Antithrombotic selection and risk factor management in ischemic stroke and transient ischemic attack

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In addition to appropriate antithrombotic therapy, the identification and treatment of modifiable ischemic stroke risk factors can reduce the likelihood of recurrent stroke. Neurosurgeons should be knowledgeable of the specific risk factors and general recommendations for ischemic stroke, as they may play a significant role in the management options for patients with intracranial and extracranial atherosclerotic disease. The authors of this article review the indications for and selection of antithrombotics in patients with cerebral ischemia. In addition, the identification and secondary prevention of select risk factors are discussed.
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STROKE is the fourth leading cause of death in the United States and is a leading cause of disability. In addition to selecting the appropriate antithrombotic, the identification and treatment of modifiable stroke risk factors can reduce the likelihood of first or recurrent stroke, prevent long-term morbidity and mortality after the first stroke or transient ischemia attack (TIA), and lower health care costs.^{19,49,60,65} While preventing recurrent cerebral ischemia is the obvious target of secondary stroke prevention, additional goals include averting other vascular disease (for example, myocardial infarction) and identifying and heading off other medical complications of cerebral ischemia (for example, depression, infection, deep vein thrombosis).

The focus of this paper is the secondary prevention of ischemic stroke or TIA. A broad overview of the indication for and selection of antithrombotics is provided. In addition, common ischemic stroke risk factors and the impact of each factor, how to diagnose it, and management for secondary prevention are reviewed. We conclude with practical information for assessing and treating risk factors.

Abbreviations used in this paper: AHA = American Heart Association; A1C = glycated hemoglobin; CPAP = continuous positive airway pressure; HDL = high-density lipoprotein; INR = international normalized ratio; LDL = low-density lipoprotein; OSA = obstructive sleep apnea; PSG = polysomnography; TIA = transient ischemic attack.

Applicability to Neurosurgery

Neurologists and/or internists typically manage risk factors associated with cerebral ischemia. However, a practicing neurosurgeon can benefit from a broad understanding of cerebrovascular risk factors and antithrombotic indications for several reasons. Patients with carotid artery disease, for instance, may be hospitalized solely on a neurosurgical service; thus, knowledge of the proper treatment of this patient beyond daily aspirin can be useful. Another example would be a neurosurgeon consulted on a patient with intracranial atherosclerosis. Endovascular treatment may be indicated when patients are “maximally” medically treated. Knowledge of what this means beyond antithrombotics may help the neurosurgeon decide whether further medical management or endovascular treatment is indicated. Finally, many patients undergoing neurosurgical procedures have cerebrovascular disease, and knowledge of the risk factors may help in the general management of these patients to help minimize perioperative ischemic stroke.

Indications for and Selection of Antithrombotics

Indications

Antithrombotics are indicated in most cerebral ischemic mechanisms or etiologies. The important distinction is whether the mechanism of cerebral ischemia requires an

antiplatelet agent or an anticoagulant (Table 1). Antiplatelet agents are indicated in most noncardioembolic etiologies of cerebral ischemia. Anticoagulants are indicated in patients with cerebral ischemia and one of the following cardioembolic etiologies: atrial fibrillation, left ventricular or left atrial thrombus, mechanical heart valve, and recent anterior wall myocardial infarction with left ventricular thrombus. Anticoagulation is also recommended in phospholipid antibody syndrome,⁵⁴ although it is not indicated for antiplatelet agent failure.^{47,88,122}

There are limited data regarding the most appropriate antithrombotic in patients with an extracranial arterial dissection and cerebral ischemia. Current American Heart Association (AHA) guidelines for the secondary prevention of ischemic stroke and TIA⁵⁴ suggest that an antiplatelet or anticoagulant agent is acceptable treatment. Similarly, there are conflicting data regarding the use of an antiplatelet agent or anticoagulation in patients with cardiomyopathy;⁵⁴ however, a recent substudy of the Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction trial¹⁰³ observed less cardioembolic ischemic stroke in the warfarin arm compared with the aspirin arm. The overall stroke rate, including all mechanisms of cerebral ischemia between the two groups, was not statistically significant.

Antiplatelet Agents

Antiplatelet agent choices for cerebral ischemia include aspirin (50–325 mg daily), clopidogrel (75 mg daily), or the combination of extended-release dipyridamole (200 mg) and aspirin (25 mg) twice daily. According to multiple clinical trials and the AHA guidelines, any of these three options is considered appropriate monotherapy for cerebral ischemia (Table 2).⁵⁴ Based on the second Cilostazol Stroke Prevention Study (CSPS 2),¹¹⁹ cilostazol may be a reasonable alternative as well, as it was noninferior to aspirin.

In clinical practice, the selection of an antiplatelet agent depends on multiple factors: cost, compliance (once- vs twice-daily dosing), side effects, interactions (for example, proton pump inhibitors and clopidogrel), and comorbidities. While no trial has studied only patients in whom aspirin has failed, it is common clinical practice to choose an alternative and/or to maximize risk factor treatment.

Prasugrel is contraindicated in cerebral ischemia. In a recent coronary artery disease trial, prasugrel was associated with a higher bleeding risk, especially in patients with prior cerebrovascular disease.¹³⁵ There are limited

efficacy and safety data on cerebral ischemia patients taking the newer antiplatelet agents such as the direct P2Y₁₂ antagonists (ticagrelor and elinogrel) and the protease-activated receptor antagonists (vorapaxar and atopaxar). There are limited data on the thromboxane receptor antagonists (terutroban and picotamide); however, they appear to be equivalent to aspirin at this time.

