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Stroke: Secondary prevention of ischemic events

A multifactorial approach is key to effective secondary stroke prevention. Here's how to individualize your plan for your at-risk patients.

PRACTICE RECOMMENDATIONS

❯ *Encourage lifestyle modifications, including smoking cessation, alcohol moderation, appropriate diet, and exercise to reduce the risk of recurrent stroke.* (A)

❯ *Optimize blood pressure control using an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker and a thiazide diuretic.* (A)

❯ *Only use beta-blockers if there is another indication for them.* (A)

Strength of recommendation (SOR)

(A) Good-quality patient-oriented evidence

(B) Inconsistent or limited-quality patient-oriented evidence

(C) Consensus, usual practice, opinion, disease-oriented evidence, case series

Patients who suffer a stroke rarely have just one vascular risk factor. Therefore, the approach to secondary stroke prevention must be multifactorial. In fact, it has been estimated that 80% of recurrent strokes could be prevented through the application of a comprehensive, multifactorial approach that includes lifestyle modification and optimal medical management.[1] Such an achievement would save millions of people from disability and functional decline, as well as millions of dollars in related medical costs.

The initial approach to patients with stroke is focused on stabilization and a rapid work-up to identify the most likely etiology. Common causes of stroke include large artery atherosclerosis, cardiac emboli, and small vessel disease; less common causes include dissection, aortic emboli, and non-atherosclerotic vascular disease. If a complete diagnostic work-up is unrevealing, the stroke is said to be cryptogenic. Determining the correct etiology of a stroke is paramount to preventing secondary stroke (**FIGURE**[2-13]).
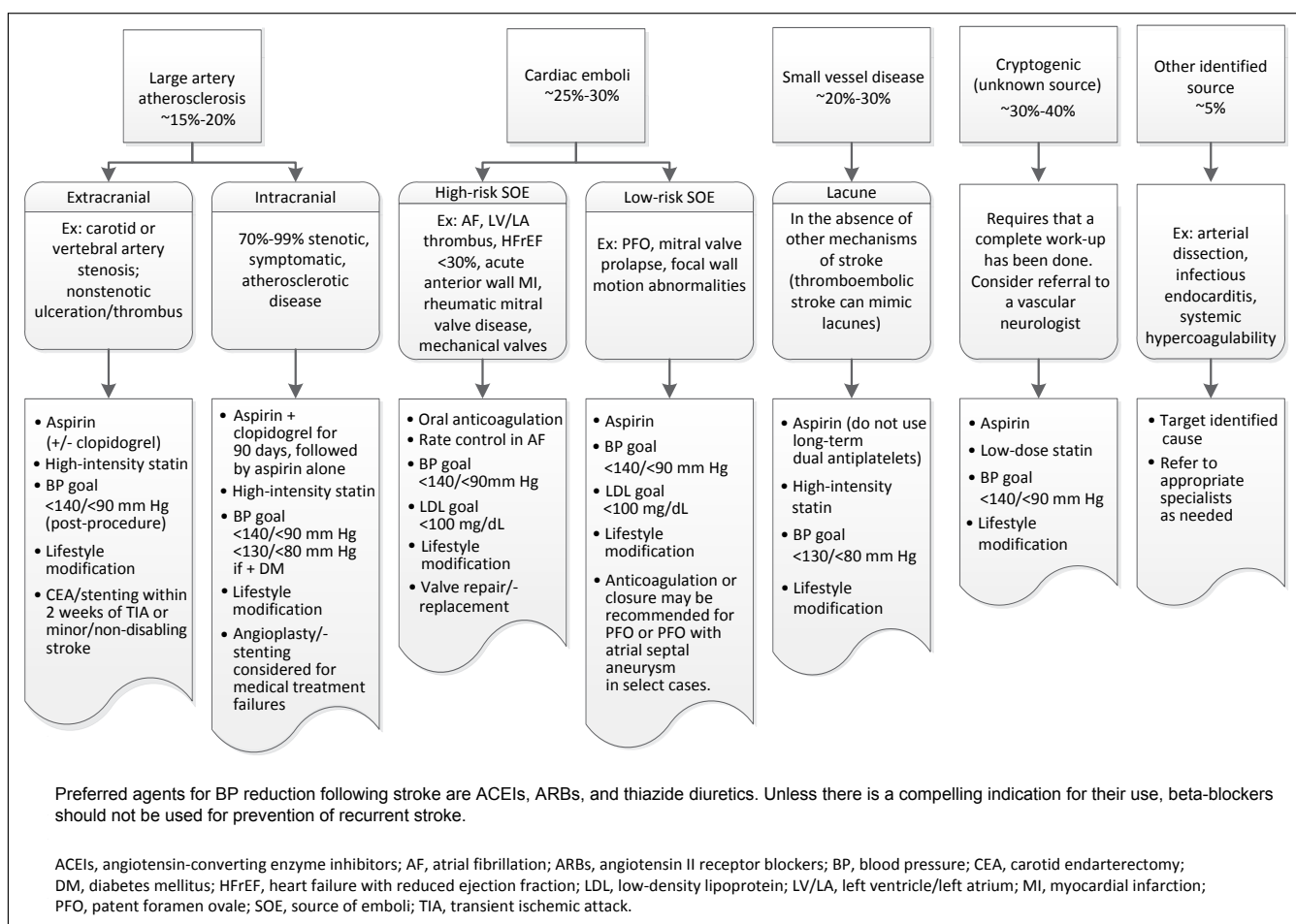
Effective secondary prevention strategies designed to prevent a stroke or transient ischemic attack (TIA) in a patient with a known history of either event include lifestyle modifications, medications, and when appropriate, mechanical interventions. As a primary care physician (PCP), you are uniquely positioned to spearhead the prevention of secondary strokes: Not only are you at the forefront of prevention and the use of techniques such as motivational interviewing, but you also have longstanding relationships with many of your patients. In fact, the success of many interventions is improved by the informed, enduring, and trusting nature of relationships between patients and their PCPs.

