



Antiplatelet Therapy and Stroke Prevention

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Stroke is the third leading cause of death in the United States and is responsible for one out of every 15 deaths. Two-thirds of all strokes occur in persons over the age of 65, therefore the risk for stroke is high in long-term care residents. Residents that have had a stroke have increased mortality, morbidity, healthcare costs, and reduced quality of life.

A symposium entitled "Antiplatelet Therapy and Stroke Prevention" was convened in conjunction with the 2000 American Society of Consultant Pharmacists' (ASCP's) 31st Annual Meeting and Exhibition in Boston, Massachusetts. Dr. Henry Bussey and Dr. Susan Fagan discussed the pathogenesis of acute ischemic stroke in the United States, as well as current trends in pharmacotherapy.

This supplement will outline the significance and epidemiology of ischemic stroke and will focus upon the importance of patient demographics, risk factors, and the role of therapeutic regimens—antiplatelet therapy and the use of aspirin and warfarin—in stroke prevention. The information provided in this monograph is intended as a resource for your daily practice.

Editorial Board

Henry I. Bussey, PharmD
Professor
Division of Pharmacotherapy
College of Pharmacy
The University of Texas at Austin
The University of Texas Health Science Center
San Antonio, Texas

Susan C. Fagan, PharmD
Professor of Pharmacy
Department of Clinical and Administrative Services
College of Pharmacy
The University of Georgia
Medical College of Georgia
Macon, Georgia

Target Audience

Antiplatelet Therapy and Stroke Prevention was designed to meet the educational needs of pharmacists in all healthcare delivery settings.

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 **MatureHealth
Communications LLC**
250 East Broad Street
Westfield, NJ 07090
P 908.317.8788
F 908.317.9555
www.maturehealth.com

Learning Objectives

After reading this monograph, the reader should be better able to:

- Understand the magnitude of the problem of acute ischemic stroke in the United States.
- Determine how comorbid conditions, heredity, and geography affect the incidence of stroke.
- Describe the processes that lead to the occlusion of a cerebral artery and cause an ischemic stroke.
- Determine whether an individual patient is at risk of ischemic stroke and recommend strategies for risk reduction.
- Discuss the advantages and disadvantages of aspirin therapy in stroke prevention.

Pharmacy Continuing Education Credits



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A symposium entitled "Antiplatelet Therapy and Stroke Prevention" was convened in conjunction with Senior Care Pharmacy 2000, ASCP's 31st Annual Meeting and Exhibition in Boston, Massachusetts. Speakers Henry I. Bussey, PharmD and Susan C. Fagan, PharmD, presented the latest information on stroke demographics and risk factors, as well as stroke management and the use of specific antiplatelet agents, such as aspirin and dipyridamole, in the prevention and treatment of stroke.

Stroke Demographics and Risk Factors

Henry I. Bussey, PharmD, a professor in the College of Pharmacy at The University of Texas at Austin, introduced the program with the observation that "many people seem to fear stroke more than death itself." In fact, stroke is the third leading cause of death in the United States and is responsible for one out of every 15 deaths. It is also the nation's leading cause of serious disability.^{1,2} The annual incidence of stroke among persons over the age of 75 is 10.7 percent for women and 12.5 percent for men.¹ Persons who have had a stroke, a myocardial infarction (MI), or peripheral artery disease (PAD) are at increased risk for future strokes and MIs. In addition, persons who have coronary artery disease (CAD) or who have had a stroke, are at increased risk for PAD (Figure 1).^{1,3}

Susan C. Fagan, PharmD, professor at the University of Georgia, College of Pharmacy, elaborated on the demographics and risk factors for stroke. Dr. Fagan stated that more than 700,000 strokes occur annually in the United States.² The most recent American Heart Association statistics indicate that African-American men and women have the highest stroke mortality in this country and bear a greater disease burden than Caucasian men and women (Figure 2).⁴ The National Institutes of Health (NIH) are currently addressing aspects of this health disparity between these two races.

For each succeeding decade lived after the age of 55, the risk of stroke doubles. Two-thirds of all strokes occur in persons over the age of 65. Additionally, their risk of dying from stroke is seven times greater than that of the general population. The lifetime cost per stroke is up to \$100,000, including rehabilitation and indirect costs.¹ Patients who have had strokes and who enter long-term care (LTC) facilities have reduced quality of life, and their care often places an additional financial burden on the healthcare system for the rest of their lives.

Stroke and Comorbid Conditions

Stroke is a leading contributor to multi-infarct dementia in this country. Dr. Fagan stated that "about 40 percent of patients over the age of 80 have this type of dementia although they may never have reported having had a stroke." Magnetic resonance imaging (MRI) or computed axial tomography (CAT) will often reveal small, deep infarcts in the brains of elderly persons who have dementia symptoms. These infarcts may be a contributing factor to multi-infarct dementia.

Figure 1—Related Atherosclerosis Events

If CAD or CVA:	Risk of PAD=33%
If PAD:	Risk of MI=50% (>4 Fold Increase) Risk of Stroke=33% (2-3 Fold Increase)
If Stroke:	9 Fold Risk of Recurrence (40% at 5 years) 2-3 Fold Risk of MI
Initial MI:	5-7 Fold Risk of Recurrence 3-4 Fold Risk of Stroke

CAD = coronary artery disease; CVA = cerebrovascular accident;
PAD = peripheral artery disease; MI = myocardial infarction

Talbert and Nappi. *US Pharmacist*. (In press).
Sacco and Elkind. *Arch Intern Med*. 2000.

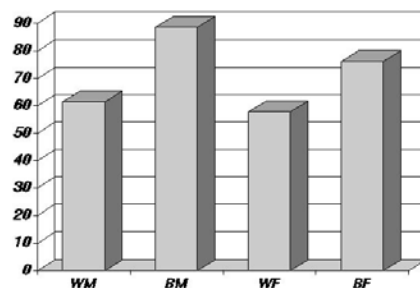
Figure 3 lists relative risk and prevalence statistics for various stroke risk factors. The most prevalent and modifiable medical risk factor for stroke is hypertension.⁵ Among the other medical risk factors are atrial fibrillation, cardiac disease, and diabetes. In patients with atrial fibrillation, the relative risk of stroke has been estimated to be as high as 17.6 times that of persons who do not have atrial fibrillation.³ Smoking and alcohol abuse are important modifiable lifestyle risk factors as well.³

"It has long been known," Dr. Fagan stated, "that hypercholesterolemia contributes to CAD and MI, but it is now known that hypercholesterolemia is also a risk factor for ischemic stroke." Diseases that affect the vasculature, such as lupus erythematosus, also increase the risk of stroke, as do hypercoagulable states such as acute promyelocytic leukemia syndrome and antiphospholipid antibody syndrome. These hypercoagulabilities are most often diagnosed in younger patients, in whom other risk factors are not present.

