A Review of Risk Factors for Stroke in Patients with Chronic Kidney Disease

Abstract

Background: Patients with chronic kidney disease (CKD) are at higher risk for stroke because of higher prevalence of traditional and non-traditional cardiovascular risk factors.

Methods: We performed an extensive literature review with pre-defined keywords. We summarized the results of the studies evaluating for risk factors predisposing to stroke in CKD patients.

Results: The incidence of stroke and stroke-related mortality is higher in CKD patients compared with the general population. Presence of anemia, hypoalbuminemia, malnutrition, uremia, and hyperhomocysteinemia in patients with CKD is associated with higher incidence of stroke. Hemodialysis and renal transplant patients are at higher risk of developing stroke compared with those who do not require renal replacement therapy.

Conclusion: The early recognition of risk factors associated with stroke in CKD population is imperative. Early interventions may potentially decrease the incidence and associated mortality of stroke in CKD patients.

Keywords: stroke; chronic kidney disease, risk factors, dialysis, renal transplant, ischemic stroke.

Almost 20 million people in United States have chronic kidney disease (CKD).1 CKD is defined as glomerular filtration rate (GFR) less than 60 ml/min/1.73 m^2.1,2 Patients with CKD have markedly increased incidence of vascular disease when compared to the general population.3 Traditional risk factors for stroke such as diabetes mellitus, hypertension, cardiac disease, hyperlipidemia and cigarette smoking are quite common in this population but little is known about the risk factors which are different from the general population. In this review article, we will emphasize on important non-traditional risk factors unique to the CKD population.

Incidence of stroke
The incidence of stroke is much higher in CKD patients than in the general population.4 The United States Renal Data System (USRDS) and National Hospital Discharge Survey (NHDS) datasets show that the incident dialysis population suffers a five to ten fold higher risk of hospitalized stroke in comparison with non-End Stage Renal Disease (ESRD) population.5 (relative risk; RR of 6.1 in ESRD population). Stroke risk is elevated for both ischemic and hemorrhagic stroke; however there is a higher risk for ischemic stroke than for hemorrhagic stroke, especially among women (ischemic stroke RR ranges from 4.3 to 10.1; hemorrhagic stroke, RR ranges from 4.1 to 6.7).6

In a study of 6685 hospitalized patients, Koren-Moreg et al7 found that an eGFR less than 60 ml/min had a hazard ratio (HR) of 1.5 for increased rate of incident stroke or transient ischemic attack in patients with CKD and pre-existing cardiovascular diseases. The risk increased with decreasing eGFR values. Preliminary results in the Kidney Early Evaluation Program (KEEP)8 found that eGFR less than 60/min/1.73m² or urine albumin to creatinine ratio >30mg/g was associated with higher risk of either myocardial infarction or stroke.

Stroke related mortality
The short and long term mortality associated with stroke appears to be higher in CKD patients than in the general population. In the Okinawa Dialysis Study (OKIDS)9, 30 day stroke mortality rate was higher in CKD patients compared with the rate observed in general population in Okinawa, Japan. The size of the lesion in hemorrhagic strokes was larger in the CKD patients than in the general
population. McWalter et al \textsuperscript{10} also found that renal dysfunc-
tion was a predictor of an increased mortality in the 7 year 
follow up study of acute stroke patients. A summary of risk 
Factors for stroke unique to the CKD population are presented in Table 1:

