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NHS R&D HTA Programme

The NHS R&D Health Technology Assessment (HTA) Programme was set up in 1993 to ensure that high-quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage and provide care in the NHS.

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Abstract

What is the best imaging strategy for acute stroke?

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Objectives: To determine the cost-effectiveness of computed tomographic (CT) scanning after acute stroke. To assess the contribution of brain imaging to the diagnosis and management of stroke, and to estimate the costs, benefits and risks of different imaging strategies in order to provide data to inform national and local policy on the use of brain imaging in stroke.

Design: A decision-analysis model was developed to represent the pathway of care in acute stroke using 'scan all patients within 48 hours' as the comparator against which to cost 12 alternative scan strategies.

Setting: Hospitals in Scotland.

Participants: Subjects were patients admitted to hospital with a first stroke and those managed as outpatients.

Interventions: The effect on functional outcome after ischaemic or haemorrhagic stroke, tumours or infections, of correctly administered antithrombotic or other treatment; of time to scan and stroke severity on diagnosis by CT or MRI; on management, including length of stay, functional outcome, and quality-adjusted life years (QALYs), of the diagnostic information provided by CT scanning; the cost-effectiveness (cost versus QALYs) of different strategies for use of CT after acute stroke.

Main outcome measures: Death and functional outcome at long-term follow-up; accuracy of CT and MRI; cost of CT scanning by time of day and week; effect of CT diagnosis on change in health outcome, length of stay in hospital and QALYs; cost-effectiveness of various scanning strategies.

Results: CT is very sensitive and specific for haemorrhage within the first 8 days of stroke only. Suboptimal scanning used in epidemiology studies suggests that the frequency of primary intracerebral haemorrhage (PICH) has been underestimated. Aspirin increases the risk of PICH. There were no reliable data on functional outcome or on the effect of antithrombotic treatment given long term after PICH. In 60% of patients with recurrent stroke after PICH, the cause is another PICH and mortality is high among PICH patients. A specific MR sequence (gradient echo) is required to identify prior PICH reliably. CT scanners were distributed unevenly in Scotland, 65% provided CT scanning within 48 hours of stroke, and 100% within 7 days for hospital-admitted patients, but access out of hours was very variable, and for outpatients was poor. The average cost of a CT brain scan for stroke was £30.23 to £89.56 in normal working hours and £55.05 to £173.46 out of hours. Average length of stay was greatest for severe strokes and those who survived in a dependent state. For a cohort of 1000 patients aged 70–74 years, the policy 'scan all strokes within 48 hours', cost £10,279,728 and achieved 1982.3 QALYS. The most cost-effective strategy was 'scan all immediately' (£9,993,676 and 1982.4 QALYS). The least cost-effective was to 'scan patients on anticoagulants, in a life-threatening condition immediately and the rest within 14 days'.

Conclusions: In general, strategies in which most patients were scanned immediately cost least and achieved the most QALYs, as the cost of providing CT (even out of hours) was less than the cost of inpatient care. Increasing independent survival by even a small proportion through early use of aspirin in the majority with ischaemic stroke, avoiding aspirin in those with haemorrhagic stroke, and appropriate early management of those who have not had a stroke, reduced costs and increased QALYs.

Contents

List of abbreviations

ABN	Association of British Neurologists
ACCP	American College of Chest Physicians
AF	atrial fibrillation
ANOVA	analysis of variance
APTT	activated partial thromboplastin time
ARI	Aberdeen Royal Infirmary
ATT	Antithrombotic Trialists' Collaboration
BG	basal ganglia
BGH	Borders General Hospital
CAST	Chinese Acute Stroke Trial
CCTR	Cochrane Controlled Trials Register
CHD	coronary heart disease
CI	confidence interval
CMA	Canadian Medical Association
CT	computed tomography
DGH	district general hospital
DWI	diffusion-weighted imaging
DVT	deep vein thrombosis
EAC	equivalent annual cost
ECG	electrocardiogram
FLAIR	fluid-attenuated inversion recovery magnetic resonance imaging
FSE T2	T2-weighted fast spin-echo
FSE	fast spin-echo
GIS	Geographical Information Service
GRE	gradient echo magnetic resonance imaging
GROS	General Registers Office of Scotland
HI	haemorrhagic infarction
HMCAS	hyperdense middle cerebral artery sign
HRQoL	health-related quality of life
HTI	haemorrhagic transformation of an infarct
ICH	intracerebral haemorrhage
ISD	Information and Statistics Division of the Scottish Office
IST	International Stroke Trial
LACI	lacunar infarction
LACS	lacunar syndrome
LOS	length of stay
LSR	Lothian Stroke Register
MCA	middle cerebral artery
MI	myocardial infarction
MR	magnetic resonance
MRI	magnetic resonance imaging
mRS	modified Rankin scale
NINDS	National Institutes of Neurological Diseases and Stroke
NSAID	non-steroidal anti-inflammatory drug
OCSP	Oxfordshire Community Stroke Project
OR	odds ratio
PACI	partial anterior circulation infarction
PACS	partial anterior circulation syndrome
PD	proton density-weighted magnetic resonance imaging
PE	pulmonary embolism
PHV	prosthetic heart valve
PICH	primary intracerebral haemorrhage
PMV	prosthetic mitral valve

continued

List of abbreviations *continued*

POCI	posterior circulation infarction
POCS	posterior circulation syndrome
QALY	quality-adjusted life year
RCR	Royal College of Radiologists
RCT	randomised controlled trial
rt-PA	recombinant tissue plasminogen activator
SAH	subarachnoid haemorrhage
SDH	subdural haematoma
SHPIC	Scottish Health Purchasing Information Centre
SIGN	Scottish Intercollegiate Guidelines Network
SPECT	single-photon emission computed tomography
SRI	Stirling Royal Infirmary
STICH	surgical treatment of intracerebral haemorrhage
T1	T1-weighted magnetic resonance imaging
T2	T2-weighted magnetic resonance imaging
TACI	total anterior circulation infarction
TACS	total anterior circulation syndrome
TIA	transient ischaemic attack
TTO	time trade-off
WHO	World Health Organization
WMHI	white matter hyperintensities

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

Objectives

- To determine the cost-effectiveness of computed tomographic (CT) scanning after acute stroke.
- To assess the contribution of brain imaging to the diagnosis and management of stroke.
- To estimate the costs, benefits and risks of different imaging strategies.
- To provide data to inform national and local policy on the use of brain imaging in stroke.

Methods

A decision-analysis model was developed to represent the pathway of care in acute stroke using 'scan all patients within 48 hours' as the comparator against which to cost 12 alternative scan strategies. Data were obtained from: systematic reviews of brain imaging, antithrombotic, anticoagulant and thrombolytic treatment, and cost-effectiveness of CT in stroke; a large UK hospital stroke registry; the Information and Statistics Division of the Scottish Office; a survey of all Scottish CT scanning departments; the Scottish Office; and a direct comparison of CT and magnetic resonance imaging (MRI).

The primary data for the model were generated in the Department of Clinical Neurosciences in Edinburgh, drawing on: the teaching hospital stroke registry (1990–9); the Cochrane Stroke Review Group; two multicentre international trials [the International Stroke Trial (IST) and the Chinese Acute Stroke Trial (CAST) of 40,000 patients conducted in 36 countries worldwide] and substudies on quality of life; a primary comparison of CT with MRI; and expert clinical knowledge where data were lacking. Data on access to CT for stroke and costs came from three representative Scottish hospitals. The health economics modelling was conducted by the Health Economics Research Unit in Aberdeen. Systematic reviews were undertaken by both departments.

Subjects were patients admitted to hospital with a first stroke and those managed as outpatients.

Interventions comprised the effect: on functional outcome after ischaemic or haemorrhagic stroke, tumours or infections, of correctly administered antithrombotic or other treatment; of time to scan and stroke severity on diagnosis by CT or MRI; on management, including length of stay, functional outcome, and quality-adjusted life years (QALYs), of the diagnostic information provided by CT scanning; the cost-effectiveness (cost versus QALYs) of different strategies for use of CT after acute stroke.

The main outcome measures were death and functional outcome at long-term follow-up (6 months, 1 year and 2 years); accuracy of CT and MRI; cost of CT scanning by time of day and week; effect of CT diagnosis on change in health outcome, length of stay in hospital and QALYs; cost-effectiveness of various scanning strategies.

Results

Clinicians disagree on the clinical diagnosis of stroke (versus not stroke) in about 20% of patients. It is impossible to differentiate infarct from haemorrhage by clinical examination. CT is very sensitive and specific for haemorrhage within the first 8 days of stroke only. Suboptimal scanning used in epidemiology studies suggests that the frequency of primary intracerebral haemorrhage (PICH) has been underestimated.

Aspirin increases the risk of PICH. There was no evidence that a few doses of aspirin given inadvertently to patients with acute PICH significantly increased the odds of death [odds ratio (OR) 0.96, 95% confidence interval (CI) 0.62 to 1.5] or recurrent intracranial haemorrhage (OR 1.02, 95% CI 0.5 to 1.8), so long as only a few doses were given. There were no reliable data on functional outcome or on the effect of antithrombotic treatment given long term after PICH. In 60% of patients with recurrent stroke after PICH, the cause is another PICH and mortality is high among PICH patients.

Among 232 patients (mainly outpatients) with mild stroke, 3% had a PICH and 15% had haemorrhagic transformation of an infarct. CT did not reliably detect PICH after 8 days. A specific

MR sequence (gradient echo) is required to identify prior PICH reliably.

CT scanners were distributed unevenly in Scotland (0.8, range 0.05–0.36/10,000). A total of 65% provided CT scanning within 48 hours of stroke, and 100% within 7 days for hospital-admitted patients, but access out of hours was very variable, and for outpatients was poor. The average cost of a CT brain scan for stroke in the NHS in Scotland ranged from £30.23 to £89.56 during normal working hours and from £55.05 to £173.46 out of hours.

Average length of stay was greatest for severe strokes and those who survived in a dependent state (alive and independent, 14 days; dependent, 51 days; and dead, 33 days).

For a cohort of 1000 patients aged 70–74 years, the policy 'scan all strokes within 48 hours' cost £10,279,728 and achieved 1982.3 QALYs. The most cost-effective strategy (least overall cost and most QALYs) was 'scan all immediately' (£9,993,676 and 1982.4 QALYs). The least cost-effective was 'scan patients on anticoagulants, in a life-threatening condition immediately and the rest within 14 days' (£12,592,666 and 1931.8 QALYs). 'Scan no patients' (but treat on the basis of clinical diagnosis alone) reduced QALYs (1904.2) at increased cost (£10,544,000).

Conclusions

In general, strategies in which most patients were scanned immediately cost least and achieved the most QALYs, as the cost of providing CT (even out of hours) was less than the cost of inpatient care. Increasing independent survival by even a small proportion through early use of aspirin in the majority with ischaemic stroke, avoiding aspirin in those with haemorrhagic stroke, and appropriate early management of those who have not had a stroke, reduced costs and increased QALYs. Sensitivity analyses to vary the cost of scanning, different age ranges, proportions of infarcts, haemorrhages or tumours/infections, accuracy of CT, utility weights, and length of stay assumptions did not alter the ranking of strategies. However, although, the model was sensitive to reducing the cost of inpatient care, 'scan all immediately' remained the dominant strategy.

Recommendations for research

Future research should obtain better data on:

- the use of antithrombotic treatment in acute PICH in patients at risk of DVT or ischaemic vascular events
- whether secondary prevention of ischaemic events with antithrombotic treatment is safe and effective in patients with prior PICH
- best management of acute PICH
- the proportion of first and recurrent stroke due to infarct or haemorrhage by age and severity
- costs of stroke care in hospital and in the community
- the accuracy of, and better methodology for assessing imaging
- improving accuracy of clinical diagnosis of stroke.
- ways of streamlining CT scanning for stroke.

Chapter 1
Background

The purpose of this chapter is to provide a brief introduction to the main research questions to be covered in the report, to summarise the evidence already available and to outline the sources of information to be used. It is intended to describe the contribution that brain imaging can make to the management of stroke and why there may be controversy about the use of brain imaging in stroke. It is therefore also intended to describe, from the perspective of the physician, radiologist, patient and carer, the important issues that the results of this project could help to resolve.

The burden of stroke: death, disability and loss of quality of life

Stroke is a major cause of death and disability in both the more developed and the less developed world.[1,2] Each year in the UK there are about 125,000 strokes,[1] causing about 10% of all deaths. About 25% of men and 20% of women can expect to suffer a stroke if they survive to 85 years.[3] The incidence and lifetime prevalence of stroke are far higher than for any other neurological disorder.[4] The incidence of first stroke is reported to be 2 per 1000 population and the overall incidence of stroke is 2.4 per 1000 population.[5,6] Stroke is currently the second most common cause of death in the UK.[7] Although the numbers of deaths from stroke are large, the major burden is chronic disability.[8] About one-third of stroke survivors are functionally dependent after 1 year;[9] survival with any degree of stroke-related impairment is likely to be associated with a reduction in health-related quality of life (HRQoL).[10] In the UK, there are about 250,000 disabled stroke survivors. Stroke is the most common cause of neurological disability in the community.[3,4,11]

The burden of stroke is projected to increase. In most developed countries, stroke mortality has declined since the early 1980s, but a large proportion of this fall has been due to a reduction in case fatality, rather than incidence.[12] In the coming decades, with the proportion of older people in the population set to rise, the total number of new strokes each year is projected to increase considerably.[1,13,14] By the year 2020, in the developed world, stroke is estimated to account for 6.2% of the total burden of illness.[14]

The cost of stroke

Stroke consumes about 2–4% of total healthcare costs (i.e. excluding social care and indirect costs) in Europe and the USA.[15] The cost of stroke in the UK is high at £2300 million per year, and accounts for about 6% of total NHS and Social Services expenditure; this is nearly twice the amount spent on coronary heart disease (CHD).[2,16] Despite this high disease burden on society and high cost, little is known about the key aspects of managing stroke and how they affect the outcome and the cost.[17] Outcome after stroke, measured as case fatality rate, clearly differs between countries, and is high in the UK compared with other European countries, although the reasons for this are unclear.[8,17,18] There is evidence of differences between countries at each stage in the assessment and treatment of patients with stroke.[19] Such variations indicate lack of agreement about the optimum approach to stroke management. Such lack of agreement among clinicians may indicate a lack of reliable research evidence. Despite the lack of evidence, less has been spent on research into stroke prevention, treatment and rehabilitation in the UK (and elsewhere) than on research into cardiovascular disease or cancer.[2]

Appropriate evidence-based strategies for the use of imaging in stroke patients could make patient care more effective and efficient. Despite that, imaging for stroke has generally not been subjected to formal economic evaluation. Thus, a systematic review of cost-effectiveness research in stroke up to 1999 identified about 2000 potential publications, but only 26 studies met the eligibility criteria.[20] Of the 26 studies in the review, only one related to acute stroke and it considered thrombolytic treatment with recombinant tissue plasminogen activator (rt-PA).[21] None were of imaging strategies.

Incidence of types of stroke and outcomes

Stroke is a clinical syndrome[22] and can be due to several different underlying pathologies. The two most common underlying pathological processes are cerebral infarction (or ischaemic stroke), which accounts for about 80% of all stroke, and intracerebral haemorrhage [or primary intracerebral haemorrhage (PICH)], which accounts for about 10–15% of all strokes.[1,23,24] Cerebral infarction is usually caused by occlusion of an artery to the brain resulting in ischaemia or infarction of the tissue supplied by that artery. It results from embolism (commonly from the heart or carotid atheroma in the neck) or *in situ* thrombosis.[25] PICH occurs as a result of a rupture of an artery wall and escape of blood into the brain parenchyma.[26] The remaining haemorrhagic strokes are due to subarachnoid haemorrhage (SAH).[27,28] SAH is so different in terms of its clinical features, immediate management and outcome to stroke (cerebral infarction or PICH) that it will not be considered further in this report. Occasionally, a tumour or an infection can present with stroke-like symptoms. In most case series, about 4% of patients presenting as 'strokes' have a non-vascular underlying cause.[5] Since the pathological processes underlying the clinical syndrome of stroke are very varied, it is not surprising that investigation, treatment and outcome of the different subtypes of stroke are also very different. Unfortunately, this has not been widely recognised until quite recently.

Implications for management

Thus, the management of a patient presenting with the clinical syndrome of stroke is predicated entirely on an accurate diagnosis of the underlying pathological process. The first step is to identify those few patients with a non-vascular cause (e.g. tumour, abscess, migraine, subdural haematoma, focal epilepsy). In such patients, surgery or biopsy may be required for treatment or to obtain a pathological diagnosis. For the remainder with vascular pathology, brain imaging by computed tomography (CT) or magnetic resonance imaging (MRI) can provide an accurate diagnosis of the nature and extent of the cerebral vascular pathology, and whether it is primarily ischaemic or haemorrhagic. Some aspects of the management of stroke are common to all pathological types (e.g. sensible control of blood pressure), but there are also key differences in the approach to primary treatment, further investigation and secondary prevention of patients with ischaemic and haemorrhagic stroke.

Clinical classification of severity of stroke

On the basis of the symptoms and signs, stroke has been classified clinically in a variety of ways. Many of these classifications were developed to describe the severity of the neurological deficit, and require detailed neurological examination. They may be useful for monitoring changes in the patient's neurological status during treatment, but do not easily relate to prognosis or risk of recurrent stroke, both of which are useful for clinical management. The Oxfordshire Community Stroke Project (OCSP) classification subdivides patients into four categories based on symptoms and signs, and these categories relate directly to prognosis, likely underlying aetiology and risk of recurrent stroke.[9] It can be applied to patients with cerebral infarction or haemorrhage and divides patients into total anterior circulation syndrome (TACS), partial anterior circulation syndrome (PACS), lacunar syndrome (LACS) and posterior circulation syndrome (POCS). If the patient is known definitely to have had an infarct (following scanning), then the 'syndrome' is replaced by 'infarction' (i.e. TACI, PACI, LACI, POCI). In general, patients with a TACS have had a severe stroke and have high mortality, and very few return to an independent existence; patients with a PACS have had a milder stroke, are less likely to die but are at greater risk of recurrent stroke soon after the first one; those with lacunar syndromes are unlikely to die but often remain dependent, though are at low risk of recurrence; patients with POCS vary in severity and prognosis, but severe POCS cases are at risk of early death due to hydrocephalus secondary to compression of the ventricular drainage system by the swollen cerebellar or brainstem infarct or haemorrhage. Among ischaemic strokes, about 20% have a TACI, 25% a LACI, 35% a PACI and about 20% a POCI, although these proportions vary between hospitals. This is a useful and widely used classification that will be used to subgroup strokes in this project.

Is brain imaging really necessary to differentiate ischaemic from haemorrhagic stroke?

Several clinical scales have been developed for this purpose, chiefly relying on the fact that haemorrhagic strokes are more often associated with symptoms of severe stroke.[29–31] Several studies have independently tested these scores, and none had sufficiently good sensitivity and specificity to be used to guide management decisions (e.g. on the use of anticoagulants).[32–35] Although patients with PICH may in general have more severe stroke symptoms, PICH can also cause

transient symptoms lasting for just a few hours [transient ischaemic attack (TIA)],[36–39] or very minor stroke.[40] However, it is not known how frequently PICH causes minor stroke or TIA. As both primary treatment and secondary prevention, investigation and treatment are quite different for ischaemic and haemorrhagic strokes (indeed, some treatments for ischaemic strokes are likely to worsen haemorrhagic strokes), on medical grounds it is important to distinguish one from the other at the very beginning of management.

Current primary treatment and secondary prevention of stroke

Ischaemic stroke: primary treatment and secondary prevention strategies

Aspirin, started within 48 hours of onset of ischaemic stroke, is the main primary treatment for patients with ischaemic stroke. Two large trials of about 20,000 patients each have provided reliable evidence that with aspirin, for every 1000 patients treated, nine avoid early death and recurrent stroke, and about 13 avoid death or dependency at 6 months.[41–43] The only other promising treatment is thrombolysis with rt-PA, which is now licensed for acute stroke treatment in the USA, Canada, Germany, and the UK. However, where it does have a licence, it is only for use in highly selected patients within 3 hours of stroke onset, and there is continuing debate about the proportion of patients that might benefit. Very few centres in the UK have the appropriate NHS infrastructure to deliver thrombolytic treatment safely and effectively to patients with acute ischaemic stroke.[44–46] Although thrombolytic therapy is therefore essentially not available to patients in the UK, large-scale trials are planned. Even if thrombolysis is not found to be cost-effective in the NHS, better services (including imaging) for the diagnosis and management of patients with acute stroke are needed.[44,45] In secondary prevention, long-term antiplatelet therapy (chiefly given as aspirin) reduces the risk of serious vascular events (recurrent stroke, myocardial infarction or vascular death).[47,48] Other secondary prevention measures specific to ischaemic stroke include carotid endarterectomy for patients with severe symptomatic carotid stenosis, and anticoagulants for patients in atrial fibrillation or with acquired thrombophilia. The role of statins in the prevention of recurrent ischaemic stroke was more controversial,[49] but the results of the Medical Research Council (MRC) British Heart Foundation (BHF) Heart Protection Study have provided clear evidence of the overall benefits of cholesterol lowering.[357] Other measures such as sensible blood pressure control apply equally to ischaemic and haemorrhagic stroke.

Primary intracerebral haemorrhage: primary treatment and secondary prevention

Patients on anticoagulants who develop PICH usually require active reversal by intravenous coagulation factors to prevent worsening of the haemorrhage,[50] although there are no randomised trials comparing active reversal of anticoagulants with conservative management. At the start of this project, the effect of inadvertent administration of antithrombotic agents to patients with PICH, in either the short or the long term, was unclear. For example, antithrombotic agents may be given by accident (thinking that the patient had had an ischaemic stroke in the absence of appropriate brain imaging) or deliberately because of the serious risk of myocardial infarction (MI) if the aspirin was stopped.

If PICH results in a large, space-occupying haematoma, then this may be surgically evacuated.[51] A randomised trial of surgical evacuation versus conservative treatment is underway (STICH), but is not due to report for some time to come.[52] A second trial of endoscopic evacuation of intracerebral haematomas is underway in India.[51] A trial of stereotactic thrombolysis of intracerebral haematomas in the Netherlands is underway.[51] PICH in the cerebellum may cause acute hydrocephalus by compressing the ventricular drainage system, which is amenable to temporary surgical drainage of the ventricles (and of the haematoma itself, if large). These patients are rare but typically present with symptoms of a posterior fossa stroke and then deteriorate neurologically over the next few hours after the stroke. (Note that patients with cerebellar infarction may also develop secondary hydrocephalus amenable to temporary ventricular drainage and present in a similar way.)

Patients with PICH should avoid antithrombotic and anticoagulant drugs in general, unless there is some particular high-risk indication (e.g. of MI, if aspirin is discontinued), in which case the balance of risk and benefit must be carefully assessed. Younger patients with a PICH may have an underlying brain lesion such as a vascular malformation that may require treatment by surgery, radiotherapy or an interventional neuroradiological procedure. However, in the

typical PICH in the older patient this is not the case. Apart from avoidance of drugs that increase bleeding tendency and control of blood pressure,[53] there is currently no other secondary preventive measure.

As a result of these different treatment strategies for ischaemic and haemorrhagic stroke (both primary and secondary prevention), the use of imaging investigations also differs between ischaemic and haemorrhagic stroke. For example, following a diagnosis of cerebral infarction (with imaging), patients in atrial fibrillation would start anticoagulants. Those not in atrial fibrillation would receive antiplatelet therapy and have carotid Doppler imaging to identify those with severe stenosis in the symptomatic artery who would benefit from carotid surgery. Some of those without carotid stenosis would undergo echocardiography to identify other possible sources of emboli, or a thrombophilia screen to identify coagulation abnormalities if indicated. None of these measures would be appropriate in patients with PICH. Following a diagnosis of PICH (with imaging), those patients with a suggestion of an underlying vascular lesion such as an arteriovenous malformation (or young patients) would undergo intra-arterial angiography and treatment. All PICH patients should avoid antiplatelet agents and have their blood pressure carefully controlled.

The need for brain imaging

As it is not possible to distinguish reliably between cerebral infarction and haemorrhage on clinical grounds,[34,35] or to identify those few patients with underlying tumours or infections mimicking a stroke, brain imaging with CT or magnetic resonance (MR) is required. Acute haemorrhage on CT appears hyperdense (or white), whereas acute infarction appears hypodense (or dark) compared with normal brain parenchyma. Thus, the two major causes of stroke are easily distinguished on CT in the acute phase. However, the haemorrhage gradually becomes isodense with normal surrounding brain, and eventually darker (hypodense) than surrounding brain[25] and so, from the point that the haematoma becomes isodense, it becomes indistinguishable from an infarct. The ability of CT to detect haemorrhage lasts from the moment the PICH occurs[54] for a variable period of up to 2 or 3 weeks depending on the initial size of the haematoma: if large, the appearance lasts longer; if small, it disappears quickly.[55] However, as there have been no studies where patients with haematomas were CT scanned serially to determine the point at which the hyperdensity disappears, the latest time when one could expect to differentiate a PICH from an infarct on CT is not precisely known. In particular, the minimum time to be able to detect a small haemorrhage reliably on CT is unknown.

Assessment of the extent of the lesion

Imaging assists the clinical management of stroke in other ways. Determining the type of cerebral infarct may help to prioritise use of limited resources; for example, by aiding the clinical diagnosis of a lacunar versus a cortical infarct: patients with cortical infarcts have a higher risk of early recurrent stroke secondary to underlying carotid stenosis, so imaging allows the prioritisation of patient referral for Doppler ultrasound.[56] Imaging added to clinical data allows a more precise prediction of outcome than clinical parameters alone.[57] Imaging can diagnose the cause of deteriorating neurological features after stroke. For example, it might show haemorrhagic transformation of the infarct, or infarct swelling with midline shift, or a new infarct elsewhere in the brain, or hydrocephalus requiring drainage. Following a PICH, the site, size and pattern of the haematoma on imaging may help to identify the likely underlying cause (e.g. hypertensive or secondary to amyloid angiopathy).[58] Imaging may identify the cause of further neurological deterioration (e.g. further new bleeding, midline shift or hydrocephalus).

Brain imaging may provide other information for which it is more difficult to quantify the benefit. The exclusion of remediable disease such as infection is crucial. Other benefits include the possible comfort that a physician may provide to relatives of a patient with a severe stroke with the knowledge that the patient has had a massive infarct (or haemorrhage) from which they are unlikely to recover and there really is nothing else that can be done. Patients are well aware that scanning is used to make the diagnosis of the cause of stroke, and may be distressed by a long wait for their test and the thought that the doctor does not know what is wrong with them until the test is done. This also may affect the time to start treatment, which can also be distressing. They may be reassured by being shown the scan and given more information about their disease and the chance of recovery.[59] Sometimes the appearance of the infarct on CT may differ from that suggested by the clinical syndrome. For example, a patient with a lacunar syndrome may have a recent cortical infarct on their scan, in which case their underlying risk factors and likelihood of

recurrence are much more like those of a cortical than a lacunar syndrome.[56] This means that patients can be fast-tracked through appropriate, although possibly limited, investigations such as carotid Doppler ultrasound to prevent a recurrence.

Reasons for the controversy over CT scanning

As stroke is a common condition, the average regional stroke service for a population of 250,000–300,000 or so will admit about one stroke patient per day, and may assess a further one or more suspected strokes per day in their outpatient clinic. CT scanning (the machines, the radiologists, the radiographers) has been a scarce resource in the UK, which means that stroke patients must compete with patients with other, equally important conditions. In dealing with a common disease such as stroke, it is important that well-organised care pathways are in place to avoid backlogs that make care less efficient. Stroke has traditionally been assigned a low priority. As most strokes are ischaemic, if one diagnosed 'ischaemic stroke' in every stroke patient one would be correct about 80% of the time. The harm that may be caused to patients with haemorrhagic stroke by this policy, and the harm that may be caused to those with ischaemic stroke by failing to implement treatment rapidly, have been unclear. Until fairly recently, there was no proven pharmacological treatment for acute stroke. The benefit of aspirin[41] is seen as marginal for the individual, which fails to recognise the benefits to the population of this widely applicable and inexpensive treatment. Similarly, the potentially large benefits of simply caring for patients with acute stroke in a coordinated and timely fashion, such as in stroke units, were overlooked and undervalued for a long time.[60] It is therefore easy to appreciate why radiologists, hard pressed to respond to demands from many different specialities for CT investigations, might question the value of CT in stroke. The immediate benefits of CT in stroke were not very clear. The importance of a more active approach to investigation of acute stroke was reflected in the first Stroke Association Survey in 1992. More than 90% of physicians who cared for stroke patients said they would prefer to have a CT scan themselves if they had a stroke, although they said that they would only request a CT in around 50% of their patients.[61] This double standard perhaps reflected an uncertainty among clinicians about the cost-effectiveness of CT, while realising that they themselves would want a CT, irrespective of cost.

In radiology departments, stroke patients may be seen as disruptive to working schedules. They are often unable to care for themselves, may not be accompanied by a nurse who can care for them while in CT, and may be unable to transfer from the chair in which they were sent (it should have been a trolley) to CT, and so the hard-pressed radiographers have to find help to place the patient on the scanning table. All of these factors slow down the throughput in a busy CT department and can be avoided by good communication between clinician and radiologist, although unfortunately this often appears to be lacking. To have this happening every day would be irritating, but it is inevitable as stroke is so common. It is easy to see how an accumulation of these factors could rapidly induce resentment amongst radiologists towards requests for scanning stroke patients, particularly if the subsequent treatment decisions were seen to offer only very marginal benefits.

Perhaps a further major source of difficulty for radiologists in deciding on an appropriate priority for stroke is that none of the stroke guidelines were produced with the input of radiologists; hence, they have been formulated without consideration for their impact on radiological services. The two national guidelines in the UK, produced by the Scottish Intercollegiate Guidelines Network (SIGN) and the Royal College of Physicians, had no radiologist included in the authorship.[50,62] It is regrettable that both guidelines have major implications for radiological workload but have not taken account of how to manage the increased workload implicit in the guideline recommendations. Furthermore, of 22 guidelines on stroke identified through a recent literature and web search (*Table 1*), with a total of at least 202 authors (among the guidelines that actually listed the number of authors; and as many guidelines did not, the total authorship will be much greater), there were only two radiologists (1%) as authors (both on the same guideline). This guideline was specifically about the investigation of TIA and stroke, the rest concerning the management of TIA or stroke but including imaging investigations as part of the management. Involvement of each relevant discipline in the production of a guideline creates a feeling of ownership, which is a key component to ensuring the guideline's subsequent implementation.[63–65] It is of little surprise therefore that the provision of CT for stroke has been perceived as suboptimal by clinicians in the UK.

TABLE 1 *Guidelines for care of stroke identified through a literature search and search of the web in August 2001*

A search of guideline websites in the USA (National Guideline Clearing House, http://www.guideline.gov/index.asp) revealed that there were 778 disease-based guidelines in the USA, of which 141 concerned nervous system diseases; of these, 18 were cerebrovascular guidelines and nine were guidelines on stroke with radiological implications. These were:

(i) Practice advisory – thrombolytic therapy for acute ischaemic stroke
American Academy of Neurology (*Stroke* 1996; **27**:1711–18)
(13 authors, specialities not stated)

(ii) Tissue plasminogen activator for acute ischaemic stroke
Daniel Freeman Hospitals (source not stated)
(authors not stated)

(iii) Fibrinolysis in acute ischaemic stroke
Mount Auburn Hospital (MI quality assurance committee)
(no radiological input)

(iv) Universe of Florida patients with acute ischaemic brain attack
Florida Agency for Health Care Administration, 5 March 1999
(3 authors, specialities not stated)

(v) 5th ACCP consensus conference on antithrombotic therapy
(*Chest* 1998; **114**(5 Suppl):439–769S)
(41 authors, specialities not stated)

(vi) Recommendations for the establishment of primary stroke centres
Brain attack coalition (*JAMA* 2000; **213**:3102–9)
(14 authors, specialities not stated)

(vii) Assessment of brain SPECT
American Academy of Neurology, 1996
(9 authors, specialities not stated)

(viii) Screening for asymptomatic carotid artery stenosis
US preventive services task force, 1996. Guideline to clinical preventive services. 2nd ed.
(13 authors, specialities not stated)

(ix) Asymptomatic carotid disease
Canadian task force on preventive healthcare, January 1994
(11 authors, no radiologist)

A search of the Canadian Guidelines (CMA clearing house, http://www.cma.ca/cpgs/index.asp) revealed two guidelines with radiological implications:

(i) Intravenous thrombolytic therapy for acute stroke
Canadian Stroke Consortium (*Can J Neurol Sci* 1998; **25**:257–9)
(no authors stated)

(ii) Thrombosis Group of Canada: Thrombolysis Guidelines
(no authors stated)

A search of a UK commercial guidelines site (http://www.eguidelines.co.uk/) revealed one in addition to SIGN:

(i) Royal College of Physicians of London: National Clinical Guidelines for Stroke
Intercollegiate working party for stroke, 1999
(30 authors, no radiologist)
(46 reviewers, no radiologists listed)

The New Zealand (http://www.nzgg.org.nz/library.htm) and the Australian (http://www.health.gov.au.nhmrc/publicat/cp-home.htm) guideline websites did not reveal any additional stroke guidelines.

Other publications assessed included:

The Association of British Neurologists. Guidelines for the care of patients with common neurological disorders in the United Kingdom. London: ABN; 1993.
(produced by the ABN, authors not listed, presumably neurologists)

Adams HP, Brott TG, Crowell RM, Furlan AJ, Gomez CR, Grotta J, *et al*. Guidelines for the management of patients with acute ischaemic stroke: a statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association. *Stroke* 1994;**25**:10901–14.
(12 authors, no radiologist)

continued

TABLE 1 *Guidelines for care of stroke identified through a literature search and search of the web in August 2001 (cont'd)*

Feinberg WM, Albers GW, Barnett HJ, *et al*. Guidelines for the management of transient ischaemic attacks: from the Ad Hoc Committee on Guidelines for the Management of Transient Ischaemic Attacks of the Stroke Council of the American Heart Association. *Circulation* 1994;**89**:2950–65.
(13 authors, no radiologist)

Culebras A, Kase C, Masdeu JC, Fox AJ, Bryan RN, Grossman CB, *et al*. Practice guidelines for the use of imaging in transient ischaemic attacks and acute stroke. A report of the Stroke Council, American Heart Association. *Stroke* 1997;**28**:1480–97.
(9 authors, 2 radiologists)

European Strategies for Early Intervention in Stroke. A Report by an Ad Hoc Consensus Group Meeting. *Cerebrovasc Dis* 1996;**6**:315–24.
(8 authors, no radiologist)

Aboderin I, Venables G. Stroke Management in Europe. Pan European Consensus Meeting on Stroke Management. *J Intern Med* 1996;**240**:173–80.
(13 authors, no radiologist)

Hacke W, Kaste M, Olsen TS, Orgogozo JM, Bogousslavsky J. European Stroke Initiative Recommendation for Stroke Management. *Cerebrovasc Dis* 2000;**10**:335–51.
(5 authors, no radiologist)

Ferguson A, McCabe CJ (Working Group on Acute Purchasing). Clinical and cost-effectiveness of CT in the management of transient ischaemic attack and stroke. Sheffield: Trent Institute of Health Services Research, Universities of Leicester, Nottingham and Sheffield. Guidance Note for Purchasers 97/01.
(2 authors, no radiologist)

Scottish Health Purchasing Information Centre (SHPIC). Draft report on stroke (unpublished).
(6 authors, no radiologist)

In summary, of 22 guidelines on stroke management identified in the world literature which included a statement on use of imaging (and there are probably many more), with at least 202 authors (among those where the authors were stated), there were only two (1%) definite radiologists as authors, both on the same guideline. Notably that guideline was specifically just about the use of imaging in the investigation of stroke and TIA, not management in general. Virtually all the rest were authored by neurologists, where that information was given.

ACCP, American College of Chest Physicians; SPECT, single-photon emission computed tomography; CMA, Canadian Medical Association; ABN, Association of British Neurologists.

Current standards of care and guidelines

Current guidelines for stroke in the UK state that patients should undergo CT within 48 hours of onset.[50,62] There is virtually no information on what proportion of patients actually are imaged within 48 hours, although during the course of the present project, the Royal College of Radiologists (RCR Audit Group, personal communication), the Royal College of Physicians and the Scottish Stroke Audit Group[66] have all undertaken surveys of clinical practice. The second Stroke Association Survey found that services for stroke patients including imaging were still very variable around the UK.[67] The National Service Framework for Older People, published in the latter months of the present project, has as its aims "to reduce the incidence of stroke in the population and ensure that those who have had a stroke have prompt access to integrated stroke services".[68] For two of the stated key interventions (prevention and immediate care), brain imaging is crucial. In 'Immediate Care' (p. 65, section 5.20) it states:

> "All patients who may have had a stroke will usually require urgent hospital admission. They should be treated by specialist stroke teams within designated stroke units. Better outcomes for patients with suspected stroke will depend on: making a diagnosis, including a brain scan to ensure patients have the best possible chance of recovery and to minimise disabilities later."

The document further specifies that patients should have "a brain scan within 48 hours" (p. 66, section 5.21).[68]

Brain imaging is a key component of the management of acute stroke, and it should be done in a timely fashion. It is, however, unclear precisely what the clinical benefits from CT scanning are, and whether the policy of CT for all stroke patients within 48 hours of onset is cost-effective.

The questions posed in this project

The aims of the present project were therefore:

- to identify the clinical benefits from CT scanning in acute stroke within 48 hours of stroke onset
- to outline a variety of strategies from which health commissioners could choose the one that best suited their local resources and needs
- to give clear estimates in financial and population terms of the cost of these different strategies and compare them by means of a cost-effectiveness analysis
- to begin to determine in which patients even more expensive investigations such as MR might be cost-effective.

What information is required to determine whether CT is cost-effective or not?

The main determinants of the cost-effectiveness of CT scanning are:

- the cost of doing the scanning itself (at different times of the day, in different sorts of hospital)
- the length of stay (LOS) in hospital for patients with stroke (of haemorrhagic or ischaemic stroke, and of different severities of stroke) and the cost of that stay in different types of hospital
- the effect of treatment decisions arising from knowledge provided by the CT scan (incorporating the effect of accuracy of diagnosis) on subsequent LOS (of haemorrhagic or ischaemic stroke and of different severities of stroke), including the effect of giving the correct or wrong treatment to patients.

The information that was needed to be able to start determining the impact of CT scanning on diagnosis and subsequent treatment decisions is shown in Appendix 2.

The cost of scanning was determined by surveying several hospitals in Scotland to obtain real data on the cost of running a CT scanning service in a teaching and district general hospital.

LOS for different subtypes and severities of stroke was determined using data from the authors' hospital stroke registry, the Lothian Stroke Register (LSR) (personal communication, 2000). This database was established to store data on all strokes admitted to the Western General Hospital in Edinburgh (a teaching hospital providing the stroke service for North Lothian with a catchment population of about 500,000 for stroke and 1,500,000 for neurosciences). Clinical, laboratory, imaging, management and follow-up data to 2 years after stroke have been recorded since 1990. Data on the cost of care in different types of hospital were obtained from standard NHS tables as these are more widely studied and standard reference tables of recently acquired data exist on the cost of patient care in hospital.[69]

The data on the effect on outcome after different types of stroke of making the right or wrong diagnosis was obtained from systematic reviews of the literature. Existing systematic reviews were used where relevant and up to date, and new reviews performed where necessary. The need for new reviews was greatest in the assessment of imaging, as there is little tradition of undertaking systematic reviews of diagnostic tests and these sorts of review are regarded as difficult, so the methodology is less well developed than for treatment reviews.[70–72] Thus, the study sought estimates of the accuracy of the clinical diagnosis of stroke (versus not stroke), of infarct versus haemorrhage; of the frequency of non-vascular pathologies that can produce a stroke-like clinical syndrome ('stroke mimics'), of infarct and haemorrhage; of the prognosis of different subtypes of stroke (i.e. risk of recurrence and functional outcome); of the accuracy of CT and MRI for detecting haemorrhage and infarction; of the benefits of aspirin in patients with cerebral infarction; of the hazard of aspirin in patients with intracerebral haemorrhage; of common management pathways in stroke; of other forms of treatment for acute stroke such as thrombolysis for ischaemic stroke and haematoma evacuation for haemorrhagic stroke; of quality of life associated with different functional outcomes after stroke; of how time in hospital related to the patient characteristics such as the severity of the stroke; of how the effect of treatment expressed as a change in functional outcome at 6 months would map onto a change in LOS in hospital; of the costs of CT scanning in different hospitals so as to be as generalisable as possible; of the cost of spending

time in different sorts of hospital; of the availability of CT scanning and what additional resource might be needed to increase access for stroke patients; and of how all this might fit together into an economic model to determine how the effect of CT and the treatment decisions arising thereafter would affect both clinical outcome and cost of stroke care. These are listed in more detail in Appendix 2. Some of this information was already available to the authors, some was sought through detailed systematic reviews, some was obtained from new primary studies or by surveying NHS departments, and some required educated estimates because there were no useful data in the literature and it was not possible to acquire these new data in the context of the present project.

Potential applications of these results

This information would be essential in practical, everyday situations in clinical medicine, for example: the planning of new stroke units (the National Service Framework has indicated that organised stroke services should be available everywhere); deciding where to site new CT scanners; guiding radiology departments on how quickly they need to scan stroke patients and therefore the sort of service they need to provide in terms of access during a 24-hour day and responsiveness; and in hospitals without CT on site, whether they should arrange transfer of patients for a scan. The intention was to determine the cost of several strategies, ranging from 'CT scan all stroke patients regardless of severity of stroke or time lapse from stroke onset' to 'scan no strokes and manage patients using clinical examination findings only', so that the financial and human costs would be absolutely clear, including the impact on hospital and community services and families.

Chapter 2

The contribution of brain imaging to the diagnosis of stroke: a systematic review of the accuracy of the clinical diagnosis of stroke

Background

In order to model the process of the diagnosis and treatment of stroke and the effect on outcome, it was necessary to attribute diagnostic probabilities to each stage in the diagnostic and decision-making process. The first step was to determine the accuracy of the clinical diagnosis of stroke in the absence of imaging. This includes the diagnosis of stroke versus not stroke and of haemorrhagic versus ischaemic stroke. Later stages in the decision model would then address the accuracy of imaging (see Chapter 3), the effect of treatment (with aspirin as the only proven treatment, Chapter 4) and then the outcomes. The present chapter is concerned with the accuracy of the clinical diagnosis of stroke.

To obtain this information systematic reviews and systematic descriptive studies of the relevant literature on the clinical diagnosis of stroke, and on the use of imaging in epidemiology studies, were conducted to determine whether there was any evidence that the incidence of PICH varied with severity of stroke and other patient characteristics.

The clinical diagnosis of stroke versus not stroke, and of infarct versus haemorrhage

Several medical conditions can present with symptoms similar or identical to those of stroke. For example, intracerebral neoplasm can present with sudden-onset hemiparesis, and vestibular neuronitis can present with sudden symptoms similar to brainstem ischaemia. Differentiating such conditions from a (vascular cause of) stroke on clinical examination can be difficult. Imaging with CT will usually determine whether the underlying lesion is vascular or non-vascular, such as a neoplasm. However, to determine the cost-effectiveness of CT, it was necessary to know precisely how often the clinical diagnosis of stroke (versus not stroke) was correct. In particular, to determine the cost-effectiveness of certain pathways of care, one needs to know whether there is any clinical diagnostic pathway (e.g. being examined by a paramedic as opposed to a medical registrar) that performed differently to others.

Distinguishing the pathological cause of stroke (i.e. ischaemic stroke or PICH) on clinical judgement alone is also difficult. Although patients with PICH are said to be more likely to be drowsy[79] or hypertensive, or to vomit more often than those with ischaemic stroke, it is well known that the distinction of infarct from haemorrhage on clinical grounds is unreliable. One study of a hospital population found the initial bedside diagnosis of infarct versus haemorrhage by physicians to be correct in only 69% of cases.[73]

To aid the clinical diagnosis of PICH, scoring systems were developed that made use of the presence or absence of factors found to be associated with PICH in hospital studies. Two of the best-known examples are the Allen probability guide (also known as Guy's Hospital Score)[29] and Siriraj score.[30] These are an improvement on unscored clinical judgement alone: using the Allen guide was said to improve clinician's accuracy in correctly distinguishing ischaemic stroke from PICH from 84% to 90%.[29] The sensitivity of a Siriraj score of greater >1 (indicating PICH) was 89.3%.[30] However, further testing of these scores showed that they were much less accurate when used in a stroke population other than the one from which they were derived.[34,35] In one study, the sensitivity of the Allen score (using a cut-off of >24 to indicate a high likelihood of haemorrhage) dropped to 31% and the sensitivity of a Siriraj score of >1, to 48%.[35]

These scores are cumbersome as well as unreliable. For example, the Siriraj score uses the following equation:

$$\text{Score} = (2.5 \times \text{Consciousness}) + (2 \times \text{Vomiting}) + (2 \times \text{Headache}) + (0.1 \times \text{Diastolic blood pressure}) - (3 \times \text{Atheroma}) - 12$$

Consciousness: alert = 0, drowsy/ stupor = 1, semicoma/coma = 2
Vomiting: no = 0, yes = 1
Headache within 2 hours: no = 0, yes = 1
Atheroma markers: none = 0, one or more = 1.

A value of > 1 indicates haemorrhage and < 1 indicates infarction with a predictive accuracy of 90.3% according to the original publication. However, according to Hawkins and colleagues,[35] a patient with a 90% chance of having a PICH on the Siriraj score still has a 50% chance of having an infarct. In other words, because these scores were developed in hospital-admitted patients, their accuracy may have been compromised by the bias towards the more severe strokes seen in hospital-admitted cases compared with patients cared for in the community.

As CT scanning has become more available, the incidence of small PICHs causing stroke has appeared to increase,[74] but this is likely to be due to better diagnosis rather than a true increase in incidence. With this has come increasing realisation that patients with PICH do not necessarily present with severe symptoms.[34,79] Might this mean that the incidence of PICH has been underestimated? As the signs of haemorrhage do not remain forever on CT (possibly not more than 10 days for small haemorrhages), patients should be scanned soon after stroke to avoid misdiagnosing small haemorrhages as infarcts.

A systematic review was performed of studies providing data on lesions that mimicked stroke and the agreement between clinicians for the clinical diagnosis of stroke. This gave a comprehensive picture of the range of conditions that can mimic stroke, the proportions of a stroke population that they represent, and the relative importance of neurological training in making a stroke diagnosis.

How reliable are the estimates of PICH?

Epidemiological studies of stroke incidence commonly attempt to determine the relative proportions of ischaemic stroke and PICH, as well as the overall incidence of all stroke. The data accrued from such studies are then used in a wide range of health economics, clinical planning and research settings. Hospital-based studies are subject to referral bias, in that more severe strokes are more likely to be admitted to hospital than mild ones. This bias is less likely in community-based studies, in which all strokes occurring in a geographically defined population are counted.

The International Stroke Incidence Collaboration identified comparable community incidence studies, mostly from the 1980s and early 1990s, and found that 73–86% of strokes were ischaemic, 8–15% were attributed to PICH and 1–5% to subarachnoid haemorrhage.[1] Some studies included an 'unknown' category for cases where the cause was uncertain. 'Unknown' usually meant that it was uncertain whether the patient had had a PICH or infarct because they had not had a CT scan, or a post-mortem if they had died. The methods used to diagnose the cause of the stroke varied between studies, although most appeared to use brain CT scanning at least to some degree. However, the precise use of CT scanning (the proportion scanned, within what time interval), and the influence that this might have had on the proportion of strokes diagnosed as ischaemic stroke or PICH has not been reviewed. Therefore, the brain imaging used in the community stroke incidence studies were systematically reviewed to determine the confidence limits around the estimate of the proportion due to infarct or PICH, and the relationship (if possible) with age, severity and other factors that may be useful in clinical practice.

Methods

Objectives

To determine:

- the proportion of patients presenting with stroke-like symptoms who turn out to not to have had a stroke (i.e. to have a non-vascular cause of their symptoms)
- the conditions that most commonly cause stroke-like symptoms
- the frequency of stroke due to cerebral infarction and PICH
- the accuracy of the estimate of the incidence of stroke due to PICH in epidemiological studies.

Criteria for considering studies

For the descriptive systematic review of the proportion of stroke mimics, stroke studies were included if they provided values for the final proportion of true strokes in a population presenting with stroke symptoms, and where it could be determined which clinician or paramedic made the first diagnosis. The review also included studies of populations presenting with stroke symptoms, in which the initial and final proportions of patients with the diagnosis of stroke (compared with non-stroke) were given, as well as details of the nature of stroke mimics.

For the systematic review of imaging usage in community-based stroke incidence studies, all community-based stroke incidence studies in which the actual proportion of ischaemic stroke and haemorrhage was reported were included. Hospital-based studies were excluded, as were studies that did not report the frequency of PICH separately from ischaemic stroke (i.e. just reported all 'stroke'), studies that documented either PICH or ischaemic stroke only, or case fatality data only.

Search strategy

To identify studies for both descriptive systematic reviews, electronic searches of the medical databases MEDLINE and EMBASE were performed (Appendix 4). To make the searches as inclusive as possible, an extended search strategy was used to identify articles relevant to stroke. This strategy, pioneered by the Cochrane Collaboration Stroke Research Group[75] for the identification of randomised controlled trials (RCTs), identifies more relevant references than a standard search that uses subject headings and specific text words. Although this strategy has not been used previously to identify observational studies, it was used here as a starting point to maximise the number of references captured. Specific methodological criteria for each review are documented separately below.

Data pertaining to the proportion of stroke mimics in a population were found in studies with differing primary purposes, so a number of searches were undertaken to be sure of identifying all relevant studies. In the electronic searches, title and text words for 'diagnosis' were added to the Cochrane Library extended stroke strategy. A separate search using title and text words for 'timing' and 'delay' was also performed, as studies pertaining to the timing of admission of patients with stroke symptoms to hospital, with reference to the potential delivery of hyperacute stroke treatment, occasionally contained relevant data. Abstracts of conference proceedings concerned with the time of arrival of patients with stroke symptoms to hospital were identified and followed-up.

Stroke incidence studies identified for the systematic review of scanning policies in epidemiological studies were also sought by searching MEDLINE and EMBASE from January 1980 to April 1999, and adding the following text words to the Cochrane Library extended search strategy:[75] 'stroke register, stroke registry, incidence, community' and subject heading 'incidence'. The electronic search went no further back than 1980 because, although CT was clinically available before this time, its use in community incidence studies was very limited. The authors also examined reference lists and had discussions with other interested investigators, notably Dr C Sudlow and Professor CP Warlow of the International Stroke Incidence Collaboration.[1]

Data extraction

For the study of stroke mimics, data were extracted on: the purpose and size of study, the profession and level of experience of the person making the diagnosis, the gold standard by which final diagnosis was made, the proportions of the study population with final diagnosis of non-stroke, ischaemic stroke or PICH, values for sensitivity and specificity of the diagnosis of stroke compared with non-stroke, and ischaemic stroke compared with PICH. Data were analysed with simple descriptive statistics. The mean sensitivity of diagnosis for different healthcare providers was determined with 95% confidence intervals (CIs). Studies in which emergency physicians had access to CT results (i.e. not truly testing clinical diagnosis on its own) were not included in these calculations.

For the systematic review of imaging in stroke incidence studies, data were extracted on year of publication and sample size of each study, the method of diagnosing the pathological cause of stroke, use of scanning, type of scanning, the proportion with ischaemic stroke or PICH, and any information on patients not scanned. Data were entered into an Access database and analysed with descriptive statistics. Patients with subarachnoid haemorrhage were excluded from both the denominator and numerator, because although there may be patients with overlapping symptoms, this condition is generally distinct from stroke due to infarction or intracerebral haemorrhage.

Details of included studies

Stroke mimics

Electronic searches captured 3794 references. Seventeen studies were identified that included data on the proportion of stroke mimics in a population presenting with stroke (*Table 2*). The total number of patients presenting with stroke symptoms was 9316, and the median study size was 411.

The studies varied widely:

- seven (6228 patients) were stroke incidence studies, in which the primary aim was not to

TABLE 2 *Studies documenting data on the proportion of patients with a final diagnosis of non-stroke in populations presenting with stroke symptoms*

Study	Date	Size	Setting	Person making initial diagnosis of stroke	Proportion of patients with non-stroke as final diagnosis (%)
OCSP[5]	88	1818	Community	GPs	1
SEPIVAC[76]	91	379	Community	GPs Hospital physicians	1
Perth[77]	93	883	Community	Physicians and nursing home supervisors	25
Belluno[78]	95	858	Community	Physicians and some neurologists	2
Innherred[92]	97	1169	Community	Multiple sources	11
Erlangen[80]	98	574	Community	GPs	2
Arcadia[81]	99	607	Community	GPs	6
Zweifler[82]	98	71	Community	Paramedics	6
Kothari[83]	95	86	Community	Paramedics	28
Wester[84]	99	834	Community	Emergency room nurse	37
Zweifler[85]	97	100	2 different hospitals	Emergency room personnel	13
Libman[86]	95	411	Emergency department	Emergency room personnel	19
Bratina[87]	95	112	8 different hospitals	Emergency physicians	0–19
Kothari[88]	95	446	Emergency department	Emergency physicians[a]	4
Horn[89]	97	229	Community	GPs	3
Martin[90]	97	565	Neurovascular clinic	GPs	27 (stroke) 40 (TIA)
Ferro[91]	98	174	Neurovascular clinic and emergency department	GPs and emergency physicians[b]	9

[a] Results of CT available.
[b] Results of CT available in 87%.

determine the accuracy of the referring clinician, rather to identify all strokes in a geographically determined area;[5,76–78,80,81,92]
- seven (1192 patients) examined the accuracy of diagnosis of various professionals concerned in the management of patients with acute stroke
- three (846 patients) were primarily concerned with the process of acute stroke care.[84,85,87]

Final diagnosis was made by a neurologist or physician with an interest in stroke and access to imaging in 14 studies, and was unspecified in the remaining three. The intention had been to identify studies in which the diagnosis by the clinician or paramedic making first contact with the patient could be compared with the second clinical contact. However, it seemed that in all the studies, the second contact had access to brain imaging (or at least was not prevented from seeing it) and therefore it was not possible to make a pure clinical-to-clinical comparison between observers. It had to be assumed that the second clinical contact used the information from brain imaging in making their clinical diagnosis, as it was not explicit that they were blind to imaging.

Stroke incidence studies

Electronic searching captured 1903 references. Twenty-five studies met the inclusion criteria (*Table 3*). One study specifically excluded SAH;[96] 23 studies (92%) included a category where the cause of stroke was 'undetermined': in 12/23 studies (48%), 'undetermined' referred only to patients who did not undergo post-mortem or scanning at any time. In the remaining 11 studies, patients could be categorised as ischaemic stroke, PICH or 'undetermined' even if no scan or post-mortem had been performed; that is, they were classified on clinical judgement alone. This was also the case for the two studies[97,98] that classified all patients as either ischaemic stroke or ICH. Two studies used the Allen score as a diagnostic aid.[24,76]

TABLE 3 *Conditions presenting with stroke-like symptoms and the ranges of their relative frequency in the stroke populations identified*

Final diagnosis	Proportion of total stroke population (%)	Study reference
Primary brain tumour	0.3–2.9	5, 76, 77, 80–82, 84, 86, 91–93
Seizure	0.3–8.5	77, 82–86, 88, 90–93
Toxic-metabolic state	0.2–3.9	77, 82–86, 88, 91, 93
Subdural haemorrhage	0.3–1.9	5, 76, 77, 80, 84, 86, 88
Systemic infection	0.5–9.3	83, 86, 91, 92, 94
Cerebral infection	0.2–1.7	77, 80, 81, 86, 88, 93
Migraine	0.4–3.0	77, 81, 82, 88, 90, 92, 93
Vertigo/vestibular	0.2–4.0	77, 86, 88, 90–93
Syncope	0.2–8.5	77, 83–85, 88, 91
Psychogenic	0.2–2.7	77, 85, 86, 88, 90, 91, 95
Peripheral neuropathy	0.5–9.3	81, 83, 85, 88, 91, 93
Cerebral metastases	0.3–1.2	5, 76, 83, 91
Transient global amnesia	0.1–1.2	77, 83, 86
Cardiac	0.6–2.3	83, 86, 92
Old stroke, nil new	1.0–1.5	84, 85
Hypertensive encephalopathy	0.2–1.0	85, 86
Dementia	0.5–0.8	81, 86
Multiple sclerosis	0.2–1.7	80, 81, 86, 88, 90

Details of excluded studies

Stroke mimics

Studies concerning the accuracy of emergency physicians unfortunately provided the results of a CT scan available at first point of contact and therefore did not represent the clinical diagnostic accuracy alone.[88,91] These were excluded.

Stroke incidence studies

Studies that were not truly community based were excluded.

Results

Stroke mimics

The proportion of the study population that was eventually diagnosed as having a condition other than stroke varied from 1 to 37% (mean 12.5%, 95% CI 6.7 to 18.3, *Table 2*). Eighteen conditions were identified that could mimic stroke often enough to be counted separately in these studies (*Table 3*). The most common stroke mimics included primary (up to 3% of patients with 'stroke') and secondary (up to 1.2%) cerebral neoplasms, seizures (up to 8%), systemic infections (up to 9%) and subdural haematoma (up to 2%).

Excluding the seven stroke incidence studies, the mean sensitivities for the diagnosis of stroke by different groups of health professionals at first point of contact with the patient with stroke symptoms were: paramedics 74.9% (95% CI 68.8 to 81.0%), general practitioners (GPs) 87.7% (95% CI 84.7 to 90.8) and emergency room personnel 71.1% (95% CI 68.6 to 73.6%), when compared with the reference standard of 'neurologist or physician with an interest in stroke', the latter operating with knowledge of the brain scan result.

TABLE 4 *Included stroke incidence studies*

Study	Date	Size
Tilburg, The Netherlands[99]	1980	152
Hisayama, Japan[100]	1981	203
Shibata, Japan[101]	1981	415
Beijing, China[102]	1983	130
Benghazi, Libya[98]	1986	329
Moscow, Russia[103]	1988	1538
Oxford, UK[24]	1990	675
Akita, Japan[104]	1990	109
Umbria, Italy[76]	1991	375
Dijon, France[105]	1991	984
Valle d'Aosta, Italy[106]	1992	254
Frederiksberg, Denmark[107]	1992	262
FINMONICA[108]	1992	3574
Malmo, Sweden[109]	1992	524
Perth, Australia[77]	1993	492
Warsaw, Poland[96]	1994	462
Brisbane, Australia[110]	1995	2056
Belluno, Italy[78]	1995	474
Rochester, USA[97]	1996	496
L'Aquila, Italy[111]	1997	819
Tartu, Estonia[112]	1997	829
Innherred, Norway[92]	1997	432
Erlangen, Germany[80]	1998	354
London, UK[113]	1999	612
Arcadia, Greece[81]	1999	555

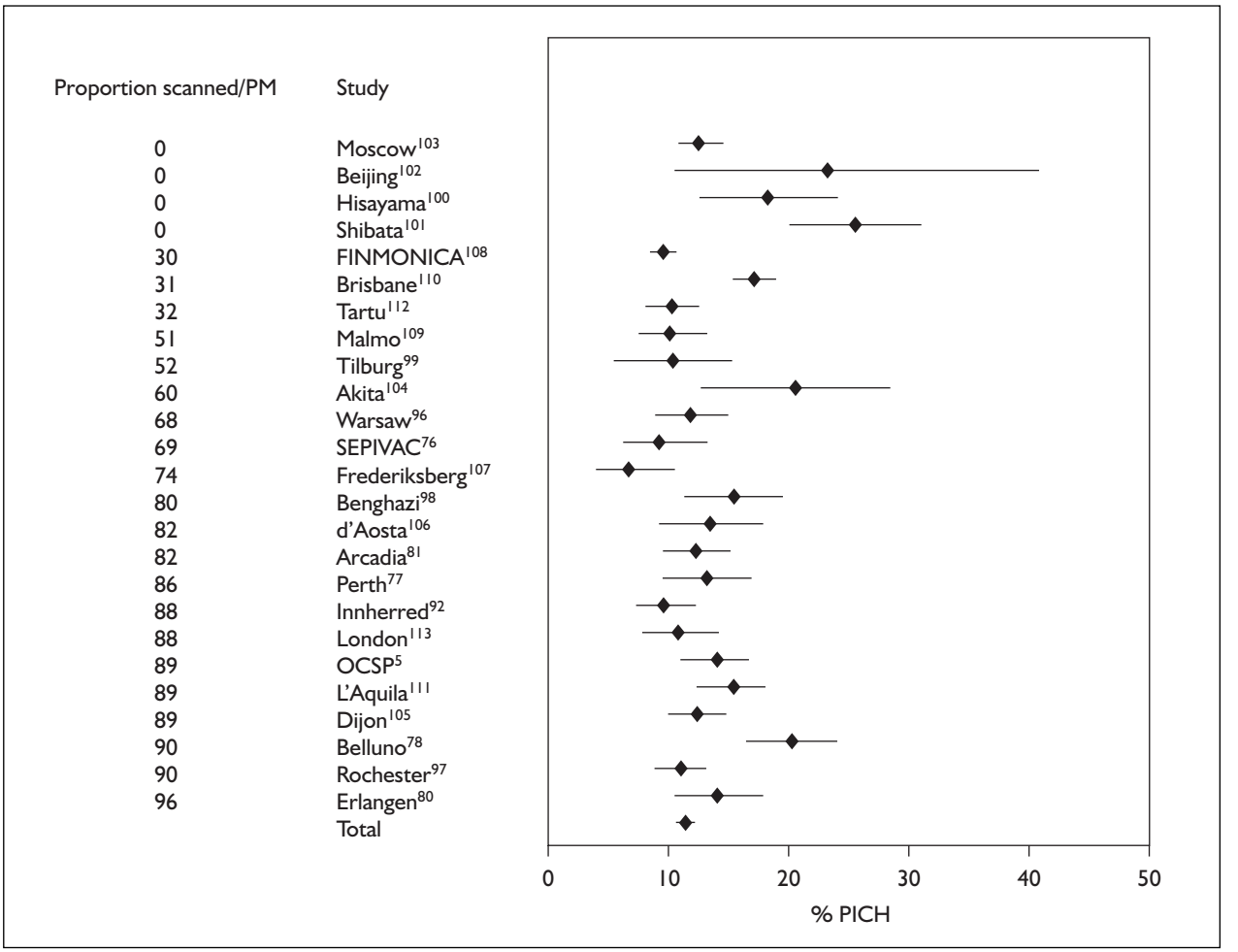


FIGURE 1 *Stroke incidence studies ranked according to proportions of strokes scanned overall (point estimates of PICH with 95% CIs). Note: scans may have been greater than 2 weeks from stroke onset (see Figure 2 for timing).*

Stroke incidence studies

In the 25 included studies (*Table 4*), the details of scanning rates, times of scanning and patient exclusions varied immensely; 5/25 (20%) studies gave no scanning details at all.[100–104] Of the 20 that did give details, the proportion of patients scanned (or who had a post-mortem) varied from less than 30% to approaching 96% (*Figure 1*). Although these 20 studies indicated the proportion of patients scanned, only 13/25 (52%) mentioned the time interval from onset of symptoms to CT scanning (*Figure 2*).

Information on timing of scanning was documented in a number of different ways; one study gave a mean time interval from onset of symptoms to scanning,[106] and two studies gave the median time interval from symptoms to scanning.[81,111] The majority of studies documented the proportion of patients scanned within a certain time interval, ranging from 7 days,[98,105,109] to 21 days[92] and 30 days.[24,76,77,78,80,113]

In no study was it possible to determine exactly what proportion of patients was scanned and when (i.e. within 1 week, 2 weeks, 3 weeks after stroke), making it impossible to estimate what proportion were scanned outside the time when CT would have distinguished infarct from haemorrhage reliably. Thus, it was not possible to calculate the confidence limits on the incidence of PICH by extrapolating from those scanned within the correct time window (for CT) to those scanned outside this (or not at all). Even studies that were published recently did not appear to have scanned a large proportion (i.e. > 90%) of patients within a time-frame that would definitely allow distinction of infarct from haemorrhage (i.e. < 10 days).[80,81,113]

Nine studies provided information on which patients were least likely to be scanned. In these nine studies, patients treated at home, those who died very early after their stroke, and the elderly were the groups most likely not to be scanned at all (*Table 5*). In the few studies that specifically

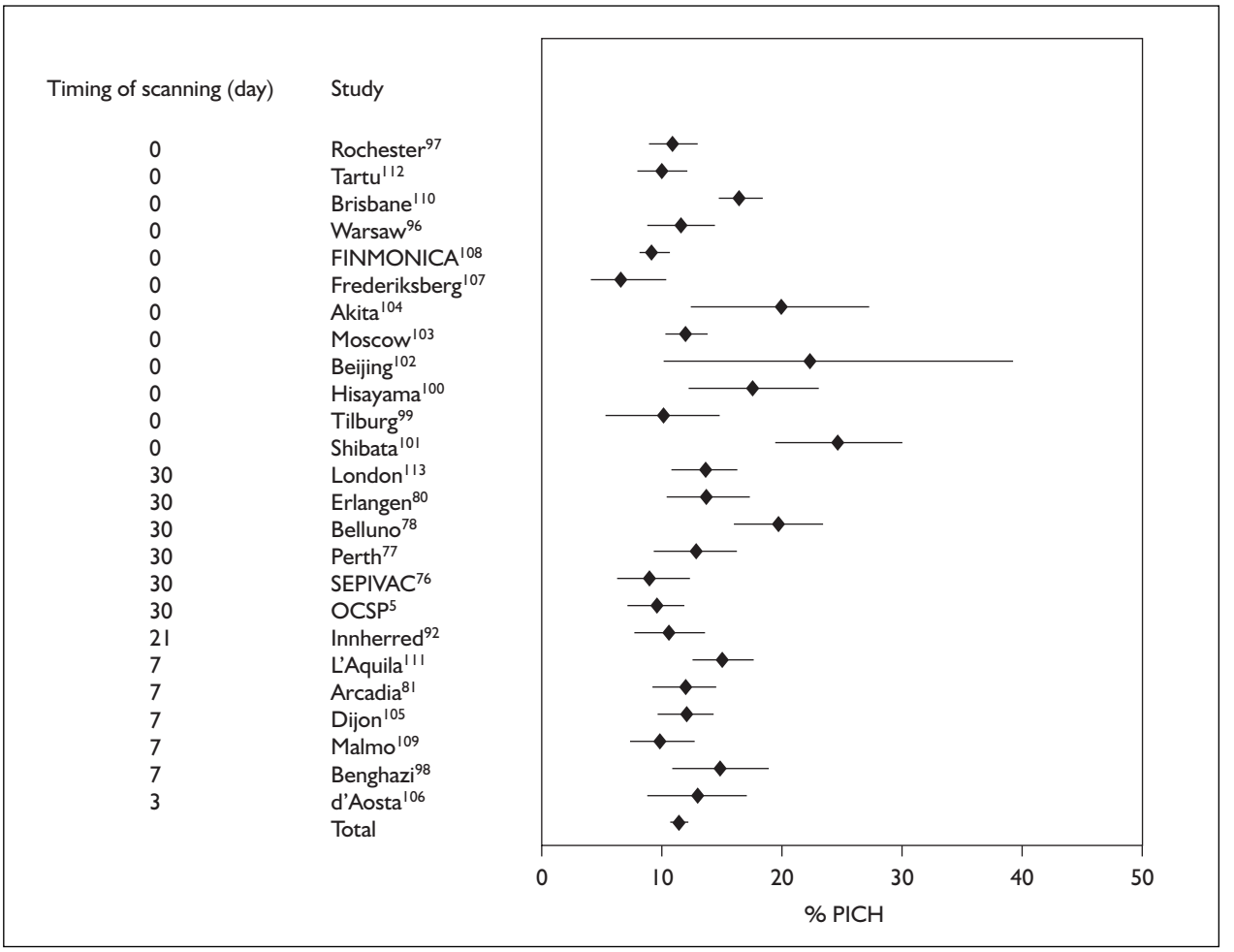


FIGURE 2 *Stroke incidence studies ranked according to speed of scanning following onset of stroke symptoms (point estimates of PICH with 95% CIs). Note: not all patients were scanned (see Figure 1 for proportion).*

TABLE 5 *Reasons mentioned for not scanning in community studies*

Study	Date	Reasons
Oxford[24]	1988	Rapidity of death, too ill to transfer, refusal, 65% of those not scanned > 75 years
Malmo[109]	1992	Mean age of those examined by CT less than those not
Perth[77]	1993	Rapidity of death, too ill, too frail, refusal, 81% of those not scanned > 75 years
Brisbane[110]	1995	Coma, lack of facility, too sick, age of the patient, attitude of the physicians
L'Aquila[111]	1997	Very early death, refusal, exclusive home care of very old patients, equipment breakdown
Tartu[112]	1997	Of the 24% with no subtype (i.e. no scan), 76% treated at home
Erlangen[80]	1998	Of those treated at home, only 37.5% scanned
London[113]	1999	Community patients, died within 2 days
Arcadia[81]	1999	Died early, very old, only home care, refusal, equipment breakdown

mentioned an age barrier, 'elderly' was greater than 75 years.

