Evidence Review on Pathways of Hyperacute Stroke Care

Aims

To review the evidence supporting the effectiveness and safety of two different routes of access to a HASU – direct transfer and indirect transfer with intermediate stop at a local hospital. To provide recommendation on undertaking a formative evaluation of the Mid and South Essex hyper-acute stroke pathway

Summary conclusions and recommendations

There seems to be little difference in patient outcomes for thrombolysis administered via both routes of access including telemedicine, despite a larger average door-to-needle time in the drip-and-ship model. The evaluation studies on the HASU models in London and Manchester are not directly comparable to the drip-and-ship approach. As such, a judgment on relative effectiveness is not possible. We would recommend a formal evaluation of the future Mid and South Essex hyper-acute stroke pathway and have spoken to Professor Naomi Fulop, University College London, who would be very interested in undertaking this work with her team.

Introduction

Stroke – prevalence, burden and outcomes

In the world, every two seconds someone suffers a stroke. With 7% of all deaths (Office for National Statistics 2016; National Records of Scotland 2016; Northern Ireland Statistics and Research Agency 2016), stroke is the fourth most common cause of death in the UK where around 95,000 people are admitted to hospital with an acute stroke every year (Stroke Association, 2017). In 2015, 40,000 people died of stroke (Office for National Statistics 2016; National Records of Scotland 2016 Northern Ireland Statistics and Research Agency 2016). In England, the treatment of stroke represents £1,7 billion in direct costs to the NHS every year (Stroke Association, 2017).

Survival has steadily increased with more people than ever before surviving a stroke (Feigin et al. 2013). Currently, there are around 1,2 million people in the UK who survived a stroke, half of whom live with stroke-related disabilities (Stroke Association, 2017). Eight-five percent of stroke patients in England, Wales and Northern Ireland survive their hospital stay and two thirds are able to return home (SSNAP 2016). Stroke survivors are subject to a higher risk of recurrent stroke at a rate of 26% within five years and 39% by ten years (Mohan et al., 2011). Around 40% of stroke survivors are alive five years after stroke (Hankey, 2003).

Ischaemic stroke – prevalence and treatment

Acute ischaemic stroke is the diagnosis in 85% of strokes (NICE Guidance 68; RCP 2016; NIHR, Roads to recovery).

The recommended treatment for acute ischaemic stroke patients is rapid assessment and, where appropriate, the timely administration of thrombolysis, i.e. intravenous recombinant tissue-type plasminogen activator (known as r-tPA or alteplase) ideally within three hours of symptom onset (NICE Guideline 68; De Keyser et al. 2007, AHA/ASA Guideline). Thrombolysis helps to dissolve the blood clot that blocks the flow of blood in the affected part of the brain (Wardlaw et al. 2014). A meta-analysis of individual patient-data concluded that a similar proportion of patients with good outcomes at three to six months post-stroke are achieved for thrombolysis administered within 3 hours (32.9%), 3 hours to 4.5 hours (35.3%), and more than 4.5 hours (32.8%) irrespective of age or stroke severity (Emberson et al. 2014). In patients receiving control treatment, only 23% had a positive outcome (Emberson et al. 2014). A systematic review on the effectiveness of thrombolysis in acute ischaemic stroke found that r-tPA significantly reduced the proportion of people who died or were left dependent (modified Rankin scale of 3 to 6) as a result of stroke (Wardlaw et al. 2014). In both reviews, the likelihood of a good outcome is greatest if thrombolysis is started within 4.5 hours of symptom onset. However, the earlier the start of thrombolysis, the better. A study by Lee et al. 2010 found that the number needed to treat (NNT) for one excellent outcome is 4.5 within 90 minutes of symptom onset, whereas NNT climbs to 9 for 91 to 180 minutes, and 14 for 181 to 270 minutes. A different study found that for every 15 minutes delay in administration of alteplase, there was a 4% decreased likelihood of independence (Southerland et al. 2016; Saver et al. 2013). The recommended door to needle time for r-tPA is 60 minutes (Jauch et al. 2013). However, this is achieved in less than 30% of patients (Fonarow et al. 2011).

Comprehensive stroke centres have been shown to have superior outcomes in terms of excellent and favourable functional outcome at 90 days compared to care in primary stroke centers or via telemedicine or telestroke alone without subsequent transfer to a comprehensive stroke unit for administration of thrombolysis (Lahr et al. 2013).

Following rapid administration of thrombolysis, the recommended treatment for an important subset of patients who suffered an acute ischaemic stroke (AIS) from major vessel occlusion – and whom fulfil certain criteria (Evans et al.

2017) - is rapid mechanical thrombectomy to remove the blood clot (RCP 2016). An evidence review found that for every four to six people with AIS undergoing mechanical thrombectomy using stent retriever devices, one person will function independently at three months compared to r-tPA alone (Public Health England review 2017). A meta-analysis demonstrated that 46% of eligible patients treated with thrombectomy achieved a good functional outcome (independence) at 90 days vs. 26.5% for thrombolysis alone independent of severity of stroke or age (Goyal et al. 2016). A meta-analysis showed that thrombectomy improved outcomes up to 7.3 hours following symptom onset (Saver et al. 2016).

Longer times until endovascular treatment are associated with significantly poorer outcomes (Menon et al. 2016; Saver et al. 2016; Khatri et al. 2014; Sun et al. 2013). The benefits of thrombectomy falls by 3.4% for every hour of delay (Public Health England review 2017) and the odds of being treated with thrombectomy decreases by 2.5% for every minute of transfer time (Prabhakaran et al. 2011). The greatest benefit can be achieved with treatment onset within the first 120 minutes following symptom onset (Saver et al. 2016).

Treatment pathways
Whilst the treatment evidence for AIS is well established, there is uncertainty around the access to treatment and the relative benefits of different treatment pathways. CT angiogram, a mandatory imaging technique and recommended in UK national guidelines, is not yet routinely available for all patients suffering AIS (RCP 2016, Evans et al. 2017). Not all emergency departments have the appropriate equipment to undertake CT angiograms or the appropriate expertise (a range of different consultants from various specialities) to make an informed judgement about whether a patient would benefit from mechanical thrombectomy or to perform endovascular treatment (Evans et al. 2017). If the admitting hospital does not have appropriate imaging, reporting and/or multi-disciplinary expertise, once thrombolysis has been started, the patient needs to be transferred or contact needs to made with a specialist or comprehensive stroke centre to interpret the CT scans or other imaging and to decide on and perform the next treatment steps including possible thrombectomy (Liebeskind 2015).

Hyperacute stroke units (HASUs) are the latest iteration in developing comprehensive stroke units further and they are the recommended place of treatment for people suffering from stroke not least because, in most places, they provide high quality, high volume, multi-disciplinary care on a 24 hours basis and may be the only place to access mechanical thrombectomy (Buecke et al. 2017; RCP 2016; Healthcare for London 2009). HASUs are targeted towards patients in the initial 72 hours after symptom onset, and are characterised, amongst other things, by multidisciplinary teams which care exclusively for patients with stroke, advanced technology including imaging, advanced treatment, 24/7 care, and at least daily ward rounds (Morris et al. 2014; Health care for London and NHS 2008).

Care provided in dedicated stroke units are associated with better patient outcomes than less specialised settings (Meretoja et al. 2010, Bray et al. 2013; Langhorne et al. 2013; Trialists' Collaboration, 2013). A prospective cohort study found that patients that are admitted to stroke centers with higher levels of organisation (defined by six key characteristics) are more likely to receive high quality care with a reduced risk of death at 30 days post-stroke in adjusted analyses (Bray et al. 2013).

