REVIEW

VASCULAR SECTION

Carotid endarterectomy has significantly lower risk in the last two decades: should the guidelines now be updated?

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ABSTRACT

Carotid endarterectomy (CEA) carries a significant risk of procedural stroke and death Guidelines recommend keeping this risk below 6% and below 3% for symptomatic and asymptomatic patients respectively. After analyzing our Institute's CEA results during the past 25 years, we found the rate of postoperative complications was now well below Guideline thresholds. Accordingly, we studied temporal changes in procedural risks in randomized controlled trials (RCTs) and in large observational studies in order to compare these against Guidelines. We found a clear temporal trend towards improving procedural outcomes, which can be explained by improvements in medical therapy, more appropriate timing of CEA, the use of local anesthesia and the use of peroperative cerebral monitoring as well as improving surgical techniques. An update of current guidelines should now be undertaken, since our findings are not unique and are supported by other studies in this review.

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Recently, our study group reported outcomes of 9897 carotid endarterectomies (CEAs) in patients with significant symptomatic or asymptomatic carotid stenosis.[1] Results from our single-center experience showed a gradual reduction in periprocedural (30-day) morbidity and mortality following CEA (Table I).[2]

It has been suggested that procedural risks have fallen over time, mainly due to improvements in medical therapy and surgical technique. However, thresholds for "acceptable levels" of procedural stroke/death in guidelines have never been updated since the introduction of current guidelines in 1995.[3, 4]

In this review, we describe temporal changes in procedural risk of stroke or death associated with CEA. We studied large randomized controlled trials (RCTs),

observational studies and registries to evaluate whether the risk reduction found at our institute was more generalizable, and to consider whether guidelines should be updated.

TABLE I.—*Temporal trend in 30-day complication rate from single center experience Dedinje.*

30-day	1991-1997	1998-2004	2005-2010
Stroke + TIA	2.1%	1.2%	1.1%
Stroke			
Fatal	1.0%	0.6%	0.3%
Disabling	0.4%	0.3%	0.3%
Nondisabling	0.7%	0.3%	0.5%
Other death	0.9%	0.8%	0.5%
Stroke/death	4.2%	2.9%	2.1%

Evolution of carotid surgery

DeBakey introduced CEA in 1953 [5] for the treatment of what was then called cerebrovascular insufficiency and this operation is now one of the most closely researched fields in surgery. Eastcott *et al.*[6] in 1954, published the first surgical case of a highly symptomatic patient with repeated ischemic neurological events and, in a later response, DeBakey [7] reported his 11 year experience of surgery in 1155 patients. Carotid reconstruction in 476 patients had a high early mortality rate of 7%. These first reports of carotid surgery were undertaken in patients with severe, often recurrent symptoms, possibly leading to higher postoperative stroke and mortality rates.

Twenty years later, Browse reported his much improved single-center results of 215 CEAs, all performed with shunting. His fatal, disabling and non-disabling stroke rate was very low at 0.47%, 0.47% and 2.35% respectively, although it must be noted that these CEAs were only performed on patients that suffered transient, often ocular symptoms.[8]

In response to controversy over whether there was any overall benefit from CEA in symptomatic patients, two major prospective randomized trials were conducted in North America (North American Symptomatic Carotid Endarterectomy Trial – NASCET) [9, 10] and Europe (European Carotid Surgery Trial - ECST).[11] Both studies confirmed that CEA prevented long-term ipsilateral stroke in symptomatic patients. In NASCET there was an absolute risk reduction of 17% (26% in medical group *versus* 9% in CEA group) for any ipsilateral stroke at 2-years of follow-up.[9, 10] ECST showed that CEA reduced major stroke or death by 11.6% (26.5% *vs.* 14.9%) over 3-years.[11]

After confirming the preventive role of CEA in symptomatic patients, trials were then conducted to determine the effects of CEA in asymptomatic carotid stenosis. To compare the outcome of CEA *versus* medical treatment alone (MT) in asymptomatic patients, Hobson *et al.*[12] conducted a multicenter clinical trial at 11 Veterans Affairs medical centers. MT was allocated to 233 patients and CEA to 211 patients. Although the combined incidence of ipsilateral neurological events was significantly reduced in the surgical group (8% *vs.* 20.6%), the ipsilateral stroke rate was non-significantly lower, 4% in the surgical group and 9.4% in the BMT (best medical treatment) group.[12] The larger Asymptomatic Carotid

Atherosclerosis Study (ACAS), also a randomized trial, examined the outcomes after CEA *vs.* medical treatment alone in 1662 asymptomatic patients with >60% carotid stenosis and found that 5-year ipsilateral stroke risk was significantly reduced following CEA (5.1% *vs.* 11% for MT alone).[13]

The largest and most recent trial comparing CEA and BMT ('best' medical treatment) in asymptomatic patients was the Asymptomatic Carotid Surgery Trial (ACST-1), where 3120 patients with severe asymptomatic carotid stenosis were randomized to immediate CEA or indefinite deferral of any CEA. There was a clearer result than in the ACAS, a significant reduction in any stroke or perioperative death in patients undergoing CEA, present after 5-years of follow-up (6.9% *vs.* 10.9%).[14]

