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**Cardiovascular risk factors following renal transplant**

Neale J *et al.* Cardiovascular risk factors following renal transplant

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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 mellitus, 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

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**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 (PD)[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 (PVD). 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 (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 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 RenalAssociation 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 greater than 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 more than 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 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 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 rapamycin (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 reduced 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 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] (HCV and CMV) 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].

CNI 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 CNI 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 m2, had significantly higher hazard ratios for any CV event compared to patients with GFR of > 60 mL/min per 1.73 m2[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 m2 compared to an eGFR > 69.7 mL/min per 1.73 m2 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 to 3.35) and CCF (HR, 2.95; 95%CI: 2.24 to 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, these 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 more than 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 World Health Organisation 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 failing 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 (ADMA), 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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**REFERENCES**

1 **Jha V**, Wang AY, Wang H. The impact of CKD identification in large countries: the burden of illness. *Nephrol Dial Transplant* 2012; **27** Suppl 3: iii32-iii38 [PMID: 23115140 DOI: 10.1093/ndt/gfs113]

2 **Matsushita K**, van der Velde M, Astor BC, Woodward M, Levey AS, de Jong PE, Coresh J, Gansevoort RT. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet* 2010; **375**: 2073-2081 [PMID: 20483451 DOI: 10.1016/S0140-6736(10)60674-5]

3 **Go AS**, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004; **351**: 1296-1305 [PMID: 15385656 DOI: 10.1056/NEJMoa041031]

4 **Levey AS**, Beto JA, Coronado BE, Eknoyan G, Foley RN, Kasiske BL, Klag MJ, Mailloux LU, Manske CL, Meyer KB, Parfrey PS, Pfeffer MA, Wenger NK, Wilson PW, Wright JT. Controlling the epidemic of cardiovascular disease in chronic renal disease: what do we know? What do we need to learn? Where do we go from here? National Kidney Foundation Task Force on Cardiovascular Disease. *Am J Kidney Dis* 1998; **32**: 853-906 [PMID: 9820460 DOI: 10.1016/S0272-6386(98)70145-3]

5 **Wolfe RA**, Ashby VB, Milford EL, Ojo AO, Ettenger RE, Agodoa LY, Held PJ, Port FK. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. *N Engl J Med* 1999; **341**: 1725-1730 [PMID: 10580071 DOI: 10.1056/NEJM199912023412303]

6 **Rao PS**, Merion RM, Ashby VB, Port FK, Wolfe RA, Kayler LK. Renal transplantation in elderly patients older than 70 years of age: results from the Scientific Registry of Transplant Recipients. *Transplantation* 2007; **83**: 1069-1074 [PMID: 17452897 DOI: 10.1097/01.tp.0000259621.56861.31]

7 **Oniscu GC**, Brown H, Forsythe JL. How great is the survival advantage of transplantation over dialysis in elderly patients? *Nephrol Dial Transplant* 2004; **19**: 945-951 [PMID: 15031354 DOI: 10.1093/ndt/gfh022]

8 **Bottomley MJ**, Harden PN. Update on the long-term complications of renal transplantation. *Br Med Bull* 2013; **106**: 117-134 [PMID: 23645842 DOI: 10.1093/bmb/ldt012]

9 **von der Lippe N**, Waldum B, Brekke FB, Amro AA, Reisæter AV, Os I. From dialysis to transplantation: a 5-year longitudinal study on self-reported quality of life. *BMC Nephrol* 2014; **15**: 191 [PMID: 25465066 DOI: 10.1186/1471-2369-15-191]

10 **Liefeldt L**, Budde K. Risk factors for cardiovascular disease in renal transplant recipients and strategies to minimize risk. *Transpl Int* 2010; **23**: 1191-1204 [PMID: 21059108 DOI: 10.1111/j.1432-2277.2010.01159]

11 **Meier-Kriesche HU**, Schold JD, Srinivas TR, Reed A, Kaplan B. Kidney transplantation halts cardiovascular disease progression in patients with end-stage renal disease. *Am J Transplant* 2004; **4**: 1662-1668 [PMID: 15367222 DOI: 10.1111/j.1600-6143.2004.00573]

12 **Holdaas H**, Fellström B, Jardine AG, Holme I, Nyberg G, Fauchald P, Grönhagen-Riska C, Madsen S, Neumayer HH, Cole E, Maes B, Ambühl P, Olsson AG, Hartmann A, Solbu DO, Pedersen TR. Effect of fluvastatin on cardiac outcomes in renal transplant recipients: a multicentre, randomised, placebo-controlled trial. *Lancet* 2003; **361**: 2024-2031 [PMID: 12814712 DOI: 10.1016/S0140-6736(03)13638-0]

13 **Willicombe M**, Kumar N, Goodall D, Clarke C, McLean AG, Power A, Taube D. Incidence, risk factors, and outcomes of stroke post-transplantation in patients receiving a steroid sparing immunosuppression protocol. *Clin Transplant* 2015; **29**: 18-25 [PMID: 25307366 DOI: 10.1111/ctr.12476]

14 **Sung RS**, Althoen M, Howell TA, Merion RM. Peripheral vascular occlusive disease in renal transplant recipients: risk factors and impact on kidney allograft survival. *Transplantation* 2000; **70**: 1049-1054 [PMID: 11045641 DOI: 10.1097/00007890-200010150-00010]

15 **Pruthi R**, Casula A, MacPhee I. UK Renal Registry 17th Annual Report: Chapter 3 Demographic and Biochemistry Profile of Kidney Transplant Recipients in the UK in 2013: National and Centre-specific Analyses. *Nephron* 2015; **129** Suppl 1: 57-86 [PMID: 25695807 DOI: 10.1159/000370273]

16 **Ghanta M**, Kozicky M, Jim B. Pathophysiologic and treatment strategies for cardiovascular disease in end-stage renal disease and kidney transplantations. *Cardiol Rev* 2014; **23**: 109-118 [PMID: 25420053 DOI: 10.1097/CRD.0000000000000044]

17 **Boerner BP**, Shivaswamy V, Desouza CV, Larsen JL. Diabetes and cardiovascular disease following kidney transplantation. *Curr Diabetes Rev* 2011; **7**: 221-234 [PMID: 21644915 DOI: 10.2174/157339911796397857]

18 **De Lima JJ**, Gowdak LH, de Paula FJ, Arantes RL, Ianhez LE, Ramires JA, Krieger EM. Influence of coronary artery disease assessment and treatment in the incidence of cardiac events in renal transplant recipients. *Clin Transplant* 2010; **24**: 474-480 [PMID: 19919611 DOI: 10.1111/j.1399-0012.2009.01150]

