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REVIEW

# Cardiovascular risk factors following renal transplant

Jill Neale, Alice C Smith

Jill Neale, Alice C Smith, Leicester Kidney Exercise Team, John Walls Renal Unit, Leicester General Hospital, Leicester LE5 4PW, United Kingdom

Jill Neale, Alice C Smith, Department of Infection, Immunity and Inflammation, University of Leicester, Leicester LE1 9HN, United Kingdom

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Correspondence to: Dr. Jill Neale, BSc, MBBS, MRCP, Academic Clinical Fellow, Department of Infection, Immunity and Inflammation, University of Leicester, University Rd, Leicester LE1 9HN, United Kingdom. jn150@student.le.ac.uk
Telephone: +44-116-2584346

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## Abstract

Kidney transplantation is the gold-standard treatment for many patients with end-stage renal disease. Renal transplant recipients (RTRs) remain at an increased risk of fatal and non-fatal cardiovascular (CV) events compared to the general population, although rates are lower than those patients on maintenance haemodialysis. Death with a functioning graft is most commonly due to cardiovascular disease (CVD) and therefore this remains an important therapeutic target to prevent graft failure. Conventional CV risk factors such as diabetes, hypertension and renal dysfunction remain a major influence on CVD in RTRs. However it is now recognised that the morbidity and mortality from CVD are not entirely accounted for by these traditional risk-factors. Immunosuppression medications exert a deleterious effect on many of these well-recognised contributors to CVD and are known to exacerbate the probability of developing diabetes, graft dysfunction and hypertension which can all lead on to CVD. Non-traditional CV risk factors such as inflammation and anaemia have been strongly linked to increased CV events in RTRs and should be considered alongside those which are classified as conventional. This review summarises what is known about risk-factors for CVD in RTRs and how, through identification of those which are modifiable, outcomes can be improved. The overall CV risk in RTRs is likely to be multifactorial and a complex interaction between the multiple traditional and non-traditional factors; further studies are required to determine how these may be modified to enhance survival and quality of life in this unique population.

**Key words:** Kidney transplantation; Cardiovascular disease; Atherosclerosis; Immunosuppression; Diabetes mellitus



**Core tip:** Cardiovascular disease (CVD) is the leading cause of death and disability in patients following a renal transplant. Identification of risk factors for CVD and strategies for their improvement are required in order to prevent graft failure in this complex patient

group. This review identifies the most important risks for CVD and seeks evidence for how they can be most successfully managed and modified to improve morbidity and mortality.

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## INTRODUCTION

Patients with chronic kidney disease (CKD), and those on dialysis in particular, have an elevated cardiovascular (CV) risk compared to the general population[1-3], with haemodialysis (HD) patients having a 10-20 times increased risk of cardiovascular disease (CVD) mortality[4]. The preferred method of renal replacement therapy is currently renal transplantation as this confers improved survival rates compared to those patients on HD or peritoneal dialysis[5]. Transplantation has been shown to reduce CV events[6,7] compared to those on dialysis[8,9], although outcomes still remain poorer than in the general population[8].

CVD is an umbrella-term which covers congestive cardiac failure (CCF), coronary artery disease (CAD), cerebrovascular disease and peripheral vascular disease. Rates of cardiac death in renal transplant recipients (RTRs) still remain higher than in the general population, with the rate of cardiac death 10-times higher and the annual rate of fatal or non-fatal CV events 50-times that of the general population[10]. Cardiac related disease accounts for 17% of all deaths in RTRs and in combination with cerebrovascular disease accounts for 22% of all deaths. The most common cardiac causes of death are cardiac arrest (45%) followed by myocardial infarction (MI) (31%) and cardiac arrhythmia (13%)[11]. These sudden cardiac deaths are often attributed to arrhythmias, rather than to MIs secondary to underlying coronary artery atherosclerosis, which suggests that the standard risk factors such as hypertension and diabetes only partly contribute to the overall CV risk. In addition, cardiac events in RTRs are more likely to be fatal than in the general population, although the rates do remain lower than in dialysis patients[12].