To reach comprehensive stroke centres or HASUs specifically, multiple routes of access exist. UCLPartners has been asked to review the evidence on the effectiveness, benefits and drawbacks of two access routes – direct transfer to a HASU or similar kind of specialist stroke center and the so called 'drip-and-ship', also known as treat and transfer access model, with indirect transfer to a HASU.

Aim
To review the evidence supporting the effectiveness and safety of two different routes of access to a HASU – direct transfer and indirect transfer with intermediate stop at a local hospital.

Search Methods
A pragmatic review has been undertaken within a timeframe including the write up of a final report of three weeks with completion by the end of October 2017.

A pragmatic literature search has been conducted to identify the most relevant and up to date primary studies and review papers evaluating the effectiveness of both access models. Only titles, and where necessary, abstracts were screened to determine eligibility.

Inclusion criteria

Study design
The inclusion of studies was restricted to studies comparing either or both models to treatment as usual or comparing both models directly, either through case series, cohort studies, simulation/modeling studies, audits, or in evidence reviews. Also, qualitative studies and commentaries were included to support impact studies.

Study focus
Studies were included if they evaluated the impact (also referred to as effectiveness, efficacy, association, outcomes etc.) of either model.

Outcomes
Study inclusion was not restricted to specific outcomes.

Population
No restriction was placed on the population studied.

Intervention

Studies evaluating the HASU or similar (e.g. centralised) model of access were included if they mentioned, amongst other things: centralisation, mothership, HASU, specialist/endovascular/or comprehensive stroke centre, or direct transfer in combination with "stroke".

Studies evaluating the drip-and-ship model of care were included if they mentioned, amongst other things: drip and ship, treat and transfer, telemedicine, local stroke centre, primary hospital in combination with stroke, or stroke centre.

The literature search focused on scientific papers written in English language published after the year 2000 and published in key peer-reviewed journals or by key sources or researchers in the field of stroke research. To identify studies the following sources were searched:

- Open Athens – NICE: Journals and databases
- Google Scholar and Google search engines
- Cochrane library
- NICE guidance
- Key documents including key reviews and guidelines from organisations incl. NIHR, Royal College of Physicians, Stroke Association, Kings Fund, SSNAP

Key words used in databases and search engines – either individually or in combination with others - were the following:

- "drip and ship" OR "drip n ship" OR "drip-and-ship" OR "drip, ship" AND stroke (AND review)
- "treat and transfer" AND stroke
- "hyper acute" OR "hyperacute" OR "hyper-acute" OR HASU AND stroke
- Centralisation OR centralising OR centralised AND stroke
- "mobile stroke" OR telestroke OR telemedicine AND stroke (AND review)

Additionally, the studies citing any of the studies included via the above method were screened and included where appropriate. The GoogleScholar function "cited by" was used. The references cited by key included studies were also screened.

All studies retrieved by NP were screened in duplicate by CD for final inclusion in the review.

Results

Search results

In total, 51 principal references were included in this review. Amongst the 51 references are 12 reviews and 39 studies.

Findings from included studies

A number of included studies evaluated the drip-and-ship transfer model either in isolation, or compared with treatment as usual or the direct transfer model.

Thrombolysis rates without direct comparison of models

An expert review by Price et al. 2014 comparing different transfer models concluded that regional collaborations, i.e. drip-and-ship approaches or direct transfer models, show the highest rates of thrombolysis administration rates compared to transfer to local hospitals alone, which may lack appropriate expertise.

There seems to be no difference in t-PA rates between centralised (Helsinki – larger hospital) and decentralised (Bavaria – smaller telemedicine-linked stroke facilities) direct transfer models (Hubert et al. 2016). The study made the evidence-based assumption that smaller hospitals have higher door-to-needle times with team experience as the key factor.

Drip-and-ship only without telemedicine

A study by Deguchi et al. 2017 investigated the drip-and-ship approach using data on 16 patients. All patients were initially transferred to primary hospitals to receive r-tPA before being shipped to neuroendovascular therapy in specialised hospitals. Mean intervals from symptom onset to r-tPA administration and endovascular treatment was 166 and 334 minutes respectively. No patient suffered intracranial haemorrhage (sICH). The study authors concluded that drip-and-ship is a safe means to transfer patients with AIS. Endovascular treatment was performed in 14 patients.

Qureshi et al. 2012 conducted a case series analysis of 602 patients receiving r-tPA either in a community hospital emergency department (ED) or via the drip-and-ship approach. Outcomes of comprehensive stroke center care were not a focus of this study. Directly referred patients had a significantly higher sICH rate (8.5% vs. 3.1%) than drip-and-ship patients with in-hospital mortality being identical. Mean hospital charges were higher for ED arrival compared to the drip-and-ship approach. No risk-adjusted results are presented.

Drip-and-ship vs. central without telemedicine

Sheth et al. 2015 undertook a case series analysis of 44,667 patients undergoing thrombolytic therapy for AIS administered at a primary hospital before transfer to a specialist hospital (drip and ship) compared to "front door" administration, i.e. direct transfer to a hospital participating in the "Get With The Guidelines-Stroke" (GWTG) program. Because allocation to the treatment arm was not random, there were substantial differences in analysed patients with differences in age, gender, and ethnicity. Also, for those transferred via the drip-and-ship model, the time between symptom onset to arrival at GWTG hospital was around five times longer than the direct group. Front-door patients had more often a history stroke and had a higher NIH Stroke Scale (NIHSS) scores than drip-and-ship patients. Only about 65% of all patients were treated in a stroke center. Risk adjusted outcomes showed that in-hospital mortality and sICH were higher in drip-and-ship patients than in front-door patients. Drip-and-ship patients were significantly less likely to be discharged home and had a higher length of stay in hospital. Absolute differences, however, are small. The authors commented that modest differences in mortality and symptomatic intracranial hemorrhage may be because of patient selection bias, post-tPA care differences, or unmeasured confounding and that the drip and ship paradigm may facilitate widespread tPA use in patients with acute stroke.

Cha et el. 2013 conducted a retrospective case series of 317 patients. Unadjusted results (with drip and ship patients with significantly larger ischemic lesions and NIHSS scores) showed that poor outcome (modified Rankin Scale score 3-6) 90 days after IVT was much higher in drip and ship patients (65.4% vs. 45.2%) whereas no difference was detected for sICH. Endovascular treatment was not mentioned.

Gerschenfeld et al. 2017 in a registry study of 159 patients treated with r-tPA and thrombectomy, adjusted analysis show no significant difference in favourable neurologic outcome at three months (61% drip and ship vs. 50.8% direct) despite longer processing times in the drip-and-ship group.

Buecke et al. 2017 in a case series study of 941 patients eligible for thrombectomy, direct admissions had significantly shorter time to recanalization (260 min vs. 348 min) though with no difference in good functional outcome, all-cause mortality at 90 days, and rate of sICH between the groups. Results were adjusted for common confounders.

Froehler et al. 2017 in a prospective observational study of 984 patients treated with r-tPA and treated with thrombectomy found significantly higher onset to revascularization time for transfer patients (312 min vs. 202 min). Adjusted clinical outcomes were significantly better in the direct group for functional independence (60% vs. 52.2%) and excellent outcome (modified Rankin score 0-1) with 47% vs. 38%. No difference was found for mortality and r-tPA did not impact on outcomes. Modelling found that in direct patients, thrombectomy could be started 91 minutes earlier.

