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GUIDELINES

VASCULAR SECTION

Guideline on carotid surgery for stroke prevention: updates from the Italian Society of Vascular and Endovascular Surgery

A trend towards personalized medicine

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ABSTRACT

BACKGROUND: This guideline (GL) on carotid surgery as updating of "Stroke: Italian guidelines for Prevention and Treatment" of the ISO-SPREAD Italian Stroke Organization-Group, has recently been published in the National Guideline System and shared with the Italian Society of Vascular and Endovascular Surgery (SICVE) and other Scientific Societies and Patient's Association.
METHODS: GRADE-SIGN version, AGREE quality of reporting checklist. Clinical questions formulated according to the PICO model. Recommendations developed based on clinical questions by a multidisciplinary experts' panel and patients' representatives. Systematic reviews performed for each PICO question. Considered judgements filled by assessing the evidence level, direction, and strength of the recommendations.
RESULTS: The panel provided indications and recommendations for appropriate, comprehensive, and individualized management of patients with carotid stenosis. Diagnostic and therapeutic processes of the best medical therapy, carotid endarterectomy (CEA), carotid stenting (CAS) according to the evidences and the judged opinions were included. Symptomatic carotid stenosis in elective and emergency, asymptomatic carotid stenosis, association with ischemic heart disease, preoperative diagnostics, types of anesthesia, monitoring in case of CEA, CEA techniques, comparison between CEA and CAS, post-surgical carotid restenosis, and medical therapy are the main topics, even with analysis of uncertainty areas for risk-benefit assessments in the individual patient (personalized medicine [PM]).
CONCLUSIONS: This GL updates on the main recommendations for the most appropriate diagnostic and medical-surgical management of patients with atherosclerotic carotid artery stenosis to prevent ischemic stroke. This GL also provides useful elements for the application of PM in good clinical practice.

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KEY WORDS: Carotid stenosis; Stroke; Prevention and control; Precision medicine; Guideline.

Introduction and objectives

The first Italian Guidelines (GL) on carotid surgery for stroke prevention dates back to 1997 as part of a corpus of Guidelines entitled "Stroke: Italian prevention and treatment guidelines," produced by an interdisciplinary Italian Stroke Organization-Stroke Prevention and Educational awareness Diffusion (ISO-SPREAD) Intersociety Group of scientific Societies. In 2017, an update on carotid endarterectomy (CEA) and carotid artery stenting (CAS) was published in the International Journal of Stroke.[1]

The Italian Society of Vascular and Endovascular Surgery (SICVE), a member of the ISO-SPREAD group, has recently updated the above GL on carotid surgery and shared it with the following scientific societies: ISA-AII-Italian Stroke Association (former ISO Italian Stroke Organization); GISE-Italian Society of Interventional Cardiology; SIAARTI-Italian Society of Anesthesiology, Analgesia and Intensive Care; SIAPAV-Italian Society of Angiology and Vascular Pathology; SIICP-Italian Interdisciplinary Society for Primary Care; SIRM-Italian Society of Medical and Interventional Radiology; SNAMI-Italian National Syndicate of Independent Doctors; 4S-SNAMI-SNAMI Scientific Society for Health, and ALICE Italia ODV Patients' Association.

To submit this new GL to the National Guidelines System (SNLG) of the Italian Institute of Health and the Ministry of Health, we followed the criteria recommended by the Methodological Manual of the SNLG. The full GL with annexes was published online on the website of the Ministry and the National Institute of Health (https://snlg.iss.it/) and the SICVE website (https://sicve.it/wp-content/uploads/2021/08/LINEA-GUIDA-Patologia-Carotidea_20.07.2021.pdf).

The present GL is shared in a multidisciplinary team of various scientific societies, and assumes that patients with carotid stenosis are to be considered "complex patients." The complexity of these patients is mainly due to: the presence of co-morbidities, the risk-benefit balance between medical-only therapy and medical/surgical therapy often challenging to define, and the frequent grey areas of uncertainty in the literature. These reasons lead to different opinions of the stakeholders that hinder to standardize and follow the medical-surgical diagnostic-therapeutic pathway. Consequently, the concordance between general practitioners, medical specialists, including vascular surgeons involved in the care process, and the patients, is mandatory. This topic lends itself to the so-called new personalized medicine o precision medicine (P-Medicine) that addresses the individual patient, complements and supplements the traditional evidence-based medicine (EBM*)*, which instead targets the standard patient as the statistical results of trials. The literature on this subject is more and more comprehensive.[2-5]

The main objective of this GL, developed in compliance with EBM and multidisciplinary consensus, was to update the recommendations for the decision-making process and the most appropriate medical-surgical diagnostic-therapeutic pathway for stroke prevention and good clinical practice in patients with atherosclerotic carotid stenosis.

This GL highlighted the increasingly decisive role of

P-Medicine in this field. While respecting the principles of EBM and the basic value of the evidence in the literature, our purpose was to display a suitable pathway for each patient, suggesting risk-benefit assessments, with a possible use of validated risk scores starting from the setting of paragraphs, questions and recommendations. Therefore, this GL pointed to general practitioners, vascular and endovascular surgeons, neurologists, radiologists, cardiologists, anesthetists, patients, family members, caregivers, public administrators, and experts.

In this paper, we described the methodology, the evidence, and assessments from the most relevant literature and developed by topics based on PICO (Patient/Population, Intervention, Comparison, Outcome) questions. We also reported some new definitions and recommendations that comply with the formulated PICO questions. These definitions and recommendations are based on EBM, Considered Judgement, and multidisciplinary Consensus of the stakeholders and could help apply P-Medicine in good clinical practice.

Methodology

We applied the GRADE-SIGN version[6] and also referred to the indications contained in the Procedures for the submission and evaluation of guidelines for publication in the SNLG-Operational Manual[7] and the Methodological Manual for the production of clinical practice guidelines[8] by the National Centre for Clinical Excellence, Quality and Safety of Care (CNEC).The present GL was developed according to the AGREE quality of reporting checklist[9] and, once completed, was assessed by the AGREE II tool.[10]

Editorial independence

No external funding was received. Declarations of conflict of interest are available on the SICVE website (https://sicve.it/about/conflitti-di-interesse-lg-patologia-carotidea/). All the authors declared that they had no financial, professional or other conflicts of interest.

Formulation of clinical questions

The first step was to formulate clinical questions structured according to the PICO model against which we issued the Recommendations. The PICO questions were formulated in agreement among the multidisciplinary panel of experts.

Systematic review of the literature

We performed a systematic review for each PICO question or homogeneous groups of questions. The studies were searched in PubMed, Cochrane Database of Systematic Reviews (CDSR), and Cochrane Central Register of Controlled Trials (CENTRAL). The detailed list of search strategies, together with the PRISMA Flow diagrams describing the selection process of the literature review, can be found online (https://snlg.iss.it/) (https://sicve.it/wp-content/uploads/2021/08/LINEA-GUIDA-Patologia-Carotidea_20.07.2021.pdf).

Selection process and critical evaluation of the literature

The literature was selected independently by pairs of authors for each clinical question or topic. Once the included articles were identified, the authors independently evaluated the methodological quality of each publication according to specific qualitative checklists provided by the GRADE-SIGN version. While other international GLs were used as an evidence base, the present GL was previously assessed using the AGREE II checklist, considering a total score of 60% as the minimum threshold of acceptability. The levels of evidence referable to the different study designs established by the checklists are displayed in Table I.

TABLE I.—*Levels of evidence.*

Level	Description
1++	High-quality meta-analysis and systematic reviews of randomized clinical trials with very low-risk of bias; single randomized clinical trials with very low-risk of bias
1+	Well-conducted meta-analysis and systematic reviews of randomized clinical trials with low-risk of bias; single randomized clinical trials with low-risk of bias
1-	Meta-analysis and systematic reviews on randomized clinical trials with high-risk of bias; single randomized clinical trials with high-risk of bias
2++	High quality systematic reviews of case-control or cohort studies; high quality case-control or cohort studies with a very low-risk of confounding or bias and a high probability of a causal relationship
2+	Well-conducted case-control or cohort studies with a low-risk of confounding or bias and a moderate probability of a causal relationship
2-	Case-control or cohort studies with a high-risk of confounding or bias and a significant risk of a non-causal relationship
3	Non-analytical studies, *e.g.* case reports and/or clinical case series
4	Expert opinion

After assessing the methodological quality of each article included for each PICO question, Evidence Tables were drawn up by describing the main characteristics of these studies: number and design of those included for the systematic reviews and meta-analysis), level of evidence, population characteristics (number of patients, pathology, age, sex), intervention(s), comparator(s), outcomes, effect measures for each outcome with their confidence intervals and p-values, and any comments regarding methodological limitations and generalizability of the results.

From evidence to recommendations

After the assessment of the methodological quality of the included articles, the authors filled in the Considered Judgement form for each clinical question. The Considered Judgement considered the characteristics of the body of evidence and the steps from the level of the evidence to the direction and strength of the recommendations. The Evidence Tables and Considered Judgements are published online (https://snlg.iss.it/)(https://sicve.it/wp-content/uploads/2021/08/LINEA-GUIDA-Patologia-Carotidea_20.07.2021.pdf).

