

# Risk Factor Management to Prevent First Stroke

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Despite substantial advances for treatment of patients with acute stroke, effective primary stroke prevention remains the best means for reducing the stroke burden [1]. More than 70% of all strokes occurring each year are first strokes and therefore primary prevention of stroke is of immense public health importance [2]. High-risk or stroke-prone individuals can be identified and targeted for specific management and interventions. The ultimate public health benefit, however, depends on not only identification of stroke risk but also on assessing global vascular risk and the management and modification of these risks [3]. Many preventive strategies are available to manage a number of factors that increase the risk of a first stroke. Such successful implementation in preventive medicine remains a great challenge worldwide.

The evidence-based guidelines for the management of risk factors to prevent first stroke have been published [4]. This article provides an overview of the management of risk factors in primary stroke prevention, the gaps in successful management, and future directions for the research and management of stroke risk factors. The management of modifiable and potentially modifiable risk factors or risk markers for a first stroke is reviewed. Nonmodifiable factors, such as age, sex, race/ethnicity, and various genetic factors, are mentioned in the context of risk stratification for a first stroke. The major focus is given to the management of modifiable risk factors for stroke, including hypertension, diabetes, dyslipidemia, atrial fibrillation and other cardiac conditions, carotid artery stenosis (CAS), smoking, poor diet, physical inactivity, and obesity. A brief discussion of the management of potentially modifiable risk factors, such as alcohol and drug abuse, sleep apnea,

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and hyperhomocysteinemia, is included, as is the use of antiplatelet therapy in primary stroke prevention. The less well documented risk factors for first stroke, such as inflammation, infection, and hypercoagulable disorders, are beyond the scope of this article. Finally, prognostic scores to assess an individual risk for a first stroke are reviewed.

### **Management of well-documented modifiable risk factors to prevent first stroke**

Evidence-based guidelines exist for the management of several modifiable risk factors of a first stroke. The modification of these risk factors clearly reduces risk of first stroke. Selected well-documented modifiable risk factors are discussed below.

#### *Hypertension*

Hypertension is one of the most important modifiable risk factors for prevention of a first stroke. The control of high blood pressure contributes to the prevention of a first stroke but also to the prevention or reduction of other end-organ damage, such as renal or heart failure [5]. A comprehensive evidence-based approach to treatment of hypertension is provided in the document published by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) [6].

The JNC 7 guidelines (Table 1) recommend lowering blood pressure to less than 140/90 mm Hg (or <130/80 mm Hg in individuals with diabetes). The optimal blood pressure target levels are still being explored in ongoing trials [6]. Overall, antihypertensive therapy is associated with a 35% to 44% reduction in the incidence of stroke [7]. Several categories of antihypertensive medications, such as thiazide diuretics, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs),  $\beta$ -adrenergic receptor blockers, and calcium channel blockers, reduce the risk of stroke in patients with hypertension [8–11].

Thiazide-type diuretics were recommended as the preferred initial drugs for treatment of hypertension in most patients [6]. Several other classes of blood pressure-lowering agents, such as ACEIs and ARBs, are recommended as next in priority.  $\beta$ -Blockers seem to have a lesser role in the management of uncomplicated hypertension [6,12].

The Systolic Hypertension in the Elderly Program (SHEP) trial found a 36% reduction in the incidence of stroke with treatment with a thiazide diuretic with or without a  $\beta$ -blocker in patients over age of 60 with isolated systolic hypertension [13]. The results from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), a randomized, double-blind, active, controlled clinical trial of 24,316 participants, showed the superiority of diuretic-based over  $\alpha$ -blocker-based antihypertensive treatment for the prevention of stroke and cardiovascular disease.

Table 1  
Classification and treatment of blood pressure according to the JNC 7

Classification	Blood pressure	Without convincing antihypertensive indication <sup>a</sup>	With convincing antihypertensive indication <sup>a</sup>
Normal	<120/80 mm Hg	No drug	No drug
Prehypertension	<139/90 mm Hg	No drug	Drugs for the compelling indication
Stage 1 hypertension	<159/99 mm Hg	Thiazide-type diuretics; may consider ACEIs, ARBs, $\beta$ -blockers, calcium channel blockers, or combination	Drugs for the compelling indication; other drugs (diuretics, ACEIs, ARBs, $\beta$ -blockers, calcium channel blockers) as needed
Stage 2 hypertension	$\geq$ 160/100 mm Hg	Two-drug combination for most <sup>b</sup> (usually thiazide-type diuretic and ACEI or ARB or $\beta$ -blocker or calcium channel blocker)	Drugs for the compelling indication and other drugs as needed

<sup>a</sup> Lifestyle modifications are encouraged for all and include (1) weight reduction if overweight, (2) limitation of ethyl alcohol intake, (3) increased aerobic physical activity (30–45 min/d), (4) reduction of sodium intake (<2.34 g), (5) maintenance of adequate dietary potassium (>120 mmol/d), (6) smoking cessation, and (7) Dietary Approaches to Stop Hypertension diet (rich in fruit, vegetables, and low-fat dairy products and reduced saturated and total fat). Compelling indications include (1) congestive heart failure, (2) myocardial infarction, (3) diabetes, (4) chronic renal failure, and (5) prior stroke.

<sup>b</sup> Initial combined therapy should be used cautiously in those at risk for orthostatic hypotension.

*Data from* Chobanian AV, Bakris GL, Black HR, et al. National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003;289:2560–72.

A meta-analysis of 18 long-term randomized trials found that both diuretics (hazard ratio, 0.49; 95% CI, 0.39–0.62) and  $\beta$ -blockers (hazard ratio, 0.71; 95% CI, 0.59–0.86) were effective in preventing stroke [12].

The Captopril Prevention Project (CAPPP) among 10,985 patients did not show a difference in efficacy in preventing cardiovascular morbidity and mortality between an ACEI-based therapeutic regimen captopril in comparison to the conventional therapy group (diuretics,  $\beta$ -blockers) in hypertension [14]. Interestingly, fatal and nonfatal stroke was more common with captopril (189 vs. 148; hazard ratio, 1.25; 95% CI, 1.01–1.55;  $P = .044$ ).

The Systolic Hypertension in Europe (Syst-Eur) Trial showed a 42% stroke risk reduction in patients treated with a calcium channel blocker (nitrendipine) compared with placebo in patients with isolated systolic hypertension [15]. Data from the Controlled Onset Verapamil Investigation of Cardiovascular Endpoints (Convince) trial, however, did not

demonstrate benefit in cardiovascular risk reduction of a calcium channel blocker (verapamil) compared with a diuretic or  $\beta$ -blocker treatment [16].

In the Anglo-Scandinavian Cardiac Output Trial—Blood Pressure—Lowering Arm (ASCOT-BPLA) with a primary cardiovascular outcome, a combination of atenolol ( $\beta$ -blocker) with a thiazide prevented more major cardiovascular events and induced less diabetes than amlodipine (a calcium channel blocker) with perindopril (ACEI) [17].

The Heart Outcomes Prevention Evaluation (HOPE) study conclusively demonstrated that ramipril (ACEI) reduces the risk of cardiovascular events in patients at risk for cardiovascular events but without heart failure [18]. The cardiovascular risk for patients treated with ACEI ramipril was reduced by approximately 20% compared with placebo. The Study to Evaluate Carotid Ultrasound Changes in Patients Treated With Ramipril and Vitamin E (Secure)substudy demonstrated that ramipril also reduced atherosclerosis [19].

The angiotensin II type 1 receptor antagonist (ARB) losartan has been shown in the Losartan Intervention for Endpoint Reduction in Hypertension (Life) study to decrease stroke risk in hypertensive patients to a substantially greater extent than conventional therapy with atenolol ( $\beta$ -blocker) for a similar reduction in blood pressure [10]. The Life study was a double-masked, randomized, parallel-group trial in 9193 participants aged 55 to 80 years with essential hypertension, and stroke occurred in 232 losartan and 309 atenolol patients (hazard ratio, 0.75; 95% CI, 0.63–0.89).

Achieving maximum benefit may require treatment with both an ACEI and ARB. The Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (Ontarget) compared the benefits of ACEI treatment, ARB treatment, and treatment with an ACEI and ARB together. Meanwhile, a parallel study, Telmisartan Randomized Assessment Study in ACEI Intolerant Patients with Cardiovascular Disease (Transcend), randomized patients unable to tolerate an ACEI to receive telmisartan or placebo [20]. The results of these landmark trials have demonstrated that telmisartan, a second-generation ARB, is equally effective as the current standard, ramipril (ACEI), in reducing the risk of stroke, myocardial infarction, cardiovascular death, and hospitalization for congestive heart failure in a broad cross-section of high-risk cardiovascular patients with normal blood pressure or controlled high blood pressure, and resulted in fewer discontinuations (hazard ratio, 1.01; 95% CI, 0.94–1.09) [20]. Telmisartan is now the only ARB to have demonstrated cardiological and vascular risk reduction benefits beyond lowering blood pressure in this high-risk population. However, a combination of an ACEI ramipril and an ARB telmisartan did not show that dual renin-angiotensin system blockade provided additional risk-reduction benefit compared with single blockade. In addition, a higher discontinuation rate was observed if telmisartan and ramipril were combined [20].

