Mechanisms of Stroke in Patients with Chronic Kidney Disease

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Keywords

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Abstract

Background: Given the increasing worldwide prevalence of chronic kidney disease (CKD), it is critical to decrease the associated risk of debilitating vascular complications, including stroke, congestive heart failure, myocardial infarction, and peripheral vascular disease. Treatment options for reducing the risk of all subtypes of stroke in patients with CKD remain limited. For patients with end-stage kidney disease (ESKD), novel applications of noninvasive imaging may help personalize the type of dialysis and dialysis prescription for patients at high-risk. **Summary:** This manuscript reviews the heightened risk of stroke in patients with nephropathy, including ischemic and hemorrhagic subtypes. Mechanisms associated with increased risk include alterations in cardiac output, platelet function, regional cerebral perfusion, accelerated systemic atherosclerosis, altered blood brain barrier, and disordered neurovascular coupling. There is great potential for noninvasive monitoring of the cerebral vasculature using transcranial Doppler (TCD) to reduce stroke risk, particularly in patients with ESKD. **Key Messages:** Compared to the general population, patients with CKD are at heightened risk for all subtypes of stroke. This is due to a multitude of mechanisms linking nephropathy with altered cerebral perfusion, cerebral neurovascular coupling, and blood ves-

sel integrity. Intracranial imaging is not currently standard of care practice in patients with CKD or ESKD. TCD may provide clinicians real-time and noninvasive measurement of brain perfusion. This could be useful for assessing risk of stroke in patients' initiating dialysis, individualizing dialysis prescriptions, and potentially reducing rates of cerebrovascular disease and stroke in high-risk patients. © 2019 S. Karger AG, Basel

Introduction

Chronic kidney disease (CKD) is an independent risk factor for stroke, including both hemorrhagic and ischemic subtypes [1–3, 6–8, 10]. Patients with end-stage kidney disease (ESKD) receiving renal replacement therapy are at four-fold to ten-fold higher risk of stroke relative to the general population and stroke risk increases by a factor of seven-fold during the initial year on dialysis [1–4]. Patients with CKD and ESKD also have significantly poorer functional outcomes and greater mortality after suffering a stroke [1, 5]. It is critical to understand the mechanisms underlying the heightened risk for cerebrovascular accidents in patients with kidney disease.

There are unique influences whereby CKD can impact the risk of stroke. Many factors are involved, including endothelial dysfunction, accelerated arteriosclerosis, and impaired cerebral autoregulation [6, 7]. However, stroke prevention measures in patients with CKD remain similar

Fig. 1. **a** TCD transtemporal view of the Circle of Willis, image shows anterior cerebral artery (ACA), middle cerebral artery (MCA), and posterior cerebral artery (PCA) vessels. **(b)** TCD transtemporal view of the MCA, with a normal waveform.

to those in populations without kidney disease. Thus, there is an unmet need for stroke prevention measures specific to individuals with CKD. Intracranial imaging is not currently standard of care in patients with CKD or ESKD. In patients with ESKD, noninvasive imaging modalities may inform individualized prescriptions for dialysis or choices of dialysis modality (discussed below). Patients at high risk for stroke might be more likely to benefit from dialysis options that reduce the risk of systemic hypotension and exacerbate cerebral hypoperfusion.

This article reviews alterations in cerebral hemodynamics in patients with kidney disease. For patients with ESKD, we discuss the role of dynamic imaging modalities such as transcranial Doppler (TCD) to assess altered cerebral hemodynamics and inform dialysis modalities and prescriptions to minimize the risk of stroke. These sections are accompanied by a brief review of stroke subtypes in patients with CKD and ESKD. This paper is intended to inform nephrologists about disease-specific stroke risk and preventive strategies for their patients.

