An Integrated Strategy to Prevent Both Ischemic and Hemorrhagic Strokes

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Disclosure Statement of Financial Interest

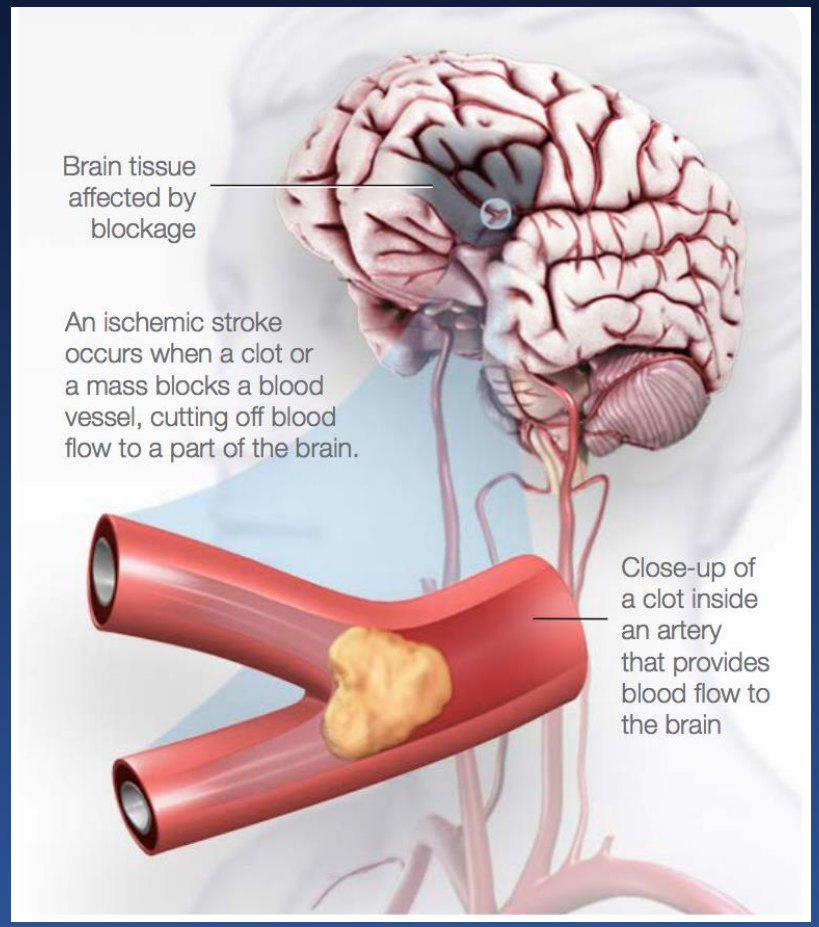
Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

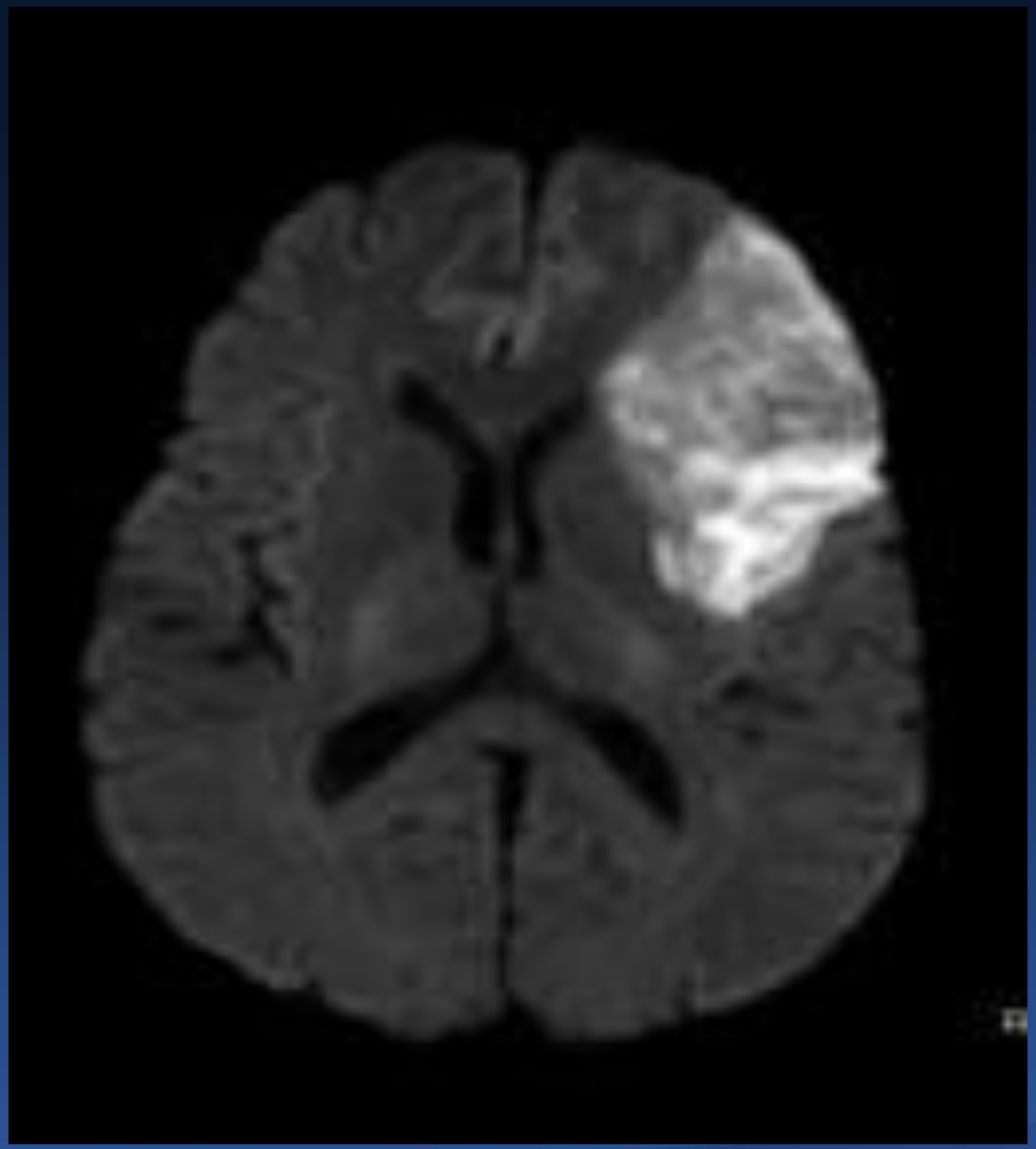
Affiliation/Financial Relationship	Company
Consulting Fees/Honoraria	St. Jude's Medical/Abbott