The first Guidelines on carotid endarterectomy, published in "Stroke" [3] and "Circulation" [4] simultaneously in 1995, were a direct result of the ACAS Trial and the earlier symptomatic trials, Level I evidence confirming CEA to be effective in long-term stroke prevention. In these first Guidelines, it was recommended that the morbidity and mortality rate should be lower than 6% in symptomatic patients and lower than 3% in asymptomatic patients.[3, 4]

Since then, many trials, registries and observational studies have published procedural risks of CEA in patients with high-grade carotid stenosis.[15-34] With improvements in surgical techniques, medical therapy and imaging techniques it is now considered that procedural risks are below the 6% and 3% thresholds in these guidelines. However, the thresholds have not changed since their first publication and have consequently also been applied to outcomes of stenting (CAS), a newer but still evolving technology.[35-37]

Development of carotid angioplasty

The development of carotid angioplasty for carotid stenosis came nearly 30 years after carotid endarterectomy. In 1967 Morris, Lechter and DeBakey were the first to describe internal carotid artery (ICA) angioplasty for fibromuscular dysplasia.[38] Gradual dilation of these lesions with biliary dilators was performed and in 12 treated patients there were no reported neurological complications. Mathias *et al.* described the first percutaneous transluminal angioplasty of ICA for carotid stenosis in 1977 [39] in a canine model and the first human

carotid angioplasty for carotid stenosis was reported by Kerber *et al.* in 1980.[40]

In 1994, Marks *et al.*[41] published the successful use of carotid angioplasty with stenting in two patients with spontaneous ICA dissection. Dietrich *et al.* (1993-1995)[42] reported the first large series using primary angioplasty and stenting, treating 110 patients with high technical success rate (89.1%), but also a high neurological complication rate (10.9%).[42] Increasing experience led to improved results after CAS; improvements in technical skill, the introduction and refinement of proximal and distal cerebral embolic devices, the newer technologies of self-expandable open and closed-cell stent design and the arrival of flow reversal devices have all contributes to greater success and acceptability of CAS.[43-47] Accordingly, RCTs have now begun to compare CAS and CEA for the primary treatment of symptomatic and asymptomatic carotid stenosis. Although CAS outcomes have improved recently, the reported rate of postoperative neurological complications after CAS is still higher than CEA.

Medical therapy for carotid stenosis

Good medical stroke prevention therapy is focused on treatment of hypertension, dyslipidemia, diabetes mellitus, metabolic disorders, smoking, modification of lifestyle, statin and antithrombotic therapy. Focus is particularly concentrated on lowering cholesterol, controlling blood pressure and stopping smoking since Wilson *et al.* showed a strong association of these three risk factors on development of carotid stenosis in 1997.[48]

Antihypertensive therapy

Apart from age, hypertension is the most significant risk factor for stroke. In the SHEP study (Systolic Hypertension in the Elderly Program), 4736 patients over 60 years of age with isolated systolic hypertension were studied. By reducing average systolic blood pressure to 143 mmHg (compared with 155 mmHg in controls) treated patients had a 36% relative risk reduction in total stroke risk (P=0.0003).[49]

Collins *et al.*[50] meta-analyzed results from 37,000 patients having antihypertensive therapy; when diastolic blood pressure was reduced by 5-6 mmHg, stroke risk was lowered by 42% (95% CI: 35-50%, P=0.0001). Af-

ter transient ischemic attack (TIA) or stroke, hypertension is an important future risk factor, but blood pressure regulation in these patients needs careful management. The Perindopril Protection Against Recurrent Stroke Study (PROGRESS) Trial [51] examined the effect of blood pressure lowering in 6105 patients with a history of TIA or stroke. Treatment with combined perindopril and indapamide was associated with a 43% reduction in stroke risk within four years, whereas single-agent therapy did not produce a significant reduction in stroke risk.

Treatment of dyslipidemia

Statins treat hyperlipidemia effectively and have benefit even when there is associated carotid atherosclerotic disease. In a meta-analysis by Amarenco *et al.*[52] 90,000 patients enrolled in statin RCTs before 2003 (when their use became widespread) had their stroke risk reduced by one fifth. Even patients with "normal" cholesterol levels can benefit. In The Cholesterol and Recurrent Events (CARE) Trial,[53] 4159 patients with a history of myocardial infarction and an 'average' total cholesterol (mean 209 mg/dL) and low density lipoprotein (LDL) level (mean139 mg/dL), were treated with either pravastatin or placebo. Pravastatin reduced total cholesterol by 20% and LDL by 32% all-cause stroke risk fell by 32%. Statins are now used in symptomatic and asymptomatic patients undergoing CEA and their pleiotropic and anti-inflammatory effects are presumed to be important for the recent decreases observed in perioperative risk neurological.[54-57]

Smoking

Smoking is significantly associated with the development of carotid atherosclerosis and increased cardiovascular risk. Wannamethee *et al.*[58] found that current smokers had a 3.7-fold higher relative risk of stroke compared to men who had never smoked. Men who quit smoking reduced this risk but the lowest risk was still in the "never-smokers".

