Carotid Artery Calcification: What We Know So Far

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Abstract

Carotid artery calcification (CAC) is a well-known marker of atherosclerosis and is linked to a high rate of morbidity and mortality. CAC is divided into two types: intimal and medial calcifications, each with its own set of risk factors. Vascular calcification is now understood to be an active, enzymatically regulated process involving dystrophic calcification and endothelial dysfunction at an early stage. This causes a pathogenic inflammatory response, resulting in calcium phosphate deposition in the form of microcalcifications, which causes plaque formation, ultimately becoming unstable with sequelae of complications. If the inflammation goes away, hydroxyapatite crystal formation takes over, resulting in macro-calcifications that help to keep the plaque stable. As CAC can be asymptomatic, it is critical to identify it early using diagnostic imaging.

The carotid artery calcification score is calculated using computed tomography angiography (CTA), which is a confirmatory test that enables the examination of plaque composition and computation of the carotid artery calcification score. Magnetic resonance angiography (MRA), which is sensitive as CTA, duplex ultrasound (DUS), positron emission tomography, and computed tomography (PET-CT) imaging with (18) F-Sodium Fluoride, and Optical Coherence Tomography (OCT) are some of the other diagnostic imaging modalities used. The current therapeutic method starts with the best medical care and is advised for all CAC patients. Carotid endarterectomy and carotid stenting are two treatment options that have mixed results in terms of effectiveness and safety. When patient age and anatomy, operator expertise, and surgical risk are all considered, the agreement is that both techniques are equally beneficial.

Introduction And Background

Carotid Artery Calcification (CAC) has been recognized as a symptom of aging for decades. Vascular calcification, once thought to be a passive and degenerative process, is now widely recognized as an active and self-regulating process involving complex cellular and enzymatic components. Vascular calcification is well documented to play a role in the progression of atherosclerosis, and it can be found in 80-90% of atheromas [1]. Calcification can develop in the medial and intimal layers of smaller elastic vessels, such as the intracranial and cervical carotid arteries [2]. Atheromatous plaques arise because of intimal calcification, which can lead to vascular stenosis, occlusion, or other secondary degenerative alterations [2]. Symptomatic carotid artery stenosis, ischemic stroke, blindness, cognitive impairment, and severe morbidity and mortality are all possible outcomes of such changes. Current research on CAC epidemiology and risk factors, pathogenesis, and the best clinical diagnostic and management approaches are reviewed in this article.

Review

In a cohort analysis of 1132 patients, predominant intimal calcification was found in 75% of males over 75-years-old and 62% of females over 75-years-old in a comprehensive review [3]. As Wu et al. point out, the Rotterdam research, the biggest population-based cohort study in a general community with 2,495 participants, backs this up [5,8]. The Rotterdam study established carotid artery calcification as a substantial risk factor for stroke in the White population after assessing cerebral carotid artery calcification volume on CT scans in 2,323 stroke-free older Caucasian patients. The findings also revealed that cerebral carotid artery calcification contributes more to all-cause strokes than large-artery
atherosclerosis, contrary to popular belief [5,9].

Diabetes, hypercholesterolemia, smoking, and hypertension are all known risk factors for the development of cardiovascular and systemic atherosclerotic disease in CAC [5]. Smoking and high blood pressure are two risk factors for dominant intimal calcification. Hypertension damages endothelial cells, resulting in pro-inflammatory activity and decreased vascular contractility, which leads to atherosclerosis.

Type 2 diabetes mellitus (T2DM), chronic kidney disease (CKD), end-stage renal disease (ESRD), and osteoporosis, all of which have an inherent calcium-phosphate imbalance, are major risk factors for Monckeberg medial calcification. Men and T2DM patients are more likely to develop this form of vascular calcification. Patients with ESRD who showed medial calcification were younger, had a higher prevalence of the calcium-phosphate problem and were hemodialysis dependent [10]. Calciphylaxis is a specific manifestation of medial calcification reported in hemodialysis patients [5,10-15].

Pathogenesis and pathophysiology

Some similarities and variations exist between the mechanisms underlying intimal and medial calcification. Microcalcifications, also known as spotty calcifications, occur during the first stage of intimal calcification, which is characterized by an acute inflammatory response. Several investigations have established that these little calcium deposits (0.5 to 1.5 m) are an insidious source of plaque instability, since they have been found in high-risk, unstable, and ruptured plaques in abundance [2,16-18].

Endothelial dysfunction of the vascular intima results in the deposition of low-density lipoprotein particles (LDLs) within the intimal layer of the artery, which starts the pathological process of microcalcification development. The presence of low-density lipoprotein cholesterol (LDLC), oxidative stress, and other harmful elements cause an inflammatory reaction within the artery wall, resulting in the release of cytokines including tumor necrosis factor (TNF) and Interleukin-1β (IL-1B) [2,19]; Monocytes, vascular smooth muscle cells (VSMCs), and other inflammatory cells in the intima migrate and proliferate in response to these cytokines [2,19]. When monocytes attempt to phagocytize deposited LDLs, they form lipid-laden macrophages, also known as foam cells. The oxidation of lipoproteins is an unpleasant and unanticipated side effect of this. These oxidized lipids are particularly hazardous to macrophages, causing apoptosis or necrosis [16]. When macrophages die, phagocytized material is released from the cells in vesicles, which act as a nidus for calcium phosphate deposition. Macrophages and VSMCs release vesicles during intimal calcification, while VSMCs release them during medial calcification [10]. A plaque forms when inflammatory material microcalcifies and develops a necrotic core beneath it.

The process of artery damage, necrosis, and surface microcalcification continue indefinitely if acute inflammation persists, and the vascular layer never entirely recovers. This creates an intrinsically unstable plaque that is prone to rupture and thrombus development [16-18].

If the inflammation eventually subsides, plaque reformation and stability can take place. Chondrocyte-like VSMCs direct a regulated mineralization process and the production of stabilizing macrocalcification, which drives plaque remodeling [16].

This calcification process resembles chondrogenesis and osteogenesis in appearance [2,5,19]. Matrix Gla Protein (MGP), Osteocalcin (OC, also known as bone Gla protein), Bone Sialoprotein (BSP), Bone Morphogenetic Proteins (BMP) 2, 4, 6, and 7, Osteopontin (OPN), and Osteonectin (ON) are only a few of the proteins that have been linked to the osteogenic transformation of VSMCs [5,19]. BMP2, BMP4, and BMP6 are the proteins that are thought to be most important in atherogenic calcification [12,17,19]. BMPs are members of the transforming growth factor-beta (TGFβ) family and are required for appropriate bone formation, angiogenesis, vascular homeostasis, and a variety of physiological activities [12,17,19].

