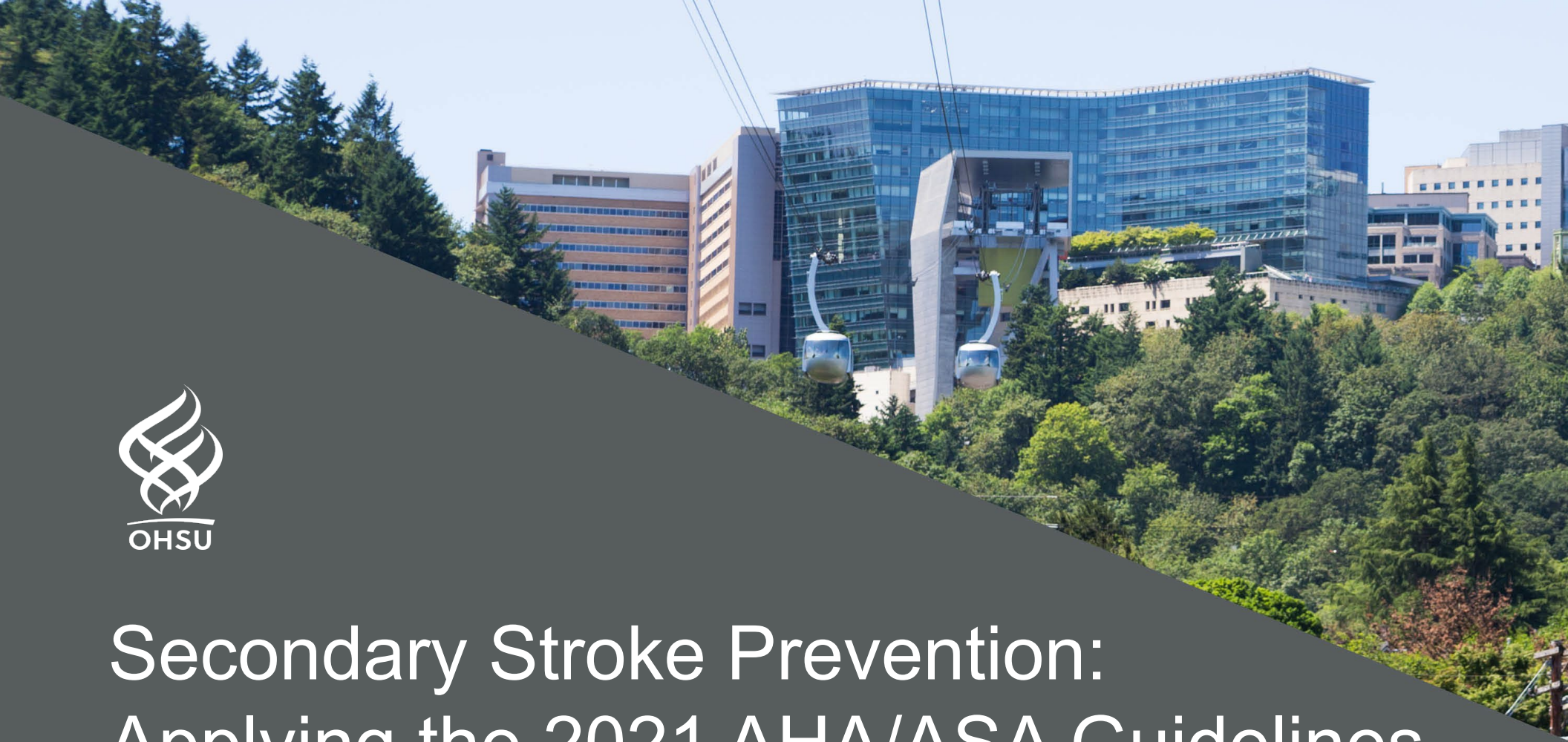

Secondary Stroke Prevention: Applying the 2021 AHA/ASA Guidelines

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Disclosures

Stroke Adjudication Committee, CREST 2, NINDS/Mayo

National Leader, Steering Committee, Bristol Myers Squib

Physician Advisory Board, Coherex Medical

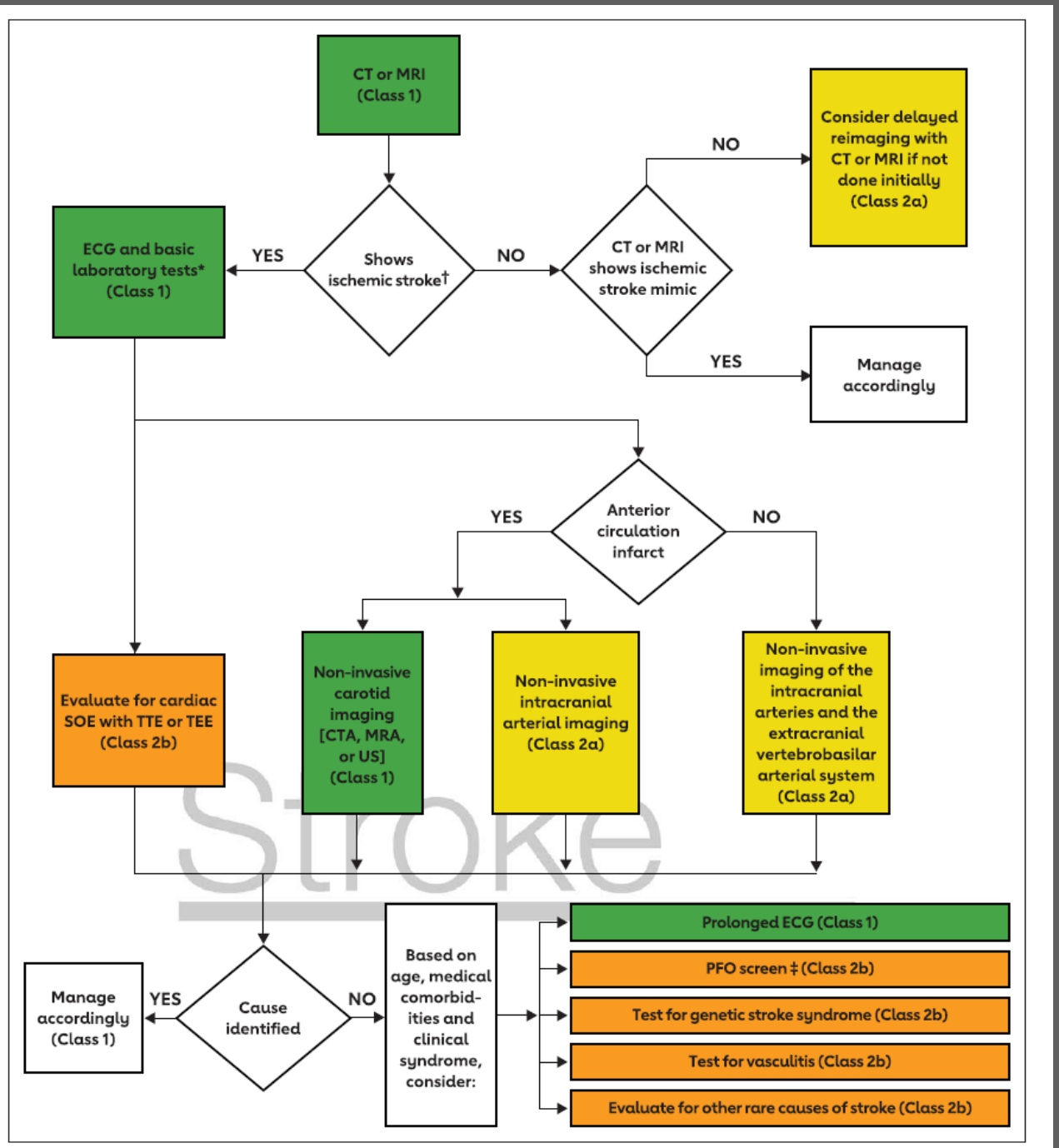
Editorial Board, Medscape Neurology

Focus on AHA/ASA 2021 Stroke Prevention Guidelines

- **Diagnosis of stroke**
- **Risk factor control**
- **Antithrombotics**
- **Large artery atherosclerosis**
- **Coagulopathies**
- **Cryptogenic stroke**
- **PFO-associated stroke**

Stroke 2021;52:e364-e467

Diagnosis



Stroke 2021;52:e364-e467

Risk Factor Control

Risk Factor Control in Secondary Stroke Prevention

Hypertension

- Blood pressure goal <130/80

Diabetes

- Hgb A1C goal <7.0

Hyperlipidemia

- LDL goal <100 without atherosclerotic disease
- LDL goal <70 with atherosclerotic disease

Stroke 2014;45:2160-2236; *NEJM* 2006; 355: 549-59; *Stroke* 2021:52:e364-e467; *NEJM* 2020;382:9-19

LDL Target <70 mg/dL

Treat Stroke to Target (TST) trial

- **Included those with cerebral infarction or high risk TIA, evidence of atherosclerotic disease (intracranial, carotid, aortic or coronary) and clear indication for statin therapy**
- **Target LDL-C <70 mg/dL was superior to a target of 90-110 mg/dL for preventing major vascular events* (8.5% vs. 10.9%, p=0.04)**
  - ***Ischemic stroke, MI, new symptoms leading to urgent coronary or carotid revascularization, or death from cardiovascular causes**

NEJM 2020;382:9-19

Vascular Risk Factor Management: Hyperlipidemia and Hypertriglyceridemia

COR		RECOMMENDATIONS
1		In patients with ischemic stroke with no known coronary heart disease, no major cardiac sources of embolism, and LDL cholesterol **(LDL-C) >100 mg/dL, atorvastatin 80 mg daily** is indicated to reduce risk of stroke recurrence
1		In patients with ischemic stroke or TIA and **atherosclerotic disease (intracranial, carotid, aortic, or coronary), lipid-lowering therapy with a statin and also ezetimibe, if needed, to a goal LDL-C of <70 mg/dL** is recommended…
2a		In patients with ischemic stroke who are **very high risk** (defined as stroke plus another major ASCVD or stroke plus multiple high-risk conditions), are taking **maximally tolerated statin and ezetimibe therapy and still have an LDL-C >70 mg/dL, it is reasonable to treat with PCSK9 inhibitor therapy** to prevent ASCVD events
