UDK: 616.831-005.1-08
Review article
Received: 15 June 2013
Accepted: 18 September 2013

CURRENT TRENDS IN STROKE MANAGEMENT

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Summary

Stroke is a major health problem despite the great efforts made worldwide to fight against it. Despite therapeutic achievements to treat ischemic stroke patients in stroke units with tissue plasminogen activator (tPA), prevention remains the most powerful strategy to cure this complex disease. Stroke is a heterogeneous and multi-factorial disease caused by the combination of vascular risk factors, environment, and genetic factors. These risk factors can be modifiable or non-modifiable.

Recently, a great emphasis has been given to the investigations of genetic factors and stroke risk, which may lead to the discovery of new biomarkers for prevention, diagnosis and to the alternative strategies for stroke treatment. Ischemic stroke must be treated as an emergency. Immediate transportation to a nearest hospital, preferably a stroke unit, cautious lowering of excessive blood pressures (>220/120mmHg) and abstention from heparin and aspirin are the most important measures in the pre-hospital care for a stroke patient. Intravenous thrombolysis in a 3-hour window is the only approved treatment, but it is time-dependent. In severe strokes with occlusion of large intracranial arteries, mechanical recanalization is increasingly used. In order to improve stroke care in rural and urban areas where there is no organized stroke unit, it is useful to establish a stroke network, which functions according to telemedicine and teleneurology rules.

Keywords: cerebrovascular disease; ischemic stroke; stroke prevention; risk factors; stroke management; thrombolysis; telemedicine; teleneurology.

INTRODUCTION

The devastating stroke consequences have enormous personal, social and economic impact on oneself and the society. Stroke is the second leading cause of death worldwide. Its burden increases as the population ages and the incidence of the factors such as hypertension and diabetes increase across the globe [1]. Therapeutic strategies such as stroke unit care and treatments including tissue plasminogen ac-

tivator (tPA) have been developed to treat acute stroke more effectively and lessen the amount of disability that the disease carries [2]. However, these modalities are not available universally in developed countries and scarcely at all in developing ones, with t-PA utilization of less than 1 in 10 patients where it is even available [3]. More than 75% of strokes each year are first-ever strokes, making the primary prevention of utmost importance. Although stroke is a clinical diagnosis with many sub-classifications and distinct yet sometime overlapping entities, the identity of the risk factors is well known with many treatments readily available. The disease can be controlled, and perhaps largely prevented, thus achieving a sizeable public health benefit.

The stroke risk factors can be subdivided into non-modifiable (age, sex, race-ethnicity, genetic variations and predispositions) and modifiable (hypertension, diabetes, dyslipidemia, atrial fibrillation, carotid artery stenosis, smoking, poor diet, physical inactivity and obesity). An individual risk factor may contribute to each subclassification of stroke differently, and there is a large overlap or risk factors with cardiovascular and peripheral vascular disease. In this paper we will discuss the management of traditional and novel risk factors in stroke prevention, as well as management of stroke itself.

STROKE PREVENTION AND MANAGEMENT

Hypertension is the most important modifiable risk factor for stroke. Several studies have concluded that it accounts for more than the third of the stroke burden and maybe as much as half of all strokes [4]. The control of high blood pressure (BP) contributes to prevention of first strokes but also of renal and heart failure and possibly cognitive decline and frank dementia [5]. It has been shown that for every 20-mmHg increase in systolic and 10-mmHg increase in diastolic BP greater than 115/75 mmHg, there is a 2-fold increase in mortality associated with stroke and coronary disease [6]. Conversely, a 10 mmHg reduction in systolic BP has been shown to lower the stroke risk by about a third in primary and secondary stroke prevention [7,8]. These benefits also extend to the elderly, where in one study, a 36% reduction was found in the incidence of stroke for patients over the age of 60 who were treated with a thiazide diuretic with or without a beta-blocker. A more recent study of patients over the age of 80 showed that lowering the mean systolic BP by 15 mmHg and mean diastolic BP by 6.1 mmHg lowered the rate of fatal strokes by 39% after 2 years of treatment [9]. A meta-analysis of 31 trials, with 190606 participants, showed the benefits for educed BP in both younger (<65 years) and older (≥65 years), implying that the benefits from better pressure control can be reaped at any age [10].

A more intensive regimen appears to be more beneficial: in the ACCORD, a 5,000 patient study of those with diabetes, the patients who were in a more intense BP lowering group < 120, had a significantly lower risk of stroke after a follow-up of 4.7 years compares to those with a BP lowering goal of <140 [11]. While the BP lowering has reduced the risk for all stroke subtypes, these findings are more pronounced for hemorrhagic strokes.

A comprehensive evidence-based approach to treatment of hypertension is provided by the Eighth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure [12]. Several categories of antihypertensive medications such as thiazide diuretics, b-adrenergic receptor blockers, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and calcium channel blockers (CCBs) have been shown to reduce the risk of stroke in patients who are hypertensive [10,13]. Thiazide-type diuretics were originally recommended as the preferred initial drugs of treatment for most patients. [14] A more recent meta-analysis, however, has shown that with a few exceptions (beta-blockers after a recent myocardial infarction and additional benefits of CCBs) all the different classes of BP-lowering medications produced a similar reduction in the incidence of stroke and cardiovascular disease for a given reduction in BP [15].

BP control can be achieved in a vast majority of patients, with most requiring combination therapies and often more than 2 antihypertensive medications. Unfortunately, BP is controlled in less than a quarter of the hypertensive population worldwide. Given the importance of hypertension as a stroke risk factor, and the abundance of effective treatments available, providing effective population-wide but patient-specific interventions remains a major public health care challenge.

