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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 II: methodology of future trials

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Abstract Based on current data and experience, the joint working group of the European Society of Minimally Invasive Neurological Therapy (ESMINT) and the European Society of Neuroradiology (ESNR) make suggestions on trial design and conduct aimed to investigate therapeutic effects of mechanical thrombectomy (MT). We anticipate that this roadmap will facilitate the setting up and conduct of successful trials in close collaboration with our neighbouring disciplines.

Keywords Stroke · Interventional neuroradiology · Thrombectomy · Thrombolysis

Abbreviations

ASPECTS	Alberta Stroke Program Early CT
BCO	Balloon guiding catheter occlusion
BMT	Best medical therapy
CAS	Carotid stenting
CBF	Cerebral blood flow

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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

Randomised Controlled Trials	
ECASS	European Cooperative Acute **S**troke **S**tudy
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

Use of clinical endpoints

A pragmatic study approach enables "hard" and established primary clinical endpoints to be used. Clinical examinations (by an independent practitioner) should be scheduled at day 90 for all study subjects preferably at the investigational site (alternatively by telephone interview). The proportion of subjects with "good" clinical outcomes as measured by Modified Rankin Scale (mRS) at 90 days post treatment should be compared between two treatment groups (Table 1). A good clinical outcome will be defined as a mRS of 0-2. Superiority of MT must be the design goal as it is more invasive and, perhaps, more expensive. Formal cost effectiveness analyses of MT are required using robust randomised controlled trial (RCT) data. As patients with proximal artery occlusions have a poorer prognosis, an improvement from mRS 5 to mRS 3 (where the patients can still walk) could be considered a success. Nevertheless, such "sub-radar-success" would be considered as poor outcome and the benefit would escape a conventional study design. In comparison to a standard fixed dichotomous approach (mRS 0-2), stroke trial power and interpretation can be substantially enhanced by full ordinal and sliding dichotomy analysis [1]. An analysis of 47 trials testing treatments with likely biological benefit or harm found that shift analysis was positive in 26 %, whereas dichotomised analysis was positive in only 9 % [2]. We suggest incorporating this analysis as pre-defined clinical secondary endpoint, as is the case in PISTE. Other suggested clinical secondary clinical endpoints suggested are: mortality; improvement in acute to 24 h National Institute of Health Stroke Scale (NIH-SS) score; the rate of subjects with NIH-SS of 0 or 1 or improvement in NIH-SS score defined as an 8 point improvement at 24 h post treatment; full neurological recovery (Rankin 0-1 vs. 2-6) and days spent at home from admission after onset to 90 days post stroke.

Imaging based patient selection and endpoints

The classical intravenous thrombolytical therapy (IVT) studies (e.g. NINDS, ECASS I-III) used non-enhanced CT (NE-CT) as sole imaging method. The lower therapy

Table 1 Key endpoints

		MT + IVT vs. IVT	IA beyond IV
Safety		Neurological deterioration (NIH-SS score increase by ≥4, or death)	
		SICH rate (24±8 h) ECASS III definition	
		Any ICH	
		Extracranial haemorrhage/groin haematoma requiring any of transfusion, evacuation, surgery or interventional radiology procedure	
		Other extracranial haemorrhage	
Clinical	Primary	mRS≤2 (day 90)	
	Secondary	sliding dichotomy analysis of mRS (day 90)	
		rate of NIH-SS of ≤1 or NIH-SS score improvement of ≥8 (24 h)	
		All cause mortality at 30 and 90 days	
		Full recovery of neurological symptoms (0-1 vs 2-6)	
		Number of days in ICU, stroke unit, general ward, and inpatient rehabilitation during hospital stay	
		Days at home: admission to 90 days	
Imaging	Primary	CT Infarct volume (24±8 h)	
	Secondary	ASPECTS difference (0 vs. 24±8 h)	
		ASPECTS difference (0 vs. later)	
		Immediate Recanalisation on DSA (graded)	
		Angiographic patency at 24 h (±8 h)on MRA/CTA,	
	Tertiary*	Time to TICI 2b or better	
		TICI grade at end of procedure	
		Number of device deployments	

