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# Cardiovascular Aspects of Patients with Chronic Kidney Disease and End-Stage Renal Disease

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Ali Osama Malik, Sumit Sehgal,  
Hashim Hussnain Ahmed, Subodh Devabhaktuni,  
Edward Co, Arhama Aftab Malik, Syed Shah and  
Chowdhury Ahsan

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## Abstract

Chronic kidney disease (CKD) is a globally recognized public health concern. Multiple studies have shown the association of CKD with cardiovascular mortality that persists after adjustment for traditional cardiovascular disease (CVD) risk factors. CKD causes accelerated coronary artery disease (CAD). In this chapter, we discuss the pathophysiological mechanisms that play a role in increasing CVD risk in patients with CKD. Further we delve into some commonly encountered challenges related to CVD in patients with CKD. These include revascularization challenges, contrast-induced nephropathy and alterations in traditional risk factors for CVD in renal transplant patients.

**Keywords:** coronary artery disease, chronic kidney disease, mortality, morbidity, public health

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## 1. Introduction

Chronic kidney disease (CKD) is recognized as a major global public health problem [1]. It is estimated that 10–25% of population from Asia, Australia, Europe and United States of America (USA) is affected by CKD [2–6].

Multiple studies have shown the association of CKD with cardiovascular mortality that persists after adjustment for traditional cardiovascular disease (CVD) risk factors. These include the Atherosclerosis Risk in Communities study (ARIC) and the Cardiovascular

Health Study [7–9]. The risk of developing congestive heart failure, atrial fibrillation, stroke, coronary artery disease (CAD) and peripheral artery disease (PAD) is increased twofold in patients with glomerular filtration rate (eGFR)  $< 70 \text{ ml/min/1.73 m}^2$  [8, 10]. Furthermore, in two separate meta-analyses of twenty-one studies from fourteen different countries eGFR and albuminuria were found to be independently associated with increased risk of all-cause and cardiovascular mortality [11, 12].

In this chapter we discuss the acute and chronic cardiovascular impact of patients with reduced kidney function. We further delve in evaluation of coronary artery disease in patients with CKD. We also address the cardiovascular aspects of patient care in renal transplant patients including modification of traditional CVD risk factors in patients taking immunosuppressive therapy.

## 2. Epidemiology

CKD is a globally recognized public health burden [13]. USA alone deals with a population of more than 20 million people with CKD [14]. Data from other developed and developing nations confirms the rising trend of the disease. Data from China estimates this number to be close to 100 million Chinese being affected with CKD [15].

CKD has long shared its associations with CVD. The prevalence of CVD among patients with CKD has been known across trials in USA, Japan, Spain, United Kingdom and, recently, across China. Highest prevalence was found in U.K., 47.2% followed by Spain, 39.1%, U.S., 33.4%, Japan, 26.8% and China 9.8% [16–19].

United States Renal Data System (USRDS) reports from 2016 revealed the prevalence of any cardiovascular event to be twice among those with CKD compared to those without it, 68.8% vs. 34.1% respectively.

### 2.1. Linear relationship of cardiovascular mortality with EGFR

CKD is an independent risk factor for progression to cardiovascular disease, known to contribute to cardiovascular morbidity and mortality [20]. Go et al., using longitudinal measurement of estimated eGFR, demonstrated the inverse relationship between eGFR and mortality rate secondary to cardiovascular events, below an eGFR of  $60 \text{ ml/min per } 1.73 \text{ m}^2$  [21]. A meta-analysis from 2011, comprising a grand total of 266,975 patients reported an exponential rise in mortality with eGFR below  $60 \text{ ml/min per } 1.73 \text{ m}^2$  [22]. (21,307,840) For cardiovascular mortality, adjusted hazard ratios at eGFR 60, 45, and  $15 \text{ ml/min per } 1.73 \text{ m}^2$  were 1.11 (0.93–1.32), 1.73 (1.49–2.00), and 3.08 (1.89–5.01), respectively [22].

Manjunath et al., also demonstrated eGFR as an independent risk factor for progression to CVD [23]. In a sample population of 4893, subjects with GFR  $90 \text{ mL/min/1.73 m}^2$  had a 15% risk of CVD over 3 years while subjects with GFR  $30 \text{ mL/min/1.73 m}^2$  had a 40% risk of CVD [23]. These findings were independent from traditional risk factors of cardiovascular diseases.

## **2.2. Albuminuria a marker of worse cardiovascular outcomes in CKD patients**

Albuminuria has been proven to be a significant risk factor for all cause and CVD related mortality in patients with CKD. Pooled data from Van der Welde et al., demonstrated a significant increase in cardiovascular mortality in patients with Albumin-to-creatinine ratio of 10 mg/dl compared to 5 mg/dl [22]. Similar results demonstrating an association of CVD mortality with albuminuria have been reported in other large scale studies [11, 12].

