

## RECOMMENDATIONS FOR THE MANAGEMENT OF PATIENTS WITH CAROTID STENOSIS

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**SUMMARY** – These are evidence based guidelines for the management of patients with carotid stenosis, developed and endorsed by Croatian Society of Neurovascular Disorders, Croatian Society of Neurology, Croatian Society of Ultrasound in Medicine and Biology, Croatian Society for Radiology, Croatian Society of Vascular Surgery and Croatian Society of Neurosurgery. They consist of recommendations for noninvasive screening of patients with carotid stenosis, best medical treatment and interventions such as carotid endarterectomy and stent placement based on international randomized clinical trials.

**Key words:** *Carotid stenosis, guidelines, carotid endarterectomy, stent placement, duplex sonography*

## Introduction

Stenosis of internal carotid artery (ICA) causes stroke, as demonstrated by randomized trials, which have shown that removing the extracranial ICA stenosis by means of carotid endarterectomy (CEA) significantly reduces the risk of subsequent ischemic stroke in ipsilateral carotid territory<sup>1,2</sup>. Observational studies suggest that about one-quarter of all first-ever ischemic strokes and transient ischemic attacks (TIAs) are caused by atherothromboembolism originating from the extracranial ICA<sup>3</sup>.

Large artery atherosclerosis may cause almost any clinical stroke syndrome, with the clinical spectrum ranging from asymptomatic arterial disease, TIA affecting the eye or the brain, and ischemic stroke of any severity in the anterior and posterior circulation. Carotid stenosis causes symptoms through two mechanisms: artery-to-artery embolism and low flow states. Artery-to-artery embolism is considered the most common mechanism, through emboli consist-

ing of platelet aggregates, from thrombus formed on atherosclerotic plaques, or from atherosclerotic debris or cholesterol crystals. The triad of vessel wall lesion, blood cells and plasma factors all contribute to thrombosis at any site. Severe stenosis alters blood flow characteristics, and turbulence replaces laminar flow when the degree of stenosis exceeds about 70%. Platelets are activated when exposed to abnormal or denuded endothelium in the region of an atheromatous plaque. Plaque hemorrhage may contribute to thrombus formation. In cases of high-grade stenosis, it can be difficult to discriminate between the two mechanisms with absolute certainty. Transcranial Doppler (TCD), an ultrasound examination of the intracranial vessels, can provide direct evidence of the hemodynamic significance of the carotid lesion, and also offers the possibility to detect the embolic signals<sup>4</sup>. Brain computerized tomography (CT) provides information on the stroke type<sup>4</sup>. Lesions of low flow states are typically localized in distal brain regions, particularly in arterial border zones, and thus referred to as 'watershed

Table 1. Classification of evidence for diagnostic and therapeutic measures

Evidence classification scheme for a diagnostic measure		Evidence classification scheme for a therapeutic intervention
Class I	A prospective study in a broad spectrum of persons with the suspected condition, using a 'gold standard' for case definition, where the test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy	An adequately powered, prospective, randomized, controlled clinical trial with masked outcome assessment in a representative population or an adequately powered systematic review of prospective randomized controlled clinical trials with masked outcome assessment in representative populations. The following are required: (a) randomization concealment (b) primary outcome(s) is/are clearly defined (c) exclusion/inclusion criteria are clearly defined (d) adequate accounting for dropouts and crossovers with numbers sufficiently low to have a minimal potential for bias; and (e) relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences
Class II	A prospective study of a narrow spectrum of persons with the suspected condition, or a well-designed retrospective study of a broad spectrum of persons with an established condition (by 'gold standard') compared to a broad spectrum of controls, where test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy	Prospective matched-group cohort study in a representative population with masked outcome assessment that meets a-e above or a randomized, controlled trial in a representative population that lacks one criterion a-e
Class III	Evidence provided by a retrospective study where either persons with the established condition or controls are of a narrow spectrum, and where test is applied in a blinded evaluation	All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome assessment is independent of patient treatment
Class IV	Evidence from uncontrolled studies, case series, case reports, or expert opinion	Evidence from uncontrolled studies, case series, case reports, or expert opinion

infarction'. Artery-to-artery embolism results in territorial infarction.

The risk of stroke ipsilateral to ICA stenosis increases with the degree of symptomatic carotid stenosis until the artery distal to the stenosis begins to collapse<sup>1,2</sup> (stenosis increase *per* 10% hazard rate (HR) 1.18; 95%CI 1.10-1.25)<sup>5</sup>. Paradoxically, these patients with ICA narrowed or collapsed due to markedly reduced post-stenotic blood flow (pseudo-occlusion, near-occlusion) have a low risk of stroke on best med-

ical treatment alone<sup>6,7</sup> (HR 0.49; 95%CI 0.19-1.24). The risk of stroke ipsilateral to ICA stenosis is greater in patients with recent neurologic symptoms of ischemia in the ipsilateral carotid territory<sup>8,9</sup>, with the presenting event as follows: major stroke (HR 2.54; 95%CI 1.48-4.35), multiple TIAs (HR 2.05; 95%CI 0.16-3.60), minor stroke (HR 1.82; 95%CI 0.99-3.34), single TIA (HR 1.41; 95%CI 0.75-2.66), and ocular event (HR 1.0)<sup>5</sup>. The high early risk of recurrence is the consequence of the instability of atherosclerotic

Table 2. Definitions of the levels of recommendation

Level A	Established as useful/predictive or not useful/predictive for a diagnostic measure or established as effective, ineffective or harmful for a therapeutic intervention; requires at least one convincing Class I study or at least two consistent, convincing Class II studies.
Level B	Established as probably useful/predictive or not useful/predictive for a diagnostic measure or established as probably effective, ineffective or harmful for a therapeutic intervention; requires at least one convincing Class II study or overwhelming Class III evidence.
Level C	Established as possibly useful/predictive or not useful/predictive for a diagnostic measure or established as possibly effective, ineffective or harmful for a therapeutic intervention; requires at least two Class III studies.
Good Clinical Practice (GCP) points	Recommended best practice based on the experience of the guideline development group. Usually based on Class IV evidence indicating large clinical uncertainty, such GCP points can be useful for health workers

plaque, and the rapid decline in the risk over the subsequent year possibly reflects the healing of the unstable atheromatous plaque or an increase in collateral blood flow to the symptomatic hemisphere<sup>7</sup>. Plaque instability is characterized by a thin fibrous cap, large lipid core, reduced smooth muscle content, and high macrophage density; complicating thrombosis occurs mainly when the thrombogenic center of the plaque is exposed to flowing blood. Other factors increasing the risk of stroke in the presence of carotid stenosis are the increasing age, irregular and ulcerated plaque morphology (HR 2.03; 95%CI 1.31-3.14)<sup>5</sup>, absence of collateral flow, impaired cerebral reactivity, TCD findings of microembolic signals, hypertension and coronary heart disease.