The proportions of subjects defined as having PICH varied widely. Also, it is very likely that some of the patients not scanned, or scanned greater than 2 weeks after stroke and diagnosed as ischaemic stroke, actually had PICH. However, it was impossible to determine from the majority of studies how many patients this bias might have affected. Therefore, to attempt to estimate what effect any underdiagnosis of PICH might have had

on the observed ratio of PICH/infarct, 'best' and 'worst' case scenarios were estimated. To do this, only studies that scanned more than 30% of patients were used. In the best case scenario, it was assumed that no patients in the uncertain (i.e. unscanned) category had PICH, and in the worst case scenario that all patients in the uncertain category had PICH, as well as those actually classified as PICH. The mean proportions per study (best and worst) and 95% confidence intervals were calculated. The mean study sample size was 529 and the proportion of PICH ranged from an estimated 13% to 25% (95% CI 10 to 29%).

Discussion

Generalisability of the results

The descriptive systematic review of studies of stroke mimics excluded virtually no studies. This is a poor quality literature. It is likely that the hospitals in which these studies were done had personnel with a particular interest in stroke, so that the proportion of misdiagnoses may have been less than might be seen in a district general hospital where the staff have no particular interest in stroke. Thus, the estimate of the proportion of patients presenting as stroke, who turn out subsequently not to have a stroke, is probably low.

Not everybody presenting with stroke symptoms is having a stroke, but who decides?

No significant difference was found between the proportion of stroke mimics misdiagnosed by paramedics as opposed to medical registrars, for example, but that may be because the studies were too small to expect to identify any significant difference. General physicians seemed to be better at making a correct diagnosis than paramedics and emergency room personnel, although confidence intervals were relatively wide. Intuitively, one would expect more experienced physicians with an interest in stroke to make fewer misdiagnoses than GPs who may only see a stroke a few times a year. If nothing more, these studies at least provide an estimate and confidence intervals of the magnitude of disagreement among different observers examining stroke patients. Whether the differences are due to experience, or new information becoming available as time passes, or true fluctuation in symptoms and signs, or differences in the primary purpose of these studies and their methodology, is not known. What these studies do highlight is that diagnosis by clinician alone, without a corroborative scan, will be incorrect a significant proportion of the time. This proportion is less when scan results are available.[88] If (as with thrombolysis) time to presentation to the acute stroke team is important, who makes the first referral is relatively immaterial.

Scanning policies in stroke incidence studies are not comprehensive

No community-based study of stroke incidence achieved a 100% CT scan rate within a time-frame that would definitely allow distinction of PICH from ischaemic stroke (i.e. within 10 days at the very most). In general, studies either scanned quickly enough but scanned relatively few patients, or scanned more patients but too late to distinguish PICH reliably. It is therefore very likely that the incidence of PICH has been underestimated, particularly the incidence of small haemorrhages, but there is really not enough information to determine by what degree. The 'best and worst' estimate of 13% to 25% gives some indication of the potential scale of the problem. Even in the latest community stroke study from Melbourne, NEMESIS (published in August 2001, after the end of the study period for the systematic review) neither made clear the precise scanning policy, nor stated exactly what proportion of patients were scanned within the first week, 2 weeks, and so on, of stroke.[114] Their methods refer to the use of CT or MR within 28 days of stroke; intracerebral haemorrhage was defined as a stroke in which a CT scan demonstrated an area of hyperdensity within the brain, or for scans performed beyond 1 week, an area of attenuation with ring enhancement after injection of contrast, or MR showed an area of hypointensity or isointensity on T1 and marked hypointensity on T2-weighted images. However, although the results state that CT, MR or autopsy was performed "soon after stroke" in 91% of those with first events (95% CI 88 to 95%), nowhere do the authors state what proportion were scanned within 1 or 2 or 3 or 4 weeks, with what modality, or anything about the proportion or timing of scanning for recurrent strokes. The discussion refers to confirmation of the pathological type of stroke with "mainly CT". They found that 14.5% of stroke was due to intracerebral haemorrhage (95% CI 10.3 to 18.6%). As with most other studies that provided the data, the majority of those not scanned at all (or autopsied) were aged over 75 years (18/24 undetermined strokes of the total 276 patients). The authors draw attention to the quite marked variation in age- and gender-adjusted annual incidence rates of haemorrhagic stroke between European stroke incidence studies, and

blame this on differences in the proportion of stroke of undetermined cause. They suggest that haemorrhagic strokes are likely to be over-represented in the 'stroke of undetermined type' category, as evidenced by the high case fatality rate in both the haemorrhage and the 'stroke of undetermined type' categories. They also suggest that the low power of the studies to detect the true incidence of haemorrhagic stroke (as it is less frequent) may be a contributing factor. It is sad that the failure to use a robust, clearly defined, imaging protocol has again gone unrecognised as a major contributing factor. Two other incidence studies (Hisayama and Shiga), also published after the search period for the present systematic review, failed even more than NEMESIS to describe their scanning.[115,116] One of these studies attempted to determine subtypes of stroke and risk factors for 32 years starting in 1961.[116] The methods refer only to 'recent' (no definition) brain imaging, but there is no indication of the proportion or time-frame for scanning. Unfortunately, it would appear that this serious flaw in the design of epidemiology studies continues unrecognised. Scanning 70% of subjects at some point might have been 'ideal' 10 or 15 years ago,[1] but is not adequate today, particularly when so much further stroke research, such as genetic studies or public health planning, depends on correct information on the proportion of ischaemic and haemorrhagic strokes.

Why were scanning policies inadequate?

The studies included in the systematic review were community based, and some of them made exhaustive attempts to record all people in the region under scrutiny who experienced stroke-like symptoms. Some studies were performed as far back as 1980, when being able to distinguish whether a stroke was ischaemic or haemorrhagic made no difference to the management of the patient. Access to CT for the investigation of stroke has improved with time, but not uniformly throughout the world, and this review included studies where access is still difficult (although Western European and Australian studies published in the late 1990s have little excuse).

Could it be that PICH is being overdiagnosed?

Very early haemorrhagic transformation of a cerebral infarct can mimic PICH,[117] but from the studies reviewed here there is no way of knowing how often this might have been the case. Whether it is important to distinguish haemorrhagic transformation from PICH is unclear, as it is unknown whether haemorrhagic transformation behaves as a clinical entity differently from cerebral infarction, or PICH, or whether it corresponds in prognosis to one or the other.[118] This can only be determined by more accurate categorisation of the condition by early scanning.

Thus, in the stroke incidence studies, the underdiagnosis of PICH is likely to be the correct current position and to reflect the problem of patients presenting late to medical attention, and so missing the window of opportunity for CT to detect PICH, even when a local community study might reasonably be expected to raise public awareness of the importance of not ignoring stroke symptoms. There was no evidence of an improvement in scanning policy in more recent compared with older studies, which is not encouraging.

Bias in scanning policies

A further bias has been introduced by the conspicuous lack of scanning in those patients managed at home, those dying early or the 'elderly'. The median age for stroke to occur is 72 years; thus, roughly half of all the strokes in a population may not have been scanned in incidence studies that failed to scan the elderly. The incidence of amyloid angiopathy, a risk factor for PICH, increases with age.[119] Increasing use of MRI has revealed that it is not uncommon to find evidence of old, apparently asymptomatic haemorrhages in the brains of older patients,[120,121] It may be that older people are particularly at risk of PICH, and thus there may be an over-representation of PICH in this group not being scanned in incidence studies. One cannot assume that the proportion of PICH to ischaemic stroke remains constant across all ages.

The community incidence studies assessed the incidence of infarct and haemorrhage as causes of first stroke. It would be wrong to assume that the proportion of PICH and infarct would be the same in recurrent stroke as in first stroke. A systematic review of studies of survivors of PICH found that PICH was a much more frequent cause of recurrent stroke than infarction.[122] In this group of patients from three community-based and seven hospital-based studies, three-quarters of recurrent strokes were due to PICH; 2.3% of patients had a recurrent stroke, 1.1% had a recurrent ischaemic stroke and 8.8% died per year of follow-up. A more recent study in which 243 patients admitted to hospital with a PICH were followed-up for an average of 5.5 years found an average recurrence of PICH of 2.1% and of vascular deaths 3.2%.

Increasing age, male gender, and use of anticoagulants increased the risk of recurrent PICH [hazard ratio (HR) for age 2.8, 95% CI 1.3 to 6.1; for male gender HR 1.8, 95% CI 1.1 to 3.0, and anticoagulants HR 3.0, 95% CI 1.3 to 7.2].[123]

There are numerous reasons why is it important to know the incidence of PICH and infarct correctly. These include (although this represents only a few):

- better understanding of the mechanism of PICH
- better understanding of the epidemiology of PICH, including for use in genetic studies
- better understanding of whether there is any variation in the proportion of stroke due to intracerebral haemorrhage with increasing age, or recurrent stroke
- improved prevention of PICH
- improved avoidance of drugs that may worsen outcome after PICH if given in the mistaken belief that the patient has had an infarct
- better methods to detect PICH.

It is well known that CT scanning will not differentiate infarct from haemorrhage reliably after 10 days, routine immediate CT imaging is available in many parts of the world for stroke, and MR should be used to diagnose haemorrhage if the patient presents too late for CT. But this fact, which is obvious to clinicians, appears to have been overlooked in the stroke epidemiology studies, even the very recent ones.

Conclusions

Implications for healthcare

About 20% of patients presenting to a hospital service with an initial diagnosis of stroke will, on further clinical assessment, turn out not to have had a stroke. There are a wide variety of stroke mimics, requiring very different management to stroke. The advent of thrombolysis highlights the problem of increasingly sophisticated (and potentially dangerous) management strategies that demand levels of diagnostic accuracy that clinicians are not capable of achieving without neuroimaging. Furthermore, it is not possible to differentiate stroke due to infarction from haemorrhage reliably on clinical grounds.

PICH has probably been underdiagnosed in community-based stroke incidence studies, especially in mild strokes, the elderly and those who died soon after the event. The weakness of scanning policies means that there is uncertainty about what proportion of strokes in various countries, or at various ages or severities, are due to PICH rather than ischaemic stroke. As a consequence, PICH may have been underestimated as a cause of mild stroke as these patients typically (in the UK) present as outpatients late after the event.

Implications for future research

There is little information on the observer reliability of clinical examination in the acute stage of stroke. More detailed information on the stability and reliability of symptoms and signs of stroke might help to improve the accuracy of clinical diagnosis of stroke versus not stroke. This would reduce the proportion of patients at risk of exposure to potentially risky treatments such as thrombolysis for whom there would be no benefit, as well as making more effective use of hospital resources. Further studies should determine which are the most robust signs of stroke, so that junior doctors, paramedics and those who see stroke rarely (such as GPs) can be given guidance on which signs are most reliable.

Community-based stroke incidence studies have been (and continue to be[115,124–127]) complacent in their attitude to neuroimaging and, as a consequence, any research relying on data from them, such as on the genetics of stroke, could be inherently flawed. The scanning policies used in any future stroke incidence studies should:

- be clearly described in terms of timing, proportion, etc.
- resort to MR with blood-sensitive sequences if it is more than 10 days after the stroke, as haemorrhage will not be reliably detected on CT after that time.

Future stroke incidence studies should look specifically and prospectively to see whether the proportion of strokes due to infarct and haemorrhage changes with age, with severity of stroke, in those who remain at home as opposed to being admitted to hospital, and whether there is a different proportion of haemorrhagic or ischaemic stroke among recurrent strokes. Ideally, a community-based incidence study would also collect data on resource use, including LOS in hospital and outpatient resources, as this would provide better data on which to plan future healthcare resources.

Chapter 3

The reliability of imaging in the diagnosis of haemorrhage and infarction

Systematic descriptive study of the diagnostic accuracy of CT and MR in stroke

Background

Distinguishing haemorrhagic from ischaemic stroke is important

The clinical diagnosis of the cause of stroke is of limited accuracy. Therefore, imaging is required to identify tumours or other non-vascular lesions presenting with stroke-like symptoms and make the distinction of infarct from haemorrhage reliably. Aspirin may be regarded as a 'safe' drug, but the long-term effects of aspirin, inadvertently given to patients with a definite intracranial haemorrhage, are unknown. Aspirin may cause less recurrent PICH than heparin following acute stroke[128] but is associated with a small but definite risk.[48,129] Delivery of current best practice[50,62] for primary and secondary stroke prevention depends on the correct diagnosis of infarct or haemorrhage, as well as the exclusion of tumours and non-vascular lesions.

Furthermore, it may no longer be sufficient to use imaging simply to exclude the presence of haemorrhage or non-vascular lesion. The clinical diagnosis of stroke (versus not stroke) is difficult, as shown in Chapter 2, where about 20% of patients initially diagnosed as stroke on first medical contact were subsequently considered not to have had a stroke when seen later by a more experienced physician. Partly, this change in diagnosis with time reflects the difficulty of clinical assessment in the acute phase when symptoms and signs may truly fluctuate, the patient may be dysphasic, so unable to give a proper history, and junior medical staff may lack confidence in eliciting or interpreting complicated neurological signs. Regardless of the cause, increasingly, physicians are turning to imaging both to confirm the diagnosis of stroke and to determine which part of the brain is affected. For example, the benefits of thrombolysis may be much greater than for antiplatelet agents but, unfortunately, so are the risks.[130] Although the latest time window for thrombolysis is uncertain, it is probably only a matter of hours. Experience from the USA, where thrombolysis has been licensed since 1996, shows that only a small fraction of patients arriving in hospital in time and eligible for thrombolysis are receiving it.[131,132] Part of the reason for this may be the reluctance of physicians to expose their patients to the (potentially fatal) risk of thrombolysis if they are not certain that the patient is definitely having a stroke. Thus, positive identification of an infarct increases the physician's confidence for the diagnosis of stroke and subsequent actions such as the use of thrombolysis.

The use of further investigations (which may themselves be of limited availability, e.g. carotid ultrasound) to guide secondary prevention may also be influenced by increased confidence in the diagnosis of infarction and its site. For example, it would not be appropriate to undertake carotid endarterectomy after mild non-disabling stroke if the infarct were in the vertebral territory rather than the carotid territory, yet with some minor strokes it can be difficult to discriminate between posterior and anterior circulation events.[133] There is also evidence that lacunar infarcts are less likely to be due to carotid stenosis than cortical infarcts,[134] and less likely to recur quickly,[56] so demonstration of a small, deep infarct in a patient who was a poor operative risk might tip the balance between operating and not operating. In patients with previous stroke and a new neurological deterioration, it may be important to know whether the deterioration is due to a new stroke or to some intercurrent illness such as a urinary tract infection. Identification of a new lesion on brain imaging is helpful in this situation. Thus, for a variety of reasons, positive identification of cerebral infarction is of increasing importance.

CT or MRI: which is 'better'?

Although access to MR for stroke has increased, CT is still the most common form of brain imaging used.[67,135] CT is widely available and easy to perform in stroke, so is likely to remain the most commonly used investigation after stroke for the foreseeable future. Haemorrhage can be demonstrated readily on CT as a hyperdense area (white) as soon as clinical symptoms appear.[54]

However, the haemorrhage remains hyperdense for only a finite amount of time.[55,136] As the haemorrhage is broken down, it loses its hyperdensity, becoming first isodense with normal brain and eventually hypodense. From the point where it loses the hyperdensity onwards, the haemorrhage is indistinguishable from an infarct. The speed with which this occurs depends on the size of the haematoma: the smaller the initial bleed, the faster it takes on the appearance identical to infarction. Thus, the issue of sensitivity of CT in the identification of PICH is less whether it can distinguish acute PICH from ischaemic stroke, but rather the length of time for which these changes remain visible and can be reliably differentiated from ischaemic stroke.

Haemorrhage remains visible on MR for much longer, probably indefinitely in most people.[137] However, MR is contraindicated for patients with pacemakers and metal implants such as intraocular metallic foreign bodies and intracranial aneurysm clips. Patients may find MR unpleasant, or be unable to tolerate it at all, because of claustrophobia. The enclosing imaging tunnel makes monitoring of sick patients difficult. MR takes longer to acquire than a CT scan, so MR is less suited to restless, confused, ill stroke patients. MR costs more than CT and, in the UK and many other countries, is less widely available. Thus, despite its increased sensitivity to haemorrhage, MR cannot simply be used in place of CT because of these practical difficulties.

Why do a systematic review of imaging studies in stroke?

In general, diagnostic tests have been much less subjected to critical systematic reviews than treatments. There was no existing systematic review of the use of CT or MR scanning in stroke at the start of this project. From the 1970s to the early 1990s, when CT scanning for stroke was less available than today, there was less perception of the need for precise estimates of its accuracy. When introduced, CT was clearly such a major advance that most publications were descriptive case series and paid little attention to defining the sensitivity or specificity of imaging. Even since then, studies of imaging have tended to be small, with little likelihood of any one study providing a definitive answer. CT is now more available, stroke is a common problem, which creates a major public health burden, and there are now treatments that depend on knowing the cause of the stroke. Misuse of imaging could be very costly to the health service. MR poses greater problems, as increasingly sophisticated and seemingly advantageous techniques are developed. Therefore, a systematic review was undertaken of the use of CT and MR, either alone or in combination, to look at all the available evidence in the identification of haemorrhagic and ischaemic stroke, not only to search for details on sensitivity, but also to assess the quality of the methodology of the studies performed.

Methods

Objectives

The aims were to determine the sensitivity and specificity of CT and MRI in the distinction of infarct from haemorrhage, in the positive diagnosis of infarct, and to identify the major factors that may affect the diagnostic accuracy. Specifically, the study aimed to determine:

- the sensitivity and specificity of CT in the diagnosis of acute PICH
- how the sensitivity and specificity of CT in the diagnosis of PICH change with time and size of haematoma
- the sensitivity and specificity of MR in the diagnosis of PICH
- how the sensitivity and specificity of MR change with time and size of haematoma
- the sensitivity and specificity of CT in the positive identification of the site and extent of ischaemic stroke
- the sensitivity and specificity of MR in the positive identification of the site and extent of ischaemic stroke
- whether there was any evidence, from direct comparisons, that CT or MR was preferable in some situations.

Criteria for considering studies for the review

All studies on the accuracy of CT and/or MR in the diagnosis of PICH or cerebral infarction were sought. These included studies where the primary aim was to identify the sensitivity and specificity of imaging, studies where the results of CT and MR imaging were reported for a group of stroke patients, and those where that was not the primary aim but it was possible to extract information relating to the accuracy of brain imaging in stroke patients. Prospective and retrospective studies were sought (there were concerns that there would be few clearly prospective studies). A further aim was to identify studies where it was clear that the 'stroke' patients had been examined by a stroke physician or neurologist, to be certain that the population was as clearly defined as possible. This was particularly important for studies assessing imaging in the diagnosis of infarction. Any studies concerned with the observer reliability of the

interpretation of images were also sought. The standard WHO definition of stroke was used.[22]

Case reports were excluded. In the review of the diagnosis of infarction, descriptive studies that were concerned with only one specific sign of ischaemia, for example, the dense middle cerebral artery sign, were excluded as these were concerned with the description of a new sign rather than its prevalence. Studies that were not primarily of stroke patients were also excluded.

Search strategy

The medical databases were searched electronically; MEDLINE from 1966 (MEDLINE databases are presented in periods, and the earliest period is 1966 to 1974, which overlaps with the inception of CT) and EMBASE from 1980 (which was as far back as it was possible to search) to December 2000. To an extended search strategy for stroke (Appendix 4[75]) were added specific search terms for accuracy, sensitivity and specificity, and for CT and MR. Patients with haemorrhagic and ischaemic stroke present with the same symptoms and were often studied together, so the main search strategy was designed to identify studies of ischaemia as well as haemorrhage. Conference abstracts were also searched, and further studies identified by examination of the reference lists of studies already found.

Preliminary searches specifically for the accuracy of scanning in PICH and infarction revealed very limited data. Therefore, the inclusion criteria were deliberately broadened to encompass all studies of the use of CT and/or MR in humans with PICH or infarction.

Data extraction

Data were extracted by one reviewer on:

- the size of study
- the primary purpose
- details of the patient population (e.g. unselected strokes, or a specific clinical type) and stroke severity
- the criteria on which the final diagnosis of stroke was made
- whether the study was prospective
- whether the patients had been assessed by a stroke physician or neurologist
- the timing of scanning in relation to onset of stroke symptoms
- the timing of CT and MR in studies comparing each type of scan to the other
- whether the order of CT and MR was random or not
- whether scans were read blind to clinical details or other imaging, and by whom
- any data on sensitivity of imaging.

Any uncertain data were discussed with a second reviewer and a consensus was reached.

It was assumed that the patients had been examined by a physician with an interest in stroke if the study was from a department of neurology or neurosurgery, even if there was no reference in the text, as opposed to being a more general collection of stroke queries referred by clinicians with less experience of stroke or, worse, based on information obtained simply from a radiology department request card with no indication of who had examined the patient. Any information on the clinical feasibility of scanning; for example, the number of patients unable to tolerate scanning, or the number of inadequate images, and whether these patients or their images had been excluded from the analysis, was noted.

Data analysis

Included studies were entered into an Access database and assessed with descriptive statistics.

Details of included studies

Studies of PICH

The search strategy identified 2467 papers concerning the use of CT and/or MRI in the diagnosis of PICH or cerebral infarction.

CT studies of haemorrhage

In total, 1047 references pertaining to the accuracy of CT alone in stroke (haemorrhagic and ischaemic) were captured. *Table 6* shows details of the included studies. Methodological detail in most of these studies was poor. Although in 36 studies (71% of total identified), patients appeared to have been assessed by a stroke physician or neurologist, information on stroke type and severity was very limited, as was the timing of scanning in relation to onset of stroke symptoms. Only two studies clearly stated that scan readers were blinded to clinical history[175] or other imaging results.[117] Only six studies (12%, 656 patients) documented that cases were collected prospectively or consecutively.[136,165,168,171,175,178] Unfortunately, the majority of studies used retrospectively collected data. There were no other standards used (e.g. post-mortem) against which CT could be judged, although admittedly this would have introduced a bias towards the more severe strokes. There were no papers identified on CT alone and PICH after 1998.

TABLE 6 *CT and intracerebral haemorrhage (ICH)*

Study	Year	Size	Purpose of study	Assessed by stroke physician?	Readings blinded?
Walshe[138]	1976	68	Clinicotopography	No	No
Greenberg[139]	1977	6	Clinicotopography	No	No
Lieberman[140]	1978	6	ICH in patients with prosthetic heart valves – outcome	No	No
Scott[141]	1979	232	Clinicotopography (thalamic ganglionic)	Yes	No
Mizukami[142]	1981	17	Clinicotopography (putaminal)	No	No
Weisberg[143]	1981	12	Clinicotopography (multiple PICH)	Yes	No
Hungerbuhler[144]	1983	108	Clinicotopography	No	No
Mayr[145]	1983	100	Prognosis	No	No
Garde[146]	1983	100	Prognosis, clinicotopography	No	No
Helweg-Larsen[147]	1984	8	Prognosis	Yes	No
Stein[148]	1984	12	Clinicotopography (caudate)	Yes	No
Steiner[149]	1984	37	Prognosis	Yes	No
Weisberg[150]	1984	8	Clinicotopography (caudate)	Yes	No
Hung[136]	1985	31	Prognosis (and serial CT characteristics)	Yes	No
Mori[151]	1985	174	Clinicotopography (lacunar)	Yes	No
Weisberg[152]	1985	50	Clinicotopography (subcortical lobar)	Yes	No
Tanaka[153]	1986	25	Prognosis	Yes	No
Gates[154]	1986	5	Clinicotopography	Yes	No
Carbonin[155]	1986	5	Clinicotopography	No	No
Dollberg[156]	1986	77	Clinicotopography	No	No
Weisberg[157]	1986	40	Clinicotopography (pontine)	Yes	No
Dennis[55]	1987	5	Serial CT characteristics		
Fieschi[158]	1988	104	Prognosis	Yes	No
Darby[159]	1988	7	Clinicotopography (solitary intraventricular haemorrhage)	Yes	No
Weisberg[160]	1988	18	Clinicotopography (occipital)	Yes	No
Iwasaki[161]	1988	10	Clinicotopography (lacunar)	No	No
Weisberg[162]	1989	25	Clinicotopography (parietal)	Yes	No
Astarloa[163]	1989	114	Prognosis	Yes	No
Jayakumar[164]	1989	15	Clinicotopography (solitary intraventricular haemorrhage)	Yes	No
Schutz[165]	1990	100	Clinicotopography	Yes	No
Cerillo[166]	1990	83	Prognosis	Yes	No
Weisberg[167]	1990	100	Clinicotopography	Yes	No
Daverat[168]	1991	166	Prognosis	Yes	No
Bogousslavsky[117]	1991	15	CT characteristics (haemorrhagic transformation)	No	Yes[a]
Kreel[169]	1991	120	CT characteristics (residual lesions)	No	No
Franke[170]	1991	42	CT characteristics (residual lesions)	Yes	No
Franke[171]	1992	157	Prognosis	Yes	No
Lisk[172]	1994	75	Prognosis	Yes	No
Berlit[173]	1994	326	Prognosis	Yes	No

continued

TABLE 6 *CT and intracerebral haemorrhage (ICH) (cont'd)*

Study	Year	Size	Purpose of study	Assessed by stroke physician?	Readings blinded?
Fujii[174]	1994	419	CT characteristics (enlargement of haematoma)	Yes	No
Halpin[175]	1994	38	CT characteristics (whether to perform angiography)	No	Yes[b]
Passero[176]	1995	112	Recurrent ICH (incidence)	Yes	No
Dandapani[177]	1995	87	Prognosis	Yes	No
Lampl[178]	1995	279	Prognosis	Yes	No
Mori[179]	1995	104	Clinicotopography (thalamic), prognosis	No	No
Qureshi[180]	1995	182	Prognosis	Yes	No
Mase[181]	1995	138	Prognosis	Yes	No
Chaves[182]	1996	17	Clinicotopography (cerebellar haemorrhagic transformation)	Yes	No
Kazui[183]	1996	204	CT characteristics (enlargement of haematoma)	Yes	No
Zhu[184]	1997	206	CT characteristics (comparing diagnoses with angiography)	Yes	No
Eshwar Chandra[185]	1998	45	CT characteristics (comparing diagnoses with angiography)	Yes	No
Butler[186]	1998	35	ICH in patients with prosthetic heart valves – outcome	No	No
Gonzalez-Duarte[187]	1998	22	Recurrent ICH, prognosis	Yes	No

[a] Blind to other imaging; [b] blind to clinical history.

MRI studies of haemorrhage

In total, 2098 references were captured concerning MR and stroke, either alone or in combination with CT. Twenty-two studies (1512 patients) concerning MR and PICH were identified (*Table 7*). Eight studies (235 patients) concentrated on MR alone in PICH. Fourteen out of 22 studies (1119 patients) included patients who had been assessed by a stroke physician or neurologist.[120,188,191,196–198,200–207] Only nine (43%) studies (756 patients) reported any details at all on the case-mix of patients.[120,188,197,200,202–204,207,208] Eight (38%) studies (865 patients) gathered data prospectively.[120,121,202–207] In only five (23%) studies (643 patients) were scans read blinded to either other imaging[204] or clinical history,[203,207] or both.[120,205] Only one (5%) study comparing CT to MR attempted to randomise the order in which imaging was performed.[207] Only five (23%) MR studies commented on the proportion of inadequate scans, for example owing to patient movement.

CT studies of cerebral infarction

Thirty-one studies (7393 patients) concerning CT and stroke were identified, 15 of which (4604 patients) documented patients who had been seen by a neurologist or a physician with an interest in stroke, and documented values from which sensitivity for CT in the positive identification of ischaemic stroke could be calculated (*Table 8*). In the 15 included studies, the population group under investigation varied: five studies (895 patients) specifically excluded haemorrhage,[57,209,211,213,219] three studies (853 patients) investigated unselected stroke populations,[210,212,216] three studies (145 patients) included infarcts of the middle cerebral artery territory only,[217,218,229] two studies (156 patients) included thrombolysis patients only,[221,222] one study included patients with various neurological diseases (1191 patients, 386 of whom had stroke symptoms)[214] and one study included patients with mild stroke symptoms only.[215] These marked differences in case-mix make it difficult to draw any generalisable conclusions.

Nine studies (3571 patients, 60% of studies) recruited patients prospectively.[57,209,210,213–218] Only six studies (3001 patients, 40% of studies) were blinded to clinical history[211,219] or clinical history and other imaging.[215,217,220,221] The gold

TABLE 7 *MRI and intracerebral haemorrhage (ICH)*

Study	Year	Size	Purpose of study	CT also performed	Assessed by stroke physician?	Readings blinded?
Linfante[188]	1999	5	Clinicotopography, hyperacute	No	Yes	No
Offenbacher[189]	1996	120	Clinicotopography, asymptomatic haemorrhage	No	No	No
Melhem[190]	1998	32	Technical (GRE sequence in haemorrhage)	No	No	No
Edelman[191]	1986	16	Technical (modification of pulse)	No	Yes	No
Gomori[192]	1985	20	Technical	No	No	No
Zimmerman[193]	1988	37	Clinicotopography	No	No	No
Shimizu[194]	1992	4	Clinicotopography	No	No	No
Liang[195]	1999	50	Technical (GRE sequence in haemorrhage)	Yes	No	No
Tanaka[196]	1999	89	Asymptomatic haemorrhage	Yes	Yes	No
Patel[197]	1996	6	Visualise haemorrhage, clinicotopography	Yes	Yes	No
Greenberg[121]	1996	25	Asymptomatic haemorrhage	Yes	No	No
Staffen[198]	1998	100	Clinical differences between haemorrhagic transformation and PICH	Yes	Yes	No
Steinbrich[199]	1990	129	Compare CT and MR	Yes	No	No
Tanaka[200]	1988	30	Compare CT and MR	Yes	Yes	No
Schellinger[201]	1999	9	Visualise haemorrhage	Yes	Yes	No
Kinoshita[202]	2000	198	Asymptomatic haemorrhage	Yes	Yes	No
Kwa[120]	1998	221	Asymptomatic haemorrhage	Yes	Yes	Yes[c]
Salgado[203]	1986	60	Compare CT and MR	Yes	Yes	Yes[b]
Kertesz[204]	1987	175	Compare CT and MR	Yes	Yes	Yes[a]
Mayer[205]	2000	36	Haemorrhagic transformation serially	Yes	Yes	Yes[c]
Arias[206]	1992	70	Compare CT and MR	Yes	Yes	No
Mohr[207]	1995	80	Compare CT and MR	Yes	Yes	Yes[b]

[a] Blind to other imaging; [b] blind to clinical history; [c] blind to both.

standard by which the final diagnosis reached was clinical progress in 11 studies (3334 patients, 73% of studies),[57,210–214,216, 218–220,222] follow-up scan in two studies (83 patients, 13% of studies),[221,223] and undefined in three studies (1233 patients, 20% of studies).[209,215,217]

MRI studies of cerebral infarction

Eighteen studies (1638 patients) were identified concerning MR alone in stroke (*Table 9*); 15 (1560 patients) included patients assessed at some stage by a neurologist or stroke physician. In only one of the four studies was imaging read blinded to clinical history.[227] As with CT, the differences in case-mix, timing of scanning and small numbers make these results of interest but difficult to generalise.

CT and MRI in the positive diagnosis of ischaemic stroke

Twenty-eight studies (1650 patients) comparing CT and MR directly in stroke were identified, of which 18 studies (808 patients) included patients who had been assessed by a neurologist or stroke physician, and of those 12 studies (609 patients) documented the number of positive findings on scans performed (*Table 10*). As previously, the patient groups under investigation differed (some studies including more than one patient group): TIA (two studies, 41 patients),[203,228] lacunar stroke (five studies, 166 patients),[203,230,232,233,235] cerebellar stroke (one study 14 patients);[229] lateral medullary syndrome (one study, six patients)[231] and unselected stroke (four studies, 356 patients).[204,206,207,234] Again, studies were uniformly small. Nine studies (75% of studies) collected data prospectively,[203,204,206,207,228,230,233–235] while six studies (50%) blinded readers of scans either to clinical history[203,207,228,234,235] or to other imaging.[204] In only one study (0.8%) was the order in which CT or MR was performed varied (although not randomised);[207] two studies performed both scans on the same day but did not document the order in which they were done;[228,232] in five studies, CT was always performed before MR.[203,204,206,234,235] The extent of the difference in times varied: in one study where all patients were scanned within 24 hours, CT was performed a

TABLE 8 *Studies on the sensitivity of CT in the positive identification of ischaemic stroke: studies where all patients seen by a neurologist or stroke physician*

Study	Year	Size	Patient group	Standard	Timing	Sensitivity
Buell[209]	1979	159	Stroke, 3 groups, not PICH	Undefined	Hours: 18 to 4 days (gp1), days: 28–65 (gp2)	0.95
Soderstrom[210]	1981	300	Cerebrovascular disease	Clinical progress	Undefined	0.53
Wall[211]	1982	26	Acute stroke, not PICH	Clinical progress/autopsy	Hours: ≤24	0.81
Sandercock[212]	1985	325	Suspected stroke, TIA	Clinical progress	Days: 34% in 7/7, 63% in 21/7	0.53
Brott[213]	1989	65	Acute stroke, not PICH	Clinical progress	Hours: ≤ 48, then 7–10 days	0.4 (admission) 0.77 (10 days)
Sotaniemi[214]	1990	1191	Various neurological diseases	Clinical progress	Days: ≤ 4 (90% of patients)	0.81
Koudstaal[215]	1992	1054	Acute stroke (minor), TIA	Undefined	Undefined	0.49
Lindgren[216]	1994	228	Acute stroke	Clinical progress	Days: ≤ 2, 3–15 (16 later), then 16–30 days	0.47 (admission) 0.74 (3–15 days)
Firlik[217]	1997	20	MCA infarcts	Undefined	Hours: < 6	0.55
Buttner[218]	1997	95	MCA infarcts	Clinical progress	Hours: ≤ 6	0.47
Al-Buhairi[219]	1998	418	Acute stroke, not PICH	Clinical progress	Unclear (60 patients scanned within 48 hours)	0.63
Wardlaw[57]	1998	639	Stroke, within 99 days, not PICH	Clinical progress	Days: ≤ 7 (part of total)	0.60 (day 1) 0.63 (day 7)
Lev[220]	1999	30	MCA infarcts	Clinical progress	Hours: ≤ 6 and controls	0.57
Scott[221]	1999	39	Acute stroke, thrombolysis recipients	Follow-up scan	Hours: ≤ 3	0.64
Barber[222]	2000	117	Acute stroke, thrombolysis recipients, anterior circulation	Clinical progress	Hours: ≤ 3 and follow-up scan	0.75

MCA, middle cerebral artery.

TABLE 9 *Studies on the sensitivity of MRI alone in the positive identification of ischaemic stroke, sensitivities available*

Study	Year	Size	Patient group	Purpose of study	Seen by stroke physician?	Images read blinded?	Sensitivity
Fazekas[224]	1996	62	TIA	Clinicotopography	Yes	No	0.31 (acute infarcts)
Cosnard[225]	1998	41	Cerebral infarcts	Technical, sensitivity (FLAIR compared with MRA)	Yes	No	0.78
Egelhof[226]	1998	34	Ischaemic cerebral infarcts	Clinicotopography (serial scans), sensitivity	Yes	No	0.88 (T2 on first scan)
Razumovsky[227]	1999	30	Acute stroke, possible	Sensitivity (with TCD, MRA)	Yes	Yes[a]	0.73

[a] Blind to clinical history.

TABLE 10 *Studies on the sensitivity of CT and MRI combined in the positive identification of ischaemic stroke*

Study	Year	Size	Study type	Images read blinded?	Patient group	Timing	Results
Salgado[203]	1986	60	Prospective	Yes[a]	TIA, lacunar or non-lacunar infarct	Days: median 12 (CT) 16 (MRI)	(i) CT 4/19, MR 13/19, (ii) CT 18/29, MR 21/29, (iii) CT 7/12, MR 10/12
Awad[228]	1986	22	Prospective	Yes[a]	TIA	Weeks: < 4 from onset. Scans performed on same or consecutive days	Clinically relevant lesions: MR only 3/22, CT better 2/22
Simmons[229]	1986	14	Retrospective	No	Cerebellar infarction on MRI	Days: within 14 in 12/14	CT findings on 6/14 (vs 14/14 on MR)
Kertesz[204]	1987	175	Prospective	Yes[b]	Acute stroke	Days and weeks: 5 groups see paper. 1 gp CT/MR within 72 h	week 1: MR 71/87, CT 44/87
Rothrock[230]	1987	31	Prospective	No	Lacunar stroke (acute, subacute, chronic)	Days to 2 years: 14 had scans same day	(i) MR 11/12, CT 2/12, (iii) MR 8/13, CT 4/13
Hommel[231]	1988	6	Retrospective	No	Lateral medullary infarction	?	CT 2/6 vs MR 5/6
Miyashita[232]	1988	9	Retrospective	No	Lacunar stroke, multiple infarcts	Days: 7–28	Enhanced MR 8/9, CT 4/9
Arboix[233]	1990	60	Prospective	No	Lacunar infarcts	Hours: 72 to 3 weeks (order unspecified)	MR 78%, CT 30% positive
Bryan[234]	1991	31	Prospective	Yes[a]	Acute stroke (clinically definite)	Hours: < 24 (CT average 4 h earlier)	Observer 1: MR 24/31, CT 15/31 Observer 2: MR 27/31, CT 21/31
Arias[206]	1992	70	Prospective	No	Acute stroke	Days: CT at presentation then MR within 1 week	MR normal in 1/52, CT normal in 25/52
Mohr[207]	1995	80	prospective	Yes[a]	Acute stroke	Hours: 68 < 4, 12 < 24 (CT first 35, MR first 45)	MR 31/61, CT 26/31 positive (not significant)
Stapf[235]	2000	54	prospective	Yes[a]	Lacunar stroke	Days: CT < 2, MR 3–5 days after onset	MR 51/54, CT 27/54

[a] Blind to clinical history; [b] blind to other imaging.

mean of 4 hours earlier,[234] in another study of imaging within the first 3 weeks of stroke, CT was performed a median of 4 days earlier,[203] and in three studies the order of scanning was not defined.[230,231,233]

Details of excluded studies

Studies of PICH

In view of the disappointing quality of the literature for CT and MR individually and the comparisons, no studies that met the basic inclusion criteria outlined above were excluded for studies concerning PICH.

Studies of cerebral infarction

Studies excluded from the analysis of CT are listed in *Table 11*. Studies were excluded from the analysis of MR (*Table 12*) because the primary purposes were: descriptions of clinicotopography or specific MRI characteristics (eight studies, 990 patients),[253,254,256,259–261,263,264] explorations around the use of contrast agent or imaging parameters (five studies, 167 patients),[251,252,255,257,262] and one study (seven patients) highlighting the important issue of negative MR scans in clinically definite stroke.[258] Studies were excluded from the analysis of CT and MR because they failed to give details on sensitivity or the patients were not examined by a stroke physician or neurologist (*Table 13*).

Results

Studies of imaging in the diagnosis of haemorrhage

CT and the identification of haemorrhage

In total, 1047 references pertaining to the accuracy of CT alone in stroke (haemorrhagic and ischaemic) were captured. Fifty-three studies (including a total of 4491 patients) specifically concerned with CT-confirmed PICH were identified (*Table 6*). Studies in which both CT and MR were performed at some stage were analysed separately (see following pages). Studies concerning interobserver reliability of image interpretation (some of which included PICH) will be addressed later.

Twenty-four studies (1310 patients) described various characteristics of PICH in an anatomically specific site, merely documenting the scan findings in groups of patients with similar clinical symptoms (often retrospectively identified). Nineteen studies (2138 patients) attempted to determine prognosis following PICH, using clinical or imaging parameters. Both of these groups of studies used CT uncritically as the tool to identify haemorrhage, and as such provided no information on accuracy.

Studies concerning haemorrhage on CT at differing time-points

Six studies (819 patients) documented CT characteristics of haemorrhage at different times after stroke.[55,136,169,170,174,183] Two of these (623 patients) reviewed a population with PICH and multiple scans within the first few days after stroke, to determine the proportion of patients with haematoma enlargement. One study (204 patients) found that 17% of haematomas continued to expand after 6 hours, but that further enlargement after 24 hours was rare.[183] The other (419 patients) found 14.3% of haematomas had expanded between the first CT (within 24 hours of onset of symptoms) and second CT (within 24 hours of admission).[174] Both used retrospectively collected data and scans were not read blinded to each other, but they highlight the important point that one scan of an acute haematoma is merely a snapshot in a dynamic process.

CT in the identification of haemorrhage late after stroke

Two studies (160 patients) investigated residual lesions late after PICH. Initial scans were taken within 1 week of onset of stroke symptoms and follow-up scans over 2 months afterwards. Between 17%[170] and 27%[169] of CT scans showed no residual lesions at all. Areas of hypodensity that would be indistinguishable from ischaemic stroke were found in 37%[169] to 52%.[170] Focal calcification was found in 5%[170] to 10%.[169] Slit-like hypodense lesions were identified in 14%[170] to 25%[169] at the site of previous haemorrhage, but it is not clear whether these were only found following PICH, or how reliably they would be recognised by a blinded observer.

Two studies (36 patients) commented on the time-course over which signs of haemorrhage could disappear. One study looking at small haemorrhages (< 20 mm diameter, comprising 6% of their PICH population) performed follow-up scanning between 6 days and 3 months in 8/31 (26%) patients. They found that 2/8 (25%) were isodense within 9 days of stroke.[136] The other study reported on five patients with PICH (maximum diameter 33 mm), identified as part of a community stroke incidence study, in whom the haematomas had become isodense on repeat CT within a few weeks of the original scan. The earliest repeat CT had been performed 13 days after stroke, and it is possible that the haematomas may have become isodense earlier.[55]

Studies of CT and haemorrhagic transformation

One study (15 patients) reported a case series of patients with ischaemic stroke who had undergone

Table 11 *Studies on the sensitivity of CT in the positive identification of ischaemic stroke: studies where patient groups were not seen by a stroke physician or were descriptive only*

Study	Year	Size	Patient group	Images read blinded?	Study design	Standard	Timing	Sensitivity	Seen by stroke physician
New[236]	1974	42	Various neurological diseases	No	Retrospective	Undefined	Undefined	?	No
Jacobs[237]	1976	79	Various neurological diseases	No	Unclear	Autopsy	Undefined	?	No
Toghi[238]	1981	87	Cerebrovascular disease	Yes[a]	Unclear	Autopsy	Days: ⩽ 110	?	No
Sipponen[239]	1984	11	Stroke, not PICH	No	Retrospective	Undefined	Days: 1 to 3 months	?	No
Panzer[240]	1985	269	Acute stroke	No	Retrospective	None stated	Unclear (majority scanned within 24 h in RGH)	?	No
Wang[241]	1988	530	Suspected stroke, CT scans	No	Retrospective	None stated	Undefined	0.77 (infarcts only)	No
Horowitz[242]	1991	50	Acute stroke, not PICH	No	Prospective	Undefined	Hours: ⩽ 5, then 5–7 days	0.56 initially, 0.74 on follow-up	No
Bendszus[243]	1997	45	MCA infarcts	Yes[a]	Retrospective	Follow-up CT	Hours: ⩽ 5	0.61 (without DDA) 0.96 with DDA	No
McAlister[244]	1997	177	Acute stroke	No	Retrospective	Clinical progress	Hours: ⩽ 24 (107), > 24 (70)	0.23 (early), 0.58 (delayed scanning)	No
Johansson[245]	1984	181	Acute stroke, negative CT	No	Retrospective	Clinical progress	Days: > 3	?	Yes
Kinkel[246]	1976	111	Cerebrovascular disease	No	Retrospective	Clinical progress	Undefined	?	Yes
Inoue[247]	1980	30	Acute stroke, positive finding on CT, not PICH	No	Prospective	Undefined	Days: ⩽ 5	?	Yes
Moulin[248]	1996	100	MCA infarcts	Yes[a]	Retrospective	Clinical progress	Days: ⩽ 10	?	Yes
Toni[249]	2000	514	Lacunar infarcts	No	Retrospective	Follow-up scan (CT) at 1 week	Hours: < 6	?	Yes
Toni[250]	1995	517	Acute stroke (but investigating sensitivity for lacunar diagnosis)	No	Retrospective	Clinical progress	Days: < 15	?	Yes

[a] Blind to clinical history. RGH, regional general hospital.

TABLE 12 *Studies on the sensitivity of MRI alone in the positive identification of ischaemic stroke, sensitivities not available*

Study	Year	Size	Patient group	Purpose	Seen by stroke physician?	Images read blinded?	Sensitivity
Bryan[251]	1983	9	Stroke	Technical (exploratory)	Yes	No	
Virapongse[252]	1986	20	Subacute and chronic stroke	Technical (contrast)	No	No	
Kinkel[253]	1986	350	Stroke, TIA	Clinicotopography	Yes	No	
Byrne[254]	1989	76	Brainstem lesions	Clinicotopography	Yes	No	
Crain[255]	1991	80	Acute stroke	Technical (contrast)	Yes	No	
Yuh[256]	1991	39	Acute ischaemic stroke	Clinicotopography	Yes	No	
Sato[257]	1991	8	Stroke	Technical (contrast)	No	No	
Alberts[258]	1992	7	Stroke, negative scan	Negative MRI-clinical stroke	Yes	No	
Shimosegawa[259]	1992	16	Stroke, embolic cerebral infarction	Clinicotopography	Yes	No	
Yin[260]	1994	81	Infratentorial stroke	Clinicotopography	Yes	No	
Kim[261]	1994	33	Lateral medullary stroke	Clinicotopography	Yes	No	
Brant-Zawadzki[262]	1996	50	Cerebrovascular accident	Technical (FLAIR)	No	Yes[a]	Overall FLAIR better in 10
Mantyla[263]	1999	395	Stroke, WMHI	MR characteristics	Yes	No	
Mantyla[264]	1999	395	Old stroke	MR characteristics	Yes	Yes	

[a]Blind to clinical history.
WMHI, white matter hyperintensities.

TABLE 13 *Studies on the sensitivity of CT and MRI combined in the positive identification of ischaemic stroke: patient groups not seen by a stroke physician or neurologist, descriptive only*

Study	Year	Size	Study type	Images read blinded?	Patient group	Timing	Results
Sipponen[265]	1983	7	Prospective	No	Acute stroke	Days: four < 1; others, 7 and 14	
Smith[266]	1985	55	Retrospective	No	Various neurological conditions	Undefined	MR 168 lesions vs CT 86, 55 patients
Steinbrich[267]	1986	55	Undefined	No	Acute stroke	Undefined	'MR demonstrated 11% more infarcts'
Kinkel[253]	1986	350	Retrospective	No	Cerebrovascular disease	Undefined	
Biller[268]	1986	10	Retrospective	No	Pontine infarction	Hours: CT within few hours of hospitalisation, MR unclear	CT 1/10, MR 9/10
Cirillo[269]	1988	192	Retrospective	No	Various neurological conditions	Undefined	MR identified 23 infarcts not seen on CT
Brown[97]	1988	21	Prospective + Retrospective	No	'Lacunar TIAs or strokes of varying chronicity'	Days: 'acute' < 3/7, subacute < 30/7, chronic > 3/12	TIAs: MR 24/25, CT 10/25, recent: MR 13/13, CT 0/12
Imakita[270]	1988	35	Prospective	No	Confirmed or suspected cerebral infarction	Hours: 4 to 27 months	MR enhancement was 'more obvious, more extensive'
Hommel[271]	1990	100	Prospective	No	Lacunar stroke	Days: CT within 4, MR on average 18 days after stroke	MR showed compatible lesions in 89%
Shuaib[272]	1992	116	Retrospective	No	Acute stroke	Days: both done within 10	MR changed management in 18.9%
Krivoshapkin[273]	1992	16	Prospective	No	Patients with EC–IC bypass	Undefined	
Boyko[274]	1992	12	Retrospective	No	Hyperintensities on T1	Undefined	
Fiorelli[275]	1993	2	Prospective	No	Acute stroke	Hours: < 4, scans within 1 h of each other	
Maeda[276]	1999	1	Case report	No	Acute right hemiparesis	Hours: < 3	Lesion seen on both

EC–IC, external cranial–intracranial artery bypass.

neuroimaging twice within the first 24 hours, the first scan negative and the second scan positive for haemorrhage.[117] They suggested that early haemorrhagic transformation may present as primary intracerebral haemorrhage if patients are not scanned very early. Unfortunately, they were unable to document the proportion of patients in their population that this group represented. This study has not been repeated since.

Increasing use of CT and apparent change in the incidence of PICH

Two studies investigated the incidence and outcome of cases of PICH compared with the use of CT. One study found that the incidence of PICH in their institution paralleled the use of CT,[74] and both found that case fatality apparently fell with increasing use of CT;[74,277] that is, smaller, less deadly PICH was being identified with increased frequency as more patients were being scanned with CT. This finding supports the observation in Chapter 2 that PICH has probably been under-recognised as a cause of mild stroke in epidemiology studies.

Summary of studies of CT and PICH

Acute PICH on CT is very characteristic and immediately visible, but the only data on the length of time these features last are anecdotal. No studies were found where the primary purpose was to establish the sensitivity of CT in the identification of haemorrhage at specific time-points after stroke and by severity of stroke. There may be features characteristic of previous haemorrhage on CT, but there are no data on how specific they are or how reliably they can be recognised. Increased use of CT has led to the realisation that PICH can cause mild stroke. This suggests that the mortality associated with PICH has probably been overestimated, owing to the use of data derived from studies with inaccurate diagnostic method and hospital-based series, hence the inherent weakness of clinical scores for determining the cause of stroke (Chapter 2).

MR and the identification of haemorrhage

In total, 2098 references were captured concerning MR and stroke, either alone or in combination with CT. Twenty-two studies (1512 patients) concerning MR and PICH were identified (*Table 7*). Eight studies (235 patients) concentrated on MR alone in PICH.

Four studies were technical, investigating specific MR sequences and their use in PICH.[190,191,195,235] Two of these (of 82 patients) demonstrated the superiority of the gradient echo (GRE) technique in the identification of PICH.[190,195] Five (of 47 patients) were descriptive case studies, documenting the clinical characteristics and signs seen on imaging of haemorrhage on MR.[188,193,194,197,201,208] Six studies (427 patients), although including a small number of patients with haemorrhage, were primarily concerned with comparing CT and MRI in ischaemic stroke, and thus little information on accuracy or sensitivity or specificity could be drawn from these.[198,203,204,206,207,267] None of these studies documented the sensitivity of MR for the identification of PICH. In 14 studies (1239 patients), CT was also performed at some stage. No study set out to determine whether all PICH remained identifiable as such, indefinitely, on MR, or to examine the sensitivity or specificity of different imaging sequences.

MR and asymptomatic haemorrhage

Five studies (653 patients) used MR to investigate the incidence of previous (asymptomatic) haemorrhage, as demonstrated by the presence of breakdown products of haemoglobin[120,121,189,196,202] (*Table 14*). The study populations varied in age and clinical history, and included patients with a history of PICH and those without. In patients with a history of PICH, MR scans were performed 3 days to 2 years after the event. Signs of asymptomatic haemorrhage on MR were identified in between 36% and 66% of patients.

Studies that directly compared CT and MR

In only two studies (165 patients) were MR and CT scanning performed at similar times, enabling some comparison of sensitivity to be made (*Table 15*). One study (published in 2000) investigated the incidence of haemorrhagic transformation in cerebral infarction[205] and the other (published in 1990) the sensitivity of both modes of scanning in intracranial haematoma.[199] Imaging was performed in both studies 'acutely' (less than 2 days), 'subacutely' (between 2 and 10 days) and in the 'chronic' phase (over 10 days). In only one of the studies were images read blinded (to clinical details but not to other imaging[205]). These studies suggested that CT was more sensitive at identifying haemorrhage in the acute phase and MR was better in the chronic phase. One study used specific blood-sensitive sequences (GRE).[199] Neither study mentioned the order in which scans were performed, or whether they were performed on the same day.

One small study (nine patients) that retrospectively compared CT and MR in patients with hyperacute PICH[90] described how MR demonstrated haemorrhage in all cases. The main

TABLE 14 *Studies investigating proportion of patients with asymptomatic haemorrhage as evidenced by haemosiderin deposits on MRI*

Study	Year	Size	Mean age (years)	Study population	Time of MRI from onset on symptoms	MRI sequences used	Proportion of asymptomatic haemorrhage (%)		
							Non-stroke	ICH	Ischaemic stroke
Greenberg[121]	1996	25	76	'Elderly' patients with lobar haematomas	Within 2 years	T1, T2, PD		60	
Offenbacher[189]	1996	120	60	Patients with ICH	Within 4 weeks	T1, T2, PD, GRE in 38 patients		33	
Kwa[120]	1998	221	62	Previous ischaemic stroke, MI or peripheral vascular disease	Mean interval 6 months	FSET2, multiplanar GRE	4		26
Tanaka[196]	1999	89	62	Patients with ICH	Not specified	FSET2, axial T2 EPI	25.4	56.7	
Kinoshita[202]	2000	198	64	Haemorrhagic or multiple lacunar stroke	Within 4 weeks	FSE T2, GRE-EPI*	5	66	68

TABLE 15 *Studies in which patients with ICH were scanned serially with both CT and MRI: proportion of scans with identified haemorrhage at each time stage*

	Year	Acute phase (%)		Subacute phase (%)		Chronic phase (%)	
		CT	MRI	CT	MRI	CT	MRI
Steinbrich[199] (haematoma)	1990	93	46	58	97	17	93
Mayer[205] (haemorrhagic transformation)	2000	0	0	33	38	37	80

TABLE 16 *Range of sensitivities of CT in the positive identification of ischaemic stroke: studies grouped according to timing of scanning from onset of stroke symptoms*

Timing of scanning	Range of sensitivity of CT	Study references
< 6 hours	0.47–0.8	215, 216, 218–221
< 2 days	0.4–0.81	57, 209, 211, 214
< 7 days	0.63–0.95	57, 207, 212
> 7 days	0.74–0.77	211, 214
Undefined	0.49–0.63	208, 213, 217

conclusion of the study was that acute haemorrhage could be detected on MR as easily as CT, which is generally held not to be the case. The methodological weakness of the study (patients were retrospectively identified from an already highly selected cohort, and images were read unblinded by stroke physicians highly trained in MR interpretation) makes their conclusion impossible to extrapolate to a more general stroke population investigated prospectively and without the benefit of concurrent CT.

Summary of studies involving MR in PICH

There were no studies investigating the length of time for which signs of haemorrhage persist on MR after stroke. There were no studies concentrating on the feasibility of MR in an unselected stroke population, or the acceptability of MR for patients. No study gave details of the absolute proportion of patients presenting to their hospital with stroke symptoms who were not scanned because MR was unavailable, or in whom MR was deemed unsafe or contraindicated. The only studies that directly compared CT to MR in the detection of ICH were small (138 patients in total) and had substantial flaws in their study method, making their conclusions difficult to generalise to an unselected stroke population.

Studies of imaging in cerebral infarction

CT and the positive identification of cerebral infarction

No study examined a population from which an estimate of specificity could be made. The sensitivity of CT in the demonstration of an appropriate ischaemic lesion varied from 0.4 to 0.95. With the exception of one study in which some images were read by two neurologists,[215] all images in included studies were read by radiologists or neuroradiologists. In an attempt to identify factors other than case-mix that had an effect upon sensitivity, studies were grouped according to timing of scanning, and whether studies were retrospective or prospective. As ischaemic lesions become more obvious with time,[25] it was assumed that if timing of scanning in relation to symptoms was the only major feature in determining sensitivity, then the lowest values would be for those studies performing scanning at the earliest time-points. This was not found to be the case; in fact, some of the highest values for sensitivity were recorded from studies in which scans were performed within 6 hours (*Table 16*). Grouping studies by whether images were read prospectively rather than retrospectively made no difference, the ranges for sensitivity of positive identification being 0.4–0.95 and 0.53–0.81, respectively.

Interobserver agreement in CT scan interpretation in cerebral infarction

Twelve studies documented the observer agreement for interpretation of CT scans, or the interobserver reliability of interpretation of scans using kappa values. The kappa statistic[278] is a measure of agreement between two observers beyond that expected from chance alone, where $\kappa = 0$ indicates agreement no better than chance, $\kappa = 1$ perfect agreement, $\kappa = 0$–0.2 poor agreement, $\kappa = 0.21$–0.4 fair agreement, $\kappa = 0.41$–0.6 moderate agreement, $\kappa = 0.61$–0.8 good agreement and $\kappa = 0.81$–1 excellent agreement.

None of the seven studies that documented kappa values (994 scans)[279–285] was designed to imitate the reading of scans in a true clinical situation. All included selections of retrospectively collected scans of patients with acute stroke (including scans from four thrombolysis trials) that were presented to different observers. They were asked to identify the presence of varying indicators of ischaemia, and kappa values were calculated for level of agreement (*Table 17*). With the exception of the identification of haemorrhagic transformation, there was no sign of ischaemia that could be identified by all observers with better than moderate agreement.

The six studies (948 scans) that documented observer agreement as either proportions in agreement or percentage accuracy, tended to mirror more closely real clinical situations[223,286–290] (*Table 18*). Two studies documenting accuracy of

TABLE 17 *Interobserver reliability of CT scan interpretation: kappa values*

Study	Year	Size	Type of CT scan (timing)	No. of observers (type)	Lesion on CT to identify	Images read blinded?	Results
Schneider[279]	1991	74	Lacunar syndromes (unspecified time)	10 (varying in expertise)	Lacunar infarcts, leucoaraiosis, cerebral atrophy	Yes[a]	κ=0.64 (decreased density), κ=0.45 (lacunar infarcts)
Wardlaw[280]	1994	119	Patients with acute stroke symptoms (2 h to 3 months)	8 (2 experts and 6 trainees)	Infarct site, swelling, haemorrhagic transformation	Yes[b]	κ=0.78 (all scans), κ=0.87 (medium/large), κ=0.59 (small), κ=0.8 (swelling), κ=0.3 (haemorrhagic transformation)
von Kummer[281]	1996	45	CTs with MCA infarct signs and normals (within 6 h of stroke)	6 neuroradiologists	HMCAS, swelling, parenchymal hypodensity	Yes[b]	κ=0.62/0.57 (HMCAS L/R). κ=0.59/0.56 (swelling), κ=0.58/0.55 (parenchymal hypodensity)
von Kummer[282]	1997	603	CTs of patients randomised in ECASS (within 6 h)	3 neuroradiologists	Whether recent ischaemia; amount of parenchymal hypoattenuation	Yes[a]	κ=0.34 (recent ischaemia), κ=0.36 (amount of swelling)
Besson[283]	1998	33	MAST-E scans (within 6 h)	3 neurologists	Early infarct signs, intracranial haematoma, haemorrhagic transformation	Yes[a]	κ=1.0 (haematoma), κ=1.0 (HTI), κ=0.43 (early infarct signs)
Marks[284]	1999	50	CTs from patients randomised in ATLANTIS (thrombolysis), (within 6 h)	3 neuroradiologists	Parenchymal hypodensity, HMCAS	Yes[b]	κ=0.65, 0.44, 0.50 for each pair of observers (hypodensity), κ=0.33, 0.2, 0.63 (HMCAS)
Grotta[285]	1999	70	CTs from NINDS thrombolysis trial (within 3 h)	16 (emergency physicians, neurologists, radiologists)	Early infarct signs	Yes[c]	κ=0.3 (parenchymal hypodensity), κ=0.2 (hypodensity > 33%), κ=0.33 (any early sign)

[a] Blind to clinical history, [b] blind to both, [c] blind to other imaging.
ATLANTIS, Acute Thrombolysis in Ischaemic Stroke; ECASS, European Cooperative Acute Stroke Study; HMCAS: hyperdense middle cerebral artery sign; MAST-E, Multicenter Acute Stroke Trial – Europe; MCA, middle cerebral artery; NINDS, National Institutes of Neurological Disorders and Stroke.

TABLE 18 *Interobserver reliability of CT scan interpretation: percentage accuracy/proportion in agreement*

Study	Year	Size	Type of CT scan	No. of observers (type)	Lesion on CT to identify	Images read blinded?	Results
Roszler[286]	1991	289	Emergency room CT	Undefined	Any pathological lesion	No	98% accuracy in interpretation
Alfaro[287]	1995	555	Emergency room CT	Undefined (emergency physicians versus radiologists)	Any pathological lesion	No	88.6% accuracy in interpretation
Pullicino[288]	1996	20	Infarcts on CT	4 (2 neurologists and 2 neuroradiologists)	Infarct size	No	Intraclass correlation coefficient values used; overall=0.98
Von Kummer[223]	1996	44	Cerebral hemisphere stroke	One	Parenchymal low-density and/or focal brain swelling	Yes[a]	82% sensitivity (36/44) for ischaemia
Schriger[289]	1998	15	Selection of old and new infarcts, calcification, haemorrhage and normal	38 emergency physicians, 29 neurologists, 36 general radiologists	Infarction (acute or old), haemorrhage, calcification	No	Overall accuracy in interpretation: emergency physicians=67%, neurologists=83%, radiologists=83%
Kalafut[290]	2000	25	Normals, acute and old infarcts	3 neuroradiologists	Amount of parenchymal hypoattenuation	No	Interpretation of >1/3 MCA territory: 64%; agreement between all 3 moderate

[a] Blind to clinical history other than 'stroke', and other imaging.

interpretation of scans by emergency physicians noted 87–98% accuracy for all pathological lesions.[286,287] Accuracy fell to 67% when emergency physicians were asked to identify lesions pertinent to the interpretation of ischaemia and haemorrhage only.[289] In this study, neurologists and radiologists interpreted ischaemia and haemorrhage on scans with greater accuracy (83%). In a study where one neuroradiologist (blinded to clinical history other than 'stroke' and all other imaging) assessed CT scans performed within 6 hours of stroke for parenchymal hypodensity and brain swelling, the sensitivity of interpretation was 82%,[223] However, in another study investigating agreement for whether there was greater than one-third involvement of the middle cerebral artery territory (a scan criterion put forward as a contraindication to thrombolysis[291]), there was still only 64% agreement between neuroradiologists.

Studies of MRI in the positive diagnosis of cerebral infarction

Among the 15 studies (1560 patients) that included patients assessed at some stage by a neurologist or stroke physician, only four studies of three quite different groups of patients reported values for sensitivity (*Table 9*). Two studies (64 patients) that scanned patients within the initial 2 days after stroke found sensitivities of 84%[227] and 88%[226] compared with follow-up MR. One study (53 patients) found a sensitivity of 65% for fluid-attenuated inversion recovery (FLAIR) MR in patients scanned within 6 hours of their stroke compared with follow-up scan.[225] One study of 79 patients with clinical transient ischaemic attacks found a sensitivity of 35% for clinically compatible lesions.[224]

Studies of CT and MRI in the positive identification of cerebral infarction

In the two studies (82 patients) that included patients with TIA, MR was markedly better at demonstrating ischaemic lesions in one study (21% on CT compared with 68% on MR[203]), but less obviously better in the other (MR demonstrated lesions not seen on CT in 14%, but CT demonstrated lesions not seen on MR in 9%[228]).

In all four studies (356 patients) of unselected stroke patients, the proportions of scans that demonstrated ischaemic lesions ranged from 43 to 68% for CT, and 51 to 98% for MR[204,206,207,234] (*Table 19*). Only one study tested the difference between the two scan findings statistically and found no significant difference.[207] In the study where the difference in positive identification was most marked, MR had been performed up to 1 week after CT.[206] One study documented the results of two observers interpreting CT and MR in stroke and found considerable differences between their interpretation of images (positive

TABLE 19 *Sensitivity of CT and MRI in the positive identification of ischaemia in unselected strokes*

Study	Proportion of images demonstrating clinically compatible lesion (%)	
	CT	MRI
Kertesz[204]	51	82
Bryan:[234]		
Observer 1	48	77
Observer 2	68	87
Arias[206]	52	98
Mohr[207]	43	51

TABLE 20 *Sensitivity of CT and MRI in the positive identification of ischaemic lacunar stroke*

Study	Proportion of images demonstrating clinically compatible lesion (%)	
	CT	MRI
Rothrock[230]	17	92
Miyashita[232]	44	89
Arboix[233]	30	78
Stapf[235]	50	94

findings on CT ranged from 48–68%, and for MR from 77 to 87%).

