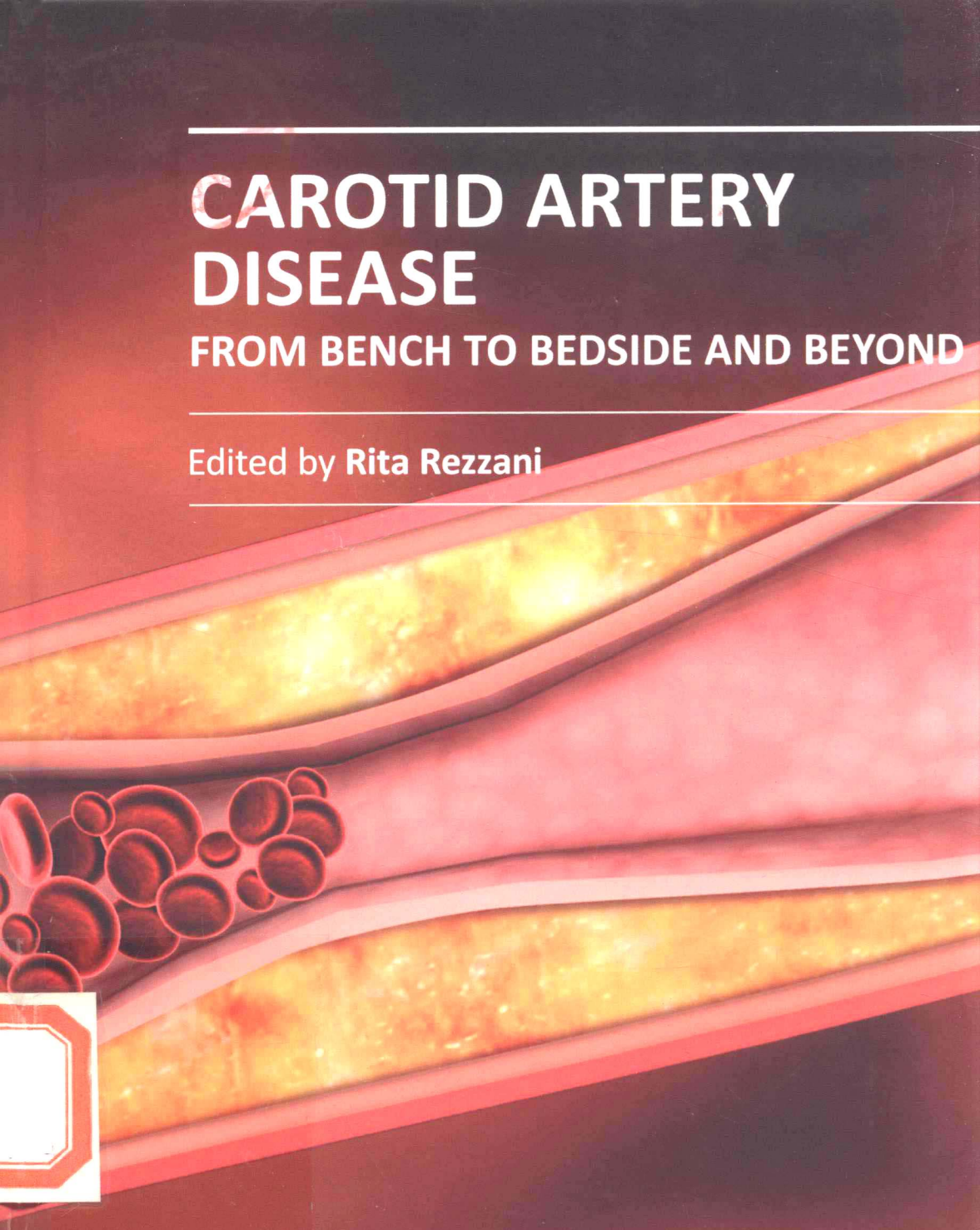
CAROTID ARTERY DISEASE

FROM BENCH TO BEDSIDE AND BEYOND

Edited by **Rita Rezzani**



INTECH

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Contributors

Reza Mofidi, Foad Abdallah, Elias Skopelitis, Dimitrios Levisianou, Sofoklis Kougialis, Helen Lydataki, Antenor Tavares Junior, Masanori Kawasaki, Jose Milei, Andres Izaguirre, Ricardo Luis Beigelman, Eric Deshaies, David Padalino, Jeffrey Indes, Lindsay Gates

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Preface

Atherosclerosis is a multifactorial and dynamic disease which makes the process of prevention and management complex.