## **3. Ischemic heart disease in chronic kidney disease**

### **3.1. Background**

Cardiovascular (CV) mortality is the leading cause of death in CKD patients and the risk of CV mortality increases with decrease in eGFR. Most of the burden of CV mortality in CKD patients is secondary to ischemic heart disease or complications associated with it including congestive heart failure. The severity and incidence of CAD increases as the kidney function declines with the prevalence of multi-vessel CAD and left main disease being significantly higher in the CKD population [24].

Coronary arteries in CKD patients have shown to exhibit more extensive atherosclerosis [25]. Multiple studies have shown the association of CKD with cardiovascular mortality that persists after adjustment for traditional cardiovascular disease (CVD) risk factors [26, 27]. Mineralocorticoid excess, oxidative stress and cellular inflammation are linked to plaque formation and rupture in CKD patients. Vitamin D deficiency a common sequela of CKD could explain the propensity of CKD patients to develop CAD. It has been shown that patients with Vitamin D deficiency have higher risk of myocardial infarction (MI). Similarly fibroblast growth factor 23 (FGF 23) a hormone usually elevated in CKD patients, to mitigate hyperphosphatemia was associated with increased CVD mortality in patients with CKD [28, 29].

In summation, the pathophysiological basis of increased CVD risk and severity in patients with CKD is due to a complex interplay of factors involving hormonal and immune mediated responses. However the risk of CAD in CKD has been well established. Hence in 2013 the American Heart Association (AHA) issued a statement to classify CKD as an independent risk factor for developing CVD [30].

### **3.2. Revascularization in CKD patients with stable CAD**

Management of patients with established CAD and CKD is challenging. Medical management in patients with renal dysfunction has been based on therapy shown to be beneficial in patient population without CKD. These medications include aspirin, beta-blockers, nitrates, hydroxymethylglutaryl co-enzyme A reductase inhibitors (statins) and angiotensin converting enzyme inhibitors. However because of routine exclusion of CKD patients from clinical trials, the efficacy of these agents in patients with CKD is still unclear.

No robust evidence is yet available to ascertain whether CKD patients with chronic stable angina who undergo revascularization have a definite survival advantage compared to CKD patients on medical therapy alone. In the only randomized study of dialysis patients comparing invasive approach (PCI and coronary artery bypass graft surgery (CABG)) with medical therapy alone, the invasive approach had a clear survival benefit [31]. However medical therapy at that time only consisted of calcium channel blockers, and use of other agents proven to have survival advantage in patients with cardiovascular disease was not the norm. Furthermore, this study only included patients with diabetes mellitus. In another study done in 2002, PCI did not significantly improve survival [32].

Multiple studies have found that patients with CKD who undergo revascularization for CAD have worst outcomes compared to patients with normal kidney function [32, 33]. Patients with CKD have more cardiovascular risk factors at baseline [32]. Furthermore, CKD itself was independently associated with worst outcomes including increased all-cause mortality and subsequent cardiac events [32].

In CKD revascularization procedures including percutaneous coronary intervention (PCI) and coronary artery bypass graft surgery (CABG) are complicated by risk of contrast induced nephropathy (CIN) and increased risk of bleeding due to dual antiplatelet therapy. CIN is discussed in detail in separate section.

CKD results in complex hemostatic disorder manifested by increased bleeding and thrombosis. Hence the use of antiplatelet therapy has the potential for both benefit and harm. Reduced platelet aggregation, intrinsic platelet dysfunction and abnormalities in platelet-endothelial interactions are found in CKD and may in part account for increased bleeding risk with PCI in these patients [34–36].

On the contrary, some studies have suggested the presence of pro-thrombotic state in CKD patients that manifest by an increase in serum fibrinogen, von Willibrand factor and reduction in antithrombin 3 [34, 37–39]. Therefore, it is unclear whether dual antiplatelet therapy after PCI is beneficial and safe in CKD patients. Furthermore, few studies have evaluated the appropriate dosing of antithrombotic agents or anticoagulants in patients with CKD [40].

Although clinical restenosis rates are not higher compared to patients with normal renal function, on repeated angiography restenosis rates were found to be as high as 60–81% [41, 42]. Thus, absence of symptoms of restenosis in patients with chronic renal insufficiency may lead to silent ischemia and contribute to high risk of subsequent cardiac events.

CKD patients have worse outcomes after CABG. One study found in-hospital mortality rate to be 14.6% [43]. Another study that was done on end-stage renal disease (ESRD) patients over course of 10 years found peri-operative mortality to be about 14% in cardiac surgery patients [44]. Even mild renal insufficiency is associated with double in-hospitality rates in one analysis [45]. CAD is more diffuse in patients with renal dysfunction which likely contributes higher complication rates and worst outcomes.

Szczzech et al. published a study in 2001 that showed survival benefit among patients with ESRD undergoing CABG as compared to PCI, while controlling for severity of CAD, LV dysfunction

and other comorbid conditions [46]. However in analysis of CREDO-Hyoto PCI/CABG registry Marui A et al. found CABG relative to PCI reduced risk of cardiac death, sudden death, myocardial infarction and need for revascularization in patients with left main disease or multi-vessel CAD only [47]. In a study by Bangalore et al., revascularization with Everolimus eluting stents was compared to CABG in patients with CKD. The authors concluded that CABG was associated with higher short term risk of death, stroke and repeat revascularization, whereas PCI with everolimus-eluting stent was associated with higher long-term risk of revascularization and perhaps MI [48]. Current American College of Cardiology (ACC) and American Heart Association (AHA) guidelines recommend CABG for patients with left main or multi-vessel disease irrespective of renal function.