1	**Monit or-ing**	In patients with stroke or TIA and hyperlipidemia, patients' adherence to changes in lifestyle and the effects of LDL-C lowering medication should be assessed by **measurement of fasting lipids and appropriate safety indicators 4-12 weeks after statin initiation or dose adjustment and every 3-12 months thereafter**, based on need to assess adherence of safety

Abbreviations: AF indicates atrial fibrillation; ASCVD, atherosclerotic cardiovascular disease; HbA1c, glycated hemoglobin A1c; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9; and TIA, transient ischemic attack.

Kernan WN, Ovbiagele B, Black HR, et al. 2021 AHA/ASA Guideline for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack. *Stroke.*

Risk Factor Control: Elevated Triglycerides

Treatment

- **Extended-release niacin and fibrates in addition to statin therapy have not improved cardiovascular outcomes**
- **Icosapent ethyl has been shown to reduce major adverse cardiovascular events when added to statin therapy**
  - **Purified preparation of the omega-3 fatty acid eicosapentaenoic acid**
  - **Vascepa, Amarin Pharmaceutics based in Ireland**

Stroke 2021;52:e364-e467

REDUCE-IT Trial

Reduction of Cardiovascular Events with Icosapent Ethyl Intervention Trial

- **Patients with cardiovascular disease or diabetes plus risk factors**
- **Fasting triglycerides of 135-499 mg/dL and LDL-C of 41-100 mg/dL on statin dose for ≥4 weeks**
- **Randomized to icosapent ethyl (IPE) 2 g twice daily plus statin vs statin alone**

Results (n=8179)

- **Major adverse cardiac events occurred in 17.2% IPE versus 22% control, p<0.001**
- **Small increase in AF with IPE**

NEJM 2019;380:11-22

Vascular Risk Factor Management: Hyperlipidemia and Hypertriglyceridemia

HYPERTRIGLYCERIDEMIA

COR	RECOMMENDATIONS
2a	In patients with ischemic stroke or TIA, with fasting **triglycerides 135 to 499** mg/dL and LDL-C of 41 to 100 mg/dL, on moderate- or high-intensity statin therapy, with HbA1c <10%, and with no history of pancreatitis, AF, or severe heart failure, treatment with **icosapent ethyl (IPE) 2 g twice a day** is reasonable to reduce risk of recurrent stroke.
2a	In patients with severe hypertriglyceridemia (ie, **fasting triglycerides ≥500** mg/dL [≥5.7 mmol/L]), it is reasonable to identify and address causes of hypertriglyceridemia… implementation of a **very low-fat diet, avoidance of refined carbohydrates and alcohol, consumption of omega-3 fatty acids**, and, if necessary to prevent acute pancreatitis, **fibrate therapy.**

Abbreviations: AF indicates atrial fibrillation; ASCVD, atherosclerotic cardiovascular disease; HbA1c, glycated hemoglobin A1c; LDL-C, low-density lipoprotein cholesterol; and TIA, transient ischemic attack.

