Received: 1 October 2019 | Revised: 16 December 2019 | Accepted: 20 January 2020

DOI: 10.1111/ctr.13803

BRIEF COMMUNICATION

Clinical TRANSPLANTATION
The Journal of Clinical and Translational Research
WILEY

Impacts of center and clinical factors in antihypertensive medication use after kidney transplantation

Farrukh M. Koraishy[1] | Hala Yamout[2] | Abhijit S. Naik[3] | Zidong Zhang[4] | Mark A. Schnitzler[4] | Rosemary Ouseph[4] | Ngan N. Lam[5] | Vikas R. Dharnidharka[6] | David Axelrod[7] | Gregory P. Hess[8] | Dorry L. Segev[9] | Bertram L. Kasiske[10] | Krista L. Lentine[2,4]

[1]Division of Nephrology, Department of Medicine, Stony Brook University, Stony Brook, NY, USA
[2]Division of Nephrology, Department of Medicine, Saint Louis University, St. Louis, MO, USA
[3]Division of Nephrology, Department of Medicine, University of Michigan, Ann Arbor, MI, USA
[4]Center for Abdominal Transplantation, Saint Louis University School of Medicine, St. Louis, MO, USA
[5]Division of Nephrology, Department of Medicine, University of Calgary, Calgary, AB, Canada
[6]Division of Nephrology, Department of Pediatrics, Washington University, St. Louis, MO, USA
[7]University of Iowa Transplant Institute, University of Iowa School of Medicine, Iowa City, IA, USA
[8]College of Medicine, Drexel University, Philadelphia, PA, USA
[9]Center for Transplantation, Johns Hopkins School of Medicine, Baltimore, MD, USA
[10]Department of Medicine, Hennepin County Medical Center, Minneapolis, MN, USA

Correspondence
Krista L. Lentine, MD, PhD, Saint Louis University Center for Abdominal Transplantation, 1402 S. Grand Blvd., St. Louis, MO 63104, USA.
Email: krista.lentine@health.slu.edu

Funding information
National Institute of Diabetes and Digestive and Kidney Diseases, Grant/Award Number: R01DK102981

Abstract

Hypertension guidelines recommend calcium channel blockers (CCBs), thiazide diuretics, and angiotensin-converting-enzyme inhibitors/angiotensin receptor blockers (ACEi/ARBs) as first-line agents to treat hypertension. Hypertension is common among kidney transplant (KTx) recipients, but data are limited regarding patterns of antihypertensive medication (AHM) use in this population. We examined a novel database that links national registry data for adult KTx recipients (age > 18 years) with AHM fill records from a pharmaceutical claims warehouse (2007-2016) to describe use and correlates of AHM use during months 7-12 post-transplant. For patients filling AHMs, individual agents used included: dihydropyridine (DHP) CCBs, 55.6%; beta-blockers (BBs), 52.8%; diuretics, 30.0%; ACEi/ARBs, 21.1%; non-DHP CCBs, 3.0%; and others, 20.1%. Both BB and ACEi/ARB use were significantly lower in the time period following the 2014 Eighth Joint National Committee (JNC-8) guidelines (2014-2016), compared with an earlier period (2007-2013). The median odds ratios generated from case-factor adjusted models supported variation in use of ACEi/ARBs (1.51) and BBs (1.55) across transplant centers. Contrary to hypertension guidelines for the general population, KTx recipients are prescribed relatively more BBs and

Koraishy and Yamout are co-first authors, equally contributed to this study.

fewer ACEi/ARBs. The clinical impact of this AHM prescribing pattern warrants further study.

KEYWORDS

antihypertensive medications, kidney transplant, pharmacoepidemiology, practice patterns

1 | INTRODUCTION

Hypertension is a highly prevalent (50%-80%) comorbid condition among kidney transplant (KTx) recipients.[1,2] Complications of uncontrolled hypertension after KTx include injury to the renal allograft, cardiovascular disease, and mortality.[3] Effective antihypertensive medications (AHMs) can control blood pressure and improve patient and graft survival.[4] Several studies have been conducted to determine the ideal blood pressure management strategy for KTx patients, primarily focused on the use of angiotensin-converting-enzyme inhibitors/angiotensin II receptor blockers (ACEi/ARBs) and calcium channel blockers (CCBs).[5] However, the optimal medical regimen in this population remains undefined. Factors to be considered in prescribing AHMs include comorbid conditions that are indications for particular agents,[6] or drug interactions with immunosuppressive therapy.[7]

In a cohort of 16 157 KTx recipients, we previously examined AHM use at the first transplant anniversary and found beta-blockers (BBs) to be the most commonly used, followed closely by CCBs.[8] This study was limited by an observation period (2005-2010) that preceded the 2014 Eighth Joint National Committee (JNC-8) hypertension guidelines,[6] and it did not consider the impact of transplant center variation practices. We recently identified center effect as a strong correlate of immunosuppressive regimen choice after transplant[9-11] and hypothesized that such center-driven variations may also affect AHM regimens.

To advance understanding of AHM use in a large, national sample of KTx recipients, we integrated US transplant registry data with national pharmacy fill records from a large pharmaceutical claims warehouse. Our primary goal was to describe current AHM prescription patterns 7-12 months post-transplant. This observation period was chosen because kidney function has typically stabilized, as have immunosuppressive regimens. We examined the impact of patient characteristics and center effects on AHM choices. In particular, we hypothesized that ACEi/ARB use may have increased, and BB use declined, after the publication of JNC-8 hypertension guidelines, based on prioritization of agent use in these guidelines for the general population.

