Carotid plaque characteristics and stroke risk: More questions — or more answers?

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DOI: 10.33963/v.phj.105231

Received:
February 25, 2025

Accepted:
February 25, 2025

Early publication date:
March 6, 2025

Despite the progress in pharmacologic therapies, atherosclerotic carotid artery stenosis remains an important mechanistic factor of ischemic stroke[1, 2]. Today, 20%–25% of strokes are caused by atherosclerotic carotid disease, and these continue to occur in people on optimized medical therapy [1–5]. Because of the large cerebral territory that can be affected, carotid-related strokes are often large and disabling [2, 3]. As the stroke burden is increasing worldwide [1, 3], it should be noted that numerous patients with stroke-related disability would prefer death to their life after stroke [1, 3]. Importantly, carotid atherosclerotic stenosis is a modifiable stroke risk factor; thus carotid-related strokes can be, in principle, prevented [1, 3].

The degree of carotid artery stenosis has been the conventional determinant of stroke risk assessment and — consequently — treatment decisions, including revascularization [1, 3, 4]. Landmark trials established the benefit of carotid endarterectomy and carotid artery stenting for patients with significant stenosis, leading to a widespread reliance on this single metric [1, 3]. However, a growing body of evidence indicates that focusing solely on the luminal "% stenosis" is an oversimplification of a complex dynamic process that occurs in the diseased artery wall [1, 3, 4, 6]. Moreover the "stenosis severity" concept, although theoretically attractive, faces significant ambiguities in every-day clinical decision-making [7]. Not all patients with asymptomatic carotid artery stenosis have the same stroke risk, and thus not all should receive the same treatment [1, 8]. Consistent with this notion, the risk scores based on stenosis luminal severity and traditional cardiovascular risk factors are not specific enough to drive evidence-based decision-making in asymptomatic patients [1, 8, 9]. Clearly, each symptomatic carotid stenosis starts is biologic "career" as an asymptomatic lesion [6]. The concept to concentrate attention on symptomatic stenoses has one fundamental limitation: frequently the treatment would arrive too late to save the functional brain and, in many instances, life [1, 2].

There is a growing body of evidence that plaque characteristics play a pathobiologic role that is far more important than the degree of luminal stenosis severity [1, 4, 10]. Plaque vulnerability is determined by a complex interplay of multiple lesion-level and patient-level factors (Table 1). Plaque morphology (the size of lipid-rich necrotic core and fibrous cap thickness, luminal surface irregularity/ulceration, plaque inflammation, neovascularization and intraplaque hemorrhage) are typical indicators of instability and increased risk of thromboembolic events [3]. For plaque characterization, the different imaging techniques have different resolution. Intravascular ultrasound with its axial resolution of 100–120 μm and tissue penetration of ~10 mm for 20 MHz transducers offers a direct live assessment of the atherosclerotic plaque with a field of view of ~15 × 15 mm but being invasive it is reserved as a primarily research tool [10]. In contrast to intravascular ultrasound, transcutaneous duplex ultrasound visualization resolution is significantly poorer (~400–800 μm for typical transcutaneous ultrasound transducers) [10]. Other commonly promoted

noninvasive techniques such as computed tomography or magnetic resonance imaging also have the fundamental limitation of image resolution (computed tomography: in-plane resolution of 400–500 μm and slice thickness of 1000 μm; magnetic resonance: in-plane resolution of 300–600 μm and slice thickness of 2000–3000 μm) [10].

A meta-analysis of 64 prospective studies in 20 751 participants with asymptomatic carotid stenosis demonstrated a pooled prevalence of high-risk plaques of 26.5% [11]. The most prevalent high-risk plaque features were neovascularization (43.4%) echolucency (42.3%), and lipid-rich necrotic core (36.3%) [11]. The incidence of ipsilateral ischemic cerebrovascular events in severe stenoses was 3.7 events per 100 person-years [11]. Plaque morphology appeared to play a greater role than stenosis severity, with the incidence of ipsilateral ischemic cerebrovascular events higher in patients with high-risk plaques (4.3 events per 100 person-years) than in those without (1.2 events per 100 person-years); odds ratio of 3.0 (95% CI, 2.1–4.3) [11].

