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KAJ JE NOVEGA V SMERNICAH OBRAVNAVE ISHEMIČNE MOŽGANSKE KAPI

WHAT IS NEW IN THE GUIDELINES FOR ISCHEMIC STROKE MANAGEMENT

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IZVLEČEK

Smernice za zdravljenje možganske kapi so bile predlagane v različnih državah z namenom izboljšanja obravnave bolnikov. Kljub temu uporaba teh smernic v klinični praksi še vedno predstavlja izziv. Namen pričujočega pregleda je predstaviti sedanjo obravnavo ishemične možganske kapi in preventivnih smernic ter poudariti novosti, ki so vključene v smernice v zadnjih nekaj letih. Zaradi pomembnih ugotovitev v nedavnih kliničnih raziskavah in študijah so posodobitve evropskih ter posebej ameriških smernic pokazale nova ali dopolnjena priporočila. Glavne opazke so, da so nujne ocenitve in obravnava v akutni fazi možganske kapi zelo pomembne, še posebej v zvezi z izvajanjem intravenske trombolize, ki ji sledi endovaskularno zdravljenje pri izbranih bolnikih. Pri preprečevanju možganske kapi obstajajo pomembne spremembe pri obravnavi atrijske fibrilacije, predvsem pri uvedbi novih (neposrednih) oralnih antikoagulantov. Glavna novost v nedavnih smernicah se nanaša na nefarmakološko preprečitev možganske kapi z vključitvijo mediteranske diete v življenjski slog.

Ključne besede: možganska kap, smernice

SUMMARY

Stroke guidelines have been proposed in different countries with the aim of improving the management of patients. Nevertheless, translation of guidelines into clinical practice remains a challenge. The aim of this review is to present current ischemic stroke management and prevention guidelines and to emphasize the novelties which were included into the guidelines in the last few years. Important findings in recent clinical trials and studies of the updates of European and especially American guidelines showed many new or revisited recommendations in the guidelines. Major remarks are that the emergency evaluation and management in the acute phase of stroke is very important, especially in terms of performing intravenous thrombolysis that should be followed with endovascular treatment in selected patients. In stroke prevention, there are important changes in atrial fibrillation management, primarily regarding the introduction of the novel (direct) oral anticoagulants. A major novelty in the most recent guidelines relates to non-pharmacological stroke prevention by the inclusion of the Mediterranean diet.

Keywords: guidelines, stroke

INTRODUCTION

The guidelines represent consensus statements by expert panels, and the process of guideline development has inherent vulnerabilities (1). Stroke guidelines have been proposed in different countries with the aim of improving the management of patients (2–14). Nevertheless, translation of guidelines into clinical practice remains a challenge. The aim of this review is to present current ischemic stroke management guidelines and to emphasize the novelties in the last few years. The American Heart Association and American Stroke Association (AHA/ASA) published comprehensive stroke guidelines which include the primary and secondary stroke prevention as well as early management of stroke. In 2008, the recently founded European Stroke Organisation (ESO) published its guidelines for the management of ischemic stroke and transient ischemic attack (9). These guidelines were translated into several languages and were updated in 2009 (15). To keep up the pace with this progress with a methodology for the development of guidelines and driven by the strong determination of the ESO to further promote stroke management, education, and research, the ESO decided to delineate a detailed standard operating procedure for its guidelines (15). To promote and publish up-to-date guidelines, the European Stroke Organisation will move from the classical model of a single Guideline Document about a major topic (e.g. management of ischemic stroke) to focused modules (i.e. subdivisions of a major topic) (15).

EARLY MANAGEMENT OF STROKE

Effective emergent evaluation of a stroke patient requires well-organized systems that maximize the speed of assessment and administration of appropriate therapies, including intravenous recombinant tissue plasminogen activator (rtPA) and endovascular therapies (16). These well-organized systems are included in AHA/ASA guidelines: primary stroke centres and comprehensive stroke centres, as well as acute stroke-ready hospitals, with the involvement of stroke units (17). ESO guidelines, on the other side, promote the certifications for ESO Stroke units and ESO Stroke centres (18).

The newest AHA/ASA guidelines from 2013 recommend that prehospital management of the emergency medical service (EMS) ensures that patient is transported to the closest available primary or the comprehensive stroke centre or to the appropriate institution (hospital) that provides emergency stroke care (17). EMS personnel should provide prehospital notification to the receiving hospital in order to mobilize appropriate hospital resources before stroke patient arrival (17). The development of regional stroke systems consists of: (a) healthcare facilities that provide initial emergency care including administration of intravenous rtPA, including primary stroke centres, comprehensive stroke centres, and other facilities; (b) centres capable of performing endovascular stroke treatment with comprehensive periprocedural care, including comprehensive stroke centres and other healthcare facilities,

to which a rapid transport can be arranged when appropriate (19). It may be useful for primary stroke centres and other healthcare facilities that provide initial emergency care including administration of intravenous rtPA, to develop the capability of performing emergency non-invasive intracranial vascular imaging to most appropriately selected patients for transfer for endovascular intervention and reduce time of endovascular treatment (19). Endovascular therapy requires the patient to be at an experienced stroke centre with rapid access to cerebral angiography and qualified neurointerventionalists (19).