In all four studies of lacunar strokes, MR demonstrated more clinically compatible lesions (*Table 20*). The proportion of ischaemic lesions identified on scans ranged from 17 to 50% for CT and 78 to 94% for MR.[230,232,233,235] In one study, MR scans were performed 1–3 days after CT;[235] in the rest, the order of scanning was not defined.

In the two remaining studies, MR was consistently superior in the positive identification of ischaemic stroke, both in the cerebellum (100%, 14/14 compared with 43%, 6/14 for CT[229]) and in lateral medullary syndrome (83%, 5/6 compared with 33%, 2/6 for CT[231]). Both studies had a very small sample of retrospectively collected data.

Primary study comparing CT with MRI

Background

It was evident from the foregoing that there was not enough specific information on the sensitivity or specificity of CT or MRI for the diagnosis of infarct or haemorrhage. In particular, the length of time that small haemorrhages might remain visible on CT, and the proportion of patients with mild strokes (i.e. the sort that would present as outpatients late after the stroke) who had a PICH as the cause of their stroke were unclear.

Small studies[55,136] have demonstrated that haemorrhage on CT will become indistinguishable from ischaemic stroke within 9 days. Were the patients in these studies isolated findings? How representative of the stroke population were they? MR can identify haemorrhage at some time after ictus,[120,121] but for how long afterwards, and does MR reliably identify *all* old haemorrhage? Detection of old haemorrhage on MR relies on the paramagnetic effects of the haemoglobin breakdown product, haemosiderin, which is thought to persist indefinitely in macrophages at the edges of old haematomas. However, pathological studies have demonstrated that not all haematomas form haemosiderin.[292] The proportion of haematomas in which this may occur, however, is unknown, as no systematic follow-up study has been performed with either pathology or MR. About 10% of old traumatic parenchymal haematomas do not show haemosiderin formation on MR.[137] Previous studies of PICH did not provide information as to whether a similar proportion of PICH do not form haemosiderin.

The 1999 Stroke Association Survey found that about 15% of patients with stroke symptoms are not admitted to hospital in the UK,[67] and are managed in the community (around 22,000 people per year). These patients are likely to be considered for aspirin or anticoagulation for secondary prevention. What proportion of this population of 22,000 people may have had PICH?

To investigate these questions, two prospective observational studies were performed.

- The late haemorrhage study: the aim was to investigate the length of time and the proportion of haemorrhages that remain visible on MR following PICH. A further aim was to investigate the sensitivity of various MRI sequences.
- The CT versus MR study. The aim was to investigate the sensitivity of CT and MR imaging in the detection of haemorrhage in patients with mild stroke symptoms presenting to an outpatient clinic. A further aim was to determine what effect this knowledge would have on clinical decision-making and determine how quickly small haemorrhages become indistinguishable from infarcts on CT.

Methods: MR late after haemorrhage study

Patient recruitment

Patients were identified from the Lothian Stroke Register (LSR).[57] Those diagnosed on CT as having a stroke due to PICH, between February 1991 and February 1999, who had had the PICH at least 3 months before this study and were still alive were invited to attend for an MR scan. Permission was obtained from the stroke physician and the patient's GP before contacting the patient. Any patients with contraindications to MR (e.g. pacemaker, intracranial aneurysm clip) were excluded from the study. Approval for the study was obtained from the Lothian Ethics Committee.

Image acquisition

The MRI was performed on an Elscint 2T Prestige scanner. The following sequences were performed: T1-weighted sagittal (T1-WI, TR 500 ms, TE 12 ms, 1 NEX), T2-weighted fast spin-echo (FSE T2, TR 5000 ms, TE 96 ms, 1 NEX), spin-echo T2-weighted (SET2), FSE proton density (PD, TR 2300 ms, 16 ms, 1 NEX), FLAIR (TR 6000 ms, TE 2000 ms, TI 126 ms, 1 NEX) and GRE (TR 510 ms, TE 18 ms, 2 NEX) axial sequences. The slice thickness was 5 mm and the slice gap 5 mm, with a 22.0 × 22.0 field of view and a 256 × 128 matrix. Total scanning time was about 30 minutes (from

the time the patient was put in the scanner to coming out). The original CT scans from the time of the PICH were retrieved from the X-ray department files.

Image analysis

MR images were read by one neuroradiologist, blind to the patient's clinical signs (other than they had had a PICH somewhere in the brain, sometime in the past) and baseline CT, or the time elapsed from the original event. MR scans were read independently of the original CT scan. MR sequences were read independently of each other in batches of the same sequence, with a suitable interval of time (minimum of 2 weeks) between batches to prevent recall of the findings of other sequences. The baseline CT scans were read after all the MR images had been read to identify the presenting PICH.

Data recorded

From the baseline CT scan, the following were noted:

- the sites of the haematoma(s) (primary lesions)
- the estimated volume of haematoma (maximum length and width, multiplied by the slice thickness (mm) and the number of slices on which the haematoma was seen)
- any other findings (secondary lesions), for example infarcts.

Lesions identified on follow-up MR sequences were coded as:

- visible as haemorrhage: if there was more than one haematoma, the largest haematoma was recorded as the primary lesion; if there was evidence of haematoma and infarct together, the lesion was documented as haematoma first, and other lesions were recorded as secondary
- visible as infarct: if there was more than one infarct, the largest infarct was recorded as the primary infarct
- uncertain
- not visible
- scans were also coded for atrophy, leucoaraiosis, enlarged perivascular spaces (on FSE T2), small-vessel disease in the white matter (FLAIR) and microhaemorrhage in the basal ganglia or elsewhere (GRE).

Once reading was complete the information from CT and MR was matched. It was then possible to determine whether any of the lesions seen on MR had developed in the interim between the original index PICH and the MR. If an MR scan demonstrated multiple haematomas, it was compared at this stage with the original CT to identify which was the primary lesion and which the secondary lesion.

Data analysis

Results were entered into a Microsoft Excel spreadsheet and an SPSS (Statistical Package for Social Sciences) database, and analysed with simple descriptive statistics.

Results: MR late after haemorrhage study

Patients, tolerability and inadequate scans

Seventy patients were identified in the LSR as having had a CT proven PICH between February 1991 and February 1999, and known to be alive at the last follow-up, but 17 were found to have died in the interim. Thus, 53 patients with PICH on CT were invited to return for follow-up MR scanning. One patient died before attending, one had aneurysm clips, 13 patients declined or were unable to attend, 11 did not attend for their appointments and one patient attended but was claustrophobic. A total of 26 people were scanned with both CT and MR. Three people had two primary haematomas on their CT scan; therefore, the MR results of a total of 29 haematomas were documented. Of a total of 156 MR images, only three were uninterpretable (two FSE T2 sequences, one FLAIR sequence) owing to patient movement or because the imaging had to be discontinued because of patient intolerance.

Baseline characteristics

The mean age of patients was at time of scanning 66.5 years (median 69 years, range 42–87 years). The mean time from PICH to follow-up MR scanning was 39.9 months (median 30.7 months, range 7.6–110.3 months). The mean haematoma volume was 23.9 cm^3 (median 18 cm^3, range 1–80 cm^3) (*Table 21*). There were five frontal lobe haematomas, 10 in the basal ganglia, two in the thalamus, four in the parietal lobe, two in the temporal lobe, three in the occipital lobe, one in the occipitoparietal lobe, and two in the brainstem/cerebellum.

Findings on follow-up MR sequences

The proportion of haemorrhages identified varied between the five MR sequences. GRE identified all haemorrhages (100%). Spin-echo T2 identified haemorrhage on 28/29 (97%), FSE T2 identified 27/29 (93%), PD identified 17/29 (59%) and FLAIR failed to identify any lesions as old haemorrhage (*Table 22*).

TABLE 21 *Late haemorrhage study: baseline characteristics*

	Mean	Median	Range	SD
Age (years)	66.5	69	42–87	10.9
Time from CT (months)	39.9	30.7	7.6–100.3	22.9
Infarct volume (cm^3)	23.9	18	1–80	22.9

TABLE 22 *Late haemorrhage study: corresponding findings on different sequences at follow-up MRI*

	MRI sequence (%)				
Scan finding	**Spin-echo T2**	**PD**	**FSE T2**	**FLAIR**	**GRE**
Lesion visible as haemorrhage	28 (97)	17 (59)	27 (93)	0	29 (100)
Lesion thought to be infarct	0	5 (17)	0	18 (62)	0
Uncertain	0	2 (7)	0	1 (3)	0
No residual lesion	1 (3)	5 (17)	0	9 (31)	0
Scan uninterpretable	0	0	2 (7)	1 (3)	0

The longest interval from CT to follow-up MR was 8.4 years, and concerned a right hemisphere 1 cm^3 basal ganglia lacunar haemorrhage that was still visible on T1, T2 and GRE sequences as haemorrhage. No patient or brain imaging features, such as timing of scan, age of patient or size of haematoma, distinguished the haematomas that did remain visible from those that did not on any of the sequences.

Any secondary lesions seen on initial CT are documented in *Table 23*, with the corresponding findings on follow-up MR. In 19/26 patients (73%), an infarct not documented on the initial CT was seen on at least one sequence of follow-up MR. In 12/26 (46.2%), there was evidence of definite new, presumably asymptomatic haemorrhage occurring since the original CT.

Other findings on follow-up MR are documented in *Table 24*. GRE identified haemorrhagic 'spots' in the basal ganglia and cortex in eight (28%) patients. FLAIR identified small-vessel disease on 18 (62%). FSE T2 identified enlarged perivascular spaces on 16 (55%). Atrophy was identified on 20 scans (69%).

Methods: the CT versus MR study

Patient recruitment

Between August 1998 and July 2000, patients presenting to the Western General Hospital with minor stroke symptoms (defined as symptoms lasting for longer than 1 day but causing little or no diminishing of functional ability), or presenting more than 5 days after onset of stroke symptoms regardless of stroke severity, were scanned on the day of presentation with CT and MRI. A few patients in whom it was felt that the MRI could contribute specifically to diagnosis and who presented within 1 day of onset of symptoms were also included. The majority of the population recruited were outpatients presenting to a neurovascular clinic, and all were assessed before scanning by a consultant stroke physician or a clinical research fellow in stroke medicine. Patients were classified according to the OCSP classification,[9] and the Canadian Neurological Score (a neurological disability score ranging from 1.5, indicating very severe stroke, to 10, indicating little or no residual disability).[299] Medically unstable patients, and patients with contraindications to MRI (e.g. pacemaker, intraocular metal, intracranial aneurysm clips) were excluded.

Image acquisition

The order of scanning was determined by the availability of each scanner; that is, not randomly. CT was performed using a GE spiral scanner (17 images, 5 mm slice thickness, total scan time from patient going into the scanner to patient coming out the scanner was about 7 minutes). MRI was performed on two scanners; up to October 1999 using an Elscint Prestige 2T scanner, and from January 2000, using a GE 1.5 Signa Horizon LX scanner. Patients underwent routine structural MRI and the imaging parameters for the two scanners were as follows: on the Elscint scanner, T1-weighted sagittal images (TR 500 ms, TE 12 ms, 1 NEX), FSE T2 (TR 5000 ms, TE 96 ms, 1 NEX), PD (TR 2300 ms, 16 ms, 1 NEX), FLAIR (TR 6000 ms, TE 2000 ms, TI 126 ms, 1 NEX) and GRE (TR 510 ms, TE 18 ms, 2 NEX) axial images. The slice thickness was 5 mm and the slice

TABLE 23 *Secondary lesions on CT and secondary findings on follow-up MRI*

CT findings		Secondary lesion finding at follow-up MRI				
Site of primary lesion (haematoma) on CT	**Secondary lesions on CT**	**T1/FES T2**	**FSE PD**	**SE T2**	**FLAIR**	**GRE T2**
R basal ganglia lacune	None	None	None	?Haemorrhage L basal ganglia, infarct L cerebellum	Infarct L lacune	Haemorrhage spots L basal ganglia, pons, R thalamus
R frontal lobe	Infarct R occipital lobe	Old secondary lesion still visible	None	Haemorrhage L parietal lobe	None	Old secondary lesion still visible and haemorrhage (and haemorrhagic transformation) L parietal lobe ×2
L basal ganglia/caudate	Infarct R centrum semiovale lacune	Old secondary lesion still visible	None	None	Infarct R centrum semiovale lacune	None
R basal ganglia	None	Haemorrhage superior cerebellum	Haemorrhage L thalamus	Haemorrhage superior cerebellum, R frontal lobe, L thalamus	None	Haemorrhage black spots everywhere
L anterior temporal lobe	None	None	None	Infarct R frontal lobe	None	None
L temporal lobe	None	None	None	None	None	Haemorrhage black spots R frontal, L parietal lobe
L basal ganglia	None	Infarct L temporal lobe	Infarct R centrum semiovale lacune	None	None	Haemorrhage R basal ganglia
R parietal lobe	Infarct L basal ganglia lacune	None	None	None	None	Old secondary lesion still visible
R basal ganglia	None	Infarct L parietal lobe, L centrum semiovale lacune	None	Haemorrhage? L basal ganglia, infarct ?old R parietal lobe	Infarct lots of lacunes	None
Mid pontine	None	Infarct R thalamus lacune L centrum semiovale lacune	None	Scan unreadable	None	Infarct L basal ganglia lacune
L parieto-occipital lobe	None	None	None, infarct R centrum semiovale lacune	None	None	Haemorrhage L thalamus dot

continued

TABLE 23 *Secondary lesions on CT and secondary findings on follow-up MRI (cont'd)*

CT findings		Secondary lesion finding at follow-up MRI				
Site of primary lesion (haematoma) on CT	**Secondary lesions on CT**	**T1/FES T2**	**FSE PD**	**SE T2**	**FLAIR**	**GRE T2**
R thalamus	None	Infarct R centrum semiovale lacune, R thalamus lacune	None	Scan unreadable	None	Haemorrhage black dots L thalamus, lentiform nucleus
L basal ganglia	Infarct L MCA, R cerebellum	Old secondary lesion still visible	None	None	Infarct L parietal border zone	
R frontal lobe and L occipital lobe	Infarct R occipital lobe	L cerebellum	None	Infarct L cerebellum	Infarct L parietal cortex	Haemorrhage R occipital lobe (not infarct as on CT), L frontal, R parietal dots
R cerebellum and R frontal lobe	None	None	None	Haemorrhage R temporal lobe, infarct R centrum semiovale lacune	Infarct R centrum semiovale lacune	Haemorrhage R posterotemporal lobe, infarct R centrum semiovale lacune, haemorrhage black dots everywhere
L basal ganglia	None	None	None	Infarct L parieto-occipital lobe	Infarct L parieto-occipital lobe	Infarct L parieto-occipital lobe
R basal ganglia	None	Infarct none, L basal ganglia lacune	None	None	None	None
L basal ganglia	None	None	None	None	None	Haemorrhage R basal ganglia
R occipital lobe and L parietal lobe	None	Infarct none, R cerebellum	None, ?haemorrhage: tiny L basal ganglia	None	Infarct R cerebellum lacune	Haemorrhage black spots everywhere
L parietal lobe	Infarct R fronto-parietal and R occipital lobe	Old secondary lesion still visible, infarct L cerebellum	Old secondary lesion still visible	Haemorrhage R frontal (not infarct as on CT)	None	Old secondary lesion still visible, haemorrhage:black spots everywhere

R, right; L, left.

TABLE 24 *Late haemorrhage study: other findings on follow-up*

	n	(%)
Atrophy	20	69
Perivascular spaces (T2)	16	55
Small-vessel disease (FLAIR)	18	62
Haemorrhage spots (GRE)	8	28
Basal ganglia spots (GRE)	8	28

gap 5 mm, with a 22.0 × 22.0 field of view and a 256 × 128 matrix. On the GE Signa Horizon scanner, T1-weighted sagittal images (TR 440 ms, TE 9 ms, 2 NEX), T2-weighted axial (TR 6300 ms, TE 106 ms, 2 NEX), PD (TR 2000 ms, TE 9.8 ms, 4 NEX), FLAIR (TR 10002 ms, TE 147 ms, TI 2500 ms, 1 NEX), and GRE (TR 2599 ms, TE 80, 4 NEX) images. The slice thickness was 5 mm and the slice gap 5 mm with a 24.0 × 24.0 field of view and a 256 × 256 matrix.

Patient preference questionnaire

Following completion of scanning, patients were asked to complete a questionnaire on the tolerability of both scanning procedures. They were asked what type of scan they had undergone first, which scanner they preferred, and whether they would have either CT or MR again if they had to. They were also asked for any additional comments.

Image analysis

CT and MR images were read independently of each other by one neuroradiologist, using forms generated using Microsoft Access, which included a brief clinical history. Scans were classified as showing:

- recent (ischaemic) infarct
- recent infarct with haemorrhagic transformation (HTI)
- recent haemorrhage
- old lesion probable infarct
- old lesion probable haemorrhage
- multiple periventricular lucencies
- cortical atrophy
- another diagnosis (e.g. tumour)
- no abnormality.

'Recent' was taken to mean consistent with the duration of symptoms given in the brief clinical history. 'Old' was taken to mean a lesion that appeared older than the clinical history.

Effect of scan results on clinical decision-making

Nine physicians with an interest in stroke were presented with a selection of anonymised histories of scanned patients, initially without imaging results. They were asked for their strategy for secondary prevention for the patient in terms of the use of antiplatelet drugs or anticoagulants, or referral for carotid endarterectomy. On the decision forms were details of ECG, echocardiography or carotid Duplex scanning if these had been performed. On each occasion, each physician was asked to rate their confidence in their diagnosis in terms of percentage for: stroke versus non-stroke, haemorrhage versus ischaemic stroke, and cause of haemorrhage or ischaemic stroke. They were not required to state a definitive diagnosis. They were initially instructed to decide on a management strategy assuming that no neuroimaging would be performed. After a number of weeks (not less than four), they were presented with the histories (each physician being given the same histories as they had had originally), along with a brief report of the CT findings, and asked again for their secondary prevention strategies. After a number of weeks, they were again given their respective patient histories, this time with the results of MRI.

Data analysis

Data on scan findings and the doctors' decisions were entered along with baseline characteristics, brief histories and relevant associated investigations onto a password-protected Access database. The proportions of haemorrhage and HTI on CT and MR were analysed with simple descriptive statistics and confidence intervals. The effect on doctor's decisions was determined by the number of altered decisions; a prospective power calculation identified that, assuming the CT result altered management in 10% of patients, and MR altered management in 10% of patients in whom the CT result is already known, a study population of 225 patients would have an 80% power to detect this 10% difference at the 95% significance level. Differences in the degree of certainty of diagnosis were analysed using a single-sample *t*-test. Differences between doctors were analysed with analysis of variance (ANOVA), using SPSS. The neurologist reading the scans completed a small sample of scans twice, and two stroke physicians

TABLE 25 *CT versus MRI study: baseline characteristics*

	Age (years)	Time from onset of symptoms to scanning (days)	Canadian Neurological Score at examination
Mean	67.5	21.5	9.5
Median	68.0	20	9.5
Range	35–89	1–112	5.5–10
SD	9.9	15.3	1.0

TABLE 26 *CT versus MRI study: distribution of stroke subtype according to the OCSP classification*

Subtype	*n*	(%)
PACS	95	42
LACS	73	32
POCS	36	16
Undefined	24	10
Total	228	100

Table 27 *CT versus MRI study: agreements, disagreements and corresponding findings on CT and MRI*

	CT findings[a]									
MRI findings[a]	RI	HTI	RH	OLPI	OLPH	MPVL	CA	Normal	Tumour	Total
RI	86	1	0	8	0	7	7	12	1	122
HTI	10	2	1	1	0	1	0	0	0	15
RH	5	0	2	1	0	0	0	0	0	8
OLPI	2	0	0	4	0	2	0	1	0	9
OLPH	2	0	0	0	0	0	1	2	0	5
MPVL	9	0	0	0	0	3	9	8	0	29
CA	1	0	0	1	0	0	6	1	0	9
Normal	4	0	0	2	0	0	3	19	0	28
Other	0	0	0	0	0	0	0	0	3	3
Total	119	3	3	17	0	13	26	43	4[b]	228

[a] Because of overlapping reporting of OLPI, OLPH and incidental meningioma with other more principal diagnoses, the only scans documented with this finding here are those where these were not associated with recent infarct, recent haemorrhage or HTI.
[b] CT identified a further meningioma in a patient with a recent infarct, thus giving a total of five meningiomas identified.
RI: recent infarct; HTI: haemorrhagic transformation; RH: recent haemorrhage; OLPI: old lesion probable infarct; OLPH, old lesion probable haemorrhage; MPVL, multiple periventricular lucencies; CA, cortical atrophy.

also completed a small sample of decisions twice to check intraobserver variation.

Results: the CT versus MR study

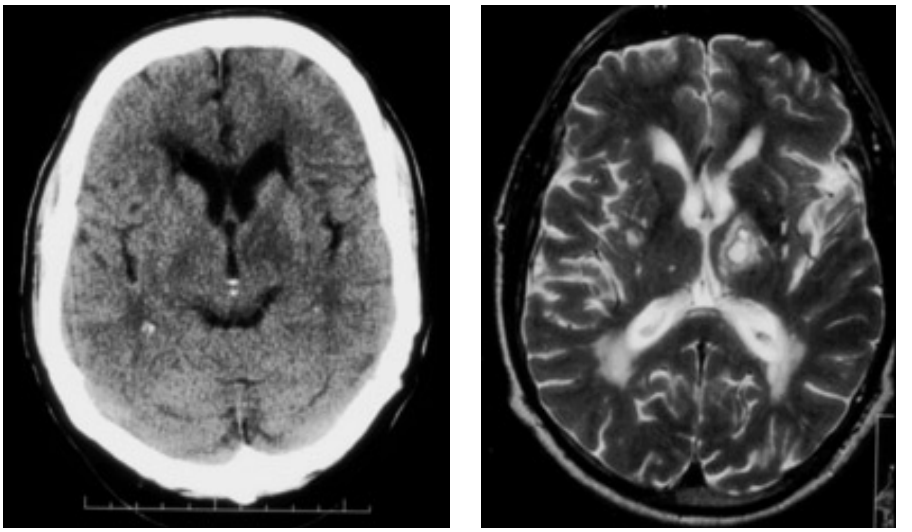
Patient baseline characteristics and tolerability of scanning

In total, 232 patients were recruited; MR was not performed in four patients (1.7%) (three patients were claustrophobic, one was too large for the scanner). A total of 228 patients had both CT and MR. No images were uninterpretable.

The mean age of the population was 67.5 years (median 68 years, range 35–89 years). The mean Canadian Neurological Score was 9.5 (median 10, range 5.5–10). The mean time from onset of stroke symptoms to scanning was 21.5 days (median 20 days, range 1–112 days) (*Table 25*). According to the OCSP classification, there were 95 (41.7%) PACS, 73 (32%) LACS, 36 (15.8%) POCS, and in 24 (10.5%) it was not possible to define a subtype (*Table 26*). Before scanning (on presentation), 144 (63.2%) were on aspirin, three (1.3%) were on warfarin and 10 (4.3%) were in atrial fibrillation.

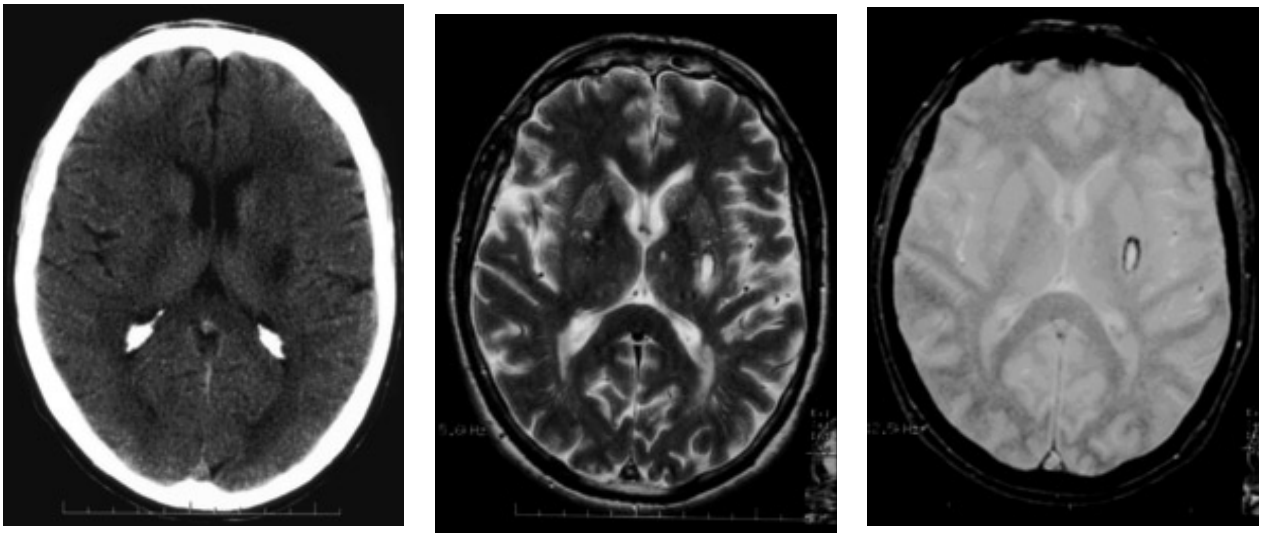
Findings on CT and MR

Table 27 documents the main findings on CT and MR. Note that more than one type of lesion could be found on the same scan (e.g. many scans with a



(a) (b)

FIGURE 3 *A 68-year-old man with right hemiparesis and dysphasia, with mild weakness persisting. (a) CT scan; (b) T2-weighted MR scan. Scans were taken at 11 days.*



(a) (b) (c)

FIGURE 4 *A 60-year-old man with right hemiparesis and right facial numbness, with residual reduced fine finger movements. (a) CT scan; (b) T2-weighted MR scan; (c) GRE MR scan. Scans were taken 21 days after the onset of symptoms.*

recent infarct also had cortical atrophy). The findings on the images of the 228 patients are documented in a hierarchy; that is, PICH, HTI and recent infarct are documented in favour of any other diagnosis. Other diagnoses are documented in the table only if they were the only significant finding on the scan. The findings with regard to haemorrhage and tumours are given below.

Recent haemorrhage

MR identified recent PICH in eight patients (3.5%, 95% CI 1.5 to 6.8%). CT agreed in only two patients (0.9%, 95% CI 0.1 to 3.1%). Corresponding findings on CT when recent haemorrhage was not identified were: recent infarct (five patients) and old lesion probable infarct (one patient). Thus, in patients with recent haemorrhage identified on MR, CT missed the diagnoses in 6/8 (75%) (*Figures 3 and 4*).

Recent infarct with HTI

MR identified HTI in 15 patients (6.6%, 95% CI 3.7 to 10.6%). The extent of haemorrhagic changes seen varied from minor petechial spots to frank haematoma. CT agreed in only two patients (0.9%, 95% CI 0.1 to 3.1%). Corresponding findings on CT when HTI was not identified were:

TABLE 28 *CT versus MRI study: scan findings in patients with haemorrhagic changes and timing of scanning in relation to onset of symptoms*

Code	Extent of haemorrhage	Time from scan (days)	X-ray history
3439	PICH	11	R hemiparesis and dysphasia, mild weakness persists
4336	PICH	13	Mild R haemiparesis including face, residual mild R facial weakness
4417	PICH	14	R arm and hand numbness lasted 2 days, persistent reduced fine finger movements
4119	PICH	17	Ataxia, blurring of R field of vision, no residual neurological signs
4636	PICH	21	Right arm and leg weakness and facial numbness, residual reduced fine finger movements
3995	PICH	28	Headache, scarred vision, persistent L inferior quadrantonopia
4548	HTI medium	6	Receptive and expressive dysphasia, R homonymous lower quadrantonopia unresolved
3996	HTI medium	19	Expressive dysphasia, mostly improved
3043	HTI medium	20	Vomited, ataxia, falling to right, no residual neurological abnormality
3766	HTI medium	28	Probable R homonymous hemianopia, no residual signs, possibly migraine
4042	HTI medium	28	4 transient episodes of right facial numbness, one associated with right hand paraesthesia
3654	HTI medium	56	20 minute episode of dysarthria followed by persistent L homonymous field deficit
4135	HTI trivial	5	R lower homonymous field defect, dysphasia, R inattention
4414	HTI trivial	14	Dysarthria, noted L facial weakness, still persists (mild)
4137	HTI trivial	21	Transient L hand weakness then following day R hand weakness; residual decreased sensation R hand
3693	HTI trivial	28	Expressive dysphasia, almost back to normal; R arm weakness when tired for last year
3824	HTI trivial	28	R arm weakness and expressive dysphasia, mostly resolved
824	HTI trivial	49	L homonymous field defect 3 days following thrombolysis for MI
4067	Seen on CT	4	Word-finding difficulty and difficulty with comprehension for 1 week
4113	Seen on CT	9	Left hand weakness, symptoms improving but still there
4403	Seen on CT	14	L hemiparesis (mild) and pins and needles; residual mild facial defect
4220	Seen on CT	17	Dysarthria, L arm sensory disturbance, L leg weakness, symptoms (mild) persist in leg
4581	Seen on CT	18	Headache followed by confusion, dressing apraxia, residual R homonymous hemianopia

recent haemorrhage (one patient), recent infarct (10 patients), old lesion probable infarct (one patient), multiple periventricular lucencies and cortical atrophy only (one patient). CT therefore missed the haemorrhagic changes seen on MR in 12/15 (80%). CT identified HTI on one scan that was interpreted as recent infarct only on MR. On review of both scans, the CT result was judged to be incorrect, the changes seen on imaging being due to the contrast of normal cortex next to infarct, as there was no evidence of haemorrhage on GRE MR.

Timing of scans identifying haemorrhage

The range of times from onset of symptoms to scan for both CT and MR in patients found to have either recent haemorrhage or HTI along with clinical presentation is documented in *Table 28*. The shortest time from onset of symptoms to scan when HTI was missed on CT was 4 days, and the shortest time PICH was missed on CT was 11 days (although this may have been sooner if scans were performed earlier). The two patients in whom CT correctly identified recent haemorrhage were scanned 9 and 14 days after stroke.

Old lesion, probable haemorrhage

Signs suggestive of an old lesion that was probably haemorrhagic were seen on 15 MR scans (6.6%, 95% CI 3.7 to 10.6%) but no CT scans. They were the only significant findings in five patients (2.3%). In the remaining ten, these signs were

TABLE 29 *CT versus MRI study: CT showed recent infarct, corresponding MR findings*

Scan findings	No. of findings on MR (%)
Recent infarct	86 (72.2)
Recent infarct and haemorrhagic transformation	11 (9.2)
Recent haemorrhage	3 (2.5)
Old lesion probable infarct	4 (3.4)
Old lesion probable haemorrhage	2 (1.7)
Multiple periventricular lucencies and/or cortical atrophy	12 (10.1)
Tumour	0 (0)
No abnormality	4 (3.4)
Total	119

TABLE 30 *CT versus MRI study. MR showed recent infarct, corresponding CT findings*

Scan findings	No. of findings on CT (%)
Recent infarct	86 (70.5)
Recent infarct and haemorrhagic transformation	1 (0.8)
Recent haemorrhage	0 (0)
Old lesion probable infarct	8 (6.6)
Old lesion probable haemorrhage	0 (0)
Multiple periventricular lucencies and/or cortical atrophy	14 (11.5)
Tumour	1 (0.8)
No abnormality	12 (9.8)
Total	122

seen alongside signs of recent infarction (eight patients) and HTI (two patients).

Recent infarction

CT scanning identified a relevant recent infarction in 119 (52.2%, 95% CI 45.7 to 58.7%). MR also showed a relevant recent infarct in 86 patients (72.2%) (*Table 29*). In the patients where MR did not agree with the CT diagnosis, the findings on MR were: HTI in 11 (9.2%), recent haemorrhage in three (2.5%), old lesion probable infarct in four (3.4%), old lesion probable haemorrhage in two (1.7%), multiple periventricular lucencies with or without cortical atrophy in 12 (10.1%) and negative scan in four (3.4%).

MR identified a relevant recent infarction in 122 patients (53.5%, 95% CI 47.0 to 60.0%) (*Table 30*). CT agreed in 86 patients (70.5%). In the patients where CT did not agree with MR diagnosis, findings on CT were: HTI in one (0.8%), old lesion probable infarct in eight (6.6%), multiple periventricular lucencies with or without cortical atrophy in 14 (11.5%), meningioma incidental to symptoms in one (0.8%) and negative scan in 12 (9.8%). Since the study was investigating the ability of MR and CT to demonstrate ischaemic stroke, MR was not taken to be the gold standard against which to make an estimate of sensitivity.

Tumours

CT scans identified five tumours in 228 patients (1.7%): two intra-axial and three extra-axial (three meningiomas; two of which were incidental, less than 1 cm in diameter and not responsible for symptoms). MR also identified the two intra-axial tumours and the symptomatic meningioma, but not the two incidental meningiomas.

Effect of CT and MRI on clinical decisions

In total, 223 clinical histories with accompanying relevant clinical details were obtained. The nine stroke physicians (five consultants and four clinical research fellows) were each given a selection of histories ranging in number from 11 to 44 according to each physician's time constraints.

Physicians' diagnoses

Physicians were not asked to say definitively whether symptoms were due to stroke versus non-stroke, or infarct versus PICH. However, taking a physician certainty of greater than 90% as a definite diagnosis, the following diagnoses were made.

- With information on clinical features, examination and general investigations (i.e. no scan findings), physicians made the diagnosis of stroke (as opposed to non-stroke) in 153 cases (69%), of which 100% were felt to be due to infarction (with greater than 90% certainty).
- When also given the corresponding findings on CT, the diagnosis of stroke was made in 166 cases (74%), of which 153 (69%) were felt to be due to infarction, two (1%) to be PICH and 11 (5%) were equivocal (diagnosis could not be made with greater than 90% certainty).
- When also given the findings on MR, the diagnosis of stroke was made in 169 cases (76%), of which 160 (72%) were felt to be due to infarction, eight (4%) to PICH and one (0.5%) was equivocal.

Thus, a CT scan increased the certainty of diagnosis of stroke versus non-stroke beyond that made on clinical features alone ($p = 0.006$), MR less so ($p = 0.5$). However, MR greatly increased

certainty in making a diagnosis of PICH ($p < 0.001$).

Decisions changed following scan results

Management decisions were changed following knowledge of CT results in 38 cases overall (17%, 95% CI 12 to 22%) (*Table 31*). With MR results, a further 28 changes (13%, 95% CI 8 to 17%) were made compared with decisions with CT findings (*Table 32*).

Decisions changed regarding the use of an antithrombotic drug in 17 patients (7.6%) when histories were reviewed with the CT results. Aspirin or another antiplatelet agent was started in seven patients (who were not previously on antithrombotic therapy), stopped in six, and continued in four when they had been stopped on history alone). Decisions regarding warfarin were changed in 12 (5.4%) patients (warfarin was started in nine patients, stopped in two patients, and continued in one patient following CT results when it had been stopped on history alone). If a warfarin decision was associated with an antiplatelet decision change, the latter was not counted separately. Decisions regarding endarterectomy were changed in 10 patients (4.5%) when CT results were available (eight patients were not referred, two patients were referred).

Decisions regarding using an antithrombotic agent were further altered in 14 (6.7%) patients with MR results. Aspirin or another antiplatelet drug was started in one patient and stopped in 13 patients. Decisions regarding warfarin were changed in five patients (2.2%) (warfarin was stopped in three patients, all of whom had PICH or HTI, and started in two patients). Endarterectomy decisions were changed in eight patients (3.6%) (six patients were referred, two patients were not).

Table 33 documents how decisions changed in patients with haemorrhage on their scans.

- In the two patients in whom PICH was also seen on CT, antithrombotic drugs were continued in one patient and another antiplatelet drug was added to aspirin in the other on history alone. These were discontinued when haemorrhage was demonstrated on CT (and remained discontinued following MR results).
- In the six patients in whom PICH was only identified on MR, four had aspirin started, one continued aspirin, and in one patient warfarin was stopped on history alone. With knowledge of CT results, aspirin or another antiplatelet agent was commenced or continued in four patients, and the one patient on warfarin continued anticoagulation. Following MR results all antithrombotic drugs or warfarin were stopped or not commenced.
- In the three patients with HTI documented on CT, aspirin was started or continued in two, and stopped in one on history alone. Following CT results, aspirin was not started in one patient, stopped in one and continued in one. Decisions were unchanged following MR results.
- In the 12 patients with HTI seen only on MR, describing the extent of HTI (as trivial or moderate, no patients had extensive HTI) seemed to have no bearing on management. Aspirin or another antiplatelet drug was commenced or continued in all 12 patients on history alone. With CT results, aspirin or another antiplatelet agent was commenced in ten patients, and warfarin commenced in two. With MR results, aspirin or another antiplatelet drug was started in all 12, and warfarin was not started in any patients.

Variability of scan reading and management decisions

The neuroradiologist interpreting scans read 20 scans twice with a gap of several weeks between readings to ensure blinding to the previous diagnosis. Diagnoses were identical in 17 (85%), and in no scans with haemorrhage was a different diagnosis reached. One stroke physician repeated ten decision forms, another repeated five. Decisions were consistent in 90% and 40%, respectively. An ANOVA on the certainty values of the different physicians making decisions showed significant variation ($p = 0.009$).

Patient scan preference questionnaire

Questionnaires were available for 192 patients. Of these patients, 82 (43%) underwent CT first and 110 (57%) underwent MR first. Altogether, 150 patients (78%) preferred CT, compared with 13 (7%) preferring MR and 29 (15%) expressing no preference. All patients felt they would agree to a further CT scan if they had to, and 99% would agree to an MR, although four patients added that it would be under duress. Twenty-one patients commented on the friendliness and helpfulness of the staff. Other comments included that the MR was noisy (11 patients), claustrophobic (six), took too long (five) and was frightening (two). One patient liked the noise of the MR scanner, while one felt more secure in the MR scanner and found it more relaxing than CT (they felt they would fall off the CT table).

TABLE 31 *Doctors' decisions: change in decision between that based on clinical features alone and that made with CT results available*

History alone	History with CT results								Total
	Start aspirin	Start aspirin and another antiplatelet agent	Stop aspirin	Continue aspirin	Start another antiplatelet agent	Continue aspirin and start another antiplatelet agent	Not applicable	Scan required for another diagnosis	
Start aspirin	44	1	0	3	3	0	3	0	54
Start aspirin and another antiplatelet agent	0	0	0	0	0	0	0	0	0
Stop aspirin	1	0	3[a]	3	0	1	0	0	8
Continue aspirin	8	0	7[b]	72	5	18	1[a]	1	112
Start another antiplatelet agent	2	0	0	2	8	0	1[a]	0	13
Continue aspirin and start another antiplatelet agent	1	0	2[a]	2	11	5	0	0	21
Not applicable	6	0	0	1	0	0	7	1	15
Scan required for another diagnosis	0	0	0	0	0	0	0	0	0
Total	62	1	12	83	27	24	12	2	223

Anticoagulation commenced in [a] one patient, [b] five patients.
Overall, following CT, anticoagulation commenced in nine patients, not started in one patient when started following history only, and continued in one patient (in 9/11, changes were also made to aspirin decisions).

TABLE 32 *Doctors' decisions: change in decision between that made with CT results, and then with MRI results*

	History with CT results								
History with CT results	**Start aspirin**	**Start aspirin and another antiplatelet agent**	**Stop aspirin**	**Continue aspirin**	**Start another antiplatelet agent**	**Continue aspirin and start another antiplatelet agent**	**Not applicable**	**Scan required for another diagnosis**	**Total**
Start aspirin	44	0	0	4	3	2	9	0	62
Start aspirin and another antiplatelet agent	1	0	0	0	0	0	0	0	1
Stop aspirin	0	0	10	1[b]	0	0	1	0	12
Continue aspirin	2	0	2[a]	69	6	2	2	0	83
Start another antiplatelet agent	2	0	1[a]	2	8	14	0	0	27
Continue aspirin and start another antiplatelet agent	0	1	0	9	2	12	0	0	24
Not applicable	1	0	2[b]	0	1	0	8[b]	0	12
Scan required for another diagnosis	0	0	0	0	0	0	0	2	2
Total	50	1	15	85	20	30	20	2	223

[a] Anticoagulation started in two patients; [b] anticoagulation stopped in three patients.

TABLE 33 *Decisions made regarding patients with haemorrhage, with and without scan results*

Patient code	Extent of haemorrhage	Time from scan (days)	Decisions made regarding antithrombotic therapy			Decisions made regarding anticoagulant therapy		
			History alone	With CT results	With MRI results	History alone	With CT results	With MRI results
3439	PICH	11	Start aspirin	Start aspirin	Not relevant	Not relevant	Not relevant	Not relevant
4336	PICH	13	Not relevant	Not relevant	Not relevant	Stop warfarin	Continue warfarin	Stop warfarin
4417	PICH	14	Start aspirin	Start aspirin	Not relevant	Not relevant	Not relevant	Not relevant
4119	PICH	17	Start aspirin	Not relevant	Not relevant	Not relevant	Not relevant	Not relevant
4636	PICH	21	Start aspirin	Start aspirin	Not relevant	Not relevant	Not relevant	Not relevant
3995	PICH	28	Continue aspirin	Continue aspirin and start another antiplatelet agent	Stop aspirin	Not relevant	Not relevant	Not relevant
4548	HTI medium	6	Continue aspirin	Continue aspirin	Continue aspirin	Not relevant	Not relevant	Not relevant
3996	HTI medium	19	Continue aspirin	Continue aspirin	Continue aspirin	Not relevant	Not relevant	Not relevant
3043	HTI medium	20	Continue aspirin	Continue aspirin	Continue aspirin	Not relevant	Not relevant	Not relevant
3766	HTI medium	28	Continue aspirin	Continue aspirin and start another antiplatelet agent	Continue aspirin	Not relevant	Not relevant	Not relevant
4042	HTI medium	28	Continue aspirin and start another antiplatelet agent	Continue aspirin	Continue aspirin	Not relevant	Not relevant	Not relevant
3654	HTI medium	56	Continue aspirin	Continue aspirin	Continue aspirin	Not relevant	Not relevant	Not relevant
4135	HTI trivial	5	Start another antiplatelet agent	Start another antiplatelet agent	Start aspirin	Not relevant	Not relevant	Not relevant
4414	HTI trivial	14	Start aspirin	Start aspirin	Start aspirin	Not relevant	Not relevant	Not relevant
4137	HTI trivial	21	Continue aspirin	Stop aspirin	Continue aspirin	Not relevant	Start warfarin	Not relevant
3824	HTI trivial	28	Start aspirin	Start aspirin	Start aspirin	Not relevant	Not relevant	Not relevant
3693	HTI trivial	28	Continue aspirin	Continue aspirin	Continue aspirin and start another antiplatelet agent	Not relevant	Not relevant	Not relevant
824	HTI trivial	49	Start another antiplatelet agent	Not relevant	Start another antiplatelet agent	Not relevant	Start warfarin	Not relevant
4067	Seen on CT	4	Start aspirin	Not relevant	Stop aspirin	Not relevant	Not relevant	Not relevant

continued

TABLE 33 *Decisions made regarding patients with haemorrhage, with and without scan results (cont'd)*

Patient code	Extent of haemorrhage	Time from scan (days)	Decisions made regarding antithrombotic therapy			Decisions made regarding anticoagulant therapy		
			History alone	With CT results	With MRI results	History alone	With CT results	With MRI results
4113	Seen on CT	9	Continue aspirin and start another antiplatelet agent	Stop aspirin	Stop aspirin	Not relevant	Not relevant	Not relevant
4403	Seen on CT	14	Continue aspirin	Stop aspirin	Stop aspirin	Not relevant	Not relevant	Not relevant
4220	Seen on CT	17	Stop aspirin	Stop aspirin	Stop aspirin	Not relevant	Not relevant	Not relevant
4581	Seen on CT	18	Continue aspirin	Continue aspirin	Continue aspirin	Not relevant	Not relevant	Not relevant

Discussion

CT identifies PICH but it is not possible to derive its sensitivity

Published studies demonstrate that PICH on CT appears acutely as an area of obvious hyperdensity, but the duration of its appearance is time dependent. Moderately sized haematomas can become isodense within 14 days[55] and smaller ones within 9 days,[136] but previous studies had failed to determine the latest reliable time to use CT. Although features of old haemorrhage have been described on CT (such as slit-like cavities and a hyperdense edge), these were not demonstrated to be reliable in the identification of haemorrhage late after stroke.[169,170] It was not possible from the published studies to derive a value for the sensitivity of CT in the identification of PICH, and there is little information on observer reliability. Two studies that investigated interobserver reliability in the identification of PICH on CT showed that not all clinicians and radiologists were equally proficient.[289,294] Therefore, although it is likely that, in good hands, CT can identify most, if not all, PICH within a few days of ictus, the rapid change in appearance over time may confuse diagnosis, meaning that the sensitivity of CT is unlikely to be 100%. However, the difficulty of finding a gold standard against which to judge CT in the acute phase of stroke (MR is likely to be more difficult to interpret in this phase, and post-mortem introduces selection bias towards the more severe strokes) may mean that determining its sensitivity is an impossible task. The epidemiological ideal is careful clinical assessment by an experienced stroke physician, CT in the acute phase, careful clinical follow-up to ensure that the patient behaves like a stroke, and a final consensus diagnosis following a panel discussion. However it was not evident that such an approach had been used in any of the identified studies.

The study comparing CT and MR in late presenting mild stroke identified that CT reliably identified small haemorrhages only up to 8 days after stroke. MR identified more haemorrhage than CT. A higher than normal field-strength MR scanner (2T) was used for many of the patients in this study (normal clinical scanners are usually 1.0 or 1.5T) but this will not have made any material difference to the assessment of MR and CT with the sequences used. MR proved superior in the detection of both PICH and HTI. CT did not identify any cases of haemorrhage that were not also identified on MRI. There are no criteria against which to judge MR, but assuming MR to be the gold standard (a reasonable assumption and the best we have at present), the sensitivity of CT in the detection of PICH and HTI in this group of patients was 50% and 20%, respectively. The patients with PICH made up 3.5% of the total group and 2.6% were misdiagnosed on CT as infarcts. This would result in 26 patients being mismanaged as ischaemic strokes per 1000 stroke patients presenting to the neurovascular clinic. This group of patients represented a typical population presenting to a neurovascular clinic and were scanned an average of 3 weeks after their stroke. A major delay before scanning was the time to presentation to the GP, as there was only a short delay once referred. This time delay definitely has a detrimental effect on the sensitivity of CT in the detection of PICH.[199,205] In this study, CT missed 19/23 (74%) of all haemorrhage identified on MR. The earliest time-point at which a PICH was missed on CT was 11 days (and because the scan was not performed any earlier, it is impossible to say precisely the earliest time-point at which this PICH would have been missed). The latest time PICH was identified on CT was 14 days. These timings, both of presentation to scan and CT findings highlight an important point. It is highly questionable to perform a CT more than 8–10 days after onset of stroke symptoms if the only reason for performing the investigation is to rule out the possibility of haemorrhage (as opposed to identifying a non-stroke lesion).

Can we derive the sensitivity of MR for haemorrhage?

The appearance of PICH on MR is more complicated than with CT. The change in appearance of PICH over time and the different appearance on each sequence are very confusing. Not all sequences are equally sensitive to PICH. Previous studies suggested that GRE sequences (which are not routinely used) are highly effective at demonstrating PICH, probably indefinitely,[120,121,190,195] but failed to demonstrate whether all haemorrhages remained identifiable as such. In the present study it was demonstrated that all 29 PICHs remained visible as haemosiderin in all 26 patients when scanned with MR up to 8 years after the stroke. Spin-echo T2 was shown to be the next most sensitive (97%), followed by fast spin-echo T2, on which about 93% of old PICH is identifiable. Although it was disappointing that only 26 patients actually underwent imaging, this is the largest (in fact only) study of its kind. The majority of the patients that we identified as still alive after the index PICH were either too disabled or had died, reflecting the high morbidity and mortality of

PICH. However the findings are in keeping with one other relevant study, although the proportion of former PICH still identifiable as such was slightly higher than in the one previous study, which examined the late MR appearance of traumatic intracerebral haemorrhage. This study found that haemosiderin was still visible in 90% of patients on spin-echo T2 up to 5 years after trauma.[135] Thus, for truly reliable identification of former PICH, a GRE sequence is required. There is less information on the reliability of MR in the identification of hyperacute haemorrhage. The two studies that have attempted to do so so far, both in academic stroke centres, are therefore important, but do not provide generalisable conclusions as the sample sizes were very small.[199,205] These studies also failed to mention the additional problems encountered with MR, of patient tolerability and contraindications, making it difficult to gauge the usefulness of MR in a non-selected stroke population. Therefore, for the present, there is reasonable (if a modest amount of) evidence that MR is very sensitive and specific for haemorrhage late after stroke.

CT in the positive identification of ischaemic stroke: values for sensitivity vary widely

Studies documenting the sensitivity of CT in the identification of ischaemic stroke demonstrate that high levels of sensitivity can be achieved, but not consistently. The range of sensitivities was wide and confounded by the variety of stroke populations investigated, as well as timing of scanning in relation to onset of stroke symptoms, and level of experience of the person interpreting the images. For instance, grouping studies according to timing of scanning (*Table 16*) did not reveal that scan interpretation was necessarily less accurate in the hyperacute stage. Neuroradiologists were generally more accurate in their interpretation of CT changes than were emergency physicians.[289,295] However, the more impressive results associated with (highly trained) neuroradiologists were from retrospective studies. Neuroradiologists may not always be available, especially within 6 hours, and hence it may not be possible to reproduce these results in real life. A good example of how different those results could be is the practice audit by general physicians in a Canadian hospital of the sensitivity of CT scanning in demonstrating a diagnostic lesion at 24 hours, where it was found to be only 23%.[244] When CT was first introduced, early investigators were content merely to describe clinicotopographical findings.[236,296] In the present era of increasingly sophisticated stroke management, such as the use of thrombolysis, it may be necessary accurately (and reliably) to demonstrate an infarct. If a sign on CT cannot be distinguished reliably by multiple observers with varying levels of ability, it is of no use as a marker on which to base clinical decisions (e.g. whether or not to give thrombolysis). So far, it seems that signs of early ischaemia on CT are too subtle for multiple observers to identify reliably and consistently.

Is MR really more sensitive than CT in the positive identification of ischaemic stroke?

Few studies so far have compared the sensitivities of CT and MR, and those that have been done were concerned with the identification of an infarct in the first few days. Those published so far seem to demonstrate that routine structural MR is consistently more sensitive in the positive identification of ischaemic stroke. This is probably the case, but inadequacies in the methodology of the studies make it unsafe to draw very robust conclusions. Sample sizes were small, and CT usually preceded MR by up to several hours, so increasing the chance that MR would show an infarct when CT did not. To derive the most accurate measure of sensitivity, scans should at the very least be performed on the same day, and ideally (especially in the hyperacute and acute stages) the order in which they are performed should be randomised. Blinding the interpreter of images to clinical history or other imaging is important to prevent bias; only 58% of studies were blinded. Only one study tested any differences found statistically (and found no difference).[207]

To the authors' knowledge, the present study is the only one to compare CT with MR in later presenting mild stroke. In this study, scans were performed on the same day. In view of the length of time from stroke to scanning (median 20 days), randomisation of the order of scanning was less important than in hyperacute studies. The patients in the study had mild strokes (median Canadian Neurological Score of 9.5) and many had few residual signs. CT and MR seemed of equal efficacy in demonstrating a recent infarct (about 50% of patients) and agreed with each other in a similar proportion (about 70%). This study was relatively large and prospective, the imaging assessment was blinded to other imaging, and the impacts on clinical decision-making and patient tolerability were systematically assessed. The MR scanning, although less liked than CT, was well tolerated by this group of older patients with stroke. CT or MR increased the clinician's

confidence of the diagnosis of stroke in about 5% of patients, and MR more than CT allowed the discrimination of infarct from haemorrhage. CT altered management in 17% and MR in 13%. The data are likely to be generalisable to hospitals elsewhere in the UK offering a similar neurovascular service.

How many minor strokes may have had haemorrhage in the general population?

The estimated number of patients being treated in the community is about 22,000 per year in the UK.[67] The use of aspirin increased dramatically during the 1990s[61,67] and stroke physicians are exhorted to consider warfarin in increasingly older populations of patients with atrial fibrillation.[297,298] The incidence of PICH in this study population was 3.5% and of HTI was 6.6%. From Stroke Association Survey estimates of patients in the community presenting with stroke symptoms, these would represent around 2200 patients per year in whom antithrombotic or anticoagulant treatment would be offered inappropriately.

What is the true incidence of asymptomatic haemorrhage?

Follow-up MRI identified evidence of new haemorrhage in 12/26 patients (46.2%) in the late haemorrhage study, which was presumed asymptomatic as there was no history of any further event in the interim. Signs of old asymptomatic haemorrhage were also found on MR in the CT versus MR study, but in far fewer patients (15/228, 6.6%). Although in patients with recent haemorrhage or haemorrhagic transformation in the CT versus MR study the proportion with asymptomatic haemorrhage was slightly higher (8.9%), it was still far from the values of up to 68% given in previous studies looking for asymptomatic haemorrhage specifically.[120,121,199,202] The most likely reasons for the large differences between the present studies and the previously published work are the difference in case-mix and timing of scanning.

Do imaging results really matter?

It may be that patients with PICH found only on MR would have come to no harm had their antithrombotic treatment been continued. In this study, knowledge of scan results made a difference to clinical management in 17% of cases following CT, and in a further 12% following MR. Whether the proportion of changes is large enough to alter scanning policy is debatable. Although clinicians prefer to have scans (certainty of diagnosis was increased) and patients prefer to have scans (personal observation), if access to imaging is relatively limited, figures such as found in here may not prove convincing enough to justify a 'scan everyone' policy. The variability within and between doctors' decisions in this study makes it impossible to say that these figures are definitive, but they do help to quantify the contribution of imaging to the overall management of the patient.

Should we be using MR more?

To be sure that a patient presenting with mild stroke symptoms more than 8–10 days after the event has not had a haemorrhagic stroke, MR is required. Access to MR is limited in the UK,[67] with many weeks' wait for a scan. If we were to wait for MR before treating all patients presenting after 10 days (assuming it was possible to obtain access to an MR machine), this would create an unacceptable level of delay in commencement of secondary prevention for the majority of patients. 'Salvage' by MR, because it is too late to CT, is not really a credible option. Patients should be encouraged to seek medical attention early after any stroke, and hospital clinics and imaging departments should offer responsive and rapid access to medical and CT assessment.

Conclusions

Implications for practice

- Patients should be encouraged to seek medical attention rapidly after suspected stroke.
- GPs should refer patients rapidly to hospital for further assessment and imaging on an in-patient or out-patient basis.
- Rapid access to CT should be considered; otherwise small PICHs will be misdiagnosed as infarcts and managed inappropriately. The data from the authors' neurovascular outpatient clinic suggest that about 26 per 1000 patients will be misdiagnosed and managed inappropriately if CT scanning is delayed to more than 8 days after stroke.
- In patients with mild stroke, CT and MR positively identify a similar proportion of recent infarcts.
- A GRE MR scan is required to exclude prior PICH reliably. If GRE is not available, then a spin-echo T2 sequence is nearly as sensitive as the GRE.

Implications for future research

- There are specific signs for old haemorrhage on CT (slit-like cavities with a hyperdense edge). Future studies should determine the sensitivity and specificity of these signs, as improved

awareness of them may lead to better detection of prior haemorrhage on CT, so perhaps avoiding the need to resort to MR in some cases.
- The proportion of patients with minor PICH will certainly have been underestimated in previous epidemiological studies. There will be about 26 per 1000 more PICHs than originally thought, and possibly more, as the study comparing CT with MR presented here was not community based.
- Future epidemiology studies should adopt more rapid scanning if using CT, or use MR instead.
- More data are required to determine the sensitivity and specificity of MR for haemorrhage early after stroke.
- More data are needed on how to improve the detection of hyperacute infarcts on CT.
- Radiologists should improve the methodology of studies to assess the accuracy or utility of new imaging modalities. They should resist pursuing new techniques when important questions remain unanswered about existing techniques. The domination of the neuroimaging literature by studies concerning more advanced neuroimaging strategies such as diffusion MR imaging, to the neglect of better understanding of the basic techniques, is a typical example. This suggests a trend towards the publication of what is 'fashionable' rather than important, and simply fuels the argument that allocation of radiological resources should not be left in the hands of clinicians and radiologists.
- Specific points to be improved in future imaging studies include accumulating a large enough prospective case series of well-characterised patients, with blinded interpretation of images, and assessment of the impact on decision-making and patient tolerability.
- Asymptomatic microhaemorrhage appears to be common in patients presenting with a haemorrhagic stroke.
- Future epidemiology studies should also examine the frequency of PICH by age and by recurrent compared with first stroke.
- As patients with PICH are more likely to have another PICH than an infarct (than patients with an infarct as their first stroke), if they have a recurrence, it is possible that the incidence of PICH is different in recurrent stroke than in first stroke.
- In particular, the influence of antithrombotic drugs on the frequency of asymptomatic haemorrhage and on PICH as a cause of recurrent stroke needs to be assessed.

Chapter 4

Contribution of brain imaging to therapeutic decision-making in stroke

This chapter presents a systematic review of the harm that may arise from failing to diagnose haemorrhage correctly and discusses antithrombotic treatment in patients with intracranial haemorrhage.

Background

The dilemma of starting antithrombotic treatment after intracranial haemorrhage

Intracranial haemorrhage, either intracerebral or subarachnoid, is usually considered an absolute contraindication to the use of antihaemostatic agents such as antiplatelet drugs or anticoagulants. However, in clinical practice, there are occasions when it is appropriate to consider using these agents in patients with definite (or possible) intracranial haemorrhage. For example, should a patient, recently started on aspirin following coronary artery bypass surgery, now admitted with a stroke due to intracerebral haemorrhage, stop or continue the aspirin? Should a patient, immobilised after an SAH, be given heparin for prophylaxis of deep vein thrombosis (DVT)? What should be done if the patient with SAH developed a clinically evident DVT before definitive treatment of any underlying aneurysm? It would be helpful to know the balance of risks and benefits in these types of patients.

A second problem is that the only way to distinguish stroke due to cerebral infarction from that due to intracerebral haemorrhage is by brain imaging with CT or MRI.[35,299] The International Stroke Trial (IST) and the Chinese Acute Stroke Trial (CAST) demonstrated the benefit of aspirin if given within 48 hours of stroke onset.[128] Consequently, there may be pressure to commence aspirin treatment as soon as possible if the clinical features suggest that the stroke was unlikely to be haemorrhagic, even if intracerebral haemorrhage has not been ruled out. For example, if brain imaging is not immediately available (or not available at all – a problem encountered in poorly resourced healthcare settings), it may well be worth starting aspirin treatment even though haemorrhagic stroke has not been reliably ruled out if the benefits for the majority with ischaemic stroke are likely to outweigh the risks in those with haemorrhagic stroke, while waiting for the brain scan.

There are numerous anecdotal reports in the literature of patients with intracranial haemorrhage who were given antithrombotic or anticoagulant drugs, for example for DVT or pulmonary embolism (PE), without apparent deterioration in their neurological status (*Table 34*). However, it is not possible to use this information to determine the risks or benefits of antithrombotic or anticoagulant treatment in patients with intracranial haemorrhage, either in patients with a clear indication for it, or in patients in whom one might want to start or continue aspirin while waiting for a CT scan but who could have an intracranial haemorrhage. It is only possible to determine the true risk to benefit ratio from an RCT in which patients with intracranial haemorrhage were randomly allocated to antithrombotic (or anticoagulant) treatment, for example for treatment of DVT. Fortunately, DVT and PE seem to be relatively rare among patients with PICH, but this makes the conduct of such a trial almost impossible because it would take so long to accrue an adequate sample size.

However, it is of serious concern that antithrombotic or anticoagulant drugs would increase the risk of further bleeding in the brain, thus worsening outcome. Meta-analyses of primary and secondary prevention studies in ischaemic stroke, TIA or ischaemic eye retinal symptoms, in patients with no prior history of intracerebral haemorrhage, have demonstrated a small but real increased risk of intracerebral haemorrhage in those given aspirin[48,129] or warfarin or heparin.[311] Patients who survive a prior intracranial haemorrhage to 1 month are also at increased risk of recurrent intracranial haemorrhage if they have another stroke.[122] In a systematic review of studies reporting recurrent stroke in survivors of PICH, the aggregate rate of all stroke was 4.3% (95% CI 3.5 to 5.4%) per patient year (higher in community-based studies at 6.2% versus 4.0% in

TABLE 34 *Observational studies of continuing antithrombotic treatment in patients with acute intracerebral haemorrhage*

Study	Year	No. of patients	Study type	Bleed type	Notes
Leker[300]	1998	4	Prospective	ICH in PMV	Warfarin reversed and all put on i.v. heparin, APTT 1.5. One patient had surgery for evacuation of haematoma, then heparin 36 h later
Boeer[301]	1991	68	Prospective	ICH (including angioma and aneurysm)	Heparin 5000 t.d.s. for DVT/PE prophylaxis starting on days 2, 4 and 10. Extra group added on to an earlier trial. No increased risk of further bleed
Butler[186]	1998	35	Retrospective	ICH and intraspinal haematomas in PHV	All had AC reversed then 10/35 restarted on heparin; only 2 had therapeutic levels, no information on outcome
Wijdicks[302]	1998	39	Retrospective	SAH/SDH/ICH in PMV	AC stopped following bleed. AC resumed at varying times (some < 3/7). 'No haemorrhagic complication on resumption of AC'
Chaves[182]	1996	17	Retrospective	Cerebellar HI	Notes pooled from Boston, Paris and Korea. All initial infarct, 9 on AC (6 heparin, 3 warfarin), 8 continued AC, no problems
Chamorro[303]	1995	5	Retrospective	HI	Looked at 171 infarcts who had heparin within 72 h. 5 had HI, 1 showed increasing size on follow-up CT, but none had clinical deterioration
Nakagawa[304]	1995	4	Retrospective	ICH/SDH in PMV	From abstract: all had warfarin reversed, 3 given i.v. heparin with no problems. One did not receive heparin because of massive bleeding
Pessin[305]	1993	12	Retrospective	HI	Mentions then excludes 2 who died of massive ICH after starting heparin for embolic stroke. AC not interrupted in 8, no problems
Kapp[306]	1987	161	Retrospective	SAH	3 groups who had adjusted-dose heparin either within 48 h of surgery (104) or after developing ischaemic deficit or not at all. Those with early heparin had fewer rebleeds and less ischaemia
Cerebral[307] Embolism Study Group	1984	30	Retrospective	ICH/HI	Of 30, 19 on AC. 16 stopped AC. 3 continued, no problems
Wang[308]	1995	1	Case report	SAH	Heparin given 13 days after event, no rebleeding
Brick[309]	1991	1	Case report	HI in PMV	Warfarin reversed, heparin started without bolus on day 2, warfarin restarted day 8.
Rothrock[310]	1989	1	Case report	HI	1/121 infarct had HI and given AC anyway (mild stroke), no problems

APTT, activated partial thromboplastin time; AC, anticoagulants; HI, haemorrhagic infarction; ICH, intracerebral haemorrhage; PHV, prosthetic heart valve; PMV, prosthetic mitral valve; SAH, subarachnoid haemorrhage; SDH, subdural haematoma.

hospital studies); about three-quarters of recurrent strokes were intracranial haemorrhage, an aggregate rate of 2.3% (95% CI 1.9 to 2.7%) per patient year; the subsequent ischaemic stroke rate was 1.1% (95% CI 0.8 to 1.7%) per patient year; and mortality was 8.8% (95% CI 5.2 to 11.0%) per patient year. It is therefore likely that aspirin or anticoagulants would increase the risk of recurrent bleeding in those who have already had an intracranial bleed, particularly in the acute phase. It would, therefore, be helpful to know the effect of antithrombotic drugs or anticoagulants on PICH in view of the occasional need to consider their use to treat DVT, and to determine whether it might be safe to use them before CT scanning in patients with suspected ischaemic stroke (but who may turn out to have a haemorrhagic stroke).

Although the primary analysis of the IST[41] did not suggest any increased risk of haemorrhage in those who started aspirin before CT scanning (some of whom were found to have an intracranial

haemorrhage when subsequently scanned), there was little information in the original publication as to how much aspirin or heparin the patients received, or how representative they were of the generality of strokes in the IST, and so what the risk of giving aspirin to acute PICH might actually be. It was also unclear whether there were other studies that might provide useful data to give a more robust estimate of the effect of antithrombotic treatment on patients with intracranial haemorrhage. Therefore, to provide a more precise estimate of how much harm (if any) or benefit might be caused by the administration of antithrombotic drugs or anticoagulants to patients with recent intracerebral haemorrhage, a systematic review of the available information on this subject was undertaken.

Methods

Objectives

The study aimed to determine the effect of antithrombotic or anticoagulant treatment given to patients with definite intracranial haemorrhage on outcome, including deaths, recurrent intracranial haemorrhage and death or dependency.

Criteria for considering studies for the review

Types of study

The authors sought to identify all reports of randomised trials (or observational studies with a concurrent comparison group), both published and unpublished, comparing antiplatelet or anticoagulant therapy with control following recent (CT or MRI confirmed) intracranial haemorrhage. Single case reports and studies with no concurrent comparison group were excluded (*Table 34*).

Types of participant

Patients had acute CT- or MR-proven intracranial haemorrhage, due to subarachnoid or acute intraparenchymal cerebral haemorrhage (which could be either PICH or HTI, i.e. any form of bleeding inside the cranial cavity).

Types of intervention

Aspirin or heparin (subcutaneous or intravenous) started within the acute period of the stroke (i.e. within the first few days) was compared with placebo or control.

Types of outcome measure

Outcome measures comprised deaths during the scheduled treatment period and at the end of follow-up; recurrent intracranial haemorrhage, recurrent ischaemic stroke, DVT or pulmonary embolus, and dependency, defined as a score of 3–5 on the modified Rankin scale (6 being dead).[312]

Search strategy

The electronic databases MEDLINE and EMBASE were screened from January 1984 to April 2001. The Cochrane Controlled Trials Register (CCTR) was also searched, and reference lists in all articles found were consulted and cross-checked for further references. The extended electronic search strategy for stroke was used (Appendix 4), combined with medical subject headings: 'anticoagulant', 'anticoagulant agent', 'aspirin', 'acetyl salicylic acid', and text words 'aspirin' and 'acetyl salicylic acid'. The search was deliberately kept broad so as to avoid missing any relevant studies in this obscure area. The search went back no further than 1984 because before that year CT scanning to identify haemorrhagic stroke correctly was not readily available.

