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See related article, "MicroRNA-23a and MicroRNA-27a Mimic Exercise by Ameliorating CKD-Induced Muscle Atrophy," on pages 2631–2640.

Synthesizing Absolute and Relative Risks and the Many Unknowns to Inform Living Kidney Donors

Emilio D. Poggio* and Jesse D. Schold†

*Department of Nephrology and Hypertension, Glickman Urological and Kidney Institute and †Department of Quantitative Health Sciences, Cleveland Clinic, Cleveland, Ohio

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Correspondence: Dr. Emilio D. Poggio, Department of Nephrology and Hypertension, Glickman Urological and Kidney Institute, 9500 Euclid Avenue, Desk Q7, Cleveland, OH 44195. Email: poggioe@ccf.org

Living kidney donation has been performed for more than six decades and contributed tremendously to the treatment of ESRD in the United States and around the world. The benefits of living kidney donation to transplant recipients and importantly, the donors themselves are of no question, making this modality the treatment of choice for many patients with ESRD. However, the continued success of living kidney donation depends on securing a favorable postdonation outcome, especially by minimizing the risk of developing kidney disease that progresses to dialysis or kidney transplantation. Initial studies on long-term outcomes of living kidney donors suggested that there was no or minimal risk for developing ESRD after kidney donation when compared with the general population primarily on the basis of studies that were mostly limited to white donors.[1,2] However, more recent publications suggested a relative increased ESRD risk among certain groups, particularly blacks and those with a family history of kidney disease.[3,4] This increased relative risk remains small in absolute numbers. Nonetheless, considering that the long-term health of each donor is paramount to the success of living kidney donation, we, as the health care community caring for these individuals, have the obligation to provide the donor candidate with the best available information for appropriate informed consent and decision making. Developing tools that help us estimate any unacceptable increased ESRD risk is an important but undoubtedly, very difficult task.

A recent draft of the upcoming Kidney Disease Improving Global Outcomes (KDIGO) Living Kidney Donor Work Group Clinical Practice Guidelines (final guidelines are not yet published) proposes a "quantitative framework" to estimate ESRD risk in potential kidney donors.[5] These guidelines recommend using this approach to determine donor candidacy or provide appropriate informed consent to facilitate decision making. In this quantitative framework, kidney donor candidate predonation ESRD risk could be estimated, and then, transplant centers could define an acceptable risk permissible of donation. This estimate would be considered the baseline risk for any individual willing to become a donor. If this risk is deemed unacceptably high as defined by the transplant center or transplant community, then a donor candidate would not be considered. To build on this framework, Grams *et al.*[6] developed a calculator using demographic (age, sex, and race) and laboratory/history (eGFR, systolic BP, use of antihypertensive medications, body mass index, history of smoking or diabetes mellitus, and urine albumin) data derived from nondonor populations that resemble potential kidney donor candidates. This calculator estimates lifelong ESRD risk if a subject does not donate a kidney (that is, baseline ESRD risk). However, it may be possible that donation *per se* increases the risk for developing progressive kidney disease in a few individuals with certain predisposing factors. Per the proposed KDIGO quantitative framework, this increased future risk is to be added to each individual baseline risk to estimate the accumulated lifetime ESRD risk for a particular prospective kidney donor. In this regard, Massie *et al.*[7] published in this issue of the *Journal of the American Society of Nephrology* a new calculator that estimates postdonation ESRD risk, complementing the predonation baseline risk proposed by

the upcoming KDIGO guidelines. Per these guidelines, it is envisioned then that transplant centers will use these two calculators to assist in the decision making to accept or not accept a prospective living kidney donor candidate.

