European Recommendations on Organisation of Interventional Care in Acute Stroke (EROICAS)

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Developed by the European Academy of Neurology (EAN), the European Association of Neurosurgical Societies (EANS), the European Society of Emergency Medicine (EuSEM), the European Society of Minimally Invasive Neurological Therapy (ESMINT), the European Society of Neuroradiology (ESNR), and the European Stroke Organisation (ESO)

Appendix A: List of the recommendations, the respective questions and the working group members

Introduction

Five recently published randomized controlled trials (RCTs)(1-5) and respective meta-analyses (6-12) provide strong evidence that endovascular thrombectomy (EVT) combined with best medical treatment (BMT), including intravenous (IV) tissue plasminogen activator (IV thrombolysis, IVT) for eligible patients, improves the outcomes of appropriately selected patients with acute ischemic stroke in the setting of proximal occlusions in the carotid circulation (large vessel occlusion, LVO).

Four out of the five studies were stopped early after a first RCT (1) showed the superiority of EVT combined with medical management over medical management alone. Such premature trial termination will on average lead to overestimation of the treatment effect.(13) Nonetheless, since all five RCTs showed consistent benefit of EVT over optimal medical management alone, and a dose-effect relation (reperfusion rates vs. clinical outcome), the benefit of EVT is considered established.

After the publication of the "Consensus statement by ESO-Karolinska Stroke Update" as timely response to the new evidence,(14) the purpose of EROICAS is to provide recommendations based on a structured collaborative process conducted by six relevant European professional societies.

Methods

A multidisciplinary group of nine clinical researchers (neurology, neurosurgery, neuroradiology, neuro-intensive care, and emergency care physicians) from seven European countries representing six European Scientific Societies [in alphabetical order: European Academy of Neurology (EAN), European Association of Neurosurgical Societies (EANS), European Society of Emergency Medicine (EuSEM), European Society of Minimally Invasive Neurological Therapy (ESMINT), European Society of Neuroradiology (ESNR), European Stroke Organisation (ESO)] was nominated by the participating societies and confirmed by the respective Executive committees.

The group discussed and decided by consensus on specific therapeutic questions. This included rating the importance of the outcomes selected, concluded by a majority consensus among the members of the working group.

The group identified all available related literature and selected eligible studies. For each question, three to five authors (**Appendix A**) screened the publications and assessed the full text of potentially relevant studies. We restricted our evidence synthesis to RCTs, systematic reviews and meta-analyses of RCTs relating to 15 questions.

The group graded quality of evidence and strength of recommendations. The final summaries of the quality and strength of evidence and recommendations for each question (based on RCT evidence only) were discussed by the whole group, and the recommendations were agreed by a majority consensus of the group of all authors. Similar to the GRADE approach,(15) quality of evidence was graded into high, moderate, low, and very low. Overall, 41 recommendations were given. Section authors generated 'additional information' based on RCTs and observational studies.

Development of guidelines that encompasses the GRADE guideline development process (15-17) is under way.

Part A. Center and operator requirements for thrombectomy

1. What service organization is associated with favourable outcome after thrombectomy?

Minimum characteristics of centres appropriate to conduct EVT common to all five studies were(1-5):

- an established organisation to support rapidly instituted IV rt-PA use
- Team organisation of a level sufficient to support clinical trial participation
- Experience with acute CT interpretation including ASPECT scoring
- Experience with CTA in acute stroke patients as a minimum additional imaging modality
- A process for monitoring door to needle / groin puncture/reperfusion, and procedural duration times, and a governance process to ensure that these are reviewed.
- Implementation of door-to-needle time minimisation strategies as for IV thrombolysis
- Minimum institutional and individual experience of cerebrovascular procedures generally, of thrombectomy for acute stroke, and of the specific device

The generalisability of the trial findings to centres or interventional teams that do not fulfil these criteria is not established by the literature.

Recommendation:

- Services should demonstrate established organization at the center to support rapidly instituted IV rt-PA use, team organization of a level sufficient to support clinical trial participation, a process for monitoring door to needle/ groin puncture, and procedural duration times, and a governance process to ensure that these are reviewed. (Quality of Evidence: **moderate**, Strength of recommendation: **strong**).
- Services should include a neuroradiological/radiological department with experience with acute CT/MR interpretation including ASPECTS, and experience with CTA in acute stroke patients as a minimum additional imaging modality. (Quality of Evidence: **moderate**, Strength of recommendation: **strong**).
- Operators and services should conform to minimum requirements for training, certification, caseload and ongoing education for acute neurovascular procedures by national/European neurointerventional/radiological organizations and national statutory bodies. (Quality of Evidence: **moderate**, Strength of recommendation: **strong**).

Additional information:

Only one trial(4) was conducted explicitly in the setting of a regional network of acute stroke care, covering a population of 7.5 million in a compact geographical region of Catalonia. No trial specified the characteristics of a network, only of individual participating centres.

EXTEND-IA(2) selected sites that were “required to have an established intravenous rt-PA program with multimodal CT or MRI imaging as standard procedure.”

SWIFT-Prime(5) selected sites and investigators based upon several criteria; in addition to general criteria related to GCP, these included:

- Previous experience with clinical research and mechanical thrombectomy procedures
- Experience in conducting randomized, controlled, clinical studies
- Currently treating subjects who meet the inclusion/exclusion criteria
- Ability to enrol an adequate number of subjects
- Ability and willingness to randomize study subjects

- Ability to perform required clinical testing, including: angiography, CT, and MRI
- Adequate staffing to conduct the study.

