

# Stroke in the Elderly

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## Abstract

Stroke is one of the oldest but least understood diseases, and it is one of the major public health problems facing the elderly. Recent epidemiological investigations have found that the incidence of stroke has been underestimated by about 50%, and that the burden of disease is highest in minority populations. Recent clinical and basic neuroscience research indicates that stroke is neither unpredictable nor irreversible. Many risk factors for stroke are readily identifiable, and evidence-based treatment may be used to reduce the likelihood of stroke among those at risk. Rapid diagnosis and evaluation of stroke and transient ischemic attack and their treatment, including surgery, anticoagulation, antiplatelet and other medical therapies, reduce the chance of recurrence. More aggressive treatment of blood pressure, even among patients who are not necessarily hypertensive, may also reduce the risk of future strokes. Once ischemic stroke has occurred, emergent therapy using thrombolysis may significantly reduce disability, even among the elderly. This review presents an update on definitions of stroke and its subtypes, stroke epidemiology, and the results of recent studies of stroke prevention and acute treatment.

**Key Words:** Cerebrovascular disorders, clinical trials, epidemiology, elderly, stroke.

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STROKE is one of the oldest recognized diseases, but remains one of the least understood. A description of one of the most classic stroke syndromes, the left middle cerebral artery embolism, may have been described in the Bible: "If I forget you, O Jerusalem, let my right hand wither! Let my tongue cleave to the roof of my mouth, if I do not remember you, if I do not set Jerusalem above my highest joy!" (Psalm 137). In some ways, the general understanding of the causes and management of stroke has not progressed much since Biblical times. Most lay people and many physicians believe, for example, that a stroke is a sudden, unpredictable, irretrievable event, like a bolt of lightning blasting a tree. The last two decades of clinical and basic neuroscience research, however, have suggested that stroke is neither unpredictable nor irreversible. This paper focuses on stroke in the elderly, the group most commonly affected by stroke.

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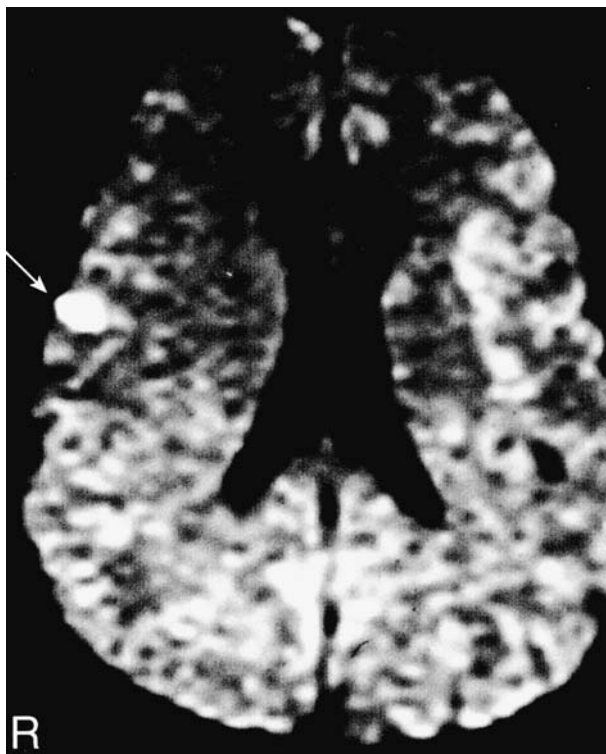
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## Definitions and Subtypes

The generally accepted definition of stroke originates with the World Health Organization (WHO) and dates back to 1980 (1): "Rapidly developing clinical signs of focal (at times global) disturbance of cerebral function, lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin." A transient ischemic attack (TIA) is generally accepted as consisting of the same symptoms, but lasting for up to 24 hours. In the past decade, however, with the advent of improved imaging technologies exquisitely sensitive to the earliest changes of ischemia, such as diffusion-weighted magnetic resonance imaging (MRI), it has become clear that changes consistent with infarction may be seen on MRI in patients whose symptoms last well under 24 hours (Fig. 1). In fact, as many as one-third of patients with symptoms lasting up to one hour have MRI evidence of brain injury (2). The artificial 24-hour line distinguishing stroke from TIA has therefore been called into question. From the neurologist's point of view, the duration of the symptoms is much less important than the cause of the event and what can be done to prevent a future, perhaps more serious — or even fatal — event.



