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 live donors (2), who have much lower lifetime ESKD risks than younger donors (3). Second, the new kidney allocation system and the longer waiting times for deceased donors disadvantage older kidney transplant candidates, who may seek older live donors as a result (1,4,5). Third, outcomes in older kidney donors have been shown to be excellent (6–8). Although older donor candidates may offer an opportunity to increase 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/history of hypertension was unavailable; thus, hypertension was defined as predonation systolic BP ≥140 or diastolic BP ≥90 mm Hg, per the seventh Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High BP (JNC7) clinical guideline (13).

Outcome Ascertainment

Donors were observed from their date of donation to the date of ESKD diagnosis, death, or end of the study (December 31, 2016). Incident ESKD was ascertained through linkage to the Center for Medicare and Medicaid Services Form 2728, as we have previously reported (25,27–29). ESKD was defined as the initiation of maintenance dialysis or receipt of a kidney transplant, and donors were censored at death or end of the study. Donors who were diagnosed with ESKD within 90 days of donation (n=3) were excluded from analysis under the assumption that these patients underwent AKI during nephrectomy rather than CKD as a long-term consequence of living with one kidney. Death was ascertained through standard OPTN follow-up and *via* linkage to the Social Security Death Master File, as we have previously reported (25,29). As such, by study design, there was no loss to follow-up.

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. First, we built multivariable Cox models to compare the risk of ESKD and mortality in older donors using 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). Third, we also estimated the association of predonation hypertension with ESKD when accounting for the competing risk of death (30).

Because of incomplete baseline data including eGFR (1%) and BMI (5%), we used multiple imputation with chained equations (20 burn-in iterations and 50 imputations) to account for missing data as per the methods of White and Royston (31). The proportions of missingness of eGFR and BMI were similar between donors with and without hypertension. All analyses were performed using Stata 14.1/MP for Linux (StataCorp.). All hypothesis tests were two-sided (α=0.05).

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 m^2, 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).

Table 1. Characteristics of older live kidney donors at donation in the United States, 1999–2016

Characteristics[a]	Hypertension, *n*=2265[b]	No Hypertension, *n*=22,268
Age, mean (SD), yr	57 (6)	56 (5)
Age category, %		
50–54	37	48
55–59	31	31
60–64	21	15
≥65	11	6
Women	60	65
Race/ethnicity, %		
White	84	82
Black	6	6
Hispanic	6	8
Asian	3	3
Other[c]	1	1
Education level, %[d]		
≤High school	30	29
Attended college	24	25
College graduate	29	29
Post college	17	17
BMI, mean (SD)[e]	28 (4)	27 (4)
BMI category, %		
≤24	24	36
25–29	48	44
≥30	28	20
Smoker[f]	25	29
BP, mm Hg, mean (SD)[g]		
Systolic BP[h]	138 (15)	123 (13)
Diastolic BP[h]	80 (10)	74 (9)
Creatinine mg/dl, mean (SD)[i]	0.88 (0.26)	0.86 (0.31)
eGFR, ml/min per 1.73 m^2, mean (SD)	87 (14)	89 (14)
Biologically related to the recipient, %	50	46

Body mass index (BMI) calculated as weight in kilograms divided by height in meters squared.
[a]Characteristics at the time of donation (1999–2016) are shown; age, sex, race/ethnicity, and biologic relationship to the recipient were available throughout the study period.
[b]Hypertension was defined as predonation documented use of antihypertensive therapy/history of hypertension for the period 2004–2016, regardless of systolic and diastolic BP; or predonation systolic BP ≥140 or diastolic BP ≥90 mm Hg when there was no available documentation of antihypertensive therapy for the period 1999–2003 (8% missing between 1999 and 2016).
[c]Race/ethnicity, the category of "Other" included American Indian or Alaskan Native, Native Hawaiian or other Pacific Islander, and multiracial.
[d]Education: 36% missing between 1999 and 2003; 23% missing between 2004 and 2009; 7% missing between 2010 and 2016.
[e]BMI: 8% missing between 1999 and 2003; 6% missing between 2004 and 2009; 0.8% missing between 2010 and 2016.
[f]Smoking status: 100% missing between 1999 and 2003; 17% missing between 2004 and 2009; 0% missing between 2010 and 2016.
[g]BP: 0.2% missing between 1999 and 2003; 8% missing between 2004 and 2009; 1% missing between 2010 and 2016.
[h]Mean (SD) systolic and diastolic BP were 132 (15) and 78 (9) mm Hg for donors with documented use of antihypertensive therapy versus 124 (14) and 74 (9) mm Hg for those not using antihypertensive therapy for the period 2004–2016.
[i]Creatinine/eGFR: 0.8% missing between 1999 and 2003; 2% missing between 2004–2009; 0.4% missing between 2010 and 2016.

