Benefits of the Novel Transcarotid Artery Revascularization (TCAR) Technique for the Treatment of Carotid Artery Stenosis

Presented to the S. Daniel Abraham Honors Program
in Partial Fulfillment of the
Requirements for Completion of the Program

Stern College for Women
Yeshiva University
May 18, 2022

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I. Abstract

Cerebrovascular diseases consist of a group of cerebral blood vessel disorders which affect blood flow to the brain. Consequences of cerebrovascular disease include cell death and stroke due to cerebral hypoxia. Unfortunately, stroke is the fifth leading cause of death in the United States and the number one leading cause of disability. Carotid Artery Stenosis is one of the most common cerebrovascular disease that often leads to ischemic stroke. Carotid Artery Stenosis is typically caused by the buildup of atherosclerotic plaque, which consists of fatty substances, cholesterol, cellular waste products, calcium, and fibrin along the inner lining of the carotid artery. As the plaque grows, it protrudes into the lumen of the artery causing stenosis; subsequently, the plaque may rupture and promote the formation of a blood clot that further occludes the artery. Medical management may be effective at controlling the effects of Carotid Artery Stenosis and preventing future strokes; in certain cases of severe stenosis, however, surgical intervention is often recommended. The Carotid Endarterectomy (CEA) has been the standard surgical intervention for revascularization for almost seventy years. Until recently, no other intervention compared to it in its effectiveness and safety. However, the Transcarotid Arterial Revascularization (TCAR) technique was introduced in 2015, and studies over the past seven years have shown promising results for this novel procedure. It combines the methods of traditional stenting with a blood flow reversal neuroprotection system to create a quick, efficient, and minimally invasive revascularization option. Future studies hope to further prove its effectiveness as it becomes a more mainstream procedure to treat Carotid Artery Stenosis.

II. Introduction

Cerebrovascular disease is a group of disorders characterized by bleeding in or restricted blood flow to a part of the brain that causes temporary or permanent patient effects and involves one or more of the cerebral blood vessels (AANS, 2022). It is essential that the heart pumps enough blood to the brain so that oxygen and important nutrients can also be transported to the brain and circulated throughout. When ischemia occurs, or blood flow to the brain is reduced or restricted, it puts the patient at an increased risk of developing a stroke. Possible causes of ischemia to areas of the brain are due to vessel stenosis (narrowing), thrombosis (blood clot formation), embolism (foreign clot or debris blockage), or hemorrhage (rupture) (University of Michigan, 2022).

III. Epidemiology

If left untreated or not managed properly, cerebrovascular disease can lead to sudden ischemia or hemorrhage that results in a cerebrovascular accident (CVA), or stroke. Unfortunately, in the United States, strokes are the fifth leading cause of death, and about 3% of adults will experience a stroke in their lifetime (Stroke, 2022). Surprisingly, the global prevalence of a stroke as of 2019 was 101.5 million people with about about fifteen million people experiencing a stroke each year. Of those fifteen million people who suffer from a stroke each year, 6.6 million of them die (AHA, 2022). In the United States, someone has a stroke every 40 seconds, and every 3.5 minutes, someone dies from a stroke (CDC, 2022). In addition, strokes are the leading cause of long-term disability, and one-third of people who suffer a stroke are left permanently disabled. These disabilities further affect the patient's family who now carry the responsibility of caretaking (Stroke, 2022). As evident by these statistics, cerebrovascular disease

and associated strokes constitute a recurrent and growing problem in healthcare, and projected estimates for the future show that the occurrence of stroke will only keep increasing if preventative measures are not taken.

IV. Types of Strokes

Cerebrovascular disease poses a great risk to individuals affected because without proper management, it often leads to stroke. A stroke is defined as "the acute onset of focal neurological findings in a vascular territory as a result of underlying cerebrovascular disease" (Tadi & Lui, 2021). Damage to blood vessels in the brain by development of cerebrovascular disease and subsequent stroke can have detrimental or even fatal consequences; deprivation of blood to the brain as a result leaves affected parts of the brain starving for oxygen (Khaku & Tadi, 2021). This brain hypoxia causes various signs and symptoms in individuals experiencing a stroke which usually includes severe headaches with possible dizziness, nausea, vomiting; confusion or disorientation; memory loss; numbness or weakness in the face, arm, or leg, usually on one side; abnormal or slurred speech; difficulty with comprehension; loss of vision or difficulty seeing; and loss of balance, coordination or the ability to walk. These signs and symptoms can occur suddenly in response to acute stroke (AANS, 2022). Therefore, recognition of stroke and sub-type early on is crucial to minimizing the damage it does to the brain. There are two main categories of stroke: ischemic and hemorrhagic. Ischemic strokes account for 85% of all strokes, while hemorrhagic strokes account for the remaining 15% (Khaku & Tadi, 2021).

Ischemic Stroke

Ischemic strokes are the most common types of strokes. They are caused by ischemia in a cerebral artery which results in a lack of perfusion to a certain area of the brain. The cerebral arteries carry oxygenated blood from the heart which supplies the brain with the oxygen and essential nutrients required to function (Tadi & Lui, 2021). Disruption to the vessel occurs by thrombosis or embolism in most cases. Thrombosis refers to the formation of a thrombus or blood clot in an artery which blocks blood from flowing properly through the vessel. An embolism, on the other hand, occurs when a piece of plaque or a blood clot breaks off and travels downstream from one artery or location within an artery to a different artery or location within the artery, thereby occluding this new site in the artery. In many cases there is not total occlusion of the artery from the thrombus or embolism as a small amount of blood can still slip through to its destination in the brain. Nevertheless, this small amount of blood is not enough for the demand of the brain, so brain cells become dysfunctional in response to oxygen and nutrient deprivation. This reaction causes the signs and symptoms of a stroke as the affected brain cells cannot function properly or maintain normal bodily processes (AANS, 2022). Unfortunately, a large portion of the affected neurons die within minutes. However, some of the affected cells form the ischemic penumbra which is brain tissue that has enough oxygen to stay alive temporarily but not enough to function properly. While the dead cells cannot be regenerated, the cells of the penumbra can stay alive for about three hours and even a little bit longer in some cases (Hakim, 1998). This allows for clot dissolution treatment such as tissue plasminogen activator (tPA) and restoration of blood flow if the patient receives medical care within three hours of stroke onset. Other methods may be done if more than three hours have passed since the

onset of the stroke, but they are not always successful at preventing cognitive disabilities or death (Khaku & Tadi, 2021).

Hemorrhagic Stroke

Hemorrhagic strokes are far less common than ischemic strokes and are caused by bleeding in the brain due to artery rupture. There are two types of hemorrhagic strokes: intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH). An ICH refers to bleeding directly into the brain tissue, while an SAH refers to bleeding into the subarachnoid space, a region filled with cerebrospinal fluid surrounding the brain. Free bleeding in the brain, a hematoma, damages surrounding brain cells by increasing the intracranial pressure, which eventually leads to severe neurological deficits (Unnithan & Mehta, 2022). Additionally, damage to the blood-brain barrier occurs along with inflammation and production of reactive oxygen species, thereby causing substantial damage to the brain (Aronowski & Zhao, 2011). Types of treatment include relieving the intracranial pressure and repairing or bypassing the ruptured blood vessel (AANS, 2022). Hemorrhagic strokes have high rates of morbidity and mortality because of their rapid progression and extensive damage to brain tissue (Chen, Zeng, & Hu, 2014). Therefore, receiving prompt treatment is essential in minimizing the **hard** caused by hemorrhagic strokes.

Transient Ischemic Attack (TIA)

There is a third type of stroke that is classified differently than an ischemic or hemorrhagic stroke. A transient ischemic attack (TIA) is a temporary stroke that causes brief neurologic dysfunction due to ischemia without permanent effects (Panuganti, Tadi, & Lui,

2021). Their symptoms mimic those of a stroke but resolve themselves quickly. In order to be considered a TIA, symptoms cannot last for more than 24 hours. Fortunately, TIAs tyically only last for an hour or less (AANS, 2022). They are not a problem on their own because the ischemia is temporary. However, TIAs usually indicate an imminent ischemic stroke as they are oftentimes caused by underlying cerebrovascular disease. The 48 hours after a TIA are crucial since an ischemic stroke is most likely to occur in that time period following a TIA (Panuganti, Tadi, & Lui, 2021). Therefore, recognizing the symptoms of a TIA, even if they resolve quickly, is crucial in getting help to prevent a possible ischemic stroke from occurring.

