold to vary from study to study[37] The presence of a threshold effect was tested for by Spearman correlation coefficients[37] and by examining ROC plots. The random effects meta-analysis method used was that described by Fleiss and colleagues to combine proportions that vary at random.[75] Heterogeneity for all sources was explored with statistical tests and forest plots using the χ^2 test and variance inflation factor (VIF). Publication bias was also assessed by funnel plots.

Sensitivity analyses

Rather than use checklists to produce a quality score,[74,76] individual prespecified items were used in sensitivity analyses.[74,76] Possible factors on which to undertake a sensitivity analysis were discussed a priori by the HTA group at the first meeting (April 2003). The factors considered (before selecting the studies) were:

- publication date, as a proxy for generation of technology
- type of less invasive technology
- patient population and spectrum of disease: although studies were only included if they complied with the prespecified criteria with regard to the patient group (e.g. symptomatic status), it was anticipated that there would still be differences between the studies in how patients had been recruited (e.g. some might have used US to screen patients and others might not)
- blinding: studies were to be included only if the index (less invasive) test was performed blind to the reference test results. However, knowledge of the less invasive test result could influence interpretation of the reference standard (IAA) test result and bias the apparent accuracy of the less invasive test.[77] It was felt important to examine the significance of this effect
- observer experience, neurovascular or vascular radiologists, being more familiar with the carotid anatomy and disease appearances, might be better at interpreting the less invasive tests than general radiologists who might be less experienced in this area. It was felt important to quantify the effect of observer experience on accuracy to help to translate the systematic review into what might happen in routine practice.

Sensitivity analyses were performed by statistical modelling of the diagnostic odds ratio (DOR)[78] using data taken from the critical appraisal and data extraction checklists (see Appendices 4–6).

Results

Results of the literature search

Included and excluded studies

In total, 3479 abstracts were identified by the electronic searches. The literature search found 194 reviews, but reference lists of only 81 were checked, as after the first 40 review reference lists this method of finding studies ceased to produce new references. Of the non-English-language publications which could not be assessed further because of lack of translation facilities, 20 German, three each of Japanese, Chinese, Spanish and Italian, two each of French and Hungarian, one each of Polish, Serbo-Croat, Norwegian, and Danish papers were excluded. Of these 40 in total, 36 appeared to be primary studies and four were reviews.

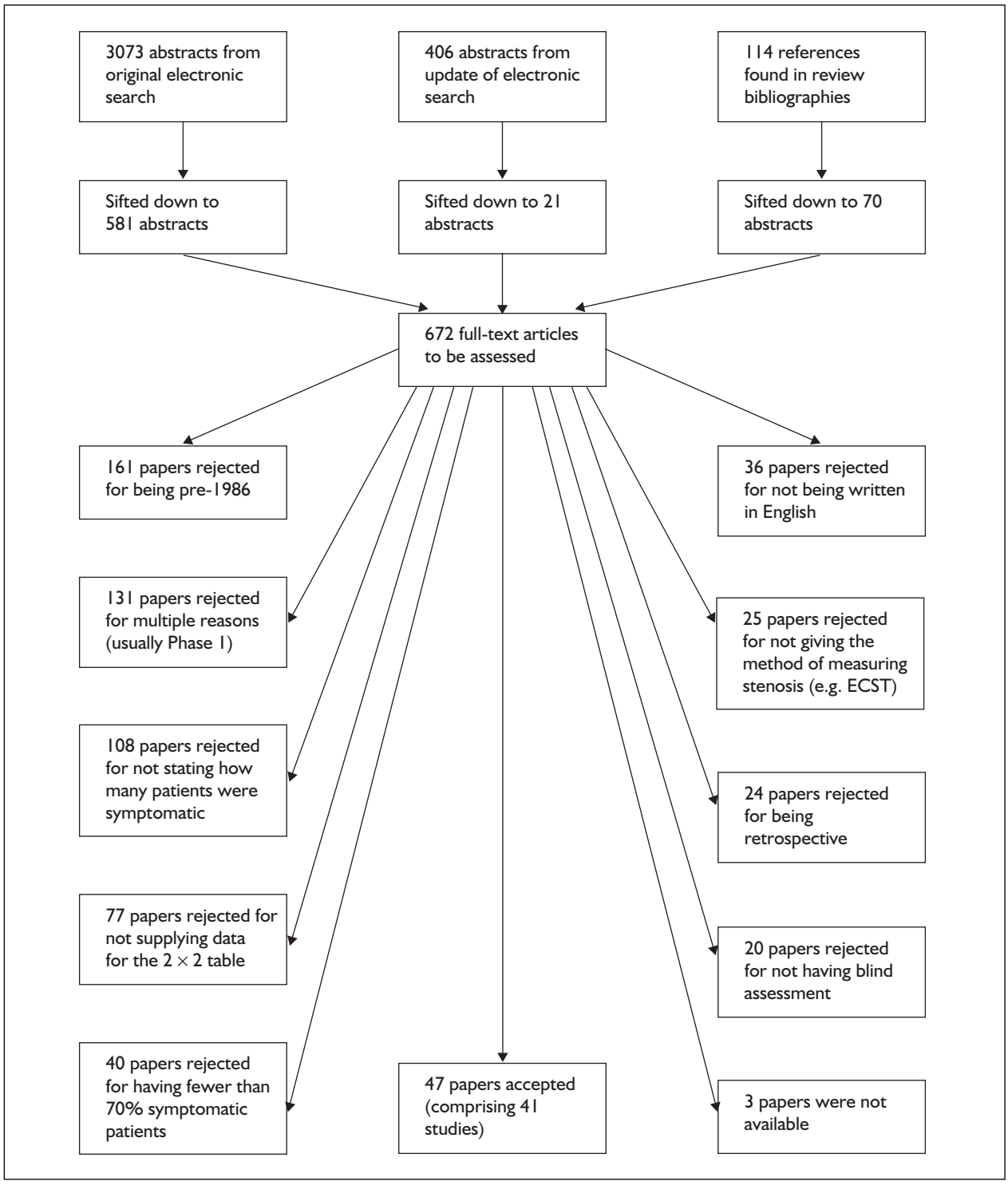

FIGURE 2 *Flowchart of the study identification and critical appraisal process*

In total, the electronic searches, review reference lists and handsearching yielded 672 primary studies for critical appraisal of the full paper. Of these, 625 were excluded for the following reasons (*Figure 2*):

- 161 studies were published in 1985 or earlier
- 131 for more than one reason, usually due to poor methodology, or for being a Phase I diagnostic study (i.e. a preliminary report of a new technology)
- 108 studies where it was not possible to ascertain the proportion of patients who were symptomatic, even by making an educated guess
- 77 studies where the data to fill a 2 × 2 table were not available

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- 40 studies where the proportion of symptomatic patients was less than 70%
- 36 non-English-language studies
- 25 studies where the method of calculating the stenosis was not given at all
- 24 studies were retrospective
- 20 studies did not blind the interpretation of the index test to the reference test
- three studies were not available in full publication

Characteristics of included studies

The remaining 47 papers, comprising 41 patient groups, were kept for critical appraisal, data extraction and meta-analysis. Six papers were secondary publications of further analyses on a data set already included in the 41 papers. *Figure 2* shows a flowchart of how many abstracts and papers were assessed and the outcome of that assessment. *Table 1* gives a summary of the characteristics of the included studies.

Most studies were not very large, the median number of patients being just 45 (*Figure 3*). The five smallest studies had just 20 patients, the smallest number acceptable by the inclusion criteria.[88,96,103,114,115] The largest study had 313 patients.[104] The 41 studies included a combined total of 2404 patients. Twelve studies did not report the average age of the patients. Of those that did, most gave an average age in the sixties (*Figure 4*). Only seven studies included some asymptomatic patients, but these studies fulfilled the inclusion criterion that at least 70% of the patients had to be symptomatic.[85,99,105–107,116]

Although many studies used more than one less invasive imaging method, it was not always possible to extract data on all techniques used, or at the stenosis cut-offs required for the meta-analysis. Thus more less invasive techniques are listed in *Table 1* than contributed to the meta-analysis. The number of studies using the less invasive imaging methods were: US (16 papers), MRA (16 papers), CTA (13 papers) and CEMRA (nine papers). Although many papers appeared to assess more than one less invasive technique, the accuracy was not comparable because different patients contributed to the analysis of accuracy for each technique. For example, 40 patients might be included in a comparison of US with IAA and only 32 of MRA with IAA in the same paper. But without knowing the US and MRA result in the same patients, the effect of combining the two cannot be determined. Only one paper described the accuracy of two less invasive tests in combination.[34]

The most common method used for defining stenosis was the NASCET method (31 studies), followed by the ECST method (six studies), and then the CCA (two studies). One study used both the NASCET and ECST methods, and one study used a method that was not NASCET, ECST or CCA (*Figure 5*).

Most papers provided data on patients in operable (70–99% stenosis) versus non-operable (0–69% or occluded) groups. Because of variation in cutpoints of stenosis used in studies, there was overlap in terms of the stenosis categories to which each study was able to contribute data. Thus, 23 studies contributed to 70–99% versus 0–69% or occluded, 11 studies contributed to 0–49% and occluded versus 50–99% only, and six studies contributed to 0–49% and occluded versus 50–69% versus 70–99% (*Figure 6*).

Results of the meta-analysis

More data were available for analysis of patients categorised as operable (70–99%) stenosis versus non-operable (0–69% or occluded) than in possibly operable (50–69%) or definitely not operable (0–49% or occluded) groups (*Figure 6*). The study therefore concentrated on the accuracy for detection of 70–99% stenosis.

The forest plots for sensitivity and specificity for each less invasive technique per included study, together with an estimate of the overall sensitivity or specificity for that technique, for 70–99% stenosis, are given in *Figures 7* and *8* respectively, and *Table 2*.

CEMRA had the highest sensitivity (0.94, 95% CI 0.88 to 0.97), closely followed by US (0.89, 95% CI 0.85 to 0.92) and MRA (0.88, 95% CI 0.82 to 0.92) and then, rather worse, CTA (0.77, 95% CI 0.68 to 0.84). The sensitivity for CTA was significantly worse than for CEMRA and US, but not MRA.

However, CTA had the highest specificity (0.94, 95% CI 0.91 to 0.97), closely followed by CEMRA (0.93, 95% CI 0.89 to 0.96), then US (0.84, 95% CI 0.77 to 0.89) and MRA (0.84, 95% CI 0.76 to 0.90). The specificity for US was significantly worse than CTA, but not any of the other techniques.

There were insufficient data to make reliable comparisons for 50–69% stenosis (*Figure 9* and *10* and *Table 2*) where only one study contributed US data, one for CTA, two for MRA and three for CEMRA. On these limited data, CEMRA appeared to have the highest sensitivity, but the 95%

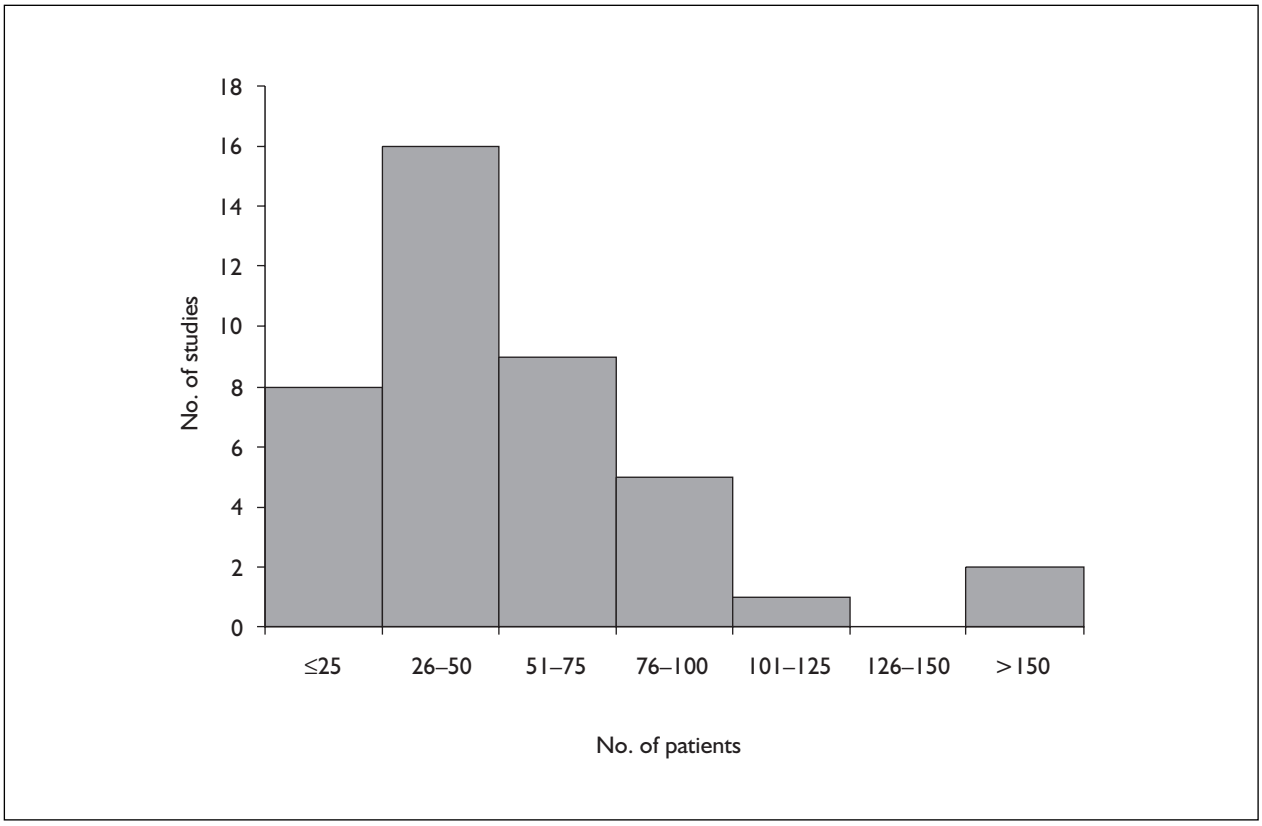

FIGURE 3 *Number of patients included in the studies used in the meta-analysis*

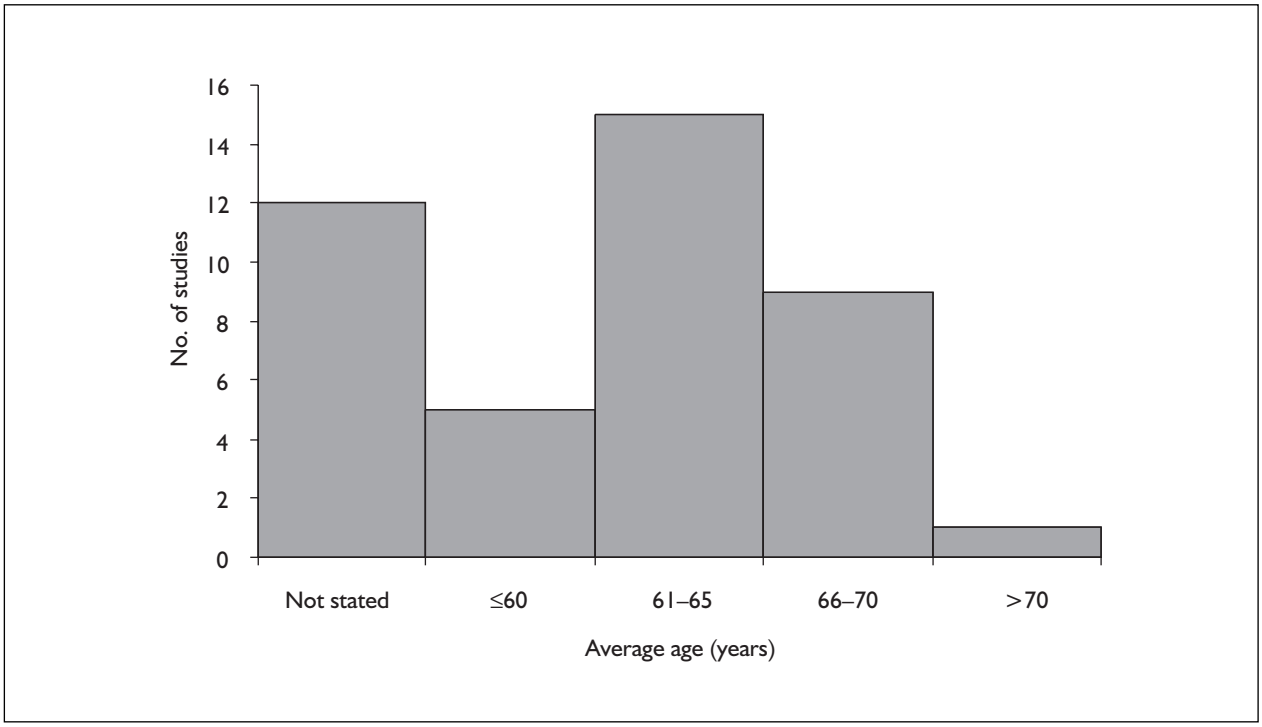

FIGURE 4 *Average age of patients in the studies in the meta-analysis (reported variously as a mean or a median)*

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TABLE I *Characteristics of included studies*

Study	No. of patients (arteries)	Mean age (range) (years)	% Symptomatic	Non-invasive imaging	Disease spectrum	Cut-off at 50% NASCET	Cut-off at 70% NASCET
Alvarez-Linera, 2003[79]	40 (80)	61.5 (42–80)	100	MRA, CTA	≥ 70% by US	Yes	Yes
Anderson, 2000[80]	40 (80)	(44–83)	100	CTA	≥ 50% by US	No	Yes
Boné, 1988[81]	67 (127)	56	100	US	0–100%	No	No
Bönig, 2000[82]	79 (158)	66.3 (40–80)	100	CTA, US	0–100%	No	Yes
Borisch, 2003[83]	39 (71)	67.4 (41–80)	100	MRA, US	0–100%	No	Yes
Catalano, 2001[84]	37 (74)	NS	100	MRA	Screened by US	No	Yes
Cosottini, 2003[85,86]	92 (188)	66.5 (45–82)	94.6	MRA	Screened by US	Yes	Yes
Cumming, 1994[87]	35 (70)	75 (51–85)	100	CTA	0–100%	No	Yes
Dadachanji, 1995[88]	20 (40)	(38–75)	100	MRA	0–100%	No	Yes
Dillon, 1993[89]	27 (50)	62.5 (37–79)	100	CTA	Screened by US	No	Yes
Elgersma, 2000[90], 1999[91]	38 (47)	65 (45–82)	100	MRA	Screened by US	Yes	Yes
Humphrey, 1990[92]	99 (168)	NS	100	US	0–100%	No	No
Huston, 1993[93]	52 (93)	67	100	MRA	Screened by US	Yes	No
Knudsen, 2002[94]	65 (129)	NS	100	US	0–100%	No	Yes
Laster, 1993[95]	101 (202)	(37-83)	100	MRA	0–100%	No	No
Leclerc, 1995[96]	20 (39)	Median 63 (39–85)	100	CTA	Screened by US	No	Yes
Leclerc, 1999[97], 1998[98]	22 (44)	Median 61 (42–84)	100	CTA	0–100%	No	Yes
Levi, 1996[99]	45 (90)	68 (33–89)	88.9	MRA	0–100%	No	Yes
Link, 1996[100] 1995[101]	46 (92)	63 (42–80)	100	CTA	0–100%	No	Yes
Link, 1997[102]	28 (56)	63 (46–77)	100	CTA, US	0–100%	No	Yes
Magarelli, 1998[103]	20 (40)	65	100	MRA, CTA	0–100%	No	Yes
Nederkoorn, 2002[104,105]	313 (313)	67 (39–88)	100	MRA,US	0–100%	Yes	Yes
Patel M, 1995[106]	88 (167)	70 (48–87)	80.0 (estimated)	US, MRA	0–100%	No	Yes
Patel S, 2002[34]	34 (34)	NS	100	US, MRA, CTA	Screened by US	No	Yes
Remonda, 1998[107]	21 (44)	68 (53–83)	81.0	MRA	Screened by US	No	Yes
Sardanelli, 1999[108]	30 (60)	64.5	100	CEMRA	0–100%	No	Yes
Scarabino, 1999[109] 1998[110]	23 (46)	(63–73)	100	MRA	0–100%	Yes	Yes
Scarabino, 1998[111]	64 (128)	NS	100	MRA, CEMRA	0–100%	No	Yes
Simeone, 1997[112]	40 (80)	(35-75)	100	CTA	0–100%	No	Yes
Sitzer, 1993[113]	56 (111)	Median 60 (39–80)	100	MRA	≥ 70% by US	No	Yes
Tetičkovič, 2001[114]	20 (40)	Median 61 (36–76)	100	CTA, US	0–100%	No	No
Turnipseed, 1993[115]	20 (34)	63	100	MRA	≥ 70% by US	No	Yes
Uehara, 1995[116]	44 (81)	60.8 (33–79)	95.5	MRA	0–100%	No	Yes
Van Merode, 1989[117]	57 (97)	NS	100	US	0–100%	No	No
Vanninen, 1995[118]	45 (90)	59 (34–72)	100	MRA, US	0–100%	No	Yes
White, 1994[119]	60 (117)	67 (44–89)	100	MRA, US	0–100%	No	No
Winkelaar, 1999[120]	99 (188)	NS	70	US	0–100%	Yes	No
Worthy, 1997[121]	73 (143)	Median 62 (47–84)	100	US	0–100%	Yes	No
Young, 1996[122] 1994[56]	70 (137)	62 (37–76)	100	MRA	Screened by US	Yes	No
Zbornikova, 1998[123]	49 (58)	63	100	US	0–100%	No	No

NS, not stated.

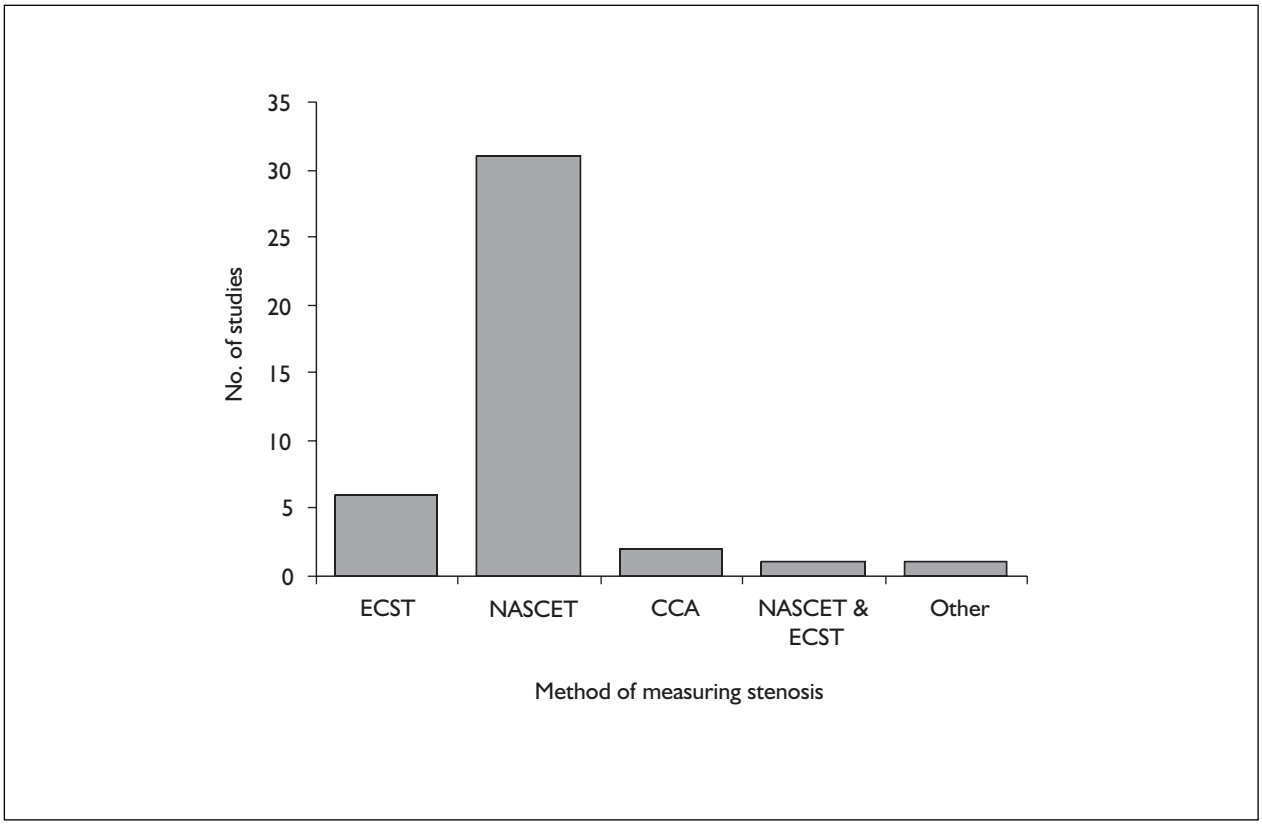

FIGURE 5 *Method used to measure stenosis in the studies included in the meta-analysis*

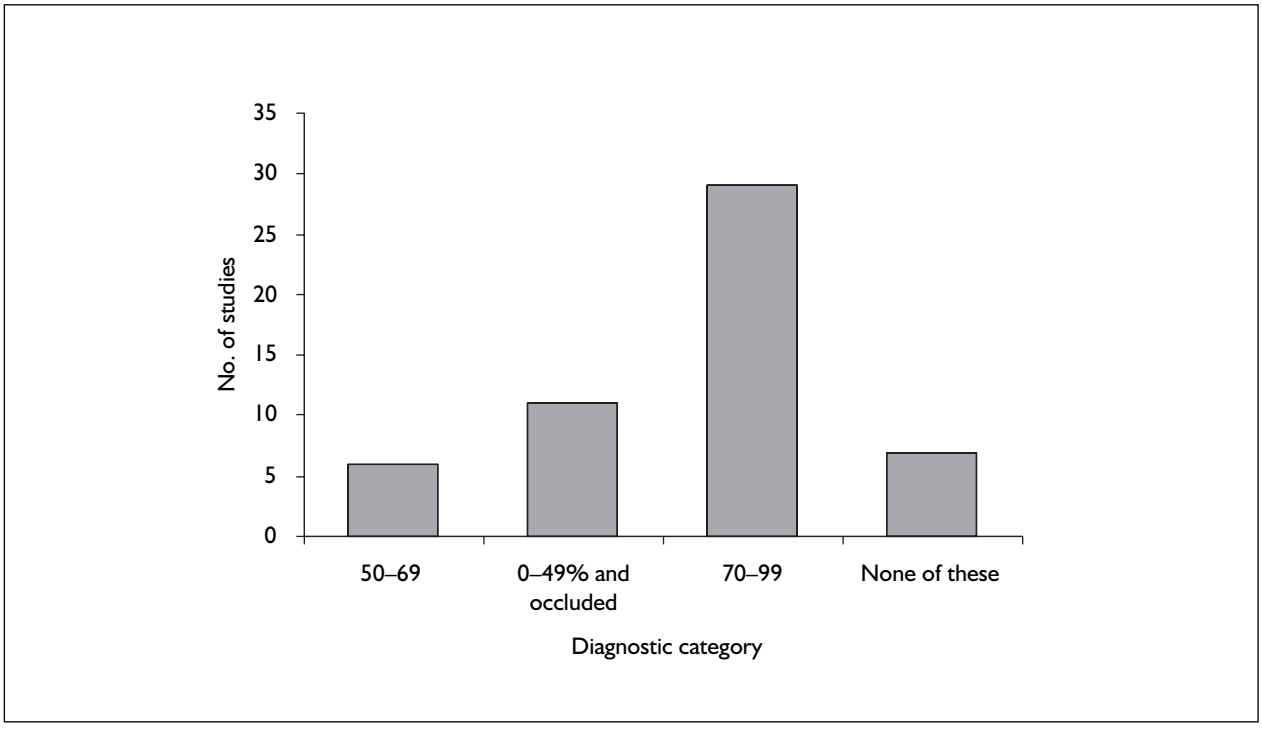

FIGURE 6 *Number of studies providing data in the required NASCET stenosis bands*

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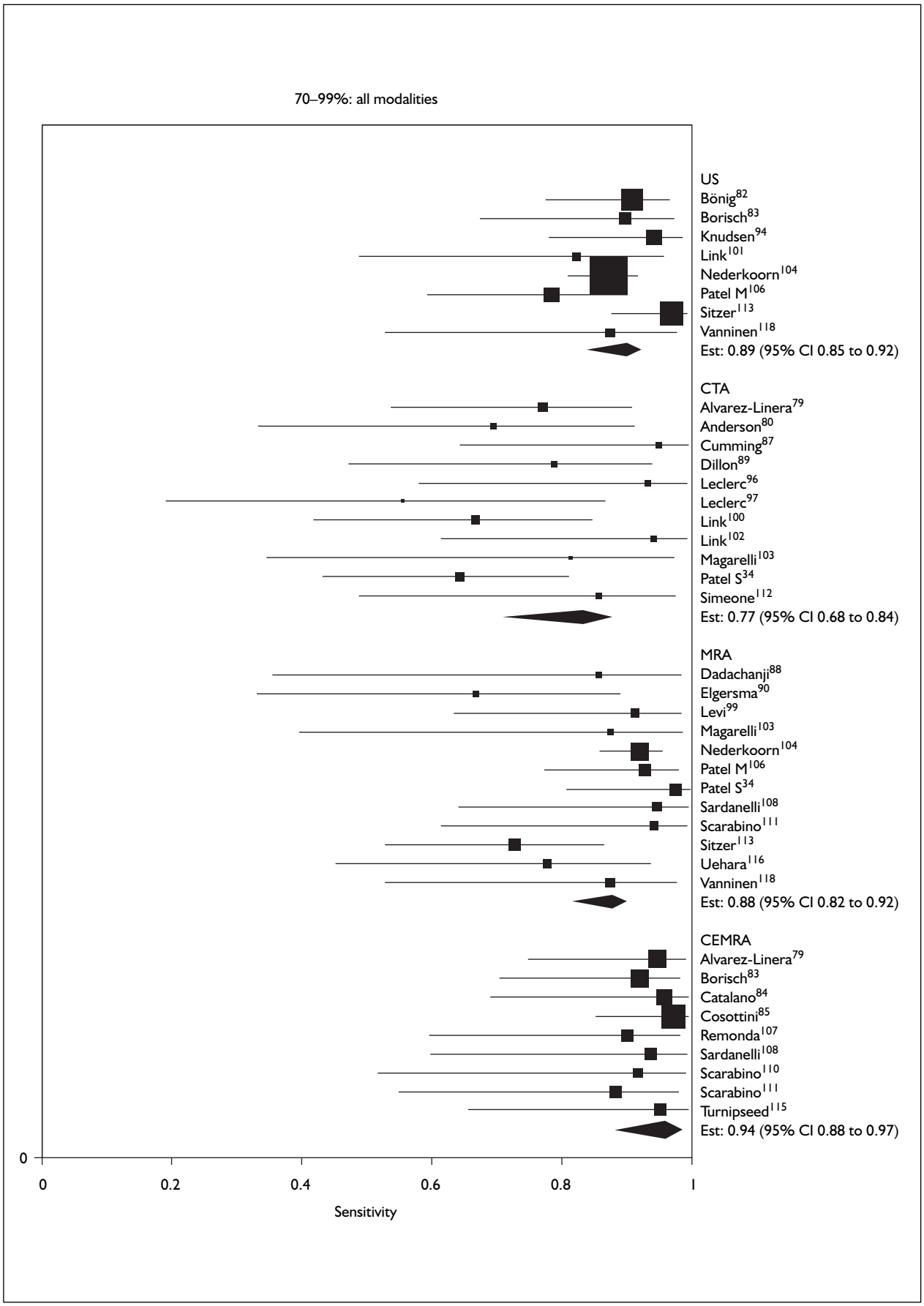

FIGURE 7 *Forest plot of sensitivity estimates (Est): 70–99% stenosis*

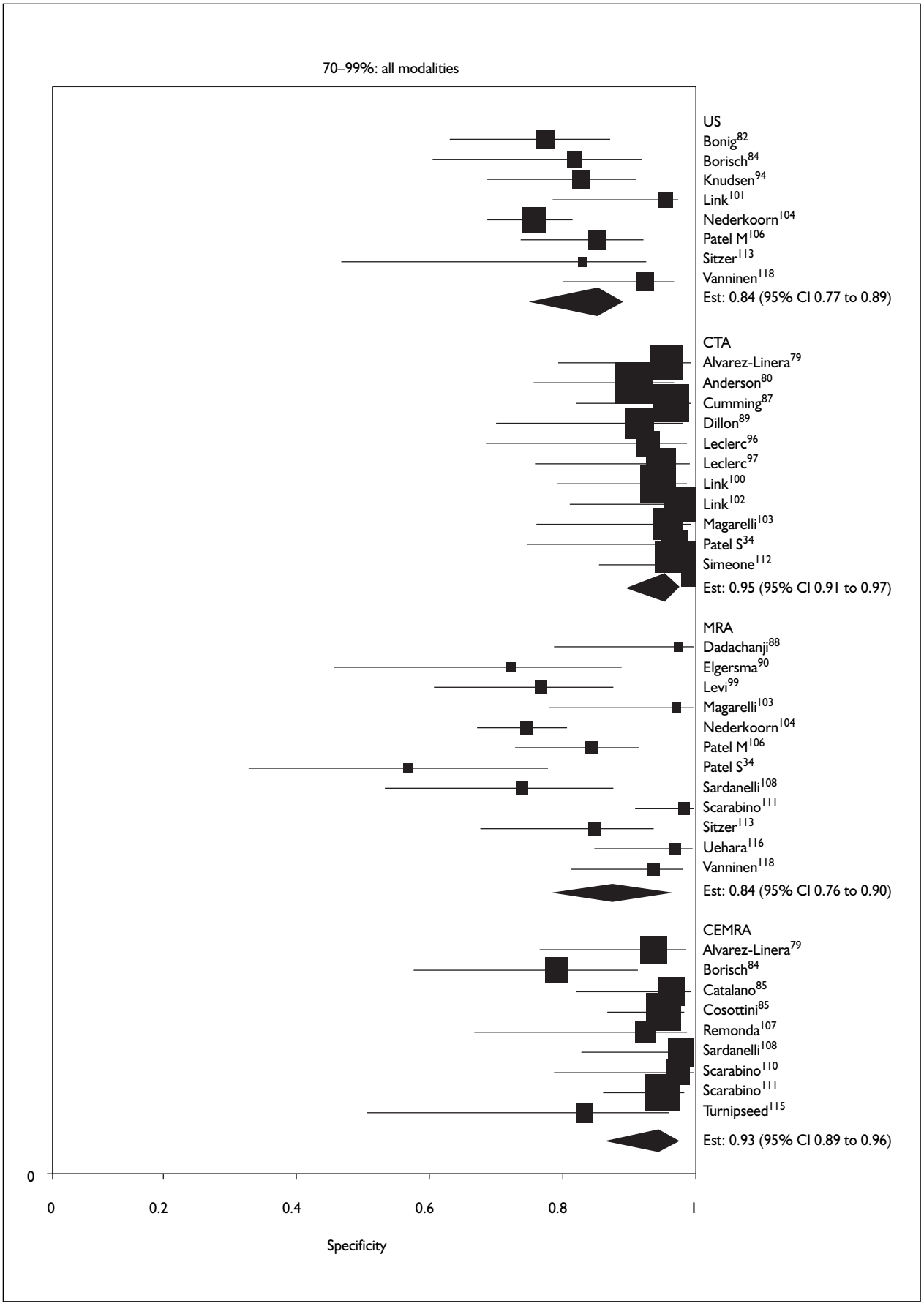

FIGURE 8 *Forest plot of specificity estimates (Est): 70–99% stenosis*

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TABLE 2 *Results of the meta-analyses for all stenosis groups and imaging modalities*

Stenosis group	Imaging	Sensitivity (95% CI)	Specificity (95% CI)
70–99%	US	0.89 (0.85 to 0.92)	0.84 (0.77 to 0.89)
	CTA	0.77 (0.68 to 0.84)	0.95 (0.91 to 0.97)
	MRA	0.88 (0.82 to 0.92)	0.84 (0.76 to 0.90)
	CEMRA	0.94 (0.88 to 0.97)	0.93 (0.89 to 0.96)
50–69%	US	0.36 (0.25 to 0.49)	0.91 (0.87 to 0.94)
	CTA	0.67 (0.30 to 0.90)	0.79 (0.63 to 0.89)
	MRA	0.37 (0.26 to 0.49)	0.91 (0.78 to 0.97)
	CEMRA	0.77 (0.59 to 0.89)	0.97 (0.93 to 0.99)
0–49,100%	US	0.83 (0.73 to 0.90)	0.84 (0.62 to 0.95)
	CTA	0.81 (0.59 to 0.93)	0.91 (0.74 to 0.98)
	MRA	0.81 (0.70 to 0.88)	0.88 (0.76 to 0.95)
	CEMRA	0.96 (0.90 to 0.99)	0.96 (0.90 to 0.99)

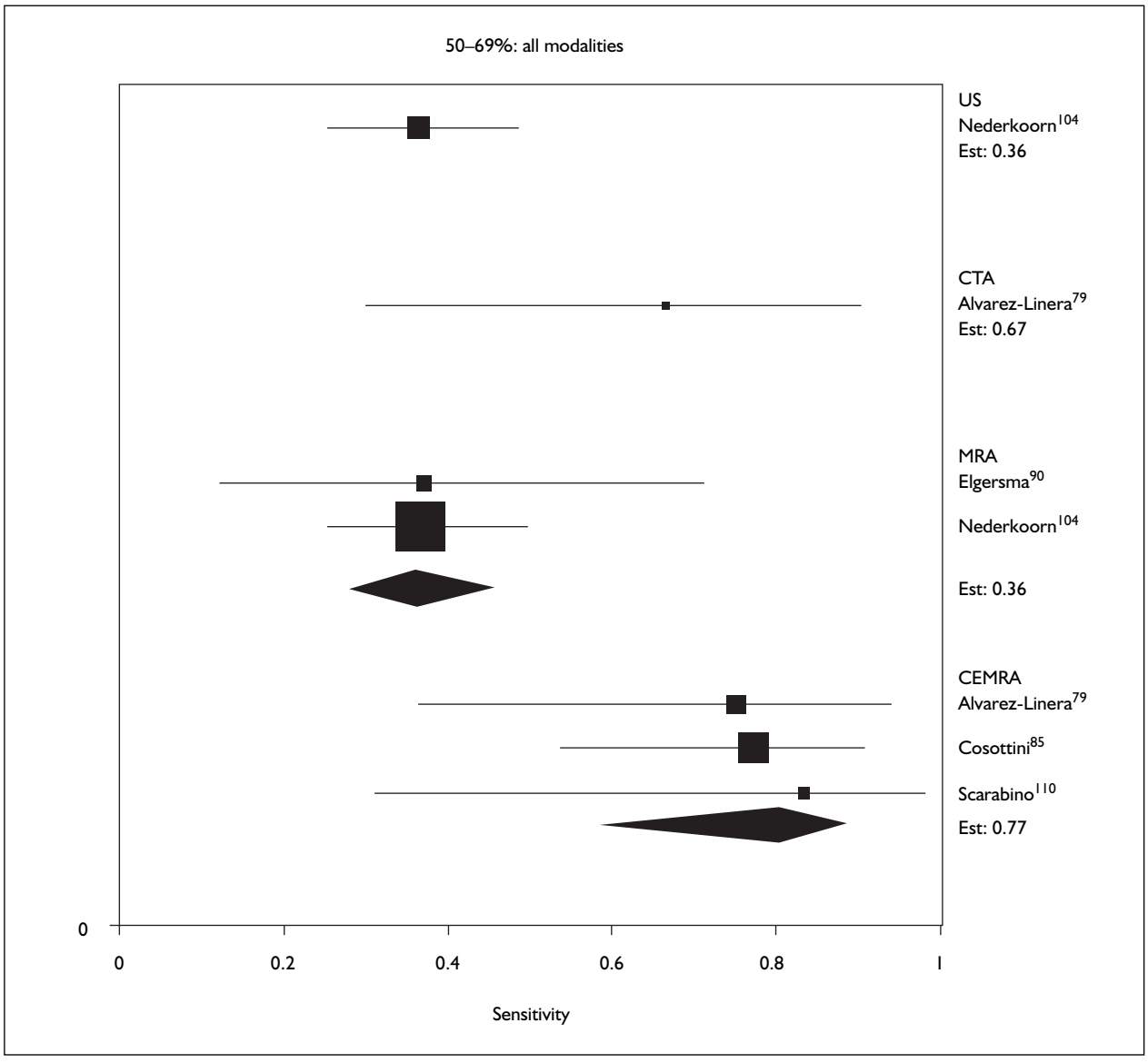

FIGURE 9 *Forest plot of sensitivity estimates (Est): 50–69% stenosis*

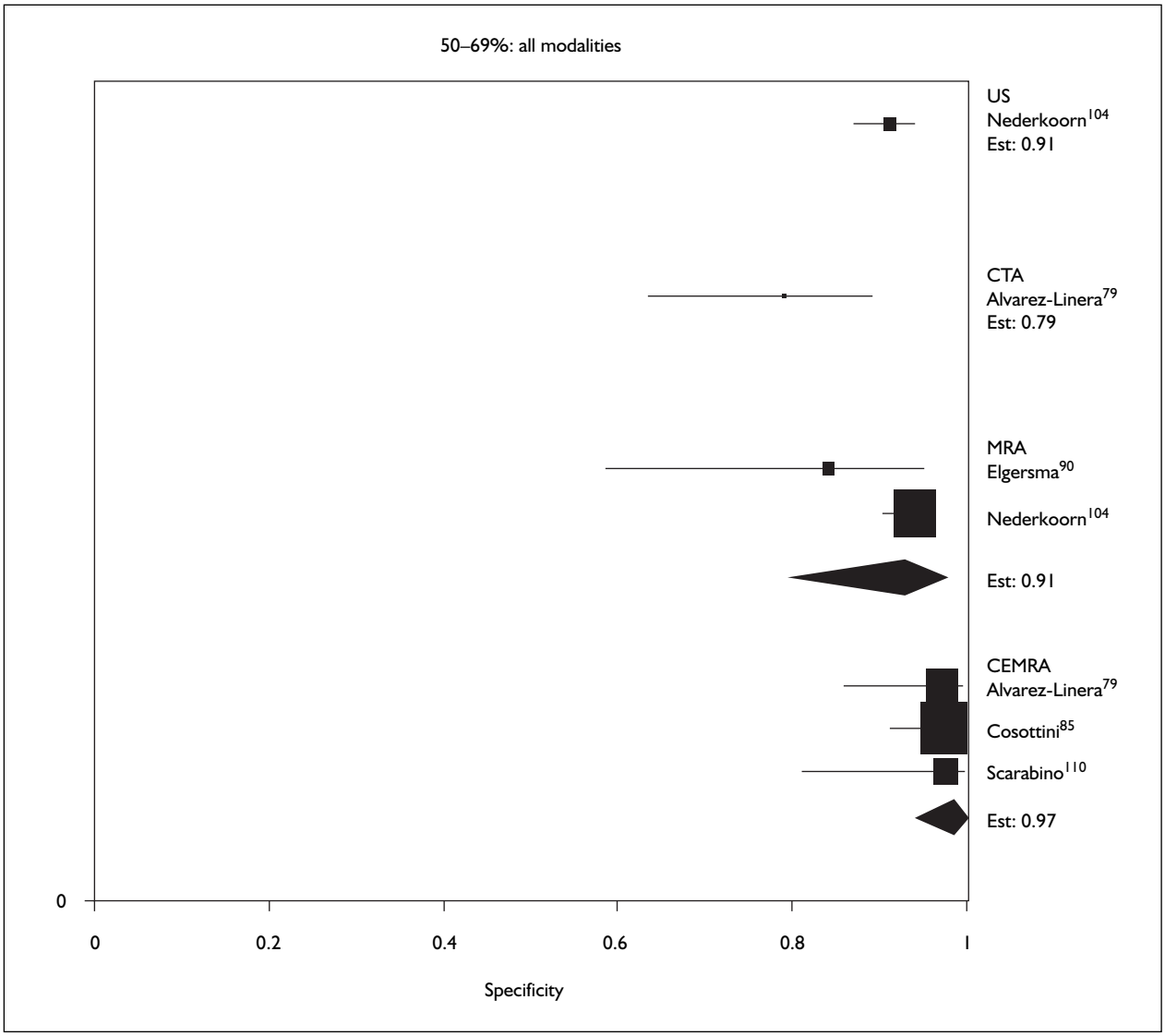

FIGURE 10 *Forest plot of specificity estimates (Est): 50–69% stenosis*

confidence intervals were very wide. In contrast to the 70–99% stenosis data, CTA appeared to have the lowest specificity, but this is based on data from very few studies. The very low sensitivities of both US and MRA in the diagnosis of 50–69% stenosis (both 36%) should be interpreted with caution owing to the paucity of data (the analyses are based on one and two studies, respectively). However, if correct, it would mean that patients with a 50–69% stenosis by IAA would be more likely to be diagnosed as having 70–99% stenosis than be given a correct diagnosis, or diagnosed with 0–49% stenosis or occlusion.

For 0–49% stenosis or occlusion, CEMRA had the highest sensitivity (*Figure 11* and *Table 2*), although the differences between the modalities were not significant and relatively few studies contributed to these analyses (four US, one CTA, four MRA and three CEMRA). The pattern was similar for specificity (*Figure 12* and *Table 2*).

Exploration of heterogeneity

Is there evidence of heterogeneity?

As sensitivity and specificity are proportions, χ^2 tests were used to test for heterogeneity between the studies. Where the χ^2 test was not appropriate, a likelihood ratio χ^2 test was used instead. In addition, the method of meta-analysis included the calculation of a VIF; heterogeneity was not statistically significant where this was equal to 1. However, these tests were interpreted carefully, as statistical methods for detecting heterogeneity can often fail.[124] Forest plots of the estimates from individual studies were also inspected for heterogeneity (*Figures 7–12*). Results of the statistical tests are given in *Tables 3* and *4*.

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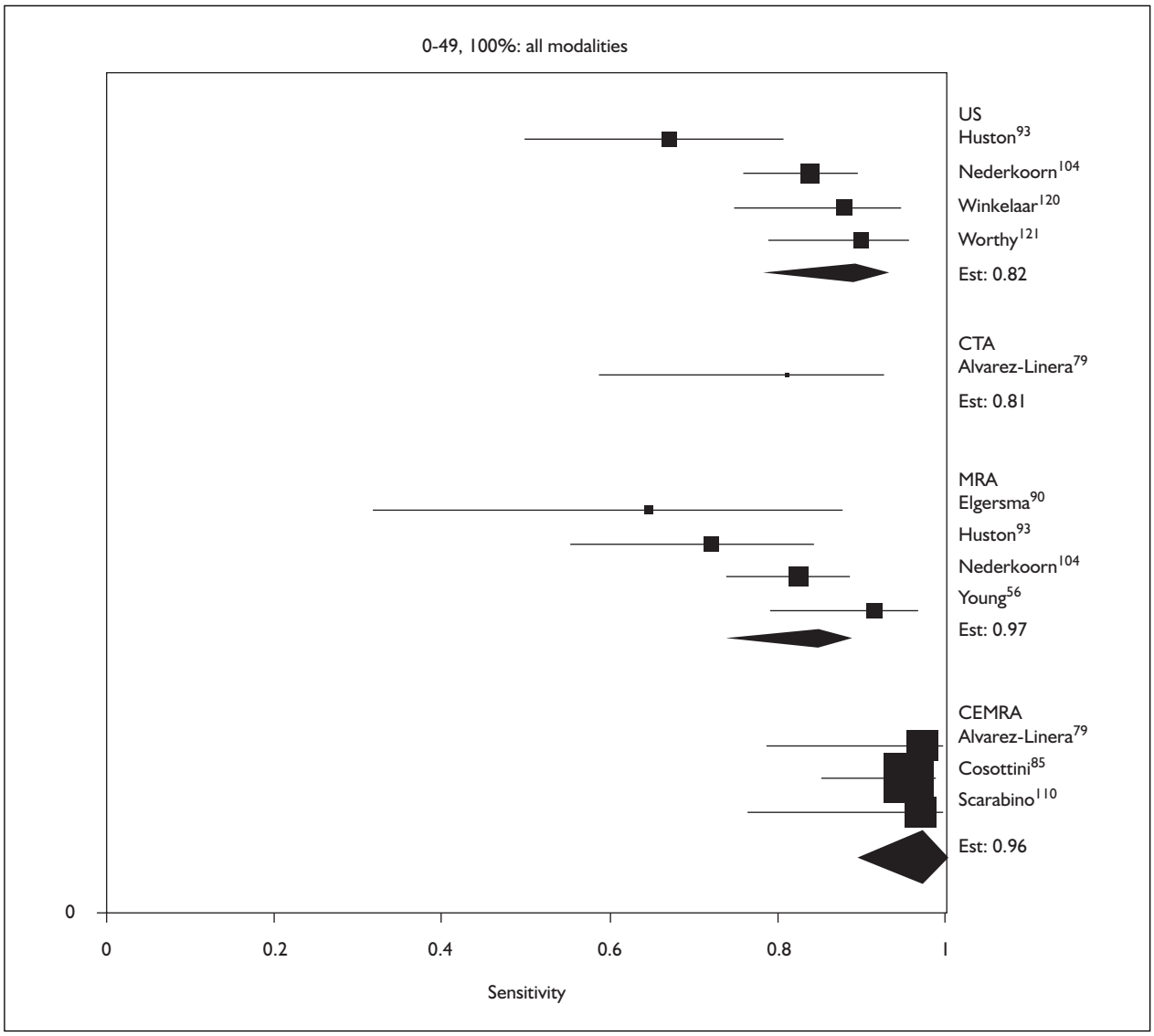

FIGURE 11 *Forest plot of sensitivity estimates (Est): 0–49, 100% stenosis*

CEMRA appears to be the imaging modality least affected by heterogeneity. Only once does the VIF indicate heterogeneity (*Table 3*) in the meta-analysis of 70–99% specificity data, and even then, the VIF is still quite small: 1.512 (a variance inflation factor of 1 indicates no heterogeneity, and the larger its value, the greater the heterogeneity).

The presence of a threshold effect was tested for with ROC plots and correlation coefficients were calculated. If a threshold effect was present, that is, there was variation among the study estimates because they were using different criteria to define positive and negative diagnoses, the data would appear to lie on an ROC curve (*Figures 13–15*). There is no obvious such curvature for US, MRA and CEMRA with regard to the 70–99% diagnostic data (*Figure 13*). The CTA data could be possibly consistent with an ROC curve, but the paucity of data creates uncertainty. The only other data that show a possibility of a threshold effect from the ROC plots are for US and MRA 0–49% or occluded stenosis data (*Figure 15*), but it is difficult to say that there is definitely an effect, owing to the paucity of data. One of the US data points appears to be an outlier.[121] This study measured stenosis using the ECST method,[72] whereas the other papers all used the NASCET method.[93,104,120] There were too few data in the ROC plot for 50–69% stenosis to say whether the points lay on a curve or not (*Figure 14*). The results of testing for threshold effects using correlation coefficients are given in *Table 5*. Only

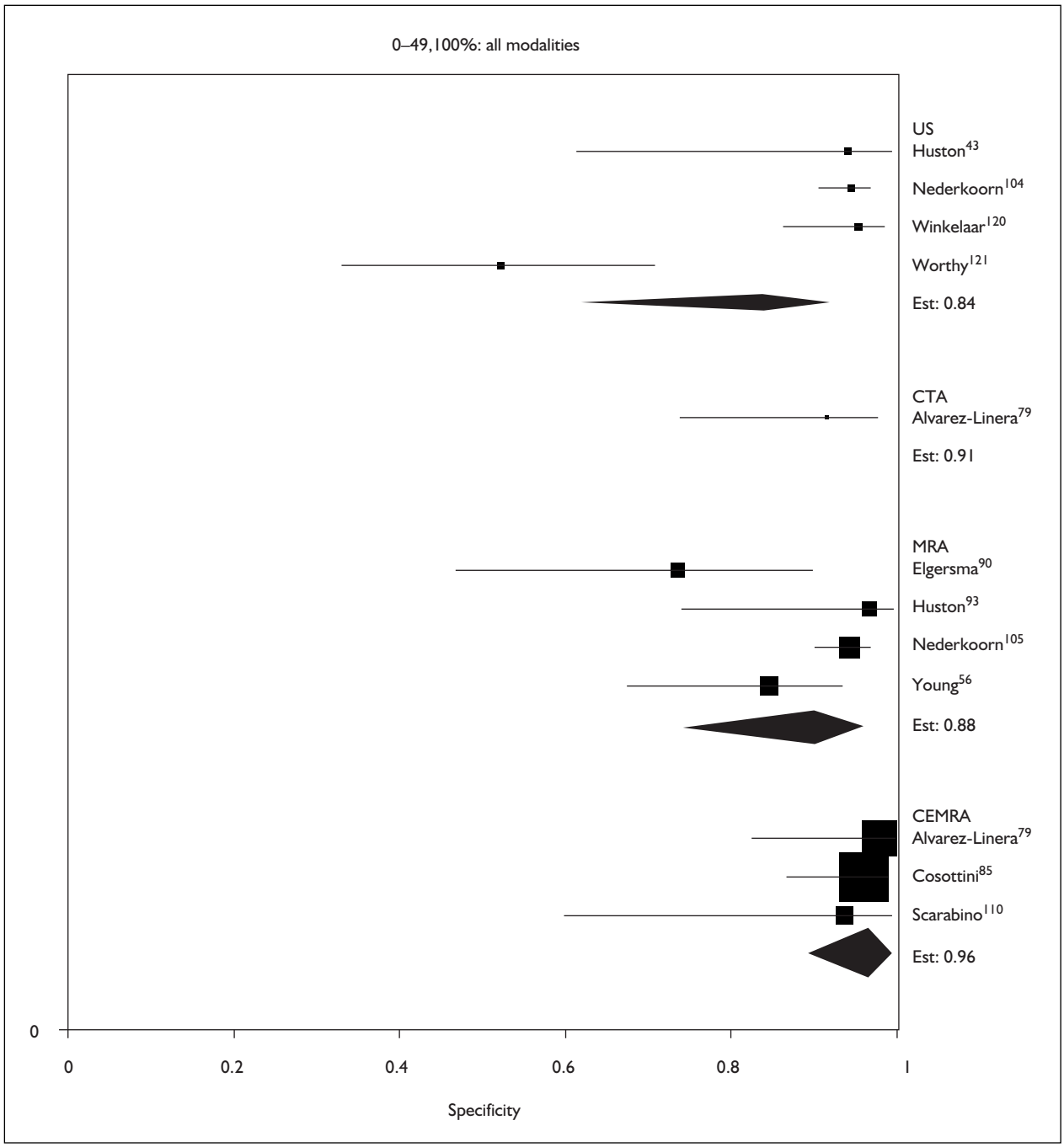

FIGURE 12 *Forest plot of specificity estimates (Est): 0–49, 100% stenosis*

one of the test results was significant, that for CEMRA 50–69% data, but as this result relies on just three data points, it cannot be taken as evidence of a threshold effect. Thus, there was no conclusive evidence of a threshold effect in any of the analyses.

Even discounting a threshold effect, there is undoubtedly heterogeneity in some of the meta-analyses. This is readily apparent from the forest plots (*Figures 7–12*), although only the meta-analysis of MRA specificity estimates in the diagnosis of 70–99% stenosis had a statistically significant χ^2 test. The VIF was more sensitive: it detected heterogeneity in all the meta-analyses for 70–99% stenosis data except those for the CTA meta-analyses. This is more in line with the inspection of the forest plots (however, the variance inflation factor appears to be very sensitive to the presence of outliers, that for US specificity in the diagnosis

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TABLE 3 *Statistical tests for heterogeneity in the meta-analyses of 70–99% data*

Imaging	No. of studies	No. of patients (adjusted)	Pearson χ^2 value	*p*	Likelihood ratio χ^2 value	*p*	VIF
Sensitivity							
US	8	316	7.62	0.37	8.16	0.32	1.22
CTA	11	111	NA	NA	9.71	0.47	1.00
MRA	12	264	NA	NA	13.04	0.29	2.78
CEMRA	9	124	NA	NA	1.58	0.99	1.00
Specificity							
US	8	357	10.53	0.16	12.08	0.10	2.84
CTA	11	250	NA	NA	2.64	0.99	1.00
MRA	12	494	NA	NA	48.59	<0.0001	6.48
CEMRA	9	257	NA	NA	8.20	0.41	1.51

NA, not applicable.

TABLE 4 *Variance inflation factors of the 50–69% and 0-49, 100% data*

Stenosis group	Imaging	No. of studies	No. of patients (adjusted)	VIF
Sensitivity				
50–69%	US	1	62	NA
	CTA	1	6	NA
	MRA	2	63	1.00
	CEMRA	3	27	1.00
0–49, 100%	US	4	233	3.48
	CTA	1	19	NA
	MRA	4	183	3.11
	CEMRA	3	81	1.00
Specificity				
50–69%	US	1	253	NA
	CTA	1	36	NA
	MRA	3	243	10.00
	CEMRA	3	136	1.00
0–49, 100%	US	4	292	45.60
	CTA	1	24	NA
	MRA	4	242	11.69
	CEMRA	3	82	1.00

of 0–49% stenosis or occluded is very high, and this meta-analysis includes a possible outlier[93]). For example, the US forest plot for specificity (*Figure 8*) does indicate heterogeneity, but the χ^2 test failed to find this (*Table 3*), and the VIF did (*Table 5*). Possible reasons for heterogeneity were explored in the sensitivity analyses.

Meaningful exploration of heterogeneity is not possible when the meta-analysis includes only a few studies. For this reason, formal statistical tests were not used for the meta-analyses of 50–69% and 0–49% or occluded diagnostic data. Inspection of the forest plots for the 50–69% data (*Figures 9 and 10*) does not suggest that heterogeneity is significant. This agrees with the VIF calculations (*Table 4*). There is some heterogeneity present in the 0–49% or occluded meta-analyses, especially the US specificity data, according to the VIF. There are four studies contributing to that meta-analysis, and one of them gives a noticeably different estimate to the other three,[121] which may, as discussed above, be an outlier.

Is there evidence of publication bias?

Funnel plots were constructed for the meta-analyses of US, CTA, MRA and CEMRA in the

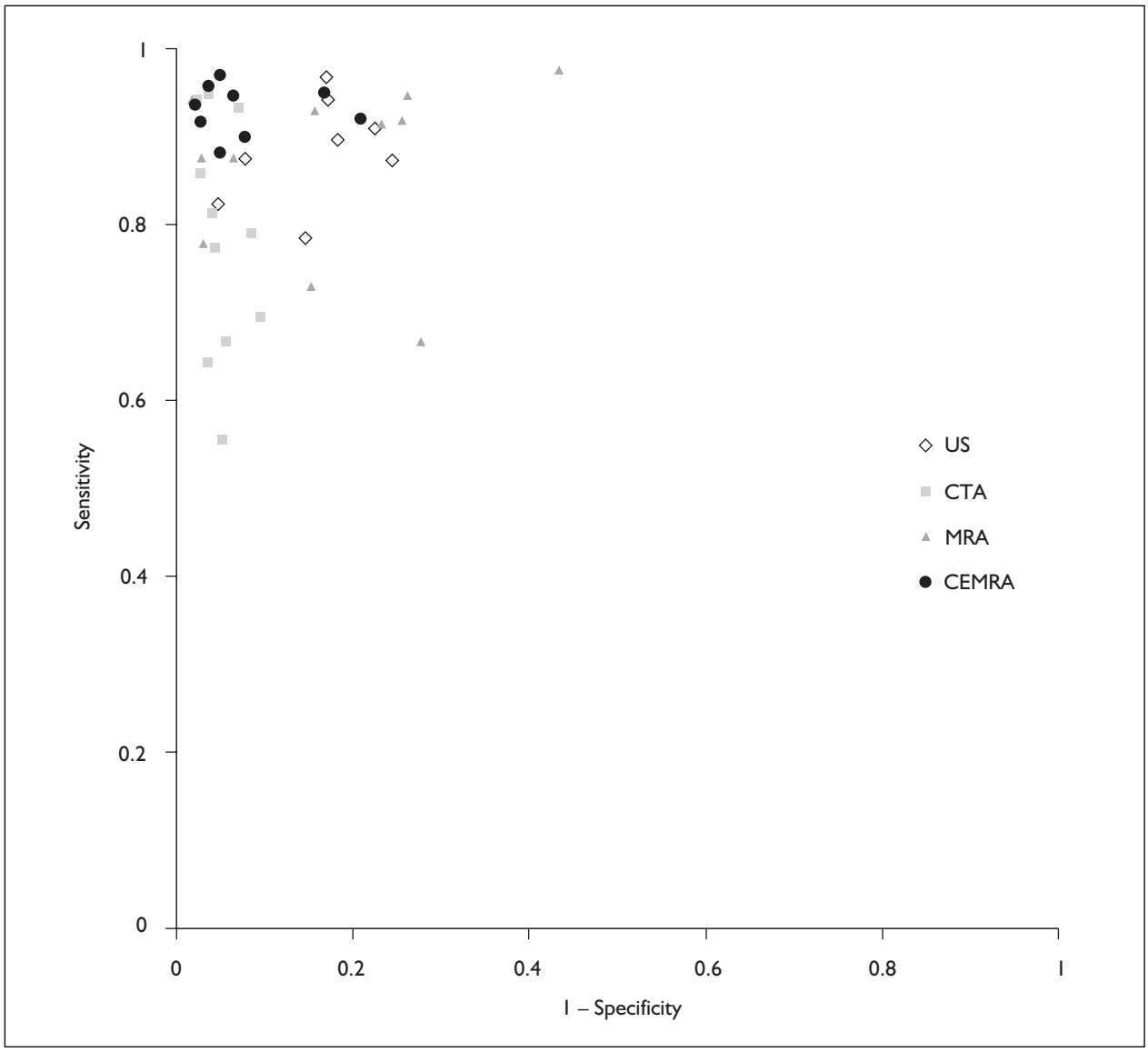

FIGURE 13 *ROC plot of US, CTA, MRA and CEMRA 70–99% data*

TABLE 5 *Threshold effect correlation coefficient tests*

Stenosis group	Imaging	No. of studies	Spearman's rho	*p*
70–99%	US	8	–0.33	0.42
	CTA	11	0.35	0.28
	MRA	12	–0.25	0.44
	CEMRA	9	0.12	0.77
50–69%	US	1	NA	NA
	CTA	1	NA	NA
	MRA	2	NA	NA
	CEMRA	3	1.00	<0.0001
0–49, 100%	US	4	–0.20	0.80
	CTA	1	NA	NA
	MRA	4	0.20	0.80
	CEMRA	3	0.50	0.67

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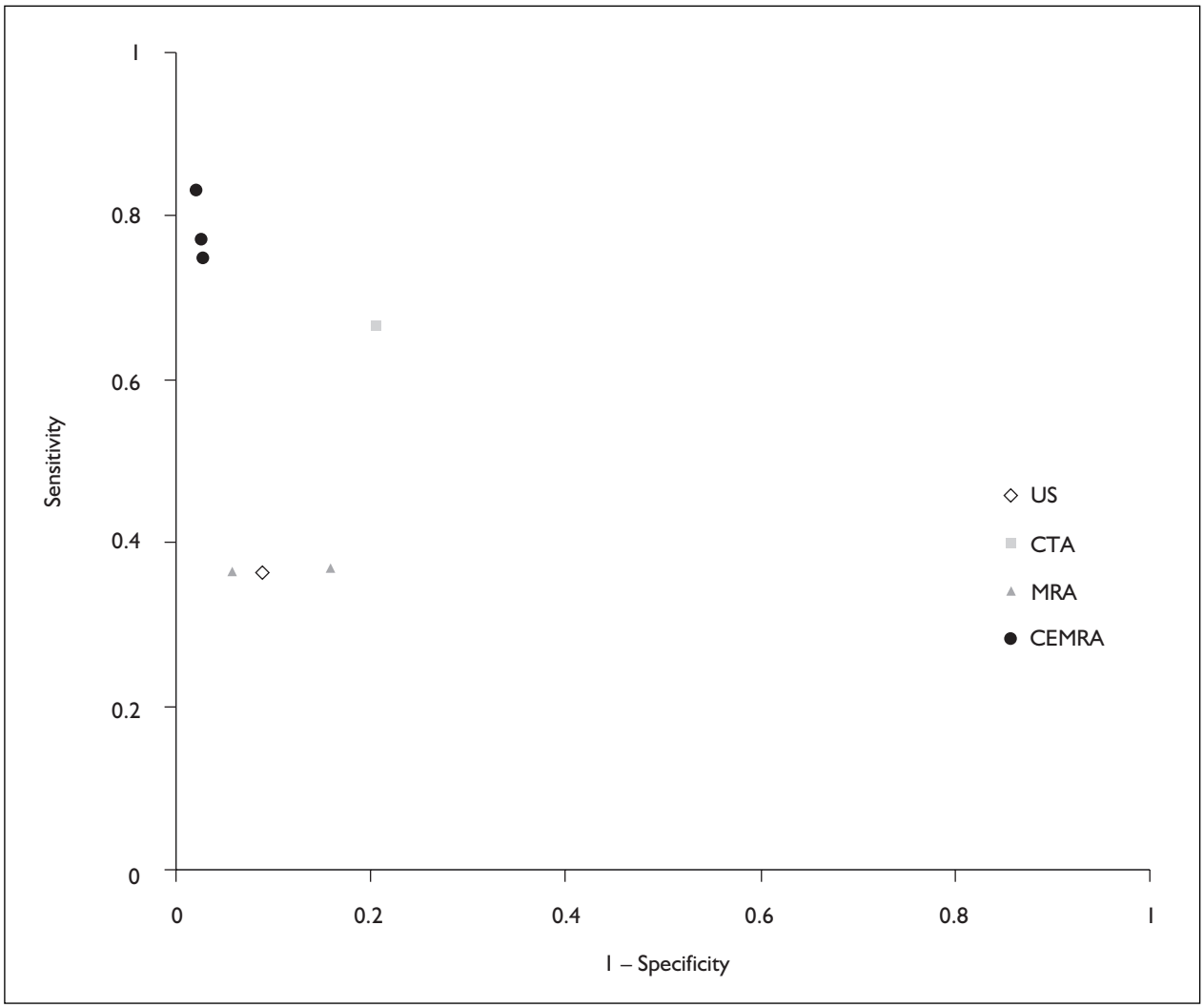

FIGURE 14 *ROC plot of US, CTA, MRA and CEMRA 50–69% data*

diagnosis of 70–99% stenosis to check for publication bias. Funnel plots were not constructed for the analyses of the 50–69% or the 0–49, or occluded diagnostic data as there were too few studies to make the plots meaningful. A 'dummy' funnel plot is shown next to *Figure 16* (see *Figure 17*); a funnel plot showing no indication of bias will have data points that are roughly symmetrical about the vertical line (true value of the quantity estimated by the meta-analysis). Where the precision of the estimates is low, they will be spread about owing to relatively large random error; where the precision is high, the random error will be small and the estimates will be much closer in value, giving the plot its characteristic funnel shape. Publication bias is suggested by asymmetrical spread about the vertical line, but is only one possible source of bias. Indeed, funnel plots have been criticised as a method for exploring publication bias,[125] and may be hard to interpret when there are few studies.

