
Article:
Pickering, A., Harnan, S., Cooper, K. et al. (3 more authors) (2016) Acute ischaemic stroke patients - direct admission to a specialist centre or initial treatment in a local hospital? A systematic review. Journal of Health Services Research and Policy, 21 (1). pp. 51-60. ISSN 1355-8196

https://doi.org/10.1177/1355819615586006

Acute ischemic stroke patients - direct transfer to a specialist centre or initial delivery to the local hospital? A systematic review

A. Pickering, S. Harnan, K. Cooper, A. Sutton, S. Mason, J Nicholl.

Keywords: Stroke, thrombolysis, systematic review

MeSH Subject codes: [44], [54], [100]

Corresponding author:

Alastair Pickering, Honorary Senior Clinical Lecturer in Emergency Medicine
A.Pickering@sheffield.ac.uk
Department of Health Services Research, School of Health And Related Research, University of Sheffield, Regent Court, 30 Regent Street, Sheffield, S1 4DA

Authors: (one common address)

S. Harnan, Research Fellow
K. Cooper, Research Fellow
A. Sutton, Information Specialist
S. Mason, Professor of Emergency Medicine
J Nicholl, Dean

School of Health And Related Research, University of Sheffield, Regent Court, 30 Regent Street, Sheffield, S1 4DA

The Authors declare that there is no conflict of interest.

Abstract

Objectives

To assess the clinical effectiveness, in acute ischemic stroke patients, of bypassing non-specialist centres in preference for a specialist stroke centre to receive the time critical intervention of thrombolysis.

Methods

Systematic review and meta-analysis using: MEDLINE; MEDLINE In-Process; EMBASE; CINAHL; Cochrane Library including Cochrane Database of Systematic Reviews, Cochrane CENTRAL Controlled Trials Register, DARE, NHS EED and HTA databases. Studies were included if they compared acute ischaemic stroke patients directly triaged to a Specialist Centre (SC) versus those initially triaged to a Non Specialist Centre (NSC) with some or all later transferred to a SC. Studies were excluded if they compared patients ever treated in a SC versus those never treated in a SC, since the aim was to assess the optimum initial triage route rather than the optimum location for overall management. The assumption being, based on previous research, that management in a SC leads to better patient outcomes.

Results

Fourteen studies investigating 2,790 patients were identified. Studies comparing commencement of thrombolysis in non-specialist centres versus the specialist centres (n=1394) showed no significant difference in unadjusted mortality (OR=0.89; 95% CI=0.61 to 1.30) or morbidity (favorable modified Rankin Score, N=899) (OR=1.16; 95% CI=0.85 to 1.59) among thrombolysed patients. In studies where thrombolysis could only be administered in a specialist centre, data for patients arriving within the therapeutic window (N=140) revealed significantly higher mortality for those initially admitted to a non-specialist centre compared to directly admitted to a specialist centre (OR=6.62; 95% CI=2.60 to 16.82); morbidity data also favored direct admission to a specialist centre, although not consistently.

Conclusions

For ischaemic stroke patients, the location of initial thrombolysis treatment does not affect outcomes. However, if thrombolysis is only available at a specialist centre, outcomes are considerably better for those patients admitted directly. However, these conclusions are based on poor quality data with small sample populations, significant heterogeneity and subject to confounding.

Introduction

In two reports for the UK Department of Health, the argument is made for the development of specialist stroke units to which stroke patients are transferred directly by the ambulance service to receive their care.[1;2] The background to this is the increasing body of evidence for early interventional therapy, predominantly thrombolysis,[3-5] and the coordinated care during rehabilitation that specialist units are able to provide. Outcomes from such services are consistently better than those reported for conventional medical ward treatment.[6]

In the National Institute for Health and Clinical Excellence (NICE) guidelines[7] the benefits of early management at 'acute' stroke units were supported by the expert panel consensus opinion. These guidelines concluded with a recommendation that all people with suspected stroke should be admitted directly to a specialist centre (SC) following initial assessment either from the community or emergency department. They also concluded that CT scans performed as early as possible provided the most cost-effective management strategy. With these conclusions and evidence that thrombolysis within 90 minutes is better than beyond this time,[5] one option to improve outcomes may be the administration of thrombolysis in the local emergency department, prior to subsequent appropriate transfer to a regional specialist centre.

The 2009 Cochrane review on thrombolysis[4] concluded that further trials were needed to identify the environment in which thrombolysis may best be given in routine practice. The key factor in improving outcomes in the initial phase of care appears to be the ability to deliver thrombolysis, but there is conflicting evidence about where it should be delivered to achieve the best outcomes. The latest stroke guidelines from the Royal College of Physicians[8] recommends the commissioning of services to deliver all acute stroke patients to a specialised hyper-acute stroke unit. This should be done within one hour but the guidelines accept that "Emergency medical staff, if appropriately trained and supported, can administer alteplase for the treatment of acute ischaemic stroke provided that patients can be managed within an acute service with appropriate neuro-radiological and stroke physician support."

A systematic review was undertaken to assess the clinical effectiveness, in acute ischaemic stroke patients, of choosing to bypass a local non-specialist hospital in preference for a specialist stroke centre to receive the time-critical intervention of thrombolysis. Throughout this review the evidence-based assumption that care within a specialist stroke centre leads to better outcomes for stroke patients has been made.

Methods

A systematic review was undertaken according to the general principles recommended in the PRISMA statement[9] (Appendix I).

Search strategy

The following databases were searched: MEDLINE; MEDLINE In-Process; EMBASE; CINAHL; Cochrane Library including Cochrane Database of Systematic Reviews, Cochrane CENTRAL Controlled Trials Register, DARE, NHS EED and HTA databases. Searches were undertaken between August and December 2010, and updated in December 2012 following recommendations from peer review of a previously submitted article and report. An initial search was conducted, and inspection of retrieved articles generated further relevant search terms that were used in an additional search. The search was limited to articles published in English from 1988 onwards, due to changes in organization of emergency care over time. The Search Strategies are included as Appendix II.

A title and initial abstract sift were undertaken by two reviewers (SH/KC), with involvement of a third reviewer where necessary (AP). Potentially relevant articles were then fully screened by two reviewers (SH/KC) and any uncertainties resolved through discussion with a third reviewer (AP). Data were extracted by one reviewer and checked by a second.

Inclusion criteria

Patients presenting with ischemic stroke were included because its management has a time-critical element (administration of thrombolytic therapy).[5;10] Studies of haemorrhagic stroke were excluded since its management does not have such a clear time-critical treatment strategy. The intervention assessed was a policy of direct triage to a SC bypassing local hospitals. The comparator was initial admission to a non-specialist centre (NSC) such as a local hospital, with potential for later transfer to a SC if indicated due to the condition and severity. Studies where transfer was not possible were excluded.

Relevant outcomes included mortality and morbidity based on validated measures. The review protocol specified the outcome of mortality measured at three time points: prehospital, 7 and 30 days postevent. In a change to the protocol, due to lack of available data at the prespecified time points, mortality was included at any time point, and these data are represented in the forest plots included. The two morbidity scales used were the modified Rankin Scale (mRS)[11] and the National Institute for Health Stroke Scale (NIHSS) [12] as these were the most commonly reported in the literature. The mRS is an ordinal scale that categorises patients from 0 (no symptoms) to 6 (dead) with 1-5 being different levels of function and independence. The NIHSS scale was developed to grade stroke severity with lower scores representing less severe disease. Time to thrombolysis has been included where the data was able to be extracted.

Studies were included if they compared patients directly triaged to a SC versus those initially triaged to a NSC with some or all later transferred to a SC. Studies were excluded if they compared patients ever treated in a SC versus those never treated in a SC, since the aim was to assess the optimum initial triage route rather than the optimum location for overall management. Studies where the pathway of care was uncertain were considered at full-text review and excluded if no data could be extracted to contribute to the analysis based on consensus opinion of all reviewers.

Data synthesis

Data were meta-analysed using Review Manager version 5.0.[13] Random effects models were used where clinical, methodological or statistical heterogeneity[14] existed between studies. Clinical heterogeneity existed where studies evaluated different components of the care pathway or different patient groups within their potential cohort. Where random effects models were not used the results are presented by subgrouping similar studies. Data were converted so all odds ratios (ORs) compared initial triage to NSCs versus direct admission to SCs; similarly, ORs for survival were converted to mortality. Hence for the presented mortality data a higher OR favours direct admission to SCs, whilst for morbidity data (reporting on favourable outcomes) a lower OR favours SCs.

Risk of bias assessment

Risk of bias within included studies was assessed using criteria developed for this review, based on the Cochrane Handbook,[14] the Critical Appraisal Skills Programme (CASP) checklist for cohort studies,[15] the Downs & Black checklist for study quality,[16] and the Newcastle-Ottowa scale.[17] Criteria that assessed potential for bias in study design, rather than quality of reporting, were selected. No criteria are reported here relating to validity of outcome measures (since this review used prespecified, standard outcomes such as mortality and validated morbidity measures) or to blinding as the primary outcome was mortality. However, the subjective nature of the morbidity tools used would warrant an assessment of blinding and this is expanded upon in 'Results' section.