V. Risk Factors

There are many risk factors for cerebrovascular disease and stroke which can be divided into two categories: nonmodifiable and modifiable risk factors. The modifiable risk factors are ones that that can be controlled by a person to minimize the risk associated with them. Nonmodifiable risk factors, on the other hand, are ones that cannot be controlled by a person because they are factors that are intrinsic to that person.

Nonmodifiable Risk Factors

Among those nonmodifiable risk factors are age, sex, race, and previous stroke. Age is currently the leading risk factor for cerebrovascular disease and subsequent strokes. A possible reason for an increased risk of stroke in older populations is duration of exposure to other risk factors such as hypertension and diabetes, which in turn, cause age to be an indicator for risk of stroke. In developed countries, the average age of experiencing a stroke is 70-75 years old. In less developed countries, such as Sub-Saharan Africa, many stroke cases occur in younger

people <60 years old, likely due to other factors such as higher prevalence of sickle cell anemia in this region which increases the risk of stroke (Donker, 2018). In general, the risk of stroke doubles every ten years past the age of 55 (CDC, 2022). In addition, the vessels in the body become stiff as a person ages, so the usual wear and tear can cause injury to the vessels and subsequent stroke. In general, individuals should take care of their body and practice healthy habits to reduce the damage done that becomes apparent in old age (Hori *et al*., 2008).

Aside from age, sex is another nonmodifiable risk factor. Statistical analysis of stroke prevalence shows that more woman than men have strokes, and women are more likely to die from a stroke than men. Specifically, women are more likely than men to experience hemorrhagic strokes. A possible reason for increased prevalence of strokes in women include women's longer life expectancy. Men, on the other hand, are more likely to experience a stroke at a younger age than woman (Bushnell *et al*., 2014).

Race and ethnicity also contribute to the likelihood of experiencing a stroke. In one study conducted in Northern Manhattan, blacks had on average a 2.4-fold increased stroke rate than whites living in the same region (Sacco *et al*., 1998). The Greater Cincinnati/Northern Kentucky Stroke Study and REGARDS national cohort study both provide additional evidence to suggest that there is a higher incidence of strokes in blacks than whites within many different sample populations (Howard *et al*., 2011). Within the Hispanic community of Northern Manhattan, stroke incidence was increased by 2-fold in Latinos compared to whites. Explanations for this disparity may be attributed to lack of education of healthy living or insurance access (Gardener *et al*., 2020).

Another nonmodifiable risk factor for incidence of a stroke includes whether or not the patient has already had a previous stroke. Someone who has experienced a prior stroke has a

much greater risk of experiencing another one. Even if a person has had a TIA, the risk for having an ischemic stroke increases by 10-fold (Stroke, 2022). A global meta-analysis from 2011 reported that of those who have a stroke, 11% will have a recurrent stroke within a year of their first, and the risk for a second stroke increases with time (Mohan *et al*., 2011). In addition, a patient who has had a prior heart attack is also at a greater risk for having a stroke. Lastly, family history of stroke also puts individuals at risk for experiencing a stroke (AANS, 2022).

Modifiable Risk Factors

Many of the nonmodifiable risk factors for cerebrovascular disease mentioned previously are linked to or exacerbated because of other modifiable risk factors. Most common of those modifiable risk factors is high blood pressure or hypertension (Wajngarten & Silva, 2019). Hypertension is one of the leading causes of strokes because elevated blood pressure damages vessels and consequently causes narrowing or rupture of the vessel over time (AHA, 2022). A 2018 study reported that 65% of recruited stroke patients also presented with hypertension. Compared with previous studies, the prevalence of hypertension in stroke patients had increased, thus suggesting that there is an increasing prevalence of hypertension in first-time stroke patients (Pathak *et al*., 2018). These statistics highlight the strong and growing frequency of hypertension as a comorbidity to stroke which will only become worse if not managed.

Smoking is another main risk factor for cerebrovascular disease and stroke (Feigin *et al*., 2005). Inhaling tobacco smoke has many physiological responses in the body that promote the occurrence of strokes. The toxic chemicals in it can raise blood pressure, inhibit oxygen from circulating in the body, promote clot formation, or cause atrial fibrillation which can cause clot embolization. Interestingly, when controlling for hypertension in a Swedish study, it was found

that aside from age, smoking accounted for most strokes in these normotensive subjects. In fact, in the study population who did not suffer from hypertension, about 39% of strokes occurred in individuals who were reported smokers (Li *et al*., 2005). Fortunately, smoking is a modifiable risk factor that can easily be managed by abolishing one's smoking habit.

Studies show that high cholesterol levels are also a contributor to cerebrovascular disease and indicator of stroke risk. Most reveal an association between high levels of low-density lipoprotein (LDL) cholesterol and an increased risk of an ischemic stroke (Tirschwell *et al*., 2004). In addition there is an inverse relationship between high-density lipoprotein (HDL) cholesterol levels and ischemic stroke, and Sacco *et al.* observed that an HDL level of at least 35 mg/dL contributed to the protection against ischemic stroke, especially in older populations (Sacco *et al*., 2001). A Copenhagen study revealed that for every 1 mmol/l increase in HDL, there is a 47% decrease in relative risk for ischemic stroke (Lindenstrom *et al*., 1994). These surprising statistics urge the general population to take precaution in maintaining cholesterol and LDL levels at an appropriate value to ensure individuals are not putting themselves at an increased risk for cerebrovascular disease and ischemic strokes.

It is important to be conscious about lowering cholesterol and LDL levels with lifestyle changes, but it is important to note that high cholesterol and LDL levels can also be caused by familial hypercholesterolemia (FH), which is an inherited disorder. Therefore, those with this condition are at an even greater risk of developing cerebrovascular disease along with other vascular diseases because the body cannot get rid of the extra cholesterol in the blood due to a genetic disposition (Rerkasem *et al*., 2008). Expressing this genetic trait means that individuals must be more diligent in their diet and lifestyle choices and in monitoring cholesterol levels.

Hyperglycemia is another risk factor for cerebrovascular disease and stroke. Someone with diabetes who has hyperglycemia is two times more likely to have a stroke than someone without diabetes, and the stroke usually occurs earlier in life. This increased stroke risk is caused by an accumulation of glucose in the blood that cannot go into the cells. The glucose buildup can then lead to the formation of fatty deposits or blood clots in the patient's arteries which block blood flow and cause stroke. Therefore, proper management of blood glucose levels in patients with type 1 and 2 diabetes is important in controlling for risk of stroke (Stroke, 2022).

Other modifiable risk factors include diet, weight, alcohol consumption, and drug use. The most important way to manage risk factors for cerebrovascular disease is to focus on living a healthy lifestyle. Of course, developing cerebrovascular disease and strokes are possible even when practicing healthy habits, but minimizing harm to the body can help in reducing the risk.

VI. Carotid Artery Stenosis

Carotid artery stenosis, also referred to as carotid artery disease, is one of the primary forms of cerebrovascular disease (AANS, 2022). The carotid arteries, along with the vertebral arteries, are the main vessels that supply the brain with oxygen and essential nutrients (Sethi *et al*., 2021). Therefore, damage to the carotid arteries, such as stenosis, can cause cerebral hypoxia, which leads to the death of the affected tissue and an ischemic stroke.

Carotid Artery Anatomy

The common carotid arteries provide the head, face and front two-thirds of the brain with oxygen and other essential nutrients. As seen in Figure 1, the right and left common carotid arteries branch off from the aortic arch with freshly oxygenated blood and extend up the

front of the neck. On either side they reach the carotid bifurcation around the area of the sinuses where they each split off into the external and internal carotid arteries. The external carotid artery (ECA) specifically provides blood to the face, head, and neck. The internal carotid artery (ICA) brings oxygenated blood into the skull where it branches off further into the anterior and middle cerebral arteries along with a few smaller arteries, thereby supplying oxygen to the front of the brain (Sethi *et al*., 2021). Disruption or injury to any branches of the ICA can result in ischemia and compromised blood flow to the brain.

