Published in final edited form as:

Ther Adv Cardiovasc Dis. 2008 August ; 2(4): 287–303. doi:10.1177/1753944708093847.

Stroke prevention: modifying risk factors

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Abstract

Risk factor modification remains as the principal aspect of care for stroke prevention. Understanding of risk factors has advanced and several options are now available to treat modifiable risk factors. However, effective treatment remains a challenging task in clinical practice. Prevention begins with awareness of risk factors by patients and clinicians. Risk factor assessment along with overall stroke risk estimation should be part of evaluation of patients with stroke, and used with careful clinical judgment. In this review we discuss the impact of modifiable traditional vascular risk factors on ischemic stroke, interventions for stroke prevention, and evidence for early treatment of risk factors where available as well as areas of research progress. Emphasis should be paid in education of patients, the community and medical personnel. Future research in the field of genetic determinants of vascular risk factors and stroke will increase our understanding of the underlying mechanisms of cerebrovascular disease and likely result in development of new therapies and individualized programs for stroke prevention.

Keywords

Stroke prevention; traditional risk factors

I. Introduction

The most effective means available for reducing the burden of stroke involve modification and treatment of vascular risk factors. Nevertheless, despite several available therapies for many of these risk factors, this task remains a challenge for clinicians and patients. Stroke remains as the leading cause of disability and the third cause of death in the United States (U.S.). Approximately 780,000 new and recurrent strokes occur annually in the US.(Williams 2001) The economic burden is tremendous, since many patients require chronic care (American-Heart-Association 1997) and long-term institutionalization, with an estimated cost of about 6.1 billion dollars for informal caregiving and total annual cost of US\$ 30 billion in the U.S. (Dobkin 1995; Hickenbottom, Fendrick et al. 2002)

Stroke prevention begins with recognition of its risk factors by a patient and clinicians treating the patient. However, patient awareness remains a limitation in the treatment of risk factors and most patients having a stroke have multiple risk factors.(Kannel 2000) In addition, effective incorporation of evidence into practice, patient education and patient encouragement to apply evidence in their lives by physicians, is also limited.(Bodenheimer 2007)

Prevention strategies have advanced over the past several years as a result of prospective epidemiological studies and several controlled clinical trials demonstrating effective therapies. These strategies target individual risk factors for the most part, but comprehensive treatment should involve overall risk assessment. For this purpose, models such as the Framingham Stroke Risk Profile (FSRP) have been developed, which are easy to use in clinical practice, providing an illustration for patient education regarding the impact of risk factors in stroke risk, and the effect of therapeutic interventions reducing this risk.

Effective modification of risk factors is a process involving patient education and a team approach, to reinforce patient understanding, follow up and confirm compliance with therapeutic measures, including medications.

In addition, knowledge of the impact of risk factors on vascular events, including stroke, is evolving as new evidence suggest that lower targets for risk factors such as hypertension, diabetes and hyperlipidemia may be better.

In this article we present an overview of the burden imposed by vascular risk factors, the impact of their modification on stroke risk and review standard recommendations for the modification of traditional stroke risk factors, as well as emerging evidence evaluating early treatment of risk factors where available and future lines of research.

II. Using the FSRP for Stroke Risk Assessment

The Framingham Stroke Risk Profile (FSRP) was developed using data from 36years follow up in the Framingham cohort and has been validated in other cohorts.(Wolf, D'Agostino et al. 1991; Voko, Hollander et al. 2004) The FSRP provides sex specific estimation of the probability of stroke using clinical information. By summing the points represented by individual risk factors, a table can be used to obtain the 10-year estimated risk of stroke (Table 1). An example of its use follows. A 65-year-old male presented to the stroke clinic, following an acute ischemic lacunar stroke that left him with mild residual left hemiparesis. He was diagnosed having hypertension (blood pressure 180/95 mm Hg), hyperlipidemia and diabetes during his recent hospitalization, and was smoking cigarettes daily. He received effective education and is now following recommendations, and compliant with treatments. He quit smoking, achieved satisfactory blood pressure and diabetes control, and is under target lipid levels. Using the FSRP, his baseline estimated 10 year stroke risk was 19.5% (15 points); with effective treatment of the 4 modifiable risk factors the estimated risk is reduced to 8.4% (9 points). It is important to note that the FSRP is a useful tool in practice but should be used along with careful clinical judgment.

III. Treatment of Risk Factors

Stroke risk factors have been classified as traditional and novel, and modifiable and non-modifiable. The non-modifiable risk factors include age, sex, ethnicity/race and family history. Stroke risk varies according to differences in these factors. Detailed review of their impact in stroke risk is available elsewhere.(Wolf 2004)

Modifiable traditional risk factors include hypertension, diabetes, hyperlipidemia, atrial fibrillation, smoking, obesity and carotid artery disease. Novel risk factors include hyperhomocysteinemia, hypercoagulable states, and select biomarkers. We will discuss further traditional risk factors, with exception of carotid artery disease reviewed in detail elsewhere. (Sacco 2001)

