2021 Guidelines Update: Secondary Prevention of Ischemic Stroke and Transient Ischemic Attack

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Introduction

- Hi. My name is Allyson Hamacher. I'm a PA practicing inpatient neurology for the past 4 years. I read the updated "AHA/ASA 2021 Guidelines for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack" so you didn't have to.
- I have no disclosures.

Objectives

- Categorize stroke etiology according to TOAST criteria
- Discuss new updates to AHA/ASA guidelines for secondary stroke prevention

Acronyms

- A fib: atrial fibrillation
- DAPT: dual anti-platelet therapy
- DASH: Dietary Approaches to Stop Hypertension
- DOAC: direct oral anticoagulant
- ICAS: intracranial atherosclerosis
- ECAS: extracranial atherosclerosis
- ESUS: embolic stroke of unknown source
- PFO: Patent Foramen Ovale
- TIA: transient ischemic attack
- VKA: Vitamin K antagonist

Trial Names

- ARISTOTLE trial (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation)
- CREST (Carotid Revascularization Endarterectomy versus Stenting Trial)
- ECST (European Carotid Surgery Trial)
- ENGAGE AF-TIMI trial (Global Study to Assess the Safety and Effectiveness of Edoxaban [DU-176b] vs Standard Practice of Dosing With Warfarin in Patients With Atrial Fibrillation
- NASCET (North American Symptomatic Carotid Endarterectomy Trial)
- NAVIGATE ESUS (Rivaroxaban Versus Aspirin in Secondary Prevention of Stroke and Prevention of Systemic Embolism in Patients With Recent Embolic Stroke of Undetermined Source)
- PREDIMED (Prevención con Dieta Mediterránea)
- RE-LY trial (Randomized Evaluation of Long-Term Anticoagulant Therapy)
- RESPECT ESUS (Dabigatran Etexilate for Secondary Stroke Prevention in Patients With Embolic Stroke of Undetermined Source)
- ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation)
- SAMMPRIS (Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis)
- SOCRATES (Soluble Guanylate Cyclase Stimulator in Heart Failure Studies)
- TOAST (Trial of Org 10172 in Acute Stroke Treatment)
- WASID (Warfarin-Aspirin Symptomatic Intracranial Disease)

Background

- AHA/ASA guidelines for secondary stroke prevention last updated in 2014
- Neary 700,000 people in the United State each year experience an ischemic stroke
  - Approx 240,000 transient ischemic attacks (TIAs) annually
- Secondary stroke prevention strategies improved annual rates of stroke recurrence from 8.7% in the 1960s to 5.0% in 2000s

Table 3. Applying Class of Recommendation and Level of Evidence to Clinical Strategies, Interventions, Treatments, or Diagnostic Testing in Patient Care (Updated May 2019)*

CLASS (STRENGTH) OF RECOMMENDATION	LEVEL (QUALITY) OF EVIDENCE‡
CLASS 1 (STRONG) — **Benefit >>> Risk** **Suggested phrases for writing recommendations:** • Is recommended • Is indicated/useful/effective/beneficial • Should be performed/administered/other • Comparative-Effectiveness Phrases†: – Treatment/strategy A is recommended/indicated in preference to treatment B – Treatment A should be chosen over treatment B	**LEVEL A** • High-quality evidence‡ from more than 1 RCT • Meta-analyses of high-quality RCTs • One or more RCTs corroborated by high-quality registry studies
CLASS 2a (MODERATE) — **Benefit >> Risk** **Suggested phrases for writing recommendations:** • Is reasonable • Can be useful/effective/beneficial • Comparative-Effectiveness Phrases†: – Treatment/strategy A is probably recommended/indicated in preference to treatment B – It is reasonable to choose treatment A over treatment B	**LEVEL B-R (Randomized)** • Moderate-quality evidence‡ from 1 or more RCTs • Meta-analyses of moderate-quality RCTs
CLASS 2b (WEAK) — **Benefit ≥ Risk** **Suggested phrases for writing recommendations:** • May/might be reasonable • May/might be considered • Usefulness/effectiveness is unknown/unclear/uncertain or not well-established	**LEVEL B-NR (Nonrandomized)** • Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies • Meta-analyses of such studies
CLASS 3: No Benefit (MODERATE) (Generally, LOE A or B use only) — **Benefit = Risk** **Suggested phrases for writing recommendations:** • Is not recommended • Is not indicated/useful/effective/beneficial • Should not be performed/administered/other	**LEVEL C-LD (Limited Data)** • Randomized or nonrandomized observational or registry studies with limitations of design or execution • Meta-analyses of such studies • Physiological or mechanistic studies in human subjects
Class 3: Harm (STRONG) — **Risk > Benefit** **Suggested phrases for writing recommendations:** • Potentially harmful • Causes harm • Associated with excess morbidity/mortality • Should not be performed/administered/other	**LEVEL C-EO (Expert Opinion)** • Consensus of expert opinion based on clinical experience

COR and LOE are determined independently (any COR may be paired with any LOE).

A recommendation with LOE C does not imply that the recommendation is weak. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials. Although RCTs are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

* The outcome or result of the intervention should be specified (an improved clinical outcome or increased diagnostic accuracy or incremental prognostic information).

