Cerebrovascular Disease in the Elderly

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6.1 Introduction

Stroke is the fifth leading cause of death and the leading cause of disability in the United States [1]. Approximately one third of all strokes are hemorrhagic, while two thirds are ischemic in origin [2].

Risk factors predisposing to stroke are more frequent among elderly (>65 year old) individuals. Consequently stroke is a common affliction of the elderly [3]. Stroke outcome is worse in the elderly. Progressive brain injury from silent infarctions may lead to "reduced cerebrovascular reserve" resulting in more catastrophic deficits for an equivalent ischemic insult. Many traditional carotid trials have excluded octogenarians, and there are few evidence-based guidelines to help determine care in this age group. In this chapter, we will define the characteristics of stroke that are unique in the elderly. We will also describe optimal and pragmatic management approaches to stroke in the elderly as related to carotid atherosclerotic occlusive disease.

6.2 Epidemiology and Rehabilitation of Stroke in the Elderly

Age is an important risk factor for stroke. The elderly, age 65 or older, are at an increased risk for stroke compared to the general population (8.1% vs. 0.8%) [3]. Among 472 stroke events in the Framingham study, risk factors included age,

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hypertension, diabetes, cigarette smoking, and atrial fibrillation [4]. The incidence of each of these risk factors is higher in the elderly and therefore explains the higher risk of stroke in this population.

Increasing age is associated with enhanced morbidity and disability after stroke. Fifteen to thirty per cent of the elderly are permanently disabled and 26% require institutionalization into a nursing home [5]. These rates are less in patients <65 suffering a stroke. Advanced age has a negative impact on stroke mortality too [6]. In an analysis of Health Care Financing Administration Medicare Part B patients in four communities in the United States, the 1-month case fatality rate for stroke was 12.6% (8.1% for ischemic strokes, and 44.6% for hemorrhagic strokes) in patients age 65 years or older [7]. In 2002, death certificates showed that the mean age at death from a stroke was 79.6 years [8].

The estimated cost of strokes in 2008 was 65.5 billion dollars [9]. Projected estimates of the total cost of stroke from 2005 to 2050 is thought to be 1.52 trillion dollars for non-Hispanic whites, 313 billion dollars for Hispanics, and $379 billion for African Americans [10].

6.3 Medical Management of Risk Factors for Stroke in the Elderly

While risk factors for stroke may be more prevalent in the elderly, control of these factors results in risk reduction regardless of age. Implementation of an effective and aggressive risk factor reduction program in elderly patients is an essential and oftentimes the best form of therapy for asymptomatic carotid atherosclerosis.

The relationship between elevated blood pressure and the risk of stroke is linear [11]. The Framingham Heart Study and the Atherosclerosis Risk in Communities (ARIC) study both concluded that reduction in blood pressure reduced the risk of future strokes [12]. Medical management with antihypertensive therapy is generally aimed at reducing blood pressure to less than 140/90 for CVA prevention.

Tight serum glucose control in patients with diabetes was traditionally thought to reduce the risk of stroke. The Action in Diabetes and Vascular diseases (ADVANCE) [13], United Kingdom Prospective Diabetes Study (UKPDS) [14], and Action to Control Cardiovascular Risk in Diabetes (ACCORD) [15] study, all tested the hypothesis that tight control of serum glucose levels would reduce their risk of future cerebrovascular events. However, they all found no reduction in stroke risk with hemoglobin A_{1c} levels less than 6.5%. Therefore, only normoglycemic serum levels with a target hemoglobin A_{1c} of less than 7% are now recommended among diabetic patients.

It is well established that smoking increases the risk for coronary and peripheral arterial disease. Similarly, the risk of a stroke is doubled with smoking and an aggressive smoking cessation program reduces this risk, based on results from the Framingham study [16]. Counseling for smoking cessation in conjunction with nicotine replacement therapy are effective approaches to reducing smoking among patients and results in a benefit regardless of age.

Antithrombotic therapy with daily aspirin is recommended by the US Preventive Services Task Force for cardiovascular prophylaxis in patients with anticipated cardiac morbidity [17]. The use of aspirin in asymptomatic carotid atherosclerosis also reduces the incidence of stroke. Similar prophylaxis has been shown to be effective for secondary prevention of recurrent stroke [18]. Based on the cardiovascular and stroke prevention benefits, it is recommended that all individuals above the age of 50–55 years should receive antithrombotic prophylaxis.