However, the funnel plots for the 70–99% diagnostic data are consistent in that they are arguably all missing data from small studies with small DORs (*Figures 16–20*), but this should be interpreted with caution.

Sensitivity analyses

Owing to the small number of studies in the meta-analyses of 50–69% and 0–49% or occluded data, sensitivity analyses were conducted only in the 70–99% data. There were not enough studies in the analyses of the other stenosis groups to make sensitivity analyses useful or robust.

It was not possible to perform a sensitivity analysis using observer experience, one of the prespecified factors, as most papers did not provide data on the experience of the test readers, or did so in a very limited way. Some papers merely specified the profession of the reader, while others said nothing at all. 'Patient population' was also excluded from

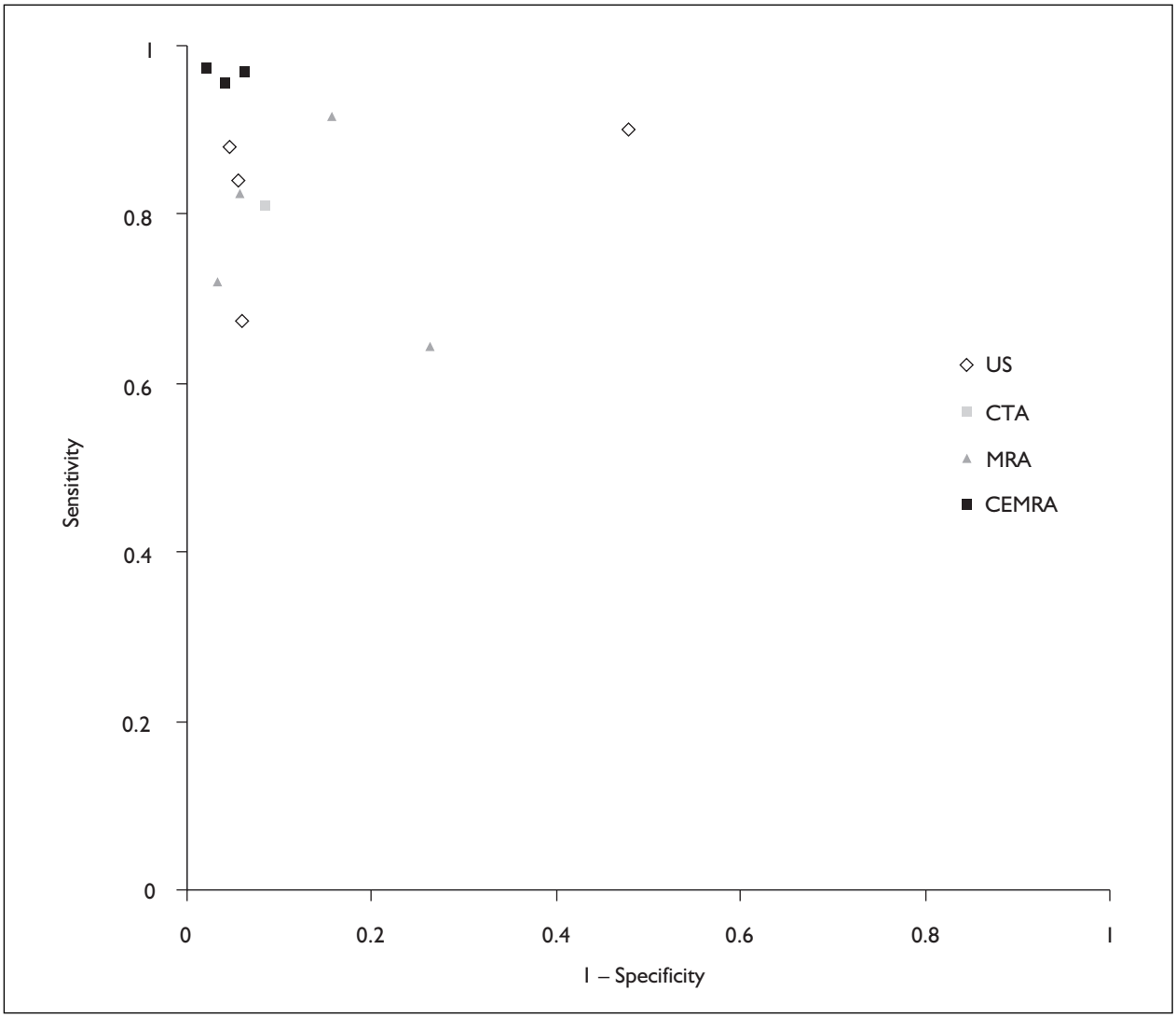

FIGURE 15 *ROC plot of US, CTA, MRA and CEMRA 0–49% and occluded data*

the sensitivity analyses, as the inclusion criteria resulted in apparently homogeneous patient groups. It was not possible to perform sensitivity analyses using patient characteristics, as those on which data were available, such as the proportion who were symptomatic, were very similar from study to study (*Table 1*). The sensitivity analysis of blinding (whether IAA had been interpreted blind to the results of the less invasive test) was not done as only one study did not state that the IAA was blind to the non-invasive test,[114] and this study did not contribute data to any of the meta-analyses as it did not provide data at the required cut-offs of 50% or 70% stenosis. This shows that most included studies were conducted with an encouraging degree of methodological rigour. However, disease spectrum was retained as a factor for sensitivity analysis. In practice, this meant comparing studies that screened patients using US with those that did not.

Year of publication did not affect diagnostic accuracy in any of the imaging modalities (*Table 6*). None of the estimated changes per year was statistically significant. This was also true for the sensitivity analysis of spectrum of disease (*Table 7*), whether the analyses were done using the answers to question 4.8, 'What was the recruitment procedure (e.g. presenting symptoms)?' or 4.14 'What was the spectrum of disease (e.g. all degrees of stenosis, severe stenosis only, occluded only)?'

Discussion

This systematic review of the less invasive carotid imaging literature identified that CEMRA is the most accurate of the techniques, and that there is little to choose between US, MRA and CTA in terms of accuracy. Most data were available for patients with 70–99% NASCET stenosis; the data

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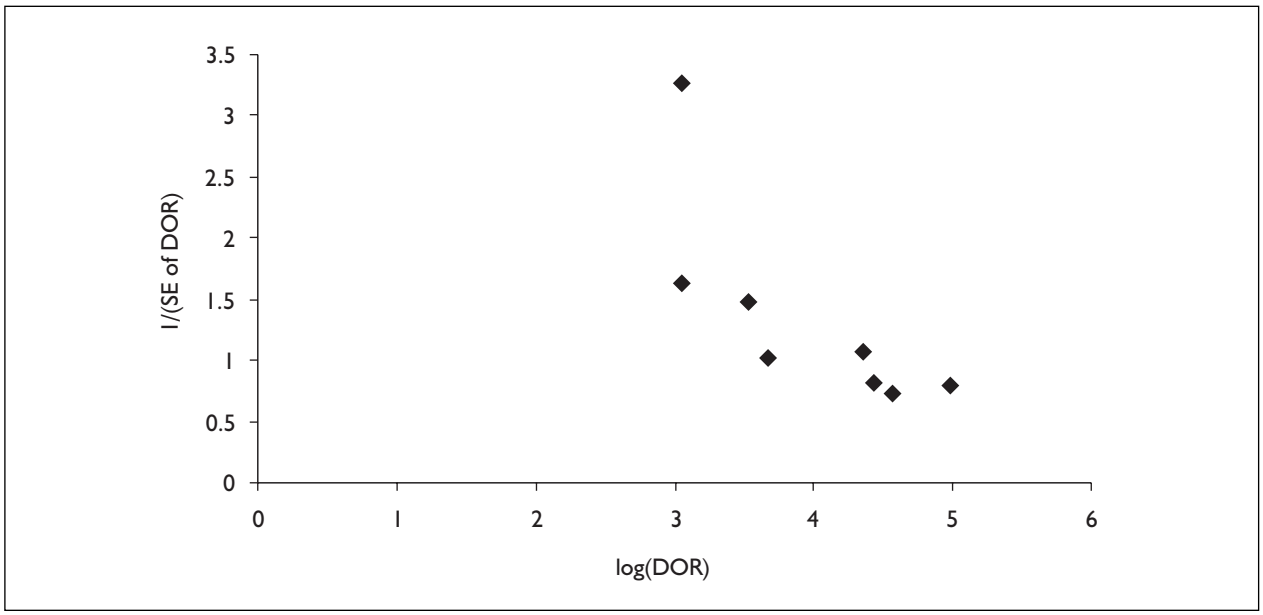

FIGURE 16 *Funnel plot of US 70–99% data: natural logarithm of the DOR versus the reciprocal of its standard error*

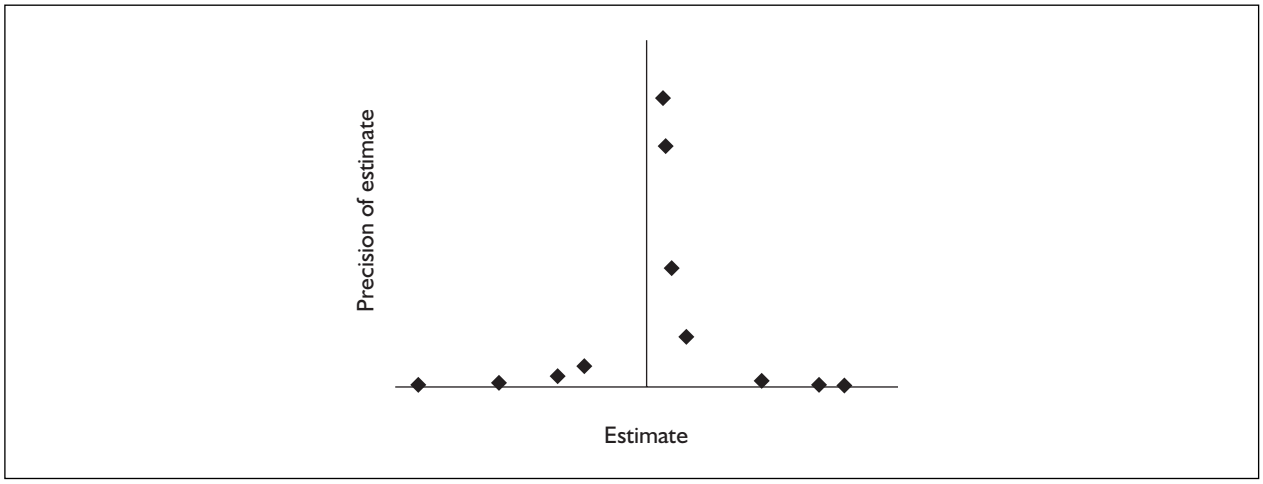

FIGURE 17 *'Dummy' funnel plot for comparison with* Figure 16*, showing no indication of bias. Note that the points are roughly symmetrical about the true value of the quantity estimated by the meta-analysis (vertical line). Where the precision of the estimates in individual papers is low, the points will be spread about owing to the relatively large random error, where the precision is high, the random error will be small, and the estimates will be much closer in value, giving the funnel plot its characteristic shape. Publication bias is one source of asymmetric funnel plots*[125]

TABLE 6 *Sensitivity analyses results for year of publication and 70–99% data*

Imaging	No. of studies	Year range in data set	Estimate (95% CI)	Multiplication factor of DOR per year
US	8	1993–2003	–0.094 (–0.29 to 0.10)	0.91
CTA	11	1993–2003	0.041 (–0.28 to 0.36)	1.04
MRA	12	1993–2002	0.060 (–0.33 to 0.45)	1.06
CEMRA	9	1988–2003	0.041 (–0.13 to 0.21)	1.04

The last column shows by how much the DOR changes with year of publication, for example a CTA odds ratio of 4 would become $4 \times 1.04 = 4.16$ for papers published a year apart, but none of these is statistically significant.

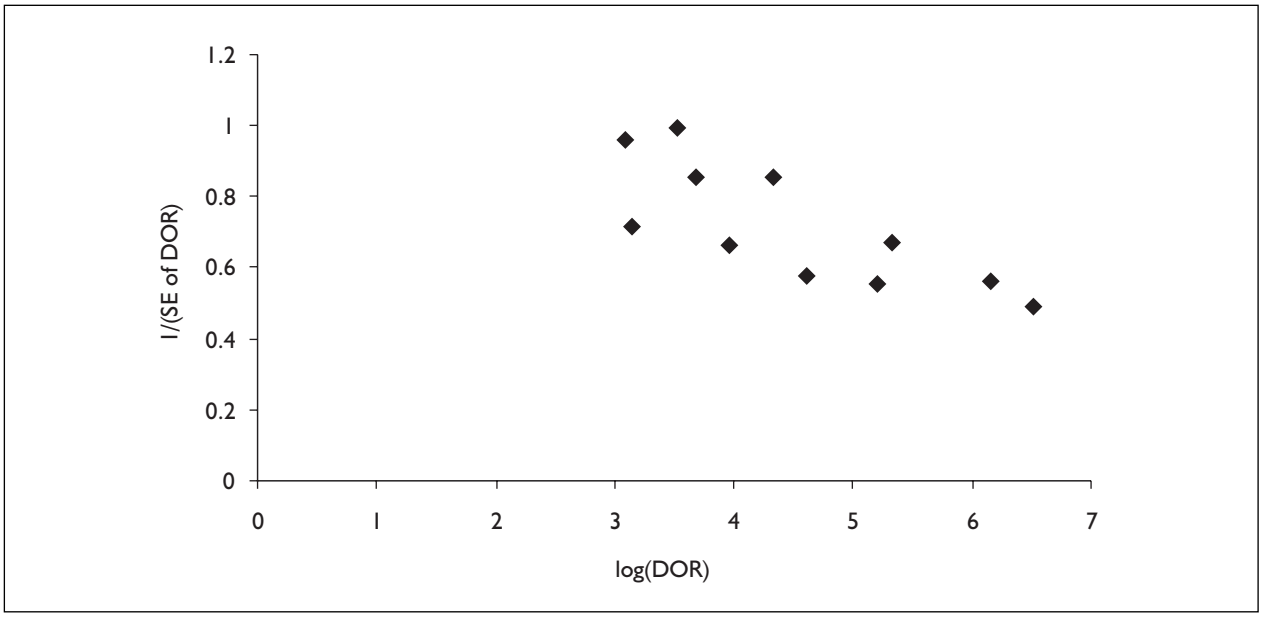

FIGURE 18 *Funnel plot of CTA 70–99% data: natural logarithm of the DOR versus the reciprocal of its standard error*

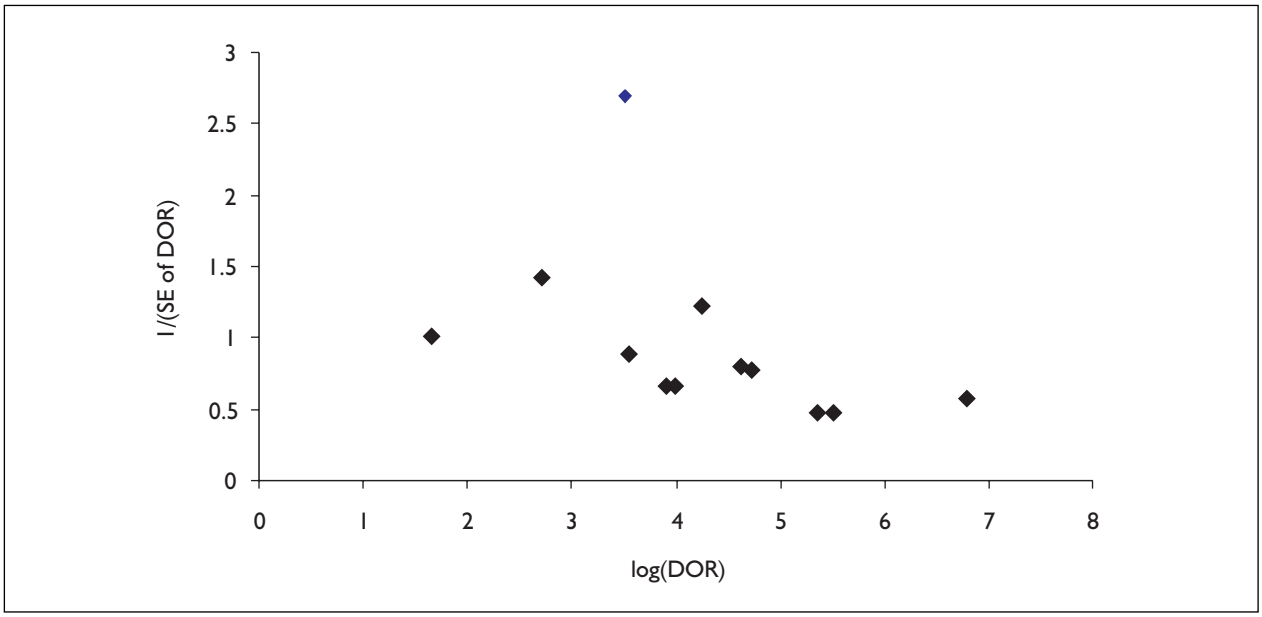

FIGURE 19 *Funnel plot of MRA 70–99% data: natural logarithm of the DOR versus the reciprocal of its standard error*

TABLE 7 *Sensitivity analyses results for spectrum of disease and 70–99% data*

Imaging	No. of studies	Estimate (95% CI)	Multiplication factor of DOR
US	8	–1.07 (–3.13 to 0.99)	0.34
CTA	11	–0.57 (–1.99 to 0.86)	0.57
MRA	12	–1.30 (–3.53 to 0.93)	0.27
CEMRA	9	0.40 (–1.41 to 2.21)	1.49

The DOR would be multiplied by the number in the last column in comparing a study with screened patients versus one with unscreened patients. For example, an unscreened MRA study with a DOR of 4 would equate to a screened MRA study with a DOR of $4 \times 0.27 = 1.08$.

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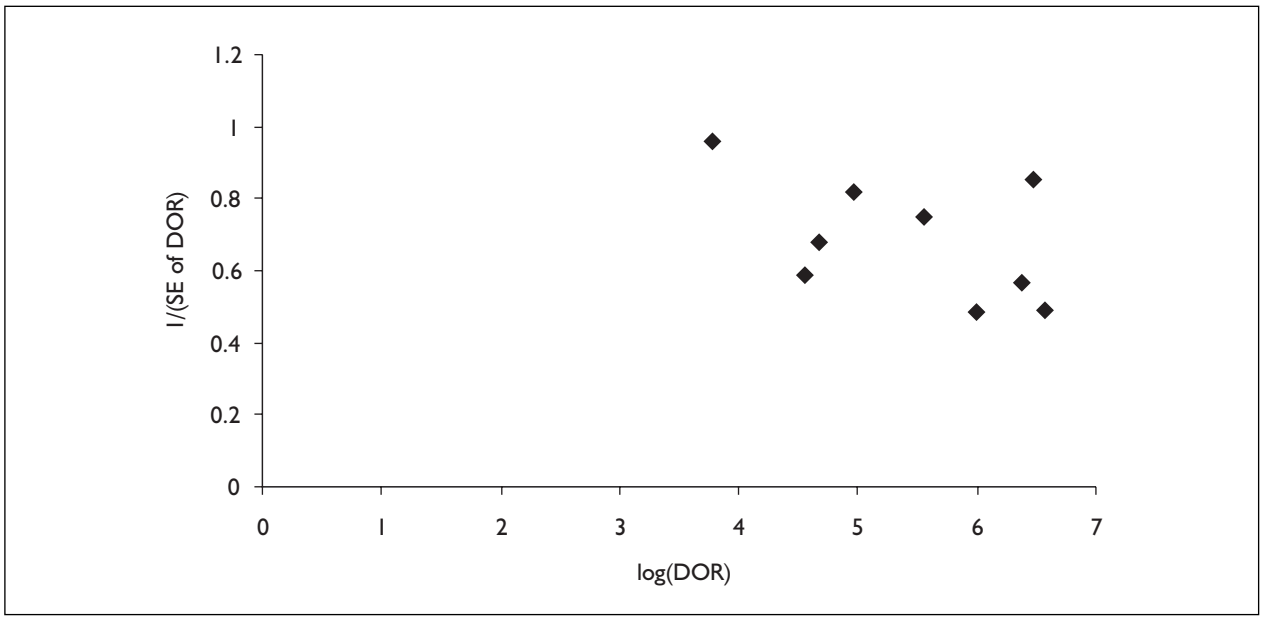

FIGURE 20 *Funnel plot of CEMRA 70–99% data: natural logarithm of the DOR versus the reciprocal of its standard error*

were too limited to provide reliable estimates of accuracy at other thresholds. In addition, there was evidence of heterogeneity between studies in the form of wide confidence limits on the estimates of sensitivity and specificity for each technique and the VIF being greater than 1. These estimates should therefore be interpreted with caution.

Furthermore, there were methodological reasons why the primary data may be limited. First, the populations from which the patients were selected, and the selection process, were in general very poorly described. Thus, it might not be unreasonable to suppose that these results, obtained in many cases from 'patients referred with symptoms of cerebrovascular disease' (a common statement in the papers' methods) would apply to patients who might be seen in neurovascular clinics in the UK. However, the details on which to base this assumption are lacking. In addition, this unfortunately made the planned sensitivity analyses using information on the patient population impossible, apart from the sensitivity analysis that used whether the patients had been screened into the study with US or not.[30] Second, details on whether patients had undergone US before entering the study were sketchy; in many studies, the patients clearly had had US. This could bias studies in two ways. First, studies that included only patients with at least 50% stenosis by the NASCET method, or 'significant stenosis', are relevant to the use of the index test as a confirmatory test in patients known to have a stenosis from US but possibly not as a primary diagnostic test. Second, studies that included patients regardless of what US showed are relevant to the use of the index test as a first line investigation, that is, in patients in whom it is not known whether there is a stenosis present. Most of the studies in the present review would appear to be the latter rather than the former, or at least there was insufficient information to quantify any bias. However, studies that included many patients without tight stenosis may have biased their results in favour of higher specificities and sensitivities than might have been the case if only patients with tight stenosis had been included. Kallmes and colleagues found that inclusion of non-diseased arteries gave falsely high estimates of diagnostic accuracy compared with the accuracy of those tests in just patients with significant stenosis.[49] Others have found that diagnostic tests may perform less well in more diseased than in less diseased populations.[33] It is difficult to quantify the effect that this would have had on the included patient population and the systematic review result. Although there was no evidence of an effect of prior screening by US ('spectrum of disease') on accuracy, this may simply be because the information given in the primary studies was too coarse to detect an effect.[43] Third, most papers described the number of arteries imaged, rather than the number of patients, in essence assuming that each artery could be treated independently as if there were no interaction between them. Only two papers used only one artery per patient.[34,104] There was no evidence that the two carotid arteries from one patient can be analysed as though they come from two different patients. This point will be explored

in the IPD meta-analysis. Therefore, adjustments had to be made to obtain a surrogate for 'number of patients' in studies that examined individual arteries. Fourth, the design of some studies may have put US at a disadvantage in that US was performed in a routine clinical setting, but other less invasive tests were performed in a research setting. Thus, the environment in which US was being used was different to that of MRA, CTA or CEMRA in many studies. Finally, the fact that US has been available for longest may also put it at a disadvantage; there are now studies of US 'in routine practice', that is, in a busy health service clinic, whereas none of the other less invasive modalities has achieved that state of maturity of use in the literature. The performance of MRA, CTA and CEMRA in routine practice may be obtainable from the IPD meta-analysis.

It was disappointing that, of the large number of potentially relevant papers identified (over 600), so few could be included in the meta-analysis. Thus, the total number of patients (2404 from all 41 studies combined) is woefully small compared with the frequency of stroke and the large numbers of patients who undergo these tests every day in the UK. In our hospital, Western General Hospital, Edinburgh, serving around half of the population of a medium-sized UK city (500,000), 1400 carotid DUSs are performed per year. Many thousands must be performed in the UK every year, and yet the data on accuracy on which this practice is based are quite limited.

About half of the studies were excluded for failing to give basic, key items of methodological information, which would have been available to the study investigators or easily obtainable during the study, but which was perhaps perceived as unimportant. Similarly, the editors and reviewers for the journals that published the papers did not feel it important to ask for this information. Instead, there was often overemphasis on technical details of the imaging technique used; these are also important, but not to the exclusion or omission of basic study design factors.[29,39] It is hoped that initiatives such as the STARD criteria (Appendix 3 and http://www.consort-statement.org/stardstatement.htm) and the Cochrane Screening and Diagnostic Test will help to focus attention on the importance of design and reporting of primary studies of diagnostic test accuracy.

The results of the meta-analysis may be optimistic for several other reasons. Small studies performed in expert centres may yield high accuracies compared with routine use of those tests in clinical practice. Patients who left the study or did not complete imaging, or whose images were of poor quality, may have been quietly left out of the analyses. Studies that achieve publication, particularly in the English-language literature, are more likely to be positive, or to be more positive than studies that are not published[46,47] or are published in the non-English-language literature.[70,71] The authors simply did not have access to translators who would have been able to supply data from the non-English-language papers in the time available, although they excluded very few possibly relevant papers because they were not in English, and they had access to the data extraction sheets of non-English publications from the review of Berry and colleagues[73] so it is very unlikely that any really important paper was excluded just because of language of publication. Furthermore, a very comprehensive literature search strategy was adopted, although some criteria on this were not published until after the review had started.[68] Thus, these included papers are more likely to describe optimum accuracies achievable than what might be achieved more routinely. The asymmetric funnel plots suggest bias; this asymmetry can occur because of publication bias, chance, artefact, poor methodological quality in smaller studies (and hence exclusion from the meta-analysis), and a relationship between study size and estimate size.[126] The exclusion criteria meant that studies with fewer than 20 patients were not included in the meta-analysis, although it is not possible to say that this is the reason for the asymmetry. It also seems plausible that a small study with unimpressive results would be less likely to be published. Given that the reason for the asymmetry cannot be ascertained, the results of the meta-analysis should be interpreted with caution as they may be overoptimistic.

The threshold effect analyses did not suggest that different application of diagnostic thresholds was an important source of heterogeneity, with the possible exception of the CTA 70–99% data. These were the only data with a reasonable number of data points and an ROC plot possibly consistent with the points lying on an ROC curve. Although the data suggest that there may be a threshold effect in this case, they are far from conclusive. All the studies were ostensibly using the same threshold and it is always possible that the CTA 70–99% results have arisen by chance.

The presence of heterogeneity means that sensitivity analyses with respect to the sensitivity and specificity estimates are vital for the cost-

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effectiveness model. Outside the context of the model, any estimate should be interpreted along with its confidence interval. CEMRA is the imaging modality with the greatest diagnostic accuracy, and therefore on accuracy criteria alone is the method of choice for diagnosing any of the stenosis groups. It is also the least affected by heterogeneity, judging from the forest plots (*Figures 7–12*). However, CEMRA is a relatively new technique, and the apparent greater accuracy and lack of heterogeneity may be due to publication of studies (so far) from research environments, rather than in routine clinical practice (the stage that the more mature techniques of MRA, DUS and CTA have reached). Furthermore, CEMRA is not as widely available as US and some patients (up to 10%) may not be able to undergo magnetic resonance (MR) because of an absolute (e.g. pacemakers) or a relative (e.g. claustrophobia) contraindication. These estimates of accuracy may also be overoptimistic because early publications concerning a new technique tend to be overpositive, compared with other techniques that have been available for longer, such as DUS.

The sensitivities of US and MRA in the diagnosis of 50–69% stenosis were both 36% (*Table 2*). Although based on very few data, if true, this is worse than one would expect if the diagnoses were made randomly, for example, by tossing a coin, which would have an average sensitivity of 50%. Moreover, the misdiagnosed patients were mostly assigned to the 70–99% group. A note of caution is required here. Although IAA is the reference standard, there is recent evidence that patients with 70–99% ICA stenosis are at risk of underdiagnosis of stenosis degree by conventional (three-view) IAA compared with three-dimensional (3D) rotational angiography (a recently introduced IAA technique).[90,91,127] It is therefore likely that these patients 'overdiagnosed' by MRA or US were in fact being underdiagnosed by IAA. Which is right? How does percentage stenosis determined by a less invasive method relate to that determined by another less invasive method? Without data from several less invasive tests and IAA in the same patients, it is not possible to tell how much of an 'overread' by one test equates to an 'underread' by another. However the 'bottom line' is that the relationship between stroke risk and percentage stenosis was calculated from three-view IAA. It might be possible to calculate adjustments to convert percentage stenosis measured by one less invasive test to another if enough data were available. However, some patients may benefit from endarterectomy at between 50 and 69% stenosis,[4] so it may be good for stroke prevention if some less invasive tests systematically 'overread' percentage stenosis and lead to more patients having CEA. In any case, the sensitivity and specificity of less invasive tests at 50–69% stenoses should be explored in future studies and in individual patient data meta-analysis, but interpreted with extreme caution until further data are available.

Year of publication was used as a proxy for generation of technology in sensitivity analyses, and was not found to affect diagnostic accuracy. It may be that technology has not changed significantly in terms of diagnostic accuracy in the past 10 years or so, or that deliberate exclusion of the pre-1986 papers removed earlier (and less accurate) versions of technology. Another explanation could be that technology has changed, but the difference in diagnostic accuracy was too small to be found by the sensitivity analyses, or that year of publication is a poor proxy for generation of technology. The technology is only one part of the process of diagnosing patients, and the rest of the process may be less dependent on time than on generation of technology.

The spectrum of disease was not found to affect diagnostic accuracy. However, this does not mean that disease spectrum is unimportant. It was very difficult to be certain about the type of patients included in the studies, as recruitment processes were in general very poorly described. The analysis is therefore based on suboptimal data. The analysis excluded studies with fewer than 70% symptomatic patients, or where it was not possible to tell what proportion was symptomatic. Furthermore, the situation may be complicated by the fact that only two of the studies used one artery per patient.[34,104] The other studies that screened patients by US only required that one artery had significant stenosis, and the other artery could have any degree of stenosis and was often also included in the study. In the studies where authors stated that only patients with significant disease were included, some of the patients had both a diseased artery and a healthy artery. As both arteries were used, the spectrum of disease would not be just 'significant disease', as the healthy arteries were unavoidably included. This difficulty in teasing out 'patients' from 'arteries', and symptomatic from asymptomatic arteries, is undoubtedly a complicating factor in the assessment of spectrum of disease on diagnostic accuracy. It will be possible to examine disease spectrum further in the IPD meta-analysis.

The heterogeneity among the studies cannot be explained by the factors used in the sensitivity analyses. Heterogeneity may simply reflect the general lack of data from these relatively small studies. However, it is possible that the sources of heterogeneity have not been reported in the studies. It has been recognised that the reporting of diagnostic studies needs to be much more complete than is often the case.[39] Until the sources of heterogeneity and their effect on diagnostic accuracy are known, the point estimates presented here should be interpreted with caution.

Comparison with previous systematic reviews of less invasive carotid imaging

How does this systematic review differ from previous systematic reviews of the accuracy of less invasive tests in the diagnosis of carotid stenosis? There have been three previous systematic reviews of MRA alone,[31,49,128] one of DUS alone[52] and four of more than one technique (*Table 8*).[48,50,51,53]

Most of these reviews found high sensitivities and specificities for less invasive imaging, particularly the most recent, by Westwood,[31] which produced a combined sensitivity and specificity estimate for MRA (mostly non-contrast) of 0.99 (95% CI 0.98 to 100) for 70–99% stenosis. These values seem even more optimistic than that obtained in the present review. There may be some important reasons for this in the methodology of the systematic reviews.

Only two previous reviews searched outside MEDLINE.[31,53] The reviews mention quite different numbers of total citations identified and actual papers included, both between these previous reviews and in comparison with the present review. For example, among the 26 papers cited in Westwood,[31] only nine were included in the present review, the other 17 being excluded. In addition, the present review included a further four papers published before 1999 that were not included in Westwood, for reasons that are unclear. Among the 17 papers included in Westwood but not in the present review, two were excluded because they included fewer than 20 patients, two because the method of calculating the stenosis was unclear, four because less than 70% of the population were symptomatic, five because it was not possible to determine the proportion with symptoms, and the remaining three for multiple reasons. Five reviews did not explicitly mention that one of their exclusion criteria was studies with non-blinded comparisons of less invasive imaging to the reference standard (*Table 8*); two reviews stated that blinding in primary publications was definitely not an inclusion/exclusion criterion,[48,53] of which one mentioned in the abstract that excluding non-blinded comparisons did not materially affect the results, but did not provide the data in the paper.[48] Only one review excluded retrospective primary studies,[53] very few mentioned whether included publications referred to symptomatic or asymptomatic patients,[31] and few mentioned the proportion of diseased arteries. There were few attempts at determining whether heterogeneity was present and the degree of formal sensitivity analyses.

Two further systematic reviews assessed the quality of the less invasive carotid imaging literature, one concentrating on MRA[28] and the other on all methods.[29] Both found methodological details lacking and major study design flaws in the primary imaging literature. Without wishing to be overcritical, it would seem that these seven previous systematic reviews have not recognised several key methodological points in the assessment of less invasive imaging tests. For example, the inclusion of non-blinded comparisons will lead to an overestimate of the diagnostic accuracy. Blinding is essential, whether it is in a study assessing a new drug (the principle underlying RCTs is to remove as far as possible any bias due to the investigators knowing whether the patient received active drug or placebo) or in observational studies.[129] The patient population should match the population in which the test is to be applied in routine practice, otherwise misleadingly good sensitivities and specificities will be found.[43] Part of the purpose of a systematic review is to indicate where new data are needed and how primary study methodology could be improved. While, in the present review, the authors regret not being able to include the non-English literature, they have been highly critical and are still concerned that the accuracy of less invasive imaging may have been overestimated. The fact that only 41 studies from 1986 to 2004 could be included suggests that over the years the primary study methodology and completeness of reporting of the methods have not improved. The analysis of individual patient data presented in Chapter 4 may help to redress that balance.

Conclusions

CEMRA has the highest diagnostic accuracy of the less invasive tests, with the highest sensitivity and specificity and the least heterogeneity. However, it is the newest test, with the least amount of published data to date. The disadvantages of

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TABLE 8 *Comparison of previous systematic reviews of carotid imaging with the present review*

Study	Tests	Years	Stenosis cut-off %	Measurement method?	No. of papers included total	No. of patients or arteries	Sensitivity	Specificity	Blind[a]	Prospective only	Sources searched; language of publication	Key methodological difference to present review
Reed, 1991[50]	DUS	1977–1989	>50	NASCET	12/18	NS	0.87–0.96	0.84–0.97	NS	NS	MEDLINE only; English only	Pulsed Doppler spectral analysis; B-mode imaging; included patients with 'cerebrovascular disease'; proportion of diseased arteries not mentioned
Blakeley, 1995[48]	DUS MRA	1977 1973	>50 >70	NS	70/568	6406 patients 12,265 arteries	0.84 0.90 (for >70% stenosis)	0.92 0.89 (for >70% stenosis)	No	No	MEDLINE only; English only	DUS: various forms of B-mode imaging; applied a quality rating; >50% had TIA; mean prevalence of >70% stenosis = 30%; mean patient age 62 years. Abstract states that exclusion of non-blind and retrospective studies did not alter results, but not mentioned in text
Reed, 1995[51]	MRA DUS	1989 1993	>50	NASCET	9/NS?	412 patients	0.78–0.95 0.93–1.0	0.71–0.88 0.64–1.00	NS	NS	MEDLINE only; English only	Symptomatic and asymptomatic proportion of diseased arteries not mentioned
Kallmes, 1996[49]	MRA	1990–1994	'Tight stenosis' (not defined)	NASCET >70; >80; >75%	17/28	NS		18–100%	NS	NS	MEDLINE only; English only	Excluded if <20 patients; recalculated specificity after excluding normal arteries: only 7/17 studies had specificity >75%
Fisher, 1998[52]	DUS	1987 1997	>70	NASCET	23/137	5063	Mean 0.80	Mean 0.91	NS	NS	MEDLINE only; English only	Symptomatic vs asymptomatic not mentioned; 34% had >70% stenosis.

continued

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TABLE 8 *Comparison of previous systematic reviews of carotid imaging with the present review (cont'd)*

Study	Tests	Years	Stenosis cut-off %	Measurement method?	No. of papers included total	No. of patients or arteries	Sensitivity	Specificity	Blind[a]	Prospective only	Sources searched; language of publication	Key methodological difference to present review
Long 2002[53]	DUS	1990–2001	>50 >60	NASCET or	13/256	1143	0.85–0.97	0.8–0.98	No	Yes	MEDLINE, HealthSTAR, EMBASE, PASCAL, Cochrane Library; English and French	Details on study selection and exclusion scant; not clear how included studies were chosen; symptomatic vs asymptomatic not mentioned; proportion of diseased arteries not mentioned
	CEMRA		>70 >80	ECST	6/158	339	0.94–1.0	0.85–1.0				
	CTA				8/92	433 (arteries not patients)	0.67–1.0 (values for >70% stenosis)	0.84–1.0 (values for >70% stenosis)				
Westwood, 2002[31]	MRA	1990–1999	70–99	NS	26/126	NS	0.99* (0.98 to 100)	(*Max. joint sensitivity plus specificity on ROC curve with 95% CI)	NS	NS	MEDLINE, EMBASE, HealthSTAR, Science Citation Index, Index to Scientific and Technical Proceedings, Cochrane Library, Inside (British Library), online computer library centre; non-English included	All symptomatic, but included some papers with asymptomatic patients; proportion of diseased arteries not mentioned; excluded papers with ≤10 patients; mean patient age 43 (range 18–63); mean sample size 40 patients (range 11–101); includes four papers on CEMRA
			50–99				0.90* (0.81 to 0.99)					

[a] Papers using blinded assessment of non-invasive tests only included.

CEMRA are that it is not suitable for all patients and it is not as accessible as some of the other non-invasive tests, such as US. There is relatively little difference in accuracy among the other three less invasive modalities, but US has the highest sensitivity and specificity overall, with MRA having the lowest.

The heterogeneity between studies for all modalities indicates that more data are needed from carefully designed studies to determine the true sensitivity and specificity of the commonly used less invasive imaging tests. Furthermore, this information is needed for the tests operating in routine practice, not in a specialised research environment.

More data are also needed on the accuracy of less invasive tests in combination. Virtually no studies reported on the accuracy of less invasive tests in the same patients. It is therefore not possible to tell whether apparent differences between tests were the result of patient differences or true differences in accuracy. Nor can it be stated with any reliability how the accuracy of two less invasive tests used in combination compares with each individual test used alone.

Key design features for future primary diagnostic accuracy studies are to ensure blinding of interpretation of the less invasive test to the reference standard, and vice versa; the inclusion of a population (with clearly stated recruitment and assessment methods) that is relevant to the clinical use of the test (i.e. with symptoms of ischaemic cerebrovascular disease); that the study is performed prospectively; a clear description of the patient selection process (did they have US as part of the selection or not?); analysis per patient and not per artery; that the proportion of diseased arteries (symptomatic and asymptomatic) is reported; and the use of clearly defined stenosis thresholds that include 70–99% and 50–69% stenosis.

Chapter 4

Individual patient data meta-analysis of studies of less invasive tests in the diagnosis of carotid stenosis

Background

Any systematic review of the published literature on carotid imaging would need to deal with the generally limited quality of methodology in diagnostic imaging research.[28,29] Moreover, where studies were conducted to an acceptable standard, the results may not have been presented in the detail required to answer the question posed by the systematic reviewer. For example, in the systematic review described in Chapter 3, seven studies[81,92,95,114,117,119,123] did not give data in the diagnostic categories of 0–49 or occluded, 50–69% and 70–99% stenosis by the NASCET criteria or equivalent.[3] It was also not possible to explore whether the accuracy of the less invasive diagnostic tests was different in different patient subgroups, as data on test performance in important subgroups were not available. Nor was it possible to determine whether diagnostic tests had similar accuracy in the symptomatic as in the asymptomatic artery, or whether it was legitimate (as many papers have done) to analyse accuracy by artery rather than by patient. Finally, there were virtually no data comparing different less invasive tests in the same patients (rather than in different cohorts of patients, in which case any apparent difference in diagnostic accuracy could have been due to patient differences, not test differences).

There is good evidence that IPD meta-analyses of randomised trials give less extreme estimates of treatment effect than literature-derived meta-analyses.[130] The main causes of this discrepancy are publication bias, patient exclusions in published studies and the generally shorter length of follow-up in literature reports than is possible in individual databases.[130] These are all likely to apply to studies of diagnostic tests. Publication bias probably affects diagnostic tests, as the tendency for studies with more positive results to be more likely to be published than those with neutral or negative results is greater in observational and laboratory-based studies than in randomised trials.[46] The failure to include non-English-language publications in the systematic literature review in Chapter 3 may have further compounded this bias as studies published in English are more likely to be positive than those published in other languages.[71] Many of the published studies were performed in expert or interested centres or in the context of a research study, where it may be possible to achieve higher accuracy than in routine day-to-day practice, or in less-expert centres. Analyses of IPD may allow some of these relationships or analyses, and opportunities to verify data not possible in the literature, to be explored.[47,131,132] Disadvantages include problems with identifying and obtaining the data.[133]

The limitations in methodological quality, details of data and sample size of the published data were anticipated from the outset because of the group's previous experience of diagnostic test systematic reviews.[29,134,135] Therefore, it was planned to supplement the systematic review with individual patient data from audit or research study databases comparing less invasive carotid imaging methods to IAA. The collaborators in this project had been responsible for several published studies of less invasive imaging and also undertook audit. At the time of seeking funding for the project, the opportunities that may exist for obtaining individual patient data from these studies had been discussed and the review group had access to several relevant data sets. Furthermore, the authors knew that it may be possible to address queries using these data that could not be solved by the literature review. In addition, the group planned to seek additional individual patient data sets during the project.

The IPD meta-analysis aimed to answer the following questions:

- Do the sensitivity and specificity estimates in the IPD meta-analysis differ from those obtained from the literature?
- Do the sensitivity and specificity estimates for the different imaging modalities differ when used on symptomatic and asymptomatic arteries?
- Do patient characteristics influence the sensitivity and specificity estimates (e.g. men versus women, or eye versus brain ischaemic

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TABLE 9 *Minimum data set requirements*

Item	Comments
Age at time of imaging or date of birth	Exact dates were not required; just month and year or year only were acceptable. The date of birth was used to calculate the age at time of imaging if this was not given directly. Needed for the age and gender group analyses
Gender	Needed for the age and gender group analyses
Symptomatic status of artery	Most data sets gave two measurements per patient from both carotids. Therefore, it was necessary to know which artery was symptomatic. Needed for the symptomatic versus asymptomatic analyses
First imaging result	Stenosis given as percentage or range. Needed to calculate sensitivity and specificity
Second imaging results	Stenosis given as percentage or range. Needed to calculate sensitivity and specificity
Dates of imaging	Needed in the time interval analyses
Stenosis criteria	Whether the stenosis was calculated according to the NASCET, ECST or CCA method
Event or symptomatic status of patient	TIA, stroke, retinal artery occlusion, amaurosis fugax. Needed to describe the patient population

symptoms) and if so, what are the different estimates? This information would be used to supplement data for the cost-effectiveness model and therefore was similar to the patient groups in the model (e.g. different age groups).
- Can sensitivity and specificity estimates be derived for different combinations of less invasive tests used on the same patients (e.g. US followed by a second US, or US followed by a CTA)?
- Do sensitivity and specificity estimates differ for less invasive imaging tests used in routine clinical practice as opposed to their use in dedicated research projects?
- Can the problem of verification bias be overcome (inherent in many of the papers assessed in the literature review, where US was used both to enter patients into the study and also in the study)? In other words, were there patients in the IPD who had not had US for study entry and did have US in the study on the same basis as they might have MRA or CTA?
- Does the time interval between the index and reference tests affect diagnostic accuracy?
- What is the relationship between repeated tests? Specifically, what is the probability of a second non-invasive test agreeing with a first?

Methods

Identification of databases

Individual patient data sets were sought from several sources. This included collaborators within the carotid study project group (from known previous publications and information given in preliminary discussions during writing of the application). Contact was made with the principal investigators of clinical trials in which patients might have had US, and of large audit studies. In addition, a notice and letter about the study were sent to neuroradiologists, stroke physicians, geriatricians and neurologists through the British Society of Neuroradiologists and the British Association of Stroke Physicians (see Appendix 7).

Minimum data requirements

A list of information was prepared which would allow the study from which the data derived to be characterised, as well as a list of key minimum items of data required for the analysis (*Table 9*) (see also Appendix 8). Files were accepted in any format as long as the data set contained the required information of stenosis measurements from at least two imaging modalities per artery (e.g. US and IAA) and the age and gender of the patient.

Determining whether the data were representative

It was not possible to ascertain whether the data used in the IPD analyses were a representative sample of all the data theoretically available. However, every effort was made to obtain as much data as possible and all the data acquired came from UK sources, making it as relevant as possible to the review group's questions. Both audit data and data taken from studies were considered suitable for the IPD analysis.

Data classification and standardisation

Each data set was checked and transformed to enable consistency of definitions and translation of data fields between data sets before the data could be used in a meta-analysis. The authors liaised with the original data holders to answer queries, and make sure that the origin of the data and their meaning and definition within each data set were understood.

Stenosis classification

To ensure consistency between data sets and with the literature systematic review, all stenosis measurements were converted to NASCET equivalent values (if not in NASCET form already) using the equation ECST or CCA = 0.6NASCET + 40.[11]

To overcome differences in the way that stenosis had been recorded in each data set, the stenosis measurements were transformed, in discussion with the source of the data set to make sure that the translation was correct, as follows:

- Where the stenosis measurements were quoted as a range rather than a single number, a single stenosis value within that range was randomly assigned to that patient. Thus, for analyses done by 'stenosis group', e.g. the 70–99% group, the patients would be analysed in the group to which they were originally assigned. This approach would result in an underestimate of diagnostic accuracy for analyses done using the individual measurements, but this only applied to one secondary analysis (to determine whether discrepancies between IAA and the non-invasive test were associated with an increasing time interval between the tests).
- Where data sets gave neither a stenosis range nor a single number, but described the stenosis as 'mild', 'moderate' or 'severe' (terminology as used in the NASCET and ECST studies,[2,136] the descriptive term was translated into the range of stenosis implied by that term.
- Other data sets used their own terminology, for example, 'operable' or 'non-significant'. These descriptive terms were also translated into the stenosis range implied by the term.
- Where it was not possible to determine the stenosis value or range from the description given (e.g. 'sluggish', which could mean very low flow beyond a critically tight stenosis, or simply relatively normal flow across a mild stenosis), the stenosis measurement was coded as 'missing'.
- Stenoses that were not measured because of technological difficulties were also coded as 'missing'.

Clarification was sought from the data provider wherever possible, but some data had been obtained from a third party (e.g. as audit, extracted from a radiological report) and the original provider was not available to interpret the description used.

Determining the status of the artery

The aim was to analyse diagnostic test accuracy in symptomatic and in asymptomatic arteries. Therefore, it was necessary to determine which artery was symptomatic. Some data sets described the arteries as either 'symptomatic' or 'asymptomatic', whereas others simply described the artery as on the left or right side. In the latter case, it was sometimes possible to determine the symptomatic status of the artery from other data on which side was symptomatic. Where it was not known whether the left or right side was symptomatic, one of the two arteries was randomly assigned as 'symptomatic' and the other as 'asymptomatic'. This was done to retain as much data as possible. However, a sensitivity analysis was performed using only the data where the true symptomatic status of the artery was known, to see whether the random assignation procedure had affected the results.

Missing data

The aim was to have as complete data sets as possible, but many of the data sets had missing data. An attempt was made to determine why the data were missing in each individual data set. Reasons for 'missing' stenosis data are given above. Such data were assumed to be missing at random and therefore would not cause systematic bias, so could be ignored in the analyses. Other data sets had missing values because patients with non-significant stenoses were not referred for a second test or included at all in the data set. These data sets were coded as having screened their patients and this information was used in the analyses.

Retaining data source information

The data source was retained as an indication of the context in which the data had been collected: data collected in routine clinical practice or audit were compared to data collected as part of a research study. This was in part to determine whether there were differences in diagnostic test performance between research studies and routine practice, but also to address concerns about pooling data from several studies as though they originated in one large study. This concern mainly applies to pooled IPD from RCTs because, in effect, this means comparing patients randomised

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in one trial to patients randomised in another.[137] However, the data from several diagnostic studies are fundamentally different to those of several RCTs because each patient (by having the index and the reference standard diagnostic test) is being compared to himself or herself, rather than one group of patients being compared to another. It is therefore acceptable to pool diagnostic data in this way.

Statistical analysis and meta-analysis

After the data sets had been prepared, they were imported into SAS (SAS Institute, Cary, NC, USA; www.sas.com) and any further formatting necessary before the final analysis was carried out. Sensitivity and specificity for degrees of carotid stenosis were calculated from contingency tables. Sensitivity and specificity were calculated for each less invasive test compared to IAA, for all the data, and then for important subgroups in sensitivity analyses:

- symptomatic and asymptomatic arteries
- different age–gender bands as defined in the cost-effectiveness model (Chapter 6)
- routine clinical or audit versus research study data
- patients prescreened by US versus those not prescreened by US.

A statistical model was derived to determine whether the time interval between IAA and the less invasive test was associated with (and therefore could explain) discrepancies between the test results.

To enable a direct comparison with the published literature, sensitivity and specificity were also calculated for the symptomatic and asymptomatic data combined, on a per artery rather than a per patient basis. This mirrored the approach used in all but two of the papers assessed in the systematic literature review.[34,104]

The DOR, which is a composite of information on sensitivity and specificity, was calculated from the equation:

$$\text{DOR} = \frac{\text{adjSens}/(1 - \text{adjSens})}{(1 - \text{adjSpec})/\text{adjSpec}}$$

where adj = adjusted, adjSens = adjusted sensitivity = adjTP/(adjTP + adjFN), adjSpec = adjusted specificity = adjTN/(adjTN + adjFP), adjTN= adjusted true negative, adjTP = adjusted true positive, adjFN = adjusted false negative and adjFP = adjusted false positive. TN, TP, FN and FP were all adjusted by adding 0.5 to the actual TN, TP, FN or FP value to avoid any zero values.

Not all the data sets had stenosis determined by IAA. The data sets that did not include IAA but did have results for more than one less invasive test in the same patients were used to calculate conditional probabilities, that is, the probability of a second less invasive test finding the same degree of stenosis as the first in that patient. This information was required for the cost-effectiveness model and was not available in the literature.

Copies of the SAS programs are available upon request.

Results

Description of the data sets

Twelve data sets were obtained (Appendix 9). One data set (number 1, Weir) was an audit of the complications of IAA only, and did not contribute further to the analysis of diagnostic test accuracy (although it did contribute to the estimate of risk of IAA used in the cost-effectiveness model, Chapters 6 and 7). The other 11 data sets included eight (1909 patients) that compared IAA and a less invasive test (numbers 2–6, 8, 10 and 12), and three data sets that included two less invasive tests in the same patients (numbers 7, 9 and 11). Three data sets included both two less invasive tests and IAA (5, 6 and 10). Data sets 7 and 9 compared US to CEMRA, as did part of data set 10. Data set 11 compared two US readings, data set 5 compared two CEMRA readings and data set 6 compared two MRA readings.

The total number of patients included in all the data sets was 2357. After cleaning and transforming the data, there were 1762 patients available for the analysis of less invasive versus IAA, 291 for US versus US, 206 for US versus CEMRA, 24 for MRA versus MRA and 133 for CEMRA versus CEMRA.

Four data sets were collected for research, seven for local audit and one for national audit projects (Appendix 9).

All data sets gave the information necessary to determine the age and gender of each patient and also which carotid artery was symptomatic (*Table 10*). However, the data sets were much more varied in their recording of the stenosis value (*Table 11*), which method of measuring the stenosis

TABLE 10 *Patient characteristics recorded per data set*

	Data set											
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Age	✓	✓			✓	✓	✓	✓		✓		
Date of birth			✓	✓		✓	✓		✓			✓
Symptoms	✓		✓	✓	✓	✓		✓	✓			✓
Symptomatic status	✓	✓	✓	✓	✓	✓		✓	✓	✓		✓
Symptomatic side	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Gender	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Other information	✓			✓	✓	✓	✓		✓			✓

TABLE 11 *Imaging recorded per data set*

	Data set											
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Stenosis given as percentages												
IAA		✓	✓	✓	✓	✓		✓		✓		✓
US	✓	✓						✓		✓	✓	✓
CTA								✓		✓		
MRA						✓						
CEMRA					✓					✓		✓
Stenosis given as percentage ranges												
IAA								✓				✓
US	✓		✓	✓	✓			✓	✓			✓
CTA								✓				
MRA												
CEMRA									✓			✓
Stenosis described in words												
IAA												✓
US	✓						✓	✓				✓
CTA								✓				
MRA								✓				
CEMRA							✓					✓

TABLE 12 *Method of measuring stenosis per data set*

	Data set											
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
NASCET		✓	✓	✓	✓	✓	✓					✓
ECST/CCA			✓			✓	✓	✓	✓	✓	✓	
Not known							✓					

had been used (*Table 12*) and the dates (of imaging or clinical events) that had been recorded (*Table 13*). Thus, considerable data manipulation was needed to transform the data into a consistent format across the data sets.

Characteristics of patients

As in the systematic literature review, the data sets had fairly homogeneous patient groups (*Table 14* and *Figure 21*). The patient population was overwhelmingly symptomatic (98%) (*Table 14*) and

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TABLE 13 *Dates recorded per data set*

	Data set											
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Date of event			✓									
Date of IAA	✓	✓	✓	✓	✓	✓		✓		✓		✓
Date of US			✓			✓		✓	✓	✓	✓	✓
Date of CTA								✓				
Date of MRA						✓		✓				
Date of CEMRA					✓		✓		✓			✓

TABLE 14 *Characteristics of patient groups of the data sets used in the sensitivity and specificity analyses*

Data set	**No. of patients**	**Median age and (range) (years)**	**Proportion of women to men[a]**		**Proportion known to be symptomatic**	
			Ratio	**% Men**	**Ratio**	**%**
2	243	67 (44–91)	65:173	71	243/243	100
3	180	67 (46–84)	58:121	67	170/180	94
4	26	65 (45–85)	7:19	73	26/26	100
5	167	71 (41–89)	45:121	72	167/167	100
6	70	63 (37–76)	21:49	70	70/70	100
8	877	68 (29–89)	367:510	58	855/877	97
10	296	66 (18–93)	121:175	59	294/296	99
12	50	65 (43–86)	13:37	74	50/50	100
Total	1909	67 (18–93)	697:1210	63	1875/1909	98

[a] The gender of two patients was not known.

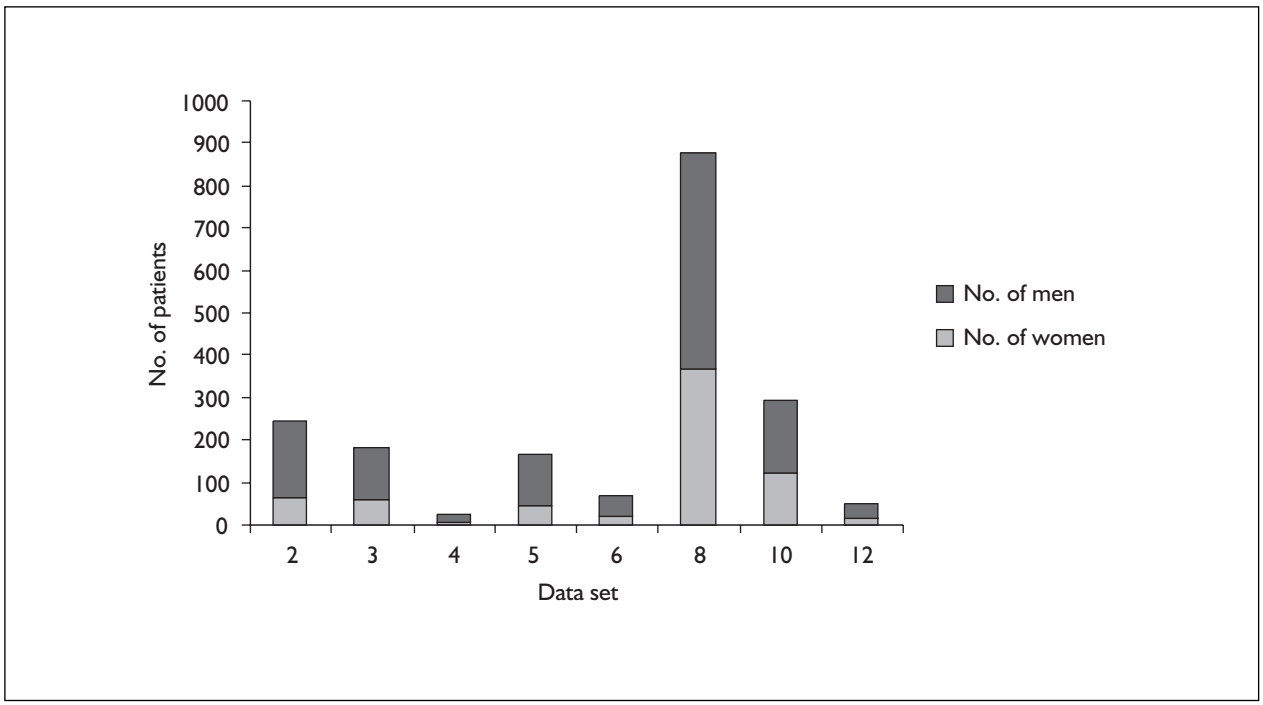

FIGURE 21 *Gender ratio in each data set*

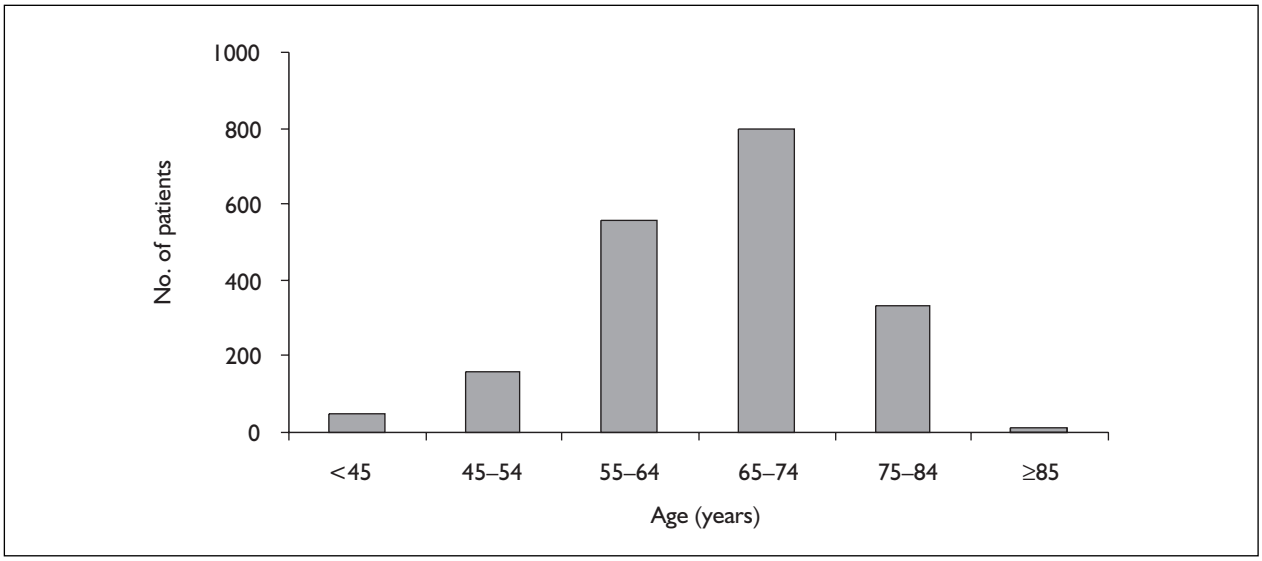

FIGURE 22 *Age of patients*

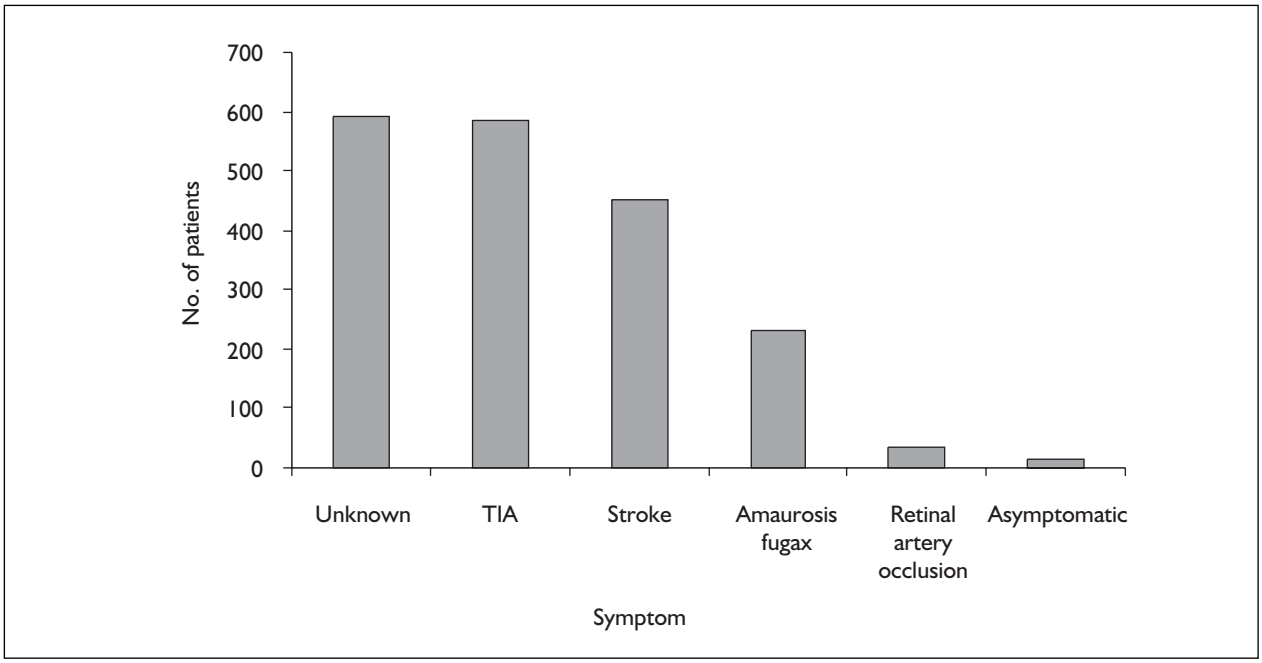

FIGURE 23 *Patients' presenting symptoms*

nearly two-thirds male. Most patients were older (*Figure 22*), with a median age of 67 years (*Table 14*). The most commonly recorded symptom (where it was recorded) was TIA (*Figure 23*).

