# National Consensus on Prevention, Diagnosis and Treatment of Cerebrovascular Diseases

**An Initiative of the Bulgarian Society of Neurology**

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# National Consensus on Prevention, Diagnosis and Treatment of Cerebrovascular Diseases

## An Initiative of the Bulgarian Society of Neurology

Today, 5.11.2024 we, the undersigned members of the Expert Group of the Bulgarian Society of Neurology reached an agreement and approved a consensus on prevention, diagnosis and treatment of the cerebrovascular diseases:

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## List of abbreviations

| | |
|---|---|
| ADCVC | Acute disorders of the cerebrovascular circulation |
| AHE | Acute Hypertensive Encephalopathy |
| AIS | Acute Ischemic Stroke |
| ASA | Acetylsalicylic Acid |
| ASPECTS | Alberta Stroke Program Early CT score |
| CAIC/DAIC | Clinic/Department of Anaesthesiology and Intensive Care |
| CCA | Common Carotid Artery |
| CTA | Computed Tomography Angiography |
| CVD | Cerebrovascular Disease |
| DSA | Digital Subtraction Angiography |
| DVT | Deep Venous Thrombosis |
| EAU | Emergency Admission Unit |
| ECC | Emergency Care Centre |
| GCP | Good Clinical Practice |
| GLCS | Glasgow-Liège Coma Scale |
| GP | General Practitioner |
| HS | Hemorrhagic Stroke |
| HTN | Arterial hypertension |
| IAT | Intra-arterial Thrombolysis |
| ICA | Internal Carotid Artery |
| IPH | Intraparenchymal Hemorrhage |
| IVT | Intravenous Thrombolysis |
| LDL-C | Low Density Lipoprotein-cholesterol |
| MCA | Middle Cerebral Artery |
| MRA | Magnetic Resonance Angiography |
| MRI | Magnetic Resonance Imaging |
| NIHSS | National Institutes of Health Stroke Scale |
| PTE | Pulmonary Thromboembolism |
| RF | Risk Factors |
| SAH | Subarachnoid Hemorrhage |
| TCVDS | Thrombosis of Cerebral Vein and Dural Sinus |
| TIA | Transient Ischemic Attack |
| VD | Vascular Dementia |

# Introduction

According to available data, every minute a citizen of the European Union has a stroke, and every six seconds there is a global death due to stroke. The survivors will be added to the 9 million Europeans with lived stroke and their families, who are forced to live with long-term health, social and financial consequences.

According to reports from the European Stroke Organisation and the European patient organisation from 2017, there are considerable inconsistencies among European countries in prophylaxis, healthcare organisation, the implementation of emergency prehospital care, treatment in the acute and subacute phases, and – most of all – in rehabilitation and post-stroke care.

The EU's Healthier Together initiative, founded by the European Commission in 2022, provides objectives and opportunity for political action to build upon the existing care standard on an EU and local national level. The European stroke action plan includes objectives and tasks in each of the following areas: primary prevention, organisation of procedural care in acute stroke, secondary prevention, and rehabilitation post-stroke. The goal of the Stroke Action Plan for Europe (SAP-E) is to reduce the absolute number of strokes in Europe by 10% through primary prevention. Since 2016, in Bulgaria the absolute number of strokes has fallen by approx. 20% – twice the required amount, and there is actionable potential for a further 10% reduction. We call on the political actors to prioritise stroke in health policy, to support the Bulgarian Society of Neurology and the proposed National Stroke Action Plan, and to take steps toward its implementation. The burden of stroke falls on all of us, particularly on stroke survivors and their carers, who have to live with the consequences daily.

We, neurologists, are convinced that 80% of strokes are preventable and treatable, and that effective primary prevention measures can alleviate the pressure on healthcare systems. There is considerable potential to reduce the burden of stroke, including its long-terms consequences. This requires collective action from multidisciplinary healthcare specialists (chiefly neurologists, but also interventional radiologists/neurologists, physiotherapists, and others), the pharmaceutical and healthcare industries, ministries of health and social policy, and other governmental and non-governmental institutions. The level of public knowledge on stroke and its symptoms and early detection must also be increased through educational campaigns.

## Health promotion and prevention of brain strokes

Attention must be paid to the widespread risk factors through lifestyle changes and the implementation of the National Strategy for Health Promotion. A legal framework to control the modifiable risk factors and unhealthy lifestyles (poor eating habits, high salt content, misuse of drugs and alcohol, etc.) must be created and implemented. Many risk factors for stroke are common for other chronic diseases, which means that implementing such measures could be effective in controlling cerebrovascular diseases, dementias, and malignant diseases.

It is important also to improve public awareness on stroke. The population must be encouraged to increase their general health knowledge, so they may make better choices regarding their health and lifestyle.

The present consensus comprises evidence-based recommendations from multicentre randomized clinical trials or meta-analyses ***(Level A of evidence)***, single-centre or non-randomized trials ***(Level B of evidence)*** and consensus of expert recommendations or therapeutic standards ***(Level C of evidence)***. Treatment and diagnostic procedures are graded as mandatory - the benefit far outweighs the risk (*Class I*), recommended (*Class IIa*) - the benefit moderately outweighs the risk, possible (*Class IIb*) - the benefit is commensurate or slightly outweighs the risk and (*Class III*) - the benefit is commensurate with the risk or the risk outweighs the benefit. The consensus is based on the National Consensus on Prevention, Diagnosis and Management of CVD, 2013, 2018, and 2020; Medical Standard "Neurological diseases", 2014; Project for Interventional Neurology Development in the P.R of Bulgaria, 2012; National Consensus on Diagnostic Ultrasound Imaging and Management of Extracranial Carotid Artery Diseases, 2011 and 2020; National Stroke Action Plan 2024 – 2030 (proposed to the Ministry of Health on 24.04.2024) and on European consensus statements on this topic.

Cerebrovascular diseases are a heterogeneous group of medical conditions, including ischemic and hemorrhagic events due to arterial and venous cerebral blood flow disorders. They include:

1. Ischemic cerebrovascular events:
    - Transient ischemic attacks (TIAs)
    - Cerebral infarctions (ischemic strokes)
2. Hemorrhagic strokes
    - Intraparenchymal hemorrhages
    - Subarachnoid hemorrhages
3. Acute hypertensive encephalopathy
4. Cerebral vein and dural venous sinus thrombosis
5. Vascular dementia

**The TIA** is a rapidly self-resolving neurological dysfunction, caused by focal cerebral, brainstem

or retinal ischemia, without indications of an established cerebral infarct zone upon imaging. It is characterised by rapid onset and resolution (several minutes to an hour) of stereotypical neurological symptoms. There is a tendency towards relapse. Lowering of the local cerebral blood flow under the ischemic threshold with rapid recovery is a characteristic factor for the occurrence of TIAs. Continued and heavier hypoperfusion leads to the development of asymptomatic (lacunar) infarction zones. Patients with TIA have an increased risk of repeated cerebrovascular ischemic incidents (up to 10% in the first 48 h). They require emergency diagnosis to treat concurrent disorders, modify risk factors, and identify specific treatable causes of TIA, particularly arterial stenosis or embolism sources. The immediate preventative treatment reduces the frequency of acute ischemic strokes (AIS), disability, and mortality. Patients with mild AIS or those with fast, spontaneous resolution have an increased risk of a second stroke. Patients with TIA must be assessed and treated in the same manner as patients with AIS because more than half of them will have an AIS within a week of their TIA. Thus, it is necessary to re-establish the Clinical Pathway "TIA" alongside the currently available Pathway "Diagnosis and treatment of ischemic stroke without thrombolysis".

Brain stroke is an emergency condition, resulting from the acute disruption of cerebral blood flow that leads to death or to heavy and irreversible morphological and functional changes in the central nervous system. Emergency hospitalisation and immediate, adequate treatment are indicated to achieve timely recanalization in the case of AIS, functional stabilisation, complete recovery of the neurological deficit, and prevention of its spread. Stroke is incredibly common. The frequency of strokes in people between 20 and 64 years of age, who represent the labour force, is ever-increasing. The global population is aging, which means that the total number of strokes will keep increasing.

Ischemic strokes are the most common acute cerebrovascular events – up to 88% of all strokes, with a death rate about 12%. According to etiology and pathogenesis, ischemic strokes are classified into four main subtypes: atherothrombotic, cardioembolic, lacunar, and cryptogenic stroke. The risk factors for ischemic stroke are defined as non-modifiable (age, race, sex, and family predisposition) and modifiable (arterial hypertension [HTN], diabetes, dyslipidemia, heart diseases, asymptomatic carotid artery stenosis, obesity, tobacco smoking, obstructive sleep apnea, sedentary lifestyle, social stress, alcohol misuse, hypercoagulability, hyperhomocysteinemia, depression, etc). Current data show that more than 150,000 Bulgarians have more than one risk factor.

Hemorrhagic strokes represent 8% to 12% of all strokes with a death rate of about 36-37%. Major RFs are age and HTN. Other RFs include cerebral amyloid angiopathy, vascular malformations, aneurismal rupture, coagulation disorders, anticoagulant treatment and thrombolytic drugs, secondary haemorrhage in cerebral infarction, bleeding brain tumors, and drug misuse.

The major RFs for non-traumatic subarachnoid hemorrhage (SAH) include HTN, tobacco smoking, alcohol misuse, and the use of sympathomimetic substances such as cocaine. The risk of SAH

is higher in patients with unruptured cerebral aneurysms (particularly symptomatic aneurysms that are larger in diameter and are located in the posterior communicating artery or the vertebrobasilar system), patients with previous SAH (with or without untreated aneurysm) and patients with familial aneurysms or SAH, arteriovenous malformations, bleeding disorders, etc.

The incidence of **stroke in infancy and childhood** varies from 2-3 to 13 per 100 000 children aged 30 days to 18 years. Morbidity of ischemic stroke varies from 2.7 to 7.8/100 000, hemorrhagic stroke – 2.9/100 000 and of cerebral vein and dural venous sinus thrombosis – 0.6/100 000. The death rate in infancy and childhood strokes is 0.6 per 100 000 children (from 7 to 28%).

The risk factors for ischemic stroke in children could be congenital or acquired, including infectious cerebral arteriopathies (in 50-80% of children with such type of stroke), congenital and acquired heart diseases as well as pro-thrombotic disorders: antithrombin, protein C and protein S deficiencies, factor V Leiden (1691G>A) or prothrombin 20210G>A (factor II) gene mutations, high plasma lipoprotein levels, antiphospholipid syndrome, etc.

Risk factors for hemorrhagic stroke in childhood are congenital cerebrovascular anomalies such as arteriovenous malformations, cavernous malformations, blood disorders, thrombocytopenia and brain tumors.

**Cerebral vein and dural venous sinus thromboses** are much rarer than arterial lesions.

# 1. Stroke prevention

## 1.1. Primary stroke prevention

Primary prevention aims to reduce stroke risk in asymptomatic people. For this reason, the World Stroke Organization (WSO) promotes the motto “One out of six” highlighting the importance of 6 simple rules to be observed:

Identification and assessment of the major modifiable RF: High blood pressure (BP; *Class I, Level A*), diabetes (*Class I, Level A*), and dyslipidemia. (*Class I, Level A*). In case of abnormalities, specific measures have to be taken for their treatment.

1. Regular physical activity (*Class III, Level B*)
2. Healthy diet for prevention of overweight/obesity (*Class III, Level B*)
3. Reduction of alcohol consumption (*Class III, Level B*)
4. Cessation of smoking (*Class III, Level B*)
5. Educational campaigns aiming to increase the awareness of the general population about symptoms and signs of stroke, as well as initial measures to be taken.

## Role of the general practitioner

**1. Identification of people at increased risk for cerebrovascular events**

- Regular BP measurement. It is recommended that high BP be treated with lifestyle changes and personalized pharmacological therapy (*Class I, Level A*), targeting BP values <130/80 mmHg, but not <120/70 mmHg in patients 18 – 65 years old and <140/80 mmHg in patients > 65 years old if well tolerated *(Class I, Level A).*
- Hypertensive patients (BP>140/90 mmHg) with congestive heart failure, myocardial infarction, diabetes or chronic renal deficiency must be treated with antihypertensive drugs (*Class 1, Level A*).
- Blood glucose should be checked regularly. Diabetes mellitus should be managed with lifestyle changes and personalized pharmacological therapy. In diabetics with concomitant HTN antihypertensive treatment should be more aggressive (*Class I, Level A*), aiming for target BP values <130/80 mmHg in patients 18-65 years old (but not <120 mmHg for the systolic pressure), <140/80 mmHg in patients >65 years old if well tolerated. Where possible, treatment should include an angiotensin-converting enzyme inhibitor (ACE-inhibitor) or angiotensin receptor blocker (ARB) (*Class I, Level A*).
- Cholesterol levels should be checked regularly. It is recommended that high blood cholesterol be managed with lifestyle changes, smoking cessation (*Class III, Level B*) and statin therapy with / without ezetimibe (*Class I, Level A*).

**2. Recommendations for comprehensive modification of the cardiovascular risk factors aimed at lifestyle changes and drug therapy**

- Restriction of alcohol consumption.
- Cessation of smoking.
- Regular physical activity.
- Healthy diet low in salt and saturated fat; consumption of plenty of fruit and vegetables, as well as wholegrain products rich in fibres.
- Subjects with pathologically increased body mass index should be recommended a weight-reducing diet.

**3. Antithrombotic therapy recommendations:**

***Patients without non-valvular atrial fibrillation***

- Low-dose aspirin (75 - 100 mg daily) for primary prevention of myocardial infarction in males does not reduce the risk of ischemic stroke (*Class I, Level A*).
- Low-dose aspirin (75 - 100 mg daily) is recommended for prevention of cerebrovascular events in patients with asymptomatic internal carotid artery stenoses >50% (*Class II, Level B*).
- Antiplatelets other than aspirin are not recommended for primary stroke prevention *(GCP*).

***Patients with non-valvular atrial fibrillation***

- Antiplatelet drugs are not recommended for primary stroke prevention.

• Unless contraindicated, either oral anticoagulants - vit. K antagonists (VKA) such as acenocoumarol with target international normalized ratio [INR] 2.0-3.0) or non-VKA (dabigatran, apixaban, edoxaban, rivaroxaban) are recommended in patients aged 65-75 years and free of cardiovascular risk factors (*Class I, Level A*).

• Unless contraindicated, oral anticoagulants are recommended for patients aged >75 or younger patients with RF such as high BP, left ventricular dysfunction or diabetes mellitus (*Class I, Level A*):

- *Acenocoumarol* – an indirect oral anticoagulant (INR range 2.0-3.0)
- *Dabigatran etexilate* – a direct thrombin inhibitor 150 mg B.I.D or 110 mg B.I.D (over 80 years old or Verapamil drugs intake).
- *Apixaban* 5 mg B.I.D – a selective inhibitor of factor Xa of the coagulation cascade;
- *Apixaban* 2.5 mg B.I.D in patients with at least two of the following conditions: age ≥80 years, body weight ≤60 kg or serum creatinine ≥133 μmol/l.
- *Rivaroxaban* 15 or 20 mg Q.D – a selective inhibitor of factor Xa of the coagulation cascade;
- *Edoxaban* at the usual daily dose of 60 mg - a direct, selective inhibitor of the active site of factor Xa. Its use is shown in one or more of the following risk factors - congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus. A daily dose of 30 mg is indicated in patients with renal insufficiency (creatinine clearance 15 - 50 mL / min), body weight ≤ 60 kg, concomitant use of P-glycoprotein inhibitors: cyclosporin, dronedarone, erythromycin, ketoconazole.

• *Aspirin* 75 – 100 mg daily to be considered for patients with contraindications to oral anticoagulants

• Patients with mechanical prosthetic valves should be considered for long-term anticoagulation VKA therapy (acenocoumarol) with target INR based on the prosthesis type, but not lower than 2.0-3.0 (*Class II, Level* B).

**4. Carotid surgery and angioplasty (see National Consensus on Ultrasound Diagnostics and therapeutic approach for Extracranial Carotid Pathology, 2020)**

• Carotid endarterectomy is not recommended in asymptomatic patients with hemodynamically significant carotid stenosis (NASCET 60-99%), except for those at high risk for stroke (*Class I, Level C*).

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

• It is recommended that patients take aspirin before and after the surgical intervention (*Class I, Level A*).

• Drugs, prescribed for improvement of cerebral microcirculation and metabolism

(antioxidants, vitamins and food supplements) have no proven beneficial effects: (*Class I, Level A*).

## 1.2. Secondary stroke prevention

Indicated for post-stroke patients with established cerebrovascular disease

## Role of the general practitioner

**1. The general practitioner** should examine post-stroke patients once a month and at each clinical deterioration after the first year of stroke.

- Visit post-stroke patients at home in case of clinical deterioration and treat all somatic complications.
- Refer immediately post-stroke patients to a neurologist for new symptoms and/or clinical signs.
- Perform prophylaxis of the cerebrovascular disease, after consulting the neurologist.
- Prescribe the monthly therapy, administered by the treating neurologist.
- Comply with the therapeutic approach, defined by a neurologist, and not changing the therapy without prior specialized consultation with the treating neurologist.
- Monitor closely the therapy of post-stroke patients discharged at home.

