

# Hypertension in Kidney Transplantation

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**Arterial hypertension in renal transplant patients plays a major role in the progression to chronic allograft failure, and in morbidity and mortality associated with cardiovascular disease. Its cause is diverse, with contributions not only from donor and/or recipient factors, but it also is influenced strongly by the type of immunosuppressive regimen. Despite increased awareness of the adverse effects of hypertension in both graft and patient survival, long-term studies have shown that arterial hypertension in the transplant population has not been controlled adequately. Ambulatory blood pressure measurements provide the advantage of a better assessment of the diurnal blood pressure variation, a predictor of target organ damage and cardiovascular morbidity and mortality events. Although the available data do not support the recommendation of any class of antihypertensive medication as preferred agents for blood pressure management in the transplant population, angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers have shown beneficial effects beyond their antihypertensive effects. Clinical data in transplant recipients are emerging that suggest that applying interventions proven to be effective in reducing cardiovascular morbidity and mortality in the general population may be effective for the transplant population.**

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Arterial hypertension is common in renal transplant patients, and plays a major role in the progression to chronic allograft failure and in the morbidity and mortality associated with cardiovascular disease (CVD). The blood pressure (BP) relationship to CVD is continuous, consistent, and independent of other risk factors.<sup>1</sup> With each increment of 20/10 mm Hg, the risk for CVD doubles across the entire BP level range starting at 115/75 mm Hg.<sup>2</sup> The benefits of sustained lowering of the BP are a 35% to 40% reduction in the incidence stroke, a 20% to 25% reduction in the incidence of acute myocardial infarction, and a 50% reduction in the incidence of congestive heart failure.

The prevalence of hypertension in the transplant population varies with the type of immunosuppressive regimen, amount of time after transplantation, and other interacting factors. The prevalence of hypertension has increased from 30% to 40% in the pre-cyclosporine (CyA) era to 75% to 80% after the introduction of CyA.<sup>3,4</sup> The recent advances in the immunosuppression have improved the short-term graft survival and have decreased early mortality.<sup>5</sup> It should be noted, however, that a growing number of kidney transplant recip-

ients are losing their grafts to premature death with functioning graft or to chronic rejection. After transplantation, hypertension has been found to be associated with a graded increase of subsequent graft failure.<sup>1</sup>

According to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, the goals of therapy for hypertension are to reduce CVD and renal morbidity and mortality.<sup>2</sup> The recommended threshold for initiation of antihypertensive treatment is systolic BP greater than 140 mm Hg or diastolic BP greater than 90 mm Hg, or BP of 130/80 mm Hg or less for patients with diabetes or chronic renal disease. The National Kidney Foundation Task Force on CVD recommended a BP goal of less than 135/85 mm Hg for renal transplant recipients without proteinuria and less than 125/75 mm Hg for patients with proteinuria.<sup>6</sup> The National Kidney Foundation [Kidney Disease Outcome Quality Initiative (K/DOQI)] guideline recommends a target BP in kidney transplant recipients of less than 130/80 mm Hg.<sup>7</sup>

Several interventional trials have established the benefits of BP reduction in the general population.<sup>8</sup> In view of reports correlating BP with adverse outcomes after transplantation, it would be unethical to conduct trials comparing treated and untreated hypertension among transplant recipients. In the absence of adequate clinical data in transplant recipients, it seems reasonable to apply interventions that have been proven to reduce CVD in the general population or in other relevant high-risk populations.

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**Table 1** Causes of Posttransplant Hypertension

<b>Recipient related</b>
Pre-existing hypertension and LVH
Body mass index
Primary kidney disease (native kidneys)
<b>Donor related</b>
Elderly and female donor
Hypertensive donor
Use of right-sided donor kidney
<b>Transplantation related</b>
Prolonged ischemia time
Delayed graft function
<b>Immunosuppressive therapy</b>
Calcineurin inhibitors (CyA and TAC)
Corticosteroids
<b>Renal transplant artery stenosis</b>
<b>Renal outflow obstruction (lymphocele, ureteral stenosis)</b>
<b>Renal transplant dysfunction (CAN, GN)</b>

Abbreviations: CAN, chronic allograft nephropathy; GN, glomerulonephritis.