The concept of quantitating ESRD risk in prospective donors is appealing, because if properly defined, it could potentially have significant applications. Examples of these would include standardization of clinical practice, the ability to provide reliable informed consent, and individualization of postdonation follow-up and care among others. However, potential misinterpretation or misuse of the information derived from these tools can lead to unnecessary exclusion of potential viable candidates or inclusion of candidates with unmeasured characteristics that are not captured in a risk model. Therefore, it is critically important that ESRD risk calculators for prospective living kidney donors be as precise and accurate as possible.

Challenges with developing models to predict individual outcomes are several fold. The natural history of progressive kidney disease is complex and multifactorial and may take decades to progress to ESRD. Although some features associated with future risk of kidney disease may be present at the time of donation (*e.g.*, race or family history of kidney disease), others are dynamic and may or may not develop until later in life whether an individual donates or does not donate (*e.g.*, hypertension, weight gain, *etc.*), making any predictive tool less accurate when applied at the time of donor evaluation. In fact, some risk factors for kidney disease, like metabolic syndrome, may improve after donation (for example, driven by a decrease in body mass index and other lifestyle modification), hence reducing long-term ESRD risk.[8] Another important issue is that most ESRD will develop at a minimum of a decade from donation (outcome to be estimated by the calculator), and the criteria used for donor selection continuously evolve over time, such as acceptance of medically complex and older donors in recent years (variables used to develop a calculator). These two characteristics further complicate the ability to develop a reliable tool that can predict an uncommon future outcome using noncontemporary donor characteristics. Reporting and missing donor data also limit the ability to construct a calculator with sufficient granularity to capture all primary factors associated with ESRD risk. For example, as a comparison with the calculator by Grams *et al.*,[6] the tool developed by Massie *et al.*[7] only uses age, sex, race, body mass index, and family history of kidney disease and does not use laboratory or clinical variables. Finally, the very low absolute number of donors who develop ESRD may limit the statistical power to develop a tool with optimal performance.

Ultimately, the pre-eminent challenge with the results of this study is how to disseminate the risk information effectively and accurately to kidney donors and caregivers. The predictive value of the model used for the calculator was moderate (concordance index $=0.71$), implying that the factors included in the model have prognostic value but that there is also significant unexplained variation. This unmeasured risk must be carefully considered for decision making, because it may strongly modify risk estimates. This includes more granular definitions of included factors (for example, using race *per se* may indeed be too coarse of a measure of risk given emerging evidence defining the subset of blacks with APOL-1 high-risk gene variants).[9,10] This also includes unmeasured risk factors, such as BP, lifestyle and diet, cardiac health, *etc.*, that may affect risk estimates. Interestingly, the interaction estimates of race and age derived from this work by Massie *et al.*[7] were much stronger than those in the study by Grams *et al.*[6] This may suggest that the population used to define risks can modify these estimates and that the donor selection process *per se* (as included in the study by Massie *et al.*[7]) refines the population on the basis of different medical, psychosocial, and logistical processes that result in systematically different populations, which also effect risk calculations. Finally, even given perfect information, the method of dissemination of these risks to many individuals that lack numeracy in a context that is often emotionally turbulent will continue to be an incredibly difficult but important challenge to overcome.

Despite these potential limitations, the calculator developed by Massie *et al.*[7] provides a tool that could add to our current approach to donor selection. This effort should be considered as a starting point in quantifying future ESRD risk. As registry data continue to accumulate and become more granular, refinements to this calculator will be needed so as to improve our ability to estimate ESRD risk after donation. At this point, a leap of faith will be needed as we apply these ESRD predictive tools in this setting; they cannot be immediately validated, because the outcome of interest is rare and takes decades to develop. Moreover, the increased risk attributed to donation remains very low in absolute numbers, with the majority of donors never developing ESRD, and despite the interesting findings, must remain an important component of the conversation to potential donors. For the transplant community caring for kidney donors, it is also important to remark that not all matters that motivate an individual showing interest in donation are quantifiable. For many donors, their desire to donate and help a loved one may benefit themselves to the point that they are willing to accept a few percentage points increase in ESRD risk beyond their baseline lifetime risk. Limiting these individuals from pursuing donation may not be beneficial to themselves, irrespective of the potential recipient.[11,12] The balanced use of calculators to estimate ESRD risk in prospective donors is welcome, because it provides another tool during the evaluation process of kidney donor candidates. However, living kidney donors voluntarily pursue donation with the knowledge of no direct medical benefit, whereas it is obligation of the transplant community to provide each donor with all available information for a final shared decision.