Cerebrovascular events are comprised of ischaemic and haemorrhagic strokes and are less common than cardiac events but still have an increased incidence compared to the general population. They represent a significant cause of morbidity, with a prevalence of around 4.5%, and ischaemic strokes account for 89%, with the remainder being classed as haemorrhagic or due to a sub-arachnoid haemorrhage[13]. The ten-year cumulative incidence of lower-limb peripheral vascular occlusive disease (PVOD) in RTRs is 5.9% and the overall survival and graft-survival rates are significantly lower than that of RTRs who do not have PVOD[14]. Infection (26%) and malignancy (24%) also contribute significantly to the causes of death in RTRs[15], especially in the first year post-transplant, suggesting that the causes of morbidity and mortality are multifactorial.

CV risk factors in RTRs can be divided into traditional and non-traditional which reflects the complex nature of RTRs. Traditional risks include co-morbidities such as hypertension, dyslipidaemia and diabetes as well as lifestyle factors such as smoking and low physical activity. The burden of CVD is not completely explained by the traditional risk factors[16] therefore there are other impacting influences which need to be considered. Non-traditional risk factors are also known to influence the morbidity and mortality of RTRs and include immunosuppression medications, anaemia, inflammation and proteinuria[17]. These will each be discussed in more detail later in the review.

## TRADITIONAL RISK FACTORS

CAD is known to play a major role in the development of CVD and subsequent cardiac events in the general population and is heavily influenced by the traditional CV risk factors. Around one third of patients undergoing assessment for renal transplant have a significant burden of CAD, identified by coronary angiogram[18], and 2.6%-4.7% have had a MI prior to their transplant[19] with 6.8% requiring revascularisation[20]. Current guidance suggests that routine coronary angiogram should only be considered in those who are high-risk (age > 50, diabetes, previous cardiac event), as only a small number of patients have CAD which subsequently requires revascularisation and there is no effect on the peri-operative rates of CV events[21].

Following transplantation, the rates of MI remain high, with a cumulative risk of 6.5%-11.1% at 36 mo, and the greatest burden of disease being seen in the first 6 mo post-transplant[22]. In fact, 86% of major adverse cardiac events occur within 180 d[23]. Other studies corroborate this pattern with prevalent CVD numbers at 20%, and 14% of RTRs having a previous MI[24]. Additionally, half of all deaths in patients who retained functioning grafts were due to ischaemic heart disease (IHD)[25] which highlights the importance of identifying risk factors which can be addressed to enhance survival rates in this complex population.

### *Hypertension*

Hypertension is a leading cause of CV events in the general population[26] and remains an important modifiable risk factor in patients with end-stage renal disease (ESRD). According to Kidney Disease: Improving Global Outcomes (KDIGO) the target for blood pressure should be ≤ 130/80 mmHg irrespective of the presence of proteinuria[27] although the United Kingdom Renal Association recommend a tighter control of ≤ 125/75 if proteinuria is present[28]. Hypertension is a frequent complication of CKD and is often difficult to control.

Eighty-five percent of those with CKD have a diagnosis of hypertension with either a blood pressure of > 140/90 mmHg or use of anti-hypertensive medications and 58% require at least three different medications suggesting that blood pressure remains a challenge even with optimum medical management[29]. After transplant, hypertension is still widespread with 55.5%-93% of RTRs consistently having a systolic blood pressure of > 140 mmHg[30,31]. There are multiple factors which can lead to hypertension including the donor and recipient characteristics as well as immunosuppressive medications and allograft function[32].

Hypertension is a leading predictor of CV events and graft dysfunction in RTRs and is seemingly independent of episodes of acute rejection and kidney function[30,33]. When blood pressure is tightly controlled with an average systolic reading of < 140 mmHg at three years post-transplant, there is improved allograft survival and reduced CV mortality at 10 years. Even if blood pressure was poorly controlled after one year, if it improved by three years following their transplant, then patients had a significantly improved long-term graft outcome compared with patients with a sustained high systolic blood pressure after three years[34].

The choice of immunosuppression also influences blood pressure. Calcineurin inhibitors (CNIs) are implicated in the development of hypertension in RTRs and cause a significant increase in blood pressure. The mechanism of the development of hypertension is complex and involves systemic and intra-renal vasoconstriction and sodium retention. Cyclosporine is thought to increase blood pressure by a number of mechanisms including activation of the sympathetic nervous system and decreasing powerful vasodilators such as prostaglandin and nitric oxide. Cyclosporine and tacrolimus both up-regulate endothelin-1 gene expression and stimulate endothelin-1 release from various renal tissues and cells[35]. Conversion from cyclosporine to tacrolimus has been shown to have a beneficial effect of reducing average systolic blood pressure in some studies[36,37] although overall, following a meta-analysis, there has been no proven beneficial effect[38].

