https://doi.org/10.23873/2074-0506-2021-13-4-382-397

Chronic kidney disease as a risk factor for acute stroke

O.N. Rzhevskaya, A.Yu. Moiseeva, A.N. Esaulenko,
A.V. Pinchuk, Kh.G. Alidzhanova✉

[1]N.V. Sklifosovsky Research Institute for Emergency Medicine,
3 Bolshaya Sukharevskaya Sq., Moscow 129090 Russia;
[2]Department of Transplantology and Artificial Organs,
A.I. Yevdokimov Moscow State University of Medicine and Dentistry,
1 Bldg. 20 Delegatskaya St., Moscow 127473 Russia;
[3]Research Institute for Healthcare Organization and Medical Management,
30 Bolshaya Tatarskaya St., Moscow 115184 Russia

✉Corresponding author: Khafiza G. Alidzhanova, Dr. Sci. (Med.), Senior Lecturer of the Training Center, Senior Researcher of the Department of Emergency Clinical Cardiology with Methods of Non-invasive Functional Diagnosis, N.V. Sklifosovsky Research Institute for Emergency Medicine, AlidzanovaHG@sklif.mos.ru

Abstract

One of the most relevant issues of nephrology, neurology, and cardiology is the management and treatment of patients with chronic kidney disease and stroke. Patients with chronic kidney disease have a risk of both thrombotic complications and bleeding, and they have a high risk of both ischemic and hemorrhagic stroke. Chronic kidney disease significantly worsens the outcome of stroke by limiting the treatment due to reduced drug clearance and side effects. Hemodialysis which causes drastic hemodynamic and biochemical changes leads to the "stress" of the cerebral vascular system, increasing the risk of stroke; kidney

transplantation reduces the risk of stroke due to functional recovery. Chronic kidney disease and stroke have significant socio-economic consequences. Patients with end-stage chronic kidney disease, as a rule, are not included in clinical trials; and stroke treatment tactics have not been developed for them.

This review examines the interaction between kidneys and brain, the pathophysiology and epidemiology of stroke in all stages of chronic kidney disease, after kidney transplantation and discusses the management and treatment of chronic kidney disease patients with stroke.

The investigation of the factors responsible for the high prevalence of brain lesions in chronic kidney disease will allow developing new treatment methods.

Keywords: chronic kidney disease, stroke, hemodialysis, kidney transplantation

Conflict of interests Authors declare no conflict of interest

Financing The study was performed without external funding

For citation: Rzhevskaya ON, Moiseeva AYu, Esaulenko AN, Pinchuk AV, Alidzhanova KhG. Chronic kidney disease as a risk factor for acute stroke. *Transplantologiya. The Russian Journal of Transplantation*. 2021;13(4):382–397. (In Russ.). https://doi.org/10.23873/2074-0506-2021-13-4-382-397

AF, atrial fibrillation

AH, arterial hypertension

AKI, Acute Kidney Injury

APD, antiplatelet drugs

APTT, activated partial thromboplastin time

BBB, blood-brain barrier

BP, blood pressure

CInf, chronic inflammation

CKD, chronic kidney disease

CNS, central nervous system

CVD, cardiovascular disease

CVE, cardiovascular event

DM, diabetes mellitus

ED, endothelial dysfunction

eGFR, estimated glomerular filtration rate

EP, erythropoietin

ESRD, end-stage renal disease

HD, hemodialysis

HS, hemorrhagic stroke

IL, interleukin

INR, International Normalized Ratio

IS, ischemic stroke

KD, kidney dysfunction

LDL, low density lipoprotein

LV, left ventricle

MR, mortality risk

NOAC, new oral anticoagulants

RAAS, renin-angiotensin-aldosterone system

RF, risk factor

RS, risk of stroke

SNS, sympathetic nervous system

TNF-α, tumor necrosis factor α

tPA, tissue plasminogen activator

Introduction

The combination of chronic kidney disease (CKD) and brain damage is becoming an increasingly relevant topic that deserves a lot of

attention. The kidneys and the brain have a complex bidirectional relationship. CKD affects both the structure and functions of the brain, which is the cause of the spread of cerebrovascular diseases at all stages of CKD [1-2]. Thus, the patients with an earlier stage of CKD are more likely than the general population show brain abnormalities: those of white matter, atrophy, and brain infarcts [3-4]. According to the US Renal Data System database, individuals with an estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2 and patients with end-stage renal disease (ESRD) have a 3.7-fold and 5.8-fold increased risk of stroke, respectively [5]. In patients with previous lacunar stroke, CKD increases the risk of recurrent stroke by 50% [2]. Regardless of concomitant cardiovascular diseases (CVD), the risk of stroke (RS) increases with the progression of CKD stage, and the prevalence of stroke is 8 times higher than in the general population, and at the beginning of dialysis it makes 6.7% [3]. Patients with CKD are at risk of both thrombotic complications and bleeding, and they have a high risk of both ischemic stroke (IS) and hemorrhagic stroke (HS) [6]. In dialysis patients, compared with the general population, RS increases three-fold for IS and six-fold for HS [4, 7]. Meantime, patients with CKD are more prone to IS than HS [8]. CKD with a stroke is more common in patients younger than 50 years of age compared to the elderly population [2].

According to the results of studies, CKD is a strong independent predictor of short-term mortality and poor outcome in patients with acute stroke [2, 9]. Most patients with CKD die from CVD, including stroke, rather than from end-stage CKD [10]. CKD is included in the QRISK3 model for predicting the risk of CVD and stroke.

Stroke is an independent predictor of CKD progression to ESRD [11]. A large-scale multicenter study showed that proteinuria or low eGFR occurs in 35% of patients with the first stroke [12]. Acute kidney

injury (AKI) after the stroke is a new independent prognostic factor for a long-term survival and the occurrence of cardiovascular events (CVS) after stroke [13]. AKI is a common complication of acute IS, accounting for 12.9-62.5%, and is associated with high mortality [14-16]. AKI and CKD are interrelated; patients with CKD have a high risk of developing AKI after stroke; AKI exacerbates the ongoing progression of CKD [13].

CKD worsens the course and outcome of stroke, and restricts the use of medications due to reduced drug clearance, a greater predisposition to bleeding, and, consequently, more side effects [17]. Patients with stage 3-5 CKD have a poorer prognosis, greater neurological deficits, and poor functional outcomes after stroke. CKD affects the choice of treatment and the secondary prevention of stroke [18]. The management of such patients is complicated by the lack of sufficient evidence to support the efficacy and safety of treatment at different stages of CKD due to their exclusion from clinical trials for safety reasons [19].

The combination of CKD and stroke has significant socio-economic consequences. The costs of managing patients with stroke and CKD is 5 times higher than the mean costs for participants in the United States Health Insurance Program (Medicare FFS) [2].

Thus, understanding the mechanisms of stroke pathogenesis in the progression of CKD is crucial for treating these patients and for stroke prevention.

The relationship between the kidneys and the brain

The relationship between the kidneys and the brain is bidirectional: there is a two-way correlation between stroke and kidney disease, since kidney dysfunction (KD) is observed in 40% of IS survivors, and the RS increases by 43% in stage 3 or more severe CKD compared to the general population [1, 11, 20]. CKD is diagnosed much more frequently in acute

stroke survivors and ranges from 20 to 40% in patients with acute IS and from 20 to 46% in patients with acute intracerebral hemorrhage [18].

The brain and kidneys share similar anatomical features: both organs have high blood flow rates and local autoregulation. The kidney consumes twice as much oxygen as the brain does, and receives ~20% of the cardiac output [6]. The brain has the system of a low vascular resistance (with local autoregulation) that provides continuous high-volume blood flow, making it vulnerable to microvascular damage caused by systemic hypertension. The blood vessels of the brain and kidneys are susceptible to damage due to high blood pressure (BP), as they have similar anatomical features [1].

