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VIA MEDICA

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Epidemiology, therapy, and prognosis after stroke in chronic kidney disease

ABSTRACT

Ischemic stroke is one of the most common causes of death worldwide. Its occurrence closely correlates with the severity of chronic kidney disease (CKD) and albuminuria. Pharmacological prevention of stroke in patients with mild-to-moderate CKD does not differ significantly from the general recommendations. However, the beneficial effect of statins on reducing the risk of stroke remains unproven in patients with advanced CKD and on dialysis. The use of acetylsalicylic acid and oral anticoagulants increases the risk of serious bleeding complications and requires special care and additional monitoring. CKD cannot be considered a contraindication for carotid artery endarterectomy or stenting in patients with symptomatic carotid artery stenosis; likewise, CKD cannot be a contraindication for thrombolysis and thrombectomy in ischemic stroke patients. Admittedly, all these procedures are associated with an increased risk of adverse events compared to non-CKD patients. Early thrombolysis and especially thrombectomy improve poor outcomes in CKD patients. Post-stroke supportive treatment of CKD patients does not differ from the general standards, but the nephrological burden should be taken into consideration, especially when using antihypertensive, anticonvulsant, or edema-reducing drugs. Statin use after stroke reduces 3-month mortality. Further research is needed to create specific CKD therapeutic algorithms for more effective management of ischemic stroke in patients with severe CKD and on dialysis.

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Key words: anticoagulants, chronic kidney disease, ischemic stroke, statins, thrombolysis, thrombectomy

INTRODUCTION

Ischemic stroke is the second leading cause of death in the world and the leading cause of severe neurological deficits. According to the 2012 definition of Kidney Disease: Improving Global Outcomes (KDIGO), chronic kidney disease (CKD) is defined as abnormalities of kidney structure or function present for over 3 months, with health implications [1]. CKD is present in about 13.4% of the general population, which poses a significant epidemiological problem and a challenge for health care systems worldwide. CKD is an independent risk factor for stroke, and CKD patients are characterized by in-hospital mortality that is several times higher than in the case of non-CKD patients; they are affected by longer recovery time and worse functioning after a stroke. Despite the high incidence of strokes in CKD patients and the impact of kidney disease on the pharmacokinetics and efficacy of many drugs, no recommendations have been proposed for stroke treatment in this particular group of patients.

EPIDEMIOLOGY OF STROKE IN PATIENTS WITH CHRONIC KIDNEY DISEASE

Strokes occur 4 to 10 times more often in CKD patients than in the general population and affect younger patients [3]. A close correlation has been shown between the estimated glomerular filtration rate (eGFR), which reflects the severity of CKD, and the risk of stroke. A meta-analysis by Masson et al. indicates a 10% increase in the relative risk of stroke, with an eGFR in the range of 60–90 mL/min/1.73 m^2 (stage 2 CKD), while with a decrease in eGFR below 30 mL/min/1.73 m^2 (stage 4 CKD) the relative risk of stroke is 70% higher. Taking that into account, we estimated that for every 10 mL/min/1.73 m^2 decrease in eGFR,

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the relative risk of stroke increases by an average of 7% [3].

Albuminuria is also a risk factor for stroke that is independent of glomerular filtration. Both micro- and macroalbuminuria have been shown to increase the relative risk of stroke by an average of 68%. It has been estimated that each increase in the albumin/creatinine ratio by 25 mg/mmol is associated with a 10% increase in stroke risk [3, 4]. Patients with CKD have a significantly higher incidence of arterial hypertension and atrial fibrillation, which predisposes them to strokes caused by cardiac embolisms. Moreover, accelerated development of atherosclerosis is observed in CKD patients, which is associated with endothelial dysfunction and increased expression of adhesion molecules and chemoattractants, which increases the infiltration of arterial walls by macrophages and predisposes to the accumulation of lipoproteins. Accelerated development of atherosclerosis also affects the carotid arteries, which significantly increases the risk of ischemic stroke [5].

Patients with chronic renal failure (CRF), including those treated with renal replacement therapy, have the highest risk of stroke. Dialysis and its type may affect the frequency and type of stroke. A meta-analysis of 1 289 572 patients with end-stage renal disease showed that peritoneal dialysis is associated with a 16% lower risk of hemorrhagic stroke when compared to hemodialysis. The high risk of stroke in patients undergoing hemodialysis is most likely associated with the use of heparin during the treatment and volume-dependent blood pressure fluctuations. This is probably why the highest frequency of strokes is recorded in the pre-dialysis period and within the first 30 days of the treatment. There was no statistical difference in the overall risk of any stroke depending on the type of hemodialysis used. However, the key factor in the interpretation of the results is the fact that the meta-analysis did not include patients with atrial fibrillation who take antiplatelet and anticoagulant drugs, which could have had a significant impact on the results of this analysis [6].