Formulation of recommendations

There are two levels of Recommendation: Strong and Weak. Usually, high-quality evidence from well-conducted studies leads to a strong recommendation. If there were substantial differences between the population described in the studies and the target population, the patients' acceptability, and the applicability of the interventions, the recommendation was deemed "weak". However, sometimes the evidence was technically modest, but there was no controversial aspects of treatment. Then, if the subject had remarkably clinical importance, a strong recommendation was issued.

The Good Clinical Practice Points (GPP) intend to support the users' decisions of guidelines through expert's panel guidance. This guidance is based on clinical experience, even though no evidence or insufficient supporting evidence on clinically relevant issues are available.

In case of strict balance or uncertainty between undesirable and desired effects a "recommendation for research" was issued.

The summary diagram of the degree of recommendations is in Table II.

TABLE II.—*Degrees of recommendation.*

Judgment	Recommendation
Undesirable effects clearly outweigh the desired effects	Strong recommendation against
Undesirable effects are likely to outweigh the desired effects	Weak recommendation against
The balance between undesirable and desired effects is either in strict balance or uncertain	Recommendation for research and limited use in trials
Desired effects are likely to outweigh the undesirable effects	Weak recommendation in favor
Desired effects clearly outweigh the undesirable effects	Strong recommendation in favor
Best practice recommendation based on clinical experience of the Working Group producing the GL	Good Clinical Practice Point (GPP)

Terminology used for the recommendations

The experts' panel decided to use the following terminology: "is recommended-not recommended" in case of strong recommendation; "is indicated-not indicated" in case of weak recommendation; "the experts' panel suggests" in case of GPP.

Main evidences and assessments from the literature

Definitions

Symptomatic carotid stenosis

As a convention from traditional clinical studies, carotid stenosis is defined as symptomatic when the last congruent cerebral or retinal ischemic episode occurred in the patient within the previous six months. However, based on reviews, analyses, and comparisons of subgroups of the same clinical studies for this GL, the experts' panel suggests that carotid stenosis should be defined as symptomatic when the last congruent cerebral or retinal ischemic episode occurred within the previous three months at most. Otherwise, the carotid stenosis should be designed as asymptomatic (see GPP recommendation 1.9).

Asymptomatic carotid stenosis

As a convention from traditional clinical studies, carotid stenosis is defined as asymptomatic when no congruent cerebral or retinal ischemic episode has ever occurred or when the last congruent cerebral or retinal ischemic episode occurred in the patient more than the last six months. However, the experts' panel suggests defining a non-symptomatic carotid stenosis as asymptomatic when no congruent cerebral or retinal ischemic episode has

ever occurred or if the last congruent cerebral or retinal ischemic episode occurred in the patient more than three months before.

Please notice that in this GL, any reference to the degree of stenosis respects the NASCET- North American Symptomatic Carotid Endarterectomy Trial criteria (1 – residual diameter/distal diameter x 100).

Symptomatic carotid stenosis: indications for carotid endarterectomy

This topic is still debatable in the literature, and the mere degree of carotid stenosis, which still supports recommendations for surgical correction, may no longer be sufficient to suggest carotid surgery in symptomatic patients.

A review of the NASCET and ECST studies already documented a greater benefit from CEA in subgroups of patients with the highest risk of stroke with only medical therapy, such as a recent event, cerebral and non-ocular symptoms, ulcerated plaque, male gender, and old age. Therefore, Rothwel *et al.*[11] proposed a score to identify the patients with the greatest benefit from CEA:

- +1 for cerebral rather than ocular events;
- +1 for carotid atheroma plaque with irregular surface;
- +1 for events within the last two months;
- +1 for each decile of stenosis from 70% to 99%, -0.5 for female, -0.5 for peripheral vascular disease, and -0.5 for systolic BP >180 mm Hg.

The greatest benefit of CEA is achieved for scores >4 and includes 70-99% stenosis. Moreover, advanced age itself does not limit the indication for CEA. Indeed, the benefits of the CEA intervention are more relevant in older patients.

In addition to the degree of stenosis, the so-called plaque vulnerability or instability needs to be assessed.

The meta-analysis of Chang *et al.*, while confirming contralateral carotid artery occlusion as a risk factor in its own right, suggested treating the patient in the same way.[12]

Evidence suggests that no valid reason exists to preclude CEA in overweight or obese patients.[13]

On the other hand, it is advisable to assess and balance the risks associated with surgery. In the literature, we can find models and predictive scores for the risk of surgery based on retrospective analyses of extended case studies. Melin *et al.* proposed considering predictive factors of increased surgical risk such as advanced age, male gender, presence of neoplasia, chronic heart disease, kidney failure, chronic pneumopathy, cognitive decline, and motor dependence.[14]

Regarding the timing of CEA according to the time interval since the last index ischemic event, the review of Rothwell's *et al.*[11] demonstrated that the benefit of surgery compared to medical therapy alone was more evident in the first two weeks after the ischemic event. Then, the benefit progressively decreased to become almost null or almost identical to that observed in the studies on asymptomatic carotid stenosis after the twelfth week after the ischemic event. Therefore, the experts' panel believes that to classify the carotid stenosis as symptomatic, the six-month time interval, conventionally adopted in NASCET and ECST studies, should be significantly reduced to no more than three months after the last cerebral ischemic event.

Carotid stenosis in urgency: indications for revascularization

Among the patients who underwent CEA within two days, those treated for TIA had a better outcome than those treated for a non-disabling stroke.[15] The data also highlighted a benefit from 7-day over 14-day surgery, suggesting the optimal timing within 48 hours for TIA and seven days for stroke.[15, 16] However, Milgrom *et al.* highlighted an increased risk of stroke in the patients who underwent surgery within 48 hours of the index event compared with those who had surgery after 48 hours, while a very early surgery does not increase the risk of death, TIA, or myocardial infarction.[17]

In their meta-analysis, Rantner *et al.* reported a stroke rate of 1.3% and 3.6% in patients undergoing CEA when treated within and after seven days from the index event.[18] Their analysis also highlighted that, compared with CEA, stenting reported higher rates of stroke or death in both patients treated within seven and after seven days.[19]

Pini *et al.* analysed the results of CEA within 14 days or within 48 hours of a stable stroke, depending on the extent of brain injury. The study highlighted that the stroke and death rates were higher in patients undergoing CEA within 48 hours than within 14 days, with a higher risk in patients with extensive ischemic brain injury (volume >4000 mm^3) and severe neurological deficit.[20] On the other hand, Bazan *et al.* reported acceptable complication rates of 3% in patients undergoing revascularization within 15 days with a mean NIHSS score of 6.6.[21] Thus, the study suggested that the neurological deficit degree could have influenced the outcome of carotid revascularization in urgency/emergency. The study also highlighted the best results achieved in patients with an NIHSS score of less than 10.[21]

In a prospective study by Capoccia *et al.*, the emergency CEA did not have any particular risks in patients with mean NIHSS values of less than 8, although including NIHSS scores of up to 22.[22] In detail, a lesion with a maximum diameter of more than 2.5 cm or that involves more than one-third of the corresponding middle-cerebral artery area would be a contraindication to urgent carotid revascularization.

However, the stability of the neurological picture is essential. In a systematic review regarding the CEA by Fereydooni *et al.*, the risk of neurological complications was higher in the case of "crescendo TIA" than in the case of a single TIA.[23]

Nevertheless, medical therapy alone cannot ensure adequate prevention of new major neurological events (stroke) that generally occur in the short term after a TIA. Thus, CEA intervention within 48 hours combined with medical therapy is still considered beneficial compared to medical therapy alone; CEA intervention within 24 hours does not seem to provide significant additional benefits or risks. The authors also confirmed that stenting was reserved for cases deemed high-risk for CEA, in line with Batchelder's observations.[24]

A single natural history study reported a stroke recurrence rate of 5.5% at four days in patients who underwent urgent intravenous thrombolysis and waiting for revascularization treatment for carotid stenosis.[25] Therefore, the timing of CEA/CAS in these patients is under debate.

In the individual cases described in the twenty-two publications that included 1170 patients who underwent CEA, regardless of the timing of surgery after thrombolysis, the recurrence rate was 5.3%, the hemorrhagic transformation 2.5% (out of 968 patients), the mortality rate 2.7% (out of 1163 patients), and the acute myocardial infarction 0.6% (out of 345 patients). Lastly, 77% of the patients who received treatment had a good outcome at 90 days, defined by a modified Rankin scale score of less than or equal to 2. However, these data were reported only for 222 patients. In the 476 patients who underwent CAS, regardless of procedural timing, the recurrence rate was 4.8%, the hemorrhagic transformation was 5.2%, the mortality rate was 14.7%, and no acute myocardial infarctions were detected. If we consider only the 476 patients treated within 14 days following thrombolysis, almost exclusively undergoing CEA, the recurrence rate was 3.4%, the hemorrhagic transformation 1.3% (out of 270 patients), the mortality rate 3.9% (out of 456 patients), while the occurrence of acute myocardial infarction was 0.4% (out of 230 patients).