19 **Farrugia D**, Cheshire J, Begaj I, Khosla S, Ray D, Sharif A. Death within the first year after kidney transplantation--an observational cohort study. *Transpl Int* 2014; **27**: 262-270 [PMID: 24138318 DOI: 10.1111/tri.12218]

20 **Pilmore HL**, Skeans MA, Snyder JJ, Israni AK, Kasiske BL. Cardiovascular disease medications after renal transplantation: results from the Patient Outcomes in Renal Transplantation study. *Transplantation* 2011; **91**: 542-551 [PMID: 21301401 DOI: 10.1097/TP.0b013e31820437bd]

21 **Aalten J**, Peeters SA, van der Vlugt MJ, Hoitsma AJ. Is standardized cardiac assessment of asymptomatic high-risk renal transplant candidates beneficial? *Nephrol Dial Transplant* 2011; **26**: 3006-3012 [PMID: 21321004 DOI: 10.1093/ndt/gfq822]

22 **Lentine KL**, Brennan DC, Schnitzler MA. Incidence and predictors of myocardial infarction after kidney transplantation. *J Am Soc Nephrol* 2005; **16**: 496-506 [PMID: 15615820 DOI: 10.1681/ASN.2004070580]

23 **Aftab W**, Varadarajan P, Rasool S, Pai RG. Predictors and prognostic implications of major adverse cardiovascular events after renal transplant: 10 years outcomes in 321 patients. *Int J Angiol* 2014; **23**: 131-138 [PMID: 25075166 DOI: 10.1055/s-0034-1372248]

24 **Carpenter MA**, Weir MR, Adey DB, House AA, Bostom AG, Kusek JW. Inadequacy of cardiovascular risk factor management in chronic kidney transplantation - evidence from the FAVORIT study. *Clin Transplant* 2012; **26**: E438-E446 [PMID: 22775763 DOI: 10.1111/j.1399-0012.2012.01676]

25 **Lindholm A**, Albrechtsen D, Frödin L, Tufveson G, Persson NH, Lundgren G. Ischemic heart disease--major cause of death and graft loss after renal transplantation in Scandinavia. *Transplantation* 1995; **60**: 451-457 [PMID: 7676492 DOI: 10.1097/00007890-199509000-00008]

26 **Sundström J**, Arima H, Woodward M, Jackson R, Karmali K, Lloyd-Jones D, Baigent C, Emberson J, Rahimi K, MacMahon S, Patel A, Perkovic V, Turnbull F, Neal B. Blood pressure-lowering treatment based on cardiovascular risk: a meta-analysis of individual patient data. *Lancet* 2014; **384**: 591-598 [PMID: 25131978 DOI: 10.1016/S0140-6736(14)61212-5]

27 Kidney disease: Improving global outcomes (KDIGO) blood pressure work group. KDIGO clinical practice guideline for the management of blood pressure in chronic kidney disease. *Kidney Inter* 2012; **2** Suppl: 337-414

28 **UK Renal Association Clinical Practice Guidelines Committee**. Guideline: Post-operative care of the kidney transplant recipient, 5th ed. 2011. Available from: URL: http://Www.renal.org/clinical/GuidelinesSection/post-operative-care-kidney-transplant-recipient.aspx

29 **Muntner P**, Anderson A, Charleston J, Chen Z, Ford V, Makos G, O'Connor A, Perumal K, Rahman M, Steigerwalt S, Teal V, Townsend R, Weir M, Wright JT. Hypertension awareness, treatment, and control in adults with CKD: results from the Chronic Renal Insufficiency Cohort (CRIC) Study. *Am J Kidney Dis* 2010; **55**: 441-451 [PMID: 19962808 DOI: 10.1053/j.ajkd.2009.09.014]

30 **Kasiske BL**, Anjum S, Shah R, Skogen J, Kandaswamy C, Danielson B, O'Shaughnessy EA, Dahl DC, Silkensen JR, Sahadevan M, Snyder JJ. Hypertension after kidney transplantation. *Am J Kidney Dis* 2004; **43**: 1071-1081 [PMID: 15168388 DOI: 10.1053/j.ajkd.2004.03.013]

31 **Zhang H**, Li X. The risk factors of cardiovascular disease in patients with renal transplantation. *Pak J Med Sci* 2014; **30**: 1228-1231 [PMID: 25674113 DOI: 10.12669/pjms.306.5610]

32 **Mangray M**, Vella JP. Hypertension after kidney transplant. *Am J Kidney Dis* 2011; **57**: 331-341 [PMID: 21251543 DOI: 10.1053/j.ajkd.2010.10.048]

33 **Mange KC**, Cizman B, Joffe M, Feldman HI. Arterial hypertension and renal allograft survival. *JAMA* 2000; **283**: 633-638 [PMID: 10665703 DOI: 10.1001/jama.283.5.633]

34 **Opelz G**, Döhler B. Improved long-term outcomes after renal transplantation associated with blood pressure control. *Am J Transplant* 2005; **5**: 2725-2731 [PMID: 16212633 DOI: 10.1111/j.1600-6143.2005.01093]

35 **Zhang R**, Leslie B, Boudreaux JP, Frey D, Reisin E. Hypertension after kidney transplantation: impact, pathogenesis and therapy. *Am J Med Sci* 2003; **325**: 202-208 [PMID: 12695725 DOI: 10.1097/00000441-200304000-00006]

36 **Artz MA**, Boots JM, Ligtenberg G, Roodnat JI, Christiaans MH, Vos PF, Blom HJ, Sweep FC, Demacker PN, Hilbrands LB. Improved cardiovascular risk profile and renal function in renal transplant patients after randomized conversion from cyclosporine to tacrolimus. *J Am Soc Nephrol* 2003; **14**: 1880-1888 [PMID: 12819249 DOI: 10.1097/01.ASN.0000071515.27754.67]

37 **Vincenti F**, Jensik SC, Filo RS, Miller J, Pirsch J. A long-term comparison of tacrolimus (FK506) and cyclosporine in kidney transplantation: evidence for improved allograft survival at five years. *Transplantation* 2002; **73**: 775-782 [PMID: 11907427 DOI: 10.1097/00007890-200203150-00021]

38 **Webster A**, Woodroffe RC, Taylor RS, Chapman JR, Craig JC. Tacrolimus versus cyclosporin as primary immunosuppression for kidney transplant recipients. *Cochrane Database Syst Rev* 2005; **5**: CD003961 [PMID: 16235347 DOI: 10.1002/14651858.CD003961.pub2]

39 **Dawidson I**, Rooth P, Lu C, Sagalowsky A, Diller K, Palmer B, Peters P, Risser R, Sandor Z, Seney F. Verapamil improves the outcome after cadaver renal transplantation. *J Am Soc Nephrol* 1991; **2**: 983-990 [PMID: 1760541]

