Published in final edited form as:

Clin Transplant. 2013 May ; 27(3): 472–480. doi:10.1111/ctr.12125.

Antihypertensive Pharmacotherapy and Long-Term Outcomes in Pediatric Kidney Transplantation

Thomas M. Suszynski¹, Michael D. Rizzari¹, Kristen J. Gillingham¹, Michelle N. Rheault², Wojciech Kraszkiewicz³, Arthur J. Matas¹, and Blanche M. Chavers²

¹Department of Surgery, Division of Transplantation, University of Minnesota, Minneapolis, Minnesota, USA

²Department of Pediatrics, Division of Nephrology, University of Minnesota, Minneapolis, Minnesota, USA

³Department of Medicine, University of Minnesota, Minneapolis, MN, USA

Abstract

Hypertension (HTN) is common in pediatric recipients following kidney transplantation (KT). We retrospectively assessed the impact of HTN on long-term (>10-year) outcomes in pediatric (aged <18 years) recipients at our center. 293 pediatric KT recipients (83% living donor [LD]) with graft survival (GS) for 5 years were studied. HTN was defined by antihypertensive medication use at 5 years post-KT. 160 (55%) recipients did not have HTN and 133 (45%) had HTN at 5 years post-KT. There were no differences in actuarial patient survival between cohorts. Actuarial GS at 15 and 20 years was 68% and 53% for recipients without HTN, and 53% and 33% for recipients with HTN ($p=0.006$). Among LD recipients using 1 antihypertensive, GS at 15 years was 100% for those using an angiotensin converting enzyme inhibitor (ACEI), and 44% for those not using an ACEI ($p=0.04$). Among these recipients, HTN treated with no ACEI was a significant risk factor for graft failure at >5 years (hazard ratio [HR] = 2.5, $p=0.02$), but HTN treated with an ACEI was not (HR=0.6, $p=0.7$). HTN at 5 years post-KT is associated with poorer long-term GS in pediatric recipients, but ACEI therapy may enable better outcomes and should be studied further.

Keywords

kidney transplantation; pediatrics; hypertension; angiotensin blockade

Introduction

The incidence of hypertension (HTN) following kidney transplantation (KT) in children is high, estimated to be 50–80% (1–3), and much higher than the estimated incidence of 2–5% in the general pediatric population (4). Post-KT HTN has been described independently as a risk factor for both decreased renal allograft function and survival in adults (3, 5–9) and children (2, 3, 10–13), but most currently available data reflect short- to intermediate-term (<5-year) outcomes. Minimal data are available on the effect of HTN on long-term (>10-year) outcomes following pediatric KT. We report our retrospective analysis on the impact of HTN and antihypertensive pharmacotherapy on actuarial patient survival (PS), graft survival (GS) and function in pediatric KT recipients with graft function for up to 20 years at our institution. We also study the impact that the use of angiotensin-converting enzyme

inhibitors (ACEIs) and other antihypertensive drugs have on long-term outcomes, with particular interest given to assess for improved GS with angiotensin blockade.

Methods

From 2/1984–8/2005, 420 KT were performed in pediatric (<18 years old) recipients at our institution. Of these recipients, 293 (51 deceased donor [DD], 242 living donor [LD]) had GS for >5 years and were included in this analysis. No recipients with <5 years GS were excluded. All donor and recipient data were retrospectively reviewed using an Institutional Review Board-approved database at the University of Minnesota. HTN was defined as use of antihypertensive(s) at the 5-year post-KT time point. Antihypertensives were prescribed by the attending nephrologist based on standard pediatric definitions of HTN at the time (14–17). Medications were stratified by class and included the following classes: alpha-1 antagonists, alpha-2 agonists, ACEIs, angiotensin receptor blockers (ARBs), beta-blockers, calcium channel blockers (CCBs), and direct vasodilators. Estimated glomerular filtration rate (eGFR) was calculated using the Schwartz formula:

$$\text{eGFR [mL/min/1.73m}^2\text{]} = (0.41 \times \text{height [cm]}) / \text{serum creatinine [mg/dL]} \quad (18).$$
 Median (interquartile range [IQR]) follow-up time was 17.3 (12.1–20.8) years for recipients without HTN and 11.6 (7.9–15.4) years for recipients with HTN ($p < 0.0001$).