**Fig. 1.** Abnormal diffusion-weighted MRI scan in a patient with 5 minutes of symptoms. Diffusion-weighted MRI scan in a 54-year-old man with a history of atrial fibrillation who presented with 5 minutes of dysarthria. Neurological examination after symptoms resolved was entirely normal. The MRI shows a small focus of diffusion signal abnormality in the right frontal operculum, consistent with acute ischemia or infarction.

Stroke comes in two major varieties, hemorrhagic and ischemic (Table 1). Approximately 15–20% of strokes are hemorrhagic, divided between subarachnoid hemorrhage and primary intracerebral hemorrhage. The former is classically related to the rupture of berry aneurysms

at the base of the brain, while the latter is due to bleeding from “microaneurysms” of smaller blood vessels, presumably weakened by hypertension. While subarachnoid hemorrhage affects people at all ages of life, the elderly can also be affected by intracerebral hemorrhage. One increasingly recognized cause of intracerebral hemorrhage is cerebral amyloid angiopathy, caused by the accumulation of amyloid beta-protein (the same amyloid protein that accumulates in the senile plaques of Alzheimer’s disease) in the walls of cerebral vessels (3). Amyloid angiopathy is important because of the high rate of recurrent hemorrhage, as much as 10% per year (4). Subclinical hemorrhages, detected by special gradient echo sequences on MRI scanning, may occur even more frequently (5). Patients with amyloid angiopathy may present with seizures, focal deficits, dementia, or transient attacks not unlike TIAs. Additional causes of cerebral hemorrhage include vascular malformations (arteriovenous malformations and cavernous angiomas), coagulopathies and blood dyscrasias, and neoplasms.

The majority of strokes, approximately 80%, are ischemic (Table 1). Unlike myocardial infarction, for which the etiology in the vast majority of patients is large artery atherosclerosis, only 20% of ischemic strokes are due to large vessel atherosclerosis affecting cerebral blood vessels. Importantly, this 20% is further subdivided between extracranial atherosclerosis (“surgical disease”) affecting the carotid or vertebral arteries, and intracranial atherosclerosis, affecting the distal carotid arteries and the vessels of the circle of Willis. Another 20% of ischemic strokes are due to cardiac embolism from a well-defined source of cardiac disease

**TABLE 1**  
*Stroke Subtypes*

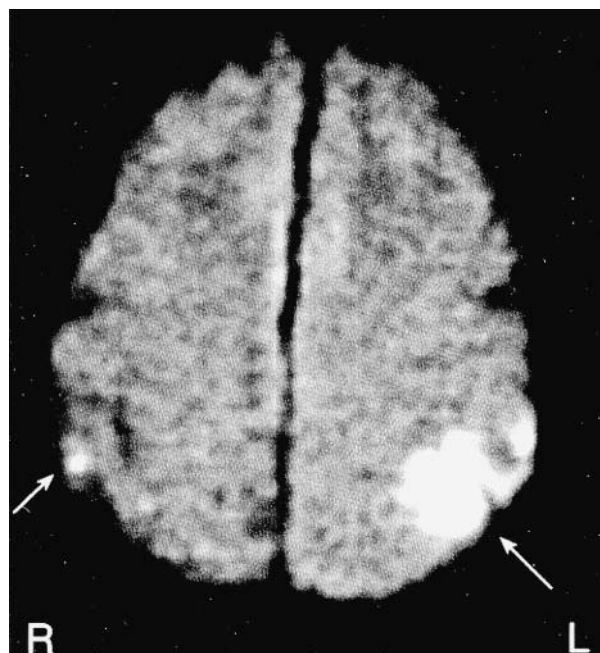
Type	Proportion of All Strokes
Hemorrhagic	15–20%
Subarachnoid hemorrhage	
Intracerebral hemorrhage	
Ischemic	80–85%
	Proportion of ischemic strokes
Extracranial atherosclerosis	10%
Intracranial atherosclerosis	10%
Cardioembolic	20%
Lacunar	20–30%
Cryptogenic	30–40%
Other (dissection, vasculitis, etc.)	<5%

such as valvular heart disease, atrial fibrillation, or mural thrombus. Approximately 20–30% of ischemic strokes are considered “lacunar,” due to small vessel disease affecting the thread-like penetrating arteriolar branches of the vessels of the circle of Willis. Lacunar infarcts typically cause a loss of elementary neurological function, causing such conditions as weakness, sensory loss, or unsteadiness, but spare more complex functions such as language and praxis, functions which localize for the most part to the surface gray matter of the hemispheres. Less than 5% of ischemic strokes are due to other specific but unusual causes, like arteritis, dissection, and hypercoagulability. Finally, about 30–40% of ischemic strokes remain unexplained even after a thorough investigation; these are usually termed “cryptogenic.” Many of these strokes are thought to be due to emboli from less well-recognized cardiac sources, including patent foramen ovale and aortic arch atheroma.

