REVIEW ARTICLE

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Diagnosis and management of ischemic stroke: time is critical

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Abstract

Background: It is predicted that stroke's incidence and impact will increase considerably over time. Proper management of stroke depends on a reliable and urgent diagnosis that includes patient / relative - emergency team - hospital chain, so the diagnosis begins with the recognition of the first signs of stroke. In order to act promptly in the acute period and subsequently assess the risk factors, the neurological service needs to be equipped with high-performance neuroimaging and clinical laboratory. The specific treatment of acute ischemic stroke is nowadays the reperfusion procedure, performed by thrombolytic therapy and, since 2015, by the endovascular treatment. Stroke is also a leading cause of severe long-term disability. The rehabilitation of post-stroke patients requires an interdisciplinary approach, in order to prevent recurrences, combat complications and reintegrate the patient into society.
Conclusions: Stroke remains one of the leading determinants of death and severe disability worldwide and the Republic of Moldova is not an exception. Considering the narrow window for recognition and administration of outcome-modifying treatment, the management of stroke focuses mainly on rapid reperfusion via intravenous thrombolysis and endovascular thrombectomy. The availability of this specialized treatment in the Stroke Unit could improve the patient's outcome and decrease the disability's level and economical burden. There is clear evidence that preventing a stroke is much more effective than treating it, so we should seize the opportunity and act involving not only the medical staff, but also the government, health decision makers, specialists in public health and international agencies.
Key words: ischemic stroke, pathogenesis, prevention, diagnosis, treatment.

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Introduction

Stroke is the second leading cause of death after heart diseases and the leading cause of death from neurological diseases. Stroke is estimated to become the leading cause of death worldwide by 2030, reaching approximately eight million deaths annually [1]. It is a serious problem, with socio-economic implications, because the surviving patients often remain with significant motor and cognitive sequelae, most of which are unable to resume their activity before the onset of the disease [2]. Like cardiovascular diseases, stroke is a suffering of elderly, but in the population of the Republic of Moldova it occurs at a much younger age. Many stroke patients do not have access to adequate, modern, highly specialized treatment and, as a result, the level of mortality at home from stroke in the Republic of Moldova is one of the highest in Europe and neighboring countries [1].

We searched in the PubMed Central and Google Scholar engines, in specialized books, guidelines and protocols, for the following keywords "ischemic stroke", "symptoms", "pathogenesis", "prevention", "diagnosis", "recovery" and "treatment". The materials were searched in English and Romanian.

At the same time, the experience and data gained within the Institute of Emergency Medicine, the Department of Neurology, Epileptology and Internal Diseases were included.

History of Stroke

The term "stroke", which is an acute event that leads to symptoms of neuronal dysfunction [3], is thought to have evolved from the ancient name "apoplexy", which also refers to a clinical concept characterized by rapid loss of consciousness and various manifestations of brain dysfunction. The concept of "apoplexy" was used to encompass various disorders, later identified as acute, vascular, and non-vascular cerebral events, as well as acute non-cerebral events [4, 5].

Since Hippocrates, or even earlier, many authors have dedicated their talent to studying "apoplexy." From Antiquity until the Renaissance, the definition was relatively stable, a concept for a wide range of conditions. The introduction in practice of autopsies in the Modern era has allowed the evolution of the concept of apoplexy. It was not until the mid-1600s that Jacob Wepfer discovered that patients who died of apoplexy had intracerebral hemorrhage or blockage of one of the cerebral blood vessels [6].

Medical science continued to study apoplexy, and in 1928 it was divided into etiological categories. This is how the term "stroke" came about. Stroke is often referred to as a "brain attack" due to the mechanism similar to a heart attack. The term "brain attack" also conveys to the general public a more urgent call for immediate action and emergency treatment.

Epidemiology. RES-Q Registry in the Republic of Moldova

Effective treatment of stroke exists, but the implementation of evidence-based treatment is limited. The main objective of the "Registry of Stroke Care Quality" (RES-Q) project is to improve the quality of healthcare provided to stroke patients by translating the data collected by RES-Q into effective health policies, both at national and European level, by collecting data over the course of one month, several years consecutively [7, 8]. The RES-Q registry was implemented in Moldova in 2016, when the pilot data collection of stroke patients in a single Stroke center took place, so that in February 2017 another 3 hospital centers would be co-opted [9], and in 2018 – other 11 from different regions of the Republic of Moldova. Thus, the number of patients admitted to the RES-Q increased from 251 in 2017 to 920 in 2019 [9,10]. In the Republic of Moldova there are only 3 Stroke Units (Institute of Neurology and Neurosurgery, Institute of Emergency Medicine, "Holy Trinity" Municipal Hospital), in which thrombolysis treatment is performed. Since 2018, thrombolysis treatment is performed in 3 more centers [10]. In 2018, the Institute of Emergency Medicine, and later, in 2019, the Institute of Neurology and Neurosurgery "Diomid Gherman" implemented the surgical method of treatment of ischemic stroke by thrombectomy.