40 **Rump LC**, Oberhauser V, Schwertfeger E, Speidel L, Zimmerhackl L, Kirste G, Grotz W. Dihydropyridine calcium antagonists and renal function in hypertensive kidney transplant recipients. *J Hypertens* 2000; **18**: 1115-1119 [PMID: 10954004 DOI: 10.1097/00004872-200018080-00017]

41 **Kuypers DR**, Neumayer HH, Fritsche L, Budde K, Rodicio JL, Vanrenterghem Y. Calcium channel blockade and preservation of renal graft function in cyclosporine-treated recipients: a prospective randomized placebo-controlled 2-year study. *Transplantation* 2004; **78**: 1204-1211 [PMID: 15502721 DOI: 10.1097/01.TP.0000137793.23371.42]

42 **Halimi JM**, Giraudeau B, Buchler M, Al-Najjar A, Etienne I, Laouad I, Bruyère F, Lebranchu Y. Enalapril/amlodipine combination in cyclosporine-treated renal transplant recipients: a prospective randomized trial. *Clin Transplant* 2007; **21**: 277-284 [PMID: 17425758 DOI: 10.1111/j.1399-0012.2007.00643]

43 **Cross NB**, Webster AC, Masson P, O'connell PJ, Craig JC. Antihypertensives for kidney transplant recipients: systematic review and meta-analysis of randomized controlled trials. *Transplantation* 2009; **88**: 7-18 [PMID: 19584673 DOI: 10.1097/TP.0b013e3181a9e960]

44 **Hiremath S**, Fergusson D, Doucette S, Mulay AV, Knoll GA. Renin angiotensin system blockade in kidney transplantation: a systematic review of the evidence. *Am J Transplant* 2007; **7**: 2350-2360 [PMID: 17845569 DOI: 10.1111/j.1600-6143.2007.01928]

45 **Duerr M**, Glander P, Diekmann F, Dragun D, Neumayer HH, Budde K. Increased incidence of angioedema with ACE inhibitors in combination with mTOR inhibitors in kidney transplant recipients. *Clin J Am Soc Nephrol* 2010; **5**: 703-708 [PMID: 20093343 DOI: 10.2215/CJN.07371009]

46 **Gonyea JE**, Anderson CF. Weight change and serum lipoproteins in recipients of renal allografts. *Mayo Clin Proc* 1992; **67**: 653-657 [PMID: 1434899 DOI: 10.1016/S0025-6196(12)60720-4]

47 **Ong CS**, Pollock CA, Caterson RJ, Mahony JF, Waugh DA, Ibels LS. Hyperlipidemia in renal transplant recipients: natural history and response to treatment. *Medicine* (Baltimore) 1994; **73**: 215-223 [PMID: 8041244 DOI: 10.1097/00005792-199407000-00004]

48 **Tse KC**, Lam MF, Yip PS, Li FK, Lai KN, Chan TM. A long-term study on hyperlipidemia in stable renal transplant recipients. *Clin Transplant* 2004; **18**: 274-280 [PMID: 15142048 DOI: 10.1111/j.1399-0012.2004.00160]

49 **Pannu HS**, Singh D, Sandhu JS. Lipid profile before and after renal transplantation--a longitudinal study. *Ren Fail* 2003; **25**: 411-417 [PMID: 12803504 DOI: 10.1081/JDI-120021153]

50 **Roodnat JI**, Mulder PG, Zietse R, Rischen-Vos J, van Riemsdijk IC, IJzermans JN, Weimar W. Cholesterol as an independent predictor of outcome after renal transplantation. *Transplantation* 2000; **69**: 1704-1710 [PMID: 10836384 DOI: 10.1097/00007890-200004270-00029]

51 **Jardine AG**, Fellström B, Logan JO, Cole E, Nyberg G, Grönhagen-Riska C, Madsen S, Neumayer HH, Maes B, Ambühl P, Olsson AG, Pedersen T, Holdaas H. Cardiovascular risk and renal transplantation: post hoc analyses of the Assessment of Lescol in Renal Transplantation (ALERT) Study. *Am J Kidney Dis* 2005; **46**: 529-536 [PMID: 16129216 DOI: 10.1053/j.ajkd.2005.05.014]

52 **Manitpisitkul W**, McCann E, Lee S, Weir MR. Drug interactions in transplant patients: what everyone should know. *Curr Opin Nephrol Hypertens* 2009; **18**: 404-411 [PMID: 19593130 DOI: 10.1097/MNH.0b013e32832edcb2]

53 **Lemahieu WP**, Hermann M, Asberg A, Verbeke K, Holdaas H, Vanrenterghem Y, Maes BD. Combined therapy with atorvastatin and calcineurin inhibitors: no interactions with tacrolimus. *Am J Transplant* 2005; **5**: 2236-2243 [PMID: 16095503 DOI: 10.1111/j.1600-6143.2005.01005]

54 **Holdaas H**, Kobashigawa J, Fellstrom JA, Jardine A. Special transplant populations: Transplant recipients. *Clin Lipidol* 2009: 486-499

55 **de Sévaux RG**, Hilbrands LB, Tiggeler RG, Koene RA, Hoitsma AJ. A randomised, prospective study on the conversion from cyclosporine-prednisone to cyclosporine-azathioprine at 6 months after renal transplantation. *Transpl Int* 1998; **11** Suppl 1: S322-S324 [PMID: 9665006 DOI: 10.1007/s001470050488]

56 **Spinelli GA**, Felipe CR, Park SI, Mandia-Sampaio EL, Tedesco-Silva H, Medina-Pestana JO. Lipid profile changes during the first year after kidney transplantation: risk factors and influence of the immunosuppressive drug regimen. *Transplant Proc* 2011; **43**: 3730-3737 [PMID: 22172836 DOI: 10.1016/j.transproceed.2011.08.074]

57 **Vathsala A**, Weinberg RB, Schoenberg L, Grevel J, Goldstein RA, Van Buren CT, Lewis RM, Kahan BD. Lipid abnormalities in cyclosporine-prednisone-treated renal transplant recipients. *Transplantation* 1989; **48**: 37-43 [PMID: 2665233 DOI: 10.1097/00007890-198907000-00009]

58 **Claes K**, Meier-Kriesche HU, Schold JD, Vanrenterghem Y, Halloran PF, Ekberg H. Effect of different immunosuppressive regimens on the evolution of distinct metabolic parameters: evidence from the Symphony study. *Nephrol Dial Transplant* 2012; **27**: 850-857 [PMID: 21617197 DOI: 10.1093/ndt/gfr238]