Stroke diagnosis is fairly straightforward when the symptoms are typical, such as right-sided weakness and nonfluent aphasia occurring together (as in Psalm 137). Many times, however, stroke syndromes are more subtle, and diagnosis may be delayed by hours, days, or even weeks. Common stroke syndromes that do not involve weakness are fluent (or Wernicke’s) aphasia and cortical visual loss. Because the inferior division of the middle cerebral artery supplies the lateral temporal and parietal lobes, including Wernicke’s area, infarcts in that vessel, usually produced by embolism, may cause a prosodic, fluent speech with multiple paraphasic errors and poor comprehension, while sparing the motor strip in the frontal lobe. The babbling, incomprehensible speech may be misinterpreted as a sign of psychosis, and the patient mistakenly triaged to the psychiatrist. Emboli traveling up the basilar artery may cause significant infarction in bilateral posterior cerebral arteries, causing complete blindness, sometimes with no awareness of the deficit on the part of the patient, due to infarction of both occipital lobes (the “top of the basilar syndrome”). Behavioral abnormalities are common. Memory loss and eye movement abnormalities may also occur, due to the involvement of the medial temporal lobe structures and the midbrain eye movement centers, respectively.

Determination of the stroke subtype requires a thorough diagnostic evaluation. At a minimum, all stroke patients should undergo diagnostic imaging of the brain (computed to-

mography [CT] or MRI), non-invasive evaluation of the blood vessels of the neck and brain (duplex Doppler ultrasound, transcranial Doppler ultrasound, magnetic resonance [MR] angiography or CT angiography), and echocardiographic evaluation (transthoracic echocardiogram or transesophageal echocardiogram), in addition to routine blood tests and electrocardiography (6). The advantages of MRI scanning include: (a) visualization of the location and extent of ischemia at its very earliest stages; (b) the ability to detect smaller infarcts (particularly in the brainstem, which is difficult to see on CT); and (c) the ability to detect additional infarcts not expected on the basis of the neurological examination, which may indicate a different cause of stroke (Fig. 2). Some medical centers which have advanced MR capability, including MR perfusion scanning, can further use the information provided to determine which patients with acute stroke are likely to benefit from thrombolytic reperfusion therapy. Non-in-



**Fig. 2.** Bilateral infarcts in setting of myocardial infarction (MI). Diffusion-weighted brain MRI scan in a 72-year-old man with acute aphasia and fluctuating right hemiparesis. Two days before, he had had chest pain for the first time. Emergency echocardiography disclosed anterior wall MI with mural thrombus. Intra-arterial thrombolysis of a branch of the left middle cerebral artery was performed with excellent results. This follow-up MRI shows abnormal signal in the left parietal region consistent with infarction, as well as an additional focus of diffusion signal abnormality in the right parietal region. These bilateral superficial infarcts are most consistent with a “shower” of emboli, and point to a proximal (i.e., cardiac) source of embolism.

vasive vascular imaging is usually adequate to answer most questions about the presence and degree of stenosis in major cerebral vessels, but occasionally conventional angiography is required when non-invasive tests are equivocal. The role of additional diagnostic imaging depends on the results of the initial evaluation and the clinical scenario.

### Epidemiology

It would be difficult to overestimate the public health impact of stroke. Stroke is the third leading cause of death and the leading cause of chronic serious disability in the United States. Recent epidemiological studies have provided evidence, moreover, that previous estimates of stroke incidence have underestimated the burden of disease. While earlier data based upon the Framingham study (7), for example, have suggested that there are 500,000 strokes annually in the United States, this data may have failed to take into account the racial and ethnic heterogeneity of the country, and the fact that minority groups are at higher risk of stroke than the predominantly white population studied in Framingham. Estimates based on data from the incidence of stroke in the more representative Cincinnati/Northern Kentucky area (8), for example, indicate that there may be as many as 750,000 strokes annually, an upward revision by 50% over previous estimates.

