RESEARCH PAPER

Clinical relevance and practical implications of trials of perfusion and angiographic imaging in patients with acute ischaemic stroke: a multicentre cohort imaging study

Joanna M Wardlaw,1 Keith W Muir,2 Mary-Joan Macleod,3 Christopher Weir,1 Ferghal McVerry,2 Trevor Carpenter,1 Kirsten Shuler,1 Ralph Thomas,1 Paul Acheampong,3 Krishna Dani,2 Alison Murray3

ABSTRACT

Background In randomised trials testing treatments for acute ischaemic stroke, imaging markers of tissue reperfusion and arterial recanalisation may provide early response indicators.

Objective To determine the predictive value of structural, perfusion and angiographic imaging for early and late clinical outcomes and assess practicalities in three comprehensive stroke centres.

Methods We recruited patients with potentially disabling stroke in three stroke centres, performed magnetic resonance (MR) or CT, including perfusion and angiography imaging, within 6 h, at 72 h and 1 month after stroke. We assessed the National Institutes of Health Stroke Scale (NIHSS) score serially and functional outcome at 3 months, tested associations between clinical variables and structural imaging, several perfusion parameters and angiography.

Results Among 83 patients, median age 71 (maximum 89), median NIHSS 7 (range 1–30), 38 (46%) received alteplase, 41 (49%) had died or were dependent at 3 months. Most baseline imaging was CT (76%); follow-up was MR (79%) despite both being available acutely. At presentation, perfusion lesion size varied considerably between parameters (p<0.0001); 40 (48%) had arterial occlusion. Arterial occlusion and baseline perfusion lesion extent were both associated with baseline NIHSS (p<0.0001). Recanalisation by 72 h was associated with 1 month NIHSS (p=0.007) and 3 month functional outcome (p=0.048), whereas tissue reperfusion, using even the best perfusion parameter, was not (p=0.11, p=0.08, respectively).

Conclusion Early recanalisation on angiography appeared to predict clinical outcome more directly than did tissue reperfusion. Acute assessment with CT and follow-up with MR was practical and feasible, did not preclude image analysis, and would enhance trial recruitment and generalisability of results.

INTRODUCTION

New treatments for acute ischaemic stroke are likely to have modest effects, so randomised controlled trials (RCTs) based on clinical outcomes need large sample sizes. Large trials are expensive and time consuming. Imaging might accelerate drug evaluation by providing markers of clinically relevant treatment effects in the initial ‘proof-of-concept’ phase and potential imaging surrogate outcome markers in phase 3 trials.

Reperfusion of the ischaemic tissue, recanalisation of the occluded artery or subacute infarct size on CT or MRI are all potential imaging markers. Arterial recanalisation was associated with more independent survival after stroke.2 Tissue reperfusion was associated with reduced final infarct size and possibly, with improved functional outcomes.3,4 Arterial recanalisation is not the same as tissue reperfusion, though these terms are often used interchangeably, adding to difficulties in interpreting previous studies.5

Perfusion and angiographic imaging have some disadvantages. Both require intravenous contrast (contraindicated in renal impairment and in diabetic patients receiving oral hypoglycaemic agents). Image acquisition and processing may delay treatment, attenuating tissue salvage. Patients must cooperate for diagnostic-quality images to be obtained. Some CT scanners have limited brain coverage for perfusion imaging. CT angiography (CTA) and perfusion imaging increase the radiation dose. Some patients with hyperacute stroke do not tolerate (or have contraindications to) MRL.6 The definition of tissue at risk of infarction varies; which of the many perfusion parameters,7 flow thresholds8 and image acquisition and processing parameters9 to use has yet to be agreed.

Whether reperfusion or recanalisation is the better or more practical marker for clinically relevant outcomes is unclear, there being few previous comparisons and these used magnetic resonance (MR) data.10 Performing either perfusion or angiographic imaging, rather than both, would make assessment of the patient with hyperacute stroke easier and faster. Being able to use either CT or MRI would also increase access by centres and patients to trials and might help to enhance recruitment rates beyond those seen in RCTs that to date have used advanced imaging to select patients for inclusion.

