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REVIEW

Endovascular treatment of carotid artery stenosis: evidences from randomized controlled trials and actual indications

Trattamento endovascolare di stenosi carotidee: evidenze dai trial clinici randomizzati e attuali indicazioni

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ABSTRACT: ***Endovascular treatment of carotid artery stenosis: evidences from randomized controlled trials and actual indications. F. Ilardi, F. Magliulo, G. Gargiulo, G.G. Schiattarella, G. Carotenuto, F. Serino, M. Ferrone, E. Visco, F. Scudiero, A. Carbone, C. Perrino, B. Trimarco, G. Esposito.***

Atherosclerotic stenosis of common and internal carotid arteries is a well-recognized risk factor for ischemic stroke, and revascularization has been proven to be the main tool of prevention, particularly for patients with stenosis-related symptoms. While for many years surgical carotid endarterectomy (CEA) has been considered the gold-standard strategy to restore vascular patency, recently the endovascular treatment through percutaneous angioplasty and stent implantation (CAS) has become a valid alternative. In the last years, interesting data about the comparison of these strategies have emerged. CAS seems to cause more peri-procedural strokes, but may also avoid many adverse events related to surgery and general anaesthesia, including peri-procedural myocardial infarction. For these reasons, it was initially considered a second-choice strategy to be adopted in patients for whom surgery was contraindicated. However, more recent trials have shown that CAS might be considered an effective alternative to CEA. Moreover, the rapid evolution of CAS technique and materials suggests its potential to improve outcome and possible superiority compared to CEA in the next future. Purpose of this review is to discuss the most recent clinical evidences concerning the treatment of carotid artery stenosis, with a special focus on the endovascular treatment.

Keywords: carotid, stenosis, endovascular, CEA, CAS, CREST.

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Introduction

Cerebrovascular disease is an important cause of mortality and long-term disability in developed countries [1]. In Italy, 10-12% of deaths are stroke-related, with almost 196000 new cases/year [1]. The vast majority of cerebrovascular events (nearly 80%) are ischemic strokes, caused by the interruption of arterial blood supply by an intravascular thrombus or a migrant embolus, while an hemorrhagic nature accounts for only the remaining 20% of the cases [1]. Atherosclerosis of the supra-aortic vessels, and especially of the common carotid bifurcation, is a major cause of recurrent ischemic stroke, accounting for approximately 20% of all strokes [2, 3].

Atherosclerotic lesions of common and internal carotid arteries are frequent in general population, and their incidence raises in the elderly population [4]. Carotid plaques may produce cerebral ischemia by three mechanisms: 1) arterial embolism of plaque debris, 2) acute thrombotic occlusion or 3) reduced cerebral perfusion resulting from critical stenosis or occlusion caused by progressive plaque growth [5]. All these three mechanisms are able to induce cerebral ischemia, however neurological symptoms only occur if the intracranial circulation becomes deficient. Therefore, it is particularly important to differentiate patients with symptoms arising from the stenosis and cases of asymptomatic carotid obstruction, which may frequently be discovered after a routine ultrasound exam of the supra-aortic trunks.

According to the largest randomized clinical trials, patients are considered symptomatic if they experienced a transient ischemic attack (TIA) or stroke in the previous three months [6, 7]. Suggestive symptoms of a carotid-related cerebrovascular event include, but are not limited to, unilateral weakness (up to paralysis), monolateral paresthesia or sensory loss, hemineglect, non-fluent aphasia, abnormal visual-spatial ability, monocular blindness and homonymous hemianopsia. In several studies the annual risk of ipsilateral stroke in asymptomatic pa-

tients assigned to medical therapy alone is approximately 2% [8-11], however such risk increases in the presence of the following conditions: elderly patients, controlateral carotid artery stenosis or occlusion, evidence of silent embolization on brain imaging, carotid plaque heterogeneity and poor collateral blood supply [12]. In contrast, the risk of stroke in symptomatic patients has been estimated to be about 13% per year [13]. Thus, the presence of symptoms appears to be the most reliable criterion to decide an appropriate strategy of intervention.