Ischemic Stroke

- In the United States, majority (~87%) of strokes occur in the setting of lack of blood flow to a part of the brain.
- Etiologies of which vary, but could be thrombotic, embolic, hemodynamic, or a combination.
- HTN remains the leading modifiable risk factor for stroke.
- Encompasses acute ischemic infarcts as well as transient ischemic attacks.

Ischemic Stroke





http://*www.strokeassociation.org/*

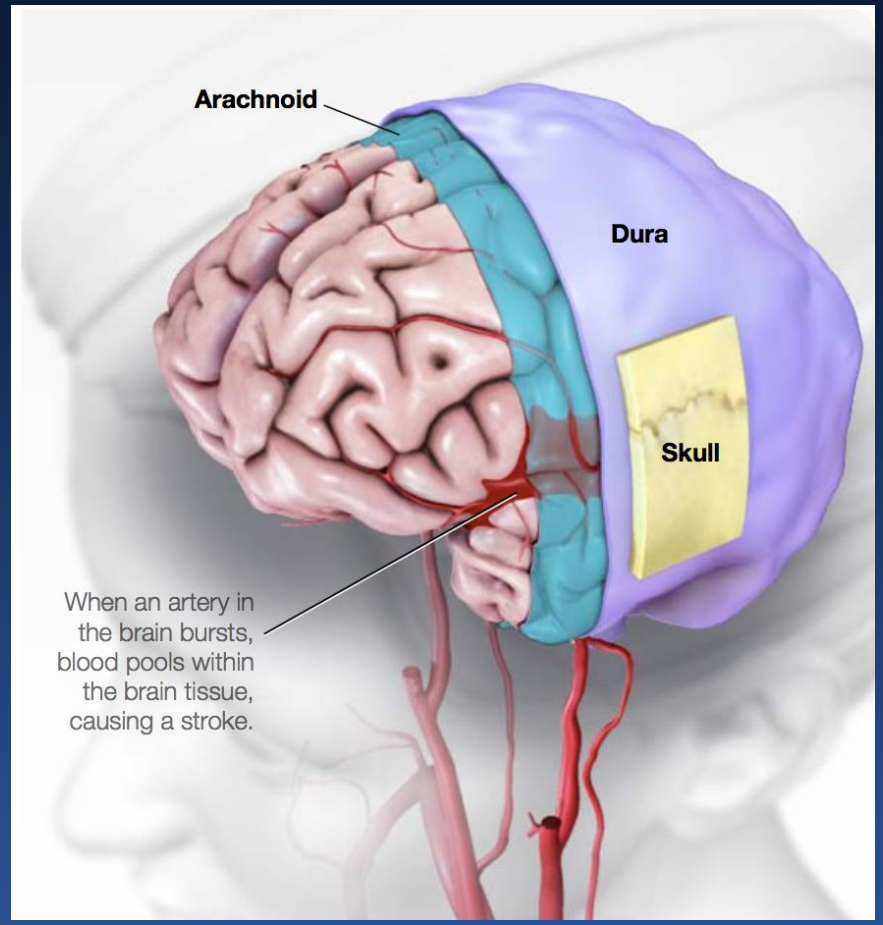
Etiologies of Acute Ischemic Stroke:

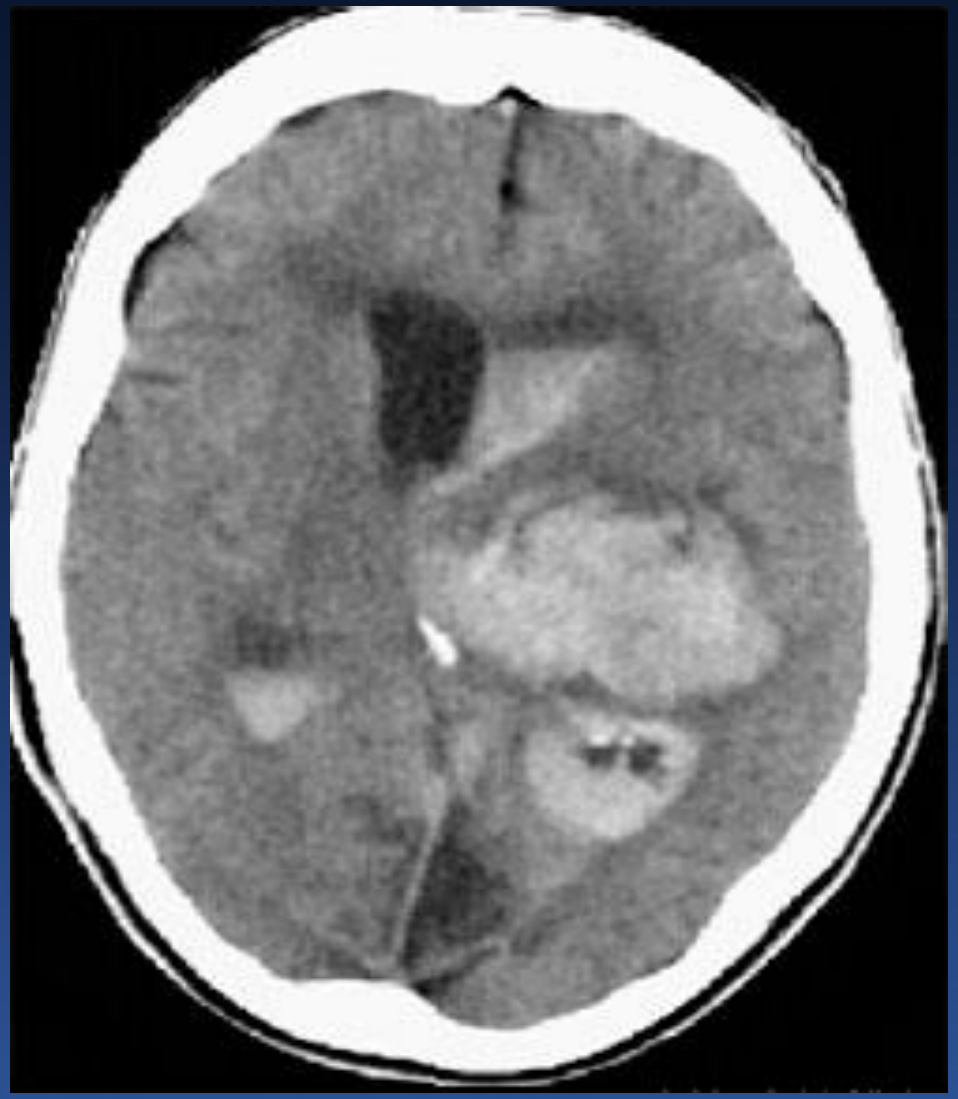
- Ischemic strokes have multiple different etiologies, including:
  - Cardioembolic
    - Atrial fibrillation
    - Cardiac thrombus
    - Hypercoagulable state
    - Infective endocarditis
  - Intracranial atherosclerotic disease
    - Hypertensive lacunar stroke syndromes
  - Large artery to artery embolization
    - Carotid stenosis
  - Hypotensive/hemodynamic
  - Paraxodoxical embolism due to shunt