† For comparative-effectiveness recommendations (COR 1 and 2a; LOE A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

‡ The method of assessing quality is evolving, including the application of standardized, widely-used, and preferably validated evidence grading tools; and for systematic reviews, the incorporation of an Evidence Review Committee.

COR indicates Class of Recommendation; EO, expert opinion; LD, limited data; LOE, Level of Evidence; NR, nonrandomized; R, randomized; and RCT, randomized controlled trial.

Takeaway 1: Work-Up

- Etiology of stroke determines secondary stroke prevention
  - Thus, comprehensive work-up is important
  - Can be taken in a step-wise approach

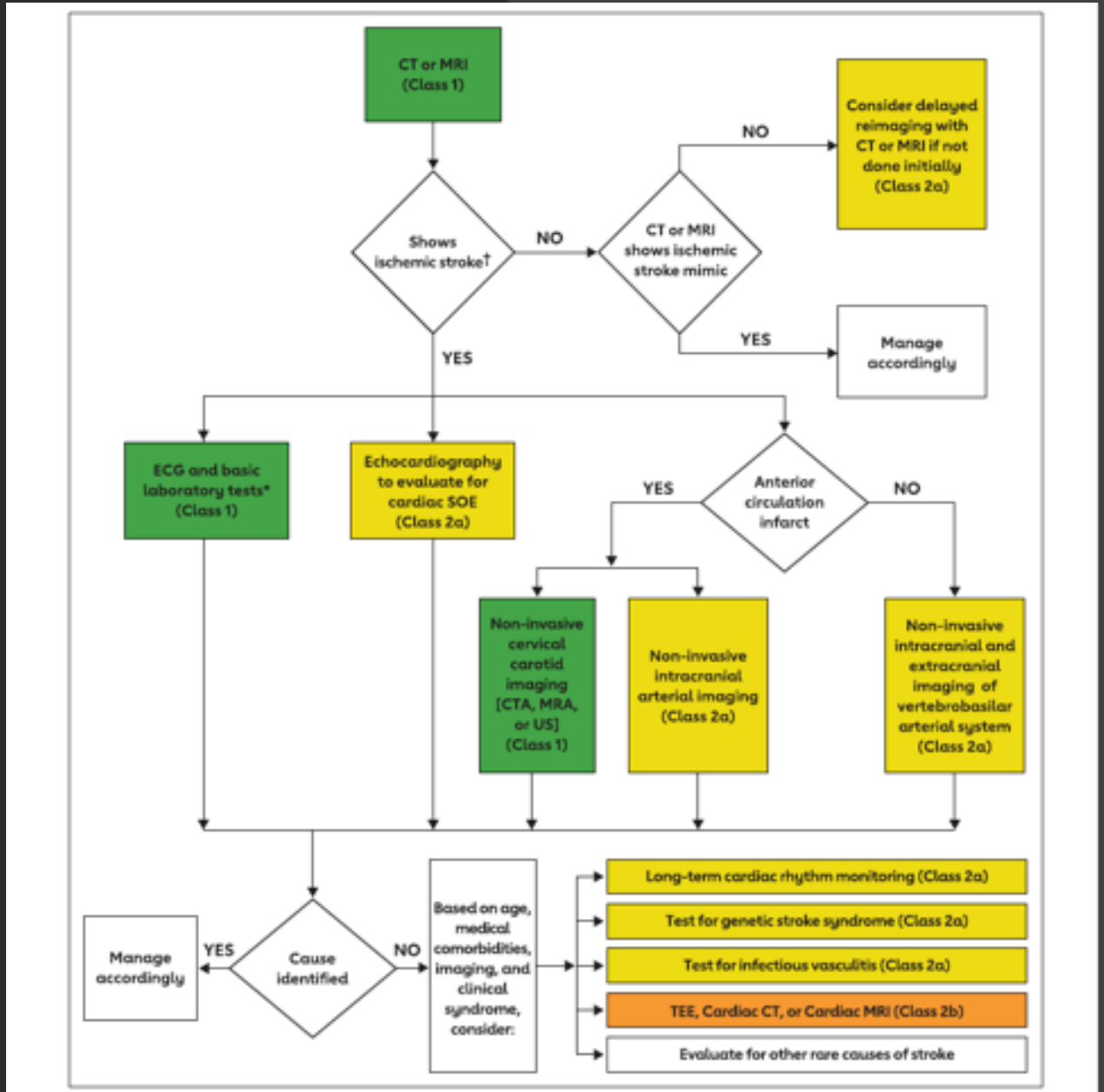
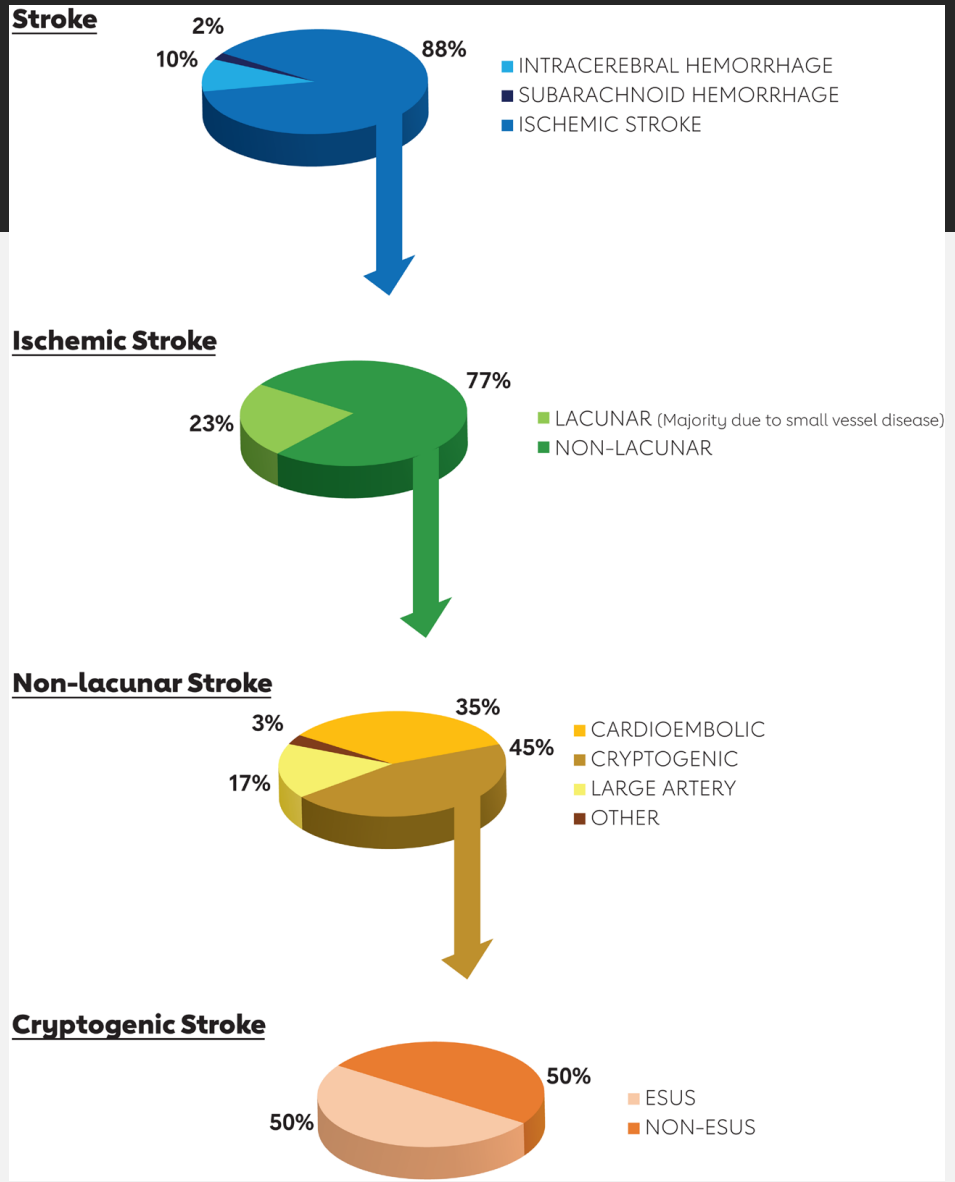


