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# Unravelling the role of carotid atherosclerosis in predicting cardiovascular disease risk: A review

**Sidhi Laksono[1,2], Hillary Kusharsamita[3]**

**Review Article**


## Abstract

Carotid atherosclerosis disease assessment can predict the patient's risk of cardiovascular disease (CVD). The purpose of this review is to provide a comprehensive review of carotid atherosclerosis disease's pathophysiology, diagnostic evaluation, imaging applications, and treatment strategies. Carotid atherosclerosis is diagnosed using a variety of techniques, including transcranial Doppler imaging (TCD), computed tomography angiography (CTA), magnetic resonance angiography (MRA), and cerebral digital subtraction angiography (DSA), with duplex ultrasound (DUS) as the primary screening. Measurements of carotid intima-media thickness (CIMT) have drawn attention recently as a marker of early-stage carotid atherosclerosis or CVD risk prediction. The classification of cardiovascular risk may be enhanced by the expanding fields of stress testing and carotid plaque screening.


**Keywords:** Carotid atherosclerosis disease; Carotid stenosis; Cardiovascular diseases; Duplex ultrasound; Carotid intima-media thickness

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## Introduction

Systemic inflammatory vascular disorders, such as atherosclerosis, involve multiple arterial beds. An association between coronary and carotid artery disease suggests that atherosclerosis is a systemic disease[1]. A study conducted by Hofmann et al. found that the prevalence of coronary artery disease (CAD) was 77.1% in both symptomatic and asymptomatic patients who were admitted to the hospital for elective carotid artery stenting[2]. 49.1% of 112 patients who underwent elective carotid artery stenting were diagnosed with CAD, according to a study. Nearly 60% of these patients experienced neurological symptoms[3]. Hence, the presence and extent of carotid atherosclerosis, characterized by identifying plaque in the carotid artery, has been employed for predicting and classifying an individual's cardiovascular risk. Carotid atherosclerosis, besides being a method of assessing risk, has been established as a reliable indicator of other CVDs, including ischemic stroke resulting from the narrowing of the artery and rupture of plaque[4].

There is a lack of consensus about specific methods to assess carotid atherosclerosis disease. However, the assessment of carotid atherosclerosis is crucial due to the great complexity of risk factors that lead to severe CVD. This study discusses the pathophysiology, diagnostic evaluation, imaging, and therapy for carotid atherosclerosis.

### *Pathophysiology of carotid atherosclerotic plaque*

The fact that atherosclerosis develops next to branch ostia, bifurcations, and bends suggests that flow dynamics are important in this process. Low flow velocity and high shear stress are typical environments for the development of atherosclerotic plaque[5]. Constricted arteries and the carotid sinus, which have slower blood flow, are affected by the pulsing pattern of the cardiac cycle's blood flow, which results in fluctuating shear rates. A thrombus occlusion or

1- Department of Cardiology and Vascular Medicine, Pertamina Central Hospital, South Jakarta, Indonesia
2- Faculty of Medicine, Universitas Muhammadiyah Prof Dr Hamka, Tangerang, Indonesia
3- General Practitioner, Pertamina Central Hospital, South Jakarta, Indonesia
**Address for correspondence:** Sidhi Laksono; FK UHAMKA Jl. Raden Patah No.01, RT.002/RW.006, Parung Serab, Kec. Ciledug, Kota Tangerang, Banten 13460; Email: sidhilaksono@uhamka.ac.id

embolization may occur as a consequence of the carotid artery gradually narrowing or of plaque rupture, both of which can induce transient ischemic attack (TIA) or strokes[6].

Additionally, the two systems most often impacted by atherosclerosis are the carotid and coronary arteries. Although the mechanisms and features of atherosclerotic plaque formation are identical in these two artery systems regardless of location, the shape and properties of the plaque vary[7]. According to the latest study, while there are differences, both of these arterial systems show a comparable phenotypic pattern of atherosclerosis. This pattern includes the thickening of the intima-media, the formation of plaques, the calcification of the arterial wall, and the narrowing or obstruction of the lumen due to large plaques. A 2021 meta-analysis provided strong evidence of a direct relationship between carotid intima-media thickness (CIMT) and the severity of CAD ($p < 0.001$). Moreover, there was a substantial correlation between CIMT and the number of coronary arteries that were affected ($p < 0.001$)[8].

