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INVITED REVIEW

Future trials of endovascular mechanical recanalisation therapy in acute ischemic stroke patients: a position paper endorsed by ESMINT and ESNR

Part I: Current situation and major research questions

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Abstract A new era of stroke treatment may have begun with mechanical thrombectomy (MT) by fully deployed closed-cell self-expanding stents (stent-triever). Multiple case series and the first randomised controlled trials (RCTs) have now been published. More studies are under way involving large numbers of patients, which in turn has resulted in less strict "pragmatic" study protocols. Problems with current trials include a lack of standardisation in the conduct of the recanalisation procedure, the definition of primary endpoints such as the grade of arterial recanalisation and tissue reperfusion, and the post-surgical care provided. In Part 1 of this two part series, we outline the current situation and the major research questions.

Keywords Stroke · Interventional neuroradiology · Thrombectomy · Thrombolysis

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Randomised Controlled Trials

ECASS	European Cooperative Acute Stroke Study
ICSS	International Carotid Stenting Study
IMS	Interventional Management of Stroke
MC CLEAN	Multicenter Randomized CLinical trial of endovascular treatment for acute ischemic stroke in The Netherlands.
NINDS	National Institute of Neurological Disorders and Stroke
TREVO	Thrombectomy REvascularization of Large Vessel Occlusions in Acute Ischemic Stroke
THRACE	Trial and Cost Effectiveness Evaluation of Intra-arterial Thrombectomy in Acute Ischemic Stroke
THERAPY	The Randomized, Concurrent Controlled Trial to Assess the Penumbra System's Safety and Effectiveness in the Treatment of Acute Stroke
PISTE	Pragmatic ischaemic stroke thrombectomy evaluation
REVASCAT	RandomizEd trial of reVascularizAtion with Solitaire FR® device vs. best mediCal therapy in the treatment of Acute stroke due to anTerior circulation large vessel occlusion presenting within 8 h of symptom onset
RIVER	Reperfuse Ischemic Vessels with Endovascular Recanalization
SPACE	Stent-Protected Angioplasty vs. Carotid Endarterectomy
SYNTHESIS EXP	SYNTHESIS Expansion
SWIFT	SOLITAIRE FR With the Intention For Thrombectomy

Abbreviations

ASPECTS	Alberta Stroke Program Early CT
BCO	balloon guiding catheter occlusion
BMT	best medical therapy
CAS	carotid stenting
CBF	cerebral blood flow
CBV	cerebral blood volume
CCA	common carotid artery
CEA	carotid endarterectomy
CS	conscious sedation
CTA	CT-angiography
CTP	CT-perfusion
DSA	digital subtraction angiography
DWI	diffusion weighted imaging
EIC	early ischemic signs
ESMINT	European Society of Minimally Invasive Neurological Therapy
ESNR	European Society of Neuroradiology
ESO	European Stroke Organisation
FU	follow up
GA	general anaesthesia
ICA	internal carotid artery
IMS III	Interventional Management of Stroke III Trial
IVT	intravenous thrombolytical therapy
MCA	middle cerebral artery
mRS	modified rankin scale
MT	mechanical thrombectomy
NE-CT	non-enhanced CT
NIH-SS	National Institute of Health Stroke Scale
PI	perfusion MRI
RCT	randomised control trial
sICH	symptomatic intracranial haemorrhage
stent-triever	self-expanding stents

Current status and outline of the problem

MT therapy for acute ischemic stroke started with Hermann Zeumer's IA thrombolysis in 1981 [1], and has been performed for many years with several devices without a widespread use of any of specific method. In recent years, the MERCI device has been used; based on Phase-I -data [2] and data from the MERCI trial [3], the device received FDA-approval to "remove blood clots from the brain in patients experiencing an ischemic stroke" [4]. Data on the MERCI device have been pooled [5] and analysed together with the Multi MERCI trial [6], particularly to characterise possible target populations for mechanical recanalisation [7, 8], the relation of recanalisation and outcome [9] and the relation of recanalisation to the vessel occlusion site [10]. The Penumbra thrombo-aspiration device has been studied within a registry that showed a remarkable discrepancy between recanalisation rate and clinical outcome [11], primarily attributed to patient selection [12].