Epidemiology

Independent from conventional cardiovascular disease (CVD) risk factors, reductions in estimated glomerular filtration rate (eGFR), and greater degrees of albuminuria increase the risk for stroke. The prospective Atherosclerosis Risk in Communities study reported that CKD, defined as an eGFR <60 mL/min/1.73 m², increased the risk for stroke nearly two-fold (hazard ratio [HR] 1.81, 95% CI 1.26–2.02), including after adjustment for conventional CVD risk factors [8]. Results were similar

to those in the multicenter Prevention Regimen for Effectively Avoiding Second Strokes Trial and a meta-analysis including 284,672 individuals [9, 10]. These reports detected an increased risk of incident stroke among participants with an eGFR <60 mL/min/1.73 m² (relative risk [RR] 1.43; 95% CI 1.31–1.57) [9, 10]. Effects may be further modulated based on the ancestry of patients. Subgroup analyses in these reports found especially high risks among patients with either an eGFR <40 mL/min/1.73 m² (RR 1.77, 95% CI 1.32–2.38) or Asian ancestry (RR 1.96, 95% CI 1.73–2.23).

Asian and West Africans with kidney disease appear to be at particularly high risk for stroke [11–13]. Large population-based studies support markedly increased stroke risk in Asian ancestry patients with Stage 3 (or higher) CKD. It remains unclear whether inherited (genetic), environmental, or a combination of these factors contribute to risk [12]. In patients with recent African ancestry, renal-risk variants in the apolipoprotein L1 gene (*APOL1*) may increase risk for kidney disease and stroke [11]. In 25,310 community-based Reasons for Geographic and Racial Differences in Stroke (REGARDS) study participants, higher urine albumin-to-creatinine ratio conferred an increased risk for stroke, particularly among African Americans [13]. A subgroup analysis in REGARDS participants without diabetes mellitus reported that carriage of an *APOL1* renal-risk genotype (2 copies of G1 and/or G2 variants) was independently associated with small vessel ischemic stroke [14]. However, it is difficult to determine whether the higher risk for cerebral small vessel disease in REGARDS related to confounding between *APOL1*-associated kidney disease and the presence of higher blood pressures (e.g., more severe second-

Table 1. Stroke subtypes and cerebral pathology in patients with kidney disease

	Effect of CKD	Effect of AKI	References
Ischemic stroke	↑	↑	[1, 5, 6, 24–36, 108, 109]
Hemorrhagic stroke	↑	↑	[18–22, 110]
Cerebral microbleeds	↑	Unknown	[20, 22, 111, 112]
SVD	↑	Unknown	[39–42, 113]

CKD, chronic kidney disease; AKI, acute kidney injury; SVD, small vessel disease.

Table 2. Mechanisms whereby kidney disease can increase risk of stroke

Mechanism	Effect of CKD	Effect of AKI	References
Cerebral autoregulation	↓	Unknown	[57, 59]
Impaired CBF	↓	Unknown	[50, 55, 60, 65]
Rate of carotid atherosclerosis	↑	Unknown	[72–75]
Risk of AF	↑	↑	[108, 114]
Uremic platelet dysfunction	↑	↑	[1–3, 6, 115]
Cerebral oxygenation	↓	↓	[67–70, 116]

CKD, chronic kidney disease; AKI, acute kidney injury; CBF, cerebral blood flow; AF, atrial fibrillation.

ary hypertension) related to nephropathy [15, 16]. No association was detected between *APOL1* genotype and incident CVD including stroke, in a meta-analysis with 16,218 African Americans without prevalent CVD [17].

Stroke Subtypes in Patients with Renal Impairment

Stroke subtypes include ischemic and hemorrhagic variants; each with a different pathogenesis. CKD uniquely affects the risk for hemorrhagic stroke, as well as cardioembolic, large vessel, and small vessel ischemic stroke subtypes [1–3, 6, 9] (Table 1).

Hemorrhagic Stroke

CKD increases the risk of intracerebral hemorrhage (ICH) and cerebral microbleeds, defined as small chronic brain hemorrhages that can act as a nidus for future hemorrhagic events [18–23]. Among patients with ICH, an eGFR <45 mL/min/1.73 m² is associated with a three-fold increase in the volume of the hematoma and a four-fold higher risk of death, compared to patients without renal impairment [18]. A retrospective cohort including more than 500,000 participants identified a stepwise association

between eGFR and ICH, where the risk of hemorrhage decreased by 9% (95% CI 8–11%) for each 10 mL/min/1.73 m² increase in eGFR, including after adjustment for medical comorbidities, albuminuria, antiplatelet therapy, and use of anticoagulants [23]. Among patients with a recent ICH or ischemic stroke, an eGFR <60 mL/min/1.73 m² was independently associated with the presence and number of cerebral microbleeds, particularly in patients with recent African ancestry [20–22]. In patients on dialysis, ICH is associated with the highest mortality risk of all stroke subtypes [20]. Uremic platelet dysfunction and use of heparin and other anticoagulants during the dialysis procedure may further increase risk of intracranial hemorrhage [21].