Diabetes is an established risk factor for all vascular events in general and ischemic stroke in particular. Individuals with type 2 diabetes also have an increased vulnerability to atherosclerosis and an increased prevalence of hypertension, hyperlipidemia and obesity. Cardiovascular disease and ischemic stroke develops earlier in patients with diabetes, and strokes in patients with diabetes tend to have a heavier morbidity burden. American Diabetes Association recommends a multi-faceted approach to optimal health in diabetics; not only controlling the blood glucose, but also aggressive treatment of associated cardiovascular risk factors, with lower targets than for the general population. Surprisingly, recent studies have shown that aggressive treatment of blood glucose was very effective in preventing mircovascular complications of diabetes, but had no statistical effect on reduction of macrovascular events, including stroke [16,17]. However, the evidence that a multifactorial approach (reduced intake of dietary fat, light to moderate exercise, ce-

ssation of smoking) reduces stroke and cardiovascular risk in type-2 diabetics is supported by subgroup analyses of diabetic patients in large clinical trials. In the UK prospective Diabetes Study Group, comparing a tight BP control group (mean BP 144/82 mmHg) vs less stringent control group (mean BP 154/87 mmHg) resulted in a reduction of 44% of fatal and non-fatal stroke between the two groups. Another study found that adding a statin to existing treatments in high risk patients resulted in a 24% reduction in strokes. The Collaborative Atorvastatin Diabetes Study evaluated statin therapy in diabetic patients as a primary prevention of vascular events (18). A total of 2838 people with type 2 diabetes were enrolled, and the trial was stopped early due to its efficacy points being met: 37% reduction the primary vascular events in general, and a 48% reduction of strokes in particular [18].

Good glycemic control involves appropriate insulin therapy and professional dietary and lifestyle therapy for type 1 diabetics and weight loss, increased physical activity and, if need be, oral and injectable hypoglycemic agents for type 2 diabetics. Treatment of adults with diabetes, especially those with additional risk factors, with a statin to lower the risk of a first stroke is recommended. Studies have shown that a multi-faceted approach to controlling diabetes and concomitant risk factors leads to significant reduction in cardiovascular events and stroke.

Many epidemiologic studies found no consistent relationship between cholesterol levels and overall stroke risks. However, there is evidence that there is a positive correlation between total and low density lipoprotein (LDL) cholesterol levels and the risk of stroke. Conversely, high density lipoprotein (HDL) cholesterol levels have been associated with reduced risk of ischemic stroke across many sub-populations. Moreover, in high risk patients, lowering cholesterol with statins (HMG-CoA reductase inhibitors) has been shown to significantly reduce the risk of transient ischemic attack or non-cardioembolic stroke [19]. Several meta-analyses have shown that lowering the LDL cholesterol by 1.0 mmol/L reduced the risk of ischemic stroke by about 20% [20]. The beneficial role of statins for primary and secondary stroke risk reduction for those with high risk for cerebrovascular disease risk has been documented [18]. It has estimated that statins prevent 9 strokes per 1000 high risk patients or in those with coronary heart disease treated over the period of 5 years. Earlier concerns of statins increasing the risk of hemorrhagic stroke have not been substantiated by a recent meta-analysis, although the topic is still under debate and caution should be exercised [21,22].

The benefit of rosuvastatin in cutting the risk of myocardial infarction in half in those patients who were apparently healthy but had elevated levels of C-reactive protein hints at the many pleotropic effects of statins [23]. Although this class of drugs is very well studied, the way it protects the brain and the heart is not entirely

clear. It may decrease platelet aggregation, stabilize plaques, lower BP and reduce inflammation. There has been further speculation that they may have neuroprotective properties, improve endothelium function, decrease smooth muscle proliferation and increase the number of circulating endothelial progenitor cells. Intriguing results have shown statins to increase nitric oxide production and P-selectin expression and up-regulate tissue-type plasminogen-activator. It is unclear if statins lower the risk of stroke by lowering the LDL, or by any of the above and maybe yet-unknown mechanisms. Other surrogate markers for artherosclerosis, such as carotid intima-media thickness (cIMT), may prove to be useful in monitoring the progression of and treatments against stroke and other vascular diseases [24].

Non-statin lipid-modifying therapies may also offer stroke protection, although the studies are less equivocal. Niacin treatment has been shown to increase HDL as part of a combination therapy. Evidence has been mixed on the exetimibe/statin combinations and if they are superior to mono-statin therapies. Fibrates have been shown to decrease the risk of coronary events and retinopathy, but not that of ischemic stroke [25]. Fibrates, Niacin, exetimibe and omega-3 fatty acids each regulate serum lipids by different mechanisms and a combination therapy may be the final answer in achieving desired lipid control. National Cholesterol Education Program III [26] guidelines for the management of patients who have not had a stroke and who have elevated total cholesterol or elevated non–HDL cholesterol in the presence of hypertriglyceridemia have been endorsed in the US [26]. The updated clinical guidelines for cholesterol testing and management (ATPIV) from the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults were published at the end of 2012 [12].

Although the benefits of statin therapy outweigh the low risk of serious side effects, there are still some populations for which more data on the safety of lipid-lowering therapies are needed to clarify the risk associated with the effect of treatment, especially for older persons (>70 years of age) and women. More clinical trials and further research for optimal lipid-lowering strategies are needed as the complex relationship between dyslipidemia, atherosclerosis, stroke and cerebrovascular disease exists and has not been entirely elucidated.