**2. Control** the main comorbid conditions that led to the stroke.

- ***Control of BP.*** It is recommended that BP be checked on regular base. Drug therapy should be prescribed if BP ≥140/90 mmHg (*Class I, Level B*).
- Drug therapy should target BP values <130/80 mmHg in patients 18-65 years old (but not <120 mmHg for the systolic pressure), <140/80 mmHg in patients >65 years old if well tolerated.
- It is recommended that antihypertensive therapy in elderly people be initiated at systolic BP ≥160 mmHg with target systolic BP <140 mmHg if well tolerated (*Class I, Level A*).
- In patients aged <80 years therapy should be initiated if SBP ≥140 mmHg with target SBP <140 if well tolerated by the patient (*Class I, Level A*).
- In patients aged >80 years with good functional and cognitive status the target SBP should be <140 mmHg (*Class I, Level A*).
- Optimal control of HTN should be achieved with diuretics or a combination of diuretics with angiotensin-converting enzyme inhibitors (*Class I, Level A*). The choice of antihypertensive therapy is individual and should be made after consideration of HTN characteristics and patient's comorbidities (*Class IIa, Level B*). It is preferred that the drugs are administered in a single-tablet formulation.
- ***Monitoring for atrial fibrillation*** during the first 6 months after stroke or TIA is

recommended (*Class IIa; Level C*).

- ***Control of dyslipidemia.*** Intensive lipid-lowering treatment with a statin is recommended for secondary stroke prevention of patients who suffered a non-cardioembolic stroke or TIA (*Class I, Level A*).
- The treatment should aim for LDL-cholesterol (LDL-C) <1.4 mmol/L
- High-intensity therapy with atorvastatin 40-80 mg or rosuvastatin 20-40 mg is recommended.
- In patients intolerant to statins or in case of failure to reach the target values, ezetimibe may be considered (*Class IIa, Level C*).
- ***Control of glucose metabolism.*** In patients who have suffered a stroke or TIA is required screening for diabetes mellitus by fasting blood glucose level test, $HbA_{1c}$ test or oral glucose tolerance test, the $HbA_{1c}$ test being a more accurate method in the phase immediately after ischemia (*Class IIa, Level C*). Regular checks of blood glucose and antidiabetic treatment are recommended.
- In patients with type 2 diabetes who do not need insulin, pioglitazone is a drug of choice after stroke (*Class III, Level B*).
- ***Echocardiography*** is applicable in specific patients to evaluate the indications for mechanical closure of a persisting foramen ovale (*Class IIa; Level B*).
- A persisting foramen ovale should be closed in patients with cryptogenic stroke.
- In acute or subacute dilated cardiomyopathy, as a diagnostic procedure to ascertain the cause of heart failure.
- ***Control of overweight/obesity.*** Regular calculation of body mass index is recommended (*Class I; Level C*).

**3. Recommend** to patients:

- Patients with overweight/obesity should be recommended a weight-reducing diet (*Class IIb; Level C*).
- Lifestyle changes as a reasonable part of a comprehensive HTN therapy (*Class IIa, Level C*) with Mediterranean-type diet, low in salt and saturated fatty acids and plenty of fruit, vegetables, fish, nuts, and low-fat dairy products with limited intake of meat and carbohydrates.
- Restriction of alcohol consumption is recommended (*Class I; Level C*)
- Increased physical activity at least 3-4 days a week for 40 minutes daily is recommended (*Class IIa; Level C*)
- Cessation of smoking is recommended (*Class I; Level C*)
- Testing for sleep apnea and when necessary, treatment with continuous positive airway

pressure breathing might be considered (*Class IIb; Level B*).

- **It is not recommended:**
  - routine screening for obstructive sleep apnea after recent AIS *(Class III, Level B).*
  - routine screening for antiphospholipid syndrome in the absence of other clinical data, as well as for a known cause of AIS *(Class III, Level C).*
  - screening for hyperhomocysteinemia after recent AIS *(Class III, Level C).*
  - The benefit of screening for thrombophilia in patients with AIS is unknown *(Class IIb, Level C).*
  - Routine supplementation with vitamins is not recommended *(Class III; Level of A)*

## Role of the primary care neurologist

**The neurologist** is a key figure in the interdisciplinary team during the diagnostic and therapeutic process of stroke patients.

**1. Patient's follow-up** in the course of 1 year:

- Clinical examination of post-stroke patients: once a month for the first 3 months and then every 3rd month till the end of the first year after stroke.
- Consultation of patients referred by a GP.
- Home visits of post-stroke patients if requested by their GP.
- Referral of post-stroke patients to their GP with detailed medical conclusion and a plan for individual treatment and follow-up.
- Referral of patients for repeated instrumental (neurosonography, CT, angiography, MRT, EEG, ECG, echocardiography, otoneurological examination, etc.) and laboratory examinations when necessary.
- Investigating for cognitive impairment is advisable, but data that support prescription of specific treatment are insufficient (*Class I, Level A*).
- Communication disorders testing is advisable, but data that support prescription of specific treatment are insufficient (*Class III, GCP*).
- In presence of indications, referral of post-stroke patients to specialized health institutions for continuous hospital treatment and rehabilitation or to hospice care.

**2. Antithrombotic therapy for secondary prevention** (*Class I, Level A*)

- ***The use of antiplatelets*** instead of oral anticoagulants is recommended in patients who have had a non-cardioembolic AIS in order to reduce the risk of recurrent AIS or other cardiovascular incident *(Class I, Level A).*
- the choice of antithrombotic medication should be individualized *(Class I, Level C).*

- It is recommended that antiplatelet therapy with aspirin (325 mg daily) be initiated within 24-48 hours after ischemic stroke for 1 month with consequent dose reduction to 75-100 mg daily.
- In patients with severe stenoses of large intracranial arteries (70-99%) who suffered a stroke within the last 30 days, clopidogrel 75 mg daily should be added to aspirin therapy for 90 days *(Class IIb, Level B).*
- In patients with 50-60% stenosis of a major intracranial artery treatment with aspirin 325 mg daily is recommended (*Class I, Level A*).
- Clopidogrel 75 mg daily alone is recommended for younger patients with TIA or ischemic stroke with concomitant diabetes mellitus, aortocoronary bypass graft, major intracranial artery stenosis, severe atherosclerosis, etc., who are intolerant to or not efficiently influenced by aspirin treatment or have adverse effect *(Class IIa, Level B.)*
- A combination of aspirin with Clopidogrel is recommended for patients with recent ischemic stroke and unstable angina, acute coronary syndrome or recent coronary stent implantation; Treatment should continue up to 12 months after the event (*Class I, Level A*). It is advisable to use proton pump inhibitors for gastroprotection.
- It is recommended that combination therapy with aspirin and clopidogrel be initiated within 24 hours after minor non-cardioembolic ischemic stroke (NIHSS score ≤ 3) for which IVT was not administered, or TIA, for 21 days *(Class I, Level A).*
- Secondary prevention after non-cardioembolic AIS with triple platelet antiaggregant therapy (ASA + clopidogrel + dipyridamole) *is harmful and should not* be used *(Class III, Level B - TARDIS Trial).*
- The benefit of increasing the dose of ASA or switching to another platelet antiaggregant medication is not well established in patients with non-cardioembolic AIS already on ASA *(Class IIb, Level B).*
- In patients with non-cardioembolic AIS on antiplatelets, switching to vit. K-antagonist is not recommended *(Class III, Level B - WARSS).*
- Anticoagulant treatment may be discussed in cases of abnormal findings in the coagulation profile after AIS depending on the underlying pathology and clinical picture. *(Class IIb, Level C).*
- ***Oral anticoagulation therapy*** is appropriate to be initiated between 4 and 14 days after an ischemic stroke, associated with ***non-valvular atrial fibrillation*** *(Class IIa, Level B).*
- No recommendation can be made on the optimum time for starting oral anticoagulation treatment (ESO Recommendations, 2019).
- In patients at high risk for haemorrhagic transformation of stroke, initiation of oral

anticoagulation might be postponed *(Class IIb, Level B).*

Drugs of choice:

- *Acenocoumarol* − INR (range 2.0-3.0)
- *Apixaban* 5 mg B.I.D
- *Apixaban* 2.5 mg B.I.D in patients with at least two of the following conditions: age ≥80 years, body weight ≤60 kg, serum creatinine ≥1,5 mg/dl (133 μmol/l).
- *Dabigatran etexilate* 110 mg B.I.D or 150 mg B.I.D
- *Rivaroxaban* 15 or 20 mg Q.D
- *Edoxaban* 15, 30, 60 mg - the dose of 60 mg Q.D or 30 mg Q.D in case of specific indications.
- In patients with non-valvular atrial fibrillation and a history of TIA or AIS, secondary prevention with new direct oral anticoagulants is recommended before the use of vit. K-antagonists (ESO Recommendations, 2019).
- For AIS associated with atrial fibrillation, it is appropriate to have antithrombotic therapy for the first 48 hours. Then, for mild strokes with a small infarction area (<1.5 cm), it is appropriate to include oral anticoagulant treatment on 3 - 4 days from the onset of AIS, on 7 days - in moderate AIS and after 14 days for massive AIS (ESO recommendations 2019).
- The safety and the benefits of treating AIS with oral direct inhibitors of factor Xa have not been well studied *(Class IIb, Level C).*
- In patients with cardioembolic stroke, not related to atrial fibrillation but at high risk for stoke recurrence oral anticoagulation is recommended [target INR 2.0-3.0]. (*Class III, Level C*).
- In selected cases - unstable angina pectoris or coronary stent, a combination of oral anticoagulants and antiplatelet agents may be administered. In patients with a history of AIS, atrial fibrillation and coronary artery disease, the addition of antithrombotic drugs to oral anticoagulant therapy has an uncertain effect *(Class IIb, Level C).*
- Advanced age alone is not a contraindication to oral anticoagulation (*Class I, Level A*).
- For patients with AIS and extracranial carotid or vertebral dissection, platelet antiaggregant or anticoagulation therapy should be considered for 3 to 6 months (Class IIa, Level B).
- In case of TCVDS low molecular weight heparins or unfractionated heparin are administered, and after the acute phase it is appropriate to have a continuous oral anticoagulant treatment with Vitamin K antagonists at INR (2.0 - 3.0) (Class IIa, Level B).
- The duration of anticoagulation in TCVDS depends on the etiology and varies within 3–12 months, or potentially throughout life, with recurrent TCVDS, at high thrombotic risk, or

subsequent deep venous thrombosis after TCVDS *(Class IIb, Level C, GCP).*

- Drugs improving microcirculation and brain metabolism have no proven therapeutic effect (*Class III, Level C*).
- In patients with AIS that has had a hemorrhagic transformation, antiplatelet treatment can be considered and continued, depending on the specific clinical picture and underlying causes (*Class IIb, Level C).*

- **It is not recommended:**
  - Oral anticoagulation in patients with comorbidities such as seizures, poor compliance, uncontrolled epilepsy, or gastrointestinal bleeding (*Class III, Level C*).
  - Oral anticoagulation after non-cardioembolic ischaemic stroke and in patients with aortic atheromas (*Class I, Level A*), except for some specific conditions such as fusiform aneurysms of the basilar artery, cervical artery dissection, or patent foramen ovale in the presence of established deep vein thrombosis or atrial septal aneurysm (*Class IIb, Level B*).
  - Administration of antiplatelets belonging to glycoprotein (GP) IIb-IIIa inhibitors (*Class I; Level A*). These selective blockers of platelet aggregation increase the risk of severe intracerebral hemorrhage after ischemic stroke.
  - Treatment and secondary prevention of ischemic stroke with neuroprotective substances *(Class III, Level A).*
  - Vasodilators such as pentoxifylline *(Class III, Level A).* In Bulgaria, physicians have experience with these drugs.

**3. Surgery and angioplasty** (see National Consensus on Ultrasound Diagnostics and Therapeutic approach in Extracranial Carotid Pathology, March 11th, 2011 and 2020)

- Among the patients with small, non-disabling AIS (mRS 0–2) in the carotid pool based on routine non-invasive neuroimaging of the cervical carotid arteries within 24 hours of admission *(Class I, Level B*) candidates for carotid endarterectomy or stenting are identified.
- In case of indications for revascularization in patients with mild non-disabling AIS (mRS 0–2), the procedure should be done in 48 hours to 16 days, in the absence of contraindication for early revascularization *(Class IIa, Level B).*

➢ **Carotid endarterectomy is recommended for:**

- Patients with 70-99% (NASCET criteria) stenosis (*Class I, Level A*). CEA should only be performed in centres with a perioperative complication rate (all types of strokes and death) <6% (*Class I, Level A*).
- CEA may be indicated for certain patients with stenosis of 50–69% (NASCET criteria). Males with very recent hemispheric symptoms are most likely to benefit (*Class III, Level C).*

- CEA for stenosis >70% (NASCET criteria) should only be performed in centres with a perioperative complication rate <3% (*Class I, Level B*).
- It is recommended that patients remain on antiplatelet treatment before and after surgery (*Class I, Level A*).

➢ **Stenting with the Wingspan stent system is not recommended in** asymptomatic patients with high-grade stenosis (70%–99%) of a major intracranial artery (*Class IIb, Level C*). Benefits of implantation of other stents and/or angioplasty are arguable even in case of worsening of clinical symptoms (*Class IIb, Level C*).

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

- It should only be performed in centres with a perioperative complication rate <6% (*Class I, Level B*).
- Combination therapy with ASA (75-100 mg) plus Clopidogrel (75 mg) is recommended prior to stent placement and for at least one month (up to ≥12) after it ( *GCP*).
- For patients aged ≥70 years CEA is a preferred therapeutic modality rather than stent-implantation because of lower risk for periprocedural complications (*Class IIa, Level B*).

➢ **It is not recommended:**

- Intracranial or extracranial (IC/EC) bypass surgery *(Class III, Level A).*
- Long-term follow-up of the extracranial carotid circulation by carotid duplex ultrasonography *(Class III, Level B).*

# 2. Diagnosis, treatment, and rehabilitation of cerebral strokes (TIAs, ischemic, and hemorrhagic strokes), cerebral vein and dural venous sinus thrombosis, acute hypertensive encephalopathy, and vascular dementia

## 2.1. Diagnosis

### 2.1.1. In primary care settings

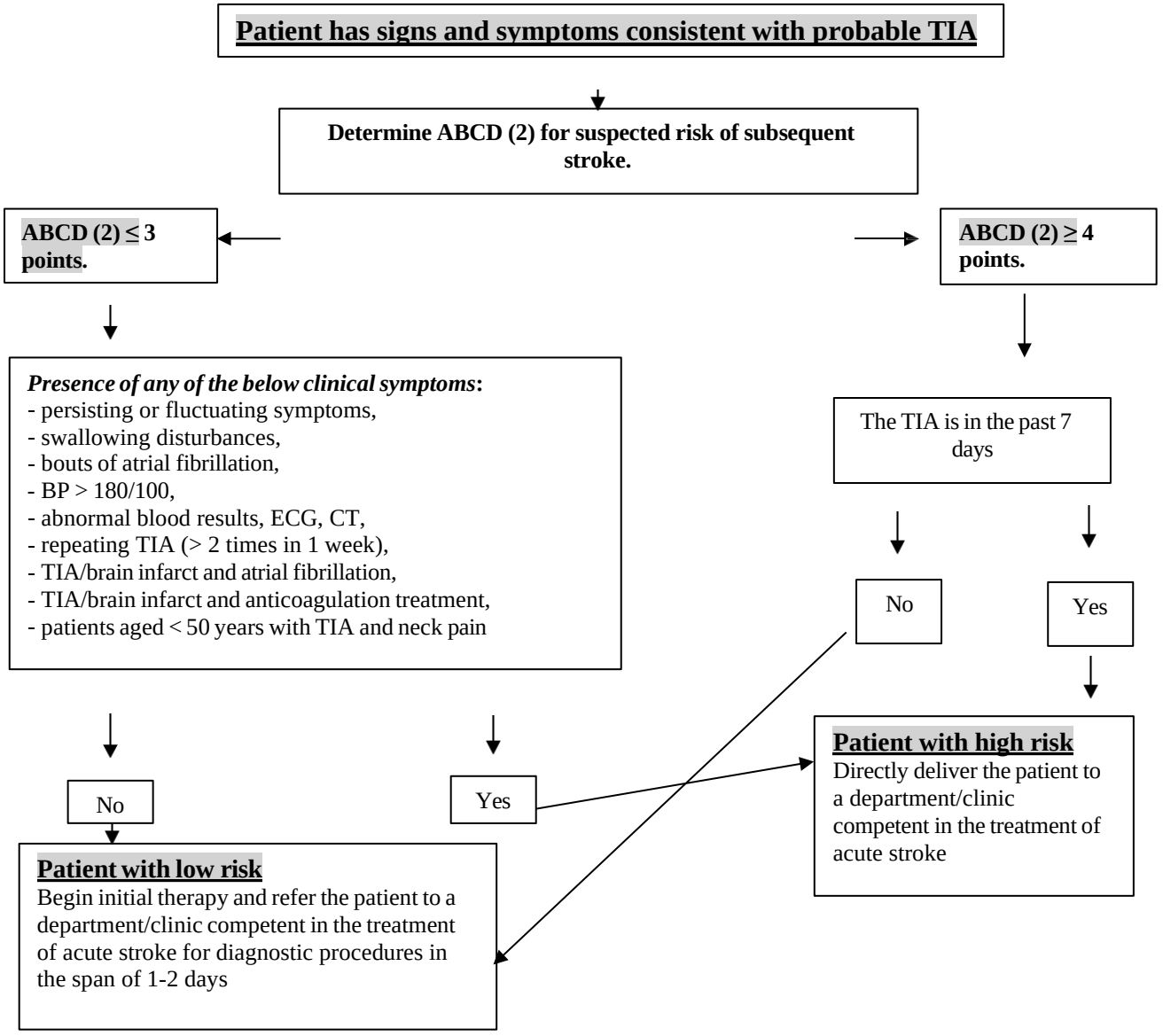
Stroke is a medical emergency requiring urgent hospitalization for its successful treatment. Identification of early mild signs and symptoms is essential for the correct diagnostic and therapeutic approach (*Class I, Level A*).

