Horses and Zebras: Common and Uncommon Causes of Acute Ischemic Stroke

Allyson Hamacher, PA-C, RD
Abigail Taylor, PA-C
Mayo Clinic, Phoenix, Arizona

DISCLOSURES

- No relevant commercial relationships to disclose for either presenter

Objectives

At the conclusion of this session, participants should be able to:

- Describe the presenting signs and symptoms of acute ischemic stroke
- List diagnostic tests performed in stroke work-up
- Recognize categories of ischemic stroke causes, including: cardioembolic, large-vessel disease, small-vessel disease, and thrombosis
- Identify specific etiologies of acute ischemic stroke and appropriately classify into above categories
- Select appropriate secondary stroke prevention measures based on etiology of acute ischemic stroke

STROKE [1,2]

- Proposed definition, “brain, spinal cord, or retinal cell death attributable to ischemia, based on neuropathological, neuroimaging, and/or clinical evidence of permanent injury.” [1]
- Includes both hemorrhagic (~20%) and ischemic strokes (~80%)
- Ranked as the second leading cause of death worldwide
  - Annual mortality rate approximately 5.5 million
- Up to 50% of stroke survivors have some chronic disability

https://www.genentechmaterials.com/strokeurgencytoolkit/items.sgi

MEDICAL EVALUATION

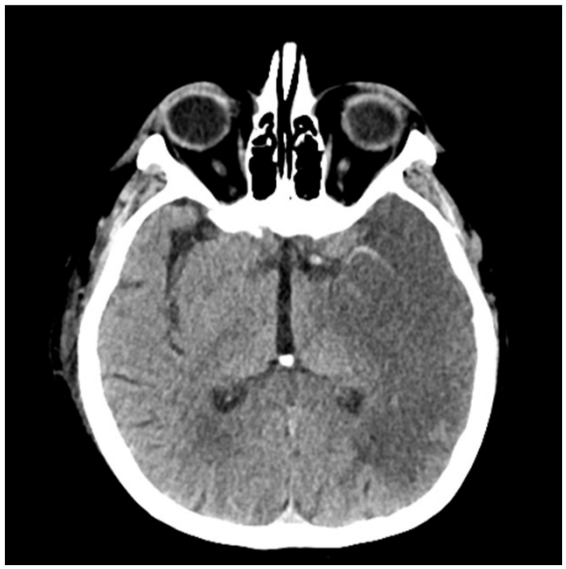
- Once a patient is diagnosed with an acute ischemic stroke/transient ischemic attack (TIA), the questions are:

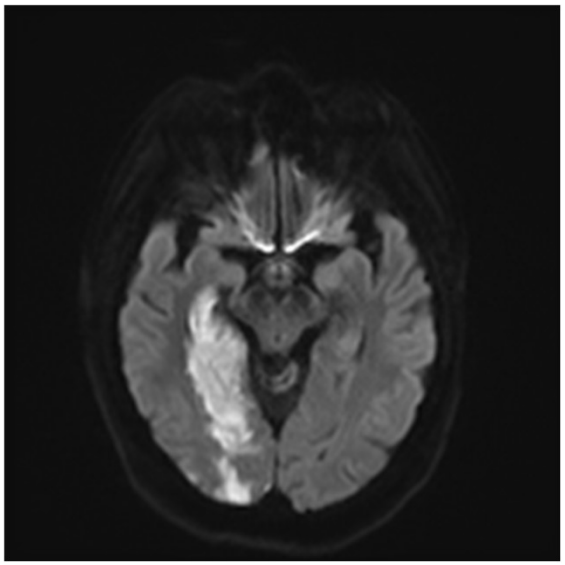
    1. Why did they have a stroke? (etiology)

    2. What can we do to prevent a future stroke? (secondary prevention)

STROKE WORK-UP

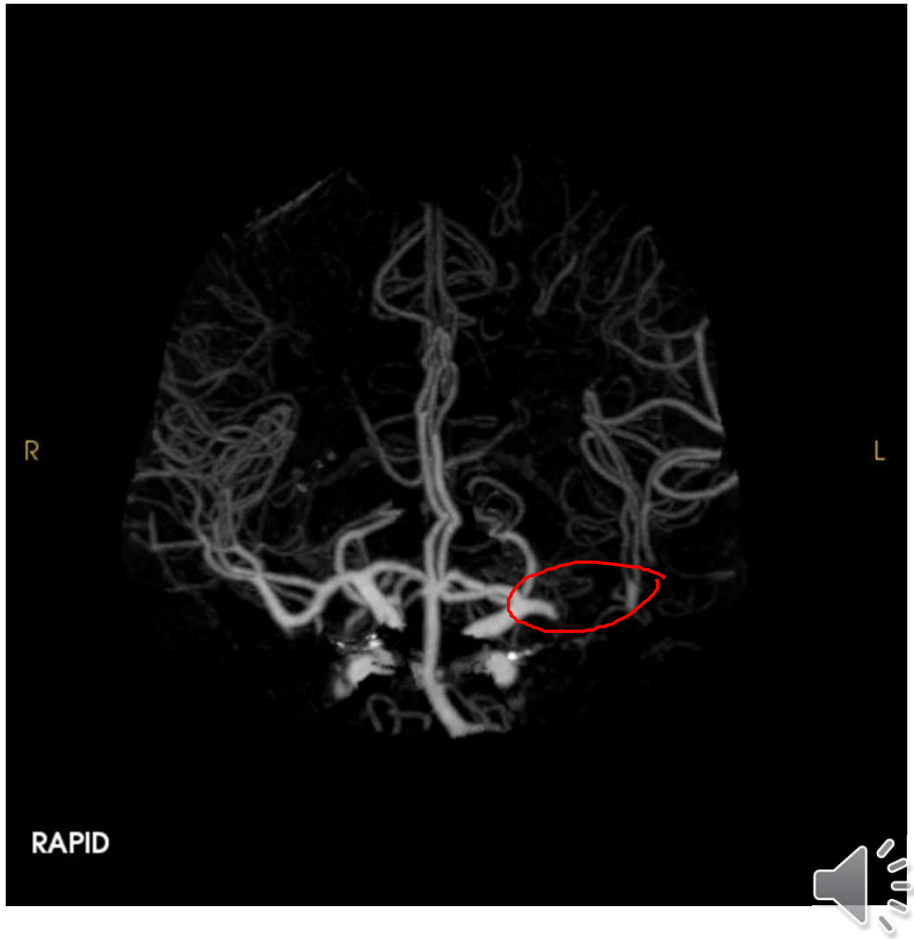
- Brain imaging
  - Computed tomography (CT) head without contrast
  - Magnetic resonance (MR) imaging brain without contrast





STROKE WORK-UP

- <u>Vessel imaging</u>
  - CT angiogram head and neck
  - MR angiogram head and neck
  - Carotid ultrasound



STROKE WORK-UP

- Cardiac imaging
  - transthoracic echocardiogram
  - transesophageal echocardiogram
- Cardiac monitoring
  - telemetry
  - Holter or implantable loop record

- Labs
  - TSH
  - HgA1c
  - lipid panel
  - liver function tests
  - In young patients or those with no vascular risk factors, hypercoagulability testing