Metabolic syndrome is defined by a cluster of interconnected factors that increase the risk of atherosclerosis, cerebrovascular disease, stroke, and diabetes mellitus type 2. Its components are dyslipidemia (elevated triglycerides and apolipoprotein B (apoB)-containing lipoproteins, and HDL), elevation of arterial BP and impaired glucose homeostasis, with abdominal obesity and/or insulin resistance [12,26,27]. More recently, other factors such as proinflammatory state, oxidative stress, and non-alcoholic fatty liver disease have been suggested to play an impor-

tant role in metabolic syndrome, making its definition even more complex. To date the most used definition for metabolic syndrome is the NCEP ATP III definition (26). All the components of metabolic syndrome are involved in conferring risk of stroke and cardiovascular disease. The adjusted hazard ratio (HR) for incident ischemic stroke associated with metabolic syndrome ranges between 2.1 and 2.5 in prospective studies, and a HR as high as 5.2 has been reported [28,29]. In a cohort of 14,284 patients, patients with metabolic syndrome but without diabetes exhibited a 1.49-fold increased risk of ischemic stroke or transitory ischemic attack, whereas those with frank diabetes had a 2.29-fold increased risk [29]. The relative odds for ischemic stroke or transitory ischemic attack, associated with presence of metabolic syndrome, were 1.39 in men and 2.10 in women. In NOMAS, a significant association between the metabolic syndrome and ischemic stroke risk was reported to be independent of other confounding factors including age, education, physical activity, alcohol use, and current smoking [30]. The prevalence of metabolic syndrome in NOMAS was 49%, and differed by sex (39% in men, 55% in women, $p<0.0001$) as well as race-ethnicity (56% in Hispanics, 41% in blacks, and 39% in whites, $p<0.0001$). Interesting, the effect of the metabolic syndrome on stroke risk was greater among women (HR=2.0; 95% CI, 1.3 to 3.1) than men (HR=1.1; 95% CI, 0.6 to 1.9) and among Hispanics (HR=2.0; 95% CI, 1.2 to 3.4) compared to blacks and whites.

Metabolic syndrome is also associated with subclinical atherosclerosis. In NOMAS, we have shown an independent association between metabolic syndrome and ultrasonographic subclinical measures of atherosclerosis including carotid plaque and carotid stiffness [31]. Therefore, an early identification of people at high risk for vascular accidents by evaluating subclinical markers of atherosclerosis is prudent in order to initiate preventive treatments.

Although the existence of metabolic syndrome as a separate entity has been recently questioned, individuals with a cluster of the risk factors that comprise metabolic syndrome should be aggressively treated for hypertension, dyslipidemia and diabetes. Patients with metabolic syndrome have a greater risk of stroke and other vascular diseases and therefore "*a major breakthrough related to the concept of the metabolic syndrome is the recognition of the high cardiovascular risk in subjects with a cluster of mild abnormalities or with a cluster of abnormalities that are not regarded as driving forces in cerebrovascular disease*" [32].

Atrial fibrillation is a common cardiac arrhythmia and a frequent cause of cardioembolic strokes. It account for up to 20% of all ischemic stroke, and the presence of atrial fibrillation independently increases the risk of these events by up to 5-fold [33]. The incidence of atrial fibrillation increases with age, with as many as 10% of the population experiencing atrial fibrillation in their 80s [34] and the number of

affected patients may reach 12 million just in the U.S. by 2050. Despite its increasing burden, atrial fibrillation is also arguably one of the best-studied causes of stroke with dozens of randomized trials and well-established evidence-based recommendations regarding effective medical treatments.

Stroke risk stratification models have been developed and validated. $CHADS_2$ (Congestive heart failure, Hypertension, Age, Diabetes, Stroke/TIA) is the most well-known stratification system [35]. It subdivides patients based on the independent predictors of stroke in those with atrial fibrillation and offers validated recommendations of anticoagulation vs antithrombotics therapy based on the scale scores. Several other models for predicting stroke risk, (such as the National Institute for Health and Clinical Excellence (NICE) guidelines and $CHADS_2$-VASc and bleeding risk (HAS-BLED) have since been developed [36].

Anticoagulation and antithrombotic therapies remain the main agents for stroke preventions for those with atrial fibrillation. Warfarin is the most commonly used anticoagulant that is cheap and exceedingly effective in preventing ischemic stroke: a recent meta-analysis showed a reduced risk of cardioembolic stroke of 64% for those on warfarin vs only 22% for those on aspirin. Warfarin also provides an almost 40% relative risk reduction compared to anti-platelet therapies [37]. Despite its effectiveness, this anticoagulant has several limitations (narrow therapeutic window, many drug and diet interactions, frequent and inconvenient monitoring) and has been under-utilized [38]. It is difficult to keep in range with only two-thirds of patients in clinical trials and little more than half in the community setting being in the therapeutic range.

Given the utilization gap for warfarin, several novel oral anticoagulants that are just as effective, have a better side effect profile and require less monitoring have been developed, tested and approved. The three novel oral anticoagulants that have shown the most promising effectiveness and safety data are Dabigatran [39], Rivaroxaban [40], and Apixaban [41]. They all exhibit a stable pharmacological profile, very few drug-drug interactions and are almost unaffected by the patients' diet. Very few patients (renal impairment or body weight extremes) require regular monitoring. They appear to be as effective, and in some cases superior to warfarin, with a much improved side effect profile. Less intracranial bleeding, arguable the most feared complication of coumadin, has been observed. These new agents will likely completely change how we treat patients with atrial fibrillation and lead to a greater reduction of cardioembolic strokes in the future [42].

