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MMA – A Promising Intervention for Subdural Hemorrhage

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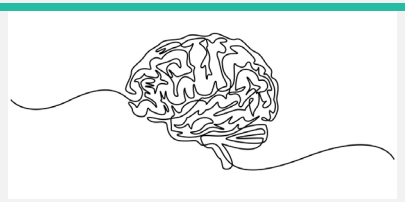


Rhode Island Stroke Symposium

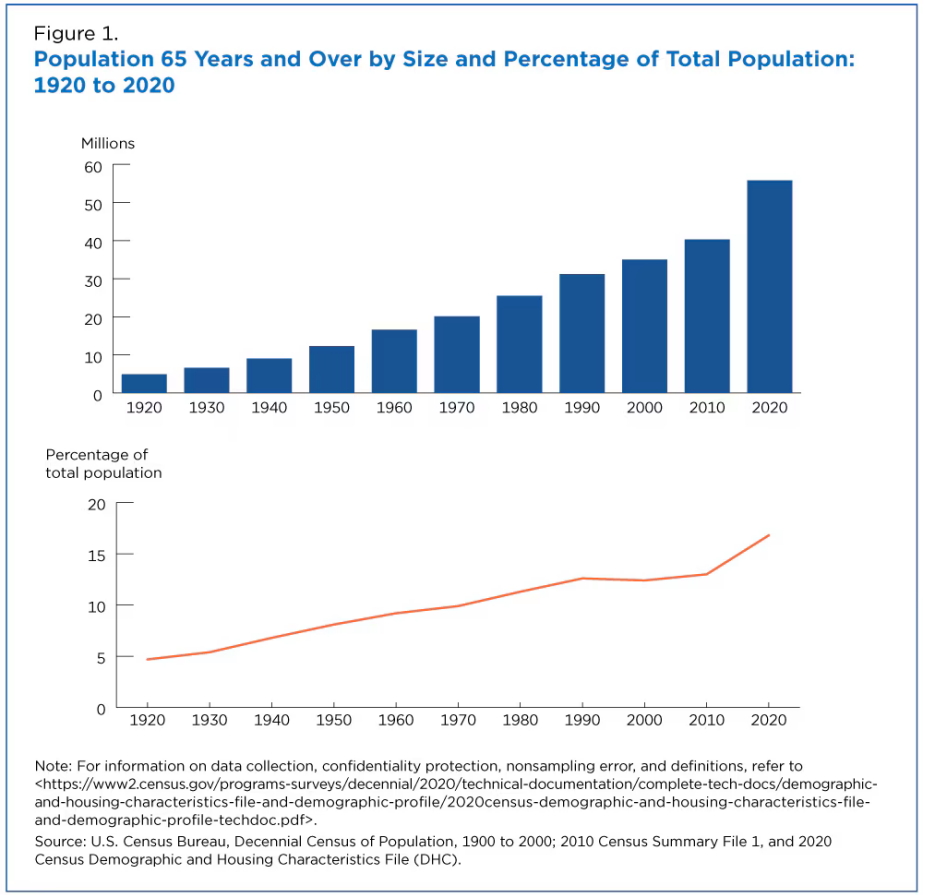
Financial Relationship Disclosure(s)

Krisztina Moldovan, MD

- Nothing to disclose

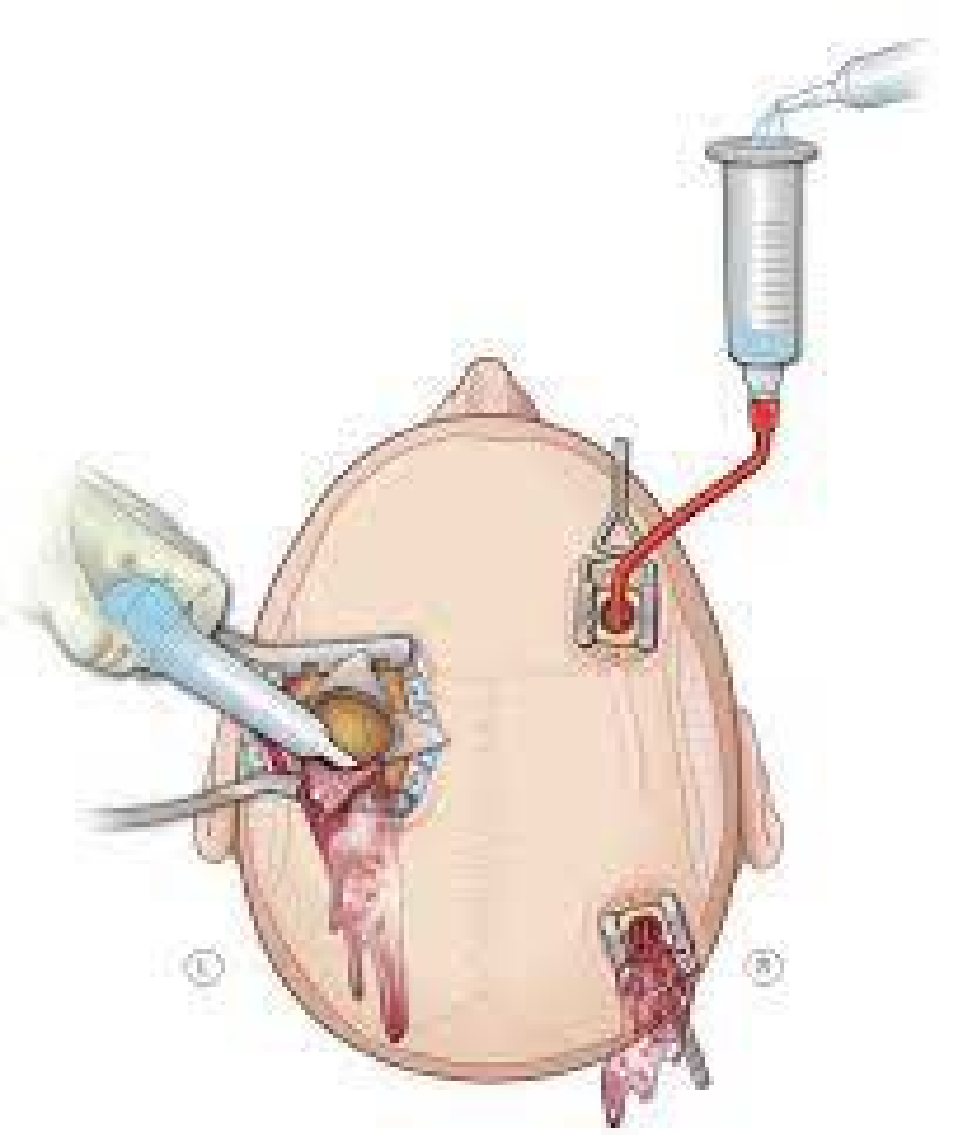
BACKGROUND

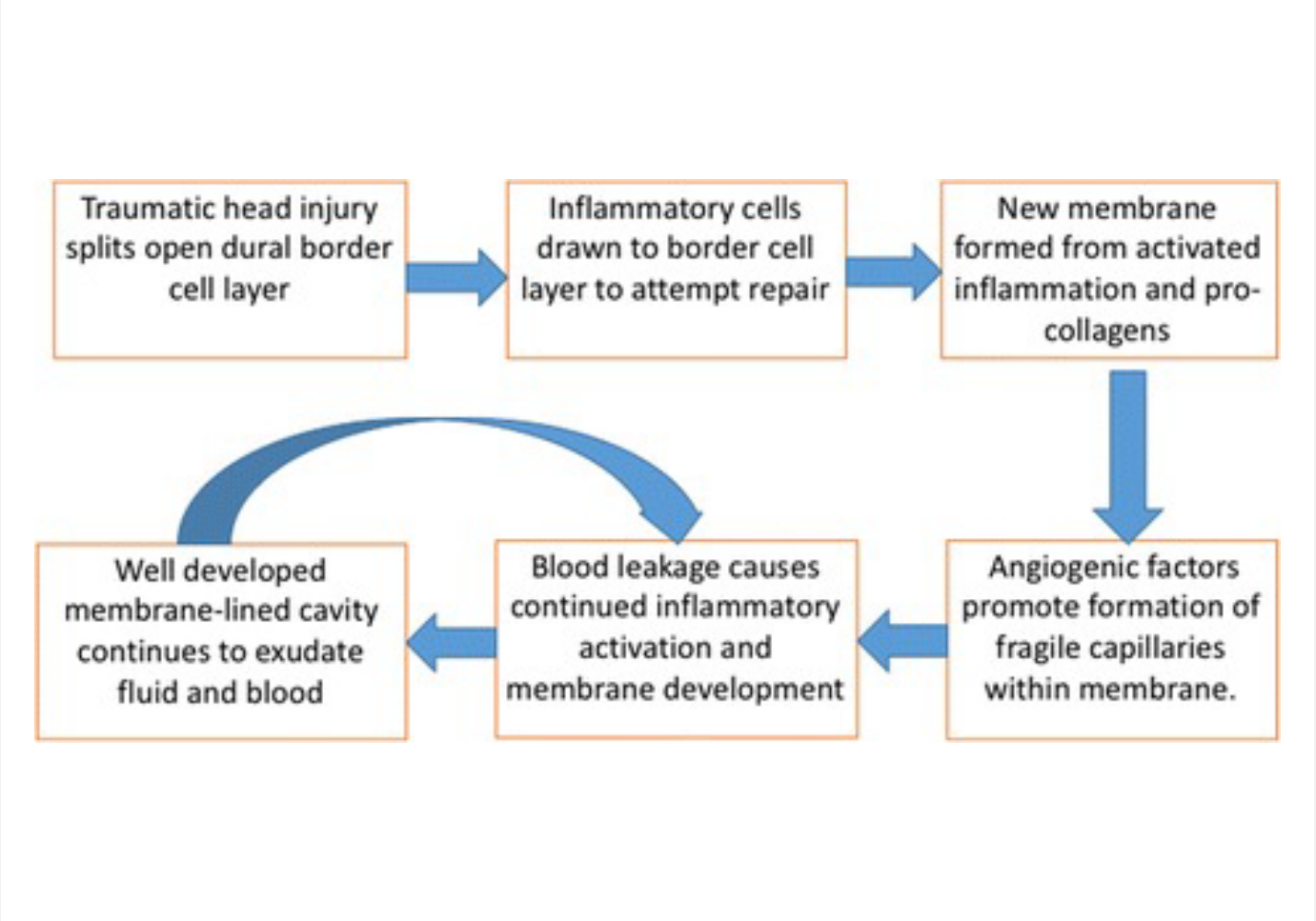
- Chronic SDH is one of the most commonly diagnosed neurosurgical conditions
- Incidence is 5/100,000/yr in general population but 58/100,000/yr in those older than 70yrs
  - Because proportion of ppl aged > 65 expected to double between 2000 – 2030, cSDH is expected to become the most common cranial surgical disease by 2030



CHRONIC SDH MANAGEMENT

- Practice patterns vary widely
- Management strategies include observation and various surgical evacuation options including craniotomy, burr holes and SEPS
- No consistent evidence-based guidelines or indications for one procedure over another
- Treatment failure rates generally very high
  - 5-50% for non-surgical management (Ban et al., Radiology 2018, Jiang JAMA Neurology 2018)
  - 2-37% for surgical management (Weigel et al., BJN 2004, JNNP 2003)

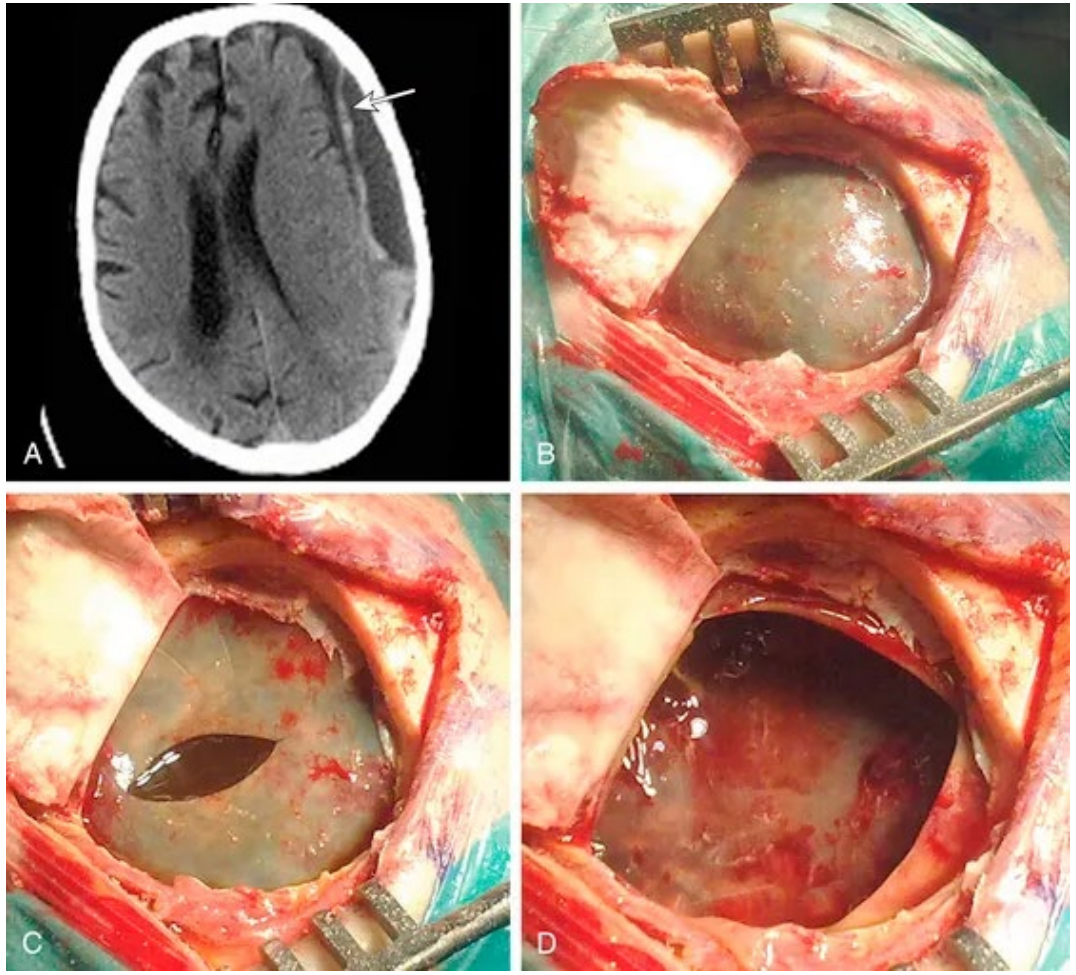




CHRONIC SDH PATHOPHYSIOLOGY

- Accumulation of blood in subdural space >> inflammatory response (fibroblast proliferation, granulation tissue formation, release of angiogenic factors)
  - >>leads to formation of neomembranes within 3-4 wks of primary injury
- Leakage from neomembrane capillaries (which contain highly permeable endothelial gap junctions) contributes to cSDH enlargement and recurrence