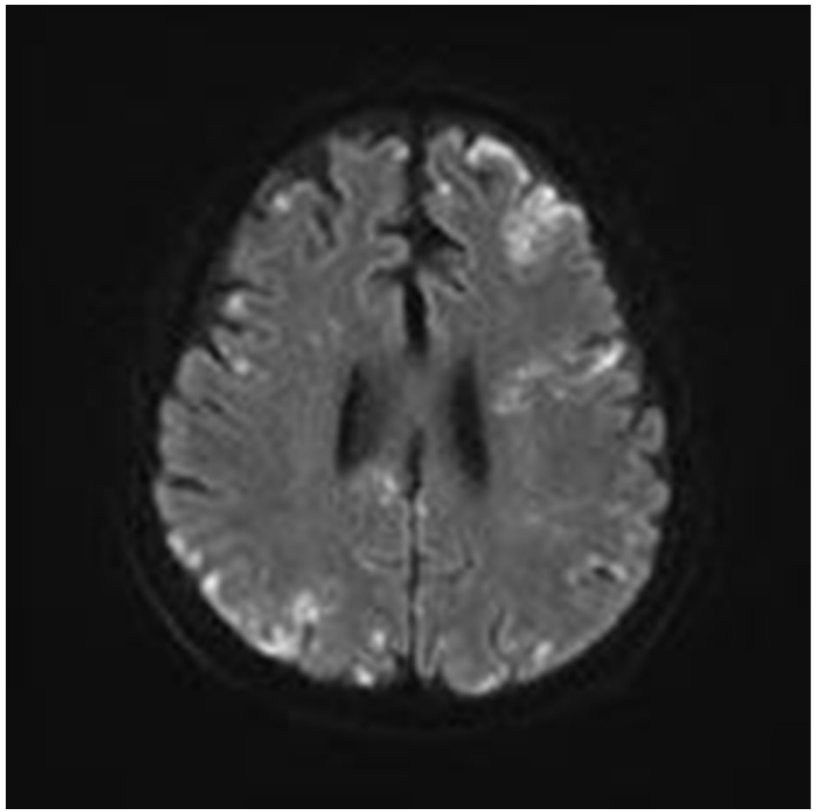
TOAST* CRITERIA[3]

Stroke Type
Cardioembolism
Large artery atherosclerosis (embolus/thrombosis)
Small-vessel occlusion (Lacune)
Stroke of other determined etiology
Stroke of undetermined etiology: cryptogenic stroke a)Two or more causes identified b)Negative evaluation c)Incomplete evaluation

*TOAST, Trial of Org 10172 in Acute Stroke Treatment.

CARDIOEMBOLIC INFARCTS[4]

- 20-30% of all strokes
- Usually more disabling than non-embolic strokes
- Multiple vascular territories: anterior, posterior, right, left
- Multiple diffusion-restricting lesions on MRI positively associated with embolic etiology
- Hemorrhagic conversion more likely than with other etiologies



Case courtesy of Dr Bruno Di Muzio, Radiopaedia.org, rID: 72391

CARDIOEMBOLIC: ATRIAL FIBRILLATION[4,6,7,8]

- Atrial fibrillation (AF) increases risk of stroke nearly 5-fold
  - Risk increases from 0.5% for those aged 50-59 years to 23.5% for those aged 80-89 years
- Pathophysiology: stasis of blood increases risk of clot formation that subsequently embolizes to brain
- May account for up to 30% of cryptogenic strokes
- Continuous hospital telemetry and short-term (24- to 48-hour) Holter monitors may miss paroxysmal AF. For patients with suspected stroke secondary to cardioembolic sources, prolonged monitoring increases the yield for detecting AF.
  - EMBRACE: significantly higher rates of AF detected in external 30-day event monitor versus 24-hour Holter (**16.1** versus **3.2%** with p-value <.001)
  - CRYSTAL AF: implantable cardiac monitor versus conventional follow-up increased detection of AF (**8.9%/12.4%** intervention group vs **1.4%/2.0%** control group at 6/12 months with p-value <.001)

CARDIOEMBOLIC: ATRIAL FIBRILLATION[9]

In patients with AF, acute ischemic stroke or TIA conveys a **score of 2** indicating a 2.2% risk per year of stroke and 2.9% risk of stroke/TIA/systemic embolism and is considered **moderate-high risk** and should be considered an **anticoagulation candidate**.

Risk Factor	Score
Congestive heart failure/Left ventricular dysfunction	1
Hypertension	1
Age ≥ 75 y	2
Diabetes mellitus	1
Stroke/TIA/Thromboembolism	2
Vascular disease (prior myocardial infarction, peripheral artery disease, aortic plaque)	1
Age 65 – 74 years	1
Sex **c**ategory (female)	1

CARDIOEMBOLIC: ATRIAL FIBRILLATION[4,10]

- **PROSPER** study showed that patients with acute ischemic stroke and atrial fibrillation who were treated with coumadin had more days at home 2 years after discharge, reduced risk of major adverse cardiovascular events, all cause mortality, and recurrent ischemic stroke

TABLE 6-6 Summary of Oral Anticoagulant Therapies[a]

	Warfarin	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Mechanism	Vitamin K antagonist	Direct thrombin inhibitor	Factor Xa inhibitor	Factor Xa inhibitor	Factor Xa inhibitor
Dose for Atrial Fibrillation	Variable	150 mg 2 times a day	20 mg/d	5 mg 2 times a day	60 mg/d
		Renal dosing: 75 mg 2 times a day	Renal dosing: 15 mg/d	2.5 mg 2 times a day if two of the following: creatinine ≥1.5, age ≥80 years, weight <60 kg (132 lb)	Renal dosing: 30 mg/d
Half-life	20–60 hours	12–17 hours; longer in renal impairment	5–9 hours;	12 hours	10–14 hours
Time to Peak Concentration	24–72 hours	1–2 hours	11–13 hours in elderly	3–4 hours	1–2 hours
			2–4 hours		
Reversal Agent	Yes; vitamin K, fresh frozen plasma, prothrombin complex concentrate, recombinant activated factor VIIa.	Yes; idarucizumab, hemodialysis, activated charcoal	No	No	No

[a] Modified with permission from Kim A, Continuum (Minneap Minn).[24] © 2014 American Academy of Neurology. *journals.lww.com/continuum/Fulltext/2014/04000/Evaluation_and_Prevention_of_Cardioembolic_Stroke.10.aspx.*

From: O'Carroll CB, Barrett KM. Cardioembolic Stroke. Continuum (Minneap Minn). 2017;23(1, Cerebrovascular Disease):111-132. doi:10.1212/CON.0000000000000419

CARDIOEMBOLIC: ATRIAL FIBRILLATION[11]

- Meta-analysis of 28 studies comparing dabigatran, rivaroxaban, & apixaban versus vitamin-K antagonists

Results	Anticoagulants
similar rates of ischemic stroke	**Apixaban** (HR 1.05; 95% CI 0.75-1.19) **dabigatran** (0.96; 95% CI 0.80-1.16), **rivaroxaban** (HR 0.89; 95% CI 0.76- 1.04)
large reduction of ICH	**Apixaban** (HR 0.54; 95% CI 0.32-0.63), **dabigatran** (HR 0.96; 95% CI 0.37-0.49), **rivaroxaban** (HR 0.89; 95% CI 0.47-0.86)
lower mortality	**Apixaban** (HR 0.65; 95% CI 0.56-0.75) & **dabigatran** (HR 0.63; 95% CI 0.53-0.75)
fewer GI & major hemorrhages	**Apixaban** (HR 0.63; 95% CI 0.42-0.95)
more GI hemorrhage	**Dabigatran** (HR 1.20; 95% CI 1.06-1.36) & **rivaroxaban** (HR 1.24; CI 1.08-1.41)