Antiplatelet agents

Ranke *et al.*[59] in 1993 showed that the effects of aspirin on carotid atherosclerosis indicated that aspirin

treatment slows carotid plaque growth, a dose of 900 mg daily being more efficient than 50 mg daily. For secondary stroke prevention, in patients presenting with TIA or minor stroke, low dose aspirin is effective. In the Swedish Aspirin Low-Dose Trial (SALT), 1360 patients with TIA or minor stroke were randomized to low-dose aspirin (75 mg daily) or placebo.[60] Treatment produced an 18% reduction in stroke or death rate. In the UKTIA (United Kingdom Transient Ischemic Attack Aspirin Trial) study of 2435 patients with TIA or minor ischemic stroke, they were randomized to 1200 mg or 300 mg of aspirin daily, or to placebo.[61] Major stroke, myocardial infarction and vascular death risk were decreased by aspirin, no difference being found between low and high-dose. In the recent Vascular Quality Initiative Registry, dual anti-platelet therapy (aspirin and clopidogrel) was given to 25% of 21,624 patients undergoing CEA and addition of Clopidogrel was associated with a 40% risk reduction in postoperative neurologic events.[62]

RCTs: symptomatic carotid disease

Results of 30-day stroke/death in both symptomatic and asymptomatic randomized trials are summarized in Table II. NASCET,[9, 10] the first RCT to evaluate outcomes of CEA, compared with best medical therapy, enrolled 659 patients and their results clearly indicated that CEA was beneficial in recently symptomatic patients with associated ipsilateral high-grade carotid stenosis. In the early postoperative period, there was a 6.5% stroke or death rate, with an overall mortality of 1.1%.[9, 10] ECST made a similar comparison and randomized 3024 patients - their 30-day risk of ma-

jor stroke or death in patients allocated to CEA was 7.0%.[11]

The newer techniques of carotid angioplasty and stenting (CAS) were first introduced in the early 1990s, results of randomized controlled trials comparing CEA with stenting alone have generally only been reported since the 2000s.[15-22] The Carotid and Vertebral Transluminal Angioplasty Study (CAVATAS), compared CEA with CAS or angioplasty, enrolled 504 mainly symptomatic (90%) patients between 1992 and 1997.[15, 16] Previous minor stroke was seen in 8% of the patients randomized to CEA, 11% had major non-disabling stroke, 7% major disabling stroke and 1% had retinal infarction. Average age in patients randomized to CEA was 68 years, 13% of the patients had diabetes while 5% of the patients were treated for atrial fibrillation. In 226 symptomatic patients assigned to CEA, the 30-day stroke/death rate was 10.2% and the disabling stroke or death rate was 6%.[15, 16] Since CAVATAS recruited patients 5-10 years later than ECST and NASCET, this is a remarkably high complication rate which might be explained by an increase in "high-risk" patients being considered for carotid intervention. The complication rate in CAVATAS highlighted that improvements in procedural outcome for CEA and CAS would be needed.

The Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) Trial designed as a non-inferiority trial, randomized 527 recently symptomatic patients to either CEA or CAS.[17, 18] Average age of patients randomized to CEA was 70.3±10.7 years with 40.5% of the patients older than 75 years. Previous stroke was seen in 20.1% of the patients, TIA in 23.1%, diabetes in 25.5% and myocar-

TABLE II.—*Results 30-day stroke/death in randomized controlled trials.*

Symptomatic: CEA *vs.* medical therapy				Asymptomatic: CEA *vs.* medical therapy			
Study	Period	Number CEA	30-day stroke/death	Study	Period	Number CEA	30-day stroke/death
ECST	1981-1994	1745	7.0%	VACS	1983-1991	211	6.1%
NASCET	1987-1991	1415	6.5%	ACAS	1987-1993	825	2.3%
				ACST-1	1993-2003	1532	2.9%
Symptomatic: CEA *vs.* CAS				Asymptomatic: CEA *vs.* CAS			
Study	Period	Number CEA	30-day stroke/death	Study	Period	Number CEA	30-day stroke/death
CAVATAS	1992-1997	226	10.2%	CAVATAS	1992-1997	22	9.09%
EVA-3S	2000-2005	259	3.9%	CREST-1	2000-2008	587	1.36%
SPACE-1	2001-2006	550	5.65%	ACT-1	2005-2013	364	1.7%
CREST-1	2000-2008	653	3.22%	SPACE-2	2009-2014	203	1.97%
ICSS	2001-2008	821	3.41%				

dial infarction in 13.1% of the patients. Results showed a significantly higher rate of 30-day any stroke or death for CAS when compared with CEA (9.6% *vs.* 3.9%, P=0.01). The difference in disabling stroke or death was non-significantly higher in CAS treated patients (3.4% *vs.* 1.5%, P=0.26).[17, 18]

The Stent-Supported Percutaneous Angioplasty of the Carotid Artery *versus* Endarterectomy (SPACE) Trial recruited during the same study period as EVA-3S and randomized 1200 patients to either CEA or CAS between 2001 and 2006.[19] The primary endpoint of the trial was ipsilateral stroke or death from time of randomization to 30 days after intervention. In a per protocol analysis, CEA had a 5.65% ipsilateral stroke or death rate, marginally lower than the risk for CAS (6.95%).[19]

The most recent CEA *vs.* CAS Trial in symptomatic patients was the International Carotid Stenting Study (ICSS) published in 2010.[20] Average age of patients randomized to CEA was 70 years, 22% of the patients had diabetes while 7% were treated for atrial fibrillation. Previous TIA was seen in 35% of the patients randomized to CEA, ischemic stroke in 44% and retinal infarction in 3% of the patients. A total of 821 patients treated with CEA, had a 30-day stroke/death rate of 3.4%. The 30-day event risk in patients undergoing stenting was more than twice as high (7.4%), with an excess of non-disabling strokes (1.3% *vs.* 4.3%).[20]

