

New Evidence for Stroke Prevention

Scientific Review

Sharon E. Straus, MD

Sumit R. Majumdar, MD

Finlay A. McAlister, MD

STROKE IS THE THIRD LEADING cause of death in most developed countries and is also a major cause of morbidity, long-term disability, and hospital admission.¹ A substantial body of evidence has established the efficacy of various strategies for stroke prevention, but surveys suggest that there is considerable interphysician variability in the application of this evidence.^{2,3}

METHODS

Searches of MEDLINE, The Cochrane Library, and the ACP Journal Club were performed by using relevant search terms (available from the author) to identify English-language articles about primary and secondary stroke prevention. The literature search focused on recent evidence in this field (from 1998-2001), with reference to several key studies that were completed before this time. The bibliography of each of the retrieved articles was also scanned, and experts in the field of stroke were contacted in an attempt to retrieve additional relevant articles. Three hundred fifty-one articles were retrieved. Each of the articles was critically appraised, and its quality was graded with levels of evidence based on specific scientific methods that affect the validity of a study's conclusions. Level 1 evidence refers to a systematic review of randomized trials or 1 or more high-

See also p 1396.

Context Stroke is a major cause of morbidity and mortality, and the application of evidence for stroke prevention varies considerably.

Objective To review the most recent, high-quality evidence for primary and secondary stroke prevention.

Data Sources and Study Selection Searches of MEDLINE, The Cochrane Library, and the ACP Journal Club were performed to identify English-language articles published from 1998 to 2001 that focused on primary and secondary stroke prevention. The references of each retrieved article were scanned, and experts in the field were contacted to identify additional relevant articles.

Data Extraction Each of the articles was appraised, and its quality was graded with levels of evidence based on specific scientific methods that affect a study's validity.

Data Synthesis For primary prevention of stroke, adequate blood pressure reduction, and treatment of hyperlipidemia, use of antithrombotic therapy in patients with atrial fibrillation and of antiplatelet therapy in patients with myocardial infarction are effective and supported by evidence from several randomized trials. Effective strategies for the secondary prevention of stroke include treatment of hypertension and hyperlipidemia, antithrombotic therapy for patients with atrial fibrillation, antiplatelet therapy, and carotid endarterectomy in patients with severe carotid artery stenosis.

Conclusions Stroke is a major public health concern, and a significant body of evidence supports many primary and secondary prevention strategies.

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quality randomized trials. High-quality observational studies (cohort, case-control, and outcomes studies) provide level 2 evidence. Level 3 evidence is provided by case reports or case series, and level 4 evidence implies expert opinion.

CLINICAL ISSUES

What Factors Increase the Risk of a Stroke?

There are a number of independent risk factors for stroke, most of them associated with atherosclerosis (TABLE 1 outlines those supported by level 2 evidence or higher).⁴⁻⁸ Nonmodifiable risk factors for stroke include older age, male sex, nonwhite race, the presence of coronary heart disease or congestive heart failure, and a positive family history for stroke or transient ischemic attack (TIA). Whether diabetes

mellitus is a modifiable risk factor remains open to debate. Patients with a history of TIA are at substantial risk for subsequent stroke, particularly within the first few days.⁹ A cohort study of 1707 patients with TIA (68% of whom were discharged and receiving aspi-

Author Affiliations: Division of General Internal Medicine, University Health Network, University of Toronto, Toronto, Ontario (Dr Straus); and Division of General Internal Medicine, University of Alberta, Edmonton (Drs Majumdar and McAlister).

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Corresponding Author: Sharon E. Straus, MD, Department of Medicine, University Health Network, Toronto General Hospital, 200 Elizabeth St, ENG 248, Toronto, Ontario, Canada M5G 2C4 (e-mail: sstraus@mtsinai.on.ca).

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Scientific Review and Clinical Applications Section Editor: Wendy Levinson, MD, Contributing Editor. We encourage authors to submit papers to "Scientific Review and Clinical Applications." Please contact Wendy Levinson, MD, Contributing Editor, *JAMA*; phone: 312-464-5204; fax: 312-464-5824; e-mail: wendy.levinson@utoronto.ca.

rin; 12%, ticlopidine; and 14%, warfarin) documented an 11% incidence of stroke within 90 days (half of these strokes occurred within 2 days of the TIA).

Attempts have been made to create clinical prediction rules for stroke. For example, using the Framingham data, D'Agostino and colleagues¹⁰ developed a prediction rule for the 10-year risk of stroke. Independent predictors included age, systolic blood pressure, hypertension, diabetes mellitus, current smoking, established cardiovascular disease (any one of myocardial infarction [MI], angina or coronary insufficiency, congestive heart failure, or intermittent claudication), atrial fibrillation (AF), and left ventricular hypertrophy on electrocardiogram (ECG). According to a patient's risk factor score, 10-year risk of stroke could vary from 1% to higher than 80%. Although this prediction rule has been independently validated, it involves a complex scoring algorithm (TABLES 2, 3, and 4), and it is not known whether its use would improve clinical decision making or health-related outcomes.

What Strategies Are Effective in the Primary Prevention of Stroke?

The impact of various primary prevention strategies is summarized in TABLE 5. However, when physicians attempt to use the results from this table in practice, they should remember that the baseline risk of stroke is variable and the resulting number needed to treat could vary by more than a thousandfold.

Treatment of Hypertension. Randomized placebo-controlled trials have established that lowering blood pressure in hypertensive individuals is effective in the primary prevention of hemorrhagic and ischemic stroke (relative risk [RR] reductions, 35%-45%).¹²⁻¹⁶ Although the

majority of this evidence arises from studies in patients with elevated diastolic (and systolic) blood pressure, a systematic review of 8 trials (15963 patients) confirmed similar reductions in stroke incidence with antihypertensive therapy in elderly patients with isolated systolic hypertension (odds reduction, 30%; 95% confidence interval [CI], 18%-41%)¹⁷ (level 1). Indeed, the benefits of antihypertensive treatment extend to patients older than 80 years (RR reduction, 34%; 95% CI, 8%-52%).¹⁸

A systematic review of early antihypertensive trials confirmed that all of the stroke reduction anticipated (on the basis of population epidemiologic stud-

Table 1. Modifiable Risk Factors for Ischemic Stroke in the General Population*

| Factor | Prevalence, % | Relative Risk |
|---|---------------|--------------------------------|
| Hypertension | 25-40 | 3-5 |
| Elevated total cholesterol level (>240 mg/dL [6.21 mmol/L]) | 6-40 | 1.8-2.6 |
| Smoking | 25 | 1.5 |
| Physical inactivity | 25 | 2.7 |
| Obesity | 18 | 1.8-2.4 |
| Asymptomatic carotid stenosis (>50%) | 2-8 | 2 |
| Alcohol consumption (>5 drinks/d) | 2-5 | 1.6 |
| Atrial fibrillation | 1 | 5 (nonvalvular); 17 (valvular) |

*Factors arranged in order of population prevalence. Data are from references 4-8.

