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Cerebrovascular Disease and Stroke (S Silverman, Section Editor)

Management of Asymptomatic Carotid Artery Stenosis

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Abstract

Purpose of review The goal of this paper is to provide the reader with a review of the evidence supporting the surgical and medical management of patients with asymptomatic internal carotid artery (ICA) stenosis.
Recent findings Based on the results of earlier clinical trials, surgical intervention with carotid endarterectomy (CEA) has long been the preferred method of management for patients with asymptomatic severe carotid stenosis. Carotid artery stenting (CAS) is another less invasive surgical option that has similar outcomes over the long-term. However, more recent improvements in medical management have reduced the risk of stroke in this population to comparable rates seen with CEA. As a result, medical management alone is advocated as well for patients with asymptomatic carotid stenosis. In addition to stenosis severity, there are a number of features of plaque morphology associated with vulnerable plaque that predict future stroke risk.
Summary Rates of stroke in patients with asymptomatic severe carotid stenosis with modern surgical techniques, CEA and CAS, are similar to modern medical therapy alone. Both surgery and medical therapy are good treatment options but it is not known which treatment is superior. The Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis Trial (CREST-2), an NIH-sponsored, multicenter, randomized trial that aims to answer this important management decision.

Introduction

Atherosclerotic carotid artery stenosis is an important cause of ischemic stroke, accounting for approximately 8–12% of all ischemic strokes [1]. The management of symptomatic severe carotid stenosis, in patients with low surgical risk, involves carotid intervention, either with carotid endarterectomy (CEA) or carotid artery stenting (CAS), and medical management. The management of asymptomatic severe carotid stenosis, however,

is more uncertain. Current guidelines recommend carotid intervention as well. But, these recommendations are based on clinical trials performed 20–30 years ago. With the advent of modern medical management, the risk of stroke in medically treated patients with asymptomatic carotid stenosis approaches that of those managed surgically. Both surgical and medical therapies have a low risk of stroke and it is uncertain which is the better treatment option. The CREST-2 trial is a NIH-sponsored, multicenter trial comparing medical with surgical treatments for patients with asymptomatic severe carotid stenosis that will hopefully answer this question in the future. For patients not interested in or eligible for the CREST-2 trial, features associated with vulnerable plaque may provide a subset of patients at higher risk of stroke, who may benefit from surgical intervention.

Prevalence of carotid artery stenosis

The prevalence of significant carotid artery stenosis in the general population is low. For moderate ≥ 50% stenosis, the prevalence ranges from 0–22.5% with a pooled prevalence of 4.2% [2]. For severe ≥ 70% stenosis, the prevalence ranges from 0–4.9% with a pooled prevalence of 1.7% [2]. In a large population study of 23,706 patients, asymptomatic moderate > 50% carotid stenosis by carotid ultrasound was found in 2% and severe > 70% stenosis in 0.5% [3]. Independent predictors of carotid stenosis were age, male sex, hypertension (HTN), diabetes mellitus (DM), current smoking, total/HDL cholesterol ratio, and history of vascular disease [3]. In another large population-based carotid artery screening study of 4657 Swedish men, 2.0% had moderate–severe 50–99% stenosis and 0.3% had carotid occlusions [4]. Independent predictors of carotid atherosclerosis in this group were smoking, HTN, coronary artery disease (CAD), and DM [4].

Screening for carotid artery stenosis

The US Preventative Services Task Force (USPSTF) recommends against screening for carotid artery stenosis in the general population [5]. Similarly, many societies also recommend against generalized screening [6–10].

Selective screening, however, in patients with known vascular disease or multiple vascular risk factors, improves the detection of asymptomatic carotid stenosis. Coronary artery disease is a risk factor for carotid atherosclerosis. Qureshi et al. in a review of 7 studies, reported a prevalence of ≥ 50% carotid stenosis of 8–21% in patients undergoing CABG [10]. Symptomatic peripheral arterial disease (PAD) is also a risk factor for carotid atherosclerosis. Studies report a prevalence of ≥ 60% carotid stenosis of > 20% in symptomatic PAD [10]. A 14-Society Guideline on the management of patients with carotid disease has Class IIb recommendations for screening carotid duplex in patients with PAD, CAD, or atherosclerotic aortic aneurysm [7].

Patients without evident atherosclerotic disease but with multiple vascular risk factors are also at risk of asymptomatic carotid stenosis. Several risk models have demonstrated the importance of selectively screening patients with vascular risk factors. Jacobowitz et al. used a modified carotid duplex protocol to screen 394 patients ≥ 60 years old with ≥ 1 risk factor of HTN, CAD, current smoking, or family history (FH) of stroke in a first-degree relative. By multivariate analysis, HTN and cardiac disease were predictors of > 50% carotid artery stenosis. In a model consisting of HTN, hyperlipidemia (HL), cardiac disease, and current smoking, the prevalence of carotid stenosis was 1.8% with 0 risk factors, 5.8% with 1 risk factor, 13.5% with 2 risk factors, 16.7% with 3 risk factors, and 66.7% with all 4 risk factors [11]. In a study by Qureshi et al., among 887 patients screened with carotid duplex, age > 65, HL, CAD, and current smoking independently predicted > 60% carotid stenosis. Patients with multiple risk factors had a greater risk of carotid stenosis than those with fewer risk factors [12]. Suri et al. externally validated the Jacobowtz and Qureshi scoring models in the Cardiovascular Health Study (CHS) database. In the 5449 patients in this database with screening carotid duplex, the prevalence of ≥ 50% carotid stenosis was 4.2%. The prevalence of ≥ 50% stenosis was 19% in patients ≥ 65 years old, with CAD, HL, and currently smoking and 21% in patients with HTN as well [13]. Rockman et al. conducted a screening program among 610 patients with vascular risk factors and found 10.8% of patients had ≥ 50% carotid stenosis. 22.1% of patients with both HTN and CAD had ≥ 50% stenosis [14]. The 14-Society Guideline has Class IIb recommendations to screen patients without atherosclerosis but who have ≥ 2 risk factors of HTN, HL, tobacco use, FH atherosclerosis in relative < 60 years old, or FH of stroke [7].