The treatment of patients with hypertension is beneficial in younger but also in older patients. In the Hypertension in the Very Elderly Trial (Hyvet)

among 3845 individuals 80 years of age or older with a sustained systolic blood pressure of 160 mm Hg or more, a 30% reduction in the rate of fatal or nonfatal stroke and a 39% reduction in the rate of death from stroke was achieved on active treatment (the diuretic indapamide with addition of ACEI perindopril if needed to achieve the target blood pressure of 150/80 mm Hg) in comparison to placebo [21]. In addition, fewer serious adverse events were reported in the active-treatment group. In the recent meta-analysis of 31 trials, with 190,606 participants, reduction of blood pressure produced benefits in younger (<65 years) and older ( $\geq 65$  years) adults, with no strong evidence that protection against stroke and other vascular events varies substantially with age [22].

The recent Avoiding Cardiovascular Events Through Combination Therapy in Patients Living with Systolic Hypertension (Accomplish) Trial was the first trial designed to compare the effects on major fatal and nonfatal cardiovascular events of two forms of antihypertensive combination therapy: benazepril plus hydrochlorothiazide and amlodipine plus benazepril in 11,454 hypertensive patients at high cardiovascular risk [23]. The study was stopped early because combination ACEI plus the calcium channel blocker amlodipine was more effective than combination treatment with benazepril plus the thiazide diuretic hydrochlorothiazide (hazard ratio, 0.80; 95% CI, 0.71–0.90).

Direct comparisons among the various types of antihypertensive agents however are still limited. In several studies comparing ACEIs and calcium-antagonists with  $\beta$ -blockers, diuretic drugs, or both, primary outcome did not differ between treatment groups [7,24,25]. The optimal blood pressure lowering for primary stroke prevention and blood pressure targets are yet to be determined.

For secondary stroke prevention, the Perindopril Protection Against Recurrent Stroke Study (Progress) trial has confirmed that a perindopril (ACEI)-based regimen reduces the incidence of secondary stroke and primary myocardial infarction [26]. In addition, combination therapy with perindopril and indapamide (non-thiazide sulphonamide diuretic) produced larger blood pressure reductions and larger stroke reductions than monotherapy with perindopril alone. Treatment with these two agents should be considered routinely for all patients with a history of previous stroke or transient ischemic attack, whether hypertensive or normotensive.

### *Summary*

It is well established that blood pressure lowering is effective for the primary prevention of stroke and other cardiovascular disorders. It has taken longer to prove that blood pressure lowering is equally effective for the prevention of recurrent stroke. Antihypertensive therapy has had a major impact on public health. Blood pressure control can be achieved in most patients, although most patients require combination therapy, often with more than two antihypertensive medications [27]. Despite this knowledge,

blood pressure levels are controlled in less than 25% of the hypertensive population worldwide [28]. There is a real need to identify hypertensive subjects and treat them with blood pressure–lowering drugs for primary prevention. Lack of diagnosis and inadequate treatment are particularly evident in minority populations and in the elderly [6,29]. The real challenge now is to implement effective strategies for the control of blood pressure. Strategies should include lifestyle measures, such as exercising, losing weight, and stopping smoking [30]. Choice of a specific regimen must be individualized, but reduction in blood pressure is generally more important than the specific agent used to achieve this goal. However, it remains unclear whether specific classes of antihypertensive drugs offer, in addition to the blood pressure–lowering effects, special protection against stroke.

### *Diabetes*

Individuals with type 2 diabetes are considered at high risk for vascular events and diabetes is a coronary heart disease (CHD) risk-equivalent with greater than 20% likelihood of a major coronary event or stroke in 10 years, according to the Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program [31]. Individuals with type 2 diabetes also have an increased vulnerability to atherosclerosis and an increased prevalence of hypertension, obesity, and abnormal blood lipids. Since 1990, the prevalence of those diagnosed with diabetes rose 61%, with an increase of 8.2% from 2000 to 2001 [1].

Cardiovascular disease develops earlier in the presence of diabetes and, to reduce this increased risk, a multifactorial approach to the management of type 2 diabetes has been advocated [32]. The American Diabetes Association recommends not only good glycemic control, but also identification and aggressive treatment of associated cardiovascular risk factors, with more stringent target levels for lipids and blood pressure than those recommended for the general population [33]. Yet, data have been lacking on the effects of such a multifactorial approach to reduce risk of stroke among individuals with type 2 diabetes. In a small trial of multifactorial-intensive interventions with 160 patients with type 2 diabetes and microalbuminuria randomized to receive conventional care or intensive treatment, the risk of cardiovascular events was reduced almost by 50% (hazard ratio, 0.47; 95% CI, 0.22–0.74;  $P = .01$ ) in those on intensive treatment [32]. Patients in the intensive-therapy group were treated with a stepwise introduction of lifestyle and pharmacologic interventions intended to maintain glycosylated hemoglobin values below 6.5%, blood pressure below 130/80 mm Hg, cholesterol levels below 175 mg/dL, and triglyceride levels below 150 mg/dL. Recommended lifestyle interventions included reduced intake of dietary fat, regular participation in light or moderate exercise, and cessation of smoking. All participants in the intensive-therapy group were advised to take aspirin and a dietary supplement, including vitamins E and C, folic acid, and chrome picolinate. In addition,

individuals in the intensive-therapy group were given an ACEI (or, if contraindicated, an ARB), regardless of the level of blood pressure. The design of this study, however, did not allow identification of which intervention or combination of interventions was responsible for the benefits, or to what extent. The evidence that a multifactorial approach substantially reduces stroke and cardiovascular risk in type 2 diabetes is also supported by subgroup analyses of diabetic participants in large clinical trials. A reduction in major cardiovascular events, including stroke, was about 50% with blood pressure reduction, 25% with statin therapy, and 15% with aspirin therapy [34].

Certainly there is good justification for aggressive treatment of elevated blood pressure and lipid levels in diabetic patients with these risk factors. Several trials have compared the effect on stroke and other cardiovascular outcomes of tight control of blood glucose and blood pressure in type 2 diabetic patients versus less stringent management. In the UK Prospective Diabetes Study (UKPDS) Group, tight blood pressure control (mean blood pressure achieved, 144/82 mm Hg) resulted in a 44% reduction of fatal and nonfatal stroke as compared with more liberal control (mean blood pressure achieved, 154/87 mm Hg) [35]. Also, over 20% risk reduction was achieved with antihypertensive treatment in diabetic subjects in SHEP [36]. In a substudy of HOPE among diabetic patients, a 25% reduction of the primary combined outcome of myocardial infarction, stroke, and cardiovascular disease and a 33% risk reduction of stroke was achieved by the addition of ACEI to the current medical regimen of high-risk patients [37]. Whether these benefits were a specific effect of the ACEI or were an effect of blood pressure lowering is still the subject of debate. In a substudy of the Life study in diabetic patients, a 24% reduction in major vascular events and a nonsignificant 21% reduction in stroke were achieved among those treated with the ARB as compared with a  $\beta$ -blocker [11].

The evidence for lipid reduction in diabetes mellitus in relation to vascular disease has, until recently, come predominantly from subgroup analyses of clinical trials, which included people with diabetes. For people with established vascular disease, several trials of statins, and one trial of the fibrate drug gemfibrozil, have all shown significant reductions in coronary and cardiovascular events in people with diabetes comparable to that seen in those without diabetes [38–41]. The Medical Research Council/British Heart Foundation Heart Protection Study found that the addition of a statin to existing treatments in high-risk patients resulted in a 24% reduction in the rate of major vascular events and a 24% reduction in strokes [42]. This treatment effect was independent of baseline cholesterol. In a subgroup analysis of the Anglo-Scandinavian Cardiac Output Trial—Lipid-Lowering Arm (ASCOT-LLA) among diabetic individuals, there was a nonsignificant 16% reduction in the primary end point of vascular events. The trial, which was stopped early, had reduced statistical power and a lower number of primary end points [43]. The Collaborative Atorvastatin Diabetes Study (CARDS) is the only trial to date to evaluate statin therapy exclusively in

diabetes in the primary prevention of vascular events. A total of 2838 people with type 2 diabetes and one risk factor (retinopathy, albuminuria, current smoking, or hypertension) were randomized to a statin or placebo [44]. Like the ASCOT-LLA trial, the CARDS trial was also stopped prematurely because the prespecified stopping rule for efficacy was met. In people with diabetes treated with a statin, the primary combined end point of acute coronary events, coronary revascularization, or stroke was reduced by 37% (hazard ratio, 0.63; 95% CI, 0.48–0.83). In particular, stroke was significantly reduced by 48%. Together, these trials provide convincing evidence that statin treatment is quite effective for prevention of stroke in individuals with diabetes mellitus.

