JAMA | Original Investigation

Meningeal Embolization for Preventing Chronic Subdural Hematoma Recurrence After Surgery
The EMPROTECT Randomized Clinical Trial

Eimad Shotar, MD; Bertrand Mathon, MD, PhD; Henri Salle, MD, PhD; Aymeric Rouchaud, MD, PhD; Charbel Mounayer, MD, PhD; Nicolas Bricout, MD; Jean-Paul Lejeune, MD, PhD; Kevin Janot, MD, PhD; Aymeric Amelot, MD, PhD; Olivier Naggara, MD, PhD; Alexandre Roux, MD, PhD; Stéphane Goutagny, MD, PhD; Alexis Guédon, MD, PhD; Emmanuel Houdart, MD, PhD; Hervé Brunel, MD; Jean-François Hak, MD, PhD; Lucas Troude, MD, PhD; Henry Dufour, MD, PhD; Anne-Laure Bernat, MD; Titien Tuilier, MD; Damien Bresson, MD, PhD; Caroline Apra, MD, PhD; Mathilde Fouet, MD; Simon Escalard, MD; Dorian Chauvet, MD; Kevin Premat, MD; Said Lebbah, MD; Agnès Dechartres, MD, PhD; Frédéric Clarencon, MD, PhD; for the EMPROTECT Investigators

IMPORTANCE Middle meningeal artery (MMA) embolization has been proposed as a potential treatment for chronic subdural hematoma (CSDH).

OBJECTIVE To assess the efficacy of MMA embolization in reducing the risk of CSDH recurrence at 6 months compared with standard care in patients who underwent an operation and were at high risk of CSDH recurrence.

DESIGN, SETTING, AND PARTICIPANTS Multicenter, open-label, randomized clinical trial with blinded end point assessment. Patients who underwent an operation for CSDH recurrence or a first CSDH episode at high risk of recurrence were recruited from July 2020 to March 2023 in 12 French neurosurgical or comprehensive neurosurgical and interventional neuroradiology centers. Last follow-up took place on November 2, 2023.

INTERVENTION Participants were randomized 1:1 to undergo MMA embolization with microparticles within 7 days of surgery (171 patients, intervention group) or standard medical care alone (171 patients, control group).

MAIN OUTCOMES AND MEASURES The primary end point was the rate of CSDH recurrence at 6 months assessed by an independent, blinded adjudication committee. There were 5 secondary end points, including rates of repeat surgery for homolateral CSDH recurrence during the 6-month follow-up period and embolization procedure–related complications.

RESULTS Among 342 randomized patients (median [IQR] age, 77 [68-83] years; 274 [80.1%] male), 308 (90.1%) completed the trial. The primary end point was observed in 24 of 162 (14.8%) and 33 of 157 (21.0%) patients in the intervention and control groups, respectively (after imputation: odds ratio, 0.64 [95% CI, 0.36-1.14]; adjusted absolute difference, −6% [95% CI, −14% to 2%]; $P = .13$). The groups did not significantly differ in any of the secondary end points. Repeat surgery was performed in 7 of 162 (4.3%) and 13 of 157 (8.3%) patients in the intervention and control groups ($P = .14$), respectively. Minor and major embolization procedure–related complications occurred in 3 of 171 (1.8%) and 1 of 171 (0.6%) patients, respectively.

CONCLUSIONS AND RELEVANCE In this randomized clinical trial, among patients who underwent an operation for CSDH recurrence or a first CSDH episode at high risk of recurrence, MMA embolization did not lead to a significantly lower rate of recurrence at 6 months compared with standard medical care alone. However, the magnitude of the effect estimate is consistent with other recent trials, including some that demonstrated the benefit of MMA embolization with nonadhesive liquid embolic agents, and these findings considered together may inform future studies and potential use of this therapeutic approach for CSDH management.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT04372147

JAMA. 2025;334(2):127-135. doi:10.1001/jama.2025.7583
Published online June 5, 2025.

Visual Abstract

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The EMPROTECT Investigators appear in Supplement 6.

Corresponding Author: Eimad Shotar, MD, Department of Neuroradiology, Pitié-Salpêtrière Hospital, 47-83 Bd de l'Hôpital, Paris 75013, France (eimad.shotar@aphp.fr).

Chronic subdural hematoma (CSDH), which is already a common disease, is expected to rapidly become the most prevalent neurosurgical disease, given current demographic trends.[1-4] CSDH is associated with increased mortality compared with standardized mortality data, which corroborates the description of CSDH as a sentinel health event.[5] Surgery is considered the standard of care for compressive symptomatic CSDH.[6,7] However, recurrence remains a significant concern, as it is observed in 1 out of 10 surgically treated patients with CSDH and negatively affects both patient survival and functional outcome.[6,8,9] Adjunct medical treatments in CSDH management are deemed modestly helpful at best[10,11] and deleterious at worst.[12]

Embolization of the middle meningeal artery (MMA) has been suggested as a stand-alone treatment for CSDH or as an adjunct to surgery.[13] A growing body of nonrandomized studies historically suggested a possible benefit of postoperative MMA embolization on CSDH recurrence, especially in patients at risk of recurrence.[13,14] Three recently published trials have assessed the efficacy of MMA embolization using nonadhesive liquid embolic agents as a stand-alone treatment or as an adjunct to surgery.[15-18]

The aim of the Embolization of the MMA for the Prevention of CSDH Recurrence in High-Risk Patients (EMPROTECT) trial was to assess the efficacy of MMA particle embolization, performed within 7 days of CSDH surgery, in reducing the risk of CSDH recurrence at 6 months compared with standard medical care alone in patients at high risk of postoperative CSDH recurrence.

Key Points

Question Does middle meningeal artery (MMA) embolization reduce the rate of chronic subdural hematoma (CSDH) recurrence in patients who underwent an operation and are at high risk of recurrence?

Findings In this randomized clinical trial that included 342 participants, the rate of CSDH recurrence was 14.8% in the MMA embolization group and 21.0% in the medical management alone group, a difference that was not statistically significant (adjusted odds ratio, 0.64 [95% CI, 0.36-1.14]).

Meaning Among patients who underwent surgery for CSDH recurrence or a first CSDH episode who are at high risk of recurrence, MMA embolization did not lead to a significantly lower rate of recurrence at 6 months compared with standard medical care alone.

