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# Hypertension in the Kidney Transplant Recipient

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## 1. Introduction

Despite normalization of renal function and improvement in volume control with kidney transplantation, the prevalence of post-transplant hypertension (HTN) is substantial. The prevalence of post-transplant HTN reported in the literature varies considerably depending on the study population and the criteria used to define HTN, although most studies report a prevalence of between 60-80% [1-3]. In one cross-sectional study of 409 adults with stable kidney allograft function, the prevalence of HTN, defined as BP > 150/90 mmHg, was 77.3% [4]. Most subjects (68.9%) required multiple antihypertensive medications. However, for patients with diabetes or estimated GFR below 60 mL/min, treatment guidelines recommend blood pressure (BP) goals below 130/80 mmHg. Applying these more stringent recommendations, the true prevalence of post-transplant HTN is likely in excess of 95%.

## 2. Pathogenesis and impact of immunosuppression

The exact pathogenesis of post-transplant HTN is poorly understood, as multiple factors impact its development. Important risk factors include preexisting recipient factors, donor specific factors, use of immunosuppressive agents, extra-allograft related issues, and both acute and chronic allograft dysfunction [1,2]. Ultimately, post-transplant HTN is characterized by sodium retention, enhanced sympathetic nervous system activity, renal vasoconstriction and relatively lower levels of plasma renin [5].

Post-transplant HTN demonstrates a distinctive characteristic regarding ambulatory BP monitoring, with patients having a high prevalence of nocturnal HTN [3]. In one prospective study, nearly 75% of subjects with post-transplant HTN demonstrated absence or reversal of the normal nocturnal fall in BP (i.e. non-dippers) [3]. In non-kidney transplant recipients, loss of nocturnal dip is associated with left ventricular hypertrophy, lacunar stroke and microalbuminuria [6].

## 3. Role of immunosuppression

Systemic steroid use contributes to the development of post-transplant HTN through various mechanisms, including sodium retention with resultant volume expansion,

decreased prostaglandin biosynthesis, and increased smooth muscle pressor response [9]. In one systematic review comparing post-transplant recipients on immunosuppression regimens containing steroids versus those on steroid-sparing regimens, steroid-attributable incidence of HTN was reported to be between 2 and 17% [10]. A more recent meta-analysis of steroid avoidance or steroid withdrawal protocols examined impact on both graft and cardiovascular outcomes [11]. Steroid avoidance or withdrawal was found to be significantly related to increased risk of acute rejection and elevated creatinine at end of follow-up, with no difference in patient survival, graft loss, or death-censored graft loss. At the same time, steroid avoidance was associated with significant reduction in the risk of cardiovascular risk factors, including a 10% reduction in risk of post-transplant HTN.

However, some evidence indicates that chronic steroid use may not alter BP control. Vincenti and colleagues evaluated one-year outcomes and cardiovascular risk factors in kidney transplant recipients randomized to immunosuppressive regimens with complete steroid avoidance, early steroid withdrawal, and chronic steroid therapy. There was no difference in systolic or diastolic BP between any of the groups and no difference in the percent of patients requiring antihypertensive therapy [12].

Perhaps the most important factor in the pathogenesis of post-transplant HTN is the use of calcineurin inhibitors. Calcineurin inhibitors lead to the development of HTN through a myriad of mechanisms, including sodium retention with resultant volume expansion, enhanced sympathetic nerve activity, up-regulation of intrarenal renin biosynthesis, and vasoconstriction of the preglomerular vasculature via decreased production of vasodilatory factors and increased production of vasoconstrictive factors [5,13-14]. It has been shown that cyclosporine-induced renal vasoconstriction precedes the development of HTN [13]. Additionally, cyclosporine has been implicated as contributing to the loss of the normal nocturnal drop in BP [3].

