INTRACRANIAL HEMORRHAGE

JONATHON COOKE, MD

GENERAL/ENDOVASCULAR NEUROSURGERY

NEUROCRITICAL CARE

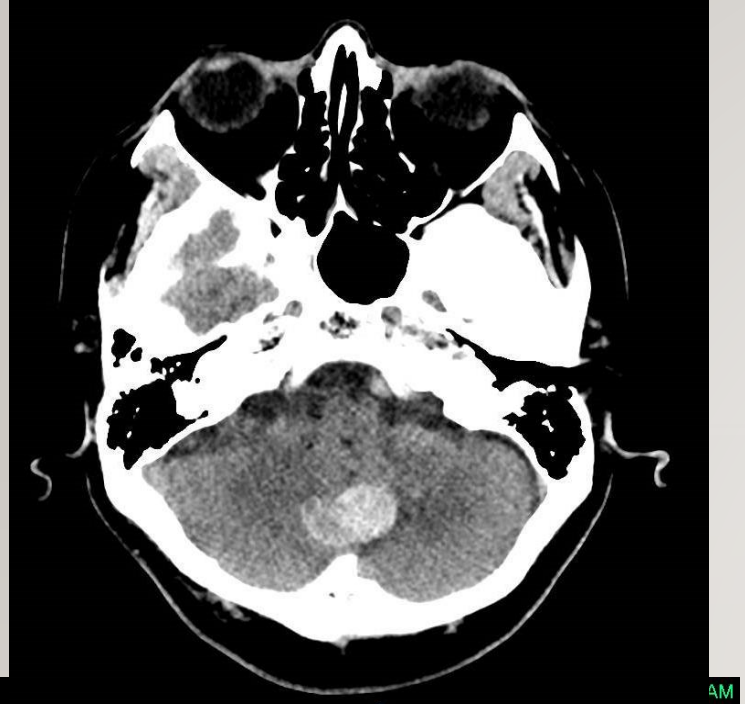
CALIFORNIA CENTER FOR NEUROINTERVENTIONAL SURGERY

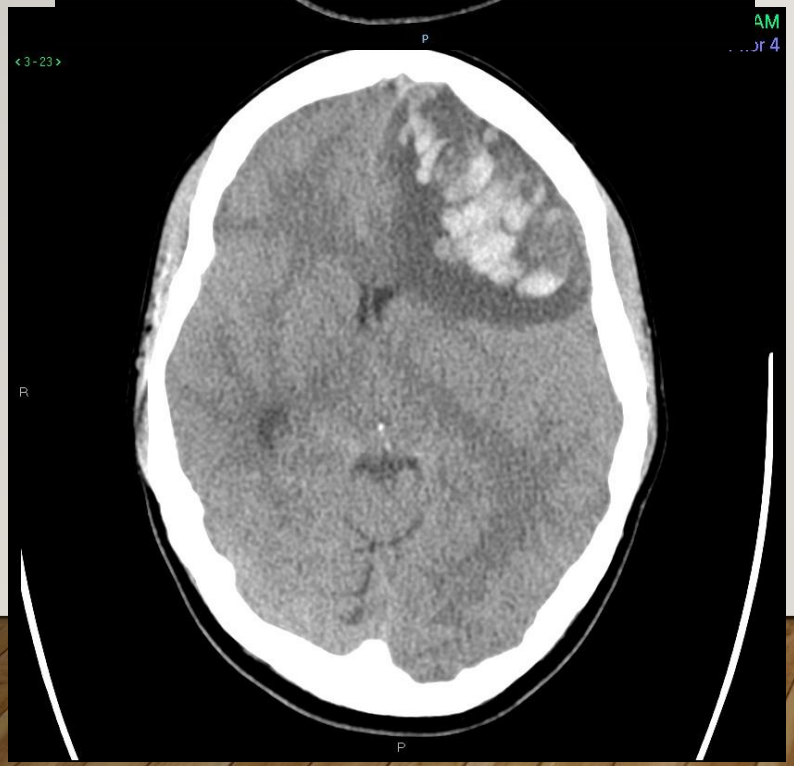
DISCLOSURES

- The views expressed are those of the author and do not reflect the official policy or position of the US Navy, Department of Defense or the US Government.

DISCUSSION

- What is an Intracranial hemorrhage (ICH)
- Risk Factors
- Causes
- Diagnosis
- Management
- Treatments