Data extraction

From the included studies, two reviewers, independently and blind to each other, sought and extracted data on the number and type of patients in the study, the mode of randomisation, the number allocated to active or control treatment, the type and dose of drug used, the duration of treatment (scheduled treatment period), the timing of latest follow-up, early (during the schedule treatment period) and late (at the end of follow-up) mortality, recurrent intracranial haemorrhage and recurrent ischaemic stroke, and functional outcome at the end of follow-up. For recurrent intracranial haemorrhage, the researchers sought the method by which the haemorrhage was identified, whether it was symptomatic (i.e. temporally associated with a worsening of neurological status) and the time when it occurred (i.e. within the scheduled treatment period or by the end of follow-up). Any disagreements regarding data extraction were resolved by discussion.

Additional individual patient data

Having identified that there were very few relevant studies in the literature, it was apparent that the majority of data would therefore come from the two largest acute stroke trials: the IST (n = 19,435)[41] and the CAST (n = 21,106),[42] both of which investigated the use of antithrombotic therapy within 48 hours of acute stroke. In these trials, about 17% of patients were randomised within 6 hours and 33% within 12 hours. Patients could be randomised before CT scanning if the clinical

suspicion of acute intracerebral haemorrhage was low and the CT scan was likely to be delayed. As a result, a small proportion of patients who were randomised without a CT scan and started the trial treatment were found to have had an acute intracerebral haemorrhage when scanned subsequently (n = 773). These patients were described as having 'haemorrhagic stroke' on the trial data forms. Before analysing the individual patient data, the researchers reviewed the individual original IST record forms to extract any additional information on the nature or timing of the intracranial haemorrhage and the duration of trial treatment (i.e. whether it was discontinued early or not). The IST was initiated and coordinated from Edinburgh and the CAST from the Clinical Trials Service Unit in Oxford. The IST data were housed in Clinical Neurosciences and the original data forms were therefore accessible directly. The CAST individual patient data, but not the original forms, were made available to the authors for this study.

Analyses

First, all trials were analysed together (i.e. in patients with any intracranial haemorrhage), then a subgroup analysis was performed of those patients with intraparenchymal cerebral haemorrhage. The effect of aspirin, heparin and other antiplatelet agents was examined at various early and late outcomes. Individual patient data were used when available. RevMan[75] software (as used in the Cochrane Database of Systematic Reviews) was used to provide an estimate of treatment effect, using the Peto odds ratio (OR), fixed effects method and 95% confidence limits. In view of the paucity of data, it did not seem appropriate to undertake further sensitivity analyses or to attempt to give the studies a quality score. Rather, the study focused on ensuring that randomised studies genuinely used random treatment allocation, and on details of follow-up and outcome, to ensure a basic minimum standard.

Details of the included trials

The search strategy (Appendix 4) identified 2779 papers on antithrombotic or anticoagulant treatment or intracranial haemorrhage, but of these, only nine described a trial of antithrombotic or anticoagulant treatment in patients with intracranial haemorrhage, and two described retrospective observational studies with a concurrent 'control' group. Of the nine trials (2043 patients) of antiplatelet drugs (1997 patients) or anticoagulants (645 patients) given after acute intracranial haemorrhage that were identified, including the IST and CAST[42,313–319] (*Tables 35 and 36*), eight were randomised trials[41,42,314–316,318–320] and one was a double-blind comparative study that gave no information on whether treatment allocation was randomised or not[317]. However, on balance, a decision was made to include it. An additional publication that added an extra group of patients to a trial already included in the review[316] was excluded.[321]

The intracranial haemorrhage was due to SAH in six trials (1224 patients),[313–315,317–319] a mixture of acute intraparenchymal cerebral haemorrhage and haemorrhagic transformation of cerebral infarction in two trials (773 patients)[41,42] and proven PICH in one trial (46 patients).[316] In two of the SAH trials, the antiplatelet trial drugs were given *after* the aneurysms had been surgically clipped to prevent rebleeding;[318,319] in one the antiplatelet trial drugs were definitely started *before* any clipping of the aneurysm;[315] and in three trials there was no indication as to whether the aneurysm had been securely treated before starting the antiplatelet trial drugs.[313,314,317]

The duration of the scheduled treatment period ranged from 8 days[318] to 3 months,[315] and three studies did not clearly specify the duration of treatment.[313,314,316] The length of follow-up ranged from 1 month[42,318] to 6 months,[41,314] and one study did not specify the length of follow-up.[316]

The primary outcome was (*Tables 35 and 36*):

- death in four studies: within the scheduled treatment period in two studies,[41,42] within the follow-up period of 6 months in one study[314] and the period was not specified in one study[316]
- 'neurological disability' measured by Glasgow Outcome Score in two studies,[315,318] the Japanese Coma Scale in one study[317] and unspecified in two studies[313,314]
- functional outcome (i.e. Rankin or simplified equivalent) in three studies[41,42,319] and pulmonary embolus and deep vein thrombosis in one study.[316]

Three studies (466 patients; two in SAH and one in intraparenchymal cerebral haemorrhage) systematically scanned patients at repeated time intervals,[313,316,317] but did not define whether any recurrent intracranial haemorrhage that occurred had been identified by routine scanning or

TABLE 35 *Characteristics of randomised trials of antithrombotic agents given after SAH primarily for the prevention of delayed ischaemic neurological deficit*

Study	Year	No. of patients	Intervention	Methods	Scheduled treatment period	Duration of follow-up (months)	Primary outcome	Comments
(a) Trial treatment started before surgical treatment of the aneurysm								
Shaw[315]	1985	677	Dipyridamole 100 mg p.o., or 10 mg i.v., o.d.	Randomised open trial	3 months	3	Neurological disability	Patients randomised immediately on admission, before investigations
(b) Uncertain whether aneurysms treated before start of trial treatment								
Mendelow[314]	1982	53	Aspirin 300 mg p.o. b.d. or placebo	Randomised placebo-controlled trial	3 days after admission until discharge	6	Death Neurological disability	All patients received tranexamic acid p.o. or i.v.
Ono[313]	1984	135	Ticlopidine 100 mg p.o. t.d.s. or placebo	Randomised double-blind placebo-controlled trial	Not stated	3	Neurological disability	No specific data on recurrent haemorrhage although quoted 'no significant increase in haemorrhagic complications occurred'
Suzuki[317]	1989	285	OKY-046[a] 80 mg i.v. b.d., 400 mg i.v. b.d., or placebo	Multicentre double-blind comparative study	10–14 days	3	Neurological disability (Japan Coma Score)	No information on method of treatment allocation. Aspirin avoided during treatment schedule
(c) Trial treatment started after surgical treatment to prevent aneurysm rebleeding								
Tokiyoshi[318]	1991	24	Cataclot[a,b] 1 μg/kg/min vs placebo	Randomised trial, post-aneurysm treatment	8–14 days	1	Neurological disability (GOS)	No information on blinding
Hop[319]	2000	50	Acetylsalicylic acid (ASA) 100 mg p.r. vs placebo	Randomised pilot trial, post-aneurysm treatment	21 days	4	Rankin	Pilot study

[a] Thromboxane synthetase inhibitor.
[b] Sodium (E)-3-[p-(1H-imidazol-1-ylmethyl) phenyl]-2-propenoate.
GOS, Glasgow Outcome Score.

TABLE 36 *Characteristics of randomised trials of antithrombotic agents given after haemorrhagic stroke or primary intracerebral haemorrhage*

Study	Year	No. of patients	Intervention	Methods	Scheduled treatment period	Duration of follow-up (months)	Primary outcome	Comments
Dickmann[316]	1988	46	Heparin 5000 U s.c. t.d.s. vs control	Randomised, open trial in patients with intracerebral haemorrhage.	Not specified	Not specified	Death, DVT, PE, rebleeding	Heparin given from day 4, compared with control (heparin started day 10).
IST[41]	1997	599	Aspirin 300 mg p.o./p.r. heparin (12,500 U b.d. 25,000 U s.c.), both or neither	Randomised, open trial in patients with acute stroke; blinded outcome assessment	14 days	6	Death within 14 days death or dependency at 6 months	Patients could be randomised before CT scanning if there was a low clinical suspicion of intracerebral haemorrhage. Total trial size: 19,435 patients
CAST[42]	1997	174	Aspirin 160 mg p.o. vs control	Randomised placebo-controlled trial in patients with acute stroke	Up to 4 weeks	Until discharge (average 4 weeks)	Death or dependency at discharge	Same CT scanning policy as IST. Total trial size 21,106 patients

because of clinical deterioration. Only two studies (773 patients) documented that recurrent intracranial haemorrhage occurred during the scheduled treatment period.[41,42] The remaining studies did not specify whether recurrent intracranial haemorrhage occurred within the scheduled treatment period or by the end of follow-up. It was therefore assumed that any recurrent intracranial haemorrhages reported had simply occurred at some point within the period of follow-up.

Additional individual patient data

The IST and CAST randomised 40,541 patients, of whom 7758 (19%) first underwent CT scans after randomisation. Of these patients, 773 (10%) were found to have an acute intracerebral haemorrhage when scanned, of whom 398 patients had been allocated to aspirin (375 to control) and 310 to heparin (289 to control). On review of the 599 individual IST forms, some additional information was gleaned in 136, but the rest added no further information. The final diagnosis of the intracerebral haemorrhages was therefore 58% PICH and 42% HTI. In general, these patients were older (68% were over 70 years of age) and had more severe strokes (30% were drowsy or comatose, 31% had a TACS, and 44% had five or more neurological deficits) than was the average in the IST. The trial treatment was stopped after the post-randomisation CT scan in 65% of these patients who therefore only received a few doses of aspirin or heparin. In the CAST, the trial treatment was discontinued in 80% of patients found to have a haemorrhagic stroke. It was not possible to compare outcomes in the patients who received only a few doses of antithrombotic treatment with those who received more antithrombotic treatment, because the sample size was too small and confidence intervals were already too wide to provide reliable conclusions (see below). Therefore, all 773 patients were included in the present analysis. The effect of time to randomisation on treatment could not be examined for the same reasons.

Details of excluded studies

Details of excluded studies are given in *Table 37*.[306,322] These studies were excluded because they were observational without a control group. Two observational studies that had a non-randomised but concurrent 'control' group were considered to provide useful information and are described at the end of the Results section. These studies did not, however, contribute data to the meta-analysis.

Results

Effect of antiplatelet treatment on outcome after acute intracranial haemorrhage (i.e. subarachnoid or intraparenchymal cerebral haemorrhage) and after intraparenchymal cerebral haemorrhage alone

All recorded deaths

In patients with any acute intracranial haemorrhage (1997 patients), the OR for death among patients allocated to antiplatelet treatment compared with control was 0.85 (95% CI 0.63 to 1.15) (*Figure 5*).

In patients with just intraparenchymal cerebral haemorrhage (773 patients), the OR for death among patients allocated to antiplatelet treatment compared with control was 0.96 (95% CI 0.62 to 1.50) (*Figure 5*).

Recurrent intracranial haemorrhage

In patients with any acute intracranial haemorrhage, the OR for recurrent intracranial haemorrhage among patients allocated antiplatelet treatment compared with control was 1.00 (95% CI 0.73 to 1.37) (*Figure 6*).

In patients with just intraparenchymal cerebral haemorrhage (773 patients), the OR for recurrent intracranial haemorrhage among patients allocated to antiplatelet treatment compared with control was 1.02 (95% CI 0.58 to 1.8).

Functional outcome

Data on functional outcome at 6 months were only available from the IST[41] (599 patients). Although data on functional outcome were collected in the CAST,[42] this was only at 1 month and therefore was regarded as being too short term. The OR for being dead or dependent among patients with intracranial parenchymal haemorrhage allocated to antiplatelet treatment compared with control was 0.68 (95% CI 0.46 to 1.02). However, 65% of patients allocated to aspirin treatment received no more than a few doses of aspirin, so this does not reflect the effect of full-dose aspirin. In any case, 42% were considered to be HTI, in which case aspirin may have had some beneficial effect.

Effect of anticoagulant treatment on outcome after acute intraparenchymal cerebral haemorrhage

There were no data on the use of anticoagulants after SAH.

TABLE 37 *Non-randomised studies*

Study	Year	No. of patients	Methods	Comments
Kapp[306]	1987	161	Retrospective observational study in patients with SAH undergoing gradual carotid ligation. 115 had heparin (2500 –3500 U, dose adjusted), 46 had no heparin	Recurrent intracranial haemorrhage: prophylactic heparin or heparin after deficit 11/115 (9.6%), no heparin 12/46 (26%)
Juvela[322]	1995	291	Observational study on retrospective use of aspirin and NSAIDs before or after SAH 62 had taken aspirin before or within 7 days of SAH, 144 had no aspirin/NSAIDs (control)	**Aspirin (*n* = 62)** / **No aspirin (*n* = 144)** Death in study period: 18% / 23% Recurrent haemorrhage: 19% / 31%

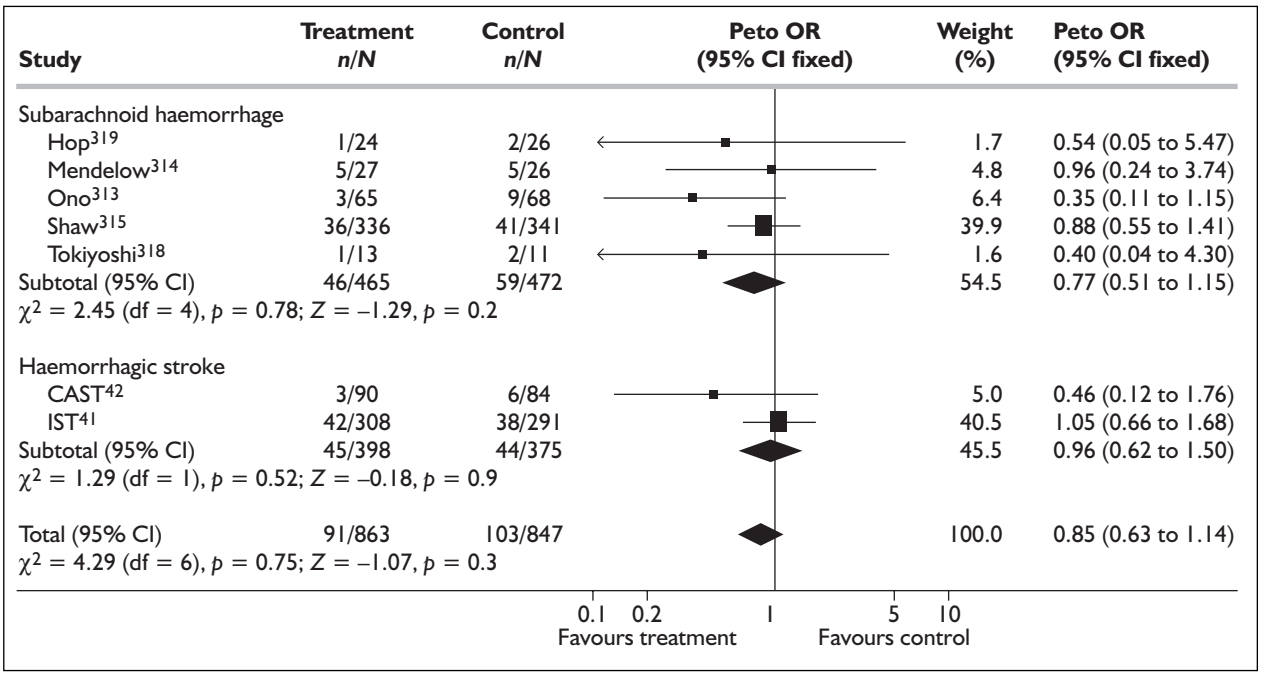


FIGURE 5 *Effect of antiplatelet treatment on death in patients with recent intracranial haemorrhage: systematic review of randomised trials comparing antiplatelet agent with control in patients with recent SAH or intracerebral haemorrhage. Treatment: patients allocated to antiplatelets; Control: patients allocated control;* n*: number of patients with event;* N*: number of patients allocated to that treatment; Peto OR: odds ratio calculated using the Peto method; Weight: proportion of the total amount of information in the whole review attributable to this study; 95% CI (fixed): 95% confidence intervals using a fixed effects model.*

All recorded deaths

In patients with any acute intraparenchymal cerebral haemorrhage (645 patients), comparing those allocated to heparin with control, the OR for death in the scheduled treatment period was 0.96 (95% CI 0.38 to 2.40) (*Figure 7*). For the 599/645 patients from the IST included in this analysis, the heparin was stopped after a few doses in 65% on discovering the intracranial haemorrhage.

Recurrent intracranial haemorrhage

In patients with acute intraparenchymal cerebral haemorrhage, the OR for recurrent intracranial haemorrhage among patients allocated heparin compared with control was 2.0 (95% CI 0.86 to 4.70) (*Figure 8*).

Functional outcome

In patients with acute intraparenchymal cerebral

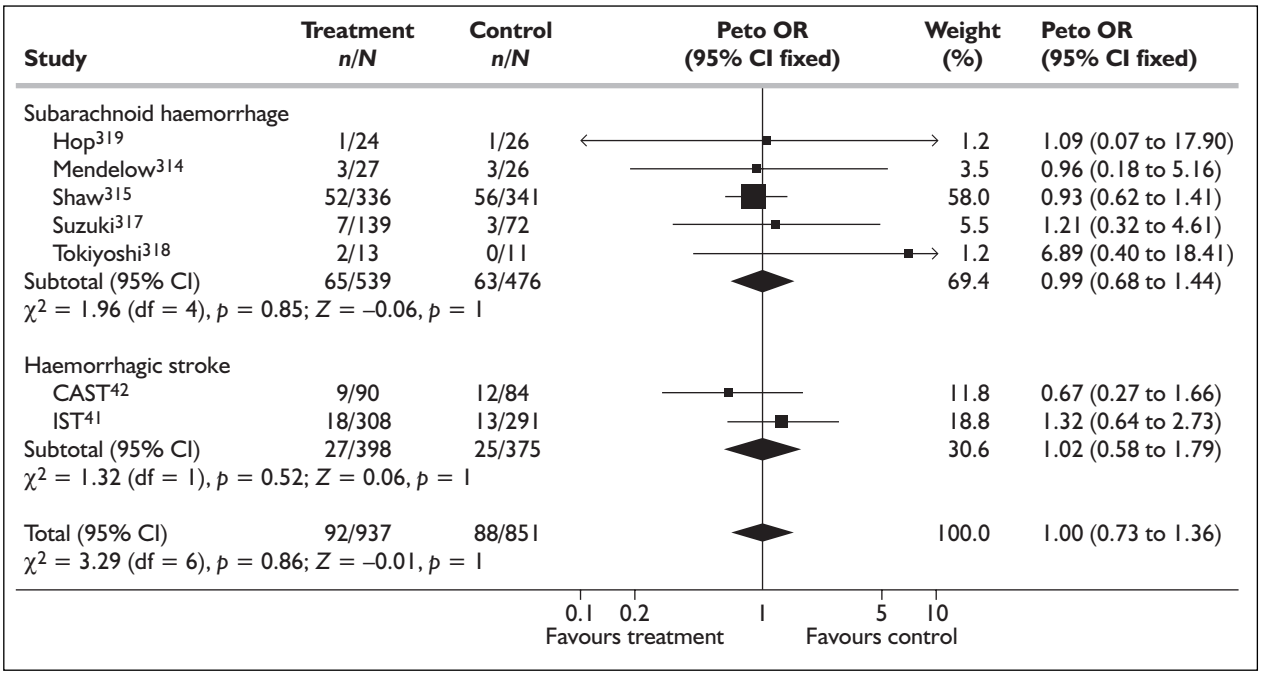


FIGURE 6 *Effect of antiplatelet treatment on recurrent intracranial haemorrhage in patients with recent intracranial haemorrhage (same conventions as Figure 5)*

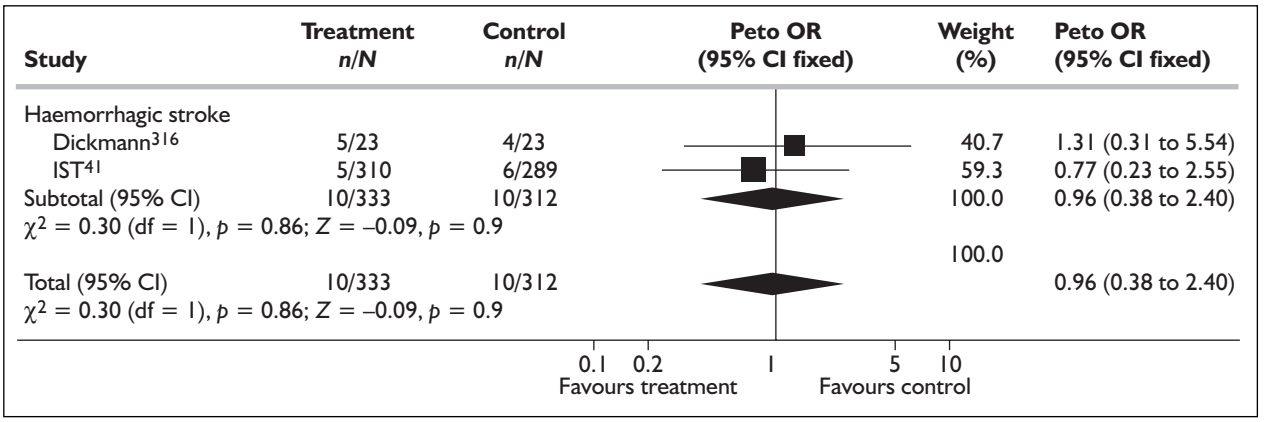


FIGURE 7 *Effect of heparin on death in patients with recent intracranial haemorrhage: systematic review of trials comparing heparin with control (same conventions as Figure 5)*

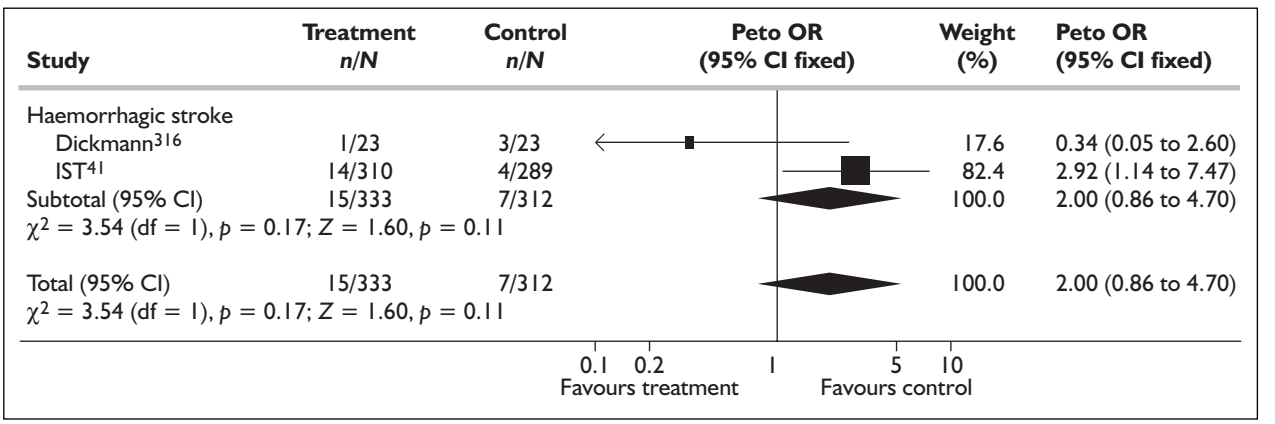


FIGURE 8 *Effect of heparin on recurrent intracranial haemorrhage in patients with recent intracranial haemorrhage (same conventions as Figure 5)*

haemorrhage, data were available only from the IST for functional outcome at 6 months (n = 599).[41] The OR for being dead or dependent among patients allocated heparin compared with control was 0.97 (95% CI 0.66 to 1.43).

Effect of antithrombotic treatment on DVT and PE

There were no data on the use of antiplatelet agents or anticoagulants to treat DVT or PE. One trial examined the effect of subcutaneous heparin in the *prevention* of DVT and PE after intraparenchymal cerebral haemorrhage.[316] However, it was not clear that the trial was truly randomised (see earlier results) and it only included 46 patients. There were eight DVTs and five PEs in the heparin-allocated patients, compared with ten DVTs and nine PEs in the control patients (p = not significant), Nine patients died, five in the heparin-treated group and four in the controls. The effects of aspirin and heparin in preventing DVT or PE in the IST and CAST have been reported previously in the main trial publications. There was no evidence that aspirin or heparin performed differently in the prevention of DVT/PE in patients with intraparenchymal cerebral haemorrhage as opposed to ischaemic stroke.

There were no data from randomised trials on the use of *intravenous* heparin to *treat* DVT/PE after intracranial haemorrhage. The trials in patients with SAH did not report the occurrence of DVT/PE.

Data from observational studies

Two observational studies were also identified (*Table 37*), both concerning patients with SAH. One retrospectively examined the effect of heparin given during surgery if a neurological deficit occurred, or after surgery as prophylaxis, compared with patients with SAH who were not given heparin.[306] In this study, there were fewer patients with recurrent haemorrhage in the group treated with heparin (9.6% versus 26.1% for controls). The study by Juvela retrospectively assessed the use of aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs) before and after SAH.[322] Since the primary mode of action of NSAIDs is not antiplatelet, analyses were restricted to the aspirin and no-aspirin groups. There were fewer deaths and fewer recurrent haemorrhages among patients receiving aspirin than among controls.

Discussion

This review summarises the totality of the evidence from randomised trials, or studies with a comparative control group, on antithrombotic or anticoagulant drugs administered (for whatever reason) after acute intracranial haemorrhage.

For antiplatelet drugs, the point estimates of effect on death and recurrent intracranial haemorrhage for patients with any intracranial haemorrhage are neutral or favourable. The estimate of treatment effect is less favourable if just patients with intraparenchymal cerebral haemorrhage are examined (the group relevant to haemorrhagic stroke). The wide confidence intervals cannot rule out modest harm, but equally they are also consistent with moderate benefit. The low risk of further intracranial bleeding in patients with intracranial haemorrhage given aspirin is consistent with the low intracerebral bleeding risk with these agents observed in other settings, although the fact that 65%–80% of patients discontinued treatment after only a few doses is very important. Thus, in certain situations, the use of an antiplatelet agent soon after acute intracranial haemorrhage would perhaps be justified if the patient were at particularly high risk of cardiac ischaemic events, as a result of a recent MI or had a history of unstable angina.[48] The data do not allow us to answer the question about the use of antithrombotic drugs in patients with a new ischaemic cerebral event who have had a known intracranial haemorrhage at some point in the more remote past, or about the long-term effects in patients with recent intracranial haemorrhage if required for prevention or treatment of some other vascular complication.

Almost all of the data (94%) on the effects of heparin in acute intraparenchymal cerebral haemorrhage come from the IST. These were a highly selected group of patients in that it was only possible to randomise patients into the IST before CT scanning if the local investigator felt that the stroke was unlikely to be haemorrhagic on clinical grounds (these would generally be mild strokes). Of 7758 patients randomised before CT, only 773 (10%) turned out to have intraparenchymal cerebral haemorrhage on CT. Thus, this group of patients is not likely to be representative of intracranial haemorrhage in general and conclusions must be drawn with great caution. In fact, in the IST, about one-third of the patients randomised without CT were drowsy and had a severe stroke. There are several interpretations of this pattern of behaviour among randomising doctors, but one possibility is that they regarded aspirin and heparin as benign drugs that were unlikely to harm patients with intracerebral haemorrhage.

What are the limitations of these data?

The data are scant and have limitations. Sixty per cent of the data on antiplatelet agents came from patients with SAH rather than intracerebral (i.e. brain parenchymal) haemorrhage, and at least some (it is not clear from the papers how many) of those patients had received definitive treatment of their aneurysm to prevent rebleeding before starting the antiplatelet trial treatment. The SAH data are of very limited relevance to patients with primary intraparenchymal cerebral haemorrhage. The patients with SAH are usually younger, with less co-morbidity, and the antithrombotic treatment was in general given to prevent ischaemic neurological deficit.

For the data on patients with intraparenchymal cerebral haemorrhage, the extent to which conclusions may be drawn on the safety of antithrombotic treatment are limited by the fact that in the majority (65% IST, 80% CAST), the aspirin or heparin was discontinued after only a few doses upon the discovery that the stroke was haemorrhagic. Therefore, the data do not describe a situation where full-dose aspirin (or heparin) was given to patients with intraparenchymal cerebral haemorrhage for 2 weeks in the acute stage. Nor do they describe the effect of administering antithrombotic treatment indefinitely, as might happen in error if a stroke was thought to be ischaemic (either in the absence of scanning, or scanning too late to discriminate infarct from haemorrhage).

The risks associated with heparin were only assessed for subcutaneous, not intravenous heparin, and only in patients with intraparenchymal cerebral haemorrhage. While the lack of effect of heparin on deaths from all causes was reassuring, the non-significant trend to a doubling of the risk of recurrent intracranial haemorrhage with heparin is a concern. Yet, patients with intracranial haemorrhage do develop indications for the use of heparin, such as symptomatic DVT. It would be useful to know precisely the balance of risk and benefit of giving heparin, and whether the reductions in venous thromboembolism are offset by an increase in intracranial haemorrhage. Given the uncertainties about the safety of heparin, it seems reasonable to encourage the use of other methods of DVT prevention (such as early mobilisation and graded compression stockings) to avoid the need for prophylactic low-dose heparin until further data from randomised trials are available. No trial has yet examined the effect of anticoagulants as a treatment for established DVT following acute intraparenchymal cerebral haemorrhage, and such a trial would be difficult to do as, fortunately, DVT after intracerebral haemorrhage is unusual. There is good evidence that the risk of intracerebral haemorrhage with heparin is dose related.[323] The risk of intravenous heparin is easier to justify if the risk of fatal PE is high (e.g. if the patient has DVT extending proximally or there is already clinically apparent PE). Where the risk of intracranial bleeding with heparin is considered too high in relation to the risk of thromboembolism, the placement of an inferior vena caval filter may be an option, but even this has drawbacks.[324] Decision-making about the balance of risk and benefit in patients with recent haemorrhage and symptomatic DVT or PE will therefore continue to be difficult.

Do these data aid scanning policy?

These data support the policy, in centres where CT resources are limited, as in parts of the developing world, of 'start aspirin pending CT if acute intracerebral haemorrhage is unlikely on clinical grounds' and 'stop the aspirin if the patient turns out to have a haemorrhage when scanned', provided the CT scan is obtained within a day or so of starting treatment. The value of aspirin where CT scanning is not performed until 5–7 days later (or more), or not at all, is not assessed by these data. A policy of widespread use of aspirin without prior imaging – a suboptimal policy – in places where CT scanning *is* available is not supported by these data. In places where CT scanning is not available *at all*, widespread use of aspirin among patients with a high probability of having an ischaemic stroke (e.g. selected with a clinical scoring system such as the Siriraj score[30]) may well be reasonable, as the population benefits of aspirin outweigh the risks. However, such a policy would require further testing and these data certainly provide no more than modest support for such an approach.

Conclusions

The data on the effects of aspirin given to patients with acute intracerebral parenchymal haemorrhage are insufficient to provide more than cautious guidance on patient management. This aspect of stroke management has been overlooked. However, it is likely that occasional patients with acute intracerebral haemorrhage will need antithrombotic treatment, that scanning will not always be immediately available even in well-resourced health services, and that intracerebral haemorrhage as a cause of stroke has been under-recognised (especially as a

cause of mild stroke). Therefore, there is a need to make the best use of the data available at present to guide management, and to obtain data in future studies to inform these areas of uncertainty.

Implications for healthcare

Aspirin and heparin should be avoided in patients with known acute intracerebral haemorrhage until further data are available better to define the balance of risk and benefit of antithrombotic treatment (for whatever reason).

There are numerous anecdotal reports of patients with intracranial haemorrhage and venous thrombosis and/or pulmonary embolism receiving anticoagulant treatment and not deteriorating neurologically, but it must be emphasised that there are no randomised comparisons of treatments in this difficult clinical situation, and the literature on anecdotal case reports may be extremely biased.

Where CT scanning resources are scarce, a policy of 'start aspirin pending the CT scan, but discontinue it immediately should the CT show a haemorrhage' is unlikely to be harmful as long as the patient is thought unlikely to have had a haemorrhagic stroke on clinical grounds using a scoring system, and the wait for the CT is unlikely to be more than a day or so.

Where CT scanning is available, it would in general be advisable not to commence aspirin for acute stroke until after the CT has excluded intracranial haemorrhage. However, the absence of a time-dependent gradient of treatment effect for aspirin within the first 48 hours after stroke suggests that scanning outside normal working hours would not normally be justified in patients who arrive at hospital in the evening if the CT can be done the following morning and then aspirin started.

Implications for further research

Further research is required to determine, in patients with a past history of definite intracranial haemorrhage, the risks and benefits of aspirin, heparin and warfarin given for:

- secondary prevention of a further cerebral, myocardial or peripheral vascular ischaemic event
- primary or secondary prevention of cerebral infarct in patients with atrial fibrillation
- treatment of symptomatic DVT and/or PE.

Chapter 5

Cost-effectiveness of CT in stroke: a systematic review of the available evidence, detailed costings and decision modelling analysis

Systematic review of previous studies of the cost-effectiveness of CT in stroke

The purpose of this systematic review was to determine what work had been done previously on the cost-effectiveness of CT scanning for stroke. In particular, the aim was to ascertain where new information was needed and what approaches had been used in the past. If indeed previous studies had shown CT to be cost-effective in stroke, then why the continuing controversy over provision of CT services for stroke?

Search strategy

A two-step process was used to identify economic evaluations of CT scanning for the diagnosis of stroke in the published literature. First, an electronic search of the literature was undertaken between 1986 and September 2001 using a series of databases including MEDLINE, EMBASE, Social Science Citation Index, Science Citation Index, NHS Economic Evaluation Database (NEED), DARE, Cochrane Library and the HTA database. A combination of MeSH headings and free text terms was used to conduct the search. Full details of the MEDLINE search are contained in Appendix 5. The syntax and search terms in the MEDLINE search were modified for the requirements of the other databases. A broad search was undertaken to maximise the number of relevant references identified for consideration for inclusion in the review. This search was supplemented with a handsearch of previous systematic reviews of the cost-effectiveness of stroke diagnosis and treatment of stroke.

Inclusion and exclusion criteria

To select the highest quality evidence in this area, inclusion and exclusion criteria were developed. Studies that met the following criteria were included:

- full economic evaluations
- evaluating diagnostic strategies involving CT scanning for stroke patients
- published in English (resources were not available for translation)
- published in peer-reviewed journals.

It was acknowledged that while partial economic evaluations can provide important information on the costs and consequences of healthcare interventions, they do not address the question of efficiency and therefore were excluded from the review.[325] Only studies that met all the inclusion criteria were included.

Study selection process

The references identified in the electronic search were initially screened on the basis of the titles and abstracts of articles by one reviewer (JS). The references from the electronic search, together with those from the handsearch, were then examined on the basis of the titles and abstracts of articles by two reviewers (JS and JC). Full manuscripts of potentially relevant references from the electronic search were obtained. Final decisions regarding inclusion and exclusion were made on the basis of the full manuscript (JS).

Results

The electronic search identified 531 references (excluding replicate references). The initial screening identified 82 potential studies evaluating the cost-effectiveness of CT scanning for the diagnosis of stroke. Of these, 127 were identified from MEDLINE, 111 from EMBASE, 241 from the Social Science Citation Index and Science Citation Index, nine from the Cochrane Database, and 43 from the DARE, NEED and HTA databases.

Two prior systematic reviews were also identified. The first, undertaken by Holloway and co-workers in 1999, examined the cost-effectiveness of a range of diagnostic, preventive or therapeutic interventions for stroke, and included studies that

were full economic evaluations in which benefits were measured in quality-adjusted life years (QALYs).[20] This study identified 26 economic evaluations of a range of stroke-related screening and treatment interventions, but no studies evaluating CT scanning for stroke.

The second systematic review, by Evers and co-workers in 2000, examined the status and quality of economic evaluations conducted in the area of cerebrovascular disease.[326] This review differed from the previous review as it only included full economic evaluations in the field of stroke research using data obtained from randomised trials, and included studies where benefits were assessed using measures other than QALYs. The purpose of the review was to examine systematically the methodological quality of the epidemiology and the economics of economic evaluations conducted in this area. This study identified a total of 23 economic evaluations that satisfied the inclusion criteria, of which three studies evaluated the cost-effectiveness of CT scanning for stroke.[327–329]

Therefore, 85 references (82 from the electronic literature search and three from the handsearch of previous reviews) were assessed for the present systematic review and full manuscripts were obtained for all 17 potential economic evaluations. Each manuscript was read and three were each considered to satisfy the inclusion criteria.

Economic evaluations of CT scanning for the diagnosis of stroke

The three studies that satisfied the inclusion criteria are summarised below.

Larson and colleagues evaluated CT scanning for patients with cerebrovascular disease as part of an assessment of the costs of diagnostic procedures, speed of work-up, institution of therapy, LOS in hospital, discharge diagnosis and follow-up plans.[328] Three groups of patients were compared, one before the installation of an EMI CT 1000 CT scanner and two groups after the CT scanner had been installed (total $n = 157$) in a general/referral hospital in the USA. The costs of procedures and LOS were estimated on the basis of 1976 billing charges in US dollars. There were no differences in LOS, speed of diagnostic work-up, treatment and discharge plans between the groups. The introduction of CT scanning, however, resulted in more specific discharge diagnoses, a reduction in the frequency of lumbar puncture and radioisotope brain scans, and an increase in the level of aggregate charges for diagnostic procedures. While this study satisfied the inclusion criteria for the present review, the results of the study are of limited use given advances in treatment for stroke since 1974 and CT scanning technology. There is also concern regarding the costs, which were based on charges that are unlikely to reflect the true opportunity cost of resource use.[325]

Britton and co-workers compared a range of diagnostic procedures for suspected stroke with CT scanning (or routine autopsy where appropriate) among 419 consecutive patients admitted to a stroke unit in Sweden between 1976 and 1979.[329] These procedures included: bedside methods; cerebrospinal fluid analysis, radioisotope scanning and CT scanning. The diagnostic validity of each strategy was assessed and costs were compared. The costs were expressed in terms of 1984 US dollars, but the methods used to estimate the costs were not reported. Results were expressed in terms of the rate of correct diagnosis achieved with each strategy. This study indicated that the most cost-effective strategy would be to use CT scanning as the sole method of investigation.

More recently, van der Meulen and co-workers compared costs and outcomes associated with CT scanning and secondary prevention with antiplatelet treatment after stroke using decision analysis.[330] Within this study a 'quality weight' was developed using decision analysis and published evidence on the excess risk of vascular events in the first 2 years after stroke compared with an optimal strategy (CT brain scan all patients and give aspirin for cerebral infarction). Secondly, these weights were applied in a follow-up study of 738 stroke patients aged over 45 years, and the data extrapolated to the whole of The Netherlands using 1991 hospital discharge statistics. No details were provided on the methods used to estimate the costs. The results were expressed as the national impact of the strategy. The investigators found that only 6% of patients had not had a CT scan anyway, and only 14% of eligible patients did not receive aspirin at hospital discharge, and therefore only a further 74 events per annum might be prevented by improving current practice. This would be equivalent to a 3% reduction in new vascular events in the first 2 years after stroke, at a total additional cost of 0.2% (250 million Dutch guilders) of the total annual hospital cost for acute stroke in The Netherlands.

Summary

This systematic review, undertaken to assess the evidence available in the published literature on

the cost-effectiveness of CT scanning for acute stroke, found that there was very little evidence regarding the cost-effectiveness of CT scanning for stroke. Only three studies met the entry criteria, but none determined the impact of CT on cost of stroke, or examined in any detail the effect of failing to diagnose intracranial haemorrhage, tumours or infection. It is therefore not possible to draw any conclusions from this review about the cost-effectiveness of CT scanning for stroke.

Several points about the studies identified in this review are worthy of note. First, none of the studies reported the methods used to estimate costs. The costs in one study were based on hospital billing charges[328] (which is not considered good practice for economic evaluations), and the remaining studies reported very little if any costing methodology.[329,330] Secondly, two of the studies were of limited relevance owing to subsequent advances in treatment and prevention of stroke and in CT technology.[329,330] In addition, both of these latter studies were really asking whether CT could replace other diagnostic methods available and in common usage around the time that CT was introduced, and did not actually model the impact on cost and health.

The electronic search may have overlooked some studies. However, a broad search strategy was used and previous systematic reviews in the area only identified a few papers, so this is considered unlikely. Therefore, one conclusion of this review is that there is very little evidence on the cost-effectiveness of CT scanning for stroke.

Only full economic evaluations were considered, so cost analyses were excluded from the review. This decision was made because only full economic evaluations are able to address questions of efficiency and so provide the most valuable findings. It could be argued that cost analyses can provide information about efficiency if it is assumed that the cheaper option is also likely to be the better one, and therefore an intervention that saves resources is more likely to be cost-effective. While this may be true, it can be strongly argued that available resources should be allocated to those interventions that are known to be both effective and cost-effective. However, in the case of CT in stroke, as there is no other way apart from scanning to diagnose the cause of stroke reliably, and as all treatments are diagnosis specific, it would be morally and ethically indefensible not to CT scan stroke patients. Therefore, although doing a scan obviously costs more than not doing a scan (in terms of scan costs) it may actually cost more not to scan if inappropriate treatment decisions result in increased dependency and LOS in hospital.

Although not full economic evaluations there were a number of studies of potential relevance. Gleason *et al*. considered the cost savings in the USA which would result from the implementation of a CT angiography–CT perfusion protocol.[331] While they did not include clinical outcomes, the main mechanism of incurring additional scanning cost in order to reduce length of inpatient stay was similar to that in the current study. Heller *et al*., in contrast, compared different CT scanning strategies in their paper but only considered death and dependency at 6 months and not the resource implications of the different strategies.[332] Finally, Grieve *et al*. developed a method for costing the management of stroke and applied it to 13 centres in 11 European countries.[333] The UK sample was, however, small and the level at which data were reported was too aggregate for useful comparison with the current study.

None of three economic evaluations identified was undertaken in the UK. Cerebrovascular disease is a major concern in the UK. It is therefore important to determine the cost-effectiveness of a variety of ways of using CT scanning for stroke to ensure that resources are used efficiently to optimise outcome after stroke.

Development of the cost-effectiveness model and decision tree, including devising a menu of representative scanning strategies

This section describes the model developed to examine the effect of CT scanning of stroke patients in terms of costs and patient outcomes, then outlines the challenges faced in the development of the model and discusses the options that were available to resolve them.

How could the cost-effectiveness of one component (imaging) in the management of a complex disease such as stroke be assessed?

The assessment of cost-effectiveness of diagnostic tests is inherently more difficult than assessments of therapeutic interventions. The difficulties stem from uncertainty about the relation between the

diagnosis and the end results (outcomes) of care.[70] However, a diagnostic test is usually a crucial first step in establishing the diagnosis, and it may substantially influence the choice of treatment. The degree to which a particular test influences outcome (and cost) will depend on the clinical context and the current level of service provision of that test.

One way to assess the effectiveness or cost-effectiveness of an intervention is to conduct an RCT comparing costs and outcomes among those who do and do not receive the diagnostic tests. There were two main reasons why an RCT was not a feasible approach to assessing CT scanning in stroke. First, it was estimated that to conduct an RCT with sufficient power to detect a clinically important difference in death or recurrent stroke, the study would require a sample of more than 40,000 patients. Secondly, it would now be considered unethical to randomise patients to whether or not they should have a CT before starting antiplatelet therapy.[41–43,334]

Therefore, modelling techniques were used to estimate the expected benefits and costs associated with different CT scanning policies. The model specifies parameters at each decision point in the care of the patient using available evidence from systematic reviews wherever possible. This approach involves developing a decision tree, incorporating key decisions and the probability of different events that can occur over time. The more detailed the model (and hence the more closely it reflects real life) and the more evidence (rather than assumptions) it contains, the more likely it will be to provide information relevant to current practice. The model provides estimates of the impact of different CT scanning strategies on treatment decisions and the consequent effects on costs and health outcomes. This enables not only the effect of each strategy on clinical outcome but also the relative cost-effectiveness of each of the scanning strategies to be assessed and the strategies to be ranked to identify, in this case, what is the best imaging strategy for stroke.

What type of model was appropriate?

The cost-effectiveness of a range of routine CT imaging strategies was examined using a deterministic model and a conventional approach to decision analysis. Data were gathered for the systematic reviews of imaging, clinical evaluation and treatment in Chapters 2–4, then the model was developed. The clinical and radiological expert authors were therefore able to identify areas where data were either unavailable or inconclusive. Thus, given the limitations of the data and the complex nature of the clinical scenario, it was constructed appropriate to use a simple, custom-designed model, rather than to build a conventional Markov model.

Identification of typical imaging strategies for stroke

Discussion among the clinical authors (a neuroradiologist, a stroke physician and a neurologist) and the health economists focused on the information required in order to evaluate scanning policies and led to the identification of 12 different strategies for CT scanning in acute stroke. These were drawn up by the expert authors from their own experience and from published studies on stroke research, audit and clinical practice in the UK. The resulting strategies had to be sufficiently different to each other to be useful, and had to reflect the fact that certain patients might have priority if CT resources were limited. A further constraint was that data should be available for most of the decision points (*Table 38*). The strategies were intended to reflect, broadly, the typical patterns of use of CT in different sorts of hospital with varying degrees of access to CT for stroke. At best, CT would be available immediately on site, and at worst only available at another hospital after a considerable delay. However, the different strategies were also designed so that they would still be relevant over the next 5 years or more. For example, rt-PA, or some other hyperacute treatment requiring CT before use, might be licensed in future for use within 3 hours of stroke, placing new pressure on CT services and leading to altered requirements and costs.

There were four main types of CT scanning strategy. The first strategy (S1) was a broad policy requiring all patients admitted to hospital suspected of having suffered an acute stroke to be scanned immediately on arrival. Strategies S2–S9 involved scanning only selected patients, selecting patients on a number of patient-based criteria and then applying a deadline by which time all eligible patients were to be scanned. The criteria included severity of the stroke, 'high-risk' patients in more urgent need of an immediate management decision (e.g. patients on anticoagulants at the time of the stroke, who might require reversal of the anticoagulation if the stroke were due to a haemorrhage) or candidates for hyperacute therapies such as thrombolysis.[130] Although thrombolytic therapy was not licensed in the UK at the start of this project (it is now), tPA is licensed in the USA, Canada and Germany, and some centres in the UK administer it to selected

TABLE 38 *CT scanning strategies*

Strategy	Imaging strategy
Comparator	Scan all within 48 hours of admission to hospital
S1	Scan all immediately
S2	Scan patients on anticoagulants or in a life-threatening condition immediately and scan all remaining patients within 24 hours of admission to hospital
S3	Scan patients on anticoagulants or in a life-threatening condition immediately and scan all remaining patients within 48 hours of admission to hospital
S4	Scan patients on anticoagulants or in a life-threatening condition immediately and scan all remaining patients within 7 days of admission to hospital
S5	Scan patients on anticoagulants or in a life-threatening condition immediately and scan all remaining patients within 14 days of admission to hospital
S6	Scan patients on anticoagulants, those in a life-threatening condition or are candidates for hyperacute treatment immediately and scan all remaining patients within 24 hours
S7	Scan patients on anticoagulants, those in a life-threatening condition or are candidates for hyperacute treatment immediately and scan all remaining patients within 48 hours
S8	Scan patients on anticoagulants, those in a life-threatening condition or are candidates for hyperacute treatment immediately and scan all remaining patients within 7 days
S9	Scan patients on anticoagulants, those in a life-threatening condition or are candidates for hyperacute treatment immediately and scan all remaining patients within 14 days
S10	Scan only patients in atrial fibrillation, on anticoagulants or on antiplatelet drugs within 7 days of admission to hospital
S11	Scan only patients with a life-threatening stroke or anticoagulants within 7 days of admission to hospital
S12	Do not scan anyone

A life-threatening stroke is defined in terms of the severity of the stroke (TACS) with an impaired level of consciousness.

patients within 3 hours of stroke. Scanning strategies S10 and S11 involved scanning select groups of patients within 7 days of admission to hospital. In the final strategy (S12), patients suspected of having suffered a stroke would not be scanned at all, and treatment was with aspirin based on clinical diagnosis alone.

Two major national guidelines for stroke in the UK were published during the project: the SIGN[50] and the RCPE.[62] A further SIGN guideline on the use of antithrombotic treatment guideline was also relevant.[335] Both stroke guidelines were for the assessment, investigation, immediate management and secondary prevention of stroke. Both guidelines used the results of the IST and CAST which showed that aspirin commenced within 48 hours of ischaemic stroke reduced early deaths and long-term death or dependency.[41,42] Thus, both guidelines recommend that patients admitted to hospital with suspected stroke should be CT scanned within 48 hours of stroke. Even though this ideal may not be achieved in all hospitals in the UK,[67] in the present study, these guidelines are assumed to represent 'best current practice' and were therefore used as the main comparator in the model. The National Service Framework for Older People,[68] subsection on stroke published in 2001, also stipulated that a brain scan should be performed within 48 hours; therefore, a base comparator of 'scan all within 48 hours of stroke' seemed reasonable.

A number of difficulties were encountered in refining the list of potential CT scanning strategies. Access to CT for stroke varies around the UK.[66,67,336] There was a clear need for the strategies not only to reflect these differences in availability, but also to take account of the wide variety of problems posed by acute stroke patients, and the different case mix in different hospitals serving different populations.[337] However, there was also a need to keep the list of strategies fairly simple. A final problem was to ensure that sufficient data were available to evaluate the expected costs and outcomes associated with each strategy. More *precise* estimates of some data (i.e. a point estimate and 95% confidence interval rather than a general estimate) only became available after some primary data collection.

In addition, it was apparent that some scanning strategies would not be relevant for some hospitals in the UK. For example, strategies that require

patients to be scanned either immediately or within a very short period assume that radiological departments have the resources to undertake emergency or out-of-hours CT scanning.[336] While this may be feasible for radiological departments in large teaching hospitals, smaller hospitals may often not have the resources to offer this service, while other hospitals do not have CT scanning facilities on site. Furthermore, hospitals with a dedicated neuroradiology department may be able to offer immediate brain CT, whereas hospitals where the brain CT is performed in the general radiology department have to slot in brain CT between more complex body CT examinations. Body CT often takes longer than a simple brain CT, and requires the use of intravenous and oral contrast, and so timing of scanning (and not interrupting it) makes immediate access for a 'quick brain CT' more difficult. All of these factors affect how quickly an individual stroke patient may gain access to CT scanning.

A survey of access to imaging facilities for patients suspected of having suffered a stroke in Scotland was undertaken to inform the modelling (see later), because there were no comprehensive data on current access to CT for stroke patients. There were data on parts of the access process, for example in a survey of UK casualty departments,[26] or in the survey of services for stroke provided in Scottish hospitals.[66] However, stroke patients may be admitted under non-stroke physicians and so would not have been included in the latter audit. In any case, both the audit and casualty department survey were based on data from at least 3 years ago. During the course of the present project, the Royal College of Radiologists undertook a survey of radiology departments in England and Wales, but these data were not available at the time of the modelling (Squires, Royal College of Radiologists Audit Committee, personal communication). There were no data at all on what *additional* resources would be required to increase the access to CT for stroke patients. The survey also sought to classify hospitals in terms of their access to CT scanning facilities, and to determine the likely scale of extra resource required to bring the service up to the level required by the 'optimal' CT scanning strategy defined by this work. The different CT scanning strategies would then be reviewed in the light of this classification.

Model structure

A decision tree was constructed to model the expected costs and outcomes associated with the strategy to 'CT scan all patients suspected of having suffered a stroke within 48 hours'. This tree was then modified to assess the effect of each of the scanning strategies listed in *Table 38*. Given that some CT scanning strategies are similar in nature, a detailed tree was required to ensure that even small differences in the costs and outcomes potentially could be identified in the analysis. The tree incorporated key decisions and events such as CT scanning, the sensitivity and specificity of scans, diagnosis, treatment options, and the effect on costs and patient outcomes. The development of the tree required considerable discussion among the clinical, radiological and health economics authors to think through carefully the implications of what might happen to patients correctly or incorrectly diagnosed at each node in the tree. This required several iterations before a final structure was agreed on.

The decision tree was constructed in accordance with a number of conventions used in decision analysis.[338] The tree depicted patients admitted to hospital with first ever stroke (but with appropriate adjustment, the model could also apply to recurrent stroke as the basic decision nodes would be the same). The main tree is displayed in *Figure 9* and the treatment and outcome subtrees are shown in *Figures 10 and 11*. A brief description of the tree is given below.

In *Figure 9*, chance nodes 1 and 2 represent the patient's true clinical status. Of the patients admitted to hospital with a suspected first stroke, a proportion would have truly had a stroke and a proportion would not (Chapter 2 and chance node 1). At chance node 2, of the patients who truly had a stroke, a proportion would have had a PICH and a proportion would have had a cerebral infarct (Chapter 2).

Stroke severity (chance nodes 3 and 4) was categorised with the Bamford classification system.[9] It includes four clinical subtypes: PACS, LACS, TACS, POCS. Of these, TACS is considered to be the most severe and these patients have the highest case fatality and worst long-term outcome. The fewer patients with a PICH (only about 15–20% of all stroke) were categorised as either TACS or non-TACS. A more detailed sub-classification of PICH would have reduced the sample sizes even further and not improved the outputs from the model.

In the base comparator, all patients in the model were CT scanned within 48 hours of stroke. A diagnosis was then made on the basis of information provided by the scan and a clinical examination. Therefore, sensitivity and specificity of the CT scans is incorporated at nodes 5–11

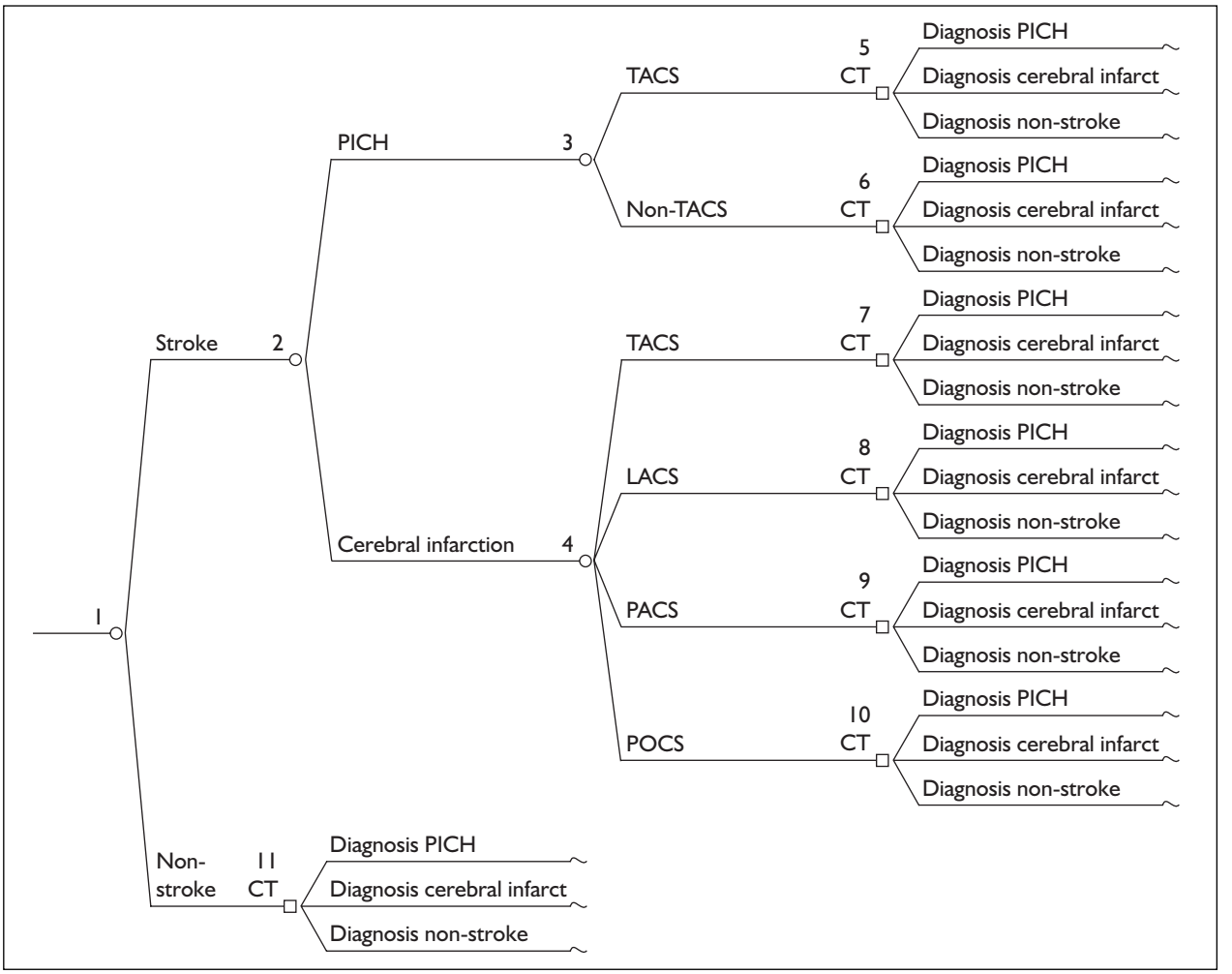


FIGURE 9 *Main decision tree for the diagnosis of patients suspected of having suffered a stroke*

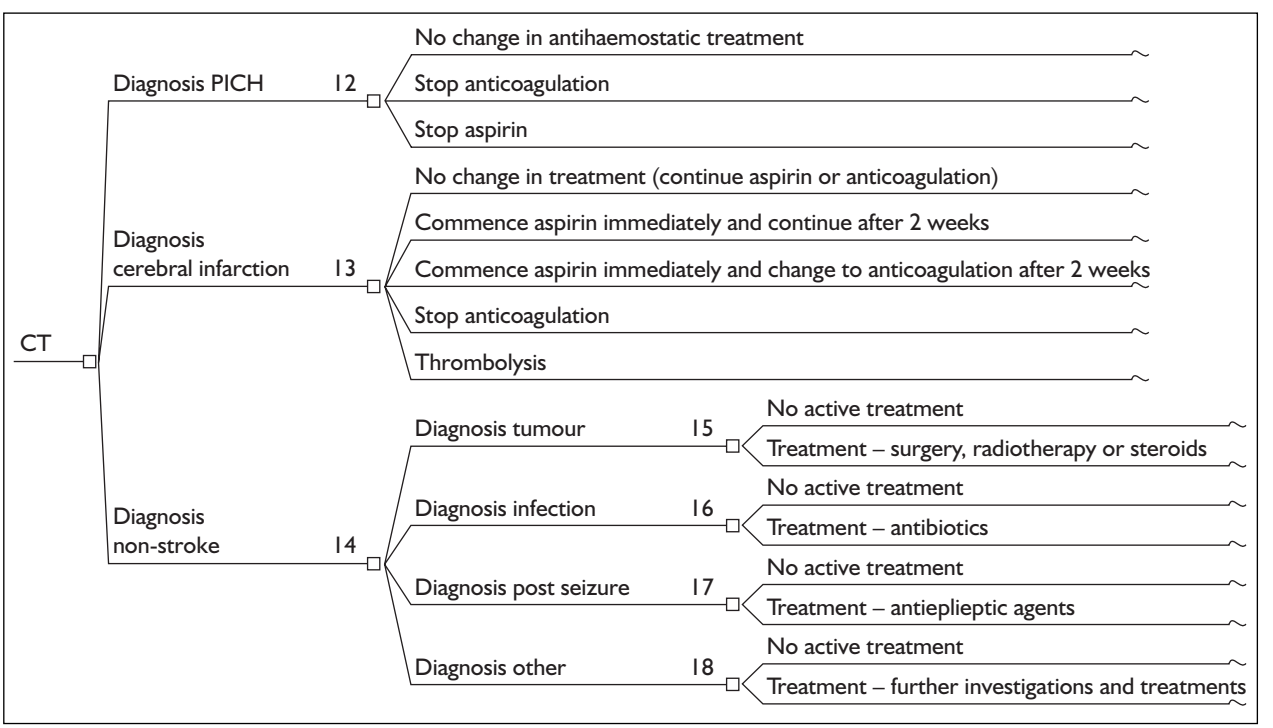


FIGURE 10 *Treatment options for patients suspected of having suffered a stroke*

(Chapter 3). For example, at node 5 patients who suffer a PICH could be given one of three possible diagnoses. First, a proportion of patients would be correctly diagnosed as having suffered a PICH. Some patients would be incorrectly diagnosed (as either a cerebral infarction or a non-stroke lesion) because the scan was misinterpreted and the PICH either overlooked or misdiagnosed as a tumour or another lesion.[287,292] If the scan had been done late (8 or more days after stroke) and the characteristic features of PICH on CT had resolved rapidly, then what was truly a PICH would be misdiagnosed as an infarct on CT (Chapter 3). Similarly, patients are diagnosed on the basis of the information provided by the CT at nodes 6–11.

A subtree was constructed to incorporate decisions regarding primary treatment (see *Figure 10* and Chapters 1 and 4). At node 12, patients diagnosed as having suffered a PICH would either have no change in antihaemostatic treatment, or be taken off anticoagulation or aspirin. Patients diagnosed as having an ischaemic stroke (node 13) would either:

- have no change in treatment
- commence aspirin immediately and continue this treatment after a period of 2 weeks
- commence aspirin immediately and then anticoagulation after 2 weeks
- have anticoagulation stopped
- or commence a hyperacute treatment such as thrombolysis.

At node 14, patients diagnosed as non-stroke were categorised as either: tumours (primary or secondary); infections such as meningitis, encephalitis or abscesses; epilepsy/postictal; or 'other', including non-vascular transient neurological events. Treatment decisions for these patients were incorporated at nodes 15, 16, 17 and 18. Patients with a tumour could have surgery, radiotherapy, steroids or no active treatment. Those suffering from infections would be treated with antibiotics or no active treatment. Patients who suffered a seizure would be treated with anti-epileptic agents. Finally, patients in the 'other' group were likely to receive further investigations to identify the cause of the event and have the appropriate treatment administered. Possible treatments include stopping or starting drugs, or procedures such as inserting a pacemaker.

Clinical outcomes were incorporated into the model in *Figure 11*. The modified Rankin scale (mRS) was used to assess the dependency of stroke survivors.[312,339] The mRS is an instrument used to measure the functional ability of stroke patients on a scale from 0 to 6. The scores of the mRS were collapsed to give three main categories: alive and independent (mRS 0–2), alive and dependent (mRS 3–5), and dead (mRS 6). Outcome was assessed at 6, 12 and 24 months after stroke. The mRS is widely used in research to assess outcome after stroke.[10,312,340–342] One concern with using this instrument in the present analysis was whether it would be sufficiently sensitive to detect changes in outcome. However, there appeared to be little alternative, as the mRS is widely used, and it was the outcome measure that was available for many of the primary data that were available for the model.

Summary of the development of the model

This section provides an overview of the model developed to assess the cost-effectiveness of CT scanning patients with suspected stroke. We have highlighted a number of challenges, such as identifying the appropriate imaging strategies to reflect likely practice, developing a model detailed enough to satisfy clinicians' awareness of the variety of acute stroke management decisions, to detect small differences in costs and outcomes between the strategies, and selecting appropriate methods to model the changes in outcomes. The next section describes the data collected to use in the model.

Data for the model: probability table, outcomes and costs

The purpose of this section is to describe the data required to analyse the model. The data include the estimates of the parameters for the main decision tree and the costs and outcomes

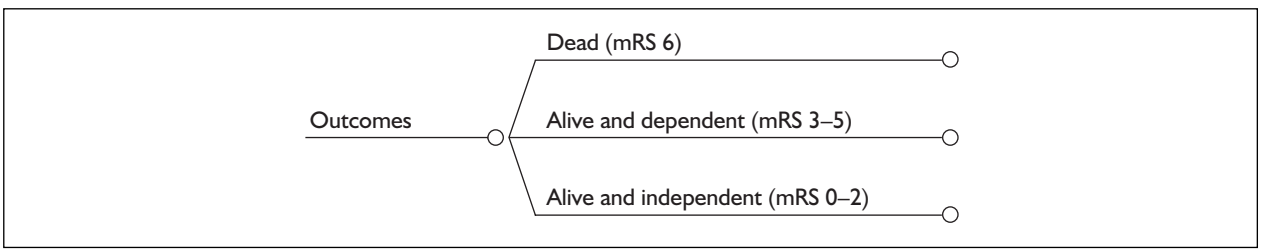


FIGURE 11 *Stroke outcomes*

associated with the comparator in the economic evaluation, that is, CT scan all patients suspected of having suffered a stroke within 48 hours. The data comprised survival data, quality-of-life data, cost information from three Scottish hospitals and resource use from the LSR.

Parameters for the main decision tree: probability tables

The parameter estimates for the main tree (*Figure 9*) were obtained from many sources. These included a series of systematic reviews of the clinical diagnosis of stroke, of CT scanning and of the effect of inadvertent administration of antithrombotic treatment to patients with PICH (see Chapters 2–4), individual studies from the literature and expert clinical opinion (only where data from primary studies or systematic reviews were lacking and it was not feasible to obtain the data in the present study). These estimates were supplemented with additional information from our own data, such as the LSR. *Tables 39–41* contain the base values for each of the parameters in the model.