ESCAPE(3)required sites to employ CTA as standard of care for acute stroke patients and have effective systems for identification of patients. In addition, "the quality of intervention will be ensured by hand-selection of sites and only be approved by the executive committee after a site visit. All sites must submit evidence within the 2 years prior to commencement of the trial that they can meet the 90 minute target of CTA-to-recanalization time. A key and critical component of the trial will be an ongoing quality assurance program to ensure that sites can meet these targets for endovascular intervention. Training will be undertaken at the sites and continued on a quarterly basis. Monitoring of interval times will be collated and provided to sites on a quarterly basis so that regular feedback might induce appropriately fast treatment processes. Sites that fail to meet these objectives in the trial will be dropped from the trial."

MR CLEAN(1) specified that "centers should meet the following minimum criteria:

- The intervention team should have ample experience with endovascular interventions for cerebrovascular disease, peripheral artery disease, or coronary artery disease. At least one member of the intervention team should have sufficient experience with intra-arterial thrombolysis (IAT).
- … At least one member of the intervention team should have sufficient experience with the particular device (defined as completion of at least 5 full procedures with the particular device). Procedures that have been carried out by two team members (for example, in a training setting) count. Procedures do not need to be successful, nor uncomplicated. Procedures consisting of mechanical thrombectomy combined with IAT count for both.
- … The possibility of treatment by an interventionalist with sufficient experience is listed as an inclusion criterion."

The same organisational components that have been shown to achieve rapid door-to-needle times for IV thrombolysis will therefore be required for provision of IAT.(18, 19) Process improvements have been documented in a number of publications and guidelines and these have been shown to improve treatment times when translated into a different healthcare environment. The additional components required for implementation of IAT should include early notification of the interventional team, and neuroradiology workflow that minimises acquisition, processing and interpretation of additional imaging to select patients for IAT.

There is evidence from national audit data in the UK that stroke centres with higher rates of IVT (≥50 cases per year) have higher numbers of admissions (550-950 ischaemic stroke patients per annum) and also have shorter door to imaging and door to needle times.(20)

2. What operator characteristics are associated with favourable outcome after thrombectomy?

In general, both patient selection and procedural expertise are critical to achieve a good clinical outcome in neurovascular procedures.(21-26) Training requires a minimum defined number of neurovascular cases, and maintenance of skills requires an ongoing minimum caseload.

Well-trained neurointerventionalists are a critical component of an organized and efficient team needed to deliver safe and effective EVT for acute ischemic stroke patients. The great majority of thrombectomies in the five stroke thrombectomy studies showing favourable outcome after EVT were performed by trained, experienced neurointerventionalists, including interventional neuroradiologists, or formally trained endovascular neurosurgeons, and interventional neurologists working routinely on neuroradiological interventional procedures.

Criteria for trial centres and staffing were stated variously in trial protocols of the five RCTs.

- REVASCAT specified "certified vascular neurologists and interventional neuroradiologists or neurologists in comprehensive stroke centers that treat more than 500 acute stroke patients and perform more than 60 acute mechanical thrombectomy procedures every year will manage patients.
- …certified interventionalists [should] have at least two years training in diagnostic angiography and endovascular treatment at a comprehensive stroke center. As first or co-interventionalists, they require to have participated in more than 200 angiographies and 150 endovascular procedures. For the purpose of the REVASCAT trial, only neurointerventionalists who have performed at least 20 thrombectomies with Solitaire device in acute ischemic stroke patients can treat subjects"
- EXTEND-IA specified "Neurointerventionalists will be credentialed to participate in the study if they have >2 years neurointerventional experience and have performed >10 intra-cranial clot retrieval procedures."

Recommendation:

- Thrombectomies should be performed by physicians competent in intracranial endovascular procedures. Competence in Interventional neurovascular procedures is based on:
  - Proven capacity to perform, conduct and interpret standard diagnostic Neuroradiology (CT, MR, multimodal-imaging) for appropriate case selection.
  - Proven capacity to perform, conduct and interpret standard intracranial endovascular procedures as well as management skills for procedural complications.
  - Skills in interdisciplinary management of hemorrhagic and ischemic stroke patients with stroke physicians or neurologists/neurosurgeons in stroke centers. Treatment in the context of an acute stroke unit is an option in geographically remote regions.
  - Meeting the minimum requirements for training, certification, caseload and ongoing education for acute neurovascular procedures by national/European neurointerventional/radiological organizations and national statutory bodies (e.g. certification by a European or National Certificate/Diploma/Master).
  - Continuous updating of the INR diagnostic and therapeutic methods and skills.

  (Quality of Evidence: **Moderate**, Strength of recommendation: **Strong**)

Additional information:

Recently, a group of international multi-disciplinary societies involved in EVT for acute ischemic stroke, have put forth training guidelines. Formal neuroscience training, stringent peer review and quality assurance processes are critical to ensuring the best possible patient outcomes. (27) The key specifications are

- The operator must have a training in radiology, neurology or neurosurgery, which should include documented training in the diagnosis and management of acute stroke, the interpretation of cerebral arteriography and neuroimaging under the supervision of a neuroradiologist, neurologist or neurosurgeon with subsequent eligibility or certification. Those physicians who did not have adequate such training during their residencies must spend an additional period (at least one year) by training in clinical neurosciences and neuroimaging. **AND**
- Dedicated training in Interventional Neuroradiology (also termed Endovascular Neurosurgery or Interventional Neurology) under the direction of a Neurointerventionalist (with Neuroradiology, Neurology or neurosurgical training background), at a high-volume center. It is preferred that this is a dedicated time (minimum of one year), which occurs after graduating (i.e., a fellowship).

