

## Inferior Mesenteric, Jejunal, Ileal, and Colic Artery Aneurysms

### Etiology

Aneurysms of the inferior mesenteric and colic arteries are extremely rare, usually anecdotally reported in the literature, and have no clear treatment modalities beyond lifesaving intervention in the setting of free rupture. Most reported lesions are small (<1 cm) compared with other visceral aneurysms.<sup>44,121,159</sup> Literature review and large case series estimate that inferior mesenteric branch aneurysms comprise less than 3% of all reported visceral artery aneurysms.<sup>12,44,160</sup> The etiologies of these aneurysms remain poorly defined, with inflammation and infection associated with one-third of the cases. A large series from the Mayo Clinic reported eight patients with these mesenteric branch aneurysms, adding that most of these had a significant smoking history and used alcohol.<sup>15</sup> Two of the three females reported a history of multiple pregnancies, but no true relationship with multiparity and these aneurysms has been established. A recent literature review showed a male-to-female predominance of nearly 5 to 1.<sup>161</sup> There is also an association with inferior mesenteric branch aneurysm formation and stenosis or occlusion of the SMA and celiac trunk.<sup>162</sup>

### Clinical Presentation

Inferior mesenteric, jejunal, ileal, and colic artery aneurysms can rupture freely into the peritoneal cavity or into adjacent intestinal segments, causing gastrointestinal hemorrhage. When rupture occurs, the mortality has been reported to be close to 20%.<sup>12</sup> Abdominal pain and hypovolemic shock are seen in approximately 85% of cases. In one series, 50% of patients presented with symptoms, whereas the other aneurysms were found incidentally.<sup>15</sup> Diagnosis can be made with cross-sectional imaging. As with other ruptured visceral aneurysms, diagnosis is often made at the time of laparotomy.

### Treatment

Current guidelines recommend elective intervention for jejunal and ileal artery aneurysms >2 cm and for all colic artery aneurysms regardless of size. Preoperative arteriography can aid in identification of the lesion and operative planning.<sup>161,163</sup> Open surgical treatment usually involves aneurysmectomy, particularly in the setting of IMAs or ligation. Cases of endovascular treatment have been limited due to the scarcity of these lesions. Treatment results have generally been favorable, with few reported technical failures.<sup>15,164</sup> Successful treatment with endovascular intervention has been reported in the setting of rupture.<sup>165</sup>

## Visceral Venous Aneurysms

Aneurysms of the visceral veins are extremely rare and seldom encountered in the clinical setting. A meta-analysis of the English and French literature identified 93 reports wherein 176 patients with 198 visceral venous aneurysms were described.<sup>166</sup> Aneurysms are usually located at the main portal vein, the junction

of the superior mesenteric and splenic veins, or the hepatic hilus.<sup>167,168</sup> Thrombosis, adjacent organ compression, and rupture are rare complications. The majority of these lesions can be followed with serial imaging. Open aneurysmorrhaphy or aneurysmectomy is indicated for symptomatic cases, thrombosis, adjacent organ compression, or rupture. Cases involving aneurysms of the splenic vein often require concomitant splenectomy and distal pancreatectomy. The role for endovascular intervention remains undefined.

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# Cerebrovascular Disease: Epidemiology and Natural History

CARON B. ROCKMAN and THOMAS S. MALDONADO

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## BACKGROUND

Until fairly recently, stroke was largely believed to be a result solely of intracranial pathology. William Osler attributed stroke mainly to intracranial hemorrhage or vasospasm and made no mention of carotid or vertebral artery occlusive disease.<sup>1</sup> Yet the relationship between extracranial carotid disease and stroke had been surmised previously as early as 1875, when Gowers reported on a patient with carotid occlusion, left visual loss, and right hemiplegia.<sup>2</sup> Subsequently, in 1905, Chiari studied 400 consecutive autopsies and discovered thrombus superimposed on carotid artery atherosclerotic plaque in seven patients, four of whom had suffered embolic strokes.<sup>3</sup> This important

observation likely represented the first description linking carotid plaque atheroembolism to ischemic stroke. Perhaps the greatest breakthrough in the study of the pathophysiology of cerebrovascular disease was Fisher's publication of clinic-anatomic correlations on occlusion of the carotid arteries in 1951 and 1954.<sup>4,5</sup> He specifically describes the atherosclerotic plaque as the culprit lesion in carotid artery disease and importantly notes that the distal internal carotid artery (ICA) is usually free of disease, raising the possibility of surgical bypass to a healthy target vessel. In 1954, Eastcott et al. reported on the first successful carotid surgery for occlusive disease, in which the carotid bifurcation was resected and in-line flow restored via a common carotid-to-ICA anastomosis.<sup>6</sup> The first successful

carotid endarterectomy (CEA) was performed by DeBakey in 1953 and reported along with a 19-year symptom-free follow-up in 1975.<sup>7,8</sup> In the 1990s, several randomized clinical trials clearly demonstrated the safety and effectiveness of CEA but also its superiority to contemporaneous medical treatment in both symptomatic as well as certain asymptomatic patients.<sup>9–13</sup>

## STROKE

### Background

Stroke, or cerebral infarction, is the acute development of a focal neurologic deficit caused by disruption of the blood supply to an area of the brain. Strokes can be ischemic, due to occlusion of a blood vessel or other causes of malperfusion, or hemorrhagic, due to rupture of a blood vessel.<sup>14</sup> The majority of strokes in the United States, approximately 87%, are in fact ischemic in etiology.<sup>14</sup> Extracranial cerebrovascular disease consisting of atherosclerotic occlusive disease of the carotid artery is considered to be one of the key preventable causes of ischemic stroke, along with atrial fibrillation and hypertension. Stroke is defined as an acute neurologic dysfunction of vascular etiology with corresponding signs and symptoms lasting more than 24 hours and resulting from infarction of focal areas of the brain. Ischemic stroke related to the carotid artery can present with sudden contralateral sensorimotor loss, speech deficit, and ipsilateral monocular blindness. In a transient ischemic attack (TIA), the ischemic parenchyma recovers and returns function to baseline. The full clinical impact of a stroke is often not apparent for up to 2 weeks, as the ischemic penumbra either recovers or evolves to infarction.

### Costs of Stroke

The estimated total direct and indirect cost of stroke in the United States in 2014–2015 was \$45.5 billion.<sup>15</sup> Between 2015 and 2035 total direct medical stroke-related costs are projected to more than double, from \$36.7 billion to \$94.3 billion, with the majority of the increase arising from the care of octogenarians.<sup>15</sup> The total cost of stroke care from 2005 to 2050 is projected to be approximately \$1.52 trillion for non-Hispanic white patients, \$313 billion for Hispanic patients, and \$379 billion for black patients.<sup>16–18</sup>

### Prevalence and Incidence

#### Stroke Prevalence

Stroke is among the major causes of mortality and disability worldwide; it is estimated that in 2013 the prevalence of stroke was 25.7 million, with 10.3 million people experiencing a first stroke.<sup>19</sup> Stroke causes 5.5 million deaths and over 44 million disabilities every year.<sup>20</sup> In the United States alone, a stroke occurs approximately every 40 seconds; this translates into about 2160 strokes each day. Each year, approximately 800,000 Americans suffer a stroke.<sup>14</sup> An estimated 70 million Americans ≥20 years of age self-report having had a stroke.<sup>15</sup> The overall stroke prevalence or proportion of the population

affected by stroke relative to the population as a whole in the United States during the years 2013–2016 was approximately 2.5%.<sup>15</sup> The prevalence of additional but clinically silent cerebral infarction is estimated to range from 6% to 28%.<sup>17,21–23</sup> Projections show that by 2030, an additional 3.4 million people will have had a stroke, a 20.5% increase in prevalence from 2012.<sup>15,24,25</sup>

The prevalence of stroke varies with the population studied, depending upon age, ethnicity, sex, and risk-factor profile (Figs. 88.1 and 88.2).<sup>17</sup> The prevalence of ischemic stroke increases with age in both men and women. In the United States, the prevalence of stroke is 6% among American Indian/Alaska Native populations, 4.0% among blacks, 2.6% among Hispanics, 2.3% among whites, and 1.6% among Asians.<sup>26</sup>

#### Stroke Incidence

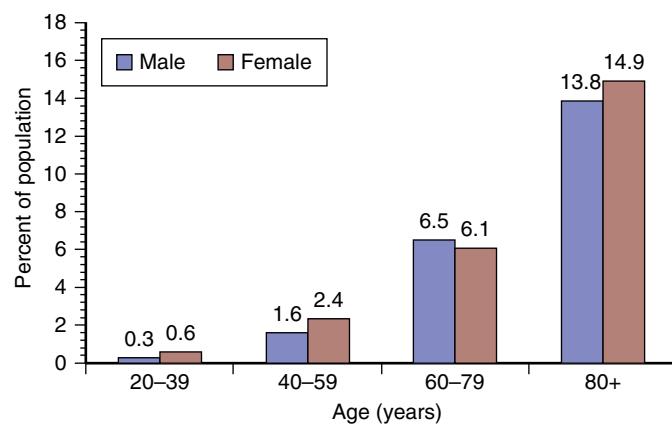
Each year in the United States approximately 800,000 people experience a new or recurrent stroke,<sup>15</sup> and approximately 185,000 are recurrent strokes.<sup>15</sup> Although women have a lower age-adjusted stroke incidence than men, women have a higher lifetime risk of stroke than men because of their longer life expectancy.<sup>15,27,28</sup> African Americans have a risk of first-ever stroke twice that of whites.<sup>15,27</sup> Data from the Framingham Heart Study indicate that the age-adjusted incidence of clinical stroke per 1000 person-years in 1950 to 1977, 1978 to 1989, and 1990 to 2004 was 7.6, 6.2, and 5.3 in men and 6.2, 5.8, and 5.1 in women, respectively.<sup>27</sup> Analysis of data from the Framingham Study additionally suggests that stroke incidence is declining over time in this largely white cohort,<sup>29</sup> although a similar decline was not noted in African Americans.

#### Trends in the Prevalence/Incidence of Stroke

Currently stroke is the fifth leading cause of death in the United States when considered separately from other cardiovascular diseases.<sup>24,30,31</sup> Several additional population-based studies have tracked stroke incidence during recent decades.<sup>32</sup> Rothwell et al. reported a decrease in stroke incidence of nearly 40% between the 1980s and 2002 in the United Kingdom.<sup>33</sup> In an additional report from the American Heart Association, the lifetime risk of stroke in a 65-year-old male decreased from 19.5% 50 years ago to 14.5% in 2013.<sup>34,35</sup> In the United States, the Framingham cohort and the Greater Cincinnati/Northern Kentucky Stroke Study (GCNKSS) also found that the incidence of stroke has been declining over the past 50 years.<sup>27,32</sup> In contrast to the prior reports, the Minnesota Stroke Study noted that the incidence of stroke appeared to be stable in both men and women between the years 1990 and 2000.<sup>36</sup>

In a 2012 report from the Atherosclerosis Risk in Communities Study (ARIC) including 14,357 participants between 1987 and 2011, stroke was diagnosed in 1051 (7%). The incidence was strongly related to older age, male sex, black race, hypertension, diabetes, coronary heart disease, and current smoking, and was negatively associated with the use of cholesterol-lowering medications. Stroke incidence decreased over time in both white and black subjects. The decrease in age-adjusted incidence was evident in participants aged 65 years and older but not in younger subjects, but was similar by sex. Additionally,

mortality after stroke was noted to decrease over time. The authors concluded that there was a demonstrable decrease in stroke incidence and mortality rates in the United States during this time period.<sup>37</sup> In a report from the Centers for Disease Control and Prevention (CDC) Behavioral Risk Factor Surveillance System in the years 2005 and 2008, the prevalence of stroke in the United States was 2.6%.<sup>38</sup> After a comprehensive review of multiple population-based studies, it was not possible to prove or disprove whether the prevalence of stroke may be decreasing, although it was felt that there was abundant evidence that the mortality attributable to acute stroke is decreasing, likely related to improvements in acute stroke treatment.<sup>38</sup> It was furthermore noted that an increase in the burden of stroke due to the aging populations of both the United States and European countries was still to be expected.

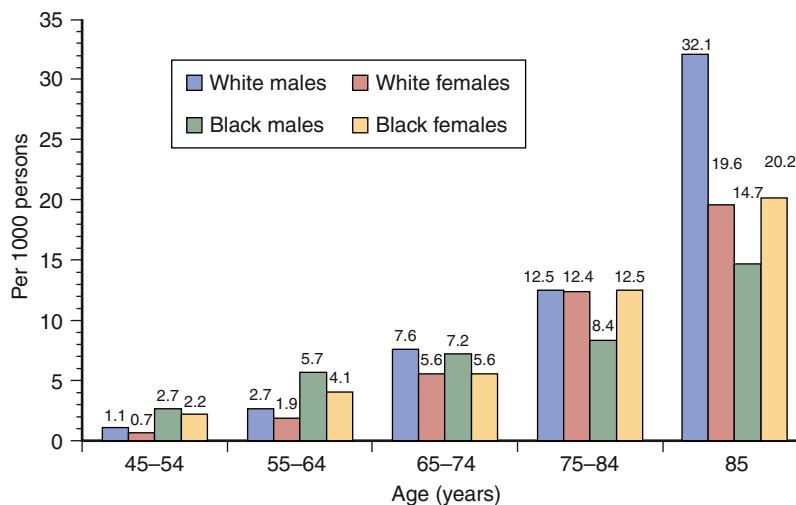


**Figure 88.1** Prevalence of stroke by age and sex. (National Health and Nutrition Examination Survey: 2011–2014). (From Benjamin EJ, et al. Heart disease and stroke statistics–2017 update: a report from the American Heart Association. *Circulation*. 2017;135:e146–e603. Used with permission.)

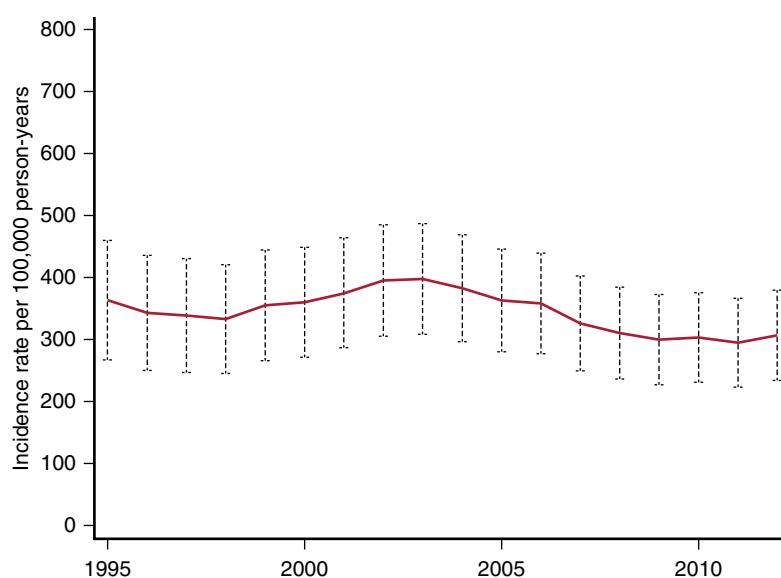
More recent data from the GCNKSS reported in 2017 showed that decreases in stroke incidence over time have been driven primarily by a decrease in ischemic stroke in men as opposed to women. In contrast to their reports from prior study periods, stroke incidence rates were noted to be similar by sex in 2010.<sup>39</sup>

In a recent update from the Tromso Study, from 1995 to 2012 the influence of improved risk factor control on the possibly declining incidence of stroke was examined.<sup>40</sup> Over the period from 1995 to 2012, the incidence of ischemic stroke decreased from 363 per 100,000 person-years to 306 per person-years<sup>40</sup> (Fig. 88.3). Changes in cardiovascular risk factors were found to account for 57% of the decrease in ischemic stroke incidence. The most important contributors were decreasing mean systolic blood pressure and smoking prevalence. Changes in total cholesterol levels surprisingly did not contribute significantly to the decline in the incidence of ischemic stroke.<sup>40</sup>

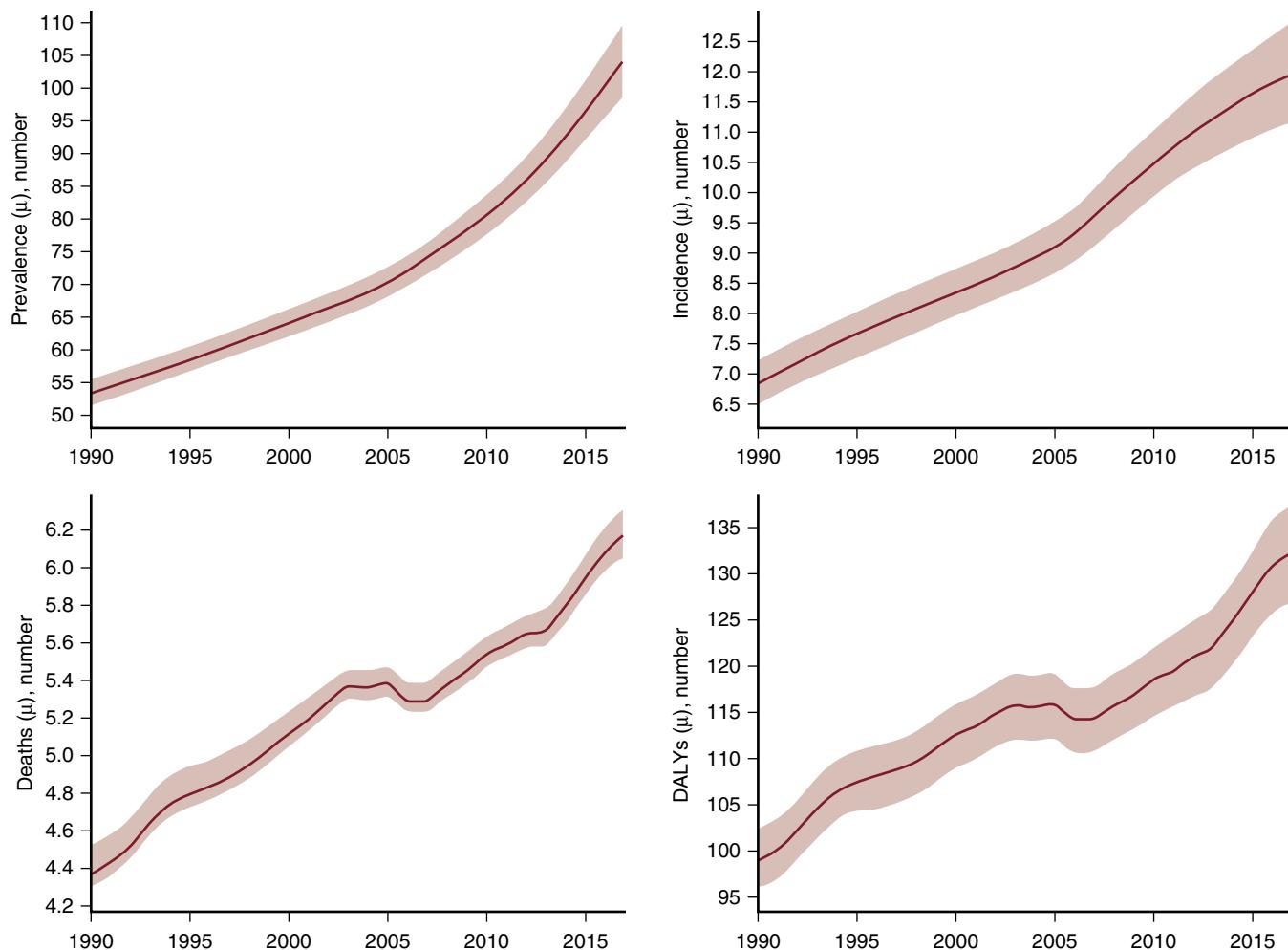
Not all relevant studies have definitively shown a decrease in stroke incidence or prevalence. Data from the Nationwide Inpatient Sample from 1995 through 2012 reveals that rates of hospitalization in the United States for acute ischemic stroke almost doubled for males aged 18–44 years.<sup>41</sup> In the Global Burden of Disease Study in 2016, there was a 2.7% overall increase in ischemic stroke prevalence worldwide from 2006 to 2016.<sup>15</sup> Regional decreases in the incidences of ischemic stroke were noted primarily in high-income countries. No significant change was seen in low- or middle-income countries.<sup>42</sup> Even more recent data in 2020 from the Global Burden of Disease Study has reported that although stroke incidence, prevalence, mortality and disability-adjusted life years did in fact decline from 1990 to 2017, the *absolute* number of people who developed new stroke, died, survived or remained disabled from stroke has almost doubled<sup>43</sup> (Fig. 88.4). The authors note



**Figure 88.2** Annual incidence of first cerebral infarction by age, sex, and race (Greater Cincinnati/Northern Kentucky Stroke Study: 1999). Rates for black men and women 45 to 54 years of age and for black men 75 years of age and above are considered unreliable. GCNKSS, Greater Cincinnati/Northern Kentucky Stroke Study. (From Unpublished data from the Greater Cincinnati/Northern Kentucky Stroke Study; From Benjamin EJ, et al. Heart disease and stroke statistics–2017 update: a report from the American Heart Association. *Circulation*. 2017;135:e146–e603. Used with permission.)



**Figure 88.3** Trends in annual incidence rates of ischemic stroke in participants aged  $\geq 30$  years. The Tromso Study, 1995 to 2012. (From Vangen-Lonne AM, et al. Declining Incidence of Ischemic Stroke: What Is the Impact of Changing Risk Factors? The Tromso Study 1995 to 2012. *Stroke* 2017;48:544–550.)



**Figure 88.4** Changes in age-specific stroke incidence, mortality and disability-adjusted life-year rates per 100,000 by sex, from 1990–2017. (From Krishnamurthi RV, et al. Global, Regional and Country-Specific Burden of Ischaemic Stroke, Intracerebral Haemorrhage and Subarachnoid Haemorrhage: A Systematic Analysis of the Global Burden of Disease Study 2017. *Neuroepidemiology* 2020;54:171–179.)

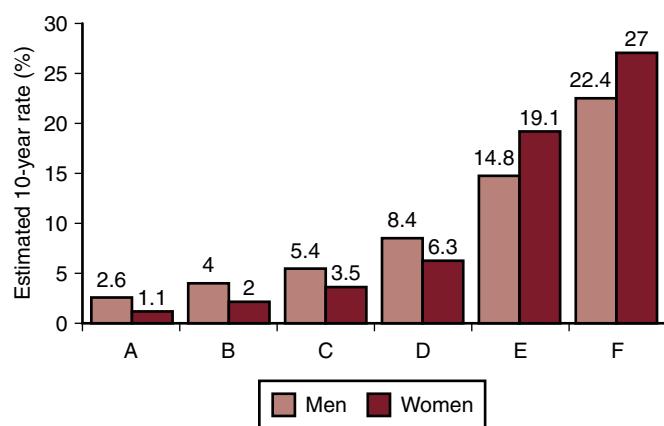
that this most recent data should supersede previous findings; stroke remains the second leading cause of death and disability worldwide.<sup>43</sup>

### Impact of Improved Medical Therapy on Stroke Incidence

Previous randomized trials have demonstrated a clear benefit of surgical therapy with CEA over contemporaneous medical therapy regarding stroke prevention in both asymptomatic and previously symptomatic patients with severe extracranial ICA stenosis.<sup>10,11,44</sup> However, recent analyses have additionally reported that the annual risk of stroke in patients with asymptomatic ICA stenosis is lower than that reported in the CEA trials, presumably due to improved medical therapy.<sup>45,46</sup> Nevertheless it remains clear that asymptomatic ICA stenosis continues to cause a significant number of strokes.<sup>47</sup> Data from the GCNKSS have resulted in conservative estimates that about 41,000 strokes may be attributed to previously asymptomatic extracranial ICA stenosis annually in the United States.<sup>47</sup> The increased usage of cholesterol-lowering medications is often cited as the likely reason behind the decreased incidence of stroke, despite evidence to the contrary from the Global Burden of Disease Study cited previously.<sup>43</sup>

The epidemiologic association between elevated cholesterol levels and stroke is inconsistent and somewhat controversial.<sup>48</sup> Treatment with statins was associated with stroke reduction in a meta-analysis of more than 90,000 patients.<sup>49</sup> It should be noted that many of the studies included in this meta-analysis involved secondary as opposed to primary stroke prevention. Nevertheless, the relative reduction in stroke risk was found to be 21%. Statins have also been demonstrated to be associated with a reduction in stroke incidence in a variety of specific patient populations, including those with known coronary artery disease,<sup>50</sup> hypercholesterolemia,<sup>50</sup> normocholesterolemia,<sup>50</sup> elderly patients,<sup>50</sup> and diabetics.<sup>51</sup> Statins have also been demonstrated to consistently reduce carotid intima-media thickness (CIMT).<sup>52</sup> A recent meta-analysis including over 113,000 patients has shown that the use of statin therapy at stroke onset is associated with improved late outcome, including both rates of functional independence and survival.<sup>53</sup> Although data regarding the utility of statin medications for the primary prevention of stroke is less conclusive than for secondary prevention, current guidelines do in fact recommend statins for the prevention of first stroke in high-risk patients, including those with LDL levels greater than 4.1 mmol/L and for males older than age 45 and females older than age 55 with the following risk factors: a positive family history, smoking, hypertension, or left ventricular hypertrophy.<sup>48</sup> However, it is unclear what exact role and effect statins have in patients with known severe carotid occlusive disease with regard to stroke prevention.

In a report authored by Writing Group Members on behalf of the American Heart Association's Stroke Council, a clear decline in stroke mortality is noted,<sup>54</sup> and it is believed that this reduction is mainly due to the treatment of hypertension as opposed to antilipid therapy. The authors note that epidemiologic studies have shown that elevated blood pressure is the



**Figure 88.5** Estimated 10-year stroke risk in adults 55 years of age according to levels of various risk factors. *A*, Fib, atrial fibrillation; *BP*, blood pressure; *CVD*, cardiovascular disease. (From Benjamin EJ, et al. Heart disease and stroke statistics; 2017 update: a report from the American Heart Association. *Circulation*. 2017;135:e146–e603. Used with permission.)

most important determinant of the risk of stroke.<sup>54</sup> This report echoes the Tromso Study, which noted that while changes in cardiovascular risk factors were found to account for 57% of the decrease in ischemic stroke incidence, the most important factor was felt to be improved control of hypertension.<sup>40</sup>

## ISCHEMIC STROKE

### Risk Factors for Stroke

The risk factors for ischemic stroke include many of the risk factors for generalized atherosclerosis (Fig. 88.5).<sup>14,17,55</sup> In addition to these risk factors for ischemic stroke, prior TIA and carotid artery atherosclerosis represent obvious major clinical risk factors for future ischemic stroke. The following factors have been clearly shown to be related to the risk of stroke in the general population:

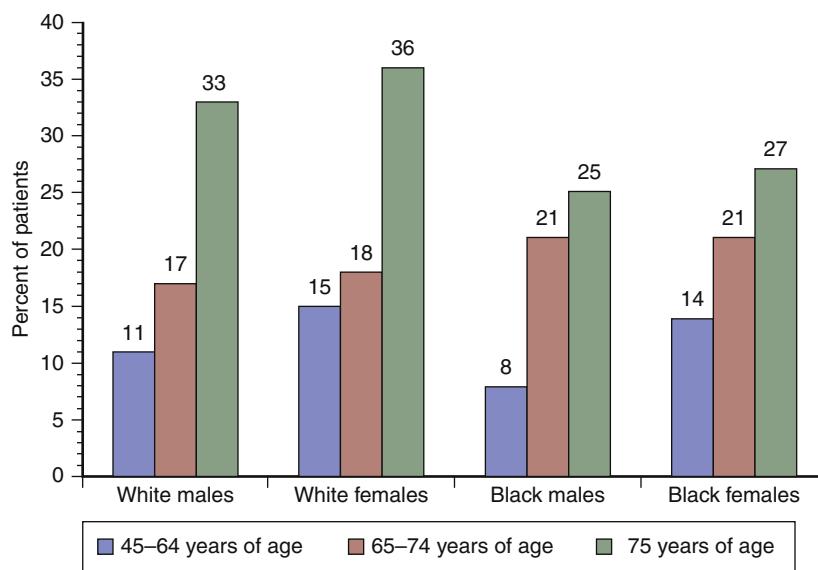
- **Sex:** The estimated 10-year stroke risk in adults 55 years of age and older differs by sex and the increasing presence of multiple risk factors.<sup>24</sup> Ischemic stroke is in general more prevalent in men than in women.<sup>56</sup> However, women tend to account for a higher percentage of stroke mortalities, likely because of greater longevity.<sup>14</sup> Additional factors unique to women that may play a role in stroke include differences in sex hormones, exogenous estrogens, and pregnancy exposure.<sup>57</sup> Females accounted for 58% of stroke deaths in the U.S. in 2016, largely because of age at time of stroke being older in females than males.<sup>15</sup>
- **Age:** Increasing age is a major risk factor for ischemic stroke. For each decade after 55 years of age, the risk of stroke approximately doubles.<sup>58</sup>

- **Race:** Blacks and Hispanics have a risk of first-ever stroke that is approximately twice that of whites.<sup>59</sup> Blacks may have a lower prevalence of carotid artery disease than whites, and it is hypothesized that the increased stroke rate among black patients is more likely related to hypertension and intracranial disease.<sup>60</sup>
  - **Hypertension:** Hypertension is a significant risk factor for both ischemic stroke and intracranial hemorrhage (see Ch. 14, Hypertension).<sup>24</sup> Appropriate treatment of blood pressure in hypertensive patients is associated with a significant reduction in the risk of ischemic stroke; patients with a blood pressure less than 120/80 have half the lifetime risk of stroke than subjects with hypertension.<sup>17,61</sup> So-called intensive blood pressure control as opposed to standard treatment has also resulted in a significantly lower risk of stroke.<sup>62</sup> Strict blood pressure control can also reduce the risk of recurrent stroke.<sup>63</sup>
  - **Family history:** A parental history of stroke, TIA, or myocardial infarction is associated with a 1.4- to 3.3-fold increased risk for stroke.<sup>64</sup>
  - **Atrial fibrillation:** Patients with atrial fibrillation have a three- to five-fold increased risk of cardioembolic ischemic stroke.<sup>65</sup>
  - **Cigarette smoking:** Current cigarette smokers have a two to four times increased risk of stroke as compared with non-smokers or those who have quit for more than 10 years (see Ch. 11, Smoking).<sup>17,66,67</sup> Discontinuation of smoking reduces future stroke risk in multiple demographic patient categories.<sup>68</sup> In a large cohort of black patients, current cigarette smoking was associated with a dose-dependent higher risk of all stroke. Past smokers did not have a significantly increased risk of stroke compared with never smokers, suggesting that smoking cessation helped to reduce the incidence of stroke.<sup>69</sup>
  - **Hypercholesterolemia:** Trials specific to ischemic stroke have demonstrated that there may be a 25% increased risk of ischemic stroke with each 38.7 mg/dL increase in total cholesterol levels,<sup>70</sup> although not all trials have consistently demonstrated a correlation between hypercholesterolemia and ischemic stroke (see Ch. 13, Hyperlipidemia).<sup>14,24</sup>
  - **Physical activity:** Increased leisure-time physical activity is protective against stroke across race, sex, and age, and related to the level of intensity and the duration of activity.<sup>71</sup> In the REGARDS study, participants who reported physical activity less than four times a week had a 20% increase in stroke risk as compared with those who exercised more than four times a week. However, it is possible that this is related to the fact that physical activity also improves traditional risk factors such as diabetes and obesity.<sup>24,72</sup>
  - **Diabetes:** Diabetes is a risk factor for ischemic stroke at all ages, but the most significant risk increase appears to occur among patients less than 65 years of age.<sup>24</sup> Diabetes mellitus nearly doubles the risk of stroke compared with others who have normal glucose levels.<sup>73</sup> The effect of diabetes on stroke risk appears to be more significant in women than in men.<sup>74</sup> Intensive glucose control did not appear to result in reduced stroke risk as compared with conventional glucose control (see Ch. 12, Diabetes).<sup>75</sup> Diabetes is also associated with post-stroke dementia.<sup>76</sup>
  - **Diet:** A protective relationship between fruit and vegetable consumption and decreased ischemic stroke risk has been reported.<sup>77</sup> A Mediterranean-style diet higher in the consumption of nuts and olive oil has been shown to be associated with a reduced risk of stroke.<sup>78</sup>
  - **Obesity:** Obesity (BMI >30) is a specific risk factor for ischemic stroke in both men and women.<sup>79,80</sup> There is an additional association between abdominal obesity and ischemic stroke in men.<sup>81</sup>
  - **Alcohol:** There is a reported increased risk of ischemic stroke with “irregular” drinking, including heavy and binge drinking.<sup>82</sup> However, moderate drinking may be associated with a decreased risk of ischemic stroke.<sup>83</sup>
  - **Renal insufficiency:** Mild to moderate renal insufficiency is an independent predictor of ischemic stroke in both asymptomatic patients and patients with peripheral arterial disease.<sup>84–86</sup>
  - **Socioeconomic status:** Low socioeconomic status appears to be an independent risk factor for stroke mortality.<sup>87</sup>
  - **COVID-19 pandemic:** During the writing of this chapter, it has become apparent that infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) appears to be related to both arterial and venous thrombotic events, and is a significant risk factor for stroke, particularly in younger patients.<sup>88</sup>
- The INTERSTROKE study, in 2010, reported a case-control study of 2337 ischemic stroke cases in 22 countries worldwide. Patients with an acute first stroke were compared with controls with no history of stroke and were matched for both age and sex.<sup>55</sup> The authors found that five factors accounted for more than 80% of the global risk of all ischemic strokes: hypertension, current smoking, abdominal obesity, poor diet, and physical inactivity.<sup>55</sup> Hypertension was the most important risk factor for all stroke subtypes.<sup>55,89</sup>

## Outcome of Stroke

Following an ischemic stroke, the risk for recurrent ischemic stroke is 2% at 7 days, 4% at 30 days, 12% at 1 year, and 29% at 5 years.<sup>90</sup> The risk of death after an initial ischemic stroke is 7% at 7 days, 14% at 30 days, 27% at 1 year, and 53% at 5 years (Fig. 88.6).<sup>90</sup> Somebody in the United States dies every 4 minutes from a stroke,<sup>17,91</sup> and strokes account for 1 out of every 18 deaths.<sup>17,91</sup> When considered separately from other cardiovascular diseases, stroke currently ranks fifth among all causes of death, behind heart disease, cancer, and chronic lower respiratory disease.<sup>17,91,92</sup>

Stroke is the leading cause of serious long-term disability in the United States.<sup>17,93</sup> Among ischemic stroke survivors who were 65 years of age or older, the following disabilities were observed at 6 months after a stroke: 50% had hemiparesis, 30% were unable to walk without assistance, 26% were dependent in activities of daily living, 19% had aphasia, 35% had depressive symptoms, and 26% were institutionalized.<sup>17,94</sup> In data from the Carotid Revascularization Endarterectomy Versus



**Figure 88.6** Probability of death within 1 year after first stroke. (Reprinted with permission *Circulation*. 2017;135:e146–e603. ©2017 American Heart Association, Inc.)

Stenting Trial (CREST), the estimated 4-year mortality after stroke was 21.1%, compared with 11.6% for those without stroke, including those who had undergone carotid revascularization. The adjusted risk of death at 4 years was higher after periprocedural stroke (hazard ratio, 2.78).<sup>95</sup>

Stroke may also be associated with long-term cognitive decline.<sup>96</sup> Although it is obvious that acute stroke may be responsible for acute changes in cognition, it has also been demonstrated that acute stroke is additionally associated with accelerated and persistent cognitive decline over 6 years (see Ch. 90, Carotid Artery Disease and Cognitive and Functional Decline).

### Recurrent Stroke Following an Initial Event

Patients who have experienced an initial stroke are additionally at greatly increased risk for subsequent events. Based upon a population cohort study of more than 10,000 patients discharged with a diagnosis of stroke, the rates of recurrent stroke were 1.8% at 1 month, 5% at 6 months, 8% at 1 year, and 18.1% at 4 years.<sup>97</sup> Recurrent stroke is associated with a greater number of baseline risk factors and with large artery occlusive disease as opposed to other causes of stroke.<sup>98,99</sup>

In the North American Symptomatic Carotid Endarterectomy Trial (NASCET), medically randomized patients with symptomatic carotid artery disease (stroke or TIA) and high-grade carotid stenosis experienced an ipsilateral stroke rate of 26% over 2 years.<sup>10</sup> Major or fatal ipsilateral stroke occurred in 13.1% of patients. In the 32-day period following randomization of medically treated symptomatic patients, 3.3% experienced stroke or death. In a large study of 500,000 Chinese adults who experienced an incident stroke, among patients who survived stroke at 28 days, 41% experienced a recurrent stroke at five years. After a first ischemic stroke, 91% of recurrent strokes were also ischemic in etiology.<sup>100</sup>

### Stroke Mortality

Stroke accounts for approximately 1 of every 20 deaths in the United States.<sup>24</sup> Data from the ARIC study revealed that all-cause mortality rate after a stroke was 10.5% at 30 days, 21.2% at 1 year, 39.8% at 5 years, and 58.4% at 24 years.<sup>37</sup> A CDC report found that among Medicare beneficiaries, the 30-day mortality following a stroke varied by age and ranged from 9% in patients 65 to 74 years of age to 23% in those over 85 years of age.<sup>101</sup>

## TRANSIENT ISCHEMIC ATTACK

### Background

A TIA, often referred to as a “ministroke,” is a neurologic event that presents with stroke-like symptoms less than 24 hours in duration. In fact, the vast majority of these symptoms last for only a few minutes. A TIA should be considered a warning sign for future stroke, as approximately 30% of patients who have had a TIA go on to suffer a stroke within 5 years.<sup>102</sup> It is important to note that a TIA is a clinical diagnosis; although neurologic baseline is restored within 24 hours, cell death may have occurred nonetheless. Indeed, brain computed tomography performed on 284 patients presenting with clinical TIA and without previous clinical stroke revealed demonstrable infarction in 24% of patients.<sup>103</sup>

Symptoms of TIA or stroke resulting from carotid disease are related to the cerebral vascular territory affected. The carotid artery supplies the anterior circulation; thus, carotid disease can result in symptoms associated with injury to brain parenchyma of the anterior cerebral artery or middle cerebral artery distribution. Motor symptoms can range from mild hemiparesis to complete hemiparalysis contralateral to the

affected hemisphere. Likewise, sensory deficits may consist of mild numbness or complete paresthesia of the contralateral extremities. Language loss (dysarthria, dysphasia, or aphasia) can occur when the dominant hemisphere is affected. Amaurosis fugax (transient monocular blindness or field cuts) resulting from emboli to the retinal artery via the ophthalmic artery, is considered to be the classic symptom of TIA related to carotid artery lesions. Unlike thromboemboli of cardiac origin, carotid emboli tend to present with TIAs rather than stroke. Moreover, TIAs of carotid artery origin tend to occur in the same vascular territory, whereas TIAs of cardioembolic origin are more haphazard in location and symptomatology.<sup>104,105</sup>

## Prevalence

As with stroke, the incidence of TIA increases with age and varies by sex and race/ethnicity.<sup>24</sup> Approximately 15% of all strokes are heralded by a TIA.<sup>106</sup> Patients who have had a TIA have a significant risk of subsequent stroke in the short term: among a cohort of patients seen in an emergency room with a TIA, 11% experienced a subsequent stroke within 90 days, and 5% experienced a subsequent stroke within 2 days.<sup>107</sup> The estimated incidence of self-reported or physician-diagnosed TIA in the United States is approximately 2.3%, but the true incidence is likely higher.<sup>17,107</sup> Additionally, the true prevalence of TIAs may actually be higher than reported because many patients who may experience subtle neurologic symptoms do not report them to a healthcare provider.<sup>24</sup>

## Natural History

The most important consideration in patients who have experienced a TIA is their future relevant stroke risk. The presence and diagnosis of a TIA, if found in the setting of ipsilateral and appropriate severity of carotid artery disease, offers the practitioner the opportunity to intervene to prevent subsequent stroke. Independent predictors of subsequent stroke following a TIA included age greater than 60 years, diabetes mellitus, the presence of focal symptoms, and TIAs that lasted longer than 10 minutes.<sup>17,107</sup> Individuals who experience a TIA and survive the initial high-risk period have a 10-year stroke risk of about 19%.<sup>17,108</sup> Two meta-analyses of TIA patients reported that the short-term risk of stroke following TIA was similar: 3% to 10% at 2 days, and 9% to 17% at 90 days.<sup>106,109</sup> Approximately one-third of episodes characterized as a TIA would probably be considered cerebral infarctions on the basis of diffusion-weighted magnetic resonance imaging (MRI) findings.<sup>17,10,111</sup> Because of the substantial risk of ischemic stroke following a TIA, patients with transient focal hemispheric symptoms should be expediently evaluated for the presence of significant carotid artery disease. In a study of more than 25,000 patients who were initially stable after a TIA or stroke, both clinical groups were at significant risk for recurrent stroke. Although patients who initially had a stroke were the higher-risk group, it is notable that 31.5% of TIA patients specifically experienced an adverse event within 5 years.<sup>112</sup>

# EXTRACRANIAL CAROTID ARTERY ATHEROSCLEROSIS

## Pathophysiology

Atherosclerotic plaque in the carotid artery causes a substantial proportion of ischemic strokes, but the mechanisms are less well understood than those of acute coronary thrombosis.<sup>113,114</sup> Carotid artery plaque can cause TIA or stroke by two mechanisms: embolization and hypoperfusion. Due to the abundant collateral circulation in the brain, global cerebral hypoperfusion is rare; it occurs only in patients with severe multivessel occlusive disease in both the carotid and vertebral artery territories. Atheroembolization of debris originating from carotid artery plaque and traveling to the brain is felt to be the predominant cause of both TIA and ischemic stroke related to carotid artery disease. Evidence for the role of embolization comes from the early reports of Hollenhorst, who found embolic debris in the retinal vessels of patients with transient monocular blindness.<sup>115</sup> The severity of carotid artery stenosis is strongly associated with stroke risk in symptomatic patients.<sup>12,113,116</sup> Currently it is the most important predictor of benefit from carotid artery intervention.<sup>117</sup> However, other factors predictive of stroke clearly exist, including plaque morphologic features (see Ch. 89, Cerebrovascular Disease: The Unstable Carotid Plaque).<sup>113,118,119</sup>

The degree of carotid artery stenosis is a critical factor involved in identifying patients at increased risk of future ischemic stroke. Although most asymptomatic patients with moderate degrees of carotid artery stenosis are at relatively low risk for future stroke, it is noteworthy that only 15% of ischemic strokes are preceded by a warning TIA. Therefore, waiting for a stenosis to become symptomatic fails to prevent most strokes caused by carotid artery disease, and highlights the critical need to improve the selection of asymptomatic patients for carotid intervention to prevent future strokes (Table 88.1).<sup>120–122</sup> The term “vulnerable” plaque is often used to denote unstable plaques, or plaques prone to complications, including embolization and subsequent stroke.

## Transcranial Doppler Detection of Microembolization

The detection of subclinical embolization may help to identify patients at high risk of future stroke.<sup>123</sup> Transcranial Doppler (TCD) testing involves the detection of microembolism in the MCA using TCD insonation; the detection of high-intensity transient signals (“HITS”) is felt to represent microemboli to the brain. HITS are detectable only in the presence of an embolic source, are undetectable days after CEA, and are absent in controls without carotid stenosis, suggesting a relationship between carotid atherosclerotic plaque and microembolization.<sup>121</sup> HITS frequency rises with increasing stenosis, and an increased rate of HITS is associated with plaque ulceration; this emphasizes the likely association between HITS and plaque instability.<sup>121</sup> Thus the concept of HITS represents an attractive option for stratifying patients with carotid artery disease who may be at

**TABLE 88.1**

Estimated Percent Risk of Ipsilateral Ischemic Cerebral Stroke Within 5 Years Based Upon Degree of Stenosis, History of Symptoms, and Plaque Characteristics

| Degree of Stenosis | History of Contralateral TIA or Stroke | DWAs Present | Plaque Area (mm <sup>2</sup> ) | GSM                |                    |                    |
|--------------------|--|--------------|--------------------------------|--------------------|--------------------|--------------------|
|                    |  |              |                                | >30                | 15–30              | <15                |
| 83% to 99% NASCET  | Present                                | Yes          | >80                            | 20.3% <sup>a</sup> | 52.8% <sup>a</sup> | <sup>b</sup>       |
|                    |  |              | 40–80                          | 13.8%              | 35.8%              | 70% <sup>a</sup>   |
|                    |  |              | <40                            | 7.8% <sup>a</sup>  | 20.1% <sup>a</sup> | <sup>b</sup>       |
|                    | Absent                                 | No           | >80                            | 13.3% <sup>a</sup> | 34.5% <sup>a</sup> | <sup>b</sup>       |
|                    |  |              | 40–80                          | 9% <sup>a</sup>    | <sup>b</sup>       | 45.7% <sup>a</sup> |
|                    |  |              | <40                            | 5.1% <sup>a</sup>  | 13.1% <sup>a</sup> | 25.7% <sup>a</sup> |
| Absent             | Yes                                    | Yes          | >80                            | 7.7% <sup>a</sup>  | 20%                | 39.1% <sup>a</sup> |
|                    |  |              | 40–80                          | 5.2%               | 13.5%              | 26.5%              |
|                    |  |              | <40                            | 2.9%               | 7.6%               | 14.9% <sup>a</sup> |
|                    | No                                     | No           | >80                            | 5% <sup>a</sup>    | 13% <sup>a</sup>   | 25.5% <sup>a</sup> |
|                    |  |              | 40–80                          | 3.4% <sup>a</sup>  | <sup>a</sup>       | 17.3%              |
|                    |  |              | <40                            | 1.9%               | 5%                 | 9.7% <sup>a</sup>  |

<sup>a</sup>Covariate combination, which occurred less than five times in observed data.

<sup>b</sup>Covariate combination, which did not occur in observed data.

DWAs, discrete white areas; GSM, gray scale median; NASCET, North American Symptomatic Carotid Endarterectomy Trial; TIA, transient ischemic attack.

Modified from Nicolaides AN, et al. Asymptomatic internal carotid artery stenosis and cerebrovascular risk stratification. *J Vasc Surg*. 2014;52:1486–1496. Used with permission.

increased risk for future stroke. In the Asymptomatic Carotid Emboli Study (ACES), the hazard ratio for stroke or TIA was 2.54 as compared with patients without embolic signals at baseline. The hazard ratio for ipsilateral stroke alone was 5.57.<sup>120</sup> The utility of TCD as a practical screening tool is limited by its time-consuming nature, the absence of a reliable automated emboli detection system, and a small proportion (10%) of subjects lack a cranial acoustic window needed for TCD.

## Types of Stroke

There are five general categories of ischemic stroke, according to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification: cardioembolic strokes, large vessel disease strokes, strokes due to small vessel disease, strokes related to unusual causes, and strokes of undetermined etiology.<sup>124</sup> Clinical studies on stroke subtype fail to identify a definitive cause of stroke in at least 25% to 39% of patients.<sup>125</sup> Traditionally it has been estimated that large vessel disease caused stroke in 50% of cases.<sup>125</sup> In a recently reported population-based study, the prevalence of large vessel occlusion in patients with acute ischemic stroke was found to be 29.2%.<sup>126</sup> Additional studies have reported that large vessel occlusions account for up to 46% of acute ischemic strokes.<sup>127</sup> Recent studies, however, have shown that small vessel disease is more frequent and large vessel disease less frequent than previously estimated.<sup>128</sup>

In the Rochester Epidemiology Project, for example, 442 patients with a first ischemic stroke from 1985 through 1989 were evaluated. Four major categories were identified: large vessel cervical or intracranial (16.7%), cardioembolic (29.9%),

lacunar (16.3%), and strokes of uncertain cause (37.1%). Therefore, the large vessel cervical etiology comprised approximately 16% of all ischemic strokes and 27% of strokes with determined causes. Interestingly, patients with large vessel strokes had the highest rates of recurrent stroke at 30 days (18.5%).<sup>129</sup>

In another study, 2204 patients with first-ever or recurrent ischemic stroke in the greater Cincinnati area in 2005 were identified, including 365 (16.6%) of the large vessel subtype. Carotid artery stenosis was associated with 8% of all ischemic strokes, while ICA occlusion was associated with an additional 3.5%. The annual rate of first-ever and recurrent stroke attributed to the extracranial carotid artery was 13.4 per 100,000 persons. Based on this analysis, it was conservatively estimated that about 41,000 strokes per year in the United States may be attributed to extracranial ICA stenosis alone (without considering additional strokes related to complete carotid artery occlusion).<sup>47</sup>

Most prior studies on this topic have examined patients who have sustained strokes, and tried to ascertain the etiology of the cerebrovascular event. One study took an alternative approach by following 1820 patients with known unilateral asymptomatic carotid artery stenosis and analyzed the types of strokes that occurred in these patients.<sup>130</sup> The risk of stroke at 5 years was 3.2% annually among the 216 patients with 60% to 99% stenosis. Among this cohort, however, the 5-year risk of a stroke in the territory of a large artery was 9.9%, that of lacunar stroke was 6%, and that of cardioembolic stroke was 2.1%. Risk factors for large artery stroke included silent brain infarction, a history of diabetes, and a higher degree of stenosis. The study concluded therefore that 45% of strokes in patients

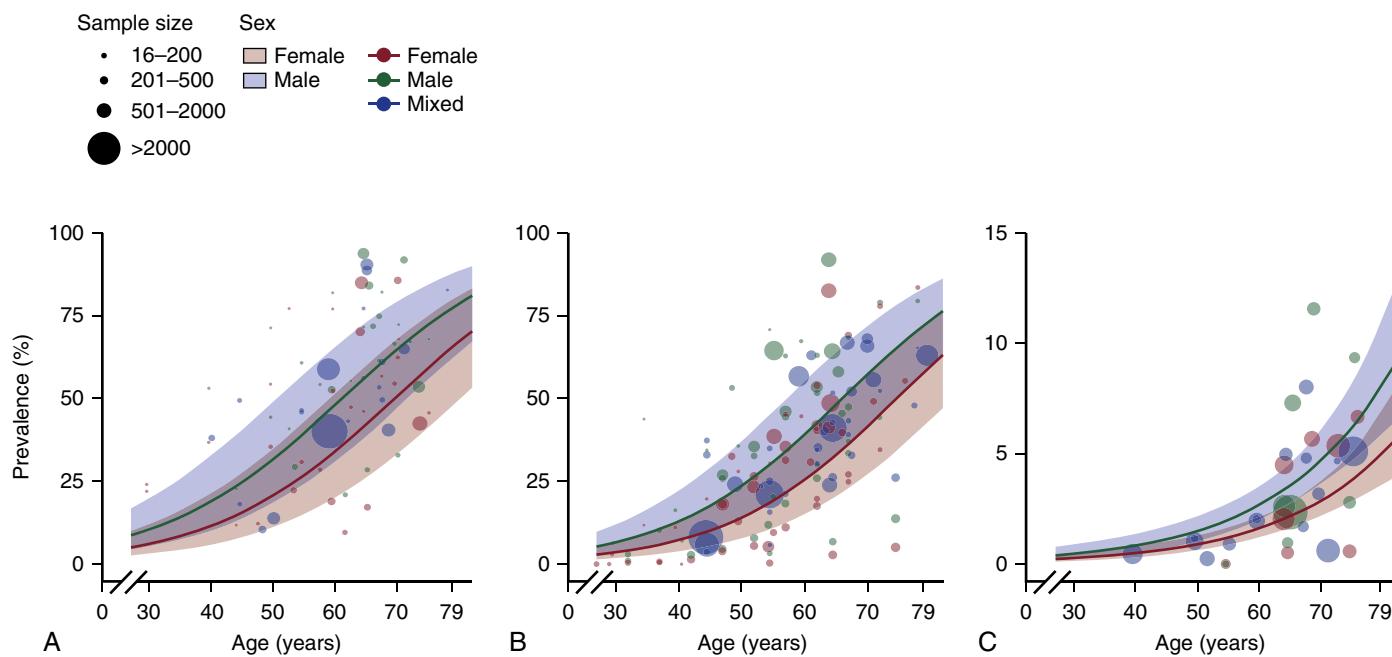
with asymptomatic stenosis of 60% to 99% are attributable to either lacunar strokes or cardioembolism and are not a direct result of large artery disease.

Racial differences have been noted in stroke subtypes.<sup>131</sup> Of ischemic stroke patients, large vessel strokes were felt to account for 10% in black patients and 12% in white patients. However, stroke cause was felt to be undetermined in approximately 50% of both racial groups. Only 60% of patients in both racial groups underwent a carotid duplex examination, and only 3% to 5% underwent a cerebral angiogram.

In a report derived from INTERSeCT, a multicenter prospective study of patients with acute ischemic stroke, it was found that in patients with embolic stroke of undetermined source, carotid plaques were significantly more common on the side of the ischemic stroke, suggesting that these plaques could represent a potential stroke etiology.<sup>132</sup> An additional review and meta-analysis examined carotid plaque morphology in patients with hemispheric embolic stroke with an undetermined source.<sup>133</sup> The prevalence of mild carotid stenosis with high risk features (including intraplaque hemorrhage, and other findings) was noted to be 32.5% in the ipsilateral carotid as compared to 4.6% in the contralateral carotid. The odds ratio of finding a plaque with high risk features in the ipsilateral carotid artery was 5.5, leading the authors to conclude that even plaques with only mild stenosis likely have a relationship with ischemic stroke.<sup>133</sup> Based on these and other studies and in consideration of the fact that most studies on this topic fail to determine with certainty the etiology of ischemic stroke in a high percentage of cases, most experts in this field feel that at least 20% of ischemic strokes are likely related to extracranial carotid artery atherosclerosis.

## Prevalence

In the Tromso Study involving nearly 7000 adults aged 25 to 84 years, ICA stenosis was detected in 3.8% of men and 2.7% of women. The prevalence increased with age, total cholesterol, systolic blood pressure, and cigarette use.<sup>134</sup> In another population-based study of older healthy patients aged 60 to 79 years, the prevalence of ICA stenosis found by duplex examination was 10.5% in men and 5.5% in women.<sup>135</sup> Despite the increased risk of carotid artery disease in known patient populations, the actual role of screening in asymptomatic patients remains controversial. In a systematic review and meta-analysis reporting on the global epidemiological burden of carotid atherosclerosis, it was noted that overall in people aged 30–79 years that the prevalence of carotid plaque is estimated to be 21.1%; the prevalence of significant carotid artery stenosis is estimated to be 1.5%, equivalent to more than 57 million people and a percentage change of nearly 60% from the year 2000<sup>136</sup> (Fig. 88.7). In a screening program of asymptomatic patients in the United States for treatable causes of ischemic stroke, 610 patients were evaluated. Unilateral or bilateral ICA stenosis of 50% or greater was detected in 66 patients (10.8%). The finding of occult ICA stenosis was more frequent than that of new hypertension (2.6%) or new atrial fibrillation (0.5%); therefore, ICA stenosis was the most frequently detected treatable cause of ischemic stroke. Patients with known hypertension were significantly more likely to have CA stenosis (12.7% vs. 7.8%) than were patients with heart disease (18.2% vs. 8%). Patients with both risk factors were significantly more likely to have CA stenosis than were patients without either risk factor (22.1% vs. 8.5%;  $P < 0.0001$ ).<sup>137</sup> A meta-analysis of nearly



**Figure 88.7** Age-specific and sex-specific prevalence of increased carotid intima-media thickness (A), carotid plaque (B), and carotid stenosis (C) for people aged 30–79 years. (Reprinted with permission from Elsevier. Song P, et al. Global and regional prevalence, burden, and risk factors for carotid atherosclerosis: a systematic review, meta-analysis, and modelling study. *Lancet Glob Health* 2020;8:e721–e729.)

24,000 subjects accumulated from large population studies reported in 2010 noted the overall prevalence of moderate-range carotid stenosis varied from 0.2% in men under 50 years of age to 7.5% in men over 80 years of age. The prevalence was lower in women. The following variables were predictive of both moderate and severe carotid stenosis in the populations: age, sex, a history of vascular disease, systolic and diastolic blood pressure, total cholesterol/high density lipoprotein (HDL) ratio, diabetes, and current smoking.<sup>138</sup>

In recent analyses of another database comprising nearly 3.5 million patients in the United States who underwent voluntary screening for vascular disease, 3.9% were found to have ICA stenosis.<sup>60,139–142</sup> Independent risk factors for ICA stenosis included advanced age, smoking, peripheral arterial disease, hypertension, coronary artery disease, diabetes, hypercholesterolemia, and abdominal aortic aneurysm. Exercise and the consumption of fruit, vegetables, and nuts were noted to have a modest protective effect.<sup>143</sup> Women had a 3.4% prevalence of ICA stenosis of 50% or more, whereas males had a 4.2% prevalence.<sup>60</sup> The prevalence increased dramatically with age. It was also noted that the prevalence of ICA stenosis varied significantly by race: Native American subjects had the highest prevalence of ICA stenosis across all age ranges and in both sexes, while Caucasian subjects had the second highest prevalence of ICA stenosis across most age ranges and in both sexes (Figs. 88.8 and 88.9). African American males and Asian females appeared to have the lowest prevalence. In all races, increasing age was the most significant risk factor for carotid stenosis. Additional risk factors included smoking history, diabetes, hypertension, and hypercholesterolemia.<sup>60</sup> It has been previously noted that African American patients may have a lower relative risk of severe carotid artery disease and that the increased stroke rate in this population is likely due to small vessel disease and hypertension.<sup>60</sup>

The prevalence of carotid artery stenosis was noted to be significantly increased in subjects with lower extremity peripheral arterial disease, and in diabetics. Increasing severity of peripheral arterial disease as quantified by the ABI was significantly associated with an increasing prevalence of carotid artery stenosis.<sup>140</sup> In this large population-based study, higher levels of physical activity were independently associated with lower odds of carotid artery stenosis.<sup>142</sup> Age remains a critical factor; after adjustment for sex, race, body mass index (BMI), family history, smoking, diabetes, hypertension, hypercholesterolemia, and physical activity, the odds of carotid artery stenosis increased with every decade of life (odds ratio, 1.8).<sup>141</sup>

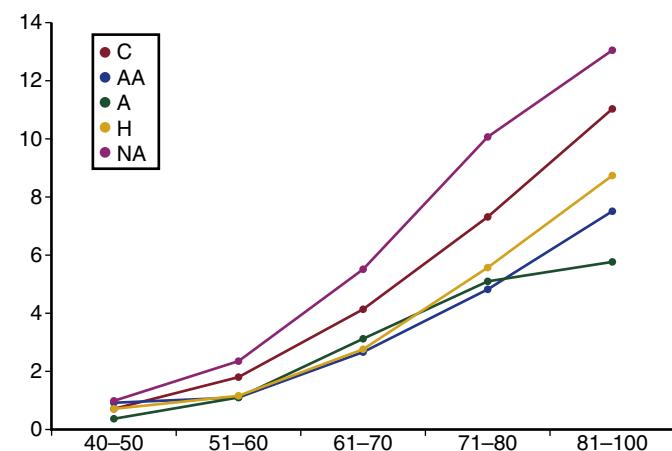
In a report examining modifiable risk factors including hypertension, hypercholesterolemia, smoking, diabetes, and sedentary lifestyle, multivariate adjusted prevalence of carotid artery stenosis with 0 to 5 risk factors was, respectively, 1.41%, 2.36%, 3.72%, 5.73%, 8.48%, and 11.58% (Fig. 88.10). Results were similar in men and women. For every additional modifiable risk factor that was present, the multivariate-adjusted odds of having carotid disease increased significantly (odds ratio, 1.57) (Fig. 88.10).<sup>139</sup>

Clearly the medical treatment of risk factors might affect the natural history of ICA stenosis.<sup>144,145</sup> Medical therapy of ICA stenosis includes treatment of hypertension with target BP of

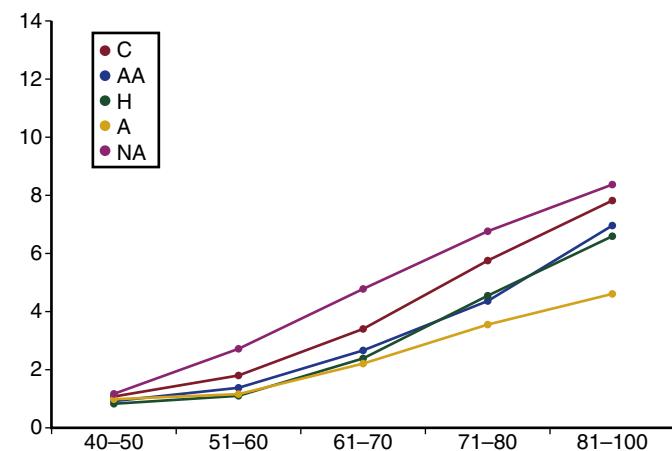
less than 140/90 and statins with a goal of decreasing LDL to less than 100, triglyceride less than 150, and increasing HDL to more than 40. Statins lower stroke risk by approximately 30%, and likely work by improving plaque stabilization.<sup>146</sup> Antiplatelet therapy in the form of aspirin or clopidogrel is also recommended for all patients with asymptomatic ICA stenosis.<sup>147</sup> Some studies have reported that the combination of aspirin and clopidogrel may be more effective than aspirin alone, but larger trials have not confirmed the benefit of adding clopidogrel (see Ch. 92, Cerebrovascular Disease: Decision Making Including Medical Therapy).<sup>148</sup> Nevertheless, progression of carotid stenosis along with the development of neurologic symptoms has been noted despite so-called optimal medical therapy.<sup>34</sup>

## Natural History

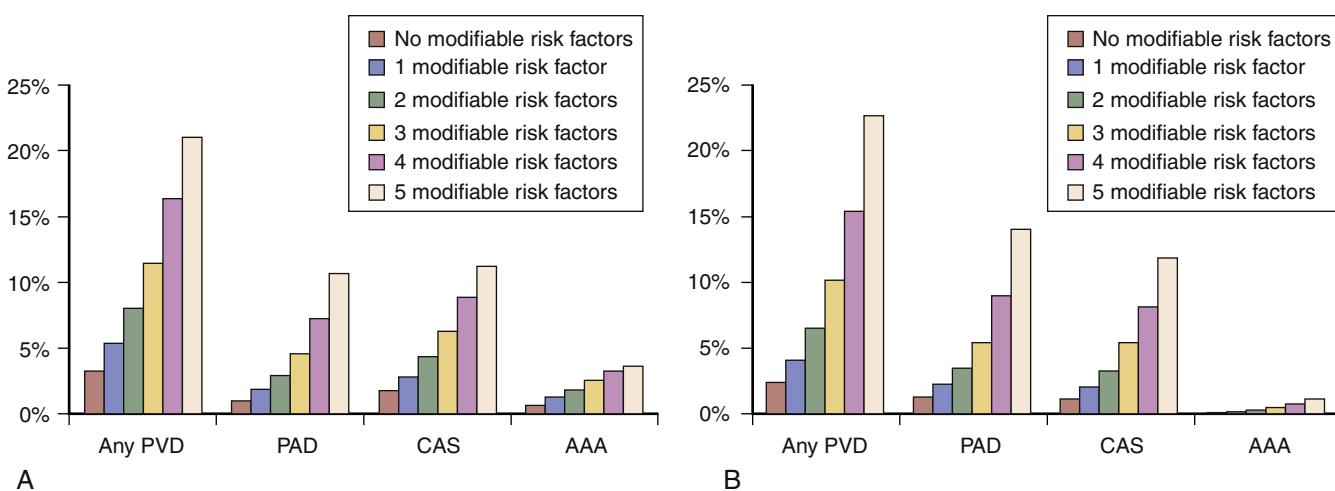
While there is little disagreement concerning the known high risk of subsequent stroke in symptomatic patients, there is



**Figure 88.8** Relationship between race, carotid artery stenosis, and age in male subjects. A, Asian; AA, African American; C, Caucasian; H, Hispanic; NA, Native American. (From Rockman CB, et al. The prevalence of carotid artery stenosis varies significantly by race. *J Vasc Surg*. 2013;57(2):327–337. Used with permission.)



**Figure 88.9** Relationship between race, carotid artery stenosis, and age in female subjects. A, Asian; AA, African American; C, Caucasian; H, Hispanic; NA, Native American. (From Rockman CB, et al. The prevalence of carotid artery stenosis varies significantly by race. *J Vasc Surg*. 2013;57(2):327–337. Used with permission.)



**Figure 88.10** Prevalence of vascular disease according to the aggregate burden of modifiable risk factors in (A) men and (B) women. Risk factors included hypertension, hypercholesterolemia, smoking, diabetes, and sedentary lifestyle. AAA, abdominal aortic aneurysm; CAS, carotid artery stenosis; PAD, peripheral artery disease; PVD, peripheral vascular disease. (From Berger JS, et al. Modifiable risk factor burden and the prevalence of peripheral artery disease in different vascular territories. *J Vasc Surg*. 2013;58:673–681.e1. Used with permission.)

ongoing debate with respect to the management of the asymptomatic patient.<sup>149</sup> Challenges to the role of CEA or CAS in the treatment of asymptomatic carotid stenosis include the arguments that modern optimal medical therapy may allow better stroke protection, obviating the need for CEA or CAS, and that the degree of stenosis alone is a poor surrogate for vulnerable plaque and does not allow the accurate prediction of patients at high risk for stroke.<sup>150</sup>

Carotid intervention should only be undertaken in asymptomatic patients who are at a high lifetime risk of stroke. In addition to age, sex, the degree of stenosis, medical comorbidities, and life expectancy, relevant factors include the severity of the stenosis,<sup>149,151</sup> progression of stenosis,<sup>149,152</sup> evidence of infarction on brain imaging,<sup>153</sup> and plaque imaging characteristics.<sup>84</sup>

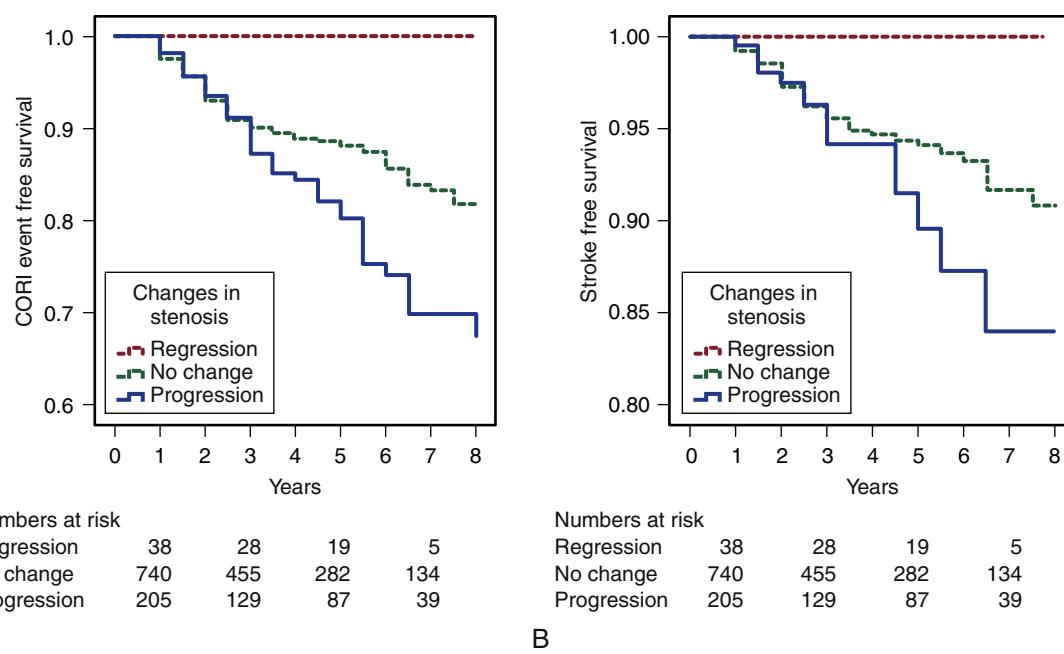
A consistent rate of stroke risk of approximately 2% per year in patients with high-grade asymptomatic stenosis was reported in ACAS, NASCET, and ACST. Although the ACAS study results have been criticized as obsolete in the current era of improved medical management of atherosclerosis, in the later years of ACST 80% of patients in fact were on statins.<sup>10,11,44,130</sup> Additionally, in the Reduction of Atherothrombosis for Continued Health Registry (REACH) a carotid stenosis of 70% or more was associated with a significantly increased stroke risk despite the fact that more than two-thirds of subjects were on statin medications.<sup>154</sup>

Progression of carotid stenosis has been shown to be a significant predictor of stroke risk in multiple natural history studies.<sup>155–157</sup> In a follow-up study from the ACSRS group of 1121 patients with asymptomatic carotid stenosis of 50% to 99%, progression occurred in 19.8% of patients with a mean follow-up of 4 years (Fig. 88.11). Independent predictors of progression included male sex, high creatinine, not taking lipid-lowering medications, low grade of stenosis, and increased plaque area. A total of 130 first ipsilateral cerebral

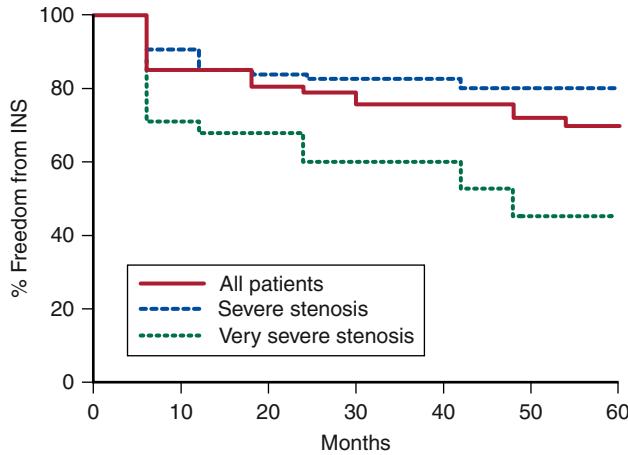
or retinal events occurred, including 59 strokes. Forty strokes (67.8%) occurred in patients whose stenosis was not changed and 19 strokes (32.2%) occurred in those with progression. For patients with baseline 70% to 99% stenosis and in the absence of progression ( $n = 349$ ), the 8-year cumulative ipsilateral ischemic stroke rate was 12%. In the presence of progression, it was 21% ( $n = 77$ ).<sup>158</sup>

In another report of 126 arteries with severe stenosis in patients who were treated medically, including 86% taking a statin medication, with a mean follow-up period of 63 months, ipsilateral neurologic symptoms developed related to 25% of the arteries (Fig. 88.12).<sup>150</sup> Of these events, 14 (45%) were strokes and 17 (55%) were TIAs or retinal events. Of this cohort of patients who initially were not considered for carotid artery intervention or were refused, 33% ultimately underwent carotid revascularization during the follow-up period.

In a series including 900 arteries in 794 patients with moderate stenosis, optimal medical therapy included aspirin and a statin with documented LDL levels less than 100 mg/dL. With a mean follow-up of 3.6 years, the 5-year freedom from progression to severe stenosis was  $61.2\% \pm 2.6\%$ , with no benefit seen from optimal medical therapy (Table 88.2). Plaque progression occurred in 262 arteries, and 36 (13.7%) of these developed symptoms. Average time to plaque progression was 32 months. Of this cohort, 90 patients (11.3%) developed ipsilateral neurologic symptoms during follow-up; 58% of these were strokes. Average time to symptom onset was 36 months. A total of 36 (40%) symptomatic patients also showed plaque progression, but the remaining 60% developed symptoms with a stable moderate stenosis. Five-year freedom from symptoms was 88.4%, with no benefit seen with OMT.<sup>34</sup> These results were supported by a study performed in Korea.<sup>159</sup> Of patients with initial moderate (50%–79%) stenosis, progression of stenosis occurred in 31.8% and development of associated neurological symptoms occurred in 3.2% over a mean follow-up



**Figure 88.11** (A) Effects of changes in stenosis on ipsilateral cerebrovascular or retinal ischemic events (CORI). (B) Effect of changes in stenosis on ipsilateral hemispheric stroke. (From Kakkos SK, et al. Predictors and clinical significance of progression or regression of asymptomatic carotid stenosis. *J Vasc Surg*. 2014;59:956–967.e1. Used with permission.)



**Figure 88.12** Kaplan-Meier curves of freedom from ipsilateral neurologic symptoms (INS) in the entire cohort and stratified according to lesion severity. (From Conrad MF, et al. The natural history of asymptomatic severe carotid artery stenosis. *J Vasc Surg*. 2014;60:1218–1225. Used with permission.)

of 49 months. The authors concluded that progression of disease was high despite the prevalent use of antiplatelet medications and statins.<sup>159</sup> In a population-based cohort in Sweden, all 65-year-old men in a single county underwent a carotid Duplex scan, and were reassessed five years later at the age of 70 years.<sup>160</sup> Among men with initially moderate (50%–79%) stenosis, 12.9% progressed to a severe stenosis, of whom two developed symptoms. Of 12 patients with initial 80%–99% stenosis, 5 (42%) developed symptoms. In multivariable analysis, smoking, coronary artery disease and hypercholesterolemia were associated with disease progression.<sup>160</sup>

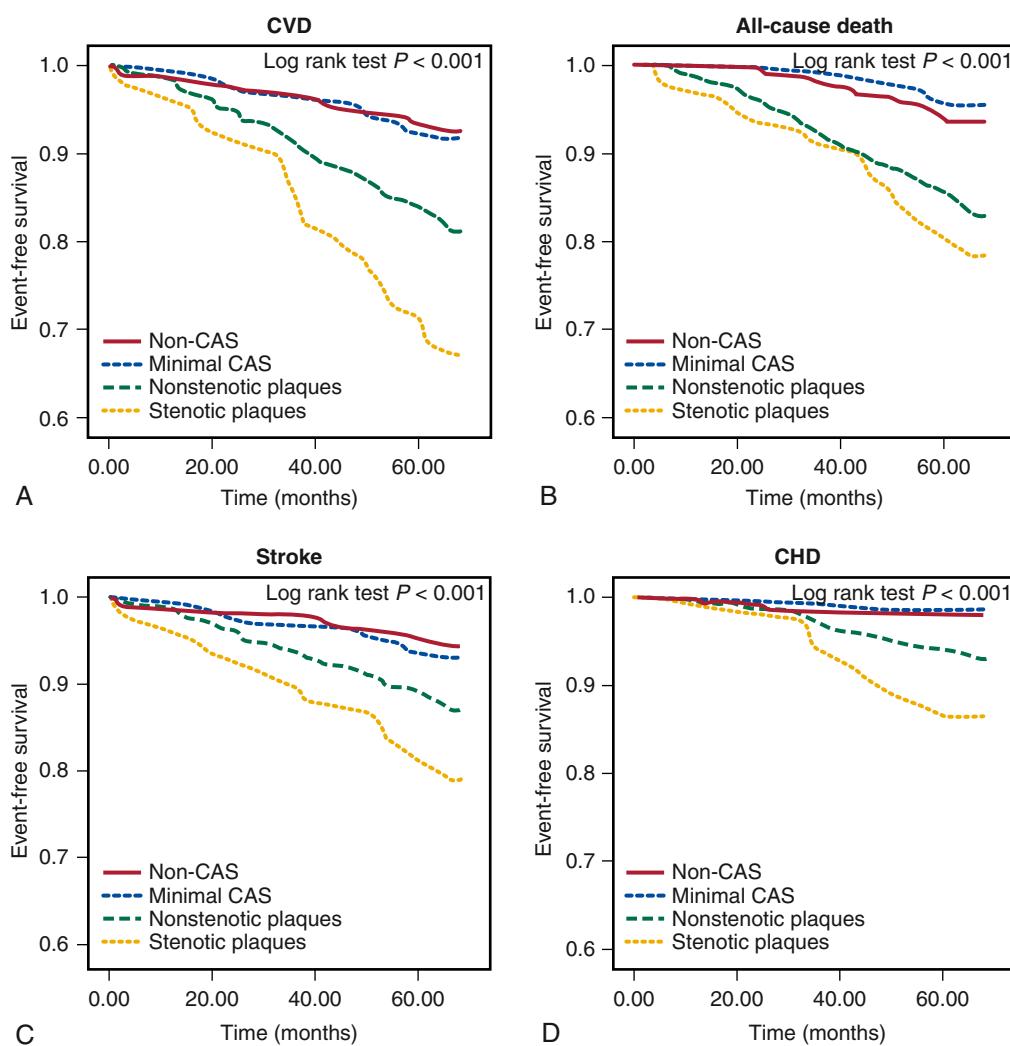
**TABLE 88.2** Multivariate Models of Outcomes

| Predictor                               | HR   | CI        | P Value |
|---|------|-----------|---------|
| <b>Predictors of Death</b>              |      |           |         |
| Age <sup>a</sup>                        | 1.1  | 1.04–1.09 | <0.0001 |
| Contralateral occlusion                 | 1.9  | 1.1–3.3   | 0.017   |
| CAD                                     | 2.1  | 1.4–3.1   | 0.0003  |
| COPD                                    | 1.8  | 1.3–2.4   | 0.0003  |
| CKD                                     | 2.4  | 1.4–4.1   | 0.0018  |
| Plavix                                  | 1.7  | 1.2–2.3   | 0.0026  |
| Aspirin                                 | 0.6  | 0.39–0.83 | 0.0033  |
| <b>Predictors of Plaque Progression</b> |      |           |         |
| CKD                                     | 2.1  | 1.2–3.7   | 0.009   |
| Aspirin                                 | 1.9  | 1.2–3.0   | 0.01    |
| CCB                                     | 1.4  | 1.1–1.8   | 0.007   |
| <b>Predictors of INS</b>                |      |           |         |
| Diabetes                                | 2.3  | 1.5–3.6   | 0.0002  |
| Warfarin                                | 1.9  | 1.2–2.9   | 0.009   |
| Statins (protective)                    | 0.37 | 0.22–0.65 | 0.0005  |

<sup>a</sup>Age was included in the model as a continuous variable.

CAD, coronary artery disease; CCB, calcium channel blocker; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; INS, ipsilateral neurologic symptoms.

From Conrad MF, et al. Progression of asymptomatic carotid stenosis despite optimal medical therapy. *J Vasc Surg*. 2013;58:128–135.e1. Used with permission.



**Figure 88.13** Kaplan–Meier curves for cardiovascular disease (all-cause death, stroke, and coronary heart disease) in participants according to the degree of carotid atherosclerosis. (A) Cardiovascular disease (CVD). (B) All-cause death. (C) Stroke. (D) Coronary heart disease (CHD). CAS, carotid artery stenosis. (From Zhang Y, et al. Carotid artery plaques, carotid intima-media thickness, and risk of cardiovascular events and all-cause death in older adults: A 5-year prospective, community-based study. *Angiology*. 2018;69:120–129. Used with permission.)

Patients with significant carotid atherosclerosis are also at increased risk for cardiovascular disease and death. In the Tromso study, a cohort of 248 individuals with greater than 35% carotid stenosis was shown to have a 3.5 times higher risk of death from any cause as compared with patients with no carotid disease, even when other risk factors were controlled for. Most deaths were from cardiovascular causes.<sup>161</sup> In another large systematic review of 12 studies involving more than 4000 patients with greater than 50% stenosis, there was an average cardiac mortality of 2.9% per year.<sup>162</sup> Most recently Zhang et al. studied the relationship between asymptomatic carotid artery stenosis and the development of cardiovascular disease (Fig. 88.13), including 1376 subjects over 55 years of age.<sup>163</sup> After adjustment for demographics and risk factors, the odds ratios for the risk of cardiovascular disease for those with minimal carotid disease, nonstenotic carotid plaque, and stenotic plaque was 0.8, 2.0, and 3.1, respectively, as compared with

patients without significant carotid artery stenosis. During a mean follow-up of 62 months, 136 new strokes occurred in this cohort.

In patients with carotid-related symptoms, almost all are in agreement regarding the appropriateness of carotid intervention. In a systematic review, the risk of recurrence of cerebrovascular events in patients with symptomatic carotid stenosis following an index neurologic event was as high as 6.4%, 19.5%, and 26.1% after 2–3, 7 and 14 days, respectively.<sup>164</sup>

### Vertebrobasilar Insufficiency

Vertebral artery origin stenosis may cause as many as 20% of posterior circulation ischemic strokes.<sup>165</sup> Additionally, symptoms may be caused by occlusion or stenosis of the subclavian artery proximal to the origin of the vertebral artery, causing the classic “subclavian steal” syndrome (see Ch. 101,

Brachiocephalic Artery Disease: Surgical Treatment and Ch. 102, Brachiocephalic Artery Disease: Endovascular Management). Vertebrobasilar ischemia can result from embolic, thrombotic, or low-flow hemodynamic mechanisms.<sup>166</sup> Vertebrobasilar insufficiency (VBI) results in ischemia to the posterior circulation of the brain, vascular territories supplied by the paired vertebral and common basilar artery (brain stem, cerebellum, thalamus, and occipital cortex). The most common causes of VBI include large artery atherosclerosis, emboli, penetrating small artery disease, and arterial dissection (see Ch. 100, Vertebral Artery Dissection and Other Conditions).<sup>167</sup> The subclavian steal phenomenon is perhaps the best example of VBI resulting from hypoperfusion, with retrograde ipsilateral vertebral flow manifesting clinically with arm pain with exertion as well as posterior cerebral neurologic symptoms, and most commonly dizziness or vertigo. Sensorimotor deficits are extremely rare in subclavian steal syndrome and usually indicate the presence of concomitant carotid occlusive disease.

Atherosclerotic lesions usually occur at the vertebral artery origins and present with transient ischemia due to hypoperfusion of the brain stem and cerebellum, resulting in dizziness, difficulty focusing visually, and loss of balance. Thromboembolic events can also result in vertebrobasilar ischemia. Large emboli often involve the intracranial vertebral arteries, resulting in cerebellar infarction, or the distal basilar artery, affecting the upper cerebellum, brain stem, and territories of the posterior cerebral arteries. Cerebellar infarction usually presents with vertigo, vomiting, blurred vision, and difficulty walking.

## ASSOCIATED CONDITIONS

### Global Cerebral Ischemia

Global ischemia or systemic hypoperfusion represents only a small fraction of all ischemic strokes from carotid occlusive disease. Patients presenting with global ischemia often present unconscious to an emergency room or with symptoms resembling near syncope.<sup>168</sup> Symptoms may include decreased visual acuity, cognitive difficulties, and bilateral upper extremity weakness, and symptoms of VBI are possible.<sup>169</sup> This can be a result of prolonged cardiogenic shock, dysrhythmias, or cardiac arrest, and treatment should initially focus on correcting cardiac failure and improving perfusion pressure to the brain.

Symptoms may be asymmetric in cases where hypoperfusion is isolated to a territory distal to a severe extracranial stenosis if inadequate collateral flow exists. Such patients may benefit most from treatment of proximal flow-limiting lesions and have been shown to fare better than those with more global hypoperfusion.<sup>170</sup>

### Lacunar Infarcts

Lacunar infarcts are defined as small subcortical infarcts that result from presumed occlusion of a single penetrating artery of the brain.<sup>171</sup> These arteries are thought to be so small that they cannot be readily imaged *in vivo*, so these lesions are presumed to be ischemic in etiology. Typical risk factors for

lacunar infarcts include increasing age, male gender, hypertension, diabetes, and smoking.<sup>171</sup> Lacunar infarcts represent roughly 20% of all ischemic strokes<sup>172</sup> and consist of small (1- to 2-cm) subcortical defects often located in the internal capsule or basal ganglia, areas supplied by the lenticulostriate vessels (small proximal branches of the intracranial carotid). The typical presentation can include pure motor hemiparesis, pure sensory syndrome, sensorimotor syndrome, ataxic hemiparesis, and dysarthria-clumsy hand syndrome.<sup>173,174</sup> Lacunar infarcts may be present in as many as 23% of persons over 65 years of age and remain asymptomatic or silent in up to 89% of patients.<sup>175</sup>

The association between atherosclerotic extracranial lesions and lacunar infarcts is controversial. Most believe that such infarcts are a result of small-vessel disease deep in the brain resulting from long-standing hypertension and/or diabetes unrelated to carotid occlusive disease.<sup>176</sup> They can occur alone or in groups and are often present in both hemispheres. Recent studies, however, show that ICA stenosis (>70%) was found more commonly on the side of lacunar infarction and may be associated with large vessel disease in up to one-third of patients.<sup>177,178</sup> This would lend support to the theory that embolization from carotid atherosclerosis to the lenticulostriate vessels may contribute to lacunar infarction in some cases.

### Cognitive Decline

The relationship between carotid stenosis itself and cognitive impairment is controversial (see Ch. 90, Carotid Artery Disease and Cognitive and Functional Decline). In a systematic review of the literature, including 18 studies examining cognitive function in patients with carotid stenosis who had not yet undergone surgery, 14 studies found deficits in patients with both symptomatic and asymptomatic lesions and four showed no cognitive impairment.<sup>179</sup> Moreover, patients with carotid occlusive disease share many of the known conventional risk factors for dementia (hypertension, diabetes, dyslipidemia, and smoking) so that carotid stenosis may be a direct cause of cognitive impairment or serve simply as a marker of intracerebral or generalized atherosclerosis.<sup>180,181</sup> Silent brain infarcts related to atheroembolization or hypoperfusion, or lacunar infarcts, may prove to be a link between carotid stenosis and cognitive impairment, although there is a paucity of data correlating degree of carotid stenosis with cognitive decline.<sup>182–185</sup>

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# Cerebrovascular Disease: The Unstable Carotid Plaque

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## INTRODUCTION

Carotid artery disease is highly prevalent, with approximately 12.5% of men and 6.9% of women over the age of 70 years in the United States having asymptomatic carotid disease.<sup>1</sup> The association between atherosclerotic disease of the carotid artery and ischemic stroke is well-documented. Carotid disease accounts for approximately 8%–37% of all strokes<sup>2,3</sup> (see Ch. 88, Cerebrovascular Disease: Epidemiology and Natural History). Early randomized controlled trials of surgical treatment of carotid atherosclerotic disease vs. medical treatment (NASCET, ACAS, ECST, and ACST) established the superiority of surgical endarterectomy in stroke prevention among asymptomatic patients with high-grade stenosis and symptomatic patients with moderate stenosis, assuming patients have a reasonable life expectancy and are appropriate surgical candidates.<sup>4–6</sup>

The vast majority of strokes from carotid artery plaques are from focal ischemic brain injury. While hemodynamic compromise due to restriction of flow in patients with high-grade carotid stenoses can contribute to ischemic stroke,<sup>7</sup> rich intracranial collateral flows from the contralateral carotid artery and vertebral arteries provide robust protection of the brain from ischemic injury. Strokes due to carotid stenosis-related hypoperfusion tend to occur in the watershed areas of arterial distribution and in the presence of inadequate cross-collateralization. A vast majority of strokes attributable to carotid disease are caused by carotid plaque disruption and distal embolization,<sup>8</sup> which is supported by detection of embolic signals in the middle cerebral artery of patients with

carotid stenosis.<sup>9</sup> Therefore, carotid plaque disruption with embolic cerebral infarction, rather than hemodynamic compromise from luminal narrowing, is the primary contributor in the pathogenesis of stroke in patients with carotid atherosclerotic stenosis.

## STABLE VERSUS UNSTABLE PLAQUE

The risk of embolization from carotid plaques varies greatly. Some have reported a 0.5% per year stroke risk in patients with high-grade stenosis,<sup>10</sup> while others have shown a risk of more than 10% per year in patients with severe carotid stenosis.<sup>11</sup> Although there were different definitions of “high-grade” stenosis in early clinical trials, most clinicians have now agreed that 70%–99% stenosis, based on NASCET criteria, is considered high-grade.<sup>5</sup> The variations in stroke risk are largely related to heterogeneity of carotid plaques. Recent advances in basic and clinical vascular sciences have shown that not all carotid plaques behave in the same manner. So-called “unstable” or “vulnerable” plaques appear to be more likely to cause cerebrovascular accident (CVA) or transient ischemic attack (TIA), even at mild or moderate levels of stenosis.<sup>12</sup> In fact, silent, micro-infarcts have been observed in patients with apparently unstable carotid artery plaques.<sup>13,14</sup> Some authors refer to these plaques as “high-risk” and stable plaques as “quiescent.” It is important to view atherosclerotic carotid plaques as dynamic lesions that may progress or regress over time.<sup>15</sup>

Plaque stability can be analyzed broadly using several different lenses, including surface characteristics, plaque content and morphology, plaque mobility, and plaque hemodynamics.

