An assessment of the cost-effectiveness of magnetic resonance, including diffusion-weighted imaging, in patients with transient ischaemic attack and minor stroke: a systematic review, meta-analysis and economic evaluation

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Scientific summary

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Introduction

Stroke, the second commonest cause of death and the commonest cause of dependency, creates a huge societal burden and costs billions of pounds in health and social care costs. Effective prevention would minimise the consequences. Eighty per cent of strokes are ischaemic. A warning transient ischaemic attack (TIA) or minor stroke may occur prior to the major disabling stroke. Rapid assessment, identification of potential causes and appropriate treatment can prevent many disabling strokes.

The diagnosis of TIA/minor stroke is difficult, particularly by non-experts. Identification of key risk factors includes imaging to identify carotid stenosis, cardiac investigations, etc. Brain imaging is critical to differentiate ischaemic from haemorrhagic stroke, and from non-vascular lesions mimicking TIA/minor stroke (e.g. tumours) to guide treatment. Until recently, this was performed with computed tomography (CT) brain scanning. Although very sensitive to haemorrhage within the first week, CT is insensitive to small ischaemic lesions. Magnetic resonance imaging (MRI) with diffusion-weighted imaging (DWI) is very sensitive to small ischaemic lesions soon after TIA/minor stroke, with T2* sensitive to haemorrhage indefinitely.

Clinical risk prediction scores, for example the ABCD2 score, may help triage patients for immediate investigation. The Department of Health guidelines currently recommend triage on ABCD2 score of ≥4 versus <4, and suggest that about 50% of TIA patients should undergo MRI to diagnose the TIA/minor stroke in order to reduce time to treatment. However, MRI is more expensive than CT, less widely available, and in considerable demand for proven indications. It is unclear whether the greater sensitivity to small ischaemic lesions is worth the additional cost, displacement of patients with other disorders for which MRI is of definite benefit, and if it is beneficial then how best to use it.

Objectives

To determine:

1. whether in most patients with TIA/minor stroke, magnetic resonance (MR) with relevant sequences is cost-effective compared with CT brain scanning
2. the cost and cost-effectiveness of increased use of MR in patients presenting at >5 days after TIA/minor stroke when CT will not identify haemorrhage reliably
3. whether 'one-stop' brain and carotid imaging is more cost-effective than separate brain/carotid examinations
4. current availability and imaging use in stroke prevention.

Methods

We performed systematic reviews/meta-analyses of published/unpublished data on prognosis after TIA/minor stroke; prediction scoring methods for stroke recurrence after TIA/minor stroke; sensitivity and specificity of CT and MRI; direct comparisons of CT and MR in TIA/minor stroke; TIA/minor stroke mimics; costs of stroke care; and imaging. We surveyed UK stroke prevention clinics and imaging services for stroke. We modelled the pathway of patients with suspected TIA/minor stroke, assessments, treatments, early and late outcome events (recurrent stroke, death, myocardial infarction), and health economic modelling on a 20-year time horizon, of strokes prevented per 1000 patients assessed, costs,

quality-adjusted life-years (QALYs), costs/QALYs for representative scenarios and key sensitivity analyses and performed deterministic and probabilistic analyses.

Results

Among 53 studies (30,558 patients) of recurrent stroke in patients presenting with TIA/minor stroke, the pooled cumulative recurrent stroke rate was 5.2% [95% confidence interval (CI) 3.9% to 5.9%] by 7 days, 6.7% (95% CI 5.2% to 8.7%) by 90 days, and 11.3% (95% CI 7.5% to 16.6%) after 90 days in 30, 35 and nine cohorts, respectively, with considerable between-study heterogeneity. Most of the larger studies reported the lower recurrence rates.

In meta-analyses of stroke after TIA/minor stroke, by ABCD2 score dichotomised at <4 or ≥4, all studies used a time-based TIA definition and excluded TIA mimics; in most, a specialist assigned the ABCD2 score; half of the studies determined ABCD2 score retrospectively from case note review; and no studies provided information on handling of key risk factors (e.g. carotid stenosis) in risk prediction analyses. Sixty-six per cent of true TIA patients had an ABCD2 score of ≥4 and 34% <4. The pooled risk of stroke by 7 and 90 days, respectively, was ABCD2 score of ≥4, 4.7% (95% CI 2.4% to 8.7%) and 8.2 (95% CI 4.7% to 14.0%); ABCD2 score of <4, 1.6% (95% CI 1.0% to 3.4%) and 2.7% (95% CI 1.5% to 4.7%). ABCD2 score did not identify key stroke risk factors or mimics: one-third of TIA patients with an ABCD2 score of ≥ 4 and one-fifth of TIA patients with an ABCD2 score of < 4 had tight carotid stenosis or atrial fibrillation (AF); 35–41% of TIA mimics had an ABCD2 score of ≥ 4. In a typical population of 1000 patients attending stroke prevention clinics including mimics, about 52% of clinic attendees would have an ABCD2 score of ≥ 4.