The purpose of revascularization of a symptomatic extracranial ICA stenosis is reduction in the risk of recurrent ipsilateral carotid territory ischemic stroke by removing the source of carotid thromboembolism.

After evaluation of the results of large international randomized controlled trials (RCTs), the Croatian Society of Neurovascular Disorders, Croatian Society of Neurology, Croatian Society of Ultrasound in Medicine and Biology, Croatian Society of Radiology, Croatian Society of Vascular Surgery and Croatian Society of Neurosurgery have reached a consensus and present herewith the guidelines based on the levels of recommendations for the treatment of patients with carotid stenosis. The classes of evidence and levels of recommendations used in these guidelines are defined according to the criteria of the European Federation of Neurological Societies (EFNS) (Tables 1 and

2)<sup>10</sup>. Recommendations are in accordance with EUSI (European Stroke Initiative) guidelines on ischemic stroke management, with the European Neurological Society, European Federation of Neurological Societies and European Stroke Council representing European Stroke Conference, as well as with other published North American stroke guidelines, American Heart Association (AHA) guidelines on intracranial neurointerventional procedures, and European Society of Vascular Surgery guidelines.

#### Transient Ischemic Attack as a Risk Factor for Stroke

Transient ischemic attack is a brief episode of neurologic dysfunction resulting from focal cerebral ischemia not associated with permanent cerebral infarction<sup>11</sup>. Among patients presenting with stroke, the prevalence of prior TIA has been reported to range from 7% to 40%. The percentage varies, depending on factors such as how TIA is defined, which stroke subtypes are evaluated, and whether the study is a population-based or hospital-based series<sup>12,13</sup>. In the population-based Northern Manhattan Stroke Study, the prevalence of TIAs among those that presented with first ischemic stroke was 8.7%<sup>14</sup>, with the majority of TIA occurring within 30 days of the patient's first ischemic stroke. An even higher rate has been reported in patients with prior stroke<sup>15,16</sup> and as great as 50% among those with atherothrombotic stroke. The timing of a TIA before stroke was highly consistent, with 17% occurring on the day of stroke, 9% on the previous day, and another 43% at the same point during the 7 days before the stroke<sup>17-20</sup>. It has long been

recognized that TIA can portend stroke<sup>21</sup>, and studies have shown elevated long-term stroke risk<sup>22-24</sup>. Studies have also shown that the short-term stroke risk is particularly high, exceeding 10% in 90 days<sup>12,20,25-28</sup>. The risk is particularly high in the first few days after TIA, and several score systems based on clinical characteristics, such as California score and ABCD score, help distinguish patients at a lower risk from those at an increased risk<sup>29</sup>. The newer ABCD<sup>2</sup> score has been derived to provide a more robust prediction standard and incorporates elements from both prior scores<sup>29</sup>. In addition, patients with severe extra- or intracranial stenosis carry a particularly high risk of recurrence<sup>30</sup>.

Imaging of the brain and supplying vessels is crucial in the assessment of patients with stroke and TIA. Brain imaging distinguishes ischemic stroke from intracranial hemorrhage and stroke mimics, and identifies the type and often also the cause of stroke; it may also help differentiate irreversibly damaged tissue from areas that may recover, thus guiding emergency and subsequent treatment, and may help predict the outcome.

Vascular evaluation for assessment may identify the site and cause of arterial obstruction, and identifies patients at a high risk of stroke or stroke recurrence<sup>31-35</sup>. Observational studies have shown that urgent evaluation at a TIA clinic and immediate initiation of treatment reduces stroke risk after TIA<sup>36,37</sup>. It has been shown that early management of TIA patients at a stroke unit leads to specific treatments in a significant proportion of cases<sup>38</sup>.

Carotid stenosis of >50% of ICA is found in 8%-31% of patients with TIA and minor stroke<sup>39,40</sup>. Carotid ultrasound provides reliable assessment of the carotid bifurcation, with reported sensitivity of 75% and specificity of 98%<sup>41</sup>, or sensitivity of 88% and specificity of 76%<sup>42</sup>. Carotid duplex examination has prognostic significance. In TIA patients, carotid duplex and TCD performed within 24 hours of symptoms revealed a 3-fold risk of stroke within 90 days of follow up in patients with moderate to severe extra- or intracranial carotid stenosis<sup>43</sup>.

TCD provides information on intracranial stenosis<sup>32</sup>, with a positive predictive value (PPV) of 36% and negative predictive value (NPV) of 86%<sup>44</sup>. The high NPV and lower PPV reflect a low prevalence of intracranial stenosis<sup>45</sup>, and the prevalence of intracra-

nial disease is much higher in non-white population.

TCD can detect microembolic signals (MESs) seen with extracranial or cardiac sources of embolism. High numbers of MESs are a marker of risk in patients with TIA of carotid origin, spurring research into optimal strategies for medical therapy and timing of endarterectomy in those with an extracranial carotid source<sup>45</sup>. In a cohort of patients unselected for stroke mechanism, MESs were more common in patients with large artery occlusive disease and were more prevalent in patients treated with anticoagulation than in those treated with antiplatelet agents<sup>46</sup>. The CARESS trial<sup>45</sup> enrolled recently symptomatic carotid disease and MESs and found fewer patients with MESs, fewer MESs *per* hour and fewer stroke in patients treated with clopidogrel and aspirin than in patients treated with aspirin alone in the first week of presentation.