In terms of surface features, plaque ulceration has been widely studied and consistently shown to correlate with vulnerable plaque and microembolic activity.<sup>5,15</sup> Studies have shown that ulcerated plaques often have an element of overlying thrombosis<sup>16</sup> and that there tends to be increased platelet aggregation and activity on the surface of ulcerated plaques.<sup>17,18</sup> Typical atherosclerotic plaques are composed of two main components: a soft, lipid-rich portion and a hard, sclerotic portion formed mainly of connective tissue elements.<sup>16</sup> The calcified, connective tissue component has been proposed to stabilize the plaque; thus, plaques with an increased calcific component may be less prone to rupture.<sup>16,19,20</sup> In contrast, the inner atheromatous component of the lesion is weak and thrombogenic, with increased macrophage activity and cellular debris.<sup>21</sup> This in turn leads to necrosis and intraplaque hemorrhage (IPH). High lipid content and necrotic core that appear echolucent or hypoechoic on ultrasound are two of the most widely accepted features of unstable plaque.<sup>12,22</sup> IPH characterized on magnetic resonance imaging (MRI) is also associated with increased necrotic core volume and decreased luminal diameter.<sup>23</sup> Both overall plaque size and necrotic core size have been related to increased risk of plaque rupture.<sup>16,21</sup> Plaque mobility has also been shown to increase the risk of microembolization and subsequent cerebral infarction.<sup>24,25</sup> One study showed that 9.3% of ICA plaques were mobile on ultrasound; those patients with mobile plaque were more likely to demonstrate progressive ischemic symptoms.<sup>25</sup>

In terms of plaque hemodynamics, extensive research has identified the relationship between shear stresses on the carotid wall and plaque development (see “Biomechanics” section below). The “upstream” region distal to the plaque has been shown to be particularly susceptible to shear stresses, with resultant changes in stability.<sup>26–28</sup> Longitudinal plaque asymmetry is linked to vulnerability and increased risk of rupture.<sup>26</sup> The implications for understanding plaque stability in this context are clear: relative differences in shear stress on the arterial wall have been linked to increased apoptosis and subsequent thinning and disruption of the overlying fibrous cap.<sup>26</sup> Plaque neovascularization (via angiogenesis) occurs in response to increasing hypoxia within a plaque’s core and has also been associated with instability.<sup>15,26,29,30</sup> At least one group has shown a disproportionate increase in neovascularization in soft, lipid-rich plaques when compared to hard, more heavily calcified plaques.<sup>30</sup>

Interestingly, the relationship between the degree of stenosis and plaque vulnerability is still unclear. Multiple studies, including ACAS and ACST, have failed to demonstrate a relationship between degree of stenosis and development of cerebrovascular symptoms.<sup>4,6</sup> However, it is thought that a higher degree of stenosis is associated with larger plaque size. Both increased overall plaque size and necrotic core size increase risk of plaque rupture.<sup>16,21</sup> The lack of clear association between plaque vulnerability and degree of stenosis is significant because treatment paradigms for those with unstable plaques may ultimately differ from those for patients with stable plaques (Table 89.1).

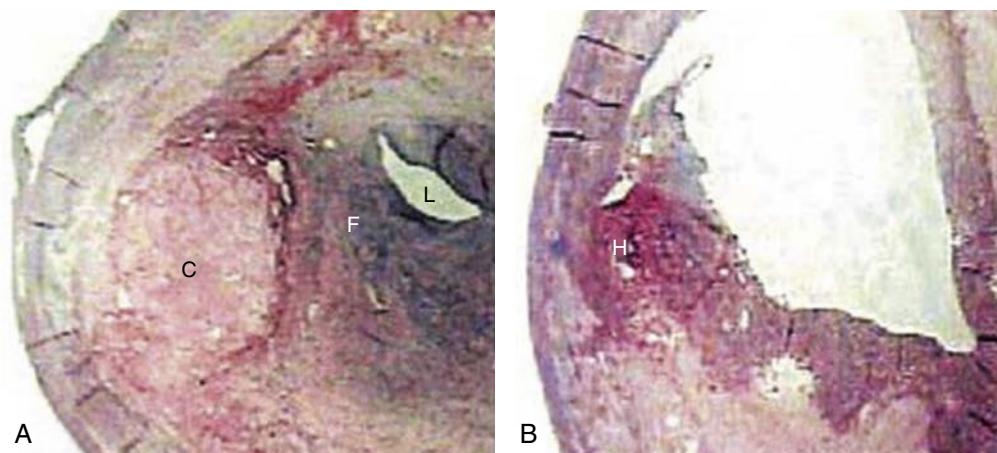
**TABLE 89.1** Stable and Unstable Plaques<sup>31–33</sup>

|                             | Stable Plaque                | Unstable Plaque                                    |
|-----------------------------|------------------------------|--|
| Core                        | Fibrous, smooth muscle cells | Necrotic, lipid rich core                          |
| Cap                         | Stable fibrous cap           | Thin/unstable fibrous cap                          |
| Intraplaque characteristics | Calcified, hard              | Intraplaque hemorrhage/necrosis; soft; ulcerations |
| Cells                       | Smooth muscle cells          | Macrophage infiltration                            |
| Biomarkers                  | High density lipoprotein     | Various inflammatory and cytokine markers          |
| Composition                 | Homogeneous                  | Heterogeneous                                      |
| US characteristics          | Echogenic                    | Echolucent   |

## HISTOMORPHOLOGY

Histologically, all atherosclerotic lesions, regardless of the vessel in which they develop, begin as a fatty streak – an accumulation of lipids and inflammatory cells within a vulnerable region of intima. Fatty streaks develop early in life, and progress to atheroma. The American Heart Association (AHA) has developed a classification system for describing atherosclerotic lesions.<sup>34–36</sup> Type I lesions consist essentially of microscopic lipid deposition within the intima and are found almost exclusively in infants and young children. The fatty streak corresponds to a type II lesion, and a type III lesion is defined by the development of extracellular lipid droplets and subsequent intimal thickening.<sup>34</sup> Lesions of types I–III precede true atheroma and have no embolic potential. Type IV lesions demonstrate a large lipid core and increased numbers of foam cells; classically, they develop within the fourth decade of life. Type V lesions have an additional fibrous tissue component, and are broken down into types Va, Vb, and Vc, depending on the presence of a lipid core and/or a calcified cap. Type VI lesions are so called “complicated” lesions: they are type IV or V lesions that also demonstrate either surface disruption, hematoma or hemorrhage, or thrombosis.<sup>35</sup> Lesions of type IV–VI have the potential to embolize.

There is general agreement between morphological features and plaque vulnerability, despite certain inconsistencies (Fig. 89.1). A large histological study of 526 carotid plaque specimens from symptomatic patients demonstrated features of AHA grade VI (cap rupture, intraplaque hemorrhage, and inflammation) in the majority of the plaques.<sup>19</sup> Interestingly, there were no significant histological differences in patients who had stroke vs. TIA vs. amarosis fugax.<sup>19</sup> A smaller analysis confirmed that unstable plaques had the thinnest fibrous caps and the largest lipid cores.<sup>16</sup> However, another study did not find significant difference in cross-sectional size, necrotic core size, or presence of IPH among those patients with clinical neurologic symptoms, compared to those without symptoms.<sup>22</sup>



**Figure 89.1** (A) Asymptomatic carotid plaque. Note the small and deep seated lipid-rich necrotic core, marked *C*. The lumen is marked *L* and fibrous cap is marked *F*. (B) Symptomatic carotid plaque. Note the fibrous cap disruption, intraplaque hemorrhage marked *H*, and exposure of the underlying lipid-rich necrotic core. (Adapted from Lal BK, Hobson RW 2nd, Pappas PJ, et al. Pixel distribution analysis of B-mode ultrasound scan images predicts histologic features of atherosclerotic carotid plaques. *J Vasc Surg*. 2002;35(6):1210–1217.<sup>37</sup>)

## BIOMECHANICS

The carotid bifurcation is important for understanding plaque stability because of unique hemodynamic stresses that occur in this region. Turbulent flow at the area of the carotid bifurcation results in changes in sheer stress and accumulation of atherosclerotic material.<sup>38,39</sup> Arterial bifurcations and branch points, such as the CCA bifurcation, are especially susceptible to mechanical stresses as cross-sectional area changes.<sup>38,40</sup> Biophysicists have hypothesized that atherosclerotic lesions develop at least in part because bioactive substances (macrophages, low density lipoproteins [LDLs], and other molecules involved in plaque progression) tend to re-circulate within turbulent flow areas, resulting in prolonged absorption times over endothelial surfaces.<sup>38,41</sup> Sheer stress has been shown to affect cellular inflammatory responses by altering ribonucleic acid (RNA) expression to upregulate inflammatory protein pathways, with resultant endothelial cell apoptosis.<sup>38,42</sup> The arterial wall initially compensates for increased mechanical stress by expanding, but at a certain point it can no longer accommodate an enlarging plaque, and luminal narrowing occurs.<sup>38</sup> Carotid atheroma tends to deposit in areas of low sheer stress.<sup>43</sup> Over time, however, stress distributions around the arterial wall change, and several fluid dynamic studies and experimental animal model studies have actually shown a correlation between elevated shear stress and plaque rupture.<sup>38,44–46</sup> The takeoff angle of the ICA has also been shown to be a prognostic indicator for plaque formation.<sup>39</sup> In a landmark paper that used high-resolution ultrasound to measure several anatomic features of carotid arteries in 1300 healthy subjects, Sitzer and colleagues identified acute angle of ICA origin (>60 degrees) as a risk factor for development of extracranial carotid disease.<sup>47</sup> A separate study using computed tomographic angiography corroborated this finding, showing that increasing ICA take-off angle (in relation to the vertical axis of the CCA) predicted

increased ICA stenosis (OR, 1.05 per degree increment; 95% CI, 1.04–1.07).<sup>48</sup> Several authors have also shown that tortuosity is a proxy for increased vessel wall exposure to disturbed flow.<sup>39,49</sup>

Mechanical forces at the area of the atheroma also appear to play a role in plaque stability.<sup>46</sup> Although low sheer stress is involved in initial plaque formation,<sup>40,50</sup> elevated shear stress in portions of the CCA and ICA has been linked to increased risk of plaque rupture and subsequent ischemic infarct.<sup>44,45</sup> Long-term increases in sheer stress lead to eccentric plaque growth and ultimately contribute to transformation of a plaque to an unstable phenotype. When arterial wall stress exceeds the strength of the fibrous cap, which is lower in thinner or ulcerated caps, plaque rupture occurs.<sup>38</sup> A study has shown that plaque wall stress appears to be higher in symptomatic patients than in asymptomatic patients,<sup>51</sup> and another study using US or MRI showed that sheer strain and axial stress correlated with plaque vulnerability.<sup>52</sup>

## Biomarkers

There is no single, widely available biomarker for carotid artery disease. Traditionally, evaluation for carotid stenosis has relied much more heavily on imaging than on laboratory testing. In recent years, several proteins, lipids, and other small molecules have emerged as potentially viable biomarkers for carotid artery disease. However, currently, they remain of investigational interest only. There is no consensus on the role of such biomarkers in the evaluation of extracranial carotid disease.<sup>53–55</sup> Serum lipid levels and HgA<sub>1c</sub> levels have been linked to an increased risk of plaque development, but they are not specific to carotid disease, nor do they predict symptomatic status or degree of stenosis.<sup>56–61</sup> Instead, they are considered markers of generalized disease states that affect all macro- and microvascular beds.<sup>62,63</sup>

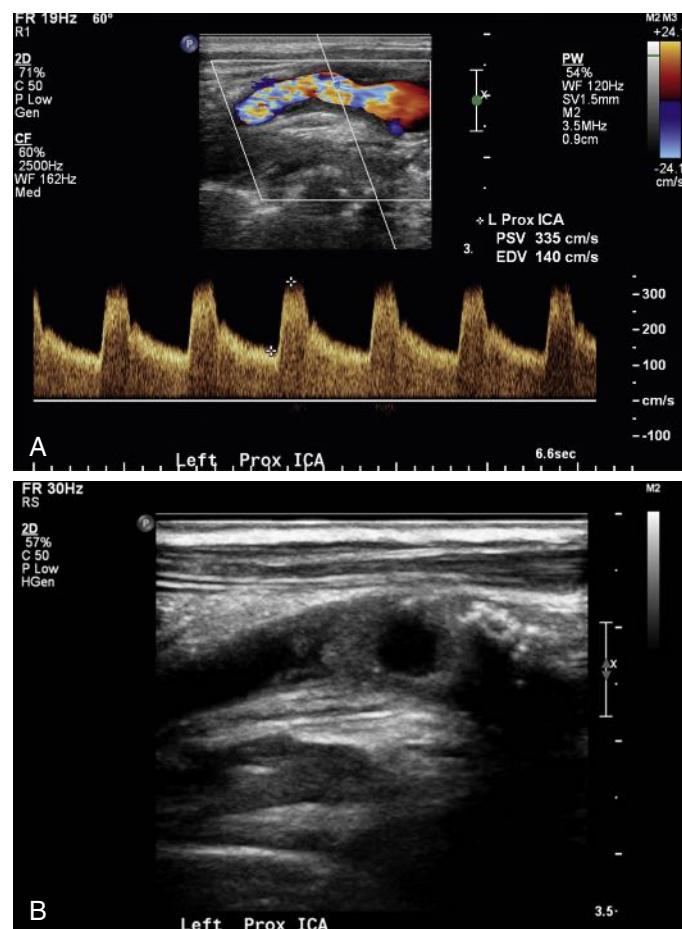
There has been significant interest in serum markers of inflammation and elevated proteolytic activity. Unstable plaques appear to have elevated frequency of proteolysis and subsequent apoptosis, as well as increased rates of inflammatory cell activity. A recent comprehensive review highlighted the potential role of several categories of serum biomarkers in extracranial carotid disease.<sup>53</sup> Matrix metalloproteinases (MMPs) are a large family of enzymes involved in catalyzing extracellular matrix breakdown and have been associated with systemic atherosclerosis and unstable carotid plaques, particularly MMP-2,<sup>64,65</sup> and MMP-1, -7, -8, -9 and -13.<sup>65–68</sup> Several studies have shown that inflammatory cytokines, such as interleukin-18 (IL-18), IL-6, tumor necrosis factor (TNF), and high sensitivity C-reactive protein (CRP), are elevated in plaques and sera of symptomatic patients.<sup>53,54,69–75</sup> However, there was a relatively small number of patients in these studies and the findings have not been corroborated by others.<sup>53</sup> Similarly, several adhesion molecules including selectins and vascular cell adhesion molecule-1 have also shown promise and controversies in their associations with plaque stability.<sup>53,54,76–79</sup> At this point in time, no single serum biomarker is proven to predict vulnerable plaques in a large-scale prospective study. Among these potential biomarkers, MMPs show the most promise.<sup>53,54</sup> Given this information, general inflammatory/lipid panels with further serum testing may be a promising adjunctive decision-making tool in the future for patients with extracranial carotid disease.

## IMAGING

Imaging plays a fundamental role in our evaluation of carotid disease and in our decision-making on carotid interventions. Several novel imaging techniques have emerged in the last decade that may allow for more widespread analysis of disease features, expanding from degree of stenosis to specific lesion features that are associated with plaque vulnerability.

### Ultrasound Imaging

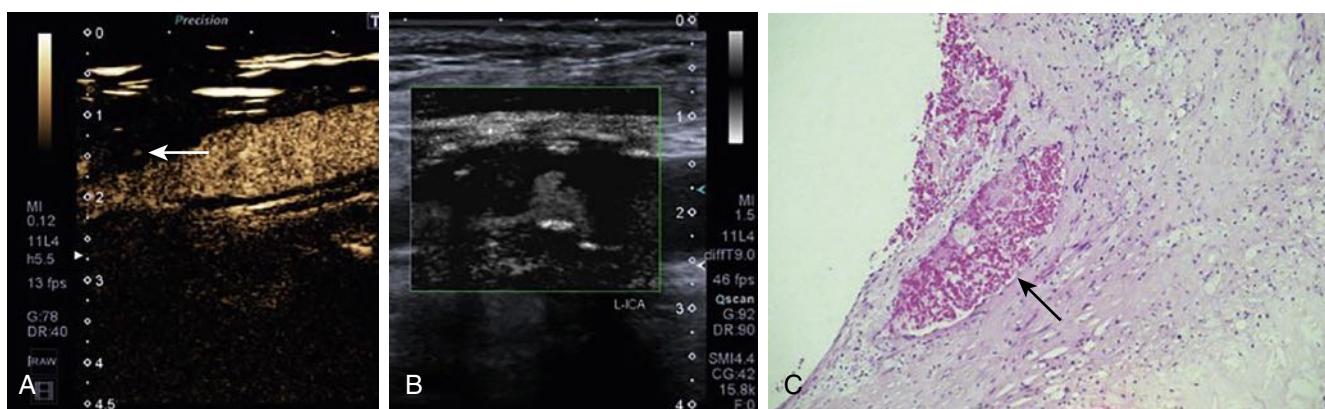
Traditional two dimensional (2-D), or B-mode (“Brightness”), ultrasound produces sound waves using a linear array of transducers. The sound waves are reflected as echoes that produce a characteristic black and white image. Classically, ultrasound for carotid artery disease has relied on flow velocity parameters in the ICA and CCA (Fig. 89.2). Gray-scale median (GSM), an ultrasound marker for plaque echogenicity that reflects increased fibrous and calcific content, has been associated with plaque stability. Low GSM, i.e., echolucency, is associated with increasing plaque AHA class, increased lipid core size, and plaque inflammation.<sup>12</sup> Multiple authors have shown that plaque echolucency correlates with soft, lipid-heavy, necrotic features that are clinically and histologically associated with instability (Fig. 89.2).<sup>22,37,80–84</sup> A recent meta-analysis concluded that plaque echolucency predicted future cerebrovascular events in asymptomatic patients, regardless of degree of stenosis, (RR 2.72, CI 1.86–3.96) and recurrence of symptoms in patients who were symptomatic (RR 2.97, CI 1.85–4.78).<sup>81</sup> In addition to echogenicity, juxtaluminal black (hypoechoic) area,



**Figure 89.2** 2-D Carotid Duplex. (A) Significant color flow disturbance and increased flow velocity. (B) Echolucent area within an atherosclerotic carotid plaque indicative of prior embolization.

defined as pixels with a greyscale value <25, has been shown to linearly predict the rate of future strokes.<sup>85</sup> Patients with a juxtaluminal black area in the highest quartile ( $>10 \text{ mm}^2$ ) had an annual stroke rate of 5% during an 8-year follow up period ( $P < 0.001$ ).<sup>85</sup> Furthermore, plaque size on 2-D ultrasound has also been linked with increased five-year risk of CVA.<sup>86</sup> The combined features of plaque area  $>95 \text{ mm}^2$  and juxtaluminal black area  $>6 \text{ mm}^2$  have been shown to have a 90% chance of predicting unstable plaque based on a histologic analysis.<sup>87</sup> However, these novel ultrasound techniques require longer scanning time, technical expertise, and clinical standardization. Therefore, they have not yet been widely adapted for routine clinical use.

Contrast-enhanced ultrasound (CEUS) and superb microvascular imaging (SMI) are two emerging technologies for enhancing 2-D ultrasound analysis of extracranial carotid disease (Fig. 89.3). SMI allows for visualization of neovascularity (a feature of vulnerable plaques) by using an algorithm specially built into the ultrasound software to separate out microvascular signals from clutter and artifact.<sup>88</sup> CEUS involves intravenous injection of contrast microbubbles diluted in saline solution followed by timed imaging of the carotid arteries. A recent study showed that SMI and CEUS demonstrate strong



**Figure 89.3** CEUS (A), SMI (B), and histological slice of plaque (C) from a patient with >70% stenosis and mostly hypoechoic plaque. The arrow in C points to a small neovessel. (Adapted from Zamani M, Skagen K, Scott H, et al. Carotid plaque neovascularization detected with superb microvascular imaging ultrasound without using contrast media. *Stroke.* 2019;50(11):3121–3127.)

agreement for grading plaque neovascularization and correlate well with echolucency ( $P < 0.001$  and  $P = 0.0002$ , respectively).<sup>88</sup> However, these advanced ultrasound imaging modalities need further validation with larger scale studies.<sup>89,90</sup> In experimental animal models, microbubbles targeted to P-selectin and VCAM1, protein ligands involved in vessel wall inflammation, have demonstrated an impressive potential as an imaging technique for unstable plaques.<sup>91</sup>

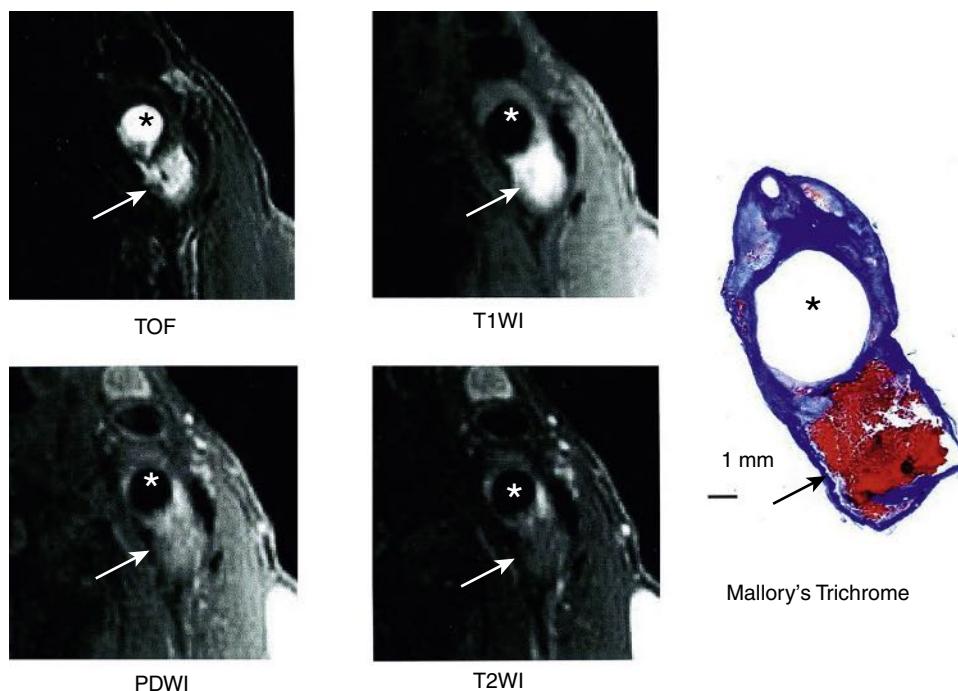
Three-dimensional ultrasound (3-D) is more sensitive to plaque changes over time than traditional 2-D duplex.<sup>92–94</sup> Recent investigations using 3-D ultrasound have analyzed both total plaque volume and plaque ulcer volume, and showed good reliability and reproducibility.<sup>92,94</sup> Using 3-D technology to detect plaque ulcers (defined as surface irregularities  $>1 \text{ mm}^3$ ), investigators demonstrated that ulcer volumes of  $>5 \text{ mm}^3$  predict future risk of CVA/TIA and all-cause death ( $P = 0.009$ ).<sup>95</sup> Drawbacks to 3-D ultrasound in current practice include the relatively heavy, motorized transducer required for use, lack of widespread operator training, high cost, and high potential for motion artifact to disrupt image acquisition. As such, it has not yet been broadly adopted in clinical practice, and further investigations into its sensitivity, specificity, and cost-benefit ratio are still required. More advanced four-dimensional (4-D) ultrasound (based on 3-D ultrasound measurements over a single cardiac cycle to study plaque surface movements<sup>96</sup>) and microbubble-targeted plaque antigen detection have also shown promise in identifying unstable plaques in small studies.<sup>88</sup>

Intravascular ultrasound (IVUS)-based virtual histology (VH) is another ultrasound tool that has been investigated to characterize carotid plaques.<sup>97</sup> Unlike the findings in cardiac imaging, the studies correlating IVUS findings with carotid plaque morphology or microembolization have not been consistent. Although the feasibility of IVUS has been demonstrated, the invasive nature of IVUS in carotid imaging will limit its routine use. The utility of IVUS may be more appropriate during carotid artery stent (CAS) procedures. Larger studies are warranted to determine the efficacy of IVUS for purely diagnostic identification of vulnerable plaques.<sup>97</sup>

## MRI Imaging

MRI is a form of cross-sectional imaging that does not use ionizing radiation and has been widely used to study carotid artery disease. Multiple large, well-designed studies have shown good correlation between MRI findings and histopathology of unstable plaques (Fig. 89.4).<sup>98–100</sup> A recent meta-analysis on the utility of MRI in analysis of carotid disease showed IPH, lipid-rich necrotic core, and a thin or ruptured fibrous cap (TRFC) were all significant predictors of future CVA/TIA, regardless of degree of stenosis.<sup>98</sup> IPH had the highest hazard ratio (4.95, CI 2.91–7.24), followed by lipid-rich necrotic core (3.00, 1.51–5.95) and TRFC (5.93 2.65–13.20), respectively.<sup>98</sup> Several additional studies have also identified a link between IPH, lipid-rich necrotic core, TRFC, and future stroke risk.<sup>101,102</sup>

In recent years, several novel MRI contrast agents and techniques have actively been investigated.<sup>102</sup> Micro iron-oxide particles targeted to bind to VCAM1 and P-selectin can differentiate high-risk plaques from low-risk ones on MRI.<sup>103</sup> A recent MRI-based fluid dynamics study using 3-D computational modelling and simulated axial stretching to analyze plaque wall stress (PWS) and mechanical shear stress showed that ulcerated plaques demonstrated 86% higher PWS than non-ulcerated plaques ( $P < 0.0001$ ); shear stress within selected ulcer nodes was 170% higher than that within non-ulcer nodes.<sup>46</sup> Additional studies using 3-D MRI have confirmed that PWS is higher in symptomatic patients than asymptomatic patients.<sup>51</sup> MR characterization of plaque composition is an emerging area of research; barriers to widespread implementation at this juncture include lack of widespread availability (some of the techniques described in small research studies require specialized carotid surface coils, for example), and difficulty distinguishing intra-plaque hemorrhage from intra-luminal thrombus.<sup>98,100</sup> Further, most studies on MR characterization of vulnerable plaques that have been performed thus far lack standardized protocols and many patients are not able to undergo MRI studies.<sup>98,100</sup> For patients who are able to receive an MRI, larger trials that correlate MR findings with histopathologic findings are required for MR to become a reliable clinical decision-making tool.



**Figure 89.4** MRI and histologic specimen of an AHA type VI lesion demonstrating mixed IPH with a high signal intensity on multiple MR sequences; the arrow indicates the area of mixed hemorrhage. (Adapted from Cai JM, Hatsukami TS, Ferguson MS, et al. Classification of human carotid atherosclerotic lesions with *in vivo* multicontrast magnetic resonance imaging. *Circulation*. 2002;106(11):1368–1373.)

## CT Imaging

CT angiography (CTA) is a widely used imaging modality for carotid disease evaluation and has shown good correlation with digital subtraction angiography (DSA) and US in defining the degree of carotid artery stenosis and also provides additional anatomical information.<sup>104–107</sup> High-resolution CTA for detection of vulnerable plaques is an emerging area of research. In a small study, there was a reasonable (72.6%) agreement between CTA detection of high-risk features and histological analysis; this was especially true for findings of lipid core and IPH.<sup>108</sup> Functional imaging studies of carotid disease, such as positron emission tomography scanning (PET), are being investigated to detect plaques with high inflammatory or metabolic activity and are gradually gaining traction.<sup>109,110</sup> Several imaging tracers, including fluorodeoxyglucose (<sup>18</sup>FDG), fluoromethyl-choline (<sup>18</sup>F-choline), and <sup>123</sup>I-VEGF<sub>165</sub>, have been proposed and studied as targeted ligands. Symptomatic plaques have been shown to take up 27% more FDG than asymptomatic ones.<sup>110,111</sup> Several other radioactive small-molecule targets (including targets for VEGF and IL-12) have been proposed and show potential for non-invasive identification of unstable plaques.

## ADDITIONAL CONSIDERATIONS

While our understanding of the histologic and imaging features of vulnerable plaques has improved significantly in recent years, investigations into clinical features of such plaques have not been incorporated into our practice guidelines. A majority

of surgeons do not offer carotid revascularization to asymptomatic patients with <70% stenosis or symptomatic patients with <50% stenosis. However, isolated case series have shown correlation between vulnerable plaque features (neovascularization and inflammation) from CEA specimens and high risk imaging features in symptomatic patients despite stenosis of less than 50%.<sup>112</sup> In addition, plaques may progress and regress over time, moving between stability categories as they face different biochemical and biomechanical stresses.<sup>87</sup> One study of CT angiography for plaque analysis discovered that plaque volume growth during a 1-year period ranged from -5.6% to 10.1%; the authors found that the relative size of plaque components could change as well.<sup>113</sup> This dynamic development makes clinical diagnosis of the unstable plaque, particularly in asymptomatic patients, extremely difficult. Needless to say, there are patients with moderate, <70% carotid stenosis but unstable plaque features that will benefit from surgical or endovascular treatment. Identification of the vulnerable carotid plaque is an evolving research field. Larger prospective studies of clinical features are needed.

## CONCLUSIONS

Carotid plaque stability is an emerging, rapidly evolving area of vascular research that has the potential for a high impact on the way we take care of patients with extracranial carotid disease. The traditional paradigms that help us identify revascularization candidates, such as degree of stenosis and symptomatic status, will change significantly as we develop a better

understanding of what types of plaques cause cerebrovascular symptoms. Ultimately, development of non-invasive, clinical methods of characterizing plaque behavior over time will change the way we understand and treat carotid disease.

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A complete reference list can be found online at [www.expertconsult.com](http://www.expertconsult.com).

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# Carotid Artery Disease and Cognitive Functional Decline

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## INTRODUCTION

A decline in cognitive function from ischemic, hypoperfused or hemorrhagic brain lesions has been termed “vascular cognitive impairment” (VCI).<sup>1</sup> While memory dysfunction is an important correlate of classic dementias, VCI is generally associated with dysfunction in executive function and processing speed. Cognitive dysfunction after stroke is a well-recognized disability. This awareness has stimulated extensive research that has established standards of diagnosis, reporting, prevention and management of cognitive impairment after stroke. The notion that atherosclerotic carotid artery occlusive disease can lead to cognitive dysfunction was first proposed by Fisher in 1951, based on a necropsy case.<sup>2</sup> He postulated that carotid stenosis can produce a dementia state, and proposed that restoration of blood supply to the brain could reverse the condition. This stimulated the first carotid reconstruction (1951) and carotid endarterectomies (CEA, 1953 and 1954) on patients with stroke and carotid artery stenosis.<sup>3–5</sup> Subsequently, stroke was recognized as a leading cause of death in the United States with about 10%–15% of instances attributable to atheroembolization from a carotid stenosis. As a result, the focus shifted to stroke prevention, which became the primary focus of carotid revascularization.<sup>6</sup>

The possibility that carotid stenosis could alter cognitive function has only recently received attention again. By 2030, 20% of the US population will be 65 years of age or older.

Cognitive dysfunction is the most frequently reported disability in this age group, prevalent in ~20%,<sup>7</sup> and often progresses to falls, frailty, loss of functional independence, dementia, disability, and death.<sup>8</sup> Older age and male sex, genetic factors (e.g., ApoE), silent brain infarctions, white matter hyperintensities, and microbleeds are known non-modifiable risk factors associated with cognitive decline.<sup>9–13</sup> Although vascular risk factors such as hypertension, diabetes, dyslipidemia, cigarette smoking and obesity respond to aggressive pharmacological and lifestyle modifications, long-term compliance remains challenging due to recidivism. The possible causative relationship between carotid disease and cognitive impairment offers the potential that carotid revascularization could restore cognitive function or delay progression. This chapter reviews the current state of knowledge about the pathophysiology, severity, and course of cognitive dysfunction in patients with stenosis or occlusion of the carotid arteries.

## COGNITIVE VERSUS NEUROLOGIC FUNCTION

Cognitive function is the term used to describe how a person produces and controls behavioral and mental processes such as thinking, learning, remembering, problem-solving, and consciousness. Clinical observations in brain-injured patients

indicate that cognitive abilities are controlled by specific regions of the brain somewhat like motor and sensory abilities. For instance, studies of the visual sensory system show that visual stimuli are initially received in the primary visual cortex. Secondary processing for detection of direction, intensity, contrast, speed, and other combined attributes of the stimulus takes place in the surrounding higher-order visual cortex. Finally, the association cortex responds exclusively to a combination of two or more sensory inputs. Therefore, cortical systems form a hierarchy based on the functions they participate in. Contemporary conceptions propose that activation and interaction of these regions occur through dedicated or shared circuits.<sup>14</sup> It is the interconnections and interactions within and between such systems that give rise to specific cognitive functions. The major difference in conceptualization between what is traditionally termed a neurologic deficit versus a cognitive deficit, is that the former is based on the loss of a localized sensory or motor function (such as movement of the left arm) whereas the latter is a loss of a system (such as ability to learn new facts). Studies have clearly shown that individuals with isolated cognitive dysfunction are at greater risk for employment problems, have difficulty with activities of daily living, may require personal assistance, and may be rendered unsafe drivers. Patients may experience problems in social situations, and the impact on family relationships is also significant. Since changes may be subtle and are not commonly sought for in a routine clinical evaluation, they may persist and progress undetected with consequent high societal and healthcare system costs.

Neurologic and cognitive deficits may occur in isolation, or occur concurrently, depending on the nature and location of the cerebral injury sustained. Evidence for the coexistence of cognitive injury in patients with neurologic injury from carotid stenosis (i.e., a stroke) is quite forthcoming.<sup>15</sup> However, exclusive cognitive dysfunction in these patients have traditionally not been looked for, and have therefore not been reported in any detail until quite recently. One informative view of the extent of the problem was provided in a subset analysis of the Cardiovascular Health Study which suggested that carotid stenosis may be a risk factor for cognitive dysfunction.<sup>16</sup> In this epidemiologic study, 32 patients were identified with asymptomatic left carotid stenosis  $\geq 75\%$ . These patients, along with the rest of the cohort, were serially tested with a modified mini-mental state examination. Based on the test scores, there was a significant decline in cognitive function in 34% of the carotid stenosis patients (12/32) over 5 years without having suffered a stroke during follow-up. A similar decline was noted when patients with stenoses  $\geq 50\%$  were analyzed. Such a decline was not observed in the remaining cohort of over 4000 patients. The authors did caution that the study was preliminary, the sample size was small, and findings needed substantiation due to the absence of an ideal cognitive test battery designed to assess patients with carotid stenosis.

## EVALUATION OF COGNITIVE FUNCTION

While neurologic examinations aim at identifying specific sensory or motor deficits, a cognitive assessment consists of administering tests that examine a set of more-or-less independent

### BOX 90.1 Key Cognitive Function Domains

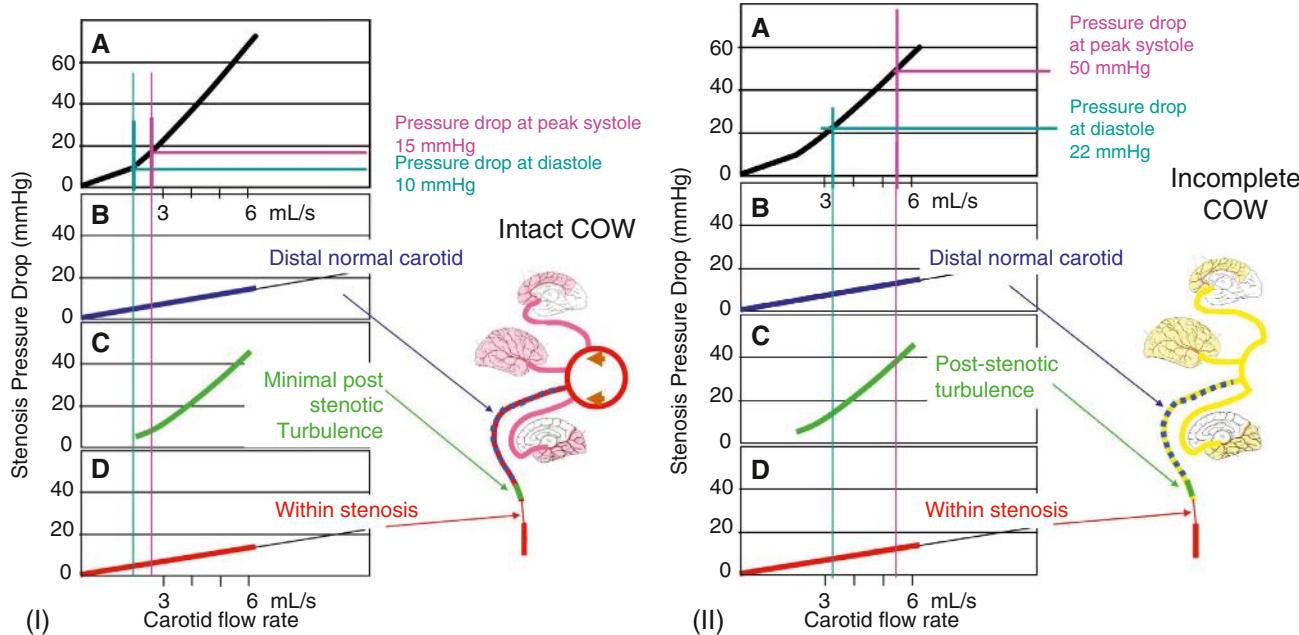
- Attention/concentration
- Memory
- Executive function
- Processing speed
- Language/verbal skills
- Perception including visuospatial
- Motor skills

functional domains that are controlled by brain systems.<sup>17</sup> Cognitive domains are further divided into component sub-domains and most cognitive tests measure one or more discrete subdomains. Therefore, more than one test is generally required to assess any particular domain completely. In addition, some tests may examine combined categories of sub-domains. The major cognitive domains that are commonly tested include: attention/concentration, memory, executive function, processing speed, language/verbal skills, perception including visuospatial, and motor skills (Box 90.1). Most broadly accepted cognitive tests have standardized administration procedures with appropriate normative comparison groups.<sup>17</sup> Guidelines for the assessment of cognition in clinical research have been published, derived largely from medical treatment outcomes studies.<sup>1</sup> However, carotid stenosis is generally a unilateral disease perturbing primarily one cerebral hemisphere, a situation quite different from the global hemispheric insult (e.g., Alzheimer's disease) suffered by patients for whom the tests were primarily developed. Cognitive batteries addressing the unique issues relating to carotid stenosis have been developed more recently. The author's ongoing Asymptomatic Carotid Stenosis and Cognitive Function (ACCOF) group of studies are one example of an attempt to develop and validate a cognitive test battery that is comprehensive and responsive to carotid stenosis patients, while maintaining clinical feasibility (e.g., taking approximately 30 minutes to implement).<sup>18–20</sup>

While assessing for specific cognitive deficits requires a composite of several tests, two commonly utilized cognitive screening tests are also available. Introduced in 1975, the Mini-Mental State Exam (MMSE) offers a quick (7 to 8 minutes) assessment of orientation, word recall, language abilities, attention and calculation, and visuospatial ability. The Montreal Cognitive Assessment (MoCA), is a newer test created in 1996 that also offers tasks such as a clock-drawing test and a trail test (10–12 minutes). While the MoCA is slightly more sensitive, neither can be considered a definitive test, and both are primarily screening tools for traditional dementias (e.g., Alzheimer's) and therefore less sensitive to VCI. They do not serve well as diagnostic or differentiating tools.

## PATHOPHYSIOLOGY OF COGNITIVE DYSFUNCTION IN CAROTID STENOSIS

Vascular cognitive impairment is widely described as a progressive disease resulting from accumulated ischemic injury. Symptomatic carotid disease is primarily associated with



**Figure 90.1** Pressure drop across a 70% carotid artery stenosis in the presence of (I) an intact circle of Willis (COW) and (II) an incomplete COW. In each of the panels, (A) depicts the net pressure drop after summing the pressure drops across the (B) distal normal carotid segment, (C) the distal end of the stenosed segment and (D) across the stenosed segment. (Adapted from: Lal BK, Beach KW, Sumner DS. Intracranial collateralization determines hemodynamic forces for carotid plaque disruption. *J Vasc Surg*. 2011;54(5):1461–1471. Copyright 2011 by the Society for Vascular Surgery. Published by Elsevier Inc.)

stroke and transient ischemic attacks through atheroembolization. On occasion, patients may also be rendered neurologically symptomatic from hypoperfusion secondary to stenosis with insufficient collateral compensation, “watershed infarction”.<sup>21,22</sup> In stroke-free patients, hypoperfusion<sup>23</sup> and showering of atheroemboli<sup>21</sup> are two important factors hypothesized to lead to cognitive dysfunction in patients with carotid stenosis or occlusion.

### Carotid Flow Restriction with Brain Hypoperfusion

Several chronic diseases in older adults such as intracranial vasculopathy, hypertension, and cardiac failure are associated with cerebral hypoperfusion, hypometabolism and cognitive dysfunction.<sup>24–27</sup> Cerebral hypoperfusion results in brain (neuronal) glucose hypometabolism measurable as reduced uptake of 2-[18F]fluoro-2-deoxy-D-glucose on positron emission tomography<sup>24</sup> that is associated with cognitive decline and progression to Alzheimer’s disease.<sup>28</sup> Balloon occlusion or clamping of the carotid artery leads to attentional deficits proportionate to the reduction in cerebral blood flow.<sup>29,30</sup> Patients undergoing carotid cross-clamping demonstrate electro-encephalogram waveform flattening, indicating decreased neural activity.<sup>30</sup> It is therefore reasonable to suspect that atherosclerotic narrowing of the carotid artery may also be associated with hypoperfusion with attendant reduced cognition.<sup>19,31</sup>

Hemodynamic theory holds that as cerebral perfusion pressure falls, cerebral blood flow is maintained by collateral circulation and autoregulatory vasodilation of cerebral

arterioles. Our computer model for cerebrovascular circulation demonstrates that incomplete intracranial collateral circulation (primarily supplied by the circle of Willis) results in large pressure drops across areas of carotid stenosis (Fig. 90.1).<sup>32</sup> Since almost half of all individuals have a partially or completely discontinuous circle of Willis,<sup>33</sup> it stands to reason that a substantial proportion of patients with carotid stenosis are inadequately collateralized. If the pressure drop across the stenosis is large enough, the intracranial arterioles become maximally dilated in an effort to maintain brain perfusion. They may fail to dilate further (flow failure) when challenged by CO<sub>2</sub> (e.g., by breath-holding) that is manifested by reduced vasoactivity on transcranial Doppler (TCD) testing.<sup>34,35</sup> We have found that at least half of asymptomatic carotid stenosis patients demonstrate flow failure as evidenced by an impaired response to breath holding on TCD.<sup>19</sup> The delay in peak contrast arriving into one hemisphere (time to peak, TTP) compared to the contralateral hemisphere on magnetic resonance imaging can be used to measure the extent of cerebral hypoperfusion from a carotid stenosis. We found that when the threshold for TTP delay was set at >0.5 seconds, 45% of patients with severe carotid stenosis demonstrated hypoperfusion in at least 50% of their brain. When the threshold was set at >1 second, 15% demonstrated hypoperfusion in over 50% of their brain. Finally, when the threshold was set at >2 seconds, 10% had at least 35% of their brain volume hypoperfused.<sup>36</sup> While extracranial carotid atherosclerosis may be a marker for more extensive intracranial occlusive atherosclerosis, this was not observed in the reported cohort.

## Silent Microembolic Injury

Cerebral microembolization is seen more frequently in patients with vascular dementia<sup>37</sup> and spontaneous cerebral microemboli are associated with accelerated cognitive decline.<sup>38</sup> In the Cardiovascular Health Study, individuals with incident neurologically silent brain infarctions detected by magnetic resonance imaging over the course of 5 years had a two-fold decrease in Modified Mini-Mental State Examination scores compared to those without infarctions ( $P < 0.01$ ).<sup>39</sup> Among 1015 participants in the Rotterdam Scan Study, silent brain infarctions at baseline were associated with a 2.26 (1.1–4.7) hazard ratio for incident dementia over 3.6 years. The new silent infarctions were associated with decreases in psychomotor skills and global cognitive function ( $P < 0.04$  for both).<sup>11</sup> These findings were confirmed by the Atherosclerosis Risk In Communities study.<sup>40</sup> Furthermore, people with pre-existing silent brain infarctions are at a higher risk for additional silent or symptomatic infarcts during follow-up<sup>41</sup> and cognitive decline occurs preferentially in these patients.<sup>11</sup> While its etiology is multifactorial, postoperative cognitive decline in patients undergoing coronary artery bypass procedures has also been correlated with silent microembolic cerebral injury.<sup>42,43</sup> The clinical impact of microembolism due to carotid stenosis, however, remains less clearly established. In experimental studies, injection of 50 µm microspheres into rat carotid arteries resulted in cerebral injury and reduced attentional performance.<sup>44</sup> Some studies have observed a relationship between procedural microembolization and cognitive dysfunction after carotid revascularization.<sup>45</sup> Most studies, however, have yet to find a relationship between carotid embolic brain injury and cognitive function.<sup>46,47</sup> Our study also did not identify a difference in microembolization rates between patients with carotid stenosis who had cognitive impairment and those who were not impaired.<sup>19</sup>

## RELATIONSHIP BETWEEN CEREBRAL HYPOPERFUSION AND COGNITIVE DYSFUNCTION

The relationship between global cerebral hypoperfusion and cognition is best exemplified by studies on patients with congestive heart failure (CHF).<sup>48</sup> Zuccala et al. were the first to demonstrate that cognition was impaired in 57 older adults with chronic CHF and an ejection fraction of  $\leq 30\%$ .<sup>25</sup> In fact, 35%–50% of patients with end-stage heart failure demonstrate evidence of cognitive dysfunction<sup>49</sup> and in severe heart failure, reduced cerebral blood flow correlates with increased prevalence of cognitive dysfunction.<sup>50</sup> Implantation of a left ventricular assist device or cardiac transplantation, restored improved cerebral blood flow and restored cognitive function in these patients.<sup>51–53</sup>

## EVIDENCE FOR COGNITIVE DYSFUNCTION IN ASYMPTOMATIC CAROTID STENOSIS

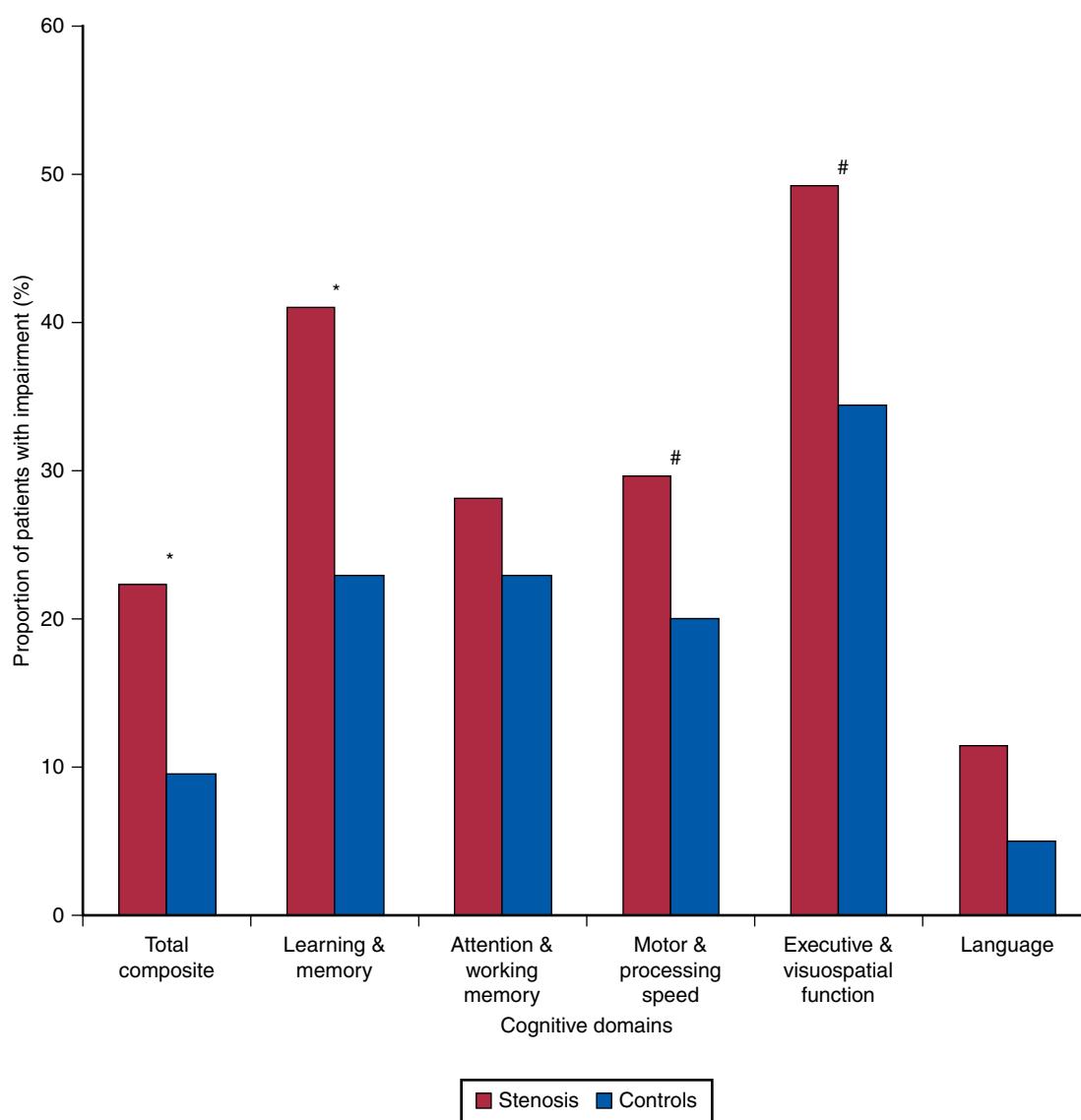
Few studies have evaluated cognitive function in patients with asymptomatic carotid stenosis. Most have focused on patients

undergoing carotid endarterectomy or stenting. Cognitive impairment has been reported in patients with carotid stenosis, although others have not found an association.<sup>54–56</sup> In most reports, the coexistence of stenosis with other confounding risk factors for cognitive impairment makes the findings difficult to interpret. Furthermore, it is challenging to design an adequately powered analysis of asymptomatic patients that uses the appropriate spectrum of cognitive assessments and controls for other confounders that predispose to cognitive dysfunction. The argument that carotid disease is an independent cause for cognitive impairment is strengthened by a select group of adequately controlled studies of patients with a stenosis in the absence of frank infarction. Bakker's review<sup>57</sup> found two studies reporting generalized cognitive dysfunction<sup>58,59</sup> and three reporting domain-specific reductions in memory,<sup>60,61</sup> learning,<sup>61</sup> psychomotor speed<sup>60</sup> and problem-solving.<sup>61,62</sup> The Trømsø study found that carotid stenosis was associated with lower scores on tests of attention, psychomotor speed and memory than controls.<sup>63</sup> In a longitudinal study, severe carotid stenosis was associated with cognitive deterioration over a 3-year follow-up period.<sup>35</sup> In one of the largest studies conducted to date, the first 1000 patients with asymptomatic carotid stenosis enrolled in the ongoing Carotid Revascularization and Medical Management Trial (CREST-2) underwent telephone-based cognitive testing. CREST-2 participants had significantly lower baseline cognitive scores than the general population.<sup>64</sup>

A hemodynamic pathophysiology assumes cerebrovascular flow failure from inadequate collateral compensation. In this scenario, patients with adequate cerebrovascular compensation would not manifest cognitive abnormalities. However, very few studies have measured cerebral hemodynamics in the context of carotid stenosis and cognitive function. This may be an important explanation for the variable cognitive outcomes reported across studies in patients with carotid stenosis. In 82 never symptomatic patients with carotid stenosis we found that approximately half had impairment in at least two cognitive domains, independent of known risk factors for vascular cognitive impairment. The deficits were driven primarily by reduced fine motor skills, processing speed, learning/memory and executive function and was mild to moderate in severity (Fig. 90.2). The mechanism for impairments was likely hemodynamic as evidenced by an impaired cerebrovascular reserve (CVR, measured as a reduced breath-holding index on TCD).<sup>19</sup> Other groups have confirmed that the presence of impaired CVR ipsilateral to a carotid stenosis is associated with an increased incidence of cognitive deterioration.<sup>35</sup> Similarly, in a longitudinal study of patients with severe asymptomatic carotid stenosis, those with an impaired CVR had the greatest decline in cognitive function over 3 years of follow-up.<sup>65</sup>

## COGNITIVE CHANGES AFTER CAROTID REVASCULARIZATION

Since cerebral hemodynamic impairment has an independent association with cognitive dysfunction, an important question is whether treatment of the hemodynamic impairment



**Figure 90.2** Proportion of carotid stenosis patients vs. vascular risk factor–matched controls demonstrating impairment in individual cognitive domains. \* $P = 0.01$ ; # $P = 0.03$ . (Adapted from: Lal BK, Dux MC, Sikdar S, et al. Asymptomatic carotid stenosis is associated with cognitive impairment. *J Vasc Surg*. 2017;66(4):1083–1092. Copyright 2017 by the Society for Vascular Surgery. Published by Elsevier Inc.)

can reverse cognitive dysfunction. The underlying mechanisms for any cognitive function improvement could be the prevention of ongoing microembolization from the plaque, or reversal of the flow restriction at the stenosis, or both. When carotid arteries of rats are ligated to produce chronic cerebral hypoperfusion, they demonstrate poor performance on water maze memory tests.<sup>66</sup> Restoration of carotid blood flow within 1 to 2 weeks restores cerebral blood flow (CBF) and memory performance. Revascularization at 3 weeks or later does not improve CBF or memory function, likely as a result of irreversible brain infarction from the chronic ligation of the artery. This indicates that neuronal ischemia with manifestations of behavioral deficits is potentially reversible for a period of time if CBF is improved by treating the flow restriction.

## EC–IC BYPASS

In 25 patients with unilateral carotid occlusion and cognitive dysfunction, revascularization by an extracranial–intracranial (EC–IC) bypass resulted in increased CBF, improved cerebrovascular reactivity and cognitive function improvement.<sup>31</sup> A small randomized trial ( $n = 41$  patients) comparing EC–IC bypass to medical therapy alone found that cognitive function improved in the subset of patients with impaired cerebrovascular hemodynamics and no prior stroke at baseline.<sup>67</sup>

## CAROTID ENDARTERECTOMY

Some studies have reported an improvement in cognitive function 3 months after CEA.<sup>68</sup> However, this improvement may

have been due to a practice effect since the same versions of the tests were used during follow-up and the interval between assessments was relatively brief, and control groups were not included. Another controlled study found a decline in 1 of 4 cognitive tests, and when all tests were combined, there was a significant decline in the composite cognitive score in the CEA group.<sup>69</sup> This study was limited by a small sample and by incomplete follow-up. The systematic reviews of Lunn et al.<sup>70</sup> and Irvine et al.<sup>71</sup> exemplify the current absence of consensus regarding cognitive function outcome after CEA. They categorized 16 of 28 studies as demonstrating cognitive improvement after surgery while the remaining 12 studies showed no improvement or even a decline in function. In their review, when Lunn et al. assessed the impact of CEA upon specific domains, they found that memory and executive function were particularly likely to benefit from surgery. However, the inconsistent results prompted the authors to conclude that reliable inferences could not be drawn without the performance of a well-controlled, adequately powered analysis. Such a study would have to include follow-up beyond 6 months to account for the effects of surgery and anesthesia and account for the wide range of confounders that affect cognitive function such as age, education level, intelligence quotient, concomitant depression, and other vascular risk factors. The study would need to include a cognitive testing battery sensitive to the unique aspects of carotid disease based on the knowledge obtained from more recent studies. Finally, the beneficial response to surgery may be restricted to only those patients with flow failure and consequent cerebral hypoperfusion. For instance, in one small study of 24 asymptomatic stenosis patients, only six had reduced flow in the middle cerebral artery on TCD at baseline. After CEA, both flow and attentional performance improved in those patients.<sup>72</sup> This suggests that in patients with carotid stenosis-related flow restriction, inadequate compensation, pressure drop and consequent cerebral hypoperfusion, CEA may improve perfusion and cognition. This hypothesis is currently under investigation in two ongoing prospective studies, CREST-Hemodynamic<sup>73</sup> and ACCOF-2,<sup>36</sup> and results will be forthcoming in the near future.

## CAROTID ARTERY STENTING

As with CEA, the impact of CAS on cognitive function remains unresolved. While it is possible that the procedure may improve cognitive function in a manner similar to CEA by improving cerebral hypoperfusion or by reducing chronic atheroembolization, it may also worsen cognitive function as a result of increased periprocedural embolization. A subset analysis of patients in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) showed no difference in cognitive outcomes between CEA and CAS, no significant impact on cognitive function 6 months after the procedures, and a possible decline in cognitive function in some patients undergoing carotid angioplasty.<sup>74</sup> Other small studies, each with fewer than 100 patients, have reported improvements in learning and executive function 2 days post-stenting,<sup>75</sup> self-reported improvements in daily function,<sup>76</sup> new learning and

memory<sup>77</sup> and executive function.<sup>78</sup> One study has measured cerebral blood flow on computed tomography perfusion scans. Patients with reduced CBF at baseline showed improvements in cerebral perfusion and in composite cognitive function 3 months after CAS.<sup>79</sup> In a non-randomized prospective study, we tested multiple cognitive domains at baseline and 6 months post-carotid revascularization in patients undergoing CEA ( $n = 25$ ) and CAS ( $n = 21$ ) for high-grade asymptomatic carotid stenosis.<sup>19</sup> We found that the composite cognitive score improved significantly after both procedures, with notable improvements in learning/memory, motor speed/coordination/executive function, language/naming, verbal fluency and processing speed, compared to baseline.

## CONCLUSION

The relationship between cerebrovascular pathophysiology and cognitive function is complex. Carotid disease can cause flow restriction at the stenosis, which, if not adequately compensated through cross collateral filling, can result in flow failure with consequent cerebral hypoperfusion. However, atherosclerotic risk factors that accompany carotid stenosis can also cause both structural pathology and chronic hemodynamic failure with cognitive dysfunction. Genetic factors and Alzheimer's disease pathology in these elderly patients may be superimposed on the vascular changes, further worsening the cognitive dysfunction. Careful studies are required and ongoing that separate out the individual contributions of these mechanisms to incident cognitive dysfunction seen in patients with carotid stenosis. There is strong evidence for a relationship between cerebrovascular hemodynamic dysfunction and cognitive dysfunction. The possibility for reversing some of these changes with carotid revascularization warrants serious clinical attention and continued scientific study.

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Vermeer SE, Prins ND, den Heijer T, et al. Silent brain infarcts and the risk of dementia and cognitive decline. *N Engl J Med.* 2003;348(13):1215–1222.

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Wolters FJ, Zonneveld HI, Hofman A, et al. Cerebral perfusion and the risk of dementia: A population-based study. *Circulation.* 2017;136(8):719–728.

*A study using 2-dimensional phase-contrast magnetic resonance imaging of 4759 participants in the Rotterdam study with a median follow-up of 6.9 years demonstrated that cerebral hypoperfusion is associated with accelerated cognitive decline and an increased risk of dementia in the general population.*

A complete reference list can be found online at [www.expertconsult.com](http://www.expertconsult.com).

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# Cerebrovascular Disease: Diagnostic Evaluation

SALIM LALA and ROBYN MACSATA<sup>†</sup>

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## DIAGNOSTIC TOOLS

### Duplex Ultrasound

Duplex ultrasound (DU) refers to two modes of ultrasound, namely B mode that obtains gray-scale imaging, and Doppler that evaluates the velocity and direction of blood flow in the vessel. DU determines the degree of carotid artery stenosis based on gray-scale plaque estimation and Doppler spectral analysis of the peak systolic velocity (PSV) and end-diastolic velocity (EDV) in the common carotid artery (CCA), internal carotid artery (ICA) and external carotid artery (ECA), as well as calculation of the ICA to CCA PSV ratio (see Ch. 22, Vascular Laboratory: Arterial Duplex Scanning). Based on these, consensus ultrasound criteria were developed to standardize carotid DU examinations and for diagnosing carotid artery stenosis severity<sup>1</sup> (Table 91.1). Criteria have been validated to diagnose a greater than 70% stenosis.<sup>2</sup> DU remains the first-line imaging modality for identifying patients with ICA stenosis because it is noninvasive, has low cost, is readily available, and has high sensitivity and specificity (Table 91.2), with now

the vast majority of carotid endarterectomy (CEA) procedures performed on the basis of DU alone.

However, there are certain limitations when interpreting DU findings. These include inability to image below the clavicle or above the mandible, overestimation of ipsilateral stenosis in the presence of contralateral severe carotid stenosis or occlusion,<sup>3,4</sup> inability to obtain accurate velocity measurements in presence of excessive calcification due to acoustic shadowing, and difficulty interpreting carotid subocclusion versus a so-called “string sign.” Additionally, due to decreased vessel wall compliance, carotid stents will increase peak systolic velocities. If this is not taken into account for post-carotid stent DU surveillance, the degree of in-stent restenosis will be overestimated. Therefore, consensus criteria have been adjusted to account for this (Table 91.3).<sup>5</sup>

Finally, extracranial DU offers limited information about flow dynamics in the vertebral arteries (VAs). DU is useful for demonstrating antegrade and/or retrograde flow, suggesting proximal subclavian or innominate artery disease. However, it is not always possible to image VA origins and only those sections running between the transverse processes can be imaged distally. Accordingly, if a patient presents with suspected vertebrobasilar symptoms, DU assessment can exclude co-existent carotid or arch vessel disease, but further diagnostic imaging is mandatory.

<sup>†</sup>Deceased.

**TABLE 91.1**

Consensus Panel Gray-Scale and Doppler Ultrasound Criteria for Diagnosis of Internal Carotid Artery Stenosis

| Degree of Stenosis (%)           | PRIMARY PARAMETERS        |                                  | ADDITIONAL PARAMETERS |                |
|----------------------------------|---------------------------|----------------------------------|-----------------------|----------------|
|                                  | ICA PSV (cm/s)            | Plaque Estimate (%) <sup>a</sup> | ICA/CCA PSV (ratio)   | ICA EDV (cm/s) |
| Normal                           | <125                      | None                             | <2.0                  | <40            |
| <50                              | <125                      | <50                              | <2.0                  | <40            |
| 50–69                            | 125–230                   | ≥50                              | 2.0–4.0               | 40–100         |
| >70 but less than near occlusion | >230                      | ≥50                              | >4.0                  | >100           |
| Near occlusion                   | High, low or undetectable | Visible                          | Variable              | Variable       |
| Total occlusion                  | Undetectable              | Visible, no detectable lumen     | Not applicable        | Not applicable |

<sup>a</sup>Plaque estimate (diameter reduction) with gray-scale and color Doppler US.

CCA, common carotid artery; EDV, end-diastolic velocity; ICA, internal carotid artery; PSV, peak systolic velocity.

Reproduced from Grant EG, Benson CB, Moneta GL, et al. Carotid artery stenosis: gray-scale and Doppler US diagnosis—Society of Radiologists in Ultrasound Consensus Conference. *Radiology*. 2003;229:340–346.

**TABLE 91.2**

Results of a Meta-Analysis of the Accuracy of Noninvasive Imaging for All Stenosis Groups and Imaging Modalities

| Stenosis Group                          | Imaging | Sensitivity (95% CI) | Specificity (95% CI) |
|---|---------|----------------------|----------------------|
| 70%–99% (0.77–0.89)<br>(0.91–0.97)      | US      | 0.89 (0.85–0.92)     | 0.84                 |
| (0.76–0.90)                             | CTA     | 0.77 (0.68–0.84)     | 0.95                 |
| (0.89–0.96)                             | MRA     | 0.88 (0.82–0.92)     | 0.84                 |
| (0.89–0.96)                             | CEMRA   | 0.94 (0.88–0.97)     | 0.93                 |
| 50%–69% (0.87–0.94)<br>(0.63–0.89)      | US      | 0.36 (0.25–0.49)     | 0.91                 |
| (0.78–0.97)                             | CTA     | 0.67 (0.30–0.90)     | 0.79                 |
| (0.93–0.99)                             | MRA     | 0.37 (0.26–0.49)     | 0.91                 |
| (0.93–0.99)                             | CEMRA   | 0.77 (0.59–0.89)     | 0.97                 |
| 0%–49%, 100% (0.62–0.95)<br>(0.74–0.98) | US      | 0.83 (0.73–0.90)     | 0.84                 |
| (0.76–0.95)                             | CTA     | 0.81 (0.70–0.88)     | 0.91                 |
| (0.90–0.99)                             | MRA     | 0.81 (0.70–0.88)     | 0.88                 |
| (0.90–0.99)                             | CEMRA   | 0.96 (0.90–0.99)     | 0.96                 |

CEMRA, contrast-enhanced magnetic resonance angiography; CTA, computed tomography angiography; MRA, magnetic resonance angiography; US, ultrasound.

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*Health Technol Assess*. 2006;10(30). Department of Health Crown copyright material is reproduced with the permission of the Controller of the HMSO and Queen's Printers for Scotland. Available at: <http://www.hta.ac.uk/fullmono/mon1030.pdf>.

**TABLE 91.3**

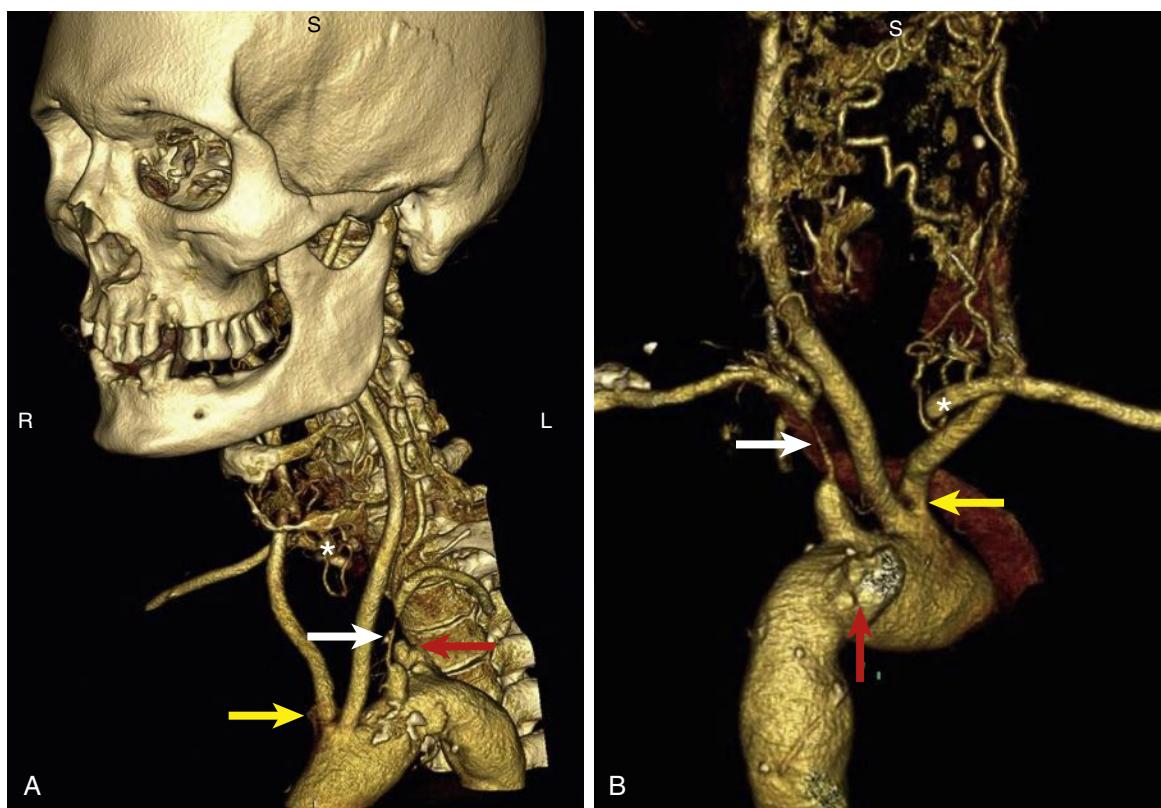
Suggested Velocity Criteria Defining Stenoses in the Stented Carotid Artery Compared to Criteria for the Native Carotid Artery

| Stenosis % | Stented Carotid Artery                   | Native Carotid Artery                                  |
|------------|--|--|
| 0%–19%     | PSV<br><150 cm/s and ICA/CCA ratio <2.15 | PSV <130 cm/s  |
| 20%–49%    | PSV 150–219 cm/s                         | PSV 130–189 cm/s                                       |
| 50%–79%    | PSV 220–339 cm/s and ICA/CCA ratio ≥2.7  | PSV 190–249 cm/s and EDV <120 cm/s                     |
| 80%–99%    | PSV ≥340 cm/s and ICA/CCA ratio ≥4.15    | PSV ≥250 cm/s and EDV ≥120 cm/s, or ICA/CCA ratio ≥3.2 |

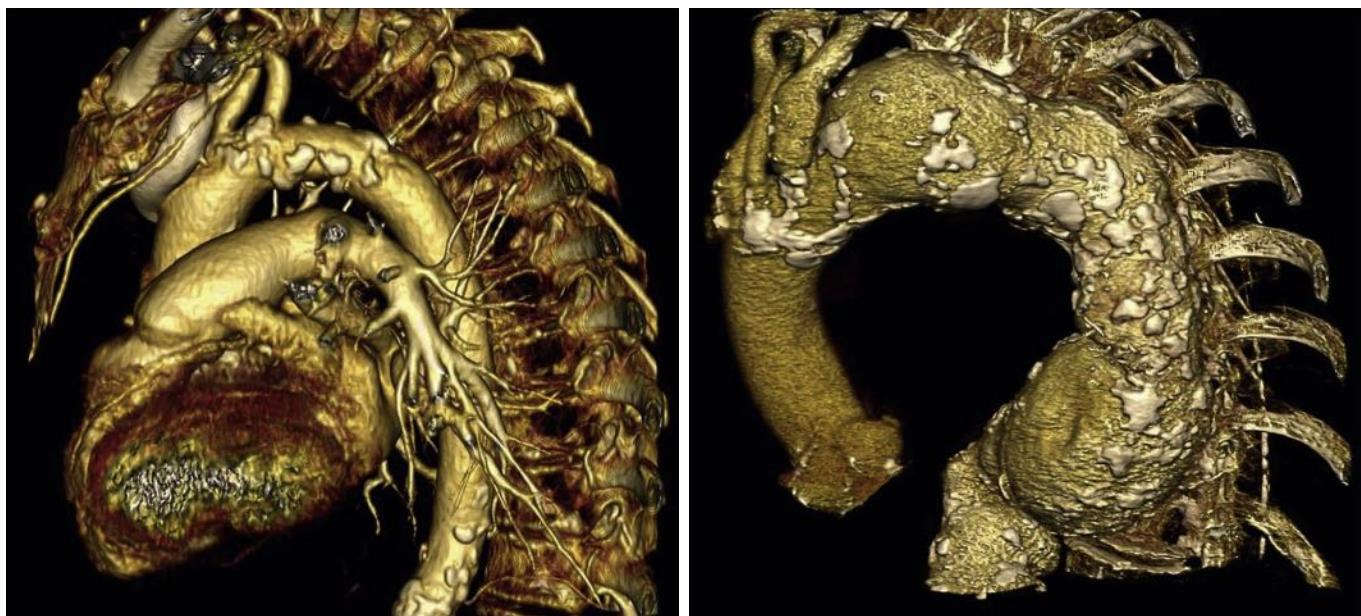
## CT Angiography

Multidetector CT angiogram (MDCTA) has revolutionized the role of CT in carotid artery disease. MDCTA is fast, offers

excellent submillimeter spatial resolution and can visualize soft tissue, bone and vessel at the same time. It can rapidly demonstrate vascular anomalies, even if occluded (Fig. 91.1), and can provide data regarding the extent of vessel calcification,



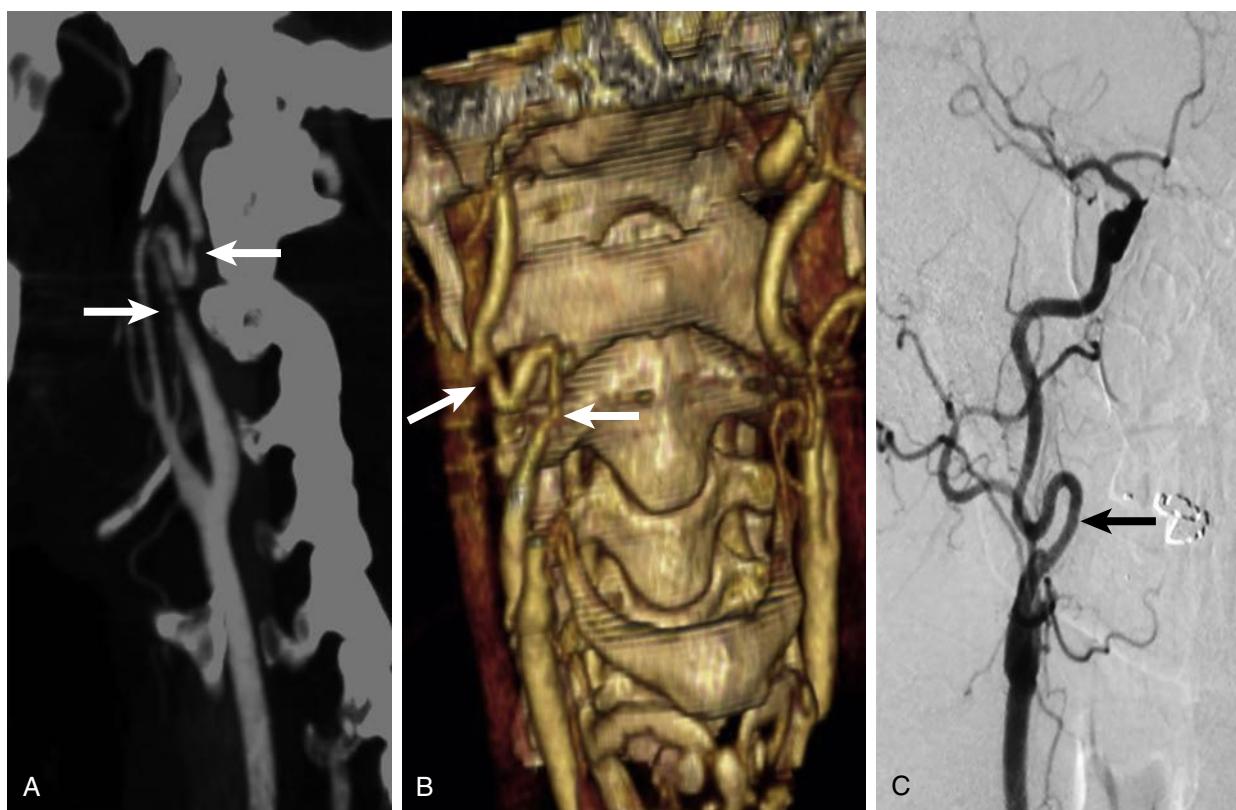
**Figure 91.1** Multidetector computed tomographic angiography showing an unexpected anomaly of the great vessels. (A) Arch viewed from its anterior aspect. (B) Arch viewed from its posterior aspect. Both common carotid arteries arise from a joint origin (yellow arrow), and there is a long, severe stenosis of the proximal left subclavian artery (white arrow). The right subclavian artery arises from an aberrant position and is occluded just beyond its origin (red arrow) with refilling distally (asterisk). The red arrow marks the “diverticulum of Kommerl.”



**Figure 91.2** Volume rendition multidetector computed tomographic angiography showing calcification in the thoracic aorta, aortic arch, and origins of the great vessels.

especially in the aortic arch (Fig. 91.2). Additionally, by utilizing rapid advances in software and hardware, combined with bolus tracking, imaging can now be achieved with a lower radiation dose and with reduced contrast than conventional CT (see Ch. 29, Computed Tomography).

MDCTA is particularly useful for patients with 50%–69% stenosis where DU has been found to be less sensitive and specific, or when further anatomic evaluation of proximal or distal arteries is needed. Additionally, it is indicated for patients undergoing evaluation for carotid artery stenting (CAS) to



**Figure 91.3** Image processing in patients with distal internal carotid artery (ICA) loops can lead to the creation of artifacts that can be interpreted as clinically important stenoses. (A) Multidetector computed tomographic angiography (MDCTA) maximum intensity projection; note the normal bifurcation and a distal looped ICA with apparent inflow and outflow stenoses (arrows). (B) Three-dimensional MDCTA in the same patient suggesting that the stenoses were real (arrows). (C) Selective intraarterial digital subtraction angiography showing the looped ICA (arrow) but no stenoses. The “stenoses” identified on A and B were caused during image processing.

delineate relevant anatomy necessary for procedural success. Given the limitations of DU, MDCTA is mandatory for diagnostic evaluation of vertebrobasilar disease as it allows for accurate visualization of the origins of these vessels as they pass through bony structures. Vessel tortuosity is easily demonstrated, and there is no problem with artifact at the VA origins.

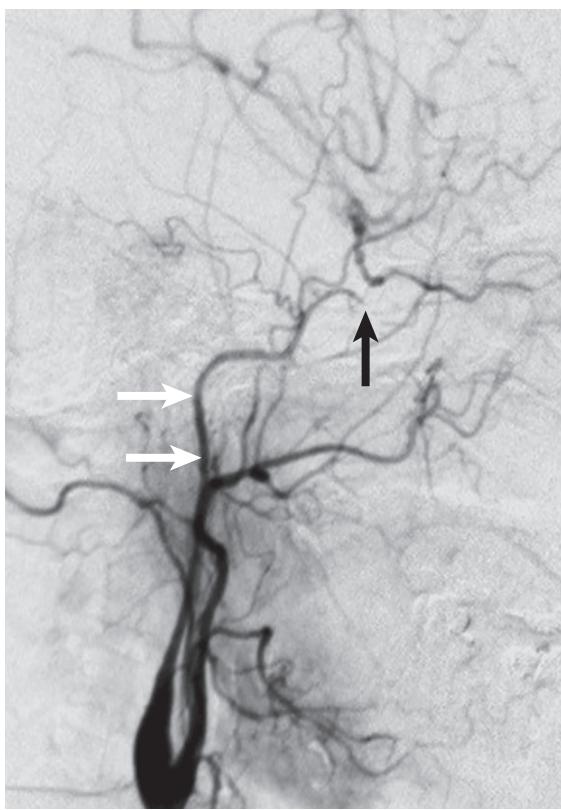
MDCTA is limited by the need for intravenous contrast, a risk of contrast-related nephropathy, not being able to provide information on flow directionality, and the exposure to radiation. Additionally, a large calcium burden can limit the ability to distinguish contrast from calcium during post-processing imaging. Finally, there are occasional situations where MDCTA and contrast-enhanced magnetic resonance angiography (CEMRA) (discussed below) cannot reliably provide accurate and diagnostic imaging information in selected complex patients, especially those with tandem syphon disease or stenoses within coiled segments of the ICA (Fig. 91.3). In these cases, high quality selective carotid digital subtraction angiography (DSA) imaging provides valuable additional information.

### Digital Subtraction Angiography

Digital subtraction angiography (DSA) remains the gold standard for carotid imaging; however, given advances in DU and MDCTA, it is rarely required prior to surgery. DSA is

performed by placing an injection catheter, usually through a femoral approach, into first the aortic arch and then individually selecting the common carotid arteries, followed by power injections of iodinated contrast (see Ch. 27, Arteriography). The degree of ICA stenosis is measured using the North American Symptomatic Carotid Endarterectomy Trial (NASCET) method, which is the calculated ratio between the residual luminal surface at the level of the ICA stenosis and the luminal surface of the distal normal ICA where there is no stenosis.<sup>6</sup> Of note, DSA usually requires imaging in more than one plane to accurately identify lesion severity. DSA provides high quality imaging that is accurate, objective, and easy to interpret. It can identify lesions from the aortic arch to the intracranial vessels. It is particularly useful for diagnosis when there is discordant imaging findings between DU and MDCTA and/or CEMRA. Additionally, DSA is useful in situations where MDCTA can provide misleading information in patients with severe distal ICA disease (Fig. 91.4) and in patients where there is marked coiling of the ICA in the upper reaches of the neck (see Fig. 91.3). Most importantly, DSA is both a diagnostic and therapeutic tool thus making it particularly useful in acute situations such as trauma or the postoperative management of stroke after surgery.

However, the performance of angiography is not without potential risks secondary to the invasive nature of the procedure



**Figure 91.4** Selective intraarterial digital subtraction angiography (IADSA) in a 38-year-old woman with stroke (middle cerebral territory infarct on computed tomography scan). Duplex ultrasound showed slow, high-resistance flow in the carotid artery but a normal bifurcation. Contrast-enhanced magnetic resonance angiography suggested a subocclusion but could not image the distal internal carotid artery (ICA). This delayed IADSA image shows a normal-caliber carotid bifurcation with a narrow-caliber ICA in its midsection (*white arrows* where flow was extremely slow). In the very distal ICA (*black arrow*), vessel diameter dwindles toward complete occlusion. The images are probably consistent with acute dissection and compression of the true lumen by thrombus in the false lumen.

and the use of contrast, stroke being the most devastating of those complications. In the Asymptomatic Carotid Atherosclerosis Study (ACAS),<sup>7</sup> angiographic related stroke accounted for 50% of the procedural complications after CEA. In a review of complications following 23,416 carotid angiograms,<sup>8</sup> groin hematomas occurred after 4% of procedures, while 2.6% of patients suffered a transient or permanent neurologic deficit. As a result, there is no role for routine catheter angiography in modern cerebrovascular practice.

### Magnetic Resonance Angiography

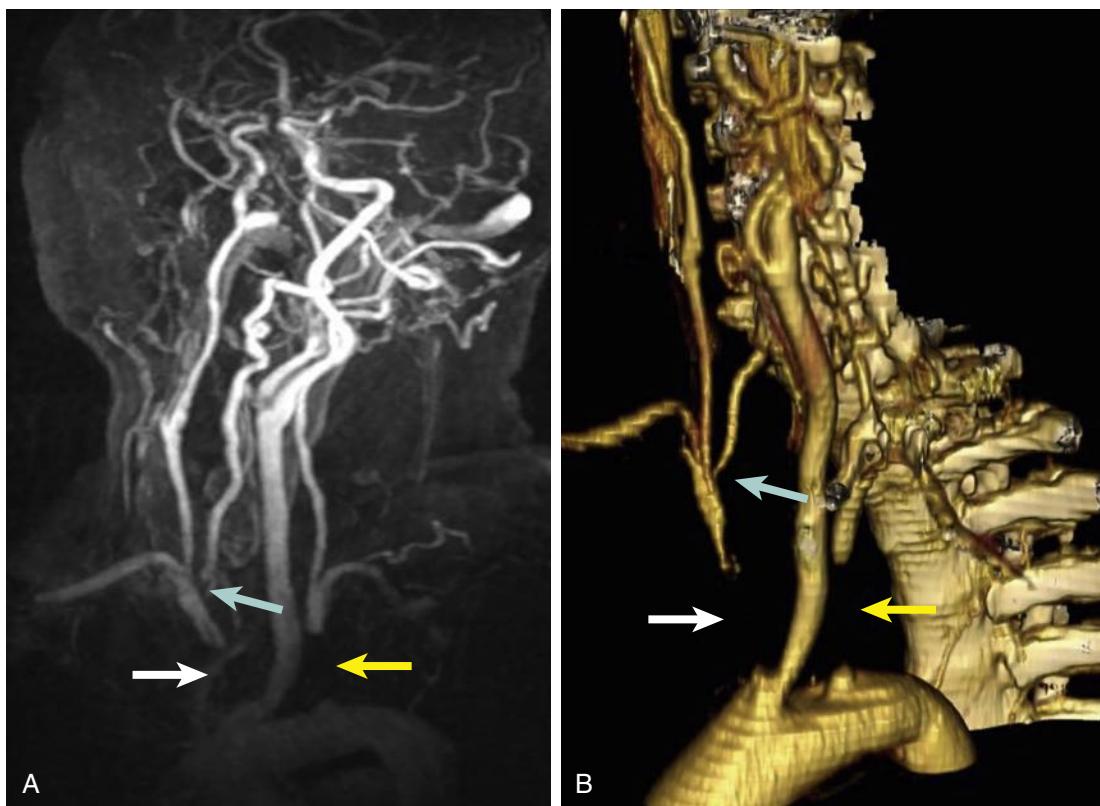
Magnetic resonance angiography (MRA) in the evaluation of extracranial carotid disease utilizes either contrast-enhanced MRA (CEMRA) or time of flight (TOF) MRA. Both have the advantage of being noninvasive, do not require ionizing radiation, and provide an unlimited number of projections of the carotid lumen from a single acquisition. It can also assess intrathoracic and intracranial lesions that are not amenable to DU interrogation. When dedicated protocols are used, MRA also can demonstrate specific plaque components, including

calcium, lipid, fibrocellular element, or thrombus within the plaques. Table 91.2 summarizes sensitivity analyses for CEMRA and TOF MRA (see Ch. 30, Magnetic Resonance Imaging and Arteriography).

CEMRA uses gadolinium as the contrast agent, and compared to MDCTA has fewer flow-related artifacts and provides a much greater field of view that enables high-resolution imaging from the aortic arch (Fig. 91.5) up to the circle of Willis (COW) while retaining the ability to evaluate flow directionality. However, unlike MDCTA, adjacent soft tissue structures are not well visualized unless unsubtracted or additional MR imaging is performed, and calcium within a plaque is not well defined, and as a result the degree of stenosis is often overestimated. Additionally, CEMRA confers the risk of nephrogenic systemic fibrosis in patients with renal insufficiency exposed to the gadolinium contrast agent. Unlike iodinated contrast-induced nephropathy, following which commonly patients recover kidney function, this is irreversible leading to permanent renal failure, along with fibrosis of the skin and joints. To avoid the risk of this devastating complication, TOF MRA is particularly useful as it does not use any contrast, provides strong vascular signals, even when flow is low, and additional three-dimensional TOF MRA can offer better spatial resolution for measuring stenosis severity and enabling assessment of flow directionality in steal phenomena. However, in practice, the lack of availability and the need for specific sequences and hardware to enable dedicated plaque imaging, along with the rare but devastating complication of nephrogenic systemic fibrosis, have left now little role for MRA.

### Transcranial Doppler

Transcranial Doppler (TCD) ultrasound provides rapid, non-invasive, real-time assessment of cerebrovascular function. TCD can be used to measure flow velocity in the basal arteries of the brain including the anterior cerebral artery (ACA), middle cerebral artery (MCA) and posterior cerebral arteries (PCA); and to assess relative changes in flow, diagnose focal vascular stenosis, or to detect embolic signals within these arteries. While there is no routine role for TCD in evaluating patients with carotid artery disease, especially given its lack of availability in most vascular labs and clinical settings, its utility in diagnosing spontaneous *in vivo* embolization can be useful.<sup>9</sup> Embolization is more commonly encountered in the MCA ipsilateral to a symptomatic carotid stenosis, and this is indicative of an unstable plaque (see Ch. 89, Cerebrovascular Disease: The Unstable Carotid Plaque). TCD-diagnosed spontaneous embolization may also assume an increasingly important role in identifying a high risk for stroke cohort of patients with asymptomatic carotid disease. A meta-analysis of six observational studies, including 1144 patients, with an asymptomatic 70%–99% stenosis observed that the presence of a single embolic signal during one hour of TCD monitoring was associated with a near eightfold increase in stroke during follow-up.<sup>10</sup> Thus, in the rare situation where TCD is available, recognition of this phenomenon should prompt the surgeon to undertake an expedited CEA.