Recent subanalysis from the ANTIQUE study, published in the current issue of *Polish Heart Journal* [12], investigated the association between plaque features by computed tomography and magnetic resonance imaging with stroke in 216 stenoses in 132 patients. Interestingly, rather than plaque morphology, the degree of stenosis (that was expressed properly, i.e., as diameter stenosis rather than area stenosis [7]) and alcohol consumption emerged as only independent predictors of recent stroke [12]. At a first glance, these results might seem to question the pathobiologic role of plaque morphology evidenced in prior, much larger and prospective studies [11]. However, it is crucial to interpret the present findings [12] within the context of the fundamental study limitations including not only its moderate size but also (and foremost) its retrospective nature. Not only part of the thromboembolic plaque material may detach and embolize when causing stroke but also carotid plaques have been shown to stabilize after stroke [13]; thus the lesion characteristics detected 3 months after the cerebrovascular event (i.e., as studied by of Pakizer et al. [12]) may not reflect the ones at the point of stroke. Furthermore, clinically asymptomatic cerebral infarcts (Table 1) were not taken into consideration in the ANTIQUE analysis[12]. The ANTIQUE study's finding that alcohol consumption was an independent predictor of stroke risk [12] is intriguing and it is likely valid clinically. While moderate alcohol consumption may be associated with some cardiovascular benefit, excessive alcohol intake is a well-established risk factor for stroke [14]. There is an ongoing controversy whether red wine consumption may be more positive than other types of alcohol [14]. Alcohol consumption may contribute to plaque instability through several mechanisms, including increasing blood pressure, promotion of inflammation, and impaired lipid metabolism. Excessive alcohol consumption correlates with poor compliance with health advice, and it may be a marker of other unhealthy lifestyle factors that contribute to stroke risk, such as poor diet, lack of exercise,

Table 1. Atherosclerotic carotid stenosis: Increased stroke risk characteristics

Feature	Imaging modality	Increase in risk[a]
Lesion level		
Intraluminal floating thrombus	DUS, Angio, IVUS	Brain/life-threatening
Thin/ruptured fibrous cap[b]	CT, IVUS	5.93 (2.65–13.20)
Intraplaque hemorrhage[b]	MRI	4.59 (2.91–7.24)
Lipid-rich necrotic core	CT, VH-IVUS, NIRS	3.00 (1.51–5.95)
Echolucent plaque	DUS	2.61 (1.47–4.63)
Stenosis severity progression	DUS, CT, MRI	1.92 (1.26–2.92)
Ulceration/Surface irregularity	CT, Angio, MRI, IVUS, DUS	1.80 (1.14–2.83)
Plaque inflammation	PET, MRI	Magnitude-dependent
Neovascularisation	MRI, DUS*	Magnitude-dependent
Intraluminal calcific nodules	IVUS, CT	Clinically significant
Intraplaque micro/nanoplastics	EM	4.53 (2.00–10.27)
Brain level		
Microembolic signals	TCD	7.46 (2.24–24.89)
Impaired cerebrovascular reserve	TCD	6.14 (1.27–29.5)
Clinically silent ipsilateral cerebral infarct	CT, MRI	3.0 (1.46–6.29)
Contralateral stroke/TIA	CT, MRI	3.0 (1.9–4.73)
Patient level		
Diabetes	N/A	2.0 (1.6–2.6)
Insulin		7.2 (3.2–16.2)
Contralateral carotid occlusion	DUS, CT, MRI, Angio	23% increase over 5 years
Family history positive for stroke	N/A	Major

[a]Fold-increase (95% confidence interval) according to the largest study(-ies) available (unless specified otherwise); for details see [3]. [b]Mechanisms of plaque growth; in mild/moderate plaque burden often clinically silent [6]
*Contrast-enhanced DUS

Abbreviations: Angio, catheter angiography; CT, computed tomography; DUS, duplex ultrasound; EM, electron microscopy; IVUS, intravascular ultrasound; MRI, magnetic resonance imaging; N/A, not applicable; NIRS, near-infrared spectroscopy; PET, positron emission tomography; VH, virtual histology

smoking, and poor compliance with cholesterol-lowering and anti-hypertensive therapy [14].

While standardized reporting systems are being developed for carotid plaque composition and morphology evaluation using different modalities (transcutaneous ultrasound, computed tomography, magnetic resonance imaging) [15], it must not be ignored that evolution of plaque morphology is a dynamic and heterogenic process [6]. Plaque progression beyond 40%–50% luminal diameter narrowing typically occurs secondary to repeated episodes of intraplaque hemorrhage and/or plaque rupture [6]. These events represent an important mechanism of plaque growth and they are often clinically silent [6]. Remarkably, the plaque rupture events are more likely to be silent in less severe lesions [6].

Overall, the present body of evidence indicates a clear need to use imaging to identify high-risk plaque composition and thus plaques (and patients!) that may benefit from more aggressive management. One fundamental question today is how to practically implement plaque-level and characteristics (Table 1) in a clinical decision-making model. Until carotid-related stroke risk prediction scores become validated (such as classic CHA_2DS_2-VASC scale or a more recent calculator of absolute stroke risk in atrial fibrillation, CARS/mCARS), the "roulette wheel" of applying (or not applying) the particular increased stroke risk characteristics in managing carotid stenosis will continue to turn over the necks of underestimated-risk patients [1].

Article information

Conflict of interest: None declared.

Funding: None.

