J R Coll Physicians Edinb 2015 45: 190–5
http://dx.doi.org/10.4997/JRCPE.2015.303

CLINICAL

Pre-hospital notification is associated with improved stroke thrombolysis timing

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ABSTRACT Intravenous thrombolysis increases disability-free survival after acute ischaemic stroke in a time-dependent fashion. We aimed to determine whether pre-hospital notification, introduction of a CT scanner near to assessment site and introduction of out-of-hours thrombolysis services affect thrombolysis timing.
Methods Timings related to thrombolysis were collected between May 2012 and June 2014 at a single hospital site; these included time to stroke physician assessment, time to cranial CT imaging and door to needle time. All thrombolysed ischaemic stroke patients admitted via the emergency department were included. Ambulance services were asked to pre-notify the emergency department of any suspected stroke patient during this period.
Results We studied 182 patients (48% female; mean age 74 years; 59% pre-notified). Pre-hospital notification was associated with a significantly higher rate of CT scanning within 25 minutes (60% vs 24%, odds ratio [OR] 4.7, 95% confidence interval [CI] 2.4–9.0; p<0.001), earlier stroke physician assessment (median 6 vs 32 minutes; p<0.001) and receiving thrombolysis within 60 minutes (89% vs 49%, OR 8.0, 95% CI 3.8–16.9; p<0.001). Being treated outside normal working hours did not alter thrombolysis timing. Logistic regression identified the introduction of a near-site CT scanner (OR 4.6 [95% CI 1.7–12.5]) and pre-hospital notification (OR 4.7, [95% CI 2.3–9.6]) as independent predictors of door to CT time ≤25 minutes, and pre-hospital notification (OR 11.6, [95% CI 4.9-30.3]) and stroke severity (OR 1.15 per point of NIHSS scale, [95% CI 1.08-1.23]) as predictors of door to thrombolysis time ≤60 minutes. The most common perceived timing delays were radiology-related (33%), the need to acutely lower blood pressure (15%) and obtaining consent (12%).
Conclusion Pre-hospital notification is associated with earlier stroke physician review, CT imaging and delivery of thrombolysis. Referral to an out of hours thrombolysis service was not associated with additional delay.

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KEYWORDS acute stroke, ambulance services, computed tomography, pre-hospital notification, thrombolysis

DECLARATION OF INTERESTS No conflict of interest declared

INTRODUCTION

Stroke is the second leading cause of death worldwide.[1] Although the prevalence of stroke in Scotland has remained static since 1995,[2] incidence and mortality rates have fallen over the past 10 years (2003–2012) by 21% and 43%, respectively.[3] In patients with acute ischaemic stroke (AIS), intravenous thrombolysis given within 4.5 hours of symptom onset increases rates of independent survival, with greater benefit the earlier it is given.[4] There are many barriers to patients receiving intravenous thrombolysis,[5] but for thrombolysis to occur in a timely fashion, a suspected stroke patient needs prompt cranial CT imaging and assessment by a stroke physician. Pre-hospital notification (PHN) of suspected stroke patients during transfer to hospital by ambulance services[6-8] can improve thrombolysis timing and increase the proportion of stroke patients eligible to receive thrombolysis within the 4.5 hour time window. Guidelines[9,10] have emphasised the importance of minimising door to thrombolysis time by several means including PHN. In addition, Quality Improvement Scotland set out seven stroke care standards in 2013, including that 80% of patients receiving thrombolysis should have the treatment initiated within one hour of hospital arrival. In 2013 the majority of stroke units in Scotland failed to meet this standard with one-third of patients, on average, receiving thrombolysis within 60 minutes of hospital arrival.[11] In our own centre, in common with many centres providing thrombolysis, the on-call stroke physicians, CT radiographer and radiologists are on-call from home outside normal working hours. Some studies describe slower time to thrombolysis out of hours,[12,13] therefore we were interested to know whether thrombolysis timing and CT imaging differed when performed outside of normal working hours.

