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

Daniel E. Weiner, MD, MS and Taimur Dad

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 the prevention of 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.

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 m²) 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,

Address reprint requests to Daniel E Weiner, MD, MS, 800 Washington St, Box 391, Boston, MA 02111. dweiner@tuftsmedicalcenter.org.

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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 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 mechanisms were 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, multi-center, 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 24 years, traditional cardiovascular

disease risk factors, including older age, smoking, higher systolic blood pressure, dyslipidemia, and obesity, were associated with incident stroke.¹⁶

Stroke Implications in the General Population

Both hemorrhagic and ischemic strokes can have devastating consequences for individual patients and populations. For ischemic stroke, age and stroke severity are the most notable predictors of clinical outcomes, with the National Institutes of Health Stroke Scale most often used to quantify stroke severity (Table 2). With stroke manifestations being fluid and rapid improvement or deterioration possible, reassessment of stroke manifestations in the hours and days after a stroke can improve prognostication.¹⁷ Among US Medicare beneficiaries, 30-day mortality for an ischemic stroke is approximately 15%, with 6% of beneficiaries dying during the index hospitalization, whereas hemorrhagic strokes have even higher associated mortality.¹⁸

CHRONIC KIDNEY DISEASE AND STROKE

Stroke Risk in CKD

Cerebrovascular disease is common at all stages of CKD. In a pooled cohort of participants in four US population cohorts, risk factors associated independently with stroke were African American race, higher baseline diastolic blood pressure, male sex, diabetes, left ventricular hypertrophy on electrocardiography, prior history of cardiovascular disease, and eGFR less than 60 mL/min per 1.73 m², as well as the traditional factors listed previously, most notably higher systolic blood pressure and older age.^{19,20} Confirming the association between kidney function and stroke, a more recent meta-analysis of 21 studies showed that an eGFR less than 60 mL/min per 1.73 m² was associated with a 43% higher risk of incident stroke.²¹ The risk of stroke also is directly proportional to increasing urine albumin levels. The European Prospective Investigation into Cancer in Norfolk population study showed that risk of stroke appeared to increase with even high normal levels of urine albumin.²² Later meta-analyses showed robust relationships between overt proteinuria and stroke risk as well as a nearly two-fold increased risk of incident stroke among individuals with a urine albumin to creatinine ratio (UACR) between 30 and 300 mg/g as compared with individuals with a UACR in the normal range (Fig. 2).^{23,24} Even higher stroke risk was seen among people with a UACR of 300 mg/g or higher.²⁵

Among dialysis patients, stroke risks are particularly high. One study that leveraged the National Health Insurance program database in Taiwan compared more than 80,000 dialysis patients with general population controls; these investigators described a nearly threefold increased risk of ischemic stroke and a six-fold increased risk of hemorrhagic stroke as compared with the general population after controlling for risk factors (Fig. 3).²⁶ Within the dialysis population, peritoneal dialysis patients were at slightly lower risk of hemorrhagic stroke than matched hemodialysis patients.²⁶ This study, however, may have limited generalizability because stroke rates may be higher among Asian populations.^{27–29} In a large single-center study of 2,384 hemodialysis patients in the United Kingdom, the incident stroke rate was 15 per 1000 patient years, an incidence similar to that seen in the Taiwan study, with major risk factors including diabetes and hypertension. There was a 24%

incidence of mortality at 1 year after an acute stroke in this study, which was similar to that seen in the general population. In the Choices for Healthy Outcomes in Caring for End-Stage Renal Disease (CHOICE) study, a prospective cohort of incident dialysis patients in the United States, there was an overall incidence of 4.9 stroke events per 100 person-years, a rate nearly 10 times higher than that seen in the general population, with ischemic strokes accounting for 76% of stroke events, and cardioembolic strokes accounting for 28% of ischemic strokes.³⁰ Of note, based on available data, no firm conclusions can be drawn on whether overall stroke risk differs by dialysis modality.