**Figure 91.5** Sixty-year-old female with a vertebrobasilar stroke and recurring unsteadiness of gait imaged by contrast-enhanced magnetic resonance angiography (CEMRA; A) and multidetector computed tomographic angiography (MDCTA; B). There is complete occlusion of the innominate artery (white arrow) and left subclavian artery (yellow arrow). The right vertebral artery has a stenosis at its origin (blue arrow). CEMRA and MDCTA have shown identical features, but MDCTA is easier to interpret because of venous contamination in the CEMRA image.

## CLINICAL RECOMMENDATIONS

The Society for Vascular Surgery (SVS) clinical recommendations for carotid imaging<sup>11</sup> recommends state that DU in an Intersocietal Commission for the Accreditation of Vascular Laboratories (ICAVL) accredited vascular laboratory is the initial diagnostic imaging of choice for evaluating the severity of stenosis in both symptomatic and asymptomatic patients. These images should be reviewed by physicians experienced in vascular ultrasound interpretation. Unequivocal identification of stenosis of 50% to 99% in neurologically symptomatic patients or 70% to 99% in asymptomatic patients is sufficient to make a decision regarding intervention. When DU is non-diagnostic or suggests stenosis of intermediate severity (50% to 69%) in an asymptomatic patient, or when evaluation of the vessels proximal or distal to the cervical carotid arteries is needed for diagnosis or to plan therapy, additional imaging with MDCTA, CEMRA or DSA is required.

### Screening

DU is the first-line modality for screening. The SVS recommends that screening be considered for asymptomatic clinically significant carotid bifurcation stenosis in certain groups of

patients, with multiple risk factors that increase the incidence of disease as long as the patients are fit for and willing to consider carotid intervention if a significant stenosis is discovered. Such groups of patients include:

- Patients with evidence of clinically significant peripheral vascular disease regardless of age.
- Patients 65 years or older with a history of one or more of the following atherosclerotic risk factors: coronary artery disease, smoking, or hypercholesterolemia. In general, the more risk factors present, the higher the yield of screening should be expected.
- Patients prior to coronary artery bypass. This is most likely to be fruitful if the patients are greater than 65, have left main disease or a history of peripheral vascular disease. The strongest indication for screening these patients from the data available is to identify patients at high risk for perioperative stroke.

Additionally, imaging of the cervical carotid artery is recommended in all patients with symptoms of carotid territory ischemia, as well as those presenting with amaurosis fugax, evidence of retinal artery embolization on fundoscopic examination (Hollenhorst plaque), or asymptomatic cerebral infarction. The SVS guidelines do not support routine screening to detect clinically asymptomatic carotid stenosis in the general population. Furthermore, screening is not recommended for presence of a

neck bruit alone without other risk factors. This recommendation is based on the low prevalence of disease in the population at large, including those with neck bruits, as well as the potential harm of indiscriminate application of carotid bifurcation intervention to a large number of asymptomatic individuals.

## Preoperative Planning

### *Carotid Endarterectomy*

CEA can be performed on DU alone in asymptomatic patients with a 70%–99% stenosis or symptomatic patients with clear unilateral identifying focal deficits with a ≥50% stenosis. Given the decreased sensitivity and specificity of DU for a 50%–69% stenosis, asymptomatic patients with this degree of stenosis may require secondary imaging, most commonly CTA. In symptomatic patients where DU is unable to accurately grade the lesion due to proximal or distal stenosis, or contralateral carotid stenosis or occlusion that may affect the peak systolic velocity and therefore stenosis severity, CTA is also warranted. Using these criteria, up to 95% of CEAs can be undertaken based on DU findings. There is no evidence that reliance on DU compromises safety or operability.<sup>12</sup>

### **Carotid Artery Stenting**

Carotid artery stenting can be performed via a transfemoral (CAS) or transcarotid (TCAR) arterial revascularization approach. This requires significantly more preoperative planning, in order to evaluate aortic arch and carotid artery anatomy and plaque burden, as well as measurements for stent sizing and selection. DU alone cannot provide this information; therefore, further imaging with either MDCTA or DSA becomes mandatory for the routine preoperative evaluation of these patients.

#### *Transfemoral Stenting*

MDCTA provides useful information regarding: (1) type of aortic arch; (2) extent of plaque burden and calcification of the great vessel origins; (3) proximal CCA tortuosity; (4) distal landing zone for a filter; and (5) the COW status, which is all necessary for optimal preoperative planning (see Ch. 94, Carotid Artery Stenting). Given DSA is necessary to perform a CAS, some surgeons may choose to forgo MDCTA and instead perform only DSA at the time of the procedure, however this leaves all decision making to the time of the procedure and leaves the surgeon with the possibility of not being able to perform the procedure due to some unanticipated anatomical issue. Therefore, we recommend performing DSA only in patients with renal insufficiency where a CTA could lead to renal failure or in emergent situations where both diagnosis and intervention can be performed in one setting.

#### *Transcarotid Artery Revascularization*

Unlike CAS, MDCTA is required for preoperative planning for TCAR (see Ch. 94, Carotid Artery Stenting). While knowledge of carotid orifice lesions, aortic arch anatomy, plaque burden, and calcifications are no longer necessary concerns,

preoperative knowledge of common carotid access site including depth of the artery, lesion characteristics, distal ICA anatomy, and intracranial atherosclerotic burden is paramount to the success of this procedure. Careful adherence to adequate anatomic requirements is necessary to ensure safe arterial sheath placement without engaging the lesion. Heavily calcified lesions should be avoided because of the known long-term adverse outcomes (recurrence, thrombosis) with stent placements in these types of lesions. MDCTA provides this information rapidly and safely and allows for appropriate patient anatomic selection to ensure continued real-world success of this novel procedure. Recent evidence from the Safety and Efficacy Study for Reverse Flow Used During Carotid Artery Stenting Procedure (ROADSTER) multicenter trial in high-risk patients undergoing transcarotid artery stenting with dynamic flow reversal reported the lowest stroke rate compared with any prospective trial of carotid artery stenting. The Society for Vascular Surgery VQI TCAR Surveillance Project (TSP) was designed to evaluate the safety and effectiveness of TCAR in real-world practice, and compared with patients undergoing transfemoral CAS, patients undergoing TCAR had significantly more medical comorbidities but similar stroke/death rates and half the risk of in-hospital TIA/stroke/death.<sup>13</sup>

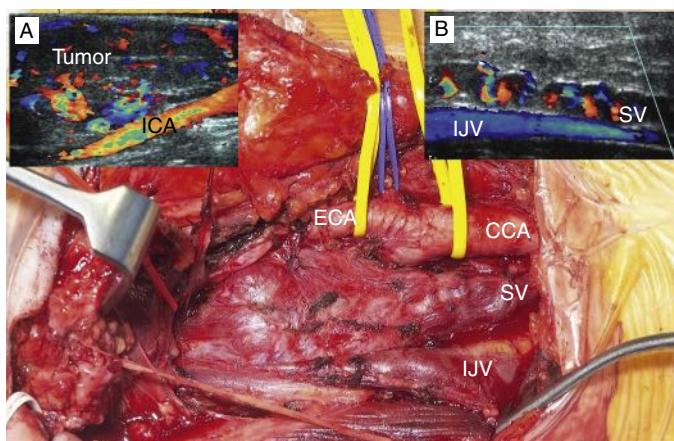
## Trauma

Duplex ultrasound (DU) offers a screening/surveillance role in patients with zone II carotid injuries (between cricoid cartilage and angle of mandible), especially intimal irregularities or small false aneurysms treated conservatively (see Ch. 180, Vascular Trauma of the Head and Neck). DU is, however, less reliable in zone I injuries (clavicle to cricoid cartilage) or zone III injuries (angle of mandible to skull base). MDCTA has an important role, because it can rapidly provide anatomical vascular images from the arch to COW, together with bony, soft tissue, and functional brain imaging during a single scan, even in a ventilated patient. CT angiography and venography of neck structures are easily incorporated into trauma whole body CT scan protocols for comprehensive vascular assessment while simultaneously evaluating for other traumatic injuries. DSA remains an important diagnostic and therapeutic option in traumatic injuries to the cerebrovascular circulation, as both diagnosis and intervention in acute dissection, hemorrhage, pseudoaneurysm and/or thrombosis. It needs to be performed rapidly and has the advantage of being able to proceed immediately with endovascular interventions (coil/balloon occlusion, thrombectomy, and stent insertion).

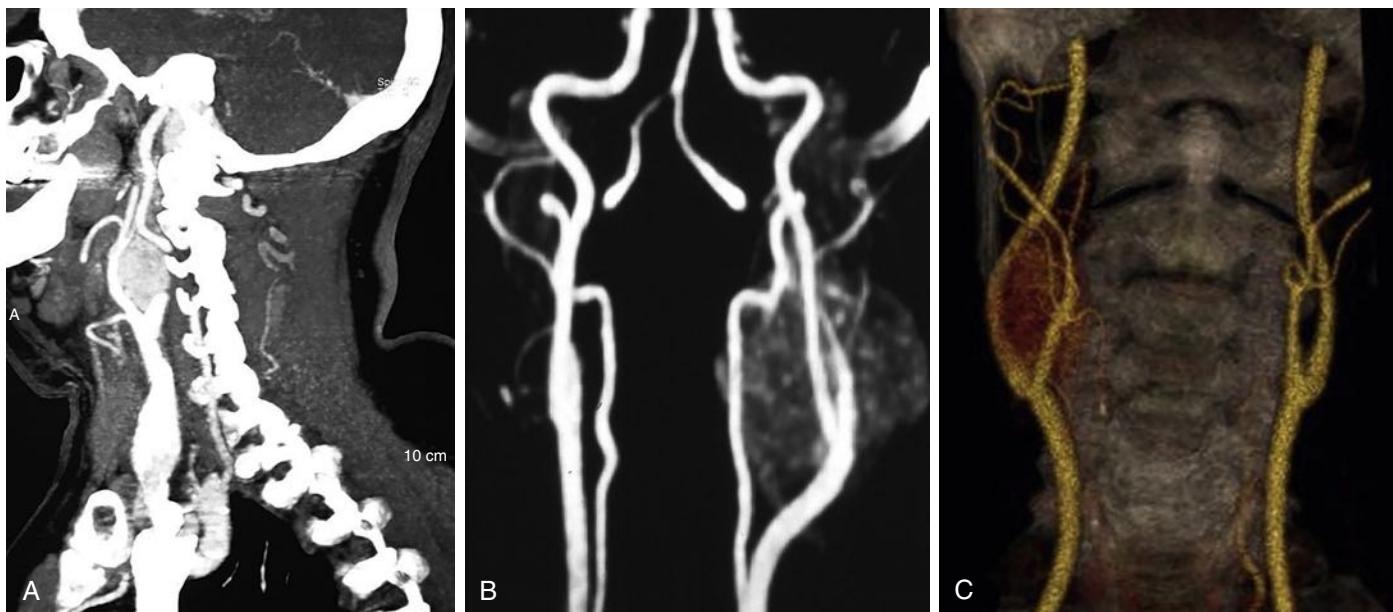
## Carotid Body Tumors

DU is ideal for diagnosing carotid body (CBT) or glomus vagale tumors (GVTs). CBTs cause splaying of the carotid bifurcation (see Ch. 98, Carotid Body Tumors). GVTs do not splay the bifurcation, but they do tend to cause displacement of the distal ICA (Fig. 91.6). However, due to its better spatial resolution and easy interpretation, MDCTA is the optimal

imaging modality for evaluating tumor circulation (see Fig. 91.7), tumor extent, whether it is bilateral, and the relationship between tumor and adjacent soft-tissue structures. This information is usually more than enough to plan a safe surgical resection and can be relied upon to warn when a high or difficult dissection might be encountered (i.e., enabling the surgeon to plan for temporomandibular subluxation as required). Finally, there is limited role for DSA in the routine evaluation of patients being considered for resection of CBTs and GVTs, but is useful for preoperative embolization of ECA feeding vessels to help reduce postoperative bleeding for larger tumors (Fig. 91.8).



**Figure 91.6** Glomus vagale tumor (*GVT, main picture*). This does not splay the bifurcation but displaces the distal internal carotid artery (ICA) (*duplex image, A*). Occasionally, preoperative ultrasound features can suggest that this is a GVT and not a carotid body tumor. Note the serpiginous feeding vessels extending down the vagus nerve (SV: *main picture* and *duplex ultrasound scan; B*). These are separate from the common carotid artery (CCA) and internal jugular vein (IJV). *ECA*, external carotid artery.



**Figure 91.7** Carotid Body Tumor. (A) Multidetector computed tomographic angiography (MDCTA) maximum intensity projection (MIP) image. (B) Contrast-enhanced magnetic resonance angiography MIP image. (C) MDCTA volume rendition image.

## Perioperative Management

### Completion Imaging

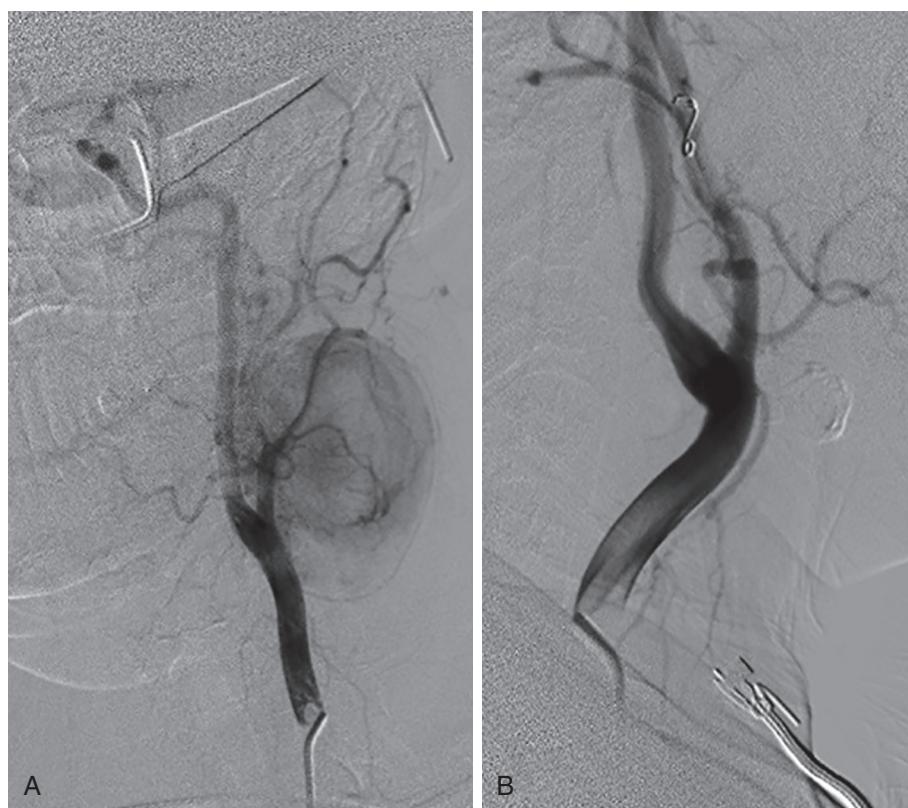
Intraoperative DU enables completion assessment following flow restoration through: (1) residual filling defects (luminal thrombus), (2) undue turbulence, and (3) evidence of intimal flaps/residual stenosis. However, this modality is limited especially due to technical difficulty and interoperator variability, as well as decreased sensitivity of results given the lack of soft tissue between the probe and the vessel and interference from the patch repair when used, and therefore left up to surgeon preference. Given the invasive nature and potential for embolization, completion DSA is not routinely performed unless there is suspicion for a distal complication such as dissection and/or embolism suspected intraoperatively.

### Immediate Postoperative Management

DU is invaluable in guiding the management of immediate postoperative neurologic deficits. These often occur when other imaging modalities are unavailable and DU can be brought immediately to the patient's bedside. Air in the deep tissues can interfere with insonation early after surgery, but it is usually possible to exclude thrombosis. If there is no thrombosis, MDCTA and DSA are both feasible options. DSA has the advantage of being both diagnostic and therapeutic, and can rapidly treat distal dissection, thrombosis or embolism. If completion DU or DSA are normal, MDCTA can be performed rapidly to evaluate for other pathologies such as intracranial hemorrhage, distal embolization, or hyperperfusion syndrome.

### Long-Term Follow-Up

The SVS guidelines recommend a postoperative DU study within 1 month of CEA. If the study shows no significant stenosis with a good postoperative result, further follow-up imaging with



**Figure 91.8** (A) Preoperative intraarterial digital subtraction arteriography of carotid vessels in a patient with a large carotid body tumor. Most of the tumor circulation is derived from external carotid artery (ECA) branches. (B) All major feeding ECA branches have been coiled. The patient went direct from the Angio suite to the operating theater for an uneventful tumor resection.

DU is recommended in patients with a primary closure or those with patch closure that have significant atherosclerotic risk factors. If the study shows a >50% carotid stenosis at the surgical site, further follow-up imaging with DU is recommended to assess for stenosis progression or resolution. Furthermore, if the patient was known to have a >50% contralateral carotid stenosis at the time of CEA, further follow-up imaging with DU is recommended to assess for contralateral stenosis progression. Given these recommendations, along with the minimally invasive and low-risk nature of DU, it is the authors' practice to follow all of our postoperative CEA patients with a one-month DU and then biannual examinations thereafter. If a >80% stenosis is identified, the patient is further imaged with MDCTA and interventions are proceeded with as indicated.

Among patients who have undergone carotid stenting (via a CAS or TCAR approach), contemporary recommendations regarding DU follow-up are limited. As DU is minimally invasive and low risk, the authors follow all of our postoperative carotid stent patients with a one-month and then biannual DU. However, we have adjusted our velocity criteria for defining stenosis in the stented portion of the carotid artery, as previously discussed (Table 91.3). Similar to CEA patients, if a >80% stenosis, or greater than 50% stenosis with recurrent symptoms is identified, the patient is further imaged with MDCTA and intervention is proceeded with as indicated.

## FUTURE DIRECTIONS

Evaluating plaque morphology is a key area of research within carotid artery disease (see Ch. 89, Cerebrovascular Disease:

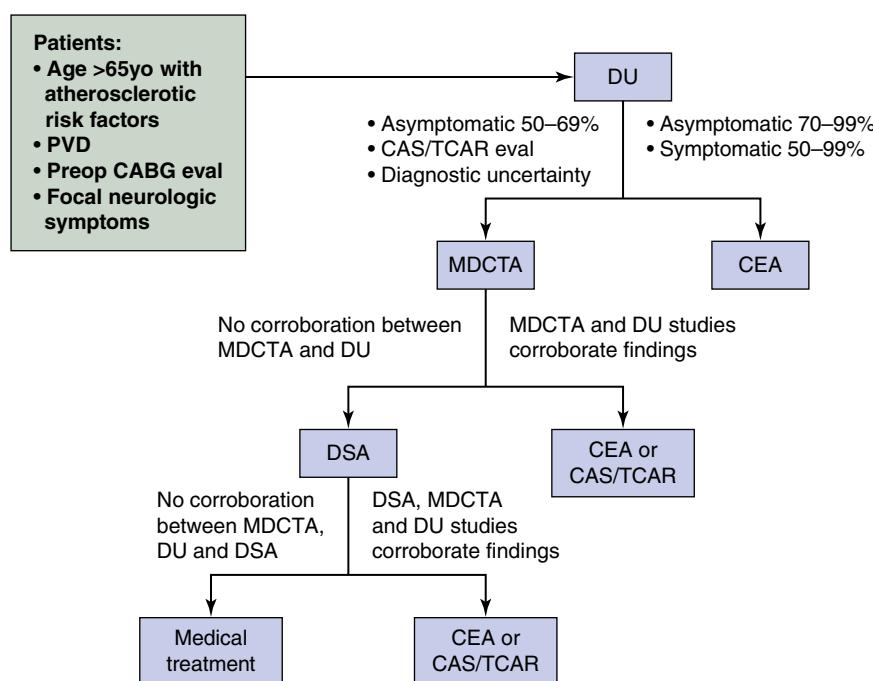
The Unstable Carotid Plaque). The ability to identify "higher risk for stroke" patients with asymptomatic carotid disease is important, as some have suggested that up to 95% of interventions in asymptomatic patients are ultimately unnecessary.<sup>14</sup> Computerized plaque analyses using DU including the gray-scale median (GSM) and measurement of overall plaque area and juxta-luminal black area (JBA)<sup>15,16</sup> are being developed to predict the risk of stroke risk. MDCTA can identify plaque ulcers, while CEMRA are useful in visualizing thrombus, fibrous cap and its rupture, as well as intraplaque hemorrhage, which is thought to be one of the most important predictors of increased stroke risk. Future application of these modalities with regards to plaque morphology will help guide intervention for asymptomatic patients based on "active plaque" and its risk of stroke, not just the degree of stenosis.

## SUMMARY

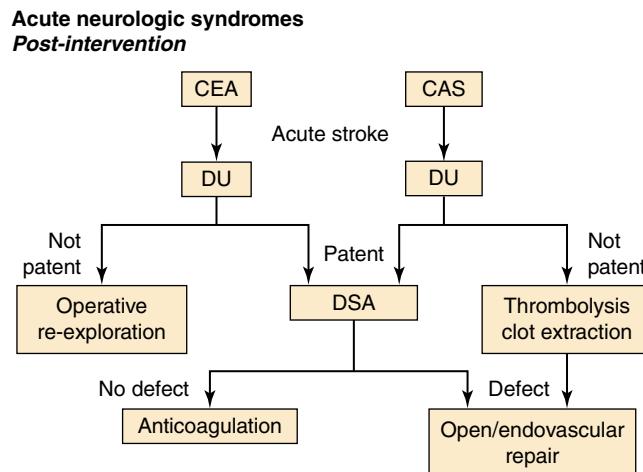
DU is the first-line modality for the diagnosis of carotid artery disease. The other diagnostic modalities of CT, MRA and DSA are useful adjuncts especially when DU is limited in its diagnostic capabilities, as mentioned in the chapter. CT is of particular importance given the increasing use of CAS, and especially among candidates being evaluated for TCAR. Given the widespread availability of DU, especially in the clinic setting, evaluation of carotid artery disease can be done rapidly and safely with high sensitivity and specificity, thus facilitating the speed of diagnostic workup and reducing time to intervention.

## CHAPTER ALGORITHMS

ALGORITHM 1



ALGORITHM 2



## SELECTED KEY REFERENCES

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A complete reference list can be found online at [www.expertconsult.com](http://www.expertconsult.com).

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# Cerebrovascular Disease: Decision Making Including Optimal Medical Therapy

A. ROSS NAYLOR and DOMINICK J.H. McCABE

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## CAROTID DISEASE AND STROKE

The management of symptomatic and asymptomatic carotid disease has been the subject of six randomized controlled trials (RCTs) comparing carotid endarterectomy (CEA) with optimal medical therapy (OMT), whereas 20 RCTs have compared CEA with either carotid angioplasty (CA) or carotid artery stenting (CAS). These 26 RCTs comprise the main evidence base for developing pragmatic decision-making in patients.

## DECISION MAKING IN SYMPTOMATIC PATIENTS

The definition of stroke and transient ischemic attack (TIA) has been detailed in Chapter 88 (Cerebrovascular Disease: Epidemiology and Natural History). Patients presenting with carotid territory symptoms, such as hemisensory/motor loss; higher cortical dysfunction (aphasia, dysphasia, visual field defect, visuospatial neglect) or monocular visual loss should undergo expedited investigation to identify the likeliest cause of their symptoms (Ch. 91, Cerebrovascular Disease: Diagnostic Evaluation). The keyword is “expedited,” as the highest risk period for recurrent stroke is the first 7–14 days after symptom onset. Accordingly, advice regarding risk factor control, OMT (everyone) and CEA/CAS (where needed) must be delivered as soon as possible.

### Management Planning

Once a diagnosis of carotid territory TIA/ischemic stroke is established, three questions require addressing: (1) what risk factors require correction; (2) is the patient receiving OMT? and (3) is there any need for CEA/CAS?

### What Risk Factors Need to Be Addressed?

Risk factors for stroke/TIA are non-modifiable and modifiable. The former includes increasing age, male sex, ethnicity and family history of stroke/TIA. Modifiable risk factors include: (i) lifestyle (smoking, alcohol intake, obesity, physical inactivity); (ii) hypertension; (iii) diabetes mellitus (DM); (iv) hyperlipidemia; (v) atrial fibrillation; (vi) carotid stenosis; (vii) structural cardiac abnormalities; and (viii) sickle cell disease.<sup>1</sup>

#### Lifestyle: symptomatic and asymptomatic patients

Patients require advice on lifestyle modification regarding diet, exercise, smoking cessation and weight reduction.<sup>2</sup> In a meta-analysis of 32 studies, smoking was associated with a significant increase in the risk of ischemic stroke (Relative Risk Increase [RRI] 1.9; 95% CI 1.7–2.2),<sup>3</sup> while moderate/high physical activity was associated with a 25% relative risk reduction (RRR) in ischemic stroke.<sup>4</sup> In a meta-analysis of 25 studies involving 2 million people, obesity was associated with a significant increase in stroke risk (RRI 1.64; 95% CI 1.36–1.99).<sup>5</sup>

### Is the Patient Receiving Optimal Medical Therapy?

#### Antiplatelet therapy

Because platelets are activated following TIA/ischemic stroke, antiplatelet agents play a key role in preventing recurrent events. The optimal antiplatelet regimen is determined by symptom status, stenosis severity, whether the patient requires CEA/CAS and whether the surgeon has a preference for performing CEA on antiplatelet monotherapy or combination therapy.

**Aspirin Monotherapy.** Most guidelines recommend aspirin monotherapy (100–325 mg daily) throughout the perioperative period, followed by 75–325 mg daily thereafter.<sup>6</sup> The Aspirin and Carotid Endarterectomy (ACE) trial, showed that lower-dose aspirin (81–325 mg daily) was superior to higher doses (650–1300 mg daily) in reducing stroke/MI/death at 30 days in CEA patients (3.7% vs. 8.2%,  $P = 0.002$ ).<sup>7</sup> However, recent evidence suggests that antiplatelet monotherapy is less effective than combination therapy in many ischemic TIA/stroke patients.

**Combination Antiplatelet Therapy.** Three RCTs (CHANCE,<sup>8</sup> POINT,<sup>9</sup> FASTER<sup>10</sup>) randomized 10,447 patients <24 hours of minor ischemic stroke (NIHSS ≤3)<sup>8–10</sup> or “high-risk TIA” (ABCD<sup>2</sup> score ≥4)<sup>8,9</sup> to aspirin monotherapy or short-term aspirin + clopidogrel combination therapy. A meta-analysis showed that, at 90 days, aspirin + clopidogrel significantly reduced nonfatal ischemic/hemorrhagic stroke, nonfatal ischemic stroke, moderate–severe functional disability and poor quality of life vs. aspirin alone.<sup>11</sup>

A British Medical Journal Guideline Panel concluded that the evidence was robust enough to recommend prescribing aspirin + clopidogrel for 21 days, followed by clopidogrel monotherapy in patients presenting with acute, high-risk TIA/minor ischemic stroke.<sup>12</sup> This was because most stroke prevention occurred in the first 10 days after symptom onset. Limiting combination therapy to 21 days reduced late bleeding complications.<sup>11</sup> A number of guidelines now recommend aspirin + clopidogrel therapy for 21 days in patients with minor non-cardioembolic ischemic stroke who have not received intravenous tissue plasminogen activator,<sup>13</sup> or for 21 days,<sup>14</sup> or 21–30 days<sup>15</sup> in patients with a high-risk TIA or minor ischemic stroke.

However, no guideline has advised surgeons regarding combination antiplatelet therapy in recently symptomatic patients with 50%–99% stenoses awaiting urgent CEA. This is mainly because they were excluded from CHANCE/POINT, in addition to concerns about increased perioperative bleeding complications with combination therapy.<sup>16</sup> Accordingly, whilst there is good evidence supporting a 21-day prescription of aspirin + clopidogrel in patients with TIA/ischemic stroke without a 50%–99% stenosis, there is no RCT evidence that the balance of benefit vs. risk also favors combination therapy in patients with 50%–99% stenoses awaiting CEA.<sup>16</sup>

Other evidence favoring combination therapy prior to CEA comes from a prospective audit, where there was a 48–72-hour delay between patients being seen in a TIA clinic and undergoing CEA. During this time, 13% experienced recurrent stroke/

TIAs.<sup>17</sup> When a decision was made to start aspirin + clopidogrel in the TIA clinic (once CT/MRI excluded parenchymal hemorrhage), recurrent clinical events prior to CEA fell fivefold from 13% to 3%, in association with a fourfold reduction in spontaneous embolization on transcranial Doppler (TCD), from 21% to 5%.<sup>17</sup> From the surgeon's perspective, performing CEA in patients on aspirin + clopidogrel was not associated with significantly increased bleeding complications (3%).<sup>17</sup> Similar observations were made by the Vascular Study Group of New England ( $n = 5264$ ), which reported that re-exploration for neck hematoma was 1.5% on no antiplatelet therapy, 1.2% on aspirin monotherapy, 0.7% on clopidogrel monotherapy and 1.4% on aspirin + clopidogrel combination therapy.<sup>18</sup>

Accordingly, clinicians now face three clinical scenarios where early institution of combination antiplatelet therapy may be the preferred option<sup>16</sup> — a patient with: (1) 0%–49% stenosis with no other cause for TIA/stroke on neurovascular work-up; (2) recent TIA/stroke and a 50%–99% stenosis, where CEA/CAS is not being considered; and (3) recent TIA/stroke and a 50%–99% stenosis where urgent CEA/CAS is planned.<sup>16</sup>

Data extrapolation from “non-carotid stenosis” patients with TIA/minor stroke for scenarios 1 and 2 support a 300-mg loading dose of clopidogrel plus 162–325 mg of aspirin (see Chapter Algorithm). Patients then receive 75 mg clopidogrel daily and 162–325 mg aspirin daily from days 2–7, followed by 75 mg clopidogrel and 75–81 mg aspirin daily through days 8–21. The patient then reverts to long-term clopidogrel monotherapy (75 mg daily). In patients with 0%–49% stenosis, an alternative would be aspirin + dipyridamole, with dosages detailed in the Chapter Algorithm. Similarly, aspirin plus full-dose dipyridamole can be considered in patients with 50%–99% symptomatic stenoses (higher risk of recurrent stroke), where a decision has been made not to undergo CEA/CAS (see Chapter Algorithm).

In the third scenario, several options are available (see Chapter Algorithm). Whilst CHANCE, POINT and FASTER only included patients <24 hours of symptom onset, if the surgeon is happy to perform expedited CEA in patients prescribed aspirin + clopidogrel, it is reasonable to start combination therapy even if patients present >24 hours after TIA/minor stroke onset (especially the first 10 days) which is the highest risk period for recurrent stroke. Parenchymal hemorrhage should be excluded on CT/MRI and the patient should receive 300–325 mg aspirin, if not already on aspirin, followed by 75–81 mg aspirin daily in combination with 75 mg clopidogrel daily from day 1 (without a 300-mg loading dose).<sup>16</sup> Expedited CEA, with careful control of postoperative BP, should be performed, as uncontrolled post-CEA hypertension increases the risk of hyperperfusion syndrome, intracranial hemorrhage (ICH) and neck hematoma formation.<sup>2</sup> Aspirin can be stopped on day 1 after CEA and clopidogrel (75 mg daily) continued indefinitely, unless contraindicated.<sup>16</sup>

If the surgeon is unwilling to perform CEA in patients prescribed aspirin + clopidogrel, an alternative would be

300–325 mg aspirin from day 1–14 and then reduce the long-term aspirin dose to 75–81 mg daily, in combination with dipyridamole MR 200 mg BD from day 1, following advice about potential side effects (see Chapter Algorithm). This regime was equally effective in reducing TCD-detected microemboli as aspirin + clopidogrel in patients with ≥50% symptomatic stenoses.<sup>19</sup>

**Antiplatelet Strategies Prior to CAS.** CAS patients are prescribed combination antiplatelet therapy, mainly based on coronary stenting RCT data,<sup>6</sup> but supported by one RCT involving 47 patients with 70%–99% carotid stenosis who underwent CAS (38 symptomatic, 9 asymptomatic).<sup>20</sup>

Ticlopidine is rarely prescribed in TIA/stroke patients due to a less favorable adverse effect profile. Accordingly, it is reasonable to prescribe 300–325 mg aspirin daily for up to 14 days, followed by 75–81 mg daily, if not already taking aspirin. Clopidogrel (75 mg daily) is started 3 days prior to CAS, or as a 300-mg loading dose in urgent cases. Combination therapy should continue for at least 4 weeks post-CAS. Thereafter, patients revert to either aspirin or clopidogrel monotherapy.<sup>6</sup> Long-term aspirin + clopidogrel therapy is rarely prescribed, unless for cardiac reasons, because the risks of long-term aspirin + clopidogrel combination therapy outweigh the benefits of monotherapy after TIA/ischemic stroke.

If intolerant of, or allergic to, aspirin and clopidogrel, 200 mg BD of dipyridamole monotherapy should be considered.<sup>2</sup> It is also important to prescribe gastric protection with proton pump inhibitors that do not interact with clopidogrel (e.g., pantoprazole) in patients prescribed combination antiplatelet therapy to reduce gastrointestinal bleeding complications.<sup>2</sup>

**Assessment of Antiplatelet “High On-Treatment Platelet Reactivity” (HTPR).** A recent meta-analysis of pooled data from several platelet function testing platforms showed a higher risk of recurrent TIA/stroke, myocardial infarction (MI) or vascular death in TIA/ischemic stroke patients with vs. without “antiplatelet HTPR” (previously referred to as “antiplatelet resistance”) on any antiplatelet regimen (OR 2.93; 95% CI: 1.90–4.51).<sup>21</sup>

Aspirin-HTPR has been reported in 23%–57% and clopidogrel-HTPR in 50%–75% of patients with 50%–99% asymptomatic carotid stenosis (ACS),<sup>22</sup> with the prevalence being positively influenced by the shear-stress levels to which platelets are exposed in the platelet function testing platform.<sup>23</sup> The prevalence of aspirin-HTPR can vary between 9.5% and 64% and the prevalence of clopidogrel-HTPR between 0% and 83% in patients with ≥50% symptomatic stenoses.<sup>24</sup> However, no studies have been adequately powered to definitively determine whether *ex vivo* HTPR status predicts the risk of clinical events in asymptomatic or symptomatic patients in the perioperative or non-perioperative periods.<sup>21–25</sup> Accordingly, evidence does not currently support routine alteration of antiplatelet therapy based on *ex vivo* antiplatelet-HTPR testing outside of research studies/clinical trials.

**Combination Antiplatelet and Direct Oral Anticoagulant Therapy in Carotid Stenosis.** There is interest in the

potential benefits of combining antiplatelet therapy with low-dose direct oral anticoagulant (DOAC) therapy in patients with vascular disease.<sup>26</sup> In the COMPASS trial, patients with coronary artery disease, peripheral arterial disease, or carotid disease (prior CEA/CAS or ≥50% ACS) were randomized to 100 mg aspirin monotherapy ( $n = 9126$ ), combination therapy with low-dose rivaroxaban (2.5 mg BD) and 100 mg aspirin daily ( $n = 9152$ ), or 5 mg BD of rivaroxaban monotherapy ( $n = 9117$ ).<sup>27</sup> Patients were excluded if they suffered a non-lacunar ischemic stroke within 1 month of randomization or had a history of hemorrhagic or lacunar stroke.<sup>28</sup>

Approximately 7% of COMPASS patients had a history of carotid disease.<sup>29</sup> In this subgroup, there was no statistically significant benefit for combination therapy with low-dose rivaroxaban + aspirin, versus aspirin alone in preventing stroke, MI or cardiovascular death (HR 0.63; 95% CI: 0.38–1.05;  $P = 0.07$ ). However, there was no significant increase in major bleeding risks (HR 1.18; 95% CI: 0.55–2.51;  $P = 0.67$ ).<sup>30</sup> There was also no benefit for rivaroxaban 5 mg BD vs. aspirin alone, in reducing major vascular events (HR 1.01; 95% CI: 0.65–1.56), but “higher-dose” rivaroxaban increased major bleeding risks (HR 2.34; 95% CI: 1.21–4.52;  $P = 0.009$ ).<sup>30</sup> Accordingly, there is no current evidence to recommend routine combination therapy with low-dose rivaroxaban and aspirin in carotid stenosis patients.

### Lipid-lowering therapy

The Heart Protection Study included a subgroup of 3280 patients with cerebrovascular disease (TIA [46%), non-disabling ischemic stroke [63%], prior CEA [10%]).<sup>31</sup> All had a baseline LDL-cholesterol >3.5 mmol/L, none were randomized <8 weeks of their TIA/stroke and the mean interval from symptom to randomization was 4 years. Simvastatin (40 mg daily) reduced the relative risk of major vascular events (stroke, non-fatal MI, death from coronary disease, and/or coronary or non-coronary revascularization) by 20%, compared with placebo ( $P = 0.001$ ) over a mean follow-up of 4.8 years. The reduction in ischemic stroke from 7.5% to 6.1% did not reach statistical significance (ARR 1.4%; RRR 19%;  $P = 0.1$ ).

FASTER randomized 392 patients within 24 hours of TIA or ischemic stroke (NIHSS <3) to receive clopidogrel + aspirin, simvastatin + aspirin, clopidogrel + simvastatin + aspirin, or placebo + aspirin.<sup>10</sup> The trial stopped prematurely due to slow recruitment and there was no significant difference in outcomes between those who were vs. were not taking simvastatin. SPARCL was the first RCT to show that atorvastatin (80 mg daily) reduced the relative risk of non-fatal or fatal stroke by 16%, compared with placebo, over approximately 5 years follow-up ( $P = 0.03$ ) in patients within 1–6 months of a non-cardioembolic TIA or ischemic stroke (MRS ≤3) and who had baseline LDL cholesterol (LDL-C) levels ≥2.6 mmol/L to <4.9 mmol/L (100 mg/dL to 190 mg/dL).<sup>32</sup> In a subgroup analysis of SPARCL patients with carotid stenosis who did not undergo carotid revascularization <30 days of randomization (mean stenosis severity 51%;  $n = 1007$ ), atorvastatin reduced the relative risk of fatal/non-fatal stroke by 33% (ARR 4.9%,  $P = 0.02$ ).<sup>33</sup>

Amarenco observed that treating patients with recent TIA/minor ischemic stroke with more aggressive lipid-lowering therapy to achieve a “lower LDL-C target” of <70 mg/dL (<1.8 mmol/L) versus a “higher LDL-C target” of 90–110-mg/dL (2.3–2.8 mmol/L), significantly reduced the incidence of major vascular events over a median follow-up of 3.5 years (8.5% vs. 10.9%, adjusted Hazard Ratio: 0.78; 95% CI: 0.61–0.98;  $p = 0.04$ ).<sup>34</sup> During the trial, 66% of patients in the lower-target LDL-C group and 94% in the higher-target LDL-C group received a statin only, whereas 33.8% and 5.8% of patients (respectively) also received ezetimibe (10 mg daily). Outcomes in patients with carotid stenosis have not been reported.

Current guidelines advise a target total cholesterol <3.5 mmol/L and LDL-C <1.8 mmol/L,<sup>34</sup> or at least a 50% reduction in LDL-C vs. baseline.<sup>13</sup> In keeping with guidelines in TIA/stroke patients overall, it is reasonable to add ezetimibe (10 mg daily) in patients with symptomatic carotid stenosis who do not reach these lipid targets on maximum doses or maximum tolerated doses of statins.<sup>13,34</sup> In the 2020 European Society for Cardiology/European Atherosclerosis Society guidelines on the management of dyslipidemia, it was recommended that the target LDL-C should be <1.4 mmol/L in patients with a symptomatic carotid stenosis in the presence of one or more additional “very-high-risk” cardiovascular risk factors (e.g., ischemic heart disease, peripheral arterial disease, type 2 DM with target organ damage or long-standing type 1 DM).<sup>35</sup>

Whilst there is no clear guidance about the optimal timing for starting statins after TIA/stroke, it is important to begin statins before CEA/CAS, because this may reduce perioperative morbidity/mortality, via their pleiotropic effects in reducing inflammation, direct plaque stabilization and general reductions in inflammatory responses to surgery. In a meta-analysis of 6 studies ( $n = 7503$ ), those taking statins prior to CEA had significantly lower perioperative mortality, compared with statin-naïve patients (OR 0.26; 95% CI 0.1–0.61).<sup>36</sup> In a second meta-analysis (11 studies,  $n = 4088$ ), patients taking statins prior to CAS had significantly lower perioperative mortality, compared with statin-naïve patients (OR 0.30; 95% CI 0.10–0.96) and significantly lower procedural stroke risk (OR 0.39; 95% CI 0.27–0.58).<sup>37</sup>

### Antihypertensive therapy

No RCTs have compared one antihypertensive regimen against another in patients with symptomatic carotid stenosis. However, hypertension treatment is an essential component of secondary prevention following TIA/stroke. In 6105 stable, post-stroke patients in the PROGRESS trial, perindopril-based therapy (perindopril alone or combined with indapamide) reduced the relative risk of recurrent stroke by 28%, versus placebo (95% CI: 17%–38%;  $P <0.0001$ ).<sup>38</sup> Combination antihypertensive therapy reduced the risk of recurrent stroke by 43% (95% CI: 30%–54%) with a mean decrease in BP of 12/5 mm Hg. A recent Cochrane Review has shown that antihypertensive medication significantly reduced the relative risk of recurrent stroke by 24% in patients with a prior ischemic stroke (OR 0.76; 95% CI: 0.64–0.89).<sup>39</sup>

Because a systolic BP >180 mm Hg is an independent predictor of stroke after CEA, it is reasonable to perform urgent CEA in patients whose preoperative BP is <180 mmHg.<sup>2</sup> Symptomatic patients with a preoperative BP >180 mm Hg should probably receive urgent antihypertensive treatment before proceeding with CEA. Persisting or worsening hypertension after CEA should be actively treated postoperatively, in order to prevent hyperperfusion syndrome, ICH, bleeding complications and cardiac events in the early postoperative period.<sup>2</sup> Data from TIA/stroke patients support the use of ACE inhibitors and thiazide diuretics, but other antihypertensive agents are acceptable.<sup>39</sup> Contemporary guidelines recommend a target BP <130 mm Hg/<80 mm Hg in non-diabetic patients under 65 years of age, and <140 mm Hg/<80 mm Hg in non-diabetic patients ≥65 years old.<sup>40</sup>

In selected patients with severe carotid stenosis with exhausted hemodynamic reserve who experience recurrent hemodynamic TIAs, despite optimal antithrombotic therapy, and who are not suitable for carotid revascularization, it would be reasonable to aim for higher systolic BP thresholds (e.g., systolic BP >140 to <160 mm Hg), in order to improve cerebral perfusion.

### Treatment of diabetes mellitus

DM is a risk factor for carotid stenosis<sup>41</sup> and DM patients in the North Manhattan study faced a doubling of stroke-risk.<sup>42</sup> However, meta-analyses found no evidence that tight glycemic control reduced late stroke,<sup>43</sup> but it did reduce other DM-related complications. The UK Prospective Diabetes Study observed that tight BP control (mean BP 144/82 mmHg) was associated with a 44% RRR in stroke (95% CI 11–65;  $P = 0.013$ ), compared with patients who had less tight BP control (mean BP 154/87 mm Hg).<sup>44</sup> In diabetic patients with a symptomatic carotid stenosis, a target systolic blood pressure <130 mm Hg (but not <120 mm Hg) and a target diastolic blood pressure <80 mm Hg (but not <70 mm Hg) is recommended in patients under 65 years of age. In diabetic patients ≥65 years of age, the target systolic blood pressure is 130–139 mm Hg, and target diastolic blood pressure is <80 mm Hg (but not <70 mm Hg).<sup>40</sup>

### Is There a Need for CEA/CAS?

#### Results of the symptomatic RCTs

Three RCTs ( $n = 6081$ ) compared CEA vs. OMT in patients with a carotid territory stroke/TIA in the preceding 6 months. These were the European Carotid Surgery Trial (ECST), the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the Veterans Affairs Administration Study (VA).<sup>45–47</sup> Although somewhat historical (having reported 30 years ago), they continue to guide practice. Table 92.1 details 5-year risk of ipsilateral stroke (including 30-day death/stroke) in 6081 patients from an individual patient meta-analysis from ECST, NASCET and VA studies by the Carotid Endarterectomy Trialists Collaboration (CETC).<sup>48–50</sup> The main findings were that CEA conferred no benefit (over OMT) in patients with <50% stenosis (NASCET method). In patients with 50%–69% stenosis, CEA conferred a small but significant benefit, while CEA conferred maximum benefit in those with 70%–99% stenosis.

Based on these level 1 data, guidelines published since 1991 have advised that “CEA is recommended in patients reporting carotid territory symptoms within the preceding 6 months and who have a 70%–99% carotid stenosis, provided the procedural death/stroke rate is <6%” (Class 1, Level A).<sup>2</sup> In addition, “CEA should be considered in patients reporting carotid territory symptoms within the preceding 6 months and who have a 50%–69% carotid stenosis, provided the procedural death/stroke rate is <6%” (Class 1, Level A).<sup>2</sup>

#### Do all patients gain similar benefit from CEA?

Because >6000 patients were randomized within the RCTs, this has enabled meaningful subgroup analyses to be undertaken which can aid clinicians in making decisions about individual patients, especially if considered “unfit” for carotid interventions. Several clinical/imaging features are predictive of a greater (lower) risk of stroke in patients with 50%–99% stenosis treated medically.

**TABLE 92.1**

5-Year Risk of Ipsilateral Stroke (Including Perioperative Death/Stroke) in 6081 Patients Randomized within ECST, NASCET & VA Studies\*

| Stenosis Severity | n =  | 30-day CEA Risk | 5-YEAR RISK |       |                          |         | Strokes Prevented Per 1000 CEAs |              |
|-------------------|------|-----------------|-------------|-------|--------------------------|---------|---------------------------------|--------------|
|                   |      |                 | CEA         | BMT   | ARR (%) ( $P =$ )        | RRR (%) |                                 |              |
| <30%              | 1746 |                 | 12.1%       | 9.8%  | -2.2% ( $P = 0.05$ )     | nb      | nb                              | 0 at 5 yrs   |
| 30%–49%           | 1429 | 6.7%            | 14.8%       | 18.1% | +3.2% ( $P = 0.6$ )      | 18%     | 38                              | 32 at 5 yrs  |
| 50%–69%           | 1549 | 8.4%            | 13.6%       | 18.2% | +4.6% ( $P = 0.04$ )     | 25%     | 13                              | 46 at 5 yrs  |
| 70%–99%           | 1095 | 6.2%            | 10.36%      | 26.2% | +15.9% ( $P < 0.00001$ ) | 61%     | 6                               | 159 at 5 yrs |
| “string sign”     | 262  | 5.4%            | 16.8%       | 15.2% | -1.6% ( $P = 0.9$ )      | nb      | nb                              | 0 at 5 yrs   |

\*Data derived from CETC individual patient meta-analysis<sup>48,49</sup> with all pre-randomization angiograms remeasured using NASCET method. nb, no benefit conferred by CEA; ARR, Absolute Risk Reduction; RRR, Relative Risk Reduction; strokes prevented per 1000 CEAs, number of strokes prevented at five years by performing 1000 CEAs.

### Clinical Features

**Increasing Age.** In the past, increasing age (especially >80 years) was considered a relative contraindication to CEA. However, a meta-analysis of RCT data showed this to be flawed logic. The absolute risk reduction (ARR) in ipsilateral stroke at 5 years conferred by CEA in patients with 50%–99% stenosis was 5.6% in patients aged <65 years, 8.6% in patients aged 65–75 years, with the maximum benefit being observed in patients aged >75 years (ARR = 19.2%).<sup>49</sup>

Amongst NASCET patients aged >75 years with 70%–99% stenosis, the ARR in ipsilateral stroke at 2 years was 28.9% (vs. 15.1% in patients aged 65–74 and 9.1% in patients aged <65). Within the NASCET cohort with symptomatic 50%–69% stenosis, the only subgroup in whom CEA conferred significant benefit were patients aged >75 years (ARR 17.3%). The number needed to treat (NNT) to prevent one stroke at 2 years was only 3 in >75-year-old patients with 70%–99% stenosis, versus 6 for similarly aged patients with 50%–69% stenosis. Of equal importance, there was no evidence that 30-day death/stroke after CEA increased with age (7.9% in patients aged <65 years; 5.5% in patients aged 65–74 and 5.2% in patients aged >75 years).<sup>51</sup> Accordingly, increasing patient age is not a contraindication to CEA, unless there are other important comorbidities.

**Patient Sex.** In a CETC meta-analysis, CEA conferred greater benefit in males with 50%–99% stenoses (ARR = 11%), versus 2.8% in females.<sup>50</sup> Female patients also rapidly lose benefit from CEA the longer the delay from symptom onset to undergoing CEA (see below).

**Presenting Symptoms.** In a CETC meta-analysis, the presenting symptom influenced outcome. The ARR in ipsilateral stroke at 5 years with CEA was 18% in patients presenting with a stroke, 15% following TIA and 5% for retinal ischemic symptoms.<sup>48</sup> Some have questioned whether CEA is beneficial in patients presenting with lacunar stroke (usually attributed to intracranial small vessel disease), but NASCET found that CEA conferred a 9% ARR in ipsilateral stroke at 3 years in these patients.<sup>52</sup>

**Multiple Comorbidities.** The issue of comorbidities often arises when deciding whether to treat symptomatic patients conservatively or with a carotid intervention. NASCET analyzed risks of late ipsilateral stroke, stratified for risk-factor burden, defined as: stroke at presentation, male sex, 80%–99% stenosis, systolic BP >160 mm Hg, diastolic BP >90 mm Hg, plaque ulceration, presenting symptom within 30 days or history of congestive cardiac failure, DM, smoking, claudication, MI, hypertension or hyperlipidaemia.<sup>46</sup> In OMT patients, the 2-year risk of ipsilateral stroke was 17% in those with <5 factors, 23% with 6 factors and 39% in patients with 7+ risk factors. The number of risk factors had no influence on CEA outcomes (9% ipsilateral stroke at 2 years, irrespective of comorbidities). Accordingly, recently symptomatic patients should not be denied a carotid intervention on the basis of comorbidities. Each case should be considered on individual merits.

**Should a Small Intracranial Aneurysm Affect Decision-Making?** About 3%–5% of symptomatic patients will have an incidental, small intracranial aneurysm and there has been

concern that these aneurysms might increase early/late stroke risks after CEA. NASCET reported that 90/2885 patients (3.1%) had 99 intracranial aneurysms.<sup>53</sup> The majority (83%) were <5 mm, with a 0.3% incidence of aneurysm >10 mm (usual threshold for neurosurgical/neuroradiological intervention). The 5-year risk of ipsilateral stroke in CEA patients was 10% with a non-repaired aneurysm, versus 14.8% in patients without an aneurysm. The 5-year risk of ipsilateral stroke in OMT patients was 22.7% with a non-repaired aneurysm, versus 22.5% in those without an aneurysm. The evidence, therefore, suggests that small intracranial aneurysms do not significantly increase risks of early/late stroke after CEA.

**Recency of Symptoms.** Most guidelines have adopted a 6-month threshold as being “recently symptomatic.” This permits substantial leeway regarding CEA timing, especially with an assumption amongst some surgeons that intervening early after symptom onset increases perioperative risks.<sup>54</sup> The momentum for changing practice and intervening early after symptom onset was driven by a 2003 CETC meta-analysis of the benefit conferred by CEA, stratified for delays from randomization to CEA.<sup>49,50</sup> In reality, CEA was performed an average of 7 days after randomization (PM Rothwell, personal communication). Table 92.2 details the results of this meta-analysis stratified for delays to CEA, stenosis severity and patient sex. The benefit conferred by CEA was greatest the earlier CEA was performed. Greater benefit was also observed in patients with 70%–99%, versus 50%–69% stenosis. Males gained greater benefit than women (as delays increased) and after about 4–6 weeks, CEA may not confer significant benefit over OMT in female patients. However, RCTs randomizing women to early vs. late interventions have not been performed.

Another important finding was that stroke risk in the first 7–14 days after symptom onset was higher than previously assumed. In a series of 549 patients who experienced their stroke after a TIA, 43% of strokes occurred within 7 days of the index TIA.<sup>55</sup> In a CETC meta-analysis, the 5-year risk of ipsilateral stroke in OMT patients was 18% in patients with 50%–69% stenosis and 26% in patients with 70%–99% stenosis<sup>48</sup> (see Table 92.1). However, data from natural history studies suggest that early stroke risk in patients with 50%–99% stenosis may be much higher, ranging from 5%–8% at 48 hours, 4%–17% at 72 hours, 8%–22% at 7 days and 11%–25% at 14 days (Table 92.3). This suggests that many high-risk patients were not randomized within ECST/NASCET and the benefit conferred by intervening in the first 7–14 days after symptom onset might be even higher than previously thought. Finally, studies have reported high rates of stroke/TIA whilst awaiting CEA. In Blaser’s series, there was a 10% risk of TIA/stroke during a median 10-day period between investigation and CEA,<sup>56</sup> whilst a Leicester study noted a 13% risk of TIA/stroke in the 48–72-hour period between being seen in a TIA clinic and undergoing CEA.<sup>17</sup> Kastrup et al. also reported a 12% risk of new MR Diffusion Weighted Image lesions over a median of 7 days between investigation and CEA.<sup>57</sup>

These data have driven a worldwide move towards performing CEA (CAS) as soon as possible after symptom onset, preferably within 7–14 days.<sup>2</sup>

**TABLE 92.2**

5-Year ARR in Ipsilateral Carotid Territory Ischemic Stroke (Including the Perioperative Risk) Conferred by CEA in Patients with a NASCET 50%–69% and 70%–99% Stenosis, Stratified for Delay from Index Event to Randomization and Patient Sex\*

| ALL PATIENTS | 50%–69% STENOSIS |     |             | 70%–99% STENOSIS |     |             |
|--------------|------------------|-----|-------------|------------------|-----|-------------|
|              | ARR              | NNT | Stroke/1000 | ARR              | NNT | Stroke/1000 |
| <2 weeks     | 14.8%            | 7   | 148         | 23.0%            | 4   | 230         |
| 2–4 weeks    | 3.3%             | 30  | 33          | 15.9%            | 6   | 159         |
| 4–12 weeks   | 4.0%             | 25  | 40          | 7.9%             | 13  | 79          |
| >12 weeks    | -2.9%            | nb  | nb          | 7.4%             | 14  | 74          |

| Males      |       |    |     |       |   |     |
|------------|-------|----|-----|-------|---|-----|
| <2 weeks   | 15.2% | 7  | 152 | 23.3% | 4 | 233 |
| 2–4 weeks  | 6.8%  | 15 | 68  | 23.8% | 4 | 238 |
| 4–12 weeks | 5.0%  | 20 | 50  | 18.3% | 5 | 183 |
| >12 weeks  | 6.3%  | 16 | 63  | 20.4% | 5 | 204 |

| Females    |        |    |     |       |    |     |
|------------|--------|----|-----|-------|----|-----|
| <2 weeks   | 13.8%  | 7  | 138 | 41.7% | 2  | 417 |
| 2–4 weeks  | -5.7%  | nb | nb  | 6.6%  | 15 | 66  |
| 4–12 weeks | -2.2%  | nb | nb  | -2.2% | nb | nb  |
| >12 weeks  | -21.7% | nb | nb  | -2.4% | nb | nb  |

\*Data derived from CETC<sup>88,91</sup> with pre-randomization angiograms remeasured using NASCET method. ARR, Absolute Risk Reduction (%); NNT, number of CEAs performed to prevent one stroke at 5 year; stroke/1000, number of ipsilateral strokes prevented at 5 years by performing 1000 CEAs; nb, no benefit conferred by CEA.

**TABLE 92.3**

Early Risk of Stroke in Patients Following a Transient Ischemic Attack Attributed to a 50%–99% Stenosis of their Ipsilateral Carotid Artery

|                               | 48 hours | 72 hours | 7 days | 14 days |
|-------------------------------|----------|----------|--------|---------|
| Fairhead 2005 <sup>118</sup>  |          |          |        | 20%     |
| Purroy 2007 <sup>119</sup>    |          |          | 10%    |         |
| Ois 2009 <sup>120</sup>       |          | 17%      | 22%    | 25%     |
| Bonifati 2011 <sup>121</sup>  | 8%       |          |        |         |
| Johansson 2013 <sup>122</sup> | 5%       |          | 8%     | 11%     |
| Mono 2013 <sup>123</sup>      |          | 4%       |        |         |
| Merwick 2013 <sup>124</sup>   |          |          | 8%     |         |
| Marnane 2014 <sup>125</sup>   | 5%       | 9%       | 9%     | 16%     |

**Timing of CEA After Disabling Stroke.** There is much debate about the optimal timing of CEA (CAS) in patients with disabling stroke. This is because of concerns about hemorrhagic transformation of an ischemic infarct, which is associated with higher rates of disability and death. The 2017 ESVS carotid guidelines advise that revascularization should be deferred in patients with 50%–99% stenosis who experience a disabling stroke (Modified Rankin Score  $\geq 3$ ), where the area of infarction exceeds one third of the middle cerebral artery territory, or who have altered consciousness/drowsiness (*Class I, Level C*).<sup>2</sup> When a decision has been made to perform CEA/

CAS in these patients (after a suitable period of recovery), it is vital to actively manage post-CEA hypertension to prevent postoperative ICH.<sup>58</sup>

#### Imaging Features

**Increasing Stenosis Severity.** Table 92.4 details the ARR conferred by CEA over OMT, stratified for stenosis severity in a CETC meta-analysis of NASCET, ECST and VA data.<sup>48</sup> CEA conferred incremental benefit as stenosis severity increased, especially in the 90%–99% subgroup. Note that patients with near-occlusion did not appear to gain benefit from CEA.

**TABLE 92.4**

Absolute Risk Reduction in Late Ipsilateral Stroke Conferred by CEA (Including any Perioperative Stroke or Death) Stratified According to Stenosis Severity\*

|                | <30%  | 30%–49% | 50%–59% | 60%–69% | 70%–79% | 80%–89% | 90%–99% | Near-Occlusion |
|----------------|-------|---------|---------|---------|---------|---------|---------|----------------|
| ARR at 3 years | -2.7% | 1.8%    | 1.8%    | 2.1%    | 14.9%   | 18.1%   | 36.1%   | 4.2%           |
| ARR at 5 years | -2.2% | 3.2%    | 4.0%    | 5.9%    | 15.8%   | 17.7%   | 32.4%   | -1.7%          |
| ARR at 8 years | -2.9% | 1.2%    | 5.2%    | 9.6%    | 14.2%   | 14.3%   | 38.1%   | -0.3%          |

\*Data derived from individual patient meta-analysis of data from ECST, NASCET and VA Studies.<sup>48</sup>

All stenoses measured using the NASCET method.

**Irregular Versus Smooth Plaques.** In a CETC meta-analysis, CEA conferred an 8% ARR in ipsilateral stroke at 5 years in patients with smooth stenoses, versus 17% in patients with irregular (ulcerated) plaques.<sup>48</sup>

**Contralateral occlusion.** In a CETC meta-analysis, the ARR in ipsilateral stroke with CEA at 5 years was 13% in patients without contralateral occlusion, vs. 24% in patients with contralateral occlusion.<sup>48</sup>

**Tandem intracranial disease.** Some clinicians are concerned that tandem intracranial disease may be a relative contraindication to CEA. NASCET undertook a subgroup analysis on the effect of tandem intracranial disease on 3-year rates of ipsilateral stroke.<sup>59</sup> In the NASCET protocol, “severe” intracranial disease was an exclusion criterion. All angiograms were reviewed and intracranial disease defined as “any atheromatous wall irregularity or stenosis in the intracranial ICA or in the main trunk of the anterior or middle cerebral arteries.” Overall, 27% of patients had mild intracranial disease, whereas 6% had moderate and 0.5% had a severe stenosis or occlusion.

**X Tandem disease had no effect on 3-year stroke rates in CEA patients.** The 3-year risk of ipsilateral stroke in OMT patients without intracranial disease increased from 15% in patients with 50%–69% extracranial stenosis, to 24% with 70%–84% stenosis and 25% for 85%–99% stenosis. OMT patients with intracranial disease (of any severity) had significantly higher rates of 3-year ipsilateral stroke, which increased with extracranial stenosis severity (19% with 50%–69% stenosis; 28% with 70%–84% stenosis and 45% with 85%–99% extracranial stenosis).<sup>59</sup> Accordingly, **tandem intracranial disease is not a reason to avoid carotid interventions in suitable symptomatic patients.**

**Impact of Collaterals.** NASCET evaluated the impact of collateral recruitment on 2-year ipsilateral stroke in patients with 70%–99% stenosis.<sup>60</sup> Collateral recruitment was defined as collateral filling via the anterior or posterior communicating arteries, or retrograde filling via the ophthalmic artery. Collateral recruitment had **no influence on stroke risk in CEA patients.** However, the **2-year risk of stroke was significantly lower in OMT patients with vs. without collateral recruitment (11% vs 28%).<sup>60</sup>**

**Should “Near-Occlusion” Influence Decision Making?** In the CETC meta-analysis, patients with near-occlusion were defined as having a 95%–99% stenosis with distal ICA collapse and/or a narrow-caliber lumen with “trickle flow” up to the skull-base.<sup>49</sup> Tables 92.1 and 92.4 indicate that the benefit

conferred by CEA over OMT alone increased with increasing stenosis severity, provided near-occlusion was not present. On the basis of these data, the 2017 ESVS guidelines advised that CEA/CAS was not recommended in symptomatic patients with chronic near-occlusion, unless associated with recurrent ipsilateral symptoms (despite OMT) and following multidisciplinary neurovascular team review (*Class III, Level C*).<sup>2</sup>

This recommendation has been challenged on the basis that the CETC data are now 30 years old and only 269 near-occlusion patients were included in the meta-analysis, some of whom underwent CEA during follow-up. More recent meta-analyses suggest that the risk of stroke in medically treated patients with near-occlusion may be higher than previously thought and that CEA/CAS may now be indicated.<sup>61,62</sup> At present, the evidence is conflicting and decisions in these patients should be individualized and based on multidisciplinary team review.

## Which Carotid Intervention: CEA or CAS?

### Perioperative Outcomes

Having established that a carotid intervention is indicated, should the patient be offered CEA or CAS? Twenty RCTs have compared CEA with CA or CAS.<sup>63</sup> Of these, 10 RCTs compared CEA vs. CAS in symptomatic patients ( $n = 5797$  patients). Table 92.5 details the results of a meta-analysis of 30-day outcomes from these 10 RCTs. As is evident, CAS (predominantly via the transfemoral route) was associated with significantly higher 30-day rates of stroke, death/stroke, death/disabling stroke and death/stroke/MI, compared with CEA.<sup>63</sup>

### Late Outcomes

The Carotid Stenting Trialists Collaboration (CSTC) undertook an individual patient data meta-analysis of late risks of ipsilateral stroke involving 4754 symptomatic patients.<sup>64</sup> After the 30-day perioperative period had elapsed (i.e. excluding perioperative risks), there was no significant difference in 5- and 9-year rates of ipsilateral stroke. The 5-year rate of ipsilateral stroke was 3.1% after CEA vs. 3.2% after CAS (HR 1.06; 95% CI 0.73–1.54), giving an average annual ipsilateral stroke rate of 0.6% after CEA and 0.64% after CAS. The 9-year rate of ipsilateral stroke was 3.9% after CEA vs. 4.5% after CAS, giving an average annual ipsilateral stroke rate of 0.43% after CEA and 0.5% after CAS.<sup>64</sup> These data indicate that once the 30-day perioperative period has elapsed, CAS is as durable as CEA in preventing late ipsilateral stroke.

**TABLE 92.5**

Meta-Analysis of 30-Day Outcomes Following CAS Versus CEA in 10 RCTs, which Included 5797 Symptomatic Patients

|                   | Death            | Stroke            | Death/Stroke     | Disabling Stroke | Death/Disabling Stroke | MI               | Death/Stroke/MI  |
|-------------------|------------------|-------------------|------------------|------------------|------------------------|------------------|------------------|
|                   | 9 RCTs n=4257    | 9 RCTs n=5535     | 10 RCTs n=5754   | 6 RCTs n=4855    | 5 RCTs n=3534          | 6 RCTs n=3980    | 6 RCTs n=3719    |
| <b>CEA</b>        | 1.4% (0.9–2.0)   | 4.6% (3.26–6.37)  | 5.08% (3.7–6.9)  | 1.8% (1.1–3.1)   | 3.2% (2.5–4.1)         | 1.6% (1.0–2.3)   | 5.1% (4.13–6.30) |
| <b>CAS</b>        | 1.9% (1.4–2.6)   | 8.5% (5.87–12.14) | 9.3% (6.8–12.6)  | 3.28% (1.6–6.7)  | 5.21% (3.0–8.9)        | 0.8% (0.5–1.4)   | 8.4% (5.0–13.8)  |
| <b>OR (95%CI)</b> | 1.38 (0.81–2.34) | 1.73 (1.38–2.18)  | 1.71 (1.38–2.11) | 1.35 (0.91–1.99) | 1.42 (1.00–2.02)       | 0.50 (0.24–1.02) | 1.61 (1.21–2.14) |

Significant benefit favoring CEA

No significant difference between CAS and CEA

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## Selecting Patients for CEA or CAS

The key message from the meta-analyses is that predicting the magnitude of the perioperative risk with CEA/CAS is essential when selecting patients for safe carotid interventions. The large number of patients randomized in the 20 RCTs ( $n = 9861$ ) has enabled meaningful subgroup analyses to be undertaken to identify clinical and/or imaging features that are associated with lower or higher risks of perioperative stroke/death after either CEA or CAS.<sup>63</sup>

### Clinical Features

#### Patient sex

In CREST, the 30-day risk of death/stroke/MI was significantly higher in females after CAS than CEA (6.8% vs. 3.8% [HR 1.84; 95% CI 1.02–3.37]). Female sex had no influence on MI risks after CEA/CAS, but stroke risk was significantly higher in females undergoing CAS vs. CEA (5.5% vs. 2.2% [HR 2.63; 95% CI 1.23–5.65]).<sup>65</sup>

#### Increasing age

A CSTC meta-analysis ( $n = 4289$ ) revealed that age had no effect on death/stroke after CEA, while there was a significant increase in death/stroke with increasing age after CAS (Table 92.6).<sup>66</sup> Compared to CEA (column 3, Table 92.6) a threshold of 70 years was statistically significant. Above 70 years, CAS patients incurred significantly higher rates of death/stroke. Below 70 years, CAS had similar 30-day death/stroke rates to CEA.

#### Intervening within 14 days of symptom onset

In a CSTC meta-analysis involving 2839 symptomatic patients,<sup>67</sup> 30-day death/stroke was significantly higher after CAS vs. CEA when performed <7 days of symptom onset (9.4% vs. 2.8% [OR 3.4; 95% CI 1.01–13.1;  $P = 0.03$ ]). Furthermore, 30-day death/stroke was also significantly higher after CAS vs. CEA when performed 8–14 days after symptom onset (8.1% vs 3.4%; OR 2.42; 95% CI 1.0–5.7;  $P = 0.04$ ). In this

meta-analysis, CAS was mainly performed via a transfemoral approach. It may be that newer technologies (e.g., transcarotid artery revascularization [TCAR]) might be associated with lower peri-procedural risks compared with transfemoral CAS, but no data have been published regarding TCAR outcomes stratified for delays to CAS.

### Imaging Predictors

#### Stenosis severity

There was no association between stenosis severity and 30-day death/stroke in CEA/CAS patients.<sup>63</sup>

#### Plaque characteristics

In CREST, sequential or remote lesions extending beyond the bulb were associated with significantly higher 30-day risks of death/stroke with CAS vs. CEA (5.8% vs. 0.7%; OR 9.01; 95% CI 1.2–6.78). In addition, plaque length >13 mm was associated with higher risks of perioperative death/stroke after CAS vs. CEA (6.1% vs. 1.9%; OR 3.42; 95% CI 1.19–9.78).<sup>68</sup>

#### Pre-existing white matter lesions on magnetic resonance imaging

ICSS scored the severity of preoperative white matter lesions (WMLs) using the Age-Related White Matter Changes (AR-WMC) score.<sup>69</sup> The median preoperative score was 7. A subgroup of ICSS patients (CAS = 536; CEA = 500) were stratified according to whether their ARWMC score was <7 or  $\geq 7$ . In CEA patients, there was no association between preoperative ARWMC score and perioperative risk. However, in CAS patients, perioperative stroke risk was significantly higher in patients with an ARWMC score  $\geq 7$ , compared to those with scores <7 (HR 2.76; 95% CI 1.17–6.51). Higher rates of disabling stroke were observed in CAS patients whose ARWMC score was  $\geq 7$  vs. <7 (HR 3; 95% CI 1.1–8.36). In addition, in patients with an ARWMC score  $\geq 7$ , the risk of stroke was significantly higher with CAS vs. CEA (HR 2.98; 95% CI 1.29–6.93;  $P = 0.011$ ). There was no difference in procedural

**TABLE 92.6**

Effect of Age on 30-Day Risk of Death/Stroke in Symptomatic Patients Randomized within EVA-3S, SPACE-1, ICSS and CREST<sup>†</sup>

|             | CAS HR (95% CI)* | CEA HR (95% CI)* | CAS vs. CEA HR (95% CI)*** |
|-------------|------------------|------------------|----------------------------|
| <60 years   | 1.0**            | 1.0**            | 0.62 (0.31–1.23)           |
| 60–64 years | 1.79 (0.89–3.60) | 1.01 (0.34–1.9)  | 1.07 (0.56–2.01)           |
| 65–69 years | 2.16 (1.13–4.13) | 0.81 (0.43–1.52) | 1.61 (0.90–2.88)           |
| 70–74 years | 4.01 (2.19–7.32) | 1.20 (0.68–2.13) | 2.09 (1.32–2.32)           |
| 75–79 years | 3.94 (2.14–7.28) | 1.29 (0.74–2.25) | 1.91 (1.21–3.01)           |
| ≥80 years   | 4.15 (2.20–7.84) | 1.09 (0.57–2.10) | 2.43 (1.35–4.38)           |

\*HR = Hazard Ratio (95% CI).

\*\*All HR age-based calculations based on comparisons against age group <60 years.

\*\*\*Age-based HR calculation for CAS compared with CEA. If HR is <1.0, CAS is associated with lower perioperative death/stroke. If HR is >1.0, CAS is associated with higher risk of perioperative stroke/death.

<sup>†</sup>Based on individual patient data meta-analysis by the Carotid Stenting Trialists Collaboration. CAS, carotid artery stenting; CEA, carotid endarterectomy; HR, Hazard Ratio; 95% CI, 95% confidence intervals.

Table reproduced with permission from Naylor AR, Ricco JB, de Borst GJ, et al. 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;55:3–86.

stroke risk in CEA/CAS patients with an ARWMC <7. This would suggest that CEA is preferred to CAS in patients with extensive WMLs on preoperative MRI.

### CEA Techniques

No aspect of CEA technique was associated with higher or lower risks of perioperative stroke. However, increased diastolic BP was an independent risk factor for stroke after CEA<sup>70</sup> but not after CAS.<sup>71</sup> In CEA patients, the relative risk of stroke increased by a factor of 1.3 per 10 mm Hg.<sup>70</sup>

### CAS Techniques

The CSTC performed a meta-analysis to assess the influence of cerebral protection devices (CPD), stent design, pre-dilatation and post-dilatation on perioperative outcomes in 1557 CAS patients.<sup>72</sup> Patients treated with open cell stents had significantly higher risks of 30-day death/stroke than those treated with closed cell stents (10.3% vs. 6%; RR 1.76; 95% CI 1.23–2.52;  $P = 0.002$ ), while filter CPDs were not associated with significant reductions in death/stroke (8.0% vs. 7.1%; RR 1.1; 95% CI 0.71–1.70;  $P = 0.67$ ). The 30-day risk of death/stroke was similar in patients who did and did not undergo pre-dilatation (7.4% vs. 7.9%; RR 0.98; 0.69–1.44;  $P = 0.919$ ) or post-dilatation (7.2% vs. 8.2%; RR 0.87; 95% CI 0.47–1.62;  $P = 0.67$ ).<sup>72</sup> CREST analyzed 1531 “lead in” and 1121 trial patients undergoing CAS and noted that when one stent was deployed, perioperative stroke was 4%, versus 15% where ≥2 stents were deployed (OR 2.9; 95% CI 1.49–5.64). Patients with ≥2 stents were significantly more likely to have ulcerated plaques ( $P = 0.006$ ), be older ( $P = 0.01$ ) and have longer lesion lengths ( $P = 0.02$ ).<sup>73</sup>

Per-protocol analysis of CAS data from the International Carotid Stenting Study (ICSS) revealed that >50% restenosis at 5 years occurred less frequently with open cell stents, versus closed cell stents (35.5% vs. 46%, unadjusted HR 0.68; 95% CI 0.53–0.88).<sup>74</sup> There was, however, no significant difference in risks of developing a 70%–99% restenosis after open cell

versus closed cell stents (8.6% vs. 12.7%; unadjusted HR 0.63; 95% CI 0.37–1.05).<sup>74</sup> The risk of ipsilateral stroke after the perioperative period was similar for open vs. closed cell stents (HR 0.78; 95% CI 0.35–1.75), i.e., both stent designs were equally effective in preventing late ipsilateral stroke.<sup>74</sup>

## DECISION MAKING IN ASYMPTOMATIC CAROTID STENOSIS PATIENTS

Clinical decision making in ACS patients, whilst also supported by level I evidence, is much more controversial than in symptomatic patients. This is because the benefits conferred by carotid interventions are much lower than in symptomatic patients and because the risk of stroke on OMT may not be as high as when patients were recruited into the original RCTs.

### Management Planning

As with symptomatic patients, once a diagnosis of ACS has been made, three issues need to be addressed: (1) what risk factors need to be addressed? (2) Is the patient receiving OMT? (3) Is there a need for CEA/CAS?

### What Risk Factors Need to Be Addressed?

It is reasonable to address modifiable risk factors in the same manner as for symptomatic patients.

### Is the Patient Receiving Optimal Medical Therapy?

In general, advice re OMT in ACS patients is similar to that for symptomatic patients, with the exception of the evidence base regarding antiplatelet therapy.

### Antiplatelet therapy

There is a paucity of quality RCT data regarding antiplatelet therapy in ACS patients. The Asymptomatic Cervical Bruit

Study randomized patients with 50%–99% ACS to 325 mg of enteric-coated aspirin ( $n = 188$ ) or placebo ( $n = 184$ ). After a 2.3-year median follow-up period, there was no difference in the annual composite risk of TIA, ischemic stroke, unstable angina, MI, or any cause death in the aspirin vs. placebo groups (11% vs. 12.3%;  $P = 0.61$ ). The risk of ipsilateral stroke was not reported separately.<sup>75</sup>

However, observational data from the Asymptomatic Carotid Emboli Study (ACES) showed that treatment with “antiplatelet therapy” significantly reduced 2-year risks of ipsilateral TIA/stroke, or stroke or any cardiovascular death, compared with “no antiplatelet therapy”.<sup>76</sup> In addition, a multicenter study, stratified for whether patients were taking aspirin prior to stroke onset, revealed that pre-existing aspirin users had less severe stroke at presentation and improved functional outcomes at discharge, even though aspirin therapy had failed to prevent their initial stroke. This beneficial effect was only seen in patients with large artery atherosclerotic strokes, as opposed to cardioembolic or lacunar strokes.<sup>77</sup> In the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance (CHARISMA) study, 7% had a 50%–99% ACS. There was no evidence that aspirin + clopidogrel combination antiplatelet therapy conferred any benefit over aspirin monotherapy.<sup>78</sup>

However, two-thirds of ACS patients have subclinical coronary artery disease. In a systematic review of 17 studies reporting 5-year mortality in 11,391 patients with 50%–99% ACS, 63% of late deaths were cardiac, representing an average annual cardiac-related mortality rate of 2.9%.<sup>79</sup> Accordingly, guidelines advise that ACS patients should be prescribed aspirin (75–325 mg daily) as the first-line strategy (mainly to prevent cardiac events), with clopidogrel monotherapy (75 mg daily) reserved for those who are aspirin intolerant.<sup>2,6</sup> Moreover, in light of data suggesting that the clinical effectiveness of aspirin for prevention of vascular events may vary according to body weight,<sup>80</sup> it is reasonable to consider prescribing 150–325 mg aspirin daily in patients weighing  $\geq 70$  kg, following assessment of whether the patients has risk factors for gastrointestinal bleeding.

### Lipid-lowering therapy

There are no large RCTs of statins in ACS patients. A *post-hoc* analysis of ACST data showed that patients prescribed statins had lower 10-year rates of non-perioperative stroke than those not taking lipid-lowering therapy (13.4% vs. 24.1%), suggesting that statins reduced long-term stroke risk in ACS patients.<sup>81</sup> Therefore, it is reasonable to prescribe lipid-lowering therapy with statins  $\pm$  ezetimibe as suggested for symptomatic patients but based on lower quality evidence.

Patients with acute ischemic stroke were excluded from many trials of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. Preliminary data from case series suggest that PCSK9 inhibitors may stabilize plaques in ACS patients,<sup>82</sup> but no RCTs have been performed. Therefore, pending such trials, in symptomatic or asymptomatic patients intolerant of, or not achieving lower LDL targets on statins,  $\pm$  ezetimibe, it

is reasonable to consider referral for additional or alternative empirical treatment with PCSK9 inhibitors.<sup>13</sup>

### Antihypertensive therapy

No RCT has specifically evaluated the impact of antihypertensive therapy on the prevention of stroke and other vascular events in ACS patients. Notwithstanding this, it is reasonable to manage hypertension as outlined for symptomatic patients.

### Treatment of patients with diabetes mellitus

There are no RCT data showing that tight glycemic control reduces risk of first stroke in the territory of a 50%–99% ACS,<sup>2</sup> but there is evidence that intensive glycemic control, compared with standard care alone, may reduce the incidence of stroke in patients with impaired glucose tolerance or type 2 DM who also have a  $BMI \geq 30$  (RR 0.86; 95% CI: 0.75–0.99;  $P = 0.041$ ).<sup>43</sup>

### *Is There a Need for CEA/CAS?*

#### RCTs comparing CEA with OMT in ACS

Two landmark RCTs, the Asymptomatic Carotid Atherosclerosis Study (ACAS) and ACST, compared CEA with OMT in patients with 60%–99% ACS.<sup>83,84</sup> The Veterans Affairs Cooperative Study (VACS) randomized 444 male patients,<sup>85</sup> but stopped early after publication of ACAS/ACST.

Table 92.7 details 5- and 10-year data from ACAS and ACST.<sup>83,84</sup> Whilst it has been suggested that both trials published similar findings, this is not strictly true. ACAS published 5-year data for ipsilateral stroke and “any stroke,” whereas ACST only published the latter. In ACAS, CEA conferred an ARR in ipsilateral stroke (including the perioperative risk) of 5.9% at 5-years, which equates to preventing 59 strokes per 1000 operations at 5-years. ACAS and ACST reported that CEA conferred a 5.4% ARR in “any stroke” at 5 years (including the perioperative risk), which equates to preventing 54 strokes per 1000 CEA operations at 5 years. ACAS did not publish 10-year data, but CEA conferred a 4.5% ARR in “any stroke” (including the perioperative risk) at 10 years in ACST.<sup>81</sup> This equates to about 45 strokes being prevented at 10 years per 1000 operations.

### *Are There Differences of Opinion Regarding the Optimal Management of ACS?*

Despite level I evidence supporting a role for CEA in suitable ACS patients, controversies exist regarding optimal decision-making in ACS patients. Advocates of a more aggressive role for CEA/CAS argue that decision-making should be based on level I evidence and that until new RCTs report, guidelines should use ACAS/ACST data, just as they do for historical NASCET/ECST data in symptomatic patients.<sup>86</sup> They also argue that performing CEA/CAS is the only way of preventing stroke in the 80% who will not experience a “warning” TIA. They also note that death/stroke risks after CEA/CAS have declined significantly, compared with ACST/ACAS, and that this should further increase the benefit conferred by any intervention. It is also argued that the apparent decline in stroke rates

**TABLE 92.7**

5- and 10-Year Data for Ipsilateral Stroke and Any Stroke (Including Perioperative Risks) in ACAS and ACST for CEA + OMT Versus OMT Alone\*

|                    | IPSILATERAL STROKE (+ PERIOPERATIVE DEATH/STROKE) |             |              |         | ANY STROKE (+ PERIOPERATIVE DEATH/STROKE) |               |               |       |                                 |
|--------------------|---|-------------|--------------|---------|---|---------------|---------------|-------|---------------------------------|
|                    | 30-day Death or Stroke after CEA                  | CEA+OMT     | OMT          | ARR (%) | Strokes Prevented Per 1000 CEAs           | CEA+OMT       | OMT           | ARR % | Strokes Prevented Per 1000 CEAs |
| ACAS <sup>83</sup> | 2.3%  | 5.1% at 5 y | 11.0% at 5 y | 5.9%    | 59 at 5 y                                 | 12.4% at 5 y  | 17.8% at 5 y  | 5.4%  | 54 at 5 y                       |
| ACST <sup>84</sup> | 2.8%  |             |              |         |   | 6.4% at 5 y   | 11.8% at 5 y  | 5.4%  | 54 at 5 y                       |
| ACST <sup>81</sup> | 2.8%  |             |              |         |   | 13.4% at 10 y | 17.9% at 10 y | 4.5%  | 45 at 10 y                      |

\*Data derived from ACAS<sup>83</sup> and ACST.<sup>81,84</sup> In the seminal papers, ACST did not publish late ipsilateral stroke data. y, years.

on modern OMT is flawed and biased by natural history studies, which included patients with 50%–69% stenosis, rather than 80%–99% stenosis, in whom it is believed that the greatest benefit will be seen.<sup>86</sup>

Opponents of this “one size fits all” approach advocate more conservative management, based on a number of “inconvenient truths,” especially awareness that only a minority of ACS patients actually benefit from CEA. Looking at the right-hand column in Table 92.7 (number of strokes prevented per 1000 CEAs), this equates to about 54 strokes prevented at 5 years and 45 at 10 years (i.e., 946/1000 were ultimately unnecessary at 5 years and 955/1000 at 10 years). This essentially means that about 95% of patients ultimately underwent an unnecessary intervention.<sup>86</sup> Whilst it may be argued that reductions in perioperative risks render this calculation irrelevant, even if one remodels Table 92.7 for a perioperative risk of 0%, the proportion of unnecessary interventions only falls from 95% to 93%.<sup>86</sup> There is also evidence that the annual stroke risk in ACS patients treated medically may be declining. In a meta-analysis of 41 studies, the rate of ipsilateral stroke was 2.3/100 person years in studies completing recruitment before 2000, compared with 1.0/100 person-years in studies recruiting between 2000 and 2010.<sup>87</sup> The 39% decline in ipsilateral stroke per decade in Hadar’s meta-analysis was attributed to improvements in OMT. Hadar observed that in studies where >25% of participants took statins, ipsilateral stroke rates were 1.2/100 person-years, compared with 2.3/100 person-years where fewer than 25% of participants took statins.<sup>87</sup> To address concerns about potential bias in prior meta-analyses of data from natural history studies which included patients with 50%–69% ACS, another meta-analysis has shown that the decline in annual stroke risks on OMT appears to apply to all categories of stenosis severity.<sup>86</sup> Similar observations were also apparent in ACAS and ACST.

In 1995, ACAS initially reported a 17.5% five-year risk of “any” stroke in OMT patients with 60%–99% stenosis (3.5% per year), which fell to 11.8%, when ACST reported its first five-year data in 2004 (2.4% per year). When ACST reported data from years 5–10, the 5-year risk of any stroke had declined to 7.2% (1.4% per year).<sup>81,83,84,88</sup> A similar phenomenon was observed for serial 5-year risks of ipsilateral stroke in OMT

patients. ACAS initially reported a 5-year ipsilateral stroke risk of 11.0% in OMT patients in 1995 (2.2% per year), which fell to 5.3% when ACST reported its first 5-year data in 2004 (1.1% per year). When ACST reported its 10-year data, the risk of ipsilateral stroke for this second 5-year period was 3.6% (0.7% per year). Overall, this represents a 60% decline in annual stroke risk in ACS patients between 1995 and 2010.<sup>81,83,84,88</sup>

### What do Existing Guidelines Recommend?

The 2011 Society for Vascular Surgery (SVS) guidelines advise that CEA may be considered in “good risk” patients with 60%–99% stenoses with a predicted 3–5-year life expectancy.<sup>89</sup> The 2014 American Heart Association (AHA) guidelines advise that it is reasonable to consider CEA in selected asymptomatic patients who have a 70%–99% ICA stenosis, if the risk of perioperative stroke/MI or death is low (<3%), whilst adding a caveat that “its effectiveness, compared with contemporary OMT, is not well established”.<sup>90</sup> In Denmark and Australia, national guidelines advise against any carotid interventions in asymptomatic patients.<sup>14,91</sup>

Most guidelines advise that patient selection is very important, but until recently, no specific guidance was provided about imaging/clinical criteria which might aid decision making in ACS patients. The 2017 ESVS guidelines<sup>2</sup> and the 2017 ESC/ESVS guidelines<sup>92</sup> were the first to address this controversial issue. Both recommended that CEA/CAS should only be considered in ACS patients with clinical/imaging features that might render them “higher-risk for stroke” on OMT.<sup>2,92</sup>

### Predicting Stroke Risk in ACS Patients

The next section summarizes the current evidence base regarding clinical/imaging features, which may assist in the selection of higher-risk cohorts for CEA/CAS.

#### General Observations

In a meta-analysis (64 cohorts;  $n = 20,751$ ), “high-risk features” (HRFs) for stroke were defined as AHA plaque type IV,V,VI; plaque echolucency; lipid-rich necrotic core (LRNC); plaque neo-vascularity; thin/ruptured fibrous cap; plaque ulceration; intra-plaque hemorrhage (IPH); impaired cerebral vascular

reserve (CVR); and spontaneous embolization on TCD.<sup>92</sup> The pooled prevalence of HRFs was 26.5% and the presence/absence of HRFs was unrelated to age, sex or stenosis severity. The incidence of ipsilateral stroke/TIA was significantly higher in patients with  $\geq 1$  HRF (4.3/100 patient years), versus 1.2/100 patient years with no HRFs (OR 3.0; 95% CI 2.1–4.3). The presence of HRFs increased the risk of late ipsilateral stroke (OR 2.0; 95% CI 1.5–2.7).<sup>93</sup>

### Stenosis Severity

The relationship between increasing stenosis severity and increased stroke risk was highly significant in symptomatic patients (Tables 92.1 and 92.4) and most assumed there would be a similar relationship in ACS patients. However, ACAS and ACST found no evidence that increasing stenosis severity was associated with increased risks of stroke.<sup>83,84</sup> Similarly, the SMART study, which followed up 293 asymptomatic patients with NASCET 50%–99% stenosis (193 with 70%–99% ACS) reported an annual stroke risk of 0.4% in patients with 50%–99% stenosis and 0.5% in those with 70%–99% stenosis.<sup>94</sup> Interpretation of data from the Asymptomatic Carotid Stenosis Risk of Stroke (ACRS) study was confounded by the stenosis measurement method. Using the ECST method, the annual risk of stroke was 0.6% in patients with 50%–69% stenosis, 1.2% for 70%–89% stenosis and 1.9% for 90%–99% stenosis. However, using the NASCET method, the annual stroke risk was 1.0% for <70% stenosis, versus 1.6% for 70%–99% stenosis.<sup>95</sup>

In a meta-analysis, HRF prevalence was unrelated to stenosis severity,<sup>93</sup> with HRFs observed in 32% of patients with 50%–69% stenosis, 30% in 50%–99% stenosis and 26% in patients with 70%–99% stenosis.<sup>93</sup> Whilst the incidence of late ipsilateral TIA/stroke was unrelated to stenosis severity (3.1/100 patient-years in patients with 50%–99% stenosis), versus 3.7/100 patient-years in those with 70%–99% stenosis, the presence of HRFs increased the risk of late events. In patients with 50%–99% stenosis, the incidence of ipsilateral stroke/TIA was 4.3/100 patient-years in patients with  $\geq 1$  HRF, versus 0.9/100 patient-years without HRFs (OR 4.5; 95% CI 1.8–10.9). In patients with 70%–99% stenosis, the incidence of ipsilateral stroke/TIA was 7.3/100 patient-years with  $\geq 1$  HRF, versus 1.7/100 patient-years without HRFs (OR 3.7; 95% CI 1.7–5.9).<sup>93</sup> These data would suggest that increasing stenosis severity assumes greater prognostic importance in the presence of HRFs.

