GENERAL REVIEW

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Carotid surgery today: an update after 14,000 carotid endarterectomy procedures

Karotidna hirurgija danas: novine nakon 14 000 karotidnih endarterektomija

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Ključne reči:
aa. carotis; aa. carotis, bolesti; endarterektomija a. carotis; hirurgija, vaskularna, procedure; angioplastika, balonska; anestezija, lokalna; antiagregaciona sredstva; lečenje, ishod.

Introduction

Atherosclerotic lesions of the extracranial part of carotid arteries are one of the most common causes of stroke. The relationship between carotid artery occlusive disease and neurologic function has been recognized for more than, 2000 years. According to Rufus of Ephesus (about 100 AD), the term carotid was derived from the Greek word κάρος (karos), meaning "to stun, to fall into deep sleep". The reason for naming the artery was that compressing it causes the loss of consciousness – "deep sleep" [1].

Hippocrates "apoplexy" in 400 BC was the first written trace of human attempt to portray conditions that we know today as transient ischemic attack (TIA) or reversible ischemic neurologic deficit [1]. Awareness of carotid arteries disease and surgical attempts to repair them led to the first successful carotid endarterectomy (CEA), performed by Michael DeBakey in 1953 [2].

Since then, carotid surgery has developed a lot, so today we have various techniques to detect and treat diseased carotid arteries [1].

Diagnostic improvement

Preoperative imaging plays irreplaceable role in successful treatment of not just carotid arteries, but any organ, as well.

Carotid duplex scan (CDS) represents the first line in the diagnostics of carotid disease. This technology, which combines the acquisition of anatomic and blood flow information, was developed in the 1970s [3]. Commercial duplex scanners became available by the 1980s, and the clinical use of CDS rapidly expanded in the past twenty years [4]. Modern CDS systems provided high-resolution B-mode ultrasound imaging of tissue and vessel anatomy, including 3D vessel reconstruction and evaluation of atherosclerotic plaque morphology, with detailed assessment of blood flow characteristics [4].

CDS is noninvasive and cost-effective and thus suitable for serial examination because it also reveals natural history of disease, including progression, regression, and response to intervention. In many patients, duplex testing can establish the definitive diagnosis the basis on which CEA or angioplasty can be performed [4]. However, the reliability of CDS depends on the expertise of the examiner and the interpreting physician.

When introduced in 1971, computed tomography (CT) scan brought a great improvement in the diagnostics [5]. Technological development led to the invention of 4-slice in 1998 and 16-slice multidetector CT (MDCT) scanner in 2002 [5, 6]. Later, the 256-slice MDCT provided ability to generate ''real time'' 3D images (Figure 1), for about the same amount of radiation as previous MDCT scanners [5]. Also, increasing use of MDCT angiography provided better visualization of the cerebral arteries, leading to an unexpected more frequent detection of unruptured intracranial aneurysms (UIAs) [7].

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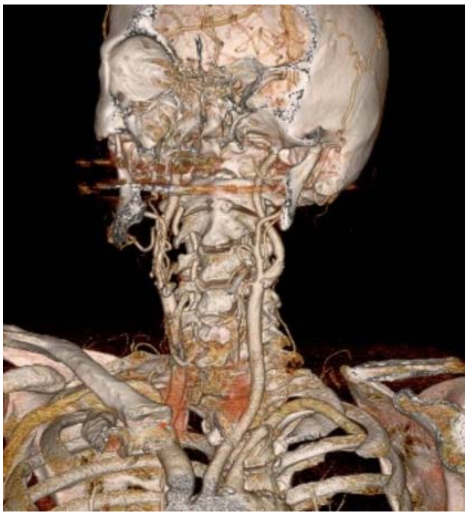

Fig. 1 – 3D model of the carotid arteries.

Dual source MDCT scanners, developed in 2006, could precisely evaluate plaque distribution in the arteries, as well as they could make difference between calcified and lipid-rich plaques (Figure 2), which is of great importance in preoperative planning [5, 8, 9].

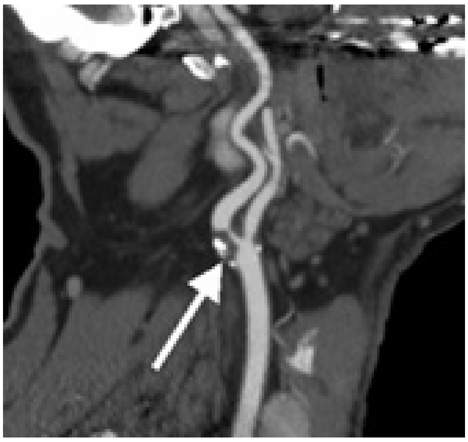

Fig. 2 – Calcified and lipid rich component of atherosclerotic plaque.

Because scanning with MDCT is done quickly, less contrast material can be administered at a faster rate, improving visibility of arteries [5, 6]. Rapid patient throughput reduces breath-holding time and received amount of radiation, which provides greater comfort for patients [5, 6]. It also raises department productivity and saves money [6].

Apart from the hardware type of a scanner, post-processing software and image management tools continue to evolve and warrants upgrade in a timely fashion.

