Thrombectomy in special populations: report of the Society of NeuroInterventional Surgery Standards and Guidelines Committee

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ABSTRACT

Background The purpose of this guideline is to summarize the data available for performing mechanical thrombectomy (MT) for emergent large vessel occlusion (ELVO) stroke in special populations not typically included in large randomized controlled clinical trials, including children, the elderly, pregnant women, patients who have recently undergone surgery, and patients with thrombocytopenia, collagen vascular disorders, and endocarditis.

Methods We performed a literature review for studies examining the indications, efficacy, and outcomes for patients undergoing MT for ischemic stroke aged <18 years and >80 years, pregnant patients, patients who have recently undergone surgery, and those with thrombocytopenia, collagen vascular diseases, or endocarditis. We graded the quality of the evidence.

Results MT can be effective for the treatment of ELVO in ischemic stroke for patients over age 80 years and under age 18 years, thrombocytopenic patients, pregnant patients, and patients with endocarditis. While outcomes are worse compared to younger patients and those with normal platelet counts (respectively), there is still a benefit in the elderly (in both mRS and mortality). Data are very limited for patients with collagen vascular diseases; although diagnostic cerebral angiography carries increased risks, MT may be appropriate in carefully selected patients in whom untreated ELVO would likely result in disabling or fatal outcome.

RECOMMENDATIONS

1. Mechanical thrombectomy (MT) should not be withheld from octogenarians and nonagenarians, but rather be evaluated on a case-by-case basis. ***(class IIa-b, level B-NR and C-LD)***
2. MT should not be withheld from thrombocytopenic patients. ***(class IIb, level C-LD)***
3. There is no absolute minimum platelet count that excludes patients from MT given the high morbidity of emergent large vessel occlusion (ELVO). The expert panel considers <20K very concerning for potential hemorrhagic conversion of infarction or procedural complication, and hematologic consultation to understand the underlying etiology of extreme thrombocytopenia is reasonable. Some experts also consider platelet transfusion to be reasonable in patients with very low platelet count. ***(class IIb, level C-EO)***
4. MT should not be withheld from neonates, infants, children, and adolescents, but rather be evaluated on a case-by-case basis. ***(class IIa-b, level B-NR and C-LD)***
5. Standard techniques for radiation dose minimization (ALARA—as low as reasonably achievable) should be applied in diagnostic and therapeutic applications for pediatric stroke. ***(class I, level B-NR)***
6. Where possible, and determined by local availability, initial radiologic work up of stroke in neonates, infants and children below the age of 10 should involve non-ionizing radiation, specifically MRI. ***(class IIa, level B-R)***
7. Potential benefits and risks of MT should be evaluated on a case-by-case basis in patients with collagen vascular diseases with reference to the specific underlying disease. ***(class IIb-III, level C-EO)***
8. Diagnostic catheter angiography in patients with collagen vascular disease carries increased risks; non-invasive imaging should be used whenever possible. ***(class III:Harm, level C-EO)***
9. MT should not be withheld from patients who have recently undergone surgery. ***(class IIa, level C-LD)***
10. MT should not be withheld from patients with endocarditis. ***(class IIb, level C-LD)***
11. Endovascular thrombectomy is a safe and feasible procedure for treating acute ischemic stroke due to ELVO in pregnancy, and should be considered for patients in a similar manner as would be indicated in a non-pregnant patient. (***class IIa, level C-LD***)
12. Fluoroscopic radiation safety features should be fully used as well as a low threshold for anesthesia and obstetrics consultation in pregnant patients. (***class IIb, level C-LD***)

INTRODUCTION

The pendulum for the usefulness of mechanical thrombectomy (MT) for ischemic stroke treatment has gone from one extreme to another in recent years. Decades from now, 2015 will be remembered

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as a pivotal year in establishing it as the standard of care for large vessel occlusions.[1–5] A pooled patient analysis of these trials concluded that MT in patients who met inclusion criteria led to significantly reduced disability compared with controls.[6] For every 100 patients treated, 58 will have improved functional status compared with controls, and approximately 20 will achieve independence.[6] As promising as the results have been in a relatively homogeneous population, the question of generalized applicability of these findings to a more heterogeneous population has been a topic of debate.[6 7] Stroke systems of care predicated on these trials, as well as protocols to consider during the COVID-19 pandemic, have been extensively reviewed and incorporated into other standards and guidelines documents from the Society of NeuroInterventional Surgery[8–18] The majority of patients treated with MT in real-life practice, would probably not have qualified for inclusion in the clinical trials, but probably do benefit from treatment.[7]

GUIDELINE SPECIFICS: CURRENT GUIDELINES FOR PATIENTS WITH EMERGENT LARGE VESSEL OCCLUSION ACUTE ISCHEMIC STROKE

Current US standards for the role of mechanical thrombectomy in emergent large vessel occlusion (ELVO) anterior circulation stroke are well summarized in the 2019 update to the 2018 guidelines for management of acute ischemic stroke published by the American Heart Association and American Stroke Association.[19] Section 3.7 of that document includes guidelines on: (1) thrombectomy after intravenous thrombolysis, (2) thrombectomy 0 to 6 hours after last seen well, (3) thrombectomy 6 to 24 hours after last seen well, (4) anatomic targets, (5) thrombectomy techniques, (6) adjunctive antiplatelet and fibrinolytic medications, and (7) postprocedural blood pressure management. Table 1 below summarizes those recommendations as well as the class (strength) of recommendation and the level (quality) of evidence for each.

The American Heart Association (AHA)/American Stroke Association (ASA) guidelines are based on randomized controlled clinical trials such as DAWN, DEFUSE 3, ARISE 2, EXTEND-IA, REVASCAT, SWIFT-PRIME, ESCAPE, and MR CLEAN, all of which enrolled adult patients (18 years old or older) and some of which excluded very elderly patients (older than 80, 85, or 90 years in some trials, and also based on case series and expert opinion. In addition to extremes of age, other common criteria that have excluded patients from randomized trials are pregnancy, thrombocytopenia, active endocarditis, recent surgery, and collagen vascular disease. Patients who have one or more of these characteristics fall outside the mainstream of medical evidence to date and, thus, will be the focus of the remainder of this guideline document.

METHODS

We systematically reviewed the literature for manuscripts with the key word ‘stroke’ and any of the following: ‘mechanical thrombectomy’, ‘elderly’, ‘octogenarian’, ‘nonagenarian’, ‘pediatric’, ‘pregnant’, ‘pregnancy’, ‘thrombocytopenia’, ‘low platelets’, ‘collagen vascular disease’, ‘connective tissue disorder’, and ‘endocarditis’. These topics were chosen to reflect conditions not typically included in randomized controlled trials of stroke that were already published in 2020 or expected to be published in 2021. We graded evidence using the Oxford Centre for Evidence-Based Medicine guidelines[20] and the American Heart Association guidelines,[19] with the latter being applied to recommendations.