Glycemic control is important for individuals with diabetes and ideally the glucose target is normoglycemia with the avoidance of hypoglycemia. Glycemic control is also effective way to reduce stroke risk. The UKPDS has shown that good glycemic control reduces the risk of stroke [45]. In type 1 diabetes, glucose control requires appropriate insulin therapy and concomitant professional dietary and lifestyle therapy. In type 2 diabetes, professional dietary advice, reduction of weight, and increased physical activity should be the first approach to achieve good glucose control. If these measures do not lead to a sufficient reduction of hyperglycemia, oral hypoglycemic drugs (biguanide, sulfonylurea, thiazolidinediones, or a combination) or insulin has to be added to the treatment regimen. In overweight and obese people, metformin is the drug of first choice [33]. Metformin in obese people with diabetes had a better cardiovascular outcome in an analysis of the UKPDS trial than those on treatment with insulin or a sulfonylurea [46]. There is also evidence of cardiovascular benefit with metformin for obese people as compared with conventional treatments. Second-line agents could include sulfonylureas, postprandial glucose regulators, and thiazolidinediones. A randomized controlled trial of a thiazolidinedione in 5238 people with type 2 diabetes did not achieve the composite primary end point (hazard ratio, 0.90; 95% CI, 0.80–1.02), but there was a reduction in the composite of all-cause mortality, nonfatal myocardial infarction, and stroke (hazard ratio, 0.84; 95% CI, 0.72–0.48). So there is now prospective trial evidence for another oral antidiabetic drug (in addition to metformin) in relation to cardiovascular events [47]. Insulin treatment should be considered as soon as treatment with oral agents fails to achieve the audit target hemoglobin A1c of 7.5% or less.

### *Summary*

A comprehensive program that includes tight control of hypertension with ACEI or ARB treatment reduces the risk of stroke in individuals with diabetes. For adults with diabetes, especially those with additional risk factors, recommendations call for treatment with a statin to lower the risk of a first stroke [31]. The role of tight glycemic control in reducing the risk of stroke is still uncertain [48]. Glycemic control reduces microvascular complications, but

evidence showing a reduction in stroke risk with tight glycemic control is lacking. Surely the most effective way to reduce cardiovascular risk associated with diabetes is to prevent diabetes itself. But for patients who already have diabetes or in whom it will develop, the advantages of a multifactorial approach to the reduction of cardiovascular risk are clear. The challenge is to ensure that this approach is widely adopted.

### *Dyslipidemia*

Most epidemiologic studies find no consistent relationship between cholesterol levels and overall stroke risk. Some studies, however, have found a positive relationship between total and low-density lipoprotein (LDL) cholesterol levels and the risk of ischemic stroke [4,49–52]. Increased high-density lipoprotein (HDL) cholesterol levels are associated with reduced risk of ischemic stroke in men and women, in the elderly, and among different racial and ethnic groups [53–56]. These data add to the evidence relating lipids to stroke and support HDL cholesterol as an important modifiable stroke-risk factor. Triglyceride levels vary considerably, making elevated levels difficult to evaluate as a risk factor for stroke. Trends toward higher triglyceride levels in patients who subsequently experience ischemic stroke have been reported [4,50]. Elevated levels of triglycerides are one of the important components of the metabolic syndrome, a modifiable risk factor for stroke. The etiologic fraction estimates suggest that elimination of the metabolic syndrome would result in a 19% reduction in overall stroke, a 30% reduction of stroke in women, and a 35% reduction of stroke among Hispanics [57].

A compelling body of evidence documents that lipid-lowering agents reduce major cardiovascular events in both secondary and primary prevention of stroke and cardiovascular disease. Current evidence suggests that high-dose lipid-lowering agents can halt and, in some cases, reverse atherosclerotic progression. Furthermore, lipid-lowering agents are in general safe and well tolerated.

Statins (hydroxymethylglutaryl coenzyme A reductase inhibitors) are agents approved by the Food and Drug Administration for the prevention of ischemic stroke in patients with coronary artery disease. The rates were reduced 27% to 32% among subjects assigned to the statin as compared with placebo in ASCOT-LLA, which enrolled high-risk hypertensive subjects, and the Heart Protection Study, which enrolled high-risk subjects mostly with previous coronary events [43,58]. In a meta-analysis of nine trials including 70,070 patients, statin treatment provided 21% relative risk reductions of stroke and 0.9% absolute risk reduction [59]. It was estimated that statins prevent nine strokes per 1000 CHD or high-risk patients treated for 5 years. Although statins prevent recurrent stroke in patients with prior stroke or transient ischemic attack (the Stroke Prevention by Aggressive Reduction in Cholesterol Levels [SPARCL] trial) [60], they

have not shown a definite benefit in the risk reduction of first stroke in the typical general population without known CHD.

However, in the population at high CHD risk but without documented CHD, statins were beneficial for first-stroke risk reduction [61]. Two (ASCOT-LLA and CARDS) out of five primary cardiovascular disease prevention statin trials showed a considerable reduction in stroke rates among individuals on 10 mg atorvastatin as compared with placebo [43,44]. In ASCOT-LLA, a relative risk reduction of stroke was 23%, and in CARDS (primary diabetic population), relative risk reduction of stroke was 48%. In two (Myocardial Ischemia Reduction With Aggressive Cholesterol Lowering [MIRACL] and Pravastatin or Atorvastatin Evaluation and Infection Therapy—Thrombolysis in Myocardial Infarction 22 [Prove-It]) out of five acute coronary syndrome trials, the prevention of first stroke was significant among individuals receiving a high-dose atorvastatin (80 mg) versus placebo (MIRACL) or versus pravastatin (Prove-It) [62]. Of secondary CHD prevention trials (Scandinavian Simvastatin Survival Study [4S], Cholesterol And Recurrent Events [CARE], Long-Term Intervention With Pravastatin in Ischaemic Disease [Lipid], the Heart Protection Study, Greek Atorvastatin and Coronary Heart Disease Evaluation [Greace], and Treating to New Targets [TNT]), which together involved more than 50,000 patients with CHD, most showed a beneficial effect of statins in stroke prevention with the relative risk reduction of fatal or nonfatal stroke by 19% to 50% [4]. In the TNT trial, which randomized 10,001 individuals with stable CHD and an LDL cholesterol level of less than 130 mg/dL, the achieved LDL cholesterol levels were 101 mg/dL among those on low-dose atorvastatin and 77 mg/dL among those on high-dose treatment [63]. Those in the high-dose group had fewer major vascular events overall and fewer strokes (3.1% vs. 2.3%; hazard ratio, 0.75; 95% CI, 0.59–0.96). In addition to the stroke risk reduction by 25% ( $P = .02$ ) on high-dose atorvastatin in the TNT trial, stroke was reduced by 47% ( $P = .03$ ) relative to “usual” care in the Greace study [64].

In a recent review and meta-analysis of 42 randomized trials evaluating statin therapy for stroke prevention ( $N = 121,285$ ), a pooled relative risk of statin therapy for all strokes was 0.84 (95% CI, 0.79–0.91) [65]. Eleven trials reported hemorrhagic stroke incidence (total  $N = 54,334$ ; relative risk 0.94; 95% CI, 0.68–1.30) and 21 trials reported on fatal strokes (total  $N = 82,278$ ; relative risk, 0.99; 95% CI, 0.80–1.21). This overview reinforces the need to consider prolonged statin treatment in patients at high risk of stroke and major vascular events, but caution remains for patients at risk of bleeds.

Nonstatin lipid-modifying therapies also may offer stroke protection, although the supporting data are less certain. Other lipid-modifying strategies include niacin, ezetimibe, bile acid sequestrants, cholesterol ester transfer protein inhibitors, and omega-3 fatty acids. Ezetimibe-statin combinations in particular provide superior lipid-modifying benefits compared with statin

monotherapy in patients with atherogenic dyslipidemia [66]. Atherogenic dyslipidemia is associated with increased levels of chylomicrons and their remnants containing three main components: apolipoprotein B-48, triglycerides, and cholesterol ester of intestinal origin. Reduction in accessibility for one of them (specifically cholesteryl ester lessening due to ezetimibe administration) could lead to a decrease of the entire production of chylomicrons and result in a decrease of the hepatic body triglyceride pool as confirmed in a number of clinical studies. However, the Enhance study (Effect of Combination Ezetimibe and High-Dose Simvastatin Versus Simvastatin Alone on the Atherosclerotic Process in Patients with Heterozygous Familial Hypercholesterolemia) showed no difference in the progression of carotid atherosclerosis between ezetimibe and simvastatin versus simvastatin alone over a 2-year period [67]. Conclusions regarding ezetimibe and statin combinations, however, should not be made until the large clinical outcome trials are completed [68].