For over fifty years the standard therapeutic strategy for significant carotid artery stenosis has been the surgical restoration of the arterial patency by surgical removal of the plaque through endarterectomy. In the last twenty years an important alternative has emerged, represented by the endovascular treatment through angioplasty and stent implantation. Even if the endovascular technique has shown good efficacy, it has been considered for many years only a second choice to surgery in patients presenting high co-morbidities or high perioperative risk due to anatomic factors. However, these assumptions have recently been challenged by the interesting results of the clinical trial Stenting versus Endarterectomy for Treatment of Carotid-Artery Stenosis (CREST), demonstrating no significant differences between surgery and stenting in a selected groups of patients [6].

The "classical" management of carotid stenosis: medical therapy and surgical endarterectomy

Being carotid stenosis a well-recognized risk factor for cerebrovascular disease development, every effort should be attempted in order to prevent such serious complications. The first step for prevention is based on non-pharmacological and pharmacological recommendations to modify the classical risk-factors for atherosclerosis: smoking cessation, blood pressure control (particularly with dihydropyridines Ca-antagonists [14]), plasma lipids lowering (by diet, lifestyle and eventually by the administration of statins [15-17]), adequate management of diabetes [18] and metabolic syndrome and encouragement to perform physical activity. In addition to these recommendation, the American Heart Association (AHA) guidelines propose the administration of antiplatelet therapy (with schemes and dosages related to risk factors, adverse reaction to drugs and risk of bleeding) for all the patients with obstructive or non-obstructive lesions of the extracranial vessels responsible for brain vascularization. While for symptomatic patients the benefit appears to be well demonstrated, there is less evidence in favor of antiplatelet therapy in asymptomatic patients with carotid stenosis [19]. Similarly, the European Society of Cardiology (ESC) guidelines suggest the use of antiplatelet therapy regardless of symptoms in all patients with an atherosclerotic lesion of a carotid vessel [20]. Moreover, antiplatelet therapy for all patients with a carotid stenosis seems to be advantageous in terms of prevention of myocardial ischemia and infarction, even though the efficacy against stroke is not completely clear [19, 21-23]. The most commonly prescribed anti-platelet regimens include aspirin at the dosage of 75-325 mg/die, clopidogrel 75 mg/die, and eventually the association of these compounds in very high-risk patients with multiple atherosclerotic lesions, as suggested by the results of the Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) study [24], or ticlodipine 250 mg/die.

In patients with an asymptomatic carotid artery stenosis greater than 50% under optimal medical therapy (including anti-hypertensive drugs, statins and aspirin or analogues), the annual event rates on medical treatment are relatively low [10], suggesting that the gold standard for such patients is medical therapy. However, revascularization may be considered even in these patients for specific situations related to a high risk of complications based on intrinsic features of the lesion. The surgical treatment restores the patency of the obstructed carotid and is commonly defined carotid endarterectomy (CEA). The first CEA was performed by Dr. Michael DeBakey in 1953 at the Methodist Hospital in Houston. Since then, a large body of evidence on its effectiveness in different patient groups has been accumulated. Three studies have clearly shown the superiority of CEA versus medical therapy in patients with a symptomatic obstruction of a carotid artery: the European Carotid Endarterectomy Surgery Trialist (ECST) [25], the North American Symptomatic Carotid Endarterectomy Trial (NASCET) [7] and the Veterans Affairs Cooperative Study (VACS) [26]. A cumulative analysis of these studies, involving a total of 35.000 patients, considering a 5-year risk of ipsilateral ischemic stroke reduction as primary endpoint, demonstrated that CEA was highly advantageous in patients with a stenosis ≥70% (n=1095, absolute risk reduction=16.0%, $p < 0.001$), with a mild benefit in those with 50-69% stenosis (n=1549, absolute risk reduction 4.6%, $p < 0.04$), no effect in patients with 30-49% stenosis (n=1429, absolute risk reduction=3.2%, $p < 0.6$), and even detrimental in those with less than 30% stenosis (n=1746, absolute risk increase= 2.2%, $p < 0.05$) [27]. On the contrary, the real benefit provided by CEA in asymptomatic patients having a carotid obstruction is not clearly understood. The two most important clinical trials on this argument are the Asymptomatic Carotid Atherosclerosis Study (ACAS) [11] and the Asymptomatic Carotid Surgery Trial (ACST) [28], randomizing patients with carotid artery stenosis in the absence of symptoms to CEA or to medical therapy. ACAS has shown an aggregate 5-year risk of ipsilateral stroke and any perioperative stroke or death of 5.1% for surgical patients and of 11.0% for patients treated only with medical therapy [11]. ACST provided a 5-year risk of stroke of 6.4% in the CEA-treated group versus 11.8% in the control group, and, respectively, a 5-year risk of 3.5% versus 6.1% for fatal or disabling strokes and 2.1% versus 4.2% for fatal strokes in the same groups [28]. Unlike ACAS, the benefit in ACST was demonstrated for overall, fatal, disabling and non-disabling strokes. Interestingly, the results of these trials showed a significant difference among men and women in terms of efficacy, with protective effects greater for men. The benefit from CEA for women was not demonstrated in the ACAS. In the