Other times of cardiac disease that contribute to the risk of ischemic stroke include congestive heart failure, myocardial infarction, dialted cardiomyopathy, valvular heart disease (eg. mechanical valves, mitral valve prolapse, etc) and con-

genital defects [eg. patent foramen ovale, atrial septal defect and aneurysm]. All patients with prosthetic valves should be anti-coagulated. The rate of thromboembolism is reduced by half with antiplatelet therapy and by more than 75% with anticoagulation. Patients with congestive heart failure have a higher risk of stroke (2-3 fold) and are more likely to incur more significant stroke-related morbidity and mortality compared to those without heart failure [43]. Low ejection fraction (especially below <30%) has been identified as a risk factor for stroke, however, studies on the best treatments for this condition remain inconclusive. Presence of aortic arch atheroma is associated with increased risk of ischemic stroke. Congenital defects, while relatively common, contribute to the burden of stroke only in relatively specific circumstances. Most of these cardiac abnormalities and the potential thrombi that they produce require all and careful cardiac workup for detection, including a transthoracic and transesophageal echocardiography, and extensive cardiac monitoring with telemetry and often a more protracted outpatient cardiac event recorder.

Carotid stenosis of 50% or greater can be found in about 5-10% of people who are older than 65, and the prevalence of a severe asymptomatic carotid stenosis has been found in 3.1% of the population [44]. Data from observational studies and clinical trials indicate an annual risk of stroke attributable to extracranial carotid to have increased with the degree of stenosis (from less than 1% a year for a <80% stenosis to 4.8% per year for a >90% occlusive lesion). In Asymptomatic Carotid Atherosclerosis Study (ACAS), patients with asymptomatic carotid artery stenosis of ≥60% were randomized to carotid endarterectomy (CEA) or best medical management, with the results showing the primary outcome of ispilateral stroke, death or any perioperative stroke to be 5.1% for surgical candidate and 11% for patients treated medically over 5 years, with an absolute risk reduction of 1% a year [45]. Asymptomatic Carotid Surgery Trial (ACST) randomized asymptomatic patients with significant carotid stenosis (>60%) for immediate surgery vs. medical management and were followed for a mean of 3.4 years. The study found the overall 5-year risk of stroke or perioperative death to be 11.8% with deferred surgery and 6.4% with immediate endarterectomy. In the subgroup analysis, CEA appeared to be more beneficial for men than women, and in younger patients, more than older individuals. A more recent study, Asymptomatic Carotid Embolic Study (ACES), of patients who were followed for 2 years and had a asymptomatic carotid stenosis of at least 70% and were noted to have embolic signals found to have a significantly higher risk of ipsilateral stroke compared to those without any emboli, suggesting the detection of embolization on transcranial Doppler may be used for additional risk stratification [46]. The benefit of endarterectomy in asymptomatic stenosis is dependent on the surgical risk. Trials of carotid surgery for asymptomatic carotid disease reduced the

risk of stroke by about 1% per annum, while the perioperative stroke rate is 3%. Medical management should be offered to most patients and only high-volume centers with complication rate of ≤3% should contemplate the surgical procedure. It appears that men and those with life expectancy of more than 5 years will derive the most benefit in appropriate centers [47,46]. Most physicians, however, are not aware of CEA complication rates at their institutions. The best medical management has been evolving with wider use of antiplatelet agents, blood pressure and lipid lowering drugs, reducing the risk of stroke to 1% [48] and therefore the above relative benefit of CEA may need to be recalibrated.

Carotid angioplasty and stenting (CAS) was developed as a less invasive procedure compared to carotid endarterectomy. It has emerged as an alternative for patients who are high surgical risks, have many medical comorbidities, previous neck radiation, contralateral laryngeal nerve palsy or surgically-suboptimal anatomy. Since its invention over 20 years ago, the technique has evolved to more sophisticated and intricate stents, embolic protection devices and increasing operator experience. The Stenting and Angioplasty with Protection in Patient at High Risk of Endarterectomy (SAPPHIRE) Trial shows that stenting was non-inferior to CEA among high-risk surgical patients. The comparison of CEA and CAS has been extensively studied, often producing contradictory and confusing results. On one hand, multiple studies have shown that CAS is not as safe as CEA, especially in symptomatic patients, with the International Carotid Stenting Study (ICSS) being the latest addition to the mix. [49] On the other hand, Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) found equal risk of composite primary outcome of stroke, MI or death in patients undergoing CAS or CEA [50]. The challenge of comparing three different modalities lie in the practice of modern medicine itself: the rapid evolution of medical management, CEA and CAS know how always slanting the risk-benefit ratio in a different direction. Overall, we have rapidly improving techniques for effective prevention of stroke from asymptomatic carotid stenosis.

Elevated plasma levels of homocysteine as a risk factor for stroke has been traditionally well recognized in atherothrombotic vascular diseases including stroke. It is believed that homocysteine induces endothelial platelet dysfunction, by reducing molecular nitric oxide. Folic acid and cobalamin have been shown to effectively reduce elevated homocysteine levels, however, clinical trials have failed to show that this translates into better cardiovascular or stroke outcomes [51,52]. Inflammation markers seem to be unaffected by lowering homocysteine in secondary stroke prevention, although it may have a role in patients with genetic predisposition to hyperhomocysteinemia or those who lack proper dietary folate intake.

Cigarette smoking is a well-established and modifiable risk factor for both ischemic and hemorrhagic strokes. Several meta-analysis have established cigarette smoking to impart a 2-fold increase in the risk of ischemic stroke an 3-fold increase of subarachnoid hemorrhages [54]. The most effective preventive measure is to not smoke or be exposed to smoke. Although quitting smoking is difficult to achieve, it does carry significant benefits, with rapid reduction in the risk of stroke within several years of cessation.

