Managing The Heart In The Failing Kidney; Challenges and Opportunities

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Introduction

Chronic kidney disease (CKD) is characterized by decreased kidney function, as determined by the glomerular filtration rate (GFR), or kidney damage (with or without albuminuria). CKD is staged according to the level of GFR (stage 1-5) and albuminuria (stage 1-3), with stage 1 representing the highest level of kidney function (GFR >90 ml/min/1.73 m^2) and stage 5 representing the lowest level of kidney function (GFR <15 ml/ min/1.73 m^2). Recent evidence indicates that the prevalence of CKD is increasing in Sudan (1) and this increase is associated with poor outcome despite the availability of state sponsored dialysis program.

Analyses from epidemiological and a large clinical trial showed that the medical community has only recently appreciated the increased risk of cardiovascular disease (CVD) across the spectrum of CKD from early (albuminuria) to transplantation (2,3). It is now evident that the risk of death, particularly due to cardiovascular disease, is typically higher than the risk of eventually requiring renal replacement therapy (4,5). This article presents a brief overview of the epidemiology, magnitude, mechanism and management of CVD at different stages in the natural history of progressive CKD.

Epidemiological links between CKD and CVD

The presence of CKD, whether it is manifested by albuminuria or reduced GFR, appears to be an independent risk factor for CVD outcomes. The CV risk increases progressively with deteriorating GFR and is increased significantly by the time serum creatinine is elevated (6). 40% of incident dialysis patients have evidence of coronary artery disease (CAD), and 85% of these patients have abnormal left ventricular structure and function (7). Epidemiological studies reported a high incidence of CV death in the dialysis population and other stages of CKD. Approximately 50% of individuals on dialysis die from a CV cause (2,5,8) with a CV mortality that is 15 to 30 times higher than the age-adjusted CV mortality in the general population (2,9). This disparity is present across all ages, but it is most marked in the younger age group (25 to 34 years old), where the CV mortality is 500-fold greater in end stage renal disease (ESRD) patients compared with age-matched controls with normal renal function (4). Patients with a functioning transplant have a much smaller increase in relative risk of around fivefold, but this group is highly selected and graft failure is associated with a dramatic increase in risk and mortality.

Patients without known coronary heart disease (CHD), such as those with diabetes, have a risk of subsequent cardiovascular events that is comparable to that seen in patients with established coronary disease. Such patients are regarded as having a CHD risk equivalent. It is therefore not surprising that CKD

is considered a CHD risk equivalent. The high prevalence of CVD in patients with CKD suggests that CKD patients are different from the general population. This difference is likely to be attributed to three unique features. The first is the course of renal disease with uraemia setting in over months to many years and leading in some patients to end stage renal disease (ESRD). The second feature is the role of extracellular fluid volume overload leading to hypertension and heart failure. The third unique feature is the characteristic vascular calcification in peripheral and coronary vessels due to secondary hyperparathyroidism in renal disease (10).

Patterns of CVD in patients with CKD

CKD is associated with increased prevalence of congestive heart failure (CHF), coronary heart disease (CHD) and cardiac arrhythmias (11-13). However, sudden death and progressive CHF is more common than classical myocardial infarction which is relatively uncommon and atypical in CKD.

Coronary heart disease (CHD)/Acute coronary syndrome in CKD

The severity, morbidity and mortality of coronary heart disease (CHD) increases as glomerular filtration rate (GFR) declines (4). The incidence of obstructive coronary artery disease (CAD) exceeds 50% in unselected dialysis patients (14,15) and is also associated with adverse outcomes in those with existing cardiovascular disease (15). This includes increased mortality after an acute coronary syndrome, after percutaneous coronary intervention (PCI) with or without stenting (16,17), and after coronary artery bypass. This increased mortality may well be due to the fact that CAD in CKD shows a pattern of diffuse multi-vessel involvement with coronary calcification and other vascular calcifications (14, 18) Figure 1 and Quick info 1. In addition, patients with CKD are more likely to present with atypical symptoms, which may delay diagnosis and adversely affect outcomes (19).