AIM

The primary aim of this study was to compare the time to stroke thrombolysis between patients with and without PHN. We also examined whether thrombolysis timing was different out of hours, or was improved by the introduction of a near-sited CT scanner in the emergency department at our hospital.

METHODS

This study was carried out at the Acute Stroke Unit (ASU), Aberdeen Royal Infirmary, as part of routine audit. This study had local Caldicott approval as an audit for the purposes of quality assurance and monitoring of practice. A stroke thrombolysis proforma was used to collect information on timing including time of symptom onset, call to emergency services, hospital arrival, review by stroke physician, CT scan, and time of commencement of thrombolysis. We also recorded whether there was any PHN from ambulance services, and whether the patient presented out of hours (i.e. outwith 9am–5pm, Monday to Friday). The proforma was completed by the treating stroke physician (five stroke consultants and one stroke speciality doctor covering the acute stroke rota) at the time of the thrombolysis treatment. The ambulance service printed record was used for the pre-hospital data. The acute stroke unit is a 16-bed unit covering a population of 523,000 in the north-east of Scotland and 42,000 in Orkney and the Shetland Isles, and admits approximately 600 patients each year. Patients who are suspected of having stroke (abnormal face, arm and speech test [FAST]),[14] with symptom onset within 4.5 hours are transported urgently to the emergency department at our hospital. During the study period, it was advised that all suspected FAST positive patients with symptom onset in the last 4.5 hours be pre-notified by ambulance staff informing the emergency department, although this was guidance and not mandatory. The emergency department staff then contacted the on-call stroke physician and on-call radiologist and radiographer, who are not resident out of hours.

Data were collected between May 2012 and June 2014. We also obtained further clinical parameters from the Safe Implementation of Thrombolysis (SITS) database[15] including baseline National Institute of Health Stroke Scale (NIHSS) score, age, sex and pre-stroke modified Rankin score. Treating physicians were prompted to document any factors perceived to have delayed initiation of thrombolysis on the proforma as free text. Factors with a similar nature were subsequently grouped together (e.g. CT scanner broken or awaiting radiologist were grouped under radiology-related). In December 2012 a near-sited CT scanner situated within the emergency department (distance of 10–30 metres from the patient assessment rooms) became operational with the opening of a new Emergency Care Centre.

We analysed timing of CT scan, stroke physician assessment and thrombolysis with regard to whether patients were pre-notified or not, whether they were treated out of hours or not, and whether they were treated before or after introduction of the near-sited CT scanner in December 2012. We also compared the proportion of patients receiving a CT scan (door to CT time) within 25 minutes of emergency department arrival, and the proportion who were thrombolysed (door to needle time) within 60 minutes of emergency department arrival. The threshold door to needle time of ≤ 60 minutes was chosen as the Scottish Stroke Care audit advises this be achieved in at least 80% of patients.[11]

Although there is no current timing standard by which stroke thrombolysis patients should have cranial CT imaging in Scotland, we have used the threshold of 25 minutes of emergency department arrival, since this was the standard first proposed in 1996 following approval of use of thrombolysis for stroke in the USA.[16] Chi square test and Student's t-test were used to test proportions and continuous data, respectively. Times are displayed as medians with inter-quartile intervals; since the timing data were not normally distributed we compared timing data using non-parametric pooled samples median testing. Significance was taken as $p < 0.05$. To identify variables that were independently associated with both door to CT time ≤25 minutes and door to needle time ≤60 minutes, we performed stepwise logistic regression analysis using the following variables; age, sex, baseline NIHSS, time period (up to May 2013 or from June 2013), pre-stroke independence, whether treated out of hours, in the era of the near-cited CT (from or before 1 December 2012), and whether there was prehospital notification. Analyses were performed using SPSS version 22 (IBM, New York, USA).