The "time is brain" concept was promoted by the World Stroke Organisation (WSO) aiming to increase public awareness about the importance of early CVD diagnosis and management. **Requirements:**

- Specific training programs targeting the community, physicians, other hospital staff, and EMS teams, aimed at reducing the time for identifying and transporting patients to treatment units and increasing the chances of thrombolytic treatment. *(Class I, Level C).*
- Educational programmes to increase awareness of stroke at population level are recommended using the Face-Arm-Speech-Test (F.A.S.T; table 7). In suspected stroke, emergency medical service (EMS) should be called immediately.
- It is recommended that dispatchers and ambulance personnel be trained to recognize stroke using simple instruments such as the Face-Arm–Speech-Test (table 7)**.**
- In patients with symptoms and signs suggesting stroke or TIA, GPs, primary care neurologists or emergency care physicians should call EMS without delay, examine blood glucose and vital clinical signs, and refer the patient for urgent hospitalization (*Class I, Level A*). Changes in consciousness, vomiting and high BP are suggestive of hemorrhagic stroke.
- Urgent transportation to the nearest stroke department/clinic is recommended with prior notification of the stroke team (*Class I, Level B*). Patients must not be transported to hospitals without capacity to treat strokes, even if they are located closer (*Class I, Level B*). Patients with onset of stroke symptoms within 3 hours should have priority in transportation. Relatives/witnesses who can describe symptom onset or the patient's medical history should accompany the patient.
- In remote areas helicopter transfer can be used in order to ensure quick access to specialized treatment (*Class III, Level C*).
- In remote areas telemedicine should be considered in order to improve access to specialized treatment (*Class I, Level B*).
- Patients with suspected TIA should be transported without delay to the nearest medical centre with stroke treatment capabilities that can provide specific assessment and urgent treatment (*Class III, Level B*).

- The medical examination of patients with TIA should be given the same priority as those with stroke because more than 20% of them will proceed to have a full-on stroke within the next 48 hours.

**Figure 1. Action algorithm for TIA, after risk evaluation of subsequent stroke**

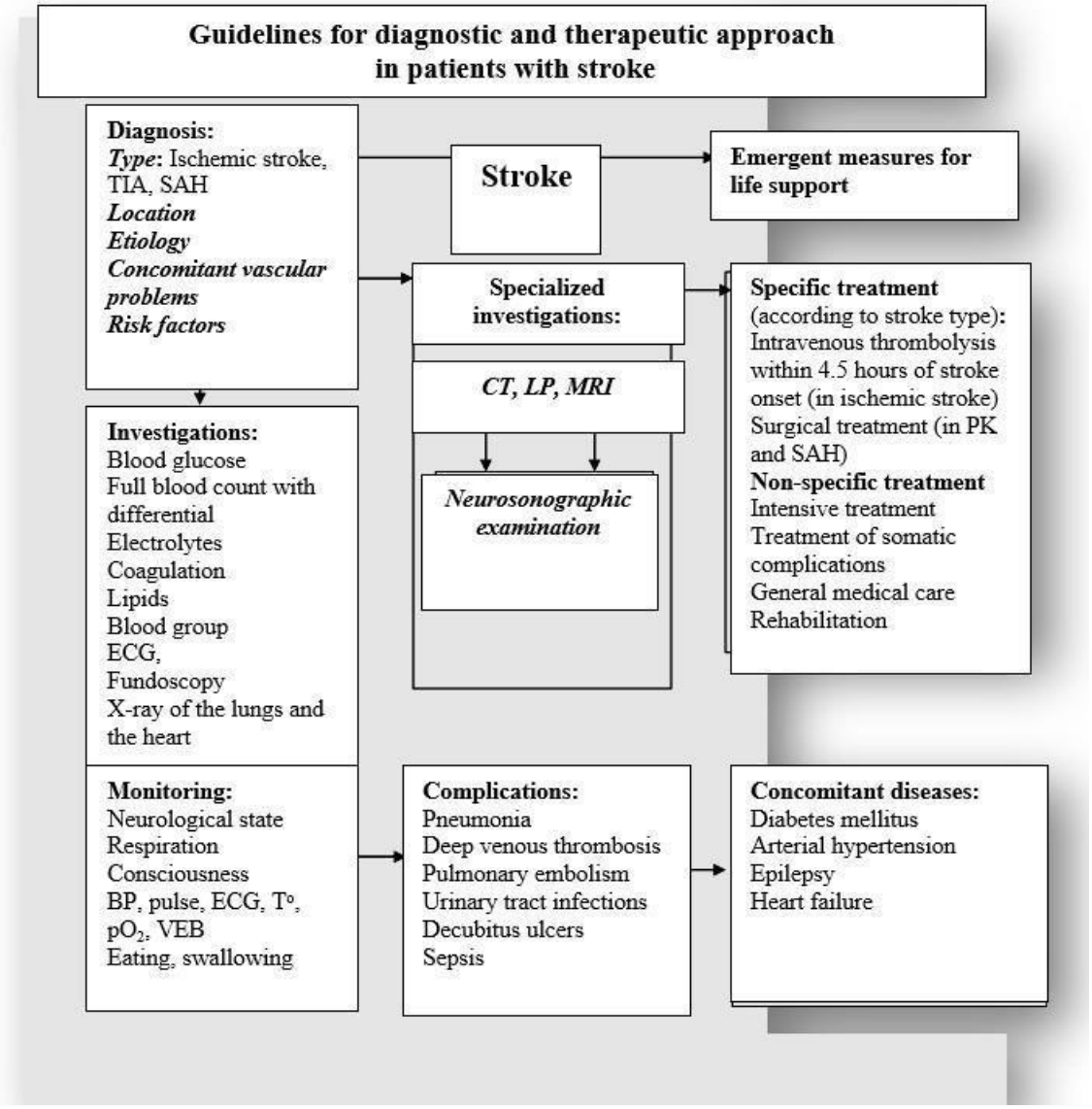



## 2.1.2. In-hospital settings

- It is recommended that all stroke patients should be diagnosed and treated in a stroke unit, intensive care unit or rooms for acute stroke treatment in neurologic clinics and departments (*Class I, Level A*).
- It is recommended that standardized diagnostic protocols be used allowing diagnosis and treatment decision within 60 minutes from patient's admission (*Class I, Level B*).

- Immediate ER triage, prompt clinical, laboratory and imaging investigations, accurate diagnosis and appropriate treatments at the receiving hospital are recommended (*Class III, Level B*).

**Figure. 2 Guidelines for diagnostic and therapeutic approach in patients with brain strokes**




- Precise history of the onset of the cerebral event (acute, subacute) with or without development of focal neurological symptoms, with or without general cerebral symptoms.
- Vital parameters including BP measurement of both arms
- Neurological status − presence or absence of: meningeal syndrome, general cerebral symptoms (headache, nausea, vomiting), respiratory and swallowing disorders, quantitative disorders of consciousness, focal neurological symptoms of different degree (hemiparesis, hemihypesthesia, hemianopsia, central or peripheral cranial nerve lesion), epileptic seizures, etc.
- Evaluation of major symptoms (*Class I, Level A*) on the basis of:

− Assessment of the severity of neurological symptoms by a neurologist using the National Institutes of Health Stroke Scale (NIHSS) (*Class I, Level B*; table 2)

− Assessment of consciousness using the Glasgow-Liège coma Scale (GLCS; table 3).

- Barthel index assessment (table 4).
- Modified Rankin score assessment (table 5)
- Hunt and Hess scale assessment of the severity of subarachnoid haemorrhage (table 6)

**Determination of:**

- Exact time of symptoms onset
- Stroke type – ischemic stroke, intraparenchymal and subarachnoid hemorrhage, TIA, cerebral vein and dural venous sinus thrombosis or acute hypertensive encephalopathy.
- Stroke location – topical diagnosis
- Etiology – etiological diagnosis
- Presence of risk factors

**Investigations**

- Stroke patients should be directed for brain imaging with priority to other patients because time is crucial. Brain imaging should be performed no later than 45 minutes from the patient's arrival at hospital and the results should be interpreted by an experienced specialist (*Class I, Level C*).
- An urgent native CT *(Class I, Level A)* or a combination of native CT and CT perfusion *(Class I, Level A)* is recommended to exclude intracerebral haemorrhage and to assess the presence of a hypodense zone. Additionally, CT perfusion allows an accurate assessment of the penumbra and the area of irreversible damage. A brain MRI *(Class I, Level B)* may also be performed if possible. CT scans (native CT or combined native CT with CT perfusion) are sufficient to make a therapeutic decision for thrombolysis.
- Fibrinolysis is recommended in the presence of early ischemic changes on native CT (ASPECTS >7), as well as on CT perfusion (*Class I, Level A*).
- If MRI is used it should include diffusion weighted imaging (DWI) for identifying the acute ischemic stroke and $T_2$-weighted gradient echo sequences to identify haemorrhage.
- CT perfusion and MRI perfusion including evaluation of the infarct core and penumbra could be used to identify candidates for reperfusion therapy out of the time window for intravenous thrombolysis. They provide additional data about the stroke severity and help taking treatment decisions (*Class I, Level B*).
- Cerebral panangiography is recommended in all young normotensive patients with unclear cause of stroke in whom surgery might be taken under consideration for exclusion of suspected brain aneurysm, malformation or another vascular pathology (*Class III, Level C*).
- Chest X-ray is recommended in patients with evidence of acute heart or lung disease provided it does not delay performance of intravenous thrombolysis (*Class IIb, Level B*).

- Non-invasive imaging of the extracranial arteries in the acute phase of stroke is recommended in patients eligible for thrombolysis or mechanical thrombectomy provided it does not delay performance of intravenous thrombolysis (*Class I, Level A*).
- Vascular imaging is advised to identify patients with advanced symptomatic arterial stenosis who could benefit from endarterectomy or angioplasty (*Class I, Level A*). Non-invasive imaging with colour-coded duplex imaging of the extracranial and intracranial arteries, CT angiography (CTA), or contrast-enhanced MR angiography (CE-MRA) are widely recommended. These imaging modalities are relatively free of risk whereas the risk of stroke during intra-arterial angiography in patients with symptomatic carotid lesions is 1-3%. Digital subtraction angiography (DSA) may be needed when other tests cannot be performed.
- Lumbar puncture (LP) and cerebral spinal fluid testing is recommended in patients contraindicated to CT or in those with negative result but with suspected SAH or history of comorbidities.
- All stroke and TIA patients are recommended the following urgent blood tests (*Class I, Level B*): complete blood count with differential, biochemistry with serum electrolytes and blood glucose, coagulation state.
- <u>Only when indicated</u>: blood group, screening for thrombophilia, homocysteinemia and antiphospholipid syndrome in children and juveniles with stroke. Subsequent tests depend on the type of stroke and suspected etiology (figure 2).
- Initial laboratory investigations are limited to avoid loss of time (*Class I, Level B*).
- Blood glucose testing should precede the initiation of intravenous thrombolysis in all patients *(Class I, Level B).*
- Troponin test is recommended provided it does not delay performance of intravenous thrombolysis or mechanical thrombectomy (*Class I, Level C*).
- 12-lead ECG and cardiologic consultation is recommended for all patients provided it does not delay performance of intravenous thrombolysis (*Class I, Level B*).
- In addition, continuous 24-hour Holter-ECG monitoring is recommended in all patients after the acute phase of stroke (*Class I, Level B*). Cardiac and ECG abnormalities are common in acute stroke patients.
- Echocardiography is recommended in selected patients with evidence for heart disease (*Class III, Level B*). Transthoracic echocardiography (TTE) is sufficient for evaluation of mural thrombi, particularly at the apex of the left ventricle.

## 2.2. Treatment

### 2.2.1. Ischemic stroke

#### 2.2.1.1. Specific treatment recommendations

Time is brain. Fewer than 10% of patients in Europe reach hospitals within 60 minutes from the onset of symptoms. A patient with stroke loses 2 million neurons per minute and they cannot be restored with available treatments. The bigger the cell loss, the greater the chance of speech disturbance, paralysis, and permanent disability.

*Quality of treatment and care for stroke.* The rapid neurological assessment and start of treatment for stroke are critical to achieve improved results and to reduce the probability of permanent disability. Stroke is a medical emergency, and the treatment result is directly proportional to how quickly it is applied. To improve the quality of stroke treatment algorithms, the actions of medical staff must be constantly observed, analysed, and compared. A periodic assessment of quality of treatment and care for stroke is needed, as well as whether the National plane for stroke is adhered to. Care for stroke patients must be provided only by properly trained and competent personnel, who are constantly audited for quality. Hospitals providing stroke care must be certified and re-certified periodically through measuring the quality of thrombolysis and thrombectomy treatments, patient outcomes, and mortality. Endovascular treatment must be done in specialised centres that have 24/7 preparedness and are staffed by certified neurologists, imaging specialists, and endovascular neurosurgeons. If the centre cannot maintain good quality values, its certification should be revoked.

*Equitable access to care must be available for all patients with acute stroke*. Increasing the coverage and rapid access to certified stroke clinics is crucial. All patients with stroke must have access to diagnostics and treatment in stroke centres as a first line of care, with guaranteed competencies to provide cerebrovascular recanalization treatments, administered in the shortest possible times from hospital entry. In Bulgaria, 92-94% of patients are treated in clinics or sectors for acute stroke treatment. In fact, intensive neurological clinics or clinics with intensive beds that have since fulfilled the requirements of a stroke unit were created in the 1990s.

It is imperative that by 2030 at least 15% of all strokes receive thrombolytic therapy and at least 5% receive endovasclar treatment. To this end, these centres must be staffed by neurologists, imaging specialists, and endovascular neurosurgeons, who are certified by a National board. These targets require the improvement of hospital organisation and logistics and the training of new certified interventionalists.

Specific treatment is carried out with minimally invasive intravascular techniques. Interventional neurology offers modern methods for the treatment of neurological vascular disorders. They include intravenous or intra-arterial thrombolysis (IVT/ IAT) or mechanical thrombectomy for treatment of AIS. Intravenous thrombolysis is just one of the possible methods for antegrade

reperfusion through lysis of the blood clots. Thrombolytic drugs stimulate fibrinolysis through conversion of fibrinogen to fibrin. The other methods use intra-arterial access – administration of fibrinolytics at the site of the occlusion (intra-arterial thrombolysis) or its mechanical fragmentation by different techniques – endovascular thrombectomy, endovascular thromboaspiration or intra-arterial angioplasty.

The results from the NINDS, ECASSI, ECASSII and ECASSIII trials showed that complete functional recovery can be expected in 1 out of every 5 patients if IVT is administered within 3 hours from onset of symptoms and in 1 out of every 15 patients if administered within 4.5 from onset of symptoms.

Clinical data show that treatment is not always successful. In proximal internal carotid artery (ICA) stenosis, successful reperfusion is achieved in 10% of all treated patients and in mid-cerebral artery (MCA) stenosis – in ~30% of the patients.

On the other hand, the increased rate of specific affinity to fibrin and activation of hemostasis induced by thrombin released during fibrinolysis substantially increase the risk for early reocclusion.

**Requirement for informed consent:**

- Interventional treatment (thrombolysis and thrombectomy) and/or decompressive craniectomy in acute stroke are performed after obtaining written informed consent from the patient or his/hers authorized representative;
- If the patient is unable to understand and sign the informed consent or in the absence of a close or authorized representative of the patient, the procedures should be performed at the discretion of the multidisciplinary team on the basis of vital signs, strictly reflected in the medical records.

## Intravenous thrombolysis

Regulatory institutions have approved two pharmacological thrombolysis agents for ischemic stroke – rtPA (Alteplase) or tenecteplase (metalyse) applied within 4.5 hours from symptom onset.

