MAYO CLINIC | School of Continuous Professional Development

SECONDARY PREVENTION OF STROKE

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- Nothing to disclose

REFERENCES TO OFF-LABEL USAGE(S) OF PHARMACEUTICALS OR INSTRUMENTS

- Nothing to disclose

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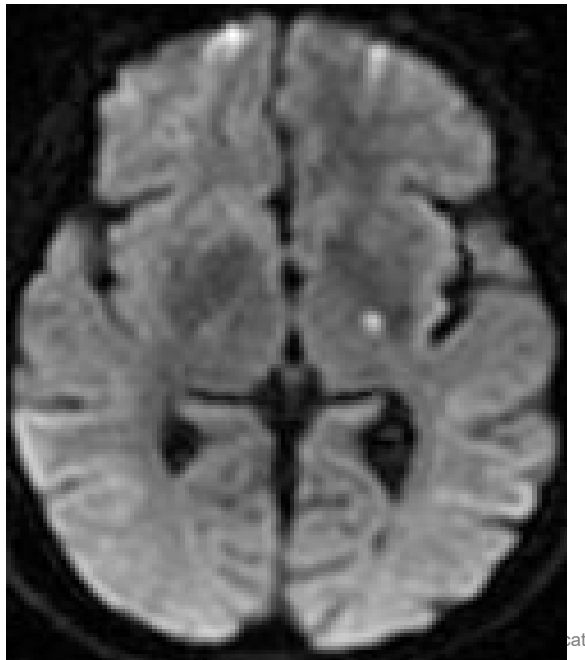
LEARNING OBJECTIVES

- Provide a practical, evidence-based treatment approach to secondary stroke prevention, highlighting key features of the 2021 AHA/ASA guidelines:
  - When to use dual antiplatelet therapy
  - Management of intracranial atherosclerotic stenosis (ICAS)
  - PFO closure after stroke
  - Prevention of stroke after ESUS
  - DOACs in patients with Afib
  - Continuous cardiac monitoring for Afib detection

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In patients presenting with minor noncardioembolic ischemic stroke (NIHSS score ≤3) who did not receive IV alteplase, treatment with dual antiplatelet therapy (aspirin and clopidogrel) started within 24 hours after symptom onset and continued for 21 days is effective in reducing recurrent ischemic stroke for a period of up to 90 days from symptom onset.

A. heparin drip
B. apixaban
C. ASA only
D. clopidogrel only
E. ASA & clopidogrel



AHA/ASA Guidelines Stroke. 2019/2021

CHANCE
CLOPIDOGREL W ASPIRIN IN ACUTE MINOR STROKE OR TIA

- Randomized 5170 pts w/in 24 hrs of minor ischemic stroke or high-risk TIA to clopidogrel & ASA x 21d vs placebo & ASA
  - Clopidogrel 300 mg x1→ 75 mg/d x 90d + ASA 75 mg/d x 21d vs placebo + ASA 75 mg/d x 90d
  - Minor stroke: NIHSS ≤3
  - High risk TIA: ABCD2 score ≥ 4
  - mRS 0-2

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

NEJM 2013 Jul 4;369(1):11-9

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CHANCE
CLOPIDOGREL W ASPIRIN IN ACUTE MINOR STROKE OR TIA

- **1°outcome**: stroke (ischemic or hemorrhagic) during 90 d

- Results: ischemic stroke **7.9%** of pts in clopidogrel–ASA grp vs **11.4%** in ASA grp (HR 0.67;P<0.001)
  - Rate of hemorrhagic stroke was 0.3% in each grp

- Conclusion: Among pts w TIA or minor stroke who can be tx'd w/in 24 hrs after the onset of sx, the **combination of clopidogrel & ASA is superior to ASA** alone for reducing the risk of stroke in the first 90 days & **does NOT increase the risk of hemorrhage**

NEJM 2013 Jul 4;369(1):11-9.

