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Updates in Management of Large Hemispheric Infarct

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Abstract

This review delves into updates in management of large hemispheric infarction (LHI), a condition affecting up to 10% of patients with supratentorial strokes. While traditional management paradigms have endured, recent strides in research have revolutionized the approach to acute therapies, monitoring, and treatment. Notably, advancements in triage methodologies and the application of both pharmacological and mechanical abortive procedures have reshaped the acute care trajectory for patients with LHI. Moreover, ongoing endeavors have sought to refine strategies for the optimal surveillance and mitigation of complications, notably space-occupying mass effect, which can ensue in the aftermath of LHI. By amalgamating contemporary guidelines with cutting-edge clinical trial findings, this review offers a comprehensive exploration of the current landscape of acute and ongoing patient care for LHI, illuminating the evolving strategies that underpin effective management in this critical clinical domain.

Keywords

cerebral edema; ischemic stroke; space-occupying mass effect; thrombectomy

Large hemispheric infarction (LHI) affects up to 10% of patients with supratentorial strokes, often from occlusions in the middle cerebral or internal carotid arteries.[1] While certain management practices for LHI have remained consistent over decades, recent breakthroughs have significantly impacted prevention, monitoring, and treatment. Our review will discuss

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Conflict of Interest

None declared.

current strategies for acute and ongoing patient care, integrating the latest guidelines and clinical trial findings.

Initial Triage

There have been several clarifications to the most immediate management strategies for LHI. Rapid transfer to facilities equipped for mechanical thrombectomy (MT) is encouraged, although uncertainty remains regarding the benefits of bypassing closer centers capable of administering intravenous (IV) thrombolytics without MT capabilities.[2]

The American Heart Association/American Stroke Association (AHA/ASA) also recommended simpler imaging protocols. The latest guidelines specified that for patients without renal disease history, pre-computed tomography (CT) angiography creatinine testing is unnecessary,[2] preventing delays in acute care. Additionally, they endorsed using magnetic resonance imaging (MRI) to pinpoint stroke timing in wake-up cases, referencing the WAKE-UP trial's fluid-attenuated inversion recovery (FLAIR)-negative lesion findings to determine thrombolysis suitability.[3]

The AHA/ASA guidelines further clarified that IV fibrinolytics is reasonable in patients with cerebral microbleeds (CMB), especially those with fewer than 10.[2] For those with greater than 10 known CMBs, the panel acknowledges that these patients may be at increased risk for symptomatic intracranial hemorrhage, but in the absence of direct evidence that fibrinolytics are of no benefit or do more harm in patients with CMBs, they state that the benefits might outweigh the risks.

Intravenous Thrombolytic Therapy

The efficacy of IV thrombolysis with rt-plasminogen activator (tPA) was first established by the National Institute of Neurological Disorders and Stroke trial in 1995, showing benefit in those treated within 3 hours of stroke onset.[4] The European Cooperative Acute Stroke Study III trial[5] expanded the eligibility for treatment to a maximum of 4.5 hours after stroke onset. This extended time window applies to nondiabetic patients less than 80 years old without prior history of stroke who have a National Institutes of Health Stroke Scale (NIHSS) ≤ 25 and are not on anticoagulation. Although further efforts to extend the treatment window for IV thrombolytic agents have shown some success in carefully selected patients, the extension beyond 4.5 hours has neither been endorsed by guidelines nor adopted widely in practice.[6] Because unknown onset time is a significant factor leading to ineligibility, the WAKE-UP and MR WITNESS trials used diffusion-weighted image (DWI)-FLAIR mismatch on MRI (DWI positive, FLAIR negative) to infer that stroke onset was within treatable limits,[3,7] further expanding the population potentially eligible for thrombolytic therapy.

The Alteplase Compared with Tenecteplase in Patients With Acute Ischemic Stroke Trial (AcT) recently demonstrated the noninferiority of tenecteplase (TNK) to alteplase in a large (N = 1,600) phase III study.[8] TNK is a modified version of tPA with four amino acid changes that increase the fibrin specificity and half-life, which allows single bolus injection without a follow-up infusion, resulting in a more rapid administration, which might lead

to more efficient thrombolysis with lower hemorrhage risk. The increasing body of work supporting the benefits of TNK have led many centers to shift to TNK as the thrombolytic agent of choice for stroke. Further trials comparing TNK to alteplase are in progress. Eligibility windows for TNK are similar to tPA and support its use in those eligible for MT.[2] It is important to note that only 25% of patients arrive to acute care hospitals at these early time windows.[9] This means that the majority of stroke patients, including those with LHI, are ineligible for IV thrombolysis, whether with tPA or TNK. Over the last decade, the acute management strategies to achieve mechanical clot retrieval have made the largest impact in reversing potential LHI injury, even at later presenting time points.

Mechanical Thrombectomy

Because many patients with proximal large artery occlusions do not respond to IV thrombolysis, efforts have been made to treat such arterial occlusions more directly with intra-arterial thrombolytic agents or with direct mechanical clot extraction.

The first successful trial of intra-arterial therapy used direct chemical thrombolysis without mechanical manipulation of the clot.[10] This approach was rapidly superseded in practice by attempts to snare and extract thrombi directly. Such therapies, often in combination with intra-arterial thrombolytic agents, were practiced for many years with variable success. The first wave of rigorous trials published in 2013 failed to demonstrate clear benefit of MT.[11-13] Improvements in patient selection, randomization processes, and enhanced devices such as stent retrievers and suction techniques led to a second wave of studies conclusively showing a significant benefit of timely MT for patients with embolic occlusions in the proximal middle cerebral artery and terminal internal carotid artery.[14-21] In the HERMES meta-analysis,[18] the adjusted odds ratio (OR) for good outcome was 2.49; the absolute benefit for modified Rankin Score (mRS) 0 to 2 was 19.5%. The number needed to treat for one patient to have reduced disability of 1 point on the mRS was 2.6. These stunning results led to subsequent recommendations regarding stroke therapy with current guidelines supporting urgent MT for all adults (≥18 years) with prestroke mRS 0 to 1 who present with proximal anterior circulation occlusion presenting in time for treatment within 6 hours of stroke onset, who have NIHSS ≥ 6, and no large established stroke on initial imaging defined as Alberta Stroke Program Early CT Score (ASPECTS) score ≥ 6.[2]

Recent studies aim to expand who is eligible for MT. The DAWN and DEFUSE 3 trials identified patients with neurological deficits out of proportion to the degree of established stroke seen on imaging (clinical imaging mismatch in DAWN and MRI or CT perfusion mismatch in DEFUSE 3), finding a benefitofMT using their criteria up to 24 hours (DAWN) or 16 hours (DEFUSE 3) poststroke onset.[22,23] It is hard to overstate the impact of extending the stroke time window. While patients who present later are undoubtedly at increased risk for subsequent complications and morbidity compared with those who present hyperacutely, the evidence supporting improved outcomes suggests that the incidence of LHI can be even further decreased with appropriate care pathways.