2 | METHODS

2.1 | Data sources and sample selection

Transplant registry data were obtained from the Scientific Registry of Transplant Recipients (SRTR), which include data on all transplant recipients in the United States, submitted by members of the Organ Procurement and Transplantation Network (OPTN). The Health Resources and Services Administration (HRSA) provides oversight of the activities of the OPTN and SRTR contractors. Pharmacy fill data were obtained from billing claims for KTx recipients from a large US pharmaceutical claims data (PCD) warehouse that collects prescription drug fill records, including self-paid fills and fills reimbursed by private and public payers. The PCD comprised National Council for Prescription Drug Program 5.1-format prescription claims aggregated from multiple sources including data clearinghouses, retail pharmacies, and prescription benefit managers for approximately 60% of US retail pharmacy transactions. Individual claim records included the dates of given pharmacy fills with National Drug Code identifying agents and dosage. After Institutional Review Board and HRSA approvals, PCD records were linked with SRTR records for kidney recipients.[8] Eligible patients had PCD data during the period 7-12 months post-transplant. We studied overall prescribing patterns for all eligible transplant recipients and examined variation in use of specific agents among recipients receiving AHMs.

2.2 | AHM regimen and covariate ascertainment

Antihypertensive medication regimens were classified based on components in the medications filled as: (a) dihydropiridine (DHP) CCBs; (b) non-DHP (NDHP) CCBs; (c) ACEi/ARBs; (d) BBs; (e) diuretics; and (f) other AHMs. Recipient characteristics (Table 1) and transplant centers were identified from the SRTR registry.

2.3 | Statistical analyses

In the initial description of prescribing patterns, distributions of recipient, donor, and transplant characteristics according to regimen (not mutually exclusive) were examined as percentages. To visually assess unadjusted variation in AHM use at the transplant center level across the United States, observed proportions of patients receiving each regimen were determined and displayed as stacked bar plots.

Among patients receiving AHMs, we examined variation in uses of BBs and of ACEi/ARBs as two regimens of key interest given particular focus in JNC-8,[6] considering clinical factors and center. Bi-level hierarchical models were constructed to adjust for clustering effects, similar to previous methods.[9,12-15] Level 1 comprised patient/donor and transplant (case) factors and level 2 represented centers, wherein use of each regimen (BBs and ACEi/ARBs) was compared with absence of use. Empirical Bayes estimates (EBEs) provided an

TABLE 1 Characteristics of kidney transplant recipients according to antihypertensive medication use 7-12 mo after transplant

	DHP CCBs	NDHP CCBs	ACEi/ARBs	BBs	Diuretics	Other AHMs
	(N = 31 814)	(N = 1699)	(N = 12 082)	(N = 30 196)	(N = 17 126)	(N = 11 479)
	%	%	%	%	%	%
Recipient factors						
Age, y						
19 to 30	7.6	8.6	7.1	7.2	3.8	7.5
31 to 44	19.8	22.5	20.8	20.6	15.2	20.6
45 to 59	39.6	38.0	41.3	39.5	38.9	39.9
≥60	33.0	31.0	30.9	32.7	42.1	32.0
Female	33.9	34.4	33.4	36.6	41.0	28.7
Race						
White	45.8	45.4	51.5	50.8	52.7	41.6
African American	32.7	34.6	28.1	29.7	30.9	38.2
Hispanic	14.9	15.2	14.3	13.4	11.9	14.1
Other	6.6	4.8	6.2	6.2	4.5	6.1
Body mass index, kg/m^2						
<18.5	1.4	1.9	1.6	1.6	1.1	1.6
18.5 to <25	26.4	28.7	25.7	26.8	18.5	27.3
25 to <30	34.1	33.2	34.0	33.2	30.3	33.6
≥30	36.3	34.7	36.4	36.5	48.0	35.2
Unknown	1.8	1.6	2.3	2.0	2.1	2.4
Cause of ESKD						
Diabetes	27.5	22.8	28.1	26.2	33.9	28.9
Glomerulonephritis	21.1	22.6	22.9	22.3	17.5	18.9
Hypertension	31.0	29.1	27.6	29.4	27.5	35.8
Polycystic kidney disease	8.3	9.7	10.3	8.6	9.0	6.3
Other	12.2	15.8	11.3	13.5	12.2	10.2
Comorbidities						
Coronary artery disease	6.1	6.1	7.0	6.6	8.6	6.9
Cerebral vascular disease	2.7	2.0	2.5	2.7	2.9	2.8
Peripheral vascular disease	6.9	5.9	5.6	6.5	9.0	7.2
COPD	1.4	1.4	1.3	1.3	1.9	1.4
eGFR at 6 mo, mL/min per 1.73 m^2						
≥60	44.2	40.8	45.0	42.0	32.2	39.3
30 to 59	48.0	50.7	48.4	49.8	54.9	50.3
<30	5.9	7.0	4.0	6.1	11.2	7.6
Missing	1.9	1.6	2.5	2.1	1.8	2.9
Donor and transplant factors						
Previous transplant	11.4	15.5	10.7	13.6	13.6	12.8
Acute rejection at 6 months	6.3	6.6	5.5	6.5	7.6	7.0
Maintenance ISx regimen at 6 mo						
mTOR inhibitor-based	4.0	4.5	5.1	4.5	7.0	6.1
Cyclosporine-based	1.3	2.9	1.6	1.3	1.9	1.6
Tac + MMF/MPA + Pred	37.0	36.6	38.7	37.6	35.5	36.8
Tac + MMF/MPA	13.9	13.4	15.5	13.8	13.0	12.1

