



Online article and related content
current as of July 2, 2008.

A 70-Year-Old Man With a Transient Ischemic Attack: Review of Internal Carotid Artery Stenosis

Louis R. Caplan

JAMA. 2008;300(1):81-90 (doi:10.1001/jama.299.21.jrr80004)

<http://jama.ama-assn.org/cgi/content/full/300/1/81>

Correction

[Contact me if this article is corrected.](#)

Citations

[Contact me when this article is cited.](#)

Topic collections

Surgery; Surgical Interventions; Vascular Surgery; Neurology; Cerebrovascular Disease; Aging/ Geriatrics; Cardiovascular System; Cardiovascular Disease/ Myocardial Infarction; Cardiovascular Intervention; Revascularization; Cardiovascular System, Other
[Contact me when new articles are published in these topic areas.](#)

CME course

[Online CME course available.](#)

Subscribe

<http://jama.com/subscribe>

Email Alerts

<http://jamaarchives.com/alerts>

Permissions

permissions@ama-assn.org
<http://pubs.ama-assn.org/misc/permissions.dtl>

Reprints/E-prints

reprints@ama-assn.org

A 70-Year-Old Man With a Transient Ischemic Attack

Review of Internal Carotid Artery Stenosis

Louis R. Caplan, MD, Discussant

DR BURNS: Mr V is a 70-year-old man with a history of coronary artery disease, including coronary angioplasty with stent placement to the left circumflex coronary artery in February 2006, peripheral vascular disease, gastrointestinal bleeding attributed to clopidogrel, hypertension, and hyperlipidemia. Mr V presented with acute onset of slurred speech and left facial droop. He has Medicare and Medicaid insurance.

Mr V was well until 4 hours before his presentation to the hospital emergency department. He had taken an afternoon nap and when he awoke an hour later, his wife noted that he had a left facial droop and garbled speech. On presentation to the emergency department, his initial vital signs were stable, including a blood pressure of 130/77 mm Hg. His speech was initially quite garbled but resolved within 5 minutes and he had a left facial droop and 1+ left arm drift. His National Institutes of Health Stroke Scale score was 2. A computed tomography (CT) scan without contrast showed old infarctions in the left caudate nucleus and cerebellum, but no acute infarction was seen. A CT angiogram of the neck was also performed and showed a very high-grade, relatively smooth, long region of right internal carotid artery (ICA) stenosis (FIGURE 1). A magnetic resonance imaging (MRI) scan was performed later that evening and showed multifocal areas of infarction in the right middle cerebral artery territory with ischemic areas in the right frontal and posterior parietal/occipital lobe border regions and acute brain infarction in both the frontal and parietal regions (FIGURE 2). T2*-weighted gradient echo images showed a thrombus in a middle cerebral artery branch.

Mr V was not considered a candidate for intravenous or intra-arterial tissue plasminogen activator, given the improvement of his symptoms and minimal deficits. He

Mr V, a man with severe coronary, aortic, and peripheral artery disease, had an episode of brain ischemia caused by severe preocclusive carotid artery disease in the neck. The major treatment options for his symptomatic carotid artery disease are optimizing medical treatment, carotid endarterectomy, and carotid artery stenting. Selection of treatment must take into consideration his severe symptomatic coronary artery disease as well as Mr V's concerns about surgery. Carotid endarterectomy presents a risk of myocardial infarction unless his coronary disease is treated effectively before surgery. Carotid stenting is problematic because the severity of the preocclusive arterial narrowing makes passing a protective device beyond the stenosis difficult without first performing potentially hazardous angioplasty. Optimizing medical treatment may be the best option for his severe systemic atherosclerosis. Treatment decisions in complex patients like Mr V require weighing the particular risks and benefits of available options, and the patient's own wishes and fears. These decisions, in this and other complex patients, often cannot be directly informed by results from randomized trials.

JAMA. 2008;300(1):81-90

www.jama.com

was thought to have an acute infarction in the right temporal lobe that likely represented an embolic event from the right ICA. He was admitted and received a heparin

This conference took place at the Neurology Grand Rounds at Beth Israel Deaconess Medical Center, Boston, Massachusetts, on December 15, 2007.

Author Affiliations: Dr Caplan is Senior Neurologist and member of the Cerebrovascular/Stroke Division at Beth Israel Deaconess Medical Center and Professor of Neurology, Harvard Medical School, Boston, Massachusetts.

Corresponding Author: Louis R. Caplan, MD, Beth Israel Deaconess Medical Center, Division of Cerebrovascular/Stroke, One Deaconess Rd, Boston, MA 02215 (lcaplan@bidmc.harvard.edu).

Clinical Crossroads at Beth Israel Deaconess Medical Center is produced and edited by Tom Delbanco, MD, Howard Libman, MD, Eileen E. Reynolds, MD, Amy N. Ship, MD, and Anjala V. Tess, MD. Risa B. Burns, MD, is series editor.

Clinical Crossroads Section Editor: Margaret A. Winker, MD, Deputy Editor.

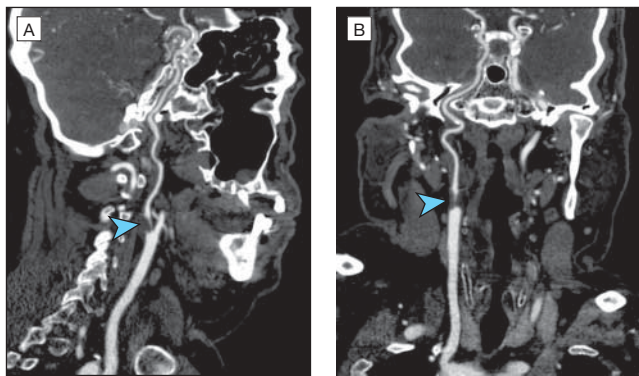


CME available online at www.jamaarchivescme.com and questions on p 120.

drip with a plan to transition him to warfarin while an inpatient. He continued to take aspirin, 325 mg/d. During his admission he had a transthoracic echocardiogram that revealed a preserved ejection fraction without an intracardiac source of emboli. He was discharged home with prescriptions for atorvastatin, 40 mg/d; pantoprazole, 40 mg/d; aspirin, 325 mg/d; metoprolol, $\frac{1}{2}$ 25-mg tablet daily; warfarin, four 1-mg tablets daily; and nitroglycerin, 0.3 mg sublingual if needed for chest pain.

Following discharge, he did well, without any new motor or sensory changes. He can walk for several hours a day without difficulty, although he has occasional chest pain at rest that lasts for a few minutes and resolves spontaneously. He also notes calf pain bilaterally only when walking fast that is relieved with rest but that has been stable for 30 years.

Figure 1. Views of a Computed Tomography Angiogram in Mr V



A, Anteroposterior view. B, Lateral view. The internal carotid artery lumen is severely narrowed (arrowheads).