Recent trials consistently show that patients with larger, established strokes on presentation defined as ASPECTS 3 to 5, also have better outcomes with MT.[24-27] The SELECT2

trial compared MT versus best medical therapy in patients with internal carotid artery or proximal middle cerebral artery occlusion and a large core infarct, defined as ASPECTS 3 to 5 or core infarct ≥ 50 mm^3 on CT perfusion or DWI imaging, treated within 24 hours of stroke onset.[26] At 90 days, patients treated with MT had lower mRS scores (4 vs. 5) and a higher rate of functional independence (20.3 vs. 7.0%).[26] This improvement in outcomes was sustained after 1 year of follow-up (International Stroke Conference 2024 Phoenix, February 9, 2024). As devices for MT are continually refined, further studies are underway to broaden the population that might benefit from MT, including ongoing trials of patients with more distal occlusions of the middle, anterior, and posterior cerebral arteries.

Finally, based on the poor prognosis of basilar artery occlusion, it is widely thought that MT will benefit patients with posterior circulation lesions as well. While it is not the primary subject of this review, large posterior circulation infarcts are similarly prone to edema, profound morbidity, and mortality. Rigorous study of thrombectomy used for basilar artery occlusion has yielded mixed results, but the most recent studies do suggest benefit, albeit with a risk of procedural complications and hemorrhage.[28-31]

Space-Occupying Mass Effect following of Large Hemispheric Infarction

Patients with LHI are unique among stroke patients because they are at risk for life-threatening, space-occupying mass effect resulting from either cerebral edema and/or hemorrhagic transformation due to their initial infarct. Because subsequent mass effect has both high mortality and morbidity,[32] society guidelines including the AHA/ASA and European Stroke Organization (ESO) have increasingly reinforced the critical nature of expeditious discussions regarding care options, ascertaining patient-centered preferences, and communication about possible outcomes including the high risk of survival with substantial disability.[2,33] Current research focuses on the use of decision aids to help surrogates and patients make decisions based on their values.[34,35] These tools are increasingly acknowledged as crucial for establishing realistic expectations about long-term outcomes and minimizing family distress (►Tables 1 and 2).[36]

Prompt identification of patients at risk of developing space-occupying mass effect is necessary to effectively triage them and monitor progression. Risk scores using information at baseline or within the first 24 hours of admission have been shown to be helpful in predicting malignant courses.[37-42] However, a recent systematic review revealed that most existing models risk overfitting or use advanced imaging variables that may not be available at all centers.[43] Future directions in this area include machine learning-derived prognostic models using many features available from the electronic medical record and dynamic models that update prognostications with new information.

However, incorporating new data into risk prediction models requires the initial step of identifying promising novel biomarkers. A persistent challenge within the field remains how to best identify clinical deterioration in the LHI patient population. Clinicians are advised to monitor for ipsilateral pupillary dysfunction, mydriasis, adduction paralysis, worsening limb power, or decreased arousal levels.[44] However, as patient exams may be confounded

by sedation, infection, fever, or metabolic abnormalities, investigation of other noninvasive monitoring modalities and biomarkers remains a priority.

Potential Quantitative Biomarkers

Radiographic imaging with either head CT or MRI are some of the most frequently used tools to identify or confirm mass effect progression. Nevertheless, the optimal frequency of radiographic surveillance (every 12, 24, 36 hours or only in response to clinical deterioration) is unknown and varies among providers. Several groups have investigated whether following quantitative neuroimaging biomarkers may assist in the early identification of developing cerebral edema.[45]

Midline shift, often measured at the septum pellucidum or foramen of Monro is a measure of lateral displacement due to edema or hemorrhage (►Fig. 1).[46] Previous studies have shown that early midline shift ≥ 5 mm is associated with malignant edema[44] and increasing shift has been shown to increase the probability of decompressive hemicraniectomy (DHC) or death.[41] Recent work suggests that the previously used measure of 5 mm may miss clinically relevant “milder” shifts that nevertheless affect outcome.[47] From a study of 1,977 patients, it was observed that midline shift as low as 3 mm was associated with worse outcome when compared with patients with lower or no midline shift.[47]

Pineal gland shift (►Fig. 1) is less commonly used but has been associated with decreased arousal in case series of patients with malignant edema.[48] Pilot studies measuring pineal gland shift in patients with LHI were underpowered to detect an effect but found a signal that it was associated with a larger difference in quantitative pupil reactivity between eyes, signifying a possible asymmetric effect on the ipsilateral third nerve and/or midbrain.[46]

More recently, investigators have sought to validate potential quantitative neuroimaging targets include decreasing cerebrospinal fluid (CSF) volume and increasing net water uptake (NWU).[49,50] After stroke as cerebral edema develops, there is a reduction in the volume of CSF due to compression of the ventricles and subarachnoid spaces. Measuring the changes in CSF volume can indicate the extent of cerebral edema. Quantitative analysis of CSF volume changes can be achieved through software that processes and segments imaging data, providing objective and reproducible measures. One study found that the rate of CSF volume reduction within the first 24 hours could be an early biomarker for the development of midline shift and worse neurological outcomes.[50]

NWU can be inferred from changes in the attenuation coefficient or directly visualized on MRI DWI sequences and reflects the extent of water uptake in the brain.[51] In a post hoc analysis of 81 patients from the GAMES-RP Trial, it was shown that NWU on the admission CT scans was higher in patients who later developed malignant edema compared with those who did not and was an independent predictor for malignant edema after adjusting for baseline midline shift.[52]

To determine whether different radiographic biomarkers predict edema endpoints, one study compared several radiographic biomarkers including change in global CSF volume, the ratio of CSF volumes between hemispheres, and NWU. The authors concluded that CSF

volumetric biomarkers could be automatically measured from almost all routine CTs and correlated better with standard edema endpoints than NWU.[51] While CSF and NWU are not yet standardly available or used in clinical practice, improved imaging processing and segmentation technology may make these measurements more widely available in the future.

