Stroke Risk Factors, Genetics, and Prevention

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Abstract: **Stroke is a heterogeneous syndrome, and determining risk factors and treatment depends on the specific pathogenesis of stroke. Risk factors for stroke can be categorized as modifiable and nonmodifiable. Age, sex, and race/ethnicity are nonmodifiable risk factors for both ischemic and hemorrhagic stroke, while hypertension, smoking, diet, and physical inactivity are among some of the more commonly reported modifiable risk factors. More recently described risk factors and triggers of stroke include inflammatory disorders, infection, pollution, and cardiac atrial disorders independent of atrial fibrillation. Single-gene disorders may cause rare, hereditary disorders for which stroke is a primary manifestation. Recent research also suggests that common and rare genetic polymorphisms can influence risk of more common causes of stroke, due to both other risk factors and specific stroke mechanisms, such as atrial fibrillation. Genetic factors, particularly those with environmental interactions, may be more modifiable than previously recognized. Stroke prevention has generally focused on modifiable risk factors. Lifestyle and behavioral modification, such as dietary changes or smoking cessation, not only reduces stroke risk, but also reduces the risk of other cardiovascular diseases. Other prevention strategies include identifying and treating medical conditions, such as hypertension and diabetes, that increase stroke risk. Recent research into risk factors and genetics of stroke has not only identified those at risk for stroke but also identified ways to target at-risk populations for stroke prevention. (*Circ Res*. 2017;120:472-495. DOI: 10.1161/CIRCRESAHA.116.308398.)**

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Stroke Risk Factors, Genetics, and Prevention

Stroke is the leading cause of long-term adult disability and the fifth leading cause of death in the United States, with ≈795 000 stroke events in the United States each year.[1,2] The aging of the population, coupled with the reduction in case fatality after stroke, is expected to increase the prevalence of stroke by 3.4 million people between 2012 and 2030.[3,4] Although stroke mortality had decreased in the United States during the past 2 decades, recent trends in mortality indicate that these decreases may have leveled off and that stroke mortality may even be rising again. Reasons for this remain uncertain but could reflect the consequences of the obesity epidemic and associated diabetes mellitus. The morbidity associated with stroke remains high, with costs estimated at $34 billion per year for healthcare services, medications, and missed days of work.[3,5] It is likely that estimates of morbidity and cost burden, moreover, based on studies of clinical stroke and using traditional measures such as physical disability and healthcare costs, underestimate the burden of cerebrovascular disease. It is

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Nonstandard Abbreviations and Acronyms	
AF	atrial fibrillation
CI	confidence interval
HR	hazard ratio
LDL	low-density lipoprotein
MET	metabolic equivalent
PM	particulate matter
SNP	single-nucleotide polymorphism

increasingly appreciated, for example, that subclinical cerebrovascular disease—including so-called silent infarction identified on brain imaging in ≤28% of the population aged >65 years[6] and ischemic white matter disease—is associated with memory loss, dementia, gait impairment, and other functional disability. Furthermore, the global burden of stroke is high, with stroke remaining the fourth leading cause of death worldwide, with a particularly large impact in developing nations.[7,8]

Stroke Risk Factors

Unlike myocardial infarction, which is almost always because of large vessel atherosclerotic disease affecting the coronary arteries, identification of risk factors for stroke is complicated by the fact that strokes come in many varieties. At the most basic level, stroke is divided into hemorrhagic and ischemic strokes. The majority (≈80%) of strokes are ischemic, although the relative burden of hemorrhagic versus ischemic stroke varies among different populations. Hemorrhagic strokes can be either primarily intraparenchymal or subarachnoid. Ischemic stroke can be further divided into what have been referred to as etiologic subtypes or categories thought to represent the causes of the stroke: cardioembolic, atherosclerotic, lacunar, other specific causes (dissections, vasculitis, specific genetic disorders, and others), and strokes of unknown cause.[9] Risk factors for hemorrhagic and ischemic stroke are similar, but there are some notable differences; there are also differences in risk factors among the etiologic categories of ischemic stroke. Hypertension is a particularly important risk factor for hemorrhagic stroke, although it contributes to atherosclerotic disease that can lead to ischemic stroke as well. Hyperlipidemia, however, is a particularly important risk factor for strokes because of atherosclerosis of extracranial and intracranial blood vessels,[10] just as it is a risk factor for coronary atherosclerosis. Atrial fibrillation (AF) is a risk factor for cardioembolic stroke.

There is evidence that a high proportion of hemorrhagic stroke, relative to ischemic stroke, can be found in developing countries, where the burden of hypertensive disorders is greater. As the recognition and treatment of hypertension has improved in those countries, often with an increase in Western style diets, the proportion of hemorrhagic strokes declines, and the proportion of ischemic strokes, as well as cardiovascular disease in general, increases. This pattern of the epidemiological transition, from hypertensive hemorrhagic stroke to ischemic strokes, and their associated risk factors, has been particularly well illustrated over a relatively short period of time in studies of stroke in Beijing, China, during that country's rapid economic development over recent decades.[11] From 1984 through 2004, for example, the incidence of hemorrhagic stroke declined by 1.7% annually, whereas the incidence of ischemic stroke increased by 8.7%. The proportion of deaths because of cerebrovascular disease declined, moreover, and the proportion of ischemic heart disease increased.

Reducing the burden of stroke in the population requires identification of modifiable risk factors and demonstration of the efficacy of risk reduction efforts. There are numerous risk factors for stroke, including both modifiable (eg, diet and comorbid conditions) and nonmodifiable risk factors (eg, age, race). In addition, risk factors may also be thought of as short-term risks or triggers (eg, infectious events, sepsis, and stress), intermediate-term risk factors (eg, hypertension and hyperlipidemia), and long-term risk factors for stroke (eg, sex and race). Risk factors for stroke in the young also likely differ from those in older patients.

Estimating stroke risk based on an individual's particular combination of risk factors, particularly for a first stroke event, is an important component of primary care. Patients indicate a preference for knowing their stroke risk.[12] Investigators have, therefore, sought to create valid risk scoring systems to identify those patients at greatest risk for stroke, with the aim of both modifying these risk factors to reduce the risk of stroke and identifying thresholds of risk that would indicate a role for preventive therapies.[13,14] The Framingham Stroke Risk Profile, a continuously-updated, well-known, and widely used score, combines stroke predictors such as age, systolic blood pressure, antihypertensive therapy, diabetes mellitus, cigarette smoking, left ventricular hypertrophy by ECG, and the presence of cardiovascular disease (coronary heart disease, peripheral vascular disease, and congestive heart failure), and can be used to estimate 10-year stroke risk stratified by sex (Table 1).[15–18] Other stroke risk scores have been developed from different sample populations, and although these additional scores include many of the same risk factors as the Framingham Stroke Risk Profile, they add additional metrics such as physical disabilities, depression, and marital status.[19–21] Risk prediction scores focused solely on stroke, however, are likely to have limited utility, because patients at risk of stroke are at risk of other cardiovascular events, as well, and so risk scores that include cardiac events and cardiovascular mortality are likely to be more useful.[22] Recently, the ASCVD risk estimator (ACC/

Table 1. The Framingham Stroke Risk Profile: 10-Year Stroke Probability for Men and Women Aged 70 Y With Systolic Blood Pressure of 160 mm Hg

% Probability							
Men	8	15	18	30	40	60	85
Women	6	10	16	34	42	80	90
Impact of other risk factors							
Hypertension medication	None	+	+	+	+	+	+
Diabetes mellitus	None		+	+	+	+	+
Cigarette use	None			+	+	+	+
Cardiovascular disease	None				+	+	+
Atrial fibrillation	None					+	+
ECG_left ventricular hypertrophy	None						+

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Table 2. Major Nonmodifiable and Modifiable Stroke Risk Factors

	Nonmodifiable Risk Factors	Modifiable Risk Factors
Ischemic stroke	Age	Hypertension
	Sex	Current smoking
	Race/ethnicity	Waist-to-hip ratio
		Diet
		Physical inactivity
		Hyperlipidemia
		Diabetes mellitus
		Alcohol consumption
		Cardiac causes
		Apolipoprotein B to A1
	Genetics*	
Hemorrhagic Stroke	Age	Hypertension
	Sex	Current smoking
	Race/ethnicity	Waist-to-hip ratio
		Alcohol consumption
		Diet
	Genetics*	

*Genetics is placed in an overlapping location between modifiable and nonmodifiable to represent the fact that genetic risk factors are increasingly recognized as potentially modifiable, either directly or through modification of gene–environment interactions.

Data on modifiable risk factors are derived from the study by O'Donnell et al.[24]

AHA Pooled Cohort 10-year atherosclerotic cardiovascular disease) was the first to include large amount of data from blacks, allowing it to incorporate race as a predictive variable and making it particularly useful in black communities.[23]

A recent international (22 nation) case–control study (INTERSTROKE) found that 10 modifiable risk factors explained 90% of the risk of stroke (Table 2).[24] The investigators enrolled 3000 patients with stroke (n=2337 ischemic and n=663 hemorrhagic) and found that hypertension, current smoking, waist-to-hip ratio, diet risk score, regular physical activity, diabetes mellitus, binge alcohol consumption, psychosocial stress and depression, cardiac disease, and ratio of apolipoprotein B to A1 were all associated with ischemic stroke risk. Risk factors for intracerebral hemorrhage included hypertension, smoking, waist-to-hip ratio, diet, and heavy alcohol consumption. Considering the majority of strokes are first strokes within this study, these findings further illustrate the importance of primary prevention through the reduction of modifiable risk factors, particularly those that confer the greatest risk, to reduce the risk of a first stroke event.[25] Although much is known about long-term stroke risk factors, such as hypertension, diabetes mellitus, and atherosclerotic disease, much less is known about short-term risk factors, or triggers, for stroke.[26]

Nonmodifiable Stroke Risk Factors

Nonmodifiable risk factors (also called risk markers) for stroke include age, sex, race-ethnicity, and genetics. In general, stroke is a disease of aging. The incidence of stroke increases with age, with the incidence doubling for each decade after 55 years of age.[27] The mean age of incident ischemic stroke in 2005 was 69.2 years. Recent evidence suggests, however, that the incidence and prevalence of ischemic stroke has been increasing in the 20 to 54-year-old age group, from 12.9% in 1993/1994 to 18.6% in 2005.[28] In a retrospective analysis of the population-based Greater Cincinnati/Northern Kentucky cohort, the proportion of incident stroke occurring among those aged 20 to 54 years increased at each of three 1-year time intervals, from 12.9% in 1993/1994, to 13.3% in 1999, to 18.6% in 2006. In an analysis of the US Nationwide Inpatient Sample, among adults aged 14 to 44 years, ischemic stroke admissions increased annually from 1995 to 2008.[29] In hemorrhagic stroke patients, the incidence increases after 45 years of age.[30] Some of the recent increases in incidence among younger people may reflect changes in diagnostic testing as well, leading to greater sensitivity for the detection of stroke among those with minor symptoms.

