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Postdonation eGFR and New-Onset Antihypertensive Medication Use After Living Kidney Donation

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Background. Limited data are available regarding clinical implications of lower renal function after living kidney donation. We examined a novel integrated database to study associations between postdonation estimated glomerular filtration rate (eGFR) and use of antihypertensive medication (AHM) treatment after living kidney donation. **Methods.** Study data were assembled by linking national U.S. transplant registry identifiers, serum creatinine (SCr) values from electronic medical records, and pharmacy fill records for 3222 living donors (1989–2016) without predonation hypertension. Estimated GFR (mL/min per 1.73 m^2) was computed from SCr values by the CKD-EPI equation. Repeated measures multivariable mixed effects modeling examined the associations (adjusted odds ratio, $_{95\%LCL}aOR_{95\% UCL}$) between AHM use and postdonation eGFR levels (random effect) with fixed effects for baseline donor factors. **Results.** The linked database identified an average of 3 postdonation SCr values per donor (range: 1–38). Lower postdonation eGFR (vs ≥75) bore graded associations with higher odds of AHM use (eGFR 30–44: aOR $_{0.95}1.47_{2.26}$; <30: aOR $_{1.08}2.52_{5.90}$). Other independent correlates of postdonation AHM use included older age at donation (aOR per decade: $_{1.08}1.23_{1.40}$), black race (aOR $_{1.03}1.51_{2.21}$), body mass index > 30 kg/m^2 (aOR $_{1.01}1.45_{2.09}$), first-degree donor–recipient relationship (aOR $_{1.07}1.38_{1.79}$), "prehypertension" at donation (systolic blood pressure 120–139: aOR $_{1.10}1.46_{1.94}$; diastolic blood pressure 80–89: aOR $_{1.06}1.45_{1.99}$). **Conclusions.** This novel linkage illustrates the ability to identify postdonation kidney function and associate it with clinically meaningful outcomes; lower eGFR after living kidney donation is a correlate of AHM treatment requirements. Further work should define relationships of postdonation renal function, hypertension, and other morbidity measures.

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Living kidney donors have lower estimated glomerular filtration rate (eGFR) due to surgical reduction in nephron mass,[1,2] and this eGFR reduction has been associated with

surrogate endpoints such as albuminuria[3] and change in left ventricular mass.[4] Yet, despite >60 years of experience with living donation, the consequences for donors of this nephron

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loss and lower eGFR remain unclear. A diagnosis of chronic kidney disease (CKD) not only implies that living kidney donors have similar cardiovascular morbidity and mortality risks to patients with native kidney CKD,[5,6] but inappropriate diagnoses of CKD may also create insurability problems for these otherwise healthy individuals.[5,7] Given that >1 in 4 donors have an eGFR below 60 mL/min/1.73 m^2 following donation,[8] the clinical implications of reduced eGFR in donors must be elucidated.

A link between nephron number, hypertension, and renal insufficiency may exist, although these pathways have not been well defined in living kidney donors. Epidemiologic studies of low-birthweight infants with prematurity-associated nephron deficit have reported a higher risk of hypertension and CKD in adulthood, thought to be due to glomerular hyperfiltration, microalbuminuria, and renal injury.[9,10] Although living kidney donors arrive at a lower nephron mass by a different mechanism, studies suggest they also may have a high risk of hypertension,[11-13] a frequently reported cause of postdonation end-stage renal disease (ESRD).[14] The association between eGFR and hypertension in living kidney donors must be considered in the context of nephron loss with normal aging.[15] This aging-related nephron loss may have confounded prior work examining birthweight and GFR in living kidney donors. In a study of 249 living kidney donors, of whom 15 reported a low birthweight, although Berglund et al did not find an association between birthweight and GFR, they did find that older donors were more likely to have low GFR and hypertension, while low-birthweight donors were more likely to have albuminuria.[16] Other researchers have also identified a higher risk of hypertension after donation in older donors.[12,17,18] A better understanding of the interplay between lower eGFR and hypertension following living kidney donation would provide insight into the physiology of low nephron number and kidney disease. This interplay has been difficult to study due to challenges of identifying measures of hypertension in datasets with sufficient power to adjust for age.