The impact of ischemic stroke on the population differs according to age, gender, and race-ethnicity, factors generally considered to be risk "markers" for stroke. Age, notably, has been consistently identified as the most important determinant of stroke. For every 10 years after age 55, the stroke rate more than doubles in both men and women (7, 8). Because stroke disproportionately affects the elderly, it is anticipated that the public health burden of stroke will increase in coming decades as the population ages. Overall, men have a greater stroke incidence rate than women by about 30%. Among younger individuals, however, the incidence of stroke among men and women is approximately the same, probably reflecting an increased risk of stroke among young women due to pregnancy and hormonal factors. In the elderly population, women stroke victims outnumber men significantly, despite a lower incidence, because women live longer than men. Stroke, therefore, particularly in the geriatric population, should not be considered simply a disease of men.

Race and ethnicity are also related to stroke incidence and mortality rates. Stroke incidence among blacks in the Cincinnati region is two to four times as high as among whites in Rochester, Minnesota (8). In the Northern Manhattan Stroke Study, blacks and Hispanics each had elevated overall annual age-adjusted relative risks of ischemic stroke compared with whites (2.0 and 3.2 for black men and women, and 1.9 and 2.3 for Hispanic men and women, respectively) (10). Several studies have shown increased mortality rates among blacks and other minority groups. Overall, blacks are more than twice as likely as whites to die of stroke (11). There is some evidence that the increased mortality among blacks is related to socioeconomic and environmental factors, although as much as 50% of the difference in mortality remains unexplained (12).

### Risk Factors and Prevention

The majority of strokes occur in people with well-established risk factors (Table 2), and in whom a first stroke can be prevented with the appropriate medications or other treatment

**TABLE 2**  
*Stroke Risk Factors*

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Non-modifiable Risk "Markers"	
	Age
	Male gender
	Race and ethnicity
	Genetic factors
Potentially Modifiable Risk Factors	
Cardiac Risk Factors	
	Well-accepted
	Atrial fibrillation
	Myocardial infarction
	Left ventricular thrombus
	Valvular heart disease
	Postulated
	Patent foramen ovale
	Atrial septal aneurysm
	Aortic arch atheroma
	Mitral annular calcification
	Mitral valve strands
	Hypertension
	Hyperlipidemia
	Cigarette smoking
	Diabetes mellitus
	Physical inactivity
	Heavy alcohol consumption
	Drug abuse (especially cocaine)
	Antiphospholipid antibodies
	Homocysteine
	Carotid artery stenosis
	Transient ischemic attack

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(primary prevention; Table 3) (13–23). Because of the limited options for treating patients once stroke has occurred (see below), recognition of risk factors and aggressive prevention efforts remain the best way to reduce the burden of stroke in the U.S. Risk factors can be divided into medical conditions, such as hypertension and diabetes mellitus, and behaviors, including cigarette smoking and physical inactivity. Physicians should attempt to address both medical conditions and behavioral risk factors when discussing stroke risk. Alcohol consumption has a complex relationship with stroke: it appears to increase the risk of hemorrhagic stroke in a linear dose-dependent fashion, but decreases the incidence of ischemic stroke in small doses (up to 2 drinks daily) and increases the risk of ischemic stroke at high doses (5 or more drinks per day). The National Stroke Association guidelines state that drinking in moderation may be protective against stroke, as long as there are no other contraindications (24).

Antihypertensive medications can reduce the risk of stroke in patients with hypertension, and warfarin can reduce the risk in patients with atrial fibrillation. Treatment of hyperlipidemia reduces the risk of a first stroke, though not to the same degree that it reduces the risk of a first myocardial infarction (MI), possibly reflecting the heterogeneity of causes of stroke compared with the causes of MI.

Surgical carotid endarterectomy reduced the risk of a first stroke among patients with asymptomatic carotid stenosis of at least 60% in the Asymptomatic Carotid Atherosclerosis Study (ACAS) (23). The benefit was of moderate clinical significance, however, reducing the incidence of stroke from about 2% to 1% annually, reflecting the low rate of stroke in the asymptomatic patient. Complication rates were higher among women than men (3.6% vs. 1.7%), and an independent, clinically significant benefit was not found in women. Patients aged 80 and older and those with symptomatic cardiac disease were not eligible for the study, so the procedure should not be routinely recommended to those over the age limit used in the study, and particularly not to those with concomitant cardiac disease. In addition, the procedure should only be performed by an experienced surgeon with a demonstrated perioperative complication rate below 3%. The role of carotid angioplasty and stenting in this population also remains unproven. Table 3 lists several interventions proven in randomized, clinical trials in recent years to prevent a first ischemic stroke.

