EDITORIAL

Improving long-term outcomes of kidney transplantation: The pressure is on

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Since the first successful operation in man in 1954, kidney transplantation has evolved from an experimental therapy to the treatment of choice for patients with end-stage renal disease (ESRD). Kidney transplantation offers a significant survival benefit to patients suffering from ESRD and improves their quality of life as compared with patients who remain dependent on dialysis.[1] In children, kidney transplantation improves growth, cognitive performance, and psychosocial well-being.[2] The number of transplantations performed each year in the Netherlands has continued to grow over the past decade and increased from 587 in 2002 to 960 in 2012.[3] This expansion can largely be ascribed to the continuing success of programs for living kidney donation. Currently, in our country, more patients with former ESRD are being maintained with a functioning kidney transplant than with dialysis (9386 *versus* 6396 patients, respectively, on 1 January 2013).[3,4]

Kidney transplantation is, however, not a cure for ESRD. Kidney transplant recipients need medical follow-up and have to take immunosuppressive medication for life. Advances in immunosuppressive drug therapy have resulted in a dramatic decrease in the incidence of acute rejection over the past 30 years and have contributed to the substantial improvement of one-year kidney allograft survival which is now ≥90% in most transplant centres.[5] Unfortunately, long-term transplantation outcome has not improved to a similar degree.[6] Kidney allograft half-lives are approximately 9.5 years for deceased-donor kidney transplants and around 16 years for living-donor kidney transplants.[4,6] Many transplanted patients will therefore at some point in their lives need a second transplant or return to dialysis.

The causes of long-term kidney allograft loss are multifactorial.[7,8] In about half of successfully operated patients, kidney transplants will fail because of diverse causes including, but not limited to, chronic rejection, late acute rejection (often related to non-adherence to immunosuppressive drug therapy), recurrent primary kidney disease, BK virus infection, or nephrotoxicity of the calcineurin inhibitors tacrolimus or ciclosporin.[7,8] The other half of all graft losses occurs because the recipient dies with a functioning kidney transplant.[7,8]

Cardiovascular disease (CVD) is the primary cause of death of kidney transplant recipients and precedes infection and malignancy.[9,10] Patients with ESRD have a greatly increased risk of CVD and although this risk is reduced after a successful kidney transplantation, it remains several times higher than in the general population.[11,12] The nature of CVD among patients with ESRD and those who have undergone a kidney transplantation also differs from that of the general population. Left ventricular hypertrophy, heart failure, sudden cardiac death, peripheral artery disease, and stroke are especially common.[11,12] Hypertension is an important and modifiable risk factor for cardiovascular morbidity and mortality in the transplant population. In addition, hypertension has been shown to negatively influence kidney transplant survival.[13-15]

In this edition of *The Netherlands Journal of Medicine*, Dobrowolski and colleagues report their findings on the prevalence and treatment efficacy of hypertension among kidney transplant recipients in the Netherlands.[16] To this end, they studied data from over 5000 patients registered in the Netherlands Organ Transplant Registry (a national registry which includes data from all eight Dutch transplant centres), as well as over 500 patients who were treated at the authors' institution and for whom more detailed data were available. Their main findings are that >75% of the patients had a blood pressure above the recommended target of 130/80 mmHg and that approximately 12.5% of these patients did not receive any antihypertensive medication. Of the hypertensive patients who did receive antihypertensive therapy, 74% were prescribed sub-maximal dosages. Furthermore, the majority of patients had a sodium intake above the recommended 90 mmol per day. The authors conclude that better blood pressure control should be possible by

intensifying pharmacological treatment and providing more advice on dietary sodium restrictions.[16]

'Less salt and more pills': is that the answer to the immense burden of CVD in the kidney transplant population? Although the easy answer may be 'yes', real-life solutions are likely to be not so simple. Excessive salt intake is associated with detrimental effects on CVD.[17,18] The results of intensive programs to modify lifestyle (smoking cessation, promoting weight loss, and reducing dietary salt intake), however, have been disappointing.[19] The question therefore arises why the patients in this study were not prescribed more intensive drug therapy. Over the past decade, the awareness of the high cardiovascular risk of transplant recipients has grown. Guidelines for cardiovascular risk management have been published and the use of potentially cardioprotective medication in this population has increased.[20,21] Medical neglect is thus an unlikely explanation. This is supported by Dobrowolski *et al*. who show that the number of 'under-treated' patients in the authors' centre, a university hospital with a long tradition of caring for transplanted patients and with a research interest in hypertension, did not differ from the rest of the Netherlands.[16]

