

Stroke in Patients with Chronic Kidney Disease...: How do we Approach and Manage it?

Abstract

Renal failure is a potent risk factor for stroke, which is a leading cause of morbidity and mortality worldwide. The risk of stroke is 5–30 times higher in patients with chronic kidney disease (CKD), especially on dialysis. Case fatality rates are also higher reaching almost 90%. It is therefore important to understand the factors that predispose to stroke in this vulnerable population to better apply preventive strategies. The heightened risk of stroke in CKD represents the interplay of the vascular co-morbidities that occur with renal impairment and factors specific to renal failure such as malnutrition-inflammation-atherosclerosis complex, the effect of uremic toxins, dialysis techniques, vascular access, and the use of anticoagulants to maintain flow in the extracorporeal circuit. Old age, hypertension, diabetes, and previous cerebrovascular disease are all risk factors for stroke with the period of dialysis initiation constituting the highest risk period for developing new stroke. Patients with CKD-stage 3–5 have worse survival and diminished functional outcomes following stroke. Thrombolytic therapy for stroke in CKD has shown an increased risk of symptomatic intracranial hemorrhage or serious systemic hemorrhage, and the therapeutic effects may be attenuated. Benefit of statin therapy in dialysis patient as preventive therapy has not been shown to be beneficial. Control of hypertension and the judicious use of antiplatelet agents form the mainstay of stroke prevention. The benefit of antiplatelet therapies and oral anticoagulants has to be balanced against the real and increased risk of bleeding that is most evident in dialysis cohorts. An increased risk of vascular calcification particularly intracerebral vascular calcification has been seen in patients receiving warfarin as prophylaxis in atrial fibrillation. Newer anticoagulants have not been tested in patients with glomerular filtration rate <30 ml/min and hence have to be used with caution. This article is a review of stroke in patients with CKD and approach to managing it.

Keywords: Antiplatelet agents, chronic kidney disease, hemorrhage, ischemic, stroke

Introduction

Cardiovascular disease is the leading cause of death in patients with kidney failure. Although much focus has been given to the high rates of cardiac disease including myocardial infarction, cardiomyopathy, and cardiac arrhythmia, equal attention needs to be given to the equally debilitating burden of cerebrovascular disease. Several conventional risk factors for atherosclerosis are more prevalent in patients with chronic kidney disease (CKD). And hence, the risk of cardiovascular diseases, including stroke in patients with end-stage renal disease (ESRD) is 5–30 times greater than that in the general population.^[1] The risk of hemorrhagic stroke has been reported to be higher than ischemic stroke in hemodialysis (HD) patients when

compared to peritoneal dialysis (PD) patients, though this has not been consistently the case, especially in recent studies. Risk factors for stroke include nonmodifiable risk factors such as older age, diabetes, male gender, non-Caucasian/Asian ethnicity, and a positive family history.^[2] Hypertension continues to be the major modifiable risk factor for both ischemic and hemorrhagic stroke with risk increasing with worsening systolic and diastolic blood pressure control. Atherosclerotic risk factors such as smoking, hyperlipidemia as well as atrial fibrillation (AF) increase risk of ischemic stroke. The prevalence of AF in CKD population is more than twice in the general population^[3] and confers a greater thromboembolic risk. Stroke rates continue to increase in the low- to middle-income countries in contrast to declining stroke risk in high-income countries.

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Stroke Risk in Predialysis Chronic Kidney Disease

The co-existence of several vascular risk factors in patients with CKD has been postulated as the reason for the observed association of renal dysfunction with stroke. Hypertension, diabetes mellitus, dyslipidemia, and proteinuria are all highly prevalent in the CKD population. Moreover, factors specific to CKD include accelerated atherosclerosis, vascular calcification, effect of uremic toxins, prothrombotic tendency, and impaired cerebral autoregulation. Intracranial arterial calcification, which is associated with stroke risk in the general population increases in prevalence in patients with CKD.