Immunosuppression

Our immunosuppressive protocol has been described previously (19–22). In brief, each KT recipient received quadruple therapy, which included: 1) an induction antibody (ATGAM or Thymoglobulin); 2) prednisone (maintenance or rapid discontinuation of prednisone [RDP]); 3) azathioprine or mycophenolate mofetil, and 4) cyclosporine. ATGAM (polyclonal horse antithymocyte globulin; Pharmacia-Upjohn, Kalamazoo, MI) was given at 15 mg/kg per dose for 14 doses; Thymoglobulin (polyclonal rabbit antithymocyte globulin; Genzyme Corp., Cambridge, MA) was given at 1.5 mg/kg per dose (per day) for 6–14 doses for recipients on steroid maintenance therapy or 5–7 doses for recipients undergoing RDP, with the first dose of Thymoglobulin given intraoperatively. For recipients on steroid maintenance therapy, prednisone was started at 2 mg/kg/day *orally* (PO), and tapered to 0.45 mg/kg/day at 1 month post-KT, then to 0.25–0.3 mg/kg/day at 1 year. For recipients following RDP, a bolus dose of prednisone was administered intraoperatively (10 mg/kg *intravenously* [IV]) and then tapered until discontinuation on day 6 post-KT (1 mg/kg IV on day 1, 0.5 mg/kg IV on days 2 and 3, 0.25 mg/kg IV on days 4 and 5, and 0 mg/kg on day 6). Azathioprine was started at 5 mg/kg/day PO on the day of KT, and then tapered to 2–2.5 mg/kg/day PO over the first week post-KT. Mycophenolate mofetil (Hoffman-La Roche, Nutley, NJ) was given at 600 mg/m²/dose PO *twice daily* and has replaced azathioprine in RDP recipients since 2002. From 2/1984 to 5/1993, cyclosporine was started on post-KT day 10–12 (5 mg/kg/day PO, then reduced by 1 mg/kg/day per month to a maintenance dose of 3 mg/kg/day). Beginning in 6/1993, cyclosporine was started (at 6–10 mg/kg/day in divided doses) on post-KT days 1–5.

Rejection protocol

Recipients with >25% increase in serum creatinine level from baseline underwent percutaneous allograft biopsy, and all rejection episodes were confirmed by histological analysis. Rejection was characterized as acute or chronic, and tubulointerstitial or vascular by established criteria (20). Rejection episodes were treated with intravenous steroids for 3 days and a rapid oral steroid taper; steroid-resistant rejection episodes and severe rejection episodes were additionally treated with OKT3 or Thymoglobulin therapy for 5–7 days. All RDP recipients who experienced an acute rejection episode were placed back on maintenance corticosteroids.

Statistical Analysis

Categorical variables were analyzed using the Chi-square test and Fisher's exact test (for small sample size). Continuous variables were analyzed using the two-sided student's *t* test. Actuarial PS, GS and death-censored GS (DCGS) rates were calculated using Kaplan-Meier analyses, and the Log-rank test was used to compare differences between cohorts. Statistical significance corresponded to *p*-values <0.05 using a 95% confidence interval.

To account for possible confounders, we studied selected pre-KT factors for possible associations with antihypertensive medication use at 5 years post-KT using a logistic regression analysis with a forward stepwise model selection process ($\alpha=0.05$). A second logistic regression analysis was implemented to determine whether selected post-KT factors were associated with antihypertensive medication use at 5 years. Starting with a logistic regression model that included significant pre-KT risk factors from the first analysis, a forward, stepwise model selection process was repeated. We also studied pre- and post-KT factors for possible associations with GS at 5 years post-KT using Cox proportional hazards modeling.

Pre-KT factors (i.e., known at the time of KT) that were studied for their possible association with antihypertensive medication use and GS at 5 years included recipient age (5–11 and 12–18 vs. <5 years) and donor age (<18 and >55 vs. 18–55 years), recipient race (African American [AA] vs. non-AA), recipient gender, donor type (DD vs. LD), pre-KT HTN, pre-KT nephrectomy, pre-KT hemodialysis (<1 year and >1 year vs. none), delayed graft function, corticosteroid use (RDP vs. standard steroid-based immunosuppression), transplant era (2000–2005 vs. 1984–1999), and primary disease process (congenital structural anomalies, glomerulonephritis, congenital nephrotic syndrome, and focal segmental glomerulosclerosis). Post-KT factors including history of acute rejection (AR) or chronic rejection (CR) at <5 years post-KT and eGFR (<60 or 60–100 vs. >100 mL/min/1.73m²) at 5 years post-KT were studied for their possible associations with antihypertensive medication use and GS at >5 years post-KT, and HTN treated with an ACEI (vs. not treated with an ACEI) and HTN treated with an ACEI or ARB (vs. not treated with an ACEI or ARB) were studied for their possible associations with GS at >5 years post-KT.

Results

Recipient demographics are shown in Table 1, and use of antihypertensives stratified by class of drug is shown in Table 2. Of the 293 recipients included in the analysis, 160 (54.6%) were not using antihypertensives at 5 years post-KT (cohort without HTN) and 133 (45.4%) were using antihypertensives at 5 years post-KT (cohort with HTN). Recipients without HTN were younger at the time of KT; median (interquartile range [IQR]) recipient age was 3.5 (1.5–10.8) years versus 9.3 (2.5–13.6) years (*p*=0.0007). Recipients without HTN were more likely to have a congenital cause of end-stage renal disease, 58% versus 44% (*p*=0.02); to have a lower frequency of pre-KT HTN, 14% versus 46% (*p*<0.0001); and to be transplanted in an earlier era (pre-2000), 88% versus 69% (*p*<0.0001). There were few recipients on the rapid discontinuation of prednisone (RDP) protocol (*n*=14) as the protocol was initiated in 2002. We did not see a decrease in the incidence of hypertension in the small number of recipients on the RDP protocol (*p*=0.01). Median (IQR) donor age was 32.8 (25.8–39.7) years for those without HTN and 35.8 (30.7–42.2) years for those with HTN (*p*=0.003). A multivariate logistical regression analysis of pre-KT variables (known at the time of KT) revealed that recipient age 5–11 years (*p*=0.006, odds ratio [OR] = 2.4), recipient age 12–18 years (*p*=0.0002, OR=3.2), pre-KT HTN (*p*<0.0001, OR=4.4), and time of KT between 2000 and 2005 (*p*=0.02, OR=2.3) were significant risk factors for predicting HTN at 5 years post-KT.