### 3.3. Non-invasive cardiac imaging in patients with CKD

As already mentioned CKD patients are at a higher risk of CVD. Imaging plays a central role in risk stratification and assessment of severity of CAD. A range of imaging modalities have been developed to assist with diagnosis and risk stratification of CVD in patients with CKD.

Myocardial perfusion imaging (MPI) is widely used for non-invasive assessment of myocardial ischemia due to CAD [49]. MPI can be performed using single photon emission computed tomography (SPECT) as well as positron emission tomography (PET). SPECT MPI is more widely available. It can be performed with a variety of stressors such as exercise or administration of vasodilatory agents (adenosine or regadenoson) or dobutamine. SPECT detects areas of reduced perfusion by measuring and comparing the distribution of injected radioactive tracers such as 99 technetium or 201 thallium, when at rest and after stressor/vasodilator agents.

For PET MPI stress perfusion is measured in the same way as SPECT. Various agents can be used as radiotracer including H<sub>2</sub> 15 O, ammonia or rubidium. With PET absolute quantification of myocardial blood flow is possible. Although both SPECT and PET MPI have widely been studied for detection of CAD in general population, data regarding their use in CKD population is limited.

Echocardiography plays a pivotal role in assessment of cardiac dysfunction in patients with or without renal insufficiency. Various cardiac abnormalities including left ventricular hypertrophy (LVH), diastolic or systolic dysfunction are predictive of poor prognosis in CKD patients and can be rapidly diagnosed using 2 D trans-thoracic echocardiogram (TTE). Stress echocardiography is an established technique used to investigate myocardial viability and ischemia. Patients can be stressed either pharmacologically with dobutamine or with exercise [50]. However, the sensitivity and specificity of stress echocardiography is modest in patients with CKD. In a systemic review by Sharma et al. sensitivity of stress echocardiography was 80% in patients with ESRD [51]. Factors limiting the role of stress echocardiography for detecting CAD in patients with CKD include LVH and blunted chronotropic response in patients with CKD [52, 53].

CT coronary angiography (CTA) has good sensitivity and specificity for detection of CAD in non-CKD population [54]. However, data is limited in patients with CKD. Iodinated contrast agent is required that increases the risk of contrast induced nephropathy. (contrast induced nephropathy

is discussed in separate section) Furthermore concerns exist that diffuse calcifications in CKD patients might render interpretation of CTA findings difficult. In patients on hemodialysis (HD) calcifications can occur in intima, where it contributes to luminal stenosis or medial where it is related to vascular stiffness. CTA might not be able to discern the difference. Despite these limitations some small studies have reported >90% sensitivity of CTA to detect CAD in patients on HD [55]. However, coronary angiography was not used as gold standard in these studies.

Leading authors have advocated for combining functional imaging technique with anatomical imaging technique for CAD screening in clinical practice. Although these hybrid techniques are potentially useful in general population, none have been validated in patients with CKD [56, 82]. Role of non-invasive imaging for pre-transplant evaluation of CAD is addressed in a separate section.

### **3.4. Contrast Induced Nephropathy**

PCI in patients with CKD is challenging due to presence of complex calcified lesions and the very high risk of CIN. PCI in patients with advanced CKD is associated with increased risk of CIN which is independently associated with major adverse clinical events [57]. Outcomes are even worse if renal replacement therapy is required [57].

Pathophysiologically several mechanisms are involved in acute kidney injury caused by CIN. Studies have shown evidence of acute tubular necrosis (ATN). Two mechanism of ATN have been postulated. Direct nephrotoxicity of contrast agents has been documented [58, 59]. Furthermore, it has also been hypothesized that renal vasoconstriction, mediated by endothelin and prostaglandins resulting in medullary hypoxia causes ATN [60–62].

Studies have demonstrated a dose-dependent relationship of acute kidney injury (AKI) caused by CIN [63]. The type of contrast alters the risk of CIN. The use of first generation hyperosmolar ionic agents is associated with a greater risk of CIN [64]. Prevention strategies for CIN that have been well established also apply to patients undergoing PCI. These include using minimal amount of contrast, avoiding ionic contrast and non-steroidal anti-inflammatory drugs (NSAIDs).

Most recently Galougahi et al. have described a case series of a unique approach toward revascularization in patients with CKD by sequential diagnostic angiography using ultra-low volumes of contrast followed by staged physiology and intravascular ultrasound (IVUS)-guided zero contrast PCI in three patients with severely calcified coronary lesions [65]. While such strategies have potential for more wider acceptance, at this time they are not practiced widely due to technical and procedural limitations.