He was seen in consultation by a vascular surgeon and an interventional cardiologist. The surgeon thought that the ICA stenosis was too severe to pass a filter device. He suggested an EMPIRE flow reversal system as part of a clinical trial or an open carotid endarterectomy.¹⁻³ The cardiologist encouraged Mr V to pursue revascularization of some form and, given his cardiac history, suggested carotid stenting.

Mr V was uncertain how to proceed and requested a carotid ultrasound to see if there had been any change in the stenosis. The ultrasound revealed velocities on the right carotid of 415 cm/s, consistent with a greater than 80% carotid stenosis. A CT angiogram was also performed and revealed extensive plaque throughout the coronary arteries and a calcium score of 2235 Agatston. The patency of the coronary stent could not be completely assessed, though there was no perceivable flow past the stent, suggesting occlusion. Mr V also had a repeat CT angiogram at another institution that revealed a mural thrombus involving the descending thoracic aorta and the right common iliac artery, which was aneurysmal.

Mr V lives with his wife. He has a 46-pack-year smoking history but quit about 18 months ago. He does not drink alcohol. He trained as a mechanical engineer but has worked as an accountant after moving to the United States 15 years ago.

He remains uncertain how to proceed. He is quite certain that he will die during a carotid endarterectomy given his underlying cardiac disease and does not know how a stent can be placed given the presence of a thrombus.

MR V: HIS VIEW

My mouth was drooped a little and I had some changes in my voice. My wife saw this—I didn't even recognize it—

Figure 2. Mr V's Diffusion-Weighted and T2*-Weighted MRI Scan



Diffusion-weighted magnetic resonance imaging (MRI) shows white hyperintense foci (restricted diffusion) that represent infarction (arrowheads) in the cerebral cortex of the right frontal lobe (A) and the parietal lobe (B). C, T2*-weighted MRI shows a cylindrical dark region that represents a thrombus in a middle cerebral artery branch (arrowhead).

and decided to take me to the hospital. They checked me with the CT first and then with an MRI. The diagnosis was acute embolic stroke. I am lucky that I didn't have a big stroke and I didn't have any disability.

At the hospital, they found that my carotid was severely blocked. They gave me Coumadin, but they said that it's not enough. They suggested I have the carotid surgery.

I saw a vascular surgeon first. He thought that I have 2 options. First, he thought I could have the surgery, but only if my heart problems were minimal. I did the CT angiogram to test the heart and lungs, and it showed a lot of heart problems. Second, he suggested I do the stent, but only with a new protection device. He is doing a study with reverse flow. I don't want to do the study because I can't believe in it.

I got a second opinion from a cardiologist. He said that he is ready to do the stent. But he has his own study, with almost new devices, with an absolutely new stent. The stent was FDA [US Food and Drug Administration]-approved January 24, 2007. And the protective device was FDA-approved in June 2006.

I read a lot about my risks factors, and I know it can happen any day. In 1 year, it's about 12%. In 5 years it's like 25%, maybe even 40%, because I have very severe blockage. I'm 100% sure that I should clean the artery, but I don't see a way I can do it.

The most important thing is that I had heart catheterization in April and it was a very bad experience. I'm afraid to do more catheterization because after the catheterization I had a thrombus.

If I have the surgery I'm afraid I will die during the operation. I almost sure that it will happen. If I have a stent thrombosis, which they're almost sure I will have, I will die definitely.

I wonder if Dr Caplan can suggest more medication, even vitamins and supplements or alternative treatment.

AT THE CROSSROADS: QUESTIONS FOR DR CAPLAN

What is the epidemiology and pathophysiology of transient ischemic attacks (TIAs) and when should carotid artery disease be suspected? How should a patient with a TIA and suspected carotid artery disease be evaluated? What are the treatment options, risks, and benefits of medical management? What are the risks and benefits of stenting and should a protective device be included? What are the risks and benefits of surgical management? How do you evaluate treatment options for an individual patient and what tools are available to guide your decision? What do you recommend for Mr V and why? What does the future hold?

DR CAPLAN: Mr V had an episode of brain ischemia caused by severe preocclusive stenosis of his right ICA in the neck. He also has severe coronary and peripheral artery atherosclerotic disease. How should this situation be managed?

Carotid artery disease is a common, important, and treatable cause of brain ischemia. Atherosclerosis of the ICA in the neck is especially common in white men and is less common in blacks and Asians and in women who do not smoke or have diabetes.^{4,5} The risk factors for development of ICA disease are similar to those for coronary artery disease and include hypertension, smoking, diabetes, and hypercholesterolemia. Mr V has hypertension, hypercholesterolemia, and coronary and peripheral vascular disease.

Pathology and Pathophysiology

Atheromas form in the distal common carotid arteries and extend into the first few centimeters of the internal and external carotid arteries, almost always more severely narrowing the ICA. Atheromatous plaques enlarge and may gradually narrow the ICA lumen. Ulceration, attachment of platelets and thrombi to crevices in plaques, and hemorrhage into plaques become more common as the arterial lumen becomes increasingly narrowed. Plaques contain a lipid core and fibrous cap. When there is a break in the fibrous cap, contact of the lipid core with the luminal contents activates platelets and can activate the coagulation cascade, promoting the deposition of white and red thrombi onto the surface of plaques.^{6,7} These thrombi can detach from the arterial wall and embolize to distal vessels, causing transient or prolonged brain and eye dysfunction. Reduction in blood flow in the ICA can cause periodic insufficiency in distal perfusion and reduced clearance (washout) of emboli.^{8,9}

Clinical Findings

The major symptoms are those due to transient or persistent brain and eye ischemia. Since the ophthalmic artery is the first branch of the ICA (FIGURE 3), the single most important clue to carotid artery localization is an attack of transient brief monocular loss of vision. Often, the visual loss is described as a dimming, darkening, or obscuration. Episodes of brain ischemia referable to the cerebral hemisphere supplied by the diseased ICA occur and are also often brief. Headaches, unusual for the patient, may also occur when the carotid narrowing is severe.^{10(pp165-198)}

In some patients, as in Mr V, an embolus arising from the ICA causes a sudden-onset stroke due to occlusion of a major intracranial branch of the ICA, most often the middle cerebral artery. Mr V suddenly developed left face and arm weakness and slurred speech caused by an embolus from his stenotic right ICA to middle cerebral artery branches. A thorough physical and neurological examination can detect signs of eye and brain involvement and can yield clues to the presence of important ICA disease. Signs that suggest the presence of carotid artery disease are noted in BOX 1.^{10(pp165-198),16}

Laboratory and Imaging Evaluation

Testing is aimed at defining the presence, nature, and severity of ICA disease, and of any concurrent cervicocranial

occlusive disease. Other potential causes of stroke (mostly cardiac and hematological) that might affect treatment decisions should also be sought.^{10(pp51-113)} Brain imaging and eye examination are important to detect biological activity of the ICA lesion even when patients report no symptoms.