Figure 2. Algorithm for evaluating patients with a clinical diagnosis of stroke for the purposes of optimizing prevention of recurrent ischemic stroke.

Stroke Etiology

Toast Criteria
Cardioembolism
Large artery atherosclerosis (embolus/thrombosis)
Small-vessel occlusion (lacunar)
Stroke of other determined etiology
Stroke of undetermined etiology a) Two or more causes identified b) Negative evaluation c) Incomplete evaluation
*TOAST, Trial of Org 10172 in Acute Stroke Treatment.



Takeaway 2: Risk Factor Modification

- Modification of vascular risk factors is key
  - Intensive medical management in multidisciplinary team with patient-centered goals is key
- 82-90% of population-attributable risk for ischemic and hemorrhagic stroke are: blood pressure (BP), diet, physical inactivity, smoking, abdominal obesity
  - Goal HgA1c 7%
  - LDL < 70 mg/dL associated with reduced vascular events compared to patients with a target of 90-100 mg/dL
  - BP goal < 130/90
- A modeling study showed that targeting multiple risk factors has additive benefits for secondary prevention; specifically, aspirin, statin, and antihypertensive medications, combined with diet modification and exercise, can result in an 80% cumulative risk reduction in recurrent vascular events.

Takeaway 3: Dietary Changes

- Mediterranean Diet

  PREDIMED

  - primary end point (MI, stroke, cardiovascular death)
  - HR of 0.72 (0.72 (95% CI, 0.54–0.95) for the Mediterranean diet with olive oil supplementation and 0.69 (95% CI, 0.53–0.91) with nut supplementation compared with a low-fat diet

- Low salt/DASH diet reduces stroke risk
  - Meta-analysis of 13 studies showed higher habitual salt intakes associated with greater stroke risk (RR 1.23 (95% CI, 1.06 – 1.43)
  - Meta-analysis of patients with established CVD showed reducing 1 g/d sodium intake associate with 20% reduction in future cardiovascular events (RR, 0.80 [95% CI, 0.66–0.97])
  - DASH-sodium trial showed reduction from 3.3 to 2.4 g/day sodium intake reduced SBP by 2.1 mm Hg and further reduction to 2.5 g/day reduced further 4.6 mm Hg.