The future of CT imaging lies in the fusion imaging technique. As a technology which enables synthesis of two dependent imaging modalities, it provides image with greater information. Positron emission tomography (PET)-CT fusion is the most relevant in the current clinical practice [5].

Eversion carotid endarterectomy

Although first described by DeBakey in 1959 [10], the modern technique of eversion CEA (ECEA) was introduced in the early 1970s [11]. However, its use became more popular about twenty years later [12]. At the end of the 20th and the beginning of the 21st century, surgeons worldwide began to report better outcomes following ECEA compared to the conventional technique (Table 1).

The majority of studies showed lower incidence of early postoperative death and neurological complications (seven days after surgery) [1–14, 16–25] in group treated with eversion technique. Also, incidence of late restenosis (follow-up period 36.4 ± 15.8 months [24]) was much lower in patients treated with ECEA versus conventional CEA (Table 2).

In addition, Gao et al. [28] documented surprisingly lower incidence of postoperative microembolic events in ECEA, compared to the standard endarterectomy.

One of the world's largest single-center series of ECEA, by Radak et al. [12], compared outcomes in patients operated on between 1991 and 1997 with those operated on in 1998–2004 period of time. The total mortality and morbidity rates and early postoperative complications were lower in the latter group. The clamping time was shorter, as well as was duration of hospital stay. At follow-up, rate of restenosis > 50% did not differ between the groups, but the incidence of < 50% restenosis was higher in the earlier group.

Improved surgical skills, shorter clamping time and better medication therapy led to preferable outcomes in patients operated on between 1998 and 2004 [12, 25].

As a technique, ECEA offers lower restenosis rates and

Table 1

Early death rates following conventional and eversion carotid endarterectomy

The author and the year	Patients (n)		Early death (%)	
	CCEA	ECEA	CCEA	ECEA
Darling et al. 1996 [13]	353	449	2.0	1.1
Entz et al. 1997 [14]	715	793	1.8	0.5
Cao et al. 1997 [15]	240	274	1.2	0.7
Cao et al. 1998 [16]	675	678	1.3	1.3
Shah et al. 1998 [17]	410	1,575	2.2	1.0
Ballotta et al. 1999 [18]	167	169	2.9	0.0
Peiper et al. 1999 [19]	388	475	1.5	1.1
Radak et al. 2000 [20]	682	2,124	1.3	0.5
Katras et al. 2001 [21]	204	118	1.3 + 2.8	0.8
Littooy et al. 2004 [22]	125	64	0.8	0.0
Marković et al. 2006 [23]	98	101	3.1	1.0

CCEA – conventional carotid endarterectomy; ECEA – eversion carotid endarterectomy.

Table 2

Long-term restenosis rates following carotid endarterectomy

Author and year	Patients (n)		Late restenosis (%)	
	CCEA	ECEA	CCEA	ECEA
Cao et al. 1997 [15]	240	274	6.9	2.2
Cao et al. 1998 [16]	675	678	4.1	2.4
Shah et al. 1998 [17]	410	1,575	1.1	0.3
Ballotta et al. 1999 [18]	167	169	1.2	0.0
Peiper et al. 1999 [19]	388	475	10.2	2.5
Radak et al. 2000 [20]	682	2,124	1.8	0.5
Cao et al. 2000 [26]	/	/	9.2	3.6
Katras et al. 2001 [21]	204	118	6.5	1.7
Littooy et al. 2004 [22]	125	64	4.9	3.1
Ballotta et al. 2004 [27]	302	848	0.6	0.5
Marković et al. 2006 [23]	98	101	6.1	0.0

CCEA – conventional carotid endarterectomy; ECEA – eversion carotid endarterectomy.

greater technical ease of performance [16, 25]. Also, ECEA has been identified as an independent factor contributing to a better outcome following surgery [29].

Still, there are certain relative contraindications to ECEA: restenosis after previous CEA, carotid stenosis due to radiation, ipsilateral surgical intervention in the past and lesions above second cervical vertebra [24, 30–33]. Therefore, alternative techniques have evolved.

Carotid artery stenting

The endovascular era began, by seeking less invasive alternative to open surgery. First successful results of percutaneous transluminal angioplasty (PTA) of carotid arteries were reported by Matthias [34] in 1977 and Kerber et al. [35] in 1980. Balloon-expandable stents were first deployed in 1989, with improving of stent material and technique over years [36].

Despite the early enthusiasm, the high likelihood of embolic stroke during carotid artery stenting (CAS) remained a major concern. The development of embolic protection devices (EPDs) in the 1990s has lowered the incidence of microembolization and consequent neurologic deficit [24, 36–38].

From the beginning of the modern endovascular period, the procedure has been largely scrutinized. Four main innovations led to dissemination of CAS technique after 2000: routine use of stenting; routine use of EPDs; introduction of new stent materials for carotid endovascular procedures and new antiplatelet drugs [36].

However, the question of CAS as an "equivalent" therapeutic option to CEA still remained. Five large randomized clinical trials were conducted seeking for answers to this dilemma (Table 3).