Trials and anecdotal reports have customarily divided patients with ICA disease into 2 groups, symptomatic and asymptomatic. Many patients have evidence of complications of their ICA disease without acknowledged symptoms. Spouses present during history-taking may remind patients of symptoms that they did not recall themselves or may have noticed symptoms the patient was unaware of, as was the case for Mr V. In other “asymptomatic” patients, neurological examination may show leg weakness or a Babinski sign, abnormalities referable to the hemisphere supplied by a stenotic ICA. Brain imaging and ophthalmoscopy can also indicate the presence of end-organ damage. In other fields of medicine, especially oncology, physicians search for clinically silent evidence of organ involvement to assess biological activity. This strategy is also useful for patients with ICA disease, rather than restricting classification to symptomatic or not. Evidence of biological activity is listed in BOX 2.

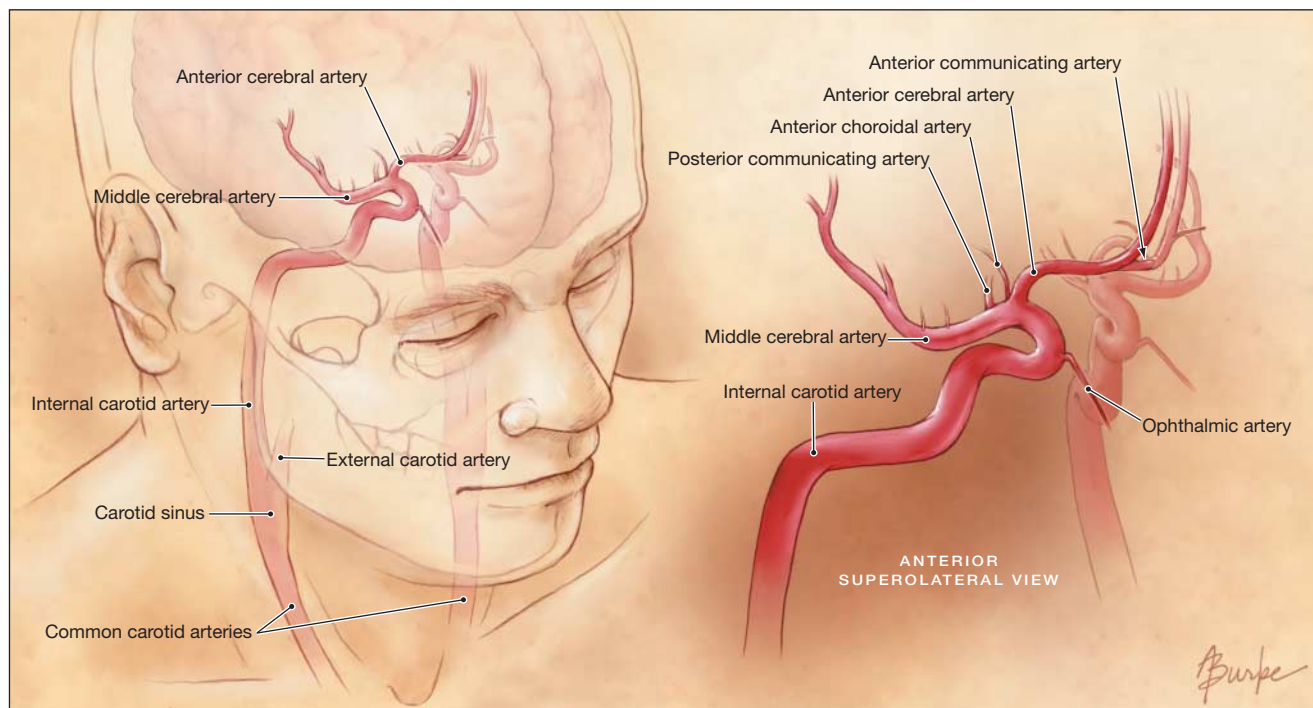
Brain imaging consists of CT or MRI. Diffusion-weighted, fluid-attenuated inversion recovery and T2*-weighted MRI images often show more than a plain T2-weighted basic MRI. In Mr V, MRI studies showed the presence of acute brain infarction in both the frontal and

parietal regions (Figure 2, A and B). T2*-weighted gradient echo images showed a thrombus in a middle cerebral artery branch (Figure 2, C). Brain infarction in the cerebral hemisphere ipsilateral to a stenotic ICA is evidence of embolism from the ICA.

Vascular imaging is performed using ultrasound, CT angiography, MR angiography, and dye-contrast catheter angiography. Ultrasound is a noninvasive, convenient way to image brain-supplying arteries in the neck and head. The most commonly used technology is Duplex scanning, which combines a B-mode picture and Doppler curves of blood-flow velocities. Duplex scanning is accurate in assessing the degree of luminal narrowing and in showing ulcerations and surface-wall characteristics of the ICAs.^{17,18} Sequential monitoring using Duplex ultrasound monitors progression of disease and the effects of treatments such as statins.¹⁹ In Mr V, Doppler ultrasound showed a peak systolic velocity of 415 cm/s in the right ICA, consistent with more than 80% stenosis. Left ICA narrowing was estimated to be less than 40%. The impact of ICA narrowing on blood flow in the major intracranial arterial branches can be studied using transcranial Doppler ultrasound, a technique that can also be used to monitor for emboli arising from the ICA, although sensitivity and specificity have not been determined.²⁰⁻²²

Magnetic resonance and CT angiography provide useful images of the ICAs and the other neck and intracranial arteries. The location and extent of arterial stenosis and char-

Figure 3. Anatomy of Internal Carotid Artery and Intracranial Branching



acteristics such as smoothness, irregularity, and ulcerations can be factors in deciding on treatment, as discussed later. Magnetic resonance angiography is a functional examination that creates an image of flow. Unlike contrast injection angiograms, the images do not show anatomy. When arterial blood flow is reduced, the vessel may appear more narrowed than shown by catheter angiography.^{23,24} Magnetic resonance angiography may overestimate the severity of stenosis but is a useful screening technique with the advantage of not requiring contrast and being performed with brain MRI. Newer MRI techniques are now sometimes used to analyze atheromatous plaque characteristics.²⁵ Computed tomography angiography uses intravenous contrast to create excellent images of the ICA. Mr V's CT angiogram showed a very high-grade, relatively smooth, long region of right ICA stenosis (Figure 1, A and B).