The systematic reviews of studies about the patients treated within 14 days, including those treated with intra-arterial thrombolysis, assessed different outcomes but identified a rate of hemorrhagic transformation between 2.6% and 7% and of stroke/death at 30 days between 3.9% and 4.9%.[16, 26, 28]

Notwithstanding the above, much of the literature agrees that revascularization treatments are safe if performed within 72 hours to at least six days after thrombolytic therapy. The reason is that, although rtPA has a short half-life, the hemorrhagic risk extends to 72 hours due to its prolonged effect on the coagulation system and a direct effect on blood-brain barrier permeability. On the other hand, surgical treatments within 48 hours after intravenous thrombolysis result in a statistically non-significant increase in hemorrhagic complications of wound or CEA-related stroke. This means that not only peri- or postoperative ischemic stroke but also hemorrhagic transformation following hyperperfusion syndrome.

Asymptomatic carotid stenosis: indications for carotid endarterectomy

The ACAS trial first documented the benefit of CEA in patients with ''asymptomatic'' 60% or more carotid stenosis (NASCET), but only after the third year of follow-up (more significant at five years).[29] Moreover, the benefit of CEA was present only if the perioperative complication rate (disabling stroke or death) was less than 3%.[29] According to a meta-analysis and a Cochrane review, CEA reduces the incidence of ipsilateral stroke in asymptomatic stenosis but with a low absolute benefit.[30] Therefore, CEA should not be recommended routinely, but it is advisable to identify subgroups of high-risk patients if not operated.

Also, the ten-year follow-up data of the ACST-1 study demonstrated a long-term benefit of CEA in patients younger than 75 years but a limited benefit in older patients.[31]

The ACSRS study yielded significant data to identify subgroups of patients most at risk of stroke with unoperated asymptomatic carotid stenosis.[32] The incidence rate of stroke was 2% per year in patients with a soft plaque and 0.14% per year in those with hard plaque, regardless of the degree of stenosis.[33] The combination of three risk factors (degree of stenosis, history of TIA, creatinine >85 μmol/L) intercepted the subgroup of patients with the highest risk of a cerebral ischemic event (4.3% per year).[34] A meta-analysis by Kamtchum-Tatuene confirmed these data.[35] However, a recent review by the Oxford group has confirmed a correlation between the severity degree of ste-

nosis and the risk of cerebral ischemic events. There was a statistically significant difference between patients with stenosis of 50-79% and those of 80-99% (P<0.001).[36]

Regarding medical therapy, a prospective study by Spence *et al.* showed that more intensive treatment could significantly reduce the incidence of cardio-cerebrovascular events and cerebral microembolism on TC Doppler in patients with asymptomatic carotid stenosis.[37] The authors concluded that patients with hemodynamically significant asymptomatic carotid stenosis should pursue intensive medical therapy in any case and only those with proven cerebral microembolism on TC Doppler.[37] The cases without cerebral microembolism should be referred for surgical treatment, provided that the risk of serious perioperative cardio-cerebral complications is less than 1%.

A systematic review by Abbott *et al.* highlighted the progress achieved in the medical therapy from the 1980s until today based on cohort studies of patients with asymptomatic carotid stenosis greater than 50% in terms of reducing the risk of ipsilateral and all types of stroke.[38] Thus, medical therapy can compete with and even cancels the benefit of surgery. The conclusion was that the best prevention in these cases is the best medical therapy (BMT), as long as it is possible to identify those patients at higher risk who could benefit from surgery. In a more recent non-randomized cohort study, Keyhani confirmed the same conclusions about BMT as an acceptable choice for patients with asymptomatic carotid stenosis.[39] Also, in a review by Pini, the risk of stroke in patients with asymptomatic carotid stenosis > 70% (NASCET) treated by medical therapy remains consistently low (1.7%).[40]

The meta-analyses by Galyfos,[41] Barkat,[42] Bisacco,[43] and Volkers[44] unanimously concluded that CEA has a benefit greater than medical therapy in the long-term prevention of cerebrovascular events (TIA/stroke) in subjects with asymptomatic carotid stenosis >70% (NASCET). However, the authors underlined the need to identify subgroups of patients at higher risk of stroke and therefore at higher benefit from surgery. In these patients, the risk-benefit balance of surgery and the assessment of procedural risk are also essential. After analysing the database of more than 17,000 patients undergoing CEA, Gupta[45] validated and proposed the following risk score for defining subgroups of asymptomatic patients at lower or higher perioperative risk:

- age: 0 points if <60; -1 points if 60-79; +2 points if ≥80;
- dyspnea: +2 points;
- chronic obstructive bronchopathy: +3 points;
- prior revascularization/amputation for peripheral arterial obstructive disease: +3 points;
- angina in previous months: +4 points;
- functional physical dependence: +5 points.

The periprocedural risk of a patient is classified as low (<3%) if the score is <4, medium (3-6%) if the score is between 4 and 7, and high (>6%) if the score is >7.

Ultimately, the recent considerations of Paraskevas *et al.* seem more than justified in this context: "Physicians should always seek to optimize patients' adherence to BMT according to current guidelines because all-cause and cardiac mortality in asymptomatic carotid stenosis are very high. Nevertheless, some patients may require specific modifications based on individual lifestyle, personal traits, social and cultural characteristics, as well as emerging advances in the field (for example, specific vulnerable carotid plaque features like intraplaque hemorrhage, neovascularization, plaque volume and inflammation that can be detected with the newer imaging approaches). A one-size-fits-all guideline policy may not be appropriate for all patients. Deciding which is the right treatment for the right patient is crucial. Some patients deserve/require a more aggressive (or a more conservative) approach than others. Consequently, the management of specific patients may need to be individualized, with active patient participation in making health and treatment choices".[5]

Carotid stenosis and ischemic heart disease

The research of the present GL is limited to the management of asymptomatic coronary artery disease with the prognostic impact in patients who are undergoing elective carotid revascularization, whether for asymptomatic or symptomatic stenosis. In addition, in patients with asymptomatic carotid stenosis, the long-term risk of acute myocardial ischemia (AMI) exceeds the risk of stroke by a factor of 4.[46] This data underscores the importance of the preprocedural cardiological management of patients with non-emergency carotid stenosis. In a recent retrospective study of patients undergoing CEA, the systematic preprocedural cardiological evaluation was compared with that performed only at the request of the anesthetist.[47] This comparison was an independent predictor of a reduction in post-procedural AMI (OR 0.61) and any post-CEA cardiac complications (OR 0.28).[47] At a 5-year follow-up, the incidence of death due to cardiovascular causes was significantly higher in patients who did not undergo systematic cardiological evaluation (8.0% vs. 4.2%).

According to Illuminati *et al.*, the systematic perfor-

mance of preoperative cardiological and coronarography evaluation in patients undergoing CEA without history suggesting coronary artery disease was associated with a significant reduction in post-CEA AMI in the long-term and an increased probability of 6-year survival.[48]

Therefore, elective preprocedural cardiological evaluation is indicated to stratify the cardiovascular risk and diagnosis of any associated coronary artery disease.

The use of validated predictive models, such as the Revised Cardiac Risk Index (RCRI) and the National Surgical Quality Improvement Program (NSQIP) indexes, combined with the estimation of functional capacity, allow to stratify the patients into categories of cardiovascular risk:

- low risk (RCRI=0, NSQIP<1%, moderate functional capacity-METs>4);
- intermediate-high risk (RCRI≥1, NSQIP≥1%;
- poor functional capacity-METs 1-4).

The RCRI and NSQIP indexes also support a correct and appropriate indication for preprocedural instrumental examinations for the diagnosis of coronary artery disease/associated myocardial ischemia. Recent recommendations from other scientific societies indicate the non-invasive *imaging* in the first instance to screen for myocardial ischemia/coronary artery disease.[49] Coronary CT can exclude critical coronary artery disease of the left main coronary artery and, in general, critical proximal coronary artery disease. Single-Photon Emission Computed Tomography (SPECT) can improve the prognostic stratification of intermediate-to-high-risk patients' undergoing vascular surgery. Exercise echocardiography or dobutamine stress echocardiography (DSE) may be examinations alternative or complementary to SPECT.

The option of preprocedural coronary investigation in selected patients (*e.g*., intermediate-to-high-risk, low functional capacity and multiple risk factors for coronary artery disease/diabetes mellitus, positive non-invasive instrumental tests) should be evaluated.

We investigated the management of patients indicated for CEA and coronary artery bypass after preprocedural cardiological evaluation, given the negative impact of carotid vasculopathy on the short-term prognosis of those subjects undergoing coronary artery bypass (20-25% of periprocedural cerebral strokes). Two recent meta-analyses compared combined myocardial and carotid surgical revascularization (in the same procedure) and sequential revascularization in the two districts.[50, 51] In the first meta-analysis, a higher incidence of postoperative stroke, perioperative death and death at 30 days was observed in the group with simultaneous treatment.[50] In the second meta-analysis, patients undergoing combined surgery had a lower risk of myocardial infarction but a higher risk of stroke and death.[51]

Given this evidence, we recommend an interdisciplinary assessment by a neurologist, cardiologist, vascular surgeon, cardiac surgeon and anesthetist, together with the patient, to make the most appropriate choice between combined or staged surgery, whether the carotid stenosis is symptomatic or asymptomatic and the indication is coronary stent or by pass.