Lifestyle Changes in Secondary Stroke Prevention

Physical activity

- **At least 10 minutes 4 times a week (moderate intensity aerobic activity)**
  - **Strongest predictor of good outcome in SAMMPRIS intracranial stenosis trial**

Neurology 2017;88:1-7; *Stroke* 2021;52:e364-e467

Guidelines for the Prevention of Stroke in Patients With Stroke and TIA

American Heart Association | American Stroke Association

Physical Activity

COR	LOE	Recommendations
1	C-LD	1. In patients with stroke or TIA who are capable of physical activity, engaging in at least moderate-intensity aerobic activity for a minimum of 10 minutes 4 times a week or vigorous-intensity aerobic activity for a minimum of 20 minutes twice a week is indicated to lower the risk of recurrent stroke and the composite cardiovascular end point of recurrent stroke, MI, or vascular death.[110]

Stroke 2021;52:e364-e467

Lifestyle Changes in Secondary Stroke Prevention

- **Stop smoking, avoid environmental smoke**
- **Drink no more than 1-2 alcoholic drinks per day**
- **Treat sleep apnea: Sleep SMART StrokeNet trial**
- **Reduce weight if overweight or obese**

Stroke 2021;52:e364-e467

Nutrition

Table 4. Dietary Details of Typical Mediterranean-Type Diets

Mediterranean diet (summarized)	DASH diet (summarized)
High monounsaturated/saturated fat ratio (use of olive oil as main cooking ingredient and/or consumption of other traditional foods high in monounsaturated fats such as tree nuts)	Limited saturated fat and cholesterol and emphasized nut consumption
High intake of plant-based foods, including fruits, vegetables, and legumes	Emphasizes fruit, vegetables, and legumes consumption
High consumption of whole grains and cereals	Emphasizes whole grains
Increased consumption of fish	
Low consumption of meat and meat products Discourages red and processed meats	Limits red and processed meats
Low to moderate red wine consumption	
Moderate consumption of milk and dairy products	Emphasizes fat-free/low-fat dairy
Discourages soda drinks, pastries, sweets, commercial bakery products, and spread fats	Limits sweets, added sugars, salt, and sugar-sweetened beverages.

DASH indicates Dietary Approaches to Stop Hypertension.
Summarized Mediterranean Diet[95,96], summarized DASH diet.[103]

Stroke 2021;52: e364-e467

Health Equity

Certain populations have documented inequities in recurrent stroke risk and vascular risk factor control

- **Caused and perpetuated by structural racism**
- **Non-White populations, women, rural dwellers, the elderly, immigrants, individuals with low socioeconomic status and lesbian, gay, bisexual, transgender and queer or questioning individuals**

Stroke 2021;52:e364-e467

Health Equity

Recommendations for Health Equity in Patients with Stroke or TIA	
COR	**RECOMMENDATIONS**
1	1. Evaluating and addressing social determinants of health (such as literacy level, language proficiency, medication affordability, food insecurity, housing, and transportation barriers) when managing stroke risk factors is recommended to reduce health care disparities. 2. Monitoring the achievement of nationally accepted, evidence-based performance measures is recommended to allow inequities to be identified and addressed. 3. Systematic adoption of the AHRQ Universal Precautions Toolkit for Health Literacy is recommended to integrate health literacy into the secondary prevention of stroke. Only 12 percent of U.S. adults have the health literacy skills needed to manage the demands of our complex health care system

Abbreviations: AHRQ indicates Agency for Healthcare Research and Quality; SES, socio-economic status; and TIA, transient ischemic attack .

AHRQ Toolkit, Tool 4 Snippet

Actions

Use strategies for communicating clearly.

- **Greet patients warmly:** Receive everyone with a welcoming smile, and maintain a friendly attitude throughout the visit.
- **Make eye contact:** Make appropriate eye contact throughout the interaction. Refer to Tool 10: Consider Culture, Customs and Beliefs for further guidance on eye contact and culture.
- **Listen carefully:** Try not to interrupt patients when they are talking. Pay attention, and be responsive to the issues they raise and questions they ask.
- **Use plain, non-medical language:** Don't use medical words. Use common words that you would use to explain medical information to your friends or family, such as stomach or belly instead of abdomen.
- **Use the patient's words:** Take note of what words the patient uses to describe his or her illness and use them in your conversation.
- **Slow down:** Speak clearly and at a moderate pace.
- **Limit and repeat content:** Prioritize what needs to be discussed, and limit information to 3-5 key points and repeat them.

Ahrq.gov

Antithrombotics in Stroke Prevention

Dual Antithrombotics: Acute

Short-Term Dual Antiplatelet (DAPT) Use

CHANCE trial (China)

- **Minor stroke and TIA patients randomized within 24 hours**
- **Randomized to either DAPT for 21 days and then clopidogrel alone for rest of 90 days, or aspirin alone for 90 days**
- **Ischemic or hemorrhagic stroke occurred less often in DAPT group (8.6% vs 11.7%)**

NEJM 2013; 269:11-19

Short-Term Dual Antiplatelet (DAPT) Use

POINT trial (U.S.)

- **Minor stroke and TIA patients randomized within 12 hours**
- **Received either DAPT or to aspirin alone for 90 days**
- **Results showed benefit, although with an increased risk of major hemorrhage**
  - **Treat 1000 patients to prevent 15 ischemic strokes and cause 5 major hemorrhages**

