Epidemiology, organization, diagnosis and treatment of acute ischemic stroke

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ABSTRACT

The management of acute ischemic stroke is changing. Over the period of 2010–2050, the number of incident strokes is expected to be more than double. Rapid access to mechanical thrombectomy for patients with large vessel occlusion is critically associated with their functional outcome. Moreover, patients with first pass effect had a better clinical outcome, lower mortality, and fewer procedural adverse events. We discuss some advances in acute ischemic stroke regarding the organization, the diagnosis and the treatment.

1. Epidemiology

In 2020, the global prevalence of all stroke subtypes was 89.13 million cases; notably the global prevalence of acute ischemic stroke (AIS) was 68.16 million people. The global prevalence of intracranial hemorrhage (ICH) and subarachnoid hemorrhage (SAH) were respectively 18.88 million and 8.09 million cases. In 2020 the global incidence of stroke was 11.71 million people and, of all strokes, ischemic stroke was approximately 65% of all cases, ICH and SAH were respectively around 29% and 6% of all cases. Regarding the mortality, in 2020, the number of deaths attributable to stroke was 7.08 million, particularly 3,48 million were caused by ischemic stroke, 3.25 million by ICH and 0.35 million were related to SAH [1].

In America, around 7.6 million people self-report having had a stroke [1]. It's estimated that between 2015 and 2035, total direct medical stroke-related costs are projected to more than double, from $36.7 billion to $94.3 billion, with much of the projected increase in costs arising from those ≥80 years of age. Indeed, each year around 795 000 people experience a new or recurrent stroke, of all strokes, 87% are ischemic, 10% are ICHs, and 3% are SAHs. Over the period of 2010–2050, the number of incident strokes is expected to more than double, especially in elderly and in people from underrepresented races and ethnicities [1]. Each year, in the US, more then 140,000 people still die from strokes, even if stroke mortality rates have declined over the past several decades due to advancements in prevention, diagnosis and treatment. In the US stroke is the fifth leading cause of death [2].

Functional and cognitive impairment and dementia are common

after stroke, with the incidence increasing with duration of follow-up. Moreover, patients with stroke are at increased risk of depression. Indeed, stroke is a leading cause of serious long-term disability in the United States [1]. In a meta-analysis, return to work after stroke occurred in 56.7% of cases at 1 year and in 66.7% of cases at 2 years [1, 3].

Etiologically, ischemic stroke is caused by embolism from the heart, artery-to-artery embolism (atherosclerotic or carotid dissection), and in-situ small vessel disease. A third of ischemic strokes remain of undetermined cause of which a subgroup is now defined as having embolic strokes of undetermined source (ESUS) [4]. ESUS comprises about 1 ischemic stroke in 6. Patients with ischemic stroke meeting criteria for ESUS were relatively young compared with other ischemic stroke subtypes and had, on average, minor strokes, consistent with small emboli [5].

Clinical trials have shown that treatment of risk factor as hypertension, hypercholesterolemia, carotid stenosis and atrial fibrillation reduces the incidence of stroke [4,6–9]. Moreover, also smoking, alcohol abuse and diabetes mellitus are casual risk factor for stroke [4].

The overwhelming majority of strokes can be prevented through blood pressure control, a healthy diet, regular physical activity, and smoking cessation. In fact, blood pressure, diet, physical inactivity, smoking, and abdominal obesity accounted for 82% and 90% of the population-attributable risk for ischemic and hemorrhagic stroke in the INTERSTROKE study (Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries) [10,11].

Similarly, the Global Burden of Disease Study showed that 90.5% of

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the global burden of stroke was attributable to modifiable risk factors [11,12].

Other risk factor that, if modified, could reduce the incidence of stroke are environmental air pollution, childhood health circumstances, sleep-disordered breathing, chronic inflammation, chronic kidney disease, migraine, hormonal contraception or hormone replacement therapy, psychosocial stress, depression, job strain and long working hours [4,10,12]. There are also several genetic loci have been associated with ischemic stroke [4].