Table 2. Scoring for Risk of Stroke Within 10 Years for Individuals Aged 55-85 Years and Free of Previous Stroke in the Framingham Heart Study

| | Points | | | | | | | | | | |
|-----------------------------|--------------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
| | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| | Men | | | | | | | | | | |
| Age, y | 54-56 | 57-59 | 60-62 | 63-65 | 66-68 | 69-72 | 73-75 | 76-78 | 79-81 | 82-84 | 85 |
| Untreated SBP, mm Hg | 97-105 | 106-115 | 116-125 | 126-135 | 136-145 | 146-155 | 156-165 | 166-175 | 176-185 | 186-195 | 196-205 |
| Treated SBP, mm Hg | 97-105 | 106-112 | 113-117 | 118-123 | 124-129 | 130-135 | 136-142 | 143-150 | 151-161 | 162-176 | 177-205 |
| Diabetes history | No | Yes | | | | | | | | | |
| Current smoker | No | Yes | | | | | | | | | |
| Cardiovascular disease* | No | Yes | | | | | | | | | |
| Atrial fibrillation history | No | Yes | | | | | | | | | |
| LVH on electrocardiogram | No | Yes | | | | | | | | | |
| | Women | | | | | | | | | | |
| Age, y | 54-56 | 57-59 | 60-62 | 63-64 | 65-67 | 68-70 | 71-73 | 74-76 | 77-78 | 79-81 | 82-84 |
| Untreated SBP, mm Hg | | 95-106 | 107-118 | 119-130 | 131-143 | 144-155 | 156-167 | 168-180 | 181-192 | 193-204 | 205-216 |
| Treated SBP, mm Hg | | 95-106 | 107-113 | 114-119 | 120-125 | 126-131 | 132-139 | 140-148 | 149-160 | 161-204 | 205-216 |
| Diabetes history | No | Yes | | | | | | | | | |
| Current smoker | No | Yes | | | | | | | | | |
| Cardiovascular disease* | No | Yes | | | | | | | | | |
| Atrial fibrillation history | No | Yes | | | | | | | | | |
| LVH on electrocardiogram | No | Yes | | | | | | | | | |

*Cardiovascular disease was defined as history of myocardial infarction, angina pectoris, coronary insufficiency, intermittent claudication, or congestive heart failure. SBP indicates systolic blood pressure; LVH, left ventricular hypertrophy. Probability of stroke based on points calculated is shown in Table 3. Adapted with permission from Stroke.¹⁰

ies) with lowering in systolic blood pressure of 5 to 6 mm Hg (the average attained in most of the early trials) was rapidly achieved (odds reduction, 42%; 95% CI, 33%-50%) within 3 years of therapy initiation¹² (level 1). A second systematic review of antihypertensive trials confirmed that the more blood pressure is lowered, the greater the number of strokes that are prevented (RR, 0.80; 95% CI, 0.65-0.98, for an extra 3/3 mm Hg reduction in blood pressure with more intensive treatment)¹⁹ (level 1). Tri-

als^{13,14,19,20} (level 1) have shown that thiazide diuretics, β -adrenergic antagonists, angiotensin-converting enzyme (ACE) inhibitors, and long-acting dihydropyridine calcium channel blockers reduce the incidence of stroke. Whether one class of drugs is superior or inferior to the others is uncertain because of methodologic flaws in the head-to-head trials; the answer awaits the results of ongoing large trials and a prospective individual patient data meta-analysis.

Treatment of Hyperlipidemia. Observational studies suggest that higher total and low-density lipoprotein (LDL) cholesterol levels are associated with a greater risk of ischemic stroke, while lower cholesterol levels (ie, LDL levels <70 mg/dL [1.81 mmol/L]) are associated with a greater risk of hemorrhagic stroke.²¹⁻²⁵ Although there have been no randomized trials evaluating lipid-lowering therapy for the prevention of stroke as a primary outcome, one can extrapolate from randomized trials of lipid-lowering therapy because most of the patients enrolled in these studies had not had a stroke or TIA.²⁶⁻²⁸ A systematic review by Bucher and colleagues²⁶ found that most lipid-lowering therapies (including resins, fibrates, and diet) did not decrease risk of stroke, although the pooled estimate from 8 trials for the relative reduction in risk of stroke with use of a statin was 24% (95% CI, 8%-38%). Warshafsky and colleagues²⁷ included 5 additional trials and, despite significant heterogeneity among these 13 trials, estimated an overall 30% reduction in stroke (95% CI, 14%-43%) with statin use. Since these 2 meta-analyses were undertaken, 2 large statin trials have been published with reporting of stroke outcomes.^{29,30} These studies had more events (455 strokes) than the previous 13 trials combined (404 strokes).^{29,30} We updated the Warshafsky et al meta-analysis and found statin therapy associated with a 25% reduction (95% CI, 14%-35%) in the risk of fatal and nonfatal stroke.

According to the available evidence, statin therapy is safe and is associated with a significant reduction in the risk of first stroke. However, the absolute

benefits of statin therapy are greater for coronary heart disease than for stroke. Therefore, the decision to initiate lipid-lowering therapy should be based on the presence or absence of other cardiovascular risk factors as well as the actual lipid levels, as suggested by the evidence-based guidelines of the National Cholesterol Education Program.³¹ Without clinically manifest atherosclerosis or diabetes, the recommended level for LDL cholesterol is less than 130 mg/dL (3.36 mmol/L).³¹ In individuals with overt atherosclerosis or diabetes mellitus, the recommended level for LDL cholesterol is less than 100 mg/dL (2.59 mmol/L).