Actuarial PS rates did not differ between cohorts ($p=0.8$). However, overall (combining DD and LD KT recipients) actuarial GS and DCGS rates differed between cohorts; 10-, 15- and 20-year overall GS was 86%, 68% and 53% for recipients without HTN, and 78%, 53% and 33% for recipients with HTN ($p=0.006$). Among recipients of LD kidneys, 10-, 15- and 20-year GS was 91%, 74%, and 59% for those without HTN, and 80%, 55% and 36% for those with HTN ($p=0.002$). There were no differences in GS rates between cohorts for recipients of DD kidneys ($p=0.9$). Overall DCGS rates showed a pattern that was similar to GS rates ($p=0.01$). DCGS rates were different between cohorts among recipients of LD kidneys ($p=0.002$), but not different among recipients of DD kidneys ($p=0.7$) (Figure 1).

There were no differences between cohorts in the actuarial rates of AR ($p=0.3$) or CR ($p=0.3$) at 5 years. Median eGFR at 5 years post-KT was higher in recipients without HTN; 68.8 versus 63.5 mL/min/1.73m² ($p=0.03$). A second logistic regression analysis which included the significant pre-KT risk factors (from the first logistic regression analysis) was performed and showed that neither prior history of AR or CR before 5 years post-KT, nor eGFR at 5 years post-KT were significantly associated with antihypertensive medication use at 5 years. Survival, rejection and functional outcomes are summarized in Table 3.

Among recipients of LD kidneys, there were no differences in actuarial PS rates by number (0, 1, 2) of antihypertensives. However, there were differences in actuarial GS and DCGS rates. 10- and 15-year GS was 90% ($n=107$) and 74% ($n=70$) for recipients not using antihypertensives, 79% ($n=40$) and 56% ($n=17$) for recipients using 1 antihypertensive, and 82% ($n=21$) and 55% ($n=4$) for recipients using 2 antihypertensives ($p=0.008$). Similarly, 10- and 15-year DCGS was 91% ($n=107$) and 76% ($n=70$) for recipients not using antihypertensives, 82% ($n=40$) and 58% ($n=17$) for recipients using 1 antihypertensive, and 82% ($n=21$) and 55% ($n=4$) for recipients using 2 antihypertensives ($p=0.008$). There were differences in GS ($p=0.003$) and DCGS ($p=0.006$) between recipients treated with 0 versus 1 antihypertensive, and in GS ($p=0.003$) and DCGS ($p=0.002$) between recipients treated with 0 versus 2 antihypertensives. However, there were no differences in GS ($p=0.3$) or DCGS ($p=0.5$) between recipients treated with 1 antihypertensive versus 2 medications.

For LD recipients using 1 antihypertensive, there were no differences in actuarial PS for those using an ACEI versus those using another antihypertensive ($p=0.7$). However, actuarial GS and DCGS were significantly higher for recipients treated with an ACEI when compared with those that were not. For recipients using an ACEI, 10- and 15-year GS was 100% and 100%; for recipients not using an ACEI, 10- and 15-year GS was 74% and 44% ($p=0.04$). Similarly, for recipients using an ACEI, 10- and 15-year DCGS was 100% and 100%; for recipients not using an ACEI, 10- and 15-year DCGS was 78% and 47% ($p=0.04$). To account for possible confounders when comparing LD recipients using an ACEI vs. no ACEI, a multivariate logistical regression analysis was performed. There were no differences in recipient or donor age, gender, or race, or cause of end-stage renal disease. Furthermore, there were no differences in the proportion of recipients having undergone pre-KT hemodialysis or nephrectomy, having received steroid-free maintenance immunosuppression or having been transplanted in the most recent era (data not shown). Of note, there were no significant differences in the median (IQR) eGFR at 5 years when comparing recipients using an ACEI (70.5 [60.6–77.5]) versus those not using an ACEI (63.4 [48.2–82.4]) ($p=0.4$). For LD recipients using 1 antihypertensive, multivariate proportional hazards modeling indicated that recipient male gender ($p=0.05$, hazard ratio [HR] = 2.1), donor age >55 years ($p=0.03$, HR=14.6), and history of AR at <5 years post-KT ($p=0.03$, 2.2) were significant risk factors for graft failure at >5 years post-KT. HTN treated with no ACEI (vs. no HTN; $p=0.02$, HR=2.5) was also a significant risk factor for graft failure at >5 years post-KT, but HTN treated with an ACEI (vs. no HTN, $p=0.7$, HR=0.6) was not.

