Clinical and Imaging Features Associated with an Increased Risk of Late Stroke in Patients with Asymptomatic Carotid Disease

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WHAT THIS PAPER ADDS
A contemporary summary of clinical and/or imaging based scoring systems, predictive algorithms and imaging parameters that may be associated with an increased (or decreased) risk of late stroke in patients with asymptomatic carotid disease.

Background: The 2011 American Heart Association Guidelines on the management of asymptomatic carotid disease recommends that carotid endarterectomy (CEA) (with carotid artery stenting (CAS) as an alternative) may be considered in highly selected patients with 70—99% stenoses. However, no guidance was provided as to what “highly selected” meant. This caveat is, however, important as up to 95% of asymptomatic individuals undergoing prophylactic CEA or CAS will ultimately undergo an unnecessary procedure. Even if the procedural risk following CEA or CAS could be reduced to 0%; 93% of patients would still undergo an unnecessary intervention. This, coupled with growing awareness that the risk of stroke in medically treated patients appears to be diminishing, has led to a renewed drive towards identifying patients with the highest risk of suffering a stroke whilst on medical therapy in whom to target CEA/CAS.

Methods: Review of clinical and/or imaging based scoring systems, predictive algorithms and imaging parameters that may be associated with an increased (or decreased) risk of stroke in patients with asymptomatic carotid disease.

Results: Parameters associated with an increased risk of late stroke include: (a) silent infarction on CT/MRI; (b) stenosis progression; (c) hypoechoic plaques or GSM <15; (d) irregular plaques; (e) evidence of spontaneous embolization on TCD; (f) AHA plaque types IV—V, VI; (g) MR diagnosed IPH; (h) plaque area >80 mm²; (i) juxtaluminal black area >10 mm²; and (j) tandem intracranial disease.

Conclusions: A number of imaging parameters have been shown to be predictive of an increased risk of late stroke in previously asymptomatic patients. None have been independently validated, but many could easily be evaluated in natural history studies or randomized trials in order to identify a “high risk for stroke” cohort in whom CEA/CAS could be prioritized.

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Keywords: Stroke, Transient ischemic attack, Carotid stenosis, Endarterectomy, Stenting

INTRODUCTION
The management of patients with asymptomatic carotid disease remains enduringly controversial. The latest American Heart Association (AHA) Guidelines (published in 2011) recommends that all patients with asymptomatic 70—99% carotid stenoses should be offered risk factor control and “optimal medical therapy” (Class I Recommendation, Level C Evidence). They further advise that carotid endarterectomy (CEA) was appropriate in highly selected patients, provided the procedural risk was <3% (Class I Recommendation, Level A Evidence) and that carotid artery stenting (CAS) might now be considered appropriate in highly selected patients (Class IIb Recommendation, Level B Evidence).1

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The key phrase, of course, is “highly selected.” This is because the AHA did not define what this term meant. As a consequence, there is evidence that some clinicians pay little attention to this caveat, while others take it to mean that the patient should simply have a predicted life-expectancy of 3–5 years.

There is no doubt that a small cohort of “high risk for stroke” patients with asymptomatic carotid stenoses will benefit from CEA/CAS, but (to date) there have been limited opportunities for defining who these patients are. The aim of this topical review was to first summarise the randomised trial evidence that is used to justify interventions in asymptomatic individuals, before reviewing contemporary clinical, biochemical and imaging based strategies that might be used in future natural history or randomized studies to define a higher (or lower) risk cohort of patients who might benefit from CEA/CAS.

### SUMMARY OF THE RANDOMIZED TRIALS

Table 1 details the 5-year risk of stroke (including perioperative stroke/death) in patients randomized to CEA or best medical therapy (BMT) in the Asymptomatic Carotid Atherosclerosis Study (ACAS) and the Asymptomatic Carotid Surgery Trial (ACST). Both trials reported a significant reduction in non-disabling stroke at 5 years, while ACST reported a significant reduction in disabling stroke. It has traditionally been reported that both studies reported similar outcomes (i.e., that CEA reduced the 5-year risk of stroke by 50%). However, this is not the case. The “11%” 5-year stroke risk in medically treated patients in ACAS refers to “ipsilateral” stroke, while the “11.8%” 5-year stroke risk in medically treated patients in ACST refers to “any” stroke.