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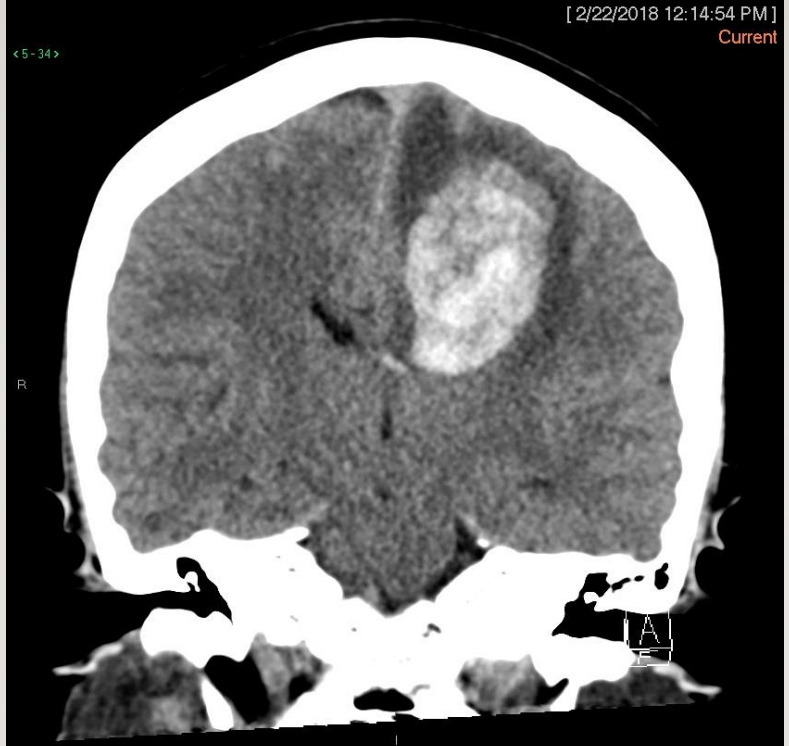
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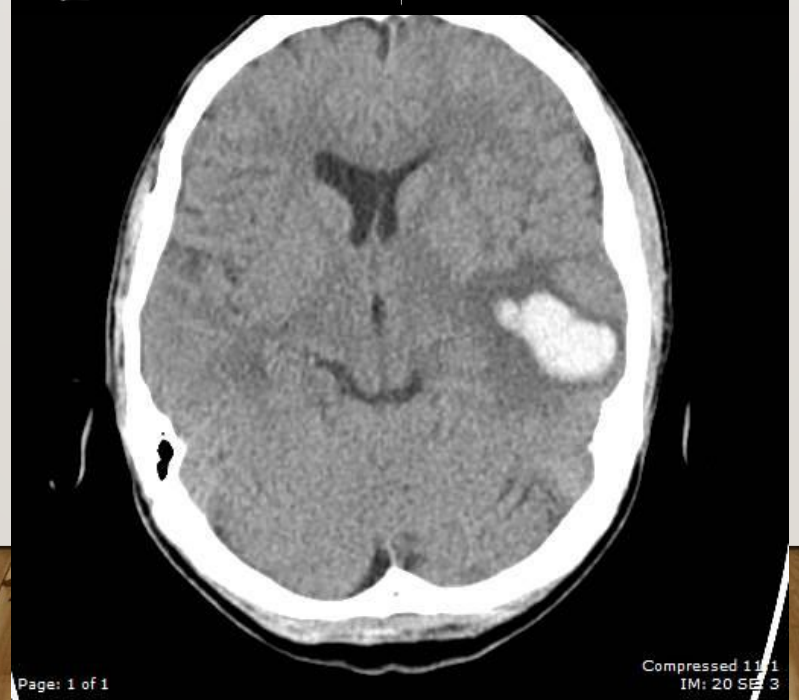
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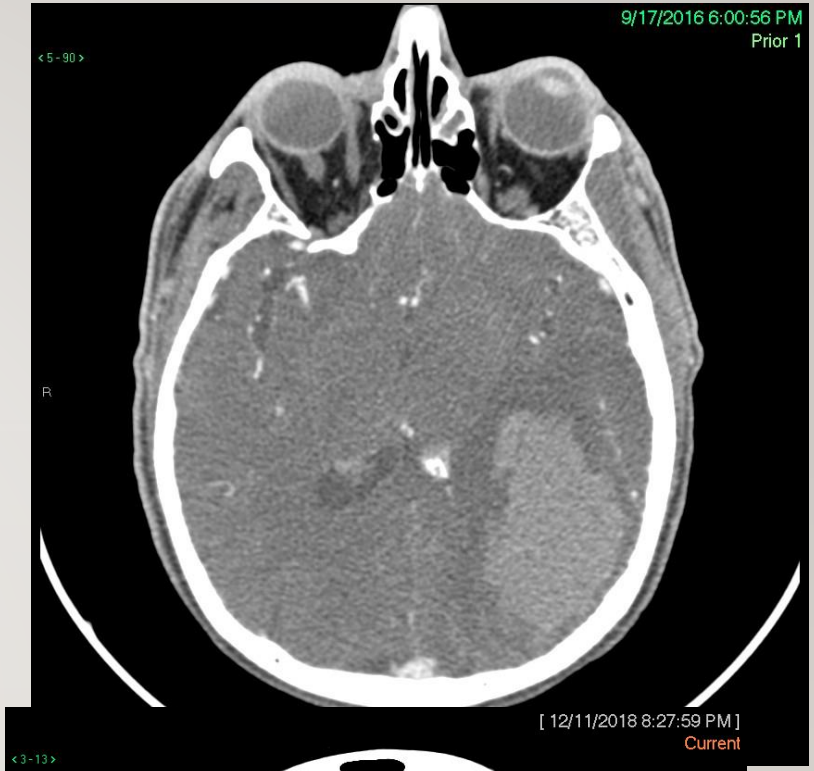
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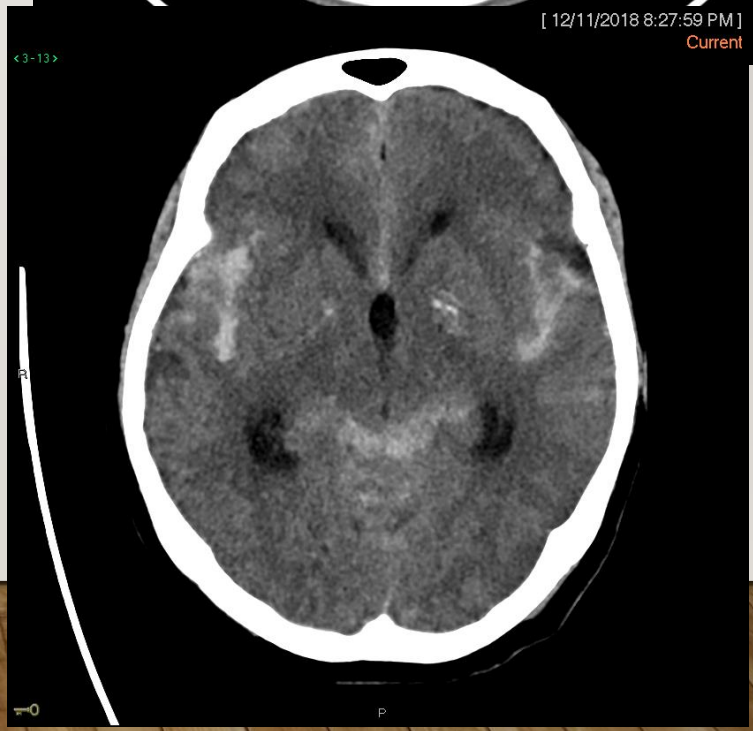
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INTRACEREBRAL HEMORRHAGE

- Spontaneous Intracerebral (Intracranial) Hemorrhage
  - "Hypertensive Hemorrhage"
  - Not due to another cause
- Second most common type of stroke (15-30% of all strokes)[1]
  - Most lethal (mortality of 35-52%)
  - 2x as common as subarachnoid hemorrhage[2]
- Medical Emergency
  - 20% of patients deteriorate by 2 GCS points between EMS and ER[3]
  - Another 15-23% deteriorate further when in hospital[4]

RISK FACTORS[5]

- Age
  - Risk doubles every decade after age 55
- Arterial Hypertension
  - Up to 46% incidence
- Race[6]
  - AA and Asians more susceptible
    - Confounder: Incidence of HTN
- EtOH[7]
  - Heavy use 7-24 hrs preceding
- Renal/Hepatic dysfunction
- DM/Cerebral Microbleeds (CROMIS2)
- Sympathomimetic drugs and opioids
- Prescription Medications
  - Cox Inhibitors
  - P2Y12 Inhibitors
  - SSRI*
  - Statin*
  - Oral Anticoagulant
- Previous Stroke (any type)
- Smoking*