CKD and brain damage have similar risk factors (RFs) (aging, diabetes, hypertension, and smoking) [8]. Atherosclerosis and vascular factors affect renal and cerebral function by ischemia, endothelial dysfunction, and blood-brain barrier (BBB) [21]. In addition to traditional and non-traditional CVD RFs, CKD is a predictor of thickening of the intima-media complex of the carotid arteries, progression of subclinical atherosclerosis, and increase in fatal and non-fatal CVEs. Patients with CKD have a significantly higher percentage of total calcification, the instability and destruction of atherosclerotic plaque [6].

CKD impairs brain autoregulation, affecting blood vessels and cerebral blood flow, which increases the RS [22]. Meanwhile, cerebrovascular diseases can induce KD, since the kidney activity is regulated by the brain through neural connections. The central pathway of brain-kidney interaction can pass through the central nervous system (CNS) and sympathetic nervous system (SNS). Peripheral signaling pathways of cross-organ interaction can be regulated by inflammatory responses, autoregulation, the neuroendocrine system, and extracellular vesicles. Stroke-induced activation of the hypothalamic-pituitary-adrenal

axis, CNS, and renin-angiotensin-aldosterone system (RAAS) can alter the release of hormones and neurotransmitters, thereby causing a KD. Inflammatory and immune responses mediate the KD after stroke. The release of inflammatory mediators by damaged brain cells can increase systemic inflammation [11].

Accelerated arteriosclerosis disrupts the cerebral blood flow autoregulation. This causes damage to the microvessels as a result of the transmission of central aortic pressure to the cerebral capillaries. Endothelial dysfunction (ED) and arteriosclerosis are deteriorated by water and sodium retention, uremic toxins, electrolyte imbalance, and hyperparathyroidism [2, 23].

Due to their similar structure, the glomerular barrier and BBB are affected by inflammatory mediators, hypoperfusion, and ischemia. BBB permeability in CKD has not been well described [6]. BBB is of paramount importance, protecting the stability of the central nervous system from fluctuations in blood composition. The BBB consists of closely related cerebral endothelial cells, astrocytes, and other components and controls the transport of various proteins and nutrients between the central nervous system and the blood. The condition of vascular endothelium affects the brain oxygenation, metabolite transport, interstitial fluid balance, and fluid clearance. ED is a cofactor of damaging processes for the brain and kidneys. RAAS should also be considered as a cofactor of degenerative changes both in CKD and small vessel diseases, since it affects the regulation of blood pressure, vasoconstriction, thrombosis, and vascular wall damage. An impaired brain perfusion in CKD has a multifactorial structure, potentially due to systemic vascular diseases and insufficient vascular reactivity. Even at an early stage of CKD, the oxidative stress and inflammation lead to the vulnerability of blood vessels and endothelium, which, in turn, threatens

the BBB integrity and facilitates the penetration of leukocytes and uremic toxins into the central nervous system [17, 11]. Models of acute kidney injury and CKD in animals showed a loss of BBB integrity against the background of uremia, which was confirmed by the results of contrast-enhanced brain magnetic resonance imaging. In this way, the development of BBB dysfunction in patients with CKD has been shown. When the BBB integrity is disrupted, there is an increase in the permeability for fluid, proteins, and other plasma components to perivascular tissues, which causes interstitial edema, thickening of the arteriole walls, disrupting further vasodilation, oxygen and nutrient transport. Fibrinogen, having overcome the BBB, is broken down to fibrin, which activates microglia and attracts peripheral macrophages, causing inflammation. Fibrinogen blocks the maturation of oligodendrocyte progenitor cells, inhibiting myelin maintenance and repair [24]. The "neurodegenerative" hypothesis suggests that the development of brain vascular dysfunction in CKD is associated with the accumulation of uremic toxins, impaired BBB integrity, an imbalance of neurotransmitters, and altered drug pharmacokinetics [3].

Chronic kidney disease: pathophysiology of stroke

Risk factors, atherosclerosis, cardiovascular diseases and uremic toxins

The occurrence of cerebrovascular disorders in CKD may be associated with the presence of traditional and non-traditional CVD RFs. The most common RFs of stroke development in CKD patients include an advanced age, prior history of CVD, arterial hypertension (AH), diabetes mellitus (DM), atrial fibrillation (AF), Smoking, obesity and a sedentary lifestyle, as well as the male gender, the left ventricle (LV) hypertrophy on the electrocardiogram, concomitant CVDs and the eGFR

lower than 60 ml/min/1.73 m^2 [3, 8]. AF is the RF of stroke which prevalence in CKD makes 3.5%-27%. AF and CKD in combination increase the RS up to 5 times [2].

CKD is often associated with hypertension and high atrial pressure, as well as with RAAS activation. Angiotensin II may contribute to atrial fibrosis, increase atrial pressure, and modulate ion channels that are involved in structural and electrophysiological atrial remodeling. In CKD, as in the general population, RS increases with high systolic blood pressure, but with reduced eGFR, there is a greater RS with a systolic blood pressure of less than 120 mm Hg. Mortality in stroke patients doubles with a 20 mmHg increase in blood pressure [25]. The presence of resistant or uncontrolled hypertension correlates with higher RS in patients with renal failure [26].

A slight decrease in the renal function is manifested by some degree of peripheral and central neurological complications due to a gradual increase in oxidative stress, inflammation, hemodynamic and vasoregulatory disorders, and uremic toxins in humans and experimental models [27-30].

In CKD, atherosclerosis is one of the leading causes of stroke [31] and is characterized by an increased collagen content and arterial calcification, which leads to arterial stiffness [32]. ED and elevated interleukin-18 (IL) levels observed in CKD also contribute to vascular calcification and plaque formation in the coronary and cerebral arteries [33-34]. Impaired hemodynamics due to plaque formation and a thromboembolic mechanism due to a malfunction in the coagulation factor system provoke the stroke development.

Uremia predisposes the brain to hypoxia, reduces metabolic activity, and causes dysregulation of excitatory and inhibitory neurotransmitters [35]. Phosphate, indoxyl sulfate, and the soluble receptor of glycation

end-products are toxic for endothelial cells. In CKD, changes in the structure and function of the gut microbiota are observed. Urea and other metabolic products diffuse into the intestinal lumen and cause changes in the microbiota, which leads to the formation of proteolytic waste products, such as indoxyl sulfate, p-cresyl sulfate, indole-3-acetic acid, N-oxide trimethylamine, and other uremic toxins of intestinal origin. Toxins increase oxidative stress, cause ED by synthesizing nitric oxide (NO), which can further cause the development of atherosclerosis and platelet dysfunction, potentiating their aggregation. Increased production of intestinal toxins is even more likely to cause uremia. These substances can activate the immune system of the intestinal mucosa and, by disrupting the permeability, move bacterial products into the blood, thereby causing the formation of inflammatory factors, the development of fibrosis and apoptosis.

Secondary hyperparathyroidism disrupts neurotransmission by increasing the level of calcium in the brain. Anemia and malnutrition in CKD interfere with the delivery of oxygen to the brain, affecting brain metabolism. Deficiency of erythropoietin (EP), which is produced in the kidneys, is another predominant cause of anemia in CKD [36]. EP production has the anti-stroke neuronal protection, which is reduced in CKD [37]. In patients with ESRD, dialysis leads to a cognitive dysfunction due to a high blood pressure variability, causing brain hypoperfusion, microembolism, edema, or accumulation of cerebral hemosiderin

Chronic inflammation

Chronic inflammation (CInf) and oxidative stress are associated with the CKD progression. CInf is present in patients at all stages of CKD [38]. Markers of oxidative stress: mitochondrial superoxide, oxidized

low-density lipoproteins (LDLs), homocysteine, superoxide dismutase, and glutathione are involved in the CKD progression [39]. Elevated levels of proinflammatory markers: IL-6, tumor necrosis factor-α (TNF-α), osteoprotegerin, osteocalcin, osteopontin, and fibroblast growth factor 23 were recorded in blood even in patients with stage 2 CKD [40]. Elevated levels of fibrinogen, IL-6, and TNF-α and decreased albumin in CKD patients are independently associated with the CKD progression [41]. Patients on hemodialysis (HD) had higher mortality if the levels of circulating proinflammatory cytokines (IL-1, IL-6, and TNF-α) were higher than those of proinflammatory cytokines (IL-2, IL-4, IL-5, IL-12, the complement system, and T-cell count) [42]. In addition, C-reactive protein is a predictor of stroke and death in dialysis patients.