A Quantitative evaluation of ischemic brain injury is made by ASPECTS (Alberta Stroke Program Early CT Score): 10-point score for quantitative topographic CT assessment used for optimal selection of patients eligible for emergency intravenous thrombolysis and thus for improvement of clinical outcomes. This method cuts the costs of hospital stay by its shortening and by improved therapeutic approach. The CT scan is native with standard slice thickness of 5 mm. The ASPECTS score divides the MCA territory into 10 areas. Seven of them are at basal ganglia level (C – nucleus caudatus “head”, I – insular ribbon, IC – internal capsule, L – nucleus lentiformis, M1, M2, M3 – cortex zones) and 3 zones are at supraganglionic level – M4, M5 and M6 cortex zones (figure 3).

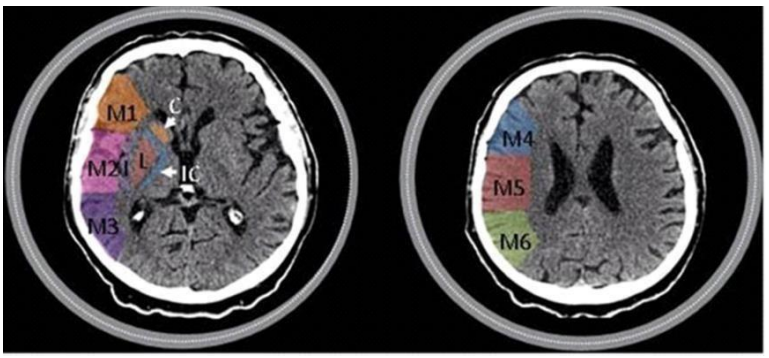



**Figure 3. Quantitative assessment of the ischemic brain injury using ASPECTS Score**

To calculate the ASPECTS score, 1 point is subtracted from a baseline of 10 for any data of early ischemic changes per each of the defined regions. The assumption whether an area is involved requires a review of all slices from the basal ganglionic or supraganglionic structures, and all slices to be visible (figure 4).

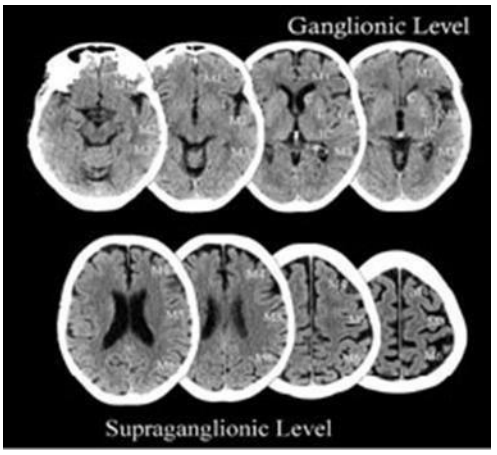



**Figure 4. Assessment of all representative slices using ASPECTS Score**

A score of 0 indicates diffuse involvement throughout the MCA territory and a normal CT scan gets 10 ASPECTS points. Lower scores might indicate more proximal arterial occlusion. Patients with ASPECTS >7 points are more likely to benefit from thrombolytic treatment. Patients with score <5 points have less probability for improvement and are at high risk of post-procedural bleeding.

**Intravenous thrombolysis:**

- Must be administered as fast as possible (*Class I, Level A*).
- Patients can benefit from thrombolysis treatment within - 4.5 hours after stroke (*Class I, Level B*).
- Door-to-needle time is recommended to be (from patient's arrival in the hospital to application of rtPA bolus) ≤60 minutes (*Class I, Level A*)
- Indicated for all eligible patients even if subsequent endovascular treatment is considered too (*Class I, Level A*)
- In patients aged ≤80 years without diabetes and previous stroke with NIHSS <25, not

on oral anticoagulants and without neuroimaging data for ischemic injury affecting more than 1/3 of MCA territory (*Class I, Level B*).

- In patients over 80 years old and with stroke onset within 3 - 4.5 hours the fibrinolysis is effective as in younger patients *(Class IIa, Level B).*
- The effect in patients with NIHSS >25 is uncertain (*Class IIb, Level C*).
- The risk/benefit ratio should be considered in patients with minor strokes (*Class* IIb, *Level* B).
- In patients with minor but disabling strokes who fulfil the inclusion criteria, it is appropriate to administrate intravenous thrombolysis within 0 to 3 hours of stroke onset *(Class I, Level B)* or within 3 to 4.5 hours of onset of stroke (*Class IIb, Level B*).
- Recommended in patients with moderate and severe stroke with rapid clinical improvement but with moderate severity of symptoms (Class IIa, Level A).
- Delay of treatment and patient monitoring for possible improvement is not recommended (*Class III Level C*).
- Acceptable alternative for basilar occlusions even if the onset of stroke is >3 hours (*Class III, Level B*)
- Intravenous thrombolysis may be beneficial in patients with ischemic stroke and sickle cell anaemia *(Class IIa, Level B).*
- Intravenous thrombolysis may be beneficial in patients with ischemic stroke and hyperdense MCA *(Class IIa, Level B).*

- CT is mandatory before fibrinolytic treatment for exclusion of intraparenchymal hemorrhage (IH), hemorrhagic stroke or large ischemic stroke, and brain tumour.
  - The use of multimodal imaging criteria may be useful for patient selection for thrombolysis but is not recommended for routine clinical practice (*Class III, Level C*).
  - Penumbral imaging in patients who meet the criteria for IV thrombolysis within 4.5 hours after stroke onset should not delay administration of IVT (*Class III, Level C*).
  - Intravenous fibrinolytic therapy is recommended for treatment in the presence of early ischemic changes on CT (*Class I, Level A*) within the therapeutic window.
  - The presence of mild to moderate early ischemic changes on CT, defined as parenchymal hypoattenuation (decreased density of brain tissue or focal brain tissue swelling) is an indication for intravenous thrombolysis (*Class I, Level A*). This treatment is contraindicated when a large area is affected or changes are severe (*Class* III, *Level* A).
- Recombinant tissue plasminogen activator (rtPA, alteplase (Actilyse)), 0.9 mg/kg, maximal dose 90 mg is administered intravenously with 10% of the dose given as a bolus followed by a 60-minute infusion of the remaining solution. Depending on the mass of the patient we recommend to combine

different volumes of drug bottles – 10 ml (10 mg), 20 ml (20 mg), and 50 ml (50 mg).

- In patients with AIS within 4.5 h of onset who are indicated for thrombolysis, tenecteplase 0.25 mg/kg can be used as a safe and effective alternative to alteplase 0.9 mg/kg. In patients with AIS who have a large vessel occlusion and who are directed for subsequent mechanical thrombectomy, thrombolysis with tenecteplase 0.25 mg/kg is still recommended. Tenecteplase has a 15x higher fibrin specificity than alteplase, a longer half-life, and a lower systemic coagulopathy. Tenecteplase has only a theoretical advantage with respect to recanalization (restoring the flow of a blocked vessel) and risk of bleeding over alteplase. It is administered by means of a single injection over 5-10 seconds.
- It is recommended that BP is lowered to <185/110 mmHg and maintained stable before thrombolysis (*Class I, Level B*).
- In patients who have not undergone intravenous thrombolysis but are scheduled for mechanical thrombectomy, BP should be maintained ≤185 / 110 mm Hg before the procedure *(Class IIa, Level B).* BP must be kept stable <180/105 the first 24 hours after thrombolysis by using Urapidil i.v.
- BP should be monitored every 15 minutes for 2 hours from the start of the thrombolysis treatment, then every 30 minutes for 6 hours, and thereafter every hour for 24 hours *(Class IIb, Level C).* When automatic measurement is used during the infusion and up to 24 hours after, there is a risk of bruising and subdermal hematomas underneath and around the sleeve due to the standard inflation of the sleeve to 200 mmHg.
- If the arterial pressure cannot be controlled or diastolic BP persists> 140 mmHg, nitroprusside sodium intravenously *(Class IIb, Level C)* may be administered.
- The thrombolytic therapy can be initiated in the hospital under the supervision of a neurologist in the absence of information on coagulation disorders or existing anticoagulation therapy before laboratory results are obtained, and immediately after the CT scan (showing no imaging contraindications). If the results of the blood samples taken during the infusion show relative deviations from the normal range the infusion should be discontinued.
- In patients undergoing fibrinolytic therapy, the treatment team should be prepared to deal with potential side effects such as bleeding and angioedema, which may cause partial airway obstruction *(Class I, Level B).*
- If the patient develops severe headache, acute hypertension, nausea or vomiting, or a worsening of neurological status is observed, the infusion should be stopped and an emergency CT scan should be performed.
- The placement of a naso-gastric tube and urethral catheter should be avoided if the patient can be safely treated without them.
- It is necessary to perform a control CT or MRI 24 hours after intravenous thrombolysis, before the administration of anticoagulants or antithrombotic drugs.

- **Intravenous rtPA may also be administered in the following patients after additional risk assessment although the current trends are in favour of endovascular treatment:**
    - When the time of the stroke onset is unknown (wake-up stroke) or more than 4.5 hours after stroke onset when the DWI-MRI lesion is less than one-third of the MCA and is not FLAIR-positive *(Class II, Level A) (AHA-ASA).*
    - With unknown time of onset, a wake-up stroke, or a time window between 4.5 – 9 h from onset, when CT perfusion or MRI (DWI, PWI) fall within the criteria of the EXTEND trial: Volume of ischemic core ≤70 ml; Mismatch ratio ≥1.2 or ≥10 ml absolute different (*Class IIa, Level B)*. Mismatch ratio = total volume of hypoperfusion (penumbra + infarct core) / volume of infarct core.
    - <18 years (*Class I, Level A*)
    - With very severe stroke, irrespective of the risk of hemorrhagic transformation (*Class I, Level A*)
    - Pregnant women with moderate and severe stroke, provided the expected benefit exceeds the risk for uterine bleeding (*Class IIb, Level C*). Emergency gynecological consultation is recommended within the span of the 4.5 h time window (*Class IIb, Level C*).
    - In the early postpartum period (up to 14 days after delivery) - clinical trial data are still insufficient (*Class IIb, Level C*).
    - Surgery in the last 14 days, provided the expected benefit exceeds the potential risk of bleeding at the site of the surgical intervention (*Class IIb, Level C*).
    - Severe trauma in the last 14 days, provided the expected benefit exceeds the potential risk for bleeding at the site of the trauma (*Class IIb, Level C*).
    - Patients with acute stroke and concomitant myocardial infarction, when, after alteplase with standard dosage, percutaneous coronary angioplasty and stenting are applicable if indicated (*Class IIb, Level C*).
    - Myocardial infarction in the last 3 months, with the exception of non-STEMI (without ST-elevation) or right or inferior STEMI (*Class IIa, Level C*) or anterior infarction (*Class IIb, Level C*).
    - Severe ischemic stroke and risk for severe disability and acute pericarditis (*Class IIb, Level C*). Emergency neurological consultation is recommended within the treatment time window.
    - Severe ischemic stroke and risk for severe disability and certain degree of left atrial and ventricular thrombosis (*Class IIb, Level C*). In patients with minor stroke the benefit/risk ratio is uncertain (*Class IIb, Level C*).
    - Cerebral stoke that is likely to be caused by extracranial cervical artery dissection within the first 4.5 hours of onset (*Class IIa, Level C*).

- Severe ischemic stroke and risk for severe disability and cardiac myxoma or papillary fibroelastoma (*Class IIb, Level C*).
- History of previous gastrointestinal or genitourinary bleeding (*Class IIb, Level C*).
- Unruptured intracranial aneurysms <10 mm in diameter (*Class IIa, Level C*). Data for patients with larger aneurysms is insufficient.
- Unruptured intracranial vascular malformations and severe stroke when the benefit exceeds the risk of intracerebral hemorrhage (*Class IIb, Level C*).
- Extraaxial intracranial brain tumors (*Class IIa, Level C*).
- End-stage renal failure and normal aPTT (*Class I, Level C*).
- Dementia (*Clas IIb, Level B*).
- Malignancy with life expectancy survival of >6 months in the absence of contraindications due to inherited bleeding disorders, recent surgery or systemic bleeding (*Class IIb, Level C*).
- Blood glucose <2.8 mmol/l or >22.2 mmol/l but after normalization within the treatment time window (*Class IIb, Level C*).
- Epileptic seizures at the time of stroke, if the residual symptoms are caused by the stroke and are not a postictal phenomenon (*Class IIa, Level C*).
- Presence of diabetic hemorrhagic retinopathy or other eye bleeding disorders after assessment of the risk for loss of vision (*Class IIa, Level B*).
- Menstruation and without history of menorrhagia although it might increase menstrual bleeding (*Class IIa, Level C*).
- Menorrhagia without clinically significant anemia or hypotonia (*Class IIb, Level C*). In patients with clinically significant anemia thrombolysis should be performed after gynecological consultation (*Class IIa, Level C*).
- In menstruation or active vaginal bleeding treatment with intravenous thrombolysis requires 24-hour follow-up (*Class I, Level C*).
- Lumbar puncture in the last 7 days (*Class IIb, Level C*).
- Stroke as a complication of cardiac or brain procedures (*Class IIa, Level A*).
- Stroke as a complication of abuse with substances such as cocaine (*Class IIa, Level C*).
- Previous antiplatelet monotherapy (*Class I, Level A*).
- Previous combined antiplatelet therapy (aspirin and clopidogrel) (*Class I, Level B*).
- History of bleeding and coagulopathy at risk assessment (*Class IIb, Level C*).
- Treatment with warfarin (sintrom) with INR <1.7 and PT<15 sec (*Class IIb, Level B*).

- **Intravenous thrombolysis is not recommended in patients with**:
  - CT evidence of acute intracranial bleeding (*Class III, Level C*).
  - Symptoms, suggestive of subarachnoid hemorrhage (*Class III, Level C*).
  - Platelet <100x$10^9$/L, INR>1.7, aPTT>40 sec or PT>15 sec (*Class III, Level C*). Since the risk is low it is recommended that platelet count and coagulation tests are performed only in suspected abnormalities (eg. splenomegaly established during physical exam) to avoid delay of emergency thrombolysis (*Class IIa, Level B*).
  - Treatment with acenocoumarol with INR >1.7 (*Class IIb, Level B*).
  - Treatment with low-molecular heparins within the past 24 hours (*Class III, Level B*).
  - Treatment with direct thrombin inhibitors or direct factor Xa inhibitors within the past 48 hours (*Class III, Level C*), except for patients with aPTT, INR, platelet count and prothrombin time in normal range and/or patients who have not received these medications for more than 48 hours.
  - Brain or spinal cord surgery within the past 3 months (*Class III, Level C*).
  - Symptoms of infective endocarditis because of increased risk for intracranial bleeding (*Class III, Level C*).
  - Gastrointestinal malignancy or bleeding in the preceding 21 days (*Class III, Level C*).
  - Arterial puncture at non-compressible punctures within the preceding 7 days (*Class IIb, Level C*).
  - Stroke that is likely to be due to aortic arch dissection (*Class III, Level C*).
  - Stroke associated with intracranial artery dissection (*Class IIb, Level C*).

**After the intravenous thrombolysis should not be administrated:**

- BP should be maintained below 180/105 mm Hg for at least the first 24 hours after intravenous thrombolysis (Class I, Level B).

## Endovascular treatment

It includes combination or separate administration of intra-arterial thrombolysis and mechanical thrombectomy.

## Intra-arterial thrombolysis

Intra-arterial thrombolysis is logically more justified – administration at the site of occlusion, lower risk for systemic complications and rapid effect in most cases. Still, according to recent randomized trials it is not recommended because the risk of hemorrhage in the ipsilateral hemisphere exceeds the chance for dissolution of already formed clots.

- Patients with indication for interventional treatment should be referred without delay to a specialized hospital unit that can provide immediate treatment (*Class I, Level A*). When necessary, air transfer by should be used.
- Intra-arterial thrombolysis should only be performed at specialized centres for

treatment of acute cerebral blood flow disorders (ACBFD) capable for emergency cerebral angiography performed by a trained and certified interventional specialist (a physician with a speciality in interventional neurology or radiology, with a valid certificate). Health care institutions with specialized centres should meet specific criteria for equipment and specialists certified for performance of intra-arterial thrombolysis (*Class I, Level C*).

**Intra-arterial thrombolysis:**

- Should only be performed in selected patients with acute MCA occlusion in the first 6 hours (*Class I, Leve B-R*).
- As an option in patients with contraindications to intravenous thrombolysis, such as recent surgery (*Class IIb, Level C*).
- Patients with acute basilar occlusion less than 6 hours (*Class III, Level B*)
- There are no approved doses for intra-arterial rtPA treatment, so it is only recommended in patients enrolled in international multicentre trials or national programs. Therefore, endovascular treatment with stent retrievers is recommended as first-line therapy to intra-arterial fibrinolysis (*Class I, Level E*).