Octogenarians and nonagenarians

The proportion of elderly (≥65 years) individuals in the United States is expected to double by the year 2050, and people older than 80 years of age have the highest incidence of acute ischemic stroke.[21] Thus, the proportion of patients aged ≥80 years who are eligible for endovascular therapy (EVT) for acute ischemic stroke (AIS) will continue to increase. This patient population was excluded from three of the six pivotal MT trials.[3 5 22] Furthermore, this population was relatively under-represented in the trials that did include them, suggesting possible selection bias.[21]

Several retrospective and prospective observational studies have reported MT for elderly patients. The generalizability of these studies is limited by small sample sizes, restriction to single centers, significant heterogeneity, and often without comparison with optimal medical management.[21] Meta-analysis data from the Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke trials (HERMES) trial showed better 90-day outcomes among patients aged >80 years treated with thrombectomy than for patients treated with intravenous thrombolysis alone (29.8% vs 13.9%; common OR=3.68, 95% CI 1.95 to 6.92).[6] Additionally, elderly patients who underwent MT had a slightly reduced risk of death (28% vs 45%; adjusted rate ratio 0.60, 95% CI 0.36 to 0.99).

Hilditch *et al* performed a systematic review of 16 observational studies involving patients aged ≥80 years who underwent MT for AIS and combined this with data from the HERMES study. Among 860 patients, the authors showed a 27% rate of functional independence at 90 days (95% CI 21% to 32%), and a mortality of 34% (95% CI 23% to 44%), with significant heterogeneity between published reports (I^2=70% and 91%, respectively). Although recanalization rates were excellent, 78% rate of Thrombolysis in Cerebral Infarction (TICI) 2b/3 recanalization (95% CI 72% to 85%), there was an 8% rate of symptomatic intracranial hemorrhage and a procedural complication rate of 11%.[21]

Even before the major stroke trials, controversy existed as to whether or not MT for anterior circulation ELVO was efficacious in patients aged 80 or older, largely due to poor outcomes in most cases (ie, 60–70%) despite good recanalization rates (~80%).[23 24] This is problematic since about one-third of ischemic strokes occur in patients of this age and are associated with particularly poor clinical outcomes.[25 26] In 2016, the trial investigators collectively pooled the data into a collaboration from the MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME, and EXTEND-IA trials into HERMES and performed a meta-analysis to evaluate whether the benefit of MT persisted when applied to specific populations of patients that were relatively under-represented in the major trials.[6] One of these populations included the elderly, as some of the trials excluded elderly patients (SWIFT PRIME excluded patients >80 years and REVASCAT excluded those >85 years), and the median age of subject in the trials when pooled was only 68. The authors found that although older age correlated with worse functional outcomes via the modified Rankin Scale (mRS), there remained a significant and fixed difference between the outcomes of the intervention (MT) and the non-intervention groups. Since then, more studies have emerged that evaluate technical feasibility with MT in the elderly and clinical outcomes, with mixed results. In the DAWN (diffusion-weighted imaging (DWI) or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention with Trevo)[27] trial, the elderly were included but only with specific core infarct sizes and/or National Institutes of Health Stroke Scale (NIHSS)

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Table 1 Summary of the mechanical thrombectomy section of the American Heart Association/American Stroke Association 2019 update of the 2018 acute ischemic stroke management guidelines (modified from Powers *et al*[19])

	COR	LOE
3.7.1 Concomitant with IV alteplase		
1. Patients eligible for IV alteplase should receive IV alteplase even if MT is being considered	I	A
2. In patients under consideration for MT, observation after IV alteplase to assess for clinical response should not be performed	III: harm	B-R
3.7.2 Zero to six hours after last seen well		
1. Patients should receive MT with a stent retriever if they meet all the following criteria: (1) prestroke mRS score of 0 to 1; (2) causative occlusion of the ICA or MCA segment 1 (M1); (3) age ≥18 years; (4) NIHSS score of ≥6; (5) ASPECTS ≥6; and (6) treatment can be initiated (groin puncture) within 6 hours of symptom onset	I	A
2. Direct aspiration thrombectomy as first-pass MT is recommended as non-inferior to stent retriever for patients who meet all the following criteria: (1) prestroke mRS score of 0 to 1; (2) causative occlusion of the ICA or M1; (3) age ≥18 years; (4) NIHSS score of ≥6; (5) ASPECTS ≥6; and (6) treatment initiation (groin puncture) within 6 hours of symptom onset	I	B-R
3. Although benefits are uncertain, MT with stent retrievers may be reasonable for carefully selected patients with AIS in whom treatment can be initiated (groin puncture) within 6 hours of symptom onset and who have causative occlusion of segment 2 (M2) or segment 3 (M3) of the MCAs	IIb	B-R
4. Although benefits are uncertain, use of MT with stent retrievers may be reasonable for patients with AIS in whom treatment can be initiated (groin puncture) within 6 hours of symptom onset and who have prestroke mRS score >1, ASPECTS <6, or NIHSS score <6, and causative occlusion of the ICA or proximal MCA (M1)	IIb	B-R
5. Although the benefits are uncertain, the use of MT with stent retrievers may be reasonable for carefully selected patients with AIS in whom treatment can be initiated (groin puncture) within 6 hours of symptom onset and who have causative occlusion of the ACAs, vertebral arteries, basilar artery, or PCAs	IIb	C-LD
3.7.3 Six to 24 hours after last seen well		
1. In selected patients with AIS within 6 to 16 hours of last known normal who have ELVO in the anterior circulation and meet other DAWN or DEFUSE 3 eligibility criteria, MT is recommended	I	A
2. In selected patients with AIS within 16 to 24 hours of last known normal who have ELVO in the anterior circulation and meet other DAWN eligibility criteria, MT is reasonable	IIa	B-R
3.7.4 Technique		
1. Use of stent retrievers is indicated in preference to the MERCI* device	I	A
2. The technical goal of MT should be reperfusion to a mTICI grade 2b/3 angiographic result to maximize the probability of a good functional clinical outcome	I	A
3. To ensure benefit, reperfusion to mTICI grade 2b/3 should be achieved as early as possible	I	A
4. In the 6- to 24-hour MT window evaluation and treatment should proceed as rapidly as possible to ensure access to treatment for the greatest proportion of patients	I	B-R
5. It is reasonable to select an anesthetic technique during EVT for AIS based on individual patient risk factors, technical performance of the procedure, and other clinical characteristics	IIa	B-R
6. The use of a proximal balloon guide catheter or a large-bore distal-access catheter, rather than a cervical guide catheter alone, in conjunction with stent retrievers may be beneficial	IIa	C-LD
7. Treatment of tandem occlusions (both extracranial and intracranial) during MT may be reasonable	IIb	B-R
8. The safety and efficacy of IV glycoprotein IIb/IIIa inhibitors administered during endovascular stroke treatment are uncertain	IIb	C-LD
9. Use of salvage technical adjuncts, including intra-arterial fibrinolysis, may be reasonable to achieve mTICI grade 2b/3 angiographic results	IIb	C-LD
3.7.5 Blood pressure management		
1. In patients undergoing MT, it is reasonable to maintain the BP at ≤180/105 mm Hg during, and for 24 hours after, the procedure	IIa	B-NR
2. In patients who undergo MT with successful reperfusion, it might be reasonable to maintain BP at a level <180/105 mm Hg	IIb	B-NR

*Mechanical Embolus Removal in Cerebral Ischemia (MERCI) device.
ACA, anterior cerebral artery; AIS, acute ischemic stroke; ASPECTS, Alberta Stroke Program Early CT Score; BP, blood pressure; COR, class of recommendation; ELVO, emergent large vessel occlusion; EVT, endovascular thrombectomy; ICA, internal carotid artery; LOE, level of evidence; MCA, middle cerebral artery; mRS, modified Rankin Scale; MT, mechanical thrombectomy; mTICI, modified Thrombolysis in Cerebral Infarction; NIHSS, National Institutes of Health Stroke Scale; PCA, posterior cerebral artery.

score, and there was no dedicated age analysis. In the DEFUSE-3 (The Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke)[28] trial, patients aged >80 years were excluded.