We undertook this study in three regional stroke centres to test strategies for use of imaging in future clinical trials: first, practical aspects for trial design such as the effect on recruitment and image analysis of allowing use of either CT or MR in patients with hyperacute stroke; and second,
whether imaging measures of tissue perfusion or arterial patency were most strongly associated with clinically relevant parameters.

METHODS
This prospective study was conducted in three comprehensive regional UK stroke centres. The study was approved by the Scotland A multicentre research ethics committee (07/MRE00/96), and written informed consent was obtained from all competent patients, or from a relative of patients incapacitated by their stroke. There were limited data on which to calculate sample size. We aimed to recruit equal proportions of patients with CT and MR, perfusion and angiography at baseline and to test feasibility by the proportion recruited with each modality. We aimed to recruit at least 80 patients within the 2 years available for the study to obtain data to enable formal sample size calculations based on proportions with perfusion or angiographic lesions and associations with clinical and imaging outcomes for future RCTs. A STROBE checklist is included in online supplementary material.

Patient recruitment
We considered all patients with potentially disabling acute ischaemic stroke who could be imaged within 6 h of stroke onset with CT or MR. Patients with MR-incompatible implants or other standard MR contraindications were excluded from MR but could still have CT; patients with impaired renal function (estimated glomerular filtration rate ≤30 ml/min) were excluded. We recorded numbers of potentially eligible patients who were not recruited and the main reason for exclusion. Alteplase and other licensed acute treatments were given according to clinical indication.

Clinical assessment
We assessed National Institutes of Health Stroke Scale (NIHSS) score at baseline, 24 h, 72 h, 7 and 30 days, and stroke subtype by the Oxfordshire Community Stroke Project (OCSP) classification. We obtained demographic data, past medical history, medications and vital signs at baseline. We assessed functional outcome using the modified Rankin Scale (mRS) by structured interview, blind to early clinical and all imaging results, at 1 and 3 months.

Image acquisition
We performed admission imaging with either plain CT brain scan, CT perfusion (CTP) with bolus tracking of intravenous contrast and circle of Willis CTA; or with MR including diffusion imaging (DWI), T2-weighted or FLAIR, T2*-weighted contrast and circle of Willis CTA; or with MR including diffusion lesion that was no more than 80% of, (c) about the same size as, or (d) 20% or more larger by visually estimated volume than the structural lesion. These cut-off points were clearly agreed or validated threshold and the extent of contrast enhancement on the dynamic source images (raw data).

We rated the extent of perfusion lesions using (1) the ASPECTS score, subtracting a point for each brain region affected, even in part, by the perfusion lesion and (2) by recording if there was (a) no visible perfusion lesion, (b) a visible perfusion lesion that was no more than 80% of, (c) about the same size as, or (d) 20% or more larger by visually estimated volume than the structural ischaemic lesion. These cut-off points were chosen to reflect previous studies. We scored all of the above perfusion parameters without thresholds (in the absence of a clearly agreed or validated threshold) and the extent of contrast enhancement on the dynamic source images (raw data). Mismatch was defined as a perfusion lesion >1 ASPECTS points larger than the structural lesion.

We scored arterial patency in the affected artery on CTA or MRA using base and maximum intensity projection angiographic images and the Mord22 23 and Thrombolysis in Myocardial Infarction (TIMI)24 scores, rating the primary occlusive lesion and patency of the immediately distal visible arteries, but not the distal arterial tree or tissue perfusion.