Hemorrhagic Stroke

- The minority (~13%) of strokes in the United States are due to rupture of blood vessels within or surrounding the brain.
- The pathophysiologic mechanism of injury in hemorrhagic stroke is different than in ischemic strokes – blood remains toxic to surround healthy neurons and glial cells, in addition to acute peri-hematomal mass effect.
- Generally intracranial hemorrhagic strokes are thought to only encompass intracerebral/intraparenchymal hemorrhage, but also include subarachnoid, intraventricular, epidural, and subdural hemorrhages as well.

Hemorrhagic Stroke





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Terminology

- **Intracranial hemorrhage** – accumulation of blood anywhere within the cranial vault, including within the brain parenchyma or the surrounding meningeal spaces.
- **Intracerebral hemorrhage** – accumulation of blood within the brain parenchyma.
- **Epidural hemorrhage** – accumulation of blood within the epidural space – i.e. middle meningeal artery.
- **Subdural hemorrhage** – accumulation of blood in the subdural space - i.e. bridging veins.
- **Subarachnoid hemorrhage** – accumulation of blood in the subarachnoid space – i.e aneurysmal bleeds.
- **Intraventricular hemorrhage** – accumulation of blood within the ventricles, oftentimes due to secondary extension.

Basics

- There are two broad categories of intracerebral hemorrhage:
  - Traumatic
    - Generally MVA's, elderly presenting with falls with frontal or temporal contusions, although more likely epidural or subdural hemorrhages rather than intraparenchymal.
  - Non-traumatic
    - Generally hypertensive etiology, amyloid, coagulopathy, vascular malformations, venous thrombosis, etc.
  - Important to differentiate the etiology because this will impact your work up and future management.

Why is it important?

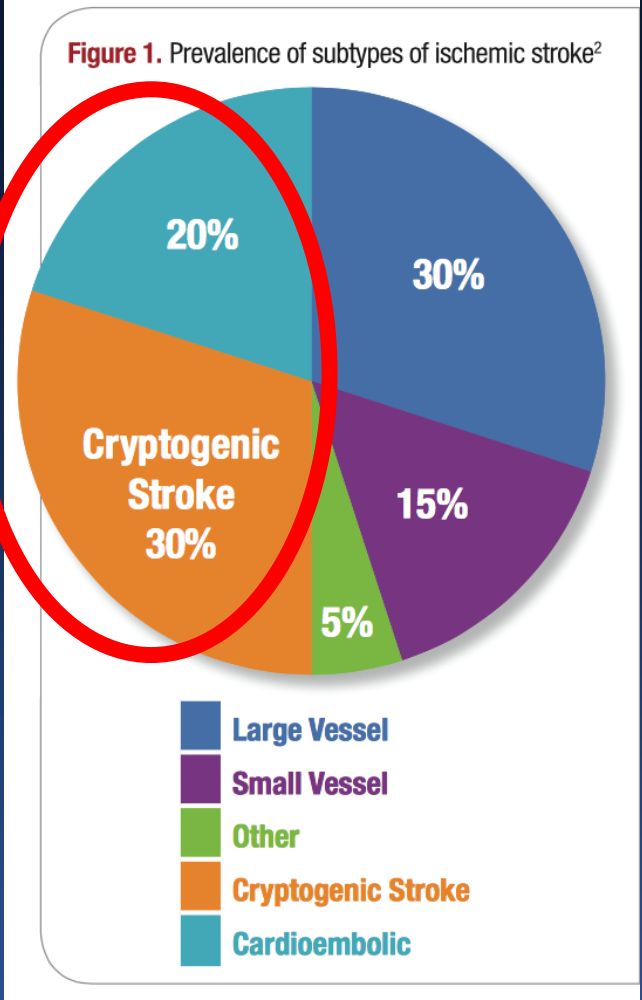

Table 1. TOAST Classification of Subtypes of Acute Ischemic Stroke²

- Large-artery atherosclerosis
- Cardioembolism
- Small-vessel occlusion
- Stroke of other determined etiology* (*Possible or probable depending on results of ancillary studies)
- Stroke of undetermined etiology
  - Two or more causes identified
  - Negative evaluation
  - Incomplete evaluation

Why is it important?