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CHANCE CRITICISMS

- trial involved Chinese pts only & this population has a higher rate of stroke & more large vessel disease than USA
  - *Limited generalizability?*
- polymorphisms affecting Plavix metabolism are more common in Chinese pts
  - *Is plavix ineffective & thus lower risk of hemorrhage?*

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POINT
CLOPIDOGREL & ASPIRIN IN ACUTE ISCHEMIC STROKE & HIGH-RISK TIA

- Randomized 4881 pts w/in 12 hrs of minor ischemic stroke or high-risk TIA to clopidogrel & ASA x **90 days** vs placebo & ASA
    - Clopidogrel 600 mg x1→ 75 mg/d from Day 2-90 + ASA ranged from **50-325** mg/day from Day 1-90

- 269 sites, in 10 countries in North America, Europe, Australia, & New Zealand (83% in the US)

- **1°outcome**: risk of a composite of ischemic stroke, MI, or death from ischemic vascular causes (major ischemic events)

NEJM 2018 Jul 19;379(3):215-225
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POINT RESULTS

- **Fewer major ischemic events** occurred in clopidogrel + ASA grp (**5.0**%) vs ASA only (**6.5**%)
  - HR, 0.75;95% CI, 0.59 to 0.95; P = 0.02

- **Fewer ischemic strokes** in clopidogrel + ASA grp (**4.6**%) vs ASA only (**6.3**%)
  - HR, 0.72; 95% CI, 0.56 to 0.92; P = 0.01

- **More major hemorrhage** occurred in clopidogrel & ASA grp (**0.9**%) vs ASA only grp (**0.4**%)
  - HR, 2.32; 95% CI, 1.10 to 4.87; P = 0.02

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POINT RESULTS

- Benefit of clopidogrel + ASA was greater in the 1st 7 days & 30 d than at 90 d

- Risk of hemorrhage w clopidogrel + ASA was greater during the period from 8-90 d than during 1st 7 d
  - **Nonfatal, nonintracranial hemorrhage accounted for most**
  - **No significant differences btw grps in hemorrhagic stroke or symptomatic ICH**

- Thus confirms (CHANCE) that limited duration of DAPT best for providing benefit while minimizing risk

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Outcomes Associated With Clopidogrel-Aspirin Use in Minor Stroke or Transient Ischemic Attack

A Pooled Analysis of Clopidogrel in High-Risk Patients With Acute Non-Disabling Cerebrovascular Events (CHANCE) and Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) Trials

- **Pooled analysis of 2 RCTs**: early & short-term clopidogrel-ASA was assoc w a ↓in risk of major ischemic events w/o increasing risk of major hemorrhage in pts w minor stroke or TIA
  - **main benefit of DAPT occurred w/in the 1st 21days**

"This analysis suggests in pts w acute minor stroke or TIA, DAPT should be initiated ASAP, but preferably w/in 24hrs after sx onset & continued for a duration of 21days"

JAMA Neurol 2019 Aug 19;76(12):1466-1473

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THALES
TICAGRELOR & ASPIRIN OR ASPIRIN ALONE IN ACUTE ISCHEMIC STROKE OR TIA

- Randomized 11,016 pts w/in 24 hrs of mild-to-moderate acute noncardioembolic ischemic stroke or high-risk TIA to ticagrelor & ASA vs placebo & ASA x 30d
  - 30-day regimen ticagrelor (180mg loading dose followed by 90 mg BID) + ASA (300-325 mg 1st day followed by 75-100 mg daily) or placebo plus ASA
  - Minor stroke: NIHSS ≤5 (no thrombolysis or thrombectomy)
  - High risk TIA: ABCD2 score ≥ 6

- **1°outcome**: composite of stroke or death w/in 30d
- **2°outcomes**: 1st subsequent ischemic stroke & incidence of disability w/in 30d
- **1° safety outcome:** severe bleeding (fatal bleeding & ICH)

N Engl J Med. 2020 Jul 16;383(3):207-217

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THALES RESULTS

- **Fewer strokes or death** occurred in ticagrelor–ASA grp **(5.5%)** vs ASA grp **(6.6%)**
  - HR 0.83; 95% CI, 0.71 to 0.96; P = 0.02
- **Fewer ischemic strokes** occurred in ticagrelor–ASA grp **(5.0%)** vs ASA grp **(6.3%)**
  - HR, 0.79; 95% CI, 0.68 to 0.93; P = 0.004
- Incidence of disability did not differ significantly btw the 2 grps

- In pts with **≥ 30% stenosis cervicocranial vasculature ipsi** to ischemic event there was **lower risk of stroke or death** in in ticagrelor-ASA grp **(8.1%)** vs ASA grp **(10.9%)**
  - HR 0.73; 95% CI, 0.56–0.96; P=0.023