The Carotid Revascularization Endarterectomy *vs.* Stenting Trial (CREST), initially designed as a trial for symptomatic patients, changed its protocol due to slow recruitment, and then included over 1000 asymptomatic patients.[21] CREST, the compared CAS with CEA in 2502 patients from 117 centers in North-America. Average age of patients randomized to CEA was 69.2±8.7 years, diabetes was seen in 30.4% of the patients while 47.3% of the patients were asymptomatic. The 30-day stroke/death rate was 3.22% in 653 symptomatic patients and 1.36% in 587 asymptomatic patients undergoing CEA. In the overall comparison, rate of stroke (4.1% **vs.** 2.3%, P=0.012) and mortality (0.7% *vs.* 0.3%, P=0.18) was higher for CAS when compared with CEA, while the MI risk was lower for CAS patients (1.1% *vs.* 2.3%, P=0.032).[21] There was no significant difference between the two groups when risk factors and preoperative characteristics were observed except for dyslipidemia with border line higher rate in CEA patients (85.8% *vs.* 82.9%, P=0.05).

RCTs: asymptomatic carotid disease

Three trials compared CEA with medical therapy in asymptomatic carotid disease. In both VACS and ACAS,[12, 13] angiographic complications were important components in the 30-risk of CEA. The 30-day stroke/death rate in VACS was 6.1%, only marginally lower than the symptomatic trials. In contrast, ACAS had a remarkably low complication rate of 2.3%, possibly because 40% of surgeons applying to join were rejected after their track records were evaluated.[12, 13]

In the large ACST-1 Trial,[22] where almost all surgeons that applied were approved, there was a low 30-day stroke/day risk of 2.9%. Use of lipid-lowering therapy increased in ACST-1 from less than 10% in 1993 to more than 80% by 2008. This may have contributed to lower procedural risk, which in patients on statins was about 2% and in statin-naïve patients was 4%.[22]

In 2016, the Asymptomatic Carotid Trial-1 (ACT-1) reported results from 1453 asymptomatic patients randomized 3:1 to CAS and CEA between 2005 and 2013.[23] The primary endpoint was 30-day death/stroke/MI and the authors concluded that CAS was not inferior to CEA (3.8% *vs.* 3.4%) although the rate of stroke/death rate within 30-days was lower in the CEA group (1.7% *vs.* 2.9%).[23]

Finally, the Stent-Protected Angioplasty in Asymptomatic Carotid artery stenosis *versus* Endarterectomy (SPACE-2) Trial, which started as a 3-armed trial (CEA *vs.* CAS *vs.* MT) changed protocol due to slow recruitment, then closed early after randomizing 513 patients, but continues follow-up, for a planned 5 years.[24] The 30-day stroke/death rate was 1.97% for CEA and 2.54% for CAS.[24]

Registries and observational studies

Although guidelines base their recommendations on Level I evidence, it is often suggested that registries and observational studies reflect "real-life" practice better. Numerous observational studies and regional registries have reported on early outcomes following CEA in the past decades. Results of registry- and observational studies for symptomatic and asymptomatic patients are shown in Table III, IV respectively.[25-34]

Several large, single-center experiences published prior to 2000 reported outcomes in symptomatic and asymptomatic patients. In 1989 Callow *et al.*[25] reported

TABLE III.—*Observational studies. Symptomatic cohorts.*

Study	Study period	Male (%)	Mean Age (years)	Type study	CEA patients	Periprocedural stroke or death
Callow *et al.*[25] Tufts University Medical Center	1970-1987	63%	64	Single center	404	3.0%
Hertzer *et al.*[26] Cleveland Clinic Registry	1989-1995	66%	69	Registry	750	2.8%*
Yates *et al.*[27] Kentucky Vascular Surgery Society	1991-1993	57%	68	Registry	568	2.3%
Cebul *et al.*[28] Medicare Beneficiary Ohio (USA)	1993-1994	54%	73	Registry	511	5.5%
Kragsterman *et al.*[29] SwedVasc Registry	1994-2003	66%	77	Registry	5511	4.3%
Sternbergh *et al.*[30] Single centre Ochsner Clinic, New Orleans	2001-2002	63%	69	Single center	148	2.7%
Nault *et al.*[31] Vascular Registry Quebec (Canada)	2004-2005	68%	69	Registry	333	3.0%
Sidawy *et al.*[32] S*VS.* Vascular Registry	2005-2007	60%	71	Registry	506	3.75%[1]
Vikatmaa *et al.*[33] (VASCUNET)	2005-2010	68%	72	Registry	28959	2.3%
Rajamani *et al.*[34] National Cardiovascular Registry Data	2005-2011	59%	78	Registry	1376	3.1%*

*In-hospital stroke or death; [1] 30-day death/stroke/MI.