The clinical studies include the thickness of intima-media tunica, evaluation of the stenosis severity and plaque morphology. These points are important for monitoring plaque stabilization, and for development of therapeutic strategies.

The book consists of 8 chapters describing the cytoarchitecture of carotid plaques from morphological and physiopathological points of view. It includes clinical applications such as the effect of statin therapy and new updates for the benefit of the patients.

The book is written for all those working in the field of atherosclerosis, cardiovascular diseases and basic scientists. Moreover, it is important for linking basic scientists to clinicians.

This book will bring out the state of art of carotid stenosis in the basic and clinical approaches for better understanding of the mechanisms and useful therapies for these disease. We hope that would be a new "current trend" understanding new aspects regarding this scientific problematic involving not only anatomical, functional but also clinical questions.

Dr. Rita Rezzani
Full Professor of Human Anatomy
Chair of Anatomy and Physiopathology Section
University of Brescia
Italy

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Evaluation and Treatment of Carotid Artery Stenosis

Lindsay Gates and Jeffrey Indes

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1. Introduction

Stroke is the fourth leading causes of death in the United States. Annually, about 795,000 people suffer from a stroke with about 140,000 people, or 1 in 19, dying each year due to stroke related causes. [1] Between 1995-2005 overall stroke death rate fell 30%, even so, annual health care related costs for stroke patients in 2012 were up to 38.6 billion. [1] It is well recognized that cerebrovascular disease, specifically carotid atherosclerosis and subsequent stenosis, is a leading cause of ischemic stroke, which makes up 87% of all strokes. Due to the significant morbidity and mortality incurred by these patients the identification, management, and treatment of carotid disease is of paramount importance.

2. Epidemiology

Cerebrovascular disease does not appear to affect all races and genders equally. In addition to the usual cardiovascular risk factors of hypertension, diabetes, and smoking; age, gender and race have also been shown to have an additive effect on stroke risk. In a study by Rockman et al. they looked at a little over 3 million patients for evidence of carotid artery stenosis. After controlling for gender and age differences, they found that there was a marked variation in the prevalence of carotid artery stenosis with Native American subjects having the highest prevalence followed by Caucasians. [2] Yet, based on CDC data, African Americans' risk of having a first stroke is nearly twice that of Caucasians. Overall, as would be expected based on the prevalence of carotid disease, American Indians/Alaska Natives are more likely to have a stroke than other groups. [1] Gender differences have also been analyzed. In a large population based study carotid artery stenosis was detected in 3.8% of men and 2.7% of women. [3] The reasons for these differences are thought in part to be due to carotid plaque differences between men and women. Sangiorgi et al. evaluated

plaque specimens from 457 patients and found that women, as compared to men of the same age, had a lower prevalence of thrombotic plaques and a smaller area of necrotic core and hemorrhage extension. Also, they found inflammatory features were less pronounced in women as compared to men. [4] These results correlate with similar studies done for evaluation of patients with coronary artery disease that showed that sex hormones seem to play a fundamental protective role in women. [5, 6] More studies still need to be conducted to determine the true role of gender in carotid artery disease. Age greater than 70 also appears to be a risk for stroke. In the Framingham study they found that seventy year olds with hypertension and the presence one additional risk factor, such as diabetes mellitus, cigarette smoking, cardiovascular disease, atrial fibrillation or electrocardiographic abnormalities had an increase in 10 year stroke risk from an average of less than 9% in women and 12.3% in men, to greater than 80%. [7].