59 **Kasiske BL**, de Mattos A, Flechner SM, Gallon L, Meier-Kriesche HU, Weir MR, Wilkinson A. Mammalian target of rapamycin inhibitor dyslipidemia in kidney transplant recipients. *Am J Transplant* 2008; **8**: 1384-1392 [PMID: 18510633 DOI: 10.1111/j.1600-6143.2008.02272]

60 **Palmer SC**, Navaneethan SD, Craig JC, Perkovic V, Johnson DW, Nigwekar SU, Hegbrant J, Strippoli GF. HMG CoA reductase inhibitors (statins) for kidney transplant recipients. *Cochrane Database Syst Rev* 2014; **1**: CD005019 [PMID: 24470059 DOI: 10.1002/14651858.CD005019.pub4]

61 **Hjelmesaeth J**, Hartmann A, Leivestad T, Holdaas H, Sagedal S, Olstad M, Jenssen T. The impact of early-diagnosed new-onset post-transplantation diabetes mellitus on survival and major cardiac events. *Kidney Int* 2006; **69**: 588-595 [PMID: 16395250 DOI: 10.1038/sj.ki.5000116]

62 **Pham PT**, Pham PM, Pham SV, Pham PA, Pham PC. New onset diabetes after transplantation (NODAT): an overview. *Diabetes Metab Syndr Obes* 2011; **4**: 175-186 [PMID: 21760734 DOI: 10.2147/DMSO.S19027]

63 **Davidson J**, Wilkinson A, Dantal J, Dotta F, Haller H, Hernández D, Kasiske BL, Kiberd B, Krentz A, Legendre C, Marchetti P, Markell M, van der Woude FJ, Wheeler DC. New-onset diabetes after transplantation: 2003 International consensus guidelines. Proceedings of an international expert panel meeting. Barcelona, Spain, 19 February 2003. *Transplantation* 2003; **75**: SS3-S24 [PMID: 12775942 DOI: 10.1097/01.TP.0000069952.49242.3E]

64 **American Diabetes Association**. Standards of medical care in diabetes--2010. *Diabetes Care* 2010; **33** Suppl 1: S11-S61 [PMID: 20042772 DOI: 10.2337/dc10-S011]

65 **Balla A**, Chobanian M. New-onset diabetes after transplantation: a review of recent literature. *Curr Opin Organ Transplant* 2009; **14**: 375-379 [PMID: 19542891 DOI: 10.1097/MOT.0b013e32832dbb98]

66 **Elmagd MM**, Bakr MA, Metwally AH, Wahab AM. Clinicoepidemiologic study of posttransplant diabetes after living-donor renal transplant. *Exp Clin Transplant* 2008; **6**: 42-47 [PMID: 18405244]

67 **Kasiske BL**, Snyder JJ, Gilbertson D, Matas AJ. Diabetes mellitus after kidney transplantation in the United States. *Am J Transplant* 2003; **3**: 178-185 [PMID: 12603213 DOI: 10.1034/j.1600-6143.2003.00010]

68 **Cosio FG**, Pesavento TE, Osei K, Henry ML, Ferguson RM. Post-transplant diabetes mellitus: increasing incidence in renal allograft recipients transplanted in recent years. *Kidney Int* 2001; **59**: 732-737 [PMID: 11168956 DOI: 10.1046/j.1523-1755.2001.059002732]

69 **Miles AM**, Sumrani N, Horowitz R, Homel P, Maursky V, Markell MS, Distant DA, Hong JH, Sommer BG, Friedman EA. Diabetes mellitus after renal transplantation: as deleterious as non-transplant-associated diabetes? *Transplantation* 1998; **65**: 380-384 [PMID: 9484755 DOI: 10.1097/00007890-199802150-00014]

70 **Moore R**, Boucher A, Carter J, Kim SJ, Kiberd B, Loertscher R, Mongeau JG, Prasad GV, Vautour L. Diabetes mellitus in transplantation: 2002 consensus guidelines. *Transplant Proc* 2003; **35**: 1265-1270 [PMID: 12826134 DOI: 10.1016/S0041-1345(03)00434-2]

71 **Hjelmesaeth J**, Hartmann A, Kofstad J, Stenstrøm J, Leivestad T, Egeland T, Fauchald P. Glucose intolerance after renal transplantation depends upon prednisolone dose and recipient age. *Transplantation* 1997; **64**: 979-983 [PMID: 9381545 DOI: 10.1097/00007890-199710150-00008]

72 **Meigs JB**, Mittleman MA, Nathan DM, Tofler GH, Singer DE, Murphy-Sheehy PM, Lipinska I, D'Agostino RB, Wilson PW. Hyperinsulinemia, hyperglycemia, and impaired hemostasis: the Framingham Offspring Study. *JAMA* 2000; **283**: 221-228 [PMID: 10634338 DOI: 10.1001/jama.283.2.221]

73 **Garg N**, Weinberg J, Ghai S, Bradauskaite G, Nuhn M, Gautam A, Kumar N, Francis J, Chen JL. Lower magnesium level associated with new-onset diabetes and pre-diabetes after kidney transplantation. *J Nephrol* 2014; **27**: 339-344 [PMID: 24609888 DOI: 10.1007/s40620-014-0072-1]

74 **Bloom RD**, Lake JR. Emerging issues in hepatitis C virus-positive liver and kidney transplant recipients. *Am J Transplant* 2006; **6**: 2232-2237 [PMID: 16869798 DOI: 10.1111/j.1600-6143.2006.01457]

75 **Boots JM**, Christiaans MH, van Hooff JP. Effect of immunosuppressive agents on long-term survival of renal transplant recipients: focus on the cardiovascular risk. *Drugs* 2004; **64**: 2047-2073 [PMID: 15341497 DOI: 10.2165/00003495-200464180-00004]

76 **Boots JM**, van Duijnhoven EM, Christiaans MH, Wolffenbuttel BH, van Hooff JP. Glucose metabolism in renal transplant recipients on tacrolimus: the effect of steroid withdrawal and tacrolimus trough level reduction. *J Am Soc Nephrol* 2002; **13**: 221-227 [PMID: 11752041]

77 **Vincenti F**, Schena FP, Paraskevas S, Hauser IA, Walker RG, Grinyo J. A randomized, multicenter study of steroid avoidance, early steroid withdrawal or standard steroid therapy in kidney transplant recipients. *Am J Transplant* 2008; **8**: 307-316 [PMID: 18211506 DOI: 10.1111/j.1600-6143.2007.02057]

