ORIGINAL RESEARCH

Endovascular therapy yields significantly superior outcomes for large vessel occlusions compared with intravenous thrombolysis: is it time to randomize?

Ansaar T Rai,[1] Jeffrey S Carpenter,[1] Karthikram Raghuram,[2] Thomas D Roberts,[1] Daniel Rodgers,[1] Gerald R Hobbs[3]

[1]Interventional Neuroradiology, West Virginia University Hospital, Morgantown, West Virginia, USA
[2]Department of Radiology, St Luke's Medical Center, Milwaukee, Wisconsin, USA
[3]Department of Biostatistics, West Virginia University, Morgantown, West Virginia, USA

Correspondence to
Dr A T Rai, Interventional Neuroradiology, West Virginia University Hospital, One Medical Center Drive, Morgantown, WV 26508, USA; ansaar.rai@gmail.com

Received 23 May 2012
Accepted 2 July 2012
Published Online First 28 July 2012

ABSTRACT

Background and purpose We compared outcomes between endovascular (EV) therapy and intravenous (IV) thrombolysis in large vessel strokes.

Methods 223 patients who had received either IV (n=100) or EV (n=123) therapy were analyzed. Only patients with strokes involving the internal carotid artery terminus (ICA-T, n=45), the middle cerebral artery (M1, n=107) or the bifurcation branches (M2, n=71) were included. The primary endpoint was 3 month outcome based on the modified Rankin Scale (mRS) score, good-outcome defined as mRS ≤2.

Results The good outcome was 44.7% in the EV group and 26% in the IV group (p=0.003, OR 2.3, 95% CI 1.3 to 4.1). There was no difference in mortality or hemorrhage. For ICA-T occlusions, the good outcome was 27.6% in the EV and 0% in the IV group (p=0.004); for M1 occlusions, 40.6% in the EV versus 10.5% in the IV group (p=0.0006, OR 5.8, 95% CI 1.9 to 18.2); and for M2 occlusions, 76% in the EV versus 47.8% in the IV group (p=0.01, OR 3.5, 95% CI 1.2 to 10.2). For M1 occlusions, the death rate was 27.5% for the EV compared with 57.9% for the IV group (p=0.002, OR 3.6, 95% CI 1.6 to 8.3) with no difference observed in mortality for ICA-T or M2 occlusions. In the univariate analysis, age, National Institutes of Health Stroke Scale score and occlusion site were significant predictors of outcome and mortality (p<0.0001 for all). In the multivariable analysis, EV therapy (p=0.0004, OR 3.9, 95% CI 1.8 to 9) and younger age (p<0.0001, OR 0.96, 95% CI 0.9 to 0.98) were significant independent predictors of good outcome.

Conclusions There are significantly higher odds of a favorable outcome with EV compared with IV therapy for large vessel strokes. The data support the rationale of a randomized trial for large vessel occlusions.

INTRODUCTION

Intravenous (IV) thrombolysis is the primary treatment for all patients with acute ischemic stroke (AIS) and improves outcomes compared with placebo.[1] Endovascular (EV) therapies have shown effectiveness in revascularization of acutely occluded cerebral blood vessels, especially the proximal larger vessels.[2–6]

Large vessel occlusions (LVOs) are responsible for significant proportions of AIS[7 8] and portend a dismal prognosis.[9–14] Intra-arterial (IA) thrombolysis has been shown to be superior to IV thrombolytic therapy for these patients.[15–17] One explanation is the lower rates of recanalization associated with IV thrombolysis[18] as opposed to either mechanical thrombectomy,[11 14] local IA thrombolysis[19] or a combination of both.[20–22] Thus there is an emerging trend incorporating EV therapy for acute stroke patients presenting with an LVO. The goal of the current study was to conduct a direct comparison of the two treatment modalities and offer preliminary data for a potential prospective trial.

METHODS

Hypothesis

The null hypothesis for this study stated that there is no difference in outcomes between IV thrombolytic therapy and EV stroke therapy for LVO in the anterior circulation.

Patient selection

Institutional review board approval was obtained for this study. We analyzed a prospectively maintained database of 425 patients who had received IV thrombolytic therapy (n=260), EV treatment (n=146) or both (n=19) for AIS over an 8 year period. Since the objective of the study was a direct comparison of IV versus EV therapy, only those patients who had received one or the other but not both were included (n=407). The vascular occlusion site was determined on the baseline CT angiogram (CTA) and patients who did not demonstrate an intracranial vascular occlusion on CTA (n=110) were excluded from the analysis. All of these were in the IV treatment group. Patients with a small vessel occlusion (n=22; IV=19, EV=3) involving either a branch of the anterior cerebral artery or a third order branch of the middle cerebral artery—for example, M3—were also excluded. Additionally, patients with posterior circulation strokes (n=37; IV=21, EV=16) were excluded.

