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

Citation for published version:

Digital Object Identifier (DOI):
10.1161/STROKEAHA.114.007036

Link:
Link to publication record in Edinburgh Research Explorer

Document Version:
Peer reviewed version

Published In:
Stroke

General rights
Copyright for the publications made accessible via the Edinburgh Research Explorer is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy
The University of Edinburgh has made every reasonable effort to ensure that Edinburgh Research Explorer content complies with UK legislation. If you believe that the public display of this file breaches copyright please contact openaccess@ed.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.
Sensitivity and specificity of the Hyperdense Artery Sign for arterial obstruction in acute ischemic stroke

Dr Grant Mair (MB ChB)\textsuperscript{1}
Dr Elena V Boyd (MBBS)\textsuperscript{2}
Dr Francesca M Chappell (PhD)\textsuperscript{1}
Prof Rüdiger von Kummer (Prof. Dr. med.)\textsuperscript{3}
Prof Richard I Lindley (MD)\textsuperscript{4}
Prof Peter Sandercock (DM)\textsuperscript{1}
Prof Joanna M Wardlaw (MD)\textsuperscript{1} and the IST-3 Collaborative Group\textsuperscript{5,6}

1. Division of Neuroimaging Sciences, University of Edinburgh, Western General Hospital, Edinburgh, UK
2. Department of Radiology, Northwick Park Hospital, Harrow, UK
3. Department of Neuroradiology, Dresden University Stroke Centre, University Hospital, Dresden, Germany
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.

Corresponding Author:
Professor Joanna M Wardlaw
Division of Neuroimaging Sciences
University of Edinburgh
Western General Hospital
Crewe Road
Edinburgh
EH4 2XU
UK

Email: joanna.wardlaw@ed.ac.uk
Phone: +44 131 537 2943
Fax: +44 131 332 5150
CONTENTS

Table I. Search strategy Page 1
Table II. Quality assessment checklist Page 2
Table III. Baseline characteristics for IST-3 patients with and without angiography Page 3
Figure I. Flow chart for systematic review Page 4
Appendix I. IST-3 investigators who contributed imaging for these analyses Page 5
Appendix II. IST-3 collaborative group Page 6
Appendix III. Funding sources for IST-3 Page 9
Table I. Strategy employed on combined Embase and Medline database search

<table>
<thead>
<tr>
<th></th>
<th>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.</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>
</tr>
<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>
</tr>
<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>
**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><strong>Age (median, IQR)</strong></td>
<td>81 years (71-86)</td>
<td>81 years (72-86)</td>
<td>0.815</td>
</tr>
<tr>
<td><strong>Male Sex</strong></td>
<td>120 (44.0%)</td>
<td>1465 (48.3%)</td>
<td>0.135</td>
</tr>
<tr>
<td><strong>NIHSS (median, IQR)</strong></td>
<td>10 (5-17)</td>
<td>11 (6-17)</td>
<td>0.020</td>
</tr>
<tr>
<td><strong>Hyperdense Artery</strong></td>
<td>69 (25.3%)</td>
<td>716/2961 (24.2%)*</td>
<td>0.687</td>
</tr>
<tr>
<td><strong>OHS (median, IQR)</strong></td>
<td>3 (1-5)</td>
<td>4 (2-6)</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Independent at 6 Months (OHS 0-2)</strong></td>
<td>120 (44.0%)</td>
<td>1088 (35.8%)</td>
<td>0.003</td>
</tr>
<tr>
<td><strong>Dead by 6 Months</strong></td>
<td>61 (22.3%)</td>
<td>815 (26.9%)</td>
<td>0.078</td>
</tr>
<tr>
<td><strong>Treated with rt-PA</strong></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 1. 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, Universitatsspital 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, Umea, 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, Universitatsspital 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, Città’ 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 Członkowska (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

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 Olav's 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 Helen Dewey
Prof Chris Bladin
Dr Jonathan Sturm
Dr Chris Levi
Dr Rohan Grimley
Dr Stephen Read
Dr Graeme J. Hankey
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
Prof Anna Czlonkowska
Prof Walenty Michal Nyka, Dr Dariusz Gasecki
<table>
<thead>
<tr>
<th>Country</th>
<th>Hospital Name</th>
<th>Medical Professional</th>
</tr>
</thead>
<tbody>
<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>
<tr>
<td></td>
<td>Hassleholm Hospital</td>
<td>Dr Magnus Esbjornsson</td>
</tr>
<tr>
<td></td>
<td>University Hospital of Northern Sweden</td>
<td>Prof Per Wester</td>
</tr>
<tr>
<td></td>
<td>Uppsala University Hospital</td>
<td>Dr Erik Lundström</td>
</tr>
<tr>
<td>SWITZERLAND</td>
<td>Universitätssspital Basel</td>
<td>Prof Philippe Lyrer</td>
</tr>
<tr>
<td></td>
<td>Universitätssspital Zürich</td>
<td>Prof Andreas Luft</td>
</tr>
<tr>
<td>UNITED KINGDOM</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>
</tr>
<tr>
<td></td>
<td>Guy's &amp; St.Thomas' Hospital</td>
<td>Prof Anthony Rudd</td>
</tr>
<tr>
<td></td>
<td>Hammersmith Hospitals &amp; Imperial College</td>
<td>Dr Pankaj Sharma</td>
</tr>
<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>
<tr>
<td></td>
<td>Norfolk and Norwich University Hospital NHS Trust</td>
<td>Dr Kneale Metcalf</td>
</tr>
<tr>
<td></td>
<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>
</tr>
<tr>
<td></td>
<td>Queen's Hospital, Barking, Havering &amp; Redbridge Hospitals NHS Trust</td>
<td>Dr Khaled Darawil</td>
</tr>
<tr>
<td></td>
<td>Royal Hallamshire Hospital</td>
<td>Prof Graham Venables</td>
</tr>
<tr>
<td></td>
<td>Southend University Hospital</td>
<td>Dr Paul Guyler</td>
</tr>
<tr>
<td></td>
<td>St George's Healthcare NHS Trust</td>
<td>Dr Geoffrey Cloud</td>
</tr>
<tr>
<td></td>
<td>The National Hospital for Neurology &amp; Neurosurgery</td>
<td>Prof Martin Brown</td>
</tr>
<tr>
<td></td>
<td>The Royal London Hospital, Barts and The London NHS Trust</td>
<td>Dr Patrick Gompertz</td>
</tr>
<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>
<tr>
<td></td>
<td>University Hospitals Coventry &amp; Warwickshire NHS Trust</td>
<td>Dr Anthony Kenton</td>
</tr>
<tr>
<td></td>
<td>Western General Hospital</td>
<td>Prof Peter Sandercock</td>
</tr>
<tr>
<td></td>
<td>William Harvey Hospital</td>
<td>Dr David Hargroves</td>
</tr>
</tbody>
</table>

8
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.