STROKE PREVENTION IN PATIENTS WITH CHRONIC KIDNEY DISEASE

In patients with CKD up to end-stage renal failure, stroke prophylaxis does not differ significantly from that recommended for patients without kidney disease and is limited to the use of low doses of acetylsalicylic acid (ASA) at eGFR ≥ 45 mL/min/1.73 m^2, warfarin at eGFR ≥ 30 mL/min/1.73 m^2, or new generation oral anticoagulants (NOACs) without antiplatelet drugs and rivaroxaban with ASA with ClCRr ≥ 15 mL/min, and statins. In symptomatic internal carotid artery stenosis (> 70%), revascularization procedures should be considered. However, the use of ASA and oral anticoagulants in dialysis patients is controversial and is associated with a risk of serious, or even fatal, hemorrhage, and in the case of statins, there is no benefit associated with their use [7, 8].

Patients with advanced CKD assessed for bleeding risk on the HAS-BLED scale score one point at baseline for their serum creatinine level, often further points for age over 65 and high systolic blood pressure (> 160 mmHg), putting them at a high risk of bleeding (Tab. 1), which is a contraindication to anticoagulant use in patients with atrial fibrillation [9].

Carotid endarterectomy and stenting are mainly recommended in symptomatic carotid artery stenoses [8]. A significant improvement in the safety of carotid artery revascularization procedures in dialysis patients has been observed in the last 2 decades [10].

THE USE OF STATINS IN CKD PATIENTS

Statins are a key element of lipid-lowering therapy, which reduces mortality due to cardiovascular diseases. A meta-analysis of 6 clinical trials evaluating the use of statins showed a 41% reduction in cardiovascular risk in patients with CKD stages 1–3 compared to placebo (RR = 0.59; 95% CI: 0.48–0.72). In the same lipid-lowering treatment group, statin therapy led to a 44% reduction in the risk of ischemic stroke (RR = 0.56; 95% CI: 0.28–1.13). The benefits of statin therapy were greater in CKD stage 3 than in stages 1 and 2 [11]. However, the benefits of statin therapy in the later stages of CKD with eGFR < 30 mL/min/1.73 m^2 have not been demonstrated [12].

ATRIAL FIBRILLATION IN PATIENTS WITH CKD

Atrial fibrillation (AF) is one of the most common cardiac arrhythmias, with a prevalence of 0.51% in the global population. It is estimated that over the past 20 years, the incidence of AF has increased by 22% [13]. Atrial fibrillation and CKD are conditions with many shared causes, remaining in a reciprocal relationship, where the presence of CKD predisposes to AF development, and AF that occurs during CKD significantly worsens its course and prognosis

Table 1. HAS-BLED scoring system. Patients with CKD have an increased risk of bleeding due to the high prevalence of uncontrolled hypertension and elevated serum creatinine, and often elderly age. Obtaining ≥ 3 points by a patient is associated with high risk of bleeding

Condition	Description	Points	Patients with CKD
H (Hypertension)	SBP > 160 mmHg	1	1
A (Abnormal renal function)	Creatinine > 200 μmol/L	1	1
(Abnormal liver function)	Bilirubin > 2× normal or ALT/AST/AP > 3× normal	1	
S (Stroke)		1	
B (Bleeding)		1	
L (Labile INR)	> 40% measurement outside of therapeutic range	1	
E (Elderly)	65+	1	1
D (Drugs)	NSAIDs	1	
	Heavy alcohol use	1	

ALT — alanine aminotransferase; AP — alkaline phosphatase; ASP — aspartic aminotransferase; CKD — chronic kidney disease; INR — international normalized ratio; NSAIDs — non-steroidal anti-inflammatory drugs; SBP — systolic blood pressure

[14, 15]. There are several paths of AF development in CKD, the common origin of which is chronic inflammation, fibrosis, and remodeling of the atria, leading to the formation of pathological ectopic foci [16]. In CKD patients, a multifactorial increase in preload and afterload is found, implying left ventricular hypertrophy, enlargement of the left atrium, and its remodeling, which increases AF risk [14]. The reasons for the development of AF in CKD should also be sought in disorders of hormonal pathways regulated by the kidneys. Chronic kidney disease is associated with increased activation of the renin-angiotensin-aldosterone system, which results in increased production of angiotensin II promoting atrial fibrosis, increased secretion of pro-inflammatory cytokines and formation of reactive oxygen species, which enhances the immune response and promotes the synthesis of extracellular matrix proteins leading to atrial fibrosis and formation of ectopic foci [14, 16].

