Review

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Progress in Risk Assessment and Treatment of Carotid Artery Atherosclerosis

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Carotid artery atherosclerosis is one of the leading causes of stroke. However, due to its insidious onset, balancing the risks and benefits of surgery for asymptomatic patients is challenging. Once it leads to a stroke, it has an extremely high mortality and disability rate. Therefore, an accurate, individualized assessment of carotid atherosclerotic plaque is necessary, combined with personalized treatment using existing therapeutic modalities. This article discusses new findings and advances in risk assessment and treatment modalities for carotid atherosclerosis.

Keywords: carotid atherosclerosis; carotid artery stenting; carotid endarterectomy

Introduction

Stroke remains one of the leading causes of death and disability worldwide, a fact underscored by its significant impact on global health systems and individual lives. According to the Global Burden of Diseases Study 2021, stroke is a major contributor to disability-adjusted life years (DALYs), with its prevalence and impact expected to rise due to global aging trends [1]. The epidemiological landscape of stroke is further complicated by its association with other cardiovascular diseases. In the Association of Southeast Asian Nations (ASEAN) region, stroke ranks among the top three cardiovascular diseases with the highest prevalence rates, alongside ischemic heart disease and peripheral arterial disease [2].

Ischemic stroke is the predominant subtype [1]. Carotid artery stenosis, or the narrowing of the carotid arteries due to atherosclerotic plaque buildup, is a critical underlying cause of ischemic stroke. This condition can lead to reduced cerebral blood flow and an increased risk of embolic events, both of which are pivotal in the pathogenesis of ischemic strokes.

Carotid atherosclerosis begins with endothelial injury [3]. Hypercholesterolemia and hypertension, for example, promote monocyte infiltration into the intima. There, monocytes differentiate into macrophages that phagocytose oxidized lipids, forming foam cells. These foam cells gradually develop into plaques, characterized by a lipid core and a fibrous cap. The stability of plaque depends on the thickness of the fibrous cap and the proportion of lipid components. A thin fibrous cap, a large lipid core, or hemorrhage within the plaque significantly increases the risk of rupture. Calcification exacerbates fragility through mechanical stress. Unstable plaques pose two risks. First, plaque rupture or ulceration can release emboli that block distal vessels. Second, the gradual growth of the plaque can cause hemodynamic disturbances, leading to reduced cerebral perfusion pressure and triggering infarction.

The clinical management of carotid artery stenosis faces two challenges. First, symptomatic stenosis, such as transient ischemic attacks or acute stroke, necessitates timely intervention to reduce disability rates [4]. Second, treatment for asymptomatic stenosis is controversial, as it entails balancing surgical risks with long-term benefits [5]. The primary intervention methods are carotid endarterectomy (CEA) and carotid artery stenting (CAS), but their efficacy depends heavily on the timing of surgery and patient selection. For instance, studies have demonstrated that performing CEA within 48 hours of an ischemic event significantly reduces the risk of recurrence [6–8]. In the management of asymptomatic carotid stenosis, advances in imaging technology have opened new avenues for identifying high-risk patients [9]. Additionally, novel high-risk biomarkers, such as plaque neovascularization, inflammation, and tissue stiffness, are being developed to help identify patients at high risk who may benefit from surgical intervention [10]. In summary, the clinical management of carotid stenosis requires treatment strategies tailored to the patient's symptomatic status, imaging findings, and individualized risk assessment.

Imaging Assessment and 3D Modeling of Carotid Artery Atherosclerosis

Carotid artery atherosclerosis is one of the leading causes of stroke. Appropriately assessing atherosclerotic plaques using suitable technical methods can directly influence treatment strategies for asymptomatic patients. In recent years, imaging techniques, such as ultrasound and magnetic resonance imaging (MRI), combined with three-dimensional (3D) reconstruction, have become more common for assessing carotid atherosclerosis. These intuitive, visual methods help clinicians comprehensively evaluate each patient's stroke risk.

