National Stroke Association

Prevention of a First Stroke: A Review of Guidelines and a Multidisciplinary Consensus Statement from the National Stroke Association

The National Stroke Association:

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Abstract

Objective.- To focus primary-care physician attention on prevention of a first stroke and to provide, in a single resource, up-to-date recommendations regarding prevention strategies for a first stroke.

Data Sources and Study Selection.- Literature review using the MEDLINE database search for 1990 through April 1998; references from text and bibliographies of guidelines, statements, meta-analyses, and overviews; and non-journal sources (i.e. textbooks, reference guides, other non-journal publications, internet web-sites). English-language guidelines, statements, meta-analyses, and overviews dealing with issues relating to prevention of a first stroke were reviewed.

Consensus Process.- The compilation of guidelines from the medical literature, addressing the prevention of a first stroke, was initially presented at a meeting of the National Stroke Association's (NSA's) Stroke Prevention Advisory Board on April 9, l998 in New York, New York. The conference attendees included recognized experts in neurology, cardiology, family practice, nursing, and health services research. From the information presented and the group discussions that followed, areas in which the current literature differed from previously published guidelines were identified, additional literature searches and reviews were performed, and recommendations were updated. The spectrum of evidence-based recommendations was critically reviewed and the highest rank was given to randomized, controlled trials and meta-analyses.

Consensus Recommendations.- After reviewing previously published guidelines and consensus statements, the NSA makes the following recommendations to reduce the risk for a first stroke: 1. Patients with hypertension should be treated according to the recommendations of the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI). 2. Patients with previous MI who do not have contraindications to warfarin should receive warfarin if there is evidence of atrial fibrillation, left ventricular thrombus, or significant left ventricular dysfunction. 3. Patients with nonvalvular atrial fibrillation who have other risk factors for stroke including previous transient ischemic attack (TIA) or stroke, hypertension, heart failure, diabetes, clinical coronary artery disease, and echocardiographic findings of enlarged left atrium or left ventricular dysfunction or who are older than 75 years, unless otherwise contraindicated, should receive warfarin. 4. Lipid lowering 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor agents should be given to post-MI patients with coronary heart disease not only for coronary heart disease prevention, but for stroke prevention

as well. 5. Carotid endarterectomy should be considered for patients with asymptomatic carotid lesions ≥60% as long as surgical complication rates are <3%. 6. Patients who smoke should quit, and those who drink excessively should be counseled to reduce alcohol intake. 7. Patients should be encouraged to exercise, limit sodium intake, replace vitamin B6, vitamin B12, and folate when such deficiencies are identified, and maintain a healthy diet that is rich in fruits and vegetables. 8. Strategies that have demonstrated efficacy in encouraging patient adherence to treatment plans should be utilized.

Conclusions.- Stroke is a substantial public health problem with a high incidence, prevalence, mortality and economic burden. Interventions that address modifiable risk factors may decrease the risk for a first stroke. Physician and patient awareness of risk factors and patient adherence to prevention regimens are critical to the success of these interventions.

INTRODUCTION

Stroke is a leading cause of death and disability worldwide. In the United States, for example, there are an annual estimated 731,000 first-ever or recurrent strokes and 4 million stroke survivors.[1;2] Stroke also exacts an enormous financial burden. It is estimated that annual direct and indirect costs for stroke care total $40 billion.[3] Although stroke remains a leading cause of death, disability, and health care expenditures, it can be prevented.[2]

Several conditions and lifestyle factors have been identified as risk factors for a first-time stroke. These include hypertension, myocardial infarction, atrial fibrillation, diabetes mellitus, blood lipids, asymptomatic carotid disease, smoking, and alcohol (Table 1). Recognition of these risk factors by patients and health care professionals is important in terms of reducing the incidence of stroke. Age-adjusted stroke incidence rates decreased from the 1950s to the early 1980s, but since then, stroke rates have been increasing.[4] This trend has been accompanied by an increase in the prevalence or fall-off in the control of key cerebrovascular risk factors.[5]

Preventing a first stroke will require a comprehensive multidisciplinary strategy to identify, educate, manage, and promote adherence to prevention protocols for the major stroke risk factors.[6] The objective of this document is to focus primary-care physician attention on prevention of a first stroke and to provide, in a single resource, up-to-date recommendations regarding prevention strategies for a first stroke. We propose evidence-based guidelines and discuss strategies to promote patient adherence to stroke prevention strategies.

BACKGROUND

We carried out an evidence-based approach to develop recommendations for prevention of a first stroke.[7;8] We assessed a wide range of "evidence-based" methodologies others have employed in developing practice recommendations, guidelines, and consensus statements for publication. The spectrum of "evidence-based" recommendations varied considerably from personal opinion to consensus of health professionals to more rigorous approaches. Some authors used a system that emphasized the importance of the study design and supporting literature, with the highest rank given to randomized, controlled trials and meta-analyses with "low false positive and false negative results" or in which "the lower limit of the confidence interval for the treatment effect exceeded the minimal clinically important benefit."[9-13] We placed

greatest emphasis on recommendations derived from studies fulfilling these latter criteria and in general gave more weight to recently published recommendations since these were found usually to reflect a more up-to-date review of the medical literature. Our review process specified that the NSA Stroke Prevention Advisory Board Members identify key stroke risk factors and strategies for prevention of a first stroke. We then reviewed the relevant primary studies or meta-analyses/review articles to update information from prior guidelines and consensus statements.

METHODS

Literature Search

We first searched the MEDLINE database from 1990 to 1998 using keyword or publication type for the exploded topics: "guideline," "consensus," "cerebrovascular disorders," (i.e. a broader MeSH heading for stroke) and "risk factors." Also, we searched the subcategory "primary prevention" for cerebrovascular disorders, hypercholesterolemia, and hyperlipidemia. We then hand-searched for all "Guidelines" and "Consensus" articles through 1995 in the following journals: Stroke, Hypertension, Circulation, Diabetes Care, Diabetes, and Neurology. We reviewed the selected articles (guidelines, statements, meta-analyses, and overviews) and identified further articles from text and/or bibliographies.

The second component of the search involved reviewing non-journal sources (i.e. textbooks, reference guides, other non-journal publications, internet web-sites). First, we performed a search for the subject "practice guidelines" on the MELVYL system (database for University of California library system). Next, we hand-searched the local medical library core collection (262) and reference collection (484) to identify publications focusing on practice guidelines. Finally, we searched the internet site www.medmatrix.org and investigated practice guideline web sites for the following institutions: NLM (National Library of Medicine); NIH (National Institutes of Health); AHCPR (U.S. Agency for Health Care Policy and Research); Canadian Medical Association; Scottish Intercollegiate Guidelines Network; American College of Cardiology; College of Physicians and Surgeons of Manitoba; Canadian Coordinating Office of Health Technology Assessment; Vermont Program for Quality in Health Care, Inc; Robert Wood Johnson Foundation; Northwestern Memorial; Greater Victoria Hospital; and McMaster University.

We excluded articles which addressed the following:

1. Prevention of recurrent stroke and transient ischemic attacks (TIAs)[10] (i.e., "secondary" prevention)[14].

2. Prevention of hypertension, hyperlipidemia, coronary heart disease, and diabetes.
3. Guidelines, consensus statements, and position statements in which a more recent update from the same organization was published.
4. Non-English language journals.