Methods

Trial Design and Oversight

The initial version of the EMPROTECT trial protocol, a table of successive protocol amendments, and appendices to the trial protocol are available as supplemental material (Supplement 1, the eTable in Supplement 2, and Supplement 3, respectively). Key aspects of trial methodology were previously published.[19] Briefly, EMPROTECT is an academic-led, multicenter, open-label randomized clinical trial (RCT) with blinded assessment of the primary end point by an adjudication committee. Patients were enrolled in 12 French centers by neurosurgery or interventional neuroradiology investigators. All patients or their representatives provided written informed consent. Trial sites were neurosurgical or comprehensive neurosurgical and interventional neuroradiology centers, all providing 24/7 neurosurgical emergency services. Ethical approval was obtained from the Comité de Protection des Personnes Ile de France III on January 10, 2020 (reference No. 3754- I). This report fully adheres to the CONSORT reporting guidelines.

Patients

Patients were eligible for enrollment if they were 18 years or older, affiliated with a social security scheme, and at high risk of CSDH recurrence after burr hole surgery for CSDH or CSDH recurrence. High risk of CSDH recurrence was defined as surgery for CSDH recurrence or surgery for a first episode of CSDH with at least 1 of the following recurrence risk factors: chronic alcoholism defined by daily alcohol consumption greater than 30 g, liver cirrhosis, antiplatelet or anticoagulant therapy, thrombocytopenia with platelet count less than $100 \times 10^3/mm^3$, or surgery without use of an external subdural drain. The definition of CSDH was pragmatically left to the discretion of the study investigators.

Patients were not eligible for inclusion if CSDH evacuation was performed by craniotomy or twist drill craniostomy rather than burr hole surgery (definitions are provided in the eMethods in Supplement 4). Additionally, patients were not eligible beyond 7 days after the index surgery (surgery for recurrent CSDH or first surgery with a risk factor indicated in the inclusion criteria); if they were functionally dependent with a modified Rankin Scale (mRS) score of 4 or above before the CSDH; they were deemed to have a life expectancy of less than 6 months; had kidney failure defined by creatinine clearance of less than 30 mL/min; were pregnant; had a history of allergy to an iodinated contrast agent; if the embolization procedure was deemed unachievable under local anesthesia (eg, because of patient agitation or discomfort) in a patient with contraindication to both conscious sedation and general anesthesia; in case of patient refusal; if follow-up was deemed problematic (eg, living abroad or homeless); or in case of legal guardianship or trusteeship.

Randomization and Trial Procedures

Patients were randomly assigned 1:1 to the experimental intervention (MMA embolization) or the control (standard medical care alone) via a central web-based randomization system (CleanWEB). Randomization involved using random permuted blocks of 2 and 4 patients with stratification for center, treatment with antiplatelet or anticoagulant medication (yes vs no), and unilateral or bilateral CSDH status.

Details of the trial procedure are available in the eMethods in Supplement 4. Briefly, in the intervention group, patients underwent computed tomography (CT) angiography of the supra-aortic and intracranial vessels followed by MMA embolization within 7 days of surgery, along with best medical treatment. During the embolization procedure, the MMA was

catheterized with a Progreat 2.4 microcatheter (Terumo Corporation) above the foramen spinosum and embolized by free-flow injection of 300- to 500-µm Embosphere (Merit Medical) trisacryl gelatin microspheres (TAGM). Standard medical management received by patients in the control group is described in the eMethods in Supplement 4. The need for a new imaging workup, a new hospital admission, or reoperation was at the discretion of the treating neurosurgeon.

End Points

The primary end point was CSDH recurrence rate at 6 months, defined as the reappearance of a homolateral CSDH with a midline shift of 5 mm or greater or a symptomatic homolateral CSDH, including leading to death; the presence of a homolateral CSDH greater than 10 mm in maximal thickness on the 6-month control head CT scan; the need for repeat surgery for homolateral CSDH recurrence; or the need for a new hospital admission related to homolateral CSDH recurrence.

Secondary end points included the rate of repeat surgery for homolateral CSDH recurrence during the 6-month follow-up period; rate of disability and dependency at 1 and 6 months, defined by an mRS score of 4 or greater; mortality rate at 1 and 6 months; total cumulative hospital stay directly or indirectly related to the CSDH during the 6-month follow-up period; and minor and major embolization procedure-related complication rates.

The primary and secondary end points were evaluated by a local neurosurgeon or interventional neuroradiologist investigator during an intermediate visit at 1 month and a final visit at 6 months. If the patient failed to attend the follow-up visits, the investigator interviewed the patient, a legal representative, or a health care professional by phone.

An independent adjudication committee evaluated the primary end point blinded to the randomization group. The committee adjudicated the following cases: CSDH recurrence reported by the local investigator; hospital admission potentially related to the CSDH; a medical visit potentially related to the CSDH other than the 1- and 6-month planned visits; a head CT or magnetic resonance imaging (MRI) scan potentially related to CSDH recurrence other than those planned at the 1- and 6-month end points; any new surgery potentially related to the CSDH; or any neurological symptoms. This list of events is in the final version of the protocol and was modified in the fourth and fifth amendments of the protocol in effect on July 27, 2021, and June 7, 2022, respectively, to be as exhaustive as possible.

Sample Size Calculation

The CSDH recurrence rate was approximately 10% in large epidemiological studies and meta-analyses.[6,20,21] Because the study population consisted of patients with prior recurrence and recurrence risk factors, the CSDH recurrence rate at 6 months was estimated at 15% in the control group. In a retrospective study comparing the impact on recurrence rate of postsurgical embolization of CSDH with a historical cohort in patients with a higher-than-average risk of recurrence, a 10% absolute difference was found in favor of embolization.[14] To show an absolute difference of 10%, with 80% power and a 2-sided overall α risk of 5%, and 20% lost to follow-up, the trial needed to include 342 patients. This sample size was calculated considering 2 sequential tests planned according to the Lan-DeMets method with an O'Brien-Fleming alpha-spending function.

Statistical Analysis

We planned a sequential analysis of the primary end point with 2 analyses: an interim analysis after the evaluation of the primary end point for the first 129 patients and a final analysis at the end of the study. The analysis was planned according to the Lan-DeMets method, with the O'Brien-Fleming alpha-spending function. The trial could be stopped after the interim analysis in case of a difference between the 2 groups attested at the α threshold of .001 or for futility in case of low conditional power. The stopping rules were not met at the interim analysis, and the data safety monitoring board recommended continuing the trial.

