Module 2. Stroke Risk Factors
Preventing Strokes

Objectives for Module 2

Knowledge

- Name at least 6 treatable or controllable risk factors for stroke
- Name at least 3 populations (groups of individuals) that have an increased risk of stroke

Clinical Applications and Reasoning

- Relate the major "modifiable" stroke risk factors to stroke pathogenesis
- Develop a series of questions that would enable you to screen a patient for major stroke risk factors, and create a stroke risk profile for that individual
- Consider ways that individuals living in a community might be encouraged to learn more about stroke, and to take part in a screening for stroke risk factors

Clinical Applications to Patient Education

- Develop 3 points that you would use in explaining *to a patient or family member* how hypertension, atrial fibrillation, or carotid stenosis is related to the risk of having a stroke.

Risk factors reflect the pathology that is responsible for the major types of strokes. Many risk factors have some role in *promoting or accelerating atherosclerotic plaque formation and ulceration*. This makes sense when you remember that 87% of all strokes are ischemic, and that atherosclerosis plays an important role in the majority of ischemic strokes. Flow-limiting stenosis of major extracranial or intracranial vessels caused by plaque may produce ischemia. However, it is usually thrombotic material that acutely occludes large or small intracranial vessels and is the immediate cause of ischemia. Also recall that a thrombus that threatens blood flow to the brain can form locally in a cerebral vessel itself, or it can form in more distant sites including the aortic arch, arteries in the neck, or the heart and then detach and travel as an embolus to reach the brain. Therefore other important stroke risk factors include conditions that *promote formation of thrombi in these more distant locations*. *Hypertension is the most significant of the stroke risk factors*. It is linked not only to atherosclerosis but also to lipohyalinosis (a major contributor to small-vessel ischemic strokes). Hypertension is also the major cause of intraparenchymal hemorrhage.

Some of the risk factors for stroke are potentially "modifiable." This means that they may be treated or controlled. In most cases, there is good evidence that treatment leads to significant reductions in the occurrence of stroke and in death from stroke. It has been estimated that if current prevention activities were uniformly performed at levels achieved by the best U.S. health care delivery systems, approximately 20% of strokes would be prevented (*Circulation*. 2008; 118:576; also see module 6).

"Modifiable" risk factors for stroke include both medical conditions (the consequences of underlying pathology of pathophysiology) and lifestyle-related factors (which may be independent risk factors and/or contribute to one or more of these medical conditions).

SOME IMPORTANT MODIFIABLE STROKE RISK FACTORS	
High Blood Pressure	**Smoking/Tobacco Use**
Diabetes Mellitus	**Physical Inactivity**
Atrial Fibrillation	**Nutrition (Poor diet patterns)**
Myocardial Infarction	**Obesity (component of Metabolic Syndrome)**
High Blood Cholesterol (and other lipids_	**Excessive Alcohol Consumption (includes binge drinking)**

Chronic Kidney Disease, Severe Sleep Apnea and Short Sleep Duration, Depression and Social Determinants including things like job loss and social isolation.

Other major risk factors for stroke are sometimes called "unmodifiable," because they are often things that neither healthcare providers nor patients can change. You need to consider "unmodifiable" risk factors, because they help you to define high-risk individuals and groups for whom treating or controlling their "modifiable" risk factors is a priority.

UNMODIFIABLE FACTORS – POPULATIONS AT SPECIAL RISK	
Age	The risk of having a stroke, and short-term risk of death after a stroke, both increase with age.
Sex	Males have more strokes than females up to the age of 65, but at older ages the difference narrows. Females tend to have greater disability after stroke than males, likely because they are on average older at stroke onset. The peripartum and post partum periods are associated with increased risk
Race/Ethnicity	Black Americans have almost twice as many first-ever ischemic strokes as whites, have a higher rate of fatal strokes, and survivors tend to have a decreased functional status compared to whites. Age-adjusted stroke incidence is also higher for Mexican Americans than non-Hispanic whites.
Family History and Genetics	An individual's risk may be increased if a first-degree relative has had a stroke. Possible mechanisms include: genetic heritability of risk factors or susceptibility to their effects; shared environmental/lifestyle factors; interaction of genetic and environmental factors. Inherited defects in blood cells or the clotting mechanism can also increase risk.
Previous Stroke or TIA	These are the most significant risk factors, since both indicate the presence of significant vascular pathology. TIAs and stroke confer substantial risk both in the short and longer term.

