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# Risk Factors for Ischemic Stroke in Younger Adults – a Focused Update

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Ischemic stroke in younger adults is far less common than among older adults, yet the underlying pathogenesis and risk factors are more diverse. Approximately 10%-15% of all strokes occur in adults ages 18-50.[1-4] In part, because of this, the diagnosis of stroke in younger adults can be challenging to differentiate from stroke mimics and to identify the cause or underlying pathogenesis. The TOAST (Trial of ORG 10172 in Acute Stroke Treatment) classification system[5] (Table 1) is parsimonious, yet many younger stroke patients have pathogeneses that are more likely to fall under cardioembolism, other determined pathogenesis, or undetermined pathogenesis rather than large artery atherosclerosis or small vessel occlusion.[1,6] Recent studies, both in the United States and Europe, have suggested that ischemic stroke in younger adults is increasing and have demonstrated increases in traditional stroke risk factors that are typically common among older adults (hypertension, dyslipidemia, diabetes mellitus, tobacco use, and obesity) to also be common among younger acute stroke patients.[1,7-13] Among younger adults presenting with acute stroke, in whom there has been an increasing prevalence of comorbid traditional cardiovascular disease risk factors, there is debate about whether or how much those traditional risk factors contribute to the cause of stroke,[4,14] particularly for those <40 years of age. This review examines some of the common and rarer pathogeneses of ischemic stroke in younger adults (Table 2).

## Epidemiology of Stroke in Younger adults

The Greater Cincinnati Northern Kentucky Stroke Study, a population-based epidemiological study, found that between 1993/1994 and 2005, the mean age of those who have a stroke declined by 2 years, while the proportion of stroke among those 20 to54 years of age increased by nearly 50% from 12.9% to 18.6%. This increase was significant among both blacks and whites and was primarily seen in ischemic stroke[8] Several other studies have

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documented recent increases in stroke among younger adults including the Dijon Stroke Registry, studies from the US National Inpatient Sample, the Swedish National Inpatient Register, and the Danish National Patient Register. Increases vary depending on the methodology and data source, including whether incidence rates or hospitalizations are reported, age ranges reported, and by individual stroke subtype. Most studies referenced above found increases primarily in ischemic stroke.[8-10, 15, 16] The Helsinki Young Stroke Registry noted relatively low stroke rates under the age 40 with sharp increases beginning at age 40. The Helsinki Young Stroke Registry also noted that overall, among ages 45 to49, men outnumbered women, but among ages 15 to30, women outnumbered men.[17] Other studies also noted an increase around age 40-45, after which large vessel atherosclerosis was a more dominant pathogenesis.[18]

### Classification of Ischemic Stroke Subtypes

Risk factors for ischemic stroke in younger adults are not unique to younger adults and overlap considerably with those of older adults but do vary in terms of the percent contribution to ischemic stroke subtypes. When considering the TOAST[5] classification, the most common types of ischemic stroke in older adults are large artery atherosclerosis and small-vessel occlusions, while these two subtypes account for only 10% to 20% of stroke in younger adults.[1, 3, 17, 19] Studies of stroke subtypes have reported a broad range and a somewhat higher prevalence (20-47%) of cardioembolism among younger stroke patients compared with all ischemic stroke patients (20-25%).[1, 3, 17, 19] Of the more traditional risk factors that are highly prevalent among older adults (hypertension, dyslipidemia and diabetes mellitus) clinical case studies and administrative studies have found that these risk factors are also highly prevalent among younger adult stroke patients although smoking is even more prevalent among younger stroke patients compared with older adults.[8,9]

## Pathogenesis

### Risk Factors Unique to or More Common among Women

Among younger stroke patients there are some risk factors that are either unique to women or more common among women. This includes use of birth control containing estrogen, pregnancy, and migraine with aura. Migraine with aura is more prevalent among younger women compared with men, and the risk of stroke is more likely in the presence of tobacco use and use of combined oral contraceptives. Studies have shown migraine with aura is associated with an approximate 2-fold increase in risk of ischemic stroke.[20, 21] However, the combination of all three risk factors (migraine with aura, use of combined oral contraceptives, and tobacco use) increases the risk of stroke approximately 9-fold compared with women who do not have any of these three risk factors.[20, 21] The increased risk of ischemic stroke in migraine with aura is associated with stroke of undetermined origin and cardioembolism, patent foramen ovale, and prothrombotic states.[20, 22, 23] Interestingly, ischemic stroke among younger women who have migraine with aura was found to be more common among those less likely to have traditional cardiovascular risk factors such as hypertension, diabetes mellitus, or high cholesterol.[20, 22]

