ONLINE SUPPLEMENT

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

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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

1	hyperdens*.mp. [mp=ti, ab, ot, nm, hw, kf, ps, rs, ui, an, sh, tn, dm, mf, dv, kw]
2	hyper-dens*.mp. [mp=ti, ab, ot, nm, hw, kf, ps, rs, ui, an, sh, tn, dm, mf, dv, kw]
3	hyperatten*.mp. [mp=ti, ab, ot, nm, hw, kf, ps, rs, ui, an, sh, tn, dm, mf, dv, kw]
4	hyper-atten*.mp. [mp=ti, ab, ot, nm, hw, kf, ps, rs, ui, an, sh, tn, dm, mf, dv, kw]
5	1 or 2 or 3 or 4
6	arter*.mp. [mp=ti, ab, ot, nm, hw, kf, ps, rs, ui, an, sh, tn, dm, mf, dv, kw]
7	vessel*.mp. [mp=ti, ab, ot, nm, hw, kf, ps, rs, ui, an, sh, tn, dm, mf, dv, kw]
8	vascula*.mp. [mp=ti, ab, ot, nm, hw, kf, ps, rs, ui, an, sh, tn, dm, mf, dv, kw]
9	6 or 7 or 8
10	5 and 9
11	hmcas.mp. [mp=ti, ab, ot, nm, hw, kf, ps, rs, ui, an, sh, tn, dm, mf, dv, kw]
12	10 or 11
13	angiogra*.mp. [mp=ti, ab, ot, nm, hw, kf, ps, rs, ui, an, sh, tn, dm, mf, dv, kw]
14	arteriogra*.mp. [mp=ti, ab, ot, nm, hw, kf, ps, rs, ui, an, sh, tn, dm, mf, dv, kw]
15	cta.mp. [mp=ti, ab, ot, nm, hw, kf, ps, rs, ui, an, sh, tn, dm, mf, dv, kw]
16	mra.mp. [mp=ti, ab, ot, nm, hw, kf, ps, rs, ui, an, sh, tn, dm, mf, dv, kw]
17	13 or 14 or 15 or 16
18	12 and 17

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

Essential	**Desirable**
Description of patient selection process	Prospective with sequential patients Randomized Inclusion/exclusion criteria provided
Image acquisition details provided	Scanner used (manufacturer and model, number of detector rows) Scan parameters (especially slice thickness) Time from stroke onset to imaging Time from non-contrast CT to angiography
Description of image analysis	Details of those analysing images Blinded to clinical details and treatment allocation (if any) Reproducibility data provided Hyperdense Artery Sign defined using previously described criteria

Table III. Baseline clinical and imaging characteristics and six-month outcome for IST-3 patients with and without pre-randomization angiography