After ischemic stroke and transitory ischemic attack (TIA), the risk of recurrent stroke without treatment is about 10–15% and 18% respectively at 1 week, 1 month and 3 months. With urgent assessment and appropriate treatment, the risk of recurrent stroke is 80% lower. The longer-term risk of recurrent stroke is about 10–25% and 40% respectively at 1 year, 5 years and 10 years [13]. The risk is higher among individuals with vascular risk factor, symptomatic atherosclerotic disease or an active source of thrombosis. Also, patients who have discontinued antiplatelet and antihypertensive drugs had a higher risk of recurrent stroke [4].

2. Organization

Intravenous thrombolysis (IVT) and mechanical thrombectomy (MT) represent the standard of care in acute stroke patient with LVO [14]. The MT is available at comprehensive stroke center (CSCs) whereas the primary stroke centers (PSC) can administer only IVT [15]. Therefore, two main prehospital stroke systems of care have been developed: the mothership (MS), in which the patient is directly brought to the CSC, and the drip and ship (DS) model, where initially the patient is brought to the PSC to have diagnostic imaging and eventual administration of IVT followed by transport to the CSC. The choice of a model over another implies clinical consequences for treated patients as well as for local health policies, including the distribution of hospital facilities over the region of interest [15,16].

In the RACECAT (Direct Transfer to an Endovascular Center Compared to Transfer to the Closest Stroke Center in Acute Stroke Patients With Suspected Large Vessel Occlusion) clinical trial [17], there was no significant difference in 90-day neurological outcomes between patients transported to a local stroke center first vs directly to a thrombectomy-capable referral center in patients with suspected large-vessel occlusion acute ischemic stroke in nonurban areas in Catalonia, Spain.

Contrary to the RACECAT trial, previous large meta-analysis on organizational paradigm suggested a possible benefit of the MS model on 90-day functional outcome independence compared with DS [18,19]. Indeed interhospital transfer of patients with acute ischemic stroke is associated with delay of endovascular treatment and worse outcomes in routine clinical practice, even in a country where between center distances are short [18]. Rapid access to MT for patients with LVO is critically associated with their functional outcome [15].

A decision-analytic model based on data from the HERMES (Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke) trial meta-analysis found that MS strategy is favored by smaller difference between distances to PSC and CSC, shorter transfer time from PSC to CSC, and longer delay in reperfusion in CSC for transferred patients. DS is favored by the reverse [20].

One advantage of the DS model is the shorter interval of IVT administration from stroke onset as the PSC is the nearest center [15]. It is essential that a new protocol to expedite transportation is needed going forward to further improve patients' outcome within regional network [15]. A major challenge for the DS model is reducing the door-in-door-out time. Gaynor et al. [21] showed that key metrics significantly improved when the ambulance crew remained with the patient on arrival at the PSC waiting for the clinical and radiological evaluation to the transferred to the CSC.

Ongoing trials like PRESTOF [Prehospital Routage of Acute Stroke Patients With Suspected Large Vessel Occlusion: Mothership Versus Drip and Ship], SWIFT DIRECT [Bridging Thrombolysis Versus Direct Mechanical Thrombectomy in Acute Ischemic Stroke] and TRIAGE [Treatment Strategy in Acute Ischemic Large Vessel STROKE: Prioritize Thrombolysis or Endovascular Treatment] could add some insights in the future [15].

Time to reperfusion has been identified as the strongest predictor of clinical outcome [22] so one of the objectives, in the stroke treatment, is to reduce the door to puncture (DTP) time. Every ten-minute increase in the DTP time is associated with a 5% reduction in the likelihood of achieving functional independence at 90 days [23,24].

There are several factors that impact in DTP time. A simple approach for achieving substantial time savings is to mobilize the neuro-interventional and anesthesia teams during patient evaluation and treatment decision making [25].