3. Which key performance indicators are required to ensure favourable thrombectomy service performance?

The interval from symptom onset to TICI IIb/III reperfusion was strongly associated with favourable clinical outcome and should be reported. In addition to general maximum time intervals for initiation of IVT and EVT, trials specified target time intervals for in-hospital processes to allow performance monitoring and minimise door-to-EVT times. The five trials reported:

- Time from symptom onset to reperfusion
- "Door to imaging" time
- Imaging to groin puncture time
- Groin puncture to clot/ first device deployment
- Degree of reperfusion (using the mTICI scale)
- Clinical outcomes: mRS at 90 days
- Procedure related complication rate: symptomatic intracranial haemorrhages (SICH)

The ability to define limits for several time variables is limited since only group average data were reported. The likelihood of favourable clinical outcome declines steeply with longer time to achieve reperfusion.(28, 29)

Recommendation:

- Services should routinely collect the key performance indicators (KPIs) listed above.
- KPIs should be reported as part of on-going audits and/or regional, national or international registries.
- Services should monitor performance to minimize door-to-reperfusion times and should report performance metrics in the public domain.
- Target for TICI IIb/III rate should be > 60%.

(Quality of Evidence: **Moderate**, Strength of recommendation: **Strong**)

- Target for imaging (in hospital where EVT is conducted) to femoral puncture time should be, if possible < 30 min and always < 90 min.

(Quality of Evidence: **Low**, Strength of recommendation: **Weak)**

Additional information:

Time metrics: Several recent trials minimised in-hospital process times. Door-to-femoral puncture and femoral puncture to-reperfusion times were generally shorter than those reported historically. Median symptom onset-to-femoral puncture times were generally approximately 4 hours. Since the four largest trials did not report screening log data, it is unknown how often patients were excluded on grounds of anticipated procedural delay.

- MR CLEAN recommended intervals from emergency department (ED) arrival as follows: Neuroimaging (CT and vascular) <20 mins; IVT start <30 mins; randomisation <60 mins if IVT eligible or <30 mins if IVT ineligible; EVT start <90 or <60 mins for IVT eligible or ineligible respectively.
- ESCAPE specified <60mins CT to femoral puncture and <90mins CT to recanalisation times and monitored site performance against these targets.
- REVASCAT specified multimodal imaging <30mins before randomisation, >30mins after IVT start, and <90mins maximum before femoral puncture (<60mins recommended).

- SWIFT-PRIME specified a 90 minute CTA to puncture requirement, with an ideal of 50 minutes CTA to puncture.
- EXTEND-IA did not specify process times, only recommending that the IAT procedure should commence as rapidly as possible and within a maximum of 6h from symptom onset.

Part B. Candidates for thrombectomy: which patients should be treated?

4. Which clinical selection criteria define candidates for additional thrombectomy compared to best medical therapy alone?

Trial inclusion criteria covered a range of clinical situations but in four of five trials set inclusion and exclusion criteria so as to maximise the probability of identifying a treatment effect by selecting a "responder" population based on clinical and imaging criteria. Many subgroups are too small to allow reliable conclusions.

Time: The maximum time permitted from symptom onset to groin puncture in the RCTs was either 6h(1, 2, 5), 8h(4) , or 12h(3). Patients with unknown time of onset have not been included in any of the completed RCTs.

Only 49 participants (15.5%) patients underwent randomization for EVT ≥6 hours after symptom in ESCAPE and the time-to groin puncture was ≥6 hours in 22/103 patients (21.4% of the EVT group) in REVASCAT. There are too few patients in these two RCTs to evaluate efficacy in the subgroup of patients within the 6-12-hour time window.

Pre-stroke function: Four of the five trials in which stent-retrievers were predominantly used, used a pre-stroke function eligibility criterion. REVASCAT, SWIFT PRIME and EXTEND-IA required a pre-stroke estimated mRS score of 0 to 1, and ESCAPE used Barthel scores of ≥90 to 100, while MR CLEAN did not set a threshold, but randomised only 25 patients with estimated mRS=2 and 21 with mRS>2. No conclusion can be drawn for patients with pre-existing functional deficits (mRS >1).

Age: All RCTs enrolled patients ≥18 years of age. Two RCTs employed an additional upper age limit of 80 or 85 years (SWIFT PRIME, REVASCAT). MR CLEAN included 81 patients ≥80 years and ESCAPE 85 patients >80 years. Treatment effects did not differ by age strata in either trial. EXTEND-IA did not report age sub-groups. Only in REVASCAT the treatment effect appeared to be less consistent in the subgroup of patients older than 70 years. There are no data from randomized trials of endovascular therapy in patients <18 years of age.

Stroke severity: Four RCTs used NIHSS scores as eligibility criteria (>2, >5, and 8–29) and the fifth enrolled patients without upper or lower limit for the NIHSS score. The median NIHSS of enrolled patients was consistently high among the RCTs (15 to 18). Based on these results, there are insufficient data to specify a lower or upper limit for the NIHSS score.

Prior IV rt-PA: All five RCTs included patients with prior IV tPA according to guidelines from professional medical societies within 4.5 hours of stroke onset (73-98% of the included patients). On aggregate, 85% of patients enrolled in the five RCTs received IV rt-PA. Two RCTs (MR CLEAN and REVASCAT) explicitly or implicitly stipulated waiting after administration of IV tPA to EVT, whereas three did not (ESCAPE, SWIFT PRIME, and EXTEND-IA).

IV rt-PA contraindications: Three trials also enrolled patients with contraindications for IV rt-PA (REVASCAT, ESCAPE, MR Clean). The therapy effect remained consistent in the subgroup with IV rt-PA contraindications, although contraindications were not defined in the trials and these subgroups constituted <10% of randomised patients.