REFERENCES

1. Musialek P, Rosenfield K, Siddiqui AH, et al. Carotid stenosis and stroke: Medicines, stents, surgery — „wait-and-see" or protect? Thromb Haemost. 2024; 124(9): 815–827, doi: 10.1055/a-1952-1159, indexed in Pubmed: 36170885.
2. Tekieli L, Dzierwa K, Grunwald IQ, et al. Outcomes in acute carotid-related stroke eligible for mechanical reperfusion: SAFEGUARD-STROKE Registry. J Cardiovasc Surg (Torino). 2024; 65(3): 231–248, doi: 10.23736/S0021-9509.24.13093-5, indexed in Pubmed: 39007556.
3. Musialek P, Bonati LH, Bulbulia R, et al. Stroke risk management in carotid atherosclerotic disease: A Clinical Consensus Statement of the ESC Council on Stroke and the ESC Working Group on Aorta and Peripheral Vascular Diseases. Cardiovasc Res. 2023: cvad135, doi: 10.1093/cvr/cvad135, indexed in Pubmed: 37632337.
4. Podlasek A, Simpson RJ. Another step toward the understanding of carotid artery pathology. AJNR Am J Neuroradiol. 2021; 42(7): 1291–1292, doi: 10.3174/ajnr.A7137, indexed in Pubmed: 33888453.
5. Hosseini AA, Simpson RJ, Altaf N, et al. Magnetic resonance imaging plaque hemorrhage for risk stratification in carotid artery disease with moderate risk under current medical therapy. Stroke. 2017; 48(3): 678–685, doi: 10.1161/STROKEAHA.116.015504, indexed in Pubmed: 28196937.
6. Sakakura K, Nakano M, Otsuka F, et al. Pathophysiology of atherosclerosis plaque progression. Heart Lung Circ. 2013; 22(6): 399–411, doi: 10.1016/j.hlc.2013.03.001, indexed in Pubmed: 23541627.
7. Tekieli L, Mazurek A, Dzierwa K, et al. Misclassification of carotid stenosis severity with area stenosis-based evaluation by computed tomography angiography: Impact on erroneous indication to revascularization or patient (lesion) migration to a higher guideline recommendation class as per ESC/ESVS/ESO/SVS and CMS-FDA thresholds. Adv Interv Cardiol. 2022; 18(4): 500–513, doi: 10.5114/aic.2023.125610, indexed in Pubmed: 36967857.
8. Paraskevas KI. Risk models for the detection of severe asymptomatic carotid stenosis and the prediction of future strokes and cardiovascular events. Stroke. 2024; 55(11): 2641–2642, doi: 10.1161/STROKEAHA.124.048875, indexed in Pubmed: 39319452.
9. Podlasek A, Grunwald IQ, Musiałek P. The evolution from an „average" study patient to patient-specific characteristics to guide interventions in vascular medicine. Pol Arch Intern Med. 2021; 131(1): 5–8, doi: 10.20452/pamw.15791, indexed in Pubmed: 33522217.
10. Musialek P, Dabrowski W, Mazurek A, et al. Quantitative virtual histology for in vivo evaluation of human atherosclerosis — a plaque biomechanics-based novel image analysis algorithm: Validation and applications to atherosclerosis research. Intravascular Ultrasound. 2020: 71–96, doi: 10.1016/b978-0-12-818833-0.00005-9.
11. Kamtchum-Tatuene J, Noubiap JJ, Wilman AH, et al. Prevalence of high-risk plaques and risk of stroke in patients with asymptomatic carotid stenosis: A meta-analysis. JAMA Neurol. 2020; 77(12): 1524–1535, doi: 10.1001/jamaneurol.2020.2658, indexed in Pubmed: 32744595.
12. Pakizer D, Netuka D, Hrbáč T, et al. MRI- and CT-derived carotid plaque characteristics and stroke: Insights from the ANTIQUE study. Pol Heart J. 2025; 83(3): 277–286, doi: 10.33963/v.phj.103740, indexed in Pubmed: 39743911.
13. Peeters W, Hellings WE, de Kleijn DPV, et al. Carotid atherosclerotic plaques stabilize after stroke: insights into the natural process of atherosclerotic plaque stabilization. Arterioscler Thromb Vasc Biol. 2009; 29(1): 128–133, doi: 10.1161/ATVBAHA.108.173658, indexed in Pubmed: 18931283.
14. Surma S, Gajos G. Alcohol, health loss, and mortality: can wine really save the good name of moderate alcohol consumption? Pol Arch Intern Med. 2024; 134(4): 16708, doi: 10.20452/pamw.16708, indexed in Pubmed: 38506256.
15. Saba L, Cau R, Kopczak A, et al. Carotid plaque-RADS: A novel stroke risk classification system. JACC Cardiovasc Imaging. 2024; 17(1): 62–75, doi: 10.1016/j.jcmg.2023.09.005, indexed in Pubmed: 37823860.