Availability of IAA and less invasive imaging data

The quantity of missing data varied between the data sets (*Table 15*, *Figure 24*). In general, the data sets with the greatest proportion of missing data tended to be audit or routinely collected data. These data were usually 'missing' because patients were not referred for a second test, simply reflecting clinical practice. US had the least amount of missing data of all the imaging modalities in the audit data sets. CTA had the most missing data. Only data sets 8 and 10 (both audit data sets) had included any CTA results. Since some of the data sets had a large proportion of patients who did not have IAA, many patients had to be excluded from the sensitivity and specificity analyses (*Figure 24*).

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TABLE 15 *Symptomatic artery imaging: number of missing data in the data sets used in the sensitivity and specificity analyses*

Data set	Audit/study	No. of patients	IAA		US		CTA		MRA		CEMRA	
			n	%	*n*	%	*n*	%	*n*	%	*n*	%
2	Audit	243	102	42	12	5	–	–	–	–	–	–
3	Study	180	14	8	14	8	–	–	–	–	–	–
4	Audit	26	0	0	0	0	–	–	–	–	–	–
5	Study	167	17	10	24	14	–	–	–	–	40	24
6	Study	70	18	26	–	–	–	–	43	61	–	–
8	Audit	877	624	71	65	7	853	97	835	95	–	–
10	Audit	296	120	41	5	2	291	98	–	–	209	71
12	Study	50	13	26	3	6	–	–	–	–	13	26

n, number of times there was no stenosis given when there could have been.

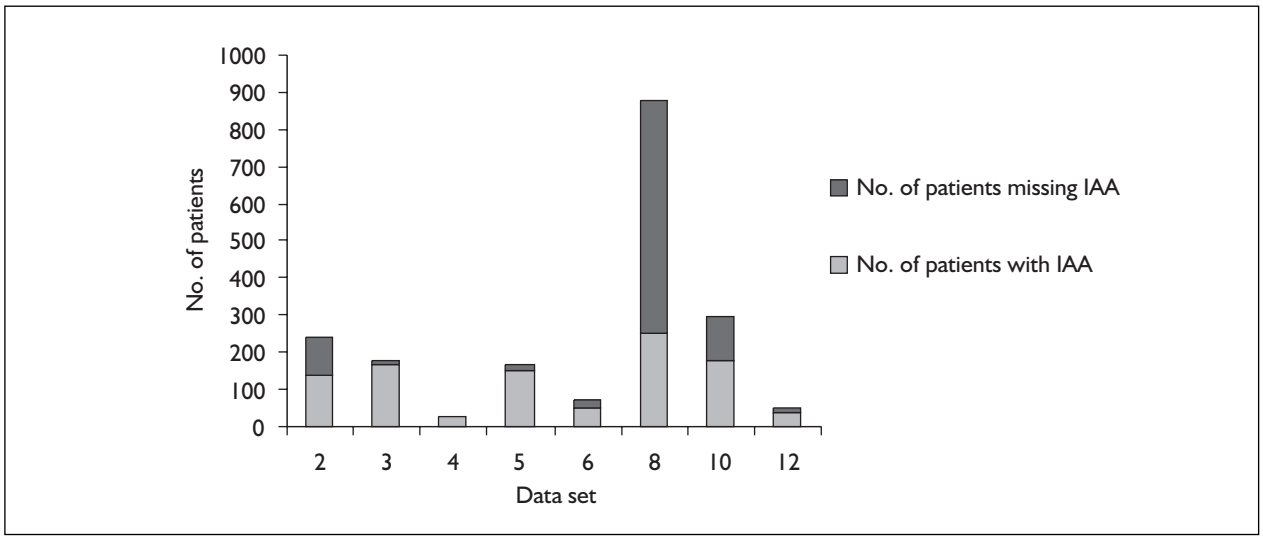

FIGURE 24 *Proportion of missing IAA data in each data set*

Data for analysis of sensitivity and specificity

The amount of data available for the analysis of sensitivity and specificity and on the proportion of arteries where the true symptomatic status was known also varied between imaging modalities (*Table 16* and *Figure 25*). US had the most data (1366 arteries, 88% of true symptomatic status known) and CTA the least (nine arteries, 100% symptomatic status known). MRA and CEMRA had a total of 67 (symptomatic status known in all) and 320 arteries (63% true symptomatic status known) contributing, respectively. The paucity of CTA data precluded further analyses (in line with the systematic review exclusion criteria of 20 patients or more) of sensitivity and specificity compared with IAA. The data available for calculating the sensitivities and specificities of US, CTA, MRA and CEMRA by degree of stenosis and whether symptomatic artery or not are presented in Appendix 10. The paucity of CTA data precluded analysis of sensitivity and specificity.

Sensitivity and specificity

Sensitivity and specificity for US, MRA and CEMRA in diagnosing the three stenosis groups of 0–49% or occluded, 50–69% and 70–99% are presented in *Tables 17–25*, by stenosis category and by true and randomly assigned artery status (true symptomatic status known or randomly assigned) to see whether this method of handling missing symptomatic status would introduce bias. In the majority of analyses, inclusion of true known artery status or not seemed to make little difference to the estimate of sensitivity and specificity. Presumably this occurs because the true symptomatic status of the majority of arteries was known. Therefore, in most further analyses (i.e. comparison with literature review, age and gender

TABLE 16 *Number of arteries contributing to the US, CTA, MRA and CEMRA versus IAA sensitivity and specificity analyses*

Artery	US	CTA	MRA	CEMRA
Randomly assigned arteries and true status known from data				
Symptomatic	886	6	32	167
Asymptomatic	480	3	35	153
Total	1366	9	67	320
True symptomatic status known from data only				
Symptomatic	803	6	32	102
Asymptomatic	395	3	35	98
Total	1198	9	67	200
Proportion of arteries with true symptomatic status known from data				
Symptomatic	91%	100%	100%	61%
Asymptomatic	82%	100%	100%	64%
Total	88%	100%	100%	63%

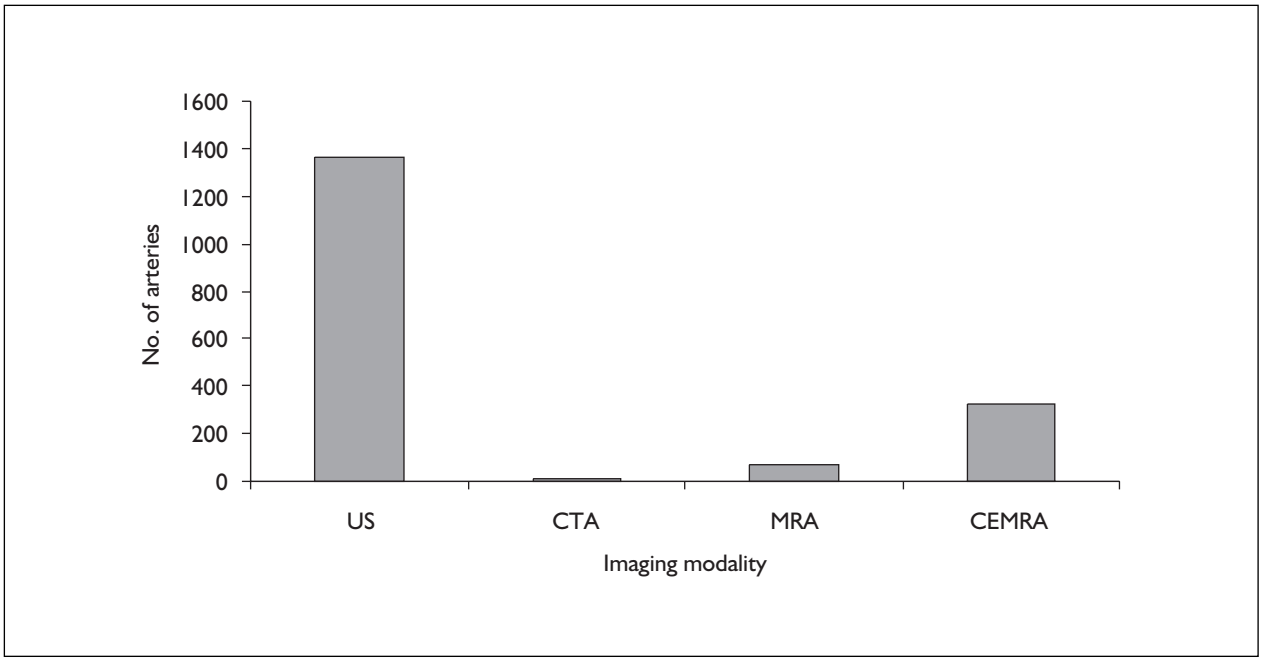

FIGURE 25 *Contribution of each imaging modality*

TABLE 17 *Sensitivity and specificity of US in diagnosing 70–99% stenosis*

Arteries included		Sensitivity (95% CI)	Specificity (95% CI)
Symptomatic	All	0.83 (0.80 to 0.86)	0.59 (0.53 to 0.64)
	True status known	0.83 (0.79 to 0.86)	0.54 (0.48 to 0.60)
Asymptomatic	All	0.71 (0.61 to 0.80)	0.91 (0.87 to 0.93)
	True status known	0.64 (0.51 to 0.75)	0.94 (0.91 to 0.96)
Both sides	All	0.82 (0.78 to 0.84)	0.76 (0.73 to 0.79)
	True status known	0.81 (0.77 to 0.84)	0.76 (0.72 to 0.79)

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TABLE 18 *Sensitivity and specificity of US in diagnosing 50–69% stenosis*

Arteries included		Sensitivity (95% CI)	Specificity (95% CI)
Symptomatic	All	0.33 (0.26 to 0.40)	0.84 (0.81 to 0.86)
	True status known	0.32 (0.25 to 0.40)	0.84 (0.81 to 0.87)
Asymptomatic	All	0.39 (0.28 to 0.52)	0.88 (0.85 to 0.91)
	True status known	0.51 (0.36 to 0.67)	0.90 (0.86 to 0.92)
Both sides	All	0.35 (0.29 to 0.41)	0.85 (0.83 to 0.87)
	True status known	0.36 (0.29 to 0.43)	0.86 (0.84 to 0.88)

TABLE 19 *Sensitivity and specificity of US in diagnosing 0–49 and 100% stenosis*

Arteries included		Sensitivity (95% CI)	Specificity (95% CI)
Symptomatic	All	0.53 (0.45 to 0.60)	0.96 (0.94 to 0.97)
	True status known	0.52 (0.43 to 0.60)	0.97 (0.95 to 0.98)
Asymptomatic	All	0.85 (0.81 to 0.88)	0.83 (0.76 to 0.88)
	True status known	0.88 (0.84 to 0.91)	0.82 (0.73 to 0.88)
Both sides	All	0.74 (0.70 to 0.77)	0.94 (0.92 to 0.95)
	True status known	0.77 (0.73 to 0.81)	0.95 (0.93 to 0.96)

TABLE 20 *Sensitivity and specificity of MRA in diagnosing 70–99% stenosis*

Arteries included	Sensitivity (95% CI)	Specificity (95% CI)
Symptomatic	0.67 (0.21 to 0.94)	0.86 (0.69 to 0.95)
Asymptomatic	1.00 (0.21 to 1.00)	0.97 (0.85 to 0.99)
Both sides	0.75 (0.30 to 0.95)	0.92 (0.83 to 0.97)
NB. The true symptomatic status of all arteries is known from the original data sets.		

TABLE 21 *Sensitivity and specificity of MRA in diagnosing 50-69% stenosis*

Arteries included	Sensitivity (95% CI)	Specificity (95% CI)
Symptomatic	0.44 (0.19 to 0.73)	0.87 (0.68 to 0.95)
Asymptomatic	0.67 (0.21 to 0.94)	0.97 (0.84 to 0.99)
Both sides	0.50 (0.25 to 0.75)	0.93 (0.83 to 0.97)
NB. The true symptomatic status of all arteries is known from the original data sets.		

TABLE 22 *Sensitivity and specificity of MRA in diagnosing 0–49 and 100% stenosis*

Arteries included	Sensitivity (95% CI)	Specificity (95% CI)
Symptomatic	0.90 (0.70 to 0.97)	0.92 (0.65 to 0.99)
Asymptomatic	0.97 (0.84 to 0.99)	1.00 (0.51 to 1.00)
Both sides	0.94 (0.84 to 0.98)	0.94 (0.72 to 0.99)
NB. The true symptomatic status of all arteries is known from the original data sets.		

TABLE 23 *Sensitivity and specificity of CEMRA in diagnosing 70–99% stenosis*

Arteries included		Sensitivity (95% CI)	Specificity (95% CI)
Symptomatic	All	0.82 (0.67 to 0.91)	0.86 (0.79 to 0.91)
	True status known	0.81 (0.63 to 0.92)	0.87 (0.77 to 0.93)
Asymptomatic	All	0.84 (0.62 to 0.94)	0.96 (0.91 to 0.98)
	True status known	0.86 (0.49 to 0.97)	0.99 (0.94 to 1.00)
Both sides	All	0.83 (0.71 to 0.90)	0.91 (0.87 to 0.94)
	True status known	0.82 (0.66 to 0.92)	0.93 (0.89 to 0.96)

TABLE 24 *Sensitivity and specificity of CEMRA in diagnosing 50–69% stenosis*

Arteries included		Sensitivity (95% CI)	Specificity (95% CI)
Symptomatic	All	0.42 (0.28 to 0.58)	0.84 (0.76 to 0.89)
	True status known	0.46 (0.28 to 0.65)	0.86 (0.76 to 0.92)
Asymptomatic	All	0.67 (0.44 to 0.84)	0.93 (0.87 to 0.96)
	True status known	1.00 (0.44 to 1.00)	0.95 (0.88 to 0.98)
Both sides	All	0.50 (0.37 to 0.63)	0.88 (0.84 to 0.92)
	True status known	0.52 (0.34 to 0.69)	0.91 (0.86 to 0.94)

TABLE 25 *Sensitivity and specificity of CEMRA in diagnosing 0–49 and 100% stenosis*

Arteries included		Sensitivity (95% CI)	Specificity (95% CI)
Symptomatic	All	0.79 (0.69 to 0.86)	0.88 (0.79 to 0.94)
	True status known	0.82 (0.70 to 0.90)	0.88 (0.77 to 0.95)
Asymptomatic	All	0.89 (0.82 to 0.93)	0.84 (0.69 to 0.92)
	True status known	0.93 (0.86 to 0.97)	0.90 (0.60 to 0.98)
Both sides	All	0.84 (0.79 to 0.89)	0.87 (0.79 to 0.92)
	True status known	0.89 (0.83 to 0.93)	0.89 (0.78 to 0.94)

groups, audit versus study data, screened versus unscreened, time interval between tests and non-invasive followed by second non-invasive test) all arteries are included whether or not their symptomatic status was given in the original data or randomised as part of the transformation process. However, only arteries where true symptomatic status was known were used in the analyses done specifically to investigate differences in sensitivity and specificity according to the symptomatic status of the artery.

For 70–99% stenosis, the sensitivities of US and CEMRA for the symptomatic artery were virtually identical, (with a point estimate of 0.83 (95% CI 0.79 to 0.86) and 0.82 (95% CI 0.69 to 0.97), respectively. The sensitivity for MRA was poorer (0.67, 95% CI 0.2 to 0.93). The sensitivities for all arteries were very similar also (*Tables 17*, *20* and *23*). The wider confidence intervals for CEMRA and MRA reflect the smaller amount of data available for these two modalities (n = 320 and 67) than for US (n = 1366). However, the pattern was not uniform, as CEMRA had better sensitivity than US for 50–69% and for 0–49% or occluded categories (*Tables 18*, *19*, *24*, *25*), and was similar to MRA for 50–69% stenosis, but worse than MRA for 0–49% or occluded (*Tables 21*, *22*, *24* and *25*).

The specificity of US and of MRA were worse for the 70–99% stenosis category than for the 50–69% and 0–49% or occluded categories, although with US this difference was more exaggerated. For example, in the symptomatic artery, the specificity of US for 70–99% stenosis was 0.58 (95% CI 0.53 to 0.63), whereas the specificity of US for 0–49% or occluded was

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TABLE 26 *DORs for US, MRA and CEMRA in diagnosing 0–49 and 100%, 50–69% or 70–99% stenosis by symptomatic status of the artery*

Artery		Stenosis group		
		70–99%	50–69%	0–49, 100%
Symptomatic	US	6.9	2.5	26.8
	MRA	9.4	4.8	56.7
	CEMRA	25.9	3.7	26.4
Asymptomatic	US	23.3	4.7	25.9
	MRA	67.0	35.0	183.0
	CEMRA	93.0	22.9	37.2
Both				
	US	13.7	3.1	42.0
	MRA	24.8	11.4	143.0
	CEMRA	44.9	7.4	34.4

0.96 (95% CI 0.94–0.97), indicating that US is very good at excluding non-operable arteries. CEMRA had high specificity in all three stenosis categories (*Tables 23–25*), with values in the symptomatic artery of 0.85 (95% CI 0.78 to 0.91), 0.84 (95% CI 0.76 to 0.89) and 0.88 (95% CI 0.79 to 0.94) for 70–99%, 50–69% and 0–49% or occluded, respectively.

Which test performs 'best' overall?

The DOR showed that CEMRA was most accurate in the symptomatic or asymptomatic arteries, but only in the 70–99% stenosis group. In the 0–49% or occluded and the 50–69% stenosed arteries, MRA performed better than CEMRA or US (*Table 26*). US performed similarly to CEMRA in the 0–49% or occluded and the 50–69% groups. However, note that these data need to be interpreted with caution given the extreme way in which the calculation of the DOR exaggerates differences in sensitivity and specificity between the less invasive imaging techniques.

How does the IPD analysis compare with the systematic review of the published literature?

To facilitate a direct comparison with the published literature, data from both symptomatic and asymptomatic arteries were used, without taking into account the fact that the symptomatic and asymptomatic data come from the same patients, to compare the sensitivity and specificity derived from the IPD analysis with the literature-derived estimate. This was to mirror the approach used in all but two papers in the literature meta-analysis.[34,104] There is a general agreement on sensitivity and specificity between the meta-analysis of published literature and of the IPD (*Tables 27–29*). However, in the majority of comparisons, there was a general trend for the IPD value for sensitivity or specificity to be lower than the estimate derived from the literature review. Only the specificity of US for 0–49% or occlusion, the sensitivity for MRA 50–69% and 0–49% or occlusion, and all specificities for MRA were higher in the IPD than in the literature meta-analysis. Some of these differences were statistically significant. Most obviously, comparison of the confidence intervals shows that they do not even overlap in three comparisons: sensitivity of US in diagnosing 70–99% stenosis (89% from the literature and 82% from the IPD), specificity of CEMRA in diagnosing 50–69% stenosis (97% in the literature and 88% from the IPD), and sensitivity of CEMRA in diagnosing 0–49 and 100% stenosis (96% from the literature and 84% from the IPD), although in all three comparisons the absolute sensitivities or specificities are still high, and indeed quite respectable. However, testing for differences using χ^2 tests (*Table 30*) reveals more significant differences between the IPD results and the systematic review results. MRA is the most consistent imaging modality, with only one of the six possible comparisons of IPD and the literature being statistically significant. CEMRA is the least consistent, with five of the six CEMRA tests being statistically significant. There is no particular pattern to the differences found, and given the number of tests performed, some of these differences could have occurred by chance.

TABLE 27 *Comparison between the US results of the literature review and the IPD analyses of all the arteries available*[a]

Stenosis group	Analysis	Sensitivity (95% CI)	Specificity (95% CI)
70–99%	Review	0.89 (0.85 to 0.92)	0.84 (0.77 to 0.89)
	IPD	0.82 (0.78 to 0.84)	0.76 (0.73 to 0.79)
50-69%	Review	0.36 (0.25 to 0.49)	0.91 (0.87 to 0.94)
	IPD	0.35 (0.29 to 0.41)	0.85 (0.83 to 0.87)
0–49, 100%	Review	0.83 (0.73 to 0.90)	0.84 (0.62 to 0.95)
	IPD	0.74 (0.70 to 0.77)	0.94 (0.92 to 0.95)

[a] This corresponds to 'Both sides, All' in *Tables 17–25*, chosen as the closest method to that used in published literature.

TABLE 28 *Comparison between the MRA results of the literature review and the IPD analyses of all the arteries available*[a]

Stenosis group	Analysis	Sensitivity (95% CI)	Specificity (95% CI)
70–99%	Review	0.88 (0.82 to 0.92)	0.84 (0.76 to 0.97)
	IPD	0.75 (0.30 to 0.95)	0.92 (0.83 to 0.97)
50–69%	Review	0.37 (0.26 to 0.49)	0.91 (0.78 to 0.97)
	IPD	0.50 (0.25 to 0.75)	0.93 (0.83 to 0.97)
0–49, 100%	Review	0.81 (0.70 to 0.88)	0.88 (0.76 to 0.95)
	IPD	0.94 (0.84 to 0.98)	0.94 (0.72 to 0.99)

[a] This corresponds to 'Both sides, All' in *Tables 17–25*, chosen as the closest method to that used in published literature.

TABLE 29 *Comparison between the CEMRA results of the literature review and the IPD analyses of all the arteries available*[a]

Stenosis group	Analysis	Sensitivity (95% CI)	Specificity (95% CI)
70–99%	Review	0.94 (0.88 to 0.97)	0.93 (0.89 to 0.96)
	IPD	0.83 (0.71 to 0.90)	0.91 (0.87 to 0.94)
50–69%	Review	0.77 (0.59 to 0.89)	0.97 (0.93 to 0.99)
	IPD	0.50 (0.37 to 0.63)	0.88 (0.84 to 0.92)
0–49, 100%	Review	0.96 (0.90 to 0.99)	0.96 (0.90 to 0.99)
	IPD	0.84 (0.79 to 0.89)	0.87 (0.79 to 0.92)

[a] This corresponds to 'Both sides, All' in *Tables 17–25*, chosen as the closest method to that used in published literature.

Do symptomatic arteries yield different sensitivities and specificities to asymptomatic arteries?

Sensitivity and specificity are given for symptomatic and asymptomatic arteries separately, and by stenosis category, in *Tables 17–25*). The values appear to differ between symptomatic and asymptomatic arteries, especially in the analyses restricted to those arteries where the true symptomatic status is known (*Tables 31* and *32*). These results should be interpreted with caution because of the problems of performing multiple tests on the same data. However, there appears to be strong evidence that sensitivity and specificity differ according to the symptomatic status of the artery (*Table 32*, all p-values are <0.0001), being significantly worse in the symptomatic artery compared with the asymptomatic one. In the analyses for each imaging modality and stenosis group (*Table 30*), the p-value is not significant at the 0.05 level for only three out of the 18 tests. Moreover, two of the non-significant p-values are

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TABLE 30 *χ^2 tests to compare IPD results with systematic review results*

		Sensitivity		Specificity	
Imaging	**Stenosis group**	χ^2	*p*	χ^2	*p*
US	70–99%	7.7	0.0054*	5.0	0.0256*
	50–69%	0.059	0.8079	5.9	0.0148*
	0–49,100%	3.0	0.0858	2.8	0.0962
MRA	70–99%	0.50	0.4815	2.1	0.1492
	50–69%	0.76	0.3824	0.076	0.7824
	0–49,100%	4.5	0.0334*	0.39	0.5307
CEMRA	70–99%	5.8	0.0160*	0.92	0.3378
	50–69%	5.7	0.0167*	9.6	0.0019*
	0–49,100%	7.6	0.0060*	5.2	0.0228*

* Significant at the 5% level.

TABLE 31 *Test results to determine whether sensitivity and specificity differ according to the symptomatic status of the artery (known from the original data set) per imaging modality/stenosis group combination*

		Sensitivity		Specificity	
Imaging	**Stenosis group**	χ^2	*p*	χ^2	*p*
US	70–99%	22.12	<0.0001*	101.30	<0.0001*
	50–69%	58.80	<0.0001*	448.33	<0.0001*
	0–49,100%	123.65	<0.0001*	598.74	<0.0001*
MRA	70–99%	0.00	1.0000	22.15	<0.0001*
	50–69%	1.29	0.2568	17.19	<0.0001*
	0–49,100%	24.50	<0.0001*	11.00	0.0009*
CEMRA	70–99%	0.09	0.7630	62.06	<0.0001*
	50–69%	6.25	0.0124*	53.39	<0.0001*
	0–49,100%	58.56	<0.0001*	42.09	<0.0001*

The McNemar test takes into account the dependence of the symptomatic and asymptomatic data because they are from the same patients.
*Significant at the 5% level.

TABLE 32 *Test results of differences between sensitivity and specificity according to symptomatic status of the artery for each stenosis group*

	Sensitivity		Specificity	
Stenosis group	**McNemar**	*p*	**McNemar**	*p*
70–99%	19.31	<0.0001	183.33	<0.0001
50–69%	65.80	<0.0001	518.88	<0.0001
0–49, 100%	202.67	<0.0001	651.80	<0.0001

TABLE 33 *US sensitivity and specificity, according to age and gender (all arteries, whether symptomatic, asymptomatic or unknown)*

Age	Stenosis group	Gender	Sensitivity (95% CI)	Specificity (95% CI)
55–64	0–49,100%	F	0.76 (0.57 to 0.88)	0.95 (0.84 to 0.99)
		M	0.83 (0.71 to 0.91)	0.95 (0.89 to 0.98)
	50–69%	F	0.20 (0.06 to 0.51)	0.82 (0.70 to 0.89)
		M	0.47 (0.28 to 0.66)	0.86 (0.78 to 0.91)
	70–99%	F	0.80 (0.63 to 0.90)	0.78 (0.63 to 0.89)
		M	0.78 (0.66 to 0.86)	0.81 (0.71 to 0.88)
65–74	0–49,100%	F	0.60 (0.42 to 0.76)	0.94 (0.86 to 0.98)
		M	0.72 (0.60 to 0.81)	0.93 (0.87 to 0.96)
	50–69%	F	0.28 (0.11 to 0.56)	0.84 (0.75 to 0.91)
		M	0.32 (0.19 to 0.47)	0.86 (0.79 to 0.90)
	70–99%	F	0.81 (0.68 to 0.89)	0.65 (0.50 to 0.78)
		M	0.83 (0.74 to 0.90)	0.73 (0.64 to 0.80)
75–84	0–49,100%	F	0.61 (0.36 to 0.81)	0.92 (0.75 to 0.98)
		M	0.77 (0.60 to 0.89)	0.93 (0.82 to 0.97)
	50–69%	F	0.42 (0.18 to 0.71)	0.81 (0.64 to 0.91)
		M	0.43 (0.22 to 0.67)	0.89 (0.79 to 0.94)
	70–99%	F	0.77 (0.53 to 0.91)	0.70 (0.50 to 0.85)
		M	0.87 (0.72 to 0.95)	0.80 (0.67 to 0.89)

The 'over 85' age group was not included owing to insufficient data (total of three patients).
F, female; M, male.

for the MRA data, for the sensitivity of MRA in diagnosing 50–69% ($p = 0.2568$) and 70–99% stenosis ($p = 1.000$), and MRA was the modality with the least amount of data in the IPD (only 67 arteries with true symptomatic status known; *Table 16*). The other non-significant p-value is for the sensitivity of CEMRA in the diagnosis of 70–99% stenosis ($p = 0.7630$).

Do sensitivity and specificity vary by gender and age?

A thorough analysis of diagnostic accuracy within gender and age groups for all the imaging modalities and stenosis groups was not possible owing to a lack of data in some of the subgroups (Appendix 10 gives numbers of arteries available for this analysis). The MRA data were particularly sparse and so were not used for further analysis. Even though it would have been desirable to perform separate analyses for the symptomatic and asymptomatic arteries, the paucity of data would not have given reliable estimates of sensitivity and specificity. Therefore, both arteries were analysed together.

There was no evidence that either age or gender affected the sensitivity or specificity of either US or CEMRA (inadequate data for analysis of CTA and MRA) when looking at the symptomatic and asymptomatic arteries together (*Tables 33* and *34*). This does not suggest that there are differences between men and women or the age groups with regard to diagnostic accuracy. This was confirmed by testing directly for differences (*Table 35*). Therefore, neither gender nor age should influence the choice of less invasive carotid imaging tests.

Are data derived from audit or routine practice different to data derived from research studies?

The only imaging modality with enough data to make analyses worthwhile on this question was US (see Appendix 10). The MRA data were too limited to allow for meaningful analyses (see Appendix 10) and there were no audit data comparing CEMRA to IAA. There was no statistically significant difference in sensitivity or specificity between audit data and research study data for either the symptomatic or asymptomatic artery (*Table 36*). When both types of artery were analysed together (with the method used in the majority of the published literature), there was no statistically significant difference (*Table 37*). However, some of the p-values were quite small, even if not less than 0.05; this could mean that there is a difference between audit and study data

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TABLE 34 *CEMRA sensitivity and specificity, according to age and gender (all arteries, whether symptomatic, asymptomatic or unknown)*

Age (years)	Stenosis group	Gender	Sensitivity (95% CI)	Specificity (95% CI)
55–64	0–49,100%	F	0.80 (0.55 to 0.93)	1.00 (0.65 to 1.00)
		M	0.92 (0.79 to 0.97)	0.78 (0.55 to 0.91)
	50–69%	F	–	0.82 (0.61 to 0.93)
		M	0.40 (0.17 to 0.69)	0.91 (0.80 to 0.97)
	70–99%	F	0.86 (0.49 to 0.97)	1.00 (0.80 to 1.00)
		M	0.75 (0.41 to 0.93)	0.94 (0.83 to 0.98)
65–74	0–49, 100%	F	0.59 (0.36 to 0.78)	0.92 (0.67 to 0.99)
		M	0.83 (0.72 to 0.91)	0.83 (0.66 to 0.93)
	50–69%	F	0.67 (0.30 to 0.90)	0.67 (0.47 to 0.82)
		M	0.43 (0.21 to 0.67)	0.88 (0.79 to 0.94)
	70–99%	F	0.57 (0.25 to 0.84)	0.87 (0.68 to 0.95)
		M	0.81 (0.57 to 0.93)	0.90 (0.82 to 0.95)
75–84	0–49, 100%	F	0.82 (0.61 to 0.93)	0.89 (0.57 to 0.98)
		M	0.86 (0.72 to 0.94)	0.88 (0.70 to 0.96)
	50–69%	F	0.67 (0.30 to 0.90)	0.92 (0.75 to 0.98)
		M	0.47 (0.25 to 0.70)	0.91 (0.80 to 0.97)
	70–99%	F	1.00 (0.44 to 1.00)	0.89 (0.73 to 0.96)
		M	1.00 (0.72 to 1.00)	0.88 (0.77 to 0.95)

The 'over 85' age group was not included owing to insufficient data (total of three patients).
F, female; M, male.

TABLE 35 *χ^2 test results for differences in sensitivity and specificity of the age and sex subgroups*

		Sensitivity		Specificity	
Subgroup		χ^2	*p*	χ^2	*p*
Men versus women	US only	1.22	0.2695	1.48	0.2245
	CEMRA only	0.38	0.5382	0.33	0.5660
	Both US and CEMRA	1.98	0.1591	1.66	0.1982
Age groups	US only	1.55	0.4599	1.28	0.5263
	CEMRA only	1.23	0.5397	1.07	0.5850
	Both US and CEMRA	2.58	0.2751	2.16	0.3404

MRA was not included owing to a lack of data; CTA was already excluded.

but the amount of data available for this analysis was inadequate.

Are patients screened by US before entering a study different to unscreened patients?

The 'screened' data sets only included patients in whom US had already demonstrated a possible significant stenosis, introducing verification bias into data sets that compare US to IAA. US was the only imaging modality with the required data to test for differences in sensitivity and specificity in screened and unscreened populations as there were no unscreened MRA/CEMRA versus IAA patients. The data used to calculate sensitivity and specificity are given in *Tables 99* and *100* in Appendix 10. The estimates of sensitivity and specificity are given in *Table 38*, and the χ^2 tests for significance of the difference are given in *Table 39*. The tests suggest that screened and unscreened populations differ in the asymptomatic artery. Inspection of the sensitivities and specificities in *Table 38* shows that the biggest difference occurs in the sensitivity of US in diagnosing 50–69% in the asymptomatic artery: 0.26 and 0.61 for screened and unscreened populations, respectively. The biggest difference

TABLE 36 *Sensitivity and specificity of US according to audit/routinely collected data versus data generated by research studies*[a]

Artery (years)	Stenosis	Context	Sensitivity (95% CI)	Specificity (95% CI)
Symptomatic	0–49,100%	Audit	0.55 (0.40 to 0.69)	0.98 (0.95 to 0.99)
		Study	0.51 (0.37 to 0.65)	0.92 (0.86 to 0.96)
	50–69%	Audit	0.30 (0.19 to 0.45)	0.84 (0.79 to 0.88)
		Study	0.36 (0.23 to 0.52)	0.83 (0.76 to 0.89)
	70–99%	Audit	0.84 (0.78 to 0.88)	0.55 (0.44 to 0.65)
		Study	0.81 (0.71 to 0.88)	0.63 (0.52 to 0.72)
Asymptomatic	0–49,100%	Audit	0.85 (0.77 to 0.90)	0.82 (0.69 to 0.90)
		Study	0.85 (0.73 to 0.92)	0.84 (0.65 to 0.94)
	50–69%	Audit	0.48 (0.28 to 0.68)	0.88 (0.81 to 0.92)
		Study	0.24 (0.08 to 0.54)	0.89 (0.79 to 0.95)
	70–99%	Audit	0.66 (0.48 to 0.80)	0.92 (0.86 to 0.95)
		Study	0.83 (0.55 to 0.95)	0.88 (0.78 to 0.94)
All	0–49,100%	Audit	0.77 (0.70 to 0.83)	0.95 (0.92 to 0.97)
		Study	0.69 (0.59 to 0.77)	0.91 (0.85 to 0.95)
	50–69%	Audit	0.36 (0.25 to 0.48)	0.85 (0.81 to 0.89)
		Study	0.33 (0.22 to 0.47)	0.85 (0.79 to 0.89)
	70–99%	Audit	0.82 (0.76 to 0.86)	0.77 (0.71 to 0.82)
		Study	0.82 (0.72 to 0.88)	0.74 (0.66 to 0.80)

[a] Calculated from data in *Tables 95* and *96*, adjusted for the number of patients contributing data.

TABLE 37 *χ^2 test results for differences in US sensitivity and specificity between audit and research study settings*

	Sensitivity		Specificity	
Artery	χ^2	*p*	χ^2	*p*
All data	3.27	0.0705	2.71	0.0997
Symptomatic artery	3.59	0.0582	2.89	0.0890
Asymptomatic artery	0.0159	0.8997	0.014	0.9066

with regard to specificity occurs in the 0–49% or occluded group: 0.79 and 0.93 for screened and unscreened populations, respectively.

Is there an association between increasing time interval between the less invasive test and IAA and the sensitivity or specificity?

No conclusive evidence was found that increasing time interval between the tests could explain lack of sensitivity or specificity (*Table 40* and *Figures 26–28*). The scatterplot of the time interval versus difference between US and IAA does not suggest any particular relationship (*Figure 26*). Some of the *p*-values in *Table 40* are statistically significant (notably those for US), but the interpretation of this is difficult, as the assumptions underlying the model were grossly violated by the data. Moreover, interpretation of the data for MRA and CEMRA are complicated by most of the individual time intervals being less than 1 day (*Figures 27* and *28*); there are not enough time intervals of different lengths for them to be modelled adequately. Thus, although any effect of increasing time interval in reducing sensitivity or specificity is most likely to be seen for US (as it was the test with the biggest time gap to IAA) and the *p*-values for US were all highly significant, the evidence of the scatterplots and the violation of the model assumptions mean that the statistically significant *p*-values in *Table 40* are of dubious reliability.

Probability that two less invasive tests will find a similar degree of stenosis: non-invasive test conditional probabilities

The data available to calculate the conditional probabilities of two less invasive tests are given in Appendix 10. Specifically, these data were used to

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TABLE 38 *Sensitivity and specificity of US according to data of screened versus unscreened patients*[a]

Artery	Stenosis	Screening	Sensitivity (95% CI)	Specificity (95% CI)
Symptomatic	0–49,100%	Yes	0.49 (0.36 to 0.63)	0.96 (0.93 to 0.98)
		No	0.57 (0.42 to 0.71)	0.96 (0.91 to 0.99)
	50–69%	Yes	0.31 (0.20 to 0.45)	0.84 (0.79 to 0.88)
		No	0.35 (0.22 to 0.51)	0.83 (0.76 to 0.89)
	70–99%	Yes	0.83 (0.77 to 0.88)	0.57 (0.48 to 0.67)
		No	0.84 (0.74 to 0.90)	0.60 (0.49 to 0.71)
Asymptomatic	0–49,100%	Yes	0.80 (0.72 to 0.87)	0.79 (0.66 to 0.88)
		No	0.92 (0.83 to 0.97)	0.93 (0.73 to 0.98)
	50–69%	Yes	0.26 (0.12 to 0.49)	0.86 (0.79 to 0.91)
		No	0.61 (0.34 to 0.83)	0.92 (0.84 to 0.97)
	70–99%	Yes	0.71 (0.54 to 0.84)	0.89 (0.82 to 0.93)
		No	0.71 (0.38 to 0.90)	0.93 (0.85 to 0.97)
All	0–49,100%	Yes	0.70 (0.63 to 0.77)	0.93 (0.89 to 0.95)
		No	0.79 (0.70 to 0.86)	0.96 (0.91 to 0.98)
	50–69%	Yes	0.30 (0.20 to 0.42)	0.84 (0.81 to 0.88)
		No	0.41 (0.29 to 0.55)	0.87 (0.81 to 0.91)
	70–99%	Yes	0.81 (0.76 to 0.86)	0.75 (0.69 to 0.80)
		No	0.82 (0.73 to 0.89)	0.77 (0.69 to 0.83)

[a] Calculated from data in *Tables 99* and *100*, adjusted for the number of patients contributing data.

TABLE 39 *χ^2 test results for differences in US sensitivity and specificity between screened and unscreened patients*

	Sensitivity		Specificity	
Artery	χ^2	*p*	χ^2	*p*
All	0.49	0.4835	0.41	0.5236
Symptomatic artery	0.59	0.4429	0.47	0.4909
Asymptomatic artery	5.7	0.0165*	5.0	0.0255*

* Significant at the 5% level.

TABLE 40 *Results of statistical modelling of the relationship between the time interval in days between IAA and the non-invasive test and the difference in percentage stenosis between the two tests*

Artery	Imaging	No. of arteries in model	Model estimate of time factor	*p*
Symptomatic only	US	588	0.0235	0.0049*
	MRA	31	0.7991	0.0067*
	CEMRA	165	0.0040	0.7844
Asymptomatic only	US	331	0.0721	0.0003*
	MRA	34	0.1938	0.5896
	CEMRA	151	0.0000	0.9976
All	US	919	0.0372	<0.0001*
	MRA	65	0.4916	0.0361
	CEMRA	316	0.0020	0.8479

* Significant at the 5% level.

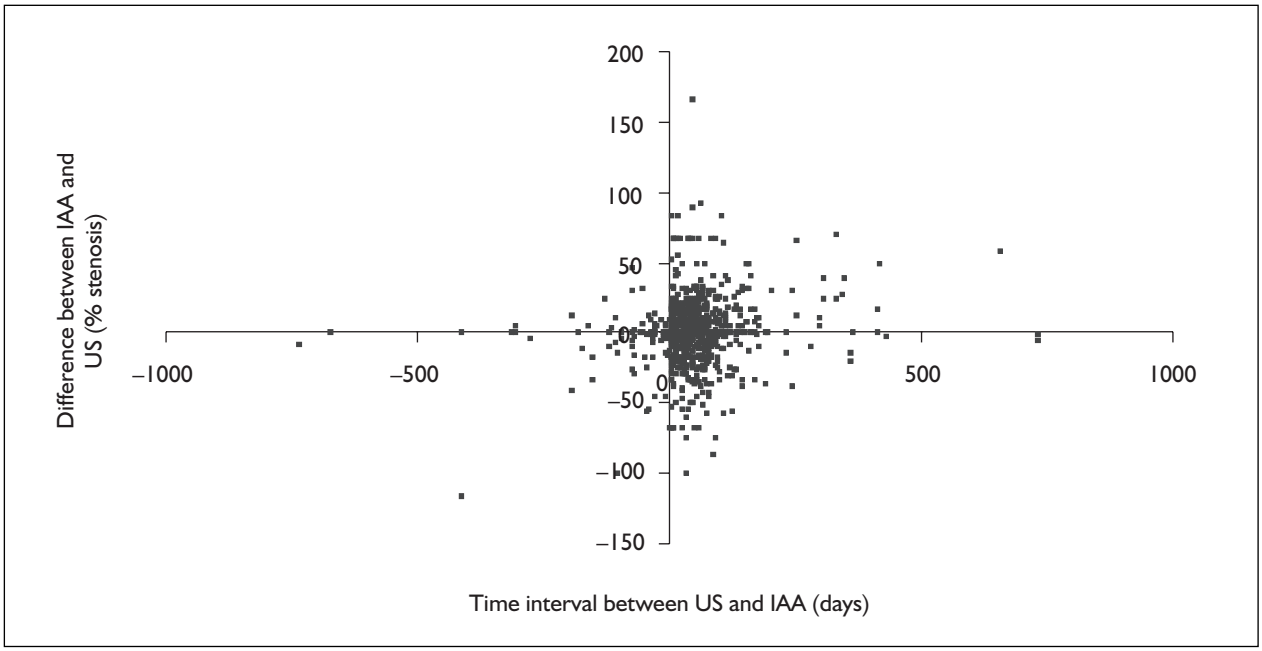

FIGURE 26 *Difference in days between time of IAA and US against the difference in percentage stenosis measured*

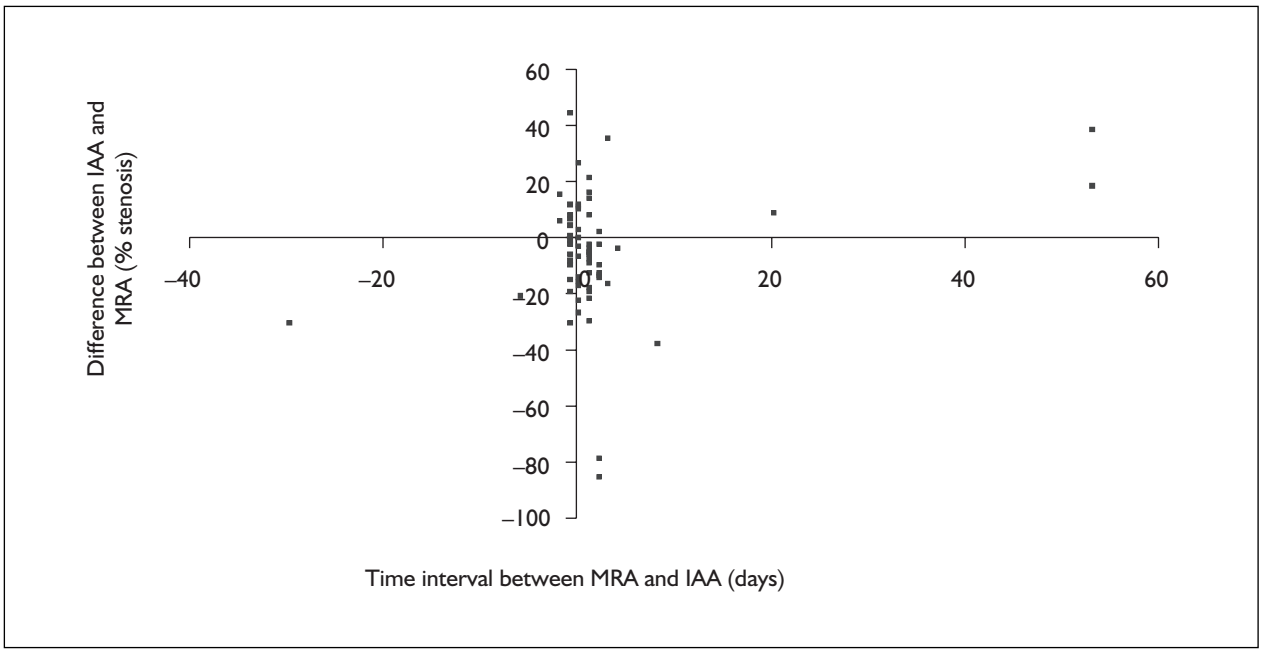

FIGURE 27 *Difference in days between time of IAA and MRA against the difference in percentage stenosis measured*

calculate the probability of a second less invasive test confirming the diagnosis made by a first. There were sufficient data on US followed by US, CEMRA followed by CEMRA, and US followed by CEMRA, but not for other combinations. The conditional probabilities given in *Table 41* show the less invasive tests are least consistent when the first diagnosis was 50–69%. This is a similar result to the comparison of less invasive tests with IAA.

Both US followed by US and CEMRA followed by CEMRA were more consistent than US followed by CEMRA, perhaps because an imaging modality is more consistent with itself than with a different imaging modality. The exception was in the diagnosis of 70–99% stenosis in the symptomatic artery (the probabilities of diagnosis being confirmed are 0.862, 0.796 and 0.922, respectively, for US followed by US, CEMRA followed by CEMRA, and US followed by

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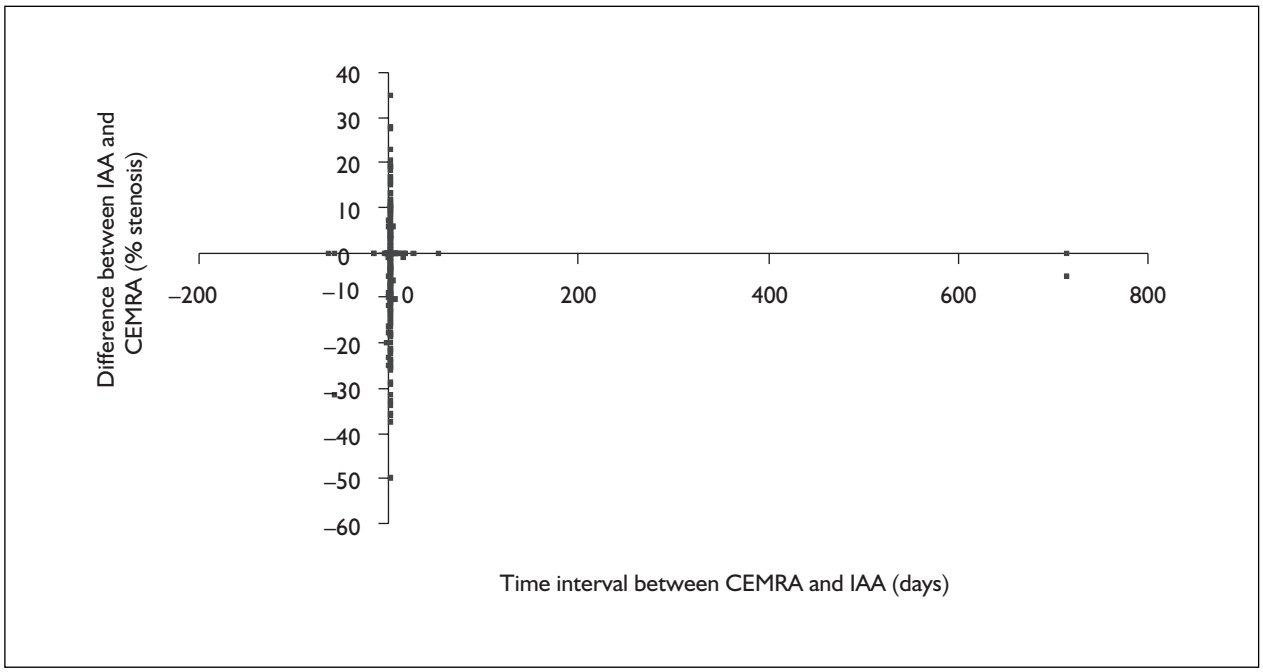

FIGURE 28 *Difference in days between time of IAA and CEMRA against the difference in percentage stenosis measured*

TABLE 41 *Conditional probabilities of a second non-invasive test agreeing with a first non-invasive test*

First and second tests	Symptomatic status of artery	Diagnosis of first test	Probability of second test confirming first diagnosis (95% CI)
US followed by US	Symptomatic	0–49, 100%	0.91 (0.82 to 0.96)
		50–69%	0.58 (0.47 to 0.69)
		70–99%	0.86 (0.79 to 0.91)
	Asymptomatic	0–49, 100%	0.97 (0.94 to 0.99)
		50–69%	0.47 (0.31 to 0.64)
		70–99%	0.86 (0.72 to 0.94)
CEMRA followed by CEMRA	Symptomatic	0–49, 100%	0.81 (0.69 to 0.89)
		50–69%	0.70 (0.52 to 0.84)
		70–99%	0.80 (0.66 to 0.89)
	Asymptomatic	0–49, 100%	0.92 (0.85 to 0.96)
		50–69%	0.70 (0.48 to 0.85)
		70–99%	0.92 (0.67 to 0.99)
US followed by CEMRA	Symptomatic	0–49, 100%	0.70 (0.61 to 0.78)
		50–69%	0.43 (0.27 to 0.61)
		70–99%	0.92 (0.83 to 0.97)
	Asymptomatic	0–49, 100%	0.89 (0.83 to 0.94)
		50–69%	0.44 (0.30 to 0.60)
		70–99%	0.73 (0.57 to 0.85)

CEMRA). The diagnosis of 70–99% stenosis in the symptomatic artery is of the most clinical interest as this is one of the CEA. However, these analyses were dependent on relatively few data; one US followed by a second US had the most data at 291 arteries.

Discussion

There are several important differences between the results of the IPD analyses and those of the systematic literature review. Most notably, the sensitivities and specificity estimates from the IPD

analyses differ from those derived from the meta-analyses of published literature, being in general poorer for all modalities in the IPD analyses, significantly so in half of the comparisons.

There are several possible reasons for this. It could be due to chance. However, it is more likely that the differences are real and due to different approaches to the analyses used in the literature and fundamental differences between data prepared for publication and data from routine practice. Four of the eight data sets that contributed to the analysis of sensitivity and specificity in the IPD were audit data sets. Although no difference was found between data collected for audit and in research projects, this analysis could only be performed for US, and the amount of data was limited, and was certainly inadequate to exclude an important difference between audit and research data.

Publication bias may be important, and previous studies have shown that not only does publication bias affect the observational literature, but it may be worse for laboratory and observational studies than for randomised trials:[46] the systematic review estimate of sensitivity or specificity was greater than the IPD estimate in 12 out of 18 cases (*Tables 27–29*) and significantly so on a χ^2 test in nine (*Table 30*).

In addition, the IPD analyses found significantly lower sensitivities and specificities for symptomatic compared with asymptomatic arteries, something completely overlooked in all but two papers in the systematic literature review.[34,104] Most published figures of sensitivity and specificity therefore may not apply to either the symptomatic or asymptomatic artery, but to somewhere in between. The vast majority of the literature does not take account of the symptomatic status of the artery in the analysis (although the studies do tend to use the symptomatic status of the patient as one of the recruitment criteria). It is biologically plausible that the accuracy of diagnostic tests may differ with the symptomatic status of the artery. In the first place, the symptomatic artery is different because its plaque has produced symptoms, presumably because it was more stenosed or ulcerated. Both features could affect the performance and interpretation of imaging tests; therefore, it should not be particularly surprising that the accuracy of less invasive tests is different between the two. Furthermore, this difference would account for the finding by Kallmes and colleagues in their systematic review of the literature that inclusion of studies reporting test accuracy in less diseased arteries produced higher estimates of sensitivity and specificity than did restricting analyses to significantly diseased arteries.[49]

Another difference is that, in contrast to the meta-analysis of published literature, in the IPD analysis there is no single imaging modality that performs best across all stenosis bands (although some of the MRA estimates are based on very sparse data compared to US and CEMRA and are therefore relatively imprecise). Furthermore, US is again at a disadvantage in that more US data came from local audit databases than for the other modalities; much of the data on CEMRA and MRA came from research studies.

With regard to the symptomatic artery, CEMRA is best in the 70–99% band (DOR 25.9 compared to 7.0 and 9.4 for US and MRA, respectively). However, it is not best across the other bands. The absolute sensitivities are almost identical for US and CEMRA for 70–99% stenosis. MRA has the highest DOR (4.8 compared to 2.5 and 3.7 for US and CEMRA, respectively) in the 50–69% stenosis band, and also for the 0–49% and occluded band (56.7 compared to 26.8 and 26.4 for US and CEMRA, respectively). US does the least well of the three imaging modalities.

The analysis for the asymptomatic artery gives a similar picture. CEMRA is again best in the 70–99% band (93.2 DOR compared to 23.3 and 67 for US and MRA, respectively). MRA is again best in the 50–69% band (35.0 compared to 4.8 and 23.0 for US and CEMRA, respectively) and again for the 0–49% and occluded band (183.0 compared to 26.0 and 37.2 for US and CEMRA, respectively). US also does least well for the asymptomatic artery.

The IPD analyses also produced some very low figures for sensitivity with regard to the diagnosis of 50–69% stenosis for all three less invasive modalities. In general, one would not expect a test to have less than 50% sensitivity as this would indicate that the test was worse at detecting positive patients than tossing a coin. As in the systematic review, most of the misdiagnosed patients who should have been put in the 50–69% stenosis group were put in the 70–99% group. A recent reanalysis of the NASCET and ECST data[4] suggested that patients with 50–69% stenosis may also benefit from CEA. Thus, the misdiagnosed patients could have benefited from their misdiagnosis.

There was no evidence of a difference in sensitivity and specificity in different age bands, or between

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genders, or in patients screened with US before entry to the study versus not screened. Therefore, neither gender nor age should influence the choice of less invasive carotid imaging tests. It is possible that the US sensitivity and specificity data are influenced by the time delay between US and IAA. The statistical model to test for this association certainly suggested that the estimates of US sensitivity and specificity were affected by the time lapse (the *p*-values were all highly statistically significant), although this may be a chance effect as the scatterplot did not suggest such an association. However, US is the test most likely to be affected by the time delay to IAA as it is usually performed first and usually not repeated at the time of IAA, and there may be delays of weeks to IAA. This is also a problem in interpretation of the literature, made worse by the fact that the time delay between the less invasive test and IAA is often not stated. Therefore, US is the most disadvantaged of the less invasive tests in the assessment of sensitivity and specificity.

The result of the conditional probability analyses is that US is more likely to agree with US, and CEMRA more likely to agree with CEMRA. The exception is in the diagnosis of 70–99% stenosis in the symptomatic artery, but this exception may well be due to chance alone. It seems plausible that each imaging modality would be more consistent with itself than another imaging modality. However, it is interesting to note that the symptomatic artery with 70–99% stenosis is the artery considered suitable for surgery. This could be a point for further research.

Conclusions

Among the three less invasive imaging modalities with sufficient data from analysis, the differences between the less invasive modalities were not large, but the least accurate imaging modality across all stenosis bands and for both arteries was US. It was marginally outperformed by both MRA and CEMRA, but caution should be exercised in the interpretation of these data as the sample sizes for some analyses were small, and the data sources for US were in general more varied and more often reflected routine audit than those for MRA or CEMRA. Other factors should be considered when determining which imaging modality is best used for stroke prevention, such as availability and costs.

The symptomatic status of the artery affects the sensitivity and specificity of all the less invasive tests in all stenosis bands and should be (1) recorded in research and audit databases, (2) included in the analysis to distinguish between symptomatic and asymptomatic arteries in studies, and (3) taken into consideration in the interpretation of less invasive tests when used in routine clinical practice. Although there were insufficient data for analysis to include CTA, there is no reason to believe that CTA would be unaffected by the symptomatic status.

The IPD analyses confirmed those of the meta-analysis of published literature in that the less invasive tests generally have a very low sensitivity for diagnosing 50–69% stenosis, and patients who have 50–69% stenosis are quite likely to be diagnosed as having 70–99% stenosis.

Implications for clinical practice

- Routine audit data should be recorded routinely.
- Radiologists and clinicians should not place undue reliance on literature values of less invasive test accuracy, as these are overoptimistic; local data should be collected and reviewed regularly where possible.
- Radiologists and clinicians should be aware of the major shortcomings in the published literature on less invasive tests.

Implications for research

- It is vital to record the symptomatic status of the artery in any research study of carotid imaging.
- It is vital to record routine audit data for CEMRA and MRA and CTA to increase IPD available for ongoing analyses.
- There is a particular need for more CTA data.
- New studies of multislice CTA in the diagnosis of carotid stenosis are needed.
- It is important to improve understanding of methodology for systematic reviews of the imaging literature, in particular, to clarify the size and impact of publication bias.
- New studies should look specifically at why sensitivity and specificity appear to be so poor in the 50–69% stenosis band and find ways to improve accuracy of interpretation at all important stenosis band levels.
- Some of the apparent difference between tests may be true difference attributed to disease progression in the time between the two tests; larger data sets are required to examine this.
- Methods of tracking the accuracy of less invasive tests over time, or as a new technique is introduced into service, are required.

Chapter 5

Costing investigation of carotid artery disease, carotid endarterectomy and stroke, and determining the effect on quality of life of having a stroke

Background

To model the cost-effectiveness of less invasive imaging tests in the diagnosis of carotid stenosis, the following costs needed to be determined: the less invasive and the conventional (or reference standard) imaging tests for carotid stenosis; the patient being assessed by a stroke physician or neurologist in the outpatient clinic, including any diagnostic brain imaging; CEA; and of having a stroke. It was important to obtain costs in sufficient detail (unit costs) for the cost-effectiveness model, and to allow sensitivity analyses of the effect of varying costs. The effect of stroke on quality of life also needed to be identified.

Unit costs refer to the resources used in clinical practice for a patient being investigated for carotid artery stenosis. The three-step intervention included: (1) clinical assessment and investigation by a neurologist or stroke physician; (2) diagnostic imaging tests for carotid stenosis; and (3) surgery. The study explicitly did not take into consideration organisational costs, such as the cost of setting up a clinic, as there is a huge amount of uncertainty in the methods to assess these costs, and huge variability depending on existing local resources and the clinic organisation.

The imaging tests considered were for carotid stenosis [intracranial angiography (IAA), colour DUS, MRA, CEMRA and CT angiography (CTA)] and for investigating the brain lesion underlying the stroke or TIA [computed tomographic (CT) scan or magnetic resonance imaging (MRI)]. The surgery considered was CEA, an intervention that has been widely used for several decades and has been exhaustively evaluated in RCTs. Other interventions are available (e.g. angioplasty and carotid stenting), although these are the subject of ongoing clinical trials.

This study was also interested in a unit cost for stroke, and the effect on quality of life of stroke occurring either as a consequence of the carotid artery stenosis or as a complication of surgery.

Approaches to costing of radiological investigations

Radiology departments provide many services (X-rays, CT scans, US, MRI) for diagnosis of a wide range of diseases. For the estimation of a unit cost to be reliable, a certain level of precision and a consistent way of allocating resources to different imaging tests are needed. The level of precision required is an important determinant for the costing methodology used. Gross-costing (a simple method of obtaining approximate costs of procedures from central finance department costs for composite data) and microcosting (a detailed bottom–up approach summing the exact cost of each item used in performing a test) represent opposite ends of the precision spectrum. The general approach in a costing study is to determine, for a specific healthcare service, the necessary amount of each input (i.e. personnel, equipment, material, floor surface, etc.).[138]

In addition to the precision, it is important to consider the cost allocation methodology. A growing literature on activity-based costing (ABC) for hospitals[139] emphasises the importance of identifying the activities and inputs that drive the final cost of a product or service. According to this logic, the costs of overhead departments are allocated to service departments based on the activities and inputs that drive them, instead of using a more generic allocation basis for all overhead departments, such as direct costs.[140] An ABC approach is desirable as, in radiology departments, most of the equipment is used for different activities and for many different medical conditions. Therefore, the equipment use attributable to each activity should be taken into account, as the cost of the test may vary depending on the disease under investigation.

Aim

The aim of this section of the work was to identify unit costs for the different diagnostic imaging tests for carotid stenosis, CEA and caring for stroke,

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and to choose estimates to use in the cost-effectiveness model. A further aim was to identify data on quality of life after stroke to use in the cost-effectiveness model.

Methods

Systematic review

A systematic review of the literature was undertaken to identify costs of imaging procedures, costs of endarterectomy, costs of stroke and data on quality of life after stroke. In addition, a microcosting exercise was conducted in two Radiology Department Directorates in Edinburgh and Sheffield to determine as precisely as possible, in year 2004 figures, the costs of the imaging tests.

Sources of cost information

MEDLINE, the HTA database, DARE and NEED databases were searched, and bibliographies and results of previous systematic reviews handsearched to identify unit costs of imaging, CEA and care of stroke. Data on unit costs were extracted from the NHS Healthcare Resource Groups (HRGs) from the year 2002 to complement the results of the search. A search was done for literature on quality of life after stroke. In addition, a microcosting exercise was performed in Edinburgh and Sheffield radiology departments to provide examples of typical UK costs of imaging tests in 2004.

Search strategy

The search strategy is detailed in Appendix 11. This was devised to optimise detection of costings papers from the literature. Reference lists of review papers were also searched. Any papers of costs or other aspects of health economics detected in the searches for papers on the accuracy of diagnostic tests (Chapter 3) were also evaluated.

Homogenising unit costs

To provide some standardisation across time and between countries, unit costs were inflated to reflect 2001/02 estimates. Inflators were taken from Unit Costs of Health and Social Care.[141] It is conventional to convert cost data from papers published outside the UK into pounds sterling according to the purchasing power parities (PPPs)[142] rather than using normal exchange rates, as the latter are heavily influenced by currency speculation and are not suitable for market imperfections in healthcare. PPPs are exchange rates that measure the purchasing power of different national currencies. The conversion rate eliminates the differences in price levels between countries. However, for the present review, non-UK studies were not converted into pounds, as it was unclear that PPP estimates would be relevant to the NHS in the UK. As a consequence of this, the data in the model came only from the UK literature and the microcosting exercise in two UK centres.

Inclusion and exclusion criteria

MEDLINE was searched from 1966 to 2003 (Appendix 11). The search included:

- studies that referred to patients undergoing the relevant imaging tests
- economic studies, such as cost-effectiveness or cost–efficacy studies, or containing economic data on costs and outcomes, and cost–analysis studies
- studies concerning investigation of patients with carotid artery stenosis
- studies of costs of caring for patients with a TIA or stroke
- studies of quality of life after stroke
- studies published in English
- studies published in peer-reviewed journals
- data from NHS HRGs.[143]

After searching MEDLINE, the authors integrated and cross-checked this literature with the literature found in the HTA, NEED and DARE databases and previous systematic reviews of economic data.

The researchers excluded studies that were not published in English, studies that did not state explicitly how the unit cost had been calculated and studies published before 1990 (as these were considered to be too old).

Data extraction

Data were extracted on costs of imaging tests in patients with carotid artery stenosis, costs of outpatient clinic attendances, costs of endarterectomy, costs of caring for stroke patients in hospital and quality of life, either as QALYs[144] or health state utility values (HSUVs).[145] Economic data from papers referring to the investigation of other medical conditions were excluded as there could be substantial differences in imaging costs when the same tests were used for different diseases. Data on the unit costs of stroke and endarterectomy were extracted. Only estimates from English studies in British pounds were used.

For each imaging test or healthcare resource use study, the aim was to provide one estimate from

TABLE 42 *Studies identified from the literature that included costs of IAA*

Source	Diagnostic test	Unit cost	How calculated	Unit cost selected for average estimate	Inflated unit cost
HRGs; National Schedule of reference costs (outpatient HRG data, 2002); vascular surgery[143]	IAA	£379	Top–down	Y	£379
Post, 2002[146]		€550	Medicare reimbursement fees	N	
Kent, 1995[60]		$2,360	Medicare reimbursement fees	N	
Hankey, 1990[147]	IAA	£520	Bottom–up cost exercise	Y	£865
Berry, 2002[73]	IAA	£204	Annual maintenance cost + capital equipment	Y	£204
U-King-Im, 2003[148]	IAA	£507	Microcosting, activity-based costing	Y	£507
Benade, 2002[149]	IAA	£950	1997/98 estimates; includes overnight hospitalisation using an estimated bed-day cost of £298	Y	£760[a]
Derdeyn, 1996[150]	IAA	$2000	1995 Medicare reimbursement fees	N	
Yin, 1998[151]	IAA	$2360	Hospital charges	N	
Berry, 2002[73]	IAA	£186	Excluding capital equipment	N	
Vanninen, 1995[118]	IAA	$783	Bottom–up cost exercise	N	
Lee, 1997[152]	IAA	$3010	Hospital and professional charges	N	

[a] Not including overnight cost.
Y, yes; No, no.

the literature to be used to populate the model. All data from the UK literature were then considered to find an average of unit cost for that modality (with 95% confidence intervals), to allow sensitivity analysis on costs to be performed in the cost-effectiveness model.