## Mechanical thrombectomy

- If left untreated, ischemic strokes due to large vessel occlusion (distal part of ICA, M1, basilar artery) are associated with high mortality.
- Mechanical thrombectomy achieves better reperfusion compared to conventional treatment, with or without IVT.
- The chances for favourable outcome are significantly higher in early vessel reperfusion.
- In some patients eligible for IVT but also with certain contraindications, endovascular treatments should be considered as part of an institutional protocol.
- In patients with contraindications to intravenous thrombolysis (vit. K-antagonist treatment with INR in the therapeutic range) mechanical thrombectomy is recommended as first line therapy for large vessel occlusion (*Class IA, Level A*).
- It is recommended that patients with acute basilar artery occlusion are assessed in centres with multimodal neuroimaging techniques and treated with mechanical thrombectomy added to intravenous thrombolysis, if indicated after CTA (*Class IIa, Level B*). Alternatively, they can be treated as participants in randomized controlled clinical trials approved by local ethics committees.
- The decision for mechanical thrombectomy is taken by a multidisciplinary team which must include at least a physician experienced in the treatment of strokes and a neurointerventionalist.

The procedure is performed in medical centres with experience in multimodal stroke treatment and qualified neuroanesthesiologists (*Class III, Level C*).

- Whenever possible, intracranial vessel occlusion should be diagnosed with non-invasive neuroimaging methods (CTA) for assessment of intracranial vessels before intra-arterial fibrinolysis or mechanical thrombectomy is considered (*Class 1, Level A*). CTA provides sufficient information for guidance of emergency intravenous thrombolysis but its performance should be followed by non-invasive neuroimaging without delay (*Class 1, Level A*).
- The usefulness of additional neuroimaging assessments other than CT, MRI, CTA or MRI angiography, such as perfusion CT or perfusion-diffusion MRI in candidates for endovascular treatment is still unclear (*Class IIb, Level C*).
- When neuroimaging cannot be performed, NIHSS scores of 9 or more points during the first 3 hours and ASPECTS scores of 7 points or more up to 6 hours should be considered as markers for large vessel occlusion (*Class IIa, Level B*).
- Mechanical thrombectomy is not recommended in patients with neuroimaging evidence of extensive infarction (assessed via the ASPECTS score) (*Class IIa, Level B*).
- Neuroimaging methods for identification of stroke area and penumbra may be used for patient selection and correlation with functional recovery after mechanical thrombectomy (*Class Ib, Level B*).
- Advanced age alone is not a contraindication to mechanical thrombectomy as adjuvant treatment (*Class Ia, Level A*).
- **Mechanical thrombectomy:**
  - If not performed in randomized clinical trials, the data should be entered in a registry and patients must be followed up for 1 year after the procedure.
  - Recommended as adjuvant therapy to intravenous thrombolysis within 6 hours after symptoms onset in stroke patients with CTA evidence of large artery occlusion in the anterior circulation (*Class I, Level A*).
  - Mechanical thrombectomy is recommended for selected patients after 6 hours of symptoms onset (up to 16 hours-AHA/ASA, 6-24 hours-SNIS) who have occlusion of a large vessel from the anterior circulation and meet the other criteria for eligibility from DAWN or DEFUSE 3 *(Class I, Level B).*
  - Mechanical thrombectomy should not prevent initiation of intravenous thrombolysis where it is appropriate and intravenous thrombolysis should not delay mechanical thrombectomy (*Class I, Level A*).
  - Mechanical thrombectomy can be done for patients with AIS and a large vessel occlusion within the 6-24 h time window if they fulfil the criteria of the DEFUSE 3 study on CT

perfusion or MRI (DWI and PWI): volume of the infarct core ≤70 ml, mismatch ≥1.8 or ≥15 ml absolute difference (*Class IIa, Level B)*.

- It is not recommended to wait for manifestation of clinical effect of intravenous thrombolysis before proceeding with endovascular therapy after prior CT angiography (*Class III, Level B*).
- When indicated, mechanical thrombectomy should be performed as soon as possible *(Class I, Level A*).
- This procedure must be performed by trained and experienced neurointerventionalists with level II certificate of competence in interventional radiology, meeting the national and international requirements (*Class II, Level* B).
- Stent retrievers approved by local health authorities should be used (*Class 1, Level A*)
- ADAPT-technique could be used (with DAC catheter for thromboaspiration), is followed by stent retrievers in case of failure.
- Stent retrievers are preferred to MERCI retrievers *(Class I, Level A*).
- At the discretion of neurointerventionalists, devices for thrombectomy and aspiration other than stent retrievers can be used in some patients (*Class IIb, Level B*) provided they are approved by relevant local health authorities and if they could also achieve rapid, complete and safe vessel revascularization (*Class IIa, Level C*).

- Patients should receive MT with a stent retriever within 6 hours from stroke onset, if they meet the following criteria *(Class I, Level A*):
  - acute stroke and IV tPA treatment within 4.5 hours from stroke onset
  - occlusion of ICA or proximal MCA (M1)
  - age ≥18 years,
  - NIHSS score ≥6
  - ASPECTS ≥ 6
  - Carefully selected patients with occlusion in the anterior circulation and contraindications to intravenous thrombolysis (*Class IIa, Level C*).
  - Despite uncertain benefits, endovascular therapy is advised in patients with modified Rankin score >1 before stroke, ASPECTS <6, NIHSS <6 and occlusion of the internal carotid artery or proximal (M1) MCA occlusion (*Class IIb, Level B*).
  - Despite uncertain benefits, endovascular therapy is advised in carefully selected patients with M2 or M3 occlusion of MCA, and anterior, vertebral, posterior artery and basilar artery occlusions (*Class IIb, Level C*).
- The aim of thrombectomy is to achieve angiographic 2b/3 TICI score (Thrombolysis In Cerebral Infarction) as a marker of favourable clinical outcome (*Class I, Level A*). For the purpose

additional techniques, such as intra-arterial fibrinolysis can be used within 6 hours of stroke onset *(Class I, Level A*).

- Angioplasty and stenting of atherosclerotic proximal cervical stenosis or in complete occlusion during thrombectomy is not contraindicated but has uncertain effect (Class IIb, Level C).
- The type of anesthesia depends on the patient's risk factors but sedation is preferred over general anesthesia (*Class IIb, Level C*). The chosen method should not delay the initiation of thombectomy (*Class IIb, Level C*).
- In patients undergoing mechanical thrombectomy, maintaining a BP of ≤180 / 105 mmHg during and 24 hours after the procedure is appropriate *(Class IIa, Level B).*
- In patients undergoing mechanical thrombectomy with successful reperfusion, maintaining a BP <180/105 mmHg *(Class IIb, Level B)* may be appropriate.

### 2.2.1.2. General (non-specific) treatment

- It is recommended that treatment is carried out in stroke units or rooms with facilities for neurorehabilitation (*Class I, Level A*).
- Aspirin should be initiated (loading dose 325 mg) 24-48 h after the stroke *(Class I, Level A).*
- Ticagrelor is not recommended for the treatment of minor ischemic stroke instead of ASA *(Class III, Level B).*
- ASA should not replace intravenous thrombolysis or mechanical thrombectomy in indicated patients (*Class III, Level B).*
- **No definite benefit has been proven in the acute phase of stroke for:**
  - Clopidogrel (*Class IIb, Level C*).
  - Emergency anticoagulation in patients with severe ipsilateral internal carotid artery stenosis (*Class IIb, Level B*).
- **Emergency anticoagulation is not recommended for:**
  - Prevention of early stroke recurrence, neurological deterioration or improvement of stroke outcome (*Class III, Level A*).
  - Treatment of non-cerebrovascular disorders in patients with moderate and severe strokes because of increased risk of serious intracranial hemorrhage (*Class III, Level A*).
- In patients who have suffered a stroke while on antiplatelet therapy, reassessment of risk factors is recommended (*GCP*).
- **It is not recommended:**
  - Early anticoagulation with unfractionated or low-molecular heparin or heparinoids is not recommended for specific treatment of patients with acute stroke (*Class I, Level A*). The use of anticoagulants is limited due to increased risk of hemorrhage or blood

infiltration in the infarct zone. Hemostasis monitoring and repeated head CT is recommended. When making a decision for use of anticoagulants the benefit/risk ratio should be considered.

- The use of vasodilators (eg. pentoxifylline), putative neuroprotectors, haemodilution by volume expansion and high doses of albumin are not recommended in the treatment of acute ischemic stroke (Class III, Level A).
- The use of mechanical devices for increasing the brain blood flow is not recommended *(Class III, Level B).*
- Hyperbaric oxygenation is not recommended in patients with acute ischemic stroke unless the cause is air embolism *(Class III, Level B).*

- **It is recommended:**
  - Oxygen should be administered if the oxygen saturation ($SaO_2$) falls below 95% (*Class I, Level C*). Oxygen is not recommended in non-hypoxic patients (*Class III, Level B)*
  - Ventilatory support is recommended in patients with impaired consciousness or bulbar symptoms (*Class I, Level C*). The aim is to prevent hypoxia and enlargement of the brain injury. Maintaining of adequate tissue oxygenation is important in the setting of AIS.
  - Hypotension and hypovolemia should be corrected to provide systemic perfusion enough to maintain organ function *(Class I, Level C).*
  - In patients with acute stroke, early treatment of hypertension is indicated when necessary to respond to available comorbid conditions (concomitant acute coronary accident, acute heart failure, aortic dissection, post fibrinolytic intracranial haemorrhage, eclampsia / pre-eclampsia) *(Class I, Level C).*
- Routine BP reduction is not recommended following acute stroke (*GCP*). In patients with arterial pressure <220/120 mmHg who are not considered for intravenous thrombolysis or mechanical thrombectomy and do not have concomitant conditions requiring an urgent reduction of the BP, the administration of antihypertensive therapy within the first 48 to 72 hours after the acute stroke has not shown a reduction in the disability or the mortality rate (class III, level A).
- In patients who are not considered as candidates for fibrinolytic therapy, cautious BP reduction is recommended in case of extremely high BP (>220/120 mmHg) on repeated measurements, or with severe cardiac failure, aortic dissection, or hypertensive encephalopathy (*Class I, Level C*).
- In patients with BP ≥220/120 who are not considered for an intravenous thrombolysis or mechanical thrombectomy and do not have concomitant conditions requiring an urgent reduction in BP, the administration of antihypertensive therapy within the first 48 to 72 hours after acute stroke has an uncertain effect. It may be appropriate to lower BP by up to 15% in the first 24

hours *(Class IIb, Level C).*

- Unless contraindicated, antihypertensive therapy may be resumed within 24 hours after acute stroke in neurologically stable hypertensive patients *(class IIa, Level B)*. Cautious treatment is recommended because in the majority of patients BP falls spontaneously in the first 24 hours after stroke (*Class IIb, Level C*)
- It is recommended that abrupt BP lowering be avoided. Systolic BP should not be lowered by more than 15% in the first 24 hours of the vascular event. (*Class I, Level C*).
- The initiation of an antihypertensive therapy during the hospital stay in patients with BP> 140/90 mmHg who are neurologically stable and without contraindications is safe and appropriate to order to improve the long-term BP control *(Class IIa, Level B).*
- Normal saline (0.9%NaCl) is recommended for fluid replacement in low BP secondary to hypovolemia and low cardiac output (*Class I, Level C*).
- Hypoglycaemia (blood glucose <3.3 mmol / L) should be treated *(Class I, Level C).*
- Severe hypoglycemia (<2.8 mmol/l) should be treated with intravenous dextrose or infusion of 10–20% glucose (*Class I, Level C*).
- Persistent hyperglycaemia during the first 24 hours of stroke onset is associated with poor prognosis, because of which blood glucose levels of 7.8 to 10.0 mmol/L should be maintained and the patient should be monitored to avoid hypoglycaemia *(Class IIa, Level C).*
- Treatment with insulin *(Class IIa, Level C)* at serum glucose levels> 10 mmol/L.
- Pyrexia (body temperature >38°C) should be treated with antipyretics and prompt the search for infections (*Class I, Level C*).
- Treatment of pyrexia (>37.5°C) with paracetamol and cooling is recommended (*Class III, Level C*)
- In patients with acute ischemic stroke, treatment with induced hypothermia has an uncertain effect *(Class IIb, Level B).*
- Routine antibiotic prophylaxis is not recommended (*Class III, Level A*)
- Antibiotic prophylaxis is not recommended in immunocompromised patients (*Class II, Level B*)
- In patients with suspected pneumonia and urinary tract infections appropriate antibiotic treatment is recommended (*Class I, Level A*).
- Prophylaxis with subcutaneous anticoagulants is indicated in patients at high risk of DVT due to immobilization. The benefit of the prophylactic dose of subcutaneous unfractionated heparin or low molecular weight heparin in patients with acute ischemic stroke is uncertain because of the increased risk of intra and extracranial bleeding *(Class IIb, Level A).*
- In case of the use of prophylactic anticoagulation, there is no reliable evidence to support the advantage of low molecular weight heparins over unfractionated heparin at prophylactic doses

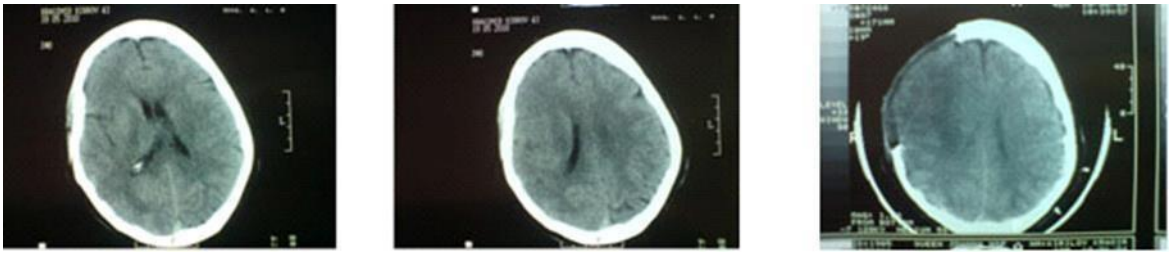
(Class IIb, Level B).

- In patients who cannot receive anticoagulants, DVT prophylaxis with aspirin is recommended (*Class IIa, Level A*).
- In immobilized patients, in order to reduce the risk of deep vein thrombosis, it is recommended that intermittent external compression be used, in the absence of contraindications, together with routine care (ASA and hydration) instead of routine care only *(Class I, Level B).*
- In patients who cannot receive anticoagulants, external intermittent compression therapy is recommended (*Class IIa, Level B*).
- Elastic compression socks *(Class III, Level B)* should not be used in patients with ischemic stroke.
- In patients with pulmonary embolism (PE) prophylaxis and treatment with low molecular heparins should be considered.
- Bedside swallowing assessment is recommended before the patient starts eating, drinking and taking oral medications (*Class I, Level B*).
- It is recommended in patients with impaired swallowing due to stroke to assess dysphagia with the ASSIST screening tool (also applicable for TIA), up to 24 hours and at discharge.
- In patients with impaired swallowing, nasogastric, nasoduodenal or PEG feeding is recommended to maintain nutrition and hydration (*Class I, Level B*).
- Nasogastric feeding (for the first 2-3 weeks after stroke) is recommended in stroke patients with swallowing problems (*Class IIa, Level B*).
- It is appropriate to introduce oral hygiene protocols to reduce the risk of pneumonia after acute stroke (*Class IIb, Level B).*
- Early mobilization and measures for prevention of stroke complications are recommended in patients with minor disability (*Class I, Level C*).
- Treatment of concomitant diseases is recommended (Class I, Level C).
- Prevention of stroke recurrence should be early initiated early *(Class I, Level C).*
- Routine administration of nutritional supplements is not recommended *(Class III, Level B).*
- It is appropriate to use nutritional supplements in patients who are malnourished or at risk of malnutrition *(Class IIa, Level B).*
- Oral dietary supplements are only recommended for non-dysphagic stroke patients who are malnourished *(Class II, Level B)*
- Calcium/vitamin-D supplements are recommended in stroke patients at risk of falls (*Class II, Level B*).
- Bisphosphonates (alendronate, etidronate and risedronate) are recommended in women with previous fractures (*Class II, Level B*).
- In stroke patients with urinary incontinence, specialist assessment and management is

recommended (*Class III, Level C*).

- Routine insertion of permanent catheters is not recommended due to increased risk of urinary tract infections (*Class III, Level C*).
- Patients with major strokes at high risk of complications as brain oedema and elevated intracranial pressure need close monitoring for neurological deterioration during the first days after stroke and preventive measures to reduce the risk of brain oedema (*Class I, Level C*). A neurosurgical intervention is recommended in patients with malignant brain oedema.
- It is appropriate to administer osmotic therapy in patients with clinical deterioration due to the development of cerebral oedema due to cerebral infarction *(Class IIa, Level C).*
- Osmotherapy can be used to treat elevated intracranial pressure prior to surgery if this is considered (*Class III, Level C*). Mannitol 1-2 g/kg/24h given as a short-term bolus infusion every 4-6 hours and/or intravenous furosemide 20-40 mg are recommended.
- The use of short-term moderate hyperventilation ($PaCO_2$ target values, 30 – 34 mmHg) is appropriate in patients with severe neurologic deterioration due to cerebral oedema, as a bridge to more invasive therapy (*Class IIa, Level C).*
- Corticosteroids in conventional or loading doses are not recommended in patients with brain oedema and elevated intracranial pressure because of increased risk of infections and lack of effect (*Class III, Level A*).
- The use of hypothermia or barbiturates in conditions associated with ischemia in cerebral or cerebral oedema is not recommended for ischemic stroke *(Class III, Level B).*
- It is recommended that surgical decompression be considered for treatment and prophylaxis of cerebral herniation and brainstem compression in patients with minor stroke (*Class I, Level B; figure 5*).