There were 13 patients without a clinical follow-up (EV=3, IV=10). Lastly, one 8-year-old male was excluded. This yielded 223 patients who presented with anterior circulation strokes secondary to an LVO and underwent either IV (n=100) or EV (n=123) therapy. This formed the cohort for the analysis.

Treatment

The IV therapy was initiated after a complete neurological assessment and comprised recombinant tissue plasminogen activator (rt-PA) administered

per standardized guidelines[1] and within 3 h of symptom onset. The rt-PA used was alteplase (Activase; Genentech Inc, San Francisco, California, USA). For EV therapy, patients had to be outside the time window for IV treatment or have other contraindications to IV thrombolysis. Compared with IV thrombolysis, which followed a fairly established and standardized protocol, there were no set standard criteria for EV therapy, as discussed in the limitations below. The most consistent criteria were the presence of cerebrovascular occlusion on CTA and absence of large area of early ischemic change on the non-contrast CT. Patients with a large cerebral blood volume abnormality on a baseline perfusion CT study were generally not treated, however the benefit of any doubt was always given to the patient, especially young patients and those who presented early on. All EV procedures were performed from a transfemoral approach, either with conscious sedation or general endotracheal anesthesia. The type of EV treatment included IA thrombolysis with r-tPA, mechanical thrombectomy or a combination of both. Mechanical thrombectomy involved the use of Food and Drug Administration (FDA) approved devices.[2 3 23] Patients in both groups were admitted to the intensive care unit following therapy.

Vascular occlusion site

The vascular occlusion site was determined based on the baseline CTA and was into the intracranial internal carotid artery with extension into the terminus (ICA-T), the main stem of the middle cerebral artery (M1) with or without extension into the middle cerebral artery bifurcation and isolated involvement of the proximal middle cerebral artery bifurcation branches (M2) (figure 1).

Outcomes

The primary endpoint was measured using the modified Rankin Scale (mRS) score at 90 days or the closest follow-up to 90 days. A good functional outcome was defined as an mRS score of ≤2. The European–Australasian Acute Stroke Study (ECASS) classification was used to grade post-treatment hemorrhages as parenchymal hematoma (PH) or hemorrhagic infarction (HI). The analysis was performed on follow-up CT or MR images reviewed by a neuroradiologist blinded to the outcomes or the treatment arm. We classified PH-1 and PH-2 as significant hemorrhages and HI-1 and HI-2 as non-significant hemorrhages. We did not include recanalization as an outcome as conclusive information regarding recanalization was only available for the EV treatment group. Recanalization as a primary endpoint has been extensively used in the stroke device trials and while this may be important to test device efficacy, a true comparison with the proven IV thrombolytic therapy can only be done with a direct comparison of the clinical outcome.

Statistical analysis

The endpoints for the analysis were clinical outcome and mortality. The significance of simple bivariate associations was assessed using Fisher's exact test for categorical variables, the Student's t test for continuous variables or logistic regression as appropriate. Initial analysis was performed to determine the predictors of outcome in the entire sample followed by a baseline analysis to assess for variations among the two treatment samples. Multivariable logistic regression was then performed assessing several factors simultaneously. The regression model was constructed to account for the effect of variables found to have a p value of <0.1 in the univariate analysis for determining predictors of outcome. All data analysis was performed using JMP statistical software, V.9 (SAS Institute Inc, Cary, North Carolina, USA).

RESULTS

Data from 223 patients were analyzed. Mean age was 71.9 (±15.3) years. There were 98 (43.9%) male and 125 (56.1%) female patients. The mean baseline National Institutes of Health Stroke Scale (NIHSS) score was 16.1 (±7.6). There were 45 (20.2%) patients with an ICA-T occlusion, 107 (48%) patients with an M1 occlusion and 71 (31.8%) patients with an M2 occlusion. The mean time from symptom onset to start of the EV procedure (groin puncture) was 5 h and 59 min (±3 h 16 min).

