Sensitivity and Specificity of the Hyperdense Artery Sign for Arterial Obstruction in Acute Ischemic Stroke

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Background and Purpose—In acute ischemic stroke, the hyperdense artery sign (HAS) on noncontrast computed tomography (CT) is thought to represent intraluminal thrombus and, therefore, is a surrogate of arterial obstruction. We sought to assess the accuracy of HAS as a marker of arterial obstruction by thrombus.

Methods—The Third International Stroke Trial (IST-3) was a randomized controlled trial testing the use of intravenous thrombolysis for acute ischemic stroke in patients who did not clearly meet the prevailing license criteria. Some participating IST-3 centers routinely performed CT or MR angiography at baseline. One reader assessed all relevant scans independently, blinded to all other data; we checked observer reliability. We combined IST-3 data with a systematic review and meta-analysis of all studies that assessed the accuracy of HAS using angiography (any modality).

Results—IST-3 had 273 patients with baseline CT or MR angiography and was the largest study of HAS accuracy. The meta-analysis (n=902+273=1175, including IST-3) found sensitivity and specificity of HAS for arterial obstruction on angiography to be 52% and 95%, respectively. HAS was more commonly identified in proximal than distal arteries (47% versus 37%; P=0.015), and its sensitivity increased with thinner CT slices (r=−0.73; P=0.001). Neither extent of obstruction nor time after stroke influenced HAS accuracy.

Conclusions—When present in acute ischemic stroke, HAS indicates a high likelihood of arterial obstruction, but its absence indicates only a 50/50 chance of normal arterial patency. Thin-slice CT improves sensitivity of HAS detection.

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Key Words: angiography □ meta-analysis □ stroke

Noncontrast computed tomography (CT) remains the primary imaging modality for hyperacute assessment of stroke in most centers. Identifying features of acute ischemic stroke on CT, therefore, remains important for routine practice. Hyperattenuation of a cerebral artery on noncontrast CT in acute ischemic stroke is thought to represent acute thrombus or embolus; the presence of the Hyperdense Artery Sign (HAS), therefore, is a surrogate of arterial obstruction and may provide useful confirmation of the diagnosis of acute ischemic stroke. The sign has been defined as any artery that subjectively appears transiently denser than adjacent or equivalent contralateral vessels although objective measures have also been applied. When compared with angiography, previous studies have shown that the HAS is a specific (although false-positives are described) but not sensitive indicator of arterial obstruction. To our knowledge, no systematic review and meta-analysis of HAS sensitivity and specificity have been published.

The Third International Stroke Trial (IST-3) was a multicenter, randomized controlled trial, which tested intravenous thrombolysis (Alteplase) given within 6 hours of ischemic stroke. Baseline (prerandomization) and follow-up (within 48 hours) brain imaging (predominantly noncontrast CT) was performed for all IST-3 patients (n=3035). In some centers, CT or MR angiography (CTA and MRA, respectively) were also routinely obtained prerandomization as part of their local stroke imaging protocol.

In a prespecified analysis, we investigated the diagnostic accuracy of HAS for arterial obstruction detected with CTA or MRA and assessed if characteristics of the noncontrast CT scan (slice-thickness), the corresponding angiographic

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*IST-3 Principal Investigators who contributed imaging for these analyses are listed in Appendix I in the online-only Data Supplement.
†The complete IST-3 Collaborative Group is listed in Appendix II in the online-only Data Supplement.

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obstruction (location, extent), or the patient (time from stroke onset) affected the accuracy of HAS. We examined data from IST-3 and performed a systematic review and meta-analysis of previous studies.

**Methods**

**Third IST**

IST-3 was an international, multicenter, prospective, randomized, open, blinded end point (PROBE) trial of intravenous recombinant tissue-type plasminogen activator (r-tPA) in acute ischemic stroke. Ethical approval, enrollment, and data collection were described elsewhere. Briefly, patients with acute stroke of any severity, with no upper age limit, were eligible for trial inclusion, if in the opinion of the responsible physician the patient might benefit from r-tPA and there was no clear indication for or contra-indications to r-tPA. If intravenous r-tPA could be started within 6 hours of stroke onset and CT/MR imaging had reliably excluded both intracranial hemorrhage and any structural stroke mimic, the patient might benefit from r-tPA. In other words, patients who definitely met the prevailing strict license criteria, or who had definite contra-indications to r-tPA were not eligible. Many patients fell outside the strict license criteria and did not have clear indications for or contra-indications and, therefore, could be randomized in the trial. Stroke severity before randomization was assessed with the National Institutes of Health Stroke Scale. Patients were randomized to receive intravenous r-tPA (0.9 mg/kg) or control. No intra-arterial therapy was used. Functional status was assessed at 6 months with the Oxford Handicap Scale. IST-3 is registered, ISRCTN25765518.