A study by Holodinsky et al. 2016 used conditional probability modelling to compare drip and ship with direct transfer to a comprehensive stroke centre based on data of the ESCAPE trial to estimate the time-dependent probability of good outcome. They concluded that the centralised approach is always superior in urban and suburban areas when transport times between final and intermediate hospital are short.

Another modelling study also used data from the ESCAPE trial for thrombectomy plus alteplase and from the GWTG trial for alteplase alone. The transfer hospital in close proximity to a specialist stroke hospital played a significant role only if it achieved a door-to-needle time of 30 minutes or less and a needle-to-door out time of 20 minutes (Milne et al. 2017).

Lahr et al. 2012 conducted a prospective observational study of 283 and 801 AIS patients on a direct and indirect transfer model. Significantly more patients in the direct model were treated with r-tPA (22% vs. 14%) in adjusted analyses. In the direct pathway, significantly more patients arrived at the hospital within 4.5 hours and patients on this pathway benefitted from shorter door-to-needle times (35 vs. 47 minutes). There was no difference in 90-day functional outcome. Thrombectomy rates and associated outcomes were not compared.

A simulation study by the same first author (Lahr et al. 2017) compared three different scenarios and their impact on cost and effects. Compared to an indirect transfer system, centralising services to two or four instead of nine facilities significantly lowers mean annual costs per patient compared to raising the quality of stroke care at community hospitals.

One model-based study looked at AIS patients for whom vessel status, and as such, eligibility for endovascular treatment, is uncertain (Schlemm et al. 2017). Based on the model, AIS patients are likely to benefit more from direct transportation to a comprehensive stroke as stroke severity increases. The mothership approach is likely to be more beneficial with shorter transfer times and longer door-to-needle and needle-to-transfer (door out) times.

Drip-and-ship vs. central with telemedicine with treatment at transfer hospital
A chart review was conducted by Martin-Schild et al. 2011 comparing patients either treated via drip-and-ship at outside hospitals or at a stroke centre. Telephone consultation was available as well as video consultation at transfer hospitals. Only 72% of the 116 drip-and-ship patients were treated within 3 hours of symptom onset. No comparative figure was given for proportion of patients treated within 3 hours for direct transfers. Mean time from onset to arrival at stroke centre was six hours for drip-and-ship patients. Endovascular treatment was administered to drip-and-ship patients in only 6% cases compared to 15.1% in direct transfers (significant difference). Drip-and-ship patients had slightly higher absolute sICH (6%) vs. 4.5% for direct transfers, whereas in-hospital mortality was nearly identical between the two groups. The study was underpowered to detect differences in this sample and no risk-adjusted difference estimates are available.

A retrospective study by Mansoor et al. 2011 compared outcomes of a total of 201 patients, some of which were treated via the drip and ship approach (14%) with patients directly admitted to a certified primary stroke centre (86%). The drip-and ship approach was based on video telemedicine in addition to phone consultation. The authors found no differences in in-hospital mortality, onset to needle time, or sICH scores. There was no mention of analyses being adjusted for confounders. Also, the drip-and-ship group was very small which may have overestimated the benefit of the drip-and-ship approach. Absolute differences in sICH were 6.3% (direct) vs. 11.5% (drip-and-ship) and mortality were 5.7% (direct) and 7.7% (drip-and-ship). Differences in rates of endovascular treatment were not mentioned.

A number of other studies were included that used some form of case series to assess the relative difference between drip-and-ship and direct transfer to a comprehensive stroke center.

Ali et al. 2013 found no association between transfer status and in-hospital mortality. No other measure was included in multivariable analyses. Median time between onset and r-tPA, whilst statistically significant between the groups, was well below the 3 hours recommendation for both groups.

Hiyama et al. 2016 in an analysis of 45 patients (all undergoing r-tPA) found a shorter onset to admission time for direct referrals (57 min vs. 164 min) whereas arrival to arterial puncture (for mechanical thrombectomy) was significantly shorter in the drip and ship group (25 min to 110 min). No differences in outcomes were found (no baseline differences).

One study using case series highlighted that the drip and ship model is associated with worse patients outcomes due to delays in endovascular therapy in the former compared to direct admissions – the differences in in-hospital mortality were 22% vs. 30% and 52% vs. 13% for patients living at home after one year for direct and secondary admissions respectively (Mueller et al. 2007). The study population was however small.

A systematic review (Pickering et al. 2015) of direct vs. indirect transfer to a specialist stroke centre for thrombolysis incorporating 14 studies found no difference in unadjusted mortality and morbidity between the two transfer models. Only three studies included in the review adjusted their analyses which carries a significant risk of selection and allocation bias, potentially confounding the results.

Telemedicine and telestroke

Telestroke refers to telemedicine in the form of videoconferencing using high quality bidirectional audiovisual systems coupled with teleradiology for remote review of brain scans. The hope for telestroke systems is for more patients to be correctly identified as suffering from stroke by emergency staff and be transported to the nearest stroke center (Schwamm et al. 2009). Telestroke networks have the potential to increase the reach of specialist stroke care to less specialised hospitals and underserved areas (Hess et al. 2005).

A review of the evidence on the use of telemedicine for stroke (Schwamm et al. 2009; Audebert and Schwamm 2009) concluded that there is general agreement of effectiveness (Class I recommendations) for the following:

- High-quality videoconferencing for NIHSS telestroke assessment for non-acute stroke (Evidence A – highest level)
- NIHSS telestroke by stroke specialist with high-quality videoconferencing when bedside assessment by specialist not available for acute stroke with identical quality achievable (Evidence A)
- Approved teleradiology systems for brain CT scan reviews in suspected stroke – and for identifying exclusion for thrombolysis by stroke specialists or radiologists (Evidence A)
- Recommendation for stroke specialist with high-quality videoconferencing to provide medical opinion on r-tPA for suspected AIS if on-site stroke expertise not available (Evidence B)

A systematic review (Johansson and Wild 2010), restricted to assessing the feasibility, acceptability, and treatment delivery reliability of telemedicine systems looking at 18 studies, found that telestroke services deliver better functional health outcomes. Hospitals with telestroke facilities had increased rates of r-tPA with patients typically being referred on to stroke centres. However, the comparator tended to be a less capable telemedicine model e.g. telephone only or conventional treatment in a hospital. Adjustment for confounders was not reported.

Another review found that telemedicine facilitates rapid patient assessment at the hospital, that it is effective in a hub and spoke setting, and that it provides more accurate treatment decisions than telephone consultations only whilst reducing the delay in diagnosis. Telemedicine is found to reduce death and dependency. Comparators tended to be telephone only or direct and longer transfer to comprehensive stroke centre without the option of ambulance-based administration of r-tPA (Birns et al. 2013). A number of studies included in this review reported higher door-to-needle times and onset-to-treatment times associated with the telemedicine model. Differences in endovascular treatment were not analysed.

A recent systematic review and meta-analysis of thrombolysis in telestroke included seven studies mostly restricted to thrombolysis administered within three hours of symptom onset. Rates of sICH were similar between patients receiving telemedicine guided r-tPA and r-tPA at stroke centers. There was no difference in mortality or functional independence at three months between the groups (Kepplinger et al. 2016). Only two studies adjusted their analyses for confounders. Differences it outcomes for those receiving endovascular therapy were not explored.