Online supplemental table 1 displays the various studies published, in chronological order, examining the relationship between elderly age and outcomes in MT. We identified 22 studies in the advanced elderly (ie, ≥80 years) and very old (ie, ≥90 years), four of which were meta-analyses, and a majority of which were retrospective, single-center analyses (10), with some multicenter studies (six), including two with national registry data. Half of the studies (11/22) performed an analysis dedicated to nonagenarians. The majority of relevant endpoints included 90-day mRS score, 90-day mortality, TICI score, and rates of symptomatic intracranial hemorrhage (sICH). A subgroup analysis of patients enrolled in MR CLEAN showed significant improvements in functional outcome with MT regardless of age or initial Alberta Stroke Program Early CT Score (ASPECTS).[29]The collective HERMES data[6] also showed

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significant improvements in outcomes with the addition of MT, despite the overall rate of good outcome being lower than for younger patients. Many single-center retrospective studies have shown the technical feasibility of MT in the elderly, good recanalization rates, but low rates of good clinical outcomes.[25 30] Some studies (including one that combines octogenarians and nonagenarians),[31] show comparable clinical outcomes to those of younger patients.[32 33] A few meta-analyses have shown poor outcomes in comparison with those for younger patients.[21 34 35] Important to note, there are limited data[6 33] comparing octogenarians receiving MT with those who did not receive MT as the comparison group, with a clear benefit in functional outcomes for the former.

Some studies (also listed in online supplemental table 1) have performed a dedicated analysis on patients who are 'very old' (ie, aged ≥90 years). Multiple multicenter retrospective studies show that MT is feasible in this population, but with low rates of good outcomes.[36–38] These data were revalidated with additional national registry data from Germany.[39] Some data from single-center studies also show that MT in nonagenarians is feasible, but with low rates of good outcomes,[40] and a particularly high rate of hemorrhagic complications.[41] Some data from single centers show no difference between octogenarians and nonagenarians[42] or younger patients,[43] and no difference in discharge disposition between younger patients (≤69 years) and nonangenarians.[44] There has been one meta-analysis for this topic showing high revascularization rates in nonagenarians with low rates of good clinical outcomes.[45]

Summary of data

- MT in octogenarians and nonagenarians is technically feasible with acceptable recanalization rates.
- Clinical outcomes, including 90-day mRS score and 90-day mortality, are improved in the elderly who receive MT compared with those who do not. Clinical outcomes in this population are worse than in younger patients (ie, aged <80) undergoing MT. It is unclear whether clinical outcomes in the very old are comparable, worse, or better in comparison with either the elderly or younger patients.
- Symptomatic intracranial hemorrhage (sICH) rates may be higher in elderly patients undergoing MT.

Recommendation

- MT should not be withheld from octogenarians and nonagenarians, but rather evaluated on a case-by-case basis. ***(class IIa-b, level B-NR and C-LD)***

Patients with thrombocytopenia

There is a paucity of data guiding decisions for MT in thrombocytopenic patients (SWIFT PRIME and EXTEND IA excluded patients with platelet counts <100 K/μL, and DAWN and DEFUSE-3 exlucded those <50 K/μL). This latter population is particularly vulnerable, since the American Heart Association and Eur0pean Stroke Organization guidelines from 2018 both suggest a platelet count of <100 K/μL to be a contraindication to IV tissue plasminogen activator (tPa).[46]

We identified three studies evaluating the impact of thrombocytopenia in MT, of which one was a retrospective review of prospectively collected trial data, and two were retrospective single-center analyses (online supplemental table 2). Nogueira *et al*[47] analyzed data retrospectively from the prospectively conducted MERCI and Muti MERCI trials. The authors identified a total of 35 patients with abnormal bleeding profiles, including thrombocytopenia (though only six of these 35 patients constituted this category), who underwent MT and compared outcomes with results for a group of 270 patients with normal bleeding profiles who underwent MT. Rates of sICH were comparable between the two groups, though the latter group did have better clinical outcomes, probably due to worse pre-stroke functional status. Mönch *et al*[48] performed a retrospective analysis specifically examining thrombocytopenia (defined here as <150 K/μL). The authors also included patients who presented with normal platelet count but experience a drop in platelet count. There was no statistical difference in rates of sICH in any of the groups, though patients with a drop in platelet count had worse mortality and functional outcomes, and thrombocytopenic patients had higher mortality. Finally, Desai *et al*[46] retrospectively reviewed patients and found largely no major differences in rates of sICH (ie, the authors used three separate definitions of sICH, and one did have statistically significant difference between groups), but worse functional outcomes and higher mortality in the thrombocytopenic group.

Summary of data

- MT in thrombocytopenic patients does not result in higher rates of sICH than in patients with normal platelets, though mortality is higher and clinical outcomes after treatment are worse, probably due to pre-existing morbidity.

Recommendations

- MT should not be withheld from thrombocytopenic patients. ***(class IIb, level C-LD)***.
- There is no absolute minimum platelet count that excludes patients from MT given the high morbidity of ELVO. The expert panel considers <20K very concerning for potential hemorrhagic conversion of infarction or procedural complication, and hematologic consultation to understand the underlying etiology of extreme thrombocytopenia is reasonable. Some experts also consider platelet transfusion to be reasonable in patients with very low platelet count. ***(class IIb, level C-EO)***.

Pediatric patients with ELVO

The incidence of AIS in children is low at approximately 2.3 per 100 000 children[49 50] but can be devastating with a very high morbidity of 70% and a mortality rate of 3–6%.[51 52] While the cause of pediatric stroke is poorly understood, it can be divided into childhood/adolescent (non-neonatal) and neonatal age groups. In the childhood/adolescent age group, common etiologies include congenital heart disease, arterial dissection, and sickle cell disease. For example, the Canadian Pediatric Stroke Registry revealed cardiac disease to be the cause in 25% of cases of pediatric AIS.[53] On the other hand, among cryptogenic strokes, a patent foramen ovale was found to be the cause in 40–50% cases as opposed to 10–27% in the general population.[54] Less common causes include inflammatory vasculopathies, head and neck trauma, and prothrombotic disorders.[55] However, in a large number of cases, the cause is can often not be identified. This has led to the diagnosis of idiopathic etiology of stroke of childhood. In childhood, arteriopathy may be due to spontaneous or traumatic dissections, or infectious etiology like varicella or moyamoya syndrome. Childhood prothrombotic disorders are broad and include antiphospholipid antibody, anticoagulant factor deficiencies, and hyperhomocysteinemia. In the neonatal population, the etiology is often more elusive but, in general, congenital cardiac anomalies and thrombophilia

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conditions presenting with stroke are more common than in the older child. Other factors in the neonatal age group includes maternal pregestational and gestational factors plus feto-maternal vertically transmitted infections. Among the above mentioned factors, the incidence of acute ischemic strokes due to ELVO is found in a small cohort of patients.