Consensus Process

The compilation of guidelines from the medical literature, addressing the prevention of a first stroke, was initially presented at a meeting of the NSA's Stroke Prevention Advisory Board on April 9, l998 in New York, New York. The conference attendees included recognized experts in neurology, cardiology, family practice, nursing, and health services research. To augment the material presented, selected Board members provided brief talks addressing a particular risk factor for stroke. From the information presented and the group discussions that followed, areas in which the current literature differed from previously published guidelines were identified and recommendations were updated. The following risk factors for first stroke were selected by the NSA Stroke Prevention Advisory Board for review: hypertension, myocardial infarction, atrial fibrillation, blood lipids, asymptomatic carotid artery stenosis, and lifestyle factors (cigarette smoking, alcohol use, physical activity, diet).

HYPERTENSION

Hypertension affects approximately 43 million men and women in the United States.[15] According to the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI) [5], 68% of persons are aware of their hypertension, but this figure may be as low as 49%. Furthermore, the general population has a less than adequate understanding that the treatment and control of hypertension reduce the risk of stroke. Clearly, however, treatment of hypertension reduces the risk of stroke: a systematic overview of 14 prospective, randomized, controlled trials demonstrated that a decrease in diastolic blood pressure of 5 to 6 mm Hg decreased the risk for stroke by 42%. [16] Also, the Systolic Hypertension in the Elderly Program (SHEP) study demonstrated that treatment of isolated systolic hypertension in the elderly decreased the risk for stroke by 36%. [17]

In the latest JNC report, less than 30% of patients being treated for hypertension have blood pressure less than 140/90 mm Hg, the suggested goal. [5] Hypertensives in all categories are at risk for

stroke whether they have systolic and diastolic, isolated systolic or diastolic hypertension. Health education programs for stroke prevention should target all hypertensive patients as hypertension may be a contributing factor in up to 70% of strokes.[18;19]

PREVIOUSLY PUBLISHED GUIDELINES

We identified two evidence-based guidelines [5;20] which provided detailed recommendations regarding the management of patients with hypertension. The more comprehensive of the two documents was the JNC VI. [5] The JNC VI report provided detailed recommendations for treatment of hypertension that included lifestyle modifications (e.g., weight reduction, physical activity), pharmacologic treatment, and strategies to improve adherence.

The JNC VI report concluded: 1. Modifying lifestyles in populations can have a major protective effect against high blood pressure and cerebrovascular disease. 2. Lowering blood pressure decreases deaths from stroke, coronary events, and heart failure; slows progression of renal failure; prevents progression to more severe hypertension; and reduces all-cause mortality. 3. A diuretic and/or a beta-blocker should be chosen as initial therapy unless there are compelling or specific indications for another drug. In the elderly population, diuretics or diuretics in combination with beta-blockers should be the first-line treatment. 4. Angiotensin converting enzyme inhibitors (ACE I) should be chosen as initial therapy for patients with diabetes mellitus, unless contraindications for ACE I therapy are present. Also, ACE I and diuretics are first-line antihypertensive agents for patients with heart failure. 5. Beta-blockers without intrinsic sympathomimetic activity are recommended for patients with myocardial infarction. ACE I therapy is recommended for patients with myocardial infarction and systolic dysfunction. 6. Special attention should be provided to the management of hypertension in ethnic and racial minorities, especially African-Americans. Compared to whites, African-Americans have a higher prevalence of hypertension, greater rate of progression to stage 3 hypertension, and a 80% higher stroke mortality.[15;21] 7. Management strategies can improve adherence through the use of multidisciplinary teams.

NSA COMMENTARY

Hypertension remains the most prevalent and modifiable of the stroke risk factors. Over 50% of the patients with sub-optimal control of hypertension demonstrate poor or only partial adherence to

antihypertensive medication. [17] We comment on three interventions directed at lowering blood pressure which may decrease the risk for a first stroke: 1. Focusing attention on blood pressure control in persons who are most likely to develop stroke due to hypertension 2. Providing blood pressure checks at each health care visit for all patients 3. Encouraging the use of home blood pressure monitoring for hypertensive patients.

Studies suggest that hypertension occurs earlier, more frequently, and at a higher level of severity in African Americans.[5;15;21] This contributes to the >60% higher risk for stroke in African-Americans.[2] Specific community-based efforts, such as church-based screening programs, health fairs, and public service announcements should be applied to increase patient awareness of hypertension as a major risk factor for stroke and help identify hypertensive patients before they develop a stroke. Treatment with antihypertensive medications, in particular diuretics, is useful in decreasing stroke morbidity and mortality in African-Americans (as well as in whites). Therefore, diuretics should be recommended as first-line agents for treating hypertension in African-Americans unless there are other reasons to initiate other types of medication.[5]

The elderly are another group in which hypertension and stroke are prevalent. Data from the third National Health and Nutrition Examination Survey (NHANES III) indicate that hypertension is present in 60-71% of persons 60 years or older.[15] Data reported from Rochester, Minnesota have shown that 55% of all strokes occur in patients 75 years of age or older.[22] As the population ages, the number of older patients with hypertension and stroke can be expected to rise over time. Additionally, patients older than 75 years of age are less likely to be able to identify correctly risk factors or warning signs for stroke than younger persons. In one report, only 56% of elderly patients could correctly identify risk factors for stroke, and were least likely to be able to list a single warning sign of stroke.[23] Since the publication of the SHEP trial results [17], emphasis has been placed on the treatment of isolated systolic hypertension in elderly individuals. A recent overview of clinical trials suggests that diuretics provide a 39% odds reduction (OR, 0.61; 95% CI, 0.51-0.72) and beta-blockers provide a 26% odds reduction (OR, 0.74; 95% CI, 0.57-0.98) of stroke events in the hypertensive elderly.[24] Efforts taken today to increase public awareness of hypertension as a risk factor for stroke, with increased attention paid towards populations with a high prevalence of hypertension and high incidence of stroke, should influence outcomes in the future. This preventive approach must be the stimulus to engage both the public and health care professionals alike.

Finally, because hypertension is often a silent condition, it may not be obvious to the patient or the health care provider until blood pressure is measured. Therefore, to promote increased detection of the condition, monitoring of blood pressure should be an essential component of regular health care visits.[5] The JNC VI concludes that self-monitoring has the advantages of identifying cases of "white-coat" hypertension, in which blood pressure is elevated during visits to health care providers, but normal during other times; assessing response to medications; improving adherence through patient involvement in the process [See Adherence sidebar]; and potentially decreasing costs. Either electronic or manual sphygmomanometers that have been proven to be accurate by using standard testing guidelines are recommended for home use.

MYOCARDIAL INFARCTION

The incidence of ischemic stroke is approximately 1-2% per year after myocardial infarction (MI).[14] This risk is greater in the first months after MI.[25-27] Possible reasons for this include the presence of left ventricular dysfunction (often times secondary to anterior wall MI[25;26;28]), the presence of atrial fibrillation, and the formation of left ventricular thrombi. [29-31] Additionally, patients with MI often have concomitant cerebrovascular conditions such as carotid disease and hyperlipidemia that, in and of themselves, are risk factors for stroke. Treatment to prevent stroke after MI may include oral anticoagulants, antiplatelet agents, and/or anti-lipid agents.

PREVIOUSLY PUBLISHED GUIDELINES

Oral anticoagulants

The Fourth Annual ACCP Conference on Antithrombotic Therapy (1995) [32], the American College of Physicians (1994) [10], the American College of Cardiology / American Heart Association (1996)[33], and the North of England Aspirin Guidelines Development Group [13] provide evidence-based recommendations that address the issue of decreasing the risk for a first stroke in patients who have sustained a myocardial infarction. Overall, the four groups reached similar conclusions regarding the use of oral anticoagulant agents in patients with MI: 1. Use of warfarin at INR levels of 2.0 to 3.0 is indicated for patients post-MI with persistent atrial fibrillation or when left ventricular thrombi are detected within a few

months after MI. 2. The evidence is less robust for benefit of administration of warfarin in patients post-MI with extensive wall motion abnormalities or with paroxysmal atrial fibrillation. 3. Warfarin cannot be recommended as a means to prevent stroke in patients with previous myocardial infarction without other known risk factors for stroke (e.g., atrial fibrillation, left ventricular thrombi) as the absolute risk reduction per year is small (i.e., 1%/year).

