Carotid Artery Stenosis, Carotid Endarterectomy & Stroke Prevention

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Cooper University Hospital
- Stroke is the third leading cause of death in the Western world
- Principal cause of permanent neurological disability
- More than half of all stroke survivors remaining dependent on others for everyday activities
- Carotid-related ischemic strokes are perhaps the most amenable to treatment to prevent further major strokes or death
Transient Monocular Blindness Associated with Hemiplegia
Charles Miller Fischer 1952

“a sort of warning that disaster threatened”
Figure 3. Schematic figure of the site of the internal carotid artery occlusion in Fisher’s first patient with transient monocular blindness associated with hemiplegia.

TEMPORARY obscuration of vision, unilateral or bilateral is not uncommon, especially if under that heading one includes the transient amaurosis associated with spasm of accommodation, glaucoma, and hysteria. The visual disturbance accompanying migraine is another common example. Rarer causes of intermittent blindness include eclampsia, lead poisoning, ergot poisoning, malaria, quinine and tobacco intoxication, polycythemia rubra vera, and paroxysmal hemoglobinuria. Circulatory deficiency in the territory of the basilar and posterior cerebral arteries may also occasion transient disturbances in vision. The bizarre, rapidly changing field defects complained of in the presence of papilledema, particularly when it is due to intracranial venous thrombosis, are less well known.

In addition to the above types, however, there is a fairly large number of cases of periodic blindness in which the principal derangement is an interruption of the retinal blood flow, usually of one eye only. It is this group of cases which is under discussion in this paper. Of obscure etiology and not lending itself to easy or simple classification, this condition has been the subject of sporadic reports during the past century. Intermittent monocular blindness due to retinal anemia constitutes a large fraction of what has been labeled amaurosis fugax, and it is probably better known under that name. Duke-Elder \(^1\) includes cases of this condition under “angiospasm” and divides them into two classes: cases occurring in young

The link between carotid disease and stroke.

"one day surgeons may even devise a method to remove the offending plaque and thereby prevent stroke"
Degree of Carotid Stenosis as a Surrogate for Stroke Risk & Rate

Guidelines for Carotid Endarterectomy
A Multidisciplinary Consensus Statement From the Ad Hoc Committee, American Heart Association
Stroke. 1995;26:188-201
The rupture prone atherosclerotic plaque has a thin fibrous cap overlaying a large necrotic core. Block Arrow: carotid plaque with a large necrotic core containing hemorrhage (red staining). The fibrous cap shows a dramatic thinning near the shoulder of the core (arrow in the lumen).
The Ruptured Carotid Plaque

- **Large arrow**: common carotid cap disruption
- **Asterisk**: fibrous cap
- **Small Arrow**: cap overlaid with thrombus on the left
- **Chevron**: organizing thrombus
Major Studies
- Symptomatic
- Asymptomatic

Controversies
- CEA vs CAS
- MicroEmboli
  - "silent stroke"

Current Guidelines
- AHA, ASA, ACCF, SVS Guidelines
- Take Away Message
Symptomatic

Asymptomatic
Symptomatic
Symptomatic

- NASCET trial (North American Symptomatic Carotid Endarterectomy Trial)
  - 2 year stroke risk 70-99% Stenosis
    - 9% w/ CEA and 26% w/ medical management
  - 2 year stroke risk 50-69% stenosis
    - 9% w/ CEA and 15% with medical management.
BENEFIT OF CAROTID ENDARTERECTOMY IN PATIENTS WITH SYMPTOMATIC MODERATE OR SEVERE STENOSIS

Asymptomatic
Asymptomatic

- ACAS - asymptomatic carotid atherosclerosis study

- 5 year stroke risk >60% Stenosis
  - 5.1% risk w/ CEA and 11% w/ medial management.
STATINS and Antiplatelet Agents
Figure 1  Statin-mediated pleiotropic activities in atherogenesis. Independently of lowering cholesterol levels, statins were shown to reduce subclinical systemic inflammation (serum C-reactive protein [CRP] levels), endothelial activation, leukocyte intraplaque infiltration, and smooth muscle cell migration.
• Reduce:
  • C-RP
  • endothelial activation
  • leukocyte intraplaque infiltration especially macrophages