In a large retrospective cohort analysis, Mallick *et al* reviewed 107 pediatric patients and found that only three patients would have been eligible for hyperacute thrombolysis with IV tPA.[56] This study and the slow recruitment of patients to the TIPS (Thrombolysis In Pediatric Stroke) trial demonstrates the degree of difficulty in achieving timely access to thrombolytic therapy in the pediatric patient group. Since 2015 the established benefit of MT in adults has shown tremendous improvement in neurological function in recanalized patients in real-world application of randomized trial results. For pediatric stroke, several case series have been published and reviewed recently, which provide an argument for the use of MT in select pediatric patients who present with ELVO who satisfy tissue viability based imaging criteria.[57–59]

As has been mentioned before the morbidity burden in pediatric ischemic stroke is immense. The plasticity of the pediatric brain can hypothetically extend the time in which to help patients with ELVO. Ravindra *et al* demonstrate that in their retrospective analysis of five centers at which pediatric AIS was treated, the median time from last known normal was 380 min (late window) and good clinical outcome from recanalization of ELVO was seen in 80% of patients.[59] In their study, eight patients were selected for MT based on perfusion imaging criteria. Zhou *et al* demonstrate that Solitaire stent-based MT is feasible and effective in pediatric ELVO, although in a small group of patients.[58] Bhatia *et al* in their review advocate a prospective multinational registry to evaluate the role of MT in anterior and posterior circulation ELVO.[57]

As with the adult population, suitability for thrombectomy in pediatric patients is determined by both clinical and radiologic parameters. In general, unnecessary exposure of neonates and children under the age of 10 to ionizing radiation should be avoided when there is a viable alternative. Targeted, limited sequence MRI/MR angiography (MRA) protocols that are designed for rapid and accurate delineation of large vessel occlusion, infarct core, and penumbra are ideal in the pediatric population. Such rapid protocols may include time of flight-MRA, 3D T2, 3D fluid-attenuated inversion recovery (FLAIR), gradient echo, and DWI sequences, or a combination thereof, and permit acquisition times of less than 15 min on modern scanners. Non-contrast MRA based on time of flight vessel imaging is the preferred mode of imaging for evaluation of ELVO. The sensitivity and specificity of this technique for ELVO detection is well established in the adult population.[60] If needed, both contrast and non-contrast techniques can be applied to enable MRI perfusion analysis of core and penumbra in the affected brain tissue. Arterial spin labeling is a promising non-contrast perfusion technique, which may prove useful in assessing tissue viability.[61] However, perfusion sequences may also be unnecessary in some patients, as a reliable surrogate determination of infarct core versus penumbra may be inferred via mismatch between regional diffusion restriction and signal hyperintensity on DWI B-1000 and FLAIR sequences, respectively. In children age 10 years or more and adolescents, the established CT based imaging protocols used in adults are appropriate (non-contrast CT, CT angiography (CTA) neck and head with or without CT perfusion). MRI techniques in older children can be used when there is iodinated contrast allergy.

Pediatric stroke intervention poses access, device, and technique related challenges. Femoral access for intervention is necessary, though appropriate sheath size is dictated by the age of the patient, which roughly correlates to femoral artery diameter. In general, the femoral artery of neonates and children up to 12 months will accommodate a 4 French sheath. In older children and adolescents, a 6Fr sheath may be the limit. This access consideration restricts the choice of guide catheter, and at the time of writing removes the availability of a balloon guide catheter for sheath sizes less then 6Fr. Alternative approaches include the use of an aspiration/intermediate catheter in place of a dedicated guide, through which routine microcatheters and micro-guidewires may be used for navigation of the aspiration catheter or the delivery and deployment of stent retrievers.

The intracerebral vessels in children may be more fragile than those in the adult population and may be damaged by minimal manipulation with intraluminal devices. The force applied to the pediatric endothelium must be titrated according to the size of the child on the operating table and the size of the cervical and intracranial blood vessels. Aspiration catheter and/or stentriever selection should be appropriately calibrated to the target vessel size diameter. The larger 6 mm stentrievers should be reserved for larger and older children. While complete reperfusion (TICI >3) should remain the goal of any stroke intervention, a lower threshold for terminating the procedure should arguably be made when multiple passes or more distal catheter positions would be required to achieve such a target. Given the current device-related limitations, one strategy has been the use of intra-arterial tPA at the site of the ELVO. Despite limited proof for this strategy in the adult literature,[62] the technique has been used in the pediatric population. Although the efficacy of intra-arterial lytic remains unproved, it might represent a potential last resort technique.

Currently, MT employs fluoroscopy which involves the application of ionizing radiation. As with all medical imaging-guided interventions, care should be taken to ensure the lowest possible dose of radiation is used to achieve the intended purpose of the intervention, also known as the ALARA (As Low As Reasonably Achievable) principle. While this principle should be applied to patients of all age groups, children are thought to be at particular risk of dose-dependent and -independent radiation-related effects (deterministic and stochastic). The dose reduction strategies employed for other pediatric neurointerventions and body interventions should be applied equally in stroke treatment.[63] Strategies applied equally to the adult and pediatric population include: limiting the use of magnification, routine use of collimation, low pulse rates for fluoroscopy, minimizing the patient to detector distance, minimizing non-essential oblique projections, shielding radiosensitive organs where possible, and eliminating unnecessary digital subtraction angiograms. These measures can all substantially reduce the radiation exposure to both the patient and operator during MT procedures.

Post-thrombectomy care is critical in maximizing the benefits of recanalized vessels to the patients for translation to improved neurological function. Postoperatively, patients should be admitted to a pediatric or neonatal intensive care unit (ICU), with close attention to blood pressure goals and to minimize possibilities of reperfusion hemorrhage following recanalization. After recovery in the ICU, attention should be on aggressive rehabilitation with dedicated goal-directed physical therapy. In recent times, advances have been made in the understanding of neuronal functional recovery and how that might be optimized further by use of artificial intelligence and novel applications of both virtual and augmented reality rehabilitation platforms.[64 65]

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Summary of data

- Data for MT vary by age in the pediatric population.

Recommendations

- Mechanical thrombectomy should not be withheld from neonates, infants, children, and adolescents with large vessel occlusive stroke but rather be evaluated on a case-by-case basis. ***(class IIa-b, level B-NR and C-LD)***
  - MT in neonates and infants (less than 1 year of age) is technically feasible and acceptable to offer in selected patients ***(class IIb, level C-LD)***
  - MT in children (age 1–9 years) is technically feasible and acceptable to offer in selected patients ***(class IIb, level C-LD)***
  - MT in adolescents (age 10–19 years) is technically feasible and acceptable to offer in selected patients ***(class IIa, level B-NR)***
- Standard techniques for radiation dose minimization (ALARA) should be applied in diagnostic and therapeutic applications for pediatric stroke. ***(class I, level B-NR)***
- Where possible, and determined by local availability, initial radiologic work up of stroke in neonates, infants, and children below the age of 10 years should involve non-ionizing radiation, specifically MRI. ***(class IIa, level B-R)***

Patients with ELVO and collagen vascular disorders

Collagen vascular disorders (CVD) make up a subset of the broader category of inherited disorders of connective tissue. These are mostly single-gene disorders that impair the structure and/or function of connective tissue. Although the most common sequelae of these disorders may not include neurologic manifestations, when they do occur these are most commonly neurovascular due to alterations in vascular connective tissue. Given the rarity of these disorders, no large sample studies have evaluated the occurrence and management of ischemic stroke in these populations; however, published case series and technical reports are numerous and can serve as a basis from which to draw general conclusions.