Ischemic Stroke

Cardioembolic

Compared to the general population, atrial fibrillation (AF) is more than twice as prevalent in patients with CKD and confers a greater risk for thromboembolism [24–31]. The Chronic Renal Insufficiency Cohort reported a prevalence of AF in patients with CKD 2–3 times higher than in the general population [26]. A report from 132,372 patients with nonvalvular AF in the Danish national registry found that patients with predialysis CKD or ESKD had

Table 3. Noninvasive modalities to image the CBF

Method	Benefits	Weaknesses	Reference
Carotid doppler ultrasound	Can be done at patient bedside Well-established guidelines for application in clinical care Dynamic study	Does not include intracranial vessel imaging	[92, 93]
Perfusion CT	Well-established guidelines for ischemia via infarct core and penumbra Well-established use for application in clinical care	Contrast administration necessary Cannot be done at bedside Not well-established for dynamic studies	[118, 119]
Perfusion MRI brain	Dynamic study Detailed spatial resolution of CBF	Contrast administration necessary Cannot be done at bedside No well-established guidelines for application in clinical care	[120, 121]
TCD ultrasound	Can be done at patient bedside Well-established guidelines for application in clinical care Dynamic study	Can be operator dependent No spatial resolution for CBF	[85–89, 95, 103, 104, 116, 117, 122, 123]

CBF, cerebral blood flow; CT, computed tomography; MRI, magnetic resonance imaging; TCD, transcranial doppler.

increased risk of stroke and increased risk of intracranial bleeding relative to those with normal kidney function [25].

Large Vessel

CKD increases the risk of large vessel stroke via its effects on carotid artery stenosis, plaque size, and carotid intima-media thickness [1–3, 32–36]. In a series of prospective carotid ultrasound and CT imaging studies of patients after a stroke, those with CKD had significantly higher internal carotid artery stenosis and plaque size, including after adjustment for conventional CVD risk factors [33–35]. CKD was independently associated with carotid atherosclerosis in patients with hypertension [35]. Many patients in these studies were of Asian descent, limiting the generalizability of results; however, the effect of CKD on large vessel and intracranial hemodynamics in other patient populations is an area of active research.

Small Vessel

The effects of reduced eGFR and increased albuminuria on small vessel ischemic stroke have been intensively studied. Small vessel disease causes 25% of ischemic strokes [37, 38]. Reduced eGFR and albuminuria are associated with higher prevalence of small vessel disease [39–42]. The Northern Manhattan Stroke Study showed an eGFR of 15–60 mL/min/1.73 m² was associated with a

higher volume of white matter hyperintensities after adjusting for conventional CVD risk factors [41]. The Rotterdam Scan Study, which focused on patients 60 years and older, found a similar higher prevalence of white matter lesions after multivariate adjustment (OR 1.11, 95% CI 0.81–1.51), as well as less deep white matter volume [40]. More recently, a subgroup analysis from the Systolic Blood Pressure Intervention Trial identified increased white matter lesion burden in patients with reduced eGFR (<60 mL/min/1.73 m²) and high urine albumin-to-creatinine ratio [65].