Once a stroke has occurred, many of the same risk-factor-modifying therapies shown to be effective in primary prevention are likely to continue to be of benefit in preventing recurrence (secondary prevention; Table 4). Moreover, investigators have recently shown that

**TABLE 3**  
*Primary Prevention of Ischemic Stroke in the Elderly*

Risk Factor	Treatment	Trial (Reference)
Hypertension	Antihypertensive	SHEP (13), others
Myocardial infarction	HMG CoA reductase inhibitors	4S (14), CARE (15), LIPID (16)
Hyperlipidemia	HMG CoA reductase inhibitors	WOSCOPS (17)
Atrial fibrillation	Warfarin	AFASAK1 (18), SPAF (19), BAATAF (20), SPINAF (21)
	Aspirin	SPAF (19)
Diabetes mellitus	Ramipril (ACE inhibitor)	HOPE
	Glycemic control	
Asymptomatic carotid stenosis	Carotid endarterectomy	ACAS (24)
Behavioral risk factors (smoking, heavy alcohol consumption, drug abuse, physical inactivity, etc.)	Stop smoking; limit or eliminate alcohol consumption; avoid drug abuse; exercise, etc.	—

HMG CoA=3-hydroxy-3-methyl glutaryl-coenzyme A; ACE=angiotensin-converting enzyme; SHEP=Systolic Hypertension in the Elderly Prevention Trial; 4S=Scandinavian Simvastatin Survival Study; CARE=Cholesterol and Recurrent Events Trial; LIPID= Long-Term Intervention with Pravastatin in Ischaemic Disease; WOSCOPS=West of Scotland Coronary Prevention Study; AFASAK=Atrial Fibrillation, Aspirin and Anticoagulation Study; SPAF=Stroke Prevention in Atrial Fibrillation; BAATAF= Boston Area Anticoagulation Trial in Atrial Fibrillation; SPINAF=Veterans Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation Study; HOPE=Heart Outcomes Prevention Evaluation; ACAS=Asymptomatic Carotid Atherosclerosis Study.

**TABLE 4**  
*Secondary Prevention of Ischemic Stroke in the Elderly*

<b>Risk Factor</b>	<b>Treatment</b>	<b>Trial (Reference)</b>
Hypertension (and consider in all patients, with or without hypertension)	Perindopril (ACE inhibitor) plus indapamide (diuretic) or ramipril	PROGRESS (25)  HOPE (26)
Atrial fibrillation	Warfarin	EAFT (22)
Other definite cardioembolic source	Warfarin	—
No cardioembolic source	Antiplatelet therapy Warfarin*	Multiple (see text) WARSS (40)
Symptomatic carotid stenosis	Carotid endarterectomy	NASCET (27)
Hyperlipidemia	HMG CoA reductase inhibitors	—
Diabetes mellitus	Glycemic control	—
Behavioral risk factors (smoking, heavy alcohol consumption, drug abuse, physical inactivity, etc.)	Stop smoking; limit or eliminate alcohol consumption; avoid drug abuse; exercise, etc.	—

\*In some cases, even in patients without cardioembolic source, such as those with severe intracranial stenosis, patent foramen ovale, aortic atheroma, or recurrent strokes despite antiplatelet therapy, anticoagulation with warfarin remains a reasonable alternative treatment (see text).

ACE=angiotensin-converting enzyme; HMG CoA=3-hydroxy-3-methyl glutaryl-coenzyme A; HOPE=Heart Outcomes Prevention Evaluation; PROGRESS=Perindopril Protection Against Recurrent Stroke Study; EAFT=European Atrial Fibrillation Trial; WARSS=Warfarin Aspirin Recurrent Stroke Study; NASCET=North American Symptomatic Carotid Endarterectomy Trial.

among patients with a first stroke or TIA, even in the absence of documented hypertension, treatment with antihypertensive therapy may reduce the risk of a recurrent event. Once a patient has had a stroke, it has been suggested, even a blood pressure traditionally defined as normal may be too high. In the Perindopril Protection against Recurrent Stroke Study (PROGRESS) trial (25), for example, an international, randomized, double-blind, placebo-controlled trial of antihypertensive therapy among 6,105 patients with a history of stroke (hemorrhagic or ischemic) or transient ischemic attack within the past 5 years, patients were enrolled independent of hypertension status, and 52% were considered non-hypertensive (i.e., systolic BP  $\leq$  160 and diastolic BP  $\leq$  90 mm Hg). The mean blood pressure among non-hypertensives was 136/79 at baseline. Active treatment with the combination of the angiotensin-converting enzyme (ACE) inhibitor perindopril 4 mg daily and the diuretic indapamide 2.5 mg daily led to a reduction in blood pressure of 12/5 mm Hg compared with placebo, and a statistically significant 43% reduction in stroke risk. The combination therapy provided a benefit of a similar magnitude among both hypertensive and non-hypertensive