Ironside N, et al. J NeuroIntervent Surg 2021;13:951–957. doi:10.1136/neurintsurg-2021-017352 Edlmann et al. Journal of Neuroinflammation (2017) 14:108 DOI 10.1186/s12974-017-0881-y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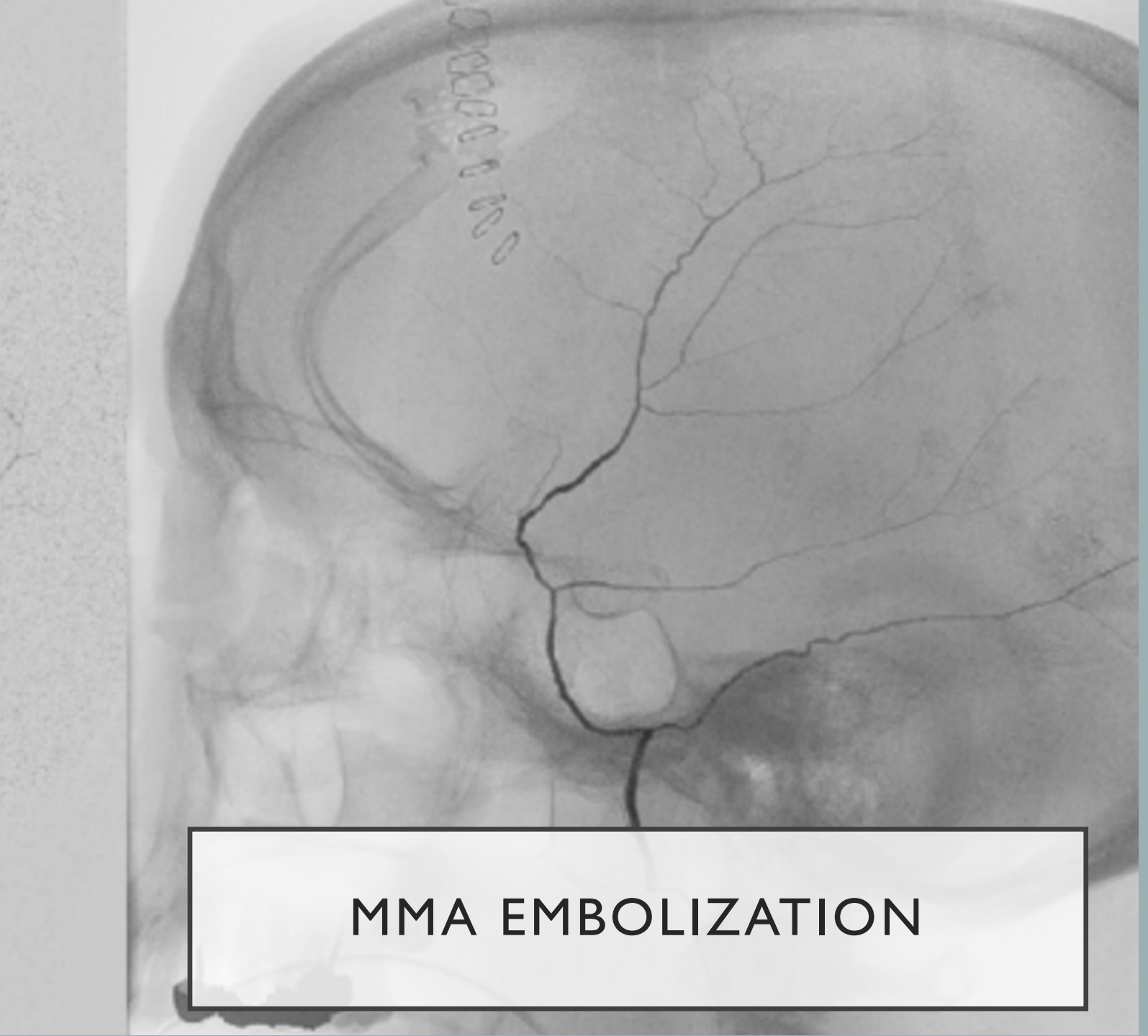


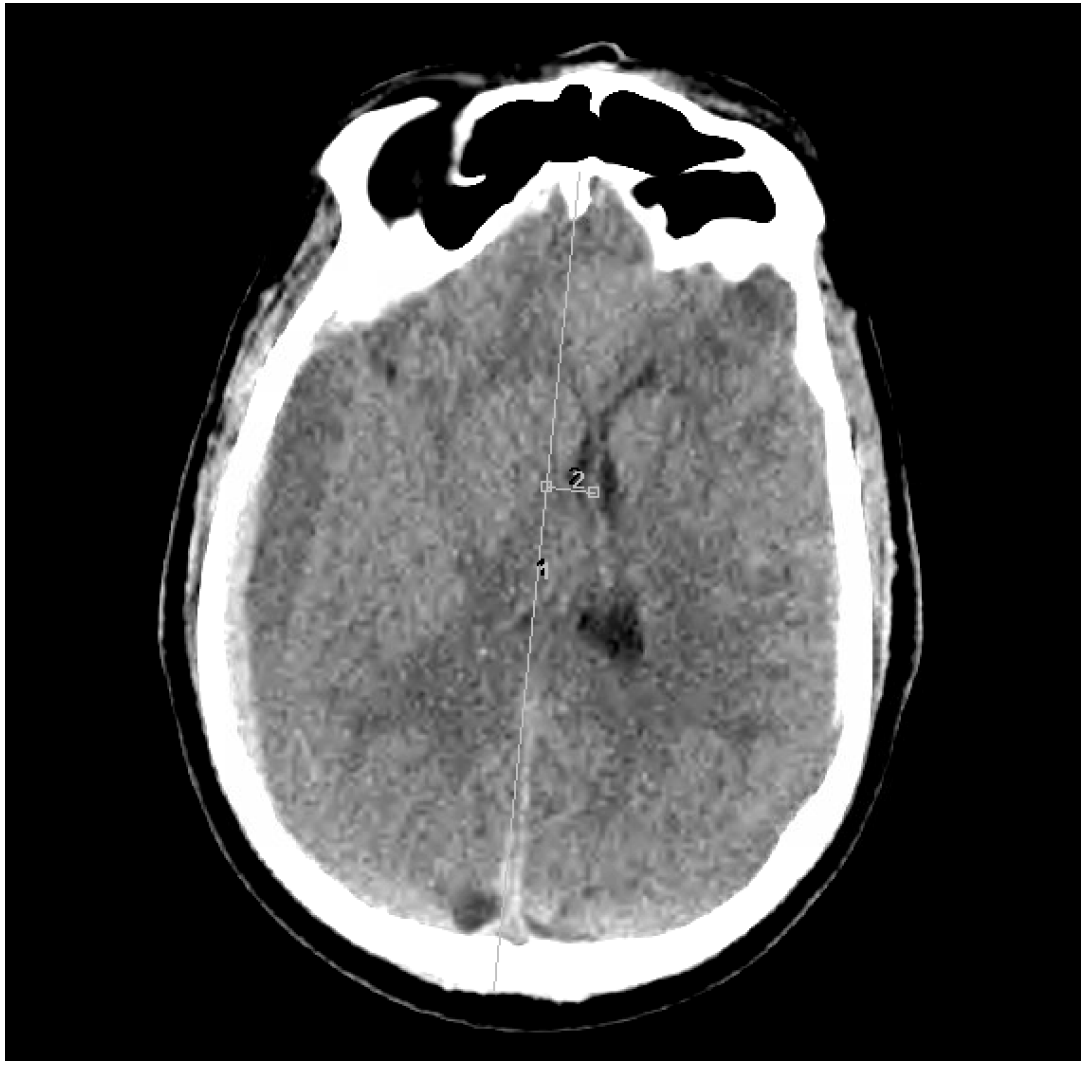
MMA EMBOLIZATION

Elimination of blood supply to SDH neomembranes by embolization of middle meningeal artery proposed as minimally invasive treatment option for cSDH

MMA Embolization with Liquid Embolic Agents introduced to manage high risk patients and surgical failures

- First case described in 2000 by Mandai et al
- Popularity increased around 2018 when first cases using Onyx-18 were performed at Stony Brook and SMC (June 2018)
- Initial Observations Presented in 2019 (Fiorella and Arthur, JNIS 2019; ABCWIN 2019)

CASE EXAMPLE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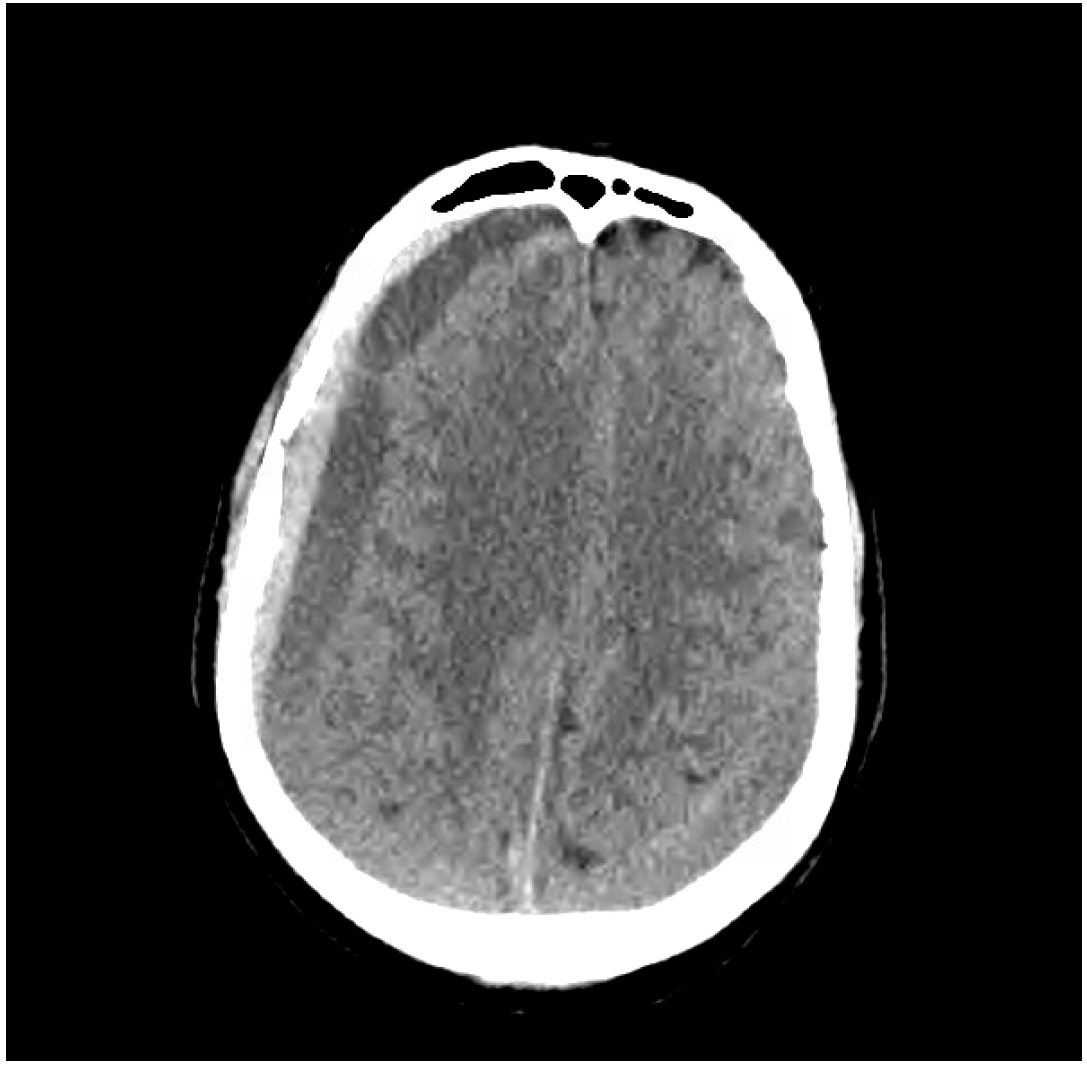