The imaging protocol required that noncontrast CT scans extend from the foramen magnum to vertex, with maximum slice-thickness 4 to 5 mm through the posterior fossa and 8 to 10 mm for the cerebral hemispheres. There was no predefined requirement for thin-slice sections, but all acquired data including spiral volumes were accepted. CTA or MRA data were also collected if available; the protocol for the IST-3 angiography substudy specified minimum acquisition standards. Only IST-3 patients who had CTA or MRA performed concurrently with baseline noncontrast CT were included in this present analysis.

All centers had to submit test imaging to the IST-3 central office for quality assessment before being certified to join the trial.

**Image Analysis**

A single neuroradiologist evaluated all relevant IST-3 images analyzing first the noncontrast CT followed by CTA or MRA sequentially and independently, blinded to any subsequent imaging or other scan reads, clinical and treatment data, using a validated, prespecified rating proforma (www.sbirc.ed.ac.uk/research/imageanalysis.html) that recorded presence, location, and extent of HAS and any angiographic obstruction.

Standard brain window settings (center, 40 Hounsfield Units; width, 80 Hounsfield Units) were used for noncontrast CT analysis, but these could be altered as required. We identified HAS on noncontrast CT if the lumen of any intracranial artery appeared more dense than adjacent or equivalent contralateral arteries but noncalcified. Thin-slice sections were used where possible to minimize volume averaging of any arterial wall calcification. We classified the internal carotid, mainstem of middle cerebral, vertebral and basilar arteries as proximal and the sylvian branches of middle cerebral and any part of the anterior or posterior cerebral arteries as distal for analysis purposes. We classified arterial obstruction on CTA/MRA using a modified 4-point Thrombolysis in Cerebral Infarction score.

To assess intraobserver reliability of HAS and CTA/MRA, the single neuroradiologist repeated ratings of 15 randomly selected patients 2 months later. To assess interobserver reliability, we compared the single neuroradiologist to the ratings performed by the IST-3 expert image reading panel performed separately using the same imaging methods (details of expert panel are provided in Appendix II in the online-only Data Supplement; these expert panel reads were not otherwise used in this present analysis).

**Systematic Review and Meta-Analysis**

We performed the systematic review and meta-analysis according to the PRISMA 2009 checklist.

**Search Strategy**

We searched Embase and Medline (Table I in the online-only Data Supplement for full strategy) between 1980 and September 2013 because HAS was first described in the early 1980s, including hand-searching references of returned articles.

**Inclusion/Exclusion Criteria and Data Extraction**

We screened abstracts for more in-depth assessment and included only peer-reviewed original articles, published in English, that contained data on patients with ischemic stroke assessed for HAS who underwent invasive or noninvasive angiography.

We assessed study quality for secondary eligibility criteria, using a modified STARD checklist (Table II in the online-only Data Supplement). We excluded articles if imaging was performed >24 hours after stroke onset (limit chosen to include articles assessing posterior fossa HAS) or if <20 patients underwent CTA, MRA, or digital subtraction angiography.

Two observers independently extracted data to calculate true and false-positive and negative rates. We only meta-analyzed articles where sensitivity or specificity (ideally both) could be calculated. We also recorded time from stroke onset to imaging, location and extent of angiographic obstruction. Disagreements were resolved by consensus.

**Statistics**

We compared clinical characteristics of the IST-3 patients with angiography to all IST-3 patients using t tests, Mann–Whitney U tests, or χ² tests as appropriate. We assessed observer reliability using the κ statistic. We used Spearman rank correlation coefficient to assess correlations between normally distributed continuous data and t tests to compare ratios of patients with and without HAS in the systematic review.

For simplicity in the present analysis and to harmonize angiographic scoring between articles, we dichotomized angiography as normal or obstructed (ie, any luminal narrowing or occlusion). We compared the angiography location of arterial obstruction with the HAS location, noting false-positives and false-negatives.

We calculated sensitivity (true-positives/[true-positives+false-negatives]), specificity (true-negatives/[true-negatives+false-positives]) in individual studies. We meta-analyzed sensitivity and specificity with a random effects model in R 8.1.2 (http://cran.r-project.org/), using the DiagMeta function, modeling within-study variation as a binomial proportion (joint meta-analysis of sensitivity and specificity was not possible because of estimation problems).

Unless stated otherwise, all analyses were performed using SPSS Statistics software, version 20.0 (IBM Corporation, New York, NY) and a value of P<0.05 was considered significant.

**Results**

In total, 273 IST-3 patients (9% of the total of 3035) had baseline CTA (n=269) or MRA (n=4). Patients with (versus without) angiography had similar baseline characteristics but less severe strokes (median National Institutes of Health Stroke Scale 10 versus 11; P=0.20) and better 6-month outcomes (median Oxford Handicap Scale 3 versus 4; P=0.002; Table III in the online-only Data Supplement).

Of the 273 IST-3 patients with angiography, 114 (42%) had some degree of luminal obstruction on angiography, whereas 69 (25%) had a HAS.

