

Stroke

American Stroke
AssociationSM

JOURNAL OF THE AMERICAN HEART ASSOCIATION

A Division of American
Heart Association



Preventing Ischemic Stroke in Patients With Prior Stroke and Transient Ischemic Attack : A Statement for Healthcare Professionals From the Stroke Council of the American Heart Association

Philip A. Wolf, G. Pat Clagett, J. Donald Easton, Larry B. Goldstein, Philip B. Gorelick, Margaret Kelly-Hayes, Ralph L. Sacco and Jack P. Whisnant
Stroke 1999;30;1991-1994

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 72514
Copyright © 1999 American Heart Association. All rights reserved. Print ISSN: 0039-2499. Online
ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://stroke.ahajournals.org/cgi/content/full/30/9/1991>

Subscriptions: Information about subscribing to Stroke is online at
<http://stroke.ahajournals.org/subscriptions/>

Permissions: Permissions & Rights Desk, Lippincott Williams & Wilkins, a division of Wolters Kluwer Health, 351 West Camden Street, Baltimore, MD 21202-2436. Phone: 410-528-4050. Fax: 410-528-8550. E-mail:
journalpermissions@lww.com

Reprints: Information about reprints can be found online at
<http://www.lww.com/reprints>

Preventing Ischemic Stroke in Patients With Prior Stroke and Transient Ischemic Attack

A Statement for Healthcare Professionals From the Stroke Council of the American Heart Association

Philip A. Wolf, MD, Chair; G. Pat Clagett, MD; J. Donald Easton, MD; Larry B. Goldstein, MD; Philip B. Gorelick, MD; Margaret Kelly-Hayes, EdD, RN; Ralph L. Sacco, MD; Jack P. Whisnant, MD

Stroke, the third leading cause of death in the United States, is a leading cause of adult neurological disability and accounts for the greatest number of hospitalizations for neurological disease. Although treatment of acute stroke has the potential of reducing death and disability, it is likely that prevention will more effectively reduce the ravages of stroke. The patient who is recovering from a mild stroke or who has had a recent transient ischemic attack (TIA) is at high risk of stroke recurrence, physical and intellectual disability, long-term institutionalization, and death.

There is substantial evidence from observational epidemiological studies and clinical trials that recurrent ischemic stroke can be prevented (Table 1). Control of risk factors is important for prevention of a first stroke and is practical after ischemic stroke and TIA have occurred. Identification of the specific ischemic stroke mechanism, eg, TIA or minor stroke ipsilateral to a moderate or severe internal carotid stenosis, guides decision making with regard to recurrent stroke prevention therapy (Table 2). A patient with symptomatic cerebrovascular disease is likely to have other cardiovascular diseases or is predisposed to develop them. Preventive measures should complement reduction in risk of atherothrombotic events in the coronary arteries and other arterial territories. Certain nonmodifiable characteristics identify persons at high risk of stroke and stroke recurrence. These include advancing age, male sex, and black and Hispanic race-ethnic backgrounds. Some risk factors, however, such as elevated blood pressure, cigarette smoking, obesity, impaired glucose tolerance, and physical inactivity, are modifiable. Other conditions, ie, prior cardiovascular diseases such as coronary heart disease with angina or prior myocardial infarction, valvular heart disease, congestive heart failure, atrial fibrillation, increased left ventricular mass, and certain other echocardiographic abnormalities, identify persons at

increased risk who may be treated with antithrombotic therapy. More recently, other modifiable risk factors for stroke have been identified. These are elevated total and low-density lipoprotein (LDL) cholesterol in patients with prior coronary heart disease and elevated plasma homocysteine levels.

Prevention

There are 3 treatment strategies to prevent recurrent stroke in patients with TIA or mild ischemic stroke. For patients with atrial fibrillation, dose-adjusted warfarin sodium is administered (international normalized ratio [INR] in the 2 to 3 range; target 2.5) unless there is a specific contraindication for that medication.^{1,2} In the latter case, the patient should be treated with aspirin 50 to 325 mg/d.

In patients with TIA or mild stroke and symptoms referable to severe (70% to 99%) carotid artery stenosis (or to moderate [50% to 69%] stenosis in a patient with significant risk factors), the treatment of choice is carotid endarterectomy by a surgeon with a low complication rate (morbidity and mortality <6%).^{3,4} For patients with TIA or mild stroke who do not have atrial fibrillation or moderate-to-severe carotid stenosis, treatment with a daily dose of 50 to 325 mg of aspirin is of demonstrated benefit. Although previous studies used doses of aspirin up to 1300 mg/d, the lower dose range is currently recommended.⁵ Other antiplatelet agents, including clopidogrel, extended-release dipyridamole plus aspirin, and ticlopidine, may be used. Recent retrospective postmarketing surveillance⁶ suggests that the use of ticlopidine with aspirin after coronary angioplasty and stenting was complicated by thrombotic thrombocytopenic purpura approximately once in every 4184 patients and was fatal in >20% of cases. In light of these findings, the use of ticlopidine must be reassessed.