Telestroke network and teleradiology systems are useful in supporting rapid imagining interpretation in time for fibrinolysis decision-making (17). Implementation of telestroke consultation in conjunction with stroke education and training for healthcare providers can be useful in increasing the use of intravenous recombinant tissue-type plasminogen activator (rtPA) at community hospitals without access to adequate on-site stroke expertise (17). An organized protocol for the emergency evaluation of patients with suspected stroke is recommended (17). Baseline electrocardiogram assessment is recommended in patients presenting with acute ischemic stroke, but should not delay initiation of intravenous rtPA, as well as baseline troponin and chest X-ray (17). In most instances, non-contrast-enhanced CT will provide the necessary information to make decisions about emergency management of stroke (17). If endovascular therapy is contemplated, a non-invasive intracranial vascular study (CTA or MRA) is strongly recommended during the initial imaging evaluation of the acute stroke patient, but should not delay intravenous rtPA, if indicated (19). For patients who qualify for intravenous rtPA, according to guidelines from professional medical societies, initiating intravenous rtPA before non-invasive vascular imaging is recommended for patients who have not had non-invasive vascular imaging as part of their initial imaging assessment for stroke (19). Non-invasive intracranial vascular imaging should then be obtained as quickly as possible (19). The benefits of additional imaging beyond CT and CTA or MR and MRA, such as CT perfusion or diffusion- and perfusion-weighted imaging, for selecting patients for endovascular therapy are unknown (19).

General supportive care includes: cardiac monitoring for at least 24 hours (to screen for atrial fibrillation and other potentially serious cardiac arrhythmias), airway support and ventilatory assistance (supplemental oxygen should be provided to maintain oxygen saturation >94%), appropriate hyperthermia treatment, correction of hypovolemia and cardiac arrhythmia, treatment of hypoglycemia and hyperglycemia to achieve normoglycemia (17). The latest ESO recommendations in regard to routine prevention of hyperthermia with antipyretics as well as induction of hypothermia are not recommended (20).

There are no data available to guide selection of medications for lowering of blood pressure in the setting of acute ischemic stroke (17). Patients with elevated blood pressure and who are otherwise eligible for treatment with intravenous rtPA should have their blood pressure carefully lowered so that their systolic blood pressure is <185 mm Hg and their diastolic blood pressure

is <110 mm Hg before fibrinolytic therapy is initiated (17). If medications are given to lower blood pressure, the clinician should be sure that the blood pressure is stabilized at the lower level before beginning treatment with intravenous rtPA and maintained below 180/105 mm Hg for at least the first 24 hours after intravenous rtPA treatment (17). In patients with markedly elevated blood pressure who do not receive fibrinolysis, a reasonable goal is to lower blood pressure by 15% during the first 24 hours after onset of stroke (17). The level of blood pressure that would mandate such treatment is not known, but consensus exists that medications should be withheld unless the systolic blood pressure is >220 mm Hg or the diastolic blood pressure is >120 mm Hg (17). Patients with malignant hypertension or other medical indications for aggressive treatment of blood pressure should be treated accordingly (17).

Intravenous rtPA (0.9 mg/kg, maximum dose 90 mg) is recommended for selected patients who may be treated within 4–5 hours of onset of ischemic stroke, in eligible patients as quickly as possible (19). The effectiveness of sonothrombolysis, tenecteplase, reteplase, desmoteplase, urokinase, or other fibrinolytic agents and the intravenous administration of ancrod or other defibrinogenating agents for treatment of patients with acute stroke is not well established (17). The use of intravenous rtPA in patients taking direct thrombin inhibitors or direct factor Xa inhibitors may be harmful and is not recommended, unless sensitive laboratory tests, such as activated partial thromboplastin time, international normalized ratio, platelet count, and ecarin clotting time, thrombin time, or appropriate direct factor Xa activity assays are normal, or the patient has not received a dose of these agents for >2 days (assuming normal renal metabolizing function) (17). Similar consideration should be given to patients being considered for intra-arterial rtPA (17).

New AHA recommendations suggest that the patients eligible for intravenous rtPA should receive intravenous rtPA, even if endovascular treatments are being considered (19). Patients should receive endovascular therapy with a stent retriever if they meet all the following criteria: (a) prestroke mRS score 0 to 1, (b) acute ischemic stroke receiving intravenous rtPA within 4.5 hours of onset, (c) causative occlusion of the internal carotid artery or proximal MCA (M1), (d) age ≥18 years, (e) NIHSS score of ≥6, (f) ASPECTS of ≥6, and (g) treatment can be initiated (groin puncture) within 6 hours of symptom onset (19).