(Continues)

TABLE 1 (Continued)

	DHP CCBs (N = 31 814) %	NDHP CCBs (N = 1699) %	ACEi/ARBs (N = 12 082) %	BBs (N = 30 196) %	Diuretics (N = 17 126) %	Other AHMs (N = 11 479) %
Tac, Tac + Pred	8.7	7.1	7.4	8.7	8.5	8.6
Other	35.1	35.5	31.7	34.1	34.3	34.7
Donor type						
Living donor	31.4	35.9	36.2	33.5	26.6	27.2
Standard criteria deceased	44.9	42.3	44.0	44.0	46.4	47.8
Expanded criteria deceased	12.5	10.1	10.3	11.5	15.0	13.3
Donation after cardiac death	11.3	11.7	9.4	11.0	12.1	11.7
Year of treatment						
2007 to 2013	66.3	74.2	78.8	70.5	70.8	73.2
2014 to 2016	33.7	25.8	21.2	29.5	29.2	26.8

Note: Column percentages reflect proportions of patients receiving a given AHM who have the indicated clinical traits.

Abbreviations: ACEi/ARBs, angiotensin-converting-enzyme inhibitors/angiotensin II receptor blockers; COPD, chronic obstructive pulmonary disease; DHP CCBs, dihydropyridine calcium channel blockers; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; ISx, immunosuppression; MMF/MPA, mycophenolate mofetil or mycophenolate acid; mTOR, mammalian target of rapamycin; NDHP CCBs, non-dihydropyridine calcium channel blockers; Pred, prednisone; Tac, tacrolimus.

adjusted proportion of use of a regimen of interest compared with the reference regimen, incorporating case-mix adjustment from the hierarchical model, where in case-level associations were quantified as adjusted odds ratios ($_{95\%LCL}$aOR$_{95\%\,UCL}$). A 95% confidence interval (CI) for a center's EBE of use of a regimen of interest not including the median national rate of use indicates a prescribing rate statistically significantly different from the expected rate of use for that regimen.

Heterogeneity in AHM prescribing across centers was quantified using median odds ratios (MORs). The MOR give the median of the odds that patients with identical characteristics will receive the AHM regimen of interest when two centers are drawn at random (performed for all possible pairs of centers). For example, a MOR of 2.0 means that if centers are selected at random across all centers, a patient with a given set of characteristics has, on an average, twice the odds of receiving the AHM regimen of interest (BB or ACEi/ARB) at one of the randomly selected centers than at the other.[16] The aORs of receiving an AHM regimen other than the reference was determined for patient and donor factors, after accounting for center effect using the hierarchical model. Data were analyzed using Stata/IC 12.0, StataCorp LP.

3 | RESULTS

A total of 147 304 patients underwent kidney-alone transplant between July 2006 and December 2015 (age > 18 years). Of these, 104 082 had pharmacy fill records for 7-12 months post-transplant; 57 185 (54.9%) used AHMs. Patients with and without captured AHM fills in the study period are compared in Table S1. Those with AHM fills were more commonly older, male, and African American; more commonly had hypertension or diabetes as the cause of end-stage kidney disease (ESKD); more commonly had comorbid coronary artery, cerebral vascular and peripheral vascular diseases; and more commonly received deceased donor (vs living donor) transplants, had acute rejection in the first 6 months, had 6-month eGFR < 60 mL/min per 1.73 m^2, and received mTOR inhibitor-based maintenance immunosuppression. CCBs were the most commonly prescribed AHM (58.6%) among recipients who used AHMs; most received DHP CCBs (55.6%, vs only 3.0% using NDHP CCBs) (Table 1), followed by BBs (52.8%), diuretics (30.0%), ACEi/ARBs (21.1%), and other agents (20.1%). Diuretic use was more common among recipients who were older, female, or obese, with lower estimated glomerular filtration rate (eGFR) and comorbid conditions such as diabetes mellitus, coronary artery disease, or peripheral vascular disease. CCB and ACEi/ARB use declined, while diuretic use increased, with lower 6-month eGFR.

We observed a modest variation in use of AHM class across transplant centers, but overall CCBs and BBs remained the most commonly used AHMs (Figure 1). Controlling for demographic and clinical factors, ACEi/ARB use was less likely in recipients with lower eGFR (aOR $_{0.58}0.64_{0.71}$), or of younger (<30 years) or older (≥ 60 years) age (aOR $_{0.82}0.89_{0.98}$ and $_{0.84}0.90_{0.96}$, respectively) or black race (aOR $_{0.84}0.89_{0.94}$) (Table 2). ACEi/ARB use was more likely in recipients with ESKD caused by diabetes (aOR $_{1.08}1.14_{1.21}$) or polycystic kidney disease (aOR $_{1.04}1.13_{1.22}$), or with a history of coronary artery disease (aOR $_{1.05}1.15_{1.25}$) at transplant registration. ACEi/ARB use was also lower in previous transplant recipients (aOR $_{0.72}0.77_{0.82}$) but higher among those using mTOR inhibitor-based immunosuppression (aOR $_{1.13}1.27_{1.42}$). Similarly, BB use was less likely in recipients aged younger than 30 or older than 60 years (aOR