The selected criteria covered four key areas:

1. **Comparability between groups:** Risk of bias due to the lack of inclusion of, or adjustment for, NSC patients not transferred to SC.
2. **Adjustment:** Risk of bias due to lack of adjustment of analyses for differences in age and severity between groups.

3. **Representative sample:** Risk of bias due to selection of patients based on condition subtype or interventions received.

4. **Exclusions:** Risk of bias due to more than 5% patients excluded due to missing data.

Results

Studies included

The review identified fourteen relevant studies (within 15 references).[18-32] (Study characteristics – Appendix III). Only controlled cohort studies were identified. Seven studies were conducted in the USA,[18;20;22-24;28;32] one in Taiwan,[29] and five in Europe (three in Spain,[26;27;30] one in Germany[31] and one in France[21]). The country was not reported in one study. [19] Two pairs of studies appeared to have overlapping cohorts. Silva 2009[22] recruited patients at the same time as Pervez 2010,[20] partly in the same hospital, but for fewer years and has only been used in synthesis where outcomes were not reported for the larger cohort in Pervez 2010.[20] Similarly, Ribo 2008[27] recruited patients at the same time as Perez de la Ossa 2009[26] and from the same region, but for fewer years and has only been used in synthesis where outcomes were not reported by Perez de la Ossa 2009.

Study size ranged from 39 to 602 patients with a total of 2790 across all studies. SCs were described as stroke centres, stroke units or neurological units. NSCs were generally described as other hospitals or community hospitals, with some studies specifying that no specific stroke care was available.

Eleven of the included studies were restricted to patients receiving thrombolysis, therefore did not capture effects on outcomes of differing thrombolysis rates between groups, which could be affected by the initial triage decision should the transfer take patients beyond the therapeutic window. The remaining three studies were not restricted to patients receiving thrombolysis but thrombolysis was only available for transfer patients at the SC if at all. The time to outcome

assessment for both mortality and morbidity data varied greatly, ranging from in-hospital to one year. These are embedded within the forest plots, listed next to each study author.

Risk of bias

Risk of bias in included studies is summarised in Appendix IV. All included studies compared patients transferred from NSC to SC versus those directly triaged to SC. No studies included or accounted for NSC patients who were not transferred to SC. Three studies adjusted at least one of their analyses for patient factors such as age and severity of injury, while the remainder were unadjusted. The between-group difference in baseline NIHSS varied across studies, sometimes being higher in transferred patients and sometimes in patients triaged direct to SC (Appendix III). The number of exclusions due to missing data was unclear for four studies while the remainder appeared to have no exclusions, although it was often unclear whether only patients with available data were included.

All studies evaluated a selected subgroup of patients; no included studies assessed all ischaemic stroke patients. Studies were sub-grouped in terms of where thrombolysis was initiated for transfer patients, as described earlier.

None of the prospective studies reported any blinding of outcome assessments to the method of delivery to the SC. The other studies were all retrospective with no reported consideration of blinding.

Studies initiating thrombolysis in NSC prior to transfer (thrombolysed patients only)

In seven studies restricted to thrombolysed patients only, transfer patients received thrombolysis in the NSC prior to transfer to the SC and were compared with patients taken directly to the SC for thrombolysis.[18-23;32] Two studies had a likely overlap of included patients so only the most recent is

included in each analysis.[20;22] In one further study (two references) 50% of transfer patients received thrombolysis in the SC and 50% in the NSC.[24;25]

Four studies reported unadjusted mortality data (total N=1,394; Figure 1) showing no significant difference in the individual studies or the pooled analysis for initial triage to NSC vs. SC (OR 0.89, 95% CI 0.61 to 1.30), with no heterogeneity between studies (I^2=0%).[18;20;21;32] A further study (N=220) in which transfer patients could receive thrombolysis in either the NSC or SC also showed no significant difference in mortality (OR 1.11, 95% CI 0.48 to 2.53).[24;25]

Five studies reported data on the proportion of patients with a favourable modified Rankin Scale (mRS) the definition of which differed between studies, as did the time of outcome assessment. There was no significant difference between groups for one study adjusting for baseline characteristics (N=296; OR 0.92, 95% CI 0.65 to 1.30; Figure 2)[20] or for four studies presenting unadjusted analyses (total N=899; pooled OR 1.16, 95% CI 0.85 to 1.59; Figure 3).[19;21;22;32]

One study reported similar reductions in mean National Institute of Health Stroke Scale (NIHSS) score at follow-up in the two groups.[23] Two studies, one in which transfer patients began thrombolysis in NSC and one in which transfer patients could receive thrombolysis in either the NSC or SC showed no significant difference between groups for the (unadjusted) proportion of patients with favourable NIHSS (score 0-5) at follow-up (Figure 4). Comparisons for transfer vs. direct triage to SC were OR 1.04 (95% CI 0.63 to 1.70, N=396) [32]and OR 1.21 (95% CI 0.67 to 2.19, N=220) [24;25]

Of the six studies reporting this outcome, three reported longer times to thrombolysis in the transfer group, [20;24;25;32] while three reported longer times in the direct-to-SC group (Table 1).[19;21;23]

Studies initiating thrombolysis in SC after transfer (thrombolysed patients only)

In three studies restricted to thrombolysed patients only, transfer patients began thrombolysis after transfer from NSC to SC; these were compared with patients triaged directly to the SC and receiving thrombolysis there.[26-28] Two studies had a likely overlap of included patients so only the most recent is included in each analysis.[26;27]

One study (N=72; Figure 1) showed no significant difference in (unadjusted) mortality for patients receiving thrombolysis after transfer vs. direct triage to SC; the small number of events in this study precludes firm conclusions (OR 0.68, 95% CI 0.13 to 3.67).[28]

One study reported data on the proportion of patients with favourable mRS. This study significantly favoured direct triage to SC when adjusting for baseline characteristics. (N=153, OR 0.40, 95% CI 0.17 to 0.94; Figure 2)[26] and showed a non-significant trend in this direction for the unadjusted analysis (N=153; OR 0.70, 95% CI 0.35 to 1.41, Figure 3)

Two studies reported unadjusted data on the proportion of patients with favourable or improved NIHSS (score 0-1 or improvement of 4 points) at follow-up. A meta-analysis of these two studies (total N=225; Figure 4) favoured direct triage to SC, though this was not statistically significant (OR 0.62, 95% CI 0.23 to 1.67).[26;28]

Two studies reported longer times from onset to thrombolysis in the transfer groups than in the direct-to-SC groups (Table 1).[26;28]

Studies initiating thrombolysis in SC after transfer (thrombolysed and non-thrombolysed patients)

Three studies did not restrict recruitment to patients receiving thrombolysis. Of these, two included only patients arriving at the SC within the time window for thrombolysis (within 4-6 hours of onset

as defined by study protocol); the proportions receiving thrombolysis were 12% (12/101) overall in one study (not reported per group)[29] with 27% (30/112) for transfers and 54% (31/57) for direct-to-SC in the other study.[30] The remaining study was restricted to patients with basilar artery occlusion, of whom 44% (7/16) of transfers and 48% (11/23) of those going direct to SC received thrombolysis.[31] In all three studies, transfer patients only received thrombolysis at the SC if at all (not at the NSC).

Two studies reported (unadjusted) mortality (total N=140; Figure 1); both significantly favoured direct triage to SC, with a pooled OR for mortality for transfers versus direct triage of 6.62 (95% CI 2.60 to 16.82).[29;31]

Two studies presented data on the proportion of patients with favourable mRS again with different definitions and time of assessment. One study adjusting for baseline characteristics favoured direct triage to SC (N=169; OR 0.34, 95% CI 0.15 to 0.77; Figure 2).[30] In unadjusted analyses, this study no longer showed a significant effect,[30] while the other study[31] significantly favoured direct triage to SC. Pooled analysis of these studies showed a non-significant trend favouring direct triage (total N=208; OR 0.29, 95% CI 0.02 to 4.28; Figure 3).

One study presenting data on the (unadjusted) proportion of patients with favourable or improved NIHSS (score 0-1 or improvement of 4 points) at follow-up significantly favoured direct triage to SC (N=169; OR 0.38, 95% CI 0.20 to 0.74; Figure 4).[30]

One study reported time from onset to thrombolysis, showing a longer time in the transfer group than in the direct-to-SC group (Table 1).[30]

Discussion

Principal findings

In studies where transfer patients were able to begin thrombolysis in a non-specialist centre (NSC) prior to transfer, mortality rates were no different to those patients triaged directly to the specialist centre (SC). There was also no difference in the proportion of patients with favourable morbidity outcomes at follow-up. These findings suggest that commencing thrombolysis for eligible patients in a local NSC can be as effective as if delivered in a regional SC within the context of the limitations identified below.