Treatment of hypertension has been the focus of several studies, investigating whether calcium channel blockers (CCB), angiotensin converting enzyme inhibitors (ACE-inhibitors) alone, or in combination are beneficial in the management of high blood pressure as well as preserving renal function. CCBs have been suggested as an option in hypertension caused by CNIs due to their effect in promoting vasodilation of the afferent arterioles. Results have been mixed when CCB are compared to placebo or no treatment, some have shown a non-significant risk reduction in graft loss[39,40] although overall graft function does seem to be improved, with an increase in the estimated glomerular filtration rate (eGFR) from 28 in controls to 44 in those receiving verapamil[39] and creatinine clearance increased from 54.2 in controls to 62.6 in those receiving lacidipine[41]. However CCB did not reduce blood pressure, the number of anti-hypertensive medications prescribed or adverse events[41]. When compared to ACE-inhibitors, CCB compare favourably, with significant improvements in creatinine clearance, potassium and haemoglobin. Additionally, ACE-inhibitors reduced albuminuria and a combination of ACE-inhibitor and CCB produced overall better results for diastolic blood pressure whilst systolic readings did not change in any group[42]. Results from meta-analyses have found that CCB compared with placebo or no treatment reduced graft loss and improved eGFR[43] whilst data from ACE-inhibitor studies were less conclusive. In direct comparison with CCB, ACE-inhibitors decreased eGFR, proteinuria and haemoglobin and increased potassium. ACE-inhibitor and angiotensin receptor blocker (ARBs) use was associated with improvements in proteinuria but decline in eGFR and equivocal results surrounding patient and graft survival[44]. In addition, there has been a reported increased incidence of angioedema in those treated with ACE-inhibitors or ARBs and mammalian target of rapamycin inhibitors (mTOR) inhibitors suggesting that this combination of treatment should be used with caution[45]. The overall recommendations were that CCBs offer greater benefit than the available alternatives, as ACE-inhibitors are associated with a decline in renal function without an improvement in CV risk, although in the presence of proteinuria ACE-inhibitors or ARBs may provide more benefit.

### *Dyslipidaemia*

Dyslipidaemia is common in those who have had a renal transplant, with a prevalence of 80% being reported in some historical studies and 57% of patients having a total serum cholesterol concentration of 240 mg/dL or more[46]. With recent advances in treatment, figures have improved, although there is still a wide range of estimates of 16%-72% depending on the patient population and the time point after transplantation when the levels were obtained[47-49]. High total cholesterol has been shown to increase the chance of having a MI in RTRs[22], similar to in the general population, and is likely due to atherosclerosis formation within coronary vessels as well as those supplying the transplant. This increases the risk of developing chronic allograft dysfunction and hypercholesterolaemia and hypertriglyceridaemia remain important independent risks factors for graft failure[50]. According to KDIGO guidance, it is recommended that all RTRs should have their lipids checked as a part of their initial assessment. However they should not be routinely checked after this for the majority of patients as the indication for pharmacological intervention is guided by CV risk rather than LDL-cholesterol levels, although a LDL-cholesterol of 2.6 mmol/L has been suggested as a target[27].

The most common pharmacological intervention for dyslipidaemia are 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (HMG Co-A reductase inhibitors, or statins). The ALERT (Assessment of lescol

in renal transplantation) trial was a large interventional study of 2100 stable RTRs treated with cyclosporine[12]. The patients received either fluvastatin (40 or 80 mg) or placebo. Follow-up was initially for six years but this was subsequently extended to eight years and patients received the higher dose of fluvastatin for the remaining two years. Following the first stage of the trial, the primary outcome measures of cardiac death, non-fatal MI and coronary intervention failed to reveal statistically significant results. There was however, a 32% reduction of LDL-cholesterol and risk of MI was decreased by 35%. The two year extension did show some significant changes in the primary composite end-points and the overall conclusion reached was that early initiation of lipid-lowering treatment was more beneficial than starting therapy later[51]. One concern regarding use of statins in RTRs is its potential for interactions with immunosuppressive medications. Cyclosporine can increase plasma levels of statins *via* a complex mechanism, possibly involving competitive inhibition of CYP3A4-mediated drug metabolism by cyclosporine. It is therefore recommended that, when used in combination with cyclosporine, the statin dose should be significantly reduced to prevent serious adverse reactions such as rhabdomyolysis[52]. The pharmacokinetics of atorvastatin has not been found to be influenced by tacrolimus[53], although further studies are needed before this can be generalised to all types of statin. Alternatives to statins, such as fibrates and nicotinic acid, should not be used as a first-line treatment for dyslipidaemia in RTRs and if they are to be used as an additional therapy, they should be monitored closely[54].