The data obtained through the RES-Q registry were presented at the annual meetings organized by the European Stroke Organization (ESO). According to the latest report, presented in September 2019 at the Summit of member countries of the IRENE-COST program, under the auspices of ESO the distribution by stroke subtype in the Republic of Moldova was as follows: 66% – ischemic strokes, 13% – hemorrhagic strokes, including 2% – subarachnoid hemorrhages (SAH), 19% – strokes of undetermined origin. It is noteworthy that the high proportion of patients with stroke of undetermined origin, a phenomenon explained by the fact that 8 participating centers are not equipped with computer tomography (CT) / magnetic resonance imaging (MRI) devices. From the category of patients who underwent CT or MRI, only in 63% the investigation was performed within one hour of hospitalization. From the category of patients who suffered hemorrhagic stroke or SAH, only 25% underwent angio-CT examination [10].

In 2019 only 2.67% of patients received thrombolytic treatment and 0.49% of patients – thrombectomy, a phenomenon explained by the fact that recanalization treatment, at that time, was performed only in 3 centers in the Republic of Moldova [10]. 36.78% of patients benefited from rehabilitation measures during the treatment provided in inpatient conditions, the majority of patients with stroke being subsequently discharged at home (75%), only 5% of patients were transferred for rehabilitation purposes to another center, and 15% died (we notice a decrease in the number of patients who died compared to previous years: 23% of patients – in 2017, 17% of patients – in 2018) [10-12].

RES-Q allows the comparative analysis of the quality of healthcare at national and international level, and is a motivational tool to improve its quality. The participation in the project will allow the dynamic evaluation of results and will be an important decision factor on changing the strategy to combat vascular diseases in the country [8-10].

Stroke Risk Factors

Stroke is a heterogeneous syndrome that can occur due to many risk factors. The risk factors can be classified into modifiable and non-modifiable. Age, sex, race/ethnicity and family history of stroke are non-modifiable risk factors, while hypertension, diabetes, obesity, metabolic syndrome, atrial fibrillation, carotid artery atherosclerosis, smoking, diet and physical inactivity are the modifiable ones. Modifiable risk factors can be further subdivided into medical conditions and behavioral risk factors [13-15].

An international case-control study showed that 90% of all stroke cases are caused by 10 risk factors: hypertension, diabetes, cardiac causes, current smoking, abdominal obesity, hyperlipidemia, physical inactivity, alcohol consumption, diet and psychosocial stress/depression [16]. Risk factors can also be categorized as short-term triggers (e.g., infectious conditions, sepsis, stress), intermediate-term (e.g., hypertension and hyperlipidemia), and long-term triggers (e.g., sex and race) [13].

In the epidemiology of stroke, a new field of research has emerged that involves the determination of stroke triggers. Thus, one study reported that a recent hospitalization for an infection was associated with an increased risk of stroke [17]. Another study showed as well that severe sepsis is associated with *de novo* onset of atrial fibrillation, and thereby, with an increased risk of stroke [18]. Therefore, identifying a short-term condition with an increased risk of stroke af-

ter an acute infection might also have direct therapeutic implications. Other potential triggers of stroke include air pollution, which has been identified as a new risk factor for stroke [13].

There are also risk factors for stroke that are specific to a certain category of population, such as women. Differences in sex hormones, exogenous estrogens and pregnancy are considered unique risk factors for women [19].

Stroke is a devastating disease worldwide, but a better identification and understanding of the stroke risk factors is essential to improve primary and secondary stroke prevention and to reduce the consequences of stroke.

Etiology and Pathophysiology of Ischemic Stroke

Ischemic stroke develops through functional and anatomical damage of the brain tissue, leading to different degree of transient or permanent neurological damage [20].

