PERIODICUM BIOLOGORUM
VOL. 114, No 3, 409–419, 2012

UDC 57:61
CODEN PDBIAD
ISSN 0031-5362

overview

Stroke prevention: recent achievements and new challenges

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Key words: ischemic stroke, prevention, risk factors, metabolic syndrome, genetics

Received November 2, 2012.

Abstract

Stroke remains a major health problem despite the great efforts made worldwide to fight against it. Despite therapeutic achievements to treat ischemic stroke patients in stroke units with tissue plasminogen activator (tPA), prevention remains the most powerful strategy to cure this complex disease. Stroke is a heterogeneous and multi-factorial disease caused by the combination of vascular risk factors, environment, and genetic factors. These risk factors can be subdivided into non-modifiable (age, sex, race-ethnicity, genetic variations and predispositions) and modifiable (hypertension, diabetes, dyslipidemia, atrial fibrillation, carotid artery stenosis, smoking, poor diet, physical inactivity and obesity). The metabolic syndrome, a cluster of metabolic risk factors within an individual, has been recognized as and important factor associated with an increased risk of stroke. Recently, a great emphasis has been given to the investigations of genetic factors and stroke risk, which may lead to the discovery of new biomarkers for prevention, diagnosis and to the alternative strategies for stroke treatment. In this review we sought to discuss the main risk factors for stroke and the current strategies of stroke prevention.

INTRODUCTION

Stroke is a devastating disease with enormous personal, social and economic consequences. It is the second leading cause of death worldwide and its burden is expected to increase as the population ages and the incidence of the disease's risk factors such as hypertension and diabetes increase across the globe *(1)* Certain therapeutic strategies such as stroke unit care and treatments including tissue plasminogen activator (tPA) have been developed to treat acute stroke more effectively and lessen the amount of disability that the disease carries. However, these modalities are not available universally in developed countries and scarcely at all in developing ones, with t-PA utilization of less than 1 in 10 patients where it is even available *(2)*. Moreover, more than 75% of strokes each year are first-ever strokes, making the primary prevention of utmost importance *(3)*. Although stroke is a clinical diagnosis with many sub-classifications and distinct yet sometime overlapping entities, the identity of the risk factors is well known with many treatments readily available. The disease can be controlled, and perhaps largely prevented, thus achieving a sizeable public health benefit. Successful implementation of the preventive tools at our disposal remains a great challenge across borders, nations and health systems.

The stroke risk factors can be subdivided into non-modifiable (age, sex, race-ethnicity, genetic variations and predispositions) and modifiable (hypertension, diabetes, dyslipidemia, atrial fibrillation, carotid artery stenosis, smoking, poor diet, physical inactivity and obesity) (Table 1). An individual risk factor may contribute to each subclassification of stroke differently, and there is a large overlap or risk factors with cardiovascular and peripheral vascular disease. This review will focus on the current updates of the management of traditional and novel risk factors in stroke prevention, the challenges of successful management and future directions for research and further therapeutic successes. Potentially modifiable stroke risk factors such as sleep apnea, alcohol, drug abuse, and hyperhomocysteinemia are discussed as is the use of antiplatelet therapy for primary stroke prevention.

Hypertension

Hypertension is the most important modifiable risk factor for stroke. Several studies have concluded that it accounts for more than the third of the stroke burden and maybe as much as half of all strokes *(4, 5)*. The control of high blood pressure (BP) contributes to prevention of first strokes but also of renal and heart failure *(6)* and possibly cognitive decline *(7, 8)* and frank dementia *(9)*. It has been shown that for every 20-mmHg increase in systolic and 10-mmHg increase in diastolic BP greater than 115/75 mmHg, there is a 2-fold increase in mortality associated with stroke and coronary disease *(10)*. Conversely, a 10 mmHg reduction in systolic BP has been shown to lower the stroke risk by about a third in primary and secondary stroke prevention *(11–13)*. These benefits also extend to the elderly, where in one study, a 36% reduction was found in the incidence of stroke for patients over the age of 60 who were treated with a thiazide diuretic with or without a beta-blocker *(14)*. A more recent study of patients over the age of 80 showed that lowering the mean systolic BP by 15 mmHg and mean diastolic BP by 6.1 mmHg lowered the rate of fatal strokes by 39% after 2 years of treatment *(15)*. A meta-analysis of 31 trials, with 190,606 participants, showed the benefits for educed BP in both younger (<65 years) and older (=65 years), implying that the benefits from better pressure control can be reaped at any age *(16)*. A more intensive regimen appears to be more beneficial: in the ACCORD, a 5,000 patient study of those with diabetes, the patients who were in a more intense BP lowering group < 120, had a significantly lower risk of stroke after a follow-up of 4.7 years compares to those with a BP lowering goal of <140 *(17)*. While the BP lowering has reduced the risk for all stroke subtypes, these findings are more pronounced for hemorrhagic strokes.