Another review found telemedicine to be both safe and effective and may be particularly beneficial in rural areas (Bowes 2015).

The most recent review on telestroke compared to on-site physician and other telemedicine systems is currently in protocol stage (Arba et al. 2016).

Based on available evidence on the effectiveness of hub-and-spoke telestroke networks (Switzer et al. 2009; Demaerschalk et al. 2009; Meyer et al. 2008; Audebert et al. 2006; Schwab et al. 2006), a modelling study (Switzer et al. 2013) found that compared with no network, a telestroke (remote review of patient files, live video and review of CT scans) system with one hub and seven spoke hospitals may lead to higher rates of r-tPA, endovascular therapies, and as a result, a higher rate of patients discharged home independently and greater cost savings.

In a study (Commiskey et al. 2017) describing the Ochsner telestroke system with a primary hub (comprehensive stroke centre), secondary hubs, and spoke centres, combined both drip and ship and drip and keep. With expansion and increasing volume of stroke patients, r-tPA utilization increased and cases of sICH fell. The average r-tPA rate was 28% with a 275% increase in r-tPA utilization pre/post. Average door to needle time was 90 minutes. The study did not discuss patient outcomes.

A before and after study (Amorim et al. 2013) evaluated the implementation of telemedicine in community hospitals in a hub-and-spoke model for AIS patients. Implementation of telestroke was found to increase thrombolytic use in remote (spoke) hospitals. The study did not compare different modes of access.

A study by Agarwal et al. 2014 evaluated the impact of introducing a horizontal telemedicine model designed for consultations out-of-hours and videoconferencing facilities for communication with two stroke hospitals providing thrombolysis seven days a week, 24 hours a day. The authors concluded for the system to be safe and effective in identifying patients for thrombolysis and the results were comparable with other telestroke trials such as TEMPiS (Audebert et al. 2005), REACH (Wang et al. 2004), STRokE DOC (Meyer et al. 2008), and Finnish Telestroke (Sairanen et al. 2011) for median NIHSS score, onset-to-needle time, door-to-needle time, sICH rates and in-hospital mortality.

Centralisation of care incl. hyper-acute stroke units

To date, a few studies have been conducted to evaluate the impact of hyper-acute stroke units (HASUs). Hunter et al. 2013 used a before-and-after design to measure differences in clinical outcomes and costs as a result of centralising specialised acute stroke care in London in eight hospitals compared to 30. Adjusted estimates suggest a small but significant improvement in survival and reduced cost by £5.2 million per year mainly as the result of reduced hospital length of stay. Rates of thrombolysis increased from 5 to 12%. The creation of HASUs in London was based on extra investment which may have had an impact on outcomes (Healthcare for London 2009, Hunter et al. 2013; Fulop et al. 2016, Davie et al. 2013). It is possible that achieved differences post-introduction of HASUs may be due to the impact of only a few rather than all eight HASUs (Brooke and Ames 2011).

Morris et al. 2014 conducted a difference-in-difference analysis for the implementation of HASUs in both Manchester and London. In London, all stroke patients are admitted to HASUs whereas Manchester defined a 4-hour time window after symptom onset, and once exceeded, patients would not be admitted to a HASU. The study found a small but significant decline of 1.1 in risk-adjusted mortality at 90 days after admission in London. Both cities showed a significant decline in length of hospital stay by 1.4 and two days respectively. Whilst the dataset is large, using an existing database carries the risk of important confounders not being included – this may have had an impact on adjusted risk estimates (Morris et al. 2014). Also, other outcomes such as functional impairment were not analysed.

A controlled before and after analysis (Ramsay et al. 2015) attempted to explain the differences found in Morris et al. 2014. The study used a non-centralized urban comparator (other areas in England). Post-centralization, the likelihood of receiving evidence-based clinical interventions increased in all areas although in London significantly more than elsewhere e.g. for brain scans within three hours. HASUs were significantly more likely to provide interventions although fewer patients were admitted to a HASU in Manchester (42% vs. 93% in London). In Manchester, one third of eligible patients were not admitted to a HASU. These differences maybe be due to different service eligibility criteria between the services and how rigorously they are followed. A simpler more inclusive model with hands-on facilitation may result in higher fidelity than a more complex model (Fulop et al. 2016).

A study to investigate the lessons about the development, provision, effects and cost of 24/7 care in London HASUs is currently ongoing as there may be different outcomes based on more services delivered during regular compared to out-of-hours (Simister et al. 2014).

An evaluation of a HASU in Ayreshire demonstrated significant improvements in acute stroke care in terms of reduced hospital length of stay and mortality compared to pre-implementation (Ghos et al. 2011).

Similar to the centralisation of stroke care in London, a Danish region also sought to centralise their stroke care reducing the number of hospitals providing specialised acute stroke care from five to two (Douw et al. 2015). The move was largely due to cut costs but also to combat variations in services depending on geographical location with some patients eligible for advanced neurological treatment not receiving it. The study does not discuss different modes of access, i.e. direct vs. drip-and-ship. Preliminary findings showed increased quality of care with reduced costs.

In any case, centralisation requires a significant re-think and adjustment in any existing system and it is likely to require a combination of top-down and bottom-up leadership to enable change. System leadership is important to provide guidance and infuse confidence whilst bottom-up approaches may provide a shared agenda and goal. To bring these two approaches together might be key in aligning interests of providers and commissioners (Turner et al. 2016). From a top-down perspective, system leadership, setting an agenda based on the promise of improved outcomes and clinical credibility in combination with "holding the line" to face pressures, may have proven vital in the run up to the introduction of HASUs in London (Fraser et al. 2017).

A review of HASUs concluded that they are clinically and cost effective due to the combination of care provided. However, favourable outcomes identified from the underlying literature can only be achieved if appropriate and optimum standards of care are maintained through continuous monitoring. The review also highlights the importance of the supportive infrastructure for HASUs (Bowes 2015).

Discussion

There seems to be little difference in patient outcomes for thrombolysis administered via both routes of access including telemedicine despite a larger average door-to-needle time in the drip-and-ship model.

It appears that the emergence of drip-and-ship access models using telestroke have increased r-tPA rates with some studies suggesting a similar or in some cases better safety profile for drip-and-ship vs. direct transfer models for the administration of thrombolysis (Muller-Barna et al. 2012; Qureshi et al. 2012). A retrospective review of consecutive r-tPA treated patients admitted to a comprehensive stroke centre (Mehta et al. 2014) was conducted. The study found a significantly higher proportion of stroke mimics (SM) which tend to present with lower NIHSS scores and whom were found to be younger. None of the stroke mimics developed sICH and all were discharged to home. The adjusted analysis found that stroke mimics were 12 times more likely to have the drip-and-ship paradigm. One explanation of that finding may be higher test accuracy of hub rather than spoke hospitals and spoke hospitals referring a higher proportion of patients on to hub hospitals for specialist treatment. Given the limited number of studies reporting adjusted estimates for both access models – this is an important confounder that needs to be considered and clearly has an impact on resource utilisation. However, identification of stroke mimics needs to be considered in both models (Mouthon-Reignier et al. 2016).

There may be other important confounders that may explain the nearly identical results reported for most studies evaluating the two access models. One study found drip-and-ship patients to less likely be black and/or and elderly (Lyerly et al. 2013; Lyverly et al. 2015), and to potentially have more favourable characteristics (Qureshi et al. 2012).

