The Latest on Ischemic Stroke

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CASE VIGNETTE

The patient is a 69-year-old construction worker with a longstanding history of hypertension, coronary artery disease, hyperlipidemia, and benign prostatic hypertrophy who woke up with symptoms of dizziness and aphasia. He fully understood the questions asked of him but often had a delay before he could "find the right words" to answer. His wife states that he was in his normal state of health when he went to bed then awoke with these symptoms. The patient is a non-smoker and denied any weakness, numbness, vision changes, chest pain, palpitations, or difficulty ambulating. He admits to having had difficulty with controlling his blood pressure despite compliance with antihypertensives and a low-salt diet. His medical regimen includes aspirin, losartan, hydrocholorthiazide, metoprolol, amlodipine, and doxazosin. Initial vital signs include a regular heart rate of 65 beats/minute, blood pressure of 170/90 mm Hg, and respiratory rate of 15. Neurological physical exam revealed an expressive aphasia. Initial laboratory findings, including complete blood count, comprehensive metabolic panel, and coagulation studies, as well as a nonconstrast computed tomogram (CT) of the head, revealed no abnormalities. Magnetic resonance imaging (MRI) showed a subacute infarct involving the left posterior frontal and left frontal-parietal-occipital junction (Figure). A magnetic resonance angiogram (MRA) of the head and neck was normal.

The patient was admitted to the hospital with a diagnosis of subacute cerebral infarction and expressive aphasia. A National Institutes of Health Stroke Scale (NIHSS) score was calculated to be four with deficits of aphasia and dysarthria. Because the patient had awoken with these symptoms, he was not eligible for thrombolysis as the last known time of normal health was when he went to sleep the night before. Antihypertensives were initially held, and the systolic blood pressure ranged from 150-170 mmHg. Aspirin, atorvastatin, and subcutaneous enoxaparin for deep venous thrombosis prophylaxis were started upon admission. The patient did not have any episodes of hyperglycemia or hyperthermia that required treatment. A fasting lipid profile revealed a low-density lipoprotein (LDL) cholesterol of 126 mg/dL (normal 63-129) and a high-density lipoprotein (HDL) cholesterol of 43 mg/dL (normal 40-75). Cardiac enzymes, serial electrocardiograms, and an echocardiogram were reportedly without abnormalities and helped exclude a cardioembolic source of the patient's cerebral infarction. The patient exhibited a moderate expressive aphasia and was enrolled in a speech therapy program. A bedside

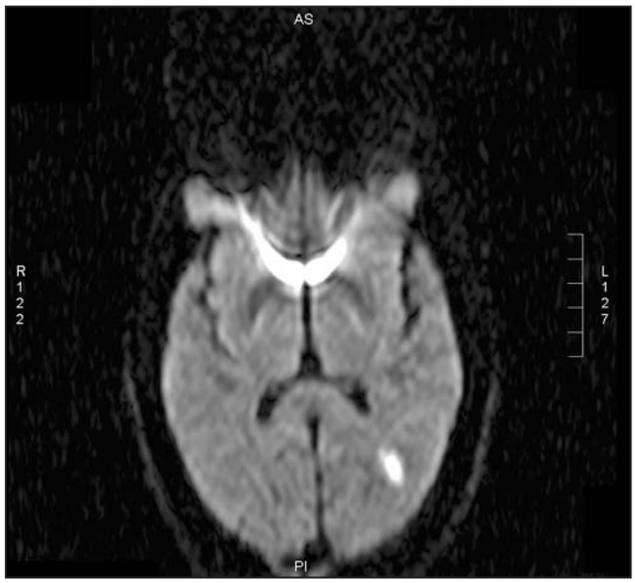

Figure. Diffusion-weighted magnetic resonance image showing subacute infarct in the left posterior parietal lobe.

swallow study resulted in a recommendation for a diet of regular textures with thin liquids. The patient's speech pattern continued to improve, and he was discharged with outpatient speech therapy follow-up. Discharge medications included clopidogrel, atorvastatin, hydrochlorothiazide, lisinopril, metoprolol, amlodipine, and doxazosin titrated to control his blood pressure. The patient's aphasia has since resolved, and he is now back at work in the construction business.