* only in MT arm

efficacy of IVT beyond 3 h after symptom onset has been attributed in part to the scarce imaging information from NE-CT, and in particular to the missed potential to accurately detect the site of arterial occlusion or spontaneous recanalisation. To overcome this drawback, NE-CT has been completed by CT-angiography (CTA) and CT-perfusion (CTP) to obtain information on the micro- and macrovascular level or has been completely replaced by MRI as primary imaging method in acute ischemic stroke in many centres [3]. To set up an imaging protocol for multicentre RCT, a balance is required between optimal patient selection and feasibility for multi-centric approach even for severely affected patients. Several authors believe that study patients should be imaged by MRI before treatment: MRA, axial T2w and T2*w, FLAIR, diffusion weighted imaging (DWI) and perfusion MRI (PI) completing image evaluation. Using DWI/PI to assess possible areas at risk might change the indication for MT [4]. MRI and CTP would also facilitate the diagnosis of reperfusion, haemorrhage and the prediction of malignant stroke progression [5, 6] and probably enhance trial safety. It has been shown in several studies that multivariate CT including CTP can also achieve a reasonable diagnostic accuracy [7]. To identify potential study participants who are most likely to benefit from MT, an appropriate vessel occlusion needs to be demonstrated and the volume of non-salvageable tissue needs to be compared to the volume of tissue at risk. In this section we discuss the major significance of using imaging protocols.

Imaging based patient selection

Non-enhanced CT The ECASS I pioneered the importance of assessing the volume of early ischemic signs (EIC) heralding irreversible tissue damage in NE-CT to predict benefit from thrombolysis and introduced the “one-third” rule [8]. In particular for non-fully trained neuroradiologists, the Alberta Stroke Program Early CT (ASPECTS) score has been developed as a systematic approach to assessing EIC on NE-CT [9–11]. Patients benefit the most with early mechanical recanalisation with an ASPECTS score >7 on baseline NE-CT [12].

A recent study employing thrombus length measurements showed that in acute middle cerebral artery stroke, IVT has almost no potential to recanalise occluded vessels if thrombus length exceeds 8 mm [13, 14]. Although not confirmed in an independent study, this finding is already in use as selection criterion for the THERAPY study.

Diffusion weighted MRI The most accurate yet practical way to determine infarct core with strong level 1 evidence is with DWI [15]. However, DWI does not necessarily reflect later infarctions as subsequent normalisations of the

hyperintensities can occur, especially in a very early phase and after recanalisation [16, 17]. Final infarct volumes of >100 mL are rarely associated with a good outcome [18].

CT/MR-angiography The demonstration of occlusion pattern prior to randomisation is essential. Proximal occlusions generally pose a larger thrombus burden and worse clinical outcome and should be excluded from primary studies. The most proximal occlusion site should be the intracranial ICA bifurcation (occlusion of the "Carotid-T") or the sphenoidal part of the middle cerebral artery (MCA). Prior to the publication of clot length measurements in NE-CT, a clot burden score was suggested based on CTA [19] that predicts the response to IVT and thereby potentially identifies candidates for a RCT. The scale is limited because it does not take into account residual flow at the site of arterial occlusion or vessel retrograde filling [10]. CTA should include at least the bifurcation of the common carotid artery (CCA) and the origin of the internal carotid artery (ICA) to identify a long vessel occlusion. Although not very responsive to IVT, this condition introduces variance and reduces the power of the study. For MRA we suggest including a contrast-enhanced MRA for evaluation of the supra-aortic vessels if possible so as to evaluate arterial access to the lesion [20].

CT/MR-perfusion In general, the region with cerebral blood volume (CBV) decrease is considered the infarct core ("irreversibly damaged") and cerebral blood flow (CBF) deficit the tissue-at-risk (often used synonymously with "penumbra") [21]. However, for individuals, this concept does not necessarily hold true. Perfusion CT (as well as perfusion MRI) is notoriously non-standardised [22] and the mismatch-concepts in their present form are often based on secondary volumetric analyses that are not applicable in the acute situation. Therefore, we do not consider CTP and PI feasible as a patient selection criterion for larger scale RCTs. The technique heavily depends on arbitrary thresholds, acquisition peculiarities, the post-processing software and the vendor [23]. Therefore, we suggest a simple approach: to enrol patients with EIC (NE-CT) less than the expected territory of the occluded artery (CTA). We suggest using CTP without thresholding as control instrument to detect deviations from this hypothesis and exclude these patients (e.g. to prove that the occlusion is more distal than diagnosed on CTA, thus violating the hypothesis of a proximal occlusion).