There are inadequate data available at this time to determine the clinical efficacy of endovascular therapy with stent retrievers for those patients whose contraindications are time-based or non-time based (e.g. prior stroke, serious head trauma, hemorrhagic coagulopathy, or receiving anticoagulant medications) (19). Although the benefits are uncertain, use of endovascular therapy with stent retrievers may be reasonable for carefully selected patients with acute ischemic stroke in whom treatment can be initiated (groin puncture) within 6 hours of symptom onset and who have causative occlusion of the M2 or M3 portion of the MCAs, anterior cerebral arteries, vertebral arteries, basilar artery, or posterior cerebral arteries (19).

Observing patients after intravenous rtPA to assess for a clinical response before pursuing endovascular therapy is not required to achieve beneficial outcomes and is not recommended (19). The use of stent retrievers is indicated in preference to the MERCI device (19). The use of mechanical thrombectomy devices other than stent retrievers may be reasonable in some circumstances (19). A clinically beneficial dose of intra-arterial rtPA is not established, and rtPA does not have FDA approval for intra-arterial use (19). As a consequence, endovascular therapy with stent retrievers is recommended over intra-arterial fibrinolysis as first-line therapy (19). Intra-arterial fibrinolysis initiated within 6 hours of stroke onset in carefully selected patients who have contraindications to the use of intravenous rtPA might be considered, but the consequences are unknown (19). It might be reasonable to favor conscious sedation over general anesthesia during endovascular therapy for acute ischemic stroke. However, the ultimate selection of anesthetic technique during endovascular therapy for acute ischemic stroke should be individualized based on patient risk factors, tolerance of the procedure, and other clinical characteristics (19).

Urgent anticoagulation is generally not recommended, except in patients with severe stenosis of an internal carotid artery ipsilateral to an ischemic stroke where is not well established as well as the usefulness of argatroban or other thrombin inhibitors, for the treatment of patients with acute ischemic stroke (17). Oral administration of aspirin (initial dose is 325 mg) within 24 to 48 hours after stroke onset is recommended for treatment of most patients (17). The usefulness of other antiplatelet agent in acute stroke are not well established (e.g. clopidogrel, intravenous tirofiban and eptifibatide), although antiplatelet agents that inhibit the glycoprotein IIb/IIIa receptor are not recommended (17).

In exceptional cases with systemic hypotension producing neurological sequelae, a physician may prescribe vasopressors to improve cerebral blood flow (17). If drug-induced hypertension is used, close neurological and cardiac monitoring is recommended (17). The administration of high-dose albumin, usage of devices to augment cerebral blood flow, and drug-induced hypertension is not well established, although hemodilution by volume expansion is not recommended (17). At present, no pharmacological agents with putative neuroprotective actions have demonstrated efficacy in improving outcomes after ischemic stroke, and therefore, other neuroprotective agents are not recommended (17). Nevertheless, among patients already taking statins at the time of onset of ischemic stroke, a continuation of statin therapy during the acute period is reasonable (17). Transcranial near-infrared laser therapy and induced hypothermia are not well established as neuroprotective strategies (17). The usefulness of emergent or urgent carotid endarterectomy is not well established (17). The use of stroke units that incorporates rehabilitation is recommended (17). Patients who cannot take solid food and liquids orally should receive nasogastric, nasoduodenal, or percutaneous endoscopic gastrostomy tube feedings to maintain hydration and nutrition while undergoing efforts to restore swallowing. In selecting between nasogastric and percutaneous endoscopic gastrostomy tube routes of feeding in patients who

cannot take solid food or liquids orally, it is reasonable to prefer nasogastric tube feeding until 2 to 3 weeks after stroke onset (17). The use of aspirin or intermittent external compression devices is reasonable for the treatment of patients who cannot receive anticoagulants for prophylaxis of deep vein thrombosis (17).

Patients with major infarctions are at high risk for complicating brain edema and increased intracranial pressure (17). Measures to lessen the risk of edema and close monitoring of the patient for signs of neurological worsening during the first days after stroke are recommended (17). Early transfer of patients at risk for malignant brain edema to an institution with neurosurgical expertise should be considered (17). Decompressive surgical evacuation of a space-occupying cerebellar infarction is effective in preventing and treating herniation and brain stem compression (17). Decompressive surgery for malignant edema of the cerebral hemisphere is effective and potentially life-saving (17). Advanced patient age and patient/family valuations of achievable outcome states may affect decisions regarding surgery (17). Placement of a ventricular drain is useful in patients with acute hydrocephalus secondary to ischemic stroke (17).