A comprehensive evidence-based approach to treatment of hypertension is provided by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) *(18)*. The JNC 7 treatment recommendations are provided in **Table 1**. The release of JNC 8 document is expected by the end of 2012 *(19)*. Several categories of antihypertensive medications such as thiazide diuretics, β-adrenergic receptor blockers, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and calcium channel blockers (CCBs) have been shown to reduce the risk of stroke in patients who are hypertensive *(20–23)*. Thiazide-type diuretics were originally recommended as the preferred initial drugs of treatment for most patients *(24)*. A more recent meta-analyses, however, has shown that with a few exceptions (beta-blockers after a recent myocardial infarction (MI) and additional benefits of CCBs) all the different classes of BP-lowering medications produced a similar reduction in the incidence of stroke and CVD for a given reduction in BP *(25)*.

BP control can be achieved in a vast majority of patients, with most requiring combination therapies and often more than 2 antihypertensive medications *(26)*. Unfortunately, BP is controlled in less than a quarter of the hypertensive population worldwide *(27)*. Given the importance of hypertension as a stroke risk factor, and the abundance of effective treatments available, providing effective population-wide but patient-specific interventions remains a major public health care challenge.

Diabetes

Diabetes is an established risk factor for all vascular events in general and ischemic stroke (IS) in particular. Individuals with type 2 diabetes also have an increased vulnerability to atherosclerosis and an increased prevalence of hypertension, hyperlipidemia and obesity. Cardiovascular disease (CVD) and IS develops earlier in patients with diabetes, and strokes in patients with diabetes tend to have a heavier morbidity burden. American Diabetes Association recommends a multi-faceted approach to optimal health in diabetics; not only controlling the blood glucose, but also aggressive treatment of associated cardiovascular risk factors, with lower targets than for the general population *(28)*. Surprisingly, recent studies have shown that aggressive treatment of blood glucose was very effective in preventing mircovascular complications of diabetes, but had no statistical effect on reduction of macrovascular events, including stroke *(29–31)*. However, the evidence that a multifactorial approach (reduced intake of dietary fat, light to moderate exercise, cessation of smoking) reduces stroke and cardiovascular risk in type-2 diabetics is supported by subgroup analyses of diabetic patients in large clinical trials. In the UK prospective Diabetes Study Group, comparing a tight BP control group (mean BP 144/82 mmHg) vs less stringent control group (mean BP 154/87 mmHg) resulted in a reduction of 44% of fatal and non-fatal stroke between the two groups *(32)*. Another study found that adding a statin to existing treatments in high risk patients resulted in a 24% reduction in strokes *(33)*. The Collaborative Atorvastatin Diabetes Study (CARDS) evaluated statin therapy in diabetic patients as a primary prevention of vascular events. A total of 2838 people with type 2 diabetes were enrolled, and the trial was stopped early due to its efficacy points being met: 37% reduction the primary

vascular events in general, and a 48% reduction of strokes in particular *(34)*.

Good glycemic control involves appropriate insulin therapy and professional dietary and lifestyle therapy for type 1 diabetics and weight loss, increased physical activity and, if need be, oral and injectable hypoglycemic agents for type 2 diabetics. Treatment of adults with diabetes, especially those with additional risk factors, with a statin to lower the risk of a first stroke is recommended *(35)*. Studies have shown that a multi-faceted approach to controlling diabetes and concomitant risk factors leads to significant reduction in cardiovascular events and stroke.