Phosphorus-calcium metabolism disorder

In patients with KD or kidney damage, the impairment of phosphorus homeostasis leads to a decreased phosphorus excretion and causes hyperphosphatemia [43]. Hyperphosphatemia is a risk factor for cerebrovascular events associated with CKD [44]. The phosphate excretion regulation is the most important role of the kidneys in maintaining the phosphate balance. M. Tonelli et al. [45] presented the data that indicate a direct relationship between increased serum phosphate levels and the incidence of stroke in dialysis and non-dialysis patients. Hyperphosphatemia increases the risk of cerebral hemorrhage, while a decrease in serum phosphate levels leads to brain infarctions in patients on HD [46].

The acid-base balance disturbance

In renal failure, a shift towards metabolic acidosis has a negative effect on the brain function [47]. L. S. Johnson et al. [48] showed a

significant correlation between an increase in serum potassium levels and an increase in RS (ischemic and hemorrhagic) and mortality. The increased RS was also seen in hyponatremia [49]. In addition, hyponatremia affects the outcome of IS and HS. Other mechanisms in stroke pathogenesis in CKD, such as homocysteinemia, albuminuria, hyperlipidemia, hyperglycemia, disorders in the neuroendocrine system and intestinal microbiota, etc. are also under discussion [50].

Hemostasis system disturbance

In CKD, there are congenital platelet abnormalities, an altered response to antiplatelet drugs, and an abnormal endothelial function, which lead to a decreased regulation of the platelet activation, as well as to a disturbed platelet interaction with the vascular wall. Nephrogenic anemia also deteriorates the platelet dysfunction. Reduced glycoprotein Ib (GPIb) in the platelets of uremic patients contributes to impaired binding to von Willebrand factor and fibrinogen-activated platelets, thereby affecting primary hemostasis. In response to ED, the elevated levels of von Willebrand factor, thromboxane A2, and a decreased prostaglandin I2 production trigger platelet aggregation [51]. Hemodynamic dysfunction in CKD contributes to hypercoagulation due to impaired platelet hemostasis. Elevated IL-6 and C-reactive protein levels in CKD provoke an inflammatory cascade and activate blood clotting mediators such as fibrinogen, von Willebrand factor, and factor VIII, thereby disrupting the normal blood clotting process [52].

Epidemiology of stroke in various stages of chronic kidney disease and treatment of end-stage renal failure

Predialysis stages of chronic kidney disease

Mild CKD causes various pathogenic mechanisms, such as inflammation, oxidative stress, neurohormonal imbalance, the formation of uremic toxins, and vascular calcification, which damage the endothelium and blood vessels. Among patients with earlier-stage CKD, the brain alterations, including the white matter disease and brain atrophy, the asymptomatic infarcts are more common than in the general population [3]. A mild KD may increase the risk of IS or transient ischemic attack [53]. Lacunar infarction is a predictor of stroke. As the CKD stage progresses, the incidence of lacunar infarction increases. A decrease in GFR of lower than 60 ml/min/1.73m^2 independently correlates with high RS and poor long-term outcomes [54]. In addition, a decrease in GFR by every 10 ml/min/1.73^{m2} increases the RS by 7% and an increase in albuminuria by every 25 mg/mmol increases the RS by 10%. Thus, the RS increases with increasing the CKD stage.

At early stages of CKD, there is a linear relationship between BP and RS. A meta-analysis including data from 33 studies reported 43% independent RS with the eGFR of no more than 60 ml/min/1.73m^2 [55]. Meanwhile, the presence of proteinuria without an eGFR reduction is an important risk factor for stroke, but the effect of interventions to reduce proteinuria on the stroke incidence is unknown. AF as a stroke risk factor makes 16% in patients with eGFR of at least 45 ml/ min/1.73m^2 and 20.4% in patients with eGFR of no more than 45 ml/ min/1.73m^2 [56].

According to a large-scale multicenter study, proteinuria or low eGFR is present in 35% of patients with the first stroke [12]. Patients with proteinuria have a 71% higher risk of stroke compared to patients without

it, since proteinuria is closely associated with hypertension and other cardiovascular risk factors [57].

Stroke while on dialysis therapy

Traditionally, patients with advanced renal failure are excluded from randomized controlled trials evaluating the impact of medical interventions on the stroke occurrence. Despite the brain hyperperfusion at rest, ESRD is associated with a reduced oxygen delivery to the brain due to anemia. HD can increase the RS. Cerebral oxygenation is further reduced during HD due to a decreased regulation of cerebral blood flow, which leads to cerebral ischemia or "stunning" of the brain. Patients on HD have an impaired autonomic function, as evidenced by lower values of their sensitivity to baroreflexes compared to the general population [58].

HD is the main method of replacement therapy for ESRD, which causes sudden and rapid fluctuations in blood pressure, osmolality, and acid-base balance, which together cause "stress" of the brain vascular network. The RS is 10 times higher in patients receiving renal replacement therapy compared to the general population. At the start of dialysis, the stroke patients had poor results, higher all-cause mortality, and lower survival rates than the non-dialysis patients. Stroke is one of the leading causes of death in dialysis patients [7-8].

Sudden hemodynamic changes, high blood pressure variability, dialysate and anticoagulants, vascular access, dialysis amyloidosis, vascular calcification, and years being on dialysis can cause either IS or HS. The IS is more common during the start of dialysis, and its incidence increases during further follow-up. An analysis of 21,000 dialysis patients in the United States found that stroke rates reached their peak within the first 30 days after starting dialysis [59]. In the Japanese cohort, IS (39%)

and HS (35%) occurred during or 30 minutes after the onset of HD [8]. In their study H.H. Wang et al. [60] showed that HS developed more frequently during peritoneal dialysis. Thus, the onset of dialysis represents the period of the greatest RS. The risk factors of stroke in dialysis patients include the vascular risk factors that develop during dialysis, the vascular risk factors that precede dialysis and develop during the course of CKD [7]. About 90% of HD patients die from stroke. As noted earlier, in patients with HD, the level of proinflammatory cytokines and CRP correlates with RS and death. MR in HD patients after acute IS is 3 times higher. Most of the data on stroke in dialysis patients were from the United States and Japan. In the European study, it was HS that prevailed among patients [8].

The majority of patients on HD are older, and they are more likely to have CVD RFs or concomitant CVD (hypertension, DM, congestive heart failure, LV hypertrophy, AF, peripheral vascular diseases, and lung diseases), which makes them predisposed to IS and HS compared to the general population. The AF prevalence in dialysis patients ranges from 3.5% to 27% [61]. Mortality was high at the hospital admission stage, at 30 days, and at one year after the stroke. In dialysis patients, IS prevails, accounting for about 70%, and has poor short- and long-term prognoses [62].