ACST has now presented/published 5- and 10-year data for “any” and “ipsilateral” stroke. When compared with parallel data from ACAS, it makes interesting reading (Table 2). The 5-year rate of “any” stroke in patients randomized to BMT in ACAS (published in 1995) was 17.5% (i.e., 3.5% pa). When ACST published its first 5-year data in 2004, the 5-year rate of “any” stroke in medically treated patients had fallen to 11.8% (2.4% pa). When ACST published its 10-year data in 2010, the 5-year rate of “any” stroke had fallen even further to 7.2% (i.e., 1.4% pa). Similarly, when ACAS published in 1995, the 5-year rate of “ipsilateral” stroke in medically treated patients was 11.0% (i.e., 2.2% pa). By 2004, the first 5-year rate of “ipsilateral” stroke in BMT patients randomized in ACST had decreased to 5.3% (1.1% pa), falling to 3.6% for the second 5-year period (0.7% pa). This represents a >60% decline in successive five year rates of “any” and “ipsilateral” stroke and would appear to corroborate data from contemporary, non-randomized, natural history studies that the risk of stroke in medically treated patients appears to be diminishing.

### WHO IS HIGH RISK FOR STROKE?

Although ACAS and ACST demonstrated that CEA conferred a small, but significant reduction in late stroke, it is an indisputable fact that even with a procedural risk of <3%, 95% of all carotid interventions in asymptomatic patients randomized within ACAS and ACST ultimately proved to be unnecessary (Table 3). It has been suggested that reducing the procedural risk after CEA and CAS will greatly improve long-term stroke prevention. Unfortunately, this is not correct. When the ACAS/ACST data in Table 3 are remodelled using a 0% procedural risk; 93% of all interventions would still be unnecessary at 5 and 10 years respectively. This observation, coupled with growing awareness that the annual risk of stroke in patients with asymptomatic carotid stenoses treated medically appears to be diminishing, has led to renewed efforts at identifying clinical, imaging or biomarker algorithms for identifying the truly “high-risk for stroke” asymptomatic patient in whom to target CEA or CAS.

### Stenosis severity

Subgroup analyses from the European Carotid Surgery Trial (ECST) and the North American Symptomatic Carotid Endarterectomy Trial (NASCET) showed that stenosis severity (but not near occlusion) was predictive of an increased risk of late stroke in medically treated patients.

However, neither ACAS nor ACST found any evidence that (a) increasing stenosis severity, (b) bilateral severe stenosis, or (c) a severe stenosis and contralateral occlusion were predictive of an increased risk of late stroke in medically treated patients. The Asymptomatic Carotid Stenosis and Risk of Stroke (ACRSRS) Study (1115 asymptomatic patients with 50–99% stenoses) has reported that patients with 50–69% stenoses (ECST measurement method) incurred a 0.8% annual risk of ipsilateral stroke, increasing to 1.4% pa for patients with 70–89% stenoses and 2.4% pa for those with 90–99% stenosis. However, “best medical therapy” in the 1998–2002 time period when ACRSRS recruited their patients was certainly much different to what would be accepted in the modern era.

### Table 1. “Traditionally” published outcomes from ACAS and ACST.

<table>
<thead>
<tr>
<th>Years of FU</th>
<th>“Stroke” risk</th>
<th>ARR</th>
<th>Strokes prevented per 1000 CEAs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CEA</td>
<td>BMT</td>
<td></td>
</tr>
<tr>
<td>ACAS</td>
<td>5</td>
<td>5.1%</td>
<td>11.0%</td>
</tr>
<tr>
<td>ACST</td>
<td>5</td>
<td>6.4%</td>
<td>11.8%</td>
</tr>
<tr>
<td>ACST</td>
<td>10</td>
<td>13.4%</td>
<td>17.9%</td>
</tr>
</tbody>
</table>

BMT = best medical therapy; CEA = carotid endarterectomy.