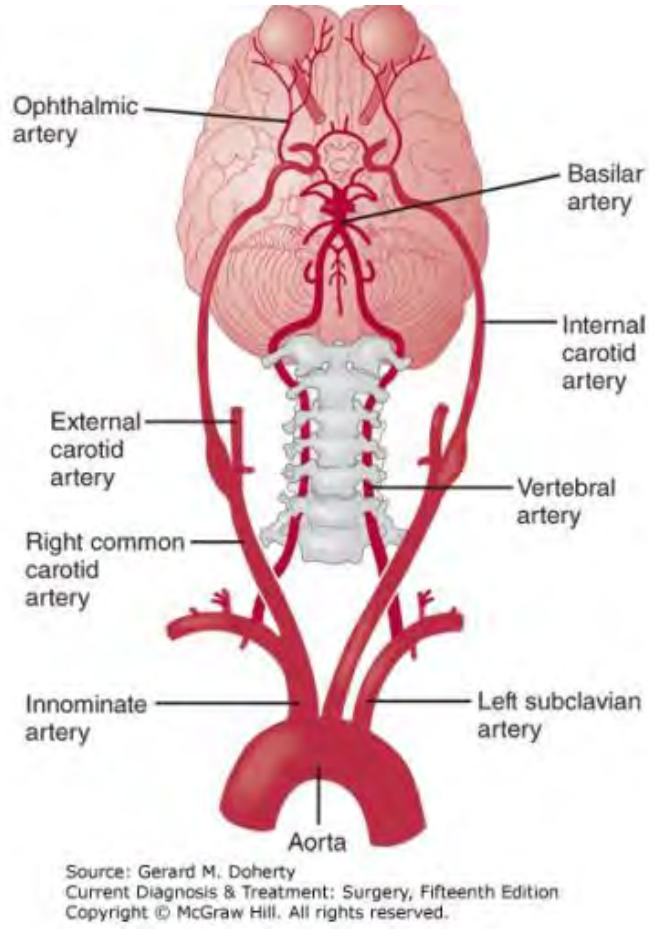


Figure 1 **Carotid Artery Anatomy**

The left and right common carotid artery branches off from the aorta and splits into the internal carotid artery (ICA) and external carotid artery (ECA) at the carotid bifurcation.

Atherosclerosis in Carotid Artery Stenosis

Carotid artery stenosis is almost always caused by atherosclerosis, or the buildup of fatty substances, cholesterol, cellular waste products, calcium, and fibrin into a plaque along the inner lining of the carotid artery, the intima layer. As seen in Figure 2, the carotid artery is made up of three layers: the intima, the smooth innermost layer; the media, the muscular middle layer; and the adventitia, the protective outer layer. As the buildup of plaque increases, the lumen of the artery narrows, and the walls of the artery become thickened and stiff. Through various mechanisms, the atherosclerotic plaque can cause significant stenosis over time, which may lead to an ischemic stroke. Therefore, is important to be proactive at managing risk factors even from a young age, which is when the atherosclerotic plaque begins building up (Hopkins Medicine, 2022).

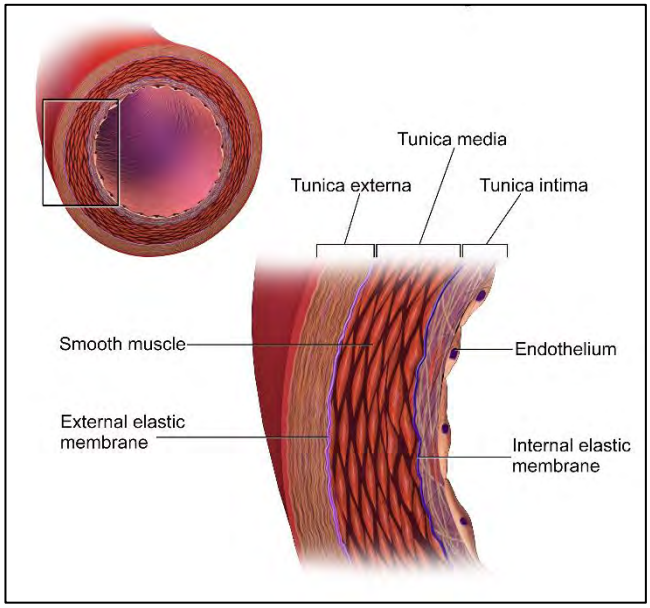


Figure 2 **The Structure of the Artery Wall**

The artery wall consists of the inner intima layer, middle media layer, and the external externa layer (or adventitia). The endothelium is on the interior of the tunica intima layer.

https://en.wikipedia.org/wiki/Tunica_media

The most common location of atherosclerosis lesions in the carotid artery is at the site of the carotid bifurcation and extending into the ICA; this specific location of atherosclerosis accounts for 10 to 12% of all ischemic strokes (Fairman, 2021). In general, extracranial arteries

including the common carotid artery are elastic due to many elastin filaments in the tunica media. Intracranial arteries, such as the ICA, lack elastin fibers, and instead, are muscular arteries. The carotid bifurcation is the location which transitions from the elastic common carotid artery to the muscular artery of the ICA (Hori *et al*., 2008). This transition in artery subtypes makes the area vulnerable which is why it is a common location of atherosclerotic plaque buildup.

Pathophysiology of Atherosclerotic Plaque Buildup

The mechanism of atherosclerosis is not entirely known but includes a complex series of cellular processes involving lipid metabolism and inflammatory signaling that interact with the vasculature of one's body. Atherosclerosis is initiated by endothelial dysfunction which leads to damage of the arterial wall (Chandra *et al*., 2017). The endothelium is a thin layer of cells that lines the interior of arteries and regulates vascular homeostasis (Figure 2). A normal and healthy endothelium secretes anticoagulant, antiplatelet, and fibrinolytic factors to maintain the structure of the vessel wall, regulate smooth muscle cell growth, and control clotting factors. The endothelium also secretes many dilator and constrictor substances to regulate vasodilation and constriction of the vessel. When all these secreted substances are not balanced properly, vascular homeostasis is disrupted and results in endothelial dysfunction (Davignon & Ganz, 2004). Endothelial dysfunction is an early indicator for atherosclerosis and begins the cascade of events that ultimately lead to atherosclerotic plaque and carotid artery stenosis.

Initial damage of endothelial cells promotes an inflammatory response. While normal endothelial cells regulate cell surface adhesin factors so that leukocytes flowing in the blood do not adhere to the endothelial layer, dysfunctional endothelial cells over-express vascular cell

adhesin molecule-1 (VCAM-1) which promotes leukocyte adherence to the endothelium (Libby, 2022). Once the leukocytes--specifically monocytes and T-lymphocytes (T-cells)--adhere to the endothelial wall, they travel through the layer of the endothelium into the tunica intima and cause inflammation (Chandra *et al*., 2017). Simultaneously, endothelial dysfunction also loosens the tight junctions between endothelial cells, thus promoting increased permeability to various molecules including LDL particles. Once the LDL molecules have entered the subendothelial space, they become oxidized. The monocytes that entered the subendothelial space previously differentiate into macrophages that phagocytose the oxidized LDL. These macrophages that have engulfed LDL acquire the lipids from the LDL and turn into foam cells. Then many foam cells accumulate to create a fatty streak in the tunica intima layer of the artery (Figure 3) (Libby, 2022).