Combination of Risk Factors for Stroke. Each risk factor that has been described is associated with an increase in stroke risk, but to varying degrees. Although an increase in the number of risk factors corresponds directly with a further increase in stroke risk, the relationship is not linear.

More About Factors That Increase Stroke Risk

High Blood Pressure (HBP)

High blood pressure has previously been defined for research purposes as SBP ≥140 mm Hg or DBP ≥ 90 mm Hg, taking antihypertensive medications, or being told at least twice one has HBP. However, recent **ACC/AHA Guidelines recommend that HBP be defined as ≥130/≥80.** *HBP is the single most important modifiable risk factor for both ischemic and hemorrhagic stroke*. Using the recent lower threshold, nearly one-half of all US adults have high blood pressure. This at least doubles their lifetime risk of stroke, independent of other risk factors. *Long-term* control of high blood pressure at target levels significantly reduces stroke risk. Recent trials suggest that intense systolic BP control (to <120 mm Hg) may have further benefit.

Populations at special risk: Of adult black American adults, 57.6% of males and 53.2% of females have high blood pressure. This population tends to develop high blood pressure earlier in life, and their average blood pressures tend to be significantly higher compared to most other U.S. populations. Several studies show that higher systolic blood pressure explains approximately 50% of the excess stroke risk among blacks compared to whites.

Relationship to stroke pathogenesis: Atherosclerotic plaque development in extracranial or intracranial arteries supplying the brain is a slowly progressive process that apparently begins in the teenage years. Arteries that are continuously subjected to high pressures are more likely to develop plaque, and it is also more likely that the endothelial surface of the vessel will be damaged, promoting plaque rupture and the formation of thrombi. A thrombus can occlude the vessel locally or can break off and potentially embolize the brain. Hypertension likely initiates lipohyalinosis of small arteries that deeply penetrate the brain, which makes their walls prone to rupture (producing an intraparenchymal brain hemorrhage) or to collapse, occluding the lumen and producing a small ischemic infarct.

A little about control/treatment: An ongoing U.S. study shows continuing increases in awareness and treatment of HBP over the past 10 years. However only approximately 25% of those being treated for HBP have their blood pressure consistently controlled; black males were significantly less likely to have their blood pressure well controlled than black females or whites.

For a small number of patients, treatment of kidney, adrenal or thyroid disease can reverse hypertension. However for most patients, the cause of hypertension is not known. The physician's challenge is to create a management plan that will enable the patient to maintain the recommended blood pressure levels *over an extended time period*. This plan usually combines risk factor modifications like more fruits/vegetables and lower fat in diet, weight loss, increased physical activity, alcohol moderation, smoking cessation, and often one or more medications.

DON'T FORGET: Recent meta-analyses indicate that systolic blood pressure <130 mmHg may be the most clinically advantageous blood pressure target in the prevention of stroke.

Myocardial Infarction

At more than 45 years of age, approximately 4% of males and 7% of females who have a first myocardial infarction (MI) will go on to have an stroke within 5 years. The risk of stroke is far greatest in the first months following an MI because of the increased risk of an embolic event.

Relationship to stroke pathogenesis: Since atherosclerosis is the underlying pathology for both MI and most ischemic strokes, this relationship should not be a surprise. Furthermore, an MI may produce damage to the heart wall or persistent atrial fibrillation, both of which promote thrombus formation. Bits of thrombus may break off and embolize the brain. Finally, the thrombolytic agents used to treat an MI by breaking up clot in the coronary vessels increase the risk of intracerebral hemorrhagic strokes.