Dyslipidemia

Many epidemiologic studies found no consistent relationship between cholesterol levels and overall stroke risks. However, there is evidence that there is a positive correlation between total and low density lipoprotein (LDL) cholesterol levels and the risk of stroke *(36, 37)*. Conversely, high density lipoprotein (HDL) cholesterol levels have been associated with reduced risk of IS across many sub-populations *(38, 39)*. Moreover, in high risk patients, lowering cholesterol with statins (HMG-CoA reductase inhibitors) has been shown to significantly reduce the risk of transient ischemic attack (TIA) or non-cardioembolic stroke *(40, 41)*. Several meta-analysis have shown that lowering the LDL cholesterol by 1.0 mmol/L reduced the risk of IS by about 20% *(42, 43)*. The beneficial role of statins for primary and secondary stroke risk reduction for those with high risk for CVD risk has been documented *(34, 44, 45)*. It has estimated that statins prevent 9 strokes per 1000 high risk patients or in those with coronary heart disease (CHD) treated over the period of 5 years. Earlier concerns of statins increasing the risk of hemorrhagic stroke *(40)* have not been substantiated by a recent meta-analysis, *(46)* although the topic is still under debate *(47)* and caution should be exercised.

The benefit of rosuvastatin in cutting the risk of myocardial infarction (MI) in half in those patients who were apparently healthy but had elevated levels of C-reactive protein (CRP) hints at the many pleotropic effects of statins *(48)*. Although this class of drugs is very well studied, the way it protects the brain and the heart is not entirely clear. It may decrease platelet aggregation, stabilize plaques, lower BP and reduce inflammation. There has been further speculation that they may have neuroprotective properties, improve endothelium function, decrease smooth muscle proliferation and increase the number of circulating endothelial progenitor cells *(49)*. Intriguing results have shown statins to increase nitric oxide (NO) production and P-selectin expression and up-regulate tissue-type plasminogen-activator *(50)*. It is unclear if statins lower the risk of stroke by lowering the LDL, or by any of the above and maybe yet-unknown mechanisms. Other surrogate markers for artherosclerosis, such as carotid intima-media thickness (cIMT), may prove to be useful in monitoring the progression of and treatments against stroke and other vascular diseases *(51)*.

Non-statin lipid-modifying therapies may also offer stroke protection, although the studies are less equivocal. Niacin treatment has been shown to increase HDL as part of a combination therapy *(52, 53)* Evidence has been mixed on the exetimibe/statin combinations and if they are superior to mono-statin therapies. Fibrates have been shown to decrease the risk of coronary events and retinopathy, but not that of IS *(54)*. Fibrates, Niacin, exetimibe and omega-3 fatty acids each regulate serum lipids by different mechanisms and a combination therapy may be the final answer in achieving desired lipid control. National Cholesterol Education Program III (NCEP ATP 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 have been endorsed in the US (**Table 1**) *(55)*. The updated clinical guidelines for cholesterol testing and management (ATPIV) from the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults are expected to be published by the end of 2012 *(56)*.

Although the benefits of statin therapy outweigh the low risk of serious side effects, there are still some populations for which more data on the safety of lipid-lowering therapies are needed to clarify the risk associated with the effect of treatment, especially for older persons (>70 years of age) and women. More clinical trials and further research for optimal lipid-lowering strategies are needed as the complex relationship between dyslipidemia, atherosclerosis, stroke and CVD exists and has not been entirely elucidated.

Metabolic Syndrome

Metabolic Syndrome (MetS) is defined by a cluster of interconnected factors that increase the risk of atherosclerosis, CVD, stroke, and diabetes mellitus type 2. Its components are dyslipidemia (elevated triglycerides and apolipoprotein B (apoB)-containing lipoproteins, and HDL), elevation of arterial BP and impaired glucose homeostasis, with abdominal obesity and/or insulin resistance (IR) *(55, 57)*. More recently, other factors such as proinflammatory state, oxidative stress, and non-alcoholic fatty liver disease have been suggested to play an important role in MetS, making its definition even more complex. To date the most used definition for MetS is the NCEP ATP III definition *(55)*. All the components of MetS are involved in conferring risk of stroke and CVD. The adjusted hazard ratio (HR) for incident IS associated with MetS ranges between 2.1 and 2.5 in prospective studies, and a HR as high as 5.2 has been reported *(58–60)*. In a cohort of 14,284 patients, patients with MetS but without diabetes exhibited a 1.49-fold increased risk of IS or TIA, whereas those with frank diabetes had a 2.29-fold increased risk *(58)*. The relative odds for IS or TIA, associated with presence of MetS, were 1.39 in men and 2.10 in women. In NOMAS, a significant association between the MetS and IS risk was reported to be independent of other confounding factors including age, education, physical activity, alcohol use, and current

TABLE 1

Stroke risk factors and treatment recommendations.