The primary analysis was the comparison of the rate of CSDH recurrence at 6 months between the 2 groups assessed by the adjudication committee, with a logistic regression model taking into account stratification factors, namely anticoagulant and antiplatelet medication vs no medication and unilateral or bilateral CSDH status with randomization group. We planned to introduce center as a random effect, but did not because variance of the random effect was estimated to be zero, indicating no significant variability between centers. An adjusted absolute risk difference in the recurrence rate at 6 months was also estimated, as was its 95% CI by using bootstrap analysis. The primary analysis involved all randomized patients according to their randomization group (full analysis set). Missing data were imputed by multiple imputation,[22] and patients who died from a neurological or unknown cause were considered to have CSDH recurrence. Details regarding the multiple imputation method are available in the eMethods in Supplement 4.

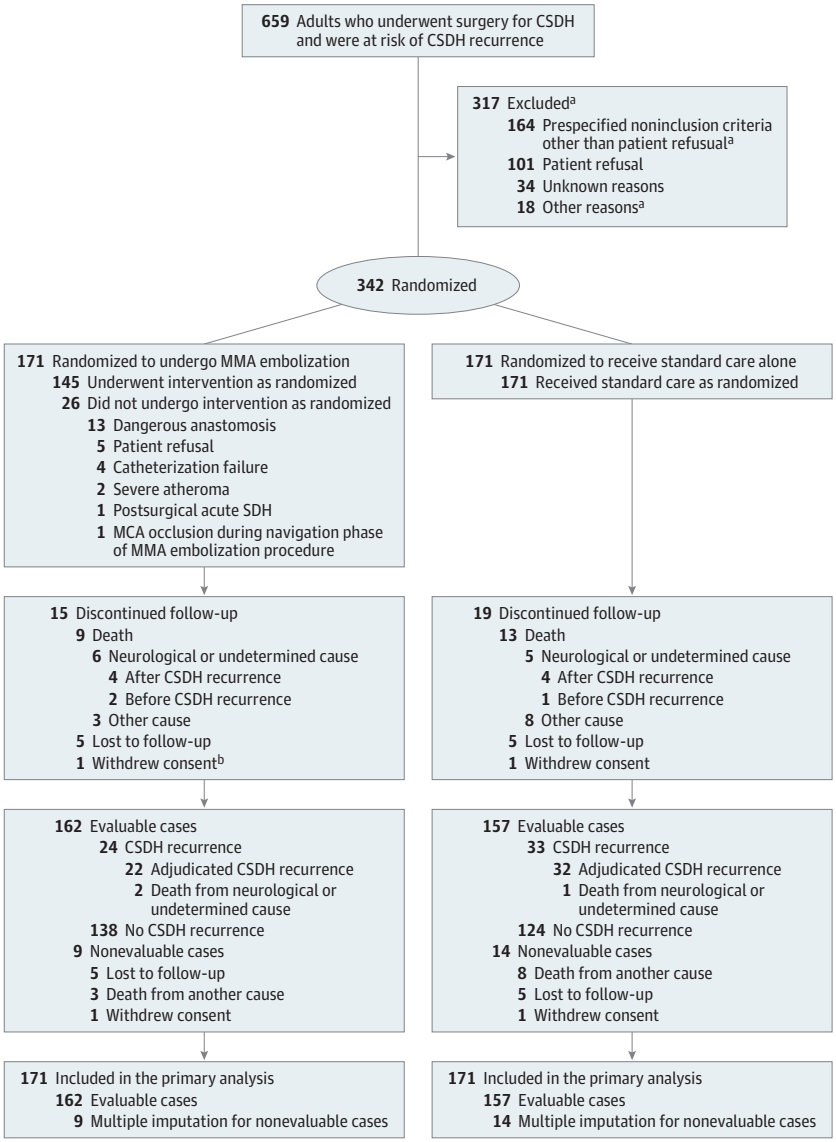
The significance threshold of the interim analysis had limited impact on the α risk. Therefore, the significance threshold for the final analysis was 0.05.

Two prespecified subgroup analyses for the primary end point were conducted: unilateral vs bilateral CSDH status and anticoagulant or antiplatelet therapy medication status (yes vs no). Interaction was tested in the logistic regression model.

We conducted the following sensitivity analyses for the primary end point: analysis without adjudication of CSDH recurrence (assessment of the primary end point by on-site investigators); analysis in the full analysis set but without imputation (ie, lost to follow-up and death from a non-neurological cause were considered no event); analysis without patients who did not undergo embolization in the experimental group (after CT angiography or for other reasons), if any; and analysis without patients wrongly included (ie, patients presenting at least 1 noninclusion criteria or not all inclusion criteria). This sensitivity analysis was not performed because of no wrongly included patients.

Regarding the secondary end points, rate of repeat surgery for homolateral CSDH recurrence, 1- and 6-month mortality rates were compared between the 2 groups by χ^2 test or

Figure 1. Study Flowchart



[a]See eFigure 1 in Supplement 4 for reasons for excluding patients with an inclusion criterion, prespecified noninclusion criteria other than patient refusal, and other reasons.

[b]Patient withdrew consent before the embolization procedure.

CSDH indicates chronic subdural hematoma; MCA, middle cerebral artery; MMA, middle meningeal artery; SDH, subdural hematoma.

Fisher exact test, as appropriate. The rate of disability and dependency at 1 and 6 months was assessed with a generalized estimating equation model. The total cumulative duration of hospital stay was compared between the 2 groups with a Wilcoxon rank-sum test. We did not apply a correction for subgroup or secondary end point analyses. Therefore, these analyses should be considered exploratory.

Statistical analysis was performed with R version 4.1.0 (R Foundation). All statistical tests were 2-sided. The full statistical analysis plan is provided in Supplement 5.

Results

Patients

From July 2020 to March 2023, of the 659 patients assessed for eligibility, 342 were included and randomized: 171 patients in each group (**Figure 1**) (eFigure 1 in Supplement 4; numbers of included patients by center are provided in eTable 1 in Supplement 4). Follow-up was discontinued for 15 and 19 patients in the intervention and control groups, the most frequent reason being death in 9 and 13 patients, respectively.