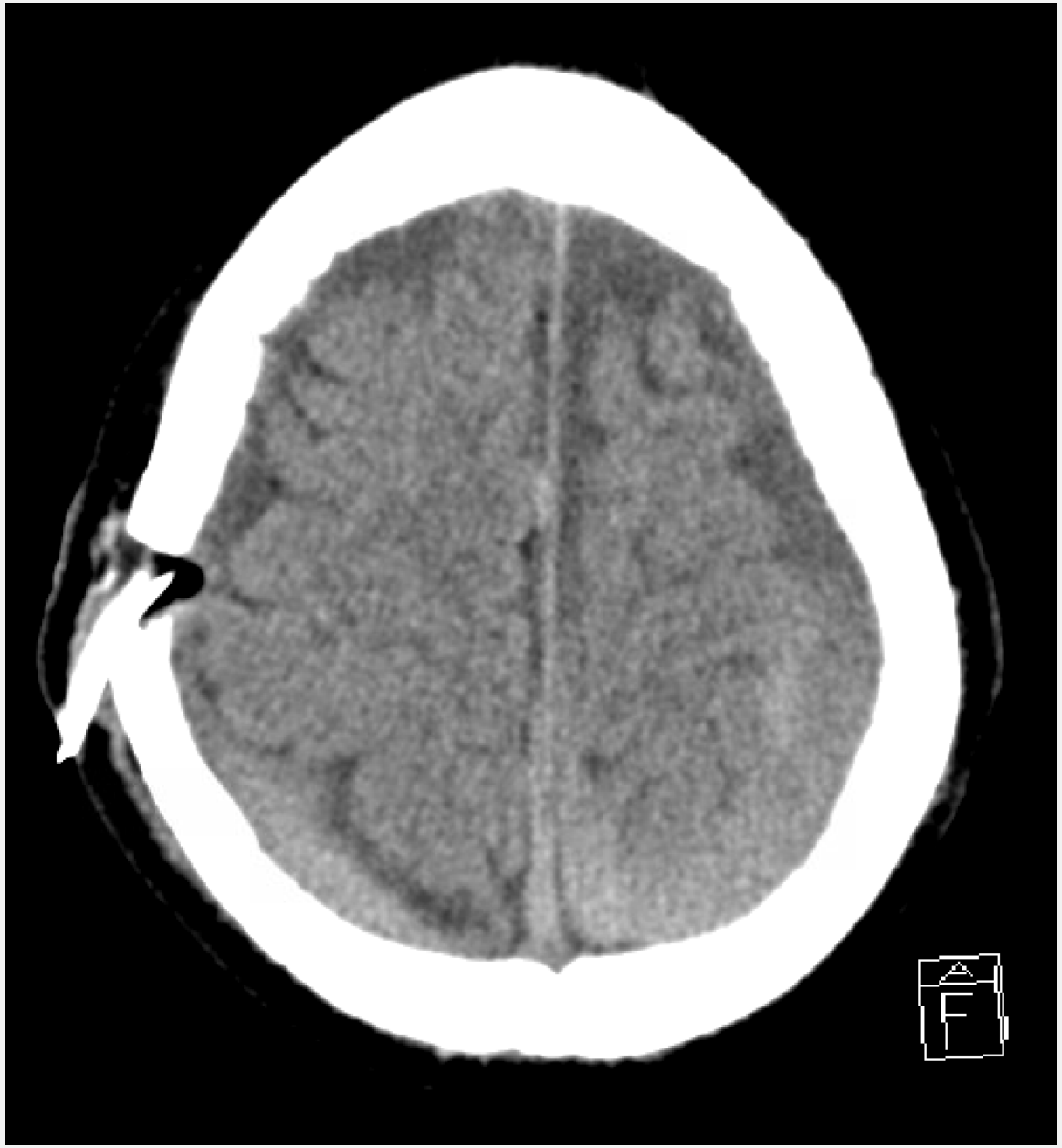
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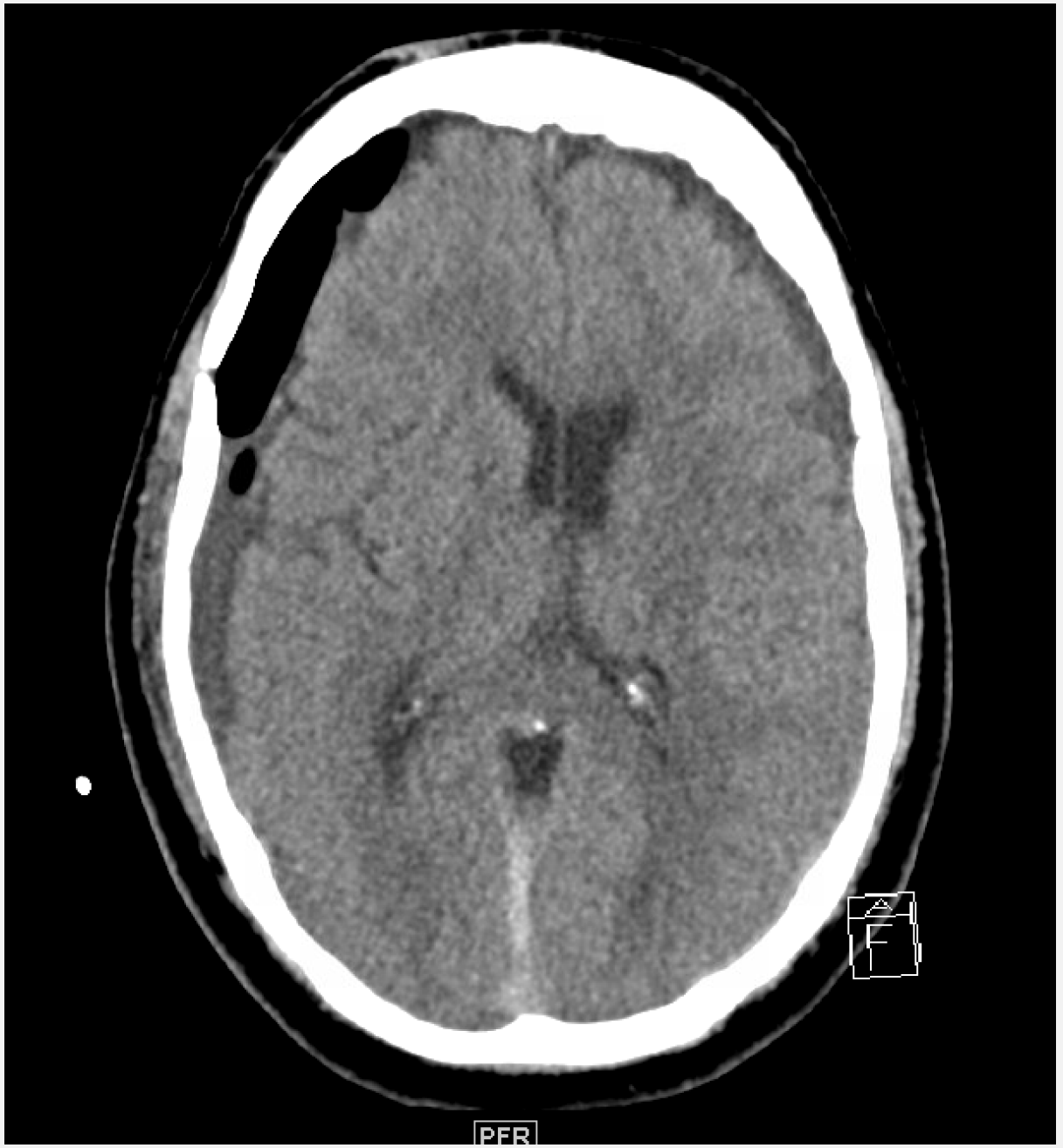
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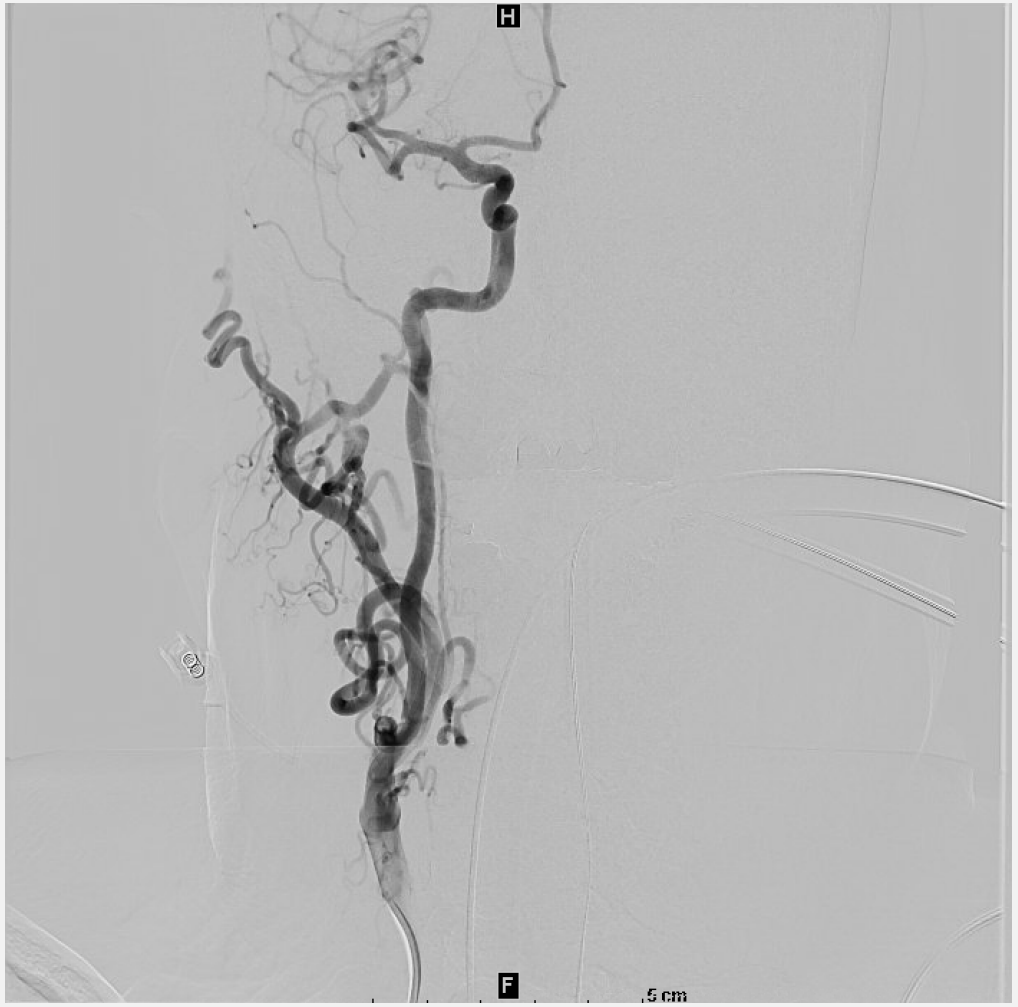
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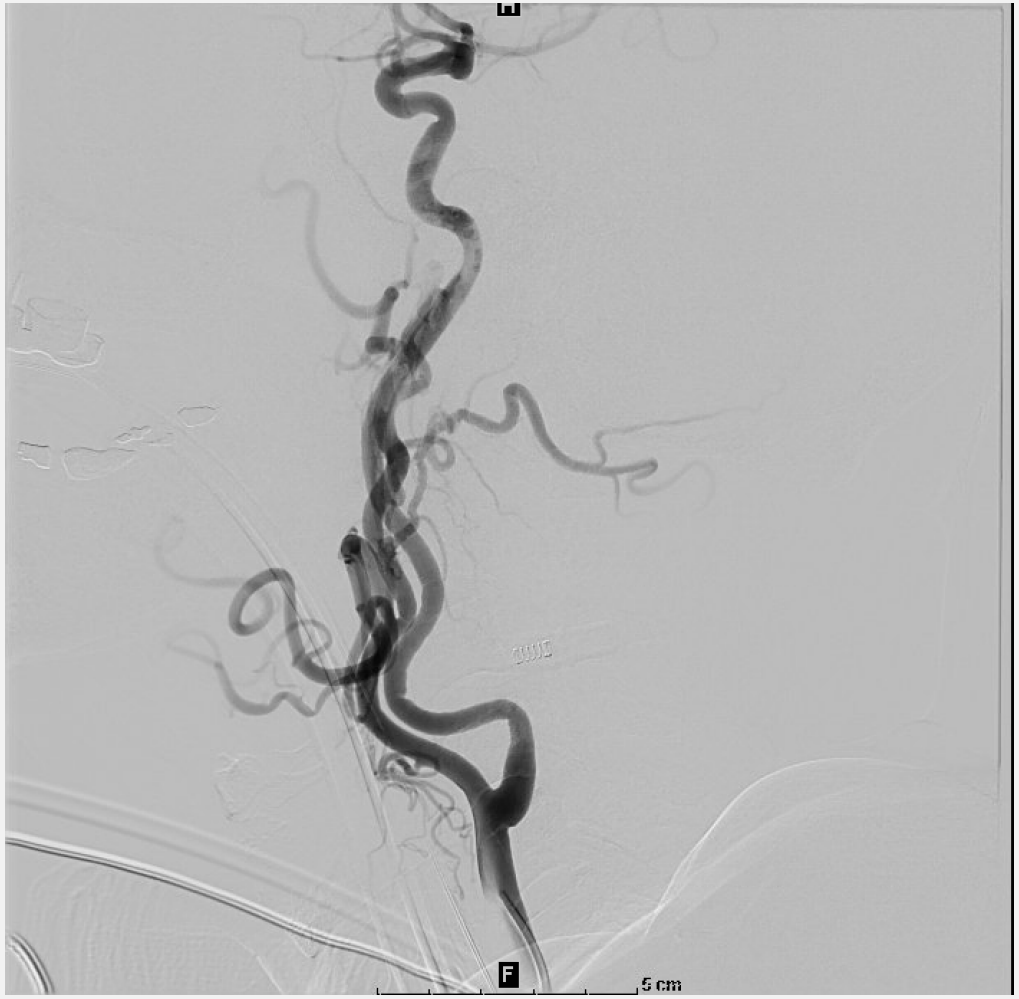
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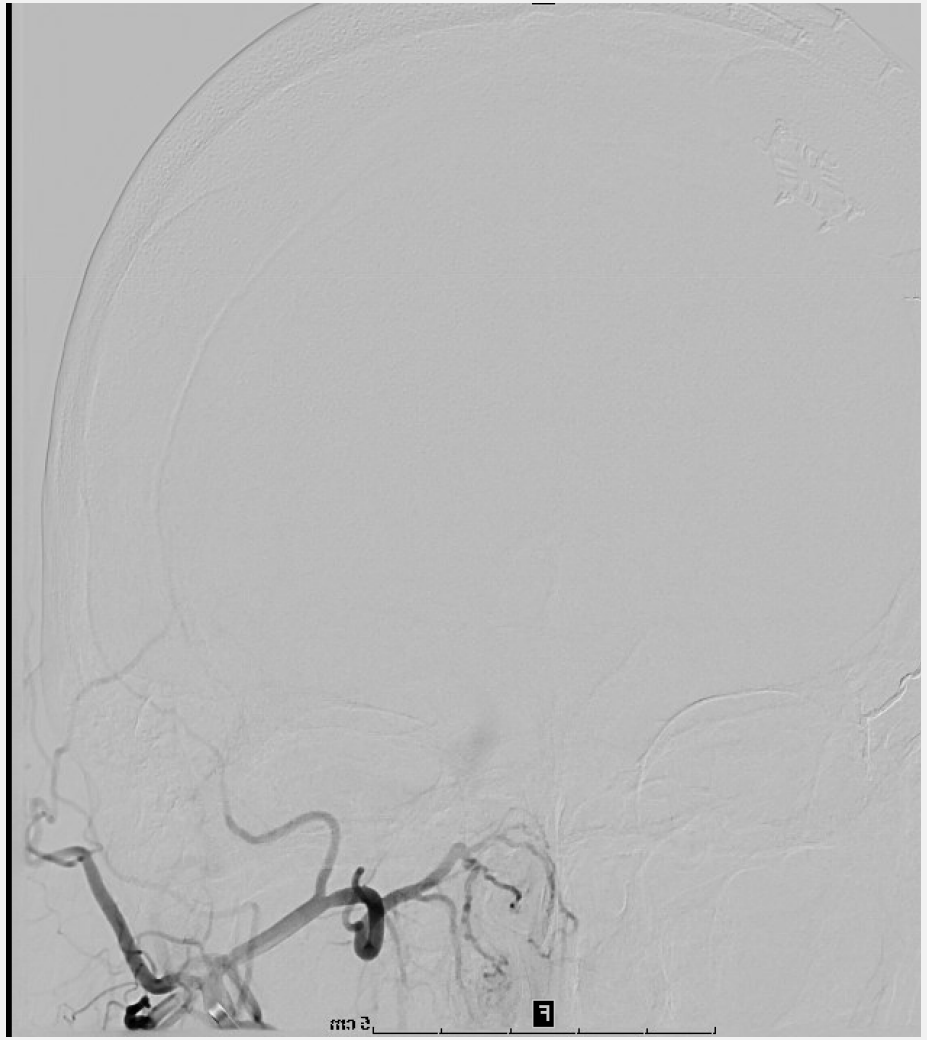

