Stroke

COMMENTS AND OPINIONS

CCaS: A New Conceptual Framework in Cerebrovascular Disease

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GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: atherosclerosis ■ carotid arteries ■ cognitive dysfunction ■ inflammation ■ stroke

Cerebrovascular diseases are a major cause of global morbidity and mortality and a leading determinant of long-term disability. Stroke has a multifactorial etiology, and atherosclerosis of carotid arteries accounts for a substantial proportion of ischemic strokes and transient ischemic attacks.[1] Traditionally, carotid atherosclerosis has been viewed as a dichotomous condition, with plaques classified as either stable and clinically silent or unstable and responsible for acute cerebrovascular events. However, this paradigm does not adequately reflect the biological and clinical complexity of the disease, as plaques may exert chronic pathological effects even when structurally stable but biologically active.[2] Increasing evidence indicates that this binary model overlooks a more continuous disease process, analogous to the conceptual evolution observed in coronary artery disease with the introduction of chronic coronary syndrome (CCS). CCS has reshaped the understanding of myocardial ischemia by acknowledging that atherosclerotic lesions may induce chronic ischemic injury long before an acute coronary event becomes manifest. This conceptual framework has promoted heightened clinical attention and the development of dedicated diagnostic and therapeutic guidelines.[3] In contrast, the absence of a similar construct for carotid atherosclerosis risks underestimates the burden of chronic cerebrovascular impairment and delays the implementation of appropriate screening and management strategies. In this context, we propose the term chronic carotid syndrome (CCaS) to define a condition of persistent but subclinical cerebrovascular dysfunction caused by stable yet hemodynamically or biologically active carotid plaques. Although not immediately responsible for overt stroke, these lesions may promote chronic cerebral hypoperfusion,[4] microembolization, and impaired cerebrovascular reactivity (CVR),[5] thereby contributing to small vessel disease and cerebral atrophy.[6] Over time, such mechanisms may result in subtle but progressive neurological deficits, cognitive decline, and an increased susceptibility to future cerebrovascular events.[7–10] The analogy between CCaS and CCS is further supported by shared pathophysiological features. Both arise from progressive atherosclerotic plaque accumulation that may remain clinically silent for prolonged periods before precipitating acute events. In both vascular territories, fixed stenosis, endothelial dysfunction, and subclinical embolization can impair tissue perfusion and vascular reserve.[11] These parallels underscore the need for refined risk stratification, advanced diagnostic modalities, and targeted therapeutic strategies. This article examines the pathophysiology, clinical relevance, and potential management of CCaS, advocating for a paradigm shift in the classification and treatment of cerebrovascular disease.

LIMITATIONS OF THE PREVAILING PARADIGM IN CAROTID ATHEROSCLEROTIC DISEASE

Current clinical practice approaches carotid atherosclerosis mainly through an acute-event–centered paradigm, in

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which the disease is considered clinically relevant primarily when presenting as transient ischemic attack or ischemic stroke, thereby focusing on short-term risk stratification and revascularization.[12] Consequently, the management of asymptomatic carotid stenosis remains controversial, with no universally accepted surgical indications and medical therapy largely confined to cardiovascular risk factor control and, in selected cases, antiplatelet treatment.[13] Contemporary guidelines advocate a multimodal diagnostic strategy, including ultrasound, computed tomography, magnetic resonance imaging, and transcranial Doppler, to detect vulnerable plaques.[14] However, recommendations for treating biologically or morphologically unstable yet asymptomatic plaques remain limited. This conceptual framework mirrors earlier views of coronary artery disease, in which emphasis was placed on acute coronary syndromes with insufficient recognition of the chronic ischemic burden imposed by subcritical or biologically active lesions. Failing to capture the chronic and multifactorial nature of carotid atherosclerosis, current guidelines underestimate the persistent, subclinical dysfunction induced by biologically active, nonocclusive plaques.[2] However, contemporary evidence indicates that inflammatory and immune-mediated activity may be present even in apparently stable lesions.[15] The absence of a nosological construct analogous to CCS further restricts the development of structured screening strategies and targeted medical therapies. As a consequence, routine practice often overlooks chronic cerebral hypoperfusion, silent microembolization, and impaired CVR, despite their association with cognitive decline and subtle neurological deficits.[16]

