Primary Prevention of Ischaemic Stroke

a report by
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Stroke is the second most common cause of death worldwide and a leading cause of long-term neurological impairment, with as many as 30% of survivors permanently disabled.[1–3] Of all strokes, approximately 70% are first-time events, thus primary-care physicians have a great opportunity to identify patients who may benefit from risk factor modification.[2] Furthermore, neurologists frequently evaluate non-stroke patients who carry modifiable stroke risk factors. In these settings, initiation of primary prevention strategies may have the greatest impact on the disease and its enormous toll on the healthcare system.

Risk Factors for Ischaemic Stroke

Numerous factors contribute to the risk of first stroke. The non-modifiable risk factors include increasing age, sex, race/ethnicity, family history, genetic factors and low birth weight. While not modifiable, these risk factors may identify those who are at highest risk of stroke and who may benefit from aggressive treatment of any modifiable risk factors. Regarding age, each decade above 55 years of age leads to a doubling of stroke risk.[4] Men carry an overall higher risk of stroke than women at younger ages, but women are at greater risk over the age of 85 years.[5] This relatively greater risk in older women may reflect changing hormonal status and/or the use of hormone replacement therapy (HRT), as well as the fact that men with stroke risk factors may die earlier from cardiovascular disease.[6–7] Race and ethnic contributions to stroke risk are difficult to separate from other risk factors such as hypertension and diabetes, which are more prevalent in certain populations. Even taking into account these risk factors, however, stroke incidence rates remain higher among some racial–ethnic groups (e.g. African-Americans).[8,9] Unidentified genetic risk factors may predispose these groups to stroke and may eventually help to explain the contribution of family history to stroke risk. Stroke is a manifestation of a variety of rare genetic disorders, but the association between most inherited coagulopathies – e.g. protein C and S deficiency – and arterial events is weak.[10–12] Finally, stroke incidence and stroke mortality are increased among individuals with low birth weight.[13,14]

The long list of modifiable stroke risk factors is best separated into two groups:

- those that clearly contribute to risk and, if modified, reduce the risk of incident stroke; and
- those that are associated with stroke, but have not been well studied or do not reduce the risk of stroke when treated.

Well-documented risk factors that clearly benefit from specific management include hypertension, cigarette smoking, atrial fibrillation, dyslipidaemia, diabetes mellitus and asymptomatic carotid stenosis (see *Table 1*).[15–17] The discussion and treatment of these risk factors will be the focus of this article. Other well-documented risk factors are cardiovascular and peripheral arterial disease, sickle cell disease and obesity. Less well documented or potentially modifiable risk factors include metabolic syndrome, hyperhomocysteinaemia, hypercoagulability, oral contraceptive use, inflammatory processes, migraine headache and sleep apnoea, among others.[18]

Hypertension

Blood pressure is a powerful determinant of stroke risk and, because hypertension is the most prevalent of the modifiable stroke risk factors throughout middle and older age, its treatment would produce the greatest impact on reducing the burden of stroke.[19] Recent evidence-based guidelines on management of hypertension recommend antihypertensive agents and lifestyle modification to keep blood pressure <140/90, with even tighter control recommended for those with additional vascular risk factors such as diabetes and chronic kidney disease (see *Table 2*).[20] Overall, across multiple classes of antihypertensive therapy, blood pressure reduction is associated with approximately 30–40% reduction in the incidence of stroke, with more intensive lowering superior to less.[21–22] Placebo-controlled studies have demonstrated the efficacy of thiazide diuretics, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers and calcium-channel blockers in reducing stroke and cardiovascular outcomes.[21–22] In general, the choice of a particular class of agents is less important than the degree of blood pressure reduction achieved.

Cigarette Smoking

Multiple studies have demonstrated that cigarette smoking independently increases the risk of ischaemic stroke approximately two-fold and places individuals at even greater risk of haemorrhagic stroke.[23–25] Moreover, smoking may act synergistically with other stroke

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Table 1: Modifiable Stroke Risk Factors

	Relative Risk	Relative Risk Reduction with Treatment
Hypertension	1.8–4.0, depending on age[60]	30–40% reduction regardless of antihypertensive used[21,22]
Cigarette smoking	2–2.6[26,27]	50% reduction at one year after cessation; excess risk disappears at five years after cessation[26–27]
Atrial fibrillation	2.6–4.5[61,62]	Adjusted dose warfarin versus placebo 62%; aspirin versus placebo 22%[29]
Dyslipidaemia	2.0 for high total cholesterol[34] 1.5–2.5 for men with low HDL-C[35–36]	21% reduction with statins[41]
Diabetes	1.8–6.0[18]	Reduction of stroke risk with blood pressure control and statins, not with tight glycaemic control[39,43–46]
Asymptomatic carotid stenosis	2.0[63]	50% risk reduction with endarterectomy in men[51–52]

HDL-C = high-density lipoprotein cholesterol.