Stroke in pregnancy is not common but does occur. Pregnancy is a pro-thrombotic state, which increases the risk for stroke, and hypertensive disorders of pregnancy increase the risk for ischemic stroke, intracerebral hemorrhage, and cerebral venous sinus thrombosis. Stroke is thought to affect approximately 30 per 100,000 pregnancies, although there is considerable variation among studies (rates varied from 10 to 65 per 100,000 pregnancies).[24] Stroke in pregnancy occurs during the antepartum, peripartum, and postpartum periods. There is also variability among studies regarding the timing of stroke in pregnancy, as some studies report peripartum stroke combined with antepartum stroke while others report peripartum stroke separately from antepartum stroke.[24, 25]

## Conditions Associated with or Potentially Associated with Cryptogenic Stroke

Patent foramen ovale (PFO) occurs in roughly 15% to 35% of the population, and it serves as a mechanism for the occurrence of paradoxical embolization from the venous circulation.[26-29] It is commonly identified among those who are diagnosed with cryptogenic stroke. The stroke risk from PFO is thought to be greater among younger patients. In patients where PFO is present and no obvious venous source of emboli is present, particularly among younger stroke patients, there is a greater prevalence of inherited and acquired thrombophilias, including Factor V Leiden mutation and prothrombin G20210A gene mutation. Both of these conditions are thought to occur in less than 6% of those of European ancestry, and are rare among those of Asian or African descent.[30-32]

## Inherited Thrombophilias and Acquired Prothrombotic or Hypercoagulable States

Factor V Leiden mutation is the most common inherited venous thrombophilia. It occurs more frequently among people of European descent. An estimated 3%-6% of people of European descent have at least one copy of this mutation.[32, 33]

G20210A gene mutation is a polymorphism of clotting factor II (prothrombin) which is associated with a 2 to 4 fold higher risk for venous thrombosis. It has been associated with ischemic stroke among those aged 15 to 42 years, but not among those aged 42 to 49 years. Even among young stroke cases, it is uncommon.[31] In the Genetics of Early Onset Stroke (GEOS) study, among those aged 15-49, the prevalence was 3.5% among cases compared with 1.4% among controls. Prothrombin thrombophilia occurs in an estimated 2% to 3% of the US white population[32, 33], but is rare among those of African descent.[34]

Proteins C and S deficiency lead to recurrent thrombotic disease. In Protein C deficiency, differences in a genetic mutation in the affected gene leading to Protein C deficiency can lead to different forms of the deficiency. It can occur in mild cases in about 1 in 500 people, whereas the severe form occurs in about 1 in 4 million cases.[35] The mild form of Protein S deficiency is estimated to occur in 1 in 500 individuals and has been reported in 4% to 12% among young stroke patients. [2, 3] Both Protein C and Protein S are important for inactivating clotting proteins.

Antithrombin (also known as Antithrombin III) is a naturally occurring anticoagulant. Deficiency of antithrombin, a hereditary genetic condition with an autosomal dominant pattern, primarily leads to venous blood clots. It is estimated to occur in about 1 in 2000 to 1

in 5000 people, although it is thought to be present in 5% to 8% of younger stroke patients.[2, 36]

Antiphospholipid syndrome, which can cause venous thrombosis, is an autoimmune disease that occurs approximately five times more often in young women, and they are more likely to be diagnosed in early adulthood ages 30-40. It is estimated that 10% to 20% of people under age 50 who have a stroke have antiphospholipid syndrome.[2] Antiphospholipid syndrome occurs frequently among individuals with systemic lupus erythematosus (SLE) and several studies have shown that stroke risk is approximately two times higher among those with SLE, particularly at younger ages.[37, 38] Approximately 10-15% of deaths among those with SLE are due to cerebrovascular disease, including stroke.[39] The highest relative risk of ischemic stroke among those with SLE occurs at younger adult ages, particularly aged <30 to 50 years, with risk ratios much higher among those ages <30 to 39 years compared with those aged 40 to 49 years.[38] Above and beyond an increase in antiphospholipid syndrome among those with SLE, patients with SLE have a high burden of cerebral small vessel disease with increased visible perivascular spaces, which increases the risk of stroke.[40]

