

Stroke and TIA: Epidemiology, Risk Factors, and the Need for Early Intervention

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Abstract

The risk of recurrent stroke in patients who have suffered a prior stroke or transient ischemic attack (TIA) is significant. It is imperative that individuals who report symptoms of a cerebrovascular event receive immediate medical attention—preferably at a hospital—to help determine its origin and impact. Many researchers recommend that any evaluation include neuroimaging studies to target those patients who would benefit most from secondary prevention, such as antithrombotic therapy.

This article defines the 2 main types of stroke and their respective subtypes and discusses the debate over how to define stroke versus TIA. Additionally, the article talks about the incidence of stroke, related morbidity and mortality rates, and several risk factors that predispose an individual to stroke and recurrent stroke. Several systems have been established to help determine the likelihood of stroke for patients with concurrent risk factors. Measures for secondary prevention can be initiated to address many of these risk factors.

The importance of early intervention cannot be underestimated. Rapid treatment following a stroke or TIA can minimize cerebrovascular damage and prevent recurrence; addressing modifiable risk factors can reduce the risk of subsequent cardiovascular and cerebrovascular events. Facilitating the initiation of effective secondary preventive therapy must become a priority in managed care.

(*Am J Manag Care. 2008;14:S204-S211*)

For author information and disclosures, see end of text.

Every 40 to 45 seconds someone in the United States suffers a stroke.^{1,2} One quarter of initial stroke survivors suffer a second stroke within 5 years.² Long before experiencing a stroke, many people have cerebrovascular risk factors that have not been adequately addressed, such as transient ischemic attacks (TIAs). TIAs are frequently followed by stroke.^{2,3} Sometimes TIAs remain unidentified because patients did not seek medical attention. TIAs may also be misdiagnosed or go untreated because baseline function returned prior to a medical evaluation.⁴ Any diagnosed stroke or TIA deserves rapid evaluation and long-term therapy to help prevent further cerebrovascular events.³

Defining Stroke and TIA

Stroke is a neurologic event related to diseases of the cerebral circulation. Symptoms of stroke include sudden severe headache, focal muscular weakness or numbness, impaired vision, dizziness, confusion, or difficulty speaking or understanding speech. Visual loss and weakness or numbness are frequently relegated to one side of the body.

TIAs are briefer episodes of neurologic deficit that occur as a result of focal cerebral or retinal ischemia.^{5,6} TIAs were once regarded as benign⁷ but are now recognized as warning signs of underlying cerebrovascular disease with the potential to cause permanent brain injury.³ Most TIAs resolve within 1 hour.^{3,6,7} Only 2% to 15% of TIAs that fail to resolve within 1 hour will do so within 24 hours.⁷

Strokes and TIAs previously were diagnosed on the basis of clinical impression alone, and traditional definitions held that TIA should be diagnosed when symptoms persisted for fewer than 24 hours, whereas a completed stroke should be diagnosed when symptoms persisted beyond 24 hours.^{3,6,7} It was also thought that TIAs left no permanent deficits.^{7,8}

The advent of sophisticated neuroimaging technologies has blurred the line between stroke and TIA.⁷ Computed tomography (CT) studies from the 1980s to the 1990s found that 15% to 20% of TIA patients had cerebral infarction in areas relevant to symptoms.⁷ Recently, diffusion-weighted magnetic resonance imaging (DWI) has demonstrated lesions suggestive of permanent ischemic injury in some TIA patients.⁷ This has led some researchers to propose that the definition of TIA be modified to specify that the condition leaves no evidence of acute infarction on neuroimaging studies.^{3,5-7} According

to this definition, imaging studies that show relevant infarction would indicate stroke, regardless of the duration of symptoms.⁷

Some researchers recommend that all TIA patients undergo brain imaging urgently—as soon as possible after the onset of symptoms—to identify causes and target secondary prevention efforts.^{7,9} CT scanning and DWI can demonstrate regions of injury and help to distinguish between hemorrhage, ischemic infarction, and other etiologies, such as tumor.^{3,5,7,10} DWI can also help differentiate an infarction from penumbra (the region surrounding the ischemic core that is hypoperfused but not yet infarcted).³ In patients who have experienced TIA or a mild-to-moderate ischemic stroke, imaging modalities such as ultrasonography, CT angiography, and magnetic resonance angiography can detect internal carotid artery stenosis,^{5,9} a condition that may benefit from early treatment with carotid endarterectomy.⁹