For LD recipients using 1 antihypertensive, we combined recipients using an ACEI or an ARB and compared outcomes in recipients using an antihypertensive whose drug action did not involve angiotensin blockade. Among these recipients, there were no differences in actuarial PS between those using an ACEI or ARB and those that were not ($p=0.7$). However, actuarial GS and DCGS were significantly higher for recipients treated with an ACEI or ARB when compared with those that were not. For recipients using an ACEI or ARB, 10- and 15-year GS was 100% and 100%; for recipients not using an ACEI or ARB, 10- and 15-year GS was 73% and 44% ($p=0.03$). Similarly, for recipients using an ACEI or ARB, 10- and 15-year DCGS was 100% and 100%; for recipients not using an ACEI or ARB, 10- and 15-year DCGS was 77% and 46% ($p=0.03$) (Figure 2). For LD recipients using 1 antihypertensive, multivariate proportional hazards modeling was performed to assess for significant risk factors for graft failure at >5 years post-KT and the analysis yielded similar conclusions as described previously for hypertensive recipients treated with an ACEI or no ACEI (data not shown).

Of LD recipients using 1 antihypertensive, there were no differences in actuarial PS for those using a CCB versus those using another antihypertensive ($p=0.7$). Similarly, there were no differences in actuarial GS and DCGS rates between those treated with a CCB and those that were not. For recipients using a CCB, 10- and 15-year GS was 78% and 55%; for recipients not using a CCB, 10- and 15-year GS was 80% and 56% ($p=0.7$). Similarly, for recipients using a CCB, 10- and 15-year DCGS was 86% and 61%; for recipients not using a CCB, 10- and 15-year DCGS was 80% and 56% ($p=0.5$). Use of an alpha-1 antagonist, alpha-2 agonist, or a beta-blocker showed no differences in PS, GS or DCGS when comparing use of 1 antihypertensive from a single drug class versus all other classes (data not shown). It is important to note that the numbers were too low to assess for effects of any particular drug class in recipients of DD kidneys.

Discussion

This study has the longest pediatric recipient follow-up (up to 20 years) to date and the data analysis indicates an association between antihypertensive medication use at 5 years post-KT and decreased long-term GS. In this study, pediatric recipients were more likely to require antihypertensive pharmacotherapy at 5 years post-KT if they were older, had an older donor, had an acquired cause of end-stage renal disease, had pre-KT HTN, and were transplanted in a more recent era (since 2000). Our analysis indicated that the use of 1 versus 2 antihypertensive(s) has a similar effect on survival outcomes.

Studies in adult KT recipients have shown that HTN negatively impacts allograft function and survival (3, 5–9, 23–29), and that the severity of HTN contributes proportionally to outcomes. Mange *et al.* showed that the relative risk of allograft failure increases by 15%, 27% and 30% with each 10-mm Hg increase in systolic, diastolic and mean arterial blood pressure (BP) at 1-year post-KT (5). Opelz and Döhler reported on a large cohort of primary DD kidney recipients, showing that recipients with systolic BPs >140 mm Hg at 1-year post-KT and controlled to 140 mm Hg by 3 years post-KT exhibited improved long-term GS when compared with recipients experiencing uncontrolled and sustained high BPs (8).

Short-term studies involving pediatric KT recipients have shown results similar to those in the adult population (2, 10–13, 30–34). Mitsnefes *et al.* reported that the 3-month systolic BP measurement was an independent predictor of 1-year measured GFR ($p<0.001$) (31). Mitsnefes *et al.* also reported that HTN within the first few months post-KT is associated with worse allograft function (at 1-year follow-up), and that systolic ($p<0.0001$) and diastolic ($p=0.02$) HTN were associated with worse GS (12). In a single-center retrospective study, Sorof *et al.* reported that antihypertensive medication use was associated with a lower

eGFR at all post-KT time intervals up to 3-years post-KT ($n=47$, $p<0.01$) (30). Similarly, Silverstein *et al.* reported that recipients with normal systolic BPs during 4.6 years of follow up post-KT had higher eGFR than hypertensive recipients (84 vs. 52 mL/min/1.73 m²; $p=0.02$) (10).

In a retrospective analysis of the North American Pediatric Renal Trials and Collaborative Study (NAPRTCS) registry database, Sorof *et al.* reported that antihypertensive medication use was associated with a relative risk of graft failure of 1.4 during a 5-year follow-up period (11). In a retrospective single center analysis of 282 LD KT recipients aged 5–20 years, El-Husseini *et al.* found that HTN within the first year post-KT was associated with a 13% reduction in the GS rate at 5-years post-KT (32). In a longer follow up, El-Husseini *et al.* found that the incidence of HTN post-KT was higher in children with GS of <10 years ($n=67$) compared to those with GS of ≥10 years ($n=30$; 79% vs 60%, $p=0.04$) (31). Analysis by Ellis *et al.* of data from the NAPRTCS registry database showed that antihypertensive medication use in the first month post-KT was associated with poorer GS beyond 10 years with a reported hazard ratio of 1.9 for graft failure ($p=0.02$) (34).

Our data indicate that long-term pediatric PS does not appear to be associated with use of antihypertensives at an advanced time point post-KT. This may be in part attributable to the young demographic, relative absence of co-morbidity in pediatric transplant recipients, and short follow-up relative to expected lifespan. However, we found that use of antihypertensives at 5 years post-KT was associated with poorer overall GS and DCGS beyond 10 years. In our study, the rate of overall graft failure at 10, 15, and 20 years post-KT was 1.6, 1.5, and 1.4 times higher, respectively, in recipients with HTN versus those without HTN. No prior study has evaluated antihypertensive medication use at 5 years post-KT as a risk factor for GS at 15 and 20 years post-KT.

