Stroke

SPECIAL REPORT

ARISE I Consensus Statement on the Management of Chronic Subdural Hematoma

Peter Kan, MD; David Fiorella, MD, PhD; Guilherme Dabus, MD; Edgar A. Samaniego, MD; Giuseppe Lanzino, MD; Adnan H. Siddiqui, MD, PhD; Huanwen Chen, MD; Alexander A. Khalessi, MD; Vitor Mendes Pereira, MD; Johanna T. Fifi, MD; Mark D. Bain, MD; Geoffrey P. Colby, MD, PhD; Ajay K. Wakhloo, MD, PhD; Adam S. Arthur, MD; on behalf of the ARISE I Academic Industry Roundtable

ABSTRACT: ARISE (Aneurysm/AVM/cSDH Roundtable Discussion With Industry and Stroke Experts) organized a one-and-a-half day meeting and workshop and brought together representatives from academia, industry, and government to discuss the most promising approaches to improve outcomes for patients with chronic subdural hematoma (cSDH). The emerging role of middle meningeal artery embolization in clinical practice and the design of current and potential future trials were the primary focuses of discussion. Existing evidence for imaging, indications, agents, and techniques was reviewed, and areas of priority for study and key questions surrounding the development of new and existing treatments for cSDH were identified. Multiple randomized, controlled trials have met their primary efficacy end points, providing high-level evidence that middle meningeal artery embolization is a potent adjunctive therapy to the standard (surgical and nonsurgical) management of neurologically stable cSDH patients in terms of reducing rates of disease recurrence. Pooled data analyses following the formal conclusion and publication of these trials will form a robust foundation upon which guidelines can be strengthened for cSDH treatment modalities and optimal patient selection, as well as delineate future lines of investigation.

Key Words: arteries ■ capillaries ■ hematoma ■ inflammation ■ neurology ■ neurosurgery ■ subdural

Chronic subdural hematoma (cSDH) is one of the most frequently encountered neurovascular pathologies across the United States, and it is treated by neurosurgeons, neurologists, neurointensivists, and neurointerventionalists. Little has been reported on the true incidence of the disease in the United States. A study in the Veterans Affairs population reported an incidence of 79.4 per 100 000 hospital admissions; based on their prediction model, the incidence will rise to 121.4 in the Veterans Affairs and 17.4 in the civilian population per 100 000 by the year 2030.[1] A steady global rise in the incidence of cSDH was also observed over the past 6 decades. The incidence was 1.7 to 2 per 100 000 persons in Finland and Sweden from 1967 to 1973 and 13.1 cases per 100 000 in Japan during the late 1980s.[2–4] This increased by approximately another 10% by 2005.[5–8]

cSDH is widely considered a disease of the elderly, and people over the age of 80 years comprise approximately one-third of the affected population.[1] Incidence in this population subset is 127.1 per 100 000 persons.[9] The cSDH incidence is, therefore, likely to rise with aging populations. However, the widely believed notion that this is a disease affecting only elderly people may be changing due to the increasing use of antiplatelet and anticoagulant medications.[10–12] However, approximately one-third of patients are <65 years of age.[1] Researchers estimate that by the year 2030, the incidence of cSDH will exceed the incidence of brain tumors (14/100 000), thus becoming the most common craniosurgical disease.[1]

CLINICAL PRESENTATION AND CONVENTIONAL MANAGEMENT

Patients with cSDH can present with a variety of symptoms of different severities. They can range from

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Correspondence to: Peter T. Kan, MD, Department of Neurosurgery, The University of Texas Medical Branch, 1005 Harborside Dr, 5th floor, Galveston, TX 77550. Email ptkan@utmb.edu

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headaches, seizures, cognitive decline, numbness, aphasia, weakness, and altered mental status.

For decompensating patients presenting with profound neurological symptoms, emergent surgical drainage is the standard of care. Surgical drainage improves neurological status and prevents further decline in patients with large cSDHs.[13] Without surgical treatment, a minority of cSDHs spontaneously resolve (≈40%); however, ≈20% of conservatively managed patients require eventual intervention.[14] There is a paucity of evidence to guide treatment decisions for patients with cSDH who do not require emergent surgery. It is estimated that between one-third to one-fifth of patients presenting with cSDH ultimately undergo either emergent or nonemergent surgical drainage.[1,15,16] Although 10 mm of thickness is sometimes cited as a possible criterion for surgical intervention, there are no evidence-based imaging criteria (including thickness of cSDH) for which surgical drainage is recommended. There are also no evidence-based clinical criteria for which surgical drainage is recommended for neurologically stable patients with cSDH. As such, clinical decision-making remains nonstandardized and varies significantly across different institutions and individual clinicians.