Introduction of retrievable stents A new era began with the first reports of permanent placement of open-cell self-expanding stents to recanalise embolic intracranial artery occlusions by compression of the occluding thrombus [13–16]. This technique claimed to provide fast and efficient recanalisation. At about the same time, retrieval of an incompletely deployed closed-cell self-expanding stent [17] used as a temporary intravascular bypass that was then also used as an thrombectomy device was reported [18]. In addition, the first thrombectomy by a fully deployed

closed-cell self-expanding stent had already been performed successfully [19]. Multiple retrospective case series (mainly small) reporting the results of these so called "stent-trievers" have been published [20–38], most from European centres. In general, recanalisation rates are high and overall clinical outcomes are comparable or superior to those reported in the IV fibrinolysis trials, despite the fact that in general the patients had more severe symptoms (higher NIHSS) and were treated at later time-points. However, the clinical outcome data were usually not externally assessed and monitored.

Recent prospective registries and RCTs Several prospective registries and RCTs are under way. A number of them are designed to gain FDA-approval for a particular device. Others address the question of clinical outcome of MT vs. IV fibrinolysis (Tables 1 and 2). For some physicians, available clinical data are so convincing that participation in a RCT is ethically impossible. This has changed slightly with the Interventional Management of Stroke III Trial (IMS III). Following enrolment of 587 of the planned 900 patients at over 50 sites worldwide, IMS III enrolment was suspended in April 2012 because of equipoise. IMS III is a RCT aiming to examine whether an IV and IA approach is superior to standard IV tPA alone (<3 h after stroke onset). Three thrombectomy devices were approved during the study period: MERCI (cleared in 2004), Penumbra (cleared 2007) and Solitaire (cleared March 2012). Stopping enrolment at the time of the approval of the first stent-triever is a very sensible decision in order to avoid discrediting stent-trievers as a concept. However, it is now up to the MT-users to demonstrate the efficacy of stent-triever in a RCT.

The challenges

- *Stroke heterogeneity:* Acute ischemic stroke is a syndrome with heterogeneous aetiologies, arterial and tissue pathologies. The heterogeneity mainly originates from type, size and location of the arterial obstruction, and the collateral blood circulation of the brain and volume of tissue that is already infarcted. To address this heterogeneity, a large number of patients have to be randomised, which in turn results in a less strict "pragmatic" study protocol allowing the use of several mechanical devices; this has been shown in several studies, namely IMS III, THRACE, PISTE and MR CLEAN.
- *Methodological heterogeneity:* Apart from the different devices, there is no standardisation in the conduct of the recanalisation procedure, the definition of primary endpoints such as the grade of arterial recanalisation and tissue reperfusion, post-surgical care and so forth. Not even the single-device THERAPY trial (Table 2) will answer all questions

Table 1 Selection of current publicly-funded RCTs of MT in acute stroke patients

	THRACE French	IMS III NIH	MR CLEAN Netherlands	PISTE UK	SYNTHESIS EXP Italian	REVASCAT Spanish
PI	S. Bracard, X. Ducrocq	J. Broderick	C. Majoie	K. Muir, P. White	A. Ciccone	A. Davalos
Randomisation	(Solitaire, Merci, Catch, Penumbra) +IV tPA vs. IV tPA	(Ekos, Penumbra, Merci, Solitaire, IA tPA) +IV tPA vs. IV tPA	EVT vs. IV tPA	all CE Marked for MT stroke	IA tPA and/or MT vs. IV tPA	Solitaire vs. IV tPA
Current status	enrolling since 10/2010	enrolment suspended	enrolling since 2010	planned	enrolling since 02/2008	planned
Hypothesis	superiority (15 %)	superiority (10 %)	non- infériority	superiority (15 %)	superiority (20 %)	superiority (15 %)
Number of centers	27	>50	11	12–15		4
Patient number at 05/2012	160/480	587/900	>120/500	400	?/350	450
IV stop	4 h	3 h	4.5 h	4.5 h	4 h	?
IA start	<5 h	5–7 h	<6 h	<6 h	<6 h	<8 h
Economic evaluation	yes	yes	yes	yes		yes
Primary Efficacy Endpoint	mRS at 90 days	Rate of mRS 0–2 at 90 days	mRS at 90 days	mRS at 90 days	Rate of mRS 0–1 at 90 days	Rate of mRS 0–2 at 90 days

Table 2 Selection of current company-driven RCTs of MT in acute stroke patients (information either from http://clinicaltrials.gov/ or from company officials)