The relationship of sex to stroke risk depends on age. At young ages, women have as high or higher risk of stroke as men, although at older ages the relative risk is slightly higher for men.[31] The higher stroke risk among women at younger ages likely reflects risks related to pregnancy and the postpartum state, as well as other hormonal factors, such as use of hormonal contraceptives. Overall, more strokes occur in women than men, because of the longer life span of women compared with men.[27,32] A study performed in 8 different European countries found that the risk of stroke increased by 9% per year in men and 10% per year in women.[33]

There are well-documented racial disparities in stroke.[34] Blacks are at twice the risk of incident stroke when compared with their white counterparts and have higher mortality associated with stroke.[34–43] Hispanic/Latino Americans also have an increased risk of stroke in some cohorts. The disparity in stroke incidence is particularly prominent among younger black adults in whom the risk for subarachnoid hemorrhage and intracerebral hemorrhage is substantially higher than age-matched whites.[37,39] Furthermore, American Indians have an increased incidence of stroke compared with non-Hispanic whites.[44] As illustrated recently by the REGARDS study (REasons for Geographic And Racial Differences in Stroke), one reason for the racial disparities could be the higher prevalence of stroke risk factors, such as hypertension, obesity, and diabetes mellitus, among blacks.[45–51] However, these additional risk factors do not completely explain the increased risk seen in these racial-ethnic groups.[52] Black race has been identified as a factor in the relationship between rurality and stroke risk,[52,53] but this could be attributed to issues with access to health care.[34,54,55] Other factors that may influence racial-ethnic differences in stroke risk include other social determinants of disease, language, and nativity.[56–59] The racial disparity in stroke mortality is being driven by the racial disparities in stroke incidence, highlighting the importance of stroke prevention interventions aimed at minority groups.[60] Interestingly, the association seen between black race and stroke, although strong for incident stroke, does not remain for recurrent stroke.[61] This could be because of stroke risk factors being addressed on discharge from the primary stroke event.

Genetic factors are also known to be nonmodifiable risk factors for stroke with parental history and family history

increasing the risk of stroke.[62–64] As is the case with other risk factors for stroke, the genetic risks of stroke vary by age, sex and race. Genetic risk factors and heritability will be more thoroughly discussed in the section on genetics below.

Modifiable Risk Factors

The modifiable risk factors are of utmost importance, as intervention strategies aimed at reducing these factors can subsequently reduce the risk of stroke. Early identification and modification of risk factors is imperative.[27] Modifiable risk factors can be further divided into medical conditions and behavioral risk factors. The role of many traditional risk factors in causing stroke, such as hypertension, diabetes mellitus, hyperlipidemia, and smoking are well established. The investigation of novel or emerging risk factors remains an area of active research.

Hypertension

Hypertension is the most important modifiable risk factor for stroke, with a strong, direct, linear, and continuous relationship between blood pressure and stroke risk.[65,66] In INTERSTROKE, hypertension was by far the most important stroke risk factor: using a definition of hypertension that included both a history of hypertension and a blood pressure measurement of 160/90 mm Hg, the population attributable risk, or proportion of strokes in the population attributable to hypertension, was 54%.[24] Although this was a case–control study, and thus measurements of blood pressure were likely confounded by recent stroke, the results still imply a major effect of blood pressure on stroke risk and are consistent with other studies. The effect of blood pressure was also greater for hemorrhagic than ischemic stroke.

Even among those who are not defined as hypertensive, the higher the blood pressure, the higher the risk of stroke.[54] Blood pressure, regardless of hypertension status, rises with increasing age, thereby increasing the lifetime risk of developing hypertension.[67,68] Of people who are ≥65 years of age, more than two thirds are hypertensive.[65] Hypertension control has improved because of heightened awareness and treatment options, with ≈50% controlled in 2008, and the prevalence of hypertension in the United States has remained at 29%.[69,70] In addition to medication for hypertension control, hypertensive patients are encouraged to engage in behavioral lifestyle changes, such as diet change and increase physical activity, to reduce the impact of hypertension.[65] Treatment of hypertension, whether through medication or lifestyle changes, remains one of the most effective strategies in reducing stroke risk, but hypertension remains undertreated in the community.

Recent studies have suggested that intraindividual variability in blood pressure measurements, or differences in blood pressure measures taken at different points in time within an individual, are associated with stroke risk beyond the risk because of elevated mean blood pressure alone. For example, British investigators, using data from 4 randomized controlled trials of patients with hypertension, previous stroke, or previous transient ischemic attack, found that variability in 2 to 10 blood pressure measures over ≈2 years is a risk factor for stroke, independent of mean blood pressure.[71] The measure of blood pressure variability may serve as an indication of the absence of cardiovascular homeostasis within the individual. These results suggest that blood pressure agents that reduce variability and not just mean blood pressure, such as calcium channel blockers, may have greater benefits. Other studies have not confirmed this association, however. In the CHS (Cardiovascular Health Study), for example, using a model that also accounted for intraindividual change in blood pressure over time, blood pressure variability was not associated with stroke risk, although it was associated with cardiac events and all-cause mortality.[72]

Diabetes Mellitus

Diabetes mellitus is an independent risk factor for stroke with a 2-fold increased risk in stroke for diabetic patients, and stroke accounts for ≈20% of deaths in diabetics. Prediabetics are also at increased risk of stroke.[73,74] Approximately 8% of Americans have diabetes mellitus, with nearly half of Americans ≥65 years of age prediabetic.[75] The duration of diabetes mellitus is also associated with increased stroke risk; in the Northern Manhattan Study, duration of diabetes mellitus was associated with ischemic stroke (adjusted hazard ratio [HR]=1.03 per year with diabetes mellitus; 95% confidence interval [CI]=1.02–1.04). Compared with nondiabetic participants, those with diabetes mellitus for 0 to 5 years (adjusted HR, 1.7; 95% CI, 1.1–2.7) and 5 to 10 years (adjusted HR, 1.8; 95% CI, 1.1–3.0) were at increased risk, and the risk for those with diabetes mellitus for ≥10 years increased markedly (adjusted HR, 3.2; 95% CI, 2.4–4.5).[73] Diabetic patients who have a stroke tend to be younger, are more likely to be black, and have a higher prevalence of other stroke risk factors. The increase in diabetes mellitus may explain some of the increase in the risk of stroke in younger populations.[76] The use of combined behavioral modification and medical therapy in diabetics has been shown to reduce the risk of stroke.[77,78] Interestingly, glycemic control alone in diabetics does not confer the reduced risk that intensive interventions with behavior modification plus medical intervention confer.[79,80]

AF and Atrial Cardiopathy

AF has long been recognized to be a major risk factor for stroke, and this has only increased with the aging of the US population. Incident stroke related to AF has nearly tripled in the past 3 decades.[81] The association between AF and stroke has long been assumed to be because of stasis of blood in the fibrillating left atrium causing thrombus formation and embolization to the brain. Recent data, however, challenge this assumption. First, there is a poor temporal relationship between AF, which may come and go at irregular and infrequent intervals, and timing of a stroke; one-third of patients do not show evidence of AF until after a stroke despite months of preceding continuous heart-rhythm monitoring.[82] Second, other paroxysmal supraventricular tachycardias, without fibrillation, have also been associated with stroke risk; in an analysis of claims-based data, paroxysmal supraventricular tachycardias was associated with a doubling in stroke risk, even after adjusting for AF.[83] Third, patients with genetic mutations associated with AF (such as in the gene for Natriuretic Peptide Precursor A) can have strokes even before the onset of AF.[84] Furthermore, in some settings, the atrium may be in electromechanical disassociation, such that there is fibrillation of the atrium even when the ECG shows normal sinus rhythm; thus, the electrocardiogram may not be a perfect indicator of the presence of normal atrial contractility.

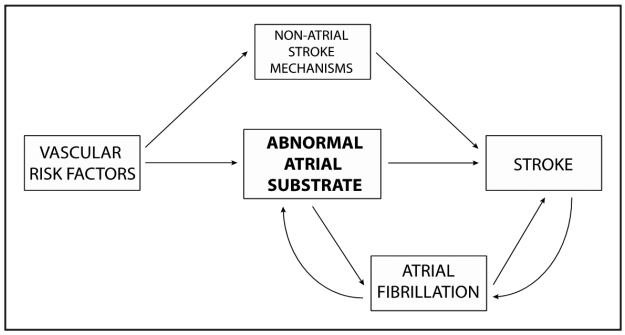

Figure 1. Atrial substrate model of thromboembolic stroke. The model emphasizes the importance of systemic and atrial substrate in explaining the relationship between atrial fibrillation (AF) and stroke. Systemic vascular risk factors produce an abnormal atrial tissue substrate that in turn causes both AF and thromboembolism. Once AF develops, the dysrhythmia causes atrial structural remodeling, worsening atrial tissue substrate and atrial dysfunction and thereby further increasing the risk of thromboembolism. Concurrently, the systemic risk factors driving this process separately increase stroke risk by driving specific mechanisms of stroke outside the atrium, such as large artery atherosclerosis, ventricular systolic dysfunction with reduced ejection fraction, and in situ cerebral small vessel occlusion. Once stroke occurs, changes in autonomic tone and a poststroke inflammatory state may transiently increase the risk of AF (Reprinted from Kamel et al[89] with permission of the publisher. Copyright ©2016, American Heart Association, Inc).

Finally, other studies have found associations between markers of atrial dysfunction and embolic stroke even in patients without diagnosed AF, suggesting that left atrial thromboembolism can occur in the absence of AF.[85] Elevated N-terminal probrain natriuretic protein is associated with a doubling of stroke risk in observational cohorts. Abnormalities of the electrocardiographic P wave on lead V1, which reflects left atrial contractility, is also associated with stroke risk independently of AF.[86–88]

These findings suggest the need for an updated model that emphasizes the atrial substrate as well as rhythm.[89] Aging and vascular risk factors, according to this model, lead to an abnormal atrial tissue substrate, or atrial cardiopathy, that causes both AF and thromboembolism (Figure 1). AF, according to this model, may be just another marker of stroke risk associated with left atrial dysfunction.[89] Once stroke occurs, the risk of subsequent AF may be further transiently increased by autonomic derangements and a poststroke inflammatory state.[89] There is even evidence from tertiary analyses of randomized trials that anticoagulation may be of benefit for ischemic stroke patients with evidence of elevations in N-terminal probrain natriuretic protein who are not known to have AF.[90] Further trials are planned to test this concept of atrial cardiopathy.