Inter- and intraobserver reliability (κ) for identification of HAS were 0.59 and 0.58, respectively; for any versus no obstruction on angiography was 0.59 and 0.82, respectively.
Reliability of HAS Versus Angiography in IST-3

In IST-3, HAS correctly identified arterial obstruction in 62, was falsely positive in 7 and falsely negative in 52, giving a sensitivity of 54% (95% confidence interval, 45%–64%) and a specificity of 96% (92%–99%).

Sensitivity, but not specificity, improved with thinner baseline noncontrast CT scan slices: ≤3 mm slices, n=162, sensitivity 62%, specificity 98%; versus >3 mm slices, n=108, sensitivity 41%, specificity 92%, (P=0.031 and P=0.089, respectively). There was no difference in the prevalence of HAS by location of arterial obstruction: proximal n=91, sensitivity 55% versus distal, n=23, sensitivity 52% (P=0.814).

More extensive angiographic obstruction, ie, involving ≥1 named artery (n=48) versus obstruction of 1 named artery (n=66), did not influence sensitivity of HAS (58% versus 52%; P=0.475). Time from stroke onset did not alter the accuracy of HAS: patients scanned ≤180 minutes (n=151), sensitivity 49%, specificity 97% versus patients scanned >180 minutes (n=122), sensitivity 61% (P=0.221), specificity 94% (P=0.500).

Systematic Review, Results of Search

We identified 326 articles by database search: 75% discussed nonintracranial HAS; 10% were published only in abstract; 10% were review articles or non-English language (Figure I in the online-only Data Supplement). Thirty-one articles underwent more in-depth assessment plus 5 further articles were found in reference lists, giving a total of 36 articles for full review. After secondary exclusion criteria, 16 of 36 original articles (n=902; Figure 1) remained for meta-analysis.6,7,15–28

Twenty articles were excluded: 7 provided insufficient raw data; 6 had <20 patients with angiography; 2 failed essential quality criteria; 2 were duplicates; 2 included patients imaged >24 hours after stroke; and 1 included nonischemic strokes.

Quality Assessment

The 16 articles identified in systematic review (n=902, not including IST-3) had a median of 52 patients (range, 20–105); most (14/16; 88%) were prospective, only 7 (44%) provided specific inclusion and exclusion criteria and none included data from a randomized controlled trial.

Most articles provided scan parameters and time from stroke onset to scan (15/16; 94% in both cases). Catheter angiography was the commonest technique (9/16; 56%); CTA and MRA were equally common (5/16; 31% and 4/16; 25%, respectively) and used almost exclusively since 2003. Most articles declared the experience or professional position of those analyzing images (14/16; 88%); with 24 neuroradiologists and 9 neurologists in the range of 1 to 6 observers per article (median, 2). Image assessors were blinded to other data in 11 of 16 (69%) articles, 12 of 16 (75%) articles used a standardized definition for HAS, only 4 articles assessed reproducibility of HAS (median κ-statistic for HAS detection 0.85; range, 0.53–0.91) and no articles assessed reproducibility of angiography.

Meta-Analysis

Among a total of 1175 patients with angiography, including IST-3, 769 had arterial obstruction and 405 had a HAS (Figure 1). The random effects summary estimate of sensitivity, based on 771 patients (384 true-positive plus 387 false-negative), was 52.4% (95% confidence interval, 41.2–63.4%). The random effects summary estimate of specificity, based on 493 patients (468 true-negative plus 25 false-positive), was 94.9% (92.5–96.6%). Four studies with missing data were omitted from specificity analysis.

HAS was more common with angiographic obstruction in proximal arteries than distal (47% versus 37%; P=0.015; Table). CT slice-thickness was significantly associated with sensitivity (Figure 2; r=−0.72; P=0.002) but not specificity of HAS and was...
Sensitivity and Specificity of the Hyperdense Artery Sign

The number of obstructed arterial segments (59% had HAS if ≥2 segments obstructed versus 49% if 1 segment obstructed; \(P=0.160\)) and time from stroke onset to scan (27% had HAS if ≤180 minutes from stroke onset versus 25% if >180 minutes; \(P=0.682\)) were not associated with HAS prevalence. Three studies with missing data were omitted from analyses of thrombus characteristics and time from stroke onset.

Discussion

We provide this first meta-analysis assessing the accuracy of HAS as a noncontrast CT marker of arterial obstruction in acute ischemic stroke and confirm using large patient numbers that HAS is highly specific and moderately sensitive for angiographically demonstrated arterial obstruction with overall specificity 95% and sensitivity 52%. IST-3, as the largest individual study of HAS sensitivity and specificity, contributes 30% more data (273/902 patients; new total 1175) than previously available. Our results are widely applicable and in situations where angiographic imaging is not currently available, can enable those performing noncontrast CT to make the best use of all available imaging information; the presence of HAS provides substantial confidence that there is a high likelihood of the diagnosis of acute ischemic stroke and of

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<th>Author</th>
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<th>Angiography, (n)</th>
<th>Location of Arterial Obstruction</th>
<th>No. of Obstructed Arterial Segments</th>
<th>Time From Stroke Onset to Scan, min</th>
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<td>Kim et al**</td>
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Results represent number of hyperdense artery sign within each total (%). Data were only included when results were available for both sides of the equation (eg, proximal and distal); 3 articles with incomplete data are not included. Unless otherwise stated, proximal arterial locations include internal carotid artery, mainstem of the middle cerebral artery (MCA), vertebral and basilar arteries. Distal arterial locations include sylvian branches of the MCA, and anterior and posterior cerebral arteries. IST-3 indicates Third International Stroke Trial.