In recent years, there has been a paradigm shift in the choice of calcineurin inhibitors from cyclosporine to tacrolimus, as short-term patient and graft survival appears to be equivalent between the two [15]. Likewise, the incidence of acute rejection is similar between the two groups when they are used in conjunction with mycophenolate mofetil. The advantage of tacrolimus over cyclosporine is a lower incidence of hyperlipidemia, hirsutism, and gingival hyperplasia. However, a difference between the two agents with regard to HTN is not as clear.

A large multi-center open label randomized controlled trial comparing cyclosporine-based versus tacrolimus-based immunosuppression regimens involving 412 kidney transplant recipients reported that at 3 years post-transplantation, the number of recipients requiring antihypertensive therapy was lower in the tacrolimus group, though this did not reach statistical significance (74.7% vs. 84.9%,  $p = 0.06$ ) [16]. Another cross-sectional study evaluating predictors of post-transplant HTN, defined as documented diagnosis of HTN or use of antihypertensive medications, determined that significantly more patients on a cyclosporine-based regimen were prescribed 2 or more antihypertensive medications compared with those on a tacrolimus-based regimen [17].

There has been interest in the use of a mammalian-target of rapamycin (m-TOR) inhibitor-based immunosuppression regimen as an alternative to calcineurin inhibitor-based regimens, partially due to concerns over long-term effects of calcineurin-induced HTN and chronic preglomerular vasoconstriction. Thus far, the data regarding the relationship between m-TOR inhibitor use and HTN have been mixed. Comparison of a small cohort of patients on tacrolimus-based vs. sirolimus-based immunosuppression demonstrated that

patients receiving sirolimus had significantly lower systolic BP on 24-hour ambulatory BP monitoring, though there was no significant difference in preserved nocturnal drop in BP [18].

However, two large randomized controlled trials evaluating the conversion of kidney transplant recipients from cyclosporine to sirolimus demonstrated no difference in BP [19-20]. The CONCEPT study, evaluating efficacy of conversion from cyclosporin to sirolimus 3-months post-transplantation in 237 kidney transplant recipients demonstrated no difference in systolic or diastolic BP one year post-transplantation [20]. There was, however, a tendency toward no need of antihypertensive medications in the sirolimus group compared to the cyclosporine group (51% vs. 38%), though this was not statistically significant. The CONVERT study, which followed a cohort of 830 subjects randomized to either sirolimus conversion or continuation of calcineurin inhibitor, found a statistically significant decrease in systolic BP at one month and in diastolic BP up to three months post-conversion [19]. However, by study endpoint two years, there was no significant difference in systolic or diastolic BP between the groups.

#### 4. Renal artery stenosis

Transplant renal artery stenosis (tRAS) is a potentially important contributor to refractory HTN and unexplained graft dysfunction. The incidence of tRAS has been reported to range from 1 to 23%, with most of this variance attributed to differences in definition and diagnostic technique employed [21]. Most episodes of tRAS in the first three post-operative months are attributed to surgical complications, such as donor vessel trauma, intra-operative kidney malpositioning, or stenosis at the surgical anastomosis [22]. Transplant RAS occurring greater than 3 months post-transplantation is rarely related to surgical complications.

Several risk factors have been implicated in the development of late tRAS, including graft rejection, CMV infection, prolonged cold ischemia time, delayed graft function, and pediatric donor source [22-26]. A recent case-control study of 29 transplant recipients with tRAS found that CMV infection was associated with a five-fold increase in the risk for tRAS, while DGF increased tRAS risk four-fold [22].

Doppler ultrasonography may be an appropriate first-line screening test for tRAS, as it is non-invasive and avoids exposure to iodinated contrast media [21]. Sensitivity and specificity have been reported as high as 94% and 100%, respectively [27]. However, this diagnostic test is very operator-dependent, and such impressive results may not be obtained in centers without strong experience in kidney transplant imaging. Ultimately, the gold standard remains angiography.