Ultrasound has several advantages over DSA for assessing carotid artery plaques. It is not only faster and more accessible but also eliminates procedural risks. Additionally, 3D ultrasound has demonstrated good accuracy and reproducibility in assessing plaque volume. For instance, a study employing 3D vascular ultrasound (3DVUS) technology revealed its high reproducibility in measuring atherosclerotic plaque volume. The results showed that the plaque volume measured by 3DVUS exhibited an extremely high correlation with the gold-standard histological measurement, achieving intra-observer consistency of 0.99 and inter-observer consistency of 0.98 [11]. Another study validated the reliability of 3D ultrasound in measuring carotid atherosclerotic plaque volume through multicenter trials. The standardized central reading protocol demonstrated an intraclass correlation coefficient (ICC) value of 0.964 among three designated readers, indicating minimal interobserver variability [12]. Furthermore, the study has shown that 3D ultrasound provides more detailed plaque information than 2D ultrasound, particularly for assessing plaque volume and surface morphology [13]. Moreover, regular carotid ultrasound examinations can monitor plaque progression in asymptomatic patients or evaluate treatment outcomes in postoperative patients [14].

Similarly, ultrasound examinations can be used to screen patients with early-stage carotid atherosclerosis. Carotid intima-media thickness (CIMT) is a significant risk factor for cardiovascular disease. An increase in CIMT is closely associated with the onset of this disease, making CIMT a valuable biomarker for subclinical atherosclerosis. Measuring CIMT with high-resolution ultrasound imaging effectively identifies high-risk individuals, adjusts cardiovascular risk assessments, and initiates timely therapeutic interventions [15,16].

Magnetic resonance imaging (MRI) technology is also increasingly used to assess carotid atherosclerosis. Compared to computed tomography (CT), MRI provides a more precise and accurate depiction of the carotid artery wall's tissue structure. 3D black-blood MRI can accurately quantify carotid artery stenosis and is consistent with digital subtraction angiography (DSA). The ICC for measuring lumen stenosis is 0.96, the sensitivity for detecting ulcers is 91.7%, and the specificity is 96.2% [17]. Additionally, 3D MRI can assess plaque composition, including the thickness of lipid cores and fibrous caps. This information is crucial for determining plaque stability [18].

Additionally, computer-based 3D modeling techniques have played a significant role in the study of carotid atherosclerosis. By combining high-resolution imaging data with computational fluid dynamics models, it is possible to simulate hemodynamic changes, thereby gaining a better understanding of the mechanisms underlying plaque formation and development [19]. This method can not only be used to assess the severity of stenosis but also to guide surgical decision-making [20].

With the widespread adoption of artificial intelligence technology, there is now greater potential for automated assessment of carotid atherosclerosis. Using deep learning algorithms, it is possible to automatically detect and classify carotid plaques, thereby improving the efficiency and accuracy of diagnosis [21].

Biomarker Assessment for Carotid Atherosclerosis

Although imaging techniques provide rich morphological information, for patients diagnosed with carotid atherosclerosis, relying solely on imaging for risk assessment is often insufficient. Clinically, some radiologically stable plaques can suddenly rupture, precipitating cerebrovascular accidents. This phenomenon is not uncommon, highlighting the limitations of current risk assessment methods. Consequently, there has been an escalating focus on research aimed at screening and assessing biomarkers. The objective of these efforts is to identify novel approaches for evaluating the risk associated with carotid plaques.

The study has identified certain oxidative stress and inflammatory markers, such as oxidized low-density lipoprotein (ox-LDL) and matrix metalloproteinase-9 (MMP-9), as predictive indicators of carotid atherosclerotic plaque instability. Laboratory findings have shown that elevated levels of ox-LDL and MMP-9 are closely associated with plaque instability, and these markers can serve as independent diagnostic tools to assess plaque instability [22]. Other inflammatory and oxidative stress biomarkers, such as indoleamine 2,3-dioxygenase (IDO) activity and neopterin levels, exhibit significant differences in patients with asymptomatic carotid artery stenosis. These biomarkers can serve as diagnostic and severity indicators for asymptomatic carotid artery stenosis [23].

