Stroke and Chronic Kidney Disease: Epidemiology, Pathogenesis, and Management Across Kidney Disease Stages

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Summary: Cerebrovascular disease and stroke are very common at all stages of chronic kidney disease (CKD), likely representing both shared risk factors as well as synergy among risk factors. More subtle ischemic brain lesions may be particularly common in the CKD population, with subtle manifestations including cognitive impairment. For individuals with nondialysis CKD, the prevention, approach to, diagnosis, and management of stroke is similar to the general, non-CKD population. For individuals with end-stage renal disease, far less is known regarding strategies to prevent stroke. Stroke prophylaxis using warfarin in dialysis patients with atrial fibrillation in particular remains of uncertain benefit. End-stage renal disease patients can be managed aggressively in the setting of acute stroke. Outcomes after stroke at all stages of CKD are poor, and improving these outcomes should be the subject of future clinical trials.
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Chronic kidney disease (CKD) is common in the United States and worldwide, with reduced kidney function (defined as an estimated glomerular filtration rate [eGFR] less than 60 mL/min per 1.73 m^2) present in almost 10% of the adult population and kidney damage (defined by the presence of albumin in the urine of at least 30 mg/g of creatinine) occurring in 5% of adults without reduced eGFR.[1,2] These rates are likely to increase modestly over the next 20 years, and, reflecting population growth, the number of Americans aged 30 years or older with CKD should reach 28 million in 2020 and nearly 38 million in 2030.[3]

Cardiovascular disease risk is high at all stages of CKD.[4,5] Similar to the general population, cardiovascular disease is the leading cause of mortality across all stages of CKD, including increased risk seen in individuals with albuminuria and increased risk in individuals with decreased GFR.[5] The magnitude of risk for individuals with CKD relative to the general population increases as kidney function decreases, with the risk of cardiovascular disease outcomes reaching levels 10 to 20 times higher than the general population in dialysis patients.[6] Critically, despite improvements in cardiovascular disease survival, the rate of improvement in patients with CKD, particularly patients treated with dialysis, has lagged behind that of the general population.[7,8]

Often neglected when discussing cardiovascular disease is cerebrovascular disease. CKD does not discriminate when it comes to blood vessels, with both the kidney disease milieu itself as well as the underlying diseases that cause CKD, such as diabetes and hypertension, affecting the vasculature throughout the body.[9] When conceptualizing cardiovascular disease risk in people with CKD, it is critical to keep other end organs beyond the heart in mind, including the effects of CKD and CKD risk factors on the brain.

This article provides an overview of stroke, including the risk factors for and subtypes of stroke, describes the burden of and risk factors for stroke in patients with chronic kidney disease, including those with earlier stages of CKD and patients treated with kidney replacement therapy, and reviews the prevention, treatment, and prognosis of stroke in patients with CKD.

DEFINING AND QUANTIFYING STROKE

Cerebrovascular diseases can be conceptualized broadly as conditions resulting from decreased brain perfusion; stroke is the most readily apparent of these conditions, although cognitive impairment related to cerebrovascular disease is a second important complication. By definition, stroke requires a clinical deficit to manifest for longer than 24 hours, although it is likely that deficits resolving within this timeframe also may have clinical sequelae.

Strokes are subdivided into two major categories: ischemic (~80%-90%) and hemorrhagic (~10%-20%) (Table 1).[10–12] The most common cause of hemorrhagic stroke likely is hypertension-related, with rupture of small lipohyalinotic aneurysms in small intracerebral vessels. Multiple etiologies exist for ischemic stroke, including large-artery atherosclerosis (embolus or thrombosis), cardioembolism, and small-vessel occlusion (lacune); other poorly defined causes include

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Table 1. Stroke Subtypes Schema

Subtype	Cause	Risk Factors/Etiologies	Pathophysiology
Ischemic			
Thrombotic	Local obstruction of an artery	Traditional cardiovascular disease risk factors resulting in arterial wall disease including atherosclerosis and arteriosclerosis; dissection and fibromuscular dysplasia are rare causes	Large-vessel disease caused most often by atherosclerosis and may predispose to hypoperfusion more distally and local thromboembolism
			Small-vessel disease refers to the lesions within the intracerebral arterial system, typically small penetrating cerebral arteries; these often are caused by lipohyalinosis, hyaline arteriosclerosis, and microatheroma, and manifest with lacunar infarcts
Embolic	Particles or clot originating elsewhere that impairs arterial flow to a brain region	Atrial fibrillation, valve disease, endocarditis, severe heart failure with akinesis, patent foramen ovale, particularly in the setting of cardiovascular disease risk factors	Results in reduced blood flow distal to the lesion, typically with abrupt onset
Hypoperfusion	Systemic reduction in blood pressure impacting either global or segmental brain perfusion	Sepsis, acute or chronic heart failure, major hemodynamic shifts, hemorrhage, pulmonary embolism, arrhythmia, and/or pericardial effusion, particularly in the setting of pre-existing vascular disease	Fewer localizing symptoms and signs, with manifestations often bilateral unless superimposed on preexisting cerebrovascular disease; watershed regions more vulnerable
Hemorrhagic			
Intracerebral	Bleeding directly into the brain parenchyma, usually from small arteries and arterioles	Hypertension, trauma with or without bleeding diatheses/ anticoagulants, amyloid angiopathy, cocaine, vascular malformations	Local hematoma formation that either because of expansion results in symptoms of diffusely increased intracranial pressure or impairs perfusion of a region of brain secondary to compression; onset may be gradual
Subarachnoid	Bleeding into the subarachnoid space surrounding the brain	Arterial aneurysm rupture and vascular malformation bleeding	Usually abrupt onset with headache and vomiting

Data were extrapolated from Amarenco et al,[98] based on the Trial of ORG 10172 in Acute Stroke Treatment.

the effects of systemic hypoperfusion, which may manifest with leukoaraiosis (also referred to as *abnormal brain white matter*). Systems differ for classifying the various subtypes of ischemic stroke, with the Northern Manhattan Study classifying the plurality of ischemic strokes as cryptogenic, suggesting more than one of these mechanism was operative; of note, most strokes classified as cryptogenic in this study likely were at least in part thrombotic in origin.[13] An estimated 6.6 million adults in the United States have had a stroke, with minorities affected disproportionately. Silent brain infarcts may be even more common, with as many as twice that number impacted.[12]

Stroke Risk Factors in the General Population

As shown in Table 1, stroke is a heterogeneous syndrome with multiple different etiologies; accordingly, although there are many shared risk factors for stroke, these risk factors do not fully account for stroke risk.[14] That stated, hypertension is a consistently strong risk factor for stroke, regardless of age (Fig. 1).[15] A meta-analysis of cohort studies investigating blood pressure and stroke found that the association between the two is continuous down to levels of at least 115/75 mm Hg; is consistent across sexes, regions, and stroke subtypes; and is consistent for fatal and nonfatal events, with the association remaining robust through age 80 years.[15] The INTERSTROKE study, an international, multicenter, case-control study including 3000 cases and 3000 matched controls from 22 countries, showed a strong association between traditional cardiovascular disease risk factors—most notably hypertension but also obesity, diabetes, dyslipidemia, and other dietary- and activity-related factors—and risk of stroke.[14] Similarly, in the Framingham Offspring Study, which followed up 4,780 predominantly white US adults for