Neurological prognosis following cSDHs and cSDH treatments cannot be easily measured as patients present with a wide range of medical comorbidities and neurological symptoms; however, it has been suggested that cSDH portends excess mortality risk up to 20 years after diagnosis, particularly for elderly patients and those with comorbidities.[17] A recent study demonstrated that the median survival time for 209 patients with cSDH was 4.4 years compared with a predicted 6 years based on actuarial life tables (hazard ratio, 1.94; $P<0.0002$).[18]

Despite rising global incidence, there has been little improvement in outcomes following cSDH treatments during the past 2 decades.[19–23] Up to 20% of surgically treated patients have poor clinical outcomes and are left with significant disability.[20,21,24–26] Perioperative mortality remains as high as 11%, and the 1-year mortality rate in the older population is 32%.[18,27] Moreover, recurrence of the collection following surgical drainage is not uncommon, with rates ranging between 5% and 30%.[22,23,28] For patients with mild symptoms or for patients who are asymptomatic, observation is frequently recommended, particularly for patients with major comorbidities that place them in a high surgical risk category.[29,30]

FINANCIAL BURDEN

Approximately 64% of patients presenting with cSDH are beyond the age of 65 years.[1] Therefore, it is likely that most of the US health care cost for this disease is borne by the federally administered Medicare program. In an National Inpatient Sample analysis, the median hospital cost was $20 341.6 (±38 327.3) for patients who did not require surgical drainage and $35 366.0 (±50 497.3) for those who did.[31] The difference not only indicates a high direct surgical cost but also may reflect the more acute nature of the disease in patients who require surgical drainage. When cSDH is the primary inpatient diagnosis, the nationally weighted estimate of mean hospital cost was $17 107.1 (±14 370.7). Based on population projection estimates, there could be as many as 60 000 cases of cSDH by the year 2030.[1,6,7] Adjusting for inflation, we estimate that the cost could go up to 2 billion US dollars per year at that point.

Aneurysm/AVM/cSDH Roundtable Discussion With Industry and Stroke Experts (ARISE) Consensus

cSDH is a common, disabling, and costly neurological condition. The incidence will likely grow with aging populations and increasing use of antiplatelet and anticoagulant therapies. Evidence-based recommendations for the management (surgical or nonsurgical) of neurologically stable patients with cSDH are lacking. Surgical treatment has a relatively high risk of cSDH recurrence necessitating further surgery. Clinical outcomes remain suboptimal for patients treated conservatively or with surgery.

PATHOGENESIS AND RATIONALE FOR MMAE

Current evidence supports the hypothesis that cSDH is a cerebrovascular disease.[32] The natural history of cSDH can be generally divided into 3 stages: an initial stage, a latent stage, and a clinical stage. During the initial stage, injury to the dural border cell layer leads to the extravasation of cerebrospinal fluid and blood into the subdural space. Thereafter, inflammatory mediators including interleukins and other cytokines are released and recruit inflammatory cells and fibroblasts. This cascade induces the release of vascular growth factors including vascular endothelial growth factor, cyclooxygenase-2, transforming growth factor-β1, and platelet-derived growth factor. These angiogenic factors then stimulate the ingrowth of a structurally incompetent neovasculature, which continues to further exude blood and inflammatory cells facilitating transudative fluid shifts into the subdural space.[33,34] In some patients, a positive feedback cycle of hyperfibrinolysis, inflammation, angiogenesis, transudation, and recurrent hemorrhage persists and ushers in the latent phase of cSDHs.[34] The latent stage can last weeks to years, and, with enough hematoma accumulation and growth, cSDHs manifest with neurological symptoms (clinical stage). The neovasculature has long been known to derive its arterial supply from the middle meningeal artery (MMA). It is hypothesized that restricting the arterial supply from the MMA may break the positive feedback cycle involved in the pathophysiology of cSDH formation and recurrence, which lays the pathophysiological basis for endovascular embolization of the MMA as a

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potential therapy for cSDH.[32] cSDH pathophysiology and rationale for middle meningeal artery embolization (MMAE) are depicted in Figure 1.

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Currently, cSDH is believed to be a cerebrovascular disease stemming from an initial dural injury inciting a positive feedback cycle of inflammation, transudation, recurrent hemorrhage, and neovascular membrane ingrowth. Physiological resorption mechanisms may be impaired. Devascularization of the dura hypothetically disrupts this positive feedback cycle. This concept forms the basis for MMA embolization as a therapeutic opportunity for cSDH. To further study the pathophysiology of cSDH, the panel recommends the creation of multicenter tissue banks and biorepositories for cSDH tissue storage (dura, membranes, hematoma fluid, and peripheral blood). Tissue can be collected from a wide spectrum of patients with symptomatic cSDH (either de novo or recurrent cSDH after failed surgery or MMAE) who undergo surgery to allow biologic-clinical correlation. Systematic elucidation of disease-related changes in the dura and membrane tissue will help us further understand the mechanisms of cSDH formation and recurrence and ultimately identify new therapeutic targets and pharmacological strategies to treat cSDH.

IMAGING OF CSDH

Diagnosis

Brain computed tomography (CT) is the most used neuroimaging modality for the diagnosis and follow-up of cSDH.[30] It usually demonstrates a mixture of iso- and hypo-dense fluid. The maximum thickness and brain midline shift are the commonly reported measurements. The maximal thickness is generally calculated on a standard CT as the maximal width of the cSDH on slices above the temporal bones and up to 2 slices above the lateral ventricles. The superior limit is taken to exclude miscalculation on high skull curvature, and the lower limit avoids measurement of tentorial bleeding and is performed by excluding slices <1 below the ventricles. Midline shift is measured as the perpendicular distance between a midline structure (usually the septum pellucidum) and a line designated by the midline. The midline will be represented as a line drawn between the anterior and posterior attachment of the falx to the inner table of the skull at the level of the foramen of Monroe. Representative images of cSDH measurements are depicted in Figure 2. Volumetric analysis of cSDHs can also be done; however, it is resource-intensive at present and not commonly used in routine clinical practice.