The importance of carotid stenosis detection

The detection of asymptomatic carotid stenosis has many implications. Approximately 10–15% of all first-ever strokes are due to previously unknown > 50% asymptomatic carotid stenosis [8•, 15]. In addition, approximately 50% of patients have progression of

stenosis at the time of the stroke [16]. In a study by Klarin et al., more than 90% of patients with carotid artery–related stroke had no prior history of carotid stenosis at the time of stroke [17]. Only 15–20% of strokes are heralded by TIAs [15, 18].

Carotid stenosis is also an important risk factor for cardiovascular disease. The importance of the detection of carotid artery stenosis is evident in cardiac disease prevention. In the SMART study, patients with ≥ 50% carotid stenosis were approximately four times more likely to have a myocardial infarction (MI) than a cerebral infarction in 5 years (8.0% vs 2.2%, respectively) [19]. In a meta-analysis of over 11,000 patients with > 50% carotid stenosis, the 5- and 10-year mortality approximates 25% and 50%, respectively, and almost two-thirds of the deaths were cardiac related [20].

Management of symptomatic carotid stenosis

The first step in the management of patients with carotid artery stenosis is to determine if the patient is symptomatic or asymptomatic. Symptomatic patients are defined as having a transient ischemic attack (TIA) or stroke secondary to the carotid artery stenosis. Ocular symptoms related to carotid stenosis include ipsilateral transient monocular blindness (TMB) or amaurosis fugax or permanent visual loss such as central retinal artery occlusion (CRAO) or branch retinal artery occlusion (BRAO). Hemispheric symptoms include contralateral hemiparesis or aphasia with dominant cerebral hemisphere involvement or neglect with non-dominant hemisphere involvement. Dizziness and lightheadedness are usually not a symptom of carotid artery stenosis.

The next step is to determine the degree of carotid artery stenosis, specifically is the artery severely (≥ 70%) stenosed. Surgical intervention is the standard of care for patients with symptomatic severe carotid stenosis who are good surgical candidates. Data supporting this comes from the North American Symptomatic Carotid Endarterectomy Trial (NASCET), which showed that patients with symptomatic severe carotid stenosis who were treated with carotid endarterectomy (CEA) had a significantly lower rate of stroke at 2 years than those treated with medical therapy only (9% vs 26%, respectively, relative risk reduction (RRR) 65%) [21]. Current AHA/ASA guidelines recommend CEA for patients with symptomatic severe (≥ 70%) ICA stenosis performed within 2 weeks if the perioperative risk is < 6% (Class I, Level A) [22].

Management of asymptomatic carotid stenosis

The management of patients with asymptomatic severe carotid artery stenosis is more controversial. The most recent AHA/ASA guidelines recommend considering CEA in asymptomatic severe (> 70%) ICA stenosis if the perioperative risk is < 3% (Class IIa, Level A) [6]. However, a caveat exists in this recommendation stating that the effectiveness of carotid intervention compared with modern medical therapy is not well known. This is the main source of contention for many physicians treating asymptomatic carotid artery stenosis. The landmark clinical trials clearly found a significant stroke risk reduction with CEA over medical treatment alone. However, medical therapies have greatly improved and the risk of stroke in medically treated patients has gone down considerably. Currently, the risks associated with surgical treatments and medical treatments are similar.

Surgical treatment of asymptomatic carotid stenosis

The data supporting surgery for patients with asymptomatic carotid stenosis comes from three main trials, the Veterans Affairs Cooperative Study (VACS) [23–26]. In VACS, 440 men with asymptomatic ≥ 50% carotid stenosis were randomized to CEA plus medical management versus medical management only. CEA significantly reduced the combined incidence of ipsilateral neurologic events (stroke or TIA) compared to the medical group (8.0% vs 20.6%, respectively; $p < 0.001$) [23]. In ACAS, 1662 patients with asymptomatic ≥ 60% carotid stenosis were randomized to medical therapy versus CEA plus medical therapy. Patients in the surgical arm had a 5.1% risk of ipsilateral stroke and perioperative stroke/death over 5 years versus 11.0% risk of ipsilateral stroke in the medical arm for a relative risk reduction of 53% ($p = 0.004$) [24]. In ACST, 3120 patients with asymptomatic ≥ 60% carotid stenosis were randomized to either immediate CEA or deferred CEA. Patients in the immediate CEA group had a significantly reduced five-year and 10-year risk of any stroke and perioperative stroke/death than the deferred CEA group (5-year, 6.9% vs 10.9%; $p = 0.0001$; 10-year, 13.4% vs 17.9%, 95% CI 1.2%–7.9%; $p = 0.009$) [25, 26]. A Cochrane review consisting of pooled data from these three pivotal trials found a 30% relative risk reduction from CEA for ipsilateral stroke or any stroke over 3 years [27].

Although CEA reduced the risk of stroke in patients with asymptomatic carotid stenosis in these trials, the absolute risk reduction from was only 5%. A. Ross Naylor contends, therefore, that 95% of all CEAs are "unnecessary" [15]. The surgical results from ACAS were

questioned regarding their generalizability to the community. ACAS accepted surgeons with low complication rates and rejected 40% of the surgical applicants [28]. When the results of ACAS were compared to other case series performed around the same time, operative mortality was eight times lower and stroke and death rates were three times lower in ACAS than in the community [28]. Many subgroups showed no benefit from CEA in these trials. There was no benefit of surgery for women in the 5-year rate of any stroke or perioperative death in ACAS and ACST [28]. The 10-year data from ACST, however, showed there was benefit from surgery for both men and women aged less than 75 at entry to the trial [26]. There was no surgical benefit in the elderly, specifically for patients older than 75 years of age at trial entry in ACST [26]. For patients with contralateral carotid artery occlusion, there was no surgical benefit in patients with asymptomatic stenosis [29].

In both ACAS and ACST, there was a delay until surgical benefit. Risks were higher early on in the CEA arm due to perioperative risks but with time the risks favored the CEA group. In ACAS, for the outcome of ipsilateral stroke or perioperative stroke or death, the Kaplan-Maier curves do not cross until 10 months and do not become significantly reduced in the CEA arm until 3 years [24]. In ACST, for the outcome of any stroke or perioperative death, the Kaplan-Maier curves do not cross until 2 years and become significant at 5 years [25] and persist at 10 years [26].