### *Type of atherosclerotic plaques*

Uncomplicated plaques are characterized by a smooth and calcified surface. On the other hand, vulnerable or complicated plaques are a kind of atherosclerotic plaque that have a strong tendency to cause thrombotic complications, such as stroke or myocardial infarction[9]. Plaques that tend to progress rapidly are also considered to be vulnerable. Imaging may reveal smoothness, irregularity, or ulceration in a vulnerable plaque[10].

In addition, a complex plaque may be classified into the following categories: plaque rupture accompanied by intraplaque hemorrhage (IPH), plaque rupture accompanied by thrombosis, plaque rupture thrombosis, and IPH without plaque rupture[11]. Utilizing modern ultrasound (US) techniques, such as transcranial Doppler (TCD) detection of microemboli that may be linked to unstable plaques, may assist in the identification of high-risk patients[12].

In persons with mild-to-moderate carotid stenosis who show symptoms, males are more prone to have a complex carotid plaque with IPH and a lipid-rich necrotic core, regardless of the total amount of plaque present[13]. Symptomatic plaques have lower levels of calcification and inflammation as compared to asymptomatic plaques. The degree of fibrous cap inflammation, as determined by the degree of macrophage infiltration, was shown to be significantly negatively correlated with the amount of calcification on the carotid plaque, regardless of the clinical result[14].

### *Diagnosis*

### *Patient's screening*

Symptomatic carotid artery stenosis refers to the narrowing of the common or internal carotid artery, accompanied by neurological symptoms on the same side of the body. These symptoms must have developed during the last six months. While symptomatic carotid artery stenosis poses a significant risk for recurrent stroke on the same side, people with this condition also have an elevated risk of cardiovascular complications. Asymptomatic carotid artery stenosis refers to the narrowing of the common or internal carotid artery without any neurological symptoms, or if such symptoms happened more than six months ago. Various studies suggest that persons with asymptomatic carotid stenosis have a higher likelihood of experiencing a heart attack rather than a stroke[15,16]. However, various risk factors contribute to the development of carotid artery stenosis in asymptomatic individuals, including advanced age, male gender, high blood pressure, smoking, high cholesterol levels, diabetes, and prior heart disease. Furthermore, research has shown that using auscultation to detect carotid bruits has a limited ability to accurately diagnose carotid stenosis or stroke, making it an unsuitable tool for screening purposes[17].

### *Imaging method for assessing carotid atherosclerosis*

Research in the field of imaging-based atherosclerosis detection and stenosis severity assessment is very promising. Imaging is also useful for assessing the stability or vulnerability of a plaque and estimating the level of risk a patient has for developing CVD[7]. There have been significant advancements in the diagnostic tools used for carotid stenosis. These include ultrasound of the carotid artery (US), transcranial Doppler imaging (TCD), computed tomography angiography (CTA), MRI (magnetic resonance angiography, MRA), and cerebral digital subtraction angiography (DSA).

*Duplex ultrasound*

One of the most used diagnostic imaging modalities for assessing carotid disease is duplex ultrasonography (DUS). This approach integrates two methodologies: conventional B-mode (greyscale) ultrasonography, which employs reflected sound waves to provide pictures of the static structure of tissues at rest, and color-Doppler ultrasound, which enables visualization of dynamic components to quantify velocity and other flow characteristics[18]. Atherosclerotic plaques may be divided into calcified (hyperechoic) and noncalcified (hypoechoic) areas using grayscale US imaging[19]. Color Doppler ultrasonography (US) displays blood flow by color-coded details to indicate velocity and direction. Pulsed Doppler assesses the speed at a certain depth inside a particular vascular region, whereas continuous Doppler waveform analyzes the flow characteristics[20]. Aside from peak systolic velocity (PSV), Grant et al. developed a set of criteria for evaluating carotid stenosis (Table 1). The specificity and sensitivity for stenosis between 70% and 90% are 0.84 and 0.89, respectively, whereas for stenosis between 50% and 69% they are 0.36 and 0.91[21].

