Review

Symptomatic non-stenotic carotid disease: current challenges and opportunities for diagnosis and treatment

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ABSTRACT
Symptomatic non-stenotic carotid plaques (SyNC) are an under-researched and under-recognized source of stroke. Various imaging markers of non-stenotic carotid plaques that are associated with stroke risk have been identified, but these causal relationships need to be confirmed in additional prospective studies. Currently, there exists neither a standardized SyNC definition nor a dedicated set of imaging protocols, although researchers have started to address these shortcomings. Moreover, many neuroradiologists are still unaware of the condition, and hence do not comment on high-risk plaque features other than stenosis in their reports. Regarding SyNC treatment, scant data exist as to whether and to what extent medical, interventional and surgical treatments could influence the course of the disease; the relative lack of data on the ‘natural’ history of untreated SyNC makes treatment comparisons difficult. In our opinion, endovascular SyNC treatment represents the most promising treatment option for SyNC, since it allows for targeted elimination of the embolic source, with few systemic side effects and without the need for general anesthesia. However, currently available carotid devices are designed to treat stenotic lesions, and thus are not optimally designed for SyNC. Developing a device specifically tailored to SyNC could be an important step towards establishing endovascular SyNC treatment in clinical practice. In this review, we provide an overview of the current state of evidence with regard to epidemiological, clinical and imaging features of SyNC, propose a SyNC definition based on imaging and clinical features, and outline a possible pathway towards evidence-based SyNC therapies, with a special focus on endovascular SyNC treatment.

BACKGROUND
Acute ischemic stroke (AIS) etiology is most often classified using the 1993 Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria.1 Large artery atherosclerosis, defined as arterio-arterial embolism from plaques in the aorta or supra-aortic branches, accounts for almost one out of four cases of AIS. The TOAST criteria only consider carotid artery plaques to be a source of stroke if a stenosis >50% is present. Patients with strokes caused by non-stenotic carotid artery plaques (<50% luminal narrowing) fall under the category of ‘embolic stroke of undetermined source’. The 50% stenosis degree cut-off was also used in the landmark carotid endarterectomy trials2-4 (the North American Symptomatic Carotid Endarterectomy Trial [NASCET] and the European Carotid Surgery Trial [ECST]), thereby finding its way into guidelines and clinical practice. Since revascularization of high-degree stenotic carotids has become the standard of care, stroke imaging has naturally prioritized identification of these high-grade (>50%) stenoses over other plaque characteristics indicative of increased stroke risk. However, in recent years it has become apparent that symptomatic non-stenotic carotid disease (SyNC) is a common and under-recognized stroke etiology.5,6 While the overall stroke risk in non-stenotic carotid plaques is on average lower compared with stenotic plaques, advanced imaging methods have allowed for identification of numerous high-risk plaque features such as intraplaque hemorrhage7 that, compared with the absence of high-risk features, are associated with increased stroke risk in non-stenotic plaques, such as intraplaque hemorrhage.8 Patients with non-stenotic but vulnerable carotid plaques seem to still carry a substantially increased risk for arterio-arterial embolic stroke.9,8 In this review, we provide an overview of epidemiological, clinical and imaging features of SyNC, propose a SyNC definition, and discuss future directions of SyNC treatment strategies.
SYNC DEFINITION
It may seem obvious that non-stenotic or mildly stenotic plaques (<50-70% luminal narrowing) can nevertheless be a source of arterial-arterial embolic strokes. However, in the presence of other, competing stroke etiologies, such as atrial fibrillation or small vessel disease, it is hard to determine the source of stroke with certainty. Thus, care needs to be taken to consider competing stroke sources when deciding whether a stroke patient suffers from SyNC. Interestingly, five out of the 17 (29%) identified original research studies and five of the 12 (42%) identified review articles avoided to define ‘SyNC’ precisely (online supplemental tables 1 and 2). The most commonly chosen stenosis threshold to define SyNC was <50%, and one study used an additional lower threshold of 30%, with SyNC being defined as 30-49% carotid stenosis. Two studies chose <70% stenosis for their SyNC definition. Additional criteria that were used included the presence of intraplaque hemorrhage or plaque thickness >3 mm. Four studies used more comprehensive definitions that incorporate morphological plaque features (stenosis degree and high-risk plaque features), clinical characteristics (competing stroke sources) and/or brain imaging findings (evidence of one or multiple strokes in the ipsilateral internal carotid artery territory). The latter points are critical, since imaging assessment of the carotid lesion itself always needs to be reviewed in the context of the brain imaging findings and clinical symptoms; without evidence of one or ideally several infarcts of the ipsilateral internal carotid artery territory, a definite diagnosis of SyNC cannot be made (table 1). Although transcranial Doppler sonography could be primarily used for brain imaging in SyNC assessment, as it is able to detect intracranial emboli, CT and MRI are less operator-dependent and more often used in the acute stroke setting. We personally believe that diffusion-weighted MRI should be the preferred brain imaging modality whenever possible.