Recommendations for Nutrition
Referenced studies that support recommendations are summarized in online Data Supplements 3 and 4.

COR	LOE	Recommendations
2a	B-R	1. In patients with stroke and TIA, it is reasonable to counsel individuals to follow a Mediterranean-type diet, typically with emphasis on monounsaturated fat, plant-based foods, and fish consumption, with either high extra virgin olive oil or nut supplementation, in preference to a low-fat diet, to reduce risk of recurrent stroke.[95,96]
2a	B-R	2. In patients with stroke or TIA and hypertension who are not currently restricting their dietary sodium intake, it is reasonable to recommend that individuals reduce their sodium intake by at least 1g/d sodium (2.5 g/d salt) to reduce the risk of cardiovascular disease (CVD) events (including stroke).[97,98]

Diet Comparison

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 mono-unsaturated 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 con-sumption	
Moderate consumption of milk and dairy products	Emphasizes fat-free/low-fat dairy
Discourages soda drinks, pastries, sweets, commercial bakery prod-ucts, 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]

Takeaway 4: Physical Activity

- Ideal recommendations for physical activity are the same as general recommendations
  - If unable to achieve these personalized recommendations
- SAMMPRIS trial showed patients who did not meet physical activity targets had OR of 6.7 (95% Ci, 2.5 – 18.1) for recurrent stroke compared to those at goal
  - Multivariate analysis demonstrated greater physical activity associated with independent 40% of risk for stroke, MI, or vascular death at 3 years (OR, 0.6 [95% CI, 0.4-0.8])

Recommendations for Physical Activity
Referenced studies that support recommendations are summarized in online Data Supplements 5 and 6.

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]
2a	B-R	2. In patients with stroke or TIA who are able and willing to increase physical activity, engaging in an exercise class that includes counseling to change physical activity behavior can be beneficial for reducing cardiometabolic risk factors and increasing leisure time physical activity participation.[111–114]
2a	C-EO	3. In patients with deficits after stroke that impair their ability to exercise, supervision of an exercise program by a health care professional such as a physical therapist or cardiac rehabilitation professional, in addition to routine rehabilitation, can be beneficial for secondary stroke prevention.
2b	B-NR	4. In individuals with stroke or TIA who sit for long periods of uninterrupted time during the day, it may be reasonable to recommend breaking up sedentary time with intervals as short as 3 minutes of standing or light exercise every 30 minutes for their cardiovascular health.[115]

Takeaway 4: Broad Treatment Approach

- Changes to diet, exercise, and medication compliance are best done with implementation of theoretical models of behavior change and may benefit form multidisciplinary team approach

Recommendations for Behavior Change Interventions Referenced studies that support recommendations are summarized in online Data Supplements 63 and 64.		
COR	**LOE**	**Recommendations**
1	B-R	1. In patients with ischemic stroke or TIA, behavior change interventions targeting stroke literacy, lifestyle factors, and medication adherence are recommended to reduce cardiovascular events.[131,134,840]
2a	B-R	2. In patients with ischemic stroke or TIA, teaching self-management skills or using behavior change theory (eg, motivational interviewing) can be beneficial in improving medication adherence.[840–843]
2a	B-R	3. In patients with stroke or TIA, combined exercise-based and behavior change interventions are probably indicated in preference to behavior interventions alone, exercise interventions alone, or usual care to reduce physiological stroke risk factors such as SBP.[111–113,829]
2a	B-R	4. In patients with TIA or nondisabling stroke, engagement in targeted secondary prevention programs (eg, cardiac rehabilitation programs or exercise and lifestyle counseling programs) can be beneficial to reduce risk factors and recurrent ischemic events.[133,134]
2a	B-NR	5. For patients with disabling stroke who are discharged from acute services, engaging in targeted secondary prevention programs (eg, an adapted cardiac rehabilitation program or structured exercise including aerobic activity and healthy lifestyle counseling) can be beneficial to reduce vascular risk factors and mortality.[111,844]
3: No Benefit	B-R	6. In patients with stroke or TIA, provision of health information or advice about stroke prevention is essential; however, information or advice alone, in the absence of a behavioral intervention, is not an effective means to change modifiable, lifestyle-related risk factors in order to reduce future ischemic events.[129,829,845]

Takeaway 4: Broad Treatment Approach

- Consider how health equity and social determinants of health will affect their ability to implement changes

Recommendations for Health Equity Referenced studies that support recommendations are summarized in online Data Supplement 65.		
COR	**LOE**	**Recommendations**
1	C-EO	1. In patients with stroke or TIA, evaluating and addressing social determinants of health (eg, literacy level, language proficiency, medication affordability, food insecurity, housing, and transportation barriers) when managing stroke risk factors is recommended to reduce healthcare disparities.
1	C-EO	2. In patients with stroke or TIA, monitoring the achievement of nationally accepted, evidence-based performance measures is recommended to allow inequities to be identified and addressed.
1	C-EO	3. In patients with stroke or TIA, systematic adoption of the Agency for Healthcare Research and Quality Universal Precautions Toolkit for Health Literacy is recommended to integrate health literacy into the secondary prevention of stroke.