**Figure 5. Surgical decompressive craniectomy**



- Surgical decompression is an efficient and life-saving procedure in patients with malignant brain edema after hemispheric stroke (*Class I, Level B; figure 5*).
- Surgical decompressive hemicraniectomy within 48 hours after symptom onset is recommended in patients up to 60 years of age with evolving malignant MCA infarcts (*Class IIa, Level A; figure 5*).
- Decompressive hemicraniectomy could be discussed in the described cases and in patients> 60 years of age *(Class IIb, Level B).*

- It is done in the presence of clinical and neuroimaging evidence for evolving intracranial hypertension, leading to coma, progression of focal neurologic symptoms and signs of brainstem dysfunction. It is recommended that osmotherapy be used prior to surgery to relieve elevated intracranial pressure.

- Consideration of ventriculostomy or surgical decompression for treatment of large cerebellar infarctions that compress the brainstem (*Class III, Level C; figure 5*).

- **Criteria for decompressive hemicraniectomy**
  - Age ≤ 60 years (in some cases over 60 years old)
  - Less than 23 h of stroke onset (no later than 48 h as an exclusion)
  - Signs on CT and MRI of an infarct area of at least 50% of MCA territory
  - Absence of contraindications to surgical treatment
  - Failed reperfusion, incl. failed thrombolysis, thrombectomy, etc.
  - Informed consent, signed by patient's relatives for procedure performance
- **Contraindications to decompressive hemicraniectomy**
  - Coma with bilateral mydriasis not induced by medication and pupil areflexia
  - The presence of more risk factors
  - Expressed comorbidity
  - Severe preceding impairment
  - Family refusal for procedure performance
- In stroke patients with acute hydrocephalus external ventricular drainage is recommended. (*Class I, Level C*).
- Recurrent epileptic seizures after stroke are treated as standard with anti-epileptic drugs, based on the specific characteristics of each patient *(Class I, Level C).*
- The prophylactic use of anticonvulsants is not recommended *(Class III, Level C).*
- **Resuscitation measures in complications**
  - Sedation
  - Orotracheal intubation
  - Tracheostomy
  - Central line placement and monitoring of central aortic pressure
  - Blood transfusion
- **In comatose patients** emergency supportive measures are recommended:
  - Airway management
  - Venous access and infusion of electrolytes
  - Antiepileptic therapy in seizures

- **General care in stroke patients:**
  - Hygiene of the mouth, eyes, genitals and body, rubbing and applying of talcum powder
  - Body repositioning every 2 hours
  - Positioning for postural drainage (not in patients with SAH)
  - Tapping and vibration massage of the chest (not in patients with SAH)
  - Breathing exercises
  - Oral and/or orotrachial aspiration
  - Bowel function and urination monitoring (24-hour diuresis).
  - Urinary catheter irrigation
  - Cleaning and dressing of wounds, pressure ulcers.
  - Application of sole dressings for prophylaxis of pressure ulcers
  - Movement rehabilitation and kinesitherapy (not in patients with SAH)
  - Massage therapy (not in patients with SAH)
  - Care for patients with quantitative disorders of consciousness
  - Care for patients with a nasogastric tube
  - Care for intubated patients
  - Care for patients with a tracheostomy.
- **Regular monitoring is necessary for (figure 2):**
  - Neurologic status
  - Body temperature
  - Pulse oximeter oxygen saturation (pO2) for 72 hours in patients with significant persisting neurological deficits (*Class IV, GCP*). In patients with SAH, the Hunt and Hess scale is used.
  - Rate, depth, rhythm and type of breathing
  - Consciousness − Glasgow-Liege Coma scale (GLCS)
  - BP, heart rate, heart rhythm
  - ECG
  - Fluid and electrolyte balance in patients with severe stroke or swallowing problems (*Class IV, GCP)*
  - Diuresis
  - Blood glucose level (*Class IV, GCP*).
  - Eating and swallowing
- **Control of concomitant somatic diseases: (figure 2)**
  - Diabetes mellitus
  - Arterial hypertension

- Heart failure and heart rhythm disorders
- Kidney diseases and renal failure
- Liver diseases
- Blood disorders
- Epilepsy
- Malignancies

- **Observation for development of complications and treatment (figure 2):**
  - Pulmonary infections, pneumonia, aspiration, atelectasis
  - Urinary infections
  - Sepsis
  - Decubitus ulcers – surgical treatment (debridement)
  - Complications related to invasive investigations
  - An assessment of falls risk is recommended for every stroke patient (*Class IV, GCP*)

### 2.2.1.3. Symptomatic management of stroke complications

➢ **Multidisciplinary care, motor functions and speech and language rehabilitation**

- Admission to a stroke unit is recommended for acute stroke patients to receive coordinated multidisciplinary rehabilitation (*Class I, Level A*)
- Early initiation of rehabilitation is recommended in all stroke patients (*Class III, Level C*), but evidence to guide specific treatment for the most severely disabled is limited (*Class II, Level B*).
- Intensive early rehabilitation within 24 hours of stroke onset should not be started due to a reduction of probability for good 3-month outcome *(class III, level B).*
- It is recommended that early discharge from stroke unit care is possible in medically stable patients with mild or moderate impairment providing that rehabilitation is delivered in the community by a multidisciplinary team with stroke expertise (*Class I, Level A*)
- It is recommended to continue rehabilitation after discharge during the first year after stroke (*Class II, Level A; figure 6*). It is recommended to increase the duration and intensity of rehabilitation (*Class II, Level B*).

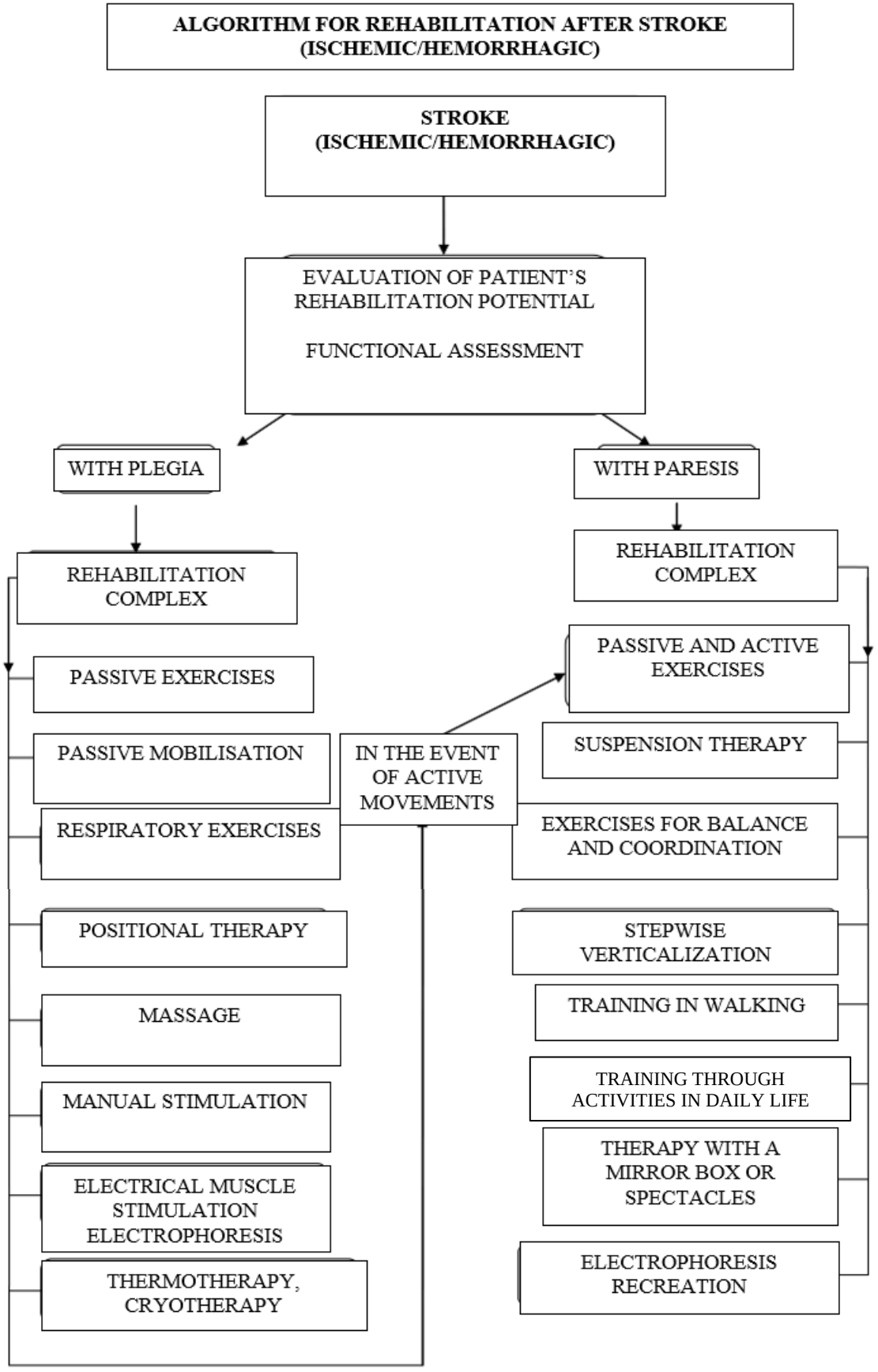



**Figure 6. Algorithm for rehabilitation after stroke**

- Physiotherapy is recommended, but the optimal mode of delivery is unclear (*Class I, Level A).*
- Occupational therapy is recommended, but the optimal mode of delivery is unclear (*Class I, Level A*).
- Depending on the patient's condition, early cognitive and language rehabilitation is recommended by a medical speech and language therapy specialist (figure 7, figure 8).

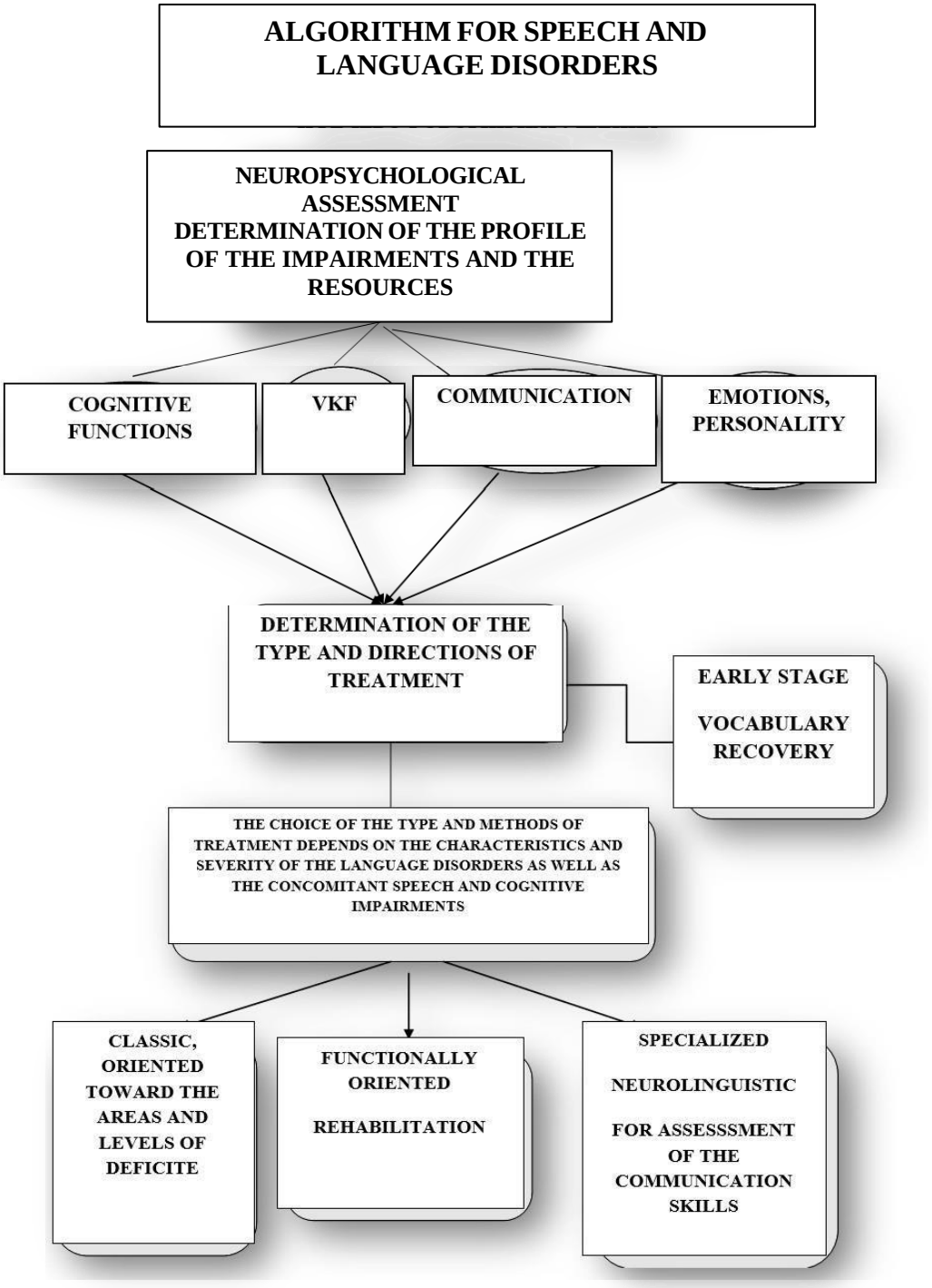



**Figure 7. Algorithm for speech and language disorders**

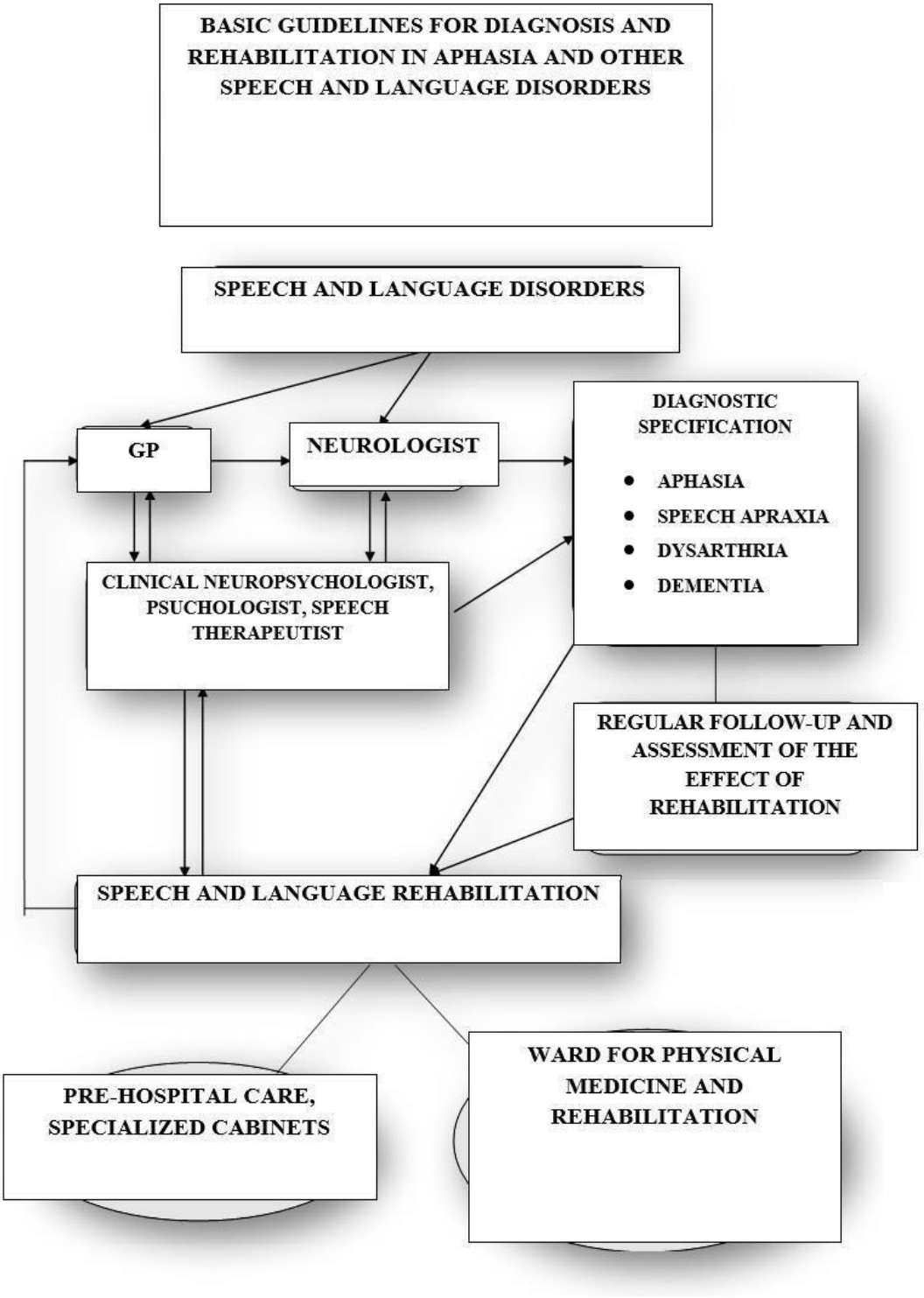



**Figure 8. Basic guidelines for diagnosis and rehabilitation in aphasia and other speech and language disorders**

- It is recommended that information is provided to patient and carers but evidence does not support use of a dedicated stroke liaison service for all patients (*Class II, Level B*)
- If necessary, refer patients and relatives to palliative care units *(Class IIa, Level C).*
- Pharmacological management of post-stroke muscle spasticity:
  - Botulinum toxin in the affected muscles (*Class III, Level B*)

- Tizanidine 12 – 24 mg daily
- Baclofen 50 – 75 mg daily

• Management of vascular cognitive impairments and mixed dementia (See National Consensus on Early Diagnosis and Treatment of Alzheimer Disease and other Forms of Dementia).