Studies in which transfer patients only began thrombolysis after transfer from NSC to SC can be divided into studies restricted to thrombolysed patients only and studies assessing all stroke patients. In both, outcomes (mortality, follow-up mRS and NIHSS scores) were generally better for patients triaged direct to SC; this was statistically significant in three analyses.

Strengths and weaknesses of this study

We focused on thrombolysis, a validated treatment available for long enough to generate sufficient evidence to enable analysis. It is recognised that there are more interventional treatments available and being developed for the management of acute stroke, many only available in specialist stroke centres.

Only three of the fourteen studies identified adjusted for age, co-morbidities or severity and these were only for morbidity data. The lack of adjustment could significantly influence outcome comparisons – in particular mortality rates – as the lack of transfer decision randomization introduces the potential for both selection and allocation bias leading to significant differences between the NSC and SC groups. Most studies were restricted to thrombolysed patients and have not captured differences in outcome due to thrombolysis rate variability. Only one study reported

this data and described a two-fold treatment rate difference,[30] which could significantly affect between-group comparison of outcomes. The higher treatment rate identified in the direct group could be considered an outcome in itself but the study does not report the number of patients delivered to the NSC who may have been eligible for treatment if taken directly to the SC.

Implications for policy

The poor quality of data identified highlights the lack of evidence available to support the current consensus recommendations for direct transfer of all suspected stroke patients to a specialist acute stroke unit.[8] However, the idea suggested from our results that delivery of all stroke patients to the nearest NSC is as effective as direct transfer to the SC cannot be supported. The restricted cohorts identified for this review limit the generalisability of our findings and, as such, must be interpreted with caution. This review found no evidence to contradict the current guidelines for the commissioning of stroke services in England. [8]

Future research

The studies identified for this review do not include a comprehensive enough cohort of patients to justify any clear conclusions, with questions remaining about the outcomes for non-thrombolysed patients in either arm, the impact of triage decisions on treatment rates in appropriate patients and the relevance of the time frame for outcome assessments.

When assessing the impact of an early intervention, such as triage to the most appropriate centre, the earlier the outcome is assessed the less likely that confounding factors can influence results. Future research should focus on a whole system approach, from the point of symptom onset, and include all suspected stroke patients managed within a network of receiving centres. In our review half of the included studies (n=7) mentioned telephone and/or telemedicine contact between NSC and SC which may have facilitated the initiation of treatment prior to SC arrival. Future work should also include both short and long-term outcomes in order to differentiate the benefit of correct

triage decisions from the recognised benefits of early, focused rehabilitation and high quality multidisciplinary care delivered in a specialist stroke centre.

Sources of funding

This project was funded by the National Institute for Health Research Service Delivery and Organisation (NIHR SDO) programme (project number 09/1001/037). Visit the SDO programme website for more information. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the SDO programme, NIHR, NHS or the Department of Health.

The Authors declare that there is no conflict of interest

All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

Contributorship statement

JN conceived the idea for the study and oversaw its running; SM assisted AP in the clinical aspects of the study and overall coordination; KC, AS & SH performed the literature searches, systematic review and meta-analysis; All authors listed made significant contributions to the final report and drafting of the article

Reference List

(1) Boyle R. Mending Hearts and Brains: Clinical case for change. 2006. London, Department of Health. 2006.

(2) Darzi L. High Quality Care for All: NHS Next Stage Review. Department of Health, editor. 2008. London, Department of Health.

(3) Hacke W, Kaste M, Bluhmki E, et al. Thrombolysis with Alteplase 3 to 4.5 Hours after Acute Ischemic Stroke. N Engl J Med 2008; 359(13).

(4) Wardlaw JM, Murray V, Berge E, et al. Thrombolysis for acute ischaemic stroke. Cochrane Database of Systematic Reviews. 4. 2009. The Cochrane Collaboration. John Wiley & Sons, Ltd.

(5) Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. The Lancet 2004; 363(9411).

(6) Stroke Unit Trialists' Collaboration. Organised inpatient (stroke unit) care for stroke. Cochrane Database of Systematic Reviews. 4. 2007. The Cochrane Collaboration. John Wiley & Sons, Ltd.

(7) National Institute for Health and Clinical Excellence. Alteplase for the treatment of acute ischaemic stroke. 2007. London, National Institute for Health and Clinical Excellence. 20-10-2011.

(8) Intercollegiate Stroke Working Party. National Clinical Guidelines for Stroke. 4th Edition. 2012. London, Royal College of Physicians.

(9) Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009; 151(4):264-9, W64.

(10) Lees KR, Bluhmki E, von KR, et al. Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. Lancet 2010; 375(9727):1695-1703.

(11) Farrell B, Godwin J, Richards S, et al. The United Kingdom transient ischaemic attack (UK-TIA) aspirin trial: final results. Journal of Neurology, Neurosurgery & Psychiatry 1991; 54(12):1044-1054.

(12) Brott T, Adams HP, Olinger CP, et al. Measurements of acute cerebral infarction: a clinical examination scale. Stroke (00392499) 1989; 20(7):864-870.

(13) Review Manager (RevMan) [Computer program]. Version 5.0. 2008. Copenhagen, The Nordic Cochrane Centre, The Cochrane Collaboration.

(14) Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions. Available from www.cochrane-handbook.org. 2011. The Cochrane Collaboration.

(15) Critical Appraisal Skills Programme (CASP). Critical appraisal checklist for cohort studies. Available from /www.casp-uk.net. 2011.

(16) Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health 1998; 52(6):377-384.

(17) Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottowa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Available from: www.ohri.ca/programs/clinical_epidemiology/oxford.asp. 2011. Oxford.

(18) Rodriguez G, Chaudhry S, Suri MF, et al. Outcomes of "drip-and-ship" paradigm among patients with acute ischemic stroke. Results of a state wide study. Neurology Conference: 64th American Academy of Neurology Annual Meeting New Orleans, LA United States Conference Start: 20120421 Conference End: 20120428 Conference Publication: (var pagings) 2012; 78(1 Meeting Abstract):22.

(19) Hsia AW, Benson RT, Pehlivanova M, et al. Evaluation of patients treated with IV tPA At regional stroke centers vs. community hospitals: Is there opportunity for a wider stroke population to be treated? Stroke Conference: 2011 International Stroke Conference Los Angeles, CA United States Conference Start: 20110209 Conference End: 20110211 Conference Publication: (var pagings) 2011; 42(3):01.

(20) Pervez MA, Silva G, Masrur S, et al. Remote supervision of IV-tPA for acute ischemic stroke by telemedicine or telephone before transfer to a regional stroke center is feasible and safe. Stroke (00392499) 2010; 41(1):e18-e24.

(21) Allibert R, Medeiros de Bustos E, Montiel P, et al. Cerebrovascular Diseases 2009; 27(Suppl 6):177.

(22) Silva GS, Lima F, Camargo EC, et al. Starting IV t-PA infusions for acute ischemic stroke at community hospitals prior to transfer to a regional stroke center is feasible and safe. Stroke (00392499) 2009; 40(4):e162 Abstract P41.

(23) Wang DZ, Rose JA, Honings DS, et al. Treating acute stroke patients with intravenous tPA. The OSF stroke network experience. Stroke (00392499) 2000; 31(1):77-81.

(24) Rymer MM, Thrutchley DE, Stroke Team at the Mid America Brain and Stroke Institute. Organizing regional networks to increase acute stroke intervention. [Review] [35 refs]. Neurological Research 2005; 27(Suppl 1):S9-S16.

(25) Rymer MM, Thrutchley DE, Thrutchley H. Community hospitals initiate thrombolytic therapy safely with good outcomes. Stroke (00392499) 2004; 35(1):291 (Abstract P198).

(26) Perez de la Ossa N, Millan M, Arenillas JF, et al. Influence of direct admission to Comprehensive Stroke Centers on the outcome of acute stroke patients treated with intravenous thrombolysis. Journal of Neurology 2009; 256(8):1270-1276.

(27) Ribo M, Molina CA, Pedragosa A, Sanclemente C, et al. Geographic differences in acute stroke care in Catalunya: impact of a regional interhospital network. Cerebrovascular Diseases 2008; 26(3):284-288.

(28) Merino JG, Silver B, Wong E, et al. Extending tissue plasminogen activator use to community and rural stroke patients. Stroke (00392499) 2002; 33(1):141-146.

(29) Li CH, Khor GT, Chen CH, et al. Potential risk and protective factors for in-hospital mortality in hyperacute ischemic stroke patients. Kaohsiung Journal of Medical Sciences 2008; 24(4):190-196.

(30) Perez de la Ossa N, Sanchez-Ojanguren J, Palomeras E, et al. Influence of the stroke code activation source on the outcome of acute ischemic stroke patients. Neurology 2008; 70(15):1238-1243.

(31) Muller R, Pfefferkorn T, Vatankhah B, et al. Admission facility is associated with outcome of basilar artery occlusion. Stroke (00392499) 2007; 38(4):1380-1383.

(32) Martin-Schild S, Morales MM, Khaja AM, et al. Is the drip-and-ship approach to delivering thrombolysis for acute ischemic stroke safe? Journal of Emergency Medicine 2011; 41(2):135-141.