The CHOICE study provides one of the better descriptions of stroke subtypes occurring in dialysis patients, describing 200 cerebrovascular events in 165 study participants.³⁰ Of 176 strokes, 13% were hemorrhagic and 87% were ischemic. Among the subset of 95 ischemic strokes that were classified with detailed chart abstraction, causes included cardioembolism in 28%, small-vessel occlusion in 20%, multiple causes in 18%, large-vessel atherosclerosis in 11%, and other or unknown causes in 23%.³⁰

Brain Perfusion in CKD

Perfusion-related brain injury, sometimes occurring during times of hypotension or hemodynamic changes, may be more frequent in people with kidney disease, particularly patients treated with dialysis. Chronic perfusion-related insults may manifest with leukoariosis, or confluent white matter lesions. These often are multifocal, symmetric, and, consistent with the fact that both are associated with vascular disease risk factors, seen coincident with lacunar infarcts.³¹ Both hemodialysis and peritoneal dialysis patients frequently have extensive brain white matter disease,^{32–34} and brain atrophy also is common among patients treated with dialysis.³⁵ Even among patients with earlier-stage CKD, brain findings, including white matter disease, silent infarcts, and atrophy, are more common than in the non-CKD general population.^{36–43}

Perfusion-related brain disease in CKD likely is multifactorial, with systemic vascular disease and insufficient vascular reactivity potentially contributing. Interestingly, one recent study showed slower cerebrovascular transit time in a small cohort of asymptomatic hemodialysis patients.⁴⁴ Hemodialysis in particular is a time of cardiovascular challenges, with fluid and electrolyte changes during the dialysis procedure itself potentially resulting in acute decreases in cardiac function and cardiac perfusion; steps taken to improve hemodynamic stability, such as a lower ultrafiltration rate and cooling the dialysate, may result in fewer adverse myocardial effects.^{45–48} It is a reasonable hypothesis that, if the heart is subject to perturbations in perfusion during dialysis, other end-organs, including the brain, also may be vulnerable to perfusion-related injury. This hypothesis is supported by a small clinical trial that showed greater hemodynamic stability and less progression in brain white matter in hemodialysis patients treated with cooler dialysate.⁴⁹

Stroke Implications in CKD

In the CHOICE cohort of incident dialysis patients, outcomes after stroke were poor: 35% of strokes were fatal (28% of ischemic strokes and 90% of hemorrhagic strokes), and only 56% of patients who experienced a stroke were able to be discharged to home or acute

rehabilitation.³⁰ In the nondialysis population, a lower eGFR and proteinuria are associated with worse outcomes after stroke.^{50,51} Similarly, a recent analysis of US dialysis patients showed a 30-day mortality rate of 18% and a 1-year mortality rate higher than 50% after ischemic stroke; outcomes after hemorrhagic stroke were even worse, with a 30-day mortality rate of 53% and a 1-year mortality rate of higher than 75%.⁵² The combination of CKD and stroke has substantial socioeconomic implications. Among Medicare beneficiaries, the combination of stroke and CKD was the most costly chronic condition dyad and comprised four of the top five most costly triads of conditions (Table 3).⁵³ Patients with stroke and chronic kidney disease had per-capita costs that were approximately 5 times higher than the average spending for Medicare FFS beneficiaries.

Stroke Risk Factors and Risk Factor Management in CKD

In all populations, hypertension is among the most prominent modifiable risk factor for stroke.¹⁵ This holds true in people with CKD. In the study described earlier that pooled four US population-based studies, among participants with an eGFR of less than 60 mL/min per 1.73 m², risk factors were similar to those with maintained kidney function.²⁰ These studies largely collected data on traditional vascular disease risk factors, defined as those associated with cardiovascular disease in the Framingham Heart Study population. In people with CKD, there is a high prevalence of nontraditional cardiovascular disease risk factors, including mineral and bone disorder, altered nitric oxide balance and vascular reactivity, fluid overload, hyperhomocysteinemia, and inflammation. Traditional and nontraditional risk factors that are associated with cardiovascular disease, and therefore likely associated with cerebrovascular disease, are summarized in Table 4. Whether these are causal or just markers of more severe kidney disease, and therefore more severe cardiovascular disease, remains uncertain for most of these risk factors.⁴

Given the strong association between hypertension and stroke, blood pressure management is an attractive strategy for both primary and secondary stroke prevention. In CKD, similar to the general population, higher stroke risk is seen with higher systolic blood pressure, although one patient-level meta-analysis of observational data did show a slightly higher risk of stroke events with a systolic blood pressure less than 120 mm Hg in people with a reduced eGFR.⁵⁴ It is uncertain whether this reflects low blood pressure itself as a stroke risk factor or suggests that low blood pressure in people with CKD identifies a high-risk cardiovascular disease cohort owing to underlying comorbid conditions. Based on a meta-analysis of more than 150,000 participants in 25 blood pressure lowering trials, there was no difference in the relative risk reduction in major cardiovascular events (including stroke) associated with decreasing blood pressure in people with eGFR less than 60 mL/min per 1.73 m² versus those with an eGFR greater than 60 mL/min per 1.73 m².⁵⁵ Critically, given the much higher event rates among people with a lower eGFR, the absolute benefit associated with blood pressure reduction among people with a reduced eGFR is greater. Notably, with a mean eGFR of 52 mL/min per 1.73 m² among individuals classified as having CKD, these results may not be generalizable to people with more advanced kidney disease.⁵⁵