Except stent protected angioplasty *vs* carotid endarterectomy (SPACE) and international carotid stenting study (ICSS) (27% and 72%, respectively), in other trials EPDs were used in > 90% of cases. Asymptomatic patients were enrolled in carotid revascularization endorterectomy *vs* stenting trial (CREST) and stenting and angioplasty unith protection in patients at high risk for endarterectomy (SAPPHIRE) trial.

The results implied to a higher perioperative stroke risk with CAS compared with CEA when it is performed in unselected patients with symptomatic or asymptomatic carotid stenosis. The association between older age and increased risk of adverse events after CAS, was reported in CREST, ICSS and SPACE trial [43–47]. The low absolute risk of recurrent stroke in CREST suggests that both CAS and CEA are clinically durable [47].

Table 3

Trials investigating outcomes of carotid artery stenting (CAS) compared to carotid endarterectomy (CEA)

Trial and year	n	Primary endpoint	Follow-up period	Results (%)	
				CAS	CEA
SAPPHIRE [39, 40] 2004, 2008	334	30-day stroke, MI, death + 1-y ipsilateral stroke, death	1-y	12.2	20.1
EVA-3S [41, 42] 2006, 2008	527	30-day stroke, death 4-y ipsilateral stroke + death	30-day 4-y	9.6 11.1	3.9 6.2
SPACE [43–45] 2006, 2008	1,196	30-day ipsilateral stroke, death 2-y ipsilateral stroke + death	30-day 2-y	6.9 9.5	6.5 8.8
ICSS [46] 2010	1,713	120-day stroke, MI, death	120-day	8.5	5.2
CREST [47] 2010	2,502	30-day stroke, MI, death 4-y ipsilateral stroke	30-day 4-y	5.2 7.2	4.5 6.8

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, n – number of patients; SAPPHIRE – stenting and angioplasty with protection in patients at high risk for endarterectomy; SPACE – stent-protected angioplasty *vs* carotid endarterectomy; y – year.

The risk of periprocedural myocardial infarction after CAS was reported with rates about half as those of CEA: 1.1% *vs* 2.3% in CREST, 0.4% *vs* 0.6% in ICSS and 0.4% *vs* 0.8% in endarterectomy *vs* angioplasty in patients with symptomatic carotid stenosis (EVA-3S) trial [41, 46, 47].

CAS should not be considered as an therapeutic option in patients with severe peripheral artery stenosis, aortic arch anomalies, carotid artery kinking/coiling and aneurysm, preocclusive lesions of the internal carotid artery (ICA), carotid stenosis longer than 2 cm, calcified, ulcerated or highly vulnerable carotid plaque and chronic renal insufficiency [24]. In such cases, open surgery remains the gold standard.

Currently, data suggest that with a careful patient and operator selection and improved technology, CAS may be considered as an alternative to CEA [36, 39–47].

Hybrid procedures

Significant atherosclerotic lesions involving carotid bifurcation and the proximal ipsilateral common carotid artery (CCA) or the innominate artery (IA) are uncommon, with the reported incidence of approximately 4.8% [48]. However, their treatment remains a great challenge. Standard CEA exposure does not allow repair of the proximal IA or CCA; it could be approached through a median sternotomy, occasionally requiring cardiopulmonary bypass [49]. On the other side, the access to skull base-level ICA stenosis mandates mandibular subluxation [50]. These procedures are associated with a prolonged operative time, increased blood loss and increased morbidity/mortality incidence [51].

In 1996, Diethrich et al. [52] described a new, hybrid technique for simultaneous treatment of carotid bifurcation and proximal lesions. This procedure consisted of surgical exposure of carotid bifurcation, retrograde stenting of the proximal CCA or IA lesions, followed by CEA.

A meta-analysis by Sfyroeras et al. [53] reported a 30-day periprocedural stroke and mortality rates of 1.5% and 0.7%, respectively. During follow-up, the incidence of restenosis in patients treated with stenting was 3.7% *vs* 14% in patients that received simple balloon angioplasty, further signalizing that proximal lesions should be solved with stent implantation. In order to assure better outcomes in patients that did not receive antiplatelet therapy, an increased dose of clopidogrel (450 mg) should be delivered immediately before the intervention [54]. Comparing mortality rates of hybrid procedures and open surgical approach (0.7% *vs* 0.5%−18.7%), stands clear that the hybrid technique made significant breakthrough in treatment of simultaneous lesions [53].

The results of hybrid procedures label that CEA and CAS should not be considered as competitive, but complementary techniques.

Local anesthesia

CEA can be performed using general anesthesia (GA) and/or local anesthesia (LA). LA comprises deep and superficial cervical block. Cervical block anesthesia (CBA) has evolved over the last 15 years with new techniques, novel methods of locating the cervical plexus and new drugs [55–57].

Using CBA, neurological function is easily assessed during carotid crossclamping, with predictable haemodynamic control. In patients with significant cardiopulmonary comorbidities or in which GA is contraindicated, LA represents a safe and effective option. Disadvantages of LA include risk of seizure or allergic reaction, discomfort for some patients and anxiety for the operating surgeon [58].