Carotid endarterectomy vs carotid artery stenting

Carotid endarterectomy is considered the gold standard for carotid intervention. Carotid artery stenting is a less invasive alternative. Comparisons between the two treatments in patients with asymptomatic carotid stenosis come from the Carotid Revascularization Endarterectomy vs Stenting Trial (CREST) and the Asymptomatic Carotid Trial (ACT) I. In CREST, symptomatic and asymptomatic patients were randomized to CEA versus CAS. There was no significant difference in the 4-year rate of the primary outcome (perioperative stroke, MI, death, or ipsilateral stroke in 4 years) between CAS and CEA (7.2% vs 6.8%, respectively; $p = 0.51$) [30]. However, in the perioperative time, there were more strokes in the CAS group (4.1% vs 2.3%; $p = 0.01$) and more MIs in the CEA group (2.3% vs 1.1%; $p = 0.03$) [30]. Over a 10-year follow-up, there was no difference in the primary outcome between CEA and CAS [31]. In addition, there was no significant difference between CEA and CAS in rates of restenosis or revascularization [31]. In ACT I, a multicenter, randomized controlled trial, patients with asymptomatic stenosis were randomized in 3:1 ratio to CAS:CEA. CAS was non-inferior to CEA for the primary endpoint (peri = operative stroke, death or MI or ipsilateral stroke at 1 year) (3.8% vs 3.4%, respectively; $p = 0.01$). Five-year follow-up between the two groups was similar as well [32].

Declining stroke rates over time

Over time, there has been a steady decline in the rate of stroke in patients with asymptomatic carotid stenosis treated with medical therapy alone. The 5-year rate of ipsilateral stroke in medically treated patients in ACAS (published 1995) was 11.0%, compared to 5.3% in the first 5 years of ACST (published 2004) and 3.6% in the second 5 years of ACST (published 2010) [15]. Similarly, the 5-year rate of any stroke in medically treated patients in ACAS was 17.5% compared to 11.8% in the first 5 years of ACST and 7.2% in the second 5 years of ACST [15]. There has been a "60–70%" decline in stroke rate over time in medically treated patients in randomized and non-randomized studies [15]. In fact, in more recent trials, the annual ipsilateral stroke rates of 0.34–1.4% in medically treated patients are considerably lower than that reported in ACAS and ACST [19, 33, 34]. In a meta-analysis, the rate of ipsilateral stroke in patients treated with medical therapy only was 1.13% per year in studies completed between 2000 and 2010 compared to 2.38% per year in studies completed before 2000 ($p < 0.001$) [35]. The biggest reason for these declining stroke rates is likely due to the progress of medical therapy. In the ACAS trial, conducted between 1987 and 1993, medical therapy consisted of ASA 325 mg per day and risk factor counseling [24]. In the ACST trial, conducted between 1993 and 2003, medical therapy was managed by the clinician, and typically consisted of anti-thrombotic, anti-hypertensive, and anti-hyperlipidemic therapy [26]. Although most patients were on aspirin throughout the ACST trial, less than 10% were on lipid-lowering therapy and about 50% on anti-hypertensive therapy at the beginning of the trial compared to greater than 80% on each drug at the end of trial [26].

Medical treatment of asymptomatic carotid stenosis

Anti-platelet therapy

In the Asymptomatic Carotid Emboli Study (ACES), anti-platelet therapy independently reduced the risk of

stroke and TIA [36]. In a multicenter stroke database, prestroke aspirin use in patients with large artery atherosclerotic stroke was associated with less severity of stroke at presentation [37]. Class IA recommendations from the 14-Society Guideline call for anti-platelet therapy, aspirin 75–325 mg per day, in patients with carotid stenosis [7].

Lipid-lowering therapy

The multiple benefits of lipid-lowering therapy, specifically statins, are well known. Statins reduce the incidence of stroke. In a meta-analysis of twelve randomized control trials, there was a 21% reduction in stroke incidence in the statin groups with a 1.0 mmol/L (39 mg/dL) reduction of LDL ($p < 0.0001$) [38]. Statins also reduce the need for carotid revascularization. In the Heart Protection Study (HPS), simvastatin significantly reduced the need for carotid revascularization (0.4% vs 0.8%; $p = 0.0003$) [38]. In the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial, in patients with carotid artery stenosis, atorvastatin resulted in a 56% reduction in carotid revascularization (HR 0.44; $p = 0.006$) [39]. Statins also cause plaque stabilization. In the Rotterdam Study, high-dose statins changed the structure of carotid plaques from vulnerable, lipid-rich plaques to stable, calcific plaques [40]. Statins also reduce the progression of carotid stenosis. In the Measuring Effects on Intima-Media Thickness: an Evaluation of Rosuvastatin (METEOR) trial, rosuvastatin significantly reduced the progression rate of intima medial thickness (IMT) in patients with subclinical carotid atherosclerosis [41]. Class IB recommendations from the 14-Society Guideline advise the use statins to reduce LDL to goal < 100 mg/dL for patients with carotid stenosis [7]. And Class IIa recommendations advise statins to reduce LDL to goal < 70 mg/dL in patients with carotid stenosis and stroke [7].

Management of hypertension

Systolic blood pressure is an independent risk factor for carotid artery stenosis [42]. In the Systolic Hypertension in the Elderly Program (SHEP) trial, treatment of hypertension in patients with ICA stenosis was associated with less progression of stenosis (14% vs 31%; $p = 0.020$) and more regression of stenosis (32% vs 0%; $p = 0.004$) compared to placebo [43]. Class IA recommendations from the 14-Society Guideline advise anti-hypertensive therapy for goal blood pressure (BP) < 140/90 mmHg in asymptomatic carotid stenosis [7]. According to the 2019 ACC/AHA guideline for the primary prevention of cardiovascular disease, new lower BP targets are recommended for goal BP < 130/80 mmHg [44]. Although this guideline does not specifically call for this lower range in patients with carotid stenosis, SBP < 130 mmHg is the new target for patients enrolled in the CREST-2 trial.

Management of diabetes

Diabetes is a risk factor for asymptomatic carotid stenosis [3]. Class IIa recommendations from the 14-Society Guideline suggest diet, exercise, and glucose-lowering medications [7]. The benefit of intensive therapy to goal HbA1c < 7.0% is not established. Statins for goal LDL < 70 mg/dL is recommended for patients with diabetes [7].

Smoking

Smoking is a risk factor for asymptomatic carotid stenosis [3, 4]. Smoking also increases the risk of carotid plaque progression [45]. Class I recommendations from the 14-Society Guideline recommend smoking cessation for patients with carotid stenosis [7].