In the first part of this 2-part series, we focused on subacute stroke management and outlined the recommended work-up for subacute stroke/TIA (see "Stroke: A road map to

Secondary stroke prevention by stroke etiology[2-13]

Large artery atherosclerosis ~15%-20%

Extracranial

Ex: carotid or vertebral artery stenosis; nonstenotic ulceration/thrombus

- Aspirin (+/- clopidogrel)
- High-intensity statin
- BP goal <140/<90 mm Hg (post-procedure)
- Lifestyle modification
- CEA/stenting within 2 weeks of TIA or minor/non-disabling stroke

Intracranial

70%-99% stenotic, symptomatic, atherosclerotic disease

- Aspirin + clopidogrel for 90 days, followed by aspirin alone
- High-intensity statin
- BP goal <140/<90 mm Hg <130/<80 mm Hg if + DM
- Lifestyle modification
- Angioplasty/-stenting considered for medical treatment failures

Cardiac emboli ~25%-30%

High-risk SOE

Ex: AF, LV/LA thrombus, HFrEF <30%, acute anterior wall MI, rheumatic mitral valve disease, mechanical valves

- Oral anticoagulation
- Rate control in AF
- BP goal <140/<90mm Hg
- LDL goal <100 mg/dL
- Lifestyle modification
- Valve repair/-replacement

Low-risk SOE

Ex: PFO, mitral valve prolapse, focal wall motion abnormalities

- Aspirin
- BP goal <140/<90 mm Hg
- LDL goal <100 mg/dL
- Lifestyle modification
- Anticoagulation or closure may be recommended for PFO or PFO with atrial septal aneurysm in select cases.

Small vessel disease ~20%-30%

Lacune

In the absence of other mechanisms of stroke (thromboembolic stroke can mimic lacunes)

- Aspirin (do not use long-term dual antiplatelets)
- High-intensity statin
- BP goal <130/<80 mm Hg
- Lifestyle modification

Cryptogenic (unknown source) ~30%-40%

Requires that a complete work-up has been done. Consider referral to a vascular neurologist

- Aspirin
- Low-dose statin
- BP goal <140/<90 mm Hg
- Lifestyle modification

Other identified source ~5%

Ex: arterial dissection, infectious endocarditis, systemic hypercoagulability

- Target identified cause
- Refer to appropriate specialists as needed

Preferred agents for BP reduction following stroke are ACEIs, ARBs, and thiazide diuretics. Unless there is a compelling indication for their use, beta-blockers should not be used for prevention of recurrent stroke.