• Increase:
  • Protective smooth muscle cell migration

• Net result is a more stable, less likely to embolize, plaque
Progression of Carotid Stenosis Detected by Duplex Ultrasonography Predicts Adverse Outcomes in Cardiovascular High-Risk Patients

Schila Sabeti, MD; Oliver Schlager, MD; Markus Exner, MD; Wolfgang Mlekusch, MD; Jasmin Amighi, MD; Petra Dick, MD; Gerald Maurer, MD; Kurt Huber, MD; Renate Koppensteiner, MD; Oswald Wagner, MD; Erich Minar, MD; Martin Schillinger, MD

Background and Purpose—The progression of carotid stenosis reflects the activity of atherosclerotic disease and may indicate a risk for systemic atherothrombotic complications. We investigated whether progressive carotid stenosis determined by duplex ultrasonography predicts adverse outcomes in cardiovascular high-risk patients.

Methods—We prospectively studied 1,065 of 1,268 consecutive patients initially asymptomatic with respect to carotid disease. Carotid ultrasound investigations at baseline and after a median of 7.5 months (range, 6 to 9 months) were performed to identify patients with progressive stenosis as defined by Doppler velocity criteria. Patients were then followed up clinically for a median of 3.2 years for the occurrence of major adverse cardiovascular events (composite MACEs: myocardial infarction, percutaneous coronary or peripheral interventions, coronary or vascular surgery, amputation, stroke, and all-cause mortality).

Results—We found progressive carotid stenosis in 93 patients (9%) by ultrasound and thereafter recorded 495 MACEs in 421 patients (40%) during clinical follow-up. Patients with progressive carotid stenosis had a significantly increased risk for cardiovascular events compared with patients with nonprogressive disease: adjusted hazard ratios and confidence intervals were 2.01 for composite MACEs (95% CI, 1.48 to 2.67, \( P < 0.001 \)), 2.38 for myocardial infarction (95% CI, 1.07 to 5.35, \( P = 0.044 \)), 1.59 for any coronary event (95% CI, 1.10 to 2.28, \( P = 0.011 \)), 2.00 for stroke (95% CI, 1.02 to 4.11, \( P = 0.035 \)), 2.42 for any peripheral vascular event (95% CI, 1.61 to 3.62, \( P < 0.001 \)), and 1.75 for cardiovascular death (95% CI, 1.03 to 2.97, \( P = 0.039 \)).

Conclusion—Progression of carotid stenosis within a 6- to 9-month interval detected by duplex ultrasound predicts midterm clinical adverse events of atherosclerosis in high-risk patients affecting the coronary, cerebrovascular, and peripheral circulations. (Stroke. 2007;38:2887-2894.)
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Results—We found progression of disease within the first year of follow-up in 421 patients (40%) for cardiovascular events. The cumulative incidence of MACEs in the first year was 11% (95% CI, 9.0% to 13.1%). The risk of MACEs in the first year was increased for patients with progression of disease (hazard ratio, 2.33; 95% CI, 1.91 to 2.84; P = 0.0005). The risk of MACEs in the first year was increased for patients with progression of disease (hazard ratio, 2.33; 95% CI, 1.91 to 2.84; P = 0.0005). The risk of MACEs in the first year was increased for patients with progression of disease (hazard ratio, 2.33; 95% CI, 1.91 to 2.84; P = 0.0005). The risk of MACEs in the first year was increased for patients with progression of disease (hazard ratio, 2.33; 95% CI, 1.91 to 2.84; P = 0.0005).

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Progression of disease was associated with a 2-fold increase in stroke risk.