Adapted from *Nephrol Dial Transplant* 17:1166-1169, 2002.

## Causes of Posttransplant Hypertension

The cause of posttransplant hypertension is diverse, with contributions not only from donor and/or recipient factors but contributions also are influenced strongly by the type of immunosuppressive regimen (Table 1). Pérez Fontán et al<sup>9</sup> reported the incidence and risk factors associated with posttransplant hypertension in 680 renal transplant patients treated with CyA. The incidence of hypertension was reported at 65% before transplantation, but at 78% at the end of the first year. The prevalence of hypertension remained greater than 70% along the duration of the study. Multivariate analyses indicated 3 independent predictors of hypertension at 3 months after transplantation: (1) pretransplant BP level, (2) basal renal disease, and (3) grafting of the right rather than the left kidney. At 1 year after transplantation, 7 independent predictors were noted: (1) pretransplant BP level, (2) grafting of the right kidney, (3) delayed graft function (DGF), (4) cold and warm ischemia, and (5) transplantation from an elderly or female donor. Immunologic variables such as early acute rejection, poor human leukocyte antigen compatibility, and increased reactivity against the lymphocyte panel were not found to be predictors of post transplant hypertension. Similarly, CyA dosage and trough levels were correlated poorly with hypertension.

A retrospective study by Ducloux et al<sup>10</sup> evaluated the retrospective roles of donor and recipient factors in the subsequent development of hypertension in 321 recipients with functioning grafts at 1 year. Hypertension was defined as systolic BP of 140 mm Hg or greater or diastolic BP of 90 mm Hg or greater, or the use of antihypertensive medications. Of the 321 patients, 263 were hypertensive according to this definition. Pretransplant hypertension, the use of calcineurin inhibitors (CNI), urinary protein excretion, body mass index,

donor age, and donor aortorenal atheroma were found to be factors associated with hypertension. Among patients receiving CNI, those receiving CyA were more prone to develop hypertension than those receiving tacrolimus. The prevalence of hypertension was 46% in patients not receiving CNI. In this study, neither donor serum creatinine level nor a history of hypertension in the donor predicted subsequent development of hypertension in the recipient. Although not statistically significant, a trend toward a greater prevalence of hypertension in male recipients from a female donor was noted. Factors such as male sex, recipient age, body mass index, acute rejection (AR), lower hemoglobin levels, administration of CyA, and higher doses of prednisone were reported recently by Kasiske et al<sup>11</sup> as predisposing to hypertension in a study comprising more than 1,600 patients followed-up for more than 2 decades.

Whether or not tacrolimus (TAC) produces more or less hypertension than CyA, is still a matter of continuing debate. A comparison of CyA and TAC with respect to renal hemodynamics and BP in normal patients was conducted by Klein et al.<sup>12</sup> When compared with TAC, patients who received CyA were found to have a higher mean BP and decreased effective renal plasma flow, glomerular filtration rate, and renal blood flow. Renal vascular resistance increased during CyA administration but did not change during TAC therapy. The investigators concluded that the use of TAC may lead to better renal function and less risk for hypertension when compared with treatment with CyA. Vincenti et al<sup>13</sup> in the 5-year study comparing TAC versus CyA, found that TAC therapy was associated with a significantly reduced requirement for antihypertensive medications. A study by the European Tacrolimus versus Cyclosporine Microemulsion Renal Transplantation Study Group<sup>14</sup> found that patients treated with CyA had significantly higher rates of hypertension when compared with the TAC group. A study by Ligtenberg et al<sup>15</sup> showed that stable renal transplant patients who were switched from CyA to TAC showed an improvement in BP as measured by ambulatory blood pressure monitoring (ABPM).