* Controversial

COMMON LOCATIONS

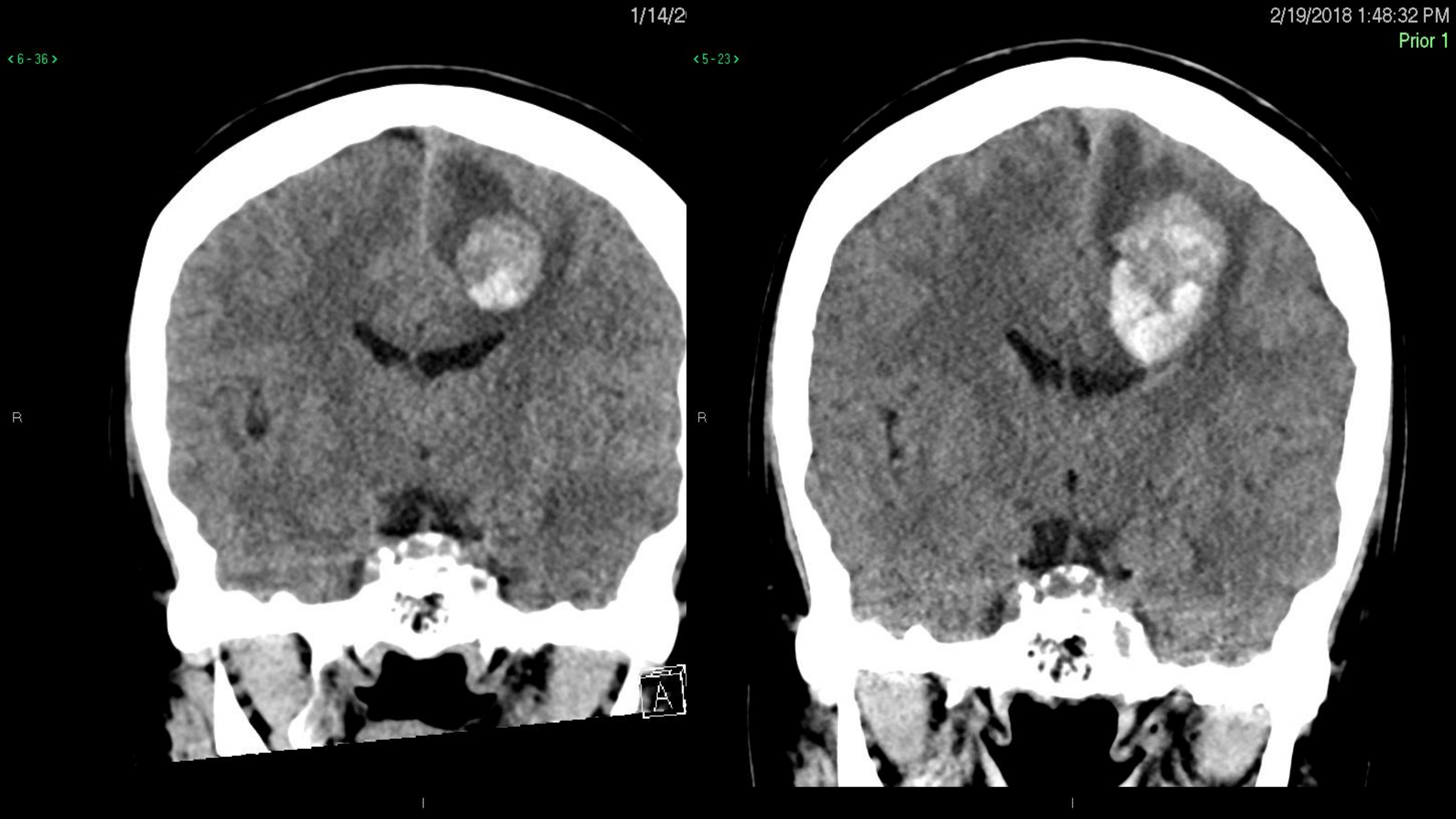
- Basal Ganglia (50%)
  - Putamen
- Thalamus (15%)
- Pons (10-15%)
  - Most likely to be hypertensive in origin
- Cerebellum (10%)
- Cerebral White Matter (10%)
- Brainstem (1-6%)

CLINICAL PRESENTATION

- A TIA like prodrome of spreading weakness, numbness, tingling
  - Putamen- contralateral hemiplegia/paresis
  - Thalamus- contralateral sensory loss
    - Spread into IC will give contralateral weakness
    - Spread to Brainstem will give ocular findings (Parinauds)
  - Cerebellum- Cerebellar signs, obstructive hydrocephalus and cranial neuropathies if floor of 4th ventricle involved
  - Lobar- initial onset of headache and symptoms localizable to injured lobe
    - Frontal- Contralateral weakness Arm > Leg, Face
    - Parietal- Contralateral Hemisensory, possible hemiparesis
    - Occipital- Contralateral Homonymous Hemianopsia
    - Temporal- Aphasia (receptive, transcortical), possible superior quadrantopsia

CLINICAL PRESENTATION

- Delayed Presentation
  - Rebleeding
  - Edema
  - Hydrocephalus
  - Seizures
  - Increased ICP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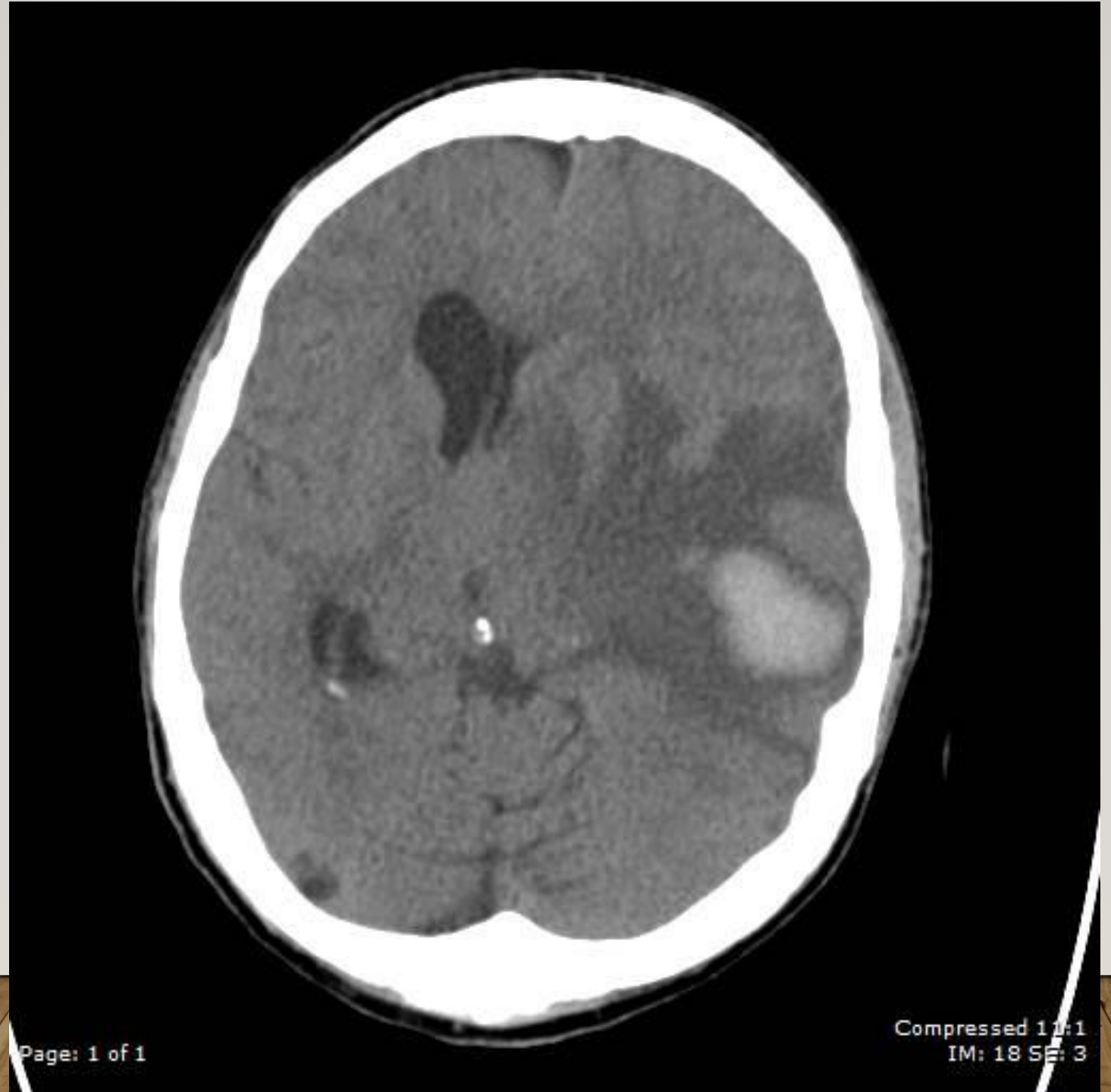
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RISK FACTORS FOR POOR OUTCOME

