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WORD COUNT	4476	TIME SUBMITTED	26-JUL-2022 09:47AM
		PAPER ID	88812592

Name of Journal: *World Journal of Transplantation*

Manuscript NO: 77440

Manuscript Type: REVIEW

Hypertension in kidney transplant recipients

Alexandrou ME *et al*. Hypertension in KTRs

Abstract

Kidney transplantation is considered the treatment of choice for end-stage kidney disease patients. However, the residual cardiovascular risk remains significantly higher in kidney transplant recipients (KTRs) than in general population. Hypertension is highly prevalent in KTRs and represents a major modifiable risk factor associated with adverse cardiovascular outcomes and reduced patient and graft survival. Proper definition of hypertension and recognition of special phenotypes and abnormal diurnal blood pressure (BP) patterns is crucial for adequate BP control. Misclassification by office BP is commonly encountered in these patients and a high proportion of masked and uncontrolled hypertension, as well as white-coat hypertension, has been revealed in these patients with the use of ambulatory BP monitoring (ABPM). The pathophysiology of hypertension in KTRs is multifactorial, involving traditional risk factors, factors related to chronic kidney disease (CKD) and factors related to the transplantation procedure. In the absence of evidence from large-scale randomized controlled trials in this population, BP targets for hypertension management in KTR have been extrapolated from CKD populations. The most recent Kidney Disease Improving Global Outcomes 2021 guidelines recommend lowering BP to less than 130/80 mmHg using standardized BP office measurements. Dihydropyridine calcium channel blockers (CCBs) and angiotensin-converting enzyme inhibitors (ACEis)/angiotensin-II receptor blockers have been established as the preferred first-line agents, on the basis of emphasis placed on their favorable outcomes on graft survival. The aim of this review is to provide previous and recent evidence on prevalence, accurate diagnosis, pathophysiology and treatment of hypertension in KTRs.

Key Words: Hypertension; Kidney transplantation; Epidemiology; Diagnosis; Physiopathology; Therapy

Alexandrou ME, Ferro CJ, Boletis I, Papagianni A, Sarafidis PA. Hypertension in kidney transplant recipients. *World J Transplant* 2022; In press

Core Tip: Kidney transplantation is considered the treatment of choice for end-stage kidney disease patients. However, the residual cardiovascular risk remains significantly higher in kidney transplant recipients (KTRs) than in general population. This article summarizes available evidence on prevalence, abnormal blood pressure phenotypes and diurnal patterns, as well as on the association of hypertension with target organ damage and clinical outcomes in kidney transplantation. The complex pathophysiology, treatment goals and recent data on therapeutic options for management of hypertension in KTRs are also discussed.

INTRODUCTION

Kidney transplantation is considered the optimal choice for renal replacement therapy in end-stage kidney disease due to improved survival and quality of life compared to dialysis modalities; this survival benefit has been attributed to kidney function improvement and delay of progression of cardiovascular disease (CVD)[1]. Nevertheless, CVD remains the leading cause of death in these patients in the early (< 10) post-transplant years[2]. Among traditional CVD risk factors, hypertension represents the most prominent comorbidity post transplantation, and a major cause of allograft dysfunction and adverse patient outcomes[3]. The diagnosis and treatment of hypertension in kidney transplantation has been traditionally based on office blood pressure (BP) measurements; BP control therefore remains suboptimal due to high rates of resistant and masked hypertension and abnormal diurnal BP patterns[4]. Controversies over BP targets and optimal antihypertensive regimen remain unresolved and should be further explored in well-designed randomized clinical trials (RCTs) in order to optimize hypertension management in this population.

