Chronic Kidney Disease Stage and Cardiovascular and Mortality Events Among Older Adults: The SPRINT Trial

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Rationale & Objective: The risk implications of the Kidney Disease: Improving Global Outcomes (KDIGO) chronic kidney disease classification in older adults are controversial. We evaluated the risk of adverse outcomes in this population across categories of estimated glomerular filtration rate (eGFR) and urinary albumin-creatinine ratio (UACR).

Study Design: Prospective cohort.

Settings & Participants: In total, 2,509 participants aged ≥75 years in the Systolic Blood Pressure Intervention Trial (SPRINT).

Exposure: KDIGO eGFR and UACR categories. We combined KDIGO categories G1 and G2, G3b and G4, as well as A2 and A3.

Outcomes: Primary SPRINT outcome (composite of myocardial infarction, other acute coronary syndromes, stroke, heart failure, or death from cardiovascular causes), and all-cause death.

Analytical Approach: Multivariable Cox proportional hazard models.

Results: Mean age was 79.8 years, and 37.4% were female. The mean eGFR was 64.0 mL/min/

1.73 m^2, and the median UACR was 13.1 mg/g. In multivariable Cox proportional hazard analysis, compared with participants with eGFR ≥ 60 mL/min/1.73 m^2 and UACR < 30 mg/g, there was no statistically significant difference in the risk of the primary outcome among participants with eGFR 45-59 or 15-44 mL/min/1.73 m^2 and UACR < 30 mg/g. However, those with eGFR 45-59 or 15-44 mL/min/1.73 m^2 and UACR ≥ 30 mg/g had higher risk of the primary outcome (HR [95% CI], 1.97 [1.27-3.04] and 3.32 [2.23-4.93], respectively). The risk for all-cause death was higher for each category of abnormal eGFR and UACR, with the highest risk observed among those with eGFR 15-44 mL/min/1.73 m^2 and UACR ≥ 30 mg/g (3.34 [2.05-5.44]).

Limitations: Individuals with diabetes and urine protein >1 g/day were excluded from SPRINT.

Conclusion: Among older adults SPRINT participants, low eGFR without albuminuria was associated with higher mortality but not with increased risk of cardiovascular events. Additional studies are needed to evaluate an adapted chronic kidney disease stage-based risk stratification for older adults.

The prevalence of chronic kidney disease (CKD) in the United States is estimated at 14% and is higher among older people (up to 38% among those aged 65 years or older).[1] Based on recommendations from Kidney Disease: Improving Global Outcomes (KDIGO), CKD is currently classified using a combination of estimated glomerular filtration rate (eGFR) and urinary albumin-creatinine ratio (UACR).[2] However, it remains controversial whether this classification should be used among older individuals.[3]

Given that the vast majority of healthy older adults experience an eGFR reduction of approximately 1 mL/min per year, with no albuminuria or hematuria, normal serum creatinine levels, minimal kidney ultrasound changes, and without the metabolic complications associated with CKD, such as anemia and alterations in bone-mineral metabolism, such people may simply have kidney aging, rather than CKD.[3-6] Kidney aging refers to the structural and functional changes that occur because of a complex interplay of genetics, environmental changes, and cellular dysfunction throughout the life cycle.[7,8] This age-related decline in kidney function can be accelerated by comorbid conditions, including hypertension and diabetes. The distinction between kidney aging and kidney disease is important because overdiagnosis of CKD in the elderly can

lead to unnecessary nephrology referral, testing, and treatments, but minimal added benefit.[3,9] On the other hand, failure to correctly identify cases of CKD, might delay the implementation of evidence-based interventions in this population.[10,11]

In this study, we evaluated the association of eGFR and UACR categories defined by KDIGO, with cardiovascular events and all-cause death among individuals older than 75 years who participated in the Systolic Blood Pressure Intervention Trial (SPRINT). We hypothesized that older adults classified as having CKD based on low eGFR without albuminuria will have similar risk of adverse outcomes compared with those without CKD.