Although the cause of CNI-induced hypertension is not well understood, the most frequently proposed mechanism involves vasoconstriction of the afferent renal arterioles and subsequent impairment of GFR and sodium excretion.<sup>16</sup> This may be secondary to several factors such as increased sympathetic nervous activity, alteration in the local renin-angiotensin system (RAS) activity, increased intracellular calcium concentrations, synthesis and release of endothelin-1, altered prostaglandin metabolism, decreased nitric oxide activity, and/or structural alterations in the kidney that impair its normal function with its possible effects on endothelial or vascular smooth muscle cells.<sup>17</sup>

Corticosteroid use is associated not only with hypertension, but also with numerous other adverse effects that lead to increased patient morbidity and mortality, adding to the long-term cost of medical care of renal transplant recipients.<sup>18</sup> Steroid-sparing protocols have been shown to improve BP control and reduce cardiovascular risk factors, with low rates of allograft rejection and graft loss, particularly

when those regimens use a combination of low-dose CNI plus sirolimus.<sup>19-24</sup> It is still too early to assess the long-term benefits of these emerging regimens.

Transplant renal artery stenosis is a potentially correctible cause of posttransplant hypertension, allograft dysfunction, and graft loss. A recent review of the topic by Bruno et al<sup>25</sup> described the pathogenesis of transplant renal artery stenosis. It accounts for approximately 1% to 5% of all cases of post-transplant hypertension. The usual presentation is difficult-to-treat hypertension and deterioration of graft function in the presence of or after introducing angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin-receptor–blocker (ARB) therapy. Transplant renal artery stenosis occurring early after transplantation most likely is related to trauma, clamping, or suturing of the donor or recipient vessels. Late causes include atherosclerotic disease of the renal artery or the proximal iliac artery. A longer artery than a vein (right kidney) may cause a functional transplant renal artery stenosis because of kinking of the artery. Another possible cause is vascular damage and fibrosis caused by prolonged cold ischemia. Different imaging techniques such as color Doppler ultrasonography and nuclear renogram, with or without captopril, are useful screening techniques.<sup>26</sup> Selective renal allograft angiography is still the gold standard for definitive diagnosis, although spiral computed tomography angiography or magnetic resonance angiography may be useful noninvasive alternatives.<sup>27</sup> Percutaneous transluminal angioplasty with stenting is the best initial treatment. Surgery is indicated for those patients with unsuccessful angioplasty or stenosis not accessible to percutaneous transluminal angioplasty.<sup>25,28</sup>

Noncompliance with required medical therapy is a recognized cause of late graft failure, late AR, and even death in renal transplantation.<sup>29</sup> It is estimated that compliance with long-term treatment for chronic asymptomatic conditions such as hypertension is approximately 50% and that the prevalence of noncompliance with immunosuppressive drugs ranges from 2% to 26%.<sup>30</sup> It has been estimated that the total cost attributed to complications resulting from noncompliance in dialysis and transplant patients exceeds \$950 million.<sup>30</sup> A positive correlation exists between medication noncompliance before and after kidney transplantation.<sup>31</sup> Factors such as young age, socioeconomic status, lack of family support, complexity of the treatment regimen, and patient beliefs and motivation are factors influencing medication compliance. Several strategies such as simplification of medication regimen, increased frequency of visits, and use of microelectronic devices to dispense medications have been recommended to improve medication compliance with varying degrees of success.<sup>30,32</sup>

## Impact of Hypertension on Graft Function

Systemic hypertension has emerged as one of the most important factors that negatively impacts the long-term graft and patient survival. Earlier studies suggested an association between pretransplant and posttransplant hypertension and

chronic allograft nephropathy.<sup>33</sup> However, these studies could not differentiate cause and effect between hypertension and deterioration of renal function. By using registry data, Opelz et al<sup>1</sup> reported a significant correlation between post-transplant hypertension and long-term graft outcome in more than 29,000 patients. Chronic graft failure was associated significantly with hypertension, even when patient death was censored. Cox regression analysis established persistent hypertension as an independent risk factor for graft failure. Most recently, Mange et al<sup>34</sup> reported a strong correlation between hypertension and graft failure after deceased donor renal transplantation. The relative risk for graft failure per each 10-mm Hg increase in BP measured at 1 year after transplantation, after adjustment for creatinine clearance, was 1.15 for systolic BP, 1.27 for diastolic BP, and 1.30 for the mean BP. This significant association between hypertension and increased risk for graft loss also has been reported by other investigators.<sup>35-37</sup>