Antiplatelet agents

The same four guidelines[10;13;32;33] discussed above suggest that aspirin reduces the risk for stroke post-MI by approximately 30%. However, due to the small absolute risk reduction of <0.5%/year, none of the guidelines promotes aspirin use as a means to prevent stroke in patients with previous MI. Such patients, however, should be placed on antiplatelet therapy for subsequent MI prevention.

NSA COMMENTARY

Oral anticoagulants

Several studies, including the WARIS[34], Sixty-Plus[35], ASPECT trials [36], have demonstrated the stroke prevention benefits of warfarin in post-MI patients. However, an overview of these trials has demonstrated that warfarin at the study INR values of 2.5 to 4.8 is associated with a tenfold increase in hemorrhagic stroke.[14] As demonstrated by the SPAF trial, INR values below 2.0 may not be effective for stroke prevention.[37] Therefore, an INR of 2 to 3 seems to be a reasonable anticoagulation goal for appropriately selected patients with previous MI who are taking warfarin.

Antiplatelet agents

The Antiplatelet Trialist's Collaboration (1994) performed a meta-analysis of trials of antiplatelet agents and concluded that in patients with previous MI, antiplatelet agents reduce the odds of nonfatal stroke by 39%, nonfatal MI by 31%, and vascular death by 15%.[38] The North of England Aspirin Guideline Development Group[13] demonstrated that aspirin use in patients with previous MI resulted in a

risk difference of 3.2% for the combined endpoint of MI, stroke, or vascular death. However, upon evaluating stroke as an outcome independent of other vascular events, the ACP[10] identified that aspirin use translated to a small absolute risk reduction of only –2 (CI, -4 to 0) for stroke, which was not strong enough evidence to conclude that antiplatelet agents are useful in preventing a first stroke in post-MI patients. Nevertheless, it is important to recognize that aspirin should be given to all post-MI patients (who do not have contraindications) due to its well-established cardio-protective effects.

The CARS trial (1997)[39] evaluated the effectiveness of combining aspirin with low dose warfarin. It demonstrated that a combination of low-dose aspirin (80 mg) with low dose warfarin (1 or 3 mg) per day was no better than 160 mg aspirin monotherapy for stroke prevention in patients with previous MI.

Recent data demonstrate potential usefulness of non-aspirin antiplatelet agents for preventing vascular events. The CAPRIE study (1996) compared clopidogrel with aspirin in a randomized, blinded trial in patients with atherosclerotic vascular disease (recent ischemic stroke, recent MI or symptomatic peripheral arterial disease) and demonstrated that clopidogrel was slightly more effective than aspirin in reducing the combined risk for stroke, MI, and vascular death (8.7% risk reduction).[40] However, this study did not have adequate statistical power to separately evaluate outcomes for patients with and without a previous stroke, and did not demonstrate a statistically significant difference in terms of stroke reduction between clopidogrel and aspirin (clopidogrel vs. aspirin, relative risk reduction 7.3% [95% CI; -5.7 to 18.7]) for those entrants in the ischemic stroke treatment subgroup. The findings of the CAPRIE trial suggest that further studies evaluating stroke as a primary independent outcome with use of non-aspirin antiplatelet agents are warranted.

Anti-lipid agents

Current evidence suggests that cholesterol lowering agents, in particular, the 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statin agents) decrease the risk of stroke in post-MI patients.[41-43] The CARE Trial (n=4159) was designed to study the effect of lowering cholesterol levels to prevent coronary events in patients post-MI. As part of its findings, this trial demonstrated that in patients with previous myocardial infarction and average cholesterol levels (<240 mg/dl), pravastatin results in a 31% risk reduction (95% CI 3,52) for stroke compared to placebo.[41] The fact that the majority of the patients in the CARE study were already taking aspirin highlights the potential for synergistic anti-stroke benefit of

these agents. Furthermore, the fact that benefit was seen for patients with average cholesterol indicates that the anti-stroke effects of the statin agents may be separate from the lipid-lowering properties.

The statin agents have also been evaluated for stroke reduction in a broader spectrum of coronary heart disease (CHD) patients (i.e, those with a history of previous MI or angina pectoris). [42;43] The Scandinavian Simvastatin Survival Study (4S) trial (n=4,444) studied the effect of lowering cholesterol with simvastatin on morbidity and mortality in patients with CHD and high cholesterol levels (cholesterol 5.5-8.0 mmol/L). Post-hoc analysis of its data demonstrated a significant reduction in stroke and TIA as a combined endpoint for patients taking simvastatin compared to the control group (relative risk 0.70, p=.024). [42] However, reduction in stroke alone was not demonstrated to be statistically significant. A larger study, the LIPID trial (n=9,014), evaluated the effect of pravastatin in patients with coronary heart disease and normal to high cholesterol (i.e., cholesterol between 155-270 mg/dl). [43] The results of the LIPID trial demonstrated a 20% risk reduction for stroke with the use of pravastatin. However, the evidence for the use of statins for stroke prevention in people with MI exists only for younger patients. There is virtually no information for those over age 70, the group where most stroke occur; it may not be appropriate to extrapolate studies from young age groups to older age groups.

The FDA recognizes the importance of statin stroke prevention in CHD patients and has recently approved pravastatin and simvastatin as agents for prevention of a first stroke or TIA. Pravastatin is approved for patients who have had a MI and have average cholesterol levels (<240 mg/dl), and simvastatin is approved for patients with CHD and high cholesterol. The NSA supports these recommendations in post-MI patients.

ATRIAL FIBRILLATION

Nonvalvular atrial fibrillation (NVAF) is a common and important risk factor for stroke. NVAF increases the risk of stroke by about 6 times compared to those without NVAF. [44;45] Over 2 million adults in the U.S. have NVAF, and this number is expected to increase as the population ages. Almost 36% of the strokes in patients between the ages of 80 and 89 are due to NVAF. [44]

PREVIOUSLY PUBLISHED GUIDELINES

We identified four guidelines and/or consensus statements that addressed the issue of preventing a first stroke in patients with NVAF. These guidelines were developed by the American College of Chest Physicians (ACCP) (1995) [32], the American College of Physicians (ACP) (1994) [10], the American Academy of Neurology (AAN) (1998)[46;47], and the American Heart Association (AHA) (1996)[48].

The recommendations by the ACCP, ACP, AAN, and AHA were in agreement that oral anticoagulation with warfarin is indicated for patients with NVAF who have certain risk factors for stroke or are older than 75 years. The ACCP specified the following risk factors: previous TIA or stroke, hypertension, heart failure, diabetes, clinical coronary artery disease, or thyrotoxicosis. The ACP did not include diabetes or thyrotoxicosis as a specific risk factor but did include the echocardiographic finding of left atrial enlargement. The AAN and AHA did not include thyroxicosis as a specific risk factor but did include echocardiographic findings of left ventricular dysfunction. The AHA also identified enlarged left atrium as a risk factor. However, patients in these groups who are unwilling or unable (e.g., have a contraindication) to take warfarin should receive aspirin 325mg/day as an alternative. These recommendations were supported by Level I evidence.[10;32]

Differences among the ACCP, ACP, AAN, and AHA recommendations lie in their discussion of management of patients younger than 75 without specified risk factors. The ACCP and AHA stated that for patients without specific risk factors and who were between the age 65 and 75, either warfarin or aspirin is recommended. The ACP and AAN did not comment on a specific recommendation for this age group. The AHA added that aspirin may be indicated for patients with NVAF who are less than 75 years and have diastolic hypertension. The ACCP and AHA recommended not giving anticoagulation to patients with NVAF and *age less than 65* and no risk factors. The ACP recommended not giving anticoagulation to patients *younger than 60 years* and without specific risk factors.