Stroke Morbidity and Mortality in Patients with CKD

Kidney disease is associated with a greater neurological deficit following ischemic stroke, a poor functional outcome, and greater mortality [43–49]. In a retrospective study of 3,778 patients with first ischemic stroke, patients with proteinuria had an approximately 1.3–1.7 times higher risk for poor functional outcome, and 3.0–4.5 times higher risk of in-hospital mortality according to severity of proteinuria. Interestingly, eGFR was not clearly associated with patient clinical outcome in this study [43]. In a large cohort study of Medicare beneficiaries with ischemic stroke, renal dysfunction was independently associated with an increased risk of in-hos-

pital mortality, with the highest mortality among ischemic stroke patients with eGFR <15 mL/min/1.73 m² (HR 2.09; 95% CI 1.66–2.63) [45]. Patients on dialysis had an increased risk of 1-year post-stroke rehospitalization (HR 2.04; 95% CI 1.9–2.18) and 1-year post-stroke mortality (HR 2.65; 95% CI 2.49–2.81) [46, 47]. In an independent longitudinal prospective study among young stroke patients (ages 18–50), an eGFR <60 mL/min/1.73 m² was independently associated with an increased risk of death (HR 4.6; 95% CI 2.6–8.2) and increased risk of incident stroke (HR 4.1, 95% CI 1.9–9.0) [48]. However, there were no changes in risk of other vascular events on an average of 11 years after stroke in young patients [48]. Small retrospective studies have found proteinuria is independently associated with poorer discharge functional activity and lower likelihood of being discharged home directly among acute ischemic stroke patients without CKD. In a study of 94 non-CKD patients with recent ICH, the likelihood of being discharged to home were lower in patients with initial proteinuria alone, but this association did not reach statistical significance [49].

Cerebrovascular Hemodynamic Changes in CKD

Kidney disease has a unique impact on stroke risk by impairing cerebral autoregulation, remodeling the cerebral vasculature, and reducing cerebral blood flow (CBF) [50–54, 57, 59, 60]. Although current research has relied on perfusion magnetic resonance imaging (MRI), TCD ultrasound is an emerging application of noninvasive bedside imaging that holds promise for screening patients with CKD at risk for stroke and is described later in this review (Table 2).

Kidney Disease and Cerebral Autoregulation

The kidney and brain share similar microvasculature and vasoregulation, leading to shared susceptibility to microvascular dysfunction [54]. Both organs are perfused by “low resistance” vascular circuits, which permit continuous high-volume blood flow during systole and diastole. While small vessels in other organs are protected by upstream vasoconstriction, small arteries in the brain and kidney are constantly exposed to fluctuations in pressure, and flow due to low vascular resistance and upstream vasodilation [50, 54, 55, 65]. To maintain relatively constant blood flow to the brain with variable systemic blood pres-

ures, the brain vasculature displays cerebral autoregulation to minimize hypoperfusion during low blood pressure states and hyperperfusion during high-blood pressure states. Cerebral autoregulation is a complex intrinsic control mechanism that maintains a constant CBF by changing cerebral vascular resistance in response to changing blood pressure, cerebral perfusion pressure, or metabolic needs. Intact cerebral autoregulation depends on preserved endothelial function and an intact blood–brain barrier [56, 58].

Individuals with a decreased eGFR have less effective cerebral autoregulation. A prospective study of patients after acute ischemic stroke found that poorer autoregulation was correlated with lower eGFR and associated with an increased risk of hemorrhagic transformation of ischemic stroke (OR 6.43; 95% CI 1.4–32.1) [57]. Hemorrhagic transformation may result from breakthrough hyperperfusion and microvascular injury in the setting of impaired autoregulation. In this study, the combination of reduced eGFR and impaired autoregulation lessened the likelihood of a good functional outcome after stroke (OR 4.39; 95% CI 3.15–25.6).

In addition to CKD, acute kidney injury (AKI) can impair cerebral autoregulation [61–64]. In renal ischemia-reperfusion injury models, AKI caused increased brain microvasculature permeability and damage to the blood–brain barrier [61, 62, 64]. CKD and AKI are commonly present in patients with posterior reversible encephalopathy syndrome. Posterior reversible encephalopathy syndrome is a result of reduced cerebral autoregulation and endothelial dysfunction that lead to hyperperfusion with protein and fluid extravasation within the parenchyma of the brain [58, 66].