Environmental and Genetic Risk Factors in Stroke

It is not known whether the geographic distribution of stroke in the United States is associated with certain climactic conditions, dietary imbalances, inadequate intake of selenium or magnesium, or the presence of some substance in the water or air.

Figure 2—Stroke Mortality



1997 Death Rates Per 100,000 Population

WM = white males; BM = black males;
WF = white females; BF = black females

<http://www.americanheart.org>—accessed Dec. 14, 2000.

The coastal plain region of North Carolina, South Carolina, and southern Georgia is called the "Stroke Belt" because of the high stroke mortality rate in this particular area of the southeast.⁶ Since the "Stroke Belt" phenomenon was analyzed by Howard and colleagues in 1995, the region has been newly described as a "necklace," because it consists of geographic pockets of elevated stroke mortality interlaced with pockets of normal stroke mortality.^{5,7} The areas of high stroke mortality remain even when all known risk factors for stroke, as well as differences in access to medical care, are considered.

Certain genetic factors, such as apolipoprotein E, have been implicated in ischemic stroke, and furthermore, genetic manipulation during an ischemic stroke may actually help to alleviate some of the damage caused by the ischemia. Pertinent preclinical genetic studies are now being performed.

Types of Stroke and Their Pathophysiologic Basis

Stroke may be broadly classified as ischemic or hemorrhagic. About 85 percent of all strokes are ischemic, while the remaining occurrences of stroke are categorized as hemorrhagic.¹ The subcategories of hemorrhagic stroke are subarachnoid hemorrhage, intracerebral hemorrhage, and subdural hematoma. The focus of this supplement is ischemic stroke, which includes atherothrombotic and cardioembolic stroke.

Atherothrombotic stroke is believed to occur after a thrombus forms in an artery of a person who has atherosclerosis. The thrombus may remain in the vessel, eventually causing it to become completely occluded, or the thrombus may break off and embolize. Cardioembolic stroke occurs when an embolus originating from a thrombus in the heart, or from an atheromatous plaque in a more distal artery, travels up the artery and lodges in a cerebral blood vessel. The occlusion of the vessel decreases cerebral blood flow and triggers a cascade of events. As quickly as 5 minutes after severe local ischemia occurs, some vulnerable neurons die. When ischemia lasts longer than 1 hour, infarction begins in the central area of lowest cerebral blood flow, expanding circumferentially towards its peak volume over several hours.⁸

Figure 3—Risk Factors for Stroke

Risk Factor	Relative Risk	Prevalence
Atrial fibrillation	5.6 – 17.6	1%
Hypertension	4.0 – 5.0	25–40%
Cardiac disease	2.0 – 4.0	10–20%
Diabetes	1.5 – 3.0	4–8%
Cigarettes	1.5 – 2.9	20–40%
Alcohol abuse	1.0 – 4.0	5–30%
Hyperlipidemia	1.0 – 2.0	6–50%

Sacco RL. *Neurology*. 1995;45(suppl 1):S10–S14.

Figure 4—The Ischemic Cascade

- Depletion of ATP and failure of Ca⁺⁺ homeostasis lead ultimately to further neuronal injury
- Lactic acidosis leads to increased free Fe⁺⁺
- Increased intracellular Na⁺ leads to cytotoxic edema
- Glutamate release causes increases in IC Ca⁺⁺ and cytotoxicity

ATP = adenosine triphosphate; Ca⁺⁺ = calcium; Fe⁺⁺ = iron; Na⁺ = sodium; IC = intracellular

Normal cerebral blood flow is about 50 to 60 mL/100 g per min.⁸ As soon as blood flow begins to decrease, the brain compensates by increasing its extraction of oxygen and glucose to preserve normal tissue functioning. As a patient's cerebral blood vessels become more atherosclerotic over the years, the brain continues to compensate for occlusion of the vessels. Eventually, when occlusion is complete, the cerebral metabolic rate of oxygen flow decreases. The release of glutamate increases, voltage-sensitive calcium channels open, calcium rushes in, a rise in pH causes acidosis, and all of the preserved ion channels start to malfunction. At this stage, the patient has neurologic symptoms, but damage may be reversible. If moderate ischemia lasts for several hours, however, cell death and irreversible damage occur.⁸

The ischemic cascade, a chain of events that leads to stroke and stroke damage, is described in Figure 4. An increase in intracellular calcium, the last event in the chain, results in the activation of proteases, endonucleases, phospholipases, and nitric oxide synthase. The activation of proteases destroys proteins necessary to maintain cell integrity. The activation of endonucleases causes damage to cell DNA. The activation of phospholipases leads to the destruction of cellular membranes and infarction. Activation of nitric oxide synthase causes the formation of nitric oxide, which can also be neurotoxic.⁸ All of the preceding events represent targets for therapy. Now molecules that target one of these pathophysiologic processes are being discovered and tested in animal models.

White blood cells become activated and attracted to damaged endothelium in a blood vessel, leading to a further influx of white blood cells and microvascular thrombus formation distal to the site of the original clot. Antagonizing the influx of white blood cells is thus one means of treating ischemic stroke. When white blood cells are in the vasculature distal to the occlusion, platelets get stuck there and increase the deposition of fibrin distal to the recanalization. Therefore, platelet antagonism may also be a target for therapy.

In addition, if a blood vessel with damaged endothelium is reperfused, blood can then extrude into the parenchyma of the brain. The most significant adverse effect of reperfusion therapy is hemorrhagic transformation or intracerebral hemorrhage. Whether this effect occurs probably depends on when the blood vessel ruptures, as well as how much damage it sustains.