#### Recommendations for Diagnostic Management of Patients with TIA or Stroke

It is recommended that all stroke patients should be treated at a stroke unit (Class I, Level A).

It is recommended that patients with suspected TIA are investigated and treated as emergencies at a TIA clinic with specialized assessment (Class III, Level B) or admitted to a stroke unit. The overall secondary prevention strategies for TIA patients do not differ from those for patients with completed stroke.

Patients with TIA, minor stroke, early spontaneous recovery or definitive stroke should undergo immediate diagnostic work-up within 24 hours of symptom onset, including urgent vascular imaging (ultrasound, CT angiography, or MR angiography) (Class I, Level A)

Noninvasive imaging of the cervicocephalic vessels should be performed routinely as part of the evaluation of patients with TIA or stroke (Class I, Level A).

#### Asymptomatic Carotid Disease

Several years ago, it was estimated<sup>47</sup> that approximately 2 million people living in Europe and North America have asymptomatic extracranial carotid artery stenosis that could be considered for treatment. Carotid endarterectomy and, recently, carotid artery stenting have been used for the treatment of carotid artery stenosis. It has been shown that the risk of stroke



increases with the degree of stenosis (less than 1% *per* year for <80% stenosis, increasing to 4.8% *per* year for >90% stenosis). Therefore, the benefit of screening for asymptomatic severe carotid artery stenosis depends on the prevalence of disease, the sensitivity and specificity of the screening tool, and the complication rates of angiography and surgery. In addition, the costs of diagnosis and treatment must be considered.

Most of the evidence in the literature regarding patient selection are based on studies using Doppler ultrasound. Therefore, a Multidisciplinary Practice Guidelines Committee of the American Society of Neuroimaging, cosponsored by the Society of Vascular and Interventional Neurology was formed to identify the group of predominantly asymptomatic patients who would benefit from screening for carotid artery stenosis<sup>48</sup>. The Committee decided that the value of screening in any subset of population was dependent on the expected prevalence and anticipated benefit from intervention (for example, the overall high incidence was evaluated against comorbidities and life expectancy in that subset of population). The grading of the strength of the scientific evidence used to create the recommendations was derived from the disease prevalence in the population subset and documented benefit of the treatment (Table 3). The anticipated benefit of treatment in asymptomatic patients with carotid stenosis was derived from three randomized clinical trials. Two trials compared carotid endarterectomy with best medical treatment in patients with asymptomatic carotid stenosis<sup>49,50</sup>, and the third trial compared carotid stenting with carotid endarterectomy<sup>51</sup>.

In the Asymptomatic Carotid Atherosclerosis Study (ACAS)<sup>49</sup>, patients with asymptomatic carotid artery stenosis of 60% or greater, defined by angiography or Doppler evaluation using a local laboratory cut-off point, were randomized to CEA or best medical management. After a median follow up of 2.7 years, the aggregate risk over 5 years for ipsilateral stroke and any perioperative stroke or death was estimated to be 5.1% for surgical patients and 11.0% for patients treated medically (aggregate risk reduction by 53%; absolute risk reduction by approximately 1% *per* year). The benefit was dependent on carotid endarterectomy being performed with less than 3% perioperative morbidity and mortality. The Asymptomatic Carotid

Surgery Trial (ACST)<sup>50</sup> randomized asymptomatic patients with significant carotid stenosis according to Doppler criteria to immediate CEA or indefinite deferral of any CEA. The mean follow up was 3.4 years. The cumulative 5-year risks were 6% *versus* 12% for all strokes, 4% *versus* 6% for fatal or disabling strokes, and 2% *versus* 4% for only fatal strokes. Subgroup-specific analyses found no significant heterogeneity in the perioperative risk or long-term postoperative benefits. A meta-analysis of three trials<sup>52</sup> has found that despite a 3% perioperative stroke or death rate, carotid endarterectomy for asymptomatic carotid stenosis reduces the risk of ipsilateral stroke and any stroke by approximately 30% over 3 years. For the outcome of any stroke or death, there was a nonsignificant trend toward fewer events in the CEA group. In subgroup analysis, CEA appeared more beneficial in men than in women and more beneficial in younger patients than in older patients, although data on age effect were inconclusive. There was no statistically significant difference between the treatment effect estimates in patients with different grades of significant stenosis, but the data were insufficient. The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE)<sup>51</sup> compared carotid stenting (CAS) (with the use of an emboli-protection device) to CEA in patients considered to be at a high surgical risk for CEA. Patients were eligible if they had either symptomatic stenosis of 50% or greater or asymptomatic stenosis of 80% or greater. The primary end point of the trial was the cumulative incidence of death, stroke, or myocardial infarction within 30 days of the procedure, or death or ipsilateral stroke between 31 days and 1 year. The primary end point occurred in 20 (12%) patients randomly assigned to undergo CAS and in 32 (20%) patients randomly assigned to undergo CEA. For patients with asymptomatic carotid artery stenosis, the cumulative incidence of the primary end point at 1 year was lower among those treated with CAS (10%) than among those that underwent CEA (22%). In the periprocedural period, the cumulative incidence of death, myocardial infarction, or stroke among patients with asymptomatic carotid artery stenosis was 5% in those that received a stent, as compared to 10% in those that underwent CEA.

The prevalence of asymptomatic ICA stenosis for determination of the screening effectiveness was grad-

Table 3. Criteria for grading the strength of scientific evidence used in the recommendations

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- A Prevalence of disease is high and detection and treatment is of documented benefit (confirmed by randomized trials)
- B Prevalence of disease is high but detection and treatment is of possible benefit (confirmed by comparison with nonrandomized concurrent or historic controls)
- C Prevalence of disease is intermediate but detection and treatment is of documented benefit (confirmed by randomized trials)
- D Prevalence of disease is intermediate and detection and treatment is of possible benefit (confirmed by comparison with nonrandomized concurrent or historic controls)
- E Prevalence of disease may be high or low but detection and treatment is documented to have no benefit, or prevalence of disease is low
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ed as high (20% or greater), intermediate (between 5% and 20%) and low (less than 5%). While screening in the high prevalence group reduces the risk of stroke in a cost-effective manner, in the intermediate group it was only recorded in some studies. In this group, the benefit is marginal and is lost if perioperative complications exceed 5%. In the low prevalence group, screening has not been shown to reduce the risk of stroke, and in some studies it could even be harmful.