Dyslipidaemia is often an unwanted side-effect of immunosuppression. It is a recognised complication of treatment with most types of immunosuppression including corticosteroids, CNIs and mTOR inhibitors. Corticosteroids affect total, HDL and LDL-cholesterol and triglycerides (TG) whereas CNIs tend to have a greater influence on total and LDL-cholesterol[55]. mTOR inhibitors work in a dose-dependent manner and influence total, HDL and LDL-cholesterol and TG suggesting that all have the potential to result in dyslipidaemia. Generally, increases in total cholesterol and TG have been found as early as 30 d after transplantation, peaking after 6 mo with stabilisation at the end of first year, regardless of the immunosuppressive regimen. However, patients receiving cyclosporine as opposed to tacrolimus, mTOR inhibitors or mycophenolate mofetil (MMF) show worse lipid profiles despite a higher proportion of mTOR inhibitor patients prescribed statins at 1 year[56,57]. Alternative findings have shown that mTOR inhibitors actually have a detrimental effect on the lipid profile[58] with more clinical trials required to determine the effect of this altered lipid profile on atherosclerotic CVD[59].

A recent Cochrane review of 22 randomised control trials (RCTs) comparing statins with placebo, no treatment or conventional treatment found that statins had uncertain effects on all-cause mortality, stroke, creatine kinase and liver enzyme derangement and withdrawal due to adverse events[60]. They significantly improved total and LDL-cholesterol, TG and HDL-cholesterol and may reduce major CV events and MIs. Statins also had uncertain effects on graft function, acute rejection and eGFR suggesting that further research is needed before it is known whether the improvement in lipid profile leads to a benefit in CV risk and allograft function.

### *Diabetes mellitus*

Post-transplant diabetes is a well-recognised complication following transplantation, and is associated with worsening of graft function and increased morbidity and mortality, especially from CV events[61]. In non-diabetic RTRs, the incidence of post-transplant diabetes ranges between 4% and 25%[62]. Making a diagnosis of post-transplant diabetes has been challenging, with no clear diagnostic criteria existing before 2003, when the American Diabetes Association and World Health Organisation (WHO) developed more focused guidelines[63]. The guidelines have been updated more recently in 2010[64] and a diagnosis of post-transplant diabetes is made if one of the following criteria are met: Symptoms of diabetes and a non-fasting plasma glucose (PG) of > 200 mg/dL (11.1 mmol/L); Fasting PG of > 126 mg/dL (7.0 mmol/L); PG > 200 mg/dL (11.1 mmol/L) 2 h following an oral glucose tolerance test; HbA1C > 6.5% (48 mmol/mol).

The prevalence has increased recently and is between 2% and 53%[65] and this is likely a reflection of the simplification and clarification of diagnosis. Post-transplant diabetes most commonly develops early in the post-transplant period, with up to half of all diagnoses occurring in the first six months[63,66,67], although the cumulative incidence does continue to rise[67]. RTRs with post-transplant diabetes or impaired glucose tolerance have a higher risk of developing CVD. Those who have existing diabetes pre-transplantation have a greater risk of having a CV related event compared to patients with post-transplant diabetes[22,61,68] and overall higher all-cause mortality[69].

There are many risk factors for the development of post-transplant diabetes and these include increasing age[68], ethnic background[67,70] (African-American, Hispanic and South Asian), positive family history[71], visceral adiposity[72], hypomagnesaemia[73], viral infections[61,74] (hepatitis C virus and Cytomegalovirus) and immunosuppression medications. Most of the commonly prescribed immunosuppressants exert negative effects on glucose metabolism leading to impaired insulin secretion and sensitivity[75]. Corticosteroids lead to insulin resistance and therefore post-transplant diabetes in a dose-dependent manner. Reduction or withdrawal of corticosteroids can reduce the risk of developing post-transplant diabetes and may actually reverse it and restore insulin sensitivity[76]. One study has compared complete steroid avoidance with early withdrawal after one week and standard steroid administration[77]. They found that, after one year, the incidence of post-