Combination of Aspirin and Clopidogrel

In general, the combination of aspirin and clopidogrel in the long term has not proven more efficacious than monotherapy in patients with cerebral ischemia,^{12,14,42} and the combination is not recommended unless there is another indication such as a carotid or coronary stent.⁵⁴ However, there are evolving data regarding the potential short-term benefit of the combination.

The Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis (CARESS)⁸⁶ study randomized patients with recently symptomatic carotid artery stenosis to aspirin and clopidogrel versus aspirin monotherapy. The results demonstrated a significant reduction in asymptomatic microembolic signals on transcranial Doppler ultrasonography in patients on the combination therapy versus aspirin alone. While the study was not powered to look at clinical outcomes, the rate of recurrent stroke was lower with combination therapy than with aspirin alone.

While the Stenting vs. Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) study was not designed to specifically assess medical management strategies,²⁶ the lower than expected risk of recurrent cerebral ischemia in the medical arm compared with that in the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID)²⁷ study was attributed in part to the antithrombotics and close attention to risk factor management in the SAMMPRIS study.

Recently the Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE)¹³⁰ study demonstrated that the combination of clopidogrel and aspirin was superior to aspirin alone for reducing stroke risk at 90 days in patients with TIA or minor stroke treated within 24 hours of symptom onset. The combination therapy was used for the first 21 days, followed by clopidogrel alone for the remaining 90-day period, which did not result in excess hemorrhage.

At present, no guidelines indicate when and in what patients the short-term combination of aspirin and clopidogrel should be used. Additional data from the Plate-

TABLE 1: Selection of antithrombotics by etiology of cerebral ischemia

Antiplatelet Agent*	Anticoagulant	Conflicting or Absent Data†
carotid artery atherosclerosis	atrial fibrillation	arterial dissection
intracranial atherosclerosis	mechanical heart valve	cardiomyopathy
lacunar disease	anterior wall myocardial infarction w/ left ventricular thrombus	
cryptogenic stroke	phospholipid antibody syndrome	

* Most noncardioembolic strokes require an antiplatelet agent. An exhaustive list of all causes in this table was not possible.

† Current guidelines suggest that either an antiplatelet agent or anticoagulation is acceptable therapy. Data are either lacking or conflicting in these areas.

Risk factor management

TABLE 2: Selected antiplatelet agent trials for the secondary prevention of cerebral ischemia*

Clinical Trial†	Agent Assessed	Primary End Point	Results
Antiplatelet Trialists' Collaborative ⁷	aspirin (30–1600 mg daily) versus placebo	stroke, myocardial infarction, or vascular death	for stroke patients, aspirin reduced risk of stroke by 4% (18% aspirin vs 22% control; 2p <0.00001)
CAPRIE ²⁵	aspirin (325mg) versus clopidogrel (75 mg daily)	stroke, myocardial infarction, or vascular death	in overall group (myocardial infarction, peripheral vascular disease, stroke), the risk of vascular outcomes was 5.83% w/ aspirin versus 5.32% w/ clopidogrel (p = 0.043)
ESPS-2 ⁴³	placebo versus aspirin (25 mg BID) versus extended-release dipyridamole (200 mg BID) versus aspirin (25 mg) & extended-release dipyridamole (200 mg) BID	stroke or death	combination of dipyridamole & aspirin resulted in 9.5% recurrent stroke versus 12.4% in the aspirin-alone group (p = 0.006)
PRoFESS ¹¹³	clopidogrel (75 mg daily) versus extended-release dipyridamole (200 mg) & aspirin (25 mg) BID	first recurrence of stroke	no significant difference in first recurrence of stroke (9.0% aspirin-dipyridamole combination vs 8.8% clopidogrel)

* BID = twice a day; CAPRIE = clopidogrel versus aspirin in patients at risk of ischaemic events; ESPS-2 = European Stroke Prevention Study 2; PRoFESS = Prevention Regimen For Effectively Avoiding Second Strokes.

† Superscripted numbers represent reference numbers.

let Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) trial is expected to help further elucidate selection.

Anticoagulation

Data from numerous clinical trials support the use of warfarin (goal INR 2–3) over an antiplatelet agent (aspirin or the combination of aspirin and clopidogrel) in patients with atrial fibrillation.⁵⁴ Emerging options for nonvalvular atrial fibrillation include novel anticoagulants such as dabigatran, rivaroxaban, and apixaban. These agents are described in more detail below under *Atrial Fibrillation*.

Overview of Ischemic Stroke Risk Factors

A number of definitive and putative risk factors predict the first ischemic stroke (Table 3). The most common major risk factors include hypertension, hyperlipidemia, tobacco use, and diabetes. Overall target goals for the secondary prevention of these major risk factors are noted in Table 4 and reviewed in more detail below.

Hypertension

Risk. High blood pressure is a risk factor for ischemic stroke as well as intracerebral hemorrhage, subarachnoid hemorrhage, and aneurysm formation. The risk of vascular complications and death begins to rise when blood pressure exceeds 115/75 mm Hg.⁷⁹ Elevated blood pressure may contribute to cerebral ischemia through its effects on small and large blood vessels (lipohyalinosis and atherosclerosis) and by contributing to cardiac disease and dysfunction.