**Table 1** Working definition for symptomatic non-stenotic carotid disease

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<tr>
<th>Disease</th>
<th>Stenosis Degree</th>
<th>High-risk Features</th>
<th>Imaging Findings</th>
<th>Competing Stroke Sources</th>
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<td>Possible</td>
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1. Plaque morphology: Certain high-risk features, most notably intraplaque hemorrhage, but also plaque ulceration and irregular plaque surface, among others, are known to be associated with an increased stroke risk, especially in non-stenotic carotid plaques. The presence of such high-risk features in a non-stenotic carotid plaque increases the likelihood of this plaque being the source of stroke. The same is true for a non-stenotic plaque that is changing in morphology, since this change may be the result of instability and active embolization.

2. Brain imaging: Presence of infarcts, especially concomitant acute/subacute and new infarcts, in the ipsilateral internal carotid artery territory are highly suggestive of an arterio-arterial embolic source in the internal carotid artery. This is especially true if there are no visible infarcts in other vascular territories. Of note, the internal carotid artery territory is variable based on the presence and caliber of the anterior and posterior communicating arteries. For example, the ipsilateral anterior cerebral artery territory is normally part of the internal carotid artery territory, except for cases in which the ipsilateral A1 segment is absent (online supplemental figure 2).

3. Absence of competing stroke etiologies: the likelihood of SyNC increases if an extensive stroke work-up, including 24-hour electrocardiogram, medium and long-term cardiac
monitoring, echocardiogram, and vasculitis work-up, is otherwise negative.

As mentioned before, these three ‘dimensions’ need to be weighed against each other when deciding about a potential SyNC case. We therefore propose a probabilistic SyNC definition based on these considerations that has been previously described by our group. In short, we suggest classifying cases as ‘definite SyNC’ if they show evidence of recurrent ipsilateral stroke exclusively in the internal carotid artery territory, an ipsilateral SyNC lesion with high-risk features and changing morphology (suggesting active embolization), as well as absence of other stroke causes. If these criteria are only partially met, we suggest classifying the case either as ‘probable’ or ‘possible’ SyNC (table 1). Certainly, clear-cut ‘definite’ SyNC cases will be the exception and, most of the time, one will encounter patients who reside somewhere along the spectrum of ‘possible’ to ‘probable’ SyNC.

**CLINICAL FEATURES OF SYNC**

Currently, it is not entirely clear whether and how clinical characteristics of SyNC patients differ from AIS patients with other stroke etiologies. Embolic stroke of undetermined source (ESUS) patients are on average younger and present with milder symptoms compared with other stroke etiologies.19–21 Since SyNC patients so far have been classified as ESUS, it is possible that the aforementioned characteristics apply to the SyNC population as well, but this is uncertain. The included SyNC studies report mean ages at stroke onset from 63 to 78 years (online supplemental table 1), which is very similar when compared with other common stroke etiologies such as small vessel disease and cardioembolic strokes. Additionally, SyNC may be associated with a general pro-inflammatory vascular state, characterized by increased fluorodeoxyglucose (FDG) uptake not only of the SyNC lesion but also other vessels, including the contralateral carotid artery.22 Indeed, carotid atherosclerotic lesions are associated with increased C-reactive protein (CRP), a systemic inflammatory marker, and the combination of carotid atherosclerosis and increased CRP is not only associated with strokes but also myocardial infarction,22 further supporting the hypothesis that SyNC may simply be a manifestation of a systemic inflammatory process. Thus, one could consider routinely obtaining CRP levels in SyNC patients to evaluate systemic inflammatory activity. Other clinical factors that may play a role in carotid plaque formation and instability, and thus also SyNC pathogenesis, need to be explored in further detail. For example, it is possible that low vitamin D levels predispose to intraplaque hemorrhage,23 but this needs to be confirmed in additional studies.