- Hematoma Size
  - Every 10% increase in hematoma volume increases mortality 5% and 16% chance of losing a point on mRS[8]
- Intraventricular Extension
  - Patients with mRS 4-6 2.25 more likely to have had IVH 2.25 (1.40-3.64)[9]
- Oral Anticoagulant Use[10]
  - Higher mortality at 90 days
  - Increased size of hematoma at 72 hrs

GOALS OF CARE

- This is an ischemic stroke until you see the blood
- Stabilize the patient
- Prevent or treat risk factors for poor outcome
  - Expansion of the hematoma
  - Reversal of Anticoagulation
  - Prevent IVH
- Prevent secondary brain injury
  - ICP Management
  - Blood Pressure Management
  - Glucose Control
  - Temperature Control
  - Treat seizures

WORK UP

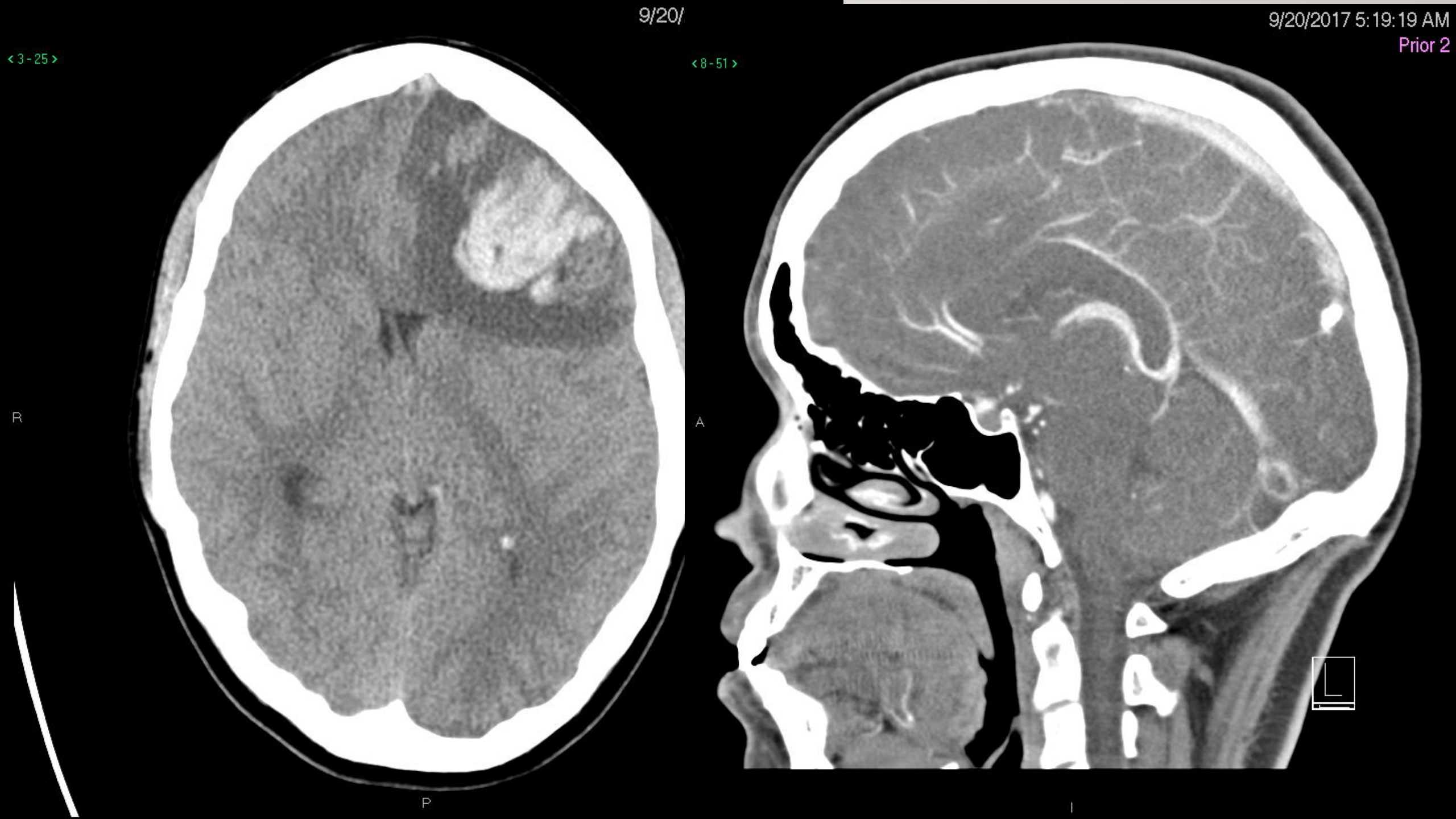
- History
  - Initial and timecourse of sx
  - Seizure
  - HTN
  - Prescription and Sympathomimetic Drug use
  - EtOH
  - Coagulopathy
  - Prior CVA, TIA
  - Aneurysm, AVM, Tumor (intra and extra cranial disease)
  - Pregnancy

WORK UP

- Stroke Labs
  - BMP
  - CBC
  - Coags
    - May not be abnormal with DOACs: History is important
  - Troponin
  - Finger stick glucose
  - Tox/Drug
  - Pregnancy