ACST study, differently from man the absolute risk reduction in women was not statistically significant, and it seems that women who undergo CEA develop many much more neurological complications [28].

According to the results of these large randomized clinical studies, both the AHA and, more recently, the ESC guidelines recommend CEA in symptomatic patients with a carotid stenosis greater than 50% (but with the highest level of evidence only for stenosis greater than 70%) as the first-line choice for patients at low or intermediate surgical risk [19, 20]. In patients with signs of progressive minor stroke, revascularization must be performed within three weeks [19, 20], while in cases of serious, disabling carotid strokes revascularization is not indicated [19]. Regarding asymptomatic patients, guidelines indications are different: in this setting AHA proposes CEA in case of stenosis greater than 70% if the risk connected to the surgical procedure (stroke, myocardial infarction or death for any causes) is acceptable [19]. For the same setup, ESC puts a lower cut-off, of more than 60%, if the surgical risk is judged to be <3% and the patient has a life expectancy greater than 5 years [20]. Guidelines do not recommend every attempt of revascularization for stenosis <50% regardless from symptoms (except in extraordinary circumstances), for totally occluded vessels and for patients who have experienced a large, severely disabling stroke, which precludes preservation of useful cerebral functions.

Endarterectomy is a serious surgical practice and presents notable risks for the patients. The risks associated with CEA involve neurological and non-neurological complications. Neurological complications include periprocedural stroke, generally due to a thromboembolic mechanism during or immediately after the procedure. In the North American Symptomatic Endarterectomy Trial (NASCET), 43 of the 1087 patients undergoing CEA (4%) had a non-disabling stroke, 17 (1.6%) had a non-fatal, disabling stroke and 7 patients died for a stroke in the 30 days after endarterectomy [13]. As a consequence of the ameliorated techniques, the CREST trial reported an incidence of 2.3% of periprocedural or ipsilateral stroke within 30 days of controlateral operation (1.4% in previously asymptomatic patients and 3.2% in symptomatic patients) [6]. Minor causes of strokes are due to cerebral low flow, for both low systemic pressure and controlateral disease, poor collateral circulation, or reduced cerebrovascular reserve. Hemorrhagic strokes are rare, occurring in <1% of the procedures and accounting for 5% of the perioperative strokes [29], as a result of a suddenly increased perfusion in a patient with prior severe stenosis and altered cerebral blood flow autoregulation. This is known as cerebral hyperperfusion syndrome (CHS) and may be accompanied by cerebral edema and seizures [30, 31]. On the other hand, it must be noted that CHS and hemorrhagic strokes are even more common after stenting procedures, probably as a consequence of the dual antiplatelet therapy [32]. The risk of stroke after CEA is greater in patients who had a symptomatic obstruction of a carotid artery, hemispheric TIA (versus retinal TIA), male gender, need for an urgent revascularization due to ongoing cerebral damage, reoperation versus primary surgery, ipsilateral ischemic lesion on computerized tomography, contralateral carotid occlusion, poor collateral circulation, impaired consciousness, and an irregular or ulcerated plaque [33, 34]. A further serious neurological side event following CEA is cranial nerve paralysis, happening in 7% of the patients undergoing surgery and generally transient. In decreasing order of frequency, hypoglossal, marginal mandibular, recurrent laryngeal, and spinal accessory nerves can be involved or the Horner syndrome can be observed. The risk of a permanent damage has been estimated of about 1%, and the only well recognized risk factor for a nerve paralysis development seems to be a duration of CEA > 2 hours [35-38]. Non-neurological adverse events of surgery mainly derive from general anesthesia and include cardiovascular complications (principally myocardial infarction, in about 2% of the treated subjects [39] hypertension or hypotension [40], congestive heart failure, arrhythmias and angina, rarely venous thromboembolism [41]), pneumonia, wound infection, acute thrombosis (prevented by the early administration of aspirin) and arterial restenosis (with a frequency of 3.6% at 1 year, yet less than after stenting). Overall mortality of CEA is reported to be of 1.3-1.8% [42]. So, there are some notable situations in which CEA brings along severe risks or is not suitable. The first is, obviously, the case of a patient at high surgical risk. More strictly, according to the Stenting and Angioplasty Procedure in Patients at High Risk for Endarterectomy (SAPPHIRE) trial, patients are considered to be at high-risk if they have, as co-morbidities, congestive heart failure (New York Heart Association class III/IV) and/or a known severe left ventricular dysfunction, open heart surgery needed within 6 weeks, a recent myocardial infarction or unstable angina (and, if a coronary revascularization is required, it should be performed after CEA), or a severe pulmonary disease [43]. Also, a severe impairment of hepatic or renal function has a significantly negative impact on the outcome of CEA [44]. Another factor which relatively contraindicates CEA is the presence of a lesion of the contralateral laryngeal nerve, being the occurrence of a bilateral paralysis threatening for the risk of laryngeal obstruction, airway limitation and the possible requirement of a tracheostomy [45, 46]. Finally, troubles may concern the anatomy of the lesion. A high carotid bifurcation or an atheromatous lesion that extends into the internal carotid artery beyond the exposed surgical field represents a technical challenge during CEA, and carotid lesions located at or above the level of the second cervical vertebra are particularly problematic. High cervical exposure increases the risk of cranial nerve injury. These “high” stenoses may represent a good field of application for an endovascular revascularization. Similarly, lesions below the clavicle, prior radical neck surgery or radiation, and controlateral carotid occlusion are associated with higher risk. In these situations, the ability and the experience of the surgeon may significantly influence the outcome [47, 48].