RESULTS

Nineteen patients with missing data or in-hospital stroke were excluded, leaving 182 patients with stroke who received thrombolysis during this period. Forty-eight percent were female with a mean age of 74 ± 13 years (ranging from 26–100), and a median NIHSS score of 12 (range 1–37). One hundred and seven patients (59%) were pre-notified by the ambulance service, and 108 (59%) patients were treated with thrombolysis out of hours. One hundred and thirty (72%) patients were thrombolysed within 60 minutes of admission. There were no differences in key characteristics between patients who had prehospital notification, or for those were treated out of hours (Tables 1 and 2). Pre-hospital notification was significantly associated with improvement in each category of in-hospital thrombolysis timing, but not pre-hospital timing (Table 1). Patients pre-notified by the ambulance service were significantly more likely to have a door to CT time of ≤25 minutes (60% vs 24%,

TABLE 1 Effect of pre-hospital notification on timing of CT scan and thrombolysis

Pre-hospital notification	Yes	No	Odds ratio (95% CI)	p
Sample size	107	75		
Mean age ± SD (years)	75 ± 12	72 ± 14		0.21
Female (%)	55 (51)	33 (43)		0.30
Median NIHSS score (IQR)	12 (7–19)	11 (6–19)		0.71
Pre-stroke independence (%)	88/93 (95)	56/65 (86)		0.09
Median time from symptom onset to ambulance call (IQR) (min)	23 (9–63)	23 (7–50)		0.97
Median time from ambulance call to hospital arrival (IQR) (min)	67 (47–91)	58 (44–76)		0.15
Median time from stroke team call to review (IQR) (min)	6 (0–15)	32 (16–43)		<0.001
Median door to CT time (IQR) (min)	21 (12–33)	39 (26–59)		<0.001
Number with door to CT time ≤25 min (%)	62/104 (60)	18/75 (24)	4.7 (2.4–9.0)	<0.001
Median door to needle time (IQR) (min)	35 (29–49)	61 (43–86)		<0.001
Number with door to needle time ≤60 min (%)	93/105 (89)	37/75 (49)	8.0 (3.8–16.9)	<0.001
Number with door to needle time ≤40 min (%)	64/105 (61)	13/75 (17)	7.4 (3.6–15.2)	<0.001

TABLE 2 Effect of out of hours on timing of CT scan and thrombolysis

Treated out of hours	Yes	No	Odds ratio (95% CI)	p
Sample size	108	74		
Mean age ± SD (years)	73 ± 14	75 ± 13		0.50
Female (%)	53 (49)	35 (47)		0.77
Median NIHSS score (IQR)	12 (6–18)	9 (6–18)		0.18
Pre-stroke independence (%)	85/93 (91)	59/65 (91)		1.0
Median time symptom onset to ambulance call (IQR) (min)	23 (9–54)	22 (5–55)		0.90
Median time call to hospital arrival (IQR) (min)	61 (47–90)	61 (45–79)		0.91
Median time stroke team call to review (IQR) (min)	15 (4–33)	13 (4–30)		0.42
Median door to CT time (IQR) (min)	30 (16–50)	25 (14–45)		0.91
Number with door to CT time ≤25 min (%)	42/104 (40)	38/74 (51)	0.64 (0.37–1.17)	0.15
Median door to needle time (IQR) (min)	44 (31–68)	46 (31–60)		0.88
Number with door to needle time ≤60 min (%)	74/106 (70)	56/74 (76)	0.74 (0.38–1.46)	0.39

odds ratio [OR] 4.7, 95% confidence interval [CI] 2.4–9.0) and door to needle time of ≤60 minutes (89% vs 49%, OR 8.0, 95% CI 3.8–16.9). Being treated out of hours did not influence timing of ambulance service response, stroke physician assessment, CT imaging or thrombolysis (Table 2).