- We have made significant strides in our ability to detect and treat atrial fibrillation, however less than half of high embolic risk patients actually receive oral anticoagulants. [11]

- A fib is associated with a 5-fold increased risk of stroke. A fib is also an independent predictor of increased mortality, and paroxysmal A fib increases stroke risk similar to sustained A fib.[9]

Current Primary Prevention of Stroke Guidelines (2014):

- Most recent AHA/ASA guidelines for Primary Prevention of Stroke recommend risk stratification – risk of cardioembolic stroke and risk for hemorrhagic complications of antithrombotic/anticoagulants.[9]
- Multiple scoring schemes have been tested in multiple cohorts – most common are $CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED.
  - Bleed risk stratification scores generally were not focused on intracranial hemorrhages, which has the greatest long-term effect on quality of life.
  - Many components on hemorrhage risk scales are also risks for cardioembolic stroke.[9]

Defining Stroke and Hemorrhage Risk in A Fib:

- CHA_2DS_2-VASc and HAS-BLED

Table 2. Assessment of Stroke (CHA_2DS_2-VASc)[14] and Bleeding Risk (HAS-BLED)[15] in Atrial Fibrillation Patients

CHA_2DS_2-VASc	Score	HAS-BLED	Score
Congestive heart failure	1	Hypertension (systolic blood pressure >160 mm Hg)	1
Hypertension	1	Abnormal renal and liver function* (1 point each)	1 or 2
Age ≥75 y	2	Stroke	1
Diabetes mellitus	1	Bleeding tendency/predisposition*	1
Stroke/TIA/TE	2	Labile INRs (if on warfarin)*	1
Vascular disease (prior MI, PAD, or aortic plaque)	1	Elderly (eg, age >65 y)	1
		Drugs or alcohol (1 point each)*	1 or 2
Aged 65 to 74 y	1		
Sex category (ie, female sex)	1		
Maximum score	9	Maximum score	9

Lane and Lip 2012

Pharmacological Risk Reduction:

- Adjusted-dose warfarin (INR 2-3), prior to NOACs, was generally the treatment of choice for cardioembolic stroke in patients with acceptably low risk of hemorrhage – specifically ICH.
  - Risk Reduction of ~64% for ischemic stroke.[9]
  - Reduces all-cause mortality by 26%.[9]
  - Anticoagulation reduces stroke severity and post-stroke mortality.[9]
- Antiplatelet agents in non-valvular atrial fibrillations:
  - Aspirin provides only modest protection – RR reduction of ~22%.
  - Dual antiplatelet resulted in significant reduction of all strokes ~28%, but at expense of increase in major bleeding RR increase 57%.[2]

NOACs/DOACs

- The NOACs (DTI and Xa inhibitors) have proved to have advantages over warfarin with non-inferiority for stroke prevention, decreased risk of ICH, lack of blood monitoring, and overall less food and drug interactions. [13]
- The generally accepted downsides of the novel agents include:
  - Slightly higher gastrointestinal bleeding
  - Higher cost
  - Questioned safety in renal dysfunction and elderly
  - Lack of an effective reversal agent – now FDA approved for Idarucizumab (DTI) and Andexanet (Xa)
  - Compliance – not protected with missed doses

Warfarin vs. NOAC ICH risk:

Table 4. Odds ratios of intracranial hemorrhage relative to warfarin with an INR of 2.0 to 3.0

Drug	Dose(s)	OR (95% CI)	Reference
Apixaban	5 mg twice daily	0.42 (0.30 to 0.58)	Granger[402]
	2.5 or 5 mg twice daily	0.17 (0.01 to 4.30)	Ogawa[321]
Dabigatran	110 to 150 mg twice daily	0.36 (0.26 to 0.49)	Connolly[392]
Rivaroxaban	20 mg daily	0.65 (0.46 to 0.92)	Patel[397]
	15 mg daily	0.50 (0.17 to 1.46)	Hori[394]

CI indicates confidence interval; INR, international normalized ratio; and OR, odds ratio. Adapted with permission from Chatterjee et al.[411] Copyright © 2013, American Medical Association. All rights reserved. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

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Current Primary Prevention of Stroke Guidelines (2014):

- For patients with nonvalvular AF, a CHA2DS2-VASc score of ≥2, and acceptably low risk for hemorrhagic complications, oral anticoagulants are recommended (*Class I*).
  - Options include warfarin (INR, 2.0 to 3.0) (*Level of Evidence A*), dabigatran (*Level of Evidence B*), apixaban (*Level of Evidence B*), and rivaroxaban (*Level of Evidence B*). The selection of antithrombotic agent should be individualized on the basis of patient risk factors (particularly risk for intracranial hemorrhage), cost, tolerability, patient preference, potential for drug interactions, and other clinical characteristics, including the time that the INR is in therapeutic range for patients taking warfarin. [9]