In summary, CEA is an effective technique for the prevention of stroke in patients having a carotid

stenosis, particularly if they are symptomatic. However, as most surgical interventions, it may entail important adverse effects, and in some situations it should not be performed. In almost all of these contexts, carotid artery stenting (CAS) has proved to be a safe and effective alternative.

The "state-of-art" of endovascular treatment

Carotid artery stenting (CAS) has been initially used as a second-choice, alternative treatment, initially in patients not eligible for surgery. Numerous non-randomized and some randomized studies have assessed safety and efficacy of carotid-artery stenting in so-called high-risk patients [43, 49-52]. Although CAS has been recommended in specialized subsets of patients [6, 53-55] such as restenosis after CEA, radiation-induced carotid stenosis, anatomically high lesions, increased cardiopulmonary risk or with unfavorable neck anatomy and in higher-risk patients, the appropriateness of its use in conventional-risk patients remains an unsolved matter.

The potential benefits of endovascular treatment (angioplasty with or without stent implantation) as an alternative to carotid endarterectomy were first highlighted by the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) [56]. This trial showed that endovascular treatment largely avoided the main complications of the endarterectomy incision (namely cranial nerve injury and severe hematoma). Besides, there was no statistical difference in terms of stroke or death at 30 days between CEA and angioplasty (the combined stroke and death rate was 9.9% for CEA and 10% for endovascular treatment, and death or disabling strokes were observed in 5.9% of CEA patients and 6.4% of endovascular patients, **Table 1**) [56]. It is worth mentioning that in the CAVATAS trial carotid stents were used in only 26% of the patients who received angioplasty, a factor that could have contributed to a high incidence of recurrent ≥70% stenosis at 1 year follow-up [57]. Despite these findings, there remained no significant difference in ipsilateral stroke between the groups with a hazard ratio of 1.04 [58]. Moreover, cerebral embolic protection devices were unavailable at the time of the study, so this adjunct was not used in the CAVATAS. Since completion of CAVATAS, stenting has largely replaced the clinical practice of angioplasty alone, and stents and protection devices specifically designed for the carotid artery have been introduced. These early encouraging results generated a great deal of interest in CAS, and so, after CAVATAS, other large randomized trials comparing CAS and CEA in symptomatic stenosis have been subsequently published exploring short-term outcomes and longer term results. Among these, the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial [43] is the only randomized trial that specifically enrolled high-risk patients to compare CEA and CAS with embolic protection devices. The primary endpoint (the composite of MI, stroke, or death within 30 days plus death because of neurological causes or ipsilateral stroke between 31 days and 1 year) occurred in 12.2% of patients assigned to CAS and 20.1% of those assigned to CEA (**Table 1**). In the periprocedural period (up to 30 days), the cumulative incidence of stroke, myocardial infarction, or death was 4.4 percent among patients who received a stent and 9.9 percent among those who underwent endarterectomy (p= 0.06). In the post-procedural period, the cumulative incidence of the primary end point at 30 days among these patients was 2.1% among those who received a stent and 9.3% among those who underwent endarterectomy. One-year analysis in patients within the CAS arm also demonstrated less cranial nerve paralysis (0% versus 4.9%; p=0.004), reduced mean hospital stay (1.84 versus 2.85 days; p=0.002), and less target vessel revascularization (0.5% versus 4.3%; p=0.04) [43]. The investigators of the SAPPHIRE trial concluded that CAS was non-inferior to CEA, leading to US Food and Drug Administration (FDA) approval of the Cordis PRECISE nitinol stent for CAS.

The Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) trial randomized 1200 symptomatic patients. The incidence of ipsilateral stroke or death at 30 days was the primary endpoint of the study and did not differ between the groups (6.3% for CEA vs. 6.8% for CAS, **Table 1**) [59]. Although the two-year stroke plus 30-day stroke and death rates were similar between the groups, the SPACE trial failed to prove the non-inferiority of CAS for the insufficient sample size. However, no differences were found between CAS and CEA with respect to the prevention of recurrent cerebrovascular events after treatment of severe symptomatic carotid artery stenosis at 2 years.

In the Endarterectomy versus Stenting in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trial the 30-day combined stroke and death rate was higher in the CAS group (9.6%) compared with 3.9% for CEA (**Table 1**) [60]. However, these results have been criticized because of the potential inexperience of CAS operators. Furthermore, 8.1% of CAS procedures were performed without an embolic protection device, and in those with embolic protection significantly fewer adverse events were observed. Results up to 4 years show that there was no difference in mortality between the two treatment groups. The 4-year estimated cumulative risks of periprocedural stroke or death and non-procedural ipsilateral stroke were significantly higher after CAS than after CEA (**Table 1**). However, this difference was largely accounted by the higher periprocedural risk of CAS compared to CEA, whereas the risk of ipsilateral stroke beyond the perioperative period was low and similar in both groups [61].

The short-term results of the International Carotid Stenting Study (ICSS), a randomized trial comparing CAS versus CEA for recently symptomatic carotid artery stenosis, show that the risk of stroke, death, or procedural myocardial infarction 120 days after randomization was significantly higher in patients in the CAS group than in patients in the CEA group (8.5% vs. 5.2%, **Table 1**) with an hazard risk (HR) in favor of surgery of 1.69 (**Table 1**). The difference between groups was mainly due to an excess of non-disabling stroke in the CAS group compared to the CEA group, but there were also more fatal strokes and fatal myocardial infarc-

Table 1. - Randomized Trials Comparing Endarterectomy With Stenting in Symptomatic and Asymptomatic Patients With Carotid Stenosis