Treatment Considerations

Atherosclerosis is a systemic disease, so that medical treatment should be optimized in all patients with documented carotid atherosclerotic plaques. The therapeutic choices in Mr V are optimal medical treatment alone, medical treatment plus carotid artery surgery, or medical treatment plus carotid artery stenting. Medical therapy is aimed at reducing embolism and preventing an increase in atherosclerotic plaque development. Surgery and stenting increase blood flow, thus improving brain perfusion and clearance of emboli.^{8,9}

Optimizing Medical Treatment

Because of their pleiotropic effects in stroke and vascular disease prevention, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) are essential in patients like Mr V. Statins not only reduce cholesterol levels but also reduce coronary artery disease-related events and mortality, even in patients with average levels of cholesterol.^{26,27} Analyses of randomized trials of statins show a clear and dramatic reduction in the incidence of stroke.²⁸⁻³³ In the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial, patients who had prior strokes or TIAs in whom low-density lipoprotein cholesterol levels were reduced by more than 50% (from a baseline mean of about 133 mg/dL) by 80 mg/d of atorvastatin had a 31% reduction in stroke risk.³² Statins have also been shown to slow the progression of carotid artery atherosclerotic plaques.^{33,34} Aggressive therapy with high doses of statins (equivalent to 80 mg/d of atorvastatin) has been shown to be more effective than lower doses in patients with coronary artery disease (plaque growth of 0.6 [SD, 5.1] mm vs 1.9 [SD, 4.9] mm with placebo)²⁷ and in preventing strokes in patients who had had TIAs or strokes (5-year absolute risk reduction, 1.9% [from 13.1% to 11.2%]).^{29,30} I recommend increasing Mr V's atorvastatin dose to 80 mg/d.

Antiplatelet therapy has also been used widely to treat patients with coronary and carotid artery disease. Mr V

Box 1. Signs of Internal Carotid Artery Disease

Neck

High-pitched, focal, long bruit at the internal carotid artery origin

Face

Increased angular, brow, cheek (ABC) pulses^{10,11}

Frontal artery sign¹²

Increase in size and pulsations in the ipsilateral superficial temporal artery

Retina

Cholesterol crystals¹³

Platelet thromboemboli¹⁴

Retinal infarctions

Reduced caliber of arteries

Less-severe hypertensive changes

Venous stasis retinopathy^{15,16}

Reduced retinal artery pressure

had a gastrointestinal bleed attributed to clopidogrel. He now takes aspirin, 325 mg/d. A combination of 325 mg/d of aspirin and modified-release dipyridamole has been shown in randomized trials to be more effective than aspirin alone in preventing strokes in patients with prior TIAs or mild strokes^{35,36} but has not been tested in trials to treat coronary or carotid artery disease. Warfarin has the potential to inhibit the formation of red erythrocyte-thrombin clots that form in very stenotic arteries. Use of warfarin in patients with severe ICA stenosis has not been studied in randomized trials but has considerable theoretical effectiveness in patients with severe stenosis, such as Mr V. He is now taking warfarin with an international normalized ratio target of 2 to 3.

While no data exist that address his particular clinical situation, I suggest continuing the warfarin if Mr V does not have surgery or stenting. A combination of 325 mg of aspirin and modified-release dipyridamole could be used instead of warfarin after surgery or stenting.^{10(pp37-138)}

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers also have theoretical advantages in patients with hypertension and occlusive vascular disease. They are posited to have endothelial actions that reduce atherosclerotic plaque development^{37,38} but their effectiveness in reducing stroke in patients with ICA disease has not been adequately studied in therapeutic trials. Mr V is now taking a β -blocker, metoprolol, 25 mg/d. Some consideration might be given to adding an ACE inhibitor depending on his blood pressures when home. It is not currently possible to quantify the benefit of adding an ACE inhibitor or angiotensin receptor blocker to the present regimen.

Box 2. Criteria for Biological Activity of a Carotid Artery Lesion*

A clinical episode of transient or persistent brain or eye ischemia

Neurological signs referable to the appropriate cerebral hemisphere

An ipsilateral brain infarction on computed tomography or magnetic resonance imaging

Ophthalmoscopy showing a Hollenhorst plaque, other retinal emboli, or retinal infarctions

Transcranial Doppler ultrasound showing microemboli in the intracranial branches of the stenotic internal carotid artery

*Based on author's clinical experience.

Carotid Endarterectomy

Carotid endarterectomy has been shown to be clearly more effective than best medical therapy in patients with neurologically symptomatic, severe (70% luminal narrowing) ICA stenosis.³⁹⁻⁴⁴ The medical therapy tested in trials was aspirin and not warfarin. In the North American Symptomatic Carotid Endarterectomy trial (NASCET), in patients with high-grade stenosis, the relative risk reduction for surgery vs medical therapy at 2-year follow-up for any ipsilateral stroke was a striking 65%, and the absolute risk reduction was 17% (number needed to treat to prevent ipsilateral stroke over 2 years was 6).³⁹ Endarterectomy not only removes the obstructing lesion, dramatically augmenting flow, but also removes the source of intra-arterial emboli. Endarterectomy has also been shown to be moderately effective (number needed to treat of 15 to prevent 1 ipsilateral stroke in NASCET) in selected patients with luminal stenosis in the 50% to 69% range.⁴⁰⁻⁴⁴ Patients must be carefully chosen in relation to their risks because neurological and cardiac morbidity and mortality are significant risks, and much depends on the experience and morbidity/mortality record of the operating surgeon.

The Carotid Endarterectomy Trialists Collaboration analyzed pooled data from the carotid endarterectomy randomized trials and reinforced the impressive benefit of surgery in symptomatic patients with severe stenosis when operated on early after development of symptoms.^{43,44} Their analysis showed that to prevent 1 ipsilateral carotid territory stroke and operative stroke or death at 5 years, only 5 patients need to be treated, and only 14 need to be operated on to prevent 1 fatal or disabling ipsilateral stroke or operative stroke or death at 5 years.^{43,44}

In patients with very severe stenosis (sometimes called "pseudo-occlusion") or thrombi, surgical risk is much higher and the benefit less.⁴³⁻⁴⁵ Mr V's stenosis is very severe and preocclusive.

The most important complications are ipsilateral stroke, accelerated hypertension, hyperperfusion syndrome with brain hemorrhage and edema after surgery, and myocardial infarction. The location and nature and extent of the carotid and other vascular disease also are factors in determining surgical risk, as are the presence of hypertension, diabetes, smoking, chronic pulmonary disease, and congestive heart failure.⁴⁶ The stroke or death rate in the pooled data collection of Rothwell et al^{43,44} was 7.1% at 30 days. The stroke and death rate of carotid endarterectomy in series of symptomatic patients usually ranges between 5% and 10%.⁴⁷ Mr V's risk would fall at the high end, nearer 10%, because of his coronary artery disease and pre-occlusive lesion.

Endarterectomy of a tightly stenotic vessel results in a sudden large increase in blood flow. Capillaries, small arterioles, and neurons are often damaged during ischemia. When flooded with blood under high pressure, these vessels then may bleed or leak fluid. The carotid sinus is also impaired during endarterectomy, leading to failure of the carotid sinus reflex, and accelerated hypertension can develop in the hours and days after carotid endarterectomy.⁴⁸⁻⁵¹ Elevated blood pressure and flooding of damaged vessels can lead to brain hemorrhage and edema after carotid endarterectomy.^{50,51} Blood pressure of patients undergoing carotid endarterectomy must be carefully monitored during the post-operative period.