Moreover, It has been demonstrated that the image to angiosuite arrival time represents both the longest and the most variable time interval in the intrahospital workflow [26] so, many recent studies, have evaluated whether bypassing the direct transfer to conventional imaging (DTCI) approach by implementing a direct transfer to angiosuite (DTAS) pathway would result in reduction of DTP times. Indeed, a meta-analysis showed that the DTAS approach resulted in reduction of time to reperfusion of approximately 33 min. It has been reported that the chances of good outcomes decrease on average by 10–15% for every 30-minute delay in reperfusion and, in the same meta-analysis, they showed that the DTAS paradigm seems to be associated with significant improvement functional outcomes with a comparable safety profile to the DTCI approach in the overall study population [26].

Another meta-analysis showed that patients undergoing the DTAS strategy had a significant reduction in door-to-puncture and door-to-reperfusion times. This resulted in an increased rate of early neurological and 90-day functional recovery without compromising safety in LVO patients undergoing endovascular thrombectomy [27].

These data are recently confirmed by a randomized clinical trial (ANGIOCAT - Evaluation of Direct Transfer to Angiography Suite vs. Computed Tomography Suite in Endovascular Treatment: Randomized Clinical Trial) [28]. It found that, for patients with LVO admitted within 6 h after symptom onset, compared with conventional workflow, the use of DTAS, increased the odds of patients undergoing EVT, decreased hospital workflow time, and improved clinical outcome [28]. Moreover, DTAS not only improves clinical outcome but also decreases the costs compared with the standard DTCT [29]. These happened because the improved clinical outcome is directly related with a decrease in costs for the hospital, mainly due to the decrease in costs of hospital stay, improved clinical outcome and fewer complications [29].

3. Diagnosis

Early stroke symptom recognition is essential for seeking timely care [14]. It is crucial improving large vessel occlusion stroke recognition and triage in the field. For example, the rapid arterial occlusion evaluation scale (RACE), designed based on the National Institutes of Health Stroke Scale (NIHSS), is a simple tool that can accurately assess stroke severity and identify patients with acute stroke with large artery occlusion at prehospital setting by medical emergency technicians [30].

In addition, mobile stroke units (MSUs) are specialized ambulances equipped with the personnel, equipment, and imaging capability to diagnose and treat acute stroke in the prehospital setting [31]. Recent trials [32,33] showed that treatment aboard MSUs was safe and led to improved functional outcomes in patients with stroke. Nevertheless, questions remain regarding the cost-effectiveness of MSUs, their utility in nonurban settings, and optimal infrastructure. Moreover, in much of the world, MSUs are currently not reimbursed by insurers nor accepted as standard care by regulatory bodies [31].

At the arrive at the hospital patient with stroke should have a careful clinical assessment, including neurological examination; the NIHSS may

be performed rapidly and, according to guideline, all patient with suspected acute stroke should receive brain imaging evaluation as quickly as possible [14].

The diagnosis of ischemic stroke can be made based on the clinical presentation and either a negative noncontrast CT (NCCT) or one showing early ischemic changes. NCCT is effective to exclude ICH [14]. MRI was as accurate as NCCT in detecting ICH [14].

In patients who awake with stroke or have unclear time of onset >4.5 h from baseline or last known well, MRI with DW-FLAIR can be useful for selecting those who can benefit from IV alteplase administration. Moreover, CT-angiography (CTA) with CT perfusion (CTP) or MR-angiography (MRA) with DW-MRI with or without MR perfusion is useful for selecting candidates for mechanical thrombectomy between 6 and 24 h after last known well [14]. Indeed, perfusion imaging, after 6 h of symptom onset, may identify the patients who are more likely to achieve favorable EVT outcomes based on infarct volume and mismatch profiles [34,35]. So, perfusion imaging profiles can predict the clinical response to mechanical thrombectomy [36].

A critical limitation for both ASPECTS and infarct volumes in treatment selection is that they do not account for tissue eloquence. The mismatch between the topographical assessment of patient's symptoms and the infarct visualized on imaging is likely the most pragmatic and reliable surrogate for penumbra and the optimal tool for an accurate decision-making [37].