### Table 2. Temporal changes in the 5-year risk of “any” and “ipsilateral” stroke in medically treated patients randomized within ACAS and ACST.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Year published</th>
<th>Study years</th>
<th>5-year rate of “any” stroke</th>
<th>5-year rate of “ipsilateral” stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACAS</td>
<td>1995</td>
<td>1–5</td>
<td>17.5%</td>
<td>11.0%</td>
</tr>
<tr>
<td>ACST</td>
<td>2004</td>
<td>1–5</td>
<td>11.8%</td>
<td>5.3%</td>
</tr>
<tr>
<td>ACST</td>
<td>2010</td>
<td>6–10</td>
<td>7.2%</td>
<td>3.6%</td>
</tr>
</tbody>
</table>

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Predicting stroke in asymptomatic patients

Table 3. Effect of modeling the procedural risk to 0% on preventing long-term stroke in ACAS and ACST.

<table>
<thead>
<tr>
<th></th>
<th>30-day death/stroke after CEA</th>
<th>Stroke rate including 30-day death/stroke CEA</th>
<th>Strokes prevented per 1000 CEAs</th>
<th>Unnecessary CEAs per 1000 CEAs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>CEA</td>
<td>BMT</td>
<td></td>
</tr>
<tr>
<td>ACST&lt;sup&gt;a&lt;/sup&gt; 5 yrs</td>
<td>2.3%</td>
<td>5.1%</td>
<td>11.0%</td>
<td>59@5 yrs</td>
</tr>
<tr>
<td></td>
<td>Modeled at 0.0%</td>
<td>2.8%</td>
<td>11.0%</td>
<td>82@5 yrs</td>
</tr>
<tr>
<td>ACST&lt;sup&gt;b&lt;/sup&gt; 10 yrs</td>
<td>2.8%</td>
<td>6.4%</td>
<td>11.8%</td>
<td>53@5 yrs</td>
</tr>
<tr>
<td></td>
<td>Modeled at 0.0%</td>
<td>3.5%</td>
<td>11.8%</td>
<td>83@5 yrs</td>
</tr>
<tr>
<td></td>
<td>Modeled at 0.0%</td>
<td>13.4%</td>
<td>17.9%</td>
<td>46@10 yrs</td>
</tr>
<tr>
<td></td>
<td>Modeled at 0.0%</td>
<td>10.5%</td>
<td>17.9%</td>
<td>74@10 yrs</td>
</tr>
</tbody>
</table>

Note. The benefits were calculated using the procedural risks observed in the constituent trial. They were then remodeled assuming a 0% procedural risk to see whether this significantly increased the number of strokes prevented. BMT = best medical therapy; CEA = carotid endarterectomy.

Clinical features

ACST found no evidence that asymptomatic patients aged >75 years gained any benefit from prophylactic CEA.<sup>5</sup> In the ACSRS Study, a history of contralateral TIA/stroke was associated with a 3.4% annual risk of stroke, compared with 1.2% in patients with no previous symptoms.<sup>11</sup> ACST has also reported that medically treated patients with a history of contralateral symptoms prior to randomization were significantly more likely to develop neurological symptoms within 5 years in the territory ipsilateral to the asymptomatic stenosis (29% risk at 5 years), compared to 22% in those with no history of contralateral symptoms (OR 1.66, 95% CI 1.28–2.15, p < .001).<sup>12</sup>

Stenosis progression

It is often assumed that stenosis progression is synonymous with plaque instability and that this will be associated with increased stroke risk. Despite the strength of this opinion, surprisingly few observational studies have demonstrated stenosis progression to be a risk factor for late stroke in asymptomatic patients. This, however, is more likely to reflect “absence of evidence rather than evidence of absence”.