Obesity and exercise

Class I guidelines from the European Society of Vascular Surgery recommend healthy diet and exercise [8•].

Modern medical therapy in other vascular territories

Evidence exists from other vascular beds that medical therapy alone is at least equivalent to intervention plus medical therapy. In the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial, percutaneous coronary intervention for patients with stable coronary artery disease did not reduce the composite outcome of death, myocardial infarction, or stroke when compared to medical therapy alone [46]. In the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial, patients with symptomatic, severe (70–99%) stenosis of an intracranial artery were randomized to aggressive medical management alone or angioplasty and stenting plus aggressive medical management. Enrollment was stopped early because the 30-

day stroke and death rate was significantly higher in the stenting group compared to the medical group (14.7% vs 5.8%; $p = 0.002$) [47]. In addition, the 1-year primary outcome in the medically treated arm of SAMMPRIS was much lower than what was expected from the Warfarin–Aspirin Symptomatic Intracranial Disease (WASID) trial (12.6% vs 25%, respectively) [47–49]. This is likely due to the more aggressive medical therapy and use of dual anti-platelet therapy used in SAMMPRIS.

Clinical equipoise

Just as the medical treatment of patients with asymptomatic carotid stenosis has improved over time, so has the surgical treatment. The perioperative stroke and death rate of vascular surgeons in the CREST trial (published 2010) was 1.1% [50]. By comparison, in ACAS (published 1995) the rate was 2.3%, and in ACST (published 2004) it was 3.1% [50]. With improvement in both medical and surgical treatments and now similar outcome rates, clinical equipoise exists for the management of patients with asymptomatic carotid stenosis. The Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis (CREST-2) Trial is a NIH-sponsored multicenter randomized controlled trial comparing intensive medical management (IMM) versus carotid intervention (CEA or CAS) plus intensive medical management. There are two parallel trials such that patients can either be randomized to the CEA trial (IMM vs CEA plus IMM) or CAS trial (IMM vs CAS plus IMM). The CREST-2 trial has passed the midpoint of enrollment and will not be completed for several years. Eligible patients should be offered enrollment in CREST-2. For patients ineligible for or uninterested in CREST-2, there are a number of risk factors associated with asymptomatic carotid stenosis that pose a higher risk of stroke.

Severity of stenosis

As the degree of carotid stenosis becomes more severe, the stroke risk increases. In the asymptomatic carotid stenosis and risk of stroke (ACSRS) study, there was an S-shaped relationship between the severity of stenosis (NASCET method) and the incidence of ipsilateral TIA or stroke, such that the event rates for 50–69% stenosis were 8.2%, for 70–89% stenosis were 10.7%, and for 90–99% were 19.3% [51]. In patients with symptomatic carotid stenosis, the benefit of CEA increases with increasing degrees of stenosis [28, 52]. In ACAS and ACST, however, there was no increase in surgical benefit for worsening stenosis [24, 25, 28, 53].

Progression of stenosis

Progression of carotid stenosis is associated with an increased risk of stroke. In the ACSRS study, patients with progression of carotid stenosis had two times the rate of ipsilateral stroke compared to patients without progression [54]. Patients in the deferred group of the ACST trial with progression of two categories and three categories of stenosis over 1 year had a 4 and 7 times, respectively, greater risk of ipsilateral stroke/TIA than those without progression [55].

High intensity transient signals on transcranial Doppler

High-intensity transient signals (HITS) are microemboli viewed with transcranial Doppler (TCD) that are a marker of unstable plaque and are associated with increased risk of stroke. Early work by Spence et al. showed that patients with >2 HITS in the middle cerebral artery ipsilateral to an asymptomatic carotid artery with $\geq$ 60% stenosis were 15 times more likely to have a stroke in 1 year (15.6% in HITS+ and 1% in HITS−; $p < 0.0001$) [56]. The Asymptomatic Carotid Emboli Study (ACES), a multicenter, prospective study in patients with $\geq 70\%$ stenosis, found that patients with ≥ 1 HITS had a 5.5 times greater risk of ipsilateral stroke in 2 years compared to patients without HITS (HR 5.57; $p = 0.007$) [18]. In a meta-analysis of five prospective studies in patients with asymptomatic carotid stenosis, HITS were a strong predictor of future stroke (OR 7.46; $p = 0.001$) [57].

Plaque echolucency

Plaque morphology on ultrasound correlates well with stability of plaque and subsequent risk of stroke. Early work by Steffan et al. and Geroulakos et al. showed that echolucent or lipid-rich plaques are unstable and more often associated with symptomatic patients compared with echogenic or fibrin-rich plaques which are more stable and associated with asymptomatic patients [58,

59]. More recent studies have shown that plaque echolucency is associated with a 2–6 times increased risk of stroke [60•]. Two meta-analyses showed that plaque echolucency in asymptomatic carotid stenosis is associated with approximately 2.5 times increased rate of ipsilateral stroke [61, 62]. In the ACES study, plaque echolucency was associated with a 6-time greater risk of ipsilateral stroke (HR 6.43; $p = 0.019$) [63]. In patients with echolucency and HITS, there was a 10 times greater risk of ipsilateral stroke (HR 10.61; $p = 0.0003$) [63].

Juxtaluminal black area

The juxtaluminal black (or hypoechoic) area on ultrasound correlates with a lipid-rich necrotic core on histologic carotid plaque specimens [64]. Several studies have shown that the presence of a juxtaluminal black (JBA) is associated with symptomatic plaques [65, 66]. Griffin et al. demonstrated the importance of the size of JBA, finding that JBA ≥ 8mm^2 without a visible fibrous cap is highly associated with symptomatic plaques regardless of the degree of stenosis [67]. In ACSRS, the size of the JBA was linearly associated with stroke risk. The average annual stroke rate was 0.4% for JBA < 4mm^2, 1.4% for JBA 4–8 mm^2, 3.2% for JBA 8–10 mm^2, and 5% for JBA > 10mm^2 was 5% ($p < .001$) [68].