Niacin (nicotinic acid or vitamin B<sup>3</sup>) treatment was associated with a 24% reduction in known or suspected stroke and transient ischemic attack [69]. The Veterans Administration HDL Intervention Trial (VA-HIT) reported a trend toward a reduction of stroke in the gemfibrozil (fibrate)-treated group (6.0% vs. 4.6%; hazard ratio, 0.75; 95% CI, 0.53–1.06;  $P = .10$ ) of men with CHD and low levels of HDL cholesterol ( $\leq 40$  mg/dL) [70]. In addition, HDL cholesterol can be increased by 25% to 40% when multiple modalities are used, in particularly when niacin is added [71,72]. Because fibrates, niacin, ezetimibe, omega-3 fatty acids, and statins each regulate serum lipids by different mechanisms, combination therapy, selected on the basis of safety and effectiveness, could be more helpful in achieving comprehensive lipid control as compared with statin monotherapy.

In primary stroke prevention by lipid-lowering agents, surrogate markers of atherosclerosis, such as carotid intima-media thickness (IMT) and small nonstenotic carotid plaque measured by B-mode ultrasound, may be useful markers to monitor the effect of lipid-lowering therapies. Carotid IMT and plaque are preclinical surrogate markers of stroke and other atherosclerotic vascular diseases [73]. Lipoprotein levels and metabolic syndrome have been correlated with carotid IMT and plaque [74–77]. In clinical trials, colestipol-niacin combination therapy, statin monotherapy, and statin-niacin combination therapy each retarded the progression of carotid IMT [78–82]. In recent clinical trials that evaluated the effect of LDL reduction and HDL elevation, however, a beneficial effect resulting in halting carotid IMT progression or IMT regression was not observed. Paradoxically some individuals experienced the growth of atherosclerotic plaque and increased carotid IMT on a combination of a statin and cholesterol ester transfer protein inhibitor. More importantly, increased cardiovascular morbidity and mortality, despite achieving an aggressive reduction in LDL cholesterol and increased HDL cholesterol, was reported [67,83,84]. This evidence

confirms the complex nature of an association between dyslipidemia, atherosclerosis, stroke, and cardiovascular diseases.

### *Summary*

Lipid-modifying medications can substantially reduce the risk of stroke in patients with CHD. Treatment with statins is associated with the reduction in the risk of a first stroke in various populations of patients at increased risk of cardiovascular events. National Cholesterol Education Program III guidelines for the management of patients who have not had a stroke and who have elevated total cholesterol or elevated non-HDL cholesterol in the presence of hypertriglyceridemia are endorsed (Table 2) [31,85]. It is recommended that, in patients with known coronary artery disease and in high-risk hypertensive patients even with normal LDL cholesterol, therapy should be initiated with lifestyle measures and a statin. Suggested treatments for patients with known coronary artery disease and low-HDL cholesterol include weight loss, increased physical activity, smoking cessation, and possibly niacin or gemfibrozil administration.

Whether lipid lowering is effective in the primary prevention of stroke in the general population without CHD is still not clear. Whether the benefit of statins in reducing the risk of stroke is due to their potent lipid-lowering effects, pleiotropic effects, or a combination of the two cannot be determined based on current clinical trial data. From a benefit/risk perspective, the benefits of statin therapy outweigh the low risk of serious side effects. However, there are still populations, especially older persons (> 70 years of age) [86] and women, for whom more data on safety of lipid-lowering therapies are needed to clarify the risk associated with the effect of treatment.

### *Atrial fibrillation*

Atrial fibrillation is an important well-documented risk factor for stroke. Atrial fibrillation is associated with a three- to fourfold increased risk of stroke [87]. Among those with atrial fibrillation but without prior stroke or transient ischemic attack, risk of first stroke is 2% to 4% per year [88]. Incidence of atrial fibrillation increases with age; approximately 6% to 10% of people older than 75 years have atrial fibrillation [89]. About one quarter of strokes in the very elderly (over 80 years) are due to atrial fibrillation [87].

Anticoagulation and antithrombotic therapies remain the main agents for stroke prevention in patients with atrial fibrillation. Several randomized controlled studies have shown that adjusted-dose warfarin reduces the overall risk of stroke by 68% with a 1% increase in the risk of major bleeds [89,90]. Risk of stroke is reduced by 20% with aspirin [91]. Warfarin reduces stroke by 45% as compared with aspirin [92]. However, reanalysis of pooled data suggests that the margin between expected benefit and harm may be less than originally believed. The reduction in annual incidence of major stroke was less than 1% and the increase in major bleeding was nearly

Table 2  
Management recommendations for dyslipidemia according to National Cholesterol Education Program Adult Treatment Panel III

Factor	LDL cholesterol goal	Recommendations
0–1 CHD risk factor <sup>a</sup>	<160 mg/dL	Diet, weight loss, physical activity; drug therapy if LDL cholesterol remains $\geq$ 190 mg/dL; if LDL cholesterol 160–189 mg/dL, drug therapy optional
$\geq$ 2 CHD risk factors and 10-y CHD risk <20%	<130 mg/dL	Diet, weight loss, physical activity; drug therapy if LDL cholesterol $\geq$ 160 mg/dL
$\geq$ 2 CHD risk factors and 10-y CHD risk 10%–20%	<130 mg/dL, or <100 mg/dL	Diet, weight loss, physical activity; drug therapy if LDL cholesterol remains $\geq$ 130 mg/dL (or $\geq$ 100 mg/dL)
CHD or CHD risk equivalent <sup>b</sup> (10-y risk >20%)	<100 mg/dL, or <70 mg/dL	Diet, weight loss, physical activity; drug therapy if LDL cholesterol is $\geq$ 130 mg/dL and optional for LDL cholesterol 70–129 mg/dL
CHD or CHD risk equivalent <sup>b</sup> (10-y risk >20%)	<100 mg/dL, or <70 mg/dL	Diet, weight loss, physical activity; drug therapy if LDL cholesterol is $\geq$ 130 mg/dL and optional for LDL cholesterol 70–129 mg/dL
Non-HDL cholesterol in persons with triglycerides $\geq$ 200 mg/dL	Goals 30 mg/dL higher than LDL cholesterol	Same as LDL cholesterol with goal 30 mg/dL higher
Low HDL cholesterol	No consensus goal	Weight loss, physical activity; consider niacin or a fibrate in high-risk individuals with HDL cholesterol <40 mg/dL

<sup>a</sup> To screen for dyslipidemia, a fasting lipoprotein profile (cholesterol, triglycerides, HDL cholesterol, and LDL cholesterol) should be obtained every 5 years in adults. It should be obtained more often if two or more CHD risk factors are present (risk factors include cigarette smoking, hypertension, HDL cholesterol <40 mg/dL, CHD in a male first-degree relative <55 years old or in a female first-degree relative <65 years old, or age  $\geq$ 45 years for men or  $\geq$ 65 years for women) or if LDL cholesterol levels are borderline or high.

<sup>b</sup> CHD risk equivalents include diabetes or other forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and symptomatic carotid artery disease).

*Data from* Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. 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;285:2486–97.

2% [93]. Although clinical trials have shown that an orally administered direct thrombin inhibitor ximelagatran is as effective as warfarin in atrial fibrillation, the Food and Drug Administration has not approved its use because of safety concerns (hepatotoxicity, a possible increased rate of myocardial infarction and coronary artery disease) [94,95].

Anticoagulation is underused in patients with atrial fibrillation in the community, and there is little information on treatment with anticoagulation in patients at low risk of stroke [96]. Several stroke risk-stratification schemes have been developed and validated [97,98]. The American College of Cardiology (ACC), the American Heart Association, and the European Society of Cardiology 2001 guideline recommends anticoagulation for patients with atrial fibrillation who are older than 60 years and have a history of hypertension, diabetes, coronary artery disease, impaired left ventricular systolic function, heart failure, or prior thromboembolism, and for all those with atrial fibrillation who are over 75 years of age [99]. However, this stratification model has not been validated. A new stratification model to assist clinicians in choosing patients for antithrombotic therapy, CHADS<sub>2</sub>, has been recently proposed and validated [97,100]. CHADS<sub>2</sub> takes its name from C for congestive heart failure, H for hypertension, A for age (greater than 75 years), D for diabetes mellitus, and S<sub>2</sub> for prior stroke or transient ischemic attack. The CHADS<sub>2</sub> score was derived from independent predictors of stroke in patients with nonvalvular atrial fibrillation [100]. The score gives 1 point each for congestive heart failure, hypertension, age 75 years or over, and diabetes mellitus, and 2 points for prior stroke or transient ischemic attack. Before prescribing anticoagulation, several factors should be considered: the absolute risk of stroke, the estimated risk of bleeding, patient preferences, and access to an anticoagulation monitoring clinic. Risk stratification in these patients is the first step in the decision-making process (Table 3).