NSA COMMENTARY

All recommendations regarding the use of antithrombotic or antiplatelet agents to prevent stroke are based on a risk-to-benefit assessment. Pooled analyses from several large, randomized trials have shown that warfarin reduces stroke occurrence by 68% (95% CI, 0.50-0.79) and aspirin reduces the risk of stroke by 21%.[49] Serious bleeding complications with warfarin occur at a rate of 1.3% per year, a rate that is

slightly higher than that seen with aspirin (1.0%).[32;50] However, even in light of the risks of antithrombotic therapy, evidence strongly supports the use of warfarin in patients with NVAF who are at highest risk for stroke.[51] These patients include those older than 75 or with specific risk factors (e.g., prior stroke, hypertension, diabetes).

Although overwhelming evidence suggests that warfarin is effective and relatively safe [52-54] in preventing ischemic events in elderly patients with NVAF, it continues to remain significantly underused in this population. [55-57] A nationwide survey of office-based practitioners suggested that over 50% of some high-risk elderly patients are not prescribed anticoagulation because of concerns for hemorrhage. [57] Under-utilization of anticoagulation may in part be due to lack of physician and patient awareness about the risks and benefits of warfarin in this group of patients. Other factors that may limit warfarin use include the logistical challenges of closely monitoring the level of anticoagulation, concerns about patient adherence, financial considerations, and patient and physician concerns about bleeding risk in the elderly.[57;58]

On the other hand, there is weaker evidence to support the role of antiplatelet agents in "lower risk" NVAF patients (i.e. those <60 years and without specific risk factors). The Antiplatelet Trialists' Collaboration reviewed two randomized trials of patients with NVAF and reported a non-significant decrease in stroke with antiplatelet therapy in unselected patients with NVAF.[38]

DIABETES

Diabetes mellitus (DM) is the most prevalent endocrinologic problem in primary care practice and has been identified as a risk factor for stroke. According to the Framingham study, the relative risk of stroke for diabetic patients aged 55-94 is 1.40 for men and 1.72 for women. [59] Data compiled by the 1994 National Diabetes Data Group revealed that diabetics were 2.5 to 4 times more likely to have a medical history of stroke. [60] In the Honolulu Heart Program[61], patients with either asymptomatic high glucose (>225 mg/dl) or with known diabetes had a 1.43 fold and 2.45 fold increased relative risk of stroke, respectively. An elevated risk was seen in both hypertensive and non-hypertensive individuals. Hemorrhagic stroke was not associated with glucose intolerance.

Diabetes may increase the risk of thromboembolic stroke through multiple and potentially synergistic mechanisms. These include acceleration of large artery atherosclerosis via glycosylation-induced

injury, adverse effects on both LDL and HDL cholesterol, and promotion of plaque formation through hyperinsulinemia. Hyperinsulinemia stimulates endothelial cell proliferation, promotion of platelet adhesion, and regulation of growth factor receptors after endothelial injury and cholesterol deposition. [62] In addition, obesity, hypertension, and insulin resistance have been linked metabolically.

PREVIOUSLY PUBLISHED GUIDELINES

Previously published guidelines addressing the management of diabetes include recommendations published by the Scottish Intercollegiate Guidelines Network (1997) [63] and those of the American Diabetes Association (1998). [64] The Scottish guidelines use a well-defined method of grading the evidence.[63] However, these recommendations regarding diabetes management are limited. While the clinical practice guidelines published by the American Diabetes Association (1998) do not utilize a method of grading/prioritizing the literature, these recommendations are more comprehensive and detailed for evaluation of patients with diabetes.

NSA COMMENTARY

Despite epidemiologic and basic science data suggesting a link between diabetes and stroke, studies have not conclusively shown that tight control of hyperglycemia reduces the risk for stroke. Some observational studies have demonstrated fewer cerebrovascular events and decreased mortality in type 2 diabetic patients with better controlled blood sugars.[65] However, a large multicenter randomized controlled trial (Diabetes Control and Complications Trial) showed that "tight control" of blood sugars with intensive insulin therapy in type 1 diabetics resulted in a reduction in the number of microvascular complications (retinopathy, nephropathy, neuropathy) [66], but not macrovascular complications such as stroke. [67] The NSA recommends tight control of blood sugars for compliant patients with type 1 diabetes mellitus to prevent microvascular complications and careful control of blood sugars for type 2 diabetes as we await more information on possible reduction in cerebrovascular events from future studies.

LIPIDS

Although plasma lipids are not as yet considered a well-documented risk factor for stroke, there is mounting epidemiologic evidence to support their relationship to cerebral infarction. [68-70] Three recent

studies, the Multiple Risk Factor Intervention Trial (MRFIT) [71], the Honolulu Heart Program [72], and the Copenhagen City Heart Study [73], have demonstrated a positive association between lipids and non-hemorrhagic stroke, although the data from the MRFIT study also suggested an inverse relationship between serum cholesterol and risk of death from hemorrhagic stroke. The link between stroke and cholesterol levels is further supported by clinical studies of extracranial carotid stenosis that show positive associations between LDL cholesterol (LDL-C), total cholesterol, triglycerides, and apoprotein B and asymptomatic carotid stenosis, and an inverse association for HDL cholesterol. [68;69]

PREVIOUSLY PUBLISHED GUIDELINES

We identified no guideline (evidence-based or non-evidence based) which specifically commented on lipid management as a method to prevent a first stroke. Biller et al., in a 1998 Statement for Healthcare Professionals from a Special Writing Group of the Stroke Council of the American Heart Association, recommended that in patients with carotid disease, lipids should be lowered to reduce the risk of carotid restenosis and concomitant coronary artery disease. [20] Firm recommendations to prevent a first stroke were not made, as the authors noted that a meta-analysis [74] of lipid-lowering trials found no benefit in terms of stroke risk reduction.

The National Cholesterol Education Program II (NCEP II) guidelines [75] made detailed recommendations for lipid management for patients with coronary heart disease (CHD) and other atherosclerotic disease, including symptomatic carotid artery disease, to decrease morbidity and mortality from CHD. The majority of the other published guidelines we identified [76-82] focused on prevention and treatment of lipids as a means of decreasing the risk for CHD but not for stroke.

NSA COMMENTARY

As noted in the 1998 AHA statement [20], a meta-analysis of previous studies failed to show a relationship between plasma lipid lowering and stroke prevention. [74] Several reasons may have accounted for this. [68;69] First, in previous studies CHD was the primary focus of the intervention strategy and stroke was evaluated as a secondary outcome endpoint. Follow-up periods in these CHD patients may have been too short to capture sufficient numbers of strokes. Second, the distinction between ischemic and hemorrhagic stroke was not made, and hemorrhagic stroke may have had an inverse relationship to

cholesterol. Third, CHD was a competing cause of mortality. Fourth, aggressive management of CHD risk factors may have lessened the subsequent likelihood of stroke. Finally, some of the earlier lipid lowering strategies were shown to be associated with significant adverse events, and these drugs may not have been as effective as more recently marketed agents.