METHODS

Study Population

The SPRINT study design, methods, and main results have been previously published.[12,13] In summary, 9,361 adult participants (older than 50 years) with hypertension and increased cardiovascular risk were enrolled from 102 clinical sites between November 2010 and March 2013 and followed until August 2015. Study participants were randomly assigned to a systolic blood pressure target

PLAIN-LANGUAGE SUMMARY

Using data from participants in the SPRINT trial, we evaluated the association of chronic kidney disease stage with adverse clinical outcomes among adults older than 75 years without diabetes. We found that low level of kidney function determined by a low estimated glomerular filtration rate with moderately or severely increased urine albumin excretion was associated with increased risk for cardiovascular events and all-cause mortality. However, low estimated glomerular filtration rate with normal or mildly increased urinary albumin excretion was not consistently associated with these adverse outcomes. This finding supports the need for additional studies to evaluate an age-adapted classification of chronic kidney disease to improve risk stratification among older adults.

of <120 mm Hg (intensive treatment) or <140 mm Hg (standard treatment). Increased cardiovascular risk was defined by one or more of the following: clinical or subclinical cardiovascular disease (CVD) other than stroke, eGFR 20-60 mL/min/1.73 m^2, a 10-year risk of CVD of 15% or greater based on the Framingham risk score, or an age of ≥75 years. Exclusion criteria included diabetes mellitus, polycystic kidney disease, proteinuria > 1 g/d, prior stroke, symptomatic heart failure, and left ventricular ejection fraction < 35%. The SPRINT protocol was approved by institutional review boards at each trial site, and all participants provided informed consent.

The current study was exempt from formal research ethics committee approval and focuses on the association of CKD based on the KDIGO classification and clinical outcomes among participants 75 years of age or older at the time of study enrollment. Of the 2,652 SPRINT participants older than 75 years, 100 were excluded because of missing data on albuminuria, and 41 because of missing data on smoking status or body mass index; 2 participants with eGFR < 15 mL/min/1.73 m^2 were also excluded. The resulting analytic sample of 2,509 participants was used for this analysis.

eGFR and UACR Classification

Participants were classified based on KDIGO eGFR categories (high, normal or mildly decreased [G1 and G2 combined, ≥60 mL/min/1.73 m^2], mildly to moderately decreased [G3a, 45-59 mL/min/1.73 m^2], and moderately to severely or severely decreased [G3b and G4 combined, 15-44 mL/min/1.73 m^2]), and UACR (normal to mildly increased [A1, <30 mg/g], and moderately or severely increased [A2 and A3 combined, ≥30 mg/g,]) according to current criteria.[14] To estimate GFR, we used the CKD Epidemiology Collaboration (CKD-EPI 2021) creatinine equation.[15] In

addition, because elderly persons have generally been underrepresented in studies of GFR equation development, we decided to also use the Berlin Initiative Study equation (BIS1) that was designed to assess kidney function in an elderly population-based cohort.[16,17] Analyses were reproduced using the CKD-EPI 2021 creatinine-cystatin C equation.

Outcomes

The main outcome was the primary SPRINT outcome, which is a composite of myocardial infarction, acute coronary syndrome not resulting in myocardial infarction, stroke, acute decompensated heart failure, or death from cardiovascular causes.[13] All-cause death was a secondary outcome. Protocol-specified clinical outcomes were adjudicated by a committee unaware of SPRINT treatment assignments.

Statistical Analysis

Baseline characteristics of study participants were summarized as mean (standard deviation) or median (interquartile range) for continuous variables, and frequency (proportion) for categorical variables. Event rates per 100 person-years were calculated for each outcome of interest. Participants were censored at time of death, loss to follow-up, or end of the follow-up period. Cox proportional hazards models were used to evaluate the association of categories of eGFR and UACR with clinical outcomes, adjusted for potential confounders selected a priori (age, sex, race and ethnicity, randomization arm, baseline systolic blood pressure, smoking status, body mass index, CVD, and total cholesterol). Whether CVD at baseline or randomization arm were effect modifiers was evaluated by separately testing interaction terms between the exposure and each potential effect modifier in the fully adjusted model. All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

RESULTS

Participants Characteristics

Among 2,509 SPRINT participants older than 75 years included in this study, the mean age at study entry was 79.8 years, and 37.4% were female. In total, 17.3% self-identified as non-Hispanic Black, 6.7% as Hispanic, and 74.2% as non-Hispanic White. In addition, 75.1% completed greater than high school education (Table 1). At baseline, mean systolic and diastolic blood pressure values were 141.7 and 71.2 mm Hg, respectively. The mean of eGFR was 64.0 mL/min/1.73 m^2, and the median UACR was 13.1 mg/g. Nearly half (46.6%) of the participants had normal eGFR (≥60 mL/min/1.73 m^2) and normal/mildly increased albuminuria (UACR < 30 mg/g), and 52.4% met the current KDIGO criteria of CKD at study entry (41.3% had eGFR <60 mL/min/1.73 m^2 and 26.3% had UACR ≥ 30 mg/g, Tables 1 and S3).