Most patients with atrial fibrillation who are less than 75 years of age and have no history of prior stroke or transient ischemic attack have a relatively low risk of stroke (1% to 2% per year) if given aspirin, and they do not benefit sufficiently from anticoagulation to warrant its use for primary stroke prevention [92,101]. It is generally agreed that atrial fibrillation patients whose estimated stroke risk exceeds 4% per year should be anticoagulated in the absence of contraindications [99].

However, warfarin therapy is underused in patients with atrial fibrillation. Only about half of patients with atrial fibrillation who are candidates for anticoagulation receive warfarin [102]. Anticoagulation is particularly underused in elderly patients [103]. In addition to age, poorly controlled hypertension and concomitant aspirin or nonsteroidal anti-inflammatory drug use confer higher bleeding risk during anticoagulation [4,98].

The optimal target international normalized ratio for primary prevention of stroke in patients with nonvalvular atrial fibrillation is in the 2 to 3 range for most atrial fibrillation patients [4,100,103,104]. Some recommend a lower

Table 3

Nonvalvular atrial fibrillation risk stratification by CHADS<sub>2</sub> scheme<sup>a</sup> and treatment recommendations

CHADS <sub>2</sub> score	Risk level	Stroke rate per year	Treatment recommendations based on risk stratification
0	Low	1.0%	Aspirin (75–325 mg/d)
1	Low–moderate	1.5%	Warfarin INR 2–3 or aspirin (75–325 mg/d) <sup>b</sup>
2 <sup>a</sup>	Moderate	2.5%	Warfarin INR 2–3 <sup>b</sup>
3	High	5.0%	Warfarin INR 2–3 <sup>c</sup>
≥4	Very high	>7%	Warfarin INR 2–3 <sup>c</sup>

One point for congestive heart failure, hypertension, age over 75 years, or diabetes; Two points for stroke or transient ischemic attack<sup>b</sup>.

Abbreviation: INR, international normalized ratio.

<sup>a</sup> All nonvalvular atrial fibrillation patients with prior stroke or transient ischemic attack should be considered high risk and treated with anticoagulants; the CHADS<sub>2</sub> scheme should be applied for primary prevention.

<sup>b</sup> Consider patient preferences, bleeding risk, and access to INR monitoring.

<sup>c</sup> If patient is more than 75 years old, an INR target of 1.6 to 2.5 is recommended by some.

Data from Gage BF, Waterman AD, Shannon W, et al. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA* 2001;285:2864–70.

target international normalized ratio of 2 in the very elderly [105]. Control of hypertension in atrial fibrillation patients is also critically important, reducing both the risk of ischemic stroke and the risk of intracerebral hemorrhage [106].

All patients with mechanical heart valves, regardless of the presence of atrial fibrillation, require anticoagulation [107]. The rate of thromboembolism in patients with mechanical heart valves is 4.4 per 100 patient-years without antithrombotic therapy, 2.2 per 100 patient-years with antiplatelet drugs, and 1 per 100 patient-years with warfarin [108].

### Summary

Atrial fibrillation is an important stroke risk factor and it can be treated successfully. Validated stroke risk-stratification models may help identify individuals with low risk (<2% per year) of first stroke who can be treated with aspirin. Anticoagulation reduces risk of stroke in those at high risk and without contraindications to this treatment. The development of safer, easier-to-use oral anticoagulants might improve the risk/benefit ratio.

### Other cardiac conditions

Other types of cardiac disease that can contribute to the risk of thromboembolic stroke include myocardial infarction, dilated cardiomyopathy, valvular heart disease (eg, mitral valve prolapse, endocarditis, prosthetic

cardiac valves), and intracardiac congenital defects (eg, patent foramen ovale, atrial septal defect, and aneurysm) [109]. Incidence of stroke is also increased in patients with reduced cardiac ejection fraction [110]. The use of warfarin for cardioembolic prophylaxis in patients with reduced left ventricular ejection fraction in the setting of idiopathic cardiomyopathy remains controversial, and clinical trials are in progress comparing warfarin with antiplatelet treatment [111]. Patients undergoing cardiac surgical procedures have a perioperative stroke risk of 1% to 7% [112]. Presence of aortic arch atheroma is also associated with increased risk of ischemic stroke [113].

### *Summary*

Various guidelines recommend strategies to reduce the risk of stroke in patients with cardiac conditions. These include the management of patients with acute myocardial infarction [114], unstable and stable angina [115,116], and valvular heart disease [108]. Studies proving the benefits of specific prophylactic procedures for patients with a variety of cardiac conditions are lacking.

### *Asymptomatic carotid stenosis*

Carotid stenosis of 50% or greater can be detected in about 5% to 10% of men and women older than 65 years of age, and stenosis of greater than 80% in 1% of the population [117–120]. An annual stroke risk between 1% and 3% occurs among individuals with asymptomatic CAS of 50% to 99% in the natural history studies [121] and is higher in those with CAS of greater than 75%, progression of CAS, and heart disease, and in men [122]. However, about 45% of ipsilateral strokes in patients with carotid stenosis could be attributable to lacunes or cardioembolism, emphasizing the need to fully evaluate patients with asymptomatic carotid stenosis for other treatable causes of stroke [120]. In summary, data from observational studies and clinical trials indicate an annual rate of stroke ipsilateral to a significant extracranial CAS of about 1% to 2%.

There have been two large published randomized controlled trials designed to assess the benefit of carotid endarterectomy (CEA) in patients with asymptomatic CAS. In the Asymptomatic Carotid Atherosclerosis Study (ACAS) designed to test the efficacy of CEA in subjects with asymptomatic CAS 60% to 99%, 1662 subjects were randomized to CEA and best medical therapy ( $n = 828$ ) or to medical therapy alone ( $n = 834$ ) [123]. The overall risk of perioperative stroke or death was 2.7% (1.2% angiography-related complications and a 1.5% risk of stroke or death among those having CEA at 30 days). The study was stopped prematurely after a median follow-up of 2.7 years because there was a significant benefit of surgery over medical treatment alone. The aggregate rate of ipsilateral stroke, any perioperative stroke, or death was estimated at

5% over 5 years in surgically treated patients, and at 11% in medically treated patients (53% risk reduction, approximate 2% per year event rate was reduced to 1% per year;  $P = .004$ ). The benefit began to accrue after 1 to 2 years. The study was not statistically powered to detect differences among patient subgroups. No surgical benefit was observed in relationship to the degree of CAS, but women appeared to benefit less than men (17% nonsignificant risk reduction in women; 95% CI, 4%–65%, vs. a 66% risk reduction in men, 95% CI, 36%–82%). This difference was partly due to a higher rate of perioperative complications in women (3.6% vs. 1.7%).

In the Medical Research Council Asymptomatic Surgery Trial (ACST), the largest randomized trial comparing a strategy of immediate versus deferred CEA, 3120 asymptomatic patients with CAS greater than 60% on carotid ultrasound were enrolled. There was a 3.1% (95% CI, 2.3%–4.1%) risk of stroke or death within 30 days of surgery [124]. Although the overall periprocedural complication rate was similar to that in ACAS, the surgical complication rate of the ACST was actually twice that of ACAS in which the complication rate of 1.5% was due to surgery only. The overall 5-year risk of any stroke or perioperative death was 11.8% with deferred surgery versus 6.4% with immediate endarterectomy ( $P < .0001$ ; 2.4% per year reduced to 1.3% per year). The benefit began to accrue after about 2 years. Although subgroup analyses need to be interpreted with caution, as in ACAS, there did not appear to be any difference in benefit based on the degree of CAS. Women also appeared to benefit less than men after CEA (4.1% [95% CI, 0.7–7.4%] in women vs. 8.2% [95% CI, 5.6%–10.8%] in men) and had a somewhat higher but nonsignificant rate of perioperative complications (3.8% vs. 2.7%).

In the pooled analyses from ACAS and ACST, surgical benefit is greater in men than in women (men: pooled interaction  $P = .01$ , odds ratio 0.49 [95% CI, 0.36–0.60]; women: odds ratio 0.96 [95% CI, 0.63–1.45]) [125]. Data presented in the ACST publication also permit calculation of the comparative rates of any stroke or death. Similar to ACAS, the overall rate of any stroke or death was 31.2% for deferred endarterectomy versus 28.9% for immediate endarterectomy (relative risk reduction of 7%; 95% CI, 3%–17%;  $P = .172$ ) and for any major stroke or death 25.5% versus 25.3% (relative risk reduction of 7%; 95% CI, –5%–18%;  $P = .242$ ). These data must be taken into account when the procedure is considered.