The median (IQR) age was 77 (68-83) years, and 274 of 342 (80.1%) patients were male (**Table 1**). At baseline, 237 (69.3%) patients were taking antiplatelet or anticoagulant medication. In total, 257 (75.1%) and 85 (24.9%) patients had a unilateral and bilateral CSDH, respectively. The study groups were comparable in baseline characteristics.

Among the 171 patients randomized to undergo embolization, 26 did not undergo the intervention, the most frequent reason being the presence of an arterial anastomosis indicating a perceived risk of nontarget embolization (13 cases). Difficult access led to catheterization failure in 4 cases and 2 patients exhibited severe atheroma, which precluded safe

Table 1. Demographic and Clinical Characteristics of Included Patients at Baseline by Treatment

Characteristic	No./total No. (%)	
	Embolization (n = 171)[a]	Standard care (n = 171)
Age, median (IQR), y	77 (68-83)	77 (69-84)
Sex, No. (%)		
Female	32 (18.7)	36 (21.1)
Male	139 (81.3)	135 (78.9)
Medical history, No. (%)		
Hypertension	101 (59.1)	103 (60.2)
Diabetes	39 (22.8)	42 (24.6)
Stroke	24 (14.0)	22 (12.9)
Myocardial infarction	18 (10.5)	17 (9.9)
Cardiac failure	16 (9.4)	9 (5.3)
Median ASA score (IQR)[b]	2.0 (1.0)	2.0 (1.0)
CSDH recurrence risk factors		
Antiplatelet or anticoagulant therapy	119/171 (69.6)	118/171 (69.0)
Chronic alcoholism	25/171 (14.6)	27/171 (15.8)
Surgery for CSDH recurrence	23/171 (13.5)	22/171 (12.9)
Surgery without external drain	16/167 (9.6)	15/163 (9.2)
Liver cirrhosis	5/171 (2.9)	3/171 (1.8)
Thrombocytopenia (platelet count <100 × 10^3/μL)	4/170 (2.4)	4/171 (2.3)
Symptoms at CSDH presentation		
Known head trauma	69/144 (47.9)	70/141 (49.6)
Hemiparesis	64/101 (63.4)	72/105 (68.6)
Gait disturbance	51/101 (50.5)	58/104 (55.8)
Headache	65/167 (38.9)	70/163 (42.9)
Speech disorder	34/100 (34.0)	31/105 (29.5)
Altered mental status (Glasgow Coma Scale score <12)[c]	9/150 (6.0)	21/149 (14.1)
Laboratory		
PR, median (IQR)	92 (82-99)	93 (83-100)
APTTr, median (IQR)	1 (0.9-1.1)	1 (0.9-1.1)
Initial imaging results		
Unilateral CSDH, No. (%)	127 (74.3)	130 (76.0)
Maximal unilateral CSDH thickness, median (IQR), mm	22 (18-26) [n = 122]	23 (20-26) [n = 122]
Bilateral CSDH, No. (%)	44 (25.7)	41 (24.0)
Median maximal bilateral CSDH thickness (IQR), mm	22 (17-26) [n = 43]	23 (15.2-26) [n=38]
Midline shift, median (IQR), mm[d]	10 (7-13) [n = 161]	10.5 (7-14) [n = 161]
Treatment		
Trepanation burr hole craniostomy[e]	150/167 (89.8)	146/163 (89.6)
Trephine craniostomy[e]	17/167 (10.2)	18/163 (11.0)
Unilateral CSDH surgery	135/171 (78.9)	137/163 (84.0)
Bilateral CSDH surgery	36/171 (21.1)	26/163 (16.0)
Corticosteroids	19/171 (11.1)	22/171 (12.9)
CSDH surgery complications		
Seizure	2/167 (1.2)	2/163 (1.2)
External drain malposition	2/152 (1.3)	0/152 (0)
Infections	1/95 (1.1)	0/86 (0)
Other[f]	7/167 (4.2)	11/163 (6.7)

Abbreviations: APTTr, activated partial thromboplastin time ratio; ASA, American Society of Anesthesiologists; CSDH, chronic subdural hematoma; PR, prothrombin rate.

[a] Data were missing for 1 patient in the embolization group.

[b] ASA scores range from 1 to 6, with higher scores indicating worse status.

[c] Glasgow Coma Scale scores range from 3 to 15, with lower scores indicating worse status.

[d] Data provided for unilateral CSDH only.

[e] Craniostomy procedures were performed either with a cranial drill (burr hole craniostomy) or a skull trephine cylindrical saw (trephine craniostomy), both allowing the creation of openings up to 30 mm, defined as burr hole craniostomy, as opposed to larger openings, defined as craniotomy.

[f] Others included acute subdural hematomas, intraparenchymal hematoma, bleeding scalp wound, confusion, diabetic ketoacidosis, acute agitation, worsening of agitation and confusion, platelet transfusion, and accidental drain removal.

endovascular navigation. Five patients refused embolization despite having agreed to inclusion in the study and 1 patient was denied embolization after a diagnosis of acute postsurgical subdural hematoma. In 1 case, the embolization procedure was terminated prematurely because of middle cerebral artery occlusion, which complicated carotid artery navigation and required mechanical thrombectomy. No patient in the control group underwent MMA embolization.

Primary End Point

The observed 6-month recurrence rate was 14.8% (24/162 patients, including 22 adjudicated CSDH recurrences and 2 deaths from a neurological or undetermined cause) in the embolization group and 21.0% (33/157 patients, including 32 adjudicated CSDH recurrences and 1 death from a neurological or undetermined cause) in the control group (**Table 2**) (event rates for each component of the outcome are provided in eTable 2 in Supplement 4). After imputation, the adjusted odds ratio (OR) was 0.64 (95% CI, 0.36-1.14), corresponding to an adjusted absolute difference of −6% (95% CI, −14% to 2%; P = .13).

On subgroup analyses of CSDH localization and anticoagulant or antiplatelet use, the 2 treatment groups did not differ, and interaction tests were not statistically significant (**Figure 2**). Sensitivity analyses gave consistent results, with no significant difference between the 2 groups (eFigure 2 in Supplement 4). In particular, when the on-site investigator's assessment of the primary end point was used instead of the adjudication committee's assessment, the difference remained not statistically significant (OR, 0.61 [95% CI, 0.35-1.06]; P = .08).