The general anaesthesia *vs* local anesthesia for carotid surgery (GALA) trial was designed to compare outcomes in patients operated on under GA or LA. The results showed no significant difference in the incidence of stroke, myocardial infarction or death at a 30-day follow up. Adverse cardiovascular events were reported in 4.8% of patients who underwent CEA under GA and 4.5% of patients who underwent CEA under LA. Also, there was no difference in hospital length of stay between the groups [59].

Since the GALA trial, several other studies have also reported subtle differences between GA and LA [55]. Referring to the results of these reports, we can say that the efficacy of vascular team looking after the patient is more important than the choice of anesthetic technique itself. Since no data showed predominance of GA or LA, selection of suitable anesthetic method remains to be discussed between the patient, his surgeon and anesthesiologist.

Best medical treatment

The invention of new, potent drugs, led to an idea of creating a novel therapeutic modality for carotid arteries disease, named the best medical treatment (BMT).

One of the most significant improvements has been the aggressive use of antiplatelet therapy, and early studies reported up to 25% reduction in overall stroke rates among patients undergoing CEA [58].

When clopidogrel bisulfate was approved by the Food and Drug Administration (FDA) in 1998 [60], a new chapter in antiplatelet therapy has been opened.

Addition of a single 75 mg dose of clopidogrel to a regular 75 mg dose of acetylsalicylic acid (ASA), administered the night before CEA, was associated with a significant reduction in postoperative neurological events, without any increase in hemorrhagic complications [61]. A study of Sharpe et al. [62] showed a lower incidence of postoperative microembolisation in patients receiving dual therapy, compared to patients receiving only ASA. Also, the need of adjuvant dextran therapy was reduced.

The utility of dual antiplatelet therapy use after CAS has been observed in the management of atherothrombosis with clopidogrel in high risk patients (MATCH) with recent transient ischemic attack or ischemic stroke and the clopidogrel for high atherothrombotic risk and ischemic stabilization, management and avoidance (CHARISMA) trials [63–65]. The benefit of combination therapy was found to be significant in patients with symptomatic carotid disease; conversely, the related risk of bleeding obviated the benefits of treatment in patients with low risk of postprocedural neurologic complications [64, 65]. A recent study showed that the use of ASA and clopidogrel 4−6 weeks after CAS is sufficient to decrease the risk of ischemic stroke, composite vascular events or death [66].

Apart from antiplatelet agents, lipid lowering drugs have significant role in prevention of major cardiovascular events. Since lovastatin had been commercialized in September 1987, 6 statins, including 2 semi-synthetic statins (simvastatin, pravastatin) and 4 synthetic statins (fluvastatin, atorvastatin, rosuvastatin, pitavastatin) have been introduced [67–69]. Statins have both lipid-lowering and anti-inflammatory effects, and have been shown to reduce risk of neurologic events in symptomatic patients and in patients after CEA or CAS [70–72]. Furthermore, it appears that the stroke prevention benefits of statins are related to their pleiotropic effects rather than their cholesterol lowering effects [58].

Numerous trials and meta-analyses since the mid-1990s, revealed a strong correlation of statin use and reduced stroke risk [58, 73–75]. In a recent series of 1,566 patients who underwent CEA, at a 30-day follow-up, statins were found to be associated with a reduced incidence of death (0.3% *vs* 2.1%), stroke (1.2% *vs* 4.5%) and TIA (1.5% *vs* 3.6%). A fivefold lower risk of death and a threefold lower risk of stroke was found in statin users group [76]. In a single-center experience, the incidence of cardiovascular events after CAS was 4% in statin users *vs* 15% in nonusers [77]. Another large series showed 1.5% *vs* 4% 30-day stroke/death rates for users and non-users [72].

In addition, according to multi-center experience, dual antiplatelet therapy and statins with angiotensin-converting enzyme (ACE) inhibitor or beta blocker after CEA or CAS, resulted in a lower incidence of restenosis and adverse postoperative effects (Table 4) [12, 36, 58, 76,78].

Recently, there has been an increasing argument to favor BMT as stand-alone treatment in all neurologically asymptomatic individuals, regardless of the degree of carotid stenosis [78]. This argument deserved serious critical analysis, because the majority of carotid interventions currently performed are in asymptomatic patients. In an effort to address the question of BMT in patients with confirmed carotid disease, Abbott et al. [79] performed meta-analyses of 11 trials that included 3724 patients with ≥ 50% carotid stenosis. Comparing their results with the results from endarterectomy for asymptomatic carotid artery stenosis (ACAS) trial, they determined that the contemporary risk of ipsilateral stroke and/or TIA did not differ, and possibly were better than the results reported for ACAS in 1995.

The latest data, which provides the most contemporary comparison of BMT alone to BMT plus CEA or CAS, indicate that CEA followed by medical therapy represents the best modality in reduction of cardiovascular events.