Data management and statistical analysis
We entered data into a purpose-designed centralised electronic case record form with consistency checks. The statistical analysis plan was finalised 6 months before recruitment completion.
There were a few differences in patient characteristics between centres, so we analysed the whole cohort together. We assessed changes in baseline clinical, structural, perfusion and angiography characteristics at 72 h and at 30 days. We analysed change in the extent of perfusion lesion between time points using (1) the change in ASPECT score and (2) change classified as ‘any reduction’, ‘no change’ or ‘any increase’ in perfusion lesion extent. We analysed change in arterial patency by change in the hyperattenuated artery sign and change in Mori/TIMI scores separately, and then created a composite score of ‘change in any of hyperattenuated artery or angiographic patency based on the TIMI score’. We did not impute missing data as the major reason for not undergoing follow-up imaging was death or being too unwell. We used the Spearman rank correlation and 95% CI, and the Wilcoxon–Mann–Whitney, Kruskal–Wallis and χ² tests to explore associations between variables. We applied Bonferroni correction for multiple comparisons to the ASPECTS measurement of multiple perfusion parameter lesion sizes at baseline; other p values are not corrected.

RESULTS

Recruitment
We screened 360 potentially eligible patients from 21 April 2008 to 31 March 2010 and recruited 83 (23%). The main reasons for exclusion were mild stroke/late arrival (125 (35%)), outside 9:00–17:00 (59 (16%)), intolerant of imaging (12 (3%)), refused consent (17 (5%)), recruited to a competing study (52 (14%)) or haemorrhagic stroke (4 (1%)).

Patient characteristics
Of the 83 recruited, median age 71 years (maximum 89), 60% were male and vascular risk factors were common (see online supplementary table S1). Almost half, 38 (46%), received alteplase open label; two patients were randomised (to control) in a trial of alteplase in acute ischaemic stroke (http://www.ist3.com). The median baseline NIHSS score was 7, range 1–30, and 62 (75%) had total or partial anterior circulation stroke. At 3 months, 41 (49.4%) were dependent or had died (mRS 3–6).

Most baseline imaging was with CT (63/83, 76%) but most follow-up imaging was with MR. The median time to first scan was 2.75 h (minimum 1.25, maximum 5.58 h), 42/83 patients (51%) being imaged <3 h and 49% from 3 to 6 h. Follow-up imaging was obtained in 72 at 72 h and 48 at 30 days (see online supplementary table S2). The main reasons for missing follow-up imaging were death (10) or being too unwell (20). Fewer patients completed perfusion and angiography imaging than structural imaging, but the completion rate did not differ between the first two modalities.

Structural imaging
At baseline, 63/83 (76%) patients had a visible ischaemic lesion on structural imaging, most (76%) in the MCA territory (see online supplementary table S2). Background brain changes included severe cerebral atrophy (9, 11%), severe white matter lesions (11, 13%) and prior infarct (24, 29%).

Perfusion imaging
The proportion of visible perfusion lesions at baseline and their size varied between perfusion parameters (figure 1). MTT-based parameters (MTT, ATF, TTP and Tmax) were larger than CBF or CBV (signed-rank test p<0.0001 for all CBV and p<0.0009 for all CBF comparisons with MTT-based parameters, Bonferroni corrected). MTT-based lesions also showed more mismatch (figure 2). MTT-based lesion sizes did not differ, so we used Tmax in all further comparisons. At baseline, a Tmax lesion was visible in 48 (61%) patients, 31 of whom (65% of those with a Tmax lesion, 39% of all patients) had mismatch (see online supplementary table S2); by 30 days, the Tmax lesion volume had decreased in 32, was unchanged in 13 and increased in three patients; mismatch persisted on Tmax in 5 (10%) at 72 h and 1 (5%) at 30 days.
Angiographic imaging

At baseline, 40/83 (48%) patients had an occluded intracranial artery, most being in the MCA main stem (22%) or MCA branch (27%, see online supplementary table S2). Sixteen patients without baseline arterial occlusion (16/43, 37%) had a baseline perfusion deficit on one or more perfusion parameters (figure 3, shows association for Tmax). Arterial occlusion persisted in 16 (40% of those with baseline occlusion or 22% of those imaged) at 72 h and in 4/48 (8%) at 30 days.

Baseline clinical and imaging associations

At baseline, a higher NIHSS score was associated with larger lesions on structural (p<0.0001) and perfusion imaging (all parameters, p<0.02–0.001) by ASPECTS and with arterial occlusion (p<0.001, table 1). Larger structural and perfusion lesions, but not arterial occlusion, were associated with increasing age; time to scanning was not associated with any imaging parameter. Arterial occlusion was associated with increasing baseline structural lesion extent (p<0.0001) and larger perfusion lesions (all p<0.0001, see online supplementary table S3).