### Patient Age

ACAS recruited patients aged 40–79 years,<sup>83</sup> but ACST had no upper age limit. Amongst ACST patients aged  $>75$  years, 5-year stroke risk (including perioperative events) was 9.2% after CEA vs. 8.8% in OMT patients. ACST concluded that CEA conferred no benefit in patients aged  $>75$  years.<sup>84</sup>

### Patient Sex

In ACAS and ACST, CEA significantly reduced stroke rates at 5 years in males undergoing CEA, but not in women.<sup>96</sup>

However, at 10 years, ACST reported significant benefit in women aged  $<75$  years (ARR = 8.2%).<sup>81</sup>

### History of Contralateral Symptoms

At 10 years, ACST reported that annual stroke risks were 3.8% in patients reporting a prior contralateral TIA/stroke vs. 1.8% in patients with no history of contralateral symptoms ( $P = \text{ns}$ ).<sup>81</sup> ACRS reported a 3.4% annual risk of stroke in patients with a history of contralateral TIA/stroke, versus 1.2% in those without prior contralateral symptoms HR 3.0; 95% CI 1.9–4.73).<sup>95</sup>

### Stenosis Progression

Sabeti observed that stenosis progression was associated with an increase in the 3-year risk of stroke from 2.5% to 5% (OR 2.00; 95% CI 1.02–4.11).<sup>97</sup> In ACRS, stenoses regressed in 4%, remained unchanged in 76%, while 20% had progression.<sup>98</sup> The 8-year risk of ipsilateral stroke was 0% with regression, 9% with unchanged stenoses (1.1% pa), and 16% with progression (2% pa). However, despite stenosis progression almost doubling the annual risk of stroke, most ipsilateral strokes (68%) still occurred in the absence of stenosis progression.<sup>98</sup>

In ACST, stenoses were divided into five NASCET categories (0%–49%; 50%–69%; 70%–89%; 90%–99%; occlusion). The annual rate of progression in OMT patients was 5%. A single author paper from this group reported that progression by  $\geq 2$  categories (e.g., 50%–69% to 90%–99%) was associated with a fivefold increase in ipsilateral TIA/stroke the following year. Using “no change” as comparator, progression by one stenosis grade was associated with a significant increase in TIA/stroke (OR 1.6; 95% CI 1.1–2.4), whilst progression by two grades was associated with higher stroke rates (OR 4.7; 95% CI 2.3–9.6). There were, however, relatively small numbers in the progression to 90%–99% group and most strokes/TIs still occurred in patients with unchanged stenoses.<sup>99</sup>

ACST evaluated the risk of progressing to occlusion and experiencing a stroke.<sup>100</sup> In OMT patients, the risk of ipsilateral occlusion was 1% pa. However, only 13.6% had a stroke at the time of ICA occlusion, whereas 10% had an ipsilateral stroke at a later date. This means that for 700 patients with a 60%–99% ACS treated medically, seven will occlude their ICA each year, at which time, one will experience an ipsilateral stroke, while another will suffer an ipsilateral stroke at a later date.

### Plaque Echolucency

In a meta-analysis (16 studies;  $n = 12,364$ ) across all stenosis grades, the prevalence of plaque echolucency using DUS was 42.3%.<sup>93</sup> Using subjective (visual) assessment, ACST reported that OMT patients with predominantly echolucent plaques did not have an increased risk of late ipsilateral stroke.<sup>84</sup> However, the Tromso study<sup>101</sup> reported that hypoechoic plaques were associated with increased stroke risks, as did the Cardiovascular Health Study Group (OR 2.8; 95% CI 1.4–5.7).<sup>102</sup>

In ACES, subjective plaque assessment categorized type I+II plaques as “predominantly echolucent” and types III+IV as “predominantly echogenic.” The combination of plaque echolucency and  $>1$  embolus detected on TCD significantly

increased rates of ipsilateral stroke, after correction for risk factors, stenosis severity and antiplatelet therapy (OR 10.6; 95% CI 2.98–37.52).<sup>103</sup> Only 6% had type I/II plaques and  $\geq 1$  microembolic signal (MES), but this small cohort had an annual ipsilateral stroke risk of 8.9%, versus 0.8% in the remaining patients.<sup>103</sup> In a 2015 meta-analysis, “predominantly echolucent” 50%–99% stenoses were associated with a 4.2% annual stroke risk, versus 1.6% without plaque echolucency (OR 2.61; 95% CI 1.47–4.63;  $P = 0.001$ ).<sup>104</sup>

### Computerized Plaque Analysis

ACRS assessed plaques with the Gray Scale Median (GSM) score, a computerized (potentially objective) measurement of plaque pixels after image normalization. Image normalization involves an area of luminal blood being scaled to zero, while the brightest area of adventitia is normalized to a gray scale of 190. Echolucent plaques have a low GSM, while echodense plaques have a high GSM. Patients with a GSM >30 (echodense) had a low annual rate of ipsilateral stroke (0.6%), increasing to 1.6% pa for a GSM of 15–30 and 3.6% with a GSM <15 (echolucent).<sup>95</sup>

The ACRS plaque classification is a computerized modification of the Gray-Weale scale and assesses plaque type according to echolucency/echogenicity based on the GSM.<sup>105</sup>

- Type 1: Uniformly echolucent with <15% of pixels being occupied by pixels with GSM >25;
- Type 2: Mainly echolucent, where pixels with GSM >25 occupy 15%–50% of the plaque
- Type 3: Mainly echogenic/echodense with pixels with GSM >25 occupying 50%–85% of the plaque
- Type 4: Uniformly echogenic/echodense with pixels with GSM >25 occupying >85% of the plaque.

Patients with type 4 plaques had a 0.4% annual risk of stroke, versus 0.8% for type 3 plaques. The annual stroke risk in patients with type 1/2 plaques was 3.0%. Three-quarters of late strokes occurred in the 38% of patients with type 1/2 (echolucent) plaques.<sup>105</sup>

Two other ACRS computerized plaque parameters (plaque area and the juxtaluminal black area (JBA) were associated with late stroke.<sup>106</sup> Patients with a plaque area <40 mm<sup>2</sup> had a low (1%) annual stroke risk, increasing to 1.4% pa with a plaque area of 40–80 mm<sup>2</sup> and 4.6% pa in patients with a plaque area >80 mm<sup>2</sup>. The JBA is defined as the area of plaque with a GSM <25 without a visible echogenic cap, which is felt to represent softer plaque components (LRNC, lipid, IPH, thrombus) adjacent to the vessel lumen.<sup>106</sup> A JBA <4 mm<sup>2</sup> was associated with an annual stroke risk of 0.4%, increasing to 1.4% with a JBA of 4–8 mm<sup>2</sup>. Patients with a JBA <8 mm<sup>2</sup> had an annual stroke risk of 0.6%, versus 4.6% pa in patients with a JBA >8 mm<sup>2</sup>.<sup>106</sup> In a separate blinded study, logistic regression analysis showed that patients with a plaque area >95 mm<sup>2</sup> and a JBA >6 mm<sup>2</sup> had a 90% probability of having a histologically unstable carotid plaque.<sup>107</sup>

### Plaque Irregularity/Ulceration on DUS

In a meta-analysis ( $n = 2086$  across all ACS grades), the prevalence of ulceration was 13.1%.<sup>93</sup> Madani undertook

serial high-resolution DUS surveillance in 253 patients with 60%–99% stenoses treated medically. The presence of  $\geq 3$  micro-plaque ulcers was associated with significant increases in stroke/death risk at 3 years (18%), versus 2% in patients with fewer or no ulcers (OR 2.4; 95% CI 0.4–13.2).<sup>108</sup> Kitamura undertook a similar study in 1358 patients with no history of cardiovascular disease. Plaque irregularity was associated with an age-adjusted increase in late stroke (OR 7.7; 95% CI 2–30).<sup>109</sup> The North Manhattan Stroke Study ( $n = 1939$ ) showed that <6% of subjects had irregular carotid plaque. The 5-year risk of ischemic stroke was 1.3% in those with no carotid plaque (0.3% pa), 3% with smooth plaques (0.6% pa), and 8.5% in patients with irregular plaques (1.7% pa).<sup>110</sup> After adjusting for risk factors, stenosis severity and plaque thickness, irregular plaques incurred significant increases in late stroke (OR 3.1; 95% CI 1.1–8.5).

### Plaque Features on MRI

In a meta-analysis, the prevalence of IPH was 19% across all ACS grades<sup>92</sup> increasing to 29% in patients with 50%–69% stenosis.<sup>111</sup> Meta-analyses of MR diagnosed AHA plaque types found that types IV,V,VI (representing LRNC, thin/ruptured fibrous caps, ulceration, IPH, thrombus) were present in 30.8% across all ACS grades.<sup>93</sup> Esposito-Bauer undertook MR scans in 77 patients with 50%–99% stenoses.<sup>112</sup> Over a median of 44 months, 9 patients (12%) experienced an ipsilateral stroke/TIA and all occurred in patients with AHA plaque types IV, V, VI. No events occurred in patients with stable plaques (AHA types III, VII, VIII).<sup>112</sup> In another meta-analysis, AHA plaque types IV, V, VI were associated with significant increases in late ipsilateral stroke/TIA (OR 28.7; 95% CI 1.6–513), and a risk of late ipsilateral stroke of 6.5/100 patient-years (95% CI 3.3–12.3).<sup>93</sup> A meta-analysis involving patients with predominantly 50%–69% ACS revealed that the annual stroke risk was higher in patients with, versus without IPH (5.6% vs. 0.8%; OR 7.9; 95% CI 1.3–47.6).<sup>111</sup>

### Spontaneous Micro-EMBOLIZATION on TCD

In a meta-analysis of 14 studies ( $n = 1648$ ),  $\geq 1$  MES was identified in 14% of patients with 70%–99% ACS.<sup>93</sup> Spontaneous embolization was associated with 9.5/100 patient-year incidence of ipsilateral stroke/TIA, significantly higher than in patients with no MES (OR 5.6; 95% CI 2.0–15.3). The presence of  $\geq 1$  MES was associated with a 10.2/100 patient-year incidence of late ipsilateral stroke.<sup>93</sup> In another meta-analysis involving 1144 with 70%–99% ACS, the presence of  $\geq 1$  MES on TCD was associated with an eight-fold increased risk of late stroke (OR 7.6; 95% CI 2.3–24.7).<sup>113</sup>

### “Silent” Brain Infarction (SBI)

In a meta-analysis, the prevalence of SBI in 2226 patients (all ACS grades) was 21.9% (95% CI 16–29).<sup>92</sup> ACRS observed that the annual risk of ipsilateral stroke was significantly higher in patients with, than without SBI (3.6% pa vs. 1.0% pa (OR 3.0; 95% CI 1.46–6.29;  $P = 0.002$ ).<sup>114</sup>

**TABLE 92.8**

Meta-analysis of 30-Day Outcomes After CAS vs. CEA in 3467 Asymptomatic Patients Randomized within 7 RCTs

|     | Death          | Stroke         | Death/Stroke   | Disabling Stroke | Death/Disabling Stroke | MI             | Death/Stroke/MI |
|-----|----------------|----------------|----------------|------------------|------------------------|----------------|-----------------|
|     | 7 RCTs n=2286  | 8 RCTs n=3467  | 8 RCTs n=3467  | 5 RCTs n=2918    | Insufficient data      | 5 RCTs n=2948  | 5 RCTs n=2948   |
| CEA | 0.7% (0.3–1.8) | 1.9% (1.3–2.9) | 2.1% (1.5–3.1) | 0.5% (0.2–1.2)   | Insufficient data      | 1.8% (1.1–2.8) | 3.1% (2.2–4.3)  |
| CAS | 0.7% (0.3–1.7) | 3.0% (2.3–3.8) | 3.1% (2.4–4.0) | 0.5% (0.3–1.0)   | Insufficient data      | 0.8% (0.5–1.4) | 3.3% (2.5–4.2)  |

Significant benefit favoring CEA

No significant difference between CAS and CEA

CAS, carotid artery stenting; CEA, carotid endarterectomy.

Reproduced with permission from: Batchelder A, Saratzis A, Naylor AR. Overview of Primary and Secondary Analyses from 20 randomised controlled trials comparing carotid artery stenting with carotid endarterectomy. *Eur J Vasc Endovasc Surg*. 2019;58:479–493.

### Impaired Cerebral Vascular Reserve

In the presence of an increasingly severe ICA stenosis (augmented by an incomplete circle of Willis), intracranial arterioles vasodilate to maintain cerebral blood flow. However, there comes a point where they cannot vasodilate further and the patient enters a state of hemodynamic compromise (impaired cerebral vascular reserve [CVR]). There is a spectrum of CVR severity, ranging from normal to impaired to exhausted. It is hypothesized that ACS patients with impaired/exhausted CVR are more likely to experience ipsilateral cerebrovascular events. In a meta-analysis, the prevalence of impaired CVR in 348 patients with 70%–99% stenoses was 29% (95% CI 15–46)<sup>92</sup> and the presence of impaired CVR is associated with a significant increase in the risk of late ipsilateral stroke (OR 6.14; 95% CI 1.27–29.5;  $P = 0.02$ ).<sup>115</sup>

### ESVS/ESC Recommendations on the Management of ACS

Based on the controversies described earlier and on an overview of imaging/clinical criteria which may be associated with higher/lower rates of late ipsilateral stroke in ACS patients, the 2017 ESVS carotid guidelines<sup>2</sup> and the 2017 ESC/ESVS guidelines<sup>92</sup> advised that: “In ‘average surgical risk’ patients with an asymptomatic 60%–99% stenosis, CEA should be considered in the presence of  $\geq 1$  imaging characteristic that are associated with an increased risk of late ipsilateral stroke, provided documented perioperative stroke/death rates are <3% and the patient’s life expectancy exceeds 5 years (Class IIa, Level B).”<sup>2,92</sup>

The clinical/imaging features adopted by the ESVS/ESC were based on RCT subgroup analyses, meta-analyses and multicenter observational studies and not on single-center studies and include: (1) history of contralateral TIA/stroke; (2) spontaneous MES on TCD; (3) impaired CVR; (4) plaque area  $>80 \text{ mm}^2$ ; (5) stenosis progression  $>20\%$ ; (6) JBA  $>8 \text{ mm}^2$ , (7) echolucent plaques; and (8) intraplaque hemorrhage.

### Which Carotid Intervention: CEA or CAS?

#### Perioperative Outcomes

Seven RCTs ( $n = 3467$ ) have compared CEA with CAS in ACS patients<sup>63</sup> and Table 92.8 summarizes a meta-analysis of 30-day outcomes. As is evident, the picture is similar to that observed in symptomatic patients (Table 92.5). CAS (predominantly via the transfemoral route) was associated with significantly higher 30-day rates of stroke and death/stroke, compared with CEA.<sup>63</sup>

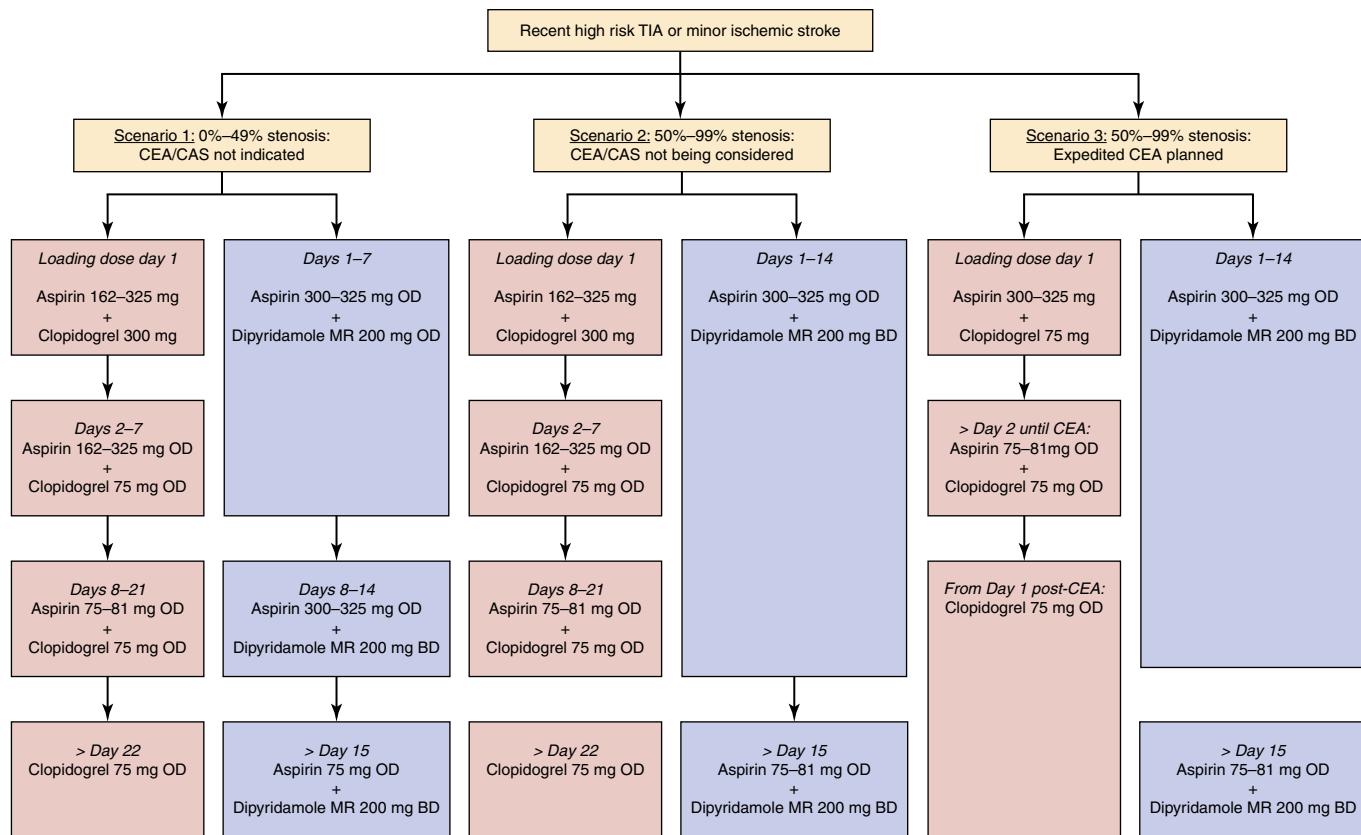
#### Late Outcomes

The two largest RCT cohorts in ACS patients with 5- or 10-year follow-up data were ACT-1 ( $n = 1420$ )<sup>116</sup> and CREST ( $n = 1181$ ).<sup>117</sup> Five-year ipsilateral stroke in ACT-1 (excluding perioperative events) was 2.2% after CAS (0.44% pa), versus 2.7% after CEA (0.54% pa).<sup>116</sup> Ten-year ipsilateral stroke in ACS patients in CREST (excluding perioperative events) was also not significantly different, being 6.9% after CAS (0.69% pa) and 5.6% after CEA (0.56% pa).<sup>117</sup> These data indicate that, as with symptomatic patients, once the perioperative period has elapsed, ipsilateral stroke is rare and CAS is as durable as CEA in preventing late ipsilateral stroke.

### Selecting Asymptomatic Patients for CEA or CAS

At present, most guidelines advise that where carotid interventions are being considered in asymptomatic patients (outwith trials), and in light of the higher perioperative risks associated with CAS in the existing RCTs, CEA is currently the preferred option.<sup>2,89,90</sup> No published RCTs have included the TCAR technique. It is likely that ACST-2 and CREST-2 will provide much more information on patient selection and advances in CAS techniques.

## CHAPTER ALGORITHM



Algorithm detailing alternative evidence-based suggestions re timing, dose and duration of antiplatelet therapy in the early phase after onset of high-risk TIA or minor ischemic stroke in patients not on antiplatelet therapy. Abbreviations: *CEA*, carotid endarterectomy; *CAS*, carotid artery stenting; *ASAP*, "as soon as possible"; *MR*, modified release; *OD*, once daily; *BD*, twice daily. (Reproduced with permission from Naylor AR, McCabe DJH. New data and the COVID-19 pandemic mandate a rethink of antiplatelet strategies in patients with TIA or minor stroke associated with atherosclerotic carotid stenosis. *Eur J Vasc Endovasc Surg.* 2020;59:861–865.)

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A complete reference list can be found online at [www.expertconsult.com](http://www.expertconsult.com).

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# Carotid Endarterectomy

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First performed in the 1950s, carotid endarterectomy (CEA) experienced remarkable growth in the 1970s and 1980s after several studies demonstrated that carotid stenosis was an important risk factor for disabling stroke and death,<sup>1–6</sup> and a randomized multicenter trial published in 1969 showed that carotid surgery reduced the incidence of stroke from symptomatic carotid lesions.<sup>7</sup> However, subsequent experience documented high complication rates, thus compromising the potential benefit of CEA.<sup>7,8</sup> However, randomized controlled trials (RCTs) performed in the 1990s definitively established the safety and efficacy of CEA and its superiority over the best medical management of patients with symptomatic and asymptomatic carotid disease.<sup>9–12</sup>

**EPIDEMIOLOGY****Incidence**

At least 750,000 strokes occur annually in the United States: approximately 15% are fatal, 15% to 20% are severely disabling, and another 15% to 20% of stroke patients who recover will experience a subsequent disabling stroke. At least 80% of these strokes are ischemic and atherosclerotic disease of the cervical carotid artery is responsible for approximately 20% of ischemic strokes.<sup>13</sup>

**Etiology**

Strokes secondary to carotid artery stenosis are a consequence of atheroembolization, thromboembolism, or are secondary to a low flow state through the carotid artery.

**INDICATIONS FOR CAROTID ENDARTERECTOMY**

Based on the most recent evidence-based guidelines published by the Society for Vascular Surgery, CEA is recommended for most symptomatic patients with a 50% to 99% internal carotid artery (ICA) stenosis. Further, CEA should be considered for patients with a 70% to 99% asymptomatic ICA stenosis if perioperative stroke and death rate is less than 3% and if the patient has at least a 3- to 5-year life expectancy.<sup>14</sup> In the symptomatic patient with a 50% to 99% ICA stenosis, and

either medical or anatomic contraindications to CEA, carotid artery stenting (CAS) should be considered (see Ch. 94, Carotid Artery Stenting). Medical therapy, rather than CEA or CAS, should be selected in symptomatic patients with a less than 50% ICA stenosis, although there is some recent evidence suggesting that CEA may be indicated for rare symptomatic patients with <50% ICA stenoses (see below). Medical therapy rather than CAS is more appropriate for asymptomatic patients with a greater than 60% stenosis and medical or surgical contraindications.<sup>14</sup>

**PREOPERATIVE IMAGING**

Duplex ultrasound in an accredited laboratory is the most appropriate first test to evaluate the patient with suspected carotid artery disease, with either CTA or MRA reserved for patients with suspected disease proximal or distal to the neck, when there are indeterminate duplex findings, or other confounding issues.<sup>15–18</sup> There is some evidence that CTA underestimates, and MRA overestimates, the degree of stenosis. It is the practice in some centers to proceed to endarterectomy based on duplex findings alone. Since the benefit of CEA is highly dependent on the degree of stenosis, others maintain that verification of duplex findings is essential before proceeding to operation.<sup>19</sup> Clearly, if the patient is found to have an intermediate stenosis and is asymptomatic, one should perform at least another noninvasive test to confirm this finding before recommending CEA. If there is discordance between these studies, one should either obtain a third noninvasive test or proceed to angiography.

**PERIOPERATIVE MEDICAL MANAGEMENT**

Risk stratification is important in determining the most appropriate preoperative cardiac work-up and perioperative management of the patient undergoing CEA (see Ch. 34, Preoperative Evaluation and Management). The American Heart Association (AHA) perioperative guidelines classify CEA as an intermediate risk procedure.<sup>20,21</sup> The perioperative medical management of the patient undergoing CEA should include blood pressure control, statin, and antiplatelet therapy, and in selected cases beta blockade.

## Beta-Blockers

Based upon early registry data, it was felt that all patients with vascular disease would benefit from perioperative beta blockade.<sup>19</sup> This recommendation has evolved based on several large trials.<sup>20–22</sup> Perioperative beta blockade, with a goal of achieving a maximum heart rate of 60 to 80 beats per minute, is recommended in the recent Society for Vascular Surgery carotid guidelines.<sup>14</sup> However, recent experience has moderated these clinical recommendations.<sup>23</sup> Specifically, beta blockers should not be started in the preoperative period to improve short-term outcomes. Among patients with indications for beta blockade treatment long-term, use may be individualized preoperatively. Patients on long-term beta-blockers should continue the use perioperatively.

## Antiplatelet Therapy

Meta-analyses of antiplatelet therapy trials published by the UK Antithrombotic Trialist Group in 1994 and 2002 concluded that antiplatelet therapy significantly reduces the incidence of stroke in high-risk patients, with a resultant 25% reduction in strokes overall.<sup>24</sup> The majority of these studies included aspirin or aspirin plus another antiplatelet agent. Recent studies of clopidogrel provide evidence that perioperative embolization is decreased without an increase in bleeding complications or transfusion requirements after CEA. Other antiplatelet agents, such as ticlopidine and glycoprotein IIb/IIIa antagonists have not been specifically studied during CEA and generally have a higher risk profile than ASA or clopidogrel. Based on this evidence, it is possible to recommend either ASA or clopidogrel, or both, for use before and after CEA. Based upon the preponderance of evidence, the author does not withhold aspirin and will continue clopidogrel if there is a clinical indication in the CEA patient.<sup>14,25</sup>

## Heparin

Unfractionated heparin (UFH) is routinely used intraoperatively to prevent carotid thrombosis despite a lack of level I evidence to support this practice. The combination of aspirin and intraoperative heparin administration appears to be especially effective in preventing thrombosis.<sup>25,26</sup>

## Protamine Administration

Numerous publications have examined whether reversing heparin with protamine during CEA is safe.<sup>27–29</sup> The preponderance of recent evidence suggests that protamine administration does not increase perioperative stroke risk, although the author prefers not to use it routinely unless there is truly unusual bleeding.<sup>30</sup>

## Dextran

Dextran is a polysaccharide that inhibits platelet aggregation.<sup>31</sup> It has been used to control embolic episodes both preoperatively and postoperatively. British investigators in 1997 showed that a 6-hour dextran infusion effectively controlled

postoperative embolic events as measured by transcranial Doppler (TCD), with a 0% stroke and mortality rate in a series of 100 patients.<sup>32–35</sup> The author favors a dextran infusion for 24 hours after CEA to control platelet aggregation on the endarterectomy site and potential microembolization.

## Statins

The potential benefits of statins in patients with carotid artery disease are several-fold. A reduction in cholesterol levels with statins may be associated with plaque regression, reduced carotid artery intima-media thickness, and also a lower rate of combined cardiovascular events.<sup>36–51</sup> Numerous trials conducted over the past decade have specifically demonstrated statin medications to be highly effective in primary and secondary stroke prevention.<sup>38–40</sup> Furthermore, it appears that the stroke prevention benefits of statins are related to the pleiotropic effects of statin medications rather than their cholesterol-lowering effects. In addition, a recent meta-analysis demonstrated that statins are associated with a reduced rate of perioperative cardiac morbidity and overall mortality in patients undergoing noncardiac surgical procedures.<sup>52</sup>

In a series of 1566 patients undergoing CEA at the author's institution, statins were associated with a reduced 30-day incidence of stroke (1.2% vs. 4.5%,  $P = 0.002$ ), TIA (1.5% vs. 3.6%,  $P = 0.01$ ), and mortality (0.3% vs. 2.1%,  $P = 0.002$ ).<sup>53</sup> A large administrative database analysis from Canada documented a significantly lower rate of perioperative stroke and death in symptomatic patients who were taking statin medications at the time of CEA.<sup>54</sup> Furthermore, LaMuraglia and coworkers reported that lipid-lowering agents were associated with significant protection against recurrent carotid stenosis after CEA.<sup>55</sup> The evidence seems clear that all patients undergoing CEA should be taking statin medications at the time of surgery, and long-term.

## OPERATIVE TECHNIQUE

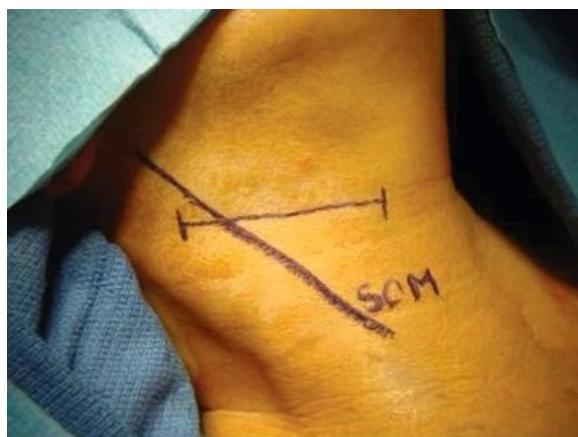
### Anesthesia

CEA may be performed under general anesthesia (GA), regional anesthesia (RA) with deep or superficial cervical block, and even under pure local anesthesia (LA), with comparable lengths of stay. The majority of studies comparing the two techniques have reported improved perioperative cardiac stability with RA, but this does not necessarily result in a reduced incidence of myocardial infarction (MI).<sup>56,57</sup>

Disadvantages of RA include patient discomfort or anxiety, risk of seizure or allergic reaction, anxiety for the operating surgeon, and compromise of technique in a teaching setting. The main benefit of LA is that it facilitates efficient selective shunting if that is the surgeon's preference (see below).

### Patient Positioning

A roll is placed behind the scapulae used in conjunction with a padded ring under the head to achieve some extension of the



**Figure 93.1** Longitudinal and Transverse Skin Incisions for Carotid Endarterectomy.

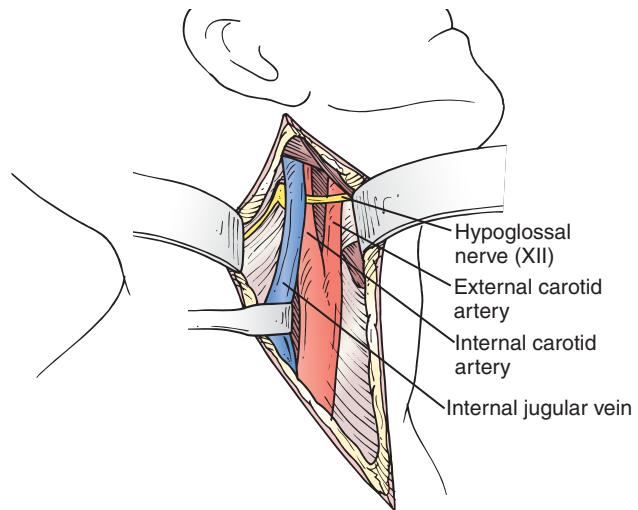
neck without being overextended. If LA or RA is used, a Mayo stand is placed over the patient's head to suspend the surgical drapes away from the patient's face to prevent sensations of claustrophobia. The patient is placed in the flexed position with the table rotated to expose the side of the neck to be operated on.

### Skin Incision

One of two skin incisions may be used (Fig. 93.1). The standard incision is a longitudinal incision parallel to the medial border of the sternocleidomastoid muscle. The upper portion of the incision is angled posterior to the earlobe if cephalic exposure above the angle of the jaw is required. An alternative method is to place the incision in an appropriately located skin crease, usually 1 to 2 cm inferior to the angle of the jaw. If the incision is made too low, more cephalic exposure can be obtained by extending the skin crease incision posteriorly. If the incision is made too high, more caudal exposure can be obtained by extending the incision more anteriorly.

### Carotid Exposure

Carotid exposure is described in Chapter 57 (Cerebrovascular Exposure). Manipulation of the carotid artery should be minimized because intraoperative embolization can result from careless handling. There are several key anatomic structures that merit emphasis. The external jugular vein lies deep to the platysma and is more commonly encountered with an oblique skin crease incision. The facial vein is identified crossing medially in the base of the wound and divided; sometimes it has an early bifurcation or trifurcation, and multiple branches need to be ligated. The vagus nerve is identified in the carotid sheath, usually located posteriorly between the jugular vein and carotid artery, although in a minority of patients it may lie anteriorly. The common carotid artery (CCA) is controlled circumferentially with an umbilical tape and a Rummel tourniquet. The ansa cervicalis nerve should be identified; it usually lies medial to the distal CCA and identifying this nerve facilitates safe dissection of the carotid bifurcation and avoids injury to the hypoglossal nerve, which crosses medially from a superior to an inferior location (Fig. 93.2). The superior thyroid artery is



**Figure 93.2** Operative Field. Note the internal jugular vein mobilized posteriorly after ligation of the anterior facial branch and the hypoglossal nerve crossing the vessels superior to the bifurcation.

controlled with a tie or plastic vessel loop and the external carotid artery (ECA) is controlled with a vessel loop. Finally, the ICA should be exposed and controlled with a vessel loop distal to the plaque, where the artery has a typical bluish appearance because of translucency of the vessel. During dissection of the carotid bifurcation and its branches, one should avoid dissecting in the crotch of the carotid bifurcation to avoid injuring the carotid body to minimize hemodynamic instability and troublesome bleeding. If hemodynamic instability results, the carotid body can be gently injected with 1% lidocaine.

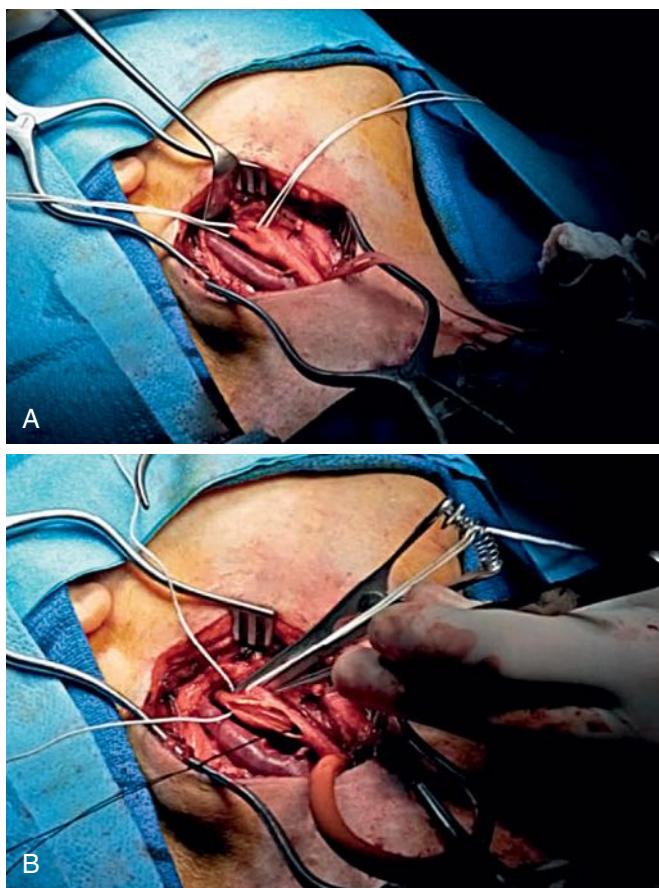
Before clamping, the patient is administered 70 to 100 U/kg of heparin, which is allowed to circulate for 3 minutes. The ICA is clamped first to prevent the embolization that can result when the CCA or ECA is clamped. Care should be taken to make sure that the ICA is clamped on a normal portion of the artery distal to the plaque.

If LA or intraoperative electroencephalography is used for selective shunting, a test clamp on the distal ICA should be applied for at least 3 minutes to check for changes in the neurologic examination or electroencephalographic (EEG) pattern. If such changes occur, the artery should be unclamped to allow reperfusion before reclamping and opening the carotid bifurcation; opening the bifurcation and placing a shunt may take 2 to 3 minutes and should not be performed while the brain is already ischemic. However, unclamping the ICA introduces the potential for embolization from disrupted plaque.

If carotid stump pressure is to be measured, clamps are placed on the CCA and the ECA, and a needle connected to a pressure line is placed into the distal CCA below the carotid bifurcation. Both clamping the CCA and placing the needle into the artery introduce the potential for embolization.

### Conventional Endarterectomy

The conventional technique for CEA consists of a vertical arteriotomy and closure usually by patch angioplasty. One should



**Figure 93.3** (A) Initial operative exposure with the Rumel tourniquet around the common carotid artery and the internal and external carotid arteries isolated with vessel loops. (B) The arteriotomy has been made and the shunt, with a silk suture attached, lies within the vessel.

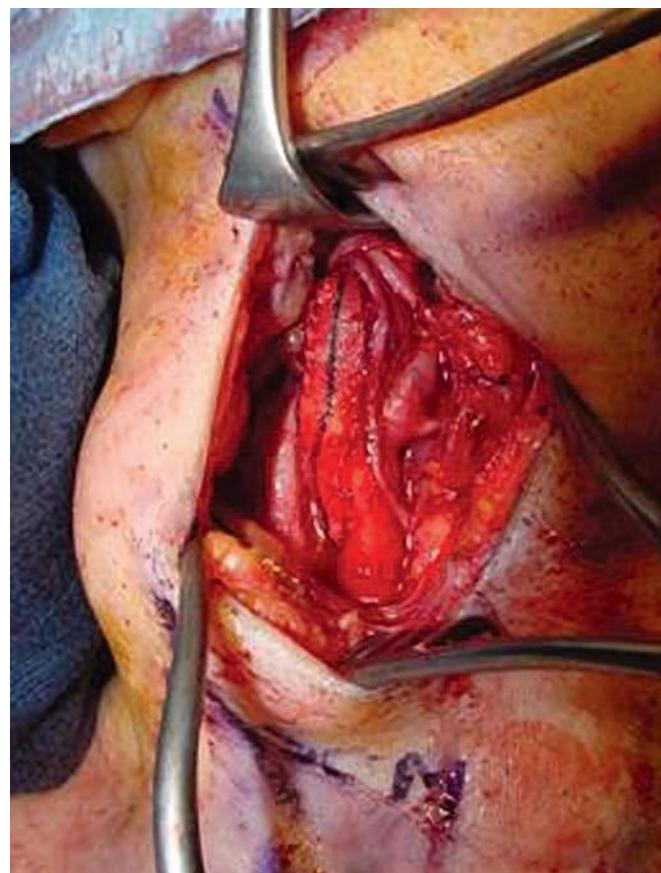
avoid making the incision too close to the flow divider at the ECA origin because this can distort the anatomy and make the closure more difficult (Fig. 93.3).

The endarterectomy is begun in the CCA in the plane between the media and the adventitia. The proximal endpoint in the distal CCA is established and the plaque is trimmed in that location in a beveled manner. The endarterectomy is continued into the orifice of the ECA, first with a Freer elevator and then with a fine clamp that is passed up into the ECA in the plane of the endarterectomy and spread to further mobilize the plaque away from the adventitia in the 6-, 9-, and 12-o'clock positions; it is usually difficult to pass the clamp in this plane at the 3-o'clock position next to the flow divider. The vessel loop on the ECA is released transiently while the plaque is everted from within the ECA. The endpoint of the plaque is inspected; an ideal endpoint is gradually tapering and feathered (Fig. 93.4). All loose bits of intima and media in the orifice of the ECA should be removed, although others believe that endarterectomy of the ECA may be neglected without compromising results.<sup>58</sup>

A technically perfect endpoint in the ICA is critical. Occasionally special maneuvers may be required to expose the distal ICA to extend the arteriotomy to achieve an acceptable endpoint, as seen in Figure 93.4. The endarterectomy is best ended by pulling the plaque transversely away from the artery with lateral traction.



**Figure 93.4** Carotid Endarterectomy Specimen. Note the smooth endpoints of the distal plaque from the external and internal (longer portion) arteries.



**Figure 93.5** Patch Closure of the Arteriotomy for Carotid Endarterectomy. Dacron was used in this case. Note the ansa cervicalis coursing along the vessel, the vagus nerve posteriorly, and the hypoglossal nerve at the apex of the incision.

One should avoid pulling out or down on the plaque, which is more likely to result in a step-off that can be difficult to correct. Tacking sutures should be used only if necessary.

Repairing the arteriotomy with a patch angioplasty represents the standard of care in contemporary practice (Fig. 93.5). A variety of patch materials are available, including autologous

vein, polytetrafluoroethylene (PTFE), woven polyester (Dacron), and bovine pericardium, and no material appears to be clearly superior to another (see below).

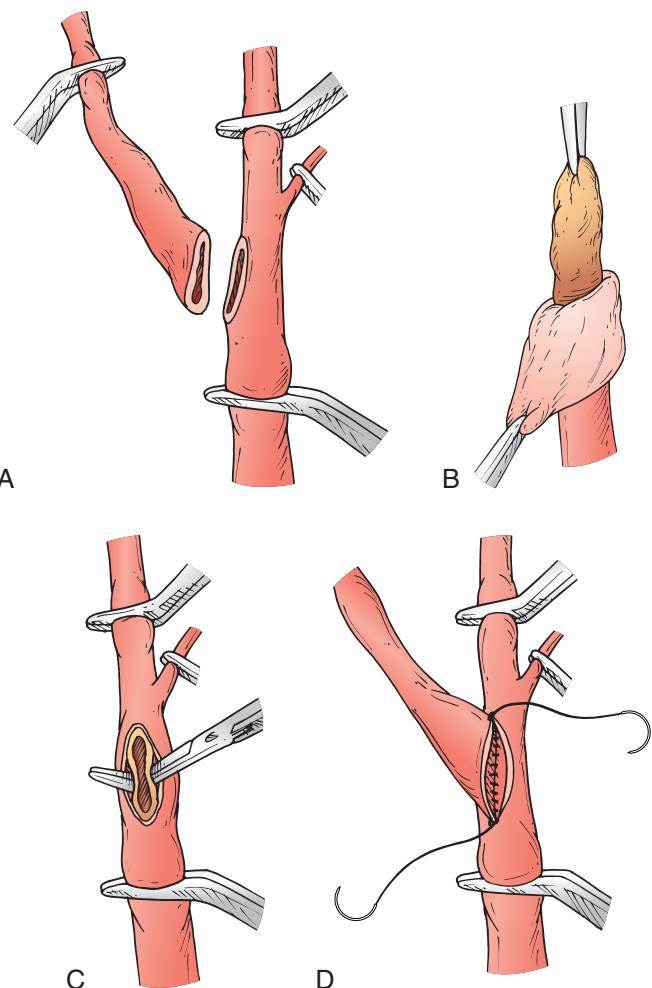
When the suture line is nearly completed, the CCA and ICA clamps are briefly sequentially released to flush air or debris (or both) out of the arteries. The carotid bifurcation is flushed vigorously with heparinized saline and inspected again for debris or intimal flaps before the arteriotomy is finally closed. Once again, the clamp on the ICA is briefly released to fill the bifurcation with blood. It is then replaced while the clamps on the CCA and ECA are released so that any remaining air or debris will be flushed up the territory of the ECA rather than the ICA. At this point the ICA clamp is removed. Any bleeding from the suture line is addressed at this time. One should avoid re-clamping unless absolutely necessary to control bleeding to avoid the risk for formation of thrombus or a fibrin-platelet aggregate on the patch or endarterectomized vessel.

### Eversion Endarterectomy

DeBakey originally described eversion endarterectomy with partial transection of the anterior portion of the carotid bifurcation.<sup>2</sup> Etheredge revised DeBakey's technique with complete transection of the bifurcation,<sup>59</sup> which allowed the origins of both the ICA and ECA to be everted for a longer distance. The endarterectomy is performed by mobilizing the entire circumference of the carotid adventitia off the plaque (described as a "circumcision" by Etheredge) and then evertting the adventitia and mobilizing it upward while gentle caudad traction is applied to the plaque. This maneuver is performed distally into the orifices of the ICA and ECA and then proximally into the CCA. Once the endarterectomy is complete, the divided bifurcation is reunited with a simple end-to-end anastomosis.

Kieny and coworkers introduced a modification of eversion endarterectomy in 1985 in which the origin of the ICA is excised obliquely off the carotid bifurcation, and is inverted on its own, and endarterectomy of the CCA and ECA is performed through an arteriotomy in the side of the carotid bifurcation.<sup>60</sup> The ICA is reanastomosed to the carotid bifurcation primarily (Fig. 93.6).

Advantages of the eversion technique are that the anastomosis can be performed rapidly and it is not prone to restenosis, and therefore patching is not required. Disadvantages of this technique are that more extensive dissection is sometimes necessary to mobilize the vessels during the eversion; the procedure does not lend itself readily to shunting (although shunting is not precluded by this technique), and it can be difficult to visualize the endpoint in the ICA after the plaque has been removed. Therefore, in the author's opinion, a completion study should be performed. This technique is particularly effective for dealing with a redundant, coiled, or kinked ICA as the ICA can be pulled down and straightened and the redundant portion excised. The remaining portion of the ICA is spatulated and reattached to the arteriotomy on the carotid bifurcation.



**Figure 93.6** Eversion Endarterectomy. (A) Internal carotid artery transected from the bifurcation. (B) Adventitia teased back off the internal carotid artery plaque. (C) Plaque endarterectomized from the common carotid and origin of the external carotid artery. (D) Reanastomosis of the internal carotid artery to the bifurcation. (Modified from Saratzis N, Saratzis A, Milaras S, et al. Eversion carotid endarterectomy illustrated: tips and tricks of the procedure. *Surg Rounds*. 2006;29(8):382–389.)

### Comparison of Conventional and Eversion Carotid Endarterectomy

In EVEREST (EVERsion CEA vs. Standard Trial study), a randomized, prospective multicenter study including more than 1400 patients randomized to eversion or standard CEA, there were no statistically significant differences in outcomes between the two techniques, although a slightly higher incidence of perioperative complications was noted with eversion CEA and a slightly higher incidence of restenosis with standard CEA. While other studies have shown better outcomes with eversion CEA,<sup>61</sup> a large meta-analysis comparing eversion to conventional CEA found no significant differences in the rate of perioperative stroke or death (1.7% vs. 2.6%, odds ratio [OR] 0.44; 95% confidence interval [CI], 0.10–1.82), but did note that eversion endarterectomy was associated with a lower rate of restenosis during follow-up (2.5% vs. 5.2%, OR 0.48; 95% CI, 0.32–0.72).<sup>62</sup>

## EXPOSURE FOR HIGH LESIONS

The carotid bifurcation can be located anywhere between the second and seventh cervical vertebrae, and a bifurcation located high in the neck poses technical challenges that can increase perioperative risk for stroke and cranial nerve injury. Ideally, one will recognize a high bifurcation on the preoperative imaging study. This is a potential advantage of CTA, in which bony anatomy is always included in the images. A conscious effort must be made to locate the bony anatomy with DSA if unsubtracted images are not provided with the study, but the anatomy can still be defined from subtracted images. Bony landmarks are never provided with carotid duplex imaging, but an astute vascular technologist will note a high bifurcation and should record it in the report.

### Nasotracheal Intubation

The initial approach is to utilize nasotracheal intubation. With the patient's mouth closed, the vertical ramus of the mandible is displaced anteriorly 1–2 cm relative to its position when the mouth is open with an oral endotracheal tube. The additional few millimeters of exposure afforded by this maneuver will often be the difference in achieving a suitable endarterectomy endpoint in the distal ICA.

### Division of the Digastric Muscle

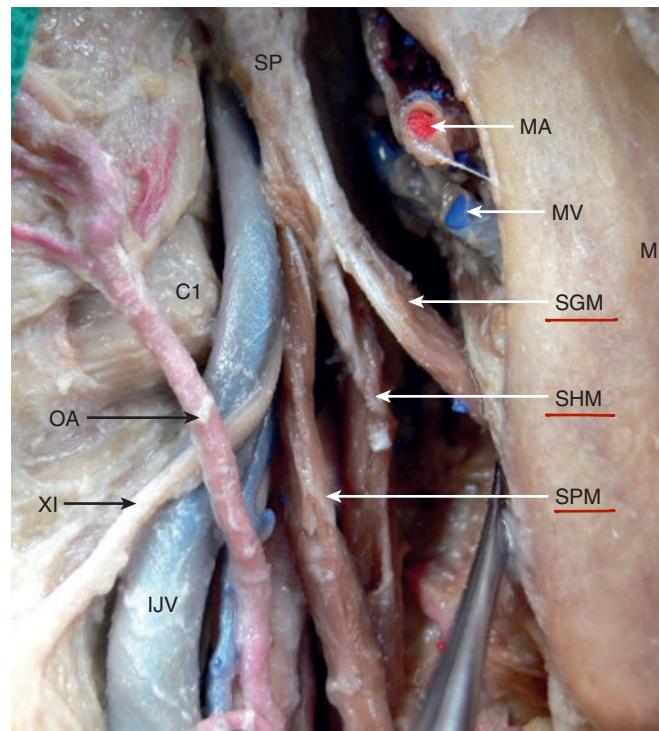
The next step to enhance distal exposure is to divide the posterior belly of the digastric muscle. The hypoglossal nerve should be carefully identified and protected before the muscle is divided. Two other nerves that can be injured high in the neck are the spinal accessory nerve, which enters the tendinous portion of the sternocleidomastoid muscle usually in the upper third of the muscle, and the glossopharyngeal nerve, which lies deep to the digastric muscle.

### Resection of the Styloid Process

The final maneuver that can be extremely effective in gaining cephalic exposure is resection of the styloid process (Fig. 93.7). After the posterior belly of the digastric muscle is divided, the insertions of the styloid apparatus: styloglossus, stylopharyngeus, and stylohyoid muscles on the styloid process are excised with a scalpel. The stylohyoid muscle can be found posterosuperior to the ECA and inserts into the posterior portion of the styloid process. In addition, the occipital artery runs along the inferior border of the posterior belly of the digastric muscle. Identification and division of the occipital artery can prevent bleeding secondary to trauma caused by retraction (Fig. 93.7). The styloid process is carefully resected with a rongeur. This can extend the exposure of the ICA by an additional 4 to 5 mm. However, damage to the underlying facial nerve is a potential complication of styloidectomy.<sup>63–65</sup>

### Anterior Subluxation of the Mandible

Two other options can be used to improve exposure of a high bifurcation, and both require preoperative planning



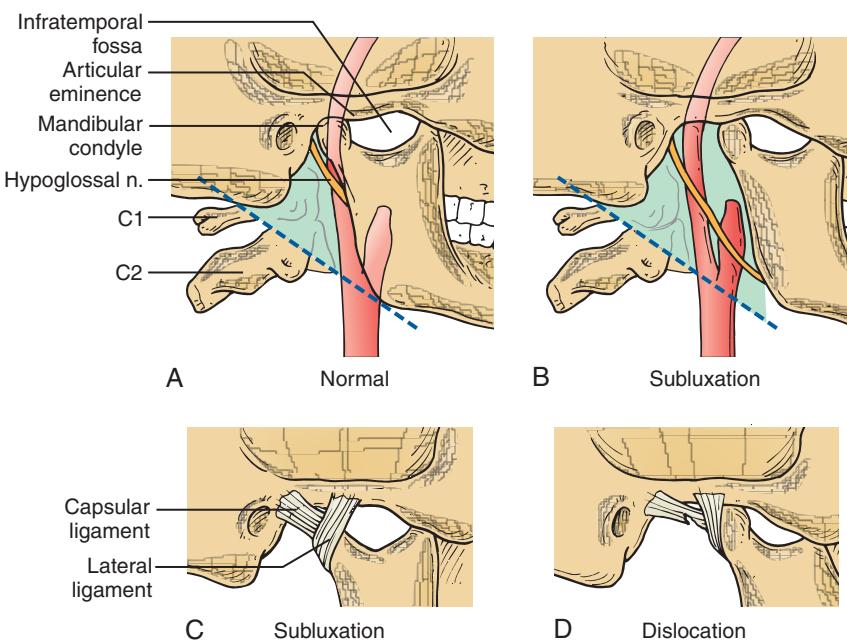
**Figure 93.7** Anatomic Relationships of the Styloid Process. *C1*, transverse process of *C1*; *IJV*, internal jugular vein; *M*, mandible; *MA*, maxillary artery; *MV*, maxillary vein; *OA*, occipital artery; *SGM*, styloglossus muscle; *SHM*, stylohyoid muscle; *SP*, styloid process; *SPM*, stylopharyngeus muscle; *XI*, spinal accessory nerve. (Modified from Icici Y, Mofakhar R, Pyle M, et al. Retromandibular fossa approach to the high cervical internal carotid artery: an anatomic study. *Neurosurgery*. 2008;62[5 Suppl 2]:ONS363–ONS369.)

and coordination with an oral or plastic surgeon (Fig. 93.8). These patients should undergo nasotracheal intubation. Anterior subluxation of the mandible was described for use in high carotid exposures in 1984. The authors describe their technique for subluxation as an evolution from full mouth arch bars with circumdental wiring to unilateral subluxation by circummandibular/transnasal wiring.<sup>66</sup> For patients with healthy dentition, anterior subluxation of the mandible can be accomplished by placing circumdental wires around the mandibular cuspid and bicuspids on the side ipsilateral to the vascular lesion. Corresponding wires should be placed around the corresponding contralateral maxillary teeth. The mandible is then subluxed anteriorly and the wires are twisted together to hold the fixation. Patients with poor dentition can have arch bars placed prior to wiring to facilitate the placement of the wires.<sup>67</sup> An even more aggressive approach involves the use of a complete vertical osteotomy through the vertical ramus of the mandible and separation of the mandible to expose the ICA.

## CEREBRAL PROTECTION AND MONITORING

### Shunting

CEA may be performed with the routine nonuse of shunts, routine shunting, or selective shunting.<sup>68–80</sup> Under GA,



**Figure 93.8** Mandibular Subluxation/Dislocation. (A) Normal bony anatomy with high carotid bifurcation. (B) The mandibular condyle is pulled forward onto the articular eminence, providing additional exposure when the subluxed mandible is fixed in place at this position. (C) Illustrates the desired position of the temporomandibular ligaments during subluxation. (D) Illustrates the potential undesired position of the temporomandibular ligaments from dislocation, which may cause a tear in the capsular ligament. (Modified from Simonian GT, Pappas PJ, Padberg FT, et al. Mandibular subluxation for distal internal carotid exposure: technical considerations. *J Vasc Surg*. 1999; 30:1116–1120. [ref. xvii].)

selective shunting may be determined by intraoperative measurement of carotid stump pressure, intraoperative monitoring of EEG or somatosensory evoked potentials (SSEP), measurement of MCA flow by TCD, and monitoring with cerebral oximetry.<sup>81–105</sup> An alternative method is to perform CEA under RA, with shunt insertion if symptoms develop after the carotid artery is clamped.<sup>106–110</sup> These adjuncts are designed to detect intraoperative cerebral ischemia, whereas TCD has the added advantage of detecting intraoperative emboli.

Placing a shunt has the capacity only to prevent ischemic stroke, but it could actually increase the risk for embolic stroke if performed poorly. Intraoperative cerebral ischemia is a relatively uncommon cause of intraoperative stroke.<sup>73–76</sup> This would support the argument of the routine nonshunters who believe that cerebral ischemia is a rare cause of stroke and that shunting may do more harm than good (by causing embolic complications) so that even selective shunting is never justified. However, it is clear that cerebral ischemia can lead to perioperative stroke<sup>73–76</sup> and can be completely relieved by placement of a shunt. This should translate into the prevention of stroke in these patients if embolic complications related to shunt placement are minimized. In fact, there is evidence that the benefits of shunting outweigh the risks in these patients.<sup>78,79</sup>

A recent meta-analysis by AbuRahma et al., including papers published from 1990 to 2010, found that the mean perioperative stroke rate for CEA with routine shunting was 1.4% and for routine nonshunting was 2%. For selective shunting, the stroke rate varied depending upon the method used for intraoperative monitoring. It ranged from 1.1% for cervical block anesthesia, 1.6% for EEG and carotid stump pressure, to 4.8% using TCD. The authors concluded that both routine and selective shunting are acceptable and should be employed at the surgeon's discretion.<sup>80</sup>

## Stump Pressure

Measurement of carotid stump pressure was the first method used to predict intraoperative ischemia.<sup>81–83</sup> In patients with measured stump pressures lower than 50 mm Hg, Hays and colleagues noted a 50% neurologic event rate in those who were not shunted versus a 10% rate in those who were in a series of 297 patients.<sup>81</sup> Kelly and coworkers measured stump pressure with concurrent EEG monitoring in 289 patients<sup>82</sup> and performed shunting only in those with evidence of ischemia by EEG criteria. They found that 6% of patients with stump pressure higher than 50 mm Hg had ischemia by EEG criteria. Stump pressure correlated well with EEG findings in patients with completed strokes but had a false-negative rate of 77% in patients with vertebral artery disease. In another report using EEG as a “gold standard,” Harada and associates found that a stump pressure lower than 50 mm Hg had a positive predictive value of only 36%.<sup>83</sup> In this series, 11% of patients with ischemia by EEG criteria would not have received shunts and 64% of patients with a stump pressure lower than 50 would have received them unnecessarily by stump pressure criteria. Similarly, Brewster and coworkers found that 11 of 17 patients with ischemic EEG findings would not have been shunted by stump pressure criteria, and 7 of 63 would have unnecessary shunts.<sup>84</sup> Finocchi and colleagues used TCD to verify stump pressure and found that stump pressure did not correlate well with ischemia by TCD criteria in patients with postoperative deficits.<sup>85</sup> Clearly, even in the setting of what appears to be a satisfactorily high stump pressure, there may still be regions of the brain that are relatively hypoperfused.

## Electroencephalographic and Somatosensory Evoked Potential Monitoring

Intraoperative EEG monitoring is the most widely used method of intraoperative cerebral monitoring.<sup>86–92</sup> Evidence suggests that electroencephalography is overly sensitive – positive

in 10% to 40% of patients with unilateral carotid disease and positive in as many as 69% with bilateral carotid disease, thereby overestimating the number of people who require shunts. Blume and coworkers observed postoperative strokes in only 9% of patients with abnormal EEG findings in whom shunts were not placed.<sup>92</sup> Furthermore, several series have documented neurologic events that occurred in the absence of EEG abnormality when shunting was not used.<sup>86</sup> Tempelhoff and associates found that 5 of 6 patients with postoperative deficits in a series of 103 patients showed EEG changes only late in the operation, when shunting was no longer feasible.<sup>93</sup>

Similarly, while there are multiple published studies on the use of SSEP suggesting that it is a useful adjunct to detect ischemia,<sup>94,95</sup> a meta-analysis of 15 studies, Wober and colleagues found that SSEP monitoring is not a reliable means of detecting ischemia and predicting neurologic outcome.<sup>111</sup>

## Transcranial Doppler

TCD was introduced by Schneider and coworkers in 1988.<sup>99</sup> Visser and coauthors reported that with normal TCD findings one could safely avoid shunting in one third of patients, but that abnormal findings on TCD predicted ischemia by EEG criteria only 60% of the time.<sup>112</sup> TCD has the unique advantage of detecting microemboli intraoperatively, which may alert the surgeon to avoid further vessel manipulation and microembolization.<sup>100,101</sup> However, Belardi and associates also reported that TCD (as well as stump pressure) was not accurate in predicting cerebral ischemia.<sup>102</sup>

## Awake Carotid Endarterectomy with Regional or Local Anesthesia

In view of these findings, performing CEA under RA is the most reliable method of predicting the need for selective shunting. Shunt rates of 5% to 15% are consistently lower than with other modalities.<sup>103,104,113</sup> In two recent prospective trials in which both stump pressure and EEG measurements were recorded before performing endarterectomy under RA, but in which the need to shunt was ultimately determined by neurologic changes, both EEG findings and stump pressure were found to inaccurately predict the need for shunting.<sup>103,104</sup> In a study by Calligaro and Dougherty published in 2005, a cost analysis found that RA saved more than \$3000 per case by avoiding EEG measurements.<sup>114</sup>

Three studies have shown decreased length of stay with RA,<sup>115–117</sup> but in two of them the length of stay in the GA group was not reflective of modern practice, approximately 5 days.<sup>115,117,118</sup> There is no evidence in the literature that demonstrates the cost effectiveness of selective shunting versus routine shunting, and insufficient data to conclude that CEA performed under RA is associated with a lower rate of MI or neurologic complications.<sup>115–117</sup>

## Routine Shunting

One risk of selective shunting is that neurologic events may be attributable to the shunt itself secondary to embolism or ischemia

and may not occur with routine shunting. Specifically, selective shunting, regardless of the adjunct used, always involves a test clamp. In the case of stump pressure measurement, instrumenting the carotid artery with a needle introduces the added risk of embolism. When a test clamp is positive, there are two options. One is to unclamp the vessels and reperfuse the brain while preparations are made to shunt. This maneuver exposes the patient to the risk of embolization. The other option is to proceed with the endarterectomy and placement of a shunt. In this instance, the brain is ischemic when the test clamp becomes positive and is exposed to an additional period of ischemia while the shunt is being placed, whereas during routine shunting, shunt placement can usually be accomplished in 1 to 2 minutes after clamping before the brain becomes ischemic.

The routine use of carotid shunts allows CEA to be performed in a consistent manner, which eliminates surgeon and patient anxiety, without the added cost or complexity of monitoring equipment. Studies consistently show that carotid shunting relieves the intracerebral ischemia caused by clamping, whether measured by neurologic status, EEG changes, MCA flow on TCD, or cerebral blood flow, and there is no convincing evidence that placement of a shunt necessarily increases embolic complications or causes arterial injury leading to more subacute or chronic complications. However, there is evidence that placing a shunt in the setting of severe ischemia decreases the stroke rate<sup>118</sup> and may limit ischemia-reperfusion injury. Further, Pärsson and associates have shown that carotid shunting diminishes the inflammatory response of ischemic brain injury, as demonstrated by the production of various inflammatory mediators.<sup>119</sup> This may be an important mechanism in the occurrence of delayed postoperative strokes, which can account for up to 70% of perioperative strokes.<sup>76</sup>

Several large series including nearly 7000 patients have documented a perioperative stroke rate of 1.0% to 1.6% with routine shunting.<sup>71,78–80</sup> In the author's practice, routine shunting is the preferred technique. Despite acceptable results in some individuals' hands, routine nonuse of shunts cannot be advocated in view of the abounding evidence that intraoperative ischemia can be a source of stroke that is preventable with shunts. Selective shunting based on stump pressure, TCD, or neurophysiologic monitoring does not accomplish the goal of improving results through decreased shunt use and only adds to the cost and complexity of the procedure. The only form of selective shunting that is truly reliable is that based on neurologic examination during RA.

## ARTERIOTOMY CLOSURE

Considerable experience indicates that patch closure yields superior clinical and anatomic outcomes compared to primary arteriotomy closure.

### Patch Material

#### Saphenous Vein Patches

Saphenous vein patching has been used extensively with good results. Complications specific to saphenous vein patching

include wound complications at the harvest site, potential compromise of a valuable conduit for later bypass procedures, and the potentially devastating complication of patch rupture, which has been reported to occur in 0.5% to 4% of cases.<sup>120–124</sup> Because most of these were ankle veins, several investigators recommended harvesting the greater saphenous vein (GSV) from above the knee. Lord and coworkers also noted that aneurysmal expansion of saphenous vein patches can occur in up to 17% patients.<sup>125</sup>

Archie and Green investigated the relationship of GSV diameter and rupture pressure and found that GSVs with diameters less than 3.5 mm were more prone to rupture.<sup>123</sup> Their group also noted that women were three times more likely to have a GSV measuring less than 3.5 mm. Applying this knowledge to their practice, Archie found that by using a GSV with a distended vein diameter of greater than 3.5 mm and maintaining a carotid bulb diameter of less than 13 mm, patch rupture was completely avoided in a series of 534 patients over an 8-year period.<sup>124</sup>

### Synthetic Patches

Synthetic materials that are commonly used include PTFE, Dacron, and bovine pericardium.

### Comparative Analyses

Pooled data from meta-analyses and large databases demonstrated no definitive clinical benefit of vein versus prosthetic patching. In a New York state database including 1972 CEAs performed at six regional hospitals, perioperative stroke was significantly more common with primary closure than with eversion endarterectomy or patching (5.6% vs. 2.2%, no difference between eversion endarterectomy and patching), as well as higher perioperative stroke and death rates with primary closure versus eversion or patching (6% vs. 2.5%).<sup>125</sup> In a review of more than 10,000 CEAs performed in several states, the use of a patch – in particular a prosthetic patch – was a statistically significant indicator for improved outcomes.<sup>126</sup> Based on these findings, the U.S. Centers for Medicare and Medicaid Services adopted patching of conventional CEA as a physician quality measure for 2009.

After these studies were published, Al-Rawi and coworkers reported an RCT that included 328 patients in which primary closure was performed by a single surgeon using microvascular techniques. There were no statistically significant differences in outcomes, but a trend toward a higher combined stroke and death rate was noted in the patched group.<sup>127</sup> Therefore, primary closure with microvascular technique may be the only instance in which it might be justified, although the preponderance of evidence supports patch closure after conventional CEA.

In a randomized trial of 160 CEAs with either external jugular vein or PTFE patches, there was no difference in stroke-free survival at 12, 30, and 60 months, and no difference in recurrent stenosis rates, but there was a trend toward improved results with a vein patch.<sup>128</sup> In an RCT comparing bovine pericardium with Dacron in 95 CEAs performed in 92 patients, there was significantly less suture line bleeding with bovine

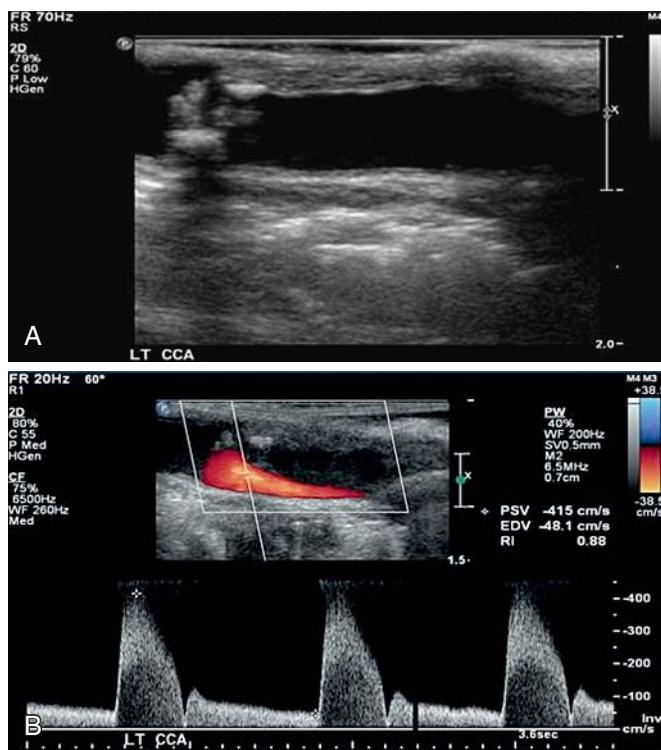
pericardium than with Dacron (4% vs. 30%) and no difference in neurologic outcomes.<sup>129</sup> Another study compared saphenous vein and internal jugular vein with knitted Dacron in 275 CEAs and found no significant differences in perioperative morbidity, mortality, or early restenosis between any of these groups.<sup>130</sup> Another report studied internal jugular vein, GSV from the thigh, and knitted Dacron, and documented a higher death rate in the jugular vein group (8% vs. 0% with GSV and 1.1% with knitted Dacron), as well as a higher stroke rate that was not statistically significant (4% vs. 1.3% and 1.1%, respectively).<sup>131</sup> In a randomized trial of primary closure versus patching with GSV, jugular vein, or PTFE, perioperative neurologic event rates were significantly higher with primary closure than with all patch methods. Event rates were slightly higher with jugular vein patches, and recurrent stenosis was also higher in this group than in the GSV or Dacron patch group and similar to primary closure.<sup>132</sup> Several other RCTs evaluating PTFE, Dacron, and vein patches have demonstrated higher perioperative stroke and restenosis rates with primary closure.<sup>132–135</sup> In the most recent meta-analysis, including 9 RCTs and 20 nonrandomized studies, and more than 13,000 CEAs, perioperative stroke rate was lower with patch closure and the rate of restenosis was higher with primary closure.<sup>136</sup> In addition, a recent report from the Vascular Quality Initiative (VQI) including more than 70,000 CEAs, superior outcomes were associated with bovine pericardial patches perioperatively and at 1-year follow-up compared with other patch materials.<sup>137</sup>

### Selective Patching

It has been suggested that carotid patching may not be necessary in all patients, and the technique does have some drawbacks, such as longer operative time, greater potential for bleeding from longer suture lines, and increased cost. To avoid these pitfalls while preventing the increased morbidity associated with primary closure, some surgeons use a policy of selective patching. Golledge and associates studied selective patching based on intraoperative measurement of the outer diameter of the ICA and found that selective patching was safe in arteries measuring at least 6 mm.<sup>138</sup> In a recent meta-analysis including 18 studies and more than 17,000 patients, risk factors for recurrent carotid stenosis and indications for selective patching included female gender, smoking, and dyslipidemia<sup>139</sup> (see below).

## COMPLETION STUDIES

A preventable cause of perioperative stroke is thromboembolism or carotid artery thrombosis resulting from technical imperfection. To minimize this risk, intraoperative completion studies have been used, including continuous wave Doppler, duplex ultrasound, and intraoperative angiography. Using continuous wave Doppler, an experienced operator can document vessel patency and a stenosis by the associated high-pitched audible signal. However, it is insensitive to small intimal flaps or more subtle stenoses, and its accuracy is operator dependent. Duplex ultrasound is a much more sensitive tool that provides



**Figure 93.9** (A) Intraoperative completion carotid B mode image revealing significant plaque disruption in the proximal common carotid artery. (B) Note the markedly elevated flow velocities at the site of plaque disruption. The vessel was re-clamped and this site was endarterectomized.

detailed anatomic imaging, as well real-time physiologic information. However, this modality is also operator-dependent. The author has found completion duplex ultrasound to be particularly helpful in identifying plaque disruption secondary to clamp or Rommel tourniquet trauma in the proximal CCA (Fig. 93.9) as well as distal intimal flaps. Intraoperative angiography has been considered the gold standard of completion studies. However, the quality of the information obtained from an angiogram may vary significantly depending on the technique used.

## Results of Completion Studies

Several studies have demonstrated the utility of completion studies to identify technical defects, with subsequent improvement of results.<sup>140,141</sup> On the other hand, not all technical imperfections, such as minor intimal flaps and especially ECA lesions, will cause strokes. In addition, attempts to revise significant lesions can convey additional morbidity from repeat manipulation of the vessels and a further risk for ischemia, embolism, thrombosis, or bleeding. In the EVEREST trial, the only significant risk factor for a major defect was plaque extension greater than 2 cm into the ICA (OR 1.5;  $P = 0.03$ ). One of the challenges with respect to completion studies is the extent of abnormality (either flap length or stenosis severity) that warrants intervention. Clearly, some workers have found no significant benefit in completion imaging.<sup>142,143</sup> However, if there is any doubt about the condition of the endpoint, a completion study should be obtained.

During eversion endarterectomy one may have only a fleeting glimpse of the endarterectomy endpoint before the artery retracts when the plaque separates from the artery, or none at all. Therefore, completion studies are more likely to be useful in this procedure.

## PERIOPERATIVE STROKE MANAGEMENT

In a comprehensive study of the etiology of perioperative stroke associated with CEA, more than 20 mechanisms were delineated.<sup>76</sup> These mechanisms can be grouped in decreasing order of frequency as perioperative arterial thrombosis and embolization, cerebral ischemia during carotid clamping, and intracerebral hemorrhage. Perioperative carotid arterial thrombosis most often results from technical imperfection in performance of the operation, such as disruption of the intima during placement of the intraluminal shunt, residual intimal flaps or atheromatous disease, or residual luminal thrombus. Completion imaging studies, as described in the previous section, will help identify technical imperfections and can reduce the incidence of neurologic complications (Fig. 93.9). Maximizing the chance for neurologic recovery is most dependent on early recognition of the deficit and immediate institution of proper therapy. Establishing the correct diagnosis is dependent on the time of onset of symptoms and is supported by selected noninvasive vascular laboratory or radiologic studies.

### Intraoperative

A patient undergoing CEA under GA should be awakened in the operating room immediately after wound closure, and a neurologic examination performed. If a new focal central neurologic deficit is identified, the incision should be immediately opened, and the ICA checked for flow with Doppler. If flow appears to be present, the surgeon should perform duplex ultrasonography or arteriography to identify a potential correctable etiology. Angiography should include intracranial imaging if no cause is found at the endarterectomy site because a distal embolus is potentially treatable by thrombolysis or extractable via microcatheter techniques. However, if the ICA does not have flow, or if a local defect is suspected, the endarterectomy must be re-explored. If there is acute thrombosis of the endarterectomy site, a meticulous search for a technical defect, such as a distal intimal ledge, should be carried out after careful thromboembolotomy. It is best not to clamp the distal ICA initially in the case of thrombosis and to extract the clot in the bulb and visible ICA so that backpressure may extrude any more distal ICA thrombus with the CCA clamped. If there is no back flow, a balloon catheter can be used, but care must be taken to prevent distention in the distal ICA to avoid causing a carotid artery–cavernous sinus fistula.<sup>144</sup> If there is a local flap, platelet accumulation, or other problem within the endarterectomy, it should be corrected. In the setting of re-exploration, great care must be taken if a shunt is reinserted to be sure that the distal endpoint is not injured and a flap created with insertion of the shunt.

At re-exploration, if the vessel is found to be patent without a local defect, the most likely cause is either ischemia during carotid clamping or, much more likely, intraoperative embolization. Despite careful technique, in a small minority of patients, excessive platelet deposition may occur acutely on the endarterectomy site and predispose to distal embolization or even acute thrombosis of the vessel. In this case, the author favors resection of the endarterectomy segment and replacement with an interposition graft and preferentially a ringed 6 mm PTFE graft. Conversely, if the vessel appears normal at re-exploration, thus suggesting that the patient experienced either embolization during vessel dissection before clamping or ischemia during clamping, treatment is medical; namely, close attention to hemodynamic monitoring, oxygenation, and blood pressure stability postoperatively or thrombolysis/microcatheter embolectomy extraction in institutions with such capability.

## Postoperative

If the patient awakens neurologically intact in the operating room and then a new deficit develops in the recovery room or later postoperatively, the differential diagnosis is more complex. Initially, the patient should undergo Duplex ultrasound if it can be performed rapidly. If this testing indicates occlusion of the vessel or abnormal flow velocities suggestive of an intimal flap or other anatomic deficit, the patient should be immediately taken to the operating room for re-exploration. Timing is crucial because most neurologic deficits are significantly reversible if flow is restored within 1 to 2 hours after vessel thrombosis. If the noninvasive studies are negative and thus suggest a patent vessel, head computed tomography (CT) should be performed immediately to rule out a cerebral hemorrhage. If negative, carotid angiography should be performed to identify any technical defect requiring revision at the operative site, or a possible intracerebral embolus.

The availability of intracerebral catheter-directed thrombolysis has provided another tool for neurologic salvage in a patient who experiences an embolic event associated with CEA. In addition, catheter-based thrombectomy of ICA and MCA emboli has been accomplished successfully in the setting of acute ischemic stroke and as “neurorescue” for carotid thrombosis.<sup>145–149</sup>

## SURGICAL RESULTS

Considerable clinical experience reported over the last three decades indicates that CEA can be performed with low rates of perioperative complications, and that it substantially reduces the risk for subsequent stroke in patients with significant symptomatic as well as asymptomatic extracranial carotid atherosclerotic lesions.<sup>9–12,150–152</sup>

### Randomized Trials

#### *Symptomatic Disease*

The National Institutes of Health (NIH)-funded North American Symptomatic Carotid Endarterectomy Trial (NASCET) included investigations of both high-grade (70%–99%) and

**TABLE 93.1**

Benefit of Carotid Endarterectomy: Randomized Trials

#### Perioperative

| Trial  | Indication  | CVA/Death          | Risk Reduction | P       |
|--------|-------------|--------------------|----------------|---------|
| NASCET | Sx: >70%    | 5.8%               | 16.5%/2 years  | <0.001  |
|        | Sx: 50%–69% | 6.7%               | 10.1%/5 years  | <0.05   |
| ECST   | Sx: 70%–99% | 7.5%, 9.6%/3 years | <0.01          | —       |
| ACAS   | Asx: >60%   | 2.3%               | 5.9%/5 years   | 0.004   |
| ACST   | Asx: >60%   | 3.1%               | 5.4%/5 years   | <0.0001 |

ACAS, Asymptomatic Carotid Atherosclerosis Study; ACST, Asymptomatic Carotid Surgery Trial; Asx, asymptomatic; ECST, European Carotid Surgery Trial; NASCET, North American Symptomatic Carotid Endarterectomy Trial; Sx, symptomatic.

Source: references 9–12, 156.

moderate-grade (50%–69%) stenosis (Table 93.1). In the NASCET high-grade stenosis investigation, 659 patients with symptomatic ICA stenoses (70%–99%) were randomized to optimal medical management versus CEA and optimal medical management. At the 2-year follow-up, there was a highly significant reduction in ipsilateral stroke incidence (9% vs. 26%) in patients who underwent CEA. This benefit became apparent within 3 months of randomization and has persisted through 8 years of follow-up.<sup>9,153</sup> In the moderate-stenosis limb of the investigation including 865 patients with 50% to 69% ICA stenoses, at 5 years of follow-up the ipsilateral stroke rate was 22.2% in medical patients and 16.7% in surgical patients ( $P = 0.045$ ), and this benefit persisted through 8 years of follow-up.<sup>153</sup>

Two recent randomized clinical trials comparing CEA to CAS have provided further evidence of the safety and efficacy of CEA. In the Carotid Revascularization Endarterectomy versus Stent Trial (CREST), the 30-day stroke and death rate was 3.2% among symptomatic patients.<sup>154</sup> In the International Carotid Surgery Trial, the 30-day stroke, death, and MI rate was 5.2%.<sup>155</sup>

#### *Asymptomatic Disease*

Management of asymptomatic carotid disease has recently become somewhat controversial because the long-term risk for stroke is not as high in asymptomatic when compared to symptomatic patients, and because the natural history of asymptomatic carotid disease may be improving due to improvements in medical therapy. In the NIH-funded Asymptomatic Carotid Atherosclerosis Study (ACAS), 1600 patients with greater than 60% asymptomatic stenosis were randomized to optimal medical management versus CEA and optimal medical management (Table 93.1). The 30-day stroke per death rate was 2.3% in the surgical cohort by intent-to-treat analysis. However, there were seven strokes and two deaths preoperatively, so the actual perioperative stroke rate was 1.3% and the mortality rate was 0.1%. At the 5-year follow-up, stroke and death rates were 5.1% in the CEA group and 11% in the medical management group ( $P = 0.004$ ).<sup>11</sup>

The Asymptomatic Carotid Surgery Trial (ACST) was carried out in Europe, was similar in design to ACAS, and

**TABLE 93.2**

## Population Studies of Carotid Endarterectomy Outcomes

| Source           | Number of Patients | Years     | % CVA/Death              |
|------------------|--------------------|-----------|--------------------------|
| North Carolina   | 1973               | 1998–1993 | 2.9                      |
| New York         | 9308               | 1998–1999 | 4.0                      |
| Maryland         | 23,237             | 1994–2003 | 1.3                      |
| California       | 51,331             | 1999–2003 | 1.0                      |
| Connecticut      | 7089               | 1997–2002 | 2.8 (VA)<br>1.2 (non-VA) |
| VSGNE            | 7649               | 2003–2010 | 1.1                      |
| Georgia Medicare | 1945               | 1993      | 3.7                      |
| NSQIP            | 13,622             | 2003–2003 | 3.4                      |
| NSQIP            | 13,316             | 2007–2008 | 2.0                      |

CVA, cerebrovascular accident; NSQIP, National Surgical Quality Improvement Project; VA, Veterans Administration hospitals; VSGNE, Vascular Study Group of New England.

Source: references 158–164.

randomized 3200 patients with greater than 60% asymptomatic ICA stenoses to best medical therapy versus CEA and best medical therapy. The 5-year stroke and death rates were 6.4% for CEA and 11.8% for medically managed patients ( $P < .0001$ ) (Table 93.1).<sup>156</sup> In CREST, the 30-day stroke and death rate was 1.2% among asymptomatic patients who underwent CEA.<sup>154</sup>

## Institutional Experience

In addition to the NASCET, ACAS, and ACST results, the safety and efficacy of CEA have been confirmed in multiple individual institutional reports. For example, in a series of 2236 CEAs performed between 1989 and 1999 at the Massachusetts General Hospital, the perioperative stroke and death rate was only 1.4%.<sup>157</sup> In a report of 1566 CEAs performed at the author's institution from 1994 through 2004, the 30-day stroke and death rates were 2.5% and 0.8%, respectively.<sup>53</sup>

## Population-Based Experience

In recent years several population-based analyses have demonstrated results of CEA in community practice comparable to the outcomes in tertiary referral centers and randomized trials (Table 93.2).<sup>158–164</sup>

## COMPLICATIONS

### Cardiac

MI is responsible for 25% to 50% of all perioperative deaths after CEA. Furthermore, more late deaths are due to MI than to stroke or other causes.<sup>157,162</sup> At least 40% to 50% of patients

**TABLE 93.3**

## Incidence of Cranial Nerve Dysfunction Following Carotid Endarterectomy

| Nerve               | Reported Incidence (%) |
|---------------------|------------------------|
| Hypoglossal         | 4.4–17.5               |
| Recurrent laryngeal | 1.5–15                 |
| Superior laryngeal  | 1.8–4.5                |
| Marginal mandibular | 1.1–3.1                |
| Glossopharyngeal    | 0.2–1.5                |
| Spinal accessory    | <1.0                   |

Source: references 170–181.

who undergo CEA have symptomatic CAD.<sup>162,165–167</sup> In a prospective angiographic study, severe surgically correctable CAD was identified in 20% of patients about to undergo treatment of carotid disease.<sup>168,169</sup> However, operative mortality has declined significantly over the past 2 decades in large measure due to a significant reduction in the incidence of major cardiac complications reflecting improvements in screening, as well as perioperative medical management of this patient population (see Ch. 44, Systemic Complications: Cardiac).

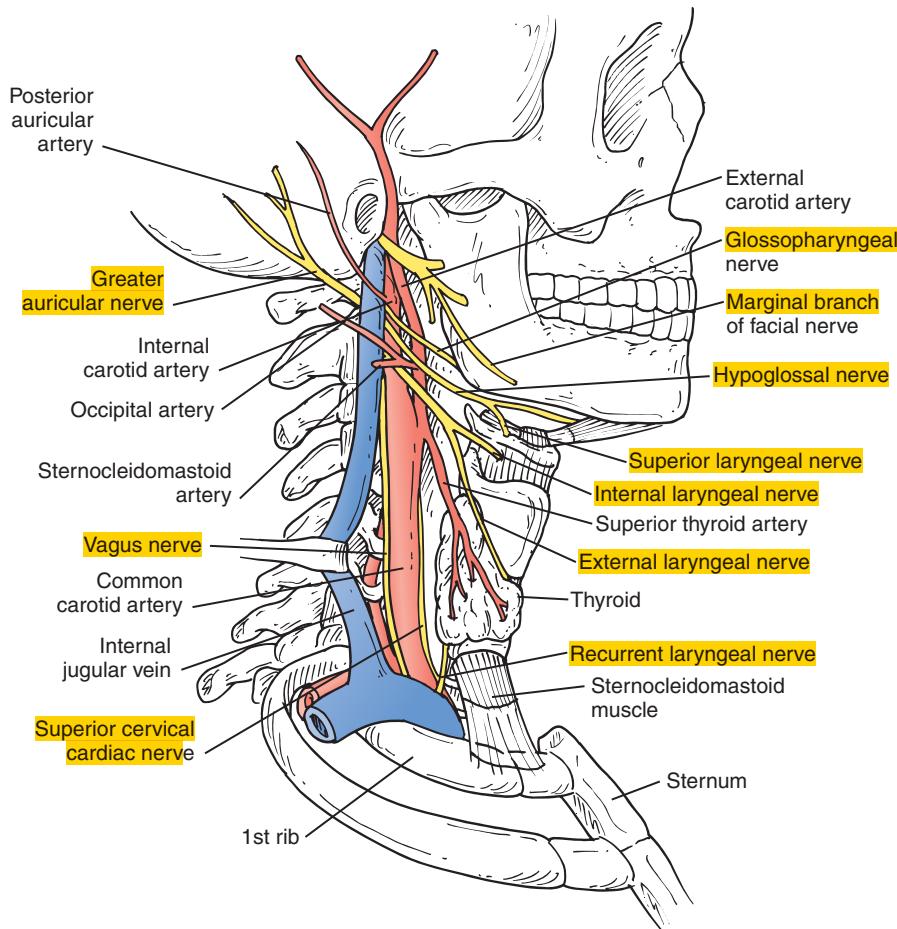
## Cranial Nerve Injury

### Incidence

Cranial nerve dysfunction is the most common neurologic complication of CEA. The incidence of postoperative dysfunction of cranial nerves ranges from 5% to 20% in several series, and a variety of nerves may be affected (Table 93.3).<sup>170–181</sup> In the CREST trial, the incidence of cranial nerve injury was 4.7%.<sup>154</sup> Many patients with documented deficits are asymptomatic and would have been missed by cursory clinical examination.<sup>177</sup> Clearly, retrospective reviews may significantly underestimate the true incidence of cranial nerve dysfunction after CEA. In a prospective study of 139 patients undergoing 162 CEA procedures and who also underwent postoperative otolaryngology examination, cranial nerve injuries were identified in 19.8% of the patients.<sup>170</sup> In another prospective series, 26 (14.2%) nerve injuries were identified in 21 patients following 183 CEA procedures. In the vast majority of cases, cranial nerve deficits are transient, with complete resolution noted within weeks to months after the procedure. In the latter series only 2 (1.1%) deficits were permanent.<sup>171</sup> In another prospective study, almost all nerve deficits resolved within 12 months after CEA, although it was noted that two patients with recurrent laryngeal nerve dysfunction regained normal function at 20 and 50 months after CEA, respectively.<sup>177</sup> In the CREST trial, there was no significant adverse impact of cranial nerve injury on the patients' quality of life 1 year later.<sup>154</sup> In the ECST randomized prospective trial, it was noted that the risk for permanent nerve injury was 0.5%.<sup>10</sup>

### Anatomic and Clinical Considerations

Iatrogenic injury to the cranial nerves results from the close anatomic proximity of these structures to the carotid bifurcation



**Figure 93.10** Relationship of the cranial nerves and their major branches to the common, internal, and external carotids in the neck. (Modified from Eisele DW, Smith RV, eds. *Complications in Head and Neck Surgery*, Philadelphia: Elsevier; 2009.)

