

Endovascular thrombectomy 2020: open issues

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Mechanical thrombectomy is now well - established first - line treatment for selected patients with large artery occlusions of the anterior circulation. However, number of technical and procedural issues remains open to assure optimal outcomes in majority of patients including those suffering from posterior circulation perfusion defects. This brief review addresses some of the open issues and refers to the ongoing trials to close the existing knowledge gaps.

Introduction

In 2015, the MR CLEAN randomized trial has proven the superior effectiveness of endovascular thrombectomy (EVT) over systemic thrombolysis (ST) in selected patients with cerebral large-vessel occlusions (LVOs).¹ Subsequent randomized trials not only confirmed the initial findings but also provided new evidence for the extension of the therapeutic time window emphasizing individual patients' collateral vessels status and penumbra tissue-related factors.² Nevertheless, a number of issues related to the practice of EVT remain open. Here, we provide a brief review of some of these issues and discuss their clinical implications.

Logistics of acute stroke interventions

Current situation in Europe

The situation in Europe in 2018 (i.e. 3 years after the new guidelines set thrombectomy as Class I.A indication) was described by the European Stroke Organization (ESO) survey.³ These data suggest that thrombectomy is performed in approximately one-third of patients, who (at least theoretically) should be treated by this method.

Importance of multidisciplinary cooperation, two levels of neurointerventional centres, involvement of interventional cardiologists

Unlike myocardial infarction (where a single specialist—interventional cardiologist is needed to manage the first in-hospital hour of STEMI)—for treatment of patients with acute ischaemic strokes (AIS) interdisciplinary stroke teams available 24 h/7 days are required.

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The ESC Council on Stroke since its foundation in 2016 is continuously recommending the involvement of interventional cardiologists in the treatment of acute stroke in those countries or regions where neuro-interventionalists are not able to cover 24/7 thrombectomy services.⁴ Involving properly trained interventional cardiologists along with establishing the required logistics would allow upgrading Level 3 to Level 2 stroke centres improving EVT availability across Europe.

Who should perform endovascular thrombectomy

Standards of practice recommendations in AIS interventions have been published by a working group composed of delegates from 13 international societies⁵ and The European Board of Neurointervention (EBNI) has defined Standards of Practice in Acute Ischaemic Stroke Intervention and Recommendations for acquiring competence in Acute Ischaemic Stroke Intervention.⁶

Applicability of results of RCTs result to other countries

All the randomized controlled trial (RCTs) were done in Europe and the USA. The question of whether the results of these trials may apply as well to other or developing countries is addressed by at least two studies.

EAST (Endovascular therapy for acute ischaemic stroke trial) evaluates the safety and efficacy of Solitaire thrombectomy in 225 Chinese patients with AIS within 12 h of symptom onset. RESILIENT (Endovascular Treatment with stent-retriever and/or thrombo-aspiration vs. best medical therapy in acute ischaemic stroke in Brazil) study results have already been presented and have shown similar results to the previous seven RCTs suggesting that in Brazil the EVT may be as efficient as in Europe and the USA.

Logistics of endovascular thrombectomy delivery: 'mothership' or 'drip and ship'

The question is whether the patient with suspected AIS should be first transported to a stroke unit without 24/7 EVT facility to receive ST if AIS has been confirmed ('drip and ship' concept) or directly sent to a stroke centre with 24/7 EVT services ('mothership' concept). Direct admission to the latter will reduce time to EVT but may delay time to ST. The RACECAT (Direct transfer to an endovascular centre compared to transfer to the closest stroke centre in acute stroke patients with suspected LVO) trial will compare direct transfer to 24/7 EVT centre compared to transfer to the closest local stroke centre in AIS patients with clinically suspected LVO identified by Emergency Medical Services (EMS) as assessed by mRS scores at 90 days in. The RACE scale will be used as a prehospital screening tool to AIS patients with suspected LVO. In this trial following candidate identification, EMS will contact a stroke neurologist on call using a prehospital tele-stroke system that will confirm inclusion criteria and will allocate the patient to a specific per-protocol temporal sequence and management.

Allocation will account for three variables; time band (two groups of 12 h), territory (metropolitan vs. provincial area), and weekday (working vs. weekend day).

Patient selection

Since the mid-1990s, the mainstay for treatment of AIS has been intravenous alteplase administration within 4.5 h of symptom onset or last know well (LKW). Although outcomes improved, the narrow therapeutic window, as well as contraindications to the drug, made the volume of eligible patients fairly restricted. Intraarterial treatment with thrombolysis and or EVT has long been considered a viable option to address this issue. Early randomized control trials failed to uncover a benefit of thrombectomy compared to medical treatment in AIS.⁷ Recent trials with better patient selection and better devices have shown an overall improvement in the outcome.