Alcohol consumption has been shown to have to have a J-shaped relation to risk of stroke, with light to moderate consumption (≤1 drink a day for women and ≤ 2 drinks a day for man) decreasing the risk of stroke to 0.3 to 0.5, but the risk increasing to 2 for heavier alcohol use (≥3 drinks) a day [54]. The relative risk is always increased for hemorrhagic strokes, regardless of the amount consumed. Alcohol in light to moderate quantities increases HDL cholesterol reduces platelet aggregation and lowers fibrinogen levels, while heavier use can lead to hypertension, hypercoagulability and atrial fibrillation [55]. Alcohol consumption should not be advocated as a way to prevent stroke, however, as alcoholism is a major public health problem and the risks of excessive intake remain great.

Abuse of illicit drugs such as cocaine in its various forms, heroin and amphetamines are associated with increased risk of both ischemic and hemorrhagic strokes by elevating the blood pressure and platelet aggregation, and inducing vasospasm and cardiac arrhythmias. Diet has been associated with the risk of stroke, with increased fruit and vegetable consumption having an inverse relationship to the risk of stroke in a dose-response manner; for example, for each serving per day increase in fruit or vegetable intake, the risk of stroke was reduced by 6% in one study. Research has shown that reducing salt intake improves cardiovascular and cerebrovascular health, although a recent review found no relation to salt intake and chronic heart disease morbidity and mortality [56]. Adherence to Mediterranean diet has also now proven to have a positive protective effect on cerebrovascular and cardiovascular disease [57].

Physical inactivity is another modifiable risk factor of stroke [58]. Physical activity has been shown to be beneficial in a dose-response pattern with more intensive physical activity providing greater benefits than light to moderate activity. The protective effects of physical activity are likely derived from lowering of body weight and BP and better glycemic control.

Obesity and body mass index (BMI) are risk factors for stroke, with associations to hypertension, dyslipidemia and glucose intolerance [59]. An obesity epidemic has been sweeping developed countries as well as developing nations such as India and China. The prevalence of metabolic syndrome worldwide, an entity that encom-

passes several stroke risk factors, was alarmingly high a decade ago (24-50%) and given the recent trends is likely to have increased since then [59]. Although no trials linking weight loss to the risk of stroke exist, evidence exists that losing weight reduces the presence of risk factors that cause stroke: in one meta-analysis an average weight loss of 5.1 kg reduced the systolic BP by 3.6-4.4 mmHg. Diet and exercise which are discussed above can be effective in controlling this modifiable risk factor.

Sleep related breathing disorders are common in patients with established cardiovascular disease. Habitual snoring and obstructive sleep apnea (OSA) have been shown to be independently associated with stroke and snoring has been strongly associated with vascular events during sleep. A recent-meta-analysis of 29 studies has shown that up to three-quarters of all patients have OSA, with the highest incidence of stroke occurring in patients with cryptogenic stroke, possibly establishing OSA an under-recognized stroke risk factor [60]. Hypoxemia, nocturnal hypertension and sympathetic surges have been postulated as some of many contributors to stroke in OSA patients. Decreased cerebral blood flow and impaired vasomotor reactivity has been observed even when the patients with OSA are not sleeping. Treatments with continuous positive airway pressure (CPAP) are non-invasive, and effective in reducing the risk of cardiovascular events and BP [61]. Further studies of OSA and other sleep disorders are on-going and may yield novels strategies and approaches in stroke prevention.

Aspirin has been shown as a well-established medication for primary stroke prevention. A recent meta-analysis showed a 32 % reduction in myocardial infarction in men but not women and a 17% reduction of the risk of stroke in women, but not men [62]. It is not clear why the sex difference exists, as the platelets seem to be inhibited equally in either sex, and no gender disparity was identified in studies in secondary prevention. A trial among diabetics with a history of atherosclerotic disease found Aspirin had no statistically significant effect on the rate of cerebrovascular events. Current guidelines indicate low-dose aspirin for women for whom the benefits may outweigh the risks and for patients with high CHD risk factors, but not for those at low risk or diabetics [63].

Stroke is a complex and multi-factorial disease caused by the combination of vascular risk factors, environment, and genetic factors. Recently, the scientific community put a great effort in understanding the genetic impact to the risk of stroke. Several epidemiological studies in families and twins have revealed a genetic component to stroke risk and experimental and clinical research using novel technologies have identified several genes directly or indirectly implicated in the mechanisms leading to stroke. The genetic contribution seems to be stronger in stroke patients younger than 70 years than in those who are older [64]. The strongest associations

have been found between stroke and single nucleotide polymorphisms (SNPs) in genes involved in inflammation, renin-angiotensin system, atherosclerosis, lipid metabolism, and obesity. (Matarin et al., 2010) However, few of these associations have been consistently replicated [65]. The innovation of a Genome-wide association study (GWAS) has allowed for identification of novel genetic loci without a specific hypothesis implicating a particular molecular pathway. The first GWAS for ischemic stroke was conducted using more than 400,000 unique SNPs in a cohort of 249 patients with IS and 268 neurologically normal controls [66]. However, these data did not reveal any single locus conferring a large effect on ischemic stroke risk. Other ischemic stroke GWASs have been conducted using a meta-analysis approach combining large populations such as CHARGE (Cohorts for Heart and Aging Research in Genomic Epidemiology), [67]. which consists of 4 prospective epidemiological cohorts of nearly 19,600 subjects with 1,544 incident strokes. In CHARGE, 2 SNPs were identified on chromosome (ch) 12, in the region of 12p13, and replication was obtained for one (rs12425791 SNP; the hazard ratio 1.3 for all stroke, and 1.0 for IS). A large International Stroke Genetic Consortium and the NINDS SiGN (Stroke Genetic Network) is currently conducting a GWAS of over 15,000 IS patients and 10,000 controls and expected to have the results available within a year.