(Fig. 93.10). Most deficits are due to direct blunt injury during dissection, stretch trauma from excessive retraction, electrocoagulation damage, inexact placement of ligatures, or pressure injury secondary to postoperative hematoma formation. Cranial nerve injury is much more likely during reoperative surgery because of excessive scar formation (see below).<sup>178</sup>

### Hypoglossal nerve

Hypoglossal nerve dysfunction, manifested by ipsilateral tongue weakness and deviation to the affected side with protrusion and difficulty masticating, is the most frequent cranial nerve deficit documented in most reports (Table 93.3). The structure descends from the hypoglossal canal (anterior condylar foramen) medial to the ICA and then courses lateral to the ECA, usually several centimeters distal to the carotid bifurcation, although in rare cases it may cross at the carotid bifurcation.<sup>177</sup> In this situation, if a patient has an unusually high carotid bifurcation or if atherosomatous plaque extends well past the origin of the ICA, cephalad mobilization of the nerve is usually required for adequate operative exposure. In most cases mobilization can be accomplished safely without morbidity by division of the ansa hypoglossi. In other cases, division of tethering branches of the ECA or internal jugular vein is required, which increases the likelihood of transient injury. Although unilateral hypoglossal nerve injury is rarely serious, bilateral deficits have been associated with serious articulation and swallowing difficulty and

upper airway obstruction requiring tracheotomy.<sup>178</sup> Therefore, it is important to assess the functional integrity of this nerve after CEA in a patient who is scheduled for early contralateral CEA.<sup>176</sup>

### Vagus nerve

The vagus nerve is easily identified within the carotid sheath posterior to the CCA, although in the occasional patient it may lie anterior to the carotid and be mistaken for the ansa hypoglossi. Therefore, before division of the latter structure, the vagus nerve should be clearly identified. The recurrent laryngeal branch usually originates from the vagus within the mediastinum, loops around the subclavian artery on the right or the aortic arch on the left side, and passes cephalad in the tracheoesophageal groove behind the strap muscles. In most cases, this nerve is not in close proximity to the operative field and is not likely to be directly injured. Typically, recurrent laryngeal nerve dysfunction results from vagus nerve trauma. In rare cases, the recurrent laryngeal nerve arises from the vagus at the level of the carotid bifurcation, the so-called nonrecurrent recurrent laryngeal nerve, and enters the larynx posterior to the CCA. Vagus or recurrent laryngeal nerve injury results in paralysis of the ipsilateral vocal cord in the paramedian position and is manifested as hoarseness and loss of an effective cough mechanism. In occasional patients, the vagus and hypoglossal nerves will be in apposition in the upper portion of the operative field,

\* artery to SCM

and no effort should be made to separate these structures to minimize the risk for injury. Patients who have previously undergone contralateral carotid, thyroid, or parathyroid surgery should have a careful examination of their vocal cords before CEA if there is any suggestion of recurrent laryngeal nerve injury because bilateral vocal cord paralysis may cause postoperative airway obstruction.

### Superior laryngeal nerve

The superior laryngeal nerve originates from the vagus near the jugular foramen and passes obliquely to the larynx posterior to the ECA and ICA where it divides into internal and external branches. It is not usually visualized during routine dissection for CEA, and it may be injured by injudicious clamping of the ICA or ECA. Injury to the external branch of the superior laryngeal nerve primarily results in loss of tensioning of the ipsilateral vocal cord and may be manifested clinically by early fatigability of the voice and difficulty with voice modulation at the high registers. Conversely, injury to the internal branch may result in decreased sensation at the laryngeal inlet and mild swallowing difficulty.

### Facial nerve: marginal mandibular branch

Injury to the marginal mandibular branch of the facial nerve causes drooping of the ipsilateral lower lip. Although this may be cosmetically bothersome to the patient, it is of little functional significance. This nerve courses from the anterior border of the parotid gland between the platysma and deep cervical fascia across the masseter muscle and ramus of the mandible. It may be drawn into the operative field as the patient's head is turned to the opposite side and the chin is extended for exposure of the carotid bifurcation. Injury is usually due to excessive stretch from self-retaining retractors in a transverse cervical incision. When a longitudinal incision is used for CEA, angling the superior aspect of the incision posteriorly toward the mastoid process below the angle of the mandible will minimize the risk of injury to the nerve.<sup>180</sup>

### Glossopharyngeal and spinal accessory nerves

Injury to the glossopharyngeal and spinal accessory nerves is exceedingly uncommon during CEA because of their anatomic location at the upper extent of the operative field. However, in rare cases in which excessive mobilization or division of the diaphragm is required for distal ICA exposure, either nerve may be encountered and traumatized. The glossopharyngeal nerve provides sensory and motor innervation to the larynx. Symptoms of glossopharyngeal nerve injury range from mild dysphasia to recurrent aspiration.<sup>174</sup>

The spinal accessory nerve exits the jugular foramen, runs posterior to the stylohyoid muscle, and enters the most cephalic extent of the sternocleidomastoid muscle. Injury is manifested as shoulder drop and pain, scapular winging, and difficulty abducting the shoulder because of weakness of the trapezius muscle.<sup>175</sup>

### Cutaneous sensory nerves

Two important cutaneous sensory nerves that are not infrequently injured during the performance of CEA are the greater

auricular and transverse cervical nerves. In one prospective study, the incidence of greater auricular and transverse cervical nerve injury was 60% and 69%, respectively, 1 week after CEA.<sup>182</sup> The greater auricular nerve courses along the most superior and the transverse cervical nerve along the most inferior area of the typical CEA longitudinal incision. Injury to the greater auricular nerve is manifested as numbness of the angle of the mandible and the lower part of the ear, and injury to the transverse cervical nerve is manifested as anesthesia of the anterior neck skin.

## Hemodynamic Instability

### Incidence and Etiology

If hypotension occurs after CEA, it usually does so within the first 2 hours postoperatively, is generally associated with bradycardia, and most likely results from disordered baroreceptor function.<sup>183–185</sup> Considerable evidence suggests that endarterectomy of fixed atheromatous plaque at the bifurcation, with its chronic dampening effect on pulse pressure, creates a heightened sensitivity of the baroreceptor mechanism that results in reduced central nervous system sympathetic activity with resultant hypotension or bradycardia, or both.<sup>183,184,186–188</sup> This reflex hypotension persists until the carotid sinus mechanism has been reset.<sup>186</sup>

Although perioperative hypertension is closely correlated with preoperative hypertension, its mechanism remains poorly understood. Baroreceptor dysfunction as a result of denervation of the carotid bulb is commonly assumed to be responsible, although there is considerable evidence to refute this hypothesis<sup>184,185</sup> and other mechanisms may be responsible, such as elevated cerebral norepinephrine or renin production.<sup>189,190</sup> In at least 80% of patients, this hypertensive response normalized within the first 24 hours, and in approximately 60% of patients within the first 16 hours after surgery.<sup>186</sup>

### Treatment

The episodic and generally unpredictable nature of post-CEA hypotension or hypertension is one of the more cogent reasons for observing the patient in a monitored unit after CEA, at least initially, with an indwelling radial artery catheter for systemic blood pressure monitoring. Hypotension should initially be treated by infusion of colloid solutions while a careful evaluation is conducted for any other causes of hypotension. Once normovolemia has been achieved, if hypotension persists, one should support the blood pressure with an intravenous infusion of phenylephrine (Neo-Synephrine), with the dosage adjusted to maintain systolic blood pressure within at least 20 mm Hg of the preoperative level. In almost all cases, the patient may be weaned from this vasoconstricting agent during the first postoperative day.

Conversely, postoperative hypertension is most effectively treated with intravenous sodium nitroprusside. Its effect is immediate, and it is quickly dissipated by stopping the infusion. The agent should be titrated to maintain systolic pressure within 20 mm Hg of the preoperative level. If myocardial ischemia is associated with these hypertensive episodes, intravenous

nitroglycerin should also be administered. Most patients are able to resume their preoperative oral antihypertensive agents on the evening of surgery or within the next 12 hours, and this often obviates the need for further and more prolonged intravenous therapy.

## Cerebral Hyperperfusion Syndrome

Cerebral hyperperfusion syndrome usually occurs several days after CEA and is often associated with severe hypertension. The reported incidence of cerebral hyperperfusion syndrome ranges from 0.4% to 7.7%.<sup>191,192</sup> Symptoms include a migraine-like headache progressing to seizures and, in its most severe manifestation, intracerebral hemorrhagic stroke. Though an infrequent complication of CEA and CAS, it is associated with a very high mortality rate that approaches 75% to 100% in some series.<sup>191,192</sup>

The cause of hyperperfusion syndrome appears to be increased regional cerebral blood flow secondary to disordered intracerebral autoregulation after relief of a high-grade carotid stenosis in the setting of severe contralateral carotid disease.<sup>193–195</sup> Systemic hypertension appears to be an important risk factor. Therefore, strict attention to postoperative blood pressure control is paramount, especially in a patient who undergoes CEA for a high-grade stenosis contralateral to complete ICA occlusion or severe stenosis. There may be some association with the use of anticoagulants and antiplatelet agents, but this evidence is speculative at best. If cerebral hemorrhage occurs, neurosurgical consultation is required to determine the necessity for craniotomy. One report noted that hyperperfusion syndrome can be predicted by a significant drop in pressure across the carotid stenosis and that it is related to temporary loss of cerebral autoregulation as evidenced by a transient increase in mean arterial velocity of the ipsilateral MCA after CEA.<sup>195–198</sup> Another study found that CEA performed less than 3 months after contralateral CEA was associated with a higher risk for hyperperfusion syndrome.<sup>198</sup>

## Other Complications

### Infections

CEA is rarely associated with infectious complications. Difficulty in primary healing is occasionally seen when this operation is performed in a previously irradiated field, but it is almost nonexistent in the absence of this complicating factor.<sup>177</sup> The reported incidence of wound infection, generally cellulitis, is well under 0.5%.<sup>199</sup> Although the true incidence of patch infection has not been established, it appears to be extremely rare. In a systematic literature review including 13 series, 123 patch infections were identified from 1962 to 2012. The overall prevalence ranged from 0.4% to 1.8%.<sup>200</sup> Most presented more than 6 months post-CEA. Staphylococci and streptococci were the most common organisms. The most common treatment was either replacement with a vein patch or placement of a vein bypass.<sup>200</sup>

### Bleeding

Postoperative hemorrhage has a reported incidence of 0.7% to 3.0%.<sup>187,201–203</sup> Most cases result from diffuse capillary oozing

secondary to the administration of heparin during the procedure and the concomitant administration of antiplatelet drugs. Though not systematically studied, at least anecdotally this degree of oozing appears to be greater in patients who are taking the antiplatelet agent clopidogrel at the time of surgery. Nevertheless, if there are indications for the administration of this agent, such as a recent coronary stent procedure or symptomatic carotid disease, one should not stop clopidogrel before surgery. In general, unless bleeding appears excessive at surgery, the author does not favor reversal of the heparin effect with protamine sulfate at completion of the procedure, but this practice varies widely.

If the neck incision has been closed over a suction drain, the acute onset of drainage of bright red blood postoperatively is suggestive of suture line disruption and is an indication for urgent re-exploration. Similarly, the development of a hematoma in the neck, often caused by inadequate function of the drain, may compress the trachea and is an indication for re-exploration of the wound. More gradual development of a neck hematoma usually results from inadequate ligation of facial veins or other muscle arterioles or venules.

## Recurrent Carotid Stenosis

Recurrent carotid stenosis has been estimated to occur in 5% to 22% of patients, although only approximately 3% of these lesions were symptomatic.<sup>204–216</sup> In a meta-analysis of 55 reports, the overall incidence of recurrent carotid stenosis after CEA was 6% to 14%, which reflected an annual incidence of restenosis or occlusion of 1.5% to 4.5%.<sup>207</sup> In another analysis of the MEDLINE database, the rate of restenosis was 10% within the first year, 3% in the second, and 2% in the third year after CEA, thus suggesting that the rate of restenosis is clearly not a linear process biologically.<sup>208</sup> In CREST, at 2 years the rate of significant restenosis or occlusion was 6.3%.<sup>214</sup>

Recurrent stenoses develop more frequently in women, in patients who continue to smoke, and in hypercholesterolemic, diabetic, and hypertensive individuals.<sup>205</sup> It has also been suggested that intraoperative injury secondary to arterial clamping, insertion of an intraluminal shunt, or placement of tacking sutures within the vessel may also predispose to early myointimal hyperplastic lesions.<sup>209</sup> As noted earlier, there is compelling evidence that closure of the arteriotomy with a patch will reduce the incidence of recurrent stenosis.

Long-term follow-up of 950 CEAs performed at the Massachusetts General Hospital demonstrated that reintervention was required in 3.8% of patients with a cumulative follow-up of 4.5 years. There was no difference in restenosis rates between patients who underwent patch closure and eversion endarterectomy.<sup>214</sup> In another series that included 1150 patients, 98.8% were free of occlusion or restenosis greater than 70% at a mean follow-up of 74 months after CEA.<sup>216</sup> In the EVEREST trial, life-table estimates of the cumulative risk for restenosis at 4 years was not significantly different between eversion CEA and conventional CEA with patch closure.<sup>217</sup> Therefore, while there may be anatomic indications for performing an eversion CEA – or it may be surgeon preference – the consensus is that this technique is not associated with a significantly lower rate of restenosis.

Early recurrent stenosis usually develops within 2 years of CEA and typically results from intimal hyperplasia, an inflammatory response that produces a firm, rubbery plaque rich in fibroblasts and smooth muscle cells surrounded by dense accumulation of collagen and acid mucopolysaccharide, and it typically develops within the endarterectomy bed (see Ch. 5, Intimal Hyperplasia). Regression of these lesions is not uncommon and is observed in as many as one third or more of cases.<sup>211,212</sup> Therefore, one should have a very high threshold for reintervention for an early restenosis. Later restenoses typically have features of atherosomatous plaque and are more widely distributed along the carotid artery. There are no prospective, randomized trials to support repeat CEA, but most available evidence supports treatment of symptomatic and very high grade asymptomatic recurrent stenoses.<sup>204,212</sup>

### Repeat Carotid Endarterectomy

Scarring typically makes the carotid dissection more technically difficult, so a higher incidence of cranial nerve injury and hematoma has been reported.<sup>218</sup> In addition, the more extensive disease within the carotid artery may necessitate carotid artery replacement with an interposition graft. This is technically more difficult, may preclude shunting, and could be associated with longer periods of cerebral ischemia, possibly leading to higher perioperative stroke rates.<sup>218</sup> However, repeat endarterectomy is often possible, even after eversion endarterectomy.<sup>219</sup> Furthermore, with careful planning and technique, excellent results can be achieved in this situation as well, and reoperative CEA has been shown to be a very durable procedure. In one series, for example, at 48 months follow-up, 100% of patients were free of recurrent stenosis after repeat CEA.<sup>220</sup>

### Carotid Artery Stenting Versus Repeat Carotid Endarterectomy

The increased technical difficulty and higher complication rate anticipated with repeat CEA has led some to advocate CAS as an alternative to CEA for recurrent stenosis. However, AbuRahma and coauthors reported lower perioperative stroke rates with repeat CEA than with CAS for recurrent stenosis.<sup>220</sup> Repeat CEA on the other hand was associated with a much greater incidence of cranial nerve injury (12% vs. 0%,  $P = 0.11$ ).<sup>221</sup> Others have not confirmed this.<sup>222,223</sup>

## SPECIAL CONSIDERATIONS

### Combined Carotid Artery and Cardiac Disease

Significant carotid disease occurs in approximately 3% to 14% of patients undergoing cardiac surgery.<sup>224</sup> Between 1970 and 2000, Naylor and colleagues found that the risk for stroke after coronary artery bypass grafting (CABG) was 2% overall – less than 2% in patients without carotid disease, 3% in asymptomatic patients with unilateral 50% to 99% stenosis, 5% in those with bilateral 50% to 99% stenosis, and 7% to 11% in patients with carotid occlusion. However, the authors noted that 50%

of CABG patients who experienced a stroke did not have significant carotid disease and that 60% of territorial infarctions on CT scan'autopsy could not be attributed to carotid disease alone. They estimated that CEA could prevent only about 40% to 50% of perioperative strokes in this patient population.<sup>225</sup> Nevertheless, carotid bifurcation disease is easily diagnosed and therefore at least one preventable cause of perioperative stroke in the cardiac surgical patient population.

### Simultaneous Carotid Endarterectomy and Coronary Artery Bypass Grafting

One strategy pursued to reduce the risk of perioperative stroke is to perform simultaneous CEA and CABG.<sup>224–230</sup> A prospective, randomized trial performed at the Cleveland Clinic demonstrated a significantly lower stroke rate in patients undergoing combined CEA/CABG (2.8%) versus staged CABG followed by CEA (14%), although mortality was not significantly different. The stroke rate was much higher if CEA was performed early after CABG than at later intervals.<sup>224</sup>

Our group reported excellent neurologic outcomes among high-risk patients undergoing combined CEA/CABG.<sup>226</sup> Other series have also documented good results among patients undergoing combined CEA/CABG.<sup>227,228</sup> Naylor and colleagues reviewed 97 published studies and found no significant difference in outcomes for staged and synchronous procedures.<sup>227</sup> Mortality was highest in patients undergoing synchronous CEA/CABG (4.6%; 95% CI, 4.1–5.2). Reverse staged procedures (CABG followed by CEA) were associated with the highest risk for ipsilateral stroke (5.8%) and any stroke (6.3%). Perioperative MI was lowest after the reverse staged procedure (0.9%) and highest in patients undergoing staged CEA/CABG (6.5%). The risk for death with or without any stroke was highest in patients undergoing synchronous CEA/CABG (8.7%) and lowest after staged CEA/CABG (6.1%). The risk of death/stroke or MI was 11.5% after synchronous procedures versus 10.2% after staged CEA and then CABG. In a related paper they found that the risk for death/stroke appeared to significantly diminish in studies published after 1993.<sup>227</sup> Patients with severe bilateral carotid disease or symptomatic stenoses were significantly more likely to suffer death or stroke (or both).<sup>227</sup> Conversely, other studies have documented increased morbidity or no benefit from combined CEA/CABG.<sup>230,231</sup> The community-wide outcomes of combined CEA/CABG in the Medicare population are inferior to those reported in many single-institution reviews.<sup>230</sup>

More recently, off-pump coronary artery bypass (OPCAB) has been introduced as an alternative method for coronary bypass, and outstanding results have been published on combined CEA/OPCAB, with combined stroke and mortality rates of 0% to 1.2%.<sup>231</sup>

In our institution, the preference has been to stage CEA followed in 1 or 2 days with CABG in patients with significant carotid disease. These are typically patients with symptomatic significant ICA stenoses, or those with bilateral severe asymptomatic ICA stenoses. A combined CEA/CABG is reserved for

patients with significant carotid artery disease and severe three-vessel or left main coronary disease, unstable angina, and/or critical aortic stenosis.

### **Carotid Artery Stenting Before Coronary Artery Bypass Grafting**

Several recent series have reported the outcomes of CAS followed by CABG with variable results.<sup>232–236</sup> In a single institution series including 97 patients who underwent same-day CAS and CABG or other cardiac surgical procedures, the in-hospital mortality and stroke rates were 2.1% and 0%, respectively.<sup>232</sup> In a meta-analysis including 31 series, staged CAS and CABG was associated with a 30-day stroke/death/MI rate of 8.5% compared to 5.9% among same-day procedures.<sup>233</sup> In another meta-analysis including more than 16,000 patients, synchronous CEA and CABG was compared to staged CAS and CABG. There was no significant difference in the rate of perioperative stroke/death/MI between the two patient populations.<sup>234</sup> Conversely, in a review of the Nationwide Inpatient Sample (NIS) database from 2004 to 2012, 22,501 concurrent carotid revascularizations and CABG surgeries during the same hospitalization were performed, including 15,402 (68.4%) combined CEA/CABG, 6297 (28.0%) staged CEA/CABG, and 802 (3.6%) staged CAS/CABG. The adjusted risk of death was greater, whereas risk of stroke was lower with both combined CEA/CABG (death odds ratio [OR]: 2.08, 95% confidence interval [CI]: 1.08 to 3.97;  $P = 0.03$ ; stroke OR: 0.65, 95% CI: 0.42 to 1.01;  $P = 0.06$ ) and staged CEA/CABG (death OR: 2.40, 95% CI: 1.43 to 4.05;  $P = 0.001$ ; stroke OR: 0.50, 95% CI: 0.31 to 0.80;  $P = 0.004$ ) approaches compared with staged CAS/CABG. The adjusted risk of death or stroke was similar in the three groups.<sup>235</sup> In another literature review including six studies and 277 patients who underwent CAS followed by CABG, the overall 30-day event rates were: minor stroke, 2.9%; major stroke, 3.2%; mortality, 7.6%; and combined death and any stroke rate was 12.3%.<sup>236</sup>

### **Advanced Age**

While the prevalence of stroke increases exponentially with advancing age, patients 80 years and older were excluded from NASCET and ACAS; therefore, it has been assumed that advanced age represents a high-risk factor for CEA and that such patients might thus be optimally treated by CAS. However, compelling evidence accumulated over the past two decades has confirmed the safety of CEA in elderly individuals. In an analysis of the Medicare database that included 140,376 patients aged 80–89 and 6446 patients older than 90, the perioperative stroke rate was 1.5% and the mortality rate was 2.2%.<sup>237</sup> In a population-based analysis of CEA in the state of Maryland from 1990 through 1995 from the author's group, the outcome in octogenarians was the same as in younger patient cohorts (perioperative stroke and death rate of 2.6%).<sup>238</sup> Considerable experience reported to date has confirmed the safety of CEA among the elderly and also excellent long-term survival and clinical results.<sup>239–242</sup>

### **Gender**

There are conflicting reports with respect to the impact of gender on the outcome of CEA. In ACAS, for example, women received less benefit in terms of stroke prevention than did men, as they experienced more strokes in both the perioperative period and long-term follow-up.<sup>11</sup> However, other studies have shown no difference in outcomes between men and women.<sup>243–245</sup>

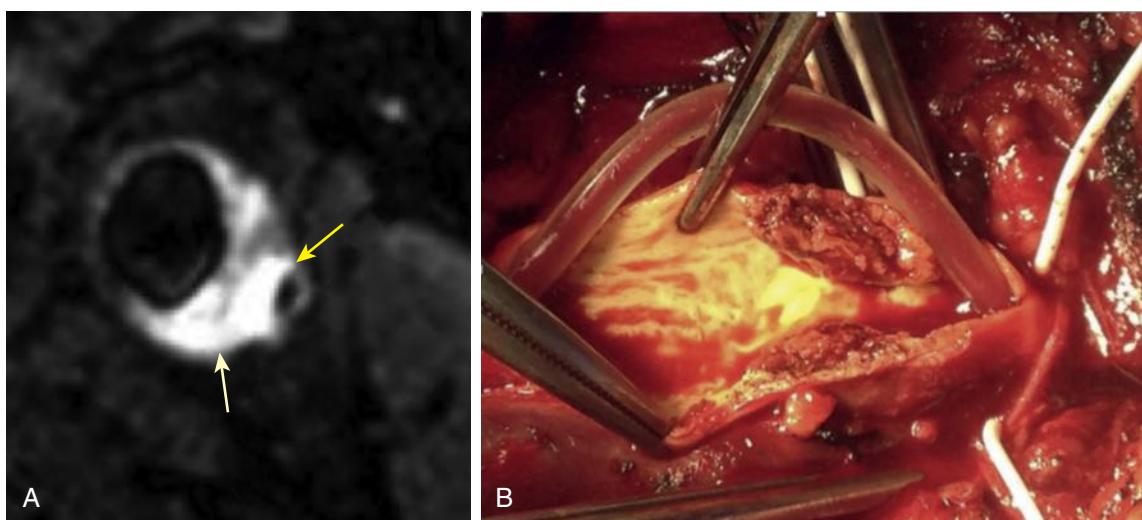
### **Race**

There are conflicting results on the impact of race on CEA outcomes. In a national Medicare database analysis, between 1994 and 1999 African American patients experienced crude mortality rates higher than white patients in seven of eight procedures, including CEA. The study suggested multiple reasons for this finding, including more frequent emergency operations and residence in low-income areas. Additionally, African Americans were more likely to receive care in lower volume hospitals and hospitals with overall higher mortality.<sup>246</sup> Likewise, a 2002 meta-analysis demonstrated a 40% greater likelihood of short-term death after CEA for African Americans than for whites undergoing CEA.<sup>247</sup> In the author's review of the Maryland state database, African American patients undergoing CEA had an increased incidence of in-hospital stroke, longer hospital stays, and higher hospital charges. This research noted that African American patients were more likely to undergo CEA in low-volume hospitals and were less likely to be treated by higher volume surgeons.<sup>248</sup>

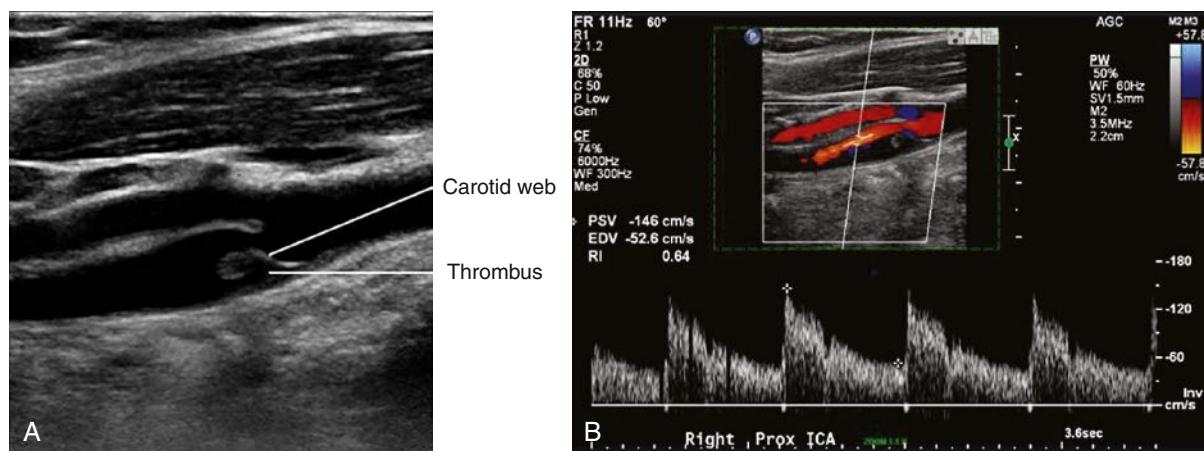
Conversely, Horner and colleagues' review of the National Surgical Quality Improvement Project (NSQIP) data revealed similarly low stroke and death rates between African American and white patients in the VA system. Among patients who presented with TIAs, however, Hispanic males experienced significantly worse outcomes in terms of stroke and death when compared with white patients.<sup>249</sup> An institutional review from Henry Ford Hospital revealed similar stroke and death rates between African American and white patients. However, African American patients in this study did have a higher incidence of all strokes in the long term than did white cohorts.<sup>250</sup> In a study of the NIS from 2005 to 2008 including 347,450 CEAs, Hispanics were found to have the greatest risk of operative mortality ( $P < 0.001$ ) and African Americans were found to have the highest stroke rate ( $P = 0.02$ ). However, on multivariable analysis, Hispanic ethnicity remained an independent risk factor for mortality after CEA whereas the increased risk of perioperative stroke in black patients was no longer significant.<sup>251</sup>

### **Symptomatic Disease with Less Than 50% Carotid Stenosis: Intraplaque Hemorrhage**

There is no level I evidence to support CEA for patients with less than 50% ICA stenoses. However, a growing body of evidence suggests that plaque morphology is an important predictor of subsequent neurologic events. For example, intraplaque hemorrhage has been shown to be associated with a high rate of recurrent ischemic events.<sup>252–254</sup> In one series of 25 patients



**Figure 93.11** Axial reconstruction of three-dimensional high-resolution blood and calcium gradient-echo sequence of magnetic resonance imaging/magnetic resonance angiography in a 72-year-old man with a history of three right hemispheric cerebral vascular accidents. A routine duplex scan revealed less than 50% right internal carotid artery stenosis but a contrast-enhanced duplex revealed hemorrhagic plaque. (A) The dark yellow arrow indicates calcification and light yellow arrow indicates hemorrhagic plaque. (B) The operative photograph demonstrates hemorrhagic plaque.



**Figure 93.12** Duplex ultrasound in a 52-year-old woman who presented with recurrent ischemic strokes. (A) Note the carotid web and probable thrombus in the cul de sac beneath the web. (B) Flow velocities consistent with a <50% ICA stenosis.

with symptomatic low-grade carotid artery stenosis with intra-plaque hemorrhage, there were 30 recurrent ischemic events (46% per patient per year).<sup>252</sup> At the author's institution, we have utilized contrast-enhanced duplex and contrast-enhanced MRA to identify plaque instability, including hemorrhage and ulceration, among symptomatic patients with less than 50% ICA stenoses, and have performed CEA with complete long-term symptomatic resolution (Fig. 93.11).<sup>254</sup>

### Carotid Webs

In addition, recent reports have identified carotid webs as another risk factor for ischemic stroke among patients with hemodynamically insignificant ICA stenoses. A carotid web is a thin membrane of tissue that typically extends from the posterior wall of the ICA into the lumen.<sup>255–270</sup> First described in the 1960s,<sup>259</sup> these webs are felt to be a variant of fibromuscular disease and can serve as the nidus for thrombus formation and cerebral emboli. Although they may be diagnosed on routine carotid duplex

imaging (Fig. 93.12), they are best depicted on CTA or MRA studies, or on lateral views on arteriography.<sup>255,262,267</sup> The most important differential diagnosis is a carotid dissection. Carotid webs are an important cause of cryptogenic strokes, and are most often seen in relatively young individuals in their 40s, there is a >50% female predominance, and African Americans are disproportionately affected.<sup>258,265,266</sup> Clinical experience to date has indicated that antiplatelet therapy has not been effective in controlling symptoms.<sup>255,261</sup> Conversely, CEA and CAS have produced excellent results in limited clinical experience.<sup>260–262</sup>

### Symptomatic Disease: Limb-Shaking Transient Ischemic Attacks

An extremely uncommon presentation of symptomatic carotid disease, first recognized by C. Miller Fisher in 1962,<sup>271</sup> is the

limb-shaking TIA. These TIAs are characterized by unilateral rhythmic or arrhythmic involuntary hyperkinesias involving the arm, leg, hand and arm, or hand, arm and leg. Symptoms may include jerking, trembling, twitching, flapping, or wavering of the affected part with an inability to control the part and lack of coordination.<sup>272–279</sup> They must be differentiated from seizures. These TIAs are almost always induced by activities that lead to hypotension and cerebral hypoperfusion, such as exercise, arising from a chair or bed, hyperextending the neck, or hyperventilation,<sup>275</sup> and are most likely related to disinhibition or release of subcortical motor systems in the setting of cortical ischemia in association with severe carotid occlusive disease.<sup>273</sup> Patients have been successfully treated with CEA,<sup>273,277</sup> CAS,<sup>279</sup> and in rare cases EC–IC bypass procedures.<sup>274</sup> It appears that the risk of post-CEA intracerebral hemorrhage is markedly increased in patients who present with these TIAs and critical carotid stenoses.<sup>276</sup>

### External Carotid Endarterectomy

In the setting of ICA occlusion, atherosclerotic disease of the ipsilateral ECA can result in embolic stroke through the collateral pathways that exist between the external carotid and intracranial circulation.<sup>280</sup> There have been several small series of patients treated successfully for symptomatic ECA stenoses with ECA endarterectomy.<sup>280–290</sup> In one series including 27 symptomatic patients undergoing external CEA, there was 1 (3.7%) stroke and 1 (3.7%) MI at 30 days with no perioperative deaths.<sup>289</sup> In a series of 19 patients who underwent 21 external carotid endarterectomy procedures, at 3-years follow-up, 86% of patients were free of stroke or death.<sup>288</sup> Using angiography or duplex ultrasonography, this report documented that two-thirds of ECAs closed primarily occluded or developed significant stenoses versus none with patch angioplasty.<sup>288</sup> In a review of 195 ECA endarterectomies and 23 ECA bypasses, the resolution of symptoms was seen in 83% of patients, with another 7% showing marked improvement. The perioperative mortality rate was 3%, mostly secondary to stroke, and the overall neurologic complication rate was 5%. A diseased contralateral carotid artery was associated with higher neurologic morbidity, whereas disease in the vertebral arteries had no impact on outcome. The best results were obtained when surgery was performed to relieve specific hemispheric or retinal symptoms as opposed to nonspecific neurologic complaints or previous stroke.<sup>290</sup> However, there is no evidence that ECA endarterectomy should be performed prophylactically for asymptomatic disease.

### Radiation-Induced Carotid Disease

Cervical irradiation is a known risk factor for carotid artery stenosis and cerebrovascular ischemic events. Carotid artery lesions secondary to irradiation therapy tend to occur at unusual locations, such as in the proximal or mid-common carotid artery. In addition to a predisposition to significant atherosclerotic disease, the effects of radiation include a fibrotic reaction and obliteration of normal tissue planes. This makes dissection and mobilization of the carotid vessels and identification of the cranial nerves more difficult. Although development of an appropriate

endarterectomy plane may be more difficult than usual, in most cases conventional endarterectomy can be successfully carried out. In the uncommon case where conventional endarterectomy cannot be performed, the obstruction may be relieved simply by placement of a patch, or vessel resection and placement of an interposition graft with placement of the anastomoses outside of the radiated field. There also may be more potential for impairing wound healing in this patient population. In the patient with particularly abnormal tissues, or if there is wound breakdown, closure with a muscle flap is an excellent option.

The reported clinical experience with CEA in this clinical scenario has been excellent, and appears superior to the results of CAS. Lesèche and associates published a series 30 cases from France, and also summarized 77 cases published by other authors.<sup>291</sup> The overall stroke and mortality rate for this entire cohort was 2%. Restenosis and recurrent stroke were not commonly encountered. The mean interval between cervical irradiation and CEA was 10 years. Bypasses from either the CCA or the subclavian artery were required to reconstruct the carotid artery in one-third of their cases.<sup>291</sup> In another early series including 24 cases, bypasses were rarely performed, although some patients required tissue flaps.<sup>292</sup> The mean time interval between irradiation and CEA in that series was even longer: 17 years.<sup>292</sup> In a more recent series of 24 patients who underwent 27 carotid revascularization procedures, including 23 vein and 3 PTFE interposition bypass grafts, and one eversion endarterectomy from 1996 to 2004, there were no perioperative strokes or deaths, and only three patients experienced transient cranial nerve dysfunction.<sup>293</sup> Follow-up ranged from 6 to 120 (mean, 28) months. There were 11 deaths, all unrelated to cerebrovascular disease. There were 3 (4.2%) strokes within the first 3 months of follow-up, with no additional strokes thereafter.<sup>293</sup>

### Hospital/Surgeon Volume

In contemporary practice, many have advocated regionalization of specialized care or high-risk procedures to higher volume centers and high-volume surgeons. A meta-analysis including 936,436 CEA procedures found that CEA stroke and death rate is significantly lower in high-volume centers, with a critical volume threshold of 79 CEAs per year.<sup>294</sup> Interestingly, this study demonstrated that patients undergoing operations performed by lower volume surgeons operating in higher volume centers also experienced lower stroke and death rates, thus suggesting that the hospital infrastructure and available resources rather than surgeon experience were more important in lowering complication rates.<sup>294</sup> Similarly, a very recent analysis including studies published between 2010 and 2018, high-quality aggregated evidence revealed an inverse relationship between hospital/surgeon CEA volume and periprocedural rate of stroke or death.<sup>295</sup> In a recent review of the NIS database including 104,918 CEA cases, surgeon volume correlated inversely with operative stroke or death rates among asymptomatic but not symptomatic patients.<sup>296</sup> A recent meta-analysis including 87 studies demonstrated a decreased risk of procedural death and stroke after CEA for high operator and high hospital volumes.<sup>297</sup> In California between 1992 and 1994,

mortality rates decreased for CEA, and higher hospital volume was inversely correlated with operative mortality.<sup>298</sup>

Conversely, a retrospective review of CEAs performed in Oregon over a 2-year period examined the outcomes between two low-volume institutions (total of 156 CEAs) and one high-volume institution (404 CEAs). There was no significant difference in 30-day stroke and death rates between the low- and high-volume centers.<sup>299</sup> This was observed despite the fact that the low-volume centers had significantly older patients, more smokers, and fewer asymptomatic patients. This paper makes a legitimate point that an individual surgeon in a low-volume institution may perform more individual high-risk procedures than another individual surgeon at a higher volume center, since ultimately it is surgeons and not hospitals that perform surgery. Furthermore, the ideal break point to define a suitably “high-volume” caseload remains to be defined.

Data published on CEA outcomes from institutional series, as well as large hospital and government databases, much of which has been summarized in this chapter, would suggest that vascular surgeons both individually and as a group have been tremendously successful in achieving published guidelines of a perioperative CVA/death rate  $\leq 3\%$  for asymptomatic and  $\leq 6\%$  for symptomatic CEA cases.<sup>300</sup> Therefore, CEA continues to be an effective treatment of carotid disease nearly 70 years after it was introduced, and it is the treatment with which all future therapies must be compared.

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PRINT

# Carotid Artery Stenting

SARAH E. DEERY and CAITLIN W. HICKS

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## INTRODUCTION

The concept of endovascular therapy for treatment of carotid artery stenosis was first proposed in 1977 by Mathias, who reported successful results of carotid artery angioplasty

using peripheral arterial angioplasty technology.<sup>1,2</sup> Balloon-expandable stents for the treatment of cerebrovascular disease were introduced 10 years later, with successful deployment of carotid artery stents in two patients with aneurysms and stenosis of the distal cervical carotid artery.<sup>3</sup> This experience

was subsequently adapted for the use of treating high-grade symptomatic carotid artery stenosis, although the initial enthusiasm was damped by high perioperative stroke rates, 6% to 9%.<sup>4–8</sup>

In 1990, Theron et al. published their technique using cerebral protection.<sup>9</sup> This led to the development of embolic protection devices (EPDs), which drastically reduced stroke rates and revitalized interest in endovascular therapy for carotid artery stenosis. More recently, transcarotid artery revascularization (TCAR) using flow reversal has been introduced as an alternative with favorable outcomes, also reinvigorating carotid artery stenting in certain populations.

## TRANSFEMORAL CAROTID STENT (TF-CAS) TRIALS

Multiple randomized controlled trials (RCTs) have compared outcomes after TF-CAS versus the “gold standard” of carotid endarterectomy (CEA) (Table 94.1). Several of these studies found TF-CAS to be noninferior to CEA.<sup>6,10–13</sup> However, the EVA-3S<sup>7,14</sup> and SPACE<sup>5,15</sup> trials showed higher rates of perioperative stroke/death with TF-CAS. Similarly, in CREST, patients undergoing TF-CAS had higher rates of periprocedural stroke, although rates of periprocedural myocardial infarction (MI) were lower.<sup>16,17</sup> These studies are criticized for limited

**TABLE 94.1**

Summary of Major Completed Randomized Controlled Trials Comparing Transfemoral Carotid Artery Stenting (TF-CAS) vs. Carotid Endarterectomy (CEA)

| Trial                     | Publication Date | Sample Size | Carotid Stenosis Criteria   | Study Design                        | EPD Use for TF-CAS | Primary Outcome  | Results TF-CAS vs. CEA  | Conclusion  |
|---------------------------|------------------|-------------|---|-------------------------------------|--------------------|--|---|---|
| SAPPHIRE <sup>11,13</sup> | 2004, 2008       | 334         | ≥50% symptomatic or ≥80% asymptomatic   | Noninferiority RCT<br>United States | 97%                | Composite death, stroke, MI within 30 days or ipsilateral stroke up to 1 year        | 1 year: 12.2% vs. 20.1%<br>3 years: 24.6% TF-CAS vs. 26.9%                    | TF-CAS noninferior to CEA   |
| EVA-3S <sup>7,14</sup>    | 2006, 2008       | 527         | >60% symptomatic carotid artery stenosis  | Noninferiority RCT<br>Europe        | 92%                | Any stroke or death within 30 days   | 30 days: 9.6% vs. 3.9%<br>6 months: 11.7% vs. 6.1%<br>4 years: 11.1% vs. 6.2% | Worse periprocedural stroke/death outcomes with TF-CAS  |
| SPACE <sup>5,15</sup>     | 2006, 2008       | 1200        | ≥70% symptomatic carotid stenosis   | Noninferiority RCT<br>Europe        | 27%                | Ipsilateral stroke or death within 30 days   | 30 days: 6.8% vs. 6.3%<br>2 years: 9.5% vs. 8.8%                              | Higher risk of periprocedural adverse events with TF-CAS  |
| ICSS <sup>6,10</sup>      | 2010, 2015       | 1713        | >50% symptomatic carotid artery stenosis  | Noninferiority RCT<br>Europe        | 72%                | 3-year fatal or disabling stroke in any territory                                    | 120 days: 8.5% vs. 5.2%<br>4.2 years: 6.4% vs. 6.5%                           | Long-term risk of disabling stroke is similar for TF-CAS and CEA                                |
| CREST <sup>16,17</sup>    | 2010, 2016       | 2502        | Symptomatic or asymptomatic carotid artery stenosis ≥70% (ultrasound) or symptomatic ≥50% (angiography) | Noninferiority RCT<br>North America | 96%                | Composite stroke, MI, or death within 30 days or ipsilateral stroke within 4 years   | 4 years: 7.2% vs. 6.8%<br>10 years: 11.8% vs. 9.9%                            | No significant long-term differences for TF-CAS vs. CEA in composite endpoint or risk of stroke |
| ACT-I <sup>12</sup>       | 2016             | 1453        | >80% asymptomatic carotid stenosis  | Noninferiority RCT<br>United States | 100%               | Composite of death, stroke, or MI within 30 days or ipsilateral stroke within 1 year | 30 days: 2.9% vs. 1.7%<br>1 year: 3.8% vs. 3.4%                               | TF-CAS not inferior to CEA for composite endpoint   |

CAS/CEA, carotid artery stenting (CAS)/carotid endarterectomy (CEA); CREST, Carotid Revascularization Endarterectomy Versus Stenting Trial; ICSS, International Carotid Stenting Study (ICSS); MI, myocardial infarction; RCT, randomized controlled trials; SAPPHIRE, Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy; SPACE, the Stent-Supported Percutaneous Angioplasty of the Carotid Artery Versus Endarterectomy.

generalizability, pre-dating modern best medical therapy, and often unbalanced training requirements between interventionists performing stenting versus CEA.

## TRANSCAROTID ARTERY REVASCULARIZATION (TCAR) TRIALS

No large, randomized controlled trials have to date been performed comparing TCAR to TF-CAS or CEA. However, clinical trial data and prospectively maintained data registries have shown promising results. The Safety and Efficacy Study for Reverse Flow Used During Carotid Artery Stenting Procedure (ROADSTER) trial overall perioperative stroke rate was 1.4%.<sup>18</sup> Although not designed as a comparative effectiveness trial, the reported perioperative stroke rates were lower than any prior prospective multicenter clinical trial of TF-CAS. One-year data from the ROADSTER trial were also favorable, with a 0.6% incidence of ipsilateral stroke and 4.2% rate of death, none neurologic in etiology.<sup>19</sup> Based on these findings, the authors suggest that TCAR offers a safe and durable revascularization option for patients who are deemed to be at high risk for CEA.

Following ROADSTER, data from all TCAR procedures performed in the US were captured in the SVS Vascular Quality Initiative (VQI) TCAR Surveillance Project registry. Retrospective analyses of these data demonstrated that despite TCAR being performed in higher risk patients, the in-hospital rates of stroke/death were similar for TCAR compared to CEA (1.6% vs. 1.4%,  $P = 0.33$ ), but the rate of cranial nerve injury was lower (0.6% vs. 1.8%,  $P < 0.001$ ).<sup>20</sup> TCAR had a lower rate of in-hospital transient ischemic attack (TIA), stroke, and death compared to TF-CAS (2.2% vs. 3.8%,  $P = 0.04$ ) that persisted after multivariable adjustment (odds ratio 2.1 [95% CI 1.08 to 4.08],  $P = 0.03$ ).<sup>21</sup> At 1 year postoperatively, TCAR was associated with a lower risk of ipsilateral stroke or death compared to TF-CAS (5.1% vs. 9.6%, hazard ratio 0.52 [95% CI 0.41 to 0.66],  $P < 0.001$ ).<sup>22</sup> Taken together, TCAR is purported to have comparable outcomes to CEA and improved outcomes compared to TF-CAS based on non-randomized data.

## CURRENT CAROTID STENT GUIDELINES

Because of the perceived higher periprocedural risk of stroke with TF-CAS compared with CEA based on results from RCTs, the indications for carotid stenting according to the current guidelines for use of TF-CAS for treating carotid artery stenosis are limited. A consensus supports the use of TF-CAS in symptomatic patients with high-grade stenoses who are deemed too high medical risk to undergo open surgery. The use of TF-CAS for low or moderate risk patients without prior neck radiation or surgery, or those who have asymptomatic carotid artery disease, is less well supported. One report supports the use of TF-CAS in lower medical risk patients with

higher anatomic risk factors for CEA such as restenosis or neck radiation.<sup>23</sup> However, many experts cite concerns about long-term viability of TF-CAS. As such, Societal guidelines addressing the appropriate use of TF-CAS are cautious (Tables 94.2 and 94.3).<sup>24–27</sup> The SVS guidelines note that asymptomatic patients who are deemed too high risk for CEA should receive medical therapy rather than carotid stenting.<sup>25</sup> Most existing guidelines were published prior to the introduction of TCAR, so the role for this technique has not been defined.

## PATIENT SELECTION

TF-CAS is currently supported only for use in a group of highly select patients meeting appropriate diagnostic criteria. According to CMS criteria (Table 94.4),<sup>28</sup> all patients must have a diagnosis of high-grade carotid artery stenosis based on duplex ultrasound or carotid artery angiography; if the diagnosis is based on duplex findings, the degree of stenosis must be confirmed via angiography at the time of the procedure prior to stenting. Patients must also be symptomatic and/or at high risk for open surgical intervention, as determined by the presence of either a significant medical comorbidity (see Table 94.4), prior neck radiation therapy or prior ipsilateral CEA. Other considerations when selecting a patient who might be appropriate for stenting are noted below.

### Age

Given the less invasive nature of carotid artery stenting, the use of TF-CAS for treating elderly patients with carotid artery stenosis was initially considered one of the main indications. Unexpectedly, data demonstrated that the opposite was true; the risk of an adverse event with TF-CAS was significantly higher than that with CEA in older patients. In post hoc analysis of the SPACE trial, ipsilateral stroke or death after TF-CAS occurred in 2.7% of patients 68 years or younger versus 10.8% in patients >68 years, whereas outcomes after CEA were not significantly different.<sup>29</sup> Similarly, an analysis of CREST demonstrated the risk of adverse events increased by 1.77 times per 10-year incremental increase in age after TF-CAS but was stable regardless of age after CEA.<sup>30</sup> These findings are confirmed by a meta-analysis of 4754 patients enrolled in CREST and the Carotid Stenting Trialists' Collaboration trials, which demonstrated a significant pattern of increased periprocedural risk with increasing age in patients assigned to TF-CAS versus CEA starting at 70 years and older ( $P < 0.001$ ).<sup>31</sup>

Population database analyses examining the effects of age on adverse events after TF-CAS and CEA report similar findings. Data from the SVS Vascular Registry demonstrated inferior 30-day composite outcomes in patients >65 years undergoing TF-CAS, regardless of symptom status.<sup>32</sup> Data from the Nationwide Inpatient Sample demonstrated worse stroke rates and cardiac complications among patients >70 years who underwent TF-CAS.<sup>33</sup>

In a Cochrane Database of Systematic Review from 2012 including 16 trials, 7572 patients supported these findings; the

**TABLE 94.2** Carotid Treatment Guidelines for Patients with Symptomatic Carotid Artery Stenosis

| Society               | Year | Recommendation   | Strength                       |
|-----------------------|------|--|--------------------------------|
| ACC/AHA <sup>24</sup> | 2011 | CAS is indicated as an alternative to CEA for symptomatic patients at average or low risk of complications associated with endovascular intervention when the diameter of the lumen of the internal carotid artery is reduced by more than 70% as documented by noninvasive imaging or more than 50% as documented by catheter angiography and the anticipated rate of periprocedural stroke or mortality is less than 6%. | Class I; level of evidence B   |
|                       |      | Among patients with symptomatic severe stenosis ( $\geq 70\%$ ) in whom the stenosis is difficult to access surgically, medical conditions are present that greatly increase the risk for surgery, or when other specific circumstances exist, such as radiation-induced stenosis or restenosis after CEA, CAS may be considered.  | Class IIb; level of evidence B |
|                       |      | CAS in the above setting is reasonable when performed by operators with established periprocedural morbidity and mortality rates of 4%–6%, similar to those observed in trials of CEA and CAS.   | Class IIa; level of evidence B |
| SVS <sup>25</sup>     | 2011 | In most patients with carotid stenosis who are candidates for intervention, CEA is preferred to CAS for reduction of all-cause and periprocedural death.   | Grade I; level of evidence B   |
|                       |      | CAS is preferred over CEA in symptomatic patients with $\geq 50\%$ stenosis and tracheal stoma, situations where local tissues are scarred and fibrotic from prior ipsilateral surgery or external beam radiotherapy, prior cranial nerve injury, and lesions that extend proximal to the clavicle or distal to the C2 vertebral body.   | Grade II; level of evidence B  |
|                       |      | CAS is preferred over CEA in symptomatic patients with $\geq 50\%$ stenosis and severe uncorrectable coronary artery disease, congestive heart failure, or chronic obstructive pulmonary disease.  | Grade II; level of evidence C  |
| ESC <sup>26</sup>     | 2011 | In patients with symptomatic 70%–99% stenosis of the internal carotid artery, CEA is recommended for the prevention of recurrent stroke.   | Class I; level of evidence A   |
|                       |      | In symptomatic patients at high surgical risk requiring revascularization, CAS should be considered as an alternative to CEA.  | Class IIa; level of evidence B |
|                       |      | In symptomatic patients requiring carotid revascularization, CAS may be considered as an alternative to CEA in high-volume centers with documented death or stroke rate <6%.   | Class IIb; level of evidence B |
| ESVS <sup>27</sup>    | 2017 | It is recommended that most patients who have suffered carotid territory symptoms within the preceding 6 months and who are aged $>70$ years and who have 50%–99% stenoses should be treated by carotid endarterectomy, rather than carotid stenting.  | Class I; level of evidence A   |
|                       |      | When revascularization is indicated in patients who have suffered carotid territory symptoms within the preceding 6 months and who are aged $<70$ years, carotid stenting may be considered an alternative to endarterectomy, provided the documented procedural death/stroke rate is $<6\%$   | Class IIb; level of evidence A |

Note: CAS (carotid artery stenting) refers to transfemoral CAS for the purposes of the 2011 guidelines, as transcarotid artery revascularization (TCAR) was not commercially available at that time.

ACC/AHA, American College of Cardiology/American Heart Association; CAS, carotid artery stenting; CEA, carotid endarterectomy; ESC, European Society of Cardiology; SVS, Society for Vascular Surgery; ESVS, European Society for Vascular Surgery

Adapted from Paraskevas KI, Mihailidis DP, Veith FJ. Comparison of the five 2011 guidelines for the treatment of carotid stenosis. *J Vasc Surg*. 2012;55(5):1504–1508.

overall risk of perioperative death or any stroke was significantly higher for TF-CAS versus CEA among patients  $>70$  years (OR 2.20, 95% confidence interval [CI] 1.47 to 3.29) but not significantly different for younger patients (OR 1.16, 95% CI 0.80).<sup>34</sup> These data suggest that TF-CAS should be reserved for younger patients.<sup>32</sup>

It is theorized that the higher stroke rate is related to the higher prevalence of aortic arch and proximal common carotid artery atheroma in this population. TCAR with flow reversal avoids this source and has been shown in small series to be equally as safe among high-risk patients regardless of age.<sup>35</sup> Furthermore, recent registry data from the VQI compared outcomes following CEA, TF-CAS, and TCAR and found no difference in outcomes following TCAR in patients  $\leq 70$ , 71–79, or  $\geq 80$  years of age.<sup>36</sup> The same analysis also found lower rates

of stroke following TCAR compared to TF-CAS in patients aged  $\geq 80$  years.<sup>36</sup> Based on these limited data, one of the current published indications for TCAR is age  $\geq 75$  years.<sup>37</sup>

## Gender

There are well-described differences in outcomes between women and men with carotid disease intervention, however the gender-specific effects on outcomes after carotid artery stenting are less clear.<sup>38</sup> A secondary analysis of CREST data suggested that the perioperative risk of an adverse event was higher in women who underwent TF-CAS versus those who underwent CEA (6.8% vs. 3.8%) but similar among men regardless of approach (4.3% vs. 4.9%).<sup>39,40</sup> These findings were attributable to an increased stroke rate in females undergoing

**TABLE 94.3** Carotid Treatment Guidelines for Patients with Asymptomatic Carotid Artery Stenosis

| Society               | Year | Recommendation  | Strength                       |
|-----------------------|------|---|--------------------------------|
| ACC/AHA <sup>24</sup> | 2011 | Prophylactic CAS might be considered in highly selected patients with asymptomatic carotid stenosis (minimum 60% by angiography, 70% by validated Doppler ultrasound), but its effectiveness compared with medical therapy alone in this situation is not well established.   | Class IIb; level of evidence B |
| SVS <sup>25</sup>     | 2011 | Neurologically asymptomatic patients with ≥60% diameter stenosis should be considered for CEA for reduction of long-term risk of stroke, provided the patient has a 3- to 5-year life expectancy and perioperative stroke/death rates can be ≤3%. There are insufficient data to recommend CAS as primary therapy for neurologically asymptomatic patients with 70% to 99% diameter stenosis. Data from CREST suggest that in properly selected asymptomatic patients, CAS is equivalent to CEA in the hands of experienced interventionalists. | Class I; level of evidence A   |
|                       |      |   | Grade II; level of evidence B  |
| ESC <sup>26</sup>     | 2011 | In asymptomatic patients with carotid artery stenosis ≥60%, CEA should be considered as long as the perioperative stroke and death rate for procedures performed by the surgical team is <3% and the patient's life expectancy exceeds 5 years.   | Class IIa; level of evidence A |
|                       |      | In asymptomatic patients with an indication for carotid revascularization, CAS may be considered as an alternative to CEA in high-volume centers with documented death or stroke rate <3%.  | Class IIa; level of evidence B |
| ESVS <sup>27</sup>    | 2017 | In "average surgical risk" patients with an asymptomatic 60%–99% stenosis in the presence of one or more imaging characteristics that may be associated with an increased risk of late ipsilateral stroke, carotid stenting may be an alternative to carotid endarterectomy, provided documented perioperative stroke/death rates are <3% and the patient's life expectancy exceeds 5 years.  | Class IIb; level of evidence B |
|                       |      | Carotid stenting may be considered in selected asymptomatic patients who have been deemed by the multidisciplinary team to be "high risk for surgery" and who have an asymptomatic 60%–99% stenosis in the presence of one or more imaging characteristics that may be associated with an increased risk of late ipsilateral stroke, provided documented procedural risks are <3% and the patient's life expectancy exceeds 5 years   | Class IIb; level of evidence B |

Note: CAS (carotid artery stenting) refers to transfemoral CAS for the purposes of the 2011 guidelines, as transcarotid artery revascularization (TCAR) was not commercially available at that time.

ACC/AHA, American College of Cardiology/American Heart Association; CAS, carotid artery stenting; CEA, carotid endarterectomy; ESC, European Society of Cardiology; SVS, Society for Vascular Surgery; ESVS, European Society for Vascular Surgery.

Adapted from Paraskevas KI, Mikhailidis DP, Veith FJ. Comparison of the five 2011 guidelines for the treatment of carotid stenosis. *J Vasc Surg*. 2012;55(5):1504–1508.

**TABLE 94.4** Medicare Decision Summary for Carotid Artery Stenting<sup>28</sup>

Carotid artery stenting with embolic protection is reasonable and necessary for the following:

1. Patients who are at high risk for CEA and who also have symptomatic carotid artery stenosis ≥70%. Coverage is limited to procedures performed using U.S. Food and Drug Administration (FDA)-approved carotid artery stenting systems and embolic protection devices.
2. Patients who are at high risk for CEA and have symptomatic carotid artery stenosis between 50% and 70%, in accordance with the Category B IDE clinical trials regulation, as a routine cost under the clinical trials policy, or in accordance with the National Coverage Determination on carotid artery stenting post-approval studies.
3. Patients who are at high risk for CEA and have asymptomatic carotid artery stenosis ≥80%, in accordance with the Category B IDE clinical trials regulation, as a routine cost under the clinical trials policy, or in accordance with the National Coverage Determination on carotid artery stenting post-approval studies.

Patients who are at high risk for CEA include those with any of the following:

Congestive heart failure class III/IV

Left ventricular ejection fraction <30%

Unstable angina

Contralateral carotid occlusion

Recent myocardial infarction

Previous CEA with recurrent stenosis

Prior radiation treatment to the neck

Other conditions that were used to determine patients at high risk for CEA in the prior carotid artery stenting trials and studies

CEA, carotid endarterectomy; IDE, Investigational Device Exemption.

**NEWER**  
TF-CAS (5.5% vs. 2.2%).<sup>39</sup> In contrast, a meta-analysis of patients enrolled in the European Carotid Stenting Trialists Collaboration (CSTC), including the EVA-3S, SPACE, and ICSS trials, demonstrated equivalent outcomes with TF-CAS and CEA for both males and females.<sup>41</sup> A subsequent meta-analysis from CREST, the CSTC, and the CAVATAS trial supported the latter conclusion that gender had no real effect on the risks following either treatment.<sup>42</sup>

Interestingly, observational data evaluating the embolic debris captured in EPDs after TF-CAS suggested that symptomatic women have a greater mean debris particle size compared with asymptomatic women, whereas the difference in debris size after carotid stenting is not statistically different between symptomatic versus asymptomatic men.<sup>43</sup> Accordingly, CREST data suggest that the main difference in stroke/death rates occurred among symptomatic women (7.5% vs. 2.7% in TF-CAS vs. CEA, respectively).<sup>39</sup> It should be noted that symptomatic women may have a different plaque morphology with greater embolic potential than their asymptomatic counterparts, which could predispose them to higher perioperative stroke risk with TF-CAS. The association of sex with outcomes after TCAR has not yet been described.

## Hostile Neck

Patients with prior neck surgery or radiation should be considered for carotid artery stenting to reduce risks of cranial nerve injury. Based on a systemic review of available literature through 2012, Kasivisvanathan et al. reported that TF-CAS is technically feasible in post-radiotherapy carotid stenosis and has a similar safety profile to that of nonirradiated necks when performed at a high-volume center.<sup>44</sup> Furthermore, in a meta-analysis of 27 articles including 533 patients, Fokkema et al. demonstrated that the perioperative risk of any cerebrovascular adverse event was similar for TF-CAS versus CEA (3.9% vs. 3.5%), but the risk of cranial nerve injury was substantially higher after CEA (9.2% vs. 0%).<sup>45</sup> Societal guidelines now include the presence of neck scarring and fibrosis from prior ipsilateral surgery such as radical neck dissection or prior CEA or external beam radiotherapy as an indication for considering TF-CAS over CEA.<sup>24–26</sup>

A hostile neck, including restenosis post-CEA, cervical spine immobility, and history of either neck irradiation or radical neck dissection, was one indication for TCAR in the ROADSTER trial, with 36% of patients having these anatomic constraints.<sup>18</sup> Despite the necessary common carotid dissection, only one transient cranial nerve injury (0.7%) occurred in the cohort.

## Restenosis

Based on data from CREST, approximately 6% of patients undergoing TF-CAS or CEA will demonstrate restenosis by 2 years postoperatively (see below).<sup>46</sup> Data from the Vascular Quality Initiative suggest that TF-CAS after prior CEA or TF-CAS is safe; estimated 30-day risk of stroke is 1.4%.<sup>47</sup> More recently, institutional data reporting outcomes following

TCAR for restenosis showed a 30-day stroke risk of zero%.<sup>48</sup> However, the clinical significance of restenosis, and indications for intervention, as well as the associated risks of adverse events after carotid artery stenting in patients with prior carotid revascularization, are currently unclear. At this time, we recommend that only patients with severe restenosis be considered for TF-CAS or TCAR, and those procedures should be performed by an expert at an institution with substantial experience.<sup>49,50</sup>

## Contraindications

Absolute contraindications to carotid artery stenting include ① active infection ② inability to gain vascular access, and ③ inability for the patient to tolerate antiplatelet therapy. Active infection confers a substantial risk of stent infection and should be avoided in all cases. Access difficulties can be minimized by using different approaches as indicated based on the patient's history, including femoral, brachial, or transcervical (see below). If none of these options are feasible, CEA should be considered. Dual antiplatelet therapy is essential to minimize the risks of acute stent thrombosis and/or embolization in the perioperative period, although the duration of therapy is controversial.<sup>51</sup> For the TCAR procedure, ④ bilateral femoral vein occlusions and common carotid artery disease are prohibitive as they preclude use of flow reversal and transcervical carotid access, respectively.

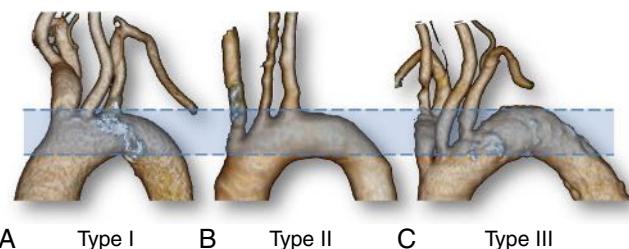
Relative contraindications include ⑤ older age (TF-CAS only), the presence of ⑥ circumferential carotid plaque with severe calcification, ⑦ severe carotid artery tortuosity (two 90-degree angles), ⑧ near occlusion of the carotid artery (i.e., string sign), and ⑨ significant aortic arch tortuosity or calcification (TF-CAS). ⑩ Inability to deploy a cerebral protection device is also a relative contraindication to TF-CAS, although this can be circumvented by using TCAR with flow reversal (see section on "Neuroprotection" later in this chapter). The high rate of peri-procedural stroke noted with TF-CAS in the European RCTs is largely attributed to variable use of EPDs. As such, the use of EPDs is now considered standard of care in the deployment of a transfemoral carotid stent.<sup>28</sup>

## ANATOMIC CONSIDERATIONS

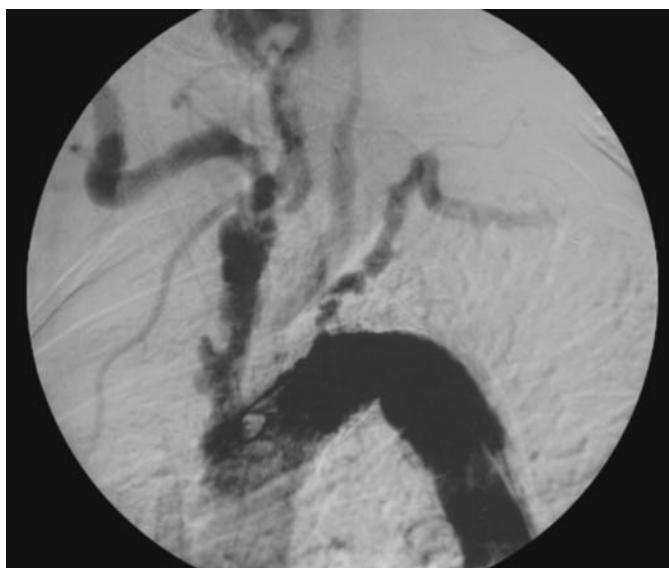
Anatomic factors can influence outcomes after carotid artery stenting. A comprehensive understanding of patient anatomy can help with appropriate selection and operative planning.

### Aortic Arch Pathology

① Aortic arch morphology can be classified into three different types depending on the position of the takeoff of the great vessels (Fig. 94.1). In type I aortic arches, the great vessels arise at or above the same horizontal plane as the outer curvature of the arch. In type II aortic arches, the origin of the innominate artery lies between the horizontal plane of the inner and outer curve of the aortic arch. In type III aortic arches, the innominate artery lies below the horizontal plane of the inner curvature of the aortic arch. As the takeoff moves more inferiorly



**Figure 94.1 Aortic Arch Classification.** (A) Type I: the great vessels arise above or in the same horizontal plane of the outer curvature of the arch. (B) Type II: the origin of the innominate artery lies between the horizontal planes of the outer and inner curvatures of the aortic arch. (C) Type III: the innominate artery lies below the horizontal plane of the inner curvature of the arch.



**Figure 94.2 Severe Atherosclerosis and Calcification in Aortic Arch (Shaggy Aorta).** The procedure should be terminated immediately; accessing the great vessels from a shaggy aortic arch should not be attempted due to potential catastrophic neurologic complications. Alternatively, a transcarotid approach will avoid the severe atheromatous arch.

(i.e., type II and type III configurations), vessel selection and the manipulation of sheath, balloon, and stent delivery system become more difficult. Reverse curvature catheters may be helpful for carotid cannulation in these scenarios. Type III aortic arch morphologies are particularly challenging and can lead to a higher risk of embolic events due to repeated and/or prolonged wire, catheter, and sheath manipulation leading to the disruption of aortic plaques.

② Aortic arches with extensive aortic wall atheroma and irregularities (i.e., shaggy aorta) and those with severe calcification (eggshell aorta) may also increase the technical complexity of TF-CAS and subsequently increase the patient's risk of stroke (Fig. 94.2). Shaggy aortas are composed of multiple atheromas that can break off upon contact with a wire or catheter, leading to atheroembolism. An eggshell aorta has poor compliance and is at risk for dissection or embolism that can similarly lead to devastating neurologic or visceral sequelae. The stiffness of an eggshell aorta can also make wire and catheter torqueability a challenge, leading to difficulty manipulating the stent delivery system into appropriate position within the target lesion. For



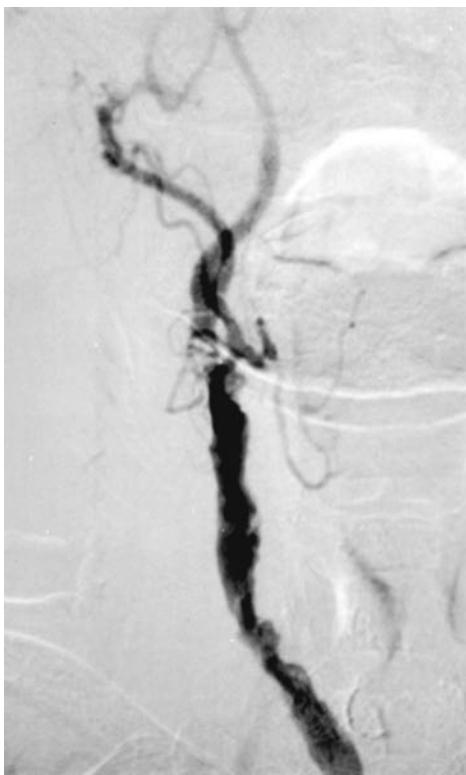
**Figure 94.3 Severe Tortuosity in the ICA.** Double 90-degree bends increase the difficulty of EPD placement and reduce its effectiveness and can cause a significant kick after stent placement.

patients with complex and/or high-risk aortic arch anatomy that have an indication for carotid artery stenting, TCAR should be considered over TF-CAS. TCAR completely avoids the manipulation of the aortic arch via direct transcervical CCA cannulation.

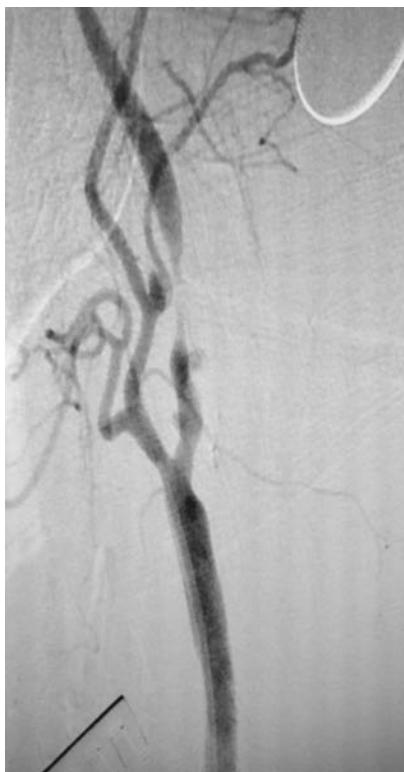
## Carotid Artery Morphology

① Carotid artery tortuosity and plaque burden can greatly affect the deliverability of both the EPD and the stent delivery system into the appropriate positions. Data from the EVA-3S trial suggests that the internal carotid artery (ICA)-CCA angulation of >60 degrees increases the relative risk of death or stroke after TF-CAS by 4.96 times (95% CI 2.29 to 10.74).<sup>52</sup> ICAs that are particularly tortuous, especially distally, can cause difficulty positioning the EPD sufficiently far enough away from the lesion to allow for stent deployment. Internal carotid arteries with severe angulation at the distal end of the stenotic lesion can cause flow limitations, or kinking due to significant changes in carotid morphology after stent deployment (Fig. 94.3). Tortuous vessels are also more prone to vasospasm at the end of the procedure.

② Carotid arteries with circumferential plaque burden and atheroma are noncompliant and thus can be difficult to access and can increase the risk of embolization during manipulation (Fig. 94.4). In addition, highly stenotic lesions with only a small area of flow (i.e., string sign; Fig. 94.5) may make stent delivery difficult and can result in inadequate stent expansion after deployment and subsequent early restenosis due to recoil.



**Figure 94.4** Severe plaque and atheroma burdens increase the risk of neurologic complications during access of the common carotid artery. These lesions should not be treated with stenting.



**Figure 94.5** Carotid Artery String Sign. These complex lesions should not be stented.

## Plaque Morphology

Both qualitative and quantitative aspects of carotid artery plaque morphology play a role in determining carotid artery stenting outcomes. In one meta-analysis, ICA stenoses >10 mm in length were associated with a 2.36 (95% CI 1.28 to 3.38) increased risk of death or stroke after TF-CAS compared to shorter lesions.<sup>52</sup> Data from CREST showed that in patients with longer lesion lengths ( $\geq 12.85$  mm), the risk of perioperative stroke or death was significantly higher for TF-CAS than CEA (OR 3.42; 95% CI 1.19 to 9.78).<sup>53</sup>

Carotid plaque echolucency, as assessed by duplex ultrasonography, has also been shown to increase the risk of stroke in TF-CAS.<sup>54,55</sup> Unfortunately, user variability results in poor reproducibility and reliability, and as such plaque morphology characteristics are not standardly used for risk-stratifying patients.<sup>56</sup>

## Contralateral Carotid Artery Occlusion

The presence of contralateral carotid artery occlusion should not influence the decision to perform a carotid stent. A subgroup analysis of 3137 patients undergoing TF-CAS who were enrolled in a German Carotid Artery Stent registry (ALKK-CAS) demonstrated a low rate of periprocedural death or major strokes among patients with contralateral carotid occlusion versus those without (1.6% vs. 1.4%).<sup>57</sup> Separate retrospective reviews of in-hospital data from two institutions similarly demonstrated both TF-CAS and CEA can both be performed with good perioperative results and acceptable midterm (approximately 2-year) mortality in patients with carotid artery stenosis and contralateral carotid artery occlusion.<sup>58,59</sup> A recent retrospective analysis from the SVS VQI demonstrated similar rates of in-hospital stroke among patients undergoing TCAR with a contralateral carotid artery occlusion compared to those with a patent contralateral carotid artery.<sup>60</sup> Notably, the risk of in-hospital stroke was higher for symptomatic patients with a history of stroke undergoing TCAR with a contralateral carotid artery occlusion. Current CMS guidelines cite contralateral carotid artery occlusion as one of the indications for carotid artery stenting, although this is not universally accepted as a high risk factor in the vascular surgical community.

## PREOPERATIVE CONSIDERATIONS

### Preoperative Imaging

Per CMS requirements, all patients require proof of diagnosis of carotid artery stenosis using angiography prior to stent placement.<sup>28</sup> This can occur either preoperatively or intraoperatively, as long as the patient has appropriate duplex ultrasound imaging to support a diagnosis of high-grade carotid artery stenosis. Duplex ultrasound allows for a comprehensive evaluation of extracranial anatomy and the hemodynamic significance of the CCA, ICA, and external carotid artery (ECA) lesions in most patients. In patients in which duplex ultrasound findings are inconclusive or unclear, magnetic resonance

imaging or computed tomographic angiography (CTA) may be helpful. CTA specifically can be helpful in patients in whom carotid plaque morphology or extent is unclear and can be used to measure the diameter of the CCA and the ICA to allow for preoperative planning of stent sizing, and to ensure that the patient meets the anatomic requirements.

## Timing of Intervention After Acute Stroke

Reported experience on the appropriate timing for carotid revascularization after an acute stroke largely supports CEA over carotid artery stenting. Data from a subgroup analysis of pooled data from two RCTs performed by the Carotid Endarterectomy Trialists Collaboration suggest that CEA confers maximum benefit if performed within 14 days of a neurologic event, assuming the patient's symptoms have stabilized and he/she is not severely disabled.<sup>61</sup> An analysis of pooled data from the EVA-3S, SPACE, and ICSS trials demonstrated that the risk of stroke or death with TF-CAS compared with CEA was highest among patients treated within seven days of symptoms.<sup>62</sup> The Carotid Acculink/Accunet Post-Approval Trial to Uncover Unanticipated or Rare Events (CAPTURE) registry also reported worse outcomes among patients undergoing TF-CAS within zero to 13 days of symptom onset, with an odds ratio of having 30-day complications of 2.52 (95% CI 1.33 to 4.78).<sup>63</sup> Most recently, the CSTC performed a pooled analysis of data from four randomized trials found that patients treated with TF-CAS within 7 days of symptom onset had a significantly higher risk of stroke or death compared to patients treated with CEA (8.3% vs. 1.3%).<sup>64</sup> This finding persisted among interventions performed after 7 days (7.1% vs. 3.6%). There are no data reporting outcomes after TCAR in a large cohort of recently symptomatic patients, especially within the first 2 weeks of symptom onset. Based on available data, the 2017 ESVS guidelines, and the SVS guidelines, recommend carotid revascularization within 14 days of symptom onset when appropriate, and support CEA over carotid stenting.<sup>25,27</sup>

## TECHNIQUE

### Perioperative Monitoring

Adequate hemodynamic monitoring in the operating room is essential during any carotid stenting procedure. All patients should have continuous electrocardiographic, pulse oximetry, and intraarterial pressure monitoring. Hypotension, hypertension, and any changes in oxygenation or cardiac tracings should be treated immediately.

TF-CAS should be performed with the patient awake using local anesthesia. This allows for continuous evaluation of neurologic function in the form of speech, alertness, and motor function, monitored by asking the patient frequent questions and having him/her squeeze a plastic toy in the contralateral hand. TCAR is frequently performed under general anesthesia but can be performed using sedation and local anesthetic in appropriate patients.

Adjunct methods of assessing neurologic status include continuous electroencephalogram (EEG) and/or transcranial Doppler (TCD). EEG can help to identify subclinical cerebrovascular changes that may aid in the early identification of a periprocedural stroke. However, the clinical utility of these changes, particularly in an awake patient with no clinical changes, is questionable. Thus, as with CEA, EEG is not essential. Although TCD is purported to differentiate the size and composition of emboli during cerebroembolic events, the accuracy is inconsistent and thus its use during carotid stenting is surgeon and center specific.<sup>65</sup>

### Arterial Access

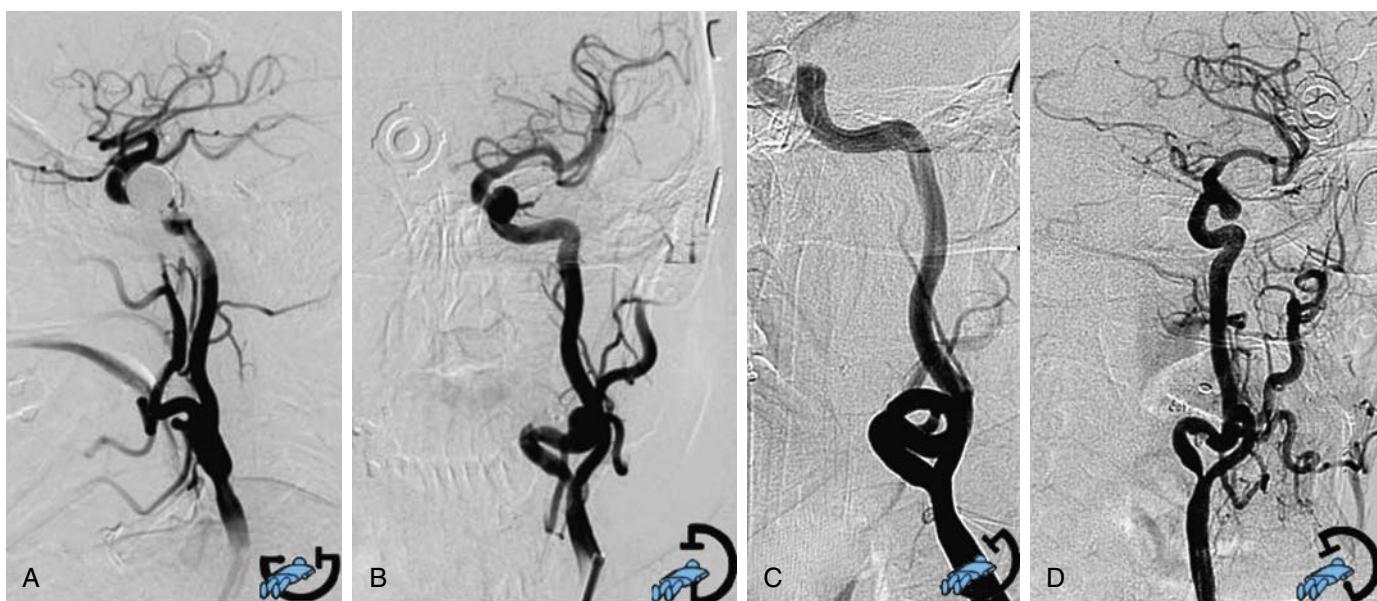
Traditional carotid stent access is transfemoral. In a right-handed operator, retrograde right transfemoral access using a 6-F introducer allows for the easiest catheter manipulation. Left transfemoral access should be the second choice if the right groin is inaccessible due to severe peripheral arterial disease, prior interventions, or other reasons. Once the working sheath is in place, a full dose of heparin should be administered.

Transcarotid access may also be used successfully in patients with hostile groin or aortic arch anatomy, or as the primary access point for TCAR. Percutaneous transcervical carotid artery access can be obtained using ultrasound guidance, with care taken to puncture the CCA at the base of the neck well below the bifurcation to allow for a stable working platform.<sup>66</sup> Alternatively, and more commonly, access to the CCA can be obtained in TCAR using surgical cutdown, allowing direct visualization of the puncture site.<sup>67</sup>

Less commonly, transbrachial or transradial access may be used. In these cases, a 6-F sheath should be used to access the artery using ultrasound guidance. Upper extremity access is indicated in patients who have either severe aortoiliac disease or shaggy or eggshell aortas and a hostile neck and are not a candidate for TCAR or CEA. A right transradial approach for patients with a bovine-type aortic arch or type III aortic arch morphology has been shown to be a safe and technically feasible approach to perform carotid artery stenting for left and right carotid artery lesions, respectively.<sup>68</sup>

### Target Lesion Access

For successful stent deployment, stable sheath access in the CCA must be obtained. In patients with remote arterial access, this can be achieved via two different platforms. In a sheath-based platform, a 6-F 90-cm Shuttle Select sheath (Cook, Inc. Indianapolis, IN) is placed in the descending aorta. A preshaped compatible 125-cm catheter (e.g., JB1, VTK, Headhunter, Simmons 1) is used to cannulate the CCA, and an exchange-length 0.035 guide wire is passed into the mid-CCA. The catheter is advanced carefully over the wire and positioned a few centimeters below the carotid bifurcation. At this point the sheath is advanced into position over the catheter. This telescopic technique provides better support and fewer working maneuvers. However, the size mismatch between the 6-F sheath and the 5-F catheter increase the risk of the sheath



**Figure 94.6** Standard Projections Showing Mild to Moderate Stenosis. The projection selected with rotational angiography shows severe stenosis. (A) Laterolateral. (B) Anteroposterior. (C) Left anterior oblique. (D) Right anterior oblique.

scraping plaque off or dissecting the arterial wall as the catheter is advanced (“snowplowing”), which can result in embolization. Alternatively, advancing a stiff glide wire into the ECA, followed by catheter withdrawal and dilator placement, can be used. The sheath and dilator are then advanced together into the mid-CCA. This technique carries a number of risks, including crossing the carotid bifurcation unprotected with a stiff wire, the dilator crossing the plaque at the bifurcation, and the need for several exchanges and manipulations.

In a guiding catheter-based platform, the CCA is directly accessed with a preshaped 6- or 7-F guiding catheter (e.g., multipurpose curve, vertebral or reversed-angle Vitek catheter), left in place for the duration of the procedure. This minimizes the number of wire and catheter exchanges needed to get the system in place, making it ideal for patients with shaggy aortic arches. The disadvantage is that the platform can be easily dislodged from the CCA during stent advancement if it is not positioned far enough into the vessel. To avoid this, a 0.014-inch coronary artery buddy wire placed in the ECA assists with platform stabilization.

For patients undergoing TCAR, access is obtained via an open CCA exposure. A 2- to 4-cm transverse or longitudinal incision is made just above the clavicle between the sternal and clavicular heads of the sternocleidomastoid. Dissection should take care to avoid the recurrent laryngeal nerve. A 3- to 4-cm segment of proximal CCA should be exposed and dissected circumferentially with an umbilical tape and Rumel tourniquet placed as proximally as possible. A U-stitch with 5-0 polypropylene suture is placed at the site of anticipated puncture, ideally >5 cm from the carotid bifurcation. A specialized micropuncture kit is used to obtain direct CCA access. Depending on the distance from the CCA access point to the carotid bifurcation, an 8-F sheath is inserted over a stiff

wire that is positioned either in the ECA or just proximal to the bifurcation. Gentle traction on the umbilical tape around the CCA throughout access and sheath insertion allows for stability and straightening of the artery for subsequent wire manipulation.

## Angiography

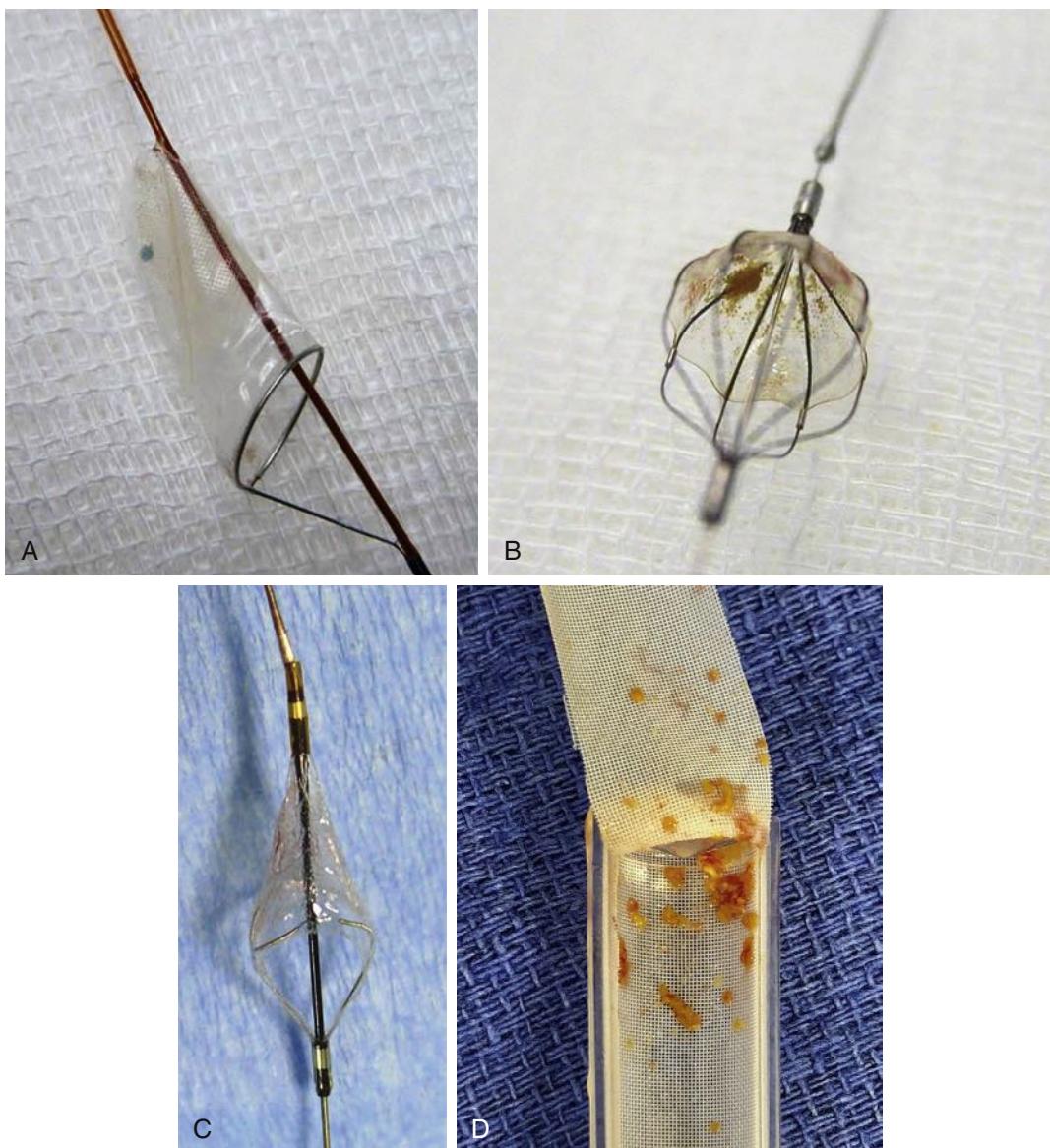
Once the working platform has been advanced into the CCA, an angiogram should be obtained through the guiding catheter or sheath using anteroposterior (AP) and lateral projections, and oblique views if needed to minimize vessel overlap (Fig. 94.6). Occasionally, rotational angiography can help to detect the true degree of stenosis. Precerebral and postcerebral images can detect distal branch embolization, although this is increasingly discouraged to minimize distal air embolization that can occur with cerebral angiography.

## Neuroprotection

After carotid angiography, neuroprotection should be employed. For TF-CAS, neuroprotection is usually established with the placement of an EPD. Current clinical guidelines all support the use of EPDs during TF-CAS,<sup>24–26</sup> and CMS mandates use of an EPD to qualify for reimbursement.<sup>28</sup> A number of different models have been developed and are available in clinical practice today.

### Filter-Type EPDs

Filter-type EPDs are the most commonly used design for TF-CAS and allow antegrade cerebral flow throughout the entire procedure (Fig. 94.7). The filter is passed across the carotid lesion over a wire and deployed distally in a straight section of



**Figure 94.7** Filter-Type Embolic Protection Devices. Different types of filters containing debris after retrieval. (A) EPI FilterWire. (B) Angioguard. (C) Emboshield. (D) ENROUTE Neuroprotection System. (A, Courtesy Boston Scientific, Natick, MA. B, Courtesy Cordis, Somerville, NJ. C, Courtesy Abbott Vascular, Redwood City, CA. D, Courtesy Caitlin Hicks, Baltimore, MD.)

the ICA to capture debris that may come loose during stenting. After the stent is successfully deployed, the filter is recaptured using a dedicated filter-retrieval system. The advantages are uninterrupted cerebral blood flow, continuous access to angiography throughout the procedure, and a low number of manipulations required within the carotid vessels. The main disadvantage is that the filter must be passed through the carotid lesion prior to deployment, which can be challenging in high-grade lesions and carries a risk of plaque dislodgement or rupture prior to filter deployment. The filter itself can also cause vasospasm or be difficult to retrieve if it becomes filled with embolic material.