Dyslipidemia

The relationship between dyslipidemia and stroke risk is complex, with an increased risk for ischemic stroke with increased total cholesterol and a decreased risk for ischemic stroke with elevated high-density lipoprotein cholesterol.[91–97] Evidence for the influence of triglycerides on stroke risk is conflicting. Risk seems to depend on stroke subtype, moreover, with a stronger association of cholesterol levels with large artery ischemic stroke than other ischemic stroke subtypes.[10] Total cholesterol, meanwhile, is inversely associated with hemorrhagic stroke, with hemorrhagic stroke risk increasing as total cholesterol decreases.[98–100] The data on lipids and intracerebral hemorrhage are further complicated by the fact that some observational studies have found no increased risk of intracerebral hemorrhage with statin therapy, whereas some treatment trials have.[101] Although these studies show potentially inconsistent and opposite findings between dyslipidemia and risk of ischemic and hemorrhagic stroke, in the general patient population, the use of statins seems to reduce the risk of total and ischemic stroke with no definite increase in the risk of hemorrhagic stroke.[102,103] The relatively large reduction in risk of ischemic stroke and other ischemic events with statins, moreover, outweighs any small increased risk of hemorrhage in most patients. Among some patients with stroke, however, and particularly those with previous hemorrhage, small vessel disease, or cerebral amyloid angiopathy, statins may be associated with an increased risk of intracerebral hemorrhage.[104,105]

Sedentary Behavior, Diet/Nutrition, Obesity, and Metabolic Syndrome

Physical inactivity is associated with many poor health effects, including stroke. People who are physically active have a lower risk of stroke and stroke mortality than those who are inactive.[106] The relationship between physical activity and stroke may be because of the associated decrease in blood pressure, reduction in diabetes mellitus, and reduction in excess body weight.[107]

Diet influences the risk of stroke and the risk of other stroke risk factors, such as diabetes mellitus, hypertension, and dyslipidemia.[108,109] There are several limitations to diet studies including recall bias and measurement error, but some specific components of diet and nutrition are well-established risk factors for stroke. Salt intake, for example, is associated with an increased risk of hypertension and stroke,[110–114] whereas increased potassium intake is associated with a decreased stroke risk.[115–118] A Mediterranean diet, or a diet high in fruits and vegetables, reduces the risk of stroke.[119,120]

Body weight and obesity are risk factors for stroke, although the specific ways in which they increase stroke risk continue to be debated. Obesity is related to stroke risk factors such as hypertension and diabetes mellitus.[121,122] A recent large meta-analysis, including 1.8 million participants from 97 cohort studies, found that 76% of the effect of body mass index (a common measure of obesity) on stroke risk was mediated by blood pressure, cholesterol, and glucose levels. Blood pressure alone accounted for 65% of the risk because of weight. The importance of distinguishing between increased abdominal adiposity, as measured by the waist-to-hip ratio, as the major contributor to risk, rather than overall increased weight, as indicated by the body mass index, is increasingly recognized.[123] In INTERSTROKE, for example, waist-to-hip ratio was associated with stroke risk, although body mass index was not.[24]

The concept of metabolic syndrome incorporates obesity, dyslipidemia, prehypertension, and prediabetes. There is evidence that a sedentary lifestyle contributes to the metabolic syndrome. Metabolic syndrome is prevalent in the United States with ≈34% of the population meeting the criteria, and although it is associated with a clear increase in risk of cardiovascular disease, the relationship between metabolic syndrome and stroke seems to be increased but not as well described.[124] The risk of ischemic stroke from metabolic syndrome seems to be double, with the

risk increasing as the number of components in the syndrome increase.[125,126] Considering that the components of the metabolic syndrome are related to stroke individually, the combination of these risk factors should be related to increased stroke risk.[126]

Alcohol Consumption, Substance Abuse, and Smoking

The relationship of alcohol consumption to stroke risk depends on stroke type. There is evidence of a J-shaped relationship between alcohol consumption and risk of ischemic stroke, with light-to-moderate alcohol consumption (≤2 drinks per day in men and ≤1 drink per day in women) being protective against stroke and heavy drinking associated with an increased risk of ischemic stroke.[127–132] Alcohol consumption has a more direct linear relationship with hemorrhagic stroke, such that consumption of even small amounts of alcohol seem to increase risk of hemorrhage. Heavy alcohol consumption is linked to hypertension, as well as poor blood pressure control in hypertensive patients who consume alcohol.[133–139]

Abuse of illicit substances, including cocaine, heroin, amphetamines, and ecstasy, is associated with an increased risk of ischemic and hemorrhagic subtypes of strokes.[140–142] Cigarette smoking remains a major risk factor for stroke, nearly doubling the risk with a dose–response relationship between pack-years and stroke risk.[15,143] It is estimated that smoking contributes to ≈15% of all stroke deaths per year.[144] Smoking cessation rapidly reduces the risk of stroke, with excess risk nearly disappearing 2 to 4 years after smoking cessation.[145–148] Secondhand smoke has been identified as an independent risk factor for stroke in the REGARDS cohort, with the risk of stroke increasing 30% after accounting for other stroke risk factors, for those who have been exposed to secondhand smoke versus those who have not been exposed.[149]

Inflammation and Infection

Levels of inflammatory biomarkers have been associated with increased risk of stroke, just as they have been associated with risk of other cardiovascular diseases and all-cause mortality. C-reactive protein, measured using a high-sensitivity assay (hsCRP), is one marker that has been particularly well studied. hsCRP has become the inflammatory marker of choice in the clinical setting because of its consistent association with cardiovascular events, long half-life, and stability when stored frozen for prolonged periods of time. A meta-analysis of 54 prospective cohort studies, including a total of >160 309 individuals, found a modest association between hsCRP levels and ischemic stroke (relative risk per SD increase in the log CRP concentration 1.27; 95% CI, 1.15–1.40).[150] Similar results were obtained in a meta-analysis of 12 observational studies of hsCRP and stroke risk.[151] Genetic studies, however, have not confirmed a causal association between hsCRP and ischemic stroke risk. In one study, single-nucleotide polymorphisms (SNPs) in the *CRP* gene were associated with elevations in hsCRP levels, but these polymorphisms were not associated with an increase in stroke risk.[152]

The reasons for the association of inflammation with stroke risk remain uncertain. Because atherosclerosis is recognized to have a highly inflammatory character, with plaque containing high levels of activated macrophages and inflammatory mediators, it may be that elevated levels of inflammatory markers reflect a high burden of atherosclerosis, or perhaps a highly active form of atherosclerosis. Thus, elevated inflammatory markers may simply serve as a marker of inflammatory burden from these plaques, making elevations in hsCRP a kind of epiphenomenon of vascular disease burden because of other conventional risk factors. Observational studies have generally tried to eliminate confounding by these other risk factors through the use of statistical adjustment, but the possibility of residual confounding, because of the inability to completely measure all such risk factors or their severity, remains. The genetic studies that have failed to confirm that *CRP* gene mutations cause an increase in risk would be consistent with possibility of residual confounding. There is, however, some evidence that CRP, an acute phase protein, may directly contribute to risk of stroke. Monomeric CRP, for example, interacts with other immune mediators to activate platelets and complement proteins.[153] Functionally, each CRP monomeric subunit has a recognition face and an effector face. The recognition face can bind to a diverse set of structural groups, including phosphocholine residues in the C-polysaccharide fraction of *Streptococcus pneumoniae* and apoptotic cells, nuclear autoantigens, and lipoproteins.[154] Binding of the recognition face induces a conformational change that allows the effector face to activate the complement pathway by binding to C1q and Fc receptors, some of which are found on endothelial cells.[155] Through this and other mechanisms, CRP, cytokines, and other inflammatory mediators may directly contribute to stroke risk.[156]

One other way in which inflammation may contribute to stroke risk is through infection. Recent data suggest that chronic exposure to common infections is a potential risk factor for stroke and that acute infections may also act as triggers for stroke. In an analysis from NOMAS (Northern Manhattan Study), for example, a composite measure of chronic infection assessed by serologies against several common bacterial and viral infections (*Chlamydia pneumoniae*, *Helicobacter pylori*, herpes simplex virus 1 and 2, and cytomegalovirus), weighted for the effect of each individual infection on stroke risk, was associated with increased long-term stroke risk.[157] Although each individual infection was positively, although not significantly, associated with stroke risk after adjusting for other risk factors, the weighted infectious burden index was associated with an increased risk of all strokes (adjusted HR per SD 1.39; 95% CI, 1.02–1.90) after adjusting for demographics and risk factors. Results were similar after adjusting for inflammatory biomarkers. This same measure of infectious burden was also associated with carotid plaque thickness and ulceration and with cognitive status and decline.[158–160]

Recent studies have also found that HIV infection is associated with a modest increased risk of both ischemic and hemorrhagic stroke, even in the era of highly active antiretroviral therapy.[161,162] Mechanisms for this increase in risk remain uncertain, but the risk seems to be higher among those with evidence of greater immunosuppression, such as lower (<200 cells/mm^3) CD4+ T-cell counts and higher number of HIV-1 RNA copies. HIV may directly injure the arterial wall. There is evidence, for example, that outward arterial remodeling, or relative thinning of the arterial wall, occurs more commonly in patients with HIV who have protracted infections and greater viral load before death.[163] Other studies do not suggest a direct effect of immunosuppression on vascular risk, although the risk may differ between cardiac and cerebrovascular events.[164] Other explanations include a higher burden of

cardiovascular risk factors among those with HIV infection and adverse metabolic effects of the antiretroviral drugs themselves.[165]