BMP2 and BMP4 cause medial VSMCs and macrophages to develop into osteoblast-like phenotypes during medial calcification. The vascular extracellular matrix is then transformed into a cartilaginous matrix by these cells. The matrix of the cartilage is calcified, and hydroxyapatite crystals develop. Endochondral ossification of bone is the same process [2,5,12]. These crystal aggregates eventually merge to generate macro-calcification calcified sheets or plaques.

Because BMPs are tightly regulated and can be suppressed by a variety of modulator proteins, including Osteopontin, Gremlin, Noggin, and uncarboxylated Matrix Gla Protein (MGP), the progressive mineralization that generates macro-calcification that stabilizes the plaque and prevents additional inflammation [5,12,16].

Clinical Manifestations

There are no specific clinical indications for carotid artery calcification. On the other side, this phenomenon is sometimes misconstrued as a proxy for atherosclerosis, leading to clinical indications being misinterpreted as atherosclerosis issues. Because it can be a marker of luminal stenosis, arterial calcification
is associated with ischemic symptoms. Signs and symptoms arise when an artery is highly stenotic or completely occluded. The most common signs and symptoms include bumps, amaurosis fugax, contralateral weakness or numbness of an extremity or face, with significant sparing of the forehead, dysarthria, aphasia, transient ischemic attack (TIA), or ischemic stroke.

**Symptomatic vs Asymptomatic Carotid Artery Plaques**

Shaalan et al. used Spiral CT to measure the percent plaque calcification area and performed an assessment of carotid plaque calcification. They discovered that asymptomatic patients had two times more plaque calcification area than symptomatic patients (48% +/-19% versus 24% +/-20%; P0.05) [20]. Shaalan et al. concluded that higher carotid artery plaque calcification is associated with plaque stability and could serve as a quantitative measure for cerebrovascular ischemia event risk based on this and other findings throughout their investigation [20]. Hunt et al. found that patients with calcified carotid plaques had fewer symptoms of stroke and transient ischemic attack (P = 0.042) than patients with non-calcified carotid plaques [21].

Shi et al. recently discovered that asymptomatic patients exhibited plaque calcification areas that were two times larger than symptomatic patients [2,22]. Intraplaque bleeding and ulceration were frequently found in plaques with a greater calcification volume and numerous calcifications. Multiple calcifications may trigger a stronger inflammatory response, increasing the risk of the plaque becoming ulcerated and hemorrhagic, according to one theory. While the authors acknowledged that plaque calcification and plaque stability are linked, they were skeptical about the information's utility in forecasting future cerebrovascular accidents [2,23-26]. Asymptomatic carotid plaques are more calcified than symptomatic plaques, according to Wu et al., and extracranial carotid plaque calcification is linked to plaque stability [5]. They also disclosed a study that used carotid-femoral pulse wave velocity and 24-hour ambulatory pulse pressure to quantify arterial stiffness. There was increased stiffness in major cerebral arteries in patients without stroke and with asymptomatic intracranial atherosclerosis, according to this study [27].

According to the findings from the various sources, calcified carotid artery plaques may be more stable than non-calcified carotid artery plaques. The findings of Fisher et al. and Wu et al., on the other hand, are in opposition to this [5,28]. Patients who were asymptomatic were compared to patients who had stroke symptoms ipsilateral or contralateral to the plaque by Fisher et al. They discovered that asymptomatic, ipsilateral symptomatic, and contralateral symptomatic patients all had similar plaque calcification averages (16%, and 15%, respectively; P0.001), leading them to conclude that the extent of carotid plaque calcification had no relation to symptoms [28].

**Stroke and Transient Ischemic Attack**

There was a decreased incidence of stroke and TIA in patients with carotid plaques composed of large calcific granules, compared to those without calcification (P = 0.021) and large calcifications were inversely related to plaque rupture [2,21]. Hunt et al. also found that 52 out of the 142 patients who had a TIA or stroke, 65% (n = 34) did not have any carotid plaque calcification, while 35% (n = 18) had a calcified plaque (P = 0.042) [21]. In contrast, Golüke et al. found that intimal and medial intracranial carotid artery calcifications were significantly associated with stroke [21]. They discovered that asymptomatic, ipsilateral symptomatic, and contralateral symptomatic patients all had similar plaque calcification averages (16%, and 15%, respectively; P0.001), leading them to conclude that the extent of carotid plaque calcification had no relation to symptoms [28].

Several studies correlated carotid artery calcifications and cardiovascular disease. Dominant intimal calcifications were significantly associated with myocardial infarction (adjusted OR 2.27 and 4.45, respectively) [29]. Patients with carotid plaques composed of large sheets of calcium were more likely to have coronary artery disease (P < 0.0535) [21]. Shaalan et al. concluded that there was no difference between the prevalence of atherosclerotic risk factors between symptomatic and asymptomatic groups, except for hypercholesterolemia, which had a higher prevalence in the group with symptomatic carotid artery plaques (56% vs 26%; P < 0.05) [20].

Other well-researched clinical manifestations associated with intracranial carotid artery calcification include deep cerebral microbleeds and white matter hyperintensities, as described by Wu et al. Cognitive decline and dementia are well studied as proposed clinical manifestations of carotid artery calcification. Suggested mechanisms relate to decreased cerebral blood flow regulation leading to cognitive deficits. Chu et al. described a significant negative correlation between carotid artery calcification scores and cognition (R = -0.359, P < 0.001), in a study of 102 patients with confirmed carotid artery calcification using color doppler ultrasound, multi-detector row spiral CT angiography, and MRI scanning [31]. Furthermore, a cross-sectional study of 2,414 non-demented people in the Rotterdam Study, followed by a subsequent longitudinal study, both demonstrated a cognitive decline in individuals with larger intracranial carotid artery calcification volume [5,8,32].
Diagnostic methods

Diagnostic techniques for carotid artery calcification have advanced in sophistication over time. Improved diagnostic tools aid in the early detection of potentially life-threatening disorders as well as clinical decision-making. Although duplex ultrasonography (DUS) is often the first diagnostic test indicated for carotid artery stenosis evaluation, confirmatory imaging modalities such as magnetic resonance angiography (MRA) or computed tomography angiography (CTA) is currently used. These diagnostic tests are used to guide therapeutic measures, such as procedure planning. Another regularly scheduled screening technique that has been shown to detect calcified atheromas in the carotid artery is panoramic radiography. The frequency of confirmed accidental carotid artery calcification identified on panoramic radiography ranges from 2% to 5%. [33]. Duplex ultrasound is frequently performed after this test, and the results are validated with computed tomography angiography or magnetic resonance angiography. More advanced imaging technologies, including optical coherence tomography (OCT), photoacoustic tomography, and infrared thermography, have been developed to characterize plaques [34]. PET-CT imaging using (18)F-Sodium Fluoride was originally developed to detect calcifying metastases, but it is currently utilized to detect and quantify microcalcification in atherosclerotic plaques. Its relationship with cardiovascular risk factors makes it a helpful noninvasive approach for determining the amount and severity of carotid artery calcification [35-37].