The benefit of endarterectomy in asymptomatic CAS is very much dependent on surgical risk, with the benefit observed only if the periprocedural complication rates are less than 2.7% as observed in ACAS or less than 3.1% as in ACST. Community-wide scrutiny of CEA in asymptomatic CAS in 10 United States states shows an overall risk for stroke or death of 3.8% (including 1% mortality) [126]. Most physicians, however, are not aware of the CEA complication rates in their respective hospitals.

Since ACAS, “standard” medical therapy has been enhanced with widespread use of antiplatelet agents and of drugs that lower blood pressure and lipids. Therefore, the risk of stroke in asymptomatic CAS may be further reduced without CEA. Although screening of general populations for CAS may not be cost-effective [127], screening for “high-risk” individuals with asymptomatic CAS, such as screening for those with impaired cerebral vasoreactivity [128] or presence of microemboli on transcranial Doppler [129], may help select those who may benefit from CEA.

Carotid angioplasty with stenting has been available for over 10 years, but data from clinical studies proving its equivalence or superiority to CEA in asymptomatic CAS are still limited. The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (Sapphire) trial showed that stenting was not inferior (within 3%,  $P = .004$ ) to CEA among CAS subjects at high risk for the surgery [130]. About 70% of the enrolled subjects had asymptomatic CAS, with 5.4% rates of stroke, myocardial infarction, or death with stenting versus 10.2% in CEA group at 30 days ( $P = .20$ ), and 9.9% versus 21.5% at 1 year, respectively ( $P = .02$ ). Because, the outcome in Sapphire included myocardial infarction, the results are not directly comparable to those from ACAS or ACST. But even in the stenting arm of Sapphire with lower rates of combined major cardiovascular outcomes of 9.9% at 1 year, it is considerably higher than the stroke risk associated with asymptomatic CAS (1% to 2% per year) in ACAS or ACST. The study did not include medically treated controls, so a comparison to the best medical treatment could not be performed.

Although pivotal stenting trials, including Sapphire, were initially limited by a lack of equipment dedicated to carotid artery stenting, including embolic protection filters, their results have compared favorably to both direct and historical surgical controls [131]. While this has led to Food and Drug Administration approval of several carotid stent systems in the United States, recent European randomized carotid stenting trials (Space [Stent-Supported Percutaneous Angioplasty of the Carotid Artery Versus Endarterectomy] and EVA-3S [Endarterectomy Versus Angioplasty in Patients With Severe Symptomatic Carotid Stenosis]) had mixed results because they failed to prove noninferiority of stenting compared with CEA and confused the perception of the place of this technology in the care of asymptomatic CAS patients [132]. The carotid stent registries with a wide range of operator experience, and patient enrollment based on surgical risk criteria (Capture II [Carotid Acculink/Accunet Post Approval Trial to Uncover Rare Events], Exact [Emboshield and Xact Post Approval Carotid Stent Trial], Cabernet [Carotid Artery Revascularization Using the Boston Scientific FilterWire and the EndoTex NexStent]) were able to meet the guidelines of 3% procedural events in the asymptomatic CAS [133]. Ongoing carotid stenting trials in the United States will further contribute to our understanding of the benefit of stent therapy in CAS patients.

### Summary

In individuals with asymptomatic CAS who are at low risk for surgery, CEA in a combination with “usual medical care” is superior to “usual medical care” alone for reduction of ischemic stroke if the perioperative complication rate is lower than 3% (Table 4) [134]. The total 5-year risk of stroke or procedural morbidity after CEA is 11.5% for deferred endarterectomy versus 6.0% for immediate endarterectomy (5.5% absolute difference, which means that to prevent one event 18 subjects need to be treated over 5 years) [124]. Perioperative risk is not balanced by benefit for 2 years. Patient selection, comorbidities, life expectancy, and patient preferences should be discussed, and the risks and benefits of the procedure should be carefully considered. The benefit of CEA in patients with asymptomatic CAS seems to be more pronounced in men, and it still

Table 4  
Guideline management recommendations

Factor	Goal	Recommendation
Asymptomatic CAS	No CAS	Endarterectomy may be considered in selected patients with $\geq 60\%$ stenosis without occlusion, performed by a surgeon with surgical morbidity and mortality $< 3\%$ ; careful patient selection should be guided by individual factors, including comorbid conditions, life expectancy, and patient preference
Cigarette smoking	Cessation	Counseling, nicotine replacement, varenicline, and formal programs are recommended
Diet/nutrition	Well-balanced diet	A diet containing $\geq 5$ servings of fruits and vegetables per day may reduce the risk of stroke
Physical activity	$\geq 30$ min of moderate activity/d	Moderate exercise (eg, brisk walking, jogging, cycling, or other aerobic activity)
Alcohol	Moderation	No more than 2 drinks per day for men, and no more than 1 drink per day for women
Drug abuse	Cessation	A history of substance abuse should be part of health evaluation
Sleep apnea	Treatment for OSA	Overnight sleep study in patients with snoring, excessive daytime sleepiness, body mass index over 30, and drug-resistant hypertension; continuous positive airway pressure treatment

remains uncertain whether there is benefit of CEA in women. One must keep in mind that women have been underrepresented in CEA trials, and some observational data have suggested benefit of CEA for women. Carotid angioplasty with stenting may be a reasonable alternative to CEA in asymptomatic CAS at high risk for the surgical procedure.

### *Cigarette smoke*

Cigarette smoking is a well-recognized and modifiable risk factor for ischemic and hemorrhagic stroke [87,135–137]. A meta-analysis of 32 studies estimated a twofold increased risk of ischemic stroke for smokers versus nonsmokers and a threefold increased risk for subarachnoid hemorrhage [138]. Passive cigarette smoke is a risk factor for stroke [139]. The stroke risk for passive smoking is close to the risk for active smoking, suggesting that tobacco exposure may have “threshold” rather than a dose–response relationship [140].

The most effective preventive measures are to never smoke and to minimize exposure to environmental smoke. The risk of stroke is also reduced with smoking cessation. Smoking cessation is associated with a rapid reduction in the risk of stroke to a level that approaches, although never reaches, the risk of those who never smoked within 2 to 5 years of cessation [141]. Sustained smoking cessation is difficult to achieve. A combination of nicotine replacement therapy, social support, and behavioral treatments offers an effective management for smoking cessation (Table 4) [142]. Varenicline is a novel smoking-cessation agent that acts at a number of nicotinic acetylcholine receptors and recently has been shown to be superior to the current standard patch in achieving abstinence and in reducing withdrawal phenomena, such as urges to smoke and withdrawal symptoms [143]. Varenicline may be an additional treatment option and is likely to become popular with patients and clinicians.

### *Summary*

Cigarette smoking is clearly associated with the risk of stroke. Comprehensive smoking cessation programs are effective. Data, however, on the effects of these programs on reduction of the risk of stroke are lacking.

### *Diet and nutrition*

Diet is associated with the risk of stroke. Increased fruit and vegetable consumption is associated with a reduced risk of stroke in a dose-response manner [144]. For each 1-serving-per-day increment in fruit and vegetable intake, the risk of stroke was reduced by 6% in the Nurses' Health Study and the Health Professionals' Follow-Up Study [145]. A higher level of sodium and lower level of potassium intake is associated with an increased risk of stroke, possibly mediated through mechanisms dependent on blood

pressure [146]. Diets rich in fruits and vegetables lower blood pressure and therefore may decrease risk of stroke [147]. Other dietary factors may affect the risk of stroke, but specific evidence is lacking. The Dietary Approaches to Stop Hypertension diet includes high consumption of fruits, vegetables, and low-fat dairy products, and reduced intake of total and saturated fat (Table 4) [147].

### *Summary*

Diets rich in fruits and vegetables and with increased potassium but reduced sodium and fat may reduce the risk of stroke. Dietary trials specifically focused to reducing the risk of stroke are lacking.

### *Physical inactivity*

Physical inactivity is a well-established and modifiable risk factor for stroke [148]. The protective effects of physical activity have been reported for different ages, sexes, and race/ethnicities in large studies, including the National Health and Nutrition Examination Survey Study and the Northern Manhattan Stroke Study [149,150]. In the Northern Manhattan Stroke Study, a dose–response relationship was reported as more intensive physical activity provided additional benefits compared with light to moderate physical activity. The protective effect of physical activity may be mediated through reduced blood pressure and weight and control of diabetes [151].

The benefits of physical activity are outlined in the Centers for Disease Control and Prevention and the National Institutes of Health guidelines (Table 4) [152,153], which recommend moderate exercise for at least 30 minutes per day. The benefits for stroke are evident for light to moderate activities, such as walking.

### *Summary*

Although clinical trials examining how physical activity affects risk of stroke do not exist, it is clear that a sedentary lifestyle increases the risk of stroke. Physical activity is beneficial in reduction of risk factors, and therefore is recommended to reduce risk of first stroke.