Recently, CIMT measures have gained popularity as a means of early detection of carotid atherosclerosis and CVD risk prediction[22]. The CIMT measures carotid artery wall thickness using ultrasonography. Carotid arterial plaque can be defined in two ways according to the American Society of Echocardiography (ASE): 1) when the CIMT is more than 1.5 mm in any segment of the carotid artery, which indicates diffuse-type plaque in the vessel walls, or 2) when there is a focal thickening that is atherosclerotic in origin and intrudes into the lumen of any segment of the carotid artery, which is known as protuberant-type plaque[23]. Research demonstrated a strong association between a maximum carotid intima-media thickness (CIMT) above 1.54 mm and the presence of severe coronary artery disease[24]. Asymptomatic people with advanced carotid artery atherosclerosis (CIMT >3.5 mm) have been shown to have a comparable elevated risk of coronary heart disease[25].

Modern technological developments have made it feasible to define plaque and the shape and function of artery walls in three-dimensional (3D) volumetric detail[26]. Research has shown that (3D) approaches are more precise than 2-dimensional (2D) ultrasonography to estimate coronary atherosclerosis[27]. The primary advantage of 3D quantification is the ability to measure the size of a lesion in all three dimensions. This technique may be used to monitor the advancement of a disease over a period of time, either for diagnostic reasons or to assess how a lesion is reacting to treatment. The ASE recommends that a 3D ultrasound be used to quantify the quantity of plaque in the left and/or right carotid arteries to estimate cardiovascular risk. There is now a 3D matrix array probe that may be used to evaluate carotid plaque. However, one disadvantage of the 3D technique is that it requires a transducer that is both bigger and heavier compared to a standard 2D array. Furthermore, a matrix transducer requires around 1-2 seconds to complete a 3D scan[23]. Moreover, the costly expense of 3D imaging equipment and software to evaluate a 3D image may restrict its practical use.

*Computed tomographic angiography*

Utilizing an intravenous iodine contrast medium, Computed Tomographic Angiography (CTA) shows

**Table 1**. DUS criteria for diagnosis of carotid stenosis[21]

| Stenosis | Parameter |
|---|---|
| **Normal** | ICA PSV < 125 cm/s and no visible plaque, additionally ICA/CCA PSV ratio < 2.0 and ICA EDV < 40 cm/s |
| **< 50** | ICA PSV < 125 cm/s and estimate plaque < 50%, additionally ICA/CCA PSV ratio < 2.0 and ICA EDV < 40 cm/s |
| **50–69** | ICA PSV 125–230 cm/s and estimate plaque 50% and more, additionally ICA/CCA PSV ratio 2.0–4.0 and ICA EDV 40–100 cm/s |
| **>70 but less than near occlusion** | ICA PSV > 230 cm/s and estimate plaque 50% and more, additionally ICA/CCA PSV ratio > 4.0 and ICA EDV > 100 cm/s |
| **Near occlusion** | ICA PSV high, low, or undetectable, estimate plaque visible, additionally variable ICA/CCA ratio and ICA EDV |
| **Total occlusion** | Undetectable flow, visible plaque, no detectable lumen |

CCA: common carotid artery, EDV: end-diastolic velocity, ICA: internal carotid artery, PSV: peak systolic velocity, US: ultrasound.

the entire carotid artery's flow from the aortic arch to intracranial regions and assesses the degree of stenosis at all levels[28]. Moreover, a completely automated CTA that is operator-independent demonstrated a 75% detection rate for the carotid artery based on study[29]. Nevertheless, the primary drawbacks of CTA are the potential for radiation exposure and the need for intravenous administration of iodine contrast material. Reduced renal function is therefore a relative contraindication to its use. CTA has a lower accuracy rate than DSA in diagnosing moderate and severe stenosis, with rates of 57% and 63%, respectively[30]. Furthermore, when comparing the effectiveness of CTA and MRA in detecting internal carotid stenosis, CTA exhibited higher sensitivity (98% compared to 70%)[31]. Non-contrast-enhanced CT (NECT) may detect calcified plaques in carotid arteries; however, it is usually utilized to assess cerebral ischemia and distinguish ischemic from hemorrhagic stroke in emergencies[32].

