Risk of ESKD in Older Live Kidney Donors with Hypertension

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Abstract

Background and objectives Hypertension in older kidney donor candidates is viewed as safe. However, hypertension guidelines have evolved and long-term outcomes have not been explored. We sought to quantify the 15-year risk of ESKD and mortality in older donors (≥50 years old) with versus those without hypertension.

Design, setting, participants, & measurements A United States cohort of 24,533 older donors from 1999 to 2016, including 2265 with predonation hypertension, were linked to Centers for Medicare and Medicaid Services data and the Social Security Death Master File to ascertain ESKD development and mortality. The exposure of interest was predonation hypertension. From 2004 to 2016, hypertension was defined as documented predonation use of antihypertensive therapy, regardless of systolic BP or diastolic BP; from 1999 to 2003, when there was no documentation of antihypertensive therapy, hypertension was defined as predonation systolic BP ≥140 or diastolic BP ≥90 mm Hg.

Results Older donors were 82% white, 6% black, 7% Hispanic, and 3% Asian. The median follow-up was 7.1 years (interquartile range, 3.4–11.1; maximum, 18). There were 24 ESKD and 252 death events during the study period. The 15-year risk of ESKD was 0.8% (95% confidence interval [95% CI], 0.4 to 1.6) for donors with hypertension (mean systolic BP, 138 mm Hg) versus 0.2% (95% CI, 0.1 to 0.4) for donors without hypertension (mean systolic BP, 123 mm Hg; adjusted hazard ratio, 3.04; 95% CI, 1.28 to 7.22; P = 0.01). When predonation antihypertensive therapy was available, the risk of ESKD was 6.21-fold higher (95% CI, 1.20 to 32.17; P = 0.03) for donors using antihypertensive therapy (mean systolic BP, 132 mm Hg) versus those not using antihypertensive therapy (mean systolic BP, 124 mm Hg). There was no significant association between donor hypertension and 15-year mortality (hazard ratio, 1.18; 95% CI, 0.84 to 1.66; P = 0.34).

Conclusions Compared with older donors without hypertension, older donors with hypertension had higher risk of ESKD, but not mortality, for 15 years postdonation. However, the absolute risk of ESKD was small.

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Introduction

The number of older (age ≥50 years old) live kidney donors in the United States has increased by 50% over the past decade (1), and will likely continue to grow for several reasons. First, the Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline on the Evaluation and Care of Living Kidney Donors allows more permissiveness for older living kidney donation (9), a substantial proportion of this population may present with common aging-related conditions such as hypertension (10).

Hypertension in healthy, screened, older live kidney donor candidates is viewed as relatively benign (11,12). However, this prevailing view is on the basis of short-term data (<5 years of follow-up), mostly from single-center studies comprising predominantly white participants (11,12), and within the context of systolic/diastolic BP targets in clinical guidelines (13–15). With longer follow-up data, a multinational meta-analysis found donor nephrectomy to be associated with a 5-mm Hg increase in systolic BP within 5–10 years after donation over that expected with normal aging (16). Because one mechanism contributing to the development of primary hypertension is a reduction in the number of nephrons (17,18), the 50% nephron mass reduction associated with donor nephrectomy may exacerbate preexisting, controlled hypertension. In a national study of 125,427 donors observed for up to 25 years, hypertension-attributed ESKD was the leading cause of ESKD by year 25 (19).
In this study, however, 78% of study participants were aged <50 years old and predonation hypertension status was not considered; as such, inferences from this cohort may not apply to older donors who have hypertension before donation.

We sought to understand the long-term clinical significance of predonation hypertension in older donors in light of hypertension guidelines that may alter practice (13,14,20–23). To accomplish this, we used a linkage of Medicare, Social Security, and national registry data from older live kidney donors between 1999 and 2016 to estimate the 15-year risk of ESKD and mortality in older donors with hypertension compared with donors without hypertension.