Table 2: Classification and Management of Hypertension[20]

Classification	Systolic Blood Pressure (mmHg)		Diastolic Blood Pressure (mmHg)	No Compelling Indication	With Compelling Indication (CHF, MI or high coronary disease risk, diabetes, chronic renal failure or prior stroke)
Normal	<120	and	<80	No antihypertensive drug	No antihypertensive drug
Pre-hypertension	120–139	or	80–90	No antihypertensive drug	Drugs for the compelling indication
Stage 1 hypertension	140–159	or	90–99	Thiazide diuretics, ACEIs, ARBs, β-blocker or calcium channel blocker	Drugs for the compelling indication; antihypertensive therapy with diuretics, ACEIs, ARBs, β-blockers, calcium channel blockers as needed
Stage 2 hypertension	≥160	or	≥100	Two-drug combination for most	Drugs for the compelling indication; antihypertensive therapy with diuretics, ACEIs, ARBs, β-blockers, calcium channel blockers as needed

CHF = congestive heart failure; MI = myocardial infarction; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker.

risk factors such as oral contraceptive pills. Smoking is thought to promote stroke by increasing thrombus generation in narrowed arteries and chronically hastening atherosclerosis. In the Framingham Study of 4,255 middle-aged men and women who were free of stroke or transient ischaemic attacks (TIAs), the risk of stroke in heavy smokers (more than 40 cigarettes per day) was twice the risk of light smokers (fewer than 10 cigarettes per day).[26] The stroke risk had decreased significantly by two years after smoking cessation and reached the level of nonsmokers by five years after smoking cessation. Another prospective study of young, healthy registered nurses found that smoking yielded a 2.58 relative risk of first stroke.[27] This excess risk largely disappeared between two and four years after smoking cessation.

Atrial Fibrillation

Nonvalvular atrial fibrillation (NVAF) confers a nearly five-fold increase in the age-adjusted risk of stroke.[28] The prevalence of NVAF increases markedly with age, as does the proportion of strokes attributable to the dysrhythmia: nearly a quarter of strokes in octogenarians can be ascribed to NVAF.[28] Multiple trials have shown that medical therapy is efficacious in the primary prevention of stroke in patients with NVAF. Overall, oral anticoagulation with warfarin reduces the risk of stroke in moderate- to high-risk patients by about 60% and aspirin by about 20%.[29] Several risk-stratification methods have been developed to guide choice of treatment in NVAF. One such scheme that has been validated in clinical trials is the CHADS$_2$, which evaluates stroke risk based on the presence of five vascular risk factors (see *Table 3*).[30] Medical therapies other than warfarin have been investigated. Ximelagatran, a direct thrombin inhibitor, was demonstrated to be equally efficacious as warfarin in reducing stroke in NVAF.[31] While ximelagatran resulted in fewer minor bleeding complications, it produced significant elevations in liver enzymes and at least one case of fatal hepatic failure – thus the drug has not been approved by either European or American regulatory agencies. The National Study for Prevention of Embolism in Atrial Fibrillation (NASPEAF) trial demonstrated the superiority of combination therapy with warfarin and the antiplatelet agent triflusal over warfarin or antiplatelet therapy alone.[32] It is important to remember that chronic and paroxysmal atrial fibrillation carry similar stroke risk and that rhythm control is not superior to rate control in reducing the risk of stroke.[33]