Table 1. Baseline Characteristics

		Urinary albumin-creatinine ratio < 30 mg/g			Urinary albumin-creatinine ratio ≥ 30 mg/g		
	Overall	eGFR ≥ 60 mL/min/1.73 m²	GFR 45-59 mL/min/1.73 m²	GFR 15-44 mL/min/1.73 m²	GFR ≥ 60 mL/min/1.73 m²	GFR 45-59 mL/min/1.73 m²	GFR 15-44 mL/min/1.73 m²
	Mean (SD), Median (IQR) or n (%)						
N (%)	2,509 (100)	1,170 (46.6)	457 (18.2)	221 (8.8)	302 (12.0)	193 (7.7)	166 (6.6)
Age, y	79.8 (3.9)	79.1 (3.5)	80.0 (4.0)	81.0 (4.2)	79.9 (3.9)	81.1 (4.1)	81.5 (4.7)
Female	939 (37.4)	441 (37.7)	173 (37.9)	106 (48.0)	109 (36.1)	54 (28.0)	56 (33.7)
Race and ethnicity							
Non-Hispanic Black	434 (17.3)	159 (13.6)	101 (22.1)	59 (26.7)	33 (10.9)	33 (17.1)	49 (29.5)
Hispanic	169 (6.7)	89 (7.6)	22 (4.8)	15 (6.8)	17 (5.6)	17 (8.8)	9 (5.4)
Non-Hispanic White	1,861 (74.2)	898 (76.8)	328 (71.8)	146 (66.1)	245 (81.1)	139 (72.0)	105 (63.3)
Other	45 (1.8)	24 (2.1)	6 (1.3)	1 (0.5)	7 (2.3)	4 (2.1)	3 (1.8)
Education							
<High school	242 (9.8)	99 (8.6)	51 (11.3)	26 (12.3)	22 (7.4)	17 (8.9)	27 (16.3)
High school	374 (15.1)	167 (14.5)	76 (16.9)	36 (17.1)	42 (14.1)	27 (14.1)	26 (15.7)
>High school	1,857 (75.1)	890 (77.0)	323 (71.8)	149 (70.6)	235 (78.6)	147 (77.0)	113 (68.1)
Smoking status							
Never	1,175 (46.8)	556 (47.5)	208 (45.5)	117 (52.9)	139 (46.0)	82 (42.5)	73 (44.0)
Former	1,252 (49.9)	585 (50.0)	231 (50.6)	91 (41.2)	151 (50.0)	107 (55.4)	87 (52.4)
Current	82 (3.3)	29 (2.5)	18 (3.9)	13 (5.9)	12 (4.0)	4 (2.1)	6 (3.6)
Randomization arm							
Intensive	1,265 (50.4)	602 (51.5)	222 (48.6)	115 (52.0)	147 (48.7)	103 (53.4)	76 (45.8)
Standard	1,244 (49.6)	568 (48.6)	235 (51.4)	106 (48.0)	155 (51.3)	90 (46.6)	90 (54.2)
Cardiovascular disease							
Clinical	554 (22.1)	229 (19.6)	103 (22.5)	55 (24.9)	69 (22.9)	53 (27.5)	45 (27.1)
Subclinical	131 (5.2)	50 (4.3)	20 (4.4)	18 (8.1)	19 (6.3)	14 (7.3)	10 (6.0)
Antihypertensive agents	1.9 (1.0)	1.8 (1.0)	2.0 (1.0)	2.1 (0.9)	2.0 (1.1)	2.1 (1.0)	2.4 (0.9)
Body mass index, kg/m²	27.8 (4.8)	27.7 (4.6)	28.2 (5.0)	27.8 (5.2)	27.7 (4.5)	27.9 (4.9)	27.06 (4.6)
Systolic BP, mm Hg	141.7 (15.8)	141.1 (15.5)	139.2 (15.5)	139.4 (15.3)	145.6 (15.0)	144.3 (16.4)	145.2 (17.4)
Diastolic BP, mm Hg	71.2 (11.0)	71.9 (10.4)	70.4 (11.0)	67.6 (11.0)	72.7 (11.1)	71.7 (12.5)	70.1 (11.7)
eGFR, mL/min/1.73 m²	64.0 (17.4)	76.4 (9.9)	53.2 (4.2)	38.0 (5.8)	74.6 (9.5)	52.1 (4.1)	34.6 (7.1)
UACR, mg/g	13.1 (7.2, 32.0)	9.2 (6.2, 14.8)	9.8 (6.0, 14.3)	11.0 (6.5, 16.7)	60.9 (40.8, 122.6)	73.1 (41.6, 153.2)	103.6 (48.6, 308.5)
Total cholesterol, mg/dL	181.1 (38.6)	182.4 (38.6)	182.8 (38.2)	183.3 (39.17)	178.2 (37.9)	172.7 (38.4)	180.0 (39.1)
LDL-cholesterol, mg/dL	103.7 (32.0)	104.62 (31.7)	105.7 (32.1)	105.0 (33.2)	100.7 (31.3)	98.1 (32.6)	101.3 (32.0)
Glucose, mg/dL	98.1 (11.8)	97.9 (11.0)	98.9 (11.8)	96.6 (10.6)	98.9 (13.8)	99.1 (11.3)	97.5 (14.8)