NEJM 2018;379:215-225

Short-Term Dual Antiplatelet (DAPT) Use

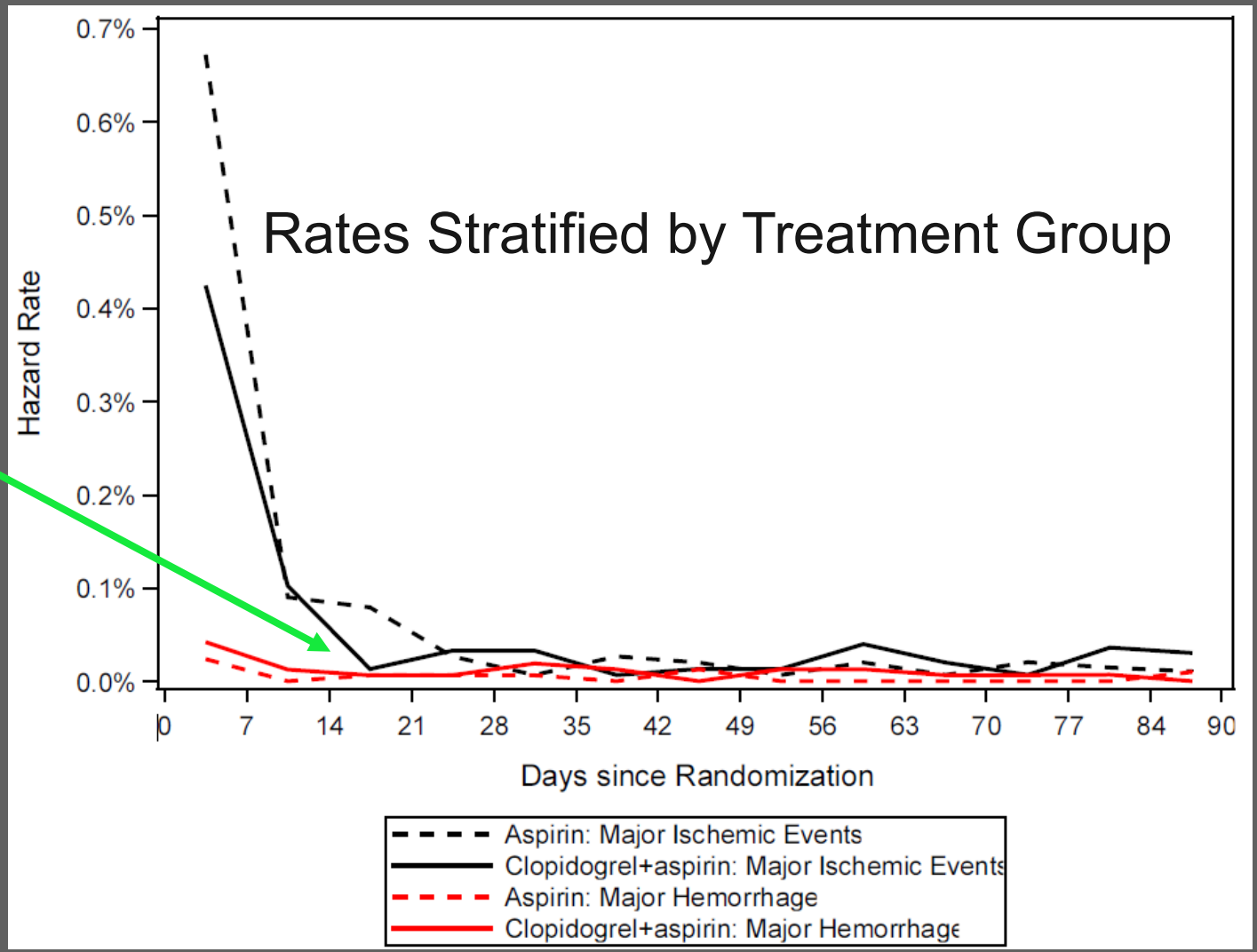
POINT trial secondary analysis

- **Benefit of clopidogrel-aspirin occurred predominantly within the first 21 says**
- **Risk of major hemorrhage remained relatively constant over 90 days**
- **For 1000 patients treated for 21 days with DAPT, prevent 20 major ischemic events and cause 2 major hemorrhages**

Circulation 2019;140:658-664

Hazard Rates By Week After Randomization for Major Ischemic Events, Major Hemorrhage

POINT Trial



Circulation 2019;140:658-664

Guidelines for the Prevention of Stroke in Patients With Stroke and TIA

American Heart Association | American Stroke Association

1	A[SR]	3. For patients with recent minor (NIHSS score ≤3) noncardioembolic ischemic stroke or high-risk TIA (ABCD² score ≥4), DAPT (aspirin plus clopidogrel) should be initiated early (ideally within 12–24 hours of symptom onset and at least within 7 days of onset) and continued for 21 to 90 days, followed by SAPT, to reduce the risk of recurrent ischemic stroke.[382,384,410,795,796]

Stroke 2021;52:e364-e467

Single Antiplatelet Agent

Single Antiplatelet Agent

Options

- **Aspirin, 50 to 325 mg daily**
  - **If already taking aspirin at the time of an ischemic stroke or TIA, effectiveness of increasing the dose or changing to another antiplatelet medication is not well established**
- **Clopidogrel, 75 mg daily**
- **Extended-release dipyridamole + aspirin twice daily**

Stroke 2021;52:e364-e467

Single Antiplatelet Agent

Cilostazol

- **Cilostazol for Prevention of Secondary Stroke (CSPS) trial showed significant reduction in recurrent stroke risk with cilostazol compared to placebo, *in particular in patients with lacunar strokes***
- **CSPS II compared cilostazol with aspirin and was associated with reduced risk of ischemic or hemorrhagic stroke but had more side effects**
  - **CSPS II has not been duplicated and was studied only in Japanese patients**

Stroke 2021;52:e364-e467

Guidelines for the Prevention of Stroke in Patients With Stroke and TIA

American Heart Association | American Stroke Association

Recommendation for Small Vessel Stroke
Referenced studies that support the recommendation are summarized in online Data Supplement 31.

COR	LOE	Recommendation
2b	B-R	1. In patients with ischemic stroke related to small vessel disease, the usefulness of cilostazol for secondary stroke prevention is uncertain.[382,384,408–410]

Stroke 2021;52:e364-e467

Dual Anti-Platelet Therapy (DAPT): Chronic Use

Dual Antiplatelets in Lacunar Strokes

SPS3 trial

- **Clopidogrel-aspirin vs aspirin alone**

DSMB terminated antiplatelet combination therapy due to risks and futility

- **Risk of major hemorrhage nearly doubled with dual antiplatelet therapy ($p<0.001$) and mortality increased ($p=0.004$)**

NEJM 2012;367:817-25

Guidelines for the Prevention of Stroke in Patients With Stroke and TIA

American Heart Association | American Stroke Association

3: Harm	**A**[SR]	6. For patients with noncardioembolic ischemic stroke or TIA, the continuous use of DAPT (aspirin plus clopidogrel) for >90 days or the use of triple antiplatelet therapy is associated with excess risk of hemorrhage.[381,382,801]

Stroke 2021;52:e364-e467

Triple Antithrombotics?

AXIOMATIC-SSP Trial

Patients with minor stroke or TIA and plaque

- **Compares aspirin + clopidogrel vs**

  Factor XIa inhibitor + aspirin + clopidogrel

- **Outcomes include stroke and covert infarction on MRI within 90 days**
- **Trial enrolled in the US, Canada and Europe until December 2021**

ClinicalTrials.gov

AXIOMATIC-SSP Trial

Factor XI

- **Factor XI may play a significant role in pathologic thrombus formation but only a limited role in hemostasis**
- **Studies suggest that targeting factor XI could produce an antithrombotic effect without significantly compromising hemostasis**

Semin Thromb Hemost 2019;45:502-508

Carotid Stenosis

Management of Extracranial Large Artery Atherosclerosis

COR	RECOMMENDATIONS
1	1. In patients with a **TIA or nondisabling ischemic stroke within the past 6 months and ipsilateral severe (70%–99%) carotid artery stenosis, carotid endarterectomy (CEA) is recommended** to reduce the risk of future stroke, provided that perioperative morbidity and mortality risk is estimated to be <6%.
1	2. …performed by operators with established periprocedural stroke and mortality rates of <6% to reduce the risk of surgical adverse events.
1	3. …intensive medical therapy
1	4. In patients with recent TIA or ischemic stroke and ipsilateral **moderate (50%–69%) carotid stenosis**…, **CEA** is recommended to reduce the risk of future stroke, **depending on patient-specific factors such as age, sex, and comorbidities**, if the perioperative morbidity and mortality risk is estimated to be <6%.