Hypertension

Hypertension is the most prevalent modifiable risk factor for stroke with a prevalence of about 30% in the U.S. (Rosamond W, Howard V et al. 2008) The prevalence of hypertension increases with age, thus as the population ages, hypertension will become an even greater threat to public health, and is likely to increase as life expectancy increases. The Framingham Heart Study investigators reported the lifetime risk of hypertension to be approximately 90% for men and women who were non-hypertensive at age 55 or 65 years and survived to ages 80–85 years old. (Vasan, Beiser et al. 2002) A meta-analysis of one million adults enrolled in 61 observational studies concluded that death from ischemic heart disease and stroke increases progressively and linearly with systolic blood pressure levels as low as 115 mm Hg and diastolic 75 mm Hg upward. This study also found that for every 20 mm Hg systolic or 10 mm Hg diastolic increase in blood pressure there is a doubling of mortality from both ischemic heart disease and stroke. The authors suggest a 10 mm Hg reduction in systolic or a 5 mm Hg reduction in diastolic blood pressure would result in a 40% lower risk of stroke death and a 30% lower risk of death from ischemic heart disease or other vascular death. (Lewington, Clarke et al. 2002) Similarly, when Framingham Heart Study investigators looked at the difference in cardiovascular mortality between participants with blood pressure of 130–139/85–89 mm Hg and compared that with participants with blood pressure below 120/80 mm Hg, a greater than twofold increase in relative risk from cardiovascular disease was found. (Vasan, Larson et al. 2001) The United Kingdom-transient ischemic attack (TIA) trial looked specifically at blood pressure and risk of stroke in patients with known cerebrovascular disease and found a direct and continuous relationship between blood pressure and recurrent strokes. Their data demonstrated that a 5 mm Hg lower diastolic blood pressure was associated with nearly one third fewer strokes. (Rodgers, MacMahon et al. 1996)

Based on data such as these the 2003 Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) redefined the classification of hypertension. (Chobanian, Bakris et al. 2003) In the new classification, blood pressure <120/80 mm Hg was changed from “optimal” to “normal” and the new term “prehypertension” was added signifying a systolic blood pressure of 120–139 mm Hg and/or diastolic blood pressure of 80–89 mm Hg. This reclassification of blood pressure was designed to encourage lifestyle changes at early stages of hypertension, and hopefully reduce the incidence of overt hypertension. The JNC-7 recommendation for treatment of pre-hypertension (in the absence of co-morbidities, such as a history of diabetes or cardiovascular disease) is lifestyle change. Lifestyle change includes diet, mainly eating more fruits and vegetables and consuming less salt, in addition to weight loss, aerobic activity and moderation of alcohol consumption. Pharmacological treatment is not recommended until systolic pressures exceed 140 mm Hg or diastolic exceeds 90 mm Hg. (Chobanian, Bakris et al. 2003) However, given that the relationship between blood pressure and risk of coronary and cerebral vascular disease is continuous down to levels of a systolic blood pressure of 115 mm Hg and a diastolic blood pressure of 75 mm Hg, it is possible that earlier pharmacological treatment may be beneficial in combating the adverse effects of sustained prehypertension.

Whereas the necessity to treat hypertension to reduce the risk of cerebrovascular events is clear, there is less clarity regarding the best choice of antihypertensive medication. Though not a trial designed to evaluate stroke risk reduction, the Heart Outcomes Prevention Evaluation (HOPE) Study demonstrated improved cardiovascular outcomes with the use of the angiotensin-converting enzyme inhibitor (ACEI) ramipril beyond its ability to lower blood pressure, which was very mild in this trial (the average reduction of systolic/diastolic blood pressure was 3/2 mm Hg). (Yusuf, Sleight et al. 2000) Subsequently, the Losartan Intervention for Endpoint reduction in hypertension (LIFE) Study compared the effects the angiotensin receptor blocker (ARB) losartan with the beta-blocker atenolol on the composite end-point of cardiovascular

death, stroke and myocardial infarction in patients with hypertension and left ventricular hypertrophy. When the endpoints were evaluated separately, a relative risk reduction of 25% was found in fatal and nonfatal stroke, favoring losartan over atenolol.(Dahlof, Devereux et al. 2002) The perindopril protection against recurrent stroke study (PROGRESS) was the first trial to be done solely on patients with known cerebrovascular disease. Patients with a history of stroke or TIA were randomized to placebo, perindopril or perindopril plus indapamide, a thiazide diuretic. There were no blood pressure criteria for enrollment into the trial and the average blood pressure at entry was 147/86 mm Hg. The combination of indapamide and perindopril produced an average reduction in blood pressure of 12/5 mm Hg and was associated with a 43% reduction in relative risk of recurrent stroke compared with perindopril alone, which produced only a 5/3 mm Hg drop in blood pressure. This study raised the question of whether or not it is the degree of reduction in blood pressure or the combination of an ACEI plus a thiazide that was responsible for the positive results.(PROGRESS-Collaborative-Group 2001) Lastly, in the Study on Cognition and Prognosis in the Elderly (SCOPE), elderly patients with isolated systolic hypertension were randomized to an ARB-based antihypertensive treatment with candesartan or non-ARB based treatment. Despite the similar degree of blood pressure lowering in the ARB arm (22/6 mm Hg) and in the non-ARB arm (20/5 mm Hg) there was a 42% relative risk reduction in stroke in the ARB arm.(Papademetriou, Farsang et al. 2004) These results suggest that ACEI and/or ARB, especially in combination with a thiazide diuretic, may be superior to other anti-hypertensive regimens in the secondary prevention of stroke.

Just as the choice of agent still is not certain, nor is the level of blood pressure reduction. Three randomized trials of more intensive versus less intensive blood pressure control have shown that the more intensive control of blood pressure was superior in reducing the number of strokes, however, these were primarily in diabetic patients and only targeted diastolic blood pressures.(Estacio, Jeffers et al. 1998; Hansson, Zanchetti et al. 1998; UKPDS-Group-Investigators 1998b) One randomized trial showed that treatment of prehypertension was feasible and suppressed the onset of stage-1 hypertension in the treatment arm.(Julius, Nesbitt et al. 2006) Clinical outcomes were not evaluated in this trial, so the effect of the medical treatment of prehypertension on reducing vascular events is not known.