Table 4

Effect of best medical therapy and risk factors reduction on major adverse cardiovascular events (MACEs)

Treatment	Comment	Outcome
Antiplatelet therapy	Single or dual therapy	Reduces both stroke rate and overall MACEs
Antihypertensive therapy	Decrease BP by 10 mm Hg systolic/5 mm Hg diastolic or to 120/80 mm Hg. Treat all patients regardless of baseline BP.	Reduces stroke recurrence and restenosis rates
Lipid lowering therapy	Reduce LDL by 50% or < 70 mg/dL. Treat hyperlipidemia and normolipemic patients with history of stroke.	May be beneficial if applied prior to CEA/CAS
Smoking cessation	Total abstinence	Reduces stroke and MACEs rates
Alcohol consumption	Avoid excessive consumption	Reduces overall MACEs rates

BP – blood pressure; CAS – carotid artery stenting; CEA – carotid endarterectomy; LDL – low density lipoprotein.

Conclusion

Overviewing the last 20 years, we stepped forward in understanding, diagnosing and treating carotid arteries disease. More sophisticated preoperative imaging, improved surgical skills, development of new stent materials and techniques and new medication therapy led to better outcome following carotid arteries treatment. Yet, there is a long way to go in order to reduce incidence of peri- and postoperative adverse effects, especially in high risk patients and the elderly population. The saga continues...

R E F E R E N C E S

1. *Popov P, Jocić D, Babić S, Tanasković S, Jovanović P, Nenezić D*, et al. Historical overview of carotid artery surgical treatment. Srp Arh Celok Lek 2008; 136(5−6): 324−30. (Serbian)
2. *Robertson JT*. Carotid endarterectomy: a saga of clinical science, personalities, and evolving technology: the Willis lecture. Stroke 1998; 29(11): 2435−41.
3. *Brott TG, Halperin JL, Abbara S, Bacharach JM, Barr JD, Bush RL*, et al. . ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS guideline on the management of patients with extracranial carotid and vertebral artery disease: executive summary. A report of the American College of

Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American Stroke Association, American Association of Neuroscience Nurses, American Association of Neurological Surgeons, American College of Radiology, American Society of Neuroradiology, Congress of Neurological Surgeons, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of NeuroInterventional Surgery, Society for Vascular Medicine, and Society for Vascular Surgery. Circulation 2011; 124(4): 489−32.