Table 1. Time and distance data

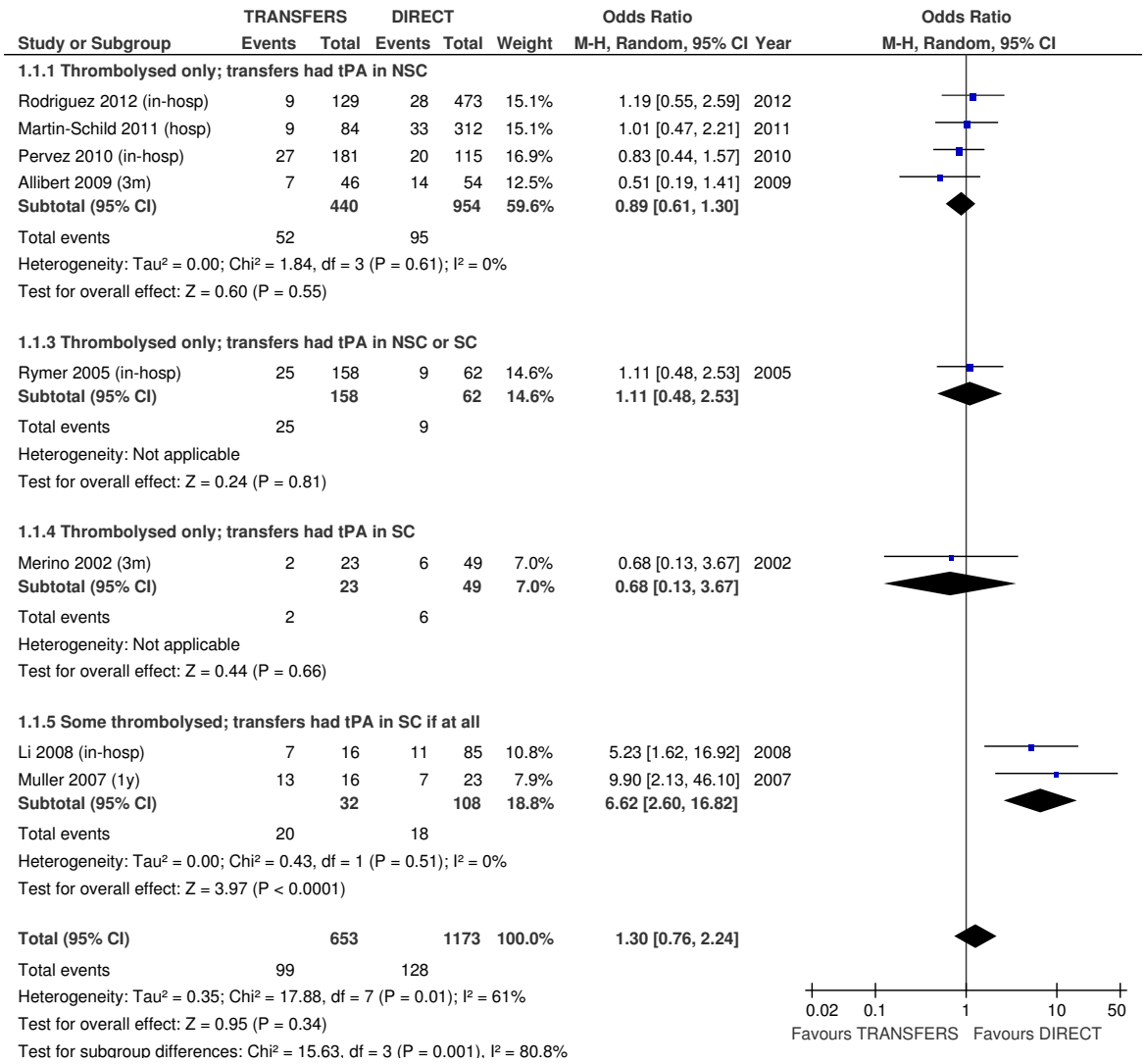
Study	Country (area)	Distances	Mean / median	Time from onset to thrombolysis (mins)		
				Transferred patients (B)	Direct to SC patients (A)	Difference: B minus A
Thrombolysed only (transfers had tPA in NSC)						
Rodriguez 2012[18]	USA (Minnesota)	NR		NR	NR	NR
Hsia 2011[19]	Country NR	NR	Mean (SD)	146 (39)	157 (24)	-11
Martin-Schild 2011[32]	USA (Houston, Texas)	Area covering more than 100 mile radius. Mean distance 77 (SD45) miles (includes patients with >3 hour treatment time)	Median (IQR)	150 (117-165)	135 (105-157)	15
Pervez 2010[20]	USA (Boston, Massachusetts)	Distance NSC to SC: median 43 miles (IQR 17-58)	Median (IQR)	140 (117-165)	130 (103-163)	10
Allibert 2009[21]	France (Besancon)	NR	Median	156	217	-61
Wang 2000[23]	USA (Illinois counties)	Network: 23 counties inc. small towns. Distance NSC to SC: range 0.25-130 miles	Mean (SD)	141 (52)	155 (53)	-14
Thrombolysed only (transfers had tPA in NSC or SC)						
Rymer 2005,[24] Rymer 2004[25]	USA (Kansas City, Missouri)	Metropolitan area. 150 miles maximum distance.	Mean (SD)	213 (117)	182 (110)	31
Thrombolysed only (transfers had tPA in SC)						
Perez de la Ossa 2009[26]	Spain (Barcelona)	Metropolitan area. 80km maximum distance.	Median (IQR)	165 (140-179)	135 (105-162)	30
Merino 2002[28]	USA (London, Ontario)	Area covers 7 counties over 7800 square miles. Distance NSC to SC: mean 41 miles (range 11-80)	Mean (range)	172 (135-203)	148 (69-191)	24
Some thrombolysed, arrived at SC within 4-6h of onset in 2 of 3 studies (transfers had tPA in SC if at all)						

Study	Country (area)	Distances	Mean / median	Time from onset to thrombolysis (mins)		
				Transferred patients (B)	Direct to SC patients (A)	Difference: B minus A
Li 2008[29]	Taiwan (Kaohsiung)	NR		NR		
Perez de la Ossa 2008[30]	Spain (Barcelona)	Metropolitan area. 80km maximum distance	Median (IQR)	165 (135-179)	125 (100-157)	40
Muller 2007[31]	Germany (Munich & Regensburgh)	NR		NR		

Abbreviations: IQR=interquartile range; NR=not reported; NSC=non-specialist centre; SC=specialist centre; SD=standard deviation; tPA=tissue plasminogen activator (thrombolysis).

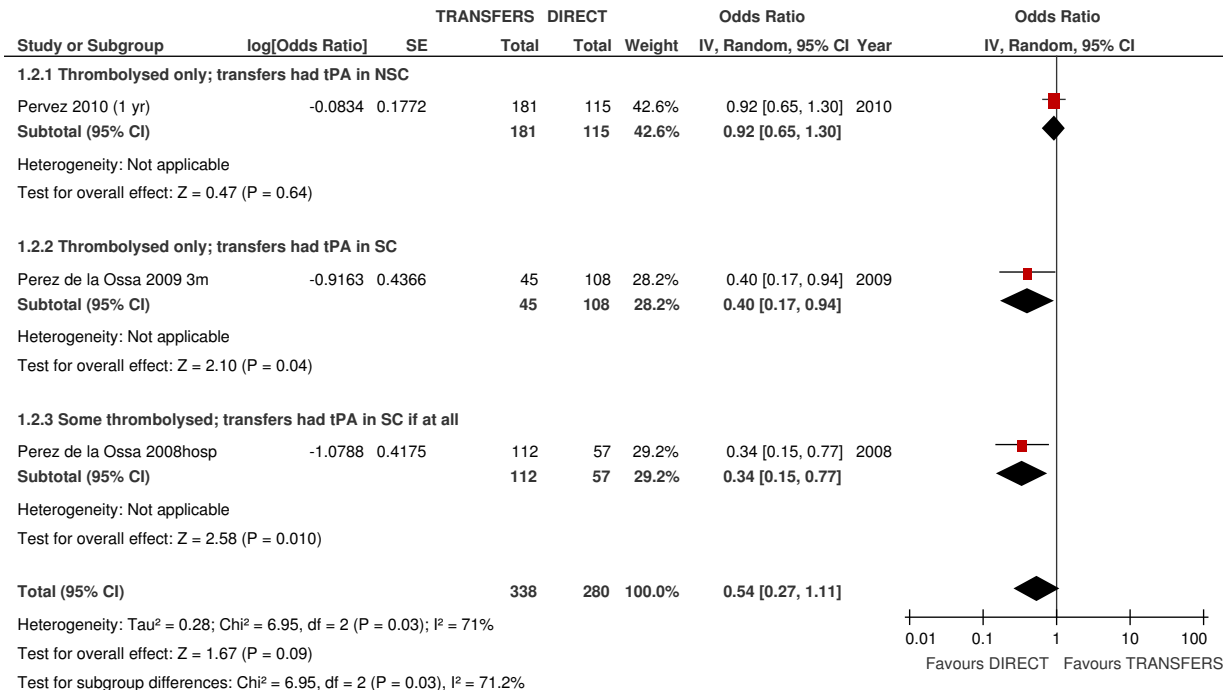
Definitions of study groups: A=direct to SC and remained there;; B=to NSC initially then transferred to SC.