3. Evaluation

Significant carotid artery atherosclerosis can put patients at a risk for stroke and/or transient ischemic attack (TIA) making it imperative that at risk populations be accurately evaluated and followed for disease progression. An ideal diagnostic imaging test could accurately and reproducibly determine the degree of luminal stenosis as well as plaque morphology in both a non-invasive and cost effective way. No one single imaging test encompasses all these traits however several have been shown to have benefit in the diagnosis and work up of carotid disease. At this time the most clinically effective first line imaging modality for identifying patients with carotid artery disease is duplex ultrasound (DUS). In 2006 Wardlaw et al published a meta-analysis looking at non-invasive imaging tests either alone or combined to determine if they could replace intra-arterial angiography for evaluation of carotid stenosis. They included 41 studies and found that contrast-enhanced magnetic resonance angiography (CEMRA) was the most accurate imaging modality for patients with 70-99% stenosis, however it was not cost-effective. Alternatively, DUS had a sensitivity of 0.89 and specificity of 0.84 for carotid stenosis between 70-90%, was cost effective and allowed for expedient diagnosis and treatment for patients recommending it as the diagnostic test of choice. In patients with lower degrees of stenosis around 50-69% the sensitivity of DUS dropped to 0.36. [8] Conversely, another meta-analysis performed by Jahromi et al found improved sensitivities and specificities of 0.98 and 0.88 for detecting greater than 50% ICA stenosis; and 0.94 and 0.90 respectively for detecting greater than 70% ICA stenosis. [9] Due to the potential risk of surgical intervention in patients with a questionable or 50-69% stenosis, a subsequent CEMRA or a multi detector computed tomographic angiogram (MDCTA), is highly recommended. [8] Principle limitations of ultrasound remain primarily operator experience. Occasionally, plaque calcification, shadowing and patient body habitus can also prevent accurate assessment of stenosis. Currently the indications for carotid duplex ultrasonography are cervical bruit, amaurosis fugax, focal or cerebral transient ischemic attacks, drop attacks, or syncope.

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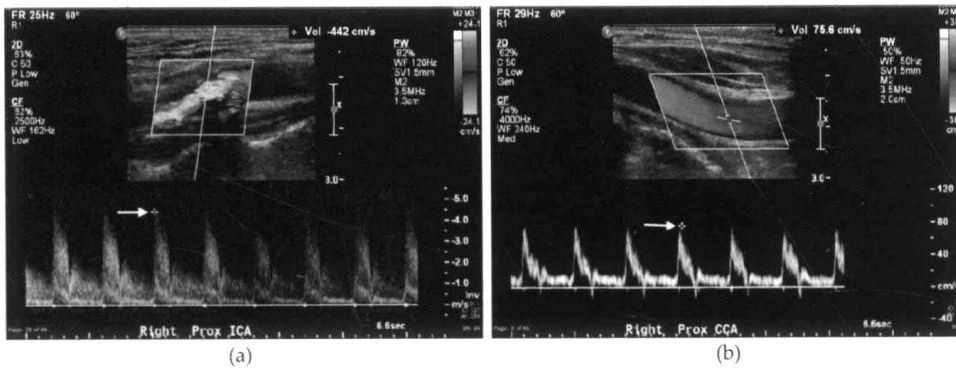

(a) (b)

Figure 1. 71 year old male presenting with history of transient ischemic attack presenting as left arm numbness and weakness. A. Ultrasound of the right internal carotid artery showing elevated velocities (arrow) up to 442 cm/s correlating with a greater than 70% stenosis by NASCET criteria. B. Same patient US of right proximal common carotid artery with baseline velocities (arrow) 75.6 cm/s.