Symptom onset or last known well within 6 h with confirmed large-vessel occlusion

The Dutch trial MR CLEAN, randomized patients with AIS and confirmed anterior circulation LVO within 6 h of LKW to EVT plus medical therapy or medical therapy alone; 33% of patients in the EVT arm achieved a good outcome (mRS 0-2) compared to 19% in the medical treatment arm [odds ratio (OR) 1.67, 95% confidence interval (CI) 1.21-2.30]. Subsequently, several trials have supported these findings. In SWIFT PRIME trial improvement of outcomes was 60% vs. 35% (Riva Rocci (RR) 1.7, 95% CI 1.23-2.33). In EXTEND IA improvement of outcomes was 71% vs. 40% (OR 4.2, 95% CI 1.4-12). For patients with anterior circulation LVO within 8 h of last know well, REVASCAT and ESCAPE found similar results, 44% EVT vs. 28% medical therapy (OR 2.1, 95% CI 1.1-4.0), and 53% vs. 29% (OR 1.8, 95% CI 1.4-2.4), respectively. While trials were stopped early because of efficacy on interim analysis or published data from other trials, the HERMES collaboration meta-analysis of the five RTC solidified the findings. Functional independence at 90 days was seen in 46% of patients in the thrombectomy group compared to 27% in medical management (RR 1.73, 95% CI 1.43-2.09).^{1,2}

It is important to note that in every one of the trials described above patients required either an Alberta Stroke Program Early Computed Tomography Score (ASPECTS) of 6-10 or infarct core of <50-70 mL measured by tomographic (CT) perfusion imaging. Furthermore, all patients had confirmed anterior circulation LVO, emphasizing the importance of appropriate patient selection.

Symptom onset or last known well within 6-24 h with confirmed large-vessel occlusion

Non-randomized trials had previously suggested a benefit to reperfusion of an occluded anterior circulation vessel beyond 6 h in patients with a favourable mismatch between infarcted tissue and tissue that might yet be salvaged. The DAWN trial randomized patients with last know well between 6 and 24 h to EVT plus medical management or medical management alone, selecting patients based on a mismatch between clinical severity and infarct volume.

Good outcome (mRS 0-2) was achieved in 49% of the EVT group vs. 13% of the medical management group. Similarly, DEFUSE 3 randomized patients based on a mismatch between infarct core and ischaemic penumbra. Results were similar with 45% and 17% (OR 2.67, 95% CI 1.60-4.48) favouring EVT group.

Interestingly, the most robust effect in outcome was seen in patients treated at a later time. These findings come to question the widely accepted notion of time being the greatest determinant of patient outcome. Both DAWN and DEFUSE showed that collateral circulation is as, if not more critical than time of onset. The question on the benefit of thrombectomy in patients outside of the 24-h window who have favourable collateral networks needs consideration. Further studies are needed to answer this question.

Patient selection: optimum imaging protocol

To minimize time loss, it appears important to clarify which imaging diagnostics should be performed or whether the patient should be sent directly to the angiography room to perform flat panel computer tomography angiography (CTA). It has been shown that younger patients with severe neurological deficits accrue greater benefits from recanalization when the symptom onset-to-reperfusion time <1 h was achieved. A recent pilot study has shown a benefit with increasing functional independence at 3 months following direct admission to the angiography room. DIRECTANGIO (Effect of direct transfer to angio-suite on functional outcome in severe acute stroke) aims to demonstrate the superiority of the direct angio-suite transfer vs. the standard management, in terms of 3-month functional independence, in 200 patients ≤ 60 years old with acute large-vessel anterior AIS.

Which type of imaging is required before indicating endovascular thrombectomy?

The success of EVT is largely related to the emergent reperfusion of the ischaemic penumbra. Multimodal brain imaging can identify the amount of salvageable penumbra. The indirect comparison of the recently published randomized trials suggests that despite common baseline clinical characteristics, (vessel site occlusion, delay, and type of treatment), the success of EVT was higher in studies enrolling exclusively patients exhibiting a significant amount of penumbra defined by a target mismatch (TMM) on CTP or magnetic resonance imaging (MRI) by comparison with those enrolling patients based on non-contrast CT scan without specific imaging criteria. There is currently no demonstration that mechanical thrombectomy (MT) must be limited to the subgroup of patients based on imaging criteria.