### 1) Age, Ethnicity and Gender:
Seliger et al \textsuperscript{11} found in their population based study that the age 
adjusted RR of stroke among dialysis patients was 6.1 [95% 
Confidence Interval (95% CI) 5.1, 7.1] compared with the gen-
eral population for Caucasian men, 4.4 (95% CI 3.3, 5.5) for 
African American men, 9.7 (95%CI 8.2, 11.2) for Caucasians 
women and 6.2 (95%CI 4.8, 7.6) for African American women. 
Overall, the RR for stroke was higher among women than in 
men. In the USRDS and NHDS datasets, African Americans 
were at lower risk for stroke than Caucasians (HR for strokes; 
0.7) among patients with cardiac disease, but opposite effect 
was observed among individuals without cardiac disease (HR 
for strokes among African Americans vs. Caucasians; HR: 1.2). 
Although age is an independent risk factor of stroke in the 
general population, this relationship was not observed among 
chronic dialysis patients\textsuperscript{6}. The lack of relationship can be 
explained either by the overall high death rate in elderly dialysis 
patients or by the relatively early onset of severe hypertension 
in CKD patients.

### 2) Anemia:
Atherosclerosis Risk in Communities Study (ARIC)\textsuperscript{12} demonstr-
ated the association between anemia and stroke in CKD 
patients. In this study, 13,716 patients with both eGFR less 
than 60ml/min and anemia (defined as hemoglobin \textless 13g/dl for 
men and \textless 12g/dl for women) were followed for 9 years. They 
found that the overall stroke risk was increased in this CKD 
population: HR 1.81, (95% CI 1.3 to 2). This risk was higher in 
patients with anemia (HR 5.4; 95% CI 2.04 to 14.4) compared 
with those without anemia (HR 1.4; 95% CI 0.93 to 2.1). This 
finding is in contrast to the general population where high 
rather than low hematocrit is associated with an increased 
risk of stroke. However, since severe anemia is uncommon in 
the non-ESRD population, these studies may have insignif-
icate power to detect such an association in the general popu-
lation. The exact reasons for this substantially higher risk of 
stroke among patients with both CKD and anemia are still not 
entirely clear. Further studies are needed to clarify this con-
cept. There are several proposed mechanisms for this associa-
tion between anemia and stroke in CKD patients. Pathophysi-
ological mechanisms of stroke in CKD are shown in Figure 1.

a) Cardiovascular disease (CVD) is prevalent in ESRD.\textsuperscript{13} Fram-
ingham Offspring Based Community Study prospectively ex-
aminied 6233 patients for 15 years and found that mild renal 
insufficiency (creatinine of 1.3 -2.9 mg/dl) carries almost two 
fold risk of CVD diseases compared with the general popula-
tion. CKD may induce oxidative stress \textsuperscript{13} which is known to 
promote atherosclerosis. \textsuperscript{14} Furthermore, 75 % of patients who 
require dialysis, have pre-existing left ventricular hypertro-
phy. \textsuperscript{15} Studies have shown that LVH is a strong predictor of 
stroke risk.\textsuperscript{16} Therefore anemia may increase the risk of stroke 
by inducing atherosclerosis and LVH in CKD patients.
b) Studies using animal models demonstrate the neuro-pro-
etective effect of erythropoietin for ischemia-induced stroke. 
\textsuperscript{17, 20} However, when renal function is reduced, the erythropoi-
etin production from kidneys is impaired, which may limit 
erthropoietin-induced neuronal protection against anemia-
associated strokes. In this way, the combination of anemia 
and reduced kidney erythropoietin production may interact 
to increase the probability of stroke.