However, a recent meta-analysis [83] of randomized, controlled trials of lipid lowering agents specifically evaluated the effect of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) in preventing a first stroke in CHD patients. It demonstrated that HMG-CoA reductase inhibitors significantly reduced the incidence of first-time nonfatal and fatal strokes (relative risk 0.76 [95% CI, 0.62 to 0.92]). Mortality from CHD and overall mortality were also decreased. Fibrates, resins, and dietary interventions failed to demonstrate significant reduction in stroke. Additionally, another meta-analysis [84] and an overview of randomized controlled trials [85] demonstrated that treatment with HMG-CoA reductase inhibitors prevented stroke in CHD patients. It remains unclear whether the beneficial effects of statin agents is obtained through antiatherosclerotic, antithrombotic, or a combination of these properties. [68;86] The NSA recognizes that the statins are useful and relatively safe [84;85;87] agents to prevent stroke and endorses their use as agents in patients who require lipid-lowering medications.

The NSA recommends following the National Cholesterol Education Program II (NCEP II) guidelines for initiating dietary therapy or drug treatment in patients with CHD or other atherosclerotic disease as a means of decreasing the risk for stroke and cardiovascular events. According to these guidelines [75], recommendations for initiating dietary therapy or drug treatment in patients with CHD or other atherosclerotic disease are based on the LDL-C level. The target LDL-C level is $\leq$100 mg/dl. In those with LDL-C $\geq$ 130mg/dl, drug treatment is generally recommended, while for those with LDL-C > 100mg/dl but <130mg/dl, dietary therapy is generally recommended as the first treatment step.

ASYMPTOMATIC CAROTID DISEASE

Carotid stenosis due to atherosclerotic disease has been demonstrated to be an important stroke risk factor. The prevalence and severity of carotid stenosis rise with advancing age, such that a large number of Americans above the age of 65 probably have some carotid narrowing detectable by duplex ultrasonography. The risk of clinical symptoms increases with the degree of stenosis. [88] The population attributable risk for stroke due to carotid stenosis is not well defined, but in the Harvard Stroke Registry

the most common single cause of stroke was cerebral atherosclerosis with thrombotic or thromboembolic obstruction. [89] At present, however, mass screening for high-grade asymptomatic carotid stenosis is not deemed to be cost-effective.[12;90]

Well-designed prospective trials in asymptomatic individuals have compared carotid endarterectomy (CE) with medical treatment. These trials have served as the basis for guidelines from several groups concerned with treatment and prevention of stroke. In every case, however, these recommendations must be interpreted in the context of the local surgical experience and the *particular characteristics* of the patient in question. Thus, they must not be applied reflexively.

PREVIOUSLY PUBLISHED GUIDELINES

We identified 14 guidelines and/or consensus statements that commented on the prevention of a first stroke in patients with asymptomatic carotid disease. The recommendations presuppose that patients have a reasonable life expectancy at the time of evaluation (typically $\geq$ 5 years) and that surgery can be done with acceptable risks (perioperative morbidity and mortality of $\leq$ 3 percent). Five organizations [12;20;90-92] used a well-defined grading system for the evidence to help assist in the formulation of their recommendations. One organization [93] used evidence-based methods to search and stratify the literature, but did not elaborate on a grading system. Another organization [94] reviewed evidence-based guidelines developed by the Canadian Task Force on the Periodic Health Examination and then held 3 rounds of Delphi consensus meetings to solicit opinion and agreement on the recommendations. These seven sets of recommendations are summarized in Table 2.

NSA COMMENTARY

In all of the guidelines reviewed, a key determinant of the need for carotid endarterectomy is the degree of carotid stenosis. No guideline supports CE for asymptomatic lesions that are less than 60% or for lesions that are 100% occlusive. The generally accepted measure of stenosis is the angiographic one championed by North American Symptomatic Carotid Endarterectomy Trial (NASCET) investigators, namely the narrowest linear diameter within the diseased segment divided by the diameter of the artery beyond the diseased segment, where the arterial walls are again approximately parallel.[95] The question of

whether noninvasive measures should be allowed to supplant angiography has been vigorously debated and remains unsettled. [96;97]

The results of the Asymptomatic Carotid Artery Surgery (ACAS) trial were published in 1995[98] In ACAS, patients with 60-99% asymptomatic stenosis showed an absolute risk reduction for stroke or death of 5.9% over 5 years, when treated with CE rather than best medical treatment only. The 1994 Canadian Task Force on the Periodic Examination recommendations[90] were published prior to the ACAS study, and did not have this information when formulating their recommendations. However, guidelines published between 1995 and 1997 did have the ACAS data available, but nevertheless were not uniformly in favor of CE for asymptomatic disease. Reasons given for this included concern about reproducibility of the low surgical morbidity rate seen in ACAS (1.1 %) and the observation that CE in ACAS did not significantly reduce the risk of major disabling stroke. (Note, however, that ACAS did not have adequate statistical power for such a subgroup analysis.) Importantly, the most recent guideline (American Heart Association, 1998) considers the value of CE for asymptomatic lesions of $\geq$ 60% as "proven" and gives it the highest level of recommendation. [20]

All the CE guidelines stipulate a perioperative morbidity and mortality of <3% as a prerequisite for CE in asymptomatic carotid stenosis. The perioperative mortality rates of CE reported from the NASCET and the ACAS studies are significantly lower than the rate observed for Medicare patients. The 30-day perioperative mortality of CE in the NASCET and ACAS studies are 0.6% and 0.1%, respectively. The mortality rate in the Medicare population (including symptomatic patients) ranges from 1.2 to 2.9%. [99] Without assurance that the local surgical risk is acceptable, CE cannot be recommended.

Several of the guidelines considered additional variables such as contralateral stenosis, plaque ulceration, rate of stenosis progression, and concomitant surgical procedures (e.g., coronary artery bypass grafting [CABG]). Unfortunately, there is insufficient data to make strong recommendations for or against surgery in these settings. Beyond those just mentioned, other potentially confounding variables must be routinely weighed. For example, in ACAS the relative risk reduction for stroke and death in men treated with CE was 66%, but for women it was only 17%. [98] (Note, however, that this gender difference was not statistically significant, and may have been related to insufficient sample size.)

To date, there is no proof that antiplatelet agents such as aspirin are effective in primary prevention of stroke [100], but new antiplatelet agents and new lipid-lowering drugs have become available. In future

studies, combinations of these may be more effective than the "best medical treatment" that was compared with CE in previous trials of asymptomatic patients. Intravascular interventions such as angioplasty and stenting are being promoted as alternatives to CE, particularly in patients considered to be poor surgical risks. Future guidelines may endorse these options as superior to the currently-accepted "best practice."

LIFESTYLE

Lifestyle factors including cigarette smoking, alcohol use, physical activity, and diet have all been associated with a variation in stroke risk.

Cigarette smoking

The Honolulu Heart Study [101] demonstrated that smoking was an independent predictor of ischemic stroke with adjusted relative risks of 2.5 for men and 3.1 for women. Case-control and prospective studies have confirmed these findings in men [101] and women. [102-104] In the Framingham Study, cigarette smoking accounted for adjusted relative risks of brain infarction of 1.7 after controlling for other cerebrovascular risk factors.[59] A meta-analysis of 32 studies found a summary relative risk of stroke for smokers of 1.5 (95% CI 1.4-1.6). [105] Dose-response relationships have been found for cigarette smoking. In the meta-analysis, stroke risk was increased twofold in heavy smokers (more than 40 cigarettes per day) compared to light smokers (fewer than 10 cigarettes per day). In middle-aged British men, stroke incidence rose with increasing number of cigarettes smoked and among hypertensive smokers. The relative risk of stroke was 12.1 for hypertensive male smokers compared to normotensive nonsmoking controls.[106] Even the effects of passive exposure to cigarette smoke have been found to increase the risk of progression of atherosclerosis.[107]