Digital subtraction angiography (DSA) A complete 4-artery-DSA should not be stipulated by the protocol because of time-limitations. However, a complete examination should be encouraged if it is achievable within <5 minutes. DSA should confirm the most proximal occlusion site. Collateral scores could be used for secondary analysis but not as patient selection criterion.

Imaging endpoints

The primary target of acute stroke therapy is to avoid disability and death by limiting the tissue damage and to avoid infarct expansion. Heterogeneity of clinical outcome is dependent on infarct localisation [24], leading to the need for large sample sizes. However, final infarct volume is a critical determinant of 3-month functional outcome and appears suitable as a surrogate biomarker in proof-of-concept intra-arterial therapy trials [18].

Non-enhanced CT Hypodensity in NE-CT is a highly specific marker for irreversible tissue damage. The volumetric analysis of infarct volume (mL) is an imaging endpoint with high reliability [18]. Possible time points for this analysis would be 24 h, 48 h, 5-7 days and 90 days. Correcting this volume in follow up (FU) imaging for the initial infarct volume and monitoring the infarct growth would increase study power. However, while EIC can be reliably detected, a clear volumetric analysis of EIC cannot be reached by manual delineation even if supported by post-processing algorithms. A possible solution would be to evaluate the changes of ASPECTS score from before treatment to follow up.

CT/MR-angiography To detect recanalisation in both arms (MT and IVT) only CTA/MRA could be used at the first FU. As data on recanalisation rates are already available, we consider this desirable.

CT/MR-perfusion Although too inaccurate to serve as patient selection criteria, thresholded CTP and MRP maps could be used as imaging outcome criteria to detect reperfusion in both arms (MT and IVT); however, only CTA/MRA can be used at the first FU. Given the difficulties with volumetric analysis of EIC, it is conceivable to use CTP parameters such as CBV as primary marker of severe ischemia and NE-CT at FU as a marker of final infarct. Based on a central core lab analysis, more advanced analysis tools such as multivariate prediction algorithms could be employed that could potentially permit subgroup analyses even with limited sample sizes (below 50) [25, 26].

Digital subtraction angiography The DSA endpoints can be applied only in the MT cohort. Among several grading schemes, TICI appears to be most reliably and closely related to clinical outcome in patients with acute ischemic stroke. A dichotomisation in patients with TICI 2b or better should be predefined as an end result of the DSA procedure. However, TICI 2b covers a wide range of perfusion

conditions that do not necessarily have uniform implications on lesion growth and prognosis. Additionally, the time from arterial puncture to initial restoration of flow to TICI 2b, the number of device deployments and the rate of embolisation in the vasculature proximal and distal to the target occlusion and their influence on the collateralisation should be measured. In an IV/MT study, the recanalisation success of IVT can be estimated in the MT arm. All DSA endpoints need to be determined by an independent core lab.

Qualification requirements for interventionalists and centres

Operator experience

Every operative therapy is dependent on the technical ability and experience of the local operators, the materials used and their preparation [27]. When studying a comparably new procedure, within-study-learning should be avoided as far as practical. The neuro-interventional community has learned this lesson the hard way from the trials comparing carotid stenting (CAS) vs. carotid endarterectomy (CEA).

MT in stroke should not be considered a trivial procedure because it not only requires technical handling of an ICA and/or MCA occlusion, but also treatment of complications (e.g. vessel perforation, dissection) and sometimes collateral procedures (e.g. carotid stenting). Moreover, compared to pharmacological trials there is a greater potential for variability in the compliance and performance of surgical operations because of differences in technology, surgeon skill and experience [28]. The magnitude of the association linking case volume to outcome varied greatly in a large systematic review [29].

