Title

Clinical events and patient-reported outcome measures during CKD progression: findings from the Chronic Renal Insufficiency Cohort Study.

Journal

Nephrology Dialysis Transplantation, 36(9)

ISSN

0931-0509

Authors

Grams, Morgan E
Surapaneni, Aditya
Appel, Lawrence J
et al.

Publication Date

2021-08-27

DOI

10.1093/ndt/gfaa364

Peer reviewed

Nephrol Dial Transplant (2021) 36: 1685–1693
doi: 10.1093/ndt/gfaa364
Advance Access publication 16 December 2020

ORIGINAL ARTICLE

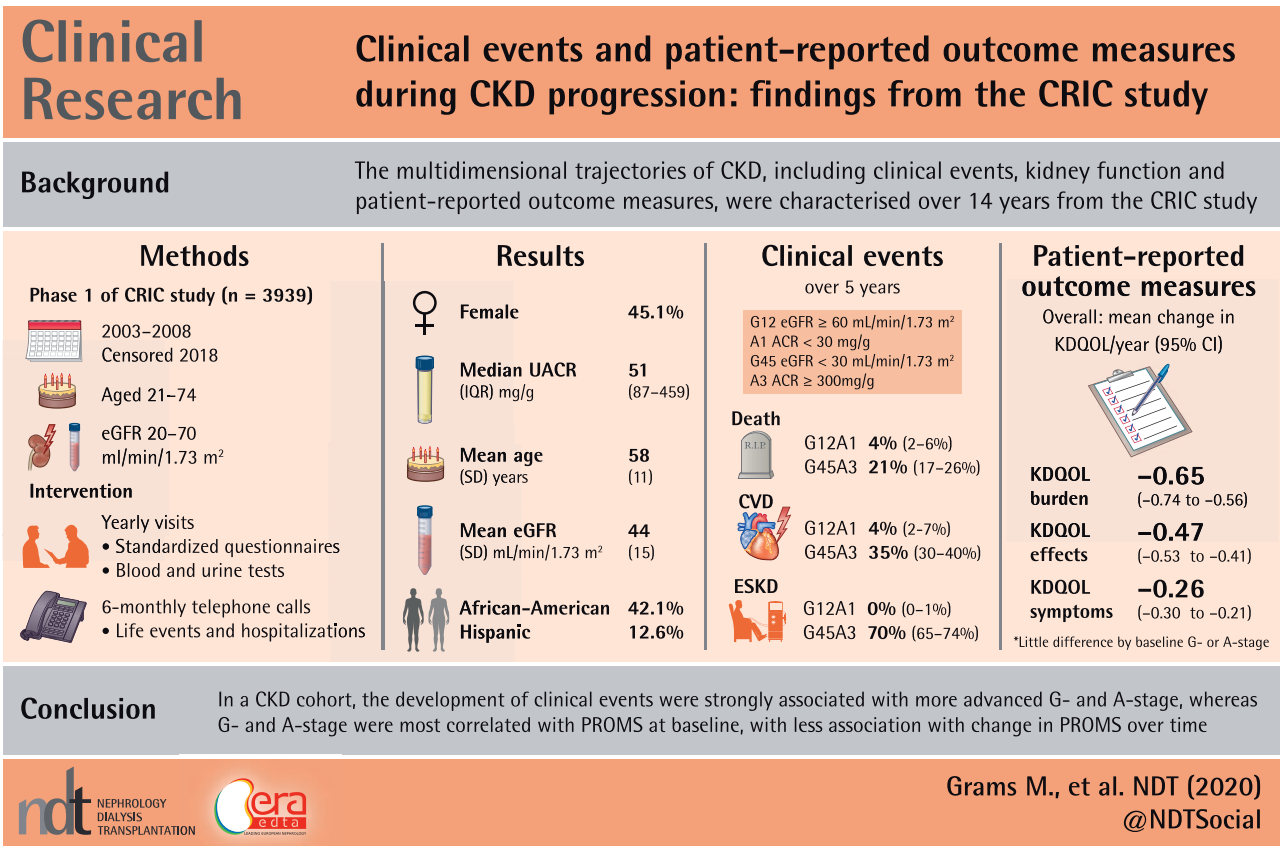
Clinical events and patient-reported outcome measures during CKD progression: findings from the Chronic Renal Insufficiency Cohort Study