The mode of action by which cigarette smoking increases the risk of stroke is not entirely clear, but acceleration of atherosclerosis is one possibility. Cigarette smoking has been found to be an independent determinant of carotid artery plaque thickness and a substantial predictor of severe extracranial carotid artery atherosclerosis.[108-111] Other biological mechanisms by which cigarette smoking may predispose to stroke include increased coagulability, blood viscosity, and fibrinogen levels, enhanced platelet aggregation, and elevated blood pressure.[112]

Alcohol use

The role of alcohol as a risk factor for ischemic stroke is controversial and may be dependent on dose. Prospective studies [113-115] have shown that alcohol consumption has a direct dose-dependent effect on the risk of hemorrhagic stroke, but the data on infarction are contradictory. Results have ranged from a definite independent effect in both men and women, an effect only in men, and no effect after controlling for other confounding risk factors such as cigarette smoking.[116] Chronic heavy drinking and acute intoxication or binge drinking have been associated with ischemic infarction in young adults.[117] In older adults, despite a significant univariate dose-response relationship, the association between weekly alcohol consumption and ischemic stroke was not significant after controlling for cigarette smoking and hypertension.[118] Cohort studies have also reported variable findings with a twofold increased stroke risk among middle-aged, British, heavy-drinking men [106] and no effect for ischemic stroke in Danes[118] and Hawaiian men of Japanese ancestry.[113]

Some studies suggest that moderate alcohol consumption confers a protective effect on the risk of ischemic stroke in some populations.[114;119-122] In Northern Manhattan, alcohol consumption of up to 2 drinks per day was protective against ischemic stroke in whites, blacks, and Hispanics. Between 2 to 5 drinks per day was indeterminate, but consumption above 5 drinks per day increased the risk of ischemic stroke. Those who previously drank heavily but had since curtailed their drinking to 2 or fewer drinks daily had no increased risk of stroke. A J-shaped relationship (i.e., plotting alcohol intake vs. stroke risk) between alcohol and ischemic stroke has been observed with a protective effect in light drinkers and an elevated stroke risk for moderate to heavy alcohol consumption when compared to non-drinkers.[123]

Alcohol may increase the risk of stroke through various mechanisms, which include hypertension, hypercoagulable states, cardiac arrhythmias, and cerebral blood flow reductions. However, there is also evidence that light to moderate drinking can reduce the risk of coronary artery disease, increase HDL-cholesterol, and increase endogenous tissue plasminogen activator. The combination of deleterious and beneficial effects of alcohol is consistent with the observation of a dose-dependent relationship between alcohol and stroke with an elevated stroke risk for heavy alcohol consumption and a protective effect in light to moderate drinkers when compared to non-drinkers. More data are needed to determine and quantify

the relationship between alcohol consumption and ischemic stroke types. Heavy alcohol consumption has been more consistently related to hemorrhagic stroke risk.

Physical Activity

Regular exercise has well-established benefits for reducing the risk of premature death and many conditions including cardiovascular disease. Only a few previous studies have evaluated the association between physical activity and the risk of stroke.[124-132] The beneficial effects have been predominately described among white populations, more apparent for men than women, and generally described for younger rather than older adults. The Honolulu Heart Program, which investigated older middle-aged men of Japanese ancestry, showed a protective effect from thromboembolic stroke of habitual physical activity among non-smokers.[125] The Framingham Study demonstrated the benefits of combined leisure and work physical activities for men, but not for women.[126] In the Oslo Study of men aged 40 to 49, increased leisure physical activity was related to a reduced stroke incidence.[127] For women 40 to 65 years old, the Nurses' Health Study showed an inverse association between level of physical activity and the incidence of stroke.[128] For white, lower and middle class urban women participating in the Copenhagen City Heart Study, lack of physical activity had a similar effect as cigarette smoking with a relative risk of stroke of 1.4.[129] In the National Health and Nutrition Examination Survey I follow-up study, a low level of recreational or non-recreational activities was associated with a slight increase in risk of stroke for both men and women and among blacks.[130] In the Northern Manhattan Stroke Study, the benefits of leisure-time physical activity were noted for all age, gender, and race-ethnic subgroups.[131]

A dose-response relationship between increasing amounts of physical activity and the reduction in the risk of stroke has not always been demonstrated. In one study the benefits of vigorous physical activity for stroke were offset by an increased risk of heart attack.[132] Among the older cohort in the Framingham study, the strongest protective effect was detected in the medium tertile physical activity subgroup with no additional benefit gained from higher levels of physical activity.[126] Among subjects in a case-control study in West Birmingham, UK, who were free of cardiac disease, peripheral vascular disease, and poor health, recent vigorous exercise (odds ratio 0.40 [95% CI 0.2, 1.0]) was just as protective as walking (odds ratio 0.30 [95% CI 0.1, 0.7]).[133] In the Northern Manhattan Stroke Study, more vigorous (heavy) forms of

physical activities provided additional benefits compared to light-moderate activities and additional protection was observed with increasing duration of exercise.[131]

The protective effect of physical activity may be partly mediated through its role in controlling various known risk factors for stroke. Exercise has been shown to lower blood pressure in African-Americans.[134] It is also associated with a lower incidence of cardiovascular disease,[135] improved diabetes control,[136] better dietary habits, and lower body weight. Other biological mechanisms are associated with physical activity, including reductions in plasma fibrinogen and platelet activity, and elevations in plasma tissue plasminogen activator activity and high-density lipoprotein (HDL) concentrations.[137-140]

Diet

Data suggest that diet may play an important role as a stroke risk factor. Dietary sodium is an important factor that may be associated with increased stroke risk. Specifically, increased sodium intake is associated with an increased risk of hypertension. Reductions in salt consumption may significantly lower blood pressure and could lead to a decrease in stroke mortality.[141]

Another important dietary component that may be associated with stroke is homocysteine. This amino acid is involved in methionine metabolism and is associated with dietary intake of folate and vitamin B12. The Framingham study found that deficiencies in folate, B12 levels, and pyridoxine accounted for the majority of elevated homocysteine levels.[142] Case -control studies have demonstrated an association between moderately elevated homocysteine and vascular disease including stroke.[143;144] The evidence corroborating this relationship is weaker in prospective studies. Finally, genetic and environmental factors may interact in the complex relationship between homocysteine and stroke.

The role of fat intake as a stroke risk factor remains undetermined. Epidemiologic studies demonstrate that higher total fat, saturated fat, and monounsaturated fat intake is associated with a lower incidence of ischemic stroke.[145;146] However, a randomized controlled, double-blinded trial demonstrated that a diet high in unsaturated fats in place of saturated fats resulted in a reduction in both serum cholesterol and incident stroke.[147]

Fruits and vegetables may contribute to stroke protection through anti-oxidant mechanisms[148;149] or through elevation of potassium levels.[150] Dietary anti-oxidants, including vitamin C, vitamin E, and beta-carotene belong to a group of antioxidants called flavonoids. These scavengers of free radicals are thought to be associated with stroke risk reduction through the free-radical oxidation of LDL, a process that inhibits the

formation of atherosclerotic plaques.[151;152] The large Western Electric study showed a moderate decrease in stroke risk associated with a higher intake of both beta-carotene and vitamin C.[153] Other dietary factors associated with a reduced risk of stroke include potassium[150], milk and calcium[154], green tea[155], and fish oils.[156;157] Overall, dietary factors are not considered well-established risk factors for stroke, but some are well-documented risk factors for cardiovascular disease in general.

PREVIOUSLY PUBLISHED GUIDELINES

Smoking

In 1996, the Agency for Health Care Policy and Research (AHCPR) published guidelines regarding smoking cessation.[12] The recommendations were graded using a standard scale from the Canadian Task Force[11] and addressed various topics that include: screening for tobacco use (Grade A); advice to quit (Grade A); interventions (Grade A); smoking cessation pharmacotherapy (Grade A); and promoting the motivation to quit and preventing relapse (Grade C).