In early studies elevated cholesterol levels were associated with an increased incidence of stroke. Subsequently, high LDL levels and high HDL/LDL ratios have all been correlated with an increased risk of stroke and other cardiovascular morbidities. A meta-analysis of randomized, placebo-controlled, double-blind trials with statin therapy reported a greater than 15% reduction in stroke rates [19]. The Education Program-Adult Treatment Panel III guidelines recommend the use of statins toward a target LDL of $\leq$100 mg/dl for low-risk patients and $\leq$70 mg/dl for high-risk patients [20]. It has been proposed that statin therapy may result in regression of carotid artery atherosclerosis. The METEOR study found regression in carotid intima-media thickness (IMT) with the use of rosuvastatin [21]. These results were confirmed by the ARBITER trial, comparing the effects of two statins (pravastatin 40 mg/day and atorvastatin 80 mg/day) on carotid IMT [22]. The benefit of statins appears to extend to patients undergoing revascularization for carotid stenosis too. Patients undergoing vascular surgery suffer fewer cerebrovascular adverse events when placed on perioperative statins [23].

6.4 The Role of Carotid Endarterectomy in Stroke Prevention for the Elderly

6.4.1 Carotid Endarterectomy

The era of carotid revascularization began in the 1950s with frequent reports of direct anastomosis between internal and common carotid artery, carotid endarterectomy, eversion endarterectomy and patch angioplasty along with shunting in quick succession. Carotid surgical revascularization experienced rapid expansion over the next four decades as a means to prevent stroke from carotid atherosclerosis.

6.4.2 Asymptomatic Carotid Stenosis

In the early 1990s, the VA Asymptomatic Carotid Stenosis Study, Asymptomatic Carotid Atherosclerosis Study (ACAS) and Asymptomatic Carotid Surgery Trial (ACST) demonstrated a benefit for carotid endarterectomy (CEA) plus best medical therapy over best medical therapy alone in asymptomatic patients that were less than 80 years of age [24–26]. It is important to note that in the era of ACAS and ACST, best medical therapy generally comprised of aspirin 325 mg/day with a very small proportion of patients receiving cholesterol-lowering medications and adequate blood pressure and glucose control. In ACAS, 1662 patients ages 40–79 with

60–99% carotid stenosis were randomized to surgery versus medical therapy alone. Perioperative stroke and death plus post-perioperative stroke were lower in the surgical group as compared to the medical group (5.6% vs. 11.0% over 4 years). The ACST randomized 3120 patients between the ages of 40 and 91 with greater than 60% asymptomatic carotid artery disease to CEA versus best medical therapy. The 5-year rate for stroke and death in CEA versus medical therapy was 6.4% and 11.8%, respectively. Patients did not show a measurable benefit until 2 years after the surgery. This is understandable, since surgery resulted in an up-front elevated risk of stroke and death in the perioperative period.

The general consensus that emerged as a result of these trials was that CEA was an optimal treatment for most patients with high-grade carotid artery stenosis, provided they survived long enough to derive prophylactic benefit (i.e. at least 2 years) and the perioperative stroke/death rate was below 3%.

The recently concluded Carotid Revascularization Endarterectomy versus Stent Trial (CREST) demonstrated the best peri-procedural outcomes associated with CEA that have been reported till date [27]. The primary endpoints were stroke, myocardial infarction (MI), and death, and octogenarians were included in the trial. The surgeons were rigorously credentialed, and this produced a perioperative stroke, death, and MI rate of 1.4% in asymptomatic patients. These excellent results have led to several clinicians proposing that the 3% threshold defining safe CEA be further reduced to 2%. The study also provided reassurance that CEA could be safely offered to octogenarians and that they would derive an equivalent benefit for stroke prevention as compared to younger patients.

6.4.3 Symptomatic Carotid Stenosis

Symptomatic carotid disease is defined based on symptoms such as weakness of the face, arm, leg, or both; sensory deficit or paresthesia of the face, arm, leg, or both; or transient blindness anosognosia, asomatognosia, neglect, visual, or sensory extinction, aphasia, alexia, anomia, and agraphesthesia within 6 months of diagnosis. Results from two landmark studies guide the current management of symptomatic carotid disease, North Atlantic Symptomatic Carotid Endarterectomy Trial (NASCET) and European Carotid Surgery Trial (ECST) [28, 29].

NASCET—a multi-center, randomized, prospective trial, commenced enrollment in the late 1980s to compare the efficacy of CEA versus best medical therapy for patients with symptomatic carotid artery disease. A total of 659 patients with history of carotid territory ischemic events within the previous 120 days were enrolled. The study was prematurely terminated at 18 months since the benefit of CEA was overwhelming. The 30-day risk of stroke and death in CEA versus medical therapy was 5.8% versus 3.3%; at 2 years the differential between the two groups had expanded to 15.8% versus 32.3%. An additional analysis confirmed that CEA also benefited patients with 50–69% symptomatic stenosis [30]. Importantly, patients age 75 and older with 50–99% stenosis benefited from CEA more than younger patients with the same degree of stenosis [31].