Sabetai et al.<sup>13</sup> observed that stenosis progression was associated with a twofold increase in the 3-year risk of stroke from 2.5% to 5% (OR 2.00; 95% CI 1.02–4.11). In practical terms, this equates to a 1.7% annual risk of stroke in patients with stenosis progression, compared to 0.7% pa in those without (i.e., not a very discriminating parameter).

The ACSRS has reported a subgroup analysis regarding stenosis regression and progression in their 1000+ patient cohort.<sup>14</sup> Regression was observed in 4% of subjects, 76% of stenoses remained unchanged, while stenosis progression occurred in 20% of patients. The 8-year cumulative risk of ipsilateral stroke was 0% in patients with duplex evidence of regression (0% pa); 9% where the stenosis was unchanged (i.e., 1.1% pa), increasing to 16% in patients with stenosis progression (i.e., 2% pa). Despite stenosis progression being associated with a doubling of the annual rate of stroke, 40 of the 59 ipsilateral strokes (68%) that occurred during follow-up affected patients with no evidence of stenosis progression.<sup>14</sup>

Hirt<sup>12</sup> has recently published a subgroup analysis from the ACST database, describing the relationship between stenosis progression and the risk of suffering an ipsilateral neurological event (i.e., any TIA or stroke) in patients randomized to medical therapy. Baseline stenoses were categorized into one of five NASCET measurement based groups (0–49%; 50–69%; 70–89%; 90–99%; occlusion). The average annual rate of stenosis progression for the overall cohort was 5.2%, while the average annual rate of stenosis regression was 4.5%. Table 4 summarizes the principle findings of this analysis. As was observed in ACSRS, stenosis regression was associated with a low rate of late ipsilateral events. Stenosis progression by more than two categories (e.g., from 50–69% to 90–99%) was associated with a fivefold increase in the risk of ipsilateral neurological events in the following year. However, it is important to be aware that the actual numbers of “at risk” patients for this particular category (n = 50) was very small compared with the overall cohort under surveillance. It is perhaps more important to note, however, that the vast majority of ipsilateral events (numerically) occurred in patients with no

Table 4. Relationship between yearly change in stenosis severity category during five years of follow-up in ACST and the risk of suffering an ipsilateral neurological event in patients randomized to medical therapy.<sup>a</sup>

<table>
<thead>
<tr>
<th>Yearly change in stenosis severity category</th>
<th>Odds ratio of suffering an ipsilateral neurological event in the year after a change in stenosis severity&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Number of ipsilateral events occurring in the year after a change in stenosis severity</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any decrease in stenosis category (i.e., regression)</td>
<td>0.716 (0.398–1.287)</td>
<td>12/427 (2.8%)</td>
<td>.264</td>
</tr>
<tr>
<td>No change in stenosis category</td>
<td>n/a</td>
<td>156/1312 (11.9%)</td>
<td></td>
</tr>
<tr>
<td>Increase by 1 stenosis category</td>
<td>1.647 (1.108–2.448)</td>
<td>29/463 (6.3%)</td>
<td>.014</td>
</tr>
<tr>
<td>Increase by 2 stenosis categories</td>
<td>4.73 (2.326–9.632)</td>
<td>9/50 (18%)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

<sup>a</sup> Data derived from Hirt.<sup>12</sup>

<sup>b</sup> Odds ratios calculated compared with where no change in yearly rate of stenosis severity was observed.
evidence of any change in stenosis severity. Apart from the small numbers of patients with significant stenosis progression in this study, another limiting feature was a failure to report the risk of late ipsilateral stroke, as Hirt combined all ipsilateral events together.

