The Secondary Prevention of Ischemic Stroke

Case Study and Commentary, Paul B. Tabereaux, MD, Lawrence M. Brass, MD, and Dawn M. Bravata, MD

Abstract

• **Objective:** To provide an overview of the evidence and clinical approach to secondary prevention for patients following an ischemic stroke or transient ischemic attack (TIA).

• **Methods:** Overview of the literature.

• **Results:** Patients with acute ischemic strokes and TIAs are at increased risk for secondary vascular events, including recurrent stroke. Nonmodifiable risk factors should be evaluated to identify patients who are at high risk of recurrent stroke. Risk factor modification includes diagnosing and treating hypertension, hyperlipidemia, and diabetes. Patients with high-grade symptomatic carotid artery stenosis should be evaluated for carotid endarterectomy. Stroke patients with atrial fibrillation should receive warfarin unless a contraindication is present. All other stroke patients should receive an antiplatelet agent unless contraindicated. Recommendations for lifestyle changes, including stopping smoking, avoiding heavy alcohol use, reducing overweight, and increasing exercise, should be made during the acute stroke period.

• **Conclusion:** Post-stroke care should involve an assessment of both nonmodifiable and modifiable risk factors in all patients. Risk factor modifications should be initiated early after the first event.

**INSTRUCTIONS**

The following article, “The Secondary Prevention of Ischemic Stroke,” is a continuing medical education (CME) article. To earn credit, read the article and complete the CME evaluation on pages 383 and 384.

**OBJECTIVES**

After participating in the continuing education activity, primary care physicians should be able to:

1. Discuss the epidemiology of secondary stroke
2. Identify the risk factors, both modifiable and nonmodifiable, that put patients at higher risk of recurrence of stroke
3. Describe lifestyle changes that should be recommended during the acute stroke period
4. Be familiar with the medical and surgical options available for recurrent stroke prevention

Stroke is a major public health problem. There are more than 700,000 new strokes each year in the United States [1,2]. Of these, 200,000 are recurrent strokes [3]. Stroke is the third leading cause of death in the United States. Short-term stroke mortality ranges from 5% to 10% [4–8]. By the end of the first year following a stroke, one quarter of patients are dead [9]. Within 5 years, 60% are dead, and by 10 years almost 80% of have died [9,10]. Stroke is also a leading cause of disability in adults. Only 10% of individuals who survive their stroke make a complete recovery, with half of patients having weakness persisting beyond 6 months [3]. Nearly 5 million people in the United States have survived a stroke and are at greatly increased risk for recurrent stroke, other vascular events, and death [3]. The annual recurrent stroke rate ranges from 4% to 14% [11]. Recurrent strokes have a higher mortality than first strokes [12,13].

Transient ischemic attacks (TIAs) are also common, with at least 300,000 new TIAs each year. Five million Americans have had a TIA [14,15]. Despite currently available therapeutic interventions, 25% of TIA patients will have a cerebrovascular or cardiovascular event or die in the 90 days post-TIA, and over the long-term 11% per year will have a stroke, myocardial infarction, or vascular death [16].

Given the high rate of recurrent events following ischemic stroke or TIA, secondary prevention strategies are an important component of care [17–19]. Unfortunately, evidence suggests that the quality of secondary stroke prevention care is lacking, even for well-established therapies. For example, among patients admitted to the hospital with a stroke associated with atrial fibrillation, approximately half of ideal candidates for anticoagulation therapy are started on warfarin [20].

In this case-based review, we describe the components of secondary ischemic stroke prevention. Our approach is to...
identify the risk and risk factors for an individual patient and identify opportunities for risk factor modification and preventive therapies.

CASE STUDY

Initial Presentation

A 64-year-old right-handed woman presents with the sudden onset of right arm weakness, facial droop, and slurred speech. The symptoms began at 10 AM while the patient was working in her garden. She arrives at the emergency department at 6 PM.

History and Physical Examination

The patient has a long-standing history of hypertension and chronic atrial fibrillation. Her medications include metoprolol and aspirin. She is not taking warfarin because she has no reliable transportation for regular blood checks (of her international normalized ratio [INR]). Rate-control on the metoprolol is good, and her atrial fibrillation remains asymptomatic. She smokes approximately 1 pack of cigarettes per day and has a 40 pack-year history of tobacco use. She drinks alcohol only on special occasions.