To advance understanding of the association between postdonation eGFR and the need for blood pressure treatment after living kidney donation, we examined a novel patient-level linkage of national registry data with laboratory data from electronic medical records (EMRs) and pharmaceutical claims data (PCD) for antihypertensive medication (AHM) use. This linkage combines the value of a confirmed patient donation history and baseline demographic and clinical characteristics with laboratory values not currently available in the national registry, as well as AHM use as a clinically meaningful outcome.

MATERIALS AND METHODS

Data Sources and Linkage

We conducted a retrospective cohort study using linked healthcare databases in the United States. 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). The Health Resources and Services Administration (HRSA), U.S. Department of Health and Human Services, provides oversight of the activities of the OPTN and SRTR contractors. Living kidney donors who

donated between 1989 and 2016 were included in the study. Donors who reported predonation hypertension, as recorded in the SRTR registry, were excluded.

Pharmacy fill data were assembled by linking SRTR records for living kidney donors with billing claims from a large U.S. PCD warehouse that maintains prescription drug fill records, including self-paid fills and fills reimbursed by private and public payers.[19-21] The PCD comprises National Council for Prescription Drug Program 5.1-format prescription claims aggregated from multiple sources, including data warehouses, retail pharmacies, and prescription benefit managers, for approximately 60% of U.S. retail pharmacy transactions. Individual claim records include the date of a given pharmacy fill with the National Drug Code identifying agent and dosage. After institutional review board and HRSA approvals, PCD records were linked with SRTR records for living donors.

Laboratory test results were integrated by further linking SRTR records for the same living kidney donors with general-purpose, multispecialty EMRs from a large U.S. healthcare data warehouse that maintains clinical records for those reimbursed by private and public payers. The EMRs comprise routine clinical data fields aggregated from multiple sources including manufacturers and healthcare systems for approximately 30% of U.S. patients seen in an outpatient setting by over 2500 practices. Individual EMRs include the date of a given visit or service, including lab testing.

We applied a deterministic deidentification strategy wherein patient identifiers (last name, first name, sex, date of birth, and ZIP code of residence) were transformed before delivery to the Saint Louis University researchers with Health Information Portability and Accountability Act and HITECH-certified encryption technology. The patient deidentification software uses multiple encryption algorithms in succession to guarantee that the resulting "token" containing encrypted patient identifiers can never be decrypted. However, the algorithm yields the same results for a given set of data elements, such that linkages by unique anonymous tokens are possible. This study was approved by the Saint Louis University Institutional Review Board. Individual participant deidentified data will not be shared due to restrictions of licensing and Data Use Agreements.

Demographic and Clinical Characteristics

Demographic and clinical characteristics ascertained from SRTR included year of donation, age, sex, race, body mass index (BMI) at donation, systolic and diastolic blood pressure at donation, predonation eGFR, and relationship with recipient. We compared baseline characteristics of all donors in the national registry (our source population) with characteristics of the subset with data available through PCD and EMR linkage (our study population) using χ^2 and t-tests as appropriate. We also compared characteristics within the study population by clinical category of predonation eGFR (>120 mL/min per 1.73 m^2, 90–120 mL/min per 1.73 m^2, <90 mL/min per 1.73 m^2, and unknown).

Postdonation Renal Function and AHM Use

Estimated GFR was calculated from linked postdonation serum creatinine (SCr) values using the CKD-EPI equation, within annual windows postdonation.[22] PCD eligibility was assessed within ±90 days of each postdonation eGFR,

followed by identification of AHM fills for donors with both eGFR data and pharmacy records eligibility. Boxplots were used to describe cross-sectional eGFR (ie, values among eligible participants at each time point). AHMs were categorized as angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, calcium channel blockers, beta blockers, diuretics, or other AHM.