**IMAGING OF SYNC**

Since the definition of SyNC relies both on imaging findings of the carotid lesion itself as well as brain imaging findings, both should be undertaken when SyNC is suspected.

As for brain imaging, only a few of the included studies specifically reported brain imaging findings as part of SyNC.13 14 24 Nevertheless, in order to establish a causal relationship, evidence of infarcts in the ipsilateral internal carotid artery territory is crucial, while infarcts in other territories would speak against SyNC. One caveat is that the internal carotid artery territory is variable depending on the circle of Willis configuration (online supplemental figure 2). Possible imaging modalities to show evidence of recent or past ischemia would be non-contrast CT and MRI. A non-contrast CT could show evidence of larger ischemic events. MRI is by far the more sensitive modality, when including both diffusion-weighted imaging to detect acute infarcts and fluid attenuated inversion recovery (FLAIR) or T2 sequences to detect subacute and old infarcts. The situation is much more complex when it comes to imaging of the carotid lesion itself. Several plaque features have been described to be indicators of ‘vulnerable’ non-stenotic lesions that are prone to embolization.

**Degree of stenosis**

The degree of stenosis as per the NASCET criteria2 can be assessed on most imaging modalities, most commonly, CT angiography (CTA), ultrasound and MRI/MR angiography. It is well-known that stenotic carotid plaques carry a higher risk of stroke than non-stenotic (<50%) plaques. Even within the group of non-stenotic plaques, it seems that a higher degree of stenosis is associated with ipsilateral stroke.10 12 Thus, the degree of stenosis seems to be an important imaging marker, even within the non-stenotic plaque subgroup. In other words, it seems that, given that all other plaque features are equal, a carotid plaque with 40% stenosis yields a higher stroke risk as compared with a plaque with 10% stenosis.

**MRI markers: intraplaque hemorrhage**

Intra-plaque hemorrhage (figure 2) is the most well-studied imaging marker in the setting of SyNC, and it has a clear, strong association with ipsilateral internal carotid artery territory strokes, irrespective of the degree of luminal narrowing.8 14 23 26 Not surprisingly, intraplaque hemorrhage was mentioned as a high-risk feature in almost every included study (online supplemental tables 1 and 2). Assessing for intraplaque hemorrhage requires a non-contrast fat-saturated T1 image, which does not require any specialized MR equipment and only takes 3–5 min to
acquire. Nevertheless, since acute stroke imaging is CT-based in the vast majority of hospitals, assessing intraplaque hemorrhage is not necessarily part of the routine stroke work-up in most centers.

Other MRI markers

Other high-risk MRI imaging markers include lipid-rich necrotic core, ulceration, ruptured fibrous cap, and possibly various quantitative fibrin, lipid and calcific component measures (see figure 2 for exemplary findings). However, the evidence, particularly for quantitative measurements, is sparse and different studies used different software packages and variable definitions to identify and quantify those components. Besides investigating the association of these individual plaque components with stroke risk, many authors have classified plaques using the American Heart Association (AHA) classification. This classification has originally been established to describe coronary artery plaques and uses histological criteria to group arterial plaques, whereby the higher groups (AHA type IV–VI plaques) are associated with a higher risk of arterial-arterial embolism. Although compelling in theory, this nomenclature is problematic in the sense that imaging findings do not translate 1:1 into histological correlates, and it is therefore hard to know the histological composition and architecture of a plaque without actually obtaining histological proof. In clinical practice, we therefore suggest a pragmatic approach for now when performing plaque MRI, that is, assessing for intraplaque hemorrhage, plaque ulceration and irregularity, without quantifying plaque components or applying any detailed classification.