Duplex Ultrasound (DUS)

Duplex ultrasonography (DUS) is one of the most used and well recommended initial diagnostic tests for carotid artery disease since it is non-invasive, low-cost, and accurate. It enables for direct visualization of vessel shape as well as flow measurement. It has a sensitivity of 86.4 for 50% stenosis and 92.1 for 100% stenosis, as well as a specificity of 90.1 for 50% stenosis and 89.5 for 100% stenosis [33]. DUS cannot tell the difference between high-grade stenosis and total occlusion, which is a disadvantage [38].

Computed Tomography Angiography (CTA) and Magnetic Resonance Angiography (MRA)

The use of intravenously supplied iodine contrast medium and complete vascular visualization to diagnose carotid artery disease using Computed Tomography Angiography (CTA) allows for the assessment of stenotic degree. This diagnostic modality allows for plaque composition characterization and calcification score computation in the carotid artery. CTA has a sensitivity of 89% for 50% stenosis and 99% for 99% stenosis, according to Anderson et al. [39]. The specificity reported was 91% for 50% stenosis and 99% for 100% stenosis [39]. CTA was proven to be nearly 100% accurate for total blockage and stenosis between 0 and 29% [39]. CTA and magnetic resonance angiography (MRA) are both sensitive, but CTA has a greater specificity [34]. The requirement for intravenous contrast injection and radiation exposure are both disadvantages of CTA [38]. MRA is a non-invasive way of detecting stenotic vessels that can be utilized with or without contrast. Similarly, to DUS, MRA may exaggerate the degree of stenosis; consequently, combining DUS and MRA is more accurate than doing either test alone [38].

PET-CT imaging with (18)F-Sodium Fluoride

PET-CT imaging with (18)F-Sodium Fluoride (18F-NaF) is a molecular imaging technique that uses an 18 Fluoride-labeled sodium fluoride radiotracer to detect areas of necrotic inflammation and metabolic activity in atherosclerotic plaques. Berlin et al. found a significantly significant connection (r = 0.85; P.0001) between the occurrence and amount of artery wall calcification and 18F-sodium fluoride absorption [36]. When compared to other PET radiotracers, 18F-sodium is cleared from circulation faster, has no superfluous soft-tissue uptake, and has a much higher absorption in important artery walls than 18F-FDG [16, 35-37]. Because CT scans can only identify large areas of calcification, they are more likely to overlook newer and smaller calcifications. With the help of x-ray attenuation, 18F-NaF was able to detect microcalcifications not evident on CT [35-37, 40]. There was also a statistically significant relationship between tracer uptake in the common carotid arteries and cardiovascular risk variables such as age, male sex, hypertension, hypercholesterolemia, and cumulative smoking exposure (P.0001) [35-37,41-45].

Optical Coherence Tomography (OCT)

The highest resolution of any intravascular imaging method is optical coherence tomography (OCT), which can be used to classify the volume of calcification. This enables the visualization of plaque shape, calcification features, and potential vulnerability in more detail. It is extremely sensitive and specific for assessing carotid artery calcification [34]. An intravascular OCT catheter was used to see the artery wall, and the imaging results were consistent with those obtained from histological inspection. When OCT was first employed during carotid artery stenting, it successfully detected fibrocalcific carotid plaque disruption, thrombosis, and plaque protrusion in 17 individuals [34]. After angioplasty and stenting, OCT has been successfully used to detect possible stenting problems such as plaque ulceration and thrombus development. However, because of its invasiveness, further research is needed before it may be used more widely [34,46].

Current management strategies
Medical Management

The goal of medical care in individuals with carotid atherosclerotic disease is to reduce the number of cerebrovascular episodes. Chimowitz et al. observed that patients who underwent a stenting surgery with intensive medical therapy had a 20.0% one-year rate of stroke or death, compared to 12.2% in patients who received aggressive medical management alone (P = 0.009) [47]. They determined that medical care alone was superior to medical management combined with percutaneous angioplasty and stenting in terms of lowering the risk of stroke [47].

Risk factor adjustment, antithrombotic treatment, and statin medication are all recommended for optimal management. Regardless of symptoms or stenosis severity, this is suggested for all individuals with carotid stenosis [48-50].

Modification of risk factors can include the following: 1) A systolic blood pressure target of 140/90 mmHg, 2) LDL cholesterol reduction, 3) smoking cessation and 4) moderate to vigorous-intensity aerobic physical exercise of at least 40 minutes per day, three to four days per week [38, 48, 50]. Clinicians should prescribe a low, moderate, or high-intensity statin depending on the patient’s 10-year risk of atherosclerotic cardiovascular disease [38, 48]. Aspirin 325 mg per day and an antiplatelet medication are used as antithrombotic treatment [38, 47].

Carotid Endarterectomy and Carotid Stenting

Carotid endarterectomy is a treatment that is performed to reduce the risk of TIA and stroke in those who have carotid atherosclerosis. A qualified surgeon should execute the surgery, which involves accessing the common and/or internal carotid arteries via the sternocleidomastoid muscle and removing atheromatous plaque material [51]. Plaque clearance should improve cerebrovascular perfusion by increasing the luminal size. Even though the technique has been used for decades, the inherent dangers of the surgery need clinicians and patients to carefully weigh the benefits and risks before opting to undergo it. The North American Symptomatic Carotid Endarterectomy Trials (NASCET) and the Asymptomatic Carotid Artery Stenosis (ACAS) trials for endarterectomy were conducted in 1987, and the current treatment recommendations and indications for endarterectomy are based on these trials [49, 51-52]. Carotid endarterectomy (CEA) is advised for symptomatic patients (those who have had a TIA or stroke in the past) if carotid stenosis is 50% or greater, and it must be conducted soon after the onset of symptoms to be useful [51]. CEA is suggested for carotid stenosis of 70% or greater in asymptomatic patients [49, 51].