Hyperhomocysteinemia is thought to cause abnormal blood clotting among other conditions and can result from a genetic mutation as well as deficiencies of folate and vitamins B6 and B12. Folate and vitamins B6 and B12 are necessary for metabolizing homocysteine. Hyperhomocysteinemia can also be due to an autosomal recessive mutation in the methylenetetrahydrofolate reductase (MTHFR) gene, which produces an enzyme necessary for converting homocysteine to methionine. It is thought to be related to thromboses and vascular lesions including atherosclerosis, small vessel disease, and arterial dissection, though the relation to ischemic stroke is emerging.[41-43] One study reported that hyperhomocysteinemia was four times more prevalent among young men with ischemic stroke than among women.[3]

Sickle cell disease is a hypercoagulable condition estimated to occur in 1 in 500 African Americans.[44] Stroke is common among young adults with this condition, including silent stroke, with about one-quarter of patients with sickle cell disease having had a stroke by age 45.[45] Studies have shown that stroke subtype varies with age among those with sickle cell disease. Early in life ischemic stroke is dominant, but at about age 18 infarction becomes less common than hemorrhagic stroke until about age 30 when infarction again predominates.[45] Risk factors for stroke in those with sickle cell disease include an increase in blood pressure, increased white blood cell count, sleep apnea, and decreased hemoglobin level.

Other acquired prothrombotic states that pose a higher risk of stroke include malignancy, and as noted above, pregnancy and use of birth control containing estrogen. Metabolic syndrome is thought to induce a prothrombotic state, although the mechanism of action for hypercoagulability in metabolic syndrome is unclear. Metabolic syndrome is accompanied with increased levels of clotting factors and inhibition of the fibrinolytic pathway.[46-49]

## Other Conditions Leading to Stroke in Younger Adults

Carotid or vertebral artery dissection is considered to be a major cause of ischemic stroke among younger adults, occurring in about 2.6 per 100,000 people per year, affecting men and women equally, with a mean age of approximately 45.[50] Some studies report a higher percentage of vertebral dissections while others report a greater frequency of carotid dissections.[50] Two hospital-based stroke registries in Zürich and Bern found that among their young stroke patients (ages 18-44 years, mean age 36 years) approximately 24% of their young stroke patients experienced cervical artery dissection.[51] Trauma is a frequent predisposing factor for carotid or vertebral dissection; however it is not always certain what role other predisposing conditions contribute to dissection, such as hyperhomocysteinemia, Ehlers-Danlos syndrome, or underlying arteriopathies.[50] Reports have been mixed on whether there are genetic factors associated with carotid artery dissection. Dissections due to trauma may show a delay between trauma and dissection from a few minutes to a few weeks. Multiple modalities have been used to diagnose a dissection, including magnetic resonance imaging (MRI), magnetic resonance angiography (MRA), computed tomographic angiography (CTA), ultrasound, and digital subtraction angiography.[52] Approximately two-thirds of those experiencing a cervical arterial dissection will have a favorable outcome.[50]

## Vasculopathy, Vasculitidies, and Arteritis

There are several rare conditions affecting arteries to consider when identifying a cause for stroke in younger adults. These include Fabry disease, reversible cerebral vasoconstriction syndrome, mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS), cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), Moyamoya disease, giant cell arteritis, Takayasu arteritis, primary cerebral arteritis, radiation-induced arteritis, fibromuscular dysplasia, and reversible vasoconstriction syndrome being among the better described of the rare conditions in this category.