patients. The role of ACE inhibitor therapy in stroke prevention is also supported by the Heart Outcomes Prevention Evaluation (HOPE) trial (26), which enrolled patients with a history of stroke, MI or diabetes, independent of blood pressure status, and randomized patients to the ACE inhibitor ramipril or placebo. Approximately 10% of patients had a history of stroke. In that study, despite a very small mean blood pressure reduction of 3/2 mm Hg, there was a statistically significant 22% risk reduction in vascular events. Trials are ongoing to determine whether lipid-lowering therapy with statins can reduce the risk of recurrent stroke in patients with normal or near-normal lipid levels (and free of concomitant heart disease) in the same way that such treatment reduces the risk of recurrent cardiac disease.

In patients with symptomatic carotid stenosis, carotid endarterectomy substantially reduces the risk of recurrent stroke. In the North American Symptomatic Carotid Endarterectomy Trial (NASCET), surgery reduced the 2-year risk of recurrent stroke from 26% with medical management alone to 9% (27). The available data suggest that there is no advantage to angioplasty and stenting over carotid surgery for the symptomatic patient (28, 29). While

coronary angioplasty has clear advantages over bypass surgery, including avoidance of a very painful sternotomy, obtaining surgical access to the carotid artery involves a small incision and minimal dissection in the neck. Patients do not have significant pain, do not require prolonged rehabilitation, and may be able to leave the hospital the day after the procedure. Carotid endarterectomy may even be performed for some patients using local anesthesia. Until large, randomized trials demonstrate its value, carotid angioplasty and stenting should be considered an experimental procedure, and endarterectomy the procedure of choice. In certain select settings, however, angioplasty offers advantages over endarterectomy. In patients with surgically inaccessible disease due to a high carotid bifurcation or intracranial atherosclerosis, for example, angioplasty may be the only option.

In addition to management of medical and behavioral risk factors, and surgery when indicated, antiplatelet therapy reduces the risk of recurrent stroke after a first event. Studies have consistently demonstrated the benefit of aspirin, the mainstay of antiplatelet treatment (30, 31). The optimal dosage of aspirin remains controversial, though recent trial data provide support for doses of 50–325 mg (32, 33). Gastrointestinal side effects are less frequent with lower aspirin doses. In a meta-analysis (34) of randomized data among more than 10,000 patients with cerebrovascular disease, investigators found that 37 future vascular events per 1,000 patients treated could be prevented ( $p < 0.000005$ ) with aspirin. The relative odds reduction was similar for those presenting with completed stroke (23%) versus TIA (22%) (34), again disparaging the notion of a strict demarcation between the two.

The past decade has witnessed the development of several new antiplatelet agents that can be used in place of or in addition to aspirin. Ticlopidine and clopidogrel, related thienopyridine-derivative compounds that inhibit adenosine diphosphate-induced platelet aggregation, are both effective (35). Ticlopidine was more effective than aspirin at preventing stroke among those with TIA or minor stroke in the Ticlopidine Aspirin Stroke Study (TASS), though its benefit in reducing a composite endpoint of stroke, MI, or vascular death was less clear (36). Side effects with ticlopidine also limit its use; they include diarrhea in more than 10% and severe neutropenia in approximately 1% of patients. Considering patients with a history of MI, stroke, and peripheral arterial disease as a group, clopidogrel, a compound ap-

proved by the FDA in 1998 and related to ticlopidine, was marginally superior to aspirin in preventing a composite outcome event; absolute risk reduction with clopidogrel was 0.5%, from 5.8% to 5.3% annual risk ( $p = 0.05$ ). There was statistically significant heterogeneity among the different patient categories in the population, however, and for the approximately 6,000 patients with cerebrovascular disease, clopidogrel was comparable to aspirin (37). Clopidogrel is generally well tolerated, although reports of thrombotic thrombocytopenic purpura have led some to recommend routine monitoring of platelet levels after initiating therapy (38).

Combination therapy with two antiplatelet agents is an emerging strategy that has been tested in the European Stroke Prevention Study 2 (ESPS 2). It utilized a factorial design comparing placebo, aspirin 25 mg twice daily, a new extended-release formulation of dipyridamole 200 mg twice daily, and the combination of aspirin and dipyridamole at these doses (39). The combined therapy arm had the greatest benefit, with reduction in risk of stroke essentially additive between the single treatment arms (risk reduction of 37%,  $p < 0.001$ , with combined treatment compared to placebo). The combination of other antiplatelet agents with distinct mechanisms of action, such as clopidogrel and aspirin, is currently being tested in stroke patients in other studies, and may play an increasing role in the future.

