New Evidence for Stroke Prevention
Scientific Review

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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. 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.

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 appraised, and its quality was graded with levels of evidence based on specific scientific methods that affect a study’s validity.

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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Financial Disclosure: Dr Strauss was a coinvestigator on an unrestricted scientific grant from Organon.

Reprints are not available from the author.

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.
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%). Although the majority of this evidence arises from studies in patients with elevated diastolic (and systolic) blood pressure, a systematic review of 8 trials (15,963 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%)(level I). Indeed, the benefits of antihypertensive treatment extend to patients older than 80 years (RR reduction, 34%; 95% CI, 8%-52%).

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

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*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-

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

<table>
<thead>
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<th>Points</th>
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*Ellipses indicate data not computed. Points are calculated using criteria in Table 2. Adapted with permission from Stroke.*

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

<table>
<thead>
<tr>
<th>Age Group, y</th>
<th>10-Year Probability, %</th>
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<td>80-84</td>
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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), between 53% and 93% of screened patients were excluded from these trials (in many cases because of perceived bleeding risks), and trial participants 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, 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.

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 |
|---------------------------------|----------------|----------------|
| **Primary Prevention Strategies** | **Relative Risk (RR) Reduction, % (95% Confidence Interval)** | **Number Needed to Treat to Prevent 1 Stroke a Year** |
| Antihypertensive therapy if blood pressure elevated | 42 (33-50) | 7937 |
| Statins if cholesterol levels elevated | 25 (14-35) | 1333 |
| Aspirin after myocardial infarction | 36 (15-51) | 400† |
| Angiotensin-converting enzyme inhibitor | 30 (15-43) | 1111 |
| 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)§ |
| 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.† Note that the baseline risk is variable (ranging from <1%-80%), and therefore the number needed to treat could vary by more than a thousand-fold, 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.‖ 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) | 152 (88-1667) |
| 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) | 54 (46-69) |
| 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) | 32 (28-42) |
| 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.† 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. 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.84

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.84 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.85-87 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 (93% CI, 7%-40%) in microvascular complications with more intensive glucose control.85 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.86 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 patients (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,88 but it is unlikely that ACE inhibitors confer more stroke prevention than other classes of antihypertensives (indeed, the data suggest a possible trend in the other direction).89 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%).89 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 unclear88 and awaits clarification from ongoing trials.62-65

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 postoperative period (RR increase, 423%; 95% CI, 127%-1107%)97 (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. 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), 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 6.

**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 disease; a systematic review of the trial literature confirms that this risk can be reduced by antihypertensive therapy (RR reduction, 28%; 95% CI, 15%-39%) (level 1). The recently published Perindopril PROtection Against REcurrent Stroke Study (PROGRESS) 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.

**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. 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, 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. 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. 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%). The Antiplatelet Trialists’ Collaboration 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 observed (level 1). Thus, the protective effect of aspirin appears to be uniform across doses of 50 to 1500 mg/d, whereas larger doses increase the risk of gastrointestinal bleeding (level 1). The lowest effective dose of aspirin has not yet been identified.

A systematic review of 4 trials (>22,000 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%) (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 (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 Tri-

alists’ Collaboration did not find that adding dipyridamole to aspirin resulted in significant benefit over the use of aspirin alone, but they noted that a single randomized trial found that the addition of extended-release dipyridamole to aspirin decreased the risk of death significantly. The ESPRIT trial (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) (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. Moreover, surgical teams whose complication rates and operative volumes would have rendered them ineligible for the NASCET trial perform most carotid endarterectomies. Not all patients with operable lesions benefit from surgery. Rothwell and colleagues performed a systematic review of the carotid endarterectomy lit-

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ure 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.

Funding/Support: Dr Straus is supported by a Ca-

reeer Scientist Award from the Ontario Ministry of Health and Long-Term Care, Drs Majumdar and McAlister are Population Health Investigators of the Alberta Heritage Foundation for Medical Research, and Drs Straus and McAlister are funded by the Canadian Stroke Network.

REFERENCES

1. American Heart Association. Heart and stroke sta-
anmericanheart.org/statistics/index.html. Accessibil-
ity verified July 29, 2002.