The morphology of cSDHs is variable. Trabeculation and septation are frequently seen. Multiple classification systems for subdural hematomas (SDHs) have been proposed, with the Nakaguchi classification system being the most widely cited.[35] This system classifies cSDH morphologies into 4 types based on hematoma density and internal architecture—homogeneous, laminar, separated, and trabecular—and each type is thought to be associated with different cSDH ages and risks of recurrence after surgical treatment. In general, the separated type is thought to represent older and matured cSDHs carrying a higher risk of recurrence, whereas the trabecular type

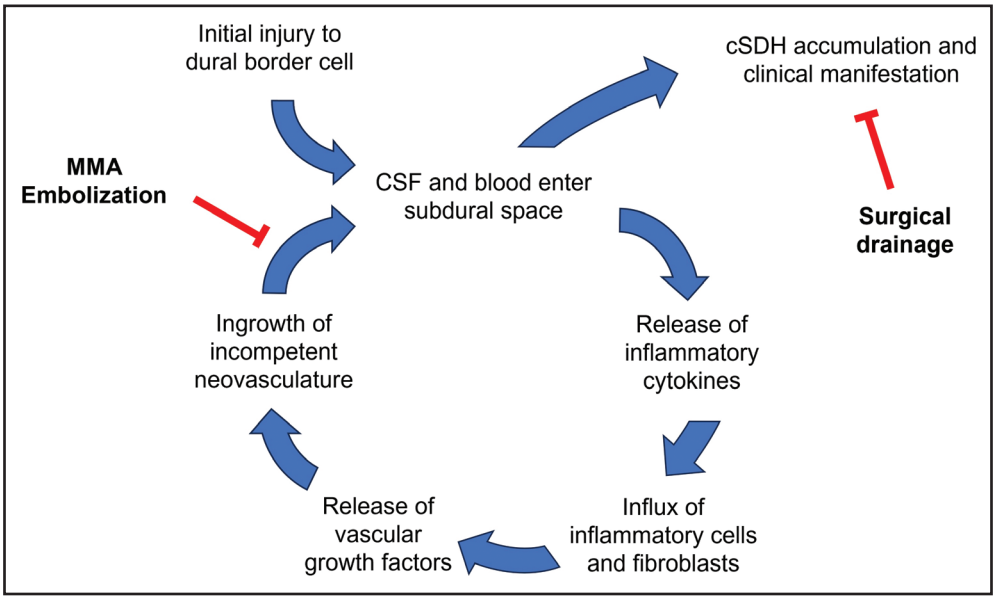

Figure 1. Pathophysiology of chronic subdural hematoma (cSDH) formation and the rationale for middle meningeal artery (MMA) embolization.
CSF indicates cerebrospinal fluid.

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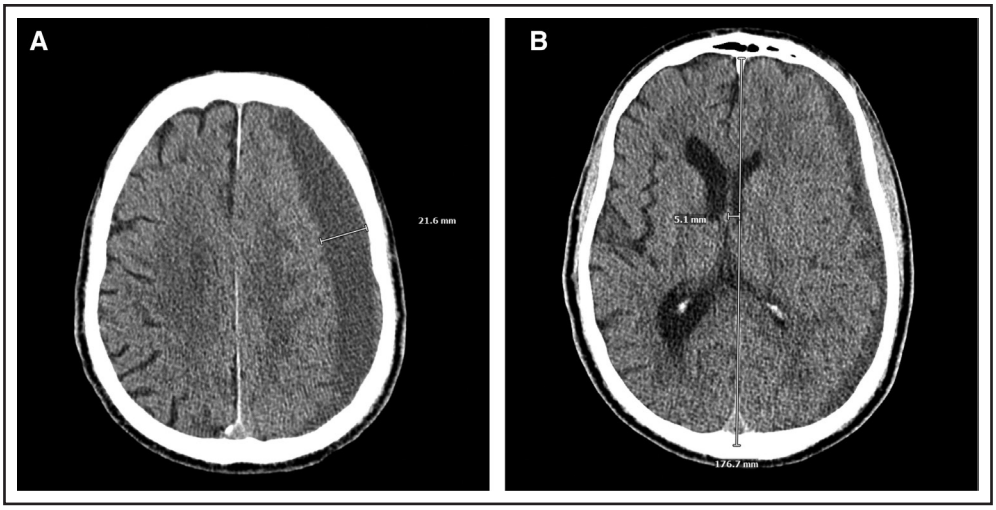

Figure 2. Representative images of chronic subdural hematomas..
Measurements of thickness (**A**) and midline shift (**B**).

is believed to represent resolving cSDHs with a lower risk of recurrence. The locations of cSDHs (cerebral convexity, cranial base, and interhemispheric) are also associated with different risks of surgical recurrence. Finally, the density of cSDH fluid also varies and may provide insight into the chronicity of cSDHs.