Since stroke is a complex disease probably related to multiple genetic loci and the interaction of environment and heredity, the study of the precursors of this complex phenotype may be more rewarding. For example, the intermediate phenotypes as markers of subclinical disease such as cIMT, carotid plaque, arterial stiffness, and left ventricular mass; may be more helpful in identifying genes related to atherosclerosis and stroke [64]. The genetic research of stroke may greatly enhance our knowledge of this complex diseases. It may contribute to the discovery of new stroke biomarkers, which ultimately may be included in the stroke prevention, diagnosis, and treatment decisions.

When ischemic stroke does occur, the earlier stroke treatment starts the better the outcome. It is essential to minimalize the delay from symptom onset to therapy. Intravenous thrombolysis with alteplase within 3 hours is the only approved specific treatment of acute ischemic stroke. The benefit of thrombolytic therapy is time dependent [68,69]. For every 10 minutes of treatment delay, within 1-3 hours after stroke onset, 1 fewer patient out of 100 has a favourable outcome after systemic thrombolysis [69].

The majority of ischemic stroke patients unfortunately do not reach the hospital early enough to receive thrombolysis. For those patients, general acute stroke treatment is of utmost importance [70].

Prehospital stroke management starts with knowlede of stroke symptoms in general population, this being the cause of biggest delay in stroke treatment. Following the imporance of recognizing stroke, emergency department is crucial for successful stroke treatment [71]. It is usually the family members rather than the patients themselves contact emergency department. Informational campaigns distributed by mass media including TV' internet, social networks, and newspapers, provide education and encouragment to make an emergency call immediately after suspecting stroke occurence.

Apart from general public, emergency personnel and paramedics should also be continuously trained to improve preclinical stroke management [72]. Patients with facial droop, prior stroke or TIA and severe clinical deficit are most probable to receive a correct preclinical diagnosis of stroke, indicating that more subtle stroke symptoms may sometimes be misinterpreted or overseen [73]. The Face-Arm-Speech Test (FAST) is a simple acronim which can help identify stroke or TIA [74].

General practitioners should also be involved in preclinical stroke management, and participate in continuous training to be able to urgently evaluate every suspected stroke and channel the patient accordingly. Emergency department transportation ensures faster hospital admission due to quicker arrival, compared to private transport [75]. Whenever possible, transportation should be to the nearest hospital with a stroke unit. Prenotification to the emergency department and stroke unit physicians during transport ensures quicker in-hospital management and better chances to receiving thrombolysis.

During transport to the nearest hospital, patients should receive 0.9% saline intravenously. Heparin or aspirin should not be given before exclusion of intracranial hemorrhage by a CT scan. Hypertension can be tolerated up to 220/120 mmHg without lowering the BP. Oxygen should be supplied if saturation falls below 95% [76]. Upon arrival to the hospital the emergency department personnel should present the patient [73,75].

Immediate triage, neurological evaluation ircluding NIHSS, general physical examination, laboratory tests, and a native CT scan are needed [73]. Stroke or TIA mimics must be ruled out (including epileptic syncopes, sepsis [74], migraine with aura [77], or hypoglycemia). It is useful to implement in-hospital algorythms to speed up the evaluation and decision making.

Irrespective of age, gender, stroke subtype or stroke severity, admission to a stroke unit significantly reduces death, post-stroke dependancy, as well as need for institutional care after stroke. Stroke units are hospital wards with spacialized multidisciplinary staff trained for treating acute stroke and stroke related complications. Stroke teams consist of doctors, nurses, physiotherapists, occupational therapists,

speech and language therapists and social workers [78]. Technical equipment in a stroke unit allows assessment of neurological status, monitoring of vital parameters within 72 hours after severe stroke, ensure early mobilization and rehabilitation after stroke.

In most cases stroke is not acutely life-treatening, but majority of patients need stabilization of vital functions during the first hours to days after stroke. Treatment strategies aim at normalizing respiratory and cardiac functions, glucose, blood pressure, fluid balance, and at preventing stroke-related complications [76].

Stroke patients are at increased risk of cardiac arrhythmias, especially atrial fibrillation, myocardial infarction, heart failure or sudden death. Troponin levels can be elevated slightly during acute stroke, even in the absence of acute coronary syndrome, and thought to be due to stroke-related sympathoadrenal activation [79], making it necessary for every patient to have an ECG on admission. Further cardiac monitoring serves to maintain normal heart rates and can reveal paroxysmal atrial fibrillation as a common cause of stroke [76].

Hyperglycemia occurs frequently (30-40%; up to 60% in non-diabetics) in acute stroke and is associated with poor outcome and death, especially in patients without known diabetes [80]. Hyperglycemia was shown to be associated with hemorrhagic transformation of stroke and larger infarct volumes (81). However, it is uncertain if correction of elevated glucose levels improves clinical outcomes. To date, correction of glucose levels above 10 mmol/L with insulin, and below 2.8mmol/L with 10-20% glucose or dextrose bolus is recommended [76].

Hypertension is also common in acute ischemic stroke, and associated with increased risk of poor outcome. Due to impaired cerebral autoregulation during acute stroke, every change in systemic blood pressure directly affects cerebral blood flow. Hypertension may result in hemorrhagic transformation of the infarcted area, whereas hypotension may cause further damage to the penumbra. Despite such pathophysiological considerations, the optimal blood pressure management in acute ischemic stroke is not known. It is also unclear whether early discontinuation from preexisting antihypertensive treatment (about 50% of patients) is necessary [82]. Beneficial effects of early hypertension control could not be reproduced [83]. In the absence of conclusive data, current guidelines recommend moderate lowering of raised blood pressure over 220/120 mmHg, and over 185 mmHg systolic in thrombolysed patients using intravenous labetolol or urapidil [76], approximately by 15—25% during the first 24 hours atrial fibrillationter stroke [84]. Sublingual nifedipine has been described to cause abrupt decrease in blood pressure, and is therefore not a drug of first choice. In clinical practice, after permissive hypertension during the first 24 hours within the mentioned limits for nonthrombolysed and thrombolysed patients, antihypertensive medication may be continued or started from day 2.