Antithrombotic Therapy for AF. Patients with AF have a mortality rate double that of age- and sex-matched controls without AF, largely because of an increased risk of stroke and systemic emboli.³² Indeed, the risk of stroke in the average patient with nonrheumatic AF is approximately 5% a year,³³ and patients with valvular AF have an even higher risk (17-fold increase above that of age- and sex-matched controls). However, the risk of stroke in an individual patient varies widely, depending on the presence of associated risk factors (TABLE 6).³⁴

Although it has long been accepted that warfarin therapy is efficacious in preventing strokes in patients with rheumatic AF,³⁵ randomized trials published in the past decade have defined the benefits of antithrombotic therapy (warfarin or aspirin) in patients with nonrheumatic AF. However, 2 points arising from the accumulated evidence deserve emphasis. First, antithrombotic therapy effectively prevents strokes of all severities, and the strokes that occur in patients receiving warfarin or aspirin are not more severe than those occurring in placebo-treated patients. Second, although retrospective studies suggested that paroxysmal AF was associated with a lower stroke risk than chronic AF, analyses of the recent trial data after controlling for confounders reveals that the stroke risks (and benefits of antithrombotic therapy) were similar for patients with paroxysmal or chronic AF.^{36,37}

Table 3. Probability of Stroke Within 10 Years for Individuals Aged 55 to 85 Years and Free of Previous Stroke in the Framingham Heart Study

| Points | 10-Year Probability, % | |
|--------|------------------------|-------|
| | Men | Women |
| 1 | 3 | 1 |
| 2 | 3 | 1 |
| 3 | 4 | 2 |
| 4 | 4 | 2 |
| 5 | 5 | 2 |
| 6 | 5 | 3 |
| 7 | 6 | 4 |
| 8 | 7 | 4 |
| 9 | 8 | 5 |
| 10 | 10 | 6 |
| 11 | 11 | 8 |
| 12 | 13 | 9 |
| 13 | 15 | 11 |
| 14 | 17 | 13 |
| 15 | 20 | 16 |
| 16 | 22 | 19 |
| 17 | 26 | 23 |
| 18 | 29 | 27 |
| 19 | 33 | 32 |
| 20 | 37 | 37 |
| 21 | 42 | 43 |
| 22 | 47 | 50 |
| 23 | 52 | 57 |
| 24 | 57 | 64 |
| 25 | 63 | 71 |
| 26 | 68 | 78 |
| 27 | 74 | 84 |
| 28 | 79 | ... |
| 29 | 84 | ... |
| 30 | 88 | ... |

*Ellipses indicate data not computed. Points are calculated using criteria in Table 2. Adapted with permission from *Stroke*.¹⁰

Table 4. Average 10-Year Probability of Stroke According to Age*

| Age Group, y | 10-Year Probability, % | |
|--------------|------------------------|-------|
| | Men | Women |
| 55-59 | 5.9 | 3.0 |
| 60-64 | 7.8 | 4.7 |
| 65-69 | 11.0 | 7.2 |
| 70-74 | 13.7 | 10.9 |
| 75-79 | 18.0 | 15.5 |
| 80-84 | 22.3 | 23.9 |
| Age-adjusted | 9.6 | 6.5 |

*Adapted with permission from *Stroke*.¹⁰

Antithrombotic therapy is not without risks (particularly of bleeding) or inconvenience. Although the trials demonstrated that the risk of major extracranial hemorrhage was minimally increased in warfarin-treated patients (by 0.3% per year),³⁸ between 53% and 93% of screened patients were excluded from these trials (in many cases because of perceived bleeding risks), and trial par-

ticipants are likely to be more compliant and more closely followed up than other patients. Although the low hemorrhage rate observed in the trials is unlikely to be duplicated in actual practice, the risk factors for hemorrhage with warfarin therapy are now relatively well defined,^{39,40} and it should be possible to target therapy to individuals with low bleeding risk. Indeed, a

prospective cohort study conducted in elderly patients with AF confirms that the excess bleeding risk with warfarin can be similar to the low rates achieved in the randomized trials.⁴¹

In summary, although there is strong trial evidence that warfarin is the most efficacious agent in preventing stroke, individual AF patients have different stroke risks and thus differ in their potential to

Table 5. Effectiveness of Stroke Prevention Strategies

| Strategy | Relative Risk (RR) Reduction, % (95% Confidence Interval) | Number Needed to Treat to Prevent 1 Stroke a Year* |
|--|--|---|
| Primary Prevention Strategies | | |
| Antihypertensive therapy if blood pressure elevated | 42 (33-50) | 7937 |
| Statins if cholesterol levels elevated | 25 (14-35) | 13 333 |
| Antiplatelet therapy Aspirin | RR increase, 7 (RR reduction of 5% to RR increase of 22%) | Not significant |
| Aspirin after myocardial infarction | 36 (15-51) | 400† |
| Angiotensin-converting enzyme inhibitor | 30 (15-43) | 11 111 |
| Carotid endarterectomy for asymptomatic stenosis | RR increase, 423 (127-1107) | Not significant |
| Secondary Prevention Strategies‡ | | |
| Antihypertensive therapy if blood pressure elevated | 28 (15-39) | 51 (16.5)§ |
| Statins if cholesterol levels elevated | 25 (14-35) | 57 (10.2)§ |
| Warfarin for nonrheumatic atrial fibrillation | 62 (48-72) | 13 (10.5)§ |
| Smoking cessation | 33 (29-38) | 43 (10.5)§ |
| Antiplatelet therapy Aspirin | 28 (19-36) | 77 (9.9)§ |
| Thienopyridines (vs aspirin) | 13 (3-22) | 64 (15.9)§ |
| Carotid endarterectomy for symptomatic moderate/severe stenosis¶ | 44 (21-60) | 26 (3.9)§ |

*Calculated by assuming that the annual risk of stroke is 0.03% (except where otherwise indicated) and using the best estimates of RR reduction from the literature, assuming constant RR reduction over time.¹¹ Note that the baseline risk is variable (ranging from <1%-80%), and therefore the number needed to treat could vary by more than a thousandfold, depending on this risk.

†Calculated by assuming that the risk of stroke is 0.01% over 2 years.

‡Calculated by assuming that the annual risk of recurrent stroke is 7% (except where otherwise indicated) and using the best estimates of RR reduction from the literature, assuming constant RR reduction over time.¹¹

§Numbers in parentheses are the percentage of all recurrent strokes avoided a year, assuming that all eligible patients receive the intervention. The percentage was calculated by factoring the absolute risk reduction from the intervention by the prevalence of the underlying risk factor in the population that has already experienced a stroke or transient ischemic attack.

||Calculated by assuming that the annual risk of recurrent stroke in a patient with nonrheumatic atrial fibrillation is 12%.