• Management of depression

- It is recommended that a structured depression interview be used as a routine screening for post-stroke depression *(Class I, Level B).*
- Patients with post-stroke depression should be treated with antidepressants in the absence of contraindications and monitored regularly for treatment effects *(Class I, Level B).*
- Drug therapy and non-drug interventions are recommended to improve mood (*Class I, Level A*).
- Treatment of post-stroke neuropathic pain is recommended *(Class III, Level B).*

• Management of psychotic and behavior disorders

- Atypical neuroleptic drugs
- Conventional neuroleptic drugs
- Treatment of sleep disorders

• Prophylaxis and treatment of deep venous thrombosis

- Subcutaneous low molecular heparins

### 2.2.2. Intraparenchymal Hemorrhage

A baseline severity score should be performed as part of the initial evaluation of patients with ICH (*Class I, Level B).* Rapid neuroimaging with CT or MRI is recommended to distinguish ischemic stroke from ICH (*Class I, Level A*).

**Conservative treatment** includes mostly treatment of the underlying cause of the cerebral hemorrhage (etiological treatment) and intensive treatment.

• The use of new oral anticoagulant agents is associated with increased risk of ICH.

• If patients are receiving hemodialysis, dabigatran is recommended (*Class IIb, Level C*).

• Protamine sulfate may be considered to reverse heparin in patients who developed acute ICH (*Class IIb, Level C*).

• The usefulness of platelet transfusions in ICH patients with thrombocytopenia is uncertain (*Class IIb, Level C).*

• After documentation of cessation of bleeding, low-dose subcutaneous low-molecular-weight heparin is recommended for prevention of venous thrombosis and thromboembolism (*Class IIb, Level B*).

- For ICH patients presenting with SBP between 150 and 220 mmHg and without contraindication to acute BP treatment, acute lowering of SBP to 140 mmHg is safe *(Class I; Level A*).
- For ICH patients presenting with SBP >220 mmHg, it may be reasonable to consider aggressive reduction of BP with a continuous intravenous infusion and frequent BP monitoring *(Class IIb, Level C*).
- Clinical seizures should be treated with antiseizure drugs *(Class I, Level A***).** Prophylactic anti-seizure medication is not recommended *(Class III, Level B***).**

**Management of complications**

- A formal screening procedure for dysphagia should be performed in all patients before the initiation of oral intake *(Class I, Level B*).
- Systematic screening for myocardial ischemia or myocardial infarction is recommended *(Class IIa, Level C*).
- When necessary analgesics and antipyretics are recommended.
- Ventricular drainage is recommended in patients with hydrocephalus (*Class IIa, Level B*).
- Corticosteroids should not be administered for treatment of elevated ICP in ICH (Class III, Level B).
- Intraventricular hemorrhage (IVH) occurs in 43% of patients with ICH. The efficacy and safety of intraventricular administration of rtPA in IVH is uncertain *(Class Iib, Level B***).** The efficacy of endoscopic treatment of IVH is also uncertain *(Class IIb, Level B*).

**Surgical treatment**

Indications depend largely on the location and size of the cerebral hemorrhage and the patient's general health status and somatic complications. Patients with minor hemorrhages which progress and obstruct ventricular drainage (*Class I, Level B*) and with lobar hematoma might benefit from surgery.

### 2.2.3. Subarachnoid Hemorrhage (SAH)

The treatment includes combined surgical and conservative approaches aiming to prevent the main reasons for poor outcome: recurrence, development of arterial vasospasm and hydrocephalus.

In comatose patients intensive treatment is recommended.

**Surgical management** includes:

- Surgical clipping up of the ruptured aneurysm as early as possible (<72 hours) in the acute phase of SAH (*Class I, Level B*). Early angiography and surgical treatment of patients with Hunt and Hess score 1 and 2 (table 6) is recommended to obliterate the source of bleeding, while the

combination of calcium channel blockers (nimodipine), adequate hemodilution and BP reduction reduces the risk of late ischemic deficit.

- Placement of ventricular or lumbar drainage is recommended in patients with acute hydrocephalus (*Class I, Level B*).
- Endovascular coiling of the ruptured aneurysm should be considered in patients considered to be technically eligible for neurosurgical treatment. This is a less invasive and less traumatic first-line therapy. In case of failure conventional craniotomy and aneurysm clipping are recommended. A number of studies showed better outcomes (lower mortality and disability rates) in favour of endovascular therapy.
- Various risk factors should be considered in patients with unruptured aneurysms planned for neurointerventional surgery.

**Conservative management** of SAH includes strict bed rest and administration of drugs for prevention of recurrence and development of arterial vasospasm for patients with contraindications or refusing surgical treatment.

***Prevention of recurrences:***

- Complete physical and emotional rest by adherence to strict bed regime for 3-4 weeks and administration of analgesic sedatives.
- Regular bowel function achieved by appropriate diet, laxatives and enemas
- Regular BP control. In unoperated patients with long-standing hypertension a decrease in systolic BP to <160 mm Hg is reasonable *(Class IIa, Level C).*
- Additional analgesia is recommended during painful procedures (lumbar puncture (LP), central venous line insertion, etc.) to avoid transient increase of BP.
- Epileptic seizures should be treated with appropriate anti-seizure drugs *(Class IIb, Level B*).
- The use of prophylactic anticonvulsants may be considered in the immediate post-hemorrhagic period *(Class IIb, Level B).*
- The routine long-term use of anticonvulsants is not recommended (*Class III, Level B*), but may be considered for patients with risk factors such as prior epilepsy, intracerebral hematoma, intractable hypertension, infarction, or aneurysm at the middle cerebral artery *(Class IIb, Level Evidence B).*

***Prevention and management of ischemic-hypoxic complications after SAH:***

- Maintenance of euvolemia and normal circulating blood volume is recommended *(Class I; Level B).*
- Hypervolemic hemodilution with hypertension may be used in patients with clipped aneurysm to increase cerebral blood flow and perfusion pressure and improve hemoreology

(maintenance of hematocrit levels between 0.33 and 0,38).

- Prophylactic hypervolemia or balloon angioplasty before the development of angiographic spasm is not recommended *(Class III, Level B).*
- The use of calcium channel blockers (nimodipine) 50 ml (10 mg) vials as continuous intravenous pump infusion 1-2 mg/h or oral intake of tablets 30 mg (total daily dose 240-300 mg) may be considered in patients with BP level over 120/75 mmHg. In lower BP values the use of nimodipine is contraindicated (*Class I, Level A*).
- Transcranial Doppler sonography is reasonable to monitor for the development of arterial vasospasm (Class IIa, Level B).
- Maintenance of higher BP values (up to 200 mm Hg) or use of cardiotonic agents is recommended in patients with clipped aneurysm and clinical signs of cerebral ischemia (*Class IIA, Level B*).
- Monitoring of central venous pressure and fluid balance is reasonable, as is treatment with crystalloid or colloid fluids *(Class IIa, Level B).*
- Central venous pressure should not be higher than 120 mm $H_2O$ because of risk of pulmonary edema, decompensated heart failure and brain swelling.
- Aggressive control of fever to a target of normothermia is recommended in the acute phase of SAH *(Class IIa, Level B).*
- Glucose management and avoidance of hypoglycemia is recommended *(Class IIb, Level B).*
- The use of fludrocortisone acetate is reasonable for preventing and correcting hyponatremia *(Class IIa, Level B).*
- Electrolyte balance control and maintenance of oxygen saturation >95% is recommended.
- The use of packed red blood cell transfusion might be reasonable in patients with SAH who are at risk of cerebral ischemia. The optimal target for hemoglobin levels is still to be determined *(Class IIb; Level B).*

### 2.2.4. Thrombosis of Cerebral Vein and Dural Venous Sinus

- To obtain an accurate history about use of hormonal contraceptives, pregnancies, puerperium conditions, open or closed head injuries, dental granulomas, blood disorders, vasculitis, neoplasms, etc.
- To make physical examination of the patient
- To evaluate the neurological status of the patient: intracranial hypertension syndrome (with headache, diplopia) with or without nausea and vomiting, possible epileptic seizures, cranial nerve lesions, motor and sensory processing disorders, aphasia, dysarthria, general cerebral symptoms

with quantitative disturbance of consciousness to the extent of coma.

- In case of history and neurological signs of TCVDS, to refer the patient immediately for urgent hospitalization through an emergency medical service.
- In case of clinical suspicion of TCVDS a complete blood count is required, biochemistry, activated partial thromboplastin time, and prothrombin time *(class I, level C)* to establish underlying hypercoagulability, infectious or inflammatory process.
- A D-dimer (ELISA) examination prior to imaging is appropriate (except in the cases of isolated headache or prolonged symptomatology over a week due to the risk of false negative results), with normal values identifying patients with a low likelihood of TCVDS *(Class IIb, Level B, GCP).*
- Imaging of the venous system is necessary to exclude TCVDS in patients with clinical presentation of idiopathic intracranial hypertension *(Class I, Level C),* in patients with headache with atypical features (*Class IIa, Level C*), and patients with lobar hematomas with unknown etiology and cerebral infarctions outside the typical arterial areas *(Class I, Level C).*
- Treatment involves the administration of low molecular weight heparin or unfractionated heparin, even with parenchymal cerebral hemorrhage *(Class IIa, Level B, GCP).*
- Together with the anticoagulant therapy, the major etiologic factors should be sought and treated, and adequate symptomatic treatment, prevention and treatment of the occurring complications.
- The consensus is based on the recommendations for optimal use of oral anticoagulants – vit. K - antagonists after the acute phase of stroke and following consultation with a hematologist. Endovascular treatment could be considered in cases of clinical deterioration against optimal anticoagulant therapy *(Class IIb, Level C).*
- A life-saving hemicranioctomy is performed in patients with severe cerebral edema and incision data *(Class IIb, Level C).*
- In cases of elevated intracranial pressure, the administration of acetazolamide is appropriate and lumbar puncture, optic nerve decompression, or shunt placement may be appropriate for progressive vision loss *(Class IIa, Level C, GCP).*
- The use of corticosteroids is associated with poor prognosis and is not recommended unless treatment is required *(Class III, Level B).*
- In the presence of an epileptic seizure, anti-epileptic therapy *(Class I and Class IIa)* is initiated but it is not indicated for the prevention of possible seizures *(Class III, Level C).*
- Treatment of TCVDS during pregnancy is performed with low molecular weight heparins *(Class I, Level C).* After birth, anticoagulant treatment with low molecular weight heparin or Vit. K-antagonist at INR (2.0 - 3.0) should be continued for at least 6 months *(Class I, Level C).*

- Patients with a history of TCVDS are at increased risk of thrombotic events, but the condition is not a contraindication for future pregnancy *(Class IIa, Level B)*, and prevention with low molecular weight heparin during subsequent pregnancy *(Class IIa, Level C)* may be recommended.

### 2.2.5. Brain Aneurysms and Vascular Malformations

**Other indications for neurointerventional treatment**

The main difference from all other indications is the lack of urgency, since saving of brain tissue in the ischemic "penumbra" within 6 hours from stroke onset is not a major goal.

Although cerebral aneurysms affect a relatively small part of the population (incidence 6 to 16 per 100 000; prevalence 0.5% to 6% in the U.S. population) the importance of their treatment is highlighted because of the severe morbidity and high mortality associated with recurrences in young age.

The management of intracranial aneurysms or brain arteriovenous malformations (BAMs), remains controversial because of the variety of their size, form and location.

- Endovascular coil occlusion of a ruptured cerebral artery aneurysm is appropriate for patients meeting the criteria for neurosurgical treatment.
- A number of factors should be considered to determine whether patients with unruptured cerebral aneurysms should receive endovascular treatment. These factors include the age of the patient, the size of the cerebral aneurysm, a history of prior subarachnoid hemorrhage, family history of cerebral aneurysms, and multiple aneurysms or concurrent pathology of other cerebrovascular disorders, such as brain arteriovenous malformation, fibromuscular dysplasia, dissection, cerebral arteritis, or other conditions that may predispose to higher risk for haemorrhage.
- Patients with unruptured cerebral aneurysms who are considered for treatment should be fully informed about the risks and benefits of the procedure as an alternative to neurosurgical treatment.
- Treatment requires the patient to be at an experienced stroke center/unit with facilities for emergency treatment of potential procedural complications

### 2.2.6. Acute Hypertensive Encephalopathy

Hypertensive encephalopathy is an acute and transient disorder of brain function caused by sudden elevation of BP. A major pathogenetic factor for development of hypertensive encephalopathy is a sudden excessive BP elevation (above 240/140 mm Hg). The most important sign is diffuse brain edema, accompanied by vasospasm in the large and middle cerebral arteries and paralytic vasodilation of the arterioles. Occasionally pinpoint hemorrhages in centrum semiovale or pons are seen or even red infarcts of varying size. The vascular wall is permeated by blood plasma. Perivascular

plasmorhagia and plasma protein extravasation is observed – increased permeability of the blood brain barrier.

The underlying cause of the majority of clinical manifestations is an increased intracranial pressure. The main symptoms are those of intracranial hypertension – severe “splitting” headache, disturbance of consciousness, generalized or partial seizures, transient focal neurological symptoms, retinal vasospasm (manifested with retinal hemorrhages and exudates), often oedema of the papilla and elevated spinal fluid pressure.

The methods for diagnosis of hypertensive encephalopathy include physical examination, BP measurement, blood tests, ECG, CT and/or MRI imaging of the head.

Hypertensive encephalopathy management consists of rapid reduction of BP, accompanied by administration of diuretics and anti-inflammatory agents, leading to resolution of clinical symptoms within several hours.

# Appendices

## Life after stroke. Neurorehabilitation

*Approximately a third of patients with stroke have lasting disabilities, reduced cognitive abilities, and worsened mental health.* Non-clinical support, specific for the distinct social and emotional needs of stroke survivors, is very important. During their hospital stay, many patients with stroke feel abandoned and this will continue, until such services become a routine part of the continuum of stroke care.

Neurorehabilitation is an important stage towards the return of stroke patients to their families. Access to early rehabilitation in the stroke unit and post-discharge through physical, cognitive, occupation, speech, and other rehabilitation programmes should be guaranteed. Pathways must be created so that stroke survivors have full access to comprehensive and coordinated long-term support.

Problems with communication, social interaction, loneliness, incontinence, tiredness, increased financial needs are often left unaddressed by current available care, which leads to poor social re-integration. Patients need coordinated personalised care and support plans after the end of the rehabilitation provided by the clinical pathway, which would guarantee improved mental health outcomes.

*Application of a European reference frame for quality in stroke care.* The reference frame must collect, measure, and publish longitudinal demographic and medical data, results from medical interventions, assess quality of life after stroke, and include national audit guidelines.

*We need to create opportunities for a dignified life after stroke. We must pay attention to stroke survivors, their families, and their unmet needs through formalising the participation of support programmes after stroke and to actively apply resolutions according to specific needs.* National recommendations for best practices and support of stroke survivors and their families must be created after a comprehensive assessment of nation-wide problems.

### Neurorehabilitation after stroke

Pharmacological intervention, combined with early and cognitive rehabilitation reduce disability after stroke.

*Nonpharmacological neurorehabilitation* consists of different therapeutic interventions that aim to restore the functional abilities of the patient and their quality of life after stroke. Examples are physiotherapy, occupational, speech and language, and cognitive behavioural therapy, biofeedback etc. Computer-assisted and robotic neurorehabilitation are contemporary techniques with great potential, and they can provide an even more intensive and personalised therapeutic programme.

Good rehabilitation includes:

- information on stroke and the available therapeutic and rehabilitation procedures that

is easily accessible for the patient and their family

- early hospital discharge with subsequent rehabilitation in the home for patients with mild stroke
- cognitive rehabilitation
- re-training and recovery of the daily routine activities of the patient; a recommended target for the recovery of these functions is up to 1 year after the stroke.