transplant diabetes was similar in all groups, although the number of RTRs who were able to be managed with diet alone was greater in those who had avoided steroids compared to those who were treated conventionally. This is supported by a Cochrane review of 30 RCTs which found that steroid-sparing and withdrawal strategies showed benefits in reducing post-transplant diabetes requiring treatment and CV events[78]. They concluded that steroid avoidance and steroid withdrawal strategies in kidney transplantation are not associated with increased mortality or graft loss despite an increase in acute rejection. These immunosuppression strategies may allow safe steroid avoidance or elimination a few days after kidney transplantation if antibody induction treatment is prescribed or after three to six months if such induction is not used[3].

CNIs are known to contribute to the development of post-transplant diabetes. They reduce pancreatic beta-cell mass, insulin production and secretion and may affect glucagon synthesis by alpha cells[75]. Tacrolimus is known to be more diabetogenic than CNIs and leads to insulin resistance, excessive insulin production and beta-cell injury[67,75]. A Cochrane review of 123 reports from 30 trials determined that tacrolimus is superior to cyclosporine in improving graft survival and preventing acute rejection after transplantation, but increases cases of post-transplant diabetes as well as neurological and gastrointestinal side effects[38]. Treating 100 RTRs with tacrolimus instead of cyclosporine would avoid 12 suffering acute rejection, two losing their graft but cause an extra five to become insulin-requiring diabetics.

Management of post-transplant diabetes is similar to that of diabetes in the general population. Strict glycaemic control and screening and treatment of common complications is well recognised to reduce morbidity and mortality. However, more transplant-specific management can include switching from tacrolimus to an alternative immunosuppressant such as cyclosporine or mTOR inhibitor and reducing or stopping corticosteroids[79] as well as careful prescribing of diuretics which are independently associated with post-transplant diabetes[80]. A pre-emptive prevention strategy and early diagnostic testing should be adopted in the first instance to promote improved outcomes for those at risk of post-transplant diabetes.

### *Renal impairment*

Having a reduced eGFR is a risk for CVD in the general population and remains a risk in RTRs as well. Although renal dysfunction itself can lead to CVD it may also be a reflection of underlying co-morbidities such as hypertension. The risk of cardiac death increases as renal function declines. In a large community study of over one million people, an independent, graded relationship was found between eGFR and rates of death, CV events and hospital admission rates. Patients with eGFRs < 60 mL/min per 1.73 $m^2$, had significantly higher hazard ratios for any CV event compared to patients with GFR of > 60 mL/min per 1.73 $m^2$[3]. RTRs experience a progressive reduction in renal function over time, which enhances their CV risk in the long-term[81] and renal function at 12 mo post-transplant, measured by serum creatinine, has been shown to be associated with overall graft survival[82]. Even mild renal insufficiency is independently associated with risk of CCF and IHD. An eGFR of < 44.8 mL/min per 1.73 $m^2$ compared to an eGFR > 69.7 mL/min per 1.73 $m^2$ at the end of the first year after transplantation was independently associated with increased risks of both acute coronary syndrome (ACS) (HR = 2.16; 95%CI: 1.39-3.35) and CCF (HR = 2.95; 95%CI: 2.24-3.90)[83]. In the event of graft failure, ACS incidence was around double that of RTRs who had a functioning graft (12.1 *vs* 6.5 per 1000 patient-years). As a time dependent variable, graft loss had a HR of 2.54[84].

Well established CV risk factors such as hypertension, dyslipidaemia and hyperglycaemia can all be worsened by graft dysfunction. Declining renal function causes hypertension by a number of mechanisms including volume overload, sodium retention and activation of the renin-angiotensin-aldosterone system (RAAS)[85] and high blood pressure in turn exacerbates the worsening eGFR, creating a negative spiral. In addition, worsening of renal function can cause insulin resistance and affect lipase function resulting in hyperglycaemia[86], and have a deleterious effect on the lipid profile, in particular a reduction in HDL levels[87] leading to an increased risk of CVD.

### *Left ventricular hypertrophy*

Left ventricular hypertrophy (LVH) is common in RTRs and is present in 40%-60%[88]. Its persistence in the first year following renal transplantation is associated with increased patient morbidity and mortality. Furthermore, in the same cohort, LVH actually proved to be the strongest predictor of all-cause mortality together with diabetes. Taken together, this data supported a role for LVH in predicting unfavourable outcomes among RTRs[89], and in particular cardiac death[51].