Abbreviations: BP, blood pressure; eGFR, estimated glomerular filtration rate; IQR, interquartile range; LDL, low-density lipoprotein; SD, standard deviation; UACR, urinary albumin-creatinine ratio.

Association of KDIGO eGFR and Albuminuria Categories with Clinical Outcomes

During a median follow-up of 3.1 years, there were 240 primary composite cardiovascular events, and 171 deaths from any cause. The event rates (95% confidence intervals [CIs]) were highest among participants with eGFR 15-44 mL/min/1.73 m^2 and ACR ≥ 30 mg/g, at 9.3 (6.7-12.2) and 6.5 (4.3-8.7) per 100 person-years, respectively, and lowest among those with normal eGFR and normal/mildly increased UACR (2.3 [1.8-2.8] and 1.2 [0.8-1.5] per 100 person-years, respectively) (Table 2). Compared with participants with eGFR ≥ 60 mL/min/1.73 m^2 and UACR < 30 mg/g, those with low eGFR (45-59 or 15-44 mL/min/1.73 m^2) and UACR < 30 mg/g did not have significantly higher risk of the primary composite cardiovascular outcome (HR [95% CI] 1.22 [0.83-1.78] and 1.22 [0.74-1.99], respectively); however, those with low eGFR (45-59 or 15-44 mL/min/1.73 m^2) and moderately or severely increased UACR (≥30 mg/g) had 2- and 3-fold higher risk (HR [95% CI] 1.97 [1.27-3.04]; and 3.32 [2.23-4.93]), respectively. The risk for all-cause death was higher for participants in most KDIGO eGFR and UACR categories compared with those with eGFR ≥60 mL/min/1.73 m^2 and normal/mildly increased UACR (<30 mg/g) (Table 2), with the highest risk observed among those with eGFR 15-44 mL/min/1.73 m^2 and UACR ≥ 30 mg/g (3.34 [2.05-5.44]). We found no significant evidence of effect modification by CVD status at study entry or by randomization arm. Similar results were observed when the BIS1 equation or the CKD-EPI 2021 creatinine-cystatin C were used to estimate GFR (Tables S1 and S2).

DISCUSSION

In this study of older adults without diabetes, we found that low eGFR was associated with adverse cardiovascular outcomes only among participants with moderately or severely increased albuminuria, but this association was not observed in those with normal to mildly increased albuminuria.

It is well documented that increased albuminuria and reduced GFR are associated with adverse clinical outcomes, including high rates of hospitalization, increased risk of mortality, and CKD progression.[18-23] Conversely, it has been shown that healthy older individuals (age ≥ 75 years) with eGFR expected for their age and no albuminuria are less likely have further decline in kidney function and are at lower risk of cardiovascular and overall mortality than adults with eGFR< 45 mL/min/1.73 m^2.[5,24,25] This phenomenon has led to the hypothesis that GFR reduction secondary to aging could be attributed to changes inherent to natural processes and not to podocyte injury or renal parenchymal damage observed in patients with CKD.[7,8] In other words, an older adult with GFR reduction expected for their age would be considered to have CKD only if at least 1 of the following parameters is present: albuminuria,

glomerular hematuria, anemia attributed to CKD, altered bone and mineral metabolism of renal origin, or significant ultrasonographic abnormalities of the kidneys.[14] Our findings provide further support for this hypothesis.