SELECT 2 is a randomized controlled trial to optimize patient selection for EVT in AIS which evaluates the efficacy and safety of EVT compared with medical management alone in AIS patients due to an LVO in the distal internal carotid artery (ICA) and MCA M1 who have large core on either CT (ASPECTS: 3-5) or advanced perfusion imaging (regional Cerebral Blood Flow <30% on CTP or ADC <620 on MRI: ≥ 50 mL) or both and are treated within 0-24 h from LKW. The second aim is to look at the correlation of imaging profiles with EVT clinical outcomes and

treatment effect. This will be evaluated by comparing the outcomes in patients with discordant imaging profile and assessing if EVT outcome rates and treatment effect will differ in patients with discordant imaging profiles (favourable CT/unfavourable perfusion imaging and unfavourable CT/favourable perfusion imaging) in 560 participants. FRAME, French acute cerebral multimodal imaging to select patient for EVT is a prospective multi-centre study to determine if multimodal imaging can identify patients who may benefit from EVT within 6 h after stroke onset. The aim is to investigate in a prospective cohort of patients treated by EVT per the current recommendations, the relationship between the prevalence of TMM on pre-treatment brain imaging with the rate of clinical recovery after EVT. MR DWI, perfusion, and CTP maps processed by RAPID software will not be as usual pushed back to the PACS but anonymized and saved on remote software leaving the investigator blinded at the time of treatment decision.

Patients with very low NIHSS (NIHSS < 6) with proximal occlusion

The management of patients with LVO presenting with minor-to-mild stroke symptoms, present in up to 28% when considering patients with an National Institutes of Health Stroke Scale (NIHSS) ≤ 4 , has not yet been studied in randomized clinical trials. Current EVT guidelines suggest cut-off of NIHSS of ≥ 6 . There are two ongoing studies aiming to answer this question. MOSTE (Minor Stroke Therapy Evaluation) targets EVT in patients with LVO presenting with NIHSS < 6 in patients last seen well < 24 h. This trial will include 824 participants. ENDOLOW (Endovascular therapy for low NIHSS ischaemic strokes) has been designed to test the hypothesis that patients (175 participants) presenting within 8 h of onset with cerebral ischaemia in the setting of LVO and baseline NIHSS 0-5 will have better 90-day clinical outcomes as assessed by mRS with immediate EVT compared to initial medical management.

Patients with large core infarct (ASPECT < 6)

To date, patients with large core defined as ASPECTS 0-5 were excluded from most randomized clinical trials resulting in a lack of evidence of benefit in this patient population. Analyses of several prospective cohorts suggest benefit of EVT in patients with large baseline core. In the prospective cohort ETIS, Panni *et al.*⁸ reported a rate of good outcome (mRS ≤ 2) of 34% in the subgroup of patient with ASPECT 4-5. In the prospective cohort analysis, RECOAT in patients presenting with ASPECT 0-5 also compared with medically treated patients EVT was favoured. In TESLA (Thrombectomy for emergent salvage of large anterior circulation ischaemic stroke) trial, the primary objective is to establish the effectiveness of EVT compared with medical management in patients with moderate to large infarcts (non-contrast CT ASPECTS 2-5) at baseline, with adaptive enrichment to better define the upper limit of infarct volume for treatment eligibility. Furthermore, the investigators aim to determine whether certain subgroups

of patients with large baseline infarcts may have a greater treatment benefit. In the LASTE (Large Stroke Therapy Evaluation) trial, the investigators aim to study the efficacy and safety of EVT in 450 patients with <7 h presenting with a large volume of infarct core defined by 0-5 ASPECT scores compared with those patients treated medically. In TENSION (Efficacy and safety of thrombectomy in stroke with extended lesion and extended time window) trial, the aim is to compare the safety and effectiveness of EVT with best medical care alone in 714 AIS patients with extended stroke lesions defined as ASPECTS scores of 3-5 and in an extended time window (up to 12 h or unknown time of symptom onset).

Patients with basilar artery occlusion

Facing the paucity of data regarding basilar artery (BA) EVT the current ESO-ESMINT guidelines recommend enrolment of patients presenting with BA occlusions into randomized trials (RT), if possible. In the absence of such an option, performance of EVT based on institutional guidelines is recommended.⁹

Strategy of endovascular thrombectomy: systemic thrombolysis yes or no

Whether IV t-PA prior to EVT is beneficial in AIS patients with anterior circulation LVO has become a matter of debate representing a relevant unanswered question in clinical practice. The aim of the SWIFT DIRECT (Bridging thrombolysis vs. direct mechanical thrombectomy in AIS) trial is to determine whether subjects with AIS due to anterior circulation LVO will have non-inferior functional outcome at 90 days when treated with direct EVT compared to subjects treated with combined IV t-PA and EVT. In Mr Clean NO IV, the primary aim is to assess the effect of direct EVT compared with ST followed by EVT on functional outcome in patients with AIS due to anterior circulation occlusion confirmed by neuro-imaging.