REFRAMING CAROTID ATHEROSCLEROSIS: THE CONCEPT OF CCaS

To address the aforementioned limitations, we propose CCaS as a unifying clinical construct encompassing the chronic, subclinical, yet pathophysiologically relevant condition associated with hemodynamically or biologically active carotid plaques. CCaS denotes a persistent state of cerebrovascular dysfunction secondary to carotid atherosclerosis that may not manifest with overt neurological events but exerts measurable and clinically meaningful effects on cerebral physiology. This dysfunction is mediated by interconnected mechanisms, including chronic cerebral hypoperfusion due to flow-limiting stenosis or impaired collateral circulation, recurrent silent microembolization from biologically active plaque surfaces,[17] and reduced CVR driven by endothelial dysfunction and inflammatory signaling.[18] By integrating hemodynamic, biological, and neurofunctional dimensions, CCaS provides a dynamic model reflecting the continuum of carotid disease and its cerebral consequences (Figure 1). This concept aligns with the growing emphasis on identifying plaque inflammation through molecular and advanced imaging, particularly positron emission tomography, which places plaque biology at the center of diagnostic and translational research and also allows evaluation of cerebral metabolism as an indirect marker of reduced cerebral blood flow in carotid stenosis.[19,20] Accordingly, CCaS offers a unifying framework that links vascular biology, immune-inflammatory mechanisms, and neurovascular dysfunction, thereby reinforcing the conceptual bridge among chronic carotid pathology, aging, and their systemic and cerebral consequences.

EVIDENCE SUPPORTING THE CCaS HYPOTHESIS

A substantial body of evidence supports the need for this revised paradigm. Advanced imaging techniques, including positron emission tomography,[19,20] magnetic resonance–based plaque characterization, and high-resolution ultrasound, consistently demonstrate marked inflammatory activity and intraplaque neovascularization even in lesions conventionally classified as stable, indicating that morphological criteria alone inadequately reflect the biological complexity of carotid disease.[21] Physiological investigations further show that CVR is frequently impaired in patients with moderate carotid stenosis, despite the absence of overt symptoms, revealing persistent disturbances in cerebral autoregulation.[22,23] In parallel, transcranial Doppler studies have identified silent microembolic signals in a subset of asymptomatic individuals that correlate with imaging markers of plaque inflammation.[24,25] Neurocognitive research provides additional confirmation, demonstrating that patients with moderate-to-severe stenosis exhibit measurable cognitive deficits and accelerated decline independent of clinically manifest cerebrovascular events.[26] Histopathologic analyses reinforce these findings by documenting sustained inflammatory and immune-mediated activity within plaques lacking conventional signs of structural instability, thereby supporting a biologically grounded distinction between active and inactive lesions.[15] Analogous to CCS, which may be suspected in patients with exertional angina, ventricular dysfunction, or instrumental abnormalities even in the absence of symptoms,[3] it is reasonable to hypothesize that so-called asymptomatic carotid atherosclerosis is frequently associated with subtle, nonspecific manifestations attributable to CCaS. Indeed, carotid atherosclerosis is an independent risk factor for cognitive decline, correlating not only with the degree of stenosis[10,27] but also with unstable plaque-related microembolization[25] and alterations in cerebral vascular stiffness. Furthermore, asymptomatic patients with reduced regional cerebral volume show a high prevalence of gait disturbances, with increasing atherosclerotic burden associated with worsening motor dysfunction.[26] The common pathophysiological