78 **Pascual J**, Zamora J, Galeano C, Royuela A, Quereda C. Steroid avoidance or withdrawal for kidney transplant recipients. *Cochrane Database Syst Rev* 2009; **(1)**: CD005632 [PMID: 19160257 DOI: 10.1002/14651858.CD005632.pub2]

79 **Palepu S**, Prasad GV. New-onset diabetes mellitus after kidney transplantation: Current status and future directions. *World J Diabetes* 2015; **6**: 445-455 [PMID: 25897355 DOI: 10.4239/wjd.v6.i3.445]

80 **Santos L**, Rodrigo E, Piñera C, Quintella E, Ruiz JC, Fernández-Fresnedo G, Palomar R, Gómez-Alamillo C, de Francisco A, Arias M. New-onset diabetes after transplantation: drug-related risk factors. *Transplant Proc* 2012; **44**: 2585-2587 [PMID: 23146462]

81 **Meier-Kriesche HU**, Baliga R, Kaplan B. Decreased renal function is a strong risk factor for cardiovascular death after renal transplantation. *Transplantation* 2003; **75**: 1291-1295 [PMID: 12717218 DOI: 10.1097/01.TP.0000061602.03327.E2]

82 **Hariharan S**, McBride MA, Cherikh WS, Tolleris CB, Bresnahan BA, Johnson CP. Post-transplant renal function in the first year predicts long-term kidney transplant survival. *Kidney Int* 2002; **62**: 311-318 [PMID: 12081593 DOI: 10.1046/j.1523-1755.2002.00424]

83 **Abbott KC**, Yuan CM, Taylor AJ, Cruess DF, Agodoa LY. Early renal insufficiency and hospitalized heart disease after renal transplantation in the era of modern immunosuppression. *J Am Soc Nephrol* 2003; **14**: 2358-2365 [PMID: 12937314 DOI: 10.1097/01.ASN.0000083008.25305.67]

84 **Abbott KC**, Bucci JR, Cruess D, Taylor AJ, Agodoa LY. Graft loss and acute coronary syndromes after renal transplantation in the United States. *J Am Soc Nephrol* 2002; **13**: 2560-2569 [PMID: 12239246 DOI: 10.1097/01.ASN.0000028800.84746.CB]

85 **Edmunds M**, Russell G, Swales J. Hypertension in renal failure. Textbook of Hypertension. London, Blackwell, 1994: 798-810

86 **Sechi LA**, Catena C, Zingaro L, Melis A, De Marchi S. Abnormalities of glucose metabolism in patients with early renal failure. *Diabetes* 2002; **51**: 1226-1232 [PMID: 11916949 DOI: 10.2337/diabetes.51.4.1226]

87 **Ardhanari S**, Alpert MA, Aggarwal K. Cardiovascular disease in chronic kidney disease: risk factors, pathogenesis, and prevention. *Adv Perit Dial* 2014; **30**: 40-53 [PMID: 25338421]

88 **Rigatto C**, Foley R, Jeffery J, Negrijn C, Tribula C, Parfrey P. Electrocardiographic left ventricular hypertrophy in renal transplant recipients: prognostic value and impact of blood pressure and anemia. *J Am Soc Nephrol* 2003; **14**: 462-468 [PMID: 12538748 DOI: 10.1097/01.ASN.0000043141.67989.39]

89 **Paoletti E**, Cannella G. Reducing the risk of left ventricular hypertrophy in kidney transplant recipients: the potential role of mammalian target of rapamycin. *Transplant Proc* 2009; **41**: S3-S5 [PMID: 19651293 DOI: 10.1016/j.transproceed.2009.06.091]

90 **Ibernon M**, Moreso F, Ruiz-Majoral A, Sarrias X, Sarrias M, Grinyó JM, Serón D. Contribution of anemia and hypertension to left ventricular hypertrophy during the initial 2 years after renal transplantation. *Transplant Proc* 2011; **43**: 2199-2204 [PMID: 21839233 DOI: 10.1016/j.transproceed.2011.05.006]

91 **Turkmen F**, Emre A, Ozdemir A, Sevinc C, Erisken E, Yesilcimen K. Relationship between aortic valve sclerosis and left ventricular hypertrophy in chronic haemodialysis patients. *Int Urol Nephrol* 2008; **40**: 497-502 [PMID: 18085423 DOI: 10.1007/s11255-007-9317-4]

92 **Zolty R**, Hynes PJ, Vittorio TJ. Severe left ventricular systolic dysfunction may reverse with renal transplantation: uremic cardiomyopathy and cardiorenal syndrome. *Am J Transplant* 2008; **8**: 2219-2224 [PMID: 18808406 DOI: 10.1111/j.1600-6143.2008.02407]

93 **Ferreira SR**, Moisés VA, Tavares A, Pacheco-Silva A. Cardiovascular effects of successful renal transplantation: a 1-year sequential study of left ventricular morphology and function, and 24-hour blood pressure profile. *Transplantation* 2002; **74**: 1580-1587 [PMID: 12490792 DOI: 10.1097/00007890-200212150-00016]

94 **Rigatto C**, Foley RN, Kent GM, Guttmann R, Parfrey PS. Long-term changes in left ventricular hypertrophy after renal transplantation. *Transplantation* 2000; **70**: 570-575 [PMID: 10972211 DOI: 10.1097/00007890-200008270-00006]

95 **Patel RK**, Mark PB, Johnston N, McGregor E, Dargie HJ, Jardine AG. Renal transplantation is not associated with regression of left ventricular hypertrophy: a magnetic resonance study. *Clin J Am Soc Nephrol* 2008; **3**: 1807-1811 [PMID: 18650407 DOI: 10.2215/CJN.01400308]

96 **Midtvedt K**, Ihlen H, Hartmann A, Bryde P, Bjerkely BL, Foss A, Fauchald P, Holdaas H. Reduction of left ventricular mass by lisinopril and nifedipine in hypertensive renal transplant recipients: a prospective randomized double-blind study. *Transplantation* 2001; **72**: 107-111 [PMID: 11468543 DOI: 10.1097/00007890-200107150-00021]

97 **Paoletti E**, Cassottana P, Amidone M, Gherzi M, Rolla D, Cannella G. ACE inhibitors and persistent left ventricular hypertrophy after renal transplantation: a randomized clinical trial. *Am J Kidney Dis* 2007; **50**: 133-142 [PMID: 17591533 DOI: 10.1053/j.ajkd.2007.04.013]

98 **Paoletti E**, Amidone M, Cassottana P, Gherzi M, Marsano L, Cannella G. Effect of sirolimus on left ventricular hypertrophy in kidney transplant recipients: a 1-year nonrandomized controlled trial. *Am J Kidney Dis* 2008; **52**: 324-330 [PMID: 18585837 DOI: 10.1053/j.ajkd.2008.04.018]