STROKE PREVENTION

Stroke prevention is a cornerstone after effective emergent evaluation and management of acute stroke. In addition to traditional risk factors such as hypertension, dyslipidemia, and diabetes mellitus, primary and secondary stroke prevention includes management of sleep apnea, diet, physical activity and other novel risk factors that are potentially modifiable (21).

Hypertension is the single most important modifiable risk factor for stroke (21). Primary stroke prevention should include regular blood pressure screening and appropriate treatment with pharmacological therapy and lifestyle modification (22).

Initiation of BP therapy is indicated for previously untreated patients with ischemic stroke or TIA who, after the first several days, have an established BP ≥140 mm Hg systolic or ≥90 mm Hg diastolic (23). Initiation of therapy for patients with BP <140 mm Hg systolic and >90 mm Hg diastolic is of uncertain benefit (23). Resumption of BP therapy is indicated for previously treated patients with known hypertension for both prevention of recurrent stroke and prevention of other vascular events in those who have had an ischemic stroke or TIA, and are beyond the first several days (23). For patients with a recent lacunar stroke, it might be reasonable to target a SBP of <130 mm Hg (23). The treatment of hypertension may include thiazide diuretic, ACE inhibitor or ARB, or its combination if it is required (24).

A large meta-analysis found that low-density lipoprotein (LDL) cholesterol level, non-high-density lipoprotein (HDL) cholesterol level, and very-low-

density lipoprotein level (but not HDL cholesterol and triglyceride levels) were associated with ischemic stroke (21). Statin therapy with intensive lipid-lowering effects is recommended to reduce the risk of stroke and cardiovascular events among patients with ischemic stroke or TIA, presumed to be of atherosclerotic origin (23). Patients with ischemic stroke or TIA and other comorbid ASCVD should be otherwise managed properly, which includes lifestyle modification, dietary recommendations, and medication recommendations (23). Statin therapy in addition to therapeutic lifestyle modification is recommended for primary stroke prevention of ischemic stroke patients estimated to have a high 10-year risk for cardiovascular events (22).

New guidelines define diabetes mellitus as a hemoglobin A1c greater than 6.5% (25). In primary stroke prevention, control of blood pressure to a target <140/90 mm Hg is recommended in patients with diabetes mellitus (22). In secondary stroke prevention, all patients should probably be screened for DM with testing of fasting plasma glucose, HbA1c, or an oral glucose tolerance test (23). In general, HbA1c may be more accurate than other screening tests in the immediate post-event period (23).

A meta-analysis of Strazullo P, et al. assessed the relationship between stroke risk and weight (patients were divided into following groups according to BMI: normal weight, BMI <25 kg/m²; overweight status, BMI 25 kg/m² to 29,99 kg/m²; and obesity, BMI >30 kg/m² (26). They concluded that the relative risk of ischemic stroke was 1.64 in obese versus healthy subjects and 1.22 in overweight versus healthy subjects (26). Therefore, all patients with TIA or stroke should be screened for obesity with measurement of BMI (23). Despite the demonstrated beneficial effects of weight loss on cardiovascular risk factors, the usefulness of weight loss among patients with a recent TIA or ischemic stroke and obesity is still uncertain (23).

The Northern Manhattan study showed that moderate- to high-intensity physical activity was protective for ischemic stroke in men, but interestingly, a protective effect of light physical activity was not observed, as it was previously reported (27, 28). In primary stroke prevention, healthy adults should perform at least moderate- to vigorous-intensity aerobic physical activity for at least 40 min per day for 3 to 4 d/wk (22). In secondary stroke prevention for patients with ischemic stroke or TIA who are capable of engaging in physical activity, at least 3 to 4 sessions per week of moderate- to vigorous-intensity aerobic physical exercise are reasonable to reduce stroke risk factors (23). Sessions should last an average of 40 minutes (23). Moderate-intensity exercise is typically defined as sufficient to break a sweat or noticeably raise the heart rate (e.g. walking briskly, using an exercise bicycle) (23). Vigorous-intensity exercise includes activity like jogging (23). For patients who are able and willing to initiate increased physical activity, referral to a comprehensive, behaviourally oriented program is reasonable (23).

Currently, the best diets for primary stroke prevention are The Dietary Approach to Stop Hypertension (DASH) with high fruit and vegetable, low-fat dairy, low animal protein and high plant protein intake as well as the Mediterranean diet which encourages vegetables, fruits, and whole grains and includes low-fat dairy products, poultry, fish, legumes, olive oil, and nuts and red wine (21). It limits intake of sweets and red meats (21). In primary stroke prevention, the Mediterranean diet supplemented with nuts may be considered in lowering risk of stroke (22). In secondary stroke prevention, it is reasonable to conduct a nutritional assessment looking for signs of overnutrition or undernutrition (23). If signs of undernutrition are present, stroke patient should be referred for individualized nutritional counseling, nevertheless routine supplementation with a single vitamin or a combination of vitamins is not recommended (23). The reduction of patients' sodium intake to less than =2.4 g/d or it is possible to <1.5 g/d. The Mediterranean-type diet instead of a low-fat diet is preferred (23).