CARDIOEMBOLIC: INFECTIVE ENDOCARDITIS[12]

- Clinical strokes occurs 10-35% of left-sided infective endocarditis (IE)
  - As many as 80% of patients with IE may have imaging evidence
- Pathophysiology: abnormality in endocardium or endothelium => thrombus formation which can embolize to brain
- Strokes in IE are prone bleeding
  - hemorrhagic transformation
  - rupture of mycotic aneurysms
  - vessel wall rupture from septic emboli

CARDIOEMBOLIC: INFECTIVE ENDOCARDITIS[12]

Definition of IE According to the Modified Duke Criteria
Definite IE
Pathological criteria Microorganisms demonstrated by culture or histological examination of a vegetation, a vegetation that has embolized, or an intracardiac abscess specimen; or pathological lesions; vegetation or intracardiac abscess confirmed by histological examination showing active endocarditis
Clinical criteria 2 Major criteria, 1 major criterion and 3 minor criteria, or 5 minor criteria
Possible IE
1 Major criterion and 1 minor criterion, or 3 minor criteria
Rejected
Firm alternative diagnosis explaining evidence of IE; or resolution of IE syndrome with antibiotic therapy for ≤4 d; or no pathological evidence of IE at surgery or autopsy with antibiotic therapy for ≤4 d; or does not meet criteria for possible IE as above

Definition of Terms Used in the Modified Duke Criteria for the Diagnosis of IE
Major Criteria
Blood culture positive for IE Typical microorganisms consistent with IE from 2 separate blood cultures, or microorganisms consistent with IE from persistently positive blood cultures defined as follows: at least 2 positive cultures of blood samples drawn >12 h apart or all 3 or a majority of ≥4 separate cultures of blood (with first and last sample drawn at least 1 h apart) Single positive blood culture for *Coxiella burnetii* or anti–phase 1 IgG antibody titer ≥1:800
Evidence of endocardial involvement Echocardiogram positive for IE defined as follows: oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation; abscess; or new partial dehiscence of prosthetic valve or new valvular regurgitation (worsening or changing or pre-existing murmur not sufficient)
Minor criteria
Predisposition, predisposing heart condition, or intravenous drug use
Fever, temperature >38°C
Vascular phenomena, major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway lesions
Immunological phenomena: glomerulonephritis, Osler nodes, Roth spots, and rheumatoid factor
Microbiological evidence: positive blood culture but does not meet a major criterion as noted above (excludes single positive cultures for coagulase-negative staphylococci and organisms that do not cause endocarditis) or serological evidence of active infection with organism consistent with IE

CARDIOEMBOLIC: INFECTIVE ENDOCARDITIS[12]

Treatment

- Appropriate antimicrobial therapy
  - May need surgical intervention
- Avoid antithrombotic medications unless a strong indication exists
  - High risk of mycotic aneurysm, intracerebral hemorrhage

Considerations for surgical intervention

Vegetation

Persistent vegetation after systemic embolization

Anterior mitral leaflet vegetation, particularly with size >10 mm

≥1 Embolic events during first 2 weeks of antimicrobial therapy

Increase in vegetation size despite appropriate antimicrobial therapy

Valvular dysfunction

Acute aortic or mitral insufficiency with signs of ventricular failure

Heart failure unresponsive to medical therapy

Valve perforation or rupture

Perivalvular extension

Valvular dehiscence, rupture, or fistula

New heart block

Large abscess or extension of abscess despite appropriate antimicrobial therapy

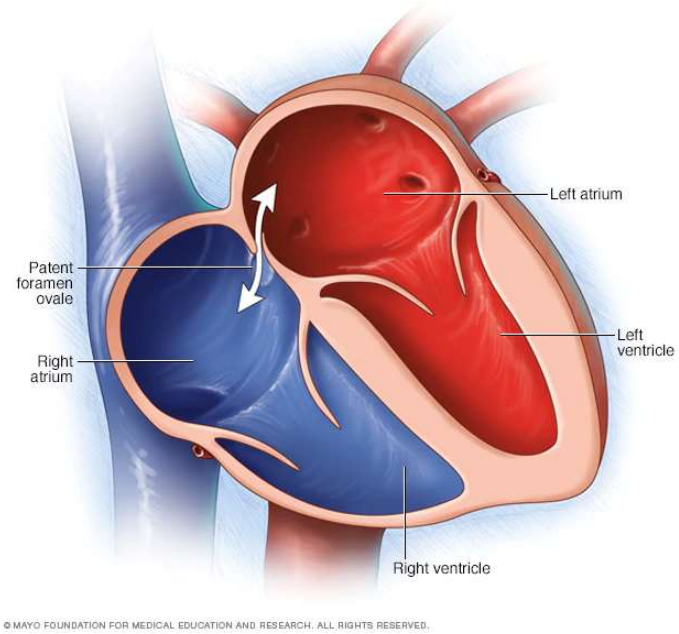
From: Baddour LM, Wilson WR, Bayer AS, et al. Infective Endocarditis in Adults: Diagnosis, Antimicrobial Therapy, and Management of Complications: A Scientific Statement for Healthcare Professionals From the American Heart Association [published correction appears in Circulation. 2015 Oct 27;132(17):e215] [published correction appears in Circulation. 2016 Aug 23;134(8):e113] [published correction appears in Circulation. 2018 Jul 31;138(5):e78-e79]. Circulation. 2015;132(15):1435-1486. doi:10.1161/CIR.0000000000000296

CARDIOEMBOLIC: NONBACTERIAL THROMBOTIC ENDOCARDITIS[13]

- Formerly called marantic endocarditis
- Libman-Sacks endocarditis is a form found in up to 11% of patients with systemic lupus erythematosus
- Associated with malignancy, antiphospholipid syndrome, hypercoagulable states, autoimmune conditions
- Pathophysiology: non-infective (fibrinoplatelet) vegetations on valves
- Treatment: manage underlying condition, anticoagulation (lovenox vs coumadin)

CARDIOEMBOLIC: PATENT FORAMEN OVALE[14]

- Patent foramen ovale (PFO) present in 10-35% of the population
- Pathophysiology: venous thrombus embolizes and crosses PFO into arterial circulation



https://www.mayoclinic.org/diseases-conditions/patent-foramen-ovale/symptoms-causes/syc-20353487

CARDIOEMBOLIC: PATENT FORAMEN OVALE[14]

- Risk of Paradoxical Embolism (ROPE) score predicts likelihood that stroke is secondary to PFO
- Highest points go to young patients with cortical infarcts and no vascular risk factors
- The higher the score, the more likely a stroke is caused by PFO

Table 4 RoPE score calculator

Characteristic	Points	RoPE score
No history of hypertension	1	
No history of diabetes	1	
No history of stroke or TIA	1	
Nonsmoker	1	
Cortical infarct on imaging	1	
Age, y		
18-29	5	
30-39	4	
40-49	3	
50-59	2	
60-69	1	
≥70	0	
Total score (sum of individual points)		
Maximum score (a patient <30 y with no hypertension, no diabetes, no history of stroke or TIA, nonsmoker, and cortical infarct)		10
Minimum score (a patient ≥70 y with hypertension, diabetes, prior stroke, current smoker, and no cortical infarct)		0

Abbreviation: RoPE = Risk of Paradoxical Embolism.