Costs of imaging determined from a detailed costing exercise in Edinburgh and Sheffield

Data were collected from the Lothian University Hospitals in Edinburgh (Western General Hospital and New Royal Infirmary) and the Northern General Hospital in Sheffield, on MRA, US, CTA and IAA.

From the Lothian University Hospitals, precise data were obtained on consumables, staffing and equipment depreciation per year, and the number of tests per year (Appendix 12). The data were derived from the Radiology Directorate central resource use data, and in a bottom-up approach (microcosting) by identifying all consumables used in an average procedure, staff, their time, the total duration of the procedure, the reporting of the procedure and the number of procedures per year. The data were obtained from staff trained in, and who frequently performed, the imaging procedure to obtain an accurate estimate of resource use. Data on fixed costs for MRA and CTA were available in the form of a lease cost per year, and data for IAA and US were available in the form of a total purchase cost. For MRA and CTA, a fixed cost per test was found by dividing the lease cost per year by the number of tests performed in that year. For IAA and US, the annual equivalent cost

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TABLE 43 *Studies identified from the literature which included costs of carotid DUS*

Source	Diagnostic test	Unit cost	How calculated	Unit cost selected for average estimate	Inflated unit cost
Post, 2002[146]	Duplex ultrasound	€63	Medicare reimbursement rates	N	
Hankey, 1990[147]		£85	Bottom–up cost exercise	Y	£141
Benade, 2002[149]		£70	1997/98 estimates	Y	£82
Derdeyn, 1995[150]		$109	1995 Medicare reimbursement fees	N	
Yin, 1998[151]		$206	Hospital charges	N	
Vanninen, 1995[118]		$130	Bottom–up cost exercise	N	
Lee, 1997[152]		$556	Hospital and professional charges	N	

was first estimated calculated on a 7-year straight line assuming no resale value and 3.5% discount. For US, once the annual equivalent cost had been calculated, this cost was averaged by the number of tests performed per year. For IAA, data were available on average time for the procedure, so a cost per minute was calculated, assuming that the equipment was run for 50 weeks per year with normal working patterns of 35 hours per week. The cost per minute estimated was £2.19 per IAA.

Sheffield estimates, obtained using a more gross-costing approach, came from the Vascular Directorate and the Finance Department of the Northern General Hospital, Sheffield. From the accounts of the Finance Departments, an amount of money was allocated to each imaging test calculated on the average use of the machine in that modality. Then, the total cost for the imaging test was averaged against the number of tests performed in that modality.

Results

Unit cost of imaging tests obtained from the literature

Eleven primary studies and one systematic review of economic evaluations[59] of diagnostic imaging tests were identified. The results for each diagnostic test are reported below.

IAA

Ten studies reporting unit cost data for IAA were identified (*Table 42*), as well as an estimate from the outpatient HRG for angiography (vascular surgery). IAA is often considered as the reference standard against which to compare other imaging tests in cost-effectiveness studies. The cost of IAA ranged from a lower value of £204 to an upper value of £760 in these studies. This may be due to differences in clinical practice or different kinds of angiography (intravenous digital subtraction versus conventional angiography), or to differences in the method of determining the costs, but few details were given in most of the publications. The most detailed costing exercise[148] was an ABC exercise where all parts (direct costs, indirect costs and fixed costs) were estimated and the approach used was clearly stated in the paper. The study by U-King-Im[148] was also the only cost–analysis study, whereas all the other studies were cost–utility evaluations where the procedure for calculating the cost was not well described.

Ultrasound

Seven studies that reported a unit cost for US for carotid stenosis were identified (*Table 43*). Of these, two only were UK studies. The lower value for these estimates was £82 and the upper value was £141. In the study by Benade and Warlow,[149] the most recent study and so more likely to reflect modern clinical practice, the cost was made up of three parts: US equipment, consumables, and human resource cost and overhead costs.

MRA and CEMRA

Four studies in total were identified in the literature. Of these, two UK studies were considered in detail. The cost of any MRA ranged from £110 for non-CEMRA to £215 for CEMRA (*Table 44*). The study by U-King Im was considered to be the most detailed as it was a proper microcosting exercise and the allocation of costs was activity based.[148] The study referred to both non-CEMRA and CEMRA. Both were required for the cost-effectiveness model. U-King-Im provided the cost for the contrast, which was then subtracted from the cost of CEMRA to provide an estimate of non-CEMRA.

TABLE 44 *Studies identified from the literature that included costs of MRA and CEMRA*

Source	Diagnostic test	Unit cost	How calculated	Unit cost selected for average estimate	Inflated unit cost
Berry, 2002[73]	MRA	£110	Annual maintenance cost + capital equipment	Y	£110
Berry, 2002[73]	MRA	£54	Excluding capital equipment	N	
Kent, 1995[60]	MRA	$560	Medicare reimbursement fees	N	
Post, 2002[146]	MRA	$510	Medicare reimbursement rates	N	
U-King-Im, 2003[148]	CEMRA	£215	Microcosting, activity-based costing	Y	£215
U-King-Im, 2003[148]	MRA	£145	Microcosting, activity-based costing	Y	£145
Berry, 2002[73]	MRA + US	£310	Excluding capital equipment	N	

TABLE 45 *Studies identified from the literature that included costs of CTA*

	Diagnostic test	Unit cost considered	Source of unit cost	Nature of investigation
Nelemans, 1998[153]	CT angiography	682.06 Dutch guilders	The cost includes personnel, material, capacity and overhead cost	Renal artery stenosis
Paterson, 2001[154]	Spiral CT (CTA)	$203 (Canadian)	Costs derived from the sum of technical, professional and capital costs	Diagnosis of acute pulmonary embolism
Lindgren, 1996[155]	β-3D CTA	$1652	This estimate is made up of three parts: procedure ($1169), physicians ($333) and other components ($150)	Renal CT
Tierney, 2000[156]	CTA (detection of the pancreas)	$1720	Medicare reimbursement rates	Adenocarcinoma of the pancreas
Visser, 2003[157]	Multidetector row CTA	$524	Medicare reimbursement rates	Patients with intermittent claudication
Van Erkel, 1996[158]	Spiral CTA	$330	Cost analysis performed from the perspective of the hospital by combining the costs for equipment, medical materials and personnel	Suspected pulmonary embolism

CTA

Six studies were identified, although these were not for carotid stenosis (*Table 45*). None of these studies was UK based. Therefore, for this particular imaging technique, the analysis had to rely on new data collected in the costing exercise performed for the present study from Sheffield and Edinburgh hospitals (see p. 64).

CT brain scan

Two UK studies on the costs of CT scanning were identified, in addition to the outpatient HRG for a CT scan (in vascular surgery) (*Table 46*). The most recent and detailed study was from data collected for an HTA-funded project in 2000 prices.[160] In the HTA-funded report, a detailed microcosting exercise was performed to estimate a unit cost of a CT scan in normal hours and out of hours, in a teaching hospital, a rural general hospital and an urban general hospital. The estimates chosen and reported in *Table 46* refer to those for an urban general hospital.

MRI of the brain

Two sources for the unit cost of MRI were identified: the outpatient HRG and an estimate provided confidentially from the pharmaceutical company Boehringer Ingelheim. The range was from £165 to £222 (*Table 47*). No relevant data were found in the literature and there was

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TABLE 46 *Studies identified from the literature that included costs of CT brain scanning*

Source	Diagnostic test	Unit cost	How calculated	Unit cost selected for average estimate	Inflated unit cost
National Schedule of reference costs (outpatient HRG data, (2002); vascular surgery[143]	CT scan	£166	Top–down	Y	£166
Ferguson, 1997[159]		£104	Mean extra contractual referral costs of the procedure within Trent Health Authority	Y	£137
Wardlaw, 2004[160]		£69.47 (58.73–84.58)	Bottom–up exercise (normal hours)	Y	£69.47
Wardlaw, 2004[160]		£72.56 (61–91)	Bottom–up exercise (out of hours)		£72.56

TABLE 47 *Studies identified from the literature that included costs of brain MRI*

Source	Diagnostic test	How calculated	Unit cost
National Schedule of reference costs (outpatient HRG data)[143]	MRI		£222
Boehringer Ingelheim Pharmaceuticals (Humphreys M: personal communication, June 1999)	MRI		£165

TABLE 48 *Detailed unit costs of imaging tests obtained by a microcosting exercise from the Radiology Directorate, Lothian University Hospitals NHS Trust, Edinburgh*

	Consumable cost per case	Staffing cost per case	Fixed cost per case	Total cost
MRA	£105.69	£50.49	£32.85	£189.03
US	£3.55	£24.16	£26.37	£54.08
CTA	£43.75	£50.78	£28.41	£122.94
IAA	£94.67	£155.04	£87.84 (43.8–131.4)	£337.50 (293.51–381.11)

All costs are in UK pounds. See Appendix 12 for full details.

insufficient information on the method of determining these two estimates to be able to rely on them. The HRGs are determined through a mixture of methods and unit costs are allocated through a top–down exercise. The estimate from Boehringer Ingelheim reflects a price rather than a cost. Therefore, it was assumed that the unit cost of MRI was the same as MRA.

Costs of less invasive carotid imaging tests obtained from Edinburgh and Sheffield

The costs obtained from the microcosting exercise in Edinburgh are given in *Table 48* (details of individual items are given in Appendix 12), and the costs from Sheffield in *Table 49*. The Sheffield unit costs seem slightly lower than the costs from Edinburgh. The biggest difference between the two estimates was for IAA, which in the Lothian hospitals was double that of the cost in Sheffield. This may be because the Sheffield estimate for IAA did not include fixed costs, or because the Sheffield estimate was based on much less detailed methods. However, broadly, these costs are similar to those obtained from the literature. Of note, none of the IAA costs included an overnight stay in hospital after the angiogram, which in most

TABLE 49 *Detailed unit costs of imaging tests obtained by a gross-costing exercise from the Northern General Hospital in Sheffield*

Imaging test	Unit cost
MRA	£165
US	£40
CTA	£125
IAA[a]	£150[a]

[a] Sheffield estimates. This estimate does not include capital cost.

TABLE 50 *Summary of point estimate and lower and upper limit of imaging costs based on the literature review and detailed costings in Edinburgh and Sheffield*

	Source of unit cost	Unit cost chosen	Maximum and minimum estimates
IAA	U-King-Im, 2003[148]	£508	£204–£865
US	Benade, 2002[149]	£82	£82–£141
CT scan	Wardlaw, 2004[160]	£69	£69–£166
CTA	Edinburgh hospital data, 2004	£123	£123–£125
MRA	U-King-Im, 2003[148]	£145	£110–£145
CEMRA	U-King-Im, 2003[148]	£215	–
MRI	Assumed the same as MRA	£145	£110–£145

TABLE 51 *Studies identified from the literature that included costs of attendance at an outpatient clinic for assessment of TIA*

Source of unit cost	Unit cost	Unit cost	How calculated	Inflated unit cost
Benade, 2002[149] 1997/98 unit cost estimate	New neurovascular attendance	£ 88	Scottish Health Service Costs 1996/97	£103
Benade, 2002[149] 1997/98 unit cost estimate	Follow-up attendance	£44	Scottish Health Service Costs 1996/97	£51

parts of the UK would be necessary after this procedure, especially in older patients with TIA.

Point estimate and range of costs for imaging

Table 50 reports the estimates chosen (based on completeness and details of study, and most recently reported) to populate the cost-effectiveness model, and the maximum and minimum estimates from the review for sensitivity analyses. For CTA the data available from the Edinburgh microcosting study were used.

Costs of outpatient clinic attendance

Data for costs of outpatient visits were collected from Benade and Warlow[149] (*Table 51*). The costs were reported separately for new neurovascular attendances and follow-up attendances. For the cost-effectiveness model, £103.00 was chosen as the cost of the first visit, £51.00 as the cost of follow-up visits and £51.00–103.00 as the range of costs.[149]

Cost of CEA

Seven studies were identified (*Table 52*). Two economic evaluations[161,162] compared endarterectomy to other interventions such as angioplasty and carotid stenting, but endarterectomy is considered the standard surgery in the present mathematical model as this represented the established technique. Four of these studies were from the UK. There was considerable variation among studies. The studies by Radestock (1992, see ref. 149) and Berry and colleagues (2002)[73] were costed according to the inpatient stay in the vascular ward, and the more recent of the two[73] suggested that length of stay after operation had decreased in recent times, and therefore endarterectomy appeared less expensive than in the previous unpublished work of Radestock from 1992. A substantial difference was noted also between the two more recent papers.[73,149] Differences in cost may depend on clinical variability and discharge policy of the hospital, and

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TABLE 52 *Studies identified from the literature that included costs of CEA, and the method of determining the costs*

Source of unit cost	Surgery	Unit cost	How calculated	Unit cost selected	Inflated unit cost
Gray, 2002[161]	Endarterectomy	$5,409 (£3,353)	Bottom–up	N	
Radestock, 1992 (see ref. 149)		£3,800 (average) £3,300 (median)	Based on the mean length of preoperative stay of 4.8 days and mean post-operative stay of 8.8 days	Y	£4,652–5,356
Berry, 2002[73]		£2,442	The cost per inpatient day is £407 and the average LOS in the hospital is 6 days	Y	£2,525
Benade, 2002[149] 1997/98 estimate		£3,716	Estimated using patient specific cost data from a prospective costing study	Y	£4,350
Kent, 1995[60]		$10,850	1993 Medicare reimbursement	N	
Kilaru, 2003[162]		$7,871	Costing exercise (not charges)	N	
Derdeyn, 1996[150]		$9,000	1995 Medicare reimbursement	N	

LOS, length of stay.

on the rate of adverse events in the different hospitals. To provide a cost for the cost-effectiveness model, £2525 was chosen from Berry and colleagues[73] as the low cost, and £4360 from Benade and Warlow[149] as the high cost.

Cost of stroke

A cost per year was sought for patients with stroke (*Tables 53* and *54*). Four systematic reviews[163,179,190,191] reporting cost per year of stroke and nine primary economic evaluations for cost of illness studies were realised, plus data from the NHS Health Care Resource Group.[143]

The most recent systematic review concerned with cost of illness studies is by Evers and colleagues (2004).[163] This included studies from January 1966 to July 2003. Fields considered in this review were whether estimation was done through an incidence or a prevalence-based method, whether studies were performed bottom–up or top–down, and whether direct and indirect costs were included. *Table 53* summarises the studies found in the review.[163]

Among the economic evaluations (reported in *Table 54*) were some data for the cost of stroke from the UK literature. Two studies,[73,187] report unit cost in the short and long term. The problem with the latter study was that these costs were estimated through a simulation model, rather than from actual data. Data from Berry (2002)[73] were derived from Healthcare Resource Group[143] and from hospital episode statistics.

The HTA report by Wardlaw and colleagues (2004) provided mean resource use data for stroke by whether the patient survived in a dependent or an independent state.[160] The data were derived from a detailed study on cost-effectiveness of CT scanning in stroke, and included mean length of stay for a stroke episode for independent survivor and dependent survivor, the cost of ambulatory rehabilitation, and the average annual cost of long-term care. These data were used to calculate a unit cost per year for either stroke dependent status or independent status and were used in the cost-effectiveness analysis.

Quality of life

Two systematic reviews were identified on health-related quality of life associated with stroke.[192,193] It is currently recommended for economic valuation that health state utility values should be obtained using a choice-based technique such as standard gamble (SG) or time trade-off (TTO) rather than a rating scale.[194]

The first review included 67 articles.[192] Quality of life estimates ranged from –0.02 to 0.71 for major stroke (n = 67), from 0.12 to 0.81 (n = 14) for moderate stroke, from 0.45 to 0.92 for minor stroke, and from 0.29 to 0.903 for any stroke. An important difference between the estimates was

TABLE 53 *Studies identified in the literature that provided data on the costs of stroke (from Evers, 2004)*[163]

Author	Year COI	Country	Study type	Discounting	Sensitivity	Unit
Adelman[164]	1976	USA	Disease-specific, preference-based, both	Y	N	Year total population
Bergman[165]	1991	Netherlands	Disease-specific, incidence-based, bottom–up	N	N	Lifetime cost + first year cost
Carstairs[166]	1974	Scotland, UK	Disease-specific, prevalence based, top–down	N	N	Year total population
Chan[167]	1994/95	Canada	Disease-specific, prevalence based, top–down	N	Y	Year total population
Dewey[168]	1997	Australia	Disease-specific, incidence-based, bottom–up	Y	Y	First year cost
Drummond[140]	1984	England, UK	Disease-specific, prevalence-based, top–down	Y	N	Year total population
Evers[169]	1993	Netherlands	Disease-specific, prevalence-based, top–down	Y	Y	Year total population
Hartunian[170]	1975	USA	General, incidence-based, top–down	Y	Y	Year total population
Health Canada[171]	1993	Canada	General, prevalence-based, top–down	N	N	Year total population
Hodgson[172]	1995	USA	General, prevalence-based, top–down	N	N	Year total population + year per patient
Isard[1]	1988	Scotland, UK	Disease-specific, prevalence-based, top–down	Y	N	Year total population
Kavanagh[173]	1994/95	UK	Disease-specific, prevalence-based, bottom–up	Y	N	Year per patient
Koopmanschap[174]	1988	Netherlands	General, prevalence-based, top–down	N	N	Year total population
Mills[175]	1975	USA	Disease-specific, prevalence based, top–down	N	N	Year total population
Persson[176]	1985	Sweden	Disease-specific, incidence-based, bottom–up	N	N	First year costs per patient + second year cost per patient
Polder[177]	1994	Netherlands	General, prevalence-based, top–down	N	Y	Year total population
Polder[178]	1999	Netherlands	General, prevalence-based, top–down	N	N	Year total population
Porsdal[179]	1994/95	Denmark	Disease-specific, incidence based, bottom–up	N	Y	First year costs per patient

continued

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TABLE 53 *Studies identified in the literature that provided data on the costs of stroke (from Evers 2004)*[163] *(cont'd)*

Author	Year COI	Country	Study type	Discounting	Sensitivity	Unit
SBU[180]	1991	Sweden	Disease-specific, incidence-based, both	Y	N	First year cost per patient + second year cost per patient
Taylor[181]	1990	USA	Disease-specific, incidence-based, unclear	Y	Y	Lifetime cost
Terent[182]	1980	Sweden	Disease-specific, incidence-based, bottom–up	Y	N	First year costs per patient + second and third year per patient
Terent[183]	1991	Sweden	Disease-specific, incidence-based, bottom–up	Y	N	First year costs per patient + second year cost per patient
Thorngren[184]	1986/87	Sweden	Disease-specific, incidence-based, bottom–up	N	N	First year cost per patient
Weill[185]	1982	France	Disease-specific, prevalence-based, top–down	Y	N	Year total population
Zethraeus[186]	1994	Sweden	General, incidence-based, bottom–up	N	N	Cost before stroke onset + first year costs per patient

COI, cost of illness, refers to the year in which the costs were obtained (i.e. not the year of study publication).

the valuation technique used to elicit HSUVs,[145] that is, whether patients valued their own state or valued hypothetical condition-specific or generic states.

The second systematic review included 23 articles,[193] many of which were also included in Tengs.[192] However, all the studies included in this systematic review were preference based (elicited by SG and TTO) or used a visual analogue scale. Patients at risk of stroke assigned a utility of 0.26 and 0.55 to major and minor stroke, respectively. Stroke survivors assigned higher utilities to both major (0.41) and minor stroke (0.72).

Even though most of the studies retrieved in the two systematic reviews had begun to use accepted methods for economic evaluation such as SG or TTO, they were limited in terms of age range, sample size, the period since the event and poor controls. To improve the reference case value data set would require the administration of a preference-based generic health status measure to a large prospective cohort and long-term follow-up. Such preference-based measures could include the EuroQol 5 dimensions (EQ-5D),[144] Health Utility Index III (HUI-III)[145] or the Short Form 6D (SF-6D),[195] which uses Short Form 36 (SF-36) data.

The only health state values related to stroke that came from a generic preference-based measure, were from Dorman and colleagues (2000),[196] and these were chosen for the economic model. Dorman and colleagues' study used the EuroQol to measure the health status of 867 UK patients enrolled in the International Stroke Trial. The utility values were 0.31 (95% CI 0.29 to 0.34) for dependent health states, 0.71 (95% CI 0.68 to 0.74) for independent health states and 0.88 (95% CI 0.84 to 0.92) for fully recovered health states.

Discussion

This review sought to identify correct estimates of the costs of imaging, clinic visits, endarterectomy and stroke care to populate the cost-effectiveness

TABLE 54 *Costs identified in the literature of stroke, expressed per patient with stroke*

Type of stroke	Description	£/$	Source of unit cost	Inflated unit cost
Short-term	First 12 weeks. Costs found through a model	£8,326	Caro, 1999[187]	£9373.6
Long-term cost per major stroke	After 12 weeks. Costs found through a model	£75,985	Caro, 1999[187]	£85,546
Long-term cost per minor stroke	After 12 weeks. Costs found through a model	£27,995	Caro, 1999[187]	£31,517
TIA	Age >69 years or with co-morbidities	£1,748	HRG	£1,748
TIA	Age <70 years without co-morbidities	£1,955	HRG	£1,955
Stroke	Age >69 years or with co-morbidities	£4,077	HRG	£4,077
Stroke	Age <70 years without co-morbidities	£3,044	HRG	£3,044
Minor stroke	Cost associated with patient hospitalised after a stroke (assumption)	£13,000	Kent, 1995[60]	£21,642
Stroke: predischarge, inpatient stay	HRG 1998–99; Department of Health, 2001	£1,619	Berry, 2002[73]	£1,823
Stroke: postdischarge, inpatient stay	HRG 1998–99; Department of Health, 2001	£2,099	Berry, 2000[73]	£2,363
Stroke disabled, per year	Hospital Episode Statistics, 1998–99	£10,525	Berry, 2000[73]	£11,849
Stroke (dependent)	Calculated on a mean LOS of 51 days inpatient, rehabilitation cost of £763 and average annual cost of £11,292	£22,255	Wardlaw, 2004[160] Sandercock, 2002[188]	£22,255
Stroke (independent)	Calculated on a mean LOS of 14 days inpatient, rehabilitation cost of £40 and average annual cost of long-term care of £876	£3,716	Wardlaw, 2004[160] Sandercock, 2002[188]	£3,716
Acute stroke	First year cost of major stroke (assumption)	$27,000 (assumed)	Kent, 1995[60]	
Acute stroke	Subsequent years (cost per year)	$12,000 (assumed)	Kent, 1995[60]	
Acute stroke	Total cost	$100,000 (assumed)	Kent, 1995[60]	
Acute stroke	Initial cost	€12,000	Post, 2002[146]	£8,982
Disability major stroke	Yearly cost	€13,000	Post, 2002[146]	£9,731
Disability minor stroke	Yearly cost	€3,700	Post, 2002[146]	£2,769
Major stroke	First year. Procedural morbidity/mortality rate for CEA and costs derived from a retrospective review of consecutive patients treated at New York Presbyterian Hospital/Cornell (n = 447)	$52,019	Kilaru, 2003[162]	
Major stroke	Annual cost for subsequent years. Procedural morbidity/mortality rate for CEA and costs (not charges) derived from a retrospective review of consecutive patients treated at New York Presbyterian Hospital/Cornell (n = 447)	$27,336	Kilaru, 2003[162]	
Major stroke	First year. Estimated fees for patients who are hospitalised ($1994)	$27,000	Yin, 1998[151]	
Major stroke	Annual cost per chronic care	$12,000	Yin, 1998[151]	

continued

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TABLE 54 *Costs identified in the literature of stroke, expressed per patient with stroke (cont'd)*

Type of stroke	Description	£/$	Source of unit cost	Inflated unit cost
Minor stroke	Average cost	$9,419	Kilaru, 2003[162]	
Minor stroke	One time cost. Estimated fees for patients who are hospitalised	$13,000	Yin, 1998[151]	
TIA stroke	Cost of hospital stay after stroke	$1,800	Porsdal, 1998[179]	
TIA stroke	Cost of the services after discharge	$1,600	Porsdal, 1998[179]	
General stroke, first year	Weighted average of the estimated cost of acute and chronic major and minor stroke from Gage *et al*. 1995[189]	$20,000	Derdeyn, 1996[150]	
General stroke, subsequent year	Weighted average of the estimated cost of acute and chronic major and minor stroke from Gage *et al*., 1995[189]	$10,000	Derdeyn, 1996[150]	
'Assumed', costs not precisely calculated but estimated roughly.				

model. These data were complemented with a point estimate and confidence intervals derived from the UK literature and data collected from two UK hospitals in 2004. However, there were considerable differences in the costs, for which there are several potential causes, but the actual reasons are uncertain.

The included studies were of patients undergoing tests for carotid stenosis, hence the researchers did not expect to find variability in costs due to investigations of different medical conditions. Differences in costs of that IAA may be due to differences in the way IAA is performed. Several different kinds of IAA were identified in the review: conventional intra-arterial film-screen angiography, intra-arterial digital subtraction angiography and intravenous digital subtraction angiography. Intravenous digital subtraction angiography is less accurate than IAA and not relevant to current practice.[197] No UK studies for CTA in patients investigated for carotid artery stenosis were found.

A limitation of the data was that most studies identified were economic evaluations, where the unit costs for tests and surgery were reported and with only short descriptions of how they were estimated. Hence, it is difficult to say how precise the costing exercise was. It is likely that methods of calculating, and the assumptions underlying, the staff and consumable costs, vary from hospital to hospital. Methods of calculating fixed costs varied and were often unclear. Further, the greater the capacity of the hospital (i.e. number of tests performed in a radiology unit), the lower the fixed cost per test. Staffing levels and amount and type of consumables are additional sources of variability.

Among the studies identified in the literature on costs of imaging, only one[148] used ABC. ABC may be considered the most appropriate way of costing in a radiology department. However, as stated by Cohen and co-workers,[198,199] ABC has also its drawbacks. ABC is resource intensive; costs are used interchangeably with charges, payment received and actual cost; there is no good standard method of measuring and allocating indirect costs (i.e. overheads); there is little knowledge of variation in costs of imaging on the basis of the severity of disease; depreciation does not have a uniformly adopted standard for calculating purchasing costs or number of years over which to depreciate it; it is difficult to calculate the maximal capacity of a system and to quantify the needed excess capacity in an emergency room environment; and labour costs in healthcare are difficult to track because staff may be simultaneously engaged in several activities for several patients.

In light of these difficulties, exemplar costs were chosen from the publication that provided the most detailed methods and represented the most up-to-date UK costs. A low and a high estimate for the costs of imaging were determined so as to explore, in sensitivity analyses, the effect of varying costs within the likely range of those found in the UK.

There was a general lack of data on the cost of CEA, which is disappointing given that it was one of the earliest surgical procedures shown to be of

benefit in large RCTs. In addition, as mentioned in two previous projects concerned with stroke performed for the HTA,[160,188] there is a lack of data on costs of caring for patients with stroke. This is even more surprising given that stroke is so common and responsible for a major public health burden. This study identified the costs of inpatient care for different survival states after stroke (alive and independent, dependent or dead) taken from previous work for the HTA, as these were the most detailed and accurate up-to-date costs. However, these were largely determined by calculating total length of hospital stay (by type of hospital) after stroke and multiplying by the average cost of inpatient care in that hospital taken from centralised NHS Scotland costs. These include a contribution for pharmaceuticals, monitoring and other commonly required facilities for the average patient, but may underestimate the cost of stroke by underestimating the cost of nursing care, physiotherapy and other therapies, which are required in greater amounts after stroke, and for longer than after many other diseases. In addition, this study did not include the cost of stroke in the community, so for that reason alone, these estimates have probably seriously underestimated the true cost of stroke.

The report by the Stroke Association (*Stroke care: reducing the burden of disease*)[200] showed that patients with stroke accounted for £2318 billion, or 5.8% of NHS and social services expenditure in 1995/96. This estimate took into account the longer term costs of support. However, costs of stroke care are set to increase by 30% in real terms by 2023, and it is difficult to take account of the amount of support that stroke patients receive from carers. Caring for people with severe disability would cost at least £672 million if productivity costs were added in (i.e. loss of patient earnings, loss of carer earnings, and the cost if the patient was in employment and has to be replaced by another paid worker).

In summary, considerable difficulties were encountered in identifying up-to-date, accurate, precise and generalisable (to the UK) costs for all aspects of the process of preventing stroke by using imaging to detect, and then treating, carotid stenosis. Exemplar costs to use in the cost-effectiveness model and a suitable range were identified. However, future research should determine more accurate and streamlined methods for calculating imaging costs, and for clinic attendances, endarterectomy and above all the cost of stroke. As stroke is the most common cause of dependency among community-dwelling adults in the Western world, it is very important to obtain a clearer picture of what this disorder is costing the UK.

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Chapter 6

Design and construction of a mathematical model to describe the investigation and treatment of patients with symptomatic carotid stenosis

Background

Patients with a symptomatic tight carotid stenosis are at increased risk of ipsilateral ischaemic stroke. Various pharmacological agents and CEA reduce the risk of stroke. CEA has a risk of causing a stroke, and the balance of risk and benefit is such that will prevent two strokes but cause one stroke for every ten patients with 70–99% stenosis, net gain one stroke in ten prevented. The risk of stroke is highest soon after the development of symptoms (usually a TIA, minor stroke or retinal artery ischaemic event) and declines to near background level by 6 months. The carotid surgery trials, in which the risk of ipsilateral ischaemic stroke in relation to the degree of carotid stenosis was determined, used IAA to visualise and measure the stenosis. IAA carries some risk, especially in patients with vascular disease, of causing a stroke or other serious complication. Newer less invasive tests are less risky and appear accurate, and so now are gradually replacing IAA. However, it is unclear whether these tests are sufficiently accurate for this purpose, whether other benefits (e.g. less delay than is incurred by IAA) may offset any loss of accuracy, or whether the costs of failing to prevent strokes by inaccurate diagnosis may offset any gain in strokes prevented by faster times to surgery.

The ideal way to assess the risk and benefit and cost-effectiveness of replacing IAA with less invasive tests would be to undertake a randomised trial in which patients were randomised to have IAA or a less invasive test to determine the need for CEA. The trial would then assess outcomes in patients diagnosed with IAA against those diagnosed with less invasive tests to see, in simple terms, which prevented most strokes at least cost. However, this would not be practical at present as, for example, it would be considered unethical by some to randomise patients to IAA when less invasive tests appear accurate. It would also be very expensive to perform such a trial and it is difficult to obtain funding for imaging studies, which are often seen as being of secondary importance to treatment trials.

The alternative approach is to model the process of assessing patients with symptomatic carotid disease, and determine mathematically the effect of replacing IAA with a less invasive test. Therefore a group of experts in stroke, neurovascular imaging, statistics, health economics and healthcare modelling was established, whose combined expertise and access to data was used to construct and populate a model to reflect the process of care of stroke prevention as accurately as possible.

Objective

The aim was to construct a mathematical model to simulate the experience of patients who had suffered a TIA or minor stroke. This model would then be used to calculate the effect on number of strokes, MIs, costs, QALYs and cost-effectiveness of different diagnostic algorithms for ascertaining whether the patient was suitable for CEA. The model would take account of differences in accuracy, costs, times to imaging and other practical implications of less invasive tests, used alone or in combination, with sensitivity analyses to check the effect of any assumptions.

Methods

It was assumed that CEA would be offered to patients with 70–99% symptomatic carotid stenosis (on NASCET criteria).[4] Patients with stenoses less than 70% (NASCET) or patients in whom the carotid artery had occluded would be offered medical therapy only. Sensitivity analyses were conducted to analyse the effect of lowering the threshold of surgical interventions to 50% stenosis. The model assumed that patients were identified in primary care or emergency departments and were then referred to an outpatient stroke prevention clinic, with no new medical treatment given before the outpatient clinic appointment.

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Model structure

A transition state model was constructed[201] to simulate the number of adverse events that occur in patients. The transition states included in the model were stroke (fatal or non-fatal), MI (fatal or non-fatal) and death due to all other causes. No distinction was made between strokes and MI caused through investigative procedures and those that occurred naturally.

The model only used one transition state for stroke, with cost and utility values calculated using a weighted average of the number of disabling and non-disabling strokes. The effects of cranial nerve palsy following surgery were considered, but this was not included as a transition state. A simplified flow diagram of the disease pathway is shown in *Figure 29*. The states of fatal stroke, fatal MI, surgical death and death through natural causes are absorbing states and cannot be exited once entered.

The model cycled through periods, starting with the day of the incident, and assigned patients into transition states based on the probability of each event occurring. Upon entering a transition state, a cost associated with the event is immediately incurred, as is any reduction in the quality of life experienced by the patient. In addition, longer term costs and quality of life values were assigned to take into account the ongoing costs of treatment and the possibility of a permanent detriment in utility.

In the period following the initial transition state, the patients were reassigned into subsequent transition states, in accordance with the probability of each event occurring. The current transition state may influence the probability of future events and such relationships were included in the model. Iterations of periods continued until the end of the modelling horizon, which was set at 20 years.

Owing to the elevated risk of stroke in the period immediately after a TIA,[6,7,9,202,203] which attenuates over time,[5,204] the model used periods of variable length. The model used seven daily periods, followed by 27 weekly periods, and then used 4-weekly periods until the end of the modelling horizon (20 years).

The beneficial effects of medical intervention were incorporated by reducing the risks of stroke and MI in accordance with efficacy values from RCTs and systematic reviews of these treatments (see below).[205–210]

The beneficial effects of surgery on reducing stroke risk and the possibility of surgical complications or complications through angiography were incorporated using the values from RCTs (details given below).[4,13,14,211–215]

For both medical therapy and surgery it was assumed that any effect would begin in the period in which the intervention was initiated.

The following outputs are produced from the model:

- the number of fatal and non-fatal strokes that have occurred at 28 days, 1 year and 5 years (including strokes suffered during angiography or surgery)
- the number of fatal and non-fatal MIs that have occurred at 28 days, 1 year and 5 years
- the number of surgical deaths suffered
- the total costs for the cohort of patients, including the costs of investigations, surgery (where applicable), medical intervention costs and the costs of any events
- the total life-years accrued for the cohort of patients
- the total QALYs accrued for the cohort of the patients.

The QALY combines increased life expectancy and improvements in health status by assigning to each period a weight ranging from 0 to 1, corresponding to the health-related quality of life during that period, where a weight of 1 corresponds to optimal health and a weight of 0 corresponds to a health state judged to be equivalent to death.[216] The QALY approach uses a utility value to 'quality adjust' survival; thus, a person expected to survive for 10 years at a quality of 0.8 has 8 QALYs. The benefits of a treatment that increases survival at a utility of 0.8 (from 10 to 20 years) or improves the quality of the 10 years (from 0.8 to 0.9) can be valued in terms of the QALY gain (i.e. gains of 8 and 1, respectively).

By comparing results from runs with different parameters, incremental cost-effectiveness ratios can be calculated. These can be provided in terms of cost per QALY gained, cost per life-year gained, cost per stroke avoided or cost per MI avoided at chosen time-points.

Population of the model

Epidemiological data: profile of patients who have suffered a TIA

Only patients aged 55 years and over and who were non-disabled were considered in the model.

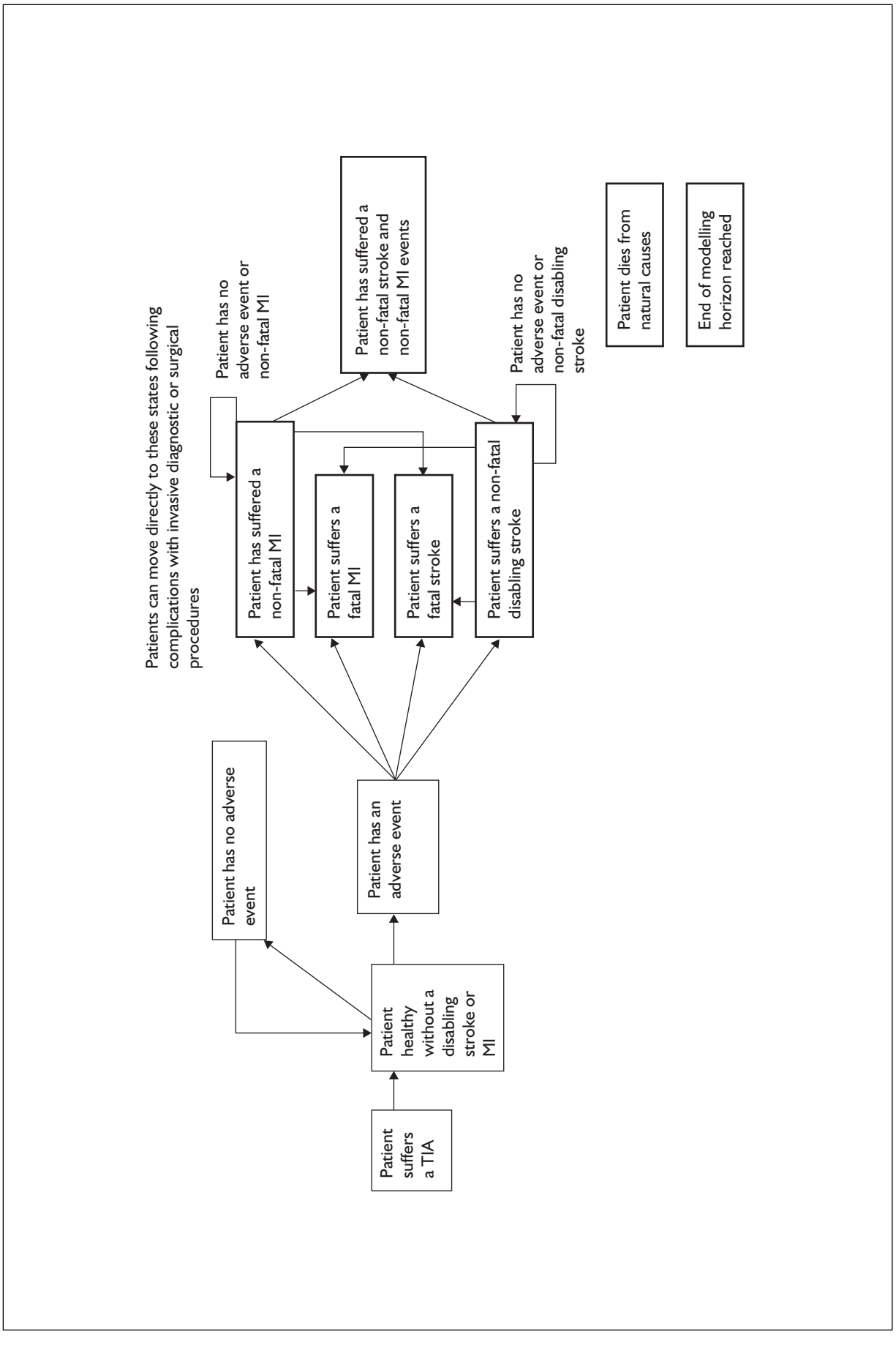

FIGURE 29 *Simplified schematic model to simulate the experience of patients who have suffered a TIA or minor stroke*

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TABLE 55 *Expected number of TIAs and minor strokes per annum in a standard population of 500,000 people*

	Age (years)				
	55–64	**65–74**	**75–84**	**≥85**	**Total**
Male	22.5 (5%)	66.3 (14%)	63.4 (13%)	25.7 (5%)	177.9 (36%)
Female	30.1 (6%)	65.3 (13%)	130.7 (27%)	86.0 (18%)	312.1 (64%)
All	52.3 (11%)	131.7 (27%)	194.2 (40%)	111.6 (23%)	490.0

Figures in parentheses indicate the percentage of the total number of TIAs or minor strokes.
Figures may not tally exactly owing to rounding.

TABLE 56 *Distribution of patients with TIA and minor stroke between stenosis bands*

Stenosis level	**Percentage of all TIAs**
70–99%	6%
50–69%	4%
0–49%, 100%	90%

The incidence of TIA per annum was taken from the OXVASC study,[217] as were the data for minor stroke, assuming that one-third of ischaemic strokes would be minor. The rates of minor stroke and TIA per age and gender band were applied to a hypothetical population of 500,000 with an age and gender mixture equal to that of England and Wales[218] which resulted in an estimated 490 minor strokes and TIAs per annum. This resulted in estimated numbers of TIAs and minor strokes per annum as given in *Table 55*.

Owing to the significant correlation between stenosis level and the risk of stroke[204] the TIAs and minor strokes were subdivided into those occurring in patients with a stenosis level of 70–99%, those in patients with a stenosis level of 50–69%, and those in patients where stenosis was less than 50% or where the carotid artery had occluded. The percentages of patients suffering a TIA or minor stroke that fall into these stenosis bands are given in *Table 56* and were assumed to be the same as those patients in the Lothian Stroke Register. It was assumed that the stenosis distribution in patients with a minor stroke was identical to that of patients with a TIA.

These groups were further subdivided between patients who were currently taking aspirin and those who were not, as this could affect the magnitude of benefit of initiating medical therapy at an earlier stage, where a diagnostic algorithm would result in treatment being initiated more rapidly (*Table 56*). It was assumed that 51% of patients would be on aspirin at the time of their TIA or minor stroke.[6,217]

It was assumed that these distributions are independent of age and gender, as there were no reliable population-based data on the age and gender distribution of patients with TIA or minor stroke that also gave information on the degree of carotid stenosis.

The risks of stroke and MI for patients within the same carotid stenosis band were assumed to be homogeneous; however, death through all other causes would vary within stenosis bands depending on the age and gender of the patient.

The risks of stroke in relation to the degree of stenosis

The longer term risks of stroke following a TIA have been well described.[4,219] However, recent data have shown that the risk in the first 3 months after an incident TIA is much higher than previously thought.[6,7,9,202] Data were available on the longer term risk stratified by stenosis level,[4] but no short-term data were available.[6] Therefore, it was assumed that the ratio of risks between stenosis bands observed in the initial year in the carotid surgery trials[4] was also applicable to the initial 3-month period. The assumed risks associated with the patients in these trials are presented in *Table 57*.

Risk of stroke in relation to medical treatment

The carotid surgery trials reported the risks of stroke following medical treatment. Antiplatelet treatment and blood pressure-lowering drugs were prescribed in the NASCET, ECST and Veterans Administration (VA) CEA trials.[4] Lipid-lowering drugs are now in widespread use and in the recent

TABLE 57 *Risk of stroke in medically-treated patients by time after TIA or minor stroke and stenosis band*

Cumulative risk of stroke in medically treated patients	Stenosis level		
	0–49, 100% and occluded	50–69%	70–99%
1 week	7%	8%	13%
1 month	9%	12%	19%
3 months	14%	18%	29%
15 months	20%	25%	39%
27 months	23%	30%	45%
39 months	26%	33%	48%

OXVASC epidemiology study, 32% of patients with TIA and 24% of those with minor stroke were on lipid-lowering agents at the time of their stroke (*Table 57*).[6]

To calculate the risks of stroke in patients who remained untreated for a period after their TIA or minor stroke, it was assumed that the efficacy of medication seen in RCTs would apply (see the section 'Efficacy of medical treatment', pp. 78–9).[205–210]

Long-term risks of stroke after TIA in the presence of carotid stenosis

It was assumed that 39 months after a TIA or minor stroke (i.e. by just over 3 years) the risks of stroke were equal regardless of stenosis level. The risk of stroke in treated patients after 3 years has been set as 2.3% per annum and is the weighted average of data presented by Clark[220] Cunningham[221] and Barnett and colleagues.[222] Therefore, immediately following successful endarterectomy in the model, the risk of stroke was set to 2.3% per annum, assuming it to be the same as in patients who had survived for 3 years or more since a TIA or minor stroke.

Long-term outcomes after stroke

The proportion of patients dying, or surviving in a dependent or independent state after stroke according to the Rankin score, by age of patient, was taken from the Lothian Stroke Registry.[223,224] A Rankin score of 0–2 indicates independent survival, a score of 3–5 indicates survival in a dependent state, and 6 is dead. The Lothian Stroke Registry is a hospital-based register of all patients with TIA or stroke attending the Western General Hospital in Edinburgh, collected between 1990 and 1999. The Western General Hospital has a catchment population of 500,000 and serves North Edinburgh. These data are not truly community based, as patients who die before hospital admission are not included in the Registry, but there were no comparable data on long-term outcome after stroke from any of the epidemiological studies published to date. The outcome values derived from the Lothian Stroke Registry are provided in *Table 58*.

These values are broadly similar to those presented by Bond and colleagues[211] where for all patients the fatality rate was 13%. The rates of disabling stroke and non-disabling stroke were 30% and 57%, respectively.

Increased risk of all-cause mortality following a stroke

Following stroke, the risk of death is increased 2.5-fold compared with patients of the same age and gender without stroke, as reported in the Perth Community Stroke Study,[225] with this effect persisting until death.

Risks of MI

The risk of MI or cardiovascular death following a TIA or non-haemorrhagic minor stroke was taken from Clark[220] and was 27.8% at 10 years, which equates to 3.2% per annum. It was assumed that these patients were taking antiplatelet therapy and blood pressure-lowering medication. The risk for patients not on antiplatelet or antihypertensive treatment was calculated assuming the efficacy of treatment as seen in RCTs (see the section 'Efficacy of medical treatment', pp. 78–9).[205–210] It was assumed that the fatality rates associated with MI were, for men, 35% for ages 55–64 years and 48%, 69% and 82% for age bands 65–74 years, 75–84 years and 85 years and older, respectively; and for women, 31%, 55%, 77% and 90%, respectively. These values were calculated by the authors from data reported by Volmink and colleagues.[226]

Risks associated with CEA

The risks associated with CEA were taken from a systematic review and meta-analysis of

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TABLE 58 *Outcome at 6 months after stroke by age of the patient*

	Outcome after stroke		
Age of patients (years)	**Rankin score 0–2**	**Rankin score 3–5**	**Fatality**
55–64	76%	22%	2%
65–74	79%	17%	4%
75–84	73%	21%	6%
≥85	52%	39%	10%

TABLE 59 *Summary of studies of risk of stroke and other complications after IAA for investigation of carotid stenosis*

	% Complications				
Study	**Stroke**	**TIA**	**Local**	**MI/other**	**Death**
Hankey, 1990[13]	1.3	1.3	0.5	0.5	0
Davies, 1992[14] Young, 1992[215]	3	5	3	1	2
Weir, 1999 (unpublished data)	3	3	1.5	5	
Cloft, 1999[214]	3.7	3			
Mean	2.4	6	2	2.5	1

symptomatic patients undergoing CEA.[4] The estimated risk of death was 1.1% and the risk of non-fatal stroke was 6.0%. This review showed that the risk of surgery was the same for patients with TIA and stroke. This work also showed no increase in mortality or complications with surgery performed early after stable stroke or TIA compared with surgery performed after a time-lapse, although the benefit of surgery was greatest when surgery was performed quickly after TIA or stroke (in patients with evolving stroke symptoms the risk of surgery was higher).[227] It was assumed that the risk of a non-fatal MI following CEA was 0.6%, using data from Barnett and colleagues[212] and Bond and colleagues[211] and that the risk of a cranial nerve palsy was 6.4%.[211]

Risks associated with an angiogram

The risk of stroke following an angiogram was set to 1% based on data presented in Johnston,[213] Hankey,[13] Cloft,[214] Davies and Humphrey[14] and Young and Humphrey (*Table 59*).[215] Although some studies suggested a higher risk of stroke, these included non-disabling stroke. Therefore, this study adopted a 1% risk of disabling stroke as the important risk. It was assumed that angiography carried a 0.1% risk of death. The data on MI after angiography were poor. Although the authors appreciate that MI is a complication of IAA for investigation of ischaemic cerebrovascular disease, there were inadequate data on which to base an assessment and therefore the risk of MI was omitted from the model. However, the main risks of disabling stroke and death were included.

Risks of death through other causes

The risks of death through other causes were taken from UK life tables.[228] These values were adjusted to avoid double counting of deaths through stroke, MI or unsuccessful CEA.

Efficacy of medical treatment

It was assumed that following a TIA a patient will be prescribed aspirin and dipyridamole, a blood pressure-lowering drug and a lipid-lowering drug.

Assumed efficacy of aspirin

It was assumed that in the initial 3-month period following a TIA, aspirin produced a 23% relative risk reduction for stroke (95% CI 13 to 31%).[205] After this period it was assumed that efficacy fell to a 15% relative risk reduction (95% CI 6 to 33%).[206] Patients already taking aspirin at the time of the TIA were assumed to have a constant 15% risk reduction of stroke throughout the duration of the model. The impact of aspirin on MI was assumed to be constant at 27% (95% CI 12 to 39%), calculated using data for combined antiplatelet therapy from the Antithrombotic Trialists' Collaboration trial.[207]

Assumed efficacy of dipyridamole

It was assumed that the additional use of dipyridamole added a further 10% relative risk reduction for stroke compared to aspirin alone.[208]

Assumed efficacy of blood pressure-lowering drugs

Data on the efficacy of blood pressure-lowering drugs were taken from the Progress Trial (2001).[209]

TABLE 60 *Assumed efficacy of combinations of medical therapy*

Time since initiation of medical therapy	Reduction in stroke risk	Reduction in MI risk	Drugs assumed to be affecting risks
<3 months[a]	33%	27%	Aspirin and dipyridamole
3–6 months	25%	27%	Aspirin and dipyridamole
6–12 months	47%	35%	Aspirin, dipyridamole and blood pressure-lowering drugs
1 year and beyond	55%	54%	Aspirin, dipyridamole, blood pressure-lowering drugs and lipid-lowering drugs

[a] Patients already taking aspirin at the time of their TIA are assumed to have less risk reduction than patients starting aspirin *de novo*; therefore, data from the 3–6 months row will be applied.

The relative reduction in non-fatal stroke was 42% (95% CI 29 to 53%) and the relative reduction in non-fatal MI 42% (95% CI 11 to 62%). From analysis of the graphs presented in the PROGRESS Trial,[209] it was assumed that the effects of blood pressure-lowering drugs would not be manifest until 6 months after starting treatment (although clearly the drugs would be pharmacologically active as soon as they were started).

Assumed efficacy of lipid-lowering drugs

The efficacy of lipid-lowering drugs was taken from Kaste.[210] The relative reduction in stroke was assumed to be 25% (95% CI 15 to 34%), while the reduction in MI was 38% (95% CI 29% to 45%). Data from the Heart Protection Study[229] imply that lipid-lowering drugs have a slow onset of effect. Accordingly, it was assumed that the effects of lipid-lowering drugs were not realised for 12 months from the start of therapy.

Estimating the combined efficacy of aspirin, dipyridamole, blood pressure-lowering drugs and lipid-lowering drugs

Few data are available on the combined efficacy of different classes of drugs. It has been hypothesised that the drugs work independently and additively, and that a reduction in stroke of 75% can be obtained (Professor R Collins: personal communication, June 2004).[230]

It was assumed that the drugs are independent and the mean efficacy estimates for aspirin and dipyridamole were used but, in view of the controversy and lack of direct data, this study conservatively used the lower 95% confidence intervals for blood pressure- and lipid-lowering drugs. The reductions in stroke and MI assumed for a patient receiving all drugs are given in *Table 60*. Note that patients already taking aspirin at the time of their TIA or minor stroke are assumed to have less risk reduction from continuing to take aspirin than would a patient starting aspirin *de novo*; therefore, the data on risk reduction between 3 and 6 months were applied (*Table 60*).

Cost and QALY data

The costs of investigative procedures were obtained in the systematic review and costing exercise described in Chapter 5, summarised in *Table 50*. The costs associated with outpatient visits, carotid surgery and adverse events used in the model are those reported in Chapter 5, *Tables 51*, *52* and *54*. The data on QALYs after stroke came from the study by Dorman and colleagues (Chapter 5). Dorman's study used the EuroQol[231] to measure the health status of 867 UK patients enrolled in the International Stroke Trial. The utility values were 0.31 (95% CI 0.29 to 0.34) for dependent health states, 0.71 (95% CI 0.68 to 0.74) for independent health states and 0.88 (95% CI 0.84 to 0.92) for fully recovered health states.[231]

It was assumed that patients who die (from whatever cause) accrue no QALYs in the period in which they die. Half-cycle correction, where it is assumed that the death was likely to occur midway through the period, was not undertaken as the effect would be small owing to the short duration of the time-cycles in the present model.

Typical structure of neurovascular (stroke prevention) clinics in the UK

It was considered important to base the model on realistic times to first seeing patients after a TIA or minor stroke, investigation, obtaining results, making decisions about treatment and implementing those decisions. There was little reliable information on how long these stages took, or the typical structure of stroke prevention clinics in the UK. Members of the project group, several of whom ran stroke prevention clinics, provided the imaging investigations for those clinics or performed the CEA, were able to

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describe their own practice. However, the group was concerned that because of their particular interests, their practice might not be representative of services routinely provided in the UK in general. Therefore, it was considered important to obtain a more representative view of the organisation and timing of stroke prevention clinics, typical numbers of patients seen, proportions with ischaemic cerebrovascular disease or other conditions mimicking TIA or stroke, the use of investigations, proportions referred for endarterectomy, timing of surgery, and so on.

A questionnaire asking about the structure of stroke prevention clinics (as above) was devised and piloted on members of the project group. Stroke physicians, geriatricians and neurologists were identified from a list of potential UK collaborators in the Third International Stroke Trial, and the questionnaire was sent to them. The details of the questionnaire and the responses are given in Appendix 13.

The main findings of the survey were that most centres surveyed held stroke prevention clinics twice a week and saw six to ten patients per clinic at between eight and 21 days after the TIA. Most respondents said that 40–60% of the patients referred were ultimately diagnosed as having carotid territory symptoms. Most clinics were run by consultants, the initial carotid imaging test was US in all but one clinic, in eight out of 17 cases this was performed on the same day as the outpatient assessment and important results were passed back to the clinic on the same day. The imaging test used to confirm significant carotid stenosis was more variable (nine IAA, eight CEMRA, five US, three CTA and two MRA; some clinics used different tests, hence the numbers do not add up to 17). In most centres, CEA was performed within 1 month of taking the decision to operate, and no centres were performing CEA more than 6 months after referral. The full details of the survey are given in Appendix 13. Although the survey is in no way intended to be a comprehensive examination of the provision of stroke prevention services in the UK, it does provide a range of scenarios and data for the model.

Devising diagnostic algorithms

Individual hospitals may have access to different types of less invasive imaging tests. In some hospitals only one modality may be available, whereas in others there may be a choice of several. Furthermore, there may be differences in the availability of some tests, so that the choice of which test to use may depend on the balance of accuracy, availability and cost. For these reasons, it was felt important to model a number of different usages (algorithms) of the less invasive tests compared with the reference standard. This would allow individual hospitals to identify the algorithm that most closely resembled their availability of tests, and to see how changing to another algorithm may affect their stroke prevention, costs or QALYs.

The following diagnostic tests were considered: US, CTA, MRA, CEMRA and IAA. The combinations shown in *Table 61* were chosen to reflect real-life availability of tests and were analysed within the model. These vary the stenosis level at which a confirmatory imaging test would be done, different combinations of initial and confirmatory tests, and different stenosis levels at which surgery would be offered. The stenosis levels used within the strategies refer only to the symptomatic artery. Note that the strategies were restricted to those for which there were reasonable data; for example, no strategies were included where two less invasive tests would be used to identify 50–99% stenosis before proceeding to surgery as there were relatively few data on sensitivity or specificity of less invasive tests in identifying 50–99% stenosis. The base comparator is: perform US first and if it shows 50–99% stenosis in the symptomatic internal carotid artery, then carry out an IAA and proceed to endarterectomy in those with 70–99% stenosis.

Applying the sensitivity and specificity of diagnostic tests in the model

The methodology used for determining the sensitivity and specificity of each less invasive imaging test is given in Chapter 3. It was assumed that angiography has 100% sensitivity and 100% specificity. The assumed sensitivity and specificity for each test by stenosis band is provided in *Table 62*.

Determining the number of patients who might be misdiagnosed by a less invasive test

Additional analyses were performed to determine how frequently a misdiagnosis would alter the treatment offered to the patient. For example, consider a patient who in reality had a 50–69% stenosis. Misdiagnosing this patient as having 0–49% carotid artery stenosis or occlusion would not alter the decision to offer medical treatment only. However, if this patient had been categorised on imaging as 70–99% stenosis, the patient would be 'incorrectly' offered surgery.

TABLE 61 *Diagnostic strategies used in the cost-effectiveness model*

Strategy no.	Strategy description
Baseline	One US alone; if 50–99% stenosis, proceed to IAA; surgery if 70–99%
1	One US alone; if 70–99% stenosis, proceed to surgery
2	One CTA alone; if 70–99% stenosis, proceed to surgery
3	One MRA alone; if 70–99% stenosis, proceed to surgery
4	One CEMRA alone; if 70–99% stenosis, proceed to surgery
5	One US; if 70–99% stenosis, then repeat US. If agreement, i.e. if both 70–99% stenosis, then offer surgery; if disagreement base on MRA
6	As 5, but deciding test is CEMRA
7	As 5, but deciding test is CTA
8	As 5, but deciding test is IAA
9	One US; if 50–99% stenosis, then repeat US. If both USs are below 70% do not offer surgery; if agreement 70–99% offer surgery; if disagreement base results on MRA
10	As 9, but deciding test is CEMRA
11	As 9, but deciding test is CTA
12	As 9, but deciding test is IAA
13	One US; if 70–99% stenosis, then do MRA. If agreement offer surgery; if disagreement base on CEMRA
14	As 13, but deciding test is CTA
15	As 13, but deciding test is IAA
16	One US; if 70–99% stenosis, then do CTA. If agreement offer surgery; if disagreement base on CEMRA
17	One US; if 70–99% proceed to IAA; if agreement, proceed to surgery
18	One US alone; if 50–99% proceed to surgery
19	One CTA alone; if 50–99% proceed to surgery
20	One MRA alone; if 50–99% proceed to surgery
21	One CEMRA alone; if 50–99% proceed to surgery

TABLE 62 *Results of the meta-analyses for patients by stenosis band and diagnostic test*

Stenosis group	Imaging	Sensitivity (95% CI)	Specificity (95% CI)
70–99%	US	0.89 (0.85 to 0.92)	0.84 (0.77 to 0.89)
	CTA	0.80 (0.70 to 0.87)	0.95 (0.91 to 0.97)
	MRA	0.8730 (0.81 to 0.92)	0.86 (0.78 to 0.97)
	CEMRA	0.9403 (0.88 to 0.97)	0.93 (0.89 to 0.96)
50–69%	US	0.36 (0.25 to 0.49)	0.91 (0.87 to 0.94)
	CTA	0.67 (0.30 to 0.90)	0.79 (0.63 to 0.89)
	MRA	0.37 (0.26 to 0.49)	0.91 (0.78 to 0.97)
	CEMRA	0.7736 (0.59 to 0.89)	0.97 (0.93 to 0.99)
0–49,100%	US	0.83 (0.73 to 0.90)	0.84 (0.62 to 0.95)
	CTA	0.81 (0.59 to 0.93)	0.91 (0.74 to 0.98)
	MRA	0.81 (0.70 to 0.88)	0.88 (0.76 to 0.95)
	CEMRA	0.96 (0.90 to 0.99)	0.96 (0.90 to 0.99)

The proportions of times that misdiagnoses in the 0–49% stenosis or occluded groups and 50–69% stenosis groups result in a patient being classified as 70–99% stenosis are given in *Tables 63–66*. This information was obtained from studies in which the same patients had two or more less invasive tests in the IPD meta-analysis (Chapter 4). There was virtually no information in the literature (Chapter 3) on the performance of less invasive tests in the same patients. Although some studies performed more than one less invasive test, it was often in overlapping groups of patients rather than actually in the same patients. It was therefore not possible to use these data directly.

Observer variability of IAA

To put the performance of the less invasive tests into context, it is worth considering the observer variability of IAA. The observer variability in the interpretation of IAA has been examined in several studies. Vanninen and colleagues[232] compared four observers' interpretations of 41

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TABLE 63 *Misdiagnosis distribution for US*

	Misdiagnosed band		
Actual stenosis band	**0–49, 100%**	**50–69%**	**70–99%**
0–49, 100%	NA	36%	64%
50–69%	24%	NA	76%
70–99%	13%	87%	NA

TABLE 64 *Misdiagnosis distribution for CTA*

	Misdiagnosed band		
Actual stenosis band	**0–49, 100%**	**50–69%**	**70–99%**
0–49, 100%	NA	88%	12%
50–69%	60%	NA	40%
70–99%	18%	82%	NA

TABLE 65 *Misdiagnosis distribution for MRA*

	Misdiagnosed band		
Actual stenosis band	**0–49, 100%**	**50–69%**	**70–99%**
0–49, 100%	NA	63%	37%
50–69%	18%	NA	82%
70–99%	42%	58%	NA

TABLE 66 *Misdiagnosis distribution for CEMRA*

	Misdiagnosed band		
Actual stenosis band	**0–49, 100%**	**50–69%**	**70–99%**
0–49, 100%	NA	79%	21%
50–69%	36%	NA	64%
70–99%	53%	47%	NA

patients' angiograms (80 arteries) and found kappa values for inter-rater reliability of 0.79 (ECST) and 0.69 (NASCET). Rothwell and colleagues[72] compared two observers' readings of 1001 angiograms and found kappa values for inter-rater agreement of 0.66 ± 0.02 (ECST), 0.72 ± 0.02 (NASCET) and 0.76 ± 0.02 for the CCA method for categorising the stenoses into mild moderate or severe groups. Observer A classified 36/1000 as moderate stenosis that observer B classed as severe, B classed 56/1000 as moderate that A classed as severe, A classed 47/1000 as moderate that B classed as mild, and B classed 40/1000 as moderate that A put into the mild group. Thus, overall about four to six of every 100 patients were put in different stenosis groups because of observer variability. Young and colleagues[233] compared three observers' readings of 179 intra-arterial angiograms in 99 patients and found kappa values of 0.6–0.7 using the

TABLE 67 *Conditional probability of a second US finding the same result as an initial US*

		Likelihood of second test falling in the specified band		
Initial reading	***n***	**0–49%**	**50–69%**	**70–99%**
0–49%	77	91%	4%	5%
50–69%	77	13%	58%	29%
70–99%	130	8%	6%	86%

n, numbers of initial readings in the specified stenosis bands.

TABLE 68 *Conditional probability of a second MRA finding the same result as an initial MRA*

		Likelihood of second test falling in the specified band		
Initial reading	***n***	**0–49%**	**50–69%**	**70–99%**
0–49%	15	100%	0%	0%
50–69%	5	80%	20%	0%
70–99%	2	0%	100%	0%

n, numbers of initial readings in the specified stenosis bands.

TABLE 69 *Conditional probability of a second CEMRA finding the same result as an initial CEMRA*

		Likelihood of second test falling in the specified band		
Initial reading	***n***	**0–49%**	**50–69%**	**70–99%**
0–49%	53	81%	17%	2%
50–69%	27	7%	70%	22%
70–99%	49	0%	20%	80%

n, refers to the numbers of initial readings in the specified stenosis bands.

ECST method. They found that clinically important differences occurred between pairs of observers in 7/179 (4%), 6/179 (3%) and 11/179 (6%) of arteries, similar to the findings of Rothwell and co-workers. These differences are clearly much less than those found between the less invasive tests.

Effect of combining diagnostic tests on the number of patients likely to be misdiagnosed: 'conditional probabilities'

In the absence of data, it was assumed that the less invasive tests performed independently of each other. This assumes that there is no correlation between the results of one test and the results from another test. Clearly, this is unlikely to be the case (e.g. two USs conducted on the same patient are likely to show similar findings), but it was easier to handle the data in this way than to assume relationships that may in turn introduce other bias into the model. At least in this way, all tests were treated the same.

A search was done for data on the variability of stenosis band readings when the same diagnostic test is repeated (Chapter 4). These data are summarised in *Tables 67–69*. Data on repeat MRA were scarce and should not be assumed to be an accurate distribution of the variability in the test.

Effect of delays occurring before each diagnostic test

The availability of each diagnostic procedure was estimated from the results of the questionnaire (Appendix 13). For each time-related question, the interviewee was given four ranges to choose from, coded 1–4. An example of such ranges is less than 1 day, less than 1 week, less than 1 month and

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TABLE 70 *Times to events as calculated from the responses to the questionnaire (Appendix 13)*

Time to (from index TIA or minor stroke)	Estimated duration since the incident (days)
Time to appointment	10
Time to initial US	11
Time to receiving US results	12
Cumulative time to the results from an additional test where test is:	
Repeat US	13
CTA	31
MRA	31
CEMRA	31
IAA	31
Additional time to endarterectomy following results of the second test	19

greater than 1 month. The responses were collated and the modal results calculated. Where the distribution was bimodal the earlier period was selected. The modal range was then translated into a time duration assuming that the midpoint of the modal range was the true delay. For example, if the mean answer from the questionnaire was the range between 1 day and 1 week, it was assumed that the delay would equate to an average of 4 days; if the modal range was between 1 week and 1 month, we have assumed that the delay would be 19 days. Given this methodology, the estimated times to each event are given in *Table 70*.