A good outcome was seen in 81 (36.3%) patients and mortality in 81 (36.3%) patients. A significant hemorrhage was seen in 27 (12.1%) patients. The predictors of outcome and mortality are listed in table 1. Patients with a favorable outcome had a lower mean age and baseline NIHSS score. Significantly more patients with a poor outcome had an ICA-T or M1 occlusion while significantly more patients with a favorable outcome had an M2 occlusion. The presence of significant hemorrhage was associated with a poor outcome. A higher NIHSS score, age, ICA-T occlusion and presence of significant hemorrhage were associated with a higher mortality (table 1).

Comparison of the two treatment groups

A comparison of the baseline characteristics among the EV and IV groups is given in table 2. A good outcome was seen in 55 patients (44.7%) who underwent EV therapy compared with 26 patients (26%) who received IV thrombolysis (p=0.003, OR 2.3, 95% CI 1.3 to 4.1). The death rate was not different in the two groups: 39 patients (31.7%) in the EV therapy group and

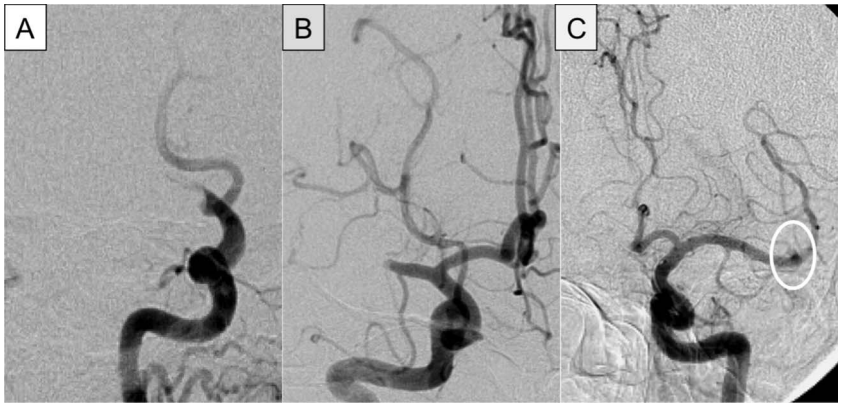

Figure 1 Occlusion site. An anterior–posterior angiogram projections shows occlusion of the right internal carotid artery terminus (A), the right M1 (B) and a left M2 (C).

Table 1 Predictors of outcome and mortality for the entire cohort (n=223)

	Favorable (n=81) (36.3%)	Poor (n=142) (63.7%)	p Value	No mortality (n=142) (63.7%)	Mortality (n=81) (36.3%)	p Value
Age (years)	64.8 (±17.6)	76 (±12.1)	<0.0001	68.4 (±16.3)	78.2 (±10.9)	<0.0001*
NIHSS score	12.8 (±6.6)	18 (±7.5)	<0.0001	13.9 (±6.7)	19.9 (±7.7)	<0.0001*
PH1/PH2 (n (%))	4 (4.9)	23 (16.2)	0.008	11 (7.8)	16 (19.8)	0.009*
Occlusion site (n (%))						
ICA-T	8 (9.9)	37 (26.1)	<0.0001	18 (12.7)	27 (33.3)	<0.0001*
M1	32 (39.5)	75 (52.8)		66 (46.5)	41 (50.6)	
M2	41 (50.6)	30 (21.1)		58 (40.9)	13 (16.1)	

*Significance level is set at 0.05.
ICA-T, internal carotid artery terminus; NIHSS, National Institutes of Health Stroke Scale; PH, parenchymal hematoma.

42 patients (42%) patients with IV thrombolysis (p=0.1, OR 1.6, 95% CI 0.9 to 2.7). Likewise, the hemorrhage rate was similar in the two treatment arms: a significant hemorrhage was seen in 17 patients (13.8%) in the EV treatment arm and in 10 (10%) patients in the IV thrombolysis arm (p=0.38, OR 0.7, 95% CI 0.3 to 1.6). As shown in table 2, mean age in the EV group was lower than that in the IV group while the composition of the occlusion site was different between the two groups. A significantly higher percentage of patients in the EV group had an M1 occlusion while a significantly higher percentage of patients in the IV group had an M2 occlusion (table 2).

An analysis of outcomes and mortality between the two groups based on site of occlusion is shown in table 3. This demonstrates that for all occlusion sites, patients undergoing EV treatment had significantly higher odds of a favorable outcome than those with IV thrombolysis and the difference was most prominent for ICA-T and M1 occlusions. For M1 occlusions, patients receiving IV thrombolysis had significantly higher odds of mortality than the EV treatment group (table 3). A multivariable logistic regression analysis was then performed for odds of good versus poor functional outcome taking into account the effect of multiple predictors of outcome as well as the different composition of age and occlusion site in the two treatment subgroups (table 4). This shows that EV therapy, younger age and M2 occlusions were the most significant independent predictors of a good outcome while a higher NIHSS score and LVO (ICA-T or M1) were the most significant independent predictors of mortality.