Nosocomial mortality increases, especially when eGFR is less than 45 ml/min/1.73 м^2 in patients with IS, but no relationship was found to the increase of nosocomial symptomatic intracranial hemorrhage and eGFR. In a Medicare study in patients over 65 years of age with acute IS, a low eGFR and the dialysis status at admission were independent predictors of adverse outcomes with a high risk of a 30-day and 1-year mortality, and rehospitalization [63]. The low level of eGFR at admission (lower than 15 ml/min/1.73 m^2) increased the risk of short-term (1 month)

mortality by 3 times, and that of a long-term (1 year) mortality rate by 4 times compared to the patients with the eGFR of at least 90 ml/min/1.73 m^2 or in the dialysis population [64]. Other studies reported that proteinuria, but not a low eGFR, was an independent predictor of a high risk of neurological deterioration, disability, and death [65].

Stroke after kidney transplantation

Kidney transplantation (KT) is the preferred treatment for ESRD patients and increases their survival rate. KT provides cardiovascular protection. The life expectancy of patients after KT has increased significantly in recent decades thanks to improved patient care, new immunosuppressive strategies, and post-transplant monitoring. The lower mortality rate among the patient undergoing KT compared to those on the waiting list for transplantation has been associated with CVE regress, but compared to the general population, they are at a higher MR and a CVD risk. KT reduced the risk of stroke by 63% compared to the subgroup of patients with ESRD. The incidence of stroke after KT has not been sufficiently studied [8]. There are insufficient data on cerebrovascular outcomes in patients who underwent KT. Although stroke is less common in people with KT, the mortality rate remains high. In Western countries, the stroke prevalence varies from 3.9 to 7.9%. According to S.T. Huang et al. [65], in the Asian population, the overall cumulative incidence of IS was 1.5%, which was significantly less than in the western cohort. This is partly due to the fact that the western cohort consisted of older patients with comorbidities. The prognostic factors for the development of HS were old age, diabetes mellitus, and peripheral vascular diseases [8, 65, 66]. HS was registered in 36.84% of patients after KT. MR and CVEs in patients undergoing KT were 6.4% higher than in the general population. KT reduces dyslipidemia, improving the endothelial function that is kept

for about 2 years after transplantation; by reducing LV mass index, the fibroblast growth factor leads to a decrease in mortality. S.M.H. Yeung et al. [67] followed-up the patients after KT over a 12.7-year period and noted a high MR in those on long-term dialysis (mortality was 37.7%). The correlation of NT-proBNP level with all-cause mortality was identified. In a retrospective cohort study of 17,628 subjects who underwent KT, the stroke-related mortality was found in 156 cases in people aged 30-49 years, more often females. A high MR from stroke was associated with an advanced age during transplantation, a graft failure, and pre-existing cerebrovascular diseases [68]. Further studies are needed to provide a better risk stratification and facilitate clinical trials to reduce the risk of stroke before and after KT. Thus, the risk of stroke after KT can be reduced by restoring kidney function.

Treatment

Kidney diseases complicate the treatment and secondary prevention of stroke. Insufficient number of clinical trials has been conducted in patients with CKD to study the effects of certain treatments and this is a subject of discussion [2, 19].

For individuals with CKD without dialysis, the stroke prevention, approaches to diagnosis and treatment of stroke are similar to those in general population without CKD. The method of both primary and secondary prevention of stroke is to reduce blood pressure. However, the targeted BP values for stroke prevention in CKD patients remain being discussed [8, 69]. The impact of intensive BP reduction in terms of protection or harm remains controversial [70]. The intensity of BP reduction in CKD and stroke has been discussed in several studies (SPS3, SPRINT, CSPPT). In accordance with the data obtained, the latest guidelines of the ESC/ESH (2018) and the Russian Society of Cardiology

(2020) recommend reducing the systolic blood pressure to lower than 130 mm Hg and the diastolic blood pressure to 70-79 mm Hg (but the systolic blood pressure should not be lower than 120 mm Hg). Overall, these BP targets seem reasonable for both primary and secondary prevention of stroke in patients with CKD. RAAS blockers can both reduce the risk of CVEs, and also delay the progression of CKD [69]. However, the treatment should be adjusted according to its effect on the renal function and electrolytes, especially in patients with advanced CKD [71]. RAAS blockers are clearly useful for the secondary prevention of stroke in CKD [72]. The PROGRESS (Perindopril Protection against Recurrent Stroke) study showed a 35% reduction in the risk of recurrent stroke in patients with kidney disease with a history of cerebrovascular pathology [73].

Lowering lipids with statins effectively reduces RS in patients with stage 3-4 CKD. Current data do not support the lipid reduction in the dialysis patients with inflammation and/or malnutrition, or in the dialysis patients who have not previously received treatment. Target LDL levels for cerebrovascular protection in patients with CKD deserve further investigation [8, 74]. KDIGO recommends statin treatment for patients with CKD over 50 years of age without any individual risk calculation [75].

Patients with CKD have an increased risk of both thromboembolic complications and bleeding, which limits the possibilities of pharmacotherapy. The use of antiplatelet drugs (APDs) as a secondary measure for the prevention of IS in patients with CKD has not gained convincing evidence. For patients with CKD, the balance of benefits and risks of using APDs remains unclear. The American Heart Association recommends aspirin for primary prevention of stroke in patients with CKD with eGFR 30-45 ml/min/1.73 m^2 [76]. An open multicenter ATTACK trial is ongoing to investigate the effect of 75 mg of aspirin on

reducing the risk of CVEs in patients with CKD [77]. Dual antiplatelet therapy for patients with CKD is probably ineffective. They have a high incidence of stroke recurrence. In patients with CKD, the antiplatelet effect of clopidogrel is reduced. In the CHARISMA study, patients with diabetes and CKD treated with clopidogrel experienced a high incidence of cardiovascular and general mortality [78]. Ticagrelor and prasugrel were more effective APDs compared to clopidogrel for patients with CKD.

Continuous anticoagulant therapy is recommended for the prevention of stroke and thromboembolic complications in patients with nonvalvular AF. Traditional recommendations for anticoagulation with warfarin or new oral anticoagulants (NOACs) for the prevention of thromboembolic stroke in severe CKD or dialysis patients with AF cannot be applied. Direct oral anticoagulants and warfarin are preferred in stage 1-3 CKD, while in stage 4 the choice depends on the pharmacokinetics of the drug and the patient's characteristics [79]. In patients with ESRD and AF, warfarin increases the risk of stroke, especially during the first 30-90 days after the start of treatment [80], due to accelerated vascular calcification that occurs as a result of antagonism of vitamin K. To prevent the risk of bleeding, the warfarin dose reduction is required by 10% in patients with eGFR 30–59 ml/min/1.73 m^2 and by 19% in patients with eGFR less than 30 ml/min/1.73 m^2 in order to maintain the international normalized ratio (INR) of no more than 4 [81]. In some patients, due to excessive hypocoagulation caused induced by warfarin, the CKD progression is accelerated and warfarin-associated nephropathy develops, which is defined as an increase in creatinine levels of more than 26.5 mmol/L detected within a week after an INR increase of more than 3 without obvious signs of bleeding [82].

NOACs are predominantly excreted by the kidneys (80% for dabigatran, 35% for rivaroxaban, and 27% for apixaban), resulting in a greater risk of bleeding associated with a long half-life of the drug. The use of these drugs during dialysis and in patients with eGFR lower than 15 ml/min/1.73 m^2 should be limited [83]. Dosage recommendations for patients with renal failure vary depending on the NOAC. The efficacy and safety of apixaban, rivaroxaban, edoxaban, or dabigatran in patients with mild to moderate CKD compared to patients without CKD has been demonstrated. Rivaroxaban, apixaban, and edoxaban (but not dabigatran) are approved in Europe for use in patients with severe CKD (stage 4, eGFR 15-29 ml/min/1.73 m^2) [84]. In the United States, apixaban is approved for the treatment of chronic stable dialysis patients.

