Moving Beyond Luminal Stenosis: Imaging Strategies for Stroke Prevention in Asymptomatic Carotid Stenosis

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Imaging studies evaluating the risk of stroke in carotid disease should clearly define asymptomatic versus symptomatic disease, use uniform definitions of clearly defined outcome measures such as ipsilateral stroke, ensure that imaging interpretations are performed in a manner blinded to treatments and other risk factors, and include cohorts which are on modern intensive medical therapy. Such studies of risk stratification for asymptomatic carotid stenosis will be most valuable if they can integrate multiple high-risk features (including clinical risk factors) into a multi-factorial risk assessment strategy in a manner that is relatively simple to implement and generalizable across a wide range of practice settings.

Key Messages:
Together, modern imaging strategies allow for a more mechanistic assessment of stroke risk in carotid disease compared to luminal stenosis measurements alone, which, with further validation in randomized controlled trials, may improve current efforts at stroke prevention in asymptomatic carotid stenosis.

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Clinical Background

Various angiographic measurements of vessel narrowing have long played a central role in stroke risk stratification in patients with carotid artery stenosis, the cause of approximately 10–15% of all ischemic strokes [1]. Lu-
minal stenosis measurements determined by catheter angiography were used to select patients for the first major treatment trials of carotid stenosis, including the North American Symptomatic Carotid Endarterectomy Trial [2] and the European Carotid Surgery Trial [3]. These trials, which began enrolling participants in the 1980s, showed that carotid endarterectomy reduced the risk of stroke in symptomatic subjects with high-grade carotid artery stenosis. Soon thereafter, randomized surgical versus medical treatment trials of asymptomatic carotid stenosis patients followed [4, 5], and though the magnitude of stroke risk reduction was less than in symptomatic patients, these studies also confirmed that carotid endarterectomy was beneficial in preventing stroke in asymptomatic patients selected based on stenosis severity.

In more recent years, however, improvements in medical therapy for stroke prevention have caused increasing controversy [6–10] about the role of surgical revascularization in the treatment of asymptomatic carotid stenosis. In the intervening 20 years since the first large treatment trials [2–5], intensive medical therapy has dramatically reduced the annual risk of stroke in asymptomatic carotid stenosis patients [11]. In a recent meta-analysis of clinical trials of asymptomatic carotid stenosis patients recruited between 2000 and 2010, Raman et al. [12] calculated an annual stroke rate of 1.13%, compared to an annual stroke rate of between 2 and 3% for studies completing recruitment before 2000. Closer inspection of these data suggest that if only the most recent studies are included, the annual stroke risk may be less than 1% per year. For this reason, the modest stroke reduction benefit seen for asymptomatic carotid stenosis in these treatment trials is of questionable current relevance [9, 12] for patients receiving modern intensive medical therapy.

**Moving Beyond Luminal Stenosis as a Risk Metric**

In the face of the advances in medical management, luminal stenosis measurements are no longer adequate to identify those asymptomatic carotid stenosis patients at greatest risk of stroke. Recent trends in stroke risk in this population are in large part the reason why in its most recent set of guidelines [13] issued in 2014, the United States Preventive Task Force made a recommendation against population-based screening efforts to detect asymptomatic carotid stenosis. In its decision, the United States Preventive Task Force cited that beyond luminal stenosis measurements and traditional stroke risk factors, ‘there are no externally validated, reliable methods to determine who is at increased risk … for stroke when carotid artery stenosis is present’. Advances in imaging in recent years, however, have allowed imaging technology to be at the forefront of a more detailed and mechanistic assessment of stroke risk in carotid disease. In particular, the two main pathophysiologic mechanisms underlying stroke risk in large vessel arterial disease – the propensity of unstable plaque to embolize [14, 15] and downstream hemodynamic compromise (low flow) from high-grade stenosis [15–17] – can both be studied with various imaging strategies with the potential to more accurately identify those carotid disease patients at the greatest stroke risk. In the subsequent sections, we will review the updated state of imaging-based risk stratification techniques. We will focus on an evidence-based approach [18], focused on those imaging strategies in which a systematic review of data of randomized controlled trials (level 1a evidence) or systematic reviews of cohort studies (level 2a) are available. As such, we will focus on studies of patients with asymptomatic carotid stenosis who had baseline imaging to measure a particular risk factor (with or without treatment randomization) and then were followed for stroke or TIA (table 1).