DISCUSSION

Acute large vessel ischemic strokes pose a significant challenge to intravenously administered thrombolytic therapy. An LVO is a significant predictor of outcome in patients undergoing stroke therapy[13 14] and unless recanalized, these patients do poorly.[13 14 24] IV rt-PA has not been shown to be effective for recanalization of these proximal vessels[18 25] due to a large thrombus burden[10 26] and hence has limited efficacy in impacting outcomes.[10–14 27–29] In 103 patients with CTA diagnosed LVO who received IV rt-PA and had a post-infusion angiogram, successful recanalization was seen in only 11.7% of patients.[30] The rate of recanalization was 4.4% for ICA-T, 32.3% for M1 and 30.8% for M2 occlusions.[30] In another study of 37 patients with documented cerebrovascular occlusion on CTA, catheter angiography following IV rt-PA administration (at a median time of 120 min) demonstrated a 12.5% recanalization rate for ICA or M1 and 27.3% for M2.[31] Another trial of 139 patients reported very low recanalization rates for both ICA-T and M1 occlusions[32] with no difference in day 1 recanalization between patients who received IV rt-PA versus those who did not.[32]

Prolyse in Acute Cerebral Thromboembolism II (PROACT-II) was one of the first EV randomized trials showing a benefit of IA thrombolysis for AIS secondary to LVO, in that case the middle cerebral artery.[6] The recent SYNTHESIS pilot trial randomizing patients presenting within 3 h to IV or IA alteplase showed improved outcomes and mortality with IA therapy compared with IV.[28] Based on the pilot data, an expanded randomized trial of IV versus EV therapy has been suggested.[29] Our mean time to groin puncture in the EV group of 6 h is similar to the stroke device trials.[2 3 23] Despite this longer time to initiation of the procedure, patients had better outcomes with EV therapy. Thus while time to treatment is important, the presence of an LVO such as the ICA-T or M1 trumps time when it comes to affecting outcomes. One valid question is why PROACT-II remains the only trial showing a positive benefit for IA thrombolysis? The Food and Drug Administration approval of IV rt-PA may have contributed to this, in addition to inadequate statistical power in some trials.[33 34] A recent meta-analysis of IA thrombolysis showed higher rates of recanalization and good functional outcomes in patients receiving IA fibrinolysis.[35]

EV therapy is currently reserved for patients who are outside the IV 'time window', ineligible for IV rt-PA or refractory to IV thrombolysis. This last criterion is arbitrarily determined, as the literature does not define a 'time period' for IV rt-PA resistance. The National Institute of Neurological Disorders and Stroke (NINDS) trial[1] demonstrated improvement in outcomes at 3 months but all the stoke device trials[3 23 36] have used inconsistent criteria, typically a lack of neurological improvement in 1 h, to determine a failed response to IV rt-PA. In reality, failure of a response to IV thrombolysis has become a surrogate to identify patients with a LVO that can then undergo EV therapy. The almost ubiquitous use of CTA in acute stroke imaging makes this selection process based on 'failed IV rt-PA' obsolete as patients presenting within 3 h of

Table 2 Comparison of baseline characteristics between the endovascular and intravenous therapy groups

	EV (n=123)	IV (n=100)	p Value
Age (years)	68.6 (±16.4)	76.1 (±12.7)	0.0002*
Female patients (n (%))	64 (52)	61 (61)	0.18
NIHSS score	16.1 (±7.3)	16.1 (±8)	0.96
Diabetes	23.7%	21.5%	0.71
Hypertension	83.2%	86.1%	0.58
Hyperlipidemia	55.1%	45%	0.16
Atrial fibrillation	44.5%	45.6%	0.88
ICA-T (n=45)	23.6%	16 (16%)	0.19
M1 (n=107)	56.1%	38 (38%)	0.007*
M2 (n=71)	20.3%	46 (46%)	0.0002*

*Significance level is set at 0.05.
EV, endovascular; ICA-T, internal carotid artery terminus; IV, intravenous; NIHSS, National Institutes of Health Stroke Scale.