EPIDEMIOLOGY OF HYPERTENSION IN KIDNEY TRANSPLANT RECIPIENTS

Prevalence of hypertension and abnormal BP phenotypes by the various metrics and definitions

The prevalence of hypertension is particularly high among kidney transplant recipients (KTRs) with previously reported rates between 70%-90%[5], and more recently even exceeding 95% of this population[6]. The source of variability in estimates of prevalence, control and different phenotypes of hypertension among KTRs is attributed to differences in the definitions used for hypertension diagnosis and in the type of BP measurement used (in office *vs* out-of-office setting) across various studies. Defining the diagnostic threshold for hypertension based on office and ambulatory BP measurements has been a matter of intense debate in chronic kidney disease (CKD) patients and more specifically in KTRs[7], with the two major existing hypertension guidelines producing confusion[8]. The cut-off values for hypertension diagnosis proposed by the 2017 American College of Cardiology/American Heart Association (ACC/AHA) guidelines for office and ambulatory BP monitoring (ABPM) measurements were ≥ 130/80 mmHg and ≥ 125/75 mmHg respectively[9] (Table 1), while those proposed by the 2018 European Society of Cardiology/European Society of Hypertension (ESC/ESH) guidelines were office BP ≥ 140/90 mmHg and ABPM ≥ 130/80 mmHg[10]. In the more recent 2021 Kidney Disease Improving Global Outcomes (KDIGO) BP guidelines (Table 1), hypertension was defined as office BP ≥ 130/80 mmHg and ABPM ≥ 125/75 mmHg[11], in agreement the 2017 ACC/AHA guidelines. Taking into consideration all the above, studies assessing the epidemiology of hypertension have previously reported presence of this disease in > 80% of patients based on the office 140/90 mmHg cut-off value[12], and in 89.5% based on the office 130/80 mmHg cut-off value, with control rates among hypertensive subjects at 45.5%[13]. The prevalence of resistant hypertension in this population (office BP ≥ 130/80 mmHg) has been previously reported in 17.5%[13] and 23.5%[14] of patients, despite intake of ≥ 1 and ≥ 3 antihypertensive drugs respectively.

Recent guidelines recommend the use of out-of-office BP measurements as a complementary tool for improving the management of hypertension. In KTRs the wider use of ABPM has led to the recognition of abnormal diurnal BP patterns and BP phenotypes[11,15]. The rates of non-dipping status have been reported to range between

36%-95%[16-18], and that of nocturnal hypertension between 69%-77% (according to the nighttime ABPM > 120/70 mmHg cut-off value for both)[18,19]. In an Italian cohort of 260 KTRs followed-up for 3.9 years, the agreement between 785 paired office and 24-ABPM measurements was assessed revealing significant discordance in 37% of all visits (κ-statistics = 0.25, indicating poor agreement)[19]. In 12% of all visits, patients were misclassified as hypertensive according to the office BP > 140/90 mmHg criterion while 24-ABPM was normal according to the < 130/80 mmHg criterion (white-coat hypertension); in 25% of all visits patients were classified as normotensive according to the office criterion, while 24-h ABPM was > 130/80 mmHg (masked hypertension). In a cross-sectional study from Spain with 868 KTRs, the prevalence of white-coat and masked hypertension was 12% and 20% respectively, applying similarly the ESC/ESH criteria[14]. Absence of SBP dipping pattern was evidenced in 80% of patients. In a retrospective study, prevalence of white-coat and masked hypertension was estimated to be at 3% and 56%, respectively with the office BP ≥ 130/80 mmHg and ABPM ≥ 125/75 mmHg thresholds[20].

In a recently published cross-sectional study with 205 KTRs[6], the prevalence of hypertension and the diagnostic performance of the two existing office BP thresholds for defining hypertension (adopted by the ESC/ESH and ACC/AHA guidelines mentioned above) was comparatively assessed. Prevalence of hypertension was 88.3% and 92.7% according to the ESC/ESH with ACC/AHA definitions for office BP measurements and 94.1% and 98.5% according to the respective ABPM thresholds. Moderate to fair agreement between office BP and 24-h ABPM was shown for both thresholds (κ-statistics = 0.52, $P < 0.001$; κ-statistics = 0.32, $P < 0.001$, respectively). Prevalence of white coat and masked hypertension was 6.7% and 39.5% using the office BP ≥ 140/90 mmHg, and 5.9% and 31.7% using the office BP ≥ 130/80 mmHg threshold. Notably, ABPM revealed significantly lower control rates among hypertensive patients compared to office BP measurements using both definitions (69.6% for office *vs* 38.3% for ABPM measurements with the ESC/ESH thresholds; 43.7% *vs* 21.3% respectively with ACC/AHA thresholds). In a sub-analysis of this study investigating presence of