*Proximal and distal arteries are defined here as internal carotid and middle cerebral arteries, respectively.
†Thick-slice (5 mm) computed tomographic data are presented here. Thin-slice data are also available.
arterial obstruction. However, absence of HAS does not predict normal arterial patency; in patients with acute ischemic stroke without HAS, approximately half will have arterial obstruction on angiography. It remains to be seen whether the presence (or absence) of acute arterial obstruction is important for intravenous thrombolysis treatment decisions; but in that context, or indeed in centers looking to perform appropriate endovascular therapy, this limitation of a negative HAS might encourage centers performing acute ischemic stroke imaging to consider providing baseline CTA or MRA in all cases.

Our meta-analysis confirmed that HAS prevalence increases with thinner CT slices, but thinner slices have no effect on HAS specificity, perhaps as HAS is already highly specific for obstruction. The mean diameter of intracranial arteries is <3 mm. A slice-thickness above this value, used in most of the included studies, may impair HAS sensitivity (especially in smaller arteries) by averaging intraluminal thrombus and surrounding cerebrospinal fluid space. Volumetric thin-slice CT is now widely available, as suggested by the highly significant inverse relationship between year of publication and CT slice-thickness in the systematic review. Allowing for the rising availability of volumetric CT, sensitivity rates in current routine clinical practice are, therefore, likely to be on the high side of those we report here.

Meta-analysis also confirmed that HAS is more likely to be identified in proximal than distal arteries, probably reflecting the larger caliber of proximal arteries and greater volumes of thrombus required for obstruction. Other factors, such as the extent of angiographic obstruction and time after stroke onset, were not significantly related to HAS prevalence.

**Strengths and Limitations**

IST-3 was conducted in many centers, so inevitably includes variability in scan parameters and protocols. However, IST-3 represents real-world practice and, combined with the systematic review, provides results that are widely applicable to centers assessing acute stroke with a range of CT scanners. Angiography in IST-3 was performed in ~10% of centers and may have been influenced by local practice, so has limitations. Nevertheless, IST-3 angiography is the largest complete data set of its kind, the only one performed in the standardized context of a randomized trial, and increases the available data by almost one third. We found only one larger data set but it only included patients with a HAS precluding assessment of sensitivity and specificity.

We used a qualitative measure to identify HAS in IST-3, which reflects routine practice. Additional work is ongoing to assess whether measuring intra-arterial thrombus density quantitatively improves the accuracy of arterial obstruction or interacts with treatment response.

Our method of dichotomizing angiography results may have included some patients with chronic atheroma in the obstructed group. This could erroneously raise the number of false-negative HAS cases and thereby seem to reduce the sensitivity of HAS. However, this is a general problem in acute stroke, no other studies that we identified in the literature had addressed this point, and we decided that the opposite approach (to only consider patients with occluded arteries as abnormal) would have been less accurate not only by having the same effect on HAS specificity but also by excluding patients with genuine nondense thrombus from our analyses entirely.

Using PRISMA and STARD, we maintained a high-quality systematic review and meta-analysis of HAS. We identified many articles, most not relevant, but we assert that evaluating several hundred abstracts was preferable to missing relevant work. Excluding abstract-only and non-English publications may have reduced the completeness and led to publication bias, but abstract-only publication provides insufficient raw data for our analyses.

The final 16 articles retained for meta-analysis were of moderate to high quality according to our criteria. In particular, most of the data were prospective and the methods were detailed enough to be replicated. More standard definitions for HAS and more consistent reporting of factors such as blinding of image assessment would improve future research.

**Conclusions**

The high specificity of HAS provides confidence for its use as a surrogate marker of angiographic obstruction and to confirm the diagnosis of acute ischemic stroke. The moderate sensitivity means that the absence of HAS cannot be used alone to indicate that angiography will be normal; those performing acute stroke imaging might, therefore, consider undertaking angiography in this context. Sensitivity of HAS is significantly improved with thin-slice volumetric CT.

**Acknowledgments**

The Third International Stroke Trial (IST-3) collaborative group thanks all patients who participated in the study. The authors gratefully acknowledge the members of the angiography reading panel, noncontrast scan reading panel, trial steering committee, and national coordinators (Appendix II in the online-only Data Supplement).

**Sources of Funding**

The Third International Stroke Trial (IST-3) main trial was funded from many sources detailed in Appendix III in the online-only Data Supplement. The angiography study was funded by the National Institute for Health Research (NIHR) Efficacy and Mechanisms Evaluation Panel (EME 08–43–52). The views are those of the authors and not of the NIHR.