Takeaway 5: Antithrombotics

- Antithrombotic (e.g. antiplatelet and anticoagulant) recommend for patients without contradictions
  - Combination of antiplatelet and anticoagulant is rare
  - DAPT not recommended long term (> 90 days) due to bleeding risk and can cause harm

Recommendations for Antithrombotic Medications
Referenced studies that support recommendations are summarized in online Data Supplements 57–59.

COR	LOE	Recommendations
1	A	1. In patients with noncardioembolic ischemic stroke or TIA, antiplatelet therapy is indicated in preference to oral anticoagulation to reduce the risk of recurrent ischemic stroke and other cardiovascular events while minimizing the risk of bleeding.[789,790]
1	A	2. For patients with noncardioembolic ischemic stroke or TIA, aspirin 50 to 325 mg daily, clopidogrel 75 mg, or the combination of aspirin 25 mg and extended-release dipyridamole 200 mg twice daily is indicated for secondary prevention of ischemic stroke.*[791–794]
1	A[SR]	3. For patients with recent minor (NIHSS score ≤3) noncardioembolic ischemic stroke or high-risk TIA (ABCD^2 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]
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]

SR indicates systematic review.
*The subgroup of patients with noncardioembolic stroke who meet clinical criteria for DAPT have a more specific recommendation for antiplatelet therapy as described in Recommendation 3.

Takeaway 5: Antithrombotics

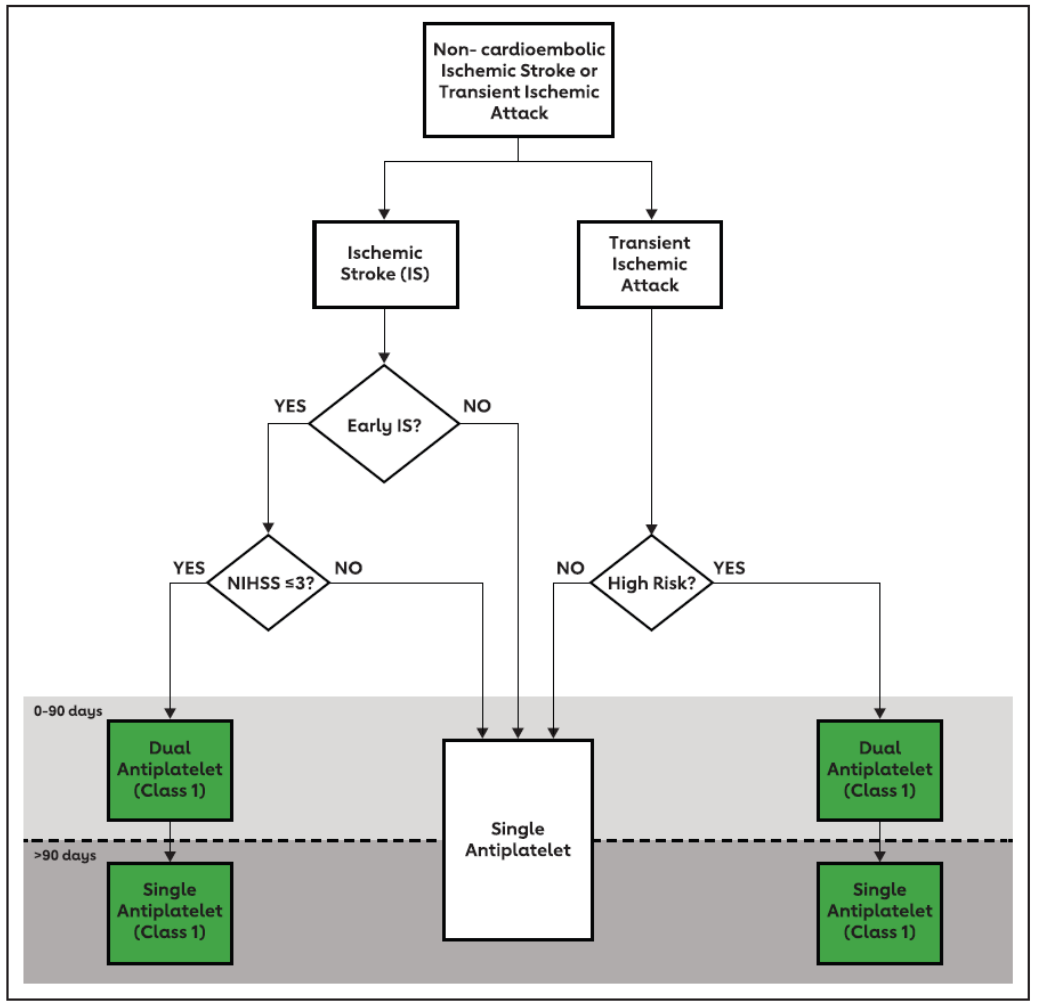


Figure 6. Antiplatelet therapy for noncardioembolic stroke and transient ischemic attack (TIA).
Note: Algorithm does not apply to patients who receive acute thrombolysis. Note: Please see Section 5.1.1 for recommendations related to severe symptomatic intracranial large vessel stenosis. Early ischemic stroke (IS), <24 hours from onset; high-risk TIA, ABCD^2 score ≥4; low-risk TIA, ABCD^2 score <4; dual antiplatelet, acetylsalicylic acid (ASA)+clopidogrel. Colors correspond to Class of Recommendation in Table 3. NIHSS indicates National Institutes of Health Stroke Scale. Data from Brown et al,[15] Pan et al,[409] and Wang et al.[410]

Etiology-Based Recommendations

Takeaway 6: Afib + TIA/Stroke = Anticoagulation

- Atrial fibrillation is a major risk factor for stroke
  - Treatment with anticoagulation if no contraindications
    - Nonvalvular: DOACs
    - Valvular or mechanical valve: warfarin

Recommendations for AF
Referenced studies that support recommendations are summarized in online Data Supplement 32.