The incidence of stroke increases in proportion to both diastolic and systolic blood pressure. It is important to recognize, however, that elevated systolic blood pressure with or without elevated diastolic blood pressure is a risk factor. The relationship between blood pressure and

risk of ischemic events (stroke and myocardial infarction) is continuous and independent of other risk factors. For each increment of 20 mm Hg in systolic or 10 mm Hg in diastolic blood pressure, the risk of cardiovascular disease doubles over the entire range from 115/75 to 185/115 mm Hg in patients aged 40–70 years.²⁸

Diagnosis. Blood pressure in the acute setting after ischemic stroke or TIA is almost always elevated.¹ While there is no definitively established time frame in which to treat blood pressure more aggressively,^{1,94} we typically wait at least 2–4 weeks after an ischemic event, a time frame consistent with many long-term secondary prevention trials and improvement in the impaired autoregulatory curve.

Once a patient is beyond the acute phase, blood pressure can be assessed and, if elevated, gradually lowered toward goal. Blood pressure can be measured in the office, at home, or via ambulatory monitoring. The latter method of monitoring can be useful in patients with “white coat hypertension,” blood pressure resistant to treatment, or episodic hypotension. If one bases the reading on an office reading, blood pressure should be mea-

TABLE 3: Risk factors for first ischemic stroke

Definitive	Putative
hypertension	impaired fasting glucose
dyslipidemia	metabolic syndrome
diabetes	alcohol abuse
tobacco smoking	drug abuse
asymptomatic carotid disease	hypercoagulability
atrial fibrillation	inflammatory processes
obesity	obstructive sleep apnea
physical inactivity	
hormone replacement therapy & oral contraceptive use	
sickle cell anemia	

TABLE 4: Secondary prevention goals for major risk factors*

Risk Factor	Goal	ARR w/ Treatment	RRR w/ Treatment†
hypertension	<140/90 mm Hg	w/ reduction by 12/5 mm Hg 6%	43% ¹⁰¹
hyperlipidemia	LDL <70 mg/dl‡	2.2% cerebrovascular (SPARCL trial§), 3.5% cardiovascular	16% cerebrovascular, 18% cardiovascular ³
blood sugar	<100 mg/dl (fasting)	—	—
diabetes	A1C <7%¶	—	—
tobacco	cessation	—	50% ¹³² ¶

* ARR = absolute risk reduction; LDL = low-density lipoprotein; RRR = relative risk reduction; SPARCL = Stroke Prevention by Aggressive Reduction in Cholesterol Levels.

† Superscripted numbers represent reference numbers.

‡ In those with cerebral ischemia and atherosclerosis or coronary artery disease or coronary artery disease “equivalent.”

§ SPARCL used a fixed dose of 80 mg of atorvastatin rather than an LDL goal.

¶ Primary prevention study.

sured at least twice, with 2 minutes between each reading and a proper technique (appropriate cuff size, positioning, cuff placement, and setting). An average blood pressure greater than 140/90 mm Hg is considered elevated.^{28,54} Some recent studies have suggested that interindividual variation (visit to visit variation) may be more important than the average blood pressure.^{110,133}

Treatment. Before treating blood pressure in a patient who has had cerebral ischemia, several precautions are in order. Blood pressure in the acute setting is often elevated in response to preserve collateral flow to the penumbra. Thus, as noted above, in secondary prevention, blood pressure is assessed and gradually lowered toward goal beginning at least 2–4 weeks after the event. Prior to aggressive treatment, one must be careful about applying a “one size fits all” blood pressure goal. For example, a patient with critical intracranial stenosis may need higher than normal blood pressure if he or she is prone to recurrent episodes of hypoperfusion. A final note: some patients may have secondary causes of elevated blood pressure and require treatment of the underlying condition rather than the increased blood pressure. For example, nonsteroidal antiinflammatory medications are commonly prescribed medications and can elevate blood pressure. In addition, unrecognized sleep apnea can make blood pressure resistant to treatment. Other secondary causes of elevated blood pressure are noted in Table 5.

An essential tactic for treating hypertension is lifestyle modification, which may include weight control; a diet rich in fruits, vegetables, and low-fat dairy products; regular aerobic physical activity; limited alcohol consumption; and moderation in sodium intake.^{20,54}

Several trials have strongly indicated that long-term treatment of hypertension reduces the relative risk of either initial or recurrent stroke.^{39,99,101,128,140,142} Clinical trials have evaluated diuretics,^{2,39,99,101} beta blockers,^{103,133} angiotensin-converting enzyme inhibitors,^{82,101,141} angiotensin receptor blockers,^{39,140} and calcium channel blockers^{70,110} in stroke prevention. The evidence is conflicting, making no compelling case for one agent over others for secondary stroke prevention. The one exception may be beta blockers, which may not reduce stroke recurrence as well

as calcium channel blockers, angiotensin inhibitors, and even placebo in some trials.^{10,11,61,133,136}

What we can conclude from multiple clinical trials is that the lowering of blood pressure, not individual classes of medication, is beneficial. In secondary prevention trials, a reduction in blood pressure by 12/5 mm Hg was associated with a relative risk reduction of approximately 43%.¹⁰¹ Medications should be selected based on patient comorbidities, preferences, and tolerances.⁵⁴

