Preventing Cardiovascular Disease in Renal Transplant Recipients

Cardiovascular disease (CVD) is the most common cause of death after kidney transplantation, accounting for between 17% and 50% of mortality [1]. In the recent United States Renal Data System report, the mortality rate per 100 patient-years from CVD was approximately 0.7 in the first year [2]. This figure slowly increased to approach 1.0 in the seventh year post-transplantation [2]. Although this compares favorably with that of patients on dialysis, it is still much higher than that of the general population, stratifying for age, gender, and race [3].

The increased risks could be categorized as follows: (1) traditional cardiac risk factors (age, sex, diabetes, hypertension, hyperlipidemia, smoking) — many of which are present among renal transplant recipients (RTRs); (2) risk factors related to the post-transplant state (immunosuppression, graft rejection, viral infections); and (3) risk factors related to loss of graft function (anemia, salt and fluid overload, hyperhomocysteinemia) [4]. With these factors in mind, it is appropriate that RTRs should be considered alongside chronic renal impairment in the highest risk group for CVD risk stratification [5].

It is important to note that CVD in RTRs does not refer to coronary artery disease alone. In RTRs, as in patients with chronic renal impairment or on dialysis, left ventricular disorders are commonly caused by ventricular remodeling in response to hemodynamic stresses in the presence of anemia and hypertension [6]. Both concentric left ventricular hypertrophy (LVH) (41%) and eccentric LVH (32%) are common [7]. Regression of LVH occurs after transplantation, continues beyond the first year, reaches a nadir at 2 years, and persists into the third and fourth post-transplant years [8]. LVH was a risk factor for death (RR, 1.9) and congestive heart failure (CHF) (RR, 2.27) [6]. Rigatto et al examined a cohort of RTRs free of cardiac disease in the first year after transplant, and found an incidence of de novo CHF of 1.2% per year [9]. This is much higher than the incidence in the general population. The major modifiable risk factors identified were anemia and hypertension [9]. De novo ischemic heart disease (IHD) occurred simultaneously with CHF in only one-third of the cases in the study, suggesting that most CHF developed independently of coronary artery disease.

The incidence of de novo IHD is 1.2–1.5% per year [1]. The 10-year cumulative risk of IHD is at least 20%, or roughly equivalent to that seen in patients with previous CVD. Cohort studies in RTRs have confirmed the importance of Framingham risk factors in the development of IHD [1,6,10]. After adjusting for hypertension, donor status, steroid use, cadaveric donation, renal function, or delayed graft function, acute rejection has been identified as an independent risk factor as well [6,10]. It is believed to lead to a state of chronic inflammation, when atherosclerosis is considered an inflammatory disorder on its own [11]. It remains controversial as to whether or not asymptomatic patients with chronic renal impairment or RTRs warrant screen testing for IHD [12]. Many of these patients would have some sort of screening prior to transplantation. Do we need to evaluate RTRs for CVD, as if they were still on the waitlist? If the answer is positive, stress imaging studies rather than standard noninvasive tests would be necessary in view of the high prevalence of coexisting LVH. Prospective trials are needed to examine the usefulness of such an approach and the accuracy of noninvasive imaging.

It is unfortunate that few clinical trials of CVD in RTRs exist. The optimum management and prevention of CVD in RTRs is, thus, not well defined and can only be based on extrapolation of data from other populations.

Approximately 60–75% of RTRs have abnormal lipids. Increased total and low-density lipoprotein cholesterol (LDL-C) levels are the most common [5]. Hypercholesterolemia has been shown to be a risk factor for CVD in RTRs [13,14]. The National Kidney Foundation’s Kidney Disease Outcomes Quality Initiative (K/DOQI) in the United States recommends treatment targets for RTRs as for the highest-risk groups of the general population [15]. The ALERT trial, a randomized controlled trial of fluvastatin in RTRs with LDL-C levels between 4 and 9 mmol/L, demonstrated a significant reduction in nonfatal myocardial infarction and cardiovascular death [16]. Unlike fluvastatin, however, most other statins are metabolized through the same microsomal cytochrome as the calcineurin inhibitors (CNI). It is recommended that toxicities can be avoided by starting at half of the usual statin dose, titrating carefully and monitoring CNI levels. In this issue of the Hong Kong Journal of Nephrology, Tse et al addressed this issue by prospectively looking at the effects of atorvastatin treatment in hypercholesterolemic RTRs [17]. Results were compared with historical controls who had been treated with simvastatin. The authors found that the use of atorvastatin reduced total
cholesterol by 31.1%, and LDL-C by 43.4%, after 3 months of treatment. These reductions were sustained throughout the 3 years of therapy. A significant reduction in triglycerides was noted after 3 and 9 months, but was not sustained. It is important to note, as Tse et al have also pointed out, that the therapy was not associated with any significant effect on cyclosporine trough level and graft function when used long-term [17]. Randomized controlled trials have also found no effects of statins on the rate of acute rejection [18].