The needs of the patient vary with time, and recovery could start a long time after the incident, so it is never too late to initiate rehabilitation.

Neurorehabilitation is most effective if started early. The process must begin with an objective assessment of the functional capabilities and limitations of the patient. The degree of recovery correlates with increasing intensity of daily rehabilitation load, especially within 3 to 6 months after the incident, when processes of neuroplasticity, healing of the lesion, and rewiring of neural networks are taking place. During this period organising rehabilitation care requires assessment and control of dysphagia, prophylaxis of contractures and bed sores, of DVTs, postictal epileptic seizures, body waste management, application of tool aids, etc.

**Occupational therapy** should be focused on all areas that impede the individual from performing their daily activities. A personalised programme with appropriate specific tasks, rehabilitation exercises, and compensatory tactics must be devised. Occupational therapy includes benefiting attending to personal needs, productivity, free time, etc. A professional therapist helps to modify the home to guarantee the patient's safety. Recommended interventions include: training on specific tasks, visual scanning, provoked movement, repetitive electric stimulation, mirror therapy, mental exercises, daily training tasks, recommendations and training on adaptive tools, sensory therapy, cognitive therapy, etc.

Recommendations for secondary prevention must include at least half an hour of daily exercise until reaching a mild aerobic effect. Training with aerobic exercises, for example with a treadmill, walking, or lie-down cycling, conditions the patient and improves speed and stamina when walking. The positive effects of computer-assisted and roboticized neurorehabilitation are several: a high intensity of the rehabilitation process, which is specialised according to the needs of the patient, a qualitative assessment of the movement characteristics, and regular feedback about the effectiveness of the rehabilitation programme. The following methods can be applied in addition to conventional therapy or on their own – Functional electrostimulator (Foot Drop System - FDS), LEXO®, Lokomat®, SafeGait 360° Balance and Mobility Trainer®, RecoveriX®, Stiwell®.

**Electrotherapy.** Functional electrical stimulation is used to optimise the rehabilitation process in the acute phase of stroke, in conjunction with physical exercises, as well as to re-learn daily activities. The sequence of movements is learned again with the help of EMG multichannel electrical

stimulation (EMG-MES) and biofeedback.

Technoconcept® is a novel method that focuses on analysing and understanding the neurobiological origin of the perception of various movements. Proprioception is used as an entry point into the sensorimotor chain, which defines the perception of movement and special orientation as a result of body stimuli.

Neurophet tES Lab is a comprehensive software for transcranial electrical stimulation (tES), simulations and computer modelling that allows the users to quantify and visualise brain effects resulting from stimuli. It performs a hyper fast and automatic topographical distribution of MRI data and can create a personalised 3D model for stimulation.

**Cognitive rehabilitation** includes several main directions: to reaffirm or recover earlier (before stroke) behavioural patterns, to create new cognitive abilities and to increase the individual's adaptive potential towards their cognitive impairments. All cognitive training programmes contribute to the recovery of the patient's cognitive potential before the stroke.

**Repetitive transcranial magnetic stimulation (rTMS)** can be applied by neurologists specially trained in the technique for the treatment of a plethora of neurological conditions. rTMS is supported by Class A evidence for its ability to improve motor deficit after stroke, especially paralysis of the arm. Treatment with rTMS yields best results if administered between 1 week and 6 months after the stroke, but can have significant efficacy after the 6-month period.

**Language therapy for neurogenic communication deficits after stroke** is done by specialists in speech and language pathology. They have a crucial role in the primary assessment, diagnosis, and therapy of the neurogenic communication deficits following stroke. The specialist consults and provides a health and education service to the patients with aphasia and dysarthria and their families. The language specialist works in a multidisciplinary team with multidisciplinary team with other specialists who are providing rehabilitation care after stroke. The speech and language therapy programme should be individualised.

The main goal of speech therapy is to restore the functional communication of the stroke patient. Language therapy in stroke patients focuses on using spoken language and should limit the use of compensatory strategies like gesticulation.

**Diagnosing aphasia** in the first instance is done while the patient is still in the hospital. Their speech and basic language capabilities are assessed, as well as comprehension. Widely applied across clinical practice to assess aphasia in the elderly is the Shipley & McAfee model (2004).

- Boston Diagnostic Aphasia Examination Test (Goodglass and Kaplan, 1983)
- Bedside Evaluation Screening Test for Aphasia (BEST-2)
- Standardised Quick Aphasia Battery (QAB)
- Scales of Cognitive and Communicative Ability for Neurorehabilitation (SCCAN)

**The therapy for aphasia** aims (i) to achieve maximal recovery of impaired function, (ii) to develop communication strategies, and (iii) to help the patient adapt to the negative consequences of brain damage. The therapeutic program must be tailored to the patient's clinical symptoms.

**Language therapy specialists offer:**

- Interventions for the limitations of activities and participation in daily life experienced by people with aphasia, as suggested by Simmons-Mackie & Kagan (2007).
- Interventions for aphasia that are focused on reducing environmental barriers by modifying it to support the patient's communication efforts (Simmons-Mackie & Kagan).
- Limited induced language therapy
- Melodic intonation therapy
- Therapy including family members

## Requirements for centres for endovascular management of acute disorders of cerebral circulation (ADCVC)

In 2009 the Working Group of the American Academy of Neurology established standards for practical skills and training in endovascular treatment of ADCVC. The accent is on the concept that neuroendovascular procedures are a technical challenge and require special training. Strict compliance with standards for performance of high-risk interventions such as endovascular procedures in ADCVC management is critically important.

- Interventional neurology should be a natural alternative of intravenous thrombolysis. Priority should be given to centres with considerable experience in intravenous thrombolysis as a way to save time and finance for setting up of medical teams with efficient logistics such as those already functioning in some hospitals in the country.
- Mechanistic transfer of experience from interventional cardiology to interventional neurology is inappropriate due to the risks involved. The accumulated skills in the performance of endovascular procedures in other vascular systems **are not directly transferable**, since the human brain is an organ with unique anatomy and physiology. The physician's knowledge of the anatomy and physiology of blood supply to the brain, the mechanisms of cerebral autoregulation, the dynamics of neurological symptoms and their hemodynamic interpretation during the procedure is of key importance in interventional neurology.

# Requirements for neurointerventionalists for performance of IAT in ischemic stroke

Neurointerventional treatment of ischemic stroke should only be performed by physicians with appropriate professional qualification in centres with interventional neurology accreditation at hospitals with level III of competence.

Neurovascular procedures at ADCVC can only be performed at certified health facilities, with the potential for intensive and neurosurgical treatment of possible complications from the procedures.

Good logistics from patient's admission to procedure performance (irrespective of whether it is IVT or IAT) are always an essential factor for successful outcome. But it is practically impossible without co-ordination of the entire process by an interdisciplinary team.

The level of competence is determined by the level of staff training and technical equipment of health institutions. The procedure should not be performed in the absence of qualified staff and without appropriate equipment.

**1. Human resource**

1.1. Interventional treatment of cerebrovascular diseases should be performed by trained specialists - physicians with one of the following specialities: neurology, neurosurgery, radiology with sufficient theoretical knowledge, professional experience and practical skills and professional certification in “Interventional neurology”;

1.2. The centres involve medical nurses and laboratory technicians who have passed successfully specialized training courses.

**Minimal requirements for the medical team:**

- Prior theoretical and practical training for diagnosis and management of acute stroke
- Technical skills and qualification
- Certification of neurointerventionalists for performance of highly specialized procedures

**2. Training**

2.1. Training for performance of highly specialized procedures in interventional neurology is conducted after approval of unified training programs by the Minister of Healthcare and professional certificate is acquired after passing a state examination. The specific conditions are stated in the current legislative provisions for medical speciality acquisition.

2.2. Theoretical and practical training, including diagnosis and management of acute stroke and interpretation of cerebral angiography and other neuroimaging techniques is required.

2.3. The training is carried out by professors in neurology, neurosurgery and neuroradiology.

2.4. The duration of training is at least 12 months.

**Technical skills and qualifications for neurointerventionalists:**

1. Preceding training that has been documented and experience in catheter arteriography, including at least 100 cerebral arteriograms. Clinical outcomes must meet or exceed the standards for technical success and complications. The training can be carried out at certified centres in Bulgaria and/or abroad.

2. Preceding training that has been documented and experience in intracranial microcatheter (≤3 French) and microguide wire (≤0.014 inch) navigation under the supervision of a certified neurointerventionalist. The training can be carried out at certified centres in Bulgaria and/or abroad.

3. Documented preceding training in assessment and performance of endovascular stroke interventional procedures as a primary operator in 50 extracranial and 20 intracranial procedures under the supervision of a certified neurointerventionalist.

4. Certified neurointerventionalists who perform intra-arterial procedures for ADCVC should document their clinical results and complication, meeting established national and international evidence-based standards.

5. Practicing neurointerventionalists should be involved in continuous stroke-specific medical education (CME) at least 10 hours annually.

All neurointerventional procedures must be entered into a hospital register.

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**Table 1. ABCD (2) scale to evaluate the risk of subsequent stroke after TIA**

| **ABCD (2) scale** – circle one result for every category | | |
|---|---|---|
| Age: | ≥ 60 years | 1 |
| | < 60 years | 0 |
| Blood pressure: | Systolic ≥ 140 mmHg OR Diastolic ≥ 90 mmHg | 1 |
| | Systolic < 140 mmHg AND Diastolic < 90 mmHg | 0 |
| Clinical presentation: | Unilateral limb weakness | 2 |
| | Speech disturbance without motor deficit | 1 |
| | Others | 0 |
| Duration of signs and symptoms: | ≥ 60 minutes | 2 |
| | Between 10 and 59 minutes | 1 |
| | < 10 minutes | 0 |
| Diabetes: | Present | 1 |
| | Absent | 0 |
| Total score (between 0 and 7 points): | | |

# Table 2. NIH Stroke Scale/Score (NIHSS)

| NIHSS Item | Definition | Response/Points | | Score |
|---|---|---|---|---|
| 1A | Level of consciousness (quantitative changes) | Alert; keenly responsive<br>Somnolence<br>Suppressed reactions<br>Coma/Irresponsive | 0<br>+1<br>+2<br>+3 | |
| 1B | 2 questions in impaired consciousness (month and age) | Answers correctly to both questions<br>Answers correctly to one of the questions<br>Wrong answers to both questions | 0<br>+1<br>+2 | |
| 1C | 2 commands in impaired consciousness: "Blink eyes" & "Squeeze hands" | Performs both tasks<br>Performs 1 task<br>Performs 0 tasks | 0<br>+1<br>+2 | |
| 2 | Horizontal extraocular movements (assess only horizontal gaze) | Normal<br>Partial gaze palsy: can be overcome<br>Complete gaze palsy: cannot be overcome | 0<br>+1<br>+2 | |
| 3 | Visual fields | No visual loss<br>Partial hemianopia<br>Complete hemianopia<br>Patient is bilaterally blind | 0<br>+1<br>+2<br>+3 | |
| 4 | Facial palsy (lesion of VII cranial nerve) | Normal symmetry<br>Minor paralysis<br>Partial paralysis<br>Unilateral complete paralysis | 0<br>+1<br>+2<br>+3 | |
| 5<br><br>5A<br><br>5B | Arm motor drift<br><br>Left arm<br><br>Right arm | No drift (pronation) for 10 seconds<br><br>Drifts in <10 seconds<br><br>Drifts in <5 seconds<br>No resistance against gravitation (falls)<br>No active movements | 0<br><br>+1<br><br>+2<br>+3<br>+4 | |
| 6<br><br>6A<br><br>6B | Leg motor drift<br><br>Left leg<br><br>Right leg | No drift (pronation) for 10 seconds<br><br>Drifts in <10 seconds<br><br>Drifts in <5 seconds<br>No resistance against gravitation (falls)<br>No active movements | 0<br><br>+1<br><br>+2<br>+3<br>+4 | |
| 7 | Limb ataxia | No ataxia<br>Ataxia in 1 limb<br>Ataxia in 2 limbs | 0<br>+1<br>+2 | |
| 8 | Sensation | Normal - no sensory loss<br>Mild-moderate loss: hemihypestesia<br>Severe or complete sensory loss | 0<br>+1<br>+2 | |
| 9 | Speech | Normal - no aphasia<br>Mild-moderate aphasia<br>Severe aphasia<br>Mute/global aphasia | 0<br>+1<br>+2<br>+3 | |
| 10 | Articulation/Dysarthria | Normal<br>Mild-Moderate dysarthria<br>Severe dysarthria/anarthria | 0<br>+1<br>+2 | |
| 11 | Extinction/inattention | No abnormality<br>Mild (extinction to 1 sensory modality)<br>Severe (extinction to ≥2 sensory modality) | 0<br>+1<br>+1 | |
| Total NIHSS Score: …… (0-42 points) | | | | |

# Scores for assessment of patients with acute cerebrovascular event

**Table 3. Glasgow-Liege Coma Scale/Score (GCS)**

| ***Eye response*** | ***Score (points)*** | ***Verbal response*** | ***Score (points)*** | ***Motor response*** | ***Score (points)*** | ***Cerebro-bulbar reflexes*** | ***Score (points)*** |
|---|---|---|---|---|---|---|---|
| Spontaneously | 4 | Oriented | 5 | Obeys commands | 6 | Fronto-orbicular | 5 |
| To verbal command | 3 | Confused | 4 | Localizes pain | 5 | Vertical oculocephalic | 4 |
| To pain | 2 | Inappropriate words | 3 | Withdrawal from pain | 4 | Pupil reaction to light | 3 |
| No eye opening | 1 | Incomprehensible sounds | 2 | Flexion to pain | 3 | Horizontal oculocephalic | 2 |
| | | No verbal response | 1 | Extension to pain | 2 | Oculocardiac | 1 |
| | | | | No motor response | 1 | Absent | 0 |

**Table 4. Barthel index for activities of daily living**

| *Activity* | *Score* |
|---|---|
| **Feeding**<br>0 = Unable<br>5 = Needs help<br>10 = Independent | |
| **Bathing**<br>0 = Unable<br>5 = Independent (or by shower) | |
| **Personal care**<br>0 = Needs help<br>5 = Independent (for face/hair/teeth/shaving) | |
| **Dressing**<br>0 = Dependent<br>5 = Needs help, but can cope with half of the activities | |
| **Bowel control**<br>0 = Incontinent (or needs to be given enemas)<br>5 = Occasional accident<br>10 = Continent | |
| **Bladder control**<br>0 = Incontinent (catheterized, unable to manage alone)<br>5 = Occasional accident<br>10 = Continent | |
| **Toilet use**<br>0 = Unable<br>5 = Accidently needs help<br>10 = Independent | |
| **Transfers (bed to chair and back)**<br>0 = Unable, not stable in a wheelchair<br>5 = Needs major help (1-2 people, physical), can sit<br>10 = Needs minor help (verbal or physical)<br>15 = Independent | |
| **Mobility**<br>0 = Immobile or < 45 m<br>5 = Wheelchair independent, including corners, >45 m<br>10 = Walks with help of one person (verbal or physical) >45 m<br>15 = Independent (but may use any aid, e.g. stick) >45 m | |
| **Stairs**<br>0 = Unable<br>5 = Needs help (verbal, physical, carrying aid)<br>10 = Independent | |
| **TOTAL SCORE = (0-100) points** | |

**Table 5. Modified Rankin Score**

| ***Points*** | ***Description*** |
|---|---|
| 0 | No symptoms |
| 1 | No significant disability despite symptoms; able to carry out all usual duties and activities |
| 2 | Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance |
| 3 | Moderate disability; requiring some help, but able to walk without assistance |
| 4 | Moderately severe disability; unable to walk and attend to bodily needs without assistance |
| 5 | Severe disability; bedridden, incontinent and requiring constant nursing care and attention |
| 6 | Death |

**Table 6. Hunt & Hess classification of subarachnoid hemorrhage**

| **Grade** | **Symptoms** |
|---|---|
| 0 | Unruptured aneurysm. |
| I | Asymptomatic or mild headache, alert and oriented, minimal (if any) nuchal rigidity. |
| II | Full nuchal rigidity, moderate-severe headache, alert and oriented, no neurological deficit (besides CN palsy) |
| III | Lethargy or confusion, mild focal neurological deficits. |
| IV | Soporous, moderate to severe hemiparesis or plegia, possible early decerebrate spasticity and neurological autonomous disorders. |
| V | Deep coma, decerebrate spasticity |

**Table. 7. FAST test for detection of early symptoms of stroke**

| ACT FAST! | |
|---|---|
| **FAST!** | **If you realize someone is having stroke, act fast and make this simple test:** |
| **F**ACE | **Ask the person to smile. Does one side of the FACE droop?** |
| **A**RM | **Ask the person to raise both arms. Does one arm drift downward?** |
| **S**PEECH | **Ask the person to repeat a simple phrase. Is speech slurred or strange?** |
| **T**IME | **If you observe any of these signs, TIME IS IMPORTANT! Call 112 immediately or take this person to a hospital FAST! BRAIN CELLS ARE DYING!** |