Primary Prevention

Lifestyle Risk Factors

The main lifestyle risk factors are cigarette smoking, alcohol use, insufficient physical activity, and a diet that is high in fat, cholesterol, and salt, and simultaneously, low in calcium, fruits, vegetables, and antioxidants.⁵

The relative risk of stroke in patients who smoke is 1.5 times greater than that of nonsmokers. Heavy smokers are twice as likely to have a stroke as light smokers. Cigarette smoking is a strong predictor of carotid artery plaque thickness.⁵ Cigarette smoking, in addition to its association with extracranial carotid artery atherosclerosis, may increase blood coagulability, viscosity, and fibrinogen levels; enhance platelet aggregation; and raise blood pressure.⁵

Although no direct link has been found between lack of exercise and stroke, physical inactivity increases the risk of heart disease, which in turn, increases the risk of stroke.⁹ Regular physical activity may reduce the risk, in part, by helping to control hypertension, diabetes, and obesity, all of which are risk factors for stroke. The current recommendation of the NIH Consensus Development Panel on Physical Activity and Cardiovascular Health is 30 minutes of moderately intense exercise, either most days or every day of the week.⁵

Eating cruciferous vegetables (eg, broccoli, cabbage) four to five times a week has been shown to reduce stroke risk by 32 percent. Additionally, drinking orange juice or eating citrus fruits daily has been shown to reduce stroke risk by 25 percent.¹⁰

Medical Risk Factors

"The most effective way to combat stroke," Dr. Fagan remarked, "is to prevent it from occurring in the first place—primary prevention." The two targets of primary prevention are medical risk factors and lifestyle risk factors. Hypertension is the most important risk factor for stroke.³ The other main medical risk factors are MI, atrial fibrillation, diabetes, hypercholesterolemia, and asymptomatic carotid artery stenosis.

According to a review of 14 prospective controlled trials, each 5 to 6 mm Hg decrease in diastolic blood pressure is associated with a 42 percent reduction in stroke risk.⁵ Even in patients over the age of 70, the risk of stroke can be reduced by 36 percent if isolated systolic hypertension is successfully treated.⁵ However, the ability of health-care providers to decrease the risk of stroke by treating hypertension may have peaked. Failure to adhere to antihypertensive regimens is the main reason why patients may not experience a significant reduction in their risk of hypertension-related stroke. Adequate strategies to promote adherence have yet to be devised.

Routine administration of antiplatelet agents to patients after an MI can prevent subsequent MIs and reduce the risk of nonfatal stroke by 39 percent.⁵ Also, using cholesterol-lowering agents such as pravastatin to reduce average cholesterol levels in patients with a previous MI was shown to reduce stroke risk by 31 percent.⁵ Therefore, physi-

cians generally prescribe statins for patients who are at risk for stroke, particularly if they have had an MI, regardless of their total cholesterol counts.

In patients who have atrial fibrillation, warfarin is very effective in reducing the risk of stroke. The overall risk reduction in pooled analyses was approximately 68 percent. However, for various reasons, many older patients are not receiving this effective treatment.⁵

There is no conclusive evidence that tight control of serum glucose levels in patients who have diabetes, reduces their stroke risk. However, there is solid evidence that tight control of blood glucose levels and intensive drug therapy reduces microvascular complications that may result from diabetes (nephropathy, retinopathy, and peripheral neuropathy).⁵ The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, has recommended that the blood pressure of hypertensive patients with diabetes be maintained at less than 130/85 mm Hg.¹¹ That recommendation is supported by the finding that tight control of blood pressure in patients who had both hypertension and type 2 diabetes reduced their stroke risk by 44 percent over patients whose blood pressure was not tightly controlled.⁵

Performing a carotid endarterectomy in asymptomatic patients whose carotid arteries are more than 60 percent stenosed can reduce their risk of stroke, but the risk of stroke is so low compared to risks associated with the procedure and the cost of screening so high that mass screening for carotid artery stenosis is not cost effective.⁵ The National Stroke Association Task Force recommends that patients, whose carotid arteries have greater than 60 percent stenosis undergo surgery, but only in centers with excellent surgical risk records.⁵ Dr. Fagan noted that carotid endarterectomy is often postponed in patients whose carotid arteries are more than 60 percent stenosed until monitoring shows them to be 90 to 95 percent stenosed.

The Asymptomatic Carotid Atherosclerosis Study (ACAS) examined the effect of carotid endarterectomy on the risk of stroke and death in asymptomatic patients who had never had a transient ischemic attack (TIA) or stroke before enrollment in the study. The relative risk reduction for stroke and death in ACAS was 66 percent for men and 17 percent for women. The relatively small number of women enrolled in the trial may explain their low risk-reduction percentage.⁵ It should be noted that surgeons who participated in ACAS were highly experienced, and the surgical morbidity rate in ACAS was only 1.1 percent.⁵

Acute Treatment

Dr. Fagan explained that healthcare providers often use the expression "time is brain" to indicate that time is of the essence in administering therapy to reduce the adverse impact of acute ischemic stroke.

Reperfusion Strategies

Current reperfusion strategies in the acute treatment of stroke are listed in Figure 5. "Probably only 1 to 2 percent of all ischemic stroke

Figure 5—Reperfusion Strategies

- IV tPA within 3 hours of onset (<5% of patients currently receive it) increases likelihood of return to normal by 30%.
- IV Ancrod® within 3 hours (not currently available) similar efficacy to tPA.
- IA Prourokinase (not available) but effective in MCA occlusion.

IV tPA = intravenous tissue plasminogen activator;
IA = intra-arterial; MCA = middle cerebral artery

patients actually receive IV tPA (tissue plasminogen activator) within 3 hours of a stroke," Dr. Fagan noted. Interventional neuroradiologists now administer intra-arterial tPA within 6 hours to patients who have occlusions of the middle cerebral artery. Other reperfusion agents are in development and are expected to be available within the next few years.

Neuroprotective Strategies

Neuroprotective drugs are effective in animals. However so far, Phase III trials have not shown them to be effective in human beings. Many neuroprotective agents are now in development or under study including gamma-aminobutyric acid (GABA) agonists, inhibitory neurotransmitters and glutamate antagonists. Modulation of potassium and sodium ion channels as well as the use of free radical scavengers are also being investigated.

Pharmacotherapy for Primary and Secondary Prevention of Stroke

Patients With Atrial Fibrillation

Dr. Bussey's presentation focused on cardioembolic and noncardioembolic stroke. "[For] patients who have atrial fibrillation," he said, "the major risk factors for stroke are hypertension, a prior thromboembolic event, and congestive heart failure. If the patient has any two of those three risk factors, the risk of stroke is approximately 18 percent per year, every year."¹² Other significant risk factors include an enlarged left atrium, diabetes, age older than 75, poor left ventricular function, and valvular heart disease."¹³

Patients with atrial fibrillation were classified in the Stroke Prevention in Atrial Fibrillation (SPAF) trials as being at low risk for stroke if they were younger than age 65 or 75, and had a stroke risk below 5 percent per year. Patients with atrial fibrillation whose annual stroke risk was 15 to 20 percent were considered high risk.¹⁴ In SPAF I, aspirin therapy reduced the risk of stroke in low-risk patients by approximately 40 percent.¹² An analysis of pooled data from five randomized, controlled trials showed that warfarin reduced stroke risk by approximately 65 to 85 percent in high-risk patients whose International Normalized Ratio (INR) range was 2 to 3. The lower percentage (65%) is based on "intention-to-treat" analysis,

which ignores whether or not patients actually took warfarin. The higher percentage (85%) reflects an "on-treatment" analysis and applies to those who actually took warfarin.¹⁵