Kent DM, Ruthazer R, Weimar C, et al. An index to identify stroke-related vs incidental patent foramen ovale in cryptogenic stroke. Neurology. 2013;81(7):619-625. doi:10.1212/WNL.0b013e3182a08d59

CARDIOEMBOLIC: PATENT FORAMEN OVALE[15]

Meta-Analysis Closure of PFO vs Medical Therapy in Pts With Cryptogenic Stroke or TIA.

5 RCTs; 3627 pts w 3.7 yr median f/u

- Ischemic stroke recurrence less in patients with PFO closure
  - 0.53 vs 1.1 per 100 pt-yrs
- Outcomes even **better** with **high-risk PFO***
  - 0.51 vs 1.4 per 100 pt-yrs
- In contrast, was **no difference** in outcomes in **low-risk** PFOs
- No difference in TIA, all-cause mortality, or MI
- New-onset **A-fib more frequent** in PFO closure group
  - 56% transient; 72% resolved w/in 45 days

* Moderate-to-large shunt and atrial septal aneurysm

CARDIOEMBOLIC: REDUCED EJECTION FRACTION[16]

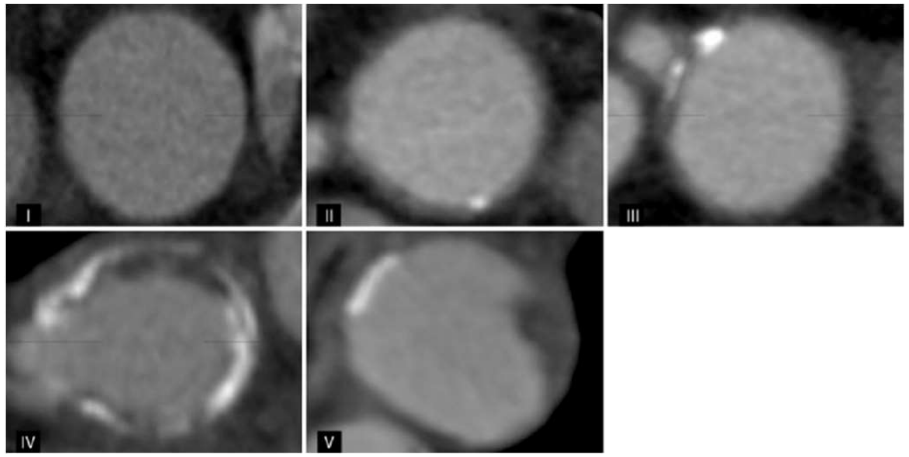
- Pathophysiology: heart failure can lead to a hypercoagulable state, stasis of blood, left ventricle thrombus, and subsequent embolism to brain
- Warfarin vs Aspirin in Reduced Cardiac EF (WARCEF)
  - ASA vs Warfarin for stroke prevention in patients with EF <35%
  - Warfarin (INR 2.0-3.5) with significantly less ischemic strokes but significantly more major hemorrhage

CARDIOEMBOLIC: LEFT VENTRICULAR THROMBUS[17]

- Pathophysiology: left ventricular thrombus embolizes to brain
- Retrospective Evaluation of DOACs and Vascular Endpoints of Left Ventricular Thrombi (RED VELVT)
  - DOAC vs warfarin for treatment of LV thrombi
  - DOAC treatment was associated with a higher risk of stroke and systemic embolism compared with warfarin use, even after adjustment for other factors

LARGE VESSEL: AORTIC ARCH ATHEROMA[18,19]

- Associated with typical vascular risk factors: increasing age, male sex, hyperlipidemia, hypertension, smoking, diabetes
- <u>Pathophysiology</u>: atherosclerotic plaques rupture => thrombosis => embolism of arteries



From: Kotelis D, Bischoff MS, Jobst B, et al. Morphological risk factors of stroke during thoracic endovascular aortic repair. *Langenbecks Arch Surg*. 2012;397(8):1267-1273. doi:10.1007/s00423-012-0997-6

LARGE VESSEL: AORTIC ARCH ATHEROMA[19,20]

- Patients with aortic arch atheromas > 4 mm is independent risk-factor for stroke and risk of recurrent ischemic stroke, up to 3-4 times higher
- French Study of Aortic Plaques in Stroke found the highest relative risk of events among patients with noncalcified, lipid-rich plaques (RR 10.3; 95% CI, 4.2–25.2; P<0.001)

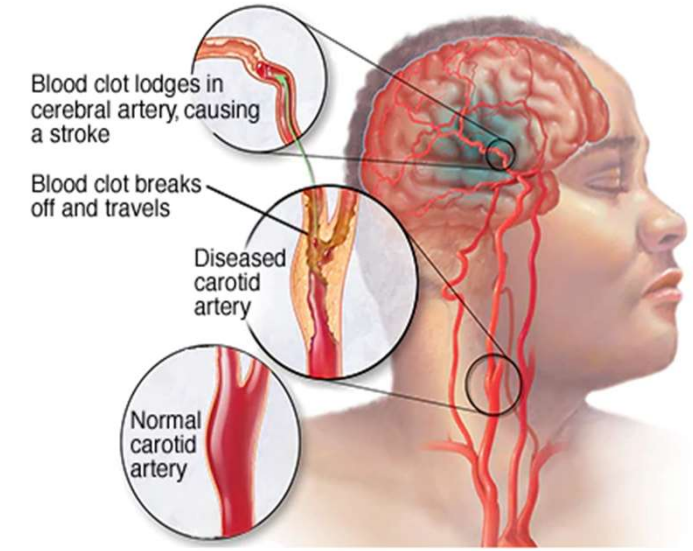
LARGE VESSEL: AORTIC ARCH ATHEROMA[21,22,23]

- Surgical aortic endartectomy associated with significant intraoperative cerebral infarction
- Aortic Arch Related Cerebral Hazard (ARCH)
  - Dual-antiplatelet treatment (DAPT) with aspirin & plavix vs coumadin for secondary stroke prevention in patients with high grade aortic arch plaque
  - Trial was inconclusive due to lack of power, stopped early
- American Heart Association/American Stroke Association Guidelines for Secondary Stroke Prevention

Aortic arch atheroma	For patients with an ischemic stroke or TIA and evidence of aortic arch atheroma, antiplatelet therapy is recommended *(Class I; Level of Evidence A)*.	New recommendation
	For patients with an ischemic stroke or TIA and evidence of aortic arch atheroma, statin therapy is recommended *(Class I; Level of Evidence B)*.	New recommendation
	For patients with ischemic stroke or TIA and evidence of aortic arch atheroma, the effectiveness of anticoagulation with warfarin, compared with antiplatelet therapy, is unknown *(Class IIb; Level of Evidence C)*.	New recommendation
	Surgical endarterectomy of aortic arch plaque for the purposes of secondary stroke prevention is not recommended *(Class III; Level of Evidence C)*.	New recommendation

LARGE VESSEL: CAROTID ARTERY STENOSIS[24,25]

- Causes up to 10% of ischemic strokes
- Pathophysiology: atherosclerotic plaques rupture => thrombosis => embolism of arteries
- Carotid endarterectomy (CEA) introduced in 1950s; carotid artery stenting (CAS) introduced in 1994



https://www.mayoclinic.org/diseases-conditions/carotid-artery-disease/symptoms-causes/syc-20360519

Large Vessel Disease: CAROTID ARTERY STENOSIS[26]