AR is a strong predictor of renal allograft survival. Cosio et al<sup>38</sup> found a significant correlation between increased BP levels posttransplant and risk for AR that was independent of graft function. Successful treatment of hypertension appeared to be associated with a decreased risk for AR. By univariate analyses, AR was associated with higher levels of systolic BP and/or diastolic BP posttransplant. Higher BP levels also were associated with earlier episodes of AR. By multivariable analysis, AR was associated significantly with systolic BP. Increased BP levels, even 3 weeks before the AR episode, were associated significantly with AR. Of the recipients whose BP increased after the transplant, 81% had AR. In contrast, only 22% of patients whose BP decreased posttransplant had AR.

Despite the evidence of the adverse effects of hypertension in graft and patient survival, 2 large studies showed that BP control has been poor despite the use of different combinations of antihypertensive medications and different immunosuppressive regimens. Opelz et al<sup>1</sup> showed that among 29,751 cadaveric recipients at 1 year, only 44.5% were normotensive as defined by a systolic BP of less than 140 mm Hg, 37.4% exhibited a systolic BP of 140 to 159 mm Hg, 13.9% exhibited a systolic BP of 160 to 179 mm Hg, and 4.2% exhibited a systolic BP of 180 mm Hg. A recent study by Kasiske et al<sup>11</sup> reported the prevalence, treatment, adequacy of control, clinical correlates of hypertension, and its association with outcomes in a cohort of 1,295 kidney transplant recipients. Hypertension was classified according to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure categories (Table 2).<sup>2</sup> Only 12.4% had normal BP, 36.3% had prehypertension, 34.2% had stage I, and 17.1% had stage 2 hypertension despite antihypertensive treatment. Of those with normal BP at 1 year, 28.1% were not treated with antihypertensive medications. Therefore, only 3.5% had truly normal BP without antihypertensive medications at 1 year posttransplantation. The control of BP improved only slightly for those undergoing a transplant procedure between 1993 and 2002 as compared with those undergoing a transplant procedure between 1976 and 1992, despite a substantial in-

**Table 2** Classification of Hypertension

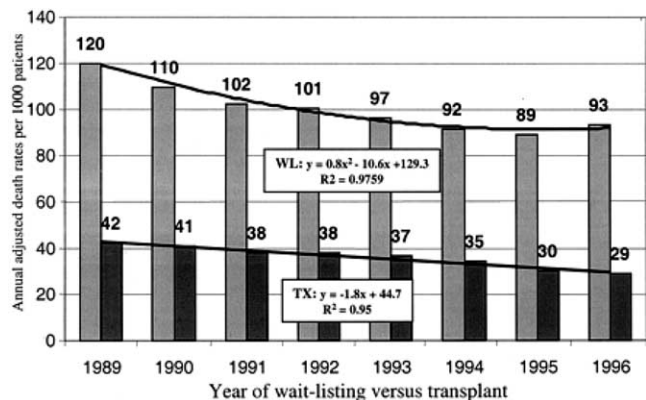
Classification	Systolic and Diastolic BP (mm Hg)
Normal	<120 and <80
Prehypertension	120-139 and 80-90
Stage 1 hypertension	140-159 and 90-99
Stage 2 hypertension	≥160 and ≥100

Adapted from Chobanian et al.<sup>2</sup>

crease in the use of antihypertensive medications. The number of patients receiving 2 or more antihypertensive medications increased from 43.5% to 54.6%. At the same time, the number of patients not receiving antihypertensive medications 1 year posttransplantation decreased from 26.7% to 5.2%. Systolic BP was an independent risk factor for graft failure, death-censored graft failure, and death, even after adjusting for AR, estimated creatinine clearance, and other recipient, donor, and transplantation variables. The adjusted relative risk for graft failure at 1 and 5 years for each 10-mm Hg increase in systolic BP was 1.13 and 1.10, respectively. After adjusting for AR, graft function, and multiple other variables, the independent effects of BP on graft failure appeared to precede graft failure by several years.