Classically recognized CVD associated with neurovascular manifestations include Ehlers-Danlos type, Marfan syndrome, pseudoxanthoma elasticum, Loeys-Dietz syndrome and neurofibromatosis, among others. Ehlers-Danlos syndrome is group of disorders with a variety of genetic defects and inheritance patterns. Vascular Ehlers-Danlos syndrome has an estimated prevalence of 0.2–1/100, 00 and is the subtype associated with the most neurovascular manifestations, including arterial dissections, carotid-cavernous fistulas, ischemic stroke, and intracranial aneurysms. The underlying pathology involves disruption in the assembly of type III collagen fibers. Marfan's disorder is another monogenic disorder with autosomal dominant inheritance. The disorder is characterized by a mutation in the fibrillin 1 gene and it has a prevalence of 1/50 000. The most common vascular complications associated with this disorder are aortic root disease and mitral valve prolapse. However, neurovascular complications, such as spinal cord ischemia, cervical artery dissection, and intracranial aneurysms, have also been reported. Pseudoxanthoma elasticum has a prevalence of approximately 1/100 000 with a varied underlying genetic etiology and inheritance pattern. The disorder is most commonly associated with cardiovascular and ocular sequelae. However, cervical artery dissection, intracranial aneurysms, and cerebral infarction secondary to premature stenosis/occlusion of carotid and vertebral arteries have been described.[66–70]

Patients with CVD are considered very high risk for endovascular procedures given the presumed increased risk of iatrogenic vessel dissection or rupture. Standard screening for intracranial aneurysms with diagnostic cerebral angiography is not generally recommended in these patients for these reasons.[67 68] Historically, some studies have even advocated that conventional angiography is absolutely contraindicated as a diagnostic tool in patients with vascular Ehlers-Danlos syndrome.[67] Additionally, transvenous approaches for treatment of intracranial fistulas, when possible, have been recommended as there is less risk of arterial injury.[71] In the setting of carotid and vertebral artery dissections, evaluations with non-invasive imaging and medical management are the recommended standards. Despite the high risk of arterial injury, some patients may be refractory to medical management, necessitating endovascular interventions. Given the rarity of these cases, there have been no technical guidelines published for these patients. However, numerous case studies describe transarterial approaches to the stenting of carotid artery dissections, treatment of carotid-cavernous fistulas, and treatment of intracranial aneurysms using a standard endovascular technique and guidelines.[72–75]

Acute ischemic stroke is rare in CVD, but most reports are associated with cervical carotid or vertebral artery dissection. Additionally, cases of cerebral infarction secondary to intracranial steno-occlusive disease, with a moyamoya pattern, have been reported in neurofibromatosis 1 and pseudoxanthoma elasticum as well.[66 67 69] There have been no reports in the literature however, of AIS secondary to thromboembolism and no studies evaluating the use of MT in this patient population. Given this lack of data, major guidelines cannot be made about the safety and efficacy of neuroendovascular procedures in this population. However, although there are some reports of successful treatment, and no absolute contraindication to endovascular intervention can be made at this time, careful clinical consideration must be made when dealing with these patients.

Summary of data

- MT in patients with CVD may carry increased procedural risks, but this varies by the specific underlying CVD.

Recommendations

- Potential benefits and risks of MT should be evaluated on a case-by-case basis in patients with collagen vascular diseases with reference to the specific underlying disease. ***(class IIb-III, level C-EO)***
- Diagnostic catheter angiography in patients with CVD carries increased risks; non-invasive imaging should be used whenever possible. ***(class III:Harm, level C-EO)***

Large vessel occlusion in patients following surgery

Acute ischemic stroke following surgery is a major cause of perioperative patient morbidity and mortality. The overall incidence of stroke is variable depending the type of procedure, with cardiothoracic surgeries having the highest risk.

One of the largest prospective institutional databases of nearly 6000 patients concluded that the average incidence of cerebrovascular ischemia was 2.48%; ELVO occurred in 10.9% of those patients.[76] Prolonged aortic cross-clamp and cardiac bypass times were both associated with higher risk of AIS and specifically, ELVO. This suggests a synergistic effect of cerebral hypoperfusion and cardioembolic events as the mechanism of ischemia. Other suggested mechanisms of stroke in these patients are aortic atherosclerosis, cerebral hypothermia, hyperglycemia, anemia,

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atrial fibrillation, and genetic predisposition.[77] In addition, the type of cardiac procedure was closely related to the incidence of AIS, which increased along with the complexity of the case. Boeken *et al* showed that the incidence of AIS in coronary artery bypass grafting (CABG) was 1.7%, CABG and valve replacement 3.3%, and multiple valve replacements 6.7%.[78] In a Denmark cohort study of 2455 patients who underwent a transcatheter aortic valve replacement (TAVR) procedure, the overall risk of AIS was highest in the early postoperative phase (0–90 days) but not in the later phase (90 days–5 years).[79] Patients who received anticoagulation during the early phase had nearly half the incidence of cerebral ischemic events as non-anticoagulated patients (1.2% vs 2.4%). Despite these data, the recommendation for prophylactic use of anticoagulants in these patients has yet to be determined.[80]

The presentation of patients with ELVO is variable, based on the timing of the ischemic event. A *JAMA* article of a large prospective study of CABG over three decades showed that the timing of the event was intraoperative in 40% of patients and postoperative, with a peak at 40 hours after surgery, in 60%.[81] Patients who have an intraoperative incidence of AIS, are less likely to be diagnosed promptly because of the duration of the surgery and long emergence from anesthesia, which does not allow for accurate neurological evaluation. Therefore, urgent CT angiography and perfusion imaging is indicated, especially in the first group of patients. If the deficit is detected promptly in the postoperative phase, then a non-contrast CT head and CT angiography are adequate for evaluation, based on the latest AHA/ASA guidelines. A thorough neurological examination protocol in the recovery unit should be strongly considered in cardiothoracic patients, in order to prevent delays in diagnosis and subsequent treatment.

Although data are limited on patient outcomes following mechanical thrombectomy for ELVO in perioperative AIS, most studies suggest that acute stroke intervention has a trend for improved functional outcomes and lower mRS scores in 3 months.[76] Therefore, these patients should be strongly considered for the expanded window of MT based on individualized perfusion imaging data.

Following the detection of ELVO and AIS, the patient should be promptly transferred to the angiography suite. An implementation of a AIS protocol in the hospital is of paramount importance for fast detection and patient transportation. As these patients may present with cardiovascular instability, the presence of the cardiothoracic team and cardiopulmonary equipment allows for safe transportation. In the angiography suite, a thorough patient examination and communication with the primary team are required prior to choosing the arterial puncture site. If the patient still has arterial access from the original surgery, then using that site may expedite revascularization time. If bilateral femoral cutdowns were performed, such as in TAVR procedures, then a transradial approach should be considered instead. Conversely, if a radial artery harvest was used, then a transfemoral approach may provide faster access times.

Intraoperative considerations in these critical patients include the ability to administer anticoagulation or thrombolytic agents. A thorough communication with the original surgical team is essential to make this decision. In general, patients who undergo an open thoracic approach are not good candidates for intravenous tPA, but they may safely receive intravenous anticoagulants or focal intra-arterial thrombolytic agents.[82] However, endovascular procedures, such as TAVR, generally do not have contraindications for either thrombolytic or anticoagulation therapies.[80] Furthermore, the consistency of the thrombus may be variable as non-traditional types, such as lipids from pericardial suction aspirate, muscle, and fat emboli, may be involved.[77] These may have a harder consistency and require aspiration thrombectomy with large-bore aspiration catheters, as opposed to stent retrievers.

The postoperative care of cardiac patients following MT requires a comprehensive approach involving both cardiothoracic and neurological teams. In general, a cardiac care unit with neurological protocol should be strongly considered. There are limited data, and therefore no recommendation, for postoperative medical management with antiplatelet or anticoagulation agents, therefore physician discretion is strongly advised.