A little about control/treatment: **Since many of the risk factors for stroke and MI are the same, preventing a second MI or a stroke will involve many of the same considerations**. These may include lifestyle changes such as smoking cessation, increasing fruits/vegetables and reducing fat in the diet, moderation of alcohol consumption, and increasing physical activity. Medical therapies that may be indicated include reducing blood pressure, antiplatelet agents, anticoagulation if cardiac problems that increase the risk of thrombus formation are present, statins or other lipid-lowering agents, and medical treatment of diabetes mellitus if it is present.

Atrial Fibrillation

Atrial Fibrillation (AF) is a powerful risk factor for ischemic stroke, independently increasing risk about 5 times, regardless of age. It is also an independent risk factor for stroke severity, recurrence, and mortality. AF is the most common cardiac dysrhythmia. Estimates of its prevalence in the U.S. ranged from about 2.7 to 6.1 million in 2010. Being white and older both increase the risk of AF. Atrial Flutter is a somewhat less significant but nonetheless important stroke risk factor.

Special Populations: The percentage of stroke attributable to atrial fibrillation increases from 1.5% at 50-59 years of age to 23.5% in *Seniors* aged 80-89. (NOTE: These numbers may be significant underestimates, as atrial fibrillation is often asymptomatic and may not be detected clinically.)

Relationship to stroke pathogenesis: Patients with atrial fibrillation have a greatly increased risk of embolic strokes. Ineffective contraction of the atrium allows blood to pool along its walls encouraging thrombus formation. Bits of these thrombi can travel through the left ventricle, enter the systemic circulation and embolize the brain.

A little about control/treatment: In some patients, atrial fibrillation resolves spontaneously. Cardioversion, ablation, or drug therapy may be used to restore a normal cardiac rhythm. However none of these approaches has been shown to reduce short-term stroke risk. By contrast, in patients with chronic nonvalvular atrial fibrillation, anticoagulation with warfarin significantly reduces stroke risk compared with untreated patients, but it requires monitoring. For patients who have a low overall stroke risk or for whom warfarin therapy is not an option, an antiplatelet agent like aspirin or clopidogrel may be considered. Anticoagulants that do not require monitoring are now available (e.g. dabagatran or apixaban) and may replace warfarin in some cases. Clinical decisions about use of these therapies must consider the risk of hemorrhagic complications.

Diabetes Mellitus

Ischemic stroke incidence is increased 2-6 fold in patients diagnosed with type 1 or type 2 diabetes mellitus compared to patients with normal glucose levels. In DM the body is unable to produce or respond properly to insulin. DM is defined as a fasting plasma glucose ≥ 126 mg/dL or HbA1c ≥ 6.5%. It is estimated that more than 10% of the adult U.S, population has diagnosed or undiagnosed diabetes. *Even when glucose levels are considered "well controlled," diabetes is associated with a 1-3 fold increased the risk of stroke in adults*. Identifying and treating diabetic patients will significantly reduce their risk of many other vascular complications of diabetes. However, since diabetes puts these patients at high risk for stroke, it is particularly important to control any of their additional risk factors for stroke, such as blood pressure. In diabetic hypertensive individuals, aggressive treatment of hypertension has been associated with significant reduction in stroke risk.

Populations at special risk: In the U.S., there is a disproportionately high prevalence of diabetes among *non-Hispanic blacks* (almost twice as high as whites), and in *Mexican Americans*.

Relationship to stroke pathogenesis: Diabetes increases the risk of ischemic strokes through several interrelated mechanisms that favor (and accelerate) the formation of atherosclerotic plaque. In patients with diabetes, plaque is much more common in the smaller branches of cerebral arteries than in non-diabetic individuals. The narrowing of these smaller vessels can directly increase the risk of stroke.