Based on the traditional definition of TIA, some clinicians might delay intervention for 24 hours after symptoms first appear to see whether they subside. Waiting could be problematic in cases where the cause of suspected TIA requires immediate treatment. Also, within this 24-hour window, the patient could experience a completed stroke following TIA.^{3,4,7} Hospital observation enables immediate intervention if the patient should experience a subsequent stroke.⁹ Damage in the penumbra of acute ischemic stroke may be reversible, and rapid treatment can prevent it from becoming incorporated into the infarct.¹⁰ Prompt thrombolysis can improve outcomes^{10,11} with an acceptable level of risk for intracranial hemorrhage (ICH), provided proper care is exercised in patient selection.¹⁰

TIAs require immediate evaluation, and treatment should be initiated promptly to prevent subsequent stroke.⁵ Most patients who report TIA-like symptoms should be sent to the emergency department.⁵ In patients who do not seek medical attention or who are not referred for imaging studies, TIAs serve as unheeded warnings of possible cerebrovascular disease.

Stroke Types and Subtypes

According to the American Stroke Association, approximately 87% of strokes are ischemic and the other 13% are hemorrhagic.^{1,2} Hemorrhagic strokes

are associated with a higher mortality rate,¹² which suggests that an even greater proportion of recurrent strokes likely have ischemic etiology.¹² Unlike brain hemorrhage, which originates from blood collecting in the extravascular space, ischemic stroke involves the occlusion of blood vessels. In the core zone of ischemia, where blood flow is lower than 10% to 25%, irreversible neuronal damage can occur within minutes.^{13,14} In the ischemic penumbra, neurons can remain viable for several hours. Rapid restoration of perfusion in this region can save penumbral cells.¹⁰

Stroke, especially in younger patients, may be associated with arterial dissection, hypercoagulable states, venous sinus thrombosis, vasculitis, hyperviscosity syndrome, thrombocytosis, sickle cell disease, or patent foramen ovale.^{6,15} Of all ischemic strokes, ≤15% are cryptogenic (without an identifiable cause).^{16,17} The etiology of a stroke, when it can be determined, affects treatment decisions, including therapy for secondary stroke prevention. For example, oral anticoagulation is a primary recommended treatment for cardioembolism, antiplatelet therapy is recommended for noncardioembolic ischemic stroke and TIA, and carotid endarterectomy is recommended for recent TIA or minor stroke occurring with severe carotid artery stenosis.⁶

Hemorrhagic Subtypes

ICH—the presence of blood within the main cellular mass of the brain—accounts for ~10% of all strokes.¹ The incidence of ICH due to the use of oral anticoagulants has increased as these therapies have become more prevalent.^{18,19} In elderly individuals, the deposition of amyloid protein into blood vessel walls may cause hemorrhage. In most cases of ICH, however, chronic hypertension leads to the degeneration of smaller brain arteries and microaneurysms; bleeding originates from tears at the bifurcation between the vessels. The patient's symptoms may change in relation to additional bleeding and expansion of the affected area; note that rupture of a cerebral artery can cause immediate death.

Subarachnoid hemorrhage (SAH) is the second hemorrhagic subtype and accounts for 3% of all strokes.¹ SAH is most prevalent among middle-aged women and has a high mortality rate.¹⁵ SAH usually results from the rupture of a cerebral aneurysm at a vessel bifurcation.²⁰ Vasospasm of brain arteries is

a common complication of SAH and can lead to a subsequent ischemic brain injury.²⁰

Ischemic Subtypes

There are 3 main subtypes of ischemic stroke, and investigators have used several systems to classify them.²¹⁻²³ Systems based only on brain imaging exclude patients with a definite ischemic stroke but no visible infarct.²² Other classification systems, such as the ones established by the National Institute of Neurological Disorders and Stroke and TOAST (Trial of Org 10172 in Acute Stroke Treatment), consider brain imaging results plus clinical features.^{22,23}

Large vessel disease (LVD) is a subtype of ischemic stroke. In LVD stroke, slowly developing atherosclerosis can result in the rupture of an intravascular plaque, development of a thrombus, and an embolus in the circulatory system, which can become lodged in part of the brain and obstruct cerebral blood flow.²³ Other LVD strokes are caused by stenosis or occlusion of a main artery, which leads to ischemic injury at the farthest branches of the artery; this is called watershed infarction.²⁴ LVD includes strokes caused by aortic arch thromboembolism.²⁵

Lacunar or small vessel disease (SVD) strokes typically involve small areas of infarction and have a better prognosis than LVD strokes.^{16,22} An SVD stroke can occur when disease develops in the smaller penetrating arteries—usually lipohyalinosis, a degeneration that forms glassy substances which block arteries. Eclampsia and arteritis commonly cause lacunar strokes.