The synergistic and prothrombotic effects of CKD and AF justify administration of anticoagulant therapy. The safety profile of direct oral anticoagulants (DOACs) in CKD patients is better than vitamin K antagonists (VKAs). This is because the use of VKAs is associated with increased calcification and progression of atherosclerotic plaques, bleeding within renal tubules (increasing their fibrosis), and suboptimal anticoagulation [17]. However, it should be noted that patients in advanced stages of CKD were not included in the study group in the clinical evaluation of DOACs, and the changed pharmacokinetics of these drugs and insufficient knowledge regarding safety assessment (reflected in the Summary of Product Characteristics [SmPC]) raise doubts about the possibility of their use [5].

Nevertheless, it seems that apixaban is the safest drug from the DOAC group for CKD patients. A meta-analysis of 19 studies (covering a group of almost 125 000 patients) showed that DOACs, especially apixaban and edoxaban, were more effective and safer than warfarin in patients with AF and CKD. Apixaban was associated with the lowest risk of major bleeding among all DOACs in CKD patients (eGFR < 30 mL/min/1.73 m^2) [18].

Patients treated with renal replacement therapy are a completely different group. A retrospective cohort study examining the use of apixaban in hemodialysis patients showed no superiority of apixaban over warfarin in reducing the risk of ischemic stroke, transient ischemic stroke, or peripheral thrombosis. Interestingly, it showed that the use of the drug in a standard dose (5 mg twice a day) was associated with higher risk of stroke, transient ischemic attack, or embolic event (OR = 2.24; 95% CI: 1.03–4, 86). At a lower dose (2.5 mg twice daily), no such association was observed (OR = 1.11; 95% CI: 0.43–2.85). In addition, a higher incidence of severe and fatal intracranial bleeding was observed in patients on apixaban therapy (OR = 2.74; 95% CI: 1.37–5.47) at the standard dose. At a reduced dose, apixaban did not increase the risk of hemorrhage. On the other hand, when the reduced dose was used, the incidence of ischemic stroke was slightly higher (RR = 1.56: 95% CI: 1.02–2.39)

Table 2. Summary of the use of new generation anticoagulants (DOACs) in patients with chronic kidney disease (CKD). Data comes from the Summary of Product Characteristics available on ema.europa.eu

CKD	Apixaban	Rivaroxaban	Dabigatran
Stage 1–2	5 mg twice a day	20 mg once a day	150 mg twice a day
Stage 3A	5 mg twice a day	150 mg twice a day for the first 3 weeks of treatment, then ≤ 15 mg once daily	150 mg twice a day, and in the case of high bleeding risk, dose reduction to 110 mg
Stage 3B	Reduced dose of 2.5 mg should be used twice a day		
Stage 4	Reduced dose should be used if 2 of the following 3 criteria are met: • serum creatinine > 1.5 mg/dL (133 μmol/L) • age ≥ 80 years or • body weight ≥ 60 kg	15 mg twice daily for the first 3 weeks of treatment, then ≤ 15 mg once daily	Use is not recommended
Stage 5	Use is not recommended	Use is not recommended	Use is not recommended
Dialysis patients	Use is not recommended	Use is not recommended	Use is not recommended
Standard drug dose	Reduced drug dose		Use is not recommended

compared to the standard dose and reference group [19].

Nevertheless, apixaban appears to be a safer option for CKD patients compared to VKAs. This point of view is presented in cardiological guidelines, in which apixaban in a reduced dose is an option in patients with creatinine clearance < 15 mL/min [20].

In the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) clinical trial, 269 patients with AF and CKD were identified, in whom ClCr was in the range of 25–30 mL/min, to assess the safety of apixaban in this group of patients. Compared to warfarin-treated patients, who reported more major bleeding complications, the hazard ratio for apixaban-treated patients was 0.34 (95% CI: 0.14–0.80). Thus, the sub-analysis indicated a higher safety of apixaban compared to warfarin in the studied group of patients [21].

In the Valkyrie study, 132 hemodialysis patients were randomized to three groups: with VKA, with a reduced dose of 10 mg rivaroxaban, and with 10 mg rivaroxaban plus vitamin K. The primary endpoint of the study was cardiovascular death and non-fatal events such as stroke, myocardial infarction, or cardiovascular events. For patients on VKAs with the highest risk of complications, the adjusted hazard ratio for the primary endpoint was 0.41 (95% CI: 0.25–0.68) for patients receiving rivaroxaban, and for patients receiving rivaroxaban plus vitamin K this ratio was 0.34 (95% CI: 0.19–0.61). The study demonstrated the superiority of using a reduced dose of rivaroxaban over VKA [22].

Table 2 presents a summary of the possibilities of using anticoagulants in the treatment of AF in patients with CKD.