American Heart Association.

Abbreviations: CAS indicates carotid artery stenting; CEA, carotid endarterectomy; and TIA, transient ischemic attack.

Kleindorfer, D. O., et al. (2021). 2021 AHA/ASA Guideline for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack. *Stroke.*

Intracranial Stenosis

Risk Factors and Outcomes in SAMMPRIS

- **Reduction of blood pressure and lipid control were important for reducing vascular events**
- **However, physical activity was the strongest predictor of good outcome in the medical arm of SAMMPRIS**

Neurology 2017:88:1-7

Physical Activity in SAMMPRIS

- **The Physician-Based Assessment and Counseling for Exercise (PACE) score target was 4-8**

PACE score of 4:

- Equates to 10-minute bouts of moderate physical activity (sufficient to break a sweat or to noticeably raise heart rate, eg, walking briskly, using an exercise bicycle) up to 4 times a week
- OR 20-minute bouts of vigorous activity (eg, jogging), up to twice a week

Lancet 2014; 383:333-41, supplementary appendix

Guidelines for the Prevention of Stroke in Patients With Stroke and TIA

American Heart Association | American Stroke Association

Management of Intracranial Large Artery Atherosclerosis

1	B-NR	6. In patients with a stroke or TIA attributable to 50% to 99% stenosis of a major intracranial artery, maintenance of SBP below 140 mm Hg, high-intensity statin therapy, and at least moderate physical activity are recommended to prevent recurrent stroke and vascular events.[110,210,337,345–349]

Stroke 2021;52:e364-e467

Guidelines for the Prevention of Stroke in Patients With Stroke and TIA

American Heart Association | American Stroke Association

Management of Intracranial Large Artery Atherosclerosis

3: Harm	A	8. In patients with stroke or TIA attributable to severe stenosis (70%–99%) of a major intracranial artery, angioplasty and stenting should not be performed as an initial treatment, even for patients who were taking an antithrombotic agent at the time of the stroke or TIA.[353–359]

Stroke 2021;52:e364-e467

Guidelines for the Prevention of Stroke in Patients With Stroke and TIA

American Heart Association | American Stroke Association

Management of Intracranial Large Artery Atherosclerosis

2a	B-NR	2. In patients with recent stroke or TIA (within 30 days) attributable to severe stenosis (70%–99%) of a major intracranial artery, the addition of clopidogrel 75 mg/d to aspirin for up to 90 days is reasonable to further reduce recurrent stroke risk.[336–339]

Stroke 2021;52:e364-e467

Management of Intracranial Large Artery Atherosclerosis

COR	RECOMMENDATIONS
	Antithrombotic Therapy
2b	3. In patients with recent (within 24 hours) minor stroke or high-risk TIA and concomitant ipsilateral >30% stenosis of a major intracranial artery, the **addition of ticagrelor 90 mg twice a day to aspirin** for up to 30 days might be considered to further reduce recurrent stroke risk.
2b	4. In patients with stroke or TIA attributable to 50% to 99% stenosis of a major intracranial artery, the **addition of cilostazol 200 mg/day to aspirin or clopidogrel** might be considered to reduce recurrent stroke risk.
2b	5. In patients with stroke or TIA attributable to 50% to 99% stenosis of a major intracranial artery, the usefulness of clopidogrel alone, the combination of aspirin and dipyridamole, ticagrelor alone, or cilostazol alone for secondary stroke prevention is not well established.

American Heart Association.

Kleindorfer, D. O., et al. (2021). 2021 AHA/ASA Guideline for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack. *Stroke.*

Comparison of Anti-coagulation vs Anti-Platelet Therapies for Intracranial Vascular Atherostenosis (CAPTIVA)

Subjects to be randomized 1:1:1 *for one year*

- **Clopidogrel plus aspirin (standard of care arm) OR**
- **Ticagrelor plus aspirin OR**
- **Low dose rivaroxaban (2.5 mg BID) plus aspirin (81 mg QD)**

Intensive risk factor management

Blinded genotyping to assess impact of CYP2C10 loss of function carrier status on outcomes

Nihstrokenet.org, ClinicalTrials.gov

Hypercoagulable States

Assessment of Hypercoagulable States

Prothrombin 20210A mutation, activated protein C resistance, elevated factor VIII levels, deficiencies of protein C, protein S, or antithrombin III

- **"In the absence of a diagnosis that would change the default treatment for ischemic stroke, it is uncertain whether testing for these hematologic traits is of benefit"**
- **If there may be a venous mechanism, testing should be deferred or repeated at least 4-6 weeks (or up to 6 months for factor VIII) after the acute stroke**

Stroke 2021;52:e364-e467

Assessment of Hypercoagulable States

Antiphospholipid syndrome

- **Persistent (repeat testing 12 weeks apart) presence of lupus anti-coagulant, anti-cardiolipin or anti-β2 glycoprotein high-titer antibodies**
- **Evidence of clinical criteria such as vascular thrombosis or pregnancy morbidity**

Stroke 2021;52:e364-e467

Hypercoagulable States: Antiphospholipid Syndrome

COR	LOE	RECOMMENDATIONS
1	B-NR	1. In patients with ischemic stroke or transient ischemic attack who have an isolated antiphospholipid antibody but **do not fulfill the criteria for antiphospholipid syndrome, antiplatelet therapy alone is recommended**
2a	B-R	**2. …confirmed antiphospholipid syndrome, treated with warfarin, it is reasonable to choose a target international normalized ratio between 2-3**…
2a	C-LD	**3. …meet the criteria for the antiphospholipid syndrome, it is reasonable to anticoagulate with warfarin**
3 HARM	B-R	4. In patients with ischemic stroke or transient ischemic attack, antiphospholipid syndrome with history of thrombosis and **triple positive aPL antibodies (i.e., lupus anticoagulant, anticardiolipin and anti-beta2-glycoprotein I), rivaroxaban is not recommended** because it is associated with excess thrombotic events compared to warfarin.