Recommendations:

- Selected patients should have a good pre-stroke functional level (mRS 0-1). (Quality of evidence: **High**, Strength of recommendation: **Strong**)
- Time from symptom onset to groin puncture should be preferably within 6 hours. (Quality of evidence: **High**, Strength of recommendation: **Strong**)
- Time from symptom onset to groin puncture should be no later than 12 hours. Advanced imaging might help in identifying patients with potential benefit in the 6-12h time window. (Quality of evidence: **Very low**, Strength of recommendation: **Weak**)
- Application of an upper age limit is not justified. (Quality of evidence: **High**, Strength of recommendation: **Strong**)
- Application of a higher or lower limit in NIHSS score is not justified. (Quality of evidence: **Moderate**, Strength of recommendation: **Strong**)
- Angiographic imaging may reasonably be undertaken even in the context of rapidly improving neurological symptoms in otherwise EVT-eligible patients (Quality of evidence: **Low**, Strength of recommendation: **Weak**)
- Waiting to evaluate IV rt-PA therapy response is not recommended. (Quality of evidence: **Low**, Strength of recommendation: **Strong**)
- EVT is recommended as first-line treatment in stroke patients with large vessel occlusions in the anterior circulation if IV rt-PA therapy is contraindicated. (Quality of evidence: **Low**, Strength of recommendation: **Weak**)

Additional information:

The benefit of thrombectomy was not different in the elderly subgroups of the two RCTs that enrolled a significant number of elderly subjects compared to younger patients. The odds for improvement in one point on the modified Rankin scale at 90 days for patients above 80 years was 3.0 (1.3–6.8) in ESCAPE and 3.2, 95% CI 1.2-8.6) in MR CLEAN: wide confidence intervals reflect imprecise effect size estimates.

There was a positive treatment effect irrespective of gender in SWIFT-PRIME (RR: 1.75 [1.11–2.78] for men; and 1.61 [1.03–2.50] for women) and ESCAPE RR 2.5 (1.4–4.5) for men and 2.6 (1.5–4.4) for women).

Eligible NIHSS score for thrombectomy varied significantly among studies: above 2 in MR CLEAN; above 5 in REVASCAT; between 8 and 30 in SWIFT-PRIME; no limit in EXTEND-IA and ESCAPE. Despite these discrepancies the median NIHSS score was 17 in the interventional arm for all these studies. There was no evidence of heterogeneity of effect across baseline NIHSS score suggesting that no specific range for NIHSS score should be recommended for thrombectomy patient selection. Apart from the NIHSS score, combined scores have been developed to predict patient outcome after therapy.

Patients with previous disability (mRS≥2) were not eligible in recent thrombectomy trials. In SWIFT prime, patients with a mRS≥2 represented 1% of the IV t-PA arm and 2% of the endovascular group. No evidence is available at present to support specific recommendations in this subset of patients.

REVASCAT explicitly waited a minimum of 30 minutes to assess the clinical effect of IV rtPA; it is likely that this also occurred in MR CLEAN given the long interval from IVT initiation to randomisation (119 mins), although this was not explicitly part of the protocol. However, those trials that pursued a policy of proceeding as fast as possible to IAT achieved significantly better outcomes. The potential role of advanced imaging selection, also deployed in trials that pursued a policy of proceeding to intervention as rapidly as possible, is not clear.

5. Which imaging selection criteria define candidates for additional thrombectomy compared to best medical therapy alone?

Type of imaging (MRI vs. CT): Parenchymal imaging to rule out hemorrhage was done predominantly by non-contrast CT with a number of patients enrolled based on MRI in MR Clean and SWIFT Prime. Imaging modality CT or MRI has not been compared in any clinical trial.

Ischemic core in non-enhanced imaging: All five positive RCTs required non-enhanced CT or MRI as baseline imaging. An ASPECTS score of 6-10 was required in two RCTs)(3, 5) and 7-10 (later 8-10) in another.(4) MR Clean had no limits for ischemic core volume by ASPECTS score but enrolled only 28 patients with ASPECTS 0-4. In EXTEND-IA)(2), patients with >1/3 MCA abnormality on non-contrast CT were excluded. In the ESCAPE and SWIFT-PRIME trials, lower ASPECTS thresholds of 5 and 6 were applied for MRI, respectively. Additional imaging selection criteria were applied in all patients in three trials, using perfusion (SWIFT-Prime and EXTEND-IA) or collateral imaging (ESCAPE) selection criteria, while REVASCAT specified perfusion imaging for patients recruited >4.5h after onset. Subgroup analyses in the studies were generally underpowered but could not identify any difference in therapeutic effect when comparing subgroups with ASPECTS scores of 5 or more points (5-7 points, OR 1.97 and 8-10 points, OR 1.61, respectively).

Demonstration of artery occlusion: In all positive studies, large artery occlusion in the carotid circulation (LVO) had to be demonstrated prior to randomization by non-invasive imaging (CT-Angiography, CTA or MR-Angiography, MRA). All studies used additional vessel imaging to identify large vessel occlusion: either CTA or MRA.(1-3) MR CLEAN and REVASCAT additionally allowed DSA to identify an occlusion minutes after start of IV tPA. All RCTs included proximal MCA occlusion (M1, total 827 patients, 66%) and four RCTs included the occlusion of the intracranial ICA (including “Carotid-T” or “Carotid-L”, total 328 patients, 26%). Patients with more distal MCA-occlusions (M2) were included in three studies (total 104 patients, 8%) and ACA-occlusion in MR Clean only (3 patients). A prospective RCT is enrolling patients with basilar artery occlusion (BASICS).(30)

Tandem pathology: Ipsilateral cervical ICA occlusions additionally to intracranial occlusions were included in three studies (in total 217 patients, 15%). Although not significantly different in these studies, the data do suggest at least a comparable therapy effect in these patients (ESCAPE, MR CLEAN). In the MR CLEAN trial, 146 (29%) patients had an additional extracranial ICA occlusion, with a trend for the treatment effect in favor of thrombectomy (OR 1.43, 95% CI 0.78-2.64). In ESCAPE, there is borderline evidence of heterogeneity of treatment effect between these subgroups suggesting higher treatment effect in patient with cervical ICA stenoses (p=0.049).