Analysing data from before and after introduction of the near-sited CT scanner in December 2012, the proportion of patients with door to CT time of ≤25 minutes increased (52% vs 18%, OR 5.0, 95% CI 2.1–12.0), but the proportion with door to needle time ≤60 minutes did not change significantly (73% vs 69%, OR 1.2, 95% CI 0.6–2.6, Table 3). Comparing data between the first and second 13-month periods of the study, the rate of prehospital notification increased (69% [67/97] vs 46% [39/85] of patients; OR 2.6, 95% CI 1.4–4.8). In multivariate analysis the independent predictors of door to CT time ≤25 minutes were prehospital notification (OR 4.7, 95% CI 2.3–9.6) and introduction of the near-sited CT scanner (OR 4.6, 95% CI 1.7–12.5). For door to needle time ≤60 minutes, the independent predictors were NIHSS (OR 1.15 per point of NIHSS scale, 95% CI 1.08–1.23) and prehospital notification (OR 11.6, 95% CI 4.9–30.3). Door to CT time was not included in logistic regression to predict door to needle time ≤60 minutes as these two variables are so intimately linked. However 71/79 (90%) of patients with door to CT time ≤25 minutes achieved a door to needle time ≤60 minutes, compared to only 58/100 (58%) of patients with door to CT time >25 minutes (OR 6.4, 95% CI 2.8–14.8).

Several factors were documented by the treating stroke physician as perceived causes of delay in thrombolysis timing. In 33 cases (33%) there were factors relating to delay in CT imaging:

- awaiting arrival of radiologist or radiographer (n=10)
- other patients in scanner (n=18)
- CT scanner broken and required to use an alternative scanner (n=5)
- treating hypertension (blood pressure >185/110 mmHg, n=15) prior to giving thrombolysis
- obtaining consent for thrombolysis (i.e. discussing

TABLE 3 Effect of introduction of near-sited CT scanner on thrombolysis and imaging timing

	Post near-sited CT scanner	Pre near-sited CT scanner	Odds ratio (95% CI)	p
n	143	39		
Mean age ± SD (years)	73 (13)	75 (13)		0.48
Female (%)	66/143 (46)	22/39 (56)		0.37
Median NIHSS score (IQR)	10 (6–19)	12 (6–18)		0.72
Pre-stroke independence (%)	114/123 (93)	30/35 (86)		0.20
Median time symptom onset to ambulance call (IQR) (min)	22 (7–56)	29 (11–47)		0.34
Median time call to hospital arrival (IQR) (min)	61 (46–82)	60 (44–91)		0.91
Median time stroke team call to review (IQR) (min)	14 (1–30)	17 (5–39)		0.60
Median door to CT time (IQR) (min)	25 (14–45)	34 (27–60)		0.008
Median door to needle time (IQR) (min)	44 (32–63)	45 (31–64)		1.00
Number with door to CT time ≤25 min (%)	73/140 (52)	7/39 (18)	5.0 (2.1–12.0)	<0.001
Number with door to needle time ≤60 min (%)	103/141 (73)	27/39 (69)	1.2 (0.6–2.6)	0.64
Number with Pre-hospital notification (%)	88/143 (62)	18/39 (46)	1.9 (0.9–3.8)	0.08

risks and benefits with patients and/or relatives and obtaining consent or assent for treatment, n=12)
- patients being medically unstable (e.g. dyspnoea, excluding fracture, n=6)
- awaiting International Normalized Ratio result (n=6)
- initial misdiagnosis or delay in contacting stroke physician (n=5)
- fluctuating symptoms (n=5)
- difficulty obtaining IV cannulation (n=5)
- multiple thrombolysis patients being treated at the same time (n=3)