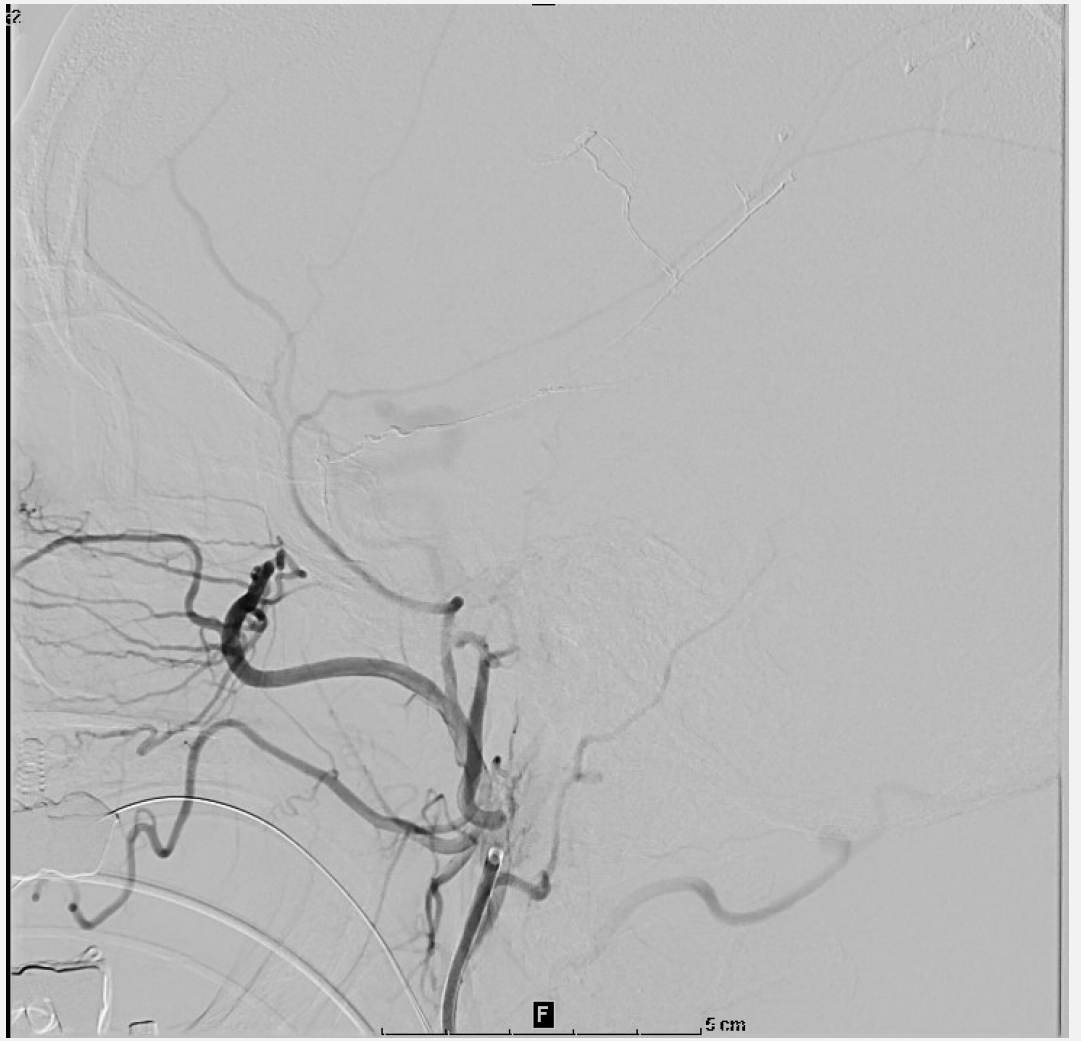
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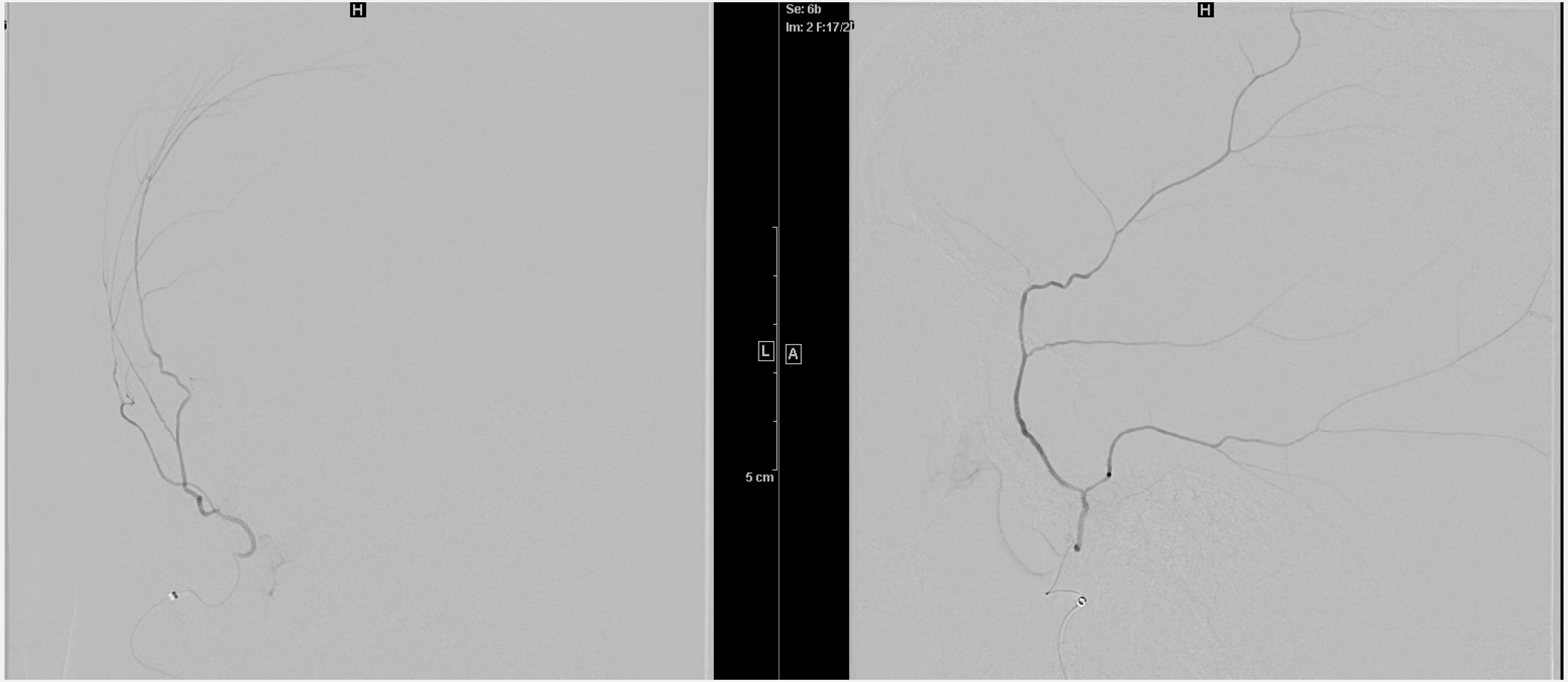
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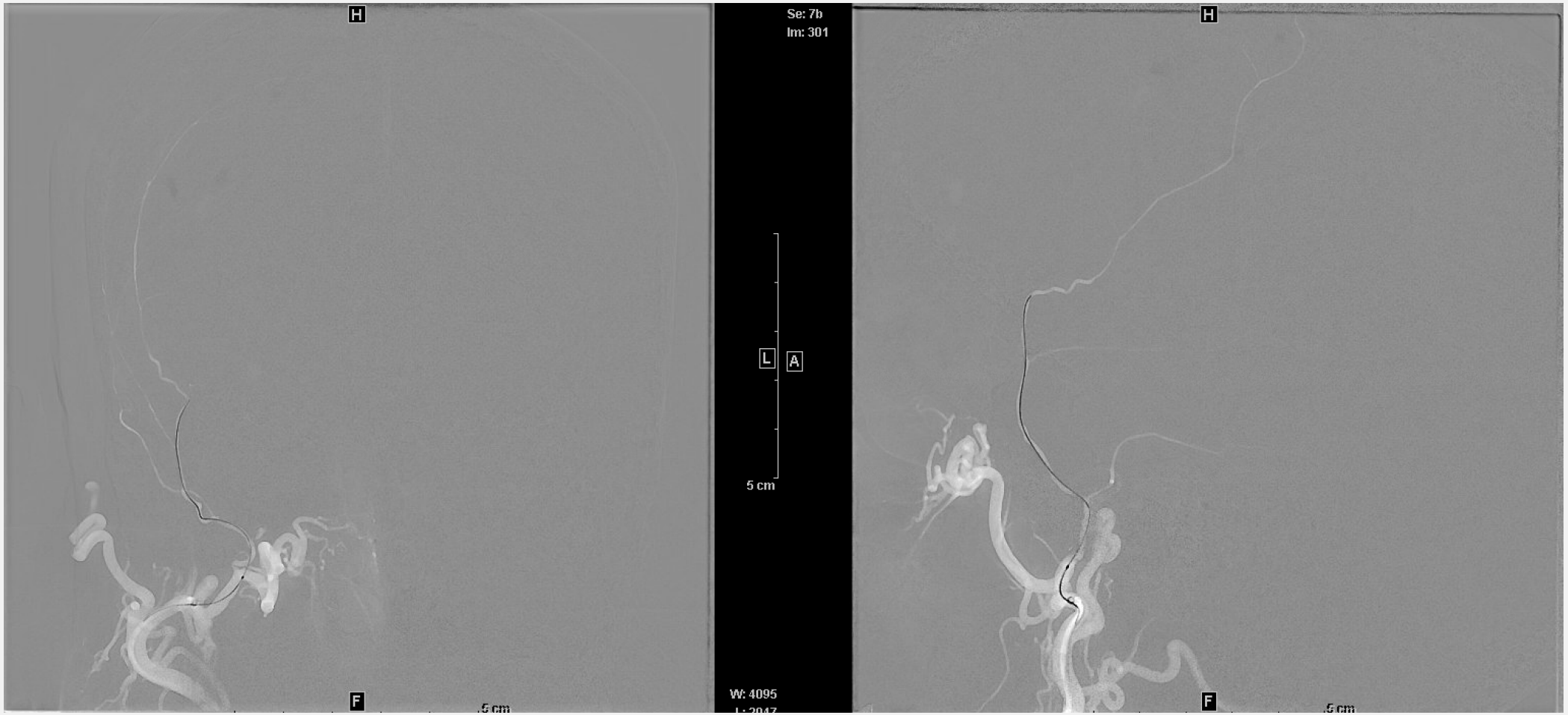
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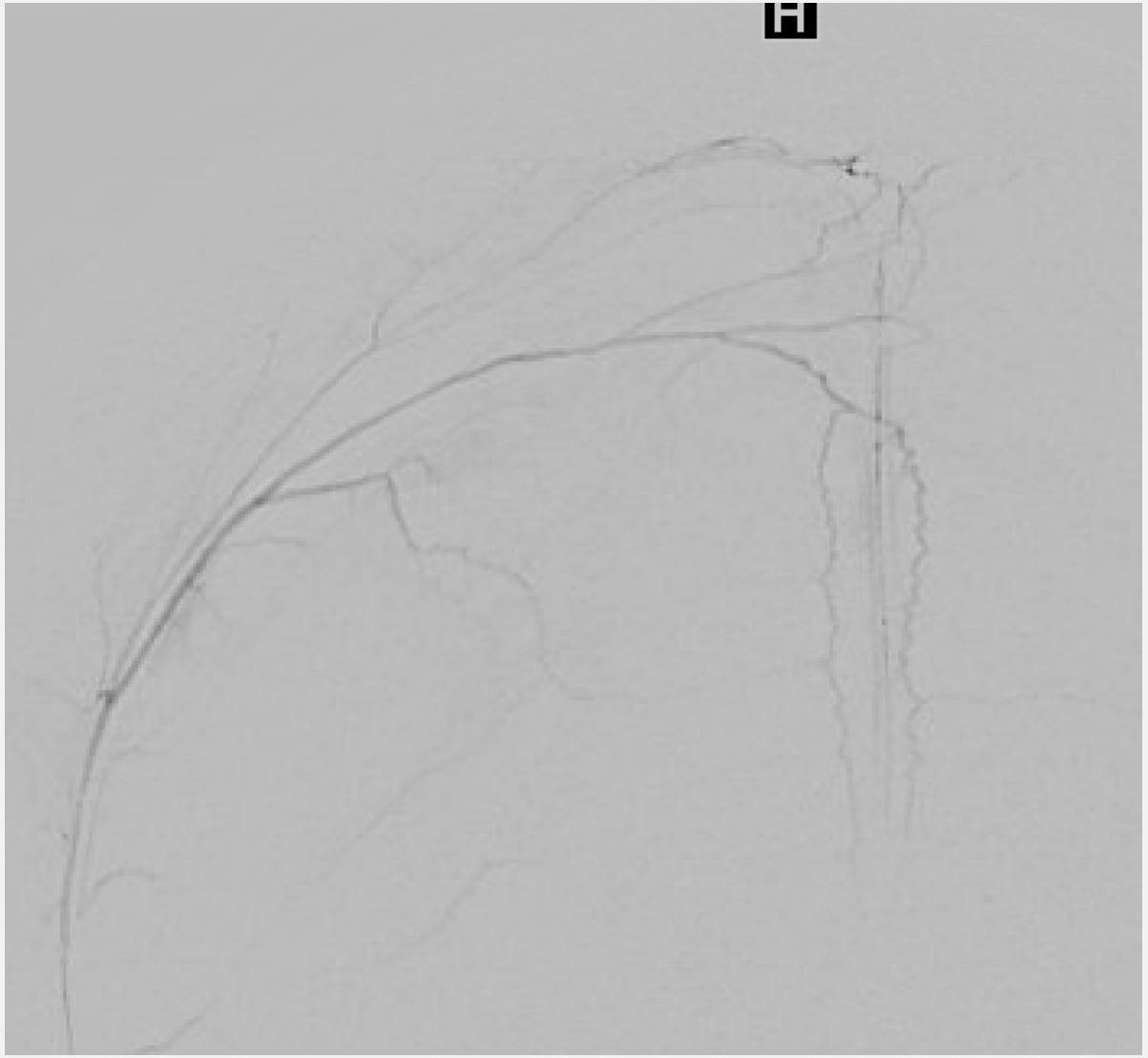

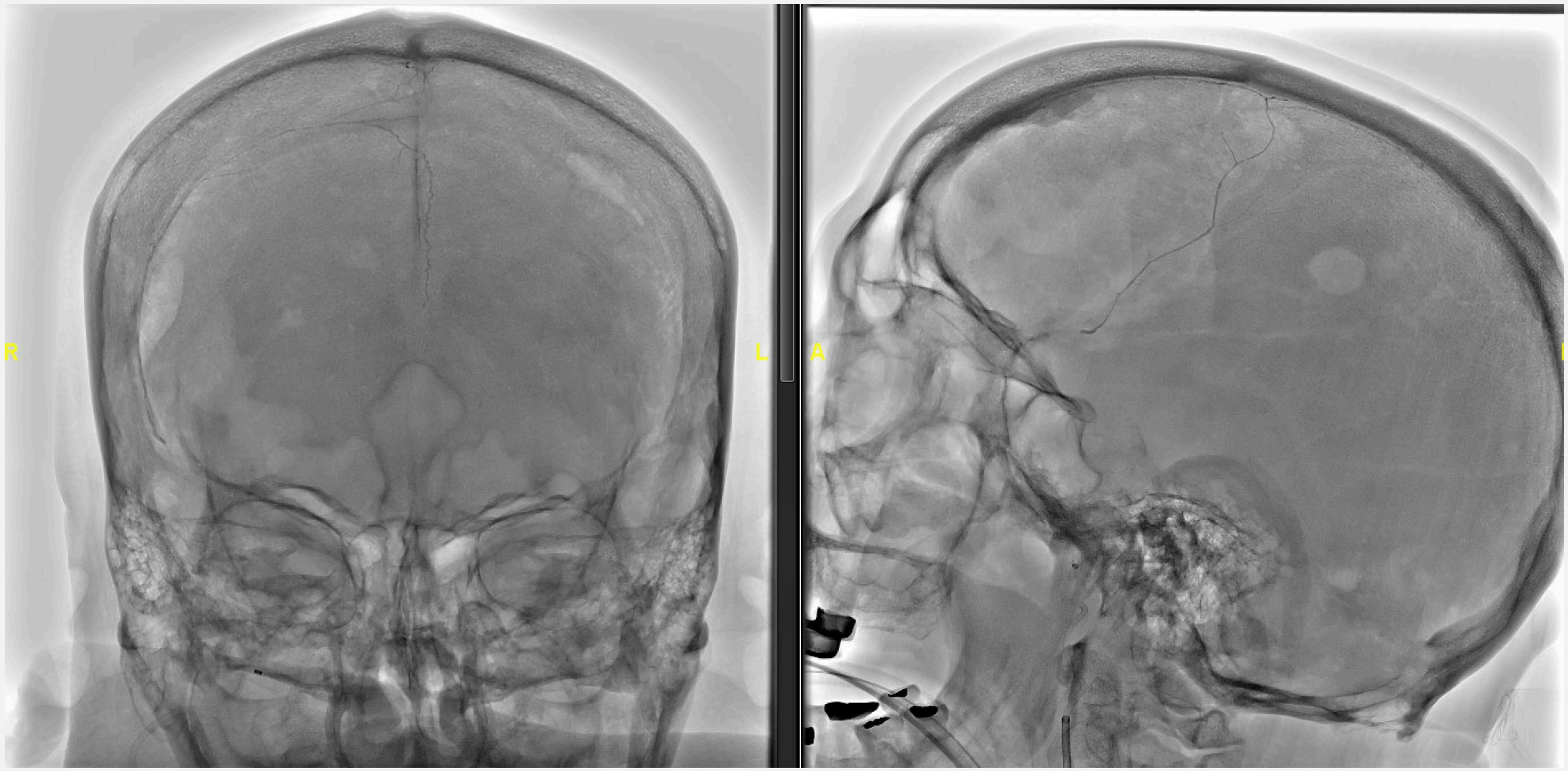
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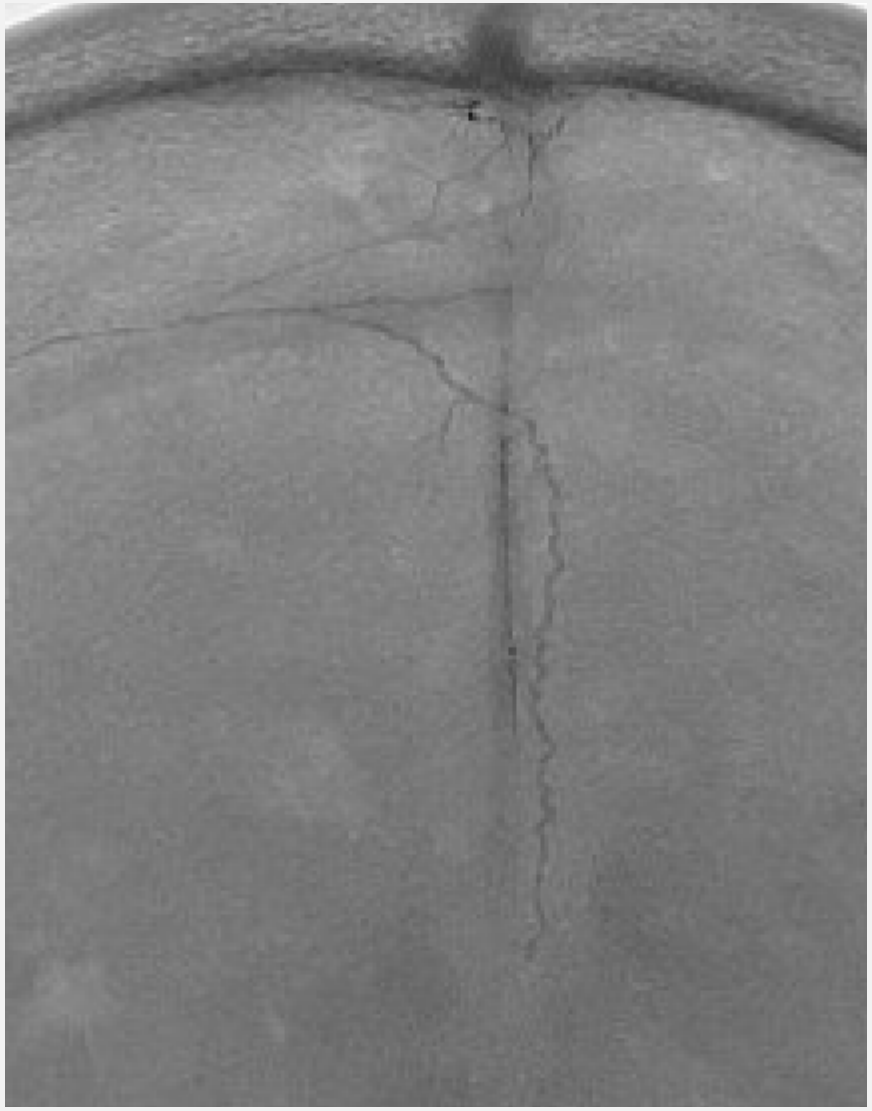