In addition to radiographic markers, there are several important adjunctive bedside monitoring techniques that can assist clinicians in monitoring edema progression. There is recent work on evaluating dynamic risk models, including vital signs, laboratory tests, and radiographic biomarkers, as predictors of life-threatening mass effect.[53] Evidence supports that quantitative pupillometry is prognostic of 6-month functional outcome in patients with acute brain injury including those with large ischemic stroke.[54] Current work is ongoing regarding pupil reactivity's correlation with developing space-occupying mass effect in LHI. Optic nerve sheath diameter is another noninvasive bedside tool used to detect elevations in intracranial pressure (ICP), although there are issues with interrater variability[55] and differences in normative values between men and women.[56] Serum markers including endothelin-1,[57] matrix metalloproteinase-9 (MMP-9),[58] and soluble serum stimulation-2[59] have been associated with edema but are not available for routine clinical use. ICP monitoring is not recommended on the basis that clinical deterioration and outcomes cannot be reliably predicted.[33]

Medical Management

Pharmaceutical management including osmotic therapy such as mannitol (dosing ranges from 0.5 to 1.5 g/kg) and hypertonic saline (HTS) (in 1.5, 3, 7.5, and 23% forms) have been mainstays of cerebral edema treatment for decades. The AHA/ASA, Neurocritical Care Society (NCS), and ESO have all stated that osmotic therapy for patients with clinical deterioration from cerebral swelling associated with infarction is reasonable,[2,33,60] but experts caution that there is insufficient evidence to recommend either agent for improving neurological outcomes.[60] No study has definitively determined that one osmotic strategy is superior to another. However, there is low- to moderate-quality evidence suggesting that clinicians can consider administration of HTS solutions for management of elevated ICP or cerebral edema who do not have an adequate response to mannitol.[60] The NCS's recommendation was based on two older prospective, randomized studies that appeared to demonstrate that the reduction in ICP from HTS was quicker, more pronounced, and more sustained compared with mannitol[61,62] and two studies that suggested that HTS may be effective even in patients in whom mannitol has failed.[62,63] There is insufficient evidence to suggest that continuous infusion of HTS versus a bolus strategy improves outcomes—the two studies investigating dosing regimens had conflicting results.[64,65] The NCS suggested against the use of prophylactic scheduled mannitol due to potential harm (low-quality evidence).[60]

To avoid adverse effects of mannitol, the NCS conditionally recommended using osmolar gap over serum osmolarity to limit dosing frequency with very low-quality evidence. Their recommendation was based on a physiological rationale that osmolar gap appears to correlate best with mannitol concentration in conjunction with the fact that elevated mannitol concentration is most associated with toxicity. They did not feel that there

was sufficient evidence to recommend a cutoff at which to hold further therapy but acknowledged that some clinicians use an osmolar gap of 20 mOsm/kg. The panel suggested that recent studies have shown that an osmolarity threshold of greater than 320 mOsm/L does not affect the incidence of acute kidney injury (AKI).[66] The incidence of AKI is estimated at 6 to 12% of patients treated with mannitol.[67] In regard to HTS-related toxicity, the panel conditionally recommended an upper serum sodium range of 155 to 160mEq/L and a serum chloride range of 110 to 115 mEq/L to decrease the risk of AKI based on the association between hypernatremia, hyperchloremia, and AKI.[60]

Recent society guidelines continue to recommend non-pharmacological strategies for reducing ICP, such as elevating the head of the bed to 30 degrees[44,60] and employing temporary, controlled hyperventilation.[60] However, hypothermia, barbiturates, and corticosteroids are not recommended due to their increased risk of harm.[44] Most societies agree that there is a need for higher quality of evidence to effectively guide medical management of cerebral edema following LHI. However, the scarcity of prospective, high-quality studies may be attributed to the large sample sizes required to show potential benefits, the associated financial costs, and deep-rooted convictions about certain medications and workflows by providers. Moreover, there have been few promising new pharmaceutical or procedural targets aimed at reducing secondary inflammation and swelling following stroke.

However, there has been growing enthusiasm surrounding glyburide, also known as glibenclamide, a second-generation sulfonylurea medication that blocks sulfonylurea receptor 1 (Sur1). Glyburide was previously used to target K_{ATP} (Sur1–Kir6.2) channels for the treatment of diabetes mellitus type 2. It was repurposed to target Sur1-transient receptor potential melastatin 4 (TRPM4) channels in acute central nervous system injury as a potential edema-reducing agent.[68]

Results of the GAMEStrial suggested that glyburide reduced midline shift, MMP-9, and potentially improved functional outcome and mortality.[69] CHARM (NCT02864953), a phase-3 Biogen sponsored study to evaluate the efficacy and safety of IV glibenclamide for severe cerebral edema following LHI has enrolled 537 subjects and was recently completed early due operational and strategic considerations. Undoubtedly, we will learn more about glibenclamide's potential role in management of space-occupying edema following LHI from the trial. Until then, societies such as the ESO stated as of 2021 that they did not have sufficient evidence to recommend glyburide as a measure to treat cerebral edema.[33]

Surgical Management

DHC within 48 hours of stroke remains the management strategy with the highest quality of evidence to reduce mortality and increase the chance of favorable outcome in LHI patients ≤ 60 years of age. The recommendation is consistent between the AHA/ASA and ESO[2,33] and is primarily based on a pooled analysis of three prospective randomized controlled trials conducted between 2007 and 2009.[70-72] The ESO further reinforced that in an individual patient data meta-analysis of randomized trials, there was no difference in benefit of DHC with regard to mortality or functional outcome in patients with and without

aphasia. The results suggest that quality of life does not appear to depend on the ability to speak, reinforcing that infarct location should not unduly bias practitioners against offering surgery.[73-75] However, controversy persists regarding the benefit of DHC in patients who (1) are 61 or older; (2) deteriorate 48 hours after stroke onset; or (3) experience concurrent symptomatic hemorrhagic transformation.

The AHA/ASA's most recent recommendation in 2019 was that DHC can be considered on a case-by-case basis in patients older than 60 years of age who experience clinical deterioration within 48 hours. They based their guidance on the mortality reduction of approximately 50% seen in the DESTINY trial.[71] A meta-analysis conducted in 2021[75] found that 0 to 12.5% of patients older than 60 years reached a favorable outcome (mRS ≤ 3) based on four primary trials from the past 15 years.[70,72,76,77] That same meta-analysis cited the DEMITUR trial, which intriguingly reported favorable outcome in 66% of patients. However, that study was later withdrawn. Overall, the data support that older patients are highly likely to be extremely dependent in their activities of living if they do survive after DC. The guidelines strongly recommend that an accurate understanding of the extent of likely disability should be conveyed to patients and families when making decisions regarding treatment.

Despite the clear benefit conferred within 48 hours of stroke, there is still uncertainty regarding the optimal timing of and trigger for surgery. Because cerebral edema typically occurs between 2 and 5 days,[44] evidence-based recommendations that recommend surgery for neurological decline within 48 hours do not apply to most patients who experience malignant edema. The ESO recommended that surgical decompression should be considered on a case-by-case basis later than 48 hours based on clinical grounds if death due to herniation appeared likely.[33]

Finally, the ESO also acknowledged there are no data or subgroup analysis of patients with concurrent hemorrhagic transformation. The guidelines make no determination regarding benefit of DHC in these patients.[33] Further investigation into more specific phenotyping of patients with and without concurrent hemorrhage, and those who swell earlier rather than later in their hospitalization are necessary to better understand how to manage these subgroups.

Additional Supportive Management

In addition to monitoring and management of space-occupying mass effect, there have also been several salient updates to supportive care, including blood pressure targets, anticoagulation initiation, complication prevention, and tracheostomy strategies in those recovering from LHI.