A graded and independent relationship between estimated glomerular filtration rate (eGFR) and stroke risk has been reported in some studies. A recent meta-analysis incorporating data from 33 studies reported a 43% independent risk of stroke with eGFR <60 ml/min.^[4] This increased risk effect was further modulated by the ethnicity of the patient with a higher stroke risk seen in Asian compared to non-Asian populations (relative risk [RR] 1.96 vs. 1.26, $P < 0.0001$). The presence of proteinuria is itself an important risk factor for stroke even in the absence of reduced GFR and after the adjustment for other vascular risk factors.^[5] A meta-analysis of observational cohort studies observed that patients with proteinuria had an adjusted risk ratio of 1.71 (95% confidence interval [CI] 1.39–2.10, $P = 0.008$). It is not known however if interventions to reduce proteinuria are effective in reducing rates of stroke.

Stroke Risk in Dialysis

Patients with ESRD on dialysis have a 8–10 times greater incidence of stroke compared to the general population with rates varying from 10 to 33 per 1000 patient years in published series.^[6–8] The age-adjusted RR of stroke among dialysis patients compared to the general population was 6.1 (CI - 5.1–7.1) for Caucasian males and 9.7 (CI - 8.2–11.2) for African American males. There are also notable differences in the type of CVA in dialysis patients versus the general population with a higher prevalence of hemorrhagic CVA. A 22-year single center study of stroke in patients on maintenance HD compared HD patients^[9] with stroke to stroke with normal kidney function. It was noticed that stroke patients receiving HD were younger (age 64 ± 10 vs. 67 ± 13 years, $P < 0.02$). In the HD group, hemorrhagic stroke was the major subtype of stroke (52%), whereas in the control group, ischemic stroke was more prevalent (68%). This may have been a reflection of uncontrolled hypertension in this cohort as well as a genetic predisposition. It is important to note that the majority of data about stroke in dialysis patients is derived from HD population from the United States and Japan. The only European study^[6] that has looked at stroke

risk in maintenance HD patients revealed a first stroke rate of 14.9/1000 patient years (95% CI - 12.2–17.9) with a predominance of ischemic compared to hemorrhagic subtypes (11.2 vs. 3.7 per 1000 patient years). Hemorrhagic strokes occurred more frequently in patients of South-Asian ethnicity compared to ischemic strokes which occurred predominantly in caucasian patients. Most studies with ESRD have focused on HD patients and less is known about the incidence, RRs, and subtypes of stroke in PD patients. Wang *et al.* looked at data of >5000 PD patients and compared it to 74,192 HD patients in a retrospective cohort study.^[8] In comparison to the HD group, it was found that PD patients had a lower risk of hemorrhagic stroke (hazard ratio [HR] 0.75, 95% CI - 0.58–0.96), and there was no significant difference in risk of ischemic stroke between HD and PD patients after adjusting for all potential confounders and competing risk of death and matched by propensity scores. In the largest PD cohort to date from the United Kingdom ($n = 1511$) with a mean age of 55 years, the overall incidence of stroke was 9.8/1000 patient years.^[10]

There are several reasons to hypothesize why patients on PD may have a lower stroke risk compared to HD patients. HD is marked both by intradialytic hypotension^[11,12] and sometimes hypertension. The initiation of dialysis itself is associated with a heightened risk of stroke. In an analysis of US Dialysis patients aged ≥ 67 years, stroke rates began to rise about 3 months before dialysis initiation and reached a peak during the first 30 days of dialysis initiation. This pattern was observed irrespective of dialysis modality and whether patients started dialysis in a planned manner.^[13] In a Japanese study, 39% of ischemic and 35% of hemorrhagic strokes occurred during or within 30 min of concluding HD suggesting that the treatment itself may mediate stroke risk.^[9] There are some risk factors distinct to the uremic process such as hyperhomocysteinemia, endothelial dysfunction, chronic inflammation and disturbances in mineral metabolism with associated calcification, which predisposes dialysis patients to accelerated atherosclerosis.

The prevalence of AF in patients with CKD is extremely high and an increasing hazard ratio for new – onset AF with decreasing kidney function has been found even in multivariate analysis. The Chronic Renal Insufficiency Cohort study reported a prevalence of 16.0% for AF in patients with eGFR >45 ml/min and 20.4% in patients with eGFR <45 ml/min.^[14] In dialysis – dependent patients with CKD, the prevalence of AF is estimated to range from 3.5% to 27% depending on AF type.^[15] The association between renal dysfunction and bleeding has long been recognized, and morbidity and mortality from bleeding remain a significant clinical problem. While the usefulness of oral anticoagulation therapy for the primary and secondary prevention of stroke in patients with AF in the non-CKD population has been well documented, it has not been consistently seen in the dialysis population.