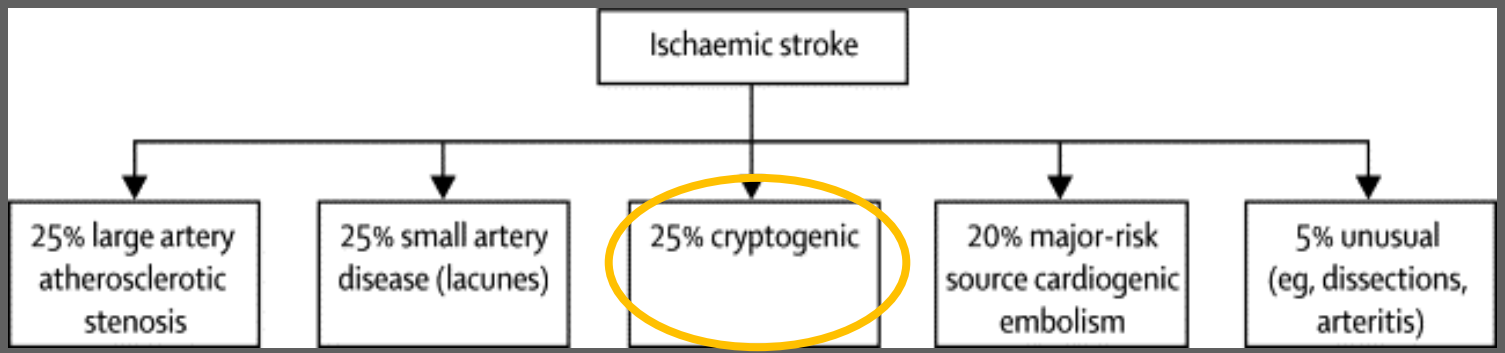
American Heart Association.

Kleindorfer, D. O., et al. (2021). 2021 AHA/ASA Guideline for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack. *Stroke.*

Cryptogenic Stroke

What is a Cryptogenic Stroke?

- **Stroke for which the cause is not found**
  - **Excludes strokes presumed due to small vessel disease, arterial stenosis of ≥ 50%, major or medium risk cardioembolic or other causes (such as dissection)**
- **Accounts for 25% of ischemic strokes**



Lancet Neurol 2014;13:429–38

What is an Embolic Stroke of Undetermined Source (ESUS)?

- **A subset of cryptogenic strokes**
- **Don’t have a major-risk cardioembolic source but can have medium-risk sources**
  - **The excluded major risk cardioembolic sources include AF and left ventricular thrombi**

Lancet Neurol 2014;13:429–38

NOAC No Better Than Aspirin in ESUS

NAVIGATE ESUS

- **Recurrent stroke risk, percent per year**
  - **Rivaroxaban 5.1% vs. aspirin 4.8%, p=0.52**
- **Major bleeding, percent per year**
  - **Rivaroxaban 1.8% vs. aspirin 0.7%, p<0.001**

RESPECT ESUS

- **Recurrent stroke risk, percent per year**
  - **Dabigatran 4.1% vs. aspirin 4.8%, p=0.10**
- **Major bleeding, percent per year**
  - **Dabigatran 1.7% vs. aspirin 1.4%, p=0.30**

NEJM 2018;378:2191-2201; *NEJM* 2019;380:1906-1917

Recommendations for ESUS

ESUS: non-lacunar cryptogenic ischemic stroke (after imaging of proximal large vessels, echocardiogram, rhythm monitoring with debate in duration of rhythm monitoring required)

COR	RECOMMENDATIONS
3 HARM	1. In patients with embolic stroke of undetermined source, treatment with direct oral anticoagulants is not recommended to reduce risk of secondary stroke.
3 HARM	2. In patients with embolic stroke of undetermined source, treatment with ticagrelor is not recommended to reduce risk of secondary stroke.

Abbreviations: ESUS indicates embolic stroke of unknown source.

American Heart Association.

Kleindorfer, D. O., et al. (2021). 2021 AHA/ASA Guideline for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack. *Stroke.*