Once the parameter estimates for the main tree had been identified, one of the main challenges in the study was to determine the way in which these estimates would be altered under the 12 different imaging strategies identified in the previous section ('Development of the cost-effectiveness model and decision tree', p. 73) (*Table 39*). The change in outcome was estimated with data from systematic reviews of randomised trials or from single randomised trials where possible. If this was not possible, expert clinical opinion was relied upon to provide an estimate of the change in outcome of less frequent problems for stroke and cerebral tumours, infections or other non-vascular causes of stroke. For example, in strategy 1 (scan all patients immediately) there were data from a systematic review to estimate change in outcome for those eligible for thrombolysis,[130] but not for those with cerebellar haematoma, or with massive PICH which might benefit from drainage of the haematoma,[51] or patients on anticoagulants who suffer a PICH, or those with tumours or infections. Therefore, for all of these latter patients, expert clinical opinion was used to interpret available data on incidence of these sorts of patient, the proportion who might have their haematoma drained, for example, and the likely effect on outcome. Patients with cerebellar haematoma and secondary hydrocephalus are at high risk of dying unless the hydrocephalus is

TABLE 39 *Parameter estimates including the probability of stroke, non-stroke and clinical subtypes*

Variable	Probability			Source
	Baseline (%)	95% CI (%)	Range (%)	
Stroke				
Proportion of actual stroke in a population presenting with stroke-like symptoms	81	77–84	73–100	Systematic review (Chapter 2)
Proportion of haemorrhagic stroke (PICH) in patients with true stroke	14.7	14.1–15.3	7.7–28.8	Systematic review (Chapter 2)
Proportion of cerebral infarctions in patients with true stroke	85.3	84.7–85.9	71.2–92.3	Systematic review (Chapter 2)
Non-stroke				
Proportion of primary brain tumours	15	8–26.3	2–15.2	Systematic review (Chapter 2)
Proportion of systemic infections	17	9–28.4	3–48.9	Systematic review (Chapter 2)
Proportion of post-seizures	17	9–28.4	2–44.7	Systematic review (Chapter 2)
Proportion of other diagnoses	51	37–68.4		Systematic review (Chapter 2)
Clinical subtypes				
PICH				
TACS	29	22–36		LSR, 2000
Non-TACS	71	64–78		LSR, 2000
Cerebral infarction				
TACS	13	11–15	13–17	LSR, 2000
LACS	28	25–30	21.3–28	LSR, 2000
PACS	42	40–45	34–52.8	LSR, 2000
POCS	17	15–19	9.4–24	LSR, 2000

TABLE 40 *Parameter estimates including the sensitivity and specificity of CT scans and stroke treatments*

Variable	Probability			Source
	Baseline (%)	95% CI (%)	Range (%)	
Sensitivity of CT scans				
Vascular versus non-vascular	0.90		0.88–0.95	Systematic review (Chapter 3)
PICH versus cerebral infarction				
Expert	1.0			Systematic review (Chapter 3)
Non-expert	0.77		0.6–0.8	
Specificity of CT scans				
Vascular versus non-vascular	0.98		0.95–1.0	Systematic review (Chapter 3)
PICH versus cerebral infarct				
Expert	1.0			Systematic review (Chapter 3)
Non-expert	0.8		0.6–0.9	
Stroke treatments				
PICH				
No change in antihaemostatic treatment	66.1	59.4–72.9		LSR, 2000
Stop anticoagulation	7.4	4.1–12.1		LSR, 2000
Stop aspirin	26.5	20.2–32.7		LSR, 2000
Infarct				
No change (continue aspirin or anticoagulation)	32.45			LSR, 2000
Commence aspirin immediately and continue after 2 weeks	61.70			LSR, 2000
Commence aspirin immediately and change to anticoagulation after 2 weeks	5.32			LSR, 2000
Stop anticoagulation	0.53			LSR, expert clinical opinion
Thrombolysis	0		0–10	LSR, expert clinical opinion

TABLE 41 *Parameter estimates for non-stroke treatments*

Variable	Probability			Source
	Baseline (%)	95% CI (%)	Range (%)	
Non-stroke treatments				
Tumour				
Surgery, radiotherapy, steroids	100			Expert clinical opinion
No active treatment	0			
Infections				
Antibiotics	100			Expert clinical opinion
No active treatment	0			
Post-seizure				
Antiepileptic agents	100			Expert clinical opinion
No active treatment	0			
Other diagnoses				
Further investigations and treatment	100			Expert clinical opinion
No active treatment	0			

drained (in which case they have a reasonable chance of making a reasonable recovery). Most clinicians would correct the haemostatic abnormality in patients on anticoagulants who have a PICH, to prevent the neurological deficit from deteriorating owing to increasing haematoma, and guidelines recommend this.[50,335] However, it is less clear that evacuating supratentorial haematomas is beneficial.[51] There are ongoing trials of evacuation versus best medical therapy for acute intraparenchymal haematomas,[51,52] but otherwise as yet no reliable evidence on specific treatment for PICH. Therefore, estimates of the proportion of patients with these types of stroke were obtained

from the literature, the LSR and expert opinion (*Tables 39–41*), but the effect on outcome had to be estimated mainly from expert opinion. However, collectively these latter patients make up only a small proportion of total strokes. While the lack of reliable evidence to indicate how outcomes after PICH might change with treatment introduced uncertainty, the majority of the more frequent stroke scenarios were covered by good evidence. These uncertainties in the model were explored using sensitivity analysis based on the upper and lower 95% confidence intervals for the point estimates of change where available or, where not available, the range of expert opinion, and the results are presented later in this chapter ('Results of the analysis of the cost-effectiveness model for CT scanning, and sensitivity analyses', p. 109).

Outcomes

The number of life years was estimated by modelling survival using 5 year survival data from the LSR (*Table 42*). Survival was modelled based on age and severity of the stroke using 6 monthly intervals over a 5 year period for 1854 first ever stroke patients using Cox's proportional hazards regression analysis. These patients represented all patients entered into the LSR with a first stroke between November 1990 and April 1999. In terms of the mRS, 83% of patients remained in the same state, 5.2% of patients improved, 8.6% of patients deteriorated, and 3.3% of patients had missing data between 12 months and 24 months after stroke. The number of years of survival was calculated, taking into consideration the age distribution, for stroke patients aged 45–89 years, in terms of 5 year age bands and severity (TACS, LACS, PACS and POCS) for a 5 year period (*Table 43*). Five year survival was initially calculated on the basis of individual years. However, it was considered to contribute very little additional information and therefore survival was aggregated in 5 year age bands.

Although modelling 5 year survival using data from the large LSR dataset has the advantage of providing a greater degree of precision, there were some limitations. For example, there was a larger proportion of milder strokes in the LSR than in some of the other Scottish hospitals for which comparable data were available[337] although, unfortunately, not in the detail that was required for the present study. There has been a major interest in stroke in the Western General Hospital (where the LSR is based) since the late 1980s, whereas other hospitals in the UK may not have had such highly developed stroke services during that time. However, that also means that the LSR data are more relevant to the immediate future as practice is changing in many hospitals in the UK in which stroke services are only now becoming more developed.[66,67] Very detailed information about treatments and management decisions was not recorded in the LSR. Although most patients with ischaemic stroke received aspirin from 1996 onwards, following publication of the IST, virtually none received thrombolysis at any time, or any neuroprotective treatment.

Clinical outcomes were assessed at 6, 12 and 24 months using data from the LSR (*Table 42* shows

TABLE 42 *Outcomes after stroke, at 6, 12 and 24 months by clinical subtype in terms of the mRS*

Outcome	Cerebral infarction (%)				PICH (%)	
	TACS	LACS	PACS	POCS	TACS	Non-TACS
60–64 years						
Alive and independent (mRS 0–2)	15.9	70.18	57.35	53.13	20.00	54.55
Alive and dependent (mRS 3–5)	47.37	19.30	20.59	37.50	20.00	27.27
Dead (mRS 6)	36.84	10.53	22.06	9.38	60.00	18.18
70–74 years						
Alive and independent (mRS 0–2)	8.3	64.87	54.16	65.91	0	42.86
Alive and dependent (mRS 3–5)	33.3	18.92	26.04	11.36	14.29	28.57
Dead (mRS 6)	58.3	16.22	19.79	22.73	85.71	28.57
80–84 years						
Alive and independent (mRS 0–2)	3.03	63.33	34.62	42.11	20.00	18.18
Alive and dependent (mRS 3–5)	24.24	20.00	25.64	21.05	60.00	36.36
Dead (mRS 6)	72.73	16.67	39.74	36.84	20.00	45.46

Source: LSR, 2000.

TABLE 43 *Mean survival (years) over the 5 years following a stroke by age and stroke severity (life years) (LSR and ISD)*

	Clinical subtype			
Age (years)	**TACS**	**PACS**	**LACS**	**POCS**
45–49	3.997	4.613	4.764	4.648
50–54	3.704	4.487	4.685	4.533
55–59	3.347	4.323	4.581	4.382
60–64	2.929	4.114	4.445	4.190
65–69	2.457	3.850	4.269	3.944
70–74	1.955	3.135	4.045	3.640
75–79	1.457	3.135	3.764	3.271
80–84	1.003	2.686	3.420	2.841
85–89	0.629	2.195	3.013	2.362

the percentages alive and independent, alive and dependent, and dead at 24 months after first stroke). While the LSR provided data on clinical outcomes at these points in time, there was no information beyond 2 years after stroke. This model examined the effect of scanning on survival over a 5 year period and therefore it was assumed that clinical outcomes remained static from 2 to 5 years after stroke. Given that there was insufficient evidence available to suggest how outcomes vary between year 2 and year 5 after stroke, this assumption was considered to be acceptable. *Table 43* shows mean survival in years over the 5 years after first stroke in the 1854 patients with first stroke in the LSR, divided into 5 year age bands according to the patient's age at the time of the stroke and by the clinical subtype of stroke.

Estimation of quality of life

Utility weights were derived to reflect the patients' opinion of the quality of life associated with 'independent survival after stroke' and 'dependent survival after stroke' health states. The utility weight is a score between 0 and 1 which reflects the quality of life associated with the health state, where 0 = death and 1 = full health. This information can reflect the opinion of the patient, carer, physician, public health doctor or government planner,[343] but the present study used data obtained previously in a survey of UK patients randomised in the IST.[10] The EQ5D health state at 18 months following stroke is known for these patients as is their modified mRS at 12 and 24 months (from the LSR) (*Table 44*).[344,345] By restricting attention to the 83% of patients whose mRS did not change, the relationship between EQ5D health state and independent and dependent survival following stroke was identified. The final step involved applying the scores that have been estimated for the relevant EQ5D states using the time trade off (TTO) tariff derived for the UK population.[346] Given that a significant proportion of stroke patients are aged 60 years and over, the TTO values for older people are used in the present study. The resulting estimated EQ5D scores for independent and dependent survival following stroke are shown in *Table 45* for all patients and those who remained in the same state between the two periods to remove any effect of the differential timing.

TABLE 44 *mRS health states for IST patients who were also in the LSR at 12 and 24 months after stroke*[10]

mRS	**12 months**	**24 months**
n	149	145
Alive and independent (mRS 0–2)	98 (65.8%)	92 (63.4%)
Alive and dependent (mRS 3–5)	51 (33.3%)	49 (33.8%)
Dead (mRS 6)	0	4 (2.8%)

These data enabled the expected number of QALYs to be calculated by multiplying utility weights, which reflect the quality of life associated with each of the health states after stroke (alive and independent, alive and dependent and dead) by the number of life years resulting from a particular treatment strategy.

A combination of evidence from the literature and expert clinical opinion was used to determine whether, and how, clinical outcomes (mRS health states) and or survival are altered in terms of each of the 12 CT imaging strategies. These results are presented later in this chapter ('Results of the analysis of the cost-effectiveness model for CT scanning, and sensitivity analyses', p. 109).

Costs

The costs in this model were estimated from the perspective of the health service. Key areas of

TABLE 45 *mRS health states and TTO tariff weights based on IST and LSR data*

mRS	TTO weights	TTO weights – constant mRS at 12 and 24 months
n	146	124
Alive and independent		
n	95	84
Mean	0.76	0.78
95% CI	0.72–0.81	0.73–0.82
Median	0.80	0.80
Minimum	0.06	0.06
Maximum	1	1
Alive and dependent		
n	51	40
Mean	0.37	0.34
95% CI	0.28–0.47	0.23–0.45
Median	0.51	0.33
Minimum	–0.57	–0.57
Maximum	1	1

resource use include CT scans, primary treatment (which consists of primary intervention and LOS for the first episode of care) and subsequent stroke-related hospital admissions within 5 years. These data were collected from a number of sources.

Information on LOS in hospital was obtained from the General Acute inpatient and day-case discharge data set (SMR01) from the ISD, Scotland (National Health Service in Scotland Information and Statistics Division). Data on LOS following a stroke were requested for the sample of 1854 first ever stroke patients from the LSR. LOS data were obtained for the period of 5 years after the first stroke, across different hospital settings, taking into account the type and severity of stroke.

To obtain the data from ISD, it was necessary to apply to the ISD Privacy Advisory Committee for permission to use the data, to supply ISD with a dataset containing sufficient identifiers to enable their statisticians to match with their data, and to decode their return dataset. This was complex, as the admissions for each patient were not already linked together and had to be matched manually to obtain total LOS. For example, if a patient had been admitted to the Western General Hospital and then transferred for rehabilitation to the adjacent hospital, this would have been recorded as two separate admissions by ISD, despite its being part of the one disease-related admission.

The ISD record linkage provided data on 1778 patients (95.9%) from the original dataset. Of the 1778 patients identified by the linkage, 1241 patients (69.8%) had at least one continuous inpatient stay for the 5 year period. The LSR records indicate that 644 of the original 1854 patients (34.7%) were not admitted to the Western General Hospital when the stroke was diagnosed and were managed as outpatients. These patients were excluded from the analysis of LOS.

The mean and median LOS for the first episode of care by type and severity of stroke are reported in *Table 46*. It is interesting to note the marked difference in LOS between patients who were alive and independent at 6 months and those who were dependent. The implication would be that a small shift in the proportion of patients from dependent to independent at 6 months would have a marked effect on reducing overall LOS. *Table 47* presents the total average LOS for subsequent stroke-related hospital admissions over the 5 year period. In both tables, LOS is presented in terms of admissions to teaching hospitals, large general hospitals and long-stay hospitals. Five observations were excluded from this analysis, where LOS of individual hospital admissions was greater than 365 days. In terms of the first episode of care, for both PICH and cerebral infarction, the average LOS was influenced by the severity of the stroke, as patients who had suffered a TACS generally had longer hospital admissions than those who suffered a less severe stroke. This difference was less apparent in terms of subsequent stroke-related hospital admissions over the 5 year period, but was still greater for the TACS than non-TACS. Note that although the majority of subsequent admissions were to the Western General Hospital or one of the immediate surrounding hospitals, patients were also admitted to hospitals as far away as Glasgow, Falkirk, Perth, Dumfries and the Borders.

TABLE 46 *Mean LOS in hospital for the first episode of care after stroke by type of stroke, functional status and type of hospital (6 month mRS)[a] (LSR data linked to ISD)*

	LOS in hospital					
Stroke by clinical subtype	**Teaching hospital**		**Large general hospital**		**Long-stay hospital**	
PICH						
TACS						
Alive and independent (*n*)	56.3	(3)	35	(1)	31.0	(2)
Alive and dependent (*n*)	79.5	(10)	–		82.8	(5)
Dead (*n*)	14.4	(18)	9.5	(2)	42.0	(1)
Non-TACS						
Alive and independent (*n*)	13.8	(34)	11.6	(8)	34.9	(8)
Alive and dependent (*n*)	67.4	(24)	16.3	(3)	49.0	(4)
Dead (*n*)	18.3	(13)	53.0	(1)	–	
Cerebral infarction						
TACS						
Alive and independent (*n*)	32.9	(15)	7.0	(1)	24.5	(2)
Alive and dependent (*n*)	75.4	(63)	26.5	(2)	90.1	(12)
Dead (*n*)	22.5	(81)	20.5	(2)	45.0	(12)
LACS						
Alive and independent (*n*)	12.3	(100)	12.7	(6)	68.6	(5)
Alive and dependent (*n*)	38.7	(65)	29.3	(6)	61.2	(11)
Dead (*n*)	25.9	(11)	–		15.7	(3)
PACs						
Alive and independent (*n*)	11.2	(156)	14.5	(18)	25.1	(19)
Alive and dependent (*n*)	49.9	(120)	17.9	(11)	67.1	(27)
Dead (*n*)	25.3	(60)	33.3	(3)	22.9	(16)
POCs						
Alive and independent (*n*)	9.6	(80)	6.4	(9)	22.7	(3)
Alive and dependent (*n*)	27.0	(33)	8.5	(6)	31.0	(6)
Dead (*n*)	13.4	(17)	–		19.7	(3)

[a] Observations with LOS = 0 or > 365 days were excluded.
Note that patients were first admitted to the teaching hospital and thence may have been transferred to the general or long-stay hospital or both.

The change in health state (mRS) and LOS then resulting from each of the 12 scanning strategies is shown in *Table 48*. This details for each of the 12 strategies by diagnosis and associated treatment, the assumed changes in clinical outcomes and in LOS. The evidence base for each of these assumptions is indicated. While many of these can be and have been explored using sensitivity analysis the table highlights the challenges of assessing the impact of different CT scanning strategies.

Unit costs were derived using a combination of both a detailed costing approach and estimates available in the published literature. Detailed costing was undertaken to calculate the cost of CT scans across a range of hospitals and during 'normal working hours' as well as 'out of hours' to provide typical examples. A detailed description of the methods and results of the CT costing study is reported in Appendix 8. This required first an approach to several Scottish hospitals to ascertain whether detailed CT costing data could be obtained within the period of the project. In each of the three different Scottish hospitals where this approach was successful, this was followed by close liaison with an NHS-funded health service manager to obtain details of capital, marginal, recurrent and staff costs to obtain a total cost for a CT scan both in normal working hours and outside normal working hours. This enabled the cost of CT scanning to be estimated for a large teaching hospital and two large general hospitals, one rural, one urban. These costs were intended to provide three suitably stylised cases against which other health care providers could compare their own costs in the model. A sensitivity analysis based on the minimum and maximum times taken to scan a patient (mainly adjusting the cost of staff time) was also performed to obtain a 'low' and 'high' estimate of cost for each hospital in and out of hours. A summary of the results of the costing study is presented in *Table 49*. The average cost of CT scanning in a teaching hospital was £42.96 during normal working hours and £79.35 out of

TABLE 47 *Mean LOS in hospital of subsequent episodes of care by type of stroke, functional status and type of hospital (24 month mRS)*[a]

	LOS in hospital					
Stroke by clinical subtype	**Teaching hospital**		**Large general hospital**		**Long-stay hospital**	
PICH						
TACS						
Alive and independent (*n*)	9.5	(2)	9	(1)	8.5	(2)
Alive and dependent (*n*)	62.0	(5)	15.0	(1)	12.0	(2)
Dead (*n*)	10.5	(6)	–		–	
Non-TACS						
Alive and independent (*n*)	13.5	(13)	10.7	(3)	60.0	(2)
Alive and dependent (*n*)	33.9	(14)	34.0	(3)	65.5	(6)
Dead (*n*)	17.5	(10)	–		64.8	(5)
Cerebral infarction						
TACS						
Alive and independent (*n*)	28.3	(3)	23.0	(1)	56.0	(3)
Alive and dependent (*n*)	36.2	(19)	42.2	(4)	64.7	(20)
Dead (*n*)	30.6	(20)	53.0	(1)	53.8	(8)
LACS						
Alive and independent (*n*)	6.7	(14)	6	(7)	33.0	(11)
Alive and dependent (*n*)	48.2	(17)	14.5	(2)	67.5	(15)
Dead (*n*)	35.7	(4)	37.0	(1)	26.0	(4)
PACS						
Alive and independent (*n*)	12.1	(39)	16.0	(9)	46.5	(10)
Alive and dependent (*n*)	30.5	(49)	23.1	(12)	68.2	(34)
Dead (*n*)	25.6	(20)	–		33.7	(13)
POCS						
Alive and independent (*n*)	19.8	(23)	8	(6)	15.2	(5)
Alive and dependent (*n*)	22.0	(8)	6.5	(2)	63.2	(5)
Dead (*n*)	9.5	(6)	–		18.8	(4)

[a] Observations with LOS = 0 or > 365 days were excluded.

hours. The average cost of CT scanning varied from £30.23–£71.47 in the large teaching hospitals during normal working hours to £55.05–£173.46 out of hours. The costs of scanning in the urban district general hospitals (DGH) were lower than those estimated for the rural DGH, but higher than those for the teaching hospital during normal working hours. The out-of-hours costs for the urban DGH were not much different to those for normal working hours, in contrast to the teaching and rural DGH, where the out-of-hours costs were substantially higher than the daytime costs. The main reason for this appeared to be that the radiographers in the urban DGH did not have a minimum billing rate per call as in the other two hospitals, possibly because the radiographer on call was able to operate CT as well as other modalities. Thus, a dedicated CT radiographer in addition to a general radiographer was not required.

The cost per inpatient day was estimated using the NHS Scottish Health Service costs.[69] An average cost per bed day was estimated for a teaching hospital, a large general hospital and a long-stay hospital using the relevant inpatient in acute specialities costs (medical and neurology). We considered obtaining more detailed costs for further investigations and primary treatment, but this would not have been practical as the costs overall are small compared with the cost of time spent in a hospital bed. In addition, the NHS Scottish Health Service costs include an amount for general investigations and treatments. The average cost per bed day for long-stay hospitals was generated using the hospital running costs for a subgroup of relevant hospitals. The subgroup of hospitals included long-stay hospitals, small long-stay hospitals, long-stay acute hospitals, long-stay acute hospitals, long-stay psychiatric hospitals and long-stay community hospitals). The average cost per bed day ranged from £116 for long-stay hospitals to £239 for teaching hospitals. Costs for stroke are also incurred in the community, but we did not have time or resources to determine these. In any case the cost of care for severely disabled patients is at least partially included in the cost of long-term care included above.

TABLE 48 *Incremental outcomes associated with the CT scanning strategies compared with the main comparator (withhold aspirin until after the CT scan)*

CT scanning strategy	Diagnosis	Treatment	Change in clinical outcomes	Change in LOS[a]
1. Scan all immediately	Cerebral infarctions which experience HTI Clinically significant HTI occurs in 1.5% (95% CI 0.8% to 2.2%) (Lindley *et al.*, unpublished)	Treat appropriately	Unable to quantify the impact on outcomes	Not calculated
	Cerebral infarctions diagnosed in 3 hours 4% of cerebral infarctions (10% of cerebral infarctions are eligible, but 6% have contraindications to tPA)	Administer tPA	Change in outcomes (Cochrane, 2001)[130]: • 140/1000 more alive and independent (95% CI 80/1000 more to 200/1000 more) • 0/1000 difference in deaths (95% CI 40/1000 fewer to 50/1000 more) • *No tPA* / *tPA* / *mRS*: 28% / 28% / dead; 32% / 27% / dependent; 39% / 45% / independent	Average LOS 31 days for one untreated patient, and 29.3 days for rt-PA-treated patients, therefore tPA ↓ LOS by 1.7 days per patient on average *No tPA* / *tPA*: 9,240 / 9,240 day/1000 pts; 16,320 / 13,770 day/1000 pts; 5,460 / 6,300 day/1000 pts
	Patients in a life-threatening condition due to cerebellar haematoma or cerebral infarct and secondary hydrocephalus	Drainage of hydrocephalus	May result in a better recovery and prevent death in the acute phase. No evidence available on the impact on outcomes	Half patients improve to independence, therefore ↓ LOS from 51 to 14 days for half patients[b]
	30% of PICH-TACS (Patients in a life-threatening condition from PICH)	Early drainage	Difficult to quantify effect on outcome but may result in better outcomes and prevent deaths in the acute phase	↓ LOS from 51 to 14 days for 20% of patients treated in this way[b]
	Patients on anticoagulants who suffer a PICH	Effects of anticoagulation are reversed more quickly	The severity of the stroke could possibly be reduced if patients were diagnosed earlier, but there is no evidence currently available on the impact on outcomes	↓ LOS by 1 week for patients treated in this way[b]
	Tumours and infections	Correct management	Change in outcomes: 1/1000 fewer deaths if infections were managed correctly Tumours occupy fewer bed days, but any reduction in LOS would be marginal if patients would otherwise be scanned within 48 hours	Infections: ↓ LOS by 1 week on average for all patients managed correctly[b] Tumours: ↓ LOS by a few days per patient. Note: strategies 1 and 2, little effect compared with base; strategy 4, add 7 days to this; strategy 5, add 14 days

[a] These figures are included here to show how mRS was converted to a treatment effect on LOS. These figures are approximate, more precise figures were used in the actual model. Similar figures were calculated for the effect of aspirin on outcome after ischaemic stroke and haemorrhagic stroke.

[b] Estimates of the effect on LOS based on clinical experience and what evidence available in the literature. However, these estimates may be inaccurate and so extensive sensitivity testing will be undertaken to vary the effect on LOS and determine the confidence limits of the effect of CT scanning on the patients in these minority groups.

continued

TABLE 48 *Incremental outcomes associated with the CT scanning strategies compared with the main comparator (withhold aspirin until after the CT scan) (cont'd)*

CT scanning strategies	Diagnosis	Treatment	Outcomes
2. Scan patients on anticoagulants or in a life-threatening condition immediately and scan all remaining patients within 24 hours	Patients in a life-threatening condition who suffer a cerebral infarction 2% of cerebral infarctions Note: this excludes patients on anticoagulants	Administer tPA	Change in outcomes (Cochrane, 2001): • 140/1000 more alive and independent (95% CI 80/1000 more to 200/1000 more) • 0/1000 difference in deaths (95% CI 40/1000 fewer to 50/1000 more) • *No tPA* *tPA* *mRS* 28% 28% dead 32% 27% dependent 39% 45% independent
	Patients in a life-threatening condition due to cerebellar haematoma or cerebral infarct and secondary hydrocephalus	Drainage of hydrocephalus	May result in a better recovery and prevent death in the acute phase. No evidence available on the impact on outcomes
	Patients on anticoagulants who suffer a PICH	Effects of anticoagulation are reversed more quickly	The severity of the stroke could possibly be reduced if patients are diagnosed earlier, but there is no evidence currently available on the impact on outcomes
	30% of PICH-TACS (Patients in a life-threatening condition from PICH)	Early drainage	Difficult to quantify effect on outcome, but may result in better outcomes and prevent deaths in the acute phase
	Tumours and infections	Correct management	Change in outcomes: • 1/1000 fewer deaths if infections were managed correctly • Tumours occupy fewer bed days, but any reduction in LOS would be marginal if patients would otherwise be scanned within 48 hours
3. Scan patients on anticoagulants or in a life-threatening condition immediately and scan all remaining patients within 48 hours	Patients in a life-threatening condition who suffer a cerebral infarction 2% of cerebral infarctions Note: this excludes patients on anticoagulants	Administer tPA	Change in outcomes (Cochrane, 2001): • 140/1000 more alive and independent (95% CI 80/1000 more to 200/1000 more) • 0/1000 difference in deaths (95% CI 40/1000 fewer to 50/1000 more) • *No tPA* *tPA* *mRS* 28% 28% dead 32% 27% dependent 39% 45% independent

continued

TABLE 48 *Incremental outcomes associated with the CT scanning strategies compared with the main comparator (withhold aspirin until after the CT scan) (cont'd)*

CT scanning strategies	Diagnosis	Treatment	Outcomes
	30% of PICH-TACS (Patients in a life-threatening condition from PICH)	Early drainage	Difficult to quantify effect on outcome, but may result in better outcomes and prevent deaths in the acute phase
	Patients in a life-threatening condition due to cerebellar haematoma or cerebral infarction and secondary hydrocephalus	Drainage of hydrocephalus	May result in a better recovery and prevent death in the acute phase. No evidence available on the impact on outcomes
	Patients on anticoagulants who suffer a PICH	Effects of anticoagulation are reversed more quickly	The severity of the stroke could possibly be reduced if patients are diagnosed earlier, but there is no evidence currently available on the impact on outcomes.
4. Scan patients on anticoagulants or in a life-threatening condition immediately and scan all remaining patients within 7 days	Patients in a life-threatening condition who suffer a cerebral infarction 2% of cerebral infarctions Note: this excludes patients on anticoagulants	Administer tPA	Change in outcomes (Cochrane, 2001)[130]: • 140/1000 more alive and independent (95% CI 80/1000 more to 200/1000 more) • 0/1000 difference in deaths (95% CI 40/1000 fewer to 50/1000 more) • *No tPA* *tPA* *mRS* 28% 28% dead 32% 27% dependent 39% 45% independent
	30% of PICH-TACS (Patients in a life-threatening condition from PICH)	Early drainage	Difficult to quantify effect on outcome, but may result in better outcomes and prevent deaths in the acute phase
	Patients in a life-threatening condition due to cerebellar haematoma or cerebral infarction and secondary hydrocephalus	Drainage of hydrocephalus	May result in a better recovery and prevent death in the acute phase. No evidence available on the impact on outcomes
	Patients on anticoagulants who suffer a PICH	Effects of anticoagulation are reversed more quickly	The severity of the stroke could possible be reduced if patients are diagnosed earlier, but there is no evidence currently available on the impact on outcomes

continued

TABLE 48 *Incremental outcomes associated with the CT scanning strategies compared with the main comparator (withhold aspirin until after the CT scan) (cont'd)*

CT scanning strategies	Diagnosis	Treatment	Outcomes
	Diagnosis of the remaining cerebral infarctions is delayed from 48 hours to 7 days	Aspirin is administered at 7 days rather than 48 hours	Change in outcomes (IST)[41–43]: • 0.5% increase in recurrent or non-fatal strokes (0.6% in the aspirin group versus 1.1% in the control group) • 0.2% increase in death without further stroke (2.6% in the aspirin group versus 2.8% in the control group) • 0.6% increase in further stroke or death (3.8% in the aspirin group versus 4.4% in the control group)
	Diagnosis of non-stroke patients is delayed from 48 hours to 7 days	Appropriate treatment is administered at 7 days rather than 48 hours	Change in outcomes: • 1/2000 more deaths from infections of the central nervous system, e.g. encephalitis and meningitis. Failure to start tumours on steroids and investigate properly would increase LOS by 7 days
5. Scan patients on anticoagulants or in a life-threatening condition immediately and scan all remaining patients within 14 days	Patients in a life threatening condition who suffer a cerebral infarction 2% of cerebral infarctions Note: this excludes patients on anticoagulants	Administer tPA	Change in outcomes (Cochrane, 2001)[130]: • 140/1000 more alive and independent (95% CI 80/1000 more to 200/1000 more) • 0/1000 difference in deaths (95% CI 40/1000 fewer to 50/1000 more) • *No tPA* / *tPA* / *mRS*: 28% / 28% / dead; 32% / 27% / dependent; 39% / 45% / independent
	30% of PICH-TACS (Patients in a life-threatening condition from PICH)	Early drainage	Difficult to quantify effect on outcome, but may result in better outcomes and prevent deaths in the acute phase
	Patients in a life-threatening condition due to cerebellar haematoma or cerebral infarction and secondary hydrocephalus	Drainage of hydrocephalus	May result in a better recovery and prevent death in the acute phase. No evidence available on the impact on outcomes
	Patients on anticoagulants who suffer a PICH	Effects of anticoagulation are reversed more quickly	The severity of the stroke could possibly be reduced if patients are diagnosed earlier, but there is no evidence currently available on the impact on outcomes

continued

TABLE 48 *Incremental outcomes associated with the CT scanning strategies compared with the main comparator (withhold aspirin until after the CT scan) (cont'd)*

CT scanning strategies	Diagnosis	Treatment	Outcomes
	Diagnosis of the remaining cerebral infarctions is delayed from 48 hours to 14 days	Aspirin is administered at 14 days rather than 48 hours	Change in outcomes: IST/CAST[41–43] • Further stroke or death A delay of 7 days results in an increase in further stroke or death by 0.6% (3.8% to 4.4%) A delay of 8–14 days results in an increase in further stroke or death by 0.3% (2.8% to 3.1%) The total increase in further stroke or death from 2 to 14 days is 0.9% • Death without further stroke A delay of 7 days results in an increase in death without further stroke by 0.2% (2.6% to 2.8%) A delay of 8–14 days results in an increase in death without further stroke by 0.3% (1.6% to 1.9%) The total increase in death without further stroke from 2 to 14 days is 0.5% • Recurrence of fatal or non-fatal cerebral infarction A delay of 7 days results in an increase in recurrence of fatal or non-fatal cerebral infarction of 0.5% (0.6% to 1.1%) A delay of 8–14 days results in an increase in recurrence of fatal or non-fatal cerebral infarction of 0.2% (0.5% to 0.7%) The total increase in recurrence of fatal or non-fatal cerebral infarction from 2 to 14 days is 0.7% • ATT[350] In acute stroke, non-fatal stroke increases by 0.4% (2.1% to 2.5%), vascular deaths increase by 0.5% (6.0% to 6.5%) and all deaths increase by 0.6% (6.1% to 6.6%)

continued

TABLE 48 *Incremental outcomes associated with the CT scanning strategies compared with the main comparator (withhold aspirin until after the CT scan) (cont'd)*

CT scanning strategies	Diagnosis	Treatment	Outcomes
	Incorrect diagnosis of PICH. The CT versus MR study presented in Chapter 3 indicates that 40% of PICH would be misdiagnosed as they would not be visible on a CT scan at 14 days. Out of 228 patients 6/8 PICH strokes would be misdiagnosed as infarcts and 13/15 haemorrhagic transformations were diagnosed as infarcts (of a population of outpatients with mild stroke). A total of 19/23 (19/228 or 30/1000) patients were misdiagnosed because bleeding was missed	Incorrect treatment is administered	Change in outcomes: • Longer term actuarial risk of recurrent PICH in survivors of PICH to 30 days was 7% per year in those not given aspirin[340] (OCSP). A 40% (30% to 50%) relative increase at 1 year in recurrent PICH was estimated if these patients were given aspirin, a 20% relative increase in death and a 20–30% increase in dependency • A systematic review of stroke and stroke survivors[109] indicated that 4.3% of survivors have any recurrent stroke (CI 3.5% to 5.4%), 2.4% have a haemorrhagic stroke (CI 1.9% to 2.7%) and there are 8.8% deaths per year (CI 5.2% to 11.0%) (assuming aspirin was not given). If aspirin was given this would result in a 3.7% (CI 2.7% to 3.8%) increase in haemorrhagic stroke and a 12.3% (a 7.3% to 15.4%) increase in deaths
	Delay in diagnosis of tumours and infections	Correct management	2/2000 more deaths from incorrectly managed infections and tumours (95% CI 1/2000 to 5/2,000)
6. Scan patients on anticoagulants, those in a life-threatening condition or candidates for hyperacute treatment immediately and scan all remaining patients within 24 hours	Patients in a life-threatening condition who suffer a cerebral infarction 4% of cerebral infarctions Note this excludes patients on anticoagulants	Administer tPA	Change in outcomes (Cochrane, 2001)[130]: • 140/1000 more alive and independent (95% CI 80/1000 more to 200/1000 more) • 0/1000 difference in deaths (95% CI 40/1000 fewer to 50/1000 more) • *No tPA* *tPA* 28% 28% 32% 27% 39% 45%
	30% of PICH-TACS	Early drainage	Difficult to quantify effect on outcome, but may result in better outcomes and prevent deaths in the acute phase.
	Patients in a life-threatening condition due to cerebellar haematoma, cerebral infarct and secondary hydrocephalus	Drainage of hydrocephalus	May result in a better recovery and prevent death in the acute phase. No evidence available on the impact on outcomes

continued

TABLE 48 *Incremental outcomes associated with the CT scanning strategies compared with the main comparator (withhold aspirin until after the CT scan) (cont'd)*

CT scanning strategies	Diagnosis	Treatment	Outcomes
	Patients on anticoagulants who suffer a PICH	Effects of anticoagulation are reversed more quickly	The severity of the stroke could possibly be reduced if patients are diagnosed earlier, but there is no evidence currently available on the impact on outcomes
	Tumours and infections	Correct management	Change in outcomes: • 1/1000 fewer deaths if infections were managed correctly • Tumours occupy fewer bed days, but any reduction in LOS would be marginal if patients would otherwise be scanned within 48 hours
7. Scan patients on anticoagulants, those in a life-threatening condition or candidates for hyperacute treatment immediately and scan all remaining patients within 48 hours	Patients in a life-threatening condition who suffer a cerebral infarction 4% of cerebral infarctions Note: this excludes patients on anticoagulants	Administer tPA	Change in outcomes (Cochrane, 2001)[130]: • 140/1000 more alive and independent (95% CI 80/1000 more to 200/1000 more) • 0/1000 difference in deaths (95% CI 40/1000 fewer to 50/1000 more) • *No tPA* *tPA* 28% 28% 32% 27% 39% 45%
	30% of PICH-TACS	Early drainage	Difficult to quantify effect on outcome, but may result in better outcomes and prevent deaths in the acute phase
	Patients in a life-threatening condition due to cerebellar haematoma, cerebral infarct and secondary hydrocephalus	Drainage of hydrocephalus	May result in a better recovery and prevent death in the acute phase. No evidence available on the impact on outcomes
	Patients on anticoagulants who suffer a PICH	Effects of anticoagulation are reversed more quickly	The severity of the stroke could possibly be reduced if patients are diagnosed earlier, but there is no evidence currently available on the impact on outcomes

continued

TABLE 48 *Incremental outcomes associated with the CT scanning strategies compared with the main comparator (withhold aspirin until after the CT scan) (cont'd)*

CT scanning strategies	Diagnosis	Treatment	Outcomes
8. Scan patients on anticoagulants, those in a life-threatening condition or candidates for hyperacute treatment immediately and scan all remaining patients within 7 days	Patients in a life-threatening condition who suffer a cerebral infarction 4% of cerebral infarctions Note this excludes patients on anticoagulants	Administer tPA	Change in outcomes (Cochrane, 2001)[130]: • 140/1000 more alive and independent (95% CI 80/1000 more to 200/1000 more) • 0/1000 difference in deaths (95% CI 40/1000 fewer to 50/1000 more) • *No tPA* *tPA* 28% 28% 32% 27% 39% 45%
	30% of PICH-TACS	Early drainage	Difficult to quantify effect on outcome, but may result in better outcomes and prevent deaths in the acute phase
	Patients in a life-threatening condition due to cerebellar haematoma and cerebral infarct and secondary hydrocephalus	Drainage of the hydrocephalus	May result in a better recovery and prevent death in the acute phase. No evidence available on the impact on outcomes
	Patients on anticoagulants who suffer a PICH	Effects of anticoagulation are reversed more quickly	The severity of the stroke could possibly be reduced if patients are diagnosed earlier, but there is no evidence currently available on the impact on outcomes
	Diagnosis of the remaining cerebral infarctions is delayed from 48 hours to 7 days	Aspirin is administered at 7 days rather than 48 hours	Change in outcomes (IST)[41–43]: • 0.5% increase in recurrent or non-fatal strokes (0.6% in the aspirin group versus 1.1% in the control group) • 0.2% increase in death without further stroke (2.6% in the aspirin group versus 2.8% in the control group) • 0.6% increase in further stroke or death (3.8% in the aspirin group versus 4.4% in the control group)
	Diagnosis of non-stroke patients is delayed from 48 hours to 7 days	Appropriate treatment is administered at 7 days rather than 48 hours	Change in outcomes: • 1/2000 more deaths from infections of the central nervous system, e.g. encephalitis or meningitis. Failure to start tumours on steroids and investigate properly would increase LOS by 7 days

continued

TABLE 48 *Incremental outcomes associated with the CT scanning strategies compared with the main comparator (withhold aspirin until after the CT scan) (cont'd)*

CT scanning strategies	Diagnosis	Treatment	Outcomes
9. Scan patients on anticoagulants, those in a life-threatening condition or are candidates for hyperacute treatment immediately and scan all remaining patients within 14 days	Patients in a life-threatening condition who suffer a cerebral infarction 4% of cerebral infarctions Note: this excludes patients on anticoagulants	Administer tPA	Change in outcomes (Cochrane, 2001)[130]: • 140/1000 more alive and independent (95% CI 80/1000 more to 200/1000 more) • 0/1000 difference in deaths (95% CI 40/1000 fewer to 50/1000 more) • *No tPA* *tPA* 28% 28% 32% 27% 39% 45%
	30% of PICH-TACS	Early drainage	Difficult to quantify effect on outcome, but may result in better outcomes and prevent deaths in the acute phase
	Patients in a life-threatening condition due to cerebellar haematoma and cerebral infarct and secondary hydrocephalus	Drainage of hydrocephalus	May result in a better recovery and prevent death in the acute phase. No evidence available on the impact on outcomes
	Patients on anticoagulants who suffer a PICH	Effects of anticoagulation are reversed more quickly	The severity of the stroke could possibly be reduced if patients are diagnosed earlier, but there is no evidence currently available on the impact on outcomes

continued

TABLE 48 *Incremental outcomes associated with the CT scanning strategies compared with the main comparator (withhold aspirin until after the CT scan) (cont'd)*

CT scanning strategies	Diagnosis	Treatment	Outcomes
	Diagnosis of the remaining cerebral infarctions is delayed from 48 hours to 14 days	Aspirin is administered at 14 days rather than 48 hours	Change in outcomes: IST/CAST[41–43] • Further stroke or death A delay of 7 days results in an increase in further stroke or death by 0.6% (3.8% to 4.4%) A delay of 8–14 days results in an increase in further stroke or death by 0.3% (2.8% to 3.1%) The total increase in further stroke or death from 2 to 14 days is 0.9% • Death without further stroke A delay of 7 days results in an increase in death without further stroke by 0.2% (2.6% to 2.8%) A delay of 8–14 days results in an increase in death without further stroke by 0.3% (1.6% to 1.9%) The total increase in death without further stroke from 2 to 14 days is 0.5% • Recurrence of fatal or non-fatal cerebral infarction A delay of 7 days results in an increase in recurrence of fatal or non-fatal cerebral infarction of 0.5% (0.6% to 1.1%) A delay of 8–14 days results in an increase in recurrence of fatal or non-fatal cerebral infarction of 0.2% (0.5% to 0.7%) The total increase in recurrence of fatal or non-fatal cerebral infarction from 2 to 14 days is 0.7% ATT[350] In acute stroke, non-fatal stroke increases by 0.4% (2.1% to 2.5%), vascular deaths increase by 0.5% (6.0% to 6.5%) and all deaths increase by 0.6% (6.1% to 6.6%)

continued

TABLE 48 *Incremental outcomes associated with the CT scanning strategies compared with the main comparator (withhold aspirin until after the CT scan) (cont'd)*

CT scanning strategies	Diagnosis	Treatment	Outcomes
	Incorrect diagnosis of PICH. The CT versus MR study presented in Chapter 3 indicates that 40% of PICH would be misdiagnosed as they would not be visible on a CT scan at 14 days. Out of 228 patients, 6/8 PICH strokes would be diagnosed as infarcts and 13/15 haemorrahagic transformations were diagnosed as infarcts of a population of 228 patients (outpatients with mild stroke). A total of 19/23 (19/228 or 30/1000) patients were misdiagnosed because bleeding was missed	Incorrect treatment is administered	Change in outcomes: • Longer term actuarial risk of recurrent PICH in survivors of PICH to 30 days was 7% per year in those not given aspirin[340] (OCSP). A 40% (30% to 50%) relative increase at 1 year in recurrent PICH was estimated if these patients were given aspirin, a 20% relative increase in death and a 20–30% increase in dependency • A systematic review of stroke and stroke survivors indicated that 4.3% of survivors have any recurrent stroke (CI 3.5% to 5.4%), 2.4% have a haemorrhagic stroke (CI 1.9% to 2.7%) and there are 8.8% deaths per year (CI 5.2% to 11.0%) (assuming aspirin was not given).[122] If aspirin was given this would result in a 3.7% (CI 2.7% to 3.8%) increase in haemorrhagic stroke and a 12.3% (CI 7.3% to 15.4%) in deaths
	Delay in diagnosis of tumours and infections	Incorrect treatment is administered	2/2000 more deaths from incorrectly managed infections and tumours (95% CI 1/2000 to 5/2000)
10. Scan only patients in AF, on anticoagulants or antiplatelet drugs within 7 days of admission to hospital	Diagnosis of patients in AF is delayed from 48 hours to 7 days	Treatment is administered at 7 days rather than 48 hours	• Recurrent stroke 2–4% would have a recurrent cerebral infarction if not on aspirin or heparin (absolute risk) 1.4–2.7% would have a recurrent cerebral infarction if on aspirin (absolute risk) • LOS AF–PICH LOS in hospital would not increase AF–cerebral infarction LOS increases by 7 days as a result of patients needing to go on anticoagulants requiring hospitalisation until they are stabilised
	Patients on anticoagulant therapy who suffer a PICH	Longer time taken to reverse effects of anticoagulation	Assume anticoagulation would be stopped before CT scanning. Outcomes would be worse because there would be a delay in reversing anticoagulation. This effect is difficult to quantify

continued

TABLE 48 *Incremental outcomes associated with the CT scanning strategies compared with the main comparator (withhold aspirin until after the CT scan) (cont'd)*

CT scanning strategies	Diagnosis	Treatment	Outcomes
	Diagnosis of patients on antiplatelet therapy is made at 7 days rather than 48 hours	Assume that antiplatelet therapy would be stopped until CT scan	Risk of an effect on outcomes. Loss of benefit: Change in outcomes cerebral infarctions (IST)[41–43]: • 0.5% increase in recurrent or non-fatal strokes (0.6% in the aspirin group versus 1.1% in the control group) • 0.2% increase in death without further stroke (2.6% in the aspirin group versus 2.8% in the control group) • 0.6% increase in further stroke or death (3.8% in the aspirin group versus 4.4% in the control group) Change in outcomes for PICH: • 30% of PICH-TACS • Drainage • Loss of benefit (difficult to quantify effect on outcome, but may result in better outcomes and prevent deaths in the acute phase)
	Remaining patients are not scanned and it is assumed that they have had a cerebral infarction	Treat with aspirin	Change in outcomes: • 10/2000 more deaths from incorrectly managed infections and tumours. 80% of infections and 60–70% of tumours will die • PICH in a life-threatening condition due to cerebellar haematoma and secondary hydrocephalus. The hydrocephalus will not be drained and therefore patients will die as a result of lack of acute treatment • PICH patients in a non-life-threatening condition have an increased risk of recurrent haemorrhagic stroke and an increased risk of death. Longer term actuarial risk of recurrent PICH in survivors of PICH to 30 days was 7% per year in those not given aspirin[340] (OCSP). A 40% (30% to 50%) relative increase at 1 year in recurrent PICH was estimated if these patients were given aspirin a 20% relative increase in death and a 20–30% increase in dependency. A systematic review of stroke and stroke survivors indicated that 4.3% of survivors have any recurrent stroke (CI 3.5% to 5.4%), 2.4% have a haemorrhagic stroke (CI 1.9% to 2.7%) and there are 8.8% deaths per year (CI 5.2% to 11.0%) (assuming aspirin was not given).[122] If aspirin was given this would result in a 3.7% (2.7% to 3.8%) increase in haemorrhagic stroke and a 12.3% (CI 7.3% to 15.4%) increase in deaths

continued

TABLE 48 *Incremental outcomes associated with the CT scanning strategies compared with the main comparator (withhold aspirin until after the CT scan) (cont'd)*

CT scanning strategies	Diagnosis	Treatment	Outcomes
11. Scan only patients with a life-threatening stroke or anticoagulants within 7 days of admission to hospital	30% of PICH-TACS	Drainage is delayed from 48 hours to 7 days	Loss of benefit: 50% more will die and the remaining patients will not recover
	Patients in a life-threatening condition due to cerebellar haematoma, cerebral infarct and secondary hydrocephalus	Drainage of hydrocephalus is delayed from 48 hours to 7 days	100% will die
	Patients on anticoagulant therapy who suffer a PICH	Longer time taken to reverse effects of anticoagulation	Assume anticoagulation would be stopped before CT scanning. Outcomes would be worse because there would be a delay in reversing anticoagulation. This effect would be difficult to quantify
	Remaining patients are not scanned and it is assumed that they have suffered a cerebral infarction	Treat with aspirin	Change in outcomes: • 8/2000 more deaths from incorrectly managed infections and tumours. 80% of infections and 60–70% of tumours will die • PICH patients in a non-life-threatening condition have an increased risk of recurrent haemorrhagic stroke and an increased risk of death. Longer term actuarial risk of recurrent PICH in survivors of PICH to 30 days was 7% per year in those not given aspirin[340] (OCSP). A 40% (30% to 50%) relative increase at 1 year in recurrent PICH was estimated if these patients were given aspirin, a 20% relative increase in death and a 20–30% increase in dependency. A systematic review of stroke and stroke survivors indicated that 4.3% of survivors have any recurrent stroke (CI 3.5% to 5.4%), 2.4% have a haemorrhagic stroke (CI 1.9% to 2.7%) and these gave 8.8% deaths per year (CI 5.2% to 11.0%) (assuming aspirin was not given).[122] If aspirin was given this would result in a 3.7% (2.7% to 3.8%) increase in haemorrhagic stroke and a 12.3% (CI 7.3% to 15.4%) increase in deaths

continued

TABLE 48 *Incremental outcomes associated with the CT scanning strategies compared with the main comparator (withhold aspirin until after the CT scan) (cont'd)*

CT scanning strategies	Diagnosis	Treatment	Outcomes
12. Do not scan anyone	It is assumed that patients have suffered a cerebral infarction	Treat with aspirin	Change in outcomes: • Longer term actuarial risk of recurrent PICH in survivors of PICH to 30 days was 7% per year in those not given aspirin (OCSP).[340] A 40% (30% to 50%) relative increase at 1 year in recurrent PICH was estimated if these patients were given aspirin, a 20% relative increase in death and a 20–30% increase in dependency. A systematic review of PICH and PICH survivors indicated that 4.3% of survivors have any recurrent stroke (CI 3.5% to 5.4%), 2.4% have a haemorrhagic stroke (CI 1.9% to 2.7%) and there are 8.8% deaths per year (5.2% to 11.0%) (assuming aspirin was not given).[122] If aspirin was given this would result in a 3.7% (CI 2.7% to 3.8%) increase in haemorrhagic stroke and a 12.3% (CI 7.3% to 15.4%) increase in deaths • 10/2000 more deaths from incorrectly managed infections and tumours. 80% of infections and 60–70% of tumours will die • Cerebral infarctions would have an immediate benefit, but however the benefit is small Change in outcomes for PICH: • 30% of PICH-TACS • No drainage • 50% will die • PICH on anticoagulants The effects of the anticoagulation would not be reversed and aspirin is administered 60–70% of patients would die • Patients with a cerebellar haematoma or cerebral infarct and secondary hydrocephalus The hydrocephalus would not be drained 100% would die • Patients in AF Patients who suffer a cerebral infarction receive aspirin and in the next year have a 20% reduced risk of recurrent stroke. After 2 weeks patients would receive anticoagulants and the risk of recurrent stroke would be reduced by 60% (i.e. a further 40% reduction compared with aspirin)

AF: atrial fibrillation.

TABLE 49 *Unit costs*

Resources	Unit cost (£)	Source
CT scanning		
Teaching hospital		
Normal working hours	42.90 (30.23–71.47)	CT costing study[a]
Out of hours	79.35 (55.05–173.46)	CT costing study
Large general hospital 1 (rural)		
Normal working hours	81.02 (71.44–89.56)	CT costing study
Out of hours	126.36 (119.52–133.16)	CT costing study
Large general hospital 2 (urban)		
Normal working hours	69.47 (58.73–84.58)	CT costing study
Out of hours	72.57 (61.43–91.48)	CT costing study
Cost per bed day		
Teaching hospital	239	NHS ISD, 2000
Large general hospital	217	NHS ISD, 2000
Long-stay hospital	116	NHS ISD, 2000

[a] See Appendix 8 for details of CT scanning costs.

Summary

This section described the data required to model the cost-effectiveness of CT scanning. The data include the parameter estimates for the main decision tree, outcomes and costs. The results of the cost-effectiveness analysis will be presented later in the chapter (p. 109).

Current provision of CT scanning for stroke: questionnaire survey of CT scanning departments in Scotland linked to population distribution

The lack of detailed information on the availability of CT for stroke has been highlighted above. Radiology departments in Scotland were surveyed to determine the current access to CT scanning for stroke patients by hospital and health board, highlight current and future potential resource constraints, and determine what additional resource(s) would be required to scan all patients within 48 hours of stroke as specified in current guidelines,[50] or to achieve the optimal CT strategy identified in this project if the latter were different. The survey was also undertaken to determine whether there were variations in access to CT scanning in Scotland. The geography and population distribution of Scotland provide examples of most of the patterns of hospital and community healthcare found elsewhere in the UK, so the results were considered to be relevant to the rest of the UK.

Methods

A postal questionnaire to send to the clinical directors of all radiology departments in Scotland was devised. The survey was developed by health economists (JS, JC) and radiologists (JW, and consultant neuroradiology colleagues Dr D Collie and Dr R Sellar), with the help of the Scottish Radiological Society. The survey (Appendices 6 and 7) contained detailed questions regarding imaging equipment, including the number of CT scanners, type of scanner, year of installation, and whether and when the scanner was used to scan stroke patients.

Access to CT scanning was assessed in several different ways:

- on the current operating hours for their CT scanning facilities: to overcome problems associated with seasonal variation and differences in the timing of when the surveys were completed, respondents were asked to describe the operating hours for a 'typical week' in October 2000. Detailed information was obtained on the number of sessions (defined as a half day), the length of sessions, the type of patients scanned in each session and the availability of out-of-hours scanning. This information was collected for normal working hours (09.00–17.00 hours Monday to Friday) and out-of-hours (17.00–09.00 hours Monday to Friday and during weekends);
- on CT scanning activity levels for the 1999 calendar year, including the number of brain

scans, the proportion of brain scans that were undertaken for suspected stroke and the proportion of scans undertaken out of hours, and the waiting times for CT scanning stroke patients during normal working hours and out of hours;
- on the effect on the department if the demand for CT scanning were increased: such effects might include introducing waiting lists, referring patients to another hospital for a scan, employing additional staff, out-of-hours scanning and purchasing additional scanning equipment.

Additional questions were included on the access to MR scanning for stroke patients during normal working hours and out of hours. The availability of MR with diffusion and/or perfusion imaging was also examined.

A list of Scottish Clinical Directors of Radiology was obtained from the ISD, Scotland. Clinical directors from 31 hospitals across 13 health boards were contacted and asked to complete the survey. Respondents were assured that the information they provided would be treated as confidential and that responses would be reported in such a way that individual hospitals could not be identified. The surveys were initially sent in January 2001, and a reminder letter and an additional copy of the survey were sent 2 weeks later.

Analysis

The data were entered into a database and analysed using descriptive statistics. Access to CT scanning was also assessed in terms of times required to travel by car for CT scanning. Drive times of 60, 90, 120 and 180 minutes were examined using the Geographical Information Service (GIS) software. An analysis was conducted using ArcView 3.2a Network Analyst software to determine the proportion of the total population and the population 'at risk' of suffering a stroke (defined as those over the age of 65 years) who were within 60, 90, 120 and 180 minutes' drive time of hospitals with CT scanners in Scotland during normal working hours. This analysis was repeated for access to CT scanning during out of hours, Monday to Friday and weekend scanning.

Four data sets were constructed, listing each hospital providing CT during normal working hours, out of hours during Monday to Friday, during the weekend including stroke, and during the weekend but not for patients with stroke. Each data set also contained the geographical coordinates (latitude and longitude) for each hospital identified using an interactive mapping facility (MultiMap, 2001, http://www.multimap.com). Population data from the 1991 Scottish Census provided by the General Registers Office of Scotland (GROS) were used in the analysis. The total population in the analysis was 4,973,459.

Survey results

Altogether, 29 of the 31 surveys (93.5%) were completed within the study period. Non-respondents were sent reminder letters and also followed up by telephone over a 3 month period. After further follow-up, the remaining three surveys were returned, giving a 100% sample.

Of the 31 respondents, 28 (90.3%) indicated that CT scanning facilities were available in their department to scan stroke patients. Four respondents reported that there were two CT scanners in their department, although only one of these was available for stroke patients. Three respondents reported that CT scanning facilities were not available at their hospital; at each, patients with stroke were referred to another hospital for CT scanning, within a radius of 2–17 miles.

On average, there were two CT scanners per health board in Scotland (range one to eight scanners in some areas. This in addition to the Orkneys and the Shetlands health boards, where CT scanning is not available). The number of CT scanners per health board was also examined in terms of the size of the population served by each health board. *Table 50* and *Figure 12* indicate the number of CT scanners per 10,000 population by health board (National Health Service in Scotland Information and Statistics Division[69]). Health boards had on average 0.085 CT scanners per 10,000 population and a median of 0.060 scanners per 10,000 population. The number of CT scanners per 10,000 population ranged from 0.047 in Argyll and Clyde to 0.363 in the Western Isles. The higher proportion of CT scanners per 10,000 population in the Western Isles reflects both the remote geographical location of the hospital and the small population. Even excluding the Western Isles, there is considerable variation in access to CT between health boards, with almost twice as many CT scanners per 10,000 in the Borders and Greater Glasgow as in the Highlands and Argyll and Clyde.

Table 51 and *Figure 13* illustrate the number of CT scanners per 1000 available staffed beds by health

TABLE 50 *Number of CT scanners per 10,000 population by health board in Scotland*

Health board	No. of CT scanners	Population[a]	10,000 population	CT scanners per 10,000 population
1. Western Isles	1	27,560	2.756	0.363
2. Borders	1	106,400	10.64	0.094
3. Greater Glasgow	8	906,000	90.60	0.088
4. Forth Valley	2	277,600	27.76	0.072
5. Dumfries & Galloway	1	146,800	14.68	0.068
6. Fife	2	349,200	34.92	0.057
7. Grampian	3	525,300	52.53	0.057
8. Ayrshire & Arran	2	374,600	37.46	0.053
9. Lanarkshire	3	562,400	56.24	0.053
10. Tayside	2	388,300	38.83	0.052
11. Lothian	4	778,500	77.85	0.051
12. Highlands	1	208,600	20.86	0.048
13. Argyll & Clyde	2	425,600	42.56	0.047

[a] Source: National Health Service in Scotland Information and Statistics Division.[69]

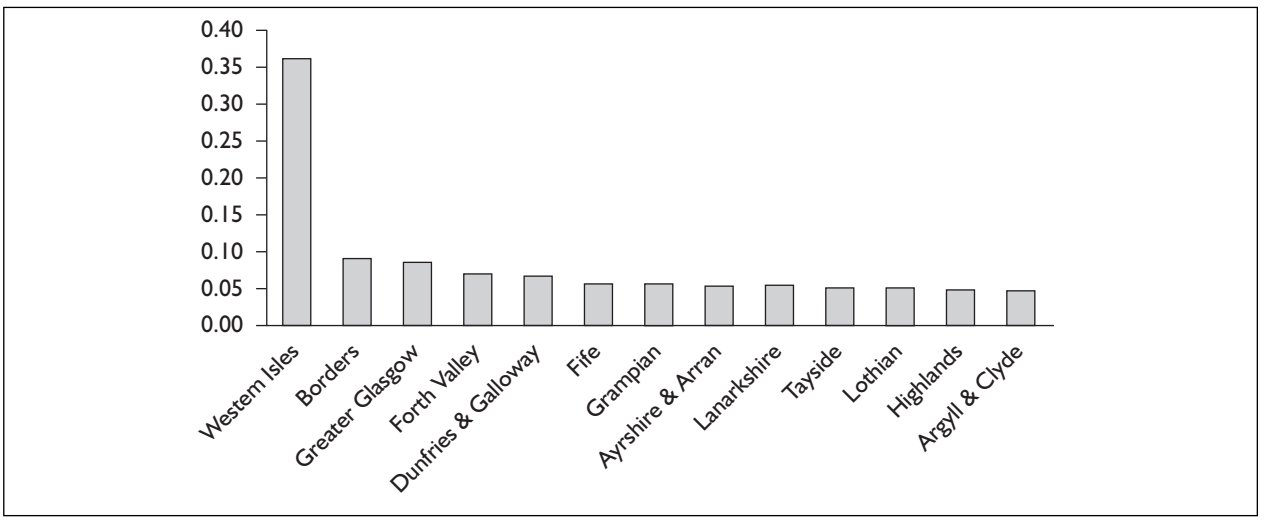


FIGURE 12 *Number of CT scanners per 10,000 population by health board in Scotland. Note: CT scanning is not available in either the Orkney or Shetland Islands.*

board (National Health Service in Scotland Information and Statistics Division[69]). Health boards on average had 1.110 CT scanners per 1000 available staffed beds and a median of 0.910 CT scanners per 1000 beds. The number of CT scanners per 1000 beds ranged from 0.616 in Argyll and Clyde to 4.016 in the Western Isles. Again, excluding the Western Isles, there are twice as many CT scanners per 1000 staffed beds in the Borders as in the Highlands, Tayside and Argyll and Clyde.

The type of CT scanner varied: spiral (71%) and non-spiral (29%) CT scanners had been installed between 1991 and 2001. The Highlands and Western Isles were the only health boards without a spiral CT scanner. A spiral scanner generally operates more quickly, so that a routine brain scan as for stroke may take about half the time that a non-spiral scanner would take.

The access to CT scanning is reported in *Table 52*. During the week, there were a mean of nine and a median of ten CT scanning sessions per scanner, varying from five to ten sessions per week. CT scanning was available for stroke patients in 92% of all sessions. Seventy per cent of scanning sessions were for a combination of inpatients, outpatients and emergencies. CT scanners operated for an average of 37 hours during the week. However, this varied across hospitals from 20 to 58 hours. Out-of-hours scanning was available in 20 hospitals (71%), Monday to Friday. Out-of-hours scanning was

TABLE 51 *Number of CT scanners per 1000 staffed hospital beds by health board in Scotland*

Health board	No. of CT scanners	Average no. of staffed beds	1000 available staffed beds[a]	CT scanners per 1000 staffed beds
1. Western Isles	1	249	0.249	4.016
2. Borders	1	690	0.690	1.449
3. Greater Glasgow	8	7139	7.139	1.121
4. Forth Valley	2	1867	1.867	1.071
5. Dumfries & Galloway	1	982	0.982	1.018
6. Fife	2	1984	1.984	1.008
7. Ayrshire & Arran	2	2153	2.153	0.929
8. Lothian	4	4537	4.537	0.882
9. Lanarkshire	3	3600	3.600	0.834
10. Grampian	3	3598	3.598	0.833
11. Highlands	1	1426	1.426	0.701
12. Tayside	2	3114	3.114	0.642
13. Argyll & Clyde	2	3248	3.248	0.616

[a] Source: National Health Service in Scotland Information and Statistics Division.[69]

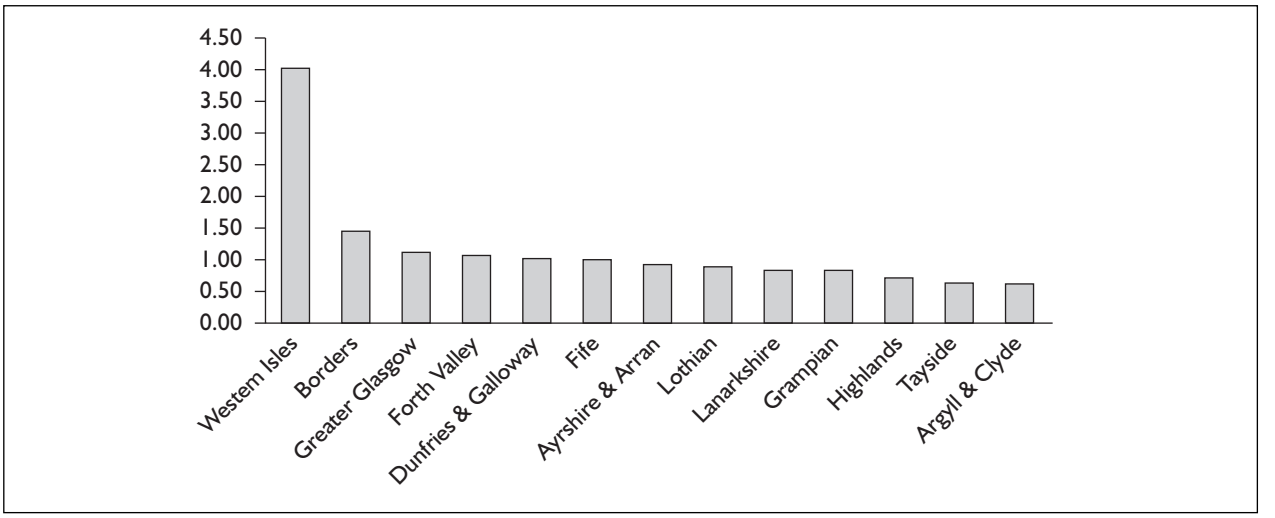


FIGURE 13 *Number of CT scanners per 1000 available staffed hospital beds by health board in Scotland. Note: CT scanning is not available in either the Orkney or Shetland Islands.*

not available at all in four hospitals, and one hospital did not scan stroke patients outside normal operating hours during the week. From the geographical location of these hospitals, it would be possible for patients to be transferred to a nearby hospital for a CT scan if necessary.

Weekend scanning (*Table 53*) was available in at least some capacity across 24 hospitals (78%). In 42%, weekend scanning was limited to out of hours and in 33% of hospitals it was restricted to emergencies only. There were ten hospitals in which CT scanning for stroke patients was not available during weekends. Most of these hospitals are relatively close to other hospitals that do provide weekend CT. At least one hospital in each health board provides out-of-hours CT scanning Monday to Friday and during weekends. There is restricted access to CT scanning facilities for stroke patients in the north-east of Scotland as there are no scanning facilities for suspected stroke patients at weekends in either Grampian or Tayside, with no alternative imaging facilities within a realistic travelling distance.

Table 54 reports the activity data for each hospital for the calendar year 1999. Ninety-six per cent of respondents provided data on the total number of CT scans and the number of brain CT scans undertaken during the period. Hospitals and directorates on average completed 4640 CT scans during the period (range 730–11,300 scans). On average, 45% of all CT scans were brain scans. On

average, 867 or 43% of all brain scans were for patients suspected of having had a stroke. This proportion varied markedly from 7 to 80% between hospitals.

During 1999 an average of 528 CT brain scans per hospital were undertaken out of hours. On average, 106 CT scans for stroke patients were conducted out of hours per hospital (i.e. about two per week); however, this varied considerably across hospitals, as some hospitals did not scan any stroke patients out of hours and another hospital scanned 543 patients during the period. It should be noted that these data were not always routinely collected in all hospitals involved in the survey. Thus, respondents were encouraged to provide estimates based on the information they had available.

Access to CT scanning was also examined by considering the time taken to provide scans for stroke patients (see *Table 55*). Thirty per cent of hospitals reported that they could provide scans without difficulty to stroke patients admitted to hospital immediately on a weekday, compared with only 15% of hospitals that could provide a CT scan regardless of the day of the week. Seventy-seven per cent of respondents could provide CT scans within 24 hours during weekdays without difficulty, whereas 35% of hospitals could provide scans within 24 hours at a weekend. Eighty-three per cent of hospitals could possibly provide CT scanning to stroke patients within 48 hours without difficulty, except at weekends, compared with 68% regardless of the day of the week. The survey did not specifically request information on outpatient access for stroke.