**Disclosures**

R. von Kummer; Lundbeck, Penumbra, Covidien, Brainsgate, Boehringer Ingelheim; R. Lindley; Boehringer Ingelheim, Covidien; P. Sandercok; Boehringer Ingelheim. The other authors report no conflicts.

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Sensitivity and specificity of the Hyperdense Artery Sign for arterial obstruction in acute ischemic stroke

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Prof Rüdiger von Kummer (Prof. Dr. med.)³
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4. Westmead Hospital Clinical School and The George Institute for Global Health, University of Sydney, Australia
5. IST-3 Principal Investigators who contributed imaging for these analyses are listed in online Appendix I.
6. The complete IST-3 Collaborative Group is listed in online Appendix II.

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<td>vessel*.mp. [mp=ti, ab, ot, nm, hw, kf, ps, rs, ui, an, sh, tn, dm, mf, dv, kw]</td>
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<td>8</td>
<td>vascula*.mp. [mp=ti, ab, ot, nm, hw, kf, ps, rs, ui, an, sh, tn, dm, mf, dv, kw]</td>
</tr>
<tr>
<td>9</td>
<td>6 or 7 or 8</td>
</tr>
<tr>
<td>10</td>
<td>5 and 9</td>
</tr>
<tr>
<td>11</td>
<td>hmcas.mp. [mp=ti, ab, ot, nm, hw, kf, ps, rs, ui, an, sh, tn, dm, mf, dv, kw]</td>
</tr>
<tr>
<td>12</td>
<td>10 or 11</td>
</tr>
<tr>
<td>13</td>
<td>angiogra*.mp. [mp=ti, ab, ot, nm, hw, kf, ps, rs, ui, an, sh, tn, dm, mf, dv, kw]</td>
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<tr>
<td>14</td>
<td>arteriogra*.mp. [mp=ti, ab, ot, nm, hw, kf, ps, rs, ui, an, sh, tn, dm, mf, dv, kw]</td>
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<td>15</td>
<td>cta.mp. [mp=ti, ab, ot, nm, hw, kf, ps, rs, ui, an, sh, tn, dm, mf, dv, kw]</td>
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<tr>
<td>16</td>
<td>mra.mp. [mp=ti, ab, ot, nm, hw, kf, ps, rs, ui, an, sh, tn, dm, mf, dv, kw]</td>
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<tr>
<td>17</td>
<td>13 or 14 or 15 or 16</td>
</tr>
<tr>
<td>18</td>
<td>12 and 17</td>
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Keywords pertaining to hyperdense arteries (in any location) and angiography were combined using the Boolean operator OR, results from these topic area searches were then combined using the Boolean operator AND.
<table>
<thead>
<tr>
<th>Essential</th>
<th>Desirable</th>
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</thead>
<tbody>
<tr>
<td>Description of patient selection process</td>
<td>Prospective with sequential patients</td>
</tr>
<tr>
<td></td>
<td>Randomized</td>
</tr>
<tr>
<td></td>
<td>Inclusion/exclusion criteria provided</td>
</tr>
<tr>
<td>Image acquisition details provided</td>
<td>Scanner used (manufacturer and model, number of detector rows)</td>
</tr>
<tr>
<td></td>
<td>Scan parameters (especially slice thickness)</td>
</tr>
<tr>
<td></td>
<td>Time from stroke onset to imaging</td>
</tr>
<tr>
<td></td>
<td>Time from non-contrast CT to angiography</td>
</tr>
<tr>
<td>Description of image analysis</td>
<td>Details of those analysing images</td>
</tr>
<tr>
<td></td>
<td>Blinded to clinical details and treatment allocation (if any)</td>
</tr>
<tr>
<td></td>
<td>Reproducibility data provided</td>
</tr>
<tr>
<td></td>
<td>Hyperdense Artery Sign defined using previously described criteria</td>
</tr>
</tbody>
</table>
Table III. Baseline clinical and imaging characteristics and six-month outcome for IST-3 patients with and without pre-randomization angiography

<table>
<thead>
<tr>
<th></th>
<th>IST-3 Patients with Baseline CT or MR Angiography n = 273</th>
<th>Entire IST-3 Group n=3035</th>
<th>p-value for Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median, IQR)</td>
<td>81 years (71-86)</td>
<td>81 years (72-86)</td>
<td>0.815</td>
</tr>
<tr>
<td>Male Sex</td>
<td>120 (44.0%)</td>
<td>1465 (48.3%)</td>
<td>0.135</td>
</tr>
<tr>
<td>NIHSS (median, IQR)</td>
<td>10 (5-17)</td>
<td>11 (6-17)</td>
<td>0.020</td>
</tr>
<tr>
<td>Hyperdense Artery</td>
<td>69 (25.3%)</td>
<td>716/2961 (24.2%)*</td>
<td>0.687</td>
</tr>
<tr>
<td>OHS (median, IQR)</td>
<td>3 (1-5)</td>
<td>4 (2-6)</td>
<td>0.002</td>
</tr>
<tr>
<td>Independent at 6 Months (OHS 0-2)</td>
<td>120 (44.0%)</td>
<td>1088 (35.8%)</td>
<td>0.003</td>
</tr>
<tr>
<td>Dead by 6 Months</td>
<td>61 (22.3%)</td>
<td>815 (26.9%)</td>
<td>0.078</td>
</tr>
<tr>
<td>Treated with rt-PA</td>
<td>138 (50.5%)</td>
<td>1515 (49.9%)</td>
<td>0.827</td>
</tr>
</tbody>
</table>

Results represent n (%) unless otherwise stated.