WORK UP

- Baseline neuro assessment
- ABCs
- Non Contrast CT Scan
- Need for Angiography To Rule out Underlying Lesion is Controversial
  - CTA- Quick, inexpensive study can be obtained a time of NCHCT
    - Sensitive and Specific for underlying vascular malformations, venous sources and signs concerning for hematoma expansion
  - MRI
    - Poor at identifying hyperacute blood
    - Slower, more expensive and requires patient be unaccompanied during study
  - Catheter Angiography
    - Largely replaced by CTA and used as confirmatory or interventional study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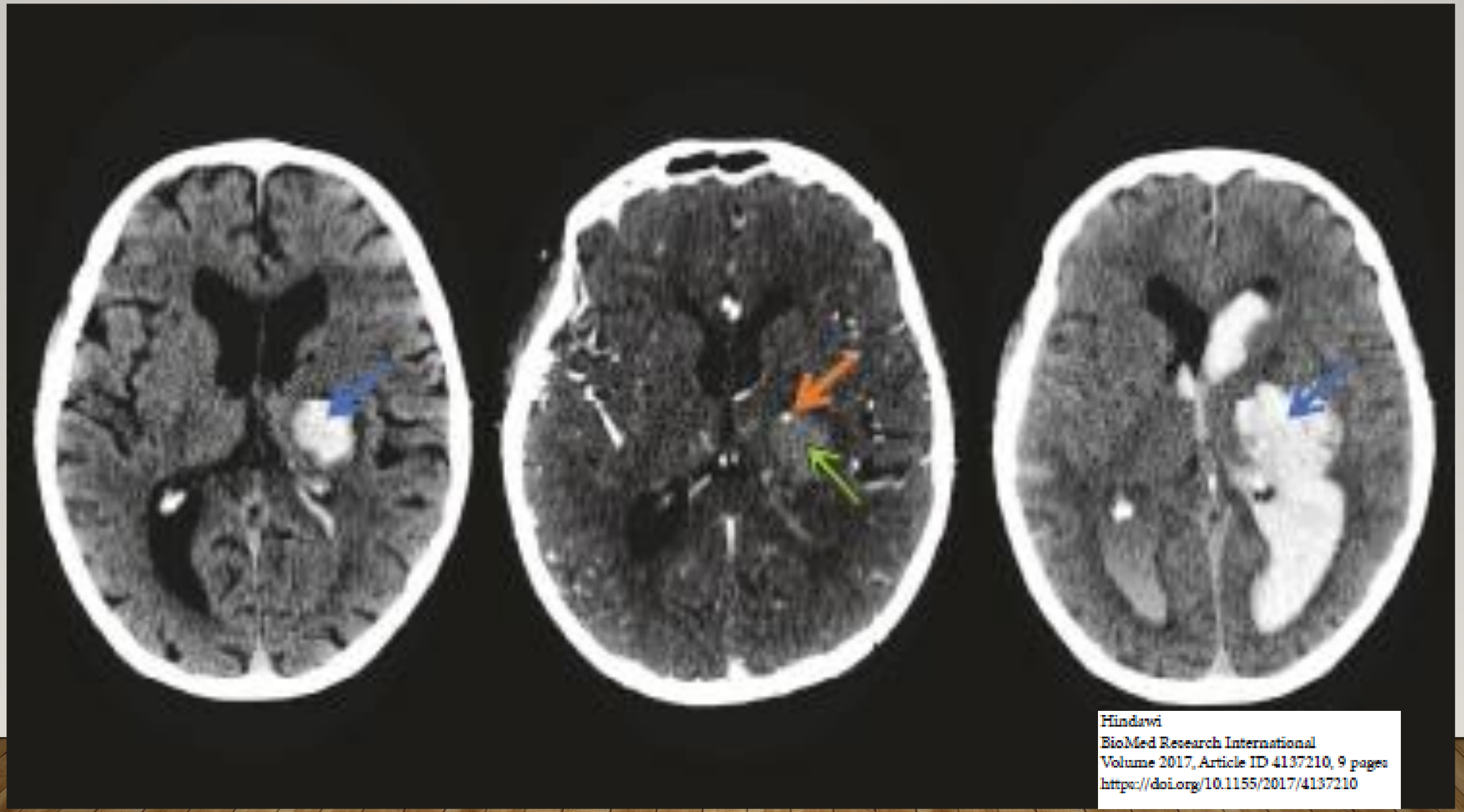

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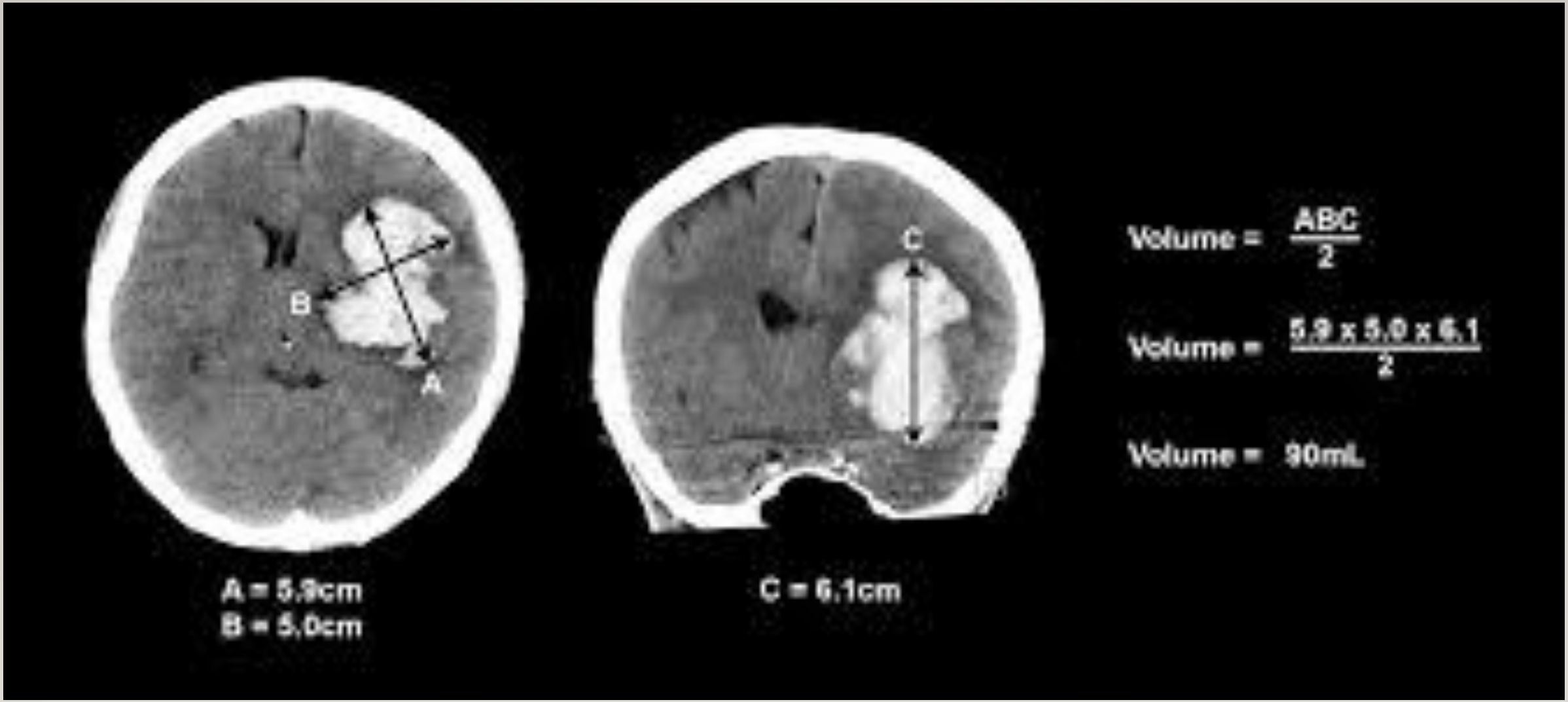
ASSESSMENT OF HEMORRHAGE SIZE

- Many scanners now do volumetric analysis
- Volume of an Ellipsoid
  - (AP Diameter x LAT Diameter x Height Diameter) ÷ 2
    - Slices with >75% counted at 1
    - Slices with 25-75% counted as ½
    - Slices with <25% not counted
- Clot decreases by about 0.75mm/day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A = 5.9cm
B = 5.0cm
C = 6.1cm
Volume = ABC / 2
Volume = 5.9 x 5.0 x 6.1 / 2
Volume = 90mL

ICH SCORES

- ICH Score
  - Predicts 30 Day Mortality
  - Use With Caution
    - Withdrawal of Care is the number one cause of death from ICH[11]
    - Odds of dying increase with use of DNR/DNI orders[12]

Intracerebral Haemorrhage

ICH Score (Hemphill et al.)