Materials and Methods

Data Source and Study Population

This study used data from the Scientific Registry of Transplant Recipients (SRTR). The SRTR data system includes data on all donors, waitlisted candidates, and transplant recipients in the United States, submitted by the members of the Organ Procurement and Transplantation Network (OPTN), and has been described elsewhere (24–26). The Health Resources and Services Administration, US Department of Health and Human Services, provides oversight to the activities of the OPTN and SRTR contractors. The SRTR data were linked to the Centers for Medicare and Medicaid Services data and the Social Security Death Master File to ascertain development of ESKD and mortality. The study population included 24,533 older (≥50 years old) live kidney donors in the United States between January 1, 1999 and December 31, 2016.

Exposure of Interest

The exposure of interest was predonation hypertension. We identified donor hypertension status using predonation clinical information of systolic/diastolic BP and history of hypertension and antihypertensive therapy that were collected in SRTR living donor registration forms. For the years of donation from 2004 to 2016, hypertension was defined as documented predonation use of antihypertensive therapy with history of hypertension, regardless of systolic BP and diastolic BP. From 1999 to 2003, documentation of antihypertensive therapy versus those not using antihypertensive therapy. We restricted the study period to 2004–2016 during which hypertension was defined on the basis of documentation of predonation use of antihypertensive therapy with history of hypertension, regardless of systolic BP/diastolic BP. In this analysis, we further adjusted for systolic BP <125 mm Hg, controlled systolic BP as per the American College of Cardiology (ACC) and American Heart Association (AHA) 2017 Guideline for the Prevention, Evaluation, and Management of High BP, and assessed effect modification by systolic BP <125 mm Hg (22,23). Second, we built multivariable Cox models to further adjust for obesity (body mass index [BMI] ≥30).

Statistical Analyses

We used Kaplan–Meier methods to estimate the 15-year cumulative incidence of ESKD and mortality in older donors with hypertension versus those without hypertension. We used multivariable Cox regression to compare the risk of ESKD and mortality in older donors with hypertension versus those without hypertension, adjusting for baseline characteristics: age, sex, race/ethnicity, eGFR, and biologic relationship to the recipient. We performed sensitivity analyses to evaluate the robustness of our results.

Results

Study Population

Between January 1, 1999 and December 31, 2016, we identified 24,533 screened older individuals (≥50 years old) who underwent donor nephrectomy in the United States, including 2265 (9%) with predonation hypertension. Donors with hypertension were 84% white, 6% black, 6% Hispanic, 3% Asian, and 1% other. Donors with hypertension had a mean age of 57 years and a mean eGFR of 87 ml/min per 1.73 m², 60% were women, 50% were biologically related to their recipient, and 25% reported having smoked cigarettes. In general, donors without hypertension were comparable with donors with hypertension with respect to these demographic and health characteristics; however, there was a greater proportion of individuals who were aged ≥60 years old (32% versus 21%) or obese (28% versus 20%) among donors with hypertension (Table 1).
Patterns of Predonation BP

The predonation mean (SD) systolic and diastolic BP were 138 (15) and 80 (10) mm Hg for donors with hypertension and 123 (13) and 74 (9) mm Hg for donors without hypertension. Among donors with predonation documented use of antihypertensive therapy, 9% were on diet-only therapy, 62% on nondiuretic only, 15% on diuretic only, 7% on dual therapy of nondiuretic and diuretic, and 7% on an unknown type of therapy; most donors (57%) had a history of hypertension for 5 years before donation; 11% for 6–10 years, 7% for >10 years, and 25% for an unknown duration. The predonation mean (SD) systolic and diastolic BP were 132 (15) and 78 (9) mm Hg for donors documented as using antihypertensive therapy, and 29% had systolic BP ≥140 mm Hg. By comparison, for donors documented as not using antihypertensive therapy during this era, predonation mean (SD) systolic and diastolic BP were 124 (14) and 74 (9) mm Hg, and 13% had systolic BP ≥140 mm Hg.