The main mechanism of the ischemic stroke could be explained by the lack of blood supply of the brain tissue as consequence of several pathological processes that affect the cerebral and extracerebral vessels [21]. Although biochemical changers in ischemic brain are approximately similar, the etiological factors are different. Atherosclerotic and atherothrombotic stenotic vascular lesions of the extracranial cervical arteries and large basal cerebral arteries can cause critical hypoperfusions and distal high-grade stenoses. Intracranial vascular occlusions are produced by embolic mechanism, both arterio-arterial from atherothrombotic lesions and systemic emboli as well (from cardiac sources, such as valve prostheses, atrial fibrillation, intracardiac thrombi, dilated cardiomyopathies, recent myocardial infarction or shunts). Another factor is the small vessel lipohialinosis, which causes microangiopathic lacunar lesions [22, 23].

The most common cause of ischemic stroke is proven to be atherosclerosis of the large and small arteries (20%). Atherosclerosis of the proximal part of the aorta, is considered to be one of the sources of cerebral emboli. In large vessel atherosclerosis, stroke develops if the cerebral perfusion drops down, because of occlusive atherosclerotic stenoses and coexisting thrombosis or arterio-arterial embolism. Occlusive diseases of small penetrating vessels, such as micro-atheromas and lipohyalinosis, are main cause of small, subcortical infarcts in 25% ("lacunar stroke"). About 20% of ischemic strokes are caused by cardiogenic embolism induced by atrial fibrillation. Uncommon causes include cervical artery dissections, vasculitis or thrombosis secondary to coagulopathies, drug abuse, etc. (5%). In more than 30%, despite of a full assessment, the cause of strokes etiology remains to be undiscovered [24-26]. Thus, seeking of the pathogenetic cause of the stroke in some patients is quite difficult, but extremely important for choosing the optimal treatment and prevention strategy.

The degree of cerebral blood flow impairment and the time when cerebral perfusion was restored, define the severity of the neurological deficit caused by ischemic stroke. This could be explained by particularities of brain's metabolism which normally is constant and permanent, but demanding a continuous supply of glucose and oxygen [20, 21, 27]. Decreasing of blood flow from normal values (50 ml / 100g / min) to <10 ml / 100 g / min, triggers the ischemic cascade reaction, which comprises a series of biochemical reactions in the brain, which usually last for 2-3 hours, but they also can be extended for several days, even after normal blood flow is restored [28].

Acute oxygen distress, caused by blood flow drawback for more than 10 seconds, deprives neurons in the affected area of the ability to produce energy and triggers anaerobic pathway, with release of lactic acid. As consequence of that, the acid-base balance in the brain is disturbed, which causes the depolarization of the cell membrane with an influx of calcium and efflux of potassium ions. Elevated intracellular calcium triggers and the release of glutamate by stimulating the AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) and NMDA (N-methyl-D-aspartate) receptors lead to more calcium influx. All these processes lead to excess of intracellular calcium with cells overexcitation, activation of proteases and free radicals' releases due to the excitotoxicity process. Activated proteases and free radicals break down the cell membrane, promoting intracellular influx of other molecules and toxic substances. These processes affect the activity of mitochondria, and results in toxins and apoptotic factors release. Those are milestones of cell death, causing irreversible changes in brain tissue [21, 29].

At the early onset of the cerebral ischemia, we can differentiate few perfusion areas around ischemic nucleus, where blood flow is reduced, but maintained. This area is defined as penumbra. It suffers from hypoxia, but remains metabolically active, containing affected, but still viable brain tissue, blood supply being ensured through the collateral vessels. Exactly this region is the target of acute therapy [28, 30]. Important issue is that the penumbra is a dynamic, time-dependent area in which brain tissue will necrotize in a few hours or days due to poor perfusion and the cascade of biochemical events. Otherwise, if blood flow and oxygen supply are restored shortly after stroke onset, these cells can survive [23, 24].

Based on these biochemical processes and supporting MRI studies, the critical time of 4.5 hours for effective reperfusion was established. At the same time it is highlighted, that earlier blood flow restore will save more brain tissue. All this is the basis of the concept "time is brain" [26].