sex differences, the prevalence of hypertension was similar between the two genders with the office BP ≥ 130/80 mmHg threshold (93.4% for men *vs* 91.3% for women, P = 0.589), but significantly higher in men with the ABPM ≥ 125/75 criterion (100% *vs* 95.7%, P = 0.014, respectively). Prevalence of white-coat hypertension (5.1% *vs* 7.6%, P = 0.493) and masked hypertension (35.3% *vs* 24.2%, P = 0.113) did not differ significantly between men and women. The above findings underline the need for more extensive use of 24-ABPM in KTRs, similarly to what is currently being increasingly recommended for the general population.

Association of hypertension with target organ damage

In KTRs, abnormal dipping status (non-dipping and reverse-dipping) independently predicts kidney function deterioration[21,22], while nighttime BP and night-day ratio are strongly associated with carotid-intimal media thickness (cIMT)[18]. Increased urinary albumin and protein excretion have been associated with hypertension in KTRs[23] and are both independent predictors of graft loss[24-26]. Several longitudinal studies have reported an association of hypertension with left ventricular hypertrophy (LVH) in KTRs, while significant reduction in left ventricular mass index (LVMI) and regression of LVH have been observed in the first 2-3 years following kidney transplantation[27,28]. However, this regression may be compromised by persistence of hypertension, high pulse pressure[27] and high sodium intake[28]. Moreover, reversion of uremic cardiomyopathy has been recently questioned according to the results of a recent meta-analysis where no difference in LVMI was detected following kidney transplantation after pooling data from 4 studies with 236 participants [standardized mean difference 0.07, 95% confidence interval (CI): 0.41-0.26][29]. Masked or sustained hypertension were independent predictors for LVH in a cohort of 221 children and young adults with kidney transplant[30]. A negative association between brachial flow-mediated dilation (FMD), a marker of endothelial function, with 24-h BP and indices of BP variability has also been reported[31]. In a recently published meta-analysis pooling data from 22 studies (2078 participants), 24-h ABPM was found to be a stronger predictor of renal

function decline and outperformed office BP with regards to LVMI, cIMT and endothelial dysfunction markers[32]. Abnormal dipping status also identified a subgroup of KTRs at risk for target organ damage.

Prognostic impact of hypertension for adverse clinical outcomes

Hypertension in KTRs has been consistently shown to be associated with a higher incidence of kidney function decline, poor graft survival[3,33-38], and worse patient survival[3,34,38,39]. In the Collaborative Transplant Study, a retrospective cohort that evaluated the impact of hypertension on long-term kidney function in 29751 KTRs, a strong graded relationship between post-transplant BP and subsequent graft failure even when patient death was censored, was reported for the first time[35]. In a subsequent sub-analysis of the Collaborative Transplant Study with data from 24404 patients, the same authors showed that SBP values consistently lower than 140 mmHg during the first 3 years post transplantation were associated with the best 10-year graft and patient outcomes; moreover successfully lowering SBP to ≤ 140 mmHg even by the third year was associated with better 10-year graft and death-censored survival (but not with total patient survival) compared to persistently uncontrolled BP[3]. With regards to different causes of death, changes in SBP were significantly associated with the risk of cardiovascular death only in the subgroup of patients < 50 years old but not in older KTRs. In another retrospective cohort of 1666 patients, each rise in SBP by 10 mmHg was associated with a 12% higher risk for graft failure [relative risk (RR) = 1.12, 95%CI: 1.08-1.15], a 17% higher risk for death-censored graft failure (RR = 1.17, 95%CI: 1.12-1.22) and a 18% higher risk for death (RR = 1.18, 95%CI: 1.12-1.23), even after adjusting for acute rejection and decreased kidney failure that were previously reported to trigger BP rises, and therefore further supported the independent beneficial effect of BP control[34]. Microalbuminuria and macroalbuminuria, both markers of target organ damage associated with hypertension, have been similarly shown to be independent predictors of death compared to normoalbuminuria [odds ratio (OR) = 5.55, 95%CI: 2.43-12.66; OR = 4.12, 95%CI: 1.65-10.29, respectively][25].