- **More severe bleeding** occurred in ticagrelor–ASA grp **(0.5%)** vs ASA grp (**0.1%**) P = 0.001

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THALES CONCLUSION

- In pts w a mild-to-moderate acute noncardioembolic ischemic stroke or TIA not undergoing IV or endovascular thrombolysis, **the risk of stroke or death w/in 30 days was lower w ticagrelor–ASA than w ASA alone**, **but the incidence of disability did not differ** significantly btw the 2 groups

- **Severe bleeding** which **included ICH** was **more frequent with ticagrelor & ASA** with the **exception of the ipsilateral atherosclerosis subgroup** which **did not** have significantly higher rates of severe bleeding

N Engl J Med. 2020 Jul 16;383(3):207-217
Stroke. 2020 Dec;51(12):3504-3513

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62 y/o F w hx of HTN & tobacco brought to ED by her husband for 3 days of “confusion”; having difficulty driving/parking her car. MRI brain reveals a R frontoparietal ischemic stroke. MRA head/neck: high-grade stenosis proximal R M1 segment middle cerebral artery w diminished flow, mild stenosis R A1 segment of the ACA & focal stenosis proximal L M2 branch of the MCA. Findings consistent with intracranial atheromatous disease. Her home meds are ASA & lisinopril.

What is the next best step in management?

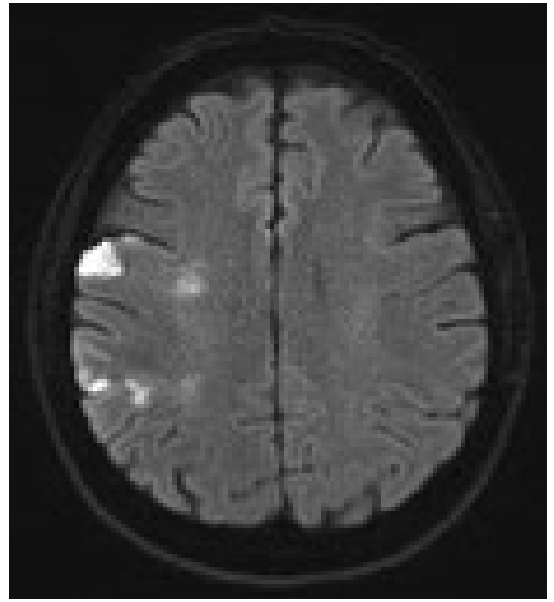
A. Consult neurosurgery for angioplasty & stenting

B. Start warfarin

C. Add clopidogrel to ASA for 90 days

D. Start high-intensity statin therapy

E. Both C & D



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SAMMPRIS TRIAL

STENTING VS AGGRESSIVE MEDICAL THERAPY FOR INTRACRANIAL ARTERIAL STENOSIS

- Randomized 451 pts w recent TIA or stroke attributed to 70- 99% stenosis of a major intracranial artery to DAPT alone or DAPT + percutaneous transluminal angioplasty & stenting (PTAS)
  - ASA 325mg daily & Plavix 75mg daily x 90 days, then ASA monotherapy
  - all pts were also on antihypertensives & rosuvastatin

- **CONCLUSION**: In patients w intracranial arterial stenosis, aggressive medical management was superior to PTAS both because the risk of early stroke after PTAS was high & because the risk of stroke with aggressive medical therapy alone was lower than expected

N Engl J Med. 2011 Sep 15;365(11):993-1003
Lancet. 2014 Jan 25;383(9914):333-41

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2021 AHA/ASA GUIDELINES
INTRACRANIAL LARGE ARTERY ATHEROSCLEROSIS

- In pts w a stroke or TIA caused by 50-99% stenosis of a major intracranial artery, **ASA 325 mg/d is recommended over warfarin** to reduce the risk of recurrent ischemic stroke

- In pts w recent stroke or TIA (w/in 30d) attributable to severe stenosis (70%–99%) of a major intracranial artery, **the addition of clopidogrel 75 mg/d to ASA for up to 90 days** is reasonable to reduce recurrent stroke risk