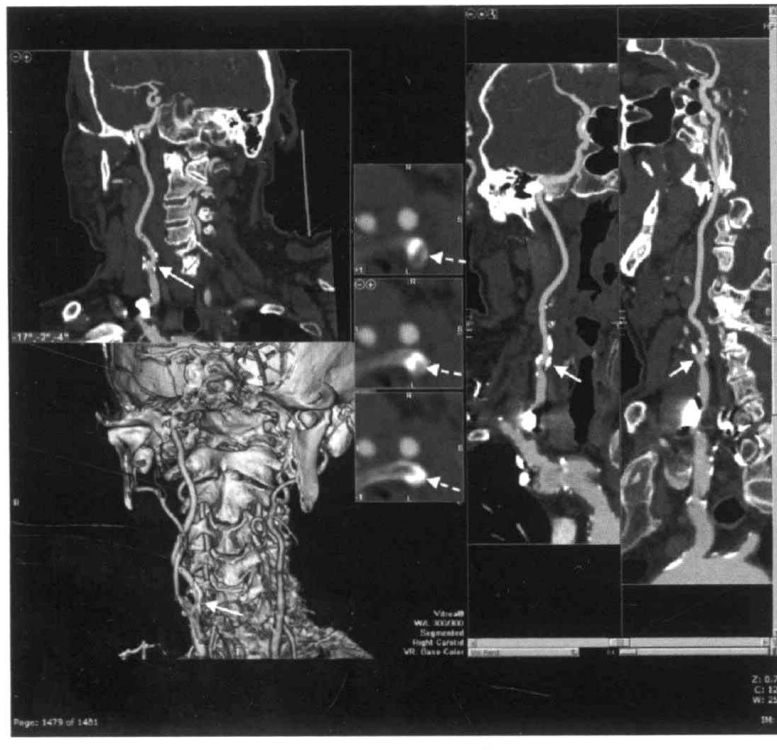

Figure 2. 79 year old male presented after transient ischemic attack. CTA obtained showing proximal right internal carotid artery stenosis (greater than 70%) with heavy calcification (arrow). Also shown cross-sectional view of area of greatest stenosis (dashed arrow).

The degree of luminal stenosis has traditionally been the most important element when considering the severity of carotid disease, however recently several studies have shown that plaque structure and composition may be an additional marker for future cerebrovascular events. [10, 11] DUS can provide only a basic view of plaque morphology, unable to consistently and accurately delineate characteristics of plaque vulnerability such as ulceration, a large lipid necrotic ore, and a thin fibrous cap. [12, 13]. Gray-Weale developed a scale, later modified by Geroulakos that identified 5 types of carotid artery plaques: type 1 (anechogenic with echogenic fibrous cap), type 2 (predominately anechogenic but with echogenic areas representing less than 25% of the plaque), type 3 (predominately hyperechogenic but with anechogenic areas representing less than 25% of the plaque), type 4 (echogenic and homogeneous plaque) and type 5 (unclassified plaques reflecting calcified plaques with areas of acoustic shadowing which hide the deeper part of the arterial layers). [14, 15]. Using this type of classification, a study by Polak et al. showed that asymptomatic elderly patients with a hypoechoic plaque have relative risk of ipsilateral ischemic stroke of 2.78, this was independent from the degree of stenosis and other cardiovascular risk factors. [16]Another, similar investigation by Mathiesen et al. found comparable results with the relative risk of ipsilateral cerebrovascular events in patients with hypo-echoic plaques to be 3.52. [17] Nevertheless in the Asymptomatic Carotid Surgery Trial (ACST), there was no evidence that the Gray-Weale classification, or plaque echolucency, showed any influence on the risk of stroke over degree of stenosis. [18]. The emergence of multi-detector computed tomographic angiography (MDCTA) came with the increased advances of improved spatial and temporal resolution for evaluating different arterial regions but also the ability to further differentiate plaque morphology between smooth, irregular and ulcerated surfaces. [19] Density of a plaque can also be determined measured in Hounsfield units (HU). This can differentiate a "soft" plaque (<50 HU) which usually has a lipid-rich core and more likely to be associated with symptoms from a "calcified" plaque (>120 HU) which generally remains asymptomatic. [20]. Even so, it seems that MRA is probably the best modality for evaluating plaque morphology. Plaque components such as lipid cores, intraplaque hemorrhage, fibrotic tissue, fibrotic caps and calcifications can all be evaluated with MRA to distinguish unstable plaques from stable ones. [21-23] In a study by Sadat et al. MRA was used to evaluate plaque morphology in acute symptomatic, recently symptomatic and asymptomatic patients. Results showed that MRA was clearly able to identify plaque features including hemorrhage and thin fibrous caps in the acutely symptomatic group that varied from the recently symptomatic and asymptomatic groups. [23] The use of MRA for further risk stratifying symptomatic patients or predicting high-risk asymptomatic patients, however requires further evaluation to determine its role in the evaluation of carotid artery disease.

Even with all of the advances of DUS, MDCTA, and MDMRA, for many practitioners intra-arterial digital subtraction arteriography (IADSA) still remains the gold standard for imaging extra cranial and intracranial circulation. Although angiography allows for detailed evaluation of the aortic arch, origins of the great vessels and the distal ICA, it is still an invasive imaging modality potentially exposing patients to unnecessary complications and even possibly death. Complications rates do vary among studies from as low as 0.4% in the Veterans Affair Cooperative Study to 1.2% in the Asymptomatic Carotid Atherosclerosis Study and as high as

12.5% in patients with severe bilateral carotid obstructive disease. [24-26]. IADSA can be forgone in most situations where noninvasive diagnostic tests are available and now usually only utilized in conjunction with planned carotid artery stenting.