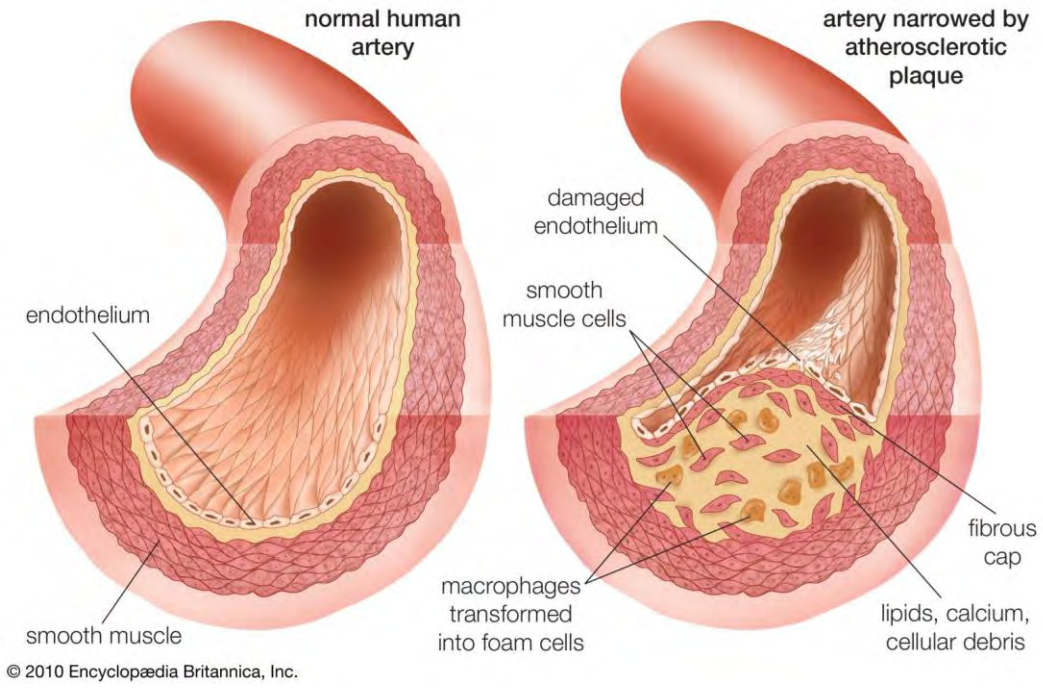


Figure 3 **Normal Artery vs. Artery with Atherosclerotic Plaque Buildup**

The left artery represents a normal, healthy artery. The right artery depicts plaque buildup inside the inner layer of the artery and the formation of foam cells due to a damaged endothelium and macrophages that phagocytosed oxidized LDL.

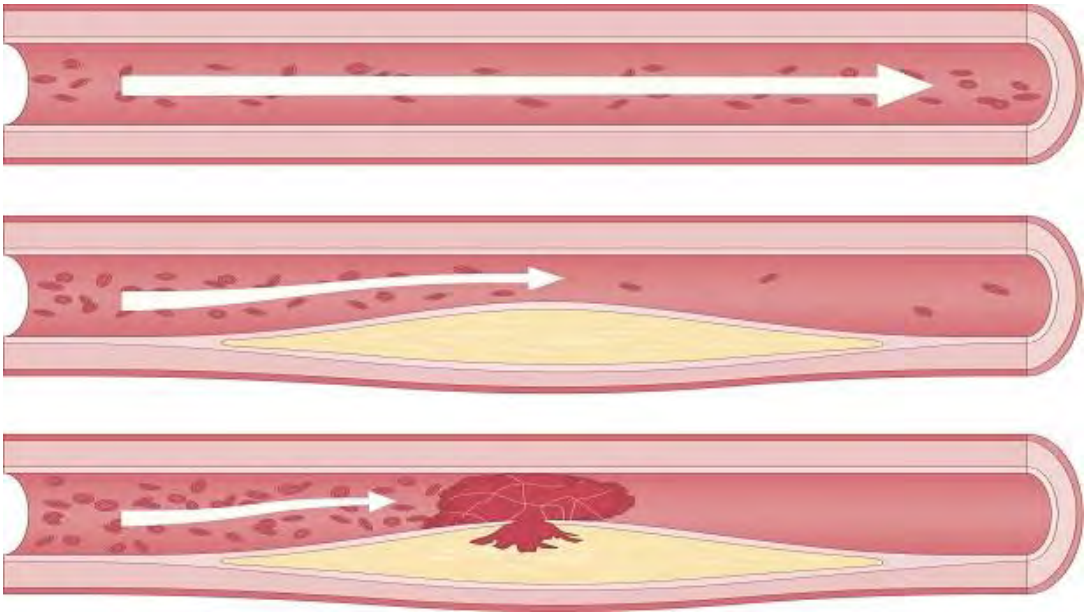
The emergence of a fatty streaks is the earliest lesion and visible sign of atherosclerosis. On its own, the fatty streak is not clinically significant, but it typically evolves to a clinically significant atherosclerotic lesion. (Berliner *et al*., 1995) Following the accumulation of foam cells into a fatty streak, the foam cells undergo apoptosis and release their fatty load into the extracellular space in the tunica intima. Over time, the fatty loads combine to produce a necrotic, lipid-rich fatty core that is surrounded by smooth muscle cells and other macrophages. These smooth muscle cells surrounding the lipid-rich fatty core had previously migrated from the tunica media layer in response to T-cell signaling due to endothelial damage. The lipid fatty core, smooth muscle cells, macrophages, and a matrix of collagen combine to form the fibrous plaque (Chandra *et al*., 2017). The formation of the fibrous plaque is the second stage of atherosclerotic pathogenesis which can have detrimental effects on the artery.

Mechanism of Stroke Due to Atherosclerosis

As a fibrous plaque grows, it accumulates more fatty lipids and cholesterol. Once the plaque has reached a certain size, it begins to protrude into the lumen of the artery. This causes partial occlusion of the vessel, or stenosis, and it may reduce the amount of blood that can flow through the artery (Chandra *et al*., 2017).

Unfortunately, thrombosis and embolization, which are other complications from atherosclerosis, can occur and contribute to a carotid stenosis-related stroke. If the atherosclerotic plaque becomes an unstable or vulnerable plaque, it is more likely to rupture (Libby, 2022). When a plaque ruptures, the cholesterol and collagen becomes exposed, and the body recognizes this occurrence as an injury. This injury stimulates the release of pro-coagulants and activates thrombosis or the clotting cascade to create a blood clot (Figure 4) (Chandra *et al*., 2017). When

thrombosis occurs at the carotid bifurcation, the most common location of carotid plaque rupture, the blood clot can do one of two things: it will either stay at the site of plaque rupture and cause occlusion of the artery or travel as an embolism to another site in the ICA and occlude that proximal portion of the carotid artery (Hori *et al*., 2008). Occlusion of any portion of the carotid artery, whether from a thrombus or embolized thrombus, may result in an ischemic stroke and cell death.



https://www.heartandstroke.ca/heart-disease/conditions/atherosclerosis

Figure 4 **Blood Clot Formation**

Atherosclerotic plaque builds up inside the artery, which begins to restrict blood flow. The plaque can rupture which stimulates thrombosis at the site of injury, thus further blocking blood flow.

Although less common, an additional consequence of atherosclerotic plaque buildup in the carotid arteries is an aneurysm. When the plaque inside the artery builds up, it may protrude out into the medial layer of the artery and cause dilation and vulnerability to the artery which promotes the formation of an aneurysm (Chandra *et al*., 2017). If the aneurysm ruptures, this

process will result in a hemorrhagic stroke which ultimately kills brain cells and can be fatal if not treated immediately.

VII. Diagnosing Carotid Artery Stenosis

Proper diagnosis and subsequent characterization of carotid stenosis is crucial in determining the plan for treatment. During a physical examination, the physician will listen with a stethoscope for the sound of a bruit, which is a vascular sound caused by stenosis in an artery (Saxena, Ng, & Lim, 2019). Because stenosis causes compromised blood flow through the artery, the sound of resultant flow is turbulent in the area surrounding stenosis (Lucerna & Espinosa, 2022). Listening for a bruit sound is a strategic starting point in diagnosing carotid artery stenosis because it is present 70 to 89% of the time in carotid arteries with at least a 2mm luminal narrowing (Grotta, 2013). If a bruit is detected, additional tests must be done to confirm the diagnose and further evaluate the extent of stenosis.