Despite not being the first-line neuroimaging modality in the management of cSDH, MRI can provide complementary information.[36,37] The architecture of the cSDH and increased vascularity of the neomembranes can be appreciated more easily on MRI, and these findings have been implicated in cSDH recurrence. Neuroimaging-based artificial intelligence can potentially have a specific and important role in the future management of cSDH. Machine learning, deep learning, and natural language processing algorithms can be applied to early disease detection and automated alerts following head CT, facilitating neurological consults, automated quantitative analysis of volume and mass effect, and outcome prediction.[38] In particular, a reproducible and accurate means of automated maximal thickness and volume measurement would represent an important contribution to the standardization of the initial assessment and follow-up imaging of these patients.

Follow-Up

The ideal interval for follow-up imaging regardless of primary management strategy—operative or nonoperative—has yet to be determined, and the time required for cSDH resorption to reach a steady state following MMA is unknown. While there is no evidence-based consensus, most of the existing literature and ongoing trials have performed imaging 1-day following interventions (surgical or MMAE) and at 1, 3, and 6 months following the initial clinical presentation. These imaging end points are performed at most institutions within the United States as part of the spectrum of care.[39] Clinical follow-up alone with less frequent neuroimaging may also be an option for clinically stable patients who had initially asymptomatic or only mildly symptomatic disease. In such patients, CT can be obtained more frequently if symptoms arise or worsen.

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CT is the mainstay imaging modality in cSDH. MR imaging may provide supplemental data, but it is not routinely used for standard diagnosis and follow-up in most cases. While not standardized, CT follow-ups early (usually at 24 hours) after intervention and at 1, 3, and 6 months after initial presentations are performed at most institutions as part of the spectrum of care. Artificial intelligence facilitated CT-based diagnosis, and follow-up may offer opportunities for standardization of key imaging biomarkers.

Medical Management

For patients with cSDH who do not require emergent or nonemergent surgery, there are few evidence-based guidelines for management. A significant proportion of patients with cSDH take anticoagulant or antiplatelet medications for prophylactic and therapeutic indications. The precise impact of these medications in facilitating the formation, progression, and recurrence of cSDH is not well understood. Currently, general practice is to seriously consider discontinuation with or without reversal for patients with symptomatic cSDH. However, decisions surrounding the discontinuation or reversal (and the optimal time for resumption) of any anticoagulant and antiplatelet medications can be challenging and are frequently made on a patient-specific basis with

consideration given to the primary indications for the medications, the hematoma size, and the presenting neurological status of the patient.[40–43]

Several adjunctive medical treatments have been investigated with varying degrees of success including statins, steroids, and tranexamic acid.[15,16,44–46] Jiang et al,[15] in a randomized controlled trial (RCT) of atorvastatin therapy in 196 patients with nonoperative cSDH with mild symptoms, reported that after 8 weeks, patients in the atorvastatin group had a better hematoma volume reduction, a better neurological outcome, and a lower rate of surgical bailout. In contrast, Hutchinson et al,[46] in a large RCT of 748 patients with mostly operative cSDH, reported that adjunctive treatment with dexamethasone resulted in fewer favorable outcomes and more adverse events than placebo at 6 months. Interestingly, Hutchinson et al[46] also observed that fewer repeat operations were performed in the dexamethasone group. Most recently, Miah et al,[16] in a trial that randomized 252 patients with symptomatic cSDH to dexamethasone or burr-hole drainage, reported that dexamethasone treatment failed to achieve noninferiority compared with surgery and was associated with more complications and a greater likelihood of additional surgery. While the pharmacological trials provide some insight into the natural history of cSDH, the outcomes of patients with cSDH with nonsurgical management and the rates of spontaneous cSDH stabilization or resolution after nonsurgical management remain poorly defined. There have been initial reports of using the antiangiogenic pharmacological agent bevacizumab to treat recurrent cSDH following failed primary attempts, and this may open a novel therapeutic target in the future.[47] Early data suggest that the percentage of patients with nonsurgically managed cSDH who ultimately require surgical drainage is ≈20%[14]; however, the rate of treatment failure with conservative management in contemporary medical practice is unknown.

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Although a significant percentage of patients with smaller, mildly symptomatic, or asymptomatic cSDH collections are managed nonsurgically, clinical practice remains nonstandardized. The radiological and clinical outcomes of nonsurgically managed patients are poorly understood. Studies of adjunctive medical therapies have yielded mixed results to date. A better appreciation of the pathophysiologic cause for cSDH raises the potential for novel adjunctive therapeutic options. The ongoing prospective clinical trials of MMAE will provide a better understanding of outcomes in patients managed nonsurgically.