Table 3 Comparison of outcome and mortality between the two treatment groups based on site of occlusion

	Good outcome (mRS ≤2)			Mortality		
	EV	IV	p Value (OR, 95% CI)	EV	IV	p Value (OR, 95% CI)
ICA-T	8/29 (27.6%)	0/16 (0%)	0.004* (N/A)	17/29 (58.6%)	10/16 (62.5%)	0.8 (1.2, 0.3 to 4.1)
M1	28/69(40.6%)	4/38(10.5%)	0.0006* (5.8, 1.9 to 18.2)	19/69 (27.5%)	22/38 (57.9%)	0.002* (3.6, 1.6 to 8.3)
M2	19/25(76%)	22/46(47.8%)	0.01* (3.5, 1.2 to 10.2)	3/25 (12%)	10/46(18.3%)	0.3 (2, 0.5 to 8.2)

*Significance level is set at 0.05.
EV, endovascular; ICA-T, internal carotid artery terminus; IV, intravenous; mRS, modified Rankin Scale.

symptom onset can be readily identified as having an LVO and the feasibility of randomizing patients based on CTA has been established.[27]

A valid argument in favor of administering IV rt-PA without any patient selection other than time is its wider availability. However, with an increasing physician work force and a push from hospitals to deliver advanced stroke therapy, EV stroke interventions have the potential of becoming more accessible. Another argument for IV rt-PA is that it may not increase the risk of hemorrhagic complications in patients subsequently undergoing an EV procedure.[36] Even if that is the case, patients with a full dose of IV rt-PA are less likely to receive local IA thrombolysis and more likely to undergo only mechanical thrombectomy. Local IA thrombolysis has been shown to be an independent predictor of favorable outcomes in patients undergoing EV stroke therapy.[19 22] Furthermore, the pharmacokinetics of alteplase[37 38] and its mechanism of action support the local delivery at the clot surface as potentially having a higher efficacy in thrombolysis than its systemic administration. None of our patients with an ICA-T occlusion and only 10% with an M1 occlusion benefitted from IV thrombolysis (table 3). These patients are least likely to achieve recanalization from IV rt-PA administration[25 39] and so constitute the ideal candidate for EV therapy. EV therapy is shown to be safe within the first 3 h[40] and an argument for instituting EV therapy for an LVO without a 'trial' of IV thrombolysis is rational.

There is a documented increase in recanalization over time—that is, early (<6 h) and late recanalization (at 24 h).[41 42] Studies have also shown that the earlier the recanalization, the better the outcome.[30 43 44] Some patients in addition may derive benefit from recanalization beyond 6 h due to a persistent penumbra.[45] Studies have also shown that improving door to needle times may improve outcomes in EV therapy.[46] Current recommendations for stroke centers include a door to CT time of 25 min and a door to needle time of 60 min for IV rt-PA.[47–49] However, there are no such mandates for EV therapy. Studies analyzing the time profiles of EV therapy[50] demonstrate sufficient room for improvement along the entire stroke therapy chain. If this is achieved, good outcomes from EV stroke therapy are likely to be higher than what are currently realized. A change in approach for LVOs may involve the concurrent administration of IV rt-PA and EV therapy rather than a linear approach of IV rt-PA, lack of symptomatic improvement and then initiation of EV treatment.

Table 4 Multivariable logistic regression for clinical outcome odds of favorable versus poor and no mortality versus mortality

	Favorable vs poor		No mortality vs mortality	
	OR (95% CI)	p Value	OR (95% CI)	p Value
NIHSS	0.95 (0.9 to 1)	0.04*	3.1 (1.6 to 5.9)	0.0006*
Age	0.96 (0.9 to 0.98)	<0.0001	2.3 (1.1 to 5.2)	0.03*
EV vs IV	3.9 (1.8 to 9)	0.0004*	2.2 (1.2 to 4.4)	0.016*
No hemorrhage vs significant hemorrhage	3.3 (1 to 13.4)	0.05*	2.4 (0.9 to 6.4)	0.07
M2 vs ICA-T	9.3 (3 to 32.5)	<0.0001*	7.7 (2.8 to 22.4)	<0.0001*
M2 vs M1	4.9 (2.1 to 12.3)	0.0002*	3.4 (1.5 to 8.3)	0.004*
M1 vs ICA-T	1.9 (0.7 to 5.4)	0.1	2.3 (1.1 to 4.9)	0.03*

*Significance level is set at 0.05.
EV, endovascular; ICA-T, internal carotid artery terminus; IV intravenous; NIHSS, National Institutes of Health Stroke Scale.