## **4. Use of troponin concentration level in patients with chronic kidney disease**

Troponin proteins are present in both cardiac and skeletal muscle [66]. Cardiac troponin C is identical to troponin C expressed in skeletal muscle. However cardiac troponin TnT and TnI are each derived from genes that are specific to the heart [66]. Hence troponin T (cTnT)

and Troponin I (cTnI) are considered the preferred biochemical markers to detect myocardial injury and to diagnose acute myocardial infarction (AMI). Since the introduction of high sensitivity cardiac troponin (hs-cTn) assays, more accurate detection of low levels of circulating cardiac troponins became feasible [67].

However the increase in sensitivity of hs-cTn for AMI is accompanied by decrease in specificity [68, 69]. In patients with chronic kidney disease elevated hs-cTn concentrations are associated with reduced renal function.

The interpretation of serum markers for myocardial injury in patients with renal insufficiency remains controversial. Large scale trials of patients with acute coronary syndrome (ACS) have documented the importance of troponin elevations in risk stratification, prognosis and therapeutic utilization. However most of these studies excluded patients with renal insufficiency.

Cardinaels et al. recently showed that in patients with acute chest discomfort hs-cTnT and hs-cTnI were strongly correlated with eGFR [70]. Although differences were small, the authors reported a greater correlation of hs-cTnT with eGFR compared to hs-cTnI. Furthermore, the association of hs-cTnT is greater with eGFR as compared to any other cardiac parameters including coronary plaque severity, coronary calcium score and left ventricular structure [70]. In contrast to hs-TnT, hs-TnI has a greater association with LV mass compared to eGFR. Hence it is possible that hs-TnT is more susceptible to renal clearance than hs-cTnI. However, these differences are yet to be completely established.

Furthermore, many investigators have hypothesized uremic-induced skeletal myopathy may be responsible for increased troponins in patients with renal failure [66]. This conclusion is centered on the notion that uremia may promote re-expression of cardiac TnT from injured or regenerating cardiac muscle fibers. Some anecdotal reports show elevated serum TnT levels in patients with skeletal muscle injury or inflammatory myopathies in the absence of any obvious myocardial ischemia [71, 72]. In marathon runners without any history of coronary artery disease cardiac TnT levels were elevated after running a marathon [73]. Hence cardiac troponin levels may be elevated in patients with renal insufficiency in the absence of AMI due to increased production from skeletal muscles and possible due to decreased renal clearance. It is imperative to evaluate troponin concentrations in patients with CKD in proper clinical context and utilization of other resources such as Electrocardiogram (EKG) to rule out AMI.

## 5. Cardio-renal Syndromes

The heart and kidneys work together to manage blood pressure, electrolyte and fluid excretion, but most importantly extracellular fluid balance [74]. Cardio-renal syndrome (CRS) is defined as a broad spectrum of diseases where both the heart and kidneys are involved in an acute or chronic setting [75]

There are five types of CRSs. Type I, or acute CRS, is acute heart failure leading to acute kidney injury [74] Type II, or chronic CRS, occurs in the setting of chronic heart failure which leads to kidney injury [75]. Type III or acute nephrocardiac is caused by acute kidney injury

| Cardiorenal type | Inciting event         | Secondary event   | Example   |
|------------------|------------------------|---|---|
| Type I           | Acute heart failure    | Acute kidney injury   | Acute coronary syndrome leading to decreased cardiac output and acute kidney injury |
| Type II          | Chronic heart failure  | Progressive kidney disease  | Chronic heart failure leading to decreased cardiac output                           |
| Type III         | Acute kidney injury    | Acute cardiac disease (heart failure, arrhythmia, pulmonary edema)                | Acute kidney failure (drug induced, glomerulonephritis)                             |
| Type IV          | Chronic kidney disease | Decreased cardiac output, Increased blood pressure leading to cardiac hypertrophy | Chronic kidney disease due to chronic hypertension or diabetic nephropathy          |
| Type V           | Systemic disease       | Both kidney and heart dysfunction and disease                                     | diabetes mellitus, sepsis, lupus  |

**Table 1.** Classification of cardio-renal syndromes.

leading to acute heart failure, example Uremic cardiomyopathy [75]. Type IV, or chronic nephrocardiac, occurs with chronic kidney disease which causes heart failure for example diastolic heart failure and kidney failure [75]. Lastly, is type V which is secondary to systemic disease leading to heart and kidney failure [75]. **Table 1** summarizes the five types of CRSs.

Management of patients with acute decompensated heart failure and worsening renal function can be challenging. A randomized control trial compared the effect of venovenous ultrafiltration with intravenous diuretics on renal function with acute decompensated heart failure and worsening renal function [76]. This study found that there was no significant difference between diuretics and ultrafiltration in weight loss, mortality or the rate of re-hospitalization for acute decompensated heart failure during a 60 day follow-up.

## 6. CAD evaluation before kidney transplant

Cardiovascular disease is the leading cause of morbidity and mortality in patients with end-stage renal disease (ESRD) and in those after kidney transplant [77, 78]. Based on Medicare billing claims incidence of myocardial infarction have ranged from 8.7 to 16.7% by 3 years after kidney transplant listing and from 4.7 to 11.1% after kidney transplantation [79]. Cardiovascular disease accounts for 30% of the overall mortality especially in the peri-transplantation period [80]. So, the preoperative cardiovascular risk assessment is of high importance before the kidney transplant surgery as these patients are closely followed up for over the 3 years and events are reported to the United Network for Organ Sharing (UNOS).