ECST—a multi-center, prospective, randomized controlled trial enrolled 2518 patients with symptomatic ischemic strokes to CEA or medical therapy. At 3 years CEA patients had a stroke incidence of 2.8% compared to 16.8% in those treated non-operatively.

Octogenarians were excluded from the ACAS and NASCET studies but were not excluded from ACST and ECST. These patients are now optimized better than ever for operative management and have been shown to be at no increased surgical risk just by virtue of their chronological age [32, 33]. In fact, subgroup analysis of patients older than 75 years was associated with an increased risk of stroke in symptomatic patients managed non-operatively, when compared to the younger-than-65-year-old patient population with similar comorbidities [34].

6.5 Carotid Artery Stenting in the Elderly

Successful endovascular revascularization of carotid disease was first reported in the 1980s [35]. Carotid artery stenting (CAS) has subsequently evolved with the introduction of nitinol stents and embolic protection devices. Several randomized trials comparing CEA to CAS have helped elucidate the potential role for CAS in the management of carotid disease.

In the early stages of its introduction, the percutaneous minimally invasive nature of CAS was thought to be of potential preferential benefit to elderly patients. The Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) trial randomized 504 symptomatic patients into angioplasty without embolic protection or CEA and achieved stroke or death rates of 10% versus 9.9% in 30-day post-procedural period respectively [36]. The results were critiqued due to the unusually high rate of stroke in the CEA arm of the study. The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) was the first multi-center randomized trial to use mandatory distal embolic protection [37]. The 30-day peri-procedural adverse event rate for CAS and CEA was 4.8% and 9.8%, respectively. The endpoint in this study included non-Q-wave MI and excluding these events resulted in elimination of the advantage of CAS over CEA. As experience with CAS continued to accumulate in the Carotid Revascularization, Endarterectomy versus Stent Trial (CREST) lead-in registry, it became apparent that while CAS could potentially achieve better results than CEA in certain high-risk patients, elderly patients were not part of that category. In fact, octogenarians were found to have a stroke rate 4 times more than patients less than 60 years of age [38]. The results were so significant that enrollment of octogenarians was halted in the registry. This finding was later confirmed in the CREST randomized trial [39]. While the composite stroke, MI, and death rate were similar in CEA compared to CAS, complications were higher in CAS compared to CEA in patients older than 70 years of age. Increasing age is generally associated with larger deposits of calcium or atheroma in the aortic arch resulting in increased atheroembolization during CAS [40]. The elderly frequently have tortuous vessels that render the procedure more technically challenging and hazardous.

The CREST study also showed that CAS resulted in a lower incidence of cardiac events compared to CEA and would therefore be ideal in patients with severe cardiac comorbidities. In addition, several anatomic conditions may increase the risk for peri-procedural adverse events with CEA and therefore benefit from preferential treatment with CAS. Distal lesions (above C2 cervical vertebral body) [41], prior neck radiation, cervical stoma, or radical neck dissection can increase the risk of wound infection or cranial nerve injury. Conversely, long-segment disease (>15 mm), circumferential heavy calcification and ulceration aortoiliac tortuosity, type III aortic arch, carotid tortuosity are some of the situations where complications from CAS are enhanced [42].

6.5.1 Cognitive Impairment and Its Association with Carotid Stenosis

Carotid artery stenosis is a long-recognized cause of atheroembolic stroke or transient ischemic attacks (TIAs). An under-appreciated but clinically significant consequence of carotid stenosis may be an insidious impairment in cognitive function without associated focal neurologic deficits (stroke, TIA). Cognitive function is the production and control of behavioral and mental processes such as thinking, learning, remembering, problem solving, and consciousness. These processes can be objectively quantified by standardized cognitive measures. Cognitive function has been documented to affect the well-being of patients and their ability to live independent productive lives [43]. As a consequence, cognitive impairment places large demands on societal support systems, hospital resources, and financial resources [44]. It is well-known that cognitive impairment co-exists in patients with stroke from carotid stenosis [45]. However, isolated cognitive deficits in carotid stenosis patients currently labeled as being "asymptomatic" in the absence of a focal neurologic deficit have not traditionally been looked for systematically and have therefore not been reported in any detail [46].