Figure 1. Unadjusted mortality for transfer NSC to SC vs. direct to SC, sub-grouped by thrombolysis setting



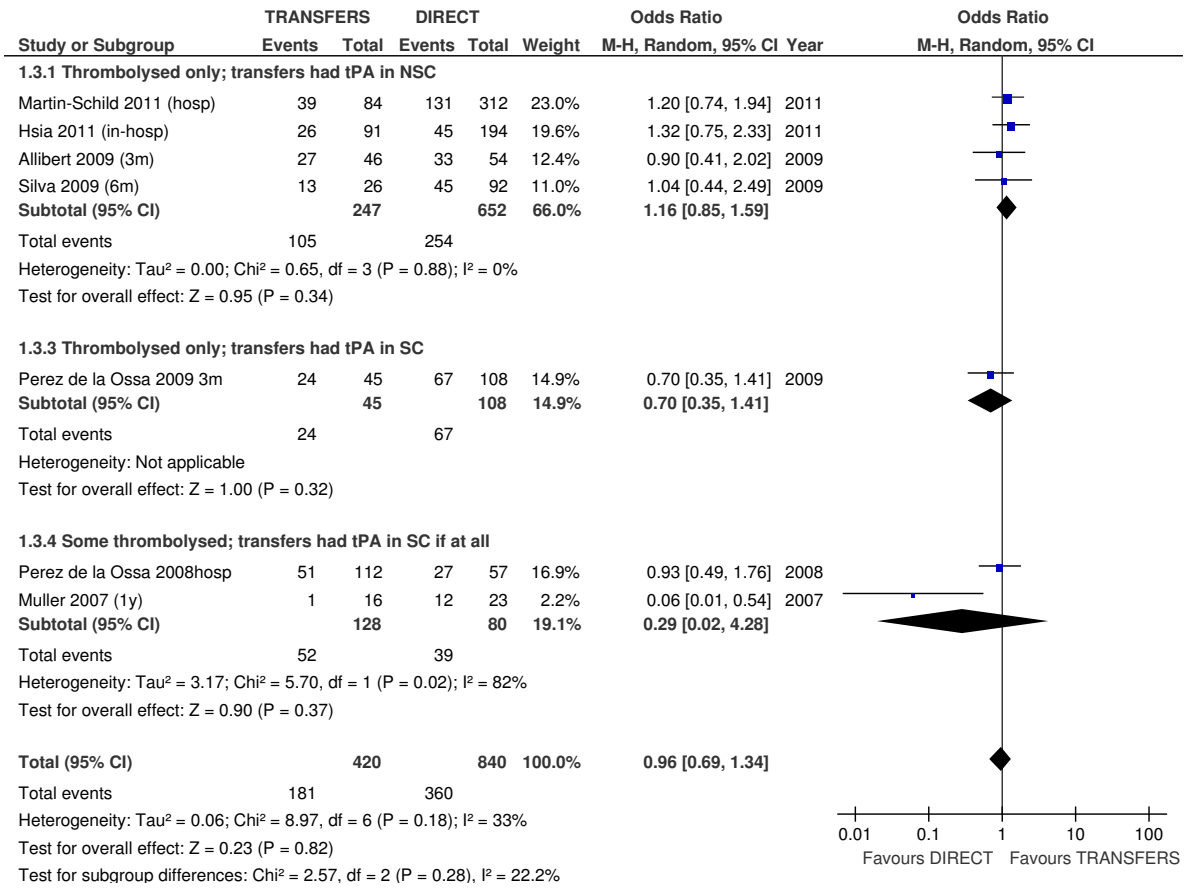
Time of outcome measurement is shown for each study following author/date.

Figure 2. Favourable mRS at follow-up (<1 or <2; adjusted analysis) for transfer NSC to SC vs. direct to SC



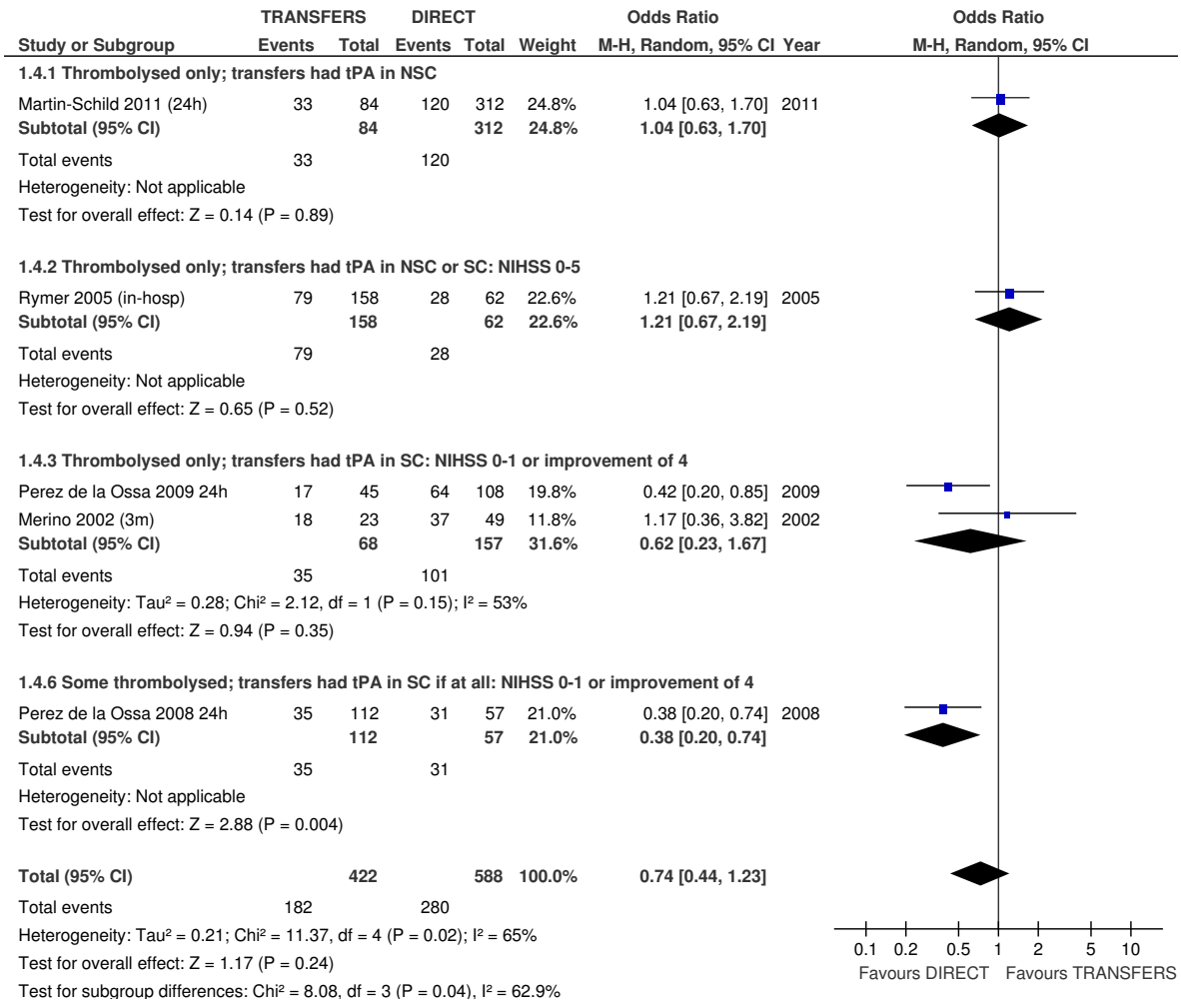
Time of outcome measurement is shown for each study following author/date.

Figure 3. Favourable mRS at follow-up (<1, <2 or <3; unadjusted analysis) for transfer NSC to SC vs. direct to SC



Time of outcome measurement is shown for each study following author/date.

Figure 4. Favourable or improved NIHSS at follow-up (unadjusted analysis) for transfer NSC to SC vs. direct to SC



Time of outcome measurement is shown for each study following author/date.