Presence of salvageable brain tissue: Advanced imaging selection criteria have the potential benefit of more accurate identification of patients most likely to respond to therapy. On the other side patients who may expect therapy effect could be excluded. Three of the RCTs attempted the confirmation of salvageable brain tissue (ESCAPE, EXTEND-IA, and SWIFT PRIME) either by defining small ischemic cores in combination with the presence of salvageable brain tissue (SWIFT PRIME and EXTEND-IA) and/or adequate collateral flow (ESCAPE). Within EXTEND-IA and SWIFT PRIME, detection of salvageable tissue was attempted by using a dedicated software in 100% and 81% of patients. REVASCAT used the same software for the first 71 patients. After enrolment of the first 71 patients, the investigators switched to the criterion to ASPECTS of ≥6 for sites that did not have CT perfusion capability. In ESCAPE, CTA was used to select patients with moderate to good collateral circulation (filling of ≥50% pial arterial circulation visualized). In ESCAPE, moderate-to good collateral circulation was defined as the filling of 50% or more of the middle-cerebral artery pial arterial circulation on CTA (preferably on multiphase CTA).(3)

A subanalysis of CT perfusion data from MR Clean revealed that this method could be useful for predicting functional outcome but not for reliable identification of patients who will not benefit from EVT.(31)

Recommendations:

- Occlusions of MCA (M1 or M2) and/or of the intracranial ICA should be diagnosed with non-invasive imaging whenever possible before considering treatment with EVT. (Quality of evidence: **High**, Strength of recommendation: **Strong**).
- EVT can be considered in patients where there is an occlusion or stenosis of the cervical ICA in addition to a suitable intracranial target vessel occlusion (tandem pathology). (Quality of evidence: **Moderate**, Strength of recommendation: **Strong**)
- The additional benefit of advanced perfusion or collateral image processing for patient selection is not established and requires further study. (Quality of evidence: **Low**, Strength of recommendation: **Strong**)

Additional information:

The ASPECTS score has only moderate to good interobserver agreement in the hyperacute stroke setting. Generally, higher baseline ASPECTS predicts more favorable outcome after thrombectomy. (32, 33) In IMS 3 however, about one fifth of patients with ASPECTS 0–4 achieved a good functional clinical outcome.(34) Lower age, faster treatment, and lower baseline stroke severity may be reasons for good outcome in this group suggesting that thrombectomy may be considered. In patients with lower initial ASPECTS, the location of the hypodensity can be taken into consideration.(32) No treatment interaction with ASPECTS has been demonstrated but ASPECTS 0-4 are barely represented in recent trials. Further RCTs in patients with ASPECTS 0-5 are warranted.

CTA-defined occlusions resolved in a proportion of patients, even with clinically severe stroke, in IMS-3 and MR CLEAN, and 10% (9/98) of SWIFT-Prime IAT-randomised patients. It is therefore inevitable that a proportion of patients with proven vessel occlusion will not require EVT by the time that the procedure is initiated. The separation of M1 occlusions from M2 occlusions can be difficult in some patients owing to early branches of the M1 such as the anterior temporal branch. If conducted, the subgroup analysis for each occlusion site for the individual RCTs showed no evidence of heterogeneity of treatment effect between the different occlusion types (SWIFT PRIME).

In a systematic review of 32 studies including 1107 patients with tandem pathology (not including the five RCTs), EVT was compared with any kind of mechanical treatment and/or stent placement. Recently published cohort studies indicate that tandem stenosis/occlusions of the ICA/MCA can be treated with acute stenting of the extracranial internal carotid and stent-retriever mechanical thrombectomy in the MCA with a reasonable risk profile.(36-44)

Acute stenting of occlusions of the extracranial ICA resulted in a higher recanalization rate (87% vs 48%, p=0.001) and favorable outcomes (68% vs 15%, p<0.001) as well as lower mortality (18% vs 41%, p=0.048) when compared to intra-arterial thrombolysis.(39)

Longer clot length as measured on thin-section NCCT has been associated in several studies with low probability of successful recanalization with IV tPA(45-47), raising the possibility that this group might derive greater benefit from EVT. The only RCT that included clot length >8 mm as a selection criterion the unpublished THERAPY trial(48), assessed the safety and effectiveness of the Penumbra System and was terminated prematurely with a sample size too small to identify a clear treatment effect. The interaction of clot length with EVT effect is therefore not established and further research is required.

Part C. Preclinical and clinical requirements in organization before thrombectomy

6. What organisation of Emergency Medical Systems (EMSs) and Emergency Departments (EDs) is required to refer appropriate patients to EVT?

Although the operational characteristics of EMSs and EDs involved in the more recent IAT trials have not been specified, all trials were undertaken at centres selected carefully for experience with acute stroke care in general and established thrombolysis pathways. The same organisational components that have been shown to achieve rapid door-to-needle times for IV thrombolysis(18, 19) will therefore be required for provision of IAT. One trial (REVASCAT) was explicitly undertaken within the context of a regional network of stroke centres organised to facilitate patient transfer to appropriate treatment centres.(4, 49)

Identifying stroke patients who are EVT candidates in the pre-hospital phase may help to shorten delay from symptom onset to EVT if the transportation times to hospitals with or without EVT capabilities are comparable. As the decision has to be taken by paramedic staff, its basis should be simple and accurate in the prediction of LVO. Several simple stroke assessment scales have been reported to identify patients with LVO.(50-53)

Among them, only the RACE scale has been prospectively validated for identifying such patients in a prehospital setting by EMS technicians.(52) A RACE scale score of ≥5 had sensitivity 0.85, specificity 0.68, positive predictive value 0.42, and negative predictive value 0.94 for LVO. The NIHSS is rarely used in the pre-hospital setting. It is usually employed in EDs to assess clinical stroke severity. There is a significant association of NIHSS scores and vessel occlusions in patients with anterior circulation strokes, but a lower threshold to identify LVOs cannot be defined. Therefore, the NIHSS cannot replace vessel imaging.(51) There is no direct evidence that patient diversion based on field diagnosis of LVO is beneficial.