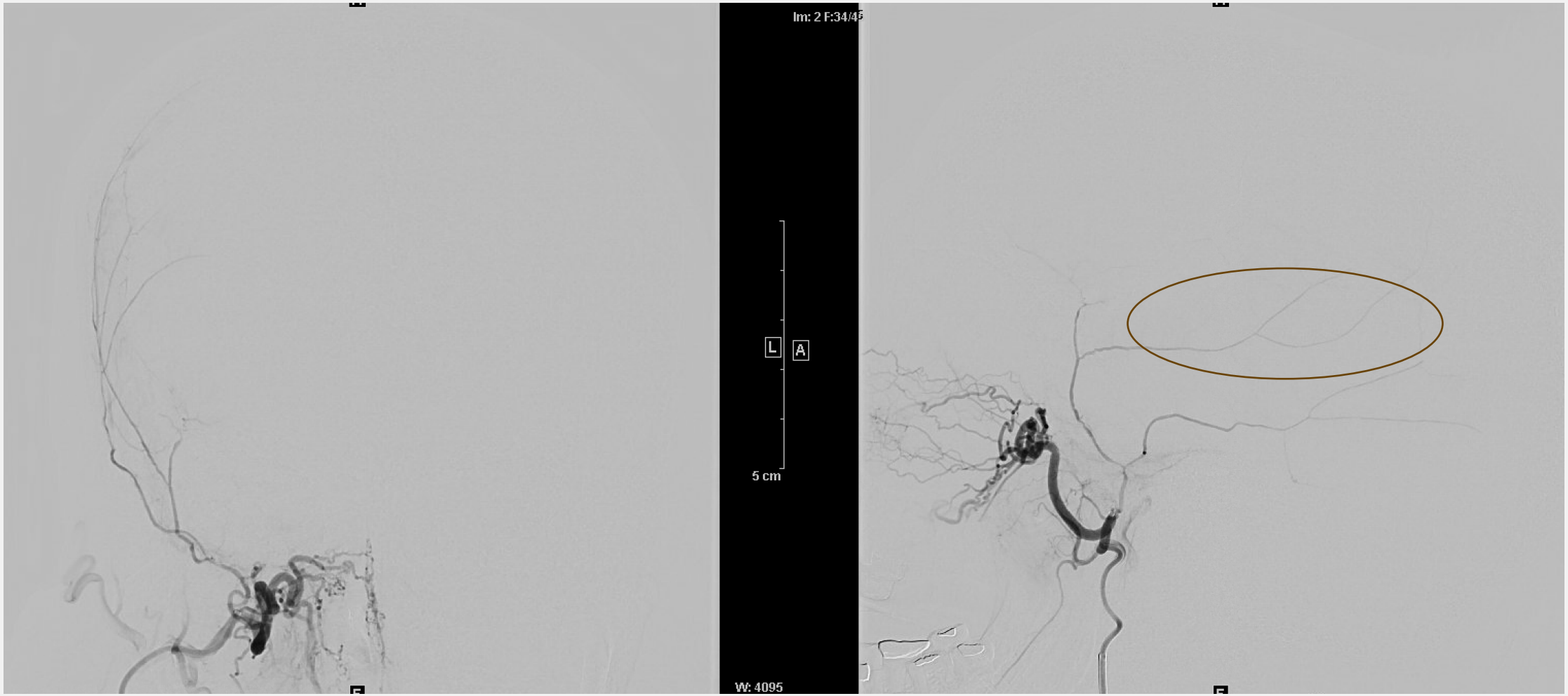
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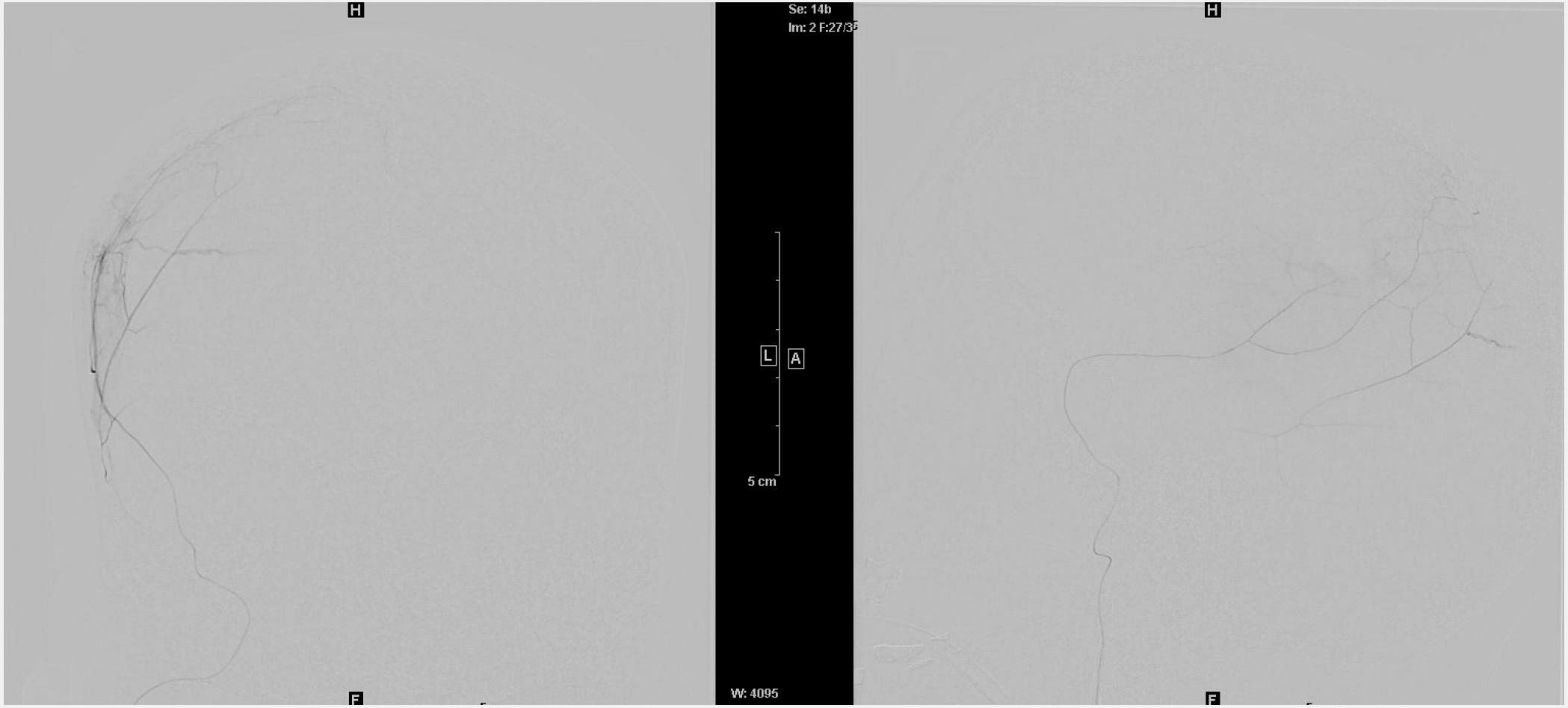
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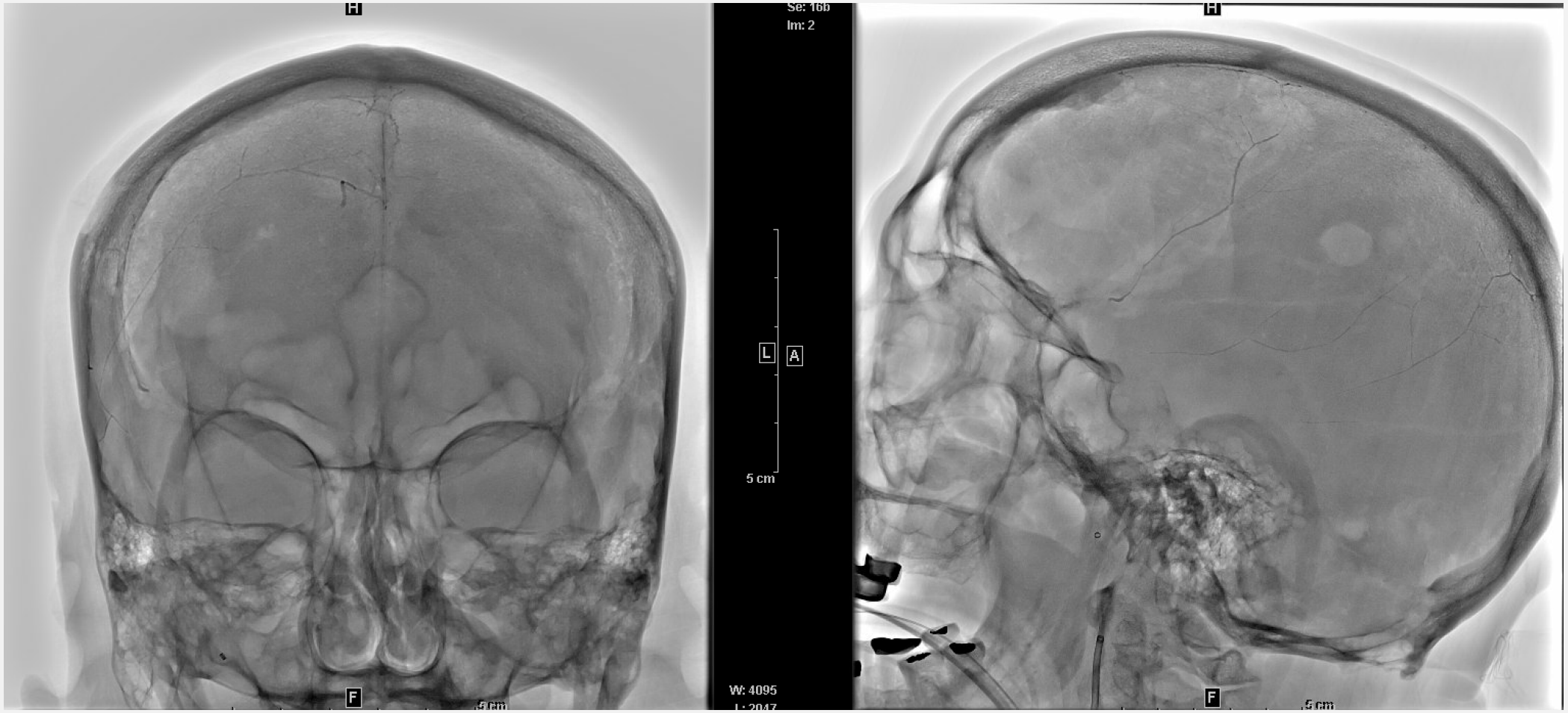
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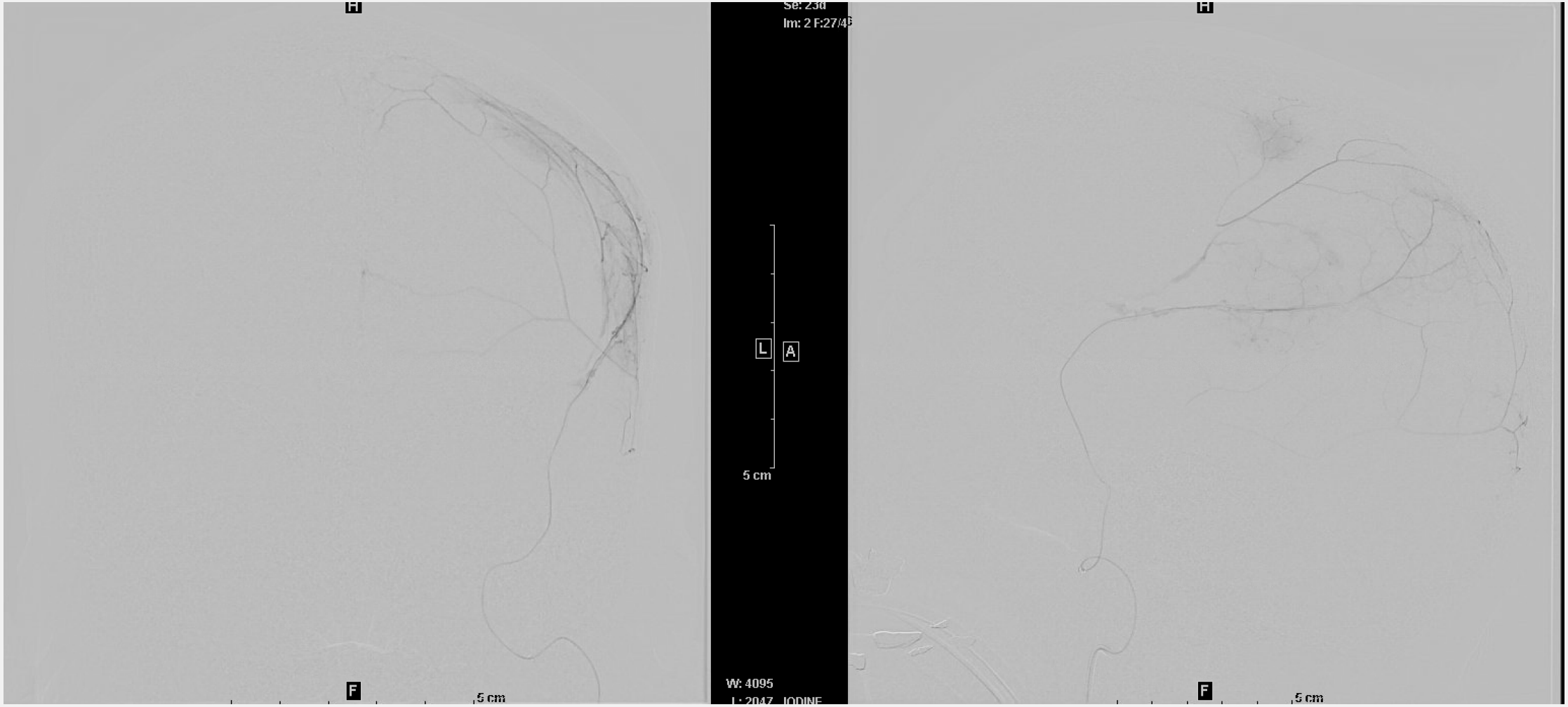
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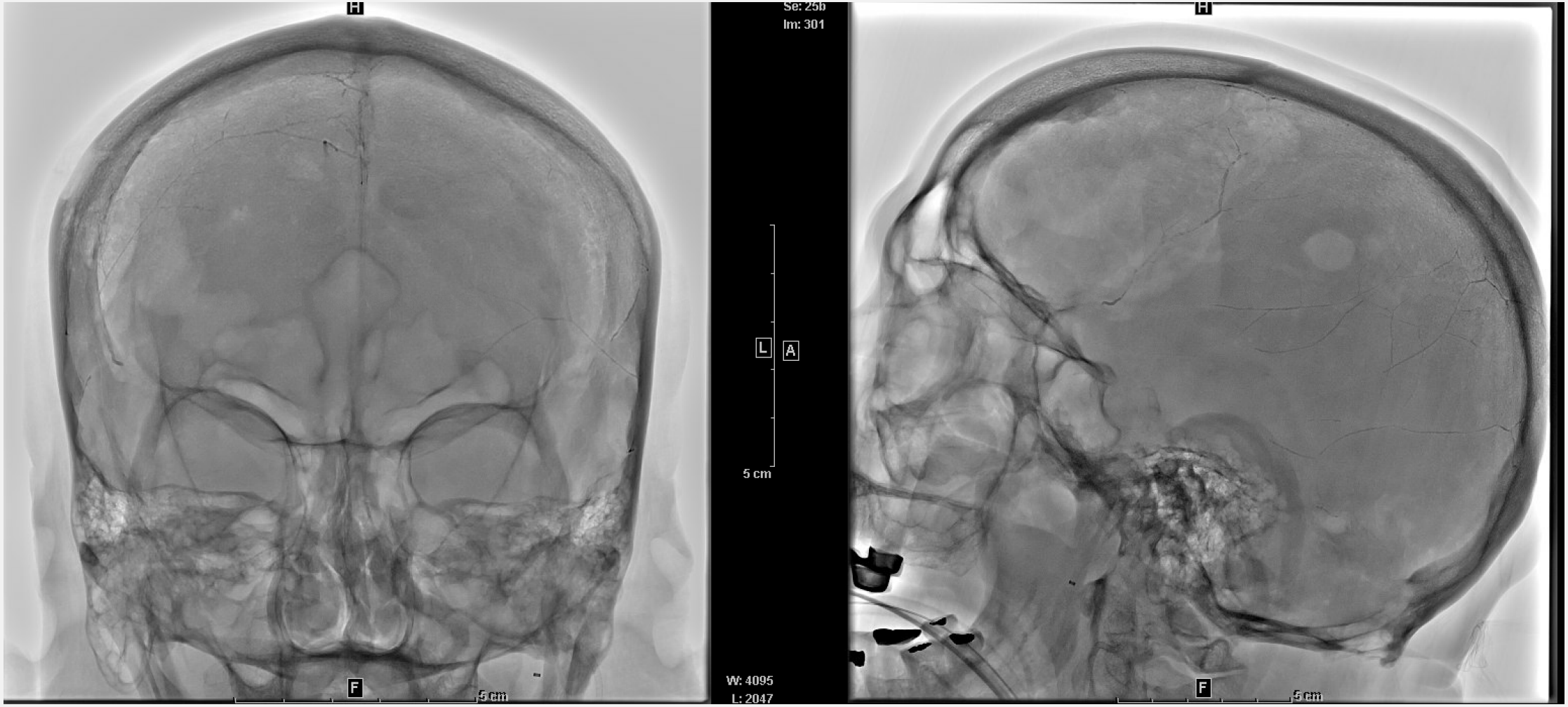
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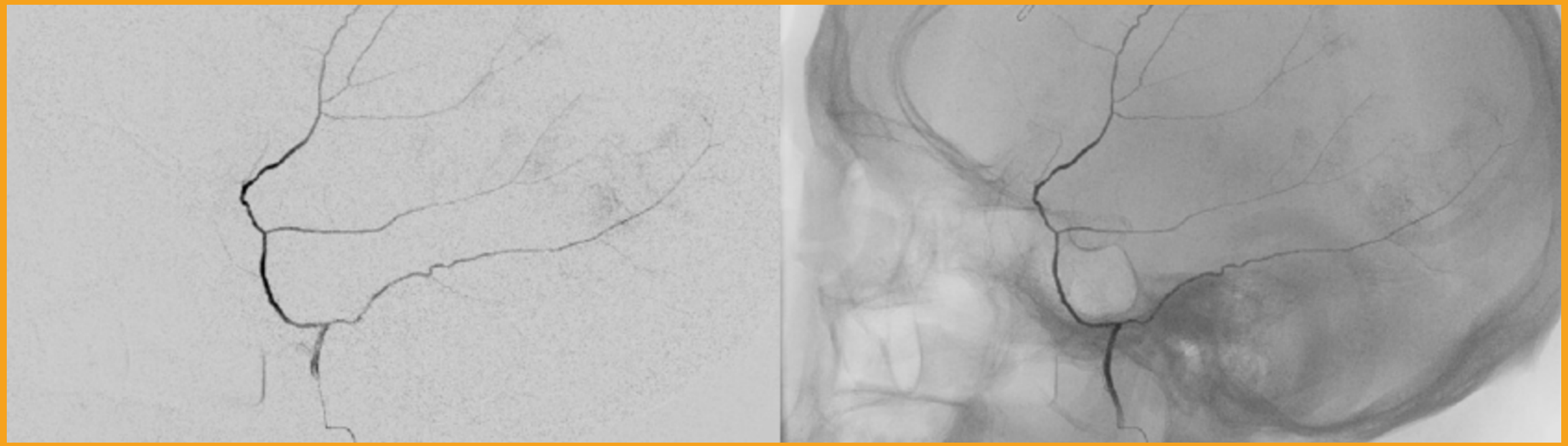