Heparin is safe in non-dialysis patients; for dialysis patients, the dose needs to be adjusted [79]. Enoxaparin is the most commonly used of the low-molecular-weight heparins and is recommended for severe CKD (1 mg/kg once daily). There are no data on dalteparin and tinzaparin in severe CKD, so it is preferable to avoid their use [85]. Although fondaparinux is preferred in cases of heparin-induced thrombocytopenia, it is not recommended in severe CKD.

An acute stroke therapy, including intravenous thrombolysis and intra-arterial interventions, such as mechanical thrombectomy, may be considered as a stroke treatment option in patients with CKD [86]. CKD is a significant predictor of poorer functional outcome and mortality in stroke patients who have received endovascular thrombectomy, but the presence of CKD should not prevent the implementation of this treatment method. Using thrombolysis with tissue plasminogen activator (tPA) is problematic for patients with CKD [8]. Thrombolysis causes a number of subclinical manifestations, such as transient infarctions, lacunar infarctions, and microbleeds, and is associated with high nosocomial

mortality and adverse outcomes [87]. The American Heart Association/American Stroke Association 2018 Guidelines for the early management of patients with acute IS indicate that patients with ESRD who are on HD and with normal activated partial thromboplastin time (APTT) are recommended to receive intravenous alteplase (Class I; evidence level C-LD), but in increased APTT, the risk of hemorrhagic complications increases.

Z.Z. Rao et al. [88] conducted a cohort study involving 18,320 patients with IS who received tPA drugs; the study results showed the relationship of eGFR with hospital mortality (mortality was 4% at eGFR lower than 45 ml/min/1.73 m^2 , and 0.9% at eGFR 45-59 ml/min/1.73 m^2) and no statistically significant differences in the development of intracerebral hemorrhage.

Thus, the stroke management and prevention in patients with CKD is a complex task that requires a multidisciplinary approach. No stroke treatment methods have been developed for ESRD patients yet, which requires clinical and research priority for them. Studying the pathophysiological basis of stroke in CKD will allow us to develop new treatment methods.

Conclusion

Chronic kidney disease is recognized as a high risk factor for stroke. Chronic kidney disease is included in the QRISK3 model for predicting the risk of cardiovascular disease and stroke. The risk of cardiovascular disease and a cardiovascular event increases in dialysis-dependent patients. Kidney transplantation reduces the risk of stroke by normalizing the kidney function. Chronic kidney disease and stroke are excluded from clinical trials, and there are no guidelines for the management and treatment of stroke. Management and treatment of patients with chronic

kidney disease and stroke is a complex task and requires an interdisciplinary collaboration. Patients with end-stage renal disease should have clinical and research priorities. Studying the pathophysiological mechanisms of stroke development at various stages of chronic kidney disease will allow us to choose the right prevention tactics and develop new treatment methods.

References

1. Silvani A, Calandra-Buonaura G, Dampney RAL, Cortelli P. Brain-heart interactions: physiology and clinical implications. *Philos Trans A Math Phys Eng Sci.* 2016;374(2067):20150181. PMID: 27044998 https://doi.org/10.1098/rsta.2015.0181

2. Dad T, Weiner DE. Stroke and chronic kidney disease: epidemio-logy, pathogenesis, and management across kidney disease stages. *Semin Nephrol.* 2015;35(4):311–322. PMID: 26355250 https://doi.org/10.1016/j.semnephrol.2015.06.003

3. Miglinas M, Cesniene U, Janusaite MM, Vinikovas A. cerebrovascular disease and cognition in chronic kidney disease patients front. *Cardiovasc Med.* 2020;7:96. PMID: 32582768 https://doi.org/10.3389/fcvm.2020.00096 eCollection 2020

4. Naganuma T, Takemoto Y. New aspects of cerebrovascular diseases in dialysis patients. *Contrib Nephrol.* 2015;185:138–146. PMID: 26023023 https://doi.org/10.1159/000380978

5. *2006 Annual data report: atlas of chronic kidney disease & end-stage renal disease in the United States.* United States renal data system. Orlando (FL): Elsevier; 2007.

6. Lau WL, Huisa BN, Fisher M. The Cerebrovascular-Chronic Kidney Disease Connection: Perspectives and Mechanisms. *Transl Stroke*

Res. 2017;8(1):67–76. PMID: 27628245 https://doi.org/10.1007/s12975-016-0499-x

7. Khrulev AE, Monashova EA, Shestakova NA, Paramonova YuA, Grigorieva VN. Stroke in dialysis patients. *Neurology bulletin.* 2019;51(4):59–65. (In Russ.).

8. Nayak-Rao S, Shenoy MP. Stroke in patients with chronic kidney disease…: How do we approach and manage it? *Indian J Nephrol.* 2017;27(3):167-171. PMID: 28553032 https://doi.org/10.4103/0971-4065.202405

9. Mahmoodi BK, Yatsuya H, Matsushita K, Sang Y, Gottesman RF, Astor BC, et al. Association of kidney disease measures with ischemic versus hemorrhagic strokes: pooled analyses of 4 prospective community-based cohorts. *Stroke.* 2014;45(7):1925–1931. PMID: 24876078 https://doi.org/10.1161/STROKEAHA.114.004900

10. Sarnak MJ, Amann K, Bangalore S, Cavalcante JL, Charytan DM, Craig JC, et al. Chronic kidney disease and coronary artery disease: JACC State-of-the-art review. *J Am Coll Cardiol.* 2019;74(14):1823–1838. PMID: 31582143 https://doi.org/10.1016/j.jacc.2019.08.1017

11. Shah B, Jagtap P, Sarmah D, Datta A, Raut S, Sarkar A, et al. Cerebrorenal interaction and stroke. *Eur J Neurosci.* 2021;53(4):1279–1299. PMID: 32979852 https://doi.org/10.1111/ejn.14983

12. Kumai Y, Kamouchi M, Hata J, Ago T, Kitayama J, Nakane H, et al. Proteinuria and clinical outcomes after ischemic stroke. *Neurology.* 2012;78(24):1909-1915. PMID: 22592359 https://doi.org/10.1212/WNL.0b013e318259e110

13. Arnold J, Ng KP, Sims D, Gill P, Cockwell P, Ferro C. Incidence and impact on outcomes of acute kidney injury after a stroke: a systematic review and meta-analysis. *BMC Nephrol.* 2018;19(1):283. PMID: 30348107 https://doi.org/10.1186/s12882-018-1085-0

14. Balch MHH, Nimjee SM, Rink C, Hannawi Y. Beyond the brain: the systemic pathophysiological response to acute ischemic stroke. *J Stroke.* 2020;22(2):159–172. PMID: 32635682 https://doi.org/10.5853/jos.2019.02978

15. Olguín-Ramírez LA, Martínez HR, Gongora-Rivera F, Maya-Quintá R, Celis Jasso JS. Acute kidney injury in acute stroke. A preliminary study in Hispanic population. *Neurology.* 2017;88(16 Suppl): Abstr AAN 69th Annual Meeting, Boston, 27 April. (P5.041).

16. Tsagalis G, Akrivos T, Alevizaki M, Manios E, Theodorakis M, Laggouranis A, et al. Long-term prognosis of acute kidney injury after first acute stroke. *Clin J Am Soc Nephrol.* 2009;4(3):616–622. PMID: 19211666 https://doi.org/10.2215/CJN.04110808

17. Gadalean F, Simu M, Parv F, Vorovenci R, Tudor R, Schiller A, et al. The impact of acute kidney injury on in-hospital mortality in acute ischemic stroke patients undergoing intravenous thrombolysis. *PLOS One.* 2017;12(10):e0185589. PMID: 29040276 https://doi.org/10.1371/journal.pone.0185589 eCollection 2017.