Duplex Ultrasound (DUS)

Typically, a carotid duplex ultrasound (DUS) is the first type of technique used to evaluate the presence of stenosis in the carotid artery. It is the preferred initial screening method because it is known to be an accurate and noninvasive imaging technique that does not pose the risk of radiation exposure. In addition, it is a low cost test which is beneficial to patients (Saxena, Ng, & Lim, 2019). The DUS combines the methods of a traditional ultrasound with that of a Doppler ultrasound. The resulting test computes real-time images of the arteries using high-frequency sound waves and detects areas with an occlusion or restricted blood flow. Therefore, this imaging technique is able to detect plaque, blood clots, and any blood flow issues in the

artery (AANS, 2022). Nevertheless, there are still limitations to this technique as it can only provide a small sectional view of the artery at one time compared to other imaging methods (Saxena, Ng, & Lim, 2019).

Cerebral Angiography (CA)

Cerebral angiography (CA) is a minimally invasive imaging technique used to look at the vasculature in the head and neck. The femoral artery is accessed through the groin with a catheter, which is then threaded through the main vessels in the abdomen and chest until it reaches the carotid artery. Contrast dye is injected into the patient, and a fluoroscope, which is an intraoperative X-ray machine, takes images of the arteries to visualize any blockages or restrictions of blood flow. Angiography has been known to be the most accurate method of vessel visualization, but it has a 1.2% risk of stroke since it is an invasive technique. Because of this, physicians often prefer to use other noninvasive methods for initial screening of carotid stenosis, such as the CTA.

Computed Tomography Angiography (CTA)

Computed tomography angiography (CTA) uses a computer tomography (CT) machine to take slice-based images of the arteries in the head and neck and generate a 3D reconstruction of the vasculature. Contrast dye is used with it to better visualize the vessels. This method is often preferable to angiography because it is noninvasive, and results in accuracy have been similar to those with angiography (Saxena, Ng, & Lim, 2019). In fact, Marks *et al*. found that CTA results were 89% accurate when compared to angiography (1993), and Anderson *et al*. discovered an almost 100% accuracy in CTA for mild stenosis and total occlusion (2019).

Magnetic Resonance Angiography (MRA)

Magnetic resonance angiography (MRA) uses a magnetic resonance imager (MRI) to take images of the arteries in the neck using large magnets and radio waves. It shows the blood movement in the vessels and produces vascular visualization similar to that of CTA (Saxena, Ng, & Lim, 2019). Meta-analysis studies done comparing CTA to MRA with contrast show that MRA is the most sensitive test to diagnose carotid artery stenosis. CTA, on the other hand, has the highest specificity (Kelly & Holloway, 2006). Nevertheless, MRA does not have the risk of radiation exposure that CTA has, which must be considered when choosing the right method of imaging after the initial DUS.

VIII. Clinical Presentation of Carotid Artery Stenosis

Together with screening for carotid artery stenosis, it is important to make the distinction between symptomatic and asymptomatic carotid artery stenosis when considering plaque progression because the course of treatment is different for each.

Symptomatic Carotid Artery Stenosis

Symptomatic carotid artery disease is defined as neurologic symptoms that are sudden in onset and ipsilateral to significant carotid atherosclerosis and include a TIA, characterized by focal neurological dysfunction or transient monocular blindness, a minor, nondisabling ischemic stroke (Barnett, 1991). In addition, in order to be considered "symptomatic," a patient must have had carotid symptoms within the past six months (Wabnitz & Turan, 2017). Management of symptomatic carotid artery stenosis is important because atherosclerotic plaques are usually

vulnerable or embologenic; therefore, they pose an increased risk of causing another stroke. Typically, the risk of an imminent TIA or stroke is highest in the first month following the initial neurological event and drops significantly after six months. Possible reasoning for this decline in risk as time goes on since initial neurological event is due to plaque stabilization, either because of spontaneous healing or medical intervention (Barnett, 1991).

Asymptomatic Carotid Artery Stenosis

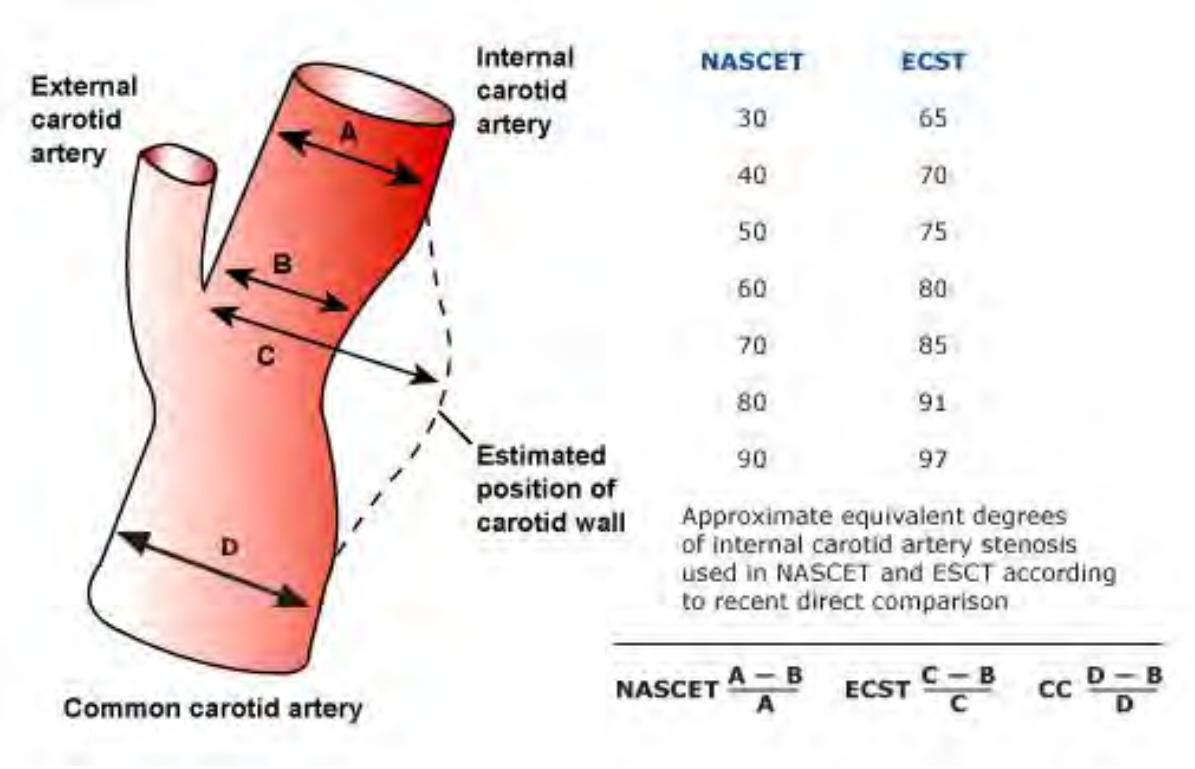
Asymptomatic carotid artery stenosis refers to stenosis of the carotid artery without accompanying neurological symptoms or stroke. Many randomized and controlled studies have shown that there is only a small risk of stroke (1-2%) in asymptomatic cases of carotid stenosis for mild (<50% stenosis) or moderate (50-69% stenosis) (Chatzikonstantinou, 2012). Therefore, medical management and longitudinal monitoring is typically the recommended course of treatment for patients with asymptomatic carotid stenosis. However, sometimes surgical intervention is recommended in cases of asymptomatic patients with a greater degree of stenosis (>80% stenosis). In addition, while asymptomatic carotid artery stenosis may not be a strong indicator for stroke, it does have a strong correlation with atherosclerotic disease in coronary arteries, thus increasing the risk of myocardial infarction (MI) (Chatzikonstantinou, 2012).

Plaque Progression

In patients with carotid artery stenosis, it is important to rank the plaque severity to determine the risk of stroke and whether medical management or surgical intervention is the best option for treatment. Using the imaging techniques mentioned above, the degree of carotid stenosis is measured by determining the diameter of the residual arterial lumen with stenosis

compared to a reference diameter. Lesion severity is graded as mild (<50% reduction in lumen), moderate (50 to 69% reduction in lumen), severe (70 to 99% reduction in lumen), or occluded.