The current standard endovascular therapy intervention for carotid atherosclerotic disease is carotid stenting [48, 53]. For patients who are unable to undergo endarterectomy, stenting is an option [48]. There are several carotid vascular access and stent implantation techniques available, each with its own set of risks and benefits [48]. Stenting can be done percutaneously with a transfemoral approach or by a tiny incision in the neck with a transcervical technique [48]. Patients aged 80 and up have a higher chance of negative outcomes after transfemoral stenting, however, this is not the case with the transcervical method [48, 54]. Several strategies are employed to prevent embolic stroke during the stenting procedure, however, there is no conclusive evidence that one method is better than the others [48].

Muller et al. conducted a systematic review that compared the safety and efficacy of stenting versus carotid endarterectomy in 5,596 participants with symptomatic and asymptomatic carotid artery stenosis. The primary outcome was death or stroke occurring up to 30 days after treatment. Up to 30 days after stenting, there was a significantly increased risk of death or stroke (OR 1.70, 95% confidence interval (CI) 1.31 to 2.19; P = 0.0001). Data from six of the trials revealed that participants over the age of 70 were twice as likely to die or have a stroke up to 30 days after stenting (OR=2.23, 95 % CI 1.61 to 3.08; P0.0007) [54]. However, after four years of follow-up data, it was determined that stenting and endarterectomy were equally effective in the long term in preventing recurrent stroke [54]. CAC risk factors vary depending on whether the calcification is intimal or medial dominant. There were 37 studies used in this review (Table 1).

| Risk factors, pathogenesis, clinical manifestations, diagnostic techniques and management of carotid artery calcification |
|--------------------------------------------------|
| **Author** | **Country** | **Study population** | **Findings** | **Conclusion** |
|-----------|---------|------------------|----------------|---------------|
| 1 Vos et al., 2018 [3] | Netherlands | 1132 patients with AIS | Dominant intimal and medial calcification was present in 30.9% and 46.9% of patients, respectively. Pulse pressure, age, and family history were risk factors for both. Adjusted risk factors for intimal calcification were smoking (OR: 2.09) and hypertension (OR:2.20), while medial calcification risk factors were diabetes mellitus (OR: 2.39) and history of vascular disease (OR:2.20) | Different risk factors exist for intracranial ICAC depending on localization to the medial or intimal layer |
| 515 studies | | | For people between the ages of 30-79 years, prevalence of increased | |
| No. | Authors, Year | Country | Study Design | Participants | Summary |
|-----|---------------|---------|--------------|--------------|---------|
| 2   | Song et al., 2020 [4] | Netherlands | Meta-analysis regarding atherosclerotic disorders | Carotid intima-media thickness was 27.6%, carotid plaque was 21.1%, and carotid stenosis was 1.5%, all of which increased with age. Common risk factors for increased carotid thickness and carotid plaque were smoking, diabetes, and hypertension Carotid atherosclerosis is highly prevalent around the world |
| 3   | Chen et al., 2006 [6] | China | 490 patients referred for brain CT | 60% of intracranial calcifications were ICAC. Age (RR= 2.795), history of ischemic stroke (RR= 3.915) and white blood cell count (RR= 1.107) were all independently associated with IAC. Many other risk factors such as hypertension, heart disease and ischemic stroke (p<0.001) were significantly prevalent in patients with artery calcification IAC is associated with white blood cell count, age, and history of ischemic stroke |
| 4   | Mak et al., 2009 [7] | China | 60 patients with TIA or ischemic stroke | Intracranial internal carotid artery was the most severely affected vessel in patients. Diabetes mellitus and age were both significant risk factors for IAC among patients, p=0.004 and p=0.02 respectively Internal carotid artery was the most severely calcified vessel, and IAC was associated with diabetes mellitus and age |
| 5   | Bos et al., 2012 [8] | Netherlands | 2495 patients who underwent brain CT | ICAC was present in 82.2% of patients. Excessive alcohol consumption (OR: 1.74) and smoking (OR: 1.72) were strong risk factors of ICAC for men; diabetes (OR: 2.02) and hypertension (OR: 1.79) were risk factors for women. Age was a risk factor in both men and women ICAC is very common and risk factors for ICAC differ in men and women |
| 6   | Bos et al., 2014 [9] | Netherlands | 2323 patients who underwent brain CT | Of patients who suffered from stroke (n=91), 74 were ischemic strokes. 75% of all strokes were related to ICAC. Increased ICAC volume was correlated with increased risk of stroke (HR: 1.43) Intracranial atherosclerosis increases risk of stroke in white population |
| 7   | Nigwekar et al., 2017 [11] | USA | 40 patients receiving hemodialysis | Patients with calciphylaxis had a lower fraction of carboxylated MGP (cMGP) compared to controls (p=0.003). Vitamin K deficiency was associated with lower cMGP (p=0.04), and low cMGP was correlated with an increase in calciphylaxis risk Vitamin K deficiency reduced cMGP concentration and may have a role in calciphylaxis |
| 8   | Bugnicourt et al., 2009 [14] | France | 340 patients with AIS | IAC in stroke patients (n=259) was associated with carotid atherosclerosis >50%, age and GFR. Calcification in non-stroke patients (n=103) was associated with age, arterial hypertension and GFR Risk factors for IAC were present in patients with and without ischemic stroke, while the frequency of calcification was greater in stroke patients |
| 9   | Power et al., 2011 [15] | United Kingdom | 2225 patients receiving hemodialysis | IAC was seen in 95% of patients with ischemic stroke and 83% of patients with no stroke (p=0.02). Age (p=0.001), hemodialysis vintage (p=0.001) and serum phosphate (p=0.05) increased severity of IAC. High grade IAC was significantly correlated to worse survival (p=0.008) IAC is especially prevalent in hemodialysis patients with AIS, and its severity is significantly associated with vascular calcification risk factors |
| 10  | Sakaguchi et al., 2016 [18] | Japan | 98 patients with acute coronary syndrome | Patients with plaque rupture (n=38) had higher frequency and significantly more spotty calcifications (p=0.006 and p<0.001) than non-plaque rupture cohort (n=60). Thin-capped fibro-atheroma (p=0.012) and macrophage infiltration (p=0.022) were significantly higher in plaque rupture group, along with largest arc and minimum depth of calcification from luminal surface. Presence of spotty calcification (p=0.030) and age (p=0.008) were independent risk factors for plaque rupture There are characteristics and positional relationships of spotty calcification plaque ruptures in patients with acute coronary syndrome |
| 11  | Dhore et al., 2001 [19] | Netherlands | 42 patients with atherosclerotic plaques | Calcified atherosclerotic plaques resulted in upregulation of BMP-2, BMP-4, osteopontin and constitutive reactivity of matrix Gla protein, osteocalcin, and bone sialoprotein. Non-diseased aortas and early atherosclerotic lesions demonstrated sustained reactivity and absence of BMP-2, BMP-4, osteopontin and osteonectin. In advanced lesions, osteoprotegerin and its ligand were present bone structures and ECM around calcium deposits, respectively There is a tight regulation of the expression of bone matrix proteins during atherosclerotic calcification Symptomatic plaques |
| Study | Countries | Plaque Type | Risk Factors | Additional Information |
|-------|-----------|-------------|--------------|------------------------|
| Shaalan et al., 2004 [20] | USA | 48 carotid bifurcation plaques | Age, Hypertension, Diabetes | Significantly higher calcium content compared to asymptomatic patients (p=0.04) |
| Hunt et al., 2002 [21] | USA | 142 carotid endarterectomy plaques | Age, Hypertension, Diabetes | Significant difference in carotid-femoral pulse wave velocity (cf-PWV) and carotid stenosis (p<0.001) |
| Miralles et al., 2006 [22] | Spain | 26 patients with internal carotid artery stenosis | Hypertension, Diabetes | Calcium deposits were significantly lower in patients with AMI and UAP (p=0.001) |
| Nadra et al., 2005 [23] | Netherlands | 10 In-vitro human monocyte derived macrophages | Monocyte-derived macrophages | Calcium deposits were significantly lower in patients with AMI and UAP (p=0.001) |
| Mizukoshi et al., 2013 [24] | Japan | 187 patients with acute MI, unstable or stable angina pectoris | Age, Hypertension, Diabetes | Calcium was more superficial in AMI and UAP (p=0.001) |
| Lin et al., 2017 [25] | China | 142 carotid artery plaques | Age, Hypertension, Diabetes | Calcium was more superficial in AMI and UAP (p=0.001) |
| van den Bouwhuijsen et al., 2015 [26] | Netherlands | 329 patients, 611 carotid arteries with plaques | Hypertension, Diabetes | Calcium was more superficial in AMI and UAP (p=0.001) |
| Zhang et al., 2011 [27] | China | 270 patients with untreated hypertension | Age, Hypertension, Diabetes | Calcium was more superficial in AMI and UAP (p=0.001) |
| Fisher et al., 2005 [28] | USA | 241 patients with carotid artery plaques | Age, Hypertension, Diabetes | Calcium was more superficial in AMI and UAP (p=0.001) |
| Gölüke et al., 2020 [29] | Netherlands | 1992 patients with ICAC or basilar artery calcifications | Diabetes, Hypertension, Smoking | Calcium was more superficial in AMI and UAP (p=0.001) |
| Study            | Country       | Number of Patients | Pathological Feature | Results                                                                 |
|------------------|---------------|--------------------|----------------------|--------------------------------------------------------------------------|
| Hong et al., 2010 | South Korea   | 445 patients       | Without large intracranial lesions | Carotid siphon calcification was associated with lacunar infarction      |
| Chu et al., 2019  | China         | 102 patients       | With carotid artery stenosis | Greater calcification scores were associated with worsened cognitive scores and can be used for early screening of cognitive impairment |
| Bos et al., 2015  | Netherlands   | 2364 patients      | Underwent brain CT    | Atherosclerosis is associated with higher risk of dementia and cognitive decline, particularly in extracranial carotid arteries |
| Huston et al., 2000 | USA          | 382 patients       | With internal carotid artery stenosis | Carotid artery stenosis of 70% or more can be accurately diagnosed using ultrasonographic criteria |
| Derlin et al., 2010 | Germany      | 75 patients        | Underwent (18)F-NaF PET/CT | (18)F-NaF PET/CT can be used to visualize deposits in arterial walls      |
| Derlin et al., 2011 | Germany      | 269 patients       | Underwent (18)F-NaF PET/CT | Carotid artery radiotracer uptake is a way to measure calcifying carotid plaques and is associated with cardiovascular risk factors |
| Derlin et al., 2011 | Germany      | 45 patients        | (18)F-FDG PET vs. (18)F-NaF PET/CT | (18)F-NaF and (18)F-FDG PET/CT may be used for evaluation of pathology in atherosclerotic lesions |
| Anderson et al., 2000 | Canada      | 40 patients        | With TIA or stroke     | CTA can be used for detection and examination of carotid occlusions if stenosis is in the 0-29% or >50% range |
| Hop et al., 2019   | Netherlands   | 23 carotid artery plaques | | There was similar uptake in (18)F-NaF in culprit and non-culprit plaques and (18)F-NaF PET is useful in a different stage of the calcification process |
| Dweck et al., 2011 | United Kingdom | 199 patients       | With and without aortic valve disease | (18)F-NaF may be used for assessment of coronary artery plaque biology |