- In pts w recent minor stroke (w/in 24 hrs) or high-risk TIA & concomitant ipsilateral >30% stenosis of a major intracranial artery, the addition of ticagrelor 90mg BID to ASA for up to 30d might be considered

Stroke. 2021 Jul;52(7):e364-e467

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2021 AHA/ASA GUIDELINES
INTRACRANIAL LARGE ARTERY ATHEROSCLEROSIS

- In pts w stroke or TIA attributable to 50-99% stenosis of a major intracranial artery, maintenance of **SBP below 140**, **high-intensity statin tx, & at least moderate physical activity** are recommended to prevent recurrent stroke

- In pts w stroke or TIA attributable to severe stenosis (70%–99%) of a major intracranial artery, **angioplasty & stenting should NOT be performed as an initial tx,** even for pts who were taking an antithrombotic at the time of the stroke or TIA

- In pts w stroke or TIA attributable to moderate stenosis (50%–69%) of a major intracranial artery, angioplasty or stenting is associated w **excess morbidity & mortality** compared with medical management

Stroke. 2021 Jul;52(7):e364-e467

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49 y/o M presents to stroke clinic s/p hospitalization last month for a L PCA ischemic stroke. No vascular risk factors. Hypercoagulability studies negative. He has been compliant w daily ASA since his stroke. TEE reveals a large PFO w R-to-L shunt at rest & w Valsalva & an associated atrial septal aneurysm. LE doppler neg for DVT. 30-day Holter: normal sinus rhythm.

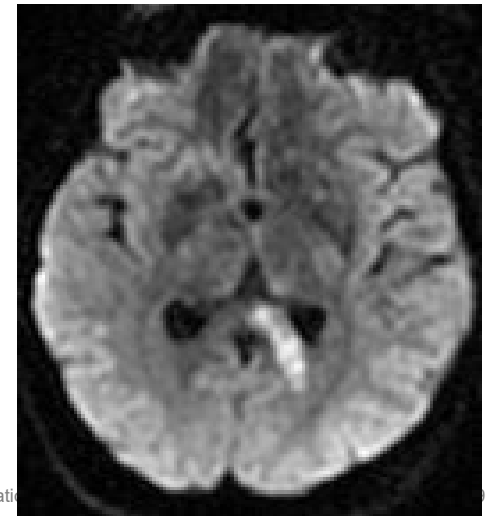
What is the next best step in management?

A. Consider referral to Cardiology for PFO closure

B. Switch to warfarin

C. Switch to clopidogrel

D. Switch to apixaban



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CLOSE TRIAL

- PFO closure + antiplatelet vs antiplatelet vs anticoagulation
  - Randomized 1:1:1; 663 pts (16 – 60yr)

- recent stroke (w/in 6 mo) attributed to PFO, w an assoc. **atrial septal aneurysm** or **large interatrial shunt**

- Results: ø stroke 238 pts PFO closure grp vs 14/235 pts antiplatelet-only grp; **HR 0.03** (p<0.001)

- New-onset Afib higher in PFO closure grp (4.6% vs 0.9% p=0.02)

- 5-yr risk of stroke was 4.9% lower w PFO closure + antiplatelet than antiplatelet alone
  - **NNT 20** to prevent 1 stroke in 5 yrs

NEJM 2017 Sep 14; 377(11): 1011-1021

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REDUCE TRIAL

- PFO closure + antiplatelet vs antiplatelet-only
  - Randomized 2:1; 664 pts (18-59 yr)

- Cryptogenic stroke w/in 6 mos

  81% had moderate or large shunt (6-25,> 25 microbubbles)

- Results: Incidence of new brain infarctions (clinical + silent MRI) was significantly lower in PFO closure grp
  - **5.7%** vs **11.3%**; **RR 0.51** (p<0.04)

- Afib higher in PFO closure grp (6.6% vs 0.4%)

- **NNT 28** to prevent 1 stroke in 24 mos

NEJM. 2017 Sep 14; 377(11): 1033-1042

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RESPECT TRIAL

- PFO closure vs med tx (ASA, warfarin, clopidogrel, or ASA & dipyridamole)
  - Cryptogenic stroke in the previous 9 mos
  - Randomized 1:1; 980 pts (18 – 60 yr)
    - Previously reported w 2.1y f/u; Extended f/u (median 5.9y)