LVH is an adaptive response to volume expansion and subsequent increase in blood pressure. The most common underlying causes include hypertension, anaemia[90], hyperparathyroidism, aortic valve calcification[91], leading to LV outflow obstruction, and worsening graft function[92]. Following renal transplant, LVH has been shown to improve when measured using echocardiography[93], this LVH regression was seen until two years following transplantation, after which the effect plateaued[94]. However, a recent report using cardiac MRI, which is accepted as the "gold standard" to assess the LV, found that there was no difference in the LV measurements in RTRs compared to those who remained on dialysis[95].

There have been several studies which have investigated potential interventions to improve LVH. ACE-inhibitors and CCBs were initially studied to identify whether they were beneficial in managing post-

transplantation hypertension, however it was also found that they had an effect on LVH, most probably due to reduction in blood pressure. There was no overall difference when CCB and ACE-inhibitors were directly compared, with both reducing LV mass index by 15%[96]. The mechanism by which ACE-inhibitors have an effect is likely to be at least partially independent of the haemodynamic effects on blood pressure[97]. The positive effect of ACE-inhibitors on LVH was only seen in those taking cyclosporine-based immunosuppression, whereas there was no such effect for RTRs taking tacrolimus[97]. One theory is that the immunosuppression may modulate the effect of anti-hypertensives on LVH in RTRs although there is no current understanding of why benefits are seen only in those taking cyclosporine. Conversion from CNIs to mTOR inhibitors such as sirolimus results in a regression of LVH within one year after conversion. This occurs mostly by reducing LV wall thickness, which suggests a non-haemodynamic effect of sirolimus on the LV mass[98].

### *Lifestyle factors*

Obesity is common in patients with ESRD and 60% of patients undergoing renal transplantation are overweight or obese at the time of the surgery. The likelihood of being obese increases with age, female sex, noninsulin-dependent diabetes mellitus, black race, and the more recent the transplant year. At 12 mo post-transplant the average increase in weight in RTRs is 9.3 kg in Caucasians and 13.5 kg in African-Americans. Conversely, the proportion of recipients with lower body mass index (BMI) fell by approximately 50%[99]. Initial BMI is an independent predictor for patient death and graft failure, and rates of morbidity (81% *vs* 89%) are higher and graft survival (71% *vs* 80%) is significantly reduced in obese RTRs at 5 years after transplantation[100]. Corticosteroids are recognised to cause a gain in weight, which may increase the risks of graft dysfunction and CV events[101]. Overall, the pattern of metabolic abnormalities caused by steroids is very similar to that seen in patients with metabolic syndrome[102].

Obesity in RTRs is strongly linked to the development of metabolic syndrome, with around 60% of patients meeting the diagnostic criteria[103] at transplantation and 9%-63% in the subsequent years[104,105]. It is independently associated with long-term graft function and is a prominent risk for allograft failure[105] and CV events secondary to atherosclerosis[106]. The cumulative incidence of coronary heart disease events by 60 mo post-transplant was 5.9% in transplant recipients with metabolic syndrome, compared with 2.3% in recipients without metabolic syndrome.

Smoking rates in RTRs at the time of transplantation are similar to that of the general population, with a prevalence of 24%[107]. Of these, 90% continued to smoke after transplantation. After adjusting for multiple predictors of graft failure, smoking > 25 pack-years at transplantation was associated with a 30% higher risk of graft failure compared to those who have never smoked[108]. The relative risk for major CV events with smoking 11-25 pack-years at transplant was 1.56 compared to 2.14 in those who had > 25 pack-year history[108]. Smoking by RTRs significantly increases the risk of CV events (29.2% *vs* 15.4%), renal fibrosis, rejection, and malignancy (HR = 2.56)[109]. Among patients with a smoking history before transplantation, death-censored graft survival was significantly higher for those who quit smoking before transplant evaluation[107]. Despite effective counselling and pharmacotherapy, up to 40% of patients will re-start smoking therefore transplant services need to be proactive in educating and implementing effective smoking cessation strategies to reduce rates of recidivism and the post-transplantation complications associated with smoking[109].

