ONLINE SUPPLEMENT

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

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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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Table I. Strategy employed on combined Embase and Medline database search

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>hyperdens*.mp. [mp=ti, ab, ot, nm, hw, kf, ps, rs, ui, an, sh, tn, dm, mf, dv, kw]</td>
</tr>
<tr>
<td>2</td>
<td>hyper-dens*.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>3</td>
<td>hyperatten*.mp. [mp=ti, ab, ot, nm, hw, kf, ps, rs, ui, an, sh, tn, dm, mf, dv, kw]</td>
</tr>
<tr>
<td>4</td>
<td>hyper-atten*.mp. [mp=ti, ab, ot, nm, hw, kf, ps, rs, ui, an, sh, tn, dm, mf, dv, kw]</td>
</tr>
<tr>
<td>5</td>
<td>1 or 2 or 3 or 4</td>
</tr>
<tr>
<td>6</td>
<td>arter*.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>7</td>
<td>vessel*.mp. [mp=ti, ab, ot, nm, hw, kf, ps, rs, ui, an, sh, tn, dm, mf, dv, kw]</td>
</tr>
<tr>
<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>
</tr>
<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>
</tr>
<tr>
<td>15</td>
<td>cta.mp. [mp=ti, ab, ot, nm, hw, kf, ps, rs, ui, an, sh, tn, dm, mf, dv, kw]</td>
</tr>
<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>
</tr>
<tr>
<td>17</td>
<td>13 or 14 or 15 or 16</td>
</tr>
<tr>
<td>18</td>
<td>12 and 17</td>
</tr>
</tbody>
</table>

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 II. Quality assessment checklist used as secondary exclusion criteria for entry into meta-analysis. All essential criteria had to be met

<table>
<thead>
<tr>
<th>Essential</th>
<th>Desirable</th>
</tr>
</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, Universitatsklinikum 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 Bladin, 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, Umeå, Sweden (1);
Prof Carlo Gandolfo, Universita degli Studi di Genova, Italy (1);
Dr Paul Guyler, Southend University Hospital, Westcliff-on-Sea, UK (1);
Dr Nicoletta Checcarelli, Ospedale Valduce di Como, Italy (1);
Dr David Nicholl, City Hospital, Sandwell & West Birmingham Hospital, Birmingham, UK (1);
Prof Andreas Luft, Universitatsklinikum 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
  - Prof Helen Dewey
- Box Hill Hospital (Monash University)
  - Prof Chris Bladin
- Gosford Hospital
  - Dr Jonathan Sturm
- John Hunter Hospital
  - Dr Chris Levi
- Nambour General Hospital
  - Dr Rohan Grimley
- Royal Brisbane and Women’s Hospital
  - Dr Stephen Read
- Royal Perth Hospital
  - Dr Graeme J. Hankey

**AUSTRIA**
- Landesklinikum Donauregion Tulln
  - Dr Karl Matz

**BELGIUM**
- Cliniques Universitaires St. Luc
  - Dr Andre Peeters

**CANADA**
- QEII Health Sciences Centre
  - Dr Gord Gubitz

**ITALY**
- Nuovo Ospedale Civile
  - Dr Federica Casoni
- Ospedale Citta di Castello
  - Dr Silvia Cenciarelli
- Ospedale di Branca (Ospedale di Gubbio)
  - Dr Tatiana Mazzoli
- Ospedale di Cattinara - Trieste
  - Dr Fabio Chiodo Grandi
- Ospedale Maggiore
  - Dr Gaetano Procacciante
- Ospedale Valduce di Como
  - Dr Nicoletta Checcarelli
- Universita degli Studi di Genova, Dipartimento di Neuroscienze Ottalmologia e Genetica
  - Prof Carlo Gandolfo

**NORWAY**
- Aalesund Sjukehus
  - Dr Yngve Müller Seljeseth
- Harstad Sykehus
  - Dr Odd Kildahl-Andersen
- St Olavs Hospital, University Hospital of Trondheim
  - Dr Bent Indredavik
- Ullevål University Hospital
  - Dr Eivind Berge
- University Hospital Northern Norway
  - Dr Stein Harald Johnsen

**POLAND**
- 2nd Department of Neurology, Institute of Psychiatry & Neurology, Medical University of Gdansk
  - Prof Anna Czlonkowska
- Institute of Psychiatry & Neurology, Medical University of Gdansk
  - Prof Walenty Michal Nyka, Dr Dariusz Gasecki
Military Medical Institute SPZZOZ w Sandomierzu  Prof A Stepien, Dr Piotr Sobolewski

PORTUGAL
Centro Hospitalar de Trás-os-Montes e Alto Douro  Dr Mário Silva

SWEDEN
Danderyds Sjukhus  Dr Veronica Murray
Hassleholm Hospital  Dr Magnus Esbjornsson
University Hospital of Northern Sweden  Prof Per Wester
Uppsala University Hospital  Dr Erik Lundström

SWITZERLAND
Universitätsspital Basel  Prof Philippe Lyrer
Universitätsspital Zürich  Prof Andreas Luft

UNITED KINGDOM
Addenbrookes Hospital  Dr Liz Warburton
City Hospital, Sandwell & West Birmingham Hospitals NHS Trust  Dr David Nicholl
Countess of Chester Hospital  Dr K Chatterjee
Guy’s & St.Thomas’ Hospital  Dr K Chatterjee
Hammersmith Hospitals & Imperial College  Dr Pankaj Sharma
King’s College Hospital  Prof Anthony Rudd
Leeds General Infirmary  Dr Ahamad Hassan
Norfolk and Norwich University Hospital NHS Trust  Dr Kneale Metcalf
Nottingham City Hospital  Dr Wayne Sunman
Queen Elizabeth the Queen Mother Hospital  Dr Gunaratnam Gunathilagan
Queen’s Hospital, Barking, Havering & Redbridge Hospitals NHS Trust  Dr Khaled Darawil
Royal Hallamshire Hospital  Prof Graham Venables
Southend University Hospital  Dr Paul Guyler
St George’s Healthcare NHS Trust  Dr Geoffrey Cloud
The National Hospital for Neurology & Neurosurgery  Prof Martin Brown
The Royal London Hospital, Barts and The London NHS Trust  Dr Patrick Gompertz
University Hospital Aintree  Dr Ramesh Durairaj
University Hospital of North Staffordshire  Prof Christine Roffe
University Hospitals Coventry & Warwickshire NHS Trust  Dr Anthony Kenton
Western General Hospital  Prof Peter Sandercock
William Harvey Hospital  Dr David Hargroves
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, 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.