- Results: recurrent ischemic stroke occurred in 3.6% PFO closure grp vs 5.8% in med tx grp; **HR 0.55** (p=0.046)

- **NNT 42 to prevent 1 stroke over 5 yrs**

- Greater benefit PFO closure among pts w an **atrial septal aneurysm** & w a **grade 3 shunt** (>20 microbubbles)

NEJM 2017 Sep 14; 377(11): 1022-1032

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	CLOSE	REDUCE	RESPECT
Number patients	663	664	980
Age	16 - 60 yo	18 - 59 yo	18 – 60 yo
Mean follow up	5.3 years	3.2 years	5.9 years
Comparator	Antiplatelet / anticoagulation	Antiplatelet	Antiplatelet and warfarin
Stroke	Cryptogenic	Cryptogenic	Cryptogenic
PFO characteristics	Large shunt Atrial septal aneurysm	All (81% moderate-to-large shunt)	All (substantial shunt 48.8%, atrial septal aneurysm 35.7%)
Primary outcome	Stroke	Ischemic stroke and new brain infarction on imaging	Composite non-fatal ischemic stroke, fatal ischemic stroke, early death (45 days)
HR	0.03	0.23	0.55
NNT	20 (in 5 years)	28 (in 2 years)	42 (in 5 years)
PFO closure success (6-12m)	93%	94.5%	93.5%
Atrial fibrillation	4.6% vs 0.9%	6.6% vs 0.4%	1.2% vs 0.8% (no sig)
Procedure/device complications	5.9%	3.9%	5%

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 pts w PFO closure
  - 0.53 vs 1.1 per 100 pt-yrs; **OR 0.43**; RRR 50.5%; NNT, **46.5 for 3.7 yrs**
- Outcomes even better w high-risk PFO
  - 0.51 vs 1.4 per 100 pt-yrs; **OR 0.39**; RRR 61%; NNT, **30 for 3.7 yrs**
- In contrast, was **no difference** in outcomes in **low-risk** PFOs
- New-onset **Afib more frequent** in PFO closure grp
  - 56% transient; **72% resolved w/in 45 days**

Ntaios et al. Stroke. 2018 Feb;49(2):412-418.

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ROPE SCORE

- Score estimates likelihood that PFO is the cause of cryptogenic stroke
- Factors in the score indicative of a higher likelihood of a PFO-dependent stroke mechanism: are absence of HTN, DM, prior stroke/TIA; cortical infarct on imaging; & younger age
- Scores range from 0 to 10, w the estimated probability that the stroke is PFO-related ranging from 0% for a ROPE score of 0 - 3 to 88% for a score of 9 to 10

Table 4 RoPE score calculator

Characteristic	Points
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

	Cryptogenic stroke (n = 3,023)			CS patients with PFO (n = 1,324)	
RoPE score	No. of patients	Prevalence of patients with a PFO, % (95% CI)[a]	PFO-attributable fraction, % (95% CI)[a]	No. of CS patients with PFO[a]	Estimated 2-y stroke/TIA recurrence rate (Kaplan-Meier), % (95% CI)
0-3	613	23 (19-26)	0 (0-4)	108	20 (12-28)
4	511	35 (31-39)	38 (25-48)	148	12 (6-18)
5	516	34 (30-38)	34 (21-45)	186	7 (3-11)
6	482	47 (42-51)	62 (54-68)	236	8 (4-12)
7	434	54 (49-59)	72 (66-76)	263	6 (2-10)
8	287	67 (62-73)	84 (79-87)	233	6 (2-10)
9-10	180	73 (66-79)	88 (83-91)	150	2 (0-4)

Neurology. 2013 Aug 13;81(7):619-25

2021 AHA/ASA GUIDELINES
PATENT FORAMEN OVALE

- In pts w a nonlacunar ischemic stroke of undetermined cause & a PFO, **recommendations for PFO closure vs medical management** should be **made jointly** by the pt, cardiologist, & neurologist, **taking into account the probability of a causal role** for the PFO

- In pts **18-60 years** of age w a **nonlacunar** ischemic stroke of **undetermined cause** despite a thorough eval & a **PFO w high-risk anatomic features,** it is **reasonable to choose closure** w a transcatheter device **& long-term antiplatelet tx** over antiplatelet tx alone for preventing recurrent stroke

Stroke. 2021 Jul;52(7):e364-e467

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73M w hx of HTN, DM admitted to hospital for aphasia & found to have an acute L MCA stroke & newly diagnosed Afib. He has dysphagia, thus a G-tube is placed. His CHA2DS2-VASc is 5 & it is determined he should be started on anticoagulation 14 days post-stroke.