Therapeutic options for tRAS include conservative management, angioplasty with or without stenting, and surgical repair. A recent case series compared the outcomes of these three strategies and determined that the highest success rate, defined as improvement in graft function, occurred in those who underwent primary angioplasty (36% conservative therapy, 82% angioplasty, 44% surgery) [28]. Graft survival at five years post-transplantation was also highest in the primary angioplasty group (63% conservative therapy, 86% angioplasty, 65% surgery). The primary angioplasty cohort was the only group in which a sustained improvement in BP was observed, with 63% of participants in this subgroup reaching target BP with a single agent post-procedure. However, angioplasty is not without risks. Four participants (6%) who underwent initial angioplasty had to undergo

a transplant nephrectomy due to post-intervention complications, specifically uncontrolled bleeding and/or thrombosis. Furthermore, the presence of large or multiple stenoses may not be appropriate for primary angioplasty, leaving surgical intervention as the only viable option.

Another case-controlled series of patients evaluated the efficacy of angioplasty with or without stenting in participants with tRAS [22]. Both serum creatinine and BP control improved significantly post-procedure. Restenosis occurred in 27% of patients at a mean time of 26 months post-procedure, and 10% experienced immediate graft loss due to procedural complications.

Transplant RAS is an important entity to consider in subjects with new-onset or refractory HTN. It can be effectively treated in most cases with angioplasty, which appears to impact positively on graft function and potentially prolonging allograft life.

## 5. Outcomes

The precise role of HTN on allograft outcome has been difficult to define due to the complex interactions between HTN and worsening allograft function. Hypertension is both a cause and consequence of kidney disease. The presence of post-transplant HTN is associated with an increased risk for acute rejection, and allograft recipients who experience an episode of acute rejection have a significantly higher BP than those without rejection [29-30]. In a historical cohort study of adult allograft recipients, Mange and colleagues characterized the relationship between BP and subsequent allograft function [31]. 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. Another cohort study by Opelz and colleagues demonstrated that systolic BP greater than 140 mmHg was associated with increased risk of graft failure, regardless of diastolic BP or history of acute rejection [32].

Post-transplant HTN is associated with increased mortality, chronic allograft nephropathy, acute rejection, and graft loss [7,30,32]. It is also an independent risk factor for the development of cardiovascular disease, the leading cause of death in kidney transplant recipients. The fact that more severe HTN 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].

## 6. Antihypertensive therapy

In patients with chronic kidney disease (CKD), therapy for HTN slows the progression of renal insufficiency [33]. This suggests that treatment of post-transplant HTN may likewise ameliorate the loss of allograft function. Current KDOQI guidelines recommend kidney transplant recipients maintain a target BP < 130/80, largely based on extrapolation from outcomes data in CKD patients [34]. Due to various contributing factors, post-transplantation HTN can be difficult to control. Multiple retrospective cohort analyses report a significant proportion of subjects fail to reach target BP, even with use of multiple anti-hypertensive agents. A review of the Collaborative Transplant Study, a database involving nearly 30,000 chronic transplant recipients at 400 international transplant centers, demonstrated that only 44.5% achieved systolic BP < 140 mmHg and that 24.5% achieved systolic BP < 130mmHg [32]. A smaller cohort study of 150 transplant recipients demonstrated that over 60% of patients required three or more anti-hypertensive

medications and that only 40% reached the target BP of < 130/80 mmHg [35]. Although the risk of HTN is well documented, there are few published reports on the management of post-transplant HTN that clearly elucidate ideal target BP or choice of individual antihypertensive agents [22].