Two studies were conducted in the 1980s concerning the carotid endarterectomy, a type of surgical intervention for carotid stenosis, but they each used different reference point diameters in the artery to compare to the portion with stenosis. These two studies have become the standard methods for measuring residual lumen diameter in North America and Europe (Figure 5) (Fairman, 2021). The North American Symptomatic Carotid Endarterectomy Trial (NASCET) compared the residual lumen diameter of the most stenotic portion of the artery to the lumen diameter in the unaffected internal carotid artery segment distal to the stenosis (Barnett, 1991). The European Carotid Surgery Trial (ECST), on the other hand, compared the residual lumen diameter at the most stenotic portion of the artery with the estimated diameter at the carotid bulb (Warlow, 1993). The carotid bulb referenced in the ECST is located at the carotid bifurcation, and it is a wider segment than the distal segment referenced in the NASCET. Therefore, the extent of stenosis appears to be greater using the ECST method. However, the two methods can be equated such that 50% stenosis with the NASCET method has an equivalent percentage of stenosis of 75% with the ECST method, and 70% stenosis with the NASCET method has an equivalent percentage of stenosis of 85% with the ECST method (Fairman, 2021). In America specifically, NASCET measurements of stenosis is the standard practice used; determining the extent of stenosis gives the physician a better idea of the plaque progression in the artery so that he can calculate the risk of stroke and decide a treatment regimen.



Modified from Donnan, GA, Davis, SM, Chambers, BR, Gates, PC, Lancet 1998; 351:1372. NASCET: North American Symptomatic Carotid Endarterectomy Trial; ECST: European Carotid Surgery Trial; CC: Common Carotid Method.

Figure 5 **NASCET and ECST Methods of Calculating Stenosis**

The figure shows the two methods of calculating percentage of stenosis. The NASCET compares the residual lumen diameter of the most stenotic portion of the artery (B) to the lumen diameter in the unaffected internal carotid artery segment distal to the stenosis (A). The ECST compares the residual lumen diameter at the most stenotic portion of the artery (B) with the estimated diameter at the carotid bulb (C).

IX. Treatment

When discussing treatment for symptomatic carotid artery stenosis, it is important to keep in mind and balance the risk of stroke and the risk of intervention for the patient. There are various medical therapies used to treat atherosclerotic disease and manage the effects of modifiable risk factors. Carotid revascularization is also an option for certain individuals to help reduce the risk of stroke or another significant neurological event. The physician must weigh the many factors present to determine the proper course of treatment for the patient.

Lifestyle Changes

Patients with carotid stenosis due to atherosclerosis should place significant emphasis on making lifestyle modifications. Many modifiable risk factors can be managed with proper diet and exercise. Recently, the Mediterranean diet has been recommended because it focuses on eating fruits, vegetables, whole grains, and olive oil instead of vegetable oil and disapproves of red meat, excess sugar or sugar sweeteners, and alcohol. Switching to a cleaner way of eating has shown reduction in blood pressure, cholesterol, blood glucose, and associated stroke risk (Estruch, 2013). Exercise is also an important lifestyle change that reduces the risk of stroke. Interestingly, physical inactivity has been associated with an increased risk of stroke, heart attack, or vascular death by five-fold. Therefore, the American Heart Association and American College of Cardiology recommend forty minutes of moderate to vigorous-intensity exercise three to four times per week (Eckel, 2014). Lastly, it is extremely important that patients stop smoking, as it can reduce the risk of a future vascular event (Kernan, 2014).

Medical Treatment

All patients presenting with atherosclerotic disease, whether symptomatic or asymptomatic, should undergo intensive medical treatment to manage the effects of carotid artery stenosis due to atherosclerosis. While lifestyle changes certainly help manage modifiable risk factors, oftentimes additional help is needed from pharmacologic agents. Antihypertensives are important medications that control hypertension and reduce the risk of stroke. Patients with blood pressure higher than 140/90 mmHg should receive antihypertensives with the intension of lowering the systolic blood pressure to <120 mmHg (Marchione, 2015).

Additional medical therapy includes statins, such as atorvastatin, which lower LDL cholesterol levels and are indicated in almost all patients with stroke or TIA. While statins are effective at lowering LDL levels, studies have also shown its benefits at slowing plaque progression and stabilizing vulnerable plaques (Marchione, 2015).

Lastly, antiplatelets are one of the most beneficial medical therapies in managing carotid stenosis due to atherosclerosis. Oftentimes, physicians will prescribe dual antiplatelet therapy (DAPT) which uses two antiplatelet drugs, aspirin and clopidogrel, to reduce the risk of stroke. Antiplatelets specifically reduce the ability of platelets to aggregate and form a blood clot in the arteries, thus reducing the risk of thrombosis or embolism of a thrombus. In addition, anticoagulants, such as heparin or warfarin, may also be used together with antiplatelets to slow the body's process of forming clots (Nogles & Galuska, 2021). In many asymptomatic and some symptomatic cases of carotid stenosis, medical treatment is enough to reduce the risk of stroke, but there are also many situations when revascularization with surgical intervention is indicated.

X. Surgical Intervention

Revascularization of the carotid artery with surgical intervention is indicated in specific cases of carotid artery stenosis. It is oftentimes indicated in patients with moderate to severe symptomatic carotid stenosis and asymptomatic patients with >80% stenosis. Interestingly, it has more benefits for men than woman, and medical management is usually the choice of treatment for woman without severe stenosis. In determining an effective course of treatment, the benefits and harms are weighed given the selected method of surgical intervention. Generally, stenosis of <50% in symptomatic cases should be managed with medical treatment because there are more risks than benefits in performing a revascularization procedure. (Fairman, 2021). In order to meet

the general criteria for any revascularization method, it is important that the risk of perioperative stroke and death for the surgeon or hospital is <6% in the last 24 months and no contraindications exist. Contraindications to revascularization include severe comorbidity due to other illness, a disabling ipsilateral stroke, and total or near occlusion of the artery. Once the physician and patient make the decision for surgical intervention, there are three procedures that can be done: carotid endarterectomy (CEA), trans-femoral carotid artery stenting (TFCAS), and trans-carotid artery revascularization (TCAR).

Carotid Endarterectomy (CEA)

The carotid endarterectomy (CEA) has been the gold standard for carotid revascularization procedures since the mid-1900s. Many randomized controlled trials show that this method is safe and effective at minimizing the risk of stroke in symptomatic patients with moderate to severe stenosis (Dacosta, Tadi & Syrowiec, 2021). As seen in Figure 6, during the procedure, the surgeon performs an arteriotomy in which he makes an incision in the neck and carotid artery at the carotid bifurcation or location of the plaque. The surgeon then removes the plaque, and the artery is repaired using sutures or a patch which widens the lumen of the artery. The patient is typically under local anesthesia with or without sedation, and in some cases general anesthesia is used. Low-dose aspirin is recommended daily following surgery to reduce the risk of thrombosis. While this method is invasive, it produces promising results for those affected by moderate to severe symptomatic carotid artery stenosis (Fairman, 2021).

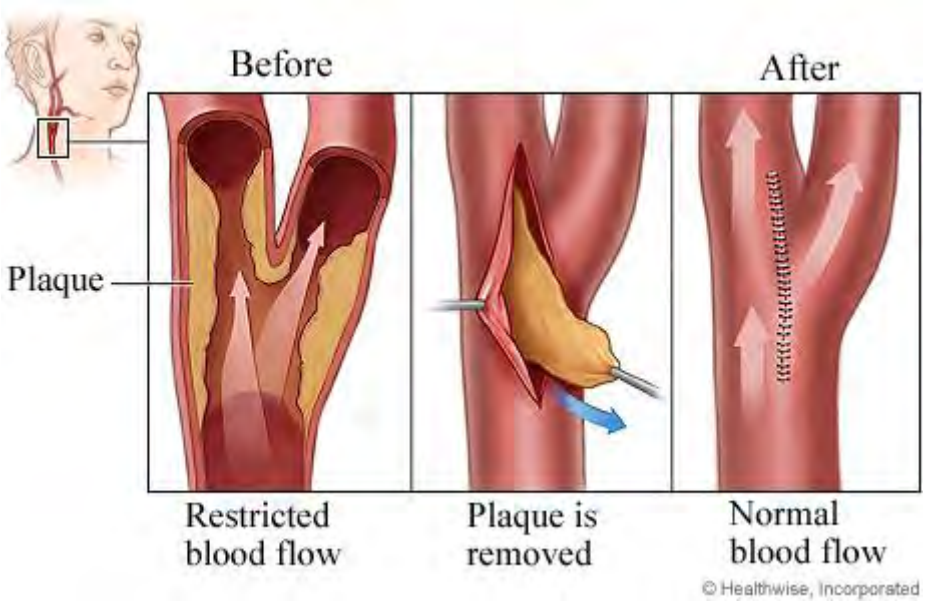


Figure 6 **Carotid Endarterectomy (CEA) Procedure**

In the CEA procedure, the surgeon makes an incision by the carotid bifurcation and manually removed the plaque, thus restoring normal blood flow to the artery