ACEIs, angiotensin-converting enzyme inhibitors; AF, atrial fibrillation; ARBs, angiotensin II receptor blockers; BP, blood pressure; CEA, carotid endarterectomy; DM, diabetes mellitus; HFrEF, heart failure with reduced ejection fraction; LDL, low-density lipoprotein; LV/LA, left ventricle/left atrium; MI, myocardial infarction; PFO, patent foramen ovale; SOE, source of emboli; TIA, transient ischemic attack.

subacute management," 2017;66:366-374). In this part, we focus on secondary prevention. The more common modifiable conditions encountered in primary care are discussed here, while many of the more rare etiologies (hypercoagulable states, sickle cell disease, and vasculitis) are outside the scope of this article.

Lifestyle interventions: Target tobacco use, obesity, alcohol intake

Lifestyle modifications can have a positive impact on many of America's most prevalent diseases, and stroke is no exception.[14] Many of the disease states identified as risk factors for stroke (type 2 diabetes, hypertension, dyslipidemia) are exacerbated by tobacco use, obesity, and excessive alcohol intake.

❚ **Does your patient smoke?** Up to 25% of all strokes are directly attributable to cigarette smoking.[15] Smoking raises an individual's risk for stroke in a dose-dependent fashion.[15,16] One study demonstrated that, compared to never-smokers, women ages 15 to 49 years who smoked a half-pack per day had an odds ratio for ischemic stroke of 2.2; those who smoked 2 packs per day had an odds ratio of 9.1.[17] After cessation, stroke risk generally returns to baseline within 5 years.[16] Thus, smoking cessation is among the most significant steps a patient can take to reduce the risk of both primary and secondary stroke.

❚ **Is your patient overweight?** While obesity in and of itself is a risk factor for stroke, a focus on nutrition and physical activity as mechanisms for weight loss is

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far superior to focusing on either element alone. Physical activity—consisting of at least 40 minutes of moderate intensity aerobic exercise 3 to 4 times per week—and a diet that emphasizes fruits and vegetables, whole grains, and healthy fats, have both independently demonstrated benefits in secondary stroke prevention and are important parts of American College of Cardiology (ACC)/American Heart Association (AHA) guidelines.[2,3]

The Mediterranean Diet, which emphasizes consumption of fruits and vegetables, legumes, tree nuts, olive oil, and lean protein, has long been associated with cardiovascular benefit.[18] One prospective, randomized, single-blinded trial involving approximately 600 patients that looked at secondary prevention of coronary heart disease found that following the diet significantly reduced mortality compared with a usual prudent post-infarct diet (number needed to treat [NNT]=30 over 4 years).[19]

▐ **Is alcohol consumption an issue?** Chronic heavy alcohol intake contributes to the development of hemorrhagic and ischemic stroke through multiple mechanisms, including alcohol-induced hypertension, alcoholic cardiomyopathy, and atrial fibrillation (AF). Light or moderate alcohol consumption has a paradoxical mild protective effect on ischemic stroke, thought to possibly be mediated by an increase in high-density lipoprotein (HDL) level and mild antiplatelet effect.[3]

AHA/American Stroke Association (ASA) guidelines indicate that no more than one standard drink per day for women and 2 drinks per day for men is reasonable.[3] Counsel patients who drink in excess of this about the benefits of decreasing alcohol intake or abstaining altogether.