Company	Codman	Codman	Covidien	Covidien	Stryker	Penumbra
Acronym	RIVER II	RIVER RCT	SWIFT	SWIFT PRIME	TREVO2	THERAPY
PI	T. Devlin, E. Levy	W. Hacke, G. Albers, O. Zaidat, M. Bendszus	J. Saver	J. Saver, C. Diener, E. Levy, V. Pereira	S. Nogueira, H. Lutsep, W. Smith	J. Mocco, P. Kathri
Randomisation	ReVive SE vs Penumbra	IV tPA + ReVive SE + IV vs. IV tPA	Solitaire FR vs. Merci	IV tPA + Solitaire FR vs. IV tPA	Trevo vs. Merci	IV tPA + Penumbra vs. IV tPA
Current status	planned	planned	completed	planned	completed	recruiting since 11/2011
Hypothesis	non-inferiority	superiority	non-inferiority	superiority (10 %)	non-inferiority	superiority (12 %)
Number of centers	tbd	tbd	18	Up to 60	27	15
Patient number	tbd	tbd	113	Up to 941 (expected 600)	178	692
Primary Efficacy Endpoint	Rate of TICI 2 in treated territory	Clinical outcome (mRS 90 days)	Rate of TIMI II/III in all treatable vessels without SICH	Reduced stroke related Disability (mRS 90 days)	Rate of TICI 2 in treated territory	Rate of mRS 0–2 (90 days)

* tbd = to be determined

regarding the efficacy of mechanical recanalisation since studies generally enrol patients who are eligible for IV tPA within an early time window, i.e. best medical therapy (BMT) and thrombectomy versus best medical treatment. Additionally, it is likely that as MT becomes more established it will become difficult to recruit patients into RCTs.

Proposal We suggest a European "family" of interventional stroke trials with the least possible overlap. In this article we outline the key research questions and trial design issues for MT which are generally supported by the authors and the respective Societies. To allow for a consensus paper that covers a broad spectrum of the current problems, we acknowledge that a few statements do not have explicit support of all authors.

What are the major research questions?

Is IVT/MT more effective than IVT?

Study objectives To establish whether IVT and MT is superior to IVT only in the subgroup of patients with large vessel occlusions in the anterior circulation.

Ethical appraisal Given the good results of previous studies and upcoming registries, such a study had been already deemed unethical by some. However, clinical equipoise may be present as MT has its own inherent risks [39]. Moreover, registry data in which outcome is self-reported is not necessarily reliable. This phenomenon has been shown elegantly for carotid surgery and carotid stenting [40, 41]. Intracranial intervention has also seen similar reports with the SAMMPRIS RCT identifying higher than expected (from registry studies) complication rates in endovascular arm and lower than expected event rate in medical arm; the trial was stopped early at request of the NINDS [42].

Ethically, it is most appropriate to test the group of patients who are eligible to receive IVT under the European Stroke Organisation (ESO) Guidelines. The trial would be conducted with a randomisation of an IV group (control) versus an IV treatment plus additional MT (experimental). A trial comparing IVT and MT (without IVT first) would deprive patients in the experimental arm of standard treatment. Such a trial could be undertaken subsequently if the IV+MT vs. IV showed benefit for MT. There is rationale for examining anterior and posterior circulation strokes separately.

Clinical patient selection Three key variables determine whether and where in the outcome spectrum clustering will

occur in stroke patients: onset to treatment time, symptoms at time of treatment and type of treatment [43]. The time window for this study is determined by the IVT studies that showed a clinical benefit (<4.5 h) [44–46]. When IST3 data are added to other trials, benefit of IVT given at 3–6 h was not demonstrated [47].

Outcomes after IVT are significantly better than in untreated comparators across baseline NIHSS 5 to 24 [48]. However, the efficacy of IVT is heterogeneous with lesser or even no benefit in the most severely affected patients [49] and in patients with proximal artery occlusions [50]. The classical CT-based IVT studies together with EPITHET enrolled patients with a mean NIHSS score of 11 (interquartile range: 7–16) [46]. In an ad-hoc secondary analysis of published data [51] for this manuscript, we found that in IVT patients the outcome of worse than mRS 0–2 (day 90) was predicted with a sensitivity of 89 % and a specificity of 48 % with NIHSS score of >10. Moreover, this threshold has been found to be a good predictor for a proximal vessel occlusion [52]. Imaging could compensate for the lower specificity (see below). An upper NIHSS threshold is not required but will be introduced by patient selection criteria (Table 3).

Based on the MERCI data, futile MT was often observed in elderly patients [8, 53]. Among patients undergoing MT for acute cerebrovascular occlusions with the MERCI device, increased age conveys a higher rate of stroke-related death, but disability at discharge in this group is similar to that of younger survivors [54]. Nevertheless, we suggest limiting the age of the included patients from 18 to 80 as in the large IVT studies though there seems to be no clear age cut-off for benefit [48, 55]. Although the IST-3 trial has confirmed the benefit of IVT beyond 80 years, the benefit in the older group seems particularly confined to IVT within 3 h and as yet there is no licence change to the use of rtPA [56].