3. Asymptomatic carotid stenosis

Patients with cerebrovascular disease can be divided into asymptomatic and symptomatic disease. Patient's with asymptomatic carotid disease generally come to the attention of practitioners because they are found to have one or more risk factor for developing cerebrovascular disease (age, diabetes mellitus, coronary artery disease, peripheral vascular disease, hypertension, or hyperlipidemia) and/or signs on clinical exam, such as carotid bruit on auscultation, that warrant further diagnostic evaluation. About 5% of the general population over 65 years of age has an asymptomatic CAS of 50% or greater. [27-28]. This is increased in patients with peripheral arterial disease up to 15% and in patients with abdominal aortic aneurysms up to about 12%. [29] The overall annual risk of ipsilateral stroke for patients found to have asymptomatic carotid stenosis that are treated medically is about 2%. Asymptomatic carotid disease, in fact, seems to be a better indicator of generalized vascular disease than of stroke risks. In this population the average annual non-stroke death rates are generally higher than those of ipsilateral stroke with more than 50% of the non-stroke related deaths due to ischemic heart disease and its complications. [30] For patients who are found to have carotid disease, optimal medical management is the cornerstone to overall treatment. The goal of medical therapy is to reduce overall cardiovascular events as well as stroke by a five pronged attack including: treatment of hypertension, treatment of diabetes mellitus, treatment of lipid abnormalities, smoking cessation, and antithrombotic treatment. As mentioned previously, hypertension has been consistently found to be an independent risk factor for carotid artery atherosclerosis with each 10-mm Hg increase in blood pressure resulting in an increase in risk for stroke of 30-45%. Conversely each 10-mm Hg reduction in blood pressure in hypertensive patients decreases risk for stroke by 33%. [31] Currently recommendations are for blood pressures to be maintained less than 140 systolic and 90 diastolic. For patients with coronary artery disease the relationship between lipid abnormalities and ischemic heart events has also been clearly identified in the literature however at this time the relationship between elevated cholesterol and stroke risk remain unclear. [32,33] Nevertheless, studies have shown that patients with known atherosclerosis have demonstrated reduced stroke rates by 15-30% when treated with lipid lowering therapy. [34] Smoking cessation is important for all patients with vascular disease, and in carotid artery disease this is no different nearly doubling the overall risk for stroke. [35] Finally both antithrombotic and anticoagulant therapy can also be utilized for prevention in patients with carotid disease. There is more robust evidence for the use of antithrombotic treatment for secondary prevention of recurrent stroke in symptomatic patients than for prevention in asymptomatic patients, however it is still recommended that patients who are at risk, or have known vascular disease, take a daily aspirin for prophylaxis. [36] Anticoagulation with Coumadin is generally reserved for patients at risk for an embolic stroke from atrial fibrillation and is not used as prophylaxis for asymptomatic or symptomatic carotid disease. [37]

For asymptomatic patients who continue to have worsening carotid disease even with best medical management the next step in treatment is to consider operative intervention. The current recommendations from the Society for Vascular Surgery is for carotid endarterectomy in asymptomatic patients with carotid stenosis of greater than or equal to 60% as long as the expected combined stroke and mortality rate for the individual surgeon was not greater than 3%. [38] These recommendations are based on three major prospective, randomized trials the Veterans Administration Asymptomatic Carotid Stenosis Study (VA ACS), the Asymptomatic Carotid Atherosclerosis Study (ACAS), and the Asymptomatic Carotid Surgery Trial (ACST).

The VA ACS evaluated a total of 444 patients over an 8 year period randomizing them to a surgical group (211) or and a medical group (233). Both groups were treated with aspirin and best medical risk factor control. For the surgical arm, the 30-day mortality rate was 1.9% and the incidence of stroke was 2.4% with a combined stroke and mortality rate of 4.3%. In total, all neurologic events were 30 (14.2%). Conversely, the medical group had a total of 55 (23.6%) neurologic events recorded. These findings were found to be statistically significant with a P value of less than 0.006. [39] However, the study did not find any difference in overall survival rates between groups. This trial gave credence that best medical treatment plus carotid endarterectomy (CEA) would reduce stroke and TIAs versus medical treatment alone in asymptomatic patients.