**Hemodynamic Stroke Risk Assessment Strategies**

**Cerebrovascular Reserve Testing**

Hypoperfusion from hemodynamically significant stenosis can result in a decrease in cerebral perfusion pressure. In such cases, autoregulation of the cerebral vasculature can respond with compensatory vasodilation of the cerebral arterioles to maintain normal cerebral blood flow [19]. If there are further decreases in cerebral perfusion pressure from progressive increases in proximal stenosis, maximally dilated arterioles may be unable to maintain CBF in a normal range and thereby result in increased ischemic stroke risk [16]. This hemodynamic parameter has been called cerebrovascular reserve, and there have been two main approaches to measure this risk factor on imaging studies. One approach involves obtaining direct brain CBF measurements using PET [20], nuclear medicine techniques [21, 22], CT perfusion [23], or MR perfusion [24, 25] before and after a vasodilatory stimulus. The second approach involves measurement of flow velocities as a surrogate for CBF [26–28] (typically in the MCA via transcranial Doppler) distal to a lesion both before and after a vasodilatory stimulus. Various vasodilatory stimuli have been reported in the literature;
they include increasing levels of CO₂ such as with breathholding or inhalation of gas mixtures [29] and pharmacological challenge with acetazolamide [30, 31].

A recent systematic review and meta-analysis [16] analyzed cerebrovascular reserve testing performed via transcranial Doppler or nuclear medicine flow studies in 13 published studies including nearly 1,000 patients with carotid stenosis or occlusion. With a mean follow-up of 3 years after baseline cerebrovascular reserve testing, the presence of impaired cerebrovascular reserve was associated with an approximately 4-fold increased risk of future stroke compared with patients with similar stenosis severity or occlusion but with a normal cerebrovascular reserve. When analysis was limited to studies with asymptomatic carotid stenosis alone, a similar risk of future stroke was found, suggesting that cerebrovascular reserve impairment is a robust hemodynamic risk metric applicable to both symptomatic and asymptomatic carotid disease. More recently, a pooled meta-analysis [26] with individual patient data focused exclusively on transcranial Doppler cerebrovascular reactivity, and found that impaired cerebrovascular reserve was independently associated with increased risk of ipsilateral stroke in carotid disease (HR 3.69) including in a subset of patients only with asymptomatic stenosis (HR 2.90).

Oxygen Extraction Fraction Assessment

Once cerebrovascular reserve is exhausted, a compensatory increase in brain tissue oxygen extraction fraction can occur to maintain aerobic metabolism in the brain [19, 32, 33]. Increase in oxygen extraction fraction as measured by ¹⁵O-PET is a well-studied hemodynamic stroke risk factor especially in symptomatic carotid occlusion [32, 34, 35]. A recent systematic review and meta-analysis of increased oxygen extraction fraction on ¹⁵O-PET in symptomatic carotid stenosis or occlusion showed that for a given degree of stenosis or occlusion of the internal carotid artery, increase in oxygen extraction is associated with a 6-fold increased stroke risk [36]. However, because of the logistical challenges associated with ¹⁵O-PET scanning (the need for a cyclotron and the 122 second half-life of the radiotracer ¹⁵O) very few reports exist on the role of oxygen extraction fraction measurement in asymptomatic carotid disease. According to the limited data published on asymptomatic carotid disease with ¹⁵O-PET, we estimate that there may be an approximately 10–20% prevalence of ¹⁵O-PET oxygen metabolism abnormalities in asymptomatic carotid stenosis patients, but there is some uncertainty about this prevalence given the limited data available for analysis.