Appendix I: PRISMA checklist

Section/topic	Item No	Checklist item	Reported on page No
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both	1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable, background, objectives, data sources, study eligibility criteria, participants, interventions, study appraisal and synthesis methods, results, limitations, conclusions and implications of key findings, systematic review registration number	2
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS)	5
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (such as web address), and, if available, provide registration information including registration number	6
Eligibility criteria	6	Specify study characteristics (such as PICOS, length of follow-up) and report characteristics (such as years considered, language, publication status) used as criteria for eligibility, giving rationale	6
Information sources	7	Describe all information sources (such as databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated	Appendix II
Study selection	9	State the process for selecting studies (that is, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis)	5

Section/topic	Item No	Checklist item	Reported on page No
Data collection process	10	Describe method of data extraction from reports (such as piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators	5
Data items	11	List and define all variables for which data were sought (such as PICOS, funding sources) and any assumptions and simplifications made	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis	7
Summary measures	13	State the principal summary measures (such as risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (such as I^2 statistic) for each meta-analysis	7
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (such as publication bias, selective reporting within studies)	N/A
Additional analyses	16	Describe methods of additional analyses (such as sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified	7
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram	8
Study characteristics	18	For each study, present characteristics for which data were extracted (such as study size, PICOS, follow-up period) and provide the citations	Appendix III
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see item 12).	Appendix IV
Results of individual studies	20	For all outcomes considered (benefits or harms), present for each study (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot	Figures 1-4
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency	Figures 1-4

Section/topic	Item No	Checklist item	Reported on page No
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see item 15)	N/A
Additional analysis	23	Give results of additional analyses, if done (such as sensitivity or subgroup analyses, meta-regression) (see item 16)	Figures 1-4
Discussion			
Summary of evidence	24	Summarise the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (such as health care providers, users, and policy makers)	13
Limitations	25	Discuss limitations at study and outcome level (such as risk of bias), and at review level (such as incomplete retrieval of identified research, reporting bias)	13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research	14
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (such as supply of data) and role of funders for the systematic review	15

Appendix II: Literature search strategies

Due to the complex, multi-faceted nature of the research question, an iterative approach to the searches was taken. Below is an example of the initial search strategy (1.1) performed in MEDLINE. This was developed following a scoping search and using "snowballing" by consulting the indexing and keywords of key papers identified by experts. This initial MEDLINE search was adapted for the other electronic databases accordingly.

MEDLINE search strategies

Search 1.1: Initial search for clinical review

Key: $=truncation; */=medical subject heading.

1 (hospital$ adj bypass$).mp.

2 (direct adj1 transfer$).mp. [changed from (direct adj transfer$) following scoping search and analysis of papers identified by experts]

3 (bypass adj protocol$).mp.

4 *Trauma Centers/

5 trauma system$.ti,ab.

6 (trauma centre$ or trauma center$).ti.

7 (prehospital adj trauma adj triage).mp.

8 (tertiary adj trauma adj cent$).mp.

9 (pre-hospital adj trauma adj triage).mp.

10 (prehospital$ or pre-hospital$).ti.

11 (ambulance$ and triage).mp.

12 *Ambulances/

13 *Triage/

14 12 and 13

15 ((prehospital or pre-hospital) and triage and protocol$).mp. [Note that the keyword triage is used in conjunction with other terms such as pre-hospital and trauma (steps 6-14) as using triage as an individual term was considered too broad, adding an additional 964 references to the MEDLINE search alone. These were checked and considered not relevant.]

16 regionali?ation.ti,ab.

17 *Delayed Diagnosis/

18 "Transportation of Patients"/ae, ec [Removed *focusing of MeSH heading following scoping search and analysis of papers identified by experts]

19 "Transportation of Patients"/st, ut [Additional sub-headings added following scoping search and analysis of papers identified by experts]

20 Patient Transfer/ec, mt, og, st, ut, sn [Economics, Methods, Organization & Administration, Standards, Utilization] [Removed *focusing of MeSH heading in conjunction with subheadings following scoping search and analysis of papers identified by experts]

21 *Patient Transfer/ [Focused MeSH heading without subheadings following scoping search and analysis of papers identified by experts]

[Terms 1-21 identified in scoping of the literature and consultation with project team]

22 (interhospital transfer$ or inter-hospital transfer$ or IHT).ti,ab.

23 (direct adj1 (admitted or admission$)).ti,ab.

24 (trauma care system$ or rapid transfer$ or integrated transfer system$).ti,ab.

25 trauma care.ti. [Terms 22-25 all added following scoping search and analysis of papers identified by experts]

26 or/1-11

27 polytrauma.ti,ab.

28 multi-system trauma.ti,ab.

29 multisystem trauma.ti,ab.

30 major trauma.ti,ab.

31 severe trauma.ti,ab.

32 *Stroke/

33 stroke$.ti,ab.

34 *Cerebral Infarction/

35 cerebral infarc$.ti,ab.

36 cerebrovascular accident$.ti,ab.

37 CVA.ti,ab.

38 significant trauma.ti,ab.

39 important trauma.ti,ab.

40 *Craniocerebral Trauma/

41 head injur$.ti,ab.

42 craniocerebral trauma$.ti,ab.

43 *Brain Injuries/

44 brain injur$.ti,ab.

45 (intra-cranial adj (haemorrhage or hemorrhage or bleed)).ti,ab.

46 (intracranial adj (haemorrhage or hemorrhage or bleed)).ti,ab.

47 *Intracranial Hemorrhages/ or *Cerebral Hemorrhage/ or *Subarachnoid Hemorrhage/ [Condition terms 27-47 identified by scoping the literature and consultation with the project team]

48 *Hematoma, Epidural, Cranial/

49 severe emergenc$.ti,ab.

50 *Critical Care/sn [Statistics & Numerical Data]

51 or/14-24

52 26 or 51

53 severe traumatic injur$.ti,ab.

54 severe$ injur$.ti.

55 trauma patient$.ti.

56 critical$ ill$.ti. [Condition terms 48-56 added following scoping search and analysis of papers identified by experts]

57 or/53-56

58 Multiple Trauma/ec, th [Economics, Therapy]

59 *Multiple Trauma/

60 or/27-50

61 or/58-59

62 57 or 60 or 61

63 52 and 62

64 limit 63 to yr="1988 - 2010" [Note that no limitations by study type were applied to the search, the aim was to identify all literature]

Search 1.2: Additional search for clinical review

An additional search was conducted following inspection of the retrieved articles from the initial search (1.1) and identification of further search terms (snowballing).

1 trauma system$.tw. [Term utilized from Search 1.1, extended to .tw (Text Word) from .ti,ab (Title or Abstract). NB Text Word searches all of the fields which contain text words and which are appropriate for a subject search.]

2 trauma cent$.tw. [Term utilized from Search 1.1, extended to .tw (Text Word) from .ti (Title)]

3 Trauma Centers/ [MesH expanded from Search 1.1 by removing *Focus]

4 1 or 2 or 3

5 non trauma cent$.tw.

6 nontrauma cent$.tw.

7 (without adj2 trauma cent$).tw.

8 (no adj2 trauma cent$).tw.

9 non trauma system$.tw.

10 nontrauma system$.tw.

11 (without adj2 trauma system$).tw.

12 (no adj2 trauma system$).tw.

13 Major Trauma Outcome Study.tw.

14 MTOS.tw.

15 Trauma Injury Severity Score.tw.

16 TRISS.tw.

17 (Trauma Audit and Research Network).tw.

18 TARN.tw. [Terms 5-18 added following analysis of references retrieved from initial search]

19 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18

20 4 and 19

21 (sever$ adj3 injur$).tw. [Term extended from Search 1.1 by adding truncation ADJ operator and .tw (Text Word) instead of .ti (Title)]

22 (sever$ adj3 trauma$).tw. [Term extended from Search 1.1 by adding truncation ADJ operator and .tw (Text Word) instead of .ti (Title)]

23 (serious$ adj3 injur$).tw.

24 ISS.tw. [Terms 23-24 added following analysis of references retrieved from initial search]

25 21 or 22 or 23 or 24

26 1 and 25

27 20 or 26

28 Stroke/ [MesH expanded from Search 1.1 by removing *Focus]

29 stroke.tw. [Term extended from Search 1.1 by searching .tw (Text Word) instead of .ti,ab (Title or Abstract). Note that truncation was removed for this search]

30 Cerebral Infarction/ [MesH expanded from Search 1.1 by removing *Focus]

31 cerebral infar$.tw. [Term utilized from Search 1.1, extended to .tw (Text Word) from .ti,ab (Title or Abstract).

32 cerebrovascular accident$.tw. [Term utilized from Search 1.1, extended to .tw (Text Word) from .ti,ab (Title or Abstract).

33 cerebrovascular event$.tw. [Terms added following analysis of references retrieved from initial search]

34 CVA.tw. [Term utilized from Search 1.1, extended to .tw (Text Word) from .ti,ab (Title or Abstract).

35 (intracranial adj (haemorrhage or hemorrhage or bleed$ or haematoma or hematoma)).tw. [Term extended from Search 1.1 by adding truncation, haematoma/hematoma terms, and .tw (Text Word) instead of .ti (Title)]

36 Intracranial Hemorrhages/

37 Cerebral Hemorrhage/

38 Subarachnoid Hemorrhage/ [Terms 36-38 extended from Search 1.1 by removing *Focus from MeSH headings]

39 cerebral hemorrhage.tw.

40 cerebral haemorrhage.tw.

41 subarachnoid hemorrhage.tw.