The Effects of Kidney Disease on CBF and Oxygenation

Impaired kidney function can lead to altered CBF and cerebral oxygen saturation (rSO₂) [65, 67–70]. CBF serves as a measure of cerebrovascular integrity, based on quantitative perfusion of the brain. Patients with impaired cerebral autoregulation are at risk for both hypoperfusion at low levels of systemic blood pressure and hyperperfusion at high levels [56, 58]. Existing studies on CBF in patients with kidney disease yielded mixed results and questions remain. In a prospective study characterizing regional CBF based on perfusion MRI in pediatric and young adults with CKD, patients with CKD had higher global CBF and impaired cerebral autoregulation with

an abnormal direct relationship between systemic blood pressure and white matter CBF [60]. Decreased hematocrit appeared to impact increased global CBF in patients with CKD. The Systolic Blood Pressure Intervention Trial study reported that reduced eGFR was independently associated with higher adjusted median CBF [65]. In contrast, lower eGFR was independently associated with lower CBF in the Rotterdam study; here, each standard deviation reduction in eGFR was associated with a 0.42 mL/min/100 mL lower CBF (95% CI 0.01–0.83) [50]. The high incidence of congestive heart failure in CKD may further impair stroke volume and CBF and cerebral perfusion [51, 52].

In addition to effects on CBF, CKD affects rSO₂ [67–69]. The majority of this literature focuses on patients with ESKD. In a prospective study, cerebral oxygenation saturation was significantly higher in patients with predialysis CKD than those on dialysis [67]. Multiple regression analysis showed lower cerebral oxygen saturation was independently associated with reduced eGFR. Diabetic patients on hemodialysis had significantly lower rSO₂ compared to those without diabetes (46.8 + 1.7 vs. 52.1 + 1.8%, $p < 0.05$), and a patient's rSO₂ was affected by blood pH, duration of hemodialysis, and serum albumin concentration [68].

Cerebrovascular Remodeling in CKD

Creatinine clearance is a strong and independent determinant of arterial stiffness and dilatation in patients with CKD [71–75]. This literature has typically focused on changes in the internal carotid artery and carotid artery intima-medial thickness (cIMT). Briet et al. [72] prospectively evaluated patients with mild to moderate CKD in order to assess the association between arterial stiffness and remodeling as CKD progressed. After 3.5-year follow-up, aortic stiffness was unchanged; however, carotid stiffness increased significantly (adjusted slope, +0.28 + 0.05 m/s per year, $p < 0.0001$). Estimated GFR was independently related to increased arterial diameter, circumferential wall stress, and carotid artery stiffness. In a multivariate Cox analysis, carotid circumferential wall stress was an independent determinate of progression to ESKD (HR 2.48 [1.63–3.78]). Arterial dilatation results from the inability of a blood vessel's elastic fibers to sustain physiological pulsatile stress [73, 75]. In the setting of a low resistance organ, such as the brain, this may lead to increased blood flow and strain on the downstream cerebral vasculature [72, 75].

cIMT has been studied as a noninvasive predictor of future CVD risk in patients with CKD [73, 74]. In a prospective longitudinal cohort study, Desbien et al. [73] found that reduced creatinine clearance was significantly associated with faster increases in cIMT. In multivariate analyses, decreased creatinine clearance (HR 1.04, 95% CI 1.02–1.23) and faster increases in cIMT (HR 1.15, 95% CI 1.11–1.93) were associated with fatal and nonfatal vascular events. Another prospective study by Kastarinen et al. [74] found that even minor reductions in eGFR were independently associated with increased cIMT, particularly among middle-aged men and post-menopausal women. These studies suggest that subclinical atherosclerosis is impacted by kidney function, and the addition of cIMT may improve noninvasive risk stratification in those with early-stage CKD.

Special Considerations for Stroke Risk in ESKD

Patients with ESKD on dialysis are at higher risk of stroke, with rates varying from 10 to 33 per 1,000 patient-years [4, 76–84]. African American men with ESKD are at particular risk compared to the general population, with an age-adjusted RR of stroke of 9.7 (95% CI 8.2–11.2), compared to European American men (RR 6.1, CI 5.1–7.1) [76]. A retrospective 7-year study from Power et al. [77] reported that first stroke occurred at a rate of 14.9/1000 patient-years in those with ESKD (95% CI 12.2–17.9). Although there was a predominance of ischemic (versus hemorrhagic subtype) strokes, patients of South Asian ethnicity were more prone to hemorrhagic strokes.