Applying algorithms in the model: some worked examples

To show how these parameter estimates and assumptions would work in the model, some worked examples are provided. In the model, patients were divided into groups dependent on their true stenosis level. The stenosis bands selected were less than 49% or occluded, 50–69% stenosis and 70–99% stenosis, as these reflect cut-off points for surgical decision-making. It was intended that patients with 70–99% stenosis would receive surgery, but owing to the inaccuracy of diagnostic tests, it is possible that patients with a stenosis level below 70% could be incorrectly diagnosed as 70–99%, while patients with a stenosis level of 70–99% could also be incorrectly diagnosed as having less severe stenoses. Where initial diagnostic tests disagree on the banding, a third test may be performed, but this may further delay the time to surgery.

The expected level of misdiagnosis and the expected delay until surgery were calculated for all the algorithms modelled. A simple example and part of a more complex example are provided here, so that the reader can understand the methodology employed.

Example 1

Algorithm 1. One US. If 70–99% stenosis, proceed to surgery.

Patients with a stenosis of 70–99%

The probability of a person with a stenosis of 70–99% being diagnosed correctly is 89% (*Table 62*). The remaining 11% will not receive surgery as they will be diagnosed into a different stenosis band with US.

Patients with a stenosis of 50–69%

The probability of a patient with 50–69% stenosis being diagnosed incorrectly is 64% (*Table 63*). The proportion of these patients that are diagnosed as 70–99% stenosis is 76%; resulting in 48% (64% × 76%) of patients with 50–69% stenosis being incorrectly diagnosed as 70–99%. The remaining 52% will not receive surgery.

Patients with a stenosis of 0–49% or an occlusion

The probability of a patient with less than 50% stenosis or an occlusion being diagnosed incorrectly is 17% (*Table 62*). The proportion of these that are diagnosed as 70–99% stenosis is 64%, resulting in 11% (17% × 64%) of patients with less than 50% stenosis or an occlusion being incorrectly diagnosed as 70–99%. The remaining 89% will not receive surgery.

As only one test is used in this algorithm, the assumed delay before surgery is 31 days for all patients. All patients will incur the cost of one US (£82).

Example 2

Algorithm 9. One US, if 50–99% stenosis, then repeat US. If agreement as below 70% stenosis do not offer surgery, if agreement 70–99% offer surgery; if disagreement base decision for surgery on MRA.

Patients with a stenosis of 70–99%
The probability of a person with a stenosis of 70–99% being diagnosed correctly is 89% (*Table 63*). Of the remaining 11%, 87% will be diagnosed as having a stenosis of 50–69% (*Table 63*), resulting in 9% (11% × 87%) of patients having a diagnosis of 50–69% stenosis. Two (rounding error) per cent (11% × 13%) of patients with a stenosis of 70–99% will be diagnosed as having a stenosis below 50% or an occlusion.

For the patients who received a diagnosis of 70–99% the probability of a second US in agreement is 86% (*Table 67*). Thus, it is expected that 77% (89%, the sensitivity of US from *Table 2* × 86%, probability of agreement) of patients with 70–99% stenoses will be offered surgery following two USs, at a cost of £164, and an expected delay of 35 days.

For the patients who received a diagnosis of 70–99% the probability of a second US diagnosing a stenosis below 70% is 14% (*Table 67*). Thus, it is expected that 12% (89% × 14%) of patients with a 70–99% stenosis will have an initial reading of 70–99% followed by a reading below 70% stenosis.

Patients with a stenosis of 50–69%
For the patients who received a diagnosis of 50–69% the probability of a second US giving a reading of 70–99% stenosis is 29% (*Table 67*). Thus, it is expected that 3% (9% × 29%) of patients with a 70–99% stenosis with have an initial reading of 50–69% followed by a 70–99% reading.

For the 15% (12% + 3%) of patients with 70–99% stenoses who have conflicting readings, an MRA would be performed. It is expected that this would give a reading of 70–99% in 89% of cases (*Table 65*). Thus, 11% (12% × 89%) of patients with a 70–99% stenosis would be offered surgery after an MRA scan, whilst 1% (12% × 11%) of patients with a 70–99% stenosis would not be offered surgery after an MRA scan. The costs for these patients would be that of two USs and an MRA scan (£309), and surgery, where appropriate, would be delayed until day 54.

The probability of a second US giving a reading of less than 70% stenosis, following an initial US of 50–69% stenosis, is 71% (*Table 67*). Therefore, 7% (9% × 71%) of patients with a 70–99% stenosis will not be offered surgery following two USs. The costs for these patients will be £164.

Patients with a stenosis of 0–49% or an occlusion
For the 4% of patients with a diagnosis of less than 50% stenosis or an occlusion, surgery will not be offered, and a cost of one US (£82) will be incurred.

The same methodology was used to distribute patients with stenoses of 50–69%, and with stenosis of less than 50% or occluded.

Discussion

The model was populated with real data in all but a very few places. Many of the estimates of probability were based on concurring data from several sources and therefore are likely to be reasonably robust. The areas where data were lacking and had to be extrapolated from other findings were in the distribution of carotid stenosis in patients with TIA or minor stroke by age and gender, the cumulative effect of multiple medical therapies (however, the estimate was conservative) and the probability of a second less invasive test finding the same result as the first. Areas where data are available but could certainly be made more robust are in the cost of imaging and the cost of stroke, as discussed in Chapter 5. The full results of the economic modelling are described in Chapter 7. The researchers plan to deal with these uncertainties by performing sensitivity analyses around the accuracy of the less invasive imaging, the times to imaging (and hence surgery), the costs of imaging and the cost of endarterectomy. Further discussion is provided at the end of Chapter 7.

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Chapter 7

Results of the cost-effectiveness analysis

Background

The approach to evaluating cost-effectiveness

Healthcare purchasers aim to maximise health gains from a limited resource. Resources may be constrained by finance, but could also involve capacity constraints, such as the number of hospital beds or time available on a US machine.

To compare interventions (pharmaceutical, surgical or diagnostic) across different disease areas, all cost-effectiveness measures must be expressed in a common denominator. Cost per life-year gained (the additional cost associated with an intervention compared to a no-treatment option, divided by the additional life-years gained compared to a no-treatment option) satisfies that criterion, but this measure is insensitive to the patient's quality of life, resulting in treatments that significantly impact on quality of life but do not prolong life having an infinite cost per life-year gained. The National Institute for Health and Clinical Excellence (NICE) has thus recommended the use of cost per quality adjusted life-year (QALY). The QALY combines increased life expectancy and improvements in health status by assigning a utility ranging from 0 to 1, corresponding to the health-related quality during a set period, where a utility of 1 corresponds to optimal health and a weight of 0 corresponds to a health state judged to be equivalent to death.[216]

The QALY approach thus 'quality adjusts' survival. A person expected to survive for 10 years at a quality of 0.8 has eight QALYs. The benefits of a treatment that increases survival at a utility of 0.8 (from 10 to 20 years), or improves the quality of the 10 years (from 0.8 to 0.9), can be valued in terms of the QALY gain (i.e. gains of 8 and 1, respectively). It is believed that NICE has set this value at £30,000 per QALY gained.[234] However, recent guidance (http://www.nice.org.uk/pdf/TAP_Methods.pdf) suggests that cost per QALY values of less than £20,000 will be deemed cost-effective, while those between £20,000 and £30,000 will need additional factors beyond the cost per QALY ratio to be deemed cost-effective. Above £30,000 the additional factors must be very strong for the intervention to be considered cost-effective.

Potential problems in interpreting cost per QALY ratios

Cost per QALY values can be difficult to interpret, as the smallest cost per QALY value is not always associated with the most optimal treatment. Thus, a treatment with a small increase in health (0.01 QALY) at a low cost (£1) would not necessarily be preferred to an intervention with higher health gains and costs (1 QALY and £10,000) despite the relative cost per QALY of the interventions being £100 and £10,000 respectively. The optimal hierarchy of interventions is calculated by ranking all interventions in order of ascending health gain and initially comparing the two least effective treatments. If the incremental cost per QALY between the more effective treatment and the lesser is below the cost per QALY threshold, the more effective treatment is selected as optimal. Similar comparisons are then iteratively conducted between the current optimal treatment and the next most efficacious treatment, until the list is exhausted, and the optimal treatment found. In the above example, the incremental cost per QALY would be £10,100 (£9,999/0.99) and if this is below an assumed threshold, the more efficacious intervention would be selected. More complex issues regarding estimating the confidence intervals of cost per QALY values exist, as the variable is not continuous. When the intervention is more costly than the comparator but the incremental health gain is zero, the cost per QALY is infinite. A slight health gain would provide high positive cost per QALY values; conversely, a slight health loss would provide a large negative cost per QALY value.

Net benefit

Owing to these potential difficulties, the use of net benefit (NB) is becoming more widespread. While these results are analogous to those presented in the more traditional cost per QALY format, there is less scope for mistakes when interpreting the data, as NB values can be directly compared across interventions and NB is a continuous variable.

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TABLE 71 *Diagnostic strategies tested in the cost-effectiveness model*

Strategy no.	Strategy description
Baseline	One US alone; if 50–99% stenosis, proceed to IAA; surgery if 70–99%
1	One US alone; if 70–99% stenosis, proceed to surgery
2	One CTA alone; if 70–99% stenosis, proceed to surgery
3	One MRA alone; if 70–99% stenosis, proceed to surgery
4	One CEMRA alone; if 70–99% stenosis, proceed to surgery
5	One US; if 70–99% stenosis, then repeat US. If agreement, i.e. if both 70–99% stenosis, then offer surgery; if disagreement base on MRA
6	As 5, but deciding test is CEMRA
7	As 5, but deciding test is CTA
8	As 5, but deciding test is IAA
9	One US; if 50–99% stenosis, then repeat US. If both USs are below 70% do not offer surgery; if agreement 70–99% offer surgery: If disagreement base results on MRA
10	As 9, but deciding test is CEMRA
11	As 9, but deciding test is CTA
12	As 9, but deciding test is IAA
13	One US; if 70–99% stenosis, then do MRA. If agreement offer surgery; if disagreement base on CEMRA
14	As 13, but deciding test is CTA
15	As 13, but deciding test is IAA
16	One US; if 70 –99% stenosis, then do CTA. If agreement offer surgery, if disagreement base on CEMRA
17	One US, if 70–99% proceed to IAA; if agreement, proceed to surgery
18	One US alone; if 50–99% proceed to surgery
19	One CTA alone; if 50–99% proceed to surgery
20	One MRA alone; if 50–99% proceed to surgery
21	One CEMRA alone; if 50–99% proceed to surgery

Net benefit is calculated from the formula:

$$NB = \lambda Q - C$$

where NB is net benefit, λ is the maximum cost per QALY that society is prepared to pay (in this example this is assumed to be £30,000), Q denotes the incremental QALY gain of the intervention, and C denotes the incremental cost of the intervention.

Where NB is positive, the treatment is cost-effective; where NB is negative, the treatment is not cost-effective; where NB is zero the cost per QALY is equal to the maximum cost per QALY that society is prepared to pay.

In this example, the NB of the first intervention would be equal to:

$$£30{,}000 \times 0.01 - £1 = £299$$

The second intervention would have an NB of:

$$£30{,}000 \times 1 - £10{,}000 = £20{,}000.$$

As both NBs are positive, both treatments are cost-effective. However, the second intervention is the more cost-effective, as it has a higher NB.

Results

Diagnostic strategies tested: a reminder

Diagnostic strategies using different less invasive carotid imaging tests were evaluated in the model. These strategies are presented in Chapter 6 (repeated in *Table 71* for clarity).

The following diagnostic tests were considered: US, CTA, MRA, CEMRA and IAA. Various combinations were chosen to reflect the real-life availability of tests. These strategies also vary the stenosis level at which a confirmatory imaging test would be done, different combinations of initial and confirmatory tests, and different stenosis levels at which surgery would be offered. The stenosis levels used within the strategies refer only to the symptomatic artery. The base comparator is: do US first and if it shows 50–99% stenosis in the symptomatic internal carotid artery, then do an IAA and proceed to endarterectomy in those with 70–99% stenosis.

Outputs of the model

The following results are presented for a cohort of 100 patients with a TIA or minor stroke. For guidance, in a standardised cohort of 500,000 patients it would be expected that 490 TIAs or

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TABLE 72 *Effect on clinical outcomes of each diagnostic strategy per 100 patients with TIA or minor stroke*

Strategy no.		All strokes at 28 days	Stroke death at 28 days	All strokes at 365 days	Stroke death at 365 days	All strokes at 5 years	Stroke death at 5 years	All MI at 28 days	MI death at 28 days	All MI at 5 years	MI death at 5 years	Surgical deaths
Baseline	US 50–99% then IAA, if 70–99% then surgery	10.58	0.72	18.59	1.43	24.60	2.32	0.10	0.20	3.57	6.70	0.07
1	US 70–99%, then surgery	10.58	0.72	18.14	1.37	23.78	2.24	0.10	0.20	3.61	6.71	0.16
2	CTA 70–99%, then surgery	10.58	0.72	18.50	1.43	24.56	2.33	0.10	0.20	3.57	6.70	0.06
3	MRA 70–99%, then surgery	10.58	0.72	18.36	1.40	24.12	2.28	0.10	0.20	3.60	6.70	0.13
4	CEMRA 70–99%, then surgery	10.58	0.72	18.43	1.42	24.47	2.32	0.10	0.20	3.57	6.70	0.06
5	US 70–99% then US, if 70–99%, then surgery, otherwise MRA	10.58	0.72	18.20	1.38	23.89	2.26	0.10	0.20	3.60	6.71	0.15
6	US 70–99% then US, if 70–99%, then surgery, otherwise CEMRA	10.58	0.72	18.20	1.38	23.90	2.26	0.10	0.20	3.60	6.71	0.14
7	US 70–99% then US, if 70–99%, then surgery, otherwise CTA	10.58	0.72	18.21	1.38	23.92	2.26	0.10	0.20	3.60	6.70	0.14
8	US 70–99% then US, if 70–99%, then surgery, otherwise IAA	10.58	0.72	18.21	1.38	23.91	2.26	0.10	0.20	3.60	6.70	0.15
9	US 50–99% then US, both 70–99% then surgery, if one 70–99% then MRA	10.58	0.72	18.18	1.37	23.85	2.25	0.10	0.20	3.60	6.71	0.15
10	US 50–99% then US, both 70–99% then surgery, if one 70–99% then CEMRA	10.58	0.72	18.18	1.38	23.87	2.25	0.10	0.20	3.60	6.71	0.15
11	US 50–99% then US, both 70–99% then surgery, if one 70–99% then CTA	10.58	0.72	18.20	1.38	23.89	2.26	0.10	0.20	3.60	6.71	0.15
12	US 50–99% then US, both 70–99% then surgery, if one 70–99% then IAA	10.58	0.72	18.21	1.38	23.89	2.25	0.10	0.20	3.60	6.70	0.15

continued

TABLE 72 *Effect on clinical outcomes of each diagnostic strategy per 100 patients with TIA or minor stroke (cont'd)*

Strategy no.		All strokes at 28 days	Stroke death at 28 days	All strokes at 365 days	Stroke death at 365 days	All strokes at 5 years	Stroke death at 5 years	All MI at 28 days	MI death at 28 days	All MI at 5 years	MI death at 5 years	Surgical deaths
13	US 70–99% then MRA. If agree then surgery, otherwise CEMRA	10.58	0.72	18.42	1.42	24.41	2.31	0.10	0.20	3.57	6.70	0.07
14	US 70–99% then MRA. If agree then surgery, otherwise CTA	10.58	0.72	18.44	1.42	24.43	2.31	0.10	0.20	3.57	6.70	0.07
15	US 70–99% then MRA. If agree then surgery, otherwise IAA	10.58	0.72	18.55	1.42	24.49	2.31	0.10	0.20	3.57	6.70	0.08
16	US 70–99% then CTA. If agree then surgery, otherwise CEMRA	10.58	0.72	18.47	1.43	24.53	2.32	0.10	0.20	3.57	6.70	0.06
17	US 70–99% then IAA. If 70–99% then surgery	10.58	0.72	18.58	1.43	24.65	2.33	0.10	0.20	3.56	6.70	0.06
18	US 50–99% then surgery	10.58	0.72	17.94	1.33	23.24	2.19	0.10	0.20	3.64	6.71	0.23
19	CTA 50–99% then surgery	10.58	0.72	18.20	1.34	23.45	2.20	0.10	0.20	3.64	6.70	0.24
20	MRA 50–99% then surgery	10.58	0.72	18.20	1.34	23.41	2.20	0.10	0.20	3.64	6.70	0.25
21	CEMRA 50–99% then surgery	10.58	0.72	18.31	1.39	24.07	2.27	0.10	0.20	3.59	6.71	0.11

TABLE 73 *Times to CEA for each diagnostic strategy*

Strategy no.	Strategy	Time to CEA (days) on one test, or if test pair agree	Delayed time to CEA (days) if third test required
Baseline	US 50–99% then IAA, if 70–99% then surgery	49	
1	US 70–99%, then surgery	31	
2	CTA 70–99%, then surgery	49	
3	MRA 70–99%, then surgery	49	
4	CEMRA 70–99%, then surgery	49	
5	US 70–99% then US, if 70–99%, then surgery, otherwise MRA	35	54
6	US 70–99% then US, if 70–99%, then surgery, otherwise CEMRA	35	54
7	US 70–99% then US, if 70–99%, then surgery, otherwise CTA	35	54
8	US 70–99% then US, if 70–99%, then surgery, otherwise IAA	35	54
9	US 50–99% then US, both 70–99% then surgery, if one 70–99% then MRA	35	54
10	US 50–99% then US, both 70–99% then surgery, if one 70–99% then CEMRA	35	54
11	US 50–99% then US, both 70–99% then surgery, if one 70–99% then CTA	35	54
12	US 50–99% then US, both 70–99% then surgery, if one 70–99% then IAA	35	54
13	US 70–99% then MRA. If agree then surgery, otherwise CEMRA	49	68
14	US 70–99% then MRA. If agree then surgery, otherwise CTA	49	68
15	US 70–99% then MRA. If agree then surgery, otherwise IAA	49	68
16	US 70–99% then CTA. If agree then surgery, otherwise CEMRA	49	68
17	US 70–99% then IAA. If 70–99% then surgery	49	
18	US 50–99% then surgery	31	
19	CTA 50–99% then surgery	49	
20	MRA 50–99% then surgery	49	
21	CEMRA 50–99% then surgery	49	

minor strokes would occur per annum (Chapter 6 and *Table 71*).[217,218]

- Clinical results: detailing the number of adverse clinical events that occur in each strategy (*Table 72*), the time to endarterectomy (*Table 73*) and the number of patients offered endarterectomy (*Table 74* and *Figure 30*) per strategy
- QALYs accrued from each strategy (*Figure 31*)
- the costs incurred from each strategy (including diagnostic and surgical costs and the costs of treating future strokes and MIs) (*Figure 32*)
- the NB compared with performing an angiogram on all patients with a US reading of greater than 49% stenosis assuming a willingness to pay a cost of £30,000 (*Figure 33*) or £20,000 (*Figure 34*) per QALY.

The researchers did not have resources to assess capacity constraints at an individual Primary Care Trust or Health Board level; in any case, this information is almost impossible to obtain in an accurate form. Therefore, the study focused on selecting the most cost-effective sequence of diagnostic tests. Strategies are highlighted that have similar NBs and alternative strategies indicated, to provide a menu of diagnostic strategies to choose from, in case the optimal strategy was logistically difficult to implement in a particular individual hospital. Also, as the value that current UK society and health purchasers are prepared to pay per QALY is uncertain, analyses have been conducted at both £20,000 and £30,000 cost per QALY.

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TABLE 74 *Proportions of patients who would undergo CEA according to each diagnostic strategy*

Strategy no.	Strategy	Total patients offered CEA	Patients with 70–99% stenosis offered CEA	Patients with 50–69% stenosis offered CEA	Patients with 0–49% stenosis or occluded offered CEA
Baseline	US 50–99% then IAA, if 70–99% then surgery	5.92	5.92	0.00	0.00
1	US 70–99%, then surgery	17.11	5.35	1.94	9.83
2	CTA 70–99%, then surgery	7.18	4.60	0.53	2.04
3	MRA 70–99%, then surgery	13.80	5.28	2.08	6.44
4	CEMRA 70–99%, then surgery	6.93	5.64	0.58	0.70
5	US 70–99% then US, if 70–99%, then surgery, otherwise MRA	15.63	3.34	1,81	8.56
6	US 70–99% then US, if 70–99%, then surgery, otherwise CEMRA	15.49	5.30	1.71	8.48
7	US 70–99% then US, if 70–99%, then surgery, otherwise CTA	15.38	5.17	1.70	8.50
8	US 70–99% then US, if 70–99%, then surgery, otherwise IAA	4.61	4.61	0.00	0.00
9	US 50–99% then US, both 70–99% then surgery, if one 70–99% then MRA	16.10	5.40	2.02	8.68
10	US 50–99% then US, both 70–99% then surgery, if one 70–99% then CEMRA	15.71	5.46	1.77	8.49
11	US 50–99% then US, both 70–99% then surgery, if one 70–99% then CTA	15.59	5.30	1.76	8.53
12	US 50–99% then US, both 70–99% then surgery, if one 70–99% then IAA	15.64	5.51	1.67	8.47
13	US 70–99% then MRA. If agree then surgery, otherwise CEMRA	7.97	5.85	1.30	0.82
14	US 70–99% then MRA. If agree then surgery, otherwise CTA	7.95	5.64	1.27	1.04
15	US 70–99% then MRA. If agree then surgery, otherwise IAA	7.63	5.92	1.01	0.70
16	US 70–99% then CTA. If agree then surgery, otherwise CEMRA	6.60	5.74	0.54	0.31
17	US 70–99% then IAA. If 70–99% then surgery	5.35	5.35	0.00	0.00

continued

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TABLE 74 *Proportions of patients who would undergo CEA according to each diagnostic strategy (cont'd)*

Strategy no.	Strategy	Total patients offered CEA	Patients with 70–99% stenosis offered CEA	Patients with 50–69% stenosis offered CEA	Patients with 0–49% stenosis or occluded offered CEA
18	US 50–99% then surgery	24.66	5.92	3.39	15.35
19	CTA 50–99% then surgery	25.98	5.75	3.20	17.03
20	MRA 50–99% then surgery	26.66	5.70	3.54	17.42
21	CEMRA 50–99% then surgery	12.84	5.81	3.67	3.36

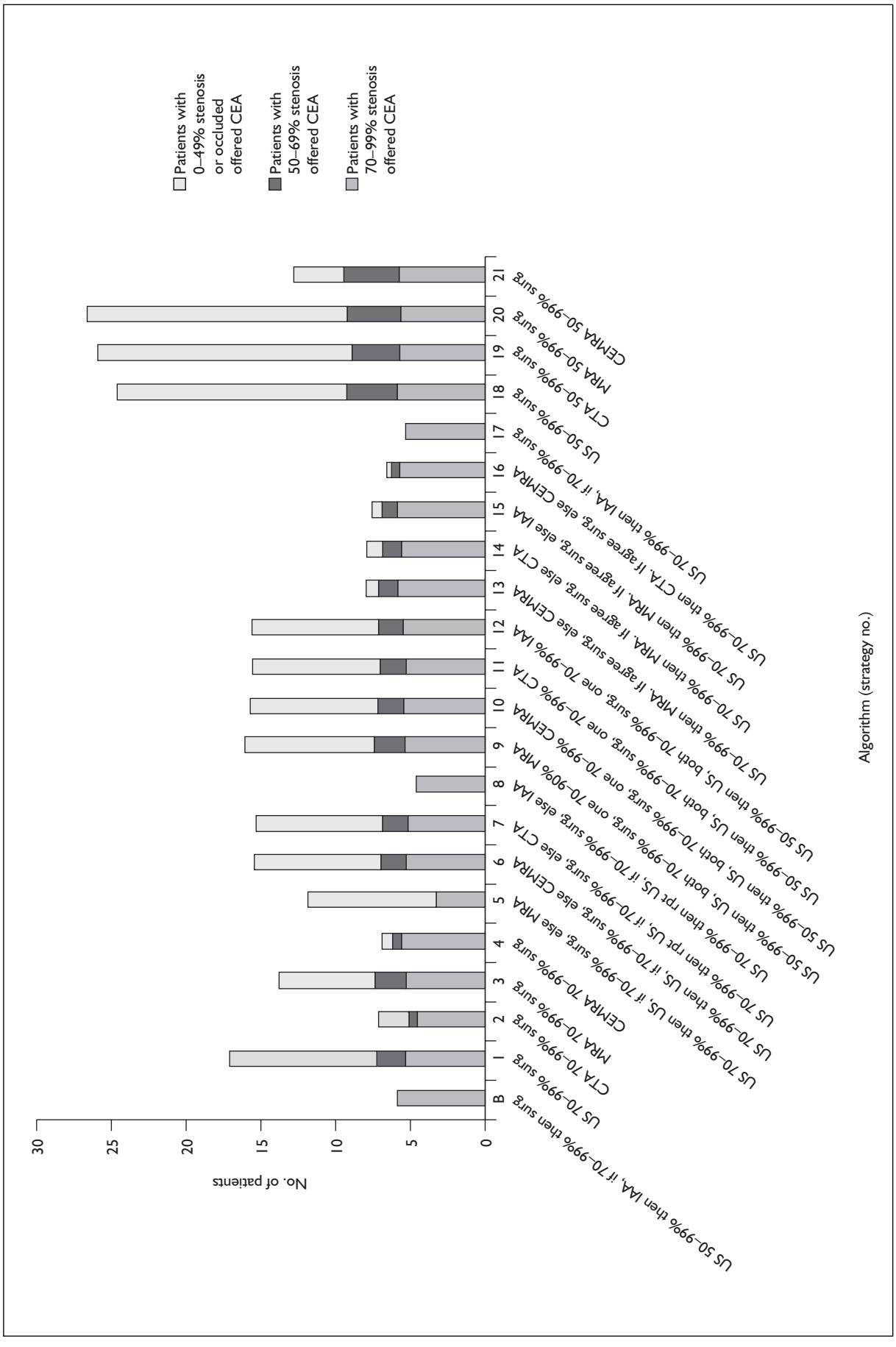

FIGURE 30 *Number of patients offered CEA per 100 patients with TIA/minor stroke by diagnostic strategy (see also* Table 74*). B, baseline comparator; surg, surgery; rpt, repeat.*

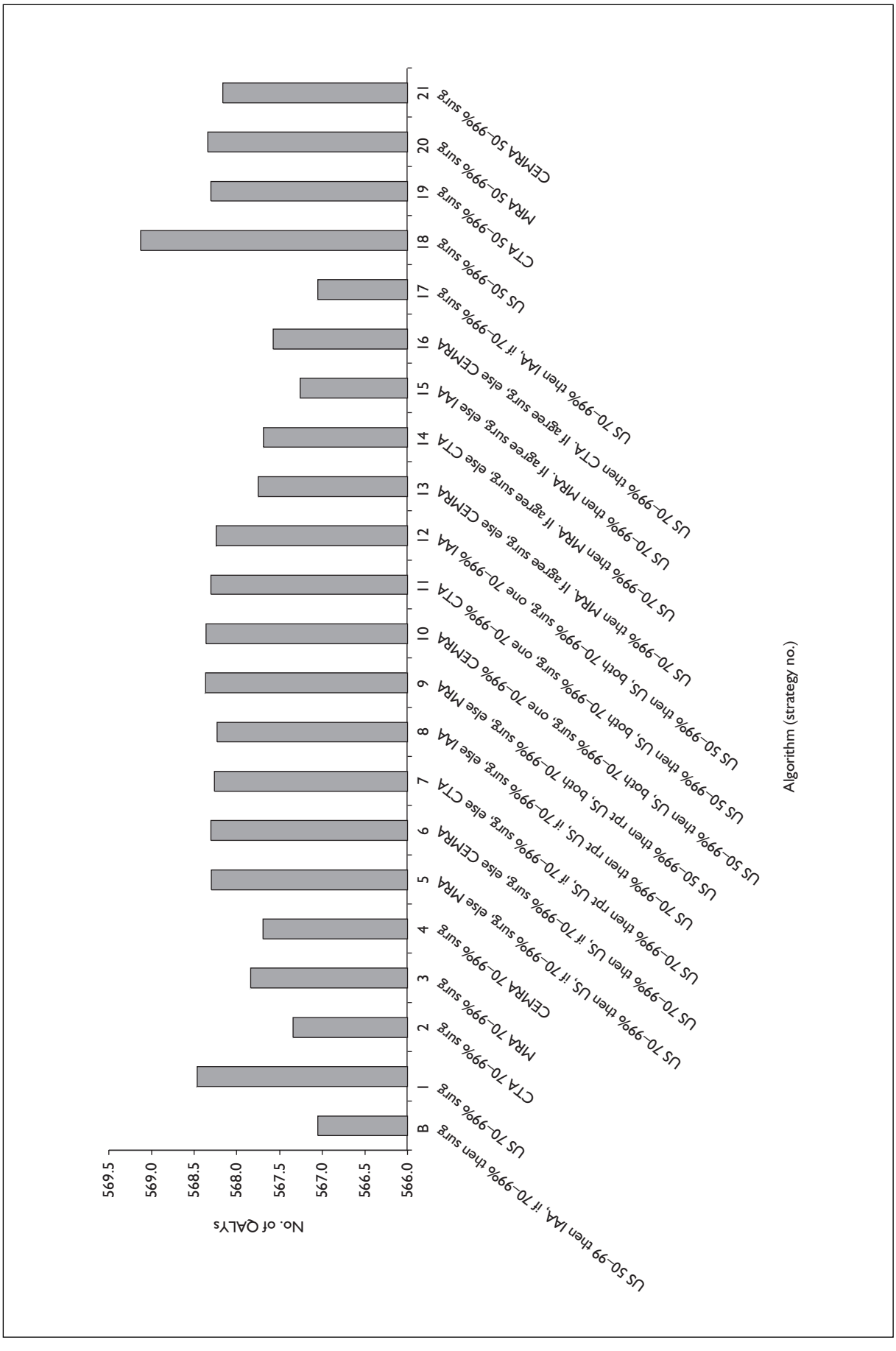

FIGURE 31 *Number of QALYs accrued over a 20-year period for secondary stroke prevention per 100 patients with TIA or minor stroke*

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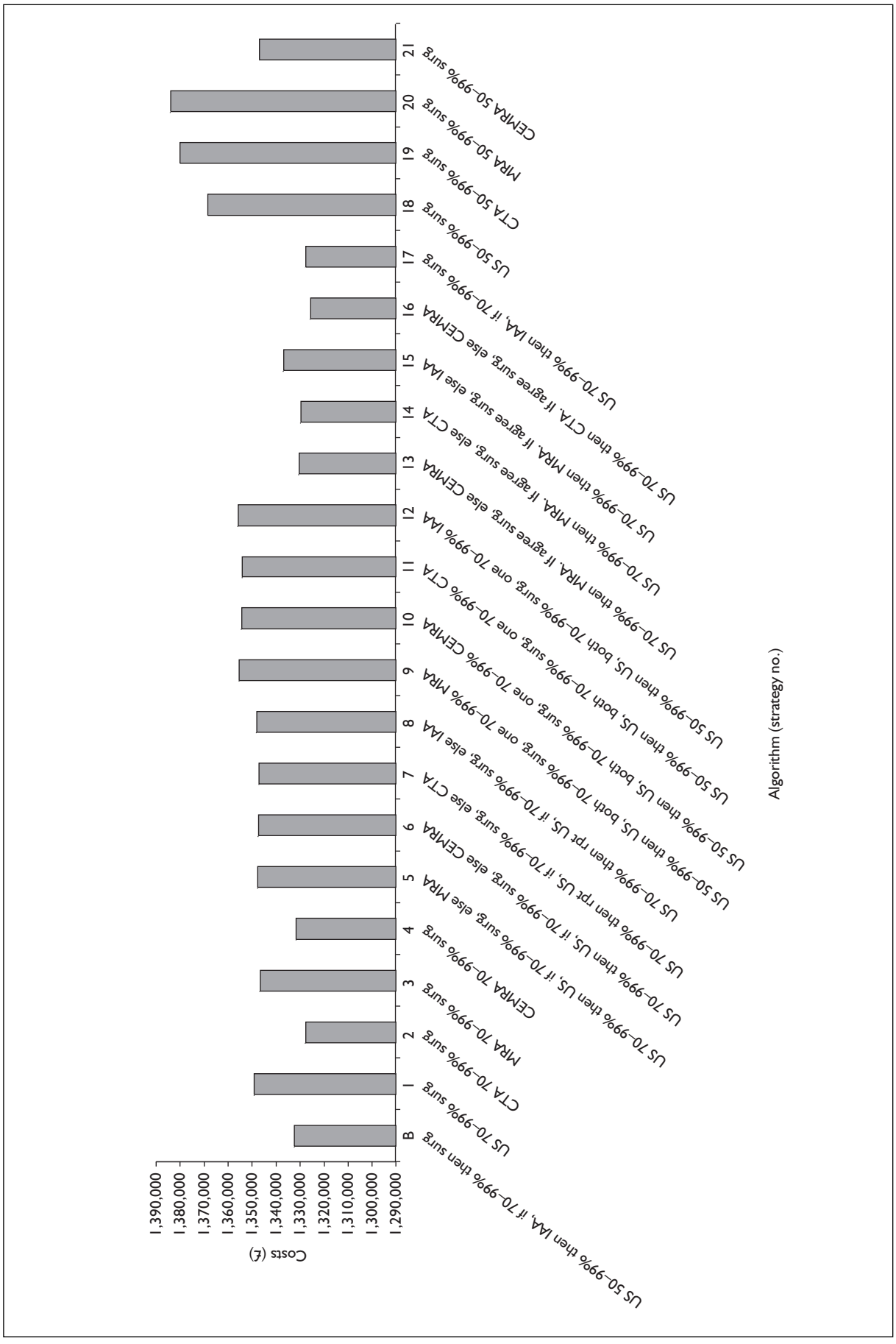

FIGURE 32 *Costs incurred over a 20-year period for secondary stroke prevention per 100 patients with TIA or minor stroke*

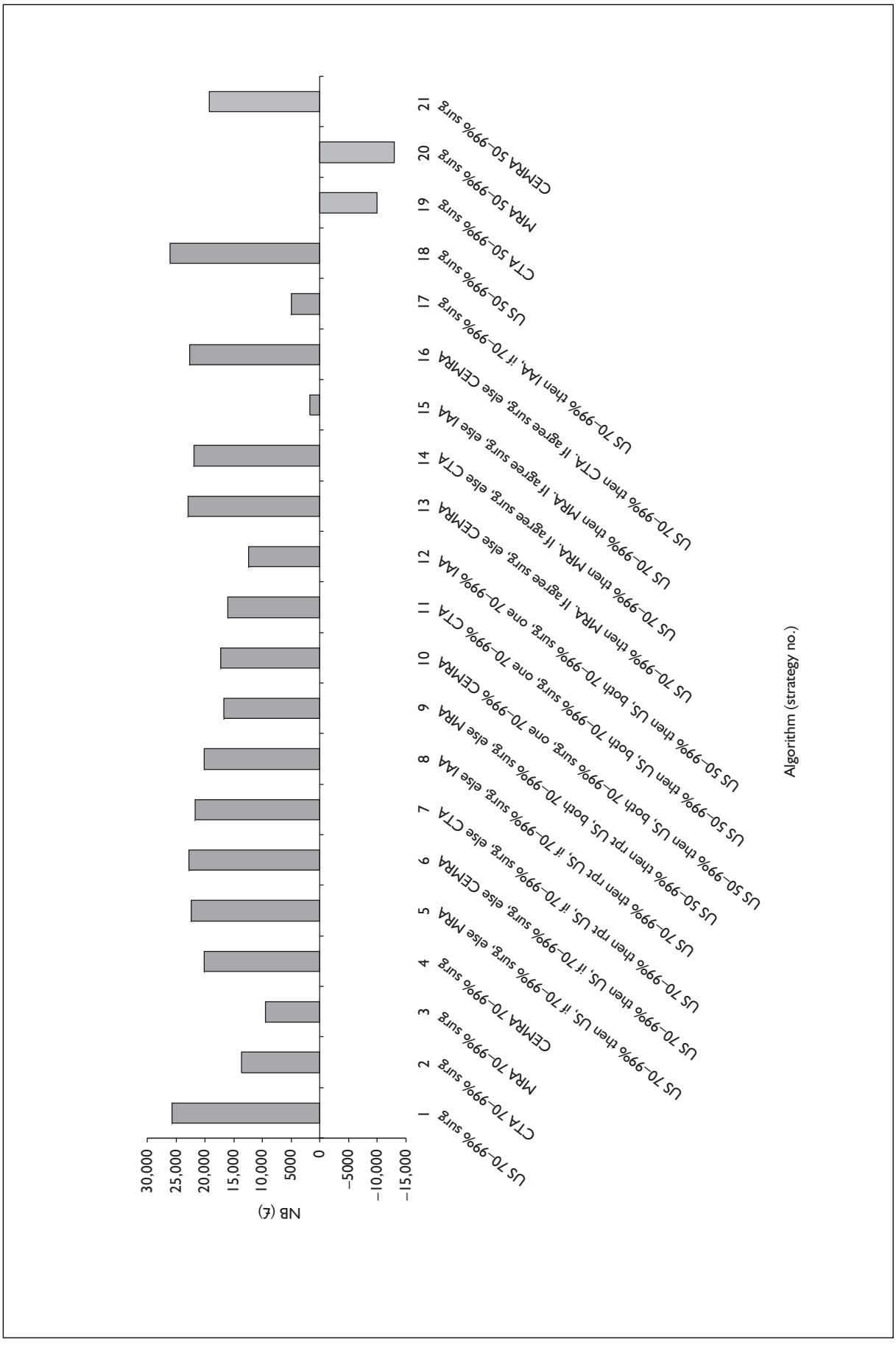

FIGURE 33 *Net benefit over a 20-year period for secondary stroke prevention per 100 patients with TIA or minor stroke. Willingness to pay £30,000 per QALY assumed.*

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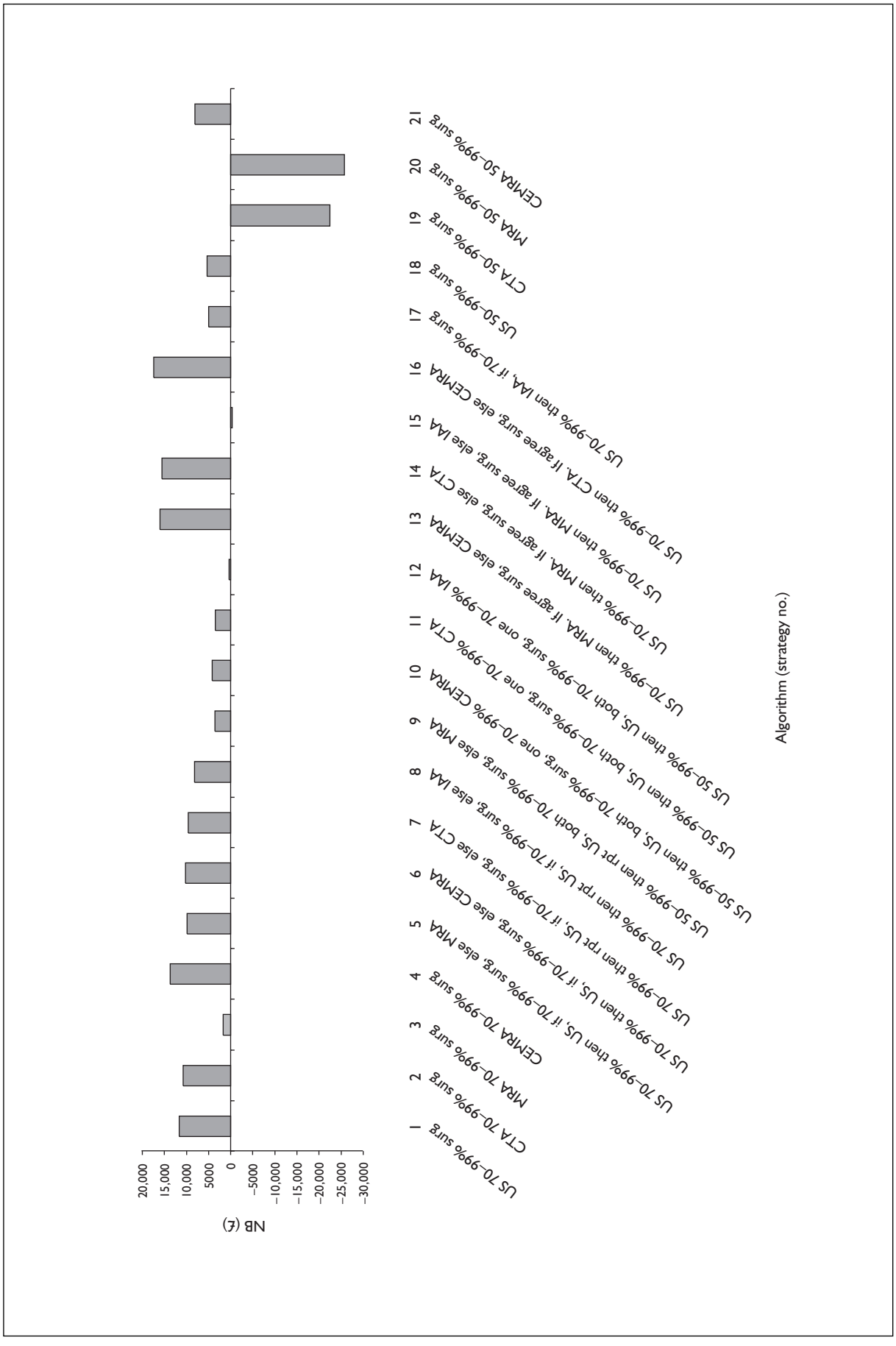

FIGURE 34 *Net benefit over a 20-year period for secondary stroke prevention per 100 patients with TIA or minor stroke. Willingness to pay £20,000 per QALY assumed.*

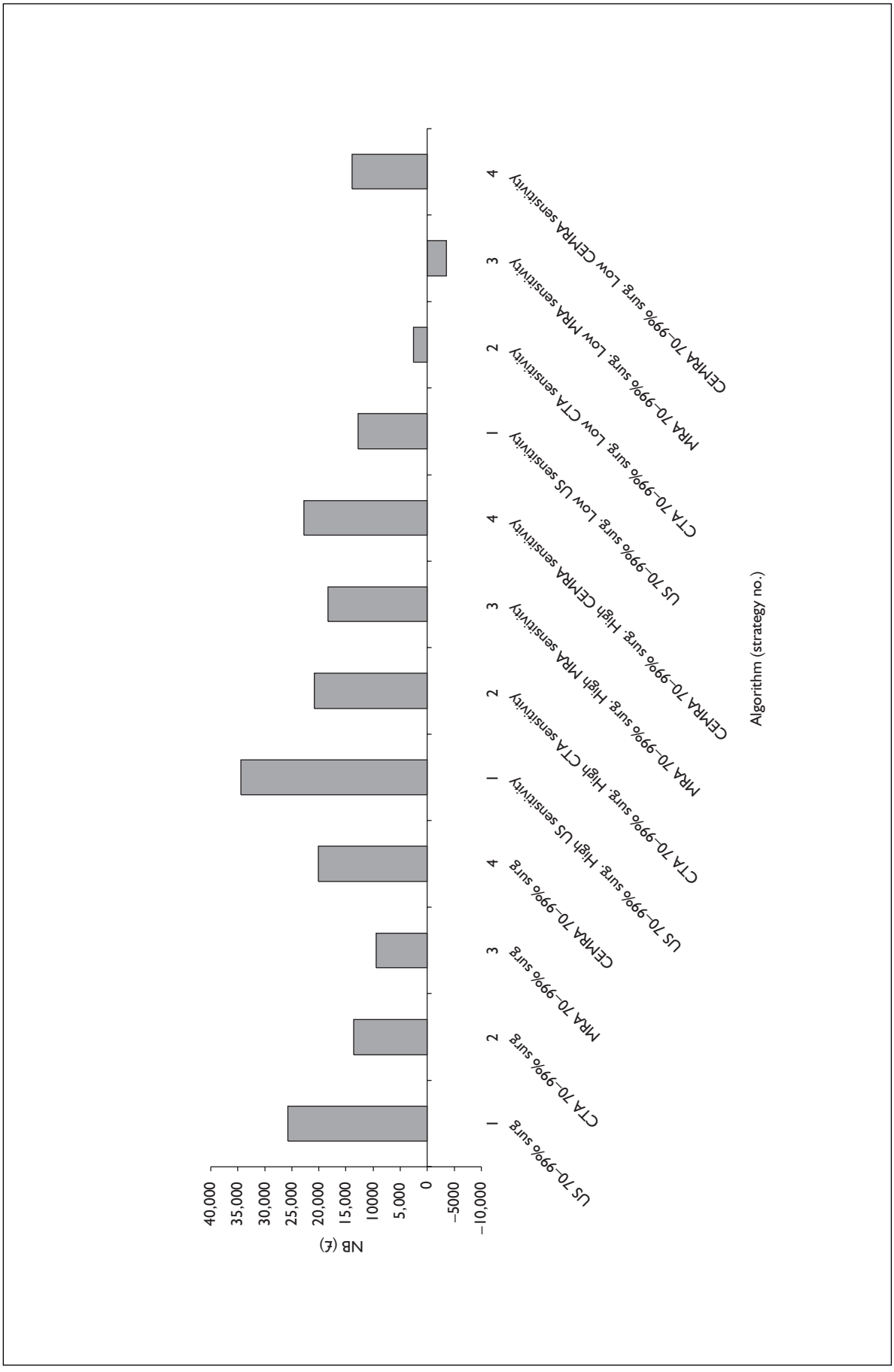

FIGURE 35 *Net benefit over a 20-year period for secondary stroke prevention per 100 patients with TIA or minor stroke. Willingness to pay £30,000 per QALY assumed. Sensitivity of diagnostic tests changed.*

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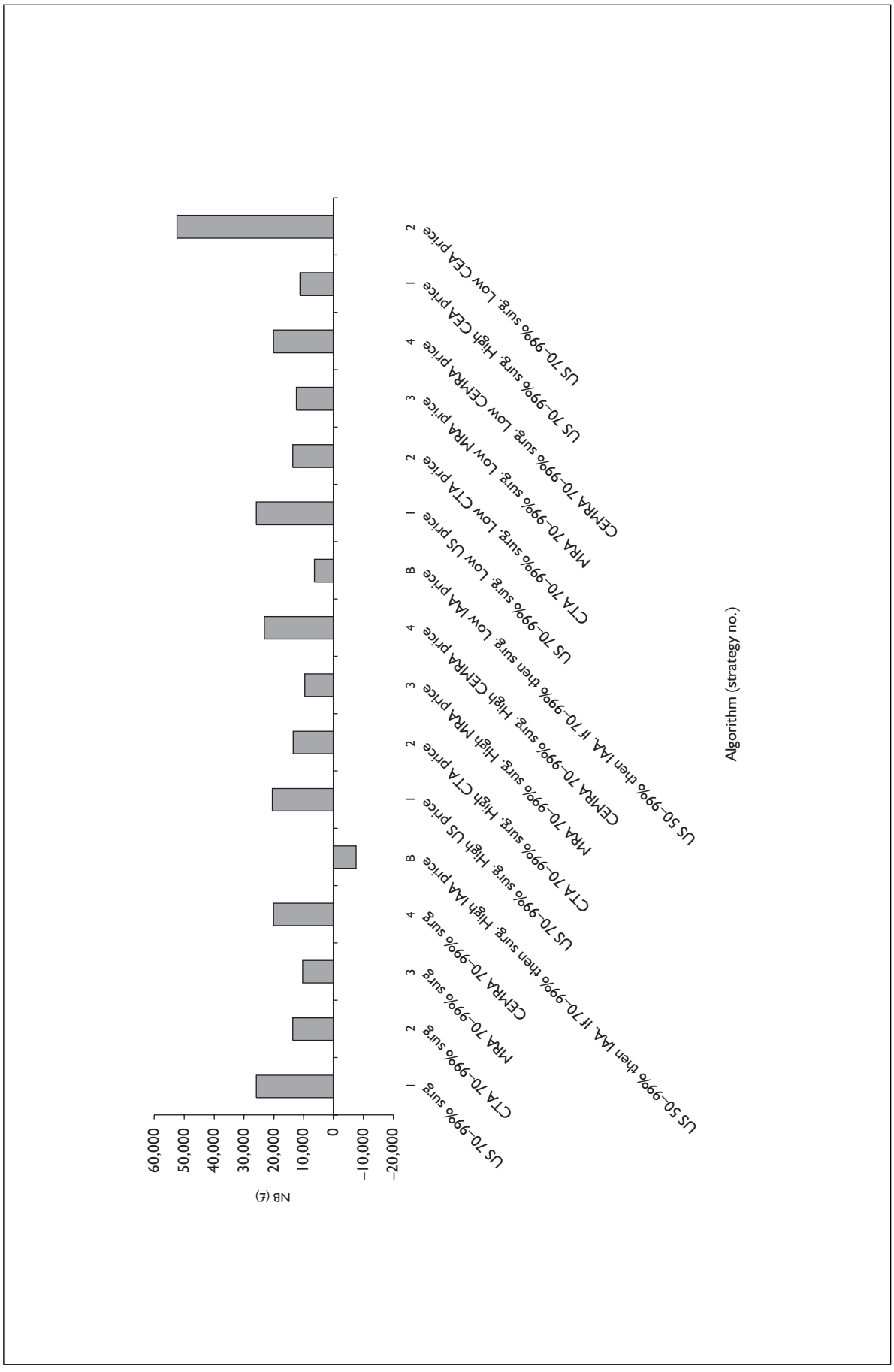

FIGURE 36 *Net benefit over a 20-year period for secondary stroke prevention per 100 patients with TIA or minor stroke. Willingness to pay £30,000 per QALY assumed. Price of diagnostic tests and endarterectomy changed.*

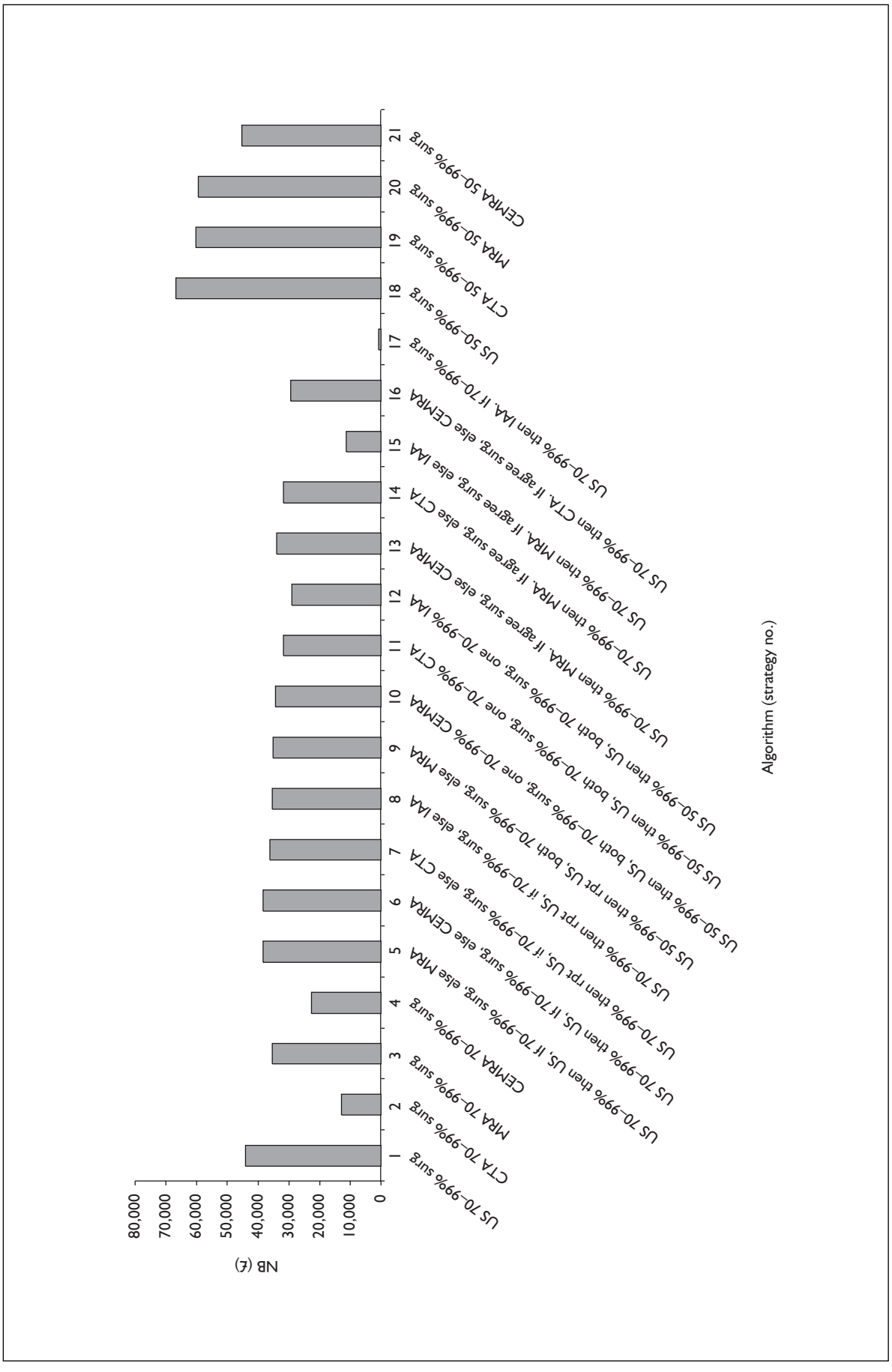

FIGURE 37 *Net benefit over a 20-year period for secondary stroke prevention per 100 patients with TIA or minor stroke. Willingness to pay £30,000 per QALY assumed. Surgery undertaken at day 14.*

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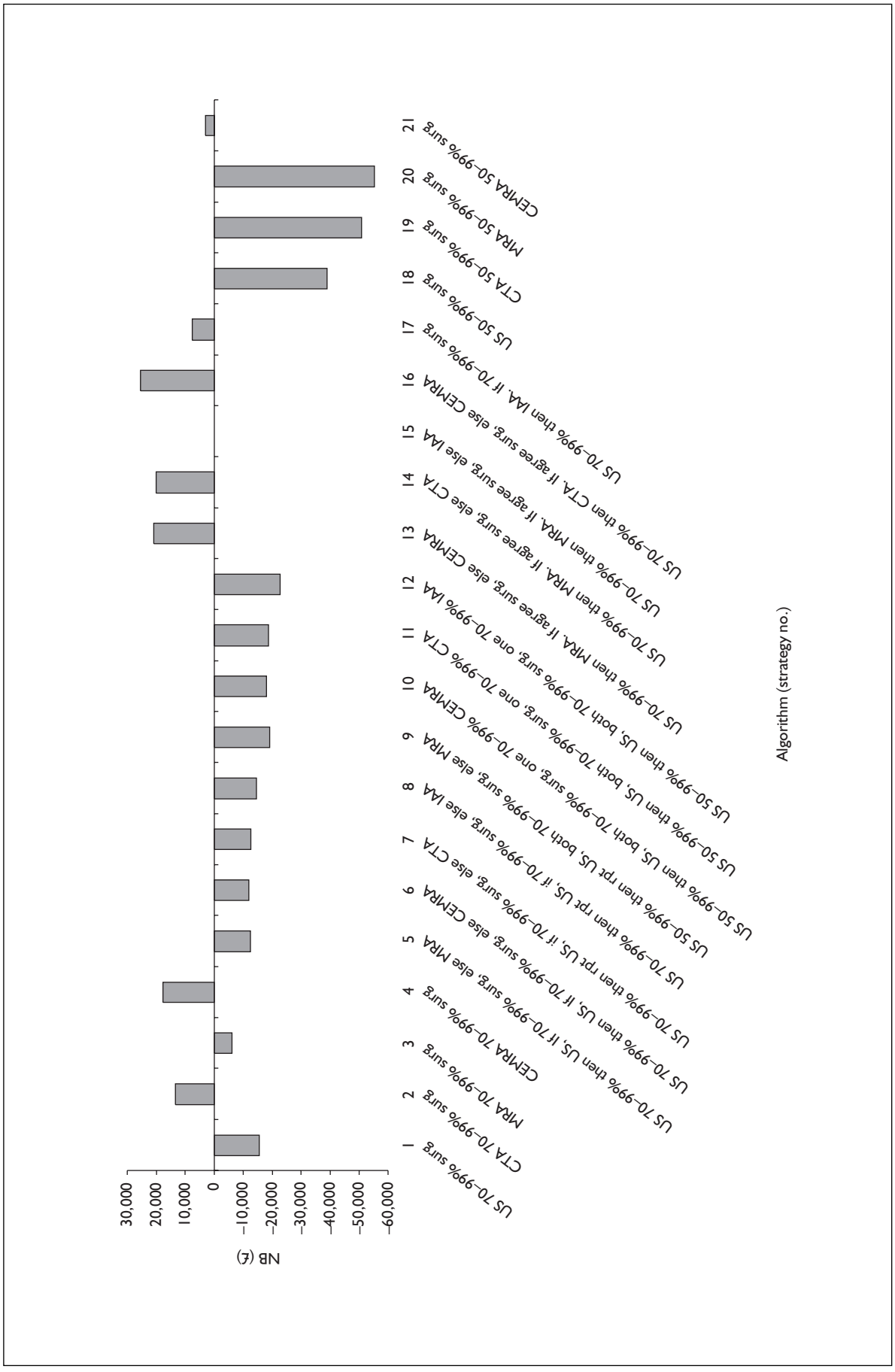

FIGURE 38 *Net benefit over a 20-year period per 100 patients with TIA or minor stroke. Willingness to pay £30,000 per QALY assumed. Surgery undertaken at day 80.*

FIGURE 39 *Net benefit over a 20-year period per 100 patients with TIA or minor stroke. Willingness to pay £30,000 per QALY assumed. Surgery undertaken at day 180.*

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Effect of different strategies on clinical outcomes of stroke and death in the short and long term

All strategies produced the same effect on outcome within the first 28 days (*Table 72*), as in the baseline strategy since no angiograms or endarterectomies would have been undertaken within this period (Chapter 6, *Table 70* and Appendix 13). Using the timings to different stages in the investigation process in Appendix 13, it was identified that most centres were able to undertake endarterectomy within 1 month of taking the decision to operate. However, even in strategies where only one diagnostic test was used to determine the carotid stenosis, this would result in the time to endarterectomy being on average about 41 days (*Table 73*). Two strategies brought the time to endarterectomy down to 31 days (strategies 1 and 18, both using only one US), eight strategies reduced the time to endarterectomy to 35 days (strategies 5–12, all used two USs to identify most patients for endarterectomy, with various tests for a third confirmatory test where the two USs disagreed).

Within the first year there was a difference in the number of total strokes suffered (*Table 72*), ranging from 17.94 to 18.59 per 100 patients with TIA or minor stroke. The number of fatal strokes ranged from 1.33 to 1.43 per 100 patients with TIA or minor stroke. The numbers of patients proceeding to endarterectomy per 100 investigated and treated are shown in *Table 74* and *Figure 30*. This ranged from 5.92 in the baseline comparator to 26.66 in strategy 20 (MRA 50–99% stenosis offer surgery). On close inspection of *Table 72*, the better strategies in terms of stroke prevention are those that enable endarterectomy to be undertaken expediently (e.g. strategy 1: one US shows stenosis of 70–99%, proceed to surgery; 18.14 strokes occur per 100 patients investigated/treated) and those where patients with greater than 49% stenosis were offered endarterectomy quickly (e.g. strategy 18: one US shows stenosis of 50–99%, proceed to surgery, 17.94 strokes occur per 100 patients investigated/treated). Strategies 9 and 10 [US 50–99% stenosis; repeat US if 70–99% offer surgery; if two USs disagree arbitrate with MRA (9) or CEMRA (10)] both perform well (18.18 strokes occur per 100 patients investigated and treated). The poorer performing strategies in terms of strokes occurring were those where the proportion of patients offered endarterectomy was smallest or where there was a delay in time to surgery (e.g. baseline, 15, 17, all of which involve IAA; *Table 73*). The benefits of the better strategies are seen to be maintained at 5 years from the incident TIA/minor stroke.

Since the model assumed that all patients received medical therapy at the same time regardless of diagnostic strategy, there was little variation between strategies in the number of MIs suffered. Those strategies that have better stroke results have marginally higher numbers of MI purely because of the increased number of patients alive, and thus susceptible to MI.

The numbers of surgical deaths were strongly related to the numbers of patients who received endarterectomy. Where these numbers were equivalent, surgical deaths were slightly higher in patients who received an IAA, owing to the assumed associated risk of mortality of IAA.

Effect of different strategies on the QALYs accrued

The number of QALYs accrued by each strategy is strongly related to the clinical results and ranges from 567.1 to 569.1 (*Figure 31*). Here it is easier to see the better strategies, which are those that offer all patients with a US reading greater than 49% stenosis endarterectomy (except for the baseline), and also offer all patients with a US reading greater than 69% stenosis endarterectomy (except for strategy 17); both baseline and 17 involve a delay while waiting for an IAA after the US, and because of the assumed 100% sensitivity of IAA, reduce the number of patients being offered endarterectomy. However, it is not just having the IAA per se that reduces QALYs, but there are two other likely reasons: first, all patients in those strategies have a longer wait for the IAA; and second, patients in the 50–69% stenosis group who may benefit from endarterectomy are weeded out (whereas with US they would be more likely to go through to endarterectomy and benefit from surgery). Thus, the strategies where IAA is still the final confirmatory test, but where a second US or another less invasive technique is used to confirm the diagnosis, allow more patients to proceed through the diagnostic system and reach endarterectomy (e.g. strategies 8 and 12 both involve IAA as the final arbiter after an initial and confirmatory US).

A large number of strategies give similar QALY results (between 568 and 569 QALYs), but there are four strategies with inferior results. These include baseline (offering endarterectomy to those patients where a US reading was more than 49% stenosis and angiography revealed a more than 69% stenosis), strategy 17 (offering endarterectomy

to those patients where a US reading was more than 69% stenosis and angiography revealed a 70–99% stenosis), strategy 2 (offering endarterectomy to those patients where a CTA showed 70–99% stenosis) and strategy 15 (offering endarterectomy to those patients where US gave a stenoses of 70–99%, MRA showed less than 70% but angiography confirmed 70–99%). These inferior strategies all reduce the number of patients who are offered endarterectomy (*Table 74* and *Figure 30*). In the case of CTA, the high specificity limits the number of patients proceeding to endarterectomy (*Figure 32*).

Effect of different strategies on the costs of stroke prevention

Owing to the high costs of both endarterectomy and stroke, in addition to those of the diagnostic tests, there is more variability in the costs associated with each strategy, with a spread of £1.33 million to £1.38 million (*Figure 32*). The strategies that incurred the highest costs were those that undertook a large number of endarterectomies, with the least costs associated with those strategies that undertook the fewest endarterectomies (*Table 74*). Contrasting these results with those for QALYs accrued (*Figure 31*), there is, using the assumptions on the timing of endarterectomy, an inverse relationship between cost and QALYs.

Effect of different strategies on NB

All NBs were compared to the baseline comparator of performing IAA on all patients with a US reading of between 49 and 99% stenosis and offering endarterectomy where the IAA reading was 70–99% stenosis in the symptomatic artery (baseline).

Where society is prepared to pay £30,000 per QALY (*Figure 33*), the baseline comparator is inferior to all but two other strategies, those offering endarterectomy to all patients with 50–99% stenosis on CTA or MRA (strategies 19 and 20). Although these strategies provided more QALYs (*Figure 31*) they incurred a large expense, making them less cost-effective than the comparator strategy 1. The best strategy was offering endarterectomy to all patients where the US reading was 50–99% stenosis, followed very closely by offering endarterectomy to all patients where the US reading was 70–99% stenosis.

Where society is willing to pay only £20,000 cost per QALY (*Figure 34*), those strategies in which a large proportion of patients receive endarterectomy become less favourable. In this instance, more selective treatment of the patients is required. The optimal strategy was 16: US followed by CTA where the US showed 70–99% stenosis; patients in whom the tests agreed should be offered endarterectomy, otherwise the decision to offer surgery should be based on CEMRA. Other favourable strategies were 13 and 14: US followed by MRA where the US showed 70–99% stenosis; patients in whom the tests agreed should be offered endarterectomy, otherwise the decision to offer surgery should be based on CEMRA or CTA.