THROMBOLYSIS

CKD patients who have experienced an ischemic stroke and are within the therapeutic window (< 4.5 hours from the onset of stroke) should not be disqualified from thrombolysis procedures using tissue plasminogen activator (tPa) due to kidney disease. CKD does not increase the risk of intracranial bleeding after successful thrombolysis. It should be noted, however, that the risk of in-hospital death is 23% higher than in patients without a nephrological burden. This risk is not related to platelet or coagulation disorders. It is worth mentioning that in stages 3 and 4 of CKD, severe atherosclerosis and thrombotic episodes are observed, while in CKD, there is an increased risk of bleeding due to the use of heparins during hemodialysis procedures, which also has a negative impact on the prognosis for these patients. After being discharged from the hospital, patients treated with tPa are characterized by 13% more frequent disability if they are additionally burdened with CKD [23]. Therapeutic failure may be associated with increased activity of the plasminogen activator inhibitor in CKD [24].

THROMBECTOMY

These treatments are more effective in restoring blood flow than thrombolysis alone. In dialysis patients with ischemic stroke, thrombectomy reduces the risk of in-hospital death by 50% relative to thrombolysis. In addition, thrombectomy reduces the percentage of patients with moderate to severe disability after ischemic stroke by up to 70% [24].

SUPPORTIVE TREATMENT

The American Heart Association (AHA)/ /American Stroke Association (ASA) guidelines on the management of patients with ischemic stroke do not formulate separate recommendations for CKD patients [25]. Until recommendations for CKD patients are developed, these guidelines must form the basis of therapy.

In all patients with ischemic stroke and hypoxia, O_2 saturation should be maintained at > 94%.

Blood pressure should also be lowered if required by comorbidities such as acute coronary syndromes, myocardial infarction, or aortic dissection. It is safe to reduce blood pressure by 15% of the baseline value since too much pressure reduction can worsen cerebral blood flow and increase cerebral ischemia during an ischemic stroke. In patients without comorbidities requiring urgent treatment of hypertension with a baseline blood pressure ≥ 220/120 mmHg who have not received thrombolysis and have not undergone thrombectomy, reduction of blood pressure by 15% within the first 24 hours of stroke may also be considered. Studies did not shown a significant improvement in the prognosis with the implementation of antihypertensive treatment on the second and third day after the stroke. On the other hand, in neurologically stable patients with blood pressure > 140/90 mmHg, antihypertensive therapy is recommended. Before thrombolysis with alteplase, a value of < 185/110 mmHg should be obtained. After thrombolysis, it is recommended to maintain blood pressure at < 180/105 mmHg. Studies have shown that higher blood pressure increases the risk of bleeding. Differences in management result from the lower effectiveness or lack of effectiveness of certain groups of drugs. It should be remembered that loop diuretics are ineffective in end-stage renal disease and in patients with anuria, and thiazide and thiazide-related drugs (except chlorthalidone) are ineffective at eGFR < 30 mL/min/1.73 m^2. Hypervolemia present in CKD limits the effectiveness of antihypertensive drugs, and its reduction may require hemodiafiltration, hemodialysis, or diafiltration.

Swelling of the brain or cerebellum should be treated by the neurosurgical team with the aid of craniectomy. If there is a deterioration in the patient's condition associated with stroke as a result of cerebral edema, osmotic therapy is indicated. It is important to emphasize that mannitol does not have a diuretic effect in patients with severe CKD and CRF, and there is no evidence that it reduces intracranial pressure in this group of patients.

Anticonvulsant therapy should be administered in accordance with the recommendations for acute neurological syndromes. Prophylactic seizure treatment is not recommended. Unfortunately, there is no data on the effectiveness of anticonvulsant therapy in patients with CKD.

POST-STROKE STATIN USE IN PATIENTS WITH CKD

Statin use reduces 3-month mortality among hospitalized stroke patients with mild to moderate CKD. This is due to the lowering of LDL cholesterol levels and other pleiotropic effects. By reducing the concentration of the LDL-C fraction, statins reduce the risk of cardiovascular events, including cerebral ones, and slow down CKD progression. It seems that reducing the production of free radicals, increasing the production of endothelial nitric oxide, and having an anti-inflammatory effect, all have an overall beneficial effect [26].

SUMMARY

Strokes are more common in patients with CKD and CRF than in those with normal renal function. Renal disease is not a contraindication to thrombolysis using tPa and thrombectomy. In the presence of atrial fibrillation in patients without a mechanical valve, apixaban or rivaroxaban is the preferred anticoagulant treatment over VKA due to the lower risk of major hemorrhage. However, until the SmPC is updated, the use of NOACs in CKD patients is not recommended. The use of ASA as an antiplatelet drug in patients with CKD and internal carotid artery stenosis increases the risk of bleeding. Symptomatic carotid artery stenosis should be treated surgically in centers with extensive experience.

The benefits of statins have not been confirmed in patients with advanced CKD and CRF. The use of statins after stroke reduces 3-month mortality but is not justified as a preventative treatment in patients with advanced CKD and CRF. There are currently no evidence-based recommendations for the treatment of patients with ischemic stroke in the course of CKD.

CONFLICT OF INTEREST

None to declared.

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