Stroke Triggers

A new area of investigation in stroke epidemiology involves the determination of stroke triggers. Addressing this issue reflects an increasing recognition that although we have a good understanding of the major stroke risk factors (the why me? question), our understanding of why strokes occur at a particular point in time (the why now? question) remains rudimentary.[26] Several potential stroke triggers have been identified, but recent infection may be one that best lends itself to modification. Evidence suggests, for instance, that acute infections may serve as a short-term trigger for stroke in patients. In a case-crossover analysis from the CHS (n=5888), for example, a recent hospitalization for infection was associated with an increased risk of stroke.[166] In this type of analysis, each individual serves as his own control, thereby limiting confounding factors and enabling the discovery of time-dependent associations. Among 669 participants who experienced a stroke, the risk of stroke was increased after hospitalization for infection within the previous 90 days (odds ratio: 3.4; 95% CI, 1.8–6.5). The risk increased as the time interval after hospitalization decreased: odds ratio 7.3 (95% CI, 1.9–40.9) for a time window of 30 days and odds ratio 8.0 (95% CI, 1.7–77.3) for a window of 14 days. In confirmatory survival analyses, hospitalization for an infection was associated with an increased risk of incident ischemic stroke in the following 30 days (adjusted HR, 2.5; 95% CI, 1.4–4.5). The finding that risk increased as shorter time windows were explored indicates that the triggering effects of the hospitalization with infection diminish over time. Other evidence suggests that more minor respiratory and urinary tract infections are associated with increased stroke risk and that vaccinations may help prevent stroke. A Cochrane review of 8 randomized controlled trials with a total of 12 029 participants provides evidence that influenza vaccination decreased cardiovascular outcomes, and a case series study that used a within-person method of comparison found that the risk of stroke was increased after respiratory tract infection but was reduced after vaccination against influenza, pneumococcal infection, and tetanus.[167,168] On the basis of this evidence, annual vaccination against influenza may affect stroke rates and could be given to individuals who are at moderate-to-high risk of stroke, as emphasized in recent guidelines.

Recent evidence also suggests that severe sepsis is associated with new-onset AF, thereby increasing risk of stroke.[169] Research using administrative data sets has identified sepsis as a risk factor for stroke, although there may be a low absolute risk of stroke after sepsis and those who are at risk seem to remain at risk for ≤1 year after their sepsis event. It is, therefore, plausible that acute infectious events lead to a prolonged proinflammatory state that can contribute to stroke risk. This phenomenon has been found for the risk of heart failure after pneumonia, for example, and it may also apply to stroke risk.[170,171] On the contrary, a population-based cohort study from Denmark showed that ≈80% of cardiovascular events after exposure to bacteremia occurred during the index hospitalization, with the risk of stroke highest in the first 3 to 15 days post-infection.[166,172,173]

The identification of a short-term state of elevated stroke risk after acute infection could have direct therapeutic implications, as well. For example, increased doses of antiplatelet agents or statins may be warranted during times of fever or infection. In addition, the period during and soon after hospitalization for infection could constitute a treatable moment, during which patients can be evaluated for cardiovascular risk and standard preventive strategies instituted.

Other potential triggers for stroke include air pollution. Air pollution, a largely ubiquitous environmental exposure, is quickly becoming a widespread public health hazard, particularly in urban areas. As of 2011, 124 million people in the United States were living in areas that did not meet the United States Environmental Protection Agency National Ambient Air Quality Standards. Air pollution has been identified as a novel risk factor for stroke. Long-term exposure to pollution has been associated with increased risk of stroke.[174–176] Evidence of the relationship between risk of ischemic stroke hospitalization and mortality and short-term peaks of pollutant levels, primarily particulate matter <2.5 μm in diameter ($PM_{2.5}$), have been seen primarily in case-crossover and time-series studies.[177] A large case crossover study of Medicare beneficiaries in 9 US cities also found that an interquartile range increase in PM_{10} was associated with a 1.03% increase in same-day stroke admissions, with similar results seen with CO, NO_2, and SO_2.[178] Long-term exposure over time has generally been shown to increase the risk of a cerebrovascular event,[179–182] although several studies have also reported null associations.[183] Meta-analyses have found a consistent positive association between air pollution and stroke; an analysis of 20 studies identified that exposure to a 5-μg/m^3 increase in $PM_{2.5}$ increases the risk of a stroke by 6% and stroke mortality by 12.5%.[184]

Genetic Risk Factors for Stroke

Hereditary factors contribute to stroke risk, although teasing apart risk because of genetic mutations and because of shared familial exposures remains challenging. The task has been complicated by the heterogeneity of stroke, the multitude of conventional risk factors that cause stroke, and the variability among populations and studies. Genetic variability may, however, contribute to stroke risk through several potential mechanisms (Table 3). First, specific rare single gene disorders may contribute to individual familial syndromes for which stroke is the primary or unique manifestation (eg, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy). Second, single gene disorders may cause a multisystem disorder of which stroke is just one manifestation (eg, sickle cell anemia). Third, some common variants of genetic polymorphisms have been associated with stroke risk, although the individual contribution of such polymorphisms is regarded as modest (eg, variants in 9p21).[185] Fourth, genetic causes of conventional stroke risk factors, such as AF, diabetes mellitus, and hypertension, are also, not surprisingly, associated with risk of stroke.[186] Emerging evidence suggests that genetic studies could help to distinguish stroke subtypes and even contribute to patient management. For example, there is an association between gene variations that confer an increased risk of AF and ischemic stroke. This raises the possibility that genetic tests could help to make the diagnosis of strokes likely to be because of AF.

Table 3. Selected Genetic Causes of Stroke

Disease	Mode of Inheritance	Gene/Protein	Mechanism of Stroke	Common Clinical Manifestations
Single gene disorders that primarily cause stroke				
Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy	Autosomal dominant	*NOTCH3*/NOTCH3	Small vessel disease	Ischemic stroke, leukoencephalopathy, migraine, psychiatric manifestations, and dementia
Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy	Autosomal recessive	*HTRA1*/ HtrA serine peptidase-1	Small vessel disease	Ischemic stroke, leukoencephalopathy, premature baldness, and spondylosis
Familial amyloid angiopathy	Autosomal dominant	*APP*/β-amyloid precursor protein	Rupture of small cortical vessels	Lobar hemorrhage, microbleeds, leukoencephalopathy, dementia, and amyloid spells
Collagen 4 (*COL4A1*) mutations	Autosomal dominant	*Col4A1*/α1 chain of collagen type 4	Rupture of cortical and subcortical vessels	Superficial and deep hemorrhages, intracranial aneurysms, hematuria, and cystic kidney disease
Genetic disorders that include stroke as manifestation				
Ehlers–Danlos type 4	Autosomal dominant	*Col3A1*/type III procollagen	Arterial dissection	Aortic, renal, splenic, iliac dissection/rupture; aneurysms/pseudoaneurysms; visceral and muscular rupture; and uterine rupture during pregnancy
Fabry disease	X-linked	*GAL*/α-galactosidase A	Large and small artery disease	Ischemic stroke and vasculopathy, angiokeratomas, corneal opacities and cataracts, neuropathy (acroparesthesias, hypohidrosis), and renal failure
Marfan syndrome	Autosomal dominant	*FBN1*/fibrillin 1	Arterial dissection and cardiac embolism	Ischemic stroke, arterial dissection, scoliosis, pectus excavatum, aortic dilatation, valvular dysfunction/heart failure, and ectopia lentis
Mitochondrial encephalopathy with lactic acid and stroke-like episodes	Maternal	Mitochondrial DNA (*MT-TL1)*/mitochondrially encoded tRNA leucine 1 (UUA/G); others	Energy failure and metabolic stroke	Ischemic stroke that does not observe vascular boundaries, short stature, developmental delay, seizures, vision loss, myopathy, and diabetes mellitus
Sickle cell disease	Autosomal recessive	*HBB*/β-globin (hemoglobin subunit)	Large and small vessel disease and moyamoya syndrome	Ischemic stroke, painful crises, vascular crises, and bacterial infections
Smooth muscle α-actin mutation–associated disorders	Autosomal dominant	*ACTA2*/smooth muscle α-actin	Moyamoya syndrome	Ischemic stroke, coronary artery disease, thoracic aortic aneurysms, and moyamoya syndrome
Common genetic variants				
TSPAN2	Common variant	*TSPAN2*/tetraspanin-2	Vascular development and atherosclerosis	Large vessel ischemic stroke
FOXF2	Common variant	*FOXF2*/forkhead transcription factor	Small vessel disease; abnormalities of smooth muscle cell and pericyte coverage of cerebral vessels	All stroke, small vessel stroke, and premature and extensive white matter disease
ABO	Common and rare variants	*ABO*/blood group protein	Thrombosis	Thrombosis and ischemic stroke
HDAC9	Common and rare variants	*HDAC9*/histone deacetylase	Atherosclerosis	Large vessel ischemic stroke
PITX2	Common and rare variants	*PITX2*	Sinoatrial node development and regulation of ion channels; modulation of cardiac conduction; and atrial fibrillation	Cardioembolic ischemic stroke and atrial fibrillation
ZFHX3	Common and rare variants	*ZFHX3*	Atrial fibrillation	Cardioembolic ischemic stroke and atrial fibrillation

Currently, heredity is generally considered a nonmodifiable risk factor, although genetic therapies may change this in the future. Some genetic factors may even be modifiable, if not curable, already; for example, those with sickle cell anemia can be treated with exchange transfusion to reduce stroke risk. Genetic factors may also be modifiable because environmental factors may also interact with genetic mutations (ie, gene–environment interactions); thus, those with a predisposition to diabetes mellitus or hypertension could engage in dietary and other lifestyle modifications to reduce their risk of disease.

Heritability of Stroke

Recent estimates of heritability using genome-wide SNP data show similar heritability for cardioembolic (32.6%) and large vessel disease (40.3%) but lower for small vessel disease (16.1%).[187] Family history of stroke increases stroke risk by 30%.[188] Monozygotic twins are at 1.65-fold higher risk of stroke than dizygotic twins.[188] Age, sex, and stroke subtype further affect stroke heritability.[63,64] Younger patients are more likely to have a first-degree relative with stroke,[63] and women with stroke are more likely to have a parental history of stroke than men.[64] Magnetic resonance imaging measures of small vessel ischemic disease, however, have concordance rates of 0.61 for monozygotic twins and 0.38 for dizygotic twins, suggesting a genetic susceptibility to small vessel ischemic stroke.[189]

Single Gene Disorders With Stroke as a Primary Manifestation

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy is a small vessel vasculopathy that affects skin and brain, although its clinical manifestations are restricted to the central nervous system. The pathology includes degeneration of the media of small vessels and a prominent and progressive leukoencephalopathy. Clinically, patients present with migraine-like headaches, psychiatric complaints including depression and psychosis, and recurrent strokes, often leading to pseudobulbar palsy and subcortical dementia. Characteristic imaging findings include white matter lesions in the external capsule and anterior temporal poles; the imaging findings can usually be distinguished from those of more typical white matter changes associated with hypertension and aging.