STROKE RISK FACTORS	CURRENT RECOMMENDATIONS	
Non-modifiable stroke risk factors		
Age, Sex, Race-ethnicity Genetic variations and predisposition		
Modifiable stroke risk factors		
Hypertension	<120/80 mmHg	No drug
	<139/90 mmHg	Drugs for the compelling indication
	<159/99 mmHg	Drugs for the compelling indication. Other drugs (diuretics, ACEIs, ARBs, β-blockers, calcium channel blockers) as needed.
	≥160/100 mmHg	Drugs for the compelling indication and other drugs as needed
	* Lifestyle modifications	
Diabetes	Glycemic control (insulin, oral anti-diabetics) Statins *Lifestyle modifications	
Dyslipidemia	0–1 CHD risk factor*	Diet, weight loss, physical activity; Drug therapy if LDL-C remains = 190 mg/dL. If LDL-C 160–189 mg/dL drug therapy optional
	2 CHD risk factors and 1y CHD risk <20%	Diet, weight loss, physical activity; Drug therapy if LDL-C =160 mg/dL
	=2 CHD risk factors and 10-y CHD risk 10–20%	Diet, weight loss, physical activity; Drug therapy if LDL-C remains =130 mg/dL (or =100 mg/dL)
	CHD or CHD risk equivalent (10-y risk >20%)	Diet, weight loss, physical activity; Drug therapy if LDL-C is =130 mg/dL and optional for LDL-C 70–129 mg/dL
	CHD or CHD risk equivalent (10-y risk >20%)	Diet, weight loss, physical activity; Drug therapy if LDL-C is =130 mg/dL and optional for LDL-C 70–129 mg/dL
	Non-HDL-C in persons with triglycerides =200 mg/dL	Same as LDL-C with goal 30 mg/dL higher
	Low HDL-C	Weight loss, physical activity. Consider niacin or a fibrate in high-risk individuals with HDL-C <40 mg/dL
Metabolic Syndrome	Control vascular risk factors (components of Metabolic Syndrome) *Lifestyle modifications	
Atrial fibrillation	Anticoagulation and antithrombotic therapies	
Other Cardiac Conditions: congestive heart failure, myocardial infarction, dilated cardiomyopathy, valvular heart disease, congenital defects	Anticoagulation and antithrombotic therapies Surgery * Lifestyle modifications	
Carotid Artery Stenosis	Endarterectomy may be considered in selected patients with >60% stenosis without occlusion. Careful patient selection should be guided by individual factors including comorbid conditions, life expectancy and patient preference.	
Smoking	Counseling, nicotine replacement, varenicline, and formal programs are recommended.	
Poor Diet	A diet containing 5 servings of fruits and vegetables per day may reduce the risk of stroke	
Obesity	Weight reduction	
Physical Inactivity	Moderate exercise (e.g., brisk walking, jogging, cycling, or other aerobic activity).	
Potentially modifiable stroke risk factors		
Sleep Apnea	Overnight sleep study in patients with snoring, excessive daytime sleepiness, body mass index over 30 and drug-resistant hypertension. CPAP treatment	
Alcohol	No more than 2 drinks/day for men, and no more than 1 drink/day for women	
Drug Abuse	A history of substance abuse should be part of health evaluation	
Hyperhomocysteinemia	Daily intake of folate (400 μg/d), B6 (1.7 mg/d), and B12 (2.4 μg/d) by consumption of vegetables, fruits, legumes, meats, fish, and fortified grains and cereals	

*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 minutes daily), (4) reduction of sodium intake (<2.34 g), (5) maintenance of adequate dietary potassium (>120 mmol/d), (6) smoking cessation, and (7) DASH diet (rich in fruit, vegetables, and low-fat dairy products and

smoking *(61)*. The prevalence of MetS in NOMAS was 49%, and differed by sex (39% in men, 55% in women, $p<0.0001$) as well as race-ethnicity (56% in Hispanics, 41% in blacks, and 39% in whites, $p<0.0001$). Interesting, the effect of the MetS on stroke risk was greater among women (HR=2.0; 95% CI, 1.3 to 3.1) than men (HR=1.1; 95% CI, 0.6 to 1.9) and among Hispanics (HR=2.0; 95% CI, 1.2 to 3.4) compared to blacks and whites.