with stroke while intimal calcifications with both stroke and MI

Calification score and cognitive scores were negatively correlated in patients other than postoperative patients (p<0.001). Calification score was significantly associated with wall area (p=0.042), total area of blood vessels (p=0.017) and plaque burden (p=0.003). Calification score was also predictive of carotid plaque lipid-rich necrotic nucleus (p=0.029) in preoperative patients

Higher risk of dementia was associated with larger calcification volume in aortic arch, extracranial vessels, and intracranial carotid arteries. Only extracranial carotid artery calcification was significantly associated with dementia (HR: 1.37). Larger calcification volumes were associated with cognitive decline

Internal carotid artery stenosis of 70% or more displayed a peak systolic velocity of at least 230cm/s, sensitivity of 96.4%, specificity of 90.1%, positive predictive value of 92.7%, negative predictive value of 92.3% and accuracy of 88.8%. Additionally, it had an end diastolic velocity of at least 70cm/s and internal carotid artery common carotid artery ratio of at least 3.2

Arterial calcification was observed in 63 patients. While radiotracer was localized to calcifications, only 12% of all arterial calcification sites had notable accumulation of radiotracer uptake

Radiotracer uptake was significantly associated with patient age (p<0.0001), male sex (p<0.0001), hypertension (p<0.002), and hypercholesterolemia (p<0.05). Calcified plaques were significantly associated with these same risk factors and diabetes (p<0.0001), smoking (p<0.001) and history of cardiovascular event (p<0.001). Radiotracer uptake and number of cardiovascular risk factors were significantly related (p<0.0001)