Further study has shown that carotid artery plaque instability is associated with the body's local immune microenvironment. By analyzing the infiltration levels of immune cell subtypes, one can identify different stages of atherosclerosis and discover potential regulatory genes that may play a role in its development and progression [24]. A study of obese populations has shown that genes such as MMP9, phospholipase A2 group VII (PLA2G7), and

secreted phosphoprotein 1 (SPP1) are associated with immune infiltration in the carotid atherosclerosis microenvironment of obese patients. These genes may serve as diagnostic markers for assessing carotid atherosclerosis in obese populations [25].

Additionally, the proportions of circulating immune markers in the blood, such as granulocytes, platelets, and lymphocytes, are associated with the characteristics of carotid atherosclerotic plaques. Studies have found that innate immune markers are associated with larger plaques, while adaptive immune markers are associated with smaller plaques and lower rates of intraplaque hemorrhage [26]. This suggests that an imbalance in the immune system may play a role in plaque vulnerability. Furthermore, circulating biomarkers, such as the cytokines interleukin-6 (IL-6) and interleukin-8 (IL-8) and the cell adhesion molecule soluble vascular cell adhesion molecule-1 (sVCAM-1), are considered potential markers for assessing the presence and severity of coronary artery disease (CAD) [22].

Screening and assessment methods for carotid atherosclerosis currently encompass a variety of genes and biomarkers, which will play a crucial role in the early detection and risk assessment of the condition.

Treatment of Carotid Atherosclerosis

Pharmacological Management Strategies for Carotid Artery Atherosclerosis

Significant progress has been made in recent years in the pharmacological management of carotid artery atherosclerosis. The goal of treatment is to reduce the incidence of adverse vascular events by lowering blood lipids, controlling blood pressure, and administering antiplatelet therapy. As our understanding of the pathophysiological mechanisms of carotid artery atherosclerosis has deepened, treatment strategies have continued to improve.

Antiplatelet therapy is crucial in managing carotid atherosclerosis and preventing ischemic stroke. Carotid atherosclerosis is a leading cause of ischemic stroke, and effective antiplatelet treatment can substantially lower the likelihood of a stroke [27]. Aspirin and clopidogrel are commonly used antiplatelet drugs that reduce the risk of thrombosis by inhibiting platelet aggregation [28]. Additionally, research also suggests that dual therapy combining low-dose anticoagulants, such as rivaroxaban, with aspirin may reduce long-term ischemic complications [28].

However, the use of antiplatelet therapy is not without controversy. For asymptomatic patients with carotid atherosclerosis, the benefits of antiplatelet therapy are unclear, especially given its limited efficacy in preventing stroke or arterial stenosis progression [29]. The balance between the risks and benefits of antiplatelet therapy is also an important consideration, especially for patients at high risk for bleeding [28]. Furthermore, antiplatelet therapy's interactions with other medications complicate its use, as these interactions may affect treatment efficacy and safety [30]. Finally, regarding optimal medical management for asymptomatic carotid stenosis patients, the study recommends enhanced medical management encompassing lifestyle modifications, such as the Mediterranean diet, exercise, and smoking cessation, alongside pharmacological interventions (antiplatelet agents, lipid-lowering drugs, blood pressure control, and glycemic management) [31]. These measures not only help reduce the risk of carotid events but may also decrease the incidence of atherosclerotic events in other critical sites. Therefore, the use of antiplatelet therapy in asymptomatic patients with carotid atherosclerosis remains controversial. However, the risk of cardiovascular events can still be reduced through appropriate individualized assessment and enhanced medical management. The specific protocols for antiplatelet therapy in this patient population and strategies to optimize treatment warrant further discussion.

In CEA and CAS, antiplatelet therapy management also involves different strategies. The study has shown that in CEA, dual antiplatelet therapy (DAPT) may increase the risk of bleeding complications, whereas in CAS, DAPT has been shown to reduce transient ischemic attacks (TIAs) [30]. In summary, antiplatelet therapy is indispensable in the management of carotid atherosclerosis and other atherosclerotic diseases. Still, its application requires individualized adjustment based on each patient's specific circumstances to maximize therapeutic efficacy and minimize risks [32].