It is well accepted that surgical skill and experience affect outcomes of comparative surgical treatments profoundly [30] and it has also been shown that complication rates at individual centres decrease with increasing patient numbers [31]. The proportion of patients being discharged home after endovascular therapy of unruptured aneurysms when treated by physicians coiling ≤5 unruptured aneurysms per year was half the rate in physicians treating at least 45 [32]. Data on CAS suggest the existence of a learning curve that involves a caseload larger than that generally accepted for credentialing [33]. In contrast, in the CAS group in EVA3S, the 30-day risk of stroke or death was 12.2 % in patients treated by interventional physicians who had experience of >50 carotid-stenting procedures, 11.0 % in patients treated by physicians who had done 50 or fewer procedures and 7.1 % in patients treated by physicians who were still in procedural training ($p=0.49$) [34]. A similarly confusing observation has been made in the ICSS study where supervised centres had a 7.1 % complication rate while experienced centres had 11.0 % (interventionalist with ≥50 CAS) [35]. Such observations might be biased by the association of patient risk factors with experience level, with the less experienced physicians treating fewer high risk patients [36]. Assessing the individual performance of a surgeon is notoriously difficult as it requires at least 200 procedures so that 95 % CIs are sufficiently tight [37]. The determination of the individual ability will be hampered by a learning curve that occurs while acquiring this number.

Centre experience

Several medical specialities are involved in MT of acute stroke and need to work in coordination and under time pressure (e.g. neuroradiologists, anaesthesiologists, neurologists, intensive care specialists). A recent editorial underlined the necessity of a systems approach to the MT of acute ischemic stroke, with focus on the overall sequence and workflow of a neurointerventional procedure rather than individual steps [38]. This emphasises that a highly experienced interventional neuroradiologist is an important - but not the only factor - that influences patient outcome. Despite highly standardised study protocols, variability will persist between centres in specific treatment aspects that may escape parameterisation (e.g. peculiarities of intensive care or anaesthesia).

In the SPACE study, the heterogeneity of CAS complication rates among centres became obvious in a secondary analysis where a within-study learning in the CAS arm but not for CEA arm was observed when a long established therapy was applied [39]. In centres with higher enrolment numbers, there was even a trend towards lower complication rates in CAS vs. CEA. The relation of complications vs. centre recruitment rate of ICSS was easier to interpret: 8.7 % in low-recruiting centres vs. 6.9 % in high-recruiting centres [35]. In a recent analysis of endovascular therapy of unruptured aneurysms, a highly significant association was noted between hospital volume and outcome [40]. A reasonable threshold seems to be somewhere between 20 and 40 UIA coiled per year. Ruptured aneurysms need to be added to the calculation of experience, which also should certainly not be below 20, with perhaps 40 to 50 total aneurysms per year as a minimum experience level.

Based on the current suggestion to the UEMS for training institutions, the INR centre caseload of endovascular interventions should be at least 150–200 cases/year. We propose not going below this minimum requirement for centres wishing to participate in the MT vs. IVT studies.

Training background

At present, there is no evidence that it is necessary or even feasible to train non-neurointerventional physicians in stroke MT [41]. The primary reason behind this observation is that physicians with interventional experience in other

vascular territories do not become competent in this demanding field as quickly. More importantly, there is no obligation to provide the unproven treatment without experienced stroke neurointerventionalist input and the time sensitivity of the condition does not favour decentralisation.

For the CREST study, a comprehensive training and credentialing process was required prior to assembling a competent team of interventionalists with low periprocedural event rates. Interventionalists submitted cases to a multidisciplinary Interventional Management Committee [42]. During the subsequent lead-in phase there were differences among training background with an OR (95 % CI) of outcome events of 0.40 (0.14–1.18) for Neuroradiology and 2.09 (1.21–3.61) for Vascular Surgery (other specialities were in between) [42]. The authors stated that duration and intensity of training in catheter-based diagnosis and treatment were substantial for Interventional Cardiology and INR specialists. Because no formal qualification for INR exists, a number of interventions need to be employed in order to define the abilities of a given interventionalist. This has been done in previous CAS vs. CEA studies [28] as well as in SAMMPRIS [43]. For SAMMPRIS, each operator's last 20 intracranial stenting procedures were reviewed by a board of INR specialists. These 20 cases included a minimum of 3 patients treated with the particular study device (Wingspan) in whom the interventionalist personally inserted a stent, performed intracranial angioplasty for intracranial stenosis or used a Neuroform stent for an intracranial aneurysm.