High Blood Cholesterol and Other Lipids

No *consistent* association has been demonstrated between levels of total cholesterol, HDL-C (good) cholesterol, or LDL-C (bad) cholesterol with overall stroke risk (all types combined). Although you will often read that high total cholesterol is a major risk factor for ischemic stroke, the data are actually conflicting. In contrast, the data associating levels of total cholesterol and other serum lipids with atherosclerotic cardiovascular disease are far more robust.

Further research is needed on any associations with ischemic stroke, specific ischemic stroke subtypes, or hemorrhagic stroke.

Populations possibly at risk: Overall, total cholesterol levels and LDL levels are somewhat higher in *Hispanic males* than in the US overall male population. However, the differences in various lipid levels between major U.S. racial/ethnic populations groups are overall small.

Relationship to pathogenesis: Concerning *cerebrovascular* disease specifically, what is known is that elevated total cholesterol and LDL-C is associated with increased degree and progression of carotid atherosclerosis, while elevated HDL-C levels have the opposite effect.

A little about control/treatment: To reduce the risk of myocardial infarction (and possibly stroke), recommended levels for adults are total cholesterol <200 mg/dL and HDL-C ≥40 mg/dL. An individual's LDL-C goal depends on how many additional risk factors they may have. The recommended levels may be achieved by diet, increased physical activity, and/or cholesterol-lowering agents (statins or other pharmacological agents).

Note that the statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) may have important effects on atherosclerotic disease in addition to their lipid-lowering properties, and recent studies show that they reduce stroke risk.

Carotid Artery Stenosis

Relationship to stroke pathogenesis: When a carotid artery is narrowed by atherosclerotic plaque so that the cross-sectional area of its lumen is reduced by 70% or more, the patient has a significantly increased risk of stroke. Narrowing of the carotid artery can be symptomatic, producing a stroke or transient ischemic attack (TIA), or asymptomatic. This depends on factors like whether the plaque surface is disrupted, increasing the likelihood of thrombus formation (a thrombus can directly block the artery or be a source of emboli) or whether there is an effective collateral circulation that supplements the blood supply to brain regions in the jurisdiction of the partially occluded carotid.

A little about control/treatment: When a carotid artery is narrowed ≥70%, carotid endarterectomy (surgical removal of fatty deposits) is often considered. This procedure has been shown to significantly reduce stroke risk for both symptomatic and asymptomatic patients, but has associated surgical risk. Early intervention after the onset of symptoms is now often recommended. More recently, minimally invasive angioplasty with or without stenting has become available. The results of clinical trials comparing long-term outcomes and considering factors such as patient age and sex continue at this time. Blockages ≤30% are often treated using lipid-lowering agents (statins) and antiplatelet therapy, with the combined goals of slowing atherosclerotic disease and reducing the risk of thrombus formation.

Smoking/Tobacco Use

In 2016, about 15% of the U.S. population age 18 years and over were currently cigarette smokers. Current smoking increases the risk of stroke 2-4 times in both males and females, compared to nonsmokers or former smokers who have quit for >10 years. Specifically, cigarette smoking has

been shown to be an independent risk factor for both ischemic stroke and subarachnoid hemorrhage). Exposure to secondhand smoke during adulthood also increases stroke risk about 30%. Discontinuation of smoking reduces stroke risk across sex, race, and age groups. When an individual quits smoking, stroke risk begins decreasing almost immediately, and after 10 years drops to nearly that of a nonsmoker. The health risks of e-cigarettes are not yet fully understood.

Populations at special risk: Smoking may impact the effect of other stroke risk factors on stroke risk. For example, Cigarette smoking increases the stroke risk of individuals with high blood pressure, and smokers with elevated systolic blood pressure who use oral contraception also have increased stroke risk..