**Figure 1** summarizes a clinical approach to preoperative cardiovascular risk assessment before kidney transplantation.



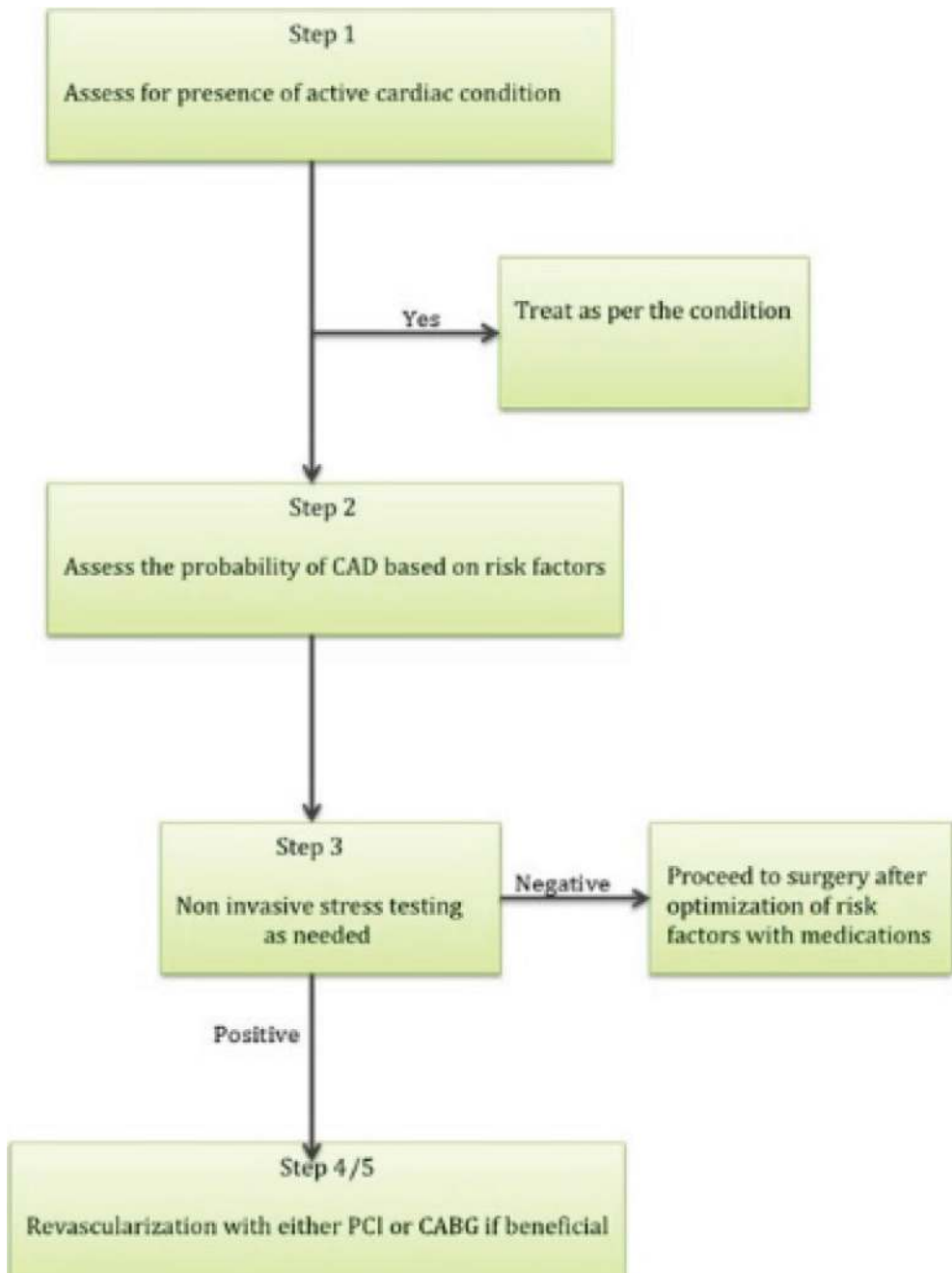


Figure 1. Pre-operative cardiovascular risk assessment before kidney transplant.

*Step 1: Assess for presence of active cardiac condition:*

Patients with active cardiac condition should be ruled out by detailed history and physical examination. Active cardiac conditions include- unstable coronary syndromes (e.g., unstable angina, severe angina, or recent MI), decompensated heart failure, significant arrhythmias, and severe valvular disease. The presence of one or more of these conditions is associated with high rates of perioperative cardiovascular morbidity and mortality and may require delay or cancellation of surgery.