Estimation of sample size All estimations of sample sizes are profoundly dependent on specific design features of the RCT. Thus, non-randomised data indicate approximately 20 % absolute benefit for MT added to IVT but are based on self assessed data in most cases. Ongoing superiority trials for MT in Europe are THRACE, PISTE and MRCLEAN (Table 1). The design and powering of these trials indicate they are likely to be positive (at 1 % significance level) if the real absolute benefit of MT added to IVT is nearer 15 %. In fact, on the basis of a pre-planned meta-analysis of PISTE/MR CLEAN, an absolute benefit of as little as 8 % could be statistically confirmed (at 5 % significance level and 80 % power).

Pre-specified subgroup analyses there are a number of important subgroup analyses to be included. These should be pre-specified. We suggest:

- Time of start of thrombectomy: <3 h versus 3–4.5 h versus >4.5 h
- Age (<60 versus 60–80)
- NIHSS at presentation (e.g. <12 versus 12–20 versus >20)
- Time to recanalisation (<45 min versus greater) from stroke onset, admission, groin puncture
- Centre volume (e.g. >12 p.a. versus 12 or fewer p.a.) differences in final infarct volume

Is MT more effective than current best medical treatment in patients ineligible for IVT?

Study objectives To establish whether MT is superior to BMT in patients ineligible for IVT.

Ethical appraisal Altogether, this is ethically much more difficult as patients in the control arm would be managed with best BMT (as many are currently) whereas patients in the MT arm would receive state of the art intra-arterial intervention. This type of study is explicitly not supported by all co-authors of this manuscript.

A multicentre RCT designed to compare intra-arterial fibrinolysis therapy vs. control in the posterior circulation was stopped after enrolment of only 16 patients in more than 7 years. The authors stated: "[…] one reason for poor recruitment to the trial may have been a growing belief in the efficacy of intra-arterial thrombolysis […] resulting in

Table 3 Key patient selection criteria for suggested studies

		MT + IVT vs. IVT	MT beyond IV
Clinical	Time after symptom onset	<4.5 h	>4.5 and <8 h
	Age	18 to <80 years	
	NIHSSS	>8	
Imaging	Maximum infarct volume (NE-CT)	ASPECTS >7	ASPECTS >7
	Clot length measurement (NE-CT)	Required?	Required?
	Occlusion site (CTA)	Carotid-T, M1	M1/2, Carotid-T
	Perfusion (TTP or MT)	Perfusion impairment >hypodensity	

patients receiving open-label treatment" [57]. Given the poor prognosis in the natural course and the different pathophysiology in the posterior circulation (more local stenoses), we believe that a trial without fibrinolysis therapy in one of the study arms might be unethical in this particular patient group.

On the other hand, as discussed above, MT might not improve or might even worsen the outcome [39]. Some information will be obtained from current trials (e.g. SYNTHESIS EXP and IMS III) but may be limited by highly heterogeneous patient groups; for example, in the case of IMS III, many interventions use devices that are not be regarded as "state of the art" in Europe. Therefore, a formal RCT of MT vs. standard medical therapy in patients ineligible for IVT would be extremely valuable.

Other patient groups ineligible for IVT such as patients with recent surgery and patients with abnormal haemostasis probably have a very different safety profile and thus need to be investigated in separate analysis that will not be further discussed within this manuscript. Finally, a RCT comparing MT versus BMT in patients with failed IVT is conceivable. The alternative to RCTs is a large European Registry to collect large volumes of non-randomised data instead very quickly, possibly developed on the back of existing IV Thrombolysis Registries.

Clinical patient selection An RCT targeting patients ineligible for IVT should be considered primarily in those presenting later than 3 h. We suggest considering >3 h rather than >4.5 h. Although IVT data shows benefit concentrated <3 h, the benefit for IVT 3–4.5 h is much weaker and even more so with higher NIHSS. Pragmatically, it would likely prove extremely hard to recruit into MT vs. standard medical therapy <3 h as it is more clinically desirable to perform active treatment in such cases. Pre-specified time window subgroups could be assessed easily e.g. 3–4.5 h, 4.5–6 h, 6–8 h. The maximum symptom duration is more controversial as there might be some patients revealing a penumbra for as long as 48 h [58] who may still benefit from MT. It has been shown that late endovascular revascularisation of carefully selected patients is safe and potentially improves the clinical outcome [59]. However, the time limit of <8 h did not show unequivocally good outcomes despite comparably good recanalisation rates [11]. Unsurprisingly, it has been found secondarily for the Penumbra pivotal stroke trial that fast recanalisation may benefit patients with a favourable image on the baseline CT scan (ASPECTS score >7) [12]. This underlines the particular importance of imaging selection criteria for this type of study. For feasibility reasons we suggest the time window of <8 h. There would be no difference in key variables in comparison the IA + IV vs. IV study (as described above).