Table 2. Results for the Primary and Secondary End Points

End point	No./total No. (%) Embolization (n = 171)	Standard care (n = 171)	Absolute difference (95% CI)	*P* value
Primary end point				
6-mo CSDH recurrence	24/162 (14.8)[a]	33/157 (21.0)[a]	−0.06 (−0.14 to 0.02)[b]	.13[c]
Adjudicated CSDH recurrence	22	32	NA	NA
Death from neurological or undetermined cause	2	1	NA	NA
Secondary end points				
Rate of repeat surgery for homolateral CSDH recurrence	7/162 (4.3)	13/157 (8.3)	−4.0 (−9.4 to 1.4)[d]	.14[e]
1-mo Disability and dependency rate, mRS score ≥4, % (95% CI)[f]	9.6 (4.8-14.4)	5.8 (2.1-9.5)	3.8 (−2.3 to 9.9)[g]	.22
6-mo Disability and dependency rate, mRS score ≥4, % (95% CI)[f]	8.2 (3.9-12.5)	7.4 (3.2-11.6)	0.8 (−5.2 to 6.8)[g]	.79
1-mo Mortality rate	3/165 (1.8)	3/165 (1.8)	0 (−3.0 to 3.0)[d]	1.00[h]
6-mo Mortality rate	9/165 (5.5)	13/165 (7.9)	−2.4 (−7.9 to 2.9)[d]	.38[e]
Total cumulative duration of hospital stay directly or indirectly related to CSDH, median (IQR), d	10 (6-26.5)	9 (5-28.5)	1 (−1 to 5)[d]	.12[i]
Embolization procedure-related complications[j]				
Major complications, No. (%)	1 (0.6)			
Mechanical thrombectomy after the occurrence of intracranial MCA occlusion during carotid catheterization	1 (0.6)			
Minor complications, No. (%)	3 (1.8)			
Transient neurological deficit	2 (1.2)			
Mild headaches	1 (0.6)			

Abbreviations: CSDH, chronic subdural hematoma; MCA, middle cerebral artery; mRS, modified Rankin Scale; NA, not applicable.

[a] Observed CSDH recurrence assessed by the blinded, independent adjudication committee. Case numbers and percentages based on observed values before multiple imputation were reported.

[b] Absolute difference adjusted for randomization stratification factors, namely the use of anticoagulants or antiplatelets and the unilateral or bilateral nature of the CSDH in the intention-to-treat population after imputation; 95% CIs were estimated using bootstrap analysis.

[c] Estimated using a logistic regression model adjusted on randomization stratification factors, namely the use of anticoagulants or antiplatelets and unilateral or bilateral nature of the CSDH in the full analysis set after multiple imputation.

[d] The absolute differences reported for secondary outcomes are unadjusted and based on observed rates without multiple imputation.

[e] *P* value of Pearson χ^2 test.

[f] The mRS evaluates the disability or dependence level in daily activities and ranges from 0 to 6, with higher scores indicating more severe disability.

[g] The treatment effect is the risk difference of 1- and 6-month disability and dependency rate with 95% CIs estimated using the generalized estimating equation for binary outcomes.

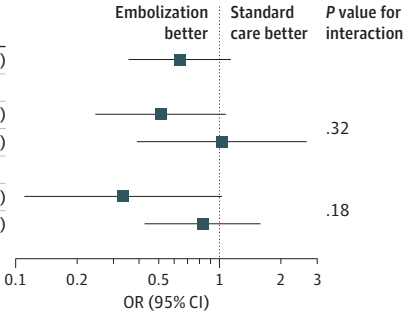
[h] *P* value of Fisher exact test for count data.

[i] *P* value of Wilcoxon rank-sum test.

[j] A detailed list of prespecified embolization procedure–related complications is provided in eTable 3 in Supplement 4.

Figure 2. Subgroup Analysis of the Primary End Point

Subgroup	No./total No. Embolization group	Standard care group	OR (95% CI)	*P* value for interaction
All patients	24/162	33/157	0.64 (0.36-1.14)	
CSDH localization				
Unilateral	12/118	22/117	0.51 (0.25-1.07)	.32
Bilateral	12/44	11/40	1.03 (0.39-2.67)	
Anticoagulant or antiplatelet medication use				
No	5/51	13/50	0.34 (0.11-1.03)	.18
Yes	19/111	20/107	0.83 (0.43-1.59)	



Subgroup plot of 6-month CSDH recurrence assessed by the adjudication committee according to CSDH localization (unilateral and bilateral) and anticoagulant or antiplatelet use (yes vs no). A logistic regression model with an interaction term tested whether the treatment effect significantly depended on the factor levels of the 2 variables.

CSDH indicates chronic subdural hematoma; OR, odds ratio.

Secondary End Points

Of the 171 patients included in the intervention group, 7 of 162 (4.3%) required repeat surgery for recurrence of the CSDH homolateral to that in the initial operation compared with 13 of 157 (8.3%) in the control group (*P* = .14). The 2 groups did not significantly differ in 1- and 6-month disability and dependence rate or mortality rate. Median (IQR) total cumulative hospital stay directly or indirectly related to the CSDH was 10 (6-26.5) days in the embolization group and 9 (5-28.5) days in the control group (*P* = .12) (Table 2).

One major complication of MMA embolization was recorded (0.6%). As mentioned earlier, a patient had a stroke

because of middle cerebral artery occlusion during MMA embolization, which led to mechanical thrombectomy, so MMA embolization was aborted. This complication did not result in severe neurological sequelae (mRS score was 2 at 1 month and 1 at 6 months). Nevertheless, we classified this event as a major complication. Three minor procedure-related complications were recorded (1.8%): 1 patient presented with transient left-sided hemiparesis, resolved in less than 10 minutes, with an MRI showing neither infarction nor vascular occlusion; 1 patient presented with transient aphasia at the end of the procedure; and 1 patient had mild headaches (Table 2). Details on all complications of interest are provided in eTable 3 in Supplement 4. The 2 groups did not differ in rate of adverse events (**Table 3**).