In contrast to studies by Sorof *et al.* (11, 30), our data did not show an association between the number of antihypertensives taken and survival outcomes. This difference may reflect comparable BP control in recipients receiving 1 versus ≥2 antihypertensive(s). However, we did find that use of an ACEI exhibited a positive association with post-KT GS and DCGS, and this may have been due to renoprotection via angiotensin blockade.

Additionally, our analysis suggested that angiotensin blockade may have a positive effect on long-term GS in recipients with HTN. Multivariate proportional hazards modeling, which accounted for other possible confounding pre- and post-KT variables, suggested that HTN requiring an antihypertensive may be a risk factor for decreased GS at >5 years, but is not when HTN is treated with an ACEI. Data also indicated that recipients with better renal function at 5 years post-KT were not disproportionately treated with an ACEI. In a retrospective analysis of 2,031 adult KT recipients, use of ACEI and/or ARB therapy post-KT was associated with improved long-term PS and GS rates (35); 10-year PS was 74% with ACEIs/ARBs and 53% without ACEIs/ARBs ($p<0.001$), whereas 10-year GS was 59% with ACEIs/ARBs and 41% without ACEIs/ARBs ($p=0.002$) (35). In contrast, a retrospective analysis of 17,209 adult kidney and 1,744 adult heart transplant recipients found no association between ACEI/ARB therapy and PS or GS post-KT (36). Furthermore, a recently published randomized, double-blind, placebo-controlled trial by Ibrahim *et al.* did not find Losartan (vs. placebo) to have a significant effect on preventing graft failure due to interstitial fibrosis and/or tubular atrophy when initiated within the first 3 months post-KT ($p=0.2$) (37). This was not a study of the effects of ARBs on PS or long-term GS. Though ACEIs and ARBs provide renoprotective benefits and are known to reduce the rate of progression of native kidney disease, their use in KT recipients is controversial due to their side effects (hyperkalemia, anemia, decreased GFR) (38).

There are several additional limitations of this study. The analysis is retrospective and not a randomized or controlled study of different antihypertensive treatment regimens. Secondly, we analyzed our recipients based on antihypertensive medication use at a single time point (5 years post-KT) and not on actual BP measurements. However, our recipient stratification was comparable to what has been done by Sorof *et al.*, El-Husseini *et al.*, and Ellis *et al.* (10, 28, 30, 32). Thirdly, there is a relative absence of racial diversity (>95% Caucasian) in our study cohort, which constrains the universality of the conclusions, especially as it pertains to AA recipients. Other limitations included not being able to determine the underlying cause of post-KT HTN, how the decision was made to use ACEI and/or ARB therapy, or to determine if the recipient had proteinuria, which is considered by some to be an indication for the use of ACEIs.

In conclusion, use of antihypertensives at 5 years post-KT is associated with poorer GS and DCGS at 10–20 years post-KT. In addition to optimization of BP control post-KT, use of ACEIs and possibly ARBs may enable achieving longer GS in pediatric recipients. Future studies should prospectively examine the impact of BP control and the use of ACEIs on GS in children after KT.

Acknowledgments

The authors would like to thank Stephanie Daily and Hang McLaughlin for their assistance with the preparation of this manuscript. This work was supported by a grant from the National Institutes of Health (NIH DK13083).

Abbreviations

AA	African-American
ACEI	angiotensin-converting enzyme inhibitor
AR	acute rejection
ARB	angiotensin receptor blocker
BP	blood pressure
CCB	calcium channel blocker
CR	chronic rejection
DCGS	death-censored graft survival
DD	deceased donor
eGFR	estimated glomerular filtration rate
GS	graft survival
HR	hazards ratio
HTN	hypertension
IQR	interquartile range
IV	<i>intravenously</i>
KT	kidney transplantation
LD	living donor
NAPRTCS	North American Pediatric Renal Transplant Collaborative Study
OR	odds ratio

PO	per os (<i>orally</i>)
PS	patient survival
RDP	rapid discontinuation of prednisone