It appears the drip-and-ship model is able to deliver similar outcomes for thrombolysis if door-to-needle and needle-to-door-out times are not significantly higher than in direct access models (Milne et al. 2016). However, the direct model is likely to be always superior in urban and suburban areas (Holodinsky et al. 2016).

A number of included studies focus on thrombolysis alone and very few focus on differences in patient outcomes for thrombectomy and the impact of the two access models. Whilst r-tPA administration within three hours appears to be a realistic target for both access models, few studies evaluating either model focus on the additional time needed in the drip-and-ship model to access endovascular treatment. For appropriate patients, good outcomes are more likely if thrombectomy is administered within 120 minutes of symptom onset (Saver et al. 2016) and that mechanical thrombectomy in addition to r-tPA may result in one in every four to six people achieving functional independence compared to r-tPA alone (Public Health England review 2017; Khatri et al. 2014). Therefore, the timely prioritisation of r-tPA at the potential cost of delays in transport to comprehensive stroke units providing endovascular treatment need to be carefully considered when planning service configurations and when considering ways to improve quality (Asif et al. 2013).

An ambulance equipped with relevant videoconferencing and imaging technology may be one option that could be considered to reduce potential treatment delays for drip and ship patients eligible for endovascular treatment (Wu et al. 2017; Yamal et al. 2017; Parker et al. 2015; Bowry et al. 2015; Espinoza et al. 2016). Also, other ambulance-based triage and pre-hospital assessment should be considered moving forward such as connecting EMS and stroke providers remotely for r-tPA assessment (Brotons et al. 2016).

Very few studies exist that directly compare the two models of access and none of those studies use a randomised controlled trial or other robust quasi-experimental design which can overcome selection bias associated with existing studies. Whilst an RCT may be difficult to conduct for these types of interventions (Hunter et al. 2013), the lack of such an evaluation makes it very difficult to evaluate the relative effectiveness of either model. The RACECAT trial is the first of its kind to directly address this gap, however the findings of this study are not expected before the year 2020 (Perez de la Ossa).

As a result, the evaluation studies on the HASU models in London and Manchester are not directly comparable to the drip-and-ship approach. As such, a judgment on relative effectiveness is not possible. Also caution needs to be exerted on the results of these studies, as the authors use a large number N (patients) in their models which can result in small changes becoming statistically significant. It will be important for decision-makers to look at study results more closely and to determine whether the differences observed are clinically significant. Also, it is important to be cautious not to generalise the results beyond London and Manchester as evaluations from HASUs in other cities are pending or not yet conducted. Thus, more research is needed to determine firstly whether HASUs are more or equally safe and effective as the drip-and-ship approach and additionally, how safe and effective HASUs are compared to other centralised systems with comprehensive stroke centres. There is clearly significant opportunity within the current service reconfiguration in Essex to undertake such evaluation. There is significant experience from applied health researchers within University College London who have contributed significantly to the current evidence and evaluation of stroke pathways in England and would be well placed to carry out such a piece of work. We have spoken to Professor Naomi Fulop from University College London, a world leading researcher in this area. She and her team would be very interested in discussing the carrying out of an evaluation of a new hyperacute stroke care pathway in Essex.

We know that HASUs are more likely to provide evidence-based clinical interventions than non-centralised systems (Ramsay et al. 2015). However, there is a need to measure whether this is due to their 24-hour availability or other factors e.g. increased funding and resources. Also, it is necessary to evaluate what other benefits are associated with 24 hour services in HASUs. The study by Simister et al. 2014 of a London HASU is likely to shed light on this. It is realistic to assume that the higher number of evidence-based clinical interventions delivered in HASUs will benefit both patients eligible for thrombolysis and/or thrombectomy and other stroke patients arriving that do not meet the eligibility criteria for either treatment. It can be assumed that quality of care is better in specialised stroke centres that more closely follow the recommendations for resources required to deliver a high-quality service (RCP 2016).

However, it might be short-sighted to think of HASUs in isolation rather than part of an intricate relationship within the whole network of providers and facilities. Caplan (2017) provides a list of suggestions including, amongst other things, upgrades to resources, adequate training to ambulance and other staff, and adequate and interoperable information systems for a stroke centre to have the ability to deliver high quality care which benefits the greatest number of patients.

References

1. Agarwal, S., Day, D. J., Sibson, L., Barry, P. J., Collas, D., Metcalf, K., ... & O'Kane, D. (2014). Thrombolysis delivery by a regional telestroke network—experience from the UK National Health Service. Journal of the American Heart Association, 3(1), e000408.

2. AHA/ASA Guideline: https://www.strokeassociation.org/idc/groups/heart-public/@wcm/@hcm/@gwtg/documents/downloadable/ucm_487907.pdf

3. Alberts, M. J., Latchaw, R. E., Selman, W. R., Shephard, T., Hadley, M. N., Brass, L. M., ... & Croft, J. B. (2005). Recommendations for comprehensive stroke centers. Stroke, 36(7), 1597-1616.

4. Ali, S. F., Singhal, A. B., Viswanathan, A., Rost, N. S., & Schwamm, L. H. (2013). Characteristics and outcomes among patients transferred to a regional comprehensive stroke center for tertiary care. Stroke, 44(11), 3148-3153.

5. Amorim, E., Shih, M. M., Koehler, S. A., Massaro, L. L., Zaidi, S. F., Jumaa, M. A., ... & Wechsler, L. R. (2013). Impact of telemedicine implementation in thrombolytic use for acute ischemic stroke: the University of Pittsburgh Medical Center telestroke network experience. Journal of Stroke and Cerebrovascular Diseases, 22(4), 527-531.

6. Arba, F., Piccardi, B., Baldereschi, M., Ricci, S., & Inzitari, D. (2016). Telemedicine for acute ischaemic stroke. The Cochrane Library

7. Asif, K. S., Lazzaro, M. A., & Zaidat, O. (2013). Identifying delays to mechanical thrombectomy for acute stroke: onset to door and door to clot times. Journal of neurointerventional surgery, neurintsurg-2013.

8. Audebert HJ, Kukla C, Clarmann von Claranau S, K€uhn J, Vatankhah B, Schenkel J, Ickenstein GW, Haberl RL, Horn M; TEMPiS Group. Telemedicine for safe and extended use of thrombolysis in stroke: the Telemedic Pilot Project for Integrative Stroke Care (TEMPiS) in Bavaria. Stroke. 2005;36:287–291.

9. Audebert HJ, Schenkel J, Heuschmann PU, Bogdahn U, Haberl RL; Telemedic Pilot Project for Integrative Stroke Care Group. Effects of the implementation of a telemedical stroke network: the Telemedic Pilot Project for Integrative Stroke Care (TEMPiS) in Bavaria, Germany. Lancet Neurol. 2006;5:742–748.

10. Audebert, H. J., & Schwamm, L. (2009). Telestroke: scientific results. Cerebrovascular Diseases, 27(Suppl. 4), 15-20. Chicago

11. Birns, J., Roots, A., & Bhalla, A. (2013). Role of telemedicine in the management of acute ischemic stroke. Clinical Practice, 10(2), 189-200.

12. Bowes, S; Varshney M.; MacRae, JD (2015). Kent and Medway Stroke Services. Evidence Review of Hyperacute Stroke Units. Kent & Medway Public Health Observatory.

13. Bowry, R., Parker, S., Rajan, S. S., Yamal, J. M., Wu, T. C., Richardson, L., ... & Grotta, J. C. (2015). Benefits of Stroke Treatment Using a Mobile Stroke Unit Compared With Standard Management. Stroke, 46(12), 3370-3374.