ACST has also published a subgroup analysis on the risk of suffering carotid occlusion and the subsequent risk of suffering a stroke. In the cohort of patients randomized to medical therapy, the risk of suffering an ipsilateral carotid occlusion was about 1% per annum. Interestingly, only 13.6% of patients who occluded their carotid artery suffered a stroke at the time of their occlusion, while a further 10% suffered an ipsilateral stroke sometime later during follow-up. In practical terms, this means that for every 700 asymptomatic patients with a 70–99% asymptomatic stenosis treated medically, seven will occlude their carotid artery each year, but only one of the 700 will suffer an ipsilateral stroke, while one further patient will suffer an ipsilateral stroke at a later date following the occlusion.

**Duplex derived plaque visualization**

The morphology of carotid plaques, as assessed by ultrasound imaging, has traditionally been done by visual (subjective) grading of the plaque’s echo-reflection (e.g., echogenicity, echolucency) and its echo pattern (e.g., heterogeneous or homogeneous). Computerized plaque analysis was not developed until the 1990s.

The literature contains conflicting findings. Using visual assessment, ACST observed that asymptomatic patients with echoluent stenoses did not have an increased risk of late stroke. By contrast, the Tromso study observed that hypoechoic plaques were associated with an increased risk of late stroke, as did the Cardiovascular Health Study Group which showed that asymptomatic patients with hypoechoic carotid stenoses had a threefold increase in late ipsilateral stroke (OR 2.8; 95% CI 1.4–5.7). In the latter study, however, these higher stroke rates were only observed in patients with the highest peak systolic velocities (>250 cm/second) and only 0.5% of the overall study cohort had this severity of stenosis.

Visual plaque assessment (types I/II = echoluent; types III/IV = echogenic) was combined with the presence/absence of spontaneous embolization using transcranial Doppler (TCD) in the Asymptomatic Carotid Embolisation Study (ACES). The combination of plaque echolucency and being embolus positive, significantly increased the rate of ipsilateral stroke after correction for risk factors, stenosis severity and antiplatelet therapy (OR 10.6; 95% CI 2.98–37.52). Only 6.3% of ACES patients had the combination of type I/II plaques and had ≥1 embolus detected, but this very small cohort of patients had an annual ipsilateral stroke rate of 8.9% versus 0.8% in the remaining patients.

**Computerized plaque analysis**

ACRS has undertaken a number of computerized plaque analysis studies after normalization of image data. The Gray Scale Median (GSM) is a computerized (objective) measurement of the “gray” values of plaque pixels after image normalization. Image normalization involves an area of blood being scaled to zero, while the brightest area of the adventitia is normalized to a gray scale of 190. Following image normalization, the lower the GSM the more echolucent is the plaque. Conversely, echogenic plaques will have a higher GSM. In the ACSRS study, asymptomatic plaques with a GSM >30 had a very low annual rate of stroke (0.6%). The annual rate of stroke increased to 1.6% pa in patients with a GSM of 15–30, while patients with a GSM <15 had a 3.6% annual risk of stroke.

By contrast, however, Gronholt et al. used a similar computerized assessment of GSM and found that neither plaque echolucency (nor severity of stenosis) was predictive of late ipsilateral stroke or death among 111 asymptomatic patients with 50–99% stenoses who were followed for 4.4 years.

The ACSRS plaque classification (plaque types I–IV) is an objective modification of the Gray–Weale scale and assigns a plaque type according to its echolucency/echogenicity based on an objective assessment of pixel gray-scale values:

- **Type 1**, uniformly echolucent with <15% of pixels in the plaque area being occupied by pixels with grayscale values <25; Type 2, mainly echolucent where pixels with gray-scale values >25 occupy 15–50% of the plaque; Type 3, mainly echogenic with pixels with grayscale values <25 occupying 50–85% of the plaque; and Type 4, uniformly echogenic with pixels with grayscale values >25 occupying <85% of the plaque. Asymptomatic patients with Type 4 plaques had a 0.4% annual risk of stroke, compared with 0.8% in Type 3 plaques. The annual rate of stroke in patients with Type 1/2 plaques was 3.0%. Of particular note was the observation that three-quarters (76%) of late strokes affecting asymptomatic patients in the ACSRS study occurred in the 38% of patients (426/1121) who had Type 1/2 plaques. To date, the ability of this particular classification to predict cohorts of patients with greater (or lesser) risks of late stroke has not been validated in any other large scale, natural history study.