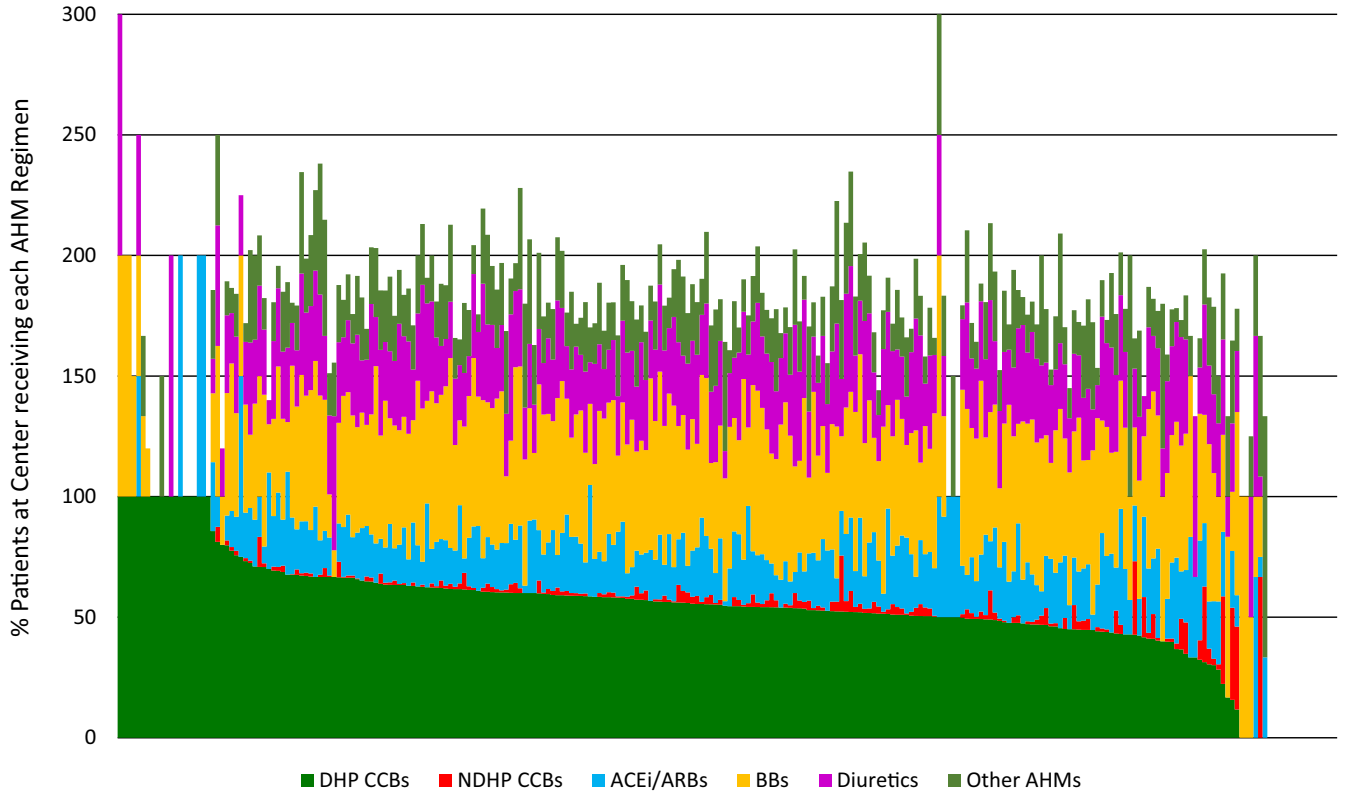

FIGURE 1 Variation of AHM regimen class prescribed in 7-12 mo post-transplant, across US transplant centers. ACEi, angiotensin-converting-enzyme inhibitor. AHM, antihypertensive medication. ARB, angiotensin II receptor blocker. BB, beta-blocker; CCB, calcium channel blocker; DHP, dihydropyridine; NDHP, non-dihydropyridine

$_{0.85}0.92_{0.99}$ and $_{0.89}0.94_{0.99}$, respectively). Regimens containing ACEi/ARBs (aOR $_{0.50}0.53_{0.56}$) and BBs (aOR $_{0.79}0.82_{0.86}$) were filled less commonly in the more recent study period of 2014-2016, compared with 2007-2013 (Table 2).

In the unadjusted model addressing center effects alone, the MOR for BB fills was 1.55; adding case factors made no difference (Table 3), suggesting that differences in case factors did not explain variation in BB fills among transplant centers. Similarly, variation in ACEi/ARB use was not explained by differences in case factors, as the MOR (1.50) did not change when case factors were added. Twenty-five percent of transplant centers were above, and 19% were below, the reference range for BB use; 18% were above and 13% below the reference range for ACEi/ARB use (Table 3, Figure 2).

4 | DISCUSSION

In this study of linked national US transplant registry and pharmacy claims data, we examined practice patterns in AHM prescription across transplant centers. We observed that in KTx recipients 7-12 months post-transplant, CCBs were the most commonly used AHMs, followed by BBs, while ACEi/ARB use remained relatively low. In addition, we observed that the odds of BB and ACEi/ARB use declined in 2014-2016 (post-JNC-8) compared with 2007-2013. Finally, while we observed some clinical associations, most variation in AHM use patterns was driven by transplant center.