Feature	Finding	Points
GCS	3-4	2
	5-12	1
	13-15	0
Age	>=80	1
	<80	0
Location	Infratentorial	1
	Supratentorial	0
ICH volume	>=30cc	1
	<30cc	0
Intraventricular Blood	Yes	1
	No	0
ICH SCORE		0-6 points

ICH Score	30 Day Mortality
0	0%
1	13%
2	26%
3	72%
4	97%
5	100%
6	100%

EXPANSION SCORES

- BRAIN Score[13]
  - 0 points 3.4% likely to have expansion
  - 24 points 85.8% likely to have expansion
- BAT Score[14]
  - >3 predicts expansion with S/S 50/89%

BRAIN score for prediction of ICH growth at 24 hours	
BRAIN score component	**Poin**
Baseline ICH volume	
≤10ml	0
10-20ml	5
>20ml	7
Recurrent ICH	
No	0
Yes	4
Anticoagulation with Warfarin at onset	
No	0
Yes	6
Intraventricular extension	
No	0
Yes	2
Number of hours to baseline CT from symptom onset	
≤1	5
1-2	4
2-3	3
3-4	2
4-5	1
>5	0

Point total	Probability of ICH growth (%)
0	3.4
1	4.2
2	5.1
3	6.3
4	7.7
5	9.4
6	11.3
7	13.7
8	16.4
9	19.5
10	23.1
11	27.2
12	31.6
13	36.4
14	41.5
15	46.7
16	52.1
17	57.4
18	62.5
19	67.4
20	71.9
21	76.0
22	79.7
23	83.0
24	85.8

Figure 1. BRAIN prediction score and predicted probabilities of intracerebral hemorrhage (ICH) growth in the development model.

Table 4. Individual Components of the BAT Score

Variable	Points
Blend sign	
Present	1
Absent	0
Any hypodensity	
Present	2
Absent	0
Time from onset to NCCT	
<2.5 h	2
≥2.5 h or unknown	0

MANAGEMENT

- ICH is a Medical Disease
- ABCs
  - Repeat checks as clinical status is fluid
- ICU or IMC admission to monitored bed
  - Admission to dedicated Neuro ICU associated with better outcomes than general CCU[15]

CLINICAL PRACTICE GUIDELINE: BP MANAGEMENT[4]

- If sBP < 220, it is safe to lower it to 140 (range 140-180) [Level I]
  - sBP < 140 may cause more renal dysfunction
- Lowering sBP to 140 may improve functional outcome [Level II]
  - However this does not prevent rebleeding
- If sBP > 220 lower by 15-20%, but can consider aggressive reduction [Level II]

CLINICAL PRACTICE GUIDELINE: BP MANAGEMENT

- ATACH2[16]
  - Randomized 1000 patients with intracerebral hemorrhage (volume, <60 cm^3) and a Glasgow Coma Scale (GCS) score of 5 or more to a systolic blood-pressure target of 110 to 139 mm Hg (intensive treatment) or a target of 140 to 179 mm Hg (standard treatment) within 4.5 hours after symptom onset.
  - The primary outcome of death or disability was observed in 38.7% of the participants (186 of 481) in the intensive-treatment group and in 37.7% (181 of 480) in the standard-treatment group (relative risk, 1.04; 95% confidence interval, 0.85 to 1.27; analysis was adjusted for age, initial GCS score, and presence or absence of intraventricular hemorrhage). Serious adverse events occurring within 72 hours after randomization that were considered by the site investigator to be related to treatment were reported in 1.6% of the patients in the intensive-treatment group and in 1.2% of those in the standard-treatment group. The rate of renal adverse events within 7 days after randomization was significantly higher in the intensive-treatment group than in the standard-treatment group (9.0% vs. 4.0%, P=0.002).

CLINICAL PRACTICE GUIDELINE: SEIZURE AND AED MANAGEMENT[4]

- Treat Seizure in patients presenting with seizure or with seizure on EEG [Level I]
- Treat seizure in patients unexplained depression of mental status commiserate with ICH [Level II]
- Do Not prophylactically treat seizure [Level III]
  - Several small trials have shown increased death and disability with AEDs
  - Prophylactic AEDs have not been shown to prevent lesion related epilepsy

CLINICAL PRACTICE GUIDELINE: HEMOSTASIS AND CORRECTION OF COAGULOPATHY[4]

- Correction of any coagulopathy is important to prevent decline from hematoma expansion and ICP elevation
- More conditions requiring anticoagulation and higher prevalence of them in an aging population
- Patients with a severe coagulation factor deficiency or severe thrombocytopenia should receive appropriate factor replacement therapy or platelets, respectively *(Class I; Level of Evidence C*). (Unchanged from the previous guideline)

CLINICAL PRACTICE GUIDELINE: HEMOSTASIS AND CORRECTION OF COAGULOPATHY[4]

- Patients with ICH whose INR is elevated because of VKA should have their VKA withheld, receive therapy to replace vitamin K–dependent factors and correct the INR, and receive intravenous vitamin K *(Class I; Level of Evidence C*).
- PCCs may have fewer complications and correct the INR more rapidly than FFP and might be considered over FFP *(Class IIb; Level of Evidence B*).
- rFVIIa does not replace all clotting factors, and although the INR may be lowered, clotting may not be restored in vivo; therefore, rFVIIa is not recommended for VKA reversal in ICH *(Class III; Level of Evidence C*). (Revised from the previous guideline)

REVERSAL OF VKA

- Vitamin K
  - Coenzyme for vitamin K-dependent carboxylase, an enzyme required for the synthesis of proteins involved in hemostasis
  - Best route of administration remains controversial
    - IV probably works faster
  - Best dose remains controversial
    - 2.5-10mg
  - Side Effects (most mitigated by slow administration)
    - Flushing
    - Rash
    - Hypotension
    - Tachycardia
    - Edema
    - Anaphylaxis