Estimation of sample size Because the natural history of a major occlusive stroke where IVT cannot be given is so poor (20–25 % or less have positive outcome at 90 days), relatively small trial(s) of MT – dependent on the design with fewer than 300 subjects - could show significant differences.

Superiority of a device over another and role of current or novel drugs

Recently, two RCTs have been completed in the US that compared one particular stent-triever with the MERCI (TREVO2-study/Trevo/Concentric [60] and SWIFT-study/Solitaire/Covidien [61]). Each study revealed clear superiority of the stent-triever versus the MERCI both in recanalisation rate and clinical outcome. Such device trials are less important than those assessing proof of concept of a novel therapy approach (namely MT); however, they do have a role and are important to ensure the momentum of development of better devices is maintained. Therefore, it is in everyone's interest to encourage the technical development. Nevertheless, these devices must be proven to be safe and at least as efficacious as those they are intended to replace. Almost inevitably, most funding for device trials will need to come from industry partners. It is here that interventionists have a key role to play. On practical grounds of size of study, feasibility and so on, frequently surrogate or non-clinical outcomes will need to be used as endpoints in such trials. This imaging-based approach is overdue to be trialled in IA therapy either in isolation or more sensibly in addition to MT (especially once the benefit of MT is confirmed by the current cohort of ongoing RCTs). We thus suggest advanced prediction analyses of tissue outcome [62–64].

The absolute benefit of IA thrombolysis over IVT is modest at best – around 2 % in the 2009 Cochrane Systematic Review. To date, trials on agents intended to replace rtPA such as Gp IIb/IIIa antagonists, desmoteplase and plasmin have been largely disappointing. However, a recent small Phase II trial of tenecteplase versus alteplase (in a highly selected population using CTA and CTP criteria) looks more promising up to 6 h with significantly more patients showing major neurologic improvement at 24 h in the tenecteplase arm, though the increased beneficial clinical outcome at 90 days did not reach statistical significance [65].

Further research questions

Many more questions are conceivable. At minimum, future studies should address the following issues:

- How are patients who are likely to benefit from MT best characterised?
- What is the clinical benefit of MT in patients with good collaterals?
- What is the clinical benefit of IVT vs. MT in acute stroke patients with basilar artery occlusions?

- What is the benefit of perfusion imaging (regardless of local protocol)?

Other issues that may be addressed include:

- IVT versus MT in patients with acute stroke caused by ICA occlusion (with and without concomitant MCA occlusion)?
- IVT versus MT in acute stroke patients with acute isolated MCA occlusion?
- IVT versus MT in acute stroke patients with M2-occlusions?
- Availability of IVT and MT for acute stroke patients and its impact on public health?
- Mechanical thrombectomy with and without pretreatment with IA thrombolytics
- The effect of IA thrombolytics after mechanical thrombectomy?
- The effect of neuroprotection (pharmacological, hypothermia) before MT?
- Relevance of pre-existing infarct volume for the effect of MT?

In all likelihood further questions will arise based on the analysis of the IMS III study and other recent data.

Conclusion

Based on current data and current experience, the key research questions are the comparisons of MT + IVT and IVT in patients both eligible and ineligible for IVT. Many more questions are conceivable and will arise based on the analysis recent data. In Part II, the joint working group of ESMINT and ESNR will make recommendations on trial design and conduct to investigate therapy effects of MT.

Conflict of interest JF consults for Stryker and Codman, and gives presentations to Covidien, Boehringer Ingelheim, Philips and Siemens MS has a Consultant agreement with Mindframe (now owned by Covidien) and is PI for the Rapid Medical study. FT consults for Stryker and Codman, is on the Codman Board, and has a proctoring agreement and holds workshops for Covidien. RVK receives personal compensation for serving on the Advisory Board of Lundbeck AC, serves as Co-Chair on the Steering Committee of the DIAS-3 and -4 trials, serves on the image adjudication committee for these trials and consults for Synarc; he is Section Editor, Interventional Neuroradiology, of the journal *Neuroradiology*. MM is a consultant for Synthes, AB Medica/Italy, gives presentations for Johnson & Johnson and has research support from ActiveO. CC consults for Covidien, Stryker, Codman and Microvention. JG is PI of the STAR Study (Covidien).