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy is associated with mutations of the *Notch3* gene, located on chromosome 19q12.[190] Most of these are missense mutations altering the number of cysteine residues expressed in an extracellular receptor domain.[191] Although *Notch3* is widely expressed in the body and plays an important role in development, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy only affects the nervous system clinically, for unknown reasons. Although the defective receptors usually do not interfere with phenotypic signaling, they have been shown to accumulate in the basal lamina of the small arteries.[192] Skin biopsy revealing granular osmiophilic material can be pathognomonic for the diagnosis, sometimes detecting the disease in patients who have relatively minor findings on imaging studies and negative genetic test results for the most common mutations.[193]

Other rare single gene disorders that cause stroke include cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy,[194] caused by mutations in the HtrA serine peptidase-1 gene[195]; arterial tortuosity syndrome, caused by mutations in the *SLC2A10* gene encoding a glucose transporter, GLUT10[196,197]; and familial cerebral amyloid angiopathy, caused by mutations affecting cystatin C.[198]

Single Gene Multisystem Disorders With Stroke as an Important Manifestation

Cerebrovascular complications are well recognized in sickle cell anemia and result from polymerized red blood cells at low oxygen tensions, leading to small vessel occlusion and sickle-related arterial disease (moyamoya syndrome). Sickle cell anemia is seen in ≈6% of children with stroke, but 25% of individuals with sickle cell anemia will experience a stroke by 45 years of age; the highest incidence for ischemic stroke is at 2 to 5 years.[199] Untreated, the risk of a recurrent stroke is as high as 90%.[200] Multiple silent infarcts may be more common than clinical infarcts, and they can impair cognitive processing and school performance.[201]

Fabry disease is an X-linked deficiency in α-galactosidase A, a lysosomal enzyme, caused by both missense and nonsense mutations in the *GLA* gene. Loss of function of α-galactosidase A leads to accumulation of globotriaosylceramide in cells throughout the body, including the vascular endothelium. Fabry disease is the second most common lysosomal storage disorder. Cerebrovascular involvement typically occurs in both large and small vessels, especially affecting the posterior circulation, and can occur in young stroke patients.[202] Mechanisms of stroke include cardioembolism from cardiac involvement, large artery thromboembolism from dolichoectasia and tortuosity of large vessels, and occlusive disease of small vessels because of glycolipid accumulation in the endothelium and vascular smooth muscle cells. In the Fabry Outcome Survey, the frequency of stroke among males aged 25 to 44 years was ≈12 times the expected frequency in the general population.[203] Enzyme replacement therapy can modify the natural course of this disease.

The syndrome of mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes is a mitochondrial disorder caused by mutations in mitochondrial DNA, leading to respiratory chain failure and reduced energy production. The most commonly reported genetic defect is an A3243G substitution within a tRNA gene, present in 80% of cases.[204] The failure of energy production leads to dysfunction and injury of brain tissues from a metabolic cause rather than from an occlusive vascular process; thus, brain lesions seen in syndrome of mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes typically do not observe classic vascular territories. Patients present with attacks of encephalopathy and focal neurological dysfunction and may also have migraine headaches, nausea, and vomiting. Episodes may be precipitated by fever, which increases metabolic demands. Multiple organ systems can be affected, leading to short stature, hearing loss, developmental delay, diabetes mellitus, and other problems. There is significant heterogeneity in the phenotype of family members, because of heteroplasmy, or the variable expression of mutated mitochondrial DNA within different tissues. Genetic

disorders of collagen can also affect multiple tissues, including the cerebral vasculature. The Ehlers–Danlos spectrum of disorders represents a group of inherited disorders characterized by connective tissue abnormalities and vascular fragility. The most worrisome is Ehlers–Danlos type 4, which is associated with arterial dissections, cerebral aneurysms, and stroke. Patients may have complications of other organs as well, however, including uterine rupture during pregnancy. Type 4 EDS (Ehlers–Danlos syndrome) is because of mutations of collagen type-III (*COL3A1*). Mutations in the gene encoding the α-1 chain of type 4 collagen (*COL4A1*) can also result in impaired vessel-wall integrity. Cerebrovascular manifestations include small vessel steno-occlusive disease, aneurysms, and dolichoectasia, with resulting ischemia, intracranial hemorrhage, leukoencephalopathy, and retinal arteriolar tortuosity.[205] An increased tendency for cerebral hemorrhage can occur with head trauma, participation in sports, and anticoagulant use.[206]

Other hereditary connective tissue diseases, such as Marfan syndrome and *ACTA2*-associated vasculopathy, are similarly associated with vascular fragility and can lead to arterial dissections. Mutations in the *ACTA2* gene, encoding actin α2, an isoform of actin found in vascular smooth muscle, leads to actin polymerization and smooth muscle cell proliferation. Phenotypically, individuals have evidence of smooth muscle dysfunction throughout the body, including fixed dilated pupils, hypotonic bladder, gut malrotation and hypoperistalsis, and pulmonary hypertension.[207] There is a risk for aortic, cervical, and intracranial arterial dissection.[208] They are also at risk for small vessel disease, moyamoya disease, and aneurysmal large vessel disease.[209]

Genes Associated With Common Ischemic Stroke and Stroke Risk Factors

There is emerging evidence that genetics contribute to the risk of common ischemic stroke. Several genetic variants have been identified, although the magnitude of effect of each variant is regarded as small. Genetic mutations in genes related to coagulation have been extensively investigated. MetaStroke is one of the largest genetic collaborations in ischemic stroke and includes 15 European, North American, and Australian case–control stroke cohorts. Participants are subtyped by ischemic stroke cause according to a modified TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification system. After detection of potential disease-causing mutations in initial somewhat smaller European cohorts, MetaStroke confirmed an association of stroke with gene variants in the blood type gene *ABO* (rs505922), which is associated with levels of the coagulation proteins von Willebrand factor and factor 8; the associations were present for large vessel and cardioembolic stroke subtypes but not for small vessel disease.[210]

Other subtype-specific genetic variants have been identified. Icelandic investigators first reported an association between genetic variants conferring an increased risk of AF and ischemic stroke, especially those thought to be cardioembolic. Interestingly, there was also a significant association in the events classified as noncardiogenic, perhaps because of underdiagnosis of AF. In a subsequent collaborative analysis among MetaStroke and several other cohorts, the *PITX2* and *ZFHX3* genes were also associated with cardioembolic stroke, and the *HDAC9* gene and 9p21 locus were associated with large vessel stroke.[186] In a separate genome-wide association study by the National Institute of Neurological Disorders and Stroke-Stroke Genetics Network project, a locus near the *TSPAN2* gene on chromosome 1 was also associated with large artery stroke.[211] These findings provide insight into the pathophysiology of stroke: *PITX2*, for example, encodes a transcriptional activator that is involved in the development of the sinoatrial node and in regulation of ion channels that modulate cardiac conduction; *ZFHX3* also encodes a transcription factor. The *HDAC9* gene encodes histone deacetylase, although its mechanism for causing atherosclerotic stroke remains uncertain. *TSPAN2* encodes tetraspanin-2, a member of a superfamily of transmembrane proteins that regulate signal transduction and play a role in cell development and growth; *TSPAN2* is expressed in arterial tissue and blood cells, and *TSPAN2* knockout mice have activation of microglia and astrocytes.

A separate meta-analysis of genome-wide association studies, including 18 population-based cohorts with almost 85 000 participants (n=4348 strokes), identified a novel locus on chromosome 6p25 (rs12204590), near the forkhead transcription factor *FOXF2* gene, that was associated with both the risk of all strokes and with the white matter hyperintensity burden seen on magnetic resonance imaging scans, a marker of small vessel disease, in a subcohort (n=21 079 individuals).[212] Deletion of *FOXF2* in young patients was associated with extensive white matter disease, and mutations in other forkhead transcription factors (*FOXC1*) have been associated with white matter disease syndromes.[213] Functional experiments in mice confirmed that deletion of Foxf2 is associated with cerebral infarction, reactive gliosis, and microhemorrhages. The zebrafish orthologs of FOXF2, moreover, are expressed in brain pericytes, and zebrafish without this gene have abnormalities of smooth muscle cell and pericyte coverage of cerebral vessels. These data suggest that FOXF2, a transcription factor that plays a role in cerebral vascular wall morphogenesis and function, may be a contributor to small vessel disease in humans, as well.

Much of the research thus far has focused on common genetic variants. More recent research, however, has confirmed that low-frequency genetic variants (ie, allele frequency <5%) may contribute to risk of large vessel and small vessel stroke.[214] *GUCY1A3*, for example, a gene that has been associated with early myocardial infarction, was associated with large vessel stroke and had an allele frequency in the lead SNP of 1.5%. This gene encodes the α1 subunit of soluble guanylyl cyclase, which plays a role both in NO-induced vasodilation and platelet inhibition.[215] Another gene, *GCH1*, also with an allele frequency of only 1.5%, was associated with small vessel stroke; *GCH1* encodes GTP cyclohydrolase 1, which plays a role in endothelial NO synthase. Thus, rare variants may account for some of the unexplained heritability in stroke risk.

Variation in chromosome 9p21 has been strongly associated with coronary artery disease and myocardial infarction in multiple cohorts.[216] Fifteen SNPs in that region were evaluated within large samples from South Germany, the United Kingdom, Europe, and North America, and 6 were associated with atherosclerotic or large vessel stroke in adjusted analyses. A population attributable risk of 20% for large vessel stroke because of SNPs at 9p21 was estimated from the analysis.[217]

Stroke Prevention

The aim of stroke prevention is to decrease stroke incidence through targeted modification of a single risk factor, or a cluster of multiple risk factors, used on a population, community, or individual level. In some cases, however, as with the use of antiplatelets, the goal may be to use an intervention that is known to reduce ischemic stroke risk among those who are deemed to be at elevated risk, rather than as a treatment for a specific risk factor. There are 3 broad levels of stroke prevention: (1) primordial prevention is the most generalizable and broadly deals with healthy living measures that, when applied on a group level, aim to decrease the population incidence of physiological stroke risk factors; (2) primary prevention, which aims to improve the risk factor profile of individuals who do not have a history of stroke or transient ischemic attack (TIA) with the goal of preventing a first cerebrovascular event; and (3) secondary prevention, which is the most targeted and is only used after an individual has experienced a stroke or TIA, with the goal of preventing stroke recurrence[218,219] (Figure 2). Examples of primordial stroke prevention include efforts to encourage smoking cessation, a healthy diet, increased physical activity, and weight control. Primary and secondary stroke prevention target a person's specific lifestyle-related and medical stroke risk factors, like hypertension and diabetes mellitus. We will focus this discussion on primordial and primary prevention of ischemic stroke.