Choosing medications to manage BP, cholesterol, and clotting

▐ **Optimize blood pressure control.** Blood pressure (BP) plays a critical role in both the management and prevention of stroke and is considered to be the most important modifiable risk factor in both primary and secondary stroke prevention.[20] In the first 24 to 48 hours following a cerebral ischemic event

that is not eligible for thrombolysis, permissive hypertension (treating BP only if it exceeds 220/120 mm Hg unless there is a concurrent medical illness that requires you do so) is appropriate, as hypotension or rapid fluctuations in BP can be harmful.[21]

This flexibility does not continue into the subacute phase of management (at a minimum, after the initial 48 hours) or into secondary prevention. Initiation and titration of oral agents to gradually achieve a BP <140/90 mm Hg or a reduction of 10/5 mm Hg for patients already within optimal range are the most widely recognized goals.[3,20] Patients with stroke secondary to small vessel disease may benefit from an even lower goal of <130/<80 mm Hg.[11] Encourage patients to monitor their BP at home for added accuracy and consistency.[22]

Pharmacologic BP management is appropriate for patients who are consistently above optimal range despite attempting recommended lifestyle modifications. The data are relatively consistent with respect to the effects of different drug classes after a stroke: beta-blockers have no effect on any outcome; thiazide diuretics significantly reduce stroke and total vascular events; angiotensin-converting enzyme (ACE) inhibitors significantly reduce myocardial infarction (MI); and the combination of an ACE inhibitor and thiazide diuretic reduces stroke, MI, and combined vascular events.[4]

This has led many stroke specialists to recommend the combination of an ACE inhibitor or angiotensin II receptor blocker (ARB) and a thiazide diuretic as a first-line approach to secondary stroke prevention rather than a beta-blocker (assuming there is no additional indication for a beta-blocker). Similarly, there is ample evidence to show that the magnitude of BP reduction is proportional to the reduction in recurrent vascular events.[3]

▐ **Make use of statin therapy—regardless of LDL.** The SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) trial[5] explored the potential role of statin medication for secondary stroke prevention. Researchers randomly assigned almost 5000 participants who'd had a stroke or TIA one to 6 months before study entry (but had

no known history of coronary artery disease) to placebo or a high-intensity statin (80 mg/d atorvastatin). The statin group demonstrated a 4.9-year absolute risk reduction in fatal or nonfatal recurrent stroke of 1.9% (NNT=53).

Given these findings and those from other studies, the AHA and ASA recommend treating patients with stroke or TIA presumed to be of atherosclerotic origin with high-intensity statin therapy, regardless of low-density lipoprotein (LDL) level.[3] Of note, statins are not indicated for the secondary prevention of hemorrhagic stroke.

❚ **Select antiplatelet therapy based on ischemic stroke subtype.** Investigators are still trying to determine the optimal antiplatelet for secondary stroke prevention; it is likely that the ideal choice depends largely on the etiology of the stroke. Trials that did not select patients based on subtype of ischemic stroke have not shown a long-term benefit from dual antiplatelet therapy (clopidogrel and aspirin),[23,24] and one double-blind, multicenter trial involving more than 3000 patients with recent stroke secondary to small vessel disease demonstrated harm from such therapy in terms of a significantly increased risk of bleeding and death.[6]

However, a 2011 study compared aggressive medical management (aspirin 325 mg/d plus clopidogrel 75 mg/d for 90 days) alone to aggressive medical management plus percutaneous transluminal angioplasty and stenting (PTAS). The study involved almost 500 patients who'd had a recent TIA or stroke attributed to intracranial atherosclerotic stenosis. The authors found that the 30-day rate of stroke or death was 14.7% in the PTAS group vs 5.8% in the medical management group.[25]

Similarly, a randomized double-blind, placebo-controlled trial published in 2013 involving over 5000 patients in China found that short-term use of dual antiplatelets (clopidogrel and aspirin for the first 21 days after an ischemic event, followed by aspirin monotherapy for 90 days) had an absolute risk reduction of 3.5% without increasing the risk of major bleeding in patients with high-risk TIA or minor stroke.[26]

All stroke patients who do not have an indication for oral anticoagulation should be placed on long-term daily aspirin (75-325 mg); research has shown that lower doses are as effective as higher doses but with a lower risk of adverse gastrointestinal effects, including bleeding.[3,20] Aspirin 81 mg/d is a common effective dose.

For patients who cannot tolerate aspirin due to allergy, clopidogrel 75 mg/d is a reasonable alternative. Long-term studies of aspirin vs clopidogrel[7] and clopidogrel vs extended-release dipyridamole[8] showed no difference in secondary stroke prevention. The International Stroke Trial[27] and Chinese Acute Stroke Trial[28] both indicate that aspirin should be started as soon as possible after the onset of an acute stroke.