MetS is also associated with subclinical atherosclerosis. In NOMAS, we have shown an independent association between MetS and ultrasonographic subclinical measures of atherosclerosis including carotid plaque and carotid stiffness *(63, 64)*. Therefore, an early identification of people at high risk for vascular accidents by evaluating subclinical markers of atherosclerosis is prudent in order to initiate preventive treatments.

Although the existence of MetS as a separate entity has been recently questioned, individuals with a cluster of the risk factors that comprise MetS should be aggressively treated for hypertension, dyslipidemia and diabetes. Patients with MetS have a greater risk of stroke and other vascular diseases and therefore *»a major breakthrough related to the concept of the MetS is the recognition of the high cardiovascular risk in subjects with a cluster of mild abnormalities or with a cluster of abnormalities that are not regarded as driving forces in CVD« (62)*.

Atrial Fibrillation

Atrial fibrillation (AF) is a common cardiac arrhythmia and a frequent cause of cardioembolic strokes. It account for up to 20% of all IS, and the presence of AF independently increases the risk of these events by up to 5-fold *(65)*. The incidence of AF increases with age, with as many as 10% of the population experiencing AF in their 80s *(66)* and the number of affected patients may reach 12 million just in the U.S. by 2050 *(67)*. Despite its increasing burden, AF is also arguably one of the best-studied causes of stroke with dozens of randomized trials and well-established evidence-based recommendations regarding effective medical treatments.

Stroke risk stratification models have been developed and validated. $CHADS_2$ (Congestive heart failure, Hypertension, Age, Diabetes, Stroke/TIA) is the most well-known stratification system *(68)*. It subdivides patients based on the independent predictors of stroke in those with AF and offers validated recommendations of anticoagulation vs antithrombotics therapy based on the scale scores. Several other models for predicting stroke risk, (such as the National Institute for Health and Clinical Excellence (NICE) guidelines [69] and $CHADS_2$-VASc [70]) and bleeding risk (HAS-BLED *(71)* have since been developed.

Anticoagulation and antithrombotic therapies remain the main agents for stroke preventions for those with AF. Warfarin is the most commonly used anticoagulant, that is cheap and exceedingly effective in preventing IS: a recent meta-analysis showed a reduced risk of cardioembolic stroke of 64% for those on warfarin vs only 22% for those on aspirin. Warfarin also provides an almost 40% relative risk reduction compared to anti-platelet therapies *(72)*. Despite its effectiveness, this anticoaguant has several limitations (narrow therapeutic window, many drug and diet interactions, frequent and inconvenient monitoring) and has been under-utilized *(73, 74)*. It is difficult to keep in range with only two-thirds of patients in clinical trials and little more than half in the community setting being in the therapeutic range *(75, 76)*.

Given the utilization gap for warfarin, several novel oral anticoagulants that are just as effective, have a better side effect profile and require less monitoring have been developed, tested and approved. The three novel oral anticoagulants that have shown the most promising effectiveness and safety data are Dabigatran *(77)*, Rivaroxaban *(78)*, and Apixaban *(79)*. They all exhibit a stable pharmacological profile, very few drug-drug interactions and are almost unaffected by the patients' diet. Very few patients (renal impairment or body weight extremes) require regular monitoring. They appear to be as effective, and in some cases superior to warfarin, with a much improved side effect profile. Less intracranial bleeding, arguable the most feared complication of coumadin, has been observed. These new agents will likely completely change how we treat patients with AF and lead to a greater reduction of cardioembolic strokes in the future.