Secondly, lipid-lowering therapy is also a key component of carotid atherosclerosis management. Statins reduce the risk of cardiovascular events by lowering low-density lipoprotein cholesterol (LDL-C) levels and stabilizing atherosclerotic plaques [33,34]. Additionally, protein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, a new class of lipid-lowering drugs, have been shown to further reduce LDL-C levels and, in some cases, reverse neovascularization within plaques [34].

For patients with hypertension, controlling blood pressure is an important measure to reduce the progression of carotid atherosclerosis. The study has shown that maintaining blood pressure within target ranges through lifestyle interventions and antihypertensive drug therapy can effectively reduce the risk of cardiovascular events [35].

Furthermore, recent studies have explored the potential roles of other drugs in the management of carotid atherosclerosis. For example, studies have found that certain natural products, such as berberine, may improve carotid atherosclerosis by regulating the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) signaling pathway [36,37]. Furthermore, the polarization of M2 macrophages is considered a promising therapeutic target, as regulating macrophage polarization may aid in reversing atherosclerosis [38].

Pharmacological management strategies for carotid atherosclerosis are continuously evolving, and combining multiple pharmacological treatment modalities can more effectively reduce the risk of cardiovascular events and improve patient outcomes. Increasing research continues to explore new drugs and treatment strategies to further optimize the management of carotid atherosclerosis.

Carotid Artery Stenting (CAS) in the Treatment of Carotid Arteriosclerosis

In recent years, CAS has garnered significant attention and application as an interventional method for treating carotid arteriosclerosis. The emergence of CAS has provided an alternative to carotid endarterectomy (CEA), particularly in high-risk surgical patients. With advancements in technology and improvements in equipment, the clinical efficacy of CAS has continued to improve; however, its value in certain situations remains controversial.

The primary advantages of CAS lie in its minimally invasive nature and lower perioperative cardiac event rates. Studies have shown that in symptomatic patients, CAS carries a slightly higher risk of perioperative stroke compared to CEA, particularly in patients over 70 years of age [39]. Additionally, CAS is equally safe as CEA in asymptomatic patients, although modern medical therapy may be as effective as any carotid intervention [39]. However, CAS has advantages in reducing perioperative cardiac events and cranial nerve palsies [39].

Some studies have considered CAS an acceptable alternative for high-risk patients. The CREST trial showed that, for standard-risk patients, CAS and CEA yielded similar outcomes [40]. However, CAS was associated with a higher incidence of minor stroke events, while CEA was associated with a higher incidence of myocardial infarction events [40,41]. Nevertheless, CAS requires high technical expertise and should be avoided in patients with unfavorable anatomical structures [41].

Another vital aspect of CAS is its impact on cerebral hemodynamics and cognitive function. Multiple studies indicate that CAS not only effectively prevents stroke but may also improve cognitive abilities. A multicenter clinical study demonstrated that improved middle cerebral artery blood flow following carotid artery reconstruction was significantly associated with enhanced executive function [42]. This suggests that CAS may help strengthen patients' cognitive abilities by enhancing cerebral blood supply. Furthermore, another observational study found that CAS significantly improved overall cognitive scores and memory in Indian patients, with particularly pronounced improvements in memory, visuospatial abilities, and language skills among those undergoing left-sided CAS [43]. Further research indicates that CAS yields more pronounced cognitive improvements in younger patients, especially those with poorer preoperative cognitive performance [44]. This age-related benefit may relate to greater neural plasticity in younger individuals. Moreover, functional magnetic resonance imaging (fMRI) studies provide direct evidence that CAS enhances cognitive function by increasing activation in specific brain regions [45]. Long-term follow-up studies also support CAS's positive impact on cognition. One study comparing CAS with medication alone demonstrated significant improvements in delayed memory in the CAS group, which correlated with increased perfusion in the middle cerebral artery territory [46]. Furthermore, another systematic review noted that, despite study heterogeneity, most studies indicate that CAS improves function in specific cognitive domains, potentially linked to enhanced cerebral blood flow [47].