Two other parameters were developed by the ACSRS (plaque area and juxta-luminal black area). Plaque area (mm²) is calculated by the imaging software using the distance scale on the side of the image frame for calibration and the plaque area outlined by the operator. The largest juxta-luminal black area (JBA) of the image, defined as the plaque area with pixels having a grayscale <25 without a visible echogenic cap, was outlined and expressed as mm². Asymptomatic patients with 50–99% stenoses who had a plaque area <40 mm² had a low annual rate of stroke (1.0%), which increased to 1.4% pa in patients with a plaque area of 40–80 mm². However, the highest annual rate of stroke (4.6% pa) was observed in patients with a plaque area >80 mm².

Juxta-luminal black areas represent softer components of the plaque adjacent to the vessel lumen (necrotic core, lipid, hemorrhage, thrombus). In the ACSRS; a JBA <4 mm² was associated with a 0.4% annual risk of stroke, which increased to 1.4% when the JBA was 4–8 mm². The highest
Predicting stroke in asymptomatic patients

The annual rate of stroke was seen in asymptomatic patients with higher JBAs (3.2% pa for a JBA of 8–10 mm² and 5.0% pa for a JBA >10 mm²). Overall, patients with a JBA <8 mm² had an annual stroke rate of 0.6%, compared to 4.6% pa in patients with a JBA >8 mm². In a recent blinded study, logistic regression analysis showed that patients with a combination of plaque area >95 mm² and a JBA >6 mm² had a 90% probability of having a histologically unstable carotid plaque.23

The ACSRS8,20 has subsequently developed an algorithm for predicting the likely annual rate of stroke for individual patients, based upon a multivariate analysis of their ultrasound-based parameters (Fig. 1). For example, a patient with an 80–99% asymptomatic stenosis with no history of contralateral TIA, whose plaque area is <40 mm² and who has a plaque GSM <30 is predicted to have an annual stroke rate of 0.5% (low risk, probably best treated medically). By contrast; someone with an 80–99% stenosis, but who reports a prior history of contralateral TIA and who has a plaque area >80 mm² and a GSM <25 would be predicted to have a 10% annual rate of stroke (very high risk, would certainly benefit from CEA/CAS).

To date, however, the ability of computerized plaque derived parameters to predict cohorts of patients with greater (or lesser) risks of suffering a late stroke has not been validated in any other large scale, natural history study. Moreover, it remains unclear whether the ability to predict higher risk cohorts might have been different had patients received modern “best medical therapy.”

**Duplex/MRI derived plaque irregularity**

Plaque irregularity has been associated with an increase in late stroke in asymptomatic patients, although not all patients in the constituent studies had 50–99% stenoses. Kitamura et al.24 undertook serial duplex ultrasound surveillance in 1358 Japanese males with no history of cardiovascular disease and observed that subjects with plaque irregularity had an age-adjusted increase in late stroke (OR 7.7; 95% CI 2–30). Kitamura et al.’s findings were corroborated by the North Manhattan Stroke Study (1939 patients), which showed that while only 5.5% of subjects had an irregular carotid plaque on duplex, the 5-year risk of ischemic stroke was 1.3% in patients with no evidence of carotid plaques (i.e., 0.3% stroke risk pa), 3% in those with a smooth carotid plaque (0.6% pa), increasing to 8.5% in patients with an irregular plaque (1.7% pa).25 After adjusting for (a) risk factors, (b) stenosis severity, and (c) plaque thickness, an irregular carotid plaque was associated with a threefold excess risk of late stroke (OR 3.1; 95% CI 1.1–8.5). Interestingly, having *bilateral* plaque irregularity significantly increased the risk of long-term stroke compared to patients with unilateral plaque irregularity (OR 3.9 (1.4–11)).25