## Hypertension and Cardiovascular Disease

Systemic hypertension, either as a result of pre-existing kidney disease and/or immunosuppressive therapy, is one of the traditional risk factors contributing to the high incidence of CVD among renal transplant recipients.<sup>39</sup> Compared with age- and sex-matched general population controls, kidney transplant recipients face a markedly increased CVD risk posttransplant.<sup>40</sup> Several studies have noted that those patients who receive a kidney transplant have a survival advantage over those who remain on dialysis (Fig 1).<sup>41-44</sup> However, the mortality rate caused by CVD is still much higher in



**Figure 1** Mortality secondary to cardiovascular disease. Adjusted annual death rates in wait-listed (WL) patients and transplant (TX) recipients per 1,000 patient-years on the basis of 5 years of actual or projected follow-up evaluation. Reprinted with permission from Meier-Kriesche et al.<sup>44</sup>

**Table 3** Conventional and Nonconventional Cardiovascular Risk Factors in Chronic Kidney Disease

Conventional Risk Factors	Nonconventional Risk Factors
Male sex	Albuminuria
Hypertension	Homocysteine
Abnormal lipid level	Anemia
Diabetes	Abnormal calcium/phosphate metabolism
Smoking	Extracellular fluid volume overload
Physical inactivity	Electrolyte imbalance
Menopause	Oxidative stress
Family history of premature CVD	Inflammation (C-reactive protein)
Cardiac hypertrophy	Malnutrition
	Thrombogenic factors

Adapted from Hypertension 42:1050-1065.

transplant patients than in the general population. Cardiovascular events are responsible for approximately 40% of the deaths with a functioning graft, with an adjusted death rate of 4.6 deaths per 1,000 patient-years.<sup>45</sup>

Hypertension has not been found consistently to have the same significant association with CVD in the transplant population as in the general population. Ponticelli et al<sup>46</sup> evaluated the causes of late graft failure in 864 kidney transplant recipients treated with CyA. Pretransplant hypertension, as well as pre-existing cardiovascular events, age greater than 45 years, and dialysis duration of more than 60 months, were variables that were associated strongly with the risk for development of a first cardiovascular event after transplantation. Pretransplant hypertension and the duration of dialysis remained significant risk factors for up to 3 years after transplantation, after which dyslipidemia gained an independent prognostic significance. Another study compared the observed and expected incidences of ischemic heart disease in a population of renal transplant recipients using equations from the Framingham Heart Study.<sup>40</sup> In this study, patients with pretransplant CVD were excluded. Most of the conventional factors of CVD prevalent in the general population were applied to renal transplant recipients. Age, diabetes mellitus, cigarette smoking, and low high-density lipoprotein levels in women were the strongest predictors of ischemic heart disease. Similar results were reported by Lindholm et al<sup>47</sup> in a cohort of Scandinavian patients. In that study, AR, diabetes mellitus, and age were the strongest factors associated with ischemic heart disease mortality. Differences in the methodology of the studies, patient selection, as well as the presence of nontraditional risk factors of CVD in transplant recipients may have contributed to this difference (Table 3). Lower levels of kidney function and the presence of inflammatory mediators (C-reactive protein, homocysteine, sialic acid, acute phase reactants) have been found to contribute to all-cause mortality and/or CVD.<sup>48-51</sup>

In addition to ischemic heart disease, left ventricular disorders, diagnosed either by electrocardiography or echocardiography, have been associated with adverse outcomes not only in patients with chronic kidney disease, but also in renal



transplant patients.<sup>52-54</sup> Increased blood pressure is known to be involved in the pathogenesis of left ventricular hypertrophy (LVH). LVH, either pre-existing or appearing de novo after transplantation, has been found to be an independent risk factor for death and congestive heart failure by univariate analysis.<sup>55</sup> In the same study, systolic BP and anemia were found to be associated with de novo congestive heart failure by multivariate analysis. Kidney transplantation may improve BP control, renal function, and anemia—factors that have been associated with the development LVH in patients with progression of chronic kidney disease. For those patients with left ventricular disorders, aggressive management of anemia and hypertension may help to reduce adverse events posttransplant.