- 70% of patients with progression of disease were being treated with statins.
- Disease progressed despite medical management.
CEA vs CAS
Carotid Endarterectomy

- Duplex US usually primary screening tool
- Followed by CT or MRA
- Look at Degree of stenosis and plaque morphology
  - >50% symptomatic
  - >70-80 asymptomatic
- Antiplatelet agents are started or maintained for patients with critical disease

- General Anesthesia or Cervical Block
- Duplex US
Carotid Endarterectomy

- General Anesthesia or Cervical Block
- Duplex US identifies exact location of the carotid bifurcation
  - Minimizes incision length
- Patient is monitored using EEG
- MAP is brought above 90 mmHg prior to clamping
- If EEG demonstrates decreased amplitudes or slowing of the wave forms, a shunt is planned
• Endarterectomy (CEA)

• Stenting (Stent)
Carotid Endarterectomy @ Cooper

• 2017
• 144 CEA’s
• Symptomatic
  • 27(18%)
• Asymptomatic
  • 117(82%)

• Cumulative Stroke
  • 3(2%)
**Fig 1. The cumulative incidence of the composite outcome of death or stroke.** CAS: Carotid Artery Stenting; CEA: Carotid Endarterectomy; ACT I: Asymptomatic Carotid Trial I; CREST: Carotid Revascularization Endarterectomy vs. Stenting Trial; ICSS: International Carotid Stenting Study; EVA-3S: Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis; BACASS: Basel Carotid Artery Stent Study; CAVATAS: Carotid and Vertebral Artery Transluminal Angioplasty Study; and Odd Ratio: adopted per 100 patient-years odd ratio.
<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>CAS</th>
<th>CEA</th>
<th>Odds Ratio M-H. Fixed, 95% CI</th>
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<tbody>
<tr>
<td>ACT1 2016</td>
<td>31/1072</td>
<td>6/348</td>
<td>1.66 [0.70, 4.04]</td>
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<tr>
<td>BACASS 2008</td>
<td>0/10</td>
<td>1/10</td>
<td>0.33 [0.01, 8.22]</td>
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<tr>
<td>CAVATAS 2009</td>
<td>25/251</td>
<td>25/253</td>
<td>1.04 [0.58, 1.76]</td>
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<tr>
<td>CREST 2016</td>
<td>55/1262</td>
<td>29/1240</td>
<td>1.87 [1.19, 2.93]</td>
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<tr>
<td>EVA-3S 2014</td>
<td>25/256</td>
<td>10/262</td>
<td>2.58 [1.24, 5.39]</td>
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<tr>
<td>ICSS 2015</td>
<td>61/853</td>
<td>28/857</td>
<td>2.21 [1.41, 3.46]</td>
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<tr>
<td>Kentucky 2014</td>
<td>0/95</td>
<td>1/94</td>
<td>0.33 [0.01, 8.10]</td>
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<tr>
<td>Markus 2008</td>
<td>0/32</td>
<td>0/29</td>
<td>Not estimable</td>
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<tr>
<td><strong>Total (95% CI)</strong></td>
<td>3799</td>
<td>3064</td>
<td>1.76 [1.38, 2.25]</td>
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</tbody>
</table>

Total events 197, 100
Heterogeneity: Chi² = 8.00, df = 6 (P = 0.24); I² = 25%
Test for overall effect: Z = 4.56 (P < 0.000001)

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### Fig 2. The cumulative incidence of stroke. 