Limitations

This is a single center retrospective analysis spread over an 8 year period. All cases that received IV rt-PA did so under standardized published guidelines. However, other than a documented LVO on CTA and lack of a large hypodensity area on non-contrast CT, no standard inclusion criteria were consistently followed for EV procedures. The EV procedures themselves evolved with time as newer devices and techniques became available. Therefore, while the IV group constituted a fairly homogeneous population, the EV group was heterogeneous. As such, any conclusions from the data have to be viewed taking into account this heterogeneity.

CONCLUSION

Large vessel strokes are a major source of morbidity, mortality and healthcare cost, and developing a focused treatment strategy for these patients is important. The current analysis of over 200 patients shows that for LVOs, EV therapy is a significant independent predictor of outcome with almost four times the odds of achieving a favorable outcome compared with IV thrombolysis. These higher odds are without any increase in hemorrhagic complications or mortality and despite being administered further out from symptom onset. These conclusions are based on a retrospective analysis without strict controls or standardized protocols. Whether these odds hold up in a controlled randomized trial remains to be seen. The data presented here and in the literature however strongly support the idea that such a trial can be rationally contemplated.

Contributors ATR contributed to the study design, methodology and analysis. GRH contributed to the statistical analysis and results. JSC and DR contributed to data collection and discussion. KR and TDR contributed to the discussion section.

Competing interests None.

Ethics approval The study was approved by the institutional review board.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1. **The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group**. Tissue plasminogen activator for acute ischemic stroke. *N Eng J Med* 1995;**333**:1581–7.
2. **Smith WS,** Sung G, Starkman S, *et al*. Safety and efficacy of mechanical embolectomy in acute ischemic stroke: results of the MERCI trial. *Stroke* 2005;**36**:1432–8.
3. **Smith WS,** Sung G, Saver J, *et al*. Mechanical thrombectomy for acute ischemic stroke: final results of the multi MERCI trial. *Stroke* 2008;**39**:1205–12.
4. **Wehrschuetz M,** Wehrschuetz E, Augustin M, *et al*. Early single center experience with the solitaire thrombectomy device for the treatment of acute ischemic stroke.