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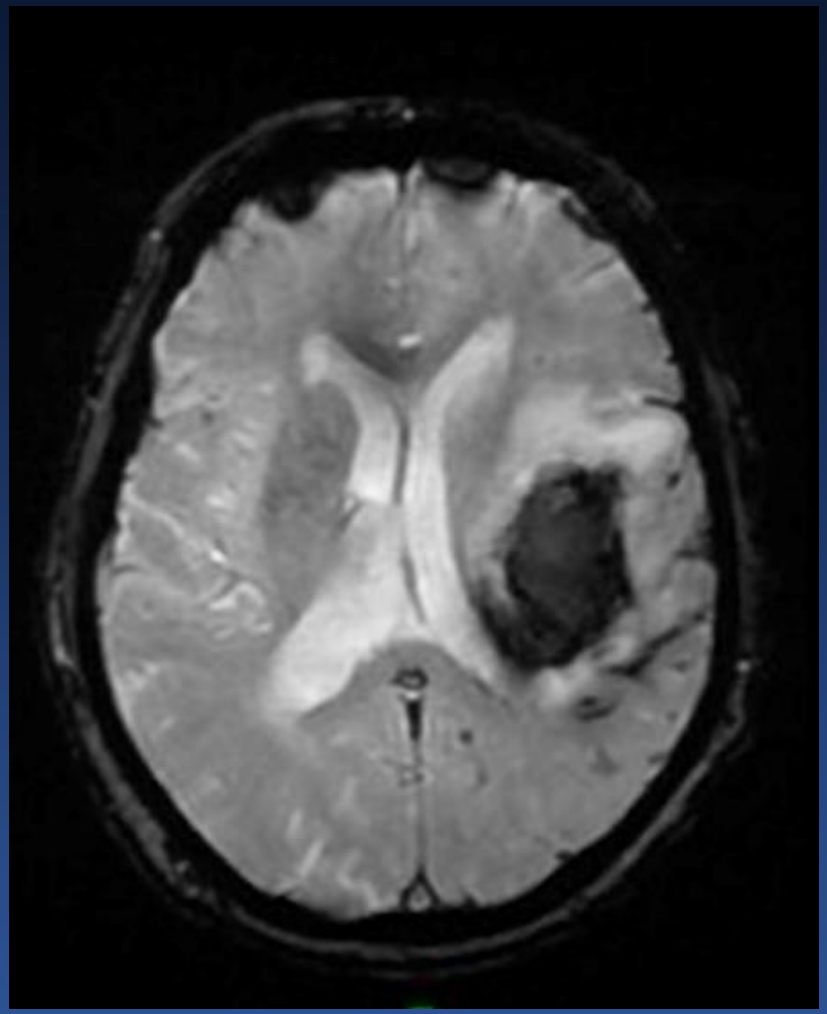
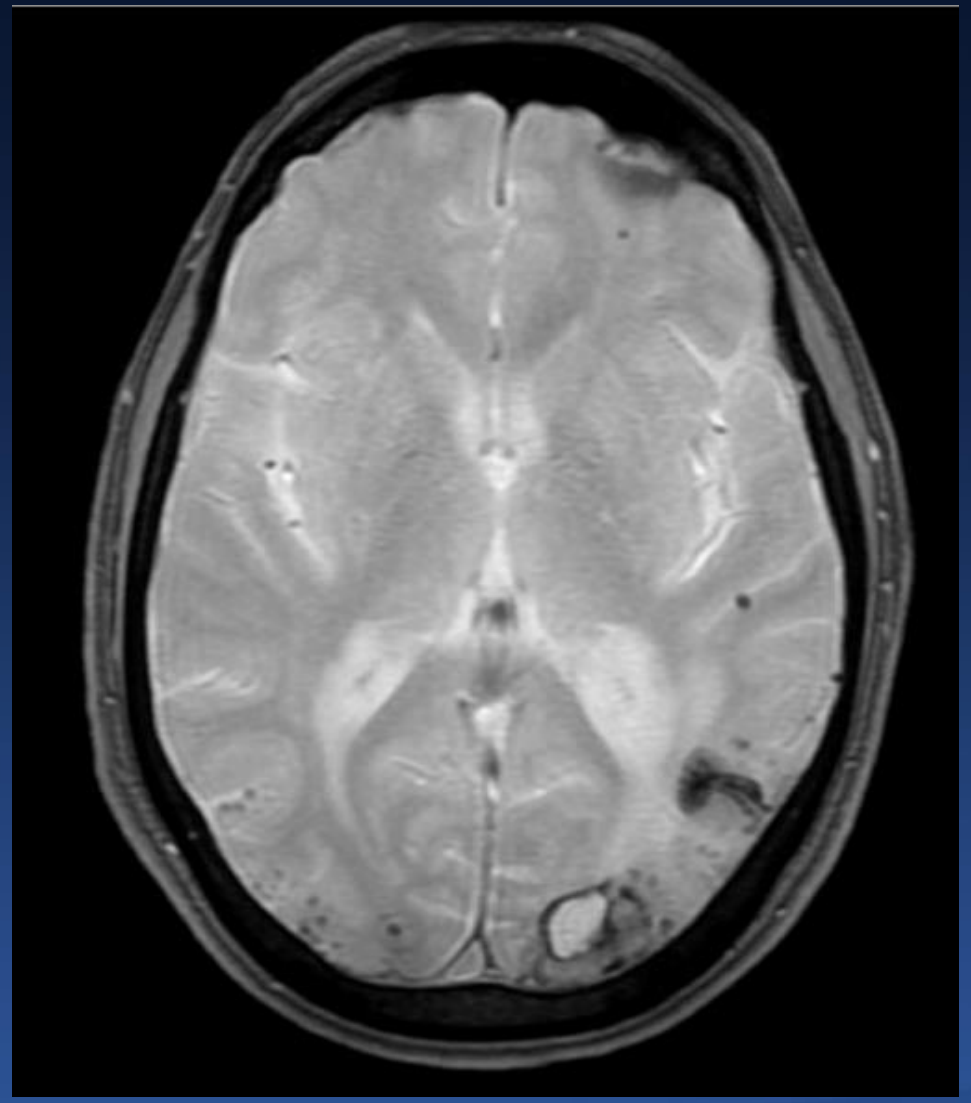
High Hemorrhage Risk Population

- OAC associated ICH have poorer outcomes when compared to non-OAC related ICH (mortality of 52% vs. 25.8%).[14]