On examination, the patient is 5'2" and weighs 150 lb. Her blood pressure on admission is 185/92 mm Hg and heart rate is 120 bpm. Funduscopic examination reveals arteriovenous nicking and arteriolar narrowing. No elevated jugular venous pressure or bruits are noted. Cardiac examination is notable for an irregularly irregular tachycardic heart beat with no murmurs or gallops; however, the point of maximal impulse is displaced to the axilla. Lung, abdominal, and extremity examinations are unremarkable. Her neurologic examination is normal except for a mild facial weakness (flattening of the nasolabial fold), weakness of the right arm (arm drifts down from the horizontal after 5 seconds), and mild slurring of her speech (dysarthria) without evidence of comprehension or expressive abnormalities.

Diagnostic Evaluation

A 12-lead electrocardiogram demonstrates left ventricular hypertrophy (LVH) and atrial fibrillation with rapid ventricular response at 110 beats per minute. There are no changes to suggest cardiac ischemia. Her laboratory testing is normal except for a serum lipid panel that reveals an elevated LDL cholesterol level of 142 mg/dL. Fasting glucose is 120 mg/dL. There is microalbuminuria. Her admission brain computed tomography (CT) scan is normal. Carotid Doppler ultrasound evaluation demonstrates a 50% stenosis of the left internal carotid artery. There is no stenosis on the right. A transesophageal echocardiogram reveals a small patent foramen ovale, without an atrial septal defect or thrombus.

Clinical Course

The patient is admitted to the hospital. She is not a candidate for thrombolysis because she arrived at the emergency department more than 3 hours after her stroke symptom onset. On the second hospital day, the patient asks her nurse what she can do to prevent a second stroke. She was living independently prior to her stroke. Her greatest fear is that she will not remain independent and will become a burden to her family.

When is the time to begin secondary prevention efforts in stroke care?

Secondary stroke prevention starts with hospital admission. The initial post-stroke care during the hours and days following hospital admission for an acute ischemic stroke should focus on 4 domains: (1) treatment of the acute stroke (eg, thrombolytic therapy), (2) prevention of secondary complications (eg, aspiration), (3) restorative (rehabilitation) care, and (4) secondary prevention therapies [21].

Although secondary prevention efforts have traditionally been deferred to the outpatient setting, evidence suggests that secondary prevention is best begun as part of acute stroke care. There are 2 main reasons to begin secondary stroke prevention early after the first stroke or TIA. First, the stroke recurrence rate is highest in the early post-stroke period; approximately one third of stroke recurrences occur within the first 30 days post-stroke [13,19]. Similarly, of strokes occurring 90 days following TIA, half occur in the first 48 hours [16]. Second, the period following a major medical event such as a stroke or TIA represents a “teachable moment” where both patients and their clinicians are focused and motivated to address risk factors. The likelihood of adherence is greatly increased for both medication and lifestyle changes. For example, patients are more likely to stop smoking if tobacco cessation efforts begin while they are in the hospital versus after discharge [22–24].

Secondary stroke prevention begins with identification of risk factors and comorbid conditions. Many factors have been associated with stroke, some of which are modifiable (Table 1).

Which nonmodifiable risk factors should be considered in patient management?

The recognition of nonmodifiable stroke risk factors allows for the identification of patients at greatest risk for recurrent stroke. Age is the strongest nonmodifiable risk factor, with the risk of stroke doubling for each successive decade after the age of 55 years [25,26]. Age influences several management
recommendations. For example, oral anticoagulation with warfarin can prevent 2 out of 3 recurrent strokes; however, it is associated with a risk of bleeding. For patients to achieve a net benefit from warfarin, the risk of recurrent stroke must be higher than the risk of serious bleeding complications. One of the major factors in the current recommendation for deciding between antiplatelet therapy and anticoagulation is age [27]. Similarly, although the risk of surgical complications associated with carotid endarterectomy (CEA) increases with age, the risk of recurrent stroke increases much more with age. Therefore, the group with the greatest net benefit from CEA are patients with symptomatic carotid stenosis who are 75 years of age or older [28].