- Carotid Revascularization Endarterectomy vs. Stenting Trial (CREST)
  - Treatment of **symptomatic** and **asymptomatic** carotid artery stenosis
    - Symptomatic patients (**Ipsilateral** ischemic stroke, TIA, amaurosis fugax) ≥ 50% (angiogram), ≥ 70% carotid ultrasound, or ≥ 70% (CTA, MRA) if ultrasounds 50-69%
    - Asymptomatic patients (≥ 60% by angiography, ≥ 70% by ultrasound, or ≥ 80% by CTA or MRA if ultrasound was 50% to 69%.
  - Carotid artery stenting (CAS) vs carotid endarterectomy (CEA)
  - The primary endpoint (death, MI, or stroke at 30 days plus ipsilateral stroke up to 4 years) was similar between the CAS and CEA arms
  - CAS carries risk of periprocedural ischemic stroke
  - CEA higher risk of periprocedural MI
  - Recommendation: patients who are older may tolerate CEA better and younger patients CAS
- CREST2 trial is currently enrolling
  - Treatment of **asymptomatic** carotid artery stenosis for primary prevention of stroke

Large Vessel Disease: EXTRACRANIAL ARTERIAL DISSECTION[27]

- Estimated incidence of 2.6 (95% CI 1.9–3.3) per 100,000 people per year
- Most common affects carotid artery > 2cm past the bifurcation, but can affect vertebral arteries as well
- Average age of patients is in the 4th decade
- Often present with preceding pain, Horner's syndrome
- Risk factors: minor trauma (chiropractic manipulation, whiplash, severe coughing), connective tissue disorders,
- Pathophysiology: mural hematoma in arterial wall embolizes to brain

Large Vessel Disease: EXTRACRANIAL ARTERIAL DISSECTION[22, 27]

- Cervical Artery Dissection In Stroke Study (CADISS)
  - Acute ischemic stroke secondary to extracranial arterial dissection
  - Antiplatelet vs anticoagulation for 3 months
  - **No significant difference** in primary endpoint (ipsilateral stroke or death within 3 months)
  - 2019: further evaluated and found no difference in recurrence of ischemic stroke at 1 year between the two groups
- AHA/ASA Guidelines for Secondary Stroke Prevention

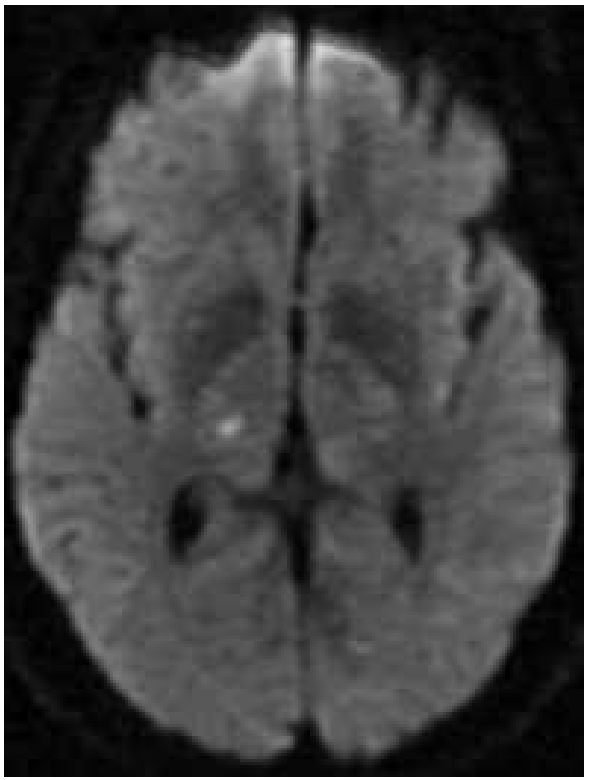
1. **For patients with ischemic stroke or TIA and extracranial carotid or vertebral arterial dissection, antithrombotic treatment with either antiplatelet or anticoagulant therapy for at least 3 to 6 months is reasonable *(Class IIa; Level of Evidence B)*.**
2. **The relative efficacy of antiplatelet therapy compared with anticoagulation is unknown for patients with ischemic stroke or TIA and extracranial carotid or vertebral arterial dissection *(Class IIb; Level of Evidence B)*.**

LARGE VESSEL: INTRACRANIAL ATHEROSCLEROSIS[28, 29]

- Patients with high-risk TIA or stroke and 70% stenosis of major intracranial artery have 23% risk of recurrent stroke
- Pathophysiology: artery-to-artery embolization, perforator disease, and impaired distal perfusion
- Stenting versus Aggressive Medical Therapy for Intracranial Arterial Stenosis (SAMMPRIS)
  - TIA or ischemic stroke 2/2 severe symptomatic intracranial atherosclerosis (70-99%)
  - Percutaneous transluminal angioplasty and stenting (PTAS) vs aggressive medical management
  - Dual-antiplatelet treatment with aspirin 325mg and plavix 75mg (600mg load) x 90 days
  - Aggressive medical management was superior to stenting
  - risk of early stroke after PTAS was high
  - risk of stroke with aggressive medical therapy alone was lower than expected

SMALL VESSEL DISEASE

- Lacunar strokes, 0.2 to 15 mm in diameter
- Located in subcortical areas of the brain
- Pathophysiology: lipohyalinosis of penetrating arteries from vascular risk factors



Case courtesy of Dr Roberto Schubert, Radiopaedia.org, rID: 14098

Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE)[30, 31]

- Minor ischemic strokes*, not always lacunar
- High risk TIA (ABCD2 ≥ 4)
- Clopidogrel + aspirin vs placebo + aspirin
  - Clopidogrel 300 mg x1, then 75 mg/d x 90d + aspirin 75 mg/d x 21 days
  - Placebo + aspirin 75 mg/d x 90 days
  - w/in 24 hrs after the onset of sx
- **Combination of clopidogrel & aspirin x21 days** is superior to aspirin alone for reducing the risk of stroke in the first 90 days & does not significantly increase the risk of hemorrhage

*National Institutes of Health Stroke Scale (NIHSS) ≤ 3

ABCD2 score for TIA patients

	Score	Feature
Age	1	≥ 60 years
Blood pressure	1	SBP > 140 or DBP ≥ 90mmHg
Clinical Features	2	Unilateral weakness
	1	Speech impairment without weakness
Duration	2	> 60 minutes
	1	10-59 minutes
	0	<10 minutes
Diabetes	1	

Early stroke rates in acute TIA patients stratified by ABCD2 score

ABCD2 score	2-day risk	7-day risk	90-day risk
0 – 3 (low risk)	1.0%	1.2%	3.1%
4 – 5 (moderate risk)	4.2%	5.9%	9.8%
6 – 7 (high risk)	8.1%	11.7%	17.8%

From: Johnston SC, Rothwell PM, Nguyen-Huynh MN, Giles MF, Elkins JS, Bernstein AL, et al. Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. Lancet. 2007 Jan 27;369(9558):283–92.

Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT)[32]

- Minor ischemic stroke and TIA
- Clopidogrel + aspirin vs placebo + aspirin
  - Clopidogrel 600 mg x1 day 1→ 75 mg/d from days 2-90 + aspirin (dosage ranged from 50-325 mg/day) from days 1-90
  - aspirin (doses ranged) + placebo
- Fewer ischemic events/strokes in clopidogrel + aspirin group, but more major hemorrhage
  - Benefit of clopidogrel + aspirin was greater in the first 7 days and 30 days than at 90 days
  - Risk of hemorrhage with clopidogrel + aspirin was greater during the period from 8-90 days than during first 7 days
- Confirmed CHANCE trial, dual-antiplatelet for limited time (21-30 days in practice) reduces risk of acute ischemic stroke and minimizes risk of hemorrhage

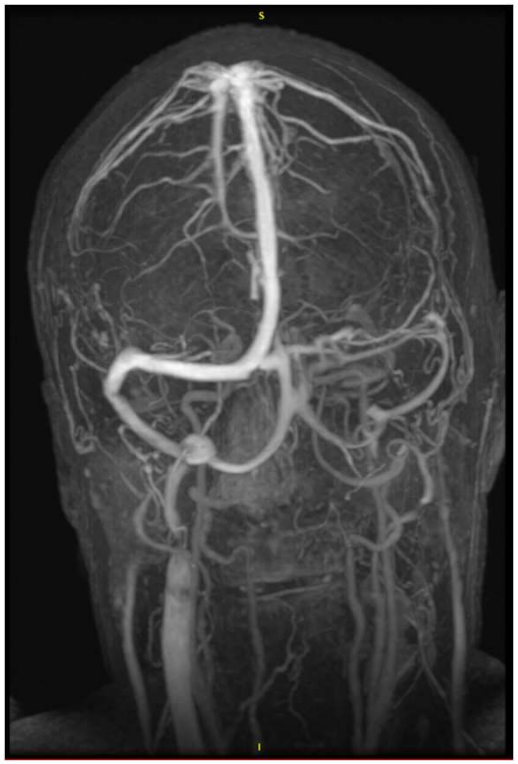
OTHER: CEREBRAL VENOUS SINUS THROMBOSIS[33]

- Estimated annual incidence of 2/100,000 per year
  - Complication of 1 in 10,000 births
- Median age of patients: 37
- Female to male: 3:1
- Typically presents with at least 1 of the following: increased ICP, focal neurologic deficits, encephalopathy, seizures
  - Headache is most common presenting symptom
- Pathophysiology: increased venous pressure => increase capillary pressure => reduced cerebral blood flow => infarction and hemorrhage

OTHER: CEREBRAL VENOUS SINUS THROMBOSIS[33]

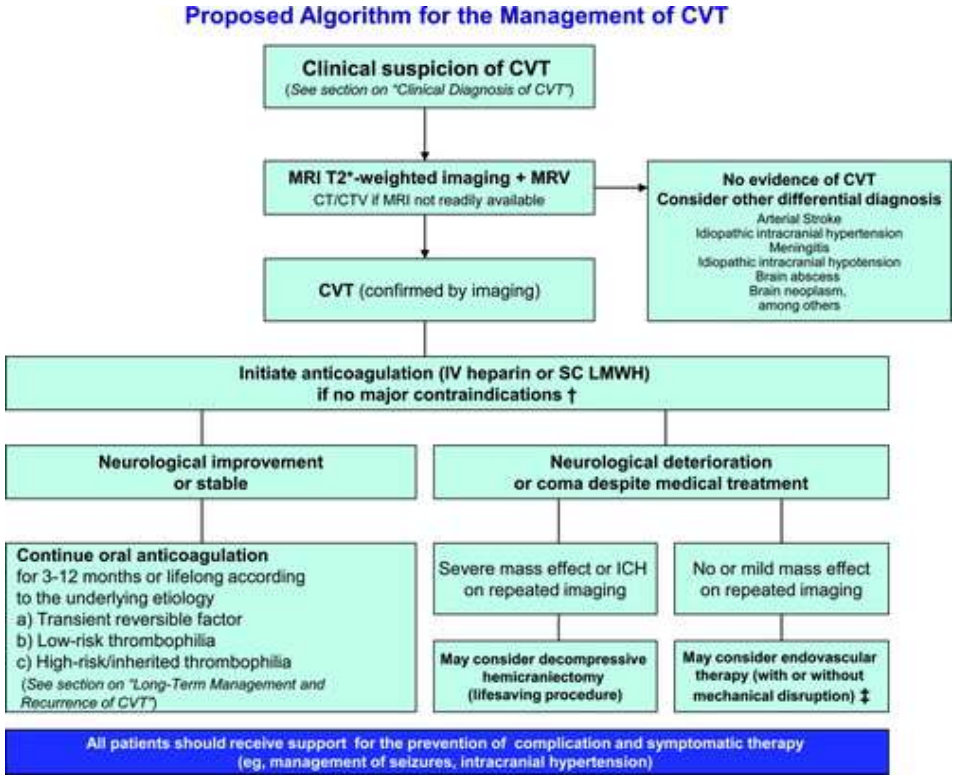
Conditions Associated with Cerebral Venous Sinus Thrombosis	
Pregnancy and puerperium	Malignancy
Oral contraceptives	Antiphospholipid antibodies
Hormone replacement therapy	Plasminogen deficiency
Dehydration	Protein S deficiency
Infection	Protein C deficiency
Head injury	Antithrombin III deficiency
Lumbar puncture	Factor V Leiden mutation
Neurosurgical procedures	Prothrombin gene mutation
Nephrotic syndrome	Inflammatory bowel disease
Behcet's disease	Polycythemia
Granulomatosis polyangiitis	Thrombocytopenia
Inflammatory bowel disease	Sickle cell disease or trait
Sarcoid	

Clinicians should maintain a high level of suspicion for CVST in patients who have any of the above risk factors, and present with a positional headache and abrupt onset neurologic symptoms.



OTHER: CEREBRAL VENOUS SINUS THROMBOSIS[33,34]

- Anticoagulation: heparin vs LMWH with transition to oral anticoagulation



Diagnosis and Management of Cerebral Venous Thrombosis. A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association

OTHER: ANTIPHOSPHOLIPID SYNDROME[35, 36]

- Autoimmune disorder causing arterial, venous, and/or small vessel **thromboembolic events** and/or pregnancy morbidity in the presence of antiphospholipid antibodies
  - May occur as primary disorder or in the setting of an systemic autoimmune condition
- Estimated incidence of 5 new cases per 100,000 persons per year and the prevalence around 40–50 cases per 100,000 person years
- Antiphospholipid antibodies:
  - Anticardiolipin antibodies
  - Anti-beta2-glycoprotein-I antibodies
  - Lupus anticoagulant

OTHER: ANTIPHOSPHOLIPID SYNDROME[36]

Antiphospholipid antibody syndrome (APS) is present if at least one of the clinical criteria and one of the laboratory criteria that follow are met

Clinical Criteria

1. Vascular thrombosis

One or more clinical episodes of arterial, venous, or small vessel thrombosis , in any tissue or organ. Thrombosis must be confirmed by objective validated criteria. For histopathologic confirmation, thrombosis should be present without significant evidence of inflammation in the vessel wall

2. Pregnancy morbidity

a) One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation, with normal fetal morphology documented by ultrasound or by direct examination of the fetus, or
b) One or more premature births of a morphologically normal neonate before the 34th week of gestation because of: (i) eclampsia or severe pre-eclampsia defined according to standard definitions, or (ii) recognized features of placental insufficiency ,or
c) Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded

Laboratory criteria

1. Lupus anticoagulant (LA) present in plasma, on two or more occasions >12 weeks apart
2. Anticardiolipin (aCL) antibody in serum or plasma, present in medium or high titer, on two or more occasions >12 weeks apart
3. Anti-b2 glycoprotein-I antibody in serum or plasma (in titer >the 99th percentile), present on two or more occasions >12 weeks apart

Adapted from Miyakis S, Lockshin MD, Atsumi T, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost*. 2006;4(2):295-306. doi:10.1111/j.1538-7836.2006.01753.x

OTHER: ANTIPHOSPHOLIPID SYNDROME[37]

Catastrophic antiphospholipid syndrome (CAPS)

Table 1
Diagnostic criteria for CAPS.