Preoperative carotid and cerebral diagnostics

To provide early intervention in carotid revascularization for symptomatic stenosis, a duplex ultrasound (DUS) of the supra-aortic trunks should be undertaken as soon as possible, preferably within the first 24 hours after a cerebral ischemic event.[52] However, the literature is against widespread screening with DUS in asymptomatic subjects for cerebrovascular events.[53] Screening seems to be justified in patients with a non-negligible cerebrovascular risk profile such as those with advanced age and/or previous diagnosis of carotid stenosis and/or previous cerebrovascular ischemic event, patients with arteriopathy in other areas, those with known coronary artery disease, subjects aged over 65 years with more than one atherothrombotic risk factor.

The accuracy of DUS is widely discussed in the literature, and several meta-analysis[54, 55] showed that the peak systolic velocity (PSV) value has a sensitivity of 0.9 and a specificity of 0.85 in diagnosing ≥70% stenosis compared to the angiography. Overlapping values can also be obtained using end-diastolic velocity (EDV) as a reference: sensitivity of 0.82 and specificity of 0.99. Additional parameters (*e.g*., ICA/CCA PSV ratio, collateral flow activation, post-stenosis flow velocity) are necessary as PSV alone is not always indicative of the degree of stenosis (*e.g*., tandem lesion, severe contralateral stenosis, hyperdynamic state or depression of cardiac function). Other hemodynamic effects of stenosis in addition to velocity must be evaluated for a more accurate classification.[56, 57]

Ultimately, it seems reasonable and supported by data to use DUS as the first and only instrumental investigation in patients potentially eligible for carotid revascularization, followed — in case of doubt — by CT angiography or MR angiography. CT angiography exposes the patient to the risk of contrast medium but, at the same time, makes it possible to study the brain parenchyma and the intracranial circulation. CT angiography is suitable also for cases of acute cerebrovascular events,[58] has a fair sensitivity and

excellent specificity compared to angiography in assessing carotid stenosis.

MR angiography is an expensive method, not always available, and with some absolute contraindications, but it prevents the patient from exposing to ionizing radiations and iodized contrast medium.[52] In case of contraindications to a paramagnetic contrast medium, specific sequences such as TOF allow the imaging of the intracranial and carotid circulation. With MR angiography, we can also study brain parenchyma and the intracranial circulation in the same examination. MR angiography is much more sensitive than CT scans in identifying silent strokes, leading to a more accurate stratification of the risk of patients undergoing revascularization of asymptomatic stenosis.[59] According to meta-analyses, MR angiography has a sensitivity of 0.76-0.88 and a specificity of 0.84-0.86 in identifying stenosis of 70-99% compared with angiography. These values significantly increased using a contrast medium (sensitivity of 0.86-0.94, specificity of 0.91-0.93).[55]

Finally, in the case of symptomatic mild-to-moderate stenosis, monitoring of microembolic signals with transcranial Doppler may help to identify patients with a vulnerable and embolizing carotid plaque at risk for invasive treatment or stricter follow-up.[60]

Carotid endarterectomy: anesthesia and cerebral monitoring

CEA is typically undertaken both under general anesthesia (GA) (with instrumental cerebral monitoring or routine intraluminal shunt) and regional anesthesia (RA).[61] More recently, a third anesthetic option of cooperative patient general anesthesia (CPGA) has been added.[62] Intraoperative clinical neurologic monitoring is the reference method for detecting intraoperative cerebral hypoperfusion. It is applicable only if the patient is cooperative as with RA or CPGA. On the other hand, general anesthetics can decrease cerebral oxygen demand and improve cerebral circulation. However, an evidence-based superiority of an anesthesia modality for these patients has been demonstrated only recently for stroke, death, or myocardial infarction. Both the large randomized controlled trial GALA[61] and a meta-analysis done on 14 randomized controlled trials failed to show the superiority of one method of anesthesia over the others.[63] For this reason, the experts' panel recommends that each surgical team choose the type of anesthesia for carotid endarterectomy according to the institution's and the patient preferences.

Although a high level of patient satisfaction has been detected for GA, RA[64] and CPGA,[62] few studies explore the patients' preference on the choice of anesthesia. Therefore, additional studies on this topic have to be encouraged.

Clinical cerebral monitoring of awake patients is currently the reference method compared to any other neurological method. Other instrumental cerebral monitoring techniques have been reported to have relatively high specificity but too low sensitivity in detecting cerebral ischemia. Although specificity was found between 81% and 96% depending on the method type,[65] a sensitivity of 70% has been reported for EEG,[64] 58% for somatosensory evoked potential,[66] 74% for near-infrared spectroscopy,[65] 81% for transcranial Doppler,[65] and 75% for stump pressure.[65]

Moreover, according to a previous Cochrane review, there are no robust data to support the preference of a specific instrumental cerebral monitoring method for CEA.[67] However, according to some observational studies, the association of multiple diagnostic modalities may improve the sensitivity of each strategy.

Carotid endarterectomy: indications for surgical technique

In a recent systematic review, CEA by eversion (e-CEA) was associated with a 30-day reduction in death, stroke, myocardial infarction, or lateral-cervical hematomas, a lower rate of restenosis >50% even in the long term (at one year).[68] Besides, no difference was revealed between e-CEA and patched CEA (p-CEA), except in the presence of a lateral-cervical hematoma, which occurred in fewer cases in patients who underwent e-CEA than p-CEA, the operating time, and the need for shunt placement.

In a cohort study, there was no perioperative difference between the two groups (e-CEA and p-CEA).[69] However, in other cohort studies, the direct suture technique was not inferior to eversion methods and patching for death, myocardial infarction, TIA/stroke, cranial nerve injury, and hematomas in the short term (<30 days) as well as for restenosis >50% and TIA/stroke in the long term.[70]

In the study by Avgerinos, there was no significant difference between CEA for direct suture, p-CEA, and e-CEA in terms of restenosis, ipsilateral stroke, perioperative, and distant mortality.[71] The only predictors of stroke, mortality, and restenosis >70% were not the different closure methods but symptomatic carotid stenosis, heart failure, no statin therapy, and severe renal failure.

This evidence would show that routine patching may be

unjustified: patients should ideally be stratified according to internal carotid artery diameter to establish where selective patching may be appropriate and offer benefits.

Another aspect concerns the pressure variations occurring in the postoperative period, depending on the technique. As demonstrated in a systematic review by Demirel, postoperative hypertension developed more frequently after e-CEA; on the other hand, postoperative hypotension was more observed with other methods.[72] However, pressure changes were observed over a few days.

Carotid endarterectomy and stenting: comparing indications

In a recent meta-analysis by Knappich *et al.*, 13,086 CAS procedures were evaluated in patients with asymptomatic and symptomatic carotid stenosis. Multivariate analysis highlighted an independent association between the use of an embolic protection device and lower rates of in-hospital stroke or death.[73]

De Waard *et al.* performed a CT angiography sub-analysis in the ICSS study to describe all anatomical characteristics related to the risk of challenges and periprocedural stroke during CAS, defined as DAR (Delphi Anatomical Risk):[74]

- low, <5;
- low-intermediate, 5-5.9;
- intermediate-high, 6-6.9; high, 7.

The DAR score was not associated with a higher periprocedural stroke, but a prolonged procedure was significantly associated with higher stroke risk.

Rots *et al.* reported that plaque vulnerability, tortuosity of the internal carotid artery (ICA), and aortic arches type II or III were associated with the occurrence of new ischemic cerebral lesions at RM-DWI in patients who underwent CAS.[75]

In a Cochrane review comparing CAS and CEA, no significant difference emerged between the two techniques related to the risk of death and any stroke type at 30 days, the 1-year risk of death or stroke, risk of death, any stroke type, and myocardial infarction.[76] Conversely, there was a statistically significant difference in cranial nerve injuries in favor of the stent.

Therefore, due to the substantial heterogeneity of the comparative studies, the early interruption of two studies for the high risk of stents, and the uncertainty of the risk of restenosis and late stroke after stenting, the authors of the Cochrane review do not currently suggest a change in trend with an advantage of CAS compared to CEA for the surgical treatment of carotid stenosis. However, analyzing the Cochrane meta-analysis by Muller *et al.* that includes 22 trials with 9753 patients, we found a higher risk of death or stroke within 30 days of treatment with CAS (OR 1.72).[76]

The evidence highlighted a lower (peri- and post-procedural) risk of myocardial infarction, when performing CAS compared to CEA. Muller *et al.* analyzed data from two RCTs (SAPPHIRE 2004; Beijing 2013). These studies demonstrated a non-inferiority of stenting for death, stroke, or myocardial infarction at 30 days or for ipsilateral death or stroke during the first year of treatment in patients at high surgical risk (severe pulmonary or cardiac disease, stenosis after the previous endarterectomy, irradiation or neck surgery, or contralateral carotid occlusion).[76] All in all, in the systematic review by Müller *et al.*, CAS was associated with higher 30-day stroke rate compared with CEA (OR 1.78, IC 95% 1.38-2.29; P <0.00001, I2 = 0%) in symptomatic carotid stenosis.[76]

Undoubtedly, the largest RCT that has provided the most convincing data on carotid stenting is the CREST study.[77] In the analysis of long-term results, the authors concluded that the composite risk of stroke, myocardial infarction, and death did not differ significantly between CAS and CEA. However, in the periprocedural period, there was a higher risk of stroke with CAS and myocardial infarction with CEA.