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

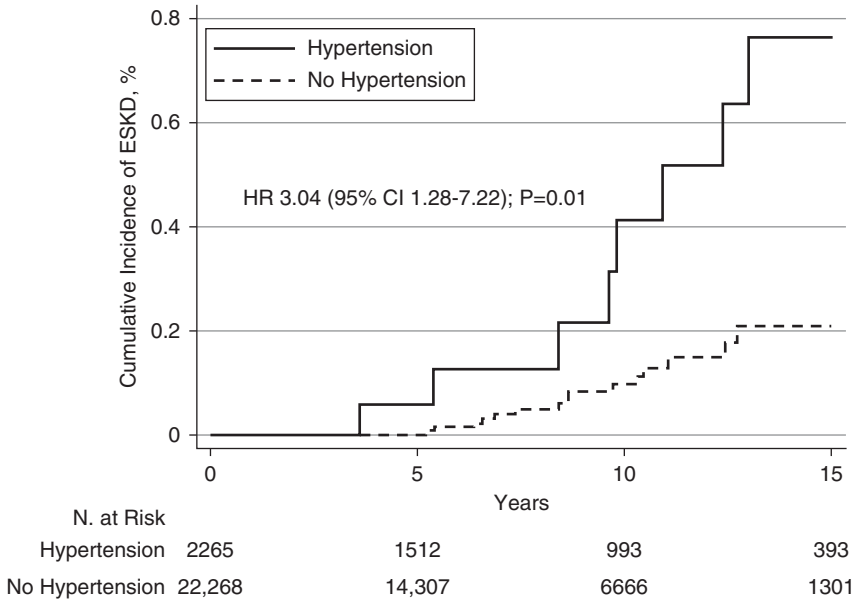

Figure 1. | **The 15-year risk of ESKD was higher for older donors with hypertension versus older donors without hypertension.** While the magnitude of the absolute risk increase was small, the risk of ESKD remained significantly higher for older donors with hypertension compared to older donors without hypertension after accounting for baseline characteristics (3.04-fold higher).

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 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).

Risk of Mortality

There were 252 deaths observed during the study period, and the death incidence rate was 13.8 per 10,000 person-years. The unadjusted 15-year cumulative incidence of mortality was 3.5% (95% CI, 2.5 to 5.0) for donors with hypertension versus 2.5% (95% CI, 2.0 to 3.0) for donors without hypertension (P=0.06) (Figure 2). In a multivariable regression accounting for age, sex, race, eGFR, and relationship to the recipient, mortality was not significantly different for donors with hypertension compared with donors without hypertension (HR, 1.18; 95% CI, 0.84 to 1.66; P=0.34) (Table 2). In sensitivity analyses, when we restricted our analysis to the 2004–2016 period, our inferences did not change (HR, 0.77; 95% CI, 0.34 to 1.76; P=0.53), and these inferences remained similar after further adjustment for systolic BP <125 mm Hg (HR, 0.81; 95% CI, 0.35 to 1.87; P=0.62), with no evidence of effect modification (P for interaction =0.89). Our inferences of mortality risk remained unchanged after further adjustment for obesity (HR, 1.17; 95% CI, 0.83 to 1.65; P=0.36).