Sensitivity analyses

Sensitivity analyses were undertaken to determine the robustness of the results to changes in:

- the assumed sensitivity of the less invasive diagnostic tests: analyses were undertaken assuming that the sensitivity of the test was at the mean, the upper 95% confidence interval or the lower 95% confidence interval of the range presented in Chapter 3
- the assumed costs of the diagnostic tests and endarterectomy: analyses were undertaken assuming that the sensitivity of the test was at the mean, the upper 95% confidence interval or the lower 95% confidence interval of the range presented in Chapter 5
- the time taken to reach endarterectomy: the time to perform diagnostic tests varies between centres owing to a number of factors, including the availability of the tests.

For the sensitivity analyses, the number of diagnostic strategies to be run in the model was reduced to a core of key strategies.

Effect on NB of varying the sensitivity of the less invasive diagnostic tests

The effect of varying sensitivity in strategies 1–4 (a single less invasive test, if 70–99% stenosis proceed to endarterectomy) was tested. *Figure 35* shows that the ranges of NB between that estimated using the upper confidence interval for sensitivity and that estimated using the lower confidence interval for sensitivity were wide and overlapping. This indicates that the results and interpretation of the stroke prevention model are sensitive to variations in the accuracy of the less invasive carotid imaging tests. For example, the NB for strategy 1 nearly trebles between assuming a low and a high sensitivity for US: with a high US sensitivity, strategy 1 has an NB of just under £35,000 compared to the baseline strategy, compared with just over £25,000 at a median and about £13,000 at low sensitivity values.

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Effect on NB of varying the price of the diagnostic tests and endarterectomy

The effect of varying costs in the baseline strategy and strategies 1–4 was tested. The unit cost for the diagnostic tests and for endarterectomy may vary by location. In *Figure 36*, the NB did not change greatly with varying cost of the less invasive tests or IAA, but was affected by changes in the cost of endarterectomy. The NB varied from just over £10,000 to just over £50,000 by moving from a high to a low endarterectomy price (Chapter 5).

Effect on NB of varying the timing of the diagnostic algorithms and time to surgery

As the time to certain diagnostic tests will vary according to Health Board area, a sensitivity analysis was undertaken assuming that diagnostic tests were finished at a certain time, and that surgery is undertaken at a certain time. The times assumed were as follows.

- Tests would be completed by day 12. Surgery would be undertaken at day 14.
- Tests would be completed by day 35. Surgery would be undertaken at day 80.
- Tests would be completed by day 120. Surgery would be undertaken at day 180.

The baseline strategy was compared to the 21 alternative diagnostic strategies. Comparing *Figures 37–39*, it is clear that when the time to surgery is lengthened, those strategies that are more selective in the patients that proceed to endarterectomy become more favourable. Thus, *Figure 37* indicates that the most strategies with the greatest NB offer surgery to patients with 50–99% stenosis the most quickly (i.e. use US rather than other techniques). Among strategies in which patients with 70–99% stenosis would be offered surgery, there is relatively little difference in NB among the strategies. However, with increasing times to surgery (*Figures 38* and *39*), strategies that offer fewer patients surgery (i.e. restricted to those with 70–99% stenosis) and rely on more accurate less invasive tests (CEMRA or CTA) achieve the highest NB, and strategies that offer surgery to many patients and use less accurate diagnostic tests create a more negative NB the greater the delay to surgery.

Table 75 shows how the NB of a strategy of offering endarterectomy to patients with a US reading of 70–99% stenosis changes with the time of surgery, compared to treating at day 41 as in the baseline analysis. It is clear that the time to surgery is a major driver in determining the cost-effectiveness of the strategy. Indeed, it may be that there is very little to choose between less invasive strategies where patients are offered endarterectomy quickly, but in regions where times to surgery are slower, the choice of diagnostic tests for carotid stenosis is very important. That said, reducing the time delay to carotid surgery of all diagnostic strategies within a Health Board region is likely to be more important than which tests are used. However, differences in the sensitivity and specificity of the four less invasive tests result in quite different numbers of patients proceeding to endarterectomy. Thus comparing strategies 1–4 (each of which used a single less invasive test; if it showed 70–99% stenosis then offer surgery), US would lead to 17.11, MRA to 13.8, CTA to 7.18 and CEMRA to 6.93 endarterectomies, respectively, per 100 TIA/minor stroke patients investigated (*Table 74*). These differences are large (almost three times as many endarterectomies if US alone were used compared with CEMRA alone) and would require major extra resources to provide the endarterectomies. However, CEMRA is much more expensive than US and using CEMRA to screen all patients would also require major extra imaging resources. In the cost–benefit analysis, as fewer strokes occur (*Table 72*) with the less sensitive imaging test of US (and the cost of caring for stroke is large), the overall effect of using the less invasive test appears to be both a net saving and more strokes prevented, but only if surgery can be performed as in the baseline strategy (31 days), or even more quickly. If surgery is delayed beyond the current baseline, then both the number of strokes suffered and the total cost rise steeply.

Discussion

This analysis, based on the most accurate and up-to-date data that the researchers could obtain on all aspects of providing a secondary stroke prevention service, indicates that the NB of stroke prevention clinics is very dependent on the speed with which patients can be investigated and treated and, for patients presenting late or where services are slow, also on the accuracy of less invasive diagnostic tests. The differences between the various strategies may seem small in terms of QALYs or NB, but on a population basis the effect is large. In addition, this analysis suggests that the current average provision of services, in which appropriate patients are unlikely to undergo CEA until 40 or so days after their warning TIA or minor stroke, could be improved. This approach, regardless of imaging strategy, is failing to prevent up to 100 strokes per 1000 patients within the first month of a warning TIA or minor stroke

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TABLE 75 *The change in costs, QALYs and strokes occurring per 100 patients with TIA or minor stroke associated with a change in the time to CEA based on strategy 1 (US, 70–99% stenosis, offer surgery)*

Time to CEA (days)	Cost incurred (£)	QALYs accrued	NB (£) £30,000 at cost per QALY	No. of strokes suffered at 1 year
14	1,335,994	570.92	86,977	17.36
31	1,349,169	568.46		18.14
80	1,358,137	566.54	–66,776	18.79
180	1,361,398	565.34	–106,067	19.23

(*Table 72*). Given that not all strokes could be prevented anyway, there is still a difference of 19 per 1000 strokes occurring between reaching endarterectomy after one US showed 70–99% stenosis by day 14 and by day 180 (*Table 75*). Given that the greatest risk of a disabling or fatal stroke is within the first few days of a warning TIA/minor stroke, current stroke prevention approaches are too slow to prevent many of the strokes that they were set up to avoid.

This analysis is somewhat crude in the sense of assuming rather fixed times to reaching medical attention and interventions (*Table 73*), whereas in real life these times would be much more variable. However, in real life, the time taken to reach endarterectomy, or even to be prescribed aspirin and other pharmacological secondary prevention therapies could be even longer: 3 months could easily lapse before the patient reached endarterectomy, given delays in obtaining the reports of examinations, referrals, waiting for a hospital bed, and so on. The possible improvements in stroke prevention have been modelled here, but more and better data are required from new trials of stroke prevention strategies to determine how much real improvement could be achieved by speeding up times to stroke prevention treatments.

The results of the model were very sensitive to changes in the accuracy of less invasive diagnostic tests. As highlighted in Chapter 3, the literature on less invasive diagnostic tests has probably overestimated their accuracy. However, while loss of accuracy might be less important if stroke prevention strategies could be implemented very quickly, in the current UK healthcare setting, where most patients will experience some delay to carotid investigation and surgery, accuracy is very important. The IPD meta-analysis in Chapter 4 reinforces this point and shows that data obtained in routine practice are likely to be even less accurate. More research is required into the sensitivity of each test, and particularly of tests in combination and at 50–69% stenosis levels, and of how interpretation of the tests could be improved, before a definitive decision can be provided as to which precise diagnostic strategy is 'best'. In the meantime, it would seem not unreasonable to stick with using US as a first line investigation, followed by US or CEMRA in those with 70–99% stenosis as a confirmatory test and offering surgery to those in whom the tests concur. However, given the operator dependence of US, it would be important to offer US only in the context of a dedicated clinic and maintain routine audit to track accuracy.

The results of the model were also very sensitive to the cost of endarterectomy. As highlighted in Chapter 5, there is a paucity of data on the costs of stroke, of running stroke prevention clinics and of endarterectomy itself. The estimates of the cost of endarterectomy were based on data from several years ago and may already be very out of date. It seems bizarre that it should be so difficult accurately to cost procedures and healthcare in the NHS when one of the major constraints governing the provision of health care in any particular region, as well as nationwide, is cost. It makes it difficult for health service staff to make sensible decisions about what technologies to use or how to perform procedures when data on costs are not available or are unreliable. More research is needed into the true costs of endarterectomy before any definitive decision can be made on the optimal diagnostic strategy.

Finally, knowledge about the benefits of CEA was obtained from the carotid surgery trials[3,10] in which the degree of carotid stenosis was determined on IAA, there were delays of weeks to months between the warning TIA/minor stroke and the endarterectomy, and the medical therapy was largely aspirin. It could be argued that these data are out of date as a result of changes in technology (which mean that many more patients can be imaged much more quickly and more safely), along with new knowledge that the peak occurrence of disabling stroke is very soon after the warning TIA, and improved medical interventions to prevent stroke (blood pressure reduction, lipid lowering, other synergistic antithrombotic drugs). Perhaps, contrary to the introductory statement, it is very important and therefore possible and ethical to conduct a randomised trial of the role of imaging before CEA.

Implications for clinical practice and research are discussed in Chapter 8.

Chapter 8

Discussion and conclusions

This study has demonstrated that the most cost-effective diagnostic strategies for carotid stenosis are those that offer surgery to a larger proportion of patients quickly after the warning TIA/minor stroke, in particular those that include patients with 50–69% as well as 70–99% NASCET symptomatic carotid stenosis. Paradoxically, this means that slightly less accurate imaging strategies may appear more cost-effective because patients with more moderate stenoses (50–69% or less) are offered surgery more often than would occur with more accurate strategies (where only patients with 70–99% stenosis would be included). However, this involves inadvertently offering surgery to some patients with less than 50% stenosis, despite which the model suggests an overall greater benefit. If operated on quickly, and the risk of surgery is low, then patients with 50–69% NASCET stenosis (approximately 70–80% ECST stenosis) may benefit more from surgery than from medical treatment. The longer the delay, the less the benefit from endarterectomy (particularly amongst those with less than 70% stenosis) and the more important it becomes that the imaging strategy is as accurate as possible to identify just those with the very tight stenoses. In general, strategies that involve mainly using US appear advantageous because, in general, in current UK clinic settings, patients can undergo imaging with US more rapidly than with other less invasive techniques or with IAA.

Strengths

The authors believe that the strengths of this work are the critical approach to the systematic review of the less invasive imaging literature, the IPD, the detailed costings, and the careful construction and population of the model with up-to-date data (wherever possible), mostly from the UK. The work also benefited from being conducted by an expert group, which included clinicians, radiologists and trialists all dealing on a daily basis with the problems posed by trying to provide stroke prevention services.

Limitations

Before discussing further the implications of this work for current health service provision, it is important to consider the limitations of the model, of the available data and of the other aspects of the work.

First, the model was sophisticated but relatively crude. For example:

- The increased risk of surgery in women compared to men was not factored in.[227]
- It was assumed that patients would reach each stage in the decision-making process at rather fixed times, whereas in fact some patients would reach these points more quickly and some more slowly, but clustered around these times.
- It was assumed that patients would not be started on any secondary prevention treatment before being seen in the stroke prevention clinic, although they would continue any drugs that they were taking before the TIA/minor stroke. In many places, patients would be started on aspirin or other secondary prevention while waiting for their outpatient clinic appointment.
- Assumptions had to be made about the efficacy of secondary prevention drugs given in combination by extrapolating from original trials in which these drugs were usually tested in isolation. Although these assumptions were supported by a philosophical paper[230] and an informed personal communication, they may nonetheless be incorrect. The authors were therefore cautious and used the lower 95% confidence limit of the calculated effect.
- The model assumed that all patients responded in a similar manner to medical or surgical interventions, whereas in reality some patients would respond better than others, and some not at all. The model dealt with the mean or median response as a way round this problem, but it is no substitute for performing an RCT to test the effect of the interventions.

Second, the data on the accuracy of the less invasive tests were obtained from the literature, supplemented by an IPD meta-analysis. The literature was rather limited and probably overoptimistic in its assessment of test accuracy, there was heterogeneity for sensitivity and specificity, and there was a lack of data on tests used in combination in the same patients as occurs

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in clinical practice. The IPP, mainly obtained from audit of routine care (but still mostly in dedicated and interested carotid imaging centres), would suggest that the accuracy achievable in routine care may be even less. There were no data on the accuracy of these tests when used in centres where there is no specialist interest in carotid imaging, and therefore these results cannot be extrapolated to such centres. A further drawback of the literature is that most studies failed to distinguish between the symptomatic and the asymptomatic carotid artery, and yet the IPD analysis suggests that the tests perform differently in symptomatic to asymptomatic arteries, for whatever reason. This may be because the symptomatic artery is more often stenosed, or perhaps the stenosis is more irregular (plaque activity is associated with plaque irregularity on angiography),[235] both of which would affect the performance of the less invasive tests, and there is some evidence of increased difficulty in interpretation of images (decreasing test accuracy) the more abnormal the artery, at least for MRA.[33] Whatever the reason, this point has been almost completely overlooked in the imaging literature. The authors were unable to obtain reliable data on the imaging determination of atheromatous plaque characteristics and stroke risk to include in the model. This is a large area to sort out and it became clear that, with the current state of the literature, it was beyond the scope of the present funding. However, the imaging appearance of plaque may be a marker for stroke risk in addition to the degree of stenosis and should be evaluated in future work.

Third, the data on costs were difficult to obtain and some costs may be out of date. For example, the cost of endarterectomy was based on costs obtained about 4 years ago. However, it is hoped that the general scale of costs (even if their absolute value has altered) will not have changed greatly in relation to other parts of the model; for example, the cost of outpatient attendance compared with the cost of imaging, and the cost of US compared with the cost of MRA.

Questions raised

This work raises several important questions for provision of stroke prevention services in the UK.

Are stroke prevention clinics optimal in the UK?

The short answer is no. This survey, mostly from among interested and motivated stroke physicians and neurologists, indicated that, in the centres surveyed, it would be unusual for patients to reach endarterectomy by 14 days. In most, reaching surgery would be at around 6 or more weeks. The timing may be much worse in centres without specialist services. More strokes will be prevented with faster access to specialist services including diagnostic imaging and endarterectomy. Methods to reduce delays to clinic referral, perhaps avoiding delays while appointment letters are typed and making better use of telephone or Internet appointments, may help. Greater awareness of TIA and stroke symptoms, and their importance, among the general public may help patients or their relatives to recognise a 'mini-stroke' and know to seek medical attention quickly. Rapid-access TIA clinics would help and GPs should be encouraged to refer rapidly.

Is IAA necessary to select patients for CEA?

As a routine test before CEA, where high-quality less invasive imaging tests are available, the short answer is no. IAA carries a risk and, on average, delays the time to surgery. IAA even appears to offer relatively low net benefits compared with other strategies, even when surgery is performed within 14 days (Chapter 7, *Figure 36*). Thus, although the debate on the use of IAA continues in the literature, in general the present synthesis of evidence does not support its continued routine use.[17–20,236]

However, there may be exceptional cases where the less invasive imaging tests simply cannot determine the anatomy and where IAA still needs to be used. In addition, in centres where IAA is currently the routine second test, ongoing audit has demonstrated the risk to be very low and the test can be done very rapidly, there may be a case for continuing to use it while introducing an alternative less invasive test.

However, the authors believe that it is extremely important that where less invasive imaging tests are used in place of IAA, they should be operated and interpreted by radiologists with a specialist interest and training in performance and interpretation of the chosen test(s). The data do not provide support for use of these tests by non-specialists or those with little training or who may see few cases per year.

What imaging tests should be used instead?

The actual choice of tests will depend on local availability of resources, but the largest amount of

(and therefore most robust) data were found on US, and the most accurate test was CEMRA. US is the most widely accessible test in most centres in the UK and therefore it seem reasonable to use it as a first line investigation. However, because of its relative insensitivity and operator dependence, it would probably be unwise to rely on one US alone, but either to repeat the US or undertake a different less invasive test (preferably CEMRA) before CEA. There is still a general wariness of the reliability of US. Of all the less invasive tests, despite its being available for the longest, it is still the one for which clinicians are most reluctant to accept the results.[23] The aim of imaging is to identify all patients with 70–99% (or 50–99%) stenosis and offer them surgery, but avoid offering surgery to those with less than 50% stenosis or occlusion because their risk of stroke is generally thought to be less than their risk of surgery. Although some imaging strategies seem to have a high NB, they achieve this at a cost of offering endarterectomy to nearly a quarter of all patients presenting to the hypothetical stroke prevention clinic, and up to half of patients offered endarterectomy (Chapter 7, *Figure 30*) would have less than 50% stenosis. Although the model suggests that these strategies would prevent more strokes, the original carotid surgery trial data indicated that the risk of surgery was greater than the risk of stroke in patients with less than 50% stenosis,[3,10] although this may have been because many of the patients in the trial did not reach endarterectomy until several months after their TIA/minor stroke, when their stroke risk may have declined substantially. The model includes the high risk of early stroke, which may be why it suggests that operating on a proportion of people with less than 50% symptomatic stenosis may be beneficial if it can be done quickly. However, operating on a quarter of all TIA/minor stroke patients would completely overwhelm current vascular surgery provision so at present the authors believe that it would be better to focus resources on those with 70–99% stenosis, speed up clinic throughput, gather more data and, if supported, work towards a strategy of operating early on lesser degrees of stenosis.[5]

Currently, there do not appear to be sufficient CT or MR scanners in the UK for CTA or MRA to be the first line imaging investigation in most centres, but there may be enough for it to be the second or third test, if the test can be performed without delay. There were relatively few data (in the literature or IPD analysis) in support of CTA, which in any case has recently undergone a significant improvement in technology to spiral multislice scanning, for which there were virtually no data. It may therefore be that the new CTA technology will be as accurate as CEMRA, but this needs to be evaluated in new studies. CEMRA rather than MRA should be performed where possible, although this does require additional hardware and software (however, many new MR scanners are now coming with these as standard). The authors believe that MRA without contrast should only be used if CEMRA is not available.

Communication between clinician and radiologist needs to be efficient and rapid

Systems need to be in place to relay important imaging results back to the referring clinician to reduce delays. Either telephoning reports or sending a paper copy of an interim report on the same day in patients with tight symptomatic stenosis could ensure that the clinician can activate the next steps in management as quickly as possible. Similarly, there needs to be good communication between the clinician and surgeon to avoid delays to surgery. This probably means that stroke prevention clinics need to be coordinated by a few people with clear roles working closely together: a stroke clinician who coordinates the patient bookings, clinical assessments and requests imaging; a radiologist who coordinates and performs the imaging tests, identifies those patients needing additional confirmatory imaging and ensures that the results are fed quickly back to the stroke clinician; and a surgeon with a special interest in carotid surgery who can respond quickly to referrals. Extra people (junior doctors, other consultant clinicians, radiographers, other radiologists, etc.) can all help to provide the service, but someone needs to be responsible for the processes at each stage. Because TIA/stroke is so common, this service has to be streamlined and there need to be well-established pathways so that all participants know what to do next.

Less invasive imaging should be audited continuously, but how?

Avoiding IAA may be good for most patients, but it presents a major problem for monitoring the accuracy of less invasive tests. IAA (conventional three-view) was the test used in the carotid surgery trials, and while some may argue about whether it is a gold standard or not, it is nonetheless the reference standard which relates the risk of stroke to the degree of carotid stenosis. Without IAA against which to compare less invasive tests, the worry is that the accuracy of less invasive tests may 'drift' and be difficult to audit. It is difficult to

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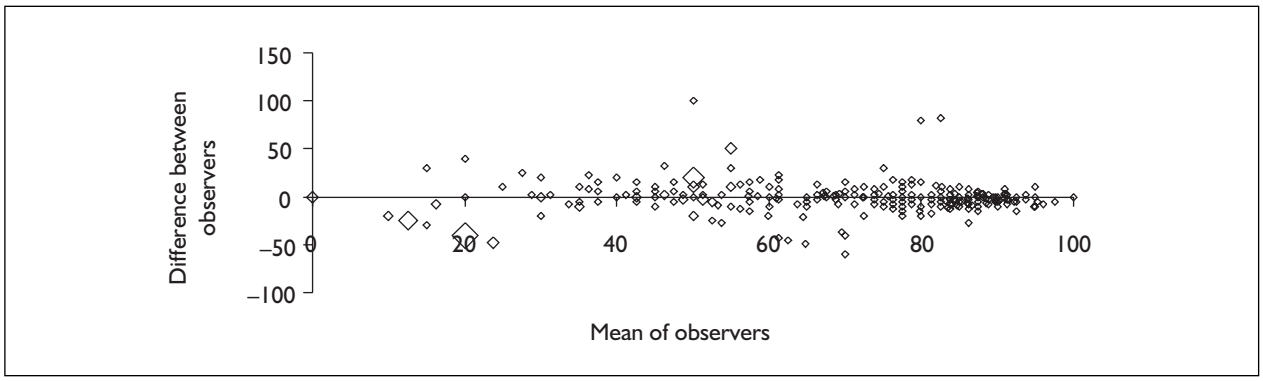

FIGURE 40 *An output of routinely collected audit data from Edinburgh Western General Hospital Neurovascular Clinic. Graph of two US examinations performed in the same patients where the operators are blind to the results of the other US. Symptomatic and asymptomatic arteries are included. Bland and Altman plot of difference between operators against the mean of operators. Note that in the stenosis range where close agreement is important (70–99%) there is very little difference between the two readings.*

assess new less invasive imaging technologies if IAA is not available as a comparator. The danger then is that new technologies are assessed against existing less invasive technologies with considerable opportunities for 'drift'. Alternatively, during the introduction of the new technology, a few centres could conduct a direct comparison with IAA, but the UK healthcare system currently is not organised or funded to provide that assessment. In addition, it would mean that radiologists in many centres may become progressively deskilled ('rusty') in the IAA technique during times when it was not in use, thereby increasing the risk to patients if it were suddenly to be reintroduced so that a new less invasive test could be evaluated. IAA itself is changing, with the recent introduction of rotational IAA. As highlighted earlier, comparison of rotational IAA and conventional three-view IAA suggests that the latter underestimates the degree of stenosis in the 70–99% group,[90,91,127] which may explain why US and MRA appear to overestimate the degree of stenosis; it is difficult to discern which tests are correct, but it is important to remember that the relationship between stroke risk and percentage stenosis was calculated from conventional three-view IAA. Therefore, any systematic difference in the estimate of stenosis by another imaging technique would need to be factored into the equation relating stenosis to stroke risk to correct for this difference. This would be possible given enough IPD collected in rigorous conditions and across the whole range of stenoses. The issue of 'tracker trials' to monitor this continuously evolving technology is very relevant to carotid imaging and is an increasingly serious problem that the UK healthcare system needs to address.[54]

In the absence of IAA, centres should at least consider auditing their less invasive tests against each other, for example, the results of two USs in the same patient, or a US followed by an MRA could be routinely recorded in an audit database. The occasional IAA could be added in when performed. The relevant information on degree of stenosis per artery could be extracted from the radiological report. If the two less invasive tests are performing optimally, there should be little difference between the results. For example, one test should not change the operative group (surgery versus no surgery) unless there is good reason to think that the disease has genuinely progressed, and should fall within about 5% stenosis of each other. A simple plot of one test against the other performed intermittently would reveal any 'drift' over time. A more sophisticated plot of sensitivity and specificity (e.g. of US against CEMRA) could also be performed. An example of this approach from the stroke prevention clinic in Edinburgh Western General Hospital is shown in *Figures 40–42*. A recent 'wobble' in *Figure 41* is due to the appointment and training of new staff. With improved NHS IT resources, data could be entered anonymously into an audit spreadsheet, extracted, sent to a central audit office for analysis and returned to the centres. This could be done on a national level. A model for this already exists through the Scottish Stroke Collaboration Audit, which collects demographic, healthcare resource use and discharge data on patients seen with stroke at hospitals in Scotland. Such a system could be expanded to record imaging data results. Central analysis would avoid the problem of requiring specialist statistical expertise in individual centres; rather, the individual centres can concentrate on collecting accurate data.

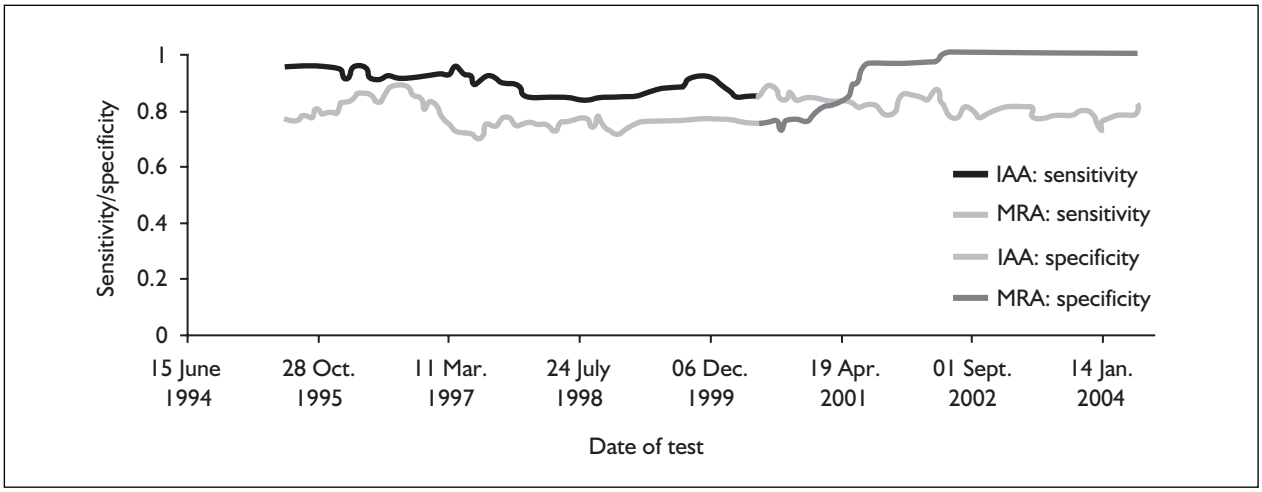

FIGURE 41 *Cumulative plot of sensitivity and specificity of US against IAA and CEMRA (data from the same source as in* Figure 40*)*

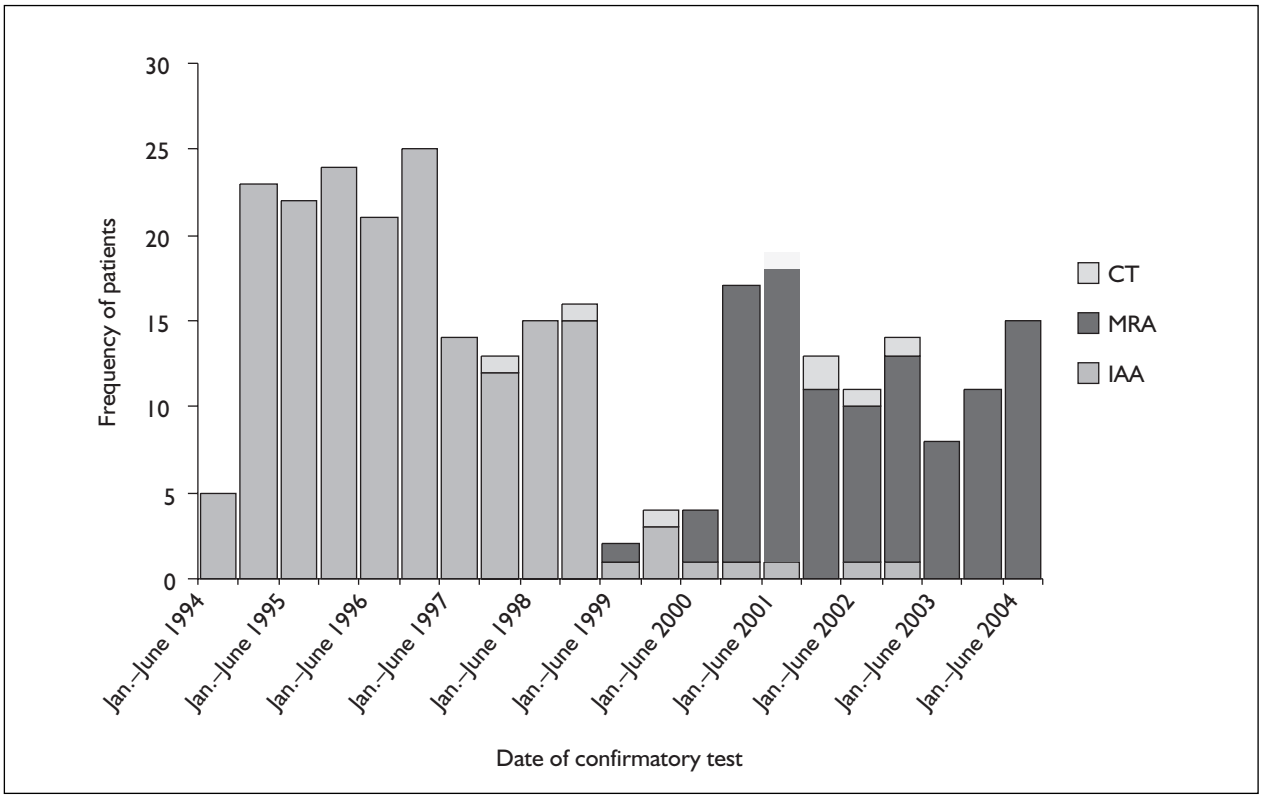

FIGURE 42 *Data from other imaging tests available for comparison with US (data from the same source as in* Figure 40*)*

One of the biggest problems in the present project was the lack of routinely collected audit data, despite many individuals indicating that they did collect such data before the start of the project. When the authors asked for the data, they were either not in a database, or not in an easily extractable form, or had been lost with a research fellow's departure. Routinely collected data can be streamlined (so not onerous to collect) and very informative, and as less invasive tests are used more and more, will be crucial for tracking the use of these tests in routine practice.

Should there be new studies of the accuracy of less invasive tests or a new randomised trial to test the role of less invasive imaging before CEA?

The present work does not provide a definitive solution to the problem of how patients should be investigated in routine practice. Rather, it provides

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a hypothesis that needs to be evaluated in trials. Worryingly, it suggests that, paradoxically, tests that are least accurate, and therefore lead to patients with less than 50% stenosis being offered endarterectomy in significant numbers, prevent the most strokes, and provide the most QALYs and the greatest NB. This is somewhat counterintuitive as stroke prevention strategies strive to avoid offering surgery to those with less than 50% stenosis, and often also those with 50–69% stenosis. It is important to sort this out. One way of approaching this would be to determine whether rapid investigation and implementation of secondary prevention measures (medical therapy or endarterectomy), based on less invasive imaging to identify patients with 50–99% NASCET stenosis, would prevent more strokes and deaths than a conventional policy of performing IAA. The other approach would be to avoid IAA altogether and to randomise patients to surgery versus best medical therapy on the basis of stenosis measured on less invasive imaging. Both approaches might be considered unethical by some, as they could result in a proven treatment (endarterectomy) being withheld from some patients, or not being implemented as quickly as possible. One way round this might be to use the first approach in patients with probable 70–99% stenosis on initial US, and the second in those with 50–99% stenosis. There are various other ways of testing the impact of less versus more invasive carotid imaging in stroke prevention. In any case, the trial would need to be multicentre to obtain a large enough sample size and to ensure generalisability to routine practice. It could also factor in the appearance of the atheroma on imaging as a marker of stroke risk.

How can individual NHS units use the analytical model to customise the findings to their own situations?

Information came from a (limited) survey of UK stroke prevention clinics to develop the model, and from the literature and several exemplar UK hospitals to obtain costs of diagnostic tests. Hopefully, therefore, many NHS units will find that their particular stroke prevention services are already represented in the model and so the results can be directly applied to their practice. However, if the population served, or costs or timings of the investigation or operation, or the accuracy of less invasive tests is very different, then an adjustment will have to be made. For example, longer delays to endarterectomy (because of delay to investigation or to surgery following investigation) would lead to less benefit with most imaging strategies (see *Figures 37–39* in Chapter 7) and would require specific less invasive tests to be used (mostly CEMRA) at high accuracy, and so would cost more. The effect of different costs of endarterectomy or less invasive tests is shown in *Figure 36*, and of different sensitivities and specificities of the less invasive tests (upper and lower 95% CI) in *Figure 35*. If a centre is currently relying on IAA to diagnose carotid stenosis, then this study provides a range of less invasive imaging strategies to choose from, one of which, it is hoped, could be implemented in most centres, as US and one or other of CTA or MRA are fairly universally available now. If a centre currently has a preferred less invasive imaging strategy, then examination of *Figures 31* and *32* (Chapter 7) shows what increase or decrease in QALYs or costs may arise in moving to another strategy. These are just a few examples of how the results of the model can be applied to specific local circumstances and used to plan changes in service.

Implications for health care

- In the majority of patients with symptoms of internal carotid artery stenosis, less invasive carotid imaging tests are sufficiently accurate, quick to obtain and cost-effective to replace IAA in the investigation of patients before CEA for secondary stroke prevention.
- The best combination in terms of availability of tests, cost of tests, strokes prevented, robustness in sensitivity analyses, NB and matching to current surgery provision appears to be US, if 70–99% repeat US, if agree offer endarterectomy, if not use CEMRA (or CTA or MRA), but the tests must be performed quickly.
- Operating on patients with 50–99% stenosis on the basis of one US has the highest NB if endarterectomy can be performed within 14 days, but involves offering endarterectomy to many more patients (up to a quarter of TIA/minor stroke) than at present.
- If there is a delay in patients reaching medical attention, then greater use should be made of CEMRA as it is more accurate and the benefit of endarterectomy for those with 50–69% stenosis appears to fall away rapidly after TIA; hence, late-presenting patients should probably only be offered endarterectomy if they have 70–99% stenosis.
- In patients with 50–69% stenosis (on NASCET criteria) the benefit of endarterectomy, if performed within the first few weeks of the TIA/minor stroke, may outweigh the risk of stroke.

- The importance of operator characteristics suggests that less invasive tests should only be used by those with a specialist interest and training and should be carefully audited, against IAA where available, otherwise against other less invasive tests.
- Stroke prevention clinics should endeavour to assess patients as quickly as possible after TIA/minor stroke. In the authors' opinion, good communication channels are necessary between the stroke clinician, the radiologist and the vascular surgeon to ensure rapid assessment and efficient management of patients.

Recommendations for future research

- More data are required to define better the accuracy of less invasive tests used at 50–69% stenoses, and in combination (e.g. US plus CEMRA).
- The methodology for primary studies of the accuracy of less invasive imaging tests needs to improve: blinding, prospective studies, in relevant patient populations, analysing the symptomatic separately from the asymptomatic artery, are essential basics.
- Clearer presentation of data in reports of primary studies of diagnostic test accuracy would enable more key sensitivity analyses to be performed in future meta-analyses.
- Methods of evaluating new technologies as they emerge (possibly involving calibration against phantoms, or other established less invasive tests) are required. Repeatedly performing studies of the new technology against IAA is no longer feasible as IAA is falling out of routine diagnostic use.
- Consideration should be given to new randomised trials to evaluate different less invasive imaging strategies before endarterectomy. For example, patients could be randomised to either a policy of less invasive imaging only (e.g US plus CEMRA or other techniques) or a policy of US followed by IAA (in centres where it is still in use) in the work-up to endarterectomy to determine the effect on number of strokes by 6 months between the two groups.
- Streamlined methods (to encourage widespread participation) of collecting data to audit less invasive tests when used in routine clinical practice are required to monitor test accuracy.
- Better information is required on the costs of caring for stroke, the costs of surgical procedures, outpatient visits and imaging tests. Standard methods agreed within the NHS Health Technology Assessment Board (or other body) and applied across the NHS would make routine estimation of the costs of procedures in the NHS not only much more accessible, but also more accurate and up to date.
- More data are required on the distribution of carotid disease by age, gender and TIA/minor stroke type.
- A more sophisticated model could be developed from the one constructed in this work to include factors such as differences in the risks of endarterectomy between men and women, and greater granularity on imaging findings (e.g. plaque characteristics), which may make the model yet more realistic.

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Contributions of authors

Joanna M Wardlaw (Professor of Neuroradiology) responded to the HTA call, conceived of the project, wrote the outline and full application, assembled the collaborative group, managed the project, coordinated the three full project meetings and had several other meetings with individual investigators, obtained data, supervised and conducted the systematic review, individual patient data analysis and UK survey of stroke prevention practice, obtained cost data, wrote the draft report and edited the revised report.

Francesca Chappell (Medical Statistician) contributed to the design of the study through discussions; performed the systematic literature review and the IPD analysis (including data transformation), attended three meetings to discuss progress and results including presenting data at meetings, kept meeting minutes, acted as information distributor for the study, performed the survey of UK stroke physicians, drafted two chapters and approved the final report.

Matt Stevenson (Senior Operational Researcher) contributed to the design of the study through discussions, designed and built the model in discussion with others, incorporated data provided by other parts of the project, ran and interpreted the model, drafted two chapters and approved the final report.

Enrico De Nigris (Research Assistant) performed the systematic literature review of costs and QALYs for stroke, obtained primary data on imaging tests in Sheffield, drafted one chapter and approved the final report.

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Steven Thomas (Senior Lecturer and Consultant Vascular Radiologist) helped to assemble the collaborative group, edited the application, helped to develop and obtained data for the model, contributed to the design of the study, attended five meetings to discuss progress and consider results, helped to edit three chapters and approved the final report.

Jonathan Gillard (Reader and Honorary Consultant Neuroradiologist) provided individual patient data and data on costs of investigations from Cambridge, contributed to the design of the study through discussions, attended two meetings to discuss progress and consider results, helped to edit one chapter and approved the final report.

Elizabeth Berry (Senior Lecturer) provided data on MRA from a recent previous systematic literature review, helped to draft the application, contributed to the design of the study through discussions, attended three meetings to discuss progress and consider results, helped to edit and approved the final report.

Gavin Young (Consultant Neurologist) contributed to the design of the study through discussions, attended three meetings to discuss progress and consider results, provided data for the individual patient data analysis, helped to edit and approved the final report.

Peter Rothwell (Professor of Clinical Neurology) provided additional data from the carotid surgery trial data set and OCSP and OXVASC studies to help to populate the model, assisted in the design of the model and underlying assumptions, and approved the final report.

Giles Roditi (Consultant Radiologist) contributed to the design of the study through discussions, attended two meetings to discuss progress and consider results, provided data for the individual patient data analysis, helped to edit and approved the final report.

Michael Gough (Consultant Vascular Surgeon) contributed to the design of the study through discussions, attended two meetings to discuss progress and consider results, suggested data sources for the individual patient data analysis, helped to edit and approved the report.

Allan Brennan (Director of Health Economics and Decision Science) helped to write the full application, supervised Matt Stevenson and Enrico De Nigris, contributed to the design of the study through discussions, supervised the construction and running of the cost-effectiveness model, attended two meetings to discuss progress and consider results and approved the final report.

John Bamford (Consultant Neurologist and Cerebrovascular Physician) contributed to the design of the study through discussions, provided data for the survey of UK stroke prevention clinics, attended a meeting to discuss progress and consider results, and approved the final report.

Jonathan Best (Professor of Medical Radiology) assisted with selection of papers and data extraction for the systematic review, attended one meeting to discuss progress and consider results, helped draft one chapter and approved the final report.

References

1. Isard PA, Forbes JF. The cost of stroke to the national service in Scotland. *Cerebrovasc Dis* 1992;**2**:47–50.
2. European Carotid Surgery Trial Collaborative Group. Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). *Lancet* 1998;**351**:1379–87.
3. North American Symptomatic Carotid Endarterectomy Trial Collaborators. Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. *N Engl J Med* 1998;**339**:1415–25.
4. Rothwell PM, Eliasziw M, Gutnikov SA, Fox AJ, Taylor DW, Mayberg MR, *et al*. Analysis of pooled data from the randomised controlled trials of endarterectomy for symptomatic carotid stenosis. *Lancet* 2003;**361**:107–16.
5. Rothwell PM, Mehta Z, Howard SC, Gutnikov SA, Warlow CP. From subgroups to individuals: general principles and the example of carotid endarterectomy. *Lancet* 2005;**365**:256–65.
6. Coull AJ, Lovett JK, Rothwell PM, on behalf of the Oxford Vascular Study. Population based study of early risk of stroke after transient ischaemic attack or minor stroke: implications for public education and organisation of services. *BMJ* 2004;**328**:326.
7. Lovett JK, Dennis MS, Sandercock PAG, Bamford J, Warlow CP, Rothwell PM. Very early risk of stroke after a first transient ischemic attack. *Stroke* 2003;**34**:1–3.
8. Johnston SC, Gress DR, Browner WS, Sidney S. Short-term prognosis after emergency department diagnosis of TIA. *JAMA* 2000;**284**:2901–6.
9. Hill MD, Yiannakoulias N, Jeerakathil T, Tu JV, Svenson LW, Schopflocher DP. The high risk of stroke immediately after transient ischemic attack: a population-based study. *Neurology* 2004;**62**:2015–20.
10. European Carotid Surgery Trialists' Collaborative Group. Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). *Lancet* 1998;**351**:1379–87.
11. Rothwell PM, Gibson RJ, Slattery J, Sellar RJ, Warlow CP. Equivalence of measurements of carotid stenosis: a comparison of three methods on 1001 angiograms. *Stroke* 1994;**25**:2435–9.
12. Rothwell PM, Gibson R, Warlow CP, on behalf of the European Carotid Surgery Trialists' Collaborative Group. Interrelation between plaque surface morphology and degree of stenosis on carotid angiograms and the risk of ischemic stroke in patients with symptomatic carotid stenosis. *Stroke* 2000;**31**:615–21.
13. Hankey GJ, Warlow CP, Molyneux AJ. Complications of cerebral angiography for patients with mild carotid territory ischaemia being considered for carotid endarterectomy. *J Neurol Neurosurg Psychiatry* 1990;**53**:542–8.
14. Davies KN, Humphrey PRD. Complications of cerebral angiography in patients with symptomatic carotid territory ischaemia screened by carotid ultrasound. *J Neurol Neurosurg Psychiatry* 1992;**55**:1215.
15. Bhatti TS, Harradine K, Davies B, Heather BP, Earnshaw JJ. First year of a fast track carotid duplex service. *J R Coll Surg Edinb* 1999;**44**:307–9.
16. 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.
17. Moore WS. For severe carotid stenosis found on ultrasound, further arterial evaluation is unnecessary. *Stroke* 2003;**34**:1816–17.
18. Davis SM, Donnan GA. Is carotid angiography necessary? Editors disagree. *Stroke* 2003;**34**:1819.
19. Norris JW, Halliday A. Is ultrasound sufficient for vascular imaging prior to carotid endarterectomy? *Stroke* 2004;**35**:370–1.
20. Powers WJ. Carotid arteriography: still golden after all these years? *Neurology* 2004;**62**:1246–7.
21. U-King-Im JM, Trivedi RA, Graves MJ, Higgins NJ, Cross JJ, Tom BD, *et al*. Contrast-enhanced MR angiography for carotid disease. Diagnostic and potential clinical impact. *Neurology* 2004;**62**:1282–90.
22. Hunter JV. Are two heads better than one? *J Neurol Neurosurg Psychiatry* 2001;**71**:147.
23. Kennedy J, Quan H, Ghali WA, Feasby TE. Importance of the imaging modality in decision making about carotid endarterectomy. *Neurology* 2004;**62**:901–4.
24. Perkins JMT, Galland RB, Simmons MJ, Magee TR. Carotid duplex imaging: variation and validation. *Br J Surg* 2000;**87**:320–2.

© Queen's Printer and Controller of HMSO 2006. All rights reserved.

25. Rodgers H, Oliver SE, Dobson R, Thomson RG. A regional collaborative audit of the practice and outcome of carotid endarterectomy in the United Kingdom. Northern Regional Carotid Endarterectomy Audit Group. *Eur J Vasc Endovasc Surg* 2000;**19**:362–9.

26. Jager HR, Moore EA, Bynevelt M, Coley S, Mounfield P, Kitchen N, *et al*. Contrast-enhanced MR angiography in patients with carotid artery stenosis: comparison of two different techniques with an unenhanced 2D time-of-flight sequence. *Neuroradiology* 2000;**42**:240–8.

27. Humphrey P. Detecting carotid stenoses. *J Neurol Neurosurg Psychiatry* 1999;**66**:4.

28. Sostman HD, Beam CA. Evaluation of the quality of clinical research studies of magnetic resonance angiography: 1991–1994. *J Magn Reson Imaging* 1996;**6**:33–8.

29. Rothwell PM, Pendlebury ST, Wardlaw J, Warlow CP. A critical appraisal of the design and reporting of studies of imaging and measurement of carotid stenosis. *Stroke* 2000;**31**:1444–50.

30. Feinstein AR. Misguided efforts and future challenges for research on 'diagnostic tests'. *J Epidemiol Community Health* 2002;**56**:330–32.

31. Westwood ME, Kelly S, Berry E, Bamford JM, Gough MJ, Airey CM, *et al*. Use of magnetic resonance angiography to select candidates with recently symptomatic carotid stenosis for surgery: systematic review. *BMJ* 2002;**324**:198.

32. Westwood ME, Kelly S, Berry E, Bamford JM, Gough MJ, Airey CM, *et al*. How to undertake a clinically relevant systematic review in a rapidly evolving field. Magnetic resonance angiography. *Int J Technol Assess Health Care* 2002;**18**:24–32.

33. Wardlaw JM, Lewis SC, Humphrey P, Young G, Collie D, Warlow CP. How does the degree of carotid stenosis affect the accuracy and interobserver variability of magnetic resonance angiography? *J Neurol Neurosurg Psychiatry* 2001;**71**:155–60.

34. Patel SG, Collie DA, Wardlaw JM, Lewis SC, Wright AR, Gibson RJ, *et al*. Outcome, observer reliability, and patient preferences if CTA, MRA, or Doppler ultrasound were used, individually or together, instead of digital subtraction angiography before carotid endarterectomy. *J Neurol Neurosurg Psychiatry* 2002;**73**:21–8.

35. Irwig L, Macaskill P, Glasziou P, Fahey M. Meta-analytic methods for diagnostic test accuracy. *J Clin Epidemiol* 1995;**48**:119–30.

36. Eisenberg JM. Ten lessons for evidence-based technology assessment. *JAMA* 1999;**282**:1865–9.

37. Deeks JJ. Systematic reviews of evaluations of diagnostic and screening tests. In Egger M, Davey Smith G, Altman DG, editors. *Systematic reviews in healthcare: meta-analysis in context*. London: *BMJ* Books; 2001. pp. 248–82.

38. Kardaun JW, Kardaun OJ. Comparative diagnostic performance of three radiological procedures for the detection of lumbar disk herniation. *Methods Inf Med* 1990;**29**:12–22.

39. Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, *et al*. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. *Clin Radiol* 2003;**58**:575–80.

40. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health* 1998;**52**:377–84.

41. Matowe L, Gilbert FJ. How to synthesize evidence for imaging guidelines. *Clinl Radiol* 2004;**59**:63–8.

42. Brenner H, Gefeller O. Variation of sensitivity, specificity, likelihood ratios and predictive values with disease prevalence. *Stat Med* 1997;**16**:981–91.

43. Ransohoff DF, Feinstein AR. Problems of spectrum and bias in evaluating the efficacy of diagnostic tests. *N Engl J Med* 1978;**299**:926–30.

44. Black WC, Welch HG. Advances in diagnostic imaging and overestimations of disease prevalence and the benefits of therapy. *N Engl J Med* 1993;**328**:1237–43.

45. Egglin TK, Feinstein AR. Context bias. A problem in diagnostic radiology. *JAMA* 1996;**276**:1752–5.

46. Easterbrook PJ, Berlin JA, Gopalan R, Matthews DR. Publication bias in clinical research. *Lancet* 1991;**337**:867–72.

47. McAuley L, Pham B, Tugwell P, Moher D. Does the inclusion of grey literature influence estimates of intervention effectiveness reported in meta-analyses? *Lancet* 2000;**356**:1228–31.

48. Blakeley DD, Oddone EZ, Hasselblad V, Simel DL, Matchar DB. Noninvasive carotid artery testing. A meta-analytic review. *Ann Intern Med* 1995;**122**:360–67.

49. Kallmes DF, Omary RA, Dix JE, Evans AJ, Hillman BJ. Specificity of MR angiography as a confirmatory test of carotid artery stenosis. *AJNR Am J Neuroradiol* 1996;**17**:1501–6.

50. Reed JFI. Meta-analysis of the reliability of noninvasive carotid studies. *Biomed Instrum Technol* 1991;**25**:465–71.

51. Reed JFI, McCullogh S, Wasser T. Magnetic resonance angiography and duplex scanning concordance in detecting severe carotid stenosis. *Vascular Surgery* 1995;**29**:177–83.

52. Fisher CM, Appleberg M, Irwig L, Macaskill P. A systematic review of the accuracy of diagnosis of

70% carotid artery stenosis by duplex scanning. *Journal of Vascular Investigation* 1998;**4**:91–8.

53. Long A, Lepoutre A, Corbillon E, Branchereau A. Critical review of non- or minimally invasive methods (duplex ultrasonography, MR- and CT-angiography) for evaluating stenosis of the proximal internal carotid artery. *Eur J Vasc Endovasc Surg* 2002;**24**:43–52.

54. Lilford RJ, Braunholtz DA, Greenhalgh R, Edwards SJ. Trials and fast changing technologies: the case for tracker studies. *BMJ* 2000;**320**:43–46.

55. Wardlaw JM, Lewis SC, Collie DA, Sellar R. Interobserver variability of magnetic resonance angiography in the diagnosis of carotid stenosis – effect of observer experience. *Neuroradiology* 2002; **44**:126–32.

56. Young GR, Humphrey PR, Shaw MD, Nixon TE, Smith ET. Comparison of magnetic resonance angiography, duplex ultrasound, and digital subtraction angiography in assessment of extracranial internal carotid artery stenosis. *J Neurol Neurosurg Psychiatry* 1994;**57**:1466–78.

57. Drummond M, O'Brien B, Stoddart G, Torrance GW. *Methods for the economic evaluation of health care programs*. 2nd ed. Oxford: Oxford University Press; 1997.

58. Hankey G, Warlow C. Cost-effective investigation of patients with suspected transient ischaemic attacks. *J Neurol Neurosurg Psychiatry* 1992; **55**:171–6.

59. Holloway RG, Benesch CG, Rahilly C, Courtright CE. A systematic review of cost-effectiveness research of stroke evaluation and treatment. *Stroke* 1999;**30**:1340–9.

60. Kent KC, Kuntz KM, Patel MR, Kim D, Klufas RA, Whittemore AD, *et al*. Perioperative imaging strategies for carotid endarterectomy. An analysis of morbidity and cost-effectiveness in symptomatic patients. *JAMA* 1995;**274**:888–93.

61. Rothwell PM, Warlow CP. Prediction of benefit from carotid endarterectomy in individual patients: a risk-modelling study. European Carotid Surgery Trialists' Collaborative Group. *Lancet* 1999;**353**:2105–110.

62. Netten A, Curtis L. *Unit costs of health and social care 2000*. Kent: Personal Social Services Research Unit; 2000. Accessed September 2001.

63. Wood BP. What's the evidence? *Radiology* 1999;**213**:635–7.

64. Medina LS. Study design and analysis in neuroradiology: a practical guide. *AJNR Am J Neuroradiol* 1999;**20**:1584–96.

65. Blackmore CC. The challenge of clinical radiology research. *AJR AM J Roentgenol* 2001;**176**:327–31.

66. Rothwell PM, Slattery J, Warlow CP. Clinical and angiographic predictors of stroke and death from carotid endarterectomy: systematic review. *BMJ* 1997;**315**:1571–7.

67. Rothwell PM, Slattery J, Warlow CP. A systematic review of the risks of stroke and death due to endarterectomy for symptomatic carotid stenosis. *Stroke* 1996;**27**:260–5.

68. Haynes RB, Wilczynski NL. Optimal search strategies for retrieving scientifically strong studies of diagnosis for MEDLINE: analytical survey. *BMJ* 2004;**328**:1040.

69. Devillé WLJM, Bezemer PD, Bouter LM. Publications on diagnostic test evaluation in family medicine journals: an optimal search strategy. *J Clin Epidemiol* 2000;**53**:65–9.

70. Moher D, Fortin P, Jadad AR, Juni P, Klassen T, Le Lorier J, *et al*. Completeness of reporting of trials published in languages other than English: implications for conduct and reporting of systematic reviews. *Lancet* 1996;**347**:363–6.

71. Egger M, Zellweger-Zahner T, Schneider M, Junker C, Lengeler C, Antes G. Language bias in randomised controlled trials published in English and German. *Lancet* 1997;**350**:326–9.

72. Rothwell PM, Gibson RJ, Slattery J, Warlow CP. Prognostic value and reproducibility of measurements of carotid stenosis. A comparison of three methods on 1001 angiograms. European Carotid Surgery Trialists' Collaborative Group. *Stroke* 1994;**25**:2440–4.

73. Berry E, Kelly S, Westwood ME, Davies LM, Gough MJ, Bamford JM, *et al*. The cost-effectiveness of magnetic resonance angiography for carotid artery stenosis and peripheral vascular disease: a systematic review. *Health Technol Assess* 2002;**6**(7).

74. Whiting P, Rutjes AWS, Reitsma JB, Bossuyt PMM, Kleijnen J. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. *BMC Med Res Methodol* 2003;**3**:25.

75. Fleiss JL, Levin B, Paik MC. The comparison of proportions from several independent samples: estimation of the marginal mean proportion. In Fleiss JL, Levin B, Paik MC, editors. *Statistical methods for rates and proportions*. Hoboken, NJ: John Wiley & Sons; 2003. pp. 212–17.

76. Jüni P, Altman DG, Egger M. Assessing the quality of controlled clinical trials. *BMJ* 2001; **323**:42–6.

77. Dix JSJ. Evaluation of carotid stenosis by angiography: potential bias toward overestimated measurements introduced by prior interpretation of Doppler sonograms. *AJNR Am J Neuroradiol* 2000;**21**:639–42.

© Queen's Printer and Controller of HMSO 2006. All rights reserved.

78. Moses LE, Shapiro D, Littenberg B. Combining independent studies of a diagnostic test into a summary ROC curve: data-analytic approaches and some additional considerations. *Stat Med* 1993;**12**:1293–316.

79. Alvarez-Linera J, Benito-Leon J, Escribano J, Campollo J, Gesto R. Prospective evaluation of carotid artery stenosis: elliptic centric contrast-enhanced MR angiography and spiral CT angiography compared with digital subtraction angiography. *AJNR Am J Neuroradiol* 2003; **24**:1012–19.

80. Anderson GB, Ashforth R, Steinke DE, Ferdinandy R, Findlay JM. CT angiography for the detection and characterization of carotid artery bifurcation disease. *Stroke* 2000;**31**:2168–74.

81. Boné G, Ladurner G, Karas I, Grobovschek M, Punzengruber J. Evaluation of the carotid bifurcation by duplex ultrasound, intravenous and intra-arterial digital subtraction angiography. *Eur Neurol* 1988;**28**:73–6.

82. Bönig L, Weder B, Schott D, Keel A, Nguyen T, Zaunbauer W. Prediction of angiographic carotid artery stenosis indexes by colour Doppler-assisted duplex imaging. A critical appraisal of the parameters used. *Eur J Neurol* 2000;**7**:183–90.

83. Borisch I, Horn M, Butz B, Zorger N, Draganski B, Hoelscher T, *et al*. Preoperative evaluation of carotid artery stenosis: comparison of contrast-enhanced MR angiography and duplex sonography with digital subtraction angiography. *AJNR Am J Neuroradiol* 2003;**24**:1117–22.

84. Catalano C, Laghi A, Pediconi F, Fraioli F, Napoli A, Passariello R. [Magnetic resonance angiography with contrast media in the study of carotid arteries] [in Italian]. *Radiol Med (Torino)* 2001;**101**:54–9.

85. Cosottini M, Pingitore A, Puglioli M, Michelassi MC, Lupi G, Abbruzzese A, *et al*. Contrast-enhanced three-dimensional magnetic resonance angiography of atherosclerotic internal carotid stenosis as the noninvasive imaging modality in revascularization decision making. *Stroke* 2003;**34**:660–4.

86. Cosottini M, Calabrese R, Puglioli M, Zampa V, Michelassi C, Ortori S, *et al*. Contrast-enhanced three-dimensional MR angiography of neck vessels: does dephasing effect alter diagnostic accuracy? *Eur Radiol* 2003;**13**:571–81.

87. Cumming MJ, Morrow IM. Carotid artery stenosis: a prospective comparison of CT angiography and conventional angiography. *AJR Am J Roentgenol* 1994;**163**:517–23.

88. Dadachanji MC, Shroff MM, Modi D, Jankharia BG. Comparison of MR angiography with contrast angiography for the diagnosis of carotid artery stenosis. *J Assoc Physicians India* 1995;**43**:92–5.

89. Dillon EH, van Leeuwen MS, Fernandez MA, Eikelboom BC, Mali WP. CT angiography: application to the evaluation of carotid artery stenosis. *Radiology* 1993;**189**:211–19.

90. Elgersma OEH, Wust AF, Buijs PC, van der Graaf Y, Eikelboom BC, Mali WPTM. Multidirectional depiction of internal carotid arterial stenosis: Three-dimensional time-of-flight MR angiography versus rotational and conventional digital subtraction angiography. *Radiology* 2000;**216**:511–16.

91. Elgersma OE, Buijs PC, Wust AF, van der Graaf Y, Eikelboom BC, Mali WP. Maximum internal carotid arterial stenosis: assessment with rotational angiography versus conventional intraarterial digital subtraction angiography. *Radiology* 1999;**213**:777–83.

92. Humphrey P, Sandercock P, Slattery J. A simple method to improve the accuracy of non-invasive ultrasound in selecting TIA patients for cerebral angiography. *J Neurol Neurosurg Psychiatry* 1990;**53**:966–71.

93. Huston J III, Lewis BD, Wiebers DO, Meyer FB, Riederer SJ, Weaver AL. Carotid artery: prospective blinded comparison of two-dimensional time- of-flight MR angiography with conventional angiography and duplex US. *Radiology* 1993;**186**:339–44.

94. Knudsen L, Johansen A, Justesen P, Jorgensen HB. Accuracy of duplex scan of internal carotid arteries. *Eur J Vasc Endovasc Surg* 2002;**24**:86–7.

95. Laster RE, Acker JD, Halford III HH, Nauer TC. Assessment of MR angiography versus arteriography for evaluation of cervical carotid bifurcation disease. *AJNR Am J Neuroradiol* 1993;**14**:681–8.

96. Leclerc X, Godefroy O, Pruvo JP, Leys D. Computed tomographic angiography for the evaluation of carotid artery stenosis. *Stroke* 1995;**29**:1577–81.

97. Leclerc X, Godefroy O, Lucas C, Benhaim JF, Michel TS, Leys D, *et al*. Internal carotid arterial stenosis: CT angiography with volume rendering. *Radiology* 1999;**210**:673–82.

98. Leclerc X, Martinat P, Godefroy O, Lucas C, Giboreau F, Ares GS, *et al*. Contrast-enhanced three-dimensional fast imaging with steady-state precession (FISP) MR angiography of supraaortic vessels: preliminary results. *AJNR Am J Neuroradiol* 1998;**19**:1405–13.

99. Levi CR, Mitchell A, Fitt G, Donnan GA. The accuracy of magnetic resonance angiography in the assessment of extracranial carotid artery occlusive disease. *Cerebrovasc Dis* 1996;**6**:231–36.

100. Link J, Brossmann J, Grabener M, Mueller-Huelsbeck S, Steffens JC, Brinkmann G, *et al*.

Spiral CT angiography and selective digital subtraction angiography of internal carotid artery stenosis. *AJNR Am J Neuroradiol* 1996; **17**:89–94.

101. Link J, Mueller-Huelsbeck S, Brossmann J, Grabener M, Stock U, Heller M. Prospective assessment of carotid bifurcation disease with spiral CT angiography in surface shaded display (SSD)-technique. *Comput Med Imaging Graph* 1995;**19**:451–6.

102. Link J, Brossmann J, Penselin V, Gluer CC, Heller M. Common carotid artery bifurcation: preliminary results of CT angiography and color-coded duplex sonography compared with digital subtraction angiography. *AJNR Am J Roentgenol* 1997;**168**:361–5.

103. Magarelli N, Scarabino T, Simeone AL, Florio F, Carriero A, Salvolini U, *et al*. Carotid stenosis: a comparison between MR and spiral CT angiography. *Neuroradiology* 1998;**40**:367–73.

104. Nederkoorn PJ, Mali WP, Eikelboom BC, Elgersma OE, Buskens E, Hunink MG, *et al*. Preoperative diagnosis of carotid artery stenosis: accuracy of noninvasive testing. *Stroke* 2002;**33**:2003–8.

105. Nederkoorn PJ, Elgersma OE, Mali WP, Eikelboom BC, Kappelle LJ, van der Graaf Y. Overestimation of carotid artery stenosis with magnetic resonance angiography compared with digital subtraction angiography. *J Vasc Surg* 2002;**36**:806–13.

106. Patel MR, Kuntz KM, Klufas RA, Kim D, Kramer J, Polak JF, *et al*. Preoperative assessment of the carotid bifucation. Can magnetic resonance angiography and duplex ultrasonography replace contrast arteriography? *Stroke* 1995;**26**:1753–8.

107. Remonda L, Heid O, Schroth G. Carotid artery stenosis, occlusion, and pseudo-occlusion: first-pass, gadolinium-enhanced, three-dimensional MR angiography – preliminary study [see comments]. *Radiology* 1998;**209**:95–102.

108. Sardanelli F, Zandrino F, Parodi RC, De Caro G. MR angiography of internal carotid arteries: breath-hold Gd-enhanced 3D fast imaging with steady-state precession versus unenhanced 2D and 3D time-of-flight techniques. *J Comput Assist Tomogr* 1999;**23**:208–15.

109. Scarabino T, Carriero A, Giannatempo GM, Marano R, De Matthaeis P, Bonomo L, *et al*. Contrast-enhanced MR angiography (CE MRA) in the study of the carotid stenosis: comparison with digital subtraction angiography (DSA). *J Neuroradiol* 1999;**26**:87–91.

110. Scarabino T, Carriero A, Balzano S, Sciannelli V, Bonomo L, Salvolini U. [Stenosis-occlusion of the carotid bifurcation. Angiography with MR and contrast media versus digital angiography] [in Italian]. *Radiol Med (Torina)* 1998;**95**:170–3.

111. Scarabino T, Carriero A, Magarelli N, Florio F, Giannatempo GM, Bonomo L, *et al*. MR angiography in carotid stenosis: a comparison of three techniques. *Eur J Radiol* 1998;**28**:117–25.

112. Simeone A, Carriero A, Armillotta M, Scarabino T, Nardella M, Ceddia A, *et al*. Spiral CT angiography in the study of the carotid stenoses. *J Neuroradiol* 1997;**24**:18–22.

113. Sitzer M, Furst G, Fischer H, Siebler M, Fehlings T, Kleinschmidt A, *et al*. Between-method correlation in quantifying internal carotid stenosis. *Stroke* 1993;**24:**1513–18.

114. Tetičkovič E, Gajsek-Marchetti M, Matela J, Flis V. Three-dimensional ultrasonography for the evaluation of atherosclerotic stenoses of the carotid trunk. *Coll Antropol* 2001;**25**:511–20.

115. Turnipseed WD, Kennell TW, Turski PA, Acher CW, Hoch JR. Combined use of duplex imaging and magnetic resonance angiography for evaluation of patients with symptomatic ipsilateral high-grade carotid stenosis. *J Vasc Surg* 1993;**17**:832–9.

116. Uehara T, Tabuchi M, Ohsumi Y, Yoneda Y, Mori E. Usefulness of three-dimensional time-of-flight MR angiography for evaluation of carotid artery bifurcation stenosis. *Cerebrovasc Dis* 1995; **5**:199–203.

117. Van Merode T, Lodder J, Smeets FAM, Hoeks APG, Reneman RS. Accurate noninvasive method to diagnose minor atherosclerotic lesions in carotid artery bulb. *Stroke* 1989;**20**:1336–40.