Alcohol

In 1998, Biller et al. published recommendations for alcohol consumption in a statement for healthcare professionals from a special writing group of the stroke council of the American Heart Association [20]. These recommendations stated that the relationship between use of alcohol and stroke is complex. Moderate consumption of alcohol may raise HDL cholesterol and lower risk of atherosclerotic heart disease. Heavy use of alcohol should be avoided. (Grade C recommendation, ACCP[9]).

Physical activity

In 1996, Burres et al. published guidelines to promote physical activity for the U.S. Preventative Services Task Force[12] . Counseling to promote regular physical activity is recommended for all children and adults. This recommendation is based on the proven efficacy of regular physical activity in reducing the risk for coronary heart disease, hypertension, obesity, and diabetes. Clinicians should determine each patient's activity level, ascertain barriers specific to that individual, and provide information on the role of physical activity in disease prevention. The clinician may then assist the patient in selecting appropriate types of physical activity. Factors that should be considered include medical limitations and activity

characteristics that both improve health (e.g., increased caloric expenditure, enhanced cardiovascular fitness, low potential for adverse effects) and enhance adherence (e.g., low perceived exertion, minimal cost and inconvenience).

Also, current guidelines endorsed by the Centers for Disease Control and Prevention [158]and the National Institutes of Health [159]recommend that Americans should exercise for at least 30 minutes of moderately intense physical activity on most, and preferably all, days of the week. An emphasis on regular, moderate intensity physical activity rather than on vigorous exercise is reasonable in sedentary persons. This emphasis encourages a variety of self-directed, moderate-level physical activities (e.g., walking or cycling to work, taking the stairs, raking leaves, mowing the lawn with a power mower, cycling for pleasure, swimming, racket sports) that can be more easily incorporated into an individual's daily routine. An appropriate short-term goal is activity that is a small increase over current levels. Over a period of several months, progression to a level of activity that achieves cardiovascular fitness (e.g., 30 minutes of brisk walking most days of the week) would be ideal. Sporadic exercise, especially if extremely vigorous in an otherwise sedentary individual, should be discouraged in favor of moderate-level activities performed consistently.

Diet

In 1996, Woolf et al. published guidelines to Promote a Healthy Diet for the U.S. Preventative Services Task Force[12] Recommendations to promote a healthy diet were graded using a standard scale from the Canadian Task Force[11] and include: limit the intake of dietary fat (especially saturated fat) to less than 30% of total calories (Grade A); limit the intake of dietary cholesterol to less than 10% of total calories (Grade B); emphasize the intake of fruits and vegetables (at least five servings per day) and products containing fiber (at least six servings per day) (Grade B); maintain caloric balance through diet and exercise; maintain adequate intake of dietary calcium (e.g., 1,200-1,500 mg/day for adolescents and young adults; 1,000 mg/day for adults age 25-50; 1,000-1,500 mg/day for post-menopausal women; 1,200-1,500 mg/day for pregnant and nursing women) (Grade B); reduce the intake of dietary sodium (Grade C); and increase the intake of beta-carotene and other antioxidants (Grade C).

NSA COMMENTARY

Observational epidemiological studies suggest that modification of lifestyle-related risk factors (smoking, alcohol, physical activity, and diet) can decrease the risk for stroke. With regards to cigarette smoking, the Nurses' Health Study and the Framingham Study both showed that the risk of ischemic stroke returns to that of non-smokers after 2 to 5 years of cessation from smoking.[160;161] It has been estimated that if we could eliminate cigarette smoking in the Unites States, we could reduce the number of strokes occurring each year by 61,500 and save $3.08 billion in stroke-related health-care costs.[162] The AHCPR guideline for smoking cessation is cost-effective[163], and its recommendations should be followed. Furthermore, recent studies suggest a role for buproprion as an effective adjunct to smoking cessation strategies.[164]

Observational studies have demonstrated that heavy drinking increases the incidence of stroke, and it has been estimated that 23,500 strokes per year could be prevented at a savings of $1.18 billion if heavy alcohol consumption could be eliminated.[162] Since some ingestion of alcohol, perhaps up to 2 drinks per day, may actually help reduce the risk of stroke, drinking in moderation should be recommended for most of the public who drink alcohol and have no health contraindications to alcohol use. However, those who do not customarily drink should not be encouraged to do so.

In terms of physical activity, the benefits for stroke reduction have been seen for even light-moderate activities, such as walking, and some data support additional benefits to be gained from increasing the level and duration of one's recreational activity. The potential deleterious consequences of extreme exercise, such as alterations in hormonal levels in women, musculoskeletal injuries, and risk of acute myocardial infarction, should be considered when advising sedentary patients to increase their physical activity. Nevertheless, physical activity is a modifiable behavior that requires greater emphasis in stroke prevention campaigns. In *Healthy People 2000*, the U.S. Department of Health and Human Services targeted physical activity in its health objectives for health promotion and disease prevention. The aim by the year 2000 is to increase the proportion of people who engage in regular physical activity and reduce the proportion of those who engage in no leisure-time physical activity, particularly among people aged 65 and older.[165] Leisure-time physical activity could translate into a cost-effective means of decreasing the public health burden of stroke and cardiovascular diseases among our aging population.

Finally, it remains unclear whether dietary changes may result in a decrease in stroke risk. Randomized trials are needed to clarify the role of dietary interventions to reduce the risk for stroke. In the

meantime, until additional data are available on other dietary interventions, it may be prudent to limit excess saturated fat and sodium intake, to replace vitamin B12 and folate when such deficiencies are identified, and to maintain a healthy diet that is rich in fruits and vegetables for stroke prevention.

[NOTE: The Adherence document will appear as a sidebar to the main document]

IMPROVING PATIENT ADHERENCE TO PREVENTION RECOMMENDATIONS

INTRODUCTION

Despite recognition of modifiable risk factors for a first stroke (e.g., hypertension, dyslipidemia, atrial fibrillation and smoking) and the availability of well-known treatments, sub-optimal control of these risk factors continues to contribute to over 700,000 strokes in the U.S. per year.[1] Hypertension remains one of the most prevalent and modifiable of these risk factors. However, data from the Health Examination Surveys indicate that only 29% of the 50 million U.S. citizens with hypertension have a blood pressure less than 140/90 mm Hg.[166] Over 50% of the patients with sub-optimal control of hypertension demonstrate poor or only partial adherence to their medication regimens.[167] A major goal of the National Stroke Association is to promote prevention of a first stroke through increased patient adherence to current recommendations.

TERMINOLOGY

Compliance vs. adherence

The terms 'compliance' and 'adherence' are often used inter-changeably. However, there are subtle differences in their connotations. Haynes et al. defined compliance as the degree to which a patient's behavior coincides with medical advice.[168] The term conveys a sense of authoritarianism, in which the physician orders and the patient obeys. Ironically, this type of interaction may actually promote *decreased* patient compliance. The term 'adherence' suggests a more active participation of the patient in the decision-making process through agreement or disagreement with the physician recommendations.[169] We prefer (and will use) the term 'adherence' rather than 'compliance' because it more appropriately describes the cooperative interaction desired between patient and physician.[169]

PREVIOUSLY PUBLISHED STUDIES

Innovative strategies to improve patient adherence have been previously described.[6] However, interventions need to be evaluated in a systematic manner to identify which are the most effective and useful. We reviewed the literature and identified meta-analyses and systematic reviews which addressed

methods to improve adherence to chronic treatment regimens or preventive lifestyle changes (e.g., smoking cessation, weight reduction, diet and exercise) in adult patients.[170-177]

Ensuring that patient follow-up occurs may be key to encouraging patient adherence to a treatment plan. Two meta-analyses [171;172] have demonstrated several methods to improve follow-up visits. These methods include providing reminders to patients, orienting patients to the clinic, educating patients about medications, and forming an agreement with the patient to return. While some studies have demonstrated that attendance at follow-up visits does not correlate with medication adherence [173;174], a meta-analysis [175] showed that follow-up visits more than 30 days from the initial visit for patients receiving counseling for nutrition and weight control was very effective in demonstrating improved outcomes.