The SPAF III study was a randomized, open-label trial that compared the use of fixed-dose warfarin plus aspirin with adjusted-dose warfarin in patients who had atrial fibrillation and were at high risk for stroke.¹⁴ The objective of the study was to compare the relative safety, efficacy, and ease of administration of the two treatments. After a mean follow-up of 1.1 years, the trial was discontinued, because the stroke risk was significantly higher in the combination-therapy group than in the adjusted-dose warfarin group. Figure 6 lists the rates of stroke, TIA, MI, and major bleeding in the two treatment groups. The higher rates of MI in the combination-therapy group compared with the adjusted-dose warfarin group raises the question of whether warfarin alone is superior to combination therapy for primary or secondary prevention of MI. The rates of major hemorrhage were not significantly different between the combination arm and adjusted-dose warfarin arm. Therefore, the results of SPAF III showed that low-intensity, fixed-dose warfarin plus aspirin is much less effective in preventing stroke and no safer than adjusted-dose warfarin in high-risk patients with atrial fibrillation.

Patients With Prosthetic Heart Valves

Long-term aspirin therapy is a currently recommended optional treatment for patients who have prosthetic tissue valves.¹⁶ Although many authorities believe that aspirin plus warfarin reduces the risk of thromboembolism in patients who have mechanical heart valves (even though it increases the risk of bleeding), whether combination therapy is superior to tight anticoagulation control using warfarin alone has not been established.¹⁶ A study by Turpie and colleagues showed that warfarin plus aspirin reduced the rate of thromboembolic events and mortality by approximately 60 to 70 percent, while increasing major bleeding by only 27 percent in patients whose heart valves had been replaced.¹⁷ However, the patients' INRs were below the targeted range approximately half the time. If their anticoagulation control had been tighter, aspirin may not have conferred any benefit.¹⁶

Data are conflicting on the efficacy of dipyridamole in combination with warfarin in preventing stroke in patients with prosthetic valves. A meta-analysis suggested that this combination is highly beneficial, but that analysis and the investigators' conclusions have been questioned.¹⁶ Other antiplatelet agents have not been studied in conjunction with warfarin for stroke prevention in patients who have prosthetic valves.

Patients With MI

In post-MI patients, warfarin has been shown to reduce the incidence of recurrent MI and stroke. The American College of Chest Physicians Consensus Conference recommends a post-MI INR target range of 2 to 3 to prevent a stroke, or 2.5 to 3.5 to prevent a recurrent MI.¹⁸ The Coumadin Aspirin Reinfarction Study (CARS) compared the efficacy of aspirin monotherapy with low, fixed-dose warfarin plus aspirin in

Figure 6—High-Risk Atrial Fibrillation: SPAF III

	Events % / Yr. (N = 1,044)	
	ASA + Warfarin INR 1.2–1.5	Warfarin INR 2–3
Stroke*	7.9	1.9
TIA	3.1	2.0
MI**	2.1	0.8
Major Bleed	2.4	2.1
IC Bleed	0.9	0.5

SPAF = Stroke Prevention in Atrial Fibrillation;
ASA = acetylsalicylic acid; TIA = transient ischemic attack;
MI = myocardial infarction; IC = intracranial;
NS = not significant; INR = international normalized ratio

* $P < 0.001$, ** $P = NS$

SPAF. *Lancet*. 1996.

post-MI patients. Patients were randomly assigned to receive either 160 mg of aspirin per day only, or 80 mg of aspirin plus 1 mg or 3 mg of warfarin daily.¹⁹ There was no significant difference in mortality in the three treatment arms of this large study, in which approximately 9,000 patients were enrolled. Furthermore, nonfatal stroke was lower in the group that received 160 mg of aspirin alone than in the warfarin/aspirin groups. In fact, adding subtherapeutic doses of warfarin appeared to increase stroke risk. Theoretically, this finding might be explained by the fact that the depletion of protein C, which occurs when warfarin is administered, may cause a prothrombotic state. This study confirmed SPAF III results, in which combination therapy was found to be less effective and no safer than single-agent therapy.¹³

Patients With Noncardioembolic Stroke

"Interpreting data pertaining to pharmacotherapy for the prevention of noncardioembolic stroke is much more complicated," Dr. Bussey remarked. Characteristics of the patients being studied are very important. Their age; whether they have had a thromboembolic event, TIA, or stroke; and other risk factors, if any, may all influence both safety and efficacy outcomes. Safety and efficacy data on the use of aspirin to prevent noncardioembolic strokes are limited. Ticlopidine and clopidogrel are reasonable alternatives, but have some significant reported adverse effects. Results of a cilostazol study appear promising, but data are limited. With respect to combination therapy, extended-release dipyridamole plus aspirin is safe and cost effective, as long as the combination is well tolerated. Other combinations have not yet been studied.

Aspirin in Stroke Prevention

Aspirin has limited safety and efficacy in the prevention of stroke. Doses of aspirin that are high enough to protect against stroke cause increased bleeding. In addition, the use of aspirin for primary prevention of cardioembolic stroke is associated with an increased risk of hemorrhagic stroke, which may cause greater disability than cardioembolic stroke. A study of more than 1,600 patients with prosthetic valves, who were taking oral anticoagulants found that 79 per-

cent of the patients who had ischemic strokes recovered either without deficits or with nondisabling deficits compared with only 33 percent of the patients who had hemorrhagic strokes.²⁰

Kronmal and colleagues compared the risk of stroke in elderly persons (mean age 72) who were frequent aspirin users (persons who took aspirin at least 10 out of 14 days before entry into the study or for whom daily aspirin had been prescribed) with the risk in nonusers. The dose of aspirin taken varied, but in most cases, totaled at least 325 mg per day. The investigators found that the female aspirin users were at increased risk for ischemic stroke, but that the male aspirin users were not. Specifically, the adjusted relative risk of ischemic stroke in the women who were persistent, frequent aspirin users was 1.93 compared with the risk in female nonusers.²¹ In the subgroup of women who were frequent aspirin users but did not have cardiovascular disease, the adjusted relative risk was 1.67. Aspirin does reduce the risk of stroke recurrence by 10 to 20 percent in persons at very high risk, but other measures have been shown to reduce the risk of recurrence by 40 to 80 percent.