Despite increased cardiovascular risk in KTx recipients compared with the general population, the optimal AHM regimen for KTx recipients is not well defined.[7,17] Based on the JNC-8 guidelines, ACEi/ARBs, thiazide diuretics, and CCBs are first-line agents for management of primary hypertension in the general population, but specific indications for use of each of these medications are based on comorbid illnesses. For example, ACEi/ARBs are recommended as first-line AHMs for all patients with chronic kidney disease (CKD), and BBs for those with a history of coronary artery disease. In this analysis, we specifically focused on ACEi/ARB and BB use in KTx recipients. The rationale for this interest was low use of ACEi/ARBs despite the 2014 JNC-8 guidelines recommendation for use as first-line agents, and high frequency of BB use (second only to CCBs) despite their being accorded a lower tier (second- or third-line) status.[6]

We observed a 48% reduction in ACEi/ARB use in the post-JNC-8 era compared with the earlier period. This pattern contrasts with JNC-8 recommendations for the general population and with observation that ACEi/ARB use has increased in general population.[18] The difference may relate to specific considerations or concerns in KTx recipients. In a systemic review of 21 trials (1549 KTx recipients), ACEi/ARB treatment was noted to significantly reduce proteinuria and GFR post-transplant, but data were insufficient to determine effects on hard outcomes such as patient or graft survival.[19] In a recent multi-center clinical trial of 213 KTx recipients with proteinuria, ACEi therapy was not associated with improved

TABLE 2 Associations of BB and ACEi/ARB use with recipient, donor, and transplant characteristics, from multi-level modeling including transplant center

	BBs	ACEi/ARBs
	aOR (95% CIs)	aOR (95% CIs)
Recipient factors		
Age, y		
19 to 30	0.92 (0.85–0.99)*	0.89 (0.82–0.98)*
31 to 44	Reference	Reference
45 to 59	0.98 (0.93–1.03)	1.01 (0.96–1.07)
≥60	0.94 (0.89–0.99)*	0.90 (0.84–0.96)*
Female	1.01 (0.97–1.04)	1.01 (0.97–1.05)
Race		
White	Reference	Reference
African American	0.99 (0.94–1.03)	0.89 (0.84–0.94)‡
Hispanic	0.96 (0.91–1.02)	0.99 (0.93–1.06)
Other	0.99 (0.92–1.07)	0.98 (0.90–1.08)
Body mass index, kg/m^2		
<18.5	0.89 (0.78–1.02)	0.99 (0.84–1.17)
18.5 to <25	Reference	Reference
25 to <30	0.97 (0.92–1.01)	1.05 (0.99–1.11)*
≥30	0.96 (0.92–1.01)	1.01 (0.95–1.06)
Unknown	1.18 (1.03–1.35)*	1.25 (1.07–1.46)*
Cause of ESRD		
Diabetes	0.91 (0.87–0.96)‡	1.14 (1.08–1.21)‡
Glomerulonephritis	0.94 (0.90–0.99)*	1.08 (1.01–1.15)*
Hypertension	Reference	Reference
Polycystic Kidney Disease	0.79 (0.74–0.85)‡	1.13 (1.04–1.22)*
Other	0.89 (0.84–0.94)‡	0.84 (0.78–0.91)‡
Comorbidities		
Coronary artery disease	1.05 (0.98–1.13)	1.15 (1.05–1.25)*
Cerebral vascular disease	1.06 (0.95–1.18)	0.99 (0.87–1.13)
Peripheral vascular disease	1.01 (0.94–1.08)	0.87 (0.79–0.96)*
COPD	0.91 (0.78–1.05)	1.06 (0.88–1.27)
eGFR at 6 mo, mL/min per 1.73 m^2		
≥60	0.95 (0.91–0.98)*	1.11 (1.06–1.16)‡
30 to 59	Reference	Reference
<30	0.97 (0.90–1.05)	0.64 (0.58–0.71)‡
Missing	1.14 (1.01–1.30)	1.44 (1.25–1.67)‡
Donor and transplant factors		
Previous transplant	1.10 (1.05–1.16)‡	0.77 (0.72–0.82)‡
Acute rejection by 6 mo	1.05 (0.98–1.13)	0.92 (0.84–1.01)
Maintenance ISx regimen at 6 mo		
mTORi-based	0.95 (0.86–1.04)	1.27 (1.13–1.42)†
Cyclosporine–based	0.89 (0.76–1.03)	1.19 (0.99–1.42)
Tac + MMF/MPA + Pred	Reference	Reference
Tac + MMF/MPA	0.99 (0.93–1.05)	1.02 (0.95–1.10)
Tac, Tac + Pred	0.98 (0.91–1.05)	0.89 (0.81–0.97)
Other	0.99 (0.94–1.04)	1.03 (0.97–1.10)
Donor type		
Living donor	0.97 (0.93–1.01)	1.06 (1.01–1.11)
Standard criteria deceased	Reference	Reference
Expanded criteria deceased	1.08 (1.02–1.14)*	0.98 (0.91–1.05)
Donation after cardiac death	1.02 (0.96–1.08)	0.89 (0.83–0.96)*
Year of treatment		
2007 to 2013	Reference	Reference
2014 to 2016	0.82 (0.79–0.86)‡	0.53 (0.50–0.56)‡

Note: *P*-value vs reference: *P < .05-0.002; †P = .001-0.0002; ‡P < .0001.