In the literature published after January 2016, there was no difference in periprocedural events between the two treatment methods (CAS *versus* CEA) for patients with asymptomatic carotid stenosis. On the other hand, the data published in 2010 for CAS versus CEA showed an HR of 1.88 for periprocedural events and of 1.86 for long-term events. Also, CAS versus CEA for the asymptomatic patients of the ACST-2 trial was recently compared.[79] There was an OR of 1.35 for periprocedural events and 1.23 for longer-term events. The ACT-1 study reported an OR of 1.69 for periprocedural events.[80] In the RCT published by Featherstone, no significant difference in disabling stroke/death between CAS (4%) and CEA (3.2%) in the case of symptomatic carotid stenosis.[81] The risk of stroke, death, or myocardial infarction was higher in CAS compared with CEA (30-day risk: 7.4% *versus* 4.0%).[81]

Rantner *et al.* reported a higher risk of postoperative stroke/death in CAS than CEA (7.3% versus 3.3%; RR 2.3) in symptomatic patients from four RCTs.[18] Batchelder *et al.* found a significantly higher postoperative stroke/death after CAS than CEA (OR 1.71) from twenty RCTs.[24] Brott *et al.* underlined the superiority of CEA compared with

CAS in combined peri- and postoperative outcomes for symptomatic patients, whereas the postoperative results were comparable.[84] Similarly, the meta-analysis of Jung *et al.* noted a higher incidence of postprocedural stroke in symptomatic patients who have undergone CAS.[85]

A systematic review of Texakalidis *et al.* showed an overlapping risk of stroke, myocardial infarction, and MACEs (major adverse cardiovascular events) between CEA and CAS in patients with contralateral carotid occlusion, even though the patients in the CAS group had a lower 30-day risk of death.[86]

Finally, Faggioli *et al.* assessed the influence of conversion of oral anticoagulant to heparin therapy on post-CEA outcomes.[87] They also evaluated the influence of unmodified oral anticoagulant therapy (TAO) in CAS.[87] There was an increased risk of stroke, death, myocardial infarction, and hematoma in the former group compared with the latter.

Post-surgical carotid restenosis

In the meta-analysis by Kumar *et al.*, the incidence of post-CEA restenosis at four years was 5.8%, with lower values in patched CEA (4.1%). In patients treated with CAS, the incidence of restenosis at five years was 10%.[88]

Regarding the correlation between restenosis and clinical events in the follow-up, the ICCS trial showed that restenosis >50% occurred more frequently in patients randomized to CAS than in those to CEA.[89] The ICCS trial also demonstrated that the risk of stroke at six years was significantly higher in patients with restenosis >50% (6.9%) than in those without (2.5%); in particular, the risk was higher in subjects who underwent CEA than in those who underwent CAS.[89] Moreover, there seemed to be no correlation between significant asymptomatic restenosis (>70%) and ipsilateral stroke in patients who underwent CAS (0.8% risk in patients with restenosis and 2% in those without at four years, OR 0.87).[88] On the other hand, in patients with asymptomatic restenosis >70% post-CEA, the 4-year stroke risk was 5.2% compared to 1.2% in those without significant restenosis (OR 4.7).

For patients with symptomatic, moderate, or severe restenosis, either post CAS or post CEA, notwithstanding a lack of comparative studies, the established practice is to apply the same indications as in the guidelines for primary symptomatic stenosis.

Two systematic reviews on the treatment of carotid restenosis analyzed the results of open and endovascular treatment after CEA and CAS.[90, 91] The limited evidence showed that, in patients with post-CEA or post-CAS restenosis, the endovascular treatment yielded results similar to the open reintervention for major neurological complications and perioperative death but reduced the risk of peripheral neurological injuries.

Medical therapy to support surgery

Systematic reviews largely agreed that antiplatelet monotherapy is preferable to a placebo and dual antiplatelet therapy, both before and after CEA surgery.[92] As for patients who underwent CAS, in the meta-analysis no significant difference emerged in terms of stroke, major bleeding, and neck hematoma between single and dual antiplatelet therapy, while there was a reduction in TIAs in patients on dual antiplatelet therapy compared to those in monotherapy.[93] Most clinical trial protocols and Good Clinical Practice protocols agree that a period of a few months (at least three) of dual antiplatelet therapy after stenting and subsequent long-term monotherapy over the years is justified. Several clinical studies assessed the use of statins before and after major vascular surgery and documented a 2-3-fold reduction in the combined end-points: myocardial infarction, stroke, and death. A meta-analysis results also demonstrated a significant reduction of the risk of periprocedural stroke and 30-day mortality, as well as improved 5-year survival in patients who underwent carotid revascularization treated with statins.[94]

Recommendations

1. Symptomatic carotid stenosis - indications for carotid endarterectomy

1.1 In patients with symptomatic carotid stenosis of less than 50% (NASCET criteria) or chronic occlusion of the internal carotid artery or disabling major ischemic stroke, endarterectomy is not recommended, as it does not improve the clinical course compared to medical therapy alone. (*Strong recommendation against, level of evidence 1++*)

1.2 In patients with even symptomatic near-occlusion of the internal carotid artery carotid, endarterectomy is not indicated, as it does not improve the clinical course compared to medical therapy alone. (*Weak recommendation against, level of evidence 1++*)

1.3 In patients with symptomatic carotid stenosis equal to or greater than 70% (NASCET criteria), endarterectomy is recommended, as it improves the clinical course compared to medical therapy alone, if the perioperative risk of death and all types of stroke is less than 6%. (*Strong recommendation in favor, level of evidence 1++*)

1.4 In patients with symptomatic carotid stenosis between 50-69% (NASCET criteria), endarterectomy is recommended, as it improves the clinical course compared to medical therapy alone if the perioperative risk of death and all types of stroke are less than 6% and if at least one of the following conditions intervenes: recent ischemia, cerebral and not ocular symptom, unstable plaque, and male gender. We should consider that the benefit is significantly reduced in diabetic patients and in any case more than 30 days after the index ischemic event. (*Strong recommendation in favor, level of evidence 1++*)

1.5 In patients with symptomatic carotid stenosis, endarterectomy (if indicated) is also recommended in the case of contralateral carotid occlusion and/or advanced age and/or high body mass index. In these cases, endarterectomy improves the clinical course compared to medical therapy alone. (*Strong recommendation in favor, level of evidence 1+*)

1.6 In patients with symptomatic carotid stenosis, to better define the risk/benefit ratio of endarterectomy, the experts' panel suggests applying validated Risk Scores that consider at least comorbidities (neoplasia, history of ischemic heart disease, chronic kidney failure, chronic obstructive pulmonary disease, cognitive impairment), gender, the extent of stenosis and morphological characteristics of the lesion, type of neurological event (cerebral or ocular), and whether there is an ipsilateral ischemic lesion on CT or MRI. (*GPP recommendation*)

1.7 In patients with symptomatic carotid stenosis with carotid web lesions, particularly in young patients (<50 years of age) and even without any cardiovascular risk factors, endarterectomy is recommended as it improves the clinical course compared to medical therapy alone. (*Strong recommendation in favor, level of evidence 1++*)

1.8 In patients with symptomatic carotid stenosis, endarterectomy (if indicated) is recommended within the first week after a congruous cerebral or retinal ischemic event as it improves the clinical course compared to endarterectomy after the first week. (*Strong recommendation in favor, level of evidence 1++*)

1.9 The comparison of clinical studies showed that, in patients with symptomatic carotid stenosis, the benefit of endarterectomy compared to medical therapy alone is appreciable if it is conducted within no more than three months after the congruous cerebral or retinal ischemic episode. After three months, the benefit of endarterectomy is almost identical to that achieved with carotid endarterectomy for asymptomatic stenosis. Therefore, the experts' panel suggests that carotid stenosis should be defined as symptomatic if the last congruous cerebral or retinal ischemic episode occurred in the patient within the previous three months at the latest; otherwise, the carotid stenosis should be defined as asymptomatic. (*GPP recommendation*)

2. Carotid stenosis in urgency: indications for revascularization

2.1 In patients with a single episode of TIA and carotid stenosis between 50-99% (NASCET criteria) carotid revascularization is recommended within seven days. If possible, carotid revascularization is recommended within 48 hours, as it improves the clinical course compared to carotid revascularization after seven days or optimal medical therapy alone. (*Strong recommendation in favor, level of evidence 1++*)