Mass Approaches

The cornerstone of lifetime cardiovascular disease (CVD) risk reduction is behavioral modification. In primordial prevention, healthy lifestyle behaviors such as abstaining from tobacco, a healthy diet, and regular exercise should start in childhood and continue through one's lifetime.[218,220] Prevention efforts targeting behavioral modification are especially well suited for mass interventions such as public health campaigns. Although the immediate result is steps removed from the outcome of stroke, such campaigns have the potential to affect multiple outcomes, including stroke, coronary artery disease, heart failure, diabetes mellitus, dementia, and others.[221,222] Furthermore, these primordial efforts are effective because of the small and widely dispersed magnitude of treatment-related adverse events.

Recently, a more specific form of population-based cardiovascular prevention has been proposed—the polypill. This is an example of a primary prevention effort used on a mass scale. The best-studied is a pill that contains 3 antihypertensives, a hydroxymethylglutaryl-coenzyme A reductase inhibitor (statin), and an antiplatelet agent.[223] In a phase 2, double-blind, randomized controlled clinical trial of healthy adults, the polypill was shown to favorably affect blood pressure, low-density lipoprotein (LDL), heart rate, and urinary thromboxane B2 level (antiplatelet effect), when compared with single-drug regimens, without increased intolerability. Such a formulation could be particularly useful in places where the infrastructure for individualized care is underdeveloped or lacking.[224] Because stroke incidence has a linear correlation with blood pressure no matter the baseline, such standardized methods can be justified.[225] In an effort to simplify pretherapy serum testing and medical follow-up, limit side effects, and ultimately decrease associated cost, the mini-polypill has recently received attention as a more refined standardized method of community cardiovascular disease prevention. The formulation that is being actively studied contains candesartan (angiotensin receptor

Figure 2. Levels of stroke prevention in a population.

blocker), hydrochlorothiazide (thiazide diuretic), and a low dose of rosuvastatin. The strongest evidence for this approach to mass primary prevention came from the HOPE trial (Heart Outcomes Prevention Evaluation-3), a 2-by-2 factorial design, double-blind, placebo-controlled trial in which 12 705 participants with intermediate risk of cardiovascular disease, but without a history of CVD, were assigned to receive rosuvastatin 10 mg+placebo, rosuvastatin 10 mg+candesartan and HCTZ (hydrochlorothiazide; polypill), candesartan and HCTZ+placebo, or a double placebo.[226–229] The analysis that reported the combined therapy with rosuvastatin and the 2 antihypertensive agents administered versus placebo included 3180 participants in the active arm versus 3168 participants in the control arm. The treatment arm was associated with a 1.4% absolute risk reduction in combined cardiovascular outcomes (HR, 71%; 95% CI, 0.56 to 0.90), half of which was driven by a decrease in stroke incidence. Except for an increase in muscle weakness and dizziness, the polypill used in this study was well tolerated, had a similar compliance rate to placebo, and led to fewer hospitalizations for cardiovascular causes.

This is the first study to validate the efficacy of a mass approach to primary prevention therapy through a standard combination of targeted drug therapies and minimal pretreatment screening. Such an effort hinges on the notion that population-wide approaches are effective in reducing outcomes in intermediate- and high-risk individuals who may otherwise be naive to individualized primary prevention efforts. The downside of this method is that those in the population who are at low risk are also exposed to the side effects of the treatment, skewing the risk to benefit ratio. Despite this evidence that the polypill approach may be effective in preventing cardiovascular outcomes, it is unclear how and where to translate such efforts into clinical practice. This is especially true in the United States, where access to health care varies but is relatively high compared with global standard.

Targeted Lifestyle Modification

Physical Activity

Classically, the lack of standard definitions of exercise intensity and variability in exercise routines, along with difficulty measuring the exposure and long time frame needed to see an effect, have all made studying the effects of exercise on the outcome of stroke difficult. It is now standard to report energy expenditure as metabolic equivalents (METs). Using this model, physical activity is classified as sedentary between 1 and 1.5 METs, light between 1.6 and 2.9 METs (eg, playing an activity-promoting video game), moderate between 3 and 5.9 METs (eg, ballet dancing), and vigorous when >6 MET (eg, outdoor bicycling).[230] Based on biological plausibility and evidence from pooled analysis from large prospective cohort and retrospective case–control studies, it is generally accepted that there is a lifelong inverse relationship between physical exercise and stroke.[222,231] Compared with physically inactive individuals (<600 MET minutes/wk), those who are highly active (>8000 MET minutes/wk or around 2 hours of daily vigorous activity) are estimated to have a 25% to 30% lower risk of stroke.[222,232] There is also evidence that the there is a gradient in protective effect depending on level of activity, although the optimal exercise regimen for specific subsets of the population have not been established.[233] At this time, a generally accepted and useful recommendation for primary stroke prevention, which can be tailored to an individual's lifestyle needs and preference, is the AHA/ACC CVD prevention guideline of at least 40 minutes per day of moderate to vigorous intensity exercise, 3 to 4 days per week[220,234] (Figure 3).

Diet

A Cochrane review in 2013 suggested that adherence to a healthy diet can decrease lifetime risk of stroke by ≈20%.[235] The Mediterranean, Dietary Approaches to Stop Hypertension, AHA, and US Department of Agriculture food patterns diets are all alike in that they promote a combination of plant-derived micro and macronutrients, decreased caloric intake related to saturated and trans fats, increased intake of fruits and vegetables, and decreased salt intake.[236] The Nurses' Health Study, a prospective cohort of 71 768 participants, followed dietary patterns from 1984 to 1998. It was the first to show that a Western diet, high in saturated fats, processed grains, and simple sugars was associated with an increase in stroke incidence (relative risk [RR] 1.58, 95% CI, 1.15–2.15; $P<0.001$), while adherence to a "prudent diet", high in fruits and vegetable, whole grains, legumes, and fish, was associated with a decreased stroke incidence when comparing extreme quintiles

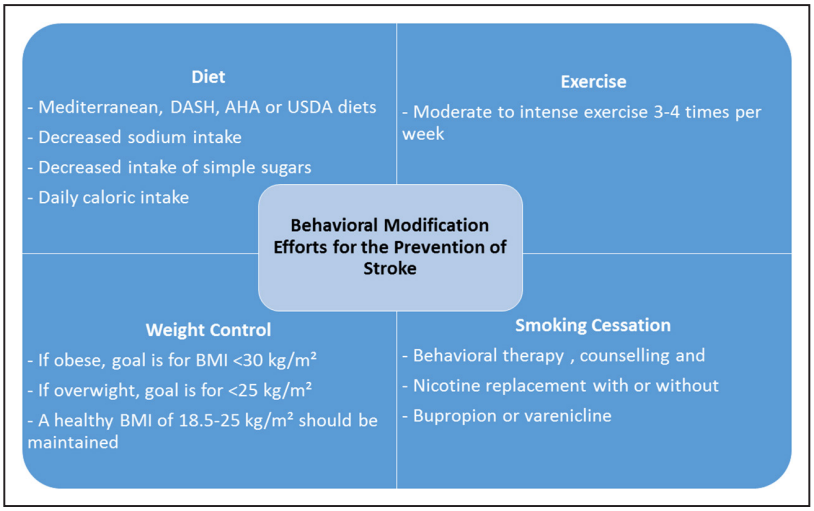

Figure 3. Healthy lifestyle-related practices for improved cardiovascular health. AHA indicates American Heart Association; DASH, Dietary Approaches to Stop Hypertension; and USDA, United States Department of Agriculture.[121,122]

(RR, 0.78; 95% CI, 0.61–1.01).[237] Perhaps the strongest evidence in favor of diet reducing cardiovascular events is the Mediterranean diet.[238] It is defined by high intake of vegetable, fruits, legumes; olive oil as the principal source of fat; preferential consumption of fish and poultry over red meat; low dairy intake; and an option of low intake of red wine.[239] The PREDIMED study (Primary Prevention of Cardiovascular Disease with a Mediterranean Diet), a multicenter randomized trial that compared the effects of the Mediterranean diet on cardiovascular outcomes found an approximate 30% (95% CI, 0.46–0.98; $P<0.04$) reduction of stroke incidence for a Mediterranean diet high in olive oil compared to a standard low fat diet, and a 50% (95% CI, 0.35–0.84; $P<0.006$) reduction for a Mediterranean diet high in mixed nuts.[119] Similar to the Mediterranean diet, a meta-analysis showed that the Dietary Approaches to Stop Hypertension diet was associated with a nearly 20% lowered risk of stroke (95% CI, 0.72–0.92).[240] In general, any diet that revolves around the high intake of plant-based nutrients, low salt, and curbing of saturated fats and simple sugars, such as the Mediterranean, Dietary Approaches to Stop Hypertension, US Department of Agriculture food patterns or AHA diets, are recommended for the purpose of good cardiovascular health and primary stroke prevention. It may also be reasonable to supplement any of these diets with a high intake of mixed nuts, defined by 6 weekly servings of 30 g of mixed nuts.[119]

Smoking Cessation

Among smokers, cessation leads to a decrease in stroke risk to levels similar to nonsmokers by 5 years.[241] The US Public Health Service Clinical Practice Guidelines Executive Summary recommends physician-led screening, counseling, and referral to further behavior support, of those who smoke, and the routine use of nicotine replacement products, bupropion and varenicline, in those who are seeking to quit smoking—unless medically contraindicated.[242] Although the benefits are likely to far outweigh the risk of therapy, the Food and Drug Administration has advised careful monitoring of patients on varenicline, based on 3 systematic reviews suggesting an increased risk of cardiovascular events, including stroke, in patients treated with varenicline compared with placebo. For the purpose of cardiovascular disease prevention, it is reasonable to use a combination of behavior therapy, nicotine replacement, and bupropion and varenicline with close monitoring of high-risk patients on varenicline.[243]