6.5.2 High Socioeconomic Burden of Cognitive Decline in the Elderly

Asymptomatic carotid stenosis has a prevalence of 4.2%, affecting ~12 million people in the United States. Among people ≥70 years, prevalence increases to 12.5% in men and 6.9% in women [47]. Small studies indicate that 34% of patients with carotid may be at risk for cognitive impairment thereby potentially affecting ~3.4 million individuals [48]. The cost of social and medical care for patients with cognitive impairment ranges from $9300 to $21,700/year [44]. Conservatively assuming mild cognitive impairment in this population, at $9300/year we may be incurring a hidden cost of up to $31.6 billion/year in the care of these patients.

6.5.3 Evidence for Cognitive Decline in Patients with Carotid Stenosis

Stroke prevention has been the dominant focus of identifying carotid disease and of carotid artery revascularization. The possibility that carotid stenosis could result in cognitive impairment in the absence of a stroke has only recently received attention [48]. A subset analysis of the Cardiovascular Health Study noted significant cognitive decline in 34% of 32 patients with asymptomatic CS (≥75%) when serially tested with a modified mini-mental state examination (MMSE) over 5 years [49]. A decline was also noted in patients with stenoses ≥50%, even after adjustments for vascular risk factors. Conversely, Martinic et al. observed normal MMSE scores in 26 patients with asymptomatic high-grade carotid stenosis, though they did have reduced Montreal Cognitive Assessment scores [50]. Benke et al. observed reduced mental speed, learning, visuospatial abilities, verbal processing, and deductive reasoning in 20 patients with asymptomatic carotid stenosis compared to unmatched controls [51]. In a subset analysis of the Framingham study, 35 participants with asymptomatic CS ≥50% had significantly worse cognitive performance compared to cohorts with increased intima-media thickness alone [52]. In the Tromso study, subjects with asymptomatic carotid stenosis performed lower in tests of attention, psychomotor speed, memory, and motor function. However, there were no significant differences in tests of speed of information processing, word association, or depression [53]. Conversely, other studies have not been able to demonstrate such associations.

Most broadly accepted cognitive tests have standardized administration procedures with normative comparison groups. Guidelines for cognitive assessment in vascular research have been published, derived largely from cardiac surgery and medical treatment studies [54, 55]. Testing of both composite and domain-specific outcomes, over long follow-up times, has been recommended. The National Institute of Neurologic Disorders (NINDS) has encouraged a harmonization of standards for identifying and describing cognitive function in patients with vascular disease [56]. The makeup of the final test battery must also accommodate practicality of testing. We have targeted this issue in a recently completed American Heart Association-funded investigation contrasting cognitive outcome after CEA versus CAS [57]. Our unique test battery was guided by NINDS recommendations and previous literature that has documented effects on motor speed, information processing, attention, and memory. It was sensitive enough to identify clinically relevant impairment in either group of patients. We compared cognitive outcome in 46 patients undergoing carotid endarterectomy (CEA = 25) versus carotid artery stenting (CAS = 21) for asymptomatic CS ≥80%. Among them, 35% were women and 54% had right-sided lesions. The 50-min cognitive battery was performed 1–3 days before and 4–6 months after each procedure. The analysis of impact was a normalized change score (change in composite cognitive score vs. baseline). Raw scores from each subtest were transformed into baseline and follow-up Z-scores by using the means and SD of the baseline test scores. The difference between the two was the "change score." A positive change score indicated improved cognition. We found that scores

for each test improved after CEA except Working Memory Index which decreased in 20/25 patients. Improvement occurred in all tests after CAS except Processing Speed Index which decreased in 18/21 patients. Both procedures improved overall cognitive function and the scores were not significantly different between the two procedures (0.51 vs. 0.47 SD, p = ns).

6.5.4 Silent Micro-embolization May Result in Cognitive Impairment

In patients with "asymptomatic" carotid stenosis transcranial Doppler (TCD) monitoring frequently identifies silent microembolization to the middle cerebral artery (MCA) [58], and computed tomography scanning identifies silent brain infarctions in 15–19% of such asymptomatic patients [59]. Cerebral microembolization is often seen in patients with vascular dementia and is associated with accelerated cognitive decline [60]. In the Rotterdam scan study, silent cerebral infarcts in elderly people doubled the risk of cognitive impairment [61]. These findings were confirmed by the Atherosclerosis Risk In Communities study and the Cardiovascular Health Study [62, 63]. Furthermore, in animal studies, injection of 50 μm microspheres into rat carotid arteries resulted in cerebral microinfarctions with reduced attentional performance [64]. Therefore, silent microembolization with cerebral microinfarction in patients with otherwise "asymptomatic" CS may result in cognitive impairment.