TABLE 52 *Operating hours of CT scanning facilities among hospitals in Scotland*

CT scanning services	
Weekly CT scanning (Monday–Friday)	
No. of sessions	
Mean (SD)	9 (2)
Range	5–10
Operating hours (hours)	
Mean (SD)	37 (7)
Range	20–58
Type of patients scanned	
Inpatients, outpatients and emergencies	19 (70.4%)
Inpatients and outpatients	2 (7.7%)
Type of patients varies	6 (23.1%)
CT scan stroke patients	
Yes	26 (92.9%)
During some sessions	2 (7.1%)
Availability of out-of-hours CT scanning	
Yes	20 (71.4%)
Emergency only	3 (10.7%)
Not available for stroke patients	1 (3.2%)
No	4 (12.9%)
Weekend CT scanning	
Availability of weekend scanning	
Yes	24 (77.5%)
No	4 (15.4%)
Type of patients scanned	
Out of hours only	10 (41.7%)
Emergencies	8 (33.3%)
Other	6 (25.0%)
Availability of CT scanning for stroke patients	
Yes	10 (41.7%)
Some sessions	3 (12.5%)
Yes if suspected bleed	1 (4.2%)
No	10 (41.7%)
Availability of 'out of hours' CT scanning	
Yes	10 (83.3%)
Yes, but not available for stroke	2 (8.3%)
Sometimes	1 (3.2%)
No	1 (3.2%)

TABLE 53 *Availability of weekend CT scanning facilities by health boards in Scotland*

Health board	Out-of-hours CT scanning Monday–Friday	Weekend CT scanning	Weekend CT scanning for suspected stroke
1. Ayrshire & Arran	✓	✓	✓
2. Borders	✓	✓	✓
3. Argyll & Clyde	✓	✓	✓
4. Fife	✓	✓	✓
5. Greater Glasgow	✓	✓	✓
6. Highlands	✓	✓	✓
7. Lanarkshire	✓	✓	✓
8. Grampian	✓	✓	✗
9. Lothian	✓	✓	✓
10. Tayside	✓	✓	✓
11. Forth Valley	✓	✓	✗
12. Western Isles	✓	✓	✓
13. Dumfries & Galloway	✓	✓	✓

TABLE 54 *Timing of CT scans for patients suspected of having suffered a stroke*

Timing of CT scanning to patients suspected of having suffered a stroke	*n*	Yes (%)	Yes, with difficulty (%)	No (%)
Provide CT scans **immediately** to suspected stroke patients on weekdays?	27	30	52	19
Provide CT scans **immediately** to suspected stroke patients on weekends?	26	15	30	58
Provide CT scans **within 24 hours** to suspected stroke patients on weekdays?	26	77	23	0
Provide CT scans **within 24 hours** to suspected stroke patients on weekends?	26	35	27	39
Provide CT scans **within 48 hours** to suspected stroke patients regardless of the day of the week?	25	68	16	16
Provide CT scans **within 48 hours** to suspected stroke patients except at weekends?	24	83	4	8
Provide CT scans **within 7 days** to suspected stroke patients?	25	100	0	0
Provide CT scans **within 14 days** to suspected stroke patients?	25	100	0	0

The question on what percentage workload increase would lead to actions such as increasing the waiting time or employing more staff was not well answered. When asked what increase in workload would lead to a waiting list of more than 4 weeks, several departments said that the waiting list was already more than 7 weeks. On the possibility of referral to another hospital, several hospitals said that this was not an option and one that it was already happening. The median increase in workload that respondents said would lead to additional radiographic staff (34%) or radiologists (30%) was inconsistent with the many comments received to the effect that most departments had at least one unfilled radiologist post and that the radiographers were already working to capacity. This suggests that the question was interpreted as 'what increase in workload would be required to convince the hospital managers to employ more radiographers or radiologists', which is different to what was actually asked, which was 'what increase in workload would lead to the need for more staff?' As many departments were already working at the capacity of the available funding, and in a climate where there are insufficient radiologists to fill existing posts (45% said that they required additional radiologists now), some of these hypothetical questions may have seemed rather redundant.

TABLE 55 *Activity data 1999 calendar year*

CT scans	No. of scans
Total no. of CT scans	
n	27
Mean (SD)	4,640 (2,342)
Minimum	730
Maximum	11,300
No. of brain CT scans	
n	27
Mean (SD)	2,096 (1,551)
Minimum	366
Maximum	6,004
No. of CT scan undertaken 'out of hours'	
n	24
Mean (SD)	528 (668)
Minimum	0
Maximum	2,840
No. of CT brain scans for patients suspected of having suffered a stroke	
n	22
Mean (SD)	867 (544)
Minimum	81
Maximum	1,840
No. of CT scans for stroke patients undertaken 'out of hours'	
n	19
Mean (SD)	106 (166)
Minimum	0
Maximum	543

GIS analysis

The proportion of the total population within 60, 90, 120 and 180 minutes' drive time from CT scanning facilities is reported in *Table 56*. The proportion of the population aged 65 years and over within 60, 90, 120 and 180 minutes' drive time from CT scanning facilities is reported in *Table 57*.

Figure 14 presents areas within 180 minutes drive time from hospitals with CT scanning

TABLE 56 *Proportion of the total population within 60, 90, 120 and 180 minutes' drive time of CT scanning facilities*

CT scanning	Population	Proportion of total population (%)
All hospitals with CT scanning facilities		
Population within 60 minutes' drive time	4,706,578	94.63
Population within 90 minutes' drive time	4,798,496	96.48
Population within 120 minutes' drive time	4,834,542	97.21
Population within 180 minutes' drive time	4,896,398	98.45
Hospitals with out-of-hours CT scanning facilities (Monday to Friday)		
Population within 60 minutes' drive time	4,708,098	94.66
Population within 90 minutes' drive time	4,798,496	96.48
Population within 120 minutes' drive time	4,834,542	97.21
Population within 180 minutes' drive time	4,896,398	98.45
Hospitals with weekend CT scanning facilities		
Population within 60 minutes' drive time	4,709,101	94.68
Population within 90 minutes' drive time	4,808,869	96.69
Population within 120 minutes' drive time	4,834,542	97.21
Population within 180 minutes' drive time	4,894,744	98.42
Hospitals with weekend CT scanning facilities for stroke patients		
Population within 60 minutes' drive time	4,210,257	84.65
Population within 90 minutes' drive time	4,373,011	87.93
Population within 120 minutes' drive time	4,516,048	90.80
Population within 180 minutes' drive time	4,903,080	98.58

TABLE 57 *Proportion of the population aged 65 years and over within 60, 90, 120 and 180 minutes' drive time of CT scanning facilities*

CT scanning	Population aged ⩾ 65 years	Proportion of total population (%)
All hospitals with CT scanning facilities		
Population within 60 minutes' drive time	711,995	14.32
Population within 90 minutes' drive time	728,192	14.64
Population within 120 minutes' drive time	733,862	14.76
Population within 180 minutes' drive time	743,611	14.95
Hospitals with out-of-hours CT scanning facilities (Monday to Friday)		
Population within 60 minutes' drive time	748,323	15.05
Population within 90 minutes' drive time	728,192	14.64
Population within 120 minutes' drive time	733,862	14.76
Population within 180 minutes' drive time	743,611	14.95
Hospitals with weekend CT scanning facilities		
Population within 60 minutes' drive time	712,335	14.32
Population within 90 minutes' drive time	730,282	14.68
Population within 120 minutes' drive time	733,862	14.76
Population within 180 minutes' drive time	743,375	14.95
Hospitals with weekend CT scanning facilities for stroke patients		
Population within 60 minutes' drive time	639,854	12.87
Population within 90 minutes' drive time	668,441	13.44
Population within 120 minutes' drive time	689,946	13.87
Population within 180 minutes' drive time	745,120	14.98

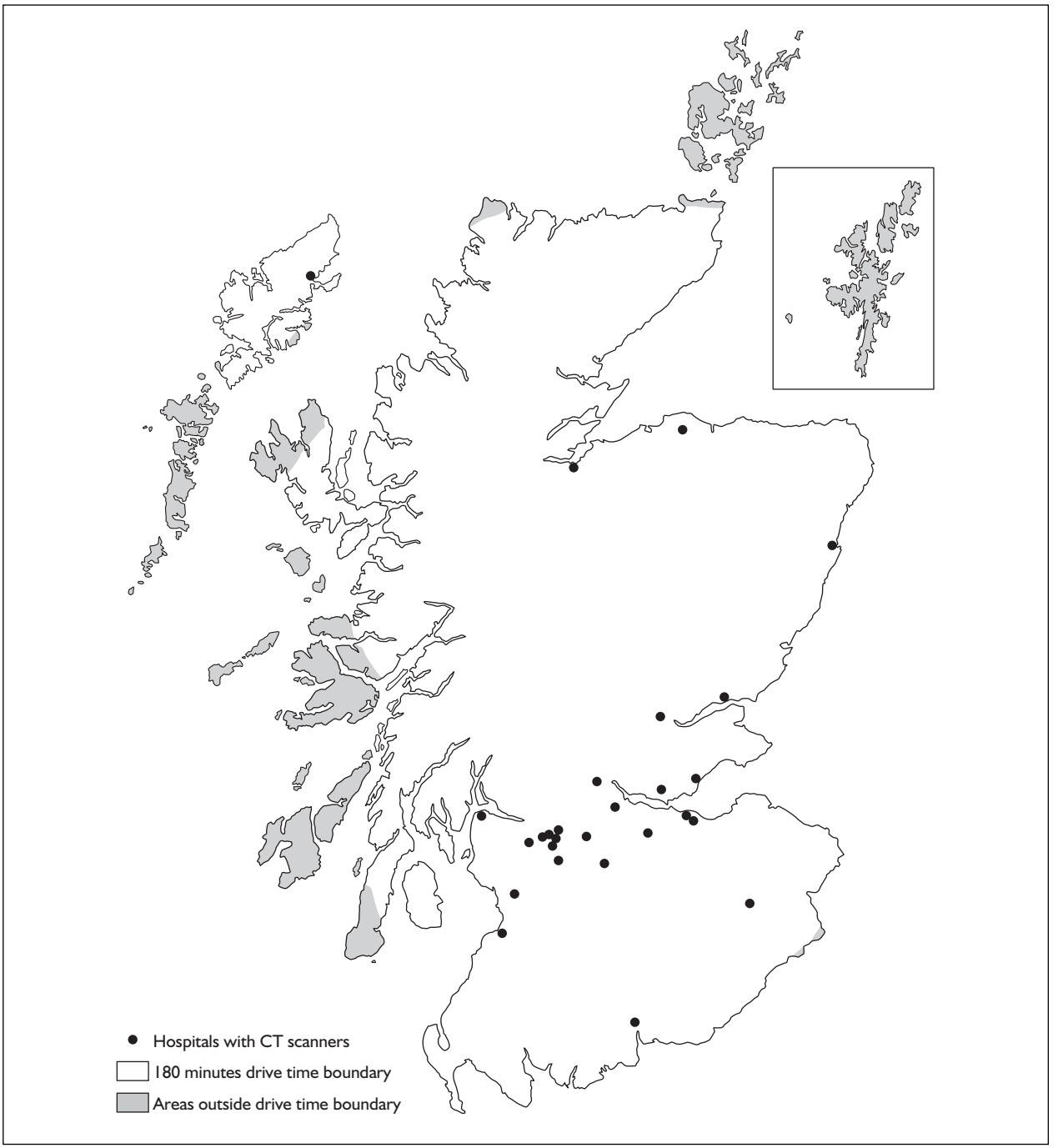


FIGURE 14 *Areas within 180 minutes drive time of a CT scanner during normal working hours*

facilities during normal working hours. This shows that despite Scotland having a geographically dispersed community, the majority of the population live within 3 hours' drive of a CT scanner. *Figure 15*, however, shows that access depends on the day of the week on which the stroke occurs, as fewer hospitals are able to provide weekend scanning for stroke.

Summary

Ninety per cent of Scottish radiology directorates have at least one CT scanner, and no hospital without a CT scanner was more than 32 km (20 miles) from a hospital that *did* have a CT scanner. However, there is considerable variation in the number of CT scanners per population and per inpatient bed, being lowest in Argyll and Clyde (0.62 CT scanners per 1000 beds) and highest in

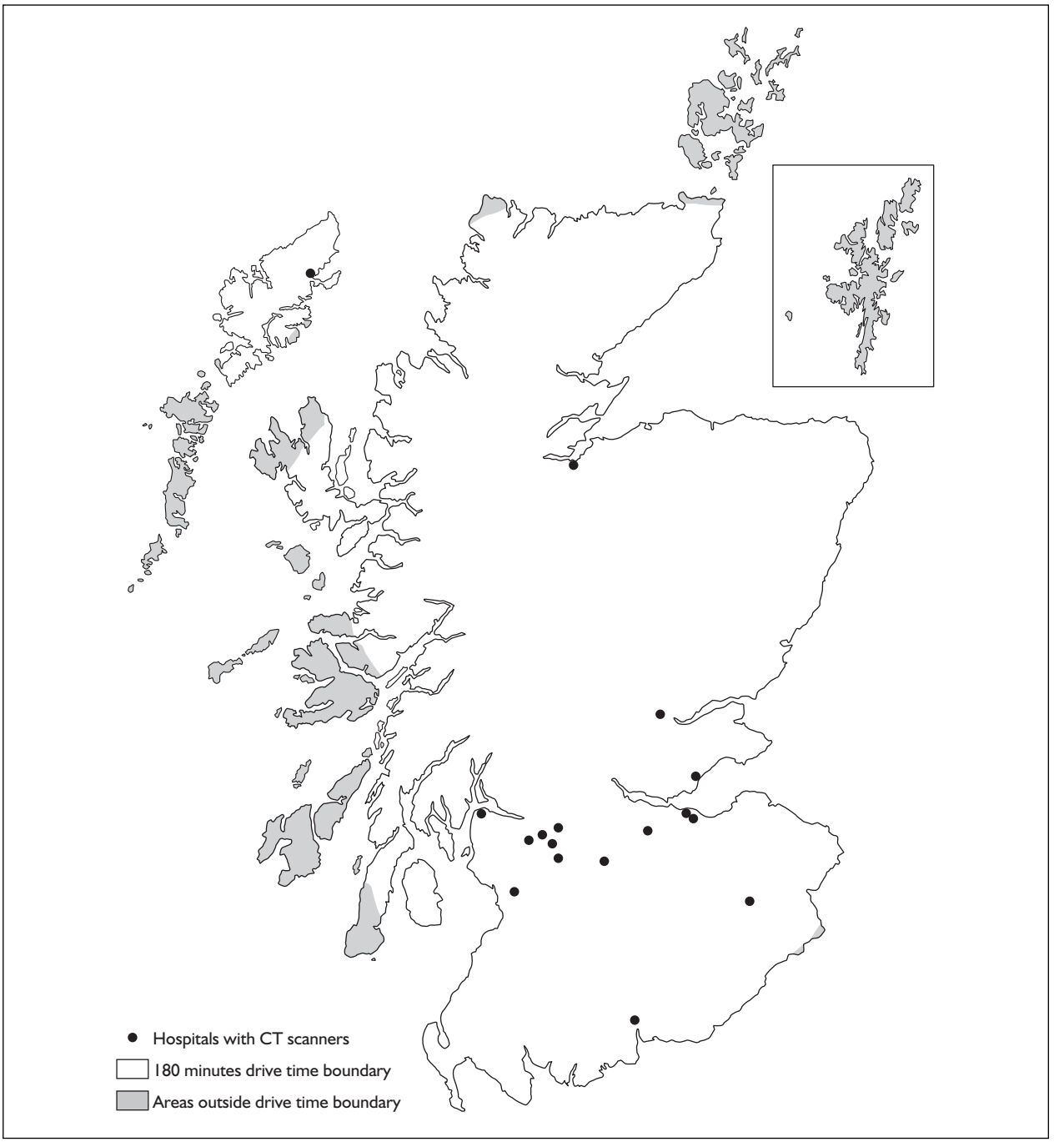


FIGURE 15 *Areas within 180 minutes drive time of weekend CT scanning for stroke*

the Western Isles (four CT scanners per 1000 beds). The average was about one scanner per 1000 beds. Furthermore, not all hospitals made their CT scanner available to patients with stroke, regardless of the day or the time of the day or night. Access for stroke was more restricted at weekends, with some hospitals simply not providing access to CT for stroke. This has important implications in a country such as Scotland where the population distribution is very skewed geographically, and resulted in two large regions having no access to CT for stroke at weekends (*Figure 15*). It would be less important in more urban areas where there would be greater likelihood of another hospital with access for stroke at weekends being close by. It is encouraging that 77% of departments provided access to CT within 24 hours of stroke on weekdays (35% could do this at weekends as well). More importantly, given that current UK guidelines state that CT should be performed within 48 hours of stroke, 83% of hospitals were

able to provide CT for stroke on weekdays within this period (68% at weekends as well). However, currently only 30% could provide immediate scanning for stroke on weekdays, and only 15% at weekends. Although there are several barriers to more patients being scanned more quickly, the single most frequently mentioned factor was lack of radiologists.

Results of the analysis of the cost-effectiveness model for CT scanning, and sensitivity analyses

Additional assumptions

The following analysis was conducted for a cohort of 1000 patients aged between 70 and 74 years. The analysis will be repeated for all other age groups in the final version of this report. It should also be noted that the modelling of functional outcomes in the preliminary analysis is based on outcome data at 24 months. Variation in outcomes between the time of stroke and 6 months, 6–12 months and 12–24 months will be incorporated in the subsequent analyses. The final assumption made in the present analysis is that the utility weights for all non-stroke diagnoses are equal to 1 (many would argue that being diagnosed as having a brain tumour would not equate to a utility weight of 1, and the effect of other utility weights for the tiny proportion of patients with tumours or infections on QALYs will be determined in sensitivity analyses). Thus, many sensitivity analyses are still to be undertaken on the results of this final analysis. At this stage robustness of the results is limited to examining the impact of varying the cost of CT scanning on the results.

Costs and outcomes associated with the 12 CT scanning strategies for patients suspected of having suffered a stroke

The cost-effectiveness of the CT scanning strategies was estimated by assessing the incremental costs and outcomes of each strategy compared with the main comparator (i.e. CT scan all patients suspected of having suffered a stroke within 48 hours). For the majority of patients (i.e. the 80% with ischaemic stroke and most of the 15% with haemorrhagic stroke), it was possible to use evidence from the published literature and secondary data sources. However, data were lacking for tumours, some PICH issues and infection, so for a minority of patients this analysis was largely based on expert clinical opinion extrapolating from the available literature and experience.

Costs

The cost of CT scanning was assessed for the main comparator and each of the scanning strategies. *Figure 16* illustrates the proportion of patients scanned during normal working hours and out of hours, and those not scanned at all for each of the 12 scanning strategies. In strategies S10, S11 and S12, a proportion of patients did not receive a CT scan. Of the remaining strategies, the proportion of patients scanned during normal working hours varied from 23.8 to 89.7% and the proportion of patients scanned out of hours ranged from 23.8 to 76.2%.

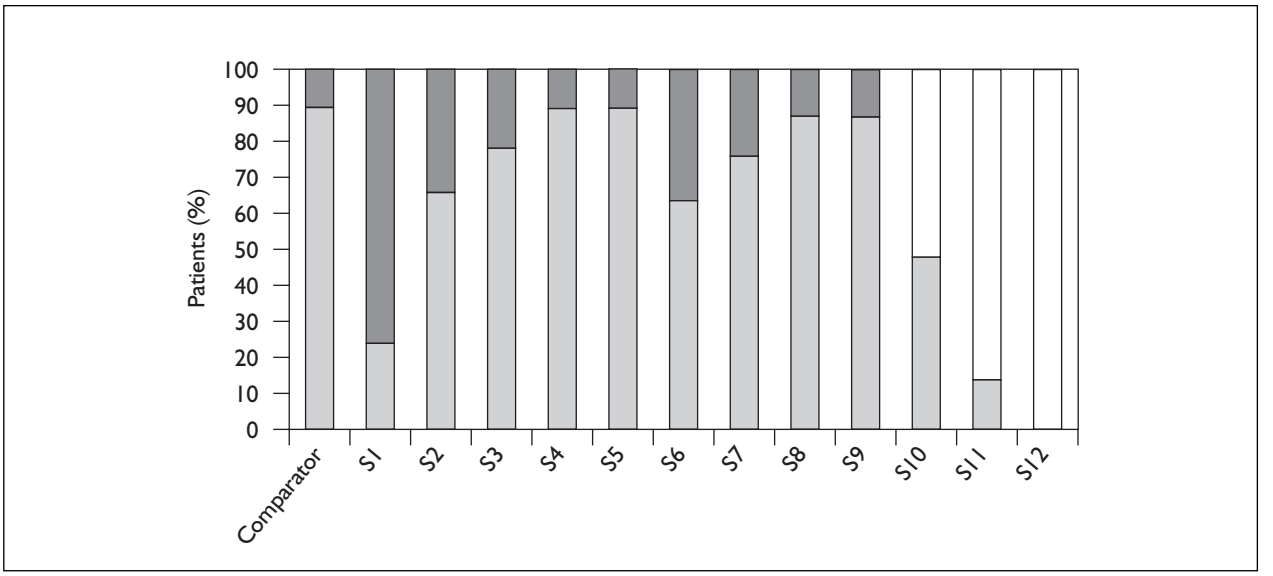


FIGURE 16 *Proportion of patients scanned during normal working hours (□), out of hours (■) and not scanned at all (□) for the comparator and the 12 CT scanning strategies*

TABLE 58 *Total cost of CT scanning for each strategy based on the cost of CT scanning at a teaching, large rural DGH and large urban DGH*

Strategy	Total cost (£)	Range (£)
Teaching hospital		
Comparator	46,728	32,834–82,177
S1	70,676	49,140–149,184
S2	55,294	38,666–106,144
S3	50,793	35,601–93,548
S4	46,666	32,791–82,003
S5	46,666	32,791–82,003
S6	55,903	39,081–107,847
S7	51,576	36,135–95,741
S8	47,614	33,437–84,655
S9	47,614	33,437–84,655
S10	20,530	14,530–34,354
S11	5,817	4,099–9,691
S12	0	0–0
Large rural DGH		
Comparator	85,770	76,487–94,139
S1	115,519	108,075–122,784
S2	96,411	87,786–104,385
S3	90,819	81,848–99,001
S4	85,693	76,405–94,065
S5	85,693	76,405–94,065
S6	97,167	88,589–105,113
S7	91,793	82,881–99,938
S8	86,871	77,655–95,199
S9	86,871	77,655–95,199
S10	38,944	34,340–43,052
S11	10,986	9,687–12,144
S12	0	0–0
Large urban DGH		
Comparator	69,797	59,010–85,306
S1	71,834	60,783–89,839
S2	70,526	59,644–86,928
S3	70,143	59,311–86,076
S4	69,792	59,005–85,294
S5	69,792	59,005–85,294
S6	70,578	59,689–87,043
S7	70,210	59,369–86,224
S8	69,873	59,075–85,474
S9	69,873	59,075–85,474
S10	33,395	28,230–40,658
S11	9,420	7,963–11,469
S12	0	0–0

The cost of CT scanning for a cohort of 1000 patients was estimated, taking into consideration the unit costs of CT scanning reported in the previous section ('Current provision of CT scanning for stroke' , p. 100). These results are presented in *Table 58*. The total cost of CT scanning for the comparator at a large teaching hospital was £46,728 and varied with the scanning strategy from £0 (S12) to £70,676 (S1). The total cost of CT scanning for the comparator at the rural DGH was £85,770 and the cost of the scanning strategies varied from £0 (S12) to £115,519 (S1). The cost of scanning at the urban DGH for the comparator was £69,797 and varied from £0 (S12) to £71,834 (S1). There was less variation in the cost of scanning between scanning strategies for the urban DGH as the unit costs for scanning during normal working hours and out of hours were similar in this hospital.

TABLE 59 *The total cost of LOS for each scanning strategy*

Strategy	Total cost (£)
S1	9,923,000
S6	10,012,000
S2	10,017,000
S7	10,178,000
S3	10,191,000
Comparator	10,233,000
S12	10,544,000
S11	10,781,000
S8	10,954,000
S4	11,004,000
S10	11,423,000
S9	12,107,000
S5	12,546,000

Cost of LOS

The total cost of LOS for each scanning strategy is reported in *Table 59*. For a cohort of 1000 patients, the cost of LOS ranged from £9,923,000 for S1 (scan all immediately) to £12,546,000 for S5 (scan patients on anticoagulants or in a life-threatening condition immediately and scan all remaining patients within 14 days). The cost of LOS for the comparator (scan all patients within 48 hours of admission to hospital) was £10,233,000, which incurred lower costs in terms of LOS than did strategies that involved scanning patients within 7 days or more (S12, S11, S8, S4, S10, S9 or S5).

Outcomes

Changes in outcomes in terms of the 12 scanning strategies were assessed by identifying possible changes in the timing or nature of the diagnosis of specific patient groups, changes in treatment and the subsequent impact on outcomes in terms of functional status, length of life and quality of life. Within each scanning strategy it was assumed that aspirin was withheld until after the result of the CT scan was known. In strategies S10, S11 and S12, it was assumed that patients with a clinical diagnosis of ischaemic stroke who did not receive a CT scan were treated with aspirin within 48 hours.

The expected number of QALYs for each of the scanning strategies ranged from 1982.4 to 1899

Table 60 *The total number of expected QALYs for each scanning strategy*

Strategies	Total QALYs		
	60–64 years	70–74 years	80–84 years
Comparator	2342.6	1982.3	1498.5
S1	2374.4	1982.4	1467
S2	2374.4	1982.4	1467
S3	2342.6	1982.3	1498.5
S4	2372.2	1980.7	1465.1
S5	2302.3	1931.8	1468.2
S6	2374.4	1982.4	1467
S7	2342.6	1982.3	1498.5
S8	2372.3	1980.7	1465.2
S9	2302.4	1931.9	1468.3
S10	2325.2	1944	1466.9
S11	2250.3	1899	1462.2
S12	2260.3	1904.2	1461.7

TABLE 61 *Total costs and expected QALYs (based on the cost of CT scanning at a teaching hospital) (please see Appendix 9 for further details)*

Strategies	QALYs	Costs (£)
S1	1982.4	9,993,676
S6	1982.4	10,067,903
S2	1982.4	10,072,294
S7	1982.3	10,229,576
S3	1982.3	10,241,793
Comparator	1982.3	10,279,728
S12	1904.2	10,544,000
S11	1899	10,786,817
S8	1980.7	11,001,614
S4	1980.7	11,050,666
S10	1944	11,443,623
S9 (LSR)	1931.9	12,154,614
S5 (LSR)	1931.8	12,592,666

for the cohort of 1000 patients (*Table 60*). In the comparator, a total of 1982.3 QALYs were expected by scanning all patients within 48 hours of admission to hospital. By scanning all patients immediately (S1), the total number of QALYs increased by 0.1, to 1982.4. When patients on anticoagulants, with a life-threatening stroke and/or candidates for hyperacute treatment were scanned immediately and the remaining patients were scanned within 24 hours of admission to hospital (S2 and S6), the same number of QALYs were expected as in S1. In the basic model, there was 0.1 reduction in the number of QALYs between the comparator and S3 and S7. When the remaining patients were scanned within 7 days (S4 and S8), rather than 48 hours, there was a loss of 1.7 QALYs, and 50.5–50.6 QALYs when the remaining patients were scanned within 14 days. When only patients in atrial fibrillation, on anticoagulants or antiplatelet drugs were scanned within 7 days of admission to hospital, this resulted in a loss of 38.4 QALYs. The greatest impact was expected when either only patients with a life-threatening stroke or patients on anticoagulants were scanned within 7 days (S11) or patients were not scanned at all (S12), where this resulted in a loss of 78.2 to 83.4 QALYs.

Results of the cost-effectiveness analysis

The results of the cost-effectiveness analysis based on the costs of scanning and LOS in a teaching hospital are presented in *Table 61* for 70–74 year olds. Following standard practice, the strategies are ranked in terms of total cost (i.e. the cost of CT scanning and LOS) from the least costly to the most expensive strategy. These results show that S1, scan all patients immediately, is the least costly strategy, closely followed by S6 and S2, which involve scanning the majority of patients within 24 hours. The results therefore indicate that S1 is the dominant strategy as it is not only the least costly strategy, but it also produces the maximum number of QALYs.

The analysis was repeated for 60–64 year olds and for 80–84 year olds. The total costs and expected QALYs for each strategy are shown in Appendix 9. S1 remains a dominant strategy yielding as many QALYs as any other strategy but at a lower cost.

One-way sensitivity analysis was conducted to assess the impact of varying the cost of CT scanning according to the type of hospital (i.e. urban or rural DGH) and the proportion of stroke patients (i.e. the proportion with a stroke or tumour or infection, and the proportion with ischaemic or haemorrhagic stroke). Sensitivity analyses indicated that the order of scanning strategies in the cost-effectiveness analysis does not change when these assumptions are varied, as S1 (scan all immediately) remains the dominant strategy because the effect of changing cost of scanning or varying the above proportions is overwhelmed by the effect of treatment on LOS (the most costly item) for the majority of patients.

Varying the probability that the suspected stroke was indeed a stroke, varying the proportion of PICHs that are TACs, and varying the utility weights attached to the different outcomes following stroke does not change the basic result. However, the results are sensitive to the cost of inpatient days. While a higher unit cost per inpatient day does not change the results, the assumption of lower costs per day causes the total

TABLE 62 *Incremental cost-effectiveness and the cost per inpatient day (please see Appendix 9 for further details)*

	Comparator		Strategy S1		
	QALYs	COSTS (£million)	QALYs	COSTS (£million)	Incremental cost per QALY (£million)
Base case cost per day	1982.3	10.280	1982.4	9.994	S1 dominant
Cost per day 5% lower	1982.3	9.763	1982.4	9.738	S1 dominant
Cost per day 10% lower	1982.3	9.246	1982.4	9.482	2.359
Cost per day 15% lower	1982.3	8.746	1982.4	9.230	4.839
Cost per day 20% lower	1982.3	8.231	1982.4	8.976	7.449

cost of S1 to fall but not as rapidly as the fall in the total cost of some other strategies (*Table 62*). However, even if inpatient costs per day are 5% lower than assumed in the base case S1 continues to be the dominant strategy. However, if the cost per day is lower than this, S1 ceases to cost less than the comparator and because of the very small expected difference in QALYs the incremental cost per QALY of scanning all immediately rises rapidly.

Interpretation of the results of the cost-effectiveness analysis

The analyses indicate that strategy S1, scan all patients immediately, is the dominant option. The costs in terms of CT scanning are highest for this option since it requires greater use of more costly out-of-hours scanning. However, these higher costs are offset by savings in the length of inpatient stay. Given the cost per inpatient bed day used in the base case, it would require the costs of out-of-hours scanning to rise markedly in order to offset these savings.

If the cost of the delayed scanning options was significantly lower than assumed currently in the model, for example, if delayed scanning was not associated with significantly longer inpatient stays, then in principle a situation could arise where delayed scanning strategies cost less than strategy S1. Then S1 would no longer be the dominant option and it would be possible to calculate incremental cost-effectiveness ratios that measured the cost-effectiveness of early scanning options compared with delayed scanning options. However, as the evidence for the majority of patients in the model (i.e. the vast majority with ischaemic stroke) is good (the effects of aspirin, anticoagulants and thrombolysis are supported by reasonably robust data), it is unlikely that the LOS effects are very inaccurate. Furthermore a sensitivity analysis of the effect of varying the assumption about the effect of delay to CT scanning on time to starting aspirin treatment did not alter the dominance of strategy S1 (Appendix 9).

The sensitivity analysis indicates that these basic findings are robust with respect to several assumptions. However, the sensitivity of the results with respect to the cost per inpatient day was marked. This suggests that further work is warranted on the inpatient costs of stroke patients. The unusual sensitivity of the incremental cost-effectiveness estimates is largely a product of the very small difference in outcome between a strategy of scanning all immediately and one of scanning all within 48 hours of admission to hospital. As the majority of patients have ischaemic stroke, the main treatment is aspirin and there is no good evidence of a time-dependency of the effect of aspirin up to 48 hours after stroke, it is perhaps not surprising that the difference between S1 and the comparator is sensitive to the cost of inpatient care.

Chapter 6
Discussion

Robustness of the conclusions

For the vast majority of patients to whom the present work applies – that is the 80% or so of patients with ischaemic stroke – sound evidence has been used to determine the effect of CT scanning on LOS, QALYs, and so the cost-effectiveness of CT scanning. The data on the effect of aspirin on functional outcome were obtained from 40,000 patients randomised in the two largest ever acute stroke trials, IST and CAST.[41,42] The data on LOS for patients with different subtypes of stroke, and severities, in relation to their functional outcome came from a large UK stroke registry collected over 10 years, linked to Scottish national hospital discharge statistics. The data on quality of life came from a study of patients who had been randomised in the IST in the UK conducted before the present study, and linked to the investigators' hospital stroke registry. Although the literature on imaging is weak and often difficult to access and summarise, the data on accuracy of CT scanning were based on the totality of the evidence and 20 years of experience with this widely used technique. Where data were lacking, for example in the duration of time that a haemorrhage might be discernible as such on CT, new data were obtained to use in the model. The researchers also relied heavily on expert opinion and drew on extensive experience of patterns of management of stroke and common diagnostic and treatment problems faced in caring for stroke in producing the model and the range of strategies for use of CT, and on extensive experience in health economics evaluations in the design and development of the model.

The data on cost of CT scanning were obtained from three different sorts of hospitals and were extremely detailed to reflect the opportunity costs of the procedure both in and out of normal working hours. A range of costs were obtained based on a range of times taken to do a CT brain scan, depending on the ease or difficulty of moving the patient into the scanner and the duration of scanning, so as to provide a range of costs to which other hospitals elsewhere could relate. These costs provide suitably stylised cases against which healthcare providers in other parts of the UK or elsewhere can compare their costs of CT scanning for stroke.

Further sensitivity analyses show that for the majority of patients (the 80% with ischaemic stroke), the model and data are robust. The sensitivity analyses have addressed the effect of varying the cost of CT scanning and bed occupancy according to the type of hospital, patient age, the proportion with actual stroke, the proportion with a severe PICH, the sensitivity and specificity of CT for differentiating an infarct from a haemorrhage, the specificity of CT in differentiating a vascular lesion from a tumour or other non-vascular lesion, different utility weights, altering assumptions about delays to starting aspirin while waiting for a scan, and the unit cost of LOS to determine whether any of these would alter the optimal strategy from 'scan all immediately'. This shows that, with one exception, the order of strategies remains the same, as the LOS and cost of bed occupancy so considerably outweigh the cost of CT scanning, even when most of the scanning has to be done out of hours. This holds true even for the patients in the minority groups, such as the 15% or so with PICH or the 4% or so with tumours presenting as a stroke, for whom the data were in general much less robust. The one exception is lowering the unit cost of LOS. A reduction in the unit cost of LOS by 10% or more changes the ranking of scanning strategies because the 'comparator' becomes less expensive than 'scan all immediately' though at the expense of a reduction in QALYs. The fact that the model is so sensitive to changes in unit cost of LOS suggests that further research is needed into costs of individual components of LOS.

It is notable that the LOS is much shorter for patients who achieved independence at 6 months compared with those who were dependent. Thus a marginal shift in the proportion of patients from dependency to independency would have a marked effect on total LOS and hence on the cost of inpatient care.

Have we failed to achieve any of the aims in the original application? The aims were to resolve issues of whether CT is cost-effective or not;

outline a variety of strategies from which health commissioners could choose that which best suits their local resources; give clear estimates in financial and population terms of the cost of these different strategies; and determine in which particular patients the even more expensive resource of MR is worth using. We believe that the study has accomplished all of those, some in greater detail than originally intended. For example, detailed information was obtained of the availability of CT and MR for stroke in the whole of Scotland and on the costs of CT at different times of the day, and it was established that CT will miss small haemorrhages as early as 8 days after stroke, and thus that the proportion of stroke due to PICH has probably been underestimated in epidemiological studies. The model developed in the cost-effectiveness analysis based on systematic reviews, and clinical expertise, could potentially be adapted by others to explore specific subquestions or subpopulations now, or used in the future to assess new healthcare directions.

We have examined first stroke only, not recurrent stroke, although the model could be used to assess the cost effectiveness of CT in recurrent stroke by altering some of the probabilities at the nodes in the decision tree, as the nodes themselves would remain the same. However there was a lack of data on proportion of different types of recurrent stroke, outcomes, and so forth that precluded useful analysis at this time.

We have obtained data on availability of MR and the cost of substituting MR for CT in certain circumstances could be determined using the model if detailed costs for MR were available. These were not available at the time of the study, nor did we have time to obtain detailed costs. However, in general MR is more expensive than CT.

We have concentrated on the cost effectiveness of CT scanning in patients admitted to hospital after a stroke, as the majority (about 80%) are admitted and create the major burden of disease. Those not admitted to hospital in general are milder strokes.

Difficulties in undertaking this work

The absence of data on treatment in some areas was very frustrating and we accept that the reliability of estimates based on expert clinical opinion for some treatment effects may be of concern. However, it is hoped that the sensitivity analyses should cover these deficiencies. But, for a very common disease such as stroke (an average DGH will admit one or two patients with stroke per day) the absence of data on some common management problems was lamentable (see below).

The imaging literature is acknowledged to be poor and biased; it is also difficult to search reliably and to extract data from the primary publications. With the introduction of each new technique, there is usually a flurry of publications stating the apparent advantages of the new technique over the existing ones, with small sample sizes, inadequate blinding (and other methodology) and hence optimistic claims regarding the sensitivity and specificity of the technique. Publication bias for positive studies is common. Studies with negative (or just less optimistic) results struggle for publication against the referees' claims that the researchers 'used the wrong machine' or 'used the wrong technique', rather than accepting that the technique may not be as good as its early proponents had suggested. It is thus virtually impossible to obtain an accurate assessment of the performance of a technique in routine clinical practice from the literature. We therefore had to extract what we could on the accuracy of CT and MRI but interpret it with caution. However, fortunately in the case of CT in stroke and the differentiation of infarct from haemorrhage there is little problem soon after stroke and so the data and assumptions in the model are valid; and real data from a study of 232 patients bridged the gap in knowledge of when small haemorrhages are no longer visible as such on CT.

A multitude of data sources were used to obtain data on the incidence of different subtypes of stroke, diagnostic accuracy, outcomes among different subtypes of stroke, treatment effects, QALYs and LOS. These included:

- re-examining trial data (IST and CAST and substudies)
- observational data (OCSP and LSR)
- national statistical data linked to our own hospital data (ISD and LSR)
- the literature (imaging, effect of aspirin on intracranial haemorrhage, bed occupancy by age)
- the Cochrane Database of Systematic Reviews (aspirin, anticoagulants, thrombolysis, secondary prevention)
- all of the CT scanning departments in Scotland (32, access to CT for stroke)

- three CT department finance and clinical managers (cost of CT)
- panel of expert clinicians (devising the CT strategies and the flow path through the model)
- generating new data (CT compared with MR for PICH)
- and analysis of secondary data (QALYs for IST patients in the LSR).

At times it was difficult to keep all of this flowing smoothly, and new data sources had to be identified when the first source that was turned to proved to be inadequate.

Had we not had the IST and CAST data (because we ran the IST and have performed an individual patient data meta-analysis of the IST and CAST in conjunction with the CAST investigators), been the authors of several Cochrane reviews (and one of the authors been the Editor of the Stroke Group), run the LSR for the past 10 years (for which we regularly obtain linked long-term outcome data from ISD) and had a research-dedicated MR scanner on which to undertake the MR arm of the CT/MR comparison, then most of this project would have been impossible or based on considerably less true evidence, or would have taken considerably longer to do and required much greater resources.

One might question whether it was really necessary to use evidence wherever possible, or whether a 'back-of-an-envelope' calculation would have arrived at the same answer. We cannot answer that as no such calculation was attempted before embarking on the project proper, and any retrospective attempt to do a back-of-an-envelope sum would now be biased. However, a model or calculation that did not take account of the evidence now available for the majority of patients would have been heavily criticised for failing to use available evidence and so probably ignored. Although there are clearly areas in the present analysis that are based on assumptions, it is hoped that readers will appreciate that these assumptions apply to the minority and so the overall conclusion is robust and evidence based. The difference between the present cost-effectiveness analysis and the three previous attempts at assessing the cost-effectiveness of CT (see Chapter 5), is the substantial lack of data in the previous attempts, the large gaps in the analysis, the broad assumptions and the very limited conclusions. The detailed model which we have developed allows individual healthcare providers to examine different components of the use of CT in stroke as each component might show regional and local variations in availability and costs. Thus, although all three previous studies concluded that CT was cost-effective,[328–330] there was no total cost provided for caring for a cohort of patients according to a particular strategy, and no assessment of the effect on functional outcome, LOS or quality of life. The generalisability was unclear and in reality two of the previous studies were actually simply comparisons of CT with another diagnostic strategy.[328,329]

Two other studies in the UK published as monographs did not develop such a detailed model, did not have such detailed evidence available (some had not been published), did not take account of the accuracy of imaging, and did not provide such a comprehensive range of CT scanning strategies as in the present study. The study by the Trent Institute for Health[351] Services Research concluded that:

> "a purchasing strategy supporting the routine CT scanning of stroke patients likely to benefit from secondary prevention should be adopted. There should be a distinction between those patients requiring an urgent scan, and those requiring a scan as soon as reasonably possible within two weeks of the onset of symptoms, i.e. before it becomes impossible to distinguish haemorrhagic from ischaemic strokes using a CT scan."

Published in 1997, this study did not include the loss of benefit incurred by failing to start aspirin within the first 48 hours identified in the IST and CAST, or the adverse effect of administering aspirin to those with PICH (regardless of any benefit that aspirin might have in reducing the risk of other ischaemic vascular events).

A second document prepared by the Wessex Institute for Health Service Research and Development (though we are unsure of its publication status)[352] did incorporate the notion of scanning within 48 hours, but only based their assessment on the cost of CT (one flat-rate cost, not by time of day) without incorporating the cost of inpatient hospital care and effect on LOS. It therefore did not achieve the comprehensive assessment and robust conclusions that were attained in the present study. Therefore, there is no place for a back-of-an-envelope calculation when data are available. We believe that our approach of accessing this large amount of detailed knowledge, put together in a very cohesive and functional way, was very cost-effective.

Limitations

The alternative approach to determining the cost-effectiveness of CT in stroke would have been to undertake a randomised trial comparing CT scanning (and subsequent management and functional outcome) with diagnosis and management based on clinical diagnosis alone. Not only would this have required a very large study (which would have been considerably more costly than the approach used in the present study), but it would have been morally and ethically insupportable in the present era of modern medical management. The time to have evaluated such an approach might have been at first introduction of CT (a lesson for the introduction of new technologies in the future), although the absence of a treatment for stroke in the 1970s would have limited the results.

Other sensitivity analyses could be undertaken, for example to vary the outcomes of patients with tumours or infections. However, it was apparent after a range of sensitivity analyses, that the major factor influencing the model was the cost of LOS. Other factors like a change in the accuracy of CT, or the proportion of patients with PICH or infarct had no effect on the ranking of the scanning strategies. Even changing the assumption about when treatment might be started while waiting for the scan did not affect the ranking. For example, the model currently works by assuming that the majority of patients placed in a particular scan strategy do not undergo CT scanning until the time specified; that is, for 'scan all patients within 7 days of stroke', most patients would be scanned near the 7 day time limit. However, in reality some might be scanned on admission, and some on day 2, and so on, rather than all near day 7. Some might start aspirin on the basis of the clinical diagnosis of ischaemic stroke pending a CT scan and therefore not lose the early benefit of aspirin, but for some with intracranial haemorrhage or tumour, incorrectly diagnosed as ischaemic stroke, starting aspirin would be inappropriate. There were no differences in cost effectiveness between younger and elderly patients.

Furthermore, the focus was on patients admitted to hospital. In the UK about 15–20% of patients are not admitted to hospital after a stroke, although current guidelines suggest that all patients with stroke should be admitted.[62] Further analyses could be run to determine the cost-effectiveness of CT scanning for those patients not admitted to hospital.

Generalisability of the results

How generalisable are our results? We have collected much of our data from hospitals in Scotland. We have sampled all CT departments and several hospital finance departments to calculate the cost of CT. We used data on cost of inpatient care from NHS Scotland Health Service Costs. The district general and teaching hospitals which provided the financial data on CT scanning are likely to be representative of at least a proportion of hospitals elsewhere in the UK, and so provide suitable examples. Similarly, amongst the range of CT departments in Scotland, it is likely that there are parallels with many hospitals elsewhere in the UK. Indeed the Royal College of Radiologists Audit of CT scanning for stroke data, although not collected in quite the same way as our survey, suggested that Scotland was at the more accessible end of the spectrum of access to CT for stroke compared with England and Wales. There were no comparable data to calculate unit costs of LOS by hospital type for England and Wales, but given that equipment costs, staffing levels and pay scales are similar, the costs we used should be relevant for England (except for London where staff and building costs are higher). Finally, Scotland offers a range of geographies, including densely populated urban areas and sparsely populated rural areas, some very remote. Across this range of geographies, there are likely to be parallels with most other parts of the UK. In all of this, even if our conditions do not match those of all other parts of the UK, it is likely that centres will be able to see where they fit in the range of available data. Furthermore, it would be possible to re-run the model with other data to explore local regional variations.

Much of our data on stroke came from the IST, CAST, the Lothian Stroke Register, or the ISD Scotland. The IST and CAST are generalisable, being very large and conducted in many hospitals in many countries worldwide. The Lothian Stroke Register is specific to our hospital, but we used data by stroke syndrome and OCSP classification thereby at least partly accounting for any local effects, and making the results more generalisable. Our outcome data however come from a setting of reasonably organised stroke care and a stroke unit has been in place for some years. Organised stroke improves functional outcome and so will reduce average LOS compared with a hospital without a stroke unit. Thus the costs of stroke care are likely to be even higher (and so CT be even more cost effective) in hospitals without organised stroke care.

Our analysis was conducted prior to the licensing of thrombolysis for treatment of acute stroke when aspirin and organised stroke care were the major common treatments. We have assumed that only a small proportion of patients would reach hospital in time to be considered for thrombolysis, but that is consistent with surveys from other parts of the world where recombinant tissue Plasminogen Activator is already licensed. If a larger proportion of patients were to become eligible for thrombolysis, say 10%, then the CT scanning strategy 'scan all immediately' would become even more cost-effective than the base comparator 'scan all within 48 hours', assuming that the estimate of thrombolysis treatment effect from current data (110 per 1000 more alive and independent) is correct.[132]

Implications for healthcare

It is not within our remit to make recommendations on whether healthcare should change as a result of this report. However, hospitals providing services for patients with stroke may wish to examine their current CT provision and see which of our 12 strategies their service matches most closely. They may then wish to determine whether they are able to move to a more cost-effective strategy by allocating resources more efficiently and reorganising services, or whether they may need to provide some additional component to be able to improve the service. For example, there is a national shortage of radiologists in the UK – many radiology departments in the UK have unfilled consultant posts. In our survey of Scottish radiology departments, although the question was not well answered, the consistent factor barring improved access to CT for patients with stroke was more radiologists. In addition, CT departments may need to identify ways of relaying the result of the scan quickly to the admitting doctor. Regardless of the barriers to scanning, in the UK, access to CT for stroke is still not good,[66] and is generally poor compared with provision in other EU countries.[18] However, even as long ago as the early 1990s, before the IST and CAST had demonstrated the benefit of aspirin, or stroke units had been recognised as beneficial, the majority of UK physicians (90%) said that they would wish to have a CT scan if they suffered a stroke themselves.[137]

The comparison of CT and MR imaging suggests that CT is unreliable for diagnosing small PICHs more than 8 days after the stroke. This is most likely to affect outpatients who may not be seen in a hospital clinic until several weeks after their stroke – they may not recognise the urgency themselves, there will be delays in obtaining appointments with the GP and then hospital clinic. By that time CT may fail to diagnose correctly even quite large PICHs. However the problem with delays may also affect some inpatients as there are difficulties in obtaining a CT scan for stroke in many parts of the UK (Royal College of Radiologists Audit Sub-committee, personal communication) so that patients may wait in hospital for up to 2 weeks for a CT scan. Anecdotal reports also suggest that patients may be sent home if well enough, rather than wait in hospital for the CT scan, occupying a bed, but may then be put on an outpatient waiting list of several months. By that time, one could argue that it is almost not worth doing the CT. The alternative for patients affected by delays is to use MR with GRE. However MR is more expensive than CT, takes longer to do, is less available and patients find it less pleasant than CT. Waiting lists for MR scans are generally thought to be much worse than for CT in most parts of the country (e.g. the waiting time for an MR in our neuroscience department is 7 months at present). If the decision to commence aspirin were to be delayed while waiting for the MR result, then the majority of patients with ischaemic stroke would be denied effective secondary prevention, and the wait would create anxiety. MR in place of CT for patients whose imaging is delayed for whatever reason is unlikely to be a realistic solution in the UK. Speedy referral to fast-track clinics with ready access to imaging is the better solution.

It is not just carrying out the scan which is important, but the result must reach the doctors caring for the patient in the most efficient way possible. In our experience, a provisional report on a duplicate sheet, with a copy sent with the patient and a copy retained in the department, not only gets the result to the attending physician quickly, but also reduces the amount of time that junior and senior doctors spend trying to get the scan result from the CT department, cuts unnecessary result-seeking phone calls to hard-pressed CT secretaries and reduces interruptions to the radiologists so that they can get on with their radiological work. There may also be other ways of streamlining the information transfer that could be evaluated.

It is worth pointing out that our model assumes that patient management is implemented correctly as described at all stages, e.g. that patients who should be treated with aspirin actually receive it.

In reality, the process of healthcare is much less precise, and so our cost-effectiveness data are likely to be the 'best case scenario'. It is likely to be even more expensive for all the strategies. For example, patients may not be sent home so quickly, and even an extra unnecessary half-day in hospital is costly, quickly adding to the financial burden of caring for stroke.

The difference in QALYs and costs between the strategies may seem marginal per patient, or per 1000 patients, and so some may wonder whether improved CT scanning is worth the extra effort and possible disadvantage to other specialties competing with stroke for access to imaging. However, stroke is so common that in the UK, our figures calculated for 1000 patients would need to be multiplied by about 120 to 140 to get the total effect per year. These differences then become substantial across the population. A marginal shift in the proportion of patients, from being dependent to independent by 6 months after stroke will have a marked effect on overall LOS and hence costs. Thus although the effect of aspirin may seem very marginal in the individual, the population effect is proportionately larger and worthwhile, and is largely what drives the ranking of scan strategies. It may help to think of the cost of caring for an average stroke in terms of some common day-to-day object. For example, each stroke patient admitted to hospital, on average, will cost about as much as to buy an average family car. Reducing the overall cost of care by reducing LOS by speedy diagnosis and increasing the chance of independent survival, would mean that not only would patients have a better health outcome, but more money would be available to 'purchase more cars'. Thus, although for the individual, the gains in functional outcome and quality of life from the rapid scan strategies may seem marginal compared with the more leisurely scan strategies, in the case of stroke every marginal gain counts towards an improved outcome, and it would be wrong even on an individual level to disregard these benefits. For the service provider dealing with the population, where large savings are possible with modest alterations in CT strategy, these gains are very important.

Implications for research

For a disease as common as stroke and with such a high mortality and morbidity, there are some rather fundamental questions about how best to manage patients for which there are few data.

1. There are inadequate data on the effect of aspirin or anticoagulant therapy in patients with intracranial haemorrhage. Although we determined that, in general, the current sparse data suggest that antithrombotic drugs should be avoided in acute PICH, there are situations where antithrombotic treatment may be required after acute PICH. For example in patients with deep vein thrombosis, or who are at high risk of myocardial infarction, or who require anticoagulation for an artificial heart valve, there are inadequate data on which to base treatment decisions. Unfortunately a randomised trial would take a long time to accrue an adequate sample size.
2. There are insufficient data on the effect of antithrombotic drugs given late (i.e. months or years later) after PICH, for example to reduce the risk of ischaemic stroke or myocardial infarction. Although patients with PICH seem to be more prone to having a further PICH, and this risk is likely to be increased with aspirin, it is still unclear whether the reduction in the risk of ischaemic vascular events with aspirin is offset by an increase in the risk of recurrent PICH.
3. The management of PICH in the hyperacute stage is uncertain. Patients on anticoagulants have their deranged clotting reversed, but there is no good guidance on when to evacuate larger haematomas or whether it is better to manage these medically. Trials in these areas are required to fill these gaps in knowledge (indeed a trial of evacuation versus medical therapy for supra-tentorial haematomas – STICH trial – is ongoing).
4. Epidemiological studies have probably underestimated the proportion of strokes due to PICH because of suboptimal scanning policies.
5. There is a lack of data on whether the proportion of stroke due to PICH varies with age, or recurrent versus first stroke, and this information will be necessary to determine the cost effectiveness of CT in recurrent stroke.
6. The data on the individual costs of the components of caring for stroke patients in hospital and in the community are lacking, as well as a general total cost. This information is needed by different types of hospital and region to calculate cost-effectiveness in detail.
7. The methodology used in studies assessing accuracy of imaging needs to be improved. Sample size, blinding of image assessment, prospective rather than retrospective data collection, and careful clinical characterisation

and documentation of the process of clinical characterisation are all too frequently overlooked.

8. There is also a surprising paucity of data on some basic components of stroke care. For example there was little evidence on the agreement between clinicians, or paramedics or nurses or general practitioners for the clinical diagnosis of stroke. What information was available tended not to be in the hyperacute phase but later on when the symptoms and signs had stopped fluctuating, and so the assessment was easier. These data may therefore not represent the true difficulty of assessing patients in the hyperacute phase. Data on how to improve the clinical diagnosis of stroke versus not a stroke in the hyperacute phase, and which symptoms or signs are particularly reliable, are required if we are to reduce delays in the process of admitting stroke patients to hospital.
9. If data on recurrent stroke and realistic MR costs were available, then further modelling could be undertaken to look at the effect of these factors on cost effectiveness.
10. Finally, there is room for improving the efficiency of the CT scanning process, from how the scan is requested through to how the result is transmitted back to the attending physicians. Different methods may be required for different departments depending on resources. What works for our department (see above) may not work for others. Some evaluation of where the system is inefficient and how this could be improved would be worthwhile. Different methods of streamlining the process of investigating stroke patients, (e.g. keep an empty appointment each day in anticipation of a stroke vs not; authorised by the consultant vs radiographer, etc) should be evaluated in randomised trials because that is the best way to avoid bias in the assessment of these strategies.

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References

1. Sudlow CLM, Warlow CP. Comparable studies of the incidence of stroke and its pathological types. Results from an international collaboration. *Stroke* 1997;**28**:491–9.
2. Rothwell PM. The high cost of not funding stroke research: a comparison with heart disease and cancer. *Lancet* 2001;**357**:1612–16.
3. Murray CJL, Lopez AD. *The global burden of disease: a comprehensive assessment of mortality and disability from diseases, injuries and risk factors in 1990 and projected to 2020*. Boston, MA: Harvard University Press; 1996.
4. MacDonald BK, Cockerell OC, Sander JW, Shorvon SD. The incidence and lifetime prevalence of neurological disorders in a prospective community-based study in the UK. *Brain* 2000;**123**:665–76.
5. Bamford J, Sandercock P, Dennis M, Warlow C, Jones L, McPherson K. A prospective study of acute cerebrovascular disease in the community: the Oxfordshire Community Stroke Project 1981–86. 1. Methodology, demography and incident cases of first-ever stroke. *J Neurol Neurosurg Psychiatry* 1988;**51**:1373–80.
6. Wade DT. Stroke (acute cerebrovascular disease). In: Stevens A, Raftery J, editors. *Health care needs assessment. The epidemiologically based needs assessment reviews*. Oxford: Radcliffe Medical Press; 1994. pp. 111–255.
7. Office of Health Economics. *OHE compendium of health statistics*. London: Office of Health Economics; 2000.
8. Wolfe CD. The impact of stroke. *Bri Med Bull* 2000;**56**:275–86.
9. Bamford J, Sandercock P, Dennis M, Burn J, Warlow C. Classification and natural history of clinically identifiable subtypes of cerebral infarction. *Lancet* 1991;**337**:1521–6.
10. 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 Neurol Neurosurg Psychiatry* 2000;**69**:487–93.
11. The Stroke Association. *Stroke care: reducing the burden of disease*. London: The Stroke Association; 1998.
12. Stegmayr B, Asplund K. Exploring the declining case-fatality in acute stroke. Population-based observations in the northern Sweden MONICA project. *J Intern Med* 1996;**240**:143–9.
13. Bonita R. Epidemiology of stroke. *Lancet* 1992;**339**:342–4.
14. Menken M, Munsat TL, Toole JF. The Global Burden of Disease Study. Implications for neurology. *Arch Neurol* 2000;**57**:418–20.
15. Evers M, Goosens M, Ament A, Maarse. Economic evaluation in stroke research. *J Cerebrovasc Dis* 2000;**11**:82–91.
16. British Heart Foundation. *Coronary heart disease statistics: British Heart Foundation statistics*. London: British Heart Foundation; 1998.
17. Grieve R, Hutton J, Bhalla A, Rastenye D, Ryglewicz D, Wolfe CD, on behalf of the Biomed II European Study of Stroke Care. A comparison of the costs and survival of hospital admitted stroke patients across Europe. *Stroke* 2001;**32**:1684–91.
18. Weir NU, Sandercock PAG, Lewis SC, Signorini DF, Warlow CP, on behalf of the IST Collaborative Group. Variations between countries in outcome after stroke in the International Stroke Trial (IST). *Stroke* 2001;**32**:1370–7.
19. Wardlaw JM, Lewis SC, Sandercock PAG, Ricci S, Spizzichino L, International Stroke Trial Collaborators in Italy and the UK. Why do Italian stroke patients receive CT scans earlier than UK patients? *Postgrad Med J* 1999;**75**:18–21.
20. Holloway R, Benesch C, Rahilly C, Courtright C, Abad-Santos F. A systematic review of cost-effectiveness research of stroke evaluation and treatment. *Stroke* 1999;**30**:1340–9.
21. Fagan S, Morgenstern L, Pettita A, Ward R, Tilley B, Marler J, *et al*. Cost-effectiveness of tissue plasminogen activator for acute ischemic stroke. *Neurology* 1998;**50**:883–90.
22. Hatano S. Experience from a multicentre stroke register: a preliminary report. *Bull World Health Organ* 1976;**54**:541–53.
23. Bamford J. Clinical examination in diagnosis and subclassification of stroke. *Lancet* 1992;**339**:400–2.
24. Bamford J, Sandercock P, Dennis M, Burn J, Warlow C. A prospective study of acute cerebrovascular disease in the community: the Oxfordshire Community Stroke Project – 1981–86. 2. Incidence, case fatality rates and overall outcome at one year of cerebral infarction,

primary intracerebral and subarachnoid haemorrhage. *J Neurol Neurosurg Psychiatry* 1990; **53**:16–22.

25. Warlow CP, Dennis MS, van Gijn J, Hankey GJ, Sandercock PAG, Bamford JM, *et al*. What pathological type of stroke is it? *Stroke: a practical guide to management.* 2nd ed. Oxford: Blackwell Scientific; 2001. pp. 151–222.
26. Warlow CP, Dennis MS, van Gijn J, Hankey GJ, Sandercock PAG, Bamford JM, *et al*. What caused this intracerebral haemorrhage? *Stroke: a practical guide to management*. 2nd ed. Oxford: Blackwell Scientific; 2001. pp. 339–75.
27. Sandercock PAG, Warlow CP, Jones LN, Starkey IR. Predisposing factors for cerebral infarction: the Oxfordshire Community Stroke Project. *BMJ* 1989;**298**:75–80.
28. Warlow CP, Dennis MS, van Gijn J, Sandercock PAG, Bamford JM, Wardlaw J. Subarachnoid haemorrhage. *Stroke: a practical guide to management*. Oxford: Blackwell Science; 1996. pp. 322–59.
29. Allen CM. Clinical diagnosis of the acute stroke syndrome. *Q J Med* 1983;**52**:515–23.
30. Poungvarin N, Viriyavejakul A, Komontri C. Siriraj stroke score and validation study to distinguish supratentorial intracerebral haemorrhage from infarction. *BMJ* 1991;**302**:1565–7.
31. Besson G, Robert C, Hommel M, Perret J. Is it clinically possible to distinguish nonhemorrhagic infarct from hemorrhagic stroke? *Stroke* 1995;**26**:1205–9.
32. Celani MG, Ceravolo MG, Duca E, Minciotti P, Caputo N, Orlandini M. Was it infarction or haemorrhage? A clinical diagnosis by means of the Allen score. *J Neurol* 1992;**239**:411–13.
33. Lindley R, Wardlaw J, Ricci S, Celani M, Sandercock P. Haemorrhagic transformation of cerebral infarction in acute stroke patients in the International Stroke Trial Pilot. *Cerebrovasc Dis* 1992;**2**:234.
34. Weir CJ, Murray GD, Adams FG, Muir KW, Grosset DG, Lees KR. Poor accuracy of stroke scoring systems for differential clinical diagnosis of intracranial haemorrhage and infarction. *Lancet* 1994;**344**:999–1002.
35. Hawkins GC, Bonita R, Broad JB, Anderson NE. Inadequacy of clinical scoring systems to differentiate stroke subtypes in population-based studies. *Stroke* 1995;**26**:1338–42.
36. Sohn YH, Kim SM, Kim JS, Kim DI. Benign brainstem haemorrhage simulating transient ischaemic attack. *Yonsei Med J* 1991;**32**:91–3.
37. Aparicio A, Sobrino J, Arboix A, Torres M. Hematoma intraparenquimatoso que simula un accidente isquemico transitorio. *Med Clin (Barc)* 1995;**104**:478–9.
38. Gunathilake SB. Rapid resolution of symptoms and signs of intracerebral haemorrhage: case reports. *BMJ* 1998;**316**:1495–6.
39. Ivo L. CT scanning can differentiate between ischaemic attack and haemorrhage. *Lancet* 1999; **319**:1197–8.
40. Scott WR, Miller BR. Intracerebral haemorrhage with rapid recovery. *Arch Neurol* 1985;**42**:133–6.
41. International Stroke Trial Collaborative Group. The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19435 patients with acute ischaemic stroke. International Stroke Trial Collaborative Group. *Lancet* 1997;**349**:1569–81.
42. Chinese Acute Stroke Trial Collaborative Group. CAST: randomised placebo-controlled trial of early aspirin use in 20,000 patients with acute ischaemic stroke. CAST (Chinese Acute Stroke Trial) Collaborative Group. *Lancet* 1997;**349**: 1641–9.
43. Chen Z, Sandercock P, Pan H, Counsell C, Collins R, Liu L, *et al*. Indications for early aspirin use in acute ischaemic stroke. A combined analysis of 40000 randomised patients from the Chinese Acute Stroke Trial and the International Stroke Trial. *Stroke* 2000;**31**:1240–9.
44. Wolfe C, Rudd A, Dennis M, Warlow C, Langhorne P. Taking acute stroke seriously. *BMJ* 2001;**323**:5–6.
45. Kennedy J, Buchan A, Barnett HJM. Thrombolysis must be considered after stroke. *BMJ* 2001;**323**:937.
46. 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* 2001;**6**(26).
47. Antithrombotic Trialists' Collaboration. Prevention of death, myocardial infarction and stroke by antiplatelet therapy in high risk patients. *BMJ* 2001;**324**:71–86.
48. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy – I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ* 1994; **308**:81–106.
49. Sandercock PAG. Statins for stroke prevention? *Lancet* 2001;**357**:1548–9.
50. Scottish Intercollegiate Guidelines Network (SIGN). Management of patients with stroke. I: Assessment, investigation, immediate management and secondary prevention. SIGN publication no. 13. Edinburgh: SIGN; 1997.
51. Prasad K, Shrivastava A. Surgery for primary supratentorial intracerebral haemorrhage

(Cochrane Review). The Cochrane Library (Issue 4), Oxford: Update Software; 2001.

52. Fernandes HM, Gregson B, Siddique S, Mendelow AD. Surgery in intracerebral haemorrhage. The uncertainty continues. *Stroke* 2001;**31**:2511–16.

53. 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.

54. Franke FL, Ramos LMP, van Gijn J. Development of multifocal haemorrhage in a cerebral infarct during computed tomography. *J Neurol Neurosurg Psychiatry* 1990;**53**:531–2.

55. Dennis MS, Bamford JM, Molyneux AJ, Warlow CP. Rapid resolution of signs of primary intracerebral haemorrhage in computed tomograms of the brain. *BMJ* 1987;**295**:379–81.

56. Mead GE, Lewis S, Wardlaw JM, Dennis MS, Warlow CP. Should computed tomography appearance of lacunar stroke influence patient management? *J Neurol Neurosurg Psychiatry* 1999;**67**:682–4.

57. Wardlaw JM, Lewis SC, Dennis MS, Counsell C, McDowall M. Is visible infarction on computed tomography associated with an adverse prognosis in acute ischemic stroke? *Stroke* 1998;**29**:1315–19.

58. Miller JH, Wardlaw JM, Lammie GA. Intracerebral haemorrhage and cerebral amyloid angiopathy: CT features with pathological correlation. *Clin Radiol* 1999;**54**:422–9.

59. Chest, Heart and Stroke Scotland. *Improving stroke services*. Patients' and carers' views. Edinburgh: Chest, Heart and Stroke Scotland; 2001.

60. Langhorne P, Williams BO, Gilchrist W, Howie K. Do stroke units save lives? *Lancet* 1993;**342**:395–8.

61. Lindley R, Amayo E, Marshall J, Sandercock PAG, Dennis MS, Warlow CP. Acute Stroke Treatment in UK hospitals: the Stroke Association survey of consultant opinion. *J R Coll Phys Lond* 1995;**29**:479–84.

62. Royal College of Physicians. Recommendations for acute treatment of stroke. *BMJ* 2000;**320**:823–5.

63. Grimshaw JM, Russell IT. Achieving health gain through clinical guidelines. I: Developing scientifically valid guidelines. *Qual Health Care* 1993;**2**:243–8.

64. Leape LL, Park RE, Kahan JP, Brook RH. Group judgement of appropriateness: the effect of panel composition. *Qual Assur Health Care* 1992;**4**:151–9.

65. Scott EA, Black N. When does consensus exist in expert panels. *J Public Health Med* 1991;**13**:35–9.

66. Roberts MA, Allen A, Langhorne P, McEwen J, D'A Semple P. Organisation of services for acute stroke in Scotland – report of the Scottish stroke services audit. *Health Bull* 2000;**58**(2):87–95.