Evidence how to handle hypotension is even more scarce. Low blood pressure at stroke onset is unusual and is recommended to be raised with saline 0.9% or volume expanders when associated with neurological deterioration. Inotropic support is only needed in patients with hypotension due to low cardiac output [76].

Oxygen should be supplied (usually 2-4 L/min via nasal tube) if saturation is below 95%. Saline 0.9% is recommended for fluid replacement during the first 24 hours after stroke. Fluid balance and electrolytes should be further monitored in dysphagic patients with severe deficit or impaired consciousness. Pyrexia (body temperature >37.5°C) should be treated with paracetamol and prompt the search for infections [76].

Bacterial pneumonia due to aspiration is one of the most frequent complications of acute ischemic stroke and should be treated with antibiotics. Aspiration occurs in patients with dysphagia or impaired consciousness and may be prevented by feeding by nasogastric tube, pulmonary physical therapy, and early mobilization [76]. Prophylactic antibiotic treatment, in contrast, may be harmful [85].

Urinary tract infections also commonly occur in hospitalized patients, mostly due to indwelling catheters. Almost half of stroke patients suffer incontinence at stroke onset (86), making urinary catheterization at least temporarily needed. Antibiotics should be used once urinary tract infection is diagnosed. Bladder catheters should be removed as soon as possible. However, 25% and 15% of patients will be incontinent at discharge and one year after stroke [86].

Immobilization due to paresis is a risk factor for deep venous thrombosis (DVT) and consecutive pulmonary embolism (PE). Early mobilization, rehydration and subcutaneous low molecular weight heparin can reduce the risk of DVT and PE in stroke patients without increasing the risk of hemorrhage [76,87].

Many stroke symptoms - hemiparesis, ataxia, vertigo, visual field defect, lower limb hypaesthesia, cognitive impairment, and depression - as well as polypharmacy lead to impaired gait balance and expose patients to increased risk of injury and falls. Hypovitaminosis D can be seen within one week after hemiplegic stroke. Falls occur in up to 25% of acute stroke patients, leading to serious injury, including hip fractures, in up to 5%. Physical exercise, mobilization, and supplementation of vitamin D, calcium, and biphosphonates can reduce fracture rates among acute stroke patients and should be provided in the acute setting. Drugs leading to postural instability, e.g. neuroleptics, should be avoided whenever possible [88-90]

Confusion, agitation and delirium are common problems in the acute phase of stroke. A search for underlying treatable causes often reveals dehydration, electrolyte dysbalance, fever, substance withdrawal, or nonconculsive epileptic seizures. When sedation or neuroleptics cannot be avoided, choice of drugs should take into

account potential side effects. Sedation can lead to impaired consciousness and thus increase the risk of aspiration and falls, so substances with short half-time periods, such as lorazepame, may be preferred. Antipsychotics, among them risperidone, have been associated with increased risk of cerebrovascular accidents in the elderly, risk of myocardial infarction in demented patients on cholinesterase inhibitors, and death [91,92]. The risk of cerebrovascular accidents seems to be greatest within the first weeks of drug intake, making the use of typical and atypical antipsychotics in the acute stroke setting even more hazardous. General recommendations are lacking, and prescription will be an individual decision based on comorbitidy and estimated harm if psychotic symptoms are left untreated.

Systemic thrombolysis with rt-PA within 3 hours is the only approved evidence-based therapy of acute ischemic stroke. Beyond 3 to 4.5 hours, intravenous thrombolysis remains effective and safe [68], but is yet unapproved by European medical authorities. Cerebral hemorrhage has to be excluded by CT scan before thrombolysis is started. As an off-label procedure, intravenous thrombolysis in the extended time window is routinely performed in experienced stroke centers. Data from the multicentre SITS-ISTR stroke registry showed that in 2009 there was a substantial increase (from 7% to 22%) in thrombolysis within 3 to 4.5 hours compared to 2008 [93]. However, the benefit of thrombolysis remains time-dependent (NNT in terms of a favourable outcome = 7 within 3 hours, 14 by 3 to 4.5 hours), [68]. Overall, the risk of SICH and mortality are slightly higher in patients thrombolysed within the extended time window, but the proportion of patients with favourable clinical outcome after 90 days is similar [93].

About 30% of strokes occur in people >80 years of age. Whereas approval criteria restrict thrombolysis to younger patients, it is now clear that older age is not a reason to preclude someone from treatment: risk and benefit must be weighted. Elderly stroke patients have higher bleeding rates. Mortality is also higher, but so is pre-stroke comorbidity. However, functional outcome in terms of mRS is significantly better in patients > 80 years after thrombolysis vs. without, and similar to younger patients [94,95].

In recent years, an increasing number of mechanical recanalization devices have been used to treat severe strokes with intracranial large artery occlusion as shown by CT angiography. The rates of good outcome (mRS = 0—2) in creased to 45 % with the latest techniques, rather acceptable for patients having very severe strokes [96]. For selection of patients the mismatch of cerebral blood flow and cerebral blood volume on contrast enhanced CT is used more and more instead of the time window. Perfusion CT has the advantage of being fast, widely available and less affected by artefacts than diffusion weighted and perfusion weighted magnetic resonance imaging.