TABLE IV.—*Observational studies. Asymptomatic cohorts.*[25-34]

Study	Study period	Male (%)	Mean Age (years)	Type study	CEA patients	Periprocedural stroke or death
Callow & Mackey Tufts University Medical Center	1970-1987	63%	64	Single center	179	1.7%
Hertzer *et al.* Cleveland Clinic Registry	1989-1995	66%	69	Registry	1174	1.5%*
Yates *et al.* Kentucky Vascular Surgery Society	1991-1993	57%	68	Registry	418	2.4%
Cebul *et al.* Medicare Beneficiary Ohio (USA)	1993-1994	54%	73	Registry	167	2.4%
Kragsterman *et al.* SwedVasc Registry	1994-2003	66%	77	Registry	671	2.1%
Sternbergh *et al.* Single centre Ochsner Clinic, New Orleans	2001-2002	63%	69	Single center	218	2.3%
Nault *et al.* Vascular Registry Quebec (Canada)	2004-2005	68%	69	Registry	227	0.9%
Sidawy *et al..* S*VS.* Vascular Registry	2005-2007	60%	71	Registry	862	1.97%[1]
Vikatmaa *et al.* (VASCUNET)	2005-2010	68%	72	Registry	19226	1.0%
Rajamani *et al.* National Cardiovascular Registry Data	2005-2011	59%	78	Registry	2773	2.0%*

* In-hospital stroke or death; [1] 30-day death/stroke/MI.

his series of 619 patients undergoing 993 CEAs. Average age of entire group was 63.9±0.3 years while 18.6% of the patients had diabetes. This 30-day stroke/death rate for symptomatic and asymptomatic patients was 3.0% and 1.7% respectively. Hertzer *et al.* from the Cleveland clinic in 1997, described 750 symptomatic

and 1174 asymptomatic patients who underwent CEA between 1989 and 1995.[26] Average age of the patients was 68 years, 63% of the patients were asymptomatic, 25% had TIA or amaurosis while 12% had prior stroke. The 30-day stroke or death rate for isolated CEA was 2.8% in symptomatic patients and 1.5% in asymptomatic patients. They found a higher risk in women undergoing CEA and for urgent interventions.[26]

Yates and Cebul [27, 28] reported CEA outcomes from regional American registries. Between 1991 and 1993, 22 vascular surgeons from the Kentucky Vascular Surgery Society Study Group performed 1490 CEAs reporting a combined stroke-mortality rate of 2.3%. Average age of the patients was 68 years, 43% of the patients were asymptomatic, 13% had amaurosis, 27% had TIA while 11% had stroke. Interestingly, there was no difference between symptomatic and asymptomatic patients (2.3% *vs.* 2.4%) in this study.[27] One year later, Cebul *et al.* reported 30-day outcome of CEA performed on 678 patients in Ohio hospitals. Overall 30-day stroke/death rate there was 4.7%, with a higher rate in symptomatic (5.5%) than asymptomatic (2.4%) patients. They found a lower complication rate in high volume hospitals, but individual surgeon volume did not affect the complication rate.[28]

The Swedish Vascular Registry reported in 2006 reported 30-day outcomes in 5511 symptomatic patients, with a relatively high stroke/death rate of 4.3%.[29] When average age was assessed the authors have found that patients at age of 78.3 had a 67% increased risk compared with the patient at age 70. Diabetes was seen in 19.2% of asymptomatic patients and 18.9% of symptomatic patients. Interestingly, they also reported improvements in outcome over time for 671 asymptomatic patients. The overall 30-day stroke/death rate was 2.1%, but decreased from 3.3% in 1994-1998 to 0.9% in 1999-2003.[29]

From 2000 to 2010, several large observational studies reported lower postoperative complication rates. Sternberg *et al.* showed, in a single-center experience, that risk of major stroke and death after CEA in 366 patients was only 1.1%.[30] Average age in this cohort was 68.9±8.6 years, diabetes was seen in 27.9% of the patients and atrial fibrillation in 1.6%. As for the symptoms, 58.1% had prior TIA, 27.7% previous cerebrovascular incident and 14.1% amaurosis. The 30-day stroke/death rate was 2.7% and 2.3% for symptomatic and as-

ymptomatic patients respectively, which was rather low, given that half these patients were considered "high-risk", and "ineligible" for RCTs.[30]

Nault *et al.* reported 2-year experience (2004-2005) results from a Canadian registry in Quebec.[31] Mean age was 69±10 years for symptomatic and 68±8 years for asymptomatic patients while diabetes was seen in 29%. 30-day outcome was collected for 560 patients showed that asymptomatic patients had a lower 30-day stroke/death risk of 0.9% when compared to 3.0% for symptomatic patients.[31]

We reported results after CEA by three different time intervals, the last one between 2005 and 2010.[2] Firstly, procedural outcomes of 1714 CEAs performed between 1991 and 1997 were compared to outcomes of 3320 CEAs performed between 1998 and 2004.[2] Results showed significantly better outcomes in the more recent cohort, which we attributed to shorter clamping time (12.4±3.1 *vs.* 14.5±4.1 min, P<0.01), lowering our 30-day total and neurological morbidity (6.41±0.47% *vs.* 4.81±0.53%, P<0.001, and 2.14±0.31% *vs.* 1.23±0.29%, P<0.001, respectively). Overall mortality was also significantly lower in the later period (1.92±0.24% *vs.* 1.36±0.50%, P<0.05). This temporal improvement in outcome found in our first analysis continued for our most recent cohort of 4863 CEAs, performed between 2005 and 2010. When overall cohort was observed, average age was 64.6±10 years, 42.8% of the patients had prior stroke, 55.1% had TIA, 25.8% of the patients had diabetes, 87.2% were treated for hypertension, 81.3% for hyperlipidemia while 41.3% of the patients were smokers. Attending neurologists of our Institute have evaluated all patients before and after the surgery and during the follow up. We have been very careful during the follow up and all strokes, minor and major have been registered. At the end of 2010 clamping time was 11.9±3.2, neurological and total morbidity was 1.1% and 3.9% respectively and overall mortality 0.8%.