No compelling evidence exists to support the idea that higher doses of aspirin confer greater benefit than lower doses. In fact, higher doses may be harmful because of a possible thrombotic effect and the dose-dependent nature of gastrointestinal side effects.^{22,23} Patrono et al studied the effect of aspirin dose size on the frequency of various vascular events in more than 47 thousand persons enrolled in 46 clinical trials.²³ As the dose size increased, the odds reduction declined, suggesting that higher doses of aspirin are not more beneficial and, in fact, may be detrimental. In addition, Patrono et al ascertained from trial data the minimum effective daily dose of aspirin needed to prevent certain thromboembolic events (see Figure 7). Those doses were 50 mg for the prevention of TIAs and ischemic strokes, 75 mg for patients with hypertension, stable angina, or unstable angina; and 160 mg for patients with acute MI or acute ischemic stroke.

The North American Symptomatic Carotid Endarterectomy Trial (NASCET) demonstrated the beneficial effect of carotid endarterectomy in reducing the risk of ipsilateral stroke in patients who had recently had hemispheric or retinal TIAs or nondisabling strokes and who had high-grade carotid stenosis.²⁴ According to a retrospective analysis of that trial published in 1999, the risk of perioperative stroke

Figure 7—Minimum Effective ASA Doses

Disorder	mg/day
Hypertension	75
Stable angina	75
Unstable angina	75
Acute MI	160
TIA & ischemic CVA	50
Acute ischemic CVA	160

MI = myocardial infarction; TIA = transient ischemic attack;
CVA = cerebrovascular accident.

Patrono C, et al. *Chest* 1998;114:470S–488S.

and death among participants with 70 to 90 percent stenosis was 6.9 percent in those taking 325 mg or less of aspirin daily, but only 1.8 percent in those taking 650 to 1,300 mg.²² That finding was not surprising, because a person who has had a carotid endarterectomy has exposed collagen, and it is reasonable to expect that large doses of aspirin would be required to prevent thrombosis. Another retrospective NASCET analysis, published in 1988, arrived at a similar finding for patients with less than 70 percent stenosis. In that cohort, the risk of stroke or death within 30 days of surgery was 8.3 percent for patients who were taking less than 650 mg of aspirin daily, and 3.7 percent for those who were taking 650 mg or more.^{22,25} Thus, both retrospective analyses supported the use of high-dose aspirin in patients who have had a carotid endarterectomy. However, unlike prospective data, retrospective data are not considered conclusive.

The ASA and Carotid Endarterectomy (ACE) trial was a prospective study designed to test whether perioperative complication rates are affected by acetylsalicylic acid (aspirin) dose size in patients who have undergone carotid endarterectomy.²² In this randomized, controlled, multinational trial, the qualifying surgeons in 74 centers were required to have achieved a stroke and death rate of less than 6 percent. Thus, only experienced surgeons working in centers in which many endarterectomies were performed, participated. Almost 3,000 patients were randomly assigned to receive one of four different aspirin doses before surgery and then followed up for three months.

Results of the ACE trial were pooled for the two lower aspirin doses, 81 mg and 325 mg, and the two higher doses, 650 mg and 1,300 mg. The patients who had received the lower aspirin doses had significantly fewer strokes, significantly fewer MIs, and a lower mortality rate. Also, when the frequencies of stroke, MI, and death were combined, the frequency was 6.2 percent in the low-dose groups versus 8.4 percent in the high-dose groups. A subgroup analysis found the difference to be even more impressive in patients who had been taking less than 650 mg of aspirin before the study. "Thus," Dr. Bussey explained, "the results of this trial reversed the conclusions of the two early post-hoc analyses by establishing that higher-dose aspirin is actually less effective than lower-dose aspirin in patients who have undergone carotid endarterectomy."

Warfarin in Stroke Prevention

Warfarin has been shown to be superior to aspirin in preventing cardioembolic stroke. The Stroke Prevention in Reversible Ischemia Trial (SPIRIT), which was conducted in the Netherlands, studied the use of warfarin in preventing noncardioembolic stroke.²⁶ It compared warfarin (INR = 3.0 to 4.5) with low-dose aspirin (30 mg/day) in 1,316 patients. This INR target range had been shown to be protective in patients who have had an MI or who have prosthetic heart valves. However, SPIRIT was stopped prematurely because 53 patients in the warfarin group had major bleeding episodes, compared with only six in the aspirin group. Of those 53 patients in the warfarin group, 27 had intracranial hemorrhages. In contrast, of the six patients in the aspirin group who experienced major bleeding, only three had intracranial hemorrhages. The number of fatal hemorrhages was 17

in the warfarin group and one in the aspirin group. In a post-hoc analysis of SPIRIT, the investigators stated that, had the subjects' INRs been maintained within a range of 2.0 to 3.0, the incidence of bleeding would have been reduced by two-thirds. Another study, the European and Australian Stroke Prevention in Reversible Ischemia Trial (ESPRIT), is now under way to evaluate the safety and efficacy of warfarin in patients whose INRs are kept within a range of 2.0 to 3.0.

Two key observations from SPIRIT were: 1) in the INR range of 3.0 to 4.5, warfarin is less safe than low-dose aspirin; 2) the high frequency of bleeding among the patients who had experienced a prior cerebrovascular event indicates that warfarin may not be as safe as previously thought. Therefore, clinicians may want to avoid using warfarin in these patients, or keep the INR below the 3.0 to 4.5 range.

Clopidogrel and Ticlopidine

Clopidogrel and ticlopidine were compared with aspirin in two well-publicized studies. The Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial enrolled more than 19,000 patients, of whom more than 6,400 had previously experienced a stroke.²⁷ Among the patients who had suffered a previous stroke, the relative-risk reduction in the cluster of ischemic stroke, MI, or vascular death was 7.3 percent in favor of clopidogrel. Among all patients who were randomly assigned to treatment, the relative-risk reduction in the same cluster was 8.7 percent in favor of clopidogrel beyond the 25 percent reduction that aspirin typically provides. Neither difference was statistically significant.

In the Ticlopidine Aspirin Stroke Study (TASS), the risk reduction in death or nonfatal stroke at three years was 12 percent for ticlopidine compared with aspirin. The risk reduction in stroke alone at three years was 21 percent for ticlopidine compared with aspirin. These differences were both statistically significant.²⁸ Ticlopidine is the only compound that has been shown to be significantly superior to aspirin in preventing ischemic stroke, MI, and vascular death in patients who have had a prior cerebrovascular event.

**Figure 8—ESPS-2 (ER-DP + ASA)
Primary Results at 2 Years**

Event	ASA N=1,649	ER-DP N=1,654	ER-DP + ASA N=1,650
Stroke	12.9	13.2	9.9
Rate Reduction %	18.1	16.3	37
Stat. Sig.	$p < 0.013$	$p < 0.039$	$p < 0.001$
TIA Rate	12.6	13.2	10.6
Reduction %	21.9	18.3	35.9
Stat. Sig.	$p < 0.01$	$p < 0.01$	$p < 0.001$

ESPS = European Stroke Prevention Study;
ER-DP = extended-release dipyridamole;
TIA = transient ischemic attack

Diener HC, et al. *J Neurol Sciences*. 1996;143:1–13.