Recommendation:

- Operational characteristics of Emergency Medical Systems and Emergency Departments must ensure that treatments for acute ischemic stroke are administered in the timeliest fashion possible. (Quality of evidence: **Moderate** Strength of recommendation: **Strong**).
- Clinical screening tools (e.g. RACE scale) to minimise unnecessary transfer of patients may be considered, depending upon local service organisation. (Quality of evidence: **Low**, Strength of recommendation: **Weak**)
- Hospitals providing EVT should do so within the context of regional or national networks in collaboration with EMS to maximise access to EVT for suitable patients, and minimise delays to appropriate treatment (Quality of evidence: **Low**, Strength of Recommendation: **Strong**)

Additional information:

In Europe, many countries have developed medical dispatch protocols and physician based pre-hospital EMS, so that the right team can be sent, the stroke pathway is activated and the right hospital ED is identified for the patient. (53)

Several studies identify probability of LVO stroke with increasing stroke severity as measured on the NIH Stroke Scale. While arbitrary NIHSS score thresholds may therefore increase the yield of potential EVT cases and avoid secondary transfer of patients, any single threshold proposed by any study achieved limited sensitivity and specificity for prediction of LVO. Studies have predominantly mixed anterior and posterior circulation strokes, and deployed various angiographic methods. It is also known that there are systematic differences between right and left hemisphere NIHSS scores due to the predominance of test items assessing language in the NIHSS, and no study has adjusted

for hemisphere. In addition, both Heldner et al.(55) and Cooray et al.(56) identified a downward shift in NIHSS threshold for predicting LVO with increasing onset to CT scan time, the threshold being NIHSS 12 for imaging at ≤60 mins, 11 with imaging at 61-120 mins, and 10 for imaging from 121-270 mins in the SITS data analysed by Cooray,(56) and 9 for imaging <180 mins but 7 for imaging 181-360 mins for the single-centre data of Heldner. Maas et al reported that all patients with NIHSS≥2 would require angiographic imaging in order to detect 90% or more of those with proximal vessel occlusions.(57)

7. Should patients with stroke from suspected large artery occlusion be directly transferred to a hospital offering thrombectomy?

All trials permitted enrolment of patients who were either admitted directly to the interventional centre or were transferred to the interventional centre from a primary stroke centre, where IV rt-PA was initiated in the great majority (the "Drip and Ship" approach).

Secondary transfer in the EVT arm was undertaken in a minority of patients where data have been presented: for EXTEND-IA (4/35; 11%) and SWIFT-Prime (31/98; 32%). No data have been presented for REVASCAT, ESCAPE or MR CLEAN.

Screening imaging with CTA or CTP (or equivalent MRI) was not undertaken at the primary stroke centre, but deferred until arrival at the interventional centre in all trials.

Primary stroke centres had to ensure that transferred patients had sufficient time to undergo clinical and imaging assessment at the EVT centre and still meet trial timelines: average onset to IV rtPA times in all trials ranged from 85 to 127 minutes (MR CLEAN 85 mins; EXTEND-IA 127 mins; SWIFT-Prime 110 mins; ESCAPE 110 mins; REVASCAT 117 mins).

Two trials (ESCAPE and SWIFT Prime) reported secondary analyses comparing treatment outcomes among direct admission to EVT centres (termed the "mother-ship" approach) with secondary transfers, and found no heterogeneity of the treatment effect of EVT. However, onset to randomisation times were substantially longer in those patients transferred secondarily (interval from IV rtPA initiation to randomisation 17 minutes versus 120 minutes in ESCAPE and interval from IVT initiation to femoral puncture 58 mins versus 160 mins in SWIFT-Prime). The absolute Benefit in terms of mRS 0-2 also did not differ between admission direct to an EVT centre and secondary transfer.

Recommendation:

- Patients should undergo diagnostic imaging as fast as possible and receive IV rt-PA as fast as possible when indicated

(Quality of evidence: **High**, Strength of recommendation: **Strong**)

- In a situation with equidistant hospitals, direct transfer of selected patients likely to have LVO to a hospital offering EVT should be considered.
- Hospitals without interventional services for stroke therapy should implement policies for transfer of patients to EVT sites, consistent with a network as recommended for EMS organisation.
- Referring hospitals should have an established IV thrombolysis service and be able to initiate treatment in appropriate cases within a timeframe sufficient to allow transfer, clinical and imaging assessment, and procedural initiation at the interventional centre within a maximum of 6h after symptom onset (or "last known well" time). This means that IV rtPA onset to treatment

times for potential EVT cases will in general be considerably shorter than the maximum time window permitted for IV rtPA therapy alone.

(Quality of evidence: **Moderate**, Strength of recommendation: **Strong**)

Part D. Methods for interventional treatment

8. What is the optimal blood pressure management during thrombectomy?

Blood pressure monitoring was not analysed systematically in any of the RCT´s. Data on blood pressure in stroke patients undergoing EVT are limited and with mixed results. While some retrospective analysis did not show a relation between periprocedural blood pressure and 90 days outcome a single center retrospective study demonstrated an association between a periprocedural hypotension (SBP<140) and a worse clinical outcome.(58) Post hoc analysis of stroke patients treated with thrombectomy showed that patients with very high or very low pressure have the worst outcome (U-shape).(59) There is limited although supportive clinical data and pathophysiologic mechanisms that suggest that hypotension in the periprocedural period of EVT and hypertension after successful recanalization may be associated with worse clinical outcome.