6.5.5 Cerebral Hypoperfusion May Result in Cognitive Impairment

Chronic cerebral hypoperfusion contributes to the onset of clinical dementia [65]. Verbal, performance, and full-scale IQ are all impaired, as are verbal fluency and Rey figure copy performance, among patients with carotid disease and reduced cerebral blood flow [66]. Carotid cross-clamping also results in EEG waveform flattening and attentional deficit [67]. While chronic or acute cerebral hypoperfusion, and systemic hypotension, are all associated with cognitive dysfunction, it is not certain whether cerebral hypoperfusion influences cognitive outcome in patients with carotid stenosis. As cerebral perfusion pressure falls, cerebral blood flow is maintained by autoregulatory arteriolar vasodilation. When the pressure falls low enough, as in some cases of severe carotid stenosis, the arterioles dilate maximally and vasodilatory challenge with CO_2 inhalation cannot be expected to dilate the arterioles further. Cerebrovascular reactivity (CVR = Δ cerebral blood flow/Δ partial pressure of CO_2) is a standard clinical measure of the ability of cerebral arterioles to respond to changes in $PaCO_2$. Under normal conditions, hypercapnia causes vasodilation and increased cerebral blood flow. A decrease in flow indicates reduced reactivity, indicating an increased risk of hypoperfusive brain injury. These tests can therefore be utilized to assess the role that a fixed carotid stenosis may play in reducing brain perfusion and thereby cognitive function.

6.5.6 Results of the ACCOF Study

The Asymptomatic Carotid Stenosis and Cognitive Function (ACCOF) study is the first attempt to identify the isolated impact of asymptomatic carotid stenosis on cognitive function [68]. Stenosis patients were compared to patients with similar vascular comorbidities but no stenosis. Cerebrovascular hemodynamic characteristics were analyzed to elucidate mechanisms impacting cognition. Sixty-nine patients with ≥50% asymptomatic carotid stenosis and 60 controls with vascular comorbidities without stenosis underwent comprehensive cognitive testing by a trained neuropsychologist. Scores were adjusted for age, sex, education, and race using normative data. An overall index of cognitive function and five domain-specific scores were computed. Breath holding index (BHI), an estimate of cerebrovascular reserve, was measured using transcranial Doppler. Patients were assigned to high versus low BHI groups using a cut-off score of 0.69. The stenosis group performed worse on the overall composite cognitive score ($p \leq .01$) and the domain-specific scores for processing speed ($p \leq .01$) and learning ($p \leq .05$). A trend of reduced performance for executive function and attention emerged ($p = .07$). Within the stenosis group, those with low BHI performed worse on learning ($p < .05$), processing speed ($p < .09$), and overall composite score ($p < .06$). These findings suggest that asymptomatic carotid stenosis is associated with cognitive impairment when compared to patients with similar risk factors but no stenosis. The deficit is driven primarily by reduced processing speed and learning and is mild to moderate in severity. A likely mechanism for this impairment is reduced cerebrovascular reserve.

Additional studies will be required to establish these findings. If substantiated, they have the potential to impact decision-making in the management of patients with asymptomatic carotid stenosis, especially in elderly individuals at higher risk for developing debilitating dementia.

6.6 Conclusions

Chronological age alone should not be utilized as a criterion to exclude patients from consideration for carotid artery revascularization. Current recommendations support optimal medical therapy for symptomatic patients with less than 50% stenosis or in asymptomatic patients with less than 70% stenosis. CEA is preferred over CAS for asymptomatic patients with high grade (≥70% stenosis) when the anticipated perioperative stroke and death rate is less than 3%. In patients that are ≥70 years of age, with a long (>15 mm) lesion, and with preocclusive stenosis, CEA is preferred over CAS. Symptomatic patients with >50% stenosis are generally best treated with CEA. However, in the presence of a prior cervical operation or radiotherapy, a low lesion that extends proximal to the clavicle or a high lesion that extends distal to the C2 vertebral body, prior cranial nerve injury, severe uncorrectable coronary disease, congestive heart failure, or chronic obstructive pulmonary disease, CAS is preferred over CEA (Fig. 6.1).