Obstructive sleep apnea has been associated with several physiologic changes, including blood pressure, cardiac structure and atrial fibrillation, all of which may contribute to an increased stroke risk (21). Several prospective studies have found sleep-disordered breathing to be an independent risk factor for stroke (21). In primary stroke prevention, screening for sleep apnea, and if indicated, polysomnography, may be considered because of its association with stroke risk (22). In secondary stroke prevention, a sleep study might be considered on the basis of the very high prevalence of sleep apnea in stroke population and the strength of the evidence that the treatment of sleep apnea improves outcomes in the general population (23). Treatment with CPAP might be considered for patients with ischemic stroke and sleep apnea given the emerging evidence in support of improved outcomes (23).

Atherosclerosis of large arteries is responsible for about 15% of all ischemic strokes (29). Carotid atherosclerosis accounts for about 7% of ischemic strokes (29). In primary stroke prevention, patients with asymptomatic carotid stenosis should be prescribed with aspirin and statin (22). It is reasonable to consider carotid endarterectomy in patients who have >70% stenosis of the internal carotid artery if the risk of perioperative stroke, myocardial infarction and death is low (<3%) (22). The Duplex ultrasound should be done annually to assess carotid artery disease progression or regression (22). Prophylactic carotid angioplasty and stenting might be considered in highly selected patients with high-grade stenosis (minimum 60% on angiography or 70% on Doppler ultrasound) (22). In secondary stroke prevention for patients with a TIA or ischemic stroke within the past 6 months and ipsilateral severe (70–99%) carotid artery stenosis as documented by non-invasive imaging, CEA is recommended if the perioperative morbidity and mortality risk is estimated to be <6%. When revascularization is indicated for patients with TIA or minor, non-disabling stroke, it is reasonable to perform the procedure within 2 weeks of the index event, rather than delay surgery if there are no contraindications to early revascularization (23). CAS is indicated as an alternative to CEA for

symptomatic patients at average or low risk of complications associated with endovascular intervention when the diameter of the lumen of the ICA is reduced by >70% by non-invasive imaging or >50% by catheter-based imaging or non-invasive imaging with corroboration and the anticipated rate of periprocedural stroke, or death is <6% in whom anatomic or medical conditions are present that greatly increase the risk for surgery, or when other specific circumstances exist such as radiation-induced stenosis, or restenosis after CEA (23). Routine, long-term follow-up imaging of the extracranial carotid circulation with carotid duplex ultrasonography is not recommended (23). For patients with recurrent or progressive ischemic symptoms ipsilateral to a stenosis or occlusion of a distal (surgically inaccessible) carotid artery, or occlusion of a mid-cervical carotid artery after institution of optimal medical therapy, the usefulness of EC/IC bypass is considered investigational (23). Optimal medical therapy, which should include antiplatelet therapy, statin therapy, and risk factor modification, is recommended for all patients with carotid artery stenosis and a TIA or stroke (23).

Intracranial atherosclerosis is an important cause of ischemic stroke, but an impressive racial difference exists with the lowest incidence among Caucasians in comparison to African Americans and Hispanic patients (30). In secondary stroke prevention, aspirin is recommended in preference to warfarin if the stroke was caused by 50 to 99% stenosis of a major intracranial artery (23). For patients with recent stroke attributable to severe stenosis (70–99%) of a major intracranial artery, the addition of clopidogrel 75 mg/d to aspirin for 90 days might be reasonable (23). For patients with a stroke or TIA attributable to 50 to 99% stenosis of a major intracranial artery, maintenance of SBP below 140 mm Hg and high-intensity statin therapy are recommended (23). For patients with a stroke or TIA attributable to moderate stenosis (50–69%) of a major intracranial artery, angioplasty or stenting is not recommended (23). For patients with stroke or TIA attributable to severe stenosis (70–99%) of a major intracranial artery, stenting with the Wingspan stent system is not recommended (23). For patients with severe stenosis (70–99%) of a major intracranial artery and recurrent TIA or stroke after institution of aspirin and clopidogrel therapy, achievement of SBP <140 mm Hg, and high-intensity statin therapy, the usefulness of angioplasty alone or placement of a Wingspan stent or other stent is unknown and is considered investigational (23). For patients with severe stenosis (70–99%) of a major intracranial artery and actively progressing symptoms after institution of aspirin and clopidogrel therapy, the usefulness of angioplasty alone or placement of a Wingspan stent or other stents is unknown and is considered investigational (23).