Studies previously conducted have specified requirements for qualifying for CEA and for the proper timing of revascularization with CEA. The NASCET and ECST trials represent the most important data on CEA procedures to date. The NASCET showed that patients with carotid stenosis of >50% are recommended to have the CEA as long as they have a history of TIA or ipsilateral stroke to atherosclerotic lesions (Barnett, 1991). The Asymptomatic Carotid Artery Stenosis (ACAS) trials show that even asymptomatic patients with stenosis of >70% are recommended to undergo the CEA procedure (Rothwell & Goldstein, 2004). Additional qualifications for undergoing the CEA procedure were defined by the NASCET and ECST and included that patients must have a surgically accessible carotid artery lesion, a life expectancy of at least five years, and no prior ipsilateral endarterectomy. In other cases in which the CEA is not

recommended, either patients should be managed with medical therapies or another surgical intervention must be considered (Fairman, 2021).

Once symptomatic candidates for CEA have been identified, it is important to perform the procedure in an appropriate time frame following the last symptomatic event. To obtain the most benefit out of the procedure, it is recommended that the procedure be done within two weeks of onset of symptoms (DaCosta, Tadi, & Surowiec, 2021). The NASCET and ECST trials showed that in the group with >70% stenosis, the CEA had a 30.2% reduction in absolute stroke risk when performed within two weeks of the patient's last neurological event. The percent reduction in absolute stroke risk dropped to 17.6% when the surgery was performed 2-4 weeks after the last neurological event. This stresses the importance of prompt surgical intervention with CEA. While prompt intervention is crucial in treatment, the physician should wait two days since the last neurological event before performing the procedure. The reason for this is that the 48 hours following the neurological event are critical, and the risk of stroke increases during that time period (Fairman, 2021). Therefore, ideally the procedure should be performed 3-14 days following the last neurological event.

Complications that may arise from CEA include myocardial infarction, hyperperfusion syndrome, cranial nerve injury (specifically the hypoglossal, vagus, glossopharyngeal, and facial nerves), perioperative stroke, restenosis, or death. However, these complications happen infrequently; a systematic review of the risks of stroke and death due to CEA in symptomatic patients found a 5.18% and 1.8% rate of 30-day complication and mortality, respectively (Rothwell & Goldstein, 2004). In addition, the skill of the surgeon contributes significantly to patient outcome which is why it is important that the surgeon has a 30-day perioperative morbidity and mortality rate of <6% (Barnett, 1991). While there are benefits and risks for CEA,

it has remained the standard of care for carotid revascularization for many decades. Until recently, the only other procedure to produce outcome results similar to it was the transfemoral carotid artery stenting technique (Fairman, 2021).

Transfemoral Carotid Artery Stenting (TFCAS)

The transfemoral carotid artery stenting (TFCAS) intervention was introduced in 1996 as an alternative, minimally invasive technique to the CEA procedure (Schermerhorn *et al*., 2019). As the standard for endovascular revascularization, it reduces the risk of embolization, thrombosis, and long-term restenosis. During the procedure, a sheath and catheter are placed in the femoral artery in the groin followed by a carotid stent. The stent is advanced until it reaches the carotid artery and then expanded. An angioplasty balloon is used to ensure the stent is positioned properly against the arterial wall and stabilizes the plaque. The surgeon will use an embolic protection device to filter and catch any debris that may break off during the procedure, and intraoperative imaging and contrast material is used to visualize the vessels. Typically, a local anesthetic is used with minimal to no sedation. After the procedure, DAPT is prescribed for at least 30 days to minimize the risk of thrombosis (Fairman, 2021).

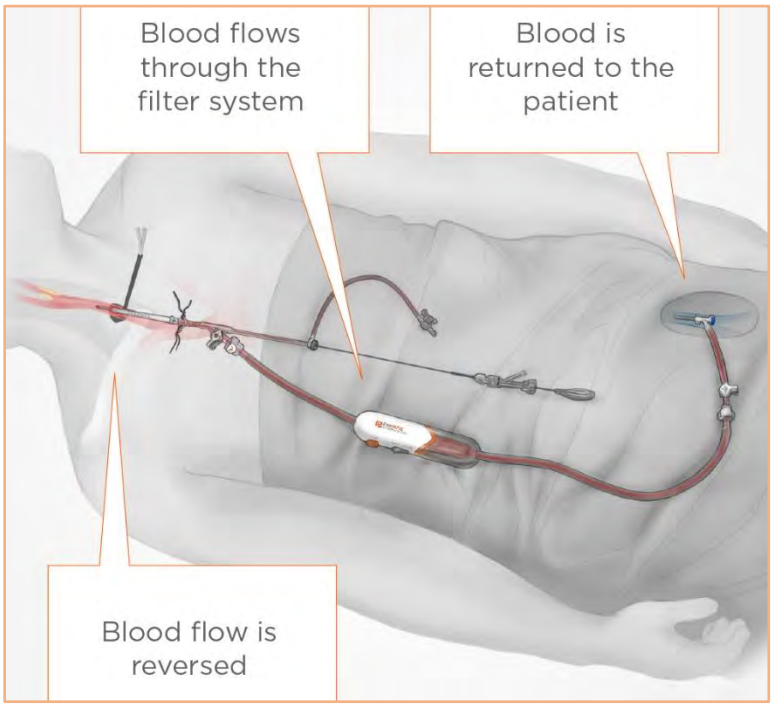
Many studies have been conducted to compare the outcomes of CEA vs. TFCAS. The Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST) determined that composite outcomes (stroke/death/MI) are similar between the two procedures. Unfortunately, the CREST trial also found that the TFCAS method has an increased risk of 30-day perioperative stroke compared to the CEA, likely due to aortic arch manipulation resulting in embolization. In fact, a meta-analysis done in 2012 found that the 30-day risk of perioperative stroke or death was 8.2% for TFCAS vs. 5.0% for CEA (Schermerhorn *et al*., 2019). Interestingly, the CREST trial

showed that outcomes of CAS were slightly better for younger patients <70 years old, while outcomes of CEA were slightly better for patients >70 years old (Mantese *et al*., 2010). Because the CEA is still the ideal method of choice for revascularization, the TFCAS is typically only used when the patient is high risk for CEA. Specific conditions for selecting TFCAS over CEA include patients who have a carotid lesion that is not suitable for surgical access; restenosis after endarterectomy; clinically significant cardiac, pulmonary, or other disease that increases the risk of surgery and anesthesia; or unfavorable neck anatomy for CEA, such as contralateral vocal cord paralysis or open tracheostomy. In all other cases of severe stenosis (70 to 99%) and a recent symptomatic event (3-14 days before), the recommended treatment is the CEA (Fairman, 2021).