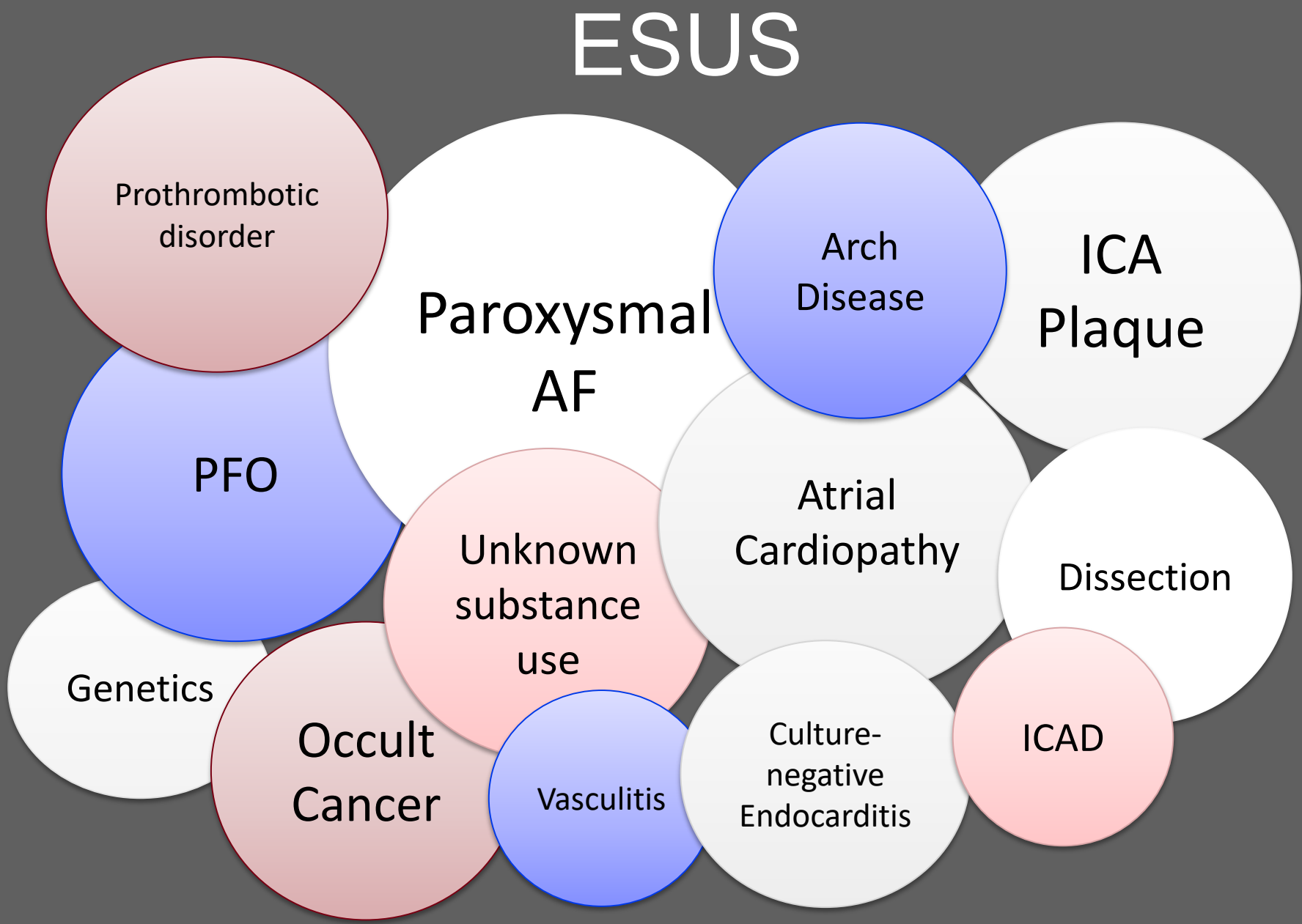
ARCADIA Stroke Trial

AtRial Cardiopathy and Antithrombotic Drugs in Prevention After Cryptogenic Stroke

NINDS Stroke-Net Consortium study

- **Apixaban 5 mg BID vs. aspirin 81 mg**
- **Patients aged 45 years or older with cryptogenic ischemic stroke and atrial cardiopathy**
- **Primary outcome is incidence of recurrent stroke**

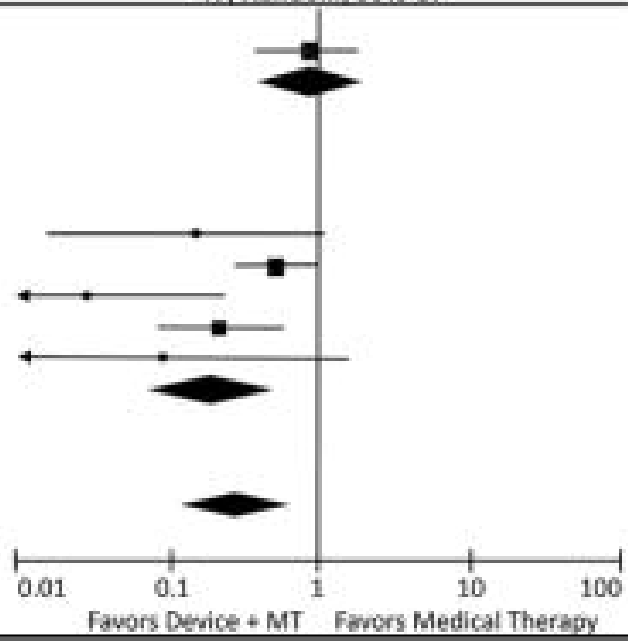
ClinicalTrials.gov


ESUS
Prothrombotic disorder
Paroxysmal AF
Arch Disease
ICA Plaque
PFO
Unknown substance use
Atrial Cardiopathy
Dissection
Genetics
Occult Cancer
Vasculitis
Culture-negative Endocarditis
ICAD

PFO in ESUS:
Now “PFO-Associated Stroke”

Trials Comparing PFO Closure Plus Antithrombotic to Antithrombotic Alone

Study or Subgroup	log[HR]	SE	Device + MT Events	Device + MT Pt-Yrs (Pts)	Medical Therapy Events	Medical Therapy Pt-Yrs (Pts)	Weight	Hazard Ratio IV, Random, 95% CI
Umbrella-clamshell devices								
CLOSURE	-0.11	0.40	12	789 (447)	13	766 (462)	24.6%	0.90 [0.41, 1.98]
Subtotal (95% CI)			**12**	**789 (447)**	**13**	**766 (462)**	**24.6%**	**0.90 [0.41, 1.98]**
Heterogeneity: Not applicable								
Test for overall effect: Z =0.27 (P = 0.79)								
Double disk devices (all or predominantly)								
PC	-1.97	1.09	1	845 (204)	7	836 (210)	10.1%	0.14 [0.02, 1.17]
RESPECT-Extended	-0.60	0.30	18	3080 (499)	28	2608 (481)	27.5%	0.55 [0.31, 0.99]
CLOSE	-3.51	1.11	0	1231 (238)	14	1222 (235)	9.7%	0.03 [0.00, 0.26]
REDUCE	-1.47	0.50	6	1529 (441)	12	703 (223)	21.7%	0.23 [0.09, 0.62]
DEFENSE-PFO	-2.40	1.47	0	95 (60)	5	92 (60)	6.4%	0.09 [0.01, 1.62]
Subtotal (95% CI)			**25**	**6780 (1442)**	**66**	**5461 (1209)**	**75.4%**	**0.20 [0.08, 0.54]**
Heterogeneity: $Tau^2 = 0.61$; $Chi^2 = 9.46$, df = 4 (P = 0.05); $I^2 = 58\%$								
Test for overall effect: Z = 3.20 (P = 0.001)								
Total (95% CI)			**37**	**7579 (1889)**	**79**	**6227 (1671)**	**100.0%**	**0.30 [0.13, 0.68]**
Heterogeneity: $Tau^2 = 0.54$; $Chi^2 = 13.52$, df = 5 (P = 0.02); $I^2 = 63\%$								
Test for overall effect: Z = 2.89 (P = 0.004)								
Test for subgroup differences: $Chi^2 = 5.38$, df = 1 (P = 0.02), $I^2 = 81.4\%$								