Given the fact that older adults with a decline in eGFR expected for their age and no albuminuria have low risk for adverse outcomes, an age-adapted classification of CKD has been previously proposed to avoid the overdiagnosis of CKD in this population.[3-5,24-27] Specifically, age-related percentiles of GFR have been proposed as an alternative age-adapted classification of CKD, in which CKD would be defined as a value below a given percentile in healthy persons.[3] In addition, a limited set of age-specific eGFR thresholds has also been proposed for 3 pivotal age categories: <40 years (eGFR cutoff of 75 mL/min/1.73 m^2), 40-65 years (eGFR cutoff 60 mL/min/1.73 m^2) and >65 years (eGFR cutoff 45 mL/min/1.73 m^2).[3] Findings from our study suggest that in the absence of albuminuria, the eGFR threshold at which risk for cardiovascular outcomes is increased and potentially even lower than 45 mL/min/1.73 m^2. Future studies with larger sample sizes should be conducted to evaluate this issue more definitively.

Over 50% of our study sample of older adults would be classified as having CKD using the KDIGO definition, with the majority meeting criteria solely based on low eGFR. This population was not at increased risk of cardiovascular events, suggesting significant risk overestimation using current KDIGO criteria. Potential consequences of misdiagnosing CKD in older adults include unnecessary diagnostic procedures and treatments, as well as negative psychological and economic burden, with no added benefit.[9,28] For example, the recommendation of a low-protein diet to patients with kidney aging rather than CKD can worsen sarcopenia in this population.[28] In addition, the prescription of medications that may not be truly indicated and may have adverse side effects, including bleeding due to antiplatelet agent use, rhabdomyolysis from statin use, hyperkalemia induced by renin-angiotensin system blockers, and urinary tract infections induced by SGTL2 inhibitors. In addition, misclassification of CKD can exacerbate polypharmacy experienced by the older adult population.[29] Furthermore, our findings provide further support for a recently proposed modification of the KDIGO classification for older individuals with eGFR < 45 mL/min/1.73 m^2 with normal/mildly increased albuminuria.[26] This modification consists of adding a recommendation to perform a careful evaluation of kidney function, metabolic parameters, and kidney ultrasound before diagnosing CKD in this population.

Our findings of higher risk for all-cause death among participants with low eGFR, even those with normal or mildly increased albuminuria is in contrast with prior studies that have shown that among older adults, GFR reduction attributed to aging is not associated with higher mortality.[24,25] These discordant results might be attributed to differences in the populations studied as well as the

Table 2. Hazard Ratio (95% Confidence Interval) for Primary Composite Outcome and Death by Categories of eGFR and Albuminuria Using the CKD-EPI eGFR Equation

UACR (mg/g) categories and eGFR (mL/min/1.73 m²)		No. of events/ No. of participants (%)	Event Rate per 100 Person-Years (95% CI)	Hazard Ratio (95% CI)[a]
Primary composite SPRINT outcome[b]				
UACR <30	eGFR ≥ 60	79/1170 (6.8)	2.3 (1.8, 2.8)	Referent
	eGFR 45-59	41/457 (9.0)	3.0 (2.1, 3.9)	1.22 (0.83-1.78)
	eGFR 15-44	21/221 (9.5)	3.2 (1.8, 4.5)	1.22 (0.74-1.99)
UACR ≥30	eGFR ≥ 60	29/302 (9.6)	3.4 (2.2, 4.6)	1.32 (0.86-2.03)
	eGFR 45-59	29/193 (15.0)	5.4 (3.5, 7.3)	1.97 (1.27-3.04)
	eGFR 15-44	41/166 (24.7)	9.3 (6.7, 12.2)	3.32 (2.23-4.93)