CT markers

In theory, using a CT-based marker for SyNC assessment would be ideal, since non-contrast CT of the head and CTA of the head and neck are routinely performed in all patients with suspected AIS. Several CT-based imaging markers have been suggested, including plaque thickness (both as a continuous variable and thickness ≥3 mm), plaque ulceration/irregularity, and non-calcified and hypodense plaques. However, the association of these features with ipsilateral strokes is weak, and many studies could not show a significant association at all. This may be related to the relatively low tissue contrast of CTA, which makes accurate distinction of different plaque components close to impossible. Some authors have also attempted to quantify histological plaque components based on differences in density, but such attempts are still experimental and suffer from the same limitations mentioned in the previous section. Limited spatial resolution and resulting volume averaging artifacts constitute additional problems. In other words, CTA should not be the primary assessment modality for SyNC. If a high-risk carotid plaque feature is seen on CTA in the appropriate context, then the suspicion of SyNC can certainly be raised, but the absence of such features on CTA should not lead us to conclude that SyNC is not present.

Ultrasound

Although carotid ultrasound is usually also not part of the acute stroke work-up, ultrasound has the advantages of being relatively inexpensive, widely available, and radiation-free. Perhaps...
the greatest disadvantage is the high inter-operator variability. High-risk ultrasound features reported in the identified studies include degree of stenosis, intraplaque hemorrhage, lipid-rich necrotic core, as well as both echolucency/high echogenicity and low echogenicity, although no quantitative thresholds were provided by the authors. One review discussed the potential advantages of contrast-enhanced ultrasound, which is, however, not routinely used in most centers.

**Positron emission tomography**
A number of studies used positron emission tomography (PET) to assess for metabolic activity of carotid lesions. Interestingly, in addition to FDG-uptake being higher in complicated (AHA type VI) lesions compared with lower-grade AHA lesions, the authors also found that patients with type VI lesions show increased uptake in the contralateral carotid artery. They hypothesized that this could indicate a possible systemic inflammatory process as an underlying etiology in patients with complicated plaques.

Other modalities such as digital subtraction angiography and optical coherence tomography have also been discussed, although no robust SynC imaging markers for these modalities exist at this point. Of note, despite increasing evidence on the importance of carotid plaque features other than the degree of stenosis, they are often not commented on in radiology reports. In a retrospective evaluation of 651 CTA reports in a large comprehensive stroke center in the USA, the degree of carotid stenosis was explicitly mentioned in >98%, but the presence or absence of most other high risk features were reported in <20%, and <1% explicitly mentioned whether there was a carotid lesion that could increase stroke risk. These data suggest that many non-stenotic high risk lesions may go unnoticed, and increasing awareness among the diagnostic neuroradiology community could substantially help in detecting SynC cases and recognizing them as such early on. Online supplemental table 3 provides an ‘SynC checklist’ for radiologists that can be used when assessing carotid CT/MR angiographies.