Madani et al.26 performed serial plaque surveillance with high-resolution ultrasound in 253 asymptomatic patients with 60–99% carotid stenoses who were treated with aggressive medical therapy. This group observed that the presence of three or more micro-plaque ulcers (in total from both carotid artery plaques) was associated with a significant increase in stroke/death at 3 years, compared with patients who had fewer or no ulcers (18% vs. 2%, p = .03). Underhill followed 85 asymptomatic subjects with 50–79% stenoses and no MRI evidence of luminal surface disruption at baseline. The size of the lipid rich necrotic core was the strongest predictor for patients developing new plaque surface disruption/micro-ulceration at a median of 36 months.27

**MRI**

Esposito-Bauer et al.28 followed 77 asymptomatic patients with 50–99% stenoses over a median of 44 months. MR scans were performed at baseline in order to classify patients according to the AHA plaque classification. Nine of 77 patients suffered recurrent ipsilateral events and these only occurred in patients with AHA plaque types IV–V (plaque with lipid or necrotic core surrounded by fibrous tissue and possible calcification) or type VI (complex plaque with possible surface defect, hemorrhage or thrombus). No recurrent cerebral events occurred in patients with plaques classified as being stable (AHA types III, VII, and VIII).28

There has been considerable interest in evaluating whether an MR diagnosis of IPH is predictive of an

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**Figure 1.** Prediction of annual risk of stroke in patients with 50–79% or 80–99% asymptomatic carotid stenosis (NASCET measurement method). The annualized risk of stroke is based upon stenosis severity, the presence or absence of prior contralateral symptoms and two computerized plaque analyses (plaque area and Gray Scale Median). Note. From “Time to rethink management strategies in asymptomatic carotid disease,” by AR Naylor, 2011, *Nature Reviews Cardiology* pp. 116–24. Reprinted with permission.
increased risk of stroke in asymptomatic patients. Underhill et al. followed 67 asymptomatic patients with 16–49% asymptomatic stenoses and observed that lesions with an MR diagnosis of IPH tended to undergo rapid expansion with luminal narrowing, while lesions with no MR evidence of IPH tended to undergo outward expansion in association with continuous remodeling, leading to preservation of luminal integrity. Takaya et al. followed 154 asymptomatic patients with 50–79% stenoses and observed that patients with an MRI diagnosis of thinned/ruptured fibrous caps, intra-plaque hemorrhage and large lipid cores incurred higher rates of ipsilateral stroke than patients without these features. Singh et al. undertook a similar study in 98 asymptomatic males with 50–70% asymptomatic stenoses. Thirty-six had MR evidence of IPH and six suffered ipsilateral stroke/TIA, compared with 0/62 patients without IPH. A univariate Cox regression analysis showed that an MR diagnosis of IPH was associated with a threefold increased risk of late ipsilateral neurological events (OR 3.6; 95% CI 2.5–4.7, p < .001).

However, there are also unexplained anomalies in the predictive value of an MR diagnosis of IPH. In Altaf et al.’s series, an MR diagnosis of IPH was highly predictive of recurrent events in the territory ipsilateral to a recently symptomatic stenosis. However, 58% of these patients also had MR evidence of IPH in the contralateral asymptomatic ICA and none suffered a stroke ipsilateral to these lesions during 36 months of follow-up.

**TCD diagnosed embolization**

A systematic review and meta-analysis of six observational studies (1144 asymptomatic patients with 70–99% stenoses) found that the presence of a single embolus detected using TCD was associated with an eightfold excess risk of late stroke (OR 7.6; 95% CI 2.3–24.7). There was also evidence that the introduction of aggressive medical therapy could significantly reduce the prevalence and magnitude of TCD embolization (from 12.6% to 3.6%), in association with a significant reduction in ipsilateral stroke and the need for CEA.