The 2019 AHA/ASA guideline indicates that early treatment of hypertension is indicated when required by comorbid conditions (concomitant acute coronary stent, acute heart failure, aortic dissection, intracranial hemorrhage, or preeclampsia). The panel suggested that initial blood pressure reduction of 15% was a reasonable goal while maintaining blood pressure ≥ 180/105 during and for first 24 hours after stroke.[2] The authors went on to

clarify that hypotension and hypovolemia should also be corrected, with either colloids or crystalloids, to maintain systemic perfusion levels necessary to support organ function.[2] Experts favor controlling blood pressure more strictly after MT. Both ESCAPE and DAWN protocols recommended controlling blood pressure (DAWN recommended systolic blood pressure [SBP] < 140 mm Hg) once reperfusion was achieved.[17,23] Despite the overall movement toward more aggressive blood pressure control, guidelines cite insufficient evidence to recommend a particular method or blood pressure lowering agent.

Newer data also suggest that direct oral anticoagulants (DOACs) may be safely started earlier in patients who need therapeutic anticoagulation for secondary stroke prevention.[78] The official guidance from the ESO and AHA/ASA recommends delaying anticoagulation for up to 14 days poststroke, depending on infarct severity and the risk of hemorrhagic conversion.[2,33] The ELAN trial, which initiated DOACs for major stroke on day 6 or 7 rather than days 12 to 14, found that patients in the earlier initiation arm had significantly less recurrent ischemic stroke, systemic embolism, major extracranial bleeding, symptomatic intracranial hemorrhage, or vascular death within 30 days compared with those randomized to standard care.[78] However, intracranial hemorrhage incidence in the major stroke subgroup was not reported. The TIMING trial similarly found improved outcomes in randomized patients receiving anticoagulation in ≤4 versus 5 to 10 days, but their study population skewed to patients with milder stroke severity. Moreover, the authors conceded that there may be an increased risk of hemorrhage in the early initiation subgroup if the initial NIHSS was greater than 15.[79] The ongoing OPTIMAS trial may provide further information on efficacy and complications of early anticoagulation, although it does not specifically focus on patients with LHI.[80] Further post hoc analyses of LHI subgroups will be necessary to better understand risks and benefits.

There are several other supportive measures worth remarking on. The AHA/ASA recommends intermittent pneumatic compression in addition to routine care to reduce the risk of deep vein thrombosis in immobile stroke patients, based on the 2015 multicenter trial CLOTS 3.[81] There was also a stronger emphasis that enteral diets should be started within 7 days.[2] For patients with LHI who are affected with dysphagia, it is reasonable to introduce a nasogastric tube within the first 7 days and to place a percutaneous gastric tube in patients with longer anticipated persistent inability to swallow.[2]

Finally, regarding long-term supportive measures, the SETPOINT2 trial[82] investigated whether patients with severe acute ischemic or hemorrhagic stroke receiving invasive ventilation assigned to early tracheostomy (≤5 days of intubation) had better outcomes than those receiving standard ventilator weaning with tracheostomy if needed from day 10. They found no significant difference in rate of survival without severe disability at 6 months. Nevertheless, the authors stated that a wide confidence interval around the effect estimate may include a clinically important difference, so that an effect of early tracheostomy could not be excluded.[82]

Future Directions

While the advances of last 10 years have unequivocally changed the landscape of LHI, particularly in preventing irreversible injury secondary to ischemia, further work is necessary to (1) understand how to decrease disparities in access and utilization of care that arise along gender, age, racial/ethnic, and socioeconomic lines, (2) identify noninvasive monitoring methods and workflows that improve patient selection for therapies, and (3) better understand how much and in whom pharmaceutical therapies (existing and potential new ones) benefit patients. Concomitantly, continued efforts in the field of neurorehabilitation can help patients who have survived LHI to achieve their maximal level of recovery.

Conclusion

The field of stroke has undergone transformative changes that will save lives and improve functionality for patients presenting with LHI. The increasing use of MT and expanded eligibility will likely reduce the incidence of patients with irreversible severe injury. However, continued work on management strategies to recognize and reduce the development of fulminant space-occupying edema remains necessary. The increasing recognition and clarification of persistent knowledge gaps has inspired investigation of promising monitoring and therapeutic targets. With continued dedication and perseverance, we can further optimize care for these critically ill patients.

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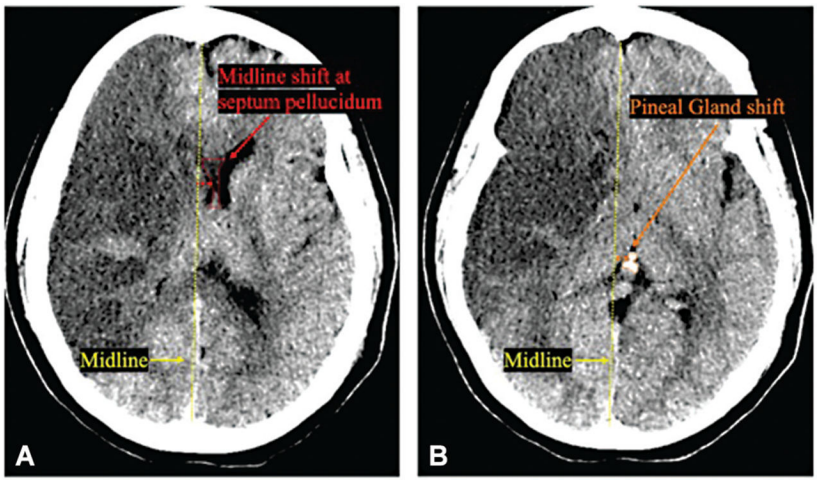

Fig. 1.

Midline shift at septum pellucidum and pineal gland shift on non-contrast CT scans. (A) Midline shift (red line) at the level of septum pellucidum (red dotted line). (B) Pineal gland shift (orange line) at the level of pineal gland (orange dotted line) have been associated with worsened outcome and arousal in large hemispheric infarction.