The atrial fibrillation management (diagnosis and treatment) in the setting of stroke prevention and as a cause of cryptogenic stroke rapidly evolved in the last few years (31). The choice of antithrombotic therapy should be based upon the absolute risks of stroke/thromboembolism and bleeding, and the net clinical benefit for a given patient (32). In primary stroke prevention for patients with valvular atrial fibrillation at high risk for stroke, and acceptably

low risk of hemorrhagic complications, chronic oral anticoagulant therapy with warfarin (CINR of 2 to 3) is recommended (32). For patients with nonvalvular atrial fibrillation, a CHA_2DS_2-VASc score of ≥2, and low risk for hemorrhagic complications, oral anticoagulants are recommended (32). Options include warfarin, dabigatran, apixaban and rivaroxaban (32). For patients with CHA_2DS_2-VASc score of 1 no antithrombotic therapy, anticoagulant therapy or aspirin therapy may be considered (32). For patients with nonvalvular atrial fibrillation and CHA_2DS_2-VASc score of 0, it is reasonable to omit antithrombotic therapy (32).

As per the new AHA/ASA guideline recommendation, for patients who have experienced an acute ischemic stroke or TIA with no other apparent cause, prolonged rhythm monitoring (=30 days) for AF is reasonable within 6 months of the index event (23).

VKA therapy (Class I; Level of Evidence A), apixaban (Class I; Level of Evidence A), and dabigatran (Class I; Level of Evidence B) are all indicated for the prevention of recurrent stroke in patients with nonvalvular AF, whether paroxysmal or permanent (23, 33).

The selection of an antithrombotic agent should be individualized on the basis of risk factors, cost, tolerability, patient preference, potential for drug interactions, and other clinical characteristics, including renal function and time in the INR therapeutic range if the patient has been taking VKA therapy (23).

Rivaroxaban is reasonable for the prevention of recurrent stroke in patients with nonvalvular AF (23). For patients with ischemic stroke or TIA with paroxysmal (intermittent), persistent, or permanent AF in whom VKA therapy is begun, a target INR of 2.5 is recommended (23, 33). The combination of oral anticoagulation (i.e. warfarin or one of the newer agents) with antiplatelet therapy is not recommended for all patients after ischemic stroke or TIA but is reasonable in patients with clinically apparent CAD, particularly an acute coronary syndrome or stent placement (23). For patients with ischemic stroke or TIA and AF who are unable to take oral anticoagulants, aspirin alone is recommended (23). The addition of clopidogrel to aspirin therapy, compared with aspirin therapy alone, might be reasonable (23). For most patients with a stroke or TIA in the setting of AF, it is reasonable to initiate oral anticoagulation within 14 days after the onset of neurological symptoms (23). In the presence of high risk for hemorrhagic conversion (i.e. large infarct, hemorrhagic transformation on initial imaging, uncontrolled hypertension, or hemorrhage tendency), it is reasonable to delay initiation of oral anticoagulation beyond 14 days (23). For patients with AF and a history of stroke or TIA who require temporary interruption of oral anticoagulation, bridging therapy with an LMWH (or equivalent anticoagulant agent if intolerant to heparin) is reasonable, depending on perceived risk of thromboembolism and bleeding (23, 33). The

usefulness of closure of the left atrial appendage with the WATCHMAN device in patients with ischemic stroke or TIA and AF is uncertain (23).

As per the AAN recommendations, in order to reduce the risk of stroke or subsequent stroke in patients with NVAF judged to require oral anticoagulants, clinicians should choose one of the following options (Level B): Warfarin, target INR 2.0–3.0; Dabigatran 150 mg twice daily (if creatinine clearance [CrCl] >30 mL/min); Rivaroxaban 15 mg/d (if CrCl 30–49 mL/ min) or 20 mg/d; Apixaban 5 mg twice daily (if serum creatinine <1.5 mg/dL) or 2.5 mg twice daily (if serum creatinine >1.5 and <2.5 mg/dL, and body weight <60 kg or age at least 80 years [or both]; Triflusal 600 mg plus Acenocoumarol, target INR 1.25–2.0 (patients at moderate stroke risk, mostly in developing countries) (34). Clinicians might recommend that patients taking warfarin, whose condition is well-controlled, continue warfarin treatment rather than switch to treatment with a new oral anticoagulant (34). Clinicians should administer dabigatran, rivaroxaban, or apixaban to patients who have NVAF requiring anticoagulant medication and are at higher risk of intracranial bleeding (34). Clinicians might offer apixaban to patients with NVAF and GI bleeding risk who require anticoagulant medication (34). Clinicians should offer dabigatran, rivaroxaban, or apixaban to patients unwilling or unable to submit to frequent periodic testing of INR levels (34). Clinicians should offer apixaban to patients unsuitable for being treated, or unwilling to be treated, with warfarin (34). Where apixaban is unavailable, clinicians might offer dabigatran or rivaroxaban (34). Where oral anticoagulants are unavailable, clinicians might offer a combination of aspirin and clopidogrel (34).