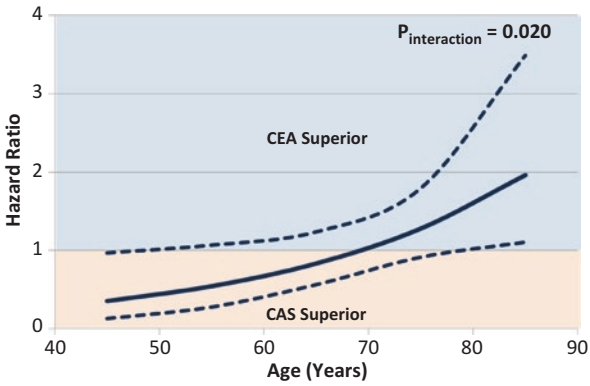

Fig. 6.1 Hazard ratio for stroke and death favors carotid artery stenting in younger patients and carotid endarterectomy in older patients with high grade carotid stenosis

Key Points

- Stroke is an important cause of death and leading cause of disability in the United States
- Risk factors predisposing to stroke are more frequent among elderly
- Stroke is more common among the elderly
- Stroke outcome is worse in the elderly
- Control of risk factors reduces stroke rates regardless of age
- Patients age 75 and older with 50–99% stenosis benefit from carotid endarterectomy more than younger patients with the same degree of stenosis
- Elderly patients with high-grade carotid artery stenosis of 70% or more also benefit from carotid endarterectomy
- Carotid artery stenting in patients aged 70 years or more is associated with an increased risk of stroke and death compared to carotid endarterectomy
- Asymptomatic high-grade carotid artery stenosis may be associated with cognitive impairment, and more information is needed to explore its impact on the functional status of older individuals

References

1. FastStats – Deaths and Mortality. at http://www.cdc.gov/nchs/fastats/deaths.htm.
2. Warlow C, Sudlow C, Dennis M, Wardlaw J, Sandercock P. Stroke. Lancet. 2003;362:1211–24.
3. Centers for Disease Control and Prevention (CDC). Prevalence of stroke – United States, 2005. MMWR Morb Mortal Wkly Rep. 2007;56:469–74.
4. Wolf PA, D'Agostino RB, Belanger AJ, Kannel WB. Probability of stroke: a risk profile from the Framingham Study. Stroke. 1991;22:312–8.
5. Kelly-Hayes M, et al. The influence of gender and age on disability following ischemic stroke: the Framingham Study. J Stroke Cerebrovasc Dis. 2003;12:119–26.
6. Kammersgaard LP, et al. Short- and long-term prognosis for very old stroke patients. The Copenhagen Stroke Study. Age Ageing. 2004;33:149–54.

7. El-Saed A, et al. Geographic variations in stroke incidence and mortality among older populations in four US communities. Stroke. 2006;37:1975–9.
8. Centers for Disease Control and Prevention (CDC). Disparities in deaths from stroke among persons aged <75 years – United States, 2002. MMWR Morb Mortal Wkly Rep. 2005; 54:477–81.
9. Rosamond W, et al. Heart disease and stroke statistics – 2007 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation. 2007;115:e69–171.
10. Brown DL, et al. Projected costs of ischemic stroke in the United States. Neurology. 2006;67:1390–5.
11. Seshadri S, et al. The lifetime risk of stroke: estimates from the Framingham Study. Stroke. 2006;37:345–50.
12. Heiss G, et al. Carotid atherosclerosis measured by B-mode ultrasound in populations: associations with cardiovascular risk factors in the ARIC study. Am J Epidemiol. 1991;134:250–6.
13. Patel A, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med. 2008;358:2560–72.
14. Laakso M. Benefits of strict glucose and blood pressure control in type 2 diabetes: lessons from the UK Prospective Diabetes Study. Circulation. 1999;99:461–2.
15. Gerstein HC, et al. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med. 2008;358:2545–59.
16. Wolf PA, D'Agostino RB, Kannel WB, Bonita R, Belanger AJ. Cigarette smoking as a risk factor for stroke. The Framingham Study. JAMA. 1988;259:1025–9.
17. Wolff T, Miller T, Ko S. Aspirin for the primary prevention of cardiovascular events: an update of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med. 2009;150:405–10.
18. Wolf PA, et al. Preventing ischemic stroke in patients with prior stroke and transient ischemic attack: a statement for healthcare professionals from the Stroke Council of the American Heart Association. Stroke. 1999;30:1991–4.
19. Bucher HC, Griffith LE, Guyatt GH. Effect of HMGcoA reductase inhibitors on stroke. A meta-analysis of randomized, controlled trials. Ann Intern Med. 1998;128:89–95.
20. Avellone G, et al. Efficacy and safety of long-term ezetimibe/simvastatin treatment in patients with familial hypercholesterolemia. Int Angiol. 2010;29:514–24.
21. Crouse JR, et al. Measuring Effects on intima media Thickness: an Evaluation Of Rosuvastatin in subclinical atherosclerosis – the rationale and methodology of the METEOR study. Cardiovasc Drugs Ther. 2004;18:231–8.
22. Taylor AJ, et al. ARBITER: Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol: a randomized trial comparing the effects of atorvastatin and pravastatin on carotid intima medial thickness. Circulation. 2002;106:2055–60.
23. Paraskevas KI, Liapis CD, Hamilton G, Mikhailidis DP. Can statins reduce perioperative morbidity and mortality in patients undergoing non-cardiac vascular surgery? Eur J Vasc Endovasc Surg. 2006;32:286–93.
24. Hobson RW, et al. Efficacy of carotid endarterectomy for asymptomatic carotid stenosis. The Veterans Affairs Cooperative Study Group. N Engl J Med. 1993;328:221–7.
25. Endarterectomy for asymptomatic carotid artery stenosis. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. JAMA. 1995;273:1421–8.
26. Halliday A, et al. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. Lancet. 2004;363:1491–502.
27. Brott TG, Hobson 2nd RW, Howard G, Roubin GS, Clark WM, Brooks W, Mackey A, Hill MD, Leimgruber PP, Sheffet AJ, Howard VJ, Moore WS, Voeks JH, Hopkins LN, Cutlip DE, Cohen DJ, Popma JJ, Ferguson RD, Cohen SN, Blackshear JL, Silver FL, Mohr JP, Lal BK, Meschia JF; CREST Investigators. Stenting versus endarterectomy for treatment of carotid-artery stenosis. N Engl J Med. 2010;363(1):11–23.
28. ACAS Investigators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. N Engl J Med. 1991;325:445–53.