¶Calculated by assuming that the annual risk of recurrent stroke in a patient with moderate to severe carotid stenosis is 8.8%.

Table 6. Stratification of Nonrheumatic Atrial Fibrillation Subjects by Biannual Stroke Risk

| Biannual Stroke Risk, % | Patient Features | 2001 ACCP Recommendations* | Number Needed to Treat to Prevent 1 Stroke |
|------------------------------------|---|---|--|
| Low (approximately 2) | Aged <65 y, no major risk factors† | Aspirin | 227 (132-2500) |
| Low moderate (approximately 3) | Aged 65-75 y, no major risk factors | Aspirin or warfarin (target international normalized ratio [INR], 2-3) | Aspirin: 152 (88-1667) Warfarin: 54 (46-69) |
| High moderate (approximately 5) | Aged 65-75 y, no major risk factors but with either diabetes mellitus or coronary artery disease | Warfarin (target INR, 2-3) | 32 (28-42) |
| High (approximately 12) | Aged <75 y, with hypertension, left ventricular dysfunction, or both or aged >75 y without other risk factors | Warfarin (target INR, 2-3) | 14 (12-17) |
| Very high (approximately 20) | Aged >75 y with hypertension, left ventricular dysfunction, or both or any age and prior stroke, transient ischemic attack, or systemic embolism | Warfarin (target INR, 2-3) | 8 (7-10) |

*Adapted from 2001 American College of Chest Physicians recommendations, which apply only to patients without contraindications to the suggested therapies.³⁵

†Major risk factors are prior stroke, systemic embolism, or transient ischemic attack; hypertension; and poor left ventricular function (either clinical history of heart failure or left ventricular ejection fraction <50% on echocardiogram).

benefit (Table 6). The decision to use warfarin, aspirin, or nothing in a patient with AF requires consideration of his or her individual risk and values.

Antithrombotic Therapy After MI.

The risk of ischemic stroke is increased after an MI, particularly in the first month and in patients with left ventricular systolic dysfunction.^{42,43} A meta-analysis of more than 140 trials (more than 72 000 patients) revealed that aspirin reduced the risk of nonfatal stroke (odds reduction, 31%; 95% CI, 24%-37%) in patients who had experienced an MI or other vascular event.⁴⁴

Treatment of Diabetes Mellitus. Diabetic patients are at increased risk for all forms of ischemic stroke and are more likely to have hypertension and hyperlipidemia.⁴⁶ We did not identify any level 1 or 2 evidence to support the tenet that better glucose control is associated with a reduced risk of stroke. None of the 3 major randomized studies that have tested the glucose control hypothesis demonstrated significant reductions in the risk of ischemic stroke or any other macrovascular outcomes.⁴⁵⁻⁴⁷ Lack of statistical power cannot be cited as a reason for the lack of benefit observed in the studies involving patients with type 2 diabetes. For example, in the United Kingdom Prospective Diabetes Study (UKPDS), there were far more macrovascular events than microvascular (eg, almost twice as many MIs as all microvascular events combined), yet the UKPDS was able to demonstrate a 25% relative reduction (95% CI, 7%-40%) in microvascular complications with more intensive glucose control.⁴⁷ Nested within the UKPDS was a smaller randomized trial of tight (<150/85 mm Hg) vs usual (<180/105 mm Hg) blood pressure control. This substudy demonstrated a 44% relative reduction (95% CI, 37%-90%) in stroke with tighter blood pressure control.⁴⁸ This stroke benefit was independent of the level of glycemic control and the antihypertensive regimen used.

Tobacco Cessation. We were unable to identify any high-quality randomized trials evaluating the effects of smoking cessation on risk of stroke. However, given the results from observational

data (Table 5), physicians should discuss smoking cessation interventions with their patients⁴⁹ (level 2). A cohort study⁵⁰ found that the risk of stroke decreased after cessation of smoking and that the elevated risk in smokers disappeared within 5 years. This decline in risk was independent of a patient's age, highlighting that it is never too late to quit. Systematic reviews have shown that 1-time advice from physicians during routine consultation results in 2% of smokers quitting for at least 1 year⁵¹⁻⁵⁴ (level 1). Similarly, nicotine replacement, some antidepressants, and advice from psychologists and nurses can enhance cessation (level 1).^{55,56}

Antiplatelet Therapy. The effectiveness of aspirin in the primary prevention of stroke is controversial because 4 observational studies demonstrated a consistent association between regular use of aspirin and increased risk of stroke.⁵⁷ However, the aspirin use in these studies was self-selected, and the studies may have been confounded by the uneven distribution of risk factors. In a meta-analysis, Hart and colleagues⁵⁷ identified 5 randomized trials that evaluated aspirin vs placebo for primary prevention of stroke (level 1). We identified another 3 eligible studies and updated their data.⁵⁸⁻⁶⁰ These 8 trials included 59 977 patients randomized to various dosages of aspirin (75-990 mg/d). Aspirin reduced the frequency of all cardiovascular events (RR, 0.89; 95% CI, 0.82-0.96) but largely because of substantial reductions in MI risk. In fact, stroke risk was marginally increased with aspirin therapy (RR, 1.07; 95% CI, 0.95-1.22), particularly hemorrhagic strokes. The risk of major bleeding was also increased with aspirin therapy (RR, 1.53; 95% CI, 1.15-2.04). Thus, although the use of aspirin may be beneficial in the primary prevention of MI, it is not efficacious for the primary prevention of stroke.

ACE Inhibitors. Data from trials comparing different antihypertensive agents are difficult to interpret because of methodologic flaws,²⁰ but it is unlikely that ACE inhibitors confer more stroke prevention than other classes of antihyper-

tensives (indeed, the data suggest a possible trend in the other direction).¹⁹ However, a systematic review of 4 randomized placebo-controlled trials demonstrated that for patients with established coronary heart disease, ACE inhibitors were associated with a 30% reduction in the risk of stroke (95% CI, 15%-43%).¹⁹ Ninety-four percent of the stroke outcomes in this meta-analysis were contributed by 1 trial, the Heart Outcomes Prevention Evaluation (HOPE) Study.⁶¹ HOPE was a randomized trial comparing ramipril with placebo in 9297 normotensive (mean blood pressure, 139/79 mm Hg) patients at "high risk of cardiovascular events."⁶¹ Although widely cited as a study of primary prevention, 88% of patients had established cardiovascular disease at study entry. Over 4 years, the reduction in the risk of stroke was 32% (95% CI, 16%-44%).⁶¹ The extent to which these benefits were related to blood pressure lowering rather than a ramipril-specific effect on atherogenesis is unclear⁶² and awaits clarification from ongoing trials.⁶³⁻⁶⁵