References

1. Zeumer H, Hacke W, Kolmann HL, Poeck K (1982) Local fibrinolysis in basilar artery thrombosis (author's transl). Dtsch Med Wochenschr 107:728–731
2. Gobin YP, Starkman S, Duckwiler GR et al (2004) MERCI 1: a phase 1 study of mechanical embolus removal in cerebral ischemia. Stroke 35:2848–2854
3. Smith WS, Sung G, Starkman S et al (2005) Safety and efficacy of mechanical embolectomy in acute ischemic stroke: results of the MERCI trial. Stroke 36:1432–1438
4. Becker KJ, Brott TG (2005) Approval of the MERCI clot retriever: a critical view. Stroke 36:400–403
5. Flint AC, Duckwiler GR, Budzik RF, Liebeskind DS, Smith WS (2007) Mechanical thrombectomy of intracranial internal carotid occlusion: pooled results of the MERCI and Multi MERCI Part I trials. Stroke 38:1274–1280
6. Smith WS, Sung G, Saver J et al (2008) Mechanical thrombectomy for acute ischemic stroke: final results of the Multi MERCI trial. Stroke 39:1205–1212
7. Nogueira RG, Smith WS (2009) Safety and efficacy of endovascular thrombectomy in patients with abnormal hemostasis: pooled analysis of the MERCI and multi MERCI trials. Stroke 40:516–522
8. Flint AC, Cullen SP, Faigeles BS, Rao VA (2010) Predicting long-term outcome after endovascular stroke treatment: the totaled health risks in vascular events score. Ajnr Am J Neuroradiol 31:1192–1196
9. Fields JD, Lutsep HL, Smith WS (2011) Higher degrees of recanalization after mechanical thrombectomy for acute stroke are associated with improved outcome and decreased mortality: pooled analysis of the MERCI and Multi MERCI trials. AJNR Am J Neuroradiol 32:2170–2174
10. Shi ZS, Loh Y, Walker G, Duckwiler GR (2010) Clinical outcomes in middle cerebral artery trunk occlusions versus secondary division occlusions after mechanical thrombectomy: pooled analysis of the mechanical embolus removal in cerebral ischemia (MERCI) and Multi MERCI trials. Stroke 41:953–960
11. Penumbra Pivotal Stroke Trial Investigators (2009) 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 40:2761–2768
12. Goyal M, Menon BK, Coutts SB, Hill MD, Demchuk AM (2011) Effect of baseline CT scan appearance and time to recanalization on clinical outcomes in endovascular thrombectomy of acute ischemic strokes. Stroke 42:93–97
13. Sauvageau E, Levy EI (2006) Self-expanding stent-assisted middle cerebral artery recanalization: technical note. Neuroradiology 48:405–408
14. Levy EI, Mehta R, Gupta R et al (2007) Self-expanding stents for recanalization of acute cerebrovascular occlusions. AJNR Am J Neuroradiol 28:816–822
15. Brekenfeld C, Schroth G, Mattle HP et al (2009) Stent placement in acute cerebral artery occlusion: use of a self-expandable intracranial stent for acute stroke treatment. Stroke 40:847–852
16. Kim SM, Lee DH, Kwon SU, Choi CG, Kim SJ, Suh DC (2012) Treatment of acute ischemic stroke: feasibility of primary or secondary use of a self-expanding stent (Neuroform) during local intra-arterial thrombolysis. Neuroradiology 54:35–41
17. Kelly ME, Furlan AJ, Fiorella D (2008) Recanalization of an acute middle cerebral artery occlusion using a self-expanding, reconstrainable, intracranial microstent as a temporary endovascular bypass. Stroke 39:1770–1773
18. Suh SH, Lee KY, Hong CK et al (2009) Temporary stenting and retrieval of the self-expandable, intracranial stent in acute middle cerebral artery occlusion. Neuroradiology 51:541–544
19. Pérez MA, Miloslavski E, Fischer S, Bäzner H, Henkes H (2011) Intracranial thrombectomy using the Solitaire stent: a historical vignette. J Neurointerv Surg. doi:10.1136/neurintsurg-2011-010149
20. Castano C, Dorado L, Guerrero C et al (2010) Mechanical thrombectomy with the Solitaire AB device in large artery occlusions of the anterior circulation: a pilot study. Stroke 41:1836–1840