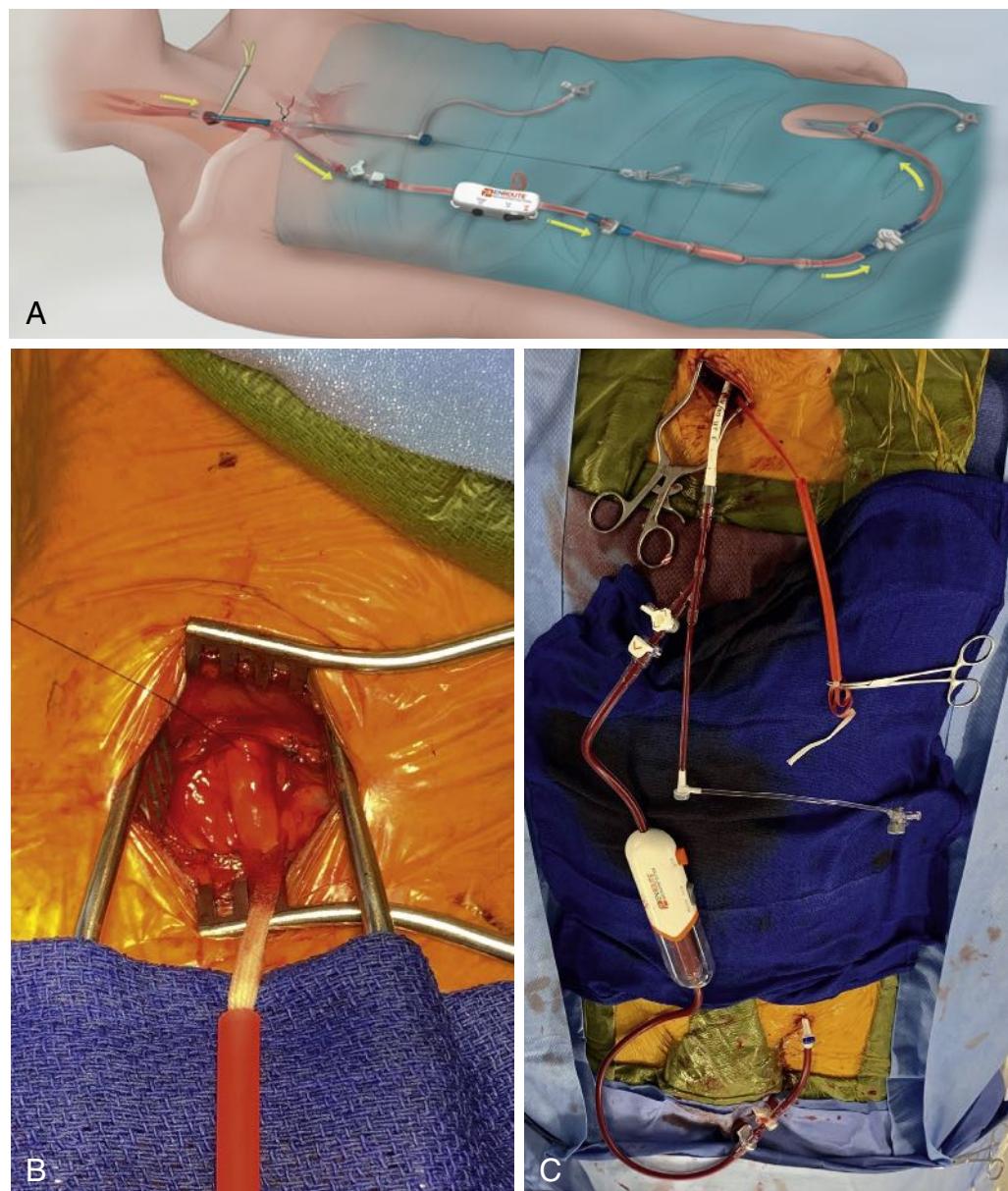
#### Flow Reversal Systems

Flow reversal, such as the ENROUTE system (Silk Road Medical, Inc.) used for TCAR, similarly employ the principles of

CCA and ECA occlusion, but an external shunt containing a filter to capture any debris is placed between the long introducer sheath in the CCA and a shorter introducer sheath in the femoral vein, allowing for continuous arteriovenous flow throughout the procedure.<sup>69,70</sup> The ENROUTE system allows for effective cerebral flow reversal at low and high flow while avoiding manipulation of the aortic arch and ECA ballooning (Fig. 94.8). *red 4-9mm vessel diameter & lesion*

#### Distal Occlusion Balloon

A distal occlusion balloon is inflated in the distal ICA, preventing antegrade blood flow during the procedure. After stent deployment, the blood and any debris material are flushed and suctioned endovascularly, and the balloon deflated and removed. Another alternative is a proximal protection EPD.



**Figure 94.8** (A) Transcarotid artery revascularization with cerebral flow reversal using the ENROUTE Neuroprotection System. In this system the arterial sheath is placed in the common carotid artery via cutdown (B), and a low-pressure venous sheath is placed in the femoral vein (C).

*Proximal Protection EPDs  $\Rightarrow$  prevents antegrade flow of debris during stenting*

This technique, such as the Mo.Ma (Invatec, Roncadelle, Italy) device, deploys an occlusion balloon in the CCA and the ECA using a single delivery catheter. This causes flow stasis during stent deployment. Debris is aspirated after the stent is deployed using intermittent syringe aspiration through the introducer sheath, after which the distal occlusion balloon is deflated.<sup>71</sup> The main advantage to proximal protection is that it prevents the need for crossing the carotid lesion prior to obtaining cerebral protection; however, a large sheath is required and 5% to 9% of patients will not tolerate flow stasis or reversal for prolonged periods of time.<sup>72</sup>

### Pre-dilatation

After neuroprotection is established, a decision must be made as to whether the lesion requires pre-dilation. When the stenosis

is severe, brief pre-dilation with a small (2.5 to 5.0 mm) coronary artery balloon to 4 to 6 atm of pressure may assist in stent positioning and deployment. Rarely, pre-dilation may be necessary to pass a filter-type EPD. In these cases, a proximal protection EPD should be considered.

### Stent Selection and Delivery

Carotid artery stents are self-expandable, made of either stainless steel (a cobalt alloy) or nitinol (a nickel–titanium alloy). Stent selection depends on the carotid anatomy and plaque characteristics. For tortuous arteries, flexible stents may be preferred to prevent kinking. In contrast, stents with better scaffolding may be preferable for plaques at risk of protruding and causing distal embolization. In general, nitinol stents have a higher radial force and may be more effective for highly calcified plaques with poor compliance. A recent analysis of data

from the ICSS compared the long-term risk of restenosis and stroke between patients with open-cell ( $N = 352$ ) versus closed-cell ( $N = 362$ ) stents and found that moderate or higher stenosis occurred more often with closed-cell configurations (open-cell 35.5% vs. closed-cell 46.0%,  $P < 0.05$ ), although this was not associated with a higher rate of stroke (hazard ratio, 0.78; 95% CI 0.35 to 1.75).<sup>73</sup> Conversely, a meta-analysis of RCTs and cohort studies showed that open-cell stents were associated with higher rates of new post-procedural ischemic lesions on MRI (relative risk 1.25, 95% CI 1.02 to 1.54,  $P = 0.03$ ), but again with no difference in stroke rates (relative risk 1.00, 95% CI 0.76 to 1.31,  $P = 0.99$ ).<sup>74</sup> There is currently no consensus regarding preferred stent type.<sup>75-78</sup>

## Post-dilatation

When TF-CAS was first adapted, it was performed using the basic tenants of peripheral arterial interventions. Balloon dilation was performed both prior to and after the stent was placed. The theory behind this practice was that pre-stenting dilation disrupts the plaque causing the lesion and allows the stent to be placed, and post-stenting ballooning allows for full stent expansion. However, an analysis using data from the VQI suggests that post-stent dilation may increase perioperative hemodynamic depression, stroke and death rates in patients undergoing TF-CAS. Compared with pre-stent ballooning only, the pre-stent and post-stent ballooning technique was associated with a 2.1-odds increase in hemodynamic depression (95% CI 1.51 to 3.01) and 2.4-odds increase in perioperative stroke and death (95% CI 1.01 to 5.620).<sup>79</sup> Continued carotid artery stent expansion has been demonstrated by duplex up to 30 days after deployment even without post-stent ballooning.<sup>80</sup> Based on these data, we suggest post-stent balloon dilation be reserved for lesions with severe residual stenosis after stent deployment for TF-CAS and TCAR.

## Completion Angiography and Retrieval of EPD

After the stent deployment, completion angiogram should be performed in two different planes while neuroprotection is still in place to evaluate for accuracy of positioning, residual stenosis, vasospasm at the distal stent endpoint, and filling defects inside the stent due to plaque protrusion. Attention should be paid to the distal ICA, which may spasm after filter-based EPD removal. If spasm occurs, waiting a few minutes usually allows for resolution, with rare need for nitroglycerin (100 to 200 µg) through the guiding sheath into the CCA to assist in vasorelaxation.

## Access Hemostasis

Heparin reversal with protamine has not been shown to increase the risk of MI, stroke, pulmonary embolism, or death in a number of CEA studies. Recent reviews of data from the VQI demonstrated that protamine can be used safely in TF-CAS and TCAR to reduce the risk of perioperative bleeding complications without increasing the risk of thrombotic events.<sup>81-85</sup>

For TF-CAS, access hemostasis should be obtained using percutaneous closure assist devices and/or manual pressure. For TCAR, the CCA arteriotomy is closed using the previously placed U-stitch without re-clamping the artery.

## PERIOPERATIVE MEDICATIONS

### Anticoagulation

For TF-CAS, patients should be fully anticoagulated with unfractionated intravenous heparin (70 to 100 units/kg) once sheath access is obtained and before starting catheter manipulation within the aortic arch. For TCAR, patients should be fully anticoagulated prior to accessing the CCA with the micropuncture needle. Activated clotting times (ACTs) should be followed and should not exceed 300 seconds to prevent hemorrhagic stroke with reperfusion following the procedure.

### Anticholinergics

Hypotension with bradycardia, or hemodynamic depression, may occur after balloon dilation or with stenting in response to carotid baroreceptor stretching. This is particularly common in older patients with long, heavily calcified plaques, and can be treated, when necessary, using atropine (0.4 to 1 mg) or glycopyrrolate (0.1 to 0.3 mg). During TCAR, pre-treatment with an anticholinergic prior to predilation is routine unless the patient has a contraindication. Hemodynamic depression may be associated with an increased risk of adverse periprocedural events including stroke<sup>86,87</sup> and should be avoided whenever possible. In patients who develop severe hypotension and bradycardia after balloon dilatation and/or stent deployment, aggressive volume resuscitation and intravenous atropine (0.4 to 1 mg) may be administered. Less commonly, vasopressors, including intravenous phenylephrine (1 to 10 µg/kg per minute) or dopamine (5 to 15 µg/kg per minute) infusion, may be necessary.<sup>84</sup> Persistent hypotension can occur, lasting 24 to 48 hours. Risk factors for persistent hypotension include distance from the carotid bifurcation to maximum stenotic lesion ( $\leq 10$  mm), type of stenosis (eccentric), plaque morphologic features (echogenic), and calcification at the carotid bifurcation.<sup>88</sup> In these cases, management generally involves pharmacologic support until the carotid baroreceptors adapt to the radial force of the stent, and the resulting hemodynamic depression is resolved.

### Vasodilators

For TF-CAS, intravenous vasodilators should be used throughout the procedure to maintain systolic blood pressure  $< 180$  mm Hg to minimize the risk of intracranial hemorrhage (ICH).<sup>24</sup> Small volumes of nitroglycerin (100 to 200 µg) may also be instilled through the guiding sheath into the CCA to assist in vasorelaxation in cases of persistent ICA spasm after EPD removal. However, excessive vasodilation in combination with hemodynamic depression after balloon dilation may exacerbate the prolonged hypotension that can be observed in some carotid stenting patients postoperatively.

## Vasopressors

For TCAR, intraoperative hypertension is preferred to improve cerebral perfusion during flow reversal. In addition to pre-treating patients with an anticholinergic prior to balloon predilation, vasopressors should be administered to maintain a systolic blood pressure goal of >160 mm Hg while the CCA is clamped. Intravenous phenylephrine (1 to 10 µg/kg per minute) is effective due to its short half-life.<sup>89</sup>

## Antiplatelet Therapy

Data from coronary revascularization studies have demonstrated a protective benefit with clopidogrel and aspirin for patients undergoing percutaneous coronary intervention, particularly in high-risk populations.<sup>90</sup> Given that periprocedural stroke is the highest concern with carotid stenting, current guidelines recommend dual antiplatelet therapy with aspirin (81 to 325 mg daily) plus clopidogrel (75 mg daily) for at least 4 days before and a minimum of 30 days after surgery for TF-CAS. For patients undergoing TCAR, clopidogrel (75 mg daily) should be started at least 7 days pre-procedure.<sup>27</sup> In urgent cases, a 450-mg loading dose of clopidogrel can be given four hours prior to the procedure.<sup>27</sup> For patients intolerant of clopidogrel, ticlopidine (90 mg twice daily) may be used.<sup>76</sup> Global intolerance to dual antiplatelet therapy (or single antiplatelet therapy with systemic anticoagulation) is a contraindication to carotid stent placement.

## Statins

All patients undergoing evaluation for carotid stenting should be initiated on statin therapy preoperatively. In a meta-analysis of 12 retrospective and 3 prospective trials including 223,010 patients, preoperative statin therapy was shown to be associated with a 59% reduction in risk of mortality after vascular surgery.<sup>77</sup> Statins have also been shown to be effective at reducing the risk of cardiovascular events in women and men<sup>78</sup> and the protective benefit likely occurs within a month of starting treatment.<sup>91</sup> Patients undergoing TF-CAS who are on preprocedural statin therapy have been shown to have a lower incidence of stroke, MI, and death within 30 days of surgery. Although the optimal timing, dosing, and agents are unclear, consensus guidelines suggest that all patients undergoing carotid revascularization should be initiated on statin therapy as early as possible.<sup>92</sup> There are no data quantifying the benefit of statin therapy among patients undergoing TCAR, but the instructions for use for the ENROUTE system specify that atorvastatin (minimum 40 mg daily) should be taken for at least seven days pre-procedure, or a loading dose of 80 mg can be given at least 12 hours prior to procedure.

## COMPLICATIONS

### Technical Complications

#### Acute Stent Thrombosis

Acute thrombosis of the stent is an emergency because it carries substantial risk of clot propagation and thromboembolic

stroke. It can be caused by stent misplacement, severe carotid artery recoil due to annular calcification, or massive plaque protrusion through the stent struts. When it occurs, the procedure should be immediately converted to CEA. Rapid reestablishment of cerebral perfusion via endarterectomy is associated with a good neurologic outcome.<sup>93</sup>

#### Kinking

Kinking may occur at the endpoints of the stent, especially when placed in vessels with severe tortuosity. Usually, this is visible on the completion angiogram. If the kink is mild and not limiting antegrade blood flow, it can be observed, as carotid remodeling occurs up to 3–6 months postoperatively and may reduce or eliminate the kink over time.<sup>94</sup> If a more severe kink leads to diminished flow, post-stenting balloon angioplasty can be performed and, if necessary, an additional stent may be placed.

#### Carotid Dissection

A carotid dissection identified on completion angiogram can also be observed and may be managed by observation, balloon apposition of the stent (i.e., post-stent dilation), or placement of an additional stent, depending on the location and extent. If the dissection is flow-limiting, use of an additional stent is indicated.<sup>75</sup> The goal of stenting for dissection is to tack down the entry tear, which may occur proximal (more common in TCAR) or distal to the stent. When a dissection is visualized, it is critical that wire position be maintained within the true lumen until the entry tear is treated and completion angiogram confirms restoration of flow.

## Neurologic Complications

Neurologic complications are the most common complications following carotid artery stenting and include embolism, ICH, hyperperfusion, and neurocognitive effects.

#### Embolism

Embolism is the most common and feared complication following carotid stenting and is usually the result of an atherosclerotic plaque or catheter-generated thrombus. The diagnosis is usually made as a result of changes in the intraoperative neurologic exam; when this occurs, an angiogram should be obtained immediately to visualize the occlusion. Depending on the location of the embolus, potential neurorescue procedures include ① catheter-directed chemical thrombolysis with urokinase or recombinant tissue plasminogen activator, ② thrombus maceration, ③ aspiration thrombectomy, ④ snare removal, and/or ⑤ glycoprotein IIb/IIIa receptor inhibitor administration. The results of each of these salvage therapies are variable, and embolus prevention remains the mainstay of carotid stenting procedures.<sup>95</sup>

#### Intracranial Hemorrhage

Intracranial hemorrhage is a rare but potentially devastating complication of carotid stenting. In a review of TF-CAS versus CEA using data from the Nationwide Inpatient Sample, TF-CAS was found to be associated with a six-fold higher risk of ICH than CEA.<sup>96</sup> However, these findings have not been

confirmed with RCTs. Data from the EVA-3S, SPACE, and CREST trials have all shown relatively equivalent risk of ICH after TF-CAS versus CEA (<1%). There is some suggestion from CREST that when ICH occurs after TF-CAS they are more severe than ICH after CEA, which may be attributable to the use of dual antiplatelet therapy.<sup>46</sup> Risk factors for ICH after carotid stent placement include patients with symptomatic carotid stenosis and those with bilateral severe carotid stenoses with associated hypertension.<sup>97</sup>

### Hyperperfusion

Hyperperfusion is a relatively uncommon complication of carotid stenting, occurring in 1% to 2% of patients. Patients often present initially with an ipsilateral headache that, in severe cases, can develop into neurologic changes and/or CT imaging showing ipsilateral cerebral edema without evidence of stroke.<sup>98</sup> Symptoms usually develop at a mean of 10 hours postoperatively and are more common in patients with hypertension or recent TIA.<sup>98</sup> The concern is progression to ICH. Treatment is largely supportive, with a focus on blood pressure control.

### Subclinical Neurocognitive Complications

Microembolic events that do not result in a clinical deficit may complicate carotid stenting. In a small prospective study, new lesions were identified by diffusion-weighted imaging in 71% of TF-CAS patients, compared with 4% of CEA patients.<sup>99</sup> The concern is that these microembolic events could lead to accelerated cognitive loss and premature senescence.<sup>100</sup> To date, existing data do not suggest that microembolic events after TF-CAS result in worse long-term neurocognitive function.<sup>101–103</sup> The longer-term effects of microembolic events that occur with carotid stenting remain to be seen.<sup>104</sup>

### Cardiovascular Complications

The risk of periprocedural MI after TF-CAS is consistently lower than that after CEA based on RCT data.<sup>5,7,16</sup> The benefit of TCAR compared to CEA for preventing MI has not been established. However, either TF-CAS or TCAR may be a good option for carotid revascularization in patients who are at high risk for having an adverse cardiac event with open surgery. Hemodynamic depression can occur, but this rarely results in ischemic events or alterations in blood pressure in the long term.<sup>105,106</sup>

### Access Complications

As with any endovascular procedure, access complications, including hematoma formation, pseudoaneurysm, peripheral embolization, and access site infections, can occur. A recent analysis of data from the VQI reported overall access site bleeding complications of 3.8% for TF-CAS and 3.5% for TCAR ( $P = 0.55$ ), although the bleeding complications with TCAR more frequently required intervention (0.8% vs. 1.3%,  $P = 0.04$ ).<sup>22</sup> Most access site complications resulting from carotid stenting are self-limited and can be managed expectantly and decrease with operator experience.<sup>107</sup> The use of duplex ultrasound to guide access, reversing anticoagulation at the end of the case,

and percutaneous closure devices following TF-CAS have all contributed to minimizing access site bleeding and pseudoaneurysm complications.

### Stent Fracture

Stent fracture has been reported after carotid stenting in approximately 9% of cases,<sup>108</sup> and occurring from 0 to 37 months after the procedure. Eleven percent of patients with stent fractures were symptomatic, including ischemic stroke in 33%, neck hematoma in 33%, and nonspecific symptoms in the remainder.<sup>108</sup> Carotid artery restenosis occurred in 55% of stent fracture cases, and 58% required reintervention.<sup>108</sup> An analysis from the ACT-I trial showed that carotid stent fractures were not associated with adverse clinical events.<sup>109</sup> The majority of stent fractures were successfully treated by *de novo* stent placement, although balloon angioplasty, CEA, carotid bypass, anticoagulation, and observation alone have also been reported.

### Restenosis

One of the major concerns with carotid stenting is that of long-term restenosis. The Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) trial reported a 10-year restenosis rate of 30.7%, compared with 11% in the CEA group.<sup>110</sup> However, the endovascular arm of CAVATAS used carotid stents in only 26% of the patients treated; the remainder underwent balloon angioplasty alone.<sup>111</sup> More recent data from the CREST trial suggest a much lower incidence of restenosis following TF-CAS; at 2 years postoperatively, carotid artery restenosis or occlusion occurred in 6.0% of TF-CAS patients and 6.3% of CEA patients.<sup>46</sup> The longer-term risks of restenosis with TF-CAS are unknown, but high-risk features include diabetes, female sex, and dyslipidemia.<sup>46</sup> Patients with carotid stenosis that is longer than 0.65 times the CCA diameter have also been shown to be at increased risk of restenosis following TF-CAS.<sup>112</sup> Restenosis following TCAR has not yet been described due to lack of available long-term follow-up.

## POSTOPERATIVE SURVEILLANCE

Duplex ultrasound should be performed in all carotid stenting patients 3 to 6 weeks postoperatively.<sup>113</sup> This allows for the establishment of new baseline flow, which is particularly important because the presence of stents has been shown to alter duplex flow velocity measurements.<sup>114</sup> Although no definitive RCT data exist, repeat surveillance is recommended 6 months after initial study and then annually thereafter for all patients undergoing carotid stenting.<sup>113</sup>

## ONGOING TRIALS

There are currently a number of trials designed to compare outcomes for TF-CAS and TCAR versus CEA for the treatment of carotid stenosis. The Asymptomatic Carotid Surgery Trial 2 (ACST-2)<sup>115</sup> and Carotid Revascularization for Primary Prevention of Stroke (CREST-2)<sup>116</sup> are designed to assess

**TABLE 94.5** Recommended Techniques to Reduce Periprocedural Adverse Events During Carotid Artery Stenting

| Timing         | Technique                                   | Comment  |
|----------------|---|--|
| Preoperative   | <u>Dual antiplatelet therapy</u>            | All patients should be initiated on dual antiplatelet therapy with aspirin (81 to 325 mg daily) plus clopidogrel (75 mg daily) for at least four days before TF-CAS <sup>24,26,27,75</sup> and at least 7 days before TCAR   |
|                | <u>Statin therapy</u>                       | All patients undergoing carotid revascularization should be initiated on statin therapy as early as possible <sup>92</sup>   |
|                | <u>Beta-blocker therapy</u>                 | Preprocedural beta blocker use for >30 days is associated with a reduction in periprocedural stroke/death risk compared to nonuse <sup>106</sup>   |
|                | <u>Adequate imaging</u>                     | Consider computed tomography angiography in patients with potential complex aortic or carotid anatomy to confirm they meet anatomic criteria for stenting and to allow for better operative planning   |
| Intraoperative | <u>Frequent awake neurologic assessment</u> | Allows for early detection of stroke   |
|                | <u>Stable sheath access</u>                 | Consider TCAR in patients with challenging aortic anatomy to reduce stroke risk <sup>18</sup>  |
|                | <u>Emboilic protection devices</u>          | Consider proximal protection EPDs (e.g. flow reversal) to reduce risk of embolic lesion caused by initial crossing of the lesion <sup>87</sup>   |
|                | <u>Appropriate blood pressure control</u>   | For TF-CAS, vasodilators should be used to maintain systolic blood pressure <180 mm Hg to minimize risk of ICH. <sup>24</sup> For TCAR, vasopressors should be used to maintain systolic blood pressure >160 mm Hg to improve cerebral perfusion during flow reversal. |
|                | <u>Anticholinergics</u>                     | Pre-treatment with an anticholinergic prior to predilation should be used to suppress the hemodynamic response to stretching of carotid baroreceptors  |
|                | <u>Appropriate stent sizing</u>             | The diameter of the stent should be slightly oversized to the largest portion of the carotid artery, which is usually the distal common carotid artery   |
|                | <u>Avoid post-stent dilation</u>            | All sizing should be confirmed by intraoperative angiography even if preoperative computed tomography angiography is obtained  |
|                | <u>Completion angiography</u>               | Hemodynamic depression and perioperative stroke and death have been shown to be lower without post-stent dilation <sup>79</sup>  |
|                | <u>Dual antiplatelet therapy</u>            | Confirm stent placement and check for distal internal carotid artery spasm   |
| Postoperative  |   | Aspirin (81–325 mg daily) plus clopidogrel (75 mg daily) is recommended for a minimum of 30 days after TF-CAS or TCAR <sup>24,26,75</sup>  |

outcomes following CEA or stenting vs. best medical therapy in patients with asymptomatic carotid artery stenosis.<sup>115</sup> The European Carotid Surgery Trial 2 (ECST-2) will compare carotid revascularization (CEA or stent) versus best medical therapy for the treatment of symptomatic or asymptomatic moderate or severe carotid stenosis.<sup>117</sup> The Reverse Flow Used During Carotid Artery Stenting Procedure 2 (ROADSTER 2) is a post-approval study to assess the efficacy of TCAR.<sup>118</sup> Preliminary results report 30-day rates of stroke and stroke/death/MI of 0.6% and 1.7%, respectively.<sup>119</sup>

## CONCLUSIONS

While TF-CAS has fallen somewhat out of favor due to high stroke rates, the advent of TCAR has reinvigorated the field of carotid stenting. Both TF-CAS and TCAR can be performed safely in select patients with appropriate neuroprotection and medical management (Table 94.5). There is a paucity of RCT data for TCAR compared to other carotid revascularization strategies, but data from observational ROADSTER trials and the Vascular Quality Initiative TCAR Surveillance Project are encouraging. Long-term results of both TF-CAS and TCAR remain to be established, especially with regard to patency, and

the role of carotid stenting for the treatment of asymptomatic carotid artery stenosis needs further investigation.

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*The International Carotid Stenting Study (ICSS) is a multicenter, randomized, British trial designed to compare TF-CAS versus CEA for patients with >50% symptomatic carotid artery stenosis. This paper describes the long-term outcomes of the study (median follow-up time 4.2 years), which demonstrated that the risk of fatal or disabling stroke was similar for TF-CAS and CEA.*

Brott TG, Hobson 2nd RW, Howard G, et al. Stenting versus endarterectomy for treatment of carotid-artery stenosis. *N Engl J Med*. 2010;363(1):11–23.

*This paper describes the original outcomes of the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST), which is the largest multicenter, randomized trial designed to compare outcomes for TF-CAS versus CEA to date. At a median follow-up of 2.5 years, there was no significant difference in the estimated 4-year rates of the primary composite endpoint (stroke, MI, or death from any cause during the periprocedural period up to 30 days or any ipsilateral stroke within 4 years after randomization) between groups. However, notably, the data from CREST demonstrated that TF-CAS had a higher risk of periprocedural stroke, whereas CEA had a higher risk of periprocedural MI.*

Brott TG, Howard G, Roubin GS, et al. Long-term results of stenting versus endarterectomy for carotid-artery stenosis. *N Engl J Med.* 2016;374(11):1021–1031.

*This paper describes the long-term follow-up data from the CREST trial. After 10 years of follow-up, there were no significant differences between TF-CAS versus CEA for the risk of perioperative stroke, myocardial infarction, or death and subsequent ipsilateral stroke. The rate of post-procedural ipsilateral stroke also did not differ between groups.*

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*This paper describes the 1-year results of the initial prospective, single-arm multicenter clinical trial evaluating the use of TCAR for high-risk symptomatic and asymptomatic patients, with an ipsilateral stroke incidence of 0.6% and death of 4.2% at 1 year postoperatively.*

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*This is a multicenter, randomized, noninferiority French trial designed to compare TF-CAS versus CEA for patients with >60% symptomatic carotid artery stenosis. This paper describes the trial's 4-year follow-up, which demonstrated worse outcomes with TF-CAS due to significantly higher rates perioperative stroke/death.*

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*This is a population-based study of patients in the Vascular Quality Initiative undergoing TF-CAS or TCAR between 2016 and 2019 that found lower rates of perioperative stroke/death with TCAR compared to TF-CAS.*

A complete reference list can be found online at [www.expertconsult.com](http://www.expertconsult.com).

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# Endovascular Management of Large Vessel Occlusion in Acute Ischemic Stroke

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## Abbreviations and Acronyms

ASPECTS, Alberta Stroke Program Early CT Score; ASTER, Contact Aspiration vs. Stent Retriever for Successful Revascularization; CAST, Committee on Subspecialty Training; COMPASS, Comparison of Direct Aspiration vs. Stent Retriever as a First Approach; CPSS, Cincinnati Prehospital Stroke Severity Scale; CSC, Comprehensive Stroke Center; CT, computed tomography; CTA, CT angiography; CTP, CT perfusion; ECASS, European Cooperative Acute Stroke Study; ELVO, emergent large vessel occlusion; DWI, diffusion-weighted imaging; ENDOLOW, Endovascular Therapy for Low NIHSS Ischemic Strokes; FDA, Food & Drug Administration; ICA, internal carotid artery; IV, intravenous; LAMS, Los Angeles Motor Scale; LVO, large vessel occlusion; MCA, middle cerebral artery; MR, magnetic resonance; MRA, MR angiography; MRI, MR imaging; MRP, MR perfusion; NCCT, noncontrast computed tomography; NIHSS, National Institutes of Health Stroke Scale; Penumbra Separator 3D, A Randomized, Concurrent Controlled Trial to Assess the Safety and Effectiveness

of the Separator 3D as a Component of the Penumbra System in the Revascularization of Large Vessel Occlusion in Acute Ischemic Stroke; RACE, Rapid Arterial Occlusion Evaluation; rtPA, recombinant tissue plasminogen activator; TESLA, Thrombectomy for Emergent Salvage of Large Anterior Circulation Ischemic Stroke; TSC, thrombectomy-capable stroke center.

## INTRODUCTION

Endovascular treatment of acute ischemic stroke from large vessel occlusion (LVO) has been revolutionized by innovations in mechanical thrombectomy devices and by knowledge of appropriate selection of patients for these procedures. Class I evidence in several randomized trials has proven the superiority of endovascular therapy over medical management alone, including the use of intravenous (IV) thrombolysis. This has created fundamental changes in stroke systems of care worldwide. In this chapter, we discuss the evaluation and modern treatment

paradigms of patients eligible for thrombectomy and overview stroke systems of care and the structure of a stroke center team.

## EVALUATION AND TRIAGE OF LARGE VESSEL OCCLUSION

Acute ischemic stroke is a true neurologic emergency. Because the history is often limited due to the patient's inability to provide a detailed description of the event, lack of witnessed onset of stroke symptoms, or medical history, the decision to proceed with endovascular stroke intervention is often based on minimal information. Stroke severity is the most critical component. Patient age and baseline level of functioning, although helpful in determining the outcome of stroke intervention, are often not available immediately upon the patient's presentation to the emergency department.

### Clinical Examination

**1** The National Institutes of Health Stroke Scale (NIHSS) is the most frequently used scale for evaluation and triage of stroke patients.<sup>1</sup> This scale is composed of 11 items such as level of alertness, motor, sensory or speech deficits, each of which is scored based on the severity of specific neurological deficits (Table 95.1). According to most stroke guidelines, candidates for endovascular therapy generally have a score of 6 or above. In most endovascular trials and registries, the majority of patients who are treated with endovascular therapy present with

severe debilitating neurologic deficits; as such, their average NIHSS scores typically fall within a 15–20 range.<sup>2</sup> The role of endovascular therapy in patients with "mild" neurological deficits (that is, NIHSS score of <6) is not well established. Although evidence from post-hoc analysis suggests that endovascular therapy may be of benefit in this patient population, it has not been confirmed in randomized clinical trials specifically targeting this population.<sup>3</sup> Ongoing trials, such as Endovascular Therapy for Low NIHSS Ischemic Strokes (ENDOLLOW; ClinicalTrials.gov identifier: NCT04167527), are evaluating the benefit of endovascular therapy in patients with mild neurologic deficits.

In addition to the NIHSS, there are multiple clinical tools that are designed to predict the likelihood of emergent large vessel occlusion (ELVO) as the cause of stroke in order to identify patients who are most likely to benefit from thrombectomy. Such clinical tools are often used in the prehospital setting when the first responders need to make a swift decision regarding the most appropriate stroke triage in each individual case. The Los Angeles Motor Scale (LAMS),<sup>4</sup> Cincinnati Prehospital Stroke Severity Scale (CPSS),<sup>5</sup> and Rapid Arterial Occlusion Evaluation (RACE)<sup>6</sup> are some of the examples of such ELVO detection tools (Tables 95.2–95.4).

### Imaging

The two main questions that various stroke imaging modalities are designed to answer are whether a patient is experiencing a stroke from ELVO and whether endovascular therapy

**TABLE 95.1** The National Institutes of Health Stroke Scale (NIHSS)

| Category  | Score Description  |
|---|--|
| Level of consciousness (LOC)                    | 0 – alert; 1 – easily arousable; 2 – requires repeated stimulation; 3 – unresponsive                               |
| LOC questions (current month and patient's age) | 0 – answers both questions correctly; 1 – one question correctly; 2 – neither question correctly                   |
| LOC one-step commands                           | 0 – performs both commands correctly; 1 – one command correctly; 2 – neither command correctly                     |
| Gaze  | 0 – normal gaze, no palsy; 1 – partial gaze palsy; 2 – forced deviation or total palsy                             |
| Visual fields                                   | 0 – intact vision; 1 – partial hemianopia; 2 – complete hemianopia; 3 – bilateral hemianopia or cortical blindness |
| Face  | 0 – symmetrical; 1 – minor paralysis; 2 – partial paralysis; 3 – complete paralysis                                |
| Motor arm                                       | 0 – no drift; 1 – drift; 2 – some effort against gravity; 3 – no effort against gravity; 4 – no movement           |
| Motor leg                                       | 0 – no drift; 1 – drift; 2 – some effort against gravity; 3 – no effort against gravity; 4 – no movement           |
| Limb ataxia                                     | 0 – absent; 1 – present in one limb; 2 – present in two limbs  |
| Sensory   | 0 – normal sensation; 1 – mild or moderate sensory loss; 2 – severe or total sensory loss                          |
| Language  | 0 – no aphasia; 1 – mild or moderate aphasia; 2 – severe aphasia; 3 – global aphasia or patient is mute            |
| Dysarthria                                      | 0 – normal; 1 – mild or moderate dysarthria; 2 – severe dysarthria   |
| Extinction and inattention                      | 0 – normal; 1 – deficit in one modality; 2 – deficit in more than one modality or profound deficit                 |

Adapted from [https://www.ninds.nih.gov/sites/default/files/NIH\\_Stroke\\_Scale.pdf](https://www.ninds.nih.gov/sites/default/files/NIH_Stroke_Scale.pdf)

**TABLE 95.2 Los Angeles Motor Scale (LAMS)**

| Category             | Score description  |
|----------------------|--|
| Facial smile/grimace | 0 - Normal<br>1 - Droop, right<br>1 - Droop, left  |
| Grip                 | 0 - Normal<br>1 - Weak grip, right<br>2 - No grip, right<br>1 - Weak grip, left<br>2 - No grip, left     |
| Arm strength         | 0 - Normal<br>1 - Drift, right<br>2 - Falls rapidly, right<br>1 - Drift, left<br>2 - Falls rapidly, left |

Adapted from Naziel B, Starkman S, Liebeskind DS, Ovbiagele B, Kim D, Sanossian N, et al. A Brief Prehospital Stroke Severity Scale Identifies Ischemic Stroke Patients Harboring Persisting Large Arterial Occlusions. *Stroke*. 2008;39:2264–2267. <https://doi.org/10.1161/STROKEAHA.107.508127>.

**TABLE 95.3 Cincinnati Prehospital Stroke Severity Scale (CPSS)**

| Category  | Score    |
|---|----------|
| Conjugate gaze deviation  | 2 points |
| Incorrectly answers at least one question (age, current month) and does not follow commands | 1 point  |
| Cannot hold arm up (right or left or both) for 10 seconds                                   | 1 point  |

Adapted from Liferidge AT, Brice JH, Overby BA, Evenson KR. Ability of laypersons to use the Cincinnati Prehospital Stroke Scale. *Prehosp Emerg Care*. 2004;8(4):384–387.

is indicated. Approximately 15%–20% of acute strokes are caused by **ELVO**,<sup>7</sup> and computed tomography angiography (CTA) is currently the most widely used modality performed in the emergency department to confirm or exclude any potential targets for thrombectomy. The choice of imaging modality to determine whether thrombectomy should or should not be performed in an individual stroke caused by ELVO varies greatly and has been a subject of ongoing debate. The **Alberta Stroke Program Early CT Score (ASPECTS)**,<sup>8</sup> magnetic resonance imaging (MRI), advanced CT perfusion (CTP) imaging, and assessment of collaterals can be used individually or in combination. The choice often depends on unique workflow patterns at individual centers, geographical aspects, and patient populations being treated.

### Alberta Stroke Program Early CT Score

ASPECTS is a noncontrast computed tomography (NCCT)-based scoring system with scores ranging from 0 to 10; it is used to evaluate the extent of early ischemic changes in the territory of the middle cerebral artery (MCA) (Fig. 95.1).<sup>8</sup> Significant variations in agreement, especially among operators with limited experience in interpreting ASPECTS, and dependence on high-resolution imaging workstations for accurate

**TABLE 95.4 Rapid Arterial Occlusion Evaluation (RACE) Scale**

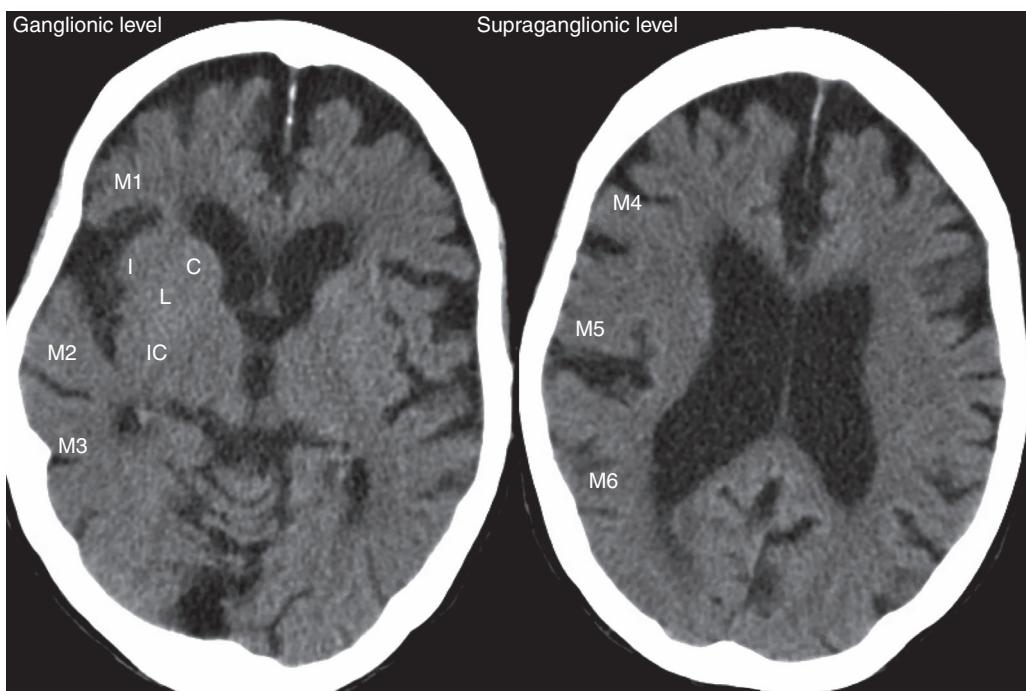
| Category                       | Score Description  |
|--------------------------------|--|
| Facial palsy                   | 0 - Absent 1 - Mild<br>2 - Moderate to severe  |
| Arm motor function             | 0 - Normal<br>1 - Moderate<br>2 - Severe   |
| Leg motor function             | 0 - Normal<br>1 - Moderate<br>2 - Severe   |
| Head and gaze deviation        | 0 - Absent 1 - Present   |
| Aphasia (if right hemiparesis) | 0 - Performs both tasks correctly<br>1 - Performs 1 task correctly<br>2 - Performs neither task  |
| Agnosia (if left hemiparesis)  | 0 - Patient recognizes his/her arm and the impairment<br>1 - Does not recognize his/her arm or the impairment<br>2 - Does not recognize his/her arm nor the impairment |

Adapted from Perez de la Ossa N, Carrera D, Gorchs M, Querol M, Millan M, Gomis M, et al. Design and validation of a prehospital stroke scale to predict large arterial occlusion: the rapid arterial occlusion evaluation scale. *Stroke*. 2014;45(1):87–91.

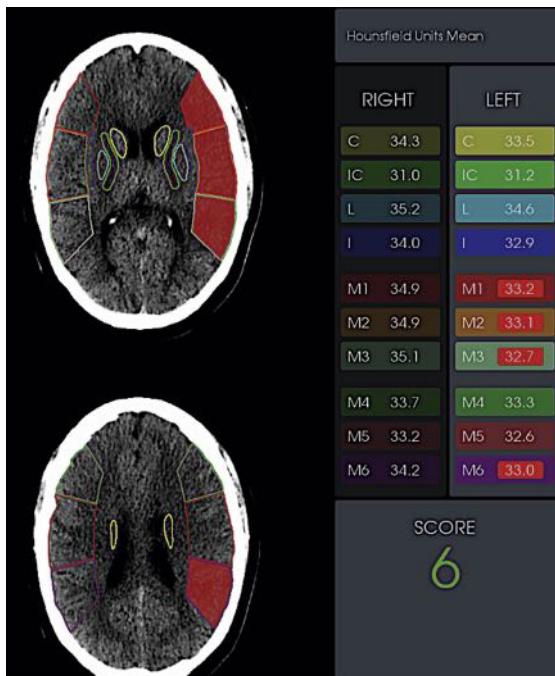
scoring are the limitations that have led to the creation of various automated ASPECTS platforms, so called “eASPECTS”<sup>9</sup> (Fig. 95.2). Automated ASPECTS notification allows fast imaging assessment, which can be done on a variety of devices including smart phones and tablets, which is highly practical and convenient. Endovascular treatment is indicated for ASPECTS of 6 and higher. Patients with lower ASPECTS are at risk of reperfusion hemorrhage and are less likely to achieve good clinical outcomes than patients with ASPECTS 6–10. However, in comparison to standard medical therapy alone, even in patients with values in the low ASPECTS range, there is still a potential benefit of endovascular recanalization.<sup>10</sup> Thrombectomy for Emergent Salvage of Large Anterior Circulation Ischemic Stroke (TESLA; ClinicalTrials.gov identifier: NCT03805308) is an ongoing randomized clinical trial of anterior circulation stroke with ASPECTS 2–5. The objective of this trial is to help determine the safety and efficacy of endovascular therapy in patients with large ischemic stroke burden.

### Perfusion Imaging

Another common imaging modality used in an acute stroke setting is perfusion imaging, especially in patients with late onset of stroke symptom onset, unknown time of stroke onset, or last known well or wake-up strokes.<sup>11</sup> MR- and CT-based perfusion studies help in assessing the volume of irreversibly infarcted brain tissue (ischemic core) and relative volume of potentially salvageable tissue at risk (ischemic penumbra).<sup>12</sup> CTP is preferred over magnetic resonance perfusion (MRP) as this can be performed in the same setting as CTA in an



**Figure 95.1** Calculating the Alberta Stroke Program Early CT Score (ASPECTS). Two axial brain cuts (one through the basal ganglia and the second at the supraganglionic level) are used. One point is deducted from the initial score of 10 for every region involved: *C*, caudate; *I*, insular; *IC*, internal capsule; *L*, lentiform nucleus; *M1–6*, six distinct middle cerebral artery (MCA) cortical regions. A score of 0 corresponds to a patient with a complete MCA stroke affecting all cortical and subcortical structures. A score of 10 describes “normal” brain computed tomography (CT).



**Figure 95.2** Automated ASPECTS. An example of ASPECTS processed with RAPID AI automated CT perfusion (CTP) software (iSchemaView, Menlo Park, CA). Using machine-learning algorithms, automated software packages such as RAPID to identify areas of irreversible brain injury and calculate ASPECTS for fast evaluation of potential stroke thrombectomy patients.

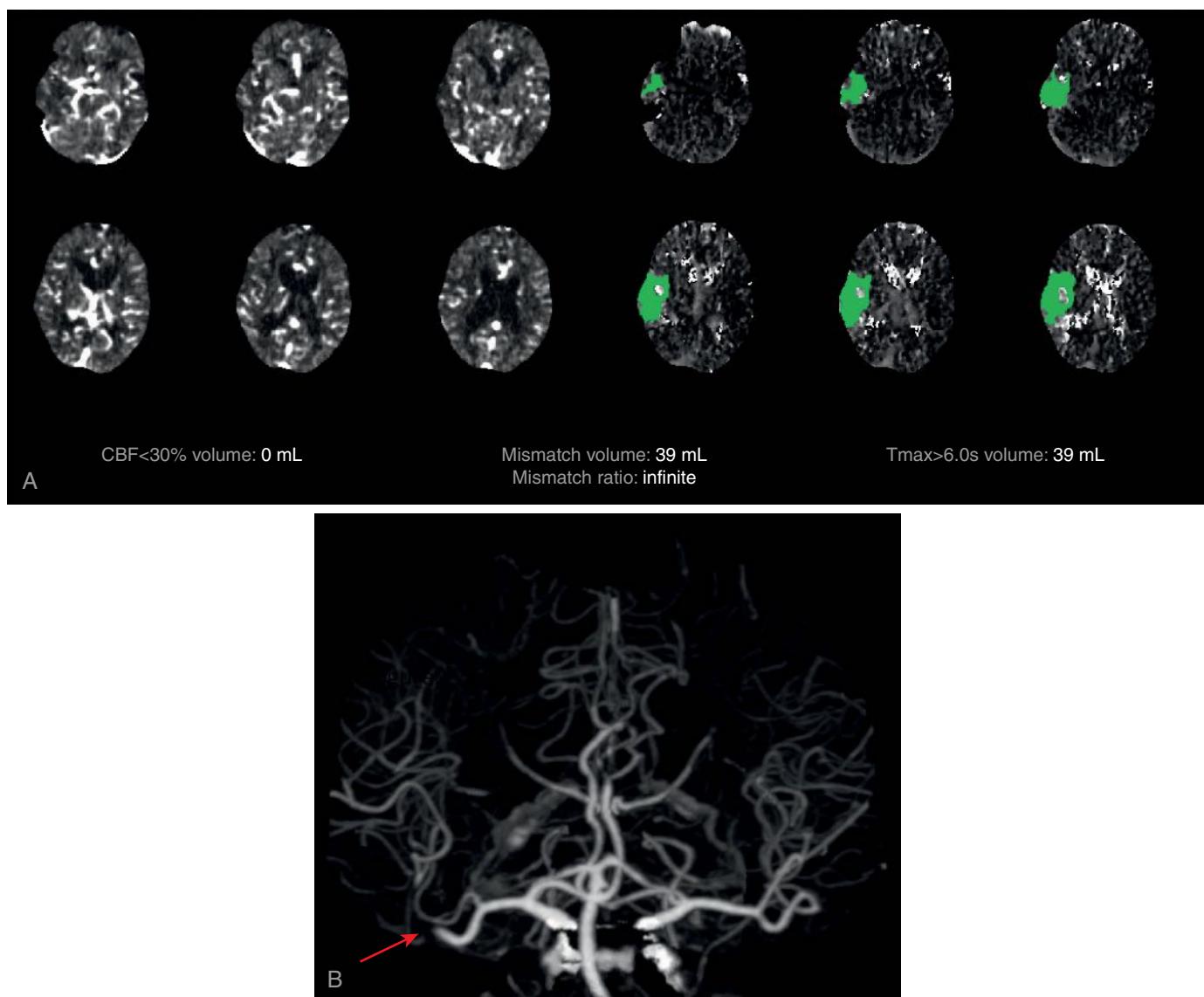
additional 4 to 5 minutes.<sup>12</sup> The practice of routine CTP and/or MRP varies between different centers as it depends on physician preference. At some comprehensive stroke centers, perfusion imaging is reserved for unclear or challenging cases, e.g., awake stroke or stroke with late presentation, while other centers routinely perform CTP for all cases of stroke.

Automated software imaging tools such as RAPID AI (iSchemaView, Menlo Park, CA) allows rapid evaluation of CT- and MR-generated perfusion maps on a desktop, tablet, or smartphone (Fig. 95.3). Perfusion imaging allows estimation of irreversibly infarcted brain (known as “core”) and salvageable tissue at risk (ischemic “penumbra”). It should be noted that within the first few hours of stroke onset, perfusion imaging may overestimate the true extent of irreversible injury, the phenomenon known as “ghost infarct core,” arguing against its use in clinical decision-making during the early hours (typically, the first 6 hours) of stroke symptom onset.<sup>13</sup>

#### Identification of Emergent Large Vessel Occlusion

ELVO is most commonly diagnosed with CTA of the head and neck and is often performed immediately after NCCT. Although some centers practice routine use of magnetic resonance angiography (MRA), this imaging modality has not been widely accepted due to its multiple restrictions, such as the need to exclude the presence of implanted metal devices or foreign bodies, which requires additional time and ultimately causes a delay in performing thrombectomy. CTA offers valuable data about the anatomy of the aortic arch and proximal vasculature. New imaging tools, such as RAPID AI or Viz.ai (Viz.ai, Inc., San Francisco, CA) use proprietary machine-learning algorithms allowing “automated” detection of suspected ELVO (Fig. 95.4). This greatly simplifies EVLO identification by healthcare workers who are less familiar with the interpretation of complex imaging modalities helping to speed up triage or transfer decision-making for patients with ischemic stroke.

More recently, research has focused on the ability of NCCT and CTA to provide imaging markers of clot morphology to help determine the most effective type of device and thrombectomy approach. These imaging approaches to determining



**Figure 95.3** CTP Imaging Assessment of Viable Brain Tissue. (A) Quantitative analysis of CTP (RAPID IA) based on  $T_{max} > 6$  seconds value shows an area of ischemic penumbra, measuring 39 mL (green color). This patient has no ischemic core (0 core volume); thus, with successful reperfusion, this patient is likely to achieve a good clinical outcome. (B) CT angiogram demonstrates a proximal right MCA M2 segment occlusion (arrow) corresponding to the location of the perfusion deficit on CTP.

clot characteristics are currently considered investigational and have not been included in any official thrombectomy treatment guidelines.

## ADJUNCTIVE USE OF INTRAVENOUS THROMBOLYSIS

### Intravenous Thrombolysis in Acute Ischemic Stroke

The Food & Drug Administration (FDA) approved IV thrombolysis with recombinant tissue plasminogen activator (rtPA) for the treatment of acute ischemic stroke for patients presenting within the first 3 hours of symptom onset based on the

results of the landmark National Institute of Neurological Disorders and Stroke rtPA stroke trial.<sup>14</sup> The trial demonstrated improved 3-month functional outcomes (assessed using modified Rankin scale and Barthel index) of stroke patients treated with IV thrombolysis when compared with placebo treatment. However, there was no significant difference in 3-month mortality between the two groups.<sup>14</sup>

The European Cooperative Acute Stroke Study (ECASS) III further demonstrated the benefit of rtPA within 3–4.5 hours of symptom onset. Favorable outcomes in the thrombolysis group were seen in 52% of patients compared to 45% in the placebo group.<sup>15</sup> On the basis of the findings of the ECASS trials, the American Heart Association recommended the use of IV thrombolysis within 3–4.5 hours of symptom onset in carefully selected patients. Patients older than 80 years, those

with severe stroke symptoms (NIHSS score >25), those receiving oral anticoagulation therapy, and those with a history of stroke and diabetes were at a higher risk for intracranial hemorrhage in ECASS III.<sup>16</sup> In comparison to patients treated within <3 hours, rtPA in the 3- to 4.5-hour window conferred benefit to half as many patients with no increase in morbidity. Numbers needed-to-treat for benefit was 6.1 (95% CI, 5.6–6.7) and the number needed to harm was 37.5 (95% CI, 34.6–40.5). Despite these findings, the FDA did not approve expansion of the time window. Currently, IV thrombolysis within the first 3 hours of stroke symptom onset remains the only FDA-approved systemic IV treatment in the US and is reserved for carefully selected patients between 3 and 4.5 hours of symptom onset.

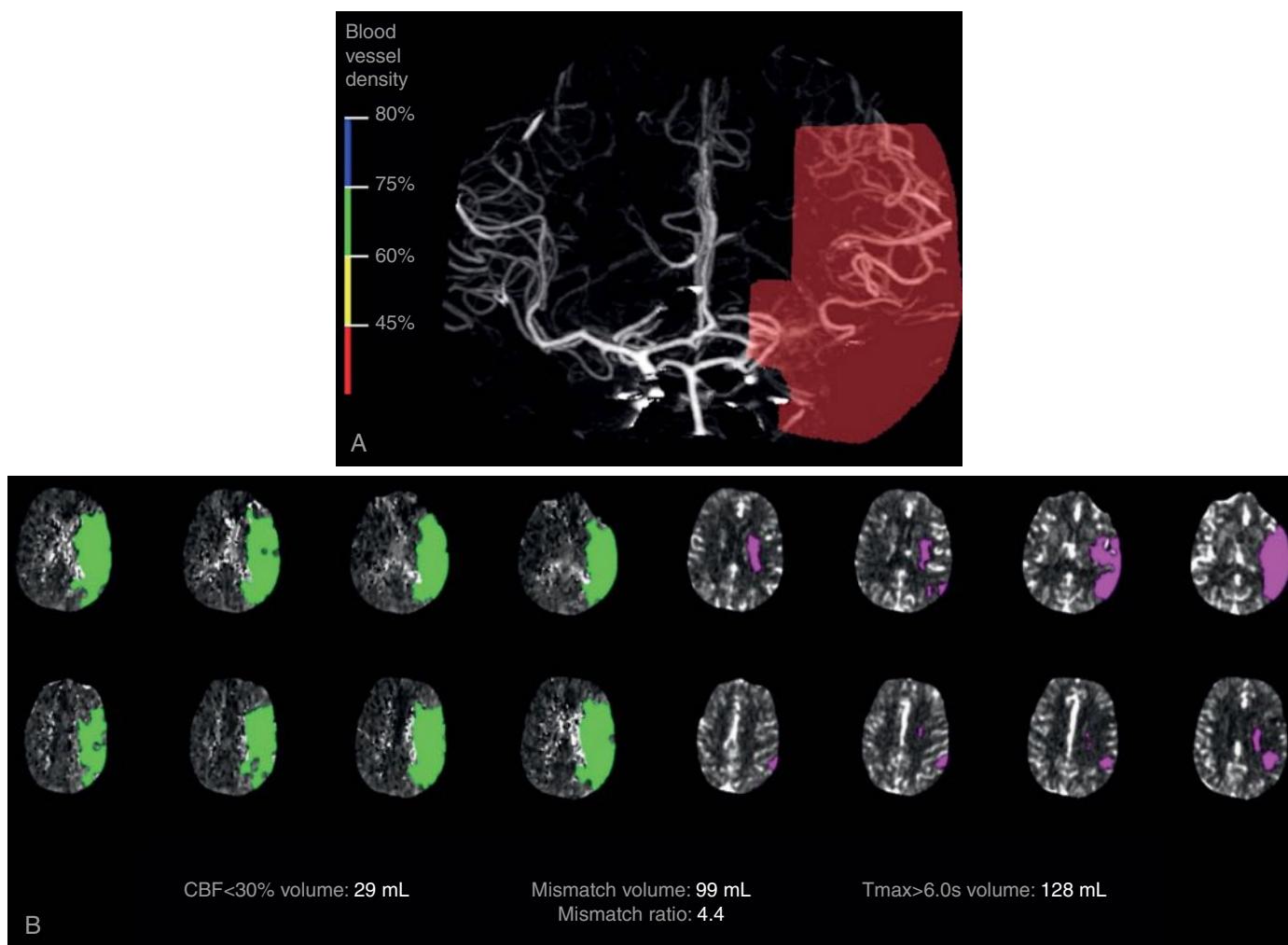
### Intravenous Thrombolysis and Large Vessel Occlusion

The utility of IV thrombolysis in patients with large vessel occlusion is limited. This is true for occlusion of the internal carotid artery (ICA), proximal middle cerebral artery (MCA) segments,

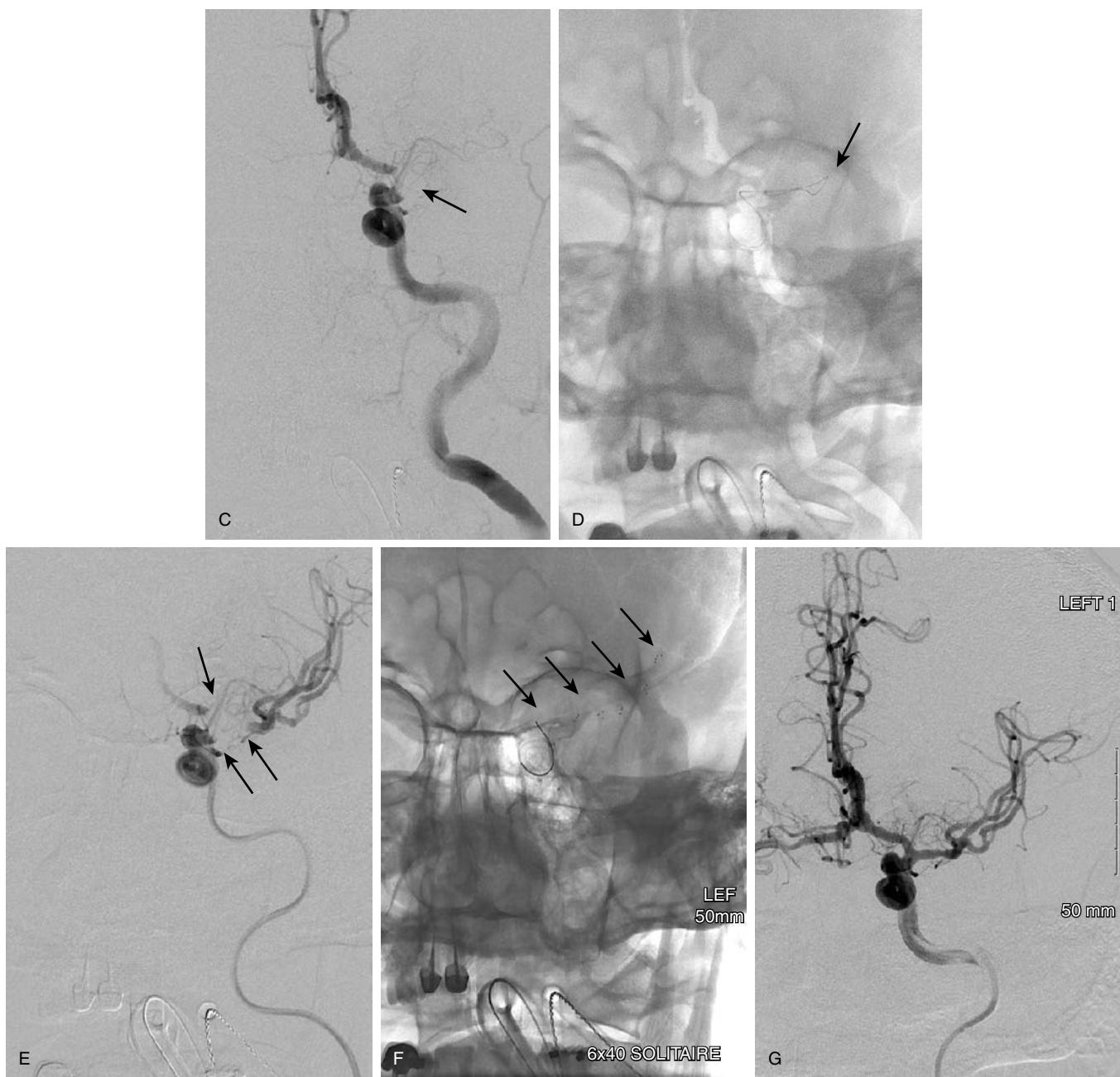
vertebral artery, and basilar artery. In fact, an occlusion of the ICA is least likely to respond to IV thrombolysis (successful in only 6%).<sup>17,18</sup> Conversely, IV thrombolysis is highly effective for smaller, more distal occlusions with success in 44% of cases when thrombus involved the M2 segment of the MCA compared to proximally located MCA occlusions with success in 30%.<sup>17</sup>

## ENDOVASCULAR THERAPY

The most common etiology of stroke from ELVO is embolic, thus effective clot extraction rather than clot disruption (which risks clot breakdown and distal embolization) provides the most effective treatment.<sup>19</sup> Mechanical thrombectomy with stent retrievers or direct aspiration (these two approaches are often used in conjunction) is currently the leading technique used by neurointerventionists to treat ELVO. It has replaced local pharmacological thrombolysis or clot disruption with wire manipulations. Scientific evidence supporting the use of mechanical thrombectomy for the treatment of ELVO is strongly based on several randomized trials (some of which are summarized in Table 95.5<sup>19–24</sup>)



**Figure 95.4** Example of Large Vessel Occlusion Thrombectomy. (A) Left internal carotid artery (ICA) terminus occlusion is identified using automated stroke imaging software (RAPID IA). The area of reduced vessel density is highlighted in red. (B) Perfusion imaging shows a large area of mismatch (mismatch ratio 4.4, mismatch volume 99 mL) corresponding to the territory of the left ICA. (*Continued*)



**Figure 95.4 cont'd** (C) The patient is taken for emergent thrombectomy. Digital subtraction angiography showing left ICA terminus occlusion (arrow). (D) During thrombectomy, the occlusion is crossed "blindly" using a guide wire (arrow) and a microcatheter. (E) A contrast injection through both the guide catheter and microcatheter helps identify the extent of the thrombus (arrows). (F) A stent retriever (Solitaire; Medtronic, Dublin, Ireland) is unsheathed and deployed, "trapping" the thrombus (arrows). (G) Withdrawing (retrieving, thus the term "stent retriever") the stent retriever device into the guide catheter removes the thrombus. This established patency of the previously occluded ICA terminus allows complete reperfusion of the downstream MCA and anterior cerebral artery branches.

evaluating thrombectomy in diverse populations of stroke patients. Angioplasty and stenting are mainly reserved for patients with acute occlusions caused by underlying atherosclerosis.

### Thrombectomy Techniques

With aspiration thrombectomy, a large-bore aspiration catheter is advanced directly to the location of the clot and a negative aspiration force is applied for several minutes to extract

the clot.<sup>25,26</sup> Multiple brands of aspiration catheters exist; they vary in length and diameter, and the choice of catheter depends on clot location and occluded vessel dimensions.

Stent retrievers are self-expandable stents that are attached to a pusher wire. These devices require traversing the clot with a microcatheter, allowing thrombus entrapment within the stent struts once the device is unsheathed. After the clot becomes fully engaged within the struts of the device, withdrawal of the stent removes the clot (see Fig. 95.4). Some operators prefer to use the

**TABLE 95.5** Examples of Landmark Randomized Trials of Endovascular Stroke Therapy

| Trial, Publication Date   | Key Inclusion Criteria   | Endovascular Therapy  | Good functional Outcome (mRS score ≤2) at 3 Months   | Comments  |
|---|--|---|--|---|
| Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke (MR CLEAN), 2015 <sup>19</sup>  | CT ASPECTS for selection. Thrombectomy initiated within 6 h.   | Stent retrievers in 97% of interventions.   | 33% with endovascular, 19% with medical management.  | This was the first endovascular stroke therapy RCT that announced its results. Subsequent similar thrombectomy RCTs were halted due to loss of equipoise. |
| Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times (ESCAPE), 2015 <sup>20</sup>   | Selection was based on multiphase CTA to evaluate collaterals. Included patients within 12 h.  | Stent retrievers in 86% of interventions.   | 53% with endovascular, 29% with medical management.  | Assessment of collaterals is used by some centers instead of perfusion imaging.   |
| Solitaire FR with the Intention for Thrombectomy as Primary Endovascular Treatment of Acute Ischemic Stroke (SWIFT PRIME), 2015 <sup>23</sup>   | Most patients were selected using CT perfusion imaging. Thrombectomy initiated within 6 h.   | Stent retrievers in all endovascular interventions.                               | 60% with endovascular, 35% with medical management.  | All patients in both groups received IV thrombolysis.   |
| Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention with Trevo (DAWN), 2018 <sup>22</sup>   | Combination of perfusion and clinical (NIHSS severity)-based patient selection. Treatment initiated within 6–24 h.                       | Stent retrievers in all interventions.  | 49% with endovascular, 13% with medical management.  | Confirmation that in appropriately selected patients thrombectomy is safe and highly effective up to 24 h of stroke symptom onset.                        |
| Contact Aspiration vs Stent Retriever for Successful Revascularization (ASTER), 2017 <sup>21</sup>  | Treatment within first 6 h. No specific imaging selection criteria.  | Aspiration-first versus stent-retriever first approach studied.                   | Similar recanalization rates in both groups: 85% with aspiration, 83% with stent retrievers. | First study that demonstrated equal technical outcomes between aspiration and stent retriever-first approach to thrombectomy                              |
| Parallel Group, Randomized Clinical Trial of Direct Intra-arterial Thrombectomy Versus Intravenous Thrombolysis with Intra-arterial Thrombectomy for Patients with Large Vessel Occlusion of the Anterior Circulation (DIRECT-MT), 2020 <sup>24</sup> | All patients required eligibility for IV thrombolysis. No specific imaging criteria other than confirmation of LVO and exclusion of ICH. | Stent retrievers were the main approach. Aspiration was used as rescue treatment. | 36% with endovascular only, 37% with IV thrombolysis + endovascular                          | Endovascular therapy alone is noninferior to endovascular thrombectomy preceded by IV thrombolysis.   |

Abbreviations: ASPECTS, Alberta Stroke Program Early CT Score; CT, computed tomography; CTA, CT angiography; h, hours; ICH, intracranial hemorrhage; IV, intravenous; LVO, large vessel occlusion; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; RCT, randomized controlled trial.

stent retriever device “alone,” often relying on a balloon-guide catheter to provide temporary flow arrest.<sup>27</sup> Others use an aspiration catheter to anchor the proximal end of the clot and thus improve the chance of full clot removal in a single pass.<sup>28</sup> With a variety of balloon-guide catheters, aspiration (intermediate) catheters, and stent retrievers available, endless combinations of approaches exist for use in a clinical setting.<sup>29,30</sup>

Three randomized controlled trials, the Contact Aspiration vs. Stent Retriever for Successful Revascularization (ASTER), a Direct Aspiration First Pass Technique (COMPASS) and A Randomized, Concurrent Controlled Trial to Assess the Safety and Effectiveness of the Separator 3D as a Component of the Penumbra System in the Revascularization of Large Vessel Occlusion in Acute Ischemic Stroke (Penumbra Separator 3D) demonstrated

**BOX 95.1****Summary of the 2019 SNIS Update on Endovascular Management of Acute Stroke****① Time from Symptom Onset**

For anterior circulation AIS, thrombectomy is indicated in select patients up to 24 hours from last known normal.

**② Imaging Selection**

- In patients with anterior circulation AIS within the first 6 hours of symptom onset and either CT ASPECTS  $\geq 6$ , MRI DWI ASPECTS  $\geq 6$ , moderate-to-good collateral status, small core infarct volumes, and/or significant penumbral-to-core mismatch on advanced perfusion imaging, thrombectomy is indicated.
- CT and CTA are recommended in the evaluation of patients with suspected posterior circulation ELVO. For late arrivals, DWI MRI could identify patients with poor posterior circulation-ASPECTS or large core infarction.

Abbreviations: AIS, acute ischemic stroke; ASPECTS, Alberta Stroke Program Early CT Score; CT, computed tomography; CTA, CT angiography; ELVO, emergent large vessel occlusion; DWI, diffusion-weighted imaging; LVO, large vessel occlusion; MCA, middle cerebral artery; MRI, magnetic resonance imaging; NIHSS, National Institutes of Health Stroke Scale; SNIS, Society of Neurointerventional Surgery

Adapted from <http://jnis.bmjjournals.org/cgi/pmidlookup?view=long&pmid=30610069> and <https://jnis.bmjjournals.com/content/11/10/1055>

similar technical efficacy and safety of these two thrombectomy approaches.<sup>31–33</sup>

**Indications for Thrombectomy**

The indications for endovascular treatment of stroke caused by ELVO are a moving target. Official guidelines and recommendation statements have often been criticized for the failure to recognize the emerging evidence, rapid technological advances, and failure to acknowledge the differences between diverse clinical practice environments versus the rigid inclusion and exclusion criteria of randomized trials.<sup>34–36</sup>

The 2019 indications for thrombectomy in AIS from ELVO endorsed by the Society of NeuroInterventional Surgery provide the most comprehensive and up-to-date summary on this subject<sup>37</sup> (Box 95.1). Examples of patient populations that are largely excluded from the most recent guidelines and are currently under investigation include those with large ischemic stroke burden (TESLA trial), those with mild neurologic deficits (ENDOLLOW trial), bypassing emergent imaging and/or intravenous thrombolysis (Solitaire™ With the Intention For Thrombectomy Plus Intravenous t-PA Versus DIRECT Solitaire™ Stent-retriever Thrombectomy in Acute Anterior Circulation Stroke, SWIFT DIRECT, ClinicalTrials.gov Identifier: NCT03192332 and Effect of DIRECT Transfer to ANGIOsuite on Functional Outcome in Patient With Severe Acute Stroke Treated With Thrombectomy: the Randomized DIRECT ANGIO Trial, ClinicalTrials.gov Identifier: NCT03969511).

See Chapter Algorithm for the triage and management of patients with acute ischemic stroke.

**STROKE SYSTEMS OF CARE AND STRUCTURE OF THE STROKE TEAM**

A typical neurointerventional team consists of a neurointerventionist (neurosurgeon, neurologist, or neuroradiologist) with dedicated neurointerventional training, which is currently

**③ Location of LVO**

- Thrombectomy is indicated in patients with occlusions of the ICA (including intracranial, cervical segments or tandem occlusion) and M1 and/or M2 segments of the MCA. The benefit of thrombectomy in more distal segments, such as MCA M3, or anterior cerebral artery is unclear.
- Thrombectomy is reasonable for posterior circulation ELVO patients to maximize the chance of a good clinical outcome.

**④ Stroke Severity**

Thrombectomy is indicated in patients with anterior circulation ELVO with NIHSS score  $\geq 6$ .

accredited through the Committee on Subspecialty Training (CAST) (<https://link.zixcentral.com/u/90299aa5/kv-blrdQ7BG5Edd5h3soMg?u=https%3A%2F%2Fabns.org%2Frfp-cnsendo%2F>) and has dedicated board certification, two technicians, and a nurse. Many busy neurointerventional programs also include residents and/or fellows. The ideal level of care for a potential thrombectomy patient requires, in addition to a neurointerventionist who will be performing the procedure, highly trained specialty physicians in areas such as stroke (vascular) neurology, neurosurgery, and neurocritical care. All of this is best achieved at a comprehensive stroke center (CSC) (<https://www.jointcommission.org/accreditation-and-certification/certification/certifications-by-setting/hospital-certifications/stroke-certification/advanced-stroke/comprehensive-stroke-center/>). In 2017, an additional certification, titled “Thrombectomy-capable Stroke Center” (TSC), was proposed. Such hospitals are designed to provide 24/7 thrombectomy interventions but otherwise do not meet all the necessary requirements for a CSC. Multiple requirements are taken into consideration when a hospital seeks a particular stroke center certification. These consist of available personnel (physicians, midlevel providers, nursing staff), a spectrum of neurosurgical and neurointerventional therapies provided, hospital infrastructure, and educational programs.

The stroke systems of care are designed to reduce time from stroke onset to reperfusion. This requires coordination between pre-hospital emergency services and the stroke centers. The Society of Neurointerventional Surgery sets various time metrics that are needed to be met to achieve optimal treatment outcomes (<https://www.snisonline.org/standards/>). These include door to administration of IV thrombolysis <30 minutes and door to groin puncture time of <60 minutes, door to recanalization time of <90 minutes. Communication between emergency medical services and the emergency room is key to achieving these targets.

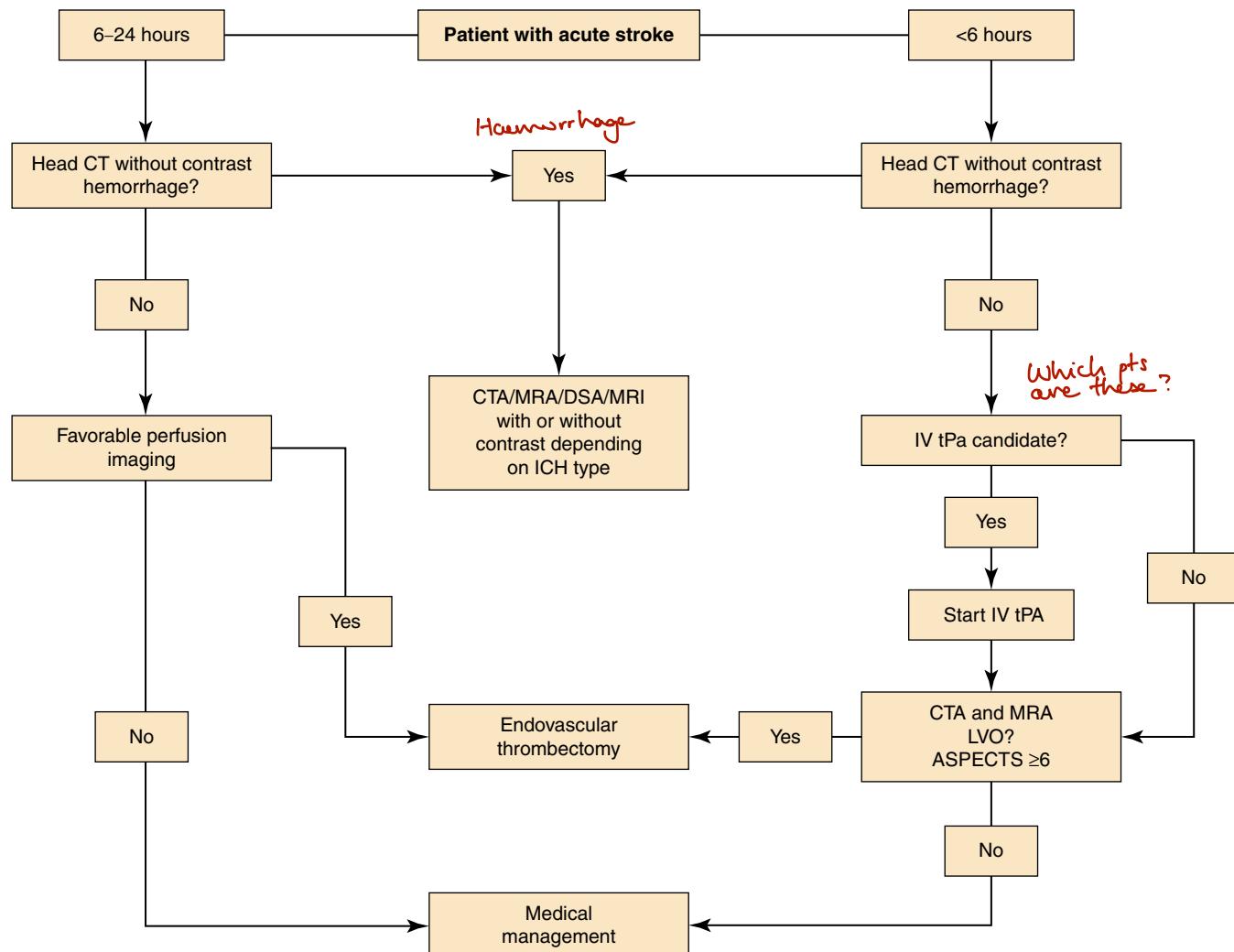
**MOBILE STROKE UNITS**

Several strategies have been implemented to increase the efficiency of the stroke systems of care. Mobile stroke units are

the most sophisticated form of prehospital triage. A mobile stroke unit is equipped with a CT scanner that is capable of performing noncontrast CT of the head and CT angiography, and medication including IV rtPA. The mobile stroke unit staff consists of first responders, a critical care nurse, a medical technician, and a CT scan technologist. Transport via mobile stroke units has been reported to be associated with higher rates of IV rtPA administration compared to traditional transport (32% vs. 22%,  $P < 0.001$ ).<sup>38</sup> Mobile stroke units have also been reported to reduce time from CT scan to intra-arterial treatment (82 vs. 165 min, respectively).<sup>39</sup> This implies that identification and triage of patients with acute ischemic stroke prior in the pre-hospital setting may expedite both pharmacologic and endovascular therapy.

Several clinical scales have been developed and used to predict large vessel occlusion in the prehospital setting.<sup>40</sup> Prehospital triage and alerting of the destination stroke facility impacts the times to CT scan, IV thrombolysis, and mechanical thrombectomy. Prehospital alerting of the stroke severity to the destination stroke facility may significantly improve the timing to CTA and time to IV thrombolysis and endovascular treatment. A nationwide study of 49,907 patients with acute large vessel occlusion stroke from Sweden showed a significant correlation between hospital alerts and reperfusion rates.<sup>41</sup> Some highly innovative stroke systems include tracking of patients and on-call team members using global positioning system-based applications. Advancements in information technology are expected to revolutionize healthcare, particularly stroke care.

## CHAPTER ALGORITHM



Algorithm for imaging and treatment of patients with acute ischemic stroke. Abbreviations: ASPECTS, Alberta Stroke Program Early CT Score; CT, computed tomography; CTA, computed tomography angiogram; DSA, digital subtraction angiogram; ICH, intracranial hemorrhage; IV, intravenous; LVO, large vessel occlusion; MRA, magnetic resonance angiogram; MRI, magnetic resonance imaging; tPA, tissue plasminogen activator. (From Waqas M, Vakharia K, Munich SA, et al. Initial Emergency Room Triage of Acute Ischemic Stroke. *Neurosurgery*. 2019;85(suppl\_1):S38–S46, with permission from Oxford University Press, License 499134135776.)

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*The study demonstrated that in carefully selected patients, thrombectomy up to 24 hours of stroke symptom onset is highly effective and safe. The trial confirmed that a much wider population of patients with large vessel occlusion including those with wake up strokes and unknown time of onset are potential candidates for thrombectomy.*

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# Cerebrovascular Disease: Carotid Artery Dissection

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Based on a previous edition chapter by Rabih A. Chaer, Peter A. Schneider, and Efthymios Avgerinos

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## INTRODUCTION

Carotid artery dissection (CAD) usually occurs secondary to a tear in the intimal layer disrupting the integrity of the arterial wall, which allows blood to leak and accumulate between arterial wall layers. CAD can occur at any age, but is more common among young adults, accounting for approximately 20% of ischemic strokes in this population.<sup>1</sup> While most carotid dissections are spontaneous or follow a minor neck trauma, CAD can also occur after severe neck trauma or interventions. It can involve either the intra- or extracranial portions of the carotid artery, but is more common in the extracranial portion as it is more mobile and in contact with head and neck bones.<sup>2</sup> Conversely, intracranial dissection is more common in children and the Asian population.<sup>3</sup> The intramural hematoma secondary to the dissection can progress to cause stenosis, occlusion, or aneurysm. Moreover, the arterial tear can provoke the coagulation system leading to acute thrombosis or cerebral embolization. In some cases, patients with CAD present with headache and neck pain. However, with thorough clinical examination along with advancements

in imaging technology, CAD can be easily diagnosed and successfully managed to prevent adverse clinical outcomes.

## SPONTANEOUS CAROTID ARTERY DISSECTION

### Epidemiology

Spontaneous CAD is a rare condition with an approximate annual incidence of 2.6 per 100,000.<sup>4</sup> However, since some cases may be clinically silent, the actual incidence may be higher. The mean age of patients with spontaneous dissection is 45 years.<sup>4</sup> Although no clear evidence of gender or ethnic predisposition in the incidence of CAD exists, women tend to be younger and with multiple dissections at the time of diagnosis.<sup>5</sup>

### Pathophysiology

Spontaneous dissection of the carotid artery results from separation of the arterial wall layers causing blood to leak between these layers and forming a false lumen within the arterial wall.

Evidence regarding the initial event causing the hemorrhage is still vague. It may be attributed to either a direct rupture of vasa vasorum or an intimal tear.<sup>6</sup> Dissections can either be subadventitial or subintimal. Luminal stenosis is more common with subintimal dissection, while aneurysms often occur with subadventitial dissection.<sup>7</sup> Examination of tissue samples from the dissected vessel reveals intramural hemorrhage. Granulation tissue replaces the intramural hematoma after 14 days of symptom onset with intimal enlargement along the false lumen.<sup>8</sup> Neovascularization within the enlarged intimal layer starts after 30 days.<sup>8</sup>

## Etiology

Spontaneous CAD develops when there is an underlying impairment in vascular wall integrity that impairs arterial wall strength and makes it more vulnerable for dissection.<sup>9</sup> In 40% of patients, there is a history of a provoking mechanical event preceding the symptoms.<sup>10</sup> CAD has been found to be associated with multiple vascular and connective tissue diseases. Fibromuscular dysplasia accounts for approximately 15% of cases (see Ch. 143, Fibromuscular Disease).<sup>11</sup> Two percent of patients with Ehlers–Danlos syndrome type IV will develop CAD (see Ch. 141, Arterial Disease in Patients with Connective Tissue Disorders).<sup>12</sup> Other connective tissue diseases that may be associated with CAD include Marfan syndrome, osteogenesis imperfecta, homocystinuria, cystic medial necrosis, and alpha-1 antitrypsin deficiency.<sup>13–17</sup> Nonetheless, it is unclear whether the incidence of CAD in these disorders is higher than the incidence by chance alone.<sup>18</sup> CAD might also be associated with the presence of long styloid process; a rare condition called Eagle syndrome.<sup>19</sup> The association between genetic factors and CAD has been suggested in light of the presence of familial cases without underlying connective tissue disease and the presence of accompanying arterial diseases, which suggests underlying arteriopathy.<sup>20</sup> Another condition that might be associated with CAD includes aortic root dilatation.<sup>21,22</sup> Although chiropractic alteration of the neck has been reported in some cases of dissection, causality has not been supported.<sup>23</sup> Recent infection was found to be associated with CAD; however, mechanical factors such as coughing, sneezing, and vomiting were not independently associated.<sup>24,25</sup> This may explain the seasonal variations of the disease during winter and autumn. Arterial hypertension and migraine were found to be independently associated with CAD.<sup>26,27</sup> However, no association has been observed between CAD and a history of smoking, diabetes, atherosclerosis, or prior oral contraceptive use.<sup>26</sup>

## Clinical Presentation

Headache and/or neck pain are the most common initial symptoms with spontaneous carotid dissection, with headache found in approximately 80% of cases.<sup>4</sup> Headache is usually gradual in onset; however, severe sudden onset has been reported in 20% of cases.<sup>28,29</sup> Almost 25% develop Horner syndrome.<sup>4</sup> Patients with internal carotid dissection may have

partial Horner syndrome, which consists of ptosis and miosis only without anhidrosis.<sup>30</sup> Transient ischemic attack and cerebral infarction occur in approximately 56% of cases.<sup>4</sup> Ocular manifestations include painful transient loss of vision secondary to ischemic optic neuropathy, anisocoria, and amaurosis fugax.<sup>30</sup> Patients with intracranial dissection can present with subarachnoid hemorrhage, which usually predicts a poor prognosis.<sup>3</sup>

 Cranial nerves are affected in about 12% of cases, particularly the lower cranial nerves (IX–XII).<sup>11</sup> The hypoglossal nerve is most commonly affected, presenting with unilateral tongue paralysis in the form of tongue deviation towards the affected side due to unopposed action of the contralateral intact muscle. Other cranial nerve-related manifestations include loss of taste sensation with injury to the glossopharyngeal nerve, dysphagia and dysphonia with the vagus nerve, and shoulder drop with the spinal accessory nerve. Patients can also have  bruit and tinnitus.<sup>31</sup>

## TRAUMATIC CAROTID ARTERY DISSECTION

### Etiology

Traumatic carotid artery dissection occurs after a blunt or sharp penetrating trauma. Intimal tear can occur secondary to rapid deceleration associated with motor vehicle accidents or any incident causing severe neck extension, lateral flexion, or rotation.<sup>32</sup> Other mechanisms of blunt trauma include trauma to the oral cavity, and fractures of the mandible, cervical vertebrae, or skull base. Iatrogenic injury can also occur secondary to endovascular procedures.

### Epidemiology

In a large study including 18,233 trauma patients, the incidence of traumatic CAD was 0.86%.<sup>33</sup> Another study including trauma patients with high risk of carotid involvement reported an incidence of traumatic internal carotid artery dissection of 3.2%.<sup>34</sup>

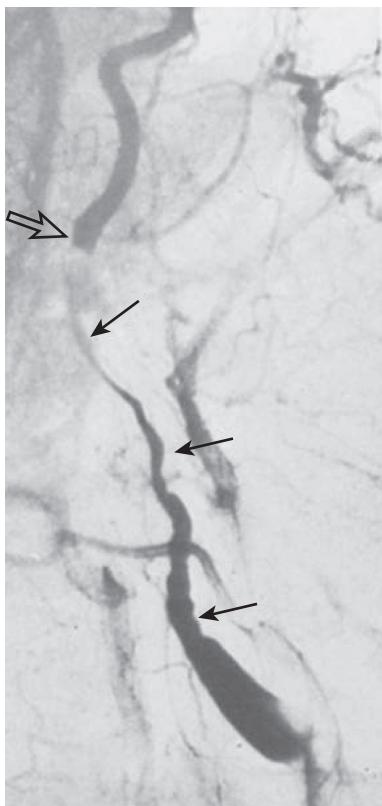
### Clinical Presentation

The symptoms of traumatic CAD are similar to those associated with spontaneous CAD. Patients may be initially asymptomatic; however, the majority will become symptomatic within 24 hours of dissection. Therefore, it is crucial to perform proper diagnostic imaging in the trauma setting, especially when there is a high suspicion of CAD such as in patients with neck bleeding, enlarging neck hematoma, Horner syndrome, carotid bruit, cerebral ischemia, maxillofacial fractures, cervical fractures, or altered level of consciousness.

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## THE DIAGNOSIS OF CAD

When CAD is suspected, it is appropriate to choose the best imaging modality based on the clinical scenario.



**Figure 96.1** Conventional angiogram showing internal carotid artery dissection in its cervical segment. Classical tapered elongated luminal narrowing is noted (solid arrows). Besides, there is abrupt reconstruction of internal carotid lumen at the base of the skull (open arrow). (From Mokri M. Dissection of the cervical and cephalic arteries. In: Meyer FB, ed. *Sundt's Occlusive Cerebrovascular Disease*. Philadelphia, PA: WB Saunders; 1994:51.)