MMAE CLINICAL TRIALS

STEM TRIAL (SQUID TRIAL FOR THE EMBOLIZATION OF THE MIDDLE MENINGEAL ARTERY FOR TREATMENT OF CHRONIC SUBDURAL HEMATOMA)

Pivotal, international, multi-center prospective stratified randomized trial

Powered to assess the comparative safety and effectiveness of standard management (surgical or non-surgical) vs. standard management + MMAE with SQUID

SQUID is a liquid embolic agent (EVOH copolymer in DMSO with micronized tantalum) which comes in various viscosity preparations

RIH served as a clinical site for STEM

N Engl J Med 2025;392:855-64.DOI: 10.1056/NEJMoa2409845

STEM INCLUSION CRITERIA

Age >30

Pre-morbid mRS 0-1

cSDH >10 mm in greatest thickness & evidence of mass effect on brain (local cortical flattening or MLS)

Chronicity: >50% of volume isodense or hypodense to normal cortical gray matter

Symptomatic:

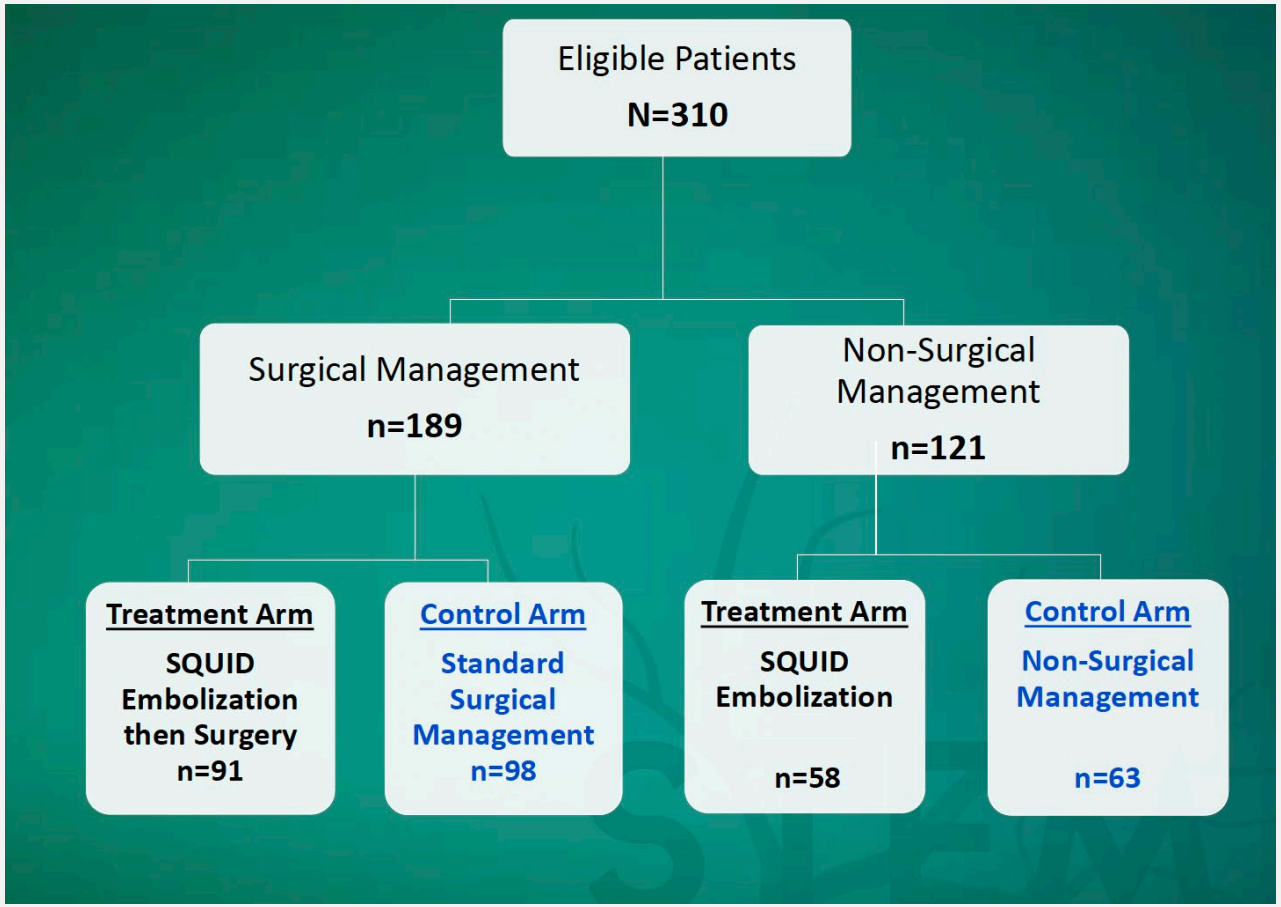
- Headache, cognitive decline, speech difficulty/aphasia, gait impairment, weakness, paresthesia or sensory deficit, facial droop or seizure

N Engl J Med 2025;392:855-64.DOI: 10.1056/NEJMoa2409845

PRIMARY ENDPOINTS

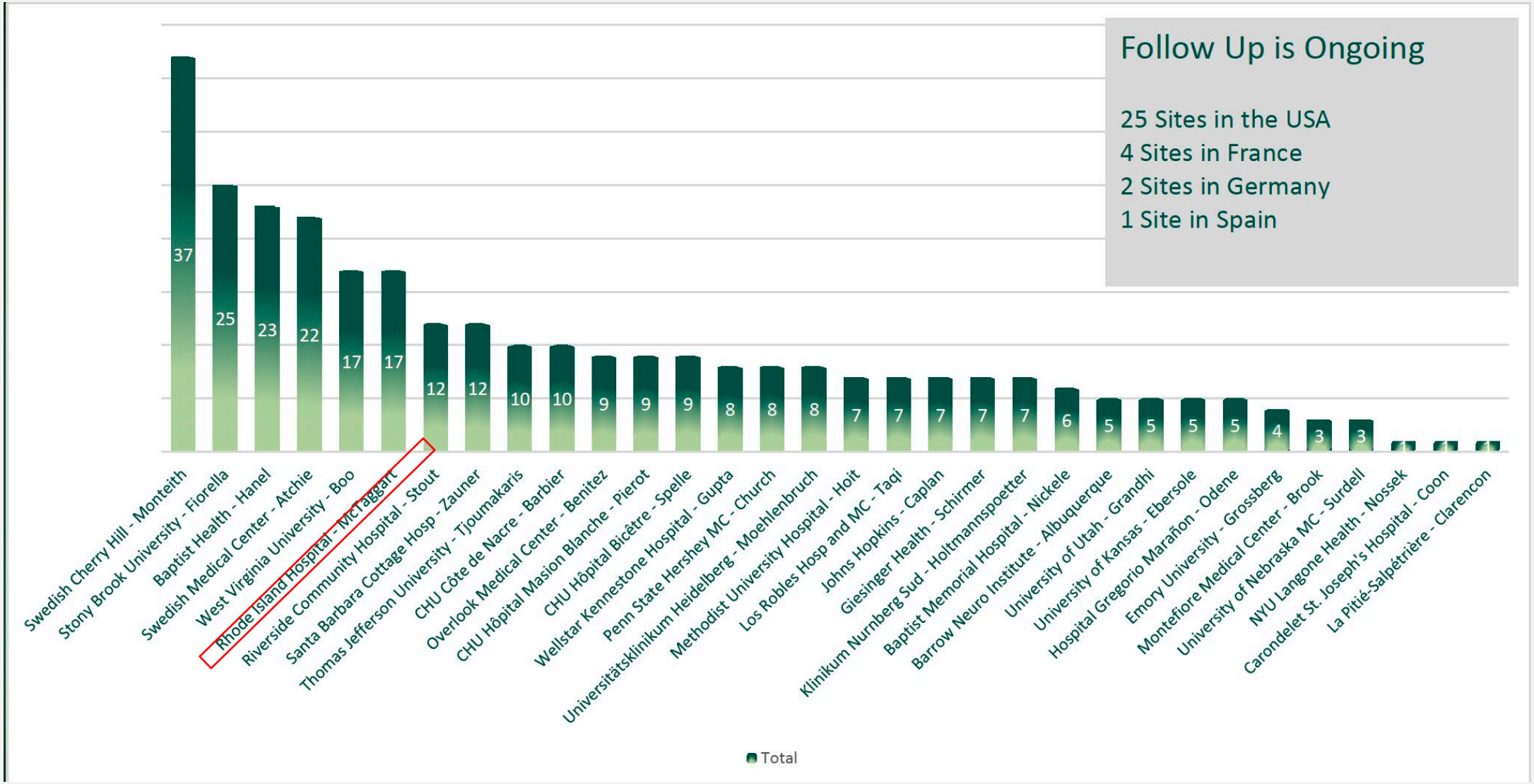
- **Primary Effectiveness Endpoint:**
  - *Residual or re-accumulation* of the SDH (≥10 mm) on 180-day scan from intervention (**Failure #1)**
  - *Re-operation* (after index procedure) or surgical rescue within 180-days of randomization (**Failure #2)**
  - Any *new, major disabling stroke, myocardial infarction (MI) or death* from any (neurological) cause within 180-days of randomization. **(Failure #3)**
- **Primary Safety Endpoint:**
  - Major disabling stroke or any death within 30-days from intervention

N Engl J Med 2025;392:855-64.DOI: 10.1056/NEJMoa2409845



- First Enrollment: November 2020
- Last Enrollment: May 2023
- Last 6 Month Follow-up: December 2023

N Engl J Med 2025;392:855-64.DOI: 10.1056/NEJMoa2409845



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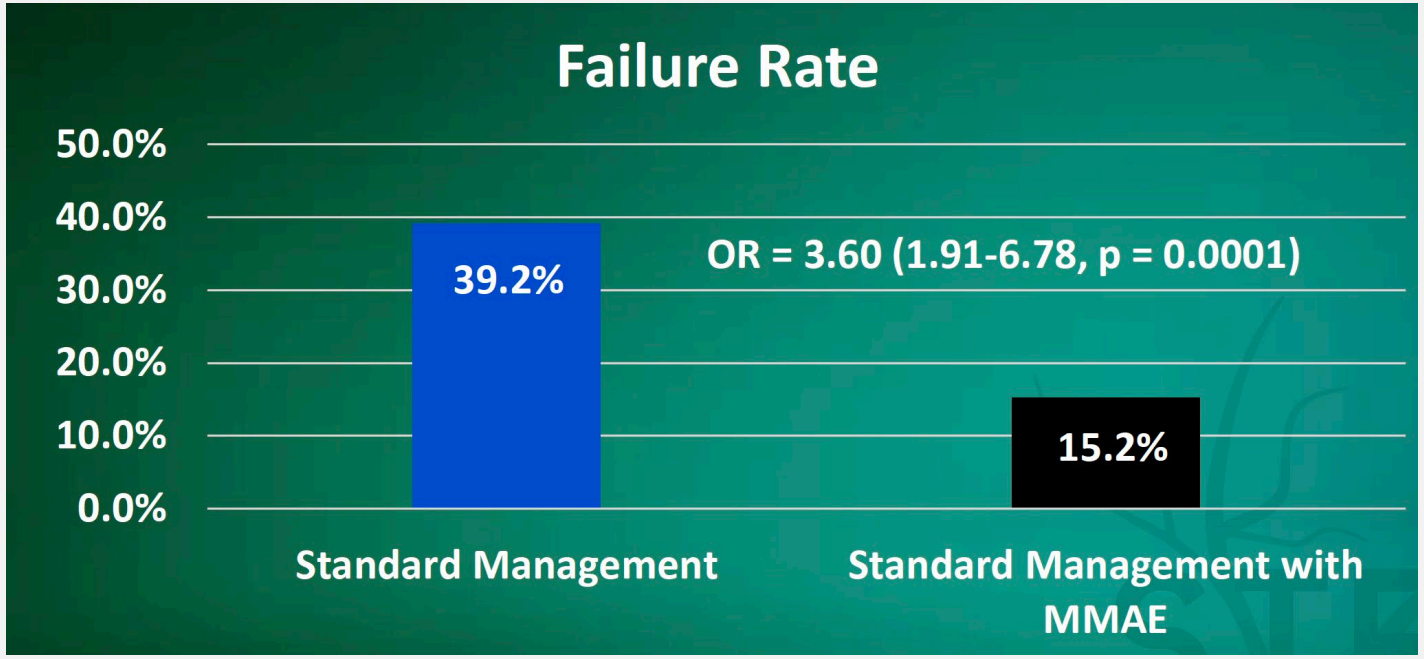
PRIMARY EFFECTIVENESS ENDPOINT