Summary of data

- MT in patients who have recently undergone surgery can be successful and is especially important to consider given that surgery is a contraindication to intravenous thrombolysis.

Recommendations

- MT should not be withheld from patients who have recently undergone surgery ***(class IIa, level C-LD)***

Endocarditis

Predicated on the high risk of hemorrhagic transformation, the use of thrombolytic agents is generally accepted as contraindicated if the etiology of infective endocarditis is suspected,[83 84] making MT the de facto only option for intervention. To establish the odds of a favorable outcome in the particular population, it is necessary to note that the rate of neurologic complications during hospitalizations for infective endocarditis is high and associated with an increased risk of death.[85] Large strokes, due to their association with ELVOs, the target population considered here, have been found to be independently associated with mortality compared with patients who had transient ischemic attacks or small strokes that remained clinically silent.[86]

D'Anna performed an extensive review of the literature using the PRISMA framework. His conclusions represent the currently highest quality data point.[87] He reports results of 30 patients reported in 19 published case series out of 431 screened records. Overall, MT was as effective as in patients presenting with ELVOs due to non-endocarditis etiologies. The median NIHSS score dropped from 15 before to 2.5 after the procedure. An intracranial hemorrhage occurred in 13.3% of patients, and the overall mortality at 90 days was 23.3%. Functional independence with an mRS score of less than 2 was achieved in 46.7% of patients.[87] Of the notable randomized trials that established the usefulness of MT for large vessel occlusion, the results of this analysis were worse than some, but not all, falling somewhere in the middle: EXTEND-IA SWIFT PRIME showed 71% and 60% good outcome, respectively, and MR CLEAN showed 33%.[1 3 4] A less rigorous review by Bolognese and coworkers found a similar number of favorable outcomes, defined here as mRS score ≤3 in 69% of patients.[88]

MT in patients with ELVO presumed to be the result of infective endocarditis has not been formally studied with a randomized controlled trial. Such a trial seems unlikely given the agreed-upon unfavorable outcome of the use of thrombolytic agents. Therefore, MT appears to be a reasonable option, with the understanding that its general safety and efficacy have not been established with high-quality data.

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Summary of data

- MT in patients with endocarditis appears to carry similar risks and benefits to those in patients without endocarditis.

Recommendations

- MT should not be withheld from patients with endocarditis ***(class IIb, level C-LD)***

Pregnancy

The incidence of stroke in pregnancy in the USA, Western and Asian countries ranges from 4.3 to 210 per 100 000 gestations.[89–91] Management of acute ischemic stroke due to large vessel occlusion in a pregnant patient is challenging, given the considerations for the developing fetus. In the largest study of stroke in pregnancy and the post partum period, Kittner *et al* found that the risk of stroke was greatest during the third trimester or puerperium, rather than throughout the entire 9 months of pregnancy.[89] Although certain conditions have a particularly strong association with stroke in pregnancy (such as eclampsia), or with the post partum period (such as cerebral venous thrombosis), most cerebral infarctions are due to arterial occlusion.[91 92]

Administration of thrombolytic agents in pregnancy for suspected stroke is a complex decision with limited evidence. Pregnancy was an exclusion criterion in all IV thrombolysis trials, and formal studies examining the effects of thrombolytic agents on the outcomes of human pregnancy do not exist. Alteplase (tPA) is far too large a molecule to cross the placenta, and there are no quality human or animal data documenting the teratogenicity of thrombolytic agents.[2 93] More than 200 reports exist in the literature of pregnant patients who have received thrombolytic therapy for various indications.[91 93] Gartman systematically reviewed reports of pregnant patients who received tPA for neurologic indications (ie, acute stroke, venous sinus thrombosis), and showed no maternal deaths, no major bleeding events, and three fetal deaths/spontaneous abortions (none of which were attributed to thrombolytic administration). Complication rates of tPA in pregnancy are comparable with those in non-pregnant patients, with overall low risks of maternal mortality (1%), maternal hemorrhage (8%), and fetal loss (6%).[2 91 93–95] The current AHA/ASA guidelines recommend IV tPA administration be considered when the expected benefits of treating life-threatening or potentially debilitating stroke outweigh the risk of uterine bleeding.[19]

Pregnancy was an exclusion criterion in the pivotal EVT clinical trials, and thus data from controlled clinical trials do not exist. Emergent EVT on the pregnant woman, like any other, requires the use of sedation and/or analgesics, iodinated contrast, and ionizing radiation. Neurointerventionalists should have a low threshold for consulting an anesthesiologist, especially for more complex cases, agitated patients, and/or for high-risk pregnancies.[96] Iodinated contrast is a category B medication, and animal studies have not reported teratogenic or mutagenic effects from exposure. Human studies have not demonstrated any inhibitory effect of free iodide on neonatal thyroid gland function.[95 96]

The National Council on Radiation Protection and Measurements states that radiation exposure less than 50 mGy to the fetus is considered negligible in comparison with baseline risks for all developmental abnormalities, but this risk increases significantly when exposure exceeds 150 mGy.[97] The most important prenatal risk and deterministic effects occur at 8 to 15 weeks after conception, when the sensitive cortical brain cells are exposed to radiation greater than the threshold of 300 mGy.[96] EVT procedures can involve cumulative radiation doses of approximately 1600±500 mGy.[98] However, all available evidence and expert opinion suggest the deterministic risks of radiation exposure should not be taken into consideration when deciding on whether to perform EVT. Notwithstanding, neurointerventionalists should fully use fluoroscopic radiation safety features as endorsed by the Society of Interventional Radiology[99] and according to ALARA principles. An experienced interventionalist(rather than a trainee) should perform as primary operator when possible, again in support of reduced fluoroscopy times. Other strategies include reducing the rate of pulsed fluoroscopy, use of last image hold, limiting the beam on-time, minimizing angiography acquisitions, limiting the use of magnification, using tight collimation, raising the patient away from the X-ray tube, minimizing the image intensifier–patient distance, removing the grid, reducing the tube current, and limiting femoral angiography.[99] Use of lead shielding does not provide significant protection, but may lend a positive psychological reassurance to patients and their families.[96]

The safety and feasibility of EVT of ELVO in pregnancy is based solely on single-center case reports and one small case series, for a total of 14 patients.[95] When examining these historical cases, despite the procedural diversity, 93% (13/14 subjects) achieved a TICI 2b or higher grade of recanalization, and all patients with follow-up data had a mRS score of 0–2 at final follow-up. Delivery outcomes consisted of seven normal full-term deliveries, one spontaneous abortion, two full-term Cesarean sections, one emergency Cesarean section with delivery of a healthy newborn, and three cases of unknown delivery status. No maternal or fetal deaths were reported. EVT is seemingly a safe and feasible procedure for treating AIS due to ELVO in pregnancy, and should be considered for patients presenting as such.

Doppler fetal monitoring should performed in the first trimester and beyond, immediately before and after the procedure, to ascertain the health of the fetus.[96] In certain circumstances, such as high-risk pregnancy and higher levels of sedation/analgesia, continuous fetal monitoring during the procedure may be appropriate. Postprocedurally, patients should receive an obstetrics consultation, and postprocedure fetal ultrasound is obtained in the first trimester to evaluate fetal viability.[96]

Summary of data

- MT in pregnant patients is technically feasible with acceptable rates of recanalization and maternal and fetal clinical outcomes.