The goal blood pressure has not been definitively established in clinical trials. Current AHA guidelines for the secondary prevention of ischemic stroke recommend following “The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure” (JNC7) guideline of a goal blood pressure < 140/90 mm Hg. While those same guidelines also recommend a goal blood pressure < 130/80 mm Hg in patients with diabetes and chronic kidney disease, studies published after the JNC7 guidelines argued against as much.^{6,35,38,123} In addition, guidelines for treatment in the elderly warn about overtreatment,⁸ and the Secondary Prevention of Small Subcortical Strokes (SPS3) study showed no significant differences in recur-

TABLE 5: Secondary causes of elevated blood pressure

Category	Cause
medications/drugs	oral contraceptives
	nonsteroidal antiinflammatory drugs
	sympathomimetics
endocrinological	alcohol use
	pheochromocytoma
	Cushing's syndrome
	primary aldosteronism
	hypothyroidism
renal disease	hyperparathyroidism
	renovascular disease
	chronic kidney disease
other	OSA
	coarctation of the aorta

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rent stroke rates in patients with lacunar stroke who had been treated to a goal systolic blood pressure < 130 mm Hg versus those treated to a rate of 130–149 mm Hg.¹³ Thus, guidelines regarding blood pressure targets may change, and we use a more conservative goal of < 140/90 mm Hg for most patients with a history of cerebral ischemia. The eighth report of the Joint National Committee guideline is eagerly anticipated in the near future.

Hyperlipidemia

Risk. Several clinical trials and epidemiological studies have not consistently found dyslipidemia to be a strong risk factor for stroke.^{45,100,102} However, these studies did not separate stroke types (hemorrhagic vs ischemic) or subtypes (lacunar, large vessel, cardioembolic, other), thus diminishing the ability to find an association.³

Some studies, including a meta-analysis of solely prospective studies on hypercholesterolemia, have shown an increased risk of stroke with high total cholesterol, high low-density lipoprotein (LDL), high non-high-density lipoprotein (HDL) cholesterol, and low HDL.^{21,41,78,104,112} The strongest association between cholesterol and stroke is with the carotid artery subtype of ischemic stroke and lacunar stroke subtypes.^{50,96,126} As regards hypertriglyceridemia, some^{52,126} but not all^{63,118} prospective epidemiological studies have suggested that hypertriglyceridemia is a moderate risk factor for ischemic stroke.

Diagnosis. A fasting lipid panel is recommended on all patients presenting with ischemic stroke or TIA. In some instances in which triglycerides are elevated, LDL cannot be calculated and the non-HDL cholesterol becomes a surrogate marker.

Treatment. Data from clinical trials in patients with known coronary artery disease have revealed relative risk reductions of first stroke between 20% and 31% over 4–5 years with statin lipid-lowering agents.^{32,81,134} Studies assessing carotid artery disease progression have reported a decrease in progression or actual regression of plaque with the use of statin medications.^{37,53,68,114,134}

In patients with hyperlipidemia, LDL lowering by other means (diet, ezetimibe, fibrate) has either no or minimal impact on the primary prevention of stroke.^{21,36} Therefore, it seems plausible that there are additional benefits from statins beyond lipid lowering, including plaque stabilization, reduced inflammation, slowing of carotid arterial disease progression, improved endothelial function, and reduced embolic stroke by preventing myocardial infarction and left ventricular dysfunction.⁵

Only 2 randomized, clinical trials have aimed at secondary prevention in stroke patients alone: a subgroup of the Heart Protection study³¹ and the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial.⁴ The latter trial included noncardioembolic ischemic stroke in addition to a minority of intracerebral hemorrhage cases with other vascular risk factors. Patients were randomized to 80 mg of atorvastatin versus placebo. After a median of 4.9 years, there was a 2.2% absolute risk reduction in recurrent stroke and a 3.5% reduction in coronary events (HR 0.65, 95% CI 0.49–0.87).⁴

Guidelines for the use of statins in the setting of stroke are slightly complex and controversial.^{89,117} While some believe a statin should be used in all patients with cerebral ischemia regardless of its mechanism,⁸⁹ others (including us) believe that selected use in patients in whom the mechanism is probably atherosclerotic makes more sense. The most recent AHA guidelines⁵⁴ suggest that patients with elevated cholesterol, cerebral ischemia, and comorbid coronary artery disease or equivalent should be treated with a statin, aiming for a goal LDL < 70 mg/dl. In patients without coronary artery disease and evidence of atherosclerosis, statin therapy with a goal LDL < 70 mg/dl or a 50% reduction in LDL is recommended. We typically treat large-vessel atherosclerosis, small-vessel disease, and cryptogenic stroke in those over 55 years of age. Patients with a nonatherosclerotic stroke mechanism should be treated according to the National Cholesterol Education Panel (NCEP) III guidelines.⁴⁸ The primary prevention goal in those with a cardiac risk < 20% over 10 years is 130 mg/dl (<http://cvdrisk.nhlbi.nih.gov>).

The risks and benefits of statins must be weighed carefully. Adverse effects can include myopathy, cognitive issues (rarely), liver dysfunction, and the possibility of an increased risk of diabetes at high doses.

Many things remain unknown about the utility of statins in the setting of cerebral ischemia. While the 2 clinical trials mentioned above used a fixed dose of a statin, the guidelines suggest a target LDL goal based mainly on cardiac studies. Thus, it remains unclear if a certain target LDL is more beneficial in stroke patients. Another issue is that many stroke patients are in their 80s and 90s, whereas the average age in the SPARCL trial was 63 years. The utility and efficacy of statins in the very elderly is not clear. Unlike in cardiac disease,^{22,116} there are no acute statin trials in ischemic stroke or carotid artery disease. Retrospective and observational studies suggest a potential protective benefit in those receiving statins early or those already taking them.^{24,93} Finally, it remains unclear whether targeting HDL or triglycerides has an impact on the secondary prevention of ischemic stroke.^{16,57} Recent cardiac studies^{16,66} have raised doubts on the pharmacological modification of HDL in improving vascular outcomes. However, one study suggested that adding extended-release niacin to statins may reduce carotid intima thickness,¹²⁴ although this was a primary prevention study.