Dyslipidaemia

Prospective studies in men and women have shown that ischaemic stroke rates increase up to 25% for every 1mmol/l increase in total cholesterol above 5.2mmol/l.[34] Low high-density lipoprotein (HDL) cholesterol level is a risk factor for stroke in men and possibly women as well.[35,36] While the association between low-density lipoprotein (LDL) cholesterol and risk of stroke is not clear, the prevention of vascular events seen in the lipid-lowering therapy trials appears to be directly proportional to the degree of LDL reduction regardless of entry-level LDL.[37,38] Two large primary prevention studies have shown that 3-hydroxy-3-methylglutaryl co-enzyme A (HMG-CoA) reductase inhibitors (statins) are effective in reducing stroke. The Heart Protection Study included over 20,000 adults with either occlusive arterial disease or diabetes mellitus who were randomly allocated to receive simvastatin 40mg or a placebo.[39] Simvastatin treatment was associated with a 25% relative reduction (1.4% absolute risk reduction) in the event rate for first non-fatal and fatal stroke. This benefit was apparent even among those with low pre-treatment LDL cholesterol below 3.0mmol/l. In the lipid-lowering arm of the Anglo–Scandinavian Cardiac Outcomes Trial, over 10,000 hypertensive patients with at least three other cardiovascular risk factors and a non-fasting total cholesterol of 6.5mmol/l were randomised to atorvastatin 10mg or placebo.[40] Fatal and non-fatal stroke were significantly reduced in the treatment group by 27% (0.7% absolute risk reduction). Meta-analyses of multiple statin trials show an overall 21% relative risk reduction for stroke with the magnitude of reduction being largely proportional to the degree of LDL reduction.[41] The Treating to New Targets (TNT) trial enrolled 10,001 patients with coronary

CHADS$_2$ Score*	Risk Level	Adjusted Stroke Rate per 100 Patient-years**	Treatment Recommendations Based on Risk
0	Low	1.9	Aspirin (75–325mg/day)
1	Low–moderate	2.8	Warfarin INR 2–3 or aspirin (75–325mg/day)
2***	Moderate	4.0	Warfarin INR 2–3
3	High	5.9	Warfarin INR 2–3
4	Very high	8.5	Warfarin INR 2–3
5	Very high	12.5	Warfarin INR 2–3
6	Very high	18.2	Warfarin INR 2–3

*CHADS$_2$ score is calculated by adding one point for recent congestive heart failure, hypertension, age greater than 75 years or diabetes, and adding two points for having had a prior stroke or transient ischaemic attack.
**The adjusted stroke rate is the expected stroke rate per 100 patient-years for patients not on antithrombotic therapy with warfarin or aspirin.
***All patients with atrial fibrillation and prior stroke or transient ischaemic attack should be considered at high risk and treated with anticoagulation.

heart disease and LDL <3.4mmol/l who were assigned to 10mg or 80mg of atorvastatin daily.[42] At five-year follow-up, the high-dose atorvastatin group had 30% fewer fatal and non-fatal strokes than the low-dose group (1.1% absolute risk reduction).

Diabetes

Type 2 diabetes is independently associated with a 1.8- to 6-fold increased stroke risk.[18] Moreover, these patients have an increased prevalence of hypertension, dyslipidaemia and obesity. Multiple studies have demonstrated the benefit of tight blood pressure control in diabetics. The UK Prospective Diabetes Study (UKPDS-36) stratified diabetic patients by 10mmHg increments of systolic blood pressure ranging from <120mmHg to >160mmHg and found that each 10mmHg decrement in mean systolic blood pressure was associated with a significant reduction in risk for any complication related to diabetes, including stroke.[43] No threshold of risk reduction was observed for any end-point. Specific classes of antihypertensive agents may offer better prevention in the diabetic population. For example, in the Losartan Intervention for End-point Reduction in Hypertension (LIFE) study, angiotensin II receptor blocker treatment resulted in a significant 24% relative risk reduction (5% absolute risk reduction) in major vascular events and a nonsignificant 21% reduction (2% absolute risk reduction) in stroke compared with beta-blocker therapy.[44] The benefit of statin therapy in diabetic patients was demonstrated in the Heart Protection Study (HPS), as discussed above.[39] Furthermore, in the Collaborative Atorvastatin Diabetes Study (CARDS), treatment with atorvastatin resulted in a 48% reduction (1.3% absolute risk reduction) in stroke among type 2 diabetics with at least one additional vascular risk factor and an LDL cholesterol <4.14mmol/l but no history of cardiovascular disease.[45] While tight blood pressure control has been proved to reduce stroke risk in diabetic patients, tight glycaemic control has not. The UKPDS-33 showed that intensive glycaemic control with sulfonylureas and insulin reduced microvascular, but not macrovascular, complications of diabetes.[46] Certain diabetic medications may offer protection through other mechanisms. In the UKPDS-34, metformin significantly reduced macrovascular events without providing tighter glycaemic control relative to the conventional treatment group.[47]