99 **Friedman AN**, Miskulin DC, Rosenberg IH, Levey AS. Demographics and trends in overweight and obesity in patients at time of kidney transplantation. *Am J Kidney Dis* 2003; **41**: 480-487 [PMID: 12552513 DOI: 10.1053/ajkd.2003.50059]

100 **Aalten J**, Christiaans MH, de Fijter H, Hené R, van der Heijde JH, Roodnat J, Surachno J, Hoitsma A. The influence of obesity on short- and long-term graft and patient survival after renal transplantation. *Transpl Int* 2006; **19**: 901-907 [PMID: 17018125 DOI: 10.1111/j.1432-2277.2006.00367]

101 **Lentine KL**, Rocca-Rey LA, Bacchi G, Wasi N, Schmitz L, Salvalaggio PR, Abbott KC, Schnitzler MA, Neri L, Brennan DC. Obesity and cardiac risk after kidney transplantation: experience at one center and comprehensive literature review. *Transplantation* 2008; **86**: 303-312 [PMID: 18645495]

102 **Wissing KM**, Pipeleers L. Obesity, metabolic syndrome and diabetes mellitus after renal transplantation: prevention and treatment. *Transplant Rev* (Orlando) 2014; **28**: 37-46 [PMID: 24507957 DOI: 10.1016/j.trre.2013.12.004]

103 **Bayer ND**, Cochetti PT, Anil Kumar MS, Teal V, Huan Y, Doria C, Bloom RD, Rosas SE. Association of metabolic syndrome with development of new-onset diabetes after transplantation. *Transplantation* 2010; **90**: 861-866 [PMID: 20724958 DOI: 10.1097/TP.0b013e3181f1543c]

104 **Ducloux D**, Kazory A, Simula-Faivre D, Chalopin JM. One-year post-transplant weight gain is a risk factor for graft loss. *Am J Transplant* 2005; **5**: 2922-2928 [PMID: 16303006 DOI: 10.1111/j.1600-6143.2005.01104]

105 **de Vries AP**, Bakker SJ, van Son WJ, van der Heide JJ, Ploeg RJ, The HT, de Jong PE, Gans RO. Metabolic syndrome is associated with impaired long-term renal allograft function; not all component criteria contribute equally. *Am J Transplant* 2004; **4**: 1675-1683 [PMID: 15367224 DOI: 10.1111/j.1600-6143.2004.00558]

106 **Israni AK**, Snyder JJ, Skeans MA, Kasiske BL. Clinical diagnosis of metabolic syndrome: predicting new-onset diabetes, coronary heart disease, and allograft failure late after kidney transplant. *Transpl Int* 2012; **25**: 748-757 [PMID: 22548293 DOI: 10.1111/j.1432-2277.2012.01488]

107 **Sung RS**, Althoen M, Howell TA, Ojo AO, Merion RM. Excess risk of renal allograft loss associated with cigarette smoking. *Transplantation* 2001; **71**: 1752-1757 [PMID: 11455254 DOI: 10.1097/00007890-200106270-00009]

108 **Kasiske BL**, Klinger D. Cigarette smoking in renal transplant recipients. *J Am Soc Nephrol* 2000; **11**: 753-759 [PMID: 10752535 DOI: 10.1097/00007890-199904150-00461]

109 **Corbett C**, Armstrong MJ, Neuberger J. Tobacco smoking and solid organ transplantation. *Transplantation* 2012; **94**: 979-987 [PMID: 23169222 DOI: 10.1097/TP.0b013e318263ad5b]

110 **Nielens H**, Lejeune TM, Lalaoui A, Squifflet JP, Pirson Y, Goffin E. Increase of physical activity level after successful renal transplantation: a 5 year follow-up study. *Nephrol Dial Transplant* 2001; **16**: 134-140 [PMID: 11209007 DOI: 10.1093/ndt/16.1.134]

111 **Zelle DM**, Corpeleijn E, Stolk RP, de Greef MH, Gans RO, van der Heide JJ, Navis G, Bakker SJ. Low physical activity and risk of cardiovascular and all-cause mortality in renal transplant recipients. *Clin J Am Soc Nephrol* 2011; **6**: 898-905 [PMID: 21372213 DOI: 10.2215/CJN.03340410]

112 **Painter PL**, Hector L, Ray K, Lynes L, Dibble S, Paul SM, Tomlanovich SL, Ascher NL. A randomized trial of exercise training after renal transplantation. *Transplantation* 2002; **74**: 42-48 [PMID: 12134097 DOI: 10.1097/00007890-200207150-00008]

113 **Mazzoni D**, Cicognani E, Mosconi G, Totti V, Roi GS, Trerotola M, Nanni Costa A. Sport activity and health-related quality of life after kidney transplantation. *Transplant Proc* 2014; **46**: 2231-2234 [PMID: 25242758 DOI: 10.1016/j.transproceed.2014.07.049]

114 **Miller TD**, Squires RW, Gau GT, Ilstrup DM, Frohnert PP, Sterioff S. Graded exercise testing and training after renal transplantation: a preliminary study. *Mayo Clin Proc* 1987; **62**: 773-777 [PMID: 3306180 DOI: 10.1016/S0025-6196(12)62329-5]

115 **Painter PL**, Hector L, Ray K, Lynes L, Paul SM, Dodd M, Tomlanovich SL, Ascher NL. Effects of exercise training on coronary heart disease risk factors in renal transplant recipients. *Am J Kidney Dis* 2003; **42**: 362-369 [PMID: 12900820 DOI: 10.1016/S0272-6386(03)00673-5]

116 **You HS**, Chung SY, So HS, Choi SJ. Effect of a DanJeon Breathing Exercise Program on the quality of life in patients with kidney transplants. *Transplant Proc* 2008; **40**: 2324-2326 [PMID: 18790224 DOI: 10.1016/j.transproceed.2008.06.051]

117 **Juskowa J**, Lewandowska M, Bartłomiejczyk I, Foroncewicz B, Korabiewska I, Niewczas M, Sierdziński J. Physical rehabilitation and risk of atherosclerosis after successful kidney transplantation. *Transplant Proc* 2006; **38**: 157-160 [PMID: 16504691 DOI: 10.1016/j.transproceed.2005.12.077]

118 **Winkelmayer WC**, Kramar R, Curhan GC, Chandraker A, Endler G, Födinger M, Hörl WH, Sunder-Plassmann G. Fasting plasma total homocysteine levels and mortality and allograft loss in kidney transplant recipients: a prospective study. *J Am Soc Nephrol* 2005; **16**: 255-260 [PMID: 15563562 DOI: 10.1681/ASN.2004070576]