Surgical Treatment

Patients with significant symptoms are typically associated with an initial hematoma thickness >10 mm or a midline shift >5 mm, and they are typically considered for surgical treatment. The surgical goal is to relieve intracranial pressure that is associated with neurological deficits or minimize secondary injury. However, surgery is associated with high mortality and morbidity rates ranging from 2.7% to 30% and 3.0% to 56.8%, respectively.[48–50] Additionally, surgery is associated with high recurrence rates ranging from 2% to 39%.[51–54] A major challenge with surgical intervention is the requirement for reversal of antiplatelet and anticoagulant therapy to reduce the risks of perioperative bleeding. Since these medications are being used to treat significant comorbidities, reversal can be associated with increased complications such as thromboembolism, especially in patients with cardiac, coronary, or peripheral arterial diseases.[55]

A variety of surgical techniques are routinely used for the evacuation of cSDH.[56] The most common is burr-hole irrigation and drainage. The technique is typically performed under general anesthesia and involves the drilling of 2 burr holes on the side of the SDH. The subdural collection is irrigated with saline until it returns clear, and a drain is inserted into the subdural space for passive closed drainage. Recurrence rates in patients who receive burr-hole irrigation surgery may be up to 25%.[48] Twist drill trephination is performed at the bedside under local anesthesia, and it is considered useful for elderly patients with multiple comorbidities and for whom risks of complex surgery are high. The technique involves the creation of a small craniostomy (<6 mm diameter) using a hand drill and the insertion of a drain connected to a closed-system drainage.[56] The latest iteration of the original twist drill technique involves the insertion of a hollow screw directly connected to a closed drainage system. This technique does not require the blind insertion of a catheter in the subdural space, potentially reducing risks of brain laceration and bleeding from cortical vessels. Recurrence rates following twist drill trephination are as high as 50% (ranging from 17.4% to 50%).[22,57] Finally, large craniotomy is the most invasive surgical treatment for cSDH. The technique requires general anesthesia and a (>25 mm) bone flap, followed by irrigation and evacuation of the SDH. The maximum access allows surgeons the best means to open membranes and wider coagulation of dural membranes and vessels. Hematoma recurrence rates with large craniotomy have been reported to range from 9.5% to 19.4% and morbidity rates up to 12.3%.[58,59] Multiple comparative studies of surgical techniques for cSDH have yielded contradicting results. A recent large meta-analysis of 34 829 patients demonstrated no significant difference in mortality, cure, or recurrence between burr-hole irrigation and twist drill trephination.[28]

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Surgical evacuation of symptomatic and larger cSDH is the standard of care; however, patient outcomes are

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variable, and rates of recurrence are high. The precise comparative value of each surgical technique remains unclear. Adjunctive MMAE may allow for less invasive surgical drainage to become more efficacious.

MIDDLE MENINGEAL ARTERY EMBOLIZATION

Clinical Data

Multiple retrospective single and multicenter studies have provided preliminary data demonstrating the feasibility of MMAE as an adjunctive treatment for patients with cSDH managed both medically and surgically. Ban et al[49] reported a case-control series of MMAE in both surgical and nonsurgical patients. For patients managed nonsurgically, 83.6% (56 of 67) of the nonembolized patients experienced treatment failure (reaccumulation) in comparison to 0% (0 of 27) of the embolized patients.[49] In the surgical group, 18% (73 of 402) of the nonembolized patients experienced treatment failure in comparison to 2.2% (1 of 45) patients who underwent preoperative embolization.[49] In a recent meta-analysis of 20 studies (718 patients in the MMAE group and 698 patients in the conventional management group), the pooled surgical rescue and in-hospital complication rates in the MMAE cohort were 4.4% (2.8% to 5.9%) and 1.7% (0.8% to 2.6%), respectively, whereas the pooled surgical rescue and in-hospital complication rates were 16.4% (5.9% to 27.0%) and 4.9% (2.8% to 7.1%) in the conventional management cohort.[60] Onyinzo et al,[61] in a study that compared 50 patients with cSDH who underwent MMAE (19 primary and 31 adjunct) to 82 patients with cSDH who underwent burr-hole drainage, reported a 5% rate of rescue surgery in the MMAE group compared with 15.1% in the surgery group. Duerinck et al[62] reported a reoperation rate of 13.1% after minicraniotomy and a 6-month mortality of 10.2%. In comparison, the reported mortality rate for MMAE ranges between 0% and 7% with the majority of studies reporting mortality rates of <5%.[53,60,63,64] In these MMAE studies, patient mortality was typically attributable to underlying comorbidities rather than the cSDH collection itself or the MMAE procedure.[65] In February 2024, preliminary results from the EMBOLISE[66] (Embolization of the Middle Meningeal Artery With ONYX Liquid Embolic System for Subacute and Chronic Subdural Hematoma), STEM[67] (The SQUID Trial for the Embolization of the Middle Meningeal Artery for Treatment of Chronic Subdural Hematoma), and MAGIC-MT[68] (Managing Non-Acute Subdural Hematoma Using Liquid Materials: A Chinese Randomized Trial of MMA Treatment) trials were presented at the International Stroke Conference. All 3 trials met their primary efficacy end points and demonstrated the safety of MMAE. For the EMBOLISE trial, MMAE with Onyx combined with surgical evacuation was significantly superior to surgical evacuation alone in terms of 90-day cSDH recurrence (4.1% versus 11.3%; P=0.008).[66] For the STEM trial, MMAE with SQUID combined with conventional management (either surgery or observation) versus conventional management alone was associated with significantly lower rates of treatment failure at 180-days, defined as the occurrence or re-accumulation of cSDH measuring 10 mm or greater in thickness, re-operation or surgical rescue, new disabling stroke, myocardial infarction, or death (15.2% versus 39.2%; P=0.0001).[67] Finally, for the MAGIC-MT trial, MMAE with Onyx combined with conventional management (either surgery or observation) was associated with a significantly lower rate of a composite death, symptomatic recurrence in the surgical arm (defined as 10 mm or greater cSDH with neurological symptoms or surgical rescue), and symptomatic progression in the medical arm (defined as 38 mm increase in cSDH thickness or requirement of surgical evacuation) compared to conventional management alone (7.2% versus 12.2%; P=0.02).[68] Given these positive results, it is likely that MMAE will be accepted as the standard of care for the management of cSDHs in select patients; however, details regarding the effectiveness of MMAE in specific patient subgroups based on symptom severity, hematoma size, anticoagulation status, etc, are currently unavailable and await eventual pooled analyses trial results. Thus, definitive guideline recommendations await the formal conclusion of these landmark trials as well as peer-review and eventual publication.