Asymptomatic Carotid Stenosis

Among the elderly in Western populations, the prevalence of extracranial carotid stenosis is as high as 10%.[18] The risk of stroke from asymptomatic carotid artery stenosis >50% is 1–3.4% per year.[48–50] Factors associated with higher risk include male sex, stenosis >75% and heart disease.[48] Two large trials have studied endarterectomy in asymptomatic carotid disease of >60% stenosis: the Asymptomatic Carotid Atherosclerosis Study (ACAS) and the Asymptomatic Carotid Surgery Trial (ACST).[51,52] The studies found

strikingly similar benefits with surgical treatment compared with medical therapy alone with a 53 and 45% relative risk reduction, respectively, corresponding to a 5.9 and 5.3% absolute risk reduction, respectively. Interestingly, after subgroup analysis, the same benefit was not seen in women, largely due to a higher rate of peri-operative complications.[53] As with many surgical trials, the benefits seen depend highly on peri-operative risk, which was approximately 3% for men in both the ACAS and ACST.[51,52] In patients with medical co-morbidities placing them at high surgical risk or in centres with less experienced surgeons, the risk–benefit ratio must be reassessed. Importantly, the observational studies on asymptomatic carotid disease as well as the endarterectomy trials were performed before the widespread use of statin medications. As primary preventative strategies with medical therapy continue to improve, the benefits of endarterectomy may need to be re-evaluated. Although carotid artery angioplasty/stenting is less invasive and possibly less costly than endarterectomy, its noninferiority to endarterectomy has not been established and thus it cannot be recommended for use outside of a trial setting. Most recently, the Endarterectomy Versus Angioplasty in Patients with Severe Symptomatic Caroid Stenosis (EVA-3S) study was stopped prematurely after interim analysis revealed that the rates of stroke and death at one and six months in patients with symptomatic stenosis (60%) were significantly higher in the stenting group.[54]

Hormone Replacement

The observation that the rate of vascular events in women dramatically increases post-menopause has led to many studies on primary and secondary prevention with HRT. The Women's Health Initiative was a primary prevention study of the effect of hormone therapy on cardiovascular disease among post-menopausal women in which stroke was a pre-specified end-point.[55,56] Two groups of women were randomised: those with an intact uterus received combined estrogen and progesterone therapy, while those with a hysterectomy received only estrogen. Both groups had a small but significant increase in vascular events with HRT compared with placebo. Thus, HRT cannot be recommended and is discouraged for prevention of ischaemic stroke.

Antiplatelet Therapy

Although antiplatelet therapy has a well-established role in secondary stroke prevention for both men and women, its value in primary prevention varies by sex and vascular risk profile. Among men, use of aspirin offers no benefit for primary prevention of ischaemic stroke or death, but, because it reduces the incidence of myocardial infarction, it is recommended for men with moderate to high risk of developing cardiovascular disease.[57,58] It has no role in primary prevention for those at low cardiovascular risk. The Women's Health Study randomised 39,876

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asymptomatic women aged 45 years or older to aspirin or placebo on alternate days followed over 10 years. The results showed a nonsignificant reduction of 9% for the primary end-point of major cardiovascular events and a significant 17% reduction in the risk of stroke (24% reduction of ischaemic stroke and a non-significant increase in haemorrhagic stroke).[59] Subgroup analysis showed that aspirin reduced the risk of ischaemic stroke and myocardial infarction largely among women aged 65 years and older. Women younger than 65 years old are unlikely to benefit from empiric antiplatelet therapy unless they carry stroke risk factors.

Summary

Substantial evidence supports the importance of a variety of modifiable stroke risk factors whose treatment offers the potential to reduce the considerable socioeconomic burden of stroke. Control of blood pressure, cessation of smoking and use of anticoagulation to prevent cardioembolism in atrial fibrillation offer the greatest impact at the population level because of the prevalence of these risk factors. The use of statins and antiplatelet agents, avoidance of HRT in older women and treatment of carotid stenosis in men contribute modest benefits to stroke risk reduction. ■

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