Patients on HD are also regularly exposed to heparin anticoagulation during the course of their treatment and this can complicate matters. Anticoagulation guidelines and frameworks for monitoring for the general population at risk for stroke may not be applicable to patients who concomitantly suffer from vascular disease and ESRD. The hazards of anticoagulation may outweigh its benefits in ESRD subpopulations. In a retrospective cohort study^[16] of incident ESRD patients with co-existing AF, warfarin use was associated with an increased risk of stroke presumably hemorrhagic stroke even after controlling for potential confounders. Warfarin may potentiate vascular calcification to increase the risk of ischemic stroke.^[17] Oral anticoagulants should therefore be carefully used in CKD patients with CHADS score ≥ 2 with careful monitoring. The role of newer non Vitamin K dependent anticoagulants such as dabigatran, rivaroxaban, and apixaban has not been tested in patients with eGFR <30 ml/min. Because of renal elimination, these have a prolonged half-life in CKD patients resulting in increased bleeding risk and have to be used cautiously. At present, there is little data about their use and safety in ESRD patients.

Outcome of Stroke in Chronic Kidney Disease and Dialysis

CKD is an independent risk factor for both ischemic as well as hemorrhagic stroke. In addition, renal impairment is associated with a greater neurological deficit following ischemic stroke, a poor functional outcome and greater mortality.^[18] Following acute ischemic stroke, advanced CKD (eGFR <30 ml/min) has been associated with a higher risk of hemorrhagic transformation (odds ratio [OR] 2.90, 95% CI - 1.26–6.68, $P = 0.01$).^[19] In patients with hemorrhagic stroke, moderate – severe CKD has been associated with 2.3 times greater hematoma volume.^[20] These findings may represent the greater co-morbid profile of patients with CKD who experience a stroke or reflect subclinical cerebral vascular disease burden seen in patients with renal failure.

Stroke Management in Chronic Kidney Disease Patients

Systemic thrombolytic therapy with recombinant tissue plasminogen activator (rTPA) is the standard of care for patients presenting within 4.5 h of onset of symptoms following ischemic stroke. Clinical trials testing rTPA for acute ischemic stroke did not specifically include patients with CKD and ESRD. The US National Get With the Guideline–stroke (GWTG-Stroke) registry analyzed the association of CKD with key hemorrhagic outcomes after IV TPA for acute ischemic stroke.^[21] Out of 44,410 patients with stroke treated with IV TPA, 34% (15,191) patients had CKD. Presence of CKD was not associated with risk-adjusted symptomatic intracranial hemorrhage (adjusted OR 1.0, 95% CI - 0.80–1.18). However, the study found

that compared to those patients with normal kidney function, those with CKD were more likely to die in hospital (OR 1.22, 95% CI - 1.14–1.32) and have an unfavorable discharge functional status (OR 1.13, 95% CI - 1.07–1.99). The risk of symptomatic hemorrhage did not actually lead to increased mortality, and other CKD related factors were responsible. These findings imply that the presence of CKD alone should not be a contraindication to administration of IV TPA for eligible patients.

Stroke Prevention in Chronic Kidney Disease and Dialysis

With greatly increased risk of stroke and poorer outcomes, in this vulnerable group of patients, it is important that preventive strategies be better applied to reduce stroke rates. Traditionally, patients with advanced renal impairment have been excluded from randomized controlled trials (RCT) involving the impact of healthcare intervention on the occurrence of stroke. It has been the norm to apply treatment algorithms from the general population and extrapolate them to patients with CKD. However, the presumption of efficacy in this group of patients with multiple co-morbidities can be misleading. Control of hypertension remains the cornerstone of primary as well as secondary stroke prevention in the general population as well as in patients with nondialysis CKD. In earlier stages of CKD such as CKD Stage 1, 2, a linear relationship^[22] was seen between attained blood pressure (BP) and stroke risk. However, earlier studies showed a J-shaped relationship in patients with CKD with systolic BP <120 mm of Hg associated with a 2.5 times greater risk.^[23] No optimum targets for BP control have been defined for hypertension control in dialysis patients and there are no data to recommend one class of antihypertensives over another.

