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DOI: 10.1159/000441096**Proper Patient Selection – The Key to Beneficial Mechanical Thrombectomy in Acute Stroke Therapy**Stephan Meckel^a, Christian Herweh^b^aDepartment of Neuroradiology, University Hospital Freiburg, Freiburg, ^bDepartment of Neuroradiology, University Hospital Heidelberg, Heidelberg, Germany*Patient Selection Criteria for Mechanical Thrombectomy*

The past few years witnessed an enormous effort of the stroke community to demonstrate that mechanical thrombectomy (MT) can complement, and in some cases even replace, the use of intravenous thrombolysis (IVT) in acute stroke. However, only 2 years ago, three randomized controlled trials (RCTs) evaluating the safety and efficacy of endovascular stroke treatment (MR RESCUE, IMS III, and SYNTHESIS Expansion), which were published in 2013, failed to show a significant clinical benefit over IVT [1–3].

In contrast, five recently published RCTs (MR CLEAN, EXTEND-IA, SWIFT PRIME, REVASCAT, and ESCAPE) [4–8] employing MT with modern stent retriever devices clearly demonstrated the superiority of endovascular treatment, which is now considered standard first-line therapy (class 1a recommendation) for selected patients with acute ischemic stroke exhibiting large cerebral artery occlusion in the anterior circulation [9].

However, this discrepancy between recent and previous trials is only superficial and can be further elucidated by comparing trial designs. For example, both IMS III and SWIFT-PRIME treated patients with MT within 6 h and exhibited similar average treatment delay, but in IMS III, patients were not screened for large vessel occlusion and the infarct core was not assessed on initial imaging, both of which were mandatory features in SWIFT-PRIME. Another case in point arises from the comparison of MR RESCUE and ESCAPE, which employed MT with IVT in an extended time window. Even though the inclusion in MR RESCUE required proof of large vessel occlusion and stratification according to penumbral imaging, MT was performed much later than in the ESCAPE trial. It seems therefore safe to state that appropriate patient selection and fast and effective recanalization achievable with state-of-the-art stent-retriever devices represent essential requirements for successful MT.

By scrutinizing the inclusion/exclusion criteria and subgroup analysis of the recent five positive trials, we can delineate selection criteria for patients who are likely to benefit from MT treatment. Many questions on the most appropriate selection criteria that were asked in the past can be answered by these current RCTs. However, there are still open or new questions arising with plenty

of room for scientific and clinical improvement. In the following, we briefly summarize the selection criteria for MT based on the current trial data.

Clinical Patient Selection by NIHSS

In four of the recent positive RCTs, treatment effects were compared in the following NIHSS subgroups: 2–15, 16–19, and ≥ 20 in MR CLEAN; 8–17 and 18–29 in SWIFT PRIME; 6–19, and ≥ 19 in ESCAPE; 6–16 and ≥ 17 in REVASCAT. Here, no significant differences in the treatment effect were disclosed. Thus, MT should be favored as treatment for all patients with proximal anterior circulation occlusion irrespective of their baseline NIHSS. However, there is still relative uncertainty on how to proceed with patients that present with very low NIHSS ≤ 5 , since most trials excluded such patients (except MR CLEAN which, however, dichotomized the respective subgroup of low NIHSS only at 15). It might be worthwhile to address this question for this particular small subgroup of stroke patients in a future trial.

Patient Selection by Age – Is There an Upper Age Limit for MT?

As is known, the likelihood of a good clinical outcome (mRS 0–2) following MT decreases with advanced age, in particular beyond 75–80 years [10, 11]. However, the age subgroup analyses did not reveal any significant loss of therapeutic benefit of MT over IVT at increased age in the recent positive RCTs. Of note, two RCTs had an upper age limit at inclusion (SWIFT PRIME, 80 years and REVASCAT, 80/85 years after addendum). Surprisingly, the OR favoring MT was higher in the advanced age group (≥ 80 years) versus younger patients in the MR CLEAN trial (3.24 vs. 1.60); however, the older age group had a wide CI due to its small group size. In summary, there is currently no evidence for an upper age limit of MT treatment, but relevant comorbidities (i.e. dementia, preexisting neurological deficits) should be considered for the indication, since all trials excluded patients with a preexisting relevant functional deficit (mRS > 1).

Patient Selection by Occlusion Type

In contrast to the previously negative reported endovascular trials, all recent positive RCTs required vascular imaging (CTA or MRA) to select a relevant proximal large vessel occlusion in the anterior circulation (i.e. MCA M1 or terminal ICA (ICAT) occlusion) for study inclusion. Subgroup analysis of these trials did not reveal significant differences in therapeutic benefit between the proximal occlusion types. There were some trends observed towards higher benefit in ICAT vs. M1 occlusion in MR CLEAN (OR 2.43 vs. 1.61), and tandem type (cervical ICA plus ICAT or M1) versus M1 occlusion in REVASCAT (OR 4.3 vs. 1.2). Likewise, there was a minor trend towards lower benefit from MT for M2 occlusion type in SWIFT PRIME. Cervical tandem stenosis or occlusions were treated in MR CLEAN, ESCAPE, and REVASCAT. In the best powered MR CLEAN trial, the therapeutic effect of MT

was equal regardless of cervical ICA tandem lesions, whereas the other two smaller trials even showed a trend towards a higher benefit (Cave: small group sizes). In summary, both MCA M1 and ICAT type occlusion equally benefit from MT. In the presence of a cervical ICA tandem lesion, MT +/- stenting of the cervical ICA should be performed.