In the early windows (within 6 h from symptoms onset) current guidelines discourage the utilization of advanced imaging to confirm EVT eligibility [14]. Indeed, time is more important than imaging [37] because generally patients with AIS, within 6 h, are fast progressor and the time is critical determinant of outcomes [37].

There was no significant interaction between any of the CTP-derived parameters and treatment effect, particularly, in the CTP cohort The Multicenter Randomized Clinical Trial of Endovascular.

Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN), there was no significant interaction between the volumes of infarct, penumbra, or mismatch and treatment effect [37,38]. Also in metanalysis conducted by the HERMES collaboration, mismatch volume, was not associated with either functional independence or functional improvement; estimated ischemic core volume was independently associated with functional independence and functional improvement but did not modify the treatment benefit of endovascular thrombectomy over standard medical therapy for improved functional outcome [39]. In the early window time to treatment is critical and trumps selection so we should "select faster, select less, and treat more". [37].

Recently Nguyen et al. [40]. showed that in patients undergoing proximal anterior circulation mechanical thrombectomy in the extended time window (from 6 h to 24 h), there were no significant differences in the clinical outcomes of patients selected with NCCT compared with those selected with CTP or MRI. These findings have the potential to widen the indication for treating patients in the extended window using a simpler and more widespread NCCT – only paradigm [26,40].

In a recent metanalysis patients with AIS treated with EVT in the late window (6–24 h) were evaluated with CTP or with NCCT only, there was no difference in recovery of functional independence in patients selected by CTP compared with patients selected by NCCT only [41].

In the past, most trials excluded patients with ASPECTS lower then 5 or with a core infarct volume larger then70 ml. A prospective randomized controlled trial [42] (Recovery by Endovascular Salvage for Cerebral Ultra-acute Embolism Japan Large IscheMIc core Trial - RESCUE-Japan LIMIT) showed that patients with ASPECTS between 3 and 5 within 6 h from onset or from 6 to 24 h since time last known well but without positive lesion on MRI-FLAIR image, had improved functional outcomes with endovascular treatment compared with standard medical management.

Moreover, the role of EVT for patients with acute large ischemic within 24 h has been studied in two recent trials (A Randomized Controlled Trial to Optimize Patient's Selection for Endovascular

Treatment in Acute Ischemic Stroke - SELECT2 and Endovascular Therapy in Acute Anterior Circulation Large VeSsel Occlusive Patients with a largE infarct core - ANGEL-ASPECT [43,44]. These trials showed that patients with low ASPECT or with a large core had better outcomes with endovascular therapy administered than with medical management alone. They evaluated patients with ASPECTS between 3 and 5 and large-core infarct (ANGEL-ASPECT, 70 – 100 ml, and SELECT2, $\geq$ 50 ml). Both trials were stopped early due to overwhelmingly improved outcomes with EVT [45]. These results may support extending the indication for thrombectomy to patients with a large ischemic core on baseline imaging [43] (Fig. 1).

4. Treatment

As healthcare providers our ethical duty is not only to the patients we decide to treat but rather to all patients we evaluate for a potential treatment [37].

IV-tPA was approved by the FDA for the treatment of AIS within 4,5 of symptom onset [14] Recently, the European Cooperative Acute Stroke Study (ECASS) IV [46] and Extending the Time for Thrombolysis in Emergency Neurological Deficits (EXTEND) [47] trials evaluated IV-tPA efficacy between the 4.5 and 9 h window in patients who were not EVT eligible and had a perfusion-to-diffusion mismatch ratio of >1.2. Moreover, the WAKE-UP trial [48] (Efficacy and Safety of MRI-based Thrombolysis in Wake-Up Stroke) randomized patients with AIS who awoke with stroke or had unclear time of onset > 4.5 h from last known well and all the patients had an ischemic lesion that was visible on MRI diffusion-weighted imaging but no parenchymal hyperintensity on FLAIR, which indicated that the stroke had occurred approximately within the previous 4.5 h. These patients had a better functional outcome at 90 days if intravenous alteplase was administered.