The prevalence of hypertension in RTRs is 70–85%, which is greater than in patients with chronic renal impairment with similar levels of renal function [19]. The pathophysiology is believed to be a combination of extracellular fluid volume overload caused by reduced renal function and vasoconstriction aggravated by immunosuppression, anti-rejection therapy, and the presence of diseased native kidneys [5]. Since RTRs are similar to patients with chronic kidney disease, a target of 130/80 mmHg or lower seems appropriate [20]. The available data on treatment of post-transplant hypertension are insufficient to recommend any class of antihypertensive agents as preferred agents. However, by analogy with chronic renal impairment, angiotensin blockade is probably indicated for RTRs with diabetes, chronic allograft nephropathy, or CVD [21].

The use of aspirin and beta-blockers following myocardial infarction in patients with chronic kidney disease has been associated with improved survival across a broad spectrum of renal function [22]. Their use for usual indications is thus warranted in RTRs as well. Little is known about the role of anemia management in the prevention of cardiomyopathy and CHF in RTRs. The data of Rigatto et al suggests that a hemoglobin level below 120 g/L may be a causal risk factor for CHF in RTRs [9]. The association of hyperglycemia with CVD outcomes in RTRs has not been studied, nor has the effect of strict glycemic control. While strict glycemic control in transplant recipients with diabetes is likely to be beneficial, the generally accepted target for HbA1c of < 7% may not be attainable in all patients as a result of the longer duration of diabetes and the increased insulin resistance with various immunosuppressive medications [5].

The use of immunosuppressive agents has been focused on lowering acute rejection rates. Now we understand that these agents also affect lipid profile, insulin resistance, blood pressure, and chronic renal allograft function. The latter, reflecting the impact of both chronic allograft nephropathy and alloantigen-independent factors, in turn affects cardiovascular mortality [23]. Corticosteroid use has been associated with hyperlipidemia, accelerated atherosclerosis, altered glucose metabolism, hypertension and exacerbation of heart failure [24]. The adverse impact occurs very early after transplantation [25]. Both steroid-free and early steroid withdrawal protocols have been tried, with improved CVD risk profiles observed [26–28]. For the CNIs, tacrolimus has been considered to have a more favorable overall cardiovascular risk profile than cyclosporine, with less reported hyperlipidemia and hypertension. While there is hot debate on the difference in CVD risk profile [29] and nephrotoxicity among the two agents, the negative impact of CNIs on long-term graft function has long been appreciated. Thus, CNI minimization, withdrawal, and even avoidance have been tested, with varying success [30–33]. Sirolimus has been used in some of these trials, and hyperlipidemia is a side effect of concern [34]. Mycophenolate mofetil, an immunosuppressive agent with favorable cardiovascular risk profile, has also been associated with better preservation of renal function [23]. This drug, with or without antibody induction, has been used in many of the steroid or CNI withdrawal protocols studied. It is tempting to have immunosuppressive regimens tailored for individual patients, considering CVD risk profile, comorbidity and relative strengths and weaknesses of specific agents [35]. Cautious drug minimalization and conversion strategies may further help to reduce drug toxicities, preserve renal function, and avoid cardiovascular injury [35].

RTRs are at high risk for LVH, CHF and IHD. Renal allograft function is influenced by donor and recipient variables, as well as post-transplantation events. Although some of these issues have been successfully addressed, it is apparent that further improvement in transplant recipient survival cannot be achieved without paying attention to CVD risk factors. Physicians looking after RTRs should attend to these cardiovascular risk factors aggressively, making use of the evidence and strategies mentioned. The usefulness of therapeutic lifestyle modifications (smoking cessation, maintenance of ideal body weight, balanced diet, regular exercise) in this context cannot be overemphasized. The American Heart Association recommends a moderate level of physical activity for 30 minutes daily. This level of activity is manageable in many of our RTRs.

While it is highly credible that interventions of proven benefit for CVD prevention in the general population will also benefit RTRs, trials of therapeutic strategies in RTRs are urgently needed to clarify the renoprotective and cardioprotective effects of these measures in the transplantation setting.

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REFERENCES