ARISE CONSENSUS ON THE CURRENT CLINICAL APPLICATION OF MMAE

Indications

Although the preliminary data are promising, with the recent positive results presented by the EMBOLISE, STEM, and MAGIC-MT trial investigators, the panel anticipates that Level 1 high quality evidence to support MMAE as a therapeutic target for cSDH will be available, pending the publication of trial results. Current data supports MMAE as an adjunct to conventional surgical or nonsurgical management. MMAE is not currently indicated to replace surgical therapy for symptomatic patients who require surgical management.

The pathophysiology of traumatic SDH is distinctly different from that of cSDH. Unlike cSDH, which forms following small dural border cell layer injuries due to a positive feedback cycle of inflammation, angiogenesis, transudation and recurrent hemorrhage and, thus, may respond to treatments that restrict arterial supply, traumatic acute SDH occurs due to tearing of the bridging veins or arteries, and MMAE is unlikely to have a direct therapeutic effect. As a result, we do not recommend this for the treatment of traumatic acute SDH.

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Embolic Agents and Procedural Techniques

Efforts are underway to study different embolic agents within RCTs. In general, there are 3 categories—liquid embolics, particles, and coils—each with different characteristics and safety profiles. Initial experiences described in the literature suggest that MAAE is feasible with all 3 categories of embolic agents, with some studies suggesting the possible superiority of liquid embolics over particles in terms of efficacy.[39,69] Coils can be used as an adjunct to liquid or particles, and some providers also deploy coils as a standalone treatment.[70,71] Overall, there is a lack of high-quality evidence on the relative efficacy of the various embolic agents.

Liquids, particles, and coils also have different safety profiles. Regardless of agents used, to minimize embolization through visible or unseen dangerous anastomoses such as a dural-pial, meningo-ophthalmic artery, and squamopetrosal branch of the MMA, embolization from a microcatheter positioned above the anterior clinoid process on the lateral image is recommended, preferentially from either the frontal (anterior) or parietal (posterior) branches of the MMA. Liquid embolics offer the highest degree of embolic penetration into distal MMA branches; however, they also carry a risk of penetrating into unseen anastomoses and lead to ischemic complications (eg, to the ophthalmic artery or pial vessels). In contrast, particles with size >150 µm do not penetrate into unseen anastomoses although they offer less penetration. Both liquid and particles can reflux into proximal vessels and branches. Finally, coils carry no risk of reflux or compromising key anastomoses, but they offer no embolic penetration into distal MMA branches.

Overall, MMAE procedures have a good safety profile, with an overall complication rate of ≈3% in the current literature.[72] The risks for stroke, hemorrhage, and visual loss are below 1% individually.[39] Thus, comparative safety profiles of embolic agents are hard to quantify and compare, and their elucidation requires larger prospective studies. In terms of other procedural details, different types of anesthesia (conscious sedation versus general anesthesia) and sites of access (radial versus femoral) are all reasonable options for MMAE. In elderly patients with coagulopathies and multiple comorbidities, conscious sedation and radial access to minimize access and anesthetic complications may be considered. If the decision is made to perform liquid embolization with dimethyl sulfoxide/Onyx under conscious sedation, intra-arterial lidocaine administration is needed to ensure patient comfort.

ARISE CONSENSUS ON THE ONGOING AND FUTURE CLINICAL TRIALS OF MMAE

Global Trial Design

Currently, there are 19 active trials of cSDH listed on https://www.clinicaltrials.gov. Three are pivotal RCTs (Table) being conducted under a US Food and Drug Agency Investigational Device Exemption. These pivotal RCTs are examining liquid embolic agents (Onyx, Medtronic Neurovascular, Irvine, CA; n-butyl cyanoacrylate (n-BCA), Cerenovus, Fremont, CA; and Squid, BALT USA, Irvine). The consensus group supports the design of the major ongoing trials that are largely synchronized