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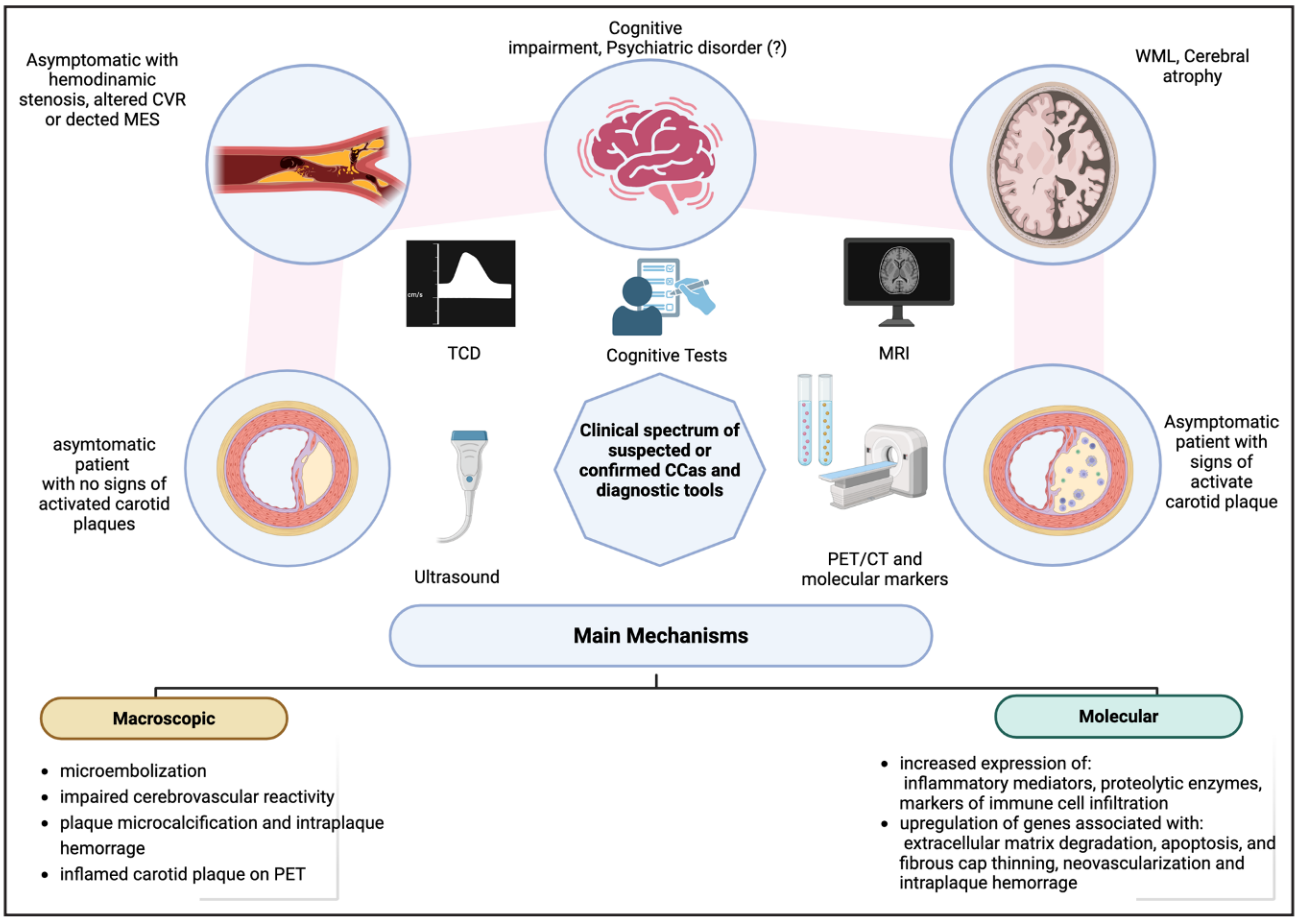

Figure 1. Chronic carotid syndrome (CCaS): clinical spectrum and underlying pathophysiological mechanisms.
Top illustrates the broad clinical continuum encompassed by the proposed nosological entity CCaS. This spectrum ranges from asymptomatic individuals to patients with hemodynamically significant carotid stenosis, impaired cerebrovascular reactivity (CVR), or microembolic signals, and those with cognitive or psychiatric impairment and magnetic resonance imaging (MRI)–detected brain changes. It includes activated plaques identified by biomarkers or positron emission tomography (PET), driven by microembolization, inflammation, and intraplaque hemorrhage. The **bottom** summarizes the principal macroscopic mechanisms involved and the associated microscopic processes. CT indicates computed tomography; MES, microembolic signals; MRI, magnetic resonance imaging; TCD, transcranial Doppler; and WML, white matter lesions. Created in BioRender. Rizzo, G. (2026) https://BioRender.com/eqbs3e5.

substrate underlying these manifestations is a shared inflammatory pathway, as reflected in characteristic cerebral changes, including white matter hyperintensities. This association between nonspecific clinical symptomatology and chronic carotid atherosclerosis further parallels CCS, highlighting the importance of early and aggressive control of vascular risk factors. Such strategies are essential to prevent progression of chronic cerebral hypoperfusion, subsequent cognitive, gait, and neuropsychological deterioration, and ultimately the occurrence of acute cerebrovascular events.