REVERSAL OF VKA

- Fresh Frozen Plasma
  - Contains all of the clotting factors, fibrinogen (400 to 900 mg/unit), plasma proteins (particularly albumin), electrolytes, physiological anticoagulants (protein C, protein S, antithrombin, tissue factor pathway inhibitor) and added anticoagulants
  - INR 1.6
  - Weight based dosing (not give em 2)
  - 1 bag (200-250cc) =1 unit (not a unit of factor activity which is 1mL)
    - Significant volume
    - Time to preparation
    - ABO/Infection/Allergen risks of RBCs
    - Half Life about 4 hours

REVERSAL OF VKA[4]

- Procoagulant Complex (K-centra)
  - 4 factor PCC
    - F 2, 7, 9, 10, Protein C and S
  - Works immediately
  - Half life around 30 hours
  - Low Volume
  - Expensive
  - Small risk of hypercoagulable side effects
  - Dosed in units/kg
    - 50u/kg for life threatening or intracranial hemorrhage

REVERSAL OF DOACS[4]

- **For patients with ICH who are taking dabigatran, rivaroxaban, or apixaban, treatment with FEIBA, other PCCs, or rFVIIa might be considered on an individual basis. Activated charcoal might be used if the most recent dose of dabigatran, apixaban, or rivaroxaban was taken <2 hours earlier. Hemodialysis might be considered for dabigatran *(Class IIb; Level of Evidence C*).** (New recommendation)

REVERSAL OF DOACS[4]

- Xa Inhibitors
  - Andexanet Alfa
    - Recombinant modified factor Xa protein approved by the FDA in May 2018 for the reversal of apixaban and rivaroxaban in patients with life-threatening or uncontrolled bleeding.
    - Acts as a decoy and sequesters rivaroxaban or apixaban, inhibiting them from binding to natural factor Xa
    - Half-life about 5 hours
    - EXPENSIVE
  - PCC and FFP have some activity against Xas
- Praxbind
  - Humanized monoclonal antibody fragment
  - Binds and immediately inactivates the active form of pradaxa

HEPARIN AND ANTIPLATELETS[4]

- **The usefulness of platelet transfusions in ICH patients with a history of antiplatelet use is uncertain *(Class IIb; Level of Evidence C*).**

- **Protamine sulfate may be considered to reverse heparin in patients with acute ICH *(Class IIb; Level of Evidence C*).** (New recommendation)

DVT PROPHYLAXIS[4]

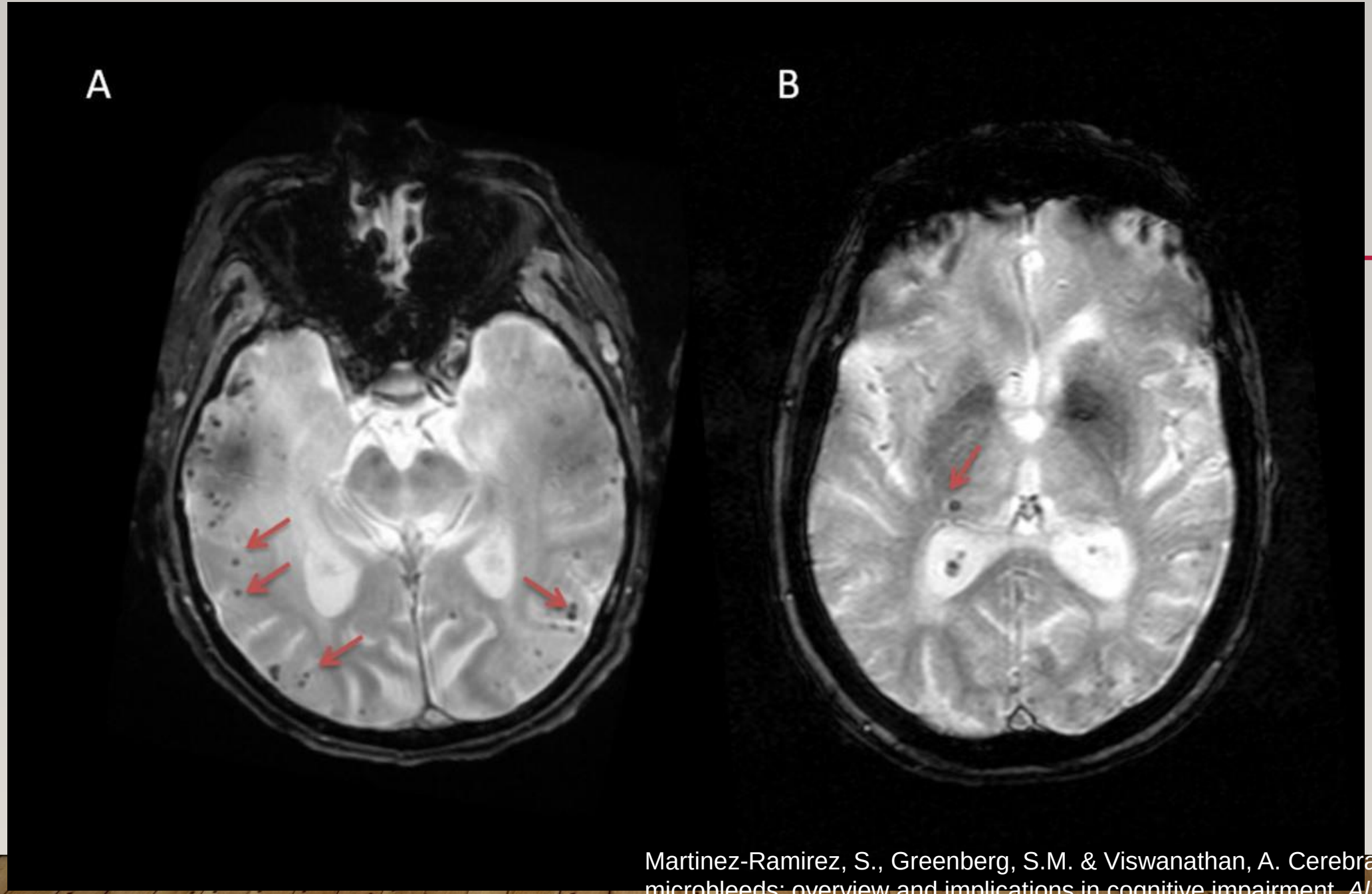
- SCDs on admission
- **After documentation of cessation of bleeding, low-dose subcutaneous low-molecular-weight heparin or unfractionated heparin may be considered for prevention of venous thromboembolism in patients with lack of mobility after 1 to 4 days from onset *(Class IIb; Level of Evidence B*).**
- **Systemic anticoagulation or IVC filter placement is probably indicated in ICH patients with symptomatic DVT or PE *(Class IIa; Level of Evidence C*). The decision between these 2 options should take into account several factors, including time from hemorrhage onset, hematoma stability, cause of hemorrhage, and overall patient condition *(Class IIa; Level of Evidence C*).** (New recommendation)

MEDICAL MANAGEMENT

- NeuroICU or Stroke Unit Care
- BP Control
- Timely Reversal of Coagulopathy
- Prevention of Secondary Brain Injury
  - Normothermic
  - Euglycemic
  - Normal oxygenation and EtCO2
  - Treatment but not prevention of seizure
- Locate a cause
- Mitigate risk factors for recurrence