14. Bray BD, Ayis S, Campbell J, Hoffman A, Roughton M, Tyrrell PJ, et al. Associations between the organisation of stroke services, process of care, and mortality in England: prospective cohort study. BMJ 2013;346:f2827.

15. Brooke, J., Kar, A., & Ames, D. (2010). Impact of hyper acute stroke unit on length of hospital stay and discharge destination; Imperial College Healthcare NHS Trust. International Journal of Stroke, 5, 30.

16. Brotons, A., Motola, I., Romano, J., Schwemmer, S., & Issenberg, B. (2016). Abstract TP254: The Use of Prehospital Telemedicine to Aid in the Decision to Airlift Patients to a Comprehensive Stroke Center From a Rural Area.

17. Bücke, P., Pérez, M. A., Schmid, E., Nolte, C. H., Bäzner, H., & Henkes, H. (2017). Endovascular thrombectomy in acute ischemic stroke: outcome in referred versus directly admitted patients. Clinical Neuroradiology, 1-10.

18. Caplan, L. R. (2017). Primary Stroke Centers vs Comprehensive Stroke Centers With Interventional Capabilities: Which Is Better for a Patient With Suspected Stroke?. Jama neurology, 74(5), 504-506.

19. Cha, J. K., Nah, H. W., Kang, M. J., Kim, D. H., Park, H. S., Kim, S. B., ... & Huh, J. T. (2014). Outcomes after tissue plasminogen activator administration under the drip and ship paradigm may differ according to the regional stroke care system. Journal of Stroke and Cerebrovascular Diseases, 23(1), 160-163.

20. Commiskey, P., Afshinnik, A., Cothren, E., Gropen, T., Iwuchukwu, I., Jennings, B., ... & Zweifler, R. M. (2017). Description of a novel telemedicine-enabled comprehensive system of care: drip and ship plus drip and keep within a system of stroke care delivery. Journal of telemedicine and telecare, 23(3), 428-436.

21. Davie, C., Hunter, R. M., Mountford, J., & Morris, S. (2013). London's hyperacute stroke units improve outcomes and lower costs'. Harvard Business Review.

22. Deguchi, I., Mizuno, S., Kohyama, S., Tanahashi, N., & Takao, M. (2017). Drip-and-Ship Thrombolytic Therapy for Acute Ischemic Stroke. Journal of Stroke and Cerebrovascular Diseases.

23. De Keyser, J., Gdovinová, Z., Uyttenboogaart, M., Vroomen, P. C., & Luijckx, G. J. (2007). Intravenous alteplase for stroke. Stroke, 38(9), 2612-2618.

24. Demaerschalk BM, Miley ML, Kiernan TE, Bobrow BJ, Corday DA, Wellik KE, Aguilar MI, Ingall TJ, Dodick DW, Brazdys K, Koch TC, Ward MP, Richemont PC; STARR Coinvestigators. Stroke telemedicine. Mayo Clin Proc. 2009;84:53–64.

25. Douw, K., Nielsen, C. P., & Pedersen, C. R. (2015). Centralising acute stroke care and moving care to the community in a Danish health region: Challenges in implementing a stroke care reform. Health Policy, 119(8),

1005-1010.

26. Emberson, J., Lees, K. R., Lyden, P., Blackwell, L., Albers, G., Bluhmki, E., ... & Grotta, J. (2014). Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. The Lancet, 384(9958), 1929-1935.

27. Espinoza, A. V., Van Hooff, R. J., De Smedt, A., Moens, M., Yperzeele, L., Nieboer, K., ... & Dupont, A. (2016). Development and Pilot Testing of 24/7 In-Ambulance Telemedicine for Acute Stroke: Prehospital Stroke Study at the Universitair Ziekenhuis Brussel-Project. Cerebrovascular Diseases, 42(1-2), 15-22. Chicago

28. Evans, M. R., White, P., Cowley, P., & Werring, D. J. (2017). Revolution in acute ischaemic stroke care: a practical guide to mechanical thrombectomy. Practical Neurology, practneurol-2017.

29. Feigin VL, et al. (2013). Global and regional burden of stroke during 1990-2010: findings from the Global Burden of Disease Study 2010. Lancet 383: 245-255.

30. Fonarow GC, Smith EE, Saver JL, et al. Timeliness of tissue-type plasminogen activator therapy in acute ischemic stroke: patient characteristics, hospital factors, and outcomes associated with door-to-needle times within 60 minutes. Circulation. 2011;123(7):750-758.

31. Fraser, A., Baeza, J. I., & Boaz, A. (2017). 'Holding the line': a qualitative study of the role of evidence in early phase decision-making in the reconfiguration of stroke services in London. Health Research Policy and Systems, 15(1), 45.

32. Froehler, M. T., Saver, J. L., Zaidat, O. O., Jahan, R., Aziz-Sultan, M. A., Klucznick, R. P., ... & Liebeskind, D. S. (2017). Interhospital Transfer Prior to Thrombectomy is Associated with Delayed Treatment and Worse Outcome in the STRATIS Registry. Circulation, CIRCULATIONAHA-117.

33. Fulop, N. J., Ramsay, A. I., Perry, C., Boaden, R. J., McKevitt, C., Rudd, A. G., ... & Morris, S. (2016). Explaining outcomes in major system change: a qualitative study of implementing centralised acute stroke services in two large metropolitan regions in England. Implementation Science, 11(1), 80.

34. Gerschenfeld, G., Muresan, I. P., Blanc, R., Obadia, M., Abrivard, M., Piotin, M., & Alamowitch, S. (2017). Two paradigms for endovascular thrombectomy after intravenous thrombolysis for acute ischemic stroke. Jama neurology, 74(5), 549-556.

35. Ghos, S. K., Barrie, E., Sommerville, C., Godfrey, J. B., Young, J., & Shah, I. M. (2011). Patient Outcomes After Development Of Hyperacute Stroke Units (hasu) In Two District General Hospitals. Cerebrovascular Diseases, 31, 221.

36. Goyal M, Menon BK, van Zwam WH, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a metaanalysis of individual patient data from five randomised trials. Lancet 2016;387:1723–31.

37. Hankey, G. J. (2003). Long-term outcome after ischaemic stroke/transient ischaemic attack. Cerebrovascular diseases, 16(Suppl. 1), 14-19.

38. Healthcare for London & NHS (2008). Acute Stroke Service Designation. 6.1 Designation criteria for provision of a HASU Service.

39. Healthcare for London (2009) Stroke acute commissioning and tariff guidance. Healthcare for London. Available: http://www.londonhp.nhs.uk/wp-content/uploads/2011/03/Stroke-Commissioning-and-Tariff-Guidance.pdf. Accessed 1 July 2013.

40. Hess, D. C., Wang, S., Hamilton, W., Lee, S., Pardue, C., Waller, J. L., ... & Adams, R. J. (2005). REACH. Stroke, 36(9), 2018-2020.

41. Hiyama, N., Yoshimura, S., Shirakawa, M., Uchida, K., Oki, Y., Shindo, S., & Tokuda, K. (2016). Safety and effectiveness of Drip, Ship, and Retrieve paradigm for acute ischemic stroke: a single center experience. Neurologia medico-chirurgica, 56(12), 731-736.

42. Holodinsky, J. K., Williamson, T. S., Kamal, N., Mayank, D., Hill, M. D., & Goyal, M. (2017). Drip and Ship Versus Direct to Comprehensive Stroke Center. Stroke, 48(1), 233-238.