Carotid Artery Stenting

Although coronary artery angioplasty began much earlier, Kerber et al⁵² reported the first endovascular treatment of the carotid artery with balloon angioplasty in 1980.⁵³ By 1995, a review of worldwide experience among 523 patients claimed favorable results: 96.2% technical success, 2.1% morbidity, 6.3% transient minor complications, and no deaths.⁵⁴ Operator experience influenced the technical success and treatment outcomes: centers with limited experience (<50 cases) reported nearly twice the rate of complications (5.9% vs 2.6%) than those with more substantial experience.⁵³⁻⁵⁵ Since then, technology has continued to change, with stenting preferred to simple angioplasty, and a variety of emboli protection strategies being used. Methods to prevent cerebral embolization during carotid instrumentation include (1) temporary balloon occlusion of the ICA distal to the stenosis followed by aspiration or lavage of the treatment area; (2) placement of a filter distal to the treatment zone that permits passage of blood components but not particles or debris; and (3) flow reversal by temporary occlusion of the ICA proximal to the treatment zone, encouraging retrograde blood flow away from the brain. Reviews show that patients with distal protection devices during carotid angioplasty/stenting have better outcomes reported than those treated without these devices, but no randomized trials have been performed.^{56,57}

Table. Selected Results of Carotid Endarterectomy (CEA) vs Carotid Angioplasty/Stenting (CAS) Trials

Source	No. of Participants	Entry Criteria	Operator Criteria	30-Day Outcome of Stroke and Death, %
CAVATAS, ^{58,59} 2001	CEA: 246 CAS: 240 (22% had stents)	Symptomatic: >70% stenosis CAS if unsuited for surgery	Not stated	CEA: 10 CAS: 10
CARESS, ⁶⁰ 2003	CEA: 254 CAS: 193	Symptomatic: >50% stenosis Asymptomatic: >75% stenosis (32% were symptomatic)	CEA: 50 surgeries per 3 y, <6% stroke and death CAS: 20 stents, <6% stroke and death	CEA: 2 CAS: 2
SAPPHIRE, ⁶¹ 2004	CEA: 167 CAS: 167	Symptomatic: >50% stenosis Asymptomatic: >80% stenosis (30% were symptomatic)	CEA: 30 surgeries per y CAS: Reviewed by committee	(Including myocardial infarction) CEA: 20.1 CAS: 12.2
SPACE, ⁶² 2006	CEA: 595 CAS: 605	Symptomatic: >50% stenosis	CEA: 25 surgeries CAS: 25 surgeries	CEA: 6.34 CAS: 6.84
EVA-3S, ⁶³ 2006	CEA: 259 CAS: 261	Symptomatic: >60% stenosis	CEA: 25 surgeries CAS: 5 surgeries	CEA: 3.9 CAS: 9.6

Carotid Endarterectomy vs Carotid Angioplasty/Stenting

In addition to stent registries, 5 randomized trials⁵⁸⁻⁶³ have compared surgery and endovascular treatment (TABLE). The Carotid and Vertebral Transluminal Angioplasty Study (CAVATAS) was a large, prospective, randomized, multicenter trial that compared carotid endarterectomy with carotid angioplasty in patients with a symptomatic stenosis of at least 70%.^{58,59} Patients "unsuitable for endarterectomy" were randomized to receive angioplasty with or without stenting or best medical treatment. Among 504 patients randomized to surgery or angioplasty during 5 years, the rate of any stroke lasting more than 7 days or death within 30 days of first treatment was 10% to 12% in both the surgical and angioplasty groups and the rate of disabling stroke or death within 30 days of first treatment was 6% in both groups. Stents were used in only 22% of patients. The rate of restenosis in the endovascular group was twice that in the surgical cohort (18% vs 9%, respectively).⁵⁶

The Carotid Revascularization Using Endarterectomy or Stenting Systems (CARESS) trial compared carotid endarterectomy with carotid stenting with protection devices in patients with carotid stenosis of at least 50% if symptomatic and at least 75% if asymptomatic.⁶⁰ The study enrolled 439 patients (254 with surgery and 143 with stenting). More than 90% of patients had more than 75% stenosis; approximately one-third were symptomatic. The 30-day combined all-cause mortality and stroke rate did not differ by Kaplan-Meier estimate between surgery (2%) and stenting (2%), and combined 30-day all-cause mortality, stroke, and myocardial infarction did not differ significantly between surgery (3%) and stenting (2%).⁶⁰

The Stenting and Angioplasty With Protection in Patients at High Risk for Endarterectomy (SAPPHIRE)⁶¹ trial compared carotid stenting using an embolic protection device with endarterectomy in 334 surgically "high-risk" patients with more than 50% symptomatic stenosis or more than 80% asymptomatic stenosis. Only 30% of patients enrolled were symptomatic. "Clinical equipoise" (stent or sur-

gery) was required for randomization. The authors concluded that stenting with distal embolic protection was not inferior to endarterectomy ($P = .004$ for noninferiority). Moreover, the results narrowly missed the mark for statistical superiority of stenting ($P = .05$). Overall the risk of stroke, death, or myocardial infarction at 30 days was 39% lower with stenting. The risk of ipsilateral stroke or death was 7.9% lower with stenting at 1 year. Fewer patients with stents required a second procedure than those who had endarterectomy.⁶¹ However, the small differences did not persist. The results of 3 years of follow-up demonstrated no significant differences between the 2 groups.⁶⁴

SAPPHIRE was the first trial to show the efficacy of distal embolic filtration protection during stent-supported angioplasty. The SAPPHIRE study was limited by the exclusion from randomization of 55% of patients who were considered poor surgical candidates, a number that appears high to surgeons.⁶⁵ Additionally, more than 20% of patients in each group had recurrent stenosis following a prior endarterectomy, a condition that potentially favors endovascular treatment. Myocardial infarction was included in the composite end point but was not included in other trials.