Standard practice guidelines from recognized organizations such as the American Heart Association and American Stroke Association (AHA/ASA) have been written in regards to secondary prevention of stroke.(Sacco, Adams et al. 2006) Currently, antihypertensive treatment is recommended for all patients who have had a TIA or a stroke, and is even to be considered in patients who are normotensive. The ideal goal blood pressure is still uncertain and should be individualized, but benefit has been seen with an average blood pressure reduction of ~10/5 mm Hg.(Sacco, Adams et al. 2006) The agent of choice depends on individual patient characteristics, but ACEI and ARB in addition to a diuretic seem to be favorable in patients with stroke, based on data from the aforementioned trials.

Future trials focusing on the outcomes of treating blood pressure at earlier stages are needed. Ideally, such a trial would compare the effects of several anti-hypertensive agents to also establish whether or not one class of drugs should be chosen over another. Currently there are two on-going trials that will hopefully partially answer these questions. The Secondary Prevention of Small Subcortical Strokes (SPS3) trial which is comparing different antiplatelet therapies in stroke prevention in patients with lacunar strokes, is also assessing the effects of different blood pressure targets, i.e. systolic blood pressure < 150 mm Hg versus a target blood pressure < 130 mm Hg. The On Going Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) is comparing the ACEI ramipril versus the ARB telmisartan versus a combination of both in high-risk patients for reductions in major vascular events.

Finally, although several treatment options exist, effective use of these treatments is limited by lack of awareness of hypertension in patients; prior studies have shown that only about 60% of hypertensive individuals were aware of having hypertension. In addition, once recognized effective treatment is achieved only in a minority. Approximately one third of hypertensive individuals are controlled to target blood pressure, according to prior studies.(Hajjar, Kotchen et al. 2006) Therefore, especial attention should be paid to patient education and follow up to ensure effective blood pressure control.

Diabetes

Diabetes affects 9.6% of Americans over the age of 20 years and 21% of Americans over the age of 60 years.(Rosamond W, Howard V et al. 2008) According to the NIH National Statistics on Diabetes, the estimated number of Americans with diabetes is 20.8 million with an additional 41 million with prediabetes.(National-Diabetes-Statistics-NIDDK 2005) With the rise in the obesity epidemic and the rising age of the population this number will undoubtedly increase in the future. The relative risk of stroke in a person with diabetes ranges from 1.8 to 6.0 and diabetics tend to have strokes at a younger age.(Rosamond W, Howard V et al. 2008) Pre-diabetes is a risk factor for the development of diabetes mellitus and, in patients with a history of TIA or stroke, impaired glucose tolerance doubles the risk of stroke.(Vermeer, Sandee et al. 2006)

In 2003 the American Diabetes Association redefined normal fasting plasma glucose levels, which had just been reduced in 1997 from < 126 mg/dl to < 110 mg/dl, even further to < 100 mg/dl. It retained the definition of a normal 75-g oral glucose tolerance test (OGTT) as < 140 mg/dl. Impaired fasting glucose (IFG) is now defined as fasting plasma glucose between 100-125 mg/dl and impaired glucose tolerance (IGT) as glucose levels during an OGTT of 140-199 mg/dl. Pre-diabetes is diagnosed either by an IFG or IGT or both. Diabetes mellitus is defined as a fasting plasma glucose ≥ 126 mg/dl or an OGTT > 200 mg/dl in the presence of symptoms of diabetes.(The-Expert-Committee-on-the-Diagnosis-and-Classification-of-Diabetes-Mellitus 1997; Genuth, Alberti et al. 2003)

While diabetes is a known risk factor for vascular disease and stroke, more data support the idea that the effects of abnormal blood glucose can have adverse health consequences, even before frank diabetes develops.(Vermeer, Sandee et al. 2006) The association of IGT and insulin resistance with an increase risk of stroke has been demonstrated in several studies. (Pyorala, Miettinen et al. 2000; Kernan, Inzucchi et al. 2002; Kaarisalo, Raiha et al. 2006; Vermeer, Sandee et al. 2006) Early intervention, including lifestyle change(Lindstrom, Ilanne-Parikka et al. 2006) and pharmacological treatment,(Knowler, Barrett-Connor et al. 2002) has been shown to reduce or delay the diagnosis of diabetes. This could have significant impact on the development of cerebrovascular disease, as well as outcome from an acute stroke. Hyperglycemia in the setting of an acute stroke is known to extend the ischemic penumbra and has an adverse effect on neurologic outcome.(Parsons, Barber et al. 2002) Diabetes increases post-stroke mortality and adversely affects post-stroke outcomes as compared with stroke patients without diabetes.(Bruno, Levine et al. 2002) However, while many trials have proven early recognition and treatment of IGT may prevent diabetes, the effect of early treatment on cardiovascular disease and stroke remains unknown.