(18)F-NaF uptake (n=27) was seen at 105 sites, and there was co-localization of radiotracer to calcified atherosclerotic lesions in 77.1% of the sites. (18)F-FDG uptake (n=34) was observed in 124 sites, and there was co-localization of radiotracer in only 14.5% of calcified lesions

Computed tomographic angiography (CTA) had nearly 100% accuracy when detecting mild carotid artery stenosis. For stenoses >50%, CTA had a sensitivity of 89%, specificity of 91% and accuracy of 90%. For stenoses 50-69% or 70-99%, CTA was much less sensitive

Average (18)F-NaF uptake was similar in culprit and non-culprit carotid plaques. A median of 10% of CT calcification of the volume of interest had increased (18)F-NaF uptake. A median of 35% of (18)F-NaF PET volume of interest displayed calcification on CT

(18)F-NaF uptake was higher in patients with coronary atherosclerosis (n=106) compared to control (p=0.003). (18)F-NaF was positively correlated with calcium score (p<0.001), and patients with increased (18)F-NaF had higher incidence of prior cardiovascular events (p=0.016), angina (p=0.023) and Framingham risk scores (p=0.011)
Table 1: Risk factors, pathogenesis, clinical manifestations, diagnostic techniques, and management of carotid artery calcification.

| Risk Factor | Study | Country | Patients | Outcome | Imaging Technique |
|-------------|-------|---------|----------|---------|------------------|
| Asymptomatic carotid stenosis | Joshi et al., 2013 [43] | United Kingdom | 80 patients with either MI or stable angina | Of the patients with MI (n=40), 93% had the highest coronary [18]F-NaF uptake in the culprit plaque compared to non-culprit (p<0.0001). There was no difference between culprit and non-culprit coronary [18]F-FDG uptake (p=0.34). Significant [18]F-NaF uptake occurred at all carotid plaque ruptures indicative of calcification, macrophage infiltration, apoptosis and necrosis. Use of [18]F-NaF PET/CT may be used to identify high-risk carotid plaques. | [18]F-NaF PET/CT is a non-invasive imaging technique to identify and localize both ruptured and high-risk plaques |
| Uneventful transient ischemic attack (TIA) | Irkle et al., 2015 [44] | United Kingdom | 7 patient’s Intimal atherosclerotic layers of human carotid arteries obtained from surgery | (18)F-NaF co-localized to calcified deposits on the plaque with both high affinity and selectivity. Areas of macro-calcification and micro-calcification were able to be deciphered by [18]F-NaF PET/CT imaging in patients undergoing surgery. | Medical management had better outcomes in patients with intracranial arterial stenosis compared to PTAS. |
| Asymptomatic carotid stenosis | Vessey et al., 2017 [45] | United Kingdom | 26 patients after TIA or stroke | (18)F-fluoride selectively localized to micro-calcifications, and carotid artery calcification was increased in culprit plaques compared to both asymptomatic contralateral plaques (p=0.001) and control patients (p=0.001). Uptake of (18)F-fluoride was significantly associated with high-risk plaque features and was a predictor of cardiovascular risk (p=0.003). | (18)F-fluoride PET/CT may be used to identify high-risk carotid plaques in patients |
| Stroke risk prediction | Chimowitz et al., 2011 [47] | USA | 451 patients after TIA or stroke | Medical management had better outcomes in patients with intracranial arterial stenosis compared to PTAS. | Medical management had better outcomes in patients with intracranial arterial stenosis compared to PTAS. |
| Asymptomatic carotid stenosis | Chambers et al., 2005 [52] | Meta-analysis | 5223 patients with asymptomatic carotid stenosis | Patients who underwent CEA had better overall results if they suffered from primary outcome- perioperative stroke, subsequent stroke, or death- (RR:0.69) or ipsilateral stroke (RR: 0.71) compared to those treated medically. | CEA slightly reduced the risk for any stroke including ipsilateral stroke over three years. |
| Asymptomatic carotid stenosis | Muller et al., 2020 [54] | Meta-analysis | 9753 patients with carotid stenosis | Transfemoral carotid artery stenting (TF-CAS) was associated with significantly increased risk of death or stroke in patients with symptomatic carotid stenosis than CEA. TF-CAS had significantly lower risk of MI, cranial nerve palsy, and hematoma compared to CEA. Asymptomatic patients had no significant increase in death or stroke between groups, but recurrent stenosis of 50-99% was significantly more prevalent after TF-CAS. | TF-CAS presents an extra risk in patients with symptomatic carotid stenosis |

**Conclusions**

Carotid artery calcification is important in clinical practice because stenosis leads to high morbidity and mortality.

The pathophysiology of CAC is an immediate inflammatory response that results in microcalcifications. Microcalcifications cause plaque instability, while macrocalcification causes plaque stabilization. Medial calcification is linked to calcium-phosphate imbalance and diabetes and chronic renal disease. These two calcifications have distinct risk factors, indicating a distinct etiology. Some studies show that increasing plaque calcification results in stenosis with minimal or no symptoms. Carotid artery calcification as a cerebrovascular risk indicator is still debated. Several methods exist to identify and characterize carotid plaque severity and shape. The initial ultrasound imaging study is quick and inexpensive. PET-CT imaging with [18]F-Sodium Fluoride ([18]F-NaF) is a newer technique that can detect new microcalcifications.

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Anticoagulants, statins, and lowering risk factors are used to treat carotid stenosis. Following medical management alone was found to be inferior in several studies. Patients over 70 were twice as likely to die or have a stroke 30 days after carotid stenting. Long-term, stenting is riskier than endarterectomy. However, both stenting and endarterectomy are effective in preventing strokes.