PROPOSED PATHWAYS FOR TESTING THE CCaS HYPOTHESIS

To validate CCaS as a clinical entity, an integrated strategy combining observational, mechanistic, and interventional studies is required. Longitudinal cohorts of asymptomatic patients with moderate carotid stenosis, assessed using multimodal imaging, silent microembolization detection, CVR testing, and serial cognitive evaluations, may clarify temporal links among plaque activity, cerebral physiology, and outcomes. Biomarker studies should identify systemic and plaque-specific inflammatory mediators as indicators of disease activity and progression. Interventional trials are needed to determine whether intensified medical therapies, lipid-lowering, anti-inflammatory, or antithrombotic, can modify physiological end points and clinical trajectories. Parallel neurofunctional assessments, including standardized cognitive testing and functional imaging, may establish whether modulation of plaque biology translates into cognitive stabilization. The conceptualization of chronic carotid atherosclerosis as a syndrome extends beyond a semantic redefinition and offers potential clinical utility analogous to that observed

with CCS. Specifically, it reframes carotid disease as a dynamic and progressive continuum rather than a binary symptomatic/asymptomatic condition, incorporates plaque biology and cerebrovascular consequences beyond luminal stenosis, and facilitates more comprehensive identification of personalized residual risk stratification. Moreover, it establishes conceptual symmetry with acute cerebrovascular syndromes, providing a coherent framework for longitudinal disease assessment.

PROPOSAL OF STEPWISE DIAGNOSTIC MANAGEMENT MODEL FOR CCaS

To translate the conceptual framework of CCaS into clinical practice, we propose a structured, stepwise diagnostic model (Figure 2) that integrates the morphological, clinical, and biological dimensions of carotid disease. This approach builds on the Plaque-RADS classification (Reporting and Data System),[28] extending it from morphological stratification to a dynamic assessment of disease activity, and is complemented by the Gray-Weale system,[29] thereby enabling a combined evaluation of plaque burden and echogenicity.

The first step should rely on carotid duplex ultrasound at spoke centers, with systematic classification according to Plaque-RADS and Gray-Weale criteria. This allows identification of stenosis severity and vulnerability features. Particular attention should be given to asymptomatic hemodynamically significant stenosis (>50%),[30] which should be referred to hub centers due to higher risk.

The CCaS model promotes early clinical integration. Patients with Plaque-RADS ≥2 should undergo neurological evaluation and cognitive screening to detect subtle dysfunction. Patients with incidental brain magnetic resonance imaging findings (white matter hyperintensities, silent infarcts, atrophy) or known cognitive decline should also be included. Ultrasound features such as hypoechogenicity, intraplaque hemorrhage, lipid-rich necrotic core, reduced distensibility, and bilateral plaque burden are associated with cognitive impairment,[7–10,16,17,27] supporting early assessment.

Escalation to second-level investigations should be guided by imaging and clinical criteria. Referral to hub