## Diagnosis of Posttransplant Hypertension

The diagnosis of hypertension based on office or clinic measurements versus ABPM is still a matter of debate. Accurate measurement of BP is essential for the diagnosis and treatment of hypertension with the aim to reduce the spectrum of CVD and other adverse outcomes after transplant. One advantage of ABPM is the ability to measure the diurnal BP variation. During normal diurnal variation, BP decreases 10% or greater with sleep in both normotensive and hypertensive patients, which is known as the *dipping pattern*. Loss of the normal diurnal BP variation (nondipping pattern) has been described to occur in patients with chronic kidney disease and has been associated with a higher rate of cardiovascular events as well as progression of renal disease.<sup>56,57</sup>

ABPM measurements generally are lower than clinic readings. Making treatment decisions based on office practice measurements, obviates the fact that, in most individuals, the BP is higher in this setting than at home or in nonclinical settings, known as *white coat hypertension*.<sup>58</sup> Although no large studies have been designed to assess the prevalence of white coat hypertension in the renal transplant population, 2 studies reported a prevalence of 12% and 32%.<sup>59,60</sup> Although the office BP measurement is more practical and the most cost efficient, the use of ABPM may be useful in the identification and evaluation of white coat hypertension, nocturnal hypertension, resistant hypertension, borderline hypertension, hypotensive symptoms complicating antihypertensive therapy, episodic hypertension, and autonomic dysfunction.<sup>2,58</sup> Also, ABPM has been considered to be superior to routine office BP measurements as a predictor of target organ damage such as LVH, hypertensive cerebrovascular disease, retinopathy, renal abnormalities, and alterations in vascular compliance.<sup>61</sup> The loss of normal diurnal BP variation is seen early after transplantation but tends to recover as the length of time after transplantation increases.<sup>62</sup> This may be related to a reduction in the dose of immunosuppressive medications (CNI and steroids), a decrease in extracellular volume, or improved kidney function.

Despite the earlier-mentioned advantages of ABPM, there is insufficient evidence whether to recommend ABPM as the

best strategy to monitor hypertension and to guide antihypertensive therapy in transplant patients.<sup>63</sup> ABPM, however, can be recommended in specific clinical situations previously described.

## Management of Posttransplant Hypertension

The goal of adequate antihypertensive therapy in the kidney transplant population is to reduce injury to the renal graft and to reduce the risk for CVD. The available data do not support the recommendation of any class of antihypertensive medication as preferred agents for long-term therapy to slow down the progression of kidney disease. In general, there are no contraindications for the use of any of the antihypertensive medications. Although calcium channel blockers (CCBs), ACEIs, and ARBs have constituted the backbone of antihypertensive therapy, diuretics and  $\beta$ -blockers continue to have a role in the antihypertensive armamentarium.

CCBs have been studied widely as effective antihypertensive medications. They effectively counteract the afferent arteriolar vasoconstriction caused by CNI, a suggested mechanism for progressive allograft dysfunction.<sup>64</sup> Several clinical studies have suggested that use of CCBs in renal transplant patients receiving CyA may be associated with a reduction in both DGF and acute rejection episodes, and possibly also a better long-term graft function.<sup>38,65-68</sup> With respect to the change of serum creatinine levels over time, CCBs have a significant nephroprotective effect that may be independent of the agent's antihypertensive actions. These findings were supported in a single-center, double-blind, randomized, parallel-group, comparative study by Midvedt et al.<sup>69</sup> A total of 154 renal transplant recipients were randomized to receive either lisinopril or nifedipine. Patients were followed-up for 2 years. In the nifedipine group, patients experienced a statistically significant improvement in renal graft function (measured Technetium Diethylenetriamine Pentaacetic Acid (Tc-DTPA)), increased effective renal plasma flow, and filtration fraction from baseline. The difference in renal graft function was sustained after 2 years treatment. BP control, however, was similar between the 2 groups throughout the study.