*According to the expected benefit of CEA in ACAS and ACST, the following recommendations for screening of patients with asymptomatic carotid stenosis have been proposed<sup>48</sup>:*

In general population, screening of the selected subpopulation aged 65 years or older with at least three cardiovascular risk factors (hypertension, coronary artery disease, current cigarette smoking or hyperlipidemia) is recommended (grade A).

In patients undergoing coronary artery bypass grafting, screening of all patients can be considered (grade D), and of selected patients is strongly recommended: age 65 years or greater with either a history of stroke or TIA, left main coronary stenosis, peripheral vascular disease, history of cigarette smoking, carotid bruit, previous carotid surgery or diabetes mellitus (grade B).

In patients with peripheral vascular disease, screening of all patients with symptomatic peripheral vascular disease is strongly recommended (grade A), but existing data do not support routine screening of asymptomatic peripheral vascular diseases (grade E).

Screening is recommended for all patients that have received unilateral or bilateral irradiation to the

neck for head or neck cancer 10 years after treatment (grade B), due to improving survival observed in these patients and availability of carotid stent placement. However, no clear relationship has been demonstrated between the dose and duration of radiation treatment to allow for incorporation of radiation dose information into the paradigm for selection of patients for screening.

In patients that have undergone CEA is recommended in those that develop ipsilateral ischemic stroke, retinal ischemic events or TIA, screening (grade B)

Screening of patients that have undergone CAS is recommended in those that develop ipsilateral ischemic stroke, retinal ischemic events, or TIA after its placement (grade C).

Screening for carotid artery stenosis is recommended for all patients with transient or permanent retinal ischemic event, particularly in the absence of migraine or cardiac sources of emboli (grade A), since most of the evidence regarding the beneficial effect of CEA derive from patients with transient retinal ischemia.

Considering patients that have undergone CEA, routine screening of all patients cannot be recommended based on the low prevalence of restenosis and lack of correlation between restenosis and late stroke (grade E). Reoperation or stenting (CEA, CAS) has been considered for patients with symptomatic restenosis or selected high-grade asymptomatic restenosis, although there is the lack of evidence demonstrating the benefit from intervening in patients with restenosis using these indications. The optimal interval between CEA/CAS and ultrasound remains unclear, but the

highest yield appears to be in studies performed between 3 and 18 months.

Further studies need to validate the practice of performing ultrasound screening at 1 month, 6 months and 12 months following carotid stent placement. Studies are required to develop Doppler ultrasound criteria with higher specificity.

No definite comments have been made regarding routine screening of all patients that have undergone CAS. There is considerable variation in the rates of restenosis following CAS. Patients with restenosis following endovascular treatment were more likely to be symptomatic compared with restenosis following carotid endarterectomy<sup>47</sup>. Repeat endovascular treatment has been considered for patients with symptomatic restenosis or selected high-grade asymptomatic restenosis, although there is the lack of evidence demonstrating benefit from intervening in patients with restenosis using these indications.

Screening of all patients or asymptomatic patients with abdominal aortic aneurysm is not recommended (grade E), but the existing data support screening of patients with abdominal aortic aneurysm and history of TIA, ischemic stroke or retinal ischemic events (grade B).

Screening of all patients with renal artery stenosis is not recommended (grade E), but the Committee acknowledges that there are limited data available and encourages further studies to evaluate the value of carotid artery disease screening among patients with atherosclerotic renal artery stenosis of 60% or greater.

In patients that have undergone CEA screening should be considered for those with contralateral carotid artery stenosis  $\geq 50\%$  (grade A). Screening may be considered for patients with contralateral disease  $< 50\%$  (grade C). Because progression of stenosis in the contralateral artery has a higher likelihood of becoming symptomatic, annual screening may be considered.

### Medical Treatment of Patients with Carotid Stenosis

In primary as well as in secondary prevention in patients with carotid stenosis, treatment of risk factors such as hypertension, diabetes mellitus, lipid or homocysteine metabolic disorders, and modification of lifestyle are of utmost importance to reduce both early and long-term risks of vascular events, dementia and death<sup>31,53</sup>.

Aspirin, a combination of aspirin and extended release dipyridamole, clopidogrel, ticlopidine and triflusal have been shown to be effective as antiplatelet agents in long-term secondary prevention of ischemic stroke<sup>54,55</sup>, but only aspirin, aspirin/extended dipyridamole and clopidogrel are widely used in clinical practice.

To date, only aspirin has been shown to be safe and effective in the acute post-ischemic phase (first 48 hours) and should be started immediately in patients with TIA/ischemic stroke after exclusion of brain hemorrhage by brain imaging. Aspirin is effective irrespective of dose (30-1,300 mg/day), but doses  $> 150$  mg/day are associated with more side effects<sup>56</sup>. In the Antithrombotic Trialists' Collaboration, a meta-analysis of  $> 60$  aspirin trials, the best risk reduction was found in trials using a 75 to 150 mg dose of aspirin<sup>57-59</sup>. Gastrointestinal side effects and bleeding rates increase with higher doses of aspirin. In patients with a history of aspirin-induced ulcer bleeding, aspirin in combination with a proton pump inhibitor was superior to clopidogrel alone in the prevention of recurrent ulcer bleeding<sup>60</sup>.

Clopidogrel (75 mg/day) was slightly more effective than aspirin monotherapy (325 mg/day) in preventing vascular events (ischemic stroke, myocardial infarction, or vascular death), resulting in a relative risk reduction (RRR) by 8.7% (95%CI 0.3-16.5)<sup>61</sup>. The highest benefit of clopidogrel was seen in patients with concomitant peripheral artery disease.

The combination of aspirin (30-300 mg/day) and extended release dipyridamole (200 mg twice a day) was shown to be more effective compared with aspirin alone in two studies<sup>62,63</sup>. Combination therapy reduced vascular events (ischemic stroke, myocardial infarction or vascular death) by 18% (95%CI 9%-26%). Reduced development of headache on combination therapy can be achieved with slower titration.