*Magnetic resonance angiography*

Magnetic resonance angiography (MRA) is utilized for assessing stenosis. This can be achieved through contrast-free time-of-flight MRA (TOF-MRA), which relies on the physical properties of the blood as it flows, or contrast-enhanced MRA (CE-MRA), which involves the injection of a gadolinium contrast agent. However, TOF-MRA is inferior to CE-MRA due to its increased susceptibility to artifacts and the potential to overestimate stenosis[28]. A meta-analysis study found that CE–MRA had a sensitivity and specificity of 0.94 and 0.93 for stenosis between 70 and 90%, respectively. On the other hand, the sensitivity and specificity are 0.77 and 0.97, respectively, for stenosis ranges from 50 to 69%[33].

One of the benefits of MRA is its non-invasive nature, which allows for the diagnosis of carotid stenosis using the TOF procedure with or without contrast. MRA produces a repeatable three-dimensional image of the carotid bifurcation and is highly sensitive for the diagnosis of high-grade carotid stenosis. MRA is less dependent on the operator and creates a comprehensive image of the entire artery compared to carotid DUS. MRA also does not involve radiation exposure, unlike DSA and CT[28].

The non-contrast MRA's disadvantage is that it is less sensitive to calcification, which leads to an underestimate of carotid stenosis. Consequently, MRA is less accurate than CTA. Meanwhile, contrast-enhanced MRA is more susceptible to aberrations, which may exaggerate the severity of stenosis. In contrast to carotid DUS and CTA, MRA is more expensive and less broadly available. In addition, patients with ferromagnetic implants, pacemakers, or claustrophobia cannot undergo MRA[28,34].

*DSA*

For accurate carotid atherosclerosis disease assessment, DSA is the gold standard, although invasive. This approach is implemented for carotid stenting and angioplasty, as well as diagnostic evaluations[34]. The sensitivity, specificity, and accuracy of DSA in the detection of carotid stenosis are 95%, 99%, and 97%, respectively. A stenosis of 70% to 99% in the internal carotid artery is classified as severe, while a stenosis of 50% to 69% is classified as moderate, according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria. A stenosis of 80% to 99% is classified as severe, while a stenosis of 70% to 79% is classified as moderate, according to the European Carotid Surgery Trial (ECST) standards[7,34].

DSA's benefits include the capacity to evaluate the degree and morphology of stenosis, particularly when an irregular border suggests plaque ulceration or thrombus. The DSA of intracranial arteries can be employed to observe collateral flow. The carotid artery system is comprehensively examined by DSA, which provides information on the presence of concomitant intracranial atherosclerotic disease, plaque morphology, and collateral circulation[28].

It is important to note that DSA is an invasive method, which is a disadvantage. Embolization associated with stroke is the most feared outcome; however, the prevalence is less than 1%. Additionally, the degree of stenosis in arteries with asymmetrical eccentric stenosis may be underestimated by a restricted number of projections[35].

*Application of carotid arterial plaque imaging and treatment in clinical practice*

Functional tests, including stress echocardiography, stress magnetic resonance imaging, stress electrocardiogram, and nuclear imaging, are employed to assess coronary artery disease. Nevertheless, they are incapable of detecting occlusions in the arteries between 50% and 70%. Stress tests with normal results offer a favourable short-term prognosis, but direct atherosclerosis evaluation may help with long-term management. Recent research indicates that imaging for atherosclerotic lesions in the carotid artery may provide supplementary prognostic information in patients who have undergone normal stress tests. Patients who do not have plaque in their carotid arteries have a favourable prognosis, while those who have atherosclerotic plaques, even though they have normal myocardial ischemia imaging, may benefit from more aggressive medical treatment[36,37]. The carotid plaque, in conjunction with the stress test, is an intriguing new discipline that enhances risk stratification. A further study indicated that patients with stable angina who did not yet have developed CAD benefited from a combination of stress echocardiography and carotid ultrasonography for improved predictive value[37]. The monitoring and modification of atherosclerosis therapy through serial plaque assessments is an intriguing application that necessitates the further development of precise methods to assess the carotid plaque load and clinical research to establish the periods and dosage modifications of therapy.