### Table 1. Summary of studies with evidence supporting brain hemodynamic or plaque imaging-based methods of stroke risk stratification

<table>
<thead>
<tr>
<th>Plaque vulnerability</th>
<th>Modality</th>
<th>Study journal and year</th>
<th>Number of asymptomatic subjects studied</th>
<th>Outcome measure</th>
<th>Ischemic event risk in the presence of imaging risk marker (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of intraplaque hemorrhage</td>
<td>carotid MRI</td>
<td>J Am Coll Cardiol, 2013 [56]</td>
<td>394</td>
<td>ipsilateral stroke or TIA</td>
<td>HR 3.50 (2.59–4.73)</td>
</tr>
<tr>
<td>Presence of lipid-rich necrotic core</td>
<td>carotid MRI</td>
<td>Stroke, 2013 [46]</td>
<td>216</td>
<td>ipsilateral stroke or TIA</td>
<td>HR 5.73 (1.46–22.51)</td>
</tr>
<tr>
<td>Presence of thinning/rupture of fibrous cap</td>
<td>carotid MRI</td>
<td>Stroke, 2013 [46]</td>
<td>216</td>
<td>ipsilateral stroke or TIA</td>
<td>HR 4.54 (0.31–65.89)</td>
</tr>
<tr>
<td>Presence of embolic signals</td>
<td>TCD</td>
<td>Lancet Neurol, 2010 [74]</td>
<td>1,144</td>
<td>ipsilateral stroke</td>
<td>OR 6.63 (2.85–15.44)</td>
</tr>
</tbody>
</table>

### Hemodynamic impairment

<table>
<thead>
<tr>
<th>Impairment of cerebrovascular reserve</th>
<th>Modality</th>
<th>Study journal and year</th>
<th>Number of asymptomatic subjects studied</th>
<th>Outcome measure</th>
<th>Ischemic event risk in the presence of imaging risk marker (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TCD or brain SPECT</td>
<td>Stroke, 2012 [16]</td>
<td>279*</td>
<td>ipsilateral stroke or TIA</td>
<td>OR 4.7 (2.00–11.07)</td>
</tr>
<tr>
<td></td>
<td>TCD</td>
<td>Neurology, 2014 [26]</td>
<td>330</td>
<td>ipsilateral stroke</td>
<td>HR 2.90 (1.02–8.30)</td>
</tr>
</tbody>
</table>

All studies in this table show class 2a evidence (systematic reviews of cohort studies) as per the Oxford levels of evidence [18] for studies related to etiology/harm/therapy/prevention. No class 1a (systematic reviews of randomized controlled trials) have been performed for these risk metrics.

* In addition to internal carotid artery stenosis, includes a subset of patients with asymptomatic occlusion.
Plaque Vulnerability for Stroke Risk Assessment

MRI Assessment of Carotid Plaque

MRI, with its high spatial resolution and tissue discrimination capabilities, has been instrumental in elucidating the tissue types that are hallmarks of histopathologically defined high-risk plaque such as hemorrhage, lipid-rich necrotic core, and a thinned or ruptured fibrous cap [37]. Early fundamental investigations to characterize the in vivo tissue types composing carotid artery plaque were focused on the accurate characterization of vulnerable plaque elements via multi-sequence MRI with a dedicated surface carotid coil [38–40] using histologic analysis of plaque as a gold standard for comparison. Subsequent work [41–45] focused on whether MRI of carotid plaque composition could predict stroke or TIA. A recent systematic review and meta-analysis [46] on this topic showed that the MRI-defined presence of intraplaque hemorrhage, fibrous cap thinning or rupture, and lipid-rich necrotic core were all predictive of future ipsilateral stroke or TIA development, though the strength of the predictive ability remains somewhat uncertain for lipid-rich necrotic core and thinning/rupture given the relatively few prospective observational studies which have characterized these particular plaque elements. Indeed, of the vulnerable plaque composition elements detectable on MRI, intraplaque hemorrhage has been the most well studied [14, 42, 43, 47–55]. Unlike the detection of lipid-rich necrotic core and characterization of the fibrous cap that require a multi-sequence MRI protocol with a carotid coil, the presence of intraplaque hemorrhage can be detected with high diagnostic accuracy using a single sequence fat-suppressed T1-weighted sequence, which can be performed in less than 5 min [46]. An additional systematic review and meta-analysis [56] focused exclusively on the predictive ability of intraplaque hemorrhage found that the presence of MRI-detected intraplaque hemorrhage conferred a 3.5-fold risk of developing future stroke or TIA for a given degree of carotid stenosis. This analysis further concluded that the predictive value of plaque hemorrhage is not significantly different whether hemorrhage is detected using a multi-sequence acquisition with a carotid coil versus a single fat-suppressed T1-weighted sequence without a carotid coil.