Between 2005 and 2007, 30-day outcomes for 1382 symptomatic and 1877 asymptomatic patients undergone CEA were collected in the Society for Vascular Surgery (SVS) Vascular Registry.[32] Mean age of CEA patients was 71.06±9.52 (range 24-99), 42.4% of the patients were symptomatic, 19.2% had stroke while 28.8% of the patients had diabetes. Their combined death/stroke/MI rate was 3.75% for symptomatic and

1.97% for asymptomatic patients, with similar risks for perioperative MI (0.59% *vs.* 0.58%).[32]

VASCUNET, a large registry for vascular surgical interventions, reported outcomes of carotid interventions in 9 European countries and Australia in 2012.[33] Large differences in practice between countries in Europe were revealed; in Denmark no interventions were performed on asymptomatic patients, whilst in Italy 70% of interventions were in asymptomatic patients. The VASCUNET results for 28,959 symptomatic CEAs and 19,226 asymptomatic patients, a 30-stroke/death rate of 2.3% and 1.0% respectively, differed substantially between countries.[33]

In elderly patients Ramajani *et al.* analyzed the outcomes of CEA in 4149 subjects, all 70 years or older, 1376 (33%) of which were symptomatic.[34] Average age was 78.1±5.2 years while diabetes was seen in 32.4% of the patients. They only reported in-hospital outcome, a 3.1% stroke/death rate for symptomatic with 2.0% for asymptomatic patients. Their complication rate was highest for the very oldest group of patients (85 years or older).[34]

Discussion

In our very large series of almost 10000 procedures, risk of CEA has decreased with time.[1] Results from other large studies of CEA suggest that risk decreased over time for both symptomatic and asymptomatic patients. For asymptomatic patients, this trend had been described previously in a meta-analysis of over 200.000 procedures, where Munster *et al.* found risk decreasing between 1991-2010 and he concluded that the new guideline or "benchmark" for procedural 30-day stroke/death in asymptomatic patients should be as low as 1.2%.[35] Paraskevas[36] undertook a very large pooled analysis of 21 registries, including over 1,500,000 carotid procedures. He compared 30-day stroke/death outcomes of "average risk" and "high risk" CEA- and CAS patients to the advised thresholds in AHA/ASA guidelines. There was a significantly higher rate of complications for CAS when compared with CEA in 11/21 (52%) registries.

In US guideline publications, 9/21 (43%) registries found procedural stroke/death rates for CAS in asymptomatic patients to be higher than the 3% threshold risk recommended by the AHA/ ASA.[36, 37, 63, 64] In the same report, only 1/21 (5%) of the registries for CEA was associated with excess procedural stroke/death rates.

In "average risk for CEA" symptomatic patients, most (11/18, 61%) registries found CAS was associated with higher stroke/death rates than CEA. In-hospital 30-day stroke/death rates for CAS exceeded the 6% AHA/ASA risk threshold in 13/18 (72%) registries, whilst for CEA procedural risks exceeding the AHA/ASA thresholds were reported in only 2/18 (11%) registries.[36, 37, 63, 64]

There are several possible explanations for the decrease in procedural risk following CEA, including newer medical therapy for carotid atherosclerosis, better selection of patients, improvements in timing of CEA, use of local anesthesia, and cerebral monitoring and changing surgical techniques, such as the introduction of eversion CEA.

Surgical techniques and introduction of eversion CEA

Carotid endarterectomy has been the "gold" standard for treatment for atherosclerotic carotid disease since publication of the first RCTs in the 1990s. Introduction of eversion in addition to conventional CEA had great impact on better overall results of carotid surgery.[65-80] Two main techniques, conventional CEA and eversion CEA, have been used since then.[65-80] Both techniques were tested in major trials,[65-79] EVEREST[65] (EVERsion carotid Endarterectomy *versus* Standard Trial) being the most influential. In 1353 patients randomly assigned to conventional or eversion CEA, eversion CEA was found to be a safe, effective and durable technique. There was a lower restenosis rate for eversion CEA, but no differences in early or late stroke or mortality outcome.[65] Several studies showed lower incidence of early postoperative death, neurological complications and restenosis in patients treated with eversion CEA when compared to patients with conventional CEA.[65, 67-70, 72-74] In addition, Gao *et al.* showed that incidence of postoperative microembolic events are also lower in patients with eversion CEA than in patients with conventional CEA.[75] These findings were later confirmed by meta-analyses comparing conventional with eversion CEA.[77, 78, 80] In published reviews and meta-analyses on these two techniques, the authors suggested that a surgeon should use the technique they are most familiar with and which provides them with a good result.[77, 78, 80] Patch angioplasty is another important technical improvement of CEA. Introduced in 1965 several meta-analyses showed patch angioplasty reduced both ipsilateral stroke as well

as restenosis.[81] These technical advancements, as well as growing experience among surgeons, may have contributed to a reduction in early complications.