DISCUSSION

This study demonstrates that a significantly higher proportion of patients with stroke had timely CT cranial imaging, earlier assessment by a stroke physician and administration of thrombolysis if the patient was pre-notified by the ambulance service. The introduction of a near-sited CT scanner increased the proportion of patients undergoing CT scanning in a timely manner, which was in turn associated with higher rates of timely thrombolysis, as has been previously noted from the SITS-EAST registry.[17] Stroke severity, as measured by NIHSS, was identified in our dataset to be an independent predictor of door to needle time of ≤60 minutes as shown in a previous study.[18] This may relate to delayed stroke diagnosis in patients with milder symptoms, less certainty of the benefit of treatment if symptoms appear to be improving, or perhaps greater urgency in the more severely affected patients. It continues to prove challenging to achieve the Quality Improvement Scotland standard for 80% of thrombolysed stroke patients having door to needle times ≥60 minutes,[11] and a minority of patients tend to be treated within 60 minutes of hospital arrival in international studies.[13,17-20] In contrast, both in England and from the SITS registry, the majority of patients treated in higher volume centres (defined as thrombolysis of >50 or >100 stroke patients/year, respectively) have door to needle times within 60 minutes.[19, 20] Earlier door to CT time is also noted in higher volume centres[18] and when prehospital notification is used.[8] In our hospital, the percentage of stroke patients treated with thrombolysis with a door to needle time of ≤60 minutes for 2011 and 2012 was 45% and 37% respectively,[11] compared to 72% for the last two years. Prehospital notification has previously been shown to increase the number of patients who can be treated within the current 4.5 hour time window.[7] In keeping with this we found that rates of prehospital notification, and the numbers of patients being thrombolysed, increased in our centre during this study period.[11] Other aspects of the pre-hospital and hospital management of stroke patients could further improve timing, e.g. direct contact either between paramedics and the stroke physician or between stroke physician and the patient's relatives before arrival.[8,12,21,22] Clearly prehospital notification is particularly relevant where stroke physicians and radiologists are not on site 24 hours a day. Such a continuous presence would be expensive, and onerous to staff, although in some centres thrombolysis is delivered by emergency physicians.[11] In Helsinki, implementation of a range of quality improvement measures had led to a progressive reduction in door to needle times for stroke patients treated with thrombolysis, resulting in median door to needle times of 20 minutes.[21] Introduction of similar measures greatly improved door to needle times in an Australian centre.[12] In addition 30 recommendations have been suggested in Canada to help achieve a median door to needle times of less than 30 minutes.[22]

Patients treated out of hours in our centre have similar timing to those treated during normal working hours, suggesting that process of care for thrombolysis patients is as effective during normal daytime working hours and out of hours. This is in contrast to one large UK study suggesting stroke patients presenting to hospital out of hours have less efficient process of care.[23] One Australian

study showed improvement in door to needle times after introduction of the Helsinki model for thrombolysis, however these were not realised 'out of hours'.[12] Analysis of the SITS database found that median door to needle times were several minutes longer for patients treated during a weeknight or at the weekend compared to treatment on a weekday.[13] The reason for the lack of difference in out of hours treated patients in our centre is unclear, although locally we have been working collaboratively with our ambulance service, radiological and emergency department colleagues to improve thrombolysis times over several years. Other reasons may include less competing clinical work out of hours, and fewer routine scans potentially delaying emergency scans. In addition, our centre could be considered as a higher volume centre with more than 10 years' experience of delivering thrombolysis; factors which have previously been associated with shorter door to needle times,[19,20] and perhaps less difference in thrombolysis timing out of hours.

An effective service that works well requires ongoing audit and review of process of care between the various members of the team assessing and treating stroke patients (i.e. stroke physician, emergency medical and nursing staff, radiologists, radiographers, paramedics). One-third of perceived delays were documented to be radiology related. The introduction of a near-sited CT scanner reduced time to CT scan, but did not in itself appear to significantly improve thrombolysis timing. It is also possible that delays in some aspects of thrombolysis timing can be compensated for, for example preparatory work while waiting for a scan (e.g. consenting patients, dose calculations). Treating significantly raised blood pressure (typically BP >185/110 mmHg) pre-thrombolysis is common practice as per the original NINDS study[24] and can lead to delay, although the blood pressure thresholds for treatment are not rigidly adhered to in all centres. The third most common perceived delay is discussion with the patient or relatives as previously recognised by Kwan et al.[5] This comprises obtaining history, understanding patients' premorbid status, explaining the risks and benefits of thrombolysis and obtaining consent from patients or their relatives if a patient lacks capacity. Another perceived delay in the emergency deparment is delay in contacting a stroke physician and initial failure to diagnose a stroke. In some cases, the departmental workload can impede rapid assessment and communication.