21. Castano C, Serena J, Davalos A (2009) Use of the new solitaire (TM) AB device for mechanical thrombectomy when Merci clot retriever has failed to remove the clot. A case report. Interv Neuroradiol 15:209–214
22. Cohen JE, Gomori JM, Leker RR, Eichel R, Arkadir D, Itshayek E (2011) Preliminary experience with the use of self-expanding stent as a thrombectomy device in ischemic stroke. Neurol Res 33:214–219
23. Cohen JE, Gomori JM, Leker RR, Moscovici S, Ramirez-Denoriega F, Itshayek E (2012) Recanalization with stent-based mechanical thrombectomy in anterior circulation major ischemic stroke. J Clin Neurosci 19:39–43
24. Costalat V, Machi P, Lobotesis K et al (2011) Rescue, combined, and stand-alone thrombectomy in the management of large vessel occlusion stroke using the solitaire device: a prospective 50-patient single-center study: timing, safety, and efficacy. Stroke 42:1929–1935
25. Machi P, Costalat V, Lobotesis K et al (2012) Solitaire FR thrombectomy system: immediate results in 56 consecutive acute ischemic stroke patients. J Neurointerv Surg 4:62–66
26. Mendonca N, Flores A, Pagola J et al (2011) Trevo system: single-center experience with a novel mechanical thrombectomy device. J Neuroimaging. doi:10.1111/j.1552-6569.2011.00666.x
27. Miteff F, Faulder KC, Goh AC, Steinfort BS, Sue C, Harrington TJ (2011) Mechanical thrombectomy with a self-expanding retrievable intracranial stent (Solitaire AB): experience in 26 patients with acute cerebral artery occlusion. AJNR Am J Neuroradiol 32:1078–1081
28. Mohlenbruch M, Seifert M, Okulla T et al (2012) Mechanical thrombectomy compared to local-intraarterial thrombolysis in carotid T and middle cerebral artery occlusions: a single center experience. Clin Neuroradiol 22(2):141–147
29. Mpotsaris A, Bussmeyer M, Loehr C, Oelerich M, Buchner H, Weber W (2012) Mechanical thrombectomy in severe acute stroke: preliminary results of the Solitaire stent. J Neurol Neurosurg Psychiatry 83:117–118
30. Nayak S, Ladurner G, Killer M (2010) Treatment of acute middle cerebral artery occlusion with a Solitaire AB stent: preliminary experience. Br J Radiol 83:1017–1022
31. Park H, Hwang GJ, Jin SC et al (2011) A retrieval thrombectomy technique with the Solitaire stent in a large cerebral artery occlusion. Acta Neurochir (Wien) 153:1625–1631
32. Pérez M, Miloslavski E, Fischer S, Bäzner H, Henkes H (2011) Intracranial thrombectomy using the Solitaire stent: a historical vignette. J Neurointerv Surg. Dec 14 (ePub)
33. Rohde S, Haehnel S, Herweh C et al (2011) Mechanical thrombectomy in acute embolic stroke: preliminary results with the revive device. Stroke 42:2954–2956
34. Roth C, Papanagiotou P, Behnke S et al (2011) Stent-assisted mechanical recanalization for treatment of acute intracerebral artery occlusions. Stroke 41:2559–2567
35. Stampfl S, Hartmann M, Ringleb PA, Haehnel S, Bendszus M, Rohde S (2011) Stent placement for flow restoration in acute ischemic stroke: a single-center experience with the Solitaire stent system. AJNR Am J Neuroradiol 32:1245–1248
36. Venker C, Stracke P, Berlit P et al (2010) New options in the therapeutic management of acute ischaemic stroke. Good results with combined i. v. and i. a. lysis and mechanical thrombectomy. Fortschr Neurol Psychiatr 78:652–657
37. Wehrschuetz M, Wehrschuetz E, Augustin M, Niederkorn K, Deutschmann H, Ebner F (2011) Early single center experience with the solitaire thrombectomy device for the treatment of acute ischemic stroke. Interv Neuroradiol 17:235–240
38. Menon BK, Kochar P, Ah-Seng A et al (2012) Initial experience with a self-expanding retrievable stent for recanalization of large vessel occlusions in acute ischemic stroke. Neuroradiology 54:147–154
39. Tomsick TA, Khatri P, Jovin T et al (2010) Equipoise among recanalization strategies. Neurology 74:1069–1076
40. Rothwell P, Warlow C (1995) Is self-audit reliable? Lancet 346:1623
41. Fiehler J (2010) On limitations of studies and limitations of therapy options for carotid stenosis: why play golf with only a sand wedge? Neuroradiology 52:597–599
42. Chimowitz MI, Lynn MJ, Derdeyn CP et al (2011) Stenting versus aggressive medical therapy for intracranial arterial stenosis. N Engl J Med 365:993–1003
43. Saver JL (2011) Optimal end points for acute stroke therapy trials: best ways to measure treatment effects of drugs and devices. Stroke 42:2356–2362
44. Hacke W, Kaste M, Bluhmki E et al (2008) Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med 359:1317–1329
45. Wahlgren N, Ahmed N, Davalos A et al (2008) Thrombolysis with alteplase 3–4.5 h after acute ischaemic stroke (SITS-ISTR): an observational study. Lancet 372:1303–1309
46. Lees KR, Bluhmki E, von Kummer R et al (2010) Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. Lancet 375:1695–1703
47. Wardlaw JM, Murray V, Berge E et al (2012) Recombinant tissue plasminogen activator for acute ischaemic stroke: an updated systematic review and meta-analysis. Lancet 379(9834):2364–2372
48. Mishra NK, Lyden P, Grotta JC, Lees KR (2010) Thrombolysis is associated with consistent functional improvement across baseline stroke severity: a comparison of outcomes in patients from the virtual international stroke trials archive (VISTA). Stroke 41:2612–2617
49. Saver JL, Yafeh B (2007) Confirmation of tPA treatment effect by baseline severity-adjusted end point reanalysis of the NINDS-tPA stroke trials. Stroke 38:414–416
50. Bhatia R, Hill MD, Shobha N et al (2010) Low rates of acute recanalization with intravenous recombinant tissue plasminogen activator in ischemic stroke: real-world experience and a call for action. Stroke 41:2254–2258
51. Thomalla G, Schwark C, Sobesky J et al (2006) Outcome and symptomatic bleeding complications of intravenous thrombolysis within 6 hours in MRI-selected stroke patients: comparison of a German multicenter study with the pooled data of ATLANTIS, ECASS, and NINDS tPA trials. Stroke 37:852–858
52. Fischer U, Arnold M, Nedeltchev K et al (2005) NIHSS score and arteriographic findings in acute ischemic stroke. Stroke 36:2121–2125
53. Hussein HM, Georgiadis AL, Vazquez G et al (2010) Occurrence and predictors of futile recanalization following endovascular treatment among patients with acute ischemic stroke: a multicenter study. Ajnr Am J Neuroradiol 31:454–458
54. Loh Y, Kim D, Shi ZS et al (2010) Higher rates of mortality but not morbidity follow intracranial mechanical thrombectomy in the elderly. AJNR Am J Neuroradiol 31:1181–1185
55. Berrouschot J, Rother J, Glahn J, Kucinski T, Fiehler J, Thomalla G (2005) Outcome and severe hemorrhagic complications of intravenous thrombolysis with tissue plasminogen activator in very old (> or =80 years) stroke patients. Stroke 36:2421–2425
56. Sandercock P, Wardlaw JM, Lindley RI et al (2012) The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the third international stroke trial [IST-3]): a randomised controlled trial. Lancet 379:2352–2363
57. Macleod MR, Davis SM, Mitchell PJ et al (2005) Results of a multicentre, randomised controlled trial of intra-arterial urokinase