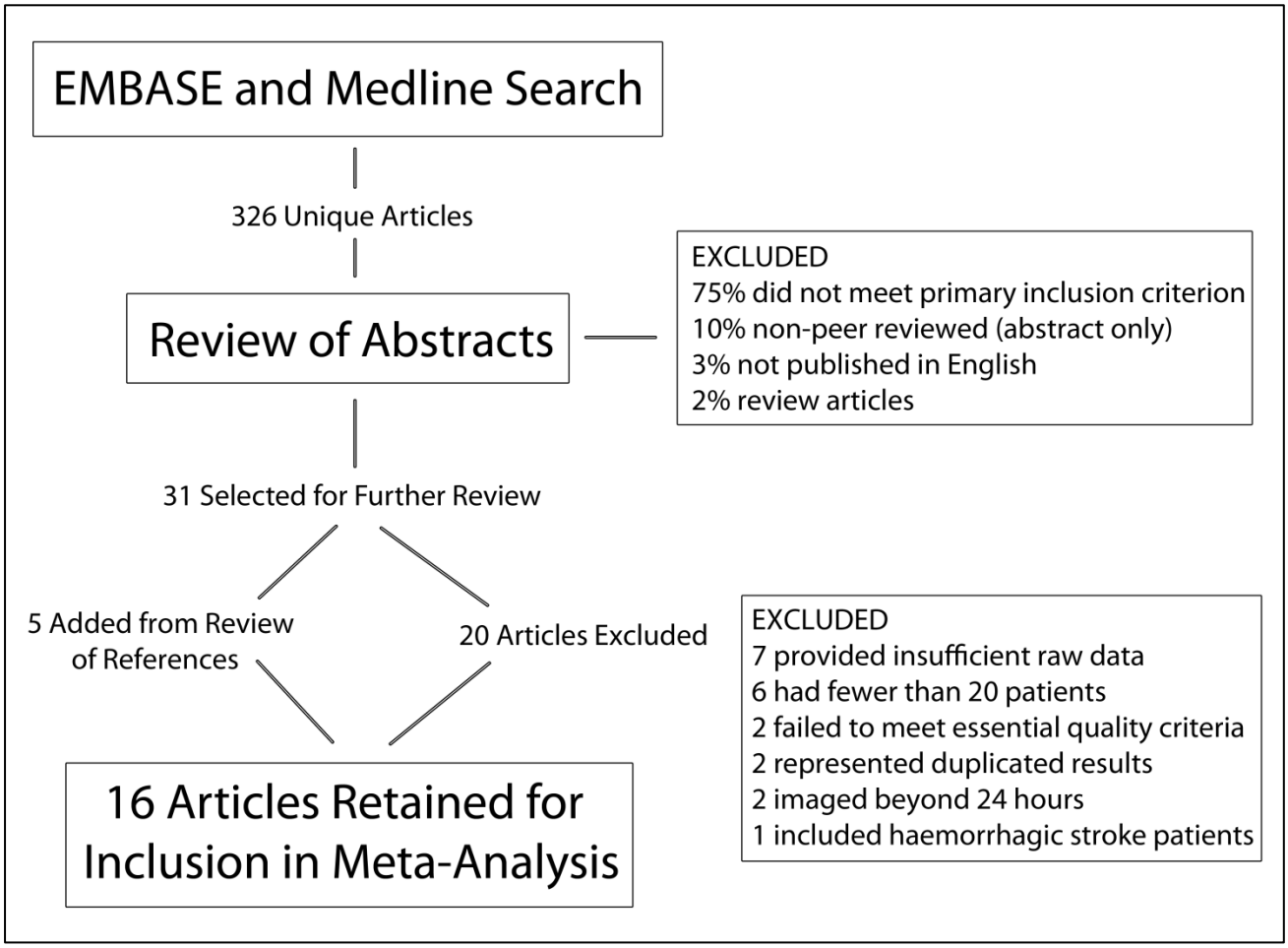
	IST-3 Patients with Baseline CT or MR Angiography n = 273	**Entire IST-3 Group n=3035**	**p-value for Difference**
Age (median, IQR)	81 years (71-86)	81 years (72-86)	0.815
Male Sex	120 (44.0%)	1465 (48.3%)	0.135
NIHSS (median, IQR)	10 (5-17)	11 (6-17)	0.020
Hyperdense Artery	69 (25.3%)	716/2961 (24.2%)*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

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



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, 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 (Dandyred 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
Independent chairmen: Colin Baigent (University of Oxford, UK); David Chadwick (University of Liverpool, UK). Independent member: Pippa Tyrrell (University of Manchester, UK); Gordon Lowe (University of Glasgow, UK). Co-principal investigators: PS; RIL. Chief investigator for Neuroradiology: JMW; Martin Dennis (University of Edinburgh, Scotland). Statistician: Geoff Cohen (University of Edinburgh, Scotland). Trial Co-ordinator: Karen Innes (University of Edinburgh, Scotland). Lay representative: Heather Goodare.

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,

Warsaw, Poland). Portugal: Manuel Correia (Hospital Geral de Santo Antonio, Porto). Switzerland: Phillippe Lyrer (University Hospital Basel, Basel,), Stefan Engelter. Sweden: Veronica Murray (Karolinska Institutet, Stockholm), Andreas Terent, Bo Norrving, Per Wester: UK: Graham Venables (Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK).

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 Procaccianti
Ospedale Valduce di Como	Dr Nicoletta Checcarelli
Universita degli Studi di Genova, Dipartimento di Neuroscienze Oftalmologia 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,	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	Prof Anthony Rudd
Hammersmith Hospitals & Imperial College	Dr Pankaj Sharma
King's College Hospital	Professor Lalit Kalra
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 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.