Statistical Analysis

The unit of analysis was a reported SCr allowing calculation of eGFR. Repeated measures multivariable mixed effects modeling examined associations (adjusted odds ratio, $_{95\%LCL}aOR_{95\%UCL}$) between AHM use and postdonation eGFR level (random effect), with fixed effects for baseline donor factors.[23] Confidence intervals are reported as per the method of Louis and Zeger: $_{95\%LCL}aOR_{95\%UCL}$.[24] Data management and analyses were performed with Statistical Analysis Software (SAS) for Windows, version 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Study Population

Of 135 464 living kidney donors who donated between 1989 and 2016, without pre-existing hypertension, 3222 had linked EMR laboratory data and PCD data postdonation. Donors in the study sample with laboratory and PCD data were slightly older (mean age: 43.6 vs 40.2 y; $P < 0.0001$), more frequently female (65.3% vs 59.5%; $P < 0.0001$), and more frequently white (79.6% vs 70.2%) than all donors without pre-existing hypertension reported in the SRTR in the study period (Table 1).

Characteristics of Sample by Baseline eGFR

The linked EMR database identified an average of 3 postdonation SCr values per donor (range 1–38). Postdonation eGFR did not vary over time (Figure 1). Median time from donation to last reported SCr was 7.8 years. Factors associated with lower baseline eGFR (<90 mL/min per 1.73 m²) included older age, white race, and elevated predonation systolic blood pressure. Donors with eGFR > 120 mL/min per 1.73 m² were more frequently obese and first-degree relatives of their recipients (Table 2).

AHM Use

Among eligible participants, AHM use increased steadily over time postdonation (Figure 2). In a multivariable mixed effects model, every 5-year increase in time since donation was associated with twice the risk of postdonation AHM use ($aOR_{1.67}2.08_{2.58}$). Other factors independently associated with new-onset AHM use included older age at donation (per decade age, $aOR_{1.08}1.23_{1.40}$), black race ($aOR_{1.03}1.51_{2.21}$), obesity ($aOR_{1.01}1.45_{2.09}$), and being a first-degree relative of the recipient ($aOR_{1.07}1.38_{1.79}$) (Figure 3). Blood pressure in the "prehypertensive range" at the time of donation (vs systolic blood pressure [SBP] < 120 and diastolic blood pressure [DBP] < 80; SBP 120–139: $aOR_{1.10}1.46_{1.94}$; DBP 80–89: $aOR_{1.06}1.45_{1.99}$) was associated with AHM use.

Postdonation eGFR had a graded association with postdonation AHM use. Compared with postdonation eGFR ≥ 75 mL/min per 1.73 m², eGFR 30–44 was associated with a trend toward higher AHM use ($aOR_{0.95}1.47_{2.26}$) while postdonation

TABLE 1.

Characteristics of living kidney donors 1989–2016 without pre-existing hypertension and the study sample with linked laboratory and pharmacy data

	Sample with linked EMR and PCD data (N = 3222)	All donors 1989–2016 without pre-existing HTN (N = 135 464)
Age at donation (mean y)	43.6	40.2
Female	65.3	59.5
Race		
White	79.6	70.2
Black	9.4	12.4
Hispanic	8.8	13.0
Other	2.3	4.4
BMI at donation (kg/m²)		
<18.5	0.7	0.8
18.5 to <25	28.7	25.1
25 to <30	33.4	29.1
≥30	18.4	16.2
Unknown	18.7	28.8
Donor–recipient relationship		
First-degree relative	54.6	58.9
Other relative	6.4	6.8
Unrelated	39.0	34.3
Predonation blood pressure (mm Hg)		
SBP < 120	37.3	30.6
SBP 120 to 140	40.3	32.8
DBP < 80	57.1	47.6
DBP 80 to 90	20.5	18.5
Predonation eGFR (ml/min per 1.73 m²)		
eGFR > 120	6.5	8.3
eGFR 90 to 120	44.2	40.4
eGFR < 90	33.9	25.7
eGFR unknown	15.5	25.6

Due to large sample size of the registry, distributions of all traits in the study sample were significantly ($P < 0.05$) different from that of all donors in the registry in the study period.
BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; EMR, electronic medical record; HTN, hypertension; PCD, pharmaceutical claims data; SBP, systolic blood pressure.

eGFR < 30 was associated with 2.5-times the likelihood of AHM use ($aOR_{1.08}2.52_{5.90}$) (Figure 3). Predonation eGFR was not associated with AHM use.