COR	LOE	Recommendations
1	A	1. In patients with nonvalvular AF and stroke or TIA, oral anticoagulation (eg, apixaban, dabigatran, edoxaban, rivaroxaban, or warfarin) is recommended to reduce the risk of recurrent stroke.[419–426]
1	B-R	2. In patients with AF and stroke or TIA, oral anticoagulation is indicated to reduce the risk of recurrent stroke regardless of whether the AF pattern is paroxysmal, persistent, or permanent.[427]
1	B-R	3. In patients with stroke or TIA and AF 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.[419–426]
1	B-NR	4. In patients with atrial flutter and stroke or TIA, anticoagulant therapy similar to that in AF is indicated to reduce the risk of recurrent stroke.[427]
1	C-EO	5. In patients with AF and stroke or TIA, without moderate to severe mitral stenosis or a mechanical heart valve, who are unable to maintain a therapeutic INR level with warfarin, use of dabigatran, rivaroxaban, apixaban, or edoxaban is recommended to reduce the risk of recurrent stroke.

DOACs vs VKA (Coumadin)

- **RE-LY** trial
  - high-dose **dabigatran** was associated with lower stroke (1.11% versus 1.69%) and similar bleeding (3.11% versus 3.36%) rates compared with warfarin after 2 years
- **ROCKET** trial
  - **Rivaroxaban** noninferior to warfarin with similar rates of stroke or systemic embolism (2.1 vs 2.4 per 100 patient-years) and major bleeding (5.6% versus 5.4%) at 2 years
- **ARISTOTLE** trial
  - **Apixaban** superior to warfarin at 1.8 years with fewer strokes or systemic embolism (1.27% versus 1.60%) and *less bleeding* (2.13% versus 3.09%)
- **ENGAGE AF-TIMI** trial
  - Edoxaban demonstrated similar rates of stroke or systemic embolism with less bleeding compared to warfarin

Meta-analysis of above studies found 19% reduction of stroke/systemic embolic, 51% reduction hemorrhagic stroke, 10% overall reduction in mortality

Takeaway 7: Carotid Stenosis and Stroke

- Extracranial carotid stenosis is a risk factor for TIA/stroke
  - Medical management for carotid artery stenosis includes antiplatelet, lipid-lowering medications, and treatment of hypertension

Recommendations for Extracranial Carotid Stenosis
Referenced studies that support recommendations are summarized in online Data Supplement 28.

COR	LOE	Recommendations
1	A	3. In patients with carotid artery stenosis and a TIA or stroke, intensive medical therapy, with antiplatelet therapy, lipid-lowering therapy, and treatment of hypertension, is recommended to reduce stroke risk.[210]

Takeaway 7: Carotid Stenosis and Stroke

- Symptomatic patients with moderate or **severe** disease should be offered intervention
  - Highest benefit of intervention in severe stenosis (70-99%)
  - either carotid endarterectomy or carotid stents, depending on multiple factors
    - Age (at/over 70)
    - Anatomy or other medical conditions
    - Cardiac risk
  - early after ischemic event
    - Greatest benefit within 2 weeks of ischemic event

Recommendations for Extracranial Carotid Stenosis
Referenced studies that support recommendations are summarized in online Data Supplement 28.

COR	LOE	Recommendations
1	A	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%.[369]
1	B-R	4. In patients with recent TIA or ischemic stroke and ipsilateral moderate (50%–69%) carotid stenosis as documented by catheter-based imaging or noninvasive imaging, 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%.[369]
2a	B-R	5. In patients ≥70 years of age with stroke or TIA in whom carotid revascularization is being considered, it is reasonable to select CEA over CAS to reduce the periprocedural stroke rate.[371]
2a	B-R	6. In patients in whom revascularization is planned within 1 week of the index stroke, it is reasonable to choose CEA over CAS to reduce the periprocedural stroke rate.[372]
2a	C-LD	8. In patients with symptomatic severe stenosis (≥70%) in whom anatomic or medical conditions are present that increase the risk for surgery (such as radiation-induced stenosis or restenosis after CEA) it is reasonable to choose CAS to reduce the periprocedural complication rate.[374]
2b	A	9. In symptomatic patients at average or low risk of complications associated with endovascular intervention, when the ICA stenosis is ≥70% by noninvasive imaging or >50% by catheter-based imaging and the anticipated rate of periprocedural stroke or death is <6%, CAS may be considered as an alternative to CEA for stroke prevention, particularly in patients with significant cardiovascular comorbidities predisposing to cardiovascular complications with endarterectomy.[375]

Takeaway 7: Carotid Stenosis and Stroke

- No evidence that intervention on <50% stenosis or in total occlusion is beneficial