## 7. Calcium channel blockers

Calcium channel blockers (CCB) are effective medications to lower BP in kidney transplant recipients. In the general population, they have proven to be robust agents to lower BP regardless of age, gender, ethnicity, and salt intake, which may explain why they are also effective in the kidney transplant population (36). In addition, they also appear to reverse some of the intra-renal vasoconstriction caused by calcineurin inhibitors (36-38). One trial of 65 transplant recipients receiving cyclosporine-based immunosuppression randomized to the CCB or placebo at the time of transplantation demonstrated that those taking felodipine had a significantly higher renal plasma flow at 6 weeks [39]. Additionally, those randomized to the felodipine also group had lower systolic and diastolic BP, higher renal plasma flow, and higher GFR (49ml/min vs. 40ml/min,  $p = 0.05$ ) at 12 weeks post-transplantation, despite a greater proportion of patients in the placebo group receiving other anti-hypertensive agents.

In a study of 123 immediate post-transplant recipients, subjects were randomized to nifedipine (CCB) or lisinopril as first line maintenance BP medication [40]. At three months post-transplantation 20% of all participants had achieved a goal diastolic BP of < 95 mmHg, with 38% in the CCB group reaching diastolic BP goal at one year. There was no difference in BP response between groups, but patients randomized to nifedipine had higher hemoglobin and lower creatinine levels compared to the lisinopril group at the study end. In an additional study comparing nifedipine and lisinopril, impact on left ventricular mass and function was assessed [41]. This study demonstrated that myocardial mass was significantly reduced in both groups one year post-transplantation, with a mean reduction of 15% in both groups. There was no statistically significant between-groups difference. The percentage of participants with persistent left ventricular hypertrophy (LVH) one year post-transplantation was similar between groups (45% nifedipine, 41% lisinopril  $p = NS$ ). Another study of 99 kidney transplant recipients one year post-transplantation randomized subjects to 1 of 3 groups: (i) amlodipine (CCB) monotherapy, (ii) enalapril monotherapy, or (iii) combination amlodipine and enalapril [42]. At six months post-randomization, there was no difference amongst the three groups in terms of systolic BP or number of antihypertensive agents used. However, participants assigned to amlodipine monotherapy demonstrated improved creatinine clearance but no change in proteinuria, as compared with either angiotensin converting enzyme (ACE)-inhibitor monotherapy or combination. Results of this study should be interpreted with some caution, as they did not reach the target number of participants for adequate power.

A recent meta-analysis of randomized controlled trials involving antihypertensive agent use in renal transplant recipients was conducted [43]. This analysis concluded that use of a CCB versus placebo did not reduce the risk of death but did reduce the risk of graft lost by 25% at 12-months post-transplantation. Additionally, subjects receiving CCB had significantly higher estimated glomerular filtration rate (eGFR). When compared to ACE-inhibition. There was no difference detected in death, graft loss, or cardiovascular event risk.

## 8. Renin-angiotensin system blockade

Use of renin-angiotensin system (RAS) blockers in kidney transplant recipients was initially limited due to a number of concerns, including ineffectiveness in BP control, potential exacerbation of anemia, potential for inducing hyperkalemia, and the risk of precipitating acute kidney injury, [44-46]. The concern for ineffective BP control with renin-angiotensin blockade was related to the fact that post-transplant HTN, characterized by a low renin, volume expanded state, has been compared with the Goldblatt single-kidney, one-clip model of HTN, which potentially would not be very responsive to these agents [47]. However, this concern has not been borne out clinically, as multiple studies have demonstrated that RAS blockers have efficacy in reducing BP in post-transplant HTN [48].

Renin-angiotensin system blockade has now become commonplace in many transplant centers. Before 1990, approximately 9% of post-transplant subjects received treatment with an ACE inhibitor, which increased to roughly 47% in 2003 [49]. In the same retrospective review, only 38.5% (781 subjects) had never received an ACE inhibitor or an angiotensin receptor blocker (ARB). Six-hundred thirty eight subjects (31.4%) used ACE inhibitor or ARB therapy for the entirety of their follow-up, and 612 subjects (30.1%) received this therapy during various times of follow-up [49].