Considering mentioned evidence that acute stroke patients benefit of specialized treatment in stroke units, but this specialized treatment is expensive and therefore not available everywhere. In most countries expertise in acute stroke treatment is mainly concentrated in academic hospitals, whereas a majority of stroke patients is treated in local general hospitals where the level of stroke care is partially suboptimal [97].

In order to improve stroke care in rural and urban areas it is useful to establish a stroke network. In order to take part in this kind of sophisticated stroke care, participating centers need to fulfill a number of requirements, such as: 24 hours availability of CT- or MR-imaging, Doppler-sonography, emergency laboratory diagnostics; securing a stroke care ward, with beds where all acute stroke patients of the hospital are concentrated, where monitoring of neurological status and vital parameters as well as early mobilization of the stroke patients is possible; continuous treatment by physiotherapists, occupational therapists and speech therapists; presence of a neurologist during the week and on call for emergencies during the weekend; the medical staff of the hospitals should be equipped with nurses, speech therapist and physiotherapist, as well as well as an additional physician [98].

These stroke teams have to complete a specific training program including: The training program is based on Standardized Optimized Procedures for diagnosis and treatment of stroke syndromes; Video training and certification in NIH-SS evaluation; Courses in transcranial Doppler sonography; Courses in swallowing disorders and dysphagia treatment.

A continuous stroke education program must include ward rounds in the local hospitals with one of the stroke experts every 3-4 months, newsletters and workshops is running in order to achieve further improvement of stroke care in the participating hospitals.

Therapeutic intervention in acute stroke requires urgent patient evaluation by physicians experienced in acute stroke to provide the best available care within critical time windows. Each hospital within the network should be equipped with a high-speed video conferencing system. In the local hospitals a second camera in a different position can be used. The interface of the local CT-scanners and MRI-scanners are connected to the workstation which is situated in a special room, close to the emergency facilities of the regional hospitals in order to facilitate rapid patient evaluation.

The stroke centers provide a 24-hours service with full-time stroke experts for teleconsultations. Contact is made up via telephone, the video connection is then established within minutes. The stroke specialist can download and analyze the CT or MRI-data from the server in the local hospital. Once the patient is in the exami-

nation room the physician at the stroke center can talk with him or with the local physician. The stroke specialist is visible on a screen in the examination room. The remote-controlled camera is operated by the stroke specialist in order to zoom and focus on the areas of interest. Mean duration of a video examination is between 15 and 20 minutes. Each teleconsultation is accomplished with a written report via electronic transmission. Indications to contact the stroke centers are clear cut [99].

CONCLUSION

Stroke remains a devastating and prevalent world-wide disease. The past several decades of research have also shown it to be a partially-preventable one, with many risk factors, strategies, and treatments identified, carefully evaluated and studied. A healthy diet and active lifestyle, careful control of modifiable stroke risk factors and access to regular health care are the keys to a successful stroke prevention strategy on both an individual and a public health level.

In stroke treatment evry minute counts. Raised stroke awareness within the population, rapid diagnosis by paramedics and primary care doctors, transportation by emergency deparment, hospital pre-notification and well organized in-hospital algorhytms contribute to rapid application of stroke treatment. The extended time window for systemic thrombolysis and recent data supporting thrombolysis in elderly patients >80 years of age offer the possibility that more patients receive this specific therapy for acute ischemic stroke. Acute general stroke management is best done at a multiprofessional stroke unit for 48-72 hours and deals with stroke-related metabolic, cardiorespiratory, inflammatory, and neuropsychiatric problems.

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Sažetak

Sadašnje smjernice za zbrinjavanje bolesnika s moždanim udarom

Unatoč konstantnoj borbi protiv moždanog udara u svijetu, on i dalje ostaje bitan zdravstveni problem. Iako je postignut velik napredak u liječenju moždanog udara primjenom aktivatora tkivnog plazminogena (tPA) u jedinicama za liječenje moždanog udara, prevencija ostaje najsnažnija strategija u liječenju te kompleksne bolesti. Moždani je udar heterogena i multifaktorijalna bolest uzrokovana kombinacijom vaskularnih čimbenika rizika, okoline i genetskih čimbenika. Na neke čimbenike rizika možemo utjecati, dok drugi ne ovise o nama.

Danas je naglasak stavljen na istraživanja genetskih čimbenika kao rizika za moždani udar. Ova istraživanja mogla bi dovesti do otkrića novih bioloških markera za prevenciju, dijagnostiku i alternativnu strategiju u zbrinjavanju bolesnika s moždanim udarom. Ishemijski moždani udar mora se zbrinjavati kao hitno stanje. Najvažnije mjere prehospitalnog zbrinjavanja bolesnika s moždanim udarom uključuju pravovremeni transport u najbližu bolnicu, ako je moguće u jedinicu za zbrinjavanje moždanog udara, pažljivo snižavanje izrazito povišenog krvnog tlaka (> 220/120 mmHg) te suzdržavanje od davanja heparina i aspirina. Intravenska tromboliza u trosatnom vremenskom prozoru jedino je odobreno liječenje, ali je vremenski ovisno. U slučaju teškog moždanog udara kod kojeg dolazi do okluzije velikih intrakranijalnih krvnih žila sve se češće izvodi zahvat mehaničke rekanalizacije. Kako bi se unaprijedila skrb za bolesnike s moždanim udarom u ruralnim i urbanim područjima gdje nema organiziranih jedinica za liječenje moždanog udara, korisno je uspostavljanje mreže za moždani udar koja funkcionira prema pravilima telemedicine i teleneurologije.

Ključne riječi: ishemijski moždani udar; prevencija; čimbenici rizika; zbrinjavanje bolesnika s moždanim udarom; tromboliza; rekombinantni tkivni plazminogen; telemedicina; teleneurologija.

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