DISCUSSION

Epidemiology

Stroke remains the third leading cause of death in the United States behind heart disease and cancer.[1] There are 780,000 new or recurrent strokes each year.[1] Strokes occur in the United States every 40 seconds, and someone dies from a stroke every three minutes.[1] Of these strokes, 87% are ischemic, and 13% are hemorrhagic.[1] Ischemic strokes are usually classified as thrombotic or embolic. Thrombotic ischemic strokes usually occur from atherosclerosis of the carotid and cerebrovascular system. These can be further divided into large vessel disease, such as strokes involving the regions of the anterior, middle, or posterior cerebral artery distribution, or small vessel disease, such as lacunar strokes from uncontrolled hyptertension. Embolic ischemic strokes, on the other hand, can occur in the absence of cerebrovascular disease and result from the migration of emboli from cardioembolic sources, such as atrial fibrillation, atrial myxoma, left atrial or ventricular thrombus, recent myocardial infarction, systolic heart failure, valvular heart disease, patent foramen ovale, or left ventricular aneurysm.

Primary Prevention

There are many non-modifiable and modifiable risk factors for ischemic stroke. Non-modifiable risk factors include age, sex, race/ethnicity, low birth weight, and genetic factors. The risk of ischemic stroke doubles for each successive decade after 55 years of age.[2] Men have a higher incidence of stroke than women in all age groups except in the 35 to 44 year-old range and in those older than 85 years. Pregnancy and the use of oral contraceptives in 35 to 44 year-old women and earlier cardiac deaths of elderly men account for these differences.[3,4] African-Americans and Hispanics have a higher incidence of stroke and increased stroke mortality compared with whites, a finding thought to be due to a higher prevalence of hypertension, diabetes, and obesity in these populations.[5,6,7] Stroke risk has also been directly linked to a paternal or maternal history of stroke, perhaps due to a combination of genetic inheritance of other stroke risk factors as well as the sharing of lifestyle patterns that could lead to an ischemic stroke.[8]

Modifiable risk factors for ischemic stroke are diverse, with many mirroring those seen in coronary artery disease (Table 1). Hypertension is a major risk factor for the development of stroke. The Systolic Hypertension in the Elderly Program was the first trial to investigate an isolated increase in systolic blood pressure and its effect on stroke and cardiovascular disease.[9] Patients were aged 60 years or older and were randomized to a thiazide diuretic or a beta blocker versus placebo. Compared to those on placebo, the patients placed on anti-hypertensives had a 36% decrease in the incidence of stroke, with those reaching a systolic blood pressure less than 150 mm Hg having a 38% decrease in stroke compared to patients on blood pressure medications who failed to reach this threshold. The Blood Pressure Lowering Treatment Trialists' Collaboration was established in 1995 and performed multiple prospective randomized trials on different blood pressure regimens and their effect on stroke and cardiovascular disease.[10] Results demonstrated that in primary prevention of stroke, the degree of blood pressure lowering dictated the amount of risk reduction. The benefit of this blood pressure lowering was independent of the class of antihypertensives used, a finding in contrast to secondary prevention of ischemic stroke.

Many scoring systems are used to determine the need for anticoagulation in patients with atrial fibrillation to prevent ischemic stroke. Universal high risk features seen on all the scoring models include older age, hypertension, and a history of stroke or transient ischemic attack (TIA). Many include left ventricular dysfunction, diabetes, and coronary artery disease as well. The CHADS2 score is the only system that is validated in a randomized trial.[11] The score gives one point each for congestive heart failure, hypertension, age >75 years, and diabetes, and two points for a history of stroke, TIA, or prior systemic embolic event. Patients with atrial fibrillation who have a stroke rate of greater than 4%per year should be placed on warfarin.[12] This would include any patient with a CHADS2 score >3 or those with a score of 2 solely from a history of TIA or stroke (Table 2).

Dyslipidemia is a risk factor for ischemic stroke as well as for coronary artery disease. Increasing levels of total cholesterol have been shown to be associated with higher rates of ischemic stroke.[13] However, no consistent association

Table 1. Modifiable risk factors for ischemic stroke.

Hypertension	Dyslipidemia	Diabetes	Inactivity	Smoking
Atrial Fibrillation	Carotid Stenosis	Obesity	Nutrition	Postmenopausal Hormones

Table 2. CHADS2 Scoring System.