Symptoms of Stroke

Stroke syndromes are clinically presented as sudden onset neurological deficits. The symptoms depend on the affected region of the brain, which in turn is defined by the arterial anatomy involved. Although some features are more or less typical of hemorrhagic forms of stroke, as distinct from ischemic stroke, none are specific to allow clinical diagnosis of the stroke type. Therefore, in the acute phase of stroke, cerebral and neurovascular imaging is required. Common symptoms of stroke in the left hemisphere include aphasia, right hemiparesis and right hemianopia, and in the right hemisphere – left spatial hemineglect, left hemiparesis and left hemianopia. The majority (90%) of strokes are

supratentorial; as such, the public can be taught to recognize and act upon stroke using the acronym FAST, for facial droop, arm drop, speech disturbance and time. Posterior circulation or infratentorial stroke has a multitude of additional symptoms, including diplopia, bulbar palsies, dysphagia, unilateral dysmetria and incoordination, as well as reduced levels of consciousness. Stroke is typically painless. The most important historical feature of stroke is the suddenness of its onset. Identification of a stroke syndrome is relatively easy: sudden onset of acute neurologic symptoms, peaking within a few minutes, is deemed a stroke until proven otherwise. However, detailed diagnosis and management are highly dependent upon clinical assessment of the history and physical examination, because symptoms and signs vary tremendously according to the region of the brain that is affected [31].

Patients with acute ischemic stroke with larger infarct volumes have a higher risk of developing symptomatic intracranial hemorrhage and worse clinical outcome following intravenous thrombolysis [32, 33]. In addition to volume, the location of an infarct is linked to neurologic deficits. Some studies reported that ischemic infarcts in the insular ribbon, lentiform nucleus, and corona radiata are associated with poor prognosis in patients with stroke [34-36].

The Pathophysiological Mechanisms of Recovery

The degree of impairment depends on many factors, such as the extent of the infarct, the identity of the damaged region and the effectiveness of the early medical care. The functional status of stroke patients spontaneously improves over 6 months after onset. More specifically, rapid recovery is achieved during the first month [37].

The term brain plasticity defines all the modifications in the organization of neural components occurring in the central nervous system during the entire life span of an individual [38]. Such plastic phenomena involve particularly the perilesional tissue in the injured hemisphere, but also the contralateral hemisphere, subcortical and spinal regions. Functional improvement overlaps with motor learning in terms of underlying mechanisms [39]. Motor learning is associated with structural changes which we report below.

Neuroblasts usually originate from the subgranular zone in the dentate gyrus of the hippocampus and the subventricular zone. These migrated neuroblasts may replace injured neurons or glial cells, and help with remodeling and reorganization processes [40]. Newly formed blood vessels might help with augmenting nutrient supply and repair processes. Proangiogenic growth factors promote survival of the neuronal, glial and endothelial cells in the peri-infarct tissues, and transient neovascularization in the ischemic brain helps with the clearance of damaged tissues. Moreover, it may create a vascular niche for neuroblast migration [41]. Axonal sprouting is mainly driven by the balance between a growth-promoting status and reduction of growth-inhibitory environment. Axonal sprouting may alter cortical sensory or motor maps, and robust evidence exists to show that new connections are formed in peri-infarct cortex areas [42]. In humans, ipsilateral perilesional cortical activation including premotor or supplementary motor area is a common finding after primary motor cortex injury. Studies suggest that ipsilateral perilesional cortical activation is associated with functional recovery, at least in the acute period. In the recovery phase, the corresponding area in the contralateral cortex frequently shows coactivation. Therefore, a decrease in the activation in the contralateral cortex is observed in patients with better functional recovery. The underlying mechanisms of change in contralateral cortical activation share similar physiologic changes, such as unmasking of latent synapse, facilitation of alternating network, synaptic remodeling, and axonal sprouting [43].

Imaging

Non-contrast Computed Tomography

Nowadays, non-contrast CT remains the "golden standard" of imaging examination for the initial evaluation of patients with suspected stroke. The CT changes can be classified as: acute (less than 24 hours), subacute (24 hours to 5 days) and chronic (weeks) (Figure 1) [44]. Acute stroke represents cytotoxic edema that causes loss of the normal gray matter/white matter differentiation and effacement of the cortical sulci. A subacute stroke represents vasogenic edema, with greater mass effect, hypo-attenuation and well-defined margins. Mass effect and risk of herniation is the greatest at this stage. Chronic strokes have loss of brain tissue and are hypo-attenuating. A non-contrast head CT may identify the early signs of stroke, but most importantly will exclude intracerebral hemorrhage and stroke mimics, such as volume occupying lesion. Non-contrast CT is also used in the evaluation of acute intracranial hemorrhage as it produces good contrast between the high attenuating ("bright") clot and the low attenuating ("dark") cerebrospinal fluid (CSF) [45]. Non-contrast CT has also been used historically to exclude patients from receiving thrombolysis based on the extent of hypo-attenuation at presentation. This criterion has, however, been removed from the 2018 American Heart Association guidelines [46].