NIHSS = National Institutes of Health Stroke Scale. OHS = Oxford Handicap Scale (six-month follow up). IQR = Inter-Quartile Range.

* From the entire IST-3 group 2961 had non-contrast CT at baseline, the remainder received MRI.
Figure I. Flowchart showing results of systematic search and effect of exclusion criteria on final number of articles included in meta-analysis

EMBASE and Medline Search

326 Unique Articles

Review of Abstracts

31 Selected for Further Review

5 Added from Review of References

20 Articles Excluded

16 Articles Retained for Inclusion in Meta-Analysis

EXCLUDED
75% did not meet primary inclusion criterion
10% non-peer reviewed (abstract only)
3% not published in English
2% review articles

EXCLUDED
7 provided insufficient raw data
6 had fewer than 20 patients
2 failed to meet essential quality criteria
2 represented duplicated results
2 imaged beyond 24 hours
1 included haemorrhagic stroke patients
Appendix I. IST-3 investigators who contributed imaging for these analyses

From their respective centres (n):

Prof Martin Brown, The National Hospital for Neurology & Neurosurgery, London, UK (67);
Prof Anna Czlonkowska, Institute of Psychiatry & Neurology, Warsaw, Poland (29);
Dr Erik Lundstrom, Uppsala University Hospital, Sweden (24);
Prof Philippe Lyrer, Universitätsspital Basel, Switzerland (18);
Dr C Levi, John Hunter Hospital, New Lambton Heights, Australia (14);
Dr C Roffe, University Hospital of North Staffordshire, Stoke-on-Trent, UK (12);
Dr J Sturm, Gosford Hospital, Australia (12);
Dr Gaetano Procaccianti, Ospedale Maggiore, Bologna, Italy (11);
Dr SH Johnsen, University Hospital North Norway, Tromso, Norway (10);
Dr Magnus Esbjornsson, Hassleholm Hospital, Sweden (10);
Dr B Indredavik, University Hospital Trondheim, Norway (9);
Dr Federica Casoni, Nuovo Ospedale Civile "S.Agostino-Estense", Modena, Italy (9);
Dr David Hargroves, William Harvey Hospital, Ashford, UK (7);
Dr Pankaj Sharma, Hammersmith Hospitals & Imperial College, London, UK (7);
Prof Peter Sandercock, Western General Hospital, Edinburgh, UK (5);
Dr Y Ronning, Ulleval Sykehus, Oslo, Norway (3);
Dr Andre Peeters, Cliniques Universitaires St Luc, Brussels, Belgium (3);
Dr Patrick Gompertz, Royal London Hospital, UK (3);
Prof Chris Bladon, Box Hill Hospital, Australia (3);
Dr E Warburton, Addenbrookes Hospital, Cambridge, UK (2);
Dr Stephen Read, Royal Brisbane and Women's Hospital, Herston, Australia (2);
Dr Fabio Chiodo Grandi, Ospedale di Cattinara Trieste, Italy (1);
Prof G Hankey, Royal Perth Hospital, Australia (1);
Prof Lalit Kalra, King's College Hospital, London, UK (1);
Dr GJ Gunathilagan, Queen Elizabeth The Queen Mother Hospital, Kent, UK (1);
Dr A Rudd, Guy's & St.Thomas Hospital, London, UK (1);
Prof Walenty M. Nyka, Medical University of Gdansk, Poland (1);
Dr Odd Roe Skogen, Alesund Sjukehus, Norway (1);
Prof Per Wester, University Hospital of Northern Sweden, Umea, Sweden (1);
Prof Carlo Gandolfo, Universita degli Studi di Genova, Italy (1);
Dr Paul Guylar, Southend University Hospital, Westcliff-on-Sea, UK (1);
Dr Nicoletta Checcharelli, Ospedale Valduce di Como, Italy (1);
Dr David Nicholl, City Hospital, Sandwell & West Birmingham Hospital, Birmingham, UK (1);
Prof Andreas Luft, Universitätsspital Zürich, Switzerland (1).
Appendix II. IST-3 Collaborative Group

For a complete list of all committees, please see the IST-3 primary publication in The Lancet (The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the third international stroke trial [IST-3]): a randomized controlled trial. *Lancet* 2012;379:2352-63).

IST-3 was conceived by the co-chief investigators, Peter Sandercock (University of Edinburgh, Scotland), Richard I Lindley (Sydney Medical School – Westmead Hospital and The George Institute for Global Health, University of Sydney, Australia), and Joanna M Wardlaw (University of Edinburgh, Scotland).