❚ **This special population should probably get antiplatelets, too.** One recent study explored the use of an antiplatelet vs anticoagulation therapy for stroke patients with carotid artery dissection. The CADISS (Cervical Artery Dissection in Stroke Study) trial[29] randomized 250 patients with extracranial carotid and vertebral artery dissection with onset of symptoms within the previous 7 days to either antiplatelet or anticoagulation therapy and found no difference in the primary outcomes of recurrent stroke or death. The study also demonstrated a low risk of recurrent stroke in this population, which was 2% at 3-month follow-up.

Most patients with cervical artery dissection, therefore, are now treated with antiplatelet therapy. That said, situations may still arise in which anticoagulation can be considered, and consultation with a neurologist for guidance on choice of therapy is recommended.

Is an anticoagulant in order? Which agent, when

❚ **The most common cause of cardioembolic stroke is AF,** which accounts for at least 15% of ischemic strokes, a number that rises in those over the age of 80.[20,30,31] A meta-analysis of more than 28,000 patients with non-valvular AF demonstrated that warfarin reduced the risk of stroke by 64%.[32]

The rate of intracerebral hemorrhages during oral anticoagulation ranges from 0.3% to 0.6% per year.[33] The risk of bleeding complications can be mitigated by keeping

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international normalized ratios ≤3.0, maintaining good BP control, and avoiding concurrent use of antiplatelets in the absence of a clear indication for them.[33]

❚ **Several risk assessment scores,** such as the HAS-BLED,[34] can help with estimating the risk of hemorrhagic complications, although these scores have their limitations.[35,36] Even in an older population (mean age 83 years) with a high risk for falls, warfarin provided a net benefit in a composite endpoint of out-of-hospital death or hospitalization for stroke, MI, or hemorrhage in a retrospective study of over 1200 Medicare beneficiaries.[37]

❚ **AF is not the only cause of cardioembolic stroke to consider.** Additional high-risk factors warranting anticoagulation include rheumatic mitral valve disease, the presence of mechanical aortic or mitral valves, known mural thrombus, and acute anterior ST segment elevation myocardial infarctions (STEMIs) with resulting anterior apical dyskinesis/akinesis and concurrent ischemic stroke/TIA.[3] (The specific management of each of these situations is beyond the scope of this paper.)

❚ **The choice of anticoagulation agent** is based on multiple factors, including cost, risk of non-reversible bleeding, drug interactions, renal function, and patient preference. Approved options currently include warfarin/vitamin K antagonist therapy, apixaban, rivaroxaban, dabigatran and edoxaban.[3] Choice of therapy will continue to evolve as reversal agents, such as idarucizumab, are developed. Idarucizumab, a reversal agent for dabigatran, received approval from the US Food and Drug Administration in October 2015.[38]

❚ **When to start anticoagulation.** There are limited data regarding the optimal timing of initiation of anticoagulation following a stroke; however, a recent multicenter prospective study supported the common practice of initiating anticoagulation therapy within 4 to 14 days of the event.[39] Individual patient factors must be taken into consideration, including the size of the stroke (the larger the stroke, the higher the risk for hemorrhagic transformation), BP control, any additional risk factors for bleeding, and the estimated risk of early recurrent stroke.

Bridging patients onto anticoagulation with unfractionated or low-molecular-weight heparin in the setting of acute stroke is not recommended.[40] Results from randomized controlled trials involving unfractionated heparin, heparinoids, and low-molecular-weight heparin have not reported any benefit to these agents over aspirin at preventing early stroke recurrence.[27,41,42]

❚ **For immobile or hospitalized patients.** Subcutaneous heparin for the prevention of deep vein thrombosis (DVT) during immobility and hospitalization is recommended.[43] Patients who cannot tolerate anticoagulation should be maintained on low-dose antiplatelet therapy. Experts do not recommend dual treatment with aspirin and anticoagulation in most cases. However, recent coronary artery stent placement does require temporary dual treatment, with duration dependent on the type of stent placed.