Table. Ongoing RCTs in the United States Under Investigational Device Exemption

	MEMBRANE	STEM	EMBOLISE
Study type	RCT	RCT	RCT
Patients	Chronic SDH	Chronic or subacute SDH	Chronic or subacute SDH
Inclusion criteria	mRS, 0–3	Premorbid mRS, 0–1	Premorbid mRS, 0–2
	No prior treatment	No prior treatment	Markwalder, ≤2
	GCS, ≥9	At least 10-mm cSDH thickness with mass effect	
	Markwalder, ≤2	Has neurological symptoms	
		Imaging evidence of chronicity (>50% hypo- or iso-dense on CT)	
Treatment groups	Conventional management (surgical or nonsurgical) vs conventional management plus MMAE	Conventional management (surgical or nonsurgical) vs conventional management plus MMAE	Conventional management (surgical or nonsurgical) vs conventional management plus MMAE
No. of patients	376	310	600
Embolic agent	NBCA (liquid)	SQUID (liquid)	Onyx (liquid)
Primary outcome	Hematoma recurrence/progression or requiring reintervention (180 d)	Residual or reaccumulation of the SDH (≥10 mm) or surgical rescue or any new, major disabling stroke after enrollment, MI, or death from any neurological cause (180 d)	Incidence of hematoma recurrence/progression requiring reintervention (90 d)

cSDH indicates chronic subdural hematoma; CT, computed tomography; EMBOLISE, Embolization of the Middle Meningeal Artery With ONYX Liquid Embolic System for Subacute and Chronic Subdural Hematoma; GCS, Glasgow Coma Scale; MEMBRANE, Middle Meningeal Artery Embolization for the Treatment of Subdural Hematomas With TRUFILL N-Butyl Cyanoacrylate; MI, myocardial infarction; MMAE, middle meningeal artery embolization; mRS, modified Rankin Scale; NBCA, N-butyl cyanoacrylate; RCT, randomized controlled trial; SDH, subdural hematoma; and STEM, The SQUID Trial for the Embolization of the Middle Meningeal Artery for Treatment of Chronic Subdural Hematoma.

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with respect to their central hypotheses, patient inclusion, randomization structure, and end point selection. This scenario lends itself well to a pooled analysis in the future.

Patient Population

In addition to the STEM and EMBOLISE trials, MEMBRANE (Middle Meningeal Artery Embolization for the Treatment of Subdural Hematomas With TRUFILL N-butyl Cyanoacrylate) is another pivotal liquid embolic RCT in the United States investigating the effectiveness and safety of MMAE as an adjunctive therapy to the standard management of non-emergent, and neurologically stable cSDH patients. All 3 trials excluded patients with cSDH who were neurologically unstable and required emergency surgical intervention. Other patient exclusion criteria are detailed in the Table. Standard management is determined at the site by the managing clinical service, with the major distinction being surgical or nonsurgical management. This determination is then used as a strata for randomization to ensure balance between groups. Patients are then randomized to MMAE or no MMAE. Two of the 3 trials were powered to compare the overall groups (MEMBRANE and STEM), while EMBOLISE was designed and powered to separately evaluate MMAE in surgical and nonsurgical subgroups. These designs, as a first pass toward the evaluation of the adjunctive role of MMAE, are both pragmatic and to some extent necessary, due to the lack of evidence-based standardization of cSDH management worldwide. As of March 2024, STEM and the surgical arm of EMBOLISE have completed patient enrollment and presented preliminary results at the International Stroke Conference (discussed above). Patient enrollment for MEMBRANE and the medical arm of EMBOLISE are ongoing.

Outcome Measures

The pivotal studies have slightly different primary outcome measures but are all prospectively collecting data on similar radiological and clinical end points. Imaging end points are based on serial CT studies being performed between 3 and 6 months after enrollment to assess for adequate regression of the hematoma volume. Adequate regression has been defined as either a reduction to <10 mm in the greatest thickness or ≥50% reduction in volume. Clinical end points include the requirement for surgical rescue (in patients originally assigned to nonsurgical management) or reoperation (for patients originally assigned to surgical management). The end point of operation/reoperation has been almost universally reported in the existing literature describing outcomes for cSDH management strategies. A primary goal of MMAE is to reduce the requirement for subsequent surgical rescue, and this end point provides direct insight into the success or failure of the technique to prevent cSDH progression. While measurements of clinical and neurological function and independence are important, they are not reliable as primary measures of the success or failure of adjunctive MMAE or of symptom resolution in the cSDH study population because patients with cSDH, in general, have a significant burden of medical comorbidities, which, in many cases, outweigh the impact of the cSDH on their functional outcomes over the 6 to 12 months following the cSDH diagnosis (and treatment).[65] In a study of age-matched mortality rates, it was found that the causes of death at follow-up for patients with cSDH were attributable to coronary artery disease, dementia/Alzheimer disease, cancer, and trauma more frequently than the cSDH.[17] When considered in the context of other cerebrovascular diseases, the distinction is more obvious. For example, a patient with a subarachnoid hemorrhage from a ruptured aneurysm or a stroke from an emergent large vessel occlusion, who is dead or disabled 90 or 180 days after the presenting event, is, in all likelihood, dead or disabled directly because of this index event. In distinction, patients presenting with cSDH who are dead or disabled 90 or 180 days after the diagnosis are as likely (or more likely) to have progressed to death or disability from other comorbidities rather than the cSDH itself. For this reason, the end points of hematoma thickness on CT and the clinical end point of operation/reoperation provide a more pragmatic, robust, and direct measure of the effectiveness of the adjunctive MMAE procedure than any measure of global clinical or quality of life outcome.