### 3) Hypoalbuminemia and malnutrition:
An elevated serum albumin concentration has been associated 
with a reduced risk of coronary heart disease,\textsuperscript{21, 22} death from 
cardiovascular disease and death from all causes in Caucasian 
men and women and African American men and women. In the 
National Health Epidemiologic Followup Study (NHEFS) da-
taset,\textsuperscript{21} a decreased serum albumin concentration or albumin/ 
globulin ratio was found to be more frequent in stroke cases 
than in controls . However, data regarding macroalbuminuria as 
a risk factor for stroke is not entirely clear. In a Japanese 
study,\textsuperscript{24} analyzing first symptomatic stroke events, reduced 
kidney function was associated with increased relative HR (HR, 3.1 in creatinine clearance < 40 ml/min, 1.9 in creatinine 
clearance 40–70 ml/min). The presence of macroalbuminuria 
tended to increase HR but was not statistical significant (HR, 
1.4). Another report from Japan\textsuperscript{25} also supported this finding 
revealing that macroalbuminuria is not a significant risk fac-
tor for death due to stroke, although it is a significant risk fac-
tor for all-cause and CVD mortality. Many authors\textsuperscript{24} speculate that the patients with macroalbuminuria are likely to have 
systemic vasculopathy and therefore the death events due to 
all-causes may be more apparent than those seen in the First 
Symptomatic Stroke Events Study.\textsuperscript{26} Malnutrition is a well 
recognized risk factor for all\textsuperscript{27, 30} and cardiovascular-specific\textsuperscript{31} 
mortality in the dialysis population. Significant protein mal-
nutrition has been ascribed to a higher incidence of intra-ce-
Figure 1: Pathophysiological mechanisms predisposing to stroke in patients with CKD

rebral hemorrhage in both the general population and dialysis patients. Seliger et al found that three markers of malnutrition specifically low serum albumin (per 1 g/dl decrease, HR = 1.4), low height-adjusted body weight (per 25% decrease, HR = 1.2), and a subjective assessment of undernourishment (HR = 1.3), were associated with a higher risk of incident stroke. This is in contrast to the general population, in which obesity, rather than malnutrition, confers a higher stroke risk. Several authors have suggested the following pathophysiological mechanisms:

a) Malnutrition reflects not merely poor nutrient intake but also the effects of a chronic micro-inflammatory state in CKD patients. Studies have shown that elevated inflammatory markers are associated with higher rates of stroke. Chronic inflammation may explain the observed association between malnutrition and stroke.

b) Low serum albumin may be an indicator of some other factor influencing the atherosclerotic process. The effect of albumin concentration on platelet function, blood viscosity, free fatty acid transport, and antioxidant levels have also been considered.

4) Uremia induced accelerated atherosclerosis: An additional factor responsible for higher stroke rates in CKD population is accelerated atherosclerotic vascular disease caused in part by uremia itself. This is supported by the reports using noninvasive imaging techniques, demonstrating a greater degree of carotid artery atherosclerosis among the dialysis patients compared to controls, even after adjusting for traditional cardiovascular risk factors. In one study, investigators found that vessel wall elasticity of the carotid artery is decreased in younger hemodialysis patients compared with age-matched healthy subjects. The enhanced stiffness of the arteries may contribute to the higher incidence of stroke in hemodialysis patients.

5) Hemodialysis procedure: Toyoda et al found that the occurrence of ischemic stroke was more common during or shortly after the dialysis procedure (34%) compared with the timing of hemorrhagic stroke. Given the relatively short exposure time during hemodialysis (3 times/wk for 5 hours) the frequency of 34% is meaningful. This result is unexpected because patients usually are administered anticoagulants during hemodialysis which would increase the tendency for hemorrhagic than the ischemic events. The potential pathophysiological mechanism may be related to drastic decrease in intravascular blood volume secondary to hemodialysis and diminished vascular responses secondary to diabetic autonomic neuropathy and advanced arteriosclerosis,
These factors result in an abrupt decrease in blood pressure and may induce brain ischemia.40

6) Blood pressure: Hypertension, notably elevated systolic blood pressure (SBP), is a risk factor for stroke in the general population. Stroke risk doubles for almost every 20/10 mmHg increase in blood pressure over 115/75 mmHg. In addition, hypertension is a major component of CKD, both as a cause and a result of impaired kidney function. Weiner et al 42 found that the individuals with CKD had a J-shaped relationship with stroke events such that those with SBP <120 mmHg were at significantly increased risk for stroke compared with the individuals with CKD and SBP 120 to 129 mmHg (HR 2.5; 95% CI 1.3 to 4.8); risk increased for SBP >130 mmHg in CKD patients. This J-shaped relationship was not seen in the individuals without CKD. Seliger et al 3 did not find this J shaped effect of BP on stroke. This J shaped effect was also not seen in Perindopril Protection against Recurrent Stroke trial (PROGRESS).43 The association of incident stroke with systolic BP and CKD is depicted in figure 2.

