

# Epidemiology and Pathophysiology of Intracranial Large Artery Stenosis

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**Abstract:** Intracranial stenosis due to atherosclerosis is a disease of significant prevalence worldwide and is responsible for a significant economic burden due to stroke-related disability. Known risk factors including age, race, sex, and medical co-morbidities contribute to its incidence. While ischemic stroke and transient ischemic attack can develop from myriad mechanisms in patients with intracranial stenosis, it is likely that an interplay of hemodynamic failure, in-situ thrombosis, and distal embolism results in brain ischemia. Knowledge of disease prevalence, risk factors, and pathophysiology is critical to development of better medical and interventional treatments for this grave condition.

**Keywords:** Ischemic stroke, intracranial stenosis, risk factors.

## INCIDENCE AND PREVALENCE

Worldwide, stroke is surpassed by only heart disease as a cause of death [1]. In the United States (US), it is third behind only heart disease and cancer in mortality [2]. It is, however, the leading cause of long term disability in adults. Annually, about 780,000 individuals have new or recurrent strokes in the US. This corresponds to one stroke every 40 seconds. As the population ages, the incidence is on the rise. In fact, it is projected that stroke incidence will reach 1 million annually by the year 2050. If developing countries adopt a “Western” diet, there may be further increase in the incidence and prevalence of cardiovascular diseases and stroke [3, 4].

The recent advances in diagnostic tools, such as magnetic resonance angiography (MRA), CT angiography, and transesophageal echocardiography, have established stroke as a heterogeneous disease with multiple distinct causative mechanisms. Identifying the responsible mechanism in an individual patient has crucial implications in relation to targeted treatment and prevention. For instance, if the mechanism of stroke is attributed to cardiac embolism from atrial fibrillation then Warfarin becomes the best strategy for preventing recurrent stroke. However, if the mechanism is attributed to severe internal carotid artery stenosis then carotid endarterectomy becomes the best approach for reducing the risk of recurrent stroke. Based on these and other observations, ischemic stroke is classified into five categories based on cause: a) cardiac embolism; b) large artery atherosclerotic disease (extra- or intra-cranial); c) small vessel disease; d) stroke of other determined cause such as a coagulopathy; and e) stroke of undetermined cause [5].

This review will focus on atherosclerotic, intracranial, large artery stenosis. The major vessels involved are the supraclinoid internal carotid artery (ICA), proximal middle

cerebral artery (MCA) and anterior cerebral artery (ACA), distal vertebral artery (VA), proximal to mid-basilar artery (BA) and proximal posterior cerebral artery (PCA). The MCA is the most commonly affected artery followed by ICA, VA and BA [6, 7]. The stem (M1) and its major superior branch (M2) are the most common sites for MCA disease. Intracranial VA disease is more common than BA involvement but less common than extracranial VA disease. As much as 20% of strokes caused by intracranial atherosclerosis occur in the vertebro-basilar (VB) circulation [8]. Of note, 39% of VA disease is bilateral with 24% and 36% of patients having associated BA and extracranial VA disease [9]. The supraclinoid ICA is the most common location in American white [4, 6]. In blacks and Hispanics, intracranial stenosis afflicts younger patients than it does in whites [10]. Women may be more likely to have posterior circulation disease than men [8].

The incidence and prevalence of the condition varies according to the population studied. It is less common in Northern Europeans and Americans of European descent and more common in Asians of China, Japan and Korea [6, 10]. In the United States (US), approximately 10% of all strokes are attributed to intracranial stenosis, 78,000 strokes a year [11, 12]. However, even in the US, the incidence differs according the racial or ethnic group studied. Of all ischemic strokes intracranial stenosis is responsible for 6-10% in whites, 11% in Hispanics and 6-29% in blacks [10]. Suri *et al.* reported an estimated prevalence of symptomatic intracranial stenosis of 1 in 100,000 whites and 15 in 100,000 blacks [13]. Based on the Northern Manhattan study, an even higher prevalence of symptomatic intracranial atherosclerosis was noted in blacks and Hispanics (4.4%). In the Hispanics, 11% of all strokes were attributed to intracranial stenosis [10].