The SPACE trial included 1183 German, Austrian, and Swiss patients with symptomatic eye or brain ischemia and more than 50% ipsilateral carotid artery stenosis who were randomized to carotid surgery ($n = 599$) or carotid artery stenting ($n = 584$).⁶² Choice of protection devices, predilatation, balloon size, and stents was left up to the interventionalists. Only 27% of patients with stents had protection devices, but end points did not differ among those treated with and without protective devices. The rate of death or ipsilateral ischemic stroke at 30 days was 6.34% with surgery and 6.84% with stenting, a clinically and statistically nonsignificant difference. Older patients and women tended to do worse with either treatment.⁶²

In a French trial of carotid endarterectomy vs stenting (EVA-3S), the stroke and death rates were higher in the stent group than in the surgical group.⁶³ The stroke or death fre-

quency at 30 days was 3.9% in the endarterectomy group and 9.6% in the group receiving stents.⁶⁶ Five different stents and 7 different protection devices were used; in about 20% of instances (mostly at the beginning of the trial), protection devices were not deployed. The requirements for prior experience of the interventionalists who performed the stenting were less restrictive than in other trials.⁶³

Complications and adverse events have been tabulated after stenting procedures. Hoffman and colleagues reviewed the risk scores for peri-interventional complications of carotid artery stenting derived from a prospective registry of 606 consecutive patients treated at a "secondary-care hospital" in Austria.⁵⁷ The acute stroke rate was 3% (including 13 minor and 5 major periprocedural nonfatal strokes), and the death rate was 1.3%, including 4 fatal strokes. Diabetes with poor glycemic control, age older than 80 years, ulceration of the carotid artery, and a severe contralateral carotid artery stenosis were the major risk factors for periprocedural complications. Patients treated with distal protection devices fared better than those who did not have protection devices.⁵⁷

A large, ongoing multicenter trial, the Carotid Revascularization Endarterectomy vs Stent Trial (CREST), supported by the National Institute of Neurological Disorders and Stroke, recruited patients in the United States and Europe, but the results have not yet been analyzed.⁶⁷

Reflections on the Trials and Suggestions for Mr V

Unfortunately, the results of the trials reviewed, as is true in many neurological conditions,⁶⁸⁻⁷⁰ do not yield much help in choosing treatment for complex individuals such as Mr V. The field of carotid artery angioplasty/stenting is a moving target, with new stents, protection devices, and techniques added annually. There is a significant learning curve for individuals performing the procedure. Outcomes of both carotid endarterectomy and angioplasty/stenting depend on patient selection, nature of the ICA lesions, presence, location, and severity of other vascular occlusive disease, and on the training, experience, and skill of the individual performing the procedure. In my experience, the location of the carotid lesion, its length, whether the lesion is smooth or irregular, calcified, echolucent (implying a soft, active plaque), or echodense (implying a calcified, inactive plaque) and whether there is any accompanying ulceration or thrombus is important in estimating the efficacy and risk of surgery and interventional treatments. None of the therapeutic trials analyzed results regarding the nature of the carotid artery lesions other than the severity of stenosis.

It is naive to think that one treatment fits all, that 1 of the 2 treatments is always superior. Each procedure might be better suited for certain carotid and cerebrovascular lesions in patients with certain neurological situations and certain comorbidities. I posit that patients with long lesions, smooth lesions, and very high bifurcations, especially those with coronary artery disease, might better be

treated using interventional stent techniques. Patients with focal irregular ulcerated lesions, especially those without important coronary artery disease, might better be treated surgically. Surgeons now learn both direct surgical and interventional techniques so that they can fit the preferred technique for an individual patient to the lesion and the patient.

Mr V's ICA lesion is relatively long and extends high into the artery, necessitating disarticulation of the jaw to reach the full plaque surgically. Moreover, he has severe coronary artery disease and is very fearful of surgery. Surgery is not a good solution for him. The risk of ipsilateral stroke, myocardial infarction, or death probably is in the range of 10%. Carotid artery stenting also has problems. The lesion, although relatively smooth, creates a severe preocclusive stenosis, so that passage of a protective device past the lesion poses a problem without first dilating the artery. Flow reversal protection is an option, but the technique is relatively new and untested. His peripheral artery disease and potential aortic atherosclerosis might make arterial access difficult and risky. The right brachial artery could provide access to the right ICA. Stent placement would require prolonged intensive antiplatelet therapy, a possible problem with his past gastrointestinal bleed. I would depend on the opinion of the potential interventionalist as to the risks of an angioplasty/stenting procedure in Mr V.

Aggressive medical treatment is a viable option. Increasing his statin treatment to 80 mg/d and adding an ACE inhibitor or angiotensin receptor blocker should be considered whether or not he has a procedure to open the ICA. If medical treatment alone is decided on, I favor continuing warfarin to prevent a red thrombus from forming in the stenotic ICA and embolizing to the brain. If surgery is decided on, treatment of his coronary artery disease, if feasible, should be performed before surgery to lessen the operative risk.

QUESTIONS AND DISCUSSION

QUESTION: How should patients with no evidence of active disease be evaluated?

DR CAPLAN: I participated in a Clinical Crossroads 12 years ago concerning management of asymptomatic carotid artery disease.⁷¹ Since then, more information is available about prognosis. The risk of stroke in patients with asymptomatic carotid stenosis is about 2% to 2.5% a year.⁷² Even when the artery occludes, many patients have no symptoms. When symptoms occur, they are often in the form of 1 or more TIAs. Many patients with severe carotid artery disease have serious comorbidities, including coronary artery disease, and the risk of surgery equals or exceeds the natural history. Asymptomatic patients by definition do not feel better after surgery. If they have a complication of the surgery, such as stroke or myocardial infarction, it occurs at that time, whereas their risk of

developing a stroke occurs over the course of years. A postsurgical stroke at age 75 years is very different from a naturally occurring stroke 10 years later at age 85 years. I do not advocate aggressive surgical treatment of asymptomatic patients. I attempt to optimize medical treatment, as discussed for Mr V.

QUESTION: The Asymptomatic Carotid Atherosclerosis Study, often used to justify treatment of asymptomatic patients,⁷³ shows that operating on those patients, even if they have relatively high-grade stenosis, reduces the risk of TIA but does not reduce the occurrence of major strokes. So there really is not a strong rationale for operating on those patients, even if you find a lesion at 70%. For that reason, I question whether individuals should even be studied by ultrasound.

DR CAPLAN: The options are either to not do anything interventional for anybody who has no symptoms or to choose among asymptomatic patients those who are at highest risk. This might be done by looking at the nature of the lesion. Echolucent, irregular, heterogeneous lesions are more biologically active. The presence of microemboli detected by transcranial Doppler ultrasound or brain infarction are posited to increase risk. It is probably wrong to never interventionally treat any asymptomatic patients. But it is also wrong to treat all of them.

Financial Disclosures: Dr Caplan reports that he has been an ad hoc consultant or advisory board member for Bayer, Bristol-Myers Squibb–Sanofi Synthelabo, and Boehringer-Ingelheim.

Additional Contributions: We thank the patient for sharing his story and for providing permission to publish it.