Imaging and clinical outcome, reperfusion and recanalisation

Infarct extent on structural imaging at 1 month was associated with baseline NIHSS (Spearman correlation ASPECTS −0.59 (95% CI −0.75 to −0.36), p<0.001; IST-3 0.44 (95% CI 0.17 to 0.65), p=0.002) and with baseline OCSP (Kruskal–Wallis test: ASPECTS p=0.0002, IST-3 p=0.0071). Reperfusion by 72 h—that is, reduction in the perfusion lesion ASPECTS score, showed no consistent association by any perfusion parameter, with NIHSS at 72 h or 1 month or mRS at 1 or 3 months (table 2). However, arterial recanalisation by 72 h was associated with NIHSS at 7 days (p=0.04) and 1 month (p=0.0007) and with mRS at 1 (p=0.04) and 3 months (p=0.03; Wilcoxon).

Figure 3 Proportions of patients with/without a perfusion defect (on Tmax) and/or arterial obstruction within 6 h, at 72 h and 30 days after stroke. Numbers on bars are numbers of patients. Tmax, time to peak of the residue function, a measure of mean transit time.

Table 1 Association between baseline clinical (stroke severity and subtype, age and time to baseline scan) and imaging (structural, perfusion, arterial patency) variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>CT or MR</th>
<th>Structural Imaging</th>
<th>Perfusion Imaging</th>
<th>Angiography data analysed by Wilcoxon–Mann–Whitney test, except for OCR which was analysed using the Kruskal–Wallis test. All other associations assessed by Spearman correlation and 95% CI, except for OCSP groups which are compared using the Kruskal–Wallis test.</th>
<th>Angiography data analysed by Wilcoxon–Mann–Whitney test, except for OCR which was analysed using the Kruskal–Wallis test. All other associations assessed by Spearman correlation and 95% CI, except for OCSP groups which are compared using the Kruskal–Wallis test.</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIHSS baseline</td>
<td>−0.67 (−0.77 to −0.57)</td>
<td>0.60 (0.04 to 0.73)</td>
<td>0.33 (0.11 to 0.22)</td>
<td>−0.63 (−0.75 to −0.57)</td>
<td>−0.63 (−0.75 to −0.57)</td>
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<tr>
<td>OCSP</td>
<td>−0.52 (−0.61 to −0.43)</td>
<td>0.23 (0.01 to 0.45)</td>
<td>0.19 (0.04 to 0.41)</td>
<td>−0.67 (−0.77 to −0.57)</td>
<td>−0.67 (−0.77 to −0.57)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>−0.35 (−0.44 to −0.26)</td>
<td>0.28 (0.06 to 0.47)</td>
<td>0.19 (0.04 to 0.41)</td>
<td>−0.27 (−0.47 to −0.07)</td>
<td>−0.27 (−0.47 to −0.07)</td>
</tr>
<tr>
<td>Time to first scan (hours)</td>
<td>0.42 (0.06 to 0.78)</td>
<td>0.38 (0.08 to 0.67)</td>
<td>0.19 (0.04 to 0.41)</td>
<td>−0.10 (−0.22 to 0.02)</td>
<td>−0.10 (−0.22 to 0.02)</td>
</tr>
<tr>
<td>Time to first scan (hours)</td>
<td>0.42 (0.06 to 0.78)</td>
<td>0.38 (0.08 to 0.67)</td>
<td>0.19 (0.04 to 0.41)</td>
<td>−0.10 (−0.22 to 0.02)</td>
<td>−0.10 (−0.22 to 0.02)</td>
</tr>
<tr>
<td>Stroke subtype</td>
<td>0.31 (0.14 to 0.47)</td>
<td>0.37 (0.10 to 0.61)</td>
<td>0.19 (0.04 to 0.41)</td>
<td>−0.10 (−0.22 to 0.02)</td>
<td>−0.10 (−0.22 to 0.02)</td>
</tr>
<tr>
<td>Project classification of stroke subtype</td>
<td>0.31 (0.14 to 0.47)</td>
<td>0.37 (0.10 to 0.61)</td>
<td>0.19 (0.04 to 0.41)</td>
<td>−0.10 (−0.22 to 0.02)</td>
<td>−0.10 (−0.22 to 0.02)</td>
</tr>
</tbody>
</table>