Recommendations for Extracranial Carotid Stenosis (Continued)		
COR	**LOE**	**Recommendations**
3: No Benefit	**A**	11. In patients with recent TIA or ischemic stroke and when the degree of stenosis is <50%, revascularization with CEA or CAS to reduce the risk of future stroke is not recommended.[369]
3: No Benefit	**A**	12. In patients with a recent (within 120 days) TIA or ischemic stroke ipsilateral to atherosclerotic stenosis or occlusion of the middle cerebral or carotid artery, extracranial-intracranial bypass surgery is not recommended.[377]

Takeaway 8: Large Intracranial Atherosclerosis

- Intracranial atherosclerosis of **≥70%** may indicate a 1-year recurrent stroke rate as high as 18%
- **WASID** trial found increased risk of major hemorrhages (relative difference, 5.1%) and all-cause death (relative difference, 5.4%) in coumadin group but did not prevent more primary end points (stroke, ICH, vascular death)
- Patients in the medical arm of **SAMMPRIS** who received DAPT with aspirin and clopidogrel for 90 days had lower rate of 1-year stroke recurrence (12.2%) compared with similar patients from WASID trial on aspirin monotherapy (25%)

Recommendations for Intracranial Large Artery Atherosclerosis
Referenced studies that support recommendations are summarized in online Data Supplements 20–27.

COR	LOE	Recommendations
		Antithrombotic Therapy
1	B-R	1. In patients with a stroke or TIA caused by 50% to 99% stenosis of a major intracranial artery, aspirin 325 mg/d is recommended in preference to warfarin to reduce the risk of recurrent ischemic stroke and vascular death.[335,336]
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]
		Risk Factor Management
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]

Takeaway 8: Large Intracranial Atherosclerosis

- Several studies have compared medical treatment (risk factor management and DAPT x 90 days) with angioplasty and stenting **and showed higher 30-day rates of cerebrovascular events and death in intervention group**
    - **First line treatment for stroke due to severe intracranial atherosclerosis is medical management with DAPT x 90 days, statin medication, blood pressure control**

COR	LOE	Recommendations
		Angioplasty and Stenting
2b	C-LD	7. In patients with severe stenosis (70%-99%) of a major intracranial artery and actively progressing symptoms or recurrent TIA or stroke after institution of aspirin and clopidogrel therapy, achievement of SBP <140 mm Hg, and high- intensity statin therapy (so-called medical failures), the usefulness of angioplasty alone or stent placement to prevent ischemic stroke in the territory of the stenotic artery is unknown.[350–352]
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]
3: Harm	B-NR	9. In patients with a stroke or TIA attributable to moderate stenosis (50%–69%) of a major intracranial artery, angioplasty or stenting is associated with excess morbidity and mortality compared with medical management alone.[336,354,355,360]

Takeaway 9: PFO Closure

- PFO closure is back (with multidisciplinary team and shared decision-making)
  - Closure recommended in patients who:
    - Are between **18-60**
    - Have a **nonlacunar stroke**
    - No other identified cause
    - **High-risk** PFO features*

Recommendations for PFO
Referenced studies that support recommendations are summarized in online Data Supplements 38 and 39.

COR	LOE	Recommendations
1	C-EO	1. In patients with a nonlacunar ischemic stroke of undetermined cause and a PFO, recommendations for PFO closure versus medical management should be made jointly by the patient, a cardiologist, and a neurologist, taking into account the probability of a causal role for the PFO.
2a	B-R	2. In patients 18 to 60 years of age with a nonlacunar ischemic stroke of undetermined cause despite a thorough evaluation and a PFO with high-risk anatomic features,* it is reasonable to choose closure with a transcatheter device and long-term antiplatelet therapy over antiplatelet therapy alone for preventing recurrent stroke.[552–557]
2b	C-LD	3. In patients 18 to 60 years of age with a nonlacunar ischemic stroke of undetermined cause despite a thorough evaluation and a PFO without high-risk anatomic features,* the benefit of closure with a transcatheter device and long-term antiplatelet therapy over antiplatelet therapy alone for preventing recurrent stroke is not well established.[552–557]
2b	C-LD	4. In patients 18 to 60 years of age with a nonlacunar ischemic stroke of undetermined cause despite a thorough evaluation and a PFO, the comparative benefit of closure with a transcatheter device versus warfarin is unknown.[554]

PFO Evaluation

Risk of Paradoxical Embolism (RoPE) Score

Identifies stroke-related PFO in patients with cryptogenic stroke.

INSTRUCTIONS

Use in patients with cryptogenic stroke found to have PFO and no other compelling cause for stroke.

When to Use | Pearls/Pitfalls | Why Use

History of hypertension	No +1	Yes 0
History of diabetes	No +1	Yes 0
History of stroke or TIA	No +1	Yes 0
Smoker	No +1	Yes 0
Cortical infarct on imaging	No 0	Yes +1
Age	29	years

10 points

88% chance that stroke is due to PFO.

2% risk of 2 year recurrence of stroke/TIA.