Possible Challenges

Although there is significant overlap, the patient selection criteria used by the 3 US pivotal RCTs have some variability (Table). Patients with cSDHs are heterogeneous. The diagnostic criteria of cSDHs and indications for treatment are not standardized, and there are no well-established tools to quantify the severity of neurological symptoms. The radiographic appearance of the cSDH may also be associated with the risk of recurrence and treatment response; however, additional imaging biomarkers on cSDH morphology were not part of the patient inclusion/exclusion criteria for the pivotal RCTs and should be considered in future trials.

It is also important to recognize that cSDHs are associated with coagulopathies (which may be due to medical comorbidities such as cancer, liver disease, and kidney disease) and antithrombotic medication use (which may be associated with cardiovascular or hematologic disorders). The degree to which these factors impact study outcomes is not well-known, and perioperative management of comorbidities and antithrombotic medications is not standardized. MMAE is generally safe and

probably remains effective for patients with thrombocytopenia[73] and those on anticoagulation medications[74]; however, perioperative antithrombotic medication use may increase the rates of cSDH recurrence following MMAE.[39,75] As such, variability in these factors may have a large impact on treatment outcomes and confound results. Finally, as previously discussed, the effect of treatment on neurological outcomes of patients with cSDH is difficult to measure as patients present with a wide range of medical comorbidities and neurological symptoms; better tools to account for comorbidities and cSDH disease severity need to be developed, and whether MMAEs improve clinical outcomes beyond the need for repeat treatment will need to be explored further. It is important to recognize that while EMBOLISE, STEM, and MAGIC-MT met their primary efficacy end points,[66–68] careful consideration of factors that contribute to patient and outcome heterogeneity remains necessary for the optimization of MMAE treatments for cSDH.

Ongoing and Future Clinical Trials

The panel recommends pooled analyses of individual patient-level data to allow a more robust analysis of the effectiveness and safety of this new adjunctive treatment modality for cSDH and to facilitate subgroup analysis for specific populations (ie, surgical and nonsurgical management groups, symptom severity, hematoma size, etc). Granular information regarding the impact of medical comorbidities and antithrombotic use on treatment outcomes will also need to be carefully analyzed to assist in optimization of their perioperative management. Future trials such as CHESS (Chronic Subdural Hematoma Treatment With Embolization Versus Surgery Study) and SWEMMA (The Swedish Trial on Embolization of Middle Meningeal Artery Versus Surgical Evacuation in Chronic Subdural Hematoma; NCT05267184) that assess whether MMAE could potentially be a first line therapy for cSDH patients who do not require urgent surgery are emerging.[76] In addition, efforts to compare different embolic agents and techniques, different anesthesia techniques, or MMA infusion of medical therapeutics (eg, bevacizumab) are possible. Finally, MMAE may allow for surgical procedures when necessary to become less invasive, more effective, and safer.

CONCLUSIONS

Multiple randomized, controlled trials have met their primary efficacy end points, providing high-level evidence that MMAE is a potent adjunctive therapy to the standard (surgical and nonsurgical) management of neurologically stable cSDH patients in terms of reducing rates of disease recurrence. Pooled data analyses following the formal publication of these trials will form a robust foundation upon which guidelines can be strengthened for cSDH treatment modalities and optimal patient selection, as well as delineate future lines of investigation.

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Affiliations

Department of Neurosurgery, The University of Texas Medical Branch, Galveston (P.K.). Department of Neurosurgery, Stony Brook University, NY (D.F.). Interventional Neuroradiology and Neuroendovascular Surgery, Miami Neuroscience Institute and Miami Cardiac and Vascular Institute-Baptist Hospital, FL (G.D.). Department of Neurology, The University of Iowa Hospitals and Clinics (E.A.S.). Department of Neurosurgery, Mayo Clinic, Rochester, MN (G.L.). Department of Neurosurgery and Radiology and Canon Stroke and Vascular Research Center, University at Buffalo Jacobs School of Medicine and Biomedical Sciences, NY (A.H.S.). National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD (H.C.). Department of Neurological Surgery, University of California, San Diego, La Jolla (A.A.K.). Division of Neuroradiology, Department of Medical Imaging and Division of Neurosurgery, Department of Surgery, University Health Network, Toronto Western Hospital, ON, Canada (V.M.P.). Department of Neurosurgery, Icahn School of Medicine at Mount Sinai, New York, NY (J.T.F.). Cerebrovascular Center, Departments of Neurology and Neurosurgery, Neurological Institute, Cleveland Clinic Foundation, OH (M.D.B.). Department of Neurosurgery, University of California Los Angeles David Geffen School of Medicine (G.P.C.). Department of Interventional Neuroradiology, Lahey Hospital & Medical Center, Burlington, MA (A.K.W.). Department of Neurosurgery, University of Tennessee Health Science Center, Memphis (A.S.A.).

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