29. ECST Investigators. Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). Lancet. 1998;351:1379–87.
30. Barnett HJ, et al. Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. N Engl J Med. 1998;339:1415–25.
31. Alamowitch S, Eliasziw M, Algra A, Meldrum H, Barnett HJ. Risk, causes, and prevention of ischaemic stroke in elderly patients with symptomatic internal-carotid-artery stenosis. Lancet. 2001;357:1154–60.
32. Kim S, et al. Multidimensional frailty score for the prediction of postoperative mortality risk. JAMA Surg. 2014;149:633–40.
33. Audisio RA, et al. Shall we operate? Preoperative assessment in elderly cancer patients (PACE) can help. A SIOG surgical task force prospective study. Crit Rev Oncol Hematol. 2008;65:156–63.
34. Rothwell P, Eliasziw M, Gutnikov S, Warlow C, Barnett H. Endarterectomy for symptomatic carotid stenosis in relation to clinical subgroups and timing of surgery. Lancet. 2004;363:915–24.
35. Mathias K. A new catheter system for percutaneous transluminal angioplasty (PTA) of carotid artery stenoses. Fortschr Med. 1977;95:1007–11.
36. Endovascular versus surgical treatment in patients with carotid stenosis in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS): a randomised trial. Lancet. 2001;357:1729–37.
37. Yadav JS, Wholey MH, Kuntz RE, Fayad P, Katzen BT, Mishkel GJ, Bajwa TK, Whitlow P, Strickman NE, Jaff MR, Popma JJ, Snead DB, Cutlip DE, Firth BG, Ouriel K; Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy Investigators. Protected carotid-artery stenting versus endarterectomy in high-risk patients. N Engl J Med. 2004;351(15):1493–501.
38. Lal BK, Brott TG. The carotid revascularization endarterectomy vs. stenting trial completes randomization: lessons learned and anticipated results. J Vasc Surg. 2009 Nov;50(5): 1224–31.
39. Voeks JH, et al. Age and outcomes after carotid stenting and endarterectomy: the carotid revascularization endarterectomy versus stenting trial. Stroke. 2011;42:3484–90.
40. Lam RC, et al. The impact of increasing age on anatomic factors affecting carotid angioplasty and stenting. J Vasc Surg. 2007;45:875–80.
41. Ricotta JJ, Aburahma A, Ascher E, Eskandari M, Faries P, Lal BK; Society for Vascular Surgery. Updated Society for Vascular Surgery guidelines for management of extracranial carotid disease: executive summary. J Vasc Surg. 2011;54(3):832–6.
42. Setacci C, et al. Siena carotid artery stenting score: a risk modelling study for individual patients. Stroke. 2010;41:1259–65.
43. Chaytor N, Schmitter-Edgecombe M. The ecological validity of neuropsychological tests: a review of the liter-ature on everyday cognitive skills. Neuropsychol Rev. 2003;13(4):181–97.
44. Rockwood K, Brown M, et al. Societal costs of vascular cognitive impairment in older adults. Stroke. 2002;33(6):1605–9.
45. Gottesman RF, Hillis AE. Predictors and assessment of cognitive dysfunction resulting from ischaemic stroke. Lancet Neurol. 2010;9(9):895–905.
46. Barnett HJ. Carotid disease and cognitive dysfunction. Ann Intern Med. 2004;140(4):303–4.
47. de Weerd M, Greving JP, et al. Prevalence of asymptomatic carotid artery stenosis according to age and sex: systematic review and metaregression analysis. Stroke. 2009;40(4):1105–13.
48. Lal BK. Cognitive function after carotid artery revascularization. Vasc Endovascular Surg. 2007;41(1):5–13.
49. Johnston SC, O'Meara ES, et al. Cognitive impairment and decline are associated with carotid artery disease in patients without clinically evident cerebrovascular disease. Ann Intern Med. 2004;140(4):237–47.
50. Martinic-Popovic I, Lovrencic-Huzjan A, et al. Assessment of subtle cognitive impairment in stroke-free pa-tients with carotid disease. Acta Clin Croat. 2009;48(3):231–40.

