Clinical associations between renal dysfunction and vascular events: A literature review
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Abstract
Chronic kidney disease affects several other organs of the human body, and causes high levels of morbidity and mortality due to these effects. The cardiovascular system is probably the most vulnerable organ to a decrease in kidney function, and responds very fast to this effect. To the extent that, more kidney disease patients die of cardiovascular events than that of the original renal disease. Moreover, cerebrovascular events have been confirmed to increase, and to have inferior outcomes on the general population. In this review article, we aim to review studies investigating effects of renal disease on vascular events.

Keywords: Renal Disease, Cardiovascular Disorders, Dialysis, Myocardial Infarction, Risk Factor

Introduction
As more new data is gained through the newly published studies, it has become more evident that kidney diseases can result in vascular disorders and ominous events. In chronic kidney diseases, it has been suggested that mortality more often occurs due to cardiovascular events than the kidney disease itself. Several explanations have been proposed for the observed connections by different authors. In this literature review, we try to summarize the existing data that relates kidney disorders to cardiovascular (CAV) and/or cerebrovascular (CBV) events.

The first part of the present review will, therefore, focus on the epidemiological evidence of links between CAV events and impairment of renal function. The second part will deal with the same relationship between CBV and kidney failure. In the third part we will focus on the newly introduced parameter of renal function, cystatin C, which has been proposed as the most accurate biomarker that shows kidney function irrespective of patients demographic factors including age, sex, muscular property, and etcetera. The forth part more delicately analyses the associations between different stages of kidney disease, and incidence and outcome of the mentioned vascular events. In the fifth part we will review data on the treatment of CAV and CBV events in renal disease patients. Finally, in the sixth and last part we make a conclusion of the reviewed articles.

Epidemiology of cardiovascular disorders in kidney dysfunction
Epidemiological evidence for the relationship between renal dysfunction and adverse CAV events is most apparent in the hemodialysis population where the mortality rate associated with cardiovascular events exceeds that of the original renal disease; at least 50% of the mortality in the population has been attributed to the CAV events. Therefore, it is observed that cardiovascular disorders are very prevalent in the dialysis population. 40% of patients starting dialysis have evidence of coronary artery disease, and 85% of the same patients represent abnormal left ventricular structure and function.

In peritoneal dialysis patients, it has been reported that 44% have left ventricular hypertrophy (LVH). In another study, this proportion in pediatric patients on peritoneal dialysis has been reportedly over 48%. In hemodialysis patients, the condition is even worse and a single center reported that 69% of their hemodialysis patients had LVH compared to 45%
in their peritoneal dialysis patients.\textsuperscript{6} In pediatric patients, hemodialysis patients have a higher rate of LVH than peritoneal dialysis patients (85\% vs. 68\%, respectively).\textsuperscript{7} Yet, progressive LVH is supposed to be the strongest predictor of sudden death in dialysis patients.\textsuperscript{8} The rate of LVH has also been attributed to the degree of creatinine clearance; with more severe hypertrophy in lower rates of creatinine clearance.\textsuperscript{9,10}

Prolonged QT interval is also a strong predictor of long term mortality in end-stage renal disease (ESRD) patients.\textsuperscript{11} It has also been shown that QTc in dialysis patients significantly increases and can be determined in up to 46\% of patients.\textsuperscript{12,13} A comparable rate of QTc prolongation has also been observed among peritoneal dialysis patients with a prevalence of 41\%.\textsuperscript{14}

The risk of cardiovascular events in pre-dialysis patients of renal function disorders is also augmented. Data from the hypertension optimal treatment (HOT) study indicates that the adjusted relative risks for total mortality and for major cardiovascular and/or cerebrovascular events were 1.65 and 1.58, respectively, in subjects with glomerular filtration rate or GFR < 60 mL/min compared with those with a GFR > 60 mL/ min.\textsuperscript{15}