The EXTEND-IA TNK trial [49] (The Tenecteplase versus Alteplase before Endovascular Therapy for Ischemic Stroke) showed that Tenecteplase administration, within 4,5 h after symptoms ones, before EVT, resulted in improved revascularization and better outcome at 90 days compared with alteplase. Recently the randomized controlled trial TRACE 2 [50] (Tenecteplase versus Alteplase in Acute Ischaemic Cerebrovascular Events) showed that tenecteplase was non-inferior to alteplase in people with ischemic stroke who were eligible for standard intravenous thrombolytic but ineligible for or refused endovascular thrombectomy and also the trial. However, Tenecteplase is currently not approved from FDA for AIS [45].

In 2015, five randomized trials [51–55] [The Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MRCLEAN), Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke (ESCAPE), Endovascular Revascularization With Solitaire Device Versus Best Medical Therapy in Anterior Circulation Stroke Within 8 h (REVASCAT), Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment (SWIFT PRIME) and Extending the Time for Thrombolysis in Emergency Neurological Deficits Intra-Arterial (EXTEND IA)] showed efficacy of endovascular thrombectomy over standard medical care in patients with acute ischemic stroke caused by occlusion of arteries of the proximal anterior circulation (Table 1) [56].

EVT is well established as a highly effective treatment for AIS due to proximal large vessel occlusion (PLVO). Available population-based and large clinical registry studies suggest that PLVOs are the cause of approximately 35–40% of AIS; instead, acute distal medium vessel occlusions (DMVOs) are the cause of 25–40% of AIS [57,58]. Medium vessels were defined as A2/A3 of anterior cerebral artery, M2/M3 of middle cerebral artery, and P2/P3 posterior cerebral artery [45]. Recently thrombectomy for DMVOs has been declared a possible next frontier of endovascular stroke treatment [59]. A metanalysis showed that MT using aspiration or stent retriever techniques appears to be effective and safe in primary and secondary DMVOs [60]. Moreover,
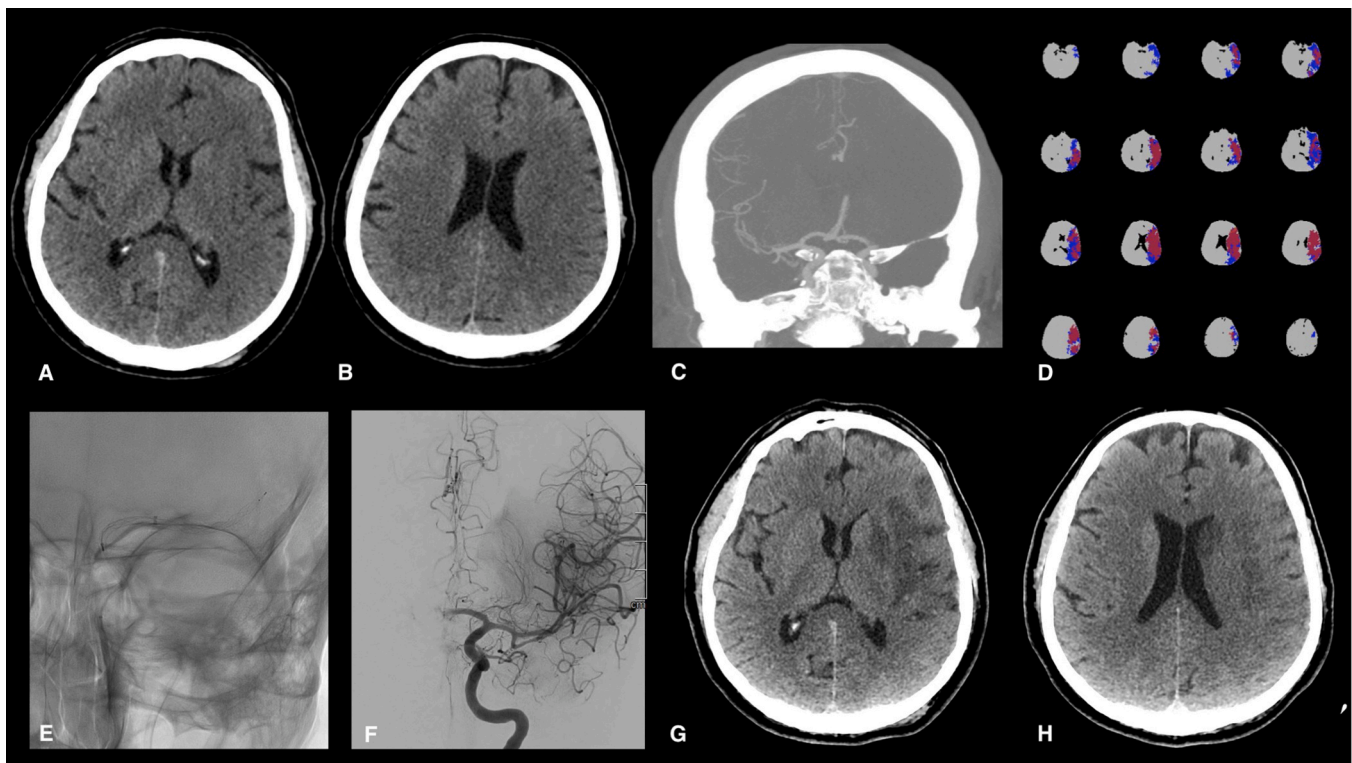
Figure 1. Patient, in his sixty, with acute ischemic stroke within 24 h, with a Glasgow Coma Scale of 8. CT brain scan (A – B) showed ASPECTS 5. CT angiogram (C) showed left M1 occlusion. CT perfusion with OLEA (D) showed core of 116.959 cc and penumbra of 201.632 cc (mismatch 1.72). Endovascular treatment was performed with combination technique and a complete recanalization was achieved after 1 pass (E – F). CT scan (G) after 24 h showed some ischemic lesions. At discharge, after 14 days, the NIHSS was 10.