The choice of agent in the treatment of prediabetes may also be important, as some agents may not be safe. In the DREAM trial the thiazolidinedione rosiglitazone reduced the frequency of diabetes in individuals with prediabetes, however the study did not have sufficient power to detect differences in cardiovascular outcomes.(Gerstein, Yusuf et al. 2006) A subsequent meta-analysis of 42 trials comparing rosiglitazone to placebo or other antidiabetic agent revealed a borderline statistically significant increase in the risk of death from cardiovascular causes (OR 1.43 for myocardial infarction and 1.64 for death from cardiovascular causes in the

rosiglitazone group).(Nissen and Wolski 2007) In contrast, the other currently available thiazolidinedione, pioglitazone, was not shown to have the same cardiovascular risk in patients with diabetes in the Proactive Study.(Dormandy, Charbonnel et al. 2005)

The UK Prospective Diabetes Study showed that glycemic control has been shown to reduce the microvascular events of nephropathy, retinopathy and peripheral neuropathy, but, its effects on macrovascular disease, such as stroke and myocardial infarction, are less clear.(UKPDS-Group-Investigators 1998a) However, if attention is focused on more rigorous control of blood pressure with a goal of < 130/80 mm Hg and lipids, with an LDL goal of < 100 mg/dl, and treatment with anti-platelet agents, the macrovascular complications of diabetes can be reduced.(Colwell 1997; Haffner 1998; Arauz-Pacheco, Parrott et al. 2002) For blood pressure reduction, ACEI and ARBs are preferred in diabetics as they have been shown to reduce microalbuminuria.(HOPE-Study-Investigators 2000) This may be significant for the reduction in cerebrovascular disease, as new data linking kidney disease and cerebrovascular disease are emerging.(Ikram, Vernooij et al. 2008)

For now, clear evidence-based data support that prediabetes is a significant risk factor for the development of diabetes and increases one's risk for cardiovascular and cerebrovascular disease. It has also been shown that early modifications in lifestyle and the initiation of medications can prevent the development of diabetes. Once a person has diabetes, aggressive blood pressure and lipid management, along with anti-platelet therapy is beneficial in reducing the macrovascular complications of diabetes. The effects of early treatment of prediabetes in reducing macrovascular events, including stroke, remains to be determined.

As in the case of hypertension, patient recognition of diabetes and effective treatment is limited in clinical practice. Therefore, emphasis should be placed on patient education and follow up to achieve glucose control.

Recently, the presumption that more aggressive blood sugar control is better has been brought into question. The Action to Control Cardiovascular Risk in Diabetes Mellitus (ACCORD) trial was designed to evaluate aggressive management of glycemia, lipidemia and blood pressure in patients with diabetes who are considered high-risk for major cardiovascular events. In addition to assessing the efficacy of a target HbA1c of < 6% versus 7-7.9% and adding a fibrate to a statin for lipid control, the target SBP of < 120 mm Hg versus < 140 mm Hg is being examined. The aggressive glucose control arm (target HbA1c <6%) of this trial has been stopped 18 months early due to an increase in death in the intensive treatment arm (1.4 deaths per 100 patients per year versus 1.1 per 100 patients per year in the standard treatment program). However, subjects in the intensive arm (HbA1c <6%) will continue to be followed for aggressive blood pressure and lipid control, but will now aim for a less-intensive glycemic target.

Research on pre-diabetes is ongoing in the Insulin Resistance Intervention After Stroke Trial (IRIS). This trial is looking at the effect of pioglitazone on secondary stroke prevention in patients with insulin resistance who have had a TIA or a stroke. This trial hopes to complete data collection on over three thousand patients by June of 2009. Future studies designed to address the appropriate timing of preventative treatment, the appropriate therapy (lifestyle modification versus medications) and the safe targets for glycemic control in the prevention of stroke and cardiovascular disease are needed.

Atrial Fibrillation—Atrial fibrillation (AF) is an independent risk factor for stroke, increasing the relative risk of stroke 2.6 to 4.5 fold depending on the age group.(Wolf, Abbott et al. 1991) Framingham Investigators have estimated that the lifetime risk for development of AF is 1 in 4 for men and women at age 40 years.(Lloyd-Jones, Wang et al. 2004) AF increases

with age, is the underlying mechanism of approximately 15% of all strokes, and is associated with strokes that carry higher mortality and disability, compared with non-AF related ischemic strokes.(Sandercock, Bamford et al. 1992; Lin, Wolf et al. 1996; Wattigney, Mensah et al. 2003)

Several prospective randomized trials have shown the benefit of anticoagulation with warfarin for stroke prevention in patients with AF (AFASAK (Petersen, Boysen et al. 1989), BAATAF, SPAF III (SPAF-III-Trial-Investigators 1996), EAFT (European-Atrial-Fibrillation-Trial-Investigators 1993). In patients treated with adjusted-dose warfarin, the relative risk reduction of stroke is 68% (95% CI, 50 to 79) and the absolute annual risk is reduced from 4.5% to 1.4%. (Atrial-Fibrillation-Investigators 1994; Sacco, Adams et al. 2006)

Since anticoagulation with warfarin carries an approximately 1% per year risk of serious and fatal hemorrhage, careful assessment of the risks and benefits should be considered. Risk assessment models have been developed for estimation of stroke risk in patients with AF, including FSRP and CHADS2 score system, which are useful when balancing the risks and benefits of anticoagulation. In patients without other risk factors (CHADS2 score <1), patients with AF have an estimated stroke risk of 1 % per year, which lessens the potential benefit of anticoagulation with warfarin compared with its potential risk.