Blacks, Hispanics, and selected groups of Japanese and Chinese populations have higher stroke rates than whites [29–38]. These racial disparities have been attributed to higher prevalence or severity of stroke risk factors in some racial groups, differential access to medical care, differential quality of medical care, biological differences, lower rates of adherence to treatment recommendations, and differences in socioeconomic status [33–35,39–43]. Although race is non-modifiable, several factors that are associated with both race and increased stroke risk are modifiable (eg, stroke risk factors such as hypertension and quality of medical care).

Lower socioeconomic status and family history of stroke both increase stroke risk modestly [44–47].

The relationship between gender and stroke risk is complex. Women have lower rates of ischemic stroke in middle age, presumably due to the protective effects of ovarian hormones prior to the menopause [48–50]. This suggested a potential role for hormone replacement therapy in stroke prevention, an observation not borne out by clinical trials [51–53]. The Women’s Health Initiative data suggest that estrogen therapy increases stroke risk in postmenopausal women [52,53]. The Women’s Estrogen for Stroke Trial demonstrated that hormone replacement therapy did not reduce the risk of recurrent stroke in women who have cerebrovascular disease [51]. There also are data to suggest that there may be gender differences with regard to provision of some therapies, such as CEA [28].

• Which modifiable risk factors should be addressed?

Medical Risk Factors

Many risk factors have been associated with increased stroke risk. However, not all factors that are associated with stroke risk are amenable to treatment. For example, elevated homocysteine levels are associated with an increased risk for ischemic stroke; however, reducing homocysteine with vitamin therapy did not reduce the risk of recurrent stroke in the Vitamin Intervention for Stroke Prevention (VISP) study [54]. It is worth noting that the study had a short follow-up period and patients had only marginally elevated homocysteine levels at baseline; other studies are ongoing.

From a public health perspective, the attributable risk can be used to prioritize stroke risk factors. The attributable risk (the product of the relative risk and the prevalence of a particular risk factor) is used to estimate the portion of stroke in the population that can be attributed to a risk factor (Table 2) [41,55,56].

Table 1. Risk Factors for Stroke

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<th>Nonmodifiable risk factors</th>
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Hypertension

Hypertension is the single most important risk factor for stroke and for stroke prevention because it is common, has a strong association with stroke risk (ie, high relative risk), and is treatable. Although hypertension is associated with other important vascular outcomes (eg, myocardial infarction), most clinical studies of hypertension have stroke as the major outcome, and stroke is the outcome that is most reduced in therapeutic clinical trials [57–60].

Blood pressures greater than 110/75 mm Hg are associated with increased incidence of both stroke and related
diseases [61]. Modest increases in blood pressure (eg, diastolic blood pressure increase of 5 mm Hg or systolic blood pressure increase of 10 mm Hg) are associated with a 30% increase in stroke risk [58,59,62]. Reducing blood pressure greatly reduces the risk of a first stroke. Numerous clinical trials have demonstrated this reduction in stroke risk with treatment of systolic or diastolic hypertension. The benefits of hypertension treatment are realized across the age spectrum [63,64].

Clinical trial evidence has demonstrated the benefits of hypertension treatment specifically for secondary stroke prevention [59]. For example, the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) enrolled 6105 patients who had a TIA or ischemic stroke within the previous 5 years. People were randomized to perindopril-based therapy (an angiotensin-converting enzyme [ACE] inhibitor) with or without a diuretic. In the mean 4 years of follow-up, those randomized to active treatment had a blood pressure reduction of 9/4 mm Hg and a relative reduction in stroke of 28% [95% CI, 17%–38%; P < 0.001]. The absolute risk reduction was 3.7%, with a number needed to treat of 27 [59]. This risk reduction is what would be expected from the increased risk associated with elevations in blood pressure [62,65,66]. Meta-analyses have also found that among patients who have had a stroke or TIA, there is benefit from reducing blood pressure, regardless of blood pressure preceding stroke [67,68].

PROGRESS addressed 2 important issues in post-stroke blood pressure reduction. First, those with a baseline blood pressure less than 140/90 mm Hg also derived a benefit from blood pressure reduction. Second, there was no evidence for a blood pressure reduction so low that the risk of stroke increased. PROGRESS did not address blood pressure reduction immediately after a stroke. In the first hours and days following an acute stroke, cerebral autoregulation is often impaired, and cerebral perfusion may become pressure dependent. During the acute phase of a stroke, aggressive blood pressure reduction is not usually recommended [21].