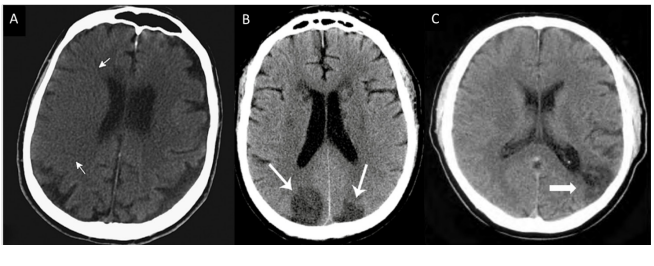

Fig. 1. Imagistic findings on brain CT in different stroke phases
Acute (A) Axial non-enhanced computer tomography demonstrates hypo-attenuating foci throughout the left-sided white matter (arrows) and sulcal effacement in the left middle cerebral artery (MCA) territory; subacute (B) "fogging effect" obtained at 36h with bilateral occipital hypodensities; chronic (C) encephalomalacia after left MCA stroke [47, 48]

Magnetic Resonance Imaging

Conventional brain MRI is not very good at detecting cytotoxic or intracellular edema that is seen in the acute or <24h phase of stroke. Standard MRI images (T1 and T2) can

help identify a subacute stroke. Fluid attenuated inversion recovery (FLAIR) sequences provide good sensitivity for acute subarachnoid hemorrhage, as compared to conventional T1 and T2 weighted images and are useful in the initial evaluation of the acute stroke patient suspected of having a subarachnoid hemorrhage. Subarachnoid hemorrhage appears bright on FLAIR images. The gradient recalled echo (GRE) sequence is also useful for the detection of blood products. Hypointensity due to paramagnetic effect of the hemosiderin, otherwise known as "blooming," affects the magnetic field and decreases the signal. Therefore, blood appears "black" on GRE images. MR diffusion is diffusion weighted images (DWI) and can be obtained within 10 minutes so the clinical determination of ischemic stroke can be confirmed quickly. DWI is used to detect early ischemic changes (acute stroke; early ischemic change; cytotoxic edema) with greater conspicuity than standard protocol. MRI with diffusion is quickly becoming the gold standard in acute stroke imaging. Once a hemorrhagic stroke has been excluded by CT, MR diffusion improves stroke detection from 50% to more than 95% [47-49]. Perfusion weighted imaging (PWI), just like CT perfusion, can identify the ischemic penumbra. The ischemic penumbra is the difference between the DWI defect (cytotoxic edema irreversible ischemia – the ischemic core) and the perfusion defect. The penumbra is the DWI/PWI mismatch. The accurate identification of this ischemic penumbra will help guide future ischemic stroke therapy and potentially aid in extending the time window for treatment [49].

Acute Treatment of Ischemic Stroke (Prehospital, Hospital, Thrombolysis, Stroke Unit)

Stroke is the main cause of long-term disability and one of the leading causes of death worldwide. About 31% of patients die during the first year, this index being higher in patients over 65 years. And concerning cost of care in the most European countries stroke has the leading position [50].

It is expected that the incidence and burden of stroke will increase considerably over time. The good news is that in the last decade was gained a substantial progress in the treatment of this devastating disease. Evidence-based treatments, aiming to restore blood flow to the affected area of the brain, such as intravenous thrombolysis and endovascular thrombectomy, show to improve functional abilities of the patients [51-54]. And the optimized operational algorithms allow to minimize "door-needle" time by rapid selection of patients, using detailed clinical evaluation as well as cerebral and vascular imaging [55-58].

A proper stroke management begins with the recognition of the first signs of the disease by the patient or family. People must be aware that "time is brain" and at first signs of a stroke to call immediately 112 for instant admission to the nearest Stroke Unit [59].

The ambulance team must be familiar with the signs of a stroke, they must perform initial assessment and stabilization of the patient and start initial management according to the protocol, hospital pre-notification is very important as well [50, 59]. Different hospitals have different stroke treatment programs; thus, time of symptoms onset is crucial point when the decision where patient will be referred to is taken [50, 60].