18. Chelluboina B, Vemuganti R. Chronic kidney disease in the pathogenesis of acute ischemic stroke. *J Cereb Blood Flow Metab.* 2019;39(10):1893–1905. PMID: 31366298 https://doi.org/10.1177/0271678X19866733

19. Kelly D, Rothwell PM. Disentangling the multiple links between renal dysfunction and cerebrovascular disease *J Neurol*

Neurosurg Psychiatry. 2020;91(1):88–97. PMID: 31511306 https://doi.org/10.1136/jnnp-2019-320526

20. Ishida JH, Johansen KL. Exclusion of patients with kidney disease from cardiovascular trials. *JAMA Intern Med.* 2016;176(1):124–125. PMID: 26618994 https://doi.org/10.1001/jamainternmed.2015.6403

21. Toyoda K, (ed.) *Brain, Stroke and Kidney.* Switzerland: Karger Med Sci Publ; 2013. https://doi.org/10.1159/isbn.978-3-318-02352-7

22. Ghoshal S, Freedman BI. Freedman mechanisms of stroke in patients with chronic kidney disease. *Am J Nephrol.* 2019;50(4):229–239. PMID: 31461699 https://doi.org/10.1159/000502446

23. Sprick JD, Nocera JR, Hajjar I, O'Neill WC, Bailey J, Park J. Cerebral blood flow regulation in end-stage kidney disease. *Am J Physiol Renal Physiol.* 2020;319(5):F782 F791. PMID: 32985235 https://doi.org/10.1152/ajprenal.00438.2020

24. Wardlaw JM, Smith C, Dichgans M. Small vessel disease: mechanisms and clinical implications. *Lancet Neurol.* 2019;18(7):684–696. PMID: 31097385 https://doi.org/10.1016/S1474-4422(19)30079-1

25. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Prospective studies collaboration age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet.* 2002;360(9349):1903–1903. PMID: 12493255 https://doi.org/10.1016/s0140-6736(02)11911-8

26. Shemetova VG, Orlova GM, Nebesnykh AL, Markhanova ES. Chronic kidney disease and cerebrocardiovascular

complications in arterial hypertension: results of perindopril A usage with indapamid. *Russian Journal of Cardiology.* 2014;(8):38–42. (In Russ.). https://doi.org/10.15829/1560-4071-2014-8-38-42

27. Jabbari B, Vaziri ND. The nature, consequences, and management of neurological disorders in chronic kidney disease. *Hemodial Int.* 2018;22(2):150–160. PMID: 28799704 https://doi.org/10.1111/hdi.12587

28. Kolachalama VB, Shashar M, Alousi F, Shivanna S, Rijal K, Belghasem ME, et al. Uremic solute-aryl hydrocarbon receptor-tissue factor axis associates with thrombosis after vascular injury in humans. *J Am Soc Nephrol.* 2018;29(3):1063–1072. PMID: 29343519 https://doi.org/10.1681/ASN.2017080929

29. Jing W, Jabbari B, Vaziri ND. Uremia induces upregulation of cerebral tissue oxidative/inflammatory cascade, down-regulation of Nrf2 pathway and disruption of blood brain barrier. *Am J Transl Res.* 2018;10(7):2137–2147. PMID: 30093950 eCollection 2018.

30. Assem M, Lando M, Grissi M, Kamel S, Massy ZA, Chillon JM, et al. The impact of uremic toxins on cerebrovascular and cognitive disorders. *Toxins (Basel).* 2018;10(7):303. PMID: 30037144 https://doi.org/10.3390/toxins10070303

31. Chue CD, Townend JN, Steeds RP, Ferro CJ. Republished paper: arterial stiffness in chronic kidney disease: causes and consequences. *Postgrad Med J.* 2010;86(1019):560–566. PMID: 20841331 https://doi.org/10.1136/pgmj.2009.184879rep

32. Derdeyn CP. Mechanisms of ischemic stroke secondary to large artery atherosclerotic disease. *Neuroimaging Clin N Am.* 2007;17(3):303–311. PMID: 17826633 https://doi.org/10.1016/j.nic.2007.03.001

33. Formanowicz D, Wanic-Kossowska M, Pawliczak E, Radom M, Formanowicz P. Usefulness of serum interleukin-18 in predicting

cardiovascular mortality in patients with chronic kidney disease–systems and clinical approach. *Sci Rep.* 2015;5:18332. PMID: 26669254 https://doi.org/10.1038/srep18332

34. Kiu Weber CI, Duchateau-Nguyen G, Solier C, Schell-Steven A, Hermosilla R, Nogoceke E, et al. Cardiovascular risk markers associated with arterial calcification in patients with chronic kidney disease Stages 3 and 4. *Clin Kidhey J.* 2014;7(2):167-173. PMID: 24683472 https://doi.org/10.1093/ckj/sfu017

35. Seifter JL, Samuels MA. Uremic encephalopathy and other brain disorders associated with renal failure. *Semin Neurol.* 2011;31(2):139–143. PMID: 21590619 https://doi.org/10.1055/s-0031-1277984

36. Babitt JL, Lin HY. Mechanisms of anemia in CKD. *J Am Soc Nephrol.* 2012;23(10):1631–1634. PMID: 22935483 https://doi.org/10.1681/ASN.2011111078

37. Abramson JL, Jurkovitz CT, Vaccarino V, Weintraub WS, Mcclellan W. Chronic kidney disease, anemia, and incident stroke in a middle-aged, community-based population: the ARIC Study. *Kidney Int.* 2003;64(2):610–615. PMID: 12846757 https://doi.org/10.1046/j.1523-1755.2003.00109.x

38. Akchurin M, Kaskel F. Update on inflammation in chronic kidney disease. *Blood Purif.* 2015;39(1–3):84–92. PMID: 25662331 https://doi.org/10.1159/000368940

39. Drożdż D, Kwinta P, Sztefko K, Kordon Z, Drożdż T, Łątka M, et al. Oxidative stress biomarkers and left ventricular hypertrophy in children with chronic kidney disease. *Oxid Med Cell Longev.* 2016;2016:7520231. PMID: 26885251 https://doi.org/10.1155/2016/7520231

40. Mihai S, Codrici E, Popescu ID, Enciu AM, Rusu E, Zilisteanu D, et al. Proteomic biomarkers panel: new insights in chronic kidney disease. *Dis Markers.* 2016;2016:3185232. PMID: 27667892 https://doi.org/10.1155/2016/3185232

41. Amdur RL, Feldman HI, Gupta J, Yang W, Kanetsky P, Shlipak M, et al. Inflammation and progression of CKD: the CRIC study. *Clin J Am Soc Nephrol.* 2016;11(9):1546–1556. PMID: 27340285 https://doi.org/10.2215/CJN.13121215

42. Cohen SD, Phillips TM, Khetpal P, Kimmel PL. Cytokine patterns and survival in haemodialysis patients. *Nephrol Dial Transplant.* 2010;25(4):1239–1243. PMID: 20007982 https://doi.org/10.1093/ndt/gfp625

43. Hruska KA, Mathew S, Lund R, Qiu P, Pratt R. Hyperphosphatemia of chronic kidney disease. *Kidney Int.* 2008;74(2):148–157. PMID: 18449174 https://doi.org/10.1038/ki.2008.130

44. Delmez JA, Slatopolsky E. Hyperphosphatemia: its consequences and treatment in patients with chronic renal disease. *Am J Kidney Dis.* 1992;19(4):303–317. PMID: 1562018 https://doi.org/10.1016/s0272-6386(12)80446-x

45. Tonelli M, Sacks F, Pfeffer M, Gao Z, Curhan G. Cholesterol and recurrent events trial investigators. Relation between serum phosphate level and cardiovascular event rate in people with coronary disease. *Circulation.* 2005;112(17):2627–2633. PMID: 16246962 https://doi.org/10.1161/CIRCULATIONAHA.105.553198

46. Yamada S, Tsuruya K, Taniguchi M, Tokumoto M, Fujisaki K, Hirakata H, et al. Association between serum phosphate levels and stroke risk in patients undergoing hemodialysis: the Q-cohort study. *Stroke.*

2016;47(9):2189–2196. PMID: 27507862 https://doi.org/10.1161/STROKEAHA.116.013195

47. Arnold R, Issar T, Krishnan AV, Pussell BA. Neurological complications in chronic kidney disease. *JRSM Cardiovasc Dis.* 2016;5:2048004016677687. PMID: 27867500 https://doi.org/10.1177/2048004016677687 eCollection 2016 Jan-Dec.