Which of the following DOACs would you avoid in this patient if he continues with tube feedings?

A. dabigatran

B. apixaban

C. edoxaban

D. rivaroxaban

E. all of the above

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IF A PATIENT HAS DYSPHAGIA

- **Can give edoxaban, apixaban, or rivaroxaban**
  - Crushed tabs admin via NG tube or orally mixed in apple puree display similar relative bioavailability compared to whole tabs administered orally

- Do **NOT** give dabigatran
  - Do **NOT** break, chew, or open capsules
  - leads to **75% increase in absorption** & potentially serious adverse reactions

Clin Pharmacokinet. 2018 Feb;57(2):221-228
Clin Ther. 2016; 38:1674-1685
Clin Pharmacol Drug Dev. 2014; 3:321-7

2021 AHA/ASA GUIDELINES ATRIAL FIBRILLATION

- In pts w stroke or TIA & Afib who do not have moderate to severe mitral stenosis or a mechanical heart valve, **apixaban, dabigatran, edoxaban, or rivaroxaban** is recommended **in preference to warfarin** to reduce the risk of recurrent stroke

- DOACs are often preferred 2/2 more predictable pharmacokinetics, greater ease of use, & equally good or better clinical outcomes

Stroke. 2021 Jul;52(7):e364-e467

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SUMMARY OF DOAC TRIALS (DIRECT ORAL ANTICOAGULANTS)

- All DOACs were found to be **non-inferior to warfarin, w dabigatran (150 mg) & apixaban meeting superiority endpoints**
- All DOACs had **lower rates of ICH** when compared to warfarin
- **More GI bleeding** w dabigatran, rivaroxaban, & edoxaban
- **Apixaban superior** to warfarin in preventing stroke & also resulted in lower mortality & less bleeding

NEJM 2009; 361: 1139–1151
NEJM 2011; 365: 981–992
NEJM 2011; 365: 883–891
NEJM 2013; 369: 2093–2104

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RIVAROXABAN VS APIXABAN IN PTS W AFIB

- Retrospective study including 581,451 Medicare pts w newly dx'd Afib, ≥ 65 yrs, on apixaban or rivaroxaban, followed for 4 yrs
  - rivaroxaban (227,572) & apixaban (353,879); standard or reduced dose (23%)

- **1° outcome:** composite of ischemic (stroke/systemic embolism) & hemorrhagic (ICH/fatal extracranial bleeding) events

- **Results:** In older adults w Afib, tx w rivaroxaban compared to apixaban was assoc w a **significantly ↑ risk of major ischemic or hemorrhagic events**
  - Incidence of 1° outcome for rivaroxaban **16.1/1000** person-yrs vs **13.4/1000** person-yrs for apixaban (**RD, 2.7** [95% CI, 1.9-3.5]; **HR, 1.18** [95% CI, 1.12-1.24])

  - Rivaroxaban grp ↑ risk nonfatal extracranial bleeding, fatal ischemic/hemorrhagic events, & total mortality

JAMA. 2021 Dec 21;326(23):2395-2404

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65 y/o F presents to stroke clinic s/p hospitalization last month for a small L frontal lobe ischemic stroke. Her only vascular risk factor is HTN. She has been compliant w newly initiated ASA since her stroke. CTA head & neck wnl. TTE & TEE wnl; no evidence of PFO. 30-day Holter: normal sinus rhythm.

What is the next best step in management?