Table 3. Adverse Events

Adverse event	No. (%)	
	Embolization (n = 171)	Standard care (n = 171)
Serious adverse events	36 (21.1)	32 (18.7)
No. of serious adverse events, median (IQR)	0	0
Adverse events	91 (53.2)	89 (52.0)
No. of adverse events, median (IQR)	1 (0-2)	1 (0-1.5)
Adverse events of interest		
Complications related to CSDH and hematoma evacuation surgery[a]	18 (10.5)	23 (13.5)
Subdural empyema	6 (3.5)	4 (2.3)
Acute subdural hematoma	1 (0.6)	0
Complications of CT angiography	1 (0.6)	0
Aspiration pneumonia	1 (0.6)	0
Urinary infection complicated by pyelonephritis	2 (1.2)	0
Deep vein thrombosis of the lower limbs and pulmonary embolism	1 (0.6)	1 (0.6)

Abbreviations: CSDH, chronic subdural hematoma; CT, computed tomography.

[a] All adverse events were reported by the study investigators to the Vigilance Department of the sponsor (Department of Clinical Research and Innovation by delegation). The adverse events were declared to be related or not to CSDH and hematoma evacuation surgery. Blinded clinical data were provided to the Vigilance Department, which had the final say in accepting or refusing to acknowledge the causal relationship.

Discussion

In this multicenter RCT conducted in France, the rate of CSDH recurrence at 6 months after surgery was not significantly lower with MMA embolization than with medical treatment alone in patients with CSDH at risk of recurrence. The 2 groups did not differ in adverse event rates. Only 1 major MMA embolization procedure-related complication was documented during the study period (0.6%).

Nonrandomized studies have suggested a possible benefit of MMA embolization in terms of recurrence and the need for surgical rescue.[13,14,23-25] First reported more than 2 decades ago as a salvage therapy in patients with surgical comorbidities, embolization has grown in popularity in recent years.[10,26] The results of 3 industry-sponsored trials (EMBOLISE, MAGIC-MT, and STEM) assessing MMA embolization using a liquid embolic agent as a stand-alone treatment or as an adjunct to surgery have recently been reported and are summarized in eTable 4 in Supplement 4.[15-18] EMBOLISE and STEM showed statistically significant results for the primary end point, while MAGIC-MT did not demonstrate a significant difference, in line with study results.

There are several possible explanations regarding the lack of a statistically significant benefit of MMA embolization in the EMPROTECT trial. First, differences across the trials in primary end point definitions may explain part of the differences in results. Problematic heterogeneity in the definitions of the outcome measures throughout the CSDH literature has been pointed out before.[27] Second, although a 10% difference in CSDH recurrence rate was expected, the observed difference was 6%, which may suggest a more modest benefit of embolization than expected. This finding could be related to the choice of embolic agent. In contrast to EMBOLISE and STEM, which reported positive results with nonadhesive liquid agents, this study used microparticles. As previously reported, the dural arterial supply is highly anastomotic.[28] TAGM particles of 300 to 500 µm are expected to fall short of occluding these anastomotic channels, in turn possibly limiting the impact on CSDH persistent exudation. However, this explanation is insufficient, as MAGIC-MT, reporting results on MMA embolization with a liquid embolic agent as well, reported negative results.

A third explanation may relate to the study population: patients with CSDH who underwent surgery and were at high risk of recurrence. In the STEM trial, the positive effect of MMA embolization was primarily driven by patients who underwent stand-alone MMA embolization compared with observation and the effect was not statistically significant in the subgroup of patients who underwent an operation.[17,18] However, in the EMBOLISE trial, the results for the surgical population indicated that MMA embolization as an adjunct to surgery met the primary end point.[16] Further studies are warranted to clarify which patients most benefit from MMA embolization and with what embolic agents. Fourth, in the EMPROTECT trial, embolization was performed within 7 days of surgery, whereas in the EMBOLISE and STEM trials, MMA embolization was performed before surgery in more than half of patients and all patients, respectively.[16,18] Fifth, play of chance is a possible explanation for missing significance, as the effect point estimate in the current trial generally aligns with those in the other trials.

Study results point to a reassuring safety profile of the MMA embolization procedure, in line with previously published data.[13-18,23-25] Only 1 procedure-related major complication was reported, and more adverse events were not observed in the intervention than control group. The MAGIC-MT trial found fewer serious adverse events within 90 days in the intervention than control group, which emphasizes the overall reassuring safety profile of MMA embolization regardless of the embolic agent used.[15,17] This result is encouraging given the profile of the CSDH population. Indeed, the median age of the study population was older than 75 years, and more than 1 in 10 patients had a history of stroke and/or myocardial infarction.

There was an overrepresentation of male individuals in the study population, but this is in line with overall prevalence of CSDH by sex in France and in the 3 aforementioned trials.[15,16,18]

Limitations

This study has limitations. First, a particular CSDH population was focused on: those who had surgery and risk factors for recurrence. This choice was made because these patients are most likely to experience CSDH recurrence and subsequent complications.[19] Therefore, study results cannot be generalized to patients with CSDH who have not had surgery. Second, only 1 embolic agent was used and the choice of the embolic agent may have affected study results. Third, and most important, the study may have lacked statistical power. Indeed, the recurrence rate defined by the primary end point was higher and the benefit smaller than expected in the sample size calculation.

Conclusions

In this multicenter RCT involving patients with surgically managed CSDH who were at high risk of CSDH recurrence, embolization of the MMA with 300- to 500-µm TAGM did not significantly reduce the rate of recurrence at 6 months. However, the magnitude of the effect estimate is consistent with other recent trials, including some that demonstrated the benefit of MMA embolization with nonadhesive liquid embolic agents, and these findings considered together may inform future studies and potential use of this therapeutic approach for CSDH management.

ARTICLE INFORMATION

Accepted for Publication: April 25, 2025.