2.2 In patients with mild to moderate acute ischemic stroke and carotid stenosis between 50-99% (NASCET criteria) and patency of the intracranial-anterior circulation, carotid revascularization is recommended between three and seven days, as it improves the clinical course compared to carotid revascularization within 48 hours or after seven days or compared to optimal medical therapy alone. (*Strong recommendation in favor, level of evidence 1++*)

2.3 In patients with severe acute ischemic stroke and large cerebral lesion (greater than 4000 mm^3 or one-third of the middle cerebral artery territory) or with hemorrhagic transformation and carotid stenosis between 50-99% (NASCET criteria) or acute occlusion of the ipsilateral extracranial internal carotid artery, carotid revascularization is not recommended, as it worsens the clinical course compared to optimal medical therapy alone. (*Strong recommendation against, level of evidence 1++*)

2.4 In patients with TIA or mild to moderate acute ischemic stroke and carotid stenosis between 50-99% (NASCET criteria) and patency of the intracranial-anterior circulation, carotid endarterectomy is recommended, as it improves the clinical course compared to carotid stenting. (*Strong recommendation in favor, level of evidence 1++*)

2.5 In patients with mild to moderate acute ischemic stroke and ipsilateral carotid stenosis between 50-99% (NASCET criteria), and patency of the anterior-intracranial circulation, comparison studies on carotid endarterectomy within 48 hours and carotid endarterectomy between three and seven days are recommended. (*Recommendation for research*)

2.6 In patients with unstable acute ischemic stroke, such as crescendo TIA or stroke in evolution, ipsilateral carotid

stenosis between 50-99% (NASCET criteria) and patency of the anterior-intracranial circulation, carotid endarterectomy is indicated as soon as possible, as it improves the clinical course compared to optimal medical therapy alone. (*Weak recommendation in favor, level of evidence 1-*)

2.7 In high-risk surgical patients with TIA or mild to moderate acute ischemic stroke or unstable acute ischemic strokes, such as crescendo TIA or stroke in evolution, ipsilateral carotid stenosis between 50-99% (NASCET criteria), and patency of the anterior-intracranial circulation, the experts' panel suggests considering carotid stenting or optimal medical therapy alone as an alternative to endarterectomy. (*GPP recommendation*)

2.8 In patients with unstable acute ischemic stroke, such as crescendo TIA or stroke in evolution, ipsilateral 50-99% carotid stenosis (NASCET criteria), and patency of the anterior-intracranial circulation, comparison studies on carotid endarterectomy within 48 hours and carotid endarterectomy between three and seven days are recommended. (*Recommendation for research*)

2.9 In patients with TIA or mild to moderate ischemic stroke or unstable acute ischemic stroke, such as crescendo TIA or stroke in evolution, and ipsilateral carotid stenosis between 50-99% (NASCET criteria) and patency of the anterior-intracranial circulation, additional comparison studies on endarterectomy and carotid stenting are recommended. (*Recommendation for research*)

2.10 In patients with mild-to-moderate acute ischemic stroke undergone intravenous thrombolysis related to the ischemic event, residual extracranial carotid stenosis between 50-99% (NASCET criteria) and patency of the anterior-intracranial circulation, with an ischemic lesion not involving more than one-third of the ipsilateral-middle cerebral artery territory and without hemorrhagic transformation at neuroimaging, carotid endarterectomy is indicated within 14 days from thrombolytic treatment, as it improves the clinical course compared to optimal medical therapy alone. (*Weak recommendation in favor, level of evidence 2+*)

2.11 In patients with mild to moderate acute ischemic stroke undergone intravenous thrombolysis, residual extracranial carotid stenosis between 50-99% (NASCET criteria) related to the ischemic event, and patency of the anterior-intracranial circulation, an ischemic lesion not involving more than one-third of the ipsilateral middle cerebral artery territory and without hemorrhagic transformation on neuroimaging, comparison studies are recommended on: a) carotid endarterectomy, carotid stenting and optimal medical therapy alone, b) carotid endarterectomy within 72 hours and 72 hours after thrombolysis. (*Recommendation for research*)

2.12 The experts' panel suggests that the indication for extracranial carotid revascularization for residual stenosis after intravenous thrombolysis related to the ischemic event should be defined in close cooperation with the vascular surgeon and the neurologist and then shared with the patient. The experts' panel also suggests that continuous postoperative monitoring should be performed in the Stroke Unit and/or by dedicated staff. (*GPP recommendation*)

2.13 In patients with severe acute ischemic stroke undergone intravenous thrombolysis related to ischemic event, residual extracranial carotid stenosis between 50-99% (NASCET criteria), patency of the anterior cerebral circulation, ischemic lesion that does not involve more than one-third of the ipsilateral-middle cerebral artery territory and without hemorrhagic transformation on neuroimaging, comparison studies on carotid endarterectomy, carotid stenting and optimal medical therapy alone are recommended. (*Recommendation for research*)

2.14 Studies on reliable advanced neuroimaging methods, such as perfusion brain CT or MRI with diffusion and perfusion sequences, are recommended in order to select patients undergoing early carotid revascularization, with patency of the intracranial anterior circulation and residual extracranial carotid stenosis between 50-99% (NASCET criteria) after intravenous thrombolysis related to the ischemic event. (*Recommendation for research*)

3. Asymptomatic carotid stenosis: indications for carotid endarterectomy

3.1 In patients with asymptomatic carotid stenosis, optimal medical therapy is still recommended. (*Strong recommendation in favor, level of evidence 1++*)

3.2 In patients with asymptomatic carotid stenosis, revascularization as an alternative to optimal medical therapy is not recommended. (*Strong recommendation against, level of evidence 1-*)

3.3 In patients with asymptomatic carotid stenosis equal to or greater than 70% (NASCET criteria) endarterectomy, combined with optimal medical treatment, is indicated in case of stenosis at high atherothromboembolic risk despite pharmacological treatment, after careful assessment of the risk/benefit ratio by a possibly multidisciplinary team. (*Weak recommendation in favor, level of evidence 1-*)

3.4 In patients with asymptomatic carotid stenosis, endarterectomy provided modest benefit compared to optimal medical therapy alone. Thus, endarterectomy is indicated if:

• stenosis is equal to or greater than 70% (NASCET criteria), given that the risk of stroke with medical therapy alone increases for stenosis of a higher degree (80-99%) (*level of evidence 1+*);

• the rate of major perioperative complications (stroke, death) is less than 3% (optimal: less than 1%) (*level of evidence 1-*);

• life expectancy is longer than three years (*level of evidence 1-*);

• the patient, despite being treated with optimal medical therapy, has a lesion "at-risk" for at least one of the following conditions: coexisting ischemic embolic silent lesion ipsilateral to brain CT/RM, vulnerable or ulcerated or rapidly growing plaque, contralateral carotid artery occlusion, and presence of ipsilateral microembolic signals on transcranial Doppler (*level of evidence 2++*). (*Weak recommendation in favor)*

3.5 In patients dependent on support in daily activities or with a short life expectancy, surgical treatment of asymptomatic carotid stenosis is not indicated. (*Weak recommendation against, level of evidence 1-*)

3.6 In patients with asymptomatic carotid stenosis, with a poor prognosis or high surgical risk, endarterectomy is not indicated. The following are considered unfavorable prognostic factors or high surgical risk factors: 1) advanced malignant tumor; 2) insulin-treated and/or decompensated diabetes mellitus; 3) congestive heart failure; 4) severe chronic obstructive pulmonary disease; 5) chronic renal failure undergoing dialysis treatment. (*Weak recommendation against, level of evidence 1*)

3.7 In patients with asymptomatic carotid stenosis undergoing revascularization, to improve the risk/benefit assessment of the procedure, the experts' panel suggests using a validated risk scale containing more evidence-based indicators, such as 1) gender; 2) age group; 3) vascular comorbidity; 4) organ damage. (*GPP recommendation*)

4. Carotid stenosis and ischemic heart disease

4.1 In patients with carotid stenosis and undergoing elective revascularization, systematic preprocedural cardiological clinical evaluation is indicated for the diagnosis of associated coronary artery disease with prognostic impact, even asymptomatic. Indeed, systematic preprocedural cardiological clinical evaluation prevents perioperative cardiovascular complications and improves short- and long-term clinical course compared to no systematic preprocedural cardiological evaluation. (*Weak recommendation in favor, level of evidence 2+*)

4.2 In patients with carotid stenosis undergoing elective revascularization, the experts' panel suggests the use of validated cardiological predictive scores (RCRI, NSQIP-MICA, NSQIP-ACS) and functional capacity estimation for low-to-intermediate-high cardiovascular risk stratification to identify patient deserving further preprocedural investigations, prevent perioperative cardiovascular complications, and improve short- and long-term clinical course. (*GPP recommendation*)

4.3 In patients with carotid stenosis undergoing elective revascularization with good functional capacity and low cardiovascular risk estimated at cardiological clinical evaluation, non-invasive preoperative instrumental examinations for the diagnosis of coronary artery disease with prognostic impact are not indicated because they do not prevent perioperative cardiovascular complications and do not improve the short- and long-term clinical course. (*Weak recommendation against, level of evidence 2-*)