there are smaller and more navigable stent retriever and thromboaspiration devices suggest EVT for DMVOs is safe and technically effective [59].

Posterior circulation LVOs may account for 7–12% of all intracranial LVOs in AIS [45]. The role of EVT in posterior circulation ischemic stroke was evaluated by two recent trials: BAOCHE [61] (Basilar Artery Occlusion Chinese Endovascular) and ATTENTION [62] (Endovascular Treatment For Acute Basilar Artery Occlusion) trials. The first one showed improved outcomes with EVT in posterior circulation stroke presenting between 6 and 24 h and the second one showed better outcomes at 90 days in patient with posterior ischemic stroke within 12 h after stroke onset. The TOPMOST (Treatment for Primary Medium Vessel Occlusion Stroke) study recently provided multicenter evidence for the feasibility of thrombectomy in posterior circulation DMVO stroke [63].

Fast and complete recanalization of the occluded vessel is associated with improved outcomes; the first pass effect (FPE) is defined as achieving a complete recanalization with a single thrombectomy device pass. Patients with FPE had a better clinical outcome, lower mortality, and fewer procedural adverse events [64]. Moreover, considering that FPE resulted in improved clinical outcomes, the healthcare resource use and estimated costs were lower [65].

Predictors of achieving first pass effect were the use of balloon guide catheter (BCG) [64]. A metanalysis showed that BCG use during mechanical thrombectomy for AIS is associated with superior clinical and angiographic outcomes [66].

The Contact Aspiration vs Stent Retriever for Successful Revascularization (ASTER) trial is a randomized trial comparing angiographic revascularization with the stent retriever and contact aspiration thrombectomy techniques showing that first-line thrombectomy with contact aspiration compared with stent retriever did not result in an increased successful revascularization rate at the end of the procedure [67]. The Direct Aspiration First Pass Technique (COMPASS) trial also showed that a direct aspiration as first pass thrombectomy conferred non-inferior functional outcome at 90 days compared with stent retriever first line thrombectomy [68]. In the ASTER trial FPE was associated with a significantly improved outcome and similar rates of FPE were achieved with stent retriever and contact aspiration [69].