Local anesthesia

CEA can be performed under general (GA) or local anesthesia (LA). Cervical block anesthesia (CBA) has evolved over the last 20 years with novel methods of locating the cervical plexus and innovative drugs.[82-84] In patients with significant cardiopulmonary comorbidities or when GA is contraindicated, LA many be a safer option. The disadvantages of LA include risk of seizure or allergic reaction, discomfort for the patients undergoing surgery and distraction to the attending surgeon.[85] The GALA (General Anaesthesia *versus* Local Anaesthesia for carotid surgery) Trial was designed to compare the outcomes of the patients operated under GA and LA.[85] There was no significant difference in the incidence of stroke, myocardial infarction or death at follow up between the two groups although the recovery is more rapid and discharge is quicker after LA.

Patient selection

More sophisticated imaging techniques are now being used to evaluate carotid disease.[86-93] Computerized tomography angiography (CTA) and magnetic resonance angiography (MRA) enable detailed but less invasive evaluation of carotid stenosis when compared with the more dangerous technique of classic angiography.[86-93] In addition to assessing degree of intraluminal stenosis, these techniques provide additional information about the plaque type and extent and the surrounding tissue (external compression, lymphadenopathy) that could influence the decision to undertake carotid surgery. Information on more distal intracranial atherosclerotic lesions, incompleteness of the circle of Willis,[92] the possible presence of intracranial aneurysms[93] or of plaque characteristics with high embolic potential can now be obtained.[94] More thorough evaluation of carotid disease with improved patient selection may have helped improve outcomes of CEA.

Timing of the surgery

The careful timing of CEA has improved results of CEA. Several studies have examined outcomes of early CEA after stroke or TIA.[95-99] Ratner *et al.*[95] analyzed 104 patients with recent stroke and concluded that there was no significant difference in the outcome of endarterectomy made within 4 weeks or 4 weeks after the stroke. Salem and colleagues examined 109 recently symptomatic patients found that CEA performed within 14 days after the ischemic event did not have a higher complication rate than CEA after 14 days.[96] Rerkasem and Rothwell in 2009 in a systematic review found an increased risk from endarterectomy after stroke-in-evolution or "crescendo" TIAs, but no difference between CEA performed before or after 14 days in stable patients with recent ischemic events.[97] Balota *et al.*, in 102 patients with recent "minor" stroke, found no differences between early and late CEA.[98] Recently, we reported our results for urgent CEA performed within 6 hours of "crescendo" TIA or stroke-in-evolution in 58 patients with significant carotid stenosis with excellent outcome.[99] All 46 patients with crescendo TIA fully recovered as well as 9 out of 12 patients with stroke in progression while 3 others with stroke in progression had significant neurological improvement. [99] National clinical guidelines for the treatment of stroke in the UK concluded that CEA could be performed safely within two weeks of recent stroke or TIA,[100] and this was later accepted by the European Stroke Organisation guidelines.[101]

Cerebral monitoring in patients undergoing CEA

Intraoperative cerebral changes during carotid endarterectomy can be monitored using electroencephalography (EEG), transcranial Doppler sonography (TCD), stump pressure (SP) measurement, somatosensory evoked potentials (SEP) and near-infrared spectroscopy (NIRS). Moritz *et al.* compared transcranial Doppler sonography (TCD), stump pressure (SP) measurement, somatosensory evoked potentials (SEP) and near-infrared spectroscopy (NIRS) in 48 patients undergoing CEA in regional anesthesia.[102] They found that TCD, NIRS, and SP measurement had similar accuracy for the detection of cerebral ischemia during CEA, while SEP was less accurate. In another study Hans *et al.*,[103] tried to correlate changes in awake patients undergoing CEA under cervical block anesthesia (CBA) with EEG and carotid artery SP measurement. They found that 10% of patients required a shunt during CEA under CBA. EEG

identified cerebral ischemia in only 59.4% of patients needing shunt placement, while both SP and EEG were poor guides for shunt placement.

Traditional methods of cerebral monitoring are now being replaced by novel, easy-to-use techniques of regional cerebral oxygen saturation monitoring.[104-106] In approximately 15% of CEA patients, an adequate TCD signal cannot be obtained due to an insufficient temporal bone window, so an alternative and promising technique of noninvasive cerebral monitoring is relative frontal lobe oxygenation (rSO(2)) measured by NIRS which provides on-line information about cerebral oxygenation. In a systematic review by Pennekamp *et al.*, the value of NIRS in predicting perioperative cerebral ischemia was compared with other cerebral monitoring techniques.[105] The authors found that NIRS correlated well with TCD and electroencephalography (EEG) values indicating ischemia. However, a threshold for postoperative cerebral ischemia could not be determined. In another study by the same author [106], NIRS and perioperative TCD are compared and assessed in relation to cerebral hyperperfusion syndrome (CHS) after CEA. The authors found that both TCD and NIRS measurements could be used to safely identify patients not at future risk of developing CHS. NIRS was described as a good alternative when a TCD signal cannot be obtained.