Trial	N. of Patients	Patients status	Carotid artery stenosis (%)	Primary endpoint	HR (95% CI)
CAVATAS	504	Symptomatic or asymptomatic	>50	Any disabling stroke or death CEA: 9.9%; CAS: 10.0%	1.04 (0.64 to 1.64), *p*=0.90
SAPPHIRE	334	70% asymptomatic 30% symptomatic	≥80 in asymptomatic patients; ≥50% in symptomatic patients	The composite of MI, stroke, or death CEA: 12.2%; CAS: 20.1%	=0.004 for non inferiority (16.4 to 0.7)
SAPPHIRE Follow up at 3 years	260	Symptomatic or asymptomatic	≥80 in asymptomatic patients; ≥50% symptomatic patients	Stroke: CEA: 9.0%;CAS: 9.0% Death: CEA: 21%; CAS: 18.6%	Stroke: *p*=0.99 (-6.1 to 6.1) Death:*p*=0.68 (10.9 to 6.1)
SPACE	1183	Symptomatic	≥70	Ipsilateral stroke or death CEA: 6.3%; CAS: 6.8%	RR 1.07 (0.70-1.63)
SPACE Follow up *p*=0.62 **at 2 years**	1214	Symptomatic	≥70	Any periprocedural stroke or death CEA: 8.8%; CAS: 9.5%	RR 1.10 (0.75-1.61)
EVA-3S	527	Symptomatic	≥60	Any stroke or death CEA: 3.9%; CAS: 9.6%	RR 2.5 (1.2-5.1), *p*=0.01
EVA-3S Follow up at 4 years	527	Symptomatic	≥60	Cumulative risks of periprocedural stroke or death and non-procedural ipsilateral stroke CEA: 6.2%; CAS: 11.1%	1.97 (1.06-3.67), *p*=0.03
ICSS	1713	Symptomatic	>50	Any stroke, death, or procedural MI at 120 days CEA: 8.5%; CAS: 5.2%	1.69 (1.16-2.45), *p*=0,006
CREST	2502	Symptomatic or asymptomatic	≥70 on ultrasound ≥50 on angiography in symptomatic patients ≥60 on angiography in asymptomatic patients	Any stroke, MI, or death during the periprocedural period or ipsilateral stroke within 4 years after randomization CEA: 6.8%; CAS: 7.2%	1.11 (0.81-1.51) *p*=0.51

CAS: Carotid Angioplasty and Stenting; CAVATAS: Carotid and Vertebral Artery Transluminal Angioplasty Study; CEA: Carotid Endarterectomy; CREST: Carotid Revascularization Endarterectomy vs Stenting Trial; EVA-3S: Endarterectomy vs Angioplasty in Patients with Symptomatic Severe Carotid Stenosis; ICSS: International Carotid Stenting Study; MI: myocardial infarction; SAPPHIRE: Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy; SPACE: Stent-protected Percutaneous Angioplasty of the Carotid vs Endarterectomy

tions in the CAS group. By contrast, disabling strokes in the two groups were identical and the rate of disabling stroke or death was not significantly different between groups. The balance of risk in favor of CEA caused by an excess of non-disabling stroke in the CAS group might be seen as partly offset by the fact that CEA was associated with more cranial nerve injuries and more severe hematomas than CAS. Fewer procedural myocardial infarctions, hematomas and cranial nerve paralyses were recorded after CAS (RR 0.02, 95% CI 0.00-0.16, p<0.0001). Taken together, the results of the CAVATAS, SAPPHIRE, SPACE and EVA-3S studies strongly suggest that CAS is as effective as CEA for the medium-term prevention of ipsilateral stroke, at least for the first 4 years after the procedure. However, none of these studies was powered to show equivalence between CAS and CEA with regard to medium-term prevention of ipsilateral stroke. More recently, the CREST trial enrolled 2522 participants across North America, representing the largest randomized clinical trial comparing the efficacy of CAS to CEA and assessing the effects of carotid revascularization in both symptomatic and asymptomatic patients with carotid artery stenosis. In this study there was no significant difference in the estimated 4-year rates of stroke, myocardial infarction, or death during the periprocedural period or ipsilateral stroke between CAS and CEA (**Table 1**). Patients randomized to CAS had more periprocedural strokes, but they had fewer myocardial infarctions compared with those receiving CEA. The incidence of major periprocedural strokes was low and not different between the two groups (0.9% vs. 0.6%; P = 0.52). Cranial nerve paralysis occurred in 0.3% of patients randomized to CAS and in 4.7% of those treated with CEA (HR 0.07, 95% CI 0.02-0.18; P = 0.0001). The rate of stroke or death among symptomatic patients after CAS (6.0%) was lower than the corresponding rate observed in the SPACE trial (6.8%, not including nonipsilateral stroke), the EVA-3S trial (9.6%), and ICSS (7.4%). The rate of stroke or death among symptomatic patients after CEA (3.2%) was also lower than the corresponding

percentage in SPACE (6.3%) and was similar to the corresponding percentage in EVA-3S (3.9%) as well as that in ICSS (3.4%).