The same meta-analysis [175] showed that patient self-monitoring was also a very effective method to help promote nutrition and weight loss, as well as decrease smoking and reduce alcohol abuse. Self-monitoring of blood pressure was shown in another meta-analysis [171] to improve medication adherence. Furthermore, a review of more than 400 meta-analyses, review articles, randomized trials, and observational studies demonstrated that interventions to promote patient participation in contributing to the design and ongoing evaluation of their treatment for chronic medical conditions improved patient outcomes.[176]

Finally, these meta-analyses and systematic reviews support the need for a multi-level approach.[6] Methods to reduce smoking and alcohol abuse are most effective when patients are exposed to recommendations from the media in addition to personal communication with the physician.[175] Also, nutrition and weight control are improved when multiple communication channels are providing the same message.[175] A systematic review performed by Haynes et al.[177] suggested that comprehensive interventions were the most effective method to improve patient adherence to blood pressure medications. The intervention which involved nurses, patient-specific dosing schemes, self-monitoring of blood pressure and pill taking, and rewards for adherence and lower blood pressure [178] was associated with both improved adherence and certain process measures (e.g., lower blood pressure).

These meta-analyses and systematic reviews demonstrate that various interventions such as reminders, self-monitoring, and multiple inputs may be effective in improving patient adherence to clinic appointments, medications, and preventive behaviors, as well as in improving patient outcomes and process measures. Recognizing and utilizing strategies that have demonstrated efficacy in encouraging patient adherence to treatment plans are important steps in preventing a first stroke.

SUMMARY

Recommendations for prevention of a first stroke by the National Stoke Association represent the best available evidence augmented by expert opinions from a multidisciplinary panel when necessary. Expert opinion is directed towards optimizing stroke prevention. Stroke prevention, however, may be best applied at the local level with care plans tailored to the individual patient by the treating physician. The NSA Stroke Prevention Advisory Board recommendations are summarized in Table 3.

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Table 1. Stroke Risk Factors, Relative Risk, Attributable Risk and Status of Prevention of First Stroke (from Gorelick PB. Stroke Prevention. Arch Neurol. 1995;52:347-355)[179]

Risk Factor	Relative Risk (RR) Framingham Study[180]*	Rochester, Minn Study[181]†	Estimated Population-Attributable Risk (PAR)[182]‡	Prevention of First Stroke Proved by Clinical Trial?
Hypertension	1.16§	4.0	High	Yes
Coronary Heart Disease	2.0||	2.2	Medium	Yes¶
Atrial fibrillation	1.82	2.9#	Low	Yes
Diabetes mellitus	1.41	1.7	Low	No
Blood lipids	…	…	??Medium	Yes¶
Cigarette smoking	1.69	…	Low	No**
Heavy alcohol consumption	…	…	Low	No**
Asymptomatic carotid artery stenosis (60-99%)	…	…	?Low-medium	Yes

* From Cox proportional hazards regressions.

† From proportional hazards model (time-dependent covariate)

‡ Low indicates PAR <15%; medium, PAR ≥15%, <40%; high, PAR ≥40%; PAR = A (1+ A), where A = prevalence x (RR – 1).[182]

§ RR is computed for an increase of 10 units (mm Hg) of systolic blood pressure

|| RR is for age group 60 to 69 years

¶ With use of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors

RR is from univariate screen

** Observational studies suggest beneficial effect for risk factor control

Table 2. Summary of "Evidence-based" Guidelines for Management of Asymptomatic Carotid Stenosis

Recommendation Source (year)	Evidence-based process	Carotid stenosis	Assessment of CE for asymptomatic lesion*
American Heart Association (1998) [20]	Well-defined grading system	≥ 60% ≥ 60% + CABG surgery† > 50% + B or C type ulcer‡	Proven Acceptable Uncertain
Canadian Neurosurgical Society (1997) [91]	Well-defined grading system	60-99% < 60%	Uncertain Not recommended
Scottish Intercollegiate Network (1997) [92]	Well-defined grading system	Mild to moderate stenosis§	Not recommended
U.S. Preventive Services Task Force (1996) [12]	Well-defined grading system	60-90%	Possibly Beneficial
Canadian Task Force on the Periodic Health Examination (1994) [90]	Well-defined grading system	Any asymptomatic stenosis	Not recommended
American College of Physicians (1994) [93]	Evidence-based literature search; decision analysis	70-99%	Possibly beneficial
Canadian Stroke Consortium (1997) [94]	Delphi method for agreement on previous evidence-based recommendations	60-99%	Not recommended

* Assuming perioperative morbidity and mortality of <3%
† Performing unilateral carotid endarterectomy at the same time as coronary artery bypass surgery
‡ Reference (Estol et al. Correlative Angiography & Pathologic Findings in the Diagnosis of Ulcerated Plaques in the Carotid Artery. Arch Neurol. 1991;48:692-694)[183]
§ Did not comment on severe asymptomatic carotid stenosis
CABG= coronary artery bypass graft
CE= carotid endarterectomy

Table 3. NSA Summary Recommendations for Prevention of a First Stroke

Condition	Recommendation
Hypertension	JNC VI recommendations[5] for lifestyle modification, initiation of specific therapy and multidisciplinary management strategies
Myocardial Infarction	Aspirin therapy if previous MI[10;13;32;33]; warfarin at an INR of 2 to 3 in post-MI patients with atrial fibrillation, left ventricular thrombus, or significant left ventricular dysfunction[10;13;32;33]; and statin agents in post-MI patients with normal to high lipid levels[83-87]
Atrial Fibrillation	Age / Risk Factors* / Treatment†
	>75 / yes / warfarin
	>75 / no / warfarin
	65-75 / yes / warfarin
	65-75 / no / warfarin or aspirin
	<65 / yes / warfarin
	<65 / no / aspirin or observe
Diabetes mellitus	ADA recommendations[64] for control of diabetes to reduce microvascular complications[66] (further studies are needed to determine if aggressive glycemic control lowers the risk of stroke)
Lipids	Statin agents in patients with CHD[83-87] and NCEP guideline principles for dietary and pharmacologic management of patients with hyperlipidemia or atherosclerotic disease[75]

Asymptomatic Carotid Disease	Carotid endarterectomy for asymptomatic carotid stenosis ≥ 60%‡ (but <100%) only where surgical morbidity and mortality is < 3%[12;20;90;91;91-94]
Lifestyle factors	Modification of smoking, alcohol, physical activity, and diet according to published guidelines[12;20;158;159] may lead to a decrease in stroke risk or reductions in risk factors such as hypertension, diabetes mellitus, blood lipids, and CHD.

* Risk factors include previous TIA or stroke, hypertension, heart failure, diabetes, clinical coronary artery disease, and echocardiographic findings of enlarged left atrium or left ventricular dysfunction

† Additional studies are needed to define the role of non-aspirin antiplatelet agents or antiplatelet-warfarin combinations to reduce the risk for a first stroke. Also, efforts to improve patient and practitioner awareness regarding the benefits and risks of warfarin will serve as a first step towards increasing appropriate usage.

‡ Replication of the ≥ 60% carotid stenosis cut-point in other studies is needed.

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