Controversy exists regarding whether one class of antihypertensive agent is superior to another in the prevention of strokes [57,58,69,70]. Given the current data, we recommend treating patients with cerebrovascular disease with antihypertensive medications to achieve target blood pressure [70]. Most often, patients will require several antihypertensive medications to reach therapeutic goals, and we often prescribe an ACE inhibitor or angiotensin receptor blocker (ARB) as part of that combination therapy [70].

**Diabetes and Insulin Resistance**

Diabetes is a risk factor for stroke [71]. Diabetes is considered to be a cardiac disease risk equivalent, meaning that diabetic patients without a previous myocardial infarction have a risk for myocardial infarction that is equivalent to the risk of nondiabetic patients who have had a myocardial infarction [72]. Therefore, for purposes of risk stratification and therapy, patients with diabetes should be treated as patients who have a history of myocardial infarction. The most effective way to reduce the risk of stroke among patients with diabetes is to reduce the blood pressure [60,71]. Among patients with stroke and diabetes, clinicians should strive to achieve and maintain goal blood pressure. The target for blood pressure control is lower among patients with diabetes, reflecting the great importance of hypertension in this population [70].

Approximately 20% to 30% of stroke patients have known diabetes, and it is estimated that an additional 15% to 25% have undiagnosed diabetes [73,74]. Among patients with stroke, there should be a systematic effort to screen for diabetes [74]. The identification and treatment of diabetes can lead to reductions in sequelae of diabetes such as vision loss, which may be particularly disabling in the post-stroke population.

Insulin resistance is also common among patients with ischemic stroke [75,76] and appears to be associated with an increased risk for recurrent stroke [75]. At this time, trials are ongoing that will address the question of whether poststroke patients with insulin resistance should be treated.

**Therapeutic Recommendations for This Patient**

The patient remained hypertensive throughout the post-stroke period. Therefore, she was started on an ACE inhibitor during her hospital stay. She has required increased titration of her ACE inhibitor dose since her discharge from the hospital. She was given a home blood pressure cuff with which she records her blood pressure and heart rate daily. The patient was noted to have several elevated fasting blood glucose measurements while in the hospital consistent with a diagnosis of impaired fasting glucose but not frank diabetes. The stroke team recommended that she use a combination of diet and exercise to normalize her fasting blood sugar.
Lifestyle Factors

Smoking
A meta-analysis of 32 studies evaluated the risk of stroke in tobacco smokers and found an increase in stroke risk (relative risk [RR], 1.5 [95% CI, 1.4–1.6]) [77]. The Physician’s Health Study also examined the relationship between nonfatal stroke and smoking and found that although a past history of smoking was not associated with increased stroke risk (RR, 1.2 [95% CI, 0.94–1.53]), current smoking was associated with increased stroke risk for both smokers of less than 20 cigarettes per day (RR, 2.02 [95% CI, 1.23–3.31]) and more than 20 cigarettes per day (RR, 2.52 [95% CI, 1.75–3.61]) [78]. In a prospective evaluation of stroke incidence, data from 4255 participants in the Framingham Heart Study cohort demonstrated that over 26 years of follow-up, smoking was significantly related to stroke after adjustment for age and hypertension but that stroke risk was equivalent between smokers and nonsmokers by 5 years after smoking cessation [79]. The Joint Commission on Accreditation of Healthcare Organizations (JCAHO) has included smoking cessation counseling as a performance measure for patients who are hospitalized with acute stroke [80]. Post-stroke patients should receive smoking cessation counseling, and smoking cessation efforts should begin during the acute stroke period in the hospital [81]. Inpatient smoking cessation programs should be multidimensional and include physician advice, nursing counseling, and postdischarge telephone contact [23].

Alcohol
Several observational studies have found an association between heavy alcohol use and increased stroke risk [82–84]. A meta-analysis was conducted that included 15 observational studies that examined the relationship between light to heavy alcohol intake and ischemic stroke risk [85]. The results of this meta-analysis indicated that compared with abstinence, heavy alcohol consumption (ie, >60 g of alcohol per day) was associated with an increased risk of ischemic stroke (RR, 1.69 [95% CI, 1.34–2.15]) [85]. This meta-analysis also demonstrated that light or moderate alcohol consumption was not associated with increased stroke risk. A report from the Physicians’ Health Study that included 1320 participants with a prior stroke found that after a mean follow-up period of 4.5 years, participants who drank 1 to 6 drinks per week had lower total mortality compared with participants who abstained (adjusted RR, 0.64 [95% CI, 0.48–0.85]) [86]. This study’s small sample size limited its ability to evaluate the effect of alcohol consumption on recurrent stroke mortality but it similarly found a reduced relative risk for participants who drank 1 to 6 drinks per week (adjusted RR, 0.65 [95% CI, 0.30–1.39]) [86].