Atrial fibrillation is an important cause of thromboembolic stroke, with other cardiac diseases also contributing, including valvular disease. Both atrial fibrillation and valve disease are very common in people with CKD. In a large cohort of patients followed up by Kaiser Permanente, 8% of beneficiaries with an eGFR less than 60 mL/min per 1.73 m² were diagnosed with atrial fibrillation whereas data from the Chronic Renal Insufficiency Cohort suggested that nearly 20% of people with nondialysis CKD may have atrial fibrillation.^{56,57} Not surprisingly, atrial fibrillation is associated with an increased risk of mortality in people with CKD, even after adjusting for other risk factors.⁵⁷ Among dialysis patients, based on administrative data, estimates of atrial fibrillation prevalence range from 8% to 20%.^{58–60} Atrial fibrillation is associated with a two-fold increase in all-cause mortality risk,^{59,60} although the association between atrial fibrillation and stroke may be less marked than seen in the general population owing to other competing risks.⁵⁸

The role for thromboprophylaxis for atrial fibrillation in CKD, particularly in dialysis patients, remains uncertain. At the current time, there is no apparent reason to treat individuals with nondialysis CKD differently from the general population with regard to anticoagulation for atrial fibrillation, although this population has not been studied specifically in clinical trials. A post hoc evaluation provided reassuring data that warfarin thromboprophylaxis was appropriate for individuals with atrial fibrillation and stage 3 CKD,⁶¹ whereas a study using administrative data encompassing Denmark's entire adult population showed significant reductions in stroke risk associated with anticoagulation.⁶²

Decisions regarding anticoagulation in dialysis patients with atrial fibrillation depend on observational data given the absence of clinical trials. Studies to date have shown discrepant results, with several studies showing either no benefit or greater mortality risk in dialysis patients with atrial fibrillation treated with warfarin,^{63–65} in contrast to the Denmark study described earlier, which showed potential benefits associated with thromboprophylaxis in dialysis patients.⁶² Although anticoagulation with warfarin is associated with a high risk of bleeding, particularly in CKD,^{64,66,67} potential nonhemorrhagic risks of warfarin are important. Specifically, warfarin, a vitamin K antagonist, inhibits carboxylation of matrix gla protein, which, in experimental models, is associated with a marked increase in vascular calcification. Given the procalcification dialysis milieu, further promotion of calcification with warfarin may be associated with increased rather than decreased cardiovascular disease risk.^{68,69} In sum, the decision to use warfarin for primary stroke prevention in dialysis patients is an individualized one that should incorporate patient input regarding their preferences given the absence of consistent data showing stroke reduction and potential risks shown in several reports.⁶⁹ In the future, novel anticoagulants that do not inhibit vitamin K may be an option for dialysis patients, but at the current time they remain insufficiently studied.⁶⁹

One previously attractive nontraditional stroke risk factor was hyperhomocysteinemia. Homocysteine levels are high in people with CKD, particularly in patients treated with dialysis, and higher levels of homocysteine have been associated with stroke in multiple cohort studies.⁷⁰ The association between homocysteine and cerebrovascular disease led some investigators to recommend decreasing homocysteine levels,⁷¹ with the American Heart Association/American Stroke Association Council on Stroke in 2006 noting that,

despite a lack of evidence for secondary prevention, daily standard multivitamin preparations are reasonable to reduce the level of homocysteine, given their safety and low cost.⁷² Given the lack of evidence, the 2014 update for recurrent stroke prevention recommends against screening homocysteine levels⁷³ whereas the 2014 update for primary prevention notes that vitamin therapy could be considered for decreasing homocysteine levels.⁷⁴ This reflects multiple negative or only borderline positive trials evaluating whether there is a benefit in stroke reduction associated with therapy that decreases homocysteine levels, both in the general and CKD populations.^{75–78} Since this update, in 2015, the China Stroke Primary Prevention Trial, a randomized, double-blind, clinical trial performed in 20,702 adults with hypertension and without history of stroke or myocardial infarction, showed a significant reduction in stroke among participants randomized to supplementation with 0.8 mg of daily folic acid. Of note, this population had normal kidney function and was recruited from a region where dietary folic acid fortification is uncommon, rendering the applicability of these results uncertain to a Western CKD population.⁷⁹