Fabry disease is an X-linked lysosomal storage disease disorder that arises from a genetic mutation in an enzyme that occurs in lysosomes. The enzyme is required to break down a fatty substance in the lysosome. When globotriaosylceramide builds up it accumulates in the cells lining blood vessels and over time can lead to both ischemic stroke and intracerebral hemorrhage.[53, 54]

MELAS causes lactic acid buildup because of a genetic mutation in several genes contained in mitochondrial DNA, and therefore is inherited from the mother. One aspect of MELAS is the occurrence of stroke-like episodes but the mechanism of injury is poorly understood. The stroke-like symptoms may evolve over days, and underlying pathology has been described as having mitochondrial accumulation in the vascular smooth muscle and endothelial cells. This microangiopathy can lead to cerebral edema. It is thought to occur in about 1 in 4,000 people. Other symptoms include muscle weakness, vomiting, and seizures, typically beginning in early childhood. Because of recurrent episodes, it can lead to permanent brain damage.[53, 55, 56]

In individuals with CADASIL, which is an autosomal dominant arteriopathy, stroke risk may begin around age 40 to 50. It is uncommon in younger adults (about 2% younger than 65 years of age). It occurs because of a mutation in the NOTCH3 gene and a common cause of hereditary cerebral small vessel disease in younger adults. It may present as ischemic stroke, TIA, or migraine with aura. The NOTCH3 gene is important for survival of vascular smooth muscle cells.[53, 57]

Moyamoya disease can be genetic or acquired, can present in childhood, but often presents in the third and fourth decades of life. A population-based study in Denmark found the incidence to be 0.047 per 100,000 person-years, with a bimodal distribution peaking at 0-9 years and 30 to 39 years. It is typically diagnosed with computed tomography (CT), CTA, MRI, or MRA. It is progressive, more common among Asians, and has been associated with Down's syndrome and neurofibromatosis. Cerebral pathology develops after a cerebral blood vessel is occluded, typically at the base of the brain. Multiple tiny blood vessels develop to try to replace the blood supply but the blood vessels are typically fragile.[58, 59]

Giant cell arteritis is one of the more common arteritis conditions, but still relatively uncommon. It is more common in people over age 50 years of age, and more often involves vertebrobasilar vessels than the anterior circulation, and typically presents with pain in shoulders, hips, and the jaw, blurred vision and an elevated erythrocyte sedimentation rate (ESR) prior to presenting with a stroke.[60] In contrast to giant cell arteritis, Takayasu arteritis typically presents in adults under age 50 years and is much more common among women. It may be proceeded by arthralgias, fever, weight loss, headaches, rashes, and may have an elevated ESR. The cerebral vascular pattern includes vascular occlusions and aneurysm formation. The typical vascular pattern can be visualized by MRI, MRA, and CTA.[61] Primary angiitis of the central nervous system (PACNS) is extremely rare, but produces a diffuse multifocal vessel disease. It can occur at all ages, including childhood, but the peak age is about 50 years. It is thought to account for about 1% of vasculitidies and is more frequent among men. It may be challenging to differentiate PACNS from reversible vasoconstriction syndrome.[62, 63] Vasculitis can occur in collagen vascular disease including SLE and Sjogren's disease, but stroke from these conditions is more likely to be due to thrombosis. Radiation-induced arteritis narrows the blood vessel wall and consequently narrowing the lumen, which can result in ischemic stroke

Fibromuscular dysplasia is a non-atherthrombotic, nonatherothrombotic, non-inflammatory disease affecting small to medium-sized arteries. It more commonly affects young women, and most commonly, the medial layer of the arterial wall becomes thickened in a multi-focal pattern, leading to a "string of beads" appearance on vessel imaging. It can also result in carotid dissection and can begin in childhood. Recurrence of stroke is common with fibromuscular dysplasia.[64, 65]

Reversible vasoconstriction syndrome typically presents with a thunderclap headache and may or may not present with focal neurological findings. Peak occurrence is around 42 years of age and is more common among women. A patient may present with recurrent episodes that eventually subside, often over a period of one to three months. Triggers may include a rapid rise in blood pressure, vasoconstrictive drugs, migraines, and the postpartum state.