Presently, intravenous thrombolytic treatment with rtPA (recombinant tissue plasminogen activator) is the only approved pharmacological treatment in acute ischemic stroke. Intravenous thrombolysis is based on the concept that most ischemic strokes are of thrombotic or thromboembolic in origin. Thus, in order to benefit from thrombolytic treatment, patient is to fulfill all inclusion and exclusion criteria [59].

As it was mentioned above, recombinant tissue plasminogen activator (rtPA) was the only treatment approved for acute ischemic stroke. However, only 3-9% of patients with ischemic stroke benefit from rtPA [61-64], in part due to the narrow therapeutic window. In 2008, after publication of ECASS-3 study results, therapeutic window for rtPA was extended from 3 to 4.5 hours from symptoms onset, with additional exclusion criteria [65]. The extension of the therapeutic window led to 20% increase in the number of patients who profited from intravenous thrombolysis [66].

Subsequently, implementation in 2015 of endovascular treatment, allowed the extension of the intervention time to 7 hours from the onset of symptoms [67]. The positive result is defined by improving by 4 or more points of the neurological deficit according to the NIHSS scale. Much better functional results for severe ischemic strokes could be obtained by combination of the pharmacological thrombolysis and endovascular therapy, this strategy will also allow to get additional time for treatment [59].

Despite the risk of bleeding complications, patients with severe stroke treated with rtPA have better prognosis. The risk of intracerebral hemorrhage is linked with severity of the neurological deficit (measured by the NIHSS) and presence of cerebral edema on CT [68, 69].

But in reality, only 25% of stroke patients are admitted in a specialized medical facility in first 4.5 hours and less than 65% arrive within 8 hours of onset, what is behind therapeutic window [70]. In such cases, DWI MRI is recommended to accurately assess the penumbra area and viable brain tissue [71].

Approach to stroke management has undergone a lot of changes in recent years, with more patients receiving treatment avoiding long-term disability. A critical step forward has been the establishment of regional systems of care, which are capable rapidly to identify stroke patients and, using the decision support, to redirect them to appropriate centers with access to the state-of-the-art treatment. Modern medicine is constantly trying to improve the management of stroke patients. One of the options is telemedicine, which allows remote audio-visual connection between comprehensive stroke center and community hospitals [72]. This comprises detailed clinical and radiological evaluation with interpretation of these results by stroke expert, with further decision about patients' eligibility for intravenous thrombolytic and endovascular therapy.

Evaluation of patients with an acute stroke is also a good time for tracing of measures for secondary prevention.

Stroke constantly confirmed to be the second cause of

mortality worldwide [73]. Proper stroke management depends on accurate and rapid diagnosis. The Specialized Neurological Facilities should be equipped with neuroimaging techniques and a high-performance clinical laboratory. The treatment concept of cerebrovascular diseases is constantly evolving. It has already been proven that prompt response and effective treatment can protect large areas of brain tissue from irreversible damage. Also, the population must be aware that "time is brain" and with the first signs of stroke immediately call 112 for immediate admission to the nearest Stroke Unit.

Endovascular Treatment of Ischemic Stroke

The history of endovascular treatment of acute ischemic stroke began as early as the end of the last millennium. PROACT I and II trials investigated the effect of intra-arterial thrombolysis with pro-urokinase in the treatment of acute ischemic stroke [74, 75]. Pro-urokinase has not been approved by FDA (Food and Drug Administration) for the treatment of stroke, due to the lack of evidence.

After PROACT II, a new tool appeared – the MERCI retriever. This was the first instrument for mechanical thrombectomy (MT) approved by FDA. The effectiveness of this device was investigated in MERCI and MULTI MERCI trials [76, 77]. These studies showed good outcome of the treated patients, but the mortality was high. However, they proved the importance of early recanalization in patients with ischemic stroke, because the promptness of recanalization was shown to be related to good outcome.

Later, second-generation devices appeared, such as the Penumbra aspiration system that was studied in the Penumbra Pivotal Stroke Trial [78]. Compared to the MERCI device, Penumbra obtained higher recanalization rates, but good clinical outcome of patients (modified Rankin Score- mRS ≤ 2) was observed only in 1/4 with high rates of complications and all-cause mortality.

The third-generation devices are stent-retrievers. Solitaire and Trevo showed promising results in the rate of recanalization and good outcomes in SWIFT and TREVO trials [79, 80].