Embolic stroke is the third main ischemic subtype; it results from clots that develop in the heart or elsewhere in the body. Embolic sources include fat emboli related to long bone fractures and particulate emboli due to intravenous drug abuse. The principal sources of cardioembolism are atrial fibrillation, acute myocardial infarction (MI), valve disease, cardiomyopathy, and endocarditis.²⁶ Cardioembolic stroke is often more severe than LVD or SVD stroke.¹⁶ Some cardioembolic strokes cause multiple acute infarctions simultaneously.

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Incidence and Prevalence

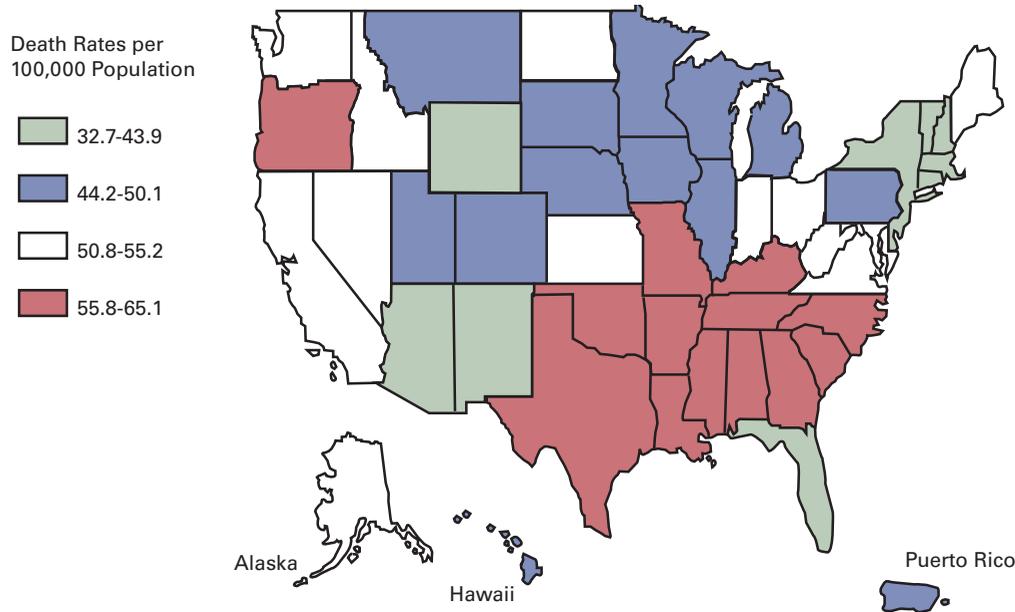
An estimated 780,000 strokes occur each year in the United States, of which 180,000 are recurrent.¹ In adults ≥ 20 years old, the prevalence of stroke is ~ 2.3 million men and ~ 3.4 million women.¹ The incidence of TIA is estimated at 200,000 to 500,000 per year.⁵ However, 15% of stroke patients report experiencing TIA previously, suggesting that the incidence is actually much higher.^{1,4} It is likely that the incidence of TIA is underestimated because up to half of individuals who suffer TIAs do not seek medical attention.^{1,5}

The incidence and prevalence of stroke in the United States can vary according to demographic factors, such as age, sex, ethnicity, geographic area, and education.^{1,27-29} The Southeast has been called the “stroke belt,” because all the states in this region, except Florida, have a rate of 55 to 65 stroke deaths per 100,000 persons (**Figure**).¹

Most strokes occur in individuals >65 years of age²⁷; in the <40 years of age demographic, stroke prevalence is only 0.5%.¹ In the 60- to 79-year age group, prevalence rises to more than 6%.¹ In persons ≥ 80 years of age, 12.4% of women and 14.8% of men have suffered a stroke.¹ The male-to-female incidence ratio is more than 1.0 for people aged 55 to 84 years, but it decreases to 0.76 in individuals ≥ 85 years of age.¹ Women have 60,000 more strokes each year than men, which may be partly attributable to their longer life span,¹ and this disparity between the sexes is growing. In the period between the 1988-1994 and 1999-2004 NHANES (National Health and Nutrition Examination Survey) surveys, the stroke rate tripled in women aged 35 to 54 years but remained the same in men of the same age group.²⁸