Furthermore, there are multiple theoretical benefits supporting the use of RAS blockers in the treatment of post-transplant HTN, such as (i) decreasing intraglomerular capillary pressure, (ii) decreasing the production and expression of the potentially damaging growth factors, (iii) decreasing proteinuria, (iv) for primary and secondary prevention of adverse cardiovascular outcomes, (v) decreasing cyclosporine nephrotoxicity, and (vi) blocking angiotensin type 1 (AT<sub>1</sub>) receptor antibodies that may be associated with vascular rejection [50-51]. In the general population, RAS blockers have been shown to reduce both primary and secondary cardiovascular events [52]. Despite these theoretical benefits for their RAS blocker use, there are no prospective studies demonstrating the advantage of RAS blockers for the protection against allograft loss or for prolonging patient survival.

The largest study to date that has evaluated the efficacy of a RAS blocker is the SECRET trial, a multi-center double-blind randomized placebo-controlled trial involving 500 participants from several transplant centers in Europe [53]. This trial was designed to evaluate the effects of Candesartan (ARB) therapy compared with placebo, on mortality, cardiovascular events, and graft failure. The study was discontinued prematurely due to a lower than expected event rate in both groups, which precluded conclusions regarding the primary endpoints. However, analysis of secondary endpoints revealed that reductions in BP and proteinuria were greater in the ARB group, but this was associated with a decrease in creatinine clearance and hemoglobin. There was no significant difference in cardiovascular or graft outcomes between the two groups, though the overall event rate was quite low (5.1% with candesartan vs. 5.3% with placebo).

A much smaller study involving fifty recipients of living unrelated kidney transplants at least six months prior to enrollment were randomized to losartan (ARB) 50 mg daily or placebo for one year [54]. Of note, the subjects were not proteinuric at randomization. There was no difference in number of antihypertensives prescribed between the two groups and no difference in creatinine clearance at study end. However, systolic BP was significantly lower in the ARB group at 12 months (113mmHg vs. 126mmHg).

Although insufficient data exist to determine the impact of RAS blockade on overall cardiovascular outcomes, a small study has evaluated the impact of ACE inhibitor therapy

on echocardiographic findings [55]. Evaluation of 74 transplant recipients randomized to lisinopril (ACE) or placebo and followed for 18 months demonstrated a significant decrease in left ventricular mass index in the ACE group while no difference was observed in the placebo group. There was no difference between the groups in terms of systolic BP, serum creatinine, urinary protein excretion, or number of antihypertensive agents used. The decrease in left ventricular mass index was observed exclusively in those concomitantly treated with ACE and cyclosporine, as opposed to tacrolimus. This small study is one more piece of evidence corroborating data from the general population, suggesting that drugs that block the RAS are capable of regressing left ventricular hypertrophy, both as part of their hemodynamic effect, but also through BP independent mechanisms. It is likely that regression of LVH may be a beneficial prognostic event that patients achieve with an appropriate BP control and an optimal class of antihypertensive therapy, with a potential for reducing adverse cardiovascular events. This study parallels efforts in older trials in the general population, illustrating the advantages of a RAS blocking drugs in the reduction of proteinuria and the risk for cardiovascular events and renal disease progression. Sadly, compelling data are still lacking in the kidney transplant population.

Although the number of randomized controlled trials regarding RAS blockade in transplant recipients has increased in recent years, much of the available data are from retrospective studies and systematic reviews. In one retrospective review of more than 2,000 recipients of kidney transplants at the University of Vienna, investigators noted that the ten-year patient survival rates were 74% in patients receiving either an ACE inhibitor or an ARB as part of their antihypertensive regimen and only 53% in patients not receiving these agents (49). Their results were even more remarkable when one considers that the group receiving the RAS blockers were older, required a higher number of antihypertensive medications, and were more likely to have type 2 diabetes and evident cardiovascular disease, when compared to the group not receiving these agents. Although selection bias limits the power of this study, the data are intriguing and suggest that there may be an important advantage to employ RAS blocking drugs as part of an antihypertensive regimen in an effort to reduce cardiovascular events.