42 subarachnoid haemorrhage.tw. [Terms 39-42 added following analysis of references retrieved from initial search]

43 Craniocerebral Trauma/

44 Brain Injuries/ [Terms 43-44 extended from Search 1.1 by removing *Focus from MeSH headings]

45 Head Injuries, Closed/ [MeSH heading added following analysis of references retrieved from initial search]

46 head injur$.tw. [Term utilized from Search 1.1, extended to .tw (Text Word) from .ti,ab (Title or Abstract).

47 craniocerebral trauma$.tw. [Term utilized from Search 1.1, extended to .tw (Text Word) from .ti,ab (Title or Abstract).

48 brain injur$.tw. (25286) [Term utilized from Search 1.1, extended to .tw (Text Word) from .ti,ab (Title or Abstract).

49 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48

50 (stroke adj (cent$ or unit$ or hospital$ or facilit$)).tw.

51 (regional adj2 (cent$ or unit$ or hospital$ or facilit$)).tw.

52 (speciali$ adj2 (cent$ or unit$ or hospital$ or facilit$)).tw.

53 (tertiary adj2 (cent$ or unit$ or hospital$ or facilit$)).tw.

54 Trauma Centers/

55 trauma cent$.tw.

56 (neurosurgical adj2 (cent$ or unit$ or hospital$ or facilit$)).tw.

57 (critical care adj (cent$ or unit$ or hospital$ or facilit$)).tw.

58 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57

59 transport$.tw.

60 transfer$.tw. [Terms 50-60 added following analysis of references retrieved from initial search]

61 59 or 60

62 49 and 58 and 61

63 27 or 62

64 limit 63 to yr="1988 -Current" [Note that no limitations by study type were applied to the search, the aim was to identify all literature]

Search 1.3 Update search (October-November 2012)

The search strategy below amalgamates searches 1.1 and 1.2 above into one strategy. Some terms were adapted following examination of the included studies from the original searches as noted below.

1 (hospital$ adj bypass$).mp.

2 (direct$ adj3 transfer$).mp. [Term extended by adding truncation ($) and broadening proximity operator (adj3 = terms appear within 3 words of each other)]

3 (bypass$ adj3 protocol$).mp. [Term extended by adding truncation ($) and broadening proximity operator (adj3 = terms appear within 3 words of each other)]

4 trauma system$.ti,ab.

5 or/1-4

6 Trauma Centers/

7 trauma cent$.tw.

8 (stroke adj (cent$ or unit$ or hospital$ or facilit$)).tw.

9 (regional adj2 (cent$ or unit$ or hospital$ or facilit$)).tw.

10 (speciali$ adj2 (cent$ or unit$ or hospital$ or facilit$)).tw.

11 (tertiary adj2 (cent$ or unit$ or hospital$ or facilit$)).tw.

12 (neurosurgical adj2 (cent$ or unit$ or hospital$ or facilit$)).tw.

13 (critical care adj (cent$ or unit$ or hospital$ or facilit$)).tw.

14 or/6-13

15 *Triage/

16 triage.ti,ab.

17 "Transportation of Patients"/ae, ec, st, ut

18 Patient Transfer/ec, mt, og, st, ut, sn

19 transfer$.ti,ab.

20 or/15-19

21 14 and 20

22 (prehospital adj triage).mp.

23 (pre-hospital adj triage).mp.

24 regionali?ation.ti,ab.

25 (direct$ adj5 transport$).ti,ab.

26 (direct$ adj5 admi$).ti,ab.

27 or/22-26

28 5 or 21 or 27

29 *Multiple Trauma/

30 trauma.ti,ab.

31 severe traumatic injur$.ti,ab.

32 (sever$ adj3 injur$).ti,ab.

33 (serious$ adj3 injur$).ti,ab.

34 ISS.ti,ab.

35 critical$ ill$.ti,ab.

36 severe emergenc$.ti,ab.

37 *Critical Care/sn [Statistics & Numerical Data]

38 Stroke/

39 stroke$.ti,ab.

40 Cerebral Infarction/

41 cerebral infar$.ti,ab.

42 cerebrovascular accident$.ti,ab.

43 CVA.ti,ab.

44 cerebrovascular event$.tw.

45 Craniocerebral Trauma/

46 head injur$.ti,ab.

47 craniocerebral trauma$.ti,ab.

48 Brain Injuries/

49 brain injur$.ti,ab.

50 ((intracranial or inta-cranial) adj (haemorrhage or hemorrhage or bleed$ or haematoma or hematoma)).tw.

51 Intracranial Hemorrhages/ or Cerebral Hemorrhage/ or Subarachnoid Hemorrhage/

52 *Hematoma, Epidural, Cranial/

53 cerebral hemorrhage.tw.

54 cerebral haemorrhage.tw.

55 subarachnoid hemorrhage.tw.

56 subarachnoid haemorrhage.tw.

57 Head Injuries, Closed/

58 or/29-57

59 28 and 58

60 limit 59 to yr="2010 -Current" [Publication date limit applied to identify studies published since original searches were conducted]

Appendix III. Study characteristics

Study	Dates, country (area), N centres	N patients	Inclusion/exclusion; definitions of groups	Severity (inclusion)	Severity (baseline): NIHSS	Age	Data source	System co-ordination	Description of centres	Pre-hospital care	Adjustments
Thrombolysed only (transfers had tPA in NSC)											
Rodriguez 2012[14]	2008-2009 USA (Minnesota) N centres NR	Total: 602 A: 473 B: 129	Thrombolysed only A: Direct to SC, tPA at SC B: tPA in NSC then transferred to SC within 24 hours	No cut-off	NR	NR	Minnesota Hospital Association data. Statewide sample.	NR	SC: Comprehensive stroke centre NSC: Community hospitals	NR	NR
Hsia 2011[15]	2005-2009 Country NR 2 SCs, NSCs	Total: 285 A: 194 B: 91	Thrombolysed only A: Direct to SC, tPA at SC B: tPA in NSC then transferred to SC Note: 100% SC patients but only 90% NSC patients had discharge diagnosis of ischaemic stroke	No cut-off	NIHSS (mean, SD) A: 13.5 (NR) B: 11.3 (NR)	Mean (SD): A: 71 (NR) B: 64 (SD)	SC database (consecutive) Retrospective analysis of prospective registry	NR	SC: Regional stroke centres NSC: Community hospitals	NR	None.
Martin-Schild 2011[28]	2004-2007 USA (Houston, Texas) 1 SC, 37 NSCs	Total:396 A: 312 B: 84	Thrombolysed only (within 3h) A: Direct to SC, tPA at SC B: tPA in NSC then transferred to SC	No cut-off	NIHSS (mean, SD): A: 13.1 (6.7) B: 10.7 (5.8)	Mean (SD): A: 65 (15) B: 65 (15)	Medical records at SC and NSC Retrospective	Stroke network, telemedicine / telephone	SC: Regional stroke unit, stroke team available 24 hours per day NSC: Regional and other hospitals Investigator based at SC	NR	None in primary analyses
Pervez 2010[16]	2003-2008 USA (Boston, Massachusetts) 1 SC, 33 NSCs	Total: 296 A: 115 B: 181	Thrombolysed only (within 3h) A: tPA in SC, may have first visited NSC B: tPA started in NSC then transferred to SC	No cut-off	NIHSS (median, IQR): A: 12 (8-19) B 13 (7-18) NIHSS >20: A: 26/115 (22.6%) B: 21/181 (11.6%)	Mean (SD): A: 74 (12) B: 72 (15)	SC database Prospective	Stroke network; telemedicine / telephone	SC: Regional stroke centre NSC: Outlying hospitals Investigator based at SC	NR	mRS analysis only: Age, NIHSS, time to tPA, follow-up time
Allibert 2009[17]	2003 onwards France (Besancon) 1 SC, NSCs	Total: 100 A: 54 B: 46	Thrombolysed only (within 3h or based on MRI) A: tPA in SC, some first visited NSC B: tPA in NSC then transferred to SC	No cut-off	NR	NR	NR	Stroke network; telemedicine	SC: Stroke unit NSC: Distant hospitals Investigator based at SC	NR	None