118. Vanninen R, Manninen H, Soimakallio S. Imaging of carotid artery stenosis: clinical efficacy and cost-effectiveness. *AJNR Am J Neuroradiol* 1995;**16**:1875–83.

119. White JE, Russell WL, Greer MS, Whittle MT. Efficacy of screening MR angiography and Doppler ultrasonography in the evaluation of carotid artery stenosis. *Am Surg* 1994;**60**:340–8.

120. Winkelaar GB, Chen JC, Salvian AJ, Taylor DC, Teal PA, Hsiang YN. New duplex ultrasound scan criteria for managing symptomatic 50% or greater carotid stenosis. *J Vasc Surg* 1999;**29**:986–94.

121. Worthy SA, Henderson J, Griffiths PD, Oates CP, Gholkar A. The role of duplex sonography and angiography in the investigation of carotid artery disease. *Neuroradiology* 1997;**39**:122–6.

122. Young GR, Humphrey PR, Nixon TE, Smith ET. Variability in measurement of extracranial internal carotid artery stenosis as displayed by both digital subtraction and magnetic resonance angiography: an assessment of three caliper techniques and visual impression of stenosis. *Stroke* 1996;**27**:467–73.

123. Zbornikova V, Johansson I. Duplex criteria for grading internal carotid artery stenosis >50%

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based on multiregression analysis. *J Neuroimaging* 1998;**8**:132–5.

124. Egger M, Davey Smith G. Principles of and procedures for systematic reviews. In Egger M, Davey Smith G, Altman DG, editors. *Systematic reviews in health care: meta-analysis in context*. London: BMJ Books; 2001. pp. 23–42.

125. Tang J-L, Liu JLY. Misleading funnel plot for the detection of bias in meta-analysis. *J Clin Epidemiol* 2000;**53**:477–84.

126. Deeks JJ, Higgins JPT, Altman DG. Analysing and presenting results. In: Higgins JPT, Green S, editors. *Cochrane Handbook for Systematic Reviews of Interventions* 4.2.5 [updated May 2005]; Section 8. http://www.cochrane.org/resources/handbook/hbook.htm. Accessed 31 May 2005.

127. Bosanac Z, Miller RJ, Jain M. Rotational digital subtraction carotid angiography: technique and comparison with static digital subtraction angiography. *Clin Radiol* 1998;**53**:682–7.

128. Kent DL, Haynor DR, Longstreth WT Jr, Larson EB. The clinical efficacy of magnetic resonance imaging in neuroimaging. *Ann Intern Med* 1994;**120**:856–71.

129. Bebarta V, Luyten D, Heard K. Emergency medicine animal research: does use of randomization and blinding affect the results? *Acad Emerg Med* 2003;**10**:684–7.

130. Stewart LA, Parmar MK. Meta-analysis of the literature or of individual patient data: is there a difference? *Lancet* 1993;**341**:418–22.

131. Lau J, Ioannidis JP, Schmid CH. Summing up evidence: one answer is not always enough. *Lancet* 1998;**351**:123–7.

132. Pogue J, Yusuf S. Overcoming the limitations of current meta-analysis of randomised controlled trials. *Lancet* 1998;**351**:47–52.

133. Stewart LA, Clarke MJ. Practical methodology of meta-analyses using updated individual patient data. In Alderson P, Green S, Higgins JPT, editors. *Cochrane Reviewers Handbook* 4.2.2. Chichester: John Wiley & Sons, 2003.

134. White P, Wardlaw J, Easton V. Can noninvasive imaging accurately depict intracranial aneurysms? A systematic review. *Radiology* 2000;**217**:361–70.

135. Keir SL, Wardlaw J. Systematic review of diffusion and perfusion imaging in acute ischaemic stroke. *Stroke* 2000;**31**:2723–31.

136. 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.

137. Stewart LA, Clarke MJ. Reviews using individual patient data. In Alderson P, Green S, Higgins JPT, editors. *Cochrane Reviewers Handbook* 4.2.2. Chichester: John Wiley, 2003.

138. Brower W, Rutten F, Koopmanschap M. Costing in economic evaluations. In Drummond MD, McGuire A, editors. *Economic evaluation in health care. Merging theory with practice*. Oxford: Oxford University Press; 2001. pp. 68–93.

139. Ramsey RH. Activity-based costing for hospitals. *Hospital Health Service Administration* 1994; **39**:385–96.

140. Drummond MF, Ward GH. The financial burden of stroke and the economic evaluation of treatment alternatives. In: Clifford RF, editor. *Stroke: epidemiological, therapeutic and socio-economic aspects*. London: Royal Society of Medicine Services; 1986. pp. 147–62.

141. Netten A, Cutis L. *Unit costs of health and social care 2003*. Canterbury: Personal Social Services Research Unit; 2003.

142. Vachris MA, Thomas J. International price comparisons based on purchasing power parity [monograph]. *Monthly Labor Review* 3–12 October 1999.

143. NHS National Health Service Care Resource Groups [monograph] 2004.

144. Brooks RG. EuroQol: the current state of the play. *Health Policy* 1996;**37**:53–72.

145. Torrance GW, Furlong W, Feeny D, Boyle M. Multi-attribute preference functions. Health Utilities Index. *Pharmacoeconomics* 1995;**7**:503–20.

146. Post PN, Kievit J, van Baalen JM, van den Hout WB, van Bockel JH. Routine duplex surveillance does not improve the outcome after carotid endarterectomy. *Stroke* 2002;**33**:749–55.

147. Hankey GJ, Warlow CP. Symptomatic carotid ischaemic events: safest and most cost effective way of selecting patients for angiography, before carotid endarterectomy. *BMJ* 1990;**300**:1485–91.

148. U-King-Im J, Trivedi R, Gillard JH. Contrast-enhanced magnetic resonance angiography carotid arteries. *Stroke* 2003;**34**:e15.

149. Benade MM, Warlow CP. Costs and benefits of carotid endarterectomy and associated preoperative arterial imaging: a systematic review of health economic literature. *Stroke* 2002; **33**:629–38.

150. Derdeyn CP, Powers WJ. Cost-effectiveness of screening for asymptomatic carotid atherosclerosis disease. *Stroke* 1996;**27**:1944–50.

151. Yin D, Carpenter JP. Cost-effectiveness of screening for asymptomatic carotid stenosis. *J Vasc Surg* 1998;**27**:245–55.

152. Lee TT, Solomon NA, Heidenreich PA, Oehlert J, Garber AM. Cost-effectiveness of screening for

carotid stenosis in asymptomatic persons. *Ann Intern Med* 1997;**126**:337–46.

153. Nelemans PJ, Kessels AGH, De Leeuw P, De Haan M, van Engelshoven J. The cost effectiveness of the diagnosis of renal artery stenosis. *Eur J Radiol* 1998;**27**:95–107.

154. Paterson DI, Schwartzman K. Strategies incorporating spiral CT for the diagnosis of acute pulmonary embolism: a cost-effectiveness analysis. *Chest* 2001;**119**:1791–800.

155. Lindgren BW, Demos T, Marsan R, Posniak H, Kostro B, Calvert D, *et al*. Renal computed tomography with 3-dimensional angiography and simultaneous measurement of plasma contrast clearance reduce the invasiveness and cost of evaluating living renal donor candidates. *Transplantation* 1996;**61**:219–23.

156. Tierney WM, Fendrick AM, Hirth RA, Scheiman JM. The clinical and economic impact of alternative strategies for adenocarcinoma of the pancreas. *Am J Gastroenterol* 2000;**95**:1708–13.

157. Visser K, Kock MC, Kuntz KM, Donaldson MC, Gazelle GS, Hunink MG. Cost-effectiveness targets for multi-detector row CT angiography in the work-up of patients with intermittent claudication. *Radiology* 2003;**227**:647–56.

158. van Erkel AR, van Rossum AB, Bloem JL, Kievit J, Pattynama PM. Spiral CT angiography for suspected pulmonary embolism: a cost-effectiveness analysis. *Radiology* 1996;**201**:29–36.

159. Ferguson A, McCabe CJ. *The clinical and cost-effectiveness of computed tomography in the management of transient ischaemic attack and stroke*. Sheffield: Trent Institute for Health Services Research; 1997.

160. Wardlaw JM, Keir SL, Seymour J, Lewis S, Sandercock PA, Dennis MS, *et al*. What is the best imaging strategy for acute stroke? *Health Technol Assess* 2004;**8**(1):1–180.

161. Gray WA, White HJ Jr, Barrett DM, Chandran G, Turner R, Reisman M. Carotid stenting and endarterectomy: a clinical and cost comparison of revascularization strategies. *Stroke* 2002;**33**:1063–70.

162. Kilaru S, Korn P, Kasirajan K, Lee TY, Beavers FP, Lyon RT, *et al*. Is carotid angioplasty and stenting more cost effective than carotid endarterectomy? *J Vasc Surg* 2003;**37**:331–9.

163. Evers SMAA, Struijs JN, Ament AJHA, van Genugten MLL, Jager C, van der Bos GAM. International comparison of stroke cost studies. *Stroke* 2004;**35**:1209–15.

164. Adelman SM. The National Survey of Stroke. Economic impact. *Stroke* 1981;**12**:I69–87.

165. Bergman L, van der Meulen J, Limburg M, Habbema DF. Cost of medical care after first-ever stroke in the Netherlands. *Stroke* 1995;**26**:1830–6.

166. Carstairs V. Stroke: resources, consumption and the costs to the community. In Gillingham FJ, Maudsley C, Williams E, editors. *Stroke*. London: Churchill Livingstone; 1976. pp. 516–28.

167. Chan B, Hayes B. Cost of stroke in Ontario, 1994/95. *CMAJ* 1998;**159**:S2–7.

168. Dewey HM, Thrift AG, Mihalopoulos C, Carter R, Macdonell RAL, McNeil JJ, *et al*. Cost of stroke in Australia from a societal perspective. Results from the North East Melbourne Stroke Incidence Study (NEMESIS). *Stro*ke 2001;**32**:2409–16.

169. Evers SM, Engel GL, Ament AJ. Cost of stroke in the Netherlands from a societal perspective. *Stroke* 1997;**28**:1375–81.

170. Hartunian NS, Smart CN, Thompson MS. The incidence and economic costs of cancer, motor vehicle injuries, coronary heart disease, and stroke: a comparative analysis. *Am J Public Health* 1980; **70**:1249–60.

171. Health Canada. *Economic burden of illness in Canada 1993*. Ottawa: Canadian Public Health Association; 1997.

172. Hodgson TA. Cost of illness studies: no aid to decision making? Comments on the second opinion by Shiell *et al*. (*Health Policy*, **8**(1987) 317–323). *Health Policy* 1989;**11**:57–60.

173. Kavanagh S, Knapp M, Patel A. Costs and disability among stroke patients. *J Public Health Med* 1999;**21**:385–94.

174. Koopmanschap MA, van Roijen L, Bonneux L. *Cost of diseases in the Netherlands 1988*. Rotterdam: Erasmus University, Department of Public Health, Institute of Medical Technology Assessment; 1991.

175. Mills E, Thompson M. The economic costs of stroke in Massachusetts. *N Engl J Med* 1978;**299**:415–18.

176. Persson U, Silverberg R, Lindgren B, Norrving B, Jadback G, Johansson B, *et al*. Direct costs of stroke for a Swedish population. *Int J Technol Assess Health Care* 1990;**6**:125–37.

177. Polder JJ, Meerding WJ, Koopmanschap MA, Bonneux L, van der Maas PJ. *Kosten van ziekten in Nederland 1994* [monograph]. Rotterdam: Instituut Maatschappelijke Gezondheidszorg, Instituut voor Medische Technology Assessment; 1997.

178. Polder JJ, Takken J, Meerding WJ, Kommer GJ, Stokx LJ. *Kosten van ziekten in Nederland*. Rotterdam/Bilthoven: Instituut Maatchappelijke Gezonndheidszorg Instituut voor Medical Technology Assessment van de Erasmus Universiteit Rotterdam/Centrum voor Volksgezondheid Tockomst Verkenningen van het Rijksinstituut voor Volksgezondheid en Milieu; 2002.

179. Porsdal V, Boysen G. Direct costs of transient ischemic attacks: a hospital-based study of resource use during the first year after transient ischemic attacks in Denmark. *Stroke* 1998;**29**:2321–4.

© Queen's Printer and Controller of HMSO 2006. All rights reserved.

180. Swedish Council on Health Techology Assessment. Economics. In: Magnusson S, Werko L, editors. *The Swedish Council on Technology Assessment in Health Care*. Stockholm: Swedish Council on Technology Assessment in Health Care, 1992. pp. 94–102.

181. Taylor TN, Davis PH, Torner JC, Holmes J, Meyer JW, Jacobson MF. Lifetime cost of stroke in the United States. *Stroke* 1996;**27**:1459–66.

182. Terent A. Medico-social consequences and direct costs of stroke in a Swedish community. *Scand J Rehabil Med* 1983;**15**:165–71.

183. Terent A, Marke LA, Asplund K, Norrving B, Jonsson E, Wester PO. Costs of stroke in Sweden. A national perspective. *Stroke* 1994;**25**:2363–9.

184. Thorngren M, Westling B. Utilization of health care resources after stroke. A population-based study of 258 hospitalized cases followed during the first year. *Acta Neurol Scand* 1991;**84**:303–10.

185. Weill C, Schneider T. The cost of cerebrovascular accidents in France in 1982. In Clifford RF, editor. *Stroke: epidemiological, therapeutic and socio-economic aspects*. London: Royal Society of Medicine Services; 1986. pp. 135–46.

186. Zethraeus N, Moulin T, Henriksson P, Jonsson B. Costs of coronary heart disease and stroke: the case of Sweden. *J Intern Med* 1999;**246**: 151–9.

187. Caro JJ, Huybrechts KF. Stroke Treatment Economic Model (STEM): predicting long-term costs from functional status. *Stroke* 1999; **30**:2574–9.

188. Sandercock P, Berge E, Dennis M, Forbes J, Hand P, Kwan J, *et al*. A systematic review of the effectiveness, cost-effectiveness and barriers to implementation of thrombolytic and neuroprotective therapy for acute ischaemic stroke in the NHS. *Health Technol Assess* 2002; **6**(26):1–112.

189. Gage BF, Cardinalli AB, Albers GW, Owens DK. Cost-effectiveness of warfarin and aspirin for prophylaxis of stroke in patients with nonvalvular atrial fibrillation. *JAMA* 1995;**274**(23):1839–45.

190. Evers SMAA, Ament AJHA, Blaauw G. Economic evaluation in stroke research. A systematic review. *Stroke* 2000;**31**:1046–53.

191. Payne KA, Huybrechts KF, Caro JJ, Craig Green TJ, Klittich WS. Long term cost-of-illness in stroke: an international review. *Pharmacoeconomics* 2002;**20**:813–25.

192. Tengs TO, Yu M, Luistro E. Health-related quality of life after stroke: a comprehensive review. *Stroke* 2001;**32**:964–72.

193. Post PN, Stiggelbout A, Wakker P. Utility of health states after stroke. A systematic review of the literature. *Stroke* 2001;**32**:1425–9.

194. Brazier JE, Deverill M, Green C. A review of the use of health status measures in economic evaluation. *Journal of Health Services Research Policy* 1999;**4**:174–84.

195. Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. *J Health Econ* 2002;**21**:271–92.

196. Dorman P, Dennis M, Sandercock P, on behalf of the United Kingdom Collaborators in the International Stroke Trial (IST). Are the modified 'simple questions' a valid and reliable measure of health related quality of life after stroke? *J Neuro Neurosurg Psychiatry* 2000;**69**:487–93.

197. Menken M, DeFriese GH, Oliver TR, Litt I. The cost-effectiveness of digital subtraction angiography in the diagnosis of cerebrovascular disease [monograph]. Health Technology Case Study 34. Washington DC: US Congress Office of Technology Assessment; 1985.

198. Cohen MD, Hawes DR, Hutchins GD, McPhee WD, LaMasters MB, Fallon RP. Activity-based cost analysis: a method of analyzing the financial and operating performance of academic radiology departments. *Radiology* 2000;**215**:708–16.

199. Cohen MD. Determining costs of imaging services. *Radiology* 2001;**220**:563–5.

200. Bosanquet N, Franks P, for the Stroke Association. *Stroke care: reducing the burden of disease*. London: Stroke Association; 1998. pp. 1–28.

201. Sonnenberg FA, Beck JR. Markov models in medical decision making: a practical guide. *Med Decis Making* 1993;**13**:322–38.

202. Coull AJ, Rothwell PM. Underestimation of the early risk of recurrent stroke. Evidence of the need for a standard definition. *Stroke* 2004;**35**:1925–9.

203. Verro P. Stroke following TIA: mounting evidence of early risk. *Stroke* 2003;**34**:4–5.

204. Rothwell PM, Gutnikov SA, Warlow CP. Reanalysis of the final results of the European Carotid Surgery Trial. *Stroke* 2003;**34**:514–23.

205. Sandercock P, Gubitz G, Foley P, Counsell C. Antiplatelet therapy for acute ischaemic stroke. *Cochrane Database Syst Rev* 2003;**2**:CD000029.

206. Johnson ES, Lanes SF, Wentworth CE III, Satterfield MH, Abebe BL, Dicker LW. A metaregression analysis of the dose–response effect of aspirin on stroke. *Arch Intern Med* 1999;**159**:1248–53.

207. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death,

myocardial infarction, and stroke in high risk patients. *BMJ* 2002;**324**:71–86.

208. De Schryver EL, Algra A, van Gijn J. Dipyridamole for preventing stroke and other vascular events in patients with vascular disease. *Cochrane Database Syst Rev* 2003;**1**:CD001820.

209. PROGRESS Collaborative Group. Randomised trial of a peridopril-based blood-pressure-lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack. *Lancet* 2001;**358**:1033–41.

210. Kaste M. Statins in threatened stroke. *Stroke* 2003;**34**:351–3.

211. Bond R, Narayan SK, Rothwell PM, Warlow CP. Clinical and radiographic risk factors for operative stroke and death in the European carotid surgery trial. *Eur J Vasc Endovasc Surg* 2002;**23**:108–16.

212. Barnett HJ, Meldrum HE, Eliasziw M. The appropriate use of carotid endarterectomy. *CMAJ* 2002;**166**:1169–79.

213. Johnston DC, Chapman KM, Goldstein LB. Low rate of complications of cerebral angiography in routine clinical practice. *Neurology* 2001;**57**:2012–14.

214. Cloft HJ, Joseph GJ, Dion JE. Risk of cerebral angiography in patients with subarachnoid hemorrhage, cerebral aneurysm, and arteriovenous malformation: a meta-analysis. *Stroke* 1999;**30**:317–20.

215. Young GR, Humphrey PR. Skepticism and carotid ultrasonography. *Stroke* 1996;**27**:768–70.

216. Weinstein MC, Stason WB. Foundations of cost-effectiveness analysis for health and medical practices. *N Engl J Med* 1977;**296**:716–21.

217. Rothwell PM, Coull AJ, Giles MF, Howard SC, Silver LE, Bull LM *et al*. Change in stroke incidence, mortality, case-fatality, severity, and risk factors in Oxfordshire, UK from 1981 to 2004 (Oxford Vascular Study). *Lancet* 2004;**363**: 1925–33.

218. Office for National Statistics. Statistics online – Census 2001 – population pyramids – United Kingdom. 2001. URL: http://www.statistics.gov.uk/census2001/pyramids/printv/uk.asp.

219. Dennis MS, Bamford JM, Sandercock PA, Warlow CP. A comparison of risk factors and prognosis for transient ischemic attacks and minor ischemic strokes. The Oxfordshire Community Stroke Project. *Stroke* 1989;**20**:1494–9.

220. Clark TG, Murphy MF, Rothwell PM. Long term risks of stroke, myocardial infarction, and vascular death in 'low risk' patients with a non-recent transient ischaemic attack. *J Neuro Neurosurg Psychiatry* 2003;**74**:577–80.

221. Cunningham EJ, Bond R, Mehta Z, Mayberg MR, Warlow CP, Rothwell PM. Long-term durability of carotid endarterectomy for symptomatic stenosis and risk factors for late postoperative stroke. *Stroke* 2002;**33**:2658–63.

222. Barnett HJ, Taylor DW, Eliasziw M, Fox AJ, Ferguson GG, Haynes RB, *et al*. Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. *N Engl J Med* 1998;**339**: 1415–25.

223. Counsell C, Dennis M, McDowall M, Warlow C. Predicting outcome after acute and subacute stroke. Development and validation of new prognostic models. *Stroke* 2002;**33**: 1041–7.

224. Mead G, Lewis S, Wardlaw JM, Dennis MS. Comparison of risk factors in patients with transient and prolonged eye and brain ischemic syndromes. *Stroke* 2002;**33**:2383–90.

225. Hankey GJ, Jamrozki K, Broadhurst RJ, Forbes S, Burvill PW, Anderson CS, *et al*. Five-year survival after first-ever stroke and related prognostic factors in the Perth Community Stroke Study. *Stroke* 2000;**31**:2080–6.

226. Volmink JA, Newton JN, Hicks NR, Sleight P, Fowler GH, Neil HA. Coronary event and case fatality rates in an English population: results of the Oxford myocardial infarction incidence study. The Oxford Myocardial Infarction Incidence Study Group. *Heart* 1998;**80**:40–4.

227. Rothwell PM, Eliasziw M, Gutnikov SA, Warlow CP, Barnett HJM, for the Carotid Endarterectomy Trialists Collaboration. Endarterectomy for symptomatic carotid stenosis in relation to clinical subgroup and timing of surgery. *Lancet* 2004;**363**:915–24.

228. Government Actuary Department. *Expectation of life, United Kingdom*. London: Government Actuary Department; 1999.

229. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;**360**:7–22.

230. Yusuf S. Two decades of progress in preventing vascular disease. *Lancet* 2002;**360**:2–3.

231. Dorman PJ, Slattery J, Farrell B, Dennis MS, Sandercock PA. A randomised comparison of the EuroQol and Short Form-36 after stroke. United Kingdom collaborators in the International Stroke Trial. *BMJ* 1997;**315**:461.

232. Vanninen R, Manninen H, Koivisto K, Tulla H, Partanen K, Puranen M. Carotid stenosis by digital

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subtraction angiography: reproducibility of the European Carotid Surgery Trial and the North American Symptomatic Carotid Endarterectomy Trial measurement methods and visual interpretation. *AJNR Am J Neuroradiol* 1994; **15**:1635–41.

233. Young GR, Sandercock PA, Slattery J, Humphrey PR, Smith ET, Brock L. Observer variation in the interpretation of intra-arterial angiograms and the risk of inappropriate decisions about carotid endarterectomy. *J Neurol Neurosurg Psychiatry* 1996;**60**:152–7.

234. Raftery J. NICE: faster access to modern treatments? Analysis of guidance on health technologies. *BMJ* 2001;**323**:1300–3.

235. Rothwell PM, Salinas R, Ferrando LA, Slattery J, Warlow CP. Does the angiographic appearance of a carotid stenosis predict the risk of stroke independently of the degree of stenosis? *Clin Radiol* 1995;**50**:830–3.

236. Rothwell PM. For severe carotid stenosis found on ultrasound, further arterial evaluation prior to carotid endarterectomy is unnecessary: the argument against. *Stroke* 2003;**34**:1817–19.

Appendix 1

Search strategy on accuracy of non-invasive imaging in the diagnosis of carotid stenosis: EMBASE

1. carotid artery obstruction/
2. carotid artery thrombosis/
3. internal carotid artery occlusion/
4. carotid stenosis.tw.
5. carotid stenoses.tw.
6. carotid artery stenosis.tw.
7. carotid artery stenoses.tw.
8. carotid arteries stenosis.tw.
9. carotid arteries stenoses.tw.
10. (narrow$ adj carotid).tw.
11. carotid artery plaque$.tw.
12. carotid plaque$.tw.
13. (carotid adj2 narrow$).tw.
14. or/1-13
15. carotid artery disease/
16. carotid artery bifurcation/
17. carotid artery bruit/
18. carotid artery/
19. internal carotid artery/
20. carotid sinus/
21. common carotid artery/
22. carotid.tw.
23. or/15-22
24. stenosis/
25. artery occlusion/
26. blood vessel occlusion/
27. "stenosis, occlusion and obstruction"/
28. occlusion/
29. obstruction/
30. blood flow velocity/
31. ulcer/
32. brain blood flow/
33. artery blood flow/
34. blood flow/
35. artery dissection/
36. stenosis.tw.
37. stenoses.tw.
38. arteriosclerosis/
39. atherosclerosis/
40. or/24-39
41. carotid artery flow/
42. carotid artery pulse/
43. 41 or 42
44. atherosclerotic plaque/
45. artery intima proliferation/
46. morphology/
47. echolucent.tw.
48. echogenic.tw.
49. echogenicity.tw.
50. hyperechoic.tw.
51. hypoechoic.tw.
52. isoechoic.tw.
53. surface characteristic$.tw.
54. surface property/
55. unstable.tw.
56. heterogenous.tw.
57. homogenous.tw.
58. homogeneity.tw.
59. or/44-58
60. carotid endarterectomy/
61. carotid endarterectomy.tw.
62. carotid artery endarterectomy.tw.
63. cea.tw.
64. amygdaloid nucleus/
65. carcinoembryonic antigen.mp.
66. (cancer or tumour or tumor or neoplasm).tw.
67. 63 not (64 or 65 or 66)
68. or/60-62,67
69. preoperative evaluation/
70. treatment indication/
71. patient selection/
72. work-up.tw.
73. or/69-72
74. magnetic resonance angiography/
75. magnetic resonance angiograph$.tw.
76. magnetic resonance angiogram$.tw.
77. mr angiograph$.tw.
78. mr angiogram$.tw.
79. mri angiograph$.tw.
80. mri angiogram$.tw.
81. mra.tw.
82. angio mr$1.tw.
83. or/74-82
84. nuclear magnetic resonance imaging/
85. magnetic resonance.tw.
86. mri.tw.
87. mr scan.tw.
88. mr scan$.tw.
89. mr imaging.tw.
90. mr image$.tw.
91. mr.tw.
92. nuclear magnetic resonance imaging agent/
93. or/84-92
94. angiography/
95. angiograph$.tw.
96. angiogram$.tw.

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97. digital subtraction angiography/
98. brain angiography/
99. or/94-98
100. ultrasound/
101. real time echography/
102. intravascular ultrasound/
103. color ultrasound flowmetry/
104. doppler flowmetry/
105. doppler flowmeter/
106. doppler echography/
107. echography/
108. ultrasound transducer/
109. ultrasound scanner/
110. transducer/
111. duplex sonograph$.tw.
112. duplex sonogram$.tw.
113. doppler.tw.
114. dus.tw.
115. b scan/
116. duplex sonographic.tw.
117. ultrasound.tw.
118. ultrasonogra$.tw.
119. or/100-118
120. spiral computer assisted tomography/
121. computer assisted tomography/
122. tomography/
123. ct scan$.tw.
124. cat scan$.tw.
125. cta.tw.
126. 3d-cta.tw.
127. 3d-ct.tw.
128. ct.tw.
129. single slice.tw.
130. multi-slice.tw.
131. tomodensitomet$.tw.
132. ct angiograph$.tw.
133. ct angiogram$.tw.
134. computer tomograph$.tw.
135. computerised tomograph$.tw.
136. computerized tomograph$.tw.
137. computer tomogram$.tw.
138. computerised tomogram$.tw.
139. computerized tomogram$.tw.
140. computed tomography scanner/
141. x-ray tomograph$.tw.
142. x-ray tomogram$.tw.
143. computer assisted tomograph$.tw.
144. computer assisted tomogram$.tw.
145. computer assisted impedance tomography/
146. or/120-145
147. image reconstruction/
148. image processing/
149. image analysis/
150. three dimensional imaging/
151. contrast enhancement/
152. image quality/
153. contrast medium/
154. imaging/
155. image intensifier/
156. image enhancement/
157. or/147-156
158. blood vessel catheterization/
159. artery catheterization/
160. artery catheter/
161. "catheters and tubes"/
162. catheter/
163. intra-arterial angiograph$.tw.
164. intra-arterial angiogram$.tw.
165. catheter angiographic.tw.
166. catheter angiography.tw.
167. catheter angiogram$.tw.
168. balloon catheter/
169. intra-arterial catheter$.tw.
170. or/158-169
171. diagnostic value/
172. diagnostic imaging/
173. diagnostic accuracy/
174. "sensitivity and specificity"/
175. receiver operating characteristic/
176. roc curve/
177. sensitivity.tw.
178. specificity.tw.
179. roc.tw.
180. receiver operator.tw.
181. receiver operating.tw.
182. diagnostic error/
183. quantitative diagnosis/
184. qualitative diagnosis/
185. computer assisted diagnosis/
186. diagnostic procedure/
187. diagnostic test/
188. diagnostic approach route/
189. differential diagnosis/
190. false negative$.tw.
191. false positive$.tw.
192. true negative$.tw.
193. true positive$.tw.
194. pre-test odds.tw.
195. pretest odds.tw.
196. pre-test probabilit$.tw.
197. pretest probabilit$.tw.
198. post-test odds.tw.
199. posttest odds.tw.
200. post-test probabilit$.tw.
201. posttest probabilit$.tw.
202. likelihood ratio$.tw.
203. positive predictive value$.tw.
204. negative predictive value$.tw.
205. diagnosis/
206. misdiagnosis.tw.
207. misdiagnoses.tw.
208. observer variation/
209. artifact reduction/
210. non-invasive measurement/

211. or/171-210
212. 14 and 83 and 211
213. 23 and 40 and 83 and 211
214. 43 and 83 and 211
215. 23 and 59 and 83 and 211
216. 68 and 73 and 83 and 211
217. 14 and 93 and 99 and 211
218. 23 and 40 and 93 and 99 and 211
219. 43 and 93 and 99 and 211
220. 23 and 59 and 93 and 99 and 211
221. 68 and 73 and 93 and 99 and 211
222. 14 and 119 and 211
223. 23 and 40 and 119 and 211
224. 43 and 119 and 211
225. 23 and 59 and 119 and 211
226. 68 and 73 and 119 and 211
227. 14 and 146 and 211
228. 23 and 40 and 146 and 211
229. 43 and 146 and 211
230. 23 and 59 and 146 and 211
231. 68 and 73 and 146 and 211
232. 14 and 157 and 211
233. 23 and 40 and 157 and 211
234. 43 and 157 and 211
235. 23 and 59 and 157 and 211
236. 68 and 73 and 157 and 211
237. 14 and 170 and 211
238. 23 and 40 and 170 and 211
239. 43 and 170 and 211
240. 23 and 59 and 170 and 211
241. 68 and 73 and 170 and 211
242. or/212-241

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Appendix 2

Search strategy on accuracy of non-invasive imaging in the diagnosis of carotid stenosis: MEDLINE

1. carotid stenosis/
2. carotid stenosis.tw.
3. carotid stenoses.tw.
4. carotid artery stenosis.tw.
5. carotid artery stenoses.tw.
6. carotid arteries stenosis.tw.
7. carotid arteries stenoses.tw.
8. (narrow$ adj carotid).tw.
9. carotid artery plaque$.tw.
10. carotid plaque$.tw.
11. (carotid adj2 narrow$).tw.
12. carotid ulcer$.tw.
13. ica.tw.
14. islets of langerhans/
15. immunohistochemistry/
16. calcium channels/
17. 13 not (14 or 15 or 16)
18. or/1-12,17
19. carotid artery diseases/
20. carotid arteries/
21. carotid artery, common/
22. carotid artery, internal/
23. carotid artery, external/
24. carotid.tw.
25. carotid sinus/
26. or/19-25
27. stenosis.tw.
28. stenoses.tw.
29. constriction, pathologic/
30. arteriosclerosis/
31. arterial occlusive diseases/
32. regional blood flow/
33. atheroscleros$.tw.
34. blood flow velocity/
35. or/27-34
36. plaque$1.tw.
37. morphology.tw.
38. heterogenous.tw.
39. homogenous.tw.
40. homogeneity.tw.
41. echolucent.tw.
42. echogenic.tw.
43. echogenicity.tw.
44. hyperechoic.tw.
45. hypoechoic.tw.
46. isoechoic.tw.
47. surface characteristic$.tw.
48. unstable.tw.
49. or/36-48
50. endarterectomy, carotid/
51. carotid endarterectomy.tw.
52. carotid artery endarterectomy.tw.
53. cea.tw.
54. carcinoembryonic antigen.tw.
55. (central nucleus adj2 amygdala).tw.
56. carcinoembryonic antigen/
57. neoplasm.mp.
58. neoplasms.mp.
59. or/54-58
60. 53 not 59
61. or/50-52,60
62. patient selection/
63. patient selection.tw.
64. work-up.tw.
65. or/62-64
66. 61 and 65
67. magnetic resonance angiography/
68. mr angiograph$.tw.
69. mr angiogram$.tw.
70. mri angiograph$.tw.
71. mri angiogram$.tw.
72. magnetic resonance angiograph$.tw.
73. magnetic resonance angiogram$.tw.
74. mra.tw.
75. angio mr$1.tw.
76. or/67-75
77. magnetic resonance imaging/
78. magnetic resonance.tw.
79. mri.tw.
80. mr imaging.tw.
81. mr image$1.tw.
82. mr.tw.
83. mri scan$.tw.
84. mr scan$.tw.
85. nmr.tw.
86. nuclear magnetic resonance, biomolecular/
87. magnetic resonance spectroscopy/
88. 85 not (86 or 87)
89. or/77-84,88
90. angiography/
91. angiography, digital subtraction/
92. angiograph$.tw.
93. angiogram$.tw.
94. cerebral angiography/
95. or/90-94
96. 89 and 95

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97. doppler.tw.
98. ultrasonics/
99. ultrasonography, doppler/
100. ultrasonography, doppler, duplex/
101. ultrasonography, doppler, pulsed/
102. ultrasonography, doppler, color/
103. ultrasonography, doppler, transcranial/
104. ultrasonography/
105. duplex sonography.tw.
106. duplex sonographic.tw.
107. duplex sonogram$.tw.
108. duplex ultra$.tw.
109. ultrasound.tw.
110. ultrasonogra$.tw.
111. transducers/
112. dus.tw.
113. or/97-112
114. ct scan$.tw.
115. cat scan$.tw.
116. tomography, x-ray computed/
117. computer tomograph$.tw.
118. computer tomogram$.tw.
119. tomography/
120. tomography scanners, x-ray computed/
121. tomography, x-ray/
122. computer assisted tomograph$.tw.
123. computer assisted tomogram$.tw.
124. ct angiography.tw.
125. cta.tw.
126. tomodensitomet$.tw.
127. 3d-cta.tw.
128. three dimensional-ct.tw.
129. multi-slice.tw.
130. single slice.tw.
131. ct.tw.
132. or/114-131
133. image enhancement/
134. imaging, three-dimensional/
135. radiographic image enhancement/
136. transducers/
137. image processing, computer assisted/
138. exp contrast media/
139. or/133-138
140. di.fs.
141. du.fs.
142. 139 and (140 or 141)
143. intra-arterial angiograph$.tw.
144. intra-arterial angiogram$.tw.
145. catheter angiography.tw.
146. catheter angiogram$.tw.
147. catheterization/
148. intra-arterial catheter$.tw.
149. or/143-148
150. diagnostic imaging/
151. diagnosis, differential/
152. diagnostic errors/
153. false negative reactions/
154. false positive reactions/
155. observer variation/
156. diagnosis, computer-assisted/
157. image interpretation, computer-assisted/
158. radiographic image interpretation, computer-assisted/
159. "sensitivity and specificity"/
160. sensitivity.tw.
161. specificity.tw.
162. predictive value of tests/
163. roc curve/
164. roc.tw.
165. receiver operating characteristic.tw.
166. receiver operator characteristic.tw.
167. reproducibility of results/
168. diagnosis/
169. "diagnostic techniques and procedures"/
170. pre-test odds.tw.
171. pretest odds.tw.
172. pre-test probabilit$.tw.
173. pretest probabilit$.tw.
174. post-test odds.tw.
175. posttest odds.tw.
176. post test probabilit$.tw.
177. posttest probabilit$.tw.
178. likelihood ratio$.tw.
179. positive predictive value$.tw.
180. negative predictive value$.tw.
181. false negative.tw.
182. false positive.tw.
183. true negative$.tw.
184. true positive$.tw.
185. misdiagnosis.tw.
186. misdiagnoses.tw.
187. or/150-185
188. carotid stenosis/ra
189. carotid stenosis/us
190. 188 or 189
191. 18 and 76 and 187
192. 26 and 35 and 76 and 187
193. 26 and 49 and 76 and 187
194. 66 and 76 and 187
195. 18 and 96 and 187
196. 26 and 35 and 96 and 187
197. 26 and 49 and 96 and 187
198. 66 and 96 and 187
199. 18 and 113 and 187
200. 26 and 35 and 113 and 187
201. 26 and 49 and 113 and 187
202. 66 and 113 and 187
203. 18 and 132 and 187
204. 26 and 35 and 132 and 187
205. 26 and 49 and 132 and 187
206. 66 and 132 and 187
207. 18 and 142 and 187
208. 26 and 35 and 142 and 187
209. 26 and 49 and 142 and 187

210. 66 and 142 and 187
211. 18 and 149 and 187
212. 26 and 35 and 149 and 187
213. 26 and 49 and 149 and 187
214. 66 and 149 and 187
215. 187 and 190
216. or/191-215

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Appendix 3

STARD initiative and related checklists

STARD Checklist (http://www.consort-statement.org/stardstatement.htm)
Note this has been slightly adapted with additional material from a previous report to the NHS Rand D HTA Panel on Diagnostic Imaging.[73]

Item numbers refer to the original STARD statement, letters to the HTA report. The original STARD checklist appears at the end of this list.

Citation:

1. Relevance
   If any of these questions can be answered with a 'No', discard the paper.
   - 1.1. Is the study a diagnostic or an agreement study? To be a diagnostic or agreement study, there must have at least two measurements of stenosis per artery. (Item 1)
   - 1.2. Are the patients people who may have carotid stenosis (e.g. presented with TIA symptoms)?
   - 1.3. Do the imaging techniques include ultrasound, CTA, MRA or IAA?

2. Quality assessment
   - 2.1. Does the study describe its aims or research questions? (Item 2)
     (a) Yes
     (b) No
     (c) Unclear or insufficient information
   - 2.2. Does the study provide enough information to fill a 2 × 2 table? If not, the paper may be discarded.
     (a) Yes
     (b) No
   - 2.3. Does the study describe its inclusion and exclusion criteria, and the setting where the data were collected? (Item 3, A1, B2)
     (a) Yes
     (b) No
     (c) Unclear or insufficient information
   - 2.4. Does the study describe from where patients are referred? (A2, A3)
     (a) Yes
     (b) No
     (c) Unclear or insufficient information
   - 2.5. Does the study describe its recruitment procedure? (Item 4)
     (a) Presenting symptoms
     (b) Results of previous tests
     (c) Results of tests/reference standard under investigation
     (d) Unclear or insufficient information
   - 2.6. Does the study describe the clinical and demographic characteristics of the patients in sufficient detail to answer Q3.3? (Item 15, C1)
     (a) Yes
     (b) Partly
     (c) No
   - 2.7. Does the study report the number of patients who dropped out or other protocol violations?
     (a) Yes
     (b) No
     (c) Unclear or insufficient information
   - 2.8. How were the patients sampled? (Item 5, B1)
     (a) Consecutive series or randomly sampled
     (b) Other
     (c) Unclear or insufficient information
   - 2.9. Was the study prospective or retrospective? (Item 6)
     (a) Prospective
     (b) Retrospective
     (c) Unclear or insufficient information
   - 2.10. What was the reference standard (this question is not relevant for studies of agreement only)? (Item 7)
     (a) IAA
     (b) MRA
     (c) Other
     (d) Unclear or insufficient information
   - 2.11. Are the tests described in sufficient detail to allow others to repeat the study? (Item 8)
     (a) Yes
     (b) Described in cited references
     (c) Unclear or insufficient information
   - 2.12. Does the study describe how stenosis was defined, and if patients were grouped into categories, how was this done? (Item 9)
     (a) Yes
     (b) No
     (c) Unclear or insufficient information

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2.13. Does the study report the results of separate readers separately? (G1, G2)
  (a) Yes
  (b) No
  (c) Unclear or insufficient information
2.14. Does the study describe the training or expertise of the readers? (Item 10)
  (a) Yes
  (b) No
  (c) Unclear or insufficient information
2.15. Did test results influence whether patients got the reference standard or not? (D1, D2)
  (a) Yes
  (b) Yes, but the authors took account of this in the analysis
  (c) No
  (d) Unclear or insufficient information
2.16. Were the readers kept blind to the results of previous tests/reference standard? (Item 11, H1, H2, H3)
  (a) Yes
  (b) No
  (c) Unclear or insufficient information
2.17. Are the results of the tests under investigation used to determine the true diagnosis of the patient? (D3)
  (a) Yes
  (b) No
  (c) Unclear or insufficient information
2.18. Does the study describe how the diagnostic accuracy measures were calculated (e.g. definition of a true positive)? (Item 12)
  (a) Yes
  (b) No
  (c) Unclear or insufficient information
2.19. For diagnostic studies only. If there was more than one reader, was inter-observer variability taken into account? (G1, G2)
  (a) Yes
  (b) No
  (c) Unclear or insufficient information
2.20. For agreement studies only: does the study describe how reproducibility was assessed? (Item 13, G4, G5)
  (a) Yes
  (b) No
  (c) Unclear or insufficient information
2.21. Does the study describe how indeterminate results were handled? (Item 22)
  (a) Yes
  (b) No
  (c) Unclear or insufficient information
2.22. Did the patients, or subgroups of patients, receive any treatment between recruitment and the tests/reference standard, or between the tests and the reference standard?
  (a) Yes
  (b) No
  (c) Unclear or insufficient information

3. Data extraction
  3.1. When was the study published? (Item 14)
  3.2. When were the patients recruited? (Item 14)
  3.3. What are the clinical and demographic characteristics of the study sample? (Item 15)
    (a) Total number of patients
    (b) Age range
    (c) Percentage of men
    (d) Percentage symptomatic
    (e) List presenting symptoms (if any)
    (f) Where patients are referred from (e.g. GPs)
  3.4. How many patients did not receive either the reference standard or the tests under investigation who satisfied the inclusion criteria? (Item 16)
  3.5. What was the time interval between the tests and the reference standard? Did the patients receive any treatment in between? (Item 17)
  3.6. What was the spectrum of disease? (Item 18)
  3.7. What were the test results (e.g. 2 x 2 table for dichotomous results, include indeterminate results if possible)? (Items 19, 23, 24)
  3.8. How many patients suffered adverse events due to the tests/reference standard, and what were these? (Item 20)
  3.9. Original STARD Checklist. (http://www.consort-statement.org/stardstatement.htm)

TABLE 76 *STARD checklist of items to improve the reporting of studies on diagnostic accuracy (test version, November 2001; for evaluation purposes only)*

Section and topic	Item	Describe	Reported on page #
TITLE/ABSTRACT/ KEYWORDS	1	The article as a study on diagnostic accuracy (recommend MeSH heading 'sensitivity and specificity')	
INTRODUCTION	2	The research question(s), such as estimating diagnostic accuracy or comparing accuracy between tests or across participant groups	
METHODS			
Participants	3	The study population: the inclusion and exclusion criteria, setting(s) and location(s) where the data were collected	
	4	Participant recruitment: was this based on presenting symptoms, results from previous tests, or the fact that the participants had received the index test(s) or the reference standard?	
	5	Participant sampling: was this a consecutive series of patients defined by selection criteria in (3) and (4)? If not specify how patients were further selected.	
	6	Data collection: were the participants identified and data collected before the index test(s) and reference standards were performed (prospective study) or after (retrospective study)?	
Reference standard	7	The reference standard and its rationale	
Test methods	8	Technical specification of material and methods involved including how and when measurements were taken, and/or cite references for index test(s) and reference standard	
	9	Definition and rationale for the units, cutoffs and/or categories of the results of the index test(s) and the reference standard	
	10	The number, training and expertise of the persons (a) executing and (b) reading the index test(s) and the reference standard	
	11	Whether or not the reader(s) of the index test(s) and reference standard were blind (masked) to the results of the other test(s) and describe any information available to them	
Statistical methods	12	Methods for calculating measures of diagnostic accuracy or making comparisons, and the statistical methods used to quantify uncertainty (e.g. 95% confidence intervals)	
	13	Methods for calculating test reproducibility, if done	
RESULTS			
Participants	14	When study was done, including beginning and ending dates of recruitment	
	15	Clinical and demographic characteristics (e.g. age, sex, spectrum of presenting symptom(s), comorbidity, current treatment(s), recruitment center)	
	16	How many participants satisfying the criteria for inclusion did or did not undergo the index test and/or the reference standard; describe why participants failed to receive either test (a flow diagram is strongly recommended)	
Reference standard	17	Time interval and any treatment administered between index and reference standard	
	18	Distribution of severity of disease (define criteria) in those with the target condition; describe other diagnoses in participants without the target condition	
Test results	19	A cross tabulation of the results of the index test(s) by the results of the reference standard; for continuous results, the distribution of the test results by the results of the reference standard	
	20	Indeterminate results, missing responses and outliers of index test(s) stratified by reference standard result and how they were handled	
	21	Adverse events of index test(s) and reference standard	

continued

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TABLE 76 *STARD checklist of items to improve the reporting of studies on diagnostic accuracy. (test version, November 2001; for evaluation purposes only) (cont'd)*

Section and topic	Item	Describe	Reported on page #
Estimation	22	Estimates of diagnostic accuracy and measures of statistical uncertainty (e.g. 95% confidence intervals)	
	23	Estimates of variability of diagnostic accuracy between subgroups of participants, readers or centres, if done	
	24	Measures of test reproducibility, if done	
DISCUSSION	25	The clinical applicability of the study findings	

Appendix 4

HTA carotid stenosis checklists 1 and 2: mandatory and desirable requirements

Citation details:
Checklist completed by:
Checklist verified by:

1. Mandatory requirements. If any of these questions can be answered with a 'No', discard the paper

		Y/N
1.1	Are the patients people who may have carotid stenosis (e.g. presented with TIA symptoms)?	
1.2	Do the imaging techniques include ultrasound, CTA, MRA, or IAA?	
1.3	Does the study provide enough information to fill a 2 x 2 table?	
1.4	Does the study state that the readers have been kept blind to the results of previous tests, particularly other carotid imaging (stated or implied)?	

2. Desirable study features. If any of these questions can be answered with a 'No', put aside the paper

		Y/N
2.1	Is the method used to calculate the percentage of stenosis given explicitly?	
2.2	Are the imaging techniques described in sufficient detail to allow others to repeat the procedure?	
2.3	Using data from the study, is it possible to calculate that at least 70% of the patients are symptomatic?	
2.4	Was the data collected prospectively?	

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Appendix 5

HTA carotid stenosis checklist 3: quality assessment

Citation details:
Checklist completed by:
Checklist verified by:

		Tick one	
		Yes/NA	**Unclear/No**
3.1	Does the study describe its aims or research questions?		
3.2	Does the study describe its inclusion and exclusion criteria, and the setting where the data were collected?		
3.3	Does the study describe from where the patients are referred?		
3.4	Does the study describe its recruitment procedure?		
3.5	Does the study describe the clinical and demographic characteristics of the patients in sufficient detail to answer Questions 4.4–4.6 (age range, gender ratio, and proportion symptomatic)?		
3.6	Does the study report the number of patients who dropped out or other protocol violations?		
3.7	Does the patient group consist of a consecutive series or people randomly sampled from a larger population?		
3.8	Does the study say explicitly that the readers were blinded rather than merely implied?		
3.9	Does the study describe the training or expertise or profession of its readers?		
3.10	Did test results **not** influence whether patients got the reference standard or not?		
3.11	Are the results of the tests under investigation **not** used to determine the true diagnosis of the patients?		
3.12	Does the study describe how the diagnostic accuracy measures were calculated (e.g. definition of a true positive)?		
3.13	Is the analysis done on a per patient (rather than per artery) basis?		
3.14	If there was more than one reader, was inter-observer variability taken into account or assessed?		
3.15	Does the study describe how indeterminate results were handled?		
3.16	Did the patients, or subgroups of patients, receive **no** treatment between recruitment and tests/reference standard, or between the tests and the reference standard?		

Comments:

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Appendix 6

HTA carotid stenosis checklist 4: data extraction

Citation details:
Checklist completed by:
Checklist verified by:

4.1	When was the study published?
4.2	When were the patients recruited?
4.3	What is the total number of patients used to generate the diagnostic/agreement data?
4.4	What is the age range and the average age?
4.5	What is the male:female ratio?
4.6	What percentage of patients is symptomatic (TIA, minor stroke, amaurosis fugax, retinal artery occlusion)?
4.7	Where are the patients referred from?
4.8	What was the recruitment procedure (e.g. presenting symptoms)?
4.9	What was the reference standard (not applicable for agreement studies)?
4.10	How is stenosis defined for angiography? E.g. ECST/NASCET/CCA
4.11	If the patients were grouped into categories (e.g. mild vs moderate vs severe stenosis) how was this done?
4.12	How many patients did not receive either the reference standard or the tests under investigation who satisfied the inclusion criteria?
4.13	What was the time interval between the tests and the reference standard?
4.14	What was the spectrum of disease (e.g. all degrees of stenosis, severe stenosis only, occluded only)?
4.15	How many patients suffered adverse events due to the tests/reference standard, and what were these?
4.16	What was the non-invasive imaging technique used?
4.17	What were the imaging parameters for angiography (if applicable)?

Arch or carotid injection	Number of views	Extras like 3D rotation of views

4.18	What were the imaging parameters for the non-invasive techniques?		
	US	MRA	Spiral CTA
	Manufacturer and model	Manufacturer and model	Manufacturer and model
	Probe frequency	Time of flight (2D or 3D) sequence	Pitch
	Area covered	Phase contrast	Slice thickness

continued

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Velocities recorded	Contrast enhanced – use of extra software like 'SLINKY'	Coverage
Measurements on images	Maximum intensity projection (MIP) or base images assessed	Contrast injected
Stenosis measured how?	Stenosis measured how?	Reconstruction MIP, base images, surface shaded display Stenosis measured how?

4.19 What were the diagnostic/agreement results?

Comments:

Appendix 7

Flyer and letter asking for individual patient data sets

DATA NEEDED

Can you help?

You could help an NHS HTA funded project – we are doing a meta-analysis of individual patient data on imaging of carotid stenosis. Do you have data from audit or primary research studies that fulfil this one criterion?

- At least 2 different imaging measures of carotid stenosis per patient, e.g. Doppler ultrasound or MRA versus intra-arterial angiography

To discuss this further please contact Prof Joanna Wardlaw on jmw@skull.dcn.ed.ac.uk or Francesca Chappell on fmc@skull.dcn.ed.ac.uk or phone 0131 537 2932

CAROTID
STENOSIS
IMAGING

This is a multicentre project in collaboration with University of Edinburgh (Clinical Neurosciences), University of Sheffield (School of Health and Related Research), universities and hospitals in Cambridge, Glasgow, Leeds, London, Middlesbrough, and Oxford.

Letter seeking data for the individual patient data meta-analysis

Dear

We are working on an HTA project *Accurate, practical, and cost-effective imaging of carotid stenosis in the UK* funded by the NHS HTA programme. This involves a systematic review of the literature with a meta-analysis of individual patient data. The systematic review is unlikely to give us a complete picture, and the individual patient data will therefore be a very important part of the project.

The data we are looking for could come from either a diagnostic study or audit data collected on ultrasound, MRA, CTA, or digital angiography. If you have any data that you think might be useful for the HTA we would be extremely grateful if you would collaborate with us on this project.

All data will be held securely and treated as confidential. The data will not be passed on to any third parties or used for any purpose other than the HTA project.

We wish to make the process as easy as possible for you and will therefore accept electronic PC files in ASCII plain text, Excel, SPSS, SAS, and most other formats. Please find enclosed a document outlining the information the data must contain for us to be able to use it in the meta-analysis, the fundamental requirement is that there must be at least two assessments of carotid stenosis per patient.

If you have any queries about the HTA project, please do not hesitate to contact us. The individual patient data meta-analysis will be immensely useful, and we hope to hear from you soon.

Yours sincerely

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Appendix 8

Minimum data set requirements

Purpose

To collect data on the imaging of carotid arteries to determine stenosis in patients at risk of stroke.

Patients

All data should be provided with a description of the inclusion/exclusion criteria and how these were assessed. e.g. if only TIA patients are to be included, how are non-TIA patients ruled out? The source of patients and any selection procedures need also to be described.

Imaging techniques

Please provide details of how the imaging was performed, e.g. use of contrast agent. The above information will be used in sensitivity analyses and to account for heterogeneity in the meta-analysis.

Data

For a given patient, diagnosis may differ because of the following sources of variation:

1. Inter-imaging technique – assessed by diagnostic studies comparing one imaging technique with another, usually a gold standard test
2. Intra-imaging technique – assessed by agreement studies that use the same imaging technique more than once on each patient to see how variable the diagnosis is
3. Inter-reader – assessed by agreement studies looking at how people differ in their interpretation of the same imaging result
4. Intra-reader – assessed by studies looking at how the same person assesses the same imaging results more than once to check the consistency of interpretation

Therefore any data used in this HTA need to have *at least two diagnostic results per artery*, obtained reasonably soon after each other and related to the same investigative episode (e.g. we do not want pre- and post-endarterectomy Doppler ultrasound). Any study where carotid stenosis is assessed just once is not suitable, as is any study where stenosis is measured before and after surgery or angioplasty.

Your data can be used to assess either (1) if there are the results of at least two different imaging techniques per artery, or (2) if you have recorded the results of the same imaging technique used more than once on the same artery, or (3) if you have recorded different interpretations by different people of the same imaging results, or (4) if you have recorded different interpretations by the same person of the same imaging result. Your data may be able to address more than one aspect of agreement listed above.

Other issues

As people have two carotid arteries, we need to know whether in your imaging you usually assess both arteries, and in what circumstances would only one artery be measured.

All imaging techniques sometimes produce inconclusive results. If your data do not include these results, could you please let us know that this is the case and give us your best estimate of the proportion of results that are inconclusive. We will also need to know how you defined stenosis, e.g. by NASCET. If you have excluded patients from your data set, it would be helpful to know why.

Structure of the minimum data set

Please explain how you have coded the data, e.g. if you have recorded gender as 1 for women, 2 for men, please let us know what the 1s and 2s mean. We also need to know how you coded missing values, common codings are 999, * or blank spaces.

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Item	Comments
Patient ID	A unique identifier for each patient, this is especially important if your data has patients with more than one record. If there is only 1 line per patient, the line number can be the unique identifier
Age	Please provide either the age at the time of imaging or the date of birth. Exact dates are not required, just month and year or year only is fine
Gender	
Event	TIA, minor stroke, retinal artery occlusion, amaurosis fugax, other, side of event (left or right or both), whether symptomatic or not
Date of event	Best estimate of when the event took place
First imaging result – left and right arteries	This will either be the degree of stenosis or the variables used to calculate the degree of stenosis. If the latter, please provide details of how you calculated stenosis from the variables: right and left hand ICA, ECA, and CCA stenosis if available. Please also say which is the symptomatic artery
Date of first imaging result	Exact date, i.e. day, month, year, of when the patient first underwent imaging
Second imaging results – left and right arteries	As for first imaging result
Date of second imaging result	As for date of first imaging result

The following, if available, would also be very useful to the HTA group

Item	Comments
CEA	Whether or not the patient underwent carotid endarterectomy
Outcome	Patient outcome within a given timeframe, e.g. stroke/death at 1 year

Appendix 9

Sources of data for individual patient data meta-analysis

Data set 1 – AngioComp_Nic Weir. Local *Audit* of complications of IAA in Edinburgh

Data set 2 – Rothwell. Local *Audit* Oxford

Data set 3 – HTA data (francesca).xls. Martin Brown's CAVATAS (Carotid and Vertebral Angioplasty versus Surgery Trial) data. *Research*

Data set 4 – randall Sheffield data.xls. Marc Randall's data. Local *Audit* Sheffield

Data set 5 – carotid.sav. Jonathan Gillard's data *Research* (study of accuracy of MRA, CEMRA vs IAA)

Data set 6 – Observer variability (caliper) DSA.xls and Observer variability (caliper) MRA.xls. Gavin Young and Peter Humphrey's data. Liverpool *Research* (study of accuracy of MRA, US vs IAA)

Data set 7 – Batch1.txt and carotid.txt. Giles Roditi's data. Local *Audit* Glasgow

Data set 8 – svag Audit Office 97 version.mdb. Jill Pell's data. National *Audit* Scotland

Data set 9 – doppler-edinburgh 2,3.xls. Brigette Yip Local *Audit* Glasgow

Data set 10 – Dopvangi.xls. DCN Local *Audit* Edinburgh

Data set 11 – USvUS.xls. DCN Local *Audit* Edinburgh

Data set 12 – Mike Gough GALA (General Anaesthetic and Local Anaesthetic for Carotid Endarterectomy) data. *Research*

Acknowledgements

Professor Martin Brown and Ms Lucy Coward (National Hospital for Neurology and Neurosurgery, London), CAVATAS.

Dr Jonathan Gillard and Dr Jean Marie U-King-Im (Department of Radiology, Addenbrookes Hospital and the University of Cambridge), research on contrast MRA.

Mr Mike Gough (Consultant Vascular Surgeon, General Infirmary at Leeds), GALA data.

Dr Jill Pell and Ms Rachel Slack (Greater Glasgow NHS Board), SVAG

Dr Marc Randall (Neurology Research Fellow) and Professor Graham Venables (Professor of Neurology, Royal Hallamshire Hospital, Sheffield), local audit data.

Dr Giles Roditi (Consultant Radiologist, Glasgow Royal Infirmary), local audit data.

Professor Peter M Rothwell (MRC Senior Clinical Research Fellow, Reader in Clinical Neurology), University Department of Clinical Neurology, Radcliffe Infirmary, Oxford, OXVASC data.

Dr Nic Weir (Stroke Fellow, Foothills Medical Centre, Calgary, Canada), Audit of Edinburgh angiography complications.

Dr Brigitte Yip (Consultant Physician in Geriatric Medicine and Stroke Service), Dr BJ Martin and Dr Fiona Gardner (Consultant Radiologist, Hairmyres Hospital, NHS Lanarkshire), local audit data.

Dr Gavin Young (Consultant Neurologist, Middlesbrough General Hospital) and Professor P Humphreys (Professor of Neurology, The Walton Centre, Liverpool), research study data.

Professor Joanna Wardlaw (Neuroradiologist, Edinburgh), local audit of US vs US, US vs IAA, US vs MRA and CEMRA.

Other potential data sources were approached, but data were not available: Vascular Surgical Society Office, RCSEng; a study of accuracy of MRA in Leeds; the Asymptomatic Carotid Surgery Trial; an audit of US and MRA in Sheffield.