**Figure 96.2** Conventional angiogram following traumatic carotid artery dissection showing luminal narrowing and pseudoaneurysm formation.

lumen, vessel wall irregularities, shifting of vessel lumen from midline due to mural thickening, and pseudoaneurysm may be present (Fig. 96.3).<sup>39</sup> Due to the lack of radiation, MRI/MRA can be safely used in children and pregnant women. It is superior to CTA in detecting subacute or chronic intramural hematoma.<sup>40-42</sup> Moreover, it can detect ischemic changes in brain tissues secondary to stroke earlier than any other imaging technique. Yet depicting hematoma with MRA in the early stages of CAD may be challenging.<sup>43</sup> Moreover, MRA may not be available in all settings, is time consuming which makes it inappropriate in most traumatic cases, not well tolerated by all patients, and carries the hazard of gadolinium use which may cause nephrogenic sclerosis.<sup>36</sup>

## Conventional Angiography

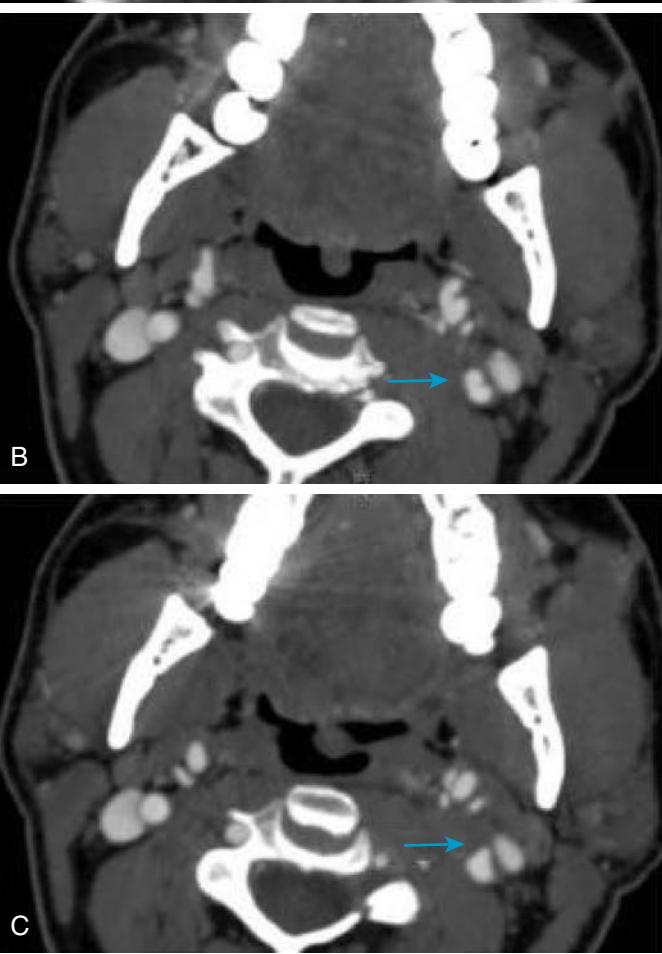
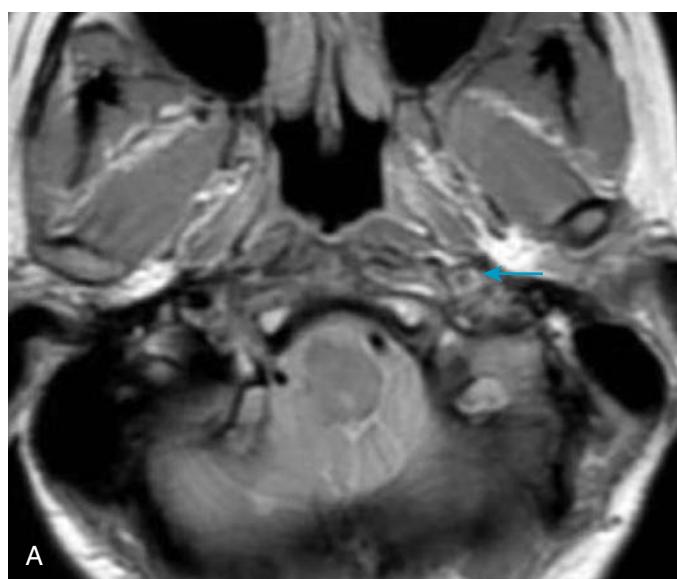
Conventional angiography has been considered the gold standard imaging modality to detect CAD. Yet it is currently being replaced by computed tomographic angiography (CTA) and magnetic resonance angiography (MRA). Conventional angiography has several drawbacks, such as cost, invasiveness, the possibility of causing iatrogenic embolization, dissection, vessel perforation, contrast nephropathy, access site complication and retroperitoneal hematoma.<sup>35</sup> Findings of CAD on conventional angiography include the classic flame-shaped narrowing of the vessel, presence of an intimal flap, pseudoaneurysm formation, and pseudo-lumen formation secondary to the vessel wall tear (Figs. 96.1 and 96.2).<sup>36</sup> However, conventional angiography does not show intramural hematoma or the abnormalities in the vessel wall.<sup>37</sup>

## Magnetic Resonance Imaging/Magnetic Resonance Angiography with Fat Suppression

This is another good imaging tool for CAD as it is noninvasive, lacks radiation exposure, and clearly shows intramural hematoma, which is characteristic for CAD.<sup>38,39</sup> Findings include crescent-shaped intramural hematoma, narrowing of vessel

## Computed Tomographic Angiography

CTA findings in CAD include a flame-shaped occlusion sparing the carotid bulb with abrupt reconstruction at the skull base (Fig. 96.4). In addition, crescent-shaped thickening of the vessel wall, a double lumen sign, intramural hematoma, luminal irregularities, and pseudoaneurysms could be seen. CTA is accurate, more tolerable and less invasive than conventional angiography.<sup>36</sup> It is more feasible to obtain in trauma settings compared to MRI/MRA, and can be performed simultaneously with brain CT scans when diagnosing hemorrhagic or embolic stroke.<sup>44,45</sup> On the other hand, it is contraindicated in patients with contrast allergies, renal insufficiency as well as children or pregnant women who are at risk of radiation exposure. The presence of severe carotid artery calcifications may affect the accuracy of CTA.<sup>38</sup> Meticulous timing of contrast injection is crucial in CTA, thus accuracy can be affected in patients with low ejection fraction.<sup>36</sup>



**Figure 96.3** MRI with fat saturation showing: (A) an increased signal and luminal narrowing of the left internal carotid artery consistent with an intramural hematoma due to dissection; (B), double lumen sign in the left internal carotid artery suggestive of dissection; (C), a small outpunching in the internal carotid artery consistent with a pseudoaneurysm. (From Blum CA, Yaghi S. Cervical artery dissection: a review of the epidemiology, pathophysiology, treatment, and outcome. *Arch Neurosci*. 2015;2(4):e26670.)



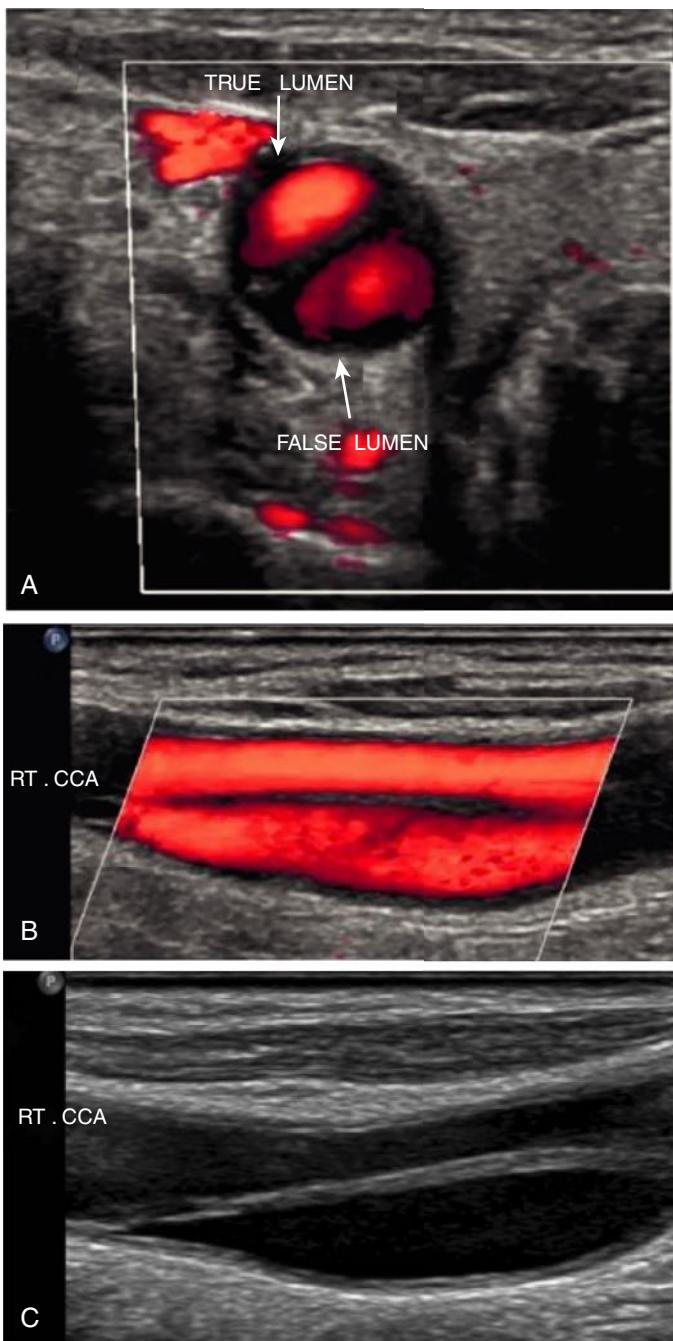
**Figure 96.4** CTA showing tapering occlusion of the right internal carotid artery with abrupt reconstitution at the skull base.

### Duplex Ultrasound

DUS is an inexpensive, noninvasive, bedside tool that has no radiation or contrast hazards (see Ch. 22, Vascular Laboratory: Arterial Duplex Scanning).<sup>36,46</sup> It is also considered a convenient tool for surveillance and follow-up. Its sensitivity in diagnosing CAD may reach 95% when properly used,<sup>46</sup> making it beneficial in trauma patients who are hemodynamically unstable to move to imaging department. Findings on DUS include intramural hematoma, the true and false lumen generated by the dissection (Fig. 96.5), and luminal narrowing or occlusion with high flow velocity.<sup>36,47–50</sup> However, DUS is operator dependent and has several limitations including inability to detect intracranial, vertebral, and above the mandible dissections and difficulty to spot small intraluminal thrombi that does not cause severe luminal narrowing.<sup>51</sup>

### TREATMENT

There are multiple options for treating CAD. Selection of the appropriate treatment depends on the presenting symptoms, patient age, medical comorbidities and underlying cause of the dissection. The main goal of treatment in the acute setting is to prevent brain ischemia, subsequent stroke and to prevent propagation of the dissection. According to the Society for Vascular Surgery (SVS) guidelines, medical treatment with antithrombotic therapy is considered initially.<sup>52</sup> For patients who continue to be symptomatic on medical therapy, the guidelines recommended balloon angioplasty and stenting over open surgery.<sup>52</sup>



**Figure 96.5** DUS of common carotid artery (CCA): (A) transverse view showing classical double lumen sign of the dissection; (B) longitudinal view showing true and false lumen of CCA; (C) B-mode image showing longitudinal view of the CCA with true and false lumen. (From Han M, Choi J, Seo GS, Nam HS. Carotid artery disease in duplex sonography: 3 cases. *Korean J Clin Lab Sci*. 2019;51(1):114–118.)

## Medical Treatment

### Antiplatelet and Antithrombotic Therapy

The mechanism of stroke in CAD is mainly due to platelet aggregation and activation of coagulation factors secondary to endothelial insult, which subsequently leads to thrombus

formation. Medical treatment with antithrombotic medications including antiplatelets and anticoagulants is usually the first line for CAD patients. Antiplatelet agents (like aspirin, dipyridamole, or clopidogrel) may be used alone or in combination with anticoagulants, such as heparin followed by warfarin, with an INR target of 2–3.<sup>53</sup> Treatment duration is usually from 3 to 6 months, as it usually takes 3 months for the arterial lumen to mend.<sup>37</sup> Prolonged treatment may be needed in some cases. There is no clear evidence with respect to when to stop antithrombotic medications. Therefore, patients' symptoms and follow-up imaging should guide the extent of medical therapy and whether further intervention is required.<sup>54</sup> Treatment with antithrombotic medications is associated with increased risk of bleeding either from trauma-related injuries or from other sources. Moreover, anticoagulants may cause the intramural hematoma to expand.<sup>54</sup> The American Heart Association Guidelines indicate no preference between antiplatelet and anticoagulant therapy for CAD treatment.<sup>55</sup> A meta-analysis of 37 randomized, quasi-randomized, or observational comparisons of antiplatelet and anticoagulant therapy in patients with cervical artery dissection revealed a large treatment effect in favor of antiplatelet agents for preventing the primary composite outcome of ischemic stroke, intracranial hemorrhage or death within the first 3 months after treatment initiation (relative risk: 0.32, 95% confidence interval: 0.12 to 0.63). However, analysis including only studies of higher methodological quality revealed a less obvious advantage of antiplatelet therapy over anticoagulation (relative risk: 0.73, 95% confidence interval: 0.17 to 2.30). In 2019, the Antiplatelet Treatment compared with Anticoagulation Treatment for Cervical Artery Dissection (CADISS) randomized clinical trial demonstrated no significant difference between antiplatelet or anticoagulant therapy in reducing the risk of recurrent stroke, mortality or recanalization outcomes after carotid and vertebral dissection.<sup>56</sup> Although there were four strokes in the antiplatelet group ( $n = 126$ ) compared to two strokes in the anticoagulation group ( $n = 124$ ), there was one major hemorrhage in the anticoagulation group.<sup>56</sup> Based on these findings and since antiplatelet agents are easier to use and less costly, the authors recommended using antiplatelet therapy as the first-line treatment unless results of an adequately powered future randomized trial suggest the opposite.<sup>57</sup>

### Thrombolytic Therapy

Thrombolytic therapy using recombinant tissue type plasminogen activator (rtPA) is an approach for the management of acute stroke associated with the dissection within 3–4.5 hours from the beginning of symptoms.<sup>58</sup> It can be administered either intravenously or intraarterially. The most important risk of thrombolytic therapy is spontaneous intracranial hemorrhage.<sup>59</sup> Thrombolytics may also lead to arterial rupture and luminal stenosis caused by the expansion of intramural hematoma, which may worsen the dissection

hemodynamics.<sup>60</sup> In addition, intraarterial thrombolysis can lead to catheter-induced thrombo-embolization and possible rupture of the dissected artery secondary to false lumen catheterization.<sup>61</sup> There is no difference in safety outcomes of thrombolytic therapy between patients with stroke due to CAD versus other stroke etiologies.<sup>60,62–64</sup> Further, there is no clear recommendations from the American Heart Association about the use of thrombolytic therapy in patients with stroke secondary to CAD.<sup>59,65</sup> Data from the Cervical Artery Dissections and Ischemic Stroke Patients (CADISP) multi-center study provides no recommendations against thrombolytic therapy in CAD stroke patients as long as they meet the criteria for thrombolysis.<sup>66,67</sup>

∴ if stroke + pt candidate for lytic  
then can give but risks:

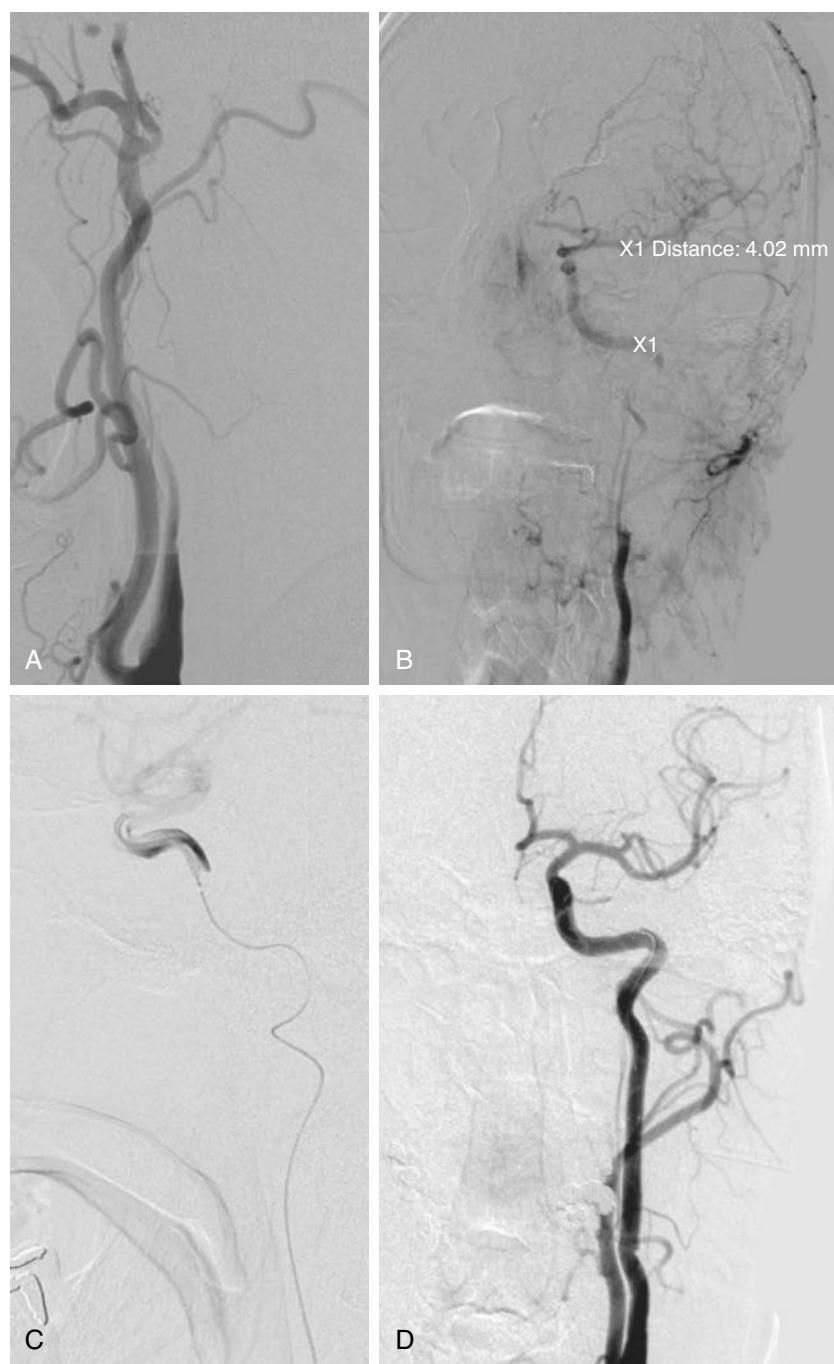
- ICH
- arterial rupture
- ↑ IMH → stenosis ↑

if CDT → catheter induced  
thromboemboli  
→ false lumen entry  
with rupture

## Endovascular Treatment

Endovascular treatment has been widely used to treat cardiovascular and cerebrovascular diseases (Fig. 96.6).<sup>68</sup> However, randomized controlled studies on the use of endovascular treatment or open surgery for CAD patients have not been reported to date and the efficacy and safety of endovascular therapy or surgical treatment have not been evaluated in CAD patients.<sup>69,70</sup> Endovascular treatment is considered in CAD patients in a few specific instances: (1) antithrombotic or thrombolytic therapy is contraindicated or fails to control symptoms; (2) the patient has both embolism and/or obvious hypoperfusion; or (3) the patient has an accompanying worsening

(3)



**Figure 96.6** The patient is a 55-year-old male who presented with left eye visual loss and right-sided weakness. He was found on noninvasive imaging to have concern for an occlusion of the internal carotid artery, likely secondary to dissection. He had a fluctuating neurological exam and this lesion was suspected to be flow-limiting. (A) Selective injection through the guiding catheter positioned in the left common carotid artery demonstrates the flame-shaped tapering of the distal cervical carotid suggestive of a dissection at the skull base. (B) Selective injection through the guiding catheter positioned in the left proximal internal carotid artery demonstrates occlusion but reconstitution of the supraclinoid carotid artery as well as middle cerebral artery and anterior cerebral artery branches. (C) Using a 0.14-inch microwire and a microcatheter the occlusion has been traversed. (D) Two overlapping 6-mm self-expanding stents were deployed and the internal carotid artery intracranially as well as the anterior and middle cerebral artery branches fill well without evidence of branch vessel occlusion.

pseudoaneurysm (see Fig. 96.2).<sup>71–73</sup> For patients with embolism/hypoperfusion, endovascular treatment can retrieve the thrombus, effectively relieve CAD-induced vascular stenosis, and restore cerebral perfusion, therefore reducing the incidence of ischemic stroke. For patients with pseudoaneurysm compression and persistent or progressive symptoms, multiple overlapping stents may reduce the blood flow velocity in pseudoaneurysms, promoting thrombosis, thereby shrinking the pseudoaneurysm or causing it to disappear.<sup>70,73</sup> Endovascular treatment provides prompt reperfusion through recanalization of the obstructed artery with the advantage of fixing possible existing pseudoaneurysms. It can be performed by either angioplasty or stenting and should always be accompanied with an embolic protection device to reduce the risk of embolism during the procedure. Antiplatelet agents should be administered following the procedure, although anticoagulation is not required.<sup>71</sup> Complications of endovascular treatment include iatrogenic arterial dissection, peripheral thromboembolism, arterial spasm, stent thrombosis, arterial wall perforation by the guide wire, stent migration, stroke, and intimal hyperplasia.<sup>73</sup>

A review of 140 patients with history of traumatic (64), spontaneous (49), and iatrogenic (21) dissections managed with stenting demonstrated that stenting is safe and reduces stroke incidence after CAD.<sup>74</sup> Another systematic review of the outcomes and safety of endovascular management with bare metal stenting or balloon-expandable stent placement in 201 patients with internal carotid artery dissections has shown promising results.<sup>71</sup> Operative complications such as access complications, retroperitoneal bleeding, intracranial hemorrhage, brain embolism, acute occlusion of the embolic protection device, and deterioration of the dissection were detected in 6% ( $n = 12$ ). Perioperative complications including transient ischemic attack (TIA) and hemorrhagic transformation were detected in 4% ( $n = 8$ ). In follow-up (mean follow-up period was 16.5 months for imaging data and 20.9 months for clinical data), 190 patients were available, of which 182 were free from any ischemic insult. Endovascular treatment has higher risks than drug therapy and should be limited to select patients, as outlined above. Moreover, CAD patients have a low risk of recurrent ischemic stroke. *vs carotid atherosclerosis*

Dissection leads to clinical events mainly through thromboembolism rather than hypoperfusion; thus, antithrombotic therapy, when indicated, has been the preferred treatment for CAD.<sup>52,75</sup> However, if drug therapy is ineffective and if the patient can generally withstand intervention and is suggested to have acute cerebral infarction, stenosis, occlusion caused by hematoma, or an expanding dissection lesion despite adequate medical treatment, the implementation of endovascular surgery would result in more benefits than risks.<sup>74</sup>

## Open Surgical Treatment

Surgical treatment is considered for the same indications as endovascular treatment. Persistent symptomatic high-grade stenosis as well as enlarging or newly developed aneurysm of the dissected internal carotid artery after medical treatment of 6 months may represent indications for surgical revascularization to prevent

recurrent ischemic or thromboembolic neurological damage.<sup>76</sup> In a study of surgical treatment of 50 carotid dissections, the indication for surgery in 54% was a concern of an aneurysm formation at the distal end of the dissection near the skull base.<sup>76</sup> The authors reported that resection of the embolizing aneurysm or of the severe stenosed artery in conjunction with vein grafting should be the preferred method of surgical treatment especially in young patients. However, surgical treatment in CAD patients is challenging since most dissections occur in the distal segment of the carotid artery ending where the artery enters the petrous bone. This requires exposure and replacement of the ICA up to the skull base in most of the cases, and special surgical expertise is warranted (see Ch. 57, Cerebrovascular Exposure and Ch. 93, Carotid Endarterectomy). The internal carotid artery is exposed by splitting the digastric muscle. Further exposure might be needed and is achieved through styloid fracture at the base, or mandibular subluxation. After that, a clamp is positioned proximal to the dissection to guard against thrombo-embolization.<sup>76</sup> Surgical management strategies include: (1) replacement of the affected internal carotid segment with a saphenous vein graft; (2) carotid artery ligation when the carotid stump pressure is more than 70 mm Hg with no neurological deficits occurring during test clamping; and (3) thromboendarterectomy with patch angioplasty.

Open repair is associated with a higher morbidity and mortality rate than surgical intervention for atherosclerotic disease at the carotid bifurcation.<sup>76</sup> Complications include stroke, cranial nerve palsy, and thrombosis of the graft. Although the endovascular approach has been widely used, open surgery may still be appropriate in cases with penetrating extracranial carotid injuries and lesions unfavorable for endovascular intervention.<sup>77</sup>

## PROGNOSIS AND FUTURE DIRECTIONS

There are multiple factors that will influence the course and overall prognosis of the patient with CAD. Establishing a correct diagnosis is imperative as timely treatment is critically important in preventing ischemia, propagation of the dissection, and in reducing mortality. The risk of recurrence is higher in patients with a positive family history of CAD and underlying connective tissue disorders (e.g., fibromuscular dysplasia, Marfan syndrome, and Ehlers–Danlos syndrome). However, a poorer prognosis is anticipated with traumatic etiology as well as patients presenting with stroke and late diagnosis. Traumatic dissections show higher tendency for aneurysm development and occlusive lesions. Moreover, stroke secondary to CAD has a worse prognosis than a stroke secondary to atherosclerotic lesions.<sup>78</sup>

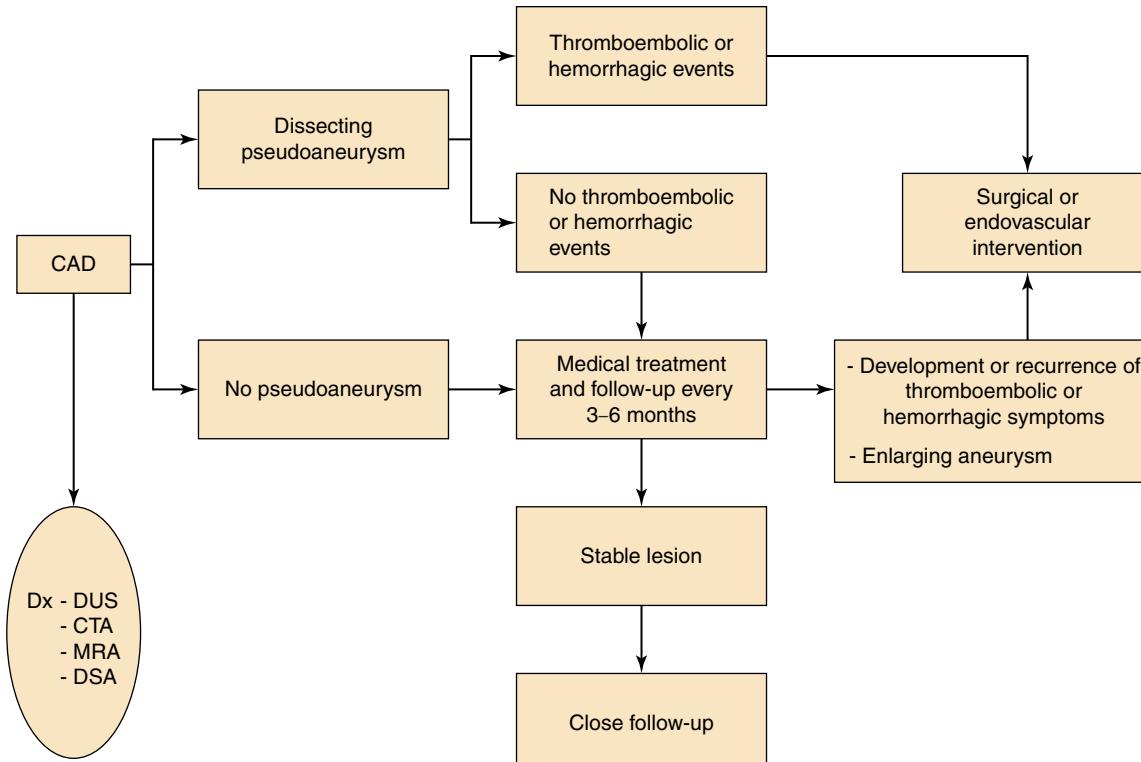
In patients with spontaneous dissections, mortality rate is less than 5% and almost 50% of patients develop a stroke earlier in the course of the disease. Approximately 75% of patients will improve with resolution of the stenotic lesions. Recurrence rate is roughly 1% per year for a 10-year period and is higher in younger people.<sup>79</sup> In a crossover cohort study including 2791 patients with dissection without ischemia, the absolute increase in stroke risk was 1.25% (95% CI, 0.84–1.67) in the first 2

weeks after dissection compared with the same time period 1 year later. The risk of stroke was no longer increased after 4 weeks.<sup>80</sup> In a retrospective cohort study including 432 patients with a history of CAD, with 31 months' follow-up, recurrent dissection developed in 4 (0.9%), recurrent stroke in 4 (0.9%), and TIA in 8 (1.9%).<sup>81</sup>

CAD is an important cause of stroke in young people. Specific risk factors should be identified and these patients should

be counseled on smoking cessation, blood pressure control, healthy eating, and avoiding heavy lifting to avoid recurrence and possible complications. It may be necessary to use antihypertensive drugs to control blood pressure and to reduce arterial wall pressure.<sup>44</sup> Although evidence on the use of statins for the treatment of CAD is lacking, statins may have a positive impact on CAD patients and merit further investigation through large multicenter randomized controlled trials.

## CHAPTER ALGORITHM



CAD, carotid artery dissection; CTA, computed tomographic angiography; DSA, digital subtraction angiography; DUS, duplex ultrasound; Dx, diagnosis; MRA, magnetic resonant angiography.

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A complete reference list can be found online at [www.expertconsult.com](http://www.expertconsult.com).

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# Carotid Artery Aneurysms

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## INTRODUCTION

Extracranial carotid artery aneurysms (ECAA) are rare in comparison with atherosclerotic occlusive disease in the same location. ECAA can occur as a result of atherosclerosis, trauma, dissection, local infection, or after carotid endarterectomy (CEA). These aneurysms occur less frequently than aneurysms involving the intracranial carotid arteries and their branches. The reported incidence of incidental intracranial aneurysms discovered in autopsy studies ranges from 0.8% to 18%.<sup>1,2</sup> The true incidence is unknown, but repair represents only 0.6% to 3.8% of procedures performed for extracranial cerebrovascular disease,<sup>3-6</sup> and is probably <2% of all carotid diseases.

An ECAA is defined as a fusiform or saccular aneurysm which occurs between the common carotid artery (CCA)

origin at the aortic arch and the internal carotid artery (ICA) at the skull base. The external carotid artery may also be involved. The definition of arterial aneurysm is “an artery having at least a 50% increase in diameter compared to the expected normal diameter of the artery.”<sup>7</sup> This definition is easily applied to fusiform aneurysms of the ICA and the CCA. However, the normal carotid bifurcation is typically 40% greater in diameter than the more distal ICA. Therefore, it does not require much dilation to reach this threshold. de Jong et al.<sup>8</sup> proposed that ECAA be defined as bulb dilation >200% of the ICA diameter or >150% of the common carotid artery diameter. This definition has been internationally accepted and applied in the surgical literature. However, strict diameter criteria have not been applied to saccular ECAA, which have been defined more loosely as a distended sac of any size affecting only part of the

\*

ICA or CCA circumference (ECCA Registry). This chapter describes contemporary management of ECAAs, including open surgery and endovascular options.

## HISTORICAL REVIEW

Sir Astley Cooper<sup>9</sup> is credited with the first unsuccessful and successful operations for ECAA in London in 1806 and 1808, respectively. Ligation of the common carotid artery was the sole treatment. Winslow<sup>10</sup> reported an exhaustive review of 124 reported cases through 1925, including 82 patients treated by carotid ligation with a mortality rate of 28%. The first resection of a carotid aneurysm with primary anastomosis was described by Shea et al. in 1955.<sup>11</sup> The first successful resection and repair was in 1952.<sup>12</sup> When inadequate length of vessels precludes primary anastomosis, an interposition graft must be used. Beall et al.<sup>13</sup> performed the first prosthetic graft replacement in 1959. By the 1970s, direct arterial reconstruction or autogenous vein grafting (or both) had supplanted carotid ligation. Endovascular techniques were first applied for ECAAs in the 1990s and continue to have an increasing role.

## EPIDEMIOLOGY

### Population Affected

The population affected and age at diagnosis are directly related to the cause of the aneurysm. The relative frequency of various causes of ECAA has changed over the years. Syphilis, tuberculosis, middle ear, and tonsillar infections were the most common causes of carotid artery aneurysms before the advent of antibiotics. The majority of these early cases were pseudoaneurysms related to trauma or “erosions” from middle ear infections and tonsillitis, rather than true atherosclerotic aneurysms.<sup>10</sup> Therefore, most patients were between 20 and 40 years of age, and the surgical morbidity and mortality were excessive. Increasing the use of antibiotics for head and neck infections significantly reduced the incidence of mycotic arterial infections from local extension of a septic process. Mycotic ECAAs should not be entirely dismissed as a problem of the past, since modern series suggest that mycotic ECAAs may still be encountered in immunocompromised patients.<sup>14</sup>

Atherosclerotic degeneration, dissection, trauma, and previous carotid surgery have supplanted infection as the most frequent causes of ECAA (Table 97.1).<sup>3,15–27</sup> True degenerative atherosclerotic carotid aneurysms affect men twice as often as women,<sup>18,28</sup> and affect right and left sides equally. Most patients are older than 60 years, but degenerative carotid artery aneurysms have also been reported in children.<sup>29</sup> There does not seem to be a specific racial distribution. Earlier reports suggested that the incidence of ECAAs in patients with other aneurysmal disease ranged from 14% to 25%.<sup>10,16</sup> Most modern series have not reported similar findings.

Blunt trauma, dissection, and penetrating injury to the neck can result in a carotid pseudoaneurysm. Such lesions are typically encountered in a younger population. Pseudoaneurysms after CEA performed for occlusive disease usually affect individuals in their sixth or seventh decades of life. ECAAs also

**TABLE 97.1** Aneurysm Characteristics

| Variables             | N    | (%) |
|-----------------------|------|-----|
| Reports included      | 39   |     |
| Patients              | 1239 |     |
| Aneurysms             | 1322 |     |
| Etiology              |      |     |
| Atherosclerosis       | 509  | 38  |
| Traumatic             | 144  | 11  |
| Mycotic               | 65   | 5   |
| Other                 | 329  | 25  |
| Not reported          | 275  | 21  |
| Symptoms <sup>a</sup> |      |     |
| Cerebral ischemia     | 476  | 36  |
| Mass                  | 442  | 33  |
| Asymptomatic          | 172  | 13  |
| Compression           | 119  | 9   |
| Local pain            | 39   | 3   |
| Other                 | 185  | 14  |
| Location              |      |     |
| ICA                   | 608  | 46  |
| Bifurcation           | 261  | 20  |
| CCA                   | 108  | 8   |
| ECA                   | 9    | 1   |
| Not reported          | 336  | 25  |

Note. Other etiology includes granulomatous diseases, connective tissue disorders, iatrogenic aneurysms, post-carotid endarterectomy cystic medial necrosis, and arteritis.

<sup>a</sup>Some patients experienced multiple symptoms from one aneurysm.

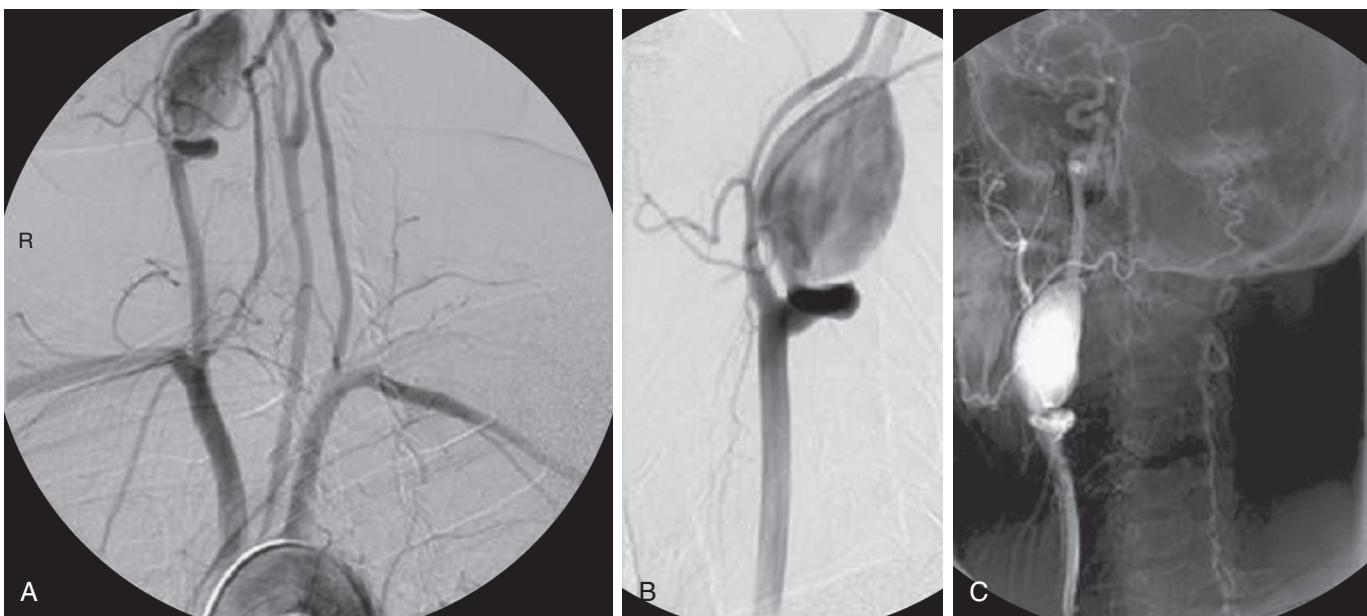
CCA, common carotid artery; ECA, external carotid artery; ICA, internal carotid artery.

From Welleweerd et al. Management of ECAA. *Eur J Vasc Surg*. 2015;50:141–147, Table 1.

occur in patients who have undergone extensive surgery and radiation therapy for head and neck cancer.<sup>30</sup> There have been several reports of ECAAs in patients with connective tissue disorders, including Ehlers–Danlos syndrome, neurofibromatosis, Behçet disease and Marfan syndrome.<sup>31</sup> In such patients, it is unwise to use autologous vein for arterial reconstruction due to unacceptable risk of late aneurysmal degeneration.

### Incidence

Because these aneurysms are rare, it is difficult to quantify the true incidence or to determine if the frequency is increasing. A search of the world's literature from 1687 to 1977 found only 853 ECAAs.<sup>4,5</sup> A more recent systematic review of single-center series with at least 10 patients from 1900 to 2014 reported 1239 patients with 1322 ECAAs.<sup>6</sup> Advances in vascular and soft tissue imaging may have contributed to greater recognition, at least partially accounting for the larger number of ECAAs reported over a shorter time period.<sup>32</sup>



**Figure 97.1** Arch (A) and right carotid (B, C) arteriograms showing a large extracranial carotid artery aneurysm involving the proximal internal carotid artery.

Other authors have quantified ECAA repairs as a percentage of their total operative carotid workload. Pooled data from the largest single-center series (1960–1995) that included CEA volume during that same period demonstrated a total of 17,854 carotid procedures, 276 of which were performed for ECAA, for a relative incidence of 1.54%. El-Sabour and Cooley<sup>3</sup> from the Texas Heart Institute reported 67 ECAs treated between 1960 and 1995. During the same period, their institution performed 7394 peripheral aneurysm repairs and 4991 carotid operations. Their 1.31% relative incidence is consistent with other published series.<sup>17,33</sup> The low incidence at large referral centers suggests that the true incidence of ECAs is probably less than 1% of all carotid disorders.

## PATHOGENESIS

### Etiology

#### Degenerative/Atherosclerotic

The most common cause of ECAs is atherosclerosis and subsequent degeneration accounting for up to 40% of ECAs. Degenerative aneurysms are true aneurysms which demonstrate disruption of the internal elastic lamina and thinning of the media on histology. They tend to be fusiform rather than saccular and are most commonly located at the bifurcation and proximal ICA, where atherosclerosis is common (Fig. 97.1). Atherosclerotic aneurysms that do not involve the carotid bifurcation are frequently saccular and occur in patients with severe hypertension. Most bilateral, nontraumatic ECAs are also saccular.

#### Post-Traumatic Causes

The incidence of carotid artery injury in civilian trauma series ranges from 12% to 17% of penetrating neck injuries (see Ch. 180, Vascular Trauma of the Head and Neck). The internal

jugular vein is the most frequently injured vascular structure and the common carotid artery is the most frequent site of arterial injury from penetrating neck trauma. Penetrating injuries involving the extracranial carotid arteries can have two important vascular sequelae: arteriovenous fistula and pseudoaneurysm formation. Carotid pseudoaneurysm has also been reported due to iatrogenic injury from attempted placement of a catheter in the internal jugular vein.

Blunt cerebrovascular injury (BCVI) occurs in 0.18% to 2.7% of blunt trauma patients, and typically involves the distal ICA just below the skull base. Traumatic dissections can degenerate into pseudoaneurysms, which can enlarge, embolize thrombus, or rupture. Some authors advocate treatment of grade 3 pseudoaneurysms that persist beyond a week.<sup>34</sup> Many of these patients have associated head injuries precluding antiplatelet therapy and anticoagulation initially. Enlarging or symptomatic pseudoaneurysms from blunt trauma are typically diagnosed some time after the original injury, at which point patients can safely be treated with preprocedural clopidogrel and intraprocedural heparin.

#### Post-Endarterectomy Aneurysms

CEA-related pseudoaneurysms are frequently reported aneurysms of the extracranial carotid arteries. El-Sabour and Cooley<sup>3</sup> demonstrated that 57% of their 67 cases were a result of previous CEA. Zhou et al.,<sup>27</sup> in a later series from the Baylor College of Medicine, found post-CEA pseudoaneurysm to be the principal etiology in 36% of 42 cases. The development of post-CEA pseudoaneurysm can be caused by suture line failure or patch degeneration with or without infection. El-Sabour and Cooley<sup>3</sup> reported seven patients in whom the silk sutures, used before the advent of monofilament sutures, degenerated. Infectious complications have been reported in a third of post-CEA pseudoaneurysms. Patients typically have local signs and

symptoms of infection, including pain and erythema at the operative site or draining neck sinuses. Infection of synthetic patches may also be identified at the time of removal, with *Staphylococcus* species being the most commonly cultured causative organism. Aneurysmal degeneration of saphenous vein patches has also been reported.

### Arterial Dysplasia

Arterial dysplasia, usually a fibromuscular variant, is a frequent reported cause of ECAAs in some smaller series.<sup>23,30,35</sup> The arteries of patients with fibromuscular dysplasia typically display a beaded appearance caused by alternating stenotic webs and dilations. These lesions may lead to ICA dissection and pseudoaneurysm formation.

### Pathology

The rarity of primary carotid artery aneurysm in comparison with carotid occlusive disease makes it difficult to accept atherosclerosis as the sole cause. Histologic study of carotid artery aneurysms, however, reveals many of the findings seen in atherosclerotic specimens: fragmentation of the elastic lamina, lipid-laden foam cells, extracellular accumulation of cholesterol, deposition of hemosiderin, degeneration of the media, and neoangiogenesis. Thinning of the media and fragmentation of the internal elastic lamina are also seen, as in aging arteries. Just as many authorities propose for abdominal aortic aneurysms, atherosclerosis is clearly a coexisting finding for many ECAAs but may not be the only cause.<sup>36,37</sup>

## CLINICAL FINDINGS

### Physical Findings/Symptoms

The symptoms of ECAAs vary according to their location, size, and etiology. The most common finding is a painless pulsatile neck mass, which was the initial symptom in 93% of patients in the series reported by Zhou et al.<sup>27</sup> Tenderness and overlying erythema, especially if associated with fever, should raise suspicion for an infected aneurysm.

An ICA aneurysm is occasionally recognized as a pulsating mass in the tonsillar fossa or pharynx with little or no manifestation of its presence externally in the neck. The classic analytic study by Shipley et al.<sup>38</sup> emphasized that aneurysms of the ICA are directed inward into the throat, whereas those of the common carotid artery are directed outward into the neck. The absence of cervical swelling in the former is attributed to the dense, deep cervical fascia and muscles attached to the styloid process anteriorly and the cervical vertebrae posteriorly, which crowd the gradually dilating aneurysm inward toward the tonsillar fossa, where the thin superior pharyngeal constrictor muscle and mucous membrane offer only minimal resistance to inward protrusion.

Aneurysms that arise at or proximal to the carotid bifurcation are readily palpable and usually pose no diagnostic difficulty. Those arising from the ICA near the base of the skull can cause diagnostic problems. A chronic unilateral swelling of

the posterior pharynx should raise the level of suspicion, especially when other physical signs are lacking, bizarre, or atypical. Otolaryngologists are often the first to see these lesions. A high index of suspicion usually leads to computed tomography angiography (CTA), magnetic resonance angiography (MRA), or catheter-based angiography, any of which is nearly always diagnostic when an aneurysm is present.

### Neurologic Symptoms

Hemispheric neurologic events may also be the initial symptom of ECAAs. In one series, 43% of the 65 patients had neurologic symptoms, including amaurosis fugax and transient ischemic attacks.<sup>3</sup> Three of these 28 patients suffered a stroke preoperatively. Zhou et al.<sup>27</sup> reported 14% of patients presented with transient ischemic attack, stroke, or Horner syndrome. Most neurologic events are secondary to embolization of thrombotic material from within the aneurysm wall, but some could be potentially related to diminished flow and compression of the ICA from the mass effect of large aneurysms. Transient ischemic attacks appear to occur twice as often as completed strokes.<sup>16,18,39</sup>

### Cranial Nerve Dysfunction

ECAAs can present with a variety of symptoms related to cranial nerve dysfunction. Distal ICA aneurysms are more frequently associated with cranial nerve dysfunction than more proximal aneurysms, but nerve injury or compression can occur with large proximal carotid aneurysms as well. The sympathetic nerve fibers of the carotid plexus accompany the ICA as it enters the cranium through the foramen lacerum and traverses the carotid canal in the petrous portion of the temporal bone. Compression of these fibers can result in Horner syndrome. Common carotid artery aneurysms can result in hoarseness from compression of the vagus or recurrent laryngeal nerve. Compression of the facial nerve can cause severe facial pain.

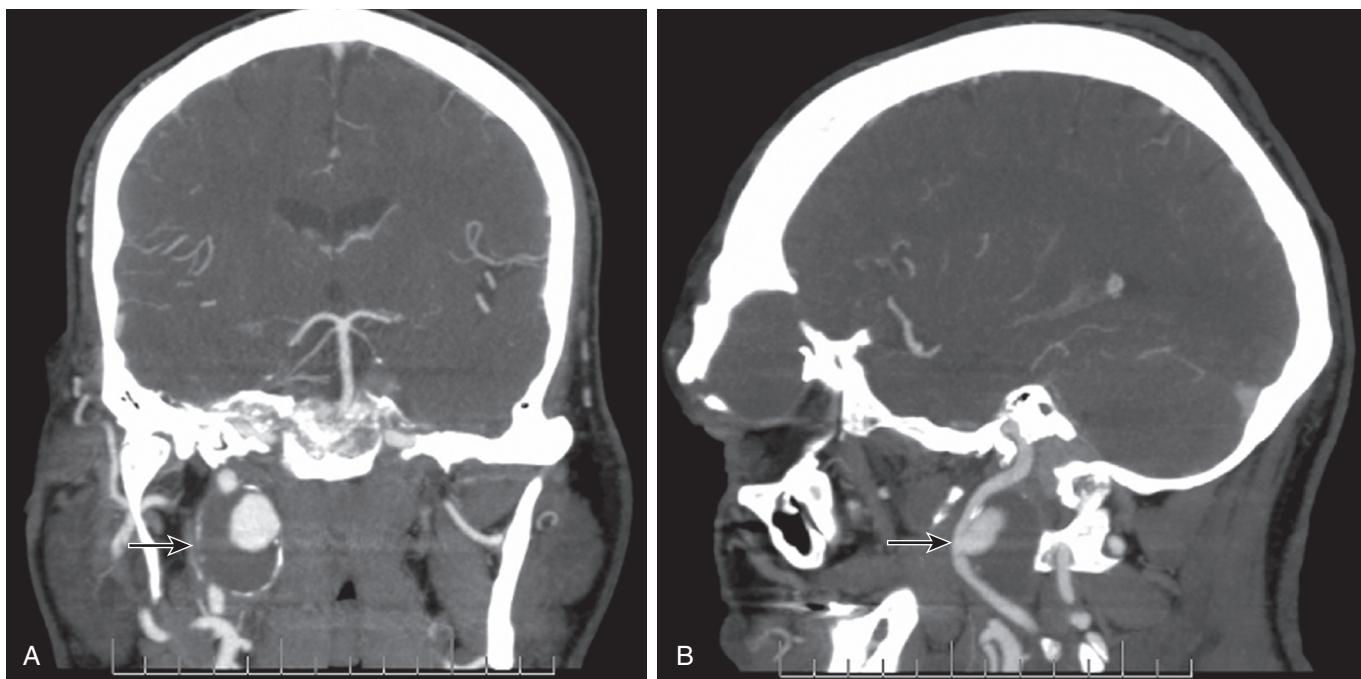
### Dysphagia

Occasionally, the mass of a large aneurysm can cause difficulty swallowing and is discovered during evaluation for dysphagia. Protrusion of the aneurysm into the pharyngeal constrictor muscles can produce dysphagia. Difficulty swallowing may also be caused by nerve compression.

### Hemorrhage and Rupture

Fortunately, hemorrhage and rupture are now infrequent manifestations of carotid artery aneurysms. Herald bleeds can occur before massive rupture. When these aneurysms do rupture into the oropharynx, the bleeding is profound and potentially lethal due to suffocation and aspiration. Mycotic aneurysms are especially susceptible to rupture and bleeding.

Another group of patients at risk for carotid blowout syndrome<sup>28</sup> are individuals following head and neck surgery and/or radiation therapy for head and neck cancer. Lesley et al.<sup>30</sup> reported their experience with 16 actual or impending carotid ruptures in 12 patients. Ten of these patients had had treatment for head and neck cancer. Risk factors



**Figure 97.2** Anterior (A) and lateral (B) computed tomography arteriogram reconstructions of a 4-cm distal internal carotid artery aneurysm (arrow). This aneurysm was treated with a covered stent graft with good result. (Courtesy, Steven Oweida, MD and John Parp Jones, MD.)

identified for the development of carotid blowout as a complication of treatment of head and neck cancer included thrombosis of the vasa vasorum secondary to wound infection, direct exposure and desiccation of the carotid artery, stripping of the carotid sheath, exposure of the artery to saliva, adjacent tissue necrosis, pharyngeal fistula formation, and previous radiation.

### Differential Diagnosis

The differential diagnosis for a pulsatile neck mass is broad. The most common cause is a tortuous, kinked, or coiled carotid artery. Duplex ultrasound and occasionally CTA are required to help differentiate this finding from an ECAA. The differential diagnosis also includes normal but prominent carotid bifurcation in a thin neck, cervical lymph nodes overlying the carotid bifurcation, carotid body tumors, glomus jugulare tumors, cervical metastatic disease, branchial cleft cysts, and cystic hygromas.

### DIAGNOSTIC EVALUATION

Duplex ultrasound is the initial diagnostic imaging modality of choice for suspected ECAs. Aneurysms located high in the distal ICA, such as those related to blunt cervical carotid dissection, are notoriously missed by ultrasound. Such aneurysms require a high index of suspicion leading to further imaging with CTA or MRA. MRA has the advantage of being able to distinguish old from recent thrombus, a differentiation that is particularly helpful in cases of carotid dissection. CTA has the benefit of visualizing the relationships of bony

anatomic landmarks, which are critical in deciding whether a lesion is considered “surgically inaccessible” and requires an endovascular intervention (Fig. 97.2). MRA and CTA, when obtained in conjunction with head and brain imaging, provide information regarding the circle of Willis and collateral cerebral circulation.

Catheter-based angiography was previously considered mandatory to obtain the detailed vascular anatomy information necessary to plan surgical treatment of ECAs.<sup>40</sup> Currently, diagnostic arteriography is usually unnecessary and may generally be reserved for endovascular interventions because of the potential stroke risk associated with this invasive diagnostic procedure. Diagnostic angiography may be used in the rare case in which open or endovascular arterial reconstruction are not considered to be feasible, and carotid ligation may be necessary. This should be considered only after exhausting all options and as a life-saving measure. Combined pre-procedure noninvasive imaging of the circle of Willis anatomy and a balloon occlusion test of the ipsilateral ICA have been recommended before carotid ligation. The latter examination involves a period of occlusion with an end-hole balloon occlusion catheter in patients who are awake, anticoagulated, and at baseline blood pressure. The end-hole catheter also allows measurement of carotid artery “stump” pressure or back-pressure. A stump pressure greater than 50% of mean systemic pressure indicates adequate cerebral blood flow during the carotid balloon occlusion test.<sup>41</sup> Occlusion of the ICA is typically performed for 30 minutes, and the awake patient is assessed for neurologic changes. Blood pressure is also pharmacologically lowered to assess tolerance of hypotension. Several reports have detailed the inadequacy of the balloon

occlusion test to accurately predict tolerance of carotid occlusion in 10% to 20% of patients.<sup>42,43</sup> Specifically, ICA ligation is associated with a 5%–25% risk of stroke even in patients who tolerated balloon occlusion<sup>44</sup> and a 20% mortality due to inadequate collaterals.<sup>45</sup> In patients in whom ipsilateral hemispheric neurologic events developed after carotid ligation, thromboembolic events secondary to disturbed flow were thought to be the cause. These reports stress the importance of anticoagulation for 6 weeks to 3 months when carotid ligation is performed.

## NATURAL HISTORY

Based on prior case series demonstrating high risk of TIA, stroke, or rupture associated with nonoperative treatment, the recommendation has classically been to intervene on almost all carotid aneurysms.<sup>10,16,18,19,27</sup> However, the etiology of ECAAs has shifted from mycotic or traumatic to degenerative or postprocedural, which have a more benign natural history. Furthermore, given advances in medical therapy with statins, antiplatelet, and anticoagulation as well as improved imaging techniques, medical management in properly selected high-risk patients with small true aneurysms may be a reasonable option. This was demonstrated in a Mayo Clinic series, including 75/141 ECAAs over a 15-year period treated nonoperatively. There were 25 true aneurysms and 116 pseudoaneurysms. Medical management with antiplatelet therapy or anticoagulation as well as serial imaging occurred in 10 patients with true aneurysms and 65 patients with pseudoaneurysms. The size of the ECAA, as well as the age of the patient, symptomatic status and comorbidities, played a major role in the decision to pursue nonoperative treatment. True aneurysms undergoing observation had a mean diameter of 12.0 mm compared with 21.2 mm in those that were treated with open surgery. Pseudoaneurysms treated medically had a diameter of 10.2 mm compared with 20.9 mm treated with open surgery and 14.5 mm undergoing endovascular intervention. During a mean follow-up of 77 months, none of these patients progressed to needing an intervention and none of them suffered death or major morbidity related to the ECAA. This is the largest series published to date and the first to demonstrate the safety of medical management in patients with small ECAAs. Clearly, more research into proper patient selection based on size, presenting symptoms, etiology, associated comorbidities, aneurysm location, and associated thrombus morphology is needed to guide treatment decisions.

①

② In summary, for ECAAs that are enlarging, greater than 2 cm, mycotic, thrombogenic or symptomatic, operative intervention is warranted in the vast majority of cases. Judicious serial observation of small, asymptomatic ECAA, especially in the elderly, is likely safe and justified.

## CLASSIFICATION

Attigah et al.<sup>46</sup> conducted a retrospective review of 57 patients who underwent 64 carotid reconstructions for ECAA

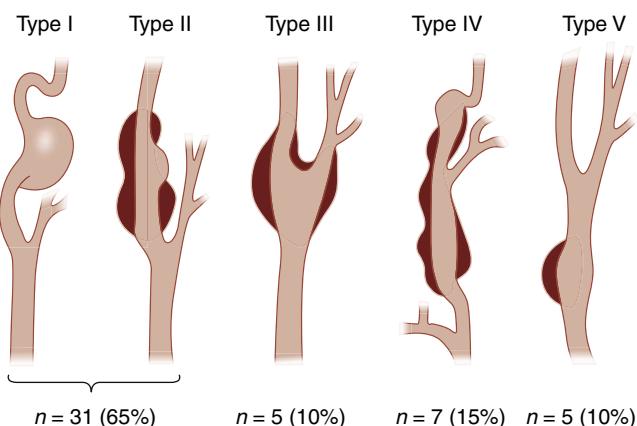


Figure 97.3 Classification of Extracranial Carotid Aneurysms.

between 1980 and 2004. Their group defined five different types of ECAA based on the anatomy of the aneurysm. This classification system has proven useful in the surgical literature for describing the morphology as well as the basis for selecting a particular surgical approach. Type I ECAAs are isolated, short aneurysms of the internal carotid artery above the carotid bulb. Type II ECAAs are long aneurysms of the ICA, ranging from the carotid bulb up to the line of Blaisdell, which is the line between the mastoid process and the angle of the mandible.<sup>33</sup> Type III ECAAs are aneurysms of the proximal ICA and the carotid bifurcation. Type IV ECAAs are extensive aneurysms involving the CCA and ICA or concomitant separate CCA and ICA aneurysms. Type V aneurysms are isolated CCA aneurysms<sup>46</sup> (Fig. 97.3).

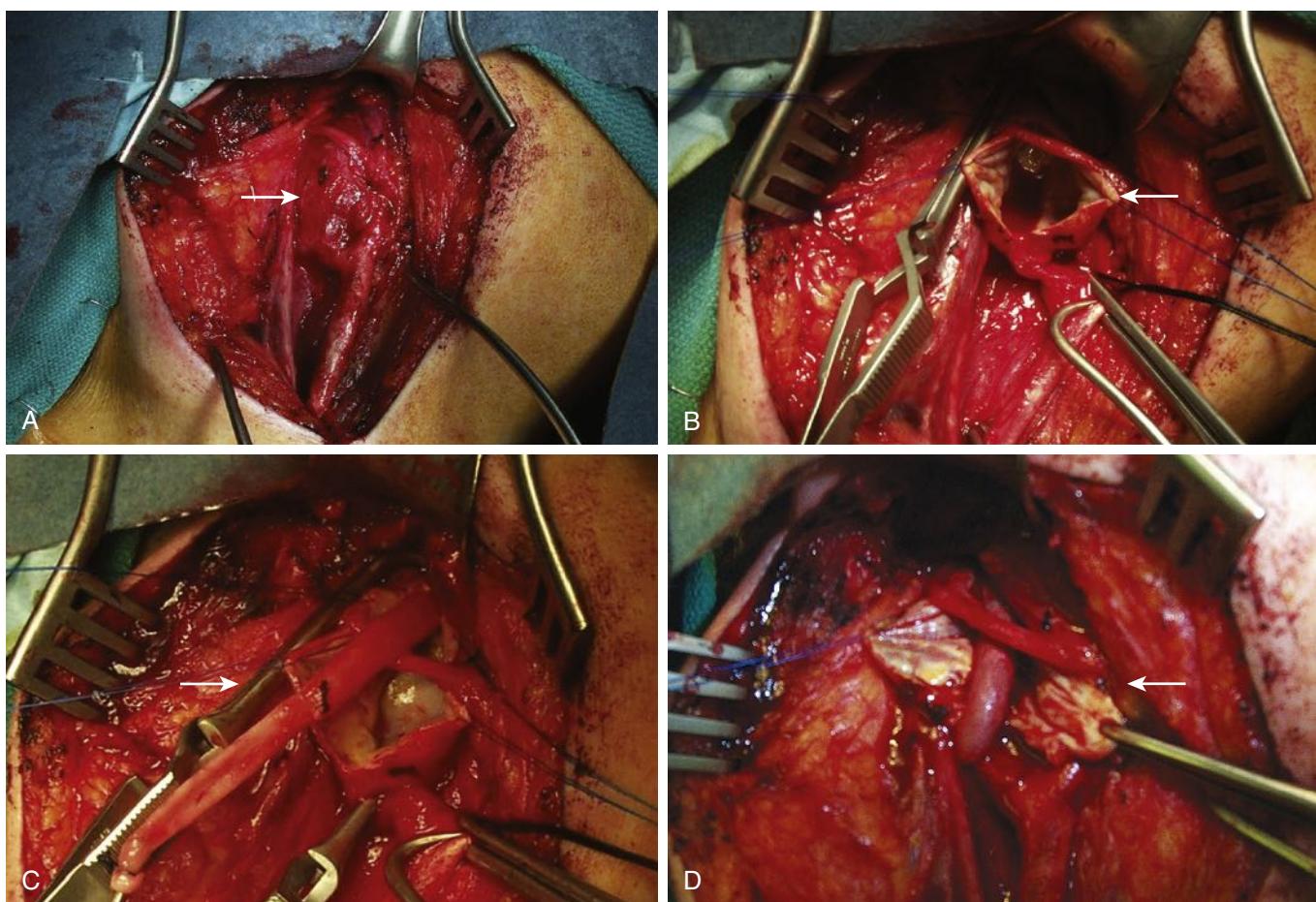
## TREATMENT

The primary objective in the treatment of ECAAs is to prevent permanent neurologic deficits that can arise from atheroembolism and thromboembolism. This is accomplished by exclusion of the aneurysm from the arterial circulation and restoration of antegrade flow. The choice of therapy should be patient-specific based on the location, size, and underlying cause as well as comorbidities. The modern vascular surgeon has a wide armamentarium of open surgical and endovascular options which have proven effective.

### Open Surgical Therapy

#### *Resection and Reconstruction*

Resection of the aneurysm with restoration of antegrade flow is the conventional treatment of ECAAs in contemporary practice (Fig. 97.4). This surgical option applies to lesions involving the common carotid artery and proximal third of the ICA. Aneurysms involving distal portions of the ICA may require further adjuncts to gain distal exposure and control.<sup>32,47</sup> Cranial nerve injury rates are between 4% and 20%, including the facial, vagus, spinal accessory, hypoglossal, and glossopharyngeal nerves. Similar to CEA, minimal aneurysm manipulation prior to vascular control is recommended to decrease risk of embolization.



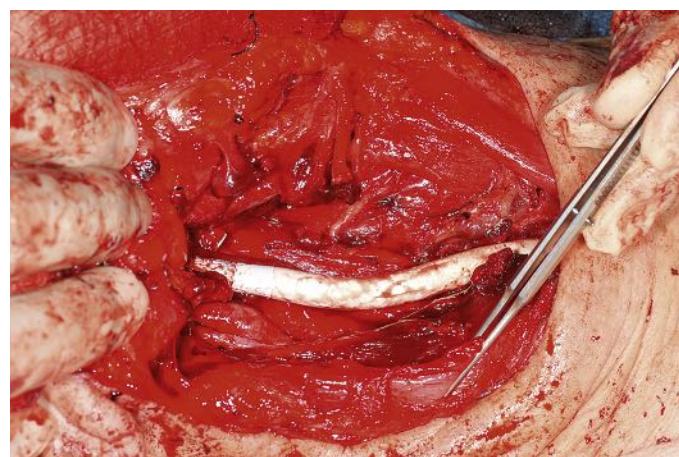
**Figure 97.4** (A–D) Open repair of the extracranial carotid artery aneurysm seen in Figure 97.1 via reversed saphenous vein interposition.

After resection of a carotid artery aneurysm, several reconstruction options are available. Small saccular aneurysms with narrow necks can be resected and closed primarily or with a patch. Mobilization of a tortuous carotid artery may be resected with primary end-to-end anastomosis. Autologous or prosthetic interposition grafts can be used with excellent results (Fig. 97.5). Autologous grafts are preferred if infectious etiology is suspected.

In cases of true ECAA, the entire aneurysmal segment should be replaced to prevent aneurysmal degeneration of abnormal artery left *in situ* after partial excision. In the treatment of patch pseudoaneurysm following prior CEA, resection back to normal arterial wall plus redo patch angioplasty with autologous conduit when infection is a possibility is an acceptable alternative to interposition grafting.

#### Pseudoaneurysm Repair After Previous Carotid Endarterectomy

Patch angioplasty during CEA has become routine in an effort to decrease the restenosis rates seen after primary closure of the arteriotomy (see Ch. 93, Carotid Endarterectomy). Non-autogenous materials currently used for patch angioplasty include Dacron, polytetrafluoroethylene, and bovine pericardium. In current practice, patch pseudoaneurysm after CEA



**Figure 97.5** Treatment option of surgical exclusion with prosthetic interposition graft for a large extracranial carotid artery aneurysm.

is more frequently related to infection than to degeneration of the patch. In one series, 28/141 ECAs were pseudoaneurysms from prior CEA, and 79% had a Dacron patch. This trend was also seen in another large case series where 58% of pseudoaneurysms were related to Dacron patch use. Some of these used silk suture or were associated with infection.

## Open Surgical Technique

Methods of cerebral monitoring and protection during carotid cross-clamping are the same as those used during conventional CEA and include electroencephalographic waveform analysis, selective shunting based on carotid stump pressure, and routine shunting. General anesthesia is usually recommended because of the difficult exposure and longer operative times for aneurysm repair than for CEA. Routine or selective shunting are acceptable.

Large aneurysms and aneurysms extending to the distal ICA can be technically challenging. Nasotracheal intubation should be considered because it allows complete closure of the jaw which opens the space around the distal ICA. Several additional techniques can be used to improve distal operative exposure, including:

1. The first step in obtaining distal exposure should always be extension of the incision to curve in a posterior fashion behind the ear to the mastoid process.
2. Divide the ansa cervicalis to allow gentle retraction on the hypoglossal nerve.
3. Divide the posterior belly of the digastric muscle.
4. Divide the occipital artery and adjacent venous branches.
5. Divide the ascending pharyngeal artery.
6. Divide the sternocleidomastoid muscle from its mastoid attachment and elevate or resect the parotid gland. Careful dissection of the facial nerve and its branches is mandatory.
7. Remove the styloid process and its attached muscles.
8. Subluxate the mandible to increase the width of exposure at the skull base by approximately 1 cm. This maneuver is in general performed by an oral surgery team after nasotracheal intubation and prior to carotid exposure.
9. Drill and remove portions of the inferior surface of the petrous portion of the temporal bone. This process usually requires a multidisciplinary approach, including the participation of nonvascular surgeons with experience in skull base surgery.
10. Use of intraluminal balloons, usually as part of a shunt (e.g., the Pruitt-Inahara shunt), to control distal internal carotid back-bleeding can be a useful adjunct when distal control is difficult.

Once proximal and distal control is obtained, the decision is made whether to perform complete aneurysm exclusion or partial resection. With a true atherosclerotic aneurysm, replacing the entire aneurysm with vein interposition or Dacron is reported. An advantage of endoaneurysmorrhaphy technique is that it may reduce the risk of cranial nerve injury since the cranial nerves are not in jeopardy during dissection of the aneurysm wall. As with repair of abdominal aortic aneurysms, the sac of the aneurysm is used to cover the interposition graft.

For prosthetic patch pseudoaneurysm, El-Sabrout and Cooley<sup>3</sup> reported good results with resection of the pseudoaneurysm back to normal arterial wall and repeat patch angioplasty. Autologous material to patch the artery should be considered because infection is frequently the cause of patch aneurysm. An in-line straight shunt, as opposed to the

Javid type, can be used during vein interposition to tailor the vein graft to the appropriate length so that kinking can be avoided. The vein interposition graft is telescoped over a straight shunt. After the distal anastomosis is performed, the vein graft is pulled to length over the shunt and trimmed accordingly. The shunt is then removed just before completion of the proximal anastomosis, and flushing maneuvers are performed in the usual fashion.<sup>29</sup> Intraoperative duplex ultrasound is helpful to confirm technical excellence of carotid reconstructions.

## Ligation

The subsequent development of modern reconstructive vascular techniques has eliminated ligation as a standard therapy for most ECAAs. Ligation was performed in just 1 of the 65 patients with carotid aneurysms treated at the Texas Heart Institute over a 35-year period.<sup>16</sup> Ligation of the carotid artery may still be necessary in emergency situations of arterial rupture, especially if infection is the cause and the artery is deemed unreconstructable. If an elective carotid ligation is being considered, preoperative evaluation with the carotid balloon occlusion test and stump pressure measurement is necessary but does not eliminate the risk of postoperative stroke and/or death. Aneurysms involving the external carotid artery alone are typically ligated without reconstruction or significant sequelae.

It is recommended that patients undergoing carotid ligation be started on heparin therapy and then switched to warfarin anticoagulation for a period to prevent distal embolization because the ICA progressively fills with thrombus, with the risk of stump embolization. This approach is analogous to management of carotid artery trauma that might require ligation of the ICA. The duration of such anticoagulation is not standardized, but several groups have recommended a 2-week to 3-month course of therapy.<sup>48,49</sup>

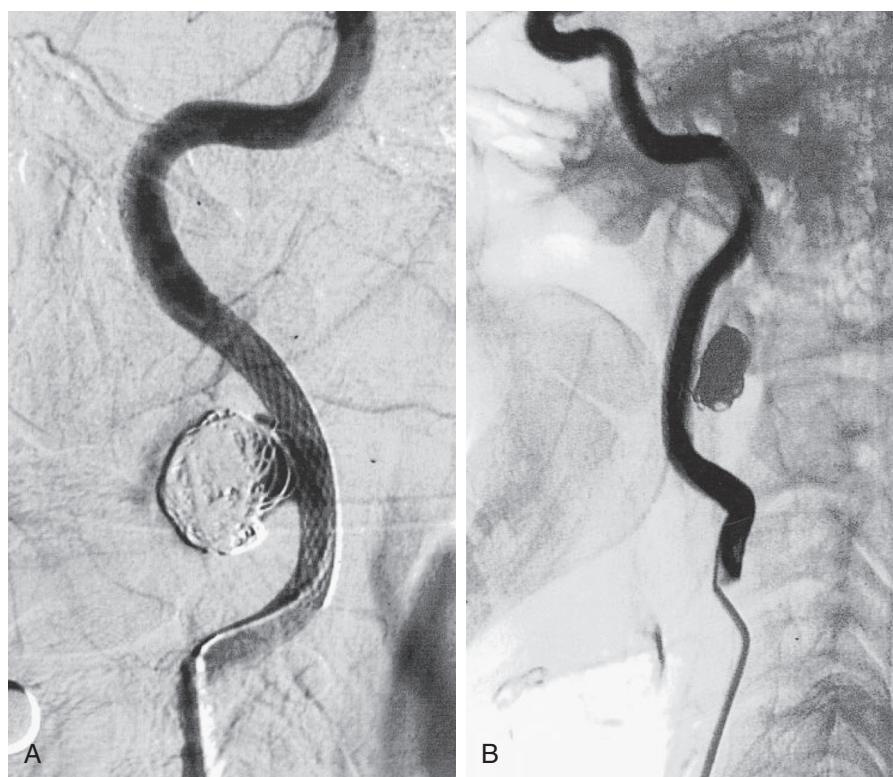
## Adjunctive Measures

*Extracranial-to-intracranial (EC-IC) bypass*, wrapping the aneurysm in fascia or mesh, and saphenous vein bypass through the aneurysm to the petrous portion of the carotid have all been described but largely abandoned due to failure to improve patient outcomes or decrease stroke risk.<sup>50,51</sup>

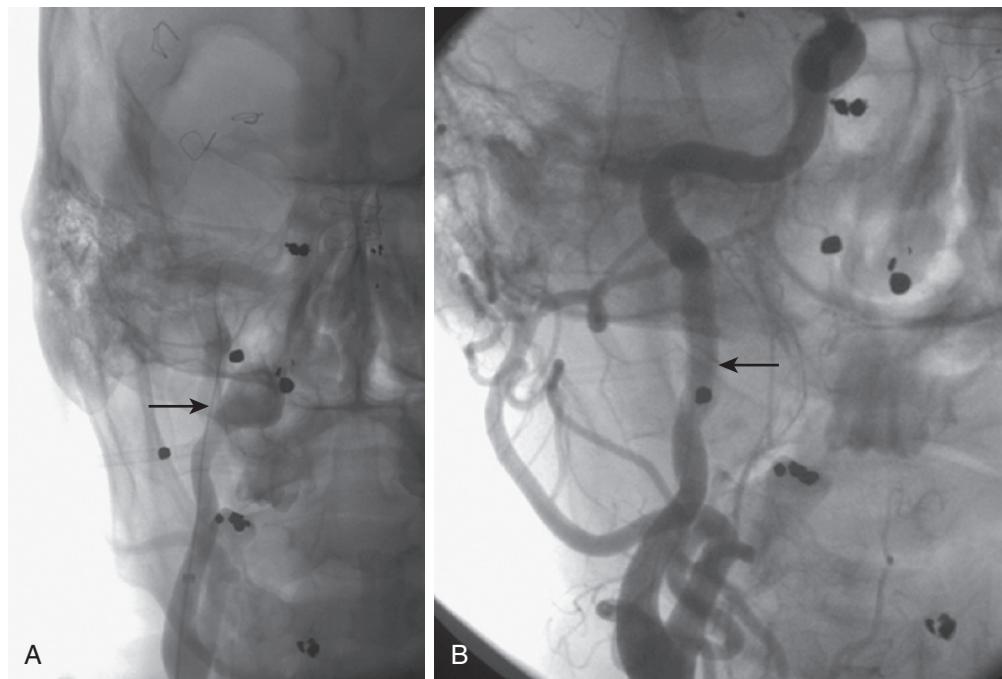
## Endovascular Therapy

Endovascular management of ECAAs offers the advantages of avoiding a difficult dissection and eliminating the need for high cervical exposure, thus reducing the risk for cranial nerve injuries and other procedure-related complications. Although most cranial nerve dysfunction is temporary, the incidence of such injuries reaches 20% in some series.<sup>27</sup> Although rare, permanent cranial nerve injuries can be devastating.

Several endovascular techniques for the treatment of ECAAs have been reported, including bare-metal stents with and without trans-stent coiling (Fig. 97.6),<sup>52</sup> placement of double stents,<sup>53</sup> autogenous vein graft-covered stents,<sup>54</sup> endovascular



**Figure 97.6** After placement of a self-expanding stent across the neck of the aneurysm, a microcatheter is used to introduce coils into the aneurysm sac. (A) Completion arteriogram documented a patent internal carotid artery (ICA) with aneurysm exclusion. (B) Arteriography after 5 months showed excellent flow through the ICA with exclusion of the pseudoaneurysm. (From Bush RL, Lin PH, Dodson TF, et al. Endoluminal stent placement and coil embolization for the management of carotid artery pseudoaneurysms. *J Endovasc Ther*. 2001;8:53–61.)



**Figure 97.7** (A) Selective right carotid arteriogram revealing the distal right internal carotid artery aneurysm demonstrated in Figure 97.2. (B) Placement of a 5 mm × 2.5 cm Gore Viabahn (W.L. Gore and Associates, Inc., Flagstaff, AZ) covered stent graft for treatment of the distal right internal carotid artery aneurysm seen in A and Figure 97.5.

coil or balloon occlusion,<sup>55</sup> and placement of covered stent grafts (Fig. 97.7).<sup>56</sup>

Percutaneous injection of thrombin under ultrasound guidance has become the treatment of choice for traumatic pseudoaneurysms of the common femoral artery. Holder et al.<sup>57</sup> reported successful thrombosis of a traumatic carotid pseudoaneurysm by endovascular balloon occlusion of the

neck of the aneurysm followed by percutaneous injection of thrombin after inadvertent central venous catheter puncture. We have had no personal experience with this technique and have concerns about the risk for embolization once the balloon is deflated.

In an early series of endovascular intervention for ECAA including 14 patients, stent grafts were used in seven patients, carotid

stenting with trans-stent coiling in six, and endovascular balloon occlusion in one.<sup>27</sup> In most series of endovascular treatment of carotid artery aneurysms, a variety of endovascular therapies have been used, and thus the small numbers in each group have precluded any meaningful comparison of the various treatments.

A 6-F Flexor Shuttle Select Sheath (Cook Medical, Inc., Bloomington, IN) may be used from a femoral approach. If one is contemplating the use of a covered stent, such as the Gore Viabahn Endoprosthesis (W.L. Gore and Associates, Inc., Flagstaff, AZ), larger sheaths may be needed. A 0.014-inch wire may be used to cross the aneurysm and a distal embolic protection device as long as there is reasonable length to land such a device above the aneurysm neck. In a circumstance of difficult transfemoral access, a cervical direct common carotid cutdown can be utilized.

### *Trans-Stent Coil Embolization*

The technique of trans-stent coiling involves initially crossing the neck of a saccular aneurysm with a self-expanding stent. If a distal embolic protection device is deployed on the 0.014-inch wire, there is adequate room to introduce a second wire ("buddy wire") to track a 3-F RAPIDTRANSIT Microcatheter (Cordis Endovascular) into the aneurysm sac between the stent interstices. Coil embolization of the entire aneurysm sac is performed with detachable or platinum coils. The stent prevents migration of the coils into the distal carotid circulation. This technique is more frequently seen for intracranial aneurysms.

### *Stent-Graft Coverage*

In patients who have a fusiform aneurysm without a discrete neck, a stent-graft prosthesis is a better treatment option as long as there is adequate length of artery for proximal and distal sealing. Typically, a larger introducer sheath is required for a stent-graft prosthesis. The stents are oversized to the artery per the instructions for use of the individual device. The stent graft with the shortest length that will have adequate seal is chosen so that a distal kink is not created in the carotid artery. Angioplasty only within the stent graft with avoidance of angioplasty of the normal adjacent proximal and distal intima of the carotid artery is prudent. Stent grafts are not FDA approved for use in the carotid distribution.

Hori et al.<sup>53</sup> described a novel double-stent technique in which overlapping uncovered stents are placed within each other. The greater surface area coverage of the two stents is thought to increase the chance of immediate aneurysmal thrombosis through decreased flow into the sac. This technique raises concerns that if aneurysm sac flow is persistent, it may be impossible to track a catheter across the double latticework of stents to place coils if an additional procedure becomes necessary.

### *Transcervical Carotid Approach with Flow Reversal*

A few case series have also described utilizing transcarotid artery revascularization (TCAR) with stenting using flow reversal technique in the treatment of ECAA.<sup>58,59</sup> Advantages of

this technique include not having to perform predilation or navigate past intramural thrombus to deploy a filter. TCAR may also be the best option in patients with distal ECAA in which there is no room for safe deployment of a distal embolic protection device. Surgeons who have selected TCAR for the treatment of ECAA cite the compelling Safety and Efficacy Study for Reverse Flow Used During Carotid Artery Stenting Procedure (ROADSTER) study data which demonstrated the lowest 30-day stroke and death rates compared with all other carotid artery stenting techniques.<sup>60</sup> Most of the authors who have published their technique describe using the ENROUTE neuroprotection system (Silk Road Medical, Sunnyvale, CA) during deployment of Viabahn endoprosthesis (W.L. Gore & Associates, Flagstaff, AZ)<sup>58,59</sup> (see Ch. 94, Carotid Artery Stenting).

### *Selection of Treatment*

The location and size of a carotid aneurysm plays a critical role in determining which therapy to offer. Large aneurysms and those involving the distal ICA, because of the difficult surgical exposure and significant morbidity, are probably best managed with endovascular techniques. On the other hand, the presence of unstable-appearing thrombus within an aneurysm or pseudoaneurysm or the occurrence of preoperative embolic symptoms may be considered a relative contraindication to endovascular repair. Aneurysms in very tortuous carotid arteries also present a relative contraindication to endovascular therapy because of the difficulty of stent tracking and conformability to the artery wall. In fact, many tortuous arteries lend themselves to aneurysm excision and primary end-to-end repair of the artery.

## **TREATMENT OUTCOME**

### *Open Surgical Repair*

Results vary widely depending on the type, size, and location of the aneurysm. Carotid ligation was previously associated with a 30% to 60% risk of stroke, and half of such patients died after stroke.<sup>10,61,62</sup> In a 2000 review of the 13 largest single-center series since 1950, El-Sabour and Cooley<sup>3</sup> found that the combined stroke/death rate associated with carotid ligation had decreased to 12%. This change probably represents improvements in anesthetic technique and medical management as well as an understanding of the importance of anti-coagulation after carotid ligation. Carotid ligation is reserved in current surgical practice for the unusual circumstance of an unreconstructable carotid artery.

In general, surgical reconstruction is associated with a combined stroke and mortality rate of about 5%–10%.<sup>3,6</sup> Transient cranial nerve dysfunction occurs in about 12%–20% of patients.<sup>3,6</sup> Pooled data reported by El-Sabour and Cooley,<sup>3</sup> including 392 cases of ECAA, showed a combined stroke and death rate of 21% in those managed nonoperatively, 12% in those treated by carotid ligation, and 9%

in those treated by surgical reconstruction.<sup>15–17,21–27</sup> Subsequent studies evaluating nonoperative management have suggested that the risks of stroke or death in select patients managed nonoperatively is much less than previously estimated.

## Endovascular Therapy

The early results of endovascular repair of ECAAs appear favorable in comparison with those of open surgical repair. In a series of 141 ECAAs spanning 14 years, including 18 repaired using endovascular techniques for pseudoaneurysms, 4 covered stents, 11 uncovered stents with trans-stent coiling, and 3 carotid embolization procedures were described, with no cranial nerve injury or strokes reported.<sup>63</sup>

In another series of 24 ECAAs in 19 patients, including 8 who underwent endovascular repair, one patient underwent coil embolization and 7 were treated with bare-metal stents. Of note, three patients required open carotid exposure with manual straightening of the artery to deploy the stents from a common carotid puncture site due to tortuosity in the ICA. No strokes were described, but two patients did have transient cranial nerve palsies from traction during the open carotid exposure.<sup>7</sup> Saatci et al.<sup>64</sup> reported using stent grafts to treat 25 distal ICA pseudoaneurysms, the majority of which were post-traumatic. Endoleak, which occurred in two patients, resolved spontaneously in one and required the additional placement of a bare-metal stent in the other. Twenty-three aneurysms were immediately excluded from the circulation after stent-graft placement. No technical adverse events – vessel dissection, vessel perforation, or thromboembolism – occurred. No mortality or morbidity developed during or after the procedure or during the follow-up period. Follow-up angiography in 21 patients showed patent reconstruction of the ICA with no aneurysm recanalization. All symptoms resolved after treatment in patients who initially had mass effect complications.

In a report of 14 patients with traumatic pseudoaneurysms after BCVI, all patients with evidence of blunt carotid dissection underwent anticoagulation with heparin for 7 days, followed by repeat arteriography. Those with flow-limiting dissections or pseudoaneurysm formation were treated with self-expanding WALLSTENT endoprostheses (Boston Scientific Corporation, Natick, MA) and warfarin anticoagulation. In the follow-up period of 2.5 years, no strokes occurred and arteriography showed all lesions to have healed by 4 months.<sup>34</sup>

Zhou et al.<sup>27</sup> compared two different treatment periods: 22 cases all treated by open repair before 1995 and 20 cases treated after 1995. Of the 20 later cases, 14 were treated with endovascular therapy by a variety of techniques. During the second treatment period, hospital length of stay was significantly shorter, the rate of cranial nerve injury was diminished, and 30-day combined stroke/death rates were lower (14% vs. 5%,  $P < 0.004$ ). No strokes occurred in the endovascular group at 30 days. At a mean follow-up of 4.6

years, 11 of 16 deaths were thought to be related to cardiovascular causes, and continued aneurysm exclusion was confirmed in all patients.

## Treatment of Carotid Blowout

In one report, 16 carotid blowout events occurring in 12 patients, the majority of whom had undergone radiation therapy or surgery (or both) for head and neck cancer, and who were deemed to be at high risk for cerebral ischemic complications because of a negative balloon occlusion test result or known incomplete circle of Willis, were managed with a variety of stent devices and techniques.<sup>28</sup> Adjunctive embolization of carotid pseudoaneurysms with platinum coils or acrylic glue was performed in five patients. Hemostasis was achieved in all cases, although one patient with traumatic carotid blowout and three patients with aggressive head and neck cancer-related carotid blowout syndrome required retreatment with endovascular therapy. Rates of recurrent carotid blowout were similar to those reported in other studies using percutaneous balloon occlusion. Overall, no treatment-related strokes or deaths occurred.<sup>30</sup>

In a systematic review of the endovascular treatment of ECAA during 1995 through 201, including 113 studies and 224 patients undergoing treatment for ECAA, procedural success was 92.8%. Endoleaks occurred in 8.1%. The perioperative stroke and death rates were 1.8% and 4.1%, respectively. The rate of cranial nerve injury was 0.5%. Follow-up of these patients averaged 15 months, and the stent patency rate was reported to be 93.2%. The investigators concluded that these intermediate results suggest that low complication and high success rates make endovascular treatment of ECAAs favorable.<sup>65</sup> As with all meta-analyses, selection bias may contribute to the favorable results reported.

## MEDICAL MANAGEMENT OF MYCOTIC ANEURYSMS

Medical management of suspected or known mycotic carotid aneurysms involves the perioperative administration of antibiotics. Gram-positive “coverage” with either vancomycin or linezolid is recommended until definitive culture and susceptibility results are available, and initial broad Gram-negative coverage is also recommended. *Staphylococcus aureus* and *Staphylococcus epidermidis* are the most frequently encountered organisms. *Escherichia coli*, *Klebsiella* species, *Corynebacterium* species, *Proteus mirabilis*, and *Yersinia enterocolitica* have also been reported. After graft removal, autologous reconstruction, debridement of perigraft tissue, muscle flap coverage, and drainage, a course of parenteral antibiotics is recommended. Patients are typically treated with parenteral culture-specific antibiotics for 4 to 6 weeks followed by oral antibiotics for 3 to 6 months or for life. However, data to establish the optimal duration of antibiotic therapy are lacking.

## PEDIATRIC PATIENTS

The clinical presentation of ECAA aneurysm in children is most frequently an expanding cervical or parapharyngeal pulsatile mass, which can be mistaken for inflammation or neoplasm of the neck or tonsillar fossa. In a review of ECAs in children, including 27 case reports of ECAs occurring in the pediatric population within the past 25 years, as in adults, symptoms included dysphagia, dyspnea, trismus, carotidynia, compression of cranial nerves (IX–XII), and Horner syndrome. More concerning symptoms on presentation include cerebral thrombosis, septic and nonseptic emboli, transient ischemic attack and life-threatening hemorrhage due to pseudoaneurysm rupture.<sup>29</sup> Initial presentation of hemorrhage occurs more frequently in the pediatric population occurring in as many as one in three children.<sup>45,66</sup>

Mortality due to hemorrhage or neurological sequelae of untreated ECAA is as high as 77% but is reduced to 35% with treatment.<sup>67,68</sup>

The most common causes of ECAA in children are infection, trauma, congenital dissections and connective tissue disorders. Infections such as meningitis, complicated pharyngitis, cervical lymphadenitis and ear infections may cause aneurysmal degeneration. Infection involving the carotid artery wall can cause arteritis and vessel wall erosion due to proinflammatory cytokines, free radicals and proteases during infection. Bacteremia with invasion of the vasa vasorum as well as iatrogenic spread of the infection due to catheterization or puncture may also result in pseudoaneurysm formation. *Staphylococcus aureus, Salmonella, Escherichia coli, Streptococcus pyogenes* and *Klebsiella* are the most common pathogens. Antibiotic therapy has reduced but not eliminated the risk of ECAA in children.<sup>45,69</sup>

Cervical ICA pseudoaneurysms may also be caused by trauma or iatrogenic injury in children. The proximity of the ICA to the tonsillar fossa is inversely proportional to the age and weight of child putting young children at increased risk of vascular injury. The distance increases to a maximum of 2.8 cm posterolateral to the tonsillar fossa at age 12 years and 56 kg.<sup>70</sup> ICA pseudoaneurysm has been reported after transcutaneous fine-needle aspiration of cervical lymph nodes, transoral drainage of peritonsillar and parapharyngeal abscesses and post-tonsillectomy as well as parapharyngeal tumor resection. Only a few cases of iatrogenic injury have been reported in children. However, these patients typically present with sudden, profuse, self-limited oral bleeding, which may be fatal or require emergent operative intervention.