4.4 In patients with carotid stenosis undergoing elective revascularization with poor functional capacity and intermediate-to-high cardiovascular risk estimated at cardiological clinical evaluation, non-invasive preoperative instrumental examinations (coronary CT and/or cardiac SPECT and/or cardiac echocardiography) for the diagnosis of coronary artery disease with prognostic impact (even asymptomatic) may be indicated to improve risk stratification, prevent perioperative cardiac complications and improve the short- and long-term clinical course. (*Weak recommendation in favor, level of evidence 2+*)

4.5 In patients with carotid stenosis undergoing elective revascularization, with good functional capacity and low cardiovascular risk estimated at cardiological clinical evaluation, preoperative coronarography is not indicated. Indeed, preoperative coronarography does not prevent perioperative cardiovascular complications and does not improve the short- and long-term clinical course. (*Weak recommendation against, level of evidence 1-*)

4.6 In patients with carotid stenosis undergoing elective revascularization with low functional capacity and intermediate-to-high cardiovascular risk estimated at cardiological clinical evaluation, the experts' panel suggests a multi-specialist interdisciplinary evaluation. Moreover, the experts' panel suggests sharing with the patient the indication for coronarography and choosing between post-carotid procedure coronarography or pre-carotid procedure coronarography with possible concomitant coronary angioplasty to prevent cardiovascular complications and improve the clinical course in the short and long term. (*GPP recommendation*)

4.7 In patients with asymptomatic carotid stenosis un-

dergoing revascularization and associated ischemic coronary artery disease undergoing aortocoronary bypass, the experts' panel suggests improving the clinical course with the interdisciplinary evaluation by the neurologist, cardiologist, vascular surgeon, cardiac surgeon and anesthetist. The experts' panel also suggest sharing with the patient the choice between combined surgery (carotid endarterectomy and aortocoronary bypass in the same session) or staged surgery, possibly preferring to prioritize aortocoronary bypass if the asymptomatic carotid stenosis to be revascularized is unilateral. The experts' panel suggests prioritizing carotid revascularization if the asymptomatic carotid stenosis to be revascularized is bilateral or unilateral with contralateral carotid occlusion. (*GPP recommendation*)

4.8 In patients with symptomatic carotid stenosis undergoing revascularization, and associated ischemic coronary artery disease undergoing aortocoronary bypass, the experts' panel suggests the interdisciplinary evaluation by the neurologist, cardiologist, vascular surgeon, cardiac surgeon, and anaesthetist to improve the clinical course. The experts' panel also suggests sharing with the patient the choice between combined surgery (carotid endarterectomy and aortocoronary bypass) or staged surgery, preferring to prioritize carotid revascularization. (*GPP recommendation*)

5. Preoperative carotid and cerebral diagnostics

5.1 In patients with ischemic stroke/TIA, color Duplex ultrasound (DUS) of the supra-aortic trunks is recommended within 24 hours or as soon as possible for appropriate etiopathogenetic assessment and to allow the diagnosis of possible symptomatic carotid stenosis, the early medical and, if indicated, surgical treatment. (*Strong recommendation in favor, level of evidence 2++*)

5.2 The experts' panel suggests that a DUS of the supra-aortic trunks for the diagnosis of carotid stenosis should be accomplished in patients undergoing major cardiovascular surgery, with a non-negligible cerebrovascular risk profile (i.e., advanced age and/or with a previous diagnosis of carotid stenosis and/or a previous cerebrovascular ischemic event). (*GPP recommendation*)

5.3 In patients undergoing major cardiovascular surgery, studies on the usefulness of DUS of the supra-aortic trunks for assessing the risk of perioperative stroke are recommended. (*Recommendation for research*)

5.4 The DUS of the supra-aortic trunks as a screening investigation for asymptomatic carotid stenosis in the general population and subjects asymptomatic for a cerebrovascular event with low cardio-cerebrovascular risk is not recommended. (*Strong recommendation against, type of evidence 2+*)

5.5 The experts' panel suggests that the DUS of the supra-aortic trunks as a screening investigation for asymptomatic carotid stenosis may be indicated in subjects asymptomatic for a cerebrovascular event with high cardio-cerebrovascular risk, such as patients with peripheral arteriopathy and/or coronary artery disease, subjects over 65 years of age and with more than one atherothrombotic risk factor. (*GPP recommendation*)

5.6 The DUS of the supra-aortic trunks is recommended as a first-line examination for diagnosis of carotid stenosis rather than the angiography of the supra-aortic trunks, provided that it is undertaken by experts and within validated parameters. The DUS should be possibly supplemented with another non-invasive second-level diagnostics (CT angiography or MR angiography) in the case of a doubtful or incomplete diagnosis with only DUS to define the degree of stenosis or the morphological or structural characteristics of atheromatous plaque. (*Strong recommendation in favour, level of evidence 2++*)

5.7 In patients with carotid stenosis, for a reliable non-invasive assessment of the degree of stenosis by DUS of the supra-aortic trunks, the multi-parameter approach (ICA/CCA-PSV ratio, pre- and post-stenosis flow velocity, morphological characteristics) is indicated to improve the diagnostic course compared to the single parameter velocimetric approach. (*Weak recommendation in favor, level of evidence 2++*)

5.8 In patients with carotid stenosis, for a reliable non-invasive assessment of the degree of stenosis by DUS of the supra-aortic trunks, the experts' panel suggests using multi-parameter criteria to be internally validated. The suggested multi-parameter criteria for carotid stenosis equal to or greater than 70% (NASCET criteria) are:

- PSV threshold (peak systolic velocity): >230 cm/s;
- post-stenosis PSV: ≥50 cm/s;
- EDV (end-diastolic velocity): >100 cm/s;
- PSV ICA/PSV CCA ratio: >4;
- pre-stenosis flow: possible reduction in diastolic velocity;
- post-stenosis flow: altered velocity;
- possible reversal flow velocity of ophthalmic test or anterior cerebral artery at transcranial Doppler.

(*GPP recommendation*)

5.9 In patients with symptomatic carotid stenosis undergoing revascularization, CT or MRI neuroimaging is recommended, considering that MRI is more sensitive and specific in the case of TIA or minor stroke to allow a cor-

rect indication for surgery. (*Strong recommendation in favor, level of evidence 2++*)

5.10 In patients with asymptomatic carotid stenosis undergoing revascularization, CT or MRI neuroimaging is indicated for the diagnosis of any previous or silent cerebral ischemia, whose presence indicates a greater benefit of revascularization than the optimal medical therapy alone. In any case, the implementation (rather than non-implementation) of CT or MRI allows a more correct indication for revascularization and improves the clinical course. (*Weak recommendation in favor, level of evidence 2+*)

5.11 In patients with asymptomatic carotid stenosis undergoing revascularization, in order to improve the assessment of the risk/benefit ratio of surgery, transcranial Doppler is indicated for diagnosis of ipsilateral microembolic signals, showing an increased benefit in case of presence of signals. (*Weak recommendation in favor, level of evidence 2+*)

5.12 In patients with carotid stenosis undergoing revascularization, additional studies on the usefulness of transcranial Doppler are recommended regarding:

- a. increased risk of cerebral reperfusion injury after revascularization;
- b. need for intraluminal shunt during carotid endarterectomy based on CO_2 reactivity tests;
- c. more benefit from revascularization in case of symptomatic mild-to-moderate carotid stenosis and with ipsilateral cerebral microembolic signals.

(*Recommendation for research*)

6. Carotid endarterectomy: anesthesia, cerebral monitoring, postoperative heparin neutralization, postoperative systemic arterial pressure monitoring

6.1 In patients undergoing carotid endarterectomy, either loco-regional or general anesthesia with instrumental cerebral monitoring and possible selective/routine temporary intraoperative intraluminal shunt or cooperative patient general anesthesia (CO.PA.GE.A) is recommended. The center's expertise, just as the patient's preference and conditions, are to be considered. (*Strong recommendation in favor, level of evidence 1++*)

6.2 In patients undergoing carotid endarterectomy, further (preferably multicenter) studies are recommended to estimate the patient's preference and satisfaction with the type of anesthesia: loco-regional, general or cooperative patient general anesthesia. (*Recommendation for research*)

6.3 In patients undergoing carotid endarterectomy, intraoperative cerebral clinical or instrumental monitoring is recommended, depending on the type of anesthesia and the intraoperative intraluminal shunt strategy, although clinical monitoring is more sensitive. (*Strong recommendation in favor, level of evidence 2+*)

6.4 The experts' panel suggests that in patients undergoing carotid endarterectomy, if possible and deemed appropriate, more than one method of instrumental neurological monitoring should be used. Indeed, the combination of multiple methods may increase sensitivity compared to a single one. (*GPP recommendation*)

6.5 In patients undergoing carotid endarterectomy, additional (preferably multicenter) studies are recommended to assess whether protamine neutralization of intraoperative heparin at the end of the procedure compared to no neutralization reduces postoperative bleeding complications without increasing the risk of postoperative thrombosis. (*Recommendation for research*)