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<th>Study or Subgroup</th>
<th>Events</th>
<th>Total</th>
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<th>Total</th>
<th>Weight</th>
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<tbody>
<tr>
<td>ACT I 2016</td>
<td>75</td>
<td>1089</td>
<td>19</td>
<td>364</td>
<td>13.2%</td>
<td>1.32 [0.80, 2.20]</td>
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<tr>
<td>CAVATAS 2009</td>
<td>67</td>
<td>251</td>
<td>48</td>
<td>253</td>
<td>21.3%</td>
<td>1.43 [0.98, 2.09]</td>
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<tr>
<td>CREST 2016</td>
<td>95</td>
<td>1262</td>
<td>71</td>
<td>1240</td>
<td>33.4%</td>
<td>1.32 [0.97, 1.79]</td>
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<tr>
<td>EVA-3S 2014</td>
<td>42</td>
<td>247</td>
<td>31</td>
<td>257</td>
<td>14.0%</td>
<td>1.42 [0.89, 2.27]</td>
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<tr>
<td>ICSS 2015</td>
<td>56</td>
<td>752</td>
<td>39</td>
<td>811</td>
<td>17.4%</td>
<td>1.56 [1.03, 2.35]</td>
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<td>Kentucky 2014</td>
<td>9</td>
<td>95</td>
<td>1</td>
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<td>8.98 [1.14, 71.03]</td>
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<tr>
<td>Markus 2008</td>
<td>4</td>
<td>42</td>
<td>0</td>
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<td>9.16 [0.49, 171.15]</td>
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<td><strong>Total (95% CI)</strong></td>
<td><strong>3738</strong></td>
<td><strong>3061</strong></td>
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Heterogeneity: Chi² = 5.14, df = 6 (P = 0.53); I² = 0%
Test for overall effect: Z = 4.17 (P < 0.0001)

Favours [CAS]  vs  Favours [CEA]
Figure 3 Preoperative, postoperative, 6-month and 12-month results of Mini-Mental State Examination in CEA and CAS patients. Significance for preoperative and 12-month comparison within groups are shown. CEA, carotid endarterectomy; CAS, carotid endarterectomy stenting.
<table>
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<tr>
<th>Coronary artery stenting</th>
<th>Carotid endarterectomy</th>
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<td><strong>DW-MRI</strong></td>
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</table>

| Mean | 25.6 | 22.9 | 23.7 | 26.1 | 25.6 | 25.9 |

−, Negative result; +, positive result; DW-MRI, diffusion-weighted magnetic resonance imaging; MMSE, Mini-Mental State Examination; Pre, preoperative; Post, ≥24 hours postoperatively.

**Boldface** type MMSE scores obtained in CAS patients presenting with new ischemic lesions at DW-MRI.
### Coronary artery stenting

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**Mean** 25.6 22.9 **23.7**

### Carotid endarterectomy

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</table>

**Mean** 26.1 25.6 25.9

−, Negative result; +, positive result; DW-MRI, diffusion-weighted magnetic resonance imaging; MMSE, Mini-Mental State Examination; Pre, preoperative; Post, ≤24 hours postoperatively.

**Boldface** indicates MMSE scores obtained in CAS patients presenting with new ischemic lesions at DW-MRI.
<table>
<thead>
<tr>
<th>Coronary artery stenting</th>
<th>Carotid endarterectomy</th>
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<td><strong>DW-MRI</strong> Pre Post Pre Post 6 mon</td>
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<td>Mean</td>
<td>25.6</td>
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</table>

\[ - , \text{Negative result; +, positive result; DW-MRI, diffusion-weighted magnetic resonance imaging; MMSE, Mini-Mental State Examination; Pre, preoperative; Post, } \leq 24 \text{ hours postoperatively.} \]

**Boldface** type MMSE scores obtained in CAS patients presenting with new ischemic lesions at DW-MRI.

- 21% of CAS patients had new DW-MRI lesions at 24 hours post op
- In CAS patients, new lesions at DW-MRI were significantly associated with a postoperative MMSE score decline >5 points (P .001).
Fig 6. Mean S100β levels are shown in carotid artery stenting (CAS) and carotid endarterectomy (CEA) patients.

Fig 3. Mean neuron-specific enolase values are shown in carotid artery stenting (CAS) and carotid endarterectomy (CEA) patients.
Silent cerebral events in asymptomatic carotid stenosis

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Joseph Shalhoub, BSc, MBBS, MRCS, and Alun H. Davies, MA, DM, FRCS, London, United Kingdom
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Silent stroke and cognitive decline in asymptomatic carotid stenosis revascularization

Laura Capoccia, Enrico Sbarigia, Annarita Rizzo, Wassim Mansour and Francesco Speziale
Fig 4. A, Combined stroke and transient ischemic attack (TIA) risk in transcranial Doppler (TCD) emboli positive and negative subjects with asymptomatic carotid stenosis. B, Stroke risk in TCD emboli positive and negative subjects with asymptomatic carotid stenosis. HITS, High intensity transient signals.
The Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis Study
Health and Hope for Patients at Risk for Stroke
Intense Medical Management