119 **Ducloux D**, Motte G, Challier B, Gibey R, Chalopin JM. Serum total homocysteine and cardiovascular disease occurrence in chronic, stable renal transplant recipients: a prospective study. *J Am Soc Nephrol* 2000; **11**: 134-137 [PMID: 10616849]

120 **Bostom AG**, Carpenter MA, Kusek JW, Levey AS, Hunsicker L, Pfeffer MA, Selhub J, Jacques PF, Cole E, Gravens-Mueller L, House AA, Kew C, McKenney JL, Pacheco-Silva A, Pesavento T, Pirsch J, Smith S, Solomon S, Weir M. Homocysteine-lowering and cardiovascular disease outcomes in kidney transplant recipients: primary results from the Folic Acid for Vascular Outcome Reduction in Transplantation trial. *Circulation* 2011; **123**: 1763-1770 [PMID: 21482964 DOI: 10.1161/CIRCULATIONAHA.110.000588]

121 **Jardine MJ**, Kang A, Zoungas S, Navaneethan SD, Ninomiya T, Nigwekar SU, Gallagher MP, Cass A, Strippoli G, Perkovic V. The effect of folic acid based homocysteine lowering on cardiovascular events in people with kidney disease: systematic review and meta-analysis. *BMJ* 2012; **344**: e3533 [PMID: 22695899 DOI: 10.1136/bmj.e3533]

122 Nutritional anaemias. Report of a WHO scientific group. *World Health Organ Tech Rep Ser* 1968; **405**: 5-37 [PMID: 4975372]

123 KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Anemia in Chronic Kidney Disease. *Am J Kidney Dis* 2006; **47**: S11-145 [PMID: 16678659 DOI: 10.1053/j.ajkd.2006.03.011]

124 **Mix TC**, Kazmi W, Khan S, Ruthazer R, Rohrer R, Pereira BJ, Kausz AT. Anemia: a continuing problem following kidney transplantation. *Am J Transplant* 2003; **3**: 1426-1433 [PMID: 14525605 DOI: 10.1046/j.1600-6135.2003.00224]

125 **Molnar MZ**, Novak M, Ambrus C, Kovacs A, Pap J, Remport A, Szeifert L, Mucsi I. Anemia in kidney transplanted patients. *Clin Transplant* 2005; **19**: 825-833 [PMID: 16313332 DOI: 10.1111/j.1399-0012.2005.00428]

126 **McClellan W**, Aronoff SL, Bolton WK, Hood S, Lorber DL, Tang KL, Tse TF, Wasserman B, Leiserowitz M. The prevalence of anemia in patients with chronic kidney disease. *Curr Med Res Opin* 2004; **20**: 1501-1510 [PMID: 15383200 DOI: 10.1185/030079904X2763]

127 **Augustine JJ**, Knauss TC, Schulak JA, Bodziak KA, Siegel C, Hricik DE. Comparative effects of sirolimus and mycophenolate mofetil on erythropoiesis in kidney transplant patients. *Am J Transplant* 2004; **4**: 2001-2006 [PMID: 15575902 DOI: 10.1111/j.1600-6143.2004.00612]

128 **Kreis H**, Cisterne JM, Land W, Wramner L, Squifflet JP, Abramowicz D, Campistol JM, Morales JM, Grinyo JM, Mourad G, Berthoux FC, Brattström C, Lebranchu Y, Vialtel P. Sirolimus in association with mycophenolate mofetil induction for the prevention of acute graft rejection in renal allograft recipients. *Transplantation* 2000; **69**: 1252-1260 [PMID: 10798738 DOI: 10.1097/00007890-200004150-00009]

129 **Choukroun G**, Kamar N, Dussol B, Etienne I, Cassuto-Viguier E, Toupance O, Glowacki F, Moulin B, Lebranchu Y, Touchard G, Jaureguy M, Pallet N, Le Meur Y, Rostaing L, Martinez F. Correction of postkidney transplant anemia reduces progression of allograft nephropathy. *J Am Soc Nephrol* 2012; **23**: 360-368 [PMID: 22193388 DOI: 10.1681/ASN.2011060546]

130 **Walker AM**, Schneider G, Yeaw J, Nordstrom B, Robbins S, Pettitt D. Anemia as a predictor of cardiovascular events in patients with elevated serum creatinine. *J Am Soc Nephrol* 2006; **17**: 2293-2298 [PMID: 16837634 DOI: 10.1681/ASN.2005020183]

131 **Kadambi PV**, Javaid B. Cardiovascular diseases in kidney transplant recipients: the role of anemia. *Adv Chronic Kidney Dis* 2004; **11**: 328-333 [PMID: 15241747 DOI: 10.1053/j.arrt.2004.04.003]

132 **EBPG Expert Group on Renal Transplantation**. European best practice guidelines for renal transplantation. Section IV: Long-term management of the transplant recipient. IV.9.1. Haematological complications. Anaemia. *Nephrol Dial Transplant* 2002; **17** Suppl 4: 48-49 [PMID: 12091647 DOI: 10.1093/ndt/17.suppl\_4.48]

133 **Linde T**, Ekberg H, Forslund T, Furuland H, Holdaas H, Nyberg G, Tydén G, Wahlberg J, Danielson BG. The use of pretransplant erythropoietin to normalize hemoglobin levels has no deleterious effects on renal transplantation outcome. *Transplantation* 2001; **71**: 79-82 [PMID: 11211199 DOI: 10.1097/00007890-200101150-00013]

134 **Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group**. KDIGO clinical practice guideline for the care of kidney transplant recipients. *Am J Transplant* 2009; **9** Suppl 3: S1-155 [PMID: 19845597 DOI: 10.1111/j.1600-6143.2009.02834]

135 **Bakri RS**, Afzali B, Covic A, Sriskantharan R, Bharma-Ariza P, Park WH, Sriharan M, Dalton N, Wierzbicki AS, Crook MA, Goldsmith DJ. Cardiovascular disease in renal allograft recipients is associated with elevated sialic acid or markers of inflammation. *Clin Transplant* 2004; **18**: 201-204 [PMID: 15016136 DOI: 10.1111/j.1399-0012.2004.00156]

136 **Dahle DO**, Mjøen G, Oqvist B, Scharnagl H, Weihrauch G, Grammer T, März W, Abedini S, Norby GE, Holme I, Fellström B, Jardine A, Holdaas H. Inflammation-associated graft loss in renal transplant recipients. *Nephrol Dial Transplant* 2011; **26**: 3756-3761 [PMID: 21511816 DOI: 10.1093/ndt/gfr163]