Cerebrovascular disease

Other imaging outcomes

Infarct swelling at 72 h was associated with larger perfusion lesions at baseline (Tmax, Spearman $-0.536$ (95% CI $-0.688$ to $-0.337$), p value $<0.0001$) and with persistent arterial occlusion at 72 h (Spearman $-0.338$, (95% CI $-0.529$ to $-0.114$), p=0.0035). Haemorrhagic transformation at 72 h was associated with baseline arterial occlusion (p=0.02) but not perfusion lesion extent or change in perfusion lesion by any parameter, or change in arterial patency.

DISCUSSION

In this direct comparison in patients with moderate to severe stroke, half of whom were receiving intravenous alteplase, we found consistent associations between arterial occlusion/recanalisation and neurological or functional outcomes, but more variable clinical associations with NIHSS and mRS for perfusion lesions and reperfusion regardless of the perfusion parameter used. Potential imaging markers should be clinically relevant. The clinical relevance of arterial occlusion and recanalisation is supported by a meta-analysis of observational data, although meta-analyses are less clear for tissue perfusion, mismatch or reperfusion. We identify several other points of value for future stroke trials. Nearly 80% had a visible ischaemic lesion on baseline structural imaging, although most had CT and more than half were scanned within 3 h of stroke, confirming the usefulness of CT in moderate to severe stroke with a structured review process. MR with DWI might have shown acute ischaemic lesions in a higher proportion, but at the risk of patient loss to recruitment. We achieved high recruitment rates, while also giving thrombolytic treatment to nearly half the patients. We demonstrate that it is feasible to recruit with CT and follow-up with MR, removing the requirement to use only one modality in clinical trials, increasing patient participation and recruitment rates. We recruited four times as many patients during the study by allowing use of CT at presentation and MR for follow-up than if we had insisted on MR at presentation, despite having research-dedicated MR scanners in all three centres. We performed early follow-up imaging at 72 h to capture peak infarct swelling and haemorrhagic transformation, but follow-up imaging could be performed earlier depending on its main purpose. These actions together, if used in RCTs, would increase the generalisability of the results, reduce time to trial completion and costs and enhance the rate at which new treatments could be tested.

Our study had limitations. We were unable to recruit some patients outside 9:00–17:00 (16%). The difficulty of performing MR at presentation mirrors experience of other observational studies and RCTs. We used three CT and three MR scanners so our data will include between-scanner variability. However, no two scanners’ performance, even the same make and model, are identical or remain static. We minimised the impact of scanner variability by using sequences optimised for each scanner and centralised analysis. Furthermore, between-patient biological variability is generally larger than between-scanner variability, large sample sizes overcome patient and centre heterogeneity and provide generalisable results. CTP may cover less brain than MRP, but we scored all brain regions showing any involvement in the perfusion lesion, minimising the effect of reduced brain coverage. Visual quantification can be performed when volume assessment cannot—for example, where there is incomplete lesion coverage, or scan quality (eg, movement artefact) precludes computational assessment. We used a composite angiographic score, including evidence of arterial occlusion on angiography or hyperattenuated artery/absent flow void, but only after testing the individual components. Hyperattenuated artery is specific for arterial occlusion, although lacks sensitivity, but its disappearance was an independent predictor of good outcome in a large alteplase registry, justifying its use in a composite arterial patency score. We did not evaluate CTP base images which may help detect small peripheral arterial branch occlusions, potentially blunting the sensitivity of the association between occlusion/recanalisation and outcome. We did not report the results by alteplase allocation because use of alteplase was non-random and the bioeffects of alteplase contribute to the analysis of reperfusion and recanalisation. We did not use apparent diffusion coefficient (ADC), CT attenuation or perfusion threshold values to define lesions. However, there is no clear ADC threshold for infarct core, the observer reliability of ADC-based lesion measurement is limited, and there is no validated perfusion threshold and different perfusion parameters produce widely different lesions.