All-cause mortality				
UACR <30	eGFR ≥ 60	42/1170 (3.6)	1.2 (0.8, 1.5)	Referent
	eGFR 45-59	32/457 (7.0)	2.2 (1.5, 3.0)	1.61 (1.01-2.56)
	eGFR 15-44	18/221 (8.1)	2.6 (1.4, 3.8)	1.66 (0.95-2.91)
UACR ≥30	eGFR ≥ 60	27/302 (8.9)	3.0 (1.9, 4.2)	2.40 (1.47-3.90)
	eGFR 45-59	20/193 (10.4)	3.4 (2.0, 4.9)	2.14 (1.24-3.69)
	eGFR 15-44	32/166 (19.3)	6.5 (4.3, 8.7)	3.34 (2.05-5.44)
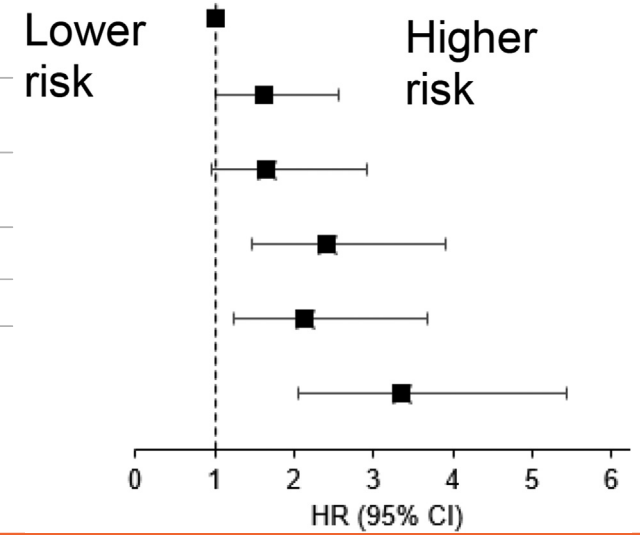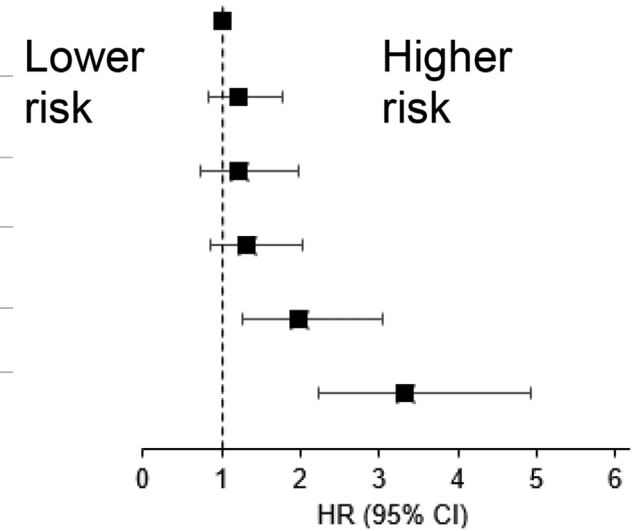
Abbreviations: UACR, urinary albumin-to-creatinine ratio; eGFR, estimated glomerular filtration rate.
[a]Adjusted for age, sex, race/ethnicity, randomization arm, baseline systolic blood pressure, smoking status, body mass index, cardiovascular disease, and total cholesterol.
[b]Myocardial infarction, other acute coronary syndromes, stroke, heart failure, or death from cardiovascular causes.

methods used to estimate GFR. Additional studies with larger samples are needed to evaluate this further.

Our study findings should be interpreted in light of its strengths and limitations. Key advantages of the SPRINT sampling strategy include the large number of participants with CKD enrolled and the comprehensive adjudication of CVD events with standardized longitudinal data collection, allowing for robust multivariable data analysis. The main limitation of this study was the low rate of renal events that did not afford us enough power to evaluate associations of eGFR and UACR KDIGO categories with progression of CKD in older adults. In addition, our analyses were conducted using a single measurement of eGFR and albuminuria at the SPRINT baseline visit, which might have led to misclassification of CKD. Furthermore, the SPRINT study did not include participants with diabetes or proteinuria > 1 g/day, and most participants self-identified as non-Hispanic White; therefore, the results of our study might not be generalizable to other populations.

In conclusion, our study showed that among older adults without diabetes enrolled in the SPRINT study, the prevalence of CKD using current KDIGO criteria was high. However, even though low eGFR with normal or mildly increased albuminuria was associated with higher mortality, it was not associated with increased risk of cardiovascular events. This finding supports the need for additional studies to evaluate an age-adapted CKD classification to improve risk stratification among adults aged 75 years or older.

SUPPLEMENTARY MATERIALS

Supplementary File (PDF)

Table S1: Hazard Ratio (95% Confidence Interval) for Primary Composite Outcome and Death by Categories of eGFR and Albuminuria Using the BIS1 eGFR Equation.

Table S2: Hazard Ratio (95% Confidence Interval) for Primary Composite Outcome and Death by Categories of eGFR and Albuminuria Using the CKD-EPI 2021 Creatinine-Cystatin C GFR Estimating Equation.

Table S3: Number (Percentage) of SPRINT Participants 75 Years or Older by KDIGO eGFR and Albuminuria Categories. Panel (A) shows the "heat map" based on current KDIGO categories while the color scheme in panel (B) is based on our Cox proportional hazards model results for the primary SPRINT outcome.

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