Among 21 published studies plus individual patient data, adding either carotid stenosis and/or CT scanning to any clinical risk prediction score improved stroke prediction over clinical scores alone. The independent hazard ratios for recurrent stroke for relevant visible infarct on CT were 1.47 (95% CI 1.01 to 2.14) and for carotid stenosis dichotomised at 70% was 2.15 (95% CI 1.42 to 3.23).

There were no direct comparisons of CT with MR in TIA/minor stroke. Therefore, we assessed the frequency of positive findings on MR DWI. Among 45 studies, 9078 TIA patients (all specialist diagnosed; excluding TIA/stroke mimics and haemorrhage; about half retrospective), a DWI ischaemic lesion was visible in 34.3% (95% CI 30.5% to 38.4%, $I^2 = 89.3\%$) of TIA and 69% of minor stroke patient. Hence, about two-thirds of TIA patients and one-third of minor stroke patients with no alternative diagnosis after specialist assessment *do not* have a DWI ischaemic lesion. There were no accuracy, sensitivity or specificity data. Some common stroke mimics (migraine, epilepsy, hypoglycaemia, multiple sclerosis) may produce apparent ischaemic lesions on DWI. Patients with acute ischaemic lesions on DWI have higher ABCD2 scores. DWI or CT added to the ABCD2 score improved prediction of recurrent stroke but still did not identify patients with key risk factors, such as carotid stenosis. The commonest TIA/minor stroke mimics do not produce specific findings on MR or CT: scanning in these patients is to exclude tumours (2.0%), subdural haematoma (1.9%) and subarachnoid haemorrhage (1.9%), not to diagnose positively the cause of the mimic.

Among 16 published/unpublished studies (total 14,542 participants), 40–45% of patients with suspected TIA/minor stroke had a mimic, with the commonest diagnoses being migraine (14.4%), cardiac disorders (8.8%), syncope (6.6%), seizure (5.0%), psychiatric conditions (4.4%), and vertigo (4.0%), with substantial heterogeneity and few data on the prognosis; recurrent stroke was lower for mimics than for TIA, but not negligible.

Stroke prevention and imaging services in the UK (45% response rate for both), confirmed that 45% of patients referred with suspected TIA/minor stroke have a mimic. Triage is by a nurse in 28% of clinics. Most patients (60–100%) had already started medical secondary prevention treatments when seen in the

clinic. Brain scanning was primarily with CT (84–86%) patients; MR was used in 51–54%, mostly in addition to CT. Most departments (55%) did not include a blood-sensitive sequence (T2*), hence will miss haemorrhages. Most CT was performed at clinic assessment, MR mostly about 1 week later, when many DWI lesions will have disappeared. Most centres used ultrasound for carotid imaging on the day of clinic assessment.

Compared with 'CT brain scan all patients' (base case), all strategies using MR instead of CT were more expensive and no more effective, either by QALYs or strokes prevented. In some strategies, for example triage into fast-track/slow-track using ABCD2 score of $< 4 / \geq 4$, treat DWI-negative patients as non-TIA/minor stroke, or start all patients on stroke prevention treatment prior to clinic assessment, MR was clearly less effective. MR or CT brain-plus-carotid imaging combined also increased costs without increasing effectiveness. MR became more effective only in patients presenting ≥ 1 week after TIA/minor stroke (CT would not exclude a haemorrhage). The results were sensitive to the costs of imaging and giving ischaemic stroke prevention drugs inadvertently to patients with haemorrhagic stroke. Data limitations (heterogeneity, lack of information for MR accuracy) precluded the estimate of some distributions.

Conclusions

The clinical utility of clinical risk scores, including the ABCD2, must be questioned: ABCD2 labels most patients as high risk, including many mimics, while failing to identify true TIA/minor stroke patients with known key causative disease needing fast-track treatment (carotid stenosis, AF). Furthermore, the system is saturated with patients with an ABCD2 score of ≥ 4 who are destined not to have a stroke, delaying rapid treatment for the most needy. One-fifth of TIA patients with an ABCD2 score of < 4 yet have tight carotid stenosis or AF, so would not be fast-tracked for investigation on current guidance, leaving those with tight carotid stenosis or AF (who require specific treatments) unprotected from recurrent stroke, and, paradoxically, resulting in the strokes that stroke prevention aims to prevent. The benefits of MRI in many unselected suspected TIA patients in routine clinical practice has yet to be demonstrated. Available information only applies to patients with definite TIA/minor stroke diagnosed by a stroke specialist. All technologies, including scoring systems, should be thoroughly evaluated, preferably in randomised trials, to determine their impact on clinically important outcomes prior to their introduction into clinical practice.