48. Johnson LS, Mattsson N, Sajadieh A, Wollmer P, Söderholm M. Serum potassium is positively associated with stroke and mortality in the large, population-based malmö preventive project cohort. Stroke. 2017;48(11):2973-2978. PMID: 28974633 https://doi.org/10.1161/STROKEAHA.117.018148

49. Zhang YZ, Qie JY, Zhang QH. Incidence and mortality prognosis of dysnatremias in neurologic critically ill patients. *Eur Neurol.* 2015;73(1–2):29–36. PMID: 25377050 https://doi.org/10.1159/000368353

50. Zhao Q, Yan T, Chopp M, Venkat P, Chen J. Brain–kidney interaction: renal dysfunction following ischemic stroke. *J Cereb Blood Flow Metab.* 2020;40(2):246–262. PMID: 31766979 https://doi.org/10.1177/0271678X19890931

51. Margetic S. Inflammation and hemostasis. *Biochem Med (Zagreb).* 2012;22(1):49–62. PMID: 22384519

52. Go AS, Chertow GM, Fan D, McCul-loch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med.* 2004;351(13):1296–1305. PMID: 15385656 https://doi.org/10.1056/NEJMoa041031

53. Masson P, Webster AC, Hong M, Turner R, Lindley RI, Craig JC. Chronic kidney disease and the risk of stroke: a systematic review and meta-analysis. *Nephrol Dial Transplant.*

2015;30(7):1162–1169. PMID: 25681099 https://doi.org/10.1093/ndt/gfv009

54. Kanamaru T, Suda S, Muraga K, Okubo S, Watanabe Y, Tsuruoka S, et al. Albuminuria predicts early neurological deterioration in patients with acute ischemic stroke. *J Neurol Sci.* 2017;372:417–420. PMID: 27836107 https://doi.org/10.1016/j.jns.2016.11.007

55. Lee M, Saver JL, Chang KH, Liao HW, Chang SC, Ovbiagele B. Low glomerular filtration rate and risk of stroke: Meta-analysis. *BMJ.* 2010;341:c4249. PMID: 20884696 https://doi.org/10.1136/bmj.c4249

56. Go AS, Fang MC, Udaltsova N, Chang Y, Pomernacki NK, Borowsky L, et al. Impact of proteinuria and glomerular filtration rate on risk of thromboembolism in atrial fibrillation: The anticoagulation and risk factors in atrial fibrillation (ATRIA) study. *Circulation.* 2009;119(10):1363–1369. PMID: 19255343 https://doi.org/10.1161/CIRCULATIONAHA.108.816082

57. Ninomiya T, Perkovic V, Verdon C, Barzi F, Cass A, Gallagher M, et al. Proteinuria and stroke: a meta-analysis of cohort studies. *Am J Kidney Dis.* 2009;53(3):417–425. PMID: 19070947 https://doi.org/10.1053/j.ajkd.2008.08.032

58. Lee DBN, Huang E, Ward HJ. Tight junction biology and kidney dysfunction. *Am J Physiol Renal Physiol.* 2006:290(1):F20–34. PMID: 16339962 https://doi.org/10.1152/ajprenal.00052.2005

59. Toyoda K, Fujii K, Fujimi S, Kumai Y, Tsuchimochi H, Ibayashi S, et al. Stroke in patients on maintenance hemodialysis: A 22-year single-center study. *Am J Kidney Dis.* 2005;45(6):1058–1066. PMID: 15957135 https://doi.org/10.1053/j.ajkd.2005.02.028

60. Wang HH, Hung SY, Sung JM, Hung KY, Wang JD. Risk of stroke in long-term dialysis patients compared with the general

population. *Am J Kidney Dis.* 2014;63(4):604–611. PMID: 24290244 https://doi.org/10.1053/j.ajkd.2013.10.013

61. Soliman EZ, Prineas RJ, Go AS, Xie D, Lash JP, Rahman M, et al. Chro-nic kidney disease and prevalent atrial fibrillation: the chronic renal insufficiency cohort (CRIC). *Am Heart J.* 2010;159(6):1102–1107. PMID: 20569726 https://doi.org/10.1016/j.ahj.2010.03.027

62. El Husseini N, Fonarow GC, Smith EE, Ju C, Sheng S, Schwamm LH, et al. Association of kidney function with 30-day and 1-year poststroke mortality and hospital readmission: get with the guidelines-stroke. *Stroke.* 2018;49(12):2896–2903. PMID: 30571413 https://doi.org/10.1161/STROKEAHA.118.022011

63. Wang IK, Liu CH, Yen TH, Jeng JS, Sung SF, Huang PH, et al. Renal function is associated with 1-month and 1-year mortality in patients with ischemic stroke. *Atherosclerosis.* 2018;269:288–293. PMID: 29254692 https://doi.org/10.1016/j.atherosclerosis.2017.11.029

64. Ovbiagele B, Sanossian N, Liebeskind DS, Kim D, Ali LK, Pineda S, et al. Indices of kidney dysfunction and discharge outcomes in hospitalized stroke patients without known renal disease. *Cerebrovasc Dis.* 2009;28(6):582–588. PMID: 19844098 https://doi.org/10.1159/000247602

65. Huang ST, Yu TM, Chuang YW, Chung MC, Wang CY, Fu PK, et al. The risk of stroke in kidney transplant recipients with end-stage kidney disease. *Int J Environ Res Public Health.* 2019 Jan 24;16(3):326. PMID: 30682846 https://doi.org/10.3390/ijerph16030326

66. Aull-Watschinger S, Konstantin H, Demetriou D, Schillinger M, Habicht A, Hörl WH, et al. Pre-transplant predictors

of cerebrovascular events after kidney transplantation. *Nephrol Dial Transplant.* 2008;23(4):1429–1435. PMID: 18045824 https://doi.org/10.1093/ndt/gfm766

67. Yeung SMH, van Londen M, Nakshbandi U, Said MY, Eisenga MF, Hepkema BG, et al. Mortality in kidney transplant recipients. *Transplantation.* 2020;104(10):2158–2165. PMID: 31978004 https://doi.org/10.1097/TP.0000000000003125

68. De La Mata NL, Kelly PJ, Wyld M, Masson P, Al-Shahi Salman R, Webster AC. Excess stroke deaths in kidney transplant recipients: a retrospective population-based cohort study using data linkage. *Transplantation.* 2020;104(10):2129–2138. PMID: 31895335 https://doi.org/10.1097/TP.0000000000003091

69. Der Mesropian PJ, Shaikh G, Cordero Torres E, Bilal A, Mathew RO. Antihypertensive therapy in nondiabetic chronic kidney disease: a review and update. *Am Soc Hypertens.* 2018;12(3):154–181. PMID: 29396103 https://doi.org/10.1016/j.jash.2018.01.005

70. Agarwal A, Cheung AK, Ma J, Cho M, Li M. Effect of baseline kidney function on the risk of recurrent stroke and on effects of intensive blood pressure control in patients with prior lacunar stroke: a post hoc analysis of the SPS3 trial (Secondary prevention of small subcortical strokes). *J Am Heart Assoc.* 2019;8(16):e013098. PMID: 31423869 https://doi.org/10.1161/JAHA.119.013098