Heinze and colleagues (49), studied 436 kidney transplant recipients who had delayed graft function. Approximately half of those patients (n=181) were given either an ACE inhibitor or ARB at the time of transplantation. Those patients who received RAS blocker had improved ten-year graft survival, when compared to those who were not treated with RAS blockers (44% vs. 32%, respectively). Hiremath and colleagues (56) performed a systematic review of 21 randomized trials of 1,549 patients to determine the effect of ACE inhibitor or ARBs on graft function and patient survival after kidney transplantation. In this analysis, drugs that block the RAS were associated with a significant decrease in GFR (-5.8 mL/min), proteinuria (-470 mg/day), and hematocrit (-3.5%)(51,57). However, there was insufficient data to determine their impact on patient or graft survival. Authors suggested that there may be a trade off between the beneficial effects of proteinuria reduction and potential cardiac protection with the development of possible anemia and lowered GFR.

## 9. Beta-blockade

Since kidney transplant patients are at much greater risk for cardiovascular events compared to the general population (58), due to both traditional and non-traditional Framingham Heart Study risk factors, beta-blocker use is often advisable. This may be

important both during the peri-operative period to protect against myocardial ischemia, but also in the long-term management of HTN and cardiovascular disease. However, these agents have not been extensively studied. A recent meta-analysis of randomized controlled trials involving antihypertensive therapy in renal transplant recipients identified four studies involving beta-blockers [43]. Currently, there is insufficient data to determine relative benefits and harms of these agents. However, data from these studies indicate that beta-blockers are effective in BP reduction without appreciable impact on renal function, proteinuria, or left ventricular mass [59-61].

## 10. Alpha-blockers

In addition to their antihypertensive effects, alpha-blockers are often used to facilitate prostatic relaxation. This is particularly important in many older patients who may have occult prostatic hypertrophy, or some degree of bladder detrusor neuropathy due to diabetes. However, these agents, in general, tend to cause significant orthostatic symptoms, and have not been proven to reduce mortality (62). Both doxazosin and prazosin have been shown to decrease HTN in transplant recipients, although the literature remains sparse (63-64).

## 11. Conclusion

Taken together, the clinical trials of antihypertensive therapeutics in kidney transplant subjects illustrates that BP can be controlled. However, it usually requires multiple drugs. Although the data is not definitive, it appears that CCB and or RAS blockers should be included in an effective antihypertensive regimen. Subjects at risk for, or who have known coronary disease, may also derive benefit from beta-blockers. More studies are needed to define optimal levels of BP control and ideal combination of agents to facilitate better long-term patient and graft survival in kidney transplant recipients.

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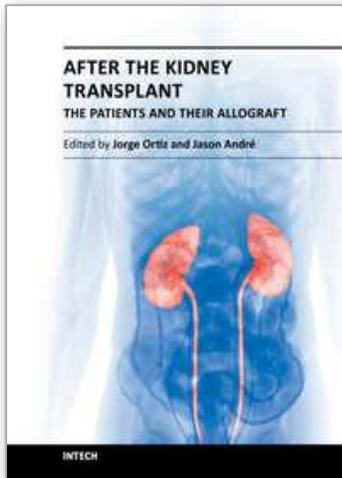
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## **After the Kidney Transplant - The Patients and Their Allograft**

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There are many obstacles in kidney transplantation. For the transplant team, there is the balance between immunosuppression to aid in the recipient's tolerance of the allograft and the infection risk of a suppressed immune system. These potential long term complications of kidney transplantation are relatively well known, but there are many other complications that patients and families do not consider when preparing themselves for a kidney transplant. Although the benefits of attempting a kidney transplant far outweigh downfalls of the long term sequelae, kidney transplantation is by no means a benign procedure. It is the hope of these authors that the reader will leave with a sense of understanding towards the kidney recipients.

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