**Epidemiology of cerebrovascular disorders in kidney dysfunction**

The topic of cerebrovascular events occurring in the context of renal disease has recently received high levels of attention. The Northern Manhattan Study (NOMAS) followed 3298 stroke-free subjects of mean follow-up time of 6.5 years for vascular outcomes. This study showed that renal failure patients with GFR levels of between 15 and 59 mL/min are at a high risk for stroke (hazard ratio (HR) 2.65; 95\% confidence interval (95\% CI) 1.47 to 4.77).\textsuperscript{16} Moreover, impaired kidney function has been associated with cerebral microbleeding.\textsuperscript{17} The incidence of stroke and associated mortality is also higher in kidney disease patients compared with the general population. Presence of anemia, hypoalbuminemia, malnutrition, uremia, and hyperhomocysteinemia in patients with kidney failure are confirmed factors associated with higher incidence of stroke.\textsuperscript{18} Hemodialysis and renal transplant patients are at a higher risk of stroke compared with those who do not require renal replacement therapy. In a large cohort of dialysis patients and people of the general population, after adjustment for age, gender, and race, estimated rates of hospitalized stroke were markedly higher for dialysis patients compared to the general population. The highest relative risk of stroke was among Caucasian females on dialysis compared to the general population (relative risk or RR: 6.1 [95\% CI 5.1-7.1] for Caucasian males, RR: 4.4 [95\%CI 3.3-5.5] for African American males, RR: 9.7 [95\% CI 8.2-11.2] for Caucasian females, and RR: 6.2 [95\%CI 4.8-7.6] for African American females).\textsuperscript{19} In a study on the United States Renal Data Systems, the rate of stroke among American dialysis patients was 33/1000 person-years. After adjustment for age and other demographics, high blood pressure (hazard ratio [HR] = 1.11) and markers of malnutrition including serum albumin (per 1 g/dl decrease, HR = 1.43), height-adjusted body weight (per 25\% decrease, HR = 1.09), and a subjective assessment of undernourishment (HR = 1.27) were found to be associated with a higher risk of stroke in this population.\textsuperscript{20} Finally, a recent meta-analysis of 21 studies which included 7863 stroke events suggested that an estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m\textsuperscript{2} is associated with the risk of stroke RR 1.43, 95\% confidence interval (95\%CI) 1.31 to 1.57; P < 0.001), but not an eGFR of 60-90 ml/min/1.73 m\textsuperscript{2} (RR: 1.07, 95\%CI: 0.98 to 1.17; P = 0.15).\textsuperscript{21} On the other hand, receiving hemodialysis, alone, worsens the outcome of acute stroke.\textsuperscript{22} A very interesting population based study in Japan showed that even a minimal kidney function decline is associated with a significantly higher rate of silent lacunar infarctions and white matter lesions.\textsuperscript{23}

**Cystatin C**

Cystatin C is a cysteine protease inhibitor excreted by almost all human cells and released into the bloodstream. It is, also, a serum index of renal function which appears to be independent of age, sex, and lean muscle mass, and is reportedly superior to GFR for this estimation. Therefore, it would be a good parameter to investigate the early stages of renal failure and, in this review article, its potential relations to cardiac diseases. This issue has recently attracted much attention. An almost 9 year cohort of 4637 elderly persons in the United States showed that higher cystatin C levels in a dose-response manner were directly associated with a higher risk of death from all causes (Compared to the first quintile, the hazard ratios and 95\% confidence intervals (HR [95\% CI]) for death were: second quintile: 1.08 [0.86-1.35]; third quintile: 1.23 [1.00-1.53]; fourth quintile: 1.34 [1.09 to 1.66]; quintile 5a: 1.77 [1.34 to 2.26]; 5b: 2.18 [1.72 to
whether the stage of kidney disease can predict the risk of development of stroke (OR: 2.09 [95% CI: 1.38–3.16]. This risk increases in patients of stages 4 and 5 (2.33 [0.1–5.46]. Another study by Tsagalis et al. investigated the risk of developing cardiovascular events and its associated mortality in renal disease patients. They found that, compared to stages 1 and 2 having kidney diseases of stage 3 or stages 4 and 5 are associated with substantial increase both in the risk of development of cardiovascular diseases. Both of the above mentioned articles have categorized their patients’ kidney disease based on creatinine-based GFR. However, Shlipak et al. in their study of significant methodology, have categorized their patients based on cystatin C, which has been shown to have a more significant correlation to renal disease than creatinine.

