Module 2. Stroke Risk Factors
Preventing Strokes

Objectives for Module 2

Knowledge

- Name at least 6 important risk factors for stroke
- Briefly relate each risk factor you named to stroke pathogenesis, based on current knowledge

Clinical Applications and Reasoning

- 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
- Discuss at least 4 ways that structural and/or social determinants of health could influence a patient's stroke risk profile.
- Propose 2 different 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
- Suggest at least 1 health policy or legislative initiative to increase primary stroke prevention programs for all U.S. residents, and address current stroke-risk factor disparities

Clinical Applications to Patient Education

- Develop 3 points that you would use in explaining *to a patient or family member* how their hypertension is related to stroke risk, and what preventive measures you recommend.

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.

Other important stroke risk factors therefore 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 can 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). **Successful preventive measures often require addressing that patient's social and economic as well as biomedical issues**. For example, a patient who is unable to obtain fresh produce and other healthy food will be unable to follow medical advice to "eat a healthy diet." A patient whose neighborhood is unsafe may be unable to "take daily walks" in order to increase physical activity.

KEY MEDICAL & BEHAVIORAL STROKE RISK FACTORS	
High Blood Pressure	**Smoking/Tobacco Use**
Diabetes Mellitus	**Physical Inactivity**
Atrial Fibrillation	**Nutrition (Poor diet patterns)**
Myocardial Infarction	**Obesity (key component of Metabolic Syndrome)**
High Blood Cholesterol (and other lipids)	**Excessive Alcohol Consumption (includes binge drinking)**

Chronic Kidney Disease, Sleep Apnea, Short Sleep Duration, Depression, Chronic Stress

ADDITIONAL FACTORS SHOWN TO INCREASE STROKE 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 postpartum periods are associated with increased risk. At this time there is no consistent evidence that current oral contraceptives or gender-affirming hormone therapies by themselves affect stroke risk.
***Family History Ethnicity Ancestry Genetics**	**Stroke is a highly complex disease, comprising a group of heterogeneous disorders in which multiple genetic and epigenetic factors interact with environmental risk factors.** Twin studies support a role for genetic factors in stroke pathogenesis, and an individual's risk may be increased if a first-degree relative has had a stroke. Possible mechanisms may include: genetic heritability of risk factors or susceptibility to their effects; shared environmental factors; interaction of genetic and environmental factors. These components are increasingly being identified and evaluated by genome-wide association studies.
Previous Stroke or TIA	**These are the most significant stroke risk factors**, **since both indicate the presence of significant vascular pathology.** TIAs and stroke confer substantial risk both in the short and longer term.

* We did not use the term "race" in this table because its definition is variable and often context dependent.. However perceived race continues to be cited in many epidemiologic studies.

KEY POINT: Biomedical factors, Health Systems structure, Health Care policy/processes, and Social Determinants of Health ALL contribute directly or indirectly to an individual's burden of Stroke Risk Factors and their ability to achieve or maintain health. Multiple interrelated considerations include biologic, social, environmental, economic factors, insurance status, availability of screening programs, exposure to racism and discrimination

Combination of Risk Factors for Stroke. Each risk factor that is listed 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*.

STROKE RISK: 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.

Although we don't yet understand the relative contributions of biomedical, structural and social determinants of health, bias and racism, multiple epidemiologic studies have shown that overall adult Black Americans of African ancestry tend to develop high systolic blood pressure relatively early in life, and this in turn is likely associated with a high number of first-ever ischemic strokes.

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.

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. Most blood pressure management plans combine 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. Adherence to such a plan is difficult for many patients—but now imagine the additional challenges posed by social and structural factors like low income level, unemployment, food insecurity, housing/neighborhood conditions, limited health literacy, lack of community-based health services, or the constant stress of structural racism. Lowering stroke risk for ALL individuals will require mitigating these issues and building additional support structures.

BOTTOM LINE: 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

STROKE RISK: 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 a 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 changes such as smoking cessation, increasing fruits/vegetables and reducing fat in the diet, moderation of alcohol consumption, and increasing physical activity. Medical therapies may 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. Again, consider the effects of social and economic determinants, biases and inequalities on a patient's ability to carry out these recommendations.

Atrial Fibrillation (AF)

Atrial fibrillation 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.

STROKE RISK: 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. 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

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.
STROKE RISK: 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. *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.

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

STROKE RISK: 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.

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

STROKE RISK: 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.

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.

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.

STROKE RISK: 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 continue to be studied.

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 also use oral contraception 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.