Recommendation:

- Blood pressure should be kept below 180/110mmHg (Quality of evidence: **Moderate**, Strength of recommendation: **strong**)
- Excessive systolic blood pressure drops during thrombectomy should be avoided (Quality of evidence: **Low**, Strength of recommendation: **strong**)

9. What kind of thrombectomy device is associated with favourable clinical outcome?

Available evidence shows superiority of stent-retrievers vs. older recanalization devices (e.g. the MERCI device) both in their recanalization rates (60, 61) and in their positive effect on clinical outcome.(6-12) A majority of this benefit appears to be attributable to the application of stent-retrievers as a class of recanalization device. In the RCTs that show superiority of EVT over IVT alone, stent-retrievers were used in 77% to 95% of the patients in the EVT group.(8) Any benefit of advances in guiding catheters and distal access/aspiration catheter technology cannot yet be derived from the RCT data.

Recommendation:

- For mechanical thrombectomy, stent-retrievers approved by regulatory authorities should be considered as first choice devices. Older generation devices should not be used. (Quality of evidence: **High**, Strength of recommendation: **Strong**)
- Other new-generation thrombectomy or aspiration devices should be used preferably in the context of clinical studies or may be used upon the neurointerventionalists´ discretion if rapid, complete and safe revascularisation of the target vessel can be achieved (Quality of evidence: Very **Low**, Strength of recommendation: **Weak**)

Additional information:

It seems that better reperfusion results are observed with stent-retrievers if a balloon guide catheter is used rather than a large bore guide catheter in the cervical carotid.(62) This method is thought to limit thrombus fragmentation while pulling out the clot. There are limited data available showing higher recanalization rates and fewer complications such as secondary embolism in new territories when stent-retrievers are used with additional techniques as proximal balloon occlusion and aspiration or additional aspiration via access catheters.(62)

Currently, there are no limited RCT data on other types of recanalization devices such as aspiration only systems. A number of observational studies suggest high recanalization rates with newer aspiration techniques.(63-78) More studies are under way to monitor the clinical outcome in these patients.

10. What kind of anaesthesia should be preferred during thrombectomy?

There are no data from prospective randomized trials available. There are several prospective randomized trials underway investigating the effect of different kind of anesthesia on clinical outcome in stroke patients undergoing EVT. Several retrospective, non-randomised comparisons of patients receiving general anesthesia (GA) or conscious sedation during EVT had shown higher rates of in-hospital mortality, secondary complications (pneumonia etc.) and worse clinical outcome with GA.(1, 79) The distinction between GA and sedation is, however, not defined. Identical drugs may be used for both. Specific agents have different profiles with respect to, for example, blood pressure lowering and neuroprotection. An expert consensus statement recommended the use of general anesthesia for patients with severe agitation, low level of consciousness (GCS <8), loss of airway protective reflexes, respiratory compromise and in patients with posterior circulation stroke

Recommendation:

- The choice of anesthesia should depend on the individual situation.
- Independently of the method chosen, all efforts should be made to avoid thrombectomy delays and severe blood pressure variations

(Quality of evidence: **Low**, Strength of recommendation: **Weak**).

11. Should high-grade extracranial carotid stenosis or occlusions be stented as part of the mechanical thrombectomy procedure?

Acute occlusion of large intracranial arteries of the anterior circulation is associated with an underlying high-grade carotid stenosis in up to 20%. These patients with a “tandem-pathology” were included in the five RCTs.

There was no heterogeneity in treatment effect between patients with such tandem lesions and those without tandem lesions. It is not reported whether these stenoses were treated with stenting or angioplasty alone. For SWIFT-PRIME, concomitant stenting of the cervical internal carotid artery was not permitted, although angioplasty could be performed to permit intracranial access.

Recommendation:

- There is no reason to withhold intraprocedural stenting in patients where high-grade stenosis or occlusion needs to be treated (Quality of evidence: **Moderate**, Strength of recommendation: **Strong**).

Additional information:

Some smaller case series and one recently published retrospective multicenter study demonstrated a rate of good clinical outcome (36%) and sICH (9%) in patients, who were treated by emergency stenting during the acute intervention, comparable to patients without a tandem lesion who underwent thrombectomy.(36) Emergency stenting in patients undergoing thrombectomy seems to be safe without an increase of sICH. The rate of sICH in EVT patients stented may be reduced if Glycoprotein IIB/IIIA – inhibitors are avoided.(44)

Part E. Patient care after thrombectomy

None of the four questions in this section has been specifically addressed in any one of the recent endovascular trials. Referral patterns and in specific where patients were managed after EVT, which specific therapy if any was used after thrombectomy, specifics as to the blood pressure management and also the use of follow up imaging outside of established protocols has neither been addressed in any of the current nor the older literature. Therefore the general recommendations from stroke guidelines are to be applied to patient care after endovascular therapy for acute ischemic stroke.