**Additional Information**

**Disclosures**

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**References**

1. Agacayak KS, Guler R, Sezgin Karatas P: Relation between the incidence of carotid artery calcification and systemic diseases. Clin Interv Aging. 2020, 15:821-6. 10.2147/CIA.S256588
2. Shi X, Gao J, Lv Q, Cai H, Wang F, Ye R, Liu X: Calcification in atherosclerotic plaque vulnerability: friend or foe?. Front Physiol. 2020, 11:56. 10.3389/fphys.2020.00656
3. Vos A, Kockelkoren R, de Vis JB, et al.: Risk factors for atherosclerotic and medial arterial calcification of the intracranial internal carotid artery. Atherosclerosis. 2018, 276:44-9. 10.1016/j.atherosclerosis.2018.07.008
4. Song P, Fang Z, Wang H, et al.: Global and regional prevalence, burden, and risk factors for carotid atherosclerosis: a systematic review, meta-analysis, and modelling study. Lancet Glob Health. 2020, 8:721-29. 10.1016/S2214-109X(20)30117-0
5. Wu XM, Chen XY, Wang LJ, Wong KS: Intracranial artery calcification and its clinical significance. J Clin Neurol. 2016, 12:253-61. 10.3988/jcn.2016.12.3.353
6. Chen XY, Lam WW, Ng HK, Fan YH, Wong KS: The frequency and determinants of calcification in intracranial arteries in Chinese patients who underwent computed tomography examinations. Cerebrovasc Dis. 2006, 21:91-7. 10.1159/000090206
7. Mak HK, Wong CW, Yau KK, Wong WM, Gu J, Khong PL, Chan BP: Computed tomography evaluation of intracranial atherosclerotic calcification in Chinese patients with transient ischemic attack or minor ischemic stroke--its distribution and association with vascular risk factors. J Cerebrovasc Dis. 2009, 18:158-63. 10.1016/j.jstrokecerebrovasdis.2008.09.011
8. Bos D, van der Rijk MJ, Geeraetsd TE, et al.: Intracranial carotid artery atherosclerosis: prevalence and risk factors in the general population. Stroke. 2012, 43:1878-84. 10.1161/STROKEAHA.111.648667
9. Bos D, Portegies ML, van der Lugt A, et al.: Intracranial carotid artery atherosclerosis and the risk of stroke in whites: the Rotterdam study. JAMA Neurol. 2014, 71:405-11. 10.1001/jamaneurol.2013.6225
10. Lanzer P, Boehr M, Sorribas V, et al.: Medial vascular calcification revisited: review and perspectives. Eur Heart J. 2014, 35:1515-25. 10.1093/eurheartj/ehu163
11. Nigwekar SU, Bloch DB, Nazarian RM, et al.: Vitamin k-dependent carboxylation of matrix gla protein influences the risk of calciphylaxis. J Am Soc Nephrol. 2017, 28:1717-22. 10.1681/ASN.2016060651
12. Yang P, Troncone L, Augur ZM, Kim SS, McNeil ME, Yu PB: The role of bone morphogenetic protein signaling in vascular calcification. Bone. 2020, 141:115542. 10.1016/j.bone.2020.115542
13. Gusberth-Tatomir P, Covic A: Causes and consequences of increased arterial stiffness in chronic kidney disease patients. Kidney Blood Press Res. 2007, 30:97-107. 10.1159/000105905
14. Bugnicourt M, Chillomon M, Massy ZA, Canaple S, Lamy C, Deramond H, Godefroy O: High prevalence of intracranial artery calcification in stroke patients with CKD: a retrospective study. Clin J Am Soc Nephrol. 2009, 4:284-90. 10.2215/CJN.02150408
15. Power A, Chan K, Haydar A, Hamady M, Cairns T, Taube D, Duncan N: Intracranial arterial calcification is highly prevalent in hemodialysis patients but does not associate with acute ischemic stroke. Hemodial Int. 2011, 15:256-63. 10.1111/j.1445-4658.2011.01054.x
16. Nakahara T, Dweck MR, Narula N, Pisapia D, Narula J, Strauss HW: Coronary artery calcification: from mechanism to molecular imaging. JACC Cardiovasc Imaging. 2017, 10:582-95. 10.1016/j.jcmg.2017.05.005
17. Lee SJ, Lee IK, Jeon JH: Vascular calcification—new insights into its mechanism. Int J Mol Sci. 2020, 21:10.3991/jms2102865
18. Sakaguchi M, Hasegawa T, Ehara S, et al.: New insights into spotty calcification and plaque rupture in acute coronary syndrome: an optical coherence tomography study. Heart Vessels. 2016, 31:1915-22. 10.1007/s00380-016-0820-5
19. Dhore CR, Cleutjens JP, Lutgen GI, et al.: Differential expression of bone matrix regulatory proteins in human atherosclerotic plaques. Arterioscler Thromb Vasc Biol. 2001, 21:1998-2005. 10.1161/hq1201.100229
20. Shaalan WE, Cheng H, Gewertz B, et al.: Degree of carotid plaque calcification in relation to symptomatic outcome and plaque inflammation. J Vasc Surg. 2004, 40:262-9. 10.1016/j.jvs.2004.04.025
21. Hunt JL, Fairman R, Mitchell ME, et al.: Bone formation in carotid plaques: a clinicopathological study. Stroke. 2002, 33:1214-9. 10.1161/01.str.0000013741.41599.67
22. Miralles M, Merino J, Busto M, Perich X, Barranco C, Vidal-Barraque F: Quantification and characterization...
of carotid calcium with multi-detector CT-angiography. Eur J Vase Endovasc Surg. 2006, 32:561-7. 10.1016/j.ejvs.2006.02.019

23. Nadra I, Mason JC, Philippidis P, et al.: Proinflammatory activation of macrophages by basic calcium phosphate crystals via protein kinase C and MAP kinase pathways: a vicious cycle of inflammation and arterial calcification? Circ Res. 2005, 96:1248-56. 10.1161/01.RES.0000171451.88616.e2

24. Mizukoshi M, Kudo T, Takarada S, et al.: Coronary superficial and spotty calcium deposits in culprit coronary lesions of acute coronary syndrome as determined by optical coherence tomography. Am J Cardiol. 2013, 112:34-40. 10.1016/j.amjcard.2013.02.048

25. Lin R, Chen S, Liu G, Xue Y, Zhao X: Association between carotid atherosclerotic plaque calcification and intraplaque hemorrhage: a magnetic resonance imaging study. Arterioscler Thromb Vasc Biol. 2017, 37:1228-35. 10.1161/ATVBHA.116.308560

26. van den Bouwhuijsen QJ, Box D, Ikram MA, et al.: Coexistence of calcification, intraplaque hemorrhage and lipid core within the asymptomatic atherosclerotic carotid plaque: the rotterdam study. Cerebrovasc Dis. 2015, 39:519-24. 10.1159/000381138

27. Zhang J, Li Y, Wang Y, et al.: Arterial stiffness and asymptomatic intracranial large arterial stenosis and calcification in hypertensive chinese. Am J Hypertens. 2011, 24:304-9. 10.1016/j.amjhyp.2010.246

28. Fisher M, Paganzini-Hill A, Martin A, Congrove M, Toole JF, Barnett HI, Norris J: Carotid plaque pathology: thrombosis, ulceration, and stroke pathogenesis. Stroke. 2005, 36:253-7. 10.1161/01.STR.0000152536.71224.21