Regular exercise is known to have positive effects on CV risk in the general population, and more recently the focus has switched to analysing the effect on RTRs. Following a kidney transplant, RTRs spontaneously increase their activity levels and this peaks at one-year post-transplantation despite an initial decrease in the first month post-operatively[110]. Those who are more physically active have a reduced CV risk[111] and exercise programmes designed for RTRs have been shown to improve a number of physiological and psychological parameters[112,113]. However, blood pressure has been measured in several studies and there are no overall significant effects of exercise[114,115]. Many patients are taking various classes of anti-hypertensive medications and exercise does not seem to interact with these either[112]. A major contributor to atherosclerotic risk, blood lipid levels, have been analysed in RTRs. There is no clear consensus as to whether exercise has a beneficial effect on cholesterol or not as some studies show an improvement[116] and others do not[115,117]. Markers of pre-diabetes in non-diabetics or of diabetic control again produce conflicting results with differences between glucose levels not necessarily reflecting activity levels[117]. Although there is undoubtedly evidence that physical activity is beneficial in the general population, more work is required to determine the overall effects in RTRs.

## NON-TRADITIONAL RISK FACTORS

RTRs have an increased probability of CVD which is only partly explained by traditional CV risk factors, therefore alternative, non-traditional, risk factors have been identified. The overall CV risk in RTRs is likely to be multifactorial and a complex interaction between the multiple traditional and non-traditional factors.

### *Homocysteine*

Homocysteine is an atherogenic amino acid and is associated with increased CVD. High plasma homocysteine levels are seen as eGFR levels decline with the

prevalence of hyperhomocysteinaemia 70%-75% in those with functioning kidney transplants[118,119]. Fasting homocysteine values were higher in those patients who experienced CV events than those who did not (31.5 ± 10.3 *vs* 17.8 ± 7.5; $P < 0.001$) and correlated with both folate concentration ($r = -0.3$; $P < 0.01$) and creatinine levels ($r = 0.54$; $P < 0.001$)[119]. Elevated homocysteine levels were associated with 1.63 times increased risk of kidney allograft loss[118] and are independently associated with CV events and mortality in stable RTRs.

The effect of folate on homocysteine has led to the development of further studies. The FAVORIT trial compared high and low doses of folic acid, vitamin B6, and vitamin B12 to determine whether decreasing total homocysteine concentrations reduced the rate of the primary composite arteriosclerotic CVD outcomes. Neither treatment reduced composite CVD outcome, all-cause mortality, or dialysis-dependent kidney failure despite significant reduction in homocysteine level[120]. These results are supported by a recent review which concluded that folic acid based homocysteine lowering does not reduce CV events in people with kidney disease and therefore folic acid based regimens should not be used for the prevention of CV events in people with hyperhomocysteinaemia and kidney disease[121].

### Anaemia

There are several different definitions used currently to define anaemia, and therefore the prevalence of anaemia depends on which of these is used. The WHO defines anaemia as a haemoglobin (Hb) level < 13 g/dL in men and < 12 g/dL in women irrespective of age[122]. In 2006, KDOQI modified this definition by giving a single criterion for diagnosing anaemia in adult males (Hb < 13.5 g/dL, regardless of age) because the decrease in Hb among males aged > 60 years is often attributable to associated co-morbidities[123]. The prevalence of anaemia is influenced by time after transplantation. During the early post-operative period 76% of patients are found to be anaemic[124], however this improves in the following years, with a reported prevalence of around one-third at any one time[124,125]. This infers that post-transplant anaemia is not directly as a result of uncorrected anaemia prior to transplant.

There are many different causes of post-transplantation anaemia and some underlying factors are shared with those with ESRD who have not undergone transplantation such as impaired kidney function, iron and nutrient deficiency and medications such as ACE-inhibitors[126]. One important transplant-specific cause includes use of immunosuppressant medications. Anaemia is a well-known side-effect of azathioprine and MMF due to their myelosuppressive qualities. Newer medications such as mTOR inhibitors are also associated with decreases in Hb. In fact in a comparison of sirolimus and MMF, anaemia was present in 57% of those taking sirolimus compared to 31% for MMF[127] and when MMF is combined with either sirolimus or cyclosporine 43% were anaemic compared to 29% respectively[128].

Most studies show that allograft function strongly correlates with anaemia, with the prevalence markedly increasing with a decline in renal function[126,129]. Anaemia is also strongly linked to increased mortality, MI and need for coronary revascularisation[130] as well as being an independent risk factor for increasing LV mass[88]. In addition, it worsens pre-existing conditions such as CCF and PVOD[88,131].