Other Cardiac Conditions

Other times of cardiac disease that contribute to the risk of IS include congestive heart failure (CHF), MI, dialted cardiomyopathy, valvular heart disease (eg. mechanical valves, mitral valve prolapse, etc) and congenital defects [eg. patent foramen ovale (PFO), atrial septal defect and aneurysm]. All patients with prosthetic valves should be anti-coagulated *(80)*. The rate of thromboembolism is reduced by half with antiplatelet therapy and by more than 75% with anticoagulation *(81)*. Patients with CHF, have a higher risk of stroke (2–3 fold) and are more likely to incur more significant stroke-related morbidity and mortality compared to those without heart failure *(82)*. Low ejection fraction (especially below <30%) has been identified as a risk factor for stroke, *(83)* however, studies on the best treatments for this condition remain inconclusive. Presence of aortic arch atheroma is associated with increased risk of IS *(84)*. Congenital defects, while relatively common, contribute to the burden of stroke only in relatively specific circumstances. Most of these cardiac abnormalities and the potential thrombi that they produce require all and careful cardiac workup for detection, including a transthoracic and transesophageal echocardiography, and extensive cardiac monitoring with telemetry and often a more protracted outpatient cardiac event recorder.

Asymptomatic Cardiac Stenosis

Carotid stenosis of 50% or greater can be found in about 5–10% of people who are older than 65, and the prevalence of a severe asymptomatic carotid stenosis has

been found in 3.1% of the population *(85, 86)*. Data from observational studies and clinical trials indicate an annual risk of stroke attributable to extracranial carotid to have increased with the degree of stenosis (from less than 1% a year for a <80% stenosis to 4.8% per year for a >90% occlusive lesion). In Asymptomatic Carotid Atherosclerosis Study (ACAS), patients with asymptomatic carotid artery stenosis of =60% were randomized to carotid endarterectomy (CEA) or best medical management, with the results showing the primary outcome of ispilateral stroke, death or any perioperative stroke to be 5.1% for surgical candidate and 11% for patients treated medically over 5 years, with an absolute risk reduction of 1% a year *(87)*. Asymptomatic Carotid Surgery Trial (ACST) randomized asymptomatic patients with significant carotid stenosis (>60%) for immediate surgery vs. medical management and were followed for a mean of 3.4 years *(88)*. The study found the overall 5-year risk of stroke or perioperative death to be 11.8% with deferred surgery and 6.4% with immediate endarterectomy. In the subgroup analysis, CEA appeared to be more beneficial for men than women, and in younger patients more than older individuals. A more recent study, Asymptomatic Carotid Embolic Study (ACES), of patients who were followed for 2 years and had a asymptomatic carotid stenosis of at least 70% and were noted to have embolic signals found to have a significantly higher risk of ipsilateralstroke compared to those without any emboli, suggesting the detection of embolization on transcranial Doppler may be used for additional risk stratification *(89)*. The benefit of endarterectomy in asymptomatic stenosis is dependent on the surgical risk. Trials of carotid surgery for asymptomatic carotid disease reduced the risk of stroke by about 1% per annum, while the perioperative stroke rate is 3%. Medical management should be offered to most patients and only high-volume centers with complication rate of =3% should contemplate the surgical procedure. It appears that men and those with life expectancy of more than 5 years will derive the most benefit in appropriate centers *(90)*. Most physicians, however, are not aware of CEA complication rates at their institutions. The best medical management has been evolving with wider use of antiplatelet agents, blood pressure and lipid lowering drugs, reducing the risk of stroke to 1% *(91, 92)*. and therefore the above relative benefit of CEA may need to be recalibrated.

Carotid angioplasty and stenting (CAS) was developed as a less invasive procedure compared to carotid endarterectomy. It has emerged as an alternative for patients who are high surgical risks, have many medical comorbidities, previous neck radiation, contralateral laryngeal nerve palsy or surgically-suboptimal anatomy. Since its invention over 20 years ago, the technique has evolved to more sophisticated and intricate stents, embolic protection devices and increasing operator experience. The Stenting and Angioplasty with Protection in Patient at High Risk of Endarterectomy (SAPPHIRE) Trial shows that stenting was non-inferior to CEA among high-risk surgical patients *(93)*. The comparison of CEA and CAS has been extensively studied, often producing contradictory and confusing results. On one hand, multiple studies have shown that CAS is not as safe as CEA, especially in symptomatic patients, with the International Carotid Stenting Study (ICSS) being the latest addition to the mix *(94)*. On the other hand, Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) found equal risk of composite primary outcome of stroke, MI or death in patients undergoing CAS or CEA *(95)*. The challenge of comparing three different modalities lie in the practice of modern medicine itself: the rapid evolution of medical management, CEA and CAS know how always slanting the risk-benefit ratio in a different direction. Overall, we have rapidly improving techniques for effective prevention of stroke from asymptomatic carotid stenosis.