Transcarotid Artery Revascularization (TCAR)

CEA has remained the standard method of revascularization due to the risks associated with TFCAS. Nevertheless, TFCAS is still done in certain situations, and for many years it was the best endovascular option for revascularization (Fairman, 2021). However, vascular surgeons wanted a safer endovascular technique for patients that was comparable to the effectiveness of CEA. Therefore, a novel stenting method was introduced in 2015 called the transcarotid artery revascularization (TCAR) procedure. It combines carotid bifurcation stenting with an advanced reversal of blood flow, so the risk of plaque embolization is minimized. In preparation for the procedure, patents are prescribed the DAPT regimen statins. During the procedure, the surgeon makes a small incision (2 to 4 cm) just above the collarbone ipsilaterally to the atherosclerotic plaque. A sheath is placed inside the carotid artery as well as a neuroprotection system. This system provides CEA-like neuroprotection for the patient through high-rate temporary flow

reversal; any blood flowing to the brain is reversed and redirected outside the body where it gets filtered through a device before it is returned to the body via a sheath in the femoral vein (Figure 7). Once the flow reversal system is in place, a stent is placed inside the carotid artery to stabilize the plaque and prevent future stroke (Figure 8). Fluoroscopy is used to monitor the procedure and visualize the arteries, and the TCAR is typically performed using a local anesthetic with or without sedation (Malas *et al*., 2017).



https://silkroadmed.com/patient-caregivers/the-tcar-procedure/

Figure 7 **TCAR Neuroprotection System Providing Flow Reversal**

The neuroprotection system is inserted into the carotid artery, and reversal of flow moves the blood out of the body where it gets filtered before returning to the patient in the femoral vein.

https://silkroadmed.com/patient-caregivers/the-tcar-procedure/

Figure 8 **TCAR Stent Insertion**

Using a catheter, a flexible mesh stent is placed inside the carotid artery and stabilizes the plaque.

The primary study conducted evaluating the TCAR procedure is the Safety and Efficacy Study for Reverse Flow Used During Carotid Artery Stenting Procedure (ROADSTER). The initial results of the TCAR procedure as described by the ROADSTER multicenter trial show that TCAR with ENROUTE neuroprotection system is a safe and effective method for preventing a stroke. The 30-day perioperative stroke rate was only 1.4% in surgical high-risk patients, which is lower than in patients who had the TFCAS procedure. Additionally, 1.4% of patients died, and 0.7% of patients suffered an MI, thus resulting in a 30-day stroke/death/MI rate of 3.5% (Kwolek *et al*., 2017). The ROADSTER 2 trial had a 30-day stroke/death/MI rate of just 1.7% (Kashyap *et al*., 2020). These low rates of stroke, death, and MI with the TCAR are most likely due to avoidance of aortic arch manipulation and the advanced neuroprotection

system. With TFCAS, it is often difficult to avoid aortic arch manipulation which results in embolization and subsequent stroke, death, or MI. With the TCAR procedure, the flow reversal system also protects against embolization by plaque that breaks free during the procedure (Kwolek *et al*., 2017).

The results of TCAR were also comparable to CEA results, as the Transcarotid Artery Revascularization Surveillance Project showed no significant differences in 30-day perioperative stroke or death outcomes between TCAR and CEA. In fact, the results for the TCAR procedure were obtained using a high-risk patient population, which shows the similar effectiveness of the TCAR compared to CEA. The main difference in outcomes between the TCAR and CEA was significantly lower rates of cranial nerve damage with the TCAR procedure because there is only one vulnerable cranial nerve that can be injured in the TCAR procedure vs. four in the CEA (TCAR Surveillance Project, 2022). Additionally, the positive results were obtained from surgeons with little to no experience in the TCAR procedure, which speaks to the safety of the procedure (Kashyap *et al*., 2020). There is also reduced operative time with the TCAR procedure, which is beneficial to both the surgeon and patient (Schermerhorn *et al*., 2019). The preliminary results of TCAR studies are promising because no other method to date has had comparative results in outcomes to CEA. Because of the introduction of the TCAR and emerging data on its effectiveness, it is likely that the TCAR will become the standard of care in the future for revascularization.

XI. Expert and Vascular Surgeon, Dr. Jaime Benarroch-Gampel

Dr. Jaime Benarroch-Gampel, a vascular surgeon at Emory University, is one of the many surgeons around the world who has begun using the novel TCAR procedure to treat carotid

artery stenosis. He can testify from first-hand experience that the technique is effective and safe and a major contribution to the field of vascular surgery. He says that over time the TCAR procedure has been used more frequently and is slowly becoming the standard for revascularization of patients with carotid stenosis. He is impressed by the results of the current studies that show that stroke and death rates for TCAR vs. CEA are essentially the same. The only major differences between the two procedures are that the TCAR has a shorter operative time; it is minimally invasive vs. an open surgery; and there is a smaller risk for nerve injury.

From his own experience, he has observed that it is easier to have the patient awake for a TCAR procedure since the incision is much smaller than in a CEA. This is beneficial to patients who are at high cardiac risk and should not be under general anesthesia. The TCAR is also an easier procedure for the surgeon to perform after he learns how to do it. Dr. Benarroch is excited about the procedure because the carotid endarterectomy has been around for almost seventy years, and the TCAR is the first procedure to date that has had similar clinical outcomes to it. He commented on the TFCAS procedure and said that it is only used in very specific circumstances, but overall, it is not performed so often. Therefore, the TCAR is really the only other procedure that rivals the CEA.

When determining which intervention to use on a patient, either the CEA or TCAR, Dr. Benarroch talks to the patients and decides with them which option is best. For example, he may recommend the TCAR procedure if the patient is at high cardiac risk. Typically, his standard procedure is still the CEA, despite his performance of many TCAR procedures. His reasoning is due to the long-term data available for the CEA; the TCAR procedure was only introduced in 2015, so there are no long-term evaluations of outcomes and restenosis. He also says that while the CEA is a more invasive procedure, the risks are minimal, and the surgery is safe. However,

he still performs the TCAR and recommends it to many patients who will benefit from it more than the CEA.

XII. Future Direction of TCAR

Because of the promising outcome results for TCAR thus far, Dr. Benarroch-Gampel has taken an interest with the procedure in his research and is invested in contributing to the available data on the effectiveness of the procedure. He says that the more data surgeons have on the procedure, the more willing they will be to implement it as a standard of care.

His current interest with the TCAR procedure involves determining its effectiveness as an initial vs. "redo" procedure to treat carotid stenosis. Oftentimes a patient will present with restenosis after an initial revascularization procedure, in which case the surgeon must determine the best course of treatment. Now that the TCAR procedure has been introduced, it can be a potential option for a "redo" revascularization procedure to treat the patient's restenosis. Therefore, Dr. Benarroch-Gampel wants to determine the TCAR's effectiveness at treating restenosis following a prior ipsilateral surgical intervention (CEA or TFCAS); additionally, he wants to compare those results to its effectiveness as an initial intervention for carotid stenosis in general.

I assisted Dr. Benarroch-Gampel with his research this past summer and helped him write a proposal to the Vascular Quality Initiative (VQI). The VQI is a national quality improvement database that has data on every vascular procedure performed. The VQI sent him the data on all CEA, TFCAS, and TCARs performed so that we could evaluate the TCAR's effectiveness as an initial vs. "redo" intervention. We plan to evaluate the data this upcoming summer and add to the research on TCAR conducted thus far.

XIII. Conclusion

Carotid artery stenosis and associated strokes have been of concern as they are one of the leading causes of death and disability worldwide. Fortunately, there are many types of treatments to manage carotid artery stenosis. Medical treatment and surgical intervention have shown promising results, and the introduction of the TCAR procedure is a significant contribution to the field of vascular surgery. Until the TCAR procedure, no other surgical procedure had been as effective at minimizing the risk of stroke or death as the CEA. The implementation of this new minimally invasive procedure has already benefitted many patients and will hopefully continue to do so in the future.

XIV. Acknowledgements

Firstly, I want to thank all the teachers at Stern College for Women who have taught me throughout my three years here. Thank you to Dr. Alayev for your mentorship and support while I wrote my thesis. Your guidance was extremely helpful, and I am so appreciative for everything you have helped me with. Thank you to Dr. Wachtell for your incredible leadership of the Honors Program. I have enjoyed the honors classes and events I have attended and am appreciative that I had those opportunities. Thank you to Dr. Jaime Benarroch-Gampel for allowing me to shadow you in surgery and clinicals and assist you with your research projects. It has been a privilege to work with you, and your mentorship over the last three years has been extremely meaningful. Thank you to my parents and family for your continuous support and love always. Lastly, thank you to my friends for always being there for me. You made the last three years so memorable, and I could not have gotten through college without you.

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