A. Consider adding warfarin

B. Continue ASA therapy

C. Switch to rivaroxaban

D. Switch to dabigatran

AHA/ASA guidelines for 2° prevention of stroke in pts who have had a cryptogenic stroke recommend administration of antiplatelet agents

Stroke. 2021 Jul;52(7):e364-e467
Stroke 2014;45(7):2160Y2236

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EMBOLIC STROKE OF UNDETERMINED SOURCE (ESUS)

IN 2014, ESUS EMERGED AS A NEW CLINICAL CONSTRUCT TO CHARACTERIZE CRYPTOGENIC STROKE

Criteria for diagnosis of ESUS

- Stroke detected by CT or MRI that is **not** lacunar
- Absence of extracranial or intracranial atherosclerosis causing ≥50% stenosis in arteries supplying the area of ischemia
- No major-risk cardioembolic source of embolism
- No other specific cause of stroke identified (eg, arteritis, dissection, vasospasm, drug misuse)

Minimum dx assessment ESUS

- Brain CT or MRI
- ECG
- TTE
- Cardiac monitoring for ≥24 h w automated rhythm detection
  - Telemetry NOT sufficient
- Imaging of both the extracranial & intracranial arteries (MRA, CTA, angiography, or carotid US + TCD)

Hart et al. Lancet Neurol 2014; 13:429–438

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NAVIGATE ESUS

- Randomized pts w ESUS to **rivaroxaban** 15mg d vs **ASA** 100mg d
  - 1° efficacy outcome: 1st recurrence of ischemic or hemorrhagic stroke or systemic embolism
  - 1° safety outcome: rate of major bleeding

- After 11mos & enrollment of 7213 pts, trial was terminated prematurely due to **higher rates of major bleeding in the rivaroxaban grp** (HR= 2.72; 95% CI 1.68–4.39)

- Results: **No clear efficacy for the 1° outcome**
  - **Recurrent ischemic stroke** was **4.7%** in **both** grps
  - **Higher rates hemorrhagic** stroke in rivaroxaban grp (HR= 6.5; 95% CI 1.47–28.8)

  - Subgroup analysis for 1° outcome favored rivaroxaban in pts w enlarged L atrium > 4.6cm

N Engl J Med 2018; 378: 2191–2201

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RE-SPECT ESUS

- Randomized 5390 pts w ESUS to **dabigatran** 110 or 150mg BID vs **ASA** 100mg d
  - 1° outcome: recurrent stroke; ischemic or hemorrhagic
  - 1° safety outcome: rate of major bleeding

- Results: Dabigatran was **NOT** superior to ASA in preventing recurrent stroke
  - Recurrent strokes 6.6% dabigatran vs 7.7% ASA grp (P=0.10)
  - Ischemic stroke occurred in 4%/yr dabigatran & 4.7%/yr in ASA grp

- Incidence of major bleeding was **NOT** greater in the dabigatran vs ASA grp (1.7%/yr vs 1.4%/yr)
  - more clinically relevant nonmajor bleeding in dabigatran grp

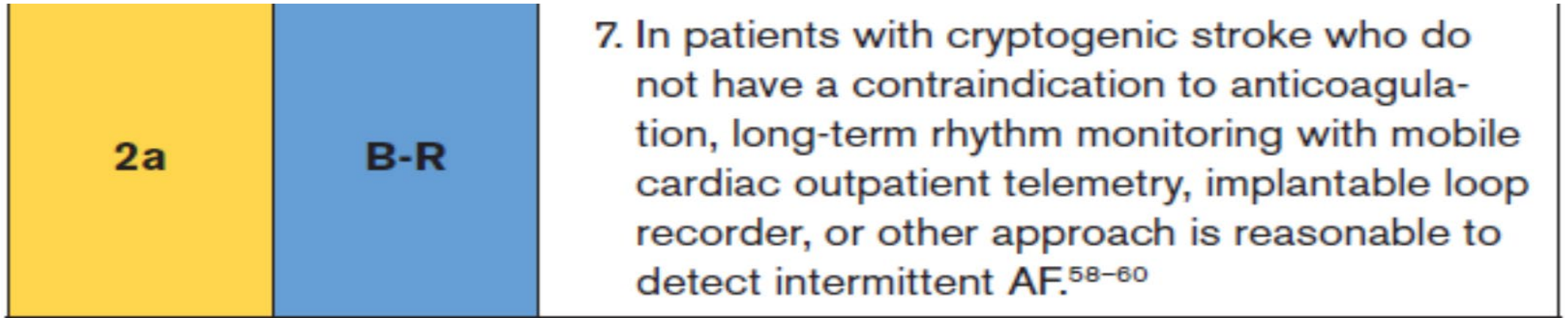
N Engl J Med. 2019 May 16;380(20):1906-1917