Clinical guidelines advocate the use of antiplatelet therapy for the presence of ischemic stroke, and there is evidence supporting its efficacy in patients with nondialysis CKD.^[24] The risk of bleeding with prophylactic antiplatelet agents is augmented in ESRD, and they have to be used with caution. Dual therapy with aspirin and clopidogrel augments the bleeding risk manifold and is therefore used with extreme caution unless there are other indications such as cardiac stent, which warrants their use. Stroke thromboprophylaxis with oral anticoagulants like warfarin or the newer agents such as dabigatran and rivaroxaban are recommended for patients with AF with CHADS score ≥ 2 .^[25] However, as has been said before, there have been no RCTs in CKD/ESRD patients and the anticoagulation targets for CKD patients are not known and guidelines applicable for the general population have been applied. Evidence-based answers in the form of a prospective clinical trial comparing dialysis patients with AF to placebo and oral anticoagulation therapy are urgently needed.

Lipid lowering with statin therapy is effective in lowering stroke risk in patients with CKD 3–4.^[26] This

was demonstrated in the Study of Heart and Renal Protection (SHARP) study. However, in a subgroup analysis of dialysis patients enrolled in SHARP as well as other RCT's statin therapy^[27] did not have any significant effect in reducing stroke risk. The rationale therefore for use of statins as prophylactic agents remains a matter of debate.

Anemia has been shown to substantially increase the risk of stroke associated with CKD.^[28] Both the Correction of Anemia with Epoetin Alfa in CKD (CHOIR)^[29] and A Trial of Darbepoetin Alfa in Type-2 Diabetes and CKD (TREAT)^[30] study have shown that hemoglobin targets >13.0 g/dl using higher doses of erythropoietin was associated with greater risk of MI, stroke or congestive cardiac failure. This may be because of the small BP increase noted with erythropoietin, lessened bleeding when hematocrit is raised, and hence a higher thrombotic tendency, increased blood viscosity. Potential carotid endarterectomy is recommended for patients with symptomatic, high grade (>70%) carotid stenosis to reduce subsequent stroke risk. In CKD Stage 3 patients, endarterectomy reduced the risk of stroke by 82% at 2 years.^[28] In this study, patients with CKD had similar rates of perioperative mortality but higher rates of cardiac events. Similar data in HD patients are not available and the long term benefits of this procedure in ESRD patients are less clear.

Stroke Risk after Kidney Transplantation

Kidney transplantation is the preferred treatment for patients with ESRD. Graft survival has increased considerably over the last decades due to the improvements in patient care, newer immunosuppressive strategies and posttransplant surveillance. Nevertheless, cardiovascular problems remain an important factor for morbidity and mortality after kidney transplantation and contribute to problem of death with functioning graft. In contrast to stroke, which has been widely reported in chronic dialysis patients, reports on cerebrovascular outcomes in kidney transplant recipients are scarce. Oliveras *et al.*^[31] reported a stroke prevalence rate of 7.9% over a 10-year period in 403 transplant patients. Hemorrhagic stroke was reported in 36.84% of stroke patients and older age, diabetes, and peripheral vascular disease were predictive factors. Other studies^[32,33] have also looked at predictive risk factors and the presence of AF, diabetes, duration of pretransplant dialysis, acute rejection, and pretransplant history of stroke were found to be significant risk factors. Beyond their ability to detect severely co-morbid patients, pretransplant screening tests such as carotid ultrasound and echocardiography were not able to identify renal transplant candidates at risk for stroke after renal transplantation. Further research is warranted to allow better risk stratification and facilitate clinical trials for risk attenuation of stroke after a kidney transplant.

Conclusions

The occurrence of stroke in CKD patients, especially the manifold increased risk in ESRD patients is an expression of increased and accelerated atherosclerosis in this group. However, in comparison to cardiac disease, this has been relatively understudied. It is therefore important to understand the risks as well as benefits of established therapy for stroke management and prevention and apply them judiciously in all stages of CKD. The need of the hour are well-designed randomized controlled trials in CKD/ESRD and postrenal transplant patients that can address and provide answers to important questions in this vulnerable group.

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Conflicts of interest

There are no conflicts of interest.

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