Table 1

Large hemispheric infarct management: endovascular treatment

Trials (chronological)	Patient sample and intervention	Major findings	Reported limitations
Intravenous (IV) rt-plasminogen activator (tPA)			
National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group (1995)[4]	Part 1: • 291 patients (n = 144 t-PA group vs. n = 147 placebo group. • Assessed clinical outcome of t-PA within 24 h of the onset of stroke Part 2: • 333 patients (n = 168 t-PA group vs. n = 165 placebo group). • Assessed clinical outcome at 3 mo	Part 1: • No significant difference between the patients in the t-PA group and the patients given placebo • Benefit was observed for the t-PA group at 3 mo for all four outcome measures Part 2: • Patients treated with t-PA were at least 30% more likely to have minimal or no disability at 3 mo compared with patients in placebo group • Symptomatic ICH within 36 h after stroke onset occurred in 6.4% of patients treated with t-PA and in 0.6% of patients given placebo (p = 0.001) • Mortality at 3 mo was 17% in the t-PA group and 21% in the placebo group (p = 0.30)	• Some patients with transient ischemic attacks whose symptoms rapidly improved were enrolled • A small percentage (2%) of patients who received a placebo showed no neurological deficits after 24 h based on NIHSS, which is unlikely to be attributed to the t-PA treatment
Hacke et al (2008)[5]	• 821 patients (418 alteplase group vs. 403 placebo) and were able to receive the study drug within 3–4h after onset	• Alteplase had more favorable outcomes than (52.4 vs. 45.2%; OR, 1.34; 95% CI, 1.02–1.76; p = 0.04) • The incidence of ICrH was higher with alteplase than with placebo for any ICrH (27.0 vs. 17.6%; p = 0.001) and for symptomatic ICrH (2.4 vs. 0.2%; p = 0.008) • Mortality did not differ between groups (7.7 and 8.4%, respectively; p = 0.68)	• Modification of the ECASS criteria for hemorrhage could have led to lower incidence of ICH in the alteplase treated • Mortality rate (8%) was lower than previous trials, probably due to inclusion of patients with less severe strokes
Schwamm et al (2018)[7]	• 80 patients were enrolled who were between 4.5 and 24 h since last known well and could receive be treated with alteplase (0.9 mg/kg) within 4.5 h of symptom discovery	• At 90 d, 39% of subjects achieved mRS 0–1 compared with 48% of patients with imaging confirming no LVO • IV thrombolysis within 4.5 h of symptom discovery in patients with unwitnessed stroke selected by DWI-FLAIR MRI mismatch, who are beyond the recommended time windows, is safe	• Small sample size • No pre- and posttreatment angiography, limiting data on recanalization rates • No perfusion imaging to assess potential candidates for late time window MT
Ma et al (2019)[6]	• 225 patients (113 alteplase group vs. 112 placebo group) between 4.5 and 9.0 h after the onset compared the proportion of patients that scored of 0 or 1 on the mRS at 90 d	• At 90 d, 40 patients (35.4%) in the alteplase group had mRS 0–1 vs. 33 patients (29.5%) in the placebo group (adjusted RR, 1.44; 95% CI, 1.01–2.06; p = 0.04)	• The study was stopped early • The “door-to-needle time” 2 h longer than recommend

Trials (chronological)	Patient sample and intervention	Major findings	Reported limitations
		• ICH occurred in 7 patients (6.2%) in the alteplase group and in 1 patient (0.9%) in the placebo group (adjusted risk ratio, 7.22; 95% CI, 0.97–53.5; $p = 0.05$)	
IV tenecteplase (TNK)			
Tong et al (2012)[9]	• 413,147 patients with acute ischemic stroke from 1287 hospitals whose data were submitted data via a web-based patient management tool • 47.0% had a documented time of stroke onset	• No substantial change in onset-to-door time over the 6-y study period • Extension of the alteplase treatment time window from 3 to 4.5 h after stroke onset increases the number of potential patients as candidate for alteplase treatment by 6.3% (30.1% relative increase)	• Data accuracy and completeness of depends on the individual hospitals. • NIHSS was missing in many patients, reflecting inconsistent use of the score in practice
Menon et al (2022)[8]	• 1,600 patients ($n = 816$ TNK group vs. $n = 784$ alteplase group) presenting within 4.5 h of symptom onset • 1,577 were the intention-to-treat population ($n = 806$ TNK vs. $n = 771$ alteplase)	• 296 (36.9%) of 802 patients in the TNK group and 266 (34.8%) of 765 in the alteplase group had mRS of 0–1 at 90–120 d (unadjusted RR difference 2.1%; 95% CI, 2.6–6.9) • 27 (3.4%) of 800 in TNK group and 24 (3.2%) of 763 in alteplase group had symptomatic ICH within 24 h • 122 (15.3%) of 796 in TNK and 117 (15.4%) of 763 in alteplase died within 90 d	• Only 6.3% of the patients in the intention-to-treat population had ischemic stroke • symptomatic intracerebral hemorrhage used in the trial was broader than that used for symptomatic intracranial hemorrhage • COVID19 pandemic might have affected the trial
Mechanical thrombectomy (MT)			
First wave of studies with negative results			
Furlan et al (1999)[10]	• Randomized, controlled, multicenter, open-label clinical trial with blinded follow-up • 180 patients ($n = 121$ intra-arterial r-proUK plus heparin vs. $n = 59$ heparin only) with acute ischemic stroke with onset within 6 h proven with angiography	• 40% treated with r-proUK patients and 25% in the heparin only group had a mRS ≤ 2 respectively ($p = 0.04$) • Mortality was 25% for the r-proUK group and 27% for the control group	• Small sample size
Ciccone et al (2013)[12]	• 362 patients with acute stroke ($n = 181$ endovascular therapy group vs. $n = 181$ alteplase group) underwent randomization within 4.5 h after symptom onset	• At 3 mo, 55 patients in the endovascular-therapy group (30.4%) and 63 in the IV t-PA group (34.8%) were alive without disability (adjusted OR 0.71; 95% CI, 0.44–1.14; $p = 0.16$) • No significant differences between groups in the rates of other serious adverse events or the case fatality rate	• 12 patients were excluded due to enrollment from one center for failure to comply with the treatment assignments • 8 other patients with major protocol deviations from six centers

Trials (chronological)	Patient sample and intervention	Major findings	Reported limitations
Kidwell et al (2013)[13]	• 118 patients, the mean time to enrollment was 5.5 h, and 58% had a favorable penumbral pattern	• Mean mRS did not differ between MT and standard medical treatment (3.9 vs. 3.9; $p = 0.99$) • MT was not superior to standard care in patients with either a favorable penumbral pattern (mean score, 3.9 vs. 3.4; $p = 0.23$)	• During the 8 y needed for the trial to be completed, advances in techniques and clinical practices • Baseline neuroimaging prediction maps may have changed by the time of recanalization with thrombectomy • Time-to-groin puncture was > 6h after symptom onset (longer than previous trials) • Follow-up imaging was not available for all patients
Broderick et al (2013)[11]	• 656 participants had undergone randomization (434 patients to endovascular therapy and 222 to IV t-PA alone)	• Findings in the endovascular-therapy and IV t-PA groups were similar for mortality at 90 d (19.1 and 21.6%, respectively; $p = 0.52$) and the proportion of patients with symptomatic ICH within 30 h after initiation of t-PA (6.2 and 5.9%, respectively; $p = 0.83$)	• The study was stopped early
Second wave of studies with positive results			
Berkhemer et al (2015)[14]	• 500 patients at 16 medical centers in the Netherlands (233 assigned to intraarterial treatment and 267 to usual care alone). Of them, 445 patients (89.0%) were treated with IV alteplase before randomization. MT with retrievable stents were used in 190 of the 233 patients (81.5%) assigned to intraarterial treatment	• Adjusted OR was 1.67 (95% CI, 1.21–2.30). There was an absolute difference of 13.5% points (95% CI, 5.9–21.2) in the rate of functional independence (mRS, 0–2) in favor of the MT (32.6 vs. 19.1%) • No significant differences in mortality or ICH	• Unbalanced randomization (more patients in control group) • Lower reperfusion rate (58.7%) than other case series • 9% of the patients in intervention group had embolization into new vascular territories • Broad inclusion criteria resulted in low proportion of patients in the control group had a mRS of 0 to 2 at the 90 d
Campbell et al (2015)[16]	• 70 patients had undergone randomization (35 patients in each group)	• Increased early neurological improvement at 3 d (80% in MT group vs. 37% in control group ($p = 0.002$) • At 90 dmRS 0–2 was 71% in MT group vs. 40% in control ($p = 0.01$)	• The trial was stopped early
Goyal et al (2015)[17]	• 316 patients from 22 hospitals worldwide were enrolled, of whom 238 received IV tPA (120 in the	• 90-day mRS 0–2 was 53.0% in MT group vs. 29.3% in the control group ($p < 0.001$)	• The trial was stopped early