## **Management of less well documented modifiable risk factors to prevent first stroke**

### *Obesity and metabolic syndrome*

Obesity is a risk factor for stroke (relative risks, 1.5–2.0) and is associated with increased risk of hypertension, dyslipidemia, hyperinsulinemia, and glucose intolerance [154]. In addition, higher weight during young adulthood and weight gain after young adulthood are associated with an increased risk of stroke [155]. Recent studies have also reported the

association between measures of the distribution of body fat, such as the waist-to-hip ratio, as a measure of abdominal obesity [156] and increased risk of stroke. About one in three adults in the United States is overweight, and the prevalence of obesity has been steadily increasing [157].

Obesity is an important component of the metabolic syndrome, a potentially modifiable risk factor for stroke. Metabolic syndrome is defined as the presence of more than three of the following: (1) abdominal obesity as determined by waist circumference greater than 102 cm or greater than 40 in for men and greater than 88 cm or greater than 35 in for women; (2) triglycerides 150 mg/dL or more; (3) HDL cholesterol less than 40 mg/dL for men and less than 50 mg/dL for women; (4) blood pressure 130/85 mm Hg or higher; and (5) fasting glucose of 110 mg/dL or more [31]. Insulin resistance is an important marker of the metabolic syndrome and may be a prevalent risk factor for stroke [57]. Insulin resistance has been incorporated into the World Health Organization definition of metabolic syndrome. Drugs that can reduce insulin resistance may also be effective in preventing stroke [158]. The metabolic syndrome is highly prevalent in the United States. Age-adjusted prevalence of metabolic syndrome is 23.7%. The highest prevalence is in Mexican Americans (31.9%) and in African American women (57%) [159].

Weight reduction is beneficial in reducing risk factors, reducing metabolic syndrome, and, therefore, in possibly reducing the risk of stroke. Clinical trials to test the effects of weight reduction on reducing the risk of stroke do not exist. Numerous studies, however, report the beneficial effects of weight reduction on blood pressure. In a meta-analysis of 25 clinical trials, blood pressure was reduced by 3.6 to 4.4 mm Hg with an average weight loss of 5.1 kg [160].

### *Summary*

Obesity and metabolic syndrome are associated with an increased risk of stroke. Individual components of the metabolic syndrome have been associated with an increased risk of ischemic stroke, and therefore should be treated by lifestyle measures and pharmacotherapy as recommended by JNC 7 and ATP III guidelines [6,31]. Despite a lack of clinical trials on the effects of weight reduction and stroke risk, weight reduction is important for lowering blood pressure and metabolic syndrome risk, which may lead to reduction of stroke risk. In addition to exercise and diet, glycemic and lipid control are important factors in reducing the risk of first stroke.

### *Alcohol and drug abuse*

The J-shaped relation of alcohol consumption to the risk of stroke has been reported [161]. The relative risk of ischemic stroke associated with moderate alcohol consumption (one to two drinks per day), as compared with nondrinking, is between 0.3 and 0.5 in some populations and increases to two for persons consuming three or more drinks per day. For

hemorrhagic stroke, the relative risk varies from 2 to 4, with some increased risk at all levels of intake [162]. Alcoholism is a major public health problem in the United States. Over 10 million adults have alcoholism and alcohol-related diseases, such as hypertension and cirrhosis [163]. Despite the potential benefit of moderate alcohol consumption, alcohol should not be considered as a preventive agent for stroke, given the health risks associated with excessive intake.

Compared to no alcohol consumption, light-to-moderate alcohol consumption (one or fewer drinks per day for women and two or fewer drinks per day for men) can increase HDL cholesterol, reduce platelet aggregation, and lower plasma fibrinogen concentration [164]. Heavy alcohol consumption can lead to hypertension, hypercoagulability, reduced cerebral blood flow, and a greater likelihood of atrial fibrillation [165]. In a meta-analysis of 35 observational studies, consumption of less than one drink per day (one drink defined as 12 g of alcohol), but not abstinence, was associated with a 20% reduced risk of stroke (95% CI, 0.67–0.96) and consumption of one to two drinks per day with 28% risk reduction (95% CI, 0.57–0.91) [166]. As compared with abstainers, those who consumed more than five drinks per day had a 69% increased stroke risk (risk ratio, 1.69; 95% CI, 1.34–2.15).

Abuse of drugs, such as heroin, cocaine, and amphetamines, is associated with an increased risk of ischemic and hemorrhagic stroke [167,168]. These drugs may cause metabolic and hematologic changes, including increased platelet aggregation and changes in blood pressure, and can lead to vasculopathy or cerebral embolization from various sources [169].

### *Summary*

Compared to no alcohol consumption, light to moderate alcohol consumption is associated with a reduced risk of stroke while heavier consumption is associated with an increased risk of stroke. Alcoholism is a major public health problem as alcohol consumption can induce dependence. Reduction of alcohol consumption in heavy drinkers is recommended [170]. A suggested consumption of alcohol in those who consume alcohol is no more than two drinks per day for men and no more than one drink per day for nonpregnant women (Table 4).

Identification and management of drug abuse is challenging. Long-term treatment strategies based on medication, psychologic support, and outreach programs play an important part in treatment of drug dependency (Table 4). When a patient is identified as having a drug addiction problem, referral for appropriate counseling is recommended.

### *Sleep apnea*

Sleep-related breathing disorders are highly prevalent in patients with established cardiovascular disease. Obstructive sleep apnea (OSA) is being increasingly recognized as an important risk factor for stroke. It is a less

well documented but modifiable risk factor. The evidence of the association of OSA with first ischemic stroke is primarily derived from the association with heart disease. OSA affects an estimated 15 million adult Americans and is present in a large proportion of patients with hypertension, obesity, and cardiovascular disease [171]. Prevalence of OSA in these populations ranges between 3% and 7%. Factors that increase vulnerability for OSA include age, male sex, obesity, family history, menopause, craniofacial abnormalities, and certain health behaviors, such as cigarette smoking and alcohol use.

OSA is characterized by repetitive interruption of ventilation during sleep caused by collapse of the pharyngeal airway or central nervous system dysfunction. The overnight polysomnogram is the standard diagnostic test for OSA. A diagnosis of OSA syndrome is made when a person has an apnea-hypopnea index (number of apneas and hypopneas per hour of sleep) greater than five and symptoms of excessive daytime sleepiness [172]. A recent analysis from more than 6000 adults participating in the Sleep Heart Health Study showed that hypopneas accompanied by oxyhemoglobin desaturation of more than 4% were associated with prevalent cardiovascular disease and stroke independent of confounders [173].

Habitual snoring and daytime sleepiness are risk factors for ischemic stroke [174]. Snoring may be a marker for sleep apnea, which can secondarily increase the risk of stroke by worsening hypertension and heart disease; reducing cerebral blood flow and autoregulation; impairing endothelial function; accelerating atherosclerosis, hypercoagulability, and inflammation; and causing paradoxical embolism in patients with patent foramen ovale [172].

Treatment of OSA is individualized and includes noninvasive continuous positive airway pressure ventilation, bilevel positive airway pressure, and automatic control of airway pressure delivery with continuous positive airway pressure devices. A variety of surgical interventions and prosthetic oral devices are available.

### *Summary*

OSA is associated with vascular risk factors and an increased risk of cardiovascular disease. Individuals with abdominal obesity and hypertension, snoring, and daytime sleepiness are more likely to have OSA and should be referred to a sleep specialist for further evaluation (Table 4). Prospective randomized studies regarding the effect of treatment of sleep apnea on stroke risk reduction do not exist. However, successful treatment of OSA can lead to a reduction in blood pressure, which may lead to a reduced risk of first stroke.

### *Hyperhomocysteinemia*

Elevated plasma levels of homocysteine (hyperhomocysteinemia) are increasingly recognized as a potential risk for atherothrombotic vascular diseases, including stroke [175,176]. In the Northern Manhattan Stroke Study,

the adjusted hazard ratio of 2.0 (95% CI, 1.0–4.1) was reported for ischemic stroke among those with a homocysteine level greater than 15  $\mu\text{mol/L}$  compared with less than 10  $\mu\text{mol/L}$  (95% CI, 1.00–4.05) [176]. The vascular effects of homocysteine were greatest among whites and Hispanics, but least among blacks.

A key event in the vascular pathobiology of hyperhomocysteinemia seems to involve the induction of endothelial dysfunction due to a reduction of the endogenous antiatherothrombotic molecular nitric oxide [177]. Elevated homocysteine levels can be efficiently and safely reduced in most hyperhomocysteinemic patients by supplementation with folic acid and cobalamin. This reduction is associated with an improvement in endothelial function and other surrogate markers of atherothrombosis, such as carotid plaque area [178]. Whether or not this translates into clinical benefits, is still under investigation. On the basis of the results of several recent clinical trials (eg, Vitamin Intervention for Stroke Prevention [VISP] trial or from ongoing Vitamins to Prevent Stroke [Vitapops] trial, which did not show a reduction of inflammatory markers by reducing homocysteine), many researchers doubt that vitamin therapy designed to lower total homocysteine concentrations is effective in reducing the risk of stroke and cardiovascular events [179,180]. However, these trials were not designed for secondary and not primary stroke prevention but rather for preventing secondary strokes, when hyperhomocysteinemia may have been less important than other factors.