Diabetes

Risk. Patients with diabetes mellitus have an increased risk of ischemic stroke, recurrence of ischemic stroke/TIA,⁵⁰ and death from ischemic stroke⁵⁹ as compared with those without diabetes mellitus. Diabetic patients have both an increased susceptibility to atherosclerosis and an increased prevalence of atherogenic risk factors, notably hypertension, hyperlipidemia, and obesity. Diabetes mellitus increases the risk of macrovascular and microvascular disease. In patients with diabetes, there is an increased prevalence of atherogenic risk factors, including hypertension, hyperlipidemia, and obesity. Some theorize that dyslipidemia, endothelial dysfunction, and platelet and

coagulation abnormalities are among the risk factors that promote the development of carotid atherosclerosis in patients with diabetes.

According to case-control and prospective epidemiological studies, the presence of diabetes translates into a 2- to 6-fold increase in the risk for stroke.^{59,71} Recently, the duration of diabetes was found to be independently associated with ischemic stroke risk. The stroke risk increases 3% each year after the diagnosis of diabetes and triples with a diabetes duration over 10 years.⁹

Diagnosis. Type 2 diabetes can be diagnosed by assessing fasting glucose, random glucose, or glycated hemoglobin (A1C). A fasting glucose level > 126 mg/dl, a random glucose level > 200 mg/dl with hyperglycemic symptoms, or an A1C level $\geq$ 6.5% indicates a diagnosis of diabetes in an adult.

Treatment. Tight glucose control reduces microvascular complications with neuropathy, retinopathy, and nephropathy.⁵⁴ Clinical trials in patients with established macrovascular disease (cardiovascular, cerebrovascular, or significant vascular risk factors) have not demonstrated a beneficial effect of intensive glucose-lowering therapy or lifestyle modification on macrovascular outcomes in patients with Type 2 diabetes.^{6,46,75,97}

Given that glucose control does prevent microvascular complications, it makes sense to aim toward a target A1C of approximately 7%.⁶ A goal of < 8% may be more appropriate in those with a history of hypoglycemia, advanced macrovascular or microvascular disease, extensive comorbid conditions, and limited life expectancy.⁶ More importantly for macrovascular disease (cardiovascular disease, cerebral vascular disease), however, is to assess and treat other concomitant risk factors such as high blood pressure, hyperlipidemia, obstructive sleep apnea (OSA), and obesity.

Atrial Fibrillation

Risk. Atrial fibrillation is the most common sustained cardiac arrhythmia in the United States, with a prevalence of approximately 1% in the general population.¹³¹ Its prevalence is strongly associated with advancing age, rising to 5% in people older than 65 years and to about 10% in those 80 years of age.¹³¹

The abnormal contraction of the atria resulting in sluggish blood flow may result in thrombus in the left atrial appendage, creating the risk of stroke due to thromboembolism.

The rate of ischemic stroke among patients with nonvalvular atrial fibrillation averages 5% per year, 2–7 times the rate in people without atrial fibrillation.⁵⁵ Approximately 16% of all strokes (1 of every 6) occur in patients with atrial fibrillation.⁵⁵ The risk of stroke increases with age; the annual risk of stroke due to atrial fibrillation is 1.5% in patients 50–59 years old,⁵⁵ 10.3% in people over 75 years of age,⁶⁷ and 23.5% in those 80–89 years.⁵⁵

A number of factors increase the risk of thromboembolism including prior thromboembolic disease. These factors are incorporated into the CHADS₂ (Table 6) and CHA₂DS₂-VAsC scores,^{56,58} which aid the clinician in

TABLE 6: The CHADS₂ score and thromboembolic risk*

CHADS ₂ Score	Adjusted Stroke Rate/Yr (range)
0	1.9% (1.2–3.0)
1	2.8% (2.0–3.8)
2	4.0% (3.1–5.1)
3	5.9% (4.6–7.3)
4	8.5% (6.3–11.1)
5	12.5% (8.2–17.5)
6	18.2% (10.5–27.4)

* Points for CHADS₂ score: 1 point each for congestive heart failure (any history), hypertension, age $\geq$ 75 years, diabetes mellitus; and 2 points for prior ischemic stroke or TIA (most experts include a systemic embolic event).

predicting thromboembolic risk in an individual patient. Patients are considered to be at low risk with a score of 0, at intermediate risk with a score of 1 or 2, and at high risk with a score $\geq$ 3. Note, however, that most experts would consider patients with prior ischemic stroke, TIA, or systemic embolic event to be at high risk even if they had no other risk factors and a score of only 2.