Congestive heart failure

CKD exposes the heart to three major mechanisms that facilitate the development of cardiomyopathy and induce left ventricular failure and these are pressure overload, volume overload, and CKD associated non-hemodynamic factors (inappropriate activation of the renin–angiotensin system, catalytic iron-dependent oxidative stress, inflammation, and stimulation of prohypertrophic and profibrogenic factors) that alter the myocardium. CKD progression is accompanied by progressive LVH, diastolic dysfunction (15) and arterial stiffening. Parfrey has characterised uraemic cardiomyopathy into three groups: systolic dysfunction, hypertrophic cardiomyopathy, and dilated cardiomyopathy

(20). It is therefore no surprise that CHF is the leading CVD in CKD patients (21,22) with the prevalence increases with declining kidney function (23,24). The mortality is slightly higher for diastolic than for systolic CHF (25,26) with the terminal events being pump failure and sudden arrhythmic death. It may well be that the abnormalities of the myocardium (left ventricular hypertrophy, systolic dysfunction, and ventricular dilatation) that predispose the patient to sudden death are of much greater importance than atherosclerotic coronary artery disease in determining the high CV mortality in this population.

Sudden cardiac death (SCD)

Sudden cardiac death (SCD) refers to the unexpected natural death from a cardiac cause within a short time period, generally 1 hour from the onset of symptoms, in a person without any prior condition that would appear fatal. Most such events are believed to be due to ventricular arrhythmias, that is, ventricular tachycardia or ventricular fibrillation (27).

SCD accounts for about one-fourth of dialysis patient deaths, with an annual rate of 5.5% (28,29) Survival of dialysis patients after sudden cardiac arrest is universally poor, with a 6-month survival of 3–11% (30,31). Reductions in GFR in CKD stages 3–5 has also been reported to be associated with a progressive increase in risk of sudden cardiac death in patients with CAD (32). There are several plausible explanations for the special vulnerability of dialysis patients to sustaining sudden cardiac death. Obstructive coronary artery disease, coupled with diminished tolerance to myocardial ischemia (in the setting of myocardial fibrosis and left ventricular hypertrophy), rapid electrolyte shifts in hemodialysis patients, and derangements in autonomic function may all contribute to this heightened risk of sudden cardiac death (33).

Diagnosis of CVD in patients with CKD

The optimal strategies for diagnosis of CVD in CKD is lacking and the evidence base for decision making is limited. However the standard diagnostic tools for diagnosis CVD in the general population continue to be used for CKD population (Quick info 2).

CKD patients usually have atypical symptoms of ACS and thus a high index of suspicion is necessary for diagnosis. In addition cardiac biomarkers, creatine kinase MB isoform and cardiac troponins, are often elevated in the absence of true myocardial necrosis, (34) and electrocardiographic changes are frequently absent or require cautious interpretation due to the influence of associated electrolyte imbalance in CKD patients (19,35).

Echocardiography has a good prognostic indicator but varies during dialysis cycle. It is recommended that that echocardiography is performed post dialysis. Exercise electrocardiography is limited by lack of specificity of the ST-segment response and by inability of many CKD patients to exercise to a diagnostic workload (36,37). The risks of contrast agents limit the use of perfusion magnetic resonance imaging and computed tomography coronary angiography, and the latter is compromised by a high prevalence of coronary calcification among CKD patients (38). Radionuclide perfusion imaging is more sensitive but less specific than stress echocardiography (39), but may be problematic in the setting of elevated left-ventricular (LV) mass index and frank LV hypertrophy (LVH) because limited spatial resolution and disturbed coronary flow reserve may lead to false results (37). It is more useful when combined with dipyridamole or dobutamine stress. Coronary angiography remains the gold standard method and is required for most CKD patients.