Intervent Neuroradiol: J Peritherapeutic Neuroradiol, Surg Proced Relat Neurosci 2011;**17**:235–40.
5. **Machi P,** Costalat V, Lobotesis K, *et al*. Solitaire FR thrombectomy system: immediate results in 56 consecutive acute ischemic stroke patients. *J Neurointervent Surg* 2011.
6. **Furlan A,** Higashida R, Wechsler L, *et al*. Intra-arterial prourokinase for acute ischemic stroke. The PROACT II study: a randomized controlled trial. Prolyse in Acute Cerebral Thromboembolism. *JAMA* 1999;**282**:2003–11.
7. **Abelson M,** Roos J, Rymer M. Mechanical thrombo-embolectomy in acute ischaemic stroke: a local experience. *Cardiovasc J Afr* 2008;**19**:204–7.
8. **Smith WS,** Lev MH, English JD, *et al*. Significance of large vessel intracranial occlusion causing acute ischemic stroke and TIA. *Stroke* 2009;**40**: 3834–40.
9. **Nogueira RG,** Smith WS. Emergency treatment of acute ischemic stroke: expanding the time window. *Curr Treat Options Neurol* 2009;**11**:433–43.
10. **Barreto AD,** Albright KC, Hallevi H, *et al*. Thrombus burden is associated with clinical outcome after intra-arterial therapy for acute ischemic stroke. *Stroke* 2008;**39**:3231–5.
11. **Flint AC,** Duckwiler GR, Budzik RF, *et al*. Mechanical thrombectomy of intracranial internal carotid occlusion: pooled results of the MERCI and multi MERCI part I trials. *Stroke* 2007;**38**:1274–80.
12. **Josephson SA,** Saver JL, Smith WS. Comparison of mechanical embolectomy and intraarterial thrombolysis in acute ischemic stroke within the MCA: MERCI and multi MERCI compared to PROACT II. *Neurocrit Care* 2009;**10**:43–9.
13. **Rai AT,** Jhadhav Y, Domico J, *et al*. Procedural predictors of outcome in patients undergoing endovascular therapy for acute ischemic stroke. *Cardiovasc Intervent Radiol*. Published Online First: 14 December 2012. doi:10.1007/s00270-011-0323-7
14. **Nogueira RG,** Liebeskind DS, Sung G, *et al*. Predictors of good clinical outcomes, mortality, and successful revascularization in patients with acute ischemic stroke undergoing thrombectomy: pooled analysis of the Mechanical Embolus Removal in Cerebral Ischemia (MERCI) and multi MERCI Trials. *Stroke* 2009;**40**:3777–83.
15. **Mattle HP,** Arnold M, Georgiadis D, *et al*. Comparison of intraarterial and intravenous thrombolysis for ischemic stroke with hyperdense middle cerebral artery sign. *Stroke* 2008;**39**:379–83.
16. **Agarwal P,** Kumar S, Hariharan S, *et al*. Hyperdense middle cerebral artery sign: can it be used to select intra-arterial versus intravenous thrombolysis in acute ischemic stroke? *Cerebrovasc Dis* 2004;**17**:182–90.
17. **Sugiura S,** Iwaisako K, Toyota S, *et al*. Simultaneous treatment with intravenous recombinant tissue plasminogen activator and endovascular therapy for acute ischemic stroke within 3 hours of onset. *AJNR* 2008;**29**:1061–6.
18. **Demchuk AM,** Christou I, Wein TH, *et al*. Specific transcranial Doppler flow findings related to the presence and site of arterial occlusion. *Stroke* 2000;**31**:140–6.
19. **Lin R,** Vora N, Zaidi S, *et al*. Mechanical approaches combined with intra-arterial pharmacological therapy are associated with higher recanalization rates than either intervention alone in revascularization of acute carotid terminus occlusion. *Stroke* 2009;**40**:2092–7.
20. The IMS Study Investigators. Combined intravenous and intra-arterial recanalization for acute ischemic stroke: the Interventional Management of Stroke Study. *Stroke* 2004;**35**:904–11.
21. **The Interventional Management of Stroke (IMS) II Study**. *Stroke* 2007;**38**:2127–35.
22. **Gupta R,** Tayal AH, Levy EI, *et al*. Intra-arterial thrombolysis or stent placement during endovascular treatment for acute ischemic stroke leads to the highest recanalization rate: results of a multicenter retrospective study. *Neurosurgery* 2011;**68**:1618–22.
23. **Penumbra Pivotal Stroke Trial Investigators**. The Penumbra Pivotal Stroke Trial: safety and effectiveness of a new generation of mechanical devices for clot removal in intracranial large vessel occlusive disease. *Stroke* 2009;40:2761–8.
24. **Rouchaud A,** Mazighi M, Labreuche J, *et al*. Outcomes of mechanical endovascular therapy for acute ischemic stroke: a clinical registry study and systematic review. *Stroke* 2011;**42**:1289–94.
25. **Saqqur M,** Uchino K, Demchuk AM, *et al*. Site of arterial occlusion identified by transcranial Doppler predicts the response to intravenous thrombolysis for stroke. *Stroke* 2007;**38**:948–54.
26. **Zivin JA,** Fisher M, DeGirolami U, *et al*. Tissue plasminogen activator reduces neurological damage after cerebral embolism. *Science* 1985;**230**:1289–92.
27. **Sen S,** Huang DY, Akhavan O, *et al*. IV vs. IA TPA in acute ischemic stroke with CT angiographic evidence of major vessel occlusion: a feasibility study. *Neurocrit Care* 2009;**11**:76–81.
28. **Ciccone A,** Valvassori L, Ponzio M, *et al*. Intra-arterial or intravenous thrombolysis for acute ischemic stroke? The SYNTHESIS pilot trial. *J Neurointervent Surg* 2010;**2**:74–9.