REFERENCES

- Parodi JC, Schönholz C, Parodi FE, Sicard G, Ferreira LM. Initial 200 cases of carotid artery stenting using a reversal-of-flow cerebral protection device. *J Cardiovasc Surg (Torino)*. 2007;48(2):117-124.
- Parodi JC, Ferreira LM, Sicard G, La Mura R, Fernandez S. Cerebral protection during carotid stenting using flow reversal. *J Vasc Surg*. 2005;41(3):416-422.
- Parodi JC, Schönholz C, Parodi FE, Sicard G, Ferreira LM. Initial 200 cases of carotid artery stenting using a reversal-of-flow cerebral protection device. *J Cardiovasc Surg (Torino)*. 2007;48(2):117-124.
- Gorelick PB, Caplan LR, Hier DB, et al. Racial differences in the distribution of anterior circulation occlusive disease. *Neurology*. 1984;34(1):54-59.
- Caplan LR, Gorelick PB, Hier DB. Race, sex, and occlusive cerebrovascular disease: a review. *Stroke*. 1986;17(4):648-655.
- Fisher CM, Ojemann RG. A clinico-pathological study of carotid endarterectomy plaques. *Rev Neurol (Paris)*. 1986;142(6-7):573-589.
- Fisher M, Paganini-Hill A, Martin A, et al. Carotid plaque pathology: thrombosis, ulceration, and stroke pathogenesis [published correction appears in *Stroke*. 2005;36(10):2330]. *Stroke*. 2005;36(2):253-257.
- Caplan LR, Hennerici M. Impaired clearance of emboli (washout) is an important link between hypoperfusion, embolism, and ischemic stroke. *Arch Neurol*. 1998;55(11):1475-1482.
- Caplan LR, Wong K-S, Gao S, Hennerici MG. Is hypoperfusion an important cause of strokes? if so, how? *Cerebrovasc Dis*. 2006;21(3):145-153.
- Caplan LR. *Caplan's Stroke: A Clinical Approach*. 3rd ed. Boston, MA: Butterworth-Heinemann; 2000.
- Fisher CM. Facial pulses in internal carotid artery occlusion. *Neurology*. 1970;20(5):476-478.
- Caplan LR. The frontal artery sign. *N Engl J Med*. 1973;288(19):1008-1009.
- Hollenhorst RW. Ocular manifestations of insufficiency or thrombosis of the internal carotid artery. *Am J Ophthalmol*. 1959;47(6):753-767.
- Fisher CM. Observations of the fundus oculi in transient monocular blindness. *Neurology*. 1959;9(5):333-347.
- Kearns TP, Hollenhorst RW. Venous-stasis retinopathy of occlusive disease of the carotid artery. *Proc Staff Meet Mayo Clin*. 1963;38:304-312.
- Carter JE. Chronic ocular ischemia and carotid vascular disease. In: Bernstein EF, ed. *Amaurosis Fugax*. New York, NY: Springer; 1988:118-134.
- Kern R, Szabo K, Hennerici M, Meairs S. Characterization of carotid artery plaques using real-time compound B-mode ultrasound. *Stroke*. 2004;35(4):870-875.
- Landry A, Spence JD, Fenster A. measurement of carotid plaque volume by 3-dimensional ultrasound. *Stroke*. 2004;35(4):864-869.
- Forteza AM, Krejza J, Koch S, Babikan VL. Ultrasound imaging of cerebrovascular disease. In: Babikan V, Wechsler LR, Higashida RT. *Imaging Cerebrovascular Disease*. Boston, MA: Butterworth-Heinemann; 2003:3-35.
- Markus H. Transcranial Doppler detection of circulating cerebral emboli: a review. *Stroke*. 1993;24(8):1246-1250.
- Siebler M, Nachtmann A, Sitzer M, et al. Cerebral microembolism and the risk of ischemia in asymptomatic high-grade internal carotid artery stenosis. *Stroke*. 1995;26(11):2184-2186.
- Molloy J, Markus HS. Asymptomatic embolization predicts stroke and TIA risk in patients with carotid artery stenosis. *Stroke*. 1999;30(7):1440-1443.
- Mittl RL, Broderick M, Carpenter JP, et al. Blinded-reader comparison of magnetic resonance angiography and Duplex ultrasonography for carotid artery bifurcation stenosis. *Stroke*. 1994;25(1):4-10.
- Levi CR, Mitchell A, Fitt G, Donnan GA. The accuracy of magnetic resonance angiography in the assessment of extracranial carotid artery occlusive disease. *Cerebrovasc Dis*. 1996;6:231-236.
- Gillard JH. Advances in atheroma imaging in the carotid. *Cerebrovasc Dis*. 2007;24(suppl 1):40-48.
- Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med*. 1996;335(14):1001-1009.
- Nissen SE, Tuzcu M, Schoenhagen P, et al; Reversal of Atherosclerosis With Aggressive Lipid Lowering (REVERSAL) Investigators. Statin therapy, LDL cholesterol, C-reactive protein, and coronary artery disease. *N Engl J Med*. 2005;352(1):29-38.
- Hebert PR, Gaziano JM, Chan KS, Hennekens CH. Cholesterol lowering with statin drugs, risk of stroke, and total mortality: an overview of randomized trials. *JAMA*. 1997;278(4):313-321.
- Blauw GJ, Lagaay AM, Smelt AHM, et al. Stroke, statins, and cholesterol: a meta-analysis of randomized placebo-controlled double-blind trials with HMG-CoA reductase inhibitors. *Stroke*. 1997;28(5):946-950.
- Bucher HC, Griffith LE, Guyatt GH. Effect of HMG-CoA reductase inhibitors on stroke: a meta-analysis of randomized controlled trials. *Ann Intern Med*. 1998;128(2):89-95.
- Amarenco P, Bogousslavsky J, Callahan A III; Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators. High-dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med*. 2006;355(6):549-559.
- Amarenco P, Goldstein LB, Szarek M, et al; SPARCL Investigators. Effects of intense low-density lipoprotein cholesterol reduction in patients with stroke or transient ischemic attack. *Stroke*. 2007;38(12):3198-3204.
- Furberg CD, Adams HP, Applegate WB, et al; Asymptomatic Carotid Artery Progression Study (ACAPS) Research Group. Effect of lovastatin on early carotid atherosclerosis and cardiovascular events. *Circulation*. 1994;90(4):1679-1687.
- Hodis HN, Mack WJ, LaBree L, et al. Reduction in carotid arterial wall thickness using lovastatin and dietary therapy: a randomized controlled clinical trial. *Ann Intern Med*. 1996;124(6):548-556.
- Diener HC. Antiplatelet agents and randomized trials. *Rev Neurol Dis*. 2007;4(4):177-183.
- Caplan LR, Fisher M. The endothelium, platelets and brain ischemia. *Rev Neurol Dis*. 2007;4(3):113-121.
- Dzau V. The cardiovascular continuum and renin-angiotensin-aldosterone system blockade. *J Hypertens Suppl*. 2005;23(1):S9-S17.
- Lonn EM, Yusuf S, Dzavik V, et al. Effects of ramipril and vitamin E on atherosclerosis: the Study to Evaluate Carotid Ultrasound Changes in Patients Treated With Ramipril and Vitamin E (SECURE). *Circulation*. 2001;103:919-925.
- North American Symptomatic Carotid Endarterectomy Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. *N Engl J Med*. 1991;325(7):445-453.
- Barnett HJ, Taylor DW, Eliasziw M, et al; North American Symptomatic Carotid Endarterectomy Trial Collaborators. Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. *N Engl J Med*. 1998;339(20):1415-1425.
- European Carotid Surgery Trialists' Collaborative Group. Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). *Lancet*. 1998;351(9113):1379-1387.
- Biller J, Feinberg WM, Castaldo JE, et al. Guidelines for carotid endarterectomy: a statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association. *Stroke*. 1998;29(2):554-562.
- Rothwell PM, Eliasziw M, Gutnikov SA, et al; Carotid Endarterectomy Trial-