The improved periprocedural outcomes in CREST as compared to previous trials may reflect the effective surgeon credentialing, assimilation of evolving endovascular technology, and rigorous training and credentialing of CAS operators [62]. These aspects are of crucial interest in determining the efficacy and safety of CAS: indeed, ESC guidelines describe the differences in CAS outcomes between centers and interventionists with low or high experience and number of cases, underlining thus the need for a great operator experience [20]. Moreover, it is worth considering that CAS technique and materials have been evolving rapidly in the last few years, also respect to CREST trial, and that outcomes analysis has been doubtless influenced by these improvements, suggesting that, in the next future, a further outcomes improvement could be obtained.

Recent large trials like CREST make it clear that with adequate training, physicians can perform CAS and CEA with low complication rates. Taken together with the results of previous trials, it appears that CAS is associated with a higher periprocedural risk of stroke or death. However, it should be considered that the aim of treatment for carotid stenosis is long-term prevention of stroke. The EVA-3S and SPACE trials showed little difference between CAS and CEA groups in the rates of ipsilateral non-perioperative stroke occurring more than 30 days after treatment, but the length of follow-up in these trials was restricted to a maximum of 4 years and 2 years, respectively. In particular, in the SPACE, at 2 years, the ipsilateral stroke rate was approximately 1% per year for CEA and CAS when periprocedural events were excluded. The clinical durability of CEA and CAS beyond 5 years cannot be clearly determined from available studies [55, 61]. CAVATAS had a longer follow-up period and reported a higher 8-year rate of non-perioperative stroke in patients who received endovascular treatment (21.1%) than in patients who received surgery (15.4%; HR 1.66, 95% CI 0.99-2.80). Most of the divergence occurred more than 2 years after randomization, which might be partly explained by a higher incidence of restenosis after endovascular treatment than after endarterectomy. However, CAVATAS included only a small proportion of patients treated by stent implantation, and the long-term rate of restenosis after this strategy remains uncertain. Follow-up is therefore continuing in ICSS and further data will become available from the current trials. In the CREST study, the rates of ipsilateral stroke during the follow-up period (2.0% with CAS and 2.4% with CEA) were similar to those in SPACE and EVA-3S, suggesting an excellent durability for up to 4 years. Hence, additional long-term data are needed before clear conclusions can be drawn regarding the relative risks and benefits of the 2 procedures [63]. Clinicians should also carefully consider the relation between patient age and outcomes of CAS and CEA. In most of these studies, an effect of age on differences between CAS and CEA was found, with younger patients having a slightly better outcome with CAS and older patients having a better outcome with CEA. The CAVATAS trial examined patients younger than 68 years and found no significant difference in the rate of stroke or perioperative death between the endovascular and surgery group. However, patients older than 68 years demonstrated a non-significant trend toward more adverse outcomes with endovascular therapy [64]. The EVA3-S trial reported excess risk associated with CAS in ≥ 70 years patients [61, 65]. Similarly, the SPACE trial demonstrated an odds ratio in favor of surgery in patients older than 75 years [66]. The CREST lead-in results demonstrated worse outcomes in patients 75 years of age and older. The 30-day rate of stroke and death in the CAS arm compared to the CEA arm was significantly higher in older subjects in both symptomatic (9.1% vs. 4.5%), as well as asymptomatic populations (7.5% vs. 2.4%). The odds ratio for advanced age and the primary endpoint of 30-day stroke, MI, and death was 2.38. Preliminary data from CREST demonstrated improved outcomes in patients younger than 69 years of age undergoing to CAS, while patients older than 70 years of age fared better with CEA [67]. Mechanisms underlying the increased risk with CAS in octogenarians probably include increased aortic arch complexity and calcification, greater vessel tortuosity and calcification [68, 69] and less cerebral reserve compared with a younger population. So that, even though the elderly patient certainly presents with increased risk to both surgical and endovascular interventions, at present, the data favor CEA in the octogenarian population.

Finally, controlateral carotid occlusion is a well-documented predictor for 30-day stroke or death in patients undergoing CEA [70]. Naggara *et al*. confirm that controlateral occlusion is not associated with an increase in risk of adverse events in CAS [71, 72], which is consistent with the fact that CAS requires shorter carotid occlusion than CEA. This result may help to identify a potential target population for CAS.