67. Ebrahim S, Redfern J. *Stroke care – a matter of chance. A national survey of stroke services*. London: The Stroke Association; 1999.

68. Department of Health. National Service Framework for older people. http://www.doh.gov.uk/nsf/olderpeople.htm. London: Department of Health; 2001.

69. National Health Service in Scotland Information and Statistics Division (NHS, ISD). *Scottish Health Service costs. Year ended 31st March 2000*. Edinburgh; ISD Publications; 2000. pp. 5–7.

70. Mushlin AI, Ruchlin HS, Callahan MA. Costeffectiveness of diagnostic tests. *Lancet* 2001; **358**:1353–5.

71. White PM, Wardlaw JM, Easton VE. Can non-invasive imaging tests accurately detect intracranial aneurysms? A systematic review. *Radiology* 2000;**217**:361–70.

72. Hobson RW II. Status of carotid angioplasty and stenting trials. *J Vasc Surg* 1998;**27**:791.

73. Von Arbin M., Brittion M, De Faire U, Helmers C, Miah K, Murray V. Accuracy of bedside diagnosis in stroke. *Stroke* 1981;**12**:288–93.

74. Rowe CC, Donnan GA, Bladin PF. Intracerebral haemorrhage: incidence and use of computed tomography. *BMJ* 1988;**297**:1177–8.

75. Cochrane Stroke Group search strategy for specialised register. The Cochrane Library (Issue 1). Oxford: Update Software; 2000.

76. Ricci S, Celani MG, La Rosa F, Vitali R, Duca E, Ferraguzzi R. SEPIVAC: a community-based study of stroke incidence in Umbria, Italy. *J Neurol Neurosurg Psychiatry* 1991;**54**:695–8.

77. Anderson CS, Jamrozik K, Burvill PW, Chakera TMH, Johnson GA, Stewart-Wynne EG. Ascertaining the true incidence of stroke: experience from the Perth Community Stroke Study, 1989–1990. *Med J Aust* 1993;**158**:80–4.

78. Lauria G, Gentile M, Fassetta G, Casetta I, Agnoli F, Andreotta G, *et al*. Incidence and prognosis of stroke in the Belluno province, Italy. First-year results of a community-based study. *Stroke* 1995;**26**:1787–93.

79. Jorgensen HS, Nakayama H, Raaschou HO, Olsen TS. Intracerebral hemorrhage versus infarction: stroke severity, risk factors, and prognosis. *Ann Neurol* 1995;**38**:45–50.

80. Kolominsky-Rabas PL, Sarti C, Heuschmann PU, Graf C, Siemonsen S, Neundoerfer B, *et al*. A prospective community-based study of stroke in Germany – the Erlangen Stroke Project (ESPro): incidence and case fatality at 1, 3, and 12 months. *Stroke* 1998;**29**:2501–6.

81. Vemmos KN, Bots ML, Tsibouris PK, Zis VP, Grobbee DE, Stranjalis GS, *et al*. Stroke incidence and case fatality in southern Greece: the Arcadia stroke registry. *Stroke* 1999;**30**:363–70.

82. Zweifler RM, York D, Tha Tha U, Mendizabal JE, Rothrock JF. Accuracy of paramedic diagnosis of stroke. *J Stroke Cerebrovasc Dis* 1998;**7**:446–8.

83. Kothari R, Barsan W, Brott T, Broderick J, Ashbrock S. Frequency and accuracy of prehospital diagnosis of acute stroke. *Stroke* 1995;**26**:937–41.

84. Wester P, Radberg J, Lundgren B, Peltonen M. Factors associated with delayed admission to hospital and in-hospital delays in acute stroke and TIA. A prospective, multicenter study. *Stroke* 1999;**30**:40–8.

85. Zweifler RM, Drinkard R, Cunningham S, Brody ML, Rothrock JF. Implementation of a stroke code system in Mobile, Alabama. Diagnostic and therapeutic yield. *Stroke* 1997;**28**:981–3.

86. Libman RB, Wirkowski E, Alvir J, Rao TH. Conditions that mimic stroke in the emergency department. Implications for acute stroke trials. *Arch Neurol* 1995;**52**:1119–22.

87. Bratina P, Greenberg L, Pasteur W, Grotta JC. Current emergency department management of stroke in Houston, Texas. *Stroke* 1995;**26**:409–14.

88. Kothari RU, Brott T, Broderick JP, Hamilton CA. Emergency physicians. Accuracy in the diagnosis of stroke. *Stroke* 1995;**26**:2238–41.

89. Horn J, Limburg M, Vermeulen M. Diagnostic accuracy of stroke by family physicians. *Neurology* 1997;**48** (Suppl):A405.

90. Martin PJ, Young G, Enevoldson TP, Humphrey PR. Overdiagnosis of TIA and minor stroke: experience at a regional neurovascular clinic. *QJM* 1997;**90**:759–63.

91. Ferro JM, Pinto AN, Falcao I, Rodrigues G, Ferreira J, Falcao F, *et al*. Diagnosis of stroke by the nonneurologist. A validation study. *Stroke* 1998;**29**:1106–9.

92. Ellekjaer H, Holmen J, Indredavik B, Terent A. Epidemiology of stroke in Innherred, Norway, 1994 to 1996. Incidence and 30-day case-fatality rate. *Stroke* 1997;**28**:2180–4.

93. Smucker WD, Disabato JA, Krishen AE. Systematic approach to diagnosis and initial management of stroke. *Am Fam Phys* 1995;**52**:225–34.

94. Gillard JH, Barker PB, van Zijl PCM, Bryan N, Oppenheimer SM. Proton MR spectroscopy in acute middle cerebral artery stroke. *AJNR Am J Neuroradiol* 1996;**17**:873–86.

95. Henneman PL, Lewis RJ. Is admission medically justified for all patients with acute stroke or transient ischemic attack? *Ann Emerg Med* 1995;**25**:458–63.

96. Czlonkowska A, Ryglewicz D, Weissbein T, Baranska-Gieruszczak M, Hier DB. A prospective community-based study of stroke in Warsaw, Poland. *Stroke* 1994;**25**:547–51.

97. Brown JJ, Hesselink JR, Rothrock JF. MR and CT of lacunar infarcts. *Am J Roentgenol* 1988;**151**: 367–72.

98. Ashok PP, Radhakrishnan K, Sridharan R, El-Mangoush M. Incidence and pattern of cerebrovascular disease in Benghazi, Libya. *J Neurol Neurosurg Psychiatry* 1986;**49**:519–23.

99. Herman B, Leyten ACM, Van Luijk JH, Frenken CWGM, Op de Coul AAW, Schulte BPM. Epidemiology of stroke in Tilburg, The Netherlands. 2. Incidence, initial clinical picture and medical care and three-week case fatality. *Stroke* 1982;**13**:629–34.

100. Ueda K, Omae T, Hirota Y, Takeshita M, Katsuki S, Tanaka M. Decreasing trend in incidence and mortality from stroke in Hisayama residents, Japan. *Stroke* 1981;**12**:154–60.

101. Tanaka H, Ueda Y, Date C, Baba T, Yamashita H, Hayashi M. Incidence of stroke in Shibata, Japan: 1976–1978. *Stroke* 1981;**12**:460–6.

102. Wang CC, Cheng XM, Li SZ, Liana Bolis C, Schoenberg B. Epidemiology of cerebrovascular disease in an urban community of Beijing, People's Republic of China. *Neuroepidemiology* 1983;**2**:121–34.

103. Scmidt VE, Smirnov VE, Ryabova VS. Results of the seven-year prospective study of stroke patients. *Stroke* 1988;**19**:942–9.

104. Kojima S, Omura T, Wakamatsu W, Kishi M, Yamazaki T, Iida M. Prognosis and disability of stroke patients after 5 years in Akita, Japan. *Stroke* 1990;**21**:72–7.

105. Giroud M, Gras P, Chadan N, Beuriat P, Milan C, Arveux P, *et al*. Cerebral haemorrhage in a French prospective population study. *J Neurol Neurosurg Psychiatry* 1991;**54**:595–8.

106. D'Alessandro G, Di Giovanni M, Roveyaz L, Iannizzi L, Compagnoni MP, Blanc S. Incidence and prognosis of stroke in the Valle d'Aosta, Italy. First-year results of a community-based study. *Stroke* 1992;**23**:1712–15.

107. Jorgensen HS, Plesner A, Hubbe P, Larsen K. Marked increase of stroke incidence in men between 1972 and 1990 in Frederiksberg, Denmark. *Stroke* 1992;**23**:1701–4.

108. Tuomilehto J, Sarti C, Narva EV, Salmi K, Sivenius J, Kaarsalo E, *et al*. The FINMONICA stroke register: community-based stroke registration and analysis of stroke incidence in Finland, 1983–1985. *Am Epidemiol* 1992;**135**:1259–70.

109. Jerntorp P, Berglund G. Stroke registry in Malmo, Sweden. *Stroke* 1992;**23**:357–61.

110. Shah S, Cooper B. The epidemiology of stroke and transient ischaemia in Brisbane, Australia. *Ital J Neurol Sci* 1995;**16**:603–12.

111. Carolei A, Marini C, Di Napoli M, Di Gianfilippo G, Santalucia P, Baldassarre M, *et al*. High stroke incidence in the prospective community-based L'Aquila registry (1994–1998). First year's results. *Stroke* 1997;**28**:2500–6.

112. Korv J, Roose M, Kaasik A-E. Stroke registry of Tartu, Estonia, from 1991 through 1993. *Cerebrovasc Dis* 1997;**7**:154–62.

113. Stewart JA, Dundas R, Howard RS, Rudd AG, Wolfe CDW. Ethnic differences in incidence of stroke: prospective study with stroke register. *BMJ* 1999;**318**:967–71.

114. Thrift AG, Dewey HM, Macdonell RAL, McNeil JJ, Donnan GA. Incidence of the major stroke subtypes. Initial findings from the North East Melbourne Stroke Incidence Study (NEMESIS). *Stroke* 2001;**32**:1732–8.

115. Kita Y, Okayama A, Ueshima H, Wada M, Nozaki A, Choudhury SR, *et al*. Stroke incidence and case fatality in Shiga, Japan 1989–1993. *Int J Epidemiol* 1999;**28**:1059–65.

116. Tanizaki Y, Kiyohara Y, Kato I, Iwamoto H, Nakayama K, Shinohara N, *et al*. Incidence and risk factors for subtypes of cerebral infarction in a general population. *Stroke* 2001;**31**:2616–22.

117. Bogousslavsky J, Regli F, Uske A, Maeder P. Early spontaneous hematoma in cerebral infarct: is primary cerebral hemorrhage overdiagnosed? *Neurology* 1991;**41**:837–40.

118. Mead GE, Wardlaw JM, Dennis MS, Lewis SC. Extensive haemorrhagic transformation of infarct: might it be an important cause of primary intracerebral haemorrhage? *Age Ageing* 2002;**31**:429–33.

119. Kase CS, Caplan LR (editors). *Intracerebral haemorrhage*. Oxford: Butterworth-Heinemann; 1994.

120. Kwa VIH, Franke CL, Verbeeten B, Jr, Stam J. Silent intracerebral microhaemorrhages in patients with ischaemic stroke. *Ann Neurol* 1998;**44**:372–7.

121. Greenberg SM, Finklestein SP, Schaefer PW. Petechial hemorrhages accompanying lobar hemorrhage: detection by gradient-echo MRI. *Neurology* 1996;**46**:1751–4.

122. Bailey RD, Hart RG, Benavente O, Pearce LA. Recurrent brain hemorrhage is more frequent than ischemic stroke after intracranial hemorrhage. *Neurology* 2001;**56**:773–7.

123. Vermeer SE, Algra A, Franke CL, Koudstaal PJ, Rinkel GJ. Long-term prognosis after recovery from primary intracerebral hemorrhage. *Neurology* 2002;**59**:205–9.

124. Jamrozik K, Broadhurst RJ, Lai N, Hankey GJ, Burvill PW, Anderson CS. Trends in the incidence, severity, and short-term outcome of stroke in Perth, Western Australia. *Stroke* 1999;**30**:2105–11.

125. Ueda K, Kiyohara Y, Fujishima M. Epidemiology: stroke risk factors in general population – the Hisayama study. *J Stroke Cerebrovasc Dis* 2000;**9**:27–8.

126. Hamad I, Ayman H, Sokrab S, Momani S, Mesraoua B, Ahmed AR. Incidence of stroke in Qatar. *J Stroke Cerebrovasc Dis* 2000;**9**:83–4.

127. Johansson B, Norrving B, Lindgren A. Increased stroke incidence in Lund-Orup, Sweden, between 1983 to 1985 and 1993 to 1995. *Stroke* 2000;**31**:481–6.

128. Chen ZM, Sandercock P, Pan HC, Counsell C, Collins R, Liu LS, *et al*. Indications for early aspirin use in acute ischemic stroke: a combined analysis of 40 000 randomized patients from the chinese acute stroke trial and the international stroke trial. On behalf of the CAST and IST collaborative groups. *Stroke* 2000;**31**:1240–9.

129. He J, Whelton PK, Vu B, Klag MJ. Aspirin and risk of haemorrhagic stroke. A meta-analysis of randomised controlled trials. *JAMA* 1998;**280**:1930–5.

130. Wardlaw JM, Yamaguchi T, del Zoppo GJ, Berge E. Thrombolytic therapy versus control in acute ischaemic stroke (Cochrane Review). The Cochrane Library (Issue 2). Oxford: Update Software; 2003.

131. Tilley BC, Lyden PD, Brott TG, Lu M, Levine SR, Welch KM. Total quality improvement method for reduction of delays between emergency department admission and treatment of acute ischemic stroke. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. *Arch Neurol* 1997;**54**:1466–74.

132. Hankey GJ, Sudlow CL, Dunbabin DW. Thienopyridines or aspirin to prevent stroke and other serious vascular events in patients at high risk of vascular disease? A systematic review of the evidence from randomized trials. *Stroke* 2000;**31**:1779–84.

133. Lindley R, Warlow CP, Wardlaw JM, Dennis MS, Sandercock PAG. Interobserver reliability of a clinical classification of acute cerebral infarction. *Stroke* 1993;**24**:1801–4.

134. Mead GE, Lewis SC, Wardlaw JM, Dennis MS, Warlow CP. Severe ipsilateral carotid stenosis and middle cerebral artery disease in lacunar ischaemic stroke: innocent bystanders? *J Neurol* 2002;**249**,266–71.

135. Lindley R, Amayo E, Marshall J, Sandercock PAG, Dennis M, Warlow CP. Hospital services for patients with acute stroke in the United Kingdom: the Stroke Association Survey of Consultant Opinion. *Age Ageing* 1995;**24**:525–32.

136. Hung TP, Lee KY. Small intracerebral haemorrhage: a study of clinical manifestations and CT findings on 31 cases. *Ann Acad Med Singapore* 1985;**14**:22–31.

137. Wardlaw JM, Statham PF. How often is haemosiderin not visible on routine MRI following traumatic intracerebral haemorrhage? *Neuroradiology* 2000;**42**:81–4.

138. Walshe TM, Hier DB, Davis KR. The diagnosis of hypertensive intracerebral hemorrhage: the contribution of computed tomography. *Computerized Tomography* 1977;**1**:63–9.

139. Greenberg JO, Skubick DL. Unexpected brain hemorrhages and the value of computerized tomography. *Computerized Tomography* 1977;**1**: 349–57.

140. Lieberman A, Hass WK, Pinto R, Isom WO, Kupersmith M, Bear G, *et al*. Intracranial hemorrhage and infarction in anticoagulated patients with prosthetic heart valves. *Stroke* 1978;**9**:18–24.

141. Scott WR, Paul FJ, Davis KR, Schnur JA. Computerized axial tomography of intracerebral and intraventricular hemorrhage. *Radiology* 1974;**112**:73–80.

142. Mizukami M, Nishijima M, Kin H. Computed tomographic findings of good prognosis for hemiplegia in hypertensive putaminal hemorrhage. *Stroke* 1981;**12**:648–52.

143. Weisberg L. Multiple spontaneous intracerebral hematomas: clinical and computed tomographic correlations. *Neurology* 1981;**31**:897–900.

144. Hungerbuhler MD, Regli MD, Van Melle PD, Bogousslavsky J. Spontaneous intracerebral haemorrhages (SICHs). Clinical and CT features; immediate evaluation of prognosis. *Schweizer Archiv fur Neurologie, Neurochirurgie und Psychiatrie* 1983;**132**:13–27.

145. Mayr U, Bauer P, Fischer J. Non-traumatic intracerebral haemorrhage. Prognostic implications of neurological and computer-tomographical findings in 100 consecutive patients. *Neurochirurgia* 1983;**26**:36–41.

146. Garde A, Bohmer G, Selden B, Neiman J. 100 cases of spontaneous intracerebral haematoma. *Eur Neurol* 1983;**22**:161–72.

147. Helweg-Larsen S, Sommer W, Strange P, Lester J, Baysen G. Prognosis for patients treated conservatively for spontaneous intracerebral haematomas. *Stroke* 1984;**15**:1045–8.

148. Stein RW, Kase DB, Hier DB, Caplan LR, Mohr JP, Hemmati M. Caudate hemorrhage. *Neurology* 1984;**34**:1549–54.

149. Steiner I, Gomori JM, Melamed E. The prognostic value of the CT scan in conservatively treated patients with intracerebral hematoma. *Stroke* 1984;**15**:279–82.

150. Weisberg L. Caudate hemorrhage. *Arch Neurol* 1984;**41**:971–4.

151. Mori E, Tabuchi M, Yamadori A. Lacunar syndrome due to intracerebral hemorrhage. *Stroke* 1985;**16**:454–9.

152. Weisberg L. Subcortical lobar intracerebral haemorrhage: clinical–computed tomographic findings. *J Neurol Neurosurg Psychiatry* 1985;**48**:1078–84.

153. Tanaka Y, Furuse M, Iwasa H, Masuzawa T, Saito K, Sato F. Lobar intracerebral hemorrhage: etiology and a long-term follow-up study of 32 patients. *Stroke* 1986;**17**:51–7.

154. Gates PC, Barnett HJM, Vinters HV, Simonsen RL, Siu K. Primary intraventricular hemorrhage in adults. *Stroke* 1986;**17**:872–7.

155. Carbonin C, Toso V, Cagnin G, Antonini D. Primary brain stem haemorrhages: clinico-radiological considerations on five cases observed. *Neurochirurgia* 1986;**29**:53–7.

156. Dollberg S, Rosin AJ, Fisher D. A new look at the natural history and clinical features of intracerebral haemorrhage: a clinical CT scan correlation. *Gerontology* 1986;**32**:211–16.

157. Weisberg L. Primary pontine haemorrhage: clinical and computed tomographic correlations. *J Neurol Neurosurg Psychiatry* 1986;**49**:346–52.

158. Fieschi C, Carolei A, Fiorelli M, Argentino C, Bozzao L, Fazio M. Changing prognosis of primary intracerebral hemorrhage: results of a clinical and computed tomographic follow-up study of 104 patients. *Stroke* 1988;**19**:192–5.

159. Darby DG, Donnan GA, Saling MA, Walsh KW, Bladin PF. Primary intraventricular haemorrhage: clinical and neuropsychological findings in a prospective series. *Neurology* 1988;**38**:68–75.

160. Weisberg LA, Stazio A. Occipital lobe hemorrhages; clinical–computed tomographic correlations. *Comput Med Imaging Graph* 1988;**12**:353–8.

161. Iwasaki Y, Kinoshita M. Lacunar syndrome and intracerebral hemorrhage: clinico-computed tomographic correlations. *Comput Med Imaging Graph* 1988;**12**:359–63.

162. Weisberg LA, Stazio A. Nontraumatic parietal subcortical hemorrhage: clinical-computed tomographic correlations. *Comput Med Imaging Graph* 1989;**13**:355–61.

163. Astarloa R, Jimenez-Scrig A, Gimeno A. [Prognostic value of CAT scanning in spontaneous supratentorial cerebral hemorrhage. Multivariate study in 114 patients]. *Archivos de Neurobiologia* 1989;**52**:234–8.

164. Jayakumar PN, Taly AB, Bhavani UR, Arya BY, Nagaraja D. Prognosis in solitary intraventricular haemorrhage. Clinical and computed tomographic observations. *Acta Neurol Scand* 1989;**80**:1–5.

165. Schutz H, Bodeker RH, Damian M, Krack P, Dorndorf W. Age-related spontaneous intracerebral hematoma in a German community. *Stroke* 1990;**21**:1412–18.

166. Cerillo A, Villano M, Vizioli L, Narciso N, Tedeschi E, Bucchiero A, *et al*. Intracerebral haemorrhage: criteria for prognosis on the grounds of clinical and CT data. *J Neurosurg Sci* 1990;**34**:123–36.

167. Weisberg LA, Stazio A, Elliott D, Shamsnia M. Putaminal hemorrhage: clinical–computed tomographic correlations. *Neuroradiology* 1990;**32**:200–6.

168. Daverat P, Castel JP, Dartigues JF, Orgogozo JM. Death and functional outcome after spontaneous intracerebral hemorrhage. *Stroke* 1991;**22**:1–6.

169. Kreel L, Kay R, Woo J, Wong HY, Nicholls MG. The radiological (CT) and clinical sequelae of primary intracerebral haemorrhage. *Br J Radiol* 1991;**64**:1096–100.

170. Franke CL, van Swieten JC, van Gijn J. Residual lesions on computed tomography after intracerebral hemorrhage. *Stroke* 1991;**22**:1530–3.

171. Franke CL, van Swieten JC, Algra A, van Gijn J. Prognostic factors in patients with intracerebral haematoma. *J Neurol Neurosurg Psychiatry* 1992;**55**:653–7.

172. Lisk DR, Pasteur W, Rhoades H, Putnam RD, Grotta JC. Early presentation of hemispheric intracerebral hemorrhage: prediction of outcome and guidelines for treatment allocation. *Neurology* 1994;**44**:133–9.

173. Berlit P, Tornow K. Outcome of intracerebral hemorrhage: clinical and CT findings in 326 patients. *Eur J Neurol* 1994;**1**:29–43.

174. Fujii Y, Tanaka R, Takeuchi S, Koike T, Minakawa T, Sasaki O. Hematoma enlargement in spontaneous intracerebral hemorrhage. *J Neurosurg* 1994;**80**:51–7.

175. Halpin SF, Britton JA, Byrne JV, Clifton A, Hart G, Moore A. Prospective evaluation of cerebral angiography and computed tomography in cerebral haematoma. *J Neurol Neurosurg Psychiatry* 1994;**57**:1180–6.

176. Passero S, Burgalassi L, D'Andrea P, Battistini N. Recurrence of bleeding in patients with primary intracerebral hemorrhage [see comments]. *Stroke* 1995;**26**:1189–92.

177. Dandapani BK, Suzuki S, Kelley RE, Reyes-Iglesias Y, Duncan RC. Relation between blood pressure and outcome in intracerebral hemorrhage. *Stroke* 1995;**26**:21–4.

178. Lampl Y, Gilad R, Eshel Y, Sarova-Pinhas I. Neurological and functional outcome in patients with supratentorial hemorrhages. A prospective study. *Stroke* 1995;**26**:2249–53.

179. Mori S, Sadoshima S, Ibayashi S, Fujishima M, Iino K. Impact of thalamic hematoma on six-month mortality and motor and cognitive functional outcome. *Stroke* 1995;**26**:620–6.

180. Qureshi AI, Safdar K, Weil J, Barch C, Bliwise DL, Colohan AR, *et al*. Predictors of early deterioration and mortality in black Americans with spontaneous intracerebral hemorrhage. *Stroke* 1995;**26**:1764–7.

181. Mase G, Zorzon M, Biasutti E, Tasca G, Vitrani B, Cazzato G. Immediate prognosis of primary intracerebral hemorrhage using an easy model for the prediction of survival. *Acta Neurol Scand* 1995;**91**:306–9.

182. Chaves CJ, Pessin MS, Chung CS, Amarenco P, Breen J, Fine J. Cerebellar haemorrhagic infarction. *Neurology* 1996;**46**:346–9.

183. Kazui S, Naritomi H, Yamamoto H, Sawada T, Yamaguchi T. Enlargement of spontaneous intracerebral hemorrhage. Incidence and time course. *Stroke* 1996;**27**:1783–7.

184. Hsiang JN, Zhu XL, Wong LK, Kay R, Poon WS. Putaminal and thalamic hemorrhage in ethnic Chinese living in Hong Kong. *Surg Neurol* 1996; **46**:441–5.

185. Eshwar Chandra N, Khandelwal N, Bapuraj JR, Mathuriya SN, Vasista RK, Kak VK, *et al*. Spontaneous intracranial hematomas: role of dynamic CT and angiography. *Acta Neurol Scand* 1998;**98**:176–81.

186. Butler AC, Tait RC. Restarting anticoagulation in prosthetic heart valve patients after intracranial haemorrhage: a 2-year follow-up. *Br J Haematol* 1998;**103**:1064–6.

187. Gonzalez-Duarte A, Cantu C, Ruiz-Sandoval JL, Barinagarrementeria F. Recurrent primary cerebral hemorrhage: frequency, mechanisms, and prognosis. *Stroke* 1998;**29**:1802–5.

188. Linfante I, Llinas RH, Caplan LR, Warach S. MRI features of intracerebral hemorrhage within 2 hours from symptom onset. *Stroke* 1999;**30**:2263–7.

189. Offenbacher H, Fazekas F, Schmidt R, Koch M, Fazekas G, Kapeller P. MR of cerebral abnormalities concomitant with primary intracerebral haematomas. *AJNR Am J Neuroradiol* 1996;**17**:573–8.

190. Melhem ER, Patel RT, Whitehead RE, Bhatia RG, Rockwell DT, Jara H. MR imaging of hemorrhagic brain lesions: a comparison of dual-echo gradient- and spin-echo and fast spin-echo techniques. *AJR AM J Roentgenol* 1998;**171**(3):797–802.

191. Edelman RR, Johnson K, Buxton R, Shoukimas G, Rosen KR, Davis KR. MR of hemorrhage: a new approach. *AJNR Am J Neuroradiol* 1986;**7**:751–6.

192. Gomori JM, Grossman RI, Goldberg HI, Zimmerman RA, Bilaniuk LT. Intracranial hematomas: imaging by high-field MR. *Radiology* 1985;**157**:87–93.

193. Zimmerman RD, Heier LA, Snow RB, Liu DPC, Kelly AB, Deck MDF. Acute intracranial hemorrhage: intensity changes on sequential MR scans at 0.5 T. *AJNR Am J Roentgenol* 1988;**150**:651–61.

194. Shimizu T, Naritomi H, Kuriyama Y, Sawada T. Sequential changes of sodium magnetic resonance images after cerebral hemorrhage. *Neuroradiology* 1992;**34**:301–4.

195. Liang L, Korogi Y, Sugahara T, Shigematsu Y, Okuda T, Ikushima I, *et al*. Detection of intracranial hemorrhage with susceptibility-weighted MR sequences. *AJNR Am J Neuroradiol* 1999;**20**:1527–34.

196. Tanaka A, Ueno Y, Nakayama Y, Takano K. Small chronic haemorrhages and ischaemic lesions in association with spontaneous intracerebral haematomas. *Stroke* 1999;**30**:1637–42.

197. Patel MR, Edelman RR, Warach S. Detection of hyperacute primary intraparenchymal hemorrhage by magnetic resonance imaging. *Stroke* 1996;**27**:2321–4.

198. Staffen W, Trinka E, McCoy M, Iglseder B, Unterrainer J, Ladurner G, *et al*. A comparison of neuroimaging and clinical findings in 100 patients with haemorrhagic infarction and intracerebral haematoma. *Aktuelle Neurologie* 1998;**25**:69–73.

199. Steinbrich W, Gross-Fengels W, Krestin GP, Heindel Schreier WG. MRI examinations of intracranial haematomas. An analysis of its sensitivity evolution and source of bleeding. *Rofo: Fortschritte auf dem Gebiete der Rontgenstrahlen und der Nuklearmedizin* 1990;**152**:534–43.

200. Tanaka T, Sakai T, Uemura K, Teramura A, Fujishima I, Yamamoto T. Magnetic resonance imaging in the acute stage of cerebrovascular disease – clinical comparison with computed tomography. *Neurol Med Chir* 1988;**2 8**: 974–80.

201. Schellinger PD, Jansen O, Fiebach JB, Hacke W, Sartor K. A standardized MRI stroke protocol: comparison with CT in hyperacute intracerebral hemorrhage. *Stroke* 1999;**30**:765–8.

202. Kinoshita T, Okudera T, Tamura H, Ogawa T, Hatazawa J. Assessment of lacunar hemorrhage associated with hypertensive stroke by echo-planar gradient-echo T2*-weighted MRI. *Stroke* 2000; **31**:1646–50.

203. Salgado ED, Weinstein M, Furlan AJ, Modic MT, Beck GJ, Estes M, *et al*. Proton magnetic resonance imaging in ischemic cerebrovascular disease. *Ann Neurol* 1986;**20**:502–7.

204. Kertesz A, Black SE, Nicholson L, Carr T. The sensitivity and specificity of MRI in stroke. *Neurology* 1987;**37**:1580–5.

205. Mayer TE, Schulte-Altedorneburg G, Droste DW, Bruckmann H. Serial CT and MRI of ischaemic cerebral infarcts: frequency and clinical impact of haemorrhagic transformation. *Neuroradiology* 2000;**42**:233–9.

206. Arias M, Requena I, Pereiro I, Amigo ME, Ventura M, Quintans L, *et al*. CT vs MRI in the diagnosis of acute stroke. *Arch Neurobiol* 1992;**55**:50–6.

207. Mohr JP, Biller J, Hilal SK, Yuh WTC, Tatemichi TK, Hedges S. Magnetic resonance versus computed tomographic imaging in acute stroke. *Stroke* 1995;**26**:807–12.

208. Van Goethem J, Van Laere M, De Moor J, Parizel PM. Subacute intracerebral hemorrhage: CT and MR characteristics. *J Belge Radiol* 1990; **73**:534–5.

209. Buell U, Kazner E, Rath M, Steinhoff H, Kleinhans E, Lanksch W. Sensitivity of computed tomography and serial scintigraphy in cerebrovascular disease. *Radiology* 1979;**131**:393–8.

210. Soderstrom CE, Ericson K, Mettinger KL, Olivecrona H. Computed tomography and CSF spectrophotometry. Diagnosis and prognosis in 300 patients with cerebrovascular disease. *Scand J Rehabil Med* 1981;**13**:65–71.

211. Wall SD, Brant-Zawadzki M, Jeffrey RB, Barnes B. High frequency CT findings within 24 hours after cerebral infarction. *AJR AM J Roentgenol* 1982; **138**:307–11.

212. Sandercock P, Molyneux A, Warlow C. Value of computed tomography in patients with stroke: Oxfordshire Community Stroke Project. *BMJ* 1985;**290**:193–7.

213. Brott T, Marler JR, Olinger CP, Adams HP, Tomsick T. Measurements of acute cerebral infarction: lesion size by computed tomography. *Stroke* 1989;**20**:871–5.

214. Sotaniemi KA, Phytinen J, Myllyla VV. Correlation of clinical and computed tomographic findings in stroke patients. *Stroke* 1990;**21**:1562–6.

215. Koudstaal PJ, van Gijn J, Frenken CW, Hijdra A, Lodder J, Vermeulen M, *et al*. TIA, RIND, minor stroke: a continuum, or different subgroups? Dutch TIA Study Group. *J Neurol Neurosurg Psychiatry* 1992;**55**:95–7.

216. Lindgren A, Norrving B, Rudling O, Johansson BB. Comparison of clinical and neuroradiological findings in first-ever stroke. A population-based study. *Stroke* 1994;**25**:1371–7.

217. Firlik AD, Kaufmann AM, Wechsler LR, Firlik KS, Fukui MB, Yonas H. Quantitative cerebral blood flow determinations in acute ischemic stroke. Relationship to computed tomography and angiography. *Stroke* 1997;**28**:2208–13.

218. Buttner T, Uffmann M, Gunes N, Koster O. Early CCT signs of supratentorial brain infarction: clinico-radiological correlations. *Acta Neurol Scand* 1997;**96**:317–23.

219. Al-Buhairi AR, Phillips SJ, Llwellyn G, Jan MSJ. Prediction of infarct topography using the Oxfordshire Community Stroke Project classification of stroke subtypes. *J Stroke Cerebrovasc Dis* 1998;**7**:339–43.

220. Lev MH, Farkas J, Gemmete JJ, Hossain ST, Hunter GJ, Koroshetz WJ, *et al*. Acute stroke: improved nonenhanced CT detection – benefits of soft-copy interpretation by using variable window width and center level settings. *Radiology* 1999;**213**:150–5.

221. Scott JN, Buchan AM, Sevick RJ. Correlation of neurological dysfunction with CT findings in early acute stroke. *Can J Neurol Sci* 1999;**26**:182–9.

222. Barber PA, Demchuk AM, Zhang J, Buchan AM. Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy. ASPECTS Study Group. Alberta Stroke Programme Early CT Score. *Lancet* 2000;**355**: 1670–4.

223. von Kummer R, Nolte PN, Schnittger H, Thron A, Ringelstein EB. Detectability of cerebral hemisphere ischaemic infarcts by CT within 6 h of stroke. *Neuroradiology* 1996;**38**:31–3.

224. Fazekas F, Fazekas G, Schmidt R, Kapeller P, Offenbacher H. Magnetic resonance imaging correlates of transient cerebral ischemic attacks. *Stroke* 1996;**27**:607–11.

225. Cosnard G, Duprez T, Grandin C, Smith AM, Munier T, Peeters A. Fast FLAIR sequence for detecting major vascular abnormalities during the hyperacute phase of stroke: a comparison with MR angiography. *Neuroradiology* 1999;**41**: 342–6.

226. Egelhof T, Essig M, von Kummer R, Dorfler A, Winter R, Sartor K. Acute ischemic cerebral infarct: prospective serial observations by magnetic resonance imaging. *Rofo: Fortschritte auf dem Gebiete der Rontgenstrahlen und der Neuen Bildgebenden Verfahren* 1998;**168**:222–7.

227. Razumovsky AY, Gillard JH, Bryan RN, Hanley DF, Oppenheimer SM. TCD, MRA and MRI in acute cerebral ischemia. *Acta Neurol Scand* 1999;**99**:65–76.

228. Awad I, Modic M, Little JR, Furlan AJ, Weinstein M. Focal parenchymal lesions in transient ischemic attacks: correlation of computed tomography and magnetic resonance imaging. *Stroke* 1986;**17**:399–403.

229. Simmons Z, Biller J, Adams HP Jr, Dunn V, Jacoby CG. Cerebellar infarction: comparison of computed tomography and magnetic resonance imaging. *Ann Neurol* 1986;**19**:291–3.

230. Rothrock JF, Lyden PD, Hesselink JR, Brown JJ, Healy ME. Brain magnetic resonance imaging in the evaluation of lacunar stroke. *Stroke* 1987;**18**: 781–6.

231. Hommel M, Pollak P, Gaio JM, Besson G, Borgel F, Le Bas JF, *et al*. Magnetic resonance imaging in lateral medullary infarction. *Rev Neurol (Paris)* 1988;**144**:272–8.

232. Miyashita K, Naritomi H, Sawada T, Nakamura M, Kuriyama Y, Ogawa M. Identification of recent lacunar lesions in cases of multiple small infarctions by magnetic resonance imaging. *Stroke* 1988;**19**:834–9.

233. Arboix A, Marti-Vilalta JL, Pujol J, Sanz M. Lacunar cerebral infarct and nuclear magnetic resonance. A review of sixty cases. *Eur Neurol* 1990;**30**:47–51.

234. Bryan RN, Levy LM, Whitlow WD, Killian JM, Preziosi TJ, Rosario JA. Diagnosis of acute cerebral infarction: comparison of CT and MR imaging. *AJNR Am J Neuroradiol* 1991;**12**:611–20.

235. Stapf C, Hofmeister C, Hartmann A, Marx P, Mast H. Predictive value of clinical lacunar syndromes for lacunar infarcts on magnetic resonance brain imaging. *Acta Neurol Scand* 2000;**101**:13–18.

236. New PJF, Scott WR, Schnur JA, Davis KR, Taveras JM. Computerized axial tomography with the EMI scanner. *Radiology* 1974;**110**:109–23.

237. Jacobs L, Kinkel WR, Heffner RR Jr. Autopsy correlations of computerized tomography: experience with 6,000 CT scans. *Neurology* 1976;**26**:1111–18.

238. Toghi H, Mochizuki H, Yamanouchi H, Iio M, Yamada H, Chiba K, *et al*. A comparison between the computed tomogram and the neuropathological findings in cerebrovascular disease. *J Neurol* 1981;**224**:211–20.

239. Sipponen JT. Visualization of brain infarction with nuclear magnetic resonance imaging. *Neuroradiology* 1984;**26**:387–91.

240. Panzer RJ, Feibel JH, Barker WH, Griner PF. Predicting the likelihood of hemorrhage in patients with stroke. *Arch Intern Med* 1985;**145**: 1800–3.

241. Wang AM, Lin JC, Rumbaugh CL. What is expected of CT in the evaluation of stroke? *Neuroradiology* 1988;**30**:54–8.

242. Horowitz SH, Zito JL, Donnarumma R, Patel M. Computed tomographic–angiographic findings within the first five hours of cerebral infarction. *Stroke* 1991;**22**:1245–53.

243. Bendszus M, Urbach H, Meyer B, Schultheiss R, Solymosi L. Improved CT diagnosis of acute middle cerebral artery territory infarcts with density-difference analysis. *Neuroradiology* 1997;**39**:127–31.

244. McAlister FA, Fisher BW, Houston SC. The timing of computed tomography in acute stroke: a practice audit. *Can Assoc Radiol J* 1997;**48**:123–9.

245. Johansson T. Cerebral infarctions with negative CT scans. *Eur Neurol* 1984;**23**:124–31.

246. Kinkel WR, Jacobs L. Computerized axial transverse tomography in cerebrovascular disease. *Neurology* 1976;**26**:924–30.

247. Inoue Y, Takemoto K, Miyamoto T, Yoshikawa N, Taniguchi S, Saiwai S. Sequential computed tomography scans in acute cerebral infarction. *Radiology* 1980;**135**:655–62.

248. Moulin T, Cattin F, Crepin-Leblond T, Tatu L, Chavot D, Piotin M, *et al*. Early CT signs in acute middle cerebral artery infarction: predictive value for subsequent infarct locations and outcome. *Neurology* 1996;**47**:366–75.

249. Toni D, Iweins F, von Kummer R, Busse O, Bogousslavsky J, Falcou A, *et al*. Identification of lacunar infarcts before thrombolysis in the ECASS I study. *Neurology* 2000;**54**:684–8.

250. Toni D, Fiorelli M, De Michele M, Bastianello S, Sacchetti ML, Montinaro E, *et al*. Clinical and prognostic correlates of stroke subtype misdiagnosis within 12 hours from onset [published erratum appears in *Stroke* 1996;**27**:152]. *Stroke* 1995;**26**:1837–40.

251. Bryan RN, Willcott MR, Schneiders NJ. Nuclear magnetic resonance evaluation of stroke. A preliminary report. *Radiology* 1983;**149**:189–92.

252. Virapongse C, Mancuso A, Quisling R. Human brain infarcts: Gd-DTPA-enhanced MR imaging. *Radiology* 1986;**161**:785–94.

253. Kinkel PR, Kinkel WR, Jacobs L. Nuclear magnetic resonance imaging in patients with stroke. *Semin Neurol* 1986;**6**:43–52.

254. Byrne JV, Kendall BE, Kingsley DPE, Moseley IF. Lesions of the brain stem: Assessment by magnetic resonance imaging. *Neuroradiology* 1989;**31**:129–33.

255. Crain MR, Yuh WTC, Greene GM, Loes DJ, Ryals TJ, Sato Y. Cerebral ischaemia: evaluation with contrast-enhanced MR imaging. *AJNR Am J Neuroradiol* 1991;**12**:631–9.

256. Yuh WTC, Crain MR, Loes DJ, Greene GM, Ryals TJ, Sato Y. MR imaging of cerebral ischaemia: findings in the first 24 hours. *AJNR Am J Neuroradiol* 1991;**12**:621–9.

257. Sato A, Takahashi S, Soma Y, Ishii K, Kikuchi Y, Watanabe T, *et al*. Cerebral infarction: early detection by means of contrast-enhanced cerebral arteries at MR imaging. *Radiology* 1991;**178**:433–9.

258. Alberts MJ, Faulstich ME, Gray L. Stroke with negative brain magnetic resonance imaging. *Stroke* 1992;**23**:663–7.

259. Shimosegawa E, Inugami A, Okudera T, Hatazawa J, Ogawa T, Fujita H, *et al*. Embolic cerebral infarction: MR findings in the first 3 hours after onset. *AJR Am J Roentgenol* 1993;**160**:1077–82.

260. Yin W-M, Nagata K, Satoh Y, Yokoyama E, Watahiki Y, Yuya H, *et al*. Infratentorial infarction: correlation of MR findings with neurological and angiographical features. *Neurol Res* 1994;**16**:154–8.

261. Kim JS, Lee JH, Suh DC, Lee MC. Spectrum of lateral medullary syndrome: correlation between clinical findings and magnetic resonance imaging in 33 subjects. *Stroke* 1994;**25**:1405–10.

262. Brant-Zawadzki M, Atkinson DJ, Detrick M, Bradley WG, Scidmore G. Fluid-attenuated inversion recovery (FLAIR) for assessment of cerebral infarction. Initial clinical experience in 50 patients. *Stroke* 1996;**27**:1187–91.

263. Mantyla R, Aronen HJ, Salonen O, Korpelainen M, Peltonen T, Standertskjold-Nordenstam C. The prevalence and distribution of white-matter changes on different MRI pulse sequences in a post-stroke cohort. *Neuroradiology* 1999;**41**:657–65.

264. Mantyla R, Aronen HJ, Salonen O, Pohjasvaara T, Korpelain M, Peltonen T. Magnetic resonance imaging white matter hyperintensities and mechanism of ischemic stroke. *Stroke* 1999;**30**:2053–8.

265. Sipponen JT, Kaste M, Ketonen L, Sepponen RE, Katevuo K, Sivula A. Serial nuclear magnetic resonance (NMR) imaging in patients with cerebral infarction. *J Comput Assist Tomography* 1983;**7**:585–9.

266. Smith AS, Weinstein MA, Modic MT. Magnetic resonance with marked T2-weighted images: improved demonstration of brain lesions, tumor, and edema. *AJR Am J Roentgenol* 1985;**145**:949–55.

267. Steinbrich W, Friedmann G, Pawlik G, Bocher-Schwarz HG, Heiss WD. MR of ischemic brain diseases. A comparison with CT, PET (18-fluorodeoxyglucose) and angiographic results. *Rofo: Fortschritte auf dem Gebiete der Rontgenstrahlen und der Nuklearmedizin* 1986;**145**:173–81.

268. Biller J, Adams HP, Dunn V, Simmons Z, Jacoby CG. Dichotomy between clinical findings and MR abnormalities in pontine infarction. *J Comput Assist Tomography* 1986;**10**:379–85.

269. Cirillo S, Simonetti L, La Tessa G, Elefante R, Smaltino F. MR imaging and CT: comparative adequacy in neuroradiology. *Radiol Med (Torino)* 1988;**76**:390–8.

270. Imakita S, Nishimura T, Yamada N, Naito H, Takamiya M, Yamada Y, *et al*. Magnetic resonance imaging of cerebral infarction: time course of Gd-DTPA enhancement and CT comparison. *Neuroradiology* 1988;**30**:372–8.

271. Hommel M, Besson G, Le Bas JF, Gaio JM, Pollak P, Borgel F, *et al*. Prospective study of lacunar infarction using magnetic resonance imaging. *Stroke* 1990;**21**:546–54.

272. Shuaib A, Lee D, Pelz D, Fox A, Hachinski VC. The impact of magnetic resonance imaging on the management of acute ischemic stroke. *Neurology* 1992;**42**:816–18.

273. Krivoshapkin AL, Jacobson MG, Rabinovich SS. Correlation of MRI and CT data with outcome of cerebral revascularization after stroke. *Neurol Res* 1992;**14**(2 Suppl):211–13.

274. Boyko OB, Burger PC, Shelburne JD, Ingram P. Non-heme mechanisms for T1 shortening: pathologic, CT, and MR elucidation. *AJNR Am J Neuroradiol* 1992;**13**:1439–45.

275. Fiorelli M, Sacchetti ML, Toni D, Argentino C, Gori C, Di Biasi C, *et al*. Feasibility and usefulness of conventional spin-echo MR imaging in hyperacute ischemic stroke: a comparison with CT scan. *Circulation et Metabolisme du Cerveau* 1993; **10**:5–10.

276. Maeda M, Abe H, Yamada H, Ishii Y. Hyperacute infarction: a comparison of CT and MRI, including diffusion-weighted imaging. *Neuroradiology* 1999;**41**:175–8.

277. Schuetz H, Dommer T, Boedeker RH, Damian M, Krack P, Dorndorf W. Changing pattern of brain hemorrhage during 12 years of computed axial tomography. *Stroke* 1992;**23**:653–6.

278. Brennan P, Silman A. Statistical methods for assessing observer variability in clinical measures. *BMJ* 1992;**304**:1491–4.

279. Schneider R, Kluge R, Willmes K. Interrater agreement for CT scans of patients with lacunar infarcts and leuko-araiosis. *Acta Neurol Scand* 1991;**84**:527–30.

280. Wardlaw J, Sellar R. A simple practical classification of cerebral infarcts on CT and its interobserver reliability. *AJNR Am J Neuroradiol* 1994;**15**:1933–9.

281. von Kummer R, Holle R, Gizyska U, Hofmann E, Jansen O, Petersen D, *et al*. Interobserver agreement in assessing early CT signs of middle cerebral artery infarction. *AJNR Am J Neuroradiol* 1996;**17**:1743–8.

282. von Kummer R, Allen KL, Holle R, Bozzao L, Bastianello S, Manelfe C, *et al*. Acute stroke: usefulness of early CT findings before thrombolytic therapy. *Radiology* 1997;**205**:327–33.

283. Besson G, Moulin T, Chavot D, Tatu L, Garnier P, Crepin-Leblond T. Intra-observer concordance of the neuroradiologic reviewing committee in CT scan reviewing in MAST-E. *Acta Neurol Scand* 1998;**98**:292–3.

284. Marks MP, Holmgren EB, Fox AJ, Patel S, von Kummer R, Froehlich J. Evaluation of early computed tomographic findings in acute ischemic stroke. *Stroke* 1999;**30**:389–92.

285. Grotta JC, Chui D, Lu M, Patel S, Levine SR. Agreement and variability in the interpretation of early CT changes in stroke patients qualifying for intravenous rTPA therapy. *Stroke* 1999;**30**:1528–33.

286. Roszler MH, McCarroll KA, Rashid T, Donovan KR, Kling GA. Resident interpretation of emergency computed tomographic scans. *Invest Radiol* 1991;**26**:374–6.

287. Alfaro D, Levitt MA, English DK, Williams V, Eisenberg R. Accuracy of interpretation of cranial computed tomography scans in an emergency medicine residency program. *Ann Emerg Med* 1995;**25**:169–74.

288. Pullicino P, Snyder W, Munschauer F, Pordell R, Greiner F. Interrater agreement of computed tomography infarct measurement. *J Neuroimaging* 1996;**6**:16–19.

289. Schriger DL, Kalafut M, Starkman S, Krueger M, Saver JL. Cranial computed tomography interpretation in acute stroke: physician accuracy in determining eligibility for thrombolytic therapy. *JAMA* 1998;**279**:1293–7.

290. Kalafut MA, Schriger DL, Saver JL, Starkman S. Detection of early CT signs of > 1/3 middle cerebral artery infarctions: interrater reliability and sensitivity of CT interpretation by physicians involved in acute stroke care. *Stroke* 2000;**31**: 1667–71.

291. Hacke W, Kaste M, Fieschi C, Toni D, Lesaffre E, von Kummer R, *et al*. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. The European Cooperative Acute Stroke Study (ECASS). *JAMA* 1995;**274**:1017–25.

292. Darrow VC, Alvord EC Jr, Mack LA, Hodson WA. Histologic evolution of the reactions to hemorrhage in the premature human infant's brain. A combined ultrasound and autopsy study and a comparison with the reaction in adults. *Am J Pathol* 1988;**130**:44–58.

293. Cote R, Hachinski VC, Shurvell BL, Norris JW, Wolfson C. The Canadian Neurological Scale: a preliminary study in acute stroke. *Stroke* 1986; **17**:731–7.

294. Kalafut M, Starkman S, Saver J, Villablanca P, Schriger D. Early infarct and haemorrhage interpretation by emergency physicians: implications for thrombolytic therapy. *Stroke* 1997;**28**:270.

295. Wardlaw JM, Dorman PJ, Lewis SC, Sandercock PAG. Can stroke physicians and neuroradiologists identify signs of early cerebral infarction on CT? *J Neurol Neurosurg Psychiatry* 1999;**67**:651–3.

296. Paxton R, Ambrose J. EMI scanner: brief review of first 650 patients. *Br J Radiol* 1974;**47**:530–65.

297. Wensley S, Keir S, Caine S, MacMahon M. Additional risk factors in atrial fibrillation patients not receiving warfarin. *Age Ageing* 1999;**28**:355–7.

298. Mead GE, Wardlaw JM, Lewis SC, McDowall M, Dennis MS. The influence of randomized trials on the use of anticoagulants for atrial fibrillation. *Age Ageing* 1999;**28**:441–6.

299. Muir KW, Weir CJ, Murray GD. Comparison of neurological scales and scoring systems for acute stroke prognosis. *Stroke* 1996;**27**:1817–20.

300. Leker RR, Abramsky O. Early anticoagulation in patients with prosthetic heart valves and intracerebral hematoma. *Neurology* 1998;**50**: 1489–91.

301. Boeer A, Voth E, Henze T, Prange HW. Early heparin therapy in patients with spontaneous intracerebral haemorrhage. *J Neurol Neurosurg Psychiatry* 1991;**54**:466–7.

302. Wijdicks EFM, Schievink WI, Brown RD, Mullany CJ, Stoodley M, Weir BKA, *et al*. The dilemma of discontinuation of anticoagulation therapy for patients with intracranial hemorrhage and mechanical heart valves. *Neurosurgery* 1998; **42**:769–73.

303. Chamorro A, Vila N, Saiz A, Alday M, Tolosa E. Early anticoagulation after large cerebral embolic infarction: a safety study. *Neurology* 1995; **45**:861–5.

304. Nakagawa T, Kubota T, Handa Y, Kawano H, Sato K. Intracranial hemorrhage due to long-term anticoagulant therapy in patients with prosthetic heart valves – four case reports. *Neurol Med Chir (Tokyo)* 1995;**35**:156–9.

305. Pessin MS, Estol CJ, Lafranchise F, Caplan LR. Safety of anticoagulation after hemorrhagic infarction. *Neurology* 1993;**43**:1298–303.

306. Kapp J, Neill WR, Salter JE, Barnes TY. Systemic heparin in the early management of ruptured intracranial aneurysms: review of 104 consecutive cases and comparison with concurrent controls. *Neurosurgery* 1987;**20**:564–70.

307. Cerebral Embolism Study Group. Immediate anticoagulation of embolic stroke: brain hemorrhage and management options. *Stroke* 1984;**15**:779–89.

308. Wang DZ, Futrell N, Taylon C, Millikan C. Anticoagulation for prevention of cerebral infarcts following subarachnoid hemorrhage. *Surg Neurol* 1995;**44**:270–4.

309. Brick JF, Cheek JC, Gutierrez AR. Hemorrhagic cardioembolic stroke: is anticoagulation absolutely contraindicated? *South Med J* 1991;**84**:927–8.

310. Rothrock JF, Dittrich HC, McAllen S, Taft BJ, Lyden PD. Acute anticoagulation following cardioembolic stroke. *Stroke* 1989;**20**:730–4.

311. Petty GW, Brown RD Jr, Whisnant JP, Sicks JD, O'Fallon WM, Wiebers DO. Frequency of major complications of aspirin, warfarin, and intravenous heparin for secondary stroke prevention. A population-based study. *Ann Intern Med* 1999; **130**:14–22.

312. Sulter G, Steen C, De Keyser J. Use of the Barthel Index and modified Rankin scale in acute stroke trials. *Stroke* 1999;**30**:1538–41.

313. Ono H, Mizukami M, Kitamura K, Kikuchi H. Subarachnoid haemorrhage. *Agents Actions* 1984;**15** (suppl):259–72.

314. Mendelow AD, Stockdill C, Steers AJW, Hayes J, Gillingham FJ. Double-blind trial of aspirin in patients receiving tranexamic acid for subarachnoid haemorrhage. *Acta Neurochir* 1982; **62**:195–202.

315. Shaw MD, Foy PM, Conway M, Pickard JD, Maloney P, Spillane JA, *et al*. Dipyridamole and postoperative ischemic deficits in aneurysmal subarachnoid hemorrhage. *J Neurosurg* 1985; **63**:699–703.

316. Dickmann U, Voth E, Schicha H, Henza T, Prange H, Emrich D. Heparin therapy, deep vein thrombosis and pulmonary embolism after intracerebral haemorrhage. *Klin Wochenschr* 1988; **66**:1182–3.

317. Suzuki S, Sano K, Handa H, Asano T, Tamura A, Yonekawa Y, *et al*. Clinical study of OKY-046, a thromboxane synthetase inhibitor, in prevention of cerebral vasospasms and delayed cerebral ischaemic symptoms after subarachnoid haemorrhage due to aneurysmal rupture: a randomized double-blind study. *Neurol Res* 1989; **11**:79–88.

318. Tokiyoshi K, Ohnishi T, Nii Y. Efficacy and toxicity of thromboxane synthetase inhibitor for cerebral vasospasm after subarachnoid haemorrhage. *Surg Neurol* 1991;**36**:112–18.

319. Hop JW, Rinkel GJ, Algra A, Berkelbach van der Sprenkel JW, van Gijn J. Randomized pilot trial of postoperative aspirin in subarachnoid hemorrhage. *Neurology* 2000;**54**:872–8.

320. Powers WJ. Acute hypertension after stroke: the scientific basis for treatment decisions. *Neurology* 1993;**43**:461–7.

321. Boeer A, Voth E, Henze Th, Prange HW. Early heparin therapy in patients with spontaneous intracerebral haemorrhage. *J Neurol Neurosurg Psychiatry* 1991;**54**:466–7.

322. Juvela S. Aspirin and delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage. *J Neurosurg* 1995;**82**:945–52.

323. Gubitz GJ, Sandercock PAG, Counsell C, Signorini D. Anticoagulants for acute ischaemic stroke (Cochrane Review). The Cochrane Library (Issue 4). Oxford: Update Software; 1999.

324. Decousus H, Leizorovicz A, Parent F, Page Y, Tardy B, Girard P, *et al*. A clinical trial of vena caval filters in the prevention of pulmonary embolism in patients with proximal deep-vein thrombosis. Prevention du Risque d'Embolie Pulmonaire par Interruption Cave Study Group. *N Engl J Med* 1998;**338**:409–15.

325. 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.

326. Evers SMAA, Ament AJHA, Blaauw G. Economic evaluation in stroke research. A systematic review. *Stroke* 2000;**31**:1046–53.

327. Bahr AE, Hodges FJ. Efficacy of computed tomography of the head in changing patient care and health costs: a retrospective study. *AJR Am J Roentgenol* 1978;**131**:45–9.

328. Larson EB, Omen GS, Loop JW. Computed tomography in patients with cerebrovascular disease: impact of a new technology on patient care. *AJR Am J Roentgenol* 1978;**131**:35–40.

329. Britton M, Jonsson E, Marke L-A, Murray V. Diagnosing suspected stroke. A cost-effectiveness analysis. *Int J Technol Assess* 1985;**1**:147–58.

330. van der Meulen JH, Limburg M, van Straten A, Habbema JD. Computed tomographic brain scans and antiplatelet therapy after stroke: a study of the quality of care in Dutch hospitals. *Stroke* 1996; **27**:633–8.

331. Gleason S, Furie K, Lev M, O'Donnell A, McMahon P, Beinfeld M. Potential influences of acute CT on inpatient costs in patients with ischaemic stroke. *Acad Radiol* 2001;**8**:955–64.

332. Heller R, Langhorne P, James E. Improving stroke outcomes: the benefits of increasing availability of technology. *Bull World Health Organ* 2002;**78**:1337–43.

333. Greive R, Dundas R, Beech R, Wolfe C. The development and use of a method to compare the costs of acute stroke across Europe. *Age Ageing* 2001;**30**:67–72.

334. Broderick JP, Adams HP, Barsan W, Feinberg W, Feldman E, Grotta J, *et al*. Guidelines for the management of spontaneous intracerebral hemorrhage. A statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association. *Stroke* 1999;**30**:905–15.

335. Scottish Intercollegiate Guidelines Network (SIGN). *Antithrombotic therapy. SIGN 36*. Edinburgh: SIGN; 1999.

336. Dorman P, Sandercock P. Access to computed tomography in British accident and emergency departments. *BMJ* 1997;**314**:440–1.

337. Weir NU, Dennis MS, on behalf of the Scottish Outcomes Group. Towards a national system for monitoring the quality of hospital-based stroke services. *Stroke* 2001;**32**:1415–21.

338. Weinstein MC, Fineberg HV. *Clinical decision analysis*. Philadelphia, PA: WB Saunders; 1980.

339. Bamford J, Sandercock P, Warlow C, Slattery J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke* 1989; **20**:828.

340. Counsell C, Boonyakarnkul S, Dennis M, Sandercock P, Bamford J, Burn J. Primary intracerebral haemorrhage in the Oxfordshire Community Stroke Project. 2. Prognosis. *Cerebrovasc Dis* 1995;**5**:26–34.

341. Hallan S, Asberg A, Indredavik B, Wideroe TE. Quality of life after cerebrovascular stroke: a systematic study of patients' preferences for different functional outcomes. *J Intern Med* 1999; **246**:309–16.

342. Dennis M, Wellwood I, Warlow C. Are simple questions a valid measure of outcome after stroke? *Cerebrovasc Dis* 1997;**7**:227–34.

343. Post PN, Stiggelbout A, Wakker P. Utility of health states after stroke. A systematic review of the literature. *Stroke* 2001;**32**:1425–9.

344. EuroQol Group. EuroQol – a new facility for the measurement of health-related quality of life. *Health Policy* 1990;**16**:199–208.

345. EuroQol Group. *A measure of health related quality of life developed by the EuroQol Group*. Rotterdam: EuroQol; 1996.

346. MVH Group. The measurement and valuation of health. Final report on the modelling of valuation

tariffs. York: Centre for Health Economics, University of York; 1995.

347. NHS Executive. Health Service Cost Index (HCHS specific price inflation) September 2000 (October 2000), Financial Matters, Appendix 1. Leeds: NHS Executive; 2000.

348. NHS Executive (2000). Health service cost index (HCHS specific price inflation), September 2001, financial matters, Appendix 1. Leeds: NHS Executive; 2000.

349. NHS Executive. Reference costs. Leeds: NHS Executive; 2001. www.doh.gov.uk/nhsexec/refcosts.htm

350. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy – III: reduction in venous thrombosis and pulmonary embolism by antiplatelet prophylaxis among surgical and medical patients. *BMJ* 1994;**308**:235–46.

351. Ferguson A, McCabe CJ, Sheffield: Trent Institute for Health Services Research, Universities of Leicester Nottingham and Sheffield. The clinical and cost-effectiveness of computed tomography in the management of transient ischaemic attack and stroke. Trent Institute for Health Services Research; 1997.

352. The Wessex Institute for Health Research & Development. CT scanning within 48 hours after stroke. Southampton: University of Southampton; 1998.

353. Drummond MF, O'Brien B, Stoddart GL, Torrance G. *Methods for the economic evaluation of health care programme*. Oxford: Oxford University Press; 1997.

354. Donaldson C, Shackley P. Economic evaluation. In Detels R, Holland W, Omenn GS, editors. *Oxford textbook of public health*. 3rd ed. Oxford: Oxford University Press; 1997.

355. Scott A, Harrold T, Russell E. Evaluation of community cardiology in Grampian (final report). Aberdeen: Health Economics Research Unit (HERU), University of Aberdeen; 1999.

356. Netten A, Curtis L. Unit cost of health and social care 2000. 2000. Kent: Personal Social Services Research Unit. http://www.ukc.ac.uk/pssru/PDFfiles/UC2000.pdf

357. 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**(9326):7–22.

Appendix 1

Definitions

Primary intracerebral haemorrhage: haemorrhage into the brain parenchyma not arising as a result of trauma

Stroke: sudden onset of a focal neurological deficit due to a vascular cause with symptoms lasting more than 24 hours.

Stroke-like syndrome: features consistent with a stroke but due to a non-vascular lesion such as an infarct or a haemorrhage

Appendix 2

Tables of information sought at start of project, likely sources and information contained therein

TABLE 63 *Module: aspirin for acute stroke treatment*

Clinical problem	Information needed	Numbers and comments
1. Subject has a stroke	Proportion who are admitted to hospital (in the UK)	From latest Stroke Association Survey[67]: 10,500 stroke patients in hospital in UK on a single day 124,000 admitted per year (~2/1000 population per year, ~ 340 per day) For UK population, can expect 111,000 first strokes and 132,000 total strokes per year ~ 85% strokes are admitted to hospital
For the proportion who are admitted to hospital:		
2. Of those referred as a 'stroke', how many are thought to have had a definite/probable/possible stroke when seen by the specialist physician?	Difference between specialist and non-specialist diagnosis of stroke in inpatients	No direct comparison studies found. Studies found looking at accuracy of diagnosis always retrospective with full notes and scans (by neurologist), with latter used as gold standard rather than comparative
3. How many definite/probable/possible strokes have an infarct/haemorrhage/non-vascular pathology, e.g. tumour on brain scanning within 5–10 days?	Proportion of strokes with infarcts/haemorrhages/tumours/abscesses, etc., on CT	From literature: misdiagnosis (i.e. admitted with possible stroke, turn out not to have one) ranges from 1.4 to 33% depending on whether CT or not (former yes, latter no). Some include non-brain primary pathology, e.g. metabolic problem
4. Of definite/probable strokes, what proportion have infarct/haemorrhage on CT by stroke syndrome (i.e. TACI, PACI, etc., or some measure of stroke severity)? *and*	How the probability of having a haemorrhage alters with stroke syndrome/severity	From Copenhagen study,[79] using Scandinavian Stroke Score. Risk of ICH increased with severity of stroke: 3.6% with mild stroke had ICH 26.4% with very severe stroke had ICH (7.3 times more likely to have ICH with very severe stroke) Note: study had major drawbacks, stacked against picking up small haemorrhages
5. Does the ability of CT to distinguish infarct from haemorrhage vary with stroke syndrome?	What is the latest time after stroke that CT can reliably detect small or large haemorrhages?	Literature suggests 5 days for small haemorrhage The CT versus MR study says 8 days
6. Are patients who are already on aspirin at the time of their stroke more likely to have had a haemorrhage than an infarct?	Does aspirin increase the likelihood of haemorrhagic stroke?	From *JAMA*[129] (systematic review of mixed primary and secondary prevention studies), there is an increased risk of haemorrhagic stroke of 12/10,000 (5–20) offset by a reduction in ischaemic stroke of 39/10,000 (17–61). Need to give 833 an aspirin to cause a haemorrhagic stroke. From Perth[77,124]: proportion of those taking aspirin or anticoagulant when had first ever stroke was significantly less for ICH than for ischaemic stroke (17% versus 35%)

continued

TABLE 63 *Module: aspirin for acute stroke treatment (cont'd)*

Clinical problem	Information needed	Numbers and comments
7. Does early aspirin use increase the risk of a poor outcome after haemorrhagic stroke?	Does aspirin increase deaths and non-fatal strokes, or reduce DVTs/PEs in patients with intracranial haemorrhage?	Systematic review: no good data in the literature IST/CAST data (treatment following ICH)[43]: Aspirin: 18/1000 reduction in non-fatal stroke or death at 2 weeks (70 fewer to 35 more) Heparin: 41/1000 increase in non-fatal stroke or death at 2 weeks (19 fewer to 102 more)
8. Does aspirin cause more harm to patients with large than small intracranial haemorrhages?	What are the absolute risks of poor outcomes in large versus small haemorrhages given aspirin, i.e. it might not cause harm to small haemorrhages, but might to large haemorrhages	No data in literature IST/CAST data sample size not large enough to use
9. Would aspirin given long term (i.e. for more than a few days) to patients with haemorrhages cause more harm?	Does aspirin cause harm if given continuously (a) in the acute phase and (b) in the long term in patients with PICH?	Systematic review: most data in literature on SAH IST/CAST: wide confidence intervals for death, recurrent intracranial haemorrhage[43] No data on long-term administration of antithrombotic treatment after ICH

Options: scan all, scan none, scan just severe strokes, scan just possibles/probables not definites, scan those on aspirin already only, scan on day of admission versus sometime within 5–10 days, but start aspirin on admission.

1. Scan all
Would pick up 2–33% of those not stroke and direct to correct management more quickly
Would pick up ~10–20% of ICH
Would therefore avoid aspirin or heparin in ICH possibly, thereby avoiding:
between 70 fewer and 35 more deaths or recurrent strokes/1000 with aspirin
between 19 fewer and 102 more deaths or recurrent strokes/1000 with heparin.

2. Scan none
Miss the above and therefore treat inappropriately up to 33% of 'strokes' (miss tumours, epilepsy, etc., thus having a knock-on effect) and 10–20% ICH, causing up to 35/1000 more deaths/recurrent strokes in the ICH group and mayhem among non-strokes.

3. Scan severe strokes (using 'very severe' data from Copenhagen)[79]
Increase the amount of bleeds found by 7.3 times, but this is the group in which stroke scores work best. Therefore, it could be argued that one should use scores on those and only scan mild strokes.

4. Scan possible/probable strokes
Not an easy distinction to make; it would be like scanning all of them.

5. Scan those on aspirin already
Very dubious data, if any, to suggest that that is a good reason to suspect an ICH.

6. Scan on day of admission
Avoid numbers in (1).

7. Stratify scanning
So that urgent ones get done on day 1 and less urgent ones on day 2 or 3, but all get done in < 5 days (might offer cheaper resource use?)