Hyperhomocysteinemia

Elevated plasma levels of homocysteine as a risk factor for stroke has been traditionally well recognized in atherothrombotic vascular diseases including stroke *(96, 97)*. It is believed that homocysteine induces endothelial platelet dysfunction, by reducing molecular nitric oxide *(98)*. Folic acid and cobalamin have been shown to effectively reduce elevated homocysteine levels, however, clinical trials have failed to show that this translates into better cardiovascular or stroke outcomes *(99–102)*. Inflammation markers seem to be unaffected by lowering homocysteine in secondary stroke prevention, *(103)* although it may have a role in patients with genetic predisposition to hyperhomocysteinemia or those who lack proper dietary folate intake.

Lifestyle Modification

Cigarette smoking is a well-established and modifiable risk factor for both ischemic and hemorrhagic strokes *(104, 105)*. Several meta-analysis have established cigarette smoking to impart a 2-fold increase in the risk of IS an 3-fold increase of subarachnoid hemorrhages *(106, 107)*. The most effective preventive measure is to not smoke or be exposed to smoke. Although quitting smoking is difficult to achieve, it does carry significant benefits, with rapid reduction in the risk of stroke within several years of cessation *(108)*.

Alcohol consumption has been shown to have to have a J-shaped relation to risk of stroke, with light to moderate consumption (=1 drink a day for women and = 2 drinks a day for man) decreasing the risk of stroke to 0.3 to 0.5, but the risk increasing to 2 for heavier alcohol use (=3 drinks) a day *(109–111)*. The relative risk is always increased for hemorrhagic strokes, regardless of the amount consumed. Alcohol in light to moderate quantities increases HDL cholesterol, reduces platelet aggregation and lowers fibrinogen levels, while heavier use can lead to hypertension, hypercoaguability and atrial fibrillation *(112)*. Alcohol consumption should not be advocated as a way to prevent stroke, however, as alcoholism is a major public health problem and the risks of excessive intake remain great.

Abuse of illicit drugs such as cocaine in its various forms, heroin and amphetamines are associated with increased risk of both ischemic and hemorrhagic strokes by elevating the blood pressure and platelet aggregation, and inducing vasospasm and cardiac arrhythmias *(113)*.

Diet has been associated with the risk of stroke, with increased fruit and vegetable consumption having an inverse relationship to the risk of stroke in a dose-response manner *(114, 115)*: for example, for each serving per day increase in fruit or vegetable intake, the risk of stroke was reduced by 6% in one study *(116)*. Research has shown that reducing salt intake improves cardiovascular and cerebrovascular health, although a recent review found no relation to salt intake and CHD morbidity and mortality *(117)*.

Physical inactivity is another modifiable risk factor of stroke *(118)*. Physical activity has been shown to be beneficial in a dose-response pattern with more intensive physical activity providing greater benefits than light to moderate activity. The protective effects of physical activity are likely derived from lowering of body weight and BP and better glycemic control *(119)*.

Obesity and body mass index (BMI) are risk factors for stroke, with associations to hypertension, dyslipidemia and glucose intolerance *(120, 121)*. An obesity epidemic has been sweeping developed countries as well as developing nations such as India and China. The prevalence of metabolic syndrome worldwide, an entity that encompasses several stroke risk factors, was alarmingly high a decade ago (24–50%) *(122)*. and given the recent trends is likely to have increased since then. Although no trials linking weight loss to the risk of stroke exist, evidence exists that losing weight reduces the presence of risk factors that cause stroke: in one meta-analysis an average weight loss of 5.1 kg reduced the systolic BP by 3.6–4.4 mmHg *(123)*. Diet and exercise which are discussed above can be effective in controlling this modifiable risk factor.