CHADS2 Score	Stroke Rate	Recommended Treatment
0	1%/yr	Aspirin
1	1.5%/yr	Aspirin
2	2.5%/yr	Aspirin/ Warfarin
3	5%/yr	Warfarin
4	>7%/yr	Warfarin
5-6	>7%/yr	Warfarin
*2 (from history of stroke or TIA)	5.9%/yr	Warfarin

has been made between LDL cholesterol and ischemic stroke,[14] while low HDL levels have been proven to be a risk factor for ischemic stroke in men.[15,16] The use of HMG-CoA reductase inhibitors (statins) has been shown to prevent ischemic stroke in patients with existing coronary artery disease. The lipid-lowering arm of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) randomized over 20,000 patients with baseline hypertension and other cardiovascular risk factors such as diabetes, smoking, peripheral arterial disease, and cerebrovascular disease.[17] These patients had a baseline LDL of less than 130 mg/dL and received either atorvastatin 10mg/day or placebo. Despite the low initial cholesterol levels, patients receiving statin therapy had a 27% decrease in fatal and nonfatal stroke. Thus, patients with known CAD[18] or high-risk hypertensive patients even, with normal LDL cholesterol levels, should be treated with lifestyle modification and statin therapy.[19]

Several studies have shown the benefit of carotid endarterectomy (CEA) in certain symptomatic and asymptomatic patients with carotid stenosis. The Asymptomatic Carotid Atherosclerosis Study (ACAS) enrolled patients with >60% asymptomatic carotid stenosis and randomized those patients to full-dose aspirin versus aspirin plus CEA.[20] The study was stopped prematurely after 2.7 years due to the obvious benefit to patients who received surgery and had a 5% rate of stroke at five years, much less than the 11% stroke rate in those patients on aspirin alone. The Asymptomatic Carotid Surgery Trial (ACST) verified the findings of the ACAS trial and also noted that patients who received carotid endarterectomies within one month of diagnosis had better outcomes than those whose operations were deferred (6.4% vs. 11.8% five-year stroke risk).[21] The benefit was not statistically significant if the patient were greater than 75 years of age and was greater in men than in women. Therefore, prophylactic CEA is now recommended in a certain population of patients with high-grade (>60%) asymptomatic carotid stenosis if the surgical risk is less than 3%.[19] However, the United States Preventive Services Task Force recommends against screening the general population for asymptomatic carotid artery stenosis, as 4,000 people would need to be screened to prevent one stroke at five years.[22]

Diabetes is a well recognized risk factor for both ischemic stroke and coronary artery disease. The UK Prospective Diabetes Study Group found that strict blood pressure control (mean, 144/82 mmHg) resulted in a 44% reduction in stroke compared to those with less rigid control (mean, 154/87 mmHg).[23] In addition, use of a statin in diabetic patients has been shown to lower the risk of a first stroke.[18] Tight glycemic control, while useful in the prevention of microvascular diabetic complications, has not been shown to decrease stroke risk in a randomized trial.[19]

There are many lifestyle factors that can affect a patient's risk of stroke. Obesity and sedentary lifestyle are associated with an increased risk of stroke.[18] Nutrition is actively being studied to evaluate the role of diet in the risk of cerebrovascular events. Increased fruit and vegetable consumption has been associated with a reduced risk of stroke.[24] Active smoking and exposure to secondhand smoke are both significant risk factors for the development of ischemic stroke, and smoking cessation is associated with a rapid reduction in the risk of stroke to that seen in nonsmokers.[18] In regards to postmenopausal hormone therapy, the Women's Health Initiative evaluated the role of hormone therapy in the primary prevention of cardiovascular disease.[25] Postmenopausal hormone therapy was found to be associated with an increased risk of myocardial infarction, deep venous thrombosis, pulmonary embolism, breast cancer, and stroke. Therefore, postmenopausal hormone therapy is not recommended for use in the primary prevention of stroke.[18]

Hospital Management

Appropriate early management of the patient hospitalized with ischemic stroke is paramount to good clinical outcomes. A complete history and physical exam, including a thorough neurological exam, should be completed upon patient arrival. Within 20 minutes, the patients should receive a noncontrast head CT or brain MRI that is read within 45 minutes to assess for evidence of hemorrhage.[26] Oxygen saturation should be checked, and routine laboratory tests, including complete blood count, platelets, routine chemistries, and coagulation studies should be ordered. An electrocardiogram (ECG), cardiac enzymes, and echocardiogram should be ordered to rule out concomitant cardiac ischemia and sources of cardioembolism. Multiple MRI modalities are available, including diffusion-weighted imaging, perfusion-weighted imaging, MR angiography, or gradient echo MRI. Diffusion-weighted MRI examines the movement of water molecules into areas of ischemia. Perfusion-weighted MRI, on the other hand, quantifies the amount of MR contrast agent after an intravenous bolus. Gradient echo MRI has the added ability to detect early hemorrhage and is an option as a sole imaging modality in the early diagnosis of stroke. Once the diagnosis of stroke is made, a formal stroke scoring system, such as the

Table 3. National Institutes of Health Stroke Scale.