51. Benke T, Neussl D, et al. Neuropsychological deficits in asymptomatic carotid artery stenosis. Acta Neurol Scand. 1991;83(6):378–81.
52. Romero JR, Beiser A, et al. Carotid artery atherosclerosis, MRI indices of brain ischemia, aging, and cogni-tive impairment: the Framingham study. Stroke. 2009;40(5):1590–6.
53. Mathiesen EB, Waterloo K, et al. Reduced neuropsychological test performance in asymptomatic carotid ste-nosis: the Tromso Study. Neurology. 2004;62(5):695–701.
54. Murkin JM, Newman SP, et al. Statement of consensus on assessment of neurobehavioral outcomes after cardiac surgery. Ann Thorac Surg. 1995;59(5):1289–95.
55. Ryan CM, Hendrickson R. Evaluating the effects of treatment for medical disorders: has the value of neuro-psychological assessment been fully realized? Appl Neuropsychol. 1998;5(4):209–19.
56. Hachinski V, Iadecola C, et al. National Institute of Neurological Disorders and Stroke-Canadian Stroke Network vascular cognitive impairment harmonization standards. Stroke. 2006;37(9):2220–41.
57. Lal BK, Younes M, Cruz G, Kapadia I, Jamil Z, Pappas PJ. Cognitive changes after surgery vs stenting for carotid artery stenosis. J Vasc Surg. 2011 Sep;54(3):691–8.
58. Spence JD, Tamayo A, et al. Absence of microemboli on transcranial Doppler identifies low-risk patients with asymptomatic carotid stenosis. Stroke. 2005;36(11):2373–8.
59. Brott T, Tomsick T, et al. Baseline silent cerebral infarction in the asymptomatic carotid atherosclerosis study. Stroke. 1994;25(6):1122–9.
60. Purandare N, Voshaar RC, et al. Asymptomatic spontaneous cerebral emboli predict cognitive and functional decline in dementia. Biol Psychiatry. 2007;62(4):339–44.
61. Vermeer SE, Prins ND, et al. Silent brain infarcts and the risk of dementia and cognitive decline. N Engl J Med. 2003;348(13):1215–22.
62. Longstreth Jr WT, Bernick C, et al. Lacunar infarcts defined by magnetic resonance imaging of 3660 El-derly people: the cardiovascular health study. Arch Neurol. 1998;55(9):1217–25.
63. Mosley Jr TH, Knopman DS, et al. Cerebral MRI findings and cognitive functioning: the atherosclerosis risk in communities study. Neurology. 2005;64(12):2056–62.
64. Craft TKS, Mahoney JH, Devries AC, Sarter M. Microsphere embolism-induced cortical cholinergic deafferentation and impairments in attentional performance. Eur J Neurosci. 2005;21(11):3117–32.
65. Ruitenberg A, den Heijer T, van Swieten JC, Koudstaal PJ, Hofman A, Breteler MM. Cerebral hypoperfusion and clinical onset of dementia: the Rotterdam Study. Ann Neurol. 2005;57(6):789–94.
66. Silvestrini M, Paolino I, Pedone C, Baruffaldi R, Gobbi B, Cagnetti C, et al. Cerebral hemodynamics and cognitive performance in patients with asymptomatic carotid stenosis. Neurology. 2009;72(12):1062–8.
67. Marshall RS. The functional relevance of cerebral hemodynamics: why blood flow matters to the injured and recovering brain. Curr Opin Neurol. 2004;17(6):705–9.
68. Lal BK, Dux MC, Sikdar S, Zhao L, AlMuhanna K, Kowalewski G, Hossian M. L1. asymptomatic carotid stenosis impairs cognitive function: preliminary results of the ACCOF study. J Vasc Surg. 2014;59(6):97S.