**RISK OF STROKE IN SYNC PATIENTS**
What is the risk of future stroke in patients with SynC? Since many studies did not use a clear SynC definition, one can only provide rough estimates on future stroke risk. Probably the most thorough, comprehensive study that was conducted on this question is the prospective, longitudinal multicenter Plaque-At-Risk (PARISK) cohort study that included patients with recent transient ischemic attack (TIA) or minor stroke and ipsilateral carotid plaques causing <70% stenosis. During 5.1 years follow-up, 37/238 (16%) patients suffered a recurrent stroke or TIA, with MRI evidence of new infarcts in 19/238 (8%) patients. Intraplaque hemorrhage and total plaque volume (both assessed on MRI) were associated with recurrent ipsilateral stroke or TIA, with hazard ratios of 2.12 (95% CI 1.02 to 4.44) and 1.07 (95% CI 1.00 to 1.15) per 100 µL increase, respectively. Although the stenosis threshold used in PARISK (<70%) is different from the one used by most studies and ourselves (<50%), most (73%) PARISK patients showed very mild stenosis with <30% luminal narrowing. Thus, the PARISK findings will likely apply to patients with <50% plaques as well. In contrast to PARISK, the majority of studies that we identified during the literature search are cross-sectional in nature, that is, patients with AIS/TIA were imaged, and ipsilateral (and contralateral) carotid plaque features were reported. For instance, a single center study by Larson et al performed routine carotid plaque imaging on 123 consecutive ESUS patients, whereby 31 patients (25.2%) had an ipsilateral hemorrhagic plaque versus five patients (4.1%) on the side contrastralateral to the stroke. The recurrent stroke risk in the ipsilateral intraplaque hemorrhage group was 16.7% compared with 2.4% in the non-intraplaque hemorrhage group, and the overall rate of recurrent ipsilateral stroke was 9.5%/year. Although numerous other studies also suggest that SynC-type lesions are found more often ipsilateral to the stroke, causality still needs to be confirmed in prospective, longitudinal studies.

One important caveat with regard to non-stenotic lesions and their association with ipsilateral stroke is that the non-stenotic plaque morphology at the time of imaging may be a result of embolization, and the initial plaque may in fact have been a stenotic one. Since serial imaging prior, during and after the stroke/TIA is neither ethical nor feasible, this possibility cannot be entirely excluded.

**POTENTIAL SYNC TREATMENT OPTIONS**
The treatment for SynC needs to be approached differently from the treatment for high-grade carotid stenosis, because the risk of future stroke is lower in SynC; this has to be taken into account when balancing treatment risks and potential benefits. Overall, it seems that a more cautious approach in SynC would be reasonable, given the better natural history of the disease.

**Medical management**
Some studies have suggested intensive medical treatment, for example, with rivaroxaban plus aspirin, dual antiplatelet agents or high-dose statins as a potential SynC treatment, the primary goal being to influence plaque remodelling in a positive way and stabilize ‘vulnerable’ plaques. Evidence for such therapeutic regimens is hitherto largely missing. The ongoing randomized Colchicine for prevention of vascular inflammation in non-cardioembolic stroke (CONVINCE) trial investigates the efficacy of low-dose colchicine to reduce non-cardioembolic strokes, which may be an interesting treatment option to counteract the inflammatory component of SynC. There are also novel treatments under investigation, for example, C-117, a compound that may potentially reduce non-stenotic carotid plaque burden based on the results of one randomized trial.

**Surgical management (carotid endarterectomy)**
Carotid endarterectomy (CEA), although commonly performed for high-grade carotid stenosis, is hardly ever used to treat SynC, because it is an invasive surgical procedure which requires general anesthesia and temporary ligation of the carotid artery and, as with any surgery, carries some perioperative risks. Although few studies have reported successful CEA for SynC, routine CEA is hardly justified, given the lack of guideline-based SynC treatment recommendations, and the perceived ‘benign’ course of SynC compared with high-grade carotid stenosis.

**Interventional management (carotid artery stenting)**
Based on the above considerations, carotid artery stenting (CAS) may be a valid alternative to CEA in SynC patients. However, the lack of randomized evidence (which in turn, has resulted in a lack of guideline-based treatment recommendations) applies to CAS as well, and for the time being there are no robust data to suggest superiority of either CEA, CAS or aggressive medical management. Furthermore, currently available stents used for CAS are intended for more severely stenotic vessel segments and have a high radial force, which comes at the cost of vessel wall

stretching and micro-injuries. To achieve this high radial force, dense wire meshes encompassing the full stent circumference (360°) are used. This high metal density results in a large thrombogenic surface area exposed in the vessel and requires lifelong antiplatelet therapy to prevent platelet adhesion and in-stent thrombosis. The high circumferential metal coverage of current carotid stents also renders subsequent CEA impossible because the dense wire mesh cannot be cut by a surgical scalpel.