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- Optimal 2° prevention for ESUS remains unknown, w current evidence from RCTs suggesting that indiscriminant anticoagulation is neither effective nor safe

- **2021 AHA/ASA guidelines**: DOACs are **NOT** recommended to reduce risk of secondary stroke in pts w ESUS

- Pursue a more comprehensive diagnostic work-up than the diagnostic requirements included in the original ESUS criteria



PER DIEM TRIAL IMPLANTABLE VS EXTERNAL LOOP RECORDER

- Randomized 300 pts w ischemic stroke & no hx of Afib to implantable electrocardiographic monitoring for 12 mos vs external monitoring x 30 d
  - Median 64 yrs, 40.3% female, 86.3% completed monitoring & 12 mo f/u
  - **66% had a stroke of undetermined etiology; included all strokes**, even pts w other potential stroke etiologies (ICAS, extracranial, small vessel)

- **1° outcome**: detection of Afib ≥ 2 min

- **Results: Implantable loop x 12 mo resulted in detection of more pts w Afib compared to external monitoring for 30 d**
  - Afib detected **15.3% pts implantable loop** vs **4.7% pts external loop recorder grp**
    - between-group difference, 10.7%; 95% CI, 4.0- 17.3%
    - Risk Ratio, 3.29 [95% CI, 1.45 - 7.42] P = .003)

JAMA. 2021 Jun 1;325(21):2160-2168

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STROKE AF TRIAL
CONTINUOUS CARDIAC MONITORING VS USUAL CARE

- Randomized 496 pts w index ischemic stroke **attributed to large- or small-vessel disease** w/in 10 d to insertable cardiac monitor (ICM) vs usual care (EKGs, Holter, telemetry or event recorders) for 12 mos
  - Median age 67 yrs, 37.6% female, 84.8% completed 12 mo f/u
  - Included pts ≥60 yrs or 50-59 yrs w at least 1 additional stroke risk factor & no contraindication to long-term OAC

- **1° outcome**: detection of Afib ≥ 30 sec

- **Results:** Afib detection at 12 mos was **significantly higher in the ICM (12.1%)** vs control grp **(1.8%),** w no significant differences btw stroke subtypes
  - Hazard Ratio 7.4 (95% CI, 2.6-21.3); P < .001

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STROKE AF TRIAL

- Prespecified 2° analysis: At 12 mos, pts w CHF and/or LAE had an Afib detection rate of **23.4%** vs **5%** for pts w neither
  - HR 5.1; 95% CI, 2.0-12.8; P < .001

JAMA Neurol. 2023 Jan 1;80(1):99-103

- Follow-up of STROKE-AF trial: 3-year incidence rates of Afib were **21.7% in the ICM grp & 2.4%** in standard of care grp w no significant differences btw stroke subtypes
  - **HR 10.0** (95% CI, 4.0-25.2); P <.001
  - > 20% of pts w ischemic stroke attributed to small or large vessel disease had Afib w the detection rate 10x greater using ICM

- **No significant differences in rates of recurrent stroke** between the ICM (17.0%) & standard of care (14.1%) grps at 3 yrs
  - HR 1.10 (95% CI, 0.67-1.78); P=.71

Schwamm L. International Stroke Conference 2023. In: Dallas, TX; 2023

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WHERE DO WE GO FROM HERE?

- An overemphasis on monitoring for Afib only in pts w an index cryptogenic embolic stroke may be doing pts a disservice by failing to detect & intervene on clinically meaningful Afib in pts w other index stroke subtypes

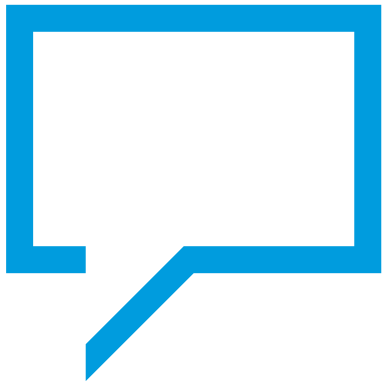
- It remains unclear whether OAC for poststroke Afib detected by ICM is beneficial to prevent 2° strokes

- What Afib burden is sufficient to produce benefit from OAC?

- Future studies are needed to determine the appropriate thresholds for initiating OAC tx in pts w ICM-detected Afib after stroke

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QUESTIONS & DISCUSSION



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