The PRoFESS trial<sup>64</sup> was a head-to-head comparison of clopidogrel and the combination of aspirin/extended release dipyridamole. There was no difference in efficacy across all endpoints and patient subgroups. The combination of aspirin/extended release dipyridamole resulted in more intracranial bleeding and a higher dropout rate due to headache compared with clopidogrel (5.9% *vs.* 0.9%).

In the MATCH trial (secondary prevention in high-risk patients with TIA or ischemic stroke)<sup>65</sup> and



CHARISMA (Combined Primary and Secondary Prevention Study) trial<sup>66</sup>, comparison of clopidogrel or aspirin monotherapy with their combination failed to show superiority of combination therapy and resulted in an increased bleeding rate. The Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis (CARESS) trial showed the combination therapy with clopidogrel and aspirin to be more effective than aspirin alone in reducing asymptomatic embolization in patients with recently symptomatic carotid stenosis<sup>45</sup>.

A systematic review identified four randomized trials directly comparing oral anticoagulants (OAC) high International Normalized Ratio (INR) (3.0-4.5) *versus* antiplatelet therapy in patients with previous TIA or minor stroke of presumed arterial origin<sup>67</sup>. Therapy with OAC was associated with a significantly higher rate of recurrent serious vascular events (1.70, 95%CI 1.12-2.59), with a highly significant excess of major bleeding complication (9.02, 95%CI 3.91-20.84) and a significant excess of recurrent serious vascular events or major hemorrhage (2.30, 95%CI 1.58-3.53) compared with antiplatelet therapy. Therapy with OAC was associated with a significant excess of death from any cause compared with antiplatelet therapy (RR 2.38, 95%CI 1.31-4.32).

#### Recommendation for Best Medical Treatment in Patients with Carotid Atherosclerosis

The best medical treatment of patients with carotid stenosis includes treatment of hypertension, diabetes mellitus, lipid or homocysteine metabolic disorders, modification of lifestyle, and statin and antithrombotic treatment (Class I, level A).

Patients presenting with ischemic symptoms not taking antiplatelet therapy should be considered for aspirin with a loading dose of 160-300 mg if they are at a low risk of recurrent event, clopidogrel if allergic or intolerant of aspirin, and clopidogrel or the combination of aspirin and dipyridamole if at a high risk of recurrent event. The two strategies being similar, the choice between combined aspirin plus dipyridamole, and clopidogrel is based on the presence of coexistent disorders, tolerability and cost. Alternatively, aspirin alone, dipyridamole alone, or triflusal alone may be used (Class I, level A).

Patients presenting with ischemic symptoms already taking aspirin should be considered to stop aspirin and start clopidogrel, or adding dipyridamole to aspirin, but not adding clopidogrel to aspirin.

Patients presenting with ischemic symptoms already taking clopidogrel should be considered to stay on clopidogrel, or changing to aspirin or the combination of dipyridamole and aspirin, but not adding aspirin to clopidogrel.

Patients presenting with ischemic symptoms already taking the combination of aspirin and clopidogrel should be considered for further therapy according to the risk of a recurrent ischemic event with all vascular risk factors well controlled. Patients at a low risk of recurrent event should be considered for aspirin monotherapy. Patients at a higher risk should be considered for clopidogrel monotherapy or the combination of dipyridamole and aspirin. Patients having received stent placement should continue dual therapy with aspirin and clopidogrel for 8 weeks, then continue therapy with aspirin alone.

It is recommended that anticoagulation should not be used after non-cardioembolic ischemic stroke (Class I, Level A). High-intensity anticoagulation (INR 3.0-4.5) is more hazardous than effective in comparison with antiplatelet therapy.

#### Carotid Endarterectomy

Carotid endarterectomy is a surgical procedure of plaque removal from the carotid artery, reducing the risk of stroke by enlarging the lumen and by removing the possible source of emboli. The ECSCCT and NASCET<sup>1,2</sup> results established CEA as the treatment of choice for moderate and severe carotid artery stenosis in secondary stroke prevention. The most important risks of CEA are death (about 1%) and stroke (about 5%)<sup>1,2</sup>. From a pooled analysis of data from the three largest RCTs of surgery for symptomatic carotid stenosis<sup>68</sup>, CEA reduced 5-year absolute risk of any stroke or death in patients with 50%-69% stenosis, according to angiographic NASCET criteria (absolute risk reduction (ARR) 7.8%, 95%CI 3.1-12.5), and was highly beneficial in patients with 70%-99% stenosis (15.3%, 95%CI 9.8-20.7), but showed no benefit in patients with near occlusion. Quantitatively similar results were seen for disabling stroke<sup>68</sup>. CEA therefore proved to be beneficial in stenosis more than 50%

according to NASCET criteria, which is equivalent to 65% stenosis by ECST criteria. In ECST trial, CEA reduced the risk of recurrent TIA in patients with near occlusion (ARR 15%;  $P=0.007$ ).

The degree of stenosis is a major determinant of benefit from CEA, but there are other clinical characteristics that influence the risks and benefits of surgery. Subgroup analyses of pooled data from the large RCT<sup>69</sup> showed the greatest benefit from CEA in men, patients aged  $\geq 75$  years, and patients randomized within 2 weeks after their last ischemic event. Both ECST and NASCET showed that for patients with  $\geq 50\%$  ICA stenosis, the number needed to treat (NNT) by CEA to prevent one ipsilateral stroke in 5 years was 9 for men *versus* 36 for women, 5 for age  $\geq 75$  years *versus* 18 for age  $< 65$  years, and 5 for patients randomized within 2 weeks after the last ischemic event *versus* 125 for patients randomized in  $> 12$  weeks. Women had a lower risk of ipsilateral ischemic stroke on medical treatment and a higher operative risk in comparison to men<sup>70</sup>. CEA was more beneficial in women with  $\geq 70\%$  stenosis, but not in women with 50%-69% stenosis. At the same time, CEA reduced the 5-year ARR by 8.0% (3.4-12.5) in men with 50%-69% stenosis. Sex difference was statistically significant even when the analysis of the interaction was confined to the group with 50%-69% stenosis<sup>70</sup>.