Abbreviations: ACEi/ARBs, angiotensin-converting-enzyme inhibitors/angiotensin II receptor blockers; CI, confidence interval; COPD, chronic obstructive pulmonary disease; DHP CCBs, dihydropyridine calcium channel blockers; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; ISx, immunosuppression; MMF/MPA, mycophenolate mofetil or mycophenolate acid; mTORi, mammalian target of rapamycin inhibitor; NDHP CCBs, non-dihydropyridine calcium channel blockers; Pred, prednisone; Tac, tacrolimus.

renal outcomes or patient survival, suggesting that findings from the non-transplant population may not extrapolate to the transplant population.[20] Another randomized controlled trial by Ibrahim et al[21] comparing losartan versus placebo found no difference in their primary outcome (composite of doubling of the fraction of renal cortical volume occupied by interstitium and graft failure from interstitial fibrosis [IF]/tubular atrophy [TA]). Notably, in a recent study by Cockfield et al, renin-angiotensin-aldosterone system (RAAS) blockade was associated with lower risk of T cell–mediated rejection even when combined with low-dose tacrolimus. In addition, the combination led to lower 24-month IF/TA compared with other regimens.[22] Further, this study did not identify reduced GFR to be a problem despite very early RAAS blockade initiation. Interestingly, we observed lower ACEi/ARB use in African Americans, a group shown to have lower rates of GFR decline with ACEi/ARBs compared with other AHMs in hypertension-associated mild-to-moderate CKD.[23] In addition to inconclusive data supporting benefits in the KTx population, the relatively lower use of ACEi/ARBs in KTx recipients compared with the general population may also reflect concern for side effects and drug interactions that

TABLE 3 (A) Heterogeneity in BB and ACEi/ARB use, from hierarchical logistic regression models adjusting for case-level characteristics. (B) Empirical Bayes estimates for BB and ACEi/ARB use adjusting for case-level characteristics

(A) Model	MOR (unadjusted)	MOR (adjusted)
BB (vs No BB)	1.55	1.55
ACEi/ARB (vs no ACEi/ARB)	1.50	1.50

(B) Model	No. of centers in pairwise comparison	No. of centers significantly above reference probability	No. of centers significantly below reference probability
BB (vs No BB)	247	62 (25%)	47 (19%)
ACEi/ARB (vs no ACEi/ARB)	247	44 (18%)	33 (13%)

Abbreviations: ACEi/ARB, angiotensin-converting-enzyme inhibitor/angiotensin II receptor blocker; BB, beta-blocker; MOR, median odds ratio.