References

1. Baluarte HJ, Gruskin AB, Ingelfinger JR, Stablein D, Tejani A. Analysis of hypertension in children post renal transplantation--a report of the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS). *Pediatr Nephrol.* 1994; 8(5):570. [PubMed: 7819003]
2. Mitsnefes MM. Hypertension and end-organ damage in pediatric renal transplantation. *Pediatr Transplant.* 2004; 8(4):394. [PubMed: 15265168]
3. Seeman T. Hypertension after renal transplantation. *Pediatr Nephrol.* 2009; 24(5):959. [PubMed: 17955265]
4. Hansen ML, Gunn PW, Kaelber DC. Underdiagnosis of hypertension in children and adolescents. *JAMA.* 2007; 298(8):874. [PubMed: 17712071]
5. Mange KC, Cizman B, Joffe M, Feldman HI. Arterial hypertension and renal allograft survival. *JAMA.* 2000; 283(5):633. [PubMed: 10665703]
6. Cosio FG, Henry M, Pesavento TE, Ferguson RM, Kim S, Lemeshow S. The relationship between donor age and cadaveric renal allograft survival is modified by the recipient's blood pressure. *Am J Transplant.* 2003; 3(3):340. [PubMed: 12614292]
7. Mange KC, Feldman HI, Joffe MM, Fa K, Bloom RD. Blood pressure and the survival of renal allografts from living donors. *J Am Soc Nephrol.* 2004; 15(1):187. [PubMed: 14694172]
8. Opelz G, Dohler B. Improved long-term outcomes after renal transplantation associated with blood pressure control. *Am J Transplant.* 2005; 5(11):2725. [PubMed: 16212633]
9. Mangray M, Vella JP. Hypertension after kidney transplant. *Am J Kidney Dis.* 2011; 57(2):331. [PubMed: 21251543]
10. Silverstein DM, Leblanc P, Hempe JM, Ramcharan T, Boudreaux JP. Tracking of blood pressure and its impact on graft function in pediatric renal transplant patients. *Pediatr Transplant.* 2007; 11(8):860. [PubMed: 17976120]
11. Sorof JM, Sullivan EK, Tejani A, Portman RJ. Antihypertensive medication and renal allograft failure: a North American Pediatric Renal Transplant Cooperative Study report. *J Am Soc Nephrol.* 1999; 10(6):1324. [PubMed: 10361872]
12. Mitsnefes MM, Khoury PR, McEnery PT. Early posttransplantation hypertension and poor long-term renal allograft survival in pediatric patients. *J Pediatr.* 2003; 143(1):98. [PubMed: 12915832]
13. Nagasako SS, Koch Nogueira PC, Machado PG, Medina Pestana JO. Arterial hypertension following renal transplantation in children-a short-term study. *Pediatr Nephrol.* 2003; 18(12):1270. [PubMed: 14586678]
14. Blumenthal S, Epps RP, Heavenrich R, Lauer RM, Lieberman E, Mirkin B, et al. Report of the task force on blood pressure control in children. *Pediatrics.* 1977; 59(5 2 suppl):I. [PubMed: 859728]
15. Report of the Second Task Force on Blood Pressure Control in Children--1987 Task Force on Blood Pressure Control in Children. National Heart, Lung, and Blood Institute, Bethesda, Maryland. *Pediatrics.* 1987; 79(1):1. [PubMed: 3797155]
16. Update on the 1987 Task Force Report on High Blood Pressure in Children and Adolescents: a working group report from the National High Blood Pressure Education Program. National High Blood Pressure Education Program Working Group on Hypertension Control in Children and Adolescents. *Pediatrics.* 1996; 98(4 Pt 1):649. [PubMed: 8885941]
17. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics.* 2004; 114(2 Suppl):555. 4th Report. [PubMed: 15286277]
18. Schwartz GJ, Munoz A, Schneider MF, Mak RH, Kaskel F, Warady BA, et al. New equations to estimate GFR in children with CKD. *J Am Soc Nephrol.* 2009; 20(3):629. [PubMed: 19158356]