Ulcerative plaque

Ulcerations in carotid plaques pose an increased risk of stroke. Moore et al. showed that the risk of stroke was proportional to the size and structure of the ulcerative plaque. Group A ulcers (small) had a more benign prognosis with 0.4% risk of stroke per year. However, group B (large) ulcers and group C (multiple or cavernous) ulcers both had a 12.5% risk of stroke per year [69]. Kuk et al. used 3D ultrasound to show that carotid ulcer volume ≥ 5 mm^3 was associated with higher risk of higher risk of stroke, TIA, or death ($p = 0.009$) [70]. In medically treated patients in the NASCET trial, patients with ulcerative plaques were significantly more likely to have an ipsilateral stroke than those without ulcers. For example, the 2-year risk of ipsilateral stroke in patients with ulcerative plaques and 75%, 85%, and 95% stenosis increased from 26%, to 44 to 73%, respectively compared to 21% for patients without ulcerative plaques and similar degree of stenosis [71].

Vulnerable plaque on MRI

Vulnerable plaque features have been shown on MRI carotid plaque imaging to predict future stroke [60•]. In symptomatic carotid stenosis, Kwee et al. demonstrated that in patients with symptomatic 30–69% stenosis, lipid-rich necrotic core (LRNC) (HR = 3.20; $p = 0.036$), a thin/ruptured fibrous cap (HR = 5.76; $p = 0.002$), and intraplaque hemorrhage (IPH) (HR = 3.54; $p = 0.04$) were associated with recurrence ipsilateral stroke/TIA [72]. And Hosseini et al. showed that in patients with symptomatic ≥ 50% stenosis, the presence of IPH was a strong predictor of recurrent stroke/TIA (HR = 12.0; $p < 0.001$) and stroke (HR = 35.0; $p = 0.001$) [73]. In asymptomatic carotid stenosis, several studies have shown similar plaque features associated with future stroke. Takaya et al. showed that in patients with asymptomatic 50–79% stenosis, a thin or ruptured fibrous cap (HR 17.0; $p \leq 0.001$), intraplaque hemorrhage (IPH) (HR 5.2; $p = 0.005$), and larger maximum % lipid-rich/necrotic core were all associated with future stroke or TIA [74]. Singh et al. found that in men with asymptomatic 50–70% stenosis, IPH was significantly associated with future stroke/TIA (HR 3.59; $p < 0.001$) [75]. Mono et al. showed that in patients with asymptomatic ≥ 50% stenosis, lipid-rich necrotic core (HR 7.21; $p = 0.037$) was associated with subsequent ipsilateral stroke or TIA [76].

Impaired cerebrovascular reserve

Impaired cerebrovascular reserve (CVR) is like a stress test for the brain. In the setting of severe carotid stenosis, autoregulation preserves cerebral blood flow by vasodilation of the brain's arterioles [60•]. When a vasodilating agent (such as inhaled carbon dioxide, breath holding, or intravenous acetazolamide) is given to a patient, in patients with normal vascular reserve there will be further vasodilation. But in patients at the limits of vasodilation, there will be impaired reserve, as the cerebral arterioles are unable to further vasodilate. Several studies have demonstrated that impairment of CVR is predictive of future stroke.

Gur et al. showed that in asymptomatic patients with severe > 70% internal carotid artery stenosis, patients with impaired reserve in response to an intravenous acetazolamide injection were more likely to have ipsilateral stroke/TIA ($p = 0.009$) [77]. Silvestrini et al. found that in patients with asymptomatic stenosis ≥ 70% stenosis, impaired breath-holding index (BHI) was associated with a 13.9% annual ipsilateral stroke/TIA rate compared to 4.1% in patients with normal BHI [78]. And Markus and Cullinane found that in patients with carotid occlusion or asymptomatic carotid stenosis, patients with impaired CVR to inhaled 8% carbon dioxide had a high likelihood of stroke/TIA (OR 14.4; $p = 0.0021$) [79].

Silent embolic infarcts

The presence of silent embolic infarcts ipsilateral to a carotid stenosis poses a high risk of future ischemic stroke in patients with asymptomatic carotid stenosis. In the ACSRS study, patients with moderate–severe (60–99%) stenosis and silent embolic infarcts on baseline head CT were 3 times more likely to have an ipsilateral stroke than those without embolic infarcts (3.6% vs 1.0% annual stroke rate, respectively; HR 3.0; $p = 0.002$) [80].

Contralateral TIAs

In the ACSRS study, patients with a history of contralateral TIAs ≥ 6 months prior to enrollment were 3 times more likely to have future stroke/TIA (RR 3.0; 95% CI 1.90–4.73) [51]. This finding is further supported by the fact that patients in the deferred arm of ACST had 2 times the rate of ipsilateral stroke when there was a history of contralateral symptoms [25, 51].

All of the above risk factors have been shown to be markers of vulnerable plaque and independently increase the risk of future stroke. The 2017 Guidelines for the European Society for Vascular Surgery have incorporated these risk factors into their Class IIa recommendation for asymptomatic stenosis. It states that CEA or CAS should be considered for patients with asymptomatic 60–99% stenosis at "average surgical risk" with one imaging marker of vulnerable plaque [8•].

Conclusion

Asymptomatic carotid artery stenosis is an important cause of ischemic stroke. Both surgical intervention (CEA and CAS) and modern medical therapy are good treatments and are associated with low and similar rates of ischemic stroke. The CREST-2 trial in a few years will hopefully provide insight into the management of these patients. As a field, we should offer enrollment in CREST-2 to all eligible patients. For patients ineligible for CREST-2, features associated with vulnerable plaque may help stratify patients at higher risk of future stroke.

Compliance with Ethical Standards

Conflict of Interest
Scott Silverman is the section editor of the Cerebrovascular Disease and Stroke section of *Current Treatment Options in Cardiovascular Medicine*.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
• Of importance