Management of CVD in patients with CKD

Modifying cardiovascular risk in patients with CKD

The traditional risk factors, listed in Quick info 3, are independent predictors of cardiovascular disease in CKD, but do not account for the total increased risk. There are also many non-traditional cardiovascular risk factors which play a potentially important role in CKD. There is randomised controlled trial evidence that timely intervention can substantially reduce the progression of renal failure, and can reduce CV risk by up to 50% (40)

Lifestyle modification

Lifestyle modification is vital and particular attention should be paid to smoking, nutrition, alcohol and physical activity. All guidelines recommend a reduction of dietary sodium for patients with hypertension and CKD. A meta-analysis of 20 randomised trials involving patients with hypertension found that halving salt intake (from approximately 10 g per day to 5 g per day) for four or more weeks had a modest but important effect on lowering systolic and diastolic blood pressure (41). In addition to direct effects on blood pressure, lowering the extra cellular volume by limiting sodium intake significantly enhances the response to most antihypertensive drugs, especially angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor antagonists.

Hypertension

Hypertension in patients with CKD is the most powerful risk factor for the progression of kidney dysfunction and the development of cardiovascular

disease. The most important goal for reducing cardiovascular risk in patients with CKD is to lower blood pressure to a target (<140/90 mmHg if proteinuria less than 1 g/day or <130/80 mmHg if proteinuria more than 1 g/day). In order to reach these targets, multiple (often 3-4) antihypertensive drugs are often needed, particularly in more advanced CKD. The activity of the renin-angiotensin-aldosterone system is increased so ACE inhibitors are the first-line therapy for patients with CKD, although angiotensin receptor antagonists may provide comparable renoprotection and therefore cardioprotection.

Dyslipidaemia

CKD is associated with hyperlipidaemia. A meta-analysis of 50 randomised trials involving over 30,000 patients found that statin use significantly reduced fatal cardiovascular events by 19% and non-fatal cardiovascular events by 22%, irrespective of the stage of CKD (42). The findings from the SHARP trial echoed the observations made in CKD subgroups from other randomized trials, treatment of patients with CKD not requiring dialysis with a statin leads to a significant reduction in cardiovascular events. Patients who received statin therapy in SHARP also received ezetimibe, although it is not clear if ezetimibe contributed to the clinical benefit (43). Current guidelines therefore recommend that statins be used to reduce cardiovascular risk in patients with chronic kidney disease. Aim for a serum total cholesterol below 4 mmol/L and a low density lipoprotein cholesterol below 2.5 mmol/L.

Glycaemic control in patients with diabetes mellitus

Diabetes is a common cause of renal failure. Intensive blood glucose control significantly reduces the risk of developing CKD and reduces CV risk. Current guidelines recommend aiming for a glycated haemoglobin (HbA1c) of less than 7%.

Anaemia

Anaemia is a common complication of CKD and is associated with the development of left ventricular hypertrophy and increased CV risk. This complication starts when the GFR is below 60 ml/min/1.73 m2 and its prevalence increases with decreasing GFR. Treatment of anaemia in CKD can be accomplished with iron supplementation and erythropoiesis stimulating drugs.

Strategies to reduce the hypervolemia

Hypervolemia can be effectively controlled in predialysis CKD with the use of diuretic and reduction of salt intake. In dialysis patients attempts to encourage fluid balance and adequate dialytic support.

Calcium and phosphate metabolism

Hyperphosphataemia and hyperparathyroidism in CKD have been associated with increased vascular calcification, cardiovascular risk and death. This often manifests when the GFR falls below 60 ml/min/1.73 m^2. It becomes more prevalent as kidney function declines and is present in most dialysis patients. Although there is no definitive evidence yet that correcting calcium-phosphate balance or secondary hyperparathyroidism improves cardiovascular outcomes, current clinical practice guidelines recommend treatment.

Aspirin

Low-dose aspirin should be considered in patients with CKD, especially in those with established cardiovascular disease. The only published controlled trial in patients with CKD found that aspirin reduced the risk of myocardial infarction, but did not reduce the overall risk of cardiovascular death (44). The potential benefit must be weighed against the risk of gastrointestinal bleeding, which is increased in patients with CKD.