With regards to specific cardiovascular events in KTRs, their burden remains high, a fact that is partly attributed to accumulation of traditional cardiovascular risk factors[40]. In a French retrospective cohort of 17526 KTRs and 3288857 non-transplanted non-dialysis participants with a 5-year follow-up, an increased incidence of myocardial infarction (MI) in the former compared to the latter (5.8% *vs* 2.8%) was shown [hazard ratio (HR) = 1.45, 95%CI: 1.35-1.55][41]. KTRs experiencing an MI were more likely to be hypertensive than their non-KTRs counterparts (76.0% *vs* 48.1%, $P < 0.0001$). Hypertension is an independent predictor of death from ischemic heart disease (IHD) and major ischemic heart events, with a reported increase by 20% in the risk for death from IHD per 10 mmHg SBP increments, during a follow-up of 5 years[39].

PATHOPHYSIOLOGY OF HYPERTENSION IN KTRS

The underlying mechanisms for development of hypertension in KTR include: (1) Traditional risk factors; (2) Those that are associated with kidney function decline; and (3) Those that are related to the kidney transplantation procedure.

Traditional risk factors

Factors considered to be associated with an increased risk of hypertension in the general population, including age, male sex, smoking status, obesity, insulin resistance, and syndrome of obstructive sleep apneas, are also present in patients undergoing kidney transplantation and may be even aggravated, further contributing to new-onset or worsening hypertension[42-46].

Factors associated with impaired kidney function

The same risk factors that are present in CKD populations and are inherent to kidney function decline are also applicable in KTRs. Among those, impaired homeostatic mechanisms handling sodium and water excretion are considered a hallmark of CKD, leading to extracellular volume accumulation, hypervolemia and increased BP[5,47]. Renal sodium retention may be even worsened by the use of immunosuppressive

regimens, mainly corticosteroids[48] and calcineurin inhibitors (CNIs)[49], as well as during episodes of acute rejection, probably indicating ischemic allograft damage[50]. Dysregulation of the renin-angiotensin-aldosterone system (RAAS)[51] and sympathetic nerve overactivity, driven in the early post transplantation period by the native kidneys (since the graft is initially denervated before becoming later re-innervated[52]), also lead to increased peripheral vascular resistance and development of hypertension[5,53,54]. Increased arterial stiffness, endothelial dysfunction and imbalance between vasoconstrictive and vasodilating agents are also pertinent to CKD and further contribute to increased BP[55,56].

Factors associated with kidney transplantation

Immunosuppressive regimens: Most current protocols for prevention of transplant rejection include as maintenance therapy a combination of a CNI (cyclosporine or tacrolimus) with either a purine pathway inhibitor that subsequently blocks lymphocyte proliferation (mycophenolate mofetil or azathioprine), or a mammalian target of rapamycin (mTOR) inhibitor (everolimus or sirolimus), with or without corticosteroids[57]. While mycophenolate mofetil and mTOR inhibitors are considered low risk agents, corticosteroids and CNIs potentially trigger hypertension and other major comorbidities in KTRs[58,57].

The burden of long-term corticosteroid exposure on corticosteroid-related adverse events and healthcare economic costs has been previously explored in the general population, as well as in KTRs, with prevalence of corticosteroid-induced hypertension estimated to exceed 30% of the total population[59], and hospitalization costs to be 2.2-fold higher in the steroid-maintenance group than in the steroid-free group one-year post living-donor kidney transplantation[60]. According to the results of a meta-analysis (34 studies, 5637 patients), complete steroids avoidance or withdrawal reduces the risk of incident hypertension and diabetes with no significant effect on graft or patient survival[61]. The main cause of corticosteroid-induced hypertension is associated with partial activation of mineralocorticoid receptors by cortisol causing urinary sodium and