Current guidelines recommend anticoagulation with adjusted-dose warfarin (target INR, 2.5; range, 2.0 to 3.0) in patients with persistent or paroxysmal AF at high risk for stroke (age > 75, prior ischemic stroke, TIA, or systemic embolism, moderate or severe left ventricular function impairment or congestive heart failure, history of hypertension or diabetes). On the other hand, for patients with non-valvular lone AF (without other risk factors) or those with contraindications for warfarin therapy, aspirin is recommended.(Sacco, Adams et al. 2006)

Despite its proven benefit, anticoagulation for stroke prevention is underutilized in patients with AF. Prior studies suggest that only 20 to 58% of patients eligible for anticoagulation actually receive it.(Go, Hylek et al. 2003; Deplanque, Leys et al. 2006) A common reason cited by physicians to deny patients treatment with warfarin is a perceived fall risk, often attributed to age. However, this should rarely be used as a justification to withhold warfarin from moderate risk patients with atrial fibrillation.(Man-Son-Hing and Laupacis 2003) According to one decision analytic model, a person with AF with an average risk of stroke (5% per year) must fall approximately 300 times a year to make the risk of a subdural hematoma outweigh the benefits of stroke reduction with warfarin.(Man-Son-Hing, Nichol et al. 1999) In addition, in clinical practice, clinicians also observe development of ecchymosis with trivial trauma, which may limit acceptance of this treatment by patients. Nevertheless, at present coumadin is the best choice for most patients despite its risks.

One of the most important aspects of treatment with warfarin is close monitoring of anticoagulation. If the INR is subtherapeutic (below 2.0) the risk of ischemic stroke increases (double at an INR of 1.7, triple at an INR of 1.5)(Hylek, Skates et al. 1996), and if the INR is supratherapeutic (above 3.0) the risk of fatal intracerebral hemorrhage increases significantly. (Levine, Raskob et al. 2004) While maintenance of the INR in this therapeutic range may be challenging, development of anticoagulation clinics has been shown to improve the safety of warfarin use and increase the likelihood of maintaining a therapeutic INR.

Although warfarin remains a “gold standard” for stroke prevention in AF patients, there is a need for new anticoagulant agents as effective, but with less hemorrhagic complications and without the rigorous monitoring schedule required. The SPORTIF III and V randomized trials showed that ximelagatran (direct thrombin inhibitor) is as effective as warfarin, with few hemorrhagic complications, but its use was associated with marked liver dysfunction, and did not meet safety requirements for approval in the U.S.(Olsson 2003) Several other direct factor

Xa inhibitors are in different stages of clinical development, including rivaroxaban, LY517717, YM150, DU-176b, apixaban, and betrixaban.(Turpie 2008) Rivaroxaban was shown to be more effective when compared to enoxaparin in postoperative prevention of venous thromboembolic events,(Fisher, Eriksson et al. 2007) and is undergoing evaluation as a treatment for prevention of stroke in AF. Similarly, a reversible thrombin inhibitor (dabigatran etexilate) is currently being studied in a phase III trial evaluating its benefit in prevention of stroke or systemic embolism in patients with AF.(Mungall 2002)

Lastly, research evaluating the genetic basis of AF as well as genetic considerations for the treatment of AF is beginning to influence treatment decisions for stroke prevention. For instance, the FDA recently approved two new genetic tests (CYP2C9 and VKORC1),(Linder, Looney et al. 2002; Rieder, Reiner et al. 2005) designed to aid in more precise initial dosing of warfarin. Although further randomized trials are required to evaluate concomitant influential factors, an economic analysis found that integration of genetic tests into warfarin therapy significantly improves health outcomes and reduces healthcare costs. Guidelines for pharmacogenomics-based warfarin dosing are under development.(Sconce, Khan et al. 2005; Hampton 2006)

Hyperlipidemia

Several large randomized trials of statins have demonstrated reduction of stroke risk associated with lowering lipid levels. However, observational prospective studies have not found a consistent relation between cholesterol levels and incidence of stroke.(Shahar, Chambless et al. 2003) The beneficial effects of statins on stroke risk reduction may be mediated by additional mechanisms of action such as improvement of endothelial function, antioxidant properties, inhibition of inflammatory responses, immunomodulatory actions, and stabilization of atherosclerotic lesions.(Endres 2005)

Although the agent used, and the dose has varied across studies, the results have been consistent, showing stroke relative risk reduction ranging approximately from 10 to 50%. (UKPDS-Group-Investigators 1998a; Athyros, Papageorgiou et al. 2002; Sever, Dahlof et al. 2003; Colhoun, Betteridge et al. 2004; Collins, Armitage et al. 2004) Most studies included patients with concomitant coronary heart disease; thus it had been less clear if the benefit in stroke risk reduction was secondary to reduction of myocardial infarction and cardiac death. The first trial evaluating directly the impact of cholesterol lowering therapy in stroke risk in patients without coronary heart disease was the Stroke Prevention by Aggressive Reduction in Cholesterol Levels Study (SPARCL). The trial compared 2365 patients with recent TIA or stroke (within 6 months of enrollment) that had no known coronary heart disease assigned to Atorvastatin 80 mg daily to 2366 patients assigned to a placebo group. This study found an absolute risk reduction in stroke rates of 2.2% (adjusted HR 0.84; 95% CI 0.71 to 0.99). This was associated with a reduction of LDL cholesterol levels of 53% ($P<0.001$). Although there were more hemorrhagic strokes in the atorvastatin group (55 versus 33 in the placebo group), the incidence of fatal hemorrhagic stroke was not significantly different between the groups. (Amarenco 2005; Amarenco, Bogousslavsky et al. 2006)