Diagnosis. The diagnosis of atrial fibrillation is usually made using electrocardiography. Many recent studies have shown that longer-term monitoring in selected patients may increase the likelihood of detecting paroxysmal atrial fibrillation. Thus, patients with an ischemic stroke that appears embolic with no other identified cause and in whom the clinician suspects paroxysmal atrial fibrillation should undergo routine electrocardiography and Holter monitoring, followed by prolonged cardiac monitoring.^{105,129}

Treatment. It is clear from many clinical trials that anticoagulation is superior to aspirin alone in preventing strokes from nonvalvular atrial fibrillation, reducing the risk by 68%.¹²¹ Anticoagulation is considered in patients with a CHADS₂ score of 2 or higher, which includes anyone with cerebral ischemia. Anticoagulation is also superior to the combination of aspirin and clopidogrel.³³

Anticoagulation using warfarin with a goal international normalized ratio (INR) of 2–3 is a common option in preventing atrial fibrillation. Recently, other options have included the novel anticoagulants dabigatran, rivaroxaban, and apixaban. When these agents were independently compared with adjusted-dose warfarin (INR 2.0–3.0) in large randomized trials of patients at intermediate to high risk for stroke, equal or better efficacy and safety was demonstrated by these newer anticoagulants compared with warfarin.^{34,62,98} The novel anticoagulants have several advantages over warfarin, including no need for monitoring and less susceptibility to dietary and drug interactions. But there are disadvantages as well: higher cost, twice-daily dosing (dabigatran, apixaban), lack of a reversing agent, impact of chronic kidney disease with dosing and effectiveness, and lack of long-term safety.

Furthermore, only warfarin (never dabigatran, apixaban, and rivaroxaban) should be used for the prevention

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of embolization in atrial fibrillation patients with prosthetic heart valves, with mitral stenosis (particularly of rheumatic origin), or with mitral regurgitation or aortic valve disease associated with heart failure that may require valve replacement in the near future.

Emerging alternative options to anticoagulation include the WATCHMAN device, LARIAT procedure,¹⁰⁶ and other procedures to obliterate or occlude the atrial appendage.

Obstructive Sleep Apnea

Risk. Obstructive sleep apnea syndrome is a common disorder attributable to recurrent partial or complete collapse of the pharyngeal airway during sleep as a result of functional and/or anatomical factors.^{40,120} The sequelae of OSA are thought to result from a sustained activation of the sympathetic nervous system leading to increased blood pressure and heart rate that, in combination with hemodynamic changes and the release of endothelin, predisposes to the development of coronary artery disease, congestive heart failure, and stroke.¹²⁰ There is a strong association between OSA and atrial fibrillation as well.²³

Obstructive sleep apnea is an independent risk factor for stroke, causing a 2-fold increase in the risk of first stroke or death.^{107,139} Sleep apnea severity is associated with stroke risk, and patients with severe sleep apnea have 3- to 4-fold increased odds of developing stroke.^{107,139} These findings were independent of obesity and were reproduced in multiple studies.^{92,107,115,139}

A recent population study demonstrated that the patients with OSA who had suffered a stroke had higher rates of atrial fibrillation even after accounting for potential confounders.⁸⁵ The most common stroke subtype associated with OSA was atrial fibrillation.⁸⁵

Diagnosis. Screening of stroke patients should be considered, particularly for those with significant hypertension and suspected or actual atrial fibrillation. The STOP BANG questionnaire is an easy screening test (Table 7) but may not be applicable to the patient with a significant breathing-related disorder associated with the stroke itself.^{29,30,92,107,115,139}

Overnight pulse oximetry may be helpful as well. While the test can be very specific, its sensitivity ranges from 50% to 90%.⁸⁴ The American Academy of Sleep Medicine's practice parameters and the Canadian Sleep

Society's guidelines both recommend overnight in-laboratory polysomnography (PSG) for the diagnosis of OSA, but access to PSG may be limited in certain areas.^{90,91} Home-based or ambulatory monitoring is increasingly becoming available and provides an alternative to in-laboratory PSG, leading to improved access to OSA diagnosis. According to the Canadian Sleep Society's guidelines, portable monitoring studies can be used to confirm the diagnosis of OSA and to institute appropriate treatment in patients with a moderate to high pretest probability of OSA.¹⁵ However, with high clinical suspicion and negative oximetry or ambulatory sleep monitoring results, an in-laboratory PSG would still be needed. The purpose of an overnight PSG is to capture repetitive obstructive apneas/hypopneas during sleep, which typically result in oxygen desaturations, hemodynamic changes, and arousals from sleep.¹⁰⁷

Treatment. The treatment of OSA with a continuous positive airway pressure (CPAP) device uses positive air pressure as a means of maintaining patency of the airway during sleep. Documented benefits of CPAP therapy in OSA include reduction in systemic blood pressure; improvement in hemodynamic parameters, vascular factors including endothelin, inflammatory markers, and insulin resistance; and attenuation of potentially fatal arrhythmias.^{40,120} Additionally, stroke patients with OSA receiving CPAP therapy may experience improvement in stroke-related impairment in functional and motor domains.^{18,40,111} However, cognitive or sensorimotor impairments may preclude the use of CPAP during the initial stroke recovery period.¹²⁷

Lifestyle Changes

A number of lifestyle changes have been recommended to reduce future stroke risk. The most recent AHA guidelines pertaining to these risk factors³⁴ are listed in Table 8. Further details are reviewed in brief below.