5. Goldstein LB, Adams R, Becker K, et al. Primary preven-

6. Benson RT, Sacco RL. Stroke prevention: hyper-

7. Bronner LL, Kanter DS, Manson JE. Primary preven-


9. Johnston SC, Gress DR, Bronner WS, Sidney S. Short-term prognosis after emergency department di-


11. McAlister FA. Relative treatment effects are consis-
tent across a spectrum of underlying risks . . . usu-

12. MacMahon S, Peto R, Cutler J, et al. Blood pressure, stroke, and coronary heart disease, I. pro-
longed systolic hypertension: prospective ob-

13. Wright JM, Lee C-H, Chambers GK. Systematic review of antihypertensive therapies: does the evi-
dence assist in choosing a first-line drug? CMAJ. 1999;

14. 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.

15. Perry HM, Davis BR, Price TR, et al. Effect of treat-
ing isolated systolic hypertension on the risk of de-


18. Gueyffier F, Bulbitt C, Boissel JP, Schron E, Ek-
brom T, Fagard R, for the INDIANA Group. Antihyper-
tensive drugs in very old people: a subgroup meta-
analysis of randomized controlled trials. Lancet. 1999;

19. 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 de-
signed overviews of randomized trials. Lancet. 2000;

20. McAlister FA, Sackett DL. Active-control equiva-


21. Cholesterol, diastolic blood pressure, and stroke: 13000 strokes in 450000 people in 45 prospective co-

rum cholesterol is a risk factor for both coronary heart disease and thromboembolic stroke in Hawaiian Japa-

23. Tasto JD. Serum cholesterol levels and six year mortal-

ity from stroke in 350,977 men screened for the Mul-

24. Byington RP, Davis BR, Plehn JF, et al. Reduction in stroke events with pravastatin: Prospective Prava-
stanol Pooling (PPP) Project. Circulation. 2001;103:

25. Pluitsky J, Ridker PM. Statins for stroke: the sec-

26. Bucher HC, Griffith LE, Guyatt GH. Effect of HMG-

27. Warshafsky S, Packard D, Marks SJ, et al. Effi-

©2002 American Medical Association. All rights reserved.
cacy of 3-hydroxy-3-methylglutaryl coenzyme A re-
ductase inhibitors on the risk of stroke. J Gen In-
28. Crouse JR III, Byington RP, Hoen HM, Furberg CD. Red-
ducer inhibit monotherapy and stroke preven-
29. White HD, Simes RJ, Anderson NE, et al. Prava-
30. Leitch I, Bogaert D, Olson AG, Ezekowitz MD, et al. Ef-
ficacy 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 Na-
tional Cholesterol Education Program (NCEP) Expert
Panel on Detection, Evaluation, and Treatment of High
Blood Cholesterol in Adults (Adult Treatment Panel
32. Feinberg WM, Blackshear JL, Laupacis A, Kron-
mal R, Hart RG. Prevalence, age distribution, and
gender of patients with atrial fibrillation: analysis and im-
33. Wolf PA, Abbott RD, Kannel WB. Atrial fibrilla-
tion: a major contributor to stroke in the elderly: the
Framingham Study. Arch Intern Med. 1987;147:1561-
1566.
34. Albers GW, Dalen JE, Laupacis A, Manning WJ,
Peterson P, Singer DE. Antithrombotic therapy in atrial
35. Albers GW, Sacco RL, Capewell S. Symbolism and an-
tiaggregant prophylaxis in rheumatic heart disease. BMJ.
36. Atrial Fibrillation Investigators. Risk factors for stroke
and efficacy of antithrombotic therapy in atrial fibrilla-
tion: analysis of pooled data from five randomized con-
fibrillation in patients with adult-onset diabetes. The
University Group Diabetes Program. A study of effect of ASA in asymptomatic patients with ca-
tilabour and office blood pressures: a HOPE substudy.
40. Landefeld CS, Goldman L. Major bleeding in out-
patients treated with warfarin: incidence and predic-
tion factors known at the start of outpatient therapy.
Am J Med. 1989;87:144-152.
41. Caro JJ, Fiegel KM, Orejuela ME, Kelley HE, Speck-
man ML, Migliaccio-Walle K. Anticoagulant prophylax-
ixis during joint surgery: effectiveness in actual practice.
CMAJ. 1999;161:493-497.
42. Tanne D, Goldberg U, Zion M, Reicher-Reiss H, Kaplinysy E, Behar S, for the SPRINT Study Group. Fre-
quency and prognosis of stroke/TIA among 4808 sur-
vivors of acute myocardial infarction. Stroke. 1993;
24:1490-1495.
43. Loh E, Sutton MS, Wun CC, et al. Venricular dys-
function and the risk of stroke after myocardial in-
44. Antiplatelet Trailists’ 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 Re-
search Group. The effect of intensive treatment of dia-
46. The University Group Diabetes Database. A study of the
characteristic of the disease in the non-insulin dependent vascu-
lar complications in patients with adult-onset diabetes. Di-
47. UK Prospective Diabetes Study Group. Intensive blood
pressure lowering with sulphonylureas or insulin compared with conventional treatment and risk of com-
plications in patients with type 2 diabetes (UKPDS 33).
48. UK Prospective Diabetes Study Group. Efficacy of an-
teiloplatin in reducing risk of macrovas-
cular and microvascular complications in type 2 dia-
289:789-794.
ing cessation and decreased risk of stroke in women. JAMA.
51. Law M, Tang JL. An analysis of the effectiveness of interventions intended to help people stop smok-
52. Lancaster T, Stead LF. Individual behavioural coun-
seling for smoking cessation [Cochrane Review on CD-
2001;issue 4.
53. Rice VH, Stead LF. Nursing interventions for smok-
ing cessation [Cochrane Review on CD-ROM]. Ox-
ford, England: Cochrane Library, Update Software;
2001;issue 4.
54. Ashenden R, Silagy C, Weller D. A systematic re-
view of the effectiveness of promoting lifestyle change in
general practitioners. The European Atrial Fibrillation Trial
Group. Sec-
ondary prevention in non-rheumatic atrial fibrillation after transient ischemic attack or minor stroke. Lan-
cet. 1993;342:1245-1262.
55. Lipton HC, Lown B. A European Stroke Preven-
patients with nonvalvular atrial fibrillation and no pre-
vious history of stroke or transient ischemic attacks. In:
Warlow C, Van Gijn J, Sandercopck P, eds. Stroke Mod-
ule of the Cochrane Database of Systematic Reviews. Ox-
57. Stroke Prevention in Atrial Fibrillation Investiga-
tors. Adjusted-dose warfarin versus low intensity, fixed-
dose warfarin plus aspirin for high-risk patients with atrial fibrillation: Stroke Prevention in Atrial Fibrillation III ran-
58. Ezekowitz MD, Levine JA. Preventing stroke in pa-
ients with atrial fibrillation. JAMA. 1999;281:1830-
1833.
59. Johnson ES, Lanes SF, Wentwork CE III, Satter-
60. Farrell B, Godwin J, Richards S, Warlow C. The United Kingdom transient ischaemic attack (UK-TIA) aspirin trial final results. Neurol. Neurosurg Psychia-
try. 1991;54:1044-1054.
61. Hankey GJ, Sadowl CLM, Dunbabin DW. Thieno-
pyridine derivatives versus ASA for preventing stroke and
other serious vascular events in high vascular risk patients
2: dipridamole and acetylsalicylic acid in the second-
63. DeSchrayer EL. Design of ESPRIT: an interna-
tional randomized trial for secondary prevention af-
64. Cina CA, Clase CM, Haynes RB. Carotid endar-
terectomy for symptomatic carotid stenosis [Coch-
65. Tu JV, Hannan EL, Anderson GM, et al. The fall of
primary and carotid endarterectomy in the United States
66. Rothwell PM, Slattery J, Warlow CP. Clinical and an-
gographic predictors of stroke and death from ca-
rotid endarterectomy: systematic review. BMJ. 1997;
315:1571-1577.

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(REPRINTED) JAMA, September 18, 2002—Vol 288, No. 11

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