Although CAS demonstrates advantages in certain aspects, its role in the management of symptomatic carotid stenosis remains controversial. Some studies suggest that CAS may be inferior to CEA in long-term outcomes, particularly with respect to recurrent stenosis and perioperative events [48]. However, as devices and operator experience continue to mature, the efficacy of CAS may improve [48].

Carotid Endarterectomy (CEA) in the Treatment of Carotid Atherosclerosis

CEA is a common surgical procedure used to treat carotid artery atherosclerosis. Its primary objective is to remove atherosclerotic plaques from the artery, restore blood flow, and thereby reduce the risk of stroke. Studies have shown that CEA is highly effective in treating carotid artery stenosis, particularly in patients with symptomatic carotid artery stenosis, where CEA can significantly reduce the incidence of stroke [49,50].

When comparing CEA with carotid artery stenting (CAS), studies have found that CEA has an advantage in reducing the risk of perioperative stroke. At the same time, CAS may be more advantageous for reducing the risk of perioperative myocardial infarction [51,52]. Additionally, CEA is considered more effective than CAS for long-term stroke prevention, particularly in terms of survival and restenosis rates, where CEA demonstrates better outcomes [53,54].

The applicability of CEA for asymptomatic carotid artery stenosis remains unexplored. However, some studies suggest that in appropriate patient populations, CEA combined with best medical therapy (BMT) may be more effective than medical therapy alone in preventing ischemic events [55,56].

Furthermore, CEA has shown potential benefits in improving cognitive function. Studies indicate that CEA can alleviate cognitive dysfunction caused by carotid stenosis by improving cerebral blood flow and metabolism [57,58].

Comparison of CAS and CEA

CAS and CEA are the two primary methods for treating carotid artery stenosis. Each method has its own advan-

tages and disadvantages, and the choice of treatment often depends on the patient's specific condition and the physician's recommendation.

From the perspective of surgical risks and complications, CAS is considered minimally invasive, making it suitable for high-risk patients who may have difficulty tolerating traditional surgery. However, studies have shown that CAS carries a higher risk of stroke during the perioperative period, particularly in patients over 70 years old [51,59]. In contrast, CEA carries a higher risk of myocardial infarction during the perioperative period, but it may have superior long-term outcomes to CAS in certain cases [60,61].

Second, CAS and CEA have comparable long-term outcomes in preventing stroke and restenosis. However, CAS may be more prone to restenosis, as confirmed by some studies [61,62]. Nevertheless, advancements in technology and accumulated operational experience are gradually improving the long-term outcomes of CAS [60].

In terms of economic costs, CAS expenses are usually higher than CEA expenses, which limits its widespread application [58]. However, for certain high-risk patients, CAS may still be a viable option.

Finally, studies have shown that CAS and CEA have similar effects on improving patients' cognitive function [63,64]. This suggests that both surgical approaches have similar potential to enhance the quality of life.

Therefore, when selecting a treatment plan, physicians must consider multiple factors, such as the patient's age, health, economic status, and surgical risks, to develop the most appropriate strategy.

Transcarotid Arterial Revascularization (TCAR) in the Treatment of Carotid Artery Atherosclerosis

In recent years, transcarotid arterial revascularization (TCAR) has emerged as a promising new technique and has garnered increasing attention. TCAR combines the advantages of carotid endarterectomy (CEA) and carotid artery stenting (CAS), utilizing a direct cervical approach for stent placement and employing retrograde protection techniques to minimize the risk of intraoperative embolism. Research has shown that TCAR demonstrates excellent efficacy in reducing the risk of stroke during and after surgery, particularly in patients with complex aortic arch anatomy [65]. Additionally, TCAR has shown promising outcomes in patients with carotid restenosis [66].

When selecting a specific treatment method, the patient's individual characteristics and risk factors are important considerations. For patients with contralateral carotid artery occlusion, studies have shown that TCAR is superior to traditional transfemoral carotid artery stenting (TFCAS) in reducing the risk of stroke or death during hospitalization, especially in asymptomatic patients [67]. Additionally, carotid revascularization not only improves cerebral hemodynamics but may also have a positive impact on cognitive function, particularly in asymptomatic patients with carotid stenosis [68].

