There is a high incidence of hypertension after kidney transplantation, which has been associated with the development of left ventricular hypertrophy, an increased risk for acute rejection, lower graft survival, and increased mortality. The pathogenesis of post-transplant hypertension is multifactorial, and therefore optimum therapy for it is not clearly defined. Historically, use of renin-angiotensin system (RAS) blockade in post-transplant hypertension has been limited given concerns of inducing worsening allograft function. Recent data demonstrated that subjects with post-transplant hypertension can be treated effectively with RAS blockers, and that these agents may offer significant additional benefits beyond blood pressure control. Review of the literature suggests that RAS blockers should be considered as useful agents for treatment of post-transplant hypertension not due to transplant renal artery stenosis.

Incidence, Prevalence, and Characterization of Post-transplant Hypertension

Despite normalization of renal function and dramatic improvement in volume control with kidney allografting, the prevalence of post-transplant hypertension is high. Poorly controlled blood pressure (BP) is common in both adult [4] and pediatric [5] kidney transplant recipients. The prevalence of post-transplant hypertension reported in the literature varies considerably depending on the study population and the criteria used to define hypertension [3,6]. In adults, the incidence of post-transplant hypertension has been estimated between 60% and 80% [7]. In one prospective study, nearly 75% of subjects with post-transplant hypertension demonstrated absence or reversal of the normal nocturnal fall in BP (ie, nondippers) [7].

Post-transplant hypertension demonstrates a distinctive characteristic on ambulatory BP monitoring: a high prevalence of nocturnal hypertension [7]. In one prospective study, nearly 75% of subjects with post-transplant hypertension demonstrated absence or reversal of the normal nocturnal fall in BP (ie, nondippers) [7]. Additionally, cyclosporine has been implicated as contrib-
Pathogenesis of Post-transplant Hypertension

The exact pathogenesis of post-transplant hypertension is poorly characterized, because multiple factors effect its development. Important associated risk factors include preexisting recipient factors (ie, pre-transplant hypertension), donor-specific factors (ie, hypertension in the donor), common immunosuppressive agents (ie, cyclosporine, tacrolimus, steroids, and sirolimus), extra-allograft–related issues (ie, transplant renal artery stenosis, and non-nephrectomized native kidneys), acute allograft dysfunction (including humoral/antibody–mediated or cellular acute rejection, and/or delayed graft function), and chronic allograft dysfunction (including calcineurin nephropathy, thrombotic microangiopathy, chronic antibody-mediated rejection, and recurrent primary disease) [3,6]. Ultimately, post-transplant hypertension is characterized by sodium retention, enhanced sympathetic nervous system activity, renal vasoconstriction, and relatively lower levels of plasma renin [10].

Of these potential pathogenic etiologies, renal artery stenosis and calcineurin inhibitors warrant further discussion.

Renal artery stenosis

As a cause of post-transplant hypertension, hemodynamically significant renal artery stenosis is thought to be an absolute contraindication to prescribing RAS blockers (ie, angiotensin-converting enzyme [ACE] inhibitors and angiotensin II receptor type 1 blockers [ARBs]). Although stenosis can occur at any time after a transplant, it tends to manifest between 3 and 24 months after engraftment [11].

Calcineurin inhibitors

The two calcineurin inhibitors currently used in transplant nephrology are cyclosporine and tacrolimus. Calcineurin inhibitors lead to the development of hypertension through a variety of mechanisms, including inducing sodium retention, which results in volume expansion [10]; enhancing sympathetic nerve activity; up-regulating intrarenal renin biosynthesis; and inducing vasoconstriction of the preglomerular vasculature [12], related in part to increased release of vasoconstrictor prostaglandins and endothelin, and activation of cytosol calcium. It has been shown that cyclosporine induces renal vasoconstriction, which precedes the development of hypertension [12].

Treatment with cyclosporine leads to overexpression of angiotensin II [13]. Angiotensin II has been shown to increase the synthesis of transforming growth factor (TGF)-β1 [14], which induces interstitial fibrosis and glomerulosclerosis [15]. Importantly, these effects of angiotensin II are mediated through the angiotensin type 1 (AT1) receptor [16], which is inhibited by ARBs.

Impact of Hypertension on Allograft Kidney Function

The precise role of hypertension in allograft outcome has been difficult to define because of the complex interactions between exacerbations of hypertension by worsening allograft function, and the resulting hypertension accelerating the rate of loss of allograft function. Stated more simply, hypertension is both a cause, and a consequence, of kidney disease. Examination of the interaction between hypertension and acute rejection further illustrates this vicious cycle. The presence of post-transplant hypertension is associated with an increased risk for acute rejection [17], and allograft recipients who experience an episode of acute rejection have significantly higher BP than those without rejection [18].

In kidney transplant recipients, hypertension is associated with decreased allograft survival [4,18,19] and the development of left ventricular hypertrophy (LVH), with LVH being an independent risk factor for increased mortality. In addition, the presence of post-transplant hypertension is associated with an increased risk for acute allograft rejection [17] and chronic allograft nephropathy [19].

In a historical cohort study of adult allograft recipients, Mange et al. [20] characterized the relationship between BP and subsequent allograft function. For each 10-mm Hg increment increase in systolic, diastolic, and mean BP, there was a 15%, 27%, and 30% reduction, respectively, in the rate of allograft survival.

Rationale Behind Treatment of Post-transplant Hypertension

Post-transplant hypertension is associated with an increased mortality, chronic allograft nephropathy [19], acute rejection [18], and graft loss [5,19]. It is also an independent risk factor for the development of cardiovascular disease, which is the leading cause of death in kidney transplant patients. The fact that more severe hypertension has been associated with a higher rate of graft dysfunction, worse graft survival, and a higher frequency of proteinuria is suggestive of a causative relationship [8].

In patients with CKD, therapy for hypertension slows the progression of renal insufficiency [21]. Therefore, inductive reasoning would suggest that treatment of post-transplant hypertension might ameliorate these deleterious events. Although the risk of hypertension is well documented, there are few published reports on the management of post-transplant hypertension, either in terms of target BP or choice of individual antihypertensive agents [22].