43. Hubert, G. J., Meretoja, A., Audebert, H. J., Tatlisumak, T., Zeman, F., Boy, S., ... & Müller-Barna, P. (2016). Stroke Thrombolysis in a Centralized and a Decentralized System (Helsinki and Telemedical Project for Integrative Stroke Care Network). Stroke, 47(12), 2999-3004.

44. Hunter, R. M., Davie, C., Rudd, A., Thompson, A., Walker, H., Thomson, N., ... & Dewan, B. (2013). Impact on clinical and cost outcomes of a centralized approach to acute stroke care in London: a comparative effectiveness before and after model. PloS one, 8(8), e70420.

45. Jauch EC, Saver JL, Adams HP Jr, et al; American Heart Association Stroke Council; Council on Cardiovascular Nursing; Council on Peripheral Vascular Disease; Council on Clinical Cardiology. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2013;44(3):870-947.

46. Johansson, T., & Wild, C. (2010). Telemedicine in acute stroke management: systematic review. International journal of technology assessment in health care, 26(2), 149-155.

47. Kepplinger, J., Barlinn, K., Deckert, S., Scheibe, M., Bodechtel, U., & Schmitt, J. (2016). Safety and efficacy of thrombolysis in telestroke A systematic review and meta-analysis. Neurology, 87(13), 1344-1351.

48. Khatri, P., Yeatts, S. D., Mazighi, M., Broderick, J. P., Liebeskind, D. S., Demchuk, A. M., ... & Goyal, M. (2014). Time to angiographic reperfusion and clinical outcome after acute ischaemic stroke: an analysis of data from the Interventional Management of Stroke (IMS III) phase 3 trial. The Lancet Neurology, 13(6), 567-574.

49. Lahr, M. M., Luijckx, G. J., Vroomen, P. C., van der Zee, D. J., & Buskens, E. (2012). Proportion of patients treated with thrombolysis in a centralized versus a decentralized acute stroke care setting. Stroke, 43(5), 1336-1340.

50. Lahr, M. M., Luijckx, G. J., Vroomen, P. C., van der Zee, D. J., & Buskens, E. (2013). The chain of care enabling tPA treatment in acute ischemic stroke: a comprehensive review of organisational models. Journal of neurology, 260(4), 960-968.

51. Lahr, M. M., van der Zee, D. J., Luijckx, G. J., Vroomen, P. C., & Buskens, E. (2017). Centralising and optimising decentralised stroke care systems: a simulation study on short-term costs and effects. BMC medical research methodology, 17(1), 5.

52. Langhorne P, Fearon P, Ronning OM, Kaste M, Palomaki H, Vemmos K, et al. Stroke unit care benefits patients with intracerebral hemorrhage systematic review and meta-analysis. Stroke 2013;44:3044-9.

53. Lees KR, Bluhmki E, von Kummer R, et al; ECASS, ATLANTIS, NINDS and EPITHET rt-PA Study Group. 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.

54. Liebeskind, D. S. (2015). Response to letter regarding article," art of expertise in stroke telemedicine: imaging and the collaterome". Stroke, 46(6), e152.

55. Lyerly, M., Albright, K., Boehme, A., Shahripour, R. B., Houston, J., Rawal, P., ... & Alexandrov, A. (2013). Potential biases in patients selected for drip and ship thrombolysis (P04. 053). Neurology, 80(7 Supplement), P04-053.

56. Lyerly, M. J., Albright, K. C., Boehme, A. K., Shahripour, R. B., Donnelly, J. P., Houston, J. T., ... & Alexandrov, A. W. (2015). Patient Selection for Drip and Ship Thrombolysis in Acute Ischemic Stroke. Southern medical journal, 108(7), 393.

57. Mansoor, S., Zand, R., Al-Wafai, A., Wahba, M. N., & Giraldo, E. A. (2013). Safety of a "drip and ship" intravenous thrombolysis protocol for patients with acute ischemic stroke. Journal of Stroke and Cerebrovascular Diseases, 22(7), 969-971.

58. Martin-Schild, S., Morales, M. M., Khaja, A. M., Barreto, A. D., Hallevi, H., Abraham, A., ... & Savitz, S. I. (2011). Is the drip-and-ship approach to delivering thrombolysis for acute ischemic stroke safe?. The Journal of emergency medicine, 41(2), 135-141.

59. Mehta, S., Vora, N., Edgell, R. C., Allam, H., Alawi, A., Koehne, J., ... & Alshekhlee, A. (2014). Stroke mimics under the drip-and-ship paradigm. Journal of Stroke and Cerebrovascular Diseases, 23(5), 844-849.

60. Menon, B. K., Sajobi, T. T., Zhang, Y., Rempel, J. L., Shuaib, A., Thornton, J., ... & Sapkota, B. (2016). Analysis of workflow and time to treatment on thrombectomy outcome in the endovascular treatment for small core and proximal occlusion ischemic stroke (ESCAPE) randomized, controlled trial. Circulation, 133(23), 2279-2286.

61. Meretoja, A., Roine, R. O., Kaste, M., Linna, M., Roine, S., Juntunen, M., ... & Sivenius, J. (2010). Effectiveness of primary and comprehensive stroke centers. Stroke, 41(6), 1102-1107.

62. Meyer BC, Raman R, Hemmen T, Obler R, Zivin JA, Rao R, Thomas RG, Lyden PD. Efficacy of site-independent telemedicine in the STRokE DOC trial: a randomised, blinded, prospective study. Lancet Neurol. 2008;7:787–795.

63. Milne, Matthew S., et al. "Drip 'n Ship vs. Mothership for Endovascular Treatment: Modeling the Best Transportation Options for Optimal Outcomes in California and Alberta." (2017): A85-A85.

64. Mohan KM, Wolfe CD, Rudd AG, Heuschmann PU, et al, 2011. Risk and cumulative risk of stroke recurrence: a systematic review and meta-analysis. Stroke, 42, 1489-94.

65. Morris, Stephen, et al. "Impact of centralising acute stroke services in English metropolitan areas on mortality and length of hospital stay: difference-in-differences analysis." Bmj 349 (2014): g4757.

66. Mouthon-Reignier, C., Bonnaud, I., Gaudron, M., Vannier-Bernard, S., Bodin, J. F., Cottier, J. P., ... & Debiais, S. (2016). Impact of a direct-admission stroke pathway on delays of admission, care, and rates of intravenous thrombolysis. Revue neurologique, 172(12), 756-760.

67. Müller, R., Pfefferkorn, T., Vatankhah, B., Mayer, T. E., Schenkel, J., Dichgans, M., ... & Audebert, H. J. (2007). Admission facility is associated with outcome of basilar artery occlusion. Stroke, 38(4), 1380-1383.

68. Müller-Barna, P., Schwamm, L. H., & Haberl, R. L. (2012). Telestroke increases use of acute stroke therapy. Current opinion in neurology, 25(1), 5-10.

69. NIHR - National Institute of Health Research (2017). Roads to recovery. Organisation and Quality of Stroke Services. NIHR Dissemination Centre.

70. National Records of Scotland. (2016). Deaths by sex, age and cause, Scotland, 2015. http://bit. ly/2h671Pu Last accessed 20 December 2016.