Unfortunately, two particularly significant adverse reactions are associated with the use of ticlopidine. In 0.9 percent of the patients who received ticlopidine, severe neutropenia developed.²⁸ Although this condition is usually reversible, it can be fatal. In a few cases (an estimated one case per 1,600 to 5,000 patients), ticlopidine therapy caused thrombotic thrombocytopenia (TTP), a disorder that can lead to fatal infarctions of vital organs.²⁹ Dr. Bussey noted that these two potentially serious complications are probably the main reason why ticlopidine was largely abandoned in favor of clopidogrel until very recently.

Severe bleeding occurred slightly less often with clopidogrel (1.38%) than with aspirin (1.55%) in the CAPRIE trial, but there was no significant difference in the incidence of neutropenia with the two agents. However, 11 cases of TTP were reported to have occurred between March 1998 and March 2000 among patients who had been taking clopidogrel. Although TTP appears to be more commonly associated with ticlopidine therapy than clopidogrel therapy, the onset of the disorder in patients who are receiving ticlopidine almost always occurs after 2 to 12 weeks of treatment, compared with less than two weeks in clopidogrel recipients.²⁹ "For short-term treatment, then," Dr. Bussey observed, "ticlopidine might be the better choice for patients, such as those who are having a stent placed."

According to clinical reports, the mortality rate due to ticlopidine-associated TTP was 18 percent in patients who underwent plasma exchange, and 58 percent in those who did not.²⁹ The mortality rate due to clopidogrel-associated TTP was 9 percent in patients who underwent plasma exchange. (All patients in these reports in whom TTP developed with clopidogrel underwent plasma exchange.) Among the 11 patients in whom TTP developed during clopidogrel therapy, there were seven instances of neurologic changes, four instances of reduced renal function, two incidences of acute liver injury, and one death. In 10 of these 11 instances, the adverse event or death occurred within the first two weeks of treatment.²⁹

Cilostazol

In a double-blind, multicenter Japanese trial, more than 1,000 patients were randomly assigned to receive either 100 mg of cilostazol twice a day or placebo.³⁰ One important outcome of the study was a highly statistically significant reduction in stroke rate of almost 42 percent compared with placebo (a stroke rate of 3.4% per year vs 5.8% with placebo). A 38.8 percent reduction occurred in stroke, MI, intracranial hemorrhage, or vascular death, and no increases in bleeding, gastrointestinal complaints, or allergic reactions were reported.

A major shortcoming of the study was the lack of an active control group. Another limitation was the use of Japanese patients exclusively. Therefore, whether cilostazol is effective in Hispanics or African-Americans, for example, is not known. Also, 77 percent of the subjects who had qualifying strokes had lacunar infarcts, which are common in hypertension,

but not characteristic of the majority of stroke patients. Thus, whether these findings would apply to patients who have had strokes from other causes is not known. The 9.2 to 62.5 percent, 95 percent confidence interval, for the effect is a wide range that is consistent with what might be expected for aspirin studies.³⁰

The frequency of withdrawal and adverse events was significantly higher with cilostazol than with placebo: withdrawal, 13.2 and 6.2 percent, respectively; headache, 12.8 and 3.2 percent, respectively; palpitations, 5.3 and 0.4 percent, respectively; and increased pulse rate, 19.0 and 7.9 percent, respectively.³⁰ The cardiovascular side effects are especially important, because cilostazol is a phosphodiesterase inhibitor, and agents in this class have been shown to increase cardiac events and arrhythmias in cardiac patients. "More data are needed before this drug can be recommended," Dr. Bussey cautioned.

Dipyridamole Plus Aspirin

Dr. Bussey stated that a few years ago there were questions regarding the utility of dipyridamole as an agent for stroke prevention, but that some encouraging, relatively new data have been released. Formerly, there was some question about the bioavailability of dipyridamole, and there was concern that the non-sustained-release formulation may induce vasodilation and cardiac ischemia. Also, two small trials from the early 1980s had shown that dipyridamole plus aspirin was no more effective in preventing stroke than aspirin alone. However, the studies were too small to detect any small differences in the efficacy of the two treatments.³¹

Results of the European Stroke Prevention Study (ESPS-1) were published in 1987. To be eligible for this placebo-controlled trial, patients had to have had a TIA, reversible ischemic neurologic deficit, or ischemic stroke. Patients who completed the treatment period and received the active treatment (75 mg dipyridamole plus 325 mg aspirin three times a day) showed a 36 percent reduction in secondary stroke or mortality during the 2-year treatment period.³² Unfortunately, the design of the study did not permit comparison of the relative contribution of dipyridamole and aspirin alone to the efficacy of the drugs in combination.

**Figure 9—ESPS-2 (ER-DP + ASA)
Secondary Results at 2 Years**

Event	Placebo N=1,649	ASA N=1,649	ER-DP N=1,654	ER-DP+ASA N=1,650	Total N=6,602	p
MI	45	39	48	35	167	NS
Other Vasc.*	54	38	35	21	148	<0.01
Combination**	307	206	271	206	1050	<0.001
Bleeding (%)	4.7	8.2	4.5	8.7		

*DVT/PE, peripheral/retinal artery occlusion **stroke/MI/sudden death

ESPS = European Stroke Prevention Study; ER-DP = extended-release dipyridamole; DVT/PE = deep vein thrombosis/pulmonary embolism

Diener HC, et al. *J Neurol Sciences*. 1996;143:1–13.

Figure 10—Summary Stroke Prevention Agents Superior to ASA

Drug	Stroke Rates	NNT/Y	30-day AWP
Ticlopidine	10% vs. 13% / 3 Yrs	100	\$112
ER-DP + ASA	9.9% vs. 12.9% / 2 Yrs	67	\$88

ER-DP + ASA: Superior to ASA alone (if tolerated) without an increase in bleeding, and is cost effective

Ticlopidine: Superior to ASA, serious adverse effects, less cost-effective

ER-DP = extended-release dipyridamole
 NNT/Y = number needed to treat per year
 AWP = average wholesale price

In 1996, the ESPS-2 results were published.³¹ This 2-year, randomized, multinational, double-blind trial compared aspirin 25 mg twice daily, extended-release dipyridamole 200 mg twice daily, and the combination of the two agents with placebo. Data were analyzed from 6,602 patients, all of whom had entered the trial after having had a TIA or stroke within the previous three months (see Figure 8). Compared with placebo, each treatment was equally beneficial in reducing stroke and TIAs, but the reductions were greater with the combination therapy.