We believe that the treatment of hypertension to appropriate target blood pressure is more important than the debate about which agent to use, since there is no clear evidence that any antihypertensive class is superior.⁶⁶ However, in patients whose blood pressure is well controlled but who remain at high risk for an event, the addition of an ACE inhibitor such as ramipril should be considered.⁶¹

Carotid Endarterectomy for Asymptomatic Stenosis. For people with asymptomatic carotid disease, the optimal treatment strategy is unclear. A systematic review of 5 randomized trials (more than 2400 patients) comparing carotid endarterectomy to medical therapy in patients with asymptomatic carotid stenosis higher than 50% found that the risk of stroke or death was increased in the immediate perioperative period (RR increase, 423%; 95% CI, 127%-1107%)⁶⁷ (level 1). However, the risk of the combined end point of stroke or death was reduced throughout the subsequent 3 years (RR reduction, 30%;

95% CI, 9%-45%), which suggests that more evidence is needed to identify subgroups of patients who are at lower risk of surgical complications and would derive more benefit from surgery.

What Strategies Are Effective in the Secondary Prevention of Stroke?

Approximately 7% of all patients with a history of TIA or stroke will have a recurrent event each year.⁶⁸ Strategies targeted to the secondary prevention of stroke are likely to be more cost-effective than primary prevention strategies, since the RR reductions are often constant across various baseline risks (at least for medical interventions),¹¹ meaning that the absolute risk reductions are substantially higher (and the numbers needed to treat are thus substantially lower) in patients at higher risk (ie, those who have already experienced an event). The impact of various secondary prevention maneuvers is summarized in Table 5.

Treatment of Hypertension. There is a continuous, strong, and graded relationship between blood pressure level and the subsequent occurrence of stroke in patients who already have cerebrovascular disease⁶⁹; a systematic review of the trial literature confirms that this risk can be reduced by antihypertensive therapy (RR reduction, 28%; 95% CI, 15%-39%)⁷⁰ (level 1). The recently published Perindopril PROtection AGAINst REcurrent Stroke Study (PROGRESS)⁷¹ further reinforces this. Although intended to test the benefit of ACE inhibitor–based blood pressure lowering on the secondary prevention of stroke, because of its complex design it may be interpreted as a test of 2 targets for blood pressure control. There was an overall 9/4 mm Hg difference in blood pressure between the perindopril-based and placebo arms, associated with a 28% relative reduction (95% CI, 17%-38%) in the risk of stroke. However, physicians had the prerandomization opportunity to state their intent with respect to treatment intensity, and if they intended to offer more intensive treatment, their patients were randomized to

combination therapy with perindopril and indapamide or double placebo. Compared with placebo, perindopril monotherapy achieved a 5/3 mm Hg difference in blood pressure and no benefit in terms of stroke (5% risk reduction; 95% CI, -19% to 23%), while perindopril/indapamide combination therapy achieved a 12/5 mm Hg difference in blood pressure and a 43% reduction (95% CI, 30%-54%) in the RR of stroke. Thus, the benefits of antihypertensive therapy appear to depend more on the blood pressure targets achieved than the agents used. However, given the paucity of controlled clinical trials, it remains unclear how acutely and by how much blood pressure should be lowered after a stroke. Data from observational studies support the familiar adage that all but the highest blood pressures should be left to settle spontaneously in the acute setting.⁷²

Treatment of Hyperlipidemia. There are no published randomized trials of lipid-lowering therapy for the secondary prevention of stroke, although 2 large-scale studies are under way.^{73,74} As mentioned in our discussion of primary prevention, statins may reduce the risk of stroke by 25%. As do the National Cholesterol Education Program guidelines, we consider that patients who have experienced an ischemic stroke or TIA have a coronary heart disease risk equivalent,³¹ and until randomized trial data show otherwise, we believe that stroke patients with hyperlipidemia will benefit from statin therapy and that their target for LDL cholesterol should be 100 mg/dL (2.59 mmol/L).

Antithrombotic Therapy for AF. Four randomized trials provide information on treatment strategies for the secondary prevention of stroke in survivors of TIA or stroke.⁷⁵⁻⁷⁸ The data from these trials confirm a substantial benefit with adjusted-dose warfarin (RR reduction, 68% vs placebo; RR reduction, 71% vs low-dose warfarin plus placebo) and a smaller but still significant benefit with aspirin (RR reduction, 17%-29% vs placebo). Although these relative benefits are similar to those seen in the AF primary prevention trials, the absolute benefit is

higher in patients with prior TIA or stroke, given their markedly higher stroke risk at baseline (Table 6).

The timing of warfarin initiation after stroke is unclear. It is generally recommended that anticoagulants not be prescribed for the first few days after an ischemic stroke, especially if the infarct is large, because of concerns about the potential for hemorrhagic transformation.⁷⁹ However, we could not identify any level 1 or 2 evidence evaluating the timing of anticoagulant administration after stroke.

Antiplatelet Therapy. A recent systematic review of 287 randomized trials in high-risk patients found that antiplatelet agents significantly decreased the risk of stroke (odds reduction, 31%; SE, 5%).⁴⁴ The Antiplatelet Trialists' Collaboration⁴⁴ did not find a significant difference between high (500-1500 mg/d) and medium (75-325 mg/d) doses of aspirin, but the number of vascular events in these studies was small. A second systematic review noted similar results: aspirin decreased the risk of stroke in patients with previous TIA or stroke, and no dose-response relationship was observed⁸⁰ (level 1). Thus, the protective effect of aspirin appears to be uniform across doses of 50 to 1500 mg/d, while larger doses increase the risk of gastrointestinal bleeding⁸¹ (level 1). The lowest effective dose of aspirin has not yet been identified.

A systematic review of 4 trials (>22000 patients) found that thienopyridines (clopidogrel and ticlopidine) are modestly more effective than aspirin at decreasing the risk of the combined end point of stroke, MI, or vascular death in patients at high risk of a vascular event (RR reduction, 8%; 95% CI, 2%-14%)⁸² (level 1). In patients with a history of stroke, thienopyridines decreased the RR of stroke by 13% (95% CI, 3%-22%) above that of aspirin.⁸² (level 1). Use of thienopyridines decreased the risk of gastrointestinal bleeds but increased the risk of rash and diarrhea, particularly with use of ticlopidine. Similarly, patients allocated to ticlopidine were at increased risk of neutropenia (odds ratio, 2.7; 95%

CI, 1.5-4.8). There are insufficient data to determine which patient subgroups would benefit most from these agents instead of aspirin.