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 (mean systolic BP, 124 mm Hg); this risk remained similar after further adjustment for systolic BP <125 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 ≥140 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 mm Hg as

Table 2. Risk of ESKD and mortality in older live kidney donors (*n*=24,533)

Outcome	ESKD	Unadjusted	Adjusted		Mortality	Unadjusted	Adjusted	
	No. of Events	Cumulative Incidence	HR (95% CI)	*P* Value	No. of Events	Cumulative Incidence	HR (95% CI)	*P* Value
Overall	24	0.3%	—		252	2.7%	—	
Risk factors[a]								
No hypertension	16	0.2%	Reference		212	2.5%	Reference	
Hypertension	8	0.8%	3.04 (1.28 to 7.22)	0.01	40	3.5%	1.18 (0.84 to 1.66)	0.34
Age, per 5-yr increase	—	—	1.26 (0.85 to 1.89)	0.25	—	—	1.57 (1.41 to 1.76)	<0.001
Sex								
Men	12	0.4%	Reference		132	3.4%	Reference	
Women	12	0.2%	0.56 (0.24 to 1.29)	0.17	120	2.0%	0.55 (0.43 to 0.72)	<0.001
Race/ethnicity								
Nonwhite	4	0.3%	Reference		36	2.0%	Reference	
White	20	0.3%	1.18 (0.39 to 3.53)	0.77	216	2.8%	1.21 (0.84 to 1.75)	0.31
eGFR, per 10-unit decrease[b]	—	—	1.13 (0.82 to 1.56)	0.46	—	—	0.97 (0.88 to 1.06)	0.48
Biologically								
Unrelated	8	0.2%	Reference		119	2.6%	Reference	
Related	16	0.4%	1.65 (0.70 to 3.89)	0.25	133	2.8%	1.03 (0.80 to 1.32)	0.79

HR, adjusted hazard ratio; 95% CI, 95% confidence interval; —, not applicable.
[a]Multivariable 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.
[b]Imputed for 1% missing eGFR (*n*=234 eGFR values). Our inferences remained unchanged in the complete-data analysis (*n*=24,299).

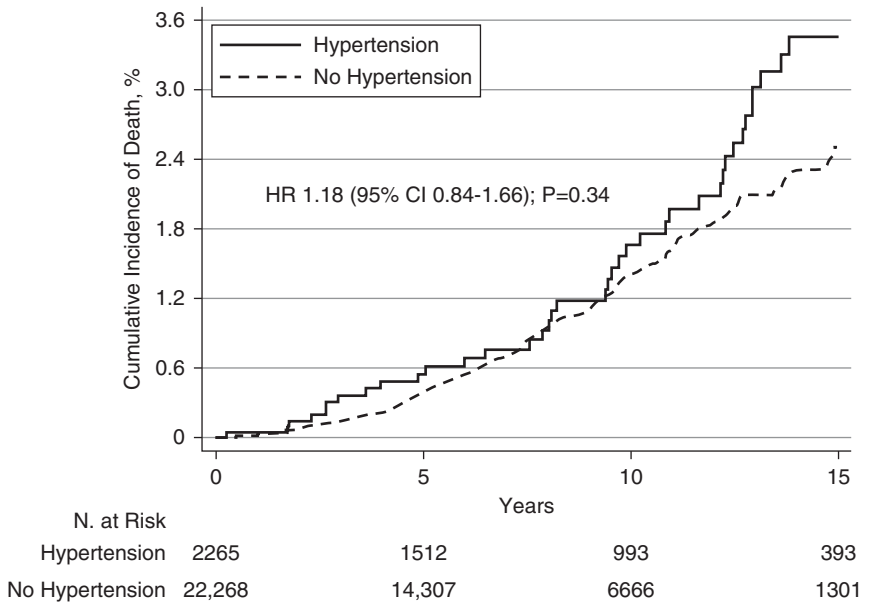

Figure 2. | The 15-year risk of mortality was not significantly different for older donors with hypertension versus older donors without hypertension. This risk of mortality remained non-significant after accounting for baseline characteristics.

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 <150 mm Hg) for individuals aged ≥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 (≥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 recommended a BP target of <130/80 mm Hg for primary prevention in individuals with atherosclerotic cardiovascular disease risk ≥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. 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 measurements 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.

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.

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