1. Flaherty ML, Kissela B, Khoury JC, Alwell K, Moomaw CJ, Woo D, et al. Carotid artery stenosis as a cause of stroke. Neuroepidemiology. 2013;40(1):36–41.
2. de Weerd M, Greving JP, de Jong AW, Buskens E, Bots ML. Prevalence of asymptomatic carotid artery stenosis according to age and sex: systematic review and metaregression analysis. Stroke. 2009;40(4):1105–13.
3. de Weerd M, Greving JP, Hedblad B, Lorenz MW, Mathiesen EB, O'Leary DH, et al. Prediction of asymptomatic carotid artery stenosis in the general population: identification of high-risk groups. Stroke. 2014;45:2366–71.
4. Högberg D, Kragsterman B, Björck M, Tjärnström J, Wanhainen A. Carotid artery atherosclerosis among 65-year-old Swedish men - a population-based screening study. Eur J Vasc Endovasc Surg. 2014;48(1):5–10.
5. LeFevre ML, U.S. Preventive Services Task Force. Screening for asymptomatic carotid artery stenosis: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2014;161:356–62.
6. Meschia JF, Bushnell C, Boden-Albala B, Braun LT, Bravata DM, Chaturvedi S, et al. Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2014;45:3754–832.
7. Brott TG, Halperin JL, Abbara S, Bacharach JM, Barr JD, Bush RL, et al. 2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS guideline on the management of patients with extracranial carotid and vertebral artery disease: executive summary. Stroke. 2011;42:e420–63.
8.• Naylor AR, Ricco JB, de Borst GJ, Debus S, de Haro J, Halliday A, et al. Editor's choice - management of atherosclerotic carotid and vertebral artery disease: 2017 Clinical Practice Guidelines of the European Society for Vascular Surgery (ESVS). Eur J Vasc Endovasc Surg. 2018;55(1):3–8.

Fantastic resource for carotid artery stenosis management.

9. Ricotta JJ, Aburahma A, Ascher E, Eskandari M, Faries P, Lal BK. Updated Society for Vascular Surgery guidelines for management of extracranial carotid disease. J Vasc Surg. 2011;54(3):e1–31.
10. Qureshi AI, Alexandrov AV, Tegeler CH, Hobson RW 2nd, Dennis Baker J, Hopkins LN. Guidelines for screening of extracranial carotid artery disease: a statement for healthcare professionals from the multidisciplinary practice guidelines committee of the American Society of Neuroimaging; cosponsored by the Society of Vascular and Interventional Neurology. J Neuroimaging. 2007;17(1):19–47.
11. Jacobowitz GR, Rockman CB, Gagne PJ, Adelman MA, Lamparello PJ, Landis R, et al. A model for predicting occult carotid artery stenosis: screening is justified in a selected population. J Vasc Surg. 2003;38(4):705–9.
12. Qureshi AI, Janardhan V, Bennett SE, Luft AR, Hopkins LN, Guterman LRD. Who should be screened for asymptomatic carotid artery stenosis? Experience from the Western New York Stroke Screening Program. J Neuroimaging. 2001;11(2):105–11.
13. Suri MF, Ezzeddine MA, Lakshminarayan K, Divani AA, Qureshi AI. Validation of two different grading schemes to identify patients with asymptomatic carotid artery stenosis in general population. J Neuroimaging. 2008;18(2):142–7.
14. Rockman CB, Jacobowitz GR, Gagne PJ, Adelman MA, Lamparello PJ, Landis R, et al. Focused screening for occult carotid artery disease: patients with known heart disease are at high risk. J Vasc Surg. 2004;39(1):44–51.
15. Naylor AR. Why is the management of asymptomatic carotid disease so controversial? Surgeon. 2015 Feb;13(1):34–43.
16. Bock RW, Gray-Weale AC, Mock PA, App Stats M, Robinson DA, Irwig L, et al. The natural history of asymptomatic carotid artery disease. J Vasc Surg. 1993;17(1):160–9.
17. Klarin D, Cambria RP, Ergul EA, Silverman SB, Patel VI, LaMuraglia GM, et al. Risk factor profile and anatomic features of previously asymptomatic patients presenting with carotid-related stroke. J Vasc Surg. 2018;68(5):1390–5.
18. Markus HS, King A, Shipley M, Topakian R, Cullinane M, Reihill S, et al. Asymptomatic embolisation for prediction of stroke in the Asymptomatic Carotid Emboli Study (ACES): a prospective observational study. Lancet Neurol. 2010;9(7):663–71.
19. Goessens BM, Visseren FL, Kappelle LJ, Algra A, van der Graaf Y. Asymptomatic carotid artery stenosis and the risk of new vascular events in patients with manifest arterial disease: the SMART study. Stroke. 2007;38(5):1470–5.
20. Giannopoulos A, Kakkos S, Abbott A, Naylor AR, Richards T, Mikhailidis DP, et al. Long-term mortality in patients with asymptomatic carotid stenosis: implications for statin therapy. Eur J Vasc Endovasc Surg. 2015;50(5):573–82.
21. Barnett HJM, Taylor DW, Haynes RB, Sackett DL, Peerless SJ, Ferguson GG, et al. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. N Engl J Med. 1991;325(7):445–53.
22. Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, et al. Guidelines for the

prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2014;45:2160–236.
23. Hobson RW, Weiss DG, Fields WS, Goldstone J, Moore WS, Towne JB, et al. Efficacy of carotid endarterectomy for asymptomatic carotid stenosis. The Veterans Affairs Cooperative Study Group. N Engl J Med. 1993;328(4):221–7.
24. Walker MD, Marler JR, Goldstein M, Grady PA, Toole JF, Baker WH, et al. Endarterectomy for asymptomatic carotid artery stenosis. JAMA. 1995;273:1421–8.
25. Halliday A, Mansfield A, Marro J, Peto C, Peto R, Potter J, et al. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. Lancet. 2004 May 8;363(9420):1491–502.
26. Halliday A, Harrison M, Hayter E, Kong X, Mansfield A, Marro J, et al. 10-year stroke prevention after successful carotid endarterectomy for asymptomatic stenosis (ACST-1): a multicentre randomised trial. Lancet. 2010;376(9746):1074–84.
27. Chambers BR, Donnan GA. Carotid endarterectomy for asymptomatic carotid stenosis. Cochrane Database Syst Rev. 2005;4:CD001923.
28. Rothwell PM, Goldstein LB. Carotid endarterectomy for asymptomatic carotid stenosis: asymptomatic carotid surgery trial. Stroke. 2004;35(10):2425–7.
29. Baker WH, Howard VJ, Howard G, Toole JF. Effect of contralateral occlusion on long-term efficacy of endarterectomy in the asymptomatic carotid atherosclerosis study (ACAS). ACAS Investigators. Stroke. 2000;31(10):2330–4.
30. Brott TG, Hobson RW 2nd, Howard G, Roubin GS, Clark WM, Brooks W, et al. Stenting versus endarterectomy for treatment of carotid-artery stenosis. N Engl J Med. 2010;363(1):11–23.
31. Brott TG, Howard G, Roubin GS, Meschia JF, Mackey A, Brooks W, et al. Long-term results of stenting versus endarterectomy for carotid-artery stenosis. N Engl J Med. 2016;374(11):1021–31.
32. Rosenfield K, Matsumura JS, Chaturvedi S, Riles T, Ansel GM, Metzger DC, et al. Randomized trial of stent versus surgery for asymptomatic carotid stenosis. N Engl J Med. 2016;374(11):1011–20.
33. Marquardt L, Geraghty OC, Mehta Z, Rothwell PM. Low risk of ipsilateral stroke in patients with asymptomatic carotid stenosis on best medical treatment: a prospective, population-based study. Stroke. 2010;41(1):e11–7.
34. Spence JD, Coates V, Li H, Tamayo A, Muñoz C, Hackam DG, et al. Effects of intensive medical therapy on microemboli and cardiovascular risk in asymptomatic carotid stenosis. Arch Neurol. 2010;67(2):180–6.
35. Raman G, Moorthy D, Hadar N, Dahabreh IJ, O'Donnell TF, Thaler DE, et al. Management strategies for asymptomatic carotid stenosis: a systematic review and meta-analysis. Ann Intern Med. 2013 May 7;158(9):676–85.
36. King A, Shipley M, Markus H. The effect of medical treatments on stroke risk in asymptomatic carotid stenosis. Stroke. 2013 Feb;44(2):542–6.
37. Park JM, Kang K, Cho YJ, Hong KS, Lee KB, Park TH, et al. Comparative effectiveness of prestroke aspirin on stroke severity and outcome. Ann Neurol. 2016;79(4):560–8.
38. Collins R, Armitage J, Parish S, Sleight P, Peto R. Effects of cholesterol-lowering with simvastatin on stroke and other major vascular events in 20536 people with cerebrovascular disease or other high-risk conditions. Lancet. 2004;363(9411):757–67.
39. Sillesen H, Amarenco P, Hennerici MG, Callahan A, Goldstein LB, Zivin J, et al. Atorvastatin reduces the risk of cardiovascular events in patients with carotid atherosclerosis: a secondary analysis of the stroke prevention by aggressive reduction in cholesterol levels (SPARCL) trial. Stroke. 2008 Dec;39(12):3297–302.
40. Mujaj B, Bos D, Selwaness M, Leening MJG, Kavousi M, Wentzel JJ, et al. Statin use is associated with carotid plaque composition: the Rotterdam study. Int J Cardiol. 2018;260:213–8.
41. Crouse JR 3rd, Raichlen JS, Riley WA, Evans GW, Palmer MK, O'Leary DH, et al. Effect of rosuvastatin on progression of carotid intima-media thickness in low-risk individuals with subclinical atherosclerosis: the METEOR Trial. JAMA. 2007;297(12):1344–53.
42. Mathiesen EB, Joakimsen O, Bønaa KH. Prevalence of and risk factors associated with carotid artery stenosis: the Tromsø study. Cerebrovasc Dis. 2001;12(1):44–51.
43. Sutton-Tyrrell K, Wolfson SK Jr, Kuller LH. Blood pressure treatment slows the progression of carotid stenosis in patients with isolated systolic hypertension. Stroke. 1994;25(1):44–50.
44. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, et al. ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019;140(11):e596–646. https://doi.org/10.1161/CIR.0000000000000678.
45. Herder M, Johnsen SH, Arntzen KA, Mathiesen EB. Risk factors for progression of carotid intima-media thickness and total plaque area: a 13-year follow-up study: the Tromsø study. Stroke. 2012;43(7):1818–23.
46. Boden WE, O'Rourke RA, Teo KK, Hartigan PM, Maron DJ, Kostuk WJ, et al. Optimal medical therapy with or without PCI for stable coronary disease. N Engl J Med. 2007;356(15):1503–16.
47. Chimowitz MI, Lynn MJ, Derdeyn CP, Turan TN, Fiorella D, Lane BF, et al. Stenting versus aggressive medical therapy for intracranial arterial stenosis. N Engl J Med. 2011;365(11):993–1003.
48. Derdeyn CP, Chimowitz MI, Lynn MJ, Fiorella D, Turan TN, Janis LS, et al. Aggressive medical treatment with or without stenting in high-risk patients with