*Step 2: Assess for presence of risk factors*

After excluding active cardiac condition, presence of risk factors for CAD should be assessed. Traditional Framingham risk score has modest to moderate ability to predict long-term coronary events among kidney transplantation patients. Risk stratification based on 2007 Lisbon conference [81] strategy improved the sensitivity and specificity for the identification of CAD (sensitivity, 94% vs. 77%; specificity, 33% vs. 24%) when compared to ACC/AHA recommended CAD risk stratification strategy. The risk factors for CAD deemed relevant to transplantation candidates in the Lisbon Conference report include diabetes mellitus, prior cardiovascular disease, >1 year on dialysis, left ventricular hypertrophy, age > 60 years, smoking, hypertension, and dyslipidemia.

Currently, the preoperative assessment is done based on the ACC/AHA scientific statement [78]. As per this "Noninvasive stress testing may be considered in kidney transplantation candidates with no active cardiac conditions based on the presence of multiple coronary artery disease (CAD) risk factors regardless of functional status. Relevant risk factors among transplantation candidates include diabetes mellitus, prior cardiovascular disease, more than 1 year on dialysis, left ventricular hypertrophy, age greater than 60 years, smoking, hypertension, and dyslipidemia. The specific number of risk factors that should be used to prompt testing remains to be determined, but the committee considers 3 or more as reasonable (Class IIb; Level of Evidence C)."

*Step 3: Non-invasive testing*

Most common non-invasive stress testing modalities include dobutamine stress echocardiogram (DSE) and MPI. The diagnostic accuracy of these tests varies with sensitivity ranging from 0.29 to 0.92 (MPI) 0.44–0.89 (DSE) and specificity of around 0.67–0.89 (MPI) and 0.71–0.94 (DSE) [78]. MPI accuracy can be affected by presence of balanced ischemia resulting in more false negative results. Recently, coronary computed tomography angiography (CCTA) was shown to be a reliable test with high sensitivity (93%) and a high negative predictive value (97%) for diagnosing obstructive CAD before kidney transplantation. Hybrid imaging techniques like combining CCTA and SPECT have a sensitivity and specificity of 67 and 86% [82]

*Step 4: Coronary angiography*

Based on the noninvasive testing, coronary angiography is performed as needed to determine the presence and extent of obstructive CAD.

### *Step 5: Revascularization*

Revascularization is done either with PCI with stent or CABG after assessment of extent of obstructive CAD and risk factors like diabetes as per the ACC/AHA guidelines for management of stable ischemic heart disease.

## **7. Cardiovascular risk in renal transplant patients**

Renal transplant (RT) has dramatically improved the survival and quality of life for successful recipients. Despite advancements in surgical methods and medical management of RT patients, cardiovascular disease (CVD) remains the leading cause of death in patients with functional grafts.

The risk of CVD improves after RT when compared to patients with end-stage renal disease (ESRD) awaiting transplantation. However, mortality due to CVD is ten times higher in renal transplant recipients than the age and sex-matched general population [83, 84].

The increased risk of CVD cannot be explained by traditional risk factors alone. Non-traditional risk factors in RT patient population also play a pivotal role [85].

Traditional CVD risk factors include Hypertension, Diabetes Mellitus, Dyslipidemia, Tobacco use, and Obesity. In this section the effect of immunosuppressive agents on these traditional risk factors will be discussed.

### **7.1. Non-traditional risk factors**

In addition to traditional CVD risk factors, RT patients develop specific risk factors related to ESRD including but not limited to endothelial dysfunction, electrolyte imbalances (calcium and phosphorous), anemia and variations in the plasma volume following dialysis.

A retrospective study using database from *Données Informatisées et Validées en Transplantation (DIVAT)* evaluated 244 RT patients post-transplant for 1 year for ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), new onset atrial fibrillation or ventricular fibrillation, and death from cardiovascular diseases.

The results revealed that a past medical history of cardiovascular disease (Hazard Ratio (HR)=2.06,  $p=0.03$ ), left ventricular hypertrophy (HR=2.04,  $p=0.04$ ) and abnormal myocardial perfusion imaging (HR=2.18,  $p=0.05$ ) were associated with a higher risk of early cardiovascular event [86].

### **7.2. Left ventricle hypertrophy**

LVH is a common co-morbidity observed in chronic kidney disease (CKD) and end-stage renal disease (ESRD) patients [87]. Multiple factors have been implicated as the cause of LVH

including over-activation of the sympathetic nervous system, volume overload, hypertension, inhibition of nitric oxide, arterial stiffness, diabetes, dyslipidemia, endothelial dysfunction, and anemia of chronic disease. Electrocardiographic (ECG) evidence of LVH in the first year after RT was found to be an independent risk factor for death and subsequent congestive heart failure [88]. Persistent or de novo LVH is also a strong independent risk factor for death after 5 years, confirming the continuing importance of LVH even in the late post-transplant period [88].

The presence of LVH is a important prognostic factor for CVD mortality and morbidity in RT patients. Whether a successful renal transplantation can reverse LVH still remains a debatable issue [87].

### **7.3. Over-activation of the sympathetic nervous system**

To entertain the hypothesis that development of LVH may be connected to excessive activation of the sympathetic nervous system, the effect of pre-transplant bilateral native nephrectomy on left ventricular mass and function has been evaluated. A study group of 32 patients who had undergone pre-transplant bilateral native nephrectomy were compared to 32 control group patients and evaluated with echocardiography and/or cardiac magnetic resonance (CMR) [89].