In the absence of specific data about the efficacy of altering alcohol consumption for secondary stroke prevention, we recommend avoiding heavy alcohol use for patients who have had a stroke based on the large body of observational data associating heavy alcohol use with increased stroke risk.

Physical Activity
Several large prospective cohort studies have found that stroke risk decreases with increasing physical activity (RR ranging from 0.37 to 0.86) [87–90]. These observational studies have further demonstrated that this association between stroke risk and physical activity is evident across all racial, ethnic, and age-groups [87–90]. In a study of 1475 post-stroke patients, almost two thirds had been told by their physician to increase their exercise level, and although 77% of patients who received such advice increased their activity level, only 39% of patients who did not receive such advice increased their exercise level [91]. Despite the difficulty that some patients have with physical activity post-stroke, given these observational data, we encourage our stroke patients to engage in regular physical activity. We routinely consult our physical therapy and occupational therapy colleagues to develop exercise programs that are tailored to individual patients’ circumstances.

Overweight
The Nurses’ Health Study found that the risk of ischemic stroke increased with higher body mass index (BMI). Compared to women with a BMI of less than 21, the adjusted RR for women with a BMI 27 to 28.9 was 1.8 (95% CI, 1.17–2.59); for BMI 29 to 31.9, the adjusted RR was 1.9 (95% CI, 1.28–2.82); for BMI of 32 or greater, the adjusted RR was 2.4 (95% CI, 1.60–3.50). P for trend < 0.001) [92]. Similarly, stroke risk increases with increasing weight gain [92,93]. Reducing obesity is likely to improve other modifiable stroke risk factors such as hypertension and diabetes. For example, weight loss in obese patients has been shown to lower blood pressure by approximately 0.3 to 1 mm Hg for every 1.0 kg lost [94–96].

Diet
Numerous studies have investigated the relationship between diet and the risk of ischemic stroke. Increased dietary consumption of fruits and vegetables has been associated with reduced risk of stroke [97–99]. Diets high in fiber have been associated with a reduction in the risk of cardiovascular disease and stroke [98,100–107]. Several studies have evaluated the relationship between fish (and fish oil) consumption and stroke risk. The results of these studies have been conflicting. However, 2 large prospective studies have reported the benefits of dietary fish consumption. In the Nurses’ Health Study, 79,839 women
were followed for 14 years, and women who ate fish at least 2 times a week had fewer ischemic strokes compared with women who ate fish less than once a month (adjusted RR, 0.49 [95% CI, 0.26–0.93]) [108]. In the Health Professional Follow-up Study, 43,671 men were followed for 12 years, and those men who ate fish 1 to 3 times a month had a lower stroke rate than those who ate fish less than once a month (adjusted RR, 0.57 [95% CI, 0.35–0.95]) [109].

There is currently no data to support the use of vitamin E, beta-carotene or vitamin C for secondary prevention in stroke [58,110,111].

**Lifestyle Modification Recommendations for This Patient**

Smoking cessation counseling was begun on the patient’s first hospital day and encouragement and reminders were provided frequently throughout her hospitalization. Smoking cessation encouragement was also provided at each of the patient’s outpatient clinic visits. Given the patient’s BMI of 27.4, the care team recommended that she engage in a weight loss program. Following hospitalization, she began participating in a water exercise program at a local swimming pool and lost 5 lb during the first month. She was pleased with both the weight loss that resulted from her exercise as well as with the social support she derived from this activity.

- Are HMG-CoA reductase inhibitors useful in post-stroke care?

**Statin Therapy**

Elevated lipids are not strongly associated with risk for stroke. Overall, early studies of lipid-lowering therapy did not find convincing reduction in the risk of stroke. However, a reduction in stroke risk was noted among patients treated with HMG-CoA reductase inhibitors (statins) following myocardial infarction [112–114]. These data, however, did not inform the clinical care for patients with cerebrovascular disease because the average age in these trials was much younger than the average age for stroke patients, and stroke following myocardial infarction may not be typical of all ischemic strokes.