Likelihood and Consequences of Stroke Recurrence

Stroke recurrence is an important public health concern.⁷ The decline in stroke mortality and the increase in life expectancy of the US population will undoubtedly increase the number of persons at risk for recurrent stroke, stroke-related disability, and the cost of medical care. The long-term stroke recurrence rates range from 4% to 14% annually. In the Framingham Study,⁸ the 5-year cumulative recurrence rate for athero-

This statement was approved by the American Heart Association Science Advisory and Coordinating Committee in June 1999. A single reprint is available by calling 800-242-8721 (US only) or writing the American Heart Association, Public Information, 7272 Greenville Ave, Dallas, TX 75231-4596. Ask for reprint No. 71-0178. To purchase additional reprints: up to 999 copies, call 800-611-6083 (US only) or fax 413-665-2671; 1000 or more copies, call 214-706-1466, fax 214-691-6342, or e-mail pubauth@heart.org. To make photocopies for personal or educational use, call the Copyright Clearance Center, 978-750-8400.

(*Stroke*. 1999;30:1991-1994.)

© 1999 American Heart Association, Inc.

Stroke is available at <http://www.strokeaha.org>

TABLE 1. Guide to Risk Reduction for Patients With Ischemic Cerebrovascular Disease (Patients Who Have Already Had Their First TIA or Stroke): General Risk-Factor-Specific Recommendations

Risk Factor	Goal	Recommendations
Hypertension	SBP <140 mm Hg and DBP <90 mm Hg; SBP <135 mm Hg and DBP <85 mm Hg if target organ damage is present	Lifestyle modification and antihypertensive medications
Smoking	Cessation	Strongly encourage patient and family to stop smoking Provide counseling, nicotine replacement, and formal programs
Diabetes mellitus	Glucose <126 mg/dL (6.99 mmol/L)	Diet, oral hypoglycemics, insulin
Lipids	LDL <100 mg/dL (2.59 mmol/L) HDL >35 mg/dL (0.91 mmol/L) TC <200 mg/dL (5.18 mmol/L) TG <200 mg/dL (2.26 mmol/L)	Start AHA Step II diet: ≤30% fat, <7% saturated fat, <200 mg/d cholesterol, and emphasize weight management and physical activity If target goal not achieved with these measures, add drug therapy (eg, statin agent) if LDL >130 mg/dL (3.37 mmol/L) and consider drug therapy if LDL 100–130 mg/dL (2.59–3.37 mmol/L)
Alcohol	Moderate consumption (≤2 drinks/d)	Strongly encourage patient and family to stop excessive drinking or provide formal alcohol cessation program
Physical activity	30–60 minutes of activity at least 3–4 times/wk	Moderate exercise (eg, brisk walking, jogging, cycling, or other aerobic activity) Medically supervised programs for high-risk patients (eg, cardiac disease) and adaptive programs depending on neurological deficits are recommended
Weight	≤120% of ideal body weight for height	Diet and exercise

SBP indicates systolic blood pressure; DBP, diastolic blood pressure; AHA, American Heart Association; HDL, high-density lipoproteins; TC, total cholesterol; and TG, triglycerides.

thrombotic brain infarction was 42% for men and 24% for women. In Rochester, Minn, the 5-year cumulative recurrence rate was 29%, with no sex difference.⁹ Recurrences were generally of the same type as the initial stroke. In the Northern Manhattan Stroke Study,¹⁰ the 5-year stroke recurrence rate was 25%. Overall, stroke recurrence is highest in the first 30 days after the initial event; 30% of recurrences occur within this time frame.¹¹ However, there may be differences in recurrence rates by stroke subtype. Lacunar infarction may have the lowest recurrence rate, atherothrombotic infarction the highest, and infarction of unknown cause

and cardioembolic stroke intermediate rates. Cardiovascular risk factors such as hypertension, glycemic control, cardiac disease, and heavy alcohol consumption may be potentially modifiable predictors of stroke recurrence.¹⁰

More than 50% of stroke survivors have significant residual physical disability and functional impairment.¹² Stroke recurrence not only may add to physical impairment and disability but may also increase mortality and length of hospital stay.⁷ In addition, stroke recurrence may lead to vascular dementia or may be an important trigger for dementia in the elderly.^{13–15} Because some first and recurrent

TABLE 2. Guide to Risk Reduction for Patients With Ischemic Cerebrovascular Disease (Patients Who Have Already Had Their First TIA or Stroke): Additional Subtype-Specific Recommendations