Targeted Risk Factor Modification

Hypertension

A meta-analysis of 147 trials, including 464 000 participants without a history of vascular disease or stroke, found that blood pressure reductions of 10 mm Hg systolic or 5 mm Hg diastolic were associated with a 40% reduction in stroke risk.[59] The effect is present even at levels below those thought to be normotensive and down to 110 mm Hg systolic and 60 mm Hg diastolic.[225,244] The disproportionately high prevalence of hypertension and diabetes mellitus among American blacks is likely a major driver of their higher rates of stroke. Furthermore, blacks are more likely to experience increased blood pressure variability and are less likely to be adequately treated, all poor prognostic factors in the development of blood pressure–related morbidity.[60] β-Blockers, thiazide diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and calcium channel blockers are the most widely studied agents, and although there are some class differences, the majority of benefit is conferred by the level of blood pressure control rather than the class of medication used.[245]

AHA/ACC guidelines recommend regular blood pressure screening and promotion of lifestyle modification for patients found to have prehypertension, defined as systolic blood pressure of 120 to 139 mm Hg or diastolic blood pressure of 80 to 89 mm Hg.[246] In hypertensive patients, blood pressure goals for the purpose of primary stroke prevention can generally be adapted from the recommendations from the Eighth Joint National Committee guidelines for blood pressure management. For individuals <60 years of age who are hypertensive, defined as a blood pressure >140 mm Hg systolic or >90 mm Hg diastolic, medical therapy is indicated. For those >60 of age who do not have a history of diabetes mellitus or kidney failure, the Eighth Joint National Committee guidelines call for a more liberal target of <150/90 mm Hg.[247] The different recommendation based on age is countered, however, by a recent large randomized control trial that included 9361 people who were ≥50 years of age and with a systolic blood pressure of ≥130 mm Hg. Intensive treatment targets of <120 mm Hg systolic, compared with standard treatment of <140 mm Hg, reduced the risk of composite cardiovascular outcomes (HR, 0.75; 95% CI, 0.64–0.89; $P<0.001$) and showed a trend toward reduced stroke risk (HR, 0.89; 95% CI, 0.63–1.25). Adverse events were not significantly different between the 2 groups, and the benefits extended out to those >75 years of age.[248] For the purpose of primary stroke prevention, lifestyle modification and pharmacological therapy should be combined to achieve strict blood pressure goals <140/90 mm Hg. Although the effects on stroke prevention are still unproven, it may be reasonable to target systolic blood pressure goals <120 mm Hg in individuals who are at low risk for complications from antihypertensive therapy. Self-measured blood pressure–monitoring devices are also recommended to better gauge treatment effects, limit adverse effects, and optimize blood pressure control.[246]

Diabetes Mellitus

Aggressive management of hyperglycemia in diabetics has not been shown to decrease the incidence of stroke and may actually be harmful. The ACCORD study (Action to Control Cardiovascular Risk in Diabetes) compared intensive glucose lowering to a goal glycohemoglobin level <6%, versus liberalized goals of 7 to 7.9%, and found no difference in stroke incidence, but a statistically significant increase in overall mortality in the intensive management group. The results suggest that it may be that the greatest effects of hyperglycemia on stroke risk accumulate early in the course of the disease and in the prediabetes stage, rather than late in the course when comorbid cardiovascular risk factors are more likely to be present. This notion is supported by a recent randomized controlled trial of pioglitazone used after stroke or TIA in those with prediabetes.[249] It enrolled 3876 individuals after a

recent stroke or TIA who also had prediabetes. The combined outcome of recurrent stroke and myocardial infarction was seen in 9.0% of the pioglitazone group and 11.8% of the placebo group (HR, 0.76; 95% CI, 0.62–0.93) during a ≈5-year follow-up. Importantly, there was also corresponding 52% reduction in incidence of diabetes mellitus. Unfortunately, treatment with pioglitazone resulted in a greater frequency of weight gain, edema, and bone fracture, limiting its practical utility. The 2016 recommendation by the American Diabetes Association calls for glycohemoglobin targets of <7% for the purpose of preventing cardiovascular complications of diabetes mellitus. It may be reasonable to liberalize the glycohemoglobin goal to 8% in the elderly or frail.[250] At this time, the presence of prediabetes necessitates intensive lifestyle intervention, although targeted medical pharmacological therapy with metformin, for example, may be optimal for certain individuals.[251]

Hyperlipidemia

The role of cholesterol reduction, particularly with hydroxymethylglutaryl-coenzyme A reductase inhibitors, or statins, has been demonstrated in several observational studies and clinical trials. Large epidemiological studies, like the MRFIT (Multiple Risk Factor Intervention Trial), which included >350 000 men, have shown a positive association between increased cholesterol levels and stroke mortality. In primary stroke prevention trials, several statins have been associated with reductions in risk of stroke ranging from 11% to 40%. The HPS (Heart Protection Study), a randomized multicenter, placebo-controlled trial of simvastatin therapy that included 20 536 individuals with coronary artery disease, peripheral vascular disease, or diabetes mellitus, showed a 5-year stroke risk reduction of 25% in the simvastatin group compared with placebo (P<0.0001).[252] The effect was driven by the decrease in ischemic strokes without an increase in risk of hemorrhagic strokes. Importantly, these benefits remained in those with LDL <100 mg/dL. More aggressive treatment was associated with a further reduction in risk. In the TNT study (Treating to New Targets), compared with atorvastatin 10 mg daily, atorvastatin 80 mg daily was associated with a 25% reduction in stroke risk that correlated with reductions in LDL. Furthermore, meta-analyses of lipid therapy and stroke showed that with each 1 mmol/L reduction in LDL cholesterol, there was an ≈20% relative risk reduction in ischemic stroke.[253,254]

The role for statin therapy in stroke prevention is also evident in secondary prevention studies. A post hoc analysis of HPS showed that in patients with a history of cerebrovascular disease without coronary disease (n=3280), simvastatin was associated with a 5% reduction in the risk of major cardiovascular events or death compared with placebo.[252] The SPARCL trial (Stroke Prevention by Aggressive Reduction in Cholesterol Levels), however, provides the most direct evidence about the role of statins in stroke patients. Patients (n=4731) with stroke or TIA and baseline LDL 100 to 190 mg/dL were randomized to atorvastatin 80 mg versus placebo beginning 1 to 6 months after their event. Atorvastatin was associated with an ≈2% absolute reduction in recurrent stroke risk (13.1% versus 11.2%) during a median follow-up of 5 years, with a relative risk reduction of 16%.[255] The benefits of statins on risk reduction were similar across subtypes of the index stroke subtype as well, implying that all ischemic stroke patients, regardless of subtype, should receive statin therapy.[256] Although there was a 0.9% absolute increase in risk of hemorrhagic stroke among patients on atorvastatin (2.3% at 5 years) compared with placebo (1.4%; HR, 1.66; 95% CI, 1.08–2.55), this detrimental effect was more than outweighed by the effect on ischemic stroke, which occurred much more commonly, such that the benefits overall favored atorvastatin for total stroke prevention (11.2% on atorvastatin versus 13.1% on placebo).

Although SPARCL was the first clinical trial to prove the benefit of high-dose statin therapy in secondary stroke prevention, the effect was modest with a number needed to treat of 50 over 5 years. Moreover, there were several limitations. For instance, patients were eligible for randomization beginning 1 month after stroke, a period where the risk of stroke recurrence falls, especially in patients with large artery atherosclerosis in whom statins may provide the most stroke prevention benefit. Ongoing trials are addressing the role of statin therapy given immediately after stroke, not only to reduce lipid levels and prevent recurrent stroke but also to ameliorate cerebral injury related to the stroke itself. For example, the NeuSTART trial (Neuroprotection with Statin Therapy for Acute Recovery) is a Phase II trial randomizing patients with acute ischemic stroke to lovastatin 640 mg daily for 3 days versus placebo to determine the safety and efficacy of lovastatin in reducing infarct size and promoting stroke recovery, which may be a function of the pleiotropic effects of statins.[257] In addition, SPARCL did not establish a target LDL.

Beyond the primary effect of statins on lowering levels of LDL, there is evidence that they may also improve endothelial function and attenuate inflammation. In one large trial in which healthy individuals with normal LDL levels and mildly elevated hsCRP levels received high-dose rosuvastatin or a placebo, after a 2-year follow-up period, the rate of stroke was 48% lower in the treatment group than in the placebo group (absolute risk reduction of 0.16%).[258] The additional reduction in risk of other cardiovascular outcomes could provide a rationale for the use of rosuvastatin for primary prevention in patients with elevated hsCRP levels but normal lipid levels. Furthermore, the absolute reduction in risk was greatest among those with the highest levels of hsCRP, reflecting the fact that these patients were at higher risk of cardiovascular events overall.

Antiplatelet Therapies

Unlike in secondary stroke prevention, where a large body of evidence supports the role for antiplatelet therapy in preventing recurrent stroke, there is little evidence to recommend the use of antiplatelet therapy for sole purpose of primary stroke prevention. A meta-analysis of vascular events in 6 primary prevention trials that included 95 000 individuals contributing 660 000 person-years, done by the Antithrombotic Trialists' Collaboration in 2009, showed no overall effect of aspirin on stroke incidence (0.20% versus 0.21% per year; P=0.4).[259] The 2015 guidelines from the US Preventive Services Task Force on aspirin use for primary CVD prevention can be applied

to primary prevention of stroke. They recommend aspirin use for primary CVD prevention only in high-risk individuals aged 50–59 years.[260] There is no convincing evidence for the use of dual antiplatelet therapies, such as aspirin and clopidogrel combined, for primary stroke prevention.[261] In the CHARISMA trial (Clopidogrel and Aspirin versus Aspirin Alone for the Prevention of Atherothrombotic Events), for example, 15 603 patients with cardiovascular disease or multiple risk factors were randomized to aspirin 75 to 162 mg daily alone or in combination with clopidogrel 75 mg daily and followed up for 28 months. The primary end point was a composite myocardial infarction, stroke, or vascular death. There was no statistical difference in outcome between those in the dual antiplatelet group (6.8%) versus those taking aspirin alone (7.3%; *P*=0.22). The risk of bleeding was higher on dual antiplatelets, however.

AF and Heart Failure

Warfarin, a vitamin K antagonist, has been for many years the standard therapy for both primary and secondary stroke prevention in patients with nonvalvular AF. In primary prevention, the AFASAK trial (Copenhagen Atrial Fibrillation, Aspirin and Anticoagulation Trial) was the first to compare warfarin to aspirin or placebo in patients with chronic AF and showed a significant reduction in stroke risk with warfarin.[262] The SPAF study (Stroke Prevention in Atrial Fibrillation), a double-blind placebo-controlled trial comparing warfarin, aspirin, and placebo in patients without a history of stroke, also showed significant benefit with warfarin and a relative risk reduction of 76% (absolute risk reduction of 5.1%) when compared with placebo.[263] There was also a reduced risk of stroke incidence when warfarin was compared with aspirin, albeit less than when compared with placebo.