71. Burgess LG, Goyal N, Jones GM, Khorchid Y, Kerro A, Chapple K, et al. Evaluation of acute kidney injury and mortality after intensive blood pressure control in patients with intracerebral hemorrhage. J Am Heart Assoc. 2018;7(8):e008439. PMID: 29654207 https://doi.org/10.1161/JAHA.117.008439

72. Weir MR, Lakkis JI, Jaar B, Rocco MV, Choi MJ, Kramer HJ, et al. Use of renin-angiotensin system blockade in advanced CKD: An

NKF-KDOQI controversies report. *Am J Kidney Dis.* 2018;72(6):873–884. PMID: 30201547 https://doi.org/10.1053/j.ajkd.2018.06.010

73. Perkovic V, Ninomiya T, Arima H, Gallagher M, Jardine M, Cass A, et al. Chronic kidney disease, cardiovascular events, and the effects of perindopril-based blood pressure lowering: data from the PROGRESS study. *J Am Soc Nephrol.* 2007;18(10):2766–2772. PMID: 17804673 https://doi.org/10.1681/ASN.2007020256

74. Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (study of heart and renal protection): a randomised placebo-controlled trial. *Lancet.* 2011;377(9784):2181–2192. PMID: 21663949 https://doi.org/10.1016/j.ymed.2011.08.055

75. Wanner C, Tonelli M. KDIGO Clinical practice guideline for lipid management in CKD: summary of recommendation statements and clinical approach to the patient. *Kidney Int.* 2014;85(6):1303–1309. PMID: 24552851 https://doi.org/10.1038/ki.2014.31

76. Gallagher H, Lown M, Fuat A, Roderick P. Aspirin for primary prevention of CVD in CKD: where do we stand? *Br J Gen Pract.* 2019;69(689):590–591. PMID: 31780468 https://doi.org/10.3399/bjgp19X706661

77. Aspirin to Target Arterial Events in Chronic Kidney Disease (ATTACK). Available at: https://www.journalslibrary.nihr.ac.uk/programmes/hta/1631127/#/ [Accessed May 25, 2021].

78. Dasgupta A, Steinhubl SR, Bhatt DL, Berger PB, Shao M, Mak KH, et al. CHARISMA Investigators. Clinical outcomes of

patients with diabetic nephropathy randomized to clopidogrel plus aspirin versus aspirin alone (a post hoc analysis of the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance [CHARISMA] trial). *Am J Cardiol.* 2009;103(10):1359–1363. PMID: 19427428 https://doi.org/10.1016/j.amjcard.2009.01.342

79. Aursulesei V, Costache II. Anticoagulation in chronic kidney disease: from guidelines to clinical practice. *Clin Cardiol.* 2019;42(8):774–782. PMID: 31102275 https://doi.org/10.1002/clc.23196

80. Chan KE, Lazarus JM, Thadhani R, Hakim RM. Warfarin use associates with increased risk for stroke in hemodialysis patients with atrial fibrillation. *J Am Soc Nephrol.* 2009;20(10):2223–2233. PMID: 19713308 https://doi.org/10.1681/ASN.2009030319

81. Limdi NA, Nolin TD, Booth SL, Centi A, Marques MB, Crowley MR, et al. Influence of kidney function on risk of supratherapeutic international normalized ratio–related hemorrhage in warfarin users: a prospective cohort study. *Am J Kidney Dis.* 2015;65(5):701–709. PMID: 25468385 https://doi.org/10.1053/j.ajkd.2014.11.004

82. Brodsky SV, Nadasdy T, Rovin BH, Satoskar AA, Nadasdy GM, Wu HM, et al. Warfarin-related nephropathy occurs in patients with and without chronic kidney disease and is associated with an increased mortality rate. *Kidney Int.* 2011;80(2):181–189. PMID: 21389969 https://doi.org/10.1038/ki.2011.44

83. Kelly DM, Rothwell PM. Prevention and treatment of stroke in patients with chronic kidney disease: an overview of evidence and current guidelines. *Kidney Int.* 2020;97(2):266–278. PMID: 31866114 https://doi.org/10.1016/j.kint.2019.09.024

84. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, et al. 2020 ESC Guidelines for the diagnosis

and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J.* 2021;42(5):373–498. PMID: 32860505 https://doi.org/10.1093/eurheartj/ehaa612

85. Hughes S, Szeki I, Nash MJ, Thachil J. Anticoagulation in chronic kidney disease patients - the practical aspects. *Clin Kidney J.* 2014;7(5):442–449. PMID: 25878775 https://doi.org/10.1093/ckj/sfu080

86. Sutherland LJ, Diprose WK, Wang MT, Barber PA. Chronic kidney disease and outcome following endovascular thrombectomy for acute ische-mic stroke. *J Stroke Cerebrovasc Dis.* 2020;29(4):104665. PMID: 32044221 https://doi.org/10.1016/j.jstrokecerebrovasdis.2020.104665

87. Naganuma M, Koga M, Shiokawa Y, Furui E, Kimura K, Yamagami H, et al. Reduced estimated glomerular filtration rate is associated with stroke outcome after intravenous rt-PA: The Stroke Acute Management with Urgent Risk-Factor Assessment and Improvement (SAMURAI) rt-PA registry. *Cerebrovasc Dis.* 2011;31(2):123–129. PMID: 21088392 https://doi.org/10.1159/000321516

88. Rao ZZ, Gu HQ, Wang XW, Xie XW, Yang X, Wang CJ, et al. Renal dysfunction and in-hospital outcomes in patients with acute ischemic stroke after intravenous thrombolytic therapy. *J Am Heart Assoc.* 2019;8(20):e012052. PMID: 31595836 https://doi.org/10.1161/JAHA.119.012052

Information about the authors

Olga N. Rzhevskaya, Dr. Sci. (Med.), Leading Researcher, Department of Kidney and Pancreas Transplantation, Department of Kidney and Pancreas Transplantation, N.V. Sklifosovsky Research Institute for Emergency Medicine; Professor of Department of Transplantology and Artificial Organs, A.I. Yevdokimov Moscow State University of Medicine and Dentistry, https://orcid.org/0000-0001-6849-1457, dr_rzhevskayaolga@mail.ru

30%, concept, design, literature review, editing, approval of the manuscript

Alexandra Yu. Moiseeva, Clinical Resident in Cardiology, N.V. Sklifosovsky Research Institute for Emergency Medicine, https://orcid.org/0000-0003-0718-5258, moiseyeva.alexandra.y@yandex.ru

24%, collection and processing of material, writing and editing the text of the manuscript

Anna N. Esaulenko, Clinical Resident in Cardiology, N.V. Sklifosovsky Research Institute for Emergency Medicine, https://orcid.org/0000-0002-4940-9574, aesaulenko95@mail.ru

22%, collection and processing of material, writing and editing the text of the manuscript

Aleksey V. Pinchuk, Dr. Sci. (Med.), Head of the Scientific Department of Kidney and Pancreas Transplantation, N.V. Sklifosovsky Research Institute for Emergency Medicine; Associate Professor of the Department of Transplantology and Artificial Organs, A.I. Yevdokimov Moscow State University of Medicine and Dentistry; Head of the Organizational and Methodological Department for Transplantology, Research Institute for Healthcare Organization and Medical Management, https://orcid.org/0000-0001-9019-9567, PinchukAV@sklif.mos.ru

14%, literature review, editing, approval of the manuscript

Khafiza G. Alidzhanova, Dr. Sci. (Med.), Senior Lecturer of the Training Center, Senior Researcher of the Department of Emergency Clinical Cardiology with Methods of Non-invasive Functional Diagnosis, N.V. Sklifosovsky Research Institute for Emergency Medicine, https://orcid.org/0000-0002-6229-8629, AlidzanovaHG@sklif.mos.ru

10%, concept, design, editing the text of the manuscript

The article was received on July 30, 2021;
Approved after reviewing August 10, 2021;
Accepted for publication September 29, 2021