Ischemic Stroke Subtype	Recommendations
Atherosclerotic carotid disease	
≥70% stenosis	Carotid endarterectomy of definite benefit if done with acceptable morbidity and mortality Antiplatelet agents Angioplasty with stent undergoing evaluation
50–69% stenosis	Carotid endarterectomy of potential benefit depending on risk factors Antiplatelet agents
<50% stenosis	Carotid endarterectomy of no benefit Antiplatelet agents
Cardiac embolism	
Definite source:	Oral anticoagulation (unless contraindicated):
Nonvalvular AF	INR 2–3 (target 2.5) lifelong therapy
LV thrombus, recent MI	INR 2–3 (target 2.5) 6-month therapy
Prosthetic VHD	INR 3–4 (target 3.5) lifelong therapy
Possible source	Antiplatelet agents (oral anticoagulation undergoing evaluation)
Other infarct subtypes including small-vessel lacunar disease and cryptogenic stroke	Antiplatelet agents (aspirin, clopidogrel, extended-release dipyridamole plus aspirin, ticlopidine) (oral anticoagulation undergoing evaluation)

AF indicates atrial fibrillation; LV, left ventricular; MI, myocardial infarction; and VHD, valvular heart disease.

strokes are preventable, vascular-associated causes of cognitive impairment might be prevented by appropriate risk-prevention measures.

Prevention of Other Cardiovascular Outcomes in Cerebrovascular Patients

Patients with stroke and TIA are also at risk for myocardial infarction and cardiovascular death. That is, they often have generalized atherosclerosis and are at risk for thrombosis in multiple vascular territories. The present report has emphasized the treatment of atherosclerotic risk factors for stroke prevention, eg, cessation of smoking, reduction of high blood pressure, control of body weight and blood glucose, and use of antithrombotic drugs. These treatments are also effective in reducing the risk of coronary artery events.

The reduction of LDL cholesterol with 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors ("statins") prevents coronary events in patients with coronary artery disease (CAD), especially when LDL cholesterol is elevated. Consequently, stroke patients with known CAD and elevated LDL cholesterol are often prescribed a statin. The value of reducing high blood LDL cholesterol for stroke prevention has been less clear. However, recent trials in patients with CAD^{16–18} have shown treatment with statins prevents stroke as well. Because many stroke patients have clinical CAD, statin use is indicated. Statin use in stroke patients without prior CAD may also reduce the risk of stroke recurrence, as well as myocardial infarction and other vascular disease, but this has not been demonstrated. Additional studies of statins in stroke patients without clinical CAD are in progress.

Educational Aspects

The synthesis of epidemiological and clinical trial data is only the first step in preventing stroke recurrence. New data must be disseminated to healthcare providers and gaps identified between current and "best" practice.¹⁹ Therapeutic decisions based on the best available evidence need to be incorporated into routine clinical practice, and the impact of treatments on patient outcomes should be systematically monitored. These problems are not trivial, because dissemination of preventive guidelines lags behind clinical trial and consensus statement results. For example, \approx 2 years after the results of 3 randomized trials became available indicating that endarterectomy was efficacious in selected symptomatic patients with high-grade carotid artery stenosis, the operation was reported as being always or often recommended by only about half of internists and noninternist primary care physicians in the United States for patients with newly symptomatic disease.²⁰ Less than 33% of the latter physicians indicated that they were considering or expecting to alter their practices.²¹ Although there are several possible explanations for this finding, targeted dissemination of clinical trial results might help address this apparent "knowledge gap" and be an important vehicle for change.

In contrast, the majority of physicians in the United States are knowledgeable regarding the use of anticoagulants in the prevention of cardiogenic embolism in patients with atrial fibrillation.²² Yet several recent studies^{22,23} show that antico-

agulants are prescribed to only \approx 50% of individuals in the United States with atrial fibrillation who are candidates for such therapy. In this case, there is a discrepancy between knowledge and practice that is unlikely to be addressed by reiterating the results of clinical trials. As illustrated by these examples, the optimal methods of translating evidence into effective clinical practice may differ depending on a variety of factors. Systematic study of these factors and the careful assessment of the impact of possible solutions on both the process of care and patient outcomes will be increasingly required in the future. Overall, healthcare organizations need to develop systems that ensure that patients at high risk for stroke are identified, screened, and treated appropriately.