Of note, there is evidence suggesting that use of statins at the time of an ischemic stroke may have beneficial effects. The Northern Manhattan Study found that the 90-day mortality rate was lower in patients who were taking a statin compared to those not taking it at the time of stroke (1.8% vs 10.6%, $p = 0.03$).(Elkind, Flint et al. 2005) Other studies support the finding of reduced degree of stroke severity and better outcomes if lipid-lowering agents were used prior to the vascular event.(Deplanque, Masse et al. 2006) In addition, withdrawal of statin treatment at the time of an acute ischemic stroke has been related to poorer neurological outcome at 90 days.(Blanco, Nombela et al. 2007) Interestingly, one small study also showed

that patients using statins prior to treatment with thrombolytics had better neurological outcome at 3 months.(Alvarez-Sabin, Huertas et al. 2007)

At present, practice guidelines recommend use of statins for secondary prevention of stroke. The target LDL level varies depending on the patient's estimated risk, < 100 mg/dL for those with symptomatic atherosclerotic disease, and < 70 mg/dL for those at very high risk. Very high risk is considered when there is established cardiovascular disease and one of the following: multiple major risk factors, poorly controlled risk factors (smoking), the metabolic syndrome (mainly triglycerides >200 mg/dL with low high-density lipoprotein (HDL) cholesterol <40 mg/dL), and acute coronary syndromes.(Sacco, Adams et al. 2006)

Additionally, although traditionally more attention is given to LDL levels, attention should also be paid to HDL levels. Prior studies in large cohorts have shown an inverse association between serum HDL cholesterol and stroke.(Curb, Abbott et al. 2004) HDL cholesterol is involved in atherosclerosis and its higher levels have been related to anti-atherosclerotic and anti-inflammatory properties in animal and human studies.(Tall 1990) A prior study found that high serum HDL levels were associated with reduced odds of having a large-vessel stroke (OR 0.8, 95% CI 0.6 – 1).(Tirschwell, Smith et al. 2004) Observations in young stroke patients demonstrated that low HDL level is associated with an increased risk of stroke.(Albucher, Ferrieres et al. 2000) Treatment considerations include the addition of niacin or fibrates in patients with HDL <40 mg/dL.(Sacco, Adams et al. 2006)

Smoking

In the U.S., nearly 25% of adults are affected by cigarette smoking.(CDC 2004) Smoking is an independent stroke risk factor, increasing the risk of stroke by about 50%.(Shinton and Beevers 1989) The risk increases proportionally with the number of cigarettes smoked per day and passive smoking also increases the risk of ischemic stroke.

Smoking cessation is an effective measure to reduce stroke risk. Several options are available for effective smoking cessation. Treatment involves counseling, and pharmacologic interventions such as nicotine replacement, antidepressant agents such as nortriptyline or bupropion, and more recently varenicline.

The value of medical counseling should not be overlooked as it increases by about 70% the success of smoking cessation (OR 1.69, 95% CI 1.45 - 1.98).(Lancaster, Stead et al. 2000) Nicotine replacement also has been found to increase the likelihood of smoking cessation by about 70% (OR 1.71, 95% CI 1.60 - 1.83), regardless of the product used.(Lancaster, Stead et al. 2000; Silagy, Mant et al. 2000) In a prior study, the antidepressant nortriptyline was effective increasing the rate of smoking cessation at 6 months with an absolute difference of 11% compared to placebo (95% CI -18% to 4%).(Prochazka, Weaver et al. 1998) Bupropion, an atypical antidepressant, also has been found to be effective attaining smoking cessation. In a study comparing bupropion alone or in combination with nicotine replacement versus placebo, treatment with bupropion resulted in higher cessation rates at 12 months compared to placebo (OR 2.3, 95% CI 1.4 to 3.9). There was a higher benefit with the combined use of bupropion and a nicotine patch (OR 3.0, 95% CI 1.8 – 4.9).(Jorenby, Leischow et al. 1999; Lancaster, Stead et al. 2000)

More recently, a randomized trial evaluated the partial nicotinic acetylcholine receptor agonist varenicline. The study included 1025 participants randomized to varenicline, bupropion or placebo for 12 weeks. This study showed a significant increase in smoking cessation rates at 52 weeks for varenicline compared to placebo (OR 3.09, 95% CI 1.95 – 4.91) and to bupropion (OR 1.46, 95%CI 0.99 – 2.17). The most common side effects were nausea (28%)

and insomnia (21%). Other studies are showing similar results, and the FDA has approved varenicline for smoking cessation, offering an alternative option for patients.

Smoking cessation is recommended for all patients with stroke or TIA, and should be encouraged during all encounters with patients. Education at the individual level along with stricter policies for global regulation for tobacco control are likely to increase the efficacy of smoking cessation strategies for the public.

Obesity

Obesity has been related to increased risk of cardiovascular events, disability and mortality. (Flegal, Graubard et al. 2005) The risk of ischemic stroke also increases with obesity, being about three times for obese individuals in prior studies (OR 3.0, 95% CI 2.1 – 4.2). (Suk, Sacco et al. 2003) Approximately a 30% prevalence of obesity has been estimated in the U.S. (Flegal, Carroll et al. 2002) Obese individuals also have more prevalent associated risk factors such as hypertension, diabetes and hyperlipidemia. Prior studies suggest that the distribution of fat may be relevant, with abdominal fat being more associated to the risk of stroke, particularly in men.

Current guidelines recommend considering weight reduction for stroke prevention, targeting body mass index 18.5 to 24.9 kg/m² and waist circumference lower than 35 inches for women and 40 inches for men. (Sacco, Adams et al. 2006) The main impact of weight loss in the risk of stroke may be mediated by improved control of other risk factors. Prior studies have shown that in obese persons, weight loss results in better control of hypertension, blood glucose and lipid levels.