water retention and therefore volume expansion[5]. This mechanism has been however called into question and a similarly important role of glucocorticoid receptors in vascular smooth cells has been proposed[62], leading to an increase in peripheral vascular resistance through attenuation of vascular response to vasodilators (nitric oxide) and upregulation of the angiotensin II receptor[48]. The mechanisms of CNI-induced hypertension are multifactorial and involve impaired sodium and water excretion, upregulation of vasoconstrictive agents (prostaglandins, thromboxane, endothelin-1), downregulation of vasodilating prostaglandins, and alterations in regulation of intracellular calcium ions, leading to vasoconstriction of afferent arteriole, a decrease in glomerular filtration rate (GFR) and an increase in peripheral vascular resistance[49,63-66]. Tacrolimus has been associated with a lower incidence of hypertension[67,68], but a higher risk for new onset diabetes compared to cyclosporine[69,70]. After complete withdrawal of CNIs was abandoned due to an increased risk of biopsy-proven acute rejection episodes[71], reduction of their dose was explored in an attempt to minimize their toxic effects. In an open-label RCT, 1645 KTRs were randomly allocated to receive standard-dose cyclosporine (target trough level 150-300 ng/mL for the first 3 mo; 100-200 ng/mL thereafter), low-dose cyclosporine (target trough level 50-100 ng/mL throughout the study), low-dose tacrolimus (target trough level 3-7 ng/mL throughout the study), or low-dose sirolimus (target trough level 4-8 ng/mL throughout the study) for 12 mo[72]. Patients in all treatment groups received mycophenolate mofetil and corticosteroids; those randomized to low dose regimens followed a 2-mo induction treatment with daclizumab. At study-end, patients in the low-dose tacrolimus group had the highest estimated GFR (eGFR) (65.4 mL/min) and highest rates of allograft survival (94.2%), followed by low-dose cyclosporine (93.1%), standard-dose cyclosporine (89.3%) and low-dose sirolimus (89.3%) (P = 0.02), therefore providing further evidence in favor of low-dose tacrolimus regimens. Accordingly, it is usually recommended to use minimal dosages of steroids (for example, 5 mg per day dose of prednisone) to achieve long-term immunosuppression in organ transplant patients without increasing the risk for hypertension[42]. Belatacept is another biologic

immunosuppressive agent that acts by inhibiting T-cell co-stimulation, approved by the United States Food and Drug Administration since 2011 on the basis of evidence of non-inferiority in preventing acute rejection in KTRs provided from three RCTs comparing belatacept to cyclosporine[69,73,74]. According to a meta-analysis (5 studies, 1535 participants) use of belatacept has been associated with lower BP levels and reduced incidence of chronic kidney scarring compared to CNIs[75].

Donor/recipient factors: Donor's age represents a major risk factor for development of post-transplant hypertension[23], along with considerable discrepancies in somatometric characteristics between donors and graft recipients (female to male transplantation, pediatric to adult transplantation, low donor/recipient body weight ratio), leading to a phenomenon of "underdosing" due to reduced donor nephron mass compared to recipient needs[76,77]. These differences result in hyperfiltration, glomerular hypertrophy and increased intraglomerular pressure. Pre-existing donor hypertension is also associated with an increased risk for post transplantation hypertension and allograft dysfunction[23,78]. Transplant recipients from donors with a family history of hypertension face a 10-fold higher risk of requiring antihypertensive treatment compared to recipients from a normotensive family[79]. Recipients of transplants from expanded criteria donors (age > 60 or 50-59 with two of the following: History of hypertension; serum creatinine > 1.5 mg/dL; cerebrovascular death) also experience a higher risk for hypertension post transplantation[80]. Other factors related to donors, predisposing to delayed graft function and increased nephrotoxicity, that could be possibly associated with development of hypertension in KTRs include the presence of genetic variants that affect the expression of cytochrome P450 3A5, apolipoprotein L1, P-glycoprotein and multidrug resistance protein 2[81-83]. With regards to recipient factors, the presence of native kidneys may further contribute to BP increments probably due to renin secretion[84]. Moreover, longstanding hypertension may be present in many recipients before transplantation, as progression of CKD is associated with atheromatosis of middle-sized conduit arteries and most importantly with reduced

compliance and arterial stiffness of aorta and the large arteries[85]. This vascular remodeling may not be fully reversible after kidney transplantation.