In this study, adjusted risk (Hazard ratio (HR) and 95% CI) of death from cardiovascular events with quintile 1 (cystatin C ≤ 0.89 mg/l) as reference were as follows: quintile 2 (cystatin C: 0.9-0.99 mg/l; HR [95%CI]: 1.33 [0.88–2.00]), quintile 3 (cystatin C: 1.0-1.1 mg/l; 1.93 [1.33–2.80]), quintile 4 (cystatin C: 1.11-1.28 mg/l; 1.99 [1.38–2.87]), quintile 5a (cystatin C: 1.29-1.39 mg/l; 2.48 [1.63–3.77]), quintile 5b (cystatin C: 1.4-1.59 mg/l; 2.73 [1.81–4.13]), and quintile 5c (cystatin C ≥ 1.6 mg/l; 2.83 [1.85–4.31]). Risk of myocardial infarction was for quintile 2 (0.97 [0.67–1.41]), quintile 3 (1.26 [0.89–1.78]), quintile 4 (1.14 [0.80–1.63]), quintile 5a (1.44 [0.91–2.28]), quintile 5b (1.30 [0.80–2.11]), and for quintile 5c (1.65 [1.03–2.64]). The risk of stroke events for each quintile was as follows: quintile 2 (1.22 [0.87–1.72]), quintile 3 (1.17 [0.83–1.65]), quintile 4 (1.15 [0.82–1.62]), quintile 5a (1.43 [0.92–2.21]), quintile 5b (1.97 [1.31–2.98]), and for quintile 5c (1.80 [1.16–2.79]). In another study, Shlipak et al. investigated a similar issue in elderly patients with normal kidney function based on creatinine based calculations. All these studies show that, irrespective of the parameter used for the definition of GFR, having higher stages of renal disease is associated with higher rates of CAV and CBV complications.

Unfortunately, not all the studies have reported their data in a comparable manner so that we could be able to summarize them into a table. For example, most studies have merged some stages together to make smaller number of patient groups to compare, or their definition of GFR was not comparable. However, higher stages indicate overall worse kidney function. In a study on an American national survey, Ovbiagile showed that, compared to patients in stages 1 and 2 of kidney disease, renal patients with CKD stage 3 have a higher risk of developing stroke (OR: 2.09 [95% CI: 1.38–3.16]. This risk increases in patients of stages 4 and 5 (2.33 [0.1–5.46]. Another study by Tsagalis et al. investigated the risk of developing cardiovascular events and its associated mortality in renal disease patients. They found that, compared to stages 1 and 2 having kidney diseases of stage 3 or stages 4 and 5 are associated with substantial increase both in the risk of development of cardiovascular diseases. Both of the above mentioned articles have categorized their patients’ kidney disease based on creatinine-based GFR. However, Shlipak et al. in their study of significant methodology, have categorized their patients based on cystatin C, which has been shown to have a more significant correlation to renal disease than creatinine.

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events, and mortality. This urges us to develop preventive strategies for patients with any stage of renal disease.

**Treatment**

Treatment of cardiovascular events in renal disease patients has no major alterations than that in the general population. Myoglobin is not a reliable biochemical marker in patients with renal failure, but both conventional isoforms of troponin seem safe in the diagnosis of a myocardial infarction. Management of acute coronary syndromes in renal failure patients is not much different from that in the general population. Moreover, medical and interventional procedures are recommended in these patients; with the suggestion of using more aggressive strategies for the prevention and treatment of acute myocardial infarction in patients on dialysis. This is because it has been shown that mortality from myocardial infarction in dialysis patients is three times greater than that in the general population. A large observational study of over 16 thousand ESRD patients with myocardial infarction showed that using reperfusion therapy improves the survival rate of these patients. Moreover, it has been shown that dialysis patients respond better to coronary artery bypass grafting (CABG) surgery than percutaneous coronary intervention. Furthermore, stent outcomes were relatively worse than CABG in diabetic patients.