19. Chavers BM, Gillingham KJ, Matas AJ. Complications by age in primary pediatric renal transplant recipients. *Pediatr Nephrol.* 1997; 11(4):399. [PubMed: 9260233]
20. Birk PE, Matas AJ, Gillingham KJ, Mauer SM, Najarian JS, Chavers BM. Risk factors for chronic rejection in pediatric renal transplant recipients--a single-center experience. *Pediatr Nephrol.* 1997; 11(4):395. [PubMed: 9260232]
21. Khositseth S, Matas A, Cook ME, Gillingham KJ, Chavers BM. Thymoglobulin versus ATGAM induction therapy in pediatric kidney transplant recipients: a single-center report. *Transplantation.* 2005; 79(8):958. [PubMed: 15849550]
22. Chavers BM, Chang YC, Gillingham KJ, Matas A. Pediatric kidney transplantation using a novel protocol of rapid (6-day) discontinuation of prednisone: 2-year results. *Transplantation.* 2009; 88(2):237. [PubMed: 19623020]
23. Ojo AO, Held PJ, Port FK, Wolfe RA, Leichtman AB, Young EW, et al. Chronic renal failure after transplantation of a nonrenal organ. *N Engl J Med.* 2003; 349(10):931. [PubMed: 12954741]
24. Kasiske BL, Anjum S, Shah R, Skogen J, Kandaswamy C, Danielson B, et al. Hypertension after kidney transplantation. *Am J Kidney Dis.* 2004; 43(6):1071. [PubMed: 15168388]
25. de Vries AP, Bakker SJ, van Son WJ, van der Heide JJ, Ploeg RJ, The HT, et al. Metabolic syndrome is associated with impaired long-term renal allograft function; not all component criteria contribute equally. *Am J Transplant.* 2004; 4(10):1675. [PubMed: 15367224]
26. Ortiz F, Paavonen T, Tornroth T, Koskinen P, Finne P, Salmela K, et al. Predictors of renal allograft histologic damage progression. *J Am Soc Nephrol.* 2005; 16(3):817. [PubMed: 15689401]
27. Paoletti E, Gherzi M, Amidone M, Massarino F, Cannella G. Association of arterial hypertension with renal target organ damage in kidney transplant recipients: the predictive role of ambulatory blood pressure monitoring. *Transplantation.* 2009; 87(12):1864. [PubMed: 19543066]
28. Vetromile F, Szwarc I, Garrigue V, Delmas S, Fesler P, Mimran A, et al. Early high pulse pressure is associated with graft dysfunction and predicts poor kidney allograft survival. *Transplantation.* 2009; 88(9):1088. [PubMed: 19898204]
29. Jardine AG, Gaston RS, Fellstrom BC, Holdaas H. Prevention of cardiovascular disease in adult recipients of kidney transplants. *Lancet.* 2011; 378(9800):1419. [PubMed: 22000138]
30. Sorof JM, Goldstein SL, Brewer ED, Steiger HM, Portman RJ. Use of anti-hypertensive medications and post-transplant renal allograft function in children. *Pediatr Transplant.* 2000; 4(1):21. [PubMed: 10731054]
31. Mitsnefes MM, Omolaja A, McEnery PT. Short-term pediatric renal transplant survival: blood pressure and allograft function. *Pediatr Transplant.* 2001; 5(3):160. [PubMed: 11422817]
32. El-Husseini AA, Foda MA, Shokeir AA, Shehab El-Din AB, Sobh MA, Ghoneim MA. Determinants of graft survival in pediatric and adolescent live donor kidney transplant recipients: a single center experience. *Pediatr Transplant.* 2005; 9(6):763. [PubMed: 16269048]
33. El-Husseini AA, Foda MA, Osman YM, Sobh MA. Characteristics of long-term live-donor pediatric renal transplant survivors: a single-center experience. *Pediatr Transplant.* 2006; 10(3):288. [PubMed: 16677350]
34. Ellis EN, Martz K, Talley L, Ilyas M, Pennington KL, Blaszkak RT. Factors related to long-term renal transplant function in children. *Pediatr Nephrol.* 2008; 23(7):1149. [PubMed: 18301925]
35. Heinze G, Mitterbauer C, Regele H, Kramar R, Winkelmayr WC, Curhan GC, et al. Angiotensin-converting enzyme inhibitor or angiotensin II type 1 receptor antagonist therapy is associated with prolonged patient and graft survival after renal transplantation. *J Am Soc Nephrol.* 2006; 17(3):889. [PubMed: 16481415]
36. Opelz G, Zeier M, Laux G, Morath C, Dohler B. No improvement of patient or graft survival in transplant recipients treated with angiotensin-converting enzyme inhibitors or angiotensin II type 1 receptor blockers: a collaborative transplant study report. *J Am Soc Nephrol.* 2006; 17(11):3257. [PubMed: 17035607]
37. Ibrahim HN, Jackson S, Connaire J, Matas A, Ney A, Najafian B, et al. Angiotensin II Blockade in Kidney Transplant Recipients. *J Am Soc Nephrol.* 2013
38. Cruzado JM, Rico J, Grinyo JM. The renin angiotensin system blockade in kidney transplantation: pros and cons. *Transpl Int.* 2008; 21(4):304. [PubMed: 18266774]

Figure 1.

Actuarial survival outcomes in pediatric kidney recipients, comparing those with and without documented use of antihypertensives at 5 years post-transplant. Overall graft survival (A) and death-censored GS (DCGS) (D), and GS and DCGS in recipients of living (B, E) or deceased (C, F) donor kidneys, comparing. There were differences in graft and death-censored graft survival outcomes between cohorts for the overall study population and for recipients of living donor kidneys ($*p < 0.05$), but no differences in these outcomes for recipients of deceased donor kidneys.

Figure 2.

Actuarial graft and death-censored graft survival in recipients of living donor kidneys using 1 antihypertensive at 5 years post-transplant, comparing recipients treated with an angiotensin-converting enzyme inhibitor (ACEI) (A, C) and with an ACEI or an angiotensin receptor blocker (ARB) (B, D) versus those that are not. There were differences in graft and death-censored graft survival outcomes between recipients using an ACEI and those not using an ACEI (* $p < 0.05$), and between those using an ACEI or ARB and those not using an ACEI or ARB (* $p < 0.05$).