4. *Cronenwett JL, Johnston KW*. Rutherford's vascular surgery. Chapter 16. 8th ed. Philadelphia, PA: Elsevier Saunders; 2014.
5. *Ghonge NP*. Computed tomography in the 21st century: current status & future prospects. JIMSA 2013; 26(1): 35−42.
6. MDCT: A Disruptive Technology Evolve. Available from: swww.axisimagingnews.com/2004/10/mdct-a-disruptive-technology-evolves/ [published 2004 October 8].
7. *Radak D, Sotirovic V, Tanaskovic S, Isenovic ER*. Intracranial aneurysms in patients with carotid disease: not so rare as we think. Angiology 2014; 65(1): 12−6.
8. *Tanasković S, Babić S, Aleksić N, Matić P, Gajin P, Jocić D*, et al. Is It Possible That This Patient is Asymptomatic? The Role of Multidetector CT Angiography in Detection of Ulcerated Plaques in Patients with Asymptomatic Carotid Stenosis: Case Report. Srp Arh Celok Lek 2015; 143(9−10): 615−8.
9. *Nenezić D, Tanasković S, Gajin P, Ilijevski N, Vucurević G*. Diagnostic dilemmas of multislice CT angiography in the evaluation of the degree of common carotid artery stenosis. Srp Arh Celok Lek 2010; 138(7−8): 494−7. (Serbian)
10. *De Bakey ME, Crawford ES, Cooley DA, Morris GCJr*. Surgical considerations of occlusive disease of innominate, carotid, subclavian, and vertebral arteries. Ann Surg 1959; 149(5): 690−710.
11. *Darling RC 3rd, Mehta M, Roddy SP, Paty PS, Kreienberg PB, Ozsvath KJ*, et al.. Eversion carotid endarterectomy: a technical alternative that may obviate patch closure in women. Cardiovasc Surg 2003; 11(5): 347−52.
12. *Radak DJ, Ilijevski NS, Nenezic D, Popov P, Vucurevic G, Gajin P*, et al. Temporal trends in eversion carotid endarterectomy for carotid atherosclerosis: single-center experience with 5,034 patients. Vascular 2007; 15(4): 205−10.
13. *Darling RC 3rd, Paty PS, Shah DM, Chang BB, Leather RP*. Eversion endarterectomy of the internal carotid artery: technique and results in 449 procedures. Surgery 1996; 120(4): 635−9; discussion 639−40.
14. *Entz L, Jaranyi Z, Nemes A*. Comparison of perioperative results obtained with carotid eversion endarterectomy and with conventional patch plasty. Cardiovasc Surg 1997; 5(1): 16−20.
15. *Cao P, Giordano G, De Rango P, Caporali S, Lenti M, Ricci S*, et al. Eversion versus conventional carotid endarterectomy: a prospective study. Eur J Vasc Endovasc Surg 1997; 14(2): 96−104.
16. *Cao P, Giordano G, De Rango P, Zannetti S, Chiesa R, Coppi G*, et al. A randomized study on eversion versus standard carotid endarterectomy: study design and preliminary results: the Everest Trial. J Vasc Surg 1998; 27(4): 595−605.
17. *Shah DM, Darling RC 3rd, Chang BB, Paty PS, Kreienberg PB, Lloyd WE*, et al. Carotid endarterectomy by eversion technique: its safety and durability. Ann Surg 1998; 228(4): 471−8.
18. *Ballotta E, Da Giau G, Saladini M, Abbruzzese E, Renon L, Toniato A*. Carotid endarterectomy with patch closure versus carotid eversion endarterectomy and reimplantation: A prospective randomized study. Surgery 1999; 125(3): 271−9.
19. *Peiper C, Nowack J, Ktenidis K, Reifenhauser W, Keresztury G, Horsch S*. Eversion endarterectomy versus open thromboendarterectomy and patch plasty for the treatment of internal carotid artery stenosis. Eur J Vasc Endovasc Surg 1999; 18(4): 339−43.
20. *Radak D, Radević B, Sternić N, Vucurević G, Petrović B, Ilijevski N*, et al. Single center experience on eversion versus standard carotid endarterectomy: a prospective non-randomized study. Cardiovasc Surg 2000; 8(6): 422−8.
21. *Katras T, Baltazar U, Rush DS, Sutterfield WC, Harvill LM, Straton PE Jr*. Durability of eversion carotid endarterectomy: comparison with primary closure and carotid patch angioplasty. J Vasc Surg 2001; 34(3): 453−8.
22. *Littooy FN, Gagovic V, Sandu C, Mansour A, Kang S, Greisler HP*. Comparison of standard carotid endarterectomy with Dacron patch angioplasty versus eversion carotid endarterectomy during a 4-year period. Am Surg 2004; 70(2): 181−5; discussion 185.
23. *Marković D*. Comparative analysis of conventional and eversion endarterectomy in the treatment of stenosis – occlusive disease of the carotid arteries [dissertation]. Belgrade: Faculty of Medicine, University of Belgrade; 2006. (Serbian)
24. *Radak D, Davidović L*. Why carotid endarterectomy is method of choice in treatment of carotid stenosis. Srp Arh Celok Lek 2008; 136(3−4): 181−6. (Serbian)
25. *Radak D, Tanasković S, Matić P, Babić S, Aleksić N, Ilijevski N*. Eversion carotid endarterectomy--our experience after 20 years of carotid surgery and 9897 carotid endarterectomy procedures. Ann Vasc Surg 2012; 26(7): 924−8.
26. *Cao P, Giordano G, De Rango P, Zannetti S, Chiesa R, Coppi G*, et al. Eversion versus conventional carotid endarterectomy: late results of a prospective multicenter randomized trial. J Vasc Surg 2000; 31(1 Pt 1): 19−30.
27. *Ballotta E, DaGian G, Piccoli A, Baracchini C*. Durability of carotid endarterectomy for treatment of symptomatic stenosis. J Vasc Surg 2004; 40(2): 270−8.
28. *Gao MY, Sillesen HH, Lorentzen JE, Schroeder TV*. Eversion carotid endarterectomy generates fewer microemboli than standard carotid endarterectomy. Eur J Vasc Endovasc Surg 2000; 20(2): 153−7.
29. *Shah DM, Darling RC 3rd, Chang BB, Paty PS, Kreienberg PB, Roddy SP*, et al. Analysis of factors contributing to improved outcome for carotid endarterectomy. Semin Vasc Surg 2004; 17(3): 257−9.
30. *Radak D, Tanasković S, Vukotić M, Babić S, Aleksić N, Kolar J*, et al. Surgical treatment of internal carotid artery restenosis following eversion endarterectomy. Srp Arh Celok Lek 2012; 140(9−10): 577−82. (Serbian)
31. *Sagić DZ, Antonić ZD, Petrović BB, Duvnjak SN, Perić MS, Masulović DM*, et al. Endovascular and surgical management of carotid artery restenosis. Acta Chir Iugosl 2007; 54(3): 43−6. (Serbian)
32. *Radak D, Tanaskovic S, Sagic D, Antonic Z, Babic S, Popov P*, et al. Carotid angioplasty and stenting is safe and effective for treatment of recurrent stenosis after eversion endarterectomy. J Vasc Surg 2014; 60(3): 645−51.
33. *Sagić D, Kecmanović V, Vidaković R, Kovacević V, Antonić Z, Stanisić M*, et al. Percutaneous transluminal angioplasty of radiotherapy induced carotid stenosis -case report. Acta Chir Iugosl 2009; 56(4): 47−9. (Serbian)
34. *Mathias K*. A new catheter system for percutaneous transluminal angioplasty (PTA) of carotid artery stenoses. Fortschr Med 1977; 95(15): 1007−11. (German)
35. *Kerber CW, Cromwell LD, Loehden OL*. Catheter dilatation of proximal carotid stenosis during distal bifurcation endarterectomy. AJNR Am J Neuroradiol 1980; 1(4): 348−9.
36. *Cronenwett JL, Johnston KW*. Rutherford's vascular surgery. Chapter 101. 8th ed. Philadelphia, PA: Elsevier Saunders; 2014.
37. *Kastrup A, Gröschel K, Krapf H, Brehm BR, Dichgans J, Schulz JB*. Early outcome of carotid angioplasty and stenting with and

without cerebral protection devices: a systematic review of the literature. Stroke 2003; 34(3): 813−9.