Trials (chronological)	Patient sample and intervention	Major findings	Reported limitations
	intervention group and 118 in the control group)	• MT was associated with reduced mortality (10.4%, vs. 19.0% in the control group; $p = 0.04$). Symptomatic ICH occurred in 3.6% of participants in intervention group and 2.7% of participants in control group ($p = 0.75$)	
Saver et al (2015)[21]	• 196 patients in 39 centers underwent randomization (98 patients in both group)	• There were no significant between-group differences in 90-day mortality (9 vs. 12%; $p = 0.50$) or symptomatic ICrH (0 vs. 3%; $p = 0.12$)	• The study was stopped early
Bracard et al (2016)[15]	• 414 patients were randomly assigned to the IV alteplase group (0·9 mg/kg, max. 90 mg, initial bolus of 10% of the total dose followed by infusion of the remaining dose over 60 min, $n = 208$) or the IV alteplase plus MT group ($n = 204$)	• Functional independence at 3 mo was achieved by 85 (42%) patients in the alteplase group vs. 106 (53%) in the alteplase plus MT group (OR, 1·55; 95% CI, 1·05–2·30; $p = 0·028$) • No significant differences in mortality at 3 mo (12% deaths in alteplase plus MT vs 13% in ; $p = 0·70$) or symptomatic intracranial hemorrhage at 24 h (four [2%] of 185 vs three [2%] of 192; $p = 0·71$)	• Treating physicians were not blinded to mRS • Protocol changes occurred while 80 were already enrolled in the study by extending the alteplase time window from 3h to 4h and MT initiation at 5h after onset • Results apply only to patients with anterior circulation stroke • Initial design was occlusion of the superior third of basilar artery with ultimately only 2 only two patients available for inclusion
Muir et al (2017)[20]	• 65 patients ($n = 32$ IV thrombolysis and $n = 35$ IV thrombolysis and adjunctive MT) enrolled in a multicentre, randomized, controlled trial with acute supratentorial ischemic stroke with onset of 4.5 h with imaging showing ICA, M1, or a single M2 artery occlusion	• No significant difference in disability-free survival at day 90 with MT (absolute difference 11%, adjusted OR, 2.12; 95% CI, 0.65–6.94; $p = 0.20$) • Greater likelihood of full neurological recovery (mRS 0–1) at day 90 (OR, 7.6; 95% CI, 1.6–37.2; $p = 0.010$) • In the per-protocol population ($n = 58$), the primary and most secondary clinical outcomes significantly favored MT (absolute difference in mRS 0–2 of 22% and adjusted OR, 4.9; 95% CI, 1.2–19.7; $p = 0.021$)	• Small sample size
Jovin et al (2022)[28]	• 217 patients with stroke due to basilar-artery occlusion who presented 6 to 24 h after symptom onset (110 in the MT group and 107 in the control group) were included in the analysis	• 51 patients (46%) in the MT group had mRS of 0 to 3 occurred in and in 26 (24%) in the control group (adjusted RR, 1.81; 95% CI, 1.26–2.60; $p < 0.001$) • The results for the original primary outcome of a mRS of 0 to 4 were 55 and 43%, respectively (adjusted RR, 1.21; 95% CI, 0.95–1.54) • Symptomatic ICrH occurred in 6 of 102 patients (6%) in the MT group and in 1 of 88 (1%) in the control group (risk ratio, 5.18; 95% CI, 0.64–42.18)	• Enrollment was stopped at a prespecified interim analysis because of the superiority of MT

Trials (chronological)	Patient sample and intervention	Major findings	Reported limitations
		• Mortality at 90 d was 31% in the MT group and 42% in the control group (adjusted RR, 0.75; 95% CI, 0.54–1.04)	
Studies on MT with extended time window from onset			
Nogueira et al (2018)[23]	• 206 patients were enrolled; 107 were assigned to the MT group and 99 to the control group	• The rate of symptomatic IcrH did not differ between the two groups (6% in the MT group and 3% in the control group; $p = 0.50$), nor did 90-day mortality (19 and 18%, respectively; $p = 1.00$)	• At 31 mo, enrollment in the trial was stopped because of the results of a prespecified interim analysis
Albers et al (2018)[22]	• 182 patients had undergone randomization (92 to the endovascular-therapy group and 90 to the medical therapy group)	• Endovascular therapy plus medical therapy was associated with a favorable mRS at 90 d (OR, 2.77; $p < 0.001$) • Higher % of patients in the endovascular-therapy group with mRS of 0 to 2 (45 vs. 17%; $p < 0.001$) • 90-day mortality rate was 14% in the endovascular-therapy group and 26% in the medical therapy group ($p = 0.05$)	• The study was stopped early
Studies on MT and large ischemic core			
Yoshimura et al (2022)[27]	• 203 patients in Japan underwent randomization (101 patients in endovascular treatment vs. 102 patients in medical treatment group) • 27% of patients in each group received alteplase	• At 90 d, 31.0% in the endovascular therapy group vs 12.7% in the medical-care group had mRS 0 to 3 (RR 2.43; 95% CI, 1.35–4.37; $p = 0.002$ • All-type IcrH occurred in 58.0 and 31.4%, respectively ($p < 0.001$)	• Limited generalizability beyond the Japanese population • Standard dose of rt-PA in Japan is lower than in other countries • No data were collected on the causes of death, no association of adverse events with endovascular therapy or thrombolysis
Huo et al (2023)[25]	• 456 patients ($n = 231$ MT group vs, $n = 225$ medical therapy alone group) in China who had stroke within 24 h	• At 90 d, MT group had better mRS compared with medical therapy alone (generalized OR, 1.37; 95% CI, 1.11–1.69; $p = 0.004$) • Symptomatic IcrH occurred in 14 of 230 patients (6.1%) in the MT group and in 6 of 225 patients (2.7%) in the medical-management group; any IcrH occurred in 113 (49.1%) and 39 (17.3%), respectively	• The trial was stopped early
Sarraj et al (2023)[26]	• 178 patients had been assigned to MT and 174 to medical care	• Mortality was similar between the two groups • MT resulted in better functional outcomes than medical therapy alone but was associated with vascular complications	• The trial was stopped early