Risk of ESKD

Over a median follow-up of 7.1 years (interquartile range, 3.4–11.1 years; maximum, 18 years), 24 ESKD events were observed, and the ESKD incidence rate was 1.3 per 10,000 person-years. The unadjusted 15-year cumulative incidence of ESKD was 0.8% (95% confidence interval [95% CI], 0.4 to 1.6) for donors with hypertension versus 0.2% (95% CI, 0.1 to 0.4) for donors without hypertension (P=0.01) (Figure 1). In a multivariable regression accounting for age, sex, race, eGFR, and relationship to the recipient, the risk of ESKD was significantly higher for donors with hypertension compared with donors without hypertension (hazard ratio [HR], 3.04; 95% CI, 1.28 to 7.22; P=0.01) (Table 2). In sensitivity analyses, when we restricted our analysis to include only donors from
the 2004 to 2016 period, during which our definition of hypertension was solely on the basis of documentation of antihypertensive therapy with history of hypertension (sample size reduced from \( n=24,533 \) to \( n=20,230 \)), we observed a stronger association between hypertension and the risk of ESKD (HR, 6.21; 95% CI, 1.20 to 32.17; \( P=0.03 \)), and these inferences remained significant even after further adjustment for systolic BP \(<125 \text{ mm Hg} \) (HR, 5.45; 95% CI, 1.04 to 28.61; \( P=0.04 \)), with no evidence of effect modification (\( P \) for interaction =0.36). Our inferences of ESKD risk remained unchanged after further adjustment for obesity (HR, 2.85; 95% CI, 1.19 to 6.78; \( P=0.02 \)) or accounting for death as a competing risk to ESKD (HR, 3.04; 95% CI, 1.27 to 7.28; \( P=0.01 \)).

**Discussion**

In this national study of older, live kidney donors from 1999 to 2016, the mean predonation systolic BP was 138 mm Hg for donors with hypertension versus 123 mm Hg for donors without hypertension. We found that hypertension was associated with higher risk of ESKD, but not mortality. The 15-year risk of ESKD was 0.8% for older donors with hypertension versus 0.2% for older donors without hypertension. Although the magnitude of the absolute risk increase was small, this risk association remained significant after accounting for baseline characteristics (3.04-fold higher). By contrast, Grams et al. (3) reported the risk of ESKD was 1.35-fold higher for healthy nondonors using antihypertensive therapy compared with those not using antihypertensive therapy. When use of antihypertensive therapy was available in our study (2004–2016), the risk of ESKD was 6.21-fold higher for donors using antihypertensive therapy (mean systolic BP, 132 mm Hg) compared with those not using antihypertensive therapy; this risk remained similar after further adjustment for systolic BP \(<125 \text{ mm Hg} \).

These findings add new information to the debate as to whether white, older donor candidates with controlled hypertension are at low risk for ESKD (11,12,32,33). In our race-adjusted analysis, we show that older donors with hypertension were still at higher risk of ESKD compared with older donors without hypertension, despite being cleared for nephrectomy with presumably controlled hypertension and otherwise healthy. These inferences held true after further adjustment for obesity. Our study shows that in clinical practice, many individuals with systolic BP \( \geq 140 \text{ mm Hg} \) have been permitted to donate over the past two decades. These practice patterns are not consistent with the JNC7 clinical guideline published during the study period, which defined systolic BP \(<140 \text{ mm Hg} \) as...
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<th>Adjusted</th>
<th>P Value</th>
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<td>HR (95% CI)</td>
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HR, adjusted hazard ratio; 95% CI, 95% confidence interval; —, not applicable.

*aMultivariable Cox regression to compare the risk of ESKD and mortality for 15 years postdonation in older (≥50 years old) donors with hypertension (n=2265) versus those without hypertension (n=22,268), accounting for age, sex, race/ethnicity, eGFR, and donor/recipient relationship.