Table 1**Recipient and Transplant Demographic Data**

	Without HTN	With HTN
Total <i>n</i> (% of total)	160 (54.6%)	133 (45.4%)
Study Variable (% of total)	<i>n</i> (% of cohort)	
<i>Age</i> ***		
< 5 years (42.8%)	86 (53.8%)	39 (29.3%)
5–11 years (25.7%)	36 (22.5%)	39 (29.3%)
11–18 years (31.5%)	38 (23.7%)	55 (41.4%)
Gender		
Female (32.9%)	54 (33.7%)	42 (31.6%)
Male (67.1%)	106 (66.3%)	91 (68.4%)
Race		
Caucasian (95.2%)	153 (95.6%)	126 (94.7%)
Non-Caucasian (4.8%)	7 (4.4%)	7 (5.3%)
<i>Pre-Transplant HTN</i> ***		
No (71.9%)	138 (86.3%)	72 (54.1%)
Yes (28.1%)	22 (13.7%)	61 (45.9%)
<i>Primary Kidney Disease</i> *		
Congenital/Obstruction/Reflux Nephropathy (51.4%)	92 (57.5%)	59 (44.4%)
Glomerulonephritis (6.5%)	8 (5.0%)	11 (8.3%)
Congenital Nephrotic Syndrome (8.2%)	17 (10.6%)	7 (5.3%)
Focal Segmental Glomerulosclerosis (7.2%)	10 (6.3%)	11 (8.3%)
Other (26.6%)	33 (20.6%)	45 (33.8%)
<i>Pre-Transplant Dialysis</i>		
No (33.1%)	60 (37.5%)	37 (27.8%)
Yes (66.9%)	100 (62.5%)	96 (72.2%)
Pre-Transplant Nephrectomy		
No (37.2%)	53 (33.1%)	56 (42.1%)
Yes (63.8%)	107 (66.9%)	77 (57.9%)
Donor Type		
Deceased (17.4%)	28 (17.5%)	23 (17.3%)
Living (82.6%)	132 (82.5%)	110 (82.7%)
<i>Transplant Era</i> **		
1984–1999 (79.5%)	141 (88.1%)	92 (69.2%)
2000–2005 (20.5%)	19 (11.9%)	41 (30.8%)

	Without HTN	With HTN
<i>Rapid Discontinuation of Prednisone</i> *		
No (95.2%)	157 (98.1%)	122 (91.7%)
Yes (4.8%)	3 (1.9%)	11 (8.3%)

*
p<0.05;

**
p<0.001;

p<0.0001; HTN, hypertension

Table 2

Summary of Antihypertensive Medication Use

	Without HTN	With HTN	
Number of Medications (% of total)	0 (54.6%)	1 (32.1%)	2 (13.3%)
Class of Medication	<i>n</i> (% of <i>With HTN</i>)		
Alpha-1 antagonist	-	5 (3.8%)	8 (6.0%)
Alpha-2 agonist	-	1 (0.8%)	5 (3.8%)
Angiotensin-converting enzyme inhibitor	-	19 (14.3%)	13 (9.8%)
Angiotensin receptor blocker	-	4 (3.0%)	5 (3.8%)
Beta-blocker	-	23 (17.3%)	21 (15.8%)
Calcium channel blocker	-	37 (27.8%)	32 (24.1%)
Direct vasodilators	-	0 (0%)	3 (2.3%)

HTN, hypertension

Table 3

Rejection, Survival, and Functional Outcomes

	Without HTN	With HTN
Total <i>n</i> (% of total)	160 (54.6%)	133 (45.4%)
Overall (All donor types)	<i>n</i> remaining (% of cohort)	
<hr/>		
Patient survival		
10-year	137 (98.7%)	83 (96.8%)
15-year	103 (94.7%)	36 (91.1%)
20-year	49 (85.8%)	15 (84.0%)
<hr/>		
<i>Graft survival</i> [*]		
10-year	124 (85.7%)	75 (78.4%)
15-year	80 (68.4%)	24 (53.0%)
20-year	30 (52.5%)	4 (33.4%)
<hr/>		
<i>Death-censored graft survival</i> [*]		
10-year	124 (86.3%)	75 (80.2%)
15-year	80 (70.2%)	24 (56.3%)
20-year	30 (57.1%)	4 (40.0%)
<hr/>		
Living donor		
<hr/>		
Patient survival		
10-year	113 (98.4%)	68 (96.2%)
15-year	85 (95.6%)	31 (92.0%)
20-year	37 (87.7%)	12 (87.1%)
<hr/>		
<i>Graft survival</i> [*]		
10-year	107 (90.5%)	61 (80.2%)
15-year	70 (73.8%)	21 (55.4%)
20-year	26 (58.5%)	3 (36.2%)
<hr/>		
<i>Death-censored graft survival</i> [*]		
10-year	107 (91.2%)	61 (82.4%)
15-year	70 (76.1%)	21 (57.0%)
20-year	26 (64.6%)	3 (42.5%)
<hr/>		
Deceased donor		
<hr/>		
Patient survival		
10-year	24 (100.0%)	15 (100.0%)
15-year	18 (91.3%)	5 (85.7%)
20-year	12 (80.1%)	2 (68.6%)
<hr/>		
Graft survival		
10-year	17 (63.8%)	14 (70.7%)
15-year	10 (44.2%)	3 (39.8%)
20-year	4 (28.4%)	1 (19.9%)
<hr/>		
Death-censored graft survival		

	Without HTN	With HTN
10-year	17 (63.8%)	14 (70.7%)
15-year	10 (44.2%)	3 (53.0%)
20-year	4 (28.4%)	1 (26.5%)
Rejection at 5 years (% of total)	<i>n</i> (% of Cohort)	
Acute Rejection		
No (56.7%)	95 (59.4%)	71 (53.4%)
Yes (43.3%)	65 (40.6%)	62 (46.6%)
Chronic Rejection		
No (91.5%)	149 (93.1%)	119 (89.5%)
Yes (8.5%)	11 (6.9%)	14 (10.5%)
Function at 5 years	Median (IQR) [mL/min/1.73m ²]	
<i>Estimated GFR</i> [*]	68.8 (52.2–86.0)	63.5 (45.6–75.5)

^{*} p<0.05; GFR, glomerular filtration rate; HTN, hypertension; IQR, interquartile range