Endarterectomy

Stenting

The Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis Study

Health and Hope for Patients at Risk for Stroke
The Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis Study
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CREST-2: Identifying the Best Method of Stroke Prevention for Carotid Artery Stenosis:
National Institute of Neurological Disorders and Stroke Organizational Update
Meghan Mott, Walter Koroshetz and Clinton B. Wright

Stroke. published online April 6, 2017;
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628
Plan to assess:
• treatment differences between IMM alone compared to carotid endarterectomy (CEA) plus IMM
• treatment differences between IMM alone compared to carotid stenting (CAS) plus IMM
<table>
<thead>
<tr>
<th>Evaluation</th>
<th>Time</th>
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<tr>
<td>Visit number</td>
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</tr>
<tr>
<td>Month</td>
<td>Baseline(^a)</td>
</tr>
<tr>
<td>Informed consent</td>
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<tr>
<td>Demographics</td>
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<tr>
<td>Medical history</td>
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<tr>
<td>Interval medical history</td>
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<tr>
<td>Stroke questionnaire (QVSS)</td>
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<td>Modified Rankin</td>
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<tr>
<td>National Institutes of Health Stroke Scale (NIHSS)</td>
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<tr>
<td>Cognitive testing</td>
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<tr>
<td>Ultrasound</td>
<td>X</td>
</tr>
<tr>
<td>CTA/MRA/CBA(^c)</td>
<td>X</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>X</td>
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<tr>
<td>Laboratory(^d)</td>
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</table>
The Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis Study

Health and Hope for Patients at Risk for Stroke

Goal to enroll 2480 participants
40% women and 12% minorities
- ≥35 years, have narrowing (≥70%) of at least 1 of their carotid arteries,
- no history of ipsilateral stroke or TIA within 180 days of randomization
- carotid stenosis that is treatable with CEA or CAS, and lack other serious medical conditions

123 CREST-2 Centers have enrolled a total of 983 of 2,480 CREST-2 Participants
Primary outcome: proportion of patients who experience the composite end point of any stroke or death within 44 days of randomization or ipsilateral stroke ≤4 years thereafter.
Secondary outcomes:
• whether IMM differs from CEA and from CAS in terms of cognitive function at 4 years
• if there are differences in major stroke, minor stroke, disabling stroke, non-disabling stroke, and tissue-based stroke at 4-years

• if the CEA or CAS versus IMM difference is affected by
  • age
  • sex
  • severity of carotid stenosis, restenosis
  • risk factor level
  • duration of asymptomatic period
## Guideline on the Management of Patients With Extracranial Carotid and Vertebral Artery Disease

**Current Guidelines & Literature**

<table>
<thead>
<tr>
<th>Stenosis (%)</th>
<th>Recommendations</th>
<th>Level of recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptomatic stenosis</strong></td>
<td></td>
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</tr>
<tr>
<td>High grade (≥70%)</td>
<td>CEA by a surgeon with perioperative mortality rate &lt;6%</td>
<td>Class I Level of evidence A</td>
</tr>
<tr>
<td>Moderate (≥50% and &lt;70%)</td>
<td>CEA, depending on patient-specific factors such as age, sex, comorbidities and severity of symptoms</td>
<td>Class I Level of evidence A</td>
</tr>
<tr>
<td>Mild (&lt;50%)</td>
<td>No indications for CEA</td>
<td>Class I Level of evidence A</td>
</tr>
</tbody>
</table>

**Asymptomatic stenosis**

| High grade (≥60%) | CEA when performed by a surgeon with a perioperative mortality rate of <3% | Class I Level of evidence A |
Conclusion

- Carotid endarterectomy is the gold standard for stroke prevention in carotid disease
- Patients with symptomatic or asymptomatic carotid disease should be referred to a vascular surgeon for further workup, surveillance and treatment.