71. NICE Guidance 68 (2005): https://www.nice.org.uk/guidance/cg68/evidence/full-guideline-pdf-196845517

72. Northern Ireland Statistics and Research Agency (NISRA). (2016). Deaths, by sex, age and cause, 2015. http://bit.ly/29ffuON Last accessed 20 December 2016.

73. Office for National Statistics. (2016). Deaths registered in England and Wales: 2015. http:// bit. ly/2h7Om7P Last accessed 20 December 2016.

74. Parker, S. A., Bowry, R., Wu, T. C., Noser, E. A., Jackson, K., Richardson, L., ... & Grotta, J. C. (2015). Establishing the first mobile stroke unit in the United States. Stroke, 46(5), 1384-1391.

75. Perez de la Ossa. Direct Transfer to an Endovascular Center Compared to Transfer to the Closest Stroke Center in Acute Stroke Patients With Suspected Large Vessel Occlusion (RACECAT). NCT02795962. Accessible via https://clinicaltrials.gov/ct2/show/NCT02795962

76. Pickering, A., Harnan, S., Cooper, K., Sutton, A., Mason, S., & Nicholl, J. (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 & policy, 21(1), 51-60.

77. Prabhakaran, S., Ward, E., John, S., Lopes, D. K., Chen, M., Temes, R. E., ... & Bleck, T. P. (2011). Transfer delay is a major factor limiting the use of intra-arterial treatment in acute ischemic stroke. Stroke, 42(6), 1626-1630.

78. Price, C. I., Clement, F., Gray, J., Donaldson, C., & Ford, G. A. (2009). Systematic review of stroke thrombolysis service configuration. Expert review of neurotherapeutics, 9(2), 211-233.

79. Public Health England review: https://www.engage.england.nhs.uk/consultation/clinical-commissioning-consultation-may-2017/user_uploads/mechanical-thrombectomy-evidence-review.pdf

80. Qureshi, A. I., Chaudhry, S. A., Rodriguez, G. J., Suri, M. F. K., Lakshminarayan, K., & Ezzeddine, M. A. (2012). Outcome of the ‘drip-and-ship’paradigm among patients with acute ischemic stroke: Results of a statewide study. Cerebrovascular diseases extra, 2(1), 1-8.

81. Ramsay, A. I., Morris, S., Hoffman, A., Hunter, R. M., Boaden, R., McKevitt, C., ... & Tyrrell, P. J. (2015). Effects of centralizing acute stroke services on stroke care provision in two large metropolitan areas in England. Stroke, 46(8), 2244-2251.

82. RCP - Royal College of Physicians. National clinical guideline for stroke, Fifth Edition, 2016. Available: https://www.strokeaudit.org/SupportFiles/Documents/Guidelines/2016-National-Clinical-Guideline-for-Stroke-5t-(1).aspx

83. Sairanen T, Soinila S, Nikkanen M, Rantanen K, Mustanoja S, F€arkkil€a M, Pieninkeroinen I, Numminen H, Baumann P, Valpas J, Kuha T, Kaste M, Tatlisumak T; For the Finnish Telestroke Task Force. Two years of Finnish Telestroke: thrombolysis at spokes equal to that at the hub. Neurology. 2011; 76:1145–1152.

84. Saver JL, Fonarow GC, Smith EE, et al. Time to treatment with intravenous tissue plasminogen activator and outcome from acute ischemic stroke. JAMA. 2013;309(23):2480-2488.

85. Schlemm, E., Ebinger, M., Nolte, C. H., Endres, M., & Schlemm, L. (2017). Optimal Transport Destination for Ischemic Stroke Patients With Unknown Vessel Status: Use of Prehospital Triage Scores. Stroke, 48(8), 2184-2191.

86. Schwab S, Vatankhah B, Kukla C, Hauchwitz M, Bogdahn U, Fürst A, Audebert HJ, Horn M; TEMPiS Group. Long-term outcome after thrombolysis in telemedical stroke care. Neurology. 2007;69:898–903.

87. Schwamm, L. H., Holloway, R. G., Amarenco, P., Audebert, H. J., Bakas, T., Chumbler, N. R., ... & Mayberg, M. (2009). A review of the evidence for the use of telemedicine within stroke systems of care. Stroke, 40(7), 2616-2634.

88. Sheth, K. N., Smith, E. E., Grau-Sepulveda, M. V., Kleindorfer, D., Fonarow, G. C., & Schwamm, L. H. (2015). Drip and Ship Thrombolytic Therapy for Acute Ischemic Stroke. Stroke, STROKEAHA-114.

89. Simister, R., Ramsay, A, Playford, D, Jager, HR, Capp, A, Rudd, A, Brown, M, Fulop, N, Morris, S (2014). Mixed methods analysis of the London Hyperacute Stroke System: identifying lessons on 24/7 working (METRO-24/7). Protocol. Accessible via: https://www.journalslibrary.nihr.ac.uk/programmes/hsdr/1212841/#/documentation

90. Southerland AM, Johnston KC, Molina CA, Selim MH, Kamal N, Goyal M. Suspected large vessel occlusion: should emergency medical services transport to the nearest primary stroke center or bypass to a comprehensive stroke center with endovascular capabilities ? Stroke. 2016;47(7):1965-1967.

91. SSNAP - Royal College of Physicians Sentinel Stroke National Audit Programme (SSNAP). National clinical audit annual results portfolio March 2015-April 2016. Available: http://bit.ly/1M5R3Op Last accessed 26 October 2016

92. Stroke Association ([2017). State of the nation: stroke statistics. www.stroke.org.uk (downloaded 22 November 2016)

93. Switzer JA, Hall C, Gross H, Waller J, Nichols FT, Wang S, Adams RJ, Hess DC. A web-based telestroke system facilitates rapid treatment of acute ischemic stroke patients in rural emergency departments. J Emerg Med. 2009;36:12–18.

94. Switzer, J. A., Demaerschalk, B. M., Xie, J., Fan, L., Villa, K. F., & Wu, E. Q. (2012). Cost-effectiveness of hub-and-spoke telestroke networks for the management of acute ischemic stroke from the hospitals' perspectives. Circulation: Cardiovascular Quality and Outcomes, CIRCOUTCOMES-112.

95. Tekle, W. G., Chaudhry, S. A., Hassan, A. E., Rodriguez, G. J., Suri, M. F. K., & Qureshi, A. I. (2012). Drip-and-ship thrombolytic treatment paradigm among acute ischemic stroke patients in the United States. Stroke, 43(7), 1971-1974.

96. Trialists'Collaboration, S. U. (2013). Organised inpatient (stroke unit) care for stroke. Cochrane Database Syst Rev, 9(9).

97. Wang S, Gross H, Lee SB, Pardue C, Waller J, Nichols FT, Adams RJ, Hess DC. Remote evaluation of acute ischemic stroke in rural community hospitals in Georgia. Stroke. 2004;35:1763–1768.

98. Wardlaw, J. M., Murray, V., Berge, E., & del Zoppo, G. J. (2014). Thrombolysis for acute ischaemic stroke. The Cochrane Library.

99. Wu, T. C., Parker, S. A., Jagolino, A., Yamal, J. M., Bowry, R., Thomas, A., ... & Grotta, J. C. (2017). Telemedicine can replace the neurologist on a mobile stroke unit. Stroke, 48(2), 493-496.

100. Yamal, J. M., Rajan, S. S., Parker, S. A., Jacob, A. P., Gonzalez, M. O., Gonzales, N. R., ... & Persse, D. (2017). Benefits of stroke treatment delivered using a mobile stroke unit trial.