intracranial artery stenosis (SAMMPRIS): the final results of a randomised trial. Lancet. 2014;383(9914):333–41.
49. Chimowitz MI, Lynn MJ, Howlett-Smith H, Stern BJ, Hertzberg VS, Frankel MR, et al. Comparison of warfarin and aspirin for symptomatic intracranial arterial stenosis. N Engl J Med. 2005;352(13):1305–16.
50. Timaran CH, Mantese VA, Malas M, Brown OW, Lal BK, Moore WS, et al. Differential outcomes of carotid stenting and endarterectomy performed exclusively by vascular surgeons in the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST). J Vasc Surg. 2013;57(2):303–8.
51. Nicolaides AN, Kakkos SK, Griffin M, Sabetai M, Dhanjil S, Tegos T, et al. Severity of asymptomatic carotid stenosis and risk of ipsilateral hemispheric ischaemic events: results from the ACSRS study. Eur J Vasc Endovasc Surg. 2005;30(3):275–84.
52. Rothwell PM, Eliasziw M, Gutnikov SA, Fox AJ, Taylor DW, Mayberg MR, et al. Analysis of pooled data from the randomised controlled trials of endarterectomy for symptomatic carotid stenosis. Lancet. 2003;361(9352):107–16.
53. Schenone AL, Cohen A, Shishehbor MH. Asymptomatic carotid artery disease: a personalized approach to management. Cleve Clin J Med. 2015;82(12):855–63.
54. Kakkos SK, Nicolaides AN, Charalambous I, Thomas D, Giannopoulos A, Naylor AR, et al. Predictors and clinical significance of progression or regression of asymptomatic carotid stenosis. J Vasc Surg. 2014;59(4):956–967.e1.
55. Hirt LS. Progression rate and ipsilateral neurological events in asymptomatic carotid stenosis. Stroke. 2014;45(3):702–6.
56. Spence JD, Tamayo A, Lownie SP, Ng WP, Ferguson GG. Absence of microemboli on transcranial Doppler identifies low-risk patients with asymptomatic carotid stenosis. Stroke. 2005;36(11):2373–8.
57. King A, Markus HS. Doppler embolic signals in cerebrovascular disease and prediction of stroke risk: a systematic review and meta-analysis. Stroke. 2009;40(12):3711–7.
58. Steffen CM, Gray-Weale AC, Byrne KE, Lusby RJ. Carotid artery atheroma: ultrasound appearance in symptomatic and asymptomatic vessels. Aust N Z J Surg. 1989;59(7):529–34.
59. Geroulakos G, Ramaswami G, Nicolaides A, James K, Labropoulos N, Belcaro G, et al. Characterization of symptomatic and asymptomatic carotid plaques using high-resolution real-time ultrasonography. Br J Surg. 1993;80(10):1274–7.
60.• Paraskevas KI, Veith FJ, Spence JD. How to identify which patients with asymptomatic carotid stenosis could benefit from endarterectomy or stenting. Stroke Vasc Neurol. 2018;3(2):92–10.
Fantastic resource for patients at high risk of stroke in asymptomatic carotid stenosis.
61. Gupta A, Kesavabhotla K, Baradaran H, Kamel H, Pandya A, Giambrone AE, et al. Plaque echolucency and stroke risk in asymptomatic carotid stenosis: a systematic review and meta-analysis. Stroke. 2015;46(1):91–7.
62. Jashari F, Ibrahimi P, Bajraktari G, Grönlund C, Wester P, Henein MY. Carotid plaque echogenicity predicts cerebrovascular symptoms: a systematic review and meta-analysis. Eur J Neurol. 2016;23(7):1241–7.
63. Topakian R, King A, Kwon SU, Schaafsma A, Shipley M, Markus HS. Ultrasonic plaque echolucency and emboli signals predict stroke in asymptomatic carotid stenosis. Neurology. 2011;77(8):751–8.
64. Sztajzel R, Momjian S, Momjian-Mayor I, Murith N, Djebaili K, Boissard G, et al. Stratified gray-scale median analysis and color mapping of the carotid plaque: correlation with endarterectomy specimen histology of 28 patients. Stroke. 2005;36(4):741–5.
65. Pedro LM, Pedro MM, Gonçalves I, Carneiro TF, Balsinha C, Fernandes e Fernandes R, et al. Computer-assisted carotid plaque analysis: characteristics of plaques associated with cerebrovascular symptoms and cerebral infarction. Eur J Vasc Endovasc Surg. 2000;19(2):118–23.
66. Sztajzel R, Momjian-Mayor I, Comelli M, Momjian S. Correlation of cerebrovascular symptoms and microembolic signals with the stratified gray-scale median analysis and color mapping of the carotid plaque. Stroke. 2006;37(3):824–9.
67. Griffin MB, Kyriacou E, Pattichis C, Bond D, Kakkos SK, Sabetai M, et al. Juxtaluminal hypoechoic area in ultrasonic images of carotid plaques and hemispheric symptoms. J Vasc Surg. 2010;52(1):69–76.
68. Kakkos SK, Griffin MB, Nicolaides AN, Kyriacou E, Sabetai MM, Tegos T, et al. The size of juxtaluminal hypoechoic area in ultrasound images of asymptomatic carotid plaques predicts the occurrence of stroke. J Vasc Surg. 2013;57(3):609–618.e1.
69. Moore WS, Boren C, Malone JM, Roon AJ, Eisenberg R, Goldstone J, et al. Natural history of nonstenotic, asymptomatic ulcerative lesions of the carotid artery. Arch Surg. 1978;113(11):1352–9.
70. Kuk M, Wannarong T, Beletsky V, Parraga G, Fenster A, Spence JD. Volume of carotid artery ulceration as a predictor of cardiovascular events. Stroke. 2014;45(5):1437–41.
71. Eliasziw M, Streifler JY, Fox AJ, Hachinski VC, Ferguson GG, Barnett HJ. Significance of plaque ulceration in symptomatic patients with high-grade carotid stenosis. North American Symptomatic Carotid Endarterectomy Trial. Stroke. 1994;25(2):304–8.
72. Kwee RM, van Oostenbrugge RJ, Mess WH, Prins MH, van der Geest RJ, ter Berg JW, et al. MRI of carotid atherosclerosis to identify TIA and stroke patients who are at risk of a recurrence. J Magn Reson Imaging. 2013;37(5):1189–94.
73. Hosseini AA, Kandiyil N, Macsweeney ST, Altaf N, Auer DP. Carotid plaque hemorrhage on magnetic resonance imaging strongly predicts recurrent ischemia and stroke. Ann Neurol. 2013;73(6):774–84.

74. Takaya N, Yuan C, Chu B, Saam T, Underhill H, Cai J, et al. Association between carotid plaque characteristics and subsequent ischemic cerebrovascular events: a prospective assessment with MRI–initial results. Stroke. 2006;37(3):818–23.
75. Singh N, Moody AR, Gladstone DJ, Leung G, Ravikumar R, Zhan J, et al. Moderate carotid artery stenosis: MR imaging-depicted intraplaque hemorrhage predicts risk of cerebrovascular ischemic events in asymptomatic men. Radiology. 2009;252(2):502–8.
76. Mono ML, Karameshev A, Slotboom J, Remonda L, Galimanis A, Jung S, et al. Plaque characteristics of asymptomatic carotid stenosis and risk of stroke. Cerebrovasc Dis. 2012;34(5–6):343–50.
77. Gur AY, Bova I, Bornstein NM. Is impaired cerebral vasomotor reactivity a predictive factor of stroke in asymptomatic patients? Stroke. 1996;27(12):2188–90.
78. Silvestrini M, Vernieri F, Pasqualetti P, Matteis M, Passarelli F, Troisi E, et al. Impaired cerebral vasoreactivity and risk of stroke in patients with asymptomatic carotid artery stenosis. JAMA. 2000;283(16):2122–7.
79. Markus H, Cullinane M. Severely impaired cerebrovascular reactivity predicts stroke and TIA risk in patients with carotid artery stenosis and occlusion. Brain. 2001;124(Pt 3):457–67.
80. Kakkos SK, Sabetai M, Tegos T, Stevens J, Thomas D, Griffin M, et al. Silent embolic infarcts on computed tomography brain scans and risk of ipsilateral hemispheric events in patients with asymptomatic internal carotid artery stenosis. J Vasc Surg. 2009;49(4):902–9.

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