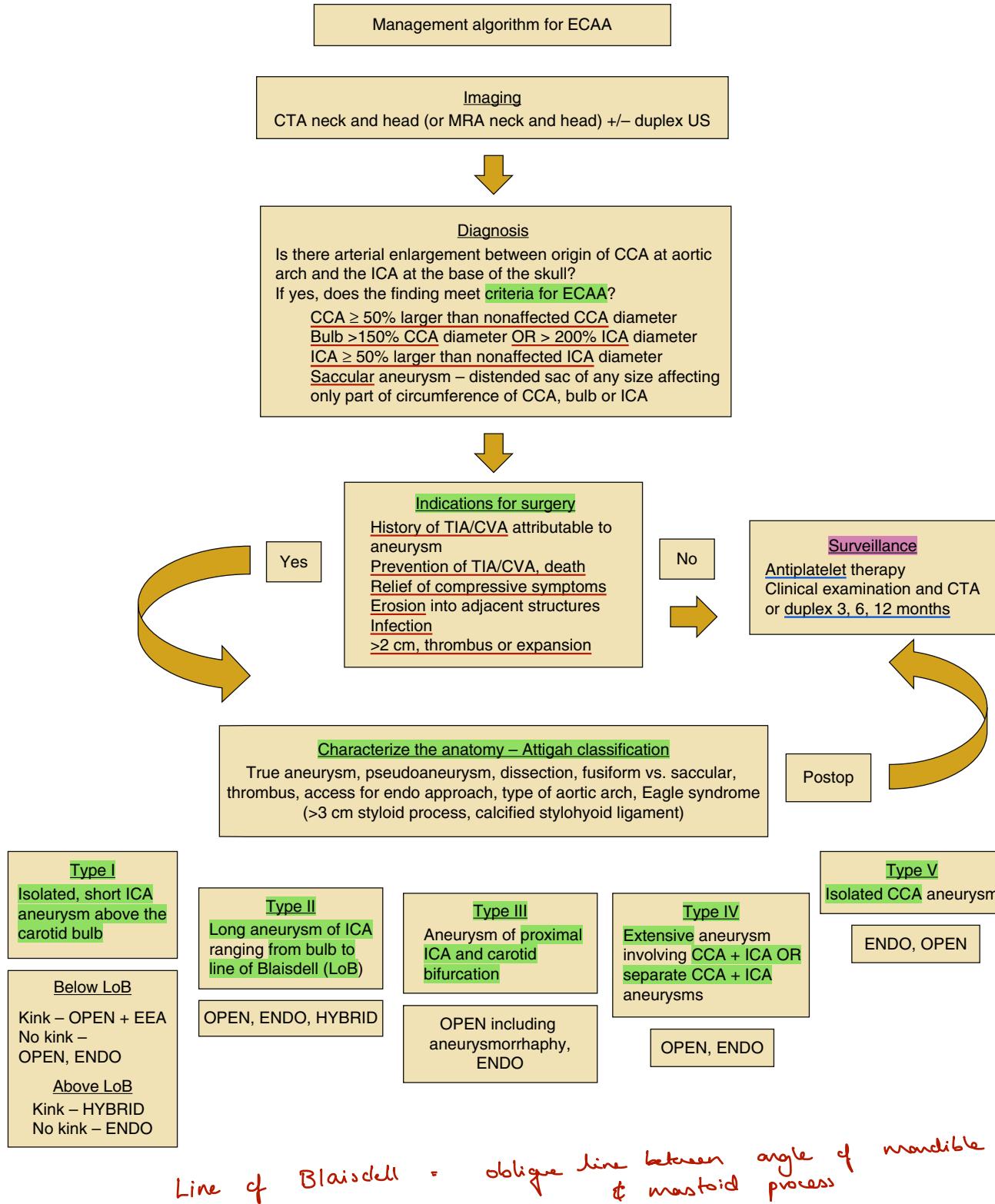
The goals of ECAA treatment in children are the same as in adults: exclude the aneurysm from circulation to prevent thromboemboli and hemorrhage, relieve compressive symptoms and preserve cerebral blood flow. A variety of techniques to achieve these operative goals have been reported with operative repair preferred for true aneurysms. In one case report, a 6-year-old boy who had undergone left common carotid artery transposition for an anomalous origin of the left common carotid artery developed aneurysmal

degeneration of the entire common carotid artery representing a particularly dramatic variant of type V ECAA. Embolization of mural thrombus resulted in transient hemispheric symptoms. He was successfully treated with therapeutic anticoagulation, ligation of the left common carotid artery and superficial femoral artery autograft from left subclavian to the left internal carotid artery. Great saphenous vein was used to replace the harvested superficial femoral artery. Superficial femoral artery was selected for the repair to maximize long-term patency, avoid aneurysmal degeneration associated with vein grafts and allow for continued patient growth.<sup>71</sup> A recent case report described a 10-year-old child with a type II ECAA treated successfully with aneurysmectomy and external to internal carotid artery transposition, providing another example of autogenous arterial reconstruction in a child with congenital ECAA.<sup>72</sup>

Experience with endovascular stenting of extracranial carotid artery pseudoaneurysms and dissections in children is limited but increasing. Special considerations in this population include vessel caliber and anticipated growth, longer life expectancy requiring surveillance and possible adverse effects of antiplatelet agents. Interestingly, the proximal internal carotid artery reaches maximum diameter by age 4<sup>73</sup> and the high cervical internal carotid artery and intracranial vasculature reach 94% of their final diameter by 5 years of age.<sup>74</sup> However, operators should note that conventional carotid stents used in adults are larger and stiffer and may be unsuitable for a pediatric patients. Careful access planning taking into account a patient's age and access vessel size as well as the ability of a particular device to navigate turns is important. Covered stent grafts such as Viabahn have been successfully used in case studies of pediatric patients for hemorrhage resulting from pseudoaneurysms.<sup>75</sup> Other similar self-expanding nitinol stents covered with PTFE are also more flexible, less thrombogenic and better conform to vessel walls compared to historical stent varieties.<sup>76</sup> Uncovered self-expanding nitinol Xpert biliary stents have also been used in case studies for nonbleeding pseudoaneurysms. These particular stents were chosen due to their similarity to intracranial aneurysm stents. These uncovered stents are compatible with smaller sheaths and catheters than covered stent grafts and allow stent crossing for coiling if needed.<sup>77</sup> Endothelial hyperplasia in response to the stent is of particular concern in pediatric patients who have smaller caliber vessels at baseline and long life expectancy. Long-term outcomes data for both treatment of extra- and intracranial internal carotid aneurysms is limited although the available short-term data is encouraging.

Finally, data regarding dose, route, duration and adverse effects of antiplatelet agents in pediatric patients is limited. Dual antiplatelet therapy has not been studied. Aspirin is most commonly used and is not associated with Reye syndrome at the lower doses used for antiplatelet therapy.<sup>78</sup> Use of clopidogrel is becoming more common but some authors are reluctant to use it due to variable response and reported adverse effects such as thrombocytopenic purpura and neutropenia.<sup>79</sup>

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# Carotid Body Tumors

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## INTRODUCTION

The carotid body tumor (CBT), first described in 1743 by Von Haller, is the only known pathologic condition of the carotid body.<sup>1</sup> The tumor is extremely rare. In 1971, only about 500 cases had been reported in the literature; doubling to more than 1000 by the early 1980s. Due to the infrequency of this disorder, very little is known about its etiology, clinical, and biologic behavior, or its malignant potential. In 1903, the first successful resection of a carotid body tumor was performed by Scudder in the United States.<sup>2</sup> Despite over a century of literature describing surgical treatment, significant controversy remains surrounding the details in the management of carotid body tumors.

## EPIDEMIOLOGY AND ETIOLOGY

The exact incidence of CBTs is unknown. Although they may be discovered in patients of all ages, they are usually diagnosed in the third to fifth decades of life. Patients with a family history of carotid body tumors may present at an earlier age.<sup>3</sup> Gender predominance has not been established, though some studies have found a higher prevalence in women.<sup>4,5</sup> They may be classified as sporadic, familial, or hyperplastic.<sup>6,7</sup> Sporadic is the most common form. Familial patterns may occur in up to 10% of cases with apparent autosomal dominant inheritance. In addition to a younger age at presentation for familial cases, rates of bilateral tumors have been reported in up to 30% of cases, in contrast to bilateral disease in 2% to 20% of nonfamilial cases.<sup>8,9</sup> Hyperplastic lesions, although not true neoplasms, are more prevalent in patients exposed to prolonged hypoxia,

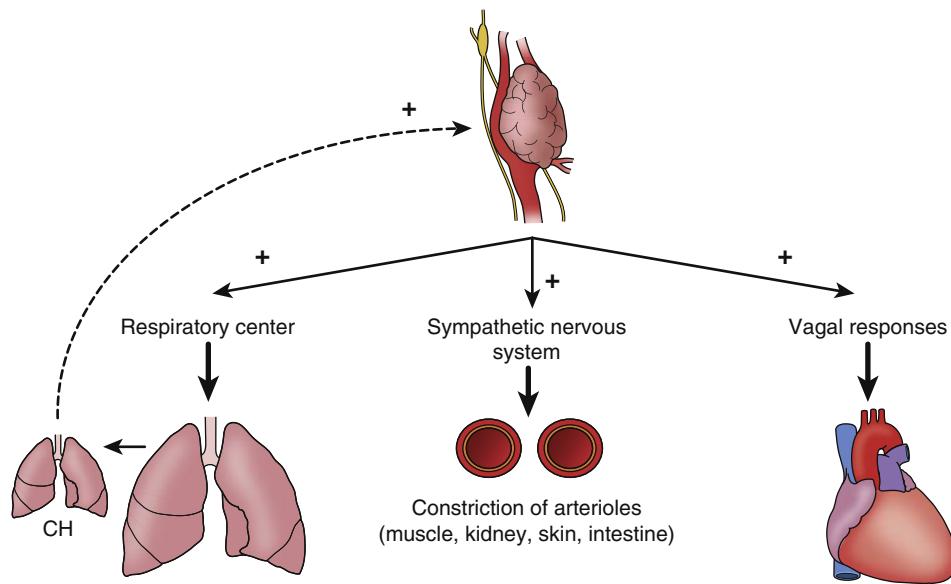
including those living at high altitudes and those suffering from chronic obstructive pulmonary disease or cyanotic heart disorders. This association has suggested chronic hypoxia as a potential etiology of CBTs.<sup>10</sup> Studies of mice deficient in the SDHD (succinyl dehydrogenase – subunit D) gene have found continued activation of the carotid body cells in response to hypoxia; such that SDHD gene mutations may be associated with formation of carotid body tumors.<sup>11–13</sup>

## ANATOMY AND PHYSIOLOGY

The carotid body is the largest mass of chemoreceptor tissue in the body. It is located within the periadventitia of the posterior surface of the carotid bifurcation. The normal carotid body is ovoid in shape and approximately 5 mm in its longest dimension. It usually receives its blood supply through branches of the external carotid artery. Blood returns through tributaries of the lingual and laryngopharyngeal veins. The carotid body derives sensory innervation through small nerve fibers from the glossopharyngeal nerve.

The embryologic origins of the carotid body are both neural crest ectoderm and mesodermal tissue from the third branchial arch. The neural crest cells migrate in close association with autonomic ganglion cells; thus, they are often referred to as paraganglioma cells.<sup>14</sup> These cells differentiate into the chemoreceptors, also known as type I glomus cells. The mesoderm forms the rich vascular stroma, made up of type II glomus cells, which support the chemoreceptor cells.

The carotid body is stimulated primarily by the partial pressure of O<sub>2</sub>, and to a lesser degree the partial pressure of



**Figure 98.1** The carotid body tumor is stimulated by partial pressure of O<sub>2</sub>, partial pressure of CO<sub>2</sub>, and arterial pH. It sends signals to multiple body systems including cardiopulmonary centers that regulate breathing and blood pressure.

CO<sub>2</sub> and arterial pH. In response, the type I glomus cells release neurotransmitters that act on the receptors of afferent nerve fibers. Signals are carried through the glossopharyngeal nerve to the medulla oblongata, affecting a number of the body's systems (Fig. 98.1). Most notable are cardiopulmonary centers in the brain that regulate breathing and blood pressure. For example, hypoxia, hypercapnia, or acidosis can stimulate the carotid body, resulting in increases in respiratory rate, tidal volume, and blood pressure with vasoconstriction.<sup>15</sup>

## PATHEOLOGY

CBTs are also known as carotid chemodectomas, carotid paragangliomas, and glomus tumors.<sup>7</sup> They represent neoplastic growths of the chemoreceptive tissue. These tumors belong to the family of paragangliomas, which are neoplastic tumors that occur along the autonomic ganglion chain from the head to pelvis. Within the head and neck, carotid body tumors are the most common type. Other cervical paragangliomas include the glomus tympanicum, glomus vagale, and glomus jugulare (Fig. 98.2).

Macroscopically, CBTs resemble normal carotid body tissue. They are reddish brown, rubbery, and well circumscribed, although they lack a true capsule. They are highly vascular, and can invade the adventitia of adjacent carotid vessels. As the tumors enlarge, they distort the carotid bifurcation and splay the internal and external carotid arteries, known as the "lyre sign" seen on angiography (Fig. 98.3).

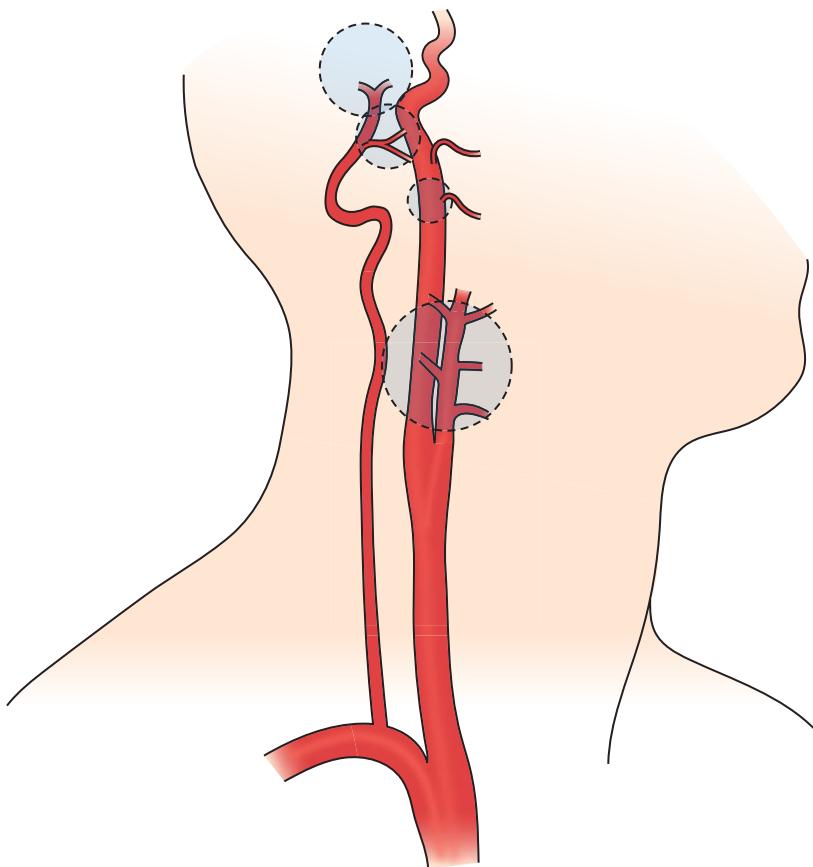
Microscopically, CBTs tend to resemble normal carotid body architecture with a well-differentiated benign appearance.<sup>16</sup> Only very rarely does histology demonstrate degenerative malignant characteristics, such as nuclear polymorphism, vascular invasion, increased mitotic activity, and necrosis. Malignant transformation cannot be predicted based on histologic findings.<sup>17,18</sup> Advanced

immunohistochemical studies have revealed that carotid body tumors can produce numerous neuroendocrine substances, often with granules rich in catecholamines seen in the cytoplasm. These tumors, in contrast to retroperitoneal paragangliomas, are usually nonfunctional and stain negative for chromaffin.

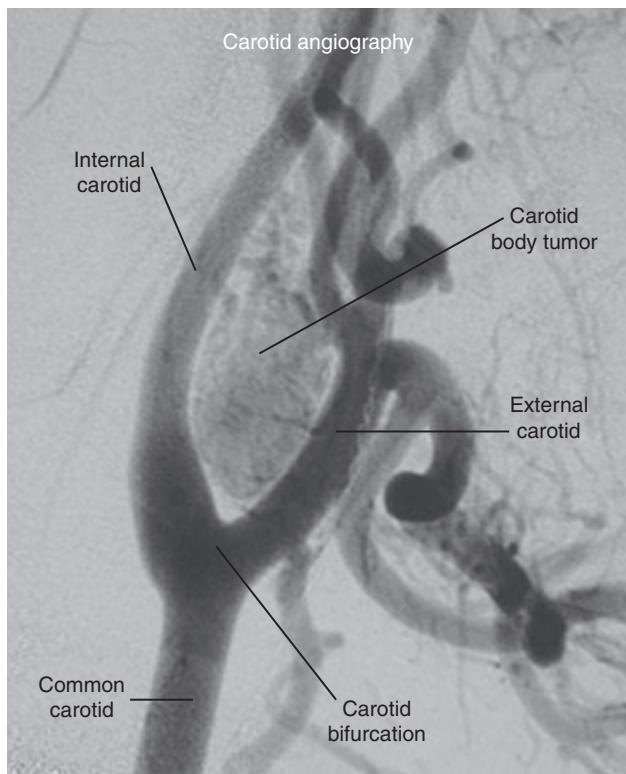
Most CBTs are benign. Malignant transformation has been reported, but the exact incidence is unknown. In contrast to many other types of cancer, malignancy of CBTs and other neuroendocrine tumors is based on clinical behavior instead of histology. Even benign tumors are capable of aggressive invasion into adjacent structures, as well as nodal and distal metastatic spread. Local growth may include adherence or encasement of neurologic and vascular structures, and even extension into the skull. Metastatic disease usually spreads into regional lymph nodes.<sup>19</sup> If carotid body cells are found in lymph nodes biopsied during surgery, this is diagnostic for malignancy; and an indication for completion of an ipsilateral modified radical neck dissection. However, routine biopsy of lymph nodes is not recommended, and only advised if lymph nodes appear clinically abnormal.<sup>20</sup> Metastases have also been seen in the cerebellum, thyroid, brachial plexus, lungs, kidney, pancreas, bones, and breast.<sup>19</sup>

## CLINICAL PRESENTATION

CBTs most commonly present as asymptomatic neck masses located below the angle of mandible. On palpation, the lesions are firm, smooth, and lobulated, and are characteristically mobile laterally but fixed longitudinally due to their association with the carotid artery.<sup>21</sup> Carotid pulsation may be transmitted through the mass, and approximately 30% to 40% of patients may have an audible bruit over the tumor. Very large carotid tumors may cause compression or local invasion, leading patients to present with nonspecific symptoms, such as localized tenderness, fullness, numbness, dysphagia, hoarseness, chronic



**Figure 98.2** Carotid body tumors belong to the family of paragangliomas, which are neoplastic tumors that occur along the autonomic ganglion chain from the head to pelvis. Carotid body tumors are the most common of the cervical paragangliomas. Others include the glomus tympanicum, glomus vagale, and glomus jugulare. The circles represent the relative incidences of these cervical paragangliomas.



**Figure 98.3** As carotid body tumors enlarge, they distort the carotid bifurcation and splay the internal and external carotid arteries, known as the “lyre sign” seen on angiography. Large tumors often encase the external carotid artery, but rarely wrap around the internal carotid artery.

cough, and tinnitus. Tumors rarely produce cranial nerve dysfunction, and if there is involvement, symptoms are typically associated with the vagal, hypoglossal, and cervical sympathetic nerves.<sup>3</sup> Occasionally, Horner syndrome has been reported in patients with this tumor.<sup>22</sup> Patients may complain of dizziness, but lateralizing neurologic signs are uncommon.

Despite possessing apparatus to synthesize and secrete catecholamines and hormones, CBTs are almost never functional. In extremely rare cases, tumors demonstrate neuroendocrine activity and patients may complain of headaches, dizziness, palpitations, tachycardia, arrhythmias, flushing, diaphoresis, and photophobia.<sup>23,24</sup> Some cases have been reported of patients with hypertension that resolves after tumor resection, which may be caused by tumor-related catecholamine release.

These neoplasms tend to grow slowly over several years, although occasional cases of rapid growth have been reported.<sup>25</sup> Although the risk of malignancy is believed to be relatively low, these tumors do progress in size and become locally invasive. Patients may live many years without treatment; however, due to the morbidity and mortality associated with progressively enlarging tumors, the low but unpredictable risk of malignancy, and the ease of excising small tumors, most surgeons recommend early diagnosis and surgical resection.

## DIAGNOSIS

The workup begins with a history and physical examination. The differential diagnosis for neck masses is broad, and

includes congenital lesions (vascular malformations, branchial cleft cysts, hygromas), inflammatory disorders (chronic lymphadenitis, reactive lymphadenopathy), infection (viral, bacterial, and parasitic lymphadenopathy), benign lesions (lipomas, cysts, parotid, and salivary tumors), and malignancies (metastatic head and neck cancer, lymphoma). Other vascular lesions (carotid artery aneurysms, kinks/atherosclerotic changes, and coils/congenital changes) and cervical paragangliomas (glomus jugulare and glomus vagale) may also present as neck masses.

Radiographic imaging is a critically important modality in the diagnostic confirmation and preoperative evaluation.<sup>26,27</sup> Conventional angiography was traditionally the gold standard, and provides excellent details about the overall size, extent, and vascularity of the lesion.<sup>28</sup> It also shows variation in blood supply and encasement of carotid vessels, both of which can significantly effect operative planning. It can also identify synchronous and contralateral tumors, carotid atherosclerotic or ulcerative disease, and other anatomic variations. It can also identify intracranial vascular lesions that may affect management. Finally, angiography provides the opportunity for preoperative embolization (see below). Limitations of angiography include high costs, risk of access complications, wound complications (hematoma, dissection, pseudoaneurysm), distal embolization with stroke, and contrast problems (allergic reaction and renal failure).

Duplex ultrasound has emerged as the most important, noninvasive method for examining carotid body tumors. It subjects the patient to minimal discomfort and essentially no risk. Ultrasound can provide excellent anatomic detail, estimate tumor vascularity with color Doppler, and determine tumor size, vessel encasement, and atherosclerotic disease. Finally, compared to angiography, ultrasound is significantly less expensive. Its limitations include an inability to clearly visualize the proximal (chest) and distal extent (intracranial) of the carotid artery and the possible extent of the tumor. The level of detail is lower compared to angiography, and it may not be as sensitive for small lesions. The reliability of carotid ultrasound is highly operator dependent.

Recently, computed tomography angiography (CTA) and magnetic resonance angiography (MRA) have supplanted conventional angiography, unless embolization is planned. These methods are noninvasive but provide high levels of anatomic and vascular detail when duplex ultrasound is insufficient.<sup>26</sup> CTA and MRA more clearly show the proximal and distal portions of the neck compared to duplex ultrasound and avoid the access/wound and embolic risks of conventional angiography. Both also have the advantage of 3D reconstruction. CTA has radiation exposure and contrast risks that are similar to conventional angiography, and MRA risks include nephrogenic systemic fibrosis associated with gadolinium contrast in patients with renal failure.

Due to the highly vascular nature of the carotid body tumor, percutaneous needle biopsy and incisional biopsies are *contraindicated*. Risks include hemorrhage, hematoma, pseudoaneurysm, and injury to adjacent neurovascular structures.<sup>29</sup> Furthermore, the ability to confirm the diagnosis with high-quality imaging renders further diagnostic tests, including biopsy, unnecessary.

Shamblin and colleagues at the Mayo Clinic developed a classification system for carotid body tumors based on tumor extent and neurovascular involvement (Fig. 98.4). Group I tumors are smaller and can be dissected easily off the walls of the carotid arteries in the periadventitial plane. Group II tumors are larger, more adherent to the adventitia, and partially surround the carotid vessels. Group III tumors have more intimate adherence to the vessels and encase the internal and external carotid arteries.<sup>30</sup> Modern imaging allows staging of carotid body tumors according to the Shamblin classification, and can assist in preoperative planning.<sup>31-34</sup> A recent multi-institutional study completed through the Very Low Frequency Disease Consortium (VLFDC) identified tumor volume and distance from base of the skull as independent factors that may assist in preoperative planning, and quantifying risks of adverse outcomes. More specifically, for every one centimeter the mass is closer to the base of the skull, the authors found 1.8 times greater risk of blood loss above 250 milliliters; 1.4 times increased risk of transfusion, 1.5 times increased risk of cranial nerve injury, and 2.7 times increased risk of multiple cranial nerve injuries<sup>35</sup> (see Chapter Algorithm).

## TREATMENT

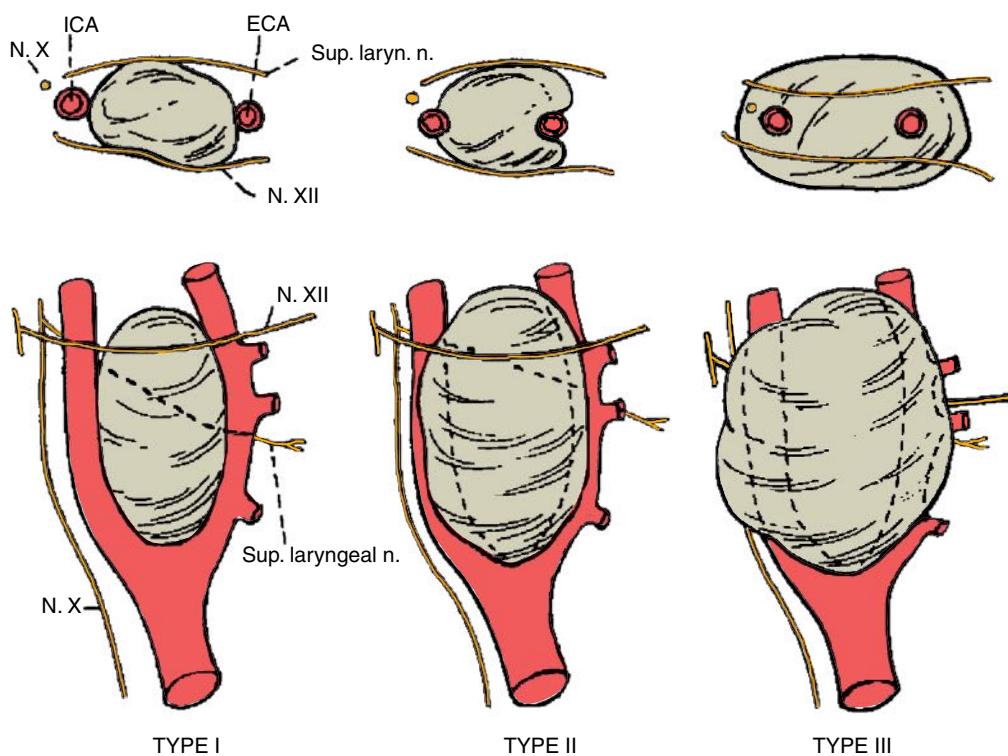
Surgical resection is the mainstay of treatment for CBTs. Although these lesions tend to be small and slow growing, they are best treated early for several reasons: smaller tumors are easier to remove; tumors may become locally invasive; lesions may grow distally into the skull or involve cranial nerves, complicating resection; and tumors may develop malignant behavior. In the absence of prohibitive comorbidities, perioperative risks, or limited life expectancy, patients with carotid body tumors should undergo surgical resection as soon as the diagnosis is made.

Radiation therapy is another treatment modality for carotid body tumors, although its use as a primary or adjunct therapy remains controversial due to conflicting studies and lack of long-term follow-up. Carotid body tumors are traditionally considered not radiosensitive, and radiation is used for suppression. Preoperative radiation may render surgery more difficult due to fibrosis. Radiation therapy is usually reserved for patients deemed poor operative candidates, and for bulky, unresectable, or recurrent tumors.<sup>36</sup>

There are currently no effective chemotherapy treatments for carotid body tumors.

## PREOPERATIVE PREPARATION

Planning should start with the evaluation of the patient's general medical condition, following current perioperative guidelines for vascular and specifically carotid artery disease. Because the operation is elective, steps should be taken to optimize the patient's health and reduce their risk factors for perioperative adverse events. Appropriate imaging should be performed to determine the tumor size and extent, and to identify other cervical paragangliomas (see Chapter Algorithm). Extension into the cranium and synchronous lesions can change operative planning. In addition, any existing cranial nerve involvement and neurologic



**Figure 98.4** The Shamblin classification describes the staging of carotid body tumors and can assist in preoperative planning. Type I tumors are smaller and can be easily dissected from the walls of the carotid arteries in the periadventitial plane. Type II tumors are larger, more adherent to the adventitia, and partially surround the carotid vessels. Type III tumors have more intimate adherence to the vessels and encase the internal and external carotid arteries.

deficits should be carefully and thoroughly documented as cranial nerve injuries are the most common postoperative complication. Although neuroendocrine activity from carotid body tumors is rare, if endocrine dysfunction or hormone imbalance is suspected, appropriate laboratory tests, including urinary catecholamines, should be ordered. Positive workup may also indicate an active synchronous lesion, such as adrenal pheochromocytomas. Medical and surgical treatment for these lesions should precede treatment for the carotid body tumor.

Preoperative embolization remains controversial. Some surgeons routinely perform embolization on Shamblin group II and III tumors. Carotid angiography is performed with selective catheterization of the ECA and embolization (Gelfoam or coils) of branch vessels feeding the tumor. Several studies demonstrate conflicting results regarding reduction in blood loss, surgical time, length of stay, and perioperative complications.<sup>31,33</sup> The disadvantages include the risk of inadvertent cerebral embolization and stroke. It also adds an additional invasive procedure with associated patient discomfort and increases the overall cost of care.

## SURGICAL TECHNIQUE

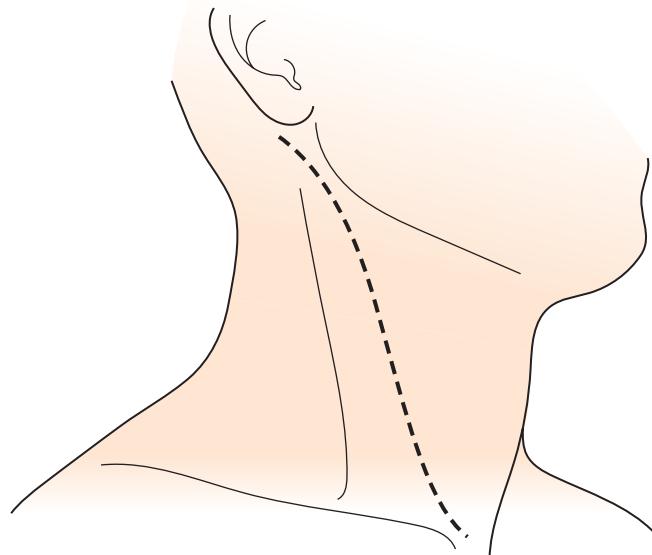
CBTs are highly vascular lesions that carry a massive hemorrhage risk during resection. The lesions may also adhere to or envelop neurovascular structures, increasing the risk of complications. The surgeon must plan his or her operative approach according to the tumor characteristics, and preservation of vital structures. The use of harmonic scalpel or bipolar forceps may

aid in decreasing overall blood loss while completing a meticulous tumor dissection.

Anesthesia for this operation could potentially be either cervical block or general anesthesia, as is the case for other carotid artery operations. However, resection of carotid body tumors usually requires more time than carotid endarterectomy and tends to be more invasive, particularly with large tumors. Therefore, most surgeons prefer the more controlled setting of general anesthesia, with better airway management and reduced patient movement during the operation. Cerebral monitoring and protection may be used for carotid body tumor resection due to potential or planned internal carotid artery occlusion or reconstruction. The choices are to use EEG monitoring or routine shunting of the internal carotid artery. Internal carotid artery back pressure is not an option due to the inability to clamp the external carotid artery due to tumor involvement. If continuous EEG monitoring shows ischemic changes with clamping of the carotid artery, a shunt can be inserted through an arteriotomy in the common carotid artery. Some surgeons have advocated doing this in all cases of carotid body tumor resection because the placement of the shunt effectively blocks inflow to the external carotid artery and may make tumor resection and hemostasis more effective.

## POSITIONING AND EXPOSURE

The setup and dissection of carotid body tumors are similar to that of carotid endarterectomy (see Ch. 93, Carotid



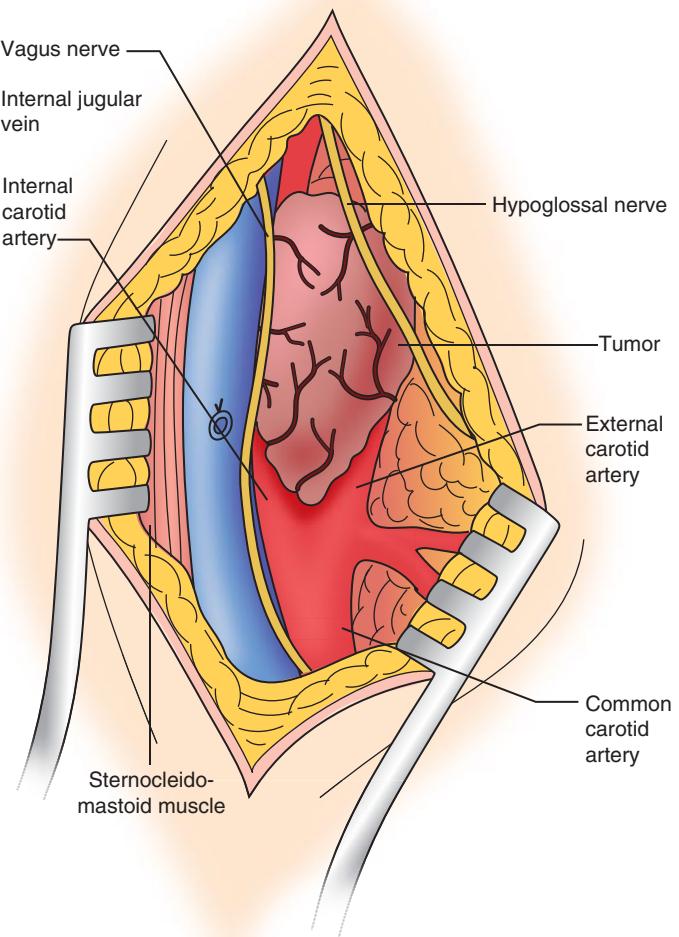
**Figure 98.5** The skin incision for carotid body tumor resection is longitudinal along the anterior border of the sternocleidomastoid muscle. The incision should be centered over the carotid bifurcation.

Endarterectomy and Ch. 57, Cerebrovascular Exposure). The patient is supine with the head rotated to the contralateral side. Depending on the patient's body habitus, a shoulder roll may be placed to extend the neck. The head of the table can be elevated 10 to 15 degrees to reduce venous pressures and incisional blood loss.

A longitudinal incision is made through the skin and subcutaneous tissues along the anterior border of the sternocleidomastoid muscle, although multiple incisions have been described relating to the size of the tumor and distal extent. The incision should be centered over the carotid bifurcation. If necessary, the incision can be extended proximally toward the sternal notch and distally toward the mastoid process (Fig. 98.5). Additional techniques for extended exposure include continuing the incision across the mastoid process behind the ear, detachment of the posterior belly of the digastric muscle from the mastoid process, division of the stylohyoid muscle with or without the styloid process, and subluxation or division of the mandible.

## RESECTION OF TUMOR

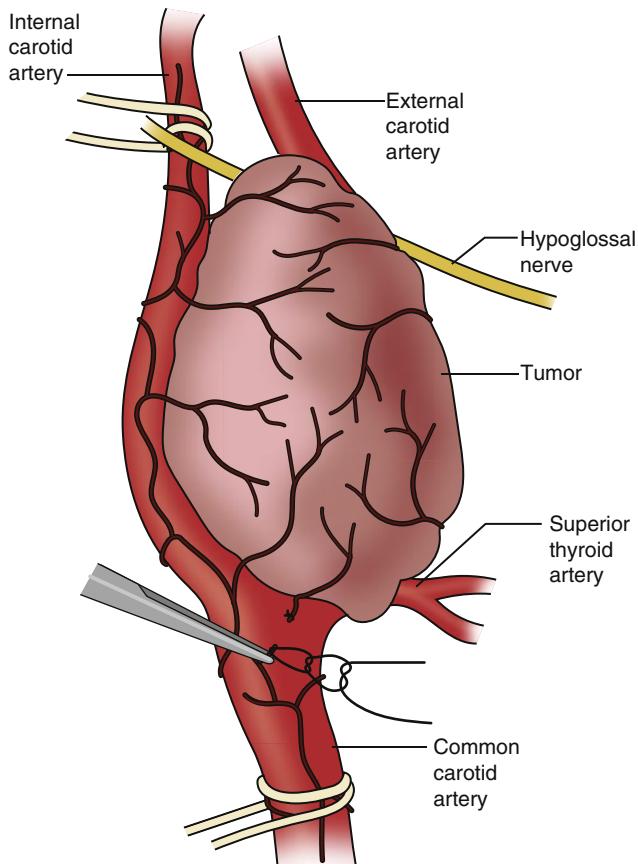
The dissection continues along the anterior border of the sternocleidomastoid until the muscle can be reflected off the carotid sheath. If the parotid gland is encountered, it can be mobilized and reflected anteriorly. The carotid sheath should be opened along the anterior border of the internal jugular vein (IJV). The common facial vein typically joins the IJV near the level of the carotid bifurcation and is a useful landmark that can be divided. The IJV can be reflected laterally to expose the carotid arteries (Fig. 98.6). The surgeon should identify and protect the hypoglossal, vagus, and laryngeal nerves. These structures may be displaced by large tumors. The proximal common carotid artery should be circumferentially mobilized



**Figure 98.6** For the exposure of the carotid body tumor, the carotid sheath should be opened along the anterior border of the jugular vein. The common facial vein, which typically joins the jugular vein near the level of the carotid bifurcation, is divided to allow lateral reflection of the jugular vein. The hypoglossal, vagus, and laryngeal nerves are identified and protected. These structures may be displaced by large tumors.

in the perivascular plane, with sufficient length obtained for possible bypass shunt (Fig. 98.7). At this point it is usually possible to see the vagus nerve. The dissection proceeds distally on the lateral aspect of the common carotid artery, in the perivascular plane, separating the artery from the vagus nerve, until a point at the upper end of the tumor mass where the internal carotid artery can be circumferentially mobilized. It is during this maneuver that the hypoglossal nerve may be encountered and must be carefully separated from the tumor mass and protected (Fig. 98.8).

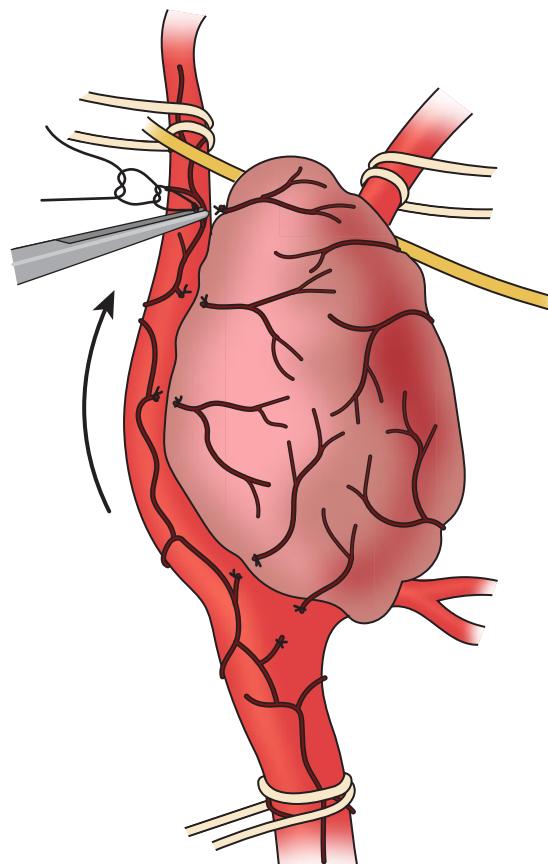
Since CBTs rarely encase the internal carotid artery, attempts are made to preserve it. The dissection is continued down the medial aspect of the internal carotid artery in the same perivascular plane, separating the tumor from the internal carotid artery to the bifurcation (Fig. 98.9). At this point, the external carotid artery can be circumferentially mobilized. For small tumors (Shamblin group I), the external carotid artery can be preserved. The dissection should stay on the tumor pseudocapsule; branches of the external carotid artery



**Figure 98.7** The common carotid artery is circumferentially mobilized in the perivascular plane to obtain proximal control of the artery. Dissection proceeds distally on the lateral aspect of the common carotid artery in the perivascular plane to a point beyond the tumor. The vagus nerve is separated from the artery and protected.

that supply the tumor can be divided and ligated with care to protect the hypoglossal nerve. Once the posterior, lateral, and medial aspects of the tumor are mobilized, the superior extent is divided between the ligature and the mass removed (Fig. 98.10). If invasion into the media is noted, the vessel requires resection.

For larger tumors that are adherent to the external carotid artery (Shamblin group II), the vessel can be divided at its origin, and the proximal stump is oversewn at the point where it was circumferentially mobilized. This maneuver is useful in reducing blood loss, and it provides a handle to rotate the tumor and aid in the dissection. The external carotid artery is resected *en bloc* with the tumor (Fig. 98.11). For tumors that cannot be dissected from the bifurcation (Shamblin group III), the bifurcation and possibly the internal and external carotid arteries must be removed with the tumor. Vascular reconstruction for the internal carotid can be performed with a prosthetic or autologous vein interposition graft (Fig. 98.12). However, it is our preference to use a 6-mm PTFE graft, because long-term patency in this position is well documented, as opposed to vein grafts.<sup>37</sup> If a carotid shunt is required, the vascular reconstruction can be performed by passing the shunt through the graft and removing the shunt before the second anastomosis is completed. In addition, if clamping of



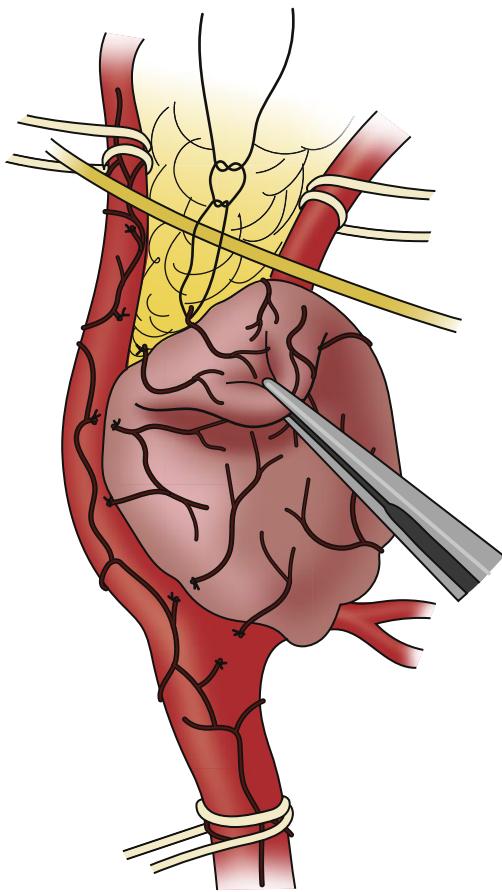
**Figure 98.8** The internal and external carotid arteries are circumferentially mobilized for distal control. The hypoglossal nerve may be encountered during the dissection; it is separated from the artery and mass and protected.

the common or internal carotid arteries must be performed, the patient should receive systemic heparin. If the neoplasm adheres to or encases nerves, attempts should be made to preserve the nerves, even by splitting the tumor. If it is necessary to split the tumor to preserve a cranial nerve, use of bipolar forces is helpful for hemostasis.

The wound is irrigated and meticulous hemostasis is obtained. The platysma is reapproximated, and the skin is closed with subcuticular sutures or skin staples. Drains are rarely needed, but if used, they can be placed beneath the platysma layer and brought out through the skin through a separate stab wound.

## POSTOPERATIVE CARE

A preliminary neurologic assessment should be performed when the patient awakens from anesthesia. The patient is brought to the recovery room where the blood pressure and neurologic function can be carefully monitored. The care team should be vigilant for neck hematomas, which can lead to an airway emergency, as well as stroke symptoms and evidence of cranial nerve injuries. If a drain is placed, it can be removed after 24 hours. Most patients are discharged 24 to 48 hours postoperatively. Although recurrence is rare, patients should be followed closely after discharge.



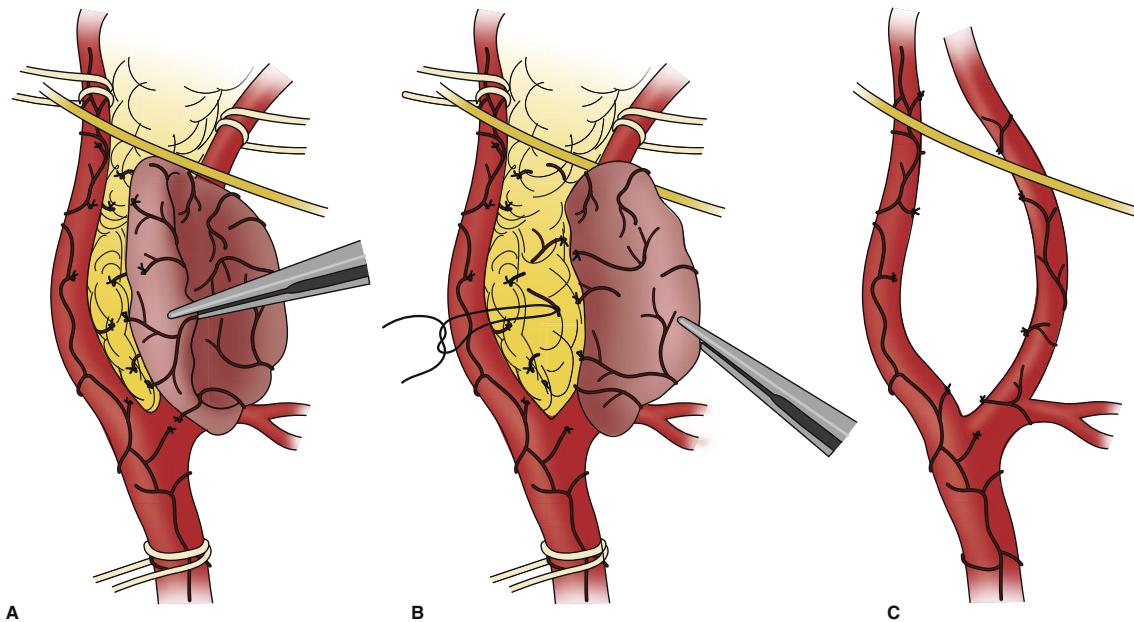
**Figure 98.9** Dissection is continued along the medial aspect of the internal carotid artery in the same perivascular plane. The carotid body tumors rarely encase the internal carotid artery, and attempts should be made to separate and preserve the internal carotid artery.

## RESULTS

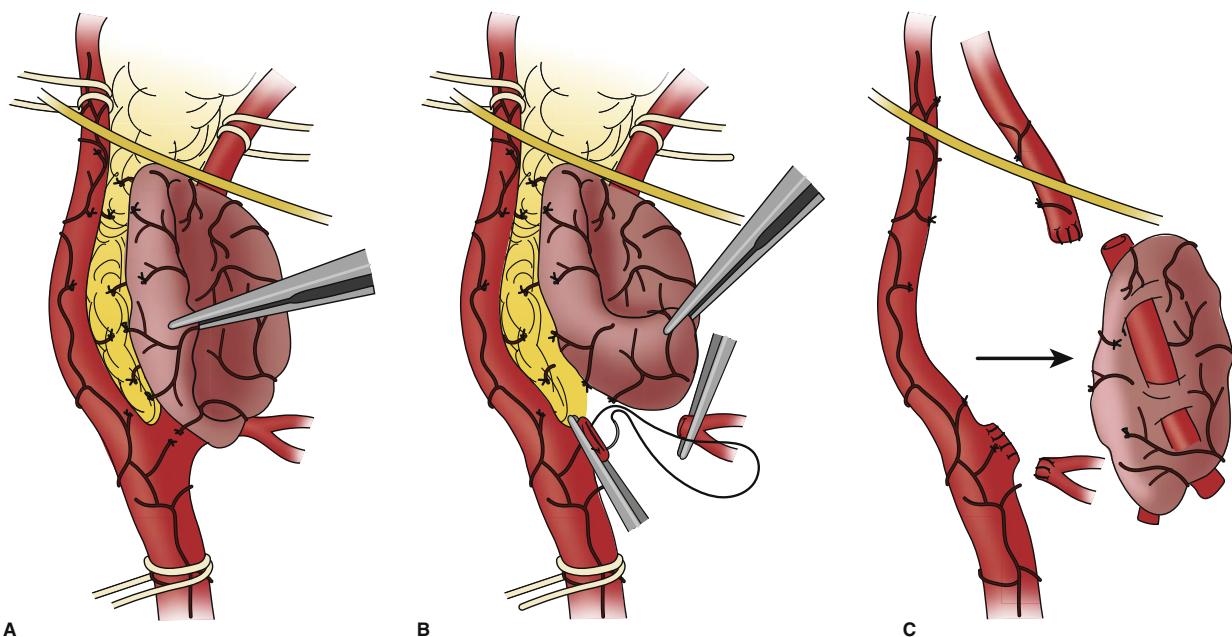
In experienced hands, the perioperative mortality should be less than 0.5%, and cerebrovascular, cranial nerve, or other minor complications occur very rarely. Particularly for tumors that appear benign, perioperative mortality and morbidity rates must be low. Other complications include hemorrhage and hematoma, especially when vascular control is inadequate. As described, several important cranial nerve structures lie within the tumor and dissection regions. Higher rates of nerve injury are seen with larger tumors. In a series of 356 tumor resections in 332 patients, the incidence of cranial nerve injury was 24%. Tumor volume and distance from the base of the skull were associated with the incidence of nerve injury, and more predictive than Shamblin classification.<sup>35</sup> Most cranial nerve dysfunction is transient. Most complications are considered technically preventable, and adequate planning by the surgeon can greatly reduce the rates of adverse events.

## CONCLUSIONS

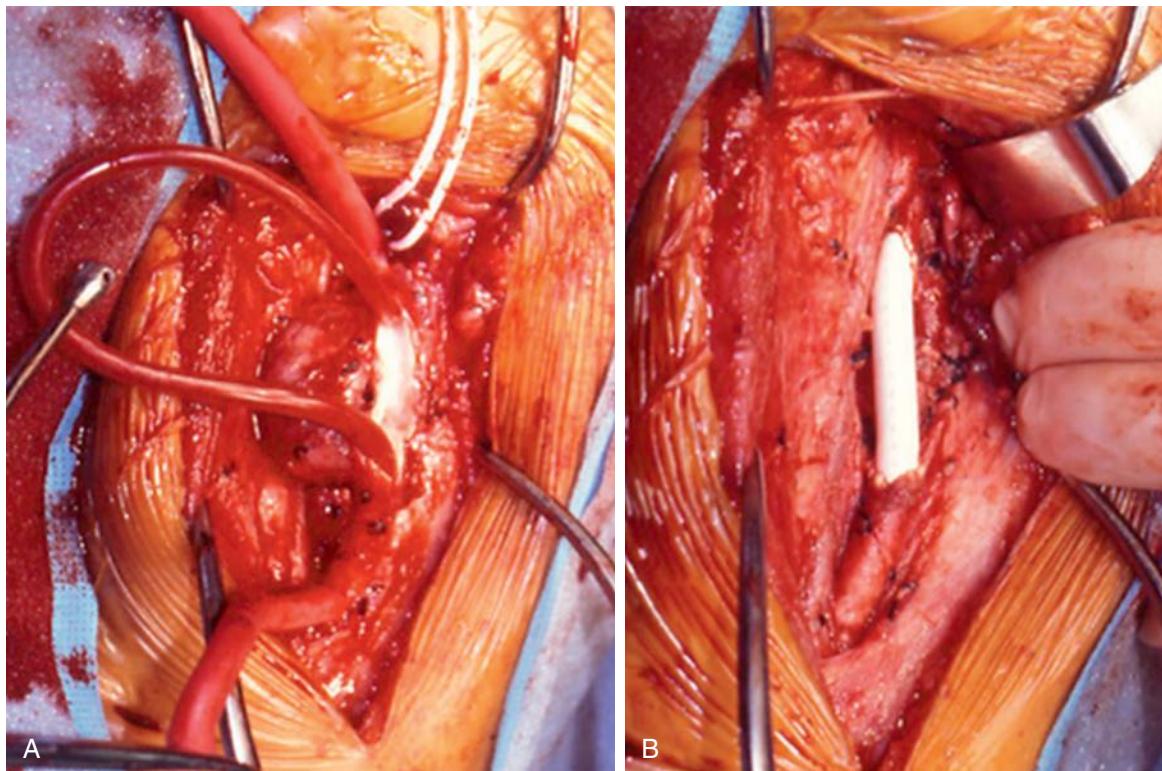
CBTs are rare neoplasms. Patients typically present with asymptomatic neck masses. These lesions are usually slow growing and benign but may exhibit locally aggressive behavior. Malignant transformation is rare. These lesions are highly vascular. Imaging (conventional angiography, duplex ultrasound, CTA, and MRA) is the primary tool for diagnosis. Early complete surgical resection is the mainstay of treatment. In experienced hands with adequate operative planning, perioperative mortality and complication rates are very low.



**Figure 98.10** For small tumors (Shamblin group I), the external carotid artery can be preserved by mobilizing the carotid body tumor along the pseudocapsule (A). The blood supply to the tumor from branches of the external carotid artery can be divided and ligated (B), thus yielding intact removal of the tumor without disruption of the carotid bifurcation (C).

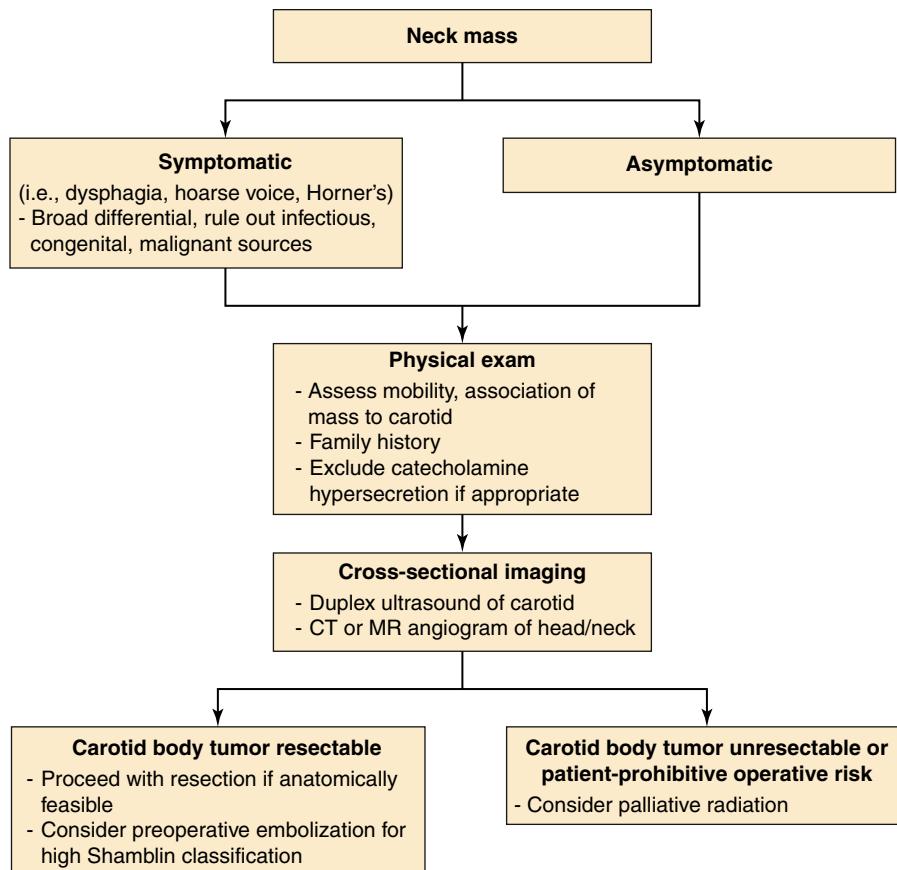


**Figure 98.11** For larger tumors (Shamblin group II) that adhere to the external carotid artery, the vessel can be resected *en bloc* with the tumor. The carotid body tumor is mobilized from the internal carotid artery and carotid bifurcation (A). The external carotid artery is divided at its origin and the proximal stump oversewn (B). The tumor is then rotated to facilitate the remaining dissection. The distal external carotid artery and remaining branches are oversewn (C).



**Figure 98.12** For tumors that involve the carotid artery bifurcation (Shamblin group III), the bifurcation and possibly the internal carotid artery must be removed with the tumor (A). A carotid shunt may be required during the reconstruction. The internal carotid artery can be revascularized with a prosthetic or autologous vein interposition graft (B).

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# Unusual Carotid Artery Conditions

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## INTRODUCTION

While cerebrovascular atherosclerotic disease is the most common pathology encountered by vascular surgeons, there are several other distinct entities that can result in cerebral ischemia, bleeding and death. This chapter discusses the rare clinical presentations and treatments for carotid body tumors, carotid sinus syndrome, intracranial carotid aneurysms, intracranial vascular lesions, carotid kinks and coils, and moyamoya disease.

## CAROTID BODY TUMORS

Carotid body tumors are described in Chapter 98 (Carotid Body Tumors), and will only be briefly summarized here. The carotid body, also known as the carotid glomus or glomus caroticum, consists of neural crest-derived chemoreceptors and associated cells found in the medial portion of the carotid bifurcation. There are two types of cells in the carotid body, glomus type I chief cells and glomus type II/sustentacular cells.

The glomus type I cells are derived from the neural crest and when tumors develop, they are referred to as extra-adrenal neuroendocrine neoplasms.<sup>1</sup> These rare but highly vascularized neoplasms are called carotid body tumors (CBT) when seen in the neck and head, although they can occur throughout the body.<sup>2</sup> Head and neck paragangliomas occur with an incidence of 1 in 30,000 or 1 in 100,000. Prevalence is higher in women, up to 25% are bilateral,<sup>3</sup> and familial incidence ranges from 30% to 40%. Early detection may prevent late diagnoses and extended resections.<sup>4-6</sup> The incidence of malignancy is low (5%); however, due to the possibility of undetected micrometastasis, any associated or large lymph nodes should be removed for histological review.<sup>7,8</sup> CBTs have an increasing incidence in inhabitants of high altitude and are predominantly female in distribution.<sup>9</sup> CBTs present as asymptomatic painless masses or focal cervical fullness. When larger, cranial nerve palsy can occur, 10%-20% with pain, hoarseness, odynophagia, stridor and dysphagia. Other symptoms include cough, tinnitus, tenderness, and dysphonia. Cervical bruits and thrills are atypical. The mass is typically located at the level of the

hyoid bone. Nerves involved can include the glossopharyngeal, vagus and hypoglossal. Patients may have Horner syndrome, vocal cord paralysis or other nerve involvement. The vertical fixation and horizontal mobility known as **Fontaine's sign** has been described in slender patients. **Sympathetic hyperactivity** such as headache, tachycardia, hypertension and palpitations are symptoms of the rare presentation of a **functional CBT**.<sup>8,9</sup>

While CBTs are typically benign, there is a potential to evolve into malignant tumor in 3%. Surgical treatment is guided by **Shamblin classification**.<sup>10–12</sup> Preoperative embolization (PAE) can be performed to decrease tumor size and vascularity in large Shamblin 2 or 3 tumors. The use of PAE varies, with considerable debate on its merits.<sup>12–17</sup> CBT resections can be performed safely and with acceptable morbidity, although **cranial nerve injury** has been reported in 1%–30% of cases.<sup>18–25</sup> Some centers report a **lymph node resection rate** of up to 54% of concomitant excisions.<sup>17</sup> Early series by Hallett and colleagues reported **improvement in perioperative stroke and morbidity** from 23% to 2.7% and 65% to 0%, respectively, over a 50-year experience.<sup>22</sup>

## CAROTID SINUS SYNDROME

The carotid sinus (CS) is a **baroreceptor** in the adventitia of the carotid bulb, often described as a dilated region at the bifurcation containing wall pressure receptors. The CS nerve, the nerve of Hering, is a branch of the glossopharyngeal (cranial nerve IX). The CS provides **baroreceptor responses** to changes in stretch or pressure in the vessel wall from manipulation or blood pressure. When stimulated, **parasympathetic fibers** are activated, while **sympathetic fibers** are inhibited, resulting in decreased systemic blood pressure and heart rate. Carotid sinus hypersensitivity (CSH) or syndrome (CSS) is an important but frequently unrecognized cause of recurrent syncope and falls in elderly patients. Aging and instability of the carotid sinus baroreceptors contribute to CSS in the elderly population.<sup>26</sup>

## Epidemiology

The prevalence of CSS is as high as 45% in individuals 35 to 60 years of age, occurring more often in men (4:1 ratio).<sup>27</sup> With CS massage, CSH is seen in 20% of elderly presenting with syncope. CSH increases with **age**, **cardiovascular**, **neurogenic** and **cerebrovascular degeneration**. The prevalence is increased in **neurodegenerative disorders** such as **Parkinson disease**, **Alzheimer dementia** and dementia with Lewy bodies. This is attributed to the **degeneration of the medullary autonomic nuclei**, which **senses the baroreceptor signals** and leads to a **stimulated response** resulting in **hypotension** and **bradycardia**.

## Classification

There are **three subtypes** of CSH. **Cardioinhibitory** carotid sinus hyperactivity (CICSH) is the **most common**, representing 70%–75% of cases, characterized by **ventricular pauses greater than or equal to 3 seconds (asystole)**. **Vasodepressor** carotid sinus hyperactivity (VDCSH) represents 5%–10% of CSH,

and displays **blood pressure drops of at least 50 mm Hg (hypotension)** without concomitant bradycardia. The **mixed CSH type**, 20%–25% of cases, shows **both ventricular pauses and a decrease in systolic blood pressure**. It is important to differentiate these classifications clinically as they dictate the approach to treatment; **CICSH** is a class 1 indication for **cardiac pacing**, whereas **VDCSH** typically requires **pharmacologic treatment**.<sup>28,29</sup>

## Physiology and Pathophysiology

Baroreceptors activate the autonomic system, balancing blood pressure and heart rate. The message is sent via the **vagus** and **glossopharyngeal nerves** to the **solitary nucleus** of the medulla. The nucleus then sends signals via the **effluent limb**. With **increases in blood pressure and vessel wall stretch**, the **parasympathetic system** is activated causing **hypotension** and **bradycardia**, while **decreased blood pressure and wall stretch** activate the **sympathetic system** causing **hypertension** and **tachycardia**. The hypersensitivity seen in CSH is not well understood but the exaggerated signal response results in dramatic physiologic changes in these patients.<sup>30</sup>

There are two proposed theories of CSS pathophysiology, one based on central disease and the other on peripheral origins. The **central theory** attributes CSS to deterioration or lesions of the **nucleus tractus solitarii**.<sup>31</sup> The **peripheral theory** focuses on disease at the CS baroreceptor and the sternocleidomastoid (SCM). The chronic loss of innervation of the SCM results in an **exaggerated sensitivity** of the baroreceptor pathway.

## Presentation and Risk Factors

Common symptoms include **dizziness** or **syncope** of sudden onset, **short duration**, and **quick recovery**; this can be more prolonged if hypotension is severe. Complications are most serious in the elderly, who have falls (typically without loss of consciousness) and sustain resulting trauma. In patients with loss of consciousness, there may be a prodrome of **visual loss** or **darkening of the visual field**. **Neurologic symptoms**, which are **rare and transient**, include abnormal sensorium, vision changes, paresthesia, paresis, and cognitive dysfunction. Spontaneous CSS can be caused by manipulation of the CS by tight collars, neck wear, shaving, neck movement, or cervical massages. Other causes include **compression** from adjacent masses such as tumors and lymph nodes. Neck irradiation and previous neck surgery increase the susceptibility to CSS. However, most CSS is induced without a predisposing maneuver or trigger.

## Diagnosis and Workup

The diagnosis involves **assessing for common causes of syncope and hypotension**, including **dehydration**, **hypoglycemia**, and **cardiovascular disease** such as **aortic stenosis** and **hypertrophic cardiomyopathy**. Serum chemistries, complete blood count, and electrocardiogram should be obtained as baseline. Holter monitor and electrophysiologic testing can also be used.

Monitored carotid sinus massage (CSM) is the most effective method for confirming CSH. The technique reproduces spontaneously occurring symptoms during 10-second sequential right and left massage,<sup>30</sup> performed both supine and erect under continuous heart rate and blood pressure monitoring. Typically, massage of the right CS is performed first, as it contains more receptors. If there is no response, similar massage for several seconds on the left is performed. The test is positive if there is asystole for greater than 3 seconds (CICSH) or greater than 50 mm Hg drop in blood pressure (VDCHS). Current guidelines from the European Society of Cardiology state that the upright position is preferred, and this is supported by Morillo (diagnostic accuracy of CSM increased by 38%).<sup>32</sup> If the test is positive, atropine is administered, and repeat massage performed to determine the degree of hypersensitivity. The mixed subtype is diagnosed when CSM produces asystole for 3 seconds and after atropine administration, greater than 30 mm Hg drop.<sup>33</sup> The differential diagnosis should include vasovagal syncope, given the potential for the coexistence in elderly patients.

Contraindications to CSM include stroke, transient ischemic attack and myocardial infarction in the previous three months. While the presence of carotid bruit is not a contraindication, documented greater than 70% stenosis on carotid duplex is a relative contraindication.

## Treatment

In asymptomatic patients, no further treatment other than trigger avoidance is needed. Treatment includes adequate fluid and salt intake and avoidance of physical manipulation and compressive clothing. If the patient is not responsive to conservative measures, medical or surgical management should be considered based on the subtype.<sup>34–36</sup>

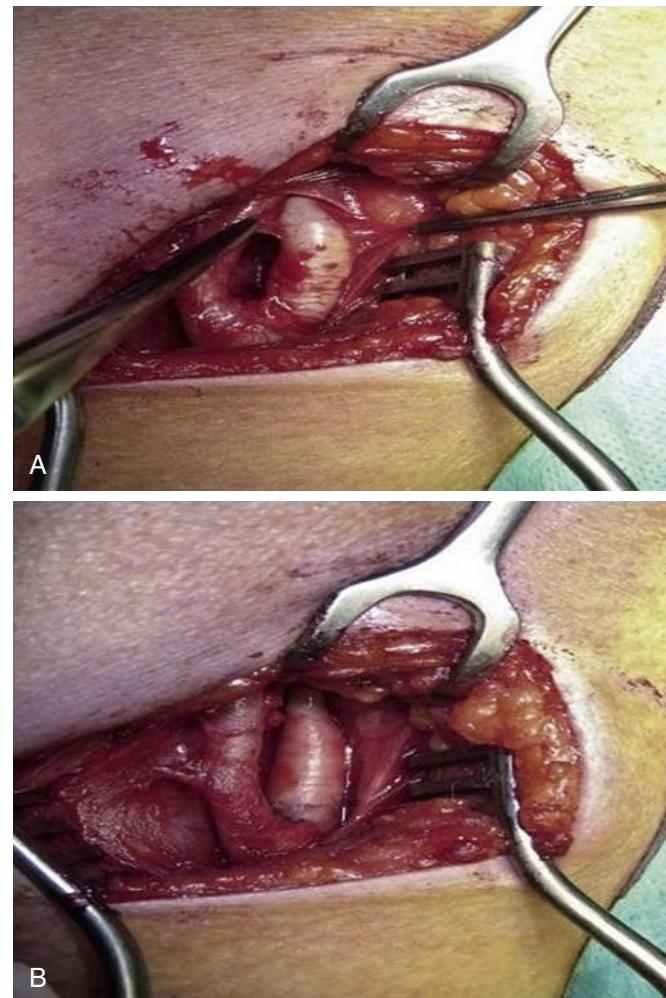
For VDCSH, appropriate salt intake (6 g/day) and hydration will suffice to control symptoms. These therapies are contraindicated in patients with congestive heart failure and hypertension. The addition of alpha-adrenergic agonist agents such as midodrine or mineralocorticoid such as cortisone can be used, albeit carefully for patients with hypertension.

In CICSH and mixed subtypes, a dual-chamber pacemaker is recommended for atrial and ventricular stimulation. DDD pacing is accepted as better for symptom reduction. The guidelines from the European Society of Cardiology (ESC) reflect this by noting that dual-chamber pacing is better than single-chamber pacing.<sup>37,38</sup> As there is an association between sick sinus syndrome (SSS) and CSH, pacemaker insertion is indicated for both.

Nonpharmacologic therapies include CS nerve denervation, glossopharyngeal nerve or CS transection and CS irradiation. Nerve transections can be morbid and ineffective. CS transection can be difficult and lead to incomplete sinus denervation. Glossopharyngeal nerve and upper rootlets of the vagus nerve transections at the level of the brain stem involves craniotomy and are typically reserved for patients unresponsive to lesser invasive therapies. Complications of glossopharyngeal transection include loss of taste, impaired gag reflex and dry mouth.

Another surgical option is adventitial stripping of the CS (Fig. 99.1).<sup>39,40</sup> Toorop and colleagues reported a review of 110 CSS patients with adventitial stripping and clinical results were encouraging. The procedure is performed under general anesthesia. The nervous tissue attached to the adventitia of the bifurcation is removed circumferentially over a 3-cm segment. Topical lidocaine application along the ICA or intravenous atropine and norepinephrine were used to treat severe bradycardia or hypotension. Concomitant carotid endarterectomy can be performed.<sup>39</sup> Complications with stripping include cervical hematoma and nerve injury. At 1-month follow-up, 93% of patients were symptom free, but long-term data has not been established.

Carotid irradiation has been utilized in the past but is limited currently. The mechanism of action is based on depression of nerve endings. The benefits are not consistent, often delayed and associated with development of CSH in patients with neck tumors.<sup>41</sup>



**Figure 99.1** Operative Photographs Depicting Adventitial Stripping of the Left Carotid Artery. (A) The process of stripping with the forceps holding the nervous tissue. (B) The 3 cm of stripped proximal internal carotid artery after the procedure. (From Toorop RJ, Scheltinga MR, Huige MC, Moll FL. Clinical results of carotid denervation by adventitial stripping in carotid sinus syndrome. *Eur J Vasc Endovasc Surg*. 2010;39:146–152.)

## MOYAMOYA DISEASE

### Background and Epidemiology

Moyamoya, a Japanese term describing “haziness like a puff of cigarette smoke in the air” was first described by Drs. Suzuki and Takaku for an angiographic picture of abnormal net-like vessels at the base of the brain in a setting of stenosis or occlusion.<sup>42</sup> Moyamoya disease (MMD), is characterized as a chronic, idiopathic, progressive cerebrovascular disease presenting with ICA stenosis and occlusion.<sup>42-44</sup> Changes are usually bilateral and accompanied by abnormalities of the anterior and middle cerebral arteries. Abnormal vascular networks seen at the brain base are common causes of stroke or transient ischemic attack; hemorrhages are possible as well. It is most commonly seen in East Asian countries (Korea, Japan, China, Taiwan). Worldwide there is a bimodal age distribution, occurring in pediatric patients, 5 to 15 years of age, and adults in their second and third decades. Incidence in females is higher than males, but geographical differences in gender distribution have been seen, such as in China, where it is equal among the sexes.<sup>45,46</sup> The differences in the US include lack of bimodal age of onset, prevalence of ischemic MMD for all age groups, benign symptoms at presentation, and better response to surgical treatment. However, in Hawaii, California and Washington, the MMD profile more closely matches that in Japan and is attributed to the higher immigrant Japanese population.<sup>47</sup>

### Presentation and Risk Factors

The clinical symptoms differ based on age. Pediatric MMD presents with transitory repetitive cerebral ischemia with progression to occlusion more common in children, paroxysmal hemiplegia, paresthesia and facial paralysis, paroxysmal headaches, fine involuntary movements of the extremities, and progressive mental impairment.<sup>48,49</sup> The repetitive symptoms can result in motor aphasia, mental retardation, and even a vegetative state. In contrast, adult-onset MMD is characterized by sudden disturbances of consciousness, intracranial hemorrhage, bleeding into the ventricles, and subarachnoid hemorrhage.<sup>50</sup> Patients often present due to headache, dizziness, palpitations, syncope, or hyperventilation.<sup>51</sup> Hemorrhages are recurrent and often fatal.

### Pathology and Genetics

Epidemiologic data point to a familial form, which constitutes 10% of cases.<sup>52-57</sup> Kamada and colleagues in 2011 identified a novel susceptibility gene, Ringin Protein 213 (RNF213), and demonstrated its association with familial MMD.<sup>58</sup> The RNF213 mutations can be heterozygous or homozygous, with the latter correlating with earlier onset, more severe symptoms and worse prognosis.<sup>59</sup> Despite genetic features, the most common form is sporadically occurring MMD.<sup>60</sup>

### Pathophysiology

Progressive bilateral or unilateral stenosis of the ICA is seen. Arterial stenosis is due to fibrocellular thickening of the intima and occlusion due to smooth muscle cell accumulation.

Histologically, the ICA shows concentric fibrocellular thickening of the intima, inducing vascular luminal stenosis, intimal elastic lamina undulation, a thickened layer of smooth muscle, and a lack of inflammation. These changes result in thrombosis and regional cerebral hypoxia. As a result, collateralization by so-called moyamoya vessels occurs, characterized by a thin media, fibrin deposition in the vessel walls, fragmented elastic laminae, and an increased tendency to form microaneurysms. Neovascularization occurs due to the expression of HIF-1, VEGF, TGF-B, hepatocyte growth factor, and MMP.<sup>61</sup> Cerebrocortical microvascularization (an increase in microvascular density and diameter) is a potential compensatory mechanism.<sup>48,49,62</sup>

Due to increased levels of multiple autoimmune antibodies, it is thought that heightened immune responses may play a role. Elevated levels of cytokines such as VEGF, basic fibroblast growth factor (bFGB), granulocyte colony stimulating factor (G-CSF) and hepatocyte growth factors are seen in plasma, cerebrospinal fluid and vessel biopsies of patients with MMD. These elevated immune factors also accelerate the arterial inflammation.<sup>63</sup>

### Diagnosis and Workup

The Japanese Ministry of Health released guidance for diagnosis and treatment of MMD.<sup>64</sup> Cerebral angiography is the gold standard for imaging, although increasingly noninvasive axial imaging has been utilized (Fig. 99.2). The Suzuki guidelines for angiographic diagnosis include: stenosis or occlusion at the end of the carotid artery, proximal anterior cerebral artery (ACA) or middle cerebral artery (MCA); an abnormal vascular network near the stenosis or occlusions in the arterial phase; and bilateral manifestations of the above findings<sup>64</sup> (Table 99.1). The guidelines were updated in 2012 to include staging based on scores of magnetic resonance angiography (MRA).<sup>65,66</sup> The new criteria include at least two obvious shadows of the blood flow seen on the same scan level at the basal ganglia, suggesting



**Figure 99.2** Cerebral Angiogram of a Patient with Moyamoya Disease. Lateral view of intracranial left internal carotid injection.

**TABLE 99.1** Moyamoya Stages and Cerebral Angiographic Findings Research Committee

| Stage | Cerebral Angiography Findings   |
|-------|---|
| I     | Narrowing of the carotid fork.  |
| II    | Initiation of the moyamoya (dilated major cerebral artery and a slight moyamoya vessel network).  |
| III   | Intensification of the moyamoya (disappearance of the anterior and middle cerebral arteries, and thick and distinct moyamoya vessels).  |
| IV    | Minimization of the moyamoya (disappearance of the posterior cerebral artery and narrowing of the individual moyamoya vessels).   |
| V     | Reduction of the moyamoya (disappearance of all the main cerebral arteries arising from the internal carotid system, further minimization of the moyamoya vessels, and an increase in the collateral pathways from the external carotid artery system). |
| VI    | Disappearance of the moyamoya (disappearance of the moyamoya vessels, with cerebral blood flow derived only from the external carotid artery and the vertebrobasilar artery systems).   |

the presence of an abnormal vascular network (Fig. 99.3). The sides are staged separately. In the evaluation system, MRA findings are totaled and collectively represent disease stages. Each artery (ICA ACA, MCA and PCA) is scored based on stenosis, discontinuity or invisibility of the proximal vessel with each variable having a score from 1 to 3. The PCA includes signal decrease in the distal vessel which scores 2 points (Table 99.2). Cerebral angiography is valuable for diagnosis and assessing progression by the Suzuki staging system. This now includes re-staging based on severity of stenosis or occlusion in the MCA and the proximal ACA and their branches on angiography.<sup>67</sup>

The differential diagnosis includes atherosclerosis, autoimmune-mediated diseases, meningitis, brain tumors and radiation damage. Moyamoya syndrome (MMS) refers to vessel morphology similar to MMD but without other characteristic indicators. The treatment is the same as MMD.

## Treatment

There is no therapy to reverse progression of MMD. Steroids, vasodilators, antibiotics, mannitol and IV calcium channel blocker infusion have not been beneficial. Due to an elevated risk of both ischemic and hemorrhagic stroke in asymptomatic patients, antiplatelet therapy is contraindicated, unless the ischemic severity justifies its use. Medical management includes the use of antihypertensive agents, lipid-lowering therapy, diabetic glycemic control, smoking cessation, weight reduction, as well as elimination of oral contraceptive agents.<sup>68,69</sup> Modifiable risk factor management and lifestyle guidance may reduce stroke recurrence. Hyperventilation can induce symptoms, so patients should avoid hot meals and strenuous exercise.

Surgical management is indicated in individuals with symptomatic ischemia or disease progression as seen in



**Figure 99.3** CTA of Intracranial Moyamoya. Arrow indicates anterior branches of moyamoya vessels.

**TABLE 99.2**

Total Score for MRA Imaging and MMD Staging

| MRA Score | MRA Stage |
|-----------|-----------|
| 0–1       | 1         |
| 2–4       | 2         |
| 5–7       | 3         |
| 8–10      | 4         |

pediatric cases. The goal of revascularization is to allow normalized cerebral perfusion, and this is the standard of care to prevent recurrent stroke and bleeding. Furthermore, revascularization has been shown to reduce the risk of transient ischemic attacks (TIAs) and cerebral infarction, to improve activities of daily living, and to ameliorate overall brain function as tracked over time.<sup>70–72</sup> Extracranial to intracranial bypass (EC-IC) has been shown to be beneficial in both ischemia and hemorrhage.<sup>73</sup> The recurrence rate of bleeding or stroke is reduced in patients treated with surgery, corroborated by several studies.<sup>73–76</sup>

Surgical techniques include three options: direct, indirect, and combined strategies. Direct revascularization most commonly is superficial temporal artery (STA) to MCA bypass, described by Yasargil in 1967. Long-term patency is dependent on presence of sufficient diameter in the STA and cortical arteries, since the later stages lead to cortical arterial shrinkage and vessel wall fragility. Chater's point is used as a landmark in searching for a large cortical branch as a distal target if the MCA target is not seen. Patency is excellent in all reports. The complication rate is up to 9%, due to increases in cerebral blood flow (CBF), intra- and perioperative ischemia, general anesthesia and symptomatic hyperperfusion. In addition, some series indicate that bypass accelerates progression of stenosis of the ICA over time.<sup>76</sup>

Indirect bypass is typically more expedient and less technically demanding, with decreased operative times and lower complication rates. It is typically performed when the STA is small or compromised, in pediatric patients with small vessels, and where direct bypass is too complex. The source of blood supply in these operations is a wide array of tissues including omental transplant. The most common inflow types are encephalomyosynangiosis (EMS), where the deep temporal artery within the temporal muscle is the supply, and encephaloduroarteriosynangiosis (EDAS), where the STA's parietal branch in the galeal crus is used. In indirect bypasses, distal anastomosis is not performed. The tissue containing the donor vessel is placed over the cerebral cortex after the arachnoid layer is removed. Collateralization occurs over time between the vessel-rich tissue and the ischemic neural tissue. While the procedure has lower risk, the increase in blood flow does not immediately occur and may take weeks to months to develop. Due to the reduced diameter of cortical arteries and longer neovascularization times, indirect revascularization may not be feasible in advanced stage patients.<sup>75</sup> The procedure also incurs a larger craniotomy and dural opening than direct bypass. Complications include seizures and overall mass effect from the tissue transfer. Indirect revascularization is recommended in pediatric patients with small caliber vessels with risk of vasospasm with direct anastomosis and greater likelihood for angiogenesis.

Combined revascularization uses both direct and indirect techniques. It is employed for unstable or acutely symptomatic patients. Houkin and colleagues reported optimal revascularization in children with STA-MCA bypass and EDAMS to improve both immediate flow and indirect flow over time.<sup>76</sup> Tandem revascularization in adults has resulted in improved outcomes.<sup>75</sup>

Advancement in techniques for assessing vessel caliber and matching with video angiography as well as ischemic preconditioning prior to surgery are on the horizon.<sup>11</sup>

## CAROTID ARTERY KINKS AND COILS

### Background

Carotid artery coiling is elongation and redundancy of the ICA resulting in an exaggerated S- or C-shaped curvature of the vessel (Fig. 99.4). Carotid kinking is elongation with angulation of one or more segments of the ICA distal to the bulb and is often associated with stenosis in the affected segment from atherosclerosis. Carotid coils and kinks were first defined by Weibel and Metz.<sup>77</sup> They may be caused by multiple factors including developmental disease, intrinsic vessel wall pathology such as fibromuscular dysplasia, age and hypertension-related degeneration, atherosclerosis or postsurgical changes. Coils and kinks can also occur as normal structural variants. These anomalies are important considerations given the association with atherosclerotic disease and the frequency of cervical procedures and manipulations.

### Epidemiology

As most patients with carotid kinks and coils are asymptomatic, the true incidence is unknown. Reported incidence rates



**Figure 99.4** Computed axial tomography angiogram with sagittal reconstruction identifying a complete 360-degree coil of the internal carotid above the carotid bulb. Arrow indicates looping carotid artery resulting in "coil". LICA, left internal carotid artery.

are likely to vary due to diagnostic modalities. Arteriographic methods report incidences from 10% to 25%, even up to 66%.<sup>78</sup> A duplex ultrasound study by Togay-Isikay et al. found a 24.6% rate.<sup>79</sup> The overwhelming majority of these patients were female (70.6%) and most over 60 years of age. The most common abnormality noted was kinking (56%), followed by tortuosity (38%) and then coiling (6%).<sup>79</sup> Infantile carotid anomalies have also been reported, with associated symptoms of seizure or stroke.

### Classification

Weibel and Fields introduced a classification system for carotid anomalies in 1965 which is still used today. They described 4 classic morphologies of the ICA: (1) straight course of ICA; (2) an S- or C-shaped elongation with medial or lateral displacement; (3) kinking of one or more segments; and (4) coiling, which may also appear as a double loop. Paulsen et al. also describe a variant of group (2) with ventral or dorsal displacement of the S- or C-shaped segment.

### Etiology and Clinical Presentation

Two main theories about the development of carotid anomalies exist.<sup>80</sup> The embryological development of the branchial arches is the basis for the first theory and notes that the ICA arises from the third aortic arch and dorsal aorta. The ICA is naturally coiled or kinked in the embryo, but stretches and elongates when the heart recedes into the thorax during normal development. Failure of this process, incomplete development or accelerated linear growth can result in persistence of

the carotid loop. However, kinking and coiling occurs in other vessels such as the vertebral artery, where no embryological explanation is found.

The second theory attributes the altered carotid morphology to aging and vessel wall changes related to atherosclerosis, degeneration and hypertension. They may also be the sequelae of prior carotid surgery such as endarterectomy, neck dissection or surgical manipulation. Typically coiling is associated with embryologic causes, whereas kinking is attributed to atherosclerosis fibromuscular dysplasia or previous surgery.

Symptoms may develop later and can be caused by vessel course deviation causing disturbances in hemodynamics or by development of atherosclerosis. Some investigators liken the coil wall hemodynamics to aneurysms, leading to denudation and possible embolic debris formation.<sup>78</sup> Several reports have also found that carotid kinking may be the source of cerebral emboli or that the kinked vessel may be temporarily occluded by rotation of the head and neck.<sup>78,81,82</sup>

## Treatment

Imaging evaluation includes duplex ultrasonography, computed tomography (CT) with imaging of the brain, magnetic resonance imaging (MRI) and biplane carotid angiography. Medical treatment includes antiplatelet therapy to reduce platelet aggregation in asymptomatic patients. Patients who exhibit lateralizing hemispheric symptoms benefit from surgical treatment.

The first randomized clinical study was performed by Ballotta and colleagues in symptomatic patients without atherosclerotic lesions. It demonstrated that surgery was significantly better than antiplatelet therapy alone for relief of neurologic symptoms and prevention of ICA thromboses and stroke.<sup>83</sup> Another study corroborated that surgery is safe and effective in symptomatic patients with isolated stenotic kinking despite antiplatelet therapy.<sup>84</sup> Surgery involves transection of the ICA at the bulb with straightening and then end-to-side reimplantation along the lateral wall of the CCA. Simple kinking is an indication for shortening angioplasty. Distal dilation of the ICA can be performed if the lumen does not return to normal after straightening or the vessel can be spatulated similar to an eversion technique.<sup>84</sup> Double kinking<sup>②</sup> anatomy can be treated with resection of the diseased arterial segment, and reconstruction with either transposition with side-to-end anastomosis onto the external carotid artery (ECA) or interposition bypass grafting preferably with autologous conduit.

Ballotta et al. found that the surgical treatment group experienced lower rates of TIAs, stroke, amaurosis fugax, deaths, carotid occlusion, and nonhemispheric symptoms than did the medically treated group with median follow-up of 5.9 years (1–10),<sup>83</sup> despite a 41% cross-over rate from the medical to surgical arm due to new or progressive hemispheric symptoms. Illuminati et al. found no postoperative deaths and a postoperative stroke rate of 1%, with 5-year primary patency of  $89\% \pm 4\%$ , and freedom from neurologic symptoms,  $92\% \pm 4\%$ .<sup>83</sup>

## INTRACRANIAL VASCULAR LESIONS

Intracranial vascular lesions include stenoses and aneurysms and are relevant to the vascular surgeon treating extracranial pathologies. Better understanding of the evolution and treatment options is critical to the management of patients with extensive vascular disease.

### Background and Epidemiology

Intracranial arterial stenosis (ICAS) is defined as large intracranial arterial luminal narrowing. Atherosclerosis and embolic phenomena from other sources are primary causes of stenoses. Entities such as arterial dissection, vasculitis, central nervous system infections, radiation, sickle cell disease, as well as moyamoya disease should also be considered. ICAS is one of the most common causes of stroke worldwide and is associated with increased risk of recurrent stroke.<sup>85</sup>

In the United States, ICAS causes approximately 100,000 strokes annually. Several multiracial studies have focused on symptomatic individuals, finding that the condition extensively affects Asians, accounting for 20% to 50% of strokes in Chinese, Korean, Thai, and Japanese populations. ICAS also accounts for 5% to 10% of strokes in Caucasians, and 15% to 29% of TIAs in African Americans. Additional studies indicate that a large proportion of strokes in the Hispanic population are also attributable to ICAS.<sup>86–90</sup> Overall, there is a lack of prevalence studies evaluating ICAS in ethnic populations leading to under-reporting of the disease.

### Risk Factors

Modifiable risk factors for ICAS include hypertension, smoking, diabetes mellitus, and dyslipidemia. Nonmodifiable risk factors include race, age, and genetic variations (angiotensin-converting enzyme polymorphisms, increased plasma endostatin/vascular endothelial growth factor, plasma homocysteine levels, glutathione S-transferase omega-1 gene polymorphism).<sup>91</sup>

The Warfarin and Aspirin Symptomatic Intracranial Disease (WASID) study sub-analysis found that women with symptomatic ICAS are at higher risk for recurrent stroke, leading to death.<sup>92</sup>

### Diagnosis

Catheter digital subtraction angiography (DSA) is the gold standard due to its ability to quantify and localize the degree and extent of intracranial luminal stenosis.<sup>93</sup> Limitations include the risk of vessel injury and stroke. For this reason, it is typically limited to therapeutic interventions. Other diagnostic imaging includes minimally invasive neuroimaging techniques, including transcranial Doppler (TCD) ultrasound, MRA, computed tomography angiography (CTA), and high-resolution MRI. The Stroke Outcomes and Neuroimaging of Intracranial Atherosclerosis (SONIA) trial<sup>93</sup> found that both TCD and MRA identify 50% to 99% intracranial stenosis