Neurovascular imaging may show typical vasoconstriction abnormalities with multiple segmental narrowings, but may appear normal in the acute phase. It can cause ischemic stroke and intracerebral hemorrhage, occurs predominantly among women, and patients may present with a combination of ischemic stroke and intracerebral hemorrhage.[66, 67]

## Common Cardiovascular and Lifestyle Risk Factors

The role of traditional risk factors in the pathogenesis of stroke in younger adults has been debated, though several studies have demonstrated a high prevalence of traditional cardiovascular risk factors among young adults presenting with acute ischemic stroke, primarily hypertension, dyslipidemia, diabetes mellitus, smoking, and obesity.[8, 13, 14, 68] It has been suggested that a high prevalence of these traditional risk factors may increase susceptibility to stroke from other causes in younger adults.[3]

Mitchell et al. found obesity to be significantly associated with increased risk for ischemic stroke risk (odds ratio 1.65) among younger adults ages 15 to 49 years in a case-control study of young ischemic stroke patients in the United States, and like other studies found high rates of hypertension (42%), diabetes mellitus (17%) and obesity (40%) among young ischemic stroke patients.[69, 70] Three studies of young men in Sweden found that body mass index (BMI) increases in puberty and adolescence were independently associated with ischemic stroke and intracerebral hemorrhage among younger adults.[71-73]

Atrial fibrillation is a far less common cause of stroke among younger adults. While valvular heart disease had been uncommon in the United States among younger adults, the rate of increase for stroke due to infective endocarditis in opioid-related hospitalizations has risen 10-fold in recent years from an annual percent increase of 1.9% from 1993 to 2008 to an annual percent increase of 20.3% from 2008 to 2015. This increase since 2008 is most pronounced among those under age 45, among non-Hispanic whites, among women, and in the southern census region.[74]

Congenital heart disease occurs in about 1% of newborns and diagnostic and surgical advances are allowing more people with congenital heart disease to live much longer in adulthood. Both ischemic stroke and hemorrhagic stroke are more common among those with congenital heart disease, and males with congenital heart disease tend to have higher incidence rates of stroke after approximately age 40. Younger adults with congenital heart disease and stroke have higher rates of atrial arrhythmias, heart failure, diabetes, tobacco and cocaine use disorders, and recent high-risk surgeries than the general population.[75] A study from Quebec found that among those aged 18 to 54 years, the incidence of ischemic stroke was 9 to 12 times higher among those with congenital heart disease compared to the general population and was 2 to 3 times higher among those aged 55 to 64 years. Similar findings were seen for hemorrhagic stroke, which was five to six times higher among those aged 18-54 and two to three times higher among those aged 55-64. The cumulative risk was higher for more severe types of congenital heart disease and higher with left-sided vs. right sided lesions.[75]

Lifestyle risk factors including smoking, physical inactivity, poor diet, heavy and/or heavy-episodic alcohol consumption, and illicit drug use (e.g., amphetamines, cocaine, and heroin)

all increase the risk for stroke. The Stroke in Young Fabry Patients (SIFAP1) study found that physical inactivity, hypertension, episodic heavy alcohol consumption, and smoking were the most important risk factors for stroke in their study of adults aged 18 t o 55 years (median age 48 years). The estimated population attributable risk (PAR) for low physical activity was 59.7% and the PAR for hypertension was 27.1% in the SIFAP1 study.[13]

Tobacco use among young ischemic stroke patients is higher than similarly aged adults in the general population and has increased over time.[8, 76] The relative risk of stroke associated with tobacco smoking has been estimated at 2.9 for ischemic stroke among those aged under 55 years.[76] A stroke patient registry from France, ages 18 to 54 years, found that tobacco use was significantly associated with cryptogenic stroke.[77] Other studies confirm a significant stroke risk among younger adult female current smokers and ischemic stroke (odds ratio of 2.6).[78] The Baltimore-Washington Young Stroke Study studied illicit drug-associated ischemic stroke among those aged 15 to 44 years, during 1988 and 1991 and found that recent illicit drug use in young adults with ischemic stroke was 12.1%, with recent cocaine use documented in 9.7% of patients, though this was lower than other studies from the same time. Of note, 21.6% of patients had a positive toxicology screen for illicit drugs despite providing a negative history of drug use.[78] Later data from this study between 1992 and 2008 found that recent cocaine use was significantly associated with ischemic stroke (adjusted odds ratio 5.7).[79, 80] A more recent study from Australia assessed fatal strokes among younger adults aged 15 to 44 years between 2009 and 2016. Of 279 fatal strokes, 50 occurred among stimulant-type drug users, (84% were among methamphetamine users) and 48 of the 50 resulted in hemorrhagic stroke, with aneurysm rupture in 16 of the 48 hemorrhagic strokes, and there were no cases of arteriovenous malformation ruptures.[81]