The ESC 2012 Update of Guidelines recommends for patients with a CHA_2DS_2-VASc score >2 an OAC therapy with: adjusted-dose VKA (INR 2–3); or a direct thrombin inhibitor (dabigatran); or an oral factor Xa inhibitor (e.g. rivaroxaban, apixaban) is recommended, unless contraindicated (32).

When patients refuse the use of any OAC (whether VKAs or NOACs), antiplatelet therapy should be considered, using combination therapy with aspirin 75–100 mg plus clopidogrel 75 mg daily (where there is a low risk of bleeding) or, less effectively, aspirin 75–325 mg daily (32). NOACs (dabigatran, rivaroxaban, and apixaban) are not recommended in patients with severe renal impairment (CrCl <30 mL/min) (23–34).

Numerous other cardiac conditions such as myocardial infarction, mural thrombus, cardiomyopathy, valvular heart disease, PFO, and aortic atheromas may require antithrombotic therapy (Table 1.) (22, 23).

Table 1. The cardiac conditions and antithrombotic therapy in primary or secondary stroke prevention (excluding atrial fibrillation)

	Primary stroke prevention	Secondary stroke prevention
Anticoagulation (indicated)	mitral stenosis and prior embolic event, mitral stenosis and left atrial thrombus, after aortic valve replacement with bileaflet mechanical or current-generation, single tilting disk prosthesis	1) acute MI complicated by LV mural thrombus formation (for 3 months); 2) sinus rhythm with left atrial of left ventricular thrombus (>3 months); 3) rheumatic valve disease and AF; 4) PFO and venous source of embolism (if it is contraindicated – an inferior vena cava filter is reasonable)
Warfarin and aspirin (indicated)	mechanical aortic valve replacement with risk factors after mitral valve replacement with any mechanical valve	1) rheumatic mitral valve disease; 2) before insertion of mechanical valve (mitral or aortic) and low risk of bleeding in patients with previous stroke or TIA
Warfarin (reasonable or considered)	STEMI and asymptomatic left ventricular mural thrombi, asymptomatic patients with severe mitral stenosis and left atrium dimension >55 mm, or an enlarged left atrium, STEMI and anterior apical akinesia or dyskinesia	1) acute anterior STEMI without demonstrable LV mural thrombus formation, but with anterior apical akinesis or dyskinesis; 2) mechanical LVAD – absence of major contraindications; 3) rheumatic mitral valve disease without AF or another likely cause for their stroke symptoms (e.g. carotid stenosis); 4) in patients with previous stroke or TIA – before insertion of mechanical aortic or mitral valve
Antiplatelet (indicated)		1) native aortic or nonrheumatic mitral valve disease with no indication for anticoagulation; 2) mitral annular calcifications; 3) mitral valve prolapse; 4) before insertion of bioprosthetic aortic or mitral valve, and no other indication for anticoagulation beyond 3–6 months after the valve placement; 5) aortic arch atheroma (with statin); 6) PFO
Aspirin (reasonable)	after aortic or mitral valve replacement with a bioprothesis	
DOACs or LMWH as an alternative to warfarin in patients with:		1) acute MI complicated by the LV mural thrombus formation or anterior or apical wall-motion abnormalities with an LV ejection fraction <40% intolerant to VKA therapy because of nonhemorrhagic events (for 3 months)

Aspirin is the main treatment option for non-cardiomebolic stroke prevention (23). Aspirin (50–325 mg/d) monotherapy or the combination of aspirin 25 mg and extended-release dipyridamole 200 mg twice a day is indicated as

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initial therapy after TIA or ischemic stroke for prevention of future stroke (23). Clopidogrel (75 mg) monotherapy is a reasonable option for secondary prevention of stroke in place of aspirin or combination aspirin/dipyridamole (23). This recommendation also applies to patients who are allergic to aspirin (23). Dual antiplatelet therapy might be considered for insertion within 24 hours of a minor ischemic stroke or TIA and continuously for 21 days (23). For patients who have an ischemic stroke or TIA while taking aspirin, there is no evidence that increasing the dose of aspirin provides additional benefit (23). Although alternative antiplatelet agents are often considered, no single agent or combination has been adequately studied in patients who have had an event while receiving aspirin (23).

For patients with a history of ischemic stroke or TIA, AF, and CAD, the usefulness of adding antiplatelet therapy to VKA therapy is uncertain for purposes of reducing the risk of ischemic cardiovascular and cerebrovascular events (23).