In a detailed assessment of the results of the recent HOPE-2 trial and a reanalysis of the VISP trial restricted to patients capable of responding to vitamin therapy, it has been suggested that higher doses of vitamin B<sub>12</sub> and perhaps new approaches to lowering total homocysteine, besides routine vitamin therapy with folate, vitamin B<sub>6</sub>, and vitamin B<sub>12</sub>, could reduce the risk of stroke [181]. Thus, therapy to lower homocysteine could still help to prevent stroke. Unfortunately, many major trials of homocysteine lowering in the general cardiovascular literature have not shown benefit of vitamin therapy for reduction of major vascular endpoints.

A single-nucleotide polymorphism in the methylenetetrahydrofolate reductase gene reduces activity of the enzyme that metabolizes homocysteine, producing an increase in serum homocysteine [182]. This single-nucleotide polymorphism can be found in 10% to 12% of the population and is associated with a 25% higher homocysteine level than in those with a wild-type genotype. In a recent meta-analysis of 72 studies, a 5- $\mu\text{mol/L}$  increase in homocysteine was associated with a 1.6-fold increased risk of stroke (95% CI, 1.2–2.0) [182]. In addition, a 3- $\mu\text{mol/L}$  decrement of homocysteine level was associated with a 24% risk reduction of stroke [183].

The current American Heart Association guidelines [4] recommend daily intake of folate (400  $\mu\text{g/d}$ ), B<sub>6</sub> (1.7 mg/d), and B<sub>12</sub> (2.4  $\mu\text{g/d}$ ) by consumption of vegetables, fruits, legumes, meats, fish, and fortified grains and cereals. This diet may be useful in reducing the risk of stroke.

### *Summary*

No randomized trials have shown that lowering elevated homocysteine levels reduces the risk of a first stroke. Until the results of more clinical trials are available, the question of whether homocysteine is a risk predictor or a modifiable risk factor for stroke remains unanswered. However, there is consistent evidence regarding overall relationship between homocysteine levels and vascular risk, and a benefit of treatment of elevated homocysteine levels cannot be excluded. There are insufficient data to recommend specific treatments to reduce the risk of first stroke in patients with elevated homocysteine. Use of folic acid and B vitamins in persons with known elevated homocysteine levels is safe and may be useful in primary stroke prevention.

### *Aspirin for primary stroke prevention*

Despite conclusive evidence of the benefits of aspirin in the secondary prevention of stroke, only a few clinical trials have addressed aspirin use in primary prevention. In the United States, the Physicians' Health Study [184] showed that the relative risk of ischemic stroke was 1.11 (95% CI, 0.82–1.50) among men using 325 mg of aspirin every other day for an average of 60.2 months versus placebo; and the relative risk of stroke of all types was 1.22 (95% CI, 0.93–1.60) on aspirin versus placebo. The risk of hemorrhagic stroke was increased (relative risk 2.14; 95% CI, 0.96–4.77). In the British Doctors' Trial with a daily dose of 500 mg of aspirin for 6 years, no significant difference in the incidence of stroke between the treatment and control groups was found, but a higher incidence of disabling stroke among those taking aspirin was reported (relative risk, 2.58;  $P < .05$ ) [185]. In a recent meta-analysis of six randomized trials (the Physicians' Health Study, the British Doctors' Trial, the Thrombosis Prevention Trial, the Hypertension Optimal Treatment study, the Primary Prevention Project, and the Women's Health Study) that evaluated the benefits of aspirin for primary prevention in a combined sample of 47,293 subjects on aspirin and 45,580 on placebo (or nonaspirin), superiority of aspirin was suggested for total cardiovascular events but there was no significant difference in the incidence of stroke [186]. Many of the patients in these studies, however, were at relatively low risk, and a study of persons at moderate risk might show a benefit of aspirin therapy.

The effects and the risk/benefit ratio of aspirin in primary prevention may be different in women and men. In the Women's Health Study [187] among 39,876 asymptomatic women 45 years old or older who were followed for 10 years for a first major vascular event, a 17% reduction in the risk of stroke (95% CI, 0.69–0.99) was found among those who received 100 mg of aspirin compared with placebo, but a nonsignificant 9% reduction (95% CI, 0.80–1.03) in the risk of the combined primary end point. The risk of hemorrhagic stroke was nonsignificant (relative risk, 1.24; 95% CI, 0.82–1.87). The overall

average stroke rates were 0.11% per year in aspirin-treated patients and 0.13% per year in placebo-treated patients (absolute risk reduction 0.02% per year, and a number needed to treat of 5000). The average gastrointestinal hemorrhage rates were 0.06% per year for aspirin and 0.05% per year for placebo (absolute risk increase 0.01% per year, number needed to harm of 10,000). The most consistent benefit for aspirin was among women 65 years old or older, a history of hypertension, hyperlipidemia, diabetes, or a 10-year cardiovascular risk of at least 10%.

### *Summary*

Aspirin is not recommended for the prevention of a first stroke in men [4]. The use of aspirin 75 mg/d is recommended for cardiovascular (including but not specific to stroke) prophylaxis for persons whose risk is sufficiently high for the benefits to outweigh the risks associated with treatment (a 10-year risk of cardiovascular events of >6%–10%) [188]. There is no evidence that this class of drugs reduces the risk of stroke in the general population of persons at low risk [188]. Aspirin can be useful for prevention of a first stroke among women whose risk is sufficiently high for the benefits to outweigh the risks associated with treatment. The reasons for the differences between men and women remain uncertain.

### **Assessing the risk of a first stroke**

Many therapeutic options exist for risk factor management to prevent a first stroke. The choice of an appropriate risk modification program depends on individual stroke risk. Each individual should have an assessment of risk of first stroke. Many factors can contribute to stroke risk. Many individuals have more than one risk factor, some of which are well documented and some less well documented. Several stroke risk assessment tools are available to use for primary stroke prevention screening programs [189]. These stroke risk estimation tools generally focus on several major vascular risk factors and do not include the full range of contributing factors, and especially do not consider different characteristics of various race/ethnic populations. The Framingham Stroke Profile is gender specific and provides a gender-specific 1-, 5-, or 10-year cumulative stroke risk [190]. Independent stroke predictors included in the Framingham Stroke Profile are age, systolic blood pressure, hypertension, diabetes mellitus, current smoking, established cardiovascular disease (any one of myocardial infarction, angina or coronary insufficiency, congestive heart failure, or intermittent claudication), atrial fibrillation, and left ventricular hypertrophy on EKG. It has been updated to include the use of antihypertensive therapy and the risk of stroke or death among individuals with atrial fibrillation (Table 5) [191]. Although very useful in some populations, the Framingham Stroke Profile has not been sufficiently studied in different race/ethnic groups.

Table 5  
Modified Framingham Stroke Profile

Risk factor	Points
Age	
54–56 y	0
57–59 y	1
60–62 y	2
63–65 y	3
66–68 y	4
69–71 y	5
72–74 y	6
75–77 y	7
78–80 y	8
81–83 y	9
84–86 y	10
Systolic blood pressure	
95–105 mm Hg	0
106–116 mm Hg	1
117–126 mm Hg	2
127–137 mm Hg	3
138–148 mm Hg	4
149–159 mm Hg	5
160–170 mm Hg	6
171–181 mm Hg	7
182–191 mm Hg	8
192–202 mm Hg	9
203–213 mm Hg	10
Treated systolic pressure	2
Diabetes mellitus	2
Cigarette smoking	3
CHD	3
Atrial fibrillation	4
Left ventricular hypertrophy on EKG	6

*Data from* Wang TJ, Massaro JM, Levy D, et al. A risk score for predicting stroke or death in individuals with new-onset atrial fibrillation in the community: the Framingham Heart Study. *JAMA* 2003;290:1049–56.

Alternative prediction models using Framingham risk factors and adding continuous levels of risk factors have been developed in other cohorts but their validity has not been well tested. [3,192,193]

### Summary

A goal is to develop a generally applicable and simple tool for assessing stroke risk. Such tools that exist each have limitations and none is widely accepted. New risk factors associated with the risk of stroke are emerging and they would need to be considered in newer stroke risk assessment tools. Validation of the current stroke risk assessment tools is needed in different age, gender, and race/ethnic groups. The complexity of risk factors predicting

stroke in an individual makes development of new stroke risk assessment tools a challenging task.

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