This study has several limitations. There may be bias in recalling factors that are perceived to cause delay in providing thrombolysis, although the proforma was completed at the time of treatment. Also the relationship between prehospital notification and earlier thrombolysis timing could have an alternative explanation: patients with less clear stroke clinical presentations may have delayed stroke diagnosis and do not get prehospital notification. Against this we found no difference in stroke severity (as measured by NIHSS) or demographic details in patients who had prehospital notification, although stroke severity was an independent predictor of door to needle time of ≤60 minutes. The median NIHSS score of 11 for non-notified patients would be consistent with a moderately severe stroke. This should be clinically evident unless symptoms were less severe when first seen by ambulance service staff. One study found prehospital notified patients tended to have higher NIHSS than non-notified patients.[8] The reasons why some patients are not pre-alerted in our study is unclear, however prehospital notification became more widely used over this study period, increasing from 46% to 69%. Ideally all suspected acute stroke patients should have their pre-hospital and hyperacute process of care and timing audited; in this study we have focused specifically on thrombolysed patients as the benefit of thrombolysis is time sensitive.[4] For the analysis of introduction of the near-sited CT scanner in December 2012, it is possible that the six-month period before its introduction may be affected by confounding by seasonal variation in case-mix and fluctuation in patient numbers at different times of the year.

CONCLUSION

Pre-hospital notification is associated with reduced delay in timings of door to CT, door to stroke physician assessment and door to thrombolysis. Being treated out of hours did not affect timing in this hospital setting. A combination of factors including increasing use of prehospital notification, greater public awareness of stroke symptoms and continuing audit of the timing process will likely improve timely delivery and increasing utilisation of thrombolysis for acute ischaemic stroke patients. It is noteworthy that the Scottish Stroke Care standards published in 2014 endorsed prehospital notification for FAST positive stroke patients to the receiving emergency department or stroke unit.[11]

REFERENCES

1 World Health Organization. *The top 10 causes of death 2013*. http://www.who.int/mediacentre/factsheets/fs310/en/ (accessed 20/2/2015).

2 Gray L, Leyland AH. *Long-Term Conditions. Scottish Health Survey 2012 – Volume 1: Main Report*. http://www.scotland.gov.uk/Publications/2013/09/3684/12 (accessed 20/2/2015).

3 Information Services Division. *Stroke Statistics Update*; 2014. https://isdscotland.scot.nhs.uk/Health-Topics/Stroke/Publications/2014-01-28/2014-01-28-Stroke-Report.pdf?21743410826 (accessed 20/2/2015).

4 Emberson J, Lees KR, Lyden P et al. 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. *Lancet* 2014; 384: 1929–35. http://dx.doi.org/10.1016/S0140-6736(14)60584-5

5 Kwan J, Hand P, Sandercock P. A systematic review of barriers to delivery of thrombolysis for acute stroke. *Age Ageing* 2004; 33: 116-121.

6 Morgenstern LB, Staub L, Chan W et al. Improving delivery of acute stroke therapy: The TLL Temple Foundation Stroke Project. *Stroke* 2002; 33: 160–6.

7 Fassbender K, Balucani C, Walter S et al. Streamlining of prehospital stroke management: the golden hour. *Lancet Neurol* 2013; 12: 585–96. http://dx.doi.org/10.1016/S1474-4422(13)70100-5

8 Casolla B, Bodenant M, Girot M et al. Intra-hospital delays in stroke patients treated with rt-PA: impact of preadmission notification. *J Neurol* 2013; 260: 635–9. http://dx.doi.org/10.1007/s00415-012-6693-1

9 Scottish Intercollegiate Guidelines Network. *Management of patients with stroke or TIA: assessment, investigation, immediate management and secondary prevention.* SIGN 108; 2008. http://www.sign.ac.uk/pdf/sign108.pdf (accessed 20/2/2015).