Trials of carotid surgery for asymptomatic carotid stenosis have concluded that, although surgery reduces the incidence of ipsilateral stroke (RR 0.47-0.54) and any stroke, the absolute benefit is small (approximately 1% *per year*)<sup>49,50,52</sup>, whereas the perioperative stroke or death rate is 3%. Medical management is the most appropriate option for most asymptomatic subjects; only centers with a perioperative complication rate of 3% or less should contemplate surgery. Patients with a high risk of stroke (men with stenosis of more than 80% and a life expectancy of more than 5 years) may derive some benefit from surgery in appropriate centers<sup>50,52</sup>.

There are different techniques of CEA. In traditional endarterectomy, the plaque is removed *via* a longitudinal arteriotomy. Eversion endarterectomy is a variant, which employs a transverse arteriotomy and re-implantation of the carotid artery. There was no significant difference in the rates of periopera-

tive stroke, stroke or death and local complication rates in a review of five RCTs comparing eversion and conventional endarterectomy performed either with primary closure or patch angioplasty<sup>71</sup>. The absolute risks were rather low (the risk of stroke or death 1.7% with eversion *versus* 2.6% with conventional endarterectomy). To reduce the risk of restenosis, many surgeons use a patch of autologous vein or synthetic material to close the artery and enlarge the lumen. Although patch increases the operative time and complication rate, it was associated with 60% reduction in the operative risk of stroke or death during the postoperative period and long-term follow up, 85% reduction in the risk of perioperative arterial occlusion and 80% reduction in the risk of restenosis during long-term follow up<sup>72</sup>. Although some surgeons routinely insert a temporary intraluminal shunt during CEA, it is associated with some risk of dissection or transmission of emboli. RCTs that included patients requiring shunting or followed different shunting policies were too small and the results were inconclusive<sup>73</sup>.

CEA was traditionally performed under general anesthesia (GA), but surgery under local anesthesia (LA) is becoming more widespread. With LA, a lower shunt rate is present due to immediate obvious need for it to restore blood flow distal to the carotid clamps. While a systematic review of seven small randomized trials showed that the use of LA was associated with a borderline statistically significant trend towards a reduced risk of operative death, but no evidence of reduction in the risk of operative stroke<sup>74</sup>, a large multicenter randomized trial (GALA) showed no major difference in the operative risk of stroke and death combined (risk ratio for LA *vs.* GA 0.94; 95% CI 0.70-1.27)<sup>75</sup>.

### Recommendation for Carotid Endarterectomy

CEA is recommended for patients with 70%-99% stenosis (Class I, Level A). CEA should only be performed in centers with a perioperative complication rate (all strokes and death) of less than 6% (Class I, Level A).

It is recommended that CEA be performed as soon as possible after the last ischemic event, ideally within 2 weeks (Class II, Level B).

It is recommended that CEA may be indicated for certain patients with stenosis of 50%-69%; males with very recent hemispheric symptoms are most likely to benefit (Class III, Level C). CEA for stenosis of 50%-69% should only be performed in centers with a perioperative complication rate (all stroke and death) of less than 3% (Class I, Level A).

CEA is not recommended for patients with stenosis of less than 50% (Class I, Level A).

There is no evidence for the routine use of shunts during CEA (Class I, Level A).

Carotid patch angioplasty reduces the risk of occlusion and restenosis, as well as the risk of combined stroke/death (Class I, Level A), but differences between the outcomes with different patch materials are small to draw firm conclusions and recommendations.

The choice of the CEA technique should depend on the experience and familiarity of the individual surgeon (Class I, Level C).

Both LA and GA are safe. The anesthetist and surgeon, in consultation with the patient, should determine the method of anesthesia. For patients with a contralateral carotid occlusion, LA might offer some benefit (Class I, Level C).

It is recommended that patients remain on antiplatelet therapy both before and after surgery (Class I, Level A)

Carotid surgery is not recommended for asymptomatic individuals with significant carotid stenosis (NASCET 60%-99%), except for those at a high risk of stroke (Class I, Level C), and then in centers with a perioperative complication rate (all strokes and death) of less than 3%.

Patients should be followed-up by both the referring physician and the surgeon (Class IV, level C).

### Extracranial-Intracranial Anastomosis (EC-IC Bypass)

About 5%-10% of patients with carotid TIA or minor stroke have occlusion of the ICA origin, or occasionally of distal ICA or proximal middle cerebral artery. These lesions can be bypassed by anastomosing a branch of the external carotid artery, usually the superficial temporal artery, *via* a skull bur hole to a cortical branch of the middle cerebral artery. Such

collateral was developed to improve blood supply in the distal middle cerebral artery bed and to reduce the risk of stroke or the severity of stroke. However, in a RCT these anastomoses between the superficial temporal and middle cerebral arteries were not beneficial in preventing stroke in patients with middle cerebral artery or ICA stenosis or occlusion<sup>76</sup>.

### Carotid Stenting

Several trials compared CAS and CEA in secondary stroke prevention<sup>51,77-82,86</sup>. None of these studies was adequately powered to show the non-inferiority (or superiority) of stenting compared to endarterectomy with regard to an endpoint combining the early risks and late benefits of the procedures. Most studies were designed to assess the non-inferiority of stenting compared to endarterectomy with regard to the early risks of the procedures. However, the SAPHIRE trial included more than 70% of asymptomatic patients and therefore should not be used for decisions about secondary prevention<sup>51</sup>. In CAVATAS (Carotid and Vertebral Artery Transluminal Angioplasty Study), the majority of patients in the endovascular group underwent angioplasty and only 26% were treated with a stent<sup>86</sup>. The studies revealed different results. SPACE (Stent-Protected Angioplasty *versus* Carotid Endarterectomy in symptomatic patients) marginally failed to prove the non-inferiority of CAS compared to CEA; for the endpoint ipsilateral stroke or death up to day 30, the event rates after 1,200 patients were 6.8% for CAS and 6.3% for CEA patients (absolute difference 0.5%; 95% CI -1.9% to +2.9%;  $P=0.09$ )<sup>84</sup>. The French EVA3S (Endarterectomy *versus* Stenting in Patients with Symptomatic Severe Carotid Stenosis) trial was stopped prematurely after the inclusion of 527 patients because of safety concerns and lack of efficacy. The RR of any stroke or death after CAS compared with CEA was 2.5 (95% CI 1.2-5.1)<sup>77</sup>.