Copy Results | Next Steps

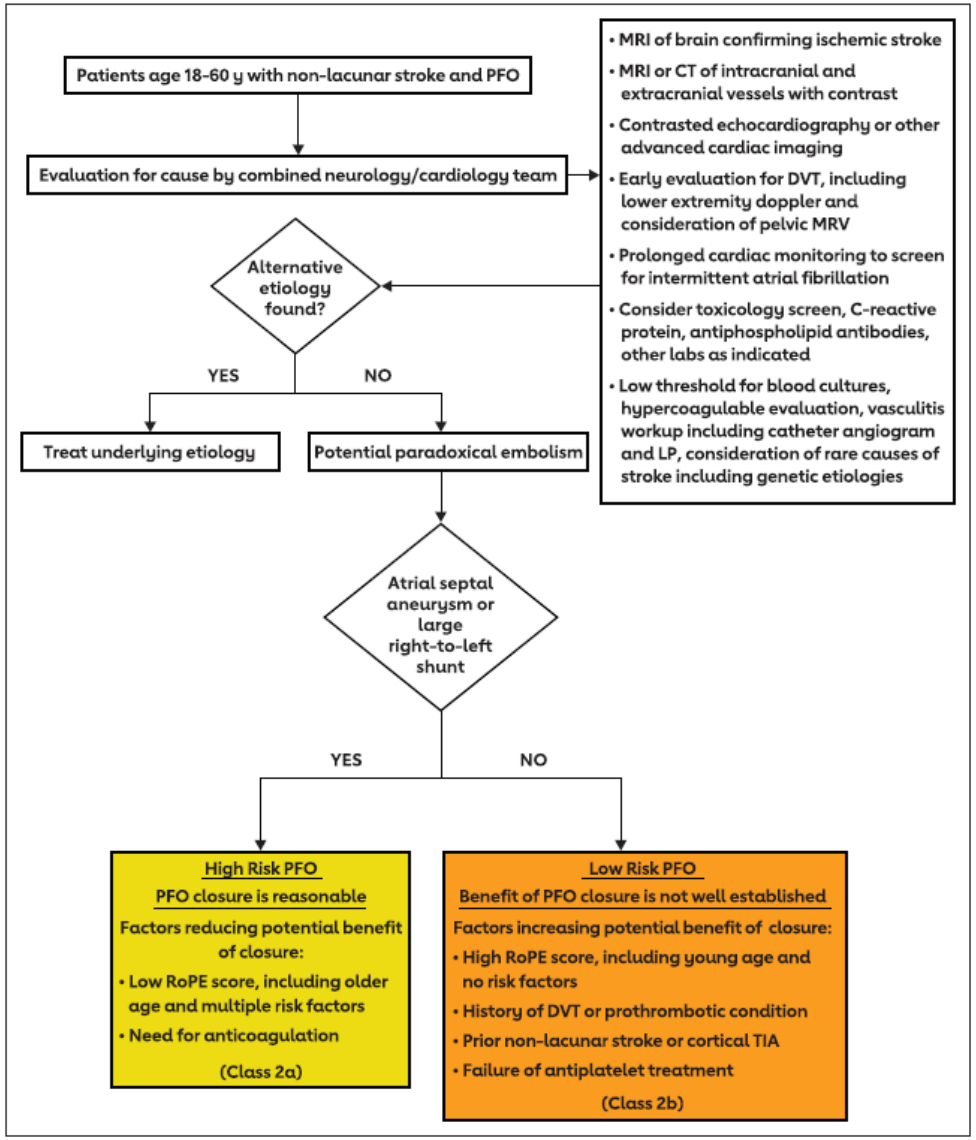


Figure 5. Patent foramen ovale (PFO) and ischemic stroke management guide.
Colors correspond to Class of Recommendation in Table 3. CT indicates computed tomography; DVT, deep vein thrombosis; LP, lumbar puncture; MRI, magnetic resonance imaging; MRV, magnetic resonance venography; RoPE, Risk of Paradoxical Embolism; and TIA, transient ischemic attack.

Takeaway 10: ESUS ≠ Anticoagulation

Recommendations for ESUS
Referenced studies that support recommendations are summarized in online Data Supplement 56.

COR	LOE	Recommendations
3: No Benefit	B-R	1. In patients with ESUS, treatment with direct oral anticoagulants is not recommended to reduce risk of secondary stroke.[779,780]
3: No Benefit	B-NR	2. In patients with ESUS, treatment with ticagrelor is not recommended to reduce the risk of secondary stroke.[781]

- ESUS is a nonlacunar stroke in which a minimum standard evaluation has been performed (arterial imaging, extended cardiac monitoring, echocardiogram lab risk factor evaluation) with no identified cause
- **NAVIGATE ESUS** study and **RESPECT ESUS** found no reduced risk of secondary stroke in patients treated with DOACs
  - Subgroup analysis suggest that patients with left atrial diameter >4.6 cm may benefit from anticoagulation but those with PFO did not
- Subgroup analysis of patients in **SOCRATES** trial with ESUS did not find ticagrelor treatment reduced vascular event risk

Questions?

Sources

- Kleindorfer DO, Towfighi A, Chaturvedi S, et al. 2021 Guideline for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack: A Guideline From the American Heart Association/American Stroke Association [published correction appears in Stroke. 2021 Jul;52(7):e483-e484]. *Stroke*. 2021;52(7):e364-e467. doi:10.1161/STR.0000000000000375