Secondary results at two years (Figure 9) reported in ESPS-2 included the number of MIs; other vascular events; stroke, MI, and sudden death combined; as well as the percentage of bleeding episodes.

Even though 36 percent of the patients in the extended-release dipyridamole group in ESPS-2 had ischemic heart disease at baseline, the MI rate associated with extended-release dipyridamole use was similar to that for placebo, allaying the concern that vasodilation due to dipyridamole might lead to an increase in MIs or other cardiac events. The frequency of bleeding was significantly lower with placebo and extended-release dipyridamole alone, than with aspirin alone and the extended-release dipyridamole/aspirin combination.

One criticism of the trial was that many of the patients who were randomly assigned to extended-release dipyridamole/aspirin therapy discontinued treatment because of side effects with extended-release dipyridamole. However, the aspirin and placebo groups also had high discontinuation rates. Another concern was that all the data from one center had to be excluded when it was discovered that they were fabricated.³⁰ However, the exclusion of those data did not alter the results.

Figure 11—Summary Stroke Prevention

- Cardioembolic stroke: warfarin superior to ASA
- Non-Cardioembolic Stroke
 - Primary prevention: only ASA in CEA with low dose better (<325mg/d) than high dose (650mg/dy)
 - Secondary prevention
 - Effective: ASA, ticlopidine, clopidogrel, DP, ER-DP+ASA, cilostazol, warfarin
 - More effective than ASA: ticlopidine, ER-DP+ASA
 - Warfarin: possibly more effective, but dangerous

"The cost-benefit ratio of extended-release dipyridamole/aspirin is another key consideration," Dr. Bussey added. Use of the combination (instead of aspirin alone) would prevent an additional 1.5 strokes annually per every 100 patients who meet ESPS-2 study criteria. The lifetime cost of a stroke in this country is roughly \$75,000 to \$100,000. Thus, preventing 1.5 strokes a year would save about \$113,250 to \$150,000. The use of dipyridamole extended-release plus aspirin, at an annual cost of \$108,000 (\$90/month x 12 months x 100 patients), would result in a net savings of \$5,250 to \$42,000 a year over the cost of using aspirin alone.

Dr. Bussey compared the cost-benefit of ticlopidine with that of extended-release dipyridamole plus aspirin in stroke prevention. Although both agents are superior to aspirin in reducing stroke rates, more strokes can be prevented in the same number of patients for the same price if extended-release dipyridamole/aspirin is used rather than ticlopidine (Figure 10). Stated another way, the advantage of extended-release dipyridamole/aspirin is that fewer patients need to receive treatment to prevent one stroke.

Other Drug Combinations

Other drug combinations involving antiplatelet drugs are likely to be effective in preventing stroke, because platelets are activated by several different mechanisms. Trial results of aspirin plus either ticlopidine or clopidogrel have shown that either combination may be superior to aspirin alone in patients who have stents. However, the only published data available on stroke prevention currently pertains to the combination of extended-release dipyridamole and aspirin.

Summary: Pharmacotherapy for Stroke Prevention

Figure 11 summarizes the key findings in stroke prevention. In the prevention of cardioembolic stroke, warfarin is generally more effective than aspirin. Whether the combination of warfarin and aspirin is better than warfarin alone in patients with prosthetic heart valves is controversial. In the primary prevention of noncardioembolic stroke, low-dose aspirin is more effective than high-dose aspirin in patients who have undergone carotid endarterectomy. In the secondary prevention of noncardioembolic stroke, agents of proven efficacy include aspirin, ticlopidine, clopidogrel, and extended-release dipyridamole, alone or in combination with aspirin. Cilostazol and warfarin may also be protective. Ticlopidine is more effective than aspirin but may cause serious adverse effects such as TTP. The combination of extended-release dipyridamole plus aspirin is also more effective than aspirin alone. Other drug combinations may show effectiveness when results of clinical trials are published.

Effective pharmacotherapeutic options are now available for stroke prevention and treatment. By choosing the most appropriate agents for their patients, taking into account each patient's risks and diagnosis, healthcare providers can help reduce the morbidity and mortality associated with stroke.