Ethnic and racial minorities have an increased risk of stroke, and African Americans have almost

■ **Figure.** 2004 Stroke Age-adjusted Death Rates by State



Adapted with permission from reference 1.

twice as many first strokes as whites.¹ Cumulative stroke incidence in Mexican Americans is 168 per 10,000 persons, compared with 136 per 10,000 in non-Hispanic whites.¹

Morbidity and Mortality

Of the 55 million annual deaths worldwide, 10% are due to stroke.²⁷ In the United States, 150,000 deaths from stroke occur each year—1 every 3 to 4 minutes.¹ For 8% to 17% of ischemic stroke patients and 37% to 38% of hemorrhagic stroke patients, death occurs within 30 days of the incident.^{1,10} African Americans of both sexes and women die at much higher rates than white men.¹ TIA patients also have a high mortality risk, and up to 25% will die within 1 year of a TIA.¹ Although stroke mortality fell 24% from 1994 to 2004,¹ stroke remains the third leading cause of death, just after heart disease and cancer.^{1,2,27}

In addition to the burden of mortality, stroke is a leading cause of disability in the United States.^{1,2} It severely restricts functionality, contributes to high costs, and reduces a patient's quality of life. More than 20% of stroke survivors will require institutional care within 3 months of the event.²⁷ Direct medical costs related to stroke and indirect costs of

lost productivity are expected to reach \$65.5 billion in 2008.¹

Risk Factors

In addition to demographic factors, various medical conditions and lifestyle factors have considerable impact on an individual's risk of stroke. During pregnancy, a woman's risk of stroke increases 2.4 times^{1,2}; depression increases the risk of stroke 4.2 times in patients <65 years of age.¹ Smokers bear twice the risk of ischemic stroke compared with nonsmokers,^{1,6} but the risk in those who quit smoking declines gradually over a 5-year-period; former smokers have no increased risk 5 years after quitting.² Heavy alcohol consumption increases the risk of stroke, whereas light-to-moderate alcohol consumption (1-2 drinks/day) may reduce the risk.⁶ A moderate-to-high level of physical activity significantly decreases stroke risk for both sexes and across all ethnicities and ages.^{1,2,6,30}

Between 15% and 33% of ischemic stroke patients have diabetes mellitus.⁶ The relative risk of stroke from diabetes ranges from 1.8 to 6.0.¹ Even prediabetes (impaired glucose tolerance) is an independent risk factor for recurrence after minor ischemic stroke or TIA.³¹ Many diabetic

Table 1. The ABCD² Score: Prediction of Short-term Risk of Stroke After TIA

Risk Factor	Points
Age ≥60 years	1
Blood pressure ≥140/90 mm Hg	1
Clinical features:	
Unilateral weakness	2
Speech impairment without weakness	1
Duration of symptoms:	
≥60 minutes	2
10-59 minutes	1
Diabetes	1

TIA indicates transient ischemic attack.
 Scoring for 2-day stroke risk after TIA: 0-3 = low, 4-5 = moderate, 6-7 = high.
 Adapted from reference 9.

patients have abdominal obesity, another stroke risk factor.⁶

Many risk factors for cerebrovascular disease are similar to those for cardiovascular disease.² Preexisting heart disease is a major risk factor for stroke; coronary artery disease doubles stroke risk, and patients with atrial fibrillation have a risk 5 times greater.² Dyslipidemia is not well established as an independent risk factor for ischemic stroke,^{2,6} but statin therapy in patients with baseline low-density lipoprotein (LDL) levels below 200 mg/dL has been associated with a reduction in stroke risk.^{3,32} Ischemic strokes have been associated with hyperhomocysteinemia, but high-dose vitamin treatment has not been shown to reduce the risk of recurrence.^{2,6}

Hypertension is the single most important modifiable risk factor for stroke.¹⁻³ A 10-mm Hg increase in arterial blood pressure can increase stroke risk by 20% to 30%,³ and the lifetime risk of stroke doubles for individuals whose blood pressure is >120/80 mm Hg.^{1,2} In meta-analyses of randomized controlled trials, lowering blood pressure reduced a person's stroke risk by 30% to 40%.⁶

It is worth noting that a person's level of education has been shown to be inversely related to stroke risk.²⁹ Identifying patients with nonmodifiable risk factors can help in targeting other risk factors for modification and thereby aid in prevention.²⁷