Study	Dates, country (area), N centres	N patients	Inclusion/exclusion; definitions of groups	Severity (inclusion)	Severity (baseline): NIHSS	Age	Data source	System co-ordination	Description of centres	Pre-hospital care	Adjustments
Silva 2009[18]	2003-2005 USA (Massachusetts & San Francisco) 2 SCs, NSCs	Total: 119 A: 92 B: 27	Thrombolysed only A: tPA in SC, may have first visited NSC B: tPA started in NSC then transferred to SC	No cut-off	NIHSS (mean, SD): A: 12.6 (6.1) B: 13.7 (6.4)	Mean (SD): A: 70 (18) B: 70 (17)	Other study Prospective	NR	SC: Stroke centres at university hospitals NSC: Community hospitals Investigator based at SC	NR	None
Wang 2000[19]	1996-1998 USA (Illinois counties) 1 SC, 13 NSCs	Total: 57 A: 23 B: 34	Thrombolysed only A: tPA in SC, may have first visited NSC B: tPA in NSC then transferred to SC	No cut-off	NIHSS (mean, SD): A: 15.5 (7.0) B: 13.7 (6.4)	Mean (SD): A: 71 (10) B: 72 (11)	Medical records (consecutive)	Stroke network; telemedicine / telephone	SC: 730-bed tertiary care centre with stroke unit, full stroke provision NSC: Community hospitals (68-350 beds) Investigator based at SC	To SC: 2 helicopters, 2 Life Flight teams	None
Thrombolysed only (transfers had tPA in NSC or SC)											
Rymer 2005,[20] Rymer 2004[21]	2000-2003 USA (Kansas City, Missouri) 1 SC, 47 NSCs	Total: 220 A: 62 B: 158	Thrombolysed only (within 3h) A: Direct to SC, tPA in SC B: 50% tPA in NSC then transferred to SC; 50% tPA in SC after transfer	No cut-off	NIHSS >20: A: 13/62 (21.0%) B: 45/158 (28.5%)	NR	SC database	Stroke network, telephone	SC: Regional stroke centre, neurologist on-call, no resident neurology cover NSC: Community hospitals (15-586 beds) Investigator based at SC	NR	None
Thrombolysed only (transfers had tPA in SC)											
Perez de la Ossa 2009[22]	2005-2007 Spain (Barcelona) 1 SC, 4 NSCs	Total: 153 A: 108 B: 45	Thrombolysed only A: Direct to SC, tPA in SC B: tPA in SC after transfer	No cut-off	NIHSS (median, IQR): A: 12 (7-18) B: 9 (6-15)	Mean (SD): A: 66 (13) B: 65 (9)	SC database (consecutive) Retrospective analysis of prospective registry	Stroke network	SC: Stroke unit, neurologic attention at all times NSC: Community hospitals, no specific stoke treatment Investigator based at SC and NSC	NR	mRS analysis only: NIHSS, prebolus glycaemia, history of atrial fibrillation

Study	Dates, country (area), N centres	N patients	Inclusion/exclusion; definitions of groups	Severity (inclusion)	Severity (baseline): NIHSS	Age	Data source	System co-ordination	Description of centres	Pre-hospital care	Adjustments
Ribo 2008[23]	2006 Spain (Catalunya) 1 SC, 4 NSCs	Total: 88 A: 61 B: 27	Thrombolysed only (within 6h), stroke code activated A: Direct to SC, tPA in SC B: tPA in SC after transfer	No cut-off	NIHSS (median, IQR): A: 16 (9-19) B: 17 (12-20)	Mean (SD): A: 69 (15) B: 70 (14)	NR	Stroke network, telephone	SC: Major university referral stroke centre NSC: Community hospitals; no neurologist on call, no thrombolysis or stroke unit Unclear whether investigator based at SC or NSC	NR	None
Merino 2002[24]	1998-2000 USA (London, Ontario) 2 SCs, 33 NSCs	Total: 72 A: 49 B: 23	Thrombolysed only (90% within 3h) A: Direct to SC, tPA in SC B: tPA in SC after transfer (only transferred if expected to arrive at SC within 3h)	No cut-off	NIHSS (median, IQR): A: 13 (10 to 19) B: 14 (9 to 16)	Mean (SD): A: 73 (10) B: 70 (11)	SC data collection Prospective	Stroke network	SC: Academic medical centres, stroke teams, 24-hour CT and MRI NSC: Rural hospitals; most lack intensive care, CT and emergency access to stroke physicians Unclear whether investigator based at SC or NSC	NR	None
Some thrombolysed, arrived at SC within 4-6h of onset in 2 of 3 studies (transfers had tPA in SC if at all)											
Li 2008[25]	2005 Taiwan (Kaohsiung) 1 SC, NSCs	Total: 101 A: 85 B: 16	Arrived SC within 4h of onset; 12% had tPA (NR per group) A: Direct to SC; tPA in SC if at all B: tPA in SC after transfer if at all	No cut-off	NIHSS (mean, SD): A+B: 11.8 (9.5)	Mean (SD): A+B: 68 (12)	SC stroke code activation Prospective, consecutive	NR	SC: Neurology department, university hospital NSC: Other hospitals Investigator based at SC	NR	None

Study	Dates, country (area), N centres	N patients	Inclusion/exclusion; definitions of groups	Severity (inclusion)	Severity (baseline): NIHSS	Age	Data source	System co-ordination	Description of centres	Pre-hospital care	Adjustments
Perez de la Ossa 2008[26]	2004-2006 Spain (Barcelona) 1 SC, 4 NSCs	Total: 262 A: 57 B: 112	Arrived SC within 6h of onset; 40% had tPA A: Direct to SC, tPA in SC if at all (54% had tPA) B: tPA in SC after transfer if at all (27% had tPA)	No cut-off	NIHSS (median, IQR): A: 11 (6 to 18) B: 5 (3 to 11)	Mean (SD): A: 64 (11) B: 67 (10)	SC data collection Prospective, consecutive	Stroke network	SC: Stroke unit, neurologic attention available at all times NSC: Community hospitals, no specific stoke treatment Investigator based at SC and NSC	NR	mRS analysis only: Age, stroke severity
Muller 2007[27]	2003-2004 Germany (Munich & Regensburgh) 4 SCs, 12 NSCs	Total: 39 A: 23 B: 16	Basilar artery occlusion only; 46% had tPA (A: 48%, B: 44%) A: Direct to SC, tPA at SC (48% had tPA) B: tPA at SC (44% had tPA)	No cut-off	NR	Mean (SD): A: 68 (16) B: 63 (15)	SC database	Stroke network, telemedicine	SC: Academic stroke centres, stroke and intensive care units, neurologic attention at all times NSC: General hospitals, no interventional facilities Unclear whether investigator based at SC or NSC	NR	None

Abbreviations: CT=computed tomography;IQR=interquartile range; MRI=magnetic resonance imaging; mRS=modified Rankin Scale; NIHSS=National Institutes of Health Stroke Scale; NR=not reported; NSC=non-specialist centre; SC=specialist centre; SD=standard deviation; telemedicine / telephone = telemedicine / telephone contact available between SC and NSCs; tPA=tissue plasminogen activator (thrombolysis). Definitions of study groups: A=direct to SC and remained there; B=to NSC initially then transferred to SC.

Appendix IV. Risk of bias in included studies

Study	**Comparability between groups:** Risk of bias due to lack of inclusion of, or adjustment for, NSC patients not transferred to SC	**Adjustment:** Risk of bias due to lack of adjustment of analyses for differences in age and severity between groups	**Representative sample:** Risk of bias due to selection of patients based on condition subtype or interventions received	**Exclusions:** Risk of bias due to more than 5% patients excluded due to missing data
Thrombolysed only (transfers had tPA in NSC)				
Rodriguez 2012[14]	High risk	High risk	High risk (thrombolysed only)	Unclear
Hsia 2011[15]	High risk	High risk	High risk (thrombolysed only)	Low risk (0%)
Martin-Schild 2011[28]	High risk	High risk	High risk (thrombolysed only)	Unclear
Pervez 2010[16]	High risk	Low risk	High risk (thrombolysed only)	Low risk (0%)
Allibert 2009[17]	High risk	High risk	High risk (thrombolysed only)	Low risk (0%)
Silva 2009[18]	High risk	High risk	High risk (thrombolysed only)	Unclear
Wang 2000[19]	High risk	High risk	High risk (thrombolysed only)	Low risk (0%)
Thrombolysed only (transfers had tPA in NSC or SC)				
Rymer 2005,[20] Rymer 2004[21]	High risk	High risk	High risk (thrombolysed only)	Low risk (0%)
Thrombolysed only (transfers had tPA in SC)				
Perez de la Ossa 2009[22]	High risk	Low risk	High risk (thrombolysed only)	Unclear
Ribo 2008[23]	High risk	High risk	High risk (thrombolysed only)	Low risk (0%)
Merino 2002[24]	High risk	High risk	High risk (thrombolysed only)	Low risk (0%)
Some thrombolysed, arrived at SC within 4-6h of onset in 2 of 3 studies (transfers had tPA in SC if at all)				

Study	**Comparability between groups:** Risk of bias due to lack of inclusion of, or adjustment for, NSC patients not transferred to SC	**Adjustment:** Risk of bias due to lack of adjustment of analyses for differences in age and severity between groups	**Representative sample:** Risk of bias due to selection of patients based on condition subtype or interventions received	**Exclusions:** Risk of bias due to more than 5% patients excluded due to missing data
Li 2008[25]	High risk	High risk	High risk (arrived within thrombolysis time window)	Low risk (0%)
Perez de la Ossa 2008[26]	High risk	Low risk	High risk (arrived within thrombolysis time window)	Low risk (0%)
Muller 2007[27]	High risk	High risk	High risk (basilar artery occlusion only)	Low risk (0%)

Abbreviations: NSC=non-specialist centre; SC=specialist centre; tPA=tissue plasminogen activator (thrombolysis).