Proposal For pragmatic reasons, there needs to be an [arbitrary] cut-off for the qualification of the individual operator since objective measures do not and will not exist. The qualification criteria need to be balanced between the optimal qualification standards (as these might determine the study outcome) and a high number of putative study centres able to enrol patients. In general, we consider these trials to be rather exploratory, reflecting the reality of management as MT cannot be considered a standard therapy at present. Therefore, we suggest the criteria as detailed in Table 2. The operator requirements for MT in acute stroke of the AAN, AANS, SNIS, SVIN and particularly the SIR have been designed for clinical application of the procedure and are easier to fulfil [41]. In essence, the requirements have been chosen to facilitate a greater number of physicians to perform MT in a clinical environment.

Table 2 Minimal requirements for study participation

	Requirement
Operator experience within the last 3 years*	> 20 MT of stroke (reports of MT to study review board**)
	> 120 endovascular INR procedures (MT, aneurysms, arteriovenous malformations, dural fistulae, carotid stentings, other supra-aortic stentings)
INR centre experience within the last 3 years*	> 450 endovascular INR procedures
	> 50 MT
	> 30 additional intracranial stent deployments
General centre qualification	> 800 strokes per year within the last 3 years
	24/7 coverage with board-certified neurologists
	24/7 coverage with mCT
	Stroke unit and ICU

* the-3-year interval is suggested because experience is cumulative and a centre that has gained lots of experience during the last 18 months is probably as experienced as a centre with longer experience but lower annual numbers

** translations to English need to be covered by the study budget

Periprocedural aspects

Periprocedural anaesthesia

The role of anaesthesia during endovascular stroke treatment is still subject to debate and there are no guidelines about whether thrombectomy should be performed under general anaesthesia (GA) or conscious sedation (CS) with local anaesthesia. The possible advantages and disadvantages of one or the other method are obvious. CS is fast to apply but intervention might be more difficult and presumably more dangerous to perform in non-compliant patients [44].

GA eliminates movement and potentially improves procedural safety and efficacy [45]. However, time delay, intubation and risk of hypotension have negative impact on neurological outcome [46]. Various retrospective studies have investigated the influence of GA on neurological outcome and mortality after endovascular stroke treatment. Most studies illustrated a significantly worse neurological outcome and higher mortality rates for patients under GA [44, 46–48]. In patients treated under GA, there was a higher incidence of post-procedural pneumonia [48]. With a higher incidence of proximal vessel occlusion (e.g. ICA terminus) and correspondingly higher NIHSS before intervention in the GA-arm, a possible selection bias towards more complicated patients can be postulated in some studies [44]. This possible bias might explain the surprisingly lower recanalisation rate [48] and higher rate of complications [44, 48] found in the GA-arm. However, a separate analysis for patients presenting with isolated M1-MCA occlusion and balanced NIHSS in both subgroups confirmed these findings [44].

Proposal Anaesthesia likely contributes significant variability to the periprocedural protocol of patients undergoing

MT. Considering the possible selection bias of retrospective data, a prospective RCT on this aspect is needed. To date, general agreement on the optimal protocol is lacking; however, CS can be recommended in all clinical settings for compliant patients. A study design on MT is needed to further address this issue, either by providing a standardised protocol for all patients or by providing subgroup analysis for GA and CS; blood pressure protocols should also be recorded.