Another explanation could be that the prevalence of hypertension was overestimated in this study as only single, office-based, blood pressure measurements were recorded.[22] Moreover, the recommended target blood pressure of <130/80 mmHg is currently debated and may have been considered too strict by the attending physicians. However, even when a cut-off of 140/90 mmHg was used, 44% of the population were still classified as being hypertensive. Other studies have reported comparable findings, suggesting that the true prevalence of under-treated hypertension is indeed this high.[23] It is also conceivable that with more detailed assessments such as 24-hour ambulatory recordings, hypertension may be more prevalent because calcineurin inhibitors reduce the nocturnal drop in blood pressure.[24]

Possibly, practical limitations prevented more intensified blood pressure-lowering pharmacotherapy. Non-compliance to immunosuppressive drug therapy among transplant recipients is very common.[25] Further increasing the pill burden is unlikely to promote adherence and there may have been a trade-off between antirejection and antihypertensive treatment. Side effects of antihypertensive therapy further complicate management. For example, ACE inhibitors and angiotensin-receptor blockers may worsen hyperkalaemia caused by tacrolimus and co-trimoxazole prophylaxis. Oedema may worsen when calcium-channel or alpha blockers are given together with glucocorticoids. Changes in serum creatinine caused by diuretics may arouse suspicion of acute rejection. Concerns about overzealous blood pressure management and the risk of fall-related injuries in the elderly are justified.[26] Fear of overdosing certain beta blockers in patients with limited graft function and interactions between immunosuppressive and antihypertensive drugs may have contributed to suboptimal blood pressure control in individual cases.[27]

Despite all these practical challenges, we believe the complexity of antihypertensive therapy in kidney transplant recipients should not lead to therapeutic nihilism. Novel antihypertensive treatments, a smarter use of existing drugs and maybe prescribing fewer drugs may do the trick. Renal denervation has been heralded as an intervention with high potential. Especially in kidney transplant recipients this technique has appeal because the native kidneys contribute to hypertension, but little to kidney function. Nonetheless, the number of patients with resistant hypertension in Dobrowolski's study was limited (7.7%) and recent reports have tempered initial enthusiasm.[28,29] With regard to a better use of existing treatments, the renewed interest in thiazide diuretics is of note. Recent research has indicated that tacrolimus (the cornerstone of modern immunosuppression) causes salt-sensitive hypertension by activating the sodium chloride cotransporter in the distal convoluted tubule, which is the target of thiazide diuretics.[30,31] Prescription of these agents, therefore, seems rational but physicians appear to be reluctant to treat transplant recipients with diuretics.[32] We are currently investigating whether chlortalidone is a more effective antihypertensive drug as compared with the calcium-channel blocker amlodipine.

A further optimisation of immunosuppressive drug therapy may have the greatest potential to reduce CVD in the transplant population. Obviously, preventing rejection and deterioration of kidney transplant function is of paramount importance. Nonetheless, the number of patients treated with maintenance glucocorticoids in Dobrowolski's study was remarkably high. Glucocorticoid-sparing or withdrawal protocols may be feasible and reduce cardiovascular risk in low-immunological risk patients treated with modern immunosuppression.[33] The optimum maintenance tacrolimus target concentrations are also a matter for debate but, again, reduction may be possible without increasing rejection risk.[34] Mycophenolate mofetil may be preferable over other antimetabolites from a cardiovascular point of view.[35] The novel immunosuppressive drug belatacept arguably has the greatest potential to reduce CVD in transplantation. This drug allows for adequate immunosuppression and results in a better kidney function, less post-transplantation diabetes mellitus, and lower serum lipids and blood pressure compared with ciclosporin-based immunosuppression.[36]

Reducing the risk of CVD is an unmet need in transplantation. It appears that the tools to do so are here. Picking the right ones for an individual patient is the challenge.

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