Recurrent Stroke

Risk factors for recurrent stroke are the same as those for a first stroke, with one important addition:

a previous stroke or TIA.^{1,4,8} Stroke survivors have a yearly 5% to 10% risk of having a second stroke.² The rate of stroke recurrence within 5 years has ranged from 29% to 42%. This rate might be underestimated because some studies exclude recurrences soon after the index event,¹² when the risk of a second event is greatest.¹⁷ About 15% of strokes are preceded by TIA.^{1,4} Patients have a 10.5% risk of suffering a stroke within 90 days of TIA. The 5-year risk of stroke for following TIA is 30%.² Almost half of strokes that occur subsequent to TIA do so within 48 hours, which is an important reason why TIA should be considered a medical emergency requiring immediate evaluation.^{3,4,6-8} Imaging is useful in targeting which patients are most likely to benefit from preventive therapy.⁸ It has been shown that TIA patients with lesions on DWI have an even higher 90-day risk of subsequent stroke (10.8%), and those who have lesion and vessel occlusion have the highest risk, at 32.6%.⁸

Other factors are known to increase the risk of recurrent stroke in patients who have suffered previous stroke or TIA. An analysis of data from more than 18,000 patients in the CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events) trial found that high baseline leukocyte counts increased a patient's risk of recurrent ischemic stroke, MI, or vascular death.³³ Subsequent leukocyte counts significantly over baseline were associated with recurrent ischemic events within 1 week.³³ In a study of 1707 patients with TIA, the significant independent risk factors for experiencing a stroke within 90 days included an age >60 years, diabetes, an episode of TIA lasting more than 10 minutes, and TIA symptoms of weakness, speech difficulty, and gait disturbance.⁴ Numbness, visual changes, and dizziness or vertigo were associated with lower stroke risk.⁴

Johnston and colleagues established and validated a scoring system (ABCD²) used to predict the risk of stroke at 2 days subsequent to TIA.⁹ The scoring system was also validated for time points at 7 and 90 days after presentation.⁹ The ABCD² score evaluates 5 risk factors (Age, Blood pressure, Clinical features, Duration, Diabetes), and a score of 7 indicates highest risk (Table 1).⁹ ABCD² helps identify those TIA patients who would benefit most from urgent intervention.⁹ Diener found slightly different predictors after index stroke and proposed

a stroke recurrence prediction model based on a subgroup analysis of stroke patients in the CAPRIE trial.¹⁷ As with ABCD², points are allotted for individual risk factors. Scores from 3 to 6 constitute high risk and scores from 7 to 10 indicate very high risk (Table 2).¹⁷

Many patients who suffer cerebrovascular events have systemic atherosclerosis.³ As a result, TIA or an initial stroke can also increase a patient's risk for cardiovascular events,^{3,17} which are the cause of death in ~40% of stroke patients.³ In the first 10 years after ischemic stroke, more patients die from cardiovascular events than from initial or recurrent stroke.³⁴ Following TIA, the patient has a 25% risk of MI or vascular death within the first 90 days.³ However, about 75% of the secondary events subsequent to a stroke are strokes.¹² This suggests different cardiovascular and cerebrovascular pathogenetic mechanisms that favor recurrence of the same type of vascular event.³⁵

Ischemic stroke is related to modifiable risk factors that have multiplied and compounded over years of life. Because patients who have experienced ischemic cerebrovascular events such as ischemic stroke or TIA are at high risk of suffering a second ischemic stroke, secondary stroke prevention to reduce modifiable risk factors is of paramount importance.

Need for Early Intervention

Acute ischemic strokes cannot be reversed completely, but they can be treated if addressed in time. Treatment is essential to minimize damage from the initial event and prevent recurrence. Unfortunately, stroke historically has been undertreated, even in a hospital setting. One study found that 32% of patients whose strokes were considered too mild for thrombolysis died prior to hospital discharge or were dependent at discharge.³⁶ In a meta-analysis by the Antithrombotic Trialists' Collaboration (ATC), antiplatelet therapy in patients who had a previous occlusive event or predisposing condition reduced the risk of stroke, MI, or vascular death, and benefits outweighed the absolute risks of major extracranial bleeding.³⁷

The risk for a second cerebrovascular event is highest in the period just following a stroke or TIA.^{3,4,8,11,17} Immediate medical care is needed to minimize damage from the first cerebrovascular

Table 2. Stroke Prediction Model Based on the Stroke Subgroup in the CAPRIE Trial