Published Online: June 5, 2025. doi:10.1001/jama.2025.7583

Author Affiliations: APHP, Department of Neuroradiology, Pitié-Salpêtrière Hospital, Paris, France (Shotar, Premat, Clarencon); Sorbonne Université, INSERM, CNRS, Institut de la Vision, Paris, France (Shotar); Sorbonne University, Paris, France (Mathon, Clarencon); APHP, Department of Neurosurgery, Pitié-Salpêtrière Hospital, Paris, France (Mathon); Department of Neurosurgery, Limoges University Hospital, Limoges, France (Salle); Department of Interventional Neuroradiology, EMIS Platform, Limoges University Hospital, F-87042, University of Limoges, XLIM, CNRS, UMR 7252, Limoges, France (Rouchaud, Mounayer); Department of Neuroradiology, Lille University Hospital, Lille, France (Bricout); Department of Neurosurgery, Lille University Hospital, Lille, France (Lejeune); Department of Neuroradiology, Tours University Hospital, Tours, France (Janot); Department of Neurosurgery, Tours University Hospital, Tours, France (Amelot); Université Paris Cité, Institute of Psychiatry and Neuroscience of Paris, INSERM U1266, IMABRAIN, GHU-Paris Psychiatrie et Neurosciences, Hôpital Sainte Anne, Neuroradiology, F-75014, Paris, France (Naggara); GHU-Paris Psychiatrie et Neurosciences, Hôpital Sainte Anne, Service de Neurochirurgie, Paris, France (Roux); Université Paris Cité, UFR Médecine Paris Nord, Inserm UMR-S1144, APHP Beaujon Hospital, Department of Neurosurgery, Paris, France (Goutagny); Department of Neuroradiology, Lariboisière Hospital, Paris, France (Guédon, Houdart); Department of Neuroradiology, La Timone Hospital, Marseille, France (Brunel, Hak); Department of Neurosurgery, Hôpital Nord, Marseille, France (Troude); Department of Neurosurgery, La Timone Hospital, Marseille, France (Dufour); Department of Neurosurgery, Lariboisière Hospital, Paris, France (Bernat); Department of Neuroradiology, Henri Mondor Hospital, Créteil, France (Tuilier); Department of Neurosurgery, Henri Mondor Hospital, Créteil, France (Bresson, Apra); Institut Mondor de Recherche Biomédicale, U955 Inserm – Université Paris Est Créteil, UPEC, Créteil, France (Apra); Department of Neurosurgery, Percy Military Teaching Hospital, Clamart, France (Fouet); Department of Interventional Neuroradiology, Fondation Adolphe de Rothschild Hospital, Paris, France (Escalard); Department of Neurosurgery, Fondation Adolphe de Rothschild Hospital, Paris, France (Chauvet); APHP, Unité de Recherche Clinique, Pitié-Salpêtrière Hospital, Paris, France (Lebbah); Sorbonne Université, INSERM, Institut Pierre Louis d'Épidémiologie et de Santé Publique, Equipe PEPITES, APHP, Hôpital Pitié-Salpêtrière, Département de Santé Publique, Paris, France (Dechartres).

Author Contributions: Drs Shotar and Dechartres had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Shotar, Mathon, Roux, Dechartres, Clarencon.
Acquisition, analysis, or interpretation of data: Shotar, Mathon, Salle, Rouchaud, Mounayer, Bricout, Lejeune, Janot, Amelot, Naggara, Roux, Goutagny, Guédon, Houdart, Brunel, Hak, Troude, Dufour, Bernat, Tuillier, Bresson, Apra, Fouet, Escalard, Chauvet, Premat, Lebbah, Dechartres.
Drafting of the manuscript: Shotar.
Critical review of the manuscript for important intellectual content: All authors.
Statistical analysis: Lebbah, Dechartres.
Obtained funding: Shotar, Dechartres.
Administrative, technical, or material support: Shotar, Naggara, Roux, Goutagny, Guédon, Houdart, Brunel, Tuillier, Apra, Fouet, Chauvet, Premat, Dechartres.
Supervision: Mathon, Salle, Bricout, Lejeune, Hak, Dufour, Tuillier, Bresson, Chauvet, Dechartres, Clarencon.

Conflict of Interest Disclosures: Dr Rouchaud reported receiving personal fees from Balt Group outside the submitted work. Dr Escalard reported receiving consulting fees from BCV Systems outside the submitted work. Dr Clarencon reported receiving personal fees from Balt Group, Medtronic, Stryker, and phenox outside the submitted work. No other disclosures were reported.

Funding/Support: The study was funded by an academic grant from Programme Hospitalier de Recherche Clinique (PHRC; IR AOR18104). Industrial support came in the form of donations of several devices. Embosphere trisacryl gelatin microspheres 300- to 500-µm microparticles were provided free of charge by Merit Medical; Optima coils and Vasco+ 10 coiling microcatheters were provided free of charge by Balt Group; and a discount was provided on Prograet microcatheters by Terumo Corporation.

Role of the Funder/Sponsor: PHRC, Merit Medical, Balt Group, and Terumo Corporation had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Data Sharing Statement: See Supplement 7.

Additional Contributions: We thank all members of the clinical research unit, including Anne Bissery, MD, and Bob-Fredy Pene, MSc, for their assistance in drafting the study protocol and conducting the trial; Sabrine Ouamri, MSc, for data monitoring; and Claudine Pardon, MSc (all of Pitié-Salpêtrière Charles Foix Hospital Group), for designing the electronic case report form and data management. We thank all members of the data safety monitoring board: Fabian Baumann, MD, PhD (Klinik für Neurochirurgie, Luzern), Paolo Machi, MD, PhD (Université de Genève), and Bruno Giraudeau, MD, PhD (Université de Tours). We thank all members of the adjudication committee: René Anxionnat, MD, PhD (CHU de Nancy), Mariette Delaitre, MD (Hôpitaux Civils de Colmar), Thiebaud Picart, MD, PhD (Lyon University Hospital), Steven Knafo, MD, PhD (Bicêtre University Hospital), and Silvia Pizzuto, MD (Foch Hospital). We also thank Julien Burel, MD (Rouen University Hospital), for helping in the practical organization of the adjudication committee. None of the abovementioned people received financial compensation for their role in the study. We also thank Laura Smales, BA (BioMedEditing), for English-language revisions; she received financial compensation.