Recommendations

- Endovascular thrombectomy is a safe and feasible procedure for treating AIS due to ELVO in pregnancy, and should be considered for patients in a similar manner as would be indicated in a non-pregnant patient. (***class IIa, level C-LD***)
- Fluoroscopic radiation safety features should be fully used as well as a low threshold for anesthesia and obstetrics consultation in pregnant patients. (***class IIb, level C-LD***)

CONCLUSIONS

Further studies are needed in patients excluded from 'standard' thrombectomy and randomized trials. As technology and techniques for thrombectomy continue to develop, evaluating their application to diverse patient populations with a variety of features or conditions that have excluded them from earlier

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trials is essential for appropriate dissemination of care. Given the rarity of some of these conditions, large randomized controlled trials may be impossible. Pragmatic design of multicenter trials and registries can help us better understand treatment for these patients.

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Author	Year	Country	Patients	Type of Study	Primary Group (n)	Comparison Group (n)	Major Endpoints	Outcomes	Comments
Duffis et al.	2014	Multiple (8 Studies)	2,729	Meta-Analysis	≥ 80 years (467)	< 80 years (2,262)	90DmRS, sICH, 90Dmortality, TIMI	≥ 80 compared to <80: TIMI 2-3 OR = 0.814, p=0.364, sICH OR = 1.604 p=0.04, mortality OR = 3.695 p<0.001 <80 compared to ≥80: 90dmRS<3 OR = 2.694, p<0.001	
Parrilla et al.	2015	Spain	150	Retrospective, Single Center	≥ 80 years (34)	< 80 years (116)	TICI, sICH, PostProcedure NIHSS, 90DmRS, 90Dmortality	≥ 80: TICI ≥ 2b =88.2%, sICH = 5.9%, PostProcedureNIHSS = 9.7, 90DmRS<3 =13.8%, mortality = 35.2% < 80: TICI ≥ 2b = 93.9%, sICH = 2.6%, PostProcedureNIHSS = 6.5, 90DmRS<3 = 56.9%, mortality = 17.2%	
Hwang et al.	2015	Korea	156	Retrospective, Single Center	> 80 years +EVT (56)	> 80 years NO EVT (100)	90DmRS, 1yrmRS, sICH, 90Dmortality	EVT: 90DmRS<3 = 35.7%, 1yrmRS = 35.7%, sICH = 10.7%, mortality = 12.5% NO EVT: 90DmRS<3 = 11%, 1yrmRS = 14%, sICH = 2%, mortality = 8%	EVT patients also had reduced in-hospital morbidity, measured via infections, etc.
Goyal et al.	2016	Multiple (5 Trials)	198	Retrospective Analysis of Prospective Trial Data	≥ 80 years +EVT (107)	≥ 80 years NO EVT (91)	90DmRS, 90Dmortality	≥ 80 +EVT vs. NO EVT: mortality = 28% versus 45%, 90DmRS<2 OR = 3.68	
Khan et al.	2017	USA	193	Retrospective, Multiple (2) Centers	≥ 90 years (18)	< 90 years (175)	90DmRS	≥ 90: 90DmRS<3 = 11% < 90: 90DmRS<3 = 48%	Older age, higher initial NIHSS, and lower degree of recanalization independent predictors of poor outcome
Mohlenbruch et al.	2017	Germany	29	Retrospective, Single Center	≥ 90 years (29)	None	TICI, 90DmRS	TICI ≥ 2b = 75.9%, 90DmRS < 3 = 17.2%	Low complication rate (only 1 minor), so suggest not excluding the elderly from MT
Alawieh et al.	2018	USA	1,346	Retrospective, Multiple (7) Centers	≥ 80 years (346)	< 80 years (1,000)	TICI, sICH, 90DmRS	< 80: TICI ≥ 2b = 88%, sICH = 4%, 90DmRS<3 =44% ≥ 80: TICI > 2b = 88%, sICH = 7%, 90DmRS<3 = 21%	Age ≥ 80 independently predicted increased mortality and poor outcome, regardless of technique (ADAPT versus SOLUMBRA), location (anterior versus posterior circulation), or TICI
Hilditch et al.	2018	Multiple (17 Studies)	860	Systematic Review and Meta-Analysis	≥ 80 years (860)	None	TICI, sICH, 90DmRS < 3	TICI ≥ 2b = 78%, sICH = 8%, 90DmRS<3 = 27%	

Wu et al.	2019	China	23	Retrospective, Multiple (2) Centers	≥ 90 years +EVT (14)	≥ 90 years NO EVT (9)	PostProcedure NIHSS, 90DmRS, 90Dmortality, sICH	EVT: PostProcedure NIHSS = 0, 90DmRS<3 = 71.4%, 90Dmortality = 28.6%, sICH = 0% NO EVT: PostProcedure NIHSS = 12, 90DmRS<3 = 44.4%, 90Dmortality = 33.3%, sICH = 33.3%	
Sussman et al.	2019	USA	108	Retrospective, Single Center	90-99 years (29)	80-89 years (79)	TICI, sICH, 90DmRS<3, 90Dmortality	>90: TICI ≥2b = 79%, 90DmRS<3 = 12.5%, sICH = 21.4%, 90Dmortality = 63% >80: TICI >2b = 79%, 90DmRS<3 = 19.7%, sICH = 6.4%, 90Dmortality = 40.9%	
Meyer et al.	2019	Germany	79	Retrospective, Multiple (3) Centers	≥ 90 years (79)	None	TICI, TTR, sICH, 90DmRS	TICI ≥ 2B = 69.6%, TTR = 39 min, sICH = 5.1%, 90DmrS < 3 = 16%	No predictors of good outcome in subgroup analysis
Kawabata et al.	2019	Japan	59	Retrospective, Single Center	≥ 80 years (19)	< 80 years (40)	TICI, 90DmRS, 90Dmortality	≥ 80: TICI ≥2b = 89.5%, 90DmRS < 3 or stable from preOP = 47.4%, 90Dmortality = 21.1% > 80: TICI >2b = 67.5%, 90DmRS < 3 or stable from preOP = 45%, 90Dmortality = 27.5%	IV tPA, TICI ≥ 2b, and out of hospital onset independent preductors of good oucome
Majidi et al.	2020	USA	113	Retrospective, Single Center	≥ 80 years (113)	None	TICI, TTR, sICH, 90DmRS<3 (Good Outcome)	TICI ≥ 2B = 89%, TTR = 53 min, sICH = 5%, 90DmRS < 3 = 22% (those with mRS < 3 baseline), and stable = 32%	Subgroup anlaysis of those with favorable outcomes at 90D (16) compared to those with unfavorable (56), only difference was baseline NIHSS (14 versus 19, p = 0.03). Anesthesia subtype did not affect outcomes
Pinto et al.	2020	Portugal	144	Retrospective, Single Center	≥ 90 years (16)	≥ 80 years, < 90 years (128)	TICI, TTR, sICH, 90DmRS<3 (Good Outcome)	> 90: TICI ≥ 2b = 81.3%, sICH = 6.3%, 90DmRS<3 = 31.3% >80: TICI ≥ 2b = 87.5%, sICH = 3.1%, 90DmRS<3 = 22.6%	No signifciant differences between 2 groups
Agarwal et al.	2020	USA	205	Retrospective, Single Center	≥ 90 years (46, 39 included in propensity)	≤ 69 years (159, 39 included in propensity)	Good discharge disposition (home, rehab), sICH, TICI	≥ 90: good discharge = 44%, sICH = 2.6%, TICI ≥ 2b = 90% ≤ 69: good discharge = 51%, sICH = 10.3%, TICI > 2b = 90%	Used propensity score matching to account for confounders. No major differences between the groups
Meyer et al.	2020	Germany	203	Retrospective, Multiple (3) Centers, Plus National Registry Data	≥ 90 years (203)	None	TICI, sICH, 90DmRS≤3 (Good Outcome)	TICI ≥ 2b = 75.9%, sICH = 3%, 90DmRS ≤ 3 = 21.6%, mortality = 27.1, 90D mortality = 48.9%	ASPECT score and NIHSS independent predictors of good outcome
Andrews et al.	2020	USA	403	Retrospective, Single Center	80-89 (86), and ≥ 90 years (14)	<80 years (303)	TICI, mortality, dischargemRS	<80: TICI ≥ 2b = 87.1%, mortality = 11.8%, sICH = 10.9%, dischargemRS≤2 =	No differences between groups