Stroke Manifestations in CKD

The physical manifestations of stroke in people with CKD are beyond the scope of this review, but mirror those of the general population. Cerebrovascular disease has protean manifestations, causing not only stroke but varying degrees of cognitive impairment. Given the high prevalence of cerebrovascular disease in people with CKD, these manifestations may be very common.⁸⁰ Cognitive impairment is far more subtle than many manifestations of cerebrovascular disease but has important implications for morbidity and mortality.⁸¹ Similarly, the hemodialysis procedure itself may contribute to brain disease, with hemodynamic perturbations leading to ischemic damage.⁸²

ACUTE TREATMENT OF ISCHEMIC STROKE

Although there are few studies specifically in people with CKD, based on similarities seen with other cardiovascular disease interventions between the non-dialysis CKD and general populations,^{83–85} it is likely that acute stroke management for most people with nondialysis CKD should be similar to the general population.⁸⁶ Among patients with very advanced CKD, including patients treated with dialysis, there is a higher risk of intracerebral bleeding than among the general population.⁸⁷ This accordingly introduces higher risk with antithrombotic treatments, such as would be administered in the setting of an acute stroke.

Current guidelines for the general population recommend that, in the absence of contraindications, patients with acute ischemic stroke presenting within the first 3 hours, as well as many within the first 4.5 hours (with several additional contraindications), should be treated with thrombolytic therapy (class IA recommendation).⁸⁶ The tissue plasminogen activator (tPA) alteplase remains the most well-studied thrombolytic in the setting of acute ischemic stroke. There are no dosage adjustments based on kidney function, although the package insert states that the risks of using alteplase (most common being bleeding) may be increased in certain conditions including “severe renal disease.”⁸⁸ There also is increasing experience with catheter-directed arterial tPA and mechanical interventions including thrombectomy with extraction and angioplasty with stent placement, although none of these

have a Food and Drug Administration clinical indication for treatment of acute ischemic stroke.⁸⁶

Table 4 shows the American Stroke Association and American Heart Association's joint current guidelines on inclusion and exclusion criteria for use of tPA in patients presenting with ischemic stroke within 3 hours of symptom onset, with additional contraindications for treatment during the first 3 to 4.5 hours detailed in the footnote.⁸⁶ The most notable contraindication for dialysis patients is recent receipt of heparin with an abnormal PTT; this is discussed in more detail later because, depending on the interpretation, it may preclude the administration of tPA in most hemodialysis patients.

Limited data exist evaluating the efficacy and safety of tPA in individuals with advanced kidney disease, with dialysis patients generally not included in clinical trials or reported in insufficient numbers in observational studies to draw meaningful conclusions. Results from retrospective database studies evaluating the efficacy and safety of tPA for ischemic stroke treatment in CKD generally show poorer outcomes among individuals with CKD as compared with the general population, including higher risk of intracerebral hemorrhage (ICH), poorer poststroke performance, and higher risk of death.^{89,90} Similarly, a retrospective study of "Get with the guidelines-Stroke" data from 1,564 US hospitals showed significantly higher risks of ICH, serious systemic hemorrhage, in-hospital mortality, and lack of independent ambulation at the time of discharge in the CKD group.⁹¹ After adjustment for baseline demographics and other risk factors, these relationships were attenuated substantially. Critically, within this cohort, patients with CKD were less likely to receive recommended therapies for acute stroke management, with the fewest recommended therapies provided to those with the poorest kidney function.⁹² Gensicke et al⁹³ evaluated data prospectively collected at 11 European stroke centers, including 4,780 patients treated with tPA, of whom 1,217 (25.5%) had an eGFR less than 60 mL/min per 1.73 m², and 1,427 patients treated without tPA, of whom 465 (32.5%) had an eGFR less than 60 mL/min per 1.73 m². In patients treated with tPA, there was a statistically significant association between low eGFR and an increased risk for poor neurologic outcome, death, and ICH in multivariable analyses. Adverse outcomes were significantly more likely among patients with an eGFR less than 60 who were treated with tPA compared with those with an eGFR less than 60 mL/min per 1.73 m² who were not treated with tPA, although there likely was substantial residual confounding, making these results difficult to interpret.⁹³