29. Golikê NM, de Brouwer EI, de Jonghe A, et al.: Intracranial artery calcifications: risk factors and association with cardiovascular disease and cognitive function. J Neuroradiol. 2020, 10.1016/j.neurad.2020.08.001

30. Hong NR, Seo HS, Lee YH, Kim JH, Seol HY, Lee NJ, Suh SI: The correlation between carotid siphon calcification and lacunar infarction. Neuroangiography. 2011, 55:643-9. 10.1016/j.sna.2011.02.004

31. Chu Z, Cheng L, Tong Q: Carotid artery calcification score and its association with cognitive impairment. Clin Interv Aging. 2019, 14:167-77. 10.2147/CIA.S192586

32. Box D, Verhoosel MW, de Bruijn RF, et al.: Atherosclerotic calcification is related to a higher risk of dementia and cognitive decline. Alzheimers Dement. 2015, 11:639-47.e1. 10.1016/j.jalz.2015.07.1578

33. Huston J 3rd, James EM, Brown RD Jr, et al.: Redefined duplex ultrasonographic criteria for diagnosis of carotid artery stenosis. Mayo Clin Proc. 2000, 75:1133-40. 10.4065/mj.2000.1133

34. Saxena A, Ng EY, Lim ST: Imaging modalities to diagnose carotid artery atherosclerosis: progress and prospect. Biomed Eng Online. 2019, 18:66. 10.1186/s12938-019-0665-7

35. Derlin T, Richter U, Bannas P, Begemann P, Buchert R, Mester J, Kutmann S: Feasibility of 18F-sodium fluoride PET/CT for imaging of atherosclerotic plaque. J Nucl Med. 2010, 51:862-5. 10.2967/jnumed.110.076471

36. Derlin T, Witoszki C, Richter U, et al.: In vivo imaging of mineral deposition in carotid plaque using 18F-sodium fluoride PET/CT: correlation with atherosclerotic risk factors. J Nucl Med. 2011, 52:562-8. 10.2967/jnumed.110.081108

37. Derlin T, Töth Z, Papp L, et al.: Correlation of inflammation assessed by 18F-FDG PET, active mineral deposition assessed by 18F-fluoride PET, and vascular calcification in atherosclerotic plaque: a dual-tracer PET/CT study. J Nucl Med. 2011, 52:1020-7. 10.2967/jnumed.111.087452

38. Meschia JF, Bushnell C, Boden-Albala B, et al.: Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2014, 45:5754-832. 10.1161/STR.0000000000000046

39. Anderson GB, Ashforth R, Steinke DE, Ferdinandy R, Findlay JM: Targeted PET/CT imaging of vulnerable atherosclerotic plaques: microcalcification with sodium fluoride and inflammation with fluorodeoxyglucose. Curr Cardiol Rep. 2013, 15:364. 10.1007/s11886-013-0364-4

40. Hop H, de Boer SA, Reijnink M, et al.: 18F-sodium fluoride positron emission tomography assessed microcalcifications in culprit and non-culprit human carotid plaques. J Nucl Med. 2019, 26:1064-7. 10.2967/jnumed.111.102070

41. DeVree MR, Chew MW, Joshi NV, et al.: Coronary arterial 18F-sodium fluoride uptake: a novel marker of plaque biology. J Am Coll Cardiol. 2012, 59:1539-48. 10.1016/j.jacc.2011.12.037

42. Chen W, Dilsizian V: Targeted PET/CT imaging of vulnerable atherosclerotic plaques: microcalcification with sodium fluoride and inflammation with fluorodeoxyglucose. Curr Cardiol Rep. 2013, 15:364. 10.1007/s11886-013-0364-4

43. Joshi NV, Vesey AT, Williams MC, et al.: 18F-fluoride positron emission tomography for identification of ruptured and high-risk coronary atherosclerotic plaques: a prospective clinical trial. Lancet. 2014, 383:705-13. 10.1016/S0140-6736(13)62015-7

44. Irlke A, Vesey AT, Lewis DY, et al.: Identifying active vascular microcalcification by (18)F-sodium fluoride positron emission tomography. Nat Commun. 2015, 6:7495. 10.1038/ncomms8495

45. Vesey AT, Jenkins WS, Irlke A, et al.: 18F-fluoride and 18F-fluorodeoxyglucose positron emission tomography after transient ischemic attack or minor ischemic stroke: case-control study. Circ Cardiovasc Imaging. 2017, 10.1161/CIRCIMAGING.116.004976

46. Cilingiroglu M, Haleem A, Feldman M, Wholey M: Optical coherence tomography imaging in asymptomatic patients with carotid artery stenosis. Cardiovasc Revasc Med. 2015, 16:453-6. 10.1016/j.carrev.2015.09.004

47. Chimowitz MI, Lynn MJ, Derdeyn CP, et al.: Stenting versus aggressive medical therapy for intracranial arterial stenosis. N Engl J Med. 2011, 365:995-1005. 10.1056/NEJMoa1105335

48. Management of asymptomatic carotid atherosclerotic disease. . (2011). Accessed: June 15, 2021: https://www.ama-assn.org/publications/contents/mobilepreview.html?m=4525979701&source=related_link

49. North American Symptomatic Carotid Endarterectomy Trial (NASCET) Steering Committee: North American symptomatic carotid endarterectomy trial: Methods, patient characteristics, and progress. Stroke, 1991, 22:711-20. 10.1161/01.str.22.6.711

50. Kernan WN, Ovbiagele B, Black HR, et al.: Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2014, 45:2160-236. 10.1161/01.STR.0000480000000024

51. DaCosta M, Tadi P, Surowiec SM: Carotid endarterectomy. Surowiec S (ed): StatPearls Publishing, Treasure Island (FL), 2021.
52. Rothwell PM, Goldstein LB: Carotid endarterectomy for asymptomatic carotid stenosis: asymptomatic carotid surgery trial. Stroke. 2004, 35:2425-7. 10.1161/01.STR.0000141706.50170.a7

53. Brott TG, Brown RD Jr, Meyer FB, Miller DA, Cloft HJ, Sullivan TM: Carotid revascularization for prevention of stroke: carotid endarterectomy and carotid artery stenting. Mayo Clin Proc. 2004, 79:1197-1208. 10.4065/79.9.1197

54. Muller M, Lyrer P, Brown M, Bonati L: Carotid artery stenting versus endarterectomy for treatment of carotid artery stenosis. J Vasc Surg. 2020, 72:748-49. 10.1016/j.jvs.2020.05.008