To stratify cardiovascular risk, the ASE recommends that plaque grading be conducted through targeted carotid vascular ultrasound by 2D or 3D plaque quantification. They have suggested that a CIMT >1.5 mm be regarded as a significant lesion in individuals under the age of 65[23]. In the European Guidelines for the Prevention of CVD in Clinical Practice, carotid artery scanning for the detection of atherosclerotic plaque was also indicated as a potential risk in the assessment of cardiovascular risk[38]. Carotid US is currently the primary screening method for the diagnosis of carotid stenosis. If this modality identifies stenosis that exceeds 50%, the subsequent step is to proceed with CTA or MRA. In patients with stenosis of 50% or less, it is recommended to undergo serial carotid duplex scanning to exclude the possibility of disease progression. The DSA is still reserved for patients who are undergoing carotid angioplasty with stenting and for situations in which the CTA or MRA findings are ambiguous[34].

Statins should be administered to patients with carotid artery disease in order to attain an LDL-cholesterol level of 1.8 mmol/L, in accordance with the established guidelines for the prevention of CVD[38]. There is substantial evidence to suggest that statin medication may reduce the risk of stroke in individuals who already have cerebrovascular disease. In a meta-analysis of randomized trials, a 21% reduction in the relative risk of stroke was associated with every 1 mmol/L decrease in LDL-C levels ($P$ = 0.009). In the secondary prevention of non-cardioembolic stroke, the intensive reduction of LDL-C levels (with statins) substantially prevented stroke and severe CV events (0.80, $P$ = 0.002)[39].

Patients with carotid artery stenosis who are not scheduled for revascularization should be assessed for additional CAD risk factors in accordance with their symptoms[40]. Nevertheless, the circumstances are distinct for individuals who have recently experienced a stroke or TIA and are exhibiting symptoms of carotid artery stenosis. A guideline recommends that individuals who have experienced a stroke or TIA undergo routine noninvasive testing for CAD in the context of severe carotid disease[41].

Carotid stenting is often advantageous for patients who have received radiation treatment in the neck, have restenosis after previous carotid endarterectomy (CEA), are under the age of 70, and have comorbid cardiac disease[42]. Nevertheless, the absolute risk of myocardial infarction may be higher, as patients who undergo carotid stenting are frequently high-risk surgical patients. In high-risk patients, comprehensive coronary angiography (CAG) prior to carotid stenting has been demonstrated to improve periprocedural and long-term outcomes. Combining coronary revascularization with carotid stenting in high-risk patients has demonstrated encouraging results in many studies[43].

If the patient is over the age of 70, carotid endarterectomy (CEA) is an alternative treatment[42]. A study reveals that 39% of the 426 patients scheduled for CEA who were randomly selected to undergo CAG prior to CEA had significant CAD, which was detected and managed with PCI. These individuals did not have a history of CAD or previous CAG evaluation. In contrast, the risk of myocardial infarction was lower among those who were randomly assigned to undergo systematic CAG six years later, and their survival rate was higher[44]. Therefore, these results indicate that patients who undergo CEA may experience significant benefits from elective CAG and revascularization.

## Conclusion

It is imperative to evaluate carotid atherosclerosis due to the numerous factors that contribute to the complexity of CVD. Currently, DUS of the carotid arteries is the primary screening method for carotid stenosis, with CIMT indicating early-stage carotid atherosclerosis or CVD risk. The subsequent measure is to proceed with CTA or MRA if DUS identifies stenosis that exceeds 50%. Serial carotid duplex scanning is advised for patients with stenosis of 50% or less to rule out any potential disease development. The addition of stress testing to carotid plaque screening may improve the classification of cardiovascular risk.

## Conflict of interests

Authors have no conflict of interests.

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## Author's Contributions

SL contributed in conception and design of the manuscript, manuscript preparation, and revising the manuscript critically for important intellectual content. HK contributed in interpretation and analysis of the data, drafting the article, and revising the manuscript critically for important intellectual content. All authors have approved the final version of manuscript.

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