Excessive Alcohol Consumption

STROKE RISK: The incidence of ischemic stroke in those who consume *small* amounts of alcohol (an average of 1-2 drinks per day for males and 1 for females) is *lower* than in nondrinkers. The reasons may involve a reduction in coronary artery disease. However, chronically drinking too much alcohol (≥ 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

STROKE RISK: Obesity, defined as a body mass index (BMI) of 30.0 kg/m^2 or greater, increases the risk of ischemic stroke relative to individuals with a lower BMI. 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

STROKE RISK: Adherence to a Mediterranean-type diet rich in nuts and olive oil, a diet that includes 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 have each 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 with chronic poverty. *Food insecurity is associated with obesity, hypertension and diabetes, which then places people at greater risk for stroke.*

Populations and Individuals at Special Risk for Stroke

A Few Introductory Thoughts and Examples

We are only at the beginning in understanding health related biological traits that may track to some extent with what is called "race" or "race/ethnicity", and other traits that instead reflect the consequences of living as a member of a particular race/ethnic group in the United States. **Both the quality of national and local U.S. healthcare systems/processes and social determinants of health, including any experiences of bias, racial discrimination and health care disparities, have major impacts on both stroke prevention and stroke outcomes, as well as verall health.**

We have selected several populations at special risk for stroke to briefly discuss. As you read about them, we urge you to consider various factors that might contribute directly or indirectly to an increased incidence of stroke and adverse health outcomes – and how those conditions might be addressed at the individual, community, and population levels.

Non-Hispanic Black individuals living in the United States

PREFACE: How closely or poorly do drivers of stroke risk (the underlying causes of stroke) correspond with racial groupings? One example to consider: Epidemiologic studies of stroke in the U.S. have generally grouped individuals whose ancestors hail from the different regions of Africa in a single "Black" or "African American" race/ethnicity category. However there is actually greater genetic diversity within this racial category than between black and white races.

Epidemiologic studies categorizing individuals based on race/ethnicity consistently report that the annual incidence for first-ever stroke is significantly higher for black individuals than white individuals for ischemic infarcts, intracerebral hemorrhage and subarachnoid hemorrhage. Between 45 and 64 years of age, both black males and females have a particularly high stroke/TIA risk. **A number of investigators now suggest that the roots of this racial disparity are likely to be environmental exposures and social processes (determinants of health).**

Of the stroke risk factors we previously discussed, level of systolic blood pressure appears to account for about half of the increased risk among black compared to white individuals. **Aggressive preventive measures in recent years are credited with decreasing average blood pressure levels in both black and white populations. However, the racial *disparity* in the prevalence of high blood pressure and in the incidence of stroke remains unchanged.**

In this example we focused on Black-White racial disparities in stroke incidence and/or mortality in the U.S. because they have been identified and studied since the 1950s. However, racial/ethnic disparities in stroke incidence and/or mortality are also reported in other U.S. populations including Hispanic or Latino, and American Indian/Native Alaskan.

QUESTION: What are several national and/or local approaches you would suggest to reduce these Black/White (and other) disparities in stroke incidence in the U.S.?

The Stroke Belt: A Geographic Region in the U.S. Whose Residents Have Unexplained High Stroke Mortality

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.

Black individuals who live in this so-called 'Stroke Belt' have sharply increased stroke mortality rates; mortality rates for whites are also increased, but remain significantly lower than for black individuals. The high rate of stroke among 'Stroke Belt' residents does not appear to be the result of poor hypertension treatment and control. Recent analyses show that stroke incidence is highest for residents who were born in the stroke belt and lived there for the first 20 years of their lives. A clear explanation for the existence of the Stroke Belt has so far eluded public health experts.

QUESTION:Do you have thoughts about factors that could contribute to creating a "Stroke Belt"? The experts seem to be baffled, so feel free to make suggestions and think outside the box.:

Older Adults

Individuals >85 years of age comprise about 17% of all stroke patients. Atrial fibrillation becomes increasingly common with age, and this may contribute to the 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, the major risk factors for stroke do not change with age. Accumulation and destabilization of atherosclerotic plaques with accompanying thrombus formation remains the pathology underlying the majority of strokes. If anything**, the influence of structural and social determinants on stroke prevention becomes at least as significant with age.**

A final point: despite the fact that strokes in older adults are more severe and are associated 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 who meet treatment guidelines.

QUESTIONS: What strategies might physicians, other health care professionals and health systems use to help SENIORS lower their stroke risk at both an individual and community level?

Sickle Cell Disease

Sickle cell disease is defined as homozygosity for the sickle cell mutation in the beta-globin gene. Among other things, the abnormal hemoglobin causes repeated episodes of erythrocyte "sickling." This damages the vascular endothelium and makes it prone to thrombus formation. Individuals, especially children, with sickle cell disease are at high risk of stroke as well ischemic damage resulting in severe pain or multisystem organ damage.

Sickle cell disease is prevalent throughout large areas of sub-Saharan Africa, the Mediterranean basin, the Middle East and India where heterozygosity for the sickle cell mutation (sickle cell trait) provides strong protection against malaria. An estimated 100,000 individuals in the U.S. currently have the disease.

The severity of sickle cell disease varies, apparently depending on both genetic modifiers (for instance, factors that control the expression of fetal hemoglobin) and non-genetic modifiers including cold exposure, air quality, infection control, and availability of screening programs. **Even in this most common inherited monogenic disorder the structural and social determinants of health play key roles in disease expression as well as in the patient's quality of life.**

POTENTIAL RACE-BASED DIAGNOSTIC BIAS: **There is a common misconception that sickle cell disease affects only Black people**. In fact, **sickle cell disease is associated with populations at risk for malaria NOT with race**. Relying on a false racial association as a diagnostic criterion could mean missing the opportunity for early diagnosis and preventive interventions like use of transcranial Doppler screening and regular blood transfusions.

QUESTION: What are several downstream negative effects of race-based diagnostic bias?