Proximal balloon occlusion catheter

All MT techniques are accompanied by the risk of thrombus dislocation. This may either occur into the distal territory of the affected vessel or during proximal thrombus retrieval into previously unaffected vessel territories. It is well established that manual suction through a balloon guide catheter is a useful and feasible technique that facilitates thrombectomy of large burden cerebral clots [49]. The presence of distal emboli during recanalisation of the target vessel is often difficult to prove as this territory has typically not been fully illustrated before recanalisation. The clinical sequelae of distal emboli mainly depends on localisation and size of vessel occlusion. Reasonable precautions and further intervention should be considered to prevent and treat distal emboli (see also rescue therapy). Nevertheless, since recanalisation of the larger proximal target vessel is achieved, improvement of brain perfusion can be assumed in the majority of cases.

Collateral infarction due to thrombus dislocation into previously unaffected vessel territories (e.g. from MCA to ACA territory) represents a major complication during MT [50, 51]. It involves ischemia in a new brain territory with the risk of new neurological deficits. Furthermore, pial collateral flow to the territory affected initially will decrease and presumably reduce salvageable tissue. For most stent-trievers and distal thrombectomy devices, proximal 8F balloon guiding catheter occlusion (BCO) and aspiration during thrombus retrieval is recommended (e.g. Trevo/Concentric, Solitaire/Covidien, ReVive/Cordis). Little data on the efficacy of BCO is available. In-vivo studies have illustrated a significant reduction of collateral infarction using distal devices when BCO is applied [52]. The largest core lab controlled study on the clinical use of stent-trievers documented a significantly lower incidence of collateral infarction when BCO was used [53]. Other approaches to reduce risk of collateral infarction such as aspiration via an intermediate/distal access catheter might be applied in complicated anatomical settings; however, their efficacy is unknown.

Proposal There is evidence that BCO reduces collateral infarction using distal devices and stent-trievers. Although clinical data is sparse, the use of BCO is recommended, especially in a RCT setting. However, only patients with an anatomical setting and occlusion pattern favourable for the application of a BCO should be considered for trial inclusion.

Adjunctive thrombolytic and antithrombotic agents

The preprocedural and intraprocedural role of fibrinolytic, anticoagulation and antiplatelet agents in endovascular stroke treatment is unclear [54].

IVT and bridging therapy Theoretically, preprocedural application of IVT might reduce thrombus burden, soften the thrombus or disintegrate distal emboli. Yet, the additional use of thrombolytic agents carries the potential increased risk of symptomatic intracranial haemorrhage (sICH). The influence of preprocedural IVT on neurological outcome and rate of sICH of patients undergoing MT has not yet been addressed in a randomised study. However, the Multi-MERCI trial which allowed prior treatment with IV rtPA and MT found a higher recanalisation rate (69.5 %) in conjunction with other treatment modalities compared to the use of the retriever alone (57.3 %) [55]. The subgroup receiving IVT prior to MT did not show differences in rates of intracranial haemorrhage or clinically significant procedural complications [55]. More recent retrospective data on the use of the Solitaire stent on 141 patients suggests a positive impact of IVT on clinical outcome after MT. One subgroup received IVT prior to MT, either following bridging IVT (BIVT) or after failed IVT. The second subgroup did not receive any IVT either because of contraindications or due to direct MT. No significant difference in age, initial NIHSS and time to groin puncture was found. However, a higher recanalisation rate and significantly better neurological outcome (mRS 0-2, 66.2 % vs. 41.8 %) in the IVT group was found without increase in sICH rate [53].

Heparin Heparin has been used inconsistently during studies of endovascular stroke treatment [54]. In the IMS [56] and PROACT [57] trials, 2,000 units of IV heparin were administered at the beginning of the procedure followed by 450 units per hour during the procedure. Additional administration of heparin to IA rpro-UK has been shown to enhance recanalisation in conjunction with a nonsignificant trend towards a higher rate of sICH [57]. A subgroup analysis of the multi MERCI trial showed no increase in the rate of sICH or mortality among the group who received periprocedural heparin (median dose of 3,000 units) during multimodal revascularisation therapy compared to those who did not [58].

Antiplatelet agents Periprocedural antiplatelet therapy is often applied after deployment of implants to reduce the risk of acute and delayed stent thrombosis. There is no consensus on safety, dosage or drug combination [54].