The study also had strengths. We used pragmatic composite imaging outcome measures but only after testing individual parameters; the composite measures were prespecified, as specific and as valid for defining recanalisation and reperfusion as possible. The qualitative image rating, performed by one observer carefully blinded to all other scan and clinical data, used extensively validated tools, and minimised observer variability. TIMI and Mori scores have been used widely by

Table 2 Imaging evidence of lesion reperfusion or arterial recanalisation and associations with clinical outcomes

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Reperfusion</th>
<th>Tmax</th>
<th>p Value</th>
<th>CBF</th>
<th>p Value</th>
<th>CBV</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIHSS day 7 (median, IQR)</td>
<td>Yes</td>
<td>6 (3, 11.5)</td>
<td>0.066</td>
<td>6 (3, 13)</td>
<td>0.15</td>
<td>6 (3, 10.5)</td>
<td>0.30</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>3 (1, 6)</td>
<td></td>
<td>3 (1, 7)</td>
<td></td>
<td>3 (1, 7)</td>
<td></td>
</tr>
<tr>
<td>NIHSS 1 month (median, IQR)</td>
<td>Yes</td>
<td>2 (1, 5)</td>
<td>0.11</td>
<td>2 (1, 6)</td>
<td>0.064</td>
<td>2 (1, 6)</td>
<td>0.16</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>1 (0, 3)</td>
<td></td>
<td>1 (0, 3)</td>
<td></td>
<td>1.5 (0, 3)</td>
<td></td>
</tr>
<tr>
<td>mRS at 3 months (median, IQR)</td>
<td>Yes</td>
<td>3 (2, 4)</td>
<td>0.076</td>
<td>3 (2, 4)</td>
<td>0.067</td>
<td>3 (2, 4)</td>
<td>0.11</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>2 (1, 3)</td>
<td></td>
<td>2 (1, 3)</td>
<td></td>
<td>2 (1, 3)</td>
<td></td>
</tr>
<tr>
<td>Age, years (median, IQR)</td>
<td>Yes</td>
<td>74 (65, 82)</td>
<td>0.074</td>
<td>74 (65, 82)</td>
<td>0.047</td>
<td>75 (67, 83)</td>
<td>0.0085</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>68 (60, 77)</td>
<td></td>
<td>69 (51, 74)</td>
<td></td>
<td>67 (51, 72)</td>
<td></td>
</tr>
</tbody>
</table>

p Values are for the Wilcoxon–Mann–Whitney test comparing groups with/without reperfusion/recanalisation. CBF, cerebral blood flow; CBV, cerebral blood volume; CTA, CT angiography; MR, magnetic resonance; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.
If imaging is to be used as a ‘biomarker’ in acute stroke trials, then it should measure a pathological process and predict resulting benefit, or harm. A ‘qualified biomarker’ is not yet validated.25 A ‘surrogate outcome marker’ is a biomarker which definitely substitutes for a clinical endpoint and measures drug efficacy or toxicity. Biomarker validation is a graded, incremental, evidentiary process. Biomarkers should reflect clinically relevant endpoints.22 Arterial recanalisation may more closely match the requirements of a biomarker than perfusion imaging, partly because tissue perfusion varies more with biological and technical factors than does angiography, so has a more complex relationship to clinical parameters. However, considerably more data from perfusion and angiography imaging are required before imaging markers can substitute for clinical outcomes. Future RCTs and observational multicentre studies using complex imaging could maximise patient recruitment by using CT or MR at baseline and for follow-up. Pragmatic use of qualitative visual scoring and quantitative analyses also minimises data loss, maximising accessibility, recruitment and generalisability.

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Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Image and numerical data are available from the authors upon request subject to a collaboration agreement. The anonymised data will be placed in the public domain once the study publication is complete.

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