MODIFIABLE RISK FACTORS FOR RECURRENCE

- Hypertension
  - OSA
- Cerebral Amyloid Angiopathy
  - Deposition of β-Amyloid in cerebral vasculature more common in elderly and with apo-E ε2, 4 alleles
  - Look for microbleeds on MRI particularly GRE sequences
- EtOH, Tobacco, Drug use



Martinez-Ramirez, S., Greenberg, S.M. & Viswanathan, A. Cerebral microbleeds: overview and implications in cognitive impairment. *Alz Res Therapy* **6,** 33 (2014). https://doi.org/10.1186/alzrt263

RESUMING ANTICOAGULATION[4]

- **Avoidance of long-term anticoagulation with warfarin as a treatment for nonvalvular atrial fibrillation is probably recommended after warfarin-associated spontaneous lobar ICH because of the relatively high risk of recurrence *(Class IIa; Level of Evidence B*).** (Unchanged from the previous guideline)
- **Anticoagulation after nonlobar ICH and antiplatelet monotherapy after any ICH might be considered, particularly when there are strong indications for these agents *(Class IIb; Level of Evidence B*).** (Revised from the previous guideline)
- **The optimal timing to resume oral anticoagulation after anticoagulant-related ICH is uncertain. Avoidance of oral anticoagulation for at least 4 weeks, in patients without mechanical heart valves, might decrease the risk of ICH recurrence *(Class IIb; Level of Evidence B*).** (New recommendation) **If indicated, aspirin monotherapy can probably be restarted in the days after ICH, although the optimal timing is uncertain *(Class IIa; Level of Evidence B*).** (New recommendation)
- **The usefulness of dabigatran, rivaroxaban, or apixaban in patients with atrial fibrillation and past ICH to decrease the risk of recurrence is uncertain *(Class IIb; Level of Evidence C*).** (New recommendation)

WHY NOT JUST TAKE IT OUT?

- Multiple surgical trials have consistently failed to show a clear benefit to surgery versus best medical management in outcomes
- Not all bleeds and not all patients are the same
- Not the presence of the hemorrhage but the tissue destruction

SURGICAL TREATMENT OF INTRACEREBRAL HEMORRHAGE (STITCH) [18]

- Determine whether early surgery reduces mortality and improves neurological outcome compared with conservative management for supratentorial ICH
- 1033 patients from 83 centers in 27 countries were randomized to early surgery (<24 hours of randomization) or initial conservative treatment.
- A favorable outcome on the 8-point extended Glasgow Outcome Scale at 6 months was used as the primary end point.
- 26% vs. 24% favorable outcome in surgical and medical arms respectively
- Subgroup analysis suggested that patients with lobar hemorrhages within 1 cm of the cortical surface might benefit from surgery.
- Additional subgroup analysis suggested that the risk for a poor outcome was increased for patients who presented as comatose (GCS score ≤8).

SURGICAL TRIAL IN LOBAR INTRACEREBRAL HAEMORRHAGE (STICH II) [19]

- Is early surgery would be beneficial for conscious patients with superficial lobar hemorrhage of 10 to 100 mm^3 within 1 cm of the cortical surface and without IVH and who were admitted within 48 hours of ictus.
- Seventy-eight centers in 27 countries participated. The study randomized patients to early surgery (within 12 hours of randomization) plus medical management or medical management alone.
- The primary outcome was a prognosis-based dichotomized (favorable or unfavorable) outcome of the extended Glasgow Outcome Scale.
- Forty-one percent of patients in the early surgery group had a favorable outcome compared with 38% in the medical arm; this difference was not statistically significant.
- A nonprespecified subgroup analysis that included only patients with a poor prognosis (as defined by a specific equation used in STICH) showed that such patients were more likely to have a favorable outcome with early surgery; however, there was no advantage to early surgery for patients in the good prognosis category. A nonsignificant survival advantage was noted for the surgical arm.

MISTIE[20]

- MISTIE III was an open-label, blinded endpoint, phase 3 trial done at 78 hospitals in the USA, Canada, Europe, Australia, and Asia. We enrolled patients aged 18 years or older with spontaneous, non-traumatic, supratentorial intracerebral haemorrhage of 30 mL or more.
- Image or endoscope guided clot aspiration and catheter placement with instillation of 1mg alteplase every 8 h for up to nine doses or standard medical care.
- Primary outcome was a modified Rankin Scale (mRS) score of 0–3 at 365 days, adjusted for group differences in prespecified baseline covariates (stability intracerebral haemorrhage size, age, Glasgow Coma Scale, stability intraventricular haemorrhage size, and clot location).
- 45% of patients in the MISTIE group and 41% patients in the standard medical care group had achieved an mRS score of 0–3 at 365 days

THROMBOLYTIC REMOVAL OF INTRAVENTRICULAR HAEMORRHAGE IN TREATMENT OF SEVERE STROKE: RESULTS OF THE RANDOMISED, MULTICENTRE, MULTIREGION, PLACEBO-CONTROLLED CLEAR III TRIAL[21]

- Randomised, double-blinded, placebo-controlled
- Participants with a routinely placed extraventricular drain, in the intensive care unit with stable, non-traumatic intracerebral haemorrhage volume less than 30 mL, intraventricular haemorrhage obstructing the 3rd or 4th ventricles, and no underlying pathology were adaptively randomly assigned (1:1), via a web-based system to receive up to 12 doses, 8 h apart of 1 mg of alteplase or 0·9% saline via the extraventricular drain.
- The treating physician, clinical research staff, and participants were masked to treatment assignment. CT scans were obtained every 24 h throughout dosing.
- The primary efficacy outcome was good functional outcome, defined as a modified Rankin Scale score (mRS) of 3 or less at 180 days per central adjudication by blinded evaluators.

CLEAR III[21]

- The primary efficacy outcome was similar in each group (good outcome in alteplase group 48% vs saline 45%; risk ratio [RR] 1·06 [95% CI 0·88-1·28; p=0·554]).
- A difference of 3·5% (RR 1·08 [95% CI 0·90-1·29], p=0·420) was found after adjustment for intraventricular haemorrhage size and thalamic intracerebral haemorrhage.
- At 180 days, the treatment group had lower case fatality (46 [18%] vs saline 73 [29%], hazard ratio 0·60 [95% CI 0·41-0·86], p=0·006), but a greater proportion with mRS 5 (42 [17%] vs 21 [9%]; RR 1·99 [95% CI 1·22-3·26], p=0·007).

SURGICAL INDICATIONS

- Hydrocephalus
  - Obstructive
  - Communicating
  - Intraventricular Hemorrhage
- Posterior fossa hemorrhage
- Lack of repeatable exam
- Failure of best medical management
  - Lobar hemorrhage > 50cc within 1cm of the cortical surface
- No optimal timing of surgery and no benefit to early (<96 hours) surgery
- Outcomes for surgical treatment of ICH mimic those of malignant MCA trials
  - Saves lives but many patients with poor long term functional status

QUESTIONS AND THANK YOU

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