Although not directly indicated for obesity, current guidelines for stroke prevention include dietary recommendations to increase the content of vegetables and fruits, as well as a diet with low fat dairy products with low content of saturated fat, in addition to reduced intake of sodium and increased intake of potassium. A diet as such is beneficial to reduce blood pressure and may therefore be beneficial for reducing stroke risk. (Goldstein, Adams et al. 2006)

IV. Ensuring practice of recommendations

Although enough evidence is available for effective modification of stroke risk factors, in practice treatments are underutilized and lack patient awareness of risk factors remains an obstacle. Recently, Bodenheimer presented a model for practicing evidence based medicine including 5 steps, from discovery of evidence by research efforts, continuing with learning of the evidence by clinicians and using it in daily practice with all patients, followed by ensuring understanding by patients and finally assisting patients to incorporate evidence in their lives. (Bodenheimer 2007) In practice, patient encounters are limited by time constraints, which interferes with application of these principles. A multidisciplinary effort aids to make this process feasible and effective.

Recent efforts by the AHA/ASA have been made to bridge the gap between theory and practice in stroke care, resulting in standardization of stroke centers and development of quality control programs such as “Get With the Guidelines”. This program provides resources for centers and clinicians to initiate risk factor modification for patients while they are in the hospital. Another program, the Preventing Recurrence Of Thromboembolic Events through Coordinated Treatment (PROTECT) program, also provides measures to initiate stroke prevention at the time of hospital admission. This model, proposes follow up 1-3 weeks after hospitalization by means of a phone call, to assess side effects of medications and compliance with medications and life style changes, a 6 week post hospitalization laboratory monitoring to ensure that targets for lipid levels are achieved and monitor liver function parameters, and 3 month and 1 year visits for comprehensive evaluation including compliance with medications, life style changes,

assessment of vascular outcomes and laboratory monitoring of lipid targets and liver parameters.(Ovbiagele and Saver 2006) Programs like these will likely improve patient care, however in clinical practice care is individualized using careful clinical judgment, and should also consider the patient's cultural background.

Conclusion

A summary of the treatment of modifiable risk factors for primary and secondary stroke prevention is presented in Tables 2a and 2b.

Modification of risk factors is the main resource for effective prevention of stroke. Many therapeutic options are available at present, and continued research efforts are expanding the available options. However, clinicians and patients face a challenge to put in practice all the evidence available. A multidisciplinary approach with organized continued education will likely improve the efficacy of these measures.

In the near future, studies embarking on the evaluation of the genetic determinants of cerebrovascular risk factors and outcomes, will increase our understanding of cerebrovascular disease and will likely result in new therapies, with individualized programs for stroke prevention.

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Table 1

Framingham Stroke Risk Profile (FSRP)

Probability of Stroke Within 10 Years for Men Aged 55–84 Years and Free of Previous Stroke: Framingham Heart Study										
RISK FACTORS	POINTS									
	0	1	2	3	4	5	6	7	8	9 10
Age (yr)	54-56	57-59	60-62	63-65	66-68	69-71	72-74	75-77	78-80	81-83 84-86
Systolic Blood Pressure	95-105	106-116	117-126	127-137	138-148	149-159	160-170	171-181	182-191	192-202 203-213
Under Hypertensive Therapy	No		Yes							
History of Diabetes Mellitus	No		Yes							
Smokes Cigarettes	No			Yes						
History of Intermittent Claudication or Congestive Heart Failure	No			Yes						
History of Atrial Fibrillation	No				Yes					
Left Ventricular Hypertrophy on EKG	No						Yes			

10 —YEARS PROBABILITY of STROKE (%)	POINTS														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
	2.6%	3.0%	3.5%	4.0%	4.7%	5.4%	6.3%	7.3%	8.4%	9.7%	11.2%	12.9%	14.8%	17.0%	19.5%
	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
	22.4%	25.5%	29.0%	32.9%	37.1%	41.7%	46.6%	51.8%	57.3%	62.8%	68.4%	73.8%	79.0%	83.7%	87.9%

Probability of Stroke Within 10 Years for Women Aged 55-84 Years and Free of Previous Stroke: Framingham Heart Study										
RISK FACTORS	POINTS									
	0	1	2	3	4	5	6	7	8	9 10
Age (yr)	54-56	57-59	60-62	63-65	66-68	69-71	72-74	75-77	78-80	81-83 84-86
Systolic Blood Pressure (SBP)	95-104	105-114	115-124	125-134	135-144	145-154	155-164	165-174	175-184	185-194 195-204
Under Hypertensive Therapy (*)	No									
History of Diabetes Mellitus	No			Yes						
Smokes Cigarettes	No			Yes						
History of Intermittent Claudications or Congestive Heart Failure	No		Yes							
History of Atrial Fibrillation	No						Yes			
Left Ventricular Hypertrophy on EKG	No				Yes					

Probability of Stroke Within 10 Years for Women Aged 55-84 Years and Free of Previous Stroke: Framingham Heart Study												
RISK FACTORS		POINTS										
		0	1	2	3	4	5	6	7	8	9	10
		95-104	105-114	115-124	125-134	135-144	145-154	155-164	165-174	175-184	185-194	195-204
(*)If currently under antihypertensive therapy, add points depending on SBP:		6	5	5	4	3	3	2	1	1	0	0

10—YEARS PROBABILITY of STROKE (%)	POINTS														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
	1.1%	1.3%	1.6%	2.0%	2.4%	2.9%	3.5%	4.3%	5.2%	6.3%	7.6%	9.2%	11.1%	13.3%	16%
	16	17	18	19	20	21	22	23	24	25	26	27			
	19.1%	22.8%	27%	31.9%	37.3%	43.4%	50.0%	57.0%	64.2%	71.4%	78.2%	84.4%			
	Adapted from reference Wolf et al., 1991 with permission.														