The ASTER-2 trial showed that an initial thrombectomy technique consisting of contact aspiration and stent retriever combined, compared with stent retriever alone, did not significantly improve the rate of near-total or total reperfusion at the end of the endovascular procedure [70].

Moreover, also a retrospective analysis showed that the first-line thrombectomy with a combined technique did not result in increased rates of first-pass reperfusion or better clinical outcomes. Although significantly higher rates of successful reperfusion prior to any rescue strategies was achieved with the first-line stent-retriever and contact aspiration treatment, so, the addition of contact aspiration after initial stent-retriever failure might be beneficial in achieving earlier reperfusion [71].

Nevertheless, considering that no randomized controlled trial has simultaneously evaluated first-line stent retriever versus contact aspiration versus the combined approach, the best recanalization strategy for mechanical thrombectomy remains unknown [72]. Data analysis from the Endovascular Treatment in Ischemic Stroke (ETIS) Registry, a prospective, multicenter, observational study of patients with AIS treated by MT, showed that fist line combine technique was associated at high recanalization rates but with higher disability and mortality [72]. Randomized controlled trials are needed to evaluate the efficacy and safety of these techniques.

The management of AIS has changed in the past decade with contributions through improvements in thrombectomy devices, medical management, and stroke workflows. It is critical for the radiologist to stay abreast of the ongoing developments to provide meaningful input and remain a useful part of the stroke team [45].

Table 1

Major clinical trial regarding the endovascular treatment for acute ischemic stroke. Comparison between thrombectomy plus standard medical care vs medical care alone.