- ists' Collaboration. Analysis of pooled data from the randomised controlled trials of endarterectomy for symptomatic carotid stenosis. *Lancet*. 2003;361(9352):107-116.
44. Rothwell PM, Eliasziw M, Gutnikov SA, Warlow CP, Barnett HJ; Carotid Endarterectomy Trialists' Collaboration. Endarterectomy for symptomatic carotid stenosis in relation to clinical subgroups and timing of surgery. *Lancet*. 2004;363(9413):915-924.
 45. Morgenstern LB, Fox AJ, Sharpe BL, et al; North American Carotid Endarterectomy Trial (NASCET) Group. The risks and benefits of carotid endarterectomy in patients with near occlusion of the carotid artery. *Neurology*. 1997;48(4):911-915.
 46. Sundt TM, Sandok BA, Whisnant JP. Carotid endarterectomy complications and pre-operative assessment of risk. *Mayo Clin Proc*. 1975;50(6):301-306.
 47. Toronto Cerebrovascular Study Group. Risks of carotid endarterectomy. *Stroke*. 1986;17(5):848-852.
 48. Wade JG, Larson C, Hickey R, et al. Effect of carotid endarterectomy on carotid chemoreceptor and baroreceptor function in man. *N Engl J Med*. 1970;282(15):823-829.
 49. Lehv MS, Salzman E, Silen W. Hypertension complicating carotid endarterectomy. *Stroke*. 1970;1(5):307-313.
 50. Caplan LR, Skillman J, Ojemann R, et al. Intracerebral hemorrhage following carotid endarterectomy: a hypertensive complication. *Stroke*. 1978;9(5):457-460.
 51. Breen JC, Caplan LR, DeWitt LD, et al. Brain edema after carotid surgery. *Neurology*. 1996;46(1):175-181.
 52. Kerber CW, Cromwell LD, Loehden OL. Catheter dilatation of proximal carotid stenosis during distal bifurcation endarterectomy. *AJNR Am J Neuroradiol*. 1980;1(4):348-349.
 53. Meyers PM, Schumacher C, Higashida RT, Leary MC, Caplan LR. Use of stents to treat extracranial cerebrovascular disease. *Annu Rev Med*. 2006;57:437-454.
 54. Kachel R. Results of balloon angioplasty in the carotid arteries. *J Endovasc Surg*. 1996;3(1):22-30.
 55. Wholey MH, Wholey M, Mathias K, et al. Global experience in cervical carotid artery stent placement. *Catheter Cardiovasc Interv*. 2000;50(2):160-167.
 56. Kastrup A, Groschel K, Krapf H, et al. Early outcome of carotid angioplasty and stenting with and without cerebral protection devices: a systematic review of the literature. *Stroke*. 2003;34(3):813-819.
 57. Hofman R, Niessner K, Kypka A, et al. Risk score for peri-interventional complications of carotid artery stenting. *Stroke*. 2006;37(10):2557-2561.
 58. Endovascular versus surgical treatment in patients with carotid stenosis in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS): a randomised trial. *Lancet*. 2001;357(9270):1729-1737.
 59. McCabe DJ, Pereira AC, Clifton A, Bland JM, Brown MM; CAVATAS Investigators. Restenosis after carotid angioplasty, stenting, or endarterectomy in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS). *Stroke*. 2005;36(2):281-286.
 60. CARESS Steering Committee. Carotid revascularization using endarterectomy or stenting systems (CARESS): phase I clinical trial. *J Endovasc Ther*. 2003;10(6):1021-1030.
 61. Yadav JS, Wholey M, Kuntz KM, et al. Protected carotid-artery stenting versus endarterectomy in high-risk patients. *N Engl J Med*. 2004;351(15):1493-1501.
 62. Ringleb PA, Allenberg J, Brückmann H, et al; SPACE Collaborative Group. 30 Day results from the SPACE trial of stent-protected angioplasty versus carotid endarterectomy in symptomatic patients: a randomized non-inferiority trial. *Lancet*. 2006;368(9543):1239-1247.
 63. Mas J-L, Chatellier G, Beyssen B, et al; EVA-3S investigators. Endarterectomy versus stenting in patients with symptomatic severe carotid stenosis. *N Engl J Med*. 2006;355(16):1660-1671.
 64. Gurm HS, Yadav JS, Fayad P, et al; SAPHIRE Investigators. Long-term results of carotid stenting versus endarterectomy in high-risk patients. *N Engl J Med*. 2008;358(15):1572-1579.
 65. Cambria RP. Stenting for carotid-artery stenosis. *N Engl J Med*. 2004;351(15):1565-1567.
 66. Adami CA, Scuro A, Spinamano L, et al. Use of the Parodi anti-embolism system in carotid stenting: Italian trial results. *J Endovasc Ther*. 2002;9(2):147-154.
 67. Hobson RW II, Howard VJ, Roubin GS, et al; CREST Investigators. Carotid artery stenting is associated with increased complications in octogenarians: 30-day stroke and death rates in the CREST lead-in phase. *J Vasc Surg*. 2004;40(6):1106-1111.
 68. Caplan LR. Evidence-based medicine: concerns of a clinical neurologist. *J Neurol Neurosurg Psychiatry*. 2001;71(5):569-576.
 69. Thibault GE. Clinical problem solving: too old for what? *N Engl J Med*. 1993;328(13):946-950.
 70. Caplan LR. Is the promise of randomized controlled trials ("evidence-based medicine") overstated? *Curr Neurol Neurosci Rep*. 2002;2(1):1-8.
 71. Caplan LR. A 79-year-old musician with asymptomatic carotid artery disease. *JAMA*. 1995;274(17):1383-1389.
 72. Perry JR, Szalai JP, Norris JW; Canadian Stroke Consortium. Consensus against both endarterectomy and routine screening for asymptomatic carotid artery stenosis. *Arch Neurol*. 1997;54(1):25-28.
 73. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. Endarterectomy for symptomatic carotid artery stenosis. *JAMA*. 1995;273(18):1421-1428.