The ACAS was a NIH-funded randomized trial which included 1662 patients between the ages of 40-79 years with greater than 60% asymptomatic stenosis. Patients were randomized to optimal medical management versus CEA and medical management. The 30-day combined mortality and stroke rate was 2.3%, which accounts for two preoperative deaths and seven preoperative strokes making the actual stroke rate 1.3% and mortality rate 0.1%. After a mean follow up of 2.7 years the overall 5-year risk for ipsilateral stroke, perioperative stroke and death was 5.1% for surgical patients and 11% for the medical group (P=0.004). [40] An absolute risk reduction for stroke and death in the surgical group was calculated to be 53%. [41] One drawback of the ACAS study is that all patients with 60%-99% carotid stenosis were analyzed together and there was no breakdown for event rates by deciles. Nevertheless, their results again favored CEA plus medical management over medical management alone.

Finally a group of European investigators embarked on an additional randomized trial, ACST, to try, in addition to validating CEA for asymptomatic patients with significant stenosis, to identify a higher-risk group of patients. They randomized 3129 patients, both men and women, with greater than 60% asymptomatic unilateral or bilateral carotid artery stenosis to CEA versus best medical therapy. The found a 5 year stroke or death rate to be 6.4% versus 11.8 % ($p<0.0001$) in the CEA versus medical group, respectively. Overall perioperative stroke or death rate was 3.1%. These results were found to be significant for bother males and females when analyzed separately [18].

4. Symptomatic carotid artery stenosis

When compared to asymptomatic patients the benefit of CEA with recent ipsilateral carotid territory symptoms and moderated to severe carotid stenosis is much greater. In patients who

experience a TIA or minor stroke the risk of subsequent stroke or death is very high, especially during the first few days and weeks after an event. [42] Traditionally the mainstay of treatment for symptomatic disease in these patients is surgical intervention with CEA. Recently there has been literature advocating aggressive medical therapy alone may be adequate in certain patients, preventing early stroke after TIA and reducing the need for urgent CEA. The Stroke Prevention Aggressive Reduction of Cholesterol Levels (SPARCL) trail tested whether treatment with atorvastatin reduced strokes in subjects with recent minor stroke or TIA. The study included 4731 participants with a mean follow up of 4.9 years and found that high does Atorvastatin use after TIA or stroke was associated with a 16% relative reduction in risk of fatal or nonfatal stroke. Also patients treated were found to have a 56% reduction in later carotid revascularization compared with placebo. Researchers postulated that the use of statins might help stabilize the arterial wall decreasing events as well as reducing intraoperative complications as well for patients who did proceed with surgery. [43,44] Merwick et al. also evaluated early high dose statin use postulating that pretreatment at TIA onset would modify early stroke risk. They found that non-procedural 7-day stroke risk was 3.8% with statin treatment compared to 13.2% in those not pretreated. [45] Another study by Chimowitz et al. evaluated a different medical treatment looking at recently symptomatic patients with intracranial 79-99% stenosis who were treated with dual antiplatelet therapy versus percutaneous transluminal angioplasty and stenting (PTAS) (gold standard for intracranial lesions). This study found a 30-day rate of stroke or death was found to be 14.7% in the PTAS group and 5.8% in the medical-management group. At one year follow this study concluded that medical management with dual antiplatelet therapy was superior to PTAS and advocates belief this data can be extrapolated to severe, symptomatic extra cranial disease as well. [46,47]. Several other older studies have compared the use of platelet antiaggregants with placebo in treating patients with cerebral ischemia secondary to extra cranial atherosclerosis. [48-51] These results however proved inferior to surgery, which was highlighted in the landmark North American Symptomatic Carotid Endarterectomy Trial.

Two major randomized control trials have reported data to date advocating for CEA in symptomatic patients with 50%-99% stenosis: The North American Symptomatic Carotid Endarterectomy Trial (NASCET) and Medical Research Council European Carotid Surgery Trial (ECST). The NASCET trial was set up to evaluate two subsets of patients those with 70-99% stenosis and those with 30-69% stenosis. In the high-grade stenosis group the 30-day operative morbidity and stroke mortality rate for patients was 5%. In the surgical group at 2-year follow-up the incidence of ipsilateral stroke was 9% compared to 26% in the medical treatment group. This difference represented an absolute risk reduction of 17% in favor of surgical management and a relative risk reduction of 71% at the end of the 18^{-month} follow up. Mortality rates were also measured at the end of 18 months yielding 12% mortality rate in the medical group compared to a significantly lower rate of 5% in the surgical group. [52,53]. The results for the moderate stenosis group were also reported. The 30-day combined mortality, disabling stroke rate, and non-disabling stroke rate was 6.7%. At 5 year follow up in this group the ipsilateral stroke rate was 22.2% in the medical patients and 16.7% in the surgical patients. [54]