References

1. Talbert R, and Nappi J. *US Pharmacist*. In press.
2. Sacco RL, Elkind MS. Update on antiplatelet therapy for stroke prevention. *Arch Intern Med*. 2000;160:1579-1582.
3. Sacco RL. Risk factors and outcomes for ischemic stroke. *Neurology*. 1995;45(suppl 1):S10-S14.
4. American Heart Association website. Available at: http://www.americanheart.org/Heart_and_Stroke_A_Z_Guide/strokes.html. Accessed Dec. 14, 2000.
5. Gorelick PB, Sacco RL, Smith DB, et al. Prevention of a first stroke: a review of guidelines and a multidisciplinary consensus statement from the National Stroke Association. *JAMA*. 1999;281:1112-1120.
6. Howard G, Evans GW, Pearce K, et al. Is the Stroke Belt disappearing? An analysis of racial, temporal, and age effects. *Stroke*. 1995;26:1153-1158.
7. Lackland DT, Bachman DL, Carter TD, et al. The geographic variation in stroke incidence in two areas of the southeastern stroke belt: the Anderson and Pee Dee Stroke Study. *Stroke*. 1998;29:2061-2068.
8. Pulsinelli W. Pathophysiology of acute ischaemic stroke. *Lancet*. 1992;339:533-536.
9. American Heart Association website. Available at: http://www.americanheart.org/Heart_and_Stroke_A_Z_Guide/strokeri.html. Accessed Feb. 22, 2001.
10. Joshipura JK, Ascherio A, Manson JE, et al. Fruit and vegetable intake in relation to risk of ischemic stroke. *JAMA*. 1999;282:1233-1239.
11. The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Arch Intern Med*. 1997;157:2413-2446.
12. Stroke Prevention in Atrial Fibrillation Investigators. Predictors of thromboembolism in atrial fibrillation: clinical features of patients at risk. *Ann Intern Med*. 1992;116:1-5.
13. Laupacis A, Albers G, Dalen J, et al. Antithrombotic therapy in atrial fibrillation. *Chest*. 1998;114:579S-589S.
14. Stroke Prevention in Atrial Fibrillation Investigators. Adjusted-dose warfarin versus low-intensity, fixed-dose warfarin plus aspirin for high-risk patients with atrial fibrillation: Stroke Prevention in Atrial Fibrillation III randomised clinical trial. *Lancet*. 1996;348:633-638.
15. Atrial Fibrillation Investigators. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation: analysis of pooled data from five randomized controlled trials. *Arch Intern Med*. 1994;154:1449-1457.
16. Bussey HI, Lyons RM. Controversies in antithrombotic therapy for patients with mechanical heart valves. *Pharmacotherapy*. 1998;18:451-455.
17. Turpie AGG, Gent M, Laupacis A, et al. A comparison of aspirin with placebo in patients treated with warfarin after heart-valve replacement. *N Engl J Med*. 1993;329:524-529.
18. Hirsh J, Dalen JE, Anderson DR, et al. Oral anticoagulants: mechanism of action, clinical effectiveness, and optimal therapeutic range. *Chest*. 1998;114:445S-469S.
19. Coumadin Aspirin Reinfarction Study (CARS) Investigators. Randomised double-blind trial of fixed low-dose warfarin with aspirin after myocardial infarction. *Lancet*. 1997;350:389-396.
20. Cannegieter SC, Rosendaal FR, Wintzen AR, et al. Optimal oral anticoagulation for patients with mechanical heart valves. *N Engl J Med*. 1995;333:11-17.
21. Kronmal RA, Hart RG, Manolio TA, et al. for the CHS Collaborative Research Group. Aspirin use and incident stroke in the Cardiovascular Health Study. *Stroke*. 1998;29:887-894.
22. Taylor W, Barnett HJM, Haynes RB, et al. Low-dose and high-dose acetylsalicylic acid for patients undergoing carotid endarterectomy: a randomized controlled trial. *Lancet*. 1999;353:2179-2184.
23. Patrono C, Collier B, Dalen JE, et al. Platelet-active drugs: the relationships among dose, effectiveness, and side effects. *Chest*. 1998;114:470S-488S.
24. NASCET. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. *N Engl J Med*. 1991;325:445-453.
25. Barnett HJM, Taylor DW, Eliasziw M, et al. Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. *N Engl J Med*. 1998;329:1415-1425.
26. Stroke Prevention In Reversible Ischemia Trial (SPIRIT) Study Group. A randomized trial of anticoagulants versus aspirin after cerebral ischemia of presumed arterial origin. *Ann Neurol*. 1997;42:857-865.
27. CAPRIE Steering Committee. A randomised, blinded trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet*. 1996;348:1329-1339.
28. Hass WK, Easton JD, Adams HP Jr, et al. A randomized trial comparing ticlopidine hydrochloride with aspirin for the prevention of stroke in high-risk patients. *N Engl J Med*. 1989;321:501-507.
29. Bennett CL, Connors JM, Carwile JM, et al. Thrombotic thrombocytopenic purpura associated with clopidogrel. *N Engl J Med*. 2000;342:1773-1777.
30. Gotto F, Tohgi H, Hirai S, et al. Cilostazol stroke prevention study: a placebo-controlled double-blind trial for secondary prevention of cerebral infarction. *J Stroke Cerebrovasc Dis*. 2000;9(4):147-157.
31. Diener HC, Cunha L, Forbes C, et al. European Stroke Prevention Study 2: dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. *J Neurol Sci*. 1996;143:1-13.
32. The ESPS Group. The European Stroke Prevention Study (ESPS): principal end-points. *Lancet*. 1987;1351-1354.

Antiplatelet Therapy and Stroke Prevention

Post-test

Please indicate your answers on the answer form located in the back of this page.

This course (ACPE #038-999-01-052-H01) qualifies for 1.00 contact hour (0.100 CEU) of continuing pharmacy credit, which will be awarded via mail within 4 weeks after submission of a successfully completed program post-test. A passing grade of 70 percent is required. Any participant who fails the examination may be re-examined one additional time. In order to apply for continuing pharmacy education credit, please complete the post-test on the answer form following this page, affix postage, and mail the form to:

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Initial release date: April 2001

Expiration date: April 2004

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Post-test Questions

- Stroke is responsible for how many deaths in the United States?
 - 1 out of 3
 - 1 out of 10
 - 1 out of 15
 - 1 out of 100
- Risk(s) associated with stroke include:
 - age
 - hypercholesterolemia
 - atrial fibrillation
 - all of the above
- The most common type of stroke is:
 - subarachnoid hemorrhage
 - intracerebral hemorrhage
 - ischemic
 - subdural hematoma
- A major lifestyle risk factor associated with stroke is:
 - smoking
 - exercise
 - diet
 - all of the above
- The main reason patients may not experience a significant reduction in hypertension-related stroke is:
 - drug costs
 - failure to adhere to antihypertensive regimens
 - lack of diet control
 - all of the above
- Patients with atrial fibrillation are at a high risk of stroke if they have the following risk factors:
 - prior thromboembolic event
 - congestive heart failure
 - hypertension
 - all of the above
- An issue of using aspirin alone for primary prevention of cardioembolic stroke is the increased risk of:
 - low tolerability
 - hemorrhagic stroke
 - noncompliance
 - none of the above
- In regards to aspirin use in stroke prevention, the following evidence exists:
 - the higher the dose, the better the efficacy
 - enteric-coated aspirin is most effective
 - higher doses do not confer greater benefit
 - one dose shows consistent efficacy for all forms of heart disease prevention
- A significant adverse reaction associated with ticlopidine is:
 - night blindness
 - thrombotic thrombocytopenia
 - cancer
 - all of the above
- The ESPS-2 trial found greatest efficacy in stroke prevention with the use of:
 - aspirin alone
 - dipyridamole alone
 - a combination of extended-release dipyridamole and aspirin
 - warfarin

Program Evaluation

- How would you rate this program overall?
 - excellent
 - good
 - fair
 - poor
- To what degree has this program improved your knowledge of the subject matter?
 - extensively improved
 - moderately improved
 - somewhat improved
 - not at all improved
- How relevant was the program content to your practice?
 - very relevant
 - moderately relevant
 - somewhat relevant
 - not at all relevant
- How effectively did the program meet the learning objectives?
 - very effective
 - moderately effective
 - somewhat effective
 - not at all effective
- The program was free from undue commercial bias:
 - strongly agree
 - agree
 - disagree

Antiplatelet Therapy and Stroke Prevention

Continuing Education Materials

This course (ACPE# 038-999-01-052-H01) qualifies for 1.00 contact hour (0.100 CEU) of continuing pharmacy credit, which will be awarded via mail within 4 weeks after submission of a successfully completed program. A passing grade of 70 percent is required. Any participant who fails the examination may be re-examined one additional time. In order to apply for continuing pharmacy education credit, complete the post-test questions on this answer sheet, copy this page, affix postage, and mail to Rutgers, The State University of New Jersey at:

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(Please circle the correct answers)

1. a b c d

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