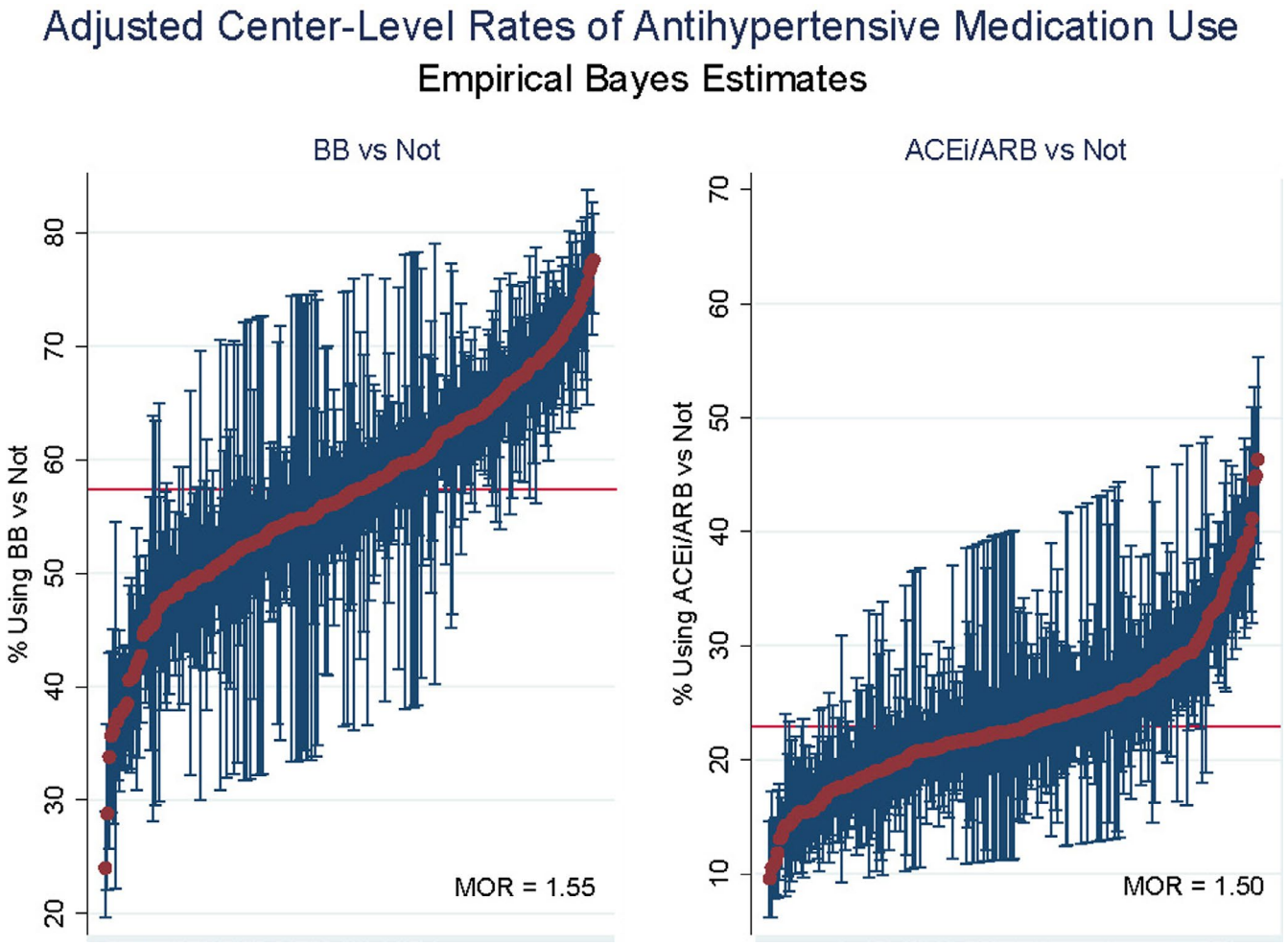

FIGURE 2 Center-level variation in BB and ACEi/ARB use in months 7-12 after KTx. ACEi, angiotensin-converting-enzyme inhibitor. AHM, antihypertensive medication. ARB, angiotensin II receptor blocker. BB, beta-blocker; MOR, median odds ratio

might be more problematic after a recent KTx, such as a decline in GFR or hyperkalemia that can be exacerbated in patients receiving calcineurin inhibitors.

We also noted an 18% reduction in BB use among KTx recipients after JNC-8. This is consistent with overall trends and data, and resonates with clinical trial meta-analysis in the non-transplant population, showing BBs to be inferior to CCBs, ACEi/ARBs and diuretics regarding cardiovascular and survival outcomes.[24,25] Despite BBs being recommended for patients with coronary artery disease, we did not note increased use among these patients.

As in the general population, CCB use appears to have increased in recent years.[18] A study directly comparing ACEi to CCB use in KTx recipients showed similar safety and efficacy; however, CCBs were associated with improved GFR 2 years post-transplant. Whether this

represents an actual improvement versus the vasodilatory properties of CCBs remains to be determined.[26] Common use of CCBs in the KTx population may also reflect efficacy in reducing blood pressure without side effects such as serum creatinine elevation or hyperkalemia, concerns that may pose barriers to ACEi/ARB use after KTx, as discussed above. For this analysis, we categorized both classes of CCBs together, partly because NDHP CCB use was very low. Low NDHP CCB use in this population is likely related to the known interactions with calcineurin inhibitors. Lastly, we noted that while some case-level factors were associated with AHM use, the variation in use was almost entirely driven by prescribing practices of transplant centers. This finding is consistent with our previous studies highlighting and quantifying center-level variation in immunosuppressive agent prescribing.[9-11] Future studies are needed to specifically assess whether centers with the best short- and long-term graft and patient outcomes employ certain practices and treatment patterns that drive those outcomes.

Our study has strengths. We identified a large, national sample of KTx recipients across US transplant centers to describe current trends and associations of AHM use, considering center and clinical factors. We compared differences in prescribing patterns before and after a major JNC guideline revision. Our study also has limitations, such as lack of indication for a given prescription and lack of data on some granular clinical factors such as blood pressure control or the presence of proteinuria. As with any observational study, we can describe associations but cannot prove causation. Notably, our capture of AHM use among 55% of the study sample is lower than some prior studies,[23] which may reflect use of different pharmacies by kidney transplant patients (eg, immunosuppression fills at a captured specialty pharmacy but AHM fills at a pharmacy not captured in the PCD), or dispersal of inexpensive generic AHMs without cost or record in the pharmacy claims warehouse. However, the pattern of characteristics of patients with versus without captured AHM fills are consistent with clinical expectations. While our data allow identification of a large national cohort, not all KTx recipients are represented, and prescribing may differ for recipients using other pharmacies.

In conclusion, we found that CCBs and BBs were the most commonly used AHMs in 7-12 months after KTx. ACEi/ARB use was noted to be lower, and BB use higher in KTx recipients than is recommended for the general population. While there were some case-level correlates of BB and ACEi/ARB use, prescribing varied across transplant centers after adjusting for case factors. Continued study is needed to provide evidence to inform AHM choice to optimize outcomes for KTx recipients.[27]

ACKNOWLEDGEMENTS

This work was conducted under the auspices of the Minneapolis Medical Research Foundation (MMRF), contractor for the Scientific Registry of Transplant Recipients (SRTR), as a deliverable under contract no. HHSH250201000018C (US Department of Health and Human Services, Health Resources and Services Administration, Healthcare Systems Bureau, Division of Transplantation). As a US Government-sponsored work, there are no restrictions on its use. The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy of or interpretation by the SRTR or the US Government. Supported in part by a grant from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), R01DK102981. KLL receives support from the Mid-America Transplant/Jane A. Beckman Endowed Chair in Transplantation. The authors thank SRTR colleague Nan Booth, MSW, MPH, ELS, for manuscript editing. An abstract describing portions of this work was presented at the American Transplant Congress 2018, Seattle, WA.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHORS' CONTRIBUTIONS

KLL and MAS: participated in study design, acquisition of data, and regulatory approvals and contributed in data analysis and writing of the paper; FMK, HY, ASN, MAS, RO, NNL, VRD, DA, GPH, DLS, and BLK: participated in study design, results interpretation, and writing of the paper as part of our outcomes consortium; ZZ: Participated in data analysis and manuscript preparation.