Relationship to stroke pathogenesis: Cigarette smoke contains carbon monoxide and nicotine as well as numerous additional toxic compounds. Cigarette smoking has a role in promoting the atherosclerotic process particularly in the carotid arteries. (It is thought that carbon monoxide may play a role in damaging the arterial endothelium). In addition, it also causes microvascular damage. Smoking also causes several changes in the blood. They include increased adhesiveness and clustering of platelets, shortened platelet survival, faster clotting time, and increased viscosity of the blood, which can affect flow velocity. Many of these same changes in the blood can also be caused by short exposures to secondhand smoke; their effects are not known.

Physical Inactivity

Higher levels of physical activity are associated with lower stroke risk across all racial/ethnic groups, ages, and in both males and females. ≥150 minutes of moderate aerobic exercise or ≥75 minutes of vigorous exercise weekly (together with strength training) is associated with lower risk of both ischemic and hemorrhagic stroke. Physical activity improves stroke risk factors as it helps control obesity and diabetes, increases levels of HDL cholesterol, and may lower blood pressure in some people. Currently, about 24% of U.S. adults self-report meeting physical activity guidelines.

Populations at special risk: Physical inactivity appears to be more prevalent among *females* than males, among *black and non-Hispanic white adults* than Hispanic adults, among *seniors* than among younger adults, and among *those reporting lower educational attainment*.

Excessive Alcohol Consumption

The incidence of ischemic stroke in those who consume *small* amounts of alcohol (an average of 1-2 drinks per day for men and 1 for women) is *lower* than in nondrinkers. The reasons may involve a reduction in coronary artery disease. However, chronically drinking too much alcohol (an average of ≥ 5 drinks per day) and/or acute binge drinking are significant risk factors for stroke.

Relationship to stroke pathogenesis: The exact pathogenic mechanism is unknown, but alcohol can contribute to high levels of triglycerides, produce cardiac arrhythmias, and cause heart failure.

A little about control/treatment: In the case of alcohol abuse, counseling and support groups.

Obesity

Obesity, defined as a body mass index (BMI) of 30.0 kg/m^2 or greater, increases the risk of ischemic stroke relative to normal-weight individuals. In 2015-16, about 38% of U.S. adults were obese. Abdominal body fat is an independent risk factor for ischemic stroke in all race/ethnic groups. In many cases obesity predisposes individuals to other stroke risk factors including diabetes, hypertension, and atrial fibrillation.

Nutrition

Adherence to a Mediterranean-type diet rich in nuts and olive oil, a diet that included fish, fruits and vegetables, oatmeal and rye bread, or a diet rich in fruits and vegetables is associated with a reduced risk of stroke. Conversely, consumption of sugar-sweetened or artificially sweetened diet soda, and a higher salt intake has been associated with a greater risk of stroke.

The proportion of adults with a "healthy diet" (as defined by the American Heart Association) has increased overall during the past 10 years. However the increase is significantly smaller for those living in poverty.

Populations at Special Risk for Stroke

Some Introductory Thoughts

When considering populations of individuals who are at special risk for stroke and stroke death, there are numerous complicated and interrelated factors to think about:

- culture-based (or population-determined) social or lifestyle factors
- extent of knowledge (and belief) that there are ways to decrease the risk of having a stroke
- health care disparities: economic and other factors governing access to preventive care and monitoring, as well as to high quality in-hospital acute emergency care and therapy at discharge (longer-term rehabilitation and follow-up care)
- potential of following medical management plans (economic and social issues, support, etc.)
- genetic factors or "pathology" especially prevalent in that population

While studies that are now underway attempt to tease apart these variables so that they can be separately identified and addressed, the results to date remain limited. Therefore what we present here about several populations at special risk for stroke is incomplete. However we hope that this information will encourage you to think about some of these issues as you continue learning about stroke and stroke prevention.

Non-Hispanic Black Americans

The annual incidence for first-ever stroke is higher for black individuals than white individuals for ischemic, intracerebral hemorrhage and subarachnoid hemorrhage. Between 45 and 64 years of age, black males and females have a particularly high stroke/TIA risk). It is estimated that about 40% of the excess stroke risk in non-Hispanic blacks can be attributed to the risk factors we have discussed. Of those, levels of systolic blood pressure account for about half of the increased risk among blacks compared to whites. The racial disparity in stroke incidence does not seem to be changing over time. Additionally, more blacks die soon after a stroke, and black stroke survivors have greater long-term activity limitations than do white stroke survivors after controlling for stroke severity and rehabilitation use.