Prevention of SCD

Dialysis patients are a special group of patients at increased risk for sudden cardiac death but they are routinely excluded from nearly all clinical trials that used sudden death as an endpoint and therefore data are not available. However, several therapeutic interventions may be of benefit. Avoiding Low-Potassium Dialysate, 0 or 1.0 mm*M* potassium dialysate (45), medical therapies with Beta-adrenergic blockers (46), ACE inhibitors (47), and ICDs in dialysis (48) and non dialysis (49) patients may all have a role in preventing these events.

Managing cardiovascular disease in CKD

Congestive heart failure

Cardiac failure is present in up to 40% of patients with CKD (50) and hospital admissions for cardiac failure are five times more common in patients with CKD than in other patients. The incidence is further increased by 30% in patients having dialysis (50) Cardiac failure in renal disease should be managed as usual. Diuretics are frequently required for symptomatic management and to control fluid retention in CKD though require frequent administration of large doses of loop diuretics (e.g. Furosemide 120 mg twice a day) to achieve an adequate diuretic response. This attempt to remove fluid must be balanced against the need to avoid dehydration and further deterioration of kidney function. Blockade of the renin-angiotensin-aldosterone system (ACE inhibitors and angiotensin

receptor antagonists) and beta blockade (bisoprolol, carvedilol or long-acting metoprolol) improves prognosis. ACE inhibitors and angiotensin receptor antagonists are underused in patients who have heart failure with CKD (51). However, prescription of these drugs is associated with a significant reduction in deaths in these patients (51). If patients cannot tolerate ACE inhibitor or angiotensin receptor antagonist therapy, consider a combination of hydralazine and nitrate therapy to improve their prognosis.

Carvedilol significantly improved all-cause mortality (49% risk reduction), cardiovascular death (68% risk reduction) and hospitalisations (56% risk reduction) in a randomised, placebo-controlled trial of 114 patients with heart failure having dialysis (46). Spironolactone and eplerenone should not be given to patients with a creatinine clearance of less than 30 ml/min/1.73 m^2. Caution should still be exercised when giving these drugs to patients with milder degrees of renal impairment, especially if they are taking an ACE inhibitor or angiotensin receptor antagonist. There is a significant potential for hyperkalaemia, as well as deterioration in renal function.

Coronary heart disease (CHD)

CHD is very common in patients with CKD. It progresses at a more rapid rate than in people without CKD and is often under treated (50). Current recommendations are that patients with CKD with CHD should be prescribed aspirin, beta blockers, ACE inhibitors and statins to achieve similar targets to those currently suggested for patients without CKD.

International best practice clinical guidelines also recommend that percutaneous coronary intervention and coronary artery bypass grafting are appropriate revascularisation techniques for patients with CKD who have obstructive lesions in their coronary arteries. When angiography is to be performed, some strategies to decrease the risk of contrast nephropathy should include; minimising contrast load; temporary cessation of drugs such as ACE inhibitors, angiotensin receptor antagonists, diuretics (if practical) and metformin around the time of contrast exposure (typically for 24-48 hours before and 24-48 hours after the procedure) and gentle pre-hydration, for example 1 L of saline infused over 12 hours before the procedure.

Patients with CKD who suffer an acute coronary syndrome or who have coronary interventions (ie, coronary artery bypass grafting, percutaneous coronary intervention) have a worse prognosis than patients with normal kidney function who have similar events or procedures. The mechanisms which underlie the poor

prognosis in patients with CKD are not entirely clear. An adverse association between mild to moderate CKD and cardiovascular prognosis in patients with ACS has been reported, both in patients with ST elevation myocardial infarction and non-ST elevation ACS. Most studies demonstrate that decreased kidney function at the time of coronary artery bypass grafting (CABG) is associated with higher risk of adverse outcomes (52,53). In-hospital complication rates and in-hospital as well as long-term mortality are highest among patients on dialysis (54-56). Patients with CKD who develop acute kidney injury after CABG may require temporary or permanent dialysis. The presence of even mild CKD appears to predict an adverse prognosis after percutaneous coronary intervention (PCI) with or without stenting (57-59).