Ultrasound Assessment of Carotid Plaque and Microemboli

Though ultrasound lacks the specificity of plaque tissue characterization possible via MRI, it remains an attractive potential means of risk stratification as it is widely available, has almost no contraindications, and is less expensive than MRI. Though various sonographically determined plaque features have been proposed to aid in the identification of high-risk plaque such as plaque ulceration [57] or stenosis progression [58], perhaps the most well-studied [59–67] risk marker for which there is level 2a evidence [68] is the presence of predominantly echolucent plaque. Histopathologic investigations [69, 70] suggest that predominantly echolucent plaque may contain a relatively high proportion of lipid-rich necrotic core or intraplaque hemorrhage, which are the known constituents of more advanced, complicated atherosclerotic plaque [37, 38]. There are two main methods of determining plaque echolucency: qualitative, subjective assessment of echolucency versus thresholded, quantitative gray-scale median value techniques. Though a few population-based studies had conflicting results about the predictive value of plaque echolucency, a recent meta-analysis [68] of over 7,000 patients from 7 studies concluded that predominantly echolucent carotid artery plaque predicted an increased relative risk of future stroke in patients with both non-stenosing and stenosing carotid plaque. In particular, in a subset analysis of patients with 50% or greater stenosis, the authors found that patients with predominantly echolucent plaque had an approximately 2.6-fold increased risk of ipsilateral stroke compared to subjects with predominantly echogenic plaque.

In addition to the direct anatomic characterization of carotid artery plaque, ultrasound techniques are also capable of detecting small, circulating emboli in the cerebral circulation via transcranial Doppler detection of embolic signals in the MCA ipsilateral to the stenotic ICA [71–74]. In this technique, which typically involves 30 to 60 min of recording of audible, high-intensity embolic signals, small microemboli can be detected with high diagnostic accuracy [75, 76]. In the Asymptomatic Carotid Emboli Study, a prospective multi-center observational trial, the presence of embolic signals ipsilateral to a stenotic carotid artery conferred an approximately six-fold increased risk of future stroke compared to those subjects without embolic signals [74]. The Asymptomatic Carotid Emboli Study investigators also performed a meta-analysis using their own data plus other studies of asymptomatic carotid stenosis and found a similar predictive ability of positive embolic signals in predicting ipsilateral stroke (HR 6.63) in a pooled analysis of nearly 1,000 patients.

256
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Gupta/Marshall
Future Directions in Stroke Risk Assessment Studies

Hemodynamic Risk Assessment Strategies

Though nuclear medicine and transcranial Doppler methods have been used to measure cerebrovascular reserve in prospective cohort studies of stroke risk in carotid stenosis, to date, no such studies have occurred using modern CT or MRI perfusion techniques. Though CT perfusion and T2* dynamic susceptibility contrast MRI perfusion are well-established methods of studying CBF, because cerebrovascular reserve testing requires two separate measurements of CBF (both at rest and after a vaso-dilatory stimulus), the need to administer two separate contrast doses may limit the role of contrast-enhanced perfusion imaging for cerebrovascular reserve testing. Arterial spin labeling MRI and blood-oxygen-level dependent (BOLD) functional MRI (fMRI) are potentially more attractive blood flow measurement techniques that have been recently shown to be accurate and feasible methods of cerebrovascular reserve testing that can be repeated without the need for intravenous contrast administration [77–83]. Future prospective observational studies will be needed to determine whether these MRI perfusion techniques can play a role in the prediction of ipsilateral ischemic stroke in asymptomatic carotid stenosis. Similarly, recent investigations have shown that MRI-based techniques can quantify brain cerebral metabolic rate of oxygen and oxygen extraction fraction, which could replace invasive PET techniques by allowing non-invasive measurement of brain oxygen metabolism via standard MRI equipment. Recent studies with susceptibility weighted imaging techniques [84, 85] and fMRI BOLD [78, 86] for example, have shown the feasibility of novel methods of oxygen metabolism quantification with MRI, though future investigations with carotid stenosis subjects are still needed to assess the clinical utility of these approaches.