38. *Sagić D, Antonić ZD, Perić MS, Duvnjak SN, Petrović BB, Ilijevski NM*, et al. Air embolism during carotid dilatation with a stent. Acta Chir Iugosl 2007; 54(3): 59−61. (Serbian)
39. *Yadav JS, Wholey MH, Kuntz RE, Fayad P, Katzen BT, Mishkel GJ*, et al. Protected carotid-artery stenting versus endarterectomy in high-risk patients. N Engl J Med 2004; 351(15): 1493−501.
40. *Gurm HS, Yadav JS, Fayad P, Katzen BT, Mishkel GJ, Bajwa TK*, et al. Long-term results of carotid stenting versus endarterectomy in high-risk patients. N Engl J Med 2008; 358(15): 1572−9.
41. *Mas JL, Chatellier G, Beyssen B, Branchereau A, Moulin T, Becquemin JP,* et al. Endarterectomy versus stenting in patients with symptomatic severe carotid stenosis. N Engl J Med 2006; 355(16): 1660−71.
42. *Mas JL, Trinquart L, Leys D, Albucher JF, Rousseau H, Viguier A*, et al. Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trial: results up to 4 years from a randomised, multicentre trial. Lancet Neurol 2008; 7(10): 885−92.
43. SPACE Collaborative Group, *Ringleb PA, Allenberg J, Brückmann H, Eckstein HH, Fraedrich G, Hartmann M,* et al. 30 day results from the SPACE trial of stent-protected angioplasty versus carotid endarterectomy in symptomatic patients: a randomised non-inferiority trial. Lancet 2006; 368(9543): 1239−47.
44. *Stingele R, Berger J, Alfke K, Eckstein HH, Fraedrich G, Allenberg J*, et al. Clinical and angiographic risk factors for stroke and death within 30 days after carotid endarterectomy and stent-protected angioplasty: a subanalysis of the SPACE study. Lancet Neurol 2008; 7(3): 216−22.
45. *Eckstein HH, Ringleb P, Allenberg JR, Berger J, Fraedrich G, Hacke W,* et al. Results of the Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) study to treat symptomatic stenoses at 2 years: a multinational, prospective, randomised trial. Lancet Neurol 2008; 7(10):893−902.
46. International Carotid Stenting Study investigators, *Ederle J, Dobson J, Featherstone RL, Bonati LH, van der Worp HB, de Borst GJ*, et al. Carotid artery stenting compared with endarterectomy in patients with symptomatic carotid stenosis (International Carotid Stenting Study): an interim analysis of a randomised controlled trial. Lancet 2010; 375(9719): 985−97.
47. *Brott TG, Hobson RW 2nd, Howard G, Roubin GS, Clark WM, Brooks W,* et al. Stenting versus endarterectomy for treatment of carotid-artery stenosis. N Engl J Med 2010; 363(1): 11−23.
48. *Akers DL, Markowitz IA, Kerstein MD*. The value of aortic arch studyin the evaluation of cerebrovascular insufficiency. Am J Surg 1987;154(2): 230−2.
49. *Makhdoomi KR, McBride M, Brittenden J, Bradbury AW, Ruckley CV*. A prospective study of internal carotid artery plication during carotid endarterectomy: early clinical and duplex outcome. Eur J Vasc Endovasc Surg 1999; 18(5): 391−4.
50. *Fisher DF Jr, Clagett GP, Parker JI, Fry RE, Poor MR, Finn RA*, et al. Mandibular subluxation for high carotid exposure. J Vasc Surg 1984; 1(6): 727−33.
51. *Rakhlin EY, Fairman RM, Carpenter JP, Wang GJ, Jackson BM, Woo EY*. Hybrid Procedures in the Treatment of Carotid Stenosis: A feasible technique applied to complex carotid plaque and anatomy. Endovasc Today 2008; 7(8): 38−40.
52. *Diethrich EB, Marx P, Wrasper R, Reid D*B. Percutaneous techniques for endoluminal carotid interventions. J Endovasc Surg 1996; 3(2): 182−202.
53. *Sfyroeras GS, Karathanos C, Antoniou GA, Saleptsis V, Giannoukas AD*. A meta-analysis of combined endarterectomy and proximal balloon angioplasty for tandem disease of the arch vessels and carotid bifurcation. J Vasc Surg 2011; 54(2): 534−40.
54. *Bazan H, Sheahan M, Dardik A*. Carotid endarterectomy with simultaneous retrograde common carotid artery stenting: technical considerations. Catheter Cardiovasc Interv 2008; 72(7): 1003−7.
55. *Stoneham MD, Stamou D, Mason J*. Regional anaesthesia for carotid endarterectomy. Br J Anaesth 2015; 114(3): 372−83.
56. *Jovic M, Unic-Stojanovic D, Isenovic E, Manfredi R, Cekic O, Ilijevski N,* et al. Anesthetics and cerebral protection in patients undergoing carotid endarterectomy. J Cardiothorac Vasc Anesth 2015; 29(1): 178−84.
57. *Ilijevski N, Krivokapić B, Smiljanić B, Nenezić D, Popov P, Sagić D*, et al. Carotid endarterectomy in cervical block anesthesia in patients with occluded contralateral internal carotid artery. Srp Arh Celok Lek 2006; 134(3−4): 122−8. (Serbian)
58. *Cronenwett JL, Johnston KW*. Rutherford's vascular surgery. Chapter 100. 8th ed. Philadelphia, PA: Elsevier Saunders; 2014.
59. GALA Trial Collaborative Group; *Lewis SC, Warlow CP, Bodenham AR, Colam B, Rothwell PM, Torgerson D,* et al. General anaesthesia versus local anaesthesia for carotid surgery (GALA): a multicentre, randomised controlled trial. Lancet 2008; 372(9656): 2132−42.
60. Drug Approval Package. Available from: www.accessdata.fda.gov/drugsatfda_docs/nda/97/020839_plavix_toc.cfm
61. *Payne DA, Jones CI, Hayes PD, Thompson MM, London NJ, Bell PR*, et al. Beneficial effects of clopidogrel combined with aspirin in reducing cerebral emboli in patients undergoing carotid endarterectomy. Circulation 2004; 109(12): 1476−81.
62. *Sharpe RY, Dennis MJ, Nasim A, McCarthy MJ, Sayers RD, London NJ,* et al. Dual antiplatelet therapy prior to carotid endarterectomy reduces post-operative embolisation and thromboembolic events: post-operative transcranial Doppler monitoring is now unnecessary. Eur J Vasc Endovasc Surg 2010; 40(2): 162−7.
63. *Diener HC, Bogousslavsky J, Brass LM, Cimminiello C, Csiba L, Kaste M*, et al. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. Lancet 2004; 364(9431): 331−7.
64. *Bhatt DL, Fox KA, Hacke W, Berger PB, Black HR, Boden WE*, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. N Engl J Med 2006; 354(16): 1706−17.
65. *Wang TH, Bhatt DL, Fox KA, Steinhubl SR, Brennan DM, Hacke W*, et al. An analysis of mortality rates with dual-antiplatelet therapy in the primary prevention population of the CHARISMA trial. Eur Heart J 2007; 28(18): 2200−7.
66. *Jhang KM, Huang JY, Nfor ON, Jian ZH, Tung YC, Ku WY*, et al. Is Extended Duration of Dual Antiplatelet Therapy After Carotid Stenting Beneficial? Medicine (Baltimore) 2015; 94(40): e1355.
67. *Endo A*. A historical perspective on the discovery of statins. Proc Jpn Acad Ser B Phys Biol Sci 2010; 86(5): 484−93.
68. *Endo A*. The discovery and development of HMG-CoA reductase inhibitors. J Lipid Res 1992; 33(11): 1569−82.
69. *Endo A*. A gift from nature: the birth of the statins. Nat Med 2008; 14(10): 1050−2.
70. *Amarenco P, Goldstein LB, Szarek M, Sillesen H, Rudolph AE, Callahan A 3rd,* et al. Effects of intense low-density lipoprotein cholesterol reduction in patients with stroke or transient ischemic attack: the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial. Stroke 2007; 38(12): 3198−204.
71. *Hindler K, Shaw AD, Samuels J, Fulton S, Collard CD, Riedel B*. Improved postoperative outcomes associated with preoperative statin therapy. Anesthesiology 2006; 105(6): 1260−72; quiz 1289−90.