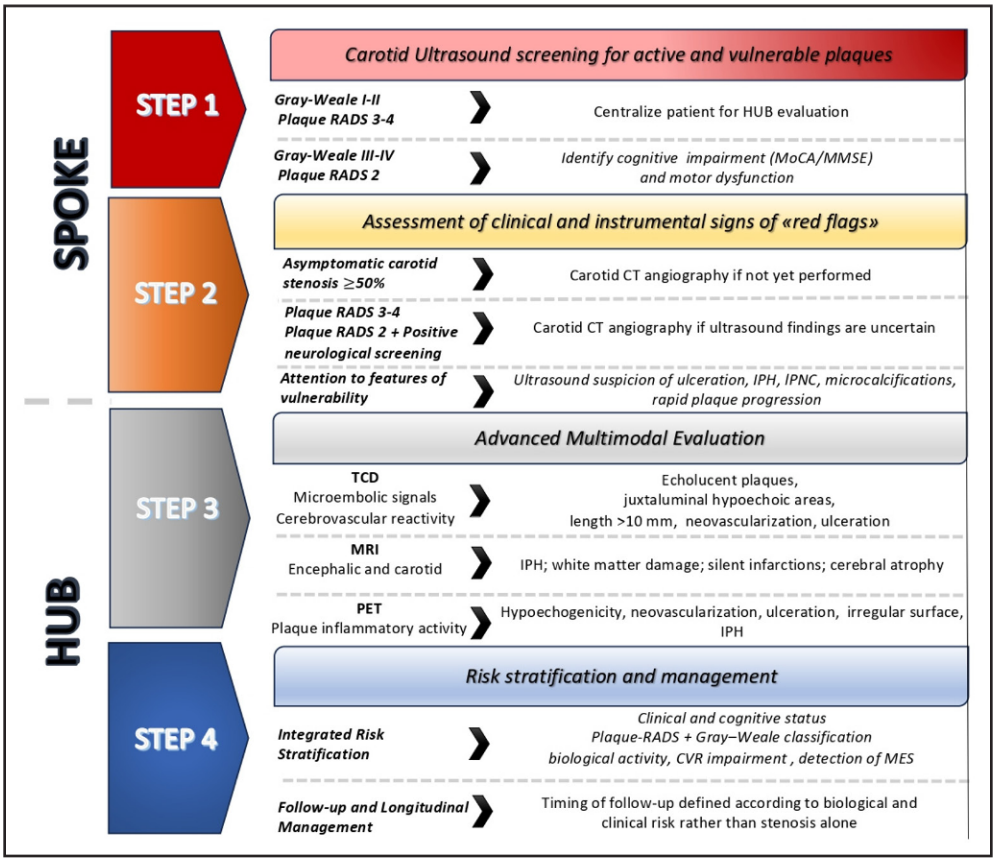

Figure 2. Stepwise diagnostic model proposal for chronic carotid syndrome.
A hub-and-spoke system proposal for a stepwise approach to chronic carotid syndrome evaluation. It includes a first step to screen for active and vulnerable plaques. A second step for recognizing red flags. Third and fourth steps: advanced multimodal evaluation and risk stratification in Hub centers. CT indicates computed tomography; CVR, cerebrovascular reactivity; IPH, intraplaque hemorrhage; IPNC, intraplaque necrotic core; MES, microembolic signals; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; MRI, magnetic resonance imaging; PET, positron emission tomography; Plaque-RADS, Plaque-Reporting and Data System; and TCD, transcranial Doppler.

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centers is recommended for Plaque-RADS ≥3 or Gray-Weale I to II, and for Plaque-RADS 2 or Gray-Weale III-IV-V when clinical or cognitive abnormalities are present. Additional triggers include ulceration, intraplaque hemorrhage, lipid core, microcalcifications, or rapid progression. Angio–computed tomography represents a key second-level modality, also feasible in spoke centers, mainly to confirm stenosis or clarify ultrasound uncertainties.

At hub centers, multimodal evaluation should be performed. Transcranial Doppler enables detection of microembolic signals and assessment of CVR. Brain magnetic resonance imaging characterizes parenchymal damage and detects intraplaque hemorrhage. Fluorodeoxyglucose labeled with Fluorine-18 (^{18}F-FDG) positron emission tomography may assess inflammatory activity, particularly in plaques with hypoechogenicity, neovascularization, ulceration, irregular surfaces, or suspected hemorrhage, adding a biological dimension. Organizationally, a hub-and-spoke system optimizes resources and standardizes care. Spoke centers perform first-line assessment and guide referrals using defined criteria, reducing variability and improving access to advanced diagnostics. Finally, this model should be considered preliminary. Its validation requires prospective studies and multidisciplinary consensus involving neurology, vascular medicine, radiology, and related fields to define standardized diagnostic pathways and fully establish the clinical role of CCaS.

CONCLUSIONS

CCaS reframes carotid atherosclerosis as a chronic cerebrovascular condition with significant functional implications even in the absence of overt stroke. By moving beyond the binary symptomatic/asymptomatic or stable/unstable classifications, CCaS provides a comprehensive paradigm that can guide more nuanced risk stratification, foster dedicated diagnostic and therapeutic guidelines, and ultimately improve neurological and cognitive outcomes for patients with carotid disease.

ARTICLE INFORMATION

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