DISCUSSION

Using a novel patient-level linkage of national registry data with pharmaceutical claims and laboratory data from EMRs, we assembled a cohort of living kidney donors to study the clinical and demographic correlates of new-onset AHM use after living kidney donation. We found a graded increase in odds of AHM use with lower eGFR after donation, such that a postdonation eGFR of <30 mL/min per 1.73 m² was associated with 2.5-times higher likelihood of AHM use (vs ≥75 mL/min per 1.73 m²). In addition, we identified other significant correlates of postdonation AHM use including older age at donation, black race, obesity, first-degree donor–recipient relationship, presence of "prehypertension" at donation, and time elapsed since donation.

While uninephrectomy performed during living donation leads to an immediate 50% reduction in functioning nephron
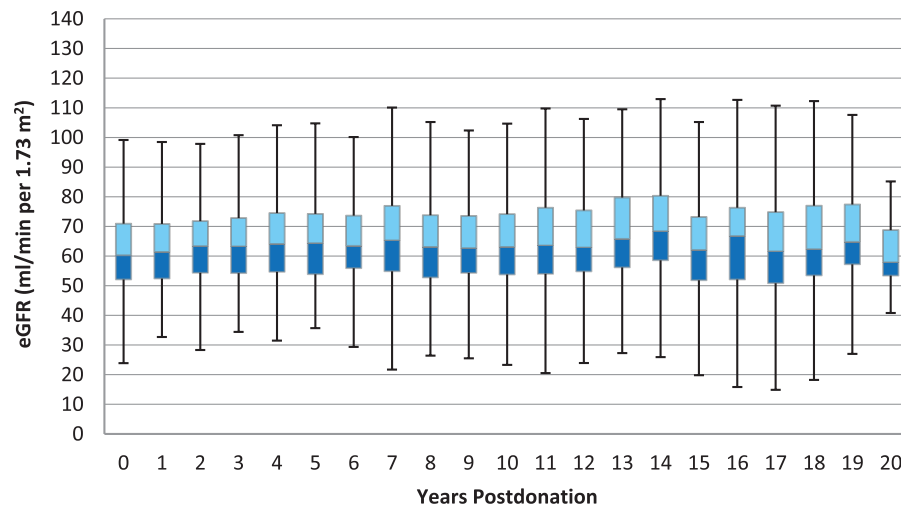
FIGURE 1. Postdonation eGFR from EMR records over follow-up time. Estimated GFR was calculated from linked postdonation serum creatinine values within annual windows postdonation. Boxplots describe cross-sectional eGFR values among eligible participants at each time point. eGFR, estimated glomerular filtration rate; EMR, electronic medical record; GFR, glomerular filtration rate.

mass among donors, adaptive compensatory hypertrophy of the remaining kidney leads to a final GFR in donors of about 70% of their predonation GFR.[25] Despite short-term safety, accumulating evidence indicates that living kidney donation is associated with a small but increased risk of ESRD,[26,27] and in one report, with increased risk of cardiovascular and all-cause mortality.[27] The mechanisms driving the increased risk of ESRD and cardiovascular mortality among living donors remain undefined, but medical conditions such as hypertension that lie on the causal pathway for both outcomes likely contribute. Low nephron number is associated with

hypertension[28] and speculated to be a risk factor for CKD.[10] In established CKD patients, worsening CKD stage was associated with higher prevalence of hypertension.[29] While the nephron mass reduction and lower GFR following living kidney donation should not be considered CKD,[8,30] we observed a stepwise increase in AHM use with lower eGFR categories, although this association was only significant at eGFR < 30 mL/min per 1.73 m². Whether a reduction in nephron mass is the shared mechanism behind hypertension in both living donors and patients with CKD merits further investigation through mechanistic studies.

TABLE 2.