Medical therapy

ANTIPLATELET THERAPY

More intensive use of appropriate medical therapies has contributed considerably to the reduction in periprocedural ischemic stroke in patients with carotid disease.[62, 108-110] The importance of aspirin for secondary prevention of cardiovascular events is well documented, but the role of antiplatelet therapy in stroke prevention in the procedural period is less clear. In an analysis of NASCET data, patients on high dose aspirin (650 mg to 1300 mg) had a significantly lower risk of procedural stroke when compared to no or low dose (325 mg) aspirin (1.8% *vs.* 6.9%).[9, 10] However, in the more recent ASA and CEA Trial, comparing low dose aspirin (81 mg or 325 mg) with high dose aspirin (650 mg or 1300 mg) patients on low dose aspirin had better outcomes.[108] Use of dual antiplatelet therapy in the perioperative period is still controversial. The addition of Clopidogrel to aspirin, although associated with 40% reduction of post-

operative neurological risk, also causes an increased risk of postoperative bleeding (odds ratio [OR], 1.71; 95% confidence interval [CI]: 1.20-2.42; P=0.003).[62] Authors concluded that the use of dual antiplatelet therapy might be beneficial in reducing postoperative neurological complication rate.[62] Another study showed that addition of a single 75 mg dose of Clopidogrel to a regular 75 mg dose of aspirin the night before CEA, was associated with a significant reduction in postoperative neurological events, without increasing hemorrhagic complications.[109] When microembolization was evaluated, Sharpe *et al.*[110] showed that patients receiving dual antiplatelet therapy had a lower incidence of microembolization compared to patients receiving only aspirin.

STATINS

Lipid-lowering therapy is important for stroke prevention. Statins have an anti-inflammatory effect, thought to be important for plaque stabilization preoperatively.[54-57] Several studies have shown that, in symptomatic and asymptomatic patients, statins significantly reduce stroke risk.[54-57] This effect is mainly attributed to their pleiotropic effects rather than to cholesterol-lowering.[111] Trials and meta-analyses show a strong correlation of statin use with reduced stroke risk.[112-114] In a series by McGirt *et al.*,[115] 1566 patients who underwent CEA were found at 30-day follow-up, to have a lower risk of death (0.3% *vs.* 2.1%), stroke (1.2% *vs.* 4.5%) and TIA (1.5% *vs.* 3.6%) when compared to patients not taking statins. Patients taking statins had fivefold lower risk of death and three fold lower risk for stroke. In addition, dual antiplatelet therapy taken with statins and angiotensin-converting-enzyme (ACE) inhibitors or beta-blocker after CEA or CAS [115, 116] may reduce restenosis and postoperative complications.

ANTICOAGULATION

A better understanding of anticoagulation therapy in patients undergoing CEA has improved perioperative risk. McMahon *et al.*[117] analyzed the administration of unfractionated heparin (UFH) and low molecular weight heparin (LMWH) prior to carotid clamping during CEA in 183 patients on aspirin. The authors found that patients on UFH had twice the risk of embolization in the first 3h after CEA, (P=0.04).[117] They

concluded that intravenous administration of LMWH reduces post-operative embolisation without increasing bleeding. As many patients are now on warfarin therapy, another study compared outcomes of antiplatelet *vs.* anticoagulation therapy in patients undergoing CEA.[118] Clopidogrel use resulted in a significant risk of developing neck hematoma and postoperative bleeding, although patients on warfarin therapy did not have this increased risk. Use of the new oral anticoagulants (dabigatran, rivaroxaban, edoxaban and apixaban) in patients with CEA is expected to increase since the recent trials have shown that these drugs are superior to warfarin for prevention of ischemic stroke, intracranial hemorrhage, systemic embolic events and all-cause mortality.[119]

Introducing carotid artery stenting

Stenting may be a reliable treatment option, but in recent RCTs, CAS has had a higher rate of postoperative neurological complications when compared with CEA.[15-23] The largest trial, CREST randomized 2502 patients between CEA and CAS and found higher rate of minor stroke after CAS and higher rates of MI after CEA.[21] Guidelines need to be clearer on indications for CAS and the influence of patient comorbidity before CAS becomes comparative with CEA and this can only happen with further randomized comparisons of these procedures.

Current guidelines and recommendations of perioperative risk changes

Current extracranial carotid disease recommendations suggest that in patients with a TIA or ischemic stroke within the past 6 months and ipsilateral severe (70-99%) carotid artery stenosis (Class I; level of evidence A) or more than 50% as documented by catheter angiography (Class I; level of evidence B), CEA is recommended if the risk is estimated to be <6%.[37, 63, 65] For asymptomatic patients with>60% diameter stenosis CEA should be considered for the reduction of long-term risk of stroke, provided the patient has a 3- to 5-year life expectancy and that perioperative risk is ≤3% (GRADE 1, level of evidence A).[37, 63, 64] We now suggest that current guidelines should be revised to decrease the acceptable perioperative risk in symptomatic severe (70-99%) carotid artery stenosis patients to <4%. In asymptom-

atic patients with >60% diameter stenosis CEA should be considered for reduction of long-term risk of stroke, provided the patient has a 3- to 5-year life expectancy and perioperative stroke/death rates are 2% or less (GRADE 1, level of evidence A).

Conclusions and perspectives

Improving drug treatment of carotid atherosclerosis, better patient selection based on timing of CEA after recent ischemic events, widespread use of local anesthesia and of better surgical techniques, such as eversion CEA and use of cerebral monitoring during operation; all these changes have led to a reduction in procedural risk from CEA, now well documented in RCTs, observational studies and registries. This may provide sufficient evidence to update guidelines and to lower the thresholds for accepted procedural complication rates in CEA, which can be then be more meaningfully compared with CAS in future trials such as ACST-2.[120]

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