In their review, the Antiplatelet Trialists' Collaboration did not find that adding dipyridamole to aspirin resulted in significant benefit over the use of aspirin alone,⁴⁴ but they noted that a single randomized trial found that the addition of extended-release dipyridamole to aspirin decreased the risk of death significantly.⁸³ The ESPRIT trial⁸⁴ (in which patients with prior stroke or TIA are randomized to warfarin, dipyridamole and aspirin, or aspirin alone) should provide additional guidance on this topic when it is completed.

Carotid Endarterectomy. A systematic review of 3 randomized trials found that carotid endarterectomy decreased the risk of stroke or death in patients with symptomatic carotid disease and severe carotid artery stenosis, defined as 70% to 99% by North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria (RR reduction, 48%; 95% CI, 27%-73%, over approximately 2.5 years)⁸⁵ (level 1). Similarly, patients with symptomatic moderate carotid artery stenosis, defined as 50% to 69% by NASCET criteria, had a decreased risk of stroke or death with surgery, although the benefits were more marginal (RR reduction, 27%; 95% CI, 15%-44%, over 5 years). However, patients with lesser degrees of stenosis (<50% by NASCET criteria) were harmed by surgery (RR increase, 20%; 95% CI, 0%-44%).

The results of these studies are applicable only if the surgical complication rate is less than 6%. Indeed, the benefits from carotid endarterectomy would be reduced by 20% for each 2% increase in perioperative stroke and death rates.⁸⁶ Moreover, surgical teams whose complication rates and operative volumes would have rendered them ineligible for the NASCET trial perform most carotid endarterectomies.⁸⁷

Not all patients with operable lesions benefit from surgery. Rothwell and colleagues⁸⁷ performed a systematic review of the carotid endarterectomy lit-

erature and identified clinical and angiographic characteristics that increase a person's risk of perioperative stroke or death. Five clinical characteristics were associated with an increased risk of perioperative stroke or death: surgery for stroke (vs surgery for amaurosis fugax), female sex, older than 75 years, systolic blood pressure higher than 180 mm Hg, and history of peripheral vascular disease. The presence of contralateral internal carotid artery occlusion and stenoses of the intracranial portion of the ipsilateral internal carotid artery and of the ipsilateral external carotid artery as seen on angiography also increased the risk of stroke or death. However, this review included retrospective studies, and its results may be an overestimate. Moreover, this prediction rule needs to be validated in an independent population before it can be recommended for clinical use.

CONCLUSIONS

Stroke is a major public health concern, and efforts should be focused on its prevention. We have provided a brief overview of some of the recent developments in stroke prevention in an attempt to bridge the gap between research and practice and to achieve knowledge translation.

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REFERENCES

- American Heart Association. Heart and stroke statistics update, 1999. Available at: <http://www.americanheart.org/statistics/index.html>. Accessibility verified July 29, 2002.
- Goldstein LB, Bonito AJ, Matchar D, et al. US national survey of physician practices for the secondary and tertiary prevention of ischemic stroke. *Stroke*. 1995; 26:1607-1615.
- Lindley RI, Amayo EO, Marshall J, et al. Acute stroke treatment in UK hospitals: the Stroke Association survey of consultant opinion. *J Coll Physicians*. 1995; 29:479-484.
- Gorelick PB, Sacco RL, Smith DB, et al. Prevention of a first stroke: a review of guidelines and a multidisciplinary consensus statement from the National Stroke Association. *JAMA*. 1999;281:1112-1120.
- Goldstein LB, Adams R, Becker K, et al. Primary prevention of ischemic stroke: a statement for healthcare professionals from the Stroke Council of the American Heart Association. *Circulation*. 2001;103:163-182.

- Benson RT, Sacco RL. Stroke prevention: hypertension, diabetes, tobacco, and lipids. *Neurol Clin*. 2000;18:309-319.
- Bronner LL, Kanter DS, Manson JE. Primary prevention of stroke. *N Engl J Med*. 1995;333:1392-1400.
- Elkind MS, Sacco RL. Stroke risk factors and stroke prevention. *Semin Neurol*. 1998;18:429-440.
- Johnston SC, Gress DR, Browner WS, Sidney S. Short-term prognosis after emergency department diagnosis of TIA. *JAMA*. 2000;284:2901-2906.
- D'Agostino RB, Wolf PA, Belanger AJ, Kannel WB. Stroke risk profile: adjustment for antihypertensive medication: the Framingham Study. *Stroke*. 1994;25:40-43.
- McAlister FA. Relative treatment effects are consistent across a spectrum of underlying risks . . . usually. *Int J Epidemiol*. 2002;31:76-77.
- MacMahon S, Peto R, Cutler J, et al. Blood pressure, stroke, and coronary heart disease, I: prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. *Lancet*. 1990;335:765-774.
- Wright JM, Lee C-H, Chambers GK. Systematic review of antihypertensive therapies: does the evidence assist in choosing a first-line drug? *CMAJ*. 1999; 161:25-32.
- Psaty BM, Smith NL, Siscovick DS, et al. Health outcomes associated with antihypertensive therapies used as first-line agents: a systematic review and meta-analysis. *JAMA*. 1997;277:739-745.
- Perry HM, Davis BR, Price TR, et al. Effect of treating isolated systolic hypertension on the risk of developing various types and subtypes of stroke. *JAMA*. 2000;284:465-471.
- Rodgers A, MacMahon S, Gamble G, et al. Blood pressure and risk of stroke in patients with cerebrovascular disease. *BMJ*. 1996;313:147.
- Staessen JA, Gasowski J, Wang JG, et al. Risks of untreated and treated isolated systolic hypertension in the elderly: meta-analysis of outcome trials. *Lancet*. 2000;355:865-872.
- Gueyffier F, Bulpitt C, Boissel JP, Schron E, Ekblom T, Fagard R, for the INDANA Group. Antihypertensive drugs in very old people: a subgroup meta-analysis of randomized controlled trials. *Lancet*. 1999; 353:793-796.
- Neal B, MacMahon S, Chapman N, for the Blood Pressure Lowering Trialists' Collaboration. Effects of ACE inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: results of prospectively designed overviews of randomized trials. *Lancet*. 2000; 356:1955-1964.
- McAlister FA, Sackett DL. Active-control equivalence trials and antihypertensive agents. *Am J Med*. 2001;111:553-558.
- Cholesterol, diastolic blood pressure, and stroke: 13000 strokes in 450000 people in 45 prospective cohorts. *Lancet*. 1995;346:1647-1653.
- Benfante R, Yano K, Hwang LJ, et al. Elevated serum cholesterol is a risk factor for both coronary heart disease and thromboembolic stroke in Hawaiian Japanese men: implications of shared risk. *Stroke*. 1994; 25:814-820.
- Iso H, Jacobs DR, Wentworth D, Neaton JD, Cohen JD. Serum cholesterol levels and six year mortality from stroke in 350,977 men screened for the Multiple Risk Factor Intervention Trial. *N Engl J Med*. 1989; 320:904-910.
- Byington RP, Davis BR, Plehn JF, et al. Reduction in stroke events with pravastatin: Prospective Pravastatin Pooling (PPP) Project. *Circulation*. 2001;103: 387-392.
- Plutzky J, Ridker PM. Statins for stroke: the second story? *Circulation*. 2001;103:348-350.
- Bucher HC, Griffith LE, Guyatt GH. Effect of HMG-CoA reductase inhibitors on stroke: a meta-analysis of randomized controlled trials. *Ann Intern Med*. 1998; 128:89-95.
- Warshafsky S, Packard D, Marks SJ, et al. Effi-