Strategy of endovascular thrombectomy: tandem occlusions

Tandem occlusion is defined AIS due to steno-occlusive disease of the extra-cranial carotid artery present in about 10% of AIS patients. Whereas EVT has shown its efficiency in AIS due to LVO, to date, there is no consensus on the endovascular management of the extra-cranial carotid artery in patients with tandem occlusions. In the available clinical randomized trials who evaluated EVT, only a small number of patients with tandem occlusions were included; in fact, tandem occlusions were often listed as exclusion criteria. Endovascular management can be complex with the need for acute stenting of the extra-cranial carotid lesion along with the potential need of antithrombotic therapy initiation. The benefit and the safety of stenting of the cervical lesion in acute phase of AIS have been suggested but not convincingly proven as yet. TITAN (Thrombectomy in tandem occlusion) trial aims to assess the superiority of the combined use of EVT and extracranial carotid stenting

compared to EVT alone using complete reperfusion rate in 432 patients with AIS due to tandem lesion.

Strategy of endovascular thrombectomy: management of blood pressure during and post-thrombectomy

Blood pressure (BP) management during and after EVT represents an important predictor of outcome. The BP should be elevated during the procedure to maintain the perfusion of the ischaemic core and penumbra. In contrast, in order to decrease the risk of haemorrhage the BP should be lower following successful recanalization. To date, no data concerning the optimal management of BP in the settings of EVT are available. BP-TARGET (Blood pressure target in acute stroke to reduce Haemorrhage after endovascular therapy) is a randomized, multicentre study comparing standard management of systolic blood pressure (SBP) per international recommendations (SBP < 185 mmHg) vs. intensive blood pressure management with SBP < 130 mmHg in 320 patients. ENCHANTED 2 (Second enhanced control of hypertension and thrombectomy stroke study) aims to evaluate different approaches to blood pressure control in 2236 AIS patients undergoing EVT. Intervention group aims to achieve SBP level of <120 mmHg within 30 min after randomization and maintaining this level at least for 72 h. Control group aims at BP lowering treatment only when BP level \geq 150 mmHg to achieve the target of \geq 140 mmHg, and maintaining this level at least 72 h.

Strategy of endovascular thrombectomy: adjunct anticoagulation and antithrombotic therapy before, during, and after revascularization

With bridging thrombolysis

All existing guidelines recommend the use of intravenous thrombolysis for AIS immediately following the indication, irrespective whether EVT follows or not. Vice versa, all guidelines recommend EVT whenever indicated, irrespective of whether the patient received (bridging) thrombolysis or not. In reality, this strategy results in about 50-75% use of periprocedural thrombolytics before/during mechanical thrombectomy. There is no indication to use thrombolysis after EVT, even if thrombectomy failed. Evidence is still lacking on the optimal selection of periprocedural anticoagulation or antiplatelet drugs use. Most centres do not use periprocedural anticoagulation during EVT in patients pretreated with thrombolysis, but other centres use very low dose (e.g. 15-20 units/kg) of unfractionated heparin during EVT. Aspirin is usually recommended after 24 h when control imaging excluded post-procedural intracranial bleeding.¹⁰

Direct thrombectomy (without thrombolysis)

Direct EVT (without thrombolysis) is recommended in patients with contraindications to such treatment and some centres use this approach also for patients who are directly admitted and intervention can start at the same time when thrombolytic infusion could start. This strategy

is based on the fact, which ST requires similar time to resume effect needed to initiate EVT. Thus, employing this strategy the risk of bleeding may be reduced. However, whenever catheter intervention is expected to start with any significant delay and thrombolysis is indicated, it should be used as bridging.

Acute stroke interventions with stent implantation

When a stent is implanted (e.g. to the internal carotid artery), dual antiplatelet therapy (clopidogrel + aspirin) is indicated. However, its initiation is debatable: immediately after stenting vs. after early control imaging (which excludes intracranial bleeding). Until new evidence becomes available, the antiplatelet management remains at the discretion of the interventionalist.

Strategy of endovascular thrombectomy

Type of anaesthesia

AMETIS (Anesthesia management in endovascular therapy for ischaemic stroke) trial aims to assess whether CS or GA in 270 patients with anterior circulation AIS treated by EVT impacts on morbidity defined by neurological outcome and peri-procedural complications. The GASS (General anaesthesia vs. sedation during intra-arterial thrombectomy: treatment for stroke) trial aims to compare CS and GA during EVT for AIS due to LVO of the anterior cerebral circulation. The main outcome will be the effect on functional neurological outcome at 3 months in 350 participants.