There are very few studies that have evaluated treatment of dialysis patients with ischemic stroke. One major barrier is that use of heparin within 48 hours of stroke onset with an increased PTT is a contraindication to receiving tPA (Table 1); hemodialysis patients almost universally receive heparin during dialysis sessions, and PTT levels frequently are increased minimally, even at times remote from dialysis. Critically, one pharmacodynamic study showed that, among patients treated with standard heparin protocols, anti-factor Xa levels were undetectable (<0.1 IU/mL) at 120 minutes after dialysis in hemodialysis patients treated with 4 hours of heparin during dialysis, suggesting that PTT may not be the optimal measure of bleeding risk in this population.⁹⁴ Kidney Disease Outcomes Quality Initiative guidelines from 2005 take heparin administration during dialysis into account and state that the original stipulation of excluding patients who have received heparin in the previous 48

hours was not designed to address patients on intermittent dialysis and that use of tPA for ischemic stroke should be considered on an individual patient basis.⁹⁵

One retrospective study examined US data from the National Inpatient Sample between 2002 and 2009, specifically focusing on ischemic stroke treated with tPA in dialysis patients. Of 82,142 patients receiving tPA, 1,007 were receiving hemodialysis and 65 were receiving peritoneal dialysis. In this select population of dialysis patients treated with tPA, the occurrence of ICH after tPA did not differ significantly from nondialysis patients, although the in-hospital mortality was significantly higher.⁹⁶ This lack of experience and comfort with treating dialysis patients with tPA was reflected in a recent survey of 40 stroke experts; only one third of the experts had experience with using tPA for ischemic stroke in dialysis patients whereas half reported reservations related to concerns about higher bleeding risk.⁹⁷ In this study, when presented with the hypothetical scenario of a hemodialysis patient presenting with an ischemic stroke shortly after finishing a session of HD with a mildly prolonged aPTT, only 17 of 40 experts would have treated with intravenous tPA whereas the rest cited guidelines regarding prolonged aPTT and heparin use being contraindicated to tPA use.

CONCLUSIONS

Cerebrovascular disease and stroke are very common at all stages of 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. For individuals with nondialysis CKD, the prevention of, approach to, and 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 the prevention of stroke. End-stage renal disease patients can be managed aggressively in the setting of acute stroke, although clinical trials are needed to better inform therapy in this population. Outcomes after stroke at all stages of CKD are poor, and improving these outcomes should be the subject of future clinical trials Table 5.

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Figure 1.

Usual SBP and the risk of stroke, stratified by age, extrapolated from multiple prospective cohort study overviews. The risk of stroke (y-axis) is plotted on a log scale. Solid squares are larger when there are more events, with the size of the squares proportional to the inverse variance. Vertical lines represent 95% confidence intervals (CIs). Reprinted with permission from Lawes et al.¹⁵

Figure 2. Association between proteinuria and stroke. RR, relative risk; CI, confidence interval. Reprinted with permission from Ninomiya et al.²³

Figure 3.

Age- and sex-matched incidence rates of hemorrhagic stroke (HS) and ischemic stroke (IS) stratified by age in hemodialysis (HD) patients, peritoneal dialysis (PD) patients, and the reference cohort (RC). Rates are plotted on a logarithmic scale. Reprinted with permission from Wang et al.²⁶

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.

Table 2

Items Assessed in the National Institutes of Health Stroke Scale

Neurologic Function	Items Assessed
Level of consciousness	Examiner assessment of level of consciousness Patient ability to state age and the current month Patient ability to follow basic commands
Best gaze	Horizontal eye movements
Visual fields assessment	Visual fields tested by confrontation
Facial palsy	Ranges from normal to complete paralysis
Motor function	Arm strength and drift against gravity Leg strength and drift against gravity
Limb ataxia	Finger-nose-finger and heel-shin tests
Sensory	Pinpricks
Best language	Description of events in a standardized picture Naming items from standardized pictures Reading form a standardized list of sentences
Dysarthria	Qualitative assessment of speech slurring

More points are given within each assessment for poorer performance.

Data from http://www.ninds.nih.gov/doctors/NIH_Stroke_Scale_Booklet.pdf.