								34.7% 80-89: TICI > 2b = 84.9%, mortality = 8.1%, sICH = 7%, dischargemRS≤2 = 18.6% ≥ 90: TICI > 2b = 100%, mortality = 7.1%, sICH = 7.7%, dischargemRS ≤2 = 28.6%	after multivariate modeling
Janssen et al.	2020	Belgium, Switzerland, Canada, Sweden	112	Retrospective, Multiple (3) Centers, Plus National Registry Data	≥ 90 years (112)	None	TICI, 90Dmortality, 90DmRS	TICI ≥ 2b = 74.6%, 90Dmortality = 62.3%, 90DmRS < 3 = 16.4%	younger age and lower pre-stroke mRS independent predictors of good clinical outcomes
Ahn et al.	2020	Korea	82	Retrospective, Single Center	≥ 80 years (82)	None	90DmRS	90DmRS≤3 = 42.7%	Subgroup analysis of patients showed higher likelihooh of poor outcomme with lower ASPECT and longer procedure time
Ospel et al.	2020	Netherlands	3,279	Retrospective anlaysis of Prospectively collected data, National Registry, Subgroup Analysis	ASPECT 6-10, ≥ 71.8 years, TICI ≥ 2b (799)	ASPECT 6-10, < 71.8 years, TICI ≥ 2b (832) ASPECT 6-10, < 71.8 years, TICI < 2b (468) ASPECT 6-10, ≥71.8 years, TICI < 2b (548) ASPECT 0-5, ≥ 71.8 years, TICI < 2b (42) ASPECT 0-5, > 71.8 years, TICI ≥ 2b (60) ASPECT 0-5, < 71.8 years, TICI < 2b (69) ASPECT 0-5, < 71.8 years, TICI ≥ 2b (70)	90DmRS	ASPECT 6-10, ≥ 71.8 years, TICI ≥ 2b (799): 90DmRS <3 = 34.8% ASPECT 6-10, < 71.8 years, TICI ≥ 2b (832): 90DmRS <3 = 67.7% ASPECT 6-10, < 71.8 years, TICI < 2b (468): 90DmRS <3 = 39.3% ASPECT 6-10, ≥71.8 years, TICI < 2b (548): 90DmRS <3 = 17.2% ASPECT 0-5, ≥ 71.8 years, TICI < 2b (42): 90DmRS <3 = 14.3% ASPECT 0-5, ≥ 71.8 years, TICI ≥ 2b (60): 90DmRS <3 = 15.1% ASPECT 0-5, < 71.8 years, TICI < 2b (69): 90DmRS <3 = 16% ASPECT 0-5, < 71.8 years, TICI ≥ 2b (70): 90DmRS <3 = 34.3%	Benefit in all groups, regardless of age or ASPECT
Zhao et al.	2020	Multiple (16 Studies)	3,954	Systematic Review and Meta-Analysis	≥ 80 years (1,059)	< 80 years (2,895)	90DmRS, 90Dmortality, sICH, TICI	≥80 compared to <80: 90DmRS<3 OR = 0.40 p <0.001, mortality OR = 2.26 p<0.001, sICH OR = 1.28 p=0.18, TICI ≥ 2b OR = 0.72 p=0.72	Better outcomes noted for studies published between 2017 and 2019 compared to earlier
Bai et al.	2021	Multiple (13 Studies)	657	Systematic Review and Meta-Analysis	≥ 90 years (657)	None	90DmRS, 90Dmortality, sICH, TICI	90DmRS<2 = 21.6%, TICI ≥2b = 80.82%, 90Dmortality = 44.38%, sICH = 3.52%	
Fujita et al.	2021	Japan	150	Retrospective Analysis of Prospective National Registry Data (46 centers)	≥ 90 years +EVT (49)	≥ 90 years NO EVT (101)	90DmRS, sICH	EVT: 90DmRS<3 or stable to prestroke = 28.6%, , sICH = 0% NO EVT: 90DmRS<3 or stable to prestroke = 6.9%, , sICH = 3.9%	EVT group had significantly higher ASPECT, shorter time to LKW, and more frequent IV tPA, all

									may have confounded analysis.

Author	Year	Country	Patients	Type of Study	Primary Group (n)	Comparison Group (n)	Major Endpoints	Outcomes	Comments
Nogueira et al.	2008	Multiple	305	Retrospective analysis of prospective trial data	Abnormal Bleeding = INR > 1.7 or PTT > 45 sec or platelet < 100K/uL (35)	Normal Bleeding = INR ≤ 1.7 and PTT ≤ 45 sec and platelet ≥ 100K/uL (270)	TIMI, sICH, 90DmRS	Abnormal: TIMI 2-3 = 60%, sICH = 8.6%, 90DmRS <3 = 9% Normal: TIMI 2-3 = 65%, sICH = 8.5%, 90DmRS <3 = 35%	Only 6/35 (17%) of the primary group had thrombocytopenia. Abnormal bleeding group also had worse pre sroke healh states, likely confounding results
Monch et al.	2019	Germany	294	Retrospective, single center	Initial thrombocytopenia (< 150K/uL) (29)	Normal Platelet (≥ 150 K/uL) (265)	sICH, 90Dmortality, 90DmRS	Thrombocytopenia: sICH = 10.3%, 90Dmortality = 48.3%, 90DmRS<3 = 24% Normal platelet: sICH = 6.8%, 90Dmortality = 22.6%, 90DmRS<3 = 37%	Only significnat difference was mortality. No adjustment for prestroke functional status. Also performed analysis of patients with and without a drop in plaelet counts (DPC) after presentation, showing that a DPC > 26% predictted mortality and worse clinical outcomes too
Desai et al.	2019	USA	555	Retrospective, single center	Thrombocytopenia (<150K/ul) (74)	Normal Platelet (≥ 150 K/uL) (481)	sICH, 90Dmortality, 90DmRS	Thrombocytopenia: sICH = 8.1-10.81%, 90Dmortality = 43.24%, 90DmRS<3 = 24.32% Normal platelet: sICH = 2.49-8.79%, 90Dmortality = 24.74%, 90DmRS<3 = 36.38%	Mortality and mRS worse. Used 3 separate definitions of sICH, with one having a statistical difference between groups, but 2 others did not. Performed subgroup anlaysis stratifying thrombocytopenic patients into (1) <100K/uL and (2) 100-150K/uL, with no real differences. Multivariate analysis: thrombocytopenia not related to rate of sICH.