Management of stroke in kidney disease patients is not suggested to be any different from that in the general population. However, according to the findings of a large prospective cohort study (CHOICE study), outcome after stroke, especially hemorrhagic stroke, was poor with a high case-fatality and low successful recovery rate with one month mortality rate of about 35%. This is quite inferior to the 10-20% adjusted stroke case-fatality in patients of non-dialysis setting. The median presentation time of stroke was over 8 hours in the CHOICE study, which is much longer than that observed in a systematic review. However, the mean length of hospital stay, surprisingly, was similar to that in the general population. Several modifiable risk factors have been suggested for renal disease patients developing stroke, which includes hypertension, smoking, diabetes, cardiac disease, and alcohol. The utmost attention must be paid to these factors, due to their substantially higher incidence and the associated inferior outcome of stroke in kidney disease patients.

Kidney transplantation has been proposed as a beneficial method of renal replacement therapy that efficiently halts the progression of cardiovascular disorders in end-stage renal disease patients. In this study, including over 60 thousand kidney transplant patients, the rates of cardiovascular diseases reached to a peak during the first 3 months post-transplantation and decreased subsequently when data was censored for graft loss. This trend was available for either living or deceased donor transplantations and even in patients whose kidney loss was due to diabetes mellitus. On the other hand, the CVD rates in the ESRD patients on the transplant waiting list substantially increased by time. These data are indicative of the apparent beneficial effects of transplantation on CAV events in ESRD patients.

Immunosuppressive agents used for preventing rejection episodes in renal transplant patients, themselves, are associated with augmented risk for cardiovascular morbidities. Corticosteroids and ciclosporin are the agents with the most negative impact on weight gain, blood pressure, and lipids. Tacrolimus increases the risk of new-onset diabetes mellitus. Sirolimus and everolimus have the most impact on risk factors for post-transplant hyperlipidaemia. Modifications in immunosuppression could improve the cardiovascular profile but there is little evidence regarding the beneficial effects of these changes on patient outcomes.

### Table 1. Stages of chronic kidney disease

| Stages | GFR mL/min per 1.73 m² | Description |
|--------|------------------------|-------------|
| 1      | ≥ 90                   | Albuminuria or structural renal abnormality with normal GFR |
| 2      | 60-89                  | Mild GFR decrease |
| 3      | 30-59                  | Moderate GFR decrease |
| 4      | 15-29                  | Severe GFR decrease |
| 5      | < 15 or on renal replacement therapy | Kidney failure |

GFR: Glomerular filtration rate
With the dissimilar effects of different immunosuppressant agents on the cardiovascular risk factors in renal recipients, one may assume that knowing this, we can improve patients’ outcome with the modification of the patients’ drug regimen based on their cardiovascular risk factors. In fact, a recent study has confirmed this presumption showing that conversion from calcineurin inhibitors to sirolimus regresses left ventricular mass thickness regardless of blood pressure changes. The same observation was also reported when everolimus was used in renal recipients whose cyclosporine dosage administration was diminished.

**Conclusion**

Even minimal kidney dysfunction is associated with increased rates of cardiovascular and cerebrovascular events. Moreover, the mortality rates associated with these conditions have also been reportedly higher in this patient population. Unfortunately, data on potential strategies which can safely decrease these risks is limited. However, knowing the major factors either in the incidence or outcome of cardiovascular or cerebrovascular disorders in renal disease patients gives us a key point for modification of these factors. Moreover, it urges us to conduct future research on the extent to which these modifications will improve the outcome of renal disease patients regarding vascular events. Nevertheless until we have strong data from large studies, preventive strategies as well as prompt diagnosis and management of the above mentioned disorders seem the best we can do to protect our kidney disease patients.

**Conflict of Interests**

Authors have no conflict of interests.

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