The role of warfarin in secondary stroke prevention among patients without definite cardioembolism has recently been revised to some extent on the basis of the Warfarin Aspirin Recurrent Stroke Study (WARSS) results (40). This study was designed to test whether warfarin (international normalized ratio [INR] 1.4–2.8) is more effective than aspirin (325 mg) in preventing recurrent stroke. The study was a randomized, blinded trial for patients who had had an ischemic stroke within 30 days prior to randomization, without severe carotid stenosis or definite cardioembolic source (i.e., patients with aortic atheroma or patent foramen ovale were eligible for enrollment). After 2 years of follow-up with 2,206 patients, there was no statistically significant advantage of warfarin over aspirin. Patients were also stratified by etiologic subtype, and in no group was warfarin more efficacious than aspirin. Notably, warfarin was not less safe than aspirin (annual risk of major hemorrhage: 2.2% on warfarin and 1.5% on aspirin,  $p = 0.10$ ). Warfarin remains

a reasonably safe alternative for some patients with ischemic stroke, such as those with severe intracranial stenosis; cryptogenic superficial, cortical infarction with patent foramen ovale; mobile aortic atheroma; or recurrent strokes despite antiplatelet therapy. Its utility in the majority of stroke patients, however, remains unproven.

### Acute Treatment for Stroke in the Elderly

As noted briefly above, stroke is not necessarily an irreversible event. Stroke evolves over a period of time, with the time required for irreversible neuronal injury dependent upon the degree of the reduction in blood flow to the brain. The longer blood flow is impaired and the lower the blood flow, the more likely it is that irreversible brain injury will occur. These facts have clinical implications. The first is that early blood flow restoration is more likely to salvage brain tissue. Thus, therapies designed to restore blood flow, such as tissue-type plasminogen activator (rt-PA), should be given as quickly as possible. The pivotal trial that demonstrated the benefit of rt-PA for acute ischemic stroke, the National Institute of Neurological Disorders and Stroke (NINDS) trial, showed that there was a statistically significant benefit in favor of rt-PA over placebo for patients treated within 3 hours of symptom onset (41). The proportion of patients that achieved functional independence in activities of daily living at 3 months after stroke was 50% in the group treated with rt-PA compared with 38% in the placebo group. Further analyses of the data from the study have shown that the earlier thrombolytic therapy was administered in the pivotal NINDS rt-PA study, the more likely patients were to have a favorable outcome, a point which was not recognized at the time tPA was first approved for stroke (42).

An understanding of the pathophysiology of stroke also leads to the recognition that levels of cerebral blood flow must be maintained as high as possible in the setting of acute ischemic stroke. Under ordinary circumstances (i.e., in the healthy brain not undergoing ischemia), cerebral arterioles are able to maintain adequate cerebral blood flow throughout a wide range of systemic blood pressures via the process of autoregulation. In the setting of stroke, however, cerebral autoregulation fails and collateral blood flow through the circle of Willis and other routes becomes heavily dependent upon systemic blood pressure. Thus, attempts to re-

duce blood pressure, though well intended by the emergency room physician most often accustomed to treating cardiac ischemia, may actually exacerbate brain ischemia and worsen an infarct. Some recent data even suggest that hypertensive therapy may be of benefit in limiting cerebral injury after stroke (43). Hypertension should be avoided, however, in patients who have received thrombolytic therapy, as it may increase the risk of hemorrhagic conversion in this setting. General principles for the management of acute ischemic stroke are given in Table 5.

The use of rt-PA for acute ischemic stroke continues to encounter resistance in some quarters, due to the increased risk of hemorrhagic conversion associated with rt-PA use after ischemic stroke. In the NINDS trial, there was a 6.4% risk of symptomatic hemorrhage within 36 hours among those treated with rt-PA, compared with a 0.6% risk among those treated with placebo (41). Not surprisingly, this tenfold increase in risk has scared many away from using rt-PA for ischemic stroke. The overall rate of neurologic worsening in 36 hours, however, was in fact similar between the two groups (17.4% in the rt-PA group and 18.3% in the