CAS has not been shown to be as safe as CEA in patients with symptomatic carotid artery stenosis in RCTs. Recent meta-analyses<sup>83-85</sup> of RCTs that compared CAS and CEA treatment of patients with mainly symptomatic carotid artery stenosis concluded that CEA should remain the first line intervention in 'standard' risk, symptomatic patients.

In RCTs, the risk of ipsilateral stroke beyond the perioperative period was low (<1% *per year*) and simi-

lar in both the stenting and endarterectomy groups, which strongly suggests that stenting is as effective as surgery for the medium-term prevention of ipsilateral stroke, at least for the first 4 years after the procedures<sup>79,80,82,86,89</sup>. As the incidence of recurrent carotid stenosis may be significantly higher after CAS than after CEA<sup>87</sup>, there is a need to assess the long-term effects of carotid stenting, and particularly the effect of restenosis.

The SAPHIRE trial selected high-risk patients with medical comorbidities that were exclusion criteria for the NASCET/ACAS trial, with one of the following features: congestive heart failure (New York Heart Association class III/IV) and/or known severe left ventricular dysfunction; open heart surgery needed within 6 weeks; recent myocardial infarction (MI); unstable angina (Canadian Cardiovascular Society class III/IV); or severe pulmonary disease. In SAPHIRE trial, the major adverse events (death, stroke and MI) at 1 year were 12.2% in the CAS group compared to 20.1% in surgically treated patients ( $P=0.053$ ). Still, it is unknown what the major adverse event rate would have been if patients had received the best medical treatment alone without any intervention. Therefore, there is no indication from the literature that a high risk for CEA is also a high risk of stroke if medically treated, and a peri-interventional stroke or death risk of >3% in high risk for surgery patients with asymptomatic carotid stenosis cannot be accepted.

Subgroup analyses from RCTs suggest some heterogeneity of risk between stenting and endarterectomy. In particular, the excess risk associated with stenting was greater in patients aged 70 years or older<sup>79,81,82</sup>. However, owing to the drawbacks of *post hoc* analyses such as low statistical power and the risk of chance findings, these subgroup analyses should be interpreted with caution. The best evidence for subgroup treatment effect interaction will be obtained from a planned combined analysis of individual patient data from current trials that compare stenting with endarterectomy.

Recently, final results of ICSS trial were presented at the European Stroke Conference 2009<sup>88</sup>. The ICSS trial was a randomized double-blind study comparing CAS and CEA in patients with symptomatic carotid stenosis of greater than 50% within 6 months prior to randomization. A total of 1710 patients were included

in the intention-to-treat (ITT) analysis, 853 randomized to CAS and 857 to CEA. The primary aim of the ICSS trial was to determine long-term survival free from disabling stroke. Sufficient follow up for this end point is expected to be completed in 2011 but the primary safety data on the 30-day rate of stroke, MI, or death, measured up to 120 days after randomization were presented. Those allocated to CAS had more events than those allocated to CEA (ITT analysis 8.5% *vs.* 5.1, *per protocol* 7.4% *vs.* 4.0%, ARR=3.4%;  $P=0.004$ ). The majority of these events were strokes, with nearly twice as many strokes in the CAS group than in the CEA group (65 *vs.* 34). In the magnetic resonance imaging (MRI) sub-study that was carried out at 5 ICSS centers, scans were analyzed blind to treatment. New ischemia was found in about half of CAS patients *vs.* about 15% of CEA patients. On follow up imaging 4 to 6 weeks later, FLAIR was abnormal at the site of early ischemia in 30% of patients after CAS *vs.* 8% of patients after CEA, also highly significant.

Immediately afterwards, the Registry of CAS patients (recruited to post-marketing surveillance in the EXACT and CAPTURE 'high risk for CEA' Registries) reported 30-day outcomes<sup>87</sup>. Subgroup analysis stratified for age was performed in a cohort of 6320 patients, 12% of them having suffered stroke or TIA 6 months prior to CAS (equivalent to recently symptomatic in ICSS). The 30-day rate of death/stroke in 589 patients aged <80 years was 5.3% (95% CI 3.6%-7.4%), compared to 10% in 172 patients aged >80 years (95%CI 3.3%-16%). The authors concluded that CAS demonstrated real-world outcomes consistent with the established American Heart Association (AHA) guidelines in symptomatic patients. There are some questions to be answered before implying these results on recommending CAS to patients at a high risk for CEA<sup>90</sup>. The low procedural risk observed in non-octogenarian patients in the amalgamated Registry must be maintained and regularly audited. If it exceeds 8%, it is unlikely that any long-term benefit will accrue to the patients and the interventionist should review his/her selection criteria. Also, a request to the interventionists is to recognize that the magnitude of the benefit conferred to the patient in terms of secondary stroke prevention will be increased if their interventions are primarily undertaken in pa-



tients who also present with criteria of 'high risk for stroke', that means male sex, hemispheric ischemic symptoms, increasing medical comorbidity, very recent symptoms, more severe degrees of stenosis, and contralateral occlusion<sup>91</sup>. A very important issue on assessing the risk for CAS is whether the patient had primary atherosclerotic disease or non-atherosclerotic disease (e.g., radiation arteritis, restenosis after CEA, etc.). In many of the 'high risk' registries published to date, up to 40% of patients had restenosis after CEA. Although this is likely to be more of a confounding factor in asymptomatic patients, secondary analyses from the Acculink for Revascularization of Carotids in High Risk Patients (ARCHeR) CAS Registry showed that the 30-day risk following CAS in patients with non-atherosclerotic disease was 14 times lower in these patients (overall risk=6.6%, but 0.7% in non-atherosclerotic patients *vs.* 9.5% in patients with atherosclerosis)<sup>92</sup>.