REFERENCES

1. Balser D, Farooq S, Mehmood T, Reyes M, Samadani U. Actual and projected incidence rates for chronic subdural hematomas in United States Veterans Administration and civilian populations. *J Neurosurg*. 2015;123(5):1209-1215. doi:10.3171/2014.9.JNS141550

2. Kudo H, Kuwamura K, Izawa I, Sawa H, Tamaki N. Chronic subdural hematoma in elderly people: present status on Awaji Island and epidemiological prospect. *Neurol Med Chir (Tokyo)*. 1992;32(4):207-209. doi:10.2176/nmc.32.207

3. Iorio-Morin C, Touchette C, Lévesque M, Effendi K, Fortin D, Mathieu D. Chronic subdural hematoma: toward a new management paradigm for an increasingly complex population. *J Neurotrauma*. 2018;35(16):1882-1885. doi:10.1089/neu.2018.5872

4. Neifert SN, Chaman EK, Hardigan T, et al. Increases in subdural hematoma with an aging population—the future of American cerebrovascular disease. *World Neurosurg*. 2020;141:e166-e174. doi:10.1016/j.wneu.2020.05.060

5. Dumont TM, Rughani AI, Goeckes T, Tranmer BI. Chronic subdural hematoma: a sentinel health event. *World Neurosurg*. 2013;80(6):889-892. doi:10.1016/j.wneu.2012.06.026

6. Almenawer SA, Farrokhyar F, Hong C, et al. Chronic subdural hematoma management: a systematic review and meta-analysis of 34,829 patients. *Ann Surg*. 2014;259(3):449-457. doi:10.1097/SLA.0000000000000255

7. Liu W, Bakker NA, Groen RJM. Chronic subdural hematoma: a systematic review and meta-analysis of surgical procedures. *J Neurosurg*. 2014;121(3):665-673. doi:10.3171/2014.5.JNS132715

8. Santarius T, Kirkpatrick PJ, Ganesan D, et al. Use of drains versus no drains after burr-hole evacuation of chronic subdural haematoma: a randomised controlled trial. *Lancet*. 2009;374(9695):1067-1073. doi:10.1016/S0140-6736(09)61115-6

9. Forster MT, Mathé AK, Senft C, Scharrer I, Seifert V, Gerlach R. The influence of preoperative anticoagulation on outcome and quality of life after surgical treatment of chronic subdural hematoma. *J Clin Neurosci*. 2010;17(8):975-979. doi:10.1016/j.jocn.2009.11.023

10. Levitt MR, Hirsch JA, Chen M. Middle meningeal artery embolization for chronic subdural hematoma: an effective treatment with a bright future. *J Neurointerv Surg*. 2024;16(4):329-330. doi:10.1136/jnis-2024-021602

11. Jiang R, Zhao S, Wang R, et al. Safety and efficacy of atorvastatin for chronic subdural hematoma in Chinese patients: a randomized clinical trial. *JAMA Neurol*. 2018;75(11):1338-1346. doi:10.1001/jamaneurol.2018.2030

12. Hutchinson PJ, Edlmann E, Bulters D, et al; British Neurosurgical Trainee Research Collaborative; Dex-CSDH Trial Collaborators. Trial of dexamethasone for chronic subdural hematoma. *N Engl J Med*. 2020;383(27):2616-2627. doi:10.1056/NEJMoa2020473

13. Ban SP, Hwang G, Byoun HS, et al. Middle meningeal artery embolization for chronic subdural hematoma. *Radiology*. 2018;286(3):992-999. doi:10.1148/radiol.2017170053

14. Shotar E, Meyblum L, Premat K, et al. Middle meningeal artery embolization reduces the post-operative recurrence rate of at-risk chronic subdural hematoma. *J Neurointerv Surg*. 2020;12(12):1209-1213. doi:10.1136/neurintsurg-2020-016048

15. Liu J, Ni W, Zuo Q, et al; MAGIC-MT Investigators. Middle meningeal artery embolization for nonacute subdural hematoma. *N Engl J Med*. 2024;391(20):1901-1912. doi:10.1056/NEJMoa2401201

16. Davies JM, Knopman J, Mokin M, et al; EMBOLISE Investigators. Adjunctive middle meningeal artery embolization for subdural hematoma. *N Engl J Med*. 2024;391(20):1890-1900. doi:10.1056/NEJMoa2313472

17. Kan P. Middle meningeal artery embolization and nonacute subdural hematoma. *N Engl J Med*. 2025;392(9):918-920. doi:10.1056/NEJMe2410915

18. Fiorella D, Monteith SJ, Hanel R, et al; STEM Investigators. Embolization of the middle meningeal artery for chronic subdural hematoma. *N Engl J Med*. 2025;392(9):855-864. doi:10.1056/NEJMoa2409845

19. Shotar E, Mathon B, Rouchaud A, et al. Embolization of the middle meningeal artery for the prevention of chronic subdural hematoma recurrence in high-risk patients: a randomized controlled trial—the EMPROTECT study protocol. *J Neurointerv Surg*. 2024;17(e1):e172-e177. doi:10.1136/jnis-2023-021249

20. Maroufi SF, Farahbakhsh F, Macdonald RL, Khoshnevisan A. Risk factors for recurrence of chronic subdural hematoma after surgical evacuation: a systematic review and meta-analysis. *Neurosurg Rev*. 2023;46(1):270. doi:10.1007/s10143-023-02175-1

21. Schmidt L, Gørtz S, Wohlfahrt J, Melbye M, Munch TN. Recurrence of subdural haematoma in a population-based cohort—risks and predictive factors. *PLoS One*. 2015;10(10):e0140450. doi:10.1371/journal.pone.0140450

22. Sterne JAC, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ*. 2009;338:b2393. doi:10.1136/bmj.b2393

23. Kan P, Maragkos GA, Srivatsan A, et al. Middle meningeal artery embolization for chronic subdural hematoma: a multi-center experience of 154 consecutive embolizations. *Neurosurgery*. 2021;88(2):268-277. doi:10.1093/neuros/nyaa379

24. Link TW, Boddu S, Paine SM, Kamel H, Knopman J. Middle meningeal artery embolization for chronic subdural hematoma: a series of 60 cases. *Neurosurgery*. 2019;85(6):801-807. doi:10.1093/neuros/nyy521

25. Ironside N, Nguyen C, Do Q, et al. Middle meningeal artery embolization for chronic subdural hematoma: a systematic review and meta-analysis. *J Neurointerv Surg*. 2021;13(10):951-957. doi:10.1136/neurintsurg-2021-017352

26. Mandai S, Sakurai M, Matsumoto Y. Middle meningeal artery embolization for refractory chronic subdural hematoma. *J Neurosurg*. 2000;93(4):686-688. doi:10.3171/jns.2000.93.4.0686

27. Chari A, Hocking KC, Edlmann E, et al. Core outcomes and common data elements in chronic subdural hematoma: a systematic review of the literature focusing on baseline and peri-operative care data elements. *J Neurotrauma*. 2016;33(17):1569-1575. doi:10.1089/neu.2015.4248

28. Kerber CW, Newton TH. The macro and microvasculature of the dura mater. *Neuroradiology*. 1973;6(4):175-179. doi:10.1007/BF00335317