Neuroprotection

Although a number of studies performed prior to the EVT era failed to demonstrate any clinical benefit with use of neuro-protectors in patients with AIS, this area remains a highly vibrant area of research. The potential benefit of new neuro-protectors must be evaluated in the setting of EVT. ESCAPE-NA1 (Safety and efficacy of NA-1 in subjects undergoing EVT for stroke) has been designed to determine the safety and efficacy of the neuro-protector (NA-1), in reducing global disability in subjects with major AIS. Subjects harbouring an AIS and who are selected for EVT in accordance with the local institutional practices and who harbour a small established infarct core and with good collateral circulation will be given a single, 2.6 mg/kg (up to a maximum dose of 270 mg) intravenous dose of NA-1 or placebo as soon as they are deemed to have met the enrolment criteria and with the intention of starting administration within 30 min of randomization. The randomization will be by stochastic minimization to balance baseline factors and will include 1120 participants.

Thrombus composition and outcomes

Thrombi are generally characterized by the relative content of erythrocytes, platelets, and fibrin. Erythrocyte-rich clots are generally soft and embolize more easily, while fibrous clots are harder and more adherent to the vessel wall.¹¹ Classical teaching states that thrombi formed in areas of low flow or stasis tend to be richer in erythrocytes,

whereas thrombi formed under arterial flow conditions, especially high shear conditions that exist at the sites of luminal narrowing, tend to comprise mainly platelets held together by a strong fibrin mesh.¹² These findings suggest that erythrocyte-rich cerebral thrombi indicate an embolic origin from the left atrium or in cases of paradoxical embolization from the venous system, whereas origin of thrombi composed of platelet-fibrin mesh suggest the arterial circulation at sites of plaque disruption. Recent studies in stroke do not support this delineation and indicate significant variability in thrombus composition between individuals experiencing strokes of the same aetiology.¹³ Irrespective of their aetiology and despite their heterogeneity, intracranial thrombi causing LVO have a core-shell structure that influences their susceptibility to thrombolysis (Di meglia *et al. Neurology* 2019 doi.org/10.1212/WNL0000000000008538). Based on the available evidence, a continuum of thrombus ultrastructure appears likely.

The structural stability of the thrombus, as well as its susceptibility to lysis and fragmentation, is determined by fibrin characteristics including density and porosity, platelet-dependent clot retraction, as well as proteins released from platelets and leucocytes, including neutrophil extracellular traps.¹⁴ Thrombi containing predominantly platelets and fibrin are more tightly packed, less compressible, and more adherent to the vessel wall than erythrocyte-rich clots.¹⁵ Such densely packed platelet-fibrin thrombi are also more difficult to extract.¹⁶ Platelet-rich thrombi undergo contraction *in situ*, which results in reduction in thrombus volume, and increased resistance to thrombolysis and embolization. The rate of clot retraction is inversely proportional to susceptibility to fibrinolysis.¹⁴

As the platelet thrombus ‘ages’, there is increasing adhesion of platelets, erythrocytes, connective tissue and neutrophils to the thrombus core, rendering it more unstable and prone to embolization.

Time and the site of origin dependent mechanical properties of thrombi are critical determinants of EVT outcome. Current imaging technology can only provide crude estimates of thrombi density.¹⁷ However, high resolution imaging of thrombus composition would be required to improve and eventually to modify decision making regarding strategy of EVT in individual patients.

Ischaemia-reperfusion injury

Successful TICI 3 revascularization of the culprit site may result in complete or incomplete reperfusion. In some cases, reperfusion may fail, the extent of the ischaemic region may increase and intracerebral haemorrhage may occur. Brain tissue injury following reperfusion, ischaemia-reperfusion injury (IRI), may be triggered by factors, such as distal thromboembolism, hyperperfusion, intracellular, or interstitial oedema formation or haemorrhage secondary to the blood-brain-barrier and the microvascular injury.¹⁸ While research is going prevention of IRI and treatment of no-reflow still remain a distant target.

Conclusion

Endovascular thrombectomy represents the uncontested first-line therapy for selected patients with AIS due to LVO. As this technique and associated technology are rapidly evolving, a number of open issues remain to be addressed by members of the involved disciplines, basic scientists and clinical researchers conducting randomized trials. Here, we have addressed some of these open clinically relevant issues have been addressed.

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