Conclusions

Recent results of large randomized clinical trials indicate that outcomes are improving for patients requiring treatment for carotid artery stenosis, either for interventional or medical treatment. While medical therapy alone is considered the gold standard for patients with asymptomatic stenosis of carotid artery, intervention confers an outcome benefit in symptomatic patients. In the last few years CAS has emerged as a valid alternative to CEA, which is still indicated as the best therapy. The results of randomized trials have not shown consistent outcome differences between CAS and CEA. CAS is associated with major periprocedural risks of stroke and death, while CEA is associated with increased incidence of myocardial infarction and cranial nerve paralysis. CAS may be superior to CEA in certain groups of patients, such as those exposed to previous neck surgery or radiation injury. When performed in conjunction with an embolic protection device, the risks associated with CAS may be lower than those associated with CEA in patients at elevated risk of surgical complications. The selection of patients for either CEA or CAS may require attention to age, with

patients younger than 60 years having a slightly better outcome with CAS, patients older than 70 years having a better outcome with CEA and those younger than 70 years having an equivalent or better aggregate outcome with CAS. Follow-up of ongoing clinical trials will provide new data regarding relative costs and benefits of CAS versus CEA, long-term restenosis rates and a better definition of subgroups that may benefit from specific interventions. However, the rapid evolution in CAS technique and materials suggests a great potential for CAS to improve outcomes and demonstrate superiority compared to CEA in the next future.

Riassunto

La stenosi aterosclerotica dei vasi carotidei è un noto fattore di rischio per lo sviluppo di ictus ischemico e la rivascolarizzazione si è dimostrata lo strumento migliore per la prevenzione, in particolare nei pazienti che presentano una sintomatologia derivante dalla stenosi. Per oltre 50 anni la strategia di rivascolarizzazione di prima scelta è stata l'endoarterectomia carotidea (CEA), ma negli ultimi anni il trattamento endovascolare mediante angioplastica ed impianto di stent (CAS) si è dimostrato una valida alternativa. Recentemente, sono emersi numerosi interessanti studi di confronto tra le due strategie terapeutiche. Il CAS sembra associato a maggior numero di ictus periprocedurali, ma con minori eventi avversi legati alla chirurgia e all'anestesia generale, e pertanto è stato inizialmente considerato la seconda scelta riservata a pazienti nei quali la chirurgia era controindicata. Tuttavia, studi clinici più recenti hanno rivelato che il CAS possa essere considerato un' efficace alternativa alla CEA. Inoltre, la rapida evoluzione delle tecniche e dei materiali utilizzati nel CAS suggerisce la possibilità che nel prossimo futuro esso possa dimostrare superiorità rispetto alla CEA. Scopo di tale revisione è approfondire lo stato dell'arte delle evidenze cliniche riguardanti il trattamento delle stenosi carotidee, con particolare attenzione alla terapia endovascolare.

Parole chiave: carotide, stenosi, CREST, CAS, CEA.

ABBREVIATIONS LIST

ACAS: Asymptomatic Carotid Atherosclerosis Study
ACST: Asymptomatic Carotid Surgery Trial
AHA: American Heart Association
CAPRIE: Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events
CAVATAS: Carotid and Vertebral Artery Transluminal Angioplasty Study
CAS: Carotid Artery Stenting
CEA: Carotid Endarterectomy
CHS: Cerebral Hyperperfusion Syndrome
CREST: Stenting versus Endarterectomy for Treatment of Carotid-Artery Stenosis
ECST: European Carotid Endarterectomy Surgery Trialist
EPD: Embolic Protection Device
ESC: European Society of Cardiology
EVA-3S: Endarterectomy versus Stenting in Patients with Symptomatic Severe Carotid Stenosis
HR: Hazard Risk;
ICSS: International Carotid Stenting Study
MI: Myocardial Infarction
NASCET: North American Symptomatic Carotid Endarterectomy Trial
RCT: Randomized Controlledlinical Trial
SAPPHIRE: Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy
SPACE: Stent-Protected Angioplasty versus Carotid Endarterectomy
TIA: Transient Ischemic Attack
VACS: Veterans Affairs Cooperative Study

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