Trials (chronological)	Patient sample and intervention	Major findings	Reported limitations
Bendszus et al (2023)[24]	• 125 patients assigned to endovascular MT vs. 128 to medical treatment alone	• At 90 d, MT was associated better outcome (adjusted OR, 2.58; 95% CI, 1·60–4·15; p = 0·0001) and with lower mortality (HR, 0.67; 95% CI, 0.46–0.98; p = 0·038)	• The trial was stopped early
Studies on MT and basilar artery infarction			
Liu et al (2020)[30]	• 131 patients (n = 66 patients in MT group and 65 in medical therapy alone group)	• No difference in outcomes of patients receiving endovascular therapy compared with those receiving standard medical therapy alone	• The trial was stopped early • Results might have been confounded by loss of equipoise over the course of the trial
Langezaal et al (2021)[29]	• 300 patients (n = 154 MT group vs. n = 146medical therapy only) with basilar-artery occlusion, within 6 h after stroke onset in a multicenter, open-label, international, randomized, controlled trial	• Good functional outcomes occurred in 68 of 154 patients (44.2%) in the MT group and 55 of 146 patients (37.7%) in the medical care group (RR, 1.18; 95% CI, 0.92–1.50) • Symptomatic ICrH occurred in 4.5% of the MT patients and in 0.7% of the medical therapy alone (RR, 6.9; 95% CI, 0.9–53.0) • Mortality at 90 d was 38.3% in MT group and 43.2% in medical therapy alone group respectively (RR, 0.87; 95% CI, 0.68–1.12)	• 29.2% of eligible patients were treated outside the trial and that 79.0% • NIHSS, used for stratification in randomization, is less sensitive to posterior-circulation stroke • Low than anticipated, our trial was underpowered for some analyses, including subgroup analyses
Jovin et al (2015)[19]	• Multicenter, prospective, randomized, sequential, open-label phase 3 study with blinded evaluation with random assignment of 206 patients who could be treated within 8 h of stroke onset • Patients were divided into thrombectomy ± IV alteplase (when appropriate) or medical therapy alone	• MT reduced the severity of disability over the range of the mRS (adjusted OR for improvement of 1 point, 1.7; 95% CI, 1.05–2.8) and led to higher rates of functional independence (a score of 0 to 2) at 90 d (43.7 vs. 28.2%; adjusted OR, 2.1; 95% CI, 1.1–4.0) • At 90 d, the rates of symptomatic ICrH were 1.9% in both the MT group and the control group (p = 1.00), and rates of death were 18.4 and 15.5%, respectively (p = 0.60)	• The trial was stopped early
Tao et al (2022)[31]	• 507 patients in China with basilar artery occlusion within 12 h after stroke onset • 340 were in the intention-to-treat population, (226 MT group vs. 114 control group)	• At 90 d, 104 patients (46%) in the MT group and in 26 (23%) in the control group had good functional outcomes (adjusted RR, 2.06; 95% CI, 1.46–2.91; p < 0.001) • Mortality at 90 d was 37% in the MT group and 55% in the control group (adjusted RR, 0.66; 95% CI, 0.52–0.82)	• Higher prevalence of intracranial large-artery atherosclerosis is known in Chinese population • Results are not generalizable to patients with milder stroke NIHSS score < 10 or onset beyond 12-h occlusion

Abbreviations: CI, confidence interval; DWI, diffusion-weighted image; FLAIR, fluid-attenuated inversion recover; HR, hazard ratio; ICH, intracerebral hemorrhage; ICrH, intracranial hemorrhage; LHI, large hemispheric infraction; LVO, large vessel occlusion; MRI, magnetic resonance imaging; mRS, modified Rankin Scale; MT, mechanical thrombectomy; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; RR, risk ratio.

Table 2

Large hemispheric infarct management: cerebral edema treatment

Trials (chronological)	Patient sample and intervention	Major findings	Reported limitations
Medical management			
Qureshi et al (1998)[65]	• 27 patients with cerebral edema including patients with head trauma (n = 8), postoperative edema (n = 5), nontraumatic intracranial hemorrhage (n = 8), and cerebral infarction (n = 6) • IV infusion of 3% saline/acetate to increase serum sodium concentrations to 145–155 mmol/L	• A reduction in mean ICP within the first 12 h correlating with an increase in the serum sodium concentration was not in patients with nontraumatic intracranial hemorrhage or cerebral infarction • In patients with head trauma, the beneficial effect of hypertonic saline on ICP was short-lasting, and after 72 h of infusion, four patients required IV pentobarbital due to poor ICP control • In repeat CT scan within 72 h of treatment lateral brain displacement was not reduced in nontraumatic ICH or cerebral infarction patients	• Retrospective chart review • Small patient population of each group and the heterogeneity in the underlying neurological illness
Schwarz et al (1998)[62]	• 9 patients with elevated ICP after acute space-occupying hemispheric stroke (n = 8) or hypertensive putaminal hemorrhage with massive perifocal edema (n = 1) • IV infusion of 100mL HS–HES or 40 g mannitol over 15 min	• ICP decreased from baseline values in both groups (p < 0.01) • The maximum ICP decrease was 11.4 mm Hg (after 25 min) in the HS–HES-treated group and 6.4 mm Hg (after 45 min) in the mannitol-treated group. • There was no constant effect on cerebral perfusion pressure in the HS–HES-treated group, whereas cerebral perfusion pressure rose significantly in the mannitol-treated group	• Small sample size
Schwarz et al (2002)[63]	• 8 patients with elevated ICP after acute space-occupying hemispheric stroke (n = 6) or supratentorial hemorrhage with massive perifocal edema (n 2) • IV 75 mL hypertonic (10%) saline, if standard treatment of 200 mL of 20% mannitol was not effective	• No constant effect on mean arterial blood pressure, whereas cerebral perfusion pressure was consistently increased • Blood osmolarity rose by 9 mmol/L and serum sodium by 5.6 mmol/L. Potassium levels, hemoglobin, hematocrit, and pH were slightly decreased. No unexpected side effects were noted	• Small sample size
Gondim et al (2005)[66]	• 95 patients treated with mannitol to determine if MI-AKI is linked to elevated osmolality	• 11 patients (11.6%) who developed MI-AKI did not have significant differences in patient age, sex, or race; history of cerebrovascular disease or smoking; baseline renal function; or GCS compared with those without MI-AKI • Renal function spontaneously returned to baseline in all patients • MI-AKI appears to be associated with history of chronic disease that affects renal function, e.g.,	• Addresses only the renal effects of increased osmolality and not the hyperosmolar effect in central nervous system function