DISCLOSURES

None.

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BP Targets in CKD, Mortality, and SPRINT: What Have We Learned?

Stephen C. Textor and Gary L. Schwartz
Division of Nephrology and Hypertension, Mayo Clinic, Rochester, Minnesota

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Correspondence: Dr. Stephen C. Textor, Division of Nephrology and Hypertension, Mayo Clinic, E19A, Rochester, MN 55905. Email: textor.stephen@mayo.edu

Control of hypertension has long been a fundamental part of the care for patients with CKD. The vast majority of patients with CKD develop disturbances in sodium balance and pressor mechanisms that lead to higher arterial pressures as GFR declines.[1] Higher BP interacts with both classic cardiovascular (CV) risk factors, which are common in patients with CKD, and additional novel risk factors unique to CKD to increase risk for CV events above that for individuals without CKD. Recognition of this higher risk led the Joint National Committee 7 (JNC 7) in 2003 to designate CKD a CV "risk equivalent" of manifest CV disease and recommend an empirical BP target of <130/80 mm Hg.[2]

However, optimal goals of BP therapy for individuals with CKD have been controversial. The relationship between BP and CV events in patients with incident CKD is complex and may differ by patient age. Several large observational studies identify a U- or J-shaped curve with rising mortality for patients with CKD as systolic BP (SBP) falls <120 mm Hg and/or diastolic BP falls <60 mm Hg.[3,4] For patients >75 years old, higher SBP adds minimal demonstrable risk at all.[3,4] Treatment trials in CKD, including the Modification of Diet in Renal Disease (MDRD) Trial and the African-American Study of Kidney Disease (AASK), specifically tested the hypothesis that intensive BP reduction would slow the rate of decline in GFR. Both of these trials failed to show benefit in patients who were not proteinuric.[5,6] Intensive antihypertensive therapy to a target SBP of 120 mm Hg compared with a conventional target of 140 mm Hg in patients with diabetes who are hypertensive enrolled in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Trial also failed to show a benefit regarding overall CV events or mortality, and indeed, the results suggested caution with intensive BP reduction because of increased risks of hypotension and AKI.[7] These observations together led the committee selected for the JNC 8 in 2014 to raise the evidence-based BP target to 140/90 mm Hg in patients <60 years old with CKD (and 150/90 mm Hg for older individuals) because of the lack of prospective data to support lower goals.[8]

Cheung *et al.*[9] now report in this issue of the *Journal of the American Society of Nephrology*, in the article "Effects of intensive BP control in CKD"—an analysis from a preidentified CKD subset of patients enrolled in the Systolic BP Intervention Trial (SPRINT). This is the largest randomized trial to date (n=2646 subjects with eGFR between 20 and 59 ml/min per 1.73 m^2) to assess different BP targets on CV and kidney outcomes in patients with CKD. The trial targeted older subjects (mean age of 71.9 years old; 43.9% aged >75 years) considered at increased CV risk with SBP between 120 and 180 mm Hg. It excluded patients with diabetes, proteinuria >1 g/d, polycystic kidney disease, prior stroke, and symptomatic heart failure or ejection fraction <35%. Importantly, multiple BP readings were obtained at 1-minute intervals and averaged at each visit using an automated oscillometric unit (Omron Healthcare 907) after the patient had been seated quietly for 5 minutes alone (unattended automated BP measurement). SBP targets of 140 mm Hg in the standard group and 120 mm Hg in the intensive group were rapidly