Transplant renal artery stenosis: Prevalence of transplant renal artery stenosis (TRAS) reportedly ranged in the past between 1%-23%, with a significant increase noted in diagnosed cases with the use of non-invasive imaging techniques[86]. Refractory hypertension and worsening kidney function are the main clinical manifestations of TRAS which usually develops 3-24 mo post transplantation and is associated with an increased risk of graft loss[84]. With regards to the anatomic site, the stenosis can be: (1) Anastomotic (due to vascular damage at the time of surgery); (2) Proximal (due to recipient's atherosclerosis); and (3) Distal (with a non-fully elucidated pathogenesis related to mechanical and immunological factors)[87]. Since the recipient's iliac artery and not the abdominal aorta is the most common site of donor renal artery anastomosis, this connection between smaller arteries is prone to narrowing and subsequent development of TRAS pathophysiology, involving impediment of blood flow, renal hypoperfusion and activation of RAAS[84]. Immunological factors leading to TRAS include immune-mediated vascular endothelial injury[88] and development of de novo class II donor-specific antibodies[89]. The association between TRAS and cytomegalovirus infection[90], as well as ischemia/reperfusion injury has been also reported[91]. In the absence of a randomized-controlled clinical trial comparing endovascular angioplasty with or without stenting *vs* surgical vascularization in KTRs, angioplasty is the preferred treatment of TRAS with reported rates of clinical success (improvements in BP or kidney function) between 65.5%-94% and of technical success > 90%[92].

Acute and chronic kidney dysfunction: Kidney function decline, whether in the context of an episode of acute cellular and antibody rejection or due to chronic allograft nephropathy, has been associated with new or worsening hypertension, with evidence with regards to a cause-effect relationship being still inconclusive[42,84,93,94]. Acute

rejection may trigger new-onset hypertension, probably *via* activation of the renin-angiotensin system according to patient's volume status; in this case treatment of rejection is accompanied by improvement in BP levels, whereas hypertension non-associated to acute rejection would be further deteriorated with modifications in doses of immunosuppression[94]. Recurrence of the primary glomerular disease, tubular atrophy, interstitial fibrosis, chronic antibody-mediated organ rejection, development of non-HLA agonistic anti-angiotensin-II type 1 receptor (AT1R) antibodies and thrombotic microangiopathy are the major contributors to chronic allograft injury leading to sudden rises of BP[5,84,94,95]. Patients with positive AT1R antibodies represent a subset of those with antibody-mediated rejection in whom kidney dysfunction is associated with malignant hypertension and acute vascular lesions on biopsy. A clinico-pathological entity including seizures on top of malignant hypertension and vasculopathy has been also described, bearing resemblance to pre-eclamptic syndromes where AT1R antibodies have been previously reported[95].

HYPERTENSION TREATMENT IN KTRS

Targets of BP therapy

Historically, no universal agreement has been achieved with regards to BP targets in CKD and more particularly in kidney transplantation, similarly to the heterogeneity observed in different BP thresholds used for diagnosis of hypertension[7-11]. In the absence of specific focus on KTRs, the BP targets of CKD population were expected to be endorsed; according to the 2018 ESC/ESH guidelines in patients with CKD the respective recommendation was lowering BP to < 140/90 mmHg and towards 130/80 mmHg[10]. However in the latest 2017 ACC/AHA and 2021 KDIGO guidelines specific recommendations targeting BP less than 130/80 mmHg have been provided for KTRs[9,11].

Non-pharmacological measures

In the absence of evidence focused on KTRs, lifestyle modifications should be adopted as a first-line approach on the basis of recommendations applied in the general population, since these interventions provide general health benefits that extend beyond BP control[96]. Low sodium intake (< 2 g/d), moderate-intensity physical activity (≥ 150 min/wk), adoption of a balanced diet and maintenance of body mass index and waist circumference within normal range (18.5 and 24.9 kg/m^2 and < 102 cm respectively), reduction in alcohol consumption and smoking cessation are encompassed by most hypertension guidelines[5,9-11,97].