1. Evidence of involvement of 3 organs, systems, and/or tissues.
2. Development of manifestations simultaneously or in less than 1 week.
3. Laboratory confirmation of the presence of aPL (LAC and/or aCL and/or anti-2GPI antibodies) in titers higher than 40 UI/l.
4. Exclude other diagnosis.

Definite CAPS:
- All 4 criteria.

Probable CAPS
- All 4 criteria, except for involvement of only 2 organs, system, and/or tissues.
- All 4 criteria, except for the absence of laboratory confirmation at least 6 weeks apart associable to the early death of a patient never tested for aPL before onset of CAPS.
- 1, 2, and 4.
- 1, 3, and 4, and the development of a third event in >1 week but <1 month, despite anticoagulation treatment.

OTHER: ANTIPHOSPHOLIPID SYNDROME[38,39]

- Treatment with anticoagulation
  - Typically heparin bridge to warfarin*
  - Systemic review from 2012[38] showed patients treated with rivaroxaban had potential increased thrombotic risk; those on DOACs may have increased risk of thrombosis compared to warfarin
  - Another study[39] comparing rivaroxaban to warfarin stopped early due to increased thrombotic and major bleeding events
- With CAPS, identify and treat any underlying condition (such as infection) that may have precipitated event
  - Anti-inflammatory treatment (high-dose steroids, plasma exchange, +/- IVIG) plus anticoagulation

*warfarin is teratogenic, LMWH used during pregnancy

OTHER CAUSES OF STROKE

- Vasculitis (including primary CNS vasculitis)
- Infection
- Reversible cerebral vasoconstriction syndrome (RCVS)
- Vasospasm after subarachnoid hemorrhage
- Moya-Moya disease
- Peri-procedural
- Fabry's disease
- MELAS (Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes)
- Giant cell arteritis
- Sickle cell anemia
- Susac's syndrome
- CARASIL (cerebral autosomal recessive arteriopathy with subcortical infarcts and leucoencephalopathy)
- CADASIL (cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy)
- …and more

CRYPTOGENIC

- When two competing mechanisms exists, clinical judgement and risk/benefit discussion on best treatment.
- Why not treat patients with suspected cardioembolic strokes or TIAs with anticoagulation rather than aspirin?
  - NAVIGATE ESUS*[40]: rivaroxaban 15 mg daily vs aspirin. No significant difference in recurrent stroke rate (4.7% recurrent ischemic stroke in both groups). Higher rates of major bleeding in rivaroxaban group compared to aspirin (1.8% vs 0.7%. Hazard ratio, 2.72; 95% CI, 1.68 to 4.39; P<0.001).
  - RESPECT ESUS**[41]: dabigatran at a dose of 150 mg or 110 mg twice daily vs 100 mg aspirin. No significant difference in rate of recurrent ischemic strokes or major bleeding, but more clinically relevant nonmajor bleeding in dagibatran group (1.6% vs 0.9%. Hazard ratio, 1.73; 95% CI 1.17–2.54)

*New Approach Rivaroxaban Inhibition of Factor Xa in a Global Trial Versus ASA to Prevent Embolism in Embolic Stroke of Undetermined Source

** Dabigatran for Prevention of Stroke after Embolic Stroke of Undetermined Source

Questions?

- Feel free to contact us
  - Allyson Hamacher: Hamacher.Allyson@mayo.edu
  - Abigail Taylor: taylor.Abigail@mayo.edu

REFERENCES

1. Sacco RL, Kasner SE, Broderick JP, et al. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association [published correction appears in Stroke. 2019 Aug;50(8):e239]. Stroke. 2013;44(7):2064-2089. doi:10.1161/STR.0b013e318296aeca

2. Donkor ES. Stroke in the 21st Century: A Snapshot of the Burden, Epidemiology, and Quality of Life. Stroke Res Treat. 2018;2018:3238165. Published 2018 Nov 27. doi:10.1155/2018/3238165

3. Adams HP Jr, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke. 1993;24(1):35-41. doi:10.1161/01.str.24.1.35

4. O'Carroll CB, Barrett KM. Cardioembolic Stroke. Continuum (Minneap Minn). 2017;23(1, Cerebrovascular Disease):111-132. doi:10.1212/CON.0000000000000419

5. Wessels T, Röttger C, Jauss M, Kaps M, Traupe H, Stolz E. Identification of embolic stroke patterns by diffusion-weighted MRI in clinically defined lacunar stroke syndromes. Stroke. 2005;36(4):757-761. doi:10.1161/01.STR.0000158908.48022.d7

6. Gladstone DJ, Spring M, Dorian P, et al. Atrial fibrillation in patients with cryptogenic stroke. N Engl J Med. 2014;370(26):2467-2477. doi:10.1056/NEJMoa1311376

7. Zhao SX, Ziegler PD, Crawford MH, Kwong C, Koehler JL, Passman RS. Evaluation of a clinical score for predicting atrial fibrillation in cryptogenic stroke patients with insertable cardiac monitors: results from the CRYSTAL AF study. Ther Adv Neurol Disord. 2019;12:1756286419842698. Published 2019 Apr 11. doi:10.1177/1756286419842698

8. Sanna T, Diener HC, Passman RS, et al. Cryptogenic stroke and underlying atrial fibrillation. N Engl J Med. 2014;370(26):2478-2486. doi:10.1056/NEJMoa1313600

9. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest. 2010;137(2):263-272. doi:10.1378/chest.09-1584

10. Xian Y, Wu J, O'Brien EC, et al. Real world effectiveness of warfarin among ischemic stroke patients with atrial fibrillation: observational analysis from Patient-Centered Research into Outcomes Stroke Patients Prefer and Effectiveness Research (PROSPER) study. BMJ. 2015;351:h3786. Published 2015 Jul 31. doi:10.1136/bmj.h3786

REFERENCES

11. Ntaios G, Papavasileiou V, Makaritsis K, Vemmos K, Michel P, Lip GYH. Real-World Setting Comparison of Nonvitamin-K Antagonist Oral Anticoagulants Versus Vitamin-K Antagonists for Stroke Prevention in Atrial Fibrillation: A Systematic Review and Meta-Analysis. Stroke. 2017;48(9):2494-2503. doi:10.1161/STROKEAHA.117.017549

12. Baddour LM, Wilson WR, Bayer AS, et al. Infective Endocarditis in Adults: Diagnosis, Antimicrobial Therapy, and Management of Complications: A Scientific Statement for Healthcare Professionals From the American Heart Association [published correction appears in Circulation. 2015 Oct 27;132(17):e215] [published correction appears in Circulation. 2016 Aug 23;134(8):e113] [published correction appears in Circulation. 2018 Jul 31;138(5):e78-e79]. Circulation. 2015;132(15):1435-1486. doi:10.1161/CIR.0000000000000296