TABLE 2a

Effects of treatment of risk factors in primary prevention of stroke

Risk factor		Evidence	Risk Reduction	Management/Comments
Hypertension ^{1,2}		Class I A	35 – 44%	Screening every 2 years. Individualized management and choice of agent. Life style modification. Goal BP <140/90mm Hg for usual care and <130/80 for compelling indications. [‡]
Pre-Hypertension ¹		No data	---	Life style modification
Diabetes	Glycemic control ³	Data lacking to support effect on stroke reduction	---	Reduction of microvascular complications, but not macrovascular. Emphasis on aggressive management of other risk factors in patients with diabetes.
	Hypertension control ^{1,2,4}	Class I A	20-44%	Goal BP < 130/80 mmHg. ACEI/ARB are preferred agents in patients with diabetes and microalbuminuria.
	Hyperlipidemia ^{2,5}	Class I A	24-48%	LDL Goal < 100 LDL <70 for high-risk patients.
Pre-Diabetes ³		No data	---	Diet, exercise and medications reduce incidence of diabetes, but the effects on vascular outcomes are not known.
Atrial fibrillation ²		Class I A	20% aspirin 68% warfarin	Anticoagulation also recommended for valvular heart disease. Goal INR 2.0-3.0. Low risk patients — aspirin or warfarin High risk patient — warfarin
Hyperlipidemia ²		Class I A	30%	If coronary artery disease or high risk hypertensive, even with normal LDL levels treat with lifestyle measures and a statin.
		Class IIa B		If coronary artery disease and low HDL levels treat with weight loss, increased physical activity, smoking cessation, and consider adding niacin or gemfibrozil.
Smoking cessation ²		Class I B	50% at 1 year, baseline by 5 years	Counseling. Nicotine replacement. Oral smoking-cessation medications.
Obesity ²		Class I A *	---	Abdominal obesity associated with an odds ratio for stroke 1.75-2.37. Weight loss affects other vascular risk factor (diabetes, HTN) but has not been shown to affect stroke directly.

Evidence class and level as defined by the AHA: Class I Evidence and/or general agreement that treatment is useful and effective; Class II Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of treatment; Class IIa Weight of evidence or opinion in favor of treatment; Class IIb Usefulness/efficacy less well established by evidence or opinion; Class III Evidence and/or general agreement that treatment is not useful/effective and may be harmful. Level A Data from multiple randomized clinical trials; Level B Data from a single randomized trial or nonrandomized studies; Level C Expert opinion or case studies.

[‡]Compelling indications = Diabetes, chronic kidney disease, myocardial infarction, congestive heart failure.

¹(Chobanian, Bakris et al. 2003).

²(Goldstein, Adams et al. 2006).

³(Ryden, Standl et al. 2007).

⁴(UKPDS-Group-Investigators 1998b).

⁵(The Expert Panel on Detection 2002).

* For weight reduction and hypertension control.

TABLE 2b

Effects of treatment of risk factors in secondary prevention of stroke

Risk factor		Evidence	Risk Reduction	Management/Comments
Hypertension ^{1,2}		Class I A	25 – 32%	Lower BP by 10/5 mm Hg. Target is < 140/90, thiazide plus ARB are preferred agents. Target is <130/80 in diabetics.
Pre-Hypertension ¹		No data	---	Life style modification. Consider antihypertensive medications.
Diabetes ^{1,2,3}	Glycemic control	Class IIb B	---	Blood glucose control with diet and medications to near normoglycemia. Goal HbA1c < 7.0.
	HTN control	Class IIa B	44%	BP goal < 130/80.
	Hyperlipidemia	Class IIa B	28%	Treatment of hyperlipidemia (statins) with goal LDL < 100 and < 70 can be considered in high-risk patients.
Pre-Diabetes ³		No data	---	Treatment shown to delay the onset of diabetes, however effects on vascular outcomes is not known.
Atrial fibrillation ¹		Class I A	As much as 68%	Degree of benefit depends highly on individual risk factors. Anticoagulation with adjusted-dose warfarin (target INR, 2.5; range, 2.0 to 3.0) ASA 325 mg if warfarin is contraindicated
Hyperlipidemia ^{1,4}		Class I A	11.2%	Life style modification. Target LDL <100 mg/dl and Target LDL <70 mg /dl in very high risk patients can be considered with statins. Consider niacin or fibrate for low HDL.
Smoking cessation ¹		Class I C	Risk disappears after 5 yrs	Smoking cessation strongly recommended. Counseling. Nicotine replacement. Oral smoking-cessation medications.
Obesity ¹		Not directly studied	---	Diet and physical activity has been linked to a reduced stroke risk. Abdominal obesity more strongly associated with stroke risk. Weight loss improves blood pressure. Consider weight reduction (diet, physical activity) for all. Goal BMI 18.5 to 24.9 kg/m ² and waist circumference of 24 inches for men, 32 for women.

Evidence class and level defined in Table 2a.

¹ (Sacco, Adams et al. 2006).² (Chobanian, Bakris et al. 2003).³ (Ryden, Standl et al. 2007).⁴ (The Expert Panel on Detection 2002). BP = Blood Pressure; BMI = body mass index.