The first trial to inform care among patients with ischemic stroke was the Heart Protection Study, which randomized 20,536 patients with varying levels of LDL cholesterol and previous coronary, cerebrovascular, or peripheral disease, diabetes mellitus, or hypertension. Patients who were randomized to receive statin therapy demonstrated a 25% reduction in fatal or nonfatal strokes [111]. The benefit was achieved in even the lowest LDL cholesterol group (< 116 mg/dL), supporting the hypothesis that statins have actions beyond just lowering LDL cholesterol (eg, plaque stabilization, reduction in inflammatory markers) [111]. In a recently published post hoc analysis from the Heart Protection Study [115], patients with preexisting cerebrovascular disease did not demonstrate a lower incidence of recurrent stroke with statin therapy as compared with placebo but did have fewer cardiovascular events.

The National Education Cholesterol Program recommends that goal LDL cholesterol should be less than 100 mg/dL in all patients requiring secondary prevention and in those with a coronary equivalent such as carotid stenosis or diabetes [116]. JCAHO recommends measuring a lipid panel for all patients who are hospitalized with acute stroke [80]. The American Heart Association recommends beginning statin therapy for patients who are hospitalized with a first ischemic stroke [117].

**Inflammatory Markers**

Many hemostatic and inflammatory markers of vascular inflammation have been evaluated for their usefulness in stratifying patients according to risk of stroke or cardiovascular disease. C-reactive protein has been used to predict stroke risk and confers additional risk stratification beyond LDL cholesterol [118–122].

- Which patients should receive oral anticoagulation?

**Oral Anticoagulation for Patients with Atrial Fibrillation**

Warfarin should be considered for all stroke patients with atrial fibrillation without a contraindication to oral anticoagulation. Atrial fibrillation is an independent risk factor for stroke. Among atrial fibrillation patients with a prior stroke, 12% will have a recurrent stroke [123,124]. Overall, atrial fibrillation increases the risk of recurrent stroke 2.1-fold [3]. Patients with atrial fibrillation have more severe strokes, are twice as likely to be disabled as a consequence of their stroke, and have greater stroke mortality than patients without atrial fibrillation [3].

Numerous studies have established the benefits of warfarin to reduce stroke risk in patients with atrial fibrillation [125–131]. For secondary stroke prevention, warfarin reduces the risk of stroke by two thirds, with an absolute risk reduction of 8.4% and a number needed to treat of 12 [131]. Warfarin therapy is underutilized even in ideal candidates [20,132]. For example, in a national study of Medicare beneficiaries, only 55% of ideal candidates were prescribed oral anticoagulation [20]. JCAHO recommends prescribing warfarin for patients hospitalized with acute stroke who have atrial fibrillation but no contraindications to oral anticoagulation [80].

For atrial fibrillation patients with contraindications to warfarin, aspirin can be used to reduce stroke risk. Aspirin
reduces the risk of stroke by one fifth, with an absolute risk reduction of 2.5% and a number needed to treat of 40 for secondary stroke prevention [125,126,129,131]. In addition, recently completed large clinical trials have shown the oral direct thrombin inhibitor ximelagatran to be equivalent in efficacy to warfarin [133].

There is no role for warfarin in the treatment of patients with acute stroke without an embolic source [134]. The Warfarin-Aspirin Recurrent Stroke Study (WARSS) randomized 2206 patients with noncardioembolic strokes to aspirin or warfarin; after 2 years of follow-up there were no significant differences in the rates of recurrent ischemic strokes, death, or major hemorrhage between the 2 groups [134].

**Oral Anticoagulation Recommendations for This Patient**

The patient’s heart rate responded to intravenous β blocker administration and she did not require cardioversion. She remained in atrial fibrillation but with excellent rate control throughout her hospitalization. The stroke team recommended that the patient receive warfarin therapy with a goal INR of 2–3 [135]. The social worker and nurse case manager worked with the patient and her family to develop a plan to ensure that the patient could receive regular blood testing to monitor her INR.

- What is the role of carotid endarterectomy?