Level of consciousness	0-alert 1-drowsy 2-obtunded 3-coma/unresponsive	**Motor function-** **Left leg** **Right leg**	0-no drift 1-drift before 5 seconds 2-falls before 5 seconds 3-no effort against gravity 4-no movement
Orientation	0-answers both questions correctly 1-answers one question correctly 2-answers neither question correctly	**Limb ataxia**	0-no ataxia 1-ataxia of 1 limb 2-ataxia of 2 limbs
Response to commands	0-performs both tasks correctly 1-performs one task correctly 2-performs neither task correctly	**Sensory**	0-no sensory loss 1-mild sensory loss 2-severe sensory loss
Gaze	0-normal horizontal movements 1-partial gaze palsy 2-complete gaze palsy	**Language**	0-normal 1-mild aphasia 2-severe aphasia 3-mute or global aphasia
Visual Fields	0-no visual defect 1-partial hemianopia 2-complete hemianopia 3-bilateral hemianopia	**Articulation**	0-normal 1-mild dysarthria 2-severe dysarthria
Facial Movement	0-normal 1-minor facial weakness 2-partial facial weakness 3-complete unilateral palsy	**Extinction/Inattention**	0-absent 1-mild (loss 1 sensory modality) 2-severe (loss 2 sensory modalities)
Motor function- **Left arm** **Right arm**	0-no drift 1-drift before 5 seconds 2-falls before 10 seconds 3-no effort against gravity 4-no movement		

NIHSS, should be calculated (Table 3). This scoring system is based on certain physical exam parameters and generates a score of 0-42, with severe strokes generally classified as greater than 15-20. The baseline NIHSS score has been validated for use by both neurologists and non-neurologists and predicts outcomes across a spectrum of patients.[27]

Once the diagnosis of acute ischemic stroke has been made, the first major principle of early management involves the consideration of thrombolytic therapy. The use of intravenous tissue plasminogen activator (IV tPA) was approved in 1996 after the release of the National Institute of Neurologic Disorders and Stroke (NINDS) trial. In this trial, 624 patients with acute ischemic stroke received IV tPA versus placebo within three hours of symptom onset.[28] Patients receiving thrombolytic therapy had a statistically significantly greater neurological improvement at 24 hours than patients receiving placebo, a finding that was sustained at one-year of follow-up.[29] Thus, eligible patients who present within the three-hour window should receive IV tPA barring any contraindications (Table 4).[26] In fact, patients who receive thrombolytics within the first 90 minutes fare better than those who receive thrombolytics in the second 90 minutes.[30] Close monitoring of blood pressure and frequent neurologic examinations are prudent once thrombolytics are given. A follow-up CT scan should be obtained 24 hours after the administration of thrombolytics and before the initiation of anticoagulants or antiplatelet agents.[26] Studies evaluating the use of thrombolytics greater than three hours after symptom onset have not demonstrated a consistently favorable outcome without significant bleeding risk, yet studies are ongoing to identify a subset of patients that may benefit during this time period.[31,32] Intra-arterial

administration of tPA, on the other hand, is an option for patients who present with middle cerebral artery strokes within six hours of presentation and who have contraindications to IV tPA.[26] There are limited indications to support the use of intra-arterial thrombolysis, such as in patients with occlusion of major cervical or intracranial arteries, as well as in patients with contraindications to IV tPA, such as recent major surgery.[26]

Patients diagnosed with ischemic stroke should be placed on continuous cardiac monitoring with frequent neurologic examinations. Physical and occupational therapy should be initiated as early as possible, and new guidelines recommend a formal evaluation of swallowing prior to the onset of oral feeding.[26] Early ambulation should be encouraged, and prophylaxis against deep vein thrombosis through chemical or barrier methods should be implemented. Hyperthermia and hyperglycemia should be corrected as both have been shown to worsen outcomes in acute ischemic stroke.[33,34] Recent guidelines have advocated the use of insulin in patients with serum glucose ≥140mg/dL.[26]