After a 90-month follow-up, bilateral native nephrectomy before transplantation was associated with a lower left ventricular mass index (LVMI;  $p = 0.001$ ), left atrial volume index (LAVI;  $p = 0.004$ ), and a lower grade (grade I) of left ventricular diastolic dysfunction [89]. In comparison with controls, the study group had lower systolic blood pressure ( $p = 0.04$ ) and required a fewer number of anti-hypertensive medications ( $p = 0.001$ ) [89].

### **7.4. Inflammatory state**

Pro-inflammatory markers have also been studied in RT patient population. Neopterin is synthesized by macrophages upon stimulation by interferon-gamma. Serum neopterin is a marker of a pro-inflammatory state in RT patients. Clinical trial data has revealed that Neopterin is associated with cardiovascular events and all-cause mortality in renal transplant patients.

The Assessment of LEscol in Renal Transplant (ALERT) trial prospectively analyzed RT patients with stable graft for an association between serum neopterin and subsequent clinical events: graft loss, major cardiovascular events (MACE) and all-cause mortality. The long-term follow-up suggests that neopterin-to-creatinine ratio is significantly associated with MACE ( $p = 0.009$ ) and all-cause mortality ( $p = 0.002$ ) [90].

### **7.5. Proteinuria**

A prospective trial of 90 RT patients with normal graft function in the post-transplantation period (3–5 years) investigated the association between proteinuria and graft/patient survival and to determine whether proteinuria may be a predictor for cardiovascular disease. High-grade ( $\geq 500$  mg/24 hours) proteinuria in RT patients is strongly associated with poor graft

survival and increased risk of cardiovascular events [91]. These findings were similar to CKD patients without transplant as previously described.

## 7.6. Anemia

According to the follow-up data from the ALERT study, anemia is a predictor of graft loss but not associated with an increased incidence of cardiovascular morbidity and mortality or all-cause mortality in RT patients [92].

## 7.7. Immunosuppressive therapy

RT patients are usually on a combination of following maintenance medications:

*Corticosteroids: Prednisone.*

*Antiproliferative agents: Mycophenolate Mofetil and Azathioprine.*

*Calcineurin inhibitors: Tacrolimus and Cyclosporine.*

*mTOR inhibitors: Sirolimus and Everolimus.*

No immunosuppressive drug has been directly associated with cardiovascular events. However, immunosuppressive drugs impact the traditional risk factors and play a crucial role.

## 8. Hypertension

### 8.1. Corticosteroids

According to the historical literature, corticosteroids were believed to cause elevated blood pressure by water and salt retention via an effect on the mineralocorticoid receptor. However, recent data points that blockade of NO formation by inhibition of both inducible and endothelial nitric oxide synthase (eNOS), inhibition of transmembrane arginine transport and inhibition of the synthesis of the NOS cofactor BH4 play a prominent role [93].

### 8.2. Antiproliferative agents

Anti-proliferative agents were thought to worsen hypertension in RT patients. However recent studies in patients with systemic lupus erythematosus suggests an improved blood pressure control with the use of mycophenolate mofetil.

### 8.3. Calcineurin inhibitors

Cyclosporine monotherapy induces hypertension to the same extent as corticosteroids [94]. The mechanism by which cyclosporine and tacrolimus increase blood pressure is complex. One proposed mechanism is that cyclosporine stimulates transmembrane influxes of calcium, thereby leading to vascular smooth muscle cell contraction and vasoconstriction.

Other proposed mechanisms include increased production of endothelin 1 (ET-1), transforming growth factor (TGF), renin, and inhibition of NO production by multiple pathways.

Recent data suggests that tacrolimus results in less renal vasoconstriction than cyclosporine. RT patients being treated with tacrolimus and equivalent dosages of corticosteroids require fewer anti-hypertensive medications than patients being treated with cyclosporine [95].

## 9. Dyslipidemia

### 9.1. Corticosteroids

Corticosteroids increase total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and hepatic synthesis of very low-density lipoprotein (VLDL) [96]. Corticosteroids lead to decreased LDL receptor synthesis and subsequent expression, thereby leading to reduced uptake and degradation of LDL [97].

### 9.2. Calcineurin inhibitors

Cyclosporine increases total cholesterol, LDL, and VLDL but decreases HDL. Cyclosporine decreases the activity of lipoprotein lipase (LPL) leading to hypertriglyceridemia. It also impairs the clearance of LDL by a similar mechanism to corticosteroids [98].

When comparing patients on tacrolimus versus cyclosporine, tacrolimus-treated patients have lower total cholesterol, LDL, and triglycerides. The levels of HDL are comparable. In a randomized, prospective trial evaluating RT patients with conversion from cyclosporine to tacrolimus, total cholesterol improved significantly by a mean of 0.5 mmol/L, LDL by 0.35 mmol/L and triglycerides by 0.4 mmol/L. These results were sustained up to 2 years after conversion [99].