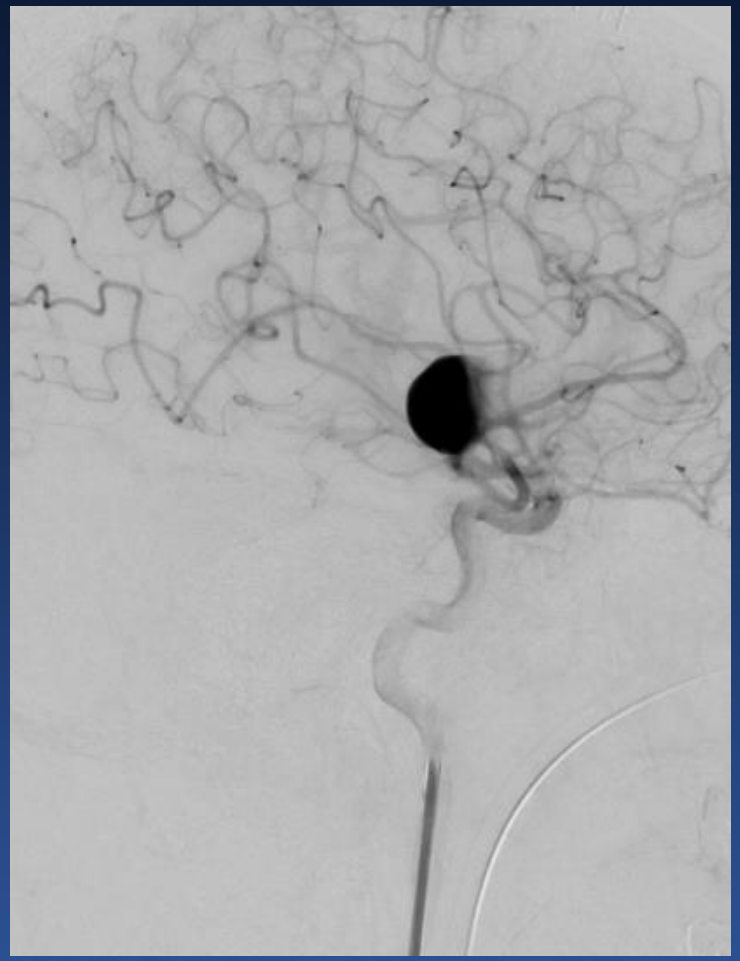
  - Patients with prior spontaneous IPH/EDH/SDH/SAH/IVH.
    - Patients with unsecured intracerebral lesions – i.e. aneurysms, fistulas, vascular malformations, etc.
  - Elderly patients, generally with high fall risk.
  - Patients with known cerebral microbleeds – possible cerebral amyloid angiopathy.
  - High systemic risk of hemorrhage without treatable lesion.

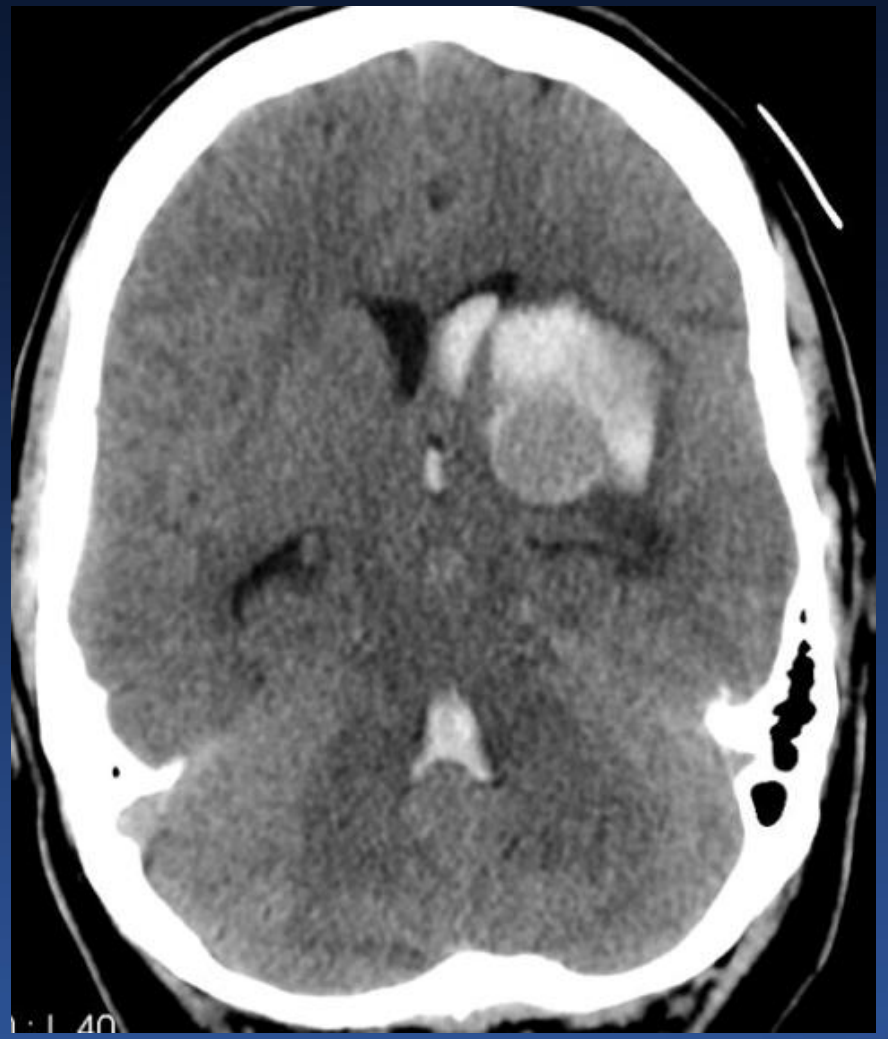
Cerebral amyloid angiopathy:



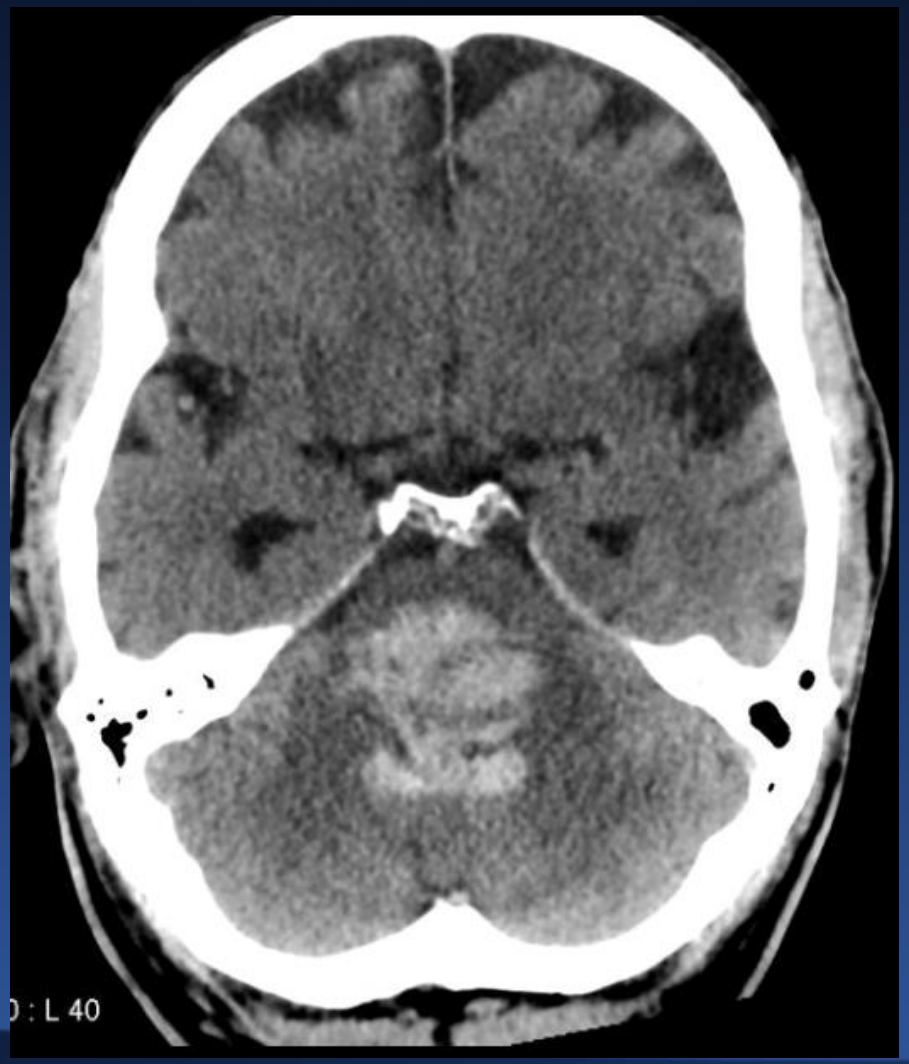


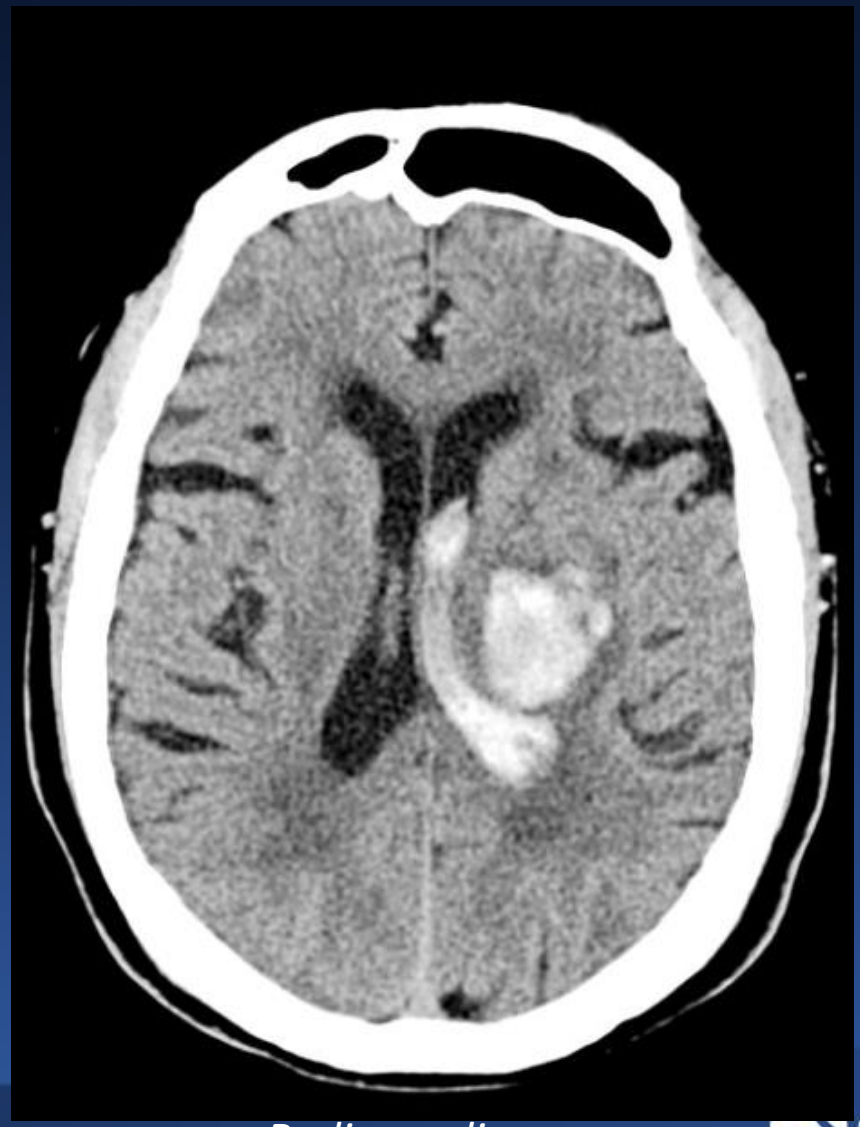
ICA Aneurysm with Rupture:





Intraparenchymal Hemorrhage:





Radiopaedia.org

Minimizing the risk of Hemorrhage with AC:

- Treatment and adequate control of hypertension in atrial fibrillation reduces both ICH and ischemic stroke risk – dual benefit.
- Addition of antiplatelet to warfarin therapy increases the risk of intracranial and extracranial hemorrhage – no strong data in patients with stable CAD and A fib.
- With unstable CAD or with PCI – recommendations are for bare metal stents to minimize time on antiplatelet in addition to anticoagulation – lower INR goal 2-2.5 while on dual antiplatelet.[3,4,5,6]

Non-pharmacological management of A fib

- Important to offer alternatives to patients with atrial fibrillation whose risks of hemorrhage (ICH or systemic) outweigh potential benefits of anticoagulation.
- The LAA is an embryonic remnant of the original left atrium, continuity with the left atrial cavity.
  - For many decades, unique anatomy thought to result in stagnant blood flow in A fib and potentially predispose to in-situ thrombus formation.
  - Internal characteristics and morphology of LAA may impact embolic stroke risk in patients with A fib.