**TABLE 5**  
*Management of Acute Ischemic Stroke*

1. Determine time window (time since patient was last known to be normal)	
0–3 hours:	Consider intravenous rt-PA 0.9 mg/kg
3–6 hours:	Consider intra-arterial thrombolysis
> 6 hours:	Aspirin 325 mg and consider addition of heparin 5000 units subcutaneously twice daily*
2. General principles of management	
ABC's (Airway, Breathing, Circulation)	
Avoid hypotension	
For patients who receive thrombolysis, maintain systolic blood pressure <180 mm Hg and diastolic blood pressure < 105 mm Hg	
Avoid hyperglycemia (goal blood sugar < 180)	
Avoid hyperthermia/treat fever and infections	
Avoid free water/hydrate with normal saline	
Treat seizures if they occur	
Consider neurosurgical intervention in setting of cerebellar infarction with edema / hydrocephalus or massive hemispheric infarction with edema / risk of herniation	

\*In some situations, including cardioembolic stroke or severe arterial stenosis, adjusted-dose unfractionated heparin may be considered the best treatment, according to the discretion of the treating physician.

See text for references.

rt-PA=recombinant tissue-type plasminogen activator

placebo group). This perhaps surprising result is due to the fact that other adverse consequences of having a stroke — brain swelling and herniation, recurrent ischemia, seizures, and others — occurred more frequently in those who did not receive rt-PA. In other words, hemorrhage is not the only adverse consequence of ischemic stroke. Also, those patients who suffered symptomatic hemorrhages were those who initially presented with large strokes; these patients may have been likely to go on to hemorrhage or to have a poor prognosis even in the absence of rt-PA. Several phase IV studies have since confirmed the generalizability of the benefits of rt-PA to the community at large (44).

The reluctance to use rt-PA is particularly strong, however, in treating elderly patients, as the elderly are thought to be at higher risk of hemorrhage after thrombolysis than are younger patients. Older patients also have a worse overall prognosis after stroke than do younger patients. A secondary analysis of the NINDS trial, however, found that elderly patients do not have a higher risk of converting to symptomatic hemorrhage, and that, on average, they demonstrate the same benefit from rt-PA as do younger patients (45). There is, therefore, no *a priori* reason to exclude the elderly patient from thrombolytic treatment on the basis of age alone. Because the benefit of treatment is primarily to increase the long-term likelihood of independence, however, it would not be unreasonable to limit treatment to those who were previously independent. The elderly, demented nursing home resident, for instance, will not be restored to independence as a result of thrombolytic therapy.

Most patients will not be treated within 3 hours of onset of their strokes. Nationwide, only about 1–2% of stroke patients are treated with thrombolytic therapy. Studies that have employed intravenous thrombolytic agents administered beyond three hours, moreover, have not found a benefit in functional outcome despite an increased risk of hemorrhage (46, 47). A pivotal clinical trial (48) using intra-arterial thrombolysis with prourokinase among patients with hemispheric infarcts treated up to 6 hours after symptom onset, however, found a benefit in terms of functional outcome at 3 months, but this form of aggressive treatment is only available in selected centers.

Beyond the 6-hour time window, except in rare cases, antiplatelet therapy and subcutaneous heparin at a dose of 5000 units twice daily remain the mainstays of treatment. Nei-

ther adjusted-dose unfractionated heparin nor heparinoids have been convincingly shown to be of benefit in acute stroke treatment, despite a long history of use. In the International Stroke Trial (IST) (49), 19,435 patients with acute ischemic stroke were randomized in a 3 × 2 factorial design study to receive either heparin 12,500 units subcutaneously twice daily, heparin 5000 units subcutaneously twice daily, or no heparin; and aspirin 300 mg daily or no aspirin. There were thus 6 possible allocation groups. At 6 months, after adjustment for severity of the stroke, there was in the aspirin group (vs. placebo, independent of heparin) a statistically significant reduction of 14 per 1000 treated in those who died or were left dependent. Other trials of aspirin in acute stroke have provided similar results (50), suggesting that aspirin is not only an effective long-term stroke preventative therapy, as discussed above, but that it might have a role to play in acute stroke management as well. There was some evidence from the IST to suggest that the combination of aspirin and low-dose subcutaneous heparin (5000 units twice daily) provided the best short-term outcome, though this was based on subgroup analysis.

## Conclusions

Stroke continues to be one of the major public health problems facing the elderly today. The past two decades of investigations into stroke imaging, epidemiology, pathophysiology, and treatment have fundamentally changed the way in which stroke is viewed by neurologists. Stroke can be prevented in many cases, and successfully treated in others when it occurs. Crucial to our success in doing so, however, is improved education of patients and physicians, the rapid and thorough evaluation of patients with symptoms of TIA and stroke, and further research into causes and treatment of stroke.

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