As a class, CCBs are relatively well tolerated. However, in the transplant population there are well-documented drug interactions that may occur with the concurrent administration of CNI and both nondihydropyridine (eg, verapamil and diltiazem) and dihydropyridine (eg, nifedipine, amlodipine, and isradipine) CCBs.<sup>70</sup> Nondihydropyridine CCBs are potent inhibitors of the cytochrome P450 3A4 isoenzyme. Co-administration of these CCBs with CNI, which are substrates of the cytochrome P450 3A4 isoenzyme, would result in a significant increase in the CNI levels. On the other hand, dihydropyridine CCBs are not inhibitors, but substrates of the cytochrome P450 3A4 isoenzyme. Co-administration of these with CNI will result in competition for metabolism and consequently an increased level of exposure to both the CNI and the CCBs.

Despite the concerns of risk for acute renal failure, hyper-

kalemia, and posttransplant anemia, ACEIs and ARBs now are considered valuable drugs for the transplant population.<sup>2</sup> ACEIs and ARBs are known to slow down the progression of chronic renal disease.<sup>71-73</sup> Possible mechanisms for these include a decrease in intracapillary pressure, a reduction in permselectivity, alterations in the function of the mesangial cells, and interference with angiotensin-mediated generation of free radical formation.<sup>74</sup> Another factor of importance is that both ACEIs and ARBs may inhibit the activation of transforming growth factor- $\beta_1$  (TGF- $\beta_1$ ), which is one of the cytokines involved in the pathogenesis of chronic allograft dysfunction.<sup>75</sup> Production of TGF- $\beta_1$  may be modulated by the intrarenal RAS and by a direct effect of CyA, which is known to stimulate its synthesis and expression.<sup>76</sup> TGF- $\beta_1$  is a profibrotic cytokine that directly stimulates the synthesis of individual extracellular matrix components, and blocks matrix degradation by stimulating inhibitors of protease activity.<sup>77</sup> Increased levels of urinary TGF- $\beta_1$  and exaggerated plasma renin activity response to ACEI therapy in renal transplant patients have been associated with the development of chronic allograft nephropathy.<sup>78</sup> The ability of ACEIs or ARBs to slow the progression of chronic allograft dysfunction remains unproven at the present time.

The administration of ACEIs and ARBs has been considered safe during the later course of kidney transplantation.<sup>79-81</sup> However, there have been concerns about their potential to exacerbate acute renal failure and DGF when used early after transplantation in the presence of high doses of CNI.<sup>82,83</sup> The blockade of the RAS may have beneficial effects on posttransplant kidney function because there is evidence that excess RAS activity in both the kidney donor and recipient are important contributors to the pathogenesis of DGF.<sup>84</sup> Lorenz et al<sup>85</sup> compared the early postoperative graft function between 260 deceased kidney transplant recipients treated with or without ACEI/ARB therapy before or early after the surgery, and its effect in kidney function during the first week after transplantation. They found that the early use of ACEIs or ARBs did not influence adversely early graft function or the occurrence of DGF. Conversely, serum creatinine levels decreased significantly faster in patients treated with ACEIs/ARBs than in those without therapy. The only variables associated with DGF were the number of previous transplants, cold ischemia time, and male sex. Among patients with DGF, those with ACEI/ARB therapy had significantly faster graft recovery times. This study draws 2 important conclusions: (1) the early use of ACEIs/ARBs is safe with no compromise of graft function, and (2) patients with DGF might benefit from blockade of the RAS system by shortening the time to graft recovery. An additional finding of the study was that posttransplantation proteinuria was lower among patients with ACEI/ARB therapy.

The benefits of ACEIs and ARBs expand beyond their antihypertensive effects; both classes have been found to improve left ventricular function and LVH associated with hypertensive heart disease.<sup>86-88</sup> Meta-analysis of randomized double-blind studies determined that they reverse LVH to a significantly greater degree than do  $\beta$ -blockers or diuretics.<sup>86</sup> In the Losartan Intervention for Endpoint reduction in hy-