High Hemorrhage Risk Patients with A fib

- LAA thought to be the origin of >90% of emboli in patients with atrial fibrillation.[9]
- Closure of LAA has been evaluated as an alternative approach to stroke prevention in non-valvular atrial fibrillation.
  - PROTECT AF: WATCHMAN device – warfarin for 45 days then DAPT x 4.5 months (if LAA echocardiographically demonstrated closure of LAA), and then ASA indefinitely.
  - LAA closure non-inferior to warfarin for preventing the primary outcome of ischemic or hemorrhagic stroke, cardiac or unexplained death, or systemic embolism.
    - Insignificantly higher risk of ischemic stroke due to procedure-related strokes.
    - FDA required another RCT – PREVAIL – higher risk patient cohort
  - AMPLATZER Amulet – another LAA occluder – SWISS-APERO – Future trial comparing Amulet to WATCHMAN, not yet enrolling.
  - External clipping – AtriClip.
- Therapeutic cardioversion and rhythm control does not reduce stroke risk.[7]
  - Intervals of asymptomatic A fib persist after apparently successful radiofrequency ablation, suggesting a persistent need for antithrombotic treatment after the procedure.[8]

Current Primary Prevention of Stroke Guidelines (2014):

- **Closure of the LAA may be considered for high-risk patients with AF who are deemed unsuitable for anticoagulation if performed at a center with low rates of peri-procedural complications and the patient can tolerate the risk of at least 45 days of post-procedural anticoagulation (*Class IIb; Level of Evidence B*).[9]**

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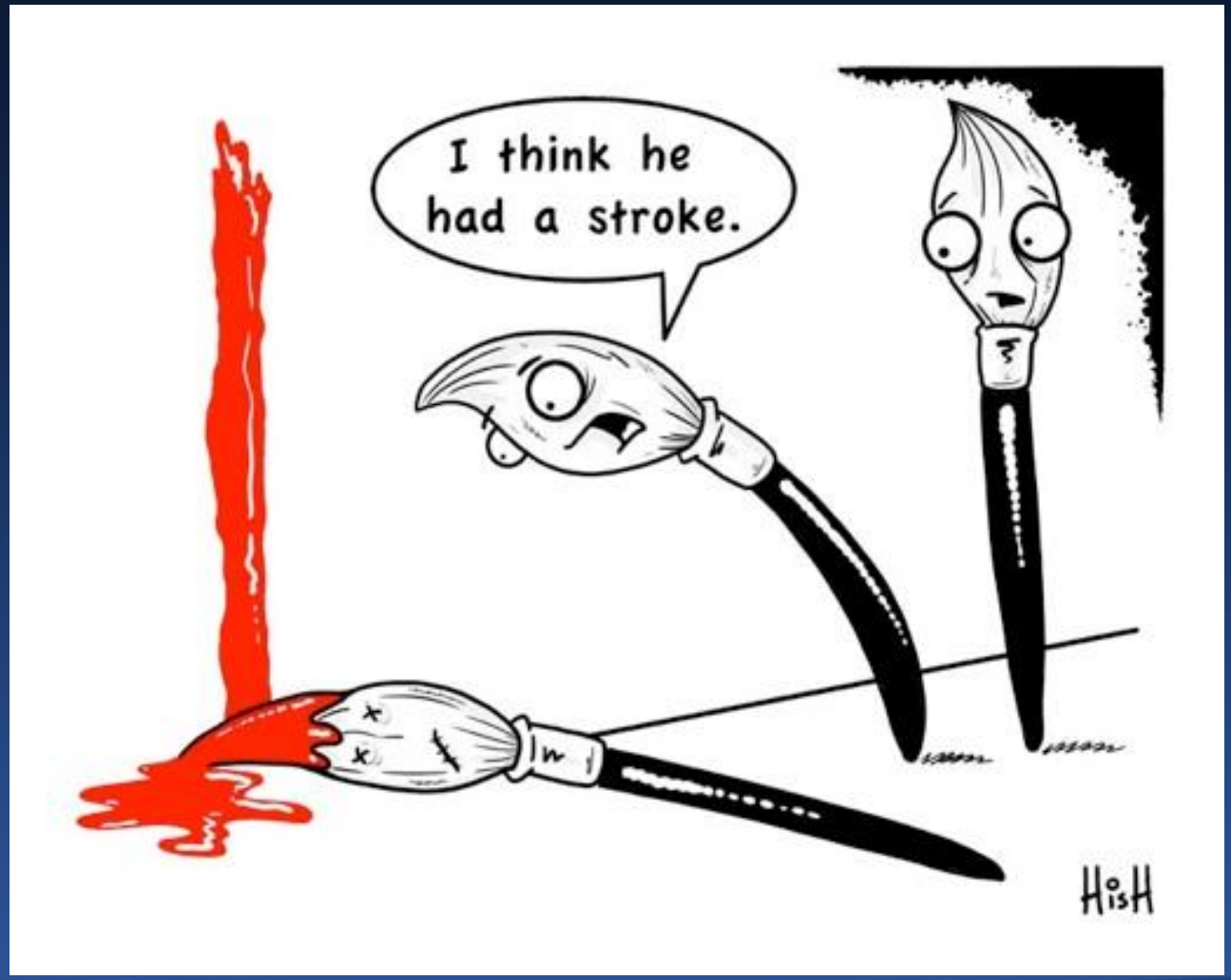
Questions?



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