7) Anticoagulation during dialysis and uremic bleeding diathesis: Routine anticoagulation during hemodialysis, combined with a uremic bleeding diathesis, may theoretically lead to an increased risk of hemorrhagic stroke. Studies showing the definitive relationship are lacking.

8) Renal transplant: Cardiovascular and cerebrovascular diseases are the main causes of death in patients with end-stage renal disease (ESRD) including those on dialysis and those who have received renal transplant. Oliveras et al 44 found that the prevalence of stroke in transplant recipients was 8% at 10 yrs. Mean time elapsed between renal transplantation and stroke was 49 months. The rate of intra-cerebral hemorrhage was found to be high in this population. The outcome of all strokes was extremely poor. They identified three predictors of stroke in these patients: diabetic nephropathy (OR = 4.8; p < 0.01), peripheral vascular disease (OR = 8.2; p < 0.001) and age > 40 yr (OR = 3.3; p < 0.02). Other analyzed risk factors including gender, renal function, cytomegalovirus infection, hyperlipidemia, hyperuricemia, erythrocytosis, or hypertensive donor failed to show any significant predictive value for stroke in these patients. This is very similar to the data from other studies evaluating such a relationship among renal transplant and hemodialysis patients. Another study 45 primarily of 1633 Caucasian patients submitted to renal transplant found a low stroke rate (3.9%) over four years. The pre-transplantation risk factors identified were atrial fibrillation (p = 0.001), and diabetes mellitus (p > 0.037). More common risk factors like prior transient ischemic attack, stroke, hypertension, hyperlipidemia, the primary cause of kidney disease, duration of renal replacement therapy, smoking, and gender were not associated with stroke.

In a recent prospective European study, a total of 184 (8.8%, 95% confidence interval 4.6–12.9) of 2102 patients experienced stroke during follow-up of 6.7 years, corresponding to an incidence of 1.3% stroke events per year. For ischemic stroke, diabetes mellitus (HR of 3.5; 95% CI 2.4–5.2), previous cerebrovascular event (HR 3.5; 95% CI 2.2–5.6), age (HR of 1.1; 95% CI 0.1–1.1), and serum creatinine (HR of 1; 95% CI 1.0–1.0) were identified as risk factors. The risk of a hemorrhagic stroke was increased by diabetes mellitus (HR of 4.9; 95% CI 2.1–11.6), polycystic kidney disease (HR of 4.2; 95% CI 1.4–11.2), left ventricular hypertrophy (HR of 3.0; 95% CI 1.2–7.2), and SBP (HR of 1; 95% CI 1.0–1.04).

9) Hyperhomocysteinemia: Wilcken et al 47 found homocysteine levels to be 2 fold higher in CKD patients than the controls. Several clinical studies have supported that hyperhomocysteinemia is an important risk factor for atherosclerosis.46,49 Mild hyperhomocysteinemia has been found in 30% of the patients having premature cerebral, vascular, and coronary artery disease. Bachmann et al 50 found that high serum homocysteine was significantly associated with occlusive arterial disease (RR = 0.2). Clark et al 51 also found a significant association between hyperhomocysteinemia and premature atherosclerosis; even after the adjustment of other atherogenic factors. Homocysteine enhances the auto oxidation of LDL cholesterol and induces a strong increase in binding of lipoprotein to fibrin. Abnormalities of lipid metabolism may explain the proatherogenic and prothrombogenic effects of homocysteine.

Future directions: Risk factors which predispose CKD population to stroke are still being analyzed. The potential importance of macroalbuminuria, hyperuricemia, hyperhomocysteinemia, and low SBP for stroke events warrants further studies. The data regarding stroke in
renal transplant patients also demands further investigation.

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