From Asian studies, intracranial stenosis is estimated to account for 33-50% of all strokes in Chinese patients; 47% of Thailand patients; 48% of Singapore patients; and 10-25% of Korean patients [14, 15]. In a study conducted on acute ischemic stroke patients in China, 33% of acute stroke was attributed to intracranial large artery stenosis [16]. In another

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study conducted in Korea utilizing transcranial Doppler (TCD) and or MRA, intracranial stenosis (symptomatic and asymptomatic) existed in 54% of subjects. Indeed, stroke is the leading cause of death in Korea and intracranial stenosis accounts for much of that public health burden [17].

These racial and ethnic differences have been demonstrated in many angiographic and autopsy studies (Table 1). Overall, the data consistently demonstrates that blacks, Asians, and Hispanics have more intracranial atherosclerotic disease in contrast to whites who have more extracranial carotid disease [10, 18-24]. As Asians, Hispanics, and blacks constitute the majority of the world's population, it may be inferred that intracranial stenosis is the most common stroke mechanism worldwide. The stroke incidence is expected to grow as the above mentioned populations expand and modernization of lifestyle and diet ensue.

**RISK FACTORS**

Risk factors for intracranial stenosis may be categorized into three groups:

1. Non-modifiable risk factors
2. Modifiable risk factors
3. Less well documented risk factors

Among the many studies of prevalence and risk factors for intracranial stenosis, age, race, hypertension, and diabetes have been most strongly and consistently observed to be associated with the disease.

**Non-Modifiable Risk Factors**

**Race (Table 1)**

As demonstrated in the first section, intracranial stenosis is more common in African and Hispanic Americans compared to white Americans. The incidence is even much higher in the Asians population. For example, the relative risk of having intracranial stenosis is 5-fold greater in American blacks and 5.85-fold greater in Hispanics

compared to American whites [13]. This is supported by data from the Northern Manhattan Stroke Study that showed the likelihood for American blacks and Hispanics to develop ischemic stroke was nearly 8-fold higher than whites [10]. This racial difference in the prevalence of intracranial stenosis was also demonstrated in autopsy studies that found African Americans had intracranial atherosclerosis more frequently compared to whites [18]. Whites had more atherosclerosis in the aorta and coronary arteries. Another autopsy study showed African Americans had more disease in the MCA stem and supraclinoid ICA, whereas whites had more frequent disease at the origin of the ICA [19]. Furthermore, the Asian population is at increased risk for developing intracranial stenosis compared to subjects of Northern European descent. In fact, it is also the most common cerebrovascular lesion in the Asian population [15, 16].

**Age**

Age is an independent risk factor for the development of intracranial atherosclerosis. In a 1967 autopsy study by Baker *et al.* [25], the prevalence of intracranial atherosclerosis was demonstrated to increase with each decade of age. It was found in 23% of those 50-59 years of age, 43% of those 60-69 years of age, 65% of those 70-79 years of age and 80% of those > 80 years of age. An autopsy study by Solberg and McGarry found similar results with respect to age [18]. A study conducted in the South Korean population observed that for every 10 years of age, the odds of intracranial disease increased by 1.2 [26]. The impact of age on developing intracranial stenosis escalates even more in the presence of other risk factors such as diabetes mellitus hypertension and hyperlipidemia [7].

**Sex**

Intracranial stenosis is more common among men, particularly in younger age groups and in particular locations, such as the basilar artery. Cross-sectional population-based and autopsy-based epidemiological studies

**Table 1. Racial Distribution of Intracranial Disease**

Study/Author	Population	Results
<b>Angiographic Studies</b>		
Gorelick [19]	26 whites, 45 blacks mixed racial population in Chicago	whites had more severe ICA origin disease; blacks had more severe MCA and supraclinoid ICA disease
Gorelick [20]	106 patients with symptomatic unilateral carotid occlusive disease	In asymptomatic vessels, black patients had more lesions of supraclinoid ICA, ACA stem, and MCA; white patients had more extracranial carotid disease
Feldmann [22]	24 whites, 24 Chinese symptomatic cerebrovascular disease	In symptomatic vascular territories, whites had more severe extracranial lesions, Chinese had more severe intracranial lesions
Northern Manhattan Stroke Study [10]	438 residents of Manhattan > age 39 years hospitalized for acute stroke	The proportion of intracranial atherosclerosis by race: 1% of whites, 6% of blacks, and 11% of Hispanics. Rate of extracranial atherosclerosis by race: 11% of whites, 8% of blacks, and 9% of Hispanics.
<b>Autopsy Studies</b>		
International Atherosclerosis Project I [8,21]	2166 autopsies performed on Blacks and Whites (from New Orleans, Jamaica, Norway)	In the 65-69 year old age group, intracranial stenosis occurred in 43% of Blacks compared to 8.5% of Whites