The prevalence of hypertension in non-Hispanic black adults in the US is currently estimated to be greater than 50%. This is among the highest in the world. Efforts to raise awareness of hypertension and its dangers in the black community have apparently been successful. But despite this success, the odds that black individuals will achieve their blood pressure targets are lower than for whites.

In a 2011-2014 survey, the prevalence of physician-diagnosed diabetes in non-Hispanic black males age 20 and older was about 15% (in non-Hispanic white males the prevalence was about 9%).

Even when the statistics are adjusted for age, hypertension, and diabetes, the relative risk of stroke among blacks is reported to be higher than among whites.

Rates of stroke mortality are highest in a region of the southeastern US which is known as the *'Stroke Belt.'* This area is variably defined, but usually includes the states of North Carolina, South Carolina, Georgia, Tennessee, Mississippi, Alabama, Louisiana, and Arkansas. In this region average stroke mortality is about 30% higher than in the rest of the US. This geographic disparity has existed more or less unchanged for the past 70 years. Even more striking, within this 'Stroke Belt' the coastal regions of North Carolina, South Carolina, and Georgia have average stroke mortality that is about 40% higher than in the rest of the nation.

Blacks who live in this so-called 'Stroke Belt' have sharply increased stroke mortality rates; whites also have somewhat increased rates. The high rate of stroke among 'Stroke Belt' residents does not appear to be the result of poor hypertension treatment and control. A clear explanation has so far eluded public health experts. However recent analyses show that stroke risks are highest for residents who were born in the stroke belt and lived there for the first 20 years of their lives.

In the US, most people with sickle cell disease are non-Hispanic blacks. Sickle cell disease is strongly associated with stroke, especially in children. In these individuals, the vascular endothelium may be damaged by repeated episodes of red cell sickling, making it prone to thrombus formation. Long-term exchange transfusion or bone marrow transplants can prevent the vascular pathology from progressing, and therefore decrease the risk of stroke. If a child with sickle cell disease has a stroke, he or she often recovers quite well, thanks perhaps to the increased plasticity of the young nervous system. However, without therapy, these children remain at high risk for additional strokes that may produce a lifetime of disability.

Mexican Americans

Stroke is one of the most common causes of death and disability among Mexican Americans. Incidence of hemorrhagic strokes and of ischemic stroke at younger ages is increased, compared with non-Hispanic whites.

Older Adults

Individuals >85 years of age comprise about 17% of all stroke patients. Atrial fibrillation becomes increasingly common in the very elderly, and this may contribute to their increased incidence of stroke. Amyloid angiopathy (and the lobar hemorrhages that are associated with this small vessel pathology) is also most common in the elderly. However, accumulation and destabilization of atherosclerotic plaques with accompanying thrombus formation remains the pathology underlying the majority of strokes, regardless of age.

Despite the fact that stroke in seniors are more severe and association with high one-month mortality, treatments for stroke are still beneficial. Evidence supports offering intravenous tPA, mechanical thrombectomy and carotid endarterectomy to elderly stroke patients.

Patients who have experienced TIAs and Stroke Survivors

Of those who survive an ischemic stroke, it is estimated that about 5% will have another stroke within the year. After 5 years that number increases to about 15%. However, it has been shown that many of these individuals can decrease their risk of a second stroke by up to 50% by surgical and medical treatments (for example, treatment of severe carotid artery stenosis and/or anticoagulation therapy) and addressing any risk factors, particularly hypertension, atrial fibrillation or smoking. For those who have had a TIA, the outlook is even more favorable. Many of these same therapies can now significantly reduce the risk that patients will go on to have a stroke.