- cacy of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors for prevention of stroke. *J Gen Intern Med.* 1999;14:763-774.
28. Crouse JR III, Byington RP, Hoen HM, Furberg CD. Reductase inhibitor monotherapy and stroke prevention. *Arch Intern Med.* 1997;157:1305-1310.
29. White HD, Simes RJ, Anderson NE, et al. Pravastatin therapy and the risk of stroke. *N Engl J Med.* 2000;343:317-326.
30. Schwartz GG, Olsson AG, Esekowitz MD, et al. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes. *JAMA.* 2001;285:1711-1718.
31. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA.* 2001;285:2486-2497.
32. Feinberg WM, Blackshear JL, Laupacis A, Kronmal R, Hart RG. Prevalence, age distribution, and gender of patients with atrial fibrillation: analysis and implications. *Arch Intern Med.* 1995;155:469-473.
33. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation: a major contributor to stroke in the elderly: the Framingham Study. *Arch Intern Med.* 1987;147:1561-1564.
34. Albers GW, Dalen JE, Laupacis A, Manning WJ, Peterson P, Singer DE. Antithrombotic therapy in atrial fibrillation. *Chest.* 2001;119(suppl):194S-206S.
35. Szekely P. Systemic embolism and anticoagulant prophylaxis in rheumatic heart disease. *BMJ.* 1964;1:1209-1212.
36. 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.
37. Hart RG, Pearce LA, Rothbart RM, McAnulty JH, Asinger RW, Halperin JL. Stroke with intermittent atrial fibrillation: incidence and predictors during ASA therapy. *J Am Coll Cardiol.* 2000;35:183-187.
38. Hart RG, Benavente O, McBride R, Pearce LA. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. *Ann Intern Med.* 1999;131:492-501.
39. Becker RC, Ansell JJ. Antithrombotic therapy. *Arch Intern Med.* 1995;155:149-161.
40. Landefeld CS, Goldman L. Major bleeding in outpatients treated with warfarin: incidence and prediction by factors known at the start of outpatient therapy. *Am J Med.* 1989;87:144-152.
41. Caro JJ, Flegel KM, Orejuela ME, Kelley HE, Speckman JL, Migliaccio-Walle K. Anticoagulant prophylaxis against stroke in atrial fibrillation: effectiveness in actual practice. *CMAJ.* 1999;161:493-497.
42. Tanne D, Goldbourt U, Zion M, Reicher-Reiss H, Kaplinsky E, Behar S, for the SPRINT Study Group. Frequency and prognosis of stroke/TIA among 4808 survivors of acute myocardial infarction. *Stroke.* 1993;24:1490-1495.
43. Loh E, Sutton MS, Wun CC, et al. Ventricular dysfunction and the risk of stroke after myocardial infarction. *N Engl J Med.* 1997;336:251-257.
44. Antiplatelet Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction and stroke in high risk patients. *BMJ.* 2002;324:71-86.
45. Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long term complications in insulin dependent diabetes mellitus. *N Engl J Med.* 1993;329:977-986.
46. The University Group Diabetes Program. A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. *Diabetes.* 1970;19(suppl):789-830.
47. UK Prospective Diabetes Study Group. Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet.* 1998;352:837-853.
48. UK Prospective Diabetes Study Group. Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes (UKPDS 39). *BMJ.* 1998;317:713-720.
49. Shinton R, Beevers G. Meta-analysis of relation between cigarette smoking and stroke. *BMJ.* 1989;298:789-794.
50. Kawachi I, Colditz GA, Stampfer MJ, et al. Smoking cessation and decreased risk of stroke in women. *JAMA.* 1993;269:232-236.
51. Law M, Tang JL. An analysis of the effectiveness of interventions intended to help people stop smoking. *Arch Intern Med.* 1995;155:1933-1941.
52. Lancaster T, Stead LF. Individual behavioural counselling for smoking cessation [Cochrane Review on CD-ROM]. Oxford, England: Cochrane Library, Update Software; 2001;issue 4.
53. Rice VH, Stead LF. Nursing interventions for smoking cessation [Cochrane Review on CD-ROM]. Oxford, England: Cochrane Library, Update Software; 2001;issue 4.
54. Ashenden R, Silagy C, Weller D. A systematic review of the effectiveness of promoting lifestyle change in general practice. *Fam Pract.* 1997;14:160-176.
55. Silagy C, Lancaster T, Stead L, Mant D, Fowler G. Nicotine replacement therapy for smoking cessation [Cochrane Review on CD-ROM]. Oxford, England: Cochrane Library, Update Software; 2001;issue 4.
56. Hughes JR, Stead L, Lancaster T. Antidepressants for smoking cessation [Cochrane Review on CD-ROM]. Oxford, England: Cochrane Library, Update Software; 2001;issue 4.
57. Hart RG, Halperin JL, McBride R, et al. Aspirin for the primary prevention of stroke and other major vascular events. *Arch Neurol.* 2000;57:326-332.
58. The DAMAD Study Group. Effect of aspirin alone and aspirin plus dipyridamol in early diabetic retinopathy. *Diabetes.* 1989;38:491-498.
59. Cote R, Battista RN, Abrahamowicz M, et al, for the Asymptomatic Cervical Bruit Study Group. Lack of effect of ASA in asymptomatic patients with carotid bruits and substantial carotid narrowing. *Ann Intern Med.* 1995;123:649-655.
60. de Gaetano G, for the Collaborative Group of the Primary Prevention Project (PPP). Low-dose aspirin and vitamin E in people at cardiovascular risk: a randomised trial in general practice. *Lancet.* 2001;357:89-95.
61. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G, for the Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin converting enzyme inhibitor, ramipril, on cardiovascular events in high risk patients. *N Engl J Med.* 2000;342:145-153.
62. Svensson P, de Faire U, Sleight P, Yusuf S, Ostergren J. Comparative effects of ramipril on ambulatory and office blood pressures: a HOPE substudy. *Hypertension.* 2001;38:E28-E32.
63. Pfeffer MA, Domanski M, Verter J, et al. The continuation of the Prevention of Events with Angiotensin-Converting Enzyme Inhibition (PEACE) Trial. *Am Heart J.* 2001;142:375-377.
64. Fox KM, Henderson JR, Bertrand ME, et al. The European Trial on reduction of cardiac events with perindopril in stable coronary artery disease (EUROPA). *Eur Heart J.* 1998;19(suppl J):J52-J55.
65. Major cardiovascular events in hypertensive patients randomized to doxazosin vs chlorthalidone: the Antihypertensive and Lipid-Lowering Treatment to prevent Heart Attack Trial (ALLHAT). *JAMA.* 2000;283:1967-1975.
66. McAlister FA, Levine M, Zarnke K, et al, for the Canadian Hypertension Recommendations Working Group. The 2000 Canadian recommendations for the management of hypertension, I: therapy. *Can J Cardiol.* 2001;17:543-559.
67. Benavente O, Moher D, Pham B. Carotid endarterectomy for asymptomatic carotid stenosis: a meta-analysis. *BMJ.* 1998;317:1477-1480.
68. Hankey GJ, Warlow CP. Treatment and secondary prevention of stroke: evidence, costs and effects on individuals and populations. *Lancet.* 1999;354:1457-1463.
69. Rodgers A, MacMahon S, Gamble G, Slattery J, Sandercock P, Warlow C. Blood pressure and risk of stroke in patients with cerebrovascular disease: the United Kingdom Transient Ischaemic Attack Collaborative Group. *BMJ.* 1996;313:147.
70. Gueyffier F, Boissel JP, Bouillon F, et al, for the INDANA Project Collaborators. Effect of antihypertensive treatment in patients having already suffered from stroke: gathering the evidence. *Stroke.* 1997;28:2557-2562.
71. PROGRESS Collaborative Group. Randomized trial of a perindopril-based blood pressure lowering regimen among 6105 individuals with previous stroke or transient ischemic attack. *Lancet.* 2001;358:1033-1041.
72. Strandgaard S. Hypertension and stroke. *J Hypertens Suppl.* 1996;14:S23-S27.
73. Collins R, Peto R. MRC/BHF Heart Protection Study. *Stroke.* 1999;30:1304.
74. Stroke prevention by aggressive reduction in cholesterol levels (SPARCL) [Stroke Center Web site]. Available at: <http://www.neuro.wustl.edu/stroke/trials>. Accessibility verified July 29, 2002.
75. European Atrial Fibrillation Trial Study Group. Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. *Lancet.* 1993;342:1255-1262.
76. Diener HC, Lowenthal A. European Stroke Prevention Study 2. *J Neurol Sci.* 1996;143:1-13.
77. Benavente O, Hart R, Koudstal P, Laupacis A, McBride R. Antiplatelet therapy for preventing stroke in patients with nonvalvular atrial fibrillation and no previous history of stroke or transient ischemic attacks. In: Warlow C, Van Gijn J, Sandercock P, eds. *Stroke Module of the Cochrane Database of Systematic Reviews*. Oxford, England: Cochrane Collaboration; 1999.
78. Stroke Prevention in Atrial Fibrillation Investigators. Adjusted-dose warfarin versus low intensity, fixed-dose warfarin plus aspirin for high-risk patients with atrial fibrillation: Stroke Prevention in Atrial Fibrillation III randomized clinical trial. *Lancet.* 1996;348:633-638.
79. Ezekowitz MD, Levine JA. Preventing stroke in patients with atrial fibrillation. *JAMA.* 1999;281:1830-1835.
80. Johnson ES, Lanes SF, Wentwork CE III, Satterfield MH, Abebe BL, Dicker LW. A meta-regression analysis of the dose-response effect of ASA on stroke. *Arch Intern Med.* 1999;159:1248-1253.
81. Farrell B, Godwin J, Richards S, Warlow C. The United Kingdom transient ischaemic attack (UK-TIA) aspirin trial: final results. *J Neurol Neurosurg Psychiatry.* 1991;54:1044-1054.
82. Hankey GJ, Sudlow CLM, Dunbabin DW. Thienopyridine derivatives versus ASA for preventing stroke and other serious vascular events in high vascular risk patients [Cochrane Review on CD-ROM]. Oxford, England: Cochrane Library, Update Software; 2001;issue 1.
83. Diener HC, Cunha L, Forbes C, Sivenius J, Smets P, Lowenthal A. European Secondary Prevention Study 2: dipyridamol and acetylsalicylic acid in the secondary prevention of stroke. *J Neurol Sci.* 1996;143:1-13.
84. DeSchrivver EL. Design of ESPRIT: an international randomized trial for secondary prevention after non-disabling cerebral ischemia of arterial origin. *Cerebrovasc Dis.* 2000;10:147-150.
85. Cina CA, Clase CM, Haynes RB. Carotid endarterectomy for symptomatic carotid stenosis [Cochrane Review on CD-ROM]. Oxford, England: Cochrane Library, Update Software; 2001;issue 1.
86. Tu JV, Hannan EL, Anderson GM, et al. The fall and rise of carotid endarterectomy in the United States and Canada. *N Engl J Med.* 1998;339:1441-1447.
87. Rothwell PM, Slattery J, Warlow CP. Clinical and angiographic predictors of stroke and death from carotid endarterectomy: systematic review. *BMJ.* 1997;315:1571-1577.