ORCID

Abhijit S. Naik https://orcid.org/0000-0003-1602-9425
Zidong Zhang https://orcid.org/0000-0002-1084-9732
David Axelrod https://orcid.org/0000-0001-5684-0613
Krista L. Lentine https://orcid.org/0000-0002-9423-4849

REFERENCES

1. Saran R, Li Y, Robinson B, et al. Renal data system 2015 annual data report: epidemiology of kidney disease in the United States. *Am J Kidney Dis*. 2016;67;Svii, S1-305.
2. Weir MR, Burgess ED, Cooper JE, et al. Assessment and management of hypertension in transplant patients. *J Am Soc Nephrol*. 2015;26:1248-1260.
3. Mange KC, Cizman B, Joffe M, Feldman HI. Arterial hypertension and renal allograft survival. *JAMA*. 2000;283:633-638.
4. Opelz G, Dohler B, Collaborative TS. Improved long-term outcomes after renal transplantation associated with blood pressure control. *Am J Transplant*. 2005;5:2725-2731.
5. Cross NB, Webster AC, Masson P, O'Connell PJ, Craig JC. Antihypertensive treatment for kidney transplant recipients. *Cochrane Database System Rev*. 2009;3:CD003598.
6. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA*. 2014;311:507-520.
7. Dunn BL, Teusink AC, Taber DJ, Hemstreet BA, Uber LA, Weimert NA. Management of hypertension in renal transplant patients: a comprehensive review of nonpharmacologic and pharmacologic treatment strategies. *Ann Pharmacother*. 2010;44:1259-1270.
8. Lentine KL, Anyaegbu E, Gleisner A, et al. Understanding medical care of transplant recipients through integrated registry and pharmacy claims data. *Am J Nephrol*. 2013;38:420-429.
9. Axelrod DA, Naik AS, Schnitzler MA, et al. National variation in use of immunosuppression for kidney transplantation: a call for evidence-based regimen selection. *Am J Transplant*. 2016;16:2453-2462.

10. Dharnidharka VR, Naik AS, Axelrod DA, et al. Center practice drives variation in choice of US kidney transplant induction therapy: a retrospective analysis of contemporary practice. *Transpl Int*. 2018;31:198-211.
11. Nazzal M, Lentine KL, Naik AS, et al. Center-driven and clinically driven variation in US liver transplant maintenance immunosuppression therapy: a national practice patterns analysis. *Transplant Direct*. 2018;4:e364.
12. King EA, Kucirka LM, McAdams-DeMarco MA, et al. Early hospital readmission after simultaneous pancreas-kidney transplantation: patient and center-level factors. *Am J Transplant*. 2016;16:541-549.
13. Orandi BJ, James NT, Hall EC, et al. Center-level variation in the development of delayed graft function after deceased donor kidney transplantation. *Transplantation*. 2015;99:997-1002.
14. Henderson ML, Thomas AG, Shaffer A, et al. The national landscape of living kidney donor follow-up in the United States. *Am J Transplant*. 2017;17(12):3131-3140.
15. Lentine KL, Naik AS, Schnitzler MA, et al. Variation in use of procurement biopsies and its implications for discard of deceased donor kidneys recovered for transplant. *Am J Transplant*. 2019;19:2241-2251.
16. Merlo J, Chaix B, Ohlsson H, et al. A brief conceptual tutorial of multilevel analysis in social epidemiology: using measures of clustering in multilevel logistic regression to investigate contextual phenomena. *J Epidemiol Community Health*. 2006;60:290-297.
17. Chatzikyrkou C, Menne J, Gwinner W, et al. Pathogenesis and management of hypertension after kidney transplantation. *J Hypertens*. 2011;29:2283-2294.
18. Jarari N, Rao N, Peela JR, et al. A review on prescribing patterns of antihypertensive drugs. *Clinical hypertension*. 2015;22:7.
19. Hiremath S, Fergusson D, Doucette S, Mulay AV, Knoll GA. Renin angiotensin system blockade in kidney transplantation: a systematic review of the evidence. *Am J Transplant*. 2007;7:2350-2360.
20. Knoll GA, Fergusson D, Chasse M, et al. Ramipril versus placebo in kidney transplant patients with proteinuria: a multicentre, double-blind, randomised controlled trial. *Lancet Diabetes Endocrinol*. 2016;4:318-326.
21. Ibrahim HN, Jackson S, Connaire J, et al. Angiotensin II blockade in kidney transplant recipients. *J Am Soc Nephrol*. 2013;24:320-327.
22. Cockfield SM, Wilson S, Campbell PM, et al. Comparison of the effects of standard vs low-dose prolonged-release tacrolimus with or without ACEi/ARB on the histology and function of renal allografts. *Am J Transplant*. 2019;19:1730-1744.
23. Wright JT Jr, Bakris G, Greene T, et al. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. *JAMA*. 2002;288:2421-2431.
24. Wiysonge CS, Bradley HA, Volmink J, Mayosi BM, Mbewu A, Opie LH. Beta-blockers for hypertension. *Cochrane Database System Rev*. 2012;11:CD002003.
25. Wiysonge CS, Bradley HA, Volmink J, Mayosi BM, Opie LH. Beta-blockers for hypertension. *Cochrane Database System Rev*. 2017;1:CD002003.
26. Midtvedt K, Hartmann A, Foss A, et al. Sustained improvement of renal graft function for two years in hypertensive renal transplant recipients treated with nifedipine as compared to lisinopril. *Transplantation*. 2001;72:1787-1792.
27. Halimi JM, Persu A, Sarafidis PA, et al. Optimizing hypertension management in renal transplantation: a call to action. *Nephrol Dial Transplant*. 2017;32:1959-1962.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Koraishy FM, Yamout H, Naik AS, et al. Impacts of center and clinical factors in antihypertensive medication use after kidney transplantation. *Clin Transplant*. 2020;34:e13803. https://doi.org/10.1111/ctr.13803