The short history of MT in stroke had ups and downs. In 2013, the results of 3 studies were published that did not provide sufficient evidence for this method. These were MR RESCUE, IMS III and SYNTHESIS. All these studies did not show better results compared to systemic intravenous thrombolysis [81-83].

But in 2015-2016 the picture changed. The results of several randomized clinical trials (MR CLEAN, ESCAPE, EXTEND-IA, SWIFT-PRIME, REVASCAT, THRACE) have been published, with promising results of endovascular treatment in patients with ischemic stroke: high degree of patient's independence at 3 months (mRS ≤ 2) and decreased mortality [57]. These trials avoided the bias of previous ones by standardizing the processes and selecting patients by detecting proximal occlusion at mandatory vascular imaging, emphasizing the importance of door-recanalization time and the use of new stent-retriever devices.

Another revolution came in 2018 with DAWN [54] and DEFUSE 3 [51] trials, which showed the efficacy of MT in patients with large vessel occlusion in the anterior circulation who were presented between 6 and 24 hours and between 6 and 16 hours, respectively, from the onset of stroke, using perfusion imaging. These studies have essentially replaced the "therapeutic window" with the "perfusion window".

Currently, endovascular therapy is the standard of treatment for patients with ischemic stroke caused by large vessel occlusion. Adequate selection of candidates and use of last generation devices give us good results in the rate of recanalization and good clinical outcome.

Stroke Prevention Strategies. Management of Stroke Risk Factors

The burden of stroke is of major importance for the global health [84], being the second leading cause of death and disability [85]. Currently, the global health system is facing a stroke pandemic, which mainly affects low and middle-income countries, where the incidence of strokes is constantly rising [86, 87]. The growing incidence of stroke and the persistence of alarmingly high rates in some parts of the world reflect significant gaps in the stroke prevention strategies [84]. The good part is that the individual risk of stroke can be reduced by about 80% [88] and the incidence of stroke by about 50% just by implementing lifestyle changes [89]. Therefore, there is an urgent need to increase the efforts towards the stroke prevention.

Currently, prevention is the main tool in the fight against stroke, whose purpose is to reduce the incidence of stroke by changing a single or several risk factors for stroke [13]. There are three levels of stroke prevention: primordial, primary and secondary prevention. The primordial prevention consists of implementation of general measures that are related to the healthy lifestyle and are applied at the population level. Primary prevention comprises the measures directed to improve the profile of cardiovascular risk factors that are present in people who have not suffered a stroke or a transient ischemic attack (TIA), in order to prevent a cerebrovascular event. Secondary prevention includes measures applied to people who have suffered a stroke or TIA, in order to prevent their recurrence [90, 91]. Primary and secondary prevention also cover the measures to control both behavioral and medical risk factors [13].

Strategies used to prevent stroke fall into 2 broad categories: strategies for people at high risk for cardiovascular diseases and population-based strategies [85]. Strategies for people at high risk for cardiovascular disease include interventions related to lifestyle changes and those related to pharmacological treatment. Lifestyle changes involve reduced salt intake, increased consumption of fruits and vegetables, physical activity, weight loss, smoking cessation, reduced alcohol consumption and management of psychosocial stress [85]. Regarding pharmacological interventions, in order to reduce the risk of cardiovascular and cerebrovascular diseases, the use of blood pressure and lipid lowering drugs together with antiplatelet agents has been suggested [85]. Both the measures related to lifestyle and pharmaco-

logical treatment have several limitations in their practical use: reduced ability to practically test the effectiveness of healthy lifestyle measures [85], practical difficulties in using cardiovascular risk scores, the need of laboratory tests for some of the risk scores, risk unawareness in rural areas, daily use of several drugs. But the major problem is that these measures are focused only on a certain category of population, failing to cover the majority of other populations [92] and even though several studies have shown their effectiveness, they are underused [88].

Population-based strategies comprise the entire population, with the aim of reducing cardiovascular risk [85]. They target several behavioral and lifestyle risk factors – tobacco use, unhealthy diet, physical inactivity, overweight, and alcohol abuse. Although these measures also prevent the risk of other diseases, such as heart diseases, lung diseases, diabetes, cancer, and dementia [85] and even though several studies have shown their effectiveness, unfortunately no country in the world has fully implemented these measures [88].