TABLE 64 *Module: aspirin for long-term secondary prevention*

Clinical problem	Information needed	Sources
1. Patient has a stroke	Proportion who are not admitted to hospital in the UK	Stroke Association Survey[67]: 15%
Of those not admitted to hospital:		
2. Of those referred as a 'stroke', how many are thought to have had a definite/probable/possible stroke when seen by the specialist physician?	Difference between specialist and non-specialist diagnosis of stroke in outpatients	73–85% outpatient referrals from GPs thought to be correct (2 papers, no information on severity of strokes)
3. How many definite/probable/possible strokes have an infarct/haemorrhage/ non-vascular pathology, e.g. tumour on brain scanning beyond10 days?	Proportion of strokes with vascular/non-vascular, etc., on CT	Nothing found in the literature on breakdown of scan pathology in late presenters or outpatients; will keep looking
4. What sort of stroke patients turn up late?	Distribution of stroke syndromes in outpatients (PACI, LACI, POCI, mild/moderate)	LSR
5. How long after stroke can CT reliably distinguish infarct from haemorrhage in this population?	Time beyond which CT is unreliable	Literature not good CT versus MR study
6. Are patients who are already on aspirin at the time of their stroke more likely to have had a haemorrhage than an infarct?	Does aspirin increase the likelihood of haemorrhagic stroke?	No good evidence in the literature or LSR
7. Does aspirin worsen outcome after mild/moderate intracranial haemorrhage?	In patients with small/medium haemorrhages, does aspirin increase the risk of worsening of the haemorrhage or of recurrent haemorrhage?	No data available
8. If do not give aspirin, what benefits are we losing out on?	What is the loss of benefit from prevention of MI and ischaemic stroke?	From *JAMA* systematic review[129]; absolute risk reduction of: All deaths: 120/10,000 (77–162) Cardiovascular death: 97/10,000 (59–135) Total MI: 137/10,000 (107–167) Fatal MI: 36/10,000 (16–55) Total stroke: 31/10,000 (5–57)

Options: although the CT/MR data are needed to see just how much better MR is, modelling options could include:

1. Scan all with CT regardless of time lapse.
2. Scan only if < 5 days from onset of symptoms with CT and use MR for any longer than 5 days.
3. Scan none.

Appendix 3

ICD-9 and ICD-10 codes

Stroke diagnostic codes

ICD-9

431*	Intracerebral haemorrhage
4329	Unspecified intracerebral haemorrhage
434*	Occlusion of cerebral arteries
436*	Acute, but ill-defined cerebrovascular disease
437*	Other ill-defined cerebrovascular disease

ICD-10

-I610	ICH in hemisphere, subcortical
-I611	ICH in hemisphere, cortical
-I612	ICH in hemisphere, unspecified
-I613	ICH in brainstem
-I614	ICH in cerebellum
-I615	ICH intraventricular
-I616	ICH multiple localised
-I618	Other intracerebral haemorrhage
-I619	Intracerebral haemorrhage, unspecified
-I629	ICH (non-traumatic), unspecified
-I630	CI due to thrombosis of precerebral arteries
-I631	CI due to embolism of precerebral arteries
-I632	CI due to unspecified occlusion/stenosis of precerebral arteries
-I633	CI due to thrombosis of cerebral arteries
-I634	CI due to embolism of cerebral arteries
-I635	CI due to unspecified occlusion/stenosis of cerebral arteries
-I636	CI due to cerebral venous thrombosis, non-pyogenic
-I638	Other cerebral infarction
-I639	Cerebral infarction, unspecified
-I64X	Stroke, not specified as haemorrhage or infarction
-I670	Dissection of cerebral arteries, non-ruptured
-I672	Cerebral atherosclerosis
-I675	Moyamoya disease
-I677	Cerebral arteritis, not elsewhere classified
-I678	Other specified cerebrovascular diseases
-I679	Cerebrovascular disease, unspecified

ICH: intracerebral haemorrhage; CI: cerebral infarction.

Appendix 4

Search strategies for imaging and epidemiology

Electronic search strategies for imaging and treatment of stroke

Glossary of search terms

/	MEDLINE subject heading (MESH)
mp.	Title, abstract, heading word, trade name, manufacturer name
.tw	Identifies the word specified in the title or abstract
ti.	Identifies word specified in title
$	Identifies any word beginning with the text preceding it
or	In the search parameter specified, the article only has to be found in one of the search terms
and	In the search specified, the article must be found in all search terms

TABLE 65 *Expanded search strategy for stroke: EMBASE*

	Search history
1	exp cerebrovasc disease/
2	stroke$.tw
3	cerebrovascular$.tw
4	(cerebral or cerebellar or brainstem or vertebrobasilar).tw
5	(infarct$ or isch?emi$ or thrombo$ or emboli$).tw
6	4 and 5
7	carotid$.tw
8	(cerebral or intraventricular or brainstem or cerebellar).tw
9	(infratentorial or supratentorial or subarachnoid).tw
10	(brain or intraventricular or brainstem or cerebellar).tw
11	8 or 9 or 10
12	(haemorrhage or hemorrhage or haematoma or hematoma).tw
13	(bleeding or aneurysm).tw
14	12 or 13
15	11 and 14
16	thrombo$.tw
17	(intracranial or (venous adj5 sinus$) or (sagittal adj5 venous) or sagittal vein).tw
18	16 and 17
19	transient isch?emic attack$.tw
20	reversible isch?emic neurologic$ deficit$.tw
21	venous malformation$.tw
22	arteriovenous malformation$.tw
23	21 or 22
24	11 and 23
25	exp aphasia/
26	dysphasia/
27	hemianopia/
28	hemiplegia/
29	hemiparesis/
30	(aphasi$ or dysphasi$ or hemianop$).tw
31	(hemipleg$ or hemipar$).tw
32	exp carotid artery surgery/
33	Or/1-3, 6-7, 18-20, 24-32

To this expanded search strategy, the following terms were added:

1. Sensitivity of CT and MRI in the identification of haemorrhagic and ischaemic stroke:
   exp computed assisted tomography/or "computed tomography".mp
   computed tomograph$.ti
   exp nuclear magnetic resonance imaging or "magnetic resonance imaging".mp
   nuclear magnetic resonance imaging or magnetic resonance.ti
   (computed tomography or CT).mp and (nuclear magnetic resonance or "magnetic resonance imaging").mp
   (accuracy or sensitivity or specificity).tw
   stroke adj10 diagnosis

   Note: using '.tw' was too non-specific when attached to scanning terms, therefore search was restricted to '.ti'

2. Scanning policies in community stroke incidence studies:
   (register or registry).tw
   exp incidence/
   incidence study.tw

   Notes: using terms for epidemiology proved too non-specific, and it was more successful in identifying studies then deciding if they were community based, rather than attempting to identify them electronically.

3. The use of antithrombotic drugs following acute intracranial haemorrhage:
   To the part of the extended search strategy that pertains to haemorrhagic stroke were added the following terms:
   exp acetylsalicylic acid/
   (aspirin or asa).tw
   exp anticoagulant agent

4. The use of magnetic resonance diffusion-weighted imaging and perfusion imaging in the identification of haemorrhagic and ischaemic stroke:
   (diffusion-weighted or DWI).tw
   (perfusion or perfusion-imaging.tw
   dynamic susceptibility.tw

TABLE 66 *Expanded search strategy for stroke: MEDLINE*

	MEDLINE terms		**MEDLINE terms**
1	exp cerebrovascular disorders/	18	16 and 17
2	stroke$.tw	19	transient isch?emic attack$.tw
3	cerebrovascular$.tw	20	reversible isch?emic neurologic$ deficit.tw
4	(cerebral or cerebellar or brainstem or vertebrobasilar).tw	21	venous malformation$.tw
		22	arteriovenous malformation$.tw
5	(infarct$ or isch?emi$ or thrombo$ or emboli$).tw	23	21 or 22
6	4 and 5	24	11 and 23
7	carotid$.tw	25	exp aphasia/
8	(cerebral or intracerebral or intracranial or parenchymal).tw	26	hemianopsia/
		27	hemiplegia/
9	(brain or intraventricular or brainstem or cerebellar).tw	28	(aphasi$ or dysphasi$ or hemianop$).tw
		29	(hemiplegi$ or hemipar$).tw
10	(infratentorial or supratentorial or subarachnoid).tw	30	25 or 26 or 27 or 28 or 29
11	8 or 9 or 10	31	or/1-3, 6-7, 15, 18-20, 24, 30
12	(haemorrhage or hemorrhage or haematoma or hematoma).tw	32	leukomalacia, periventricular/
		33	cerebral anoxia/
13	(bleeding or aneurysm).tw	34	exp dementia, vascular/
14	12 or 13	35	exp vascular headache/
15	11 and 14	36	migrain$.tw
16	thrombo$.tw	37	32 or 33 or 34 or 35 or 36
17	(intracranial or (venous adj5 sinus$) or sagittal adj5 venous) or (sagittal adj5 vein)).tw	38	31 not 37

To the expanded search strategy were added the following terms:

1. Sensitivity of CT and MRI in the identification of haemorrhagic and ischaemic stroke:
   exp tomography Xray computed/ or computed tomography.mp
   (computed tomograph$ or CT).ti
   exp magnetic resonance imaging/ magnetic resonance imaging.mp
   (magnetic resonance or MR).ti
   ((computed tomography or CT) adj10 (magnetic resonance or MR)).ti
   (accuracy or sensitivity or specificity).tw
   stroke adj10 diagnosis.tw

2. Scanning policies in community stroke incidence studies
   register or registry.tw
   incidence study.tw

3. The use of antithrombotic drugs following acute intracranial haemorrhage:
   To the part of the extended search strategy that pertains to haemorrhagic stroke were added the following terms:
   exp aspirin/
   aspirin.tw
   acetyl salicylic acid.tw
   exp anticoagulants/

4. The use of magnetic resonance diffusion-weighted imaging and perfusion imaging in the identification of haemorrhagic and ischaemic stroke:
   (diffusion-weighted or DWI).tw
   (perfusion or perfusion-imaging.tw
   dynamic susceptibility.tw

Electronic search strategies for CT cost-effectiveness studies

MEDLINE (Ovid)

1. exp cerebrovascular disorders/
2. stroke$.tw.
3. cerebrovascular$.tw.
4. (cerebral or cerebellar or brainstem or vertebrobasilar).tw.
5. (infarct$ or isch?emi$ or thrombo$ or emboli$).tw.
6. 4 and 5
7. (cerebral or intracerebral or intracranial or parenchymal).tw.
8. (brain or intraventricular or brainstem or cerebellar).tw.
9. (infratentorial or supratentorial or subarachnoid).tw.
10. or/7-9
11. (haemorrhage or hemorrhage or haematoma or hematoma).tw.
12. (bleeding or aneurysm).tw.
13. 11 or 12
14. 10 and 13
15. carotid$.tw.
16. thrombo$.tw.
17. (intracranial or (venous adj5 sinus$) or (sagittal adj5 venous) or (sagittal adj5 vein)).tw.
18. 16 and 17
19. transient isch?emic attack$.tw.
20. reversible isch?emic neurologic$ defecit.tw.
21. venous malformation$.tw.
22. arteriovenous malformation$.tw.
23. 21 or 22
24. 10 and 23
25. exp aphasia/
26. hemianopsia/
27. hemiplegia/
28. (aphasi$ or dysphasi$ or hemianop$).tw.
29. (hemiplegi$ or hemipar$).tw.
30. or/25-29
31. or/1-3,6,14-15,18-20,24,30
32. leukomalacia, periventricular/
33. cerebral anoxia/
34. exp dementia, vascular/
35. exp Vascular Headaches/
36. migrain$.tw.
37. or/32-36
38. 31 not 37
39. Tomography, X-Ray Computed/
40. (computed tomograph$ or ct).tw.
41. 39 or 40
42. 38 and 41
43. exp economics/
44. economic evaluation.tw.
45. economic$.tw.
46. cost effective$.tw.
47. Tomography, X-Ray Computed/ec [Economics]
48. or/43-47
49. 42 and 48
50. limit 49 to english language
51. cost$.tw.
52. 48 or 51
53. 42 and 52
54. limit 53 to english language
55. Magnetic Resonance Imaging/
56. mri.tw.
57. 55 or 56
58. magnetic resonance imaging/ec
59. or/43-46,51,58
60. 38 and 57 and 59

61. 60 not 53
62. limit 61 to english language
63. from 62 keep 1-29

EMBASE (Ovid)

1. exp cerebrovascular disease/
2. stroke$.tw.
3. cerebrovascular$.tw.
4. (cerebral or cerebellar or brainstem or vertebrobasilar).tw.
5. (infarct$ or isch?emi$ or thrombo$ or emboli$).tw.
6. 4 and 5
7. carotid$.tw.
8. (cerebral or intracerebral or intracranial or parenchymal).tw.
9. (infratentorial or supratentorial or subarachnoid).tw.
10. (brain or intraventricular or brainstem or cerebellar).tw.
11. or/8-10
12. (haemorrhage or hemorrhage or haematoma or hematoma).tw.
13. (bleeding or aneurysm).tw.
14. 12 or 13
15. 11 and 14
16. thrombo$.tw.
17. (intracranial or (venous adj5 sinus$) or (sagittal adj5 venous) or (sagittal adj5 vein)).tw.
18. 16 and 17
19. transient isch?emic attack$.tw.
20. reversible isch?emic neurologic$ defecit.tw.
21. venous malformation$.tw.
22. atriovenous malformation$.tw.
23. 21 or 22
24. 11 and 23
25. exp aphasia/
26. Hemianopia/
27. hemiplegia/
28. (aphasi$ or dysphasi$ or hemianop$).tw.
29. or/25-28
30. or/1-3,6-7,15,18-20,24,29
31. exp Computer Assisted Tomography/
32. (computed tomograph$ or ct).tw.
33. 31 or 32
34. 30 and 33
35. exp economic aspect/
36. economic evaluation.tw.
37. cost effective$.tw.
38. cost$.tw.
39. economic$.tw.
40. or/35-39
41. 34 and 40
42. limit 41 to english
43. Nuclear Magnetic Resonance Imaging/
44. mri.tw.
45. 43 or 44
46. 30 and 40 and 45
47. 46 not 41
48. limit 47 to english
49. from 48 keep 1-39

SCIENCE CITATION INDEX AND SOCIAL CITATION INDEX DATABASES (Web of Science) (stroke or cerebrovascular or vascular or cerebral or subarachnoid) AND (tomography OR ct OR magnetic resonance OR mri) AND (economic* OR cost*)

NHS CRD DATABASES (DARE, NHS EED, HTA) (stroke or cerebrovascular or vascular or cerebral or subarachnoid)/All Fields OR dementia/Subject Headings) AND (tomography OR ct OR magnetic OR mri/All fields)

Appendix 5

Search strategies: systematic review of cost-effectiveness of CT scanning for stroke

MEDLINE (Ovid)

1. exp cerebrovascular disorders/
2. stroke$.tw.
3. cerebrovascular$.tw.
4. (cerebral or cerebellar or brainstem or vertebrobasilar).tw.
5. (infarct$ or isch?emi$ or thrombo$ or emboli$).tw.
6. 4 and 5
7. (cerebral or intracerebral or intracranial or parenchymal).tw.
8. (brain or intraventricular or brainstem or cerebellar).tw.
9. (infratentorial or supratentorial or subarachnoid).tw.
10. or/7-9
11. (haemorrhage or hemorrhage or haematoma or hematoma).tw.
12. (bleeding or aneurysm).tw.
13. 11 or 12
14. 10 and 13
15. carotid$.tw.
16. thrombo$.tw.
17. (intracranial or (venous adj5 sinus$) or (sagittal adj5 venous) or (sagittal adj5 vein)).tw.
18. 16 and 17
19. transient isch?emic attack$.tw.
20. reversible isch?emic neurologic$ defecit.tw.
21. venous malformation$.tw.
22. arteriovenous malformation$.tw.
23. 21 or 22
24. 10 and 23
25. exp aphasia/
26. hemianopsia/
27. hemiplegia/
28. (aphasi$ or dysphasi$ or hemianop$).tw.
29. (hemiplegi$ or hemipar$).tw.
30. or/25-29
31. or/1-3,6,14-15,18-20,24,30
32. leukomalacia, periventricular/
33. cerebral anoxia/
34. exp dementia, vascular/
35. exp Vascular Headaches/
36. migrain$.tw.
37. or/32-36
38. 31 not 37
39. Tomography, X-Ray Computed/
40. (computed tomograph$ or ct).tw.
41. 39 or 40
42. 38 and 41
43. exp economics/
44. economic evaluation.tw.
45. economic$.tw.
46. cost effective$.tw.
47. Tomography, X-Ray Computed/ec [Economics]
48. or/43-47
49. 42 and 48
50. limit 49 to english language
51. cost$.tw.
52. 48 or 51
53. 42 and 52
54. limit 53 to english language
55. Magnetic Resonance Imaging/
56. mri.tw.
57. 55 or 56
58. magnetic resonance imaging/ec
59. or/43-46,51,58
60. 38 and 57 and 59
61. 60 not 53
62. limit 61 to english language
63. from 62 keep 1-29

EMBASE (Ovid)

1. exp cerebrovascular disease/
2. stroke$.tw.
3. cerebrovascular$.tw.
4. (cerebral or cerebellar or brainstem or vertebrobasilar).tw.
5. (infarct$ or isch?emi$ or thrombo$ or emboli$).tw.
6. 4 and 5
7. carotid$.tw.
8. (cerebral or intracerebral or intracranial or parenchymal).tw.
9. (infratentorial or supratentorial or subarachnoid).tw.
10. (brain or intraventricular or brainstem or cerebellar).tw.
11. or/8-10
12. (haemorrhage or hemorrhage or haematoma or hematoma).tw.
13. (bleeding or aneurysm).tw.
14. 12 or 13
15. 11 and 14

16. thrombo$.tw.
17. (intracranial or (venous adj5 sinus$) or (sagittal adj5 venous) or (sagittal adj5 vein)).tw.
18. 16 and 17
19. transient isch?emic attack$.tw.
20. reversible isch?emic neurologic$ defecit.tw.
21. venous malformation$.tw.
22. atriovenous malformation$.tw.
23. 21 or 22
24. 11 and 23
25. exp aphasia/
26. Hemianopia/
27. hemiplegia/
28. (aphasi$ or dysphasi$ or hemianop$).tw.
29. or/25-28
30. or/1-3,6-7,15,18-20,24,29
31. exp Computer Assisted Tomography/
32. (computed tomograph$ or ct).tw.
33. 31 or 32
34. 30 and 33
35. exp economic aspect/
36. economic evaluation.tw.
37. cost effective$.tw.
38. cost$.tw.
39. economic$.tw.
40. or/35-39
41. 34 and 40
42. limit 41 to english
43. Nuclear Magnetic Resonance Imaging/
44. mri.tw.
45. 43 or 44
46. 30 and 40 and 45
47. 46 not 41
48. limit 47 to english
49. from 48 keep 1-39

SCIENCE CITATION INDEX AND SOCIAL CITATION INDEX DATABASES (Web of Science) (stroke or cerebrovascular or vascular or cerebral or subarachnoid) AND (tomography OR ct OR magnetic resonance OR mri) AND (economic* OR cost*)

NHS CRD DATABASES (DARE, NHS EED, HTA) (stroke or cerebrovascular or vascular or cerebral or subarachnoid)/All Fields OR dementia/Subject Headings) AND (tomography OR ct OR magnetic OR mri/All fields)

Appendix 6

Questionnaire for Scottish CT scanning departments

TABLE 67 *Hospitals included in the survey*

Crosshouse Hospital
Vale of Leven Hospital
Borders General Hospital
Victoria Hospital
Falkirk & District Royal Infirmary
Woodend General Hospital
The Ayr Hospital
Royal Alexandra Hospital
Inverclyde Royal Hospital
Dumfries & Galloway Royal Infirmary
Queen Margaret Hospital
Aberdeen Royal Infirmary
Glasgow Royal Infirmary
Dr Gray's Hospital
Hairmyres Hospital
Stobhill Hospital
Southern General Hospital
Victoria Infirmary
Western Infirmary/Gartnavel Hospital
Raigmore Hospital
Law Hospital
Monklands District General Hospital
Eastern General Hospital
Royal Infirmary of Edinburgh
Western General Hospital
St John's Hospital
Perth Royal Infirmary
Western Isles Hospital
Institute of Neurological Sciences – Southern General Hospital
Ninewells Hospital
Stirling Royal Infirmary

Covering letter sent with survey

15 January 2001

Dear «Title» «Surname»

ACCESS TO IMAGING FACILITIES FOR THE DIAGNOSIS OF ACUTE STROKE IN SCOTLAND

We are writing to seek your cooperation in a research project designed to examine the role of imaging in the management of patients with suspected stroke in Scotland. This research has been funded by an NHS Health Technology Assessment (HTA) Primary Research Grant led by Dr Joanna Wardlaw, Dr Peter Sandercock, Dr Martin Dennis from the University of Edinburgh and Mr John Cairns from the University of Aberdeen. The primary objective of this research is to draw up evidence-based strategies to guide clinicians, radiologists and health care commissioners on the use of computerised axial tomography (CT) and magnetic resonance (MR) scanning after stroke.

We are contacting the Clinical Directors of radiology departments in hospitals throughout Scotland asking them to assist with this research by completing the enclosed survey. This survey is specifically designed to provide current information on access to imaging facilities for the diagnosis of acute stroke. The survey contains questions regarding current imaging facilities, operating hours, waiting times and the impact of increasing demand for CT scanning on radiology departments.

Please attempt to answer every question in the survey. We expect that a number of questions may be difficult to answer, however we urge you to provide an answer based on the information that you have available. The information in this survey will be treated in the strictest confidence. Your answers will be reported in such a way that it will not identify your hospital.

This survey is an important component of the research project and has the support of the Scottish Radiological Society. It is envisaged that the findings of this survey will be presented at one of the Scottish Radiological Society meetings. We would be extremely grateful if you would be able to complete this survey and return it in the reply paid envelope by Monday 29th January. If you have any questions please feel free to contact myself at the Health Economics Research Unit (HERU), University of Aberdeen on 01224 553733 or by email (j.seymour@abdn.ac.uk).

We greatly appreciate you taking the time to complete this survey. As this is a national survey, your response is vital for the success of the research. Thank you in anticipation for your support of this project.

Yours sincerely,

Janelle Seymour
Health Economics Research Unit, University of Aberdeen

Reference no _____

ACCESS TO IMAGING FACILITIES FOR THE DIAGNOSIS OF STROKE IN SCOTLAND

This research has been funded by an NHS Health Technology Assessment Primary Research Grant lead by Dr Joanna Wardlaw, Dr Peter Sandercock, Dr Martin Dennis from the University of Edinburgh and Mr John Cairns from the University of Aberdeen.

If you have any questions please contact:

Janelle Seymour
Health Economics Research Unit (HERU), University of Aberdeen
Telephone: 01224 553733
Email: j.seymour@abdn.ac.uk

Computerised axial tomography (CT) is widely used in the diagnosis and management of patients with acute stroke. The Stroke Association recently reported that although the provision of CT scanning facilities has improved, urgent access to CT scanners is often limited[1].

This survey examines access to scanning facilities for patients with suspected stroke. Please answer the following questions in relation to your department/directorate. Please note that throughout this survey, we refer to patients who are suspected of having suffered either an ischaemic stroke or primary intracerebral haemorrhage but NOT a subarachnoid haemorrhage.

[1] Ebrahim S, Redfern J (1999) *Stroke care – a matter of chance. A national survey of stroke services*. The Stroke Association, London.

Question 1a

Are CT scanning facilities available in your department/directorate? (Please tick)

☐ Yes If Yes, how many CT scanners are there? _____ ***Go to Question 1b***

☐ No ***Go to Question 1c***

Question 1b

Are CT scanning facilities available for patients with suspected stroke in your department/directorate? (Please tick)

☐ Yes ***Go to Question 2***

☐ No ***Go to Question 1c***

Question 1c

Are patients with suspected stroke referred from your hospital, to another hospital/s for CT scanning?

☐ Yes If so what hospital/s are they referred to? _____

_____

If there are CT scanners in your department/directorate, go to Question 2, if not, go to Question 7

☐ No ***If there are CT scanners in your department/directorate, go to Question 2, if not, go to Question 7***

Question 2

For each CT scanner, please list the type of scanner (e.g. spiral CT), the date of installation and whether that machine is used to scan patients with suspected stroke.

CT scanner	**Type of CT scanner**	**Date installed**	**Used to scan suspected stroke patients? (tick below)**
CT scanner 1		____ / ____ / ____	☐ Yes ☐ No
CT scanner 2		____ / ____ / ____	☐ Yes ☐ No
CT scanner 3		____ / ____ / ____	☐ Yes ☐ No

Question 3a

One way of assessing current access to CT scanning facilities is to identify the **current operating hours** of CT scanning facilities. Please list the following information for **each** of your CT scanners for what you would consider to **be 'a typical week' in October 2000**;

- each session
- the start and end times of each session
- the type of patients scanned during each session (i.e. inpatients, outpatients and/or emergencies)
- whether patients suspected of having suffered are scanned in the session
- whether 'out of hours CT scanning' (i.e. after 5pm – 8am) is available.

For example, for this particular scanner, there is one 3 hour session on a Monday for outpatients. Patients suspected of having suffered a stroke are scanned during this session. Out of hours scanning is not available on a Monday.

EXAMPLE	Sessions (tick if Yes)	Start/end times	Type of patients (IP=inpatient OP=outpatients E=emergency)	Stroke patients (tick if Yes)	Out of hours CT scanning (tick if Yes)
Monday AM PM	☐ ☐	9–12	OP	☐ ☐	☐

Please complete a table for each scanner.

Scanner 1

	Sessions (tick if Yes)	Start/end times	Type of patients (IP=inpatient OP=outpatients E=emergency)	Stroke patients (tick if Yes)	Out of hours CT scanning (tick if Yes)
Monday AM	☐			☐	☐
PM	☐			☐	
Tuesday AM	☐			☐	☐
PM	☐			☐	
Wednesday AM	☐			☐	☐
PM	☐			☐	
Thursday AM	☐			☐	☐
PM	☐			☐	
Friday AM	☐			☐	☐
PM	☐			☐	
Saturday	☐			☐	☐
Sunday	☐			☐	☐

Scanner 2

	Sessions (tick if Yes)	Start/end times	Type of patients (IP=inpatient OP=outpatients E=emergency)	Stroke patients (tick if Yes)	Out of hours CT scanning (tick if Yes)
Monday AM	☐			☐	☐
PM	☐			☐	
Tuesday AM	☐			☐	☐
PM	☐			☐	
Wednesday AM	☐			☐	☐
PM	☐			☐	
Thursday AM	☐			☐	☐
PM	☐			☐	
Friday AM	☐			☐	☐
PM	☐			☐	
Saturday	☐			☐	☐
Sunday	☐			☐	☐

Scanner 3

	Sessions (tick if Yes)	Start/end times	Type of patients (IP=inpatient OP=outpatients E=emergency)	Stroke patients (tick if Yes)	Out of hours CT scanning (tick if Yes)
Monday AM	☐			☐	☐
PM	☐			☐	
Tuesday AM	☐			☐	☐
PM	☐			☐	
Wednesday AM	☐			☐	☐
PM	☐			☐	
Thursday AM	☐			☐	☐
PM	☐			☐	
Friday AM	☐			☐	☐
PM	☐			☐	
Saturday	☐			☐	☐
Sunday	☐			☐	☐

Question 3b

How much do the operating hours of your CT scanners vary throughout the year? (Please tick)

☐ Not at all

☐ Not very much

☐ A great deal

Is the variation due to seasonal effects? Please comment:

_____

_____

_____

IF out of hours CT scanning is available, please go to Question 4a

Question 3c

Are patients referred to another hospital if out of hours scanning is not available? (Please tick)

☐ Yes If yes, which hospital/s are they referred to? _____

☐ No

Question 4a

Please answer each of the following questions for your directorate the **1999 calendar year**. If you do not have ready access to these data, could you please give **approximate figures**.

Questions	Answers
i. What was the total number of CT scans conducted in 1999?	
ii. How many CT brain scans were conducted in 1999?	
iii. What proportion of the CT brain scans were conducted after hours?	
iv. How many of the CT brain scans were for patients who were suspected to have had a stroke?	
v. What proportion of the CT brain scans for patients with suspected stroke were conducted out of hours?	

Question 4b

Please answer the following questions by placing a tick in the most appropriate box.

Questions	Yes	Yes, with difficulty	No
1. Could you provide CT scans **immediately** to suspected stroke patients on week days?	☐	☐	☐
2. Could you provide CT scans **immediately** to suspected stroke patients on weekends?	☐	☐	☐
3. Could you provide CT scans **within 24 hours** to suspected stroke patients on week days?	☐	☐	☐
4. Could you provide CT scans **within 24 hours** to suspected stroke patients on weekends?	☐	☐	☐
5. Could you provide CT scans **within 48 hours** to suspected stroke patients regardless of the day of the week?	☐	☐	☐
6. Could you provide CT scans **within 48 hours** to suspected stroke patients except at weekends?	☐	☐	☐
7. Could you provide CT scans **within 7 days** to suspected stroke patients?	☐	☐	☐
8. Could you provide CT scans **within 14 days** to suspected stroke patients?	☐	☐	☐

Question 5

Imagine your department/directorate were to undertake **more CT brain scans**. Please **indicate what percentage increase in workload** would result in the need for any of the subsequent actions listed below.

For example, an XX% increase in workload would require the introduction of a waiting list for CT scans of more than 4 weeks.

Increase in workload (%)	Actions
XX% EXAMPLE	i. Introduce a waiting list of more than 4 weeks for CT scans

Please complete the following table;

Increase in activity (%)	Actions
____ %	i. Introduce a waiting list of more than 4 weeks for CT scans
____ %	ii. Patients would be referred to another hospital for a CT scan
____ %	iii. Employ additional radiographic staff
____ %	iv. Employ additional radiologists
____ %	v. Undertake any additional CT scans out of hours
____ %	vi. Purchase an additional CT scanner

Question 6
Is CT angiography available in your department/directorate? (Please tick)

☐ Yes

☐ No

Question 7
Are magnetic resonance (MR) scanning facilities currently available in your department/directorate? (Please tick)

☐ Yes ***Go to Question 8***

☐ No ***Go to Question 13***

Question 8
Is MR scanning available for patients suspected of having suffered a stroke? (Please tick)

☐ Yes ***Go to Question 9***

☐ No ***Go to Question 13***

Question 9
Is out of hours MR scanning available at your department/directorate? (Please tick)

☐ Yes

☐ No

Question 10
Is out of hours MR scanning available for patients suspected of having suffered a stroke at your department/directorate? (Please tick)

☐ Yes

☐ No

Question 11
Is MR with diffusion imaging available at your department/directorate? (Please tick)

☐ Yes

☐ No

Question 12
Is MR with perfusion available at your department/directorate? (Please tick)

☐ Yes

☐ No

Question 13
Are stroke patients referred to another hospital/mobile scanner if MR scanning is not available? (Please tick)

☐ Yes

If so what hospital/s are they referred to? _____

☐ No

If you have any additional comments regarding the survey, please make them below.

Thank you for completing the survey

Please return the survey as soon as possible in the pre-paid envelope

If you have any questions please contact:

Janelle Seymour
Health Economics Research Unit (HERU), University of Aberdeen
Telephone: 01224 553733
Email: j.seymour@abdn.ac.uk

Appendix 7

Current provision of CT scanners in Scotland

CT scanners:

CE CTI
Elscint Elite (NS)
Elscint Scanner (S)
Elsent Twin Spiral (S)
GE Helical (S)
GE Spiral CT (S)
GT Cytec 3000 (NS)
IGE Prospeed (S)
IGE Prospeed UX (NS)
IGEbLX1, replaced IGVE 9800 (NS)
Marconi CT Twin Flash (S)
Philips Tomoscan av (NS)
Phillips SR 7000 (NS)
Phillips Tomoscan 3rd Generation Surge Slice (S)
Seimens Helical (S)
Siemems Somatom Arstar (S)
Siemens Plus 4 (S)
Siemens Somatom Plus 4 (S)
Siemens Somatom Plus 4 (S)
Siemens Somaton SR (S)
Spiral (S)
Toshiba Astewn (NS)
Toshiba Express Spiral (S)

S: spiral scanner; NS: non-spiral scanner. Spiral scanners can provide more rapid imaging.

Appendix 8

Costings of CT scanning services from three hospitals in Scotland within normal working hours and out of hours

Introduction

As CT scanning is a key component of the cost-effectiveness analysis presented in Chapter 5, it is important that an accurate estimate is used in the model. The costs of CT scanning were estimated to reflect the difference in resource use between scanning during 'normal working hours' as well as 'out of hours'. In addition, as CT scanning is conducted in both teaching hospitals and general hospitals, it was important that unit costs were estimated in a number of sites to determine whether there is any difference in resource use associated with CT scanning patients at different types of hospital.

Costs were estimated at three sites in Scotland: a large teaching hospital (TH) and two general hospitals (DGH).

Methods

The cost of CT scanning was estimated in terms of costs to the health service in this study. A detailed, bottom–up approach was adopted using standardised costing methods.[353] A three-step process involving identification, measurement and valuation of resources was undertaken to estimate the cost of scanning.[354] The first step involved identifying the main areas of resource use required for scanning this group of patients. Once these had been determined, the quantity of resource use was measured. Finally, a unit cost was calculated to value resource use for CT scanning at each site. All costs were estimated in 1999–2000 prices and exclude value added tax.

The Clinical Director of Radiology at each hospital was approached to participate in the costing study. With their agreement health service resource use data were obtained for each hospital. The main types of resource use were identified as a result of discussions with radiologists. These included allocated costs (overheads), labour (neuroradiologists, radiographers, nursing, clerical staff and porters), capital (buildings and equipment), and consumables (medical supplies). It was indicated that only staff time is likely to vary when scanning is undertaken during normal working hours compared with out of hours. Given resource constraints, it was not possible to collect data on resource use prospectively, therefore a costing questionnaire, supplemented by discussions with radiologists, was used to collect resource use data. The quantity of resource use was identified by asking each hospital the average resource use required for CT scanning patients suspected of having suffered a stroke during normal working hours and out of hours.

Unit costs were estimated for health service resources. Allocated costs were estimated from the 2000 Scottish Health Service Cost manual[69] and allocated on the basis of floor space and throughput. Estimates of throughput were obtained from the activity level data reported in the Access to CT Scanning Survey (see Chapter 5). Staff costs were calculated using the mid-point of NHS salary scales, taking into account national insurance and superannuation. Building costs were estimated using a cost per metre squared,[355] converted into an equivalent annual cost (EAC) and allocated on the basis of throughput.[355] A discount rate of 6% was used to calculate the EAC; however, this was varied from 0% to 10% in the sensitivity analysis. The cost of equipment was estimated using purchase price, converted into an EAC and allocated in a similar manner. The costs of medical supplies were estimated using existing market prices (various personal communications). All costs not estimated in 1999–2000 prices were adjusted using the NHS Heath Service Cost Index.[348,356]

Results

Tables 68–77 report the quantity of resource use and costs in terms of allocated costs, staff, capital and consumables required for CT scanning patients suspected of having suffered a stroke for

each of the hospitals. *Tables 78 and 79* summarise the cost of CT scanning during normal working hours and out of hours.

The average cost of CT scanning at the teaching hospital is £42.90 (£30.23–£71.47) during normal working hours and £79.35 (£55.05–£173.46) when scanning is undertaken out of hours. The average cost of CT scanning at the rural DGH is £81.02 (£71.44–£89.56) during normal working hours and £126.30 (£119.52–£133.16) when scanning is undertaken out of hours. Finally, the cost of CT scanning at the urban DGH is £69.47 (£58.73–£84.58) during normal working hours and £72.57 (£61.43–£91.48) when scanning is undertaken out of hours.

TABLE 68 *Teaching hospital allocated costs*

Allocated costs	Total costs	CT scanning costs
Cleaning	£2,103,000	£2,072
Linen services	£984,000	£969
Building	£870,000	£857
Engineering	£781,000	£769
Rent and rates	£1,675,000	£1,650
Energy	£1,039,000	£1,024
Medical	£1,763,000	£1,737
Medical records	£696,000	£686
Nursing	£862,000	£849
General	£5,263,000	£5,185
Recharged agency	£705,000	£695
Total	£16,741,000	£16,494
Proportion of floor space of CT scanning/hospital		0.001
Proportion of stroke CT scans/total CT scans		0.206
Proportion of allocated costs for CT scanning stroke patients		£3,400
Cost per CT scan		£2.62

TABLE 69 *Rural DGH allocated costs*

Allocated costs	Total costs	CT scanning costs
Cleaning	£591,000	£2,477
Linen services	£136,000	£570
Building	£1,545,000	£6,476
Engineering	£338,000	£1,417
Rent and rates	£877,000	£3,676
Energy	£270,000	£1,132
Medical	£537,000	£2,251
Medical records	£243,000	£1,018
Nursing	£221,000	£926
General	£2,196,000	£9,204
Recharged agency	£568,000	£2,381
Total	£7,522,000	£31,527
Proportion of floor space of CT scanning/hospital		0.004
Proportion of stroke CT scans/total CT scans		0.243
Proportion of allocated costs for CT scanning stroke patients		£7,657
Cost per CT scan		£9.01

TABLE 70 *Urban DGH allocated costs*

Allocated costs	Total costs	CT scanning costs
Cleaning	£804,000	£1,347
Linen services	£238,000	£399
Building	£1,833,000	£3,072
Engineering	£639,000	£1,071
Rent and rates	£752,000	£1,260
Energy	£314,000	£526
Medical	£684,000	£1,146
Medical records	£636,000	£1,066
Nursing	£216,000	£362
General	£2,450,000	£4,106
Recharged agency	–	–
Total	£8,566,000	£14,356
Proportion of floor space of CT scanning/hospital		0.002
Proportion of stroke CT scans/total CT scans		0.262
Proportion of allocated costs for CT scanning stroke patients		£3,758
Cost per CT scan		£4.40

TABLE 71 *Teaching hospital labour costs*

Staff	Normal working hours			Out of hours		
	Average (minutes)	Minimum (minutes)	Maximum (minutes)	Average (minutes)	Minimum (minutes)	Maximum (minutes)
Nurse grade E/D Cost per minute = £0.17	40 £6.80	20 £3.40	60 £10.20	45 £7.65	22 £3.74	67 £11.39
Senior I radiographer Cost per minute = £0.21	15 £3.15	10 £2.10	30 £6.30	45 £9.45	30 £6.30	120 £25.20
Superintendent III radiographer Cost per minute = £0.23	15 £3.45	10 £2.30	30 £6.90	45 £10.35	30 £6.90	120 £27.60
Consultant Cost per minute = £0.56	5 £2.80	2 £1.12	30 £16.80	45 £25.20	30 £16.80	120 £67.20
Medical secretary[a] Cost per minute = £0.13	10 £1.30	10 £1.30	10 £1.30	10 £1.30	10 £1.30	10 £1.30
Porter Cost per minute = £0.08	40 £3.20	20 £1.60	60 £4.80	40 £3.20	20 £1.60	60 £4.80
Senior house officer (ward) Cost per minute = £0.24	–	–	–	–	–	45 £10.80
Average cost per scan	£20.70	£11.82	£46.30	£57.15	£36.64	£148.29

[a] Average across grades.

TABLE 72 *Rural DGH labour costs*

Staff	Normal working hours			Out of hours		
	Average (minutes)	Minimum (minutes)	Maximum (minutes)	Average (minutes)	Minimum (minutes)	Maximum (minutes)
Nurse grade D Cost per minute = £0.16	12 £1.92	7 £1.12	15 £2.40	–	–	–
Senior radiographers × 2 Cost per minute = £0.20[a]	12 £4.80	7 £2.80	15 £6.00	60 £24.00	60 £24.00	60 £24.00
Radiologist Cost per minute = £0.56	10 £5.60	10 £5.60	10 £5.60	60 £33.60	60 £33.60	60 £33.60
Clerical secretary[b] Cost per minute = £0.13	10 £1.30	10 £1.30	10 £1.30	10 £1.30	10 £1.30	10 £1.30
Average cost per scan	£13.62	£10.82	£15.30	£58.90	£58.90	£58.90

[a] Average cost per minute of a Senior I and Senior II radiographer.
[b] Average across grades.

TABLE 73 *Urban DGH labour costs*

Staff	Normal working hours			Out of hours		
	Average (minutes)	Minimum (minutes)	Maximum (minutes)	Average (minutes)	Minimum (minutes)	Maximum (minutes)
1 Auxiliary/staff nurse[a]	15	10	30	20	15	45
Cost per minute = £0.14	£2.10	£1.40	£4.20	£2.80	£2.10	£6.30
2 Senior radiographers[b]	15	10	30	20	15	40
Cost per minute = £0.20	£6.00	£4.00	£12.00	£8.00	£6.00	£16.00
1 Neuroradiologist	5	5	5	5	5	5
Cost per minute = £0.60	£2.80	£2.80	£2.80	£2.80	£2.80	£2.80
1 Clerical/administration	5	5	5	5	5	5
Cost per minute = £0.13	£0.65	£0.65	£0.65	£0.65	£0.65	£0.65
1 Porter	15	10	30	20	10	40
Cost per minute = £0.08	£1.20	£0.80	£2.40	£1.60	£0.80	£3.20
Average cost per scan	£12.75	£9.65	£22.05	£15.85	£12.35	£28.95

[a] Average cost per minute of a staff nurse and an auxiliary nurse.
[b] Average cost per minute of a Senior I, Senior II and Superintendent IV radiographer.

TABLE 74 *Teaching hospital capital costs*

Capital	Cost	Minimum	Maximum
Equipment			
Siemens Somatom Plus 4 spiral CT scanner			
Life span (years)	10	10	10
Replacement cost	£509,025	£509,025	£509,025
Discount rate (%)	6	0	10
Equivalent annual cost	£69,177	£50,903	£82,818
Proportion of stroke CT scans/total CT scans	0.206	0.206	0.206
Cost per CT scan	£10.97	£8.07	£13.13
Maintenance			
Annual maintenance	£27,500	£27,500	£27,500
Proportion of stroke CT scans/total CT scans	0.206	0.206	0.206
Cost per CT scan	£4.36	£4.36	£4.36
Buildings			
CT room			
Floor space (m^2)	95	95	95
Unit cost	£919	£919	£919
Replacement cost	£86,394	£86,394	£86,394
Discount rate (%)	6	0	10
Equivalent annual cost	£5,284	£1,423	£8,563
Proportion of stroke CT scans/total CT scans	0.206	0.206	0.206
Cost per CT scan	£0.84	£0.23	£1.36
Cost of capital per CT scan	£16.17	£12.66	£18.85

TABLE 75 *Rural DGH capital costs*

Capital	Cost	Minimum	Maximum
Equipment			
Elsent Twin Slice Spiral			
Life span (years)	5	5	5
Replacement cost	£600,000	£600,000	£600,000
Discount rate (%)	6	0	10
Equivalent annual cost	£138,600	£120,000	£158,280
Proportion of stroke CT scans/total CT scans	0.243	0.243	0.243
Cost per CT scan	£39.60	£34.29	£45.22
Maintenance			
Annual maintenance	£50,000	£50,000	£50,000
Proportion of stroke CT scans/total CT scans	0.243	0.243	0.243
Cost per CT scan	£14.29	£14.29	£14.29
Buildings			
CT room			
Floor space (m^2)	126	126	126
Unit cost	£919	£919	£919
Replacement cost	£114,586	£114,586	£114,586
Discount rate (%)	6	0	10
Equivalent annual cost	£7,093	£1,910	£11,493
Proportion of stroke CT scans/total CT scans	0.243	0.243	0.243
Cost per CT scan	£2.00	£0.54	£3.24
Cost of capital per CT scan	£55.89	£49.11	£62.75

TABLE 76 *Urban DGH capital costs*

Capital	Cost	Minimum	Maximum
Equipment			
IGE CT Lxi helical scanner			
Life span (years)	10	10	10
Replacement cost	£585,000	£585,000	£585,000
Discount rate (%)	6	0	10
Equivalent annual cost	£79,502	£58,500	£95,180
Proportion of stroke CT scans/total CT scans	0.262	0.262	0.262
Cost per CT scan	£24.34	£17.91	£29.14
Maintenance			
Annual maintenance	£52,000	£52,000	£52,000
Proportion of stroke CT scans/total CT scans	0.263	0.263	0.263
Cost per CT scan	£15.92	£15.92	£15.92
Dry Laser Printer – Kodak Dry View 8100			
Life span (years)	10	10	10
Replacement cost	£20,000	£20,000	£20,000
Discount rate (%)	6	0	10
Equivalent annual cost	£2,728	£2,000	£3,254
Proportion of stroke CT scans/total CT scans	0.262	0.262	0.262
Cost per CT scan	£0.83	£0.61	£1.00
Maintenance			
Annual maintenance	£2,955	£2,955	£2,955
Proportion of stroke CT scans/total CT scans	0.262	0.262	0.262
Cost per CT scan	£0.90	£0.90	£0.90

continued

TABLE 76 *Urban DGH capital costs (cont'd)*

Capital	Cost	Minimum	Maximum
Buildings			
CT room			
Floor space (m^2)	80	80	80
Unit cost	£919	£919	£919
Replacement cost	£71,890	£71,890	£71,890
Discount rate (%)	6	0	10
Equivalent annual cost	£4,450	£1,198	£7,211
Proportion of stroke CT scans/total CT scans	0.262	0.262	0.262
Cost per CT scan	£1.36	£0.37	£2.21
Cost of capital per CT scan	£43.36	£35.72	£49.17

TABLE 77 *Cost of consumables*

Capital	Unit cost (£)	Cost per scan (£)
Teaching hospital		
Optical disc	35.20	1.42
Film and processing	–	2.00
Total	–	3.42
Rural DGH		
Optical disc	–	0.50
Film and processing	–	2.00
Total	–	2.50
Urban DGH		
Optical disc	28.00	0.01
Film	1,119.66	8.96
Total	–	8.97

TABLE 78 *Cost of CT scanning for stroke patients: normal working hours*

	Cost per scan (£)		
Resources	**TH**	**RDGH**	**UDGH**
Average cost			
Allocated costs	2.62	9.01	4.40
Labour	20.70	13.62	12.75
Capital	16.17	55.89	43.36
Consumables	3.42	2.50	8.97
Cost per scan	42.90	81.02	69.47
Low estimate			
Allocated costs	2.62	9.01	4.40
Labour	11.82	10.82	9.65
Capital	12.66	49.11	35.72
Consumables	3.13	2.50	8.97
Cost per scan	30.23	71.44	58.73
High estimate			
Allocated costs	2.62	9.01	4.40
Labour	46.30	15.30	22.05
Capital	18.85	62.75	49.18
Consumables	3.70	2.50	8.97
Cost per scan	71.47	89.56	84.58

RDGH, rural DGH; UDGH, urban DGH; TH, teaching hospital.

TABLE 79 *Cost of CT scanning for stroke patients: out of hours*

	Cost per scan (£)		
Resources	**TH**	**RDGH**	**UDGH**
Average cost			
Allocated costs	2.62	9.01	4.40
Labour	57.15	58.90	15.85
Capital	16.17	55.89	43.36
Consumables	3.42	2.50	8.97
Cost per scan	79.35	126.30	72.57
Low estimate			
Allocated costs	2.62	9.01	4.40
Labour	36.64	58.90	12.35
Capital	12.66	49.11	35.72
Consumables	3.13	2.50	8.97
Cost per scan	55.05	119.52	61.43
High estimate			
Allocated costs	2.62	9.01	4.40
Labour	148.29	58.90	28.95
Capital	18.85	62.75	49.17
Consumables	3.70	2.50	8.97
Cost per scan	173.46	133.16	91.48

RDGH, rural DGH; UDGH, urban DGH; TH, teaching hospital.

Appendix 9

Results of the sensitivity analysis

TABLE 80 *Total costs and expected QALYs (based on the cost of CT scanning at a teaching hospital for a cohort aged 60–64 years*

Strategies	QALYs	COSTS
S1	2374.4	£10,136,676
S6	2374.4	£10,210,903
S2	2374.4	£10,214,294
S7	2342.6	£10,370,576
S3	2342.6	£10,382,793
Comparator	2342.6	£10,419,728
S12	2260.3	£10,810,000
S11	2250.3	£11,066,817
S8	2372.3	£11,136,614
S4	2372.2	£11,184,666
S10	2325.2	£11,616,623
S9 (LSR)	2302.4	£12,334,614
S5 (LSR)	2302.3	£12,771,666

TABLE 81 *Total costs and expected QALYs (based on the cost of CT scanning at a teaching hospital for a cohort aged 80–84 years*

Strategies	QALYs	COSTS
S1	1467	£11,213,676
S6	1467	£11,287,903
S2	1467	£11,292,294
S7	1498.5	£11,449,576
S3	1498.5	£11,460,793
Comparator	1498.5	£11,498,728
S12	1461.7	£11,619,000
S11	1462.2	£11,990,817
S8	1465.2	£12,219,614
S4	1465.1	£12,268,666
S10	1466.9	£12,659,623
S9 (LSR)	1468.3	£13,364,614
S5 (LSR)	1468.2	£13,798,666

TABLE 82 *Sensitivity analysis – proportion of actual stroke in a population (0.77)*

Strategies	QALYs	COSTS
S1	2063.6	£9,654,676
S6	2063.6	£9,729,903
S2	2063.6	£9,733,294
S7	2063.4	£9,874,576
S3	2063.4	£9,885,793
Comparator	2063.4	£9,920,728
S12	1989.1	£10,220,000
S11	1984.3	£10,460,817
S8	2062	£10,639,614
S4	2061.9	£10,687,666
S10	2027	£11,072,623
S9 (LSR)	2015.5	£11,745,614
S5 (LSR)	2015.4	£12,170,666

TABLE 83 *Sensitivity analysis – proportion of actual stroke in a population (0.84)*

Strategies	QALYs	COSTS
S1	1921.5	£10,247,676
S6	1921.5	£10,321,903
S2	1921.5	£10,325,294
S7	1921.4	£10,467,576
S3	1921.4	£10,478,793
Comparator	1921.4	£10,514,728
S12	1840.4	£10,788,000
S11	1835.1	£11,038,817
S8	1919.8	£11,272,614
S4	1919.7	£11,322,666
S10	1881.8	£11,722,623
S9	1869.2	£12,461,614
S5	1869.1	£12,909,666

TABLE 84 *Proportion of TACs haemorrhagic stroke (PICH) patients (0.22)*

Strategies	QALYs	COSTS
S1	1994.1	£10,029,676
S6	1994.1	£10,104,903
S2	1994.1	£10,108,294
S7	1994	£10,254,576
S3	1994	£10,265,793
Comparator	1944	£10,301,728
S12	1909.9	£10,602,000
S11	1905.1	£10,851,817
S8	1992.4	£11,037,614
S4	1992.4	£11,086,666
S10	1952.2	£11,488,623
S9 (LSR)	1939	£12,201,614
S5 (LSR)	1938.9	£12,640,666

TABLE 85 *Proportion of TACs haemorrhagic stroke (PICH) patients (0.36)*

Strategies	QALYs	COSTS
S1	1970.7	£9,956,676
S6	1970.7	£10,030,903
S2	1970.7	£10,035,294
S7	1970.6	£10,173,576
S3	1970.6	£10,183,793
Comparator	1970.6	£10,218,728
S12	1898.7	£10,488,000
S11	1893.2	£10,722,817
S8	1969	£10,964,614
S4	1969	£11,014,666
S10	1935.8	£11,398,623
S9 (LSR)	1924.8	£12,106,614
S5 (LSR)	1924.7	£12,545,666

TABLE 86 *Sensitivity of CT scans for the diagnosis of PICH (versus cerebral infarct) (0.77)*

Strategies	QALYs	COSTS
S1	1994.6	£9,993,676
S6	1944.6	£10,067,903
S2	1994.6	£10,072,294
S7	1944.4	£10,213,576
S3	1994.4	£10,224,793
Comparator	1994.4	£10,259,728
S12	1874.6	£10,544,000
S11	1863.9	£10,786,817
S8	1942.9	£11,001,614
S4	1942.9	£11,050,666
S10	1907.5	£11,443,623
S9	1896.5	£12,154,614
S5	1896.4	£12,592,666

TABLE 87 *Specificity of CT scans for the diagnosis of vascular (versus non-vascular) events (0.95)*

Strategies	QALYs	COSTS
S1	1953.8	£9,993,676
S6	1953.8	£10,067,903
S2	1953.8	£10,072,294
S7	1953.7	£10,213,576
S3	1953.7	£10,224,793
Comparator	1953.7	£10,259,728
S12	1882.5	£10,544,000
S11	1873.8	£10,786,817
S8	1952.2	£11,001,614
S4	1952.1	£11,050,666
S10	1917.1	£11,443,623
S9	1904.8	£12,150,614
S5	1904.7	£12,588,666

TABLE 88 *Specificity of CT scans for the diagnosis of vascular (versus non-vascular) events (1)*

Strategies	QALYs	COSTS
S1	2001.5	£9,993,676
S6	2001.5	£10,067,903
S2	2001.5	£10,072,294
S7	2001.4	£10,213,576
S3	2001.4	£10,224,793
Comparator	2001.4	£10,259,728
S12	1918.6	£10,544,000
S11	1915.9	£10,786,817
S8	1999.8	£11,001,614
S4	1999.7	£11,050,666
S10	1961.9	£11,443,623
S9 (LSR)	1950	£12,156,614
S5 (LSR)	1949.9	£12,595,666

TABLE 89 *Specificity of CT scans for the diagnosis of PICH (versus cerebral infarction) (0.6)*

Strategies	QALYs	COSTS
S1	1916.6	£9,993,676
S6	1916.6	£10,067,903
S2	1916.6	£10,072,294
S7	1916.5	£10,213,576
S3	1916.5	£10,224,793
Comparator	1916.5	£10,259,728
S12	1852.8	£10,544,000
S11	1837.9	£10,786,817
S8	1915	£11,001,614
S4	1914.9	£11,050,666
S10	1880.5	£11,443,623
S9	1870.4	£12,154,614
S5	1870.3	£12,592,666

TABLE 90 *Utility weights (alive and dependent 0.15, alive and independent 0.65)*

Strategies	QALYs	COSTS
S1	1689.6	£9,993,676
S6	1689.6	£10,067,903
S2	1689.6	£10,072,294
S7	1689.5	£10,213,576
S3	1689.5	£10,224,793
Comparator	1689.5	£10,259,728
S12	1626	£10,544,000
S11	1620	£10,786,817
S8	1687.9	£11,001,614
S4	1687.8	£11,050,666
S10	1656.2	£11,443,623
S9	1646.3	£12,154,614
S5	1646.1	£12,592,666

TABLE 91 *Utility weights (alive and dependent –0.04, alive and independent 0.64)*

Strategies	QALYs	COSTS
S1	1565.5	£9,993,676
S6	1565.5	£10,067,903
S2	1565.5	£10,072,294
S7	1565.4	£10,213,576
S3	1565.4	£10,224,793
Comparator	1565.4	£10,259,728
S12	1505.6	£10,544,000
S11	1496.9	£10,786,817
S8	1563.5	£11,001,614
S4	1563.4	£11,050,666
S10	1530.8	£11,443,623
S9	1521	£12,154,614
S5	1520.9	£12,592,666

TABLE 92 *Unit cost of LOS – 25% lower (teaching hospital £179, large general hospital £163 and long stay hospital £87)*

Strategies	QALYs	COSTS
Comparator	1982.3	£7,713,728
S3	1982.3	£7,851,793
S7	1982.3	£7,891,576
S12	1904.2	£8,079,000
S11	1899	£8,274,817
S1	1982.4	£8,719,676
S6	1982.4	£8,811,903
S2	1982.4	£8,816,294
S10	1944	£9,266,623
S8	1980.7	£9,469,614
S4	1980.7	£9,505,666
S9	1931.9	£10,345,614
S5	1931.8	£10,673,666

TABLE 93 *Unit cost of LOS – 25% higher (teaching hospital £284, large general hospital £258 and long stay hospital £138)*

Strategies	QALYs	COSTS
S1	1982.4	£11,267,676
S6	1982.4	£11,323,903
S2	1982.4	£11,327,294
S8	1980.7	£12,533,614
S7	1982.3	£12,558,576
S4	1980.7	£12,630,666
S3	1982.3	£12,631,793
Comparator	1982.3	£12,845,728
S12	1904.2	£13,009,000
S11	1899	£13,298,817
S10	1944	£13,621,623
S9 (LSR)	1931.9	£13,963,614
S5 (LSR)	1931.8	£14,512,666

TABLE 94 *Removing LOS assumptions for strategies that involve scanning after 48 hours of admission to hospital (an additional 5 or 12 days)*

Strategies	QALYs	COSTS
S1	1982.4	£9,993,676
S2	1982.4	£10,072,294
S6	1982.4	£10,076,903
S7	1982.3	£10,229,576
S8	1980.7	£10,235,614
S3	1982.3	£10,241,793
S4	1980.7	£10,247,666
Comparator	1982.3	£10,279,728
S12	1904.2	£10,292,000
S9 (LSR)	1931.9	£10,356,614
S11	1899	£10,356,817
S10	1944	£10,360,623
S5 (LSR)	1931.9	£10,410,666

TABLE 95 *Unit cost of LOS – 20% lower (teaching hospital £191, large general hospital £174 and long stay hospital £93)*

Strategies	QALYs	COSTS
Comparator	1982.3	£8,230,728
S3	1982.3	£8,332,793
S7	1982.3	£8,362,577
S12	1904.2	£8,576,000
S11	1899	£8,780,817
S1	1982.4	£9,975,675
S6	1982.4	£9,063,903
S2	1982.4	£9,068,294
S10	1944	£9,704,623
S8	1980.7	£9,776,614
S4	1980.7	£9,815,667
S9 (LSR)	1931.9	£10,707,614
S5 (LSR)	1931.8	£11,058,667

TABLE 96 *Unit cost of LOS – 15% lower (teaching hospital £203, large general hospital £184 and long stay hospital £99)*

Strategies	QALYs	COSTS
Comparator	1982.3	£8,745,728
S3	1982.3	£8,811,793
S7	1982.3	£8,831,577
S12	1904.2	£9,070,000
S1	1982.4	£9,229,675
S11	1899	£9,283,817
S6	1982.4	£9,314,903
S2	1982.4	£9,319,294
S8	1980.7	£10,083,614
S4	1980.7	£10,124,667
S10	1944	£10,140,623
S9 (LSR)	1931.9	£11,069,614
S5 (LSR)	1931.8	£11,442,667

TABLE 97 *Unit cost of LOS – 10% lower (teaching hospital £215, large general hospital £195 and long stay hospital £104)*

Strategies	QALYs	COSTS
Comparator	1982.3	£9,245,728
S3	1982.3	£9,278,793
S7	1982.3	£9,287,577
S1	1982.4	£9,481,675
S12	1904.2	£9,551,000
S6	1982.4	£9,563,903
S2	1982.4	£9,568,294
S11	1899	£9,774,817
S8	1980.7	£10,386,614
S4	1980.7	£10,430,667
S10	1944	£10,568,623
S9 (LSR)	1931.9	£11,428,614
S5 (LSR)	1931.8	£11,822,667

TABLE 98 *Unit cost of LOS – 5% lower (teaching hospital £227, large general hospital £206 and long stay hospital £110)*

Strategies	QALYs	COSTS
S1	1982.4	£9,737,675
S7	1982.3	£9,758,577
S3	1982.3	£9,759,793
Comparator	1982.3	£9,762,728
S6	1982.4	£9,815,903
S2	1982.4	£9,820,294
S12	1904.2	£10,048,000
S11	1899	£10,280,817
S8	1980.7	£10,694,614
S4	1980.7	£10,740,667
S10	1944	£11,006,623
S9 (LSR)	1931.9	£11,791,614
S5 (LSR)	1931.8	£12,207,667

Appendix 10

Publications and presentations

Publications

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

Keir SL, Sandercock PAG, Wardlaw JM. Antithrombotic therapy in patients with any form of intracranial haemorrhage: a systematic review of the available controlled studies. *Cerebrovasc Dis* 2002;**14**:197–206.

Keir SL, Wardlaw JM, Warlow CP. Stroke epidemiology studies have underestimated the frequency of intracerebral haemorrhage. A systematic review of imaging in epidemiological studies. *J Neurology* 2002;**249**:1226–31.

Wardlaw JM, Dennis MS, Warlow CP, Sandercock PAG. Imaging appearance of the symptomatic perforating artery in patients with lacunar infarction: occlusion or other vascular pathology? *Ann Neurol* 2001;**50**: 208–15.

Guy S, Wardlaw JM. Who writes guidelines, and who should? *Clinical Radiology* 2002;**57**:891–7.

Wardlaw JM, Keir SL, Dennis MS. The impact of delays in CT brain imaging on the accuracy of diagnosis and subsequent management in patients with minor stroke. *J Neurol Neurosurg Psychiatry* 2003;**74**:77–81.

In preparation

Keir SL, Wardlaw JM, Dennis MS. A comparison of CT and MR imaging in the detection of haemorrhage – are we managing stroke correctly?

Keir SL, Wardlaw JM, Dennis MS. The effect of the result of a CT or MR scan on doctor's decisions for primary treatment and secondary prevention of stroke. *Age and Aging*. Under review.

Keir SL, Djimigen M, Wardlaw JM. Accuracy of MR in detection of intracerebral haemorrhage late after stroke. Under review.

Seymour J, Wardlaw JM, Cairns J. Provision of CT scanning for stroke – a matter of chance? Submitted.

Wardlaw JM, Seymour J, Keir SL, Cairns J, Sandercock PAG, Dennis MS. Cost effectiveness of CT scanning after stroke. *Stroke*. Submitted.

Presentations

Keir S, Wardlaw J, Warlow CP. Have epidemiological studies of stroke incidence underestimated the frequency of primary intracerebral haemorrhage? 9th European Stroke Conference, Vienna, May 25th–27th 2000 (Platform Session IV: Hemorrhage). *Cerebrovasc Dis* 2000;**10**(Suppl 2):50.

Keir SL, Lewis SC, Wardlaw JM, Sandercock PAG, Chen ZM, on behalf of the IST and CAST Collaborative Groups. Effects of aspirin or heparin inadvertently given to patients with haemorrhagic stroke. 25th International Stroke Conference, New Orleans, USA, 10–12 Feb 2000. *Stroke* 2000;**31**:314.

Keir S, Wardlaw J, Dennis M. What are the benefits of brain imaging in patients presenting with minor stroke? 10th European Stroke Conference, Lisbon, Portugal, May 16th–19th 2001 (Oral Session II: Neuro-and Vascular Imaging). *Cerebrovasc Dis* 2001;**11**(Suppl 4):56.

Wardlaw JM, Dennis MS, Warlow CP, Sandercock PAG. Imaging appearance of the symptomatic perforating artery in patients with lacunar infarction: occlusion, or other vascular pathology? 10th European Stroke Conference, Lisbon, Portugal, May 16th–19th 2001 (Oral Session: Neuroimaging). *Cerebrovasc Dis* 2001;**11**(Suppl 4):27.

Wardlaw J, Seymour J, Sandercock PAG, Cairns J, Keir S, Dennis M. Cost-effectiveness of CT scanning in acute stroke. 11th European strke Conference, Geneva, Switzerland, May 29–June 1 2002 (One Session/Management Economics). *Cerebrovasc Dis* 2002;**13**(Suppl. 3):61.

Appendix 11

Authors' declared conflicts of interest

Joanna Wardlaw
- is the contact reviewer for the Cochrane systematic review of thrombolytic treatment for acute stroke
- is a member of the third International Stroke Trial (IST-3) management group and leads a collaborative neuroradiological group assessing the scans of patients entered in the trial
- is director of the SHEFC Brain Imaging Research Centre for Scotland. This is located within the Department of Clinical Neurosciences at the University of Edinburgh. The Centre houses a research magnetic resonance scanner which was funded by the UK Research Council's Joint Research Equipment Initiative, supplemented by grants and donations from various other sources. Boehringer Ingelheim was one of the commercial enterprises which gave a grant towards the purchase of the scanner
- has also attended meetings held by Boehringer Ingelheim to discuss the licensing of rt-PA. She attended as an unpaid independent external adviser but was refunded her travel expenses.

Peter Sandercock
- was the Principal Investigator of the IST-2 to evaluate a neuroprotective compound (619c89). The trial was to be conducted independently of the manufacturer (Glaxo-Wellcome). Peter Sandercock received an initial grant of £800,000 from Glaxo-Wellcome for the first phases of the study, but the compound was withdrawn from clinical development and IST-2 was terminated before any patients had been randomised
- is Chairman of the Steering Committee for the IST-3 of thrombolysis in acute stroke. The start-up phase of the trial is currently funded by a grant from the Stroke Association. Boehringer Ingelheim have donated trial drug and placebo for the 300 patients to be included in the start-up phase
- is a member of the Trial Steering Committee for the MRC IMAGES trial (of magnesium, a potentially neuroprotective agent).

Martin Dennis
- received a grant of £18,000 from UCB Pharma for work on the risk of seizures after stroke
- received a grant of £20,000 from Sanofi to support work on stroke prevention
- received funding from Glaxo-Wellcome (£100,000) to establish a series of clinical training fellowships in stroke medicine
- is a member of the IST-3 Steering Committee and is participating as a collaborator in IST-3
- is responsible for running stroke services at the Western General Hospital. This has been supported by Boehringer Ingelheim, who supplied £800 worth of patient leaflets
- was founding president of the British Association of Stroke Physicians. Boehringer donated £4000 towards the cost of establishing the Association.

Sarah Keir
Has no conflict of interest (see below).

John Cairns
Has no conflict of interest.

Janelle Seymour
Has no conflict of interest.

Both John Cairns and Janelle Seymour work in the Health Economics Research Unit, Aberdeen, which receives funding from the Chief Scientist's Office of the Scottish Parliament. The views expressed in this report are not those of the Scottish Office.

J Wardlaw, P Sandercock, M Dennis and S Keir
have at some time received lecture fees or travel expenses to attend conferences from a variety of pharmaceutical companies, including Boehringer Ingelheim and Glaxo Wellcome. None of the authors has a contractual consultancy arrangement with any pharmaceutical company. Furthermore, none of us knowingly has any financial interest in any of the companies whose products are mentioned in this report.

Book royalties
Joanna Wardlaw, Peter Sandercock and Martin Dennis are co-authors of *Stroke: a practical guide to management*, published by Blackwell Science.

Servier, the manufacturers of the antihypertensive drug Perindopril, bought 2000 copies of the book; each author will receive royalties on these sales to the value of £762 as a result.

S Lewis
Does not, to the best of their knowledge, have any personal, financial or scientific conflicts of interest.

Signed declarations of potential conflicts have been lodged with Joanna Wardlaw.

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We look forward to hearing from you.

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