Initiation of dialysis per se is associated with a heightened risk of stroke, well above the general increased risk seen in prevalent patients with ESKD [4, 78, 79, 82]. In a 22-year single-center retrospective study, 39% of ischemic and 35% of hemorrhagic strokes occurred during or shortly after a hemodialysis session [80].

A population-based study of elderly U.S. dialysis patients reported that irrespective of the dialysis modality, stroke rates begin to rise approximately 3 months prior to the initiation of renal replacement therapy and peaked during the first 30 days after dialysis initiation [4]. In a Taiwanese study, Wang et al. [79] observed that patients on hemodialysis and peritoneal dialysis had similarly high HRs for ischemic stroke (2.88 for hemodialysis, 3.21 for peritoneal dialysis) and hemorrhagic stroke (6.83 for hemodialysis, 6.15 for peritoneal dialysis), a finding reproduced by other investigators [82, 83].

Polinder-Bos et al. [70] studied the acute effects of conventional hemodialysis on CBF and found that the hemodialysis session had significant, though largely asymptomatic, declines in global CBF. The long-term effects of repeated episodes of reduced CBF on cognitive performance remain to be determined.

Intracranial Imaging in Kidney Disease

Intracranial imaging is not currently a standard of care practice prior to dialysis initiation. Patients are not routinely screened for carotid stenosis or intracranial stenosis and their cerebral autoregulatory capacity is not assessed. Taking preexisting intracranial pathology in these patients into account may better inform selection of dialysis modality, individualize prescriptions, ultrafiltration goals, and intradialytic blood pressure goals to minimize stroke risk. For nondialysis CKD patients, imaging may help assess for overall stroke risk and progression.

Practical cranial vascular imaging options for patients with kidney disease include carotid duplex ultrasonography, computed tomography angiography (CTA), magnetic resonance imaging angiography (MRA), and TCD ultrasonography. Of these options, carotid duplex ultrasonography is appealing as a cost-effective, dynamic, noninvasive bedside modality to measure carotid plaque and stenosis, though it is limited by its inability to assess intracranial circulation [84]. CTA and MRA are useful modalities to assess morphology of intracranial vessels, though they are static studies and cannot relay flow dynamics or cerebral autoregulatory capacity. CTA is further limited by its dependence on IV contrast. MRA may be completed with or without contrast. Perfusion MRI and perfusion computed tomography of the head are less practical in CKD populations, in part due to necessity of contrast administration. TCD, an established imaging technique, may be a practical, informative tool to assess intracranial hemodynamics in CKD (Table 3).

Role of TCD Ultrasound in Kidney Disease

TCD ultrasonography is a useful bedside tool used for repeated, noninvasive monitoring of cerebrovascular hemodynamics as a marker for CBF, resistance to flow, and vessel autoregulation (Fig. 1). Common TCD variables include a cerebral vessel's peak systolic velocity, mean flow velocity (MFV), and Gosling pulsatility index (PI). PI measures the variability of blood velocity in a vessel

and describes distal cerebrovascular resistance. The TCD waveform itself shows a low resistance pattern characteristic of cerebral hemodynamics, with a sharp systolic upstroke and slow decay. Cerebrovascular autoregulation is measured by increased MFV and decreased PI with increased arterial carbon dioxide as the vessel vasodilates. In impaired cerebral autoregulation, MFV and PI do not respond to changes in carbon dioxide [90, 98].

TCD waveform analysis, combined with trends in MFV and PI, serves as useful noninvasive bedside markers for changes in CBF. TCD is an emerging tool in dialysis medicine, although studies have largely focused on monitoring declines in MFV during hemodialysis [85–89, 91, 94, 95]. An observational study of MFV fluctuations in patients receiving chronic maintenance hemodialysis found significant reductions in the middle cerebral and basilar arteries through the procedure. Amount of fluid removed and change in hematocrit significantly correlated with change in MFV [86]. Separate studies corroborated with similar MCA MFV drops during hemodialysis, which inversely correlated to ultrafiltration volume [87, 95]. In contrast, a small study found no significant intradialytic changes in MFV even with significant changes in mean arterial pressure [88]. Dynamic cerebral autoregulation and carbon dioxide reactivity remained normal in patients with chronic renal failure and were not significantly altered by hemodialysis, though this observation is limited by small study population [89].