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Appendix 10

Data in the individual patient data meta-analysis available for the analyses presented in Chapter 4

TABLE 77 *Data available for IAA versus US data: symptomatic arteries only*

			IAA			
Arteries included			**0–49, 100%**	**50–69%**	**70–99%**	**Total**
All	US	0–49, 100%	93	18	10	121
		50–69%	36	56	81	173
		70–99%	47	96	449	592
		Total	176	170	540	886
True status known only	US	0–49, 100%	68	14	9	91
		50–69%	22	48	81	151
		70–99%	42	88	431	561
		Total	132	150	521	803

TABLE 78 *Data available for IAA versus US data: asymptomatic arteries only*

			IAA			
Arteries included			**0–49, 100%**	**50–69%**	**70–99%**	**Total**
All	US	0–49, 100%	285	14	11	310
		50–69%	37	24	13	74
		70–99%	14	23	59	96
		Total	336	61	83	480
True status known only	US	0–49, 100%	266	7	10	283
		50–69%	26	18	11	55
		70–99%	10	10	37	57
		Total	302	35	58	395

TABLE 79 *Data available for IAA versus US data: all arteries*

			IAA			
Arteries included			**0–49, 100%**	**50–69%**	**70–99%**	**Total**
All	US	0–49, 100%	378	32	21	431
		50–69%	73	80	94	247
		70–99%	61	119	508	688
		Total	512	231	623	1366
True status known only	US	0–49, 100%	334	21	19	374
		50–69%	48	66	92	206
		70–99%	52	98	468	618
		Total	434	185	579	1198

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TABLE 80 *Data available for IAA versus CTA data: symptomatic arteries only (the symptomatic status of all arteries contributing to the CTA data was known)*

			IAA			
Arteries included			**0–49, 100%**	**50–69%**	**70–99%**	**Total**
True status known only	CTA	0–49, 100%	1	–	–	1
		50–69%	–	–	1	1
		70–99%	1	–	3	4
		Total	2	0	4	6

TABLE 81 *Data available for IAA versus CTA data: asymptomatic arteries only (the symptomatic status of all arteries contributing to the CTA data was known)*

			IAA			
Arteries included			**0–49, 100%**	**50–69%**	**70–99%**	**Total**
True status known only	CTA	0–49, 100%	1	–	–	1
		5–69%	–	–	–	0
		70–99%	–	1	1	2
		Total	1	1	1	3

TABLE 82 *Data available for IAA versus CTA data: all arteries (the symptomatic status of all arteries contributing to the CTA data was known)*

			IAA			
Arteries included			**0–49, 100%**	**50–69%**	**70–99%**	**Total**
True status known only	CTA	0–49, 100%	2	–	–	2
		50–69%	–	–	1	1
		70–99%	1	1	4	6
		Total	3	1	5	9

TABLE 83 *Data available for IAA versus MRA data: symptomatic arteries only (the symptomatic status of all arteries contributing to the MRA data was known)*

			IAA			
Arteries included			**0–49, 100%**	**50–69%**	**70–99%**	**Total**
True status known only	MRA	0–49, 100%	18	1	–	19
		50–69%	2	4	1	7
		70–99%	–	4	2	6
		Total	20	9	3	32

TABLE 84 *Data available for IAA versus MRA data: asymptomatic arteries only (the symptomatic status of all arteries contributing to the MRA data was known)*

			IAA			
Arteries included			**0–49, 100%**	**50–69%**	**70–99%**	**Total**
True status known only	MRA	0–49, 100%	30	–	–	30
		50–69%	1	2	–	3
		70–99%	–	1	1	2
		Total	31	3	1	35

TABLE 85 *Data available for IAA versus MRA data: all arteries (the symptomatic status of all arteries contributing to the MRA data was known)*

			IAA			
Arteries included			**0–49, 100%**	**50–69%**	**70–99%**	**Total**
True status known only	MRA	0–49, 100%	48	1	–	49
		50–69%	3	6	1	10
		70–99%	–	5	3	8
		Total	51	12	4	67

TABLE 86 *Data available for IAA versus CEMRA data: symptomatic arteries only*

			IAA			
Arteries included			**0–49, 100%**	**50–69%**	**70–99%**	**Total**
All	CEMRA	0–49, 100%	71	6	3	80
		50–69%	17	16	4	37
		70–99%	2	16	32	50
		Total	90	38	39	167
True status known only	CEMRA	0–49, 100%	42	4	2	48
		50–69%	8	11	3	22
		70–99%	1	9	22	32
		Total	51	24	27	102

TABLE 87 *Data available for IAA versus CEMRA data: asymptomatic arteries only*

			IAA			
Arteries included			**0–49, 100%**	**50–69%**	**70–99%**	**Total**
All	CEMRA	0–49, 100%	103	3	3	109
		50–69%	10	12	–	22
		70–99%	3	3	16	22
		Total	116	18	19	153
True status known only	CEMRA	0–49, 100%	82	–	1	83
		50–69%	5	3	–	8
		70–99%	1	–	6	7
		Total	88	3	7	98

TABLE 88 *Data available for IAA versus CEMRA data: all arteries*

			IAA			
Arteries included			**0–49, 100%**	**50–69%**	**70–99%**	**Total**
All	CEMRA	0–49, 100%	174	9	6	189
		50–69%	27	28	4	59
		70–99%	5	19	48	72
		Total	206	56	58	320
True status known only	CEMRA	0–49, 100%	124	4	3	131
		50–69%	13	14	3	30
		70–99%	2	9	28	39
		Total	139	27	34	200

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TABLE 89 *Data available for US for women in the age bands specified by the cost-effectiveness model (all arteries whether symptomatic, asymptomatic or unknown)*

		IAA		
Age band (years)	**US**	**0–49, 100%**	**50–69%**	**70–99%**
55–64	0–49, 100%	41	3	1
	50–69%	10	4	12
	70–99%	3	13	52
65–74	0–49, 100%	33	2	5
	50–69%	10	7	14
	70–99%	12	16	80
75–84	0–49,100%	17	2	2
	50–69%	6	8	5
	70–99%	5	9	24
≥ 85	0–49, 100%	–	–	–
	50–69%	–	–	–
	70–99%	–	–	–

TABLE 90 *Data available for US for men in the age bands specified by the cost-effectiveness model (all arteries whether symptomatic, asymptomatic or unknown)*

		IAA		
Age band (years)	**US**	**0–49, 100%**	**50–69%**	**70–99%**
55–64	0–49, 100%	87	6	2
	50–69%	7	20	27
	70–99%	11	17	101
65–74	0–49,100%	98	12	6
	50-69%	22	25	22
	70-99%	17	42	140
75–84	0–49,100%	48	5	2
	50–69%	8	13	7
	70–99%	6	12	61
>85	0–49,100%	1	–	1
	50–69%	–	–	1
	70–99%	1	–	1

TABLE 91 *Data available for MRA for women in the age bands specified by the cost-effectiveness model (all arteries whether symptomatic, asymptomatic or unknown)*

		IAA		
Age band (years)	**MRA**	**0–49, 100%**	**50–69%**	**70–99%**
55–64	0–49,100%	6	–	–
	50–69%	2	1	–
	70–99%	–	1	–
65–74	0–49, 100%	5	–	–
	50–69%	–	–	–
	70–99%	–	1	1
75–84	0–49, 100%	–	–	–
	50–69%	–	1	–
	70–99%	–	–	–
≥85	0–49,100%	–	–	–
	50–69%	–	–	–
	70–99%	–	–	–

TABLE 92 *Data available for MRA for men in the age bands specified by the cost-effectiveness model (all arteries whether symptomatic, asymptomatic or unknown)*

		IAA		
Age band (years)	**MRA**	**0–49, 100%**	**50–69%**	**70–99%**
55–-64	0–49, 100%	17	–	–
	50–69%	–	1	–
	70–99%	–	–	1
65–74	0–49, 100%	11	1	–
	50–69%	–	1	–
	70–99%	–	3	1
75–84	0–49, 100%	1	–	–
	50–69%	–	–	–
	70–99%	–	–	–
≥85	0–49, 100%	–	–	–
	50–69%	–	–	–
	70–99%	–	–	–

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TABLE 93 *Data available for CEMRA for women in the age bands specified by the cost-effectiveness model (all arteries whether symptomatic, asymptomatic or unknown)*

		IAA		
Age band (years)	**CEMRA**	**0–49, 100%**	**50–69%**	**70–99%**
55–64	0–49, 100%	12	–	–
	50–69%	3	–	1
	70–99%	–	–	6
65–74	0–49, 100%	10	–	1
	50–69%	6	4	2
	70–99%	1	2	4
75–84	0–49, 100%	18	1	–
	50–69%	2	4	–
	70–99%	2	1	3
≥85	0–49,100%	–	–	–
	50–69%	–	–	–
	70–99%	–	–	–

TABLE 94 *Data available for CEMRA for men in the age bands specified by the cost-effectiveness model (all arteries whether symptomatic, asymptomatic or unknown)*

		IAA		
Age band (years)	**CEMRA**	**0–49, 100%**	**50–69%**	**70–99%**
55–64	0-49, 100%	35	3	1
	50–69%	3	4	1
	70–99%	–	3	6
65–74	0–49, 100%	49	2	3
	50–69%	9	6	–
	70–99%	1	6	13
75–84	0–49, 100%	32	3	–
	50–69%	4	7	–
	70–99%	1	5	10
≥85	0–49, 100%	–	–	1
	50–69%	–	–	–
	70–99%	–	–	2

TABLE 95 *Data available for IAA versus US data: audit/routinely collected data (all arteries are included whether their symptomatic status was randomised or the true status known from original data)*

			IAA			
Arteries included			**0–49, 100%**	**50–69%**	**70–99%**	**Total**
Symptomatic	US	0–49, 100%	45	8	1	54
		50–69%	14	28	60	102
		70–99%	23	56	319	398
		Total	82	92	380	554
Asymptomatic	US	0–49, 100%	195	9	9	213
		50–69%	25	19	11	55
		70–99%	10	12	39	61
		Total	230	40	59	329
All	US	0–49, 100%	240	17	10	267
		50–69%	39	47	71	157
		70–99%	33	68	358	459
		Total	312	132	439	883

TABLE 96 *Data available for IAA versus US data: research study data (all arteries are included whether their symptomatic status was randomised or the true status known from original data)*

			IAA			
Arteries included			**0–49, 100%**	**50–69%**	**70–99%**	**Total**
Symptomatic	US	0–49, 100%	48	10	9	67
		50–69%	22	28	21	71
		70–99%	24	40	130	194
		Total	94	78	160	332
Asymptomatic	US	0–49, 100%	90	5	2	97
		50–69%	12	5	2	19
		70–99%	4	11	20	35
		Total	106	21	24	151
All	US	0–49, 100%	138	15	11	164
		50–69%	34	33	23	90
		70–99%	28	51	150	229
		Total	200	99	184	483

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TABLE 97 *Data available for IAA versus MRA data: audit/routinely collected data (all arteries are included whether their symptomatic status was randomised or the true status known from original data)*

			IAA			
Arteries included			**0–49, 100%**	**50–69%**	**70–99%**	**Total**
Symptomatic	MRA	0–49, 100%	2	–	–	2
		50–69%	–	–	–	0
		70–99%	–	1	2	3
		Total	2	1	2	5
Asymptomatic	MRA	0–49, 100%	4	–	–	4
		50–69%	–	–	–	0
		70–99%	–	–	1	1
		Total	4	0	1	5
All	MRA	0–49, 100%	6	–	–	6
		50–69%	–	–	–	0
		70–99%	–	1	3	4
		Total	6	1	3	10

TABLE 98 *Data available for IAA versus MRA data: research study data (all arteries are included whether their symptomatic status was randomised or the true status known from original data)*

			IAA			
Arteries included			**0–49, 100%**	**50–69%**	**70–99%**	**Total**
Symptomatic	MRA	0–49, 100%	16	1	–	17
		50–69%	2	4	1	7
		70–99%	–	3	–	3
		Total	18	8	1	27
Asymptomatic	MRA	0–49, 100%	26	–	–	26
		50–69%	1	2	–	3
		70–99%	–	1	–	1
		Total	27	3	0	30
All	MRA	0–49, 100%	42	1	–	43
		50–69%	3	6	–	9
		70–99%	–	4	–	4
		Total	45	11	0	56

TABLE 99 *Data available for IAA versus US data: screened patients*

			IAA			
Arteries included			**0–49, 100%**	**50–69%**	**70–99%**	**Total**
Symptomatic	US	0–49, 100%	49	10	10	69
		50–69%	23	30	56	109
		70–99%	27	56	321	404
		Total	99	96	387	582
Asymptomatic	US	0–49, 100%	168	11	11	190
		50–69%	31	10	8	49
		70–99%	10	17	47	74
		Total	209	38	66	313
All	US	0–49, 100%	217	21	21	259
		50–69%	54	40	64	158
		70–99%	37	73	368	478
		Total	308	134	453	895

TABLE 100 *Data available for IAA versus US data: unscreened patients*

			IAA			
Arteries included			**0–49, 100%**	**50–69%**	**70–99%**	**Total**
Symptomatic	US	0–49, 100%	44	8	–	52
		50–69%	13	26	25	64
		70–99%	20	40	128	188
		Total	77	74	153	304
Asymptomatic	US	0–49, 100%	117	3	–	120
		50–69%	6	14	5	25
		70–99%	4	6	12	22
		Total	127	23	17	167
All	US	0–49, 100%	161	11	–	172
		50–69%	19	40	30	89
		70–99%	24	46	140	210
		Total	204	97	170	471

TABLE 101 *Data used to calculate the probability of a second US agreeing with a first US (symptomatic arteries only)*

	Second US			
First US	**0–49, 100%**	**50–69%**	**70–99%**	**Total**
0–49, 100%	70	3	4	77
50–69%	10	45	22	77
70–99%	10	8	112	130
Total	90	56	138	284

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TABLE 102 *Data used to calculate the probability of a second US agreeing with a first US (asymptomatic arteries only)*

	Second US			
First US	**0-49, 100%**	**50-69%**	**70-99%**	**Total**
0–49, 100%	209	2	4	215
50–69%	8	15	9	32
70–99%	2	3	32	37
Total	219	20	45	284

TABLE 103 *Data used to calculate the probability of a second MRA agreeing with a first MRA (symptomatic arteries only)*

	Second MRA			
First MRA	**0–49, 100%**	**50–69%**	**70–99%**	**Total**
0–49, 100%	15	–	–	15
50–69%	4	1	–	5
70–99%	–	2	–	2
Total	19	3	0	22

TABLE 104 *Data used to calculate the probability of a second MRA agreeing with a first MRA (asymptomatic arteries only)*

	Second MRA			
First MRA	**0-49, 100%**	**50–69%**	**70–99%**	**Total**
0–49, 100%	13	1	–	14
50–69%	6	1	–	7
70–99%	3	–	–	3
Total	22	2	0	24

TABLE 105 *Data used to calculate the probability of a second CEMRA agreeing with a first CEMRA (symptomatic arteries only)*

	Second CEMRA			
First CEMRA	**0–49, 100**	**50–69**	**70–99**	**Total**
0–49, 100%	43	9	1	53
50–69%	2	19	6	27
70–99%	–	10	39	49
Total	45	38	46	129

TABLE 106 *Data used to calculate the probability of a second CEMRA agreeing with a first CEMRA (asymptomatic arteries only)*

	Second CEMRA			
First CEMRA	**0–49, 100%**	**50–69%**	**70–99%**	**Total**
0–49, 100%	92	8	–	100
50–69%	4	14	2	20
70–99%	–	1	12	13
Total	96	23	14	133

TABLE 107 *Data used to calculate the probability of a CEMRA agreeing with a prior US (symptomatic arteries only)*

	Second CEMRA			
First US	**0–49, 100**	**50–69**	**70–99**	**Total**
0–49, 100%	76	14	18	108
50–69%	5	12	11	28
70–99%	4	1	59	64
Total	85	27	88	200

TABLE 108 *Data used to calculate the probability of a CEMRA agreeing with a prior US (asymptomatic arteries only)*

	Second CEMRA			
First US	**0–49, 100%**	**50–69%**	**70–99%**	**Total**
0–49, 100%	119	9	5	133
50–69%	11	16	9	36
70–99%	6	4	27	37
Total	136	29	41	206

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Appendix 11

Search strategy for the systematic review of costs of diagnostic tests, clinics, stroke patient care, carotid endarterectomy and quality of life after stroke

Search terms list for MEDLINE

Computed tomography

1. exp economics
2. exp Technology assessment
3. exp health resources
4. cost$.tw
5. charge$.tw
6. economic$tw
7. finan$.tw
8. economic evaluation.tw
9. cost effective$.tw.
10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11. exp cerebrovascular disorders/
12. stroke$.tw.
13. cerebrovascular$.tw.
14. (cerebral or cerebellar or brainstem or vertebrobasilar).tw.
15. (infarct$ or isch?emi$ or thrombo$ or emboli$).tw.
16. 14 and 15
17. exp Ischemic Attack, Transient/
18. 11 or 12 or 13 or 16 or 17
19. Tomography, X-Ray Computed/ec [Economics]
20. 18 and 19

Magnetic resonance angiography

1 exp economics
2 exp Technology assessment
3 exp health resources
4 cost$.tw
5 charge$.tw
6 economic$tw
7 finan$.tw
8 economic evaluation.tw
9. cost effective$.tw.
10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11. exp cerebrovascular disorders/
12. stroke$.tw.
13. cerebrovascular$.tw.
14. (cerebral or cerebellar or brainstem or vertebrobasilar).tw.
15. (infarct$ or isch?emi$ or thrombo$ or emboli$).tw.
16. 14 and 15
17. exp Ischemic Attack, Transient/
18. 11 or 12 or 13 or 16 or 17
    Magnetic Resonance Angiography/ ec
20. 18 and 19

Ultrasound

1. exp economics
2. exp Technology assessment
3. exp health resources
4. cost$.tw
5. charge$.tw
6. economic$tw
7. finan$.tw
8. economic evaluation.tw
9. cost effective$.tw.
10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11. exp cerebrovascular disorders/
12. stroke$.tw.
13. cerebrovascular$.tw.
14. (cerebral or cerebellar or brainstem or vertebrobasilar).tw.
15. (infarct$ or isch?emi$ or thrombo$ or emboli$).tw.
16. 14 and 15
17. exp Ischemic Attack, Transient/
18. 11 or 12 or 13 or 16 or 17
    Ultrasound/ ec
20. 18 and 19

MRI

1. exp economics
2. exp Technology assessment
3. exp health resources
4. cost$.tw
5. charge$.tw
6. economic$tw
7. finan$.tw
8. economic evaluation.tw
9. cost effective$.tw.
10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11. exp cerebrovascular disorders/
12. stroke$.tw.
13. cerebrovascular$.tw.

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14. (cerebral or cerebellar or brainstem or vertebrobasilar).tw.
15. (infarct$ or isch?emi$ or thrombo$ or emboli$).tw.
16. 14 and 15
17. exp Ischemic Attack, Transient/
18. 11 or 12 or 13 or 16 or 17
19. MRI/ ec
20. 18 and 19

Angiography

1. exp economics
2. exp Technology assessment
3. exp health resources
4. cost$.tw
5. charge$.tw
6. economic$tw
7. finan$.tw
8. economic evaluation.tw
9. cost effective$.tw.
10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11. exp cerebrovascular disorders/
12. stroke$.tw.
13. cerebrovascular$.tw.
14. (cerebral or cerebellar or brainstem or vertebrobasilar).tw.
15. (infarct$ or isch?emi$ or thrombo$ or emboli$).tw.
16. 14 and 15
17. exp Ischemic Attack, Transient/
18. 11 or 12 or 13 or 16 or 17
19. angiography/ ec
20. 18 and 19

Appendix 12

Cost of investigations

Costs of carotid imaging presented here were derived from a microcosting exercise in Edinburgh.

Costings for MRA

	Cost per item (£)	No. of items	Cost (£)	Incl. VAT @ 17.5%
Consumable costs per MRA				
30-ml Omniscan	33.00	2	66.00	77.55
Injector pack	12.75	1	12.75	14.98
Injection pack (venflon, etc.), saline, mediswab, tape, 5-ml syringe, gauze	6.00	1	6.00	7.05
Earplugs	0.10	1	0.10	0.12
35 × 43 film	1.15	4	4.60	5.41
Film bag and labels, green card	0.50	1	0.50	0.59
Total				**105.69**

	Top of scale (£)	Top of scale + 22% emp. costs (£)	Weekly rate (£)	Hourly rate (£)	Time taken (hours)	Cost (£)
Staffing costs						
Consultant radiologist	68,505.00	83,576.10	1,607.23	45.92	0.50	22.96
Senior I	26,966.00	32,898.52	632.66	18.08	0.60	10.85
Senior I	26,966.00	32,898.52	632.66	18.08	0.60	10.85
Nurse/Spr (Venflon)	34,095.00	41,595.90	799.92	22.85	0.16	3.66
RDA	12,250.00	14,945.00	287.40	8.21	0.16	1.31
A&C 2	16,124.00	19,671.28	378.29	10.81	0.08	0.86
Total staff cost						**50.49**

MR equipment	£230,000 p.a. lease and servicing (inc. VAT)

Radiology costs not including equipment or room costs

Room costs: not known (size 13 × 6 m)	
Consumable costs	£105.69
Staffing costs	£50.49
Actual cost per case	£156.18
Number of MRAs p.a.	75
Costs per annum/study	11,713.37618

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Costings for carotid Doppler US

	Cost per item (£)	No. of items	Cost (£)	Incl. VAT @ 17.5%
Consumable costs per US				
Gel 1 bottle/200 patients	10.00	0.05	0.50	0.59
Paper rolls, paper towels: large, small	1.00	0.02	0.02	0.02
Film bag and labels, green card, report forms	0.50	1.00	0.50	0.59
Printer paper colour/black and white	2.00	1.00	2.00	2.35
Total				**3.55**

	Top of scale (£)	Top of scale + 22% emp. costs (£)	Weekly rate (£)	Hourly rate (£)	Time taken (hours)	Cost (£)
Staffing costs						
Consultant radiologist	68,505.00	83,576.10	1,607.23	45.92	0.33	15.15
Senior I	26,966.00	32,898.52	632.66	18.08	0.33	5.97
A&C 4	16,124.00	19,671.28	378.29	10.81	0.16	1.73
RDA	12,250.00	14,945.00	287.40	8.21	0.16	1.31
Total staff cost						**24.16**

Equipment costs purchase	250,000.00
Servicing p.a.	4,000.00

Radiology costs not including equipment or room costs

Room costs: not known (size 5 × 6 m)	
Consumable costs	£3.55
Staffing costs	£24.16
Actual cost per case	£27.71
Number of USs	1,500
Costs per annum/study	41,566.07093

Costings for CTA

	Cost per item (£)	No. of items	Cost (£)	Incl. VAT @ 17.5%
Consumable costs per US				
150-ml Visipaque 270	18.83	1	18.83	22.13
Injector pack	11.25	1	11.25	13.22
Injection pack (venflon, etc.), saline, tape, gauze, mediswab	6.00	1	6.00	7.05
35 × 43 film	1.15	3	1.15	1.35
Film bag and labels, green card, report paper	0.50	1	0.10	0.00
Totals				**43.75**

	Top of scale (£)	Top of scale + 22% emp. (£)	Weekly rate (£)	Hourly rate (hours)	Time taken (£)	Cost
Staffing costs						
Consultant radiologist	68,505.00	83,576.10	1,607.23	45.92	0.50	22.96
SPR	34,095.00	41,595.90	799.92	22.85	0.25	5.71
Senior I	26,966.00	32,898.52	632.66	18.08	0.40	7.23
Senior I	26,966.00	32,898.52	632.66	18.08	0.40	7.23
Staff nurse	24,495.00	29,883.90	574.69	16.42	0.20	3.28
Nurse (grade A)	12,250.00	14,945.00	287.40	8.21	0.40	3.28
A&C 4	16,124.00	19,671.28	378.29	10.81	0.10	1.08
Total staff cost						**50.78**

CT equipment	249,100 p.a. lease and servicing
Replacement X-ray tubes (need at least 2 over 10 years)	30,000 per tube

Radiology costs not including equipment or room costs

Room costs: not known (size 6 × 1 m)	
Consumable costs	£43.75
Staffing costs	£50.78
Actual cost per case	£94.53
Number of CTAs	75.00
Costs per annum/study	7,089.72956

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Costings for IAA

	Cost per item (£)	No. of items	Cost (£)	Incl. VAT @ 17.5%
Consumable costs per IAA				
100-ml Visipaque	12.55	1	12.55	14.75
Basic pack	6.00	1	6.00	7.05
Diagnostic pack (inc. syringes, razor, drape)	23.50	1	23.50	27.61
Steel J guidewire	4.05	1	4.05	4.76
Catheter pigtail 4F	8.50	1	8.50	9.99
Catheter Simmons 5F	8.50	1	8.50	9.99
Sheath 5F	8.50	1	8.50	9.99
19-G Seldinger needle	2.50	1	2.50	2.94
Iodine skin prep.	0.11	1	0.11	0.13
Sterile gloves	0.26	4	1.04	1.22
Non-sterile gloves	0.08	3	0.24	0.28
Saline solution 500 ml	0.35	1	0.35	0.41
CD for archiving	1.25	1	1.25	1.47
10-ml lignocaine	0.68	1	0.68	0.80
35 × 43 film	1.15	2	2.30	2.70
Film bag and labels, green card, report form	0.50	1	0.50	0.59
Total				**94.67**

	Top of scale (£)	Top of scale + 22% emp. costs (£)	Weekly rate (£)	Hourly rate (£)	Time taken (hours)	Cost (£)
Staffing costs						
Consultant radiologist	68,505.00	83,576.10	1,607.23	45.92	1.50	68.88
Senior I	26,966.00	32,898.52	632.66	18.08	1.00	18.08
Senior I	26,966.00	32,898.52	632.66	18.08	1.00	18.08
Sister (grade G)	27,240.00	33,232.80	639.09	18.26	1.25	22.82
Staff nurse	24,495.00	29,883.90	574.69	16.42	1.25	20.52
RDA	12,250.00	14,945.00	287.40	8.21	0.60	4.93
A&C 4	16,124.00	19,671.28	378.29	10.81	0.16	1.73
Total staff cost						**155.04**

Equipment purchase	1,410,000.00
Servicing p.a.	47,000.00

Radiology costs not including equipment or room costs

Room costs: not known (size 8 × 12 m)	
Consumable costs	£94.67
Staffing costs	£155.04
Actual cost per case	£249.71[a]
Number of IAAs	75.00[b]
Costs per annum/study	18728.17643

[a] Not including overnight stay or stay in recovery area for 8–12 hours.
[b] We do very few now, but we used to do about 75 per year.

Appendix 13

Questionnaire on organisation of stroke prevention clinics in the UK

Background

The cost-effectiveness model required data on the range of ways in which TIA clinics are run in the UK. This would allow the model to include different scenarios reflecting real day-to-day UK practice, and so allow clinicians to compare their own TIA clinic with one of the scenarios in the model. However, there were no published data with the required level of detail. In addition, the model required data on individual clinics so as to be able to reconstruct the patient pathway, and not summary statistics of a number of TIA clinics.

Given the needs of the model and the lack of publicly available data, the only practical solution was to conduct a survey of different kinds of UK TIA clinics by e-mail/postal questionnaire.

Methodology

The HTA group sampled centres so as to be certain of including both general and teaching hospitals, with clinics run by neurologists, geriatricians or stroke physicians. Even though this meant that the sample would not be random or necessarily representative of TIA clinics as a whole, the data needs of the cost-effectiveness model would be met. Moreover, obtaining a random sample of TIA clinics would pose immense practical difficulties as there is no easy way of finding out where these clinics are and a full-scale survey of TIA clinics in the UK was beyond the scope of the project.

Although it is not easy to identify where and by whom a clinic is run, the HTA group did have access to a number of individuals working in UK TIA clinics, namely themselves and UK collaborators in the IST-3 Trial (http://www.dcn.ed.ac.uk/ist3/default.asp). These were individuals known to have an interest in stroke and therefore were more likely to respond to the questionnaire. These clinics would not be representative of all UK TIA clinics. The data could not be used to make reliable inferences about the 'average' TIA clinic; but they would provide the necessary information for the cost-effectiveness model, that is, allow a range of clinics to be described with the level of required detail.

An initial questionnaire was drawn up by a neuroradiologist (JMW) who runs a carotid imaging service for a neurovascular clinic and a statistician (FMC) and discussed with the people developing the cost-effectiveness model (ST, MS, E De N). In order to make the questionnaire simple and quick to fill in, tick boxes were used wherever possible. This also made the data extraction and manipulation process easier as well as making a high response rate more likely. The questions were designed to extract data on the patient pathway from initial presentation to surgery. The specific needs of the cost-effectiveness model were related to knowing how often the clinics were run, what volume of patients they dealt with, what resources they consumed and the timing of events, for example, the number of days after the initial appointment to carotid imaging.

When agreement had been reached on the form and content of the questionnaire, it was piloted among the members of the HTA group who had not been involved in its development. The members were specifically asked for any suggestions to improve the questionnaire and to point out any weaknesses or ambiguities. The data from the pilot phase showed that the questionnaire was understood by the respondents and generated useful data. The questionnaire was then sent to UK collaborators in the IST-3 trial after one question was added at the request of the cost-effectiveness model developers. This was question 29, 'What is your approximate clinic catchment population?' No other changes were made to the questionnaire.

The data were extracted from the returned questionnaires and sent to the cost-effectiveness model developers. Each individual TIA clinic's data was given to the developers, though they did not know which centres had provided which data. Summary statistics and other analyses would not have been appropriate, not only because of the sampling procedure, but also because the

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TABLE 109 *Frequency of dedicated TIA clinic and numbers of patients attending (data from Q2 and Q3)*

No. of patients per clinic	Daily	Twice weekly	Once a week	Other[a]	Total
1–5	1	0	0	0	1
6–10	0	4	4	1	9
11–15	0	1	2	0	3
16–20	0	1	0	0	1
>20	0	0	2	0	2
Total	1	6	8	1	16

[a] There was one clinic that ran three times a week.

TABLE 110 *Frequency of dedicated TIA clinic and proportion of patients ultimately diagnosed as having carotid territory disease (data from Q2 and Q4)*

No. of patients per clinic	Daily	Twice weekly	Once a week	Other[a]	Total
≤ 20%	0	1	0	0	1
21–40%	0	0	2	1	3
41–60%	1	4	5	0	10
61–80%	0	1	1	0	2
80–100%	0	0	0	0	0
Total	1	6	8	1	16

[a] There was one clinic that ran three times a week.

developers potentially needed to be able to reconstruct the set-up of each clinic.

Results

The questionnaire was sent to 17 centres offering TIA/stroke prevention clinics and the response rate was 100%. Full results are given in the questionnaire; parts marked with an asterisk have been added to the questionnaire to indicate where people left questions blank. Some of the replies that the respondents gave were inconsistent, but these were not amended.

All but one of the respondents worked in a dedicated TIA clinic, all of which were run at least once a week. The other respondent saw patients who had already attended a TIA clinic. *Table 109* shows how often and how many patients attended the dedicated clinics. The most common scenario was for a clinic to be held once or twice a week with six to ten patients attending each clinic. The data suggested that clinics that are run more often have fewer patients attending each clinic (*Table 109*), although given the sampling procedure and the small number of questionnaires, this does not constitute reliable evidence. Again the most common scenario was for a clinic to be held once or twice per week with 41–60% of its patients being diagnosed with carotid territory disease (*Table 110*).

Most clinics were run by consultants. Only one respondent said that a non-consultant helped to run the clinic, in that case a stroke nurse (*Figure 43*). Most patients' final diagnoses were made either by or with input from a consultant (see question 13). No clinic had more than four doctors and only four respondents said that nurses or nurse specialists were involved in the medical assessment or triaging of patients (see questions 12 and 14). A wide variety of professions was involved in assessing the patients' medical state (*Figure 44*).

Patients were referred from a variety of sources. All respondents said that they had referrals from GPs and other doctors working within the same hospital. The majority (12 out of 17) also said that they accepted referrals from doctors working at different hospitals. Up to a quarter of TIA and minor stroke patients at a centre could be seen in clinics other than the dedicated TIA clinic (*Figure 45*). These clinics may or may not be at the same hospital (see question 8).

In no clinic did patients have to wait more than 1 month for an appointment at the clinic after referral. Data from the respondents who gave a

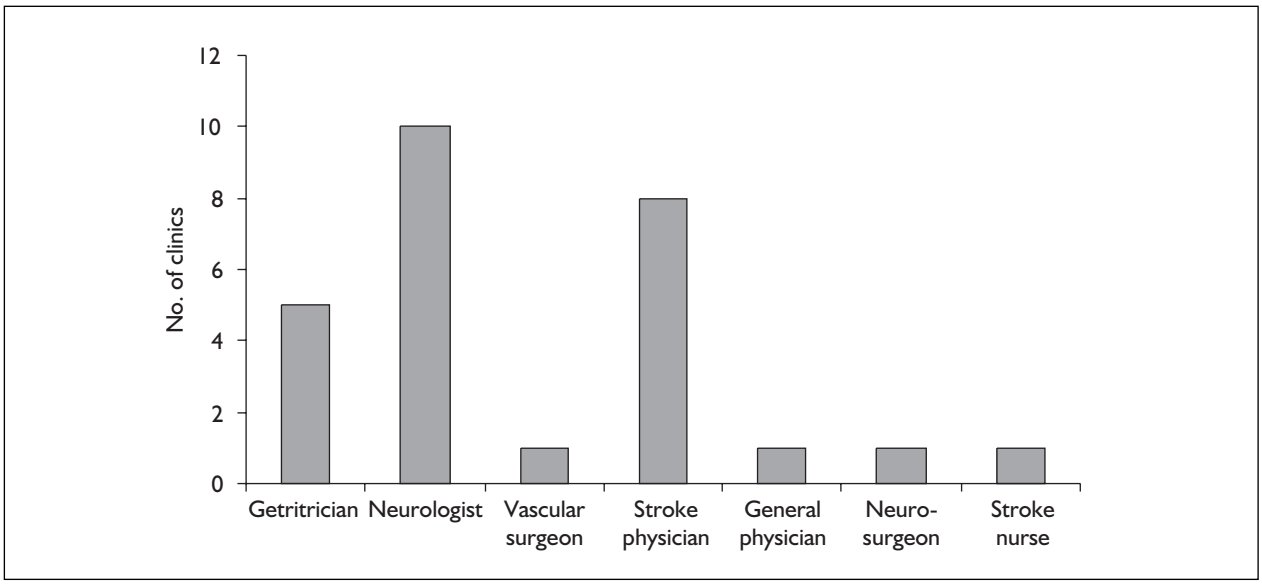

FIGURE 43 *Professions of people running dedicated TIA clinics (data from Q6)*

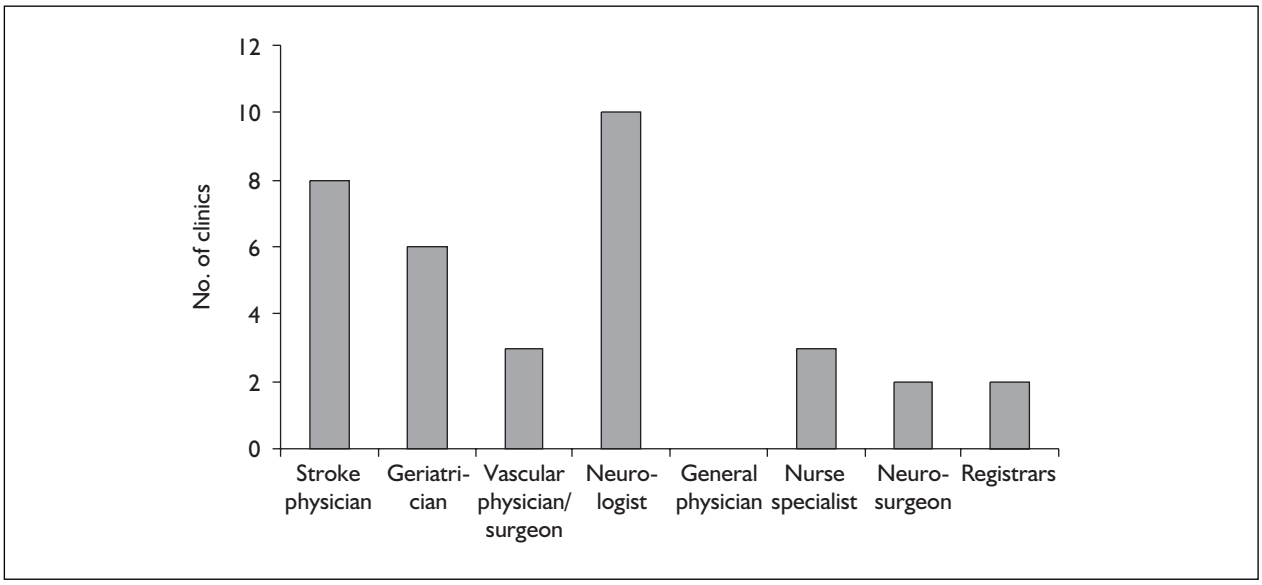

FIGURE 44 *Professions involved in assessing patients' medical state (data from Q11)*

figure of median waiting times indicated a range of 8–21 days. Only one respondent said that imaging of the carotid or vertebral arteries usually took place before this appointment (*Table 111*). Of those who said that the imaging took place after the appointment, most (six to nine clinics) tried to have it done during the same hospital visit (*Figure 46*) and in more than half of the clinics the imaging results were received back at the clinic within 24 hours (*Figure 47*). In other words, in seven to ten out of 17 clinics, patients underwent their initial carotid imaging on the same day as the clinic attendance. All respondents, apart from two who did not reply to the question, said that important positive imaging results were either always or sometimes given back to the clinic immediately (see question 20). Only one clinic did not offer routine imaging of the neck arteries at the same hospital.

In all but one case, the first line carotid imaging was done with US (*Table 112*). However, there was more variety among the clinics with regard to confirmatory imaging; the most common modality was IAA (*Table 113*). US was the only modality where it was possible for tests to be requested and results received within 24 hours. The data suggested that other tests, especially MRA and

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TABLE 111 *Time to appointment to clinic after initial referral and times to imaging of the carotid/vertebral arteries from the appointment (data from Q10 and Q15)*

	Timing of imaging				
Time to appointment	**Same day, before**	**Same day, after**	**After (>1 day)**	**Various timings**	**Total**
<3 days	0	0	1	0	1
<1 week	1	0	1	1	3
<2 weeks	0	3	2	2	7
<1 month	0	3	3	0	6
Total	1	6	7	3	17

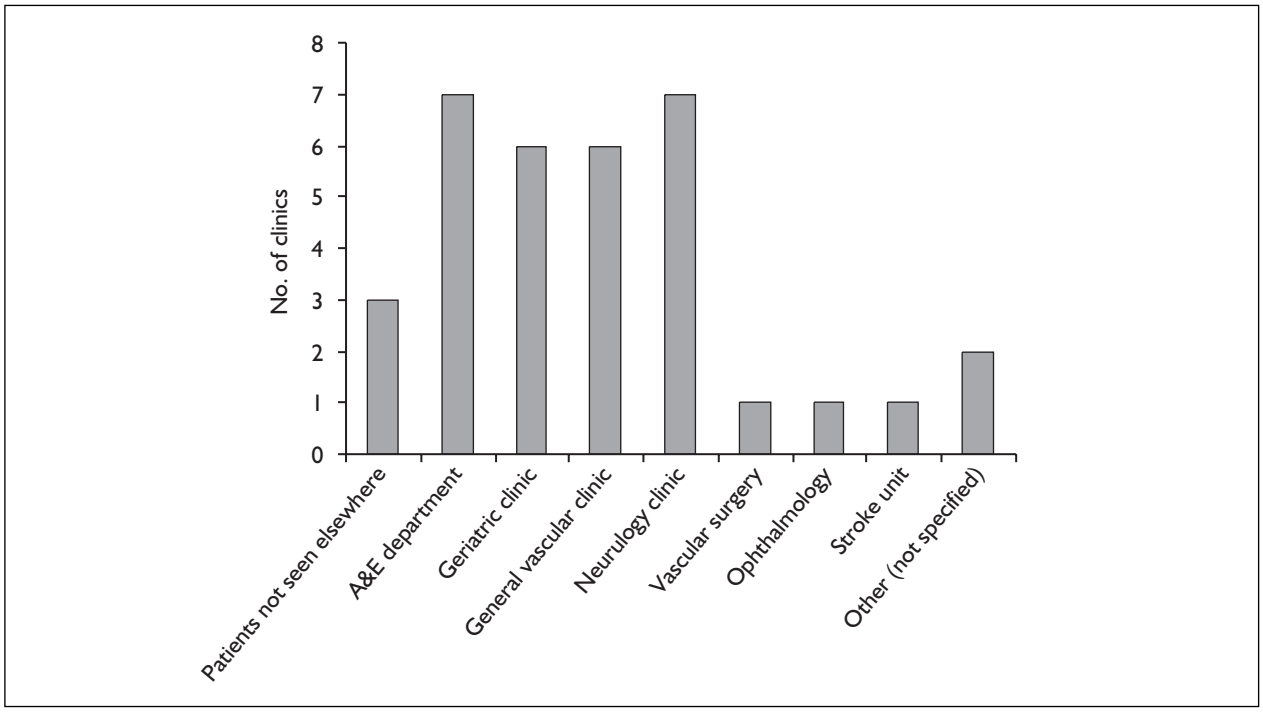

FIGURE 45 *Clinics other than dedicated TIA clinics that accept TIA or minor stroke patients (data from Q7)*

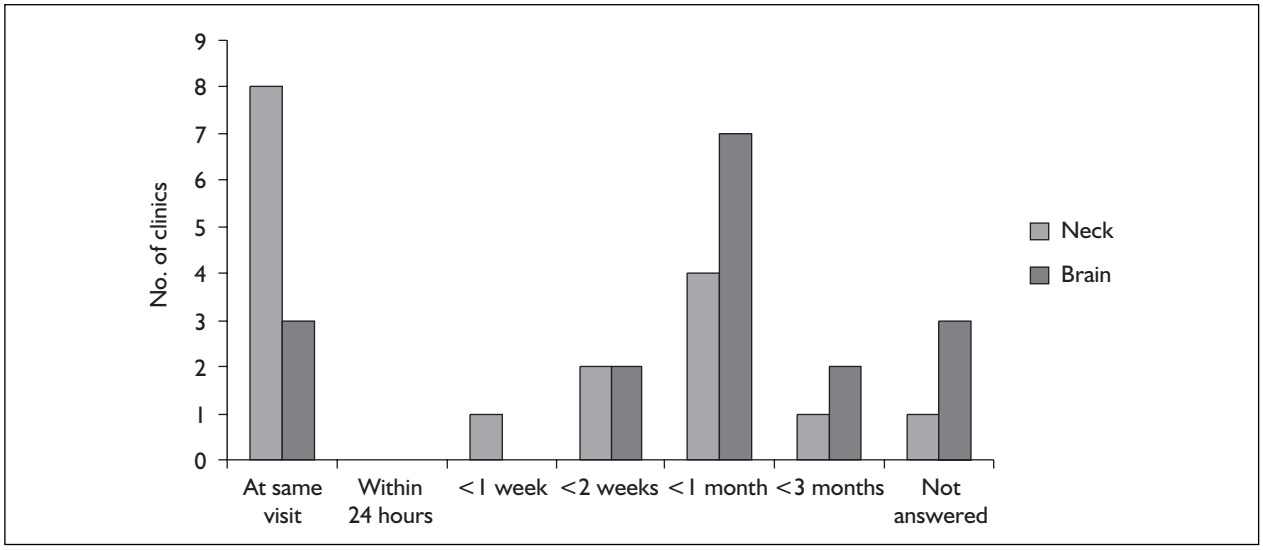

FIGURE 46 *Time to neck and brain imaging after initial appointment (data from Q16)*

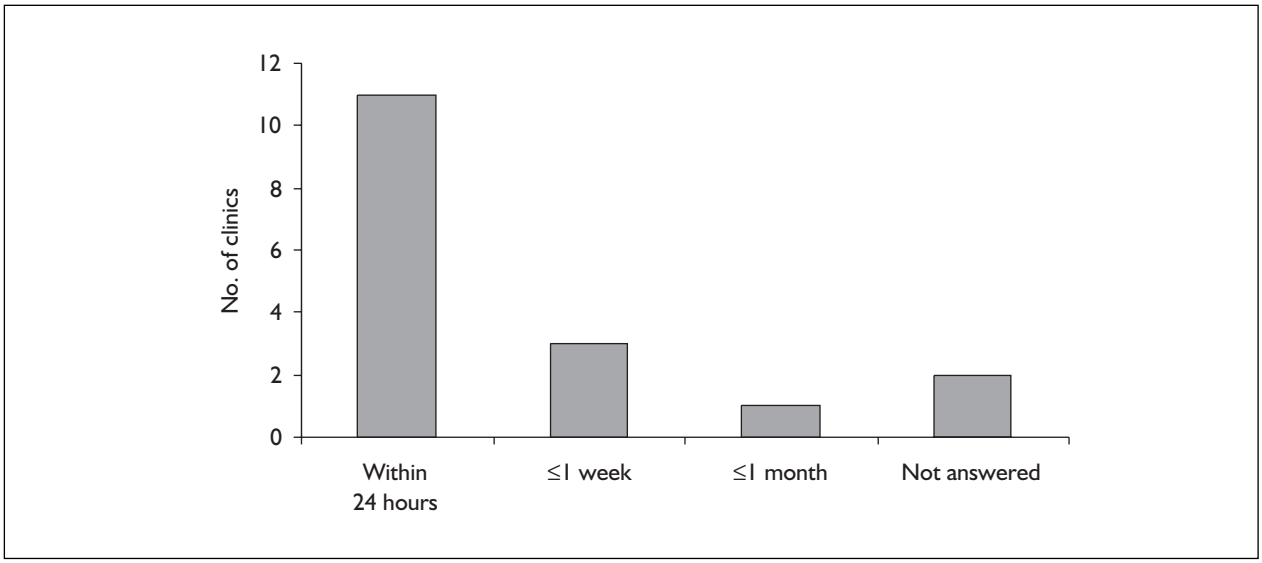

FIGURE 47 *Time for imaging results to reach clinic (data from Q19)*

TABLE 112 *Location (relative to clinic) and modality used for first line carotid imaging (data from Q17 and 18)*

	First line carotid imaging			
Location	**US**	**CTA**	**Not answered**	**Total**
Same hospital	13	1	0	14
Different hospital	1	0	0	1
Not applicable	1	0	0	1
Not answered	0	0	1	1
Total	15	1	1	17

TABLE 113 *Choice of imaging modality for confirmatory imaging (data from Q21)*

Imaging modality	**Most frequently used**	**Sometimes used**	**Total**
US	4	1	5
CTA	0	3	3
MRA: non-contrast	2	5	7
MRA: with contrast	3	5	8
IAA	5	4	9
Three respondents did not reply to this question			

TABLE 114 *Time to surgery and location where surgeon is based (data from Q24 and Q25)*

	Location		
Time to surgery	**At same hospital**	**Not at same hospital**	**Total**
<1 week	1	2	3
<1 month	6	3	9
<3 months	1	2	3
<6 months	2	0	2
Total	10	7	17

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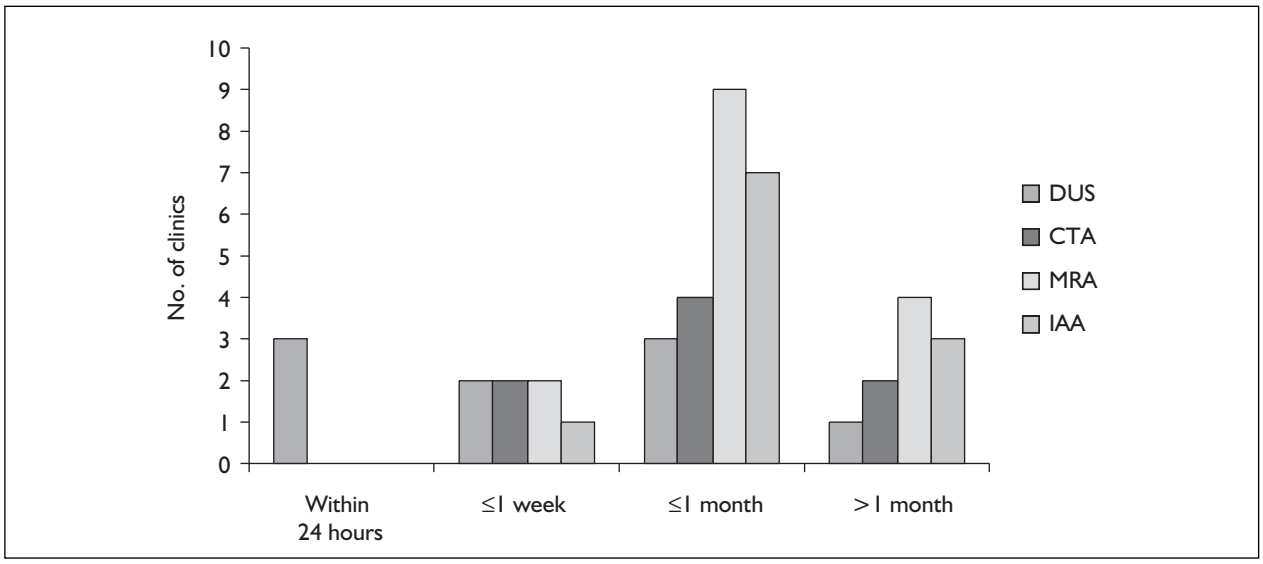

FIGURE 48 *Times for results of further tests to be received from time requested (data from Q22)*

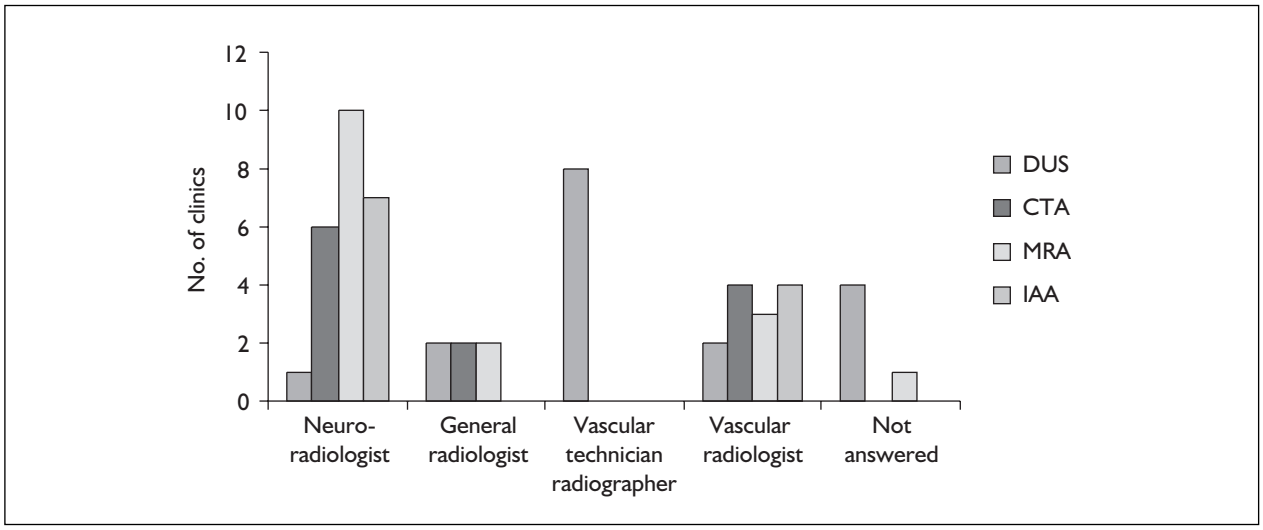

FIGURE 49 *Who performs and interprets further tests (data from Q23)*

IAA, took longer (*Figure 48*). US was also the only modality to be generally interpreted by a vascular technician or radiographer (*Figure 49*).

In no clinic was surgery performed more than 6 months after the decision to operate had been taken. The sampling procedure and the number of respondents mean that it is not possible to decide whether the location where the surgeon is based (at the same hospital or not) makes a difference to the time to surgery (*Table 114*). All patients spent less than 1 week in hospital for the operation (*Figure 50*).

Only three respondents felt that their clinic had extra capacity. Two of the respondents who said that they did not have extra capacity pointed out that this did not mean that they actually turned patients away. The two most common requirements to be able to expand clinic capacity were more consultants and more imaging capacity (*Figure 51*). Where more imaging capacity was needed, access to more US was the most common reason cited (*Figure 52*).

Discussion

Given the sampling procedure, the data from the questionnaire cannot be used to generate valid summary statistics such as mean number of patients seen per week. However, the respondents

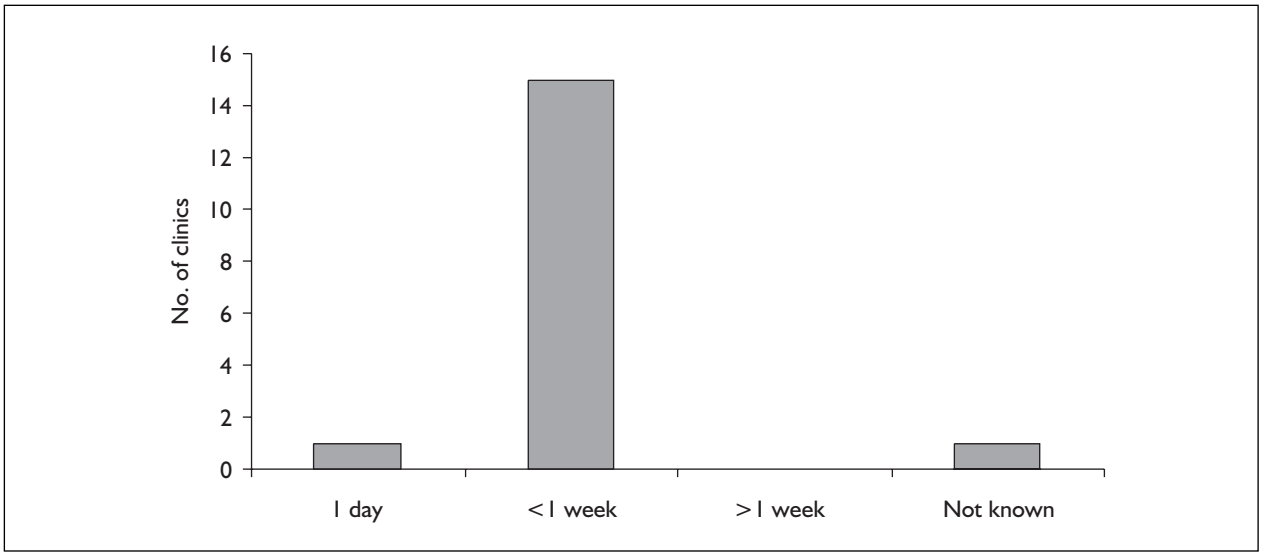

FIGURE 50 *Time spent in hospital for CEA counting from day of surgery (data from Q26)*

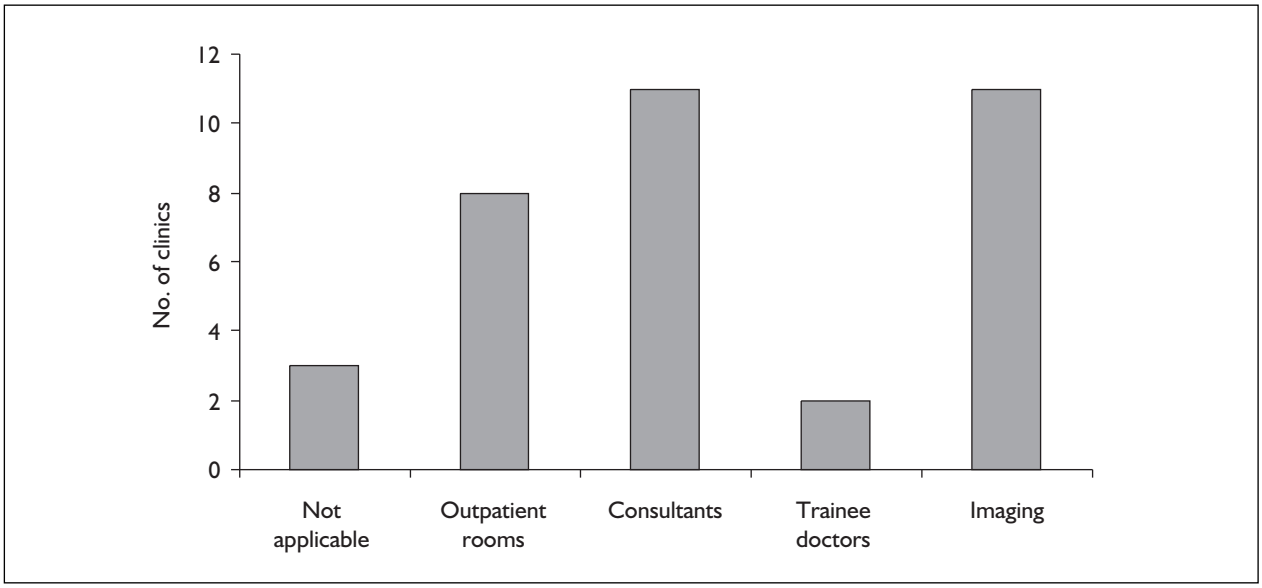

FIGURE 51 *Resources needed to expand capacity in fully saturated TIA clinics (data from Q28)*

work in different kinds of hospital in TIA clinics set up in different ways. It is therefore hoped that the data represent the range of parameters that these clinics can have. Although an e-mail/postal questionnaire to a limited number of selected centres may not be the ideal way to gather data on TIA clinics, it was the only practical solution, and provided the above caveat is borne in mind when interpreting the data, it can generate useful information.

The questionnaire provided helpful data for the cost-effectiveness model, especially with regard to the times between events on the patient pathway. Timing of imaging and surgery are critical factors in the model and the questionnaire provided up-to-date information on the range of times taken in UK TIA clinics. In this way the questionnaire was invaluable.

The questionnaire also confirmed the common use of US as the first line carotid imaging. The model includes several scenarios where various combinations of imaging test are used to confirm a patient's suitability for CEA, many of which have US as the initial test. The confirmatory test could be any one of US, CTA, MRA or IAA, and so the cost-effectiveness model included scenarios where all these tests are used. It was useful to note that about half of those surveyed still use IAA as a

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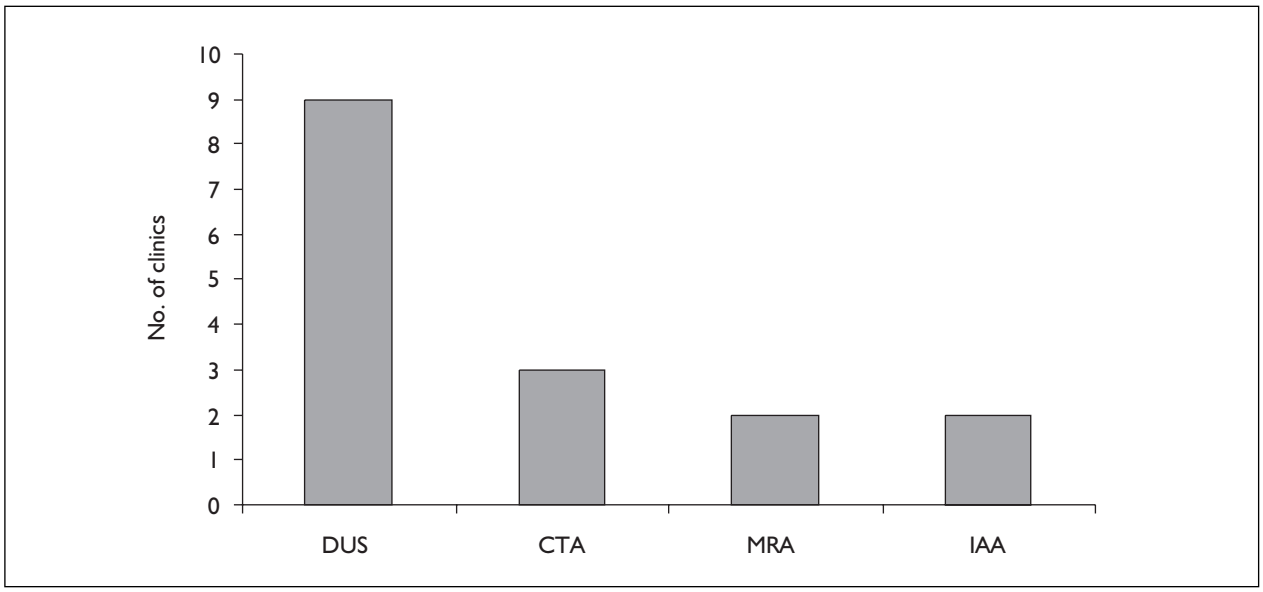

FIGURE 52 *Type of imaging needed to expand capacity (data from Q 28)*

confirmatory test, even if not as the routine confirmatory test.

These and other data from the questionnaire allowed the model developers to create true-to-life TIA clinic scenarios: they had data on how often these clinics were run, how many patients they handled, who worked in the clinics and what imaging resources were used.

Conclusion

It is encouraging that such a high proportion of stroke prevention clinics have access to at least initial carotid imaging on the same day as the clinic attendance. All of the less invasive tests evaluated in this work are in use in UK stroke prevention clinics. It is interesting that nearly half still use IAA.

Letter to HTA project participants inviting them to complete the questionnaire regarding the configuration of their stroke prevention clinic

Dear HTA group

Please find a copy of a questionnaire drafted by me and Joanna with feedback from our colleagues in Sheffield. This questionnaire aims to survey the variation in practice in TIA clinics with regard to referral patterns, clinic structures, and imaging policies as discussed at the first meeting in March (see page two of the minutes for further details – if anyone would like another copy of the minutes, just let me know).

Could you please take five minutes to fill in the questionnaire? We have tried to make it as user-friendly as possible, with tick-boxes for almost every question. It would be great if it could be sent back to me by 31st August 2003.

We would like you to complete the questionnaire for two major reasons: 1. the information will be tremendously useful for the HTA project 2. the questionnaire will be sent out to people who are not involved in the HTA and so will have less motivation to fill it in – we need to know if any of the questions are ambiguous or if it is difficult to complete.

We would also like to hear any suggestions you may have to improve the questionnaire – the current version is the usual compromise between being easy to fill in and completeness. If you have any ideas for making it more palatable or if there are any areas not covered which you feel are important, please do let me know.

Many thanks, and I hope to see as many of you as possible at the meeting on 2nd September.

best wishes

Francesca

Letter to UK participants in the Third International Stroke Trial inviting them to complete the questionnaire regarding the configuration of their stroke prevention clinic

Dear

We are working on an HTA project *Accurate, practical, and cost-effective imaging of carotid stenosis in the UK* funded by the NHS HTA programme. Part of this project requires a cost-effectiveness analysis, which involves modelling the pathway of care that patients go through when they present with TIA or minor stroke symptoms.

We feel that it is very important that our economic model is as close as possible to what actually happens in the UK, and so we are surveying people who run TIA clinics with regard to imaging techniques used, volume of work, and timing of procedures. It would be immensely helpful to us if you would fill in the enclosed questionnaire. If, however, you do not feel that you are the right person, please do pass on the questionnaire to an appropriate colleague.

We have tried to make the questionnaire as quick and easy to fill in as possible – when piloted, it took only 3 minutes to complete. We would be extremely grateful if you could help us and we hope to hear from you soon.

Yours sincerely

HTA Questionnaire: questions and results

1. Do you have a dedicated TIA/minor stroke outpatient clinic for stroke prevention?

	TICK ONE	
Yes	16	Go to Question 2
No	1	Go to Question 9

2. If you do have a dedicated TIA/minor stroke clinic, how often does it run?

	TICK ONE	
Daily	1	
Twice weekly	6	
Once a week	8	
Every two weeks	0	
Once a month	0	
Less than once a month	0	
Other (please specify)	1	*3 times a week*

3. In your dedicated TIA/minor stroke clinic, approximately how many patients attend each time it runs?

	TICK ONE
1–5 patients	1
6–10 patients	9
11–15 patients	3
16–20 patients	1
More than 20 patients	2

4. Approximately what proportion of patients attending the TIA/minor stroke clinic is ultimately diagnosed as having carotid territory cerebrovascular disease?

	TICK ONE
20% or less	1
21–40%	3
41–60%	10
61–80%	2
81–100%	0
Not known	0

5. Are patients referred to the dedicated TIA clinic/minor stroke clinic from other hospitals?

	TICK ONE
Yes	11
No	5

6. Who runs the dedicated TIA/minor stroke clinic?

	TICK ALL THAT APPLY	
Geriatrician	5	
Neurologist	10	
Vascular surgeon	1	
Stroke physician	8	
General physician	1	
Other (please specify)	2	*1 stroke nurse* *1 neurosurgeon*

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7. Are a proportion of TIA/minor stroke patients seen in other clinics, i.e. not in a dedicated TIA/minor stroke clinic? If so, where?

TICK ALL THAT APPLY		Approx. proportion if known
Patients not seen elsewhere	3	
A&E department	7	5–15%
Geriatric clinic	6	5–25%
General vascular clinic	6	1–20%
Neurology clinic	7	1–20%
Other (please specify)	5	10–20%

Vascular Surgery
Ophthalmology
Stroke Unit

8. Are these other clinics at the same hospital as you?

	TICK ONE
Yes	6
No	2
Some of them	4
Not applicable	4

If you have a dedicated TIA/minor stroke clinic, please answer the following questions with respect to it. If **not**, please answer with respect to the clinic in which you see the most TIA/minor stroke patients.

9. Who refers patients to your clinic?

	TICK ALL THAT APPLY
GP	17
Doctors within your hospital	17
Doctors from other hospitals	12
Other (please specify)	0

10. Once patients have been referred to your clinic, on average how long do they wait for an appointment?

	TICK ONE
Less than 3 days	1
Less than 1 week	3
Less than 2 weeks	7
Less than 1 month	6
Less than 3 months	0
Other (please specify)	0

NB. If you have data on median waiting times and range, please state 8–21 days

11. Who assesses the patients' medical state? Please tick for all those who are involved.

	TICK ALL THAT APPLY
Stroke physician	8
Geriatrician	6
Vascular physician/surgeon	3
Neurologist	10
General physician	0
Nurse specialist	3
Other (please specify)	2

Neurosurgeon
Neurology & Geriatric Medicine Registrars

12. Do nurses or nurse specialists undertake the medical assessment or triaging of patients?

	TICK ONE
Yes	4
No	13

13. If trainee doctors or nurse specialists assist in the clinic, how is the final diagnosis decided? Please comment:

*Patients' diagnoses always made with or by consultant	11
*Patients' diagnoses sometimes made with or by consultant	2
*Not applicable	2
*Blank – 2 replies	2

14. Approximately how many doctors are involved in patient assessment in the clinic?

	TICK ONE
1–2 doctors	7
3–4 doctors	10
5–6 doctors	0
More than 6 doctors	0

15. Are the patients' carotid/vertebral arteries usually scanned before or after the doctor's assessment?

	TICK ONE
Same day, but before	1
Before (more than 1 day)	0
Same day, but after	6
After (more than 1 day)	7
Mixture of the above	3

16. If a patient is to undergo imaging of the neck arteries or brain parenchyma after the clinical doctor's assessment, generally when does the imaging take place?

	TICK ONE Neck arteries	TICK ONE Brain parenchyma
At the same hospital visit	8	3
Within 24 hours	0	0
Less than 1 week	1	0
Less than 2 weeks	2	2
Less than 1 month	4	7
Less than 3 months	1	2
More than 3 months	0	0
*Not answered	1	3

17. Where do patients usually go for routine imaging (e.g. ultrasound) of the neck arteries?

	TICK ONE
At same hospital	14
At different hospital	1
Not applicable	1
*Not answered	1

18. Is ultrasound (DUS) used routinely in your clinic as the first line carotid/vertebral imaging investigation?

	TICK ONE	
Yes	15	
No (please say what is used)	1	CTA
*Not answered	1	

19. In general when are the imaging results received back at the clinic?

	TICK ONE
Within 24 hours	11
Less than 1 week	3
Less than 1 month	1
More than 1 month	0
Not applicable	0
*Not answered	2

20. Are important positive results (e.g. 70–99% stenosis) fed back to the clinic immediately?

	TICK ONE
Yes	12
No	0
Sometimes	3
Not applicable	2

21. If further tests are needed to confirm the ultrasound/initial neck imaging results, e.g. prior to referral for endarterectomy, what tests are used? Please put a * by the one most frequently used.

	TICK ALL THAT APPLY	
Ultrasound	5	****
CTA	3	
MRA – non-contrast	7	**
MRA – with contrast	8	***
Intra-arterial angiography (IAA)	9	*****
Other (please specify)	0	_____
*Not answered	3	

22. If further tests are required, approximately how long do you wait in total for the test to be done and the results sent to you?

	TICK ALL THAT APPLY DUS	CTA	MRA	IAA
Within 24 hours	3	0	0	0
1 week or less	2	2	2	1
1 month or less	3	4	9	7
More than 1 month	1	2	4	3

23. Who generally performs and interprets the tests?

	TICK ALL THAT APPLY DUS	CTA	MRA	IAA
Neuroradiologist	1	6	10	7
General radiologist	2	2	2	0
Vascular technician/ radiographer	8	0	0	0
Vascular radiologist	2	4	3	4
Other	0	0	0	0
*Not answered	4	0	1	0

24. If it is decided that a patient should have a carotid endarterectomy, in general what is the delay between deciding to operate and the operation?

	TICK ONE
Less than 1 week	3
Less than 1 month	9
Less than 3 months	3

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Less than 6 months	2
More than 6 months	0
Not applicable	0

25. Is the surgeon performing the carotid endarterectomy based in the same hospital as the clinic?

	TICK ONE
Yes	10
No	7
Other (please specify)	0 _____
Not applicable	0

26. Counting day 1 as day of surgery, on average how many days in total do patients stay in hospital for carotid endarterectomy?

	TICK ONE
1 day	1
Less than 1 week	15
More than 1 week	0
Not applicable	0
Not known	1

27. Is there capacity to expand your clinic to see more patients or is your current set-up saturated?

More capacity	3
Fully saturated	14

28. If there is no extra capacity in your clinic, what extra facilities are needed to expand the clinic?

Not applicable	3
More outpatient rooms	8
More consultants	11
More trainee doctors	2
More imaging capacity	11

Please tick which imaging method

9	DUS
3	CTA
2	MRA
2	IAA

29. What is your approximate catchment population? 150,000–1,700,000

Name of person filling in questionnaire:

Designation:

Name of hospital:

NHS Board/Health Authority/NHS Trust:

THANK YOU FOR FILLING IN THIS QUESTIONNAIRE

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We look forward to hearing from you.

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