The European best practices guidelines for kidney transplantation recommend regular screening and careful evaluation of anemia[132]. They also identify immunosuppressive agents, ACE-inhibitors and ARBs as causative agents. They advocate following the European best practices guidelines for anaemia management, which advise that an erythropoietin stimulating agent (ESA) not normally be discontinued in patients undergoing surgery or who develop an intercurrent illness[133]. No recommendation was made on whether to continue or stop ESAs in the immediate post-transplant period. Patients with a failing kidney transplant should be monitored as for any other patient with reduced kidney function[134].

### Inflammation

Systemic inflammation is widely acknowledged to influence outcomes in RTRs. High-sensitivity C-reactive protein (hsCRP) has been found to be independently associated with major CV events and all-cause mortality in RTRs[135,136], although this is not supported unanimously by all studies[137]. Those with a CRP > 5 have an increased mortality compared to patients below that threshold[138] and there is a J-shaped association between hsCRP and mortality suggesting that RTRs with very low hsCRP may also be at increased risk of death[139]. More novel markers such as asymmetric dimethylarginine, which is associated with endothelial dysfunction, are also associated with higher risk of mortality (HR = 2.18) and developing CVD (HR = 2.59) in ESRD[140]. Poorer graft outcomes are predicted by IL-6[136,141] and elevated symmetric dimethylarginine[142] (HR = 5.51). Troponin-T, usually used in the diagnosis of ACS, is a strong independent predictor of all-cause mortality in stable RTRs[143]. Interestingly, use of immunosuppression in general, correlated negatively with CRP ($P = 0.05$) and even more closely with MMF in particular ($P = 0.003$)[144] although a prospective study of the effect of MMF on other non-traditional CV risks is needed before firm conclusions can be made.

### Proteinuria

Proteinuria has been reported in up to 30% of RTRs[145]. The underlying aetiology of post-transplant proteinuria involves many factors, such as the presence of pre-transplant renal lesions, immunologic damage during allograft rejection, ischemia/reperfusion injury, chronic allograft nephropathy, and *de novo* or recurrent glomerulonephritis[145]. Persistent proteinuria is strongly

correlated to reduced function and graft survival[146].

In renal transplantation, the presence of proteinuria at 12 mo is associated with a two-fold risk of CV death[147]. Furthermore, persistent proteinuria is predictive of subsequent IHD and PVOD[148]. Even low-grade proteinuria detected at early time points after renal transplantation is associated with inferior graft and patient outcomes[149]. Both proteinuria and hypertension are associated with poor graft survival and the combination of the two led to the worst outcomes. Importantly, hypertension was associated with significantly worse outcomes in patients with proteinuria[150]. In addition, microalbuminuria has also been found to be a powerful risk factor for increased mortality from CVD[151].

Investigation into the management of proteinuria has found that ACE-inhibitors and ARBs are effective in reducing levels of proteinuria, although their overall effect on allograft function and survival are less clear[152,153]. Sirolimus increases levels of proteinuria compared to CNIs at 6 mo (40.8% *vs* 21.4%, $P = 0.006$) and 12 mo (37.8% *vs* 18.4%, $P = 0.004$), although the clinical relevance has yet to be established[154].

A systematic review has found that use of RAAS blockade is associated with a significant decrease in eGFR and a reduction in proteinuria (-0.47 gm/d; 95%CI: -0.86 to -0.08)[44]. However, given that there are few trials with long follow-up, the findings need to be viewed with some caution until findings from further RCTs are available. Given the tradeoff between the beneficial effect of proteinuria reduction and potential cardiac protection with the impact of anaemia and lower eGFR, an adequately powered RCT of sufficient duration that examines meaningful outcomes such as patient or allograft survival is necessary to address whether ACE-inhibitor or ARB use is beneficial in RTRs.

## CONCLUSION

Renal transplantation is the gold-standard treatment for selected patients with ESRD. It has been shown to reduce CV events compared to those that remain on dialysis but RTRs still continue to be at higher risk when compared to the general population. As traditional risk factors do not entirely explain the elevated CVD seen in RTRs, there are other influential factors which need to be considered when attempting to determine how to improve morbidity and mortality in this complex population. Management should focus on identifying and optimising modifiable risk factors and maintaining allograft function in order to reduce CV events. Acknowledging that immunosuppression plays a vital role in preserving the graft, medications should be optimised in order to prevent toxicity causing a worsening of CVD.

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