Characteristics of the study sample of living kidney donors by baseline eGFR levels (N = 3222)

	eGFR > 120 (N = 209)	eGFR 90–120 (N = 1423)	eGFR < 90 (N = 1092)	Unknown (N = 498)
Age at donation (mean y)	30.4	42.5[a]	48.0[a]	42.8[a]
Female	76.1	67.1[b]	62.8[c]	61.24[c]
Race		[a]	[a]	[a]
White	44.0	77.7	88.4	80.3
Black	30.6	8.5	6.0	10.4
Hispanic	21.5	11.0	3.9	7.6
Other	3.8	2.7	1.8	1.6
BMI at donation (kg/m²)		[b]		[a]
<18.5	1.9	0.7	0.7	0.2
18.5 to <25	27.8	35.4	31.6	3.8
25 to <30	37.3	37.1	41.7	3.0
≥30	27.3	21.0	20.4	3.0
Unknown	5.7	5.8	5.6	90.0
Donor–recipient relationship		[b]	[c]	[c]
First-degree relative	59.8	51.9	48.3	73.9
Other relative	9.1	6.2	6.1	6.4
Unrelated	31.1	41.9	45.6	19.7
Predonation blood pressure (mm Hg)			[b]	[a]
SBP < 120	58.9	53.7	50.4	97.8
SBP 120 to 140	41.2	46.3	49.6	2.2
DBP < 80	78.5	76.7	74.4	99.2
DBP 80 to 90	21.5	23.3	25.6	0.8