A role for glycemic control? Still to be determined

The specific role of diabetic management in secondary stroke prevention remains unclear. The 2008 ACCORD trial,[44] a randomized study involving over 10,000 patients with a median glycated hemoglobin level of 8.1%, investigated intensive hyperglycemic control (targeting a glycated hemoglobin level <6.0% vs <7.9%) as a means of decreasing cardiovascular risk. However, the trial ended 17 months early because of an increase in all-cause mortality in the intensive treatment arm compared with the standard management group. The same trial was also unable to demonstrate a decrease in stroke risk with a decrease in A1c.[44]

❚ **More recently,** the IRIS (Insulin Resistance Intervention after Stroke) trial[45] (2016) found a 2.8% absolute risk reduction in stroke or MI among participants who had a stroke or TIA in the previous 6 months who were treated with pioglitazone vs placebo over 4.8 years (NNT=36). Participants were required to have insulin resistance, but were excluded if they had diabetes. The authors did, however, report a notable increase in the risk of bone fractures requiring surgery or hospitalization in the pioglitazone arm

> **All ischemic stroke patients who do not have an indication for oral anticoagulation should be placed on long-term daily aspirin.**

(5.1% vs 3.2%; number needed to harm [NNH]=53).

The impact this single study should have on standard secondary prevention is not yet clear. The authors concluded, "It seems reasonable to consider individual treatment preference and risk of drug-related adverse events in addition to potential benefits when making patient-specific decisions regarding therapy."[45]

Determining whether mechanical interventions are needed

Almost all conditions leading to stroke warrant active medical management, but a few benefit from procedural intervention, as well.

❚ **Extracranial carotid atherosclerosis.** Carotid endarterectomy or carotid artery stenting is recommended as secondary prevention for patients with a history of stroke or TIA who have ipsilateral high-grade extracranial carotid stenosis of 70% to 99% and, in some cases, 50% to 69%.[3,9,20] In patients with mild non-disabling stroke, the optimal timing for these procedures is within 2 weeks of the ischemic event. A delay of 6 weeks is generally preferred for moderate or larger strokes to allow for some healing of the injured brain.

The choice of procedure is based on risk profile, with the most important factor being age. For patients >70 years, endarterectomy is preferred because stenting is associated with an increased risk of stroke.[3,9,10] Experts do not recommend either procedure for patients who have had a severe disabling stroke. Generally speaking, these procedures have higher rates of success when they are performed in centers that perform a higher number of these procedures.[10]

❚ **Vertebrobasilar atherosclerosis.** Due to generally good compensatory blood flow of the contralateral vertebral artery in the setting of vertebral artery stenosis, and an unacceptably high complication rate of angioplasty and stenting in the basilar artery, medical management is typically the first-line approach. If a patient has recurrent symptoms in the setting of optimal medical management and a focal lesion that is amenable to an endovascular intervention (most commonly a vertebral artery origin high-grade stenosis), angioplasty and stenting may be considered.[10]

❚ **Intracranial atherosclerosis.** Similarly, medical management is the preferred strategy for intracranial atherosclerosis. Angioplasty and/or stenting are reserved for complex cases or recurrence despite adherence to secondary stroke prevention measures. Ideally, these patients should be managed with long-term aspirin 81 mg/d, adjunctive clopidogrel 75 mg/d for 90 days post stroke, a high-intensity statin, BP optimization, and any relevant lifestyle interventions.[13]

❚ **Patent foramen ovale.** Research to date has not shown that closure of a patent foramen ovale (PFO) is superior to medical therapy for secondary stroke prevention in patients <60 years with cryptogenic stroke.[12,46,47] The decision to anticoagulate these patients should be based on the presence or absence of a DVT and not on a PFO alone. In patients with an identified DVT and a contraindication to oral anticoagulation, inferior vena cava filter placement should be considered. For patients with ongoing prothrombotic risk thought to increase the chances of future paradoxical embolism, closure of the PFO may be considered.   JFP

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> **Treat patients with stroke or TIA presumed to be of atherosclerotic origin with high-intensity statin therapy, regardless of low-density lipoprotein level.**

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