The management of blood pressure in the early period of acute ischemic stroke has been the subject of a multitude of research and studies. Extremes of blood pressure, both high and low, in the first days of ischemic stroke worsen outcomes.[35] Unless the patient presents with severe hypertension (>220/120 mmHg), antihypertensives should initially be held.[26] For patients not receiving thrombolytics, blood pressure should be acutely lowered by 15% in the first 24 hours if ≥ 220/120 mmHg.[26] If the patient is eligible for thrombolytics but presents with a blood pressure ≥ 185/110, labetolol through intermittent boluses or as an intravenous drip, as well as nicardipine or nitropaste, may be given to lower the blood pressure below this threshold in an attempt to give the thrombolytics within the three hour window.[26] If the patient presents with hypotension, the source of the decreased blood pressure should be discovered and treated. Intravenous fluids can be used to correct hypovolemia, and cardiac arrythmias should be corrected to minimize their effect on blood pressure.[26] The results of the Controlling Hypertension and Hypotension Immediately Post-Stroke (CHHIPS) trial have recently been released.[36] This study divided patients not on antihypertensive therapy into those who presented with a systolic blood pressure below 140mmHg (pressor arm) and above 160 mmHg (depressor arm). Patients in the pressor arm all received intravenous fluids, while half received vasopressors to raise the systolic blood pressure to 150mmHg. Patients in the depressor arm received either lisinopril or labetolol titrated to reach the same goal. Results showed no early neurologic deterioration or change in 14-day mortality , but a statistically significant benefit at three months for those patients in the depressor arm. Unfortunately, the subgroup analysis regarding the use of vasopressors was thrown out due to lack of recruitment secondary to strict exclusion criteria. Currently, the use of vasopressors in the setting of acute ischemic stroke outside the setting of clinical trials is not advocated.[26] The ACCESS trial showed an improvement in 12 month mortality in hypertensive patients started on candesartan at 24 hours after diagnosis of ischemic stroke.[37] Results of the ACCESS trial suggest that blood pressure medications in patients with pre-existing hypertension can be restarted at 24 hours if the patient is neurologically stable.[26] Further studies will be needed to delineate the optimal strategy for managing blood pressure in the early period of an acute ischemic stroke. The ongoing COSSACS trial (Continue or Stop Antihypertensives Collaborative) is currently evaluating the possibility of continuing antihypertensives on admission in patients who present with ischemic stroke.

Medical therapy in the early management of acute ischemic stroke aside from thrombolytics and blood pressure management is minimal. Aspirin therapy is a mainstay in the early management of acute ischemic stroke. It is recommended that full-dose aspirin (325mg) be given within 24-48 hours of stroke onset.[26] The major benefit of aspirin, rather than affecting the current stroke, is in the prevention of early recurrence of ischemic stroke.[38] Other antiplatelet agents, such as clopidogrel, ticlopidine, and glycoprotein IIb/IIIa inhibitors have not been evaluated in the acute management of ischemic stroke. Statins should be continued in patients on chronic therapy and started in statin-naive patients to avoid worsening outcomes.[39] The early administration of anticoagulants, such as heparin, on the other hand, are not recommended for treatment of

Table 4. Contraindications to use intravenous tissue plasminogen activator.

Historical exclusion criteria	• Major surgery within 14 days • Stroke, myocardial infarct, or head trauma within 3 months • History of intracerebral hemorrhage • Gastrointestinal or genitourinary bleeding within 21 days • Arterial or lumbar puncture within 7 days	*Clinical exclusion criteria*	• Very minor or very severe neurological deficits • Signs of resolving deficits • Persistent BP > 185/110 mmHg with treatment • Pregnancy or lactation • Active bleeding • Symptoms of myocardial infarct or subarachnoid hemorrhage
Laboratory exclusion criteria	• International normalized ratio (INR) ≥1.7 on warfarin • Prolonged partial thromboplastin time (PTT) on heparin • Platelet count ≤ 100,000/mm^3 • Serum glucose ≤ 50 mg/dL	*Radiologic exclusion criteria*	• Evidence of hemorrhage

acute ischemic stroke, even in those strokes precipitated by cardioembolism secondary to atrial fibrillation. Early studies showed a potential benefit of heparin therapy in patients with large-artery atherosclerosis,[40] a finding that was negated with the recent FISS-tris trial.[41] Data concerning the possible use of anticoagulation in patients with ischemic stroke secondary to intracardiac or intra-arterial thrombi and intracranial stenosis, such as vertebrobasilar insufficiency, is not conclusive, and clinical decisions should be individualized. However, unfractionated heparin, or a low-molecular weight equivalent, can be used for deep vein thrombosis (DVT) prophylaxis early in the management of ischemic stroke.[26]