### 9.3. mTOR inhibitors

Sirolimus is notorious for causing hyperlipidemia; increasing VLDL and LDL. One hypothesis is that sirolimus increases hepatic production of triglycerides and secretion of VLDL [100]. In clinical trials evaluating serum lipid profile, the addition of sirolimus 10 milligrams to cyclosporine and corticosteroids for 6 weeks increased both total cholesterol and LDL by 50% and triglycerides by almost 100%. The effects were fully reversible after discontinuation of sirolimus [100].

## 10. Diabetes mellitus

Post-transplantation diabetes mellitus (PTDM) has evolved into a concerning challenge in RT patients. Approximately one-third of nondiabetic kidney transplant recipients develop persistent impaired glucose metabolism by 6 months post-transplantation [101]. Risk factors for PTDM include age, obesity, African American race and Hispanic ethnicity, family history

and impaired glucose tolerance. Additionally, transplant related risk factors also play a role: immunosuppressive medications, HLA mismatch, donor gender, type of underlying renal disease and viral infections (HCV and CMV) [102].

The implications of PTDM in patient outcomes are not well established, but data from the USRDS/UNOS have shown that PTDM increases the risk of post-transplant myocardial infarction [103].

### **10.1. Corticosteroids**

Corticosteroids lead to development of PTDM by enhancing insulin resistance. PTDM is reversible by cessation of corticosteroids.

### **10.2. Antiproliferative agents**

There is no data suggesting that mycophenolate mofetil or azathioprine play a role in development of PTDM.

### **10.3. Calcineurin inhibitors**

RT patients receiving calcineurin inhibitors have a higher incidence of PTDM. The etiology is impairment in pancreatic beta-cell secretory function [104]. Dose reduction has been shown to reverse diabetes in majority of the affected patients. The incidence of PTDM with tacrolimus is postulated to be as high as 20%. The higher incidence of PTDM with tacrolimus versus cyclosporine is believed to be due to stronger potency of tacrolimus in calcineurin inhibition than cyclosporine [105].

Tacrolimus leads to PTDM in a dose-dependent manner. It leads to complete reversible inhibition of the insulin gene transcription with no acute effects on insulin secretion or the glucose uptake by insulin. Therefore, in majority of patients, PTDM is reversible after reducing the dose of tacrolimus and withdrawing corticosteroids.

### **10.4. mTOR inhibitors**

There is no data suggesting that sirolimus or everolimus plays a role in development of PTDM.

## **11. Management of immunosuppressive agents in controlling risk factors**

### **11.1. Corticosteroids**

Corticosteroids negatively impact blood pressure, lipid profile, and glucose metabolism. Randomized trials have shown that corticosteroid withdrawal or corticosteroid-free immunosuppression improves hypertension, dyslipidemia, and glucose metabolism [106].

## 11.2. Calcineurin inhibitors

In patients receiving cyclosporine combined with mycophenolate mofetil, a 50% reduction in cyclosporine dose or complete cyclosporine withdrawal from a mycophenolate mofetil or sirolimus-based regimen results in fewer anti-hypertensive medications [106]. Tacrolimus increases the risk of PTDM more than cyclosporine, therefore, switching from tacrolimus to cyclosporine may lead to improvement in PTDM.

## 12. Conclusion

Renal transplantation is the single most effective intervention for reducing CV risk in appropriately selected patients with ESRD. Even though renal transplant has significantly improved survival for successful recipients, CVD remains the leading cause of death in patients with functional grafts [107].

In addition to traditional CVD risk factors, RT patients develop specific risk factors related to ESRD including but not limited to left ventricular hypertrophy, over-activation of the sympathetic nervous system, pro-inflammatory state, and proteinuria.

Post-transplantation, patients are maintained on a regimen of immunosuppressive medications. Even though immunosuppressive drugs have not been directly associated with cardiovascular events, they play pivotal role in risk associated with traditional risk factors of hypertension, dyslipidemia, and diabetes.

Strategies targeting transplant-specific CV risk factors should include optimization of renal function, limiting risk of rejection, avoidance of PTDM and anticipation of CV side effects of immunosuppression.

## Author details

Ali Osama Malik<sup>1</sup>, Sumit Sehgal<sup>2</sup>, Hashim Hussnain Ahmed<sup>3</sup>, Subodh Devabhaktuni<sup>2</sup>, Edward Co<sup>1</sup>, Arhama Aftab Malik<sup>5</sup>, Syed Shah<sup>4</sup> and Chowdhury Ahsan<sup>2\*</sup>

\*Address all correspondence to: [chahsan92@yahoo.com](mailto:chahsan92@yahoo.com)

1 Department of Internal Medicine, University of Nevada, School of Medicine, Reno, Nevada

2 Department of Cardiovascular Medicine, University of Nevada, School of Medicine, Reno, Nevada

3 Department of Surgery, Shaukat Khanum Memorial Cancer and Research Center, Pakistan

4 Kidney Specialist of Southern Nevada, Nevada, USA

5 Aga Khan University, Karachi, Pakistan



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