The ECST trial was a European randomized control trial that enrolled patients over 10 years almost concurrently with the NASCET trial. There were 2518 patients with nondisabling ischemic stroke, TIA or retinal infarct due to a stenotic lesion in the ipsilateral carotid artery

randomized to either medical management with aspirin or surgery. At 3 years, the risk of stroke was found to be 26.5% in the medical group compared to 7% in the surgery group with an absolute reduction of 14.9%. The actual incidence of ipsilateral stroke was 2.8% in the surgery group versus 16.8% in the medical group. [55] ECST trial also evaluated gender, age, severity of stenosis, plaque morphology, and time since last event. They found that risk of events increased with age and with male gender. They did not find any benefit for surgery over medical treatment in the mild stenosis group (10%-29%) unlike the severe stenosis group, which showed a 6-fold reduction in subsequent strokes over 3 years. [56]

Based on these randomized studies there seems to be a consensus on which patients would benefit from operative intervention after an ischemic event, however the timing of intervention has been much debated. The risk of recurrent stroke after TIA or minor stroke is the highest within the first 7-10 days. According to a meta-analysis by Giles et al the risk of stroke after TIA is 6.7% at 48 hours and 10% at 7 days with more than half of the strokes occurring within the first 7 days doing so within the first 24 hours after the inciting event. [57,58] In another study by Ois et al. the rate of recurrent stroke in symptomatic patients with greater then 50% stenosis was determined to be 20.9% in the first 72 hours, 6.7% between 72 hours and 7 days and 3.7% between 7 and 14 days. [59] These results support early intervention in the first 48 hours because the risk of recurrent stroke appears to outweigh the operative risk in patients who are medically stable and have relatively small or no infarcts on imaging studies. Alternatively, for a completed stroke researchers advocate delayed surgical intervention for at least 4-6 weeks due to the risk of converting an ischemic cerebral infarction into a hemorrhagic one. Giordano et al reported on 49 CEAs done after a completed acute stroke. 27 of these were performed within 5 weeks of the event and 22 were done between 5 and 20 weeks. The early intervention group had a morbidity and mortality of 18.5% compared to nothing for the later group. [60] These results seem to corroborate with observations in both the NASCET and ECST trials.

5. Carotid artery stenting

Along with CEA, carotid artery stenting (CAS) has emerged as an alternative treatment strategy for patients with carotid artery disease. Initially proponents of angioplasty and stenting projected that this procedure could overcome the risks associated with CEA and provide a minimally invasive alternative for patients. However at this time the utility of CAS is highly debated with CEA remaining the standard of care in most asymptomatic and symptomatic patients.

There have been very few studies that have specifically addressed CAS in asymptomatic patients and most of the data available comes from high-risk registries which include patients with lesions located at or above the level of C2, contralateral carotid occlusion, severe ulceration and tandem intracranial stenosis, age over 80, active coronary artery disease or congestive heart failure, and patient's with "hostile necks" (immobile neck, previous irradiation, previous surgery on the ipsilateral side or previous surgery on the contralateral side with vocal cord paralysis). In the SAPPHIRE trial, which population included 70% asymptomatic high-risk patients, their results found cumulative perioperative incidence of death, stroke, and MI of

5.4% for CAS and 10.2% for CEA. [61] Their results found that CAS with cerebral protection was not inferior to CEA. This study, however had several limitations including failure to randomize >50% of patients, unaccounted for elevated incidence of perioperative stroke, and possible reporting bias. The Carotid Revascularization Endarterectomy versus Stent Trial (CREST) enrolled more than 1000 asymptomatic patients. Stroke and death rates after CAS were 2.6% and 1.1% respectively with a difference between CAS and CEA in asymptomatic patients for any periprocedural stroke being 2.5% versus 1.4%. [62-64] These results did not show significant difference between CAS and CEA. The results from this study, however, were based on procedures performed by highly experienced operators and have not been replicated by other trials. [65]