Pharmacological measures

In CKD populations, use of an ACEi or an angiotensin receptor blocker (ARB) has been established as first-line treatment, followed by combinations with a CCB and/or diuretic[98]. In KTRs, the use of a dihydropyridine CCB is commonly advocated notably in the early post transplantation period because of their demonstrated efficacy in improving graft function and minimizing the vasoconstrictive effects of CNIs[15,93,99]. To support this choice, CCBs have been uniformly associated with improved patient and graft outcomes in several studies[99-103]. In contrast, the use of ACEis/ARBs in KTRs was considered a source of controversy for many years[4]. Treatment with an ACEi/ARB led to impressively better patient (HR = 0.57; 95%CI: 0.40-0.81) and graft (HR = 0.56; 95%CI: 0.40-0.78) survival rates in a retrospective cohort with 2031 KTRs[104], but not in a subsequent analysis of data from 17208 KTRs[105].

According to the results of an RCT with 154 hypertensive KTRs, allocated to receive nifedipine 30 mg or lisinopril 10 mg 3 wk post transplantation, no differences were noted in BP control. Nevertheless, a significant increase was observed in measured GFR for nifedipine compared to lisinopril (mean between-group difference 9.6 mL/min, 95%CI: 5.5-13.7 mL/min) at 1 year, an improvement that was maintained at 2 years[106]. The results of a 2009 Cochrane systematic review claimed that patients receiving ACEis were exposed to a higher risk of hyperkalemia and anemia and that in direct comparisons with CCBs their use was associated with worse kidney function (mean

between-group difference for eGFR -11.48 mL/min, 95%CI: -15.75 to -7.21). Data on graft loss were available from only one study, showing no significant differences (RR = 7.37, 95%CI: 0.39-140.35)[100]. Among the main limitations of this meta-analysis was the fact that data for head-to-head comparisons were pooled from 6 studies with only 296 participants; 4 of them had a follow-up between 4 wk and 6 mo[25,107-109], 2 of them being published after the year 2000[25,106], and no one comparing ARBs to CCBs directly. In a more recent meta-analysis conducted by Pisano *et al*[99] pooling data from 71 RCTs and providing evidence on both ACEis and ARBs, a significant reduction in the risk for graft loss was observed by 42% with CCBs (16 studies, 1327 participants) and by 38% with ACEi/ARBs (9 studies, 1246 participants). When pooling results from head-to-head comparisons between CCBs and ACEis/ARBs, an increase in GFR (11.07 mL/min, 95%CI: 6.04-16.09) was noted for CCBs, along with a reduction in serum potassium levels (-0.24 mEq/L, 95%CI: -0.38 to -0.10). In the 2021 KDIGO guidelines, use of a dihydropyridine CCB or an ARB has received a Grade 1C recommendation for first-line treatment in KTRs, with potential benefits on graft survival (RR for graft loss compared to placebo: Dihydropyridine CCBs 0.62, 95%CI: 0.43-0.90; ARBs: 0.35, 95%CI: 0.15-0.84) outweighing side effects related to each class of agent[11]. No significant effect on mortality or CV events was detected with either of these classes.

CONCLUSION

The accurate diagnosis of hypertension and adequate BP control in KTRs remains an area of controversy among different guidelines, with BP thresholds and treatment goals mostly extrapolated from CKD populations. The diagnostic performance of office measurements has been recently questioned, with more recent studies using ABPM suggesting a higher prevalence of uncontrolled, masked and nocturnal hypertension in KTRs than previously believed that is further increased when new lower BP thresholds are applied. Recent analyses provide evidence that 24-h ABPM outperforms office BP measurements with regards to markers of target organ damage, including LVMI, cIMT and FMD, and represents an independent predictor of kidney function decline and graft

loss. Except from pre-existing or *de novo* traditional risk factors and factors associated with CKD, immunosuppressive drugs, donor-recipient mismatches, TRAS, recurrence of primary glomerular disease, presence of native kidneys, as well as episodes of acute and chronic allograft injury contribute to development of hypertension post transplantation. Recent guidelines recommend the use of dihydropyridine CCBs[15], as they exhibit a favorable profile due to their vasodilatory effects counteracting vasoconstriction induced by CNIs and their favorable effects on outcomes or ARBs due to their favorable effects on graft survival, despite previously reported undesirable effects on risk of hyperkalemia and anemia. High-quality large-scale RCTs comparatively assessing the effect of different antihypertensive agents on mortality and major cardiovascular events are warranted to provide definite evidence.

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