**Non-contrast CT and MRI reading panel**
Joanna M Wardlaw, Andrew Farrall (University of Edinburgh, Scotland), Zoe Morris (University of Edinburgh, Scotland), Rüdiger von Kummer (Dresden University Stroke Centre, Germany), Lesley Cala (University of Western Australia, Crawley, Australia), Anders von Heijne (Danderyd Hospital, Stockholm, Sweden), Alessandro Adami (Sacro Cuore-Don Calabria Hospital, Verona, Italy), Andre Peeters (Cliniques Universitaires Saint-Luc, Bruxelles, Belgium), Gillian Potter (Salford Royal NHS Foundation Trust, England), Nick Brady (Neuroradiology, James Cook University Hospital, South Tees Hospital NHS Trust, Middlesborough, UK).

**Angiography reading panel**
Joanna M Wardlaw, Rüdiger von Kummer, Andrew Farrall, Robin Sellar (University of Edinburgh, Scotland), Alessandro Adami, Philip White (Newcastle University, UK), Andrew Demchuk (University of Calgary, Canada), Matthew Adams (Great Ormond Street Hospital, London, UK), Grant Mair (University of Edinburgh, Scotland), Bernard Yan (The Royal Melbourne Hospital, Parkville, Australia).

**Trial steering committee**

**National coordinators and associate national coordinators**
Australia: RIL, Graeme J Hankey (Royal Perth Hospital, Perth). Austria: Karl Matz (Landesklinikum Donauregion Tulln, Tulln), Michael Brainin. Belgium: AP. Canada: Gord Gubitz (Dalhousie University and Queen Elizabeth II Health Sciences Centre, Halifax), Stephen J Phillips (Dalhousie University and Queen Elizabeth II Health Sciences Centre, Halifax). Italy: Stefano Ricci (Department of Neurology ASL1, Ospedale, Citta’ di Castello). Mexico: Antonio Arauz (Instituto Nacional de Neurologia, Mexico City). Norway: Eivind Berge (Oslo University Hospital, Oslo), Karsten Bruins Slot (Oslo University Hospital, Oslo). Poland: Anna Czlonkowska (Institute of Psychiatry and Neurology, Warsaw, and Medical University of Warsaw, Warsaw), Adam Kobayashi (Institute of Psychiatry and Neurology,

Centres in IST-3 that performed angiography

AUSTRALIA
Austin Health - Repatriation Campus
Box Hill Hospital (Monash University)
Gosford Hospital
John Hunter Hospital
Nambour General Hospital
Royal Brisbane and Women's Hospital
Royal Perth Hospital

AUSTRALIA
Prof Helen Dewey
Prof Chris Bladin
Dr Jonathan Sturm
Dr Chris Levi
Dr Rohan Grimley
Dr Stephen Grimley
Dr Graeme J. Hankey

AUSTRIA
Landesklinikum Donauregion Tulln

BELGIUM
Cliniques Universitaires St. Luc

CANADA
QEII Health Sciences Centre

ITALY
Nuovo Ospedale Civile
Ospedale Citta di Castello
Ospedale di Branca (Ospedale di Gubbio)
Ospedale di Cattinara - Trieste
Ospedale Maggiore
Ospedale Valduce di Como
Universita degli Studi di Genova, Dipartimento di Neuroscienze Oftalmologia e Genetica

NORWAY
Aalesund Sjukehus
Harstad Sykehus
St Olavs Hospital, University Hospital of Trondheim
Ullevål University Hospital
University Hospital Northern Norway

POLAND
2nd Department of Neurology,
Institute of Psychiatry & Neurology, Medical University of Gdansk

PROF Anna Czlonkowska
Prof Walenty Michal Nyka, Dr Dariusz Gasecki

Dr Karl Matz

Dr Andre Peeters

Dr Gord Gubitz

Dr Federica Casoni
Dr Silvia Cenciarelli
Dr Tatiana Mazzoli
Dr Fabio Chiodo Grandi
Dr Gaetano Procaccianti
Dr Nicoletta Checcarelli
Prof Carlo Gandolfo