6.6 In patients undergoing carotid endarterectomy, postoperative monitoring of systemic blood pressure and possible treatment of hypertension is indicated, as it improves the clinical course compared to no monitoring. (*Weak recommendation in favor, level of evidence 2-*)

7. Carotid endarterectomy: indications for surgical technique

7.1 In patients undergoing carotid endarterectomy, the patch angioplasty technique or the eversion or semi-eversion technique (the choice is determined by the center and operator's expertise) is recommended, as it improves the clinical course compared with the primary closure technique. (*Strong recommendation in favor, level of evidence 1++*)

7.2 In patients undergoing carotid endarterectomy, the primary closure technique is indicated if performed in centers with a peri- and postoperative major complication rates (death, stroke, restenosis) similar to those observed with patch angioplasty or eversion or semi-eversion technique. In case of primary closure technique, a preoperative score should be applied to the patient, considering the main predictors of higher risk of cerebral ischemic complications or carotid restenosis, such as severe kidney failure and/or internal carotid artery diameter less than 5 mm and/or absence of statin therapy and/or a previous cerebral ischemic event and/or heart failure. (*Weak recommendation in favor, level of evidence 2+*)

7.3 In patients undergoing carotid endarterectomy with patch angioplasty technique, no particular type of patch (bovine pericardium, Dacron, polyurethane) is indicated. Indeed, a different type of patch is not associated with

a significant difference in complications such as stroke, death, bleeding, infection, and restenosis. (*Weak recommendation against, type of evidence 2+*)

7.4 The experts' panel suggests that, in patients undergoing carotid endarterectomy, the choice between selective intraluminal shunt with cerebral monitoring and routine intraluminal shunt without cerebral monitoring should be based on the expertise of the center and operator. Also, the choice should take into account clinical and/or anatomical predictive factors for risk/benefit balance in the single patient. (*GPP recommendation*)

7.5 In several cohort studies and experiences the trend is for the selective intraluminal shunt with cerebral monitoring during carotid endarterectomy. In many centers, at the same time, the tendency is toward the routine intraluminal shunt without cerebral monitoring. Therefore, further (preferably randomized) comparative controlled studies are recommended. (*Recommendation for research*)

8. Carotid endarterectomy and stenting: comparing indications

8.1 In patients with carotid stenosis and indication for stenting, the use of proximal or distal cerebral protection device is recommended, as it improves the clinical course compared to non-use. (*Strong recommendation in favor, level of evidence 1++*)

8.2 In patients with carotid stenosis and indication for stenting, is indicated to consider vulnerable carotid plaque and/or vessel tortuosity and/or aortic arch calcifications and/or type III or bovine arch as individual periprocedural risk factors greater than with endarterectomy. Indeed, the assessment of these elements improves the clinical course compared to not considering them. (*Weak recommendation in favor, level of evidence 1+*)

8.3 In patients with asymptomatic carotid stenosis between 70-99% (NASCET criteria) and mild to moderate surgical risk, endarterectomy is indicated as the method of choice to improve the clinical course compared to stenting. As an alternative to endarterectomy, stenting may be indicated in centers with documented expertise and a periprocedural risk rate no higher than that for endarterectomy in asymptomatic patients. (*Weak recommendation in favor, level of evidence 1++*)

8.4 In patients with asymptomatic carotid stenosis between 70-99% (NASCET criteria) and high surgical risk, carotid stenting is indicated as an alternative to endarterectomy if it is performed in centers with documented expertise, and a periprocedural risk rate not higher than that for endarterectomy in asymptomatic patients. Patient with one of the following characteristics is deemed at high surgical risk:

- clinically significant heart disease (congestive heart failure, positive ergometric test or need for cardiac surgery);
- severe pulmonary disease;
- contralateral laryngeal nerve paralysis;
- ongoing oral anticoagulant therapy;
- previous major cervical radiotherapy;
- restenosis after endarterectomy or stenting.

(*Weak recommendation in favor, level of evidence 1++*)

8.5 When the indication for carotid revascularization and/or the choice between endarterectomy and stenting are not clear-cut, the experts' panel suggests considering:

- integrated interdisciplinary approach involving specialists with different cardio-cerebrovascular skills in diagnostic imaging and both traditional and endovascular surgical procedures and sharing with the patient;
- the center and the operators' expertise;
- the option of optimal medical therapy alone, especially in the case of patients with asymptomatic carotid stenosis and/or at high surgical risk.

(*GPP recommendation*)

8.6 In patients with symptomatic carotid stenosis greater than 50% (NASCET criteria) with mild-to-moderate surgical risk, endarterectomy is recommended as it is associated with a lower risk of periprocedural neurological events (TIA, stroke). Endarterectomy improves the clinical course compared to stenting. (*Strong recommendation in favor, level of evidence 1++*)

8.7 In patients with symptomatic carotid stenosis greater than 50% (NASCET criteria) with high surgical risk, stenting is indicated as an alternative to endarterectomy if the documented periprocedural stroke/death rate is less than 6%, like for endarterectomy.

Patient with one of the following characteristics is deemed at high surgical risk:

- clinically significant heart disease (congestive heart failure, positive ergometric test or need for conventional cardiac surgery);
- severe pulmonary disease;
- contralateral laryngeal nerve paralysis;
- ongoing oral anticoagulant therapy;
- previous major cervical radiotherapy;
- restenosis after endarterectomy or stenting.

(*Weak recommendation in favor, level of evidence 1+*)

9. Carotid restenosis, medical therapy to support surgery

9.1 In patients with symptomatic or asymptomatic carotid stenosis undergoing endarterectomy or stenting, the

experts' panel suggests intra-operative or postoperative pre-discharge carotid procedural quality control. Also, the experts' panel suggests identifying and repairing any technical operative defects that could be responsible for perioperative or late complications. (*GPP recommendation*)

9.2 In patients with symptomatic carotid restenosis greater than 50% (NASCET criteria) after endarterectomy or stenting, surgical correction is recommended in addition to optimal medical therapy, as it improves the clinical course compared to optimal medical therapy alone. (*Strong recommendation in favor, level of evidence 1++*)

9.3 In patients with asymptomatic carotid restenosis greater than 70% (NASCET criteria) after endarterectomy and a careful evaluation of risks and benefits and adequate patient information, the surgical correction is indicated in addition to the optimal medical therapy, as it improves the clinical course compared to the optimal medical therapy alone. (*Weak recommendation in favor, level of evidence 1-*)

9.4 In patients with asymptomatic carotid restenosis greater than 70% (NASCET criteria) after stenting, surgical correction is not indicated, as it does not improve the clinical course compared to optimal medical therapy alone. (*Weak recommendation against, level of evidence 1-*)

9.5 In patients with carotid restenosis and indication for surgical correction after endarterectomy or stenting, endovascular treatment with stenting is indicated after a multidisciplinary evaluation of the case and an adequate information of the patient about the risks and the choice of the procedure. Indeed, the endovascular treatment can improve the clinical course compared to redo endarterectomy. (*Weak recommendation in favor, level of evidence 2++*)

9.6 In patients with carotid stenosis or restenosis, waiting for and after surgical correction, the best medical therapy is recommended in the absence of contraindications. Indeed, the best medical therapy improves the clinical course compared to no best medical therapy. (*Strong recommendation in favor, level of evidence 1++*)

9.7 In patients undergone carotid stenting, dual antiplatelet therapy for at least the first three months and antiplatelet monotherapy (the best medical therapy) for the following months are recommended if there are no contraindications, as they improve the clinical course. (*Strong recommendation in favor, level of evidence 1+*)

9.8 In patients waiting for and after carotid endarterectomy or stenting, statin therapy and blood pressure management are indicated, as they improve the clinical course compared to no statin therapy and no blood pressure management. (*Weak recommendation in favor, level of evidence 1+*)

Final considerations

Our primary purpose was to provide a GL suitable to trace and suggest appropriate and more complete diagnostic and therapeutic indications for the medical and surgical management of patients with atherosclerotic carotid stenosis at risk of ischemic stroke, according to the most recent evidence in the current literature, selected and processed according to the EBM methodological criteria.

The unique nature of the field and topics, many of which are still widely discussed in the academic community and often with different opinions, led the authors and reviewers of this GL to analyze and assess the proofs, compare and share topics of considerable clinical and management importance with experts from various medical and surgical specialties, many stakeholders, and the contribution of a patients' association.

More or fewer clear-cut recommendations were issued when the evidence (or absence of evidence in case of GPP) in the literature and the assessments of the multidisciplinary authors and the various stakeholders allowed it. Vice versa, when this was not possible, recommendations "for research" were shared and formulated concerning grey areas that are still to be investigated and clarified.

This GL is characterized by the constant consideration of Personalized Medicine, from the beginning and at each step, of topics definition, research questions, analysis of the evidence in the literature, sharing of the judgments, and final recommendations.

Beyond the EBM, we evaluated the trend toward the Personalized Medicine to invite to take it into account in good clinical practice. Indeed, in the real world, we address single patients, who often are very different from the standard patients described in the trials and in the literature.

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