12. Where should stroke patients be managed after thrombectomy?

There is no information available from the recent RCTs pertaining to allocation of stroke patients after EVT. In general, stroke patients should be treated on specialized wards, so called stroke units. Specialized stroke unit care reduces morbidity and mortality in stroke patients and therefore this is a high quality grade of evidence and a strong recommendation.(76) While this has not been addressed in the context of EVT and the recent RCTs the general recommendation stands.(81-83)

Patients, who for whatever reason (instable vital parameters, need for pressor agents, intubation, ventilation, general anesthesia, increased ICP etc.) are not able to be managed on a stroke unit and need a critical care environment should be managed on dedicated neurocritical care units, as this also leads to a reduced morbidity and mortality, albeit this has not convincingly been shown for ischemic or hemorrhagic stroke but only neurotrauma.(84-89)

Despite of that, specific neurocritical care appears to be best suited for treating patients, who cannot be admitted to a non-critical care stroke unit.

Recommendations:

- Stroke patients undergoing thrombectomy should be treated on stroke units (Quality of evidence: **Moderate**, Strength of recommendation: **Strong**).
- Stroke patients, who are not able to be managed on a stroke unit and need a critical care environment, should be managed on dedicated neurocritical care units (Quality of evidence: **Low**, Strength of recommendation: **Strong**).

13. Should a specific medical therapy be used in stroke patients after thrombectomy?

Beyond general guideline recommendations (blood pressure management, statins etc.) there is no specific therapy to be used after EVT. The exception is double platelet inhibition, which is used as a standard for 6-12 weeks after PTA with bare metal stent (BMS) implantation

Recommendations:

- Stroke patients undergoing thrombectomy should receive medication according to published guideline recommendations based on high quality evidence derived from multiple large randomized trials (Quality of evidence: **Moderate**, Strength of recommendation: **Strong**).
- Stroke patients undergoing thrombectomy AND implantation of a stent for proximal carotid stenosis should receive double platelet medication with ASA and clopidogrel to prevent secondary thromboembolism or in stent stenosis (Quality of evidence: **Very low**, Strength of recommendation: **Weak**).

14. Should stroke patients after thrombectomy undergo blood pressure control in a given range?

About 85% of the patients in the five RCTs were treated with intravenous rt-PA before the thrombectomy procedure. Therefore, guidelines and recommendations for intravenous thrombolysis apply. Accordingly, BP should not exceed 180-185 / 105-110 mmHg for intravenous thrombolysis (or endovascular treatment) to commence.(79)

An analysis of the SITS registry showed that high systolic BP 2 to 24 hours after intravenous thrombolysis was associated with worse outcomes and had a linear association with symptomatic hemorrhage and a U-shaped association with mortality and independence. (90) Systolic BP at 141 to 150 mm Hg was associated with the most favorable outcomes in general population treated with intravenous rt-PA. Following these recommendations is recommended also with regard to maintaining BP when inducing or performing general anesthesia to prevent BP drops which are associated with poor clinical outcome.(83)

The patient population after successful EVT in patients with large vessel occlusions is not necessarily comparable to the general population treated with intravenous rt-PA. There is no evidence to actively modify the blood pressure. Blood pressure drops after successful reperfusion might still impair collateral flow to areas with disturbed microcirculation or in TICI 2b patients. On the other hand, an artificial maintenance of BP at 141-150 mmHg might increase the risk for secondary symptomatic intracranial hemorrhage. Research on blood pressure intervention after thrombectomy is encouraged.

Recommendations:

- Blood pressure in stroke patients undergoing thrombectomy should not exceed 180 mmHg systolic and 110 mmHg diastolic (Quality of evidence: **Low**, Strength of recommendation: **Strong**).
- Active titration to other, as of yet unknown optimum blood pressure levels is not recommended (Quality of evidence: **Very Low**, Strength of recommendation: **Weak**).

15. Is there a specific kind of imaging follow-up after thrombectomy?

Outside of clinical trials, where specific imaging findings are acquired as surrogate outcomes and endpoints the need for follow up imaging has not been studied at all, neither in- nor outside the context of endovascular therapy. While several assessments may follow common sense (6-12h or

24h assessment of vessel status, follow up CT or MRI to assess infarct size and/or haemorrhage, space occupying edema etc.), this has not been the topic of focussed research, i.e. not performing routine follow up imaging has not been shown to be associated with poor outcome.

In patients, who return (close) to normal after IVT and EVT, are awake, clinically assessable, have no indication of haemorrhage or a large stroke, follow up imaging is superfluous and costly and in case of CT associated with additional X-ray exposure, especially if follow up CTA and perfusion CT are performed. On the other hand, if a patient is intubated and sedated after IVT and EVT, the development of space occupying oedema, bleeding or both may remain undetected until irreversible damage and herniation occurs.

As decompressive surgery for malignant MCA infarction within 48 h reduces morbidity and mortality, this must not be missed in patients otherwise not clinically assessable.(91, 92) Therefore, it is recommended to perform follow up imaging of choice after IVT and EVT within 12-36 h whenever the patient is not clinically assessable or whenever therapeutic or prognostic consequences may potentially be derived from imaging findings.

Recommendations:

- Follow-up brain imaging should be performed 12-36 h after treatment to inform therapeutic and prognostic decisions and monitor service safety and additionally whenever required by clinical circumstances (Quality of evidence: **Moderate**, Strength of recommendation: **Strong**).

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Appendix A

Section	Title	Questions	Working group members*
A	Center and operator requirements for thrombectomy	1-3	Christophe Cognard, Olav Jansen, Adam Kobayashi, Keith Muir
B	Candidates for thrombectomy: which patients should be treated?	4-5	Jens Fiehler, Mikael Mazighi, Olav Jansen
C	Preclinical and clinical requirements in organization before thrombectomy	6-7	Keith Muir, Peter Schellinger, Mauro Gallitelli, Adam Kobayashi, Heinrich Mattle
D	Methods for interventional treatment	8-11	Olav Jansen, Christophe Cognard, Jens Fiehler
E	Patient care after thrombectomy	12-15	Peter Schellinger, Karl Schaller, Christophe Cognard

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