10 Ringleb AP, Bousser M-G, Ford G et al. *Guidelines for Management of Ischaemic Stroke and Transient Ischaemic Attack 2008*. European Stroke Organization; 2008. p. 14–15. http://www.congrex-switzerland.com/fileadmin/files/2013/eso-stroke/pdf/ESO08_Guidelines_Original_english.pdf (accessed 20/2/2015).

11 Scottish Stroke Care Audit. *2014 National Report – Stroke Services in Scottish Hospitals*; 2014. http://www.strokeaudit.scot.nhs.uk/Downloads/2014_report/SSCA-report-2014-web.pdf (accessed 20/2/2015).

12 Meretoja A, Weir L, Ugalde M et al. Helsinki model cut stroke thrombolysis delays to 25 minutes in Melbourne in only 4 months. *Neurology* 2013; 81: 1071–6. http://dx.doi.org/10.1212/WNL.0b013e3182a4a4d2

13 Lorenzano S, Ahmed N, Tatlisumak T et al. Within-day and weekly variations of thrombolysis in acute ischemic stroke: results from safe implementation of treatments in stroke-international stroke thrombolysis register. *Stroke* 2014; 45: 176–84. http://dx.doi.org/10.1161/STROKEAHA.113.002133

14 Stroke Association. *Act FAST: Recognise the symptoms of a stroke*. http://www.stroke.org.uk/FAST (accessed 20/2/2015).

15 Safe Implementation of Treatments in Stroke. https://sitsinternational.org/ (accessed 20/2/2015).

16 National Institute of Neurological Disorders and Stroke. *Proceedings of a National Symposium on Rapid Identification and Treatment of Acute Stroke*; 1996. http://www.ninds.nih.gov/news_and_events/proceedings/stroke_proceedings/execsum.htm (accessed 20/2/2015).

17 Haršány M, Kadlecová P, Švigelj V et al. Factors influencing door-to-imaging time: analysis of the safe implementation of treatments in Stroke-EAST registry. *J Stroke Cerebrovasc Dis* 2014; 23: 2122–9. http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2014.03.019

18 Mikulík R, Kadlecová P, Czlonkowska A et al. Safe Implementation of Treatments in Stroke-East Registry (SITS-EAST) Investigators. Factors influencing in-hospital delay in treatment with intravenous thrombolysis. *Stroke* 2012; 43: 1578–83. http://dx.doi.org/10.1161/STROKEAHA.111.644120

19 Bray BD, Campbell J, Cloud GC et al. Intercollegiate Stroke Working Party Group. Bigger, faster? Associations between hospital thrombolysis volume and speed of thrombolysis administration in acute ischemic stroke. *Stroke* 2013; 44: 3129–35. http://dx.doi.org/10.1161/STROKEAHA.113.001981

20 Strbian D, Ahmed N, Wahlgren N et al. Trends in Door-to-Thrombolysis Time in the Safe Implementation of Stroke Thrombolysis Registry: Effect of Center Volume and Duration of Registry Membership. *Stroke* 2015; 46: 1275–80. http://dx.doi.org/10.1161/STROKEAHA.114.007170

21 Meretoja A, Strbian D, Mustanoja S et al. Reducing in-hospital delay to 20 minutes in stroke thrombolysis. *Neurology* 2012; 79: 306–13. http://dx.doi.org/10.1212/WNL.0b013e31825d6011

22 Kamal N, Benavente O, Boyle K et al. Good is not Good Enough: The Benchmark Stroke Door-to-Needle Time Should be 30 Minutes. *Can J Neurol Sci* 2014; 41: 694–6. http://dx.doi.org/10.1017/cjn.2014.41

23 Bray BD, Ayis S, Campbell J et al. Associations between stroke mortality and weekend working by stroke specialist physicians and registered nurses: prospective multicentre cohort study. *PLoS Med* 2014; 11: e1001705. http://dx.doi.org/10.1371/journal.pmed.1001705

24 National Institute of Neurological Disorders and Stroke. Tissue Plasminogen Activator for Acute Ischemic Stroke. *N Engl J Med* 1995; 333:1581–8.