ICA = internal carotid artery, ACA = anterior cerebral artery MCA = middle cerebral artery.

have observed an increased odds ratio of men for developing the disease [13, 21, 27, 28].

### **Genetic Factors**

Multiple genetic factors have been identified that may enhance and promote premature atherosclerosis in the whole vascular system including intracranial large arteries. These include angiotensin converting enzyme polymorphism, plasma to vascular endothelial growth factor ratio, glutathione S-transferase, omega-1 gene polymorphism, and plasma homocysteine level [13, 29-32]. They exert their action *via* various mechanisms such as vascular endothelial injury, proliferation of vascular smooth muscle cell, and impairment of angiogenesis.

### **Modifiable Risk Factors**

#### ***Hypertension***

It is the major independent modifiable risk factor for intracranial stenosis. In fact, the impact of hypertension as a risk factor for intracranial atherosclerosis was already established from autopsy studies [18]. Based on epidemiological studies, hypertension is associated with increased odds for the development of intracranial stenosis that ranged from 5 to 9.7 [18, 27]. Moreover, the risk further increased when hypertension was associated with other risk factors [7].

#### ***Disorders of Lipid Metabolism***

Intracranial stenosis has been associated with dyslipidemia, specifically elevated total cholesterol but also its various components. High lipoprotein is an independent marker for a greater extent of disease. There is actually a synergic effect between lipoprotein "a" and diabetes mellitus and resultant intracranial occlusive disease [12]. Elevated LDL has also been shown to be a risk factor for intracranial stenosis [12].

#### ***Diabetes Mellitus***

Diabetes is an independent risk factor for intracranial stenosis. It promotes the accelerated formation of atherosclerotic stenosis through a decrease in fibrinolytic activity [12, 25]. Based on epidemiological studies, the odds ratio associated with diabetes ranges from 4 to 5.9 [12, 25, 27]. In fact, data from the Northern Manhattan Stroke study revealed that patients with intracranial atherosclerosis had a higher prevalence of diabetes (67%) when compared to those with extracranial atherosclerosis or non-atherosclerotic (60% and 48% respectively) [33]. Additionally, the impact of diabetes was also established in autopsy study done in Hong Kong [25]. Based on these studies, it may be the strongest risk factor for intracranial stenosis.

#### ***Metabolic Syndrome***

Results from the Northern Manhattan Stroke Study [33] also demonstrated a higher prevalence of metabolic syndrome in patient with intracranial atherosclerosis when compared to those with extracranial atherosclerosis, non-atherosclerotic stroke, and controls (62%, 40%, 40%, and 35% respectively).

Other potential though less well-studied factors include sickle cell disease, meningitis, cranial radiation therapy, tobacco exposure, family history, and presence of extracranial carotid atherosclerosis and aortic plaques [13].

### **Mechanisms and Pathophysiology**

Intracranial arteries are composed of endothelium, smooth muscle cells and an extracellular matrix consisting of collagen and elastin fibers. The luminal tunica intima includes a single layer of endothelial cells overlying delicate connective tissue which is supported by a dense elastic band, the internal elastic lamina. The middle layer, or intima media, consists of smooth muscle cells. The outermost tunica adventitia is mainly composed of collagen and is predominantly surrounded by only cerebrospinal fluid. A cascade of events including macrophage recruitment and low-density lipoprotein accumulation results in atherosclerotic plaque formation.

The several mechanisms of ischemic stroke related to intracranial atherosclerosis include hemodynamic failure, in-situ thrombosis from plaque disruption, distal thromboembolism, and perforator artery occlusion by plaque within the parent artery. Perforator artery occlusion seems to be the least frequent mechanism as most subsequent strokes in WASID were non-lacunar (91%) [34]. An impaired washout concept has also been a proposed mechanism that results from a combination of hypoperfusion and distal thromboembolism [35]. Thus, progressive arterial narrowing, plaque instability and thromboembolism, and/or exhausted collateral flow with impaired vasomotor reactivity are inter-woven mechanisms that may contribute to ischemic stroke due to intracranial stenosis (Table 2).