pertension (LIFE) trial, losartan was compared with atenolol in patients with essential hypertension with electrocardiogram evidence of LVH.<sup>89</sup> The study was aimed to establish whether selective blockade of angiotensin II improved LVH by mechanisms beyond reducing BP and, consequently, its ability to reduce cardiovascular morbidity and death. The study showed that losartan, when compared with atenolol, resulted in a significant reduction in the primary end point of cardiovascular morbidity and mortality and a greater reduction in electrocardiographically defined LVH. Losartan was more effective in the prevention of cardiovascular morbidity and death than atenolol for a similar reduction in BP. The atenolol arm was associated with a higher incidence of newly diagnosed diabetes. In studies comparing quinapril with atenolol as the antihypertensive treatment in renal transplant recipients, both agents showed similar positive effects on BP.<sup>90,91</sup> Quinapril was found to reduce albuminuria to a significantly greater degree than atenolol, with no negative effect on graft function. This may suggest a beneficial effect of ACEIs on long-term graft function.

$\beta$ -blockers are known to reduce morbidity and mortality after myocardial infarction and are also of benefit in the management of heart failure not only in the general population but also in patients with kidney disease.<sup>92</sup> These agents could be considered as a possible first-line therapy for posttransplant hypertension in patients with concomitant coronary heart disease. However, in the general population,  $\beta$ -blockers have been found to have an adverse lipid profile (increase triglyceride levels and decreased high-density lipoprotein cholesterol levels), and have been associated with increased risk for new-onset diabetes mellitus.<sup>93,94</sup> This shows a potential limitation in patients receiving CNI, Target of Rapamycin (TOR) inhibitors, and/or corticosteroids because these medications have been associated with both problems.<sup>95</sup> These concerns may be preventing physicians from prescribing these agents. Although evidence from earlier clinical trials justifies some of these concerns, newer third-generation  $\beta$ -blockers (eg, carvedilol) have been shown to have a neutral or positive effect on dyslipidemia and insulin resistance.<sup>96</sup>

## Summary

Arterial hypertension plays a major role in the progression to chronic allograft failure and in morbidity and mortality associated with CVD. Its prevalence varies with the type of immunosuppressive regimen, time after transplantation, and other interacting factors. Although several interventional trials have established the benefits of BP reduction in the general population, large studies are needed in the transplant population. However, in view of reports correlating BP with adverse outcomes after transplantation, it seems reasonable to apply interventions that have proven to reduce CVD in the general population or in other relevant high-risk populations.

Despite the evidence of the adverse effects of hypertension in graft and patient survival, BP control has been poor despite the use of different combinations of antihypertensive medications and different immunosuppressive regimens. It is still

too early to assess the long-term benefits of CNI-free regimens. Steroid-sparing protocols have been shown to improve BP control and reduce cardiovascular risk factors, with low rates of allograft rejection and graft loss, particularly when those regimens use a combination of low-dose CNI plus TOR inhibitors.

Hypertension has not been found consistently to have the same significant association with CVD in the transplant population as in the general population. Lower levels of kidney function and the presence of inflammatory cytokines may be contributing to all-cause mortality and/or CVD. Kidney transplantation may improve BP control, renal function, and anemia—factors that have been associated with the development of LVH in patients with progression of chronic kidney disease.

The diagnosis of hypertension based on office or clinic measurements versus ABPM is still a matter of debate. There is still insufficient evidence whether to recommend ABPM as the best strategy to monitor hypertension and to guide antihypertensive therapy in transplant patients. However, there are specific clinical situations in which ABPM can be recommended.

The available data do not support the recommendation of any class of antihypertensive medications as preferred agents for long-term therapy to slow down the progression of kidney disease. CCB, ACEI, and ARB diuretics, and  $\beta$ -blockers continue to have a role in the antihypertensive armamentarium. Despite the concerns of risk for acute renal failure, hyperkalemia, and posttransplant anemia, ACEIs and ARBs are now considered valuable drugs for the transplant population. However, the ability of ACEIs or ARBs to slow the progression of chronic allograft dysfunction remains unproven at the present time.

## Uncited References

This section comprises references that occur in the Tables but not in the reference list. Please position each reference in the reference list or delete it. Any references not dealt with will be retained in this section: *Nephrol Dial Transplant* 17:1166-1169, 2002 (Oxford University Press); *Hypertension* 42:1050-1065.

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