Trials (chronological)	Patient sample and intervention	Major findings	Reported limitations
		diabetes mellitus rather than mannitol dose or osmolality	
Harutjunyan et al (2005)[61]	• 40 patients at risk of increased ICP were randomized to receive either 7.2% NaCl/HES 200/0.5 (NaCl/HES) or 15% mannitol targeting ICP < 15mm Hg. Of them, 17 patients received the NaCl/HES regimen, 15 received the mannitol regimen, and 8 patients did not require treatment due to their ICP not going over 20mm Hg	• Both treatment regimens lowered ICP below 15 mm Hg ($p < 0.0001$). The NaCl/HES lowered the ICP within a median of 6.0 min while the mannitol within a median of 8.7 min ($p < 0.0002$) • The NaCl/HES caused a pronounced decrease in ICP than mannitol (57% vs 48%; $p < 0.01$). Cerebral perfusion pressure was increased from a median 60 to 72 mm Hg by infusion with NaCl/HES ($p < 0.0001$) while with the mannitol regimen increased from a median 61 to 70 mm Hg with mannitol ($p < 0.0001$) • The mean arterial pressure was increased by 3.7% from NaCl/HES 200/0.5 and was not altered by mannitol	• Small patient population of each group and the heterogeneity in the underlying neurological illness
Hauer et al (2011)[64]	• 100 patients with severe ICH signs of increased ICP received a continuous infusion of 3% hypertonic saline within ≤72 h after symptom onset over a mean period of 13 d • The findings were compared previously treated control group ($n = 115$) with equal underlying disease	• Fewer episodes of critically elevated ICP (92 vs. 167; $p = 0.027$) in fewer patients (50.0 vs. 60.0%; $p = 0.091$) and in-hospital mortality was significantly decreased (17.0 vs. 29.6%; $p = 0.037$)	• Pilot character of study • Compared findings with a previous cohort with known outcomes risk of bias • Heterogeneous patient cohort with three different pathologies of cerebrovascular diseases
Lin et al (2015)[67]	• 432 patients of whom 62.3% had ischemic stroke, received mannitol treatment	• The incidence of MI-AKI was 6.5% (95% CI, 4.5–9.3%) in acute stroke patients, 6.3% in patients with ischemic stroke, and 6.7% in patients with ICH • Multivariate analysis revealed that diabetes, lower eGFR at baseline, higher baseline NIHSS, and use of diuretics increased the risk of MI-AKI	• Decision to initiate osmotic therapy and the dose depended only on the treating physician's expertise • Retrospective nature of the study that cannot exclude missing data in the analysis • The causative relationship between concurrent medications and the development of MI-AKI were not easily clarified
Sheth et al (2016)[69]	• 86 patients with anterior circulation LHI within 10 h from onset assigned to placebo or IV glyburide in a double-blind, randomized, placebo-controlled trial	• At 90 d, 17 (41%) patients in the IV glyburide group and 14 (39%) in the placebo group had an mRS 0–4 without surgery (adjusted OR, 0.87; 95% CI, 0.32–2.32; $p = 0.77$)	• Enrollment was stopped because of funding reasons
Surgical management			

Trials (chronological)	Patient sample and intervention	Major findings	Reported limitations
Jüttler et al (2007)[71]	• 32 patients were randomized to either surgical plus conservative treatment or to conservative treatment alone in a prospective, multicenter, randomized, controlled, clinical trial and patients	• At 30 d, 88% patients in surgery group survived compared with 47% patients in medical therapy group ($p = 0.02$)	• 81% of patients originated from two centers • Possibility of bias introduced due to nonblinding of evaluation of clinical outcome
Vahedi et al (2007)[72]	• 38 patients in a multicenter, randomized trial in France involving patients with large MCA infarction comparing functional outcomes with or without surgery	• The proportion of patients with a mRS ≤3 at the 6-mo and 1-y follow-up was 25 and 50%, respectively, in the surgery group compared with 5.6 and 22.2%, respectively, in the no-surgery group ($p = 0.18$ and 0.10, respectively) • There was a 52.8% absolute reduction of death after craniectomy compared with medical therapy only ($p < 0.0001$)	• The trial stopped because of slow recruitment
Hofmeijer et al (2009)[70]	• 64 patients were included; 32 were randomly assigned to surgical decompression and 32 to best medical treatment • Patients with LHI with cerebral edema were randomly assigned within 4 d of stroke onset to surgical decompression or best medical treatment	• Surgical decompression had no effect on the primary outcome measure (absolute risk reduction 0%; 95% CI, −21 to 21) but did reduce case fatality (absolute risk reduction 38%, 15–60)	• Unknown number of patients who were screened • Possibility of selection bias due to the small number of patients with aphasia in the referral of patients for inclusion in this trial
Slezins et al (2012)[76]	• 28 patients with a malignant MCA stroke • Random assignment to surgery plus best medical therapy group or best medical therapy alone	• 6 patients survived: 5 in the DCE group (none of them was older than 60 y) and 1 in the BMT group ($p = 0.03/0.06$) • All survivors in the DCE group had favorable outcomes. There was no significant difference in the NIHSS and GCS scores between the groups and survivors/nonsurvivors ($p > 0.05$)	• Small sample size
Zhao et al (2012)[77]	• 47 patients ($n = 24$ surgery plus medical treatment vs. $n = 23$ medical treatment alone) with MCA infarction with cerebral edema in a randomized controlled trial	• At 6 and 12 mo, reduced mortality was observed in surgery plus medical therapy compared with medical therapy alone (12.5 vs. 60.9%; $p = 0.001$ and 16.7 vs. 69.6%; $p < 0.001$, respectively) • At 6 and 12 mo, fewer patients had mRS >4 postsurgery (33.3 vs. 82.6%; $p = 0.001$ and 25.0 vs. 87.0%; $p < 0.001$, respectively)	• 63.8% of patients were from one single center • Unknown number of patients that have been screened • Outcome measurement was based on questionnaires replied by patients' caregivers • No data quality of life, neuropsychiatric status, or aphasia

Trials (chronological)	Patient sample and intervention	Major findings	Reported limitations
Hofmeijer et al (2013)[73]	• 20 patients underwent surgery within 48 h of MCA infarction due to life-threatening edema, underwent detailed neuropsychological examination at a median of 14.5 mo after stroke onset	• Poorer cognitive performance was associated with worse functional outcomes on the mRS scale (b −0.4; 95% CI, −0.6 to −0.1) • No differences were observed between operated and nonoperated patients	• Small sample size • Investigator who performed the examinations was not blinded to treatment assignment and functional outcome

Abbreviations: CI, confidence interval; GCS, Glasgow Coma Scale; HS–HES, hypertonic saline–hydroxyethyl starch; ICH, intracerebral hemorrhage; ICP, intracranial pressure; LHI, large hemispheric infraction; MCA, middle cerebral artery; MI-AKI, mannitol-induced acute kidney injury; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.