Clinical trial	Number of patient	Time criteria (h)	NIHSS	Imaging criteria	Functional independence at 90 days	sICH	Mortality
MR CLEAN [51]	500	0–6 h since time last known well	NIHSSS ≥ 2	-distal ICA or M1/M2 or A1/A1 occlusion	32.6% vs 19.1% (AOR, 2.16, 95% CI,1.39–3.38)	7.7% vs 6.45%	18.9% vs 18.4%
REVASCAT [54]	206	0–8 h since time last known well	NIHSSS ≥ 6	Distal ICA or M1 occlusion or proximal ICA and M1 occlusion	43.7% vs. 28.2%; (AOR, 2.1; 95% CI, 1.1–4.0)	1.9% vs 1.9% (P = 1.00)	18.4% vs 15.5%
ESCAPE[52]	316	0–12 h since time last known well	NIHSS > 5	-M1 occlusion or M1 occlusion and terminal ICA occlusion -ASPECTS 6–10	53.0%, vs. 29.3% (RR, 1.8; 95% CI, 1.4–2.4; P < 0.001)	3.6% vs 2.7% (RR, 1.4; 95% CI, 0.4–4.7; P = 0.75)	10.4% vs 19% (RR, 0.5; 95% CI, 0.3–1.0; P = 0.04)
SWIFT-PRIME[53]	196	0–6 h since time last known well	NIHSS 8–29	Intracranial ICA and/or M1 occlusion	60% vs 35% (RR, 1.7; 95% CI, 1.23–2.33; P < .001)	0% vs 3% (P = 0.12)	9% vs 12% (P = 0.50)
EXTEND-IA [55]	70	0–4.5 h since time last known well	NIHSS 0–42	ICA or M1/M2 occlusion	71% vs 40% (P = 0.01)	0% vs 6% (P = 0.49)	9% vs 20% (P = 0.18)
DAWN[35]	206	6–24 h since time last known well	NIHSSS ≥ 10 or NIHSS≥ 20 depending on the age and infarct core volume	-distal ICA and or M1 occlusion -age< 80 years and NIHSS ≥ 10 and infarct core volume 0–30 ml; age < 80 years and NIHSS≥ 20 and infarct core volume 31–51 ml; age≥ 80 and NIHSS score ≥ 10 and infarct core volume 0–20 ml	49% vs 13% (aDiff 33 pp; 95% CrI, 24–44; posterior probability of superiority, >0.999)	6% vs 3% (P = 0.50)	19% vs 18% (P = 1.00)
DEFUSE3[34]	182	6–16 h since time last known well	NIHSSS ≥ 6	-cervical or intracranial ICA or M1. -infarct core volume < 70 and mismatch volume > 15 ml and mismatch ratio> 1.8	45% vs 17% (RR, 2.67; 95% CI, 1.60–4.48; P < 0.001)	7% vs 4% (P = 0.75)	14% vs 26% (P = 0.05)
BAOCHE[61]	217	6–24 h since time last known well	NIHSSS ≥ 6	-Basilar artery occlusion or both intracranial verterbal artery occlusion. -PC-ASPECTS ≥ 6	46% vs 24% (aRR, 1.81; 95% CI, 1.26–2.60, P < 0.001)	6% vs. 1%; (RR 5.18; 95% CI, 0.64–42.18)	31% vs 42% (aRR, 0.75; 95% CI, 0.54–1.04)
ATTENTION [62]	340	0–12 h since time last known well	NIHSSS ≥ 10	-Basilar artery occlusion -PC ASPECTS ≥ 6 (for patient < 80 years old; ≥ 8 for patient ≥ 80 years old.	46% vs 23% (aRR, 2.06; 95% CI, 1.46–2.91, P < 0.001)	5% VS 0% (aRR no estimate)	37% vs 55% (aRR 0.66; 95% CI 0.52–0.82)
RESCUE Japan LIMIT[42]	203	0–6 h since time last known well or 6–24 h since time last known well without positive lesion on MRI-FLAIR image	NIHSSS ≥ 6	ICA or M1 occlusion -ASPECT 3–5 and if from 6 h to 24 h since time last know well, no positive lesion on MRI-FLAIR image	31.0% vs 12.7% (RR 2.43; 95% CI, 1.35–4.37; P = 0.002)	9.0% vs 4.9% (P = 0.25)	18.0% vs 23.5% (P = 0.33)
SELECT 2[43]	352	0–24 h since time last known well	NIHSSS ≥ 6	Cervical or intracranial ICA or M1. -ASPECT 3–5 or infarct core volume ≥ 50 ml	20.3% vs 7.0% (RR 2.97; 95% CI, 1.60–5.51)	0.6% vs 1.1% (RR 0.49; 95% CI, 0.04–5.36)	38.4% vs 41.5% (RR 0.91; 95%CI, 0.71–1.18)
ANGEL ASPECT [44]	456	0–24 h since time last known well	NIHSS 6–30	Terminal ICA and/or M1 -ASPECT 3–5 Or ASPECT 0–2 and infarct core volume 70–100 ml or ASPECTS> 5 and infarct core volume 70–100 ml.	30% vs 11.6% (RR 2.62; 95% CI, 1.69–4.06)	6.1% vs 2.7% (P = 0.12)	21.7% vs 20.0% (P = 0.99)

Abbreviation: aDiff = adjusted difference, AOR = adjusted odd ratio, aRR = adjusted risk ratio, CI = confidence interval, CrI = credible interval, ICA = internal carotid artery, NIHSS = national institutes of health stroke scale, pp = percentage point, RR = risk ratio.

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Renieri Leonardo: Writing – review & editing, Visualization, Validation, Conceptualization. **Capirossi Carolina:** Writing – review & editing, Writing – original draft, Conceptualization. **Laiso Antonio:** Writing – original draft, Visualization, Validation. **Capasso Francesco:** Visualization, Validation, Conceptualization. **Limbucci Nicola:** Writing – review & editing, Visualization, Validation, Supervision, Data curation, Conceptualization.

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