P values for difference in distribution of donor characteristics according to baseline eGFR levels: [a]$P < 0.0001$; [b]$0.02 \le P < 0.05$; [c]$0.0001 \le P < 0.01$.
BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate (ml/min/1.73 m²); SBP, systolic blood pressure.
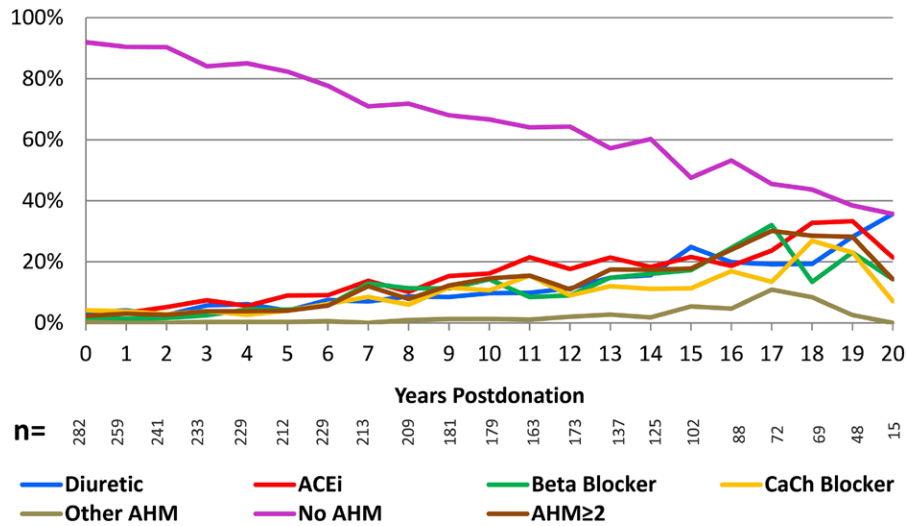
FIGURE 2. AHM fills by category of medication over postdonation time. ACEi, angiotensin-converter enzyme inhibitor; AHM, antihypertensive medication; CaCh, calcium channel blocker.
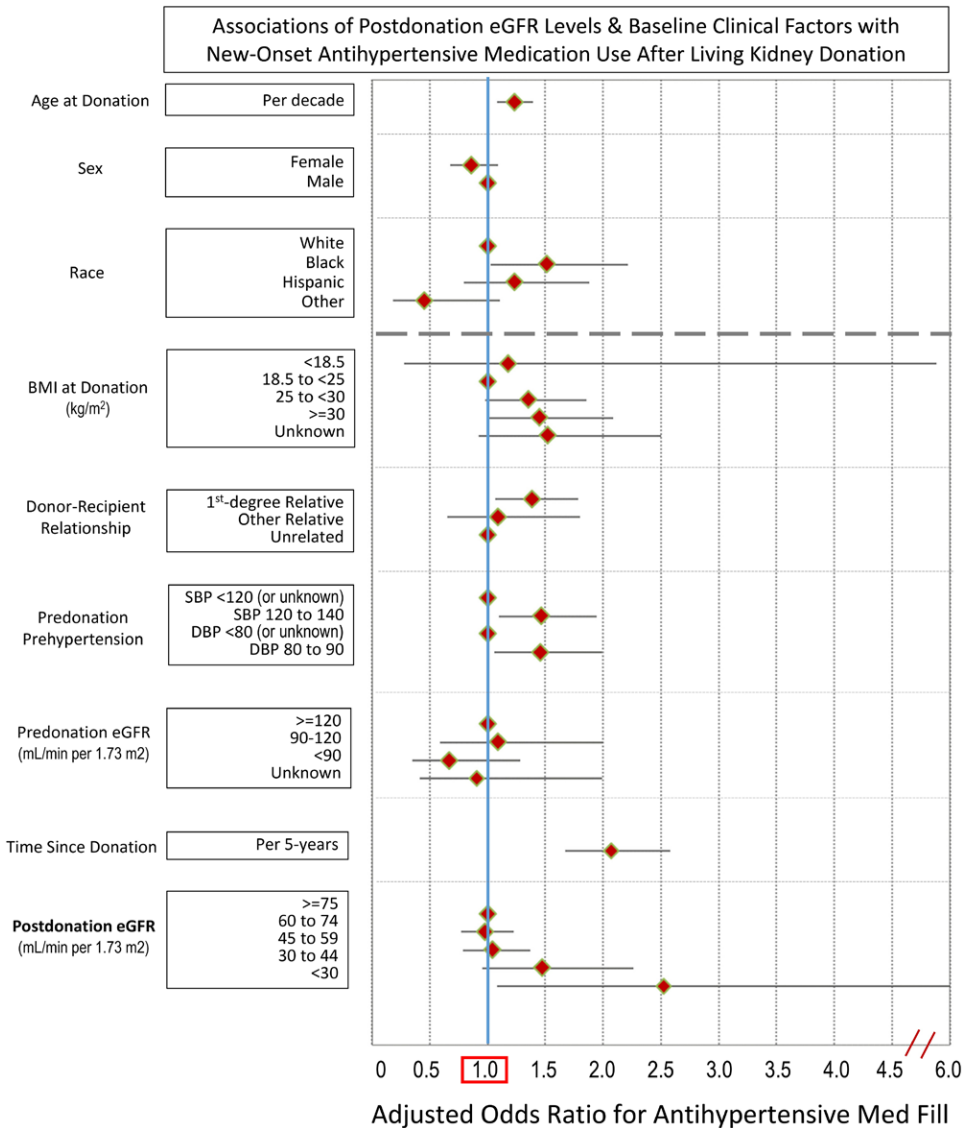
FIGURE 3. Association of postdonation eGFR and baseline factors with new-onset antihypertensive medication use after living kidney donation. BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure.

Many previous studies have investigated the epidemiology of hypertension after living donation but are limited by short duration of follow-up and lack of accompanying clinical and laboratory data. In a study using an administrative health database from Ontario, Canada, donors were found to have a 40% higher risk for hypertension than matched healthy nondonors (age, sex, income) at a median of 6.2 years postdonation.[31] Another study that linked OPTN data to private insurer billing claims noted an incidence of 17.8% at a median 7.7-year follow-up. This study noted a higher risk of hypertension among black (vs white) donors, a group identified as being at increased risk of ESRD after living donation.[13] In the longest single-center study of a predominantly white cohort, a quarter of patients (26.8%) developed hypertension at a mean of 16.6 years postdonation. While the prevalence of hypertension in this cohort was still lower than in a general U.S. cohort (National Health and Nutrition Examination Survey, 2011–2014), no comparison was made with age- and baseline-comorbidity-matched population controls who did not donate. In our study, we observed that approximately 60% of donors contributing data at 20 years postdonation were using AHMs at that time point. Whether this reflects selection bias (from sampling), time elapsed since donation, or characteristics of our cohort (older, obese, higher prevalence of "prehypertension") remains unclear. Long-term longitudinal studies with well-matched controls are needed to better define relationships.