Carotid endarterectomies are generally not performed emergently in the setting of acute ischemic stroke. However, surgery is indicated for symptomatic patients with carotid stenosis ≥ 50% if the surgical risk is deemed to be ≤ 6%.[42] The optimal timing of the CEA has not been established, but the benefit is greater if the CEA is done within two weeks of the TIA or CVA.[42] In addition, stenting has been shown not to be inferior to CEA in high-risk patients.[43]

Secondary Prevention

The secondary prevention of patients that have suffered an ischemic stroke involves the use of certain antihypertensives, statins, and antiplatelet agents. Unlike primary prevention in which the degree of blood pressure lowering dictated the risk reduction, the particular antihypertensive used is important in the secondary prevention of ischemic stroke.[44] There are several studies that look at a wide array of antihypertensives in the secondary prevention of stroke. The Perindopril Protection Against Recurrent Stroke Study (PROGRESS) evaluated over 6,000 patients who had a history of prior cerebrovascular disease and randomized them to treatment with an angiotensin-converting enzyme (ACE) inhibitor versus an ACE inhibitor with a thiazide diuretic.[45] Those patients treated with an ACE inhibitor alone had a minor 5% reduction in stroke, while patients on combination therapy had a 43% reduction in stroke, a finding that could not be explained by the change in blood pressure itself. This finding was consistent across all ischemic and non-subarachnoid hemorrhagic stroke subtypes and was regardless of whether the patient had a history of hypertension or not. A meta-analysis from the International Society of Hypertension found a significant decrease in both fatal and nonfatal stroke with the use of diuretics or the combination of ACE inhibitors and diuretics but not with beta-blockers or ACE inhibitors alone,[46] a finding consistent with recent guidelines advocating their use in the management of hypertension to prevent recurrent stroke.[44]

Recent trials have supported the use of statins in both the primary and secondary prevention of ischemic stroke, regardless of baseline cholesterol levels. The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) randomized patients with a history of stroke or TIA in the preceding one to six months to atorvastatin 80mg versus placebo.[47] Patients receiving statin therapy had, on average, a significant 2.2% absolute 5-year risk reduction in the secondary prevention of stroke as well as a

5.2% 5-year reduction in cardiovascular events, despite the fact that none of these patients had known coronary artery disease. The study showed that only 46 patients would need to be treated to prevent one ischemic stroke at five years. There was an increase in the number of hemorrhagic strokes in patients treated with atorvastatin, a finding that has been seen in other statin studies and is thought possibly to be a class effect. However, due to the results of this study, a new update issued by the American Heart Association and American Stroke Association recommends the administration of statin therapy for patients with atherosclerotic ischemic stroke or TIA to reduce the risk of ischemic stroke and cardiovascular events.[48]

There are several independent studies to support the use of clopidogrel[49,50] or extended-release dipyridamole[51,52] with aspirin in the secondary prevention of ischemic stroke. The Management of Atherothrombosis With Clopidogrel in High-Risk Patients with TIA or Stroke (MATCH) trial assigned patients with prior stroke or TIA to clopidogrel or clopidogrel plus aspirin.[53] The patients using combination therapy exhibited no decrease in cardiac or cerebrovascular disease but had an increase in major hemorrhage.[53] Thus, recent guidelines advocate the use of aspirin 50-325 mg, clopidogrel monotherapy, or the combination of aspirin and extended-release dipyridamole to reduce the risk of recurrent stroke.[48] Recently, the PROFESS trial (Prevention Regimen for Effectively avoiding Second Strokes) became the first major published trial directly comparing clopidogrel versus the combination of aspirin and extended-release dipyridamole.[54] It involved over 20,000 patients in over 35 countries and is the world's largest secondary stroke prevention trial. The results showed similar rates of recurrent stroke and stroke, myocardial infarction, and vascular mortality. The patients receiving the combination of aspirin plus dipyridamole had more major hemorrhagic events and intracranial bleeds, a result that did not reach statistical significance. The findings of the PROFESS trial validate the recent guidelines advocating the use of either clopidogrel monotherapy or the combination of aspirin and extended-release dipyridamole as initial antiplatelet agents in the secondary prevention of stroke.

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