Since those trials, there have been advances in thromboembolism prevention with the addition of a number of novel anticoagulants from 2 separate classes. Dabigatran (a direct thrombin inhibitor) and edoxaban, rivaroxaban, and apixaban (all factor Xa inhibitors) were shown to be noninferior in efficacy to warfarin in reducing strokes in patients with AF.[264–267] The rates of major hemorrhage have also been compared between the new agents and warfarin in a meta-analysis that included 102 607 patients. The novel agents as a group were associated with a lower risk of major hemorrhage (RR, 0.72; *P*<0.01), including intracerebral hemorrhage (ICH; RR, 0.53; *P*<0.01), without any difference in risk of gastrointestinal bleeding. The incidence of ICH was 0.51% in the novel agents group and 1.08% in the warfarin group.[268]

To assist with clinical decision making, validated AF scoring systems such as $CHADS_2$ or the newer CHA_2DS_2-VASc score, can be used to approximate ischemic stroke event rates from underlying AF.[269,270] Depending on the scoring system used, many comorbid conditions act as additional predictors of stroke risk (Tables 4 and 5). For both scoring systems, anticoagulation is generally recommended for those with scores of ≥2.

A new alternative to anticoagulation for patients with AF is left atrial appendage closure. Because an estimated 90% of thromboembolic material originates in the atrial appendage in patients with nonrheumatic AF,[271] closing the atrial appendage was theorized as a way to prevent AF-related thromboembolism. The 2 ways to achieve atrial appendage closure and make it functionally obsolete are through surgical ligation and through a transaortic catheter approach using the Watchman or Amplatzer transaortic devices.[272,273] Patients are generally expected to be on therapeutic doses of warfarin for at least 45 days after a closure procedure, followed by 6 months of dual antiplatelet therapy and indefinite aspirin use. There is a small subset of patients in whom there has been inadequate seeding of the device, necessitating a longer course of anticoagulation. Two randomized controlled trials compared the Watchman device to warfarin in patients with nonvalvular AF: the PROTECT-AF trial (Watchman Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation) and the more recent PREVAIL trial (Prospective Randomized Evaluation of the Watchman Left Atrial Appendage Closure device in patients with atrial fibrillation versus long-term warfarin therapy). In both trials, the Watchman device was noninferior in efficacy for the prevention of ischemic stroke.[274,275] Pericardial effusion, periprocedural stroke, and device embolization accounted for the major complications. Based on these 2 studies, the Watchman device was approved by the Food and Drug Administration for use in patients who: (1) have nonvalvular AF, (2) carry an increased risk of stroke, (3) are indicated for and may take warfarin, and (4) have a reason to seek a nondrug alternative to anticoagulation.[276]

The WARCEF study (Warfarin and Aspirin in Patients with Heart Failure and Sinus Rhythm) evaluated the role of anticoagulation with warfarin, versus aspirin, for the prevention of ischemic stroke, intracerebral hemorrhage, or death in patients with congestive heart failure and an ejection fraction <35%.[277] It included 2305 participants with a mean ejection fraction of 27%, followed up for ≤6 years. There was no difference in the composite outcome (26.4% versus 27.5%; HR, 0.93; 95% CI, 0.79–1.10; *P*=0.4), but there was a reduction in ischemic stroke (2.5% versus 4.7%; HR, 0.52; 95% CI, 0.33–0.82; *P*=0.005)

Table 4. Commonly Used risk stratification schemes for Atrial Fibrillation

$CHADS_2$ Items	Points	CHA_2DS_2-VASc Items	Points
C=congestive heart failure	1	C=congestive heart failure	1
H=hypertension	1	H=hypertension	1
A=age ≥75 y	1	A_2=age ≥75 y (double value)	2
D=diabetes mellitus	1	D=siabetes mellitus	1
S_2=history of stroke, TIA, or thromboembolism (double value)	2	S_2=history of stroke, TIA, or thromboembolism (double value)	2
		V=vascular disease (previous MI, peripheral arterial disease, and aortic plaque)	1
		A=age 65–74 y	1
		Sc=sex category (female sex)	1
Range	0–6	...	0–9
Maximum	6	…	9

MI indicates myocardial infarction; and TIA, transient ischemic attack.

Table 5. Commonly Used Risk Prediction Schemes, Annual Stroke Risk, and Antithrombotic Recommendations Based on Guidelines for Patients With Atrial Fibrillation

$CHADS_2$ Score	Stroke Risk (%/y)	CHA_2DS_2-VASc Score	Stroke Risk (%/y)	Recommended Antithrombotic Treatment Based on CHA_2DS_2-VASc (Class of Recommendation, Level of Evidence)
0	1.9	0	0	None (IIb, B)
1	2.8	1	1.3	None, aspirin, or anticoagulant (IIb, C)
2	4.0	2	2.2	Anticoagulant (I, A [warfarin], and B [dabigatran, rivaroxaban, and apixaban])
3	5.9	3	3.2	
4	8.5	4	4.0	
5	12.5	5	6.7	
6	18.2	6	9.8	
		7	9.6	
		8	6.7	
		9	15.2	

with no increase in ICH. Further accounting for time on treatment, there was a marginal benefit of warfarin over aspirin by the 4th year of follow-up, but there was also higher rate of major systemic hemorrhage, mostly gastrointestinal hemorrhage, with warfarin. The study concluded that a reduced risk of ischemic stroke with anticoagulation was offset by an increased risk of major hemorrhage. A secondary analysis showed that increasing the time that patients are in the therapeutic range with warfarin was significantly associated with better outcomes and improved net clinical benefit.[278] Based on a meta-analysis that included 3663 patients, there is no clear evidence at this time to recommend the use of anticoagulation in this subgroup of patients.[279] With the availability of newer oral anticoagulants with a more favorable risk profile, however, it is possible that future trials could demonstrate a benefit.

Extracranial and Intracranial Atherosclerotic Disease

Another major source of preventable cerebral infarction is large vessel atherosclerotic disease and specifically internal carotid artery stenosis. In asymptomatic (ie, those without a history of recent stroke or TIA on the side of the stenosis) men with >60% carotid stenosis and low perioperative risk, carotid endarterectomy was shown beneficial; ≈20 procedures must be performed to prevent one stroke over a 5-year period. There is no clear benefit in women or those with a perioperative risk of >3%.[280,281] There is no benefit of carotid endarterectomy in asymptomatic patients with <50% stenosis.[282,283]

For patients with symptomatic extracranial carotid stenosis of at least 70% (ie, those with stroke or TIA and a stenosis on the symptomatic side), there is evidence that carotid endarterectomy reduces the risk of stroke by 50% in relative terms, with an absolute risk reduction of ≈13% over 2 years.[284] The studies that demonstrated a benefit of surgical revascularization were conducted 10 to 25 years ago, however. Since the advent of more aggressive medical approaches to atherosclerotic disease, particularly statins, there have been temporal changes in the rates of stroke among medically treated patients with atherosclerotic carotid artery disease. Stroke rates among medically treated patients were significantly lower in studies that completed recruitment after 2000 (1.13% per year) than in those that completed recruitment earlier (2.38% per year; $P<0.001$).[285] More recent studies (eg, the Carotid Revascularization Endarterectomy Versus Stenting Trial 2) are ongoing.[286]

For patients with asymptomatic intracranial stenosis, there is no evidence of benefit to stenting or angioplasty. Even for those with symptomatic intracranial stenosis, recent trials do not provide any evidence of a benefit to stenting intracranial arteries of ≥50% stenosis. The WASID trial (Comparison of Warfarin and Aspirin for Symptomatic Intracranial Stenosis) studied aspirin versus warfarin in patients with symptomatic intracranial stenosis of 50% to 99%. It was stopped early because of a high rate of adverse events in the warfarin group, leading to a conclusion that warfarin does not provide a benefit over aspirin and may even be harmful in this subset of patients. The subsequent SAMMPRIS trial (Stenting Versus Aggressive Medical Management of Intracranial Atherosclerotic Stenosis) enrolled patients with symptomatic high-grade intracranial stenosis (>70%), comparing percutaneous stenting to best medical management with aggressive risk factor control and dual antiplatelet therapy for 3 months.[287] During a median follow-up of 32 months, the primary end-point of recurrent stroke or death was seen in 23% of the stenting group and 15% in the medical management group.[288] Interestingly, the medical group had a lower-than-expected recurrence of stroke, compared with that which was predicted from previous studies. The results suggested that aggressive medical therapy is superior to intervention for high-grade intracranial stenosis with currently available technology, particularly in the context of current medical approaches, as was seen with extracranial disease, as noted above, as well.

Conclusions

Recent years have witnessed tremendous strides in our understanding of risk factors and prevention of stroke. Research into stroke risk factors has increasingly addressed the heterogeneous subtypes of strokes, including not only hemorrhagic versus ischemic stroke but also the several etiologic subtypes of stroke. Thus, studies have confirmed that lipids are a risk factor for atherosclerotic stroke, whereas AF and related atrial cardiopathies are associated with cardioembolic strokes. Genetic analyses have benefited in particular from the emphasis on specific categories of stroke. Mutations in particular genes have now been associated with, and replicated in, large vessel, cardioembolic, and small vessel stroke subtypes. Genetic studies have also suggested new avenues to pursue in teasing out stroke pathogenesis. These studies suggest that in the future, precision medicine will enable clinicians to better focus treatments in cerebrovascular disease. Meanwhile, several large clinical trials have provided evidence of the benefits of several medical and behavioral treatments in reducing stroke risk. Blood pressure reduction, statin therapy, antiplatelets, anticoagulants, carotid revascularization, and dietary changes have all been proven to reduce stroke risk in various

patient populations. Just as importantly, some treatments, such as stenting of stenosed intracranial vessels, have not yet been proven of benefit. Observational studies provide strong evidence for other behavioral approaches, including smoking cessation and regular physical activity. Considerations of alternative approaches to prevention, in general, such as the mass approach using therapies like the polypill, using risk estimation in primary care and focusing on high-risk intervals of time after stroke triggers, also have the potential to dramatically change the future of stroke prevention.

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