Conclusion

Accelerated CVD is now the leading cause of death in patients with progressive renal disease and managing the heart in the failing kidney is encountered with many challenges but equally there are many opportunities to support patients with CKD during their long journey with the disease.

CKD is CHD risk equivalent and as such all patients should be offered prevention from the earliest phases of progressive renal disease, when serum creatinine is just above the normal range or the presence of albuminuria. It is also clear that some of this risk is modifiable and can be improved by controlling of blood pressure, aggressive treatment of dyslipidemia, control of protein intake, minimization of bone resorption by managing serum calcium, phosphorous and parathyroid hormone and reducing the hypercoagulability state.

Extracellular fluid volume overload is a major cause of hypertension and meticulous control of fluid balance will limit the development of left ventricular hypertrophy and limit, or regress, ventricular abnormalities in CKD. Patients and clinicians should be encouraged to appreciate that thrice a week dialysis is the minimal requirement to manage volume overload and uraemia.

Renal transplantation offer a better quality of life and a reduced CVD risk and should be encouraged in designed centres with a multidisciplinary team to ensure patient safety and staff training.

Finally, there should be a low threshold for the investigation of patients with advanced renal disease even in the absence of symptoms. Overall, the message is clear, improved understanding and management of CVD in CKD patients will reduce the morbidity and mortality.

Figure 1: Extensive vascular calcification in a 78 year old Arab female with non diabetic CKD stage 4 (GFR 22).

Quick info 1: Promoters of Vascular Calcification in CKD
Promoters of calcification
<u>Traditional factors</u> **Older age, male gender, hypertension, diabetes, smoking high LDL cholesterol, low HDL cholesterol, genetics** **<u>Uraemia-related factors</u>** **Uremic serum, hyperphosphatemia, increased Ca_P product, exogenous vitamin D therapy, elevated parathyroid hormone levels, dialysis vintage, calcium load and hypercalcemia, chronic inflammation, warfarin, elevated leptin levels**

Quick info 2: Cardiac assessment of patients with CKD
• Echocardiography: good prognostic indicator but varies during dialysis cycle • Standard exercise test: little use because of poor exercise capacity and resting ECG Abnormalities • Isotope scanning: useful when combined with dipyridamole or dobutamine stress • Coronary angiography: required for most patients

Quick info 3:Cardiovascular risk factors in CKD	
Traditional risk factors	**Nontraditional risk factors**
• Hypertension • Smoking • Diabetes • Elevated LDL cholesterol • Reduced HDL cholesterol • Older age • Male gender • Menopause • Psychosocial stress • Physical inactivity • Family history of CHD	• Type of CKD (CHD risk equivalent) • Decreased GFR • Albuminuria • Dialysis therapy (↑oxidant stress, ↑complement & cytokines, ↑adhesion molecules) • Dialysis vintage (duration on dialysis) • Extra cellular fluid volume overload • ↑vascular calcification (coronary artery calcification) • Retention of uremic toxins • Anaemia • Abnormal calcium and phosphate metabolism • Hyperhomocysteinemia • Inflammation • Oxidative stress • Mineralocorticoid excess • Physical inactivity • Inhibition of nitric oxide synthesis due to ↑ Asymmetrical dimethylarginine (ADMA) • Renin-Angiotensin System activity • Dyslipidemia • Elevated lipoprotein (a) • Malnutrition • Thrombogenic factors

Quick info 4: Intervention for coronary artery disease
• High risk in patients with end stage renal failure • Angioplasty has unacceptably high failure rate • Coronary stenting unproven • Coronary bypass graft surgery remains treatment of choice for most patients

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