in the treatment of acute posterior circulation ischaemic stroke. Cerebrovasc Dis 20:12–17
58. Heiss WD, Huber M, Fink GR et al (1992) Progressive derangement of periinfarct viable tissue in ischemic stroke. J Cereb Blood Flow Metab 12:193–203
59. Natarajan SK, Snyder KV, Siddiqui AH, Ionita CC, Hopkins LN, Levy EI (2009) Safety and effectiveness of endovascular therapy after 8 hours of acute ischemic stroke onset and wake-up strokes. Stroke 40:3269–3274
60. Nogueira RG, Lutsep H, Gupta R et al (2012) Results from the TREVO 2 study (thrombectomy revascularization of large vessel occlusions in acute ischemic stroke): randomized data comparing Trevo with Merci for thrombectomy in acute stroke. In: European Stroke Conference. Lisbon, 2012
61. Saver J, Jahan R, Clark W et al (2012) Primary results of the solitaireTM FR with the intention for thrombectomy (SWIFT) multicenter, randomized clinical trial. In: International Stroke Conference. Los Angeles, USA, 2012; Presentation Number CT P40
62. Wu O, Christensen S, Hjort N et al (2006) Characterizing physiological heterogeneity of infarction risk in acute human ischaemic stroke using MRI. Brain 129:2384–2393
63. Lansberg MG, Lee J, Christensen S et al (2011) RAPID automated patient selection for reperfusion therapy: a pooled analysis of the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET) and the Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution (DEFUSE) Study. Stroke 42:1608–1614
64. Willats L, Connelly A, Christensen S, Donnan GA, Davis SM, Calamante F (2012) The role of bolus delay and dispersion in predictor models for stroke. Stroke 43(4):1025–1031
65. Parsons M, Spratt N, Bivard A et al (2012) A randomized trial of tenecteplase versus alteplase for acute ischemic stroke. N Engl J Med 366:1099–1107