Obstructive Sleep Apnea

Sleep related breathing disorders are common in patients with established CVD. Habitual snoring and obstructive sleep apnea (OSA) have been shown to be independently associated with stroke and snoring has been strongly associated with vascular events during sleep *(124, 125)*. A recent-meta-analysis of 29 studies has shown that up to three-quarters of all patients have OSA, with the highest incidence of stroke occurring in patients with cryptogenic stroke, possibly establishing OSA an under-recognized stroke risk factor *(126)*. Hypoxemia, nocturnal hypertension and sympathetic surges have been postulated as some of many contributors to stroke in OSA patients. Decreased cerebral blood flow and impaired vasomotor reactivity has been observed even when the patients with OSA are not sleeping *(127)*. Treatments with continuous positive airway pressure (CPAP) are non-invasive, and effective in reducing the risk of cardiovascular events and BP *(128, 129)*. Further studies of OSA and other sleep disorders are on-going and may yield novels strategies and approaches in stroke prevention.

Aspirin for Primary Stroke Prevention

Aspirin has been shown as a well-established medication for primary stroke prevention. A recent meta-analysis showed a 32% reduction in MI in men but not women and a 17% reduction of the risk of stroke in women, but not men *(130)*. It is not clear why the sex difference exists, as the platelets seem to be inhibited equally in either sex, and no gender disparity was identified in studies in secondary prevention. A trial among diabetics with a history of atherosclerotic disease found Aspirin had no statistically significant effect on the rate of cerebrovascular events *(131)*. Current guidelines indicate low-dose aspirin for women for whom the benefits may outweigh the risks and for patients with high CHD risk factors, but not for those at low risk or diabetics *(132)*.

Genetics of Stroke

Stroke is a complex and multi-factorial disease caused by the combination of vascular risk factors, environment, and genetic factors. Recently, the scientific community put a great effort in understanding the genetic impact to the risk of stroke *(133)*. Several epidemiological studies in families and twins have revealed a genetic component to stroke risk *(134)*. and experimental and clinical research using novel technologies have identified several genes directly or indirectly implicated in the mechanisms leading to stroke *(135)*. The genetic contribution seems to be stronger in stroke patients younger than 70 years than in those who are older *(136, 137)*.

The strongest associations have been found between stroke and single nucleotide polymorphisms (SNPs) in genes involved in inflammation, renin-angiotensin system, atherosclerosis, lipid metabolism, and obesity *(133)*. However, few of these associations have been consistently replicated *(138)*. The innovation of a Genome-wide association study (GWAS) has allowed for identification of novel genetic loci without a specific hypothesis implicating a particular molecular pathway. The first GWAS for IS was conducted using more than 400,000 unique SNPs in a cohort of 249 patients with IS and 268 neurologically normal controls *(139)*. However, these data did not reveal any single locus conferring a large effect on IS risk. Other IS GWASs have been conducted using a meta-analysis approach combining large populations such as CHARGE (Cohorts for Heart and Aging Research in Genomic Epidemiology), *(140)* which consists of 4 prospective epidemiological cohorts of nearly 19,600 subjects with 1,544 incident strokes. In CHARGE, 2 SNPs were identified on chromosome (ch) 12, in the region of 12p13, and replication was obtained for one (rs12425791 SNP; the hazard ratio 1.3 for all stroke, and 1.0 for IS). A large International Stroke Genetic Consortium and the NINDS SiGN (Stroke Genetic Network) is currently conducting a GWAS of over 15,000 IS patients

and 10,000 controls and expected to have the results available within a year.

Since stroke is a complex disease probably related to multiple genetic loci and the interaction of environment and heredity, the study of the precursors of this complex phenotype may be more rewarding. For example, the intermediate phenotypes as markers of subclinical disease such as cIMT, carotid plaque, arterial stiffness, and left ventricular mass; may be more helpful in identifying genes related to atherosclerosis and stroke *(133)*. The genetic research of stroke may greatly enhance our knowledge of this complex diseases. It may contribute to the discovery of new stroke biomarkers, which ultimatelly may be included in the stroke prevention, diagnosis, and treatment decisions.

CONCLUSION

Stroke remains a devastating and prevalent world--wide disease. The past several decades of research have also shown it to be a partially-preventable one, with many risk factors, strategies, and treatments identified, carefully evaluated and studied. A healthy diet and active lifestyle, careful control of modifiable stroke risk factors and access to regular health care are the keys to a successful stroke prevention strategy on both an individual and a public health level.

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