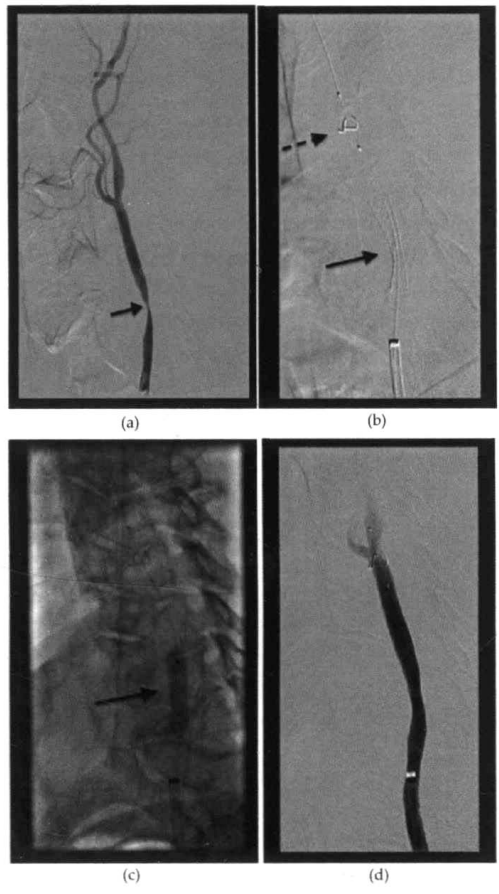

Figure 3. 70 year old Male with a history of squamous cell carcinoma status post neck radiation and hemiglossectomy found to have a 90% asymptomatic left common carotid artery stenosis. A: Angiogram of left common carotid artery stenosis (arrow) B. Angiogrom showing cerebral protection device located in the left internal carotid artery (dashed arrow) and stent placed in common carotid artery stenosis (black arrow). C. Post stent placement angioplasty balloon inflated (arrow) D. Completion angiogram showing minimal residual stenosis after stent placed.

For symptomatic patients several major randomized trials comparing CEA versus CAS have been completed. These include the International Carotid stenting Study (ICSS), the Stent-Supported Percutaneous Angioplasty of the Carotid Artery Versus Endarterectomy (SPACE) trial, the Endarterectomy versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3s) trial, the Stenting and Angioplasty with Protection in Patients at high risk for Endarterectomy (SAPPHIRE) trial and the Carotid Revascularization Endarterectomy Versus Stenting Trial (CREAST).

Trial	Methods	Results	Conclusions
ICSS	1713 patient with symptomatic stenosis >50% CEA vs CEA -Primary endpoint at 120 days was stroke, death or MI	-Primary endpoints: Stroke: 7.7% CAS vs 4.1% CEA Death: 2.3% CAS vs. 0.8% CEA MI: 8.5% CAS vs. 5.2% CEA	-CAS higher rates of any stroke and all cause death -No significant difference between groups in disabling stroke
SPACE	European study 1196 patients with symptomatic stenosis randomly assigned 180 days after TIA or stroke to CAS vs. CEA -Primary endpoint: ipsilateral stroke or death at 30 days	-Stroke or Death: -6.9% CAS vs. 6.5% CEA -2 year follow up showed no significant difference btw CAS and CEA - 9.5% CAS vs. 8.8% CEA	-failed to prove noninferiority of CAS vs. CEA -2 year restenosis more frequent in CAS group -10.7% vs 4.6%
EVA-3S	French multicenter study 259 patients with severe symptomatic stenosis >60% CAS vs. CEA -Evaluate hypothesis that CAS in not inferior to CEA (similar to SPACE) -Primary endpoint: stroke or death at 30 days	- Stroke and/or Death: -9.6% CAS vs. 3.9% CEA -RR 2.5 -4 year follow up Stroke and/or Death - 11.1% CEA vs. 6.2% CAS	-Stopped premature 2/2 deaths in CAS group -CEA needs to be safer before it can be alternative to CEA *CPD were optional
CREST	RCT largest comparing CAS vs. CEA in both symptomatic and asymptomatic patients -2502 enrolled; 47% asymptomatic	- Death: 0.7% CAS vs. 0.3% CE - Stroke: 4.1% CAS vs. 2.3% CEA - MI: 1.1% CAS vs. 2.3% CEA - Combined endpoints: 7.2% CAS vs. 6.8% CEA -4 year follow up combined endpoints:	-overall effectiveness and safety were similar -similar results male vs. female and symptomatic vs. asymptomatic -Periprocedural higher risk of stroke with CAS and higher risk MI with CEA -Subanalysis: - No difference in primary endpoint based