The largest (individual) observational study (ACES) has now published a subgroup analysis correlating spontaneous embolization with plaque morphology and late stroke risk. The combination of plaque echolucency (defined as ACSRS plaque type I/II) and being embolus positive, significantly increased the rate of ipsilateral stroke after correction for risk factors, stenosis severity and antiplatelet therapy (OR 10.6; 95% CI 2.98–37.52). Only 6.3% of ACES patients had type I/II plaques and had ≥1 embolus detected, but this very small cohort of patients had an annual ipsilateral stroke rate of 8.9% versus 0.8% in the remaining patients. Interestingly, the ACES trial found no correlation between plaque lucency, stenosis severity and embolus status at baseline, suggesting that lumot plaques became more unstable during follow-up with the secondary development of spontaneous embolization and ipsilateral symptoms.

**“Silent” infarction on CT**

About 20% of patients with asymptomatic carotid stenoses will have evidence of “silent” infarction on CT/MRI. ACSRS and ACST have performed secondary analyses to establish whether “silent” infarcts were associated with an increased risk of late stroke. ACSRS observed that patients with ipsilateral “silent” infarction had a significantly higher annual rate of ipsilateral stroke (3.6% pa), than patients with no evidence of infarction (1.0% pa; p = .002). ACST undertook a similar study; 1331 patients with evidence of either ipsilateral infarction on baseline CT/MRI or a history of cerebral symptoms had a 5.8% absolute risk increase in stroke at 10 years (95% CI 1.8–9.8; p = .004), compared to patients with no prior symptoms or infarction. No further information is available regarding this subgroup analysis as it has only appeared in abstract form.

**Biomarkers**

Plasma lipoprotein-associated phospholipase A2 (Lp-PLA2) is significantly elevated in patients with 70–99% asymptomatic carotid stenoses who have evidence of unstable plaque features on independent histological examination. It remains to be seen, however, whether elevated Lp-PLA2 levels can identify high-risk for stroke asymptomatic patients.

**Intracranial disease**

Madani et al. observed that the presence of asymptomatic tandem lesions (intracranial and extracranial) was associated with a significantly higher rate of stroke/TIA/ death at 3 years (p = .001) and stroke and/or TIA at 3 years (p = .004).

**SUMMARY**

**Asymptomatic patients**

There is little evidence that increasing stenosis severity is associated with an increased risk of late stroke. Parameters associated with an increased risk of late stroke in asymptomatic patients with carotid disease include: (a) silent infarction on CT/MRI; (b) stenosis progression; (c) hypoechoic plaques or GSM <15; (d) irregular plaques; (e) evidence of spontaneous embolization on TCD; (f) AHA plaque types IV–V, VI; (g) MR diagnosed IPH; (h) plaque area ≥80 mm²; (i) juxta-luminal black area >10 mm² and (j) tandem intracranial disease. Clinical features associated with an increased risk of late stroke include (k) a history of prior ipsilateral and contralateral TIA/minor stroke.

Clinical/imaging parameters associated with a lower intermediate/late risk of stroke include: (a) patients aged >75 years; (b) stenosis regression or no progression; (c) a GSM >30; and (d) AHA plaque types III, VII, and VIII.

However, many of the parameters that have been reported to be associated with a greater (or lesser) risk of suffering a stroke have not been subject to independent validation and most of the patients in the constituent studies were not receiving what would now be considered...
optimal medical therapy. There is also the unanswered question relating to dynamic plaque changes; i.e., can a single “snap-shot” be used to predict late stroke risk or is serial surveillance required? It is, therefore, essential that any new natural history studies or randomized trials in asymptomatic patients includes an analysis of one or more of these imaging strategies in order to identify the small cohort of “high risk for stroke” patients who will benefit from CEA/CAS.

**FUNDING**

None.

**CONFLICT OF INTEREST**

None.

**REFERENCES**