For patients with ischemic stroke or TIA and extracranial carotid or vertebral arterial dissection, antithrombotic treatment with either antiplatelet or anticoagulant therapy for at least 3 to 6 months is reasonable (23). The relative efficacy of antiplatelet therapy compared with anticoagulation therapy is unknown in patients with ischemic stroke or TIA and extracranial carotid or vertebral artery dissection (23). For patients with stroke or TIA and extracranial carotid or vertebral artery dissection who have definite recurrent cerebral ischemic events despite medical therapy, endovascular therapy (stenting) may be considered (23). Patients with stroke or TIA and extracranial carotid or vertebral artery dissection who have definite recurrent cerebral ischemic events despite medical therapy, who are not candidates for endovascular therapy or in whom it has failed, may be considered for surgical treatment (23).

Among patients with recent ischemic stroke or TIA for hyperhomocysteinemia and for antiphospholipid antibodies who have no other manifestations of the APS and who have an alternative explanation for their ischemic event, routine screening is not indicated (23). For patients with ischemic stroke or TIA who have an antiphospholipid antibody, but do not fulfill the criteria for APS, antiplatelet therapy is recommended (23). For patients with ischemic stroke or TIA who meet the criteria for the APS, anticoagulant therapy might be considered, depending on the perception of risk for recurrent thrombotic events and bleeding (23). For patients with ischemic stroke or TIA who meet the criteria for the APS, but in whom anticoagulation is not begun, antiplatelet therapy is indicated (23).

For patients with sickle cell disease and prior ischemic stroke or TIA, chronic blood transfusions to reduce hemoglobin S to <30% of total hemoglobin are recommended, and alternative treatment with hydroxyurea may be considered (23).

During pregnancy, in the presence of a high-risk condition that would require anticoagulation, the following options are reasonable: (a) LMWH twice a day throughout pregnancy, with dose adjusted to achieve the LMWH manufacturer's recommended peak anti-Xa activity 4 hours after injection, or (b) adjusted-dose UFH throughout pregnancy, administered subcutaneously every 12 hours in doses adjusted to keep the mid-interval activated partial thromboplastin time at least twice to control or to maintain an anti-Xa heparin level of 0.35 to 0.70 U/mL, or (c) UFH or LMWH (as above) until the 13th week, followed by substitution of a VKA until close to delivery, when UFH or LMWH is resumed (23). For pregnant women receiving adjusted-dose LMWH therapy for a high-risk condition that would require anticoagulation outside of pregnancy, and when delivery is planned, it is reasonable to discontinue LMWH ≥24 hours before induction of labor or cesarean section (23). In the presence of a low-risk situation in which antiplatelet therapy would be the treatment recommendation outside of pregnancy, UFH or LMWH, or no treatment may be considered during the first trimester of pregnancy, depending on the clinical situation (23). In the presence of a low-risk situation in which antiplatelet therapy would be the treatment recommendation outside of pregnancy, low-dose aspirin (50–150 mg/d) is reasonable after the first trimester of pregnancy (23). During breastfeeding in the presence of a high-risk condition that would require anticoagulation, it is reasonable to use warfarin, UFH, or LMWH. Nevertheless, in the presence of a low-risk situation in which antiplatelet therapy would be the treatment recommendation outside of pregnancy, low-dose aspirin use may be considered (23).

The decision to restart antithrombotic therapy after ICH related to antithrombotic therapy depends on the risk of subsequent arterial or venous thromboembolism, the risk of recurrent ICH, and the overall status of the patient and must, therefore, be individualized to each patient (23). For patients with a comparatively lower risk of cerebral infarction (e.g. AF without prior ischemic stroke), and a higher risk of recurrent ICH (e.g. elderly patients with lobar ICH or presumed amyloid angiopathy), or with very poor overall neurological function, an antiplatelet agent may be considered for prevention of ischemic stroke (23). For patients who require resumption or initiation of anticoagulation after an acute ICH, subarachnoid hemorrhage, or subdural hematoma, the optimal timing is uncertain (23). For most patients, however, it might be reasonable to wait ≥1 week (23). For patients with hemorrhagic cerebral infarction, a continuation of anticoagulation may be considered, depending on the specific clinical scenario and underlying indication for anticoagulant therapy (23).

CONCLUSION

Due to important findings in recent clinical trials and studies, the updates of European and especially American guidelines showed many new or revised recommendations. Major remarks are that the emergency evaluation and management in the acute phase of stroke is very important, especially in

terms of performing intravenous thrombolysis that should be followed by endovascular treatment in selected patients. In stroke prevention, there are important changes in atrial fibrillation management, primarily regarding the introduction of the novel (direct) oral anticoagulants. A major novelty in the most recent guidelines relates to non-pharmacological stroke prevention by the inclusion of the Mediterranean diet.

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