Prevalence of and Per-Capita Costs Associated With Medical Conditions Among US Medicare Fee-for-Service beneficiaries in 2010

Table 3

Costly Dyads			Costly Triads		
Dyad	Prevalence	Per Capita	Triad	Prevalence	Per Capita
Stroke and CKD	2.0%	\$51,715	Stroke, CKD, asthma	0.2%	\$69,980
Stroke and COPD	1.4%	\$49,025	Stroke, CKD, COPD	0.8%	\$68,956
Stroke and heart failure	2.3%	\$47,568	Stroke, CKD, depression	0.8%	\$65,153
Stroke and asthma	0.4%	\$46,913	Stroke, CKD, heart failure	1.5%	\$63,242
COPD and CKD	4.9%	\$45,011	Stroke, heart failure, asthma	0.3%	\$62,819

The five most costly dyads and triads are presented.

Abbreviation: COPD, chronic obstructive pulmonary disease.

Data derived from Centers for Medicare and Medicaid Services.⁵³

Table 4

Traditional and Nontraditional Cardiovascular Disease Risk Factors

Traditional Risk Factors	Nontraditional Factors
Older age	Atrial fibrillation
Male sex	Extracellular fluid volume overload
Hypertension	Abnormal calcium/ phosphate metabolism
Diabetes	Anemia
Smoking	Oxidative stress and inflammation
Dyslipidemia	Homocysteine
Left ventricular hypertrophy	Malnutrition
Physical inactivity	Albuminuria
Obesity	Thrombogenic factors
Menopause	Sleep disturbances
Family history of cardiovascular disease	Altered nitric oxide/ endothelin balance
	Other uremic toxins

Risk factors for cerebrovascular disease and coronary heart disease appear similar across cohort studies. Traditional risk factors were identified in the Framingham Heart Study as predisposing to cardiovascular disease whereas nontraditional risk factors were identified subsequently, predispose to cardiovascular disease, and are more common in people with kidney disease.

Table 5

Inclusion and Exclusion Criteria for Treatment of Ischemic Stroke With Intravenous Recombinant Tissue-Type Plasminogen Activator Within 3 Hours of Symptom Onset

Inclusion criteria
Diagnosis of ischemic stroke causing measurable neurologic deficit
Onset of symptoms fewer than 3 hours before beginning treatment
Age 18 y
Exclusion criteria
Significant head trauma or prior stroke in previous 3 months
Symptoms suggestive of subarachnoid hemorrhage
Arterial puncture at a noncompressible site in previous 7 days
History of previous intracranial hemorrhage
Recent intracranial or intraspinal surgery
Intracranial neoplasm, AV malformation, or aneurysm
Increased blood pressure (systolic >185 mm Hg or diastolic >110 mm Hg)
Active bleeding
Acute bleeding diathesis
Platelet count <100,000/mm ³
Heparin received within 48 hours, resulting in abnormally increased aPTT greater than the upper limit of normal
Concurrent use of anticoagulants with INR >1.7 or PT >15 seconds
Current use of direct thrombin inhibitors or direct factor Xa inhibitors with increased laboratory test results (such as aPTT, INR, ECT, TT; or appropriate factor Xa activity assays)
Blood glucose concentration <50 mg/dL
Computed tomography scan of the head showing multilobar infarction (hypodensity >1/3 cerebral hemisphere)
Relative exclusion criteria*
Only minor or rapidly improving stroke symptoms (clearing spontaneously)
Pregnancy
Seizure at onset with postictal residual neurologic impairments
Major surgery or serious trauma within previous 14 days
Recent gastrointestinal or urinary tract hemorrhage (within previous 21 days)
Recent acute myocardial infarction (within previous 3 months)

Additional exclusion criteria for treatment during the 3- to 4.5-hour window are age older than 80 years, oral anticoagulant use regardless of international normalized ratio, baseline National Institutes of Health Stroke Scale score greater than 25, imaging evidence of ischemic injury involving more than one third of the MCA territory, or history of both stroke and diabetes mellitus.

Abbreviations: aPTT, activated thromboplastin time; ECT, ecarin clotting time; INR, international normalized ratio; PT, partial thromboplastin time; TT, thrombin time.

* May receive recombinant tissue-type plasminogen activator therapy despite 1 or more relative contraindications with careful consideration of risks and benefits

Data were abstracted from the 2013 American Stroke Association/American Heart Association's guideline for early management of acute ischemic stroke.⁸⁶