29. **Ciccone A,** Valvassori L, Nichelatti M. SYNTHESIS expansion: design of a nonprofit, pragmatic, randomized, controlled trial on the best fast-track endovascular treatment vs. standard intravenous alteplase for acute ischemic stroke. *Int J Stroke: Official J Int Stroke Soc* 2011;**6**:259–65.
30. **Bhatia R,** Hill MD, Shobha N, *et al*. Low rates of acute recanalization with intravenous recombinant tissue plasminogen activator in ischemic stroke: real-world experience and a call for action. *Stroke* 2010;**41**:2254–8.
31. **Lee KY,** Han SW, Kim SH, *et al*. Early recanalization after intravenous administration of recombinant tissue plasminogen activator as assessed by pre- and post-thrombolytic angiography in acute ischemic stroke patients. *Stroke* 2007;**38**:192–3.
32. **Rother J,** Schellinger PD, Gass A, *et al*. Effect of intravenous thrombolysis on MRI parameters and functional outcome in acute stroke <6 hours. *Stroke* 2002;**33**:2438–45.
33. **Macleod MR,** Davis SM, Mitchell PJ, *et al*. Results of a multicentre, randomised controlled trial of intra-arterial urokinase in the treatment of acute posterior circulation ischaemic stroke. *Cerebrovasc Dis* 2005;**20**:12–17.
34. **Ogawa A,** Mori E, Minematsu K, *et al*. Randomized trial of intraarterial infusion of urokinase within 6 hours of middle cerebral artery stroke: the middle cerebral artery embolism local fibrinolytic intervention trial (MELT) Japan. *Stroke* 2007;**38**:2633–9.
35. **Lee M,** Hong KS, Saver JL. Efficacy of intra-arterial fibrinolysis for acute ischemic stroke: meta-analysis of randomized controlled trials. *Stroke* 2010;**41**:932–7.
36. **Smith WS.** Safety of mechanical thrombectomy and intravenous tissue plasminogen activator in acute ischemic stroke. Results of the multi Mechanical Embolus Removal in Cerebral Ischemia (MERCI) trial, part I. *AJNR* 2006;**27**:1177–82.
37. **Acheampong P,** Ford GA. Pharmacokinetics of alteplase in the treatment of ischaemic stroke. *Expert Opin Drug Metab Toxicol* 2012;**8**:271–81.
38. **Vance DL.** Treating acute ischemic stroke with intravenous alteplase. *Crit Care Nurse* 2001;**21**:25–7, 29–32.
39. **Mendonca N,** Rodriguez-Luna D, Rubiera M, *et al*. Predictors of tissue-type plasminogen activator nonresponders according to location of vessel occlusion. *Stroke* 2012;**43**:417–21.
40. **Mathews MS,** Sharma J, Snyder KV, *et al*. Safety, effectiveness, and practicality of endovascular therapy within the first 3 hours of acute ischemic stroke onset. *Neurosurgery* 2009;**65**:860–5.
41. **Mori E,** Minematsu K, Nakagawara J, *et al*. Effects of 0.6 mg/kg intravenous alteplase on vascular and clinical outcomes in middle cerebral artery occlusion: Japan Alteplase Clinical Trial II (J-ACT II). *Stroke* 2010;**41**:461–5.
42. **Zanette EM,** Roberti C, Mancini G, *et al*. Spontaneous middle cerebral artery reperfusion in ischemic stroke. A follow-up study with transcranial Doppler. *Stroke* 1995;**26**:430–3.
43. **Christou I,** Alexandrov AV, Burgin WS, *et al*. Timing of recanalization after tissue plasminogen activator therapy determined by transcranial Doppler correlates with clinical recovery from ischemic stroke. *Stroke* 2000;**31**:1812–16.
44. **Mazighi M,** Serfaty JM, Labreuche J, *et al*. Comparison of intravenous alteplase with a combined intravenous-endovascular approach in patients with stroke and confirmed arterial occlusion (RECANALISE study): a prospective cohort study. *Lancet Neurol* 2009;**8**:802–9.
45. **Kidwell CS,** Alger JR, Saver JL. Evolving paradigms in neuroimaging of the ischemic penumbra. *Stroke* 2004;**35**(Suppl 1):2662–5.
46. **Khatri P,** Abruzzo T, Yeatts SD, *et al*. Good clinical outcome after ischemic stroke with successful revascularization is time-dependent. *Neurology* 2009;**73**:1066–72.
47. **Alberts MJ,** Hademenos G, Latchaw RE, *et al*. Recommendations for the establishment of primary stroke centers. Brain Attack Coalition. *JAMA* 2000;**283**:3102–9.
48. **Adams HP Jr,** Brott TG, Furlan AJ, *et al*. Guidelines for thrombolytic therapy for acute stroke: a supplement to the guidelines for the management of patients with acute ischemic stroke. A statement for healthcare professionals from a Special Writing Group of the Stroke Council, American Heart Association. *Circulation* 1996;**94**:1167–74.
49. **Marler JR,** Jones PW, Emr M, National Institute of Neurological Disorders and Stroke (US). Office of Scientific and Health Reports. *Setting new directions for stroke care: Proceedings of a National Symposium on Rapid Identification and Treatment of Acute Stroke*. Bethesda, MD: The Institute, 1997.
50. **Eesa M,** Menon BK, Hill MD, *et al*. Achieving faster recanalization times by IA thrombolysis in acute ischemic stroke: where should we direct our efforts? *Intervent Neuroradiol: J Peritherapeutic Neuroradiol, Surg Proced Relat Neurosci* 2011;**17**:228–34.