There is growing evidence for these specific individual mechanisms and their potential synergism [36-40]. Thromboembolic mechanisms include in-situ thrombosis with resultant large artery occlusion, perforator (small artery) occlusion, and/or distal embolism. In one study, among 63 patients with middle cerebral artery stenosis and acute ischemic stroke, 32 showed multiple lesions in the MCA territory [38]. The majority had perforating artery infarcts, alone or in combination with distal territory infarcts while a minority had borderzone infarcts suggesting flow failure. Another study noted that 60% of patients with multi-infarct pattern on diffusion-weighted imaging had microembolic signals on transcranial Doppler monitoring of the middle cerebral artery compared to only 6% in those with a single perforator or single infarction pattern [49]. Hemodynamic impairment is likely in a subset of patients with intracranial occlusive disease. With progressive stenosis, the tissue distal to the lesion may depend heavily on collateral blood flow. In one study, 30% of patients with middle cerebral artery occlusive disease had impaired cerebral hemodynamics on vasomotor reactivity testing [39]. In a small positron emission tomography study, 25% of patients with symptomatic middle cerebral artery stenosis had abnormal hemodynamics [36]. Using quantitative MRA to estimate vessel-specific flow among those with symptomatic vertebrobasilar stenosis, 16 of 50 patients had impaired flow [37].

**Table 2. Stroke Mechanism of Large Artery Intracranial Stenosis**

Mechanisms	Imaging Markers (See Chapter 2)
Decreased antegrade flow	Degree of stenosis Vessel-specific cerebral blood flow
Plaque instability	Hi-resolution MRI plaque imaging
Poor proximal collateral flow	Circle of Willis cerebral blood flow
Poor distal collateral flow	Leptomeningeal cerebral blood flow
Limited cerebrovascular reserve	Vasomotor reactivity
Artery-to-artery embolism	Microembolic signals

These data support thromboembolism with local small vessel occlusion and distal embolization as the predominant mechanisms of stroke, though up to one-quarter of patients with severe stenosis or poor collateral flow may develop infarcts due to perfusion failure. It may be that biologic factors that promote plaque changes (i.e. rupture, hemorrhage) and/or a critical level of stenosis must be reached and that leads to a cascade of in-situ events at the level of the atherosclerotic plaque. Antithrombotic agents, statins and elevated blood pressure may favorably influence these events in the setting of acute ischemia.

In clinical practice, the mechanism of stroke due to intracranial stenosis is often inferred by the pattern of infarction on brain imaging, usually magnetic resonance imaging. Deep infarcts suggest local thrombosis at the ostia of perforators. Complete territorial infarction distal to the site of stenosis suggests complete occlusion of the segment. Single or multiple distal cortical infarct patterns suggest thromboembolism from the site of proximal stenosis. Lastly, a borderzone pattern with impaired washout is suggested by “rosary bead” or “string of pearls” appearance in the deep white matter territory of the middle cerebral artery. Often, a mixed or combined pattern is noted which makes definitive determination of stroke mechanism a challenge. A recent case study highlighted how these may interact and provided *in vivo* evidence of the impaired washout hypothesis [41].

### ECONOMIC IMPACT

The impact of stroke on the individual and on society is enormous. In the US, the costs associated with stroke are estimated to be \$57 billion annually [2]. A significant portion is due to loss of productivity. Intracranial stenosis alone may be responsible for \$1 billion annually. Given the increased prevalence of the condition in Asia, the financial and social impact of the disease there may be even greater.

In summary, intracranial stenosis is highly prevalent stroke mechanism, especially in the Asian population that constitute one third of the globe population. Unfortunately, despite the current maximal medical therapy, intracranial stenosis is associated with substantial risk for recurrent stroke and vascular death. Endovascular angioplasty and stent is emerging as a promising alternative modality and its efficacy and safety is currently being assessed in a large multi-center clinical trial. In the mean time, every effort must be made to identify and aggressively control risk factors associated with intracranial atherosclerosis.

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