Risk factors for increased AHM use in our study were black race, obesity, first-degree relative with hypertension, "prehypertension," and time since donation. These findings are similar to those from the study by Sanchez et al in a predominantly white cohort, in which older age at donation, family history of hypertension, higher BMI, higher systolic and diastolic blood pressures, hyperlipidemia, and smoking status were associated with incident hypertension after donation.[17] Similar to our prior study,[13] we identified black race as associated with an increased risk of hypertension compared with nonblack race. These findings reaffirm prior studies and validate the novel cohort linkage.

Presence of an association between lower eGFR and postdonation AHM use should not be viewed as an indication that hypertension is a causal risk factor for lower eGFR after donation. This relation can be bidirectional; that is, CKD by itself might drive hypertension as shown by increased prevalence of hypertension with higher stages of CKD as observed by Cheng et al.[29] In the longitudinal cohort from Sanchez et al, while postdonation hypertension was associated with higher CKD stages and proteinuria, there was no increased risk of ESRD among patients who developed hypertension. Further, a large meta-analysis has demonstrated that among individuals with CKD and nonmalignant hypertension, hypertension treatment per se did not affect chosen renal endpoints.[32] Together, these data thus suggest a complex relation between CKD and hypertension. Importantly, however, the current study does highlight the need for (1) mechanistic clinical studies, (2) long-term longitudinal follow-up of living donors and development of databases for matched controls, and (3) collecting parallel health information (laboratory, medications, other clinical conditions) by leveraging available technology and other data warehouses, thereby expanding the "proof of concept" linkage accomplished

in this study. We expect that using such clinical data will improve our ability to track and evaluate the health outcomes of kidney donors.

Several limitations of these data merit discussion. First, the study population was a convenience sample of living kidney donors with laboratory values and PCD available for linkage. Like other studies using national registry data, ours is limited by the granularity of donor registration data. Although unlikely, it is possible that some donors with predonation hypertension were misclassified as not having hypertension at donation. This was not a longitudinal cohort, rather our design was chosen to maximize the power of the available data to estimate associations of postdonation eGFR with AHM use. These data lack clinical granularity to describe the indication for AHM use, as well as measured systolic and diastolic blood pressures and other clinical parameters after donation. The study medications may have other indications than treatment of hypertension; most likely, inclusion of medication fills for other indications (eg, beta-blocker use for migraine) would attenuate associations with eGFR and hypertension risk factors. Finally, as in many previous studies, we did not have available data to construct a nondonor comparison cohort.

Strengths of this study include the novel linkage of national registry data to laboratory values beyond the current mandated follow-up time. This pilot demonstration can be leveraged to examine other potential complications and outcomes following living kidney donation. PCD offers useful surrogate measures of medically-treated clinical conditions among donors. For now, while we do not believe donors have a "disease" and advocate strongly against misclassification that leads to insurance discrimination,[6] we do believe that donors should have access to health care and engage in long-term follow-up, including monitoring and early treatment of any medical comorbidity, such as hypertension that arises after donation, to help ensure optimal long-term health outcomes.

In summary, linking national donor registry with pharmacy and laboratory data enabled a novel approach to collection of postdonation eGFR information and demonstrated associations of lower eGFR after donation with higher odds of AHM use. Additional baseline factors associated with higher odds of AHM use after donation included black race, obesity, first-degree donor–recipient relationship, and "prehypertension," and these findings validate results of prior studies. This novel epidemiologic design can be applied to future studies of delivered health care among living kidney donors. Further work should continue elucidating the clinical implications of lower postdonation renal function, including relationships between eGFR, hypertension, and "hard" renal, and cardiovascular endpoints.

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