Tobacco Use

Tobacco use is a significant alterable risk factor contributing to premature morbidity and mortality in the United States, accounting for 443,000 premature deaths from smoking-related illnesses annually.¹⁰⁸ Smoking has been associated with an increased risk for all stroke subtypes and has a strong dose-response relationship for both

TABLE 7: STOP BANG Questionnaire to screen for OSA*

Yes	No	Snoring: Do you snore loudly?
Yes	No	Tired: Do you often feel tired, fatigued, or sleepy during the daytime?
Yes	No	Observed: Has anyone observed you stop breathing during your sleep?
Yes	No	Pressure: Do you have or are being treated for high blood pressure?
Yes	No	Body mass index >35?
Yes	No	Age older than 50 years?
Yes	No	Neck size large? (Do you have a neck that measures more than 16 in (40 cm)?)
Yes	No	Gender = male?

* Results: Score 5–8, high risk; Score 3–4, intermediate risk; Score 0–2, low risk. Reprinted with permission from Chung F et al: High STOP-Bang score indicates a high probability of obstructive sleep apnoea. *Br J Anaesth* 108:768–775, 2012.

TABLE 8: Guidelines for lifestyle changes*

Factor	Recommendations
Smoking	Health care providers should strongly advise every patient w/ stroke or TIA who has smoked in the past yr to quit
Alcohol	Light to moderate levels of alcohol consumption (no more than 2 drinks per day for men and 1 drink per day for nonpregnant women) may be reasonable; nondrinkers should not be counseled to start drinking
Obesity	Weight reduction should be considered to achieve goal body mass index
Physical inactivity	For patients w/ ischemic stroke or TIA who are capable of engaging in physical activity, at least 30 mins of moderate-intensity physical exercise, typically defined as vigorous activity sufficient to break a sweat or noticeably raise heart rate, 1–3 times a wk (for example, walking briskly, using an exercise bicycle) may be considered to reduce risk factors & comorbid conditions that increase the likelihood of recurrent stroke
Estrogen use	Discontinue

* Recommendations for the factors of smoking, alcohol, and physical inactivity based on those from Furie et al.

ischemic stroke and subarachnoid hemorrhage as well as aneurysm formation.^{74,76,80,137} Smoking contributes to atherosclerosis and alteration of the coagulation systems (increased fibrinogen, increased platelet aggregation, decreased HDL, and increased hematocrit).

Those who smoke have approximately double the risk of incurring a stroke during their lifetime compared with never smokers.^{72,125} Recent estimates indicate that approximately 19% of the stroke burden is faulted from current smoking practices.⁹⁵

Studies suggest a 50% reduction in stroke risk in patients who recently ceased smoking,¹³² and by 5 years after smoking cessation, the risk level can be reduced to that of a never smoker.^{74,132} Therefore, national guidelines recommend smoking cessation for patients with stroke or TIA and suggest the avoidance of environmental tobacco smoke.⁵⁴ Tobacco cessation clinics, quit lines, and nurse-led stroke prevention/transitional programs may be useful adjuncts for patients.

Physical Activity

Regular physical activity has been established as reducing cardiovascular disease. In addition, it appears that physical activity can also decrease stroke in primary prevention studies.^{44,87} A 2010 meta-analysis demonstrated that an increased level of physical activity has the potential to reduce stroke incidence and stroke-related outcomes.⁴⁴

Physical activity is probably beneficial because of its positive effects on blood pressure, weight, diabetes, and cardiovascular disease. There may also be reductions in plasma fibrinogen and platelet activities and triglycerides, as well as an increase in HDL concentration.

While no existing clinical trial has suggested that physical activity decreases recurrent stroke risk, physical activity is beneficial in reducing risk factors contributing to cerebral ischemia.⁸⁷ Current secondary prevention guidelines make the following recommendations: For patients with ischemic stroke or TIA who are capable of engaging in physical activity, at least 30 minutes of moderate-intensity physical exercise 1–3 times a week may be considered to reduce risk factors and comorbid conditions that increase the likelihood of recurrent stroke.⁵⁴ Several studies are assessing the feasibility of cardiac rehabilitation after cerebral ischemia.⁸³

Maintaining Normal Weight

“Overweight” is defined as a body mass index > 25 kg/m²; and “obesity,” as a body mass index > 30 kg/m². Obesity predisposes one to both coronary and cerebrovascular disease. Obesity can also be associated with hypertension, hyperlipidemia, OSA, and elevated glucose. Reducing the risk for recurrent stroke through weight reduction has not been proven, but weight loss is recommended to reduce comorbid conditions.⁵⁴

Nutrition

A variety of dietary changes can be implemented to lower blood pressure, maintain a healthy weight, and reduce cholesterol. While clinical trial data do not exist on secondary prevention, diets high in grain, fruit, and vegetable intake are recommended.⁵⁴

Alcohol Use

Several studies have found a “J-shaped” curve relationship between alcohol and stroke risk. One to two drinks per day may protect against cardiovascular disease and stroke, whereas more than 4–5 drinks per day is deleterious.

The AHA recommends no more than two drinks per day for men and one drink per day for women,⁵⁴ where one drink is equal to 12 ounces of beer, 5 ounces of wine, or 1 ounce of hard alcohol.

Hormone Replacement Therapy

The AHA currently recommends the discontinuation of estrogen in patients with ischemic stroke or TIA.⁵⁴ We believe, in general, that this strategy is appropriate unless the estrogen is not implicated in the mechanism of stroke. For example, we believe that a patient who has a dissection that heals could return to estrogen-based products as necessary.