**Symptomatic Carotid Artery Stenosis**

Two large randomized controlled trials demonstrated the benefit of treating recently symptomatic carotid artery stenosis greater than 70% with CEA [136,137]. In the North American Symptomatic Carotid Endarterectomy Trial (NASCET), 659 patients with either a nondisabling stroke or TIA within the 120 prior days and a 70% to 99% stenosis in the symptomatic carotid artery were randomized to either medical care, including antiplatelet therapy, or CEA [136]. After 2 years of follow-up, the ipsilateral stroke risk was 26% in the patients assigned to medical therapy and 9% to the patients assigned to CEA (P < 0.001) [136]. Similarly, patients assigned to medical therapy had higher rates of major or fatal ipsilateral stroke (13.1% versus 2.5%, P < 0.001) [136]. As noted above, elderly patients derived the most benefit from CEA [28].

A meta-analysis of the European Carotid Surgery Trial (ECST) [137], NASCET [136], and the Veterans Affairs Trial [138] confirmed that the benefits of surgery increase with increasing degree of carotid artery stenosis (relative risk of ipsilateral stroke or operative death for 50% to 69% stenosis: RR, 0.75 [95% CI, 0.56–0.94]; for 70%–99% stenosis: RR, 0.39 [95% CI, 0.28–0.51]) [139]. The American Heart Association recommends ipsilateral CEA for patients with 70% to 99% carotid artery stenosis [140].

Given the benefit of CEA for patients with symptomatic carotid artery stenosis, a patient with a stroke or TIA should receive noninvasive testing for carotid artery stenosis. Also, given the benefits of early CEA and the high rates of recurrent events early after a first stroke or TIA, this evaluation should be completed as soon as possible after the first event [16]. Evaluation of the carotid arteries can be performed with either B-mode and Doppler ultrasound or magnetic resonance angiography (MRA). The sensitivity and specificity of ultrasounds have been demonstrated to be 86% and 87% versus 85% and 90% for MRA [141]. Ultrasonography and MRA are cost-effective alternatives to angiography [141–144].

**Antiplatelet Therapy**

Randomized controlled trials have demonstrated that aspirin reduces the risks of recurrent or disabling stroke by 20% to 48% [145–148]. The Canadian Cooperative study reported a 48% relative risk reduction in the combined outcome of stroke or death [145]. Two meta-analyses from the Antiplatelet Trialists Collaboration included data from 29,000 and 100,000 patients and reported reductions in the nonfatal stroke risk of 27% and 23%, respectively [146,147]. JCAHO has recommended that all patients with acute ischemic stroke should receive an antithrombotic agent on discharge unless a contraindication is present [80].

Controversy exists as to the most appropriate dose of aspirin following stroke. Aspirin is currently FDA-approved for doses at 50 to 325 mg per day for secondary prevention of stroke [148–151]. Clinical trials have used doses ranging from 30 to 1300 mg, showing benefit over placebo at all doses; however, no trial has demonstrated a benefit of higher doses versus lower doses of aspirin [152].

The secondary stroke prevention benefits of ticlopidine were demonstrated in the Ticlopidine Aspirin Stroke Study (TASS), where patients receiving ticlopidine had a 21% lower stroke rate compared with patients receiving aspirin [153]. Ticlopidine is associated with side effects such as diarrhea, rash, and neutropenia. The combination of aspirin plus dipyridamole was associated with a 19% reduction in stroke risk compared with aspirin alone [154]. Clopidogrel appears to be slightly more effective than aspirin in reducing MI, stroke, and vascular death among patients with a history of vascular disease (stroke, MI or peripheral arterial disease) [155]. The MATCH Trial, recently presented at the European Stroke Conference, indicated that the addition of aspirin to
clopidogrel conferred no additional net benefit in terms of MI, ischemic stroke, vascular death or hospitalization for ischemic events [156].

SUMMARY

Patients with acute ischemic stroke are at increased risk for recurrent stroke especially early after the first stroke or TIA. Nonmodifiable risk factors should be evaluated to identify patients who are at high risk for recurrent events. Risk factor modification includes diagnosing and treating hypertension, hyperlipidemia, and diabetes. Patients with high-grade symptomatic carotid artery stenosis should be evaluated for CEA early after the first stroke or TIA. Stroke patients with atrial fibrillation should receive warfarin unless a contraindication is present. All other stroke patients should receive an antiplatelet medication unless contraindicated. Lifestyle changes, including recommendations to stop smoking and increase exercise, should be made during the acute stroke period.

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SECONDARY STROKE PREVENTION


SECONDARY STROKE PREVENTION