Aspirin and thienopyridinem The most commonly used agents are aspirin and thienopyridinem (e.g. Clopidogrel) derivatives. Oral antiplatelet therapy is routinely withheld following IVT or MCT for 12-24 h for potential risk of increasing the incidence of sICH. Both are typically used for secondary stroke prevention.

Abciximab Initial studies indicated administration of abciximab was safe in stroke treatment up to 24 h from symptom onset [59, 60]. The AbESTT-II trial, however, was terminated prematurely due to an increased risk of sICH [61]. Few case series have reported on its use in variable interventions [62–64] with no definite conclusion on the use of abciximab during MT. The role of Abciximab in endovascular stroke treatment remains unclear.

Other GP IIb/IIIa inhibitors Due to their shorter half-life, GP IIb/IIIa inhibitors such as tirofiban and epitifibatide are frequently used during or after endovascular stroke treatment [54, 65, 66]. The SaTIS trial, a randomised, placebo-controlled trial, demonstrated the safety of Tirofiban and demonstrated no significant increase in bleeding risk (Stroke Trials Registry. Available at: http://www.strokecenter.org/trials/TrialDetail.aspx?tid593). A review of various endovascular reperfusion therapies in combination with GP IIb/IIIa inhibitors and MT suggested that the inhibitors are an independent predictor of recanalisation [67].

Proposal RCT trials of MT should record the use of thrombolytic and antithrombotic agents, and subgroup analyses should be used to explore associations with sICH. The adjuvant use of IVT prior to MT is likely to be a significant variable. The sparse data available suggests a possible impact of tPA prior to MT on clinical outcome without increasing the rate of sICH. However, a prospective RCT on this aspect is needed. With regard to time span most centres need to begin the procedure, BIVT or even IVT can be applied without delaying MT. For the time being, preprocedural BIVT might be advocated for eligible patients in trials on MT. The standard procedural protocol might include heparin dosage up to 5,000 units throughout the intervention. Current data does not support the routine intraprocedural administration of antiplatelet agents unless a stent is implanted. In cases of in-stent thrombosis, rescue therapy using parental GP IIb/IIIa inhibitors appears to be beneficial.

Number of passes

In the study by Costalat et al. only one pass was sufficient to obtain a TICI2b/TICI3 recanalisation in 22 patients (44 %) [51]. These results are supported by other recent Solitaire FR device studies. Castaño et al. also demonstrated a recanalisation rate of 90 % (TICI 2B/TICI3) in 18 of the 20 patients using the Solitaire device in MCA occlusions. The mean number of passes were 2.9, 2 and 1.4 as reported by Shi [68], Castaño et al. [69] and Machi et al. [70] respectively. Optimal number of passes results from a trade-off between increasing efficiency and safety concerns. Loh reported a series of patients treated using MERCI in which up to 3 retrieval attempts correlated with good revascularisation, and when ≥4 attempts were performed, the end result was more often failed revascularisation and procedural complications [71]. More passes carry the risk of damaging the endothelium. Yin et al. [72] reported endothelium alterations after MERCI thrombectomy. This data should be considered with caution since the purpose of preserving the endothelium of an occluded vessel is dubious. What's more, one has to take into consideration company recommendations about the number of passes with a given device, although the use of another device during the same procedure goes beyond this limitation. Iterative passes may also prolong the procedure duration beyond a safe time window.

Proposal A suggested cut off time for thrombectomy is 8 h (as in SWIFT, THERAPY, PISTE and IMS III) or a 1 h delay to achieve the procedure (SYNTHESIS EXP), and a maximum number of passes (5 being an accepted number) beyond which the benefit of additional passes is unlikely.

Conclusion

Neurointerventional care is growing, with an increasing number of procedures and increasing number of centres where procedures are performed [73]. These developments present new possibilities for performing clinical trials that could allow Interventional Neuroradiology to progress from a discipline predominantly resting on experience-based decision making into a medical specialty underpinned by clinical trial evidence [74]. At present, the field of MT in patients with acute ischemic stroke is the most dynamic development in Interventional Neuroradiology and provides the greatest chance for successful trials. We sincerely hope that this first roadmap might help in designing and conducting successful trials in close collaboration with our neighbouring disciplines.

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).

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