Vitamins and Supplementation

No known supplements are clearly beneficial for patients with cerebral ischemia. Large clinical trials have failed to show stroke reduction through dietary supplementation with the antioxidant vitamins beta-carotene,

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TABLE 9: Website references for patients

General Stroke References	Nutrition	Exercise
American Heart/Stroke Association: www.americanheart.org National Stroke Association: www.stroke.org Brain Attack Coalition: www.stroke-site.org National Aphasia Association: www.aphasia.org National Institute of Neurologic Disorders and Stroke: www.stroke.nih.gov Family Caregiver Alliance: www.caregiver.org Heart and Stroke Foundation: www.heartandstroke.com (search term: stroke) National Institute of Neurologic Disorders and Stroke: www.stroke.nih.gov	American Heart/Stroke Association: www.americanheart.org (search term: nutrition stroke) USDA Food and Nutrition Center: http://fnic.nal.usda.gov Government Nutrition Information: Choose My Plate www.choosemyplate.gov Academy of Nutrition and Dietetics: www.eatright.org	American Heart Association: www.americanheart.org (search term: exercise after stroke) National Stroke Association: www.americanheart.org (search term: exercise) Government-Supported Fitness Guideline: www.fitness.gov
Tobacco	Stress Management, Behavior Changes After Stroke, and Suicide Prevention	Weight Loss
Become an Ex: www.becomeanex.org Nicotine Anonymous: www.nicotine-anonymous.org Smokefree: www.smokefree.gov Centers for Disease Control: www.cdc.gov/tobacco American Lung Association: www.lungusa.org	American Heart/Stroke Association: www.americanheart.org (search term: depression or emotional changes after stroke) National Stroke Association: www.stroke.org (search term: depression) Suicide Prevention: www.suicidepreventionlifeline.org 1-800-273-8255 National Institute of Mental Health: www.nimh.nih.gov	Healthy Weight: Centers for Disease Control: www.cdc.gov/healthyweight Food and Activity Tracker: www.supertracker.usda.gov
Diabetes	Blood Pressure	Cholesterol
American Diabetes Association: www.diabetes.org American Heart/Stroke Association: www.americanheart.org (search term: diabetes)	American Heart/Stroke Association: www.americanheart.org (search term: blood pressure) National Stroke Association: www.stroke.org (search term: blood pressure)	American Heart/Stroke Association: www.americanheart.org (search term: cholesterol) National Stroke Association: www.stroke.org (search term: cholesterol)
Alcohol	Communication Tips/Aphasia	Atrial Fibrillation
Alcoholics Anonymous: www.aa.org	National Aphasia Association: www.aphasia.org American Heart Association: www.americanheart.org (search term: communication after stroke)	American Heart/Stroke Association: www.americanheart.org (search term: atrial fibrillation) National Stroke Association: www.stroke.org (search term: atrial fibrillation) Heart and Stroke Foundation: www.heartandstroke.com (search term: atrial fibrillation)
Sleep	Dietary Supplements	Reading Materials
National Sleep Foundation: www.sleepfoundation.org Better Sleep Council: www.bettersleep.org	National Institutes of Health Information on Nutritional Supplements: www.dietary-supplements.info.nih.gov	American Heart Association: magazine: <i>Stroke Connection</i> book: <i>Life After Stroke: The Guide to Recovering Your Health and Preventing Another Stroke</i> www.americanheart.org

vitamin C, and vitamin E.⁶⁴ In populations with vitamin-fortified foods, there is no reliable evidence that supplementation with folic acid and vitamin B12 prevents stroke.⁶⁴ While not specifically assessed in stroke patients, accumulating evidence leads one to question whether fish oil supplementation reduces vascular events in the secondary prevention of coronary artery disease.^{77,109} Recently, calcium supplements have been shown to potentially increase the risk of vascular disease.^{17,138} In patients with cerebral ischemia, the risk/benefit ratio should be assessed until further data are available.

Practical Issues in Stroke Prevention

Despite existing knowledge, there is a lack of systematic assessment, and secondary stroke prevention strategies are underutilized, resulting in a gap between existing evidence and actual practice.^{69,73} Several strategies to address the problems that exist in the evidence-practice gap must tackle each of the categories of patient factors, physician factors, and health care factors. These strategies must address the education of patients, the systematic identification and early treatment of risk factors, and the long-term follow-up and surveillance of patients.

A nurse or other member of the neurosurgical team can perform a systematic review of risk factors to ensure that none are missed. Education on individual risk factors can be provided to patients and their families. Many websites with reliable information on individual risk factors are available (Table 9). Setting realistic targets and assisting patients in reaching their goals can be useful. In addition to websites and written brochures, there are many self-help smartphone applications that allow patients to track their weight, blood pressure, and other health measurements. Assisting patients in consultations or follow-ups appropriate for their risk factors is also key to their success. While a neurosurgeon may not be the appropriate person to follow up on the lipids and the safety labs for statins, ensuring appropriate follow-up is very important. Stroke prevention and transitional programs can also be incorporated into the practice to ensure ongoing commitment and education toward goals.⁵¹

Conclusions

Identification and treatment of modifiable stroke risk factors can significantly reduce ischemic stroke and myocardial infarction as well as prevent long-term morbidity and mortality after first stroke or TIA. Neurosurgeons should be aware of the specific risk factors and general recommendations for stroke patients. A select member of the neurosurgical team may be useful in aiding the neurosurgeon to assess risk factors and assist patients for long-term success.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript prepara-

tion include the following. Conception and design: both authors. Acquisition of data: both authors. Drafting the article: both authors. Reviewed submitted version of manuscript: both authors.

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