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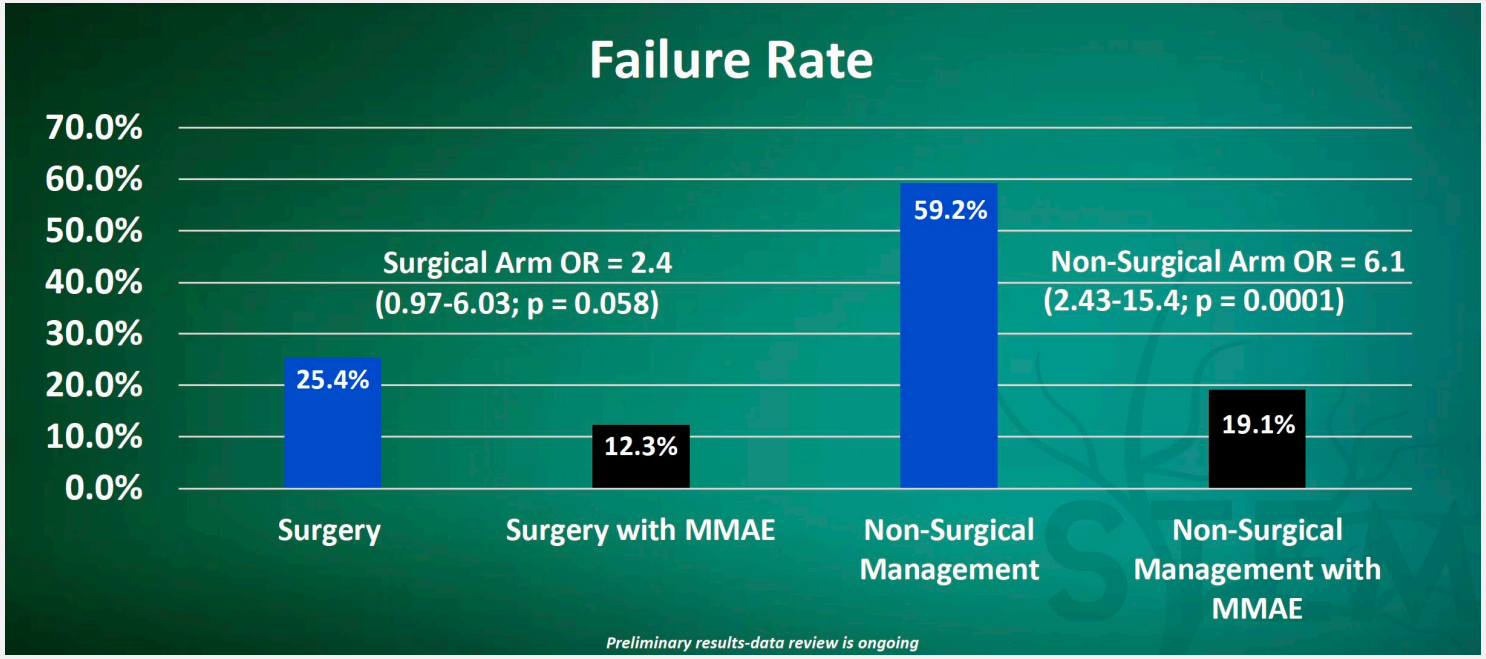
PRIMARY EFFECTIVENESS ENDPOINT SUBGROUPS



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30 DAY SAFETY OUTCOMES

	Treatment	Control
All Cause Death	4 (2.7%)	5 (3.1%)
Major Disabling Stroke*	0 (0%)	1 (0.6%)

N Engl J Med 2025;392:855-64.DOI: 10.1056/NEJMoa2409845

EMBOLISE

Study Design

OBJECTIVE	To evaluate the safety and efficacy of embolization of the MMA using Onyx™ LES for treatment of symptomatic subacute or chronic SDH
STUDY DESIGN	Multicenter, prospective, randomized, interventional, controlled, open label, adaptive design, IDE clinical trial
SITES	Up to 60 across the U.S.
SAMPLE SIZE	600 patients overall (400 in Surgery Cohort – per DMC assessment of Interim Analysis; 200 in Observation Cohort – pending Interim Analysis)
COHORTS	**Two Separately Powered Cohorts (Surgery and Observation) – "2 trials in 1" – Different Disease Severity**

N Engl J Med 2024;391:1890-900.DOI: 10.1056/NEJMoa2313472

EMBOLISE-RESULTS

Primary Endpoint Results

SDH Recurrence/Progression Requiring Surgical Drainage Through 90 Days Per CEC Adjudication – With Multiple Imputation – ITT Population

Outcome	Onyx Embo + Surgery (Treatment) (N=197)	Surgery Only (Control) (N=203)	Relative Risk [95% CI]	P-Value
SDH Recurrence/ Progression Requiring Surgical Drainage Through 90 Days	**4.1%** [1.8%, 7.8%][1]	**11.3%** [7.3%, 16.5%][2]	0.36 [0.11, 0.80]	**0.0081**

Outcome is imputed for subjects who failed to attend the 90-day evaluation visit (based on completion of the 90-day subject visit or the 90-day imaging requirement) and who did not have CEC-adjudicated hematoma recurrence/progression requiring surgical drainage within 90 days post-treatment.

[1]Note: 2 patients in the ITT population who exhibited recurrence/progression requiring surgical drainage had not been embolized with Onyx due to presence of dangerous anatomical variants.

[2] Does not include an additional 3 patients who experienced hematoma recurrence/progression and were retreated outside protocol (with Onyx Embo only). As these 3 patients were not retreated surgically, they did not contribute to the primary endpoint. However, they met clinical criteria to warrant retreatment.

Key Takeaway

Statistically significant ~3-fold reduction in recurrence requiring surgical re-drainage for subacute/chronic SDH after MMA embolization with Onyx™

N Engl J Med 2024;391:1890-900.DOI: 10.1056/NEJMoa2313472

Safety Endpoint Results

Device- and Procedure-Related AEs - Per CEC Adjudication - ITT Population

AEs	Onyx Embo + Surgery (Treatment)	Surgery Only (Control)
SAEs related to surgery procedure, up to 30 days[1,2]	15.7% (31/197) [45]	21.7% (44/203) [55]
Related to surgery	7.6% (15/197) [22]	21.7% (44/203) [55]
Related to embolization and surgery	10.2% (20/197) [23]	-
SAEs related to embolization procedure only, up to 30 days	2.0% (4/197) [4]	-
Onyx device-related SAEs up to 30 days	0%	-
Onyx device-related AEs up to 90 days	0%	-

Numbers are % (n/N) [# of events]

[1] A patient in the Onyx Embo + Surgery group may have an SAE related to surgery and a different SAE related to surgery and embolization. Such patients are only counted once in the overall rate of 15.7%.

[2] P-value = non-significant

Types of SAEs Related to Surgery

Neurologic*	Non-Neurologic*
• Brain abscess • Cerebellar/cerebral hemorrhage • Cerebral infarction • Dementia • Encephalopathy • Extradural hematoma • Gait disturbance • Headache • Neurological decompensation • Neurological symptom • Pneumocephalus • Procedural complication • Seizure/status epilepticus • SDH • Subdural hygroma • Wound infection	• Anemia • Asthenia • Atrial fibrillation • Cardiac arrest • Dysphagia • Hepatic encephalopathy • Hypotension • Malnutrition • Neuropathy (peripheral) • Pneumonia • Respiratory failure

*Neurological classification per NPIs

Key Takeaways

- Low rate of SAEs related to the Onyx MMA embolization procedure alone within 30 days
- No (0%) AEs related to the Onyx™ device through 90 days

N Engl J Med 2024;391:1890-900.DOI: 10.1056/NEJMoa2313472

MEMBRANE TRIAL (N-BCA)

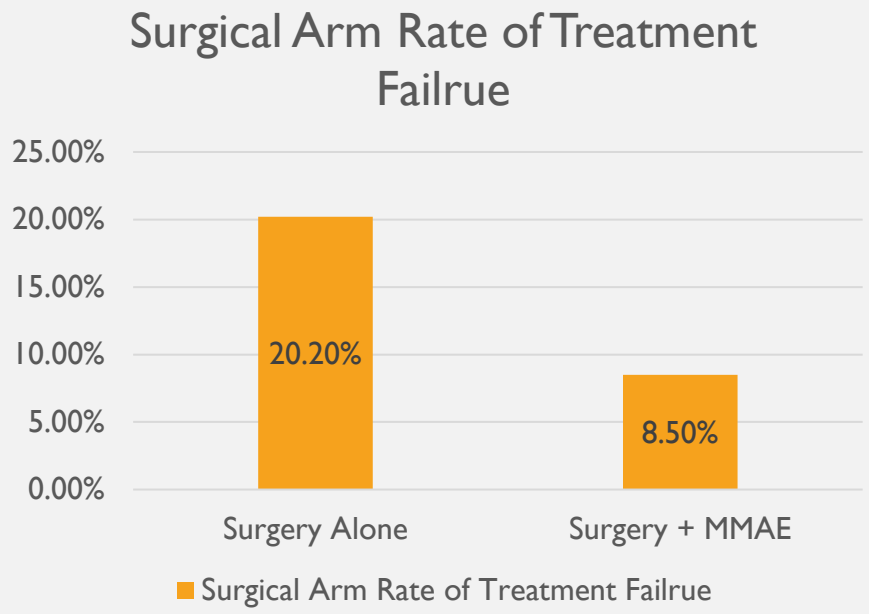
RCT enrolled 376 cSDH across 28 sites in US and 2 sites in China

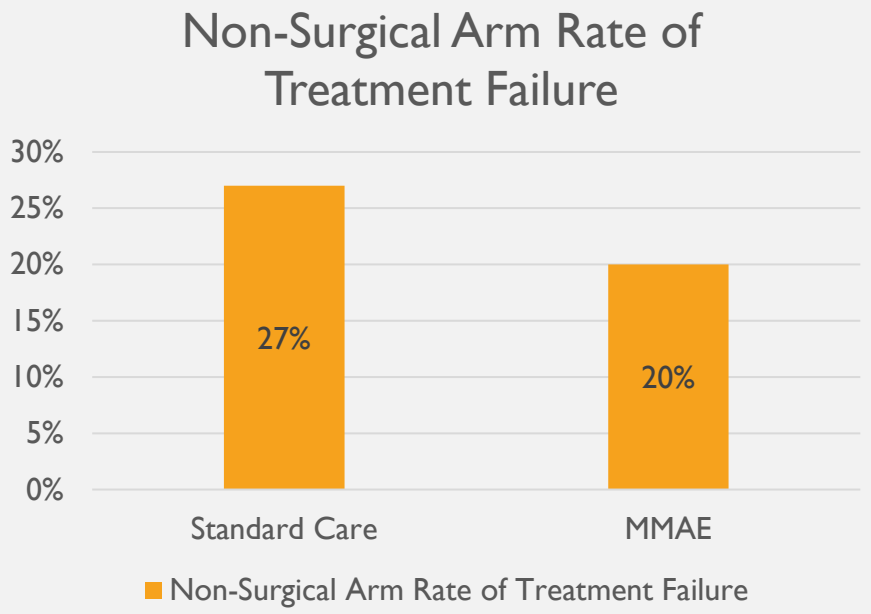
Two arms (surgical and non-surgical) randomized to standard care vs MMA embolization with n-BCA

Primary endpoint: cSDH re-accumulation (>10 mm) at 6mo or re-operation within 6 mo

Rai et al, SVIN Nov 2024, San Diego

MEMBRANE RESULTS





Rai et al, SVIN Nov 2024, San Diego

MAGIC-MT

- Multi-center RCT conducted at 31 sites in China
- 727 subjects enrolled in surgical and non-surgical arm, randomized to MMAE vs standard care
  - Excluded those requiring crani, only burr holes accepted for surgical arm
- MMAE with Onyx
- Primary endpoint: symptomatic recurrence or progression at 90 days

N Engl J Med 2024;391:1901-12. DOI: 10.1056/NEJMoa2401201

MAGIC –MT TRIAL

Table 2. Primary and Secondary Outcomes.*

Outcome	Embolization (N=360)	Usual Care (N=362)	Measure of Effect†	Value (95% CI)‡
Primary outcome				
Symptomatic recurrence or progression of subdural hematoma within 90 days — no. (%)§	24 (6.7)	36 (9.9)	Percentage-point difference	−3.3 (−7.4 to 0.8)¶
Symptomatic recurrence	17 (4.7)	19 (5.2)		
Symptomatic progression	7 (1.9)	17 (4.7)		
Secondary outcomes				
Clinical outcomes				
Modified Rankin scale score at 90 days				
Median (IQR)‖	0 (0 to 1)	0 (0 to 1)	Common odds ratio	1.10 (0.82 to 1.46)
0, 1, or 2 — no. (%)	335 (93.1)	333 (92.0)	Percentage-point difference	1.1 (−2.8 to 5.0)
0 to 3 — no. (%)	352 (97.8)	349 (96.4)	Percentage-point difference	1.4 (−1.2 to 4.1)
Mean EQ-5D-5L score at 90 days**	0.95	0.94	Mean difference	0.01 (−0.01 to 0.03)
Length of hospital stay — days††	10.2±4.3	9.6±4.8	Mean difference	0.6 (0.0 to 1.3)
Rehospitalization — no. (%)	25 (6.9)	28 (7.7)	Percentage-point difference	−0.8 (−4.6 to 3.0)
Destination after discharge: rehabilitation hospital — no. (%)	11 (3.1)	10 (2.8)	Percentage-point difference	0.3 (−2.4 to 2.9)

Safety outcomes (Intention-to-Treat Population)

Variable	Embolization (n=360)	Usual-care (n=362)	Odds Ratio (95% CI)	P Value
	number (precent)			
Safety outcomes				
Death within 90 days†	2 (0.6)	8 (2.2)	0.25 (0.05 to 1.17)	0.10‡
Serious adverse events within 90 days	24 (6.7)	42(11.6)	0.54 (0.32 to 0.92)	0.02
Adverse events within 90 days	49 (13.6)	63 (17.4)	0.75 (0.50 to 1.12)	0.16
MMA embolization-related complications within 30 days	3 (0.8)	0	NA	0.12‡
Facial nerve paralysis	1 (0.3)	0		
Contrast agent allergy	2 (0.6)	0		
Burr-hole surgery-related complications within 30 days§	9 (2.5)	4 (1.1)	2.30 (0.70 to 7.52)	0.16
Symptomatic intracranial hemorrhage	1 (0.3)	1 (0.3)		
Asymptomatic intracranial hemorrhage	0	1 (0.3)		
Central nervous system infection	1 (0.3)	0		
Non-central nervous system infection	4 (1.1)	1 (0.3)		
Incision complications	2 (0.6)	0		
Epilepsy	3 (0.8)	1 (0.3)		