Radak Dj, et al. Vojnosanit Pregl 2016; 73(5): 472–479.

72. *Verzini F, De Rango P, Parlani G, Giordano G, Caso V, Cieri E,* et al. Effects of statins on early and late results of carotid stenting. J Vasc Surg 2011; 53(1): 71−9; discussion 79.
73. *Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C,* et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet 2005; 366(9493): 1267−78.
74. *Amarenco P, Labreuche J, Lavallée P, Touboul P*J. Statins in stroke prevention and carotid atherosclerosis: systematic review and up-to-date meta-analysis. Stroke 2004; 35(12): 2902−9.
75. *Athyros VG, Katsiki N, Karagiannis A, Radak D.* Editorial: effect of statins on rates of long-term cardiovascular events and restenosis following carotid endarterectomy. Curr Vasc Pharmacol 2015; 13(2): 223−5.
76. *McGirt MJ, Perler BA, Brooke BS, Woodworth GF, Coon A, Jain S,* et al. 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors reduce the risk of perioperative stroke and mortality after carotid endarterectomy. J Vasc Surg 2005; 42(5): 829−36; discussion 836−7.
77. *Gröschel K, Ernemann U, Schulz JB, Nägele T, Terborg C, Kastrup A.* Statin therapy at carotid angioplasty and stent placement: effect on procedure-related stroke, myocardial infarction, and death. Radiology 2006; 240(1): 145−51.
78. *Cronenwett JL, Johnston KW.* Rutherford's vascular surgery. Chapter 99. 8th ed. Philadelphia, PA: Elsevier Saunders; 2014.
79. *Abbott AL, Bladin CF, Levi CR, Chambers BR.* What should we do with asymptomatic carotid stenosis? Int J Stroke 2007; 2(1): 27−39.

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