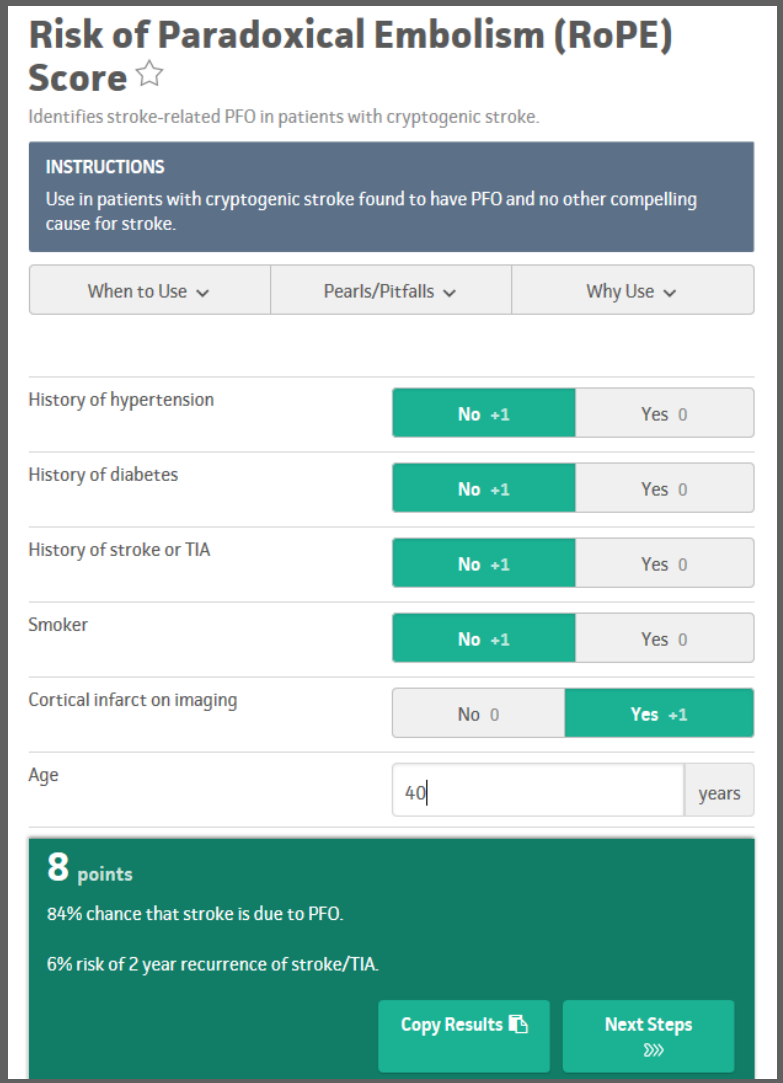
Device Medical Therapy

Stroke 2018;49:1541-48

Neurologist Approach to Patient Assessment for PFO Closure

Cryptogenic stroke in patient generally <60 years of age

- **RoPE score (MDCalc)**
  - **Emphasizes younger age, cortical infarcts, lack of usual risk factors**
  - **Score of >6 suggests probable PFO-related stroke**



Neurology 2013;81:619-625;
Neurology 2014;83:221-226

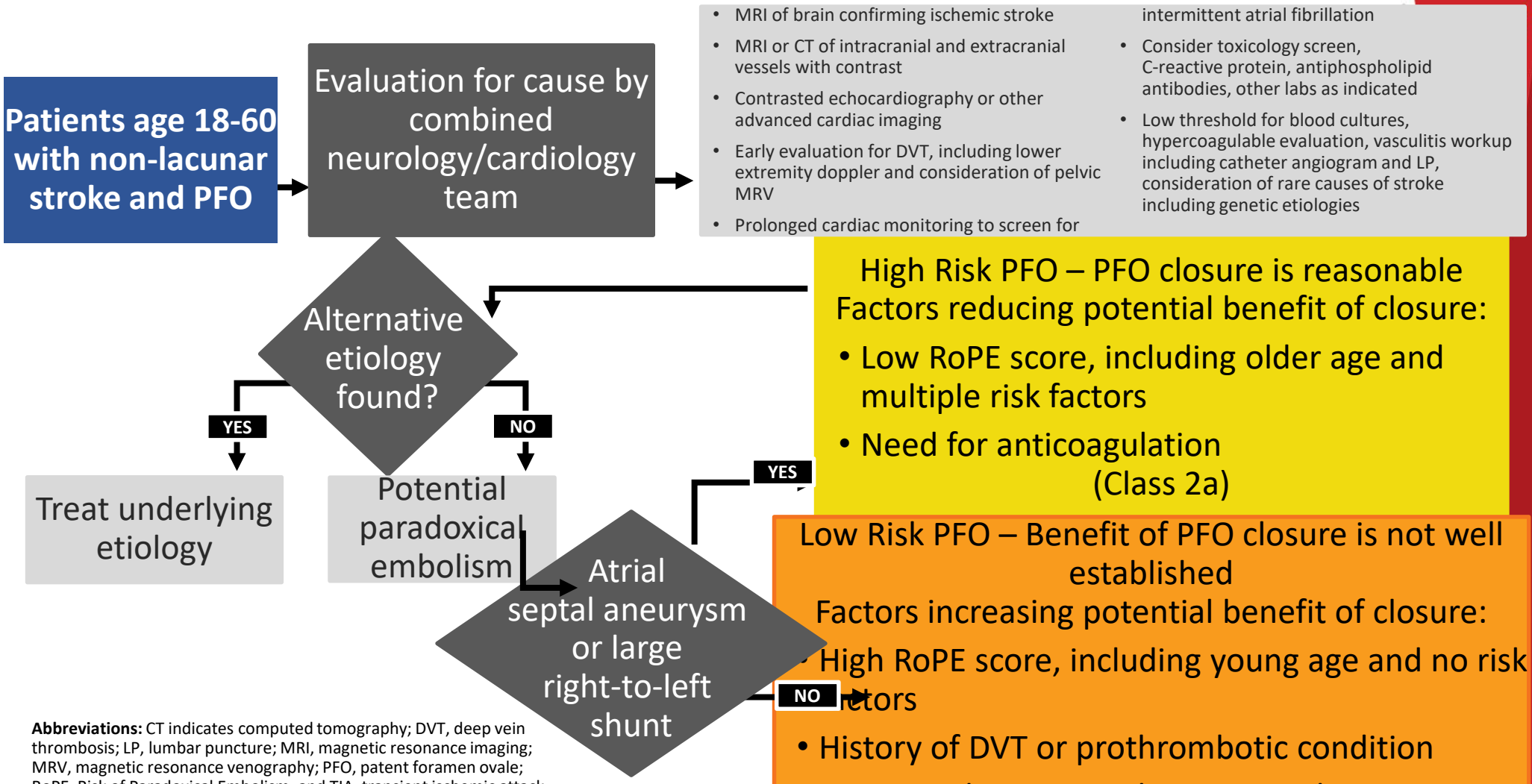
Further Assessment of Likelihood of PFO-Associated Stroke

Other risk factors

- **History of DVT or PE**
- **Recent prolonged travel**
- **Migraine**
- **Valsalva preceding the onset**
- **Waking up with the stroke**

Neurol 2013;81:619-625; *Neurol* 2014;83:221-226; *J Neurol Sci* 2008:275:121-127

Figure 5. Secondary Stroke Prevention with PFO



Abbreviations: CT indicates computed tomography; DVT, deep vein thrombosis; LP, lumbar puncture; MRI, magnetic resonance imaging; MRV, magnetic resonance venography; PFO, patent foramen ovale; RoPE, Risk of Paradoxical Embolism; and TIA, transient ischemic attack.

American Heart Association.

Secondary Stroke Prevention Summary

- **Risk factor control is key, including lack of exercise**
- **Consider endarterectomy for symptomatic carotid stenosis of 50-99%**
- **Some coagulopathy findings are treated with antiplatelets**
- **Strokes of undetermined source are treated with antiplatelets**
- **Selected patients <60 years of age may benefit from PFO closure**

Stroke 2021;52:e364-e467

Thank you!