13. Liu J, Frishman WH. Nonbacterial Thrombotic Endocarditis: Pathogenesis, Diagnosis, and Management. Cardiol Rev. 2016;24(5):244-247. doi:10.1097/CRD.0000000000000106

14. Kent DM, Ruthazer R, Weimar C, et al. An index to identify stroke-related vs incidental patent foramen ovale in cryptogenic stroke. Neurology. 2013;81(7):619-625. doi:10.1212/WNL.0b013e3182a08d59

15. Ntaios G, Papavasileiou V, Sagris D, et al. Closure of Patent Foramen Ovale Versus Medical Therapy in Patients With Cryptogenic Stroke or Transient Ischemic Attack: Updated Systematic Review and Meta-Analysis. Stroke. 2018;49(2):412-418. doi:10.1161/STROKEAHA.117.020030

16. Homma S, Thompson JL, Pullicino PM, et al. Warfarin and aspirin in patients with heart failure and sinus rhythm. N Engl J Med. 2012;366(20):1859-1869. doi:10.1056/NEJMoa1202299

17. Robinson AA, Trankle CR, Eubanks G, et al. Off-label Use of Direct Oral Anticoagulants Compared With Warfarin for Left Ventricular Thrombi. JAMA Cardiol. 2020;5(6):685-692. doi:10.1001/jamacardio.2020.0652

18. Capmany RP, Ibañez MO, Pesquer XJ. Complex atheromatosis of the aortic arch in cerebral infarction. Curr Cardiol Rev. 2010;6(3):184-193. doi:10.2174/157340310791658712

19. Kotelis D, Bischoff MS, Jobst B, et al. Morphological risk factors of stroke during thoracic endovascular aortic repair. Langenbecks Arch Surg. 2012;397(8):1267-1273. doi:10.1007/s00423-012-0997-6

20. Cohen A, Tzourio C, Bertrand B, Chauvel C, Bousser MG, Amarenco P. Aortic plaque morphology and vascular events: a follow-up study in patients with ischemic stroke. FAPS Investigators. French Study of Aortic Plaques in Stroke. Circulation. 1997;96(11):3838-3841. doi:10.1161/01.cir.96.11.3838

REFERENCES

21. Amarenco P, Davis S, Jones EF, et al. Clopidogrel plus aspirin versus warfarin in patients with stroke and aortic arch plaques. *Stroke*. 2014;45(5):1248-1257. doi:10.1161/STROKEAHA.113.004251

22. Meschia JF, Bushnell C, Boden-Albala B, et al. Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014;45(12):3754-3832. doi:10.1161/STR.0000000000000046

23. Cohen A, Tzourio C, Bertrand B, Chauvel C, Bousser MG, Amarenco P. Aortic plaque morphology and vascular events: a follow-up study in patients with ischemic stroke. FAPS Investigators. French Study of Aortic Plaques in Stroke. Circulation. 1997;96(11):3838-3841. doi:10.1161/01.cir.96.11.3838

24. Prasad K. Pathophysiology and Medical Treatment of Carotid Artery Stenosis. *Int J Angiol*. 2015;24(3):158-172. doi:10.1055/s-0035-1554911

25. Mantese VA, Timaran CH, Chiu D, Begg RJ, Brott TG; CREST Investigators. The Carotid Revascularization Endarterectomy versus Stenting Trial (CREST): stenting versus carotid endarterectomy for carotid disease. *Stroke*. 2010;41(10 Suppl):S31-S34. doi:10.1161/STROKEAHA.110.595330

26. Debette S, Leys D. Cervical-artery dissections: predisposing factors, diagnosis, and outcome. *Lancet Neurol*. 2009;8(7):668-678. doi:10.1016/S1474-4422(09)70084-5

27. Markus HS, Levi C, King A, Madigan J, Norris J; Cervical Artery Dissection in Stroke Study (CADISS) Investigators. Antiplatelet Therapy vs Anticoagulation Therapy in Cervical Artery Dissection: The Cervical Artery Dissection in Stroke Study (CADISS) Randomized Clinical Trial Final Results. *JAMA Neurol*. 2019;76(6):657-664. doi:10.1001/jamaneurol.2019.0072

28. Chimowitz MI, Lynn MJ, Derdeyn CP, et al. Stenting versus aggressive medical therapy for intracranial arterial stenosis [published correction appears in N Engl J Med. 2012 Jul 5;367(1):93]. *N Engl J Med*. 2011;365(11):993-1003. doi:10.1056/NEJMoa1105335

29. Flusty B, de Havenon A, Prabhakaran S, Liebeskind DS, Yaghi S. Intracranial Atherosclerosis Treatment: Past, Present, and Future. *Stroke*. 2020;51(3):e49-e53. doi:10.1161/STROKEAHA.119.028528

30. Wang Y, Wang Y, Zhao X, et al. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. *N Engl J Med*. 2013;369(1):11-19. doi:10.1056/NEJMoa1215340

REFERENCES

31. Johnston SC, Rothwell PM, Nguyen-Huynh MN, Giles MF, Elkins JS, Bernstein AL, et al. Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. Lancet. 2007 Jan 27;369(9558):283–92.

32. Johnston SC, Easton JD, Farrant M, et al. Platelet-oriented inhibition in new TIA and minor ischemic stroke (POINT) trial: rationale and design. *Int J Stroke*. 2013;8(6):479-483. doi:10.1111/ijs.12129

33. Agrawal K, Burger K, Rothrock JF. Cerebral Sinus Thrombosis. Headache. 2016 Sep;56(8):1380-9. doi: 10.1111/head.12873. Epub 2016 Jun 28. PMID: 27350588.

34. Saposnik G, Barinagarrementeria F, Brown RD Jr, et al. Diagnosis and management of cerebral venous thrombosis: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2011;42(4):1158-1192. doi:10.1161/STR.0b013e31820a8364

35. Cervera R. Antiphospholipid syndrome. *Thromb Res*. 2017;151 Suppl 1:S43-S47. doi:10.1016/S0049-3848(17)30066-X

36. Miyakis S, Lockshin MD, Atsumi T, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost*. 2006;4(2):295-306. doi:10.1111/j.1538-7836.2006.01753.x

37. Cervera R, Rodríguez-Pintó I, Colafrancesco S, et al. 14th International Congress on Antiphospholipid Antibodies Task Force Report on Catastrophic Antiphospholipid Syndrome. *Autoimmun Rev*. 2014;13(7):699-707. doi:10.1016/j.autrev.2014.03.002

38. Dufrost V, Risse J, Zuily S, Wahl D. Direct Oral Anticoagulants Use in Antiphospholipid Syndrome: Are These Drugs an Effective and Safe Alternative to Warfarin? A Systematic Review of the Literature. *Curr Rheumatol Rep*. 2016;18(12):74. doi:10.1007/s11926-016-0623-7

39. Pengo V, Denas G, Zoppellaro G, et al. Rivaroxaban vs warfarin in high-risk patients with antiphospholipid syndrome. *Blood*. 2018;132(13):1365-1371. doi:10.1182/blood-2018-04-848333

40. Harloff A, Schlachetzki F. Rivaroxaban for Stroke Prevention after Embolic Stroke of Undetermined Source. *N Engl J Med*. 2018;379(10):986-987. doi:10.1056/NEJMc1809065

41. Diener HC, Sacco RL, Easton JD, et al. Dabigatran for Prevention of Stroke after Embolic Stroke of Undetermined Source. *N Engl J Med*. 2019;380(20):1906-1917. doi:10.1056/NEJMoa1813959