## Risk of Recurrence

Young adults who have had a stroke are at high risk for a subsequent admission for stroke or myocardial infarction, death, long-term continuing care for complex health conditions, and admission to a long-term care facility compared with matched controls. The Ontario Stroke Registry followed young stroke patients up to 5 years poststroke and found that they had a hazard ratio of 5.2 at five years for incurring one of these events, whereas among older stroke patients the 5-year hazard ratio was only 1.3 compared with their matched controls.[82] Several studies have found high rates of hypertension, hyperlipidemia, and diabetes mellitus among younger adult stroke patients and stroke survivors.

## Conclusion

While stroke in younger adults is less common, the pathogenesis of stroke in younger adults requires consideration of several less common risk factors. A thorough workup including testing for hypercoagulable causes, vascular imaging, and echocardiography can often identify or narrow down a list of potential pathogenesis, which is critical for prevention of recurrent strokes in younger adults. Regardless of stroke pathogenesis, young stroke survivors with high rates of traditional risk factors should have these risk factors aggressively managed for long-term risk reduction.

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**Table 1.**

TOAST Classification of Subtypes of Acute Ischemic Stroke

| |
|---|
| Large-artery atherosclerosis (embolism/thrombosis) * |
| Cardioembolism (high-risk/medium-risk) * |
| Small-vessel occlusion (lacune) * |
| Stroke of other determined etiology * |
| Stroke of undetermined etiology |
| a. Two or more causes identified |
| b. Negative evaluation |
| c. Incomplete evaluation |

TOAST, Trial of Org 10172 in Acute Stroke Treatment.

* Possible or probable depending on results of ancillary studies.

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**Table 2.**

Risk Factors for Stroke in Younger Adults

| | |
|---|---|
| *Risk Factors Unique To or More Common Among Women* | |
| | Use of contraception containing estrogen (unique to women) |
| | Pregnancy (unique to women) |
| | Migraine with aura (more common among women) |
| *Conditions Associated with or Potentially Associated with Cryptogenic Stroke* | |
| | Patent foramen ovale |
| *Inherited Thrombophilias and Acquired Prothrombotic or Hypercoagulable States* | |
| | Factor V Leiden mutation (more common among European descent) |
| | G20210A gene mutation (more common among U.S. whites) |
| | Proteins C and S deficiency |
| | Antithrombin III deficiency |
| | Antiphospholipid syndrome (5 times more common among women) |
| | Systemic lupus erythematosus (more common among women and African Americans) |
| | Hyperhomocysteinemia, with or without mutation in the methylenetrahydrofolate reductase (MTHFR) gene (more common among males) |
| | Sickle cell disease |
| | Malignancy (hematologic and non-hematologic) |
| | Pregnancy (unique to women) |
| | Use of estrogen containing contraception (unique to women) |
| | Metabolic syndrome |
| *Carotid or Vertebral Artery Dissection* | |
| *Vasculopathy and Vasculitidies and related conditions* | |
| | Fabry disease (X-linked) |
| | Mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS) |
| | Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) |
| | Moyamoya disease (more common among Asians) |
| | Giant cell arteritis (more common among those over age 50) |
| | Takayasu arteritis (more common among women and under age 50) |
| | Primary angiitis (more frequent among men) |
| | Radiation-induced arteritis |
| | Fibromuscular dysplasia (more common among women) |
| | Reversible vasoconstriction syndrome (more common among women) |
| *Cardiovascular Risk Factors* | |
| | Hypertension |
| | Dyslipidemia |
| | Diabetes |
| | Atrial fibrillation |

| | |
|---|---|
| | Cardiomyopathy |
| | Valvular heart disease |
| | Obesity |
| | Infective endocarditis |
| | Congenital Heart Disease |
| *Lifestyle Risk Factors* | |
| | Tobacco use |
| | Physical inactivity |
| | Poor diet |
| | Heavy or heavy-episodic alcohol consumption |
| | Illicit drug use (methamphetamine, cocaine, heroin, etc.) |