Changes in MFV and other TCD metrics have significant clinical impact. In a recent prospective observational study of 97 patients receiving chronic hemodialysis, patients showed significant intradialytic decline in MFV. Percentage decline in MFV correlated significantly with MRI white matter disease burden as well as poor executive function on cognitive testing [91]. Serial TCD may be helpful in assessing progression of known white matter disease burden in patients with CKD, as TCD and MRI studies have found strong correlation between TCD PI and white matter disease severity [92–94].

TCD may help identify dialysis-dependent patients at particular risk of hypoperfusion or cerebral ischemia and personalize dialysis prescription. For patients with ESKD who are initiating dialysis, detection of intracranial stenoses and altered cerebral autoregulation may assist in selecting the appropriate dialysis modality, goal intradialytic blood pressures, and length of treatment sessions [96]. An observational study found significant intradialytic MFV decreases in a subset of chronic hemodialysis patients, but especially marked drops in patients with concomitant carotid stenosis on study ultrasound [87]. Chronicity of di-

alysis dependence may also be a significant factor in intradialytic cerebral hemodynamics. A prospective study compared intradialytic MFV changes in critically ill patients with AKI compared to patients with ESKD. Significant MFV decreases among those with AKI, but not ESKD [85].

Real-time TCD results are an exciting addition to the field. They may provide significant benefits, but there are also important limitations. TCD has the potential for continuous noninvasive monitoring of cerebral perfusion during dialysis, as well as serial longitudinal measurements to assess white matter disease burden and guide changes in individualized dialysis prescription over time.

Nephrologists can modify selection of renal-replacement modalities in patients at high risk of stroke or cognitive decline. A prospective study found that cognitive function declined faster with hemodialysis compared with peritoneal dialysis, despite similar baseline cognitive scores and adjustment for education and demographics [97]. Peritoneal dialysis, particularly nocturnal supine treatments, may be attractive in patients with the requisite skill set and a supportive home environment. Additional alterations to treatment that nephrologists can employ to preserve cerebral perfusion and reduce systemic hypotension include use of midodrine hydrochloride (an α 1-receptor agonist), more frequent in-center hemodialysis (4 treatments per week), home hemodialysis (5 treatments per week), extending treatment durations during hemodialysis, or instituting weight-based ultrafiltration limits [99]. Real-time TCD can be applied with different renal replacement modalities and prescriptions to optimize therapy. However, TCD measurements may be limited on operator experience as well as patient anatomy [100–102]. An estimated 8–9% of patients do not have an appropriate transtemporal or occipital acoustic window for vessel insonation due to skull thickness [102]. Despite these limitations, the use of TCD has expanded with improved technology and improved access to formal TCD training programs [91, 103].

Unmet Needs and Future Directions

The prevalence of CKD and ESKD is increasing, as is the risk of stroke. Effective noninvasive screening and primary prevention tools are urgently needed to minimize stroke-related morbidity and mortality in this population. At present, there are no primary stroke prevention measures that are specific for patients with CKD, nor are there measures for screening patients at particularly high risk. Studies employing renin-angiotensin system modulators in patients with CKD did not identify reductions in the short-term risk of stroke [104, 106]. The potential benefit of reducing albuminuria to lower the risk of stroke in patients with CKD is also unclear [3].

Research regarding the effects of arterial remodeling and altered autoregulation in patients with moderate reductions in eGFR is ongoing. In patients with reduced cerebral autoregulation or intracranial stenosis due to accelerated atherosclerosis, a lower blood pressure target may paradoxically worsen the risk of hypoperfusion and ischemic stroke [104, 105]. TCD may prove beneficial in setting patient-specific blood pressure goals and identifying patients at particularly high risk of stroke. Thus, TCD may soon change our approach to choosing dialysis modalities and delivering dialysis in patients with underlying CVD and cerebrovascular disease, particularly during the initial period of dialysis initiation and when changing therapies. TCD provides an exciting potential advance in stroke prevention in patients with advanced kidney disease.

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