*bImputed for 1% missing eGFR (n=234 eGFR values). Our inferences remained unchanged in the complete-data analysis (n=24,299).
the therapeutic goal for individuals with primary hypertension and without diabetes or CKD (13), as is typical of healthy, screened donors. They are more consistent with a subsequent update to these guidelines (the Eighth Joint National Committee), which set a higher therapeutic goal (systolic BP $\leq 150$ mm Hg) for individuals aged $\geq 60$ years (14). Neither of these guidelines, however, are specific enough to guide practices for a population of otherwise healthy, screened individuals with hypertension who have donated 50% of their nephron mass.

The Systolic Blood Pressure Intervention Trial reports, published at the end of our study period, recommend more intensive systolic BP targets (<120 mm Hg) for older ($\geq 50$ years old) nondonors without diabetes who have an increased risk of cardiovascular disease (20,21). Furthermore, the ACC and AHA 2017 Guideline for the Prevention, Evaluation, and Management of High BP in adults recommends a BP target of $<130/80$ mm Hg for primary prevention in individuals with atherosclerotic cardiovascular disease risk $\geq 10\%$ (22,23,34,35). In our study, we cannot extend these inferences to healthy, screened older donors with documented use of antihypertensive therapy. Also, we do not establish a safety threshold of systolic BP control for risk reduction. However, we do show that despite meeting systolic BP targets proposed by JNC7 and the Eighth Joint National Committee (mean systolic BP, 132 mm Hg), older donors with hypertension had significantly higher risk of ESKD (36). In a population who may already have a diminished number of nephrons because of primary hypertension (17,18), the 50% reduction in nephron mass may further exacerbate this preexisting condition (36), and the drastic alteration of kidney physiology associated with donor nephrectomy might be a potential target of first-line antihypertensive therapy.

A key strength of our approach was the use of national registry data and highly reliable linkage-based ESKD ascertainment to study the largest cohort of older donors to date, allowing us to make inferences specific to a small but growing subgroup of donors. Because donors are rigorously evaluated before nephrectomy, another strength of our approach is that donors with hypertension were unlikely to have occult kidney disease according to markers such as creatinine clearance and urine albumin-to-creatinine ratio (37). As such, the inferences we make here may be generalizable to the majority of older donor candidates with primary hypertension.

The limitations of this study merit consideration. Despite being the largest study of older donors with hypertension to date, we recognize the potential limitations of using registry-based data. First, our definition of hypertension from 1999 to 2003 was on the basis of BP measurements. But regardless of whether predonation BP reflected single in-office readings, white coat hypertension, or masked hypertension, our analysis of donors with documented use of antihypertensive therapy found that these donors had a mean systolic BP of 132 mm Hg and significantly higher risk of ESKD. Second, there was no information on urine albumin, so we cannot rule out the possibility that ESKD arose from underlying kidney disease at donation (38,39). However, clinical practice guidelines such as the Amsterdam Forum and KDIGO specify that older donor candidates who have been cleared for nephrectomy should have no evidence of target organ damage (e.g., proteinuria, microalbuminuria, left ventricular hypertrophy) (2,40). Third, we were unable to adjust for factors such as antihypertensive therapy regimen, dosing, or adherence to assess whether intensive therapy may minimize hypertension-attributable ESKD after donation (14,41,42). Despite these limitations, national registries constitute the only comprehensive data source for studying the rare event of ESKD development among live donors.

Figure 2. The 15-year risk of mortality was not significantly different for older donors with hypertension versus older donors without hypertension. This risk of mortality remained non-significant after accounting for baseline characteristics.
In conclusion, compared with older donors without hypertension, older donors with hypertension had higher risk of ESKD, but not mortality, for 15 years postdonation. However, the absolute risk of ESKD was small. These findings may help inform discussions with older candidates considering kidney donation. Long-term monitoring of systolic BP and kidney profile is suggested.

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Disclosures
Dr. Al Ammary, Dr. Luo, Dr. Muzaale, Dr. Massie, Dr. Snyder, Dr. Segev, Dr. Coresh, Dr. Brennan, Dr. Crews, Dr. Waldram, Dr. Qadi, Dr. Garonzik-Wang, Dr. Henderson, Dr. Wiseman, and Dr. Lindrooth have nothing to disclose.

References