Risk Factor	Points
<65 years	0
65-75 years	1
>75 years	2
Hypertension	1
Diabetes	1
Previous MI	1
Other cardiovascular disease (except MI and AF)	1
Peripheral arterial disease	1
Smoker	1
Additional TIA or ischemic stroke in addition to qualifying event	1

AF indicates atrial fibrillation; MI, myocardial infarction; TIA, transient ischemic attack.
Scoring for risk of stroke recurrence: 0-3 = low, 3-6 = high, 7-10 = very high.
Adapted from reference 17.

event and reduce the risk of a second event. Paramedics can begin stroke evaluation before or during transport, to rule out hypoglycemia, intoxication, or other causes. Ideally, a physician in the emergency department should perform a physical examination followed by laboratory and imaging evaluations within 1 hour of the patient's arrival. This can enable immediate pharmacologic intervention for ischemic stroke, if indicated. Administering tissue plasminogen activator (tPA) within 3 hours of symptom onset may improve neurologic and functional outcomes.^{10,11} Stroke interventions depend on the patient's or caregiver's initial response to the onset of symptoms, which may rely on the level of public education and awareness. Primary care clinicians and managed care organizations can assist in informing the public about TIA and stroke signs and symptoms and emphasizing the importance of seeking immediate medical attention.

A recent study of suspected TIA or stroke in the United Kingdom compared standard management (evaluation by appointment, treatment recommended to primary care but not initiated at stroke clinic) with expedited care (no appointment necessary, immediate treatment on diagnosis).³⁸ Expedited care resulted in an 80% reduction in 90-day recurrent stroke risk.³⁸

The ATC meta-analysis showed smaller effects in patients treated during acute stroke.³⁷ However, the net benefit was achieved in less than 1 month of treatment, compared with 29 months for patients with previous stroke or TIA, demonstrating greater reduction in the risk of recurrent events when initiating treatment during or immediately after an acute stroke. The authors concluded that antiplatelet therapy should begin as soon as possible after the event.³⁷ Those stroke and TIA patients with multiple risk factors are most likely to benefit from early, aggressive interventions.⁴

Current Quality of Care

The American Heart Association/American Stroke Association has designed a program called Get With The Guidelines (GWTG)-Stroke to improve quality of care after TIA or stroke.¹ GWTG-Stroke tracked the performance of 778 participating hospitals involving 141,449 patients admitted with ischemic stroke or TIA in 2006. The GWTG-Stroke observed the following regarding 7 key performance indicators¹:

- 63% of patients who arrived at the hospital less than 2 hours after symptom onset received intravenous tPA
- 95% of inpatients received antithrombotics within 48 hours of admission
- 83% received deep vein thrombosis prophylaxis by the second day of hospitalization
- 98% received antithrombotics at discharge
- 98% received anticoagulation for atrial fibrillation at discharge
- 84% received counseling in regard to smoking cessation
- 82% received cholesterol-lowering therapy at discharge if their low-density lipoprotein level was >100 mg/dL or if they were on therapy at admission

GWTG-Stroke concluded that the quality of hospital care, including secondary preventive care, was generally good for patients admitted for stroke symptoms. Challenges remain in ensuring continuity of care posthospitalization³ and especially in getting prompt care to all patients who experience cerebrovascular events. Stroke patients should receive immediate emergency evaluation, including neuroimaging and appropriate urgent therapy to halt neuronal damage, and long-term therapy to

prevent future vascular events. TIAs are also medical emergencies, and patients who have one should seek medical attention as soon as possible. Primary care providers, in turn, should conduct full evaluations and send patients to the emergency department if they present within a few days of a suspected TIA or refer them to a neurologist if they present later.

Conclusion

Stroke is a leading cause of death and disability in the United States and worldwide. In addition to neurologic impairment, ischemic stroke survivors face an increased risk of recurrent stroke. In patients who have experienced a TIA or initial stroke, risk of recurrent stroke can be quantified based on concurrent risk factors such as age, hypertension, and diabetes. Lifestyle modifications and medical interventions can help reduce the risk. Pharmacotherapies for secondary prevention are most effective when initiated soon after the initial cerebrovascular event, when risk of suffering a second event is highest. With the inherent danger of recurrence, prompt attention to strokes and TIAs and wider application of effective secondary preventive therapy must become leading healthcare priorities.

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Funding Source: This supplement was supported by Boehringer Ingelheim.

Author Disclosures: Consultant: Boehringer Ingelheim and Servier.

Authorship Information: Concept, design, and drafting of the manuscript and critical revision of the manuscript for important intellectual content.

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