Patient Selection by Extent of Infarct Core – Is Perfusion Imaging Necessary?

Most of the positive RCTs utilized the ASPECTS (Alberta Stroke Program Early CT Score) [12] to determine the extent of early core infarct in the MCA territory on plain CT imaging. Thereby, these trials included only patients with small baseline core infarcts: ASPECTS 6–10 in ESCAPE and SWIFT PRIME; ASPECTS 7–10 in REVASCAT. MR CLEAN did not exclude patients with larger core infarcts; however, no benefit of MT was demonstrated for this subgroup (ASPECTS <5, OR 1.09). In addition, this subgroup was particularly small (only 5.6%), indicating a potential selection bias. In ESCAPE, the status of collateral circulation was additionally assessed for study inclusion on a dedicated multiphase CTA protocol [13]. Patient inclusion based on CT perfusion criteria only with penumbral selection was performed in the smallest Australian EXTEND-IA trial (target-mismatch criteria: core <70 ml of rCBF (CT-P) or DWI (MRI); penumbra: Tmax >6 s; mismatch ratio >1.2; absolute mismatch >10 ml). Hence, 25% of patients with qualifying vessel occlusion were excluded from this trial by penumbral selection, which would have been treated with ASPECTS-based selection. SWIFT PRIME utilized an automated perfusion-based neuroimaging selection (RAPID-Software) for the first 71 patients, but then amended their protocol to ASPECTS-based selection only. When comparing therapeutic efficacy between the positive RCTs, three trials with more stringent neuroimaging selection criteria (ESCAPE, EXTEND-IA, SWIFT PRIME) versus two trials with rather unselective neuroimaging criteria (MR CLEAN and REVASCAT) showed a better clinical outcome and higher treatment effect of MT (mRS 0–2 in MT arm: 53–71 vs. 33–44%; absolute difference between MT and IVT arms: 24–31 vs. 14–16%). However, the latter two trials showed also longer timing performance owing to their ‘failed IVT’ strategy (‘last seen normal to groin’: 200–224 vs. 260/269 min), which may also have negative impact on the clinical outcome.

In summary, perfusion imaging is currently not mandatory for patient selection to MT treatment within the 6 h time window. Patients may even get excluded by penumbral selection, which could potentially benefit from MT. Baseline ASPECTS (on CT or DWI MRI) analysis should be performed to exclude patients with larger core infarcts that are unlikely to benefit from MT (ASPECTS <6). Within a stroke network, the recipient thrombectomy center may individually decide whether a second neuroimaging study (CT or DWI MRI) for verification of a small infarct core and/or exclusion of infarct growth should be done prior to MT treatment in case of longer delays from patient transfer and/or very early initial CT imaging. The usefulness of advanced neuroimaging (perfusion or multiphase CTA) should be subject to future studies beyond the 6 h time window or in patients with larger core infarcts (ASPECTS <6).

Patient Selection by Time Window

In most positive MT trials (MR CLEAN, EXTEND-IA, SWIFT PRIME), patients were treated within 6 h time window (‘symptom onset – groin puncture’). In REVASCAT (8 h) and ESCAPE (12 h),

time windows were extended, and these trials also showed a positive therapy effect of MT without increased rate of intracranial hemorrhage. Subgroup analysis of the trials did not reveal significant change in therapy effect between shorter and longer time windows. Important to note, only the time from symptom onset to randomization was regarded (and not until start of MT), and the times were dichotomized differently (at 2 h in MR CLEAN; at 3 h in SWIFT PRIME, ESCAPE; at 4.5 h in REVASCAT). However, in ESCAPE (longest time window, 12 h), only 15.5% of patients were treated in the extended time window (6–12 h, wake up strokes) and no separate analysis for this important subgroup was presented. Moreover, this trial also had more stringent neuroimaging inclusion criteria (CTA collateral assessment, see above); hence, a general recommendation for indication of MT in the extended time window >6 h is currently not possible. However, there is a positive signal that patients with good collaterals and a small infarct core in the extended time window may also benefit from MT treatment, which necessitates future studies for affirmation.

Is MT Better with or without Prior IVT?

A small proportion of patients showed clinical improvement following IVT prior to MT or even thrombus recanalization on first angiographic series (2.9–3.4% clinical improvement in MR CLEAN/EXTEND IA; 4.9–11.4% TICI 2b/3 on first DSA in EXTEND, ESCAPE, SWIFT PRIME, REVASCAT). It remains uncertain whether clinical improvement relates to vessel recanalization, augmented collateral circulation, or non-visible tissue reperfusion, and if patients with clinical improvement despite persistent occlusion should still receive MT. In all trials that allowed MT treatment without IVT (ESCAPE, MR CLEAN, REVASCAT), subgroup analysis did not show significant differences in therapeutic efficacy of MT with or without preceding IVT. Notably, the subgroups without IVT were smaller (wide CI), and these subgroups are subject to selection bias due to inclusion/exclusion criteria for IVT (foremost time window). Thus, the question whether MT should be necessarily combined with MT cannot be answered yet. However, the indicated valuable trend justifies a future study of sole MT versus MT with IVT. Until then, the addition of IVT is currently indicated within the 4.5 h window meeting all medical exclusions. According to the ‘time is brain’ concept, MT treatment should be immediately started following the application of IVT.

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