Still, the biggest question is why the reduction in the procedural risk after CAS in non-randomized, observational studies is lower than in RCT. In 2001, CAVATAS was heavily criticized for the high procedural risk after both CEA and CAS. However, while the 30-day risk after CEA improved from 9.9% observed in CAVATAS (SPACE 6.3%, EVA-3S 3.9%, and ICSS 5.1%), the same does not apply to CAS (CAVATAS 10.0%, SPACE 6.8%, EVA-3S 9.6%, and ICSS 8.5%). Numerous factors are likely to be responsible for the excess risk of procedural stroke observed in RCT. There is a number of methodological criticisms regarding CAS practice in each of these trials; the biggest one is the interventionist experience, but also the use of protection devices. Also, other factors should be taken in consideration such as stent types, protection type devices, sex, age, presenting symptoms, symptoms to intervention, medical comorbidity, and patient selection criteria in order to identify cohorts of recently symptomatic patients that are predicted to be at either high or low risk of suffering procedural stroke after CAS. A very important question is whether rapid intervention influences the early procedural risk, but also enables the biggest benefit of intervention. The risk of stroke after a TIA or minor stroke is highest in the first seven days of symptom onset. There is compelling evidence that any delay in intervention rapidly diminishes the benefit accruing

to the patient<sup>93</sup>. Accordingly, the CAS Registries and any future meta-analyses of the RCT must go back and evaluate the relationship between the time from symptom onset to treatment and then specifically relate it to the procedural risk. It is no longer acceptable to simply provide outcome risk data for patients treated within 6 months of symptoms. Consecutively, better information on outcomes of the preferred intervention (CEA or CAS) in patients treated within 7 or 14 days of symptom onset would be available. This could mean that one intervention might be safer in the hyperacute phase of treatment, while the other might be preferable after some time has elapsed. Especially, results of the CAPTURE CAS Registry<sup>94</sup> have pointed to this, showing by subgroup analysis that the 30-day risk of death/stroke was 2.5 times higher if CAS was performed within two weeks of the most recent symptom ( $P<0.05$ ), whereas there was no difference in the procedural risk after four weeks.

Certain vascular and local anatomic features are considered as relative contraindications depending on the experience of interventional radiologist and type of procedural material for CAS, e.g., complex bifurcation disease with long, multifocal lesions or extensive aortic or brachiocephalic trunk plaque, severe tortuosity or calcification of the aortic arch vessel, or ring-like, heavy calcifications of the carotid bifurcation. Contrary, based on experts' opinion and not on RCTs<sup>95</sup>, CAS is indicated in patients with contralateral laryngeal nerve palsy and previous radical neck dissection or cervical irradiation and with prior CEA (restenosis), because the rate of cranial nerve injuries following surgery is higher in this subset. Also, CAS can be offered to patients with high bifurcation or intracranial extension of a carotid lesion, where surgical access could be difficult, or in patients at a high risk of cerebral ischemia during carotid clamping (occlusion of the contralateral ICA and anomalies of the Willis circle).

While pending CREST publication, carotid stenting in symptomatic patient with standard risk should be offered in high volume CAS centers that already treat 'standard risk' symptomatic patients only if the 30-day risk of death/stroke is independently audited and maintained at <6% and patients are treated without delay, preferably within 14 days. If these two caveats cannot be achieved, the patient should be referred for CEA.

### Recommendation for Carotid Stent Placement

Until the results of the ongoing trials are available for a pooled analysis of safety and long-term effectiveness, stenting should not be routinely offered to patients suitable for carotid endarterectomy.

Carotid percutaneous transluminal angioplasty and stenting (CAS) is recommended in selected patients (Class I, Level A). It should be restricted to the following subgroups of patients with severe symptomatic carotid artery stenosis: those with contraindications for CEA, stenosis at a surgically inaccessible site, restenosis after earlier CEA, and post-radiation stenosis (Class IV, GCP).

The procedure should be restricted to high volume CAS centers, with interventional radiologists experienced in different stent types and protection devices, and with the known perioperative complication rate of <6%.

Patients should receive a combination of clopidogrel and aspirin immediately before and for at least 1 month after stenting (Class IV, GCP).

Carotid angioplasty, with or without stenting, is not recommended for patients with asymptomatic carotid stenosis (Class IV, GCP).

### Stenting of Intracranial Artery Stenosis

Patients with symptomatic intracranial stenosis of  $\geq 50\%$  are at a high risk of recurrent strokes, both in the anterior and posterior circulation (12% after 1 year and 15% after 2 years in the territory of the stenosed artery)<sup>96,97</sup>. Severe stenosis ( $\geq 70\%$ ) carries a higher risk than moderate stenosis (50% to <70%)<sup>97</sup>. Since no RCTs were designed to evaluate angioplasty, stenting or both for intracranial stenosis, data derive from several non-randomized trials that showed feasibility and acceptable safety of intracranial stenting with the high risk of restenosis<sup>98,99</sup>. The incidence of complications after either angioplasty or stenting may be up to 6%<sup>98</sup>.

### Recommendations for Stenting of Intracranial Artery Stenosis

For patients with hemodynamically significant intracranial stenosis that have symptoms despite medical therapies (antithrombotics, statins, and other treatments for risk factors), the usefulness of endovascular therapy (angioplasty and/or stent placement) is

uncertain and is considered investigational (Class II, Level C).

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#### Sažetak

### PREPORUKE ZA LIJEČENJE BOLESNIKA S KAROTIDNOM STENOZOM

U ovom članku objavljujemo preporuke za zbrinjavanje bolesnika sa stenozom karotidnih arterija, prihvaćene od Hrvatskoga društva za neurovaskularne poremećaje, Hrvatskoga neurološkog društva, Hrvatskoga društva za ultrazvuk u medicini i biologiji, Hrvatskoga radiološkog društva, Hrvatskoga društva za vaskularnu kirurgiju i Hrvatskoga društva za neurokirurgiju. Sastoje se od preporuka za neinvazivni probir bolesnika s karotidnom stenozom, preporuke za najbolje medikamentno liječenje te preporuka za intervenciju kao što je karotidna endarterektomija i postavljanje stenta, a zasnovane su na rezultatima internacionalnih randomiziranih kliničkih pokusa.

*Ključne riječi: stenozna karotidne arterije, preporuke, karotidna endarterektomija, postavljanje stenta, duplex sonografija*