Lastly, the pores of currently used stents are relatively large, and allow small plaque fragments to migrate into the vessel lumen, increasing the risk of periprocedural embolic strokes. Proximal and distal protection devices are available to minimize that risk, although they cannot completely prevent distal embolization, and earlier reviews suggest no significant differences in periprocedural strokes and death with versus without protection devices.40 41

ENDOVASCULAR SYNC TREATMENT: HOW TO MOVE FORWARD?

Despite the above-mentioned issues, we personally believe that of all treatment options, endovascular treatment is the most promising option. Several challenges need to be overcome first: more (prospective) knowledge about the ‘natural history’ of SyNC should be gathered, the role of systemic inflammatory conditions in SyNC patients should be further investigated, and robust evidence for all three treatment options needs to be created. The neurointerventional community seems to agree with this approach: in a multinational web-based survey (ESCAPE ALICE: EndovaSCular TreAtment Preference Evaluation at the Advanced Live Interventionsal Course of Essen),62 43 we asked 248 neurointerventionists from 48 countries how they see the future of SyNC treatment. The majority of physicians thought that essential prerequisites to successful interventional SyNC treatment are (1) a standard definition for SyNC, and (2) a standardized imaging protocol (online supplemental figure 3A,B). Two thirds believed that now is the time for a randomized trial comparing medical versus interventional versus surgical SyNC therapy, while 23% believed that, first, better data on the natural history of non-stenotic carotid plaques are needed (online supplemental figure 3D). With regard to potential endovascular SyNC treatment devices, four out of five physicians thought that an uncovered stent is preferable to a covered device (online supplemental figure 3C). Self-expanding properties and appropriate mesh design with small pores were thought to be the most critical features of an endovascular SyNC treatment device, while a strong outward force was considered the least desirable of all provided answer options (online supplemental figure 3D).

Indeed, SyNC is by definition non-stenotic, and thus it is not necessary to widen the vessel lumen by applying an outward force. In fact, only focal coverage by the stent material at the site of the plaque is needed to eliminate the embolic lesion. Not only would focal metal coverage reduce the thrombogenic risks, it would also allow for subsequent CEA because the device could be cut at the site of minimal metal coverage. Further design specifications, such as anti-inflammatory coating or a resorbable material for temporary plaque stabilization, could be considered as well. Figure 3 outlines a suggested timeline for establishing endovascular SyNC treatment in clinical practice. Of note, these considerations are purely speculative at this point and, currently, no such SyNC treatment device exists.

CONCLUSION

SyNC is an under-researched and under-reported source of stroke. Although it is well known that certain imaging modalities, each having their advantages and disadvantages, can identify non-stenotic carotid plaques associated with increased stroke risk, most studies are cross-sectional in nature and only little prospective data are available. Furthermore, SyNC definitions vary between studies, and many neuroradiologists seem to be unaware of the stroke risks associated with certain carotid plaque features, and hence do not comment on them in their reports. Given the high recurrent stroke risk in SyNC patients with approximately one out of seven patients suffering a repeat stroke or TIA,11 the neuroradiology community should be sensitized for SyNC, and a consensus on a standardized SyNC definition that includes plaque and brain imaging findings, as well as clinical features, should be prioritized. Next, observational studies need to be conducted to determine the natural history of SyNC and the risk of stroke recurrence. These data can serve as a baseline and comparator for randomized controlled trials that may be conducted after endovascular SyNC devices have been tested and validated. While we acknowledge that such trials will be challenging to conduct, we believe they are feasible and are critical to guide the medical care of SyNC patients, for whom no good treatment currently exists. To ensure that potential short-term benefits from any treatment found by trials translate into long-term benefits in clinical practice, randomized controlled trials should be followed by registries for long-term follow-up. Such registries, although they may be subject to enrollment bias, could complement randomized trials and may provide a more realistic picture of SyNC treatment benefits in clinical routine as opposed to the highly standardized clinical trial setting. These steps will hopefully soon lead to increased recognition and targeted treatment of SyNC.
REFERENCES