Stroke prevention is a complex medical and political issue but there is clear evidence that stroke prevention is effective and we need to seize the opportunity and act now [14, 93]. This health issue also requires the involvement and support of governments, health decision-makers, public health professionals and international agencies [84].

Post-Stroke Recovery and Rehabilitation

According to statistics, 10% of post-stroke patients recover almost completely, 25% have minimal functional impairment, 40% have moderate to severe functional impairment and need special care, 10% require special care at home or in long-term medical facilities, 15% die shortly after stroke, 14% of stroke survivors suffer repeated stroke in the first year [94]. Rehabilitation of post-stroke patients is a complex process that requires a multidisciplinary approach, consisting of neurologist, physiotherapist, social therapist, speech therapist, clinical psychologist, and other specialists, the main purpose being the application of contemporary recovery methods and techniques, preventing recurrences, combating complications and reintegrating the patient into society [95]. The objectives of neurorehabilitation are to minimize disability, increase the degree of functional independence, prevent recurrences and complications, help in social integration, increase the quality of life, reduce costs [96]. A crucial contribution to establishing the staging of rehabilitation by identifying deficiencies that cause disabilities is neurological assessment with a focus on functional testing, gait, balance, muscle strength, physiological and pathological reflexes, cognitive and psychoemotional status, and the degree of independence. It is also essential to use functional ability assessment scales, such as Barthel score, Rankin scale, ADL (Daily Living Activities) scale, FIM (functional independence measurement) scale, modified Ashworth spasticity scale, MRC (Medical Research Council) muscle strength scale, Mini Mental test for cognitive functions [97]. Cognitive and behavioral symptoms can be seen frequently in people who have had a stroke. Post-stroke depression is probably the most common emotional disorder and the most important long-term psychosocial consequence of a stroke, and has a negative effect on patients' functional outcome. As the functional status of patients improves rapidly in the early rehabilitation period, it is necessary to focus on the treatment of depression. Also, the support of family caregivers can improve the patient's psycho-emotional state, and later become a modifiable factor. Therefore, the rehabilitation team should take this into account and reflect this in planning a treatment program [98].

The patient's level of disability, concomitant illness, cognitive and mental functions can have a significant impact on both treatment decisions and outcomes. Psychosocial factors, such as the availability of support networks, financial resources, the patient's sense of control over the disease can affect the results and therefore must be evaluated. Stroke is a difficult living condition. Patients who have found an acceptable way to live with the disease are distinguished by the following: they dare to prepare for a more difficult future, they do not withdraw from the world of the healthy, they develop topics of interest other than stroke, they evolve towards a more conscious life, based on fundamental values [2].

Conclusions

Stroke remains one of the leading determinants of death and severe disability worldwide. It is a medical emergency with a narrow window for recognition and administration of outcome-modifying treatment in the emergency department, that's why the management of stroke focuses mainly on rapid reperfusion that can be achieved with intravenous thrombolysis and endovascular thrombectomy. Both methods reduce disability in patients after stroke but are time-critical. The key to maximizing the benefits of reperfusion therapies and to achieve good outcomes we need to improve our health system of care that will minimize the treatment delays and errors. For acute treatment of stroke, the intravenous thrombolysis will reduce disability only if it is administered within 4.5h of the onset of stroke. Thrombolysis also can benefit selected patients with evidence from perfusion imaging of salvageable brain tissue for up to 9h and in patients who have woken up stroke symptoms. The endovascular thrombectomy reduces disability in a broad group of patients with large vessel occlusion when performed within 6h of stroke onset and in patients selected by perfusion imaging up to 24h following stroke onset. Admission to specialized stroke units is associated with improved outcome in patients suffering from acute stroke.

Primary and secondary prevention of ischemic stroke has many common elements with cardiovascular risk management from other fields, including blood pressure control, cholesterol management and antithrombotic medications. Other preventative interventions are tailored to the mechanism of stroke, such as anticoagulation for atrial fibrillation and carotid endarterectomy for severe symptomatic carotid artery stenosis.

Most survivors of a stroke are left with chronic disability. Rehabilitation efforts during the initial three to six months after stroke should aim to maximize patients' physical, communicative, and cognitive functioning.

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SG conceptualized the project and designed the research; EZ, AB, AG, EM conducted literature review, EZ, AB, AG, EM, PL, DE, IC, DG, TB drafted the first manuscript; SG, EZ, AB, AG, EM revised the final version of the manuscript. All the authors approved the final version of the manuscript.

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