137 **Stojanovic D**, Cvetkovic T, Stojanovic M, Bojanic V, Stefanovic N, Radenkovic S, Ljubisavljevic S, Pavlovic D. Crosstalk of inflammatory mediators and lipid parameters as early markers of renal dysfunction in stable renal transplant recipients with regard to immunosuppression. *Ann Transplant* 2013; **18**: 414-423 [PMID: 23946969 DOI: 10.12659/AOT.889239]

138 **Winkelmayer WC**, Lorenz M, Kramar R, Födinger M, Hörl WH, Sunder-Plassmann G. C-reactive protein and body mass index independently predict mortality in kidney transplant recipients. *Am J Transplant* 2004; **4**: 1148-1154 [PMID: 15196074 DOI: 10.1111/j.1600-6143.2004.00477]

139 **Winkelmayer WC**, Schaeffner ES, Chandraker A, Kramar R, Rumpold H, Sunder-Plassmann G, Födinger M. A J-shaped association between high-sensitivity C-reactive protein and mortality in kidney transplant recipients. *Transpl Int* 2007; **20**: 505-511 [PMID: 17362474 DOI: 10.1111/j.1432-2277.2007.00472]

140 **Tripepi G**, Mattace Raso F, Sijbrands E, Seck MS, Maas R, Boger R, Witteman J, Rapisarda F, Malatino L, Mallamaci F, Zoccali C. Inflammation and asymmetric dimethylarginine for predicting death and cardiovascular events in ESRD patients. *Clin J Am Soc Nephrol* 2011; **6**: 1714-1721 [PMID: 21642364 DOI: 10.2215/CJN.11291210]

141 **Abedini S**, Holme I, März W, Weihrauch G, Fellström B, Jardine A, Cole E, Maes B, Neumayer HH, Grønhagen-Riska C, Ambühl P, Holdaas H. Inflammation in renal transplantation. *Clin J Am Soc Nephrol* 2009; **4**: 1246-1254 [PMID: 19541816 DOI: 10.2215/CJN.00930209]

142 **Pihlstrøm H**, Mjøen G, Dahle DO, Pilz S, Midtvedt K, März W, Abedini S, Holme I, Fellström B, Jardine A, Holdaas H. Symmetric dimethylarginine as predictor of graft loss and all-cause mortality in renal transplant recipients. *Transplantation* 2014; **98**: 1219-1225 [PMID: 24999963 DOI: 10.1097/TP.0000000000000205]

143 **Connolly GM**, Cunningham R, McNamee PT, Young IS, Maxwell AP. Troponin T is an independent predictor of mortality in renal transplant recipients. *Nephrol Dial Transplant* 2008; **23**: 1019-1025 [PMID: 18065785 DOI: 10.1093/ndt/gfm738]

144 **Wong BM**, Huang M, Zaltzman JS, Prasad GV. Mycophenolate mofetil and C-reactive protein in renal transplant recipients. *Transplantation* 2007; **83**: 48-53 [PMID: 17220790 DOI: 10.1097/01.tp.0000248864.21574.92]

145 **Peddi VR**, Dean DE, Hariharan S, Cavallo T, Schroeder TJ, First MR. Proteinuria following renal transplantation: correlation with histopathology and outcome. *Transplant Proc* 1997; **29**: 101-103 [PMID: 9122914 DOI: 10.1016/S0041-1345(96)00022]

146 **Hohage H**, Kleyer U, Brückner D, August C, Zidek W, Spieker C. Influence of proteinuria on long-term transplant survival in kidney transplant recipients. *Nephron* 1997; **75**: 160-165 [PMID: 9041535 DOI: 10.1159/000189525]

147 **Roodnat JI**, Mulder PG, Rischen-Vos J, van Riemsdijk IC, van Gelder T, Zietse R, IJzermans JN, Weimar W. Proteinuria after renal transplantation affects not only graft survival but also patient survival. *Transplantation* 2001; **72**: 438-444 [PMID: 11502973 DOI: 10.1097/00007890-200108150-00014]

148 **Fernández-Fresnedo G**, Escallada R, Rodrigo E, De Francisco AL, Cotorruelo JG, Sanz De Castro S, Zubimendi JA, Ruiz JC, Arias M. The risk of cardiovascular disease associated with proteinuria in renal transplant patients. *Transplantation* 2002; **73**: 1345-1348 [PMID: 11981434 DOI: 10.1097/00007890-200204270-00028]

149 **Cherukuri A**, Welberry-Smith MP, Tattersall JE, Ahmad N, Newstead CG, Lewington AJ, Baker RJ. The clinical significance of early proteinuria after renal transplantation. *Transplantation* 2010; **89**: 200-207 [PMID: 20098283 DOI: 10.1097/TP.0b013e3181c352c5]

150 **Cherukuri A**, Tattersall JE, Lewington AJ, Newstead CG, Baker RJ. Resolution of low-grade proteinuria is associated with improved outcomes after renal transplantation-a retrospective longitudinal study. *Am J Transplant* 2015; **15**: 741-753 [PMID: 25648199 DOI: 10.1111/ajt.13013]

151 **Halimi JM**, Buchler M, Al-Najjar A, Laouad I, Chatelet V, Marlière JF, Nivet H, Lebranchu Y. Urinary albumin excretion and the risk of graft loss and death in proteinuric and non-proteinuric renal transplant recipients. *Am J Transplant* 2007; **7**: 618-625 [PMID: 17217438 DOI: 10.1111/j.1600-6143.2007.01665]

152 **Heinze G**, Mitterbauer C, Regele H, Kramar R, Winkelmayer WC, Curhan GC, Oberbauer R. Angiotensin-converting enzyme inhibitor or angiotensin II type 1 receptor antagonist therapy is associated with prolonged patient and graft survival after renal transplantation. *J Am Soc Nephrol* 2006; **17**: 889-899 [PMID: 16481415 DOI: 10.1681/ASN.2005090955]

153 **Opelz G**, Zeier M, Laux G, Morath C, Döhler B. No improvement of patient or graft survival in transplant recipients treated with angiotensin-converting enzyme inhibitors or angiotensin II type 1 receptor blockers: a collaborative transplant study report. *J Am Soc Nephrol* 2006; **17**: 3257-3262 [PMID: 17035607 DOI: 10.1681/ASN.2006050543]

154 **Stephany BR**, Augustine JJ, Krishnamurthi V, Goldfarb DA, Flechner SM, Braun WE, Hricik DE, Dennis VW, Poggio ED. Differences in proteinuria and graft function in de novo sirolimus-based vs. calcineurin inhibitor-based immunosuppression in live donor kidney transplantation. *Transplantation* 2006; **82**: 368-374 [PMID: 16906035 DOI: 10.1097/01.tp.0000228921.43200.f7]

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