Dr Yngve Müller Seljeseth
Dr Odd Kildahl-Andersen
Dr Bent Indredavik
Dr Eivind Berge
Dr Stein Harald Johnsen
<table>
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<tr>
<th>Country</th>
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<th>Contact Person</th>
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<tr>
<td>Portugal</td>
<td>Centro Hospitalar de Trás-os-Montes e Alto Douro</td>
<td>Dr Mário Silva</td>
</tr>
<tr>
<td>Sweden</td>
<td>Danderyds Sjukhus</td>
<td>Dr Veronica Murray</td>
</tr>
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<td></td>
<td>Hassleholm Hospital</td>
<td>Dr Magnus Esbjornsson</td>
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<td>University Hospital of Northern Sweden</td>
<td>Prof Per Wester</td>
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<td>Switzerland</td>
<td>Universitätsspital Basel</td>
<td>Prof Philippe Lyrer</td>
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<td>Prof Andreas Luft</td>
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<td>UK</td>
<td>Addenbrookes Hospital</td>
<td>Dr Liz Warburton</td>
</tr>
<tr>
<td></td>
<td>City Hospital, Sandwell &amp; West Birmingham Hospitals NHS Trust</td>
<td>Dr David Nicholl</td>
</tr>
<tr>
<td></td>
<td>Countess of Chester Hospital</td>
<td>Dr K Chatterjee</td>
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<tr>
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<td>Guy's &amp; St. Thomas' Hospital</td>
<td>Prof Anthony Rudd</td>
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<tr>
<td></td>
<td>Hammersmith Hospitals &amp; Imperial College</td>
<td>Dr Pankaj Sharma</td>
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<tr>
<td></td>
<td>King's College Hospital</td>
<td>Professor Lalit Kalra</td>
</tr>
<tr>
<td></td>
<td>Leeds General Infirmary</td>
<td>Dr Ahamad Hassan</td>
</tr>
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<td></td>
<td>Norfolk and Norwich University Hospital NHS Trust</td>
<td>Dr Kneale Metcalf</td>
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<td>Nottingham City Hospital</td>
<td>Dr Wayne Sunman</td>
</tr>
<tr>
<td></td>
<td>Queen Elizabeth the Queen Mother Hospital</td>
<td>Dr Gunaratnam Gunathilagan</td>
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<td></td>
<td>Queen's Hospital, Barking, Havering &amp; Redbridge Hospitals NHS Trust</td>
<td>Dr Khaled Darawil</td>
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<td>Dr Paul Guyler</td>
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<td>Dr Geoffrey Cloud</td>
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<td>The National Hospital for Neurology &amp; Neurosurgery</td>
<td>Prof Martin Brown</td>
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<td>The Royal London Hospital, Barts and The London NHS Trust</td>
<td>Dr Patrick Gompertz</td>
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<tr>
<td></td>
<td>University Hospital Aintree</td>
<td>Dr Ramesh Durairaj</td>
</tr>
<tr>
<td></td>
<td>University Hospital of North Staffordshire</td>
<td>Prof Christine Roffe</td>
</tr>
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<td></td>
<td>University Hospitals Coventry &amp; Warwickshire NHS Trust</td>
<td>Dr Anthony Kenton</td>
</tr>
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<td>Western General Hospital</td>
<td>Prof Peter Sandercock</td>
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<tr>
<td></td>
<td>William Harvey Hospital</td>
<td>Dr David Hargroves</td>
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</table>
Appendix III. Funding sources for IST-3

The start-up phase of IST-3 was supported by a grant from the Stroke Association, UK (TSA 04/99). The expansion phase was funded by the Health Foundation UK (2268/1282). The scan reading development was funded by Chest, Heart Stroke Scotland (R100/7).

The main phase of the trial is funded by: UK Medical Research Council (MRC) (grant numbers G0400069 and EME 09-800-15) and managed by NIHR on behalf of the MRC-NIHR partnership; the Research Council of Norway; Arbetsmarknadens Partners Forsakringsbolag (AFA) Insurances Sweden; the Swedish Heart Lung Fund; The Foundation of Marianne and Marcus Wallenberg, Stockholm County Council; Karolinska Institute Joint ALF-project grants Sweden, the Polish Ministry of Science and Education (grant number 2PO5B10928); the Australian Heart Foundation; Australian National Health and Medical Research Council (NHMRC); the Swiss National Research Foundation; the Swiss Heart Foundation; the Foundation for Health and Cardio-/Neurovascular Research, Basel, Switzerland; the Assessorato alla Sanita, Regione dell’Umbria, Italy; and, Danube University, Krems, Austria.

Boehringer-Ingelheim GmbH donated drug and placebo for the 300 patients in the double-blind phase, but thereafter had no role whatsoever in the trial.

The UK Stroke Research Network (SRN study ID 2135) adopted the trial in 01/05/2006, supported the initiation of new UK sites, and in some centres, and, after that date, data collection was undertaken by staff funded by the network or working for associated NHS organisations.

IST-3 gratefully acknowledges the extensive support of the NIHR Stroke Research Network, NHS Research Scotland (NRS), through the Scottish Stroke Research Network, and the National Institute for Social Care and Health Research Clinical Research Centre (NISCHR CRC).

The central imaging work was undertaken at the Brain Imaging Research Centre (www.bric.ed.ac.uk), a member of the Scottish Imaging Network A Platform for Scientific Excellence (SINAPSE) collaboration (www.sinapse.ac.uk), at the Division of Clinical Neurosciences, University of Edinburgh. SINAPSE is funded by the Scottish Funding Council (SFC) and the Chief Scientist Office of the Scottish Executive (CSO).

Additional support was received from Chest Heart and Stroke Scotland, DesAcc, University of Edinburgh, Danderyd Hospital R&D Department, Karolinska Institutet, Oslo University Hospital, and the Dalhousie University Internal Medicine Research Fund.