Discussion

Carotid atherosclerosis is a complex disease, and its risk assessment and treatment options require consideration of multiple factors. In recent years, advances in imaging technology and treatment methods have led to the evolution of management strategies for carotid atherosclerosis.

Currently, non-invasive imaging techniques play an increasingly important role in the risk assessment of carotid atherosclerosis. Using imaging techniques such as ultrasound, CT, and MRI, it is possible to better assess plaque characteristics, inflammation, and neovascularization, thereby improving the accuracy of risk stratification [69]. Additionally, carotid ultrasound has demonstrated clinical value in determining stroke risk in asymptomatic individuals, particularly when combined with intima-media thickness (IMT) and plaque volume [70,71].

In terms of treatment, CEA and CAS are the two primary revascularization procedures. For asymptomatic patients with carotid artery stenosis, selecting an appropriate intervention requires consideration of multiple factors, including the patient's overall health status, life expectancy, and risk of surgical complications [72,73]. Studies have shown that imaging assessments can help identify high-risk plaques, thereby guiding surgical decision-making [74].

Additionally, due to the significant variability among patients with carotid atherosclerosis, individualized treatment management is particularly important. When determining the treatment plan, clinicians must tailor the approach to the patient's specific circumstances, including age, gender, ethnicity, and comorbidities, to enhance treatment efficacy and minimize unnecessary interventions [73,75].

Finally, pharmacological therapy is equally indispensable in the management of carotid atherosclerosis. Recent studies have shown that aggressive multimodal pharmacological treatment can significantly reduce the incidence of stroke, prompting new clinical trials to compare the efficacy of revascularization with that of pharmacological therapy [76].

Looking ahead, the deep integration of multidisciplinary approaches promises revolutionary breakthroughs in the diagnosis and treatment of carotid atherosclerosis. Imaging technologies will advance toward higher resolution and functional imaging capabilities. Biomarker research will leverage multi-omics analysis to uncover additional potential targets, while artificial intelligence will become deeply embedded in personalized treatment decision-making. Drug development will focus on precise targets with minimal side effects, surgical techniques will continue to innovate, and combined treatment strategies will become mainstream. Through sustained research, we are confi-

dent in delivering superior treatment options for carotid atherosclerosis patients, reducing stroke risk, and significantly improving their quality of life.

Conclusion

This review explores risk assessment and therapeutic advances for carotid atherosclerosis. For risk evaluation, imaging techniques (e.g., ultrasound, MRI) combined with 3D reconstruction enable intuitive visualization of plaque information, supporting clinical decision-making. 3D ultrasound ensures high accuracy in plaque volume assessment, while MRI details the carotid intima-media structure. Integrating imaging data with 3D fluid-dynamics modeling helps clarify mechanisms of plaque formation. Additionally, biomarker assessment (e.g., oxidative stress, inflammatory markers, and immune cell-related parameters) has become a new focus, aiding in the evaluation of plaque stability and disease progression.

Therapeutic strategies center on pharmacologic interventions: lipid-lowering, blood pressure control, and platelet aggregation inhibition. Antiplatelet therapy remains controversial for asymptomatic patients but is critical for preventing ischemic stroke. Statins and PCSK9 inhibitors reduce cardiovascular event risk in lipid management, while blood pressure control significantly slows disease progression. For surgical interventions, CEA and CAS are primary revascularization methods. CEA excels in reducing perioperative and long-term stroke risk, while CAS offers minimally invasive benefits for high-risk patients, with both improving cognitive function similarly. The emerging TCAR technique combines the advantages of CEA and CAS, further reducing intraoperative and postoperative stroke risk.

Availability of Data and Materials

Not applicable.

Author Contributions

ZL was responsible for the design, drafting and critical revision. ZZ was responsible for part of the drafting and literature collection. YL was responsible for part of the literature collection and critical revision. DG was responsible for design and critical revision. All authors gave final approval of the version to be published. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity are addressed.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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