Implications for health care

1. In all patients with probable TIA/minor stroke, diagnostic efficiency and stroke prevention could be maximised if investigations are focused to identify key risk factors and implement appropriate treatment rapidly (e.g. of tight symptomatic carotid stenosis or AF).
2. Patients thought to have a TIA/minor stroke mimic (45%), many of which are cardiac or neurological, require different treatment to avoid costly and potentially harmful effects of unnecessary antiplatelet, statin and antihypertensive treatment.
3. The benefits of the ABCD2 score have not yet been demonstrated in reliable, generalisable studies.
4. Initial triage using the ABCD2 score alone risks relegating patients with key underlying causative lesions but low ABCD2 scores to 'slow stream' investigation and treatment leaving them exposed to higher early recurrent stroke risk that rapid endarterectomy or anticoagulation would have avoided.
5. The evidence suggests that caution is required when translating the results of these studies to routine practice as there are no data on how accurately TIAs are diagnosed, how well the ABCD2 score performs, how accurately mimics are identified or on the proportion of TIAs with positive DWI findings when patients are assessed by non-specialists.
6. The justification for routine use of MR in most TIA/minor stroke is unclear. Exceptionally, the data support the use of MR in patients presenting at > 1 week after TIA when MR with T2* is better than CT for identifying haemorrhage, possibly when an unusual cause of symptoms is considered or when there is doubt if a TIA/minor stroke is in the territory of a tight carotid stenosis. However, in most

'typical' TIA/minor stroke patients presenting soon after onset, use of MR inflates costs substantially, confers no advantage in stroke prevention, may increase risk through increasing delays to treatment, and potentially delays patients with other non-cerebrovascular conditions for which there is evidence of benefit.

7. The evidence indicates that patients diagnosed as true TIA/minor stroke by a stroke specialist, but without a visible ischaemic lesion on DWI, will nonetheless benefit from secondary stroke prevention treatment; if not treated, about two-thirds of patients with TIA and one-third of patients with minor stroke who have no lesion on DWI would remain at high risk of recurrent stroke.

8. Failure to include T2* sequence as part of the MR examination for stroke or TIA, as in 55% of UK services, will fail to diagnose haemorrhage, and risks recurrent haemorrhage if patients with haemorrhage are treated with antithrombotic drugs.

9. Triage on the basis of MR DWI alone will fail to identify underlying risk factors, not correctly differentiate stroke/TIA from mimic, not identify haemorrhage or correctly identify positively all true TIAs or minor strokes.

10. The use of MR in addition to CT is not justified, at least not at its current frequency (50% of patients). Using CT or MR, but not both together, would help streamline TIA/minor stroke investigations.

11. There was strong evidence to support ultrasound as the most widely used routine investigation for carotid stenosis; CT or MR angiography are not cost-effective alternatives, even when combined into one examination session with brain CT or MR.

12. The justification for changing the definition of TIA from time based to tissue based is unclear: two-thirds of specialist-diagnosed TIAs and one-third of minor stroke do not have a DWI-visible lesion.

13. There are still many delays during the assessment of patients with suspected TIA/minor stroke, including delay to endarterectomy; identifying and overcoming those delays would increase speed of investigation and prevent more strokes.

Recommendations for research

1. We identified a lack of reliable, relevant and generalisable data on use of MR in TIA/minor stroke, specifically no direct comparisons of CT and MR.

2. There is a strong case to perform a randomised controlled trial to test a policy of 'early CT brain scan' compared with 'early MR DWI and T2* brain scan' with a primary outcome of recurrent stroke and vascular death.

3. Use of ABCD2 score by non-specialists should be tested against stroke experts to determine the reliability and clinical utility of the ABCD2 score in different settings.

4. The effect of changing TIA definition from time based to tissue based is required in large populations across multiple stroke centres and scanners to determine the effect on TIA/stroke incidence, prevalence and outcome, preferably before the definition is changed.

5. Research should examine why MR is frequently used after CT; reducing duplicate examinations and effective triage in one examination would help to improve efficient use of staff and equipment.

6. Reliable data are required on all costs for stroke including imaging and their variation with different health-care scenarios.

7. Research into the reasons for substantial heterogeneity between studies on all topics related to TIA is required to improve consistency of diagnosis. The wide variation observed is unlikely to reflect true differences in disease frequency.

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