Plaque Imaging Assessment Strategies

With the exception of echolucency on ultrasound, most existing plaque-imaging techniques that we have described are relatively expensive and require access to MRI, thereby somewhat limiting simple and widespread implementation of these risk stratification strategies. Future work should emphasize those plaque-imaging strategies which can be generalized and used in a wide range of clinical settings. One such approach is the evaluation of carotid artery stenosis progression with serial sonography. Though to our knowledge there is no systematic review or meta-analysis on this topic, there are several studies [58, 87–90] suggesting that the progression of carotid stenosis detected by duplex sonography predicts adverse cardiovascular clinical events and ipsilateral stroke. The most recent of these studies by Hirt [58] analyzed about 1,500 carotid subjects from the Asymptomatic Carotid Stenosis Trial (ACST) and provides detailed stroke risk information based on stenosis progression over time in strictly defined NASCET stenosis subgroups (50–69%, 70–89%, 90–99%, and 100%). Clearly, though evaluation of high-risk plaque composition is highly valuable as it provides stroke risk information at a single time point, future stroke risk prediction studies would be strengthened by combining plaque vulnerability assessment with stenosis progression data, as most asymptomatic carotid stenosis patients do undergo periodic surveillance imaging.

Although rapidly evolving MRI technology has been improving the imaging of vulnerable carotid artery plaque, future investigations would also benefit from increased standardization of imaging sequences and interpretation parameters so that such technology could be more amenable to multicenter trials and would also be more generalizable in clinical practice [56]. Similarly, there is significant variability in the sonographic criteria used to define plaque echolucency, and therefore techniques that rely upon a quantitative imaging parameter, such as a normalized gray-scale median, may improve standardization of image assessment [63]. In addition, though to-date CT has to date performed relatively poorly in discriminating between specific tissue types in carotid plaque [53, 91, 92], recent work [93–97] suggests that plaque with greater volumes of ‘soft’ or low-attenuation plaque relative to calcified plaque may represent a relatively simple scheme for identifying those carotid plaques most likely to cause ischemic symptoms. Prospective studies using these CT techniques to predict stroke risk are warranted now. Finally, the use of molecular and physiologic imaging with either radionuclides specific for plaque inflammation [98] or contrast-enhanced ultrasound [99] are emerging techniques that may also improve our ability to discriminate between high- and low-risk carotid plaques.

Conclusion

There is converging evidence to suggest that modern imaging techniques assessing cerebral hemodynamics and plaque vulnerability can improve risk stratification in asymptomatic carotid stenosis. The highest quality evidence thus far in the literature includes only systematic
reviews and meta-analyses of cohort studies with no randomized trials having yet been performed to show how these newer imaging biomarkers could be used to inform treatment decisions in asymptomatic carotid stenosis. Beyond the need for randomized trials, there are additional important steps needed to improve the relevance of evidence supporting risk assessment strategies [6]. Imaging studies evaluating the risk of stroke in carotid disease should clearly define asymptomatic versus symptomatic disease, use uniform definitions of clearly defined outcome measures such as ipsilateral stroke, ensure that imaging interpretations are performed in a manner blinded to treatments and other risk factors, and include cohorts that are on modern intensive medical therapy. Such studies of risk stratification for asymptomatic carotid stenosis will be most valuable if they can integrate multiple high-risk features (including clinical risk factors) into a multifactorial risk assessment strategy in a manner that is relatively simple to implement and generalizable across a wide range of practice settings. Such high-quality evidence is needed to ensure that imaging techniques remain relevant with the evolving treatment and stroke risk trends that are major determinants of optimal stroke-prevention strategies.

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