References

1. 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.
2. EAFT Study Group. Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. *Lancet.* 1993;342:1255–1262.
3. North American Symptomatic Carotid Endarterectomy Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. *N Engl J Med.* 1991;325:445–453.
4. Barnett HJ, Taylor DW, Eliasziw M, Fox AJ, Ferguson GG, Haynes RB, Rankin RN, Clagett GP, Hachinski VC, Sackett DL, Thorpe KE, Meldrum HE. Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis: North American Symptomatic Carotid Endarterectomy Trial Collaborators. *N Engl J Med.* 1998;339:1415–1425.
5. Albers GW, Easton JD, Sacco RL, Teal P. Antithrombotic and thrombolytic therapy for ischemic stroke. *Chest.* 1998;114(suppl):683S–698S.
6. Steinhilb SR, Tan WA, Foody JM, Topol EJ. Incidence and clinical course of thrombotic thrombocytopenic purpura due to ticlopidine following coronary stenting: EPISTENT Investigators: Evaluation of Platelet IIb/IIIa Inhibitor for Stenting. *JAMA.* 1999;281:806–810.
7. Sacco RL, Benjamin EJ, Broderick JP, Dyken M, Easton JD, Feinberg WM, Goldstein LB, Gorelick PB, Howard G, Kittner SJ, Manolio TA, Whisnant JP, Wolf PA. American Heart Association Prevention Conference, IV: prevention and rehabilitation of stroke: risk factors. *Stroke.* 1997;28:1507–1517.
8. Sacco RL, Wolf PA, Kannel WB, McNamara PM. Survival and recurrence following stroke: the Framingham Study. *Stroke.* 1982;13:290–295.
9. Petty GW, Brown RD Jr, Whisnant JP, Sicks JD, O'Fallon WM, Wiebers DO. Survival and recurrence after first cerebral infarction: a population-based study in Rochester, Minnesota, 1975 through 1989. *Neurology.* 1998;50:208–216.
10. Sacco RL, Shi T, Zamanillo MC, Kargman DE. Predictors of mortality and recurrence after hospitalized cerebral infarction in an urban community: the Northern Manhattan Stroke Study. *Neurology.* 1994;44:626–634.
11. Hier DB, Foulkes MA, Swiontoniowski M, Sacco RL, Gorelick PB, Mohr JP, Price TR, Wolf PA. Stroke recurrence within 2 years after ischemic infarction. *Stroke.* 1991;22:155–161.
12. Dombovy ML, Basford JR, Whisnant JP, Bergstralh EJ. Disability and use of rehabilitation services following stroke in Rochester, Minnesota, 1975–1979. *Stroke.* 1987;18:830–836.
13. Gorelick PB. Status of risk factors for dementia associated with stroke. *Stroke.* 1997;28:459–463.
14. Kokmen E, Whisnant JP, O'Fallon WM, Chu CP, Beard CM. Dementia after ischemic stroke: a population-based study in Rochester, Minnesota (1960–1984). *Neurology.* 1996;46:154–159.
15. Snowden DA, Greiner LH, Mortimer JA, Riley KP, Greiner PA, Markesbery WR. Brain infarction and the clinical expression of Alzheimer disease: the Nun Study. *JAMA.* 1997;277:813–817.
16. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with

- pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med*. 1998;339:1349–1357.
17. Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, Brown L, Warnica JW, Arnold JM, Wun CC, Davis BR, Braunwald E. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels: Cholesterol and Recurrent Events Trial Investigators. *N Engl J Med*. 1996;335:1001–1009.
 18. Plehn JF, Davis BR, Sacks FM, Rouleau JL, Pfeffer MA, Bernstein V, Cuddy TE, Moyé LA, Piller LB, Rutherford J, Simpson MS, Braunwald E, for the CARE Investigators. Reduction of stroke incidence after myocardial infarction with pravastatin: the Cholesterol And Recurrent Events (CARE) Study. *Circulation*. 1999;99:216–223.
 19. Miller NH, Hill M, Kottke T, Ockene IS. The multilevel compliance challenge: recommendations for a call to action: a statement for healthcare professionals. *Circulation*. 1997;95:1085–1090.
 20. Goldstein LB, Bonito AJ, Matchar DB, Duncan PW, Samsa GP. US national survey of physician practices for the secondary and tertiary prevention of ischemic stroke: carotid endarterectomy. *Stroke*. 1996;27:801–806.
 21. Goldstein LB, Cohen SJ, Matchar DB, Bonito AJ, Samsa GP. Physician-reported readiness to change stroke prevention practices. *J Stroke Cerebrovasc Dis*. 1998;7:358–363.
 22. Munschauer FE, Priore RL, Hens M, Castilone A. Thromboembolism prophylaxis in chronic atrial fibrillation: practice patterns in community and tertiary-care hospitals. *Stroke*. 1997;28:72–76.
 23. Stafford RS, Singer DE. National patterns of warfarin use in atrial fibrillation. *Arch Intern Med*. 1996;156:2537–2541.

KEY WORDS: AHA Scientific Statements ■ stroke ■ ischemia ■ prevention