MAGIC-MT

N Engl J Med 2024;391:1901-12. DOI: 10.1056/NEJMoa2401201

EMPROTECT TRIAL (PARTICLES)

Multicenter RCT conduced at 12 French centers assessing use of surgery + adjunct MMA vs surgery alone

Included 342 patients with cSDH recurrence or first cSDH episode at high risk of recurrence

Embolization with 300-500 um microparticles within 7 days of surgery

Shotar et al *JAMA July 8, 2025 Volume 334, Number 2*

EMPROTECT TRIAL

- Primary Endpoint: cSDH recurrence at 6 months defined as
  - return of cSDH with >/= 5 mm shift
  - return of cSDH with associated symptoms
  - Presence of cSDH >10 mm
  - Need for repeat surgery or admission due to homolateral cSDH

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EMPROTECT RESULTS

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)			

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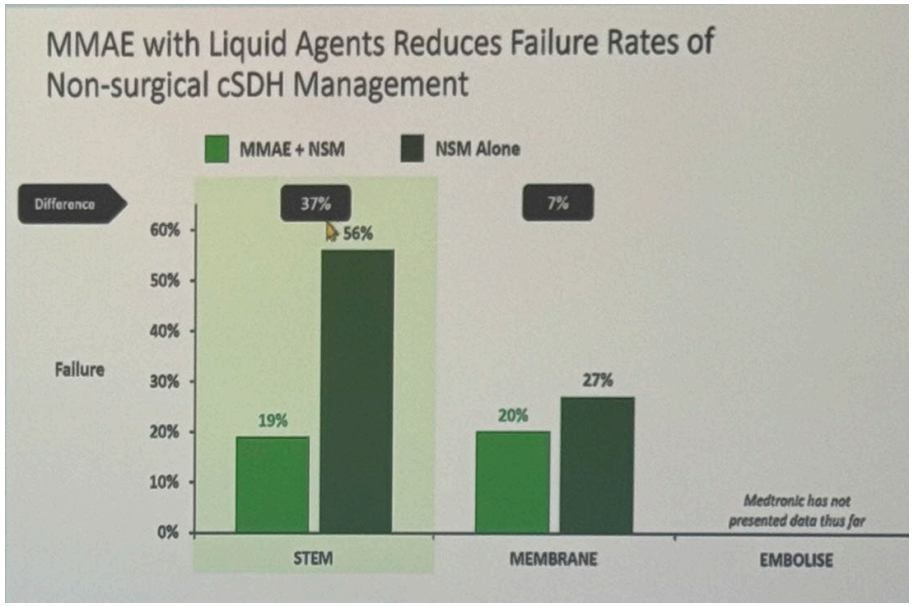
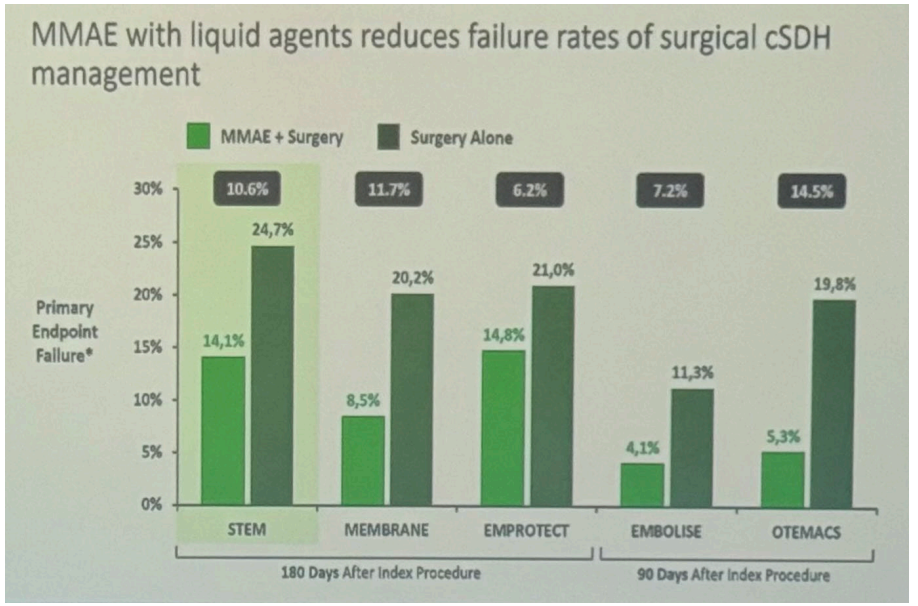


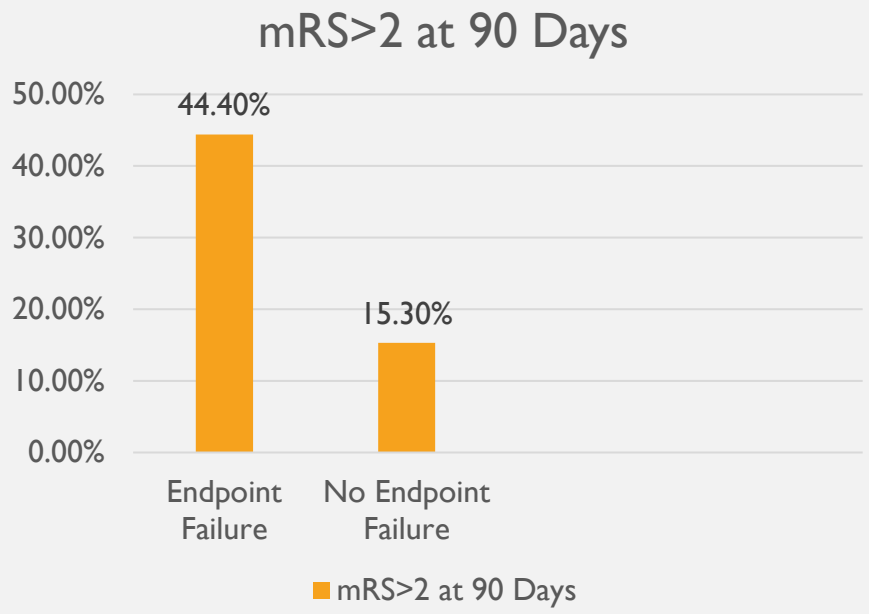


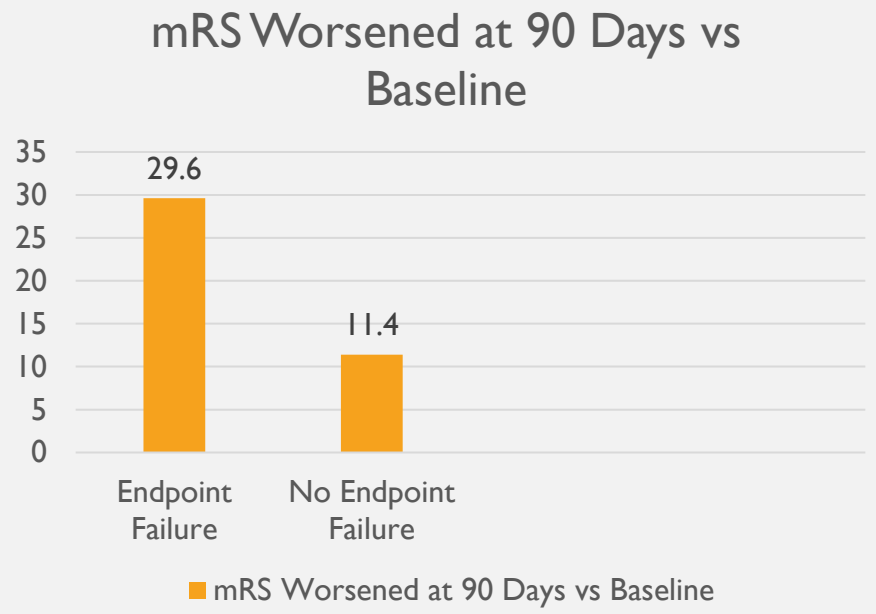
LESSONS OF MMAE TRIALS

Fiorella ESMINT September 2025, Marseille.

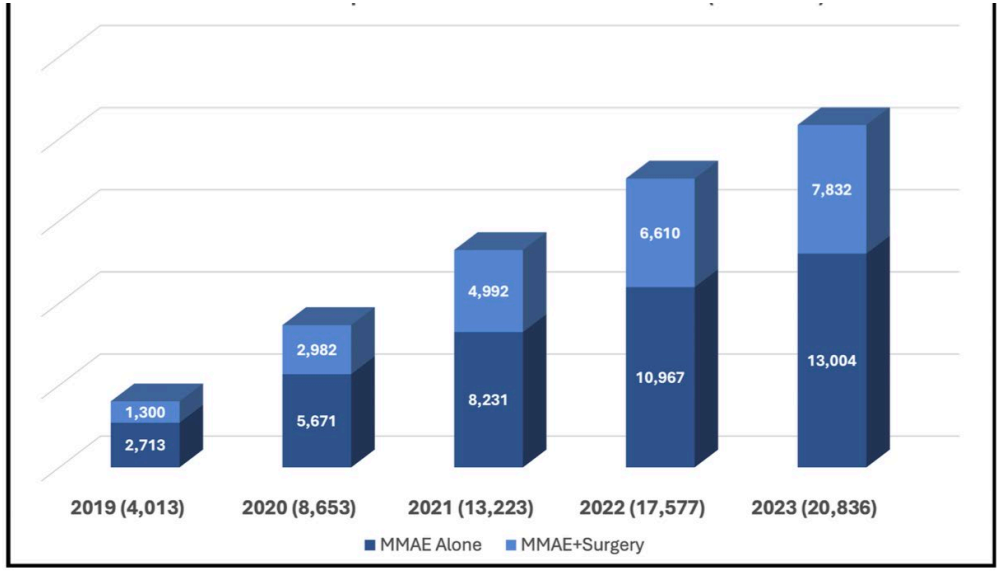
HOW RELEVANT IS PRIMARY ENDPOINT FAILURE VS NON-FAILURE?

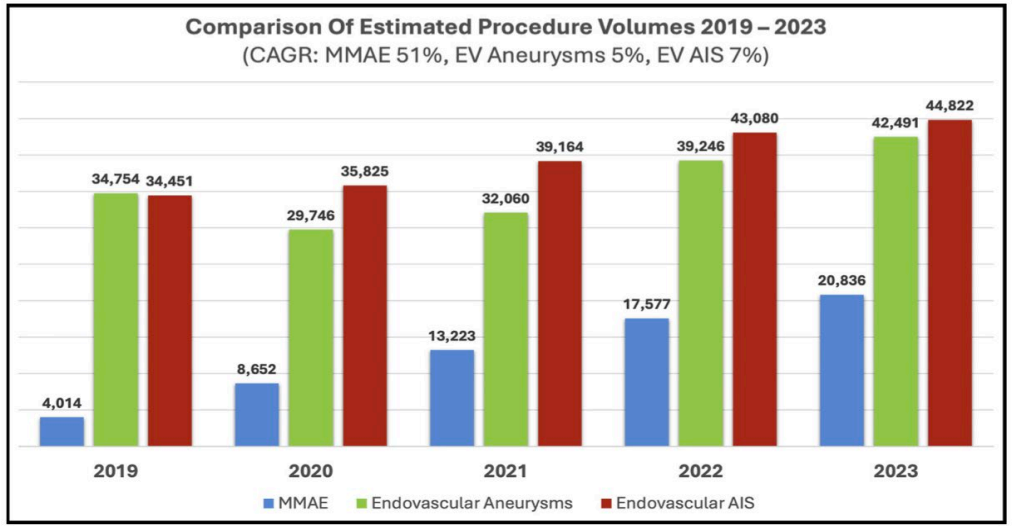
mRS > 2 a5 90 days & mRS worsening at 90 days, SDH recurrence/progression requiring surgical drainage through 90 days





Treating SDH IN 2024: A Multimodal Approach Jason Davies CNS September 2024 (EMBOLISE Study)

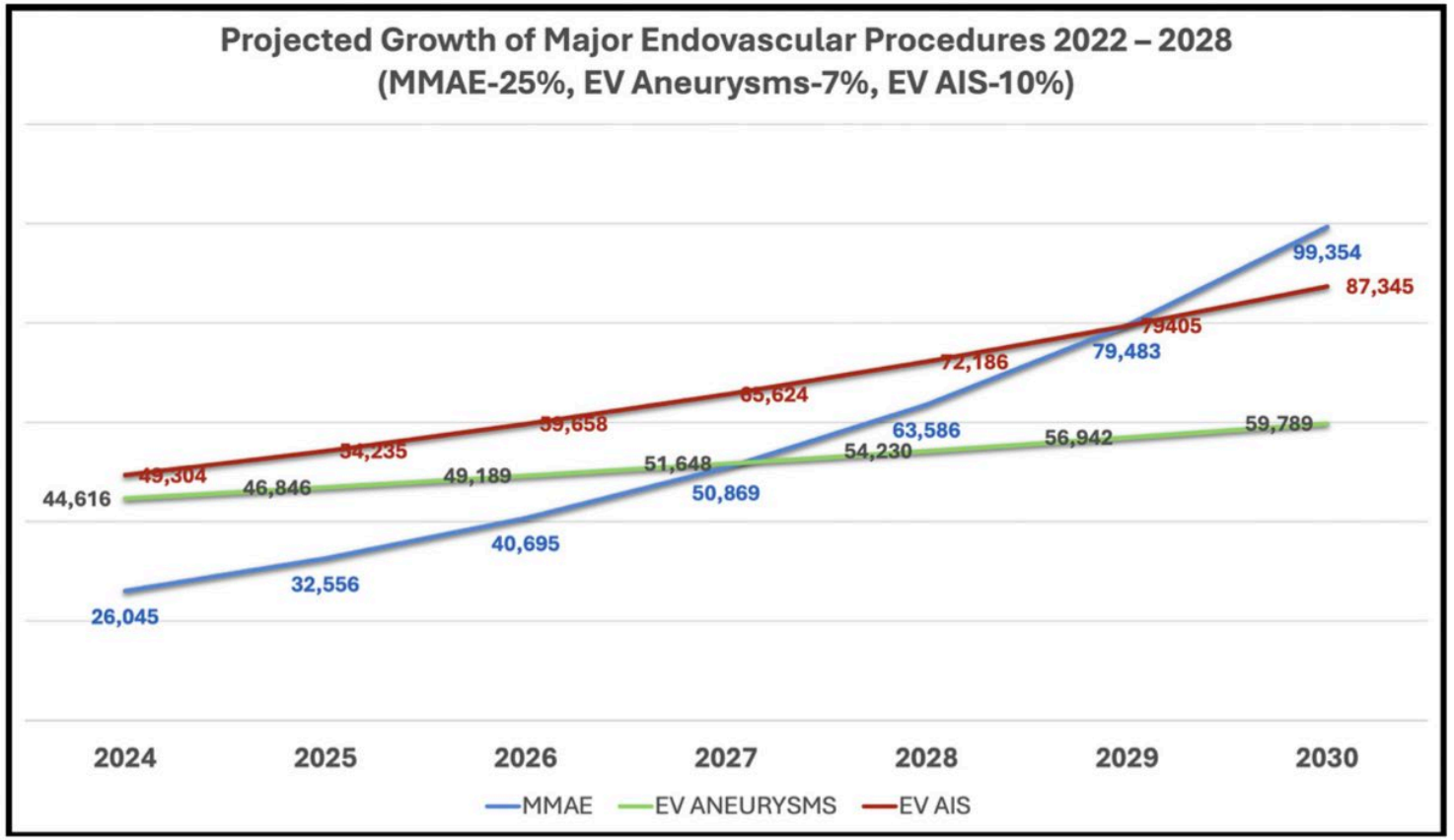




UTILIZATION OF MMAE FOR CSDH OVER TIME

Rai AT, et al. J NeuroIntervent Surg 2025;0:1–5. doi:10.1136/jnis-2025-023109

PROJECTED GROWTH RATE OF MMAE



Rai AT, et al. J NeuroIntervent Surg 2025;0:1–5. doi:10.1136/jnis-2025-023109

QUESTIONS?