Morgan E. Grams[1], Aditya Surapaneni[1], Lawrence J. Appel[1], James P. Lash[2], Jesse Hsu[3], Clarissa J. Diamantidis[4], Sylvia E. Rosas[5], Jeffrey C. Fink[6], Julia J. Scialla[4,7], James Sondheimer[8], Chi-Yuan Hsu[9], Alfred K. Cheung[10], Bernard G. Jaar[1], Sankar Navaneethan[11], Debbie L. Cohen[3], Sarah Schrauben[3], Dawei Xie[3], Pandu Rao[12] and Harold I. Feldman[3] the CRIC study investigators*

[1]Departments of Medicine and Epidemiology, Johns Hopkins University, Baltimore, MD, USA, [2]Department of Medicine, University of Illinois at Chicago, Chicago, IL, USA, [3]Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA, [4]School of Medicine, Duke University, Durham, NC, USA, [5]Joslin Diabetes Center, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA, USA, [6]Department of Medicine, University of Maryland, Baltimore, MD, USA, [7]Department of Medicine and Public Health Sciences, University of Virginia School of Medicine, Charlottesville, VA, USA, [8]Department of Internal Medicine, Wayne State University, Detroit, MI, USA, [9]Department of Medicine, University of California, San Francisco, San Francisco, CA, USA, [10]Veterans Affairs Salt Lake City Health Care System, University of Utah, Salt Lake City, UT, USA, [11]Baylor College of Medicine, Houston, TX, USA and [12]Department of Internal Medicine, University of Michigan, Ann Arbor, MI, USA

Correspondence and offprint requests to: Morgan E. Grams; E-mail: mgrams2@jhmi.edu
*The Chronic Renal Insufficiency Cohort Study investigators additionally include Alan S. Go, Jiang He, Mahboob Rahman and Raymond R. Townsend

GRAPHICAL ABSTRACT



KEY LEARNING POINTS

What is already known about this subject?

- Patients with chronic kidney disease (CKD) have a higher risk of end-stage kidney disease (ESKD), cardiovascular disease (CVD) and death.
- Less is known about changes in patient-reported quality of life (QOL) and mental and physical well-being and how they relate to the existing CKD staging system.

What this study adds?

- More advanced stages of CKD were associated with a higher risk of clinical outcomes over time.
- More advanced stages of CKD were associated with a lower QOL and mental and physical well-being.
- Changes in patient-reported outcome measures (PROMs) over time were generally small and distinct from the existing CKD staging system.

What impact this may have on practice or policy?

- Important PROMs, including physical and mental well-being and other QOL metrics, capture distinct information from the existing CKD staging system.

ABSTRACT

Background. Patients with chronic kidney disease (CKD) face risks of not only end-stage kidney disease (ESKD), cardiovascular disease (CVD) and death, but also decline in kidney function, quality of life (QOL) and mental and physical well-being. This study describes the multidimensional trajectories of CKD using clinical events, kidney function and patient-reported outcome measures (PROMs). We hypothesized that more advanced CKD stages would associate with more rapid decline in each outcome.

Methods. Among 3939 participants enrolled in the Chronic Renal Insufficiency Cohort (CRIC) Study, we evaluated multidimensional disease trajectories by G- and A-stages of enrollment estimated glomerular filtration rate (eGFR) and albuminuria, respectively. These trajectories included clinical events (ESKD, CVD, heart failure and death), eGFR decline and PROMs [kidney disease QOL (KDQOL) burden, effects and symptoms questionnaires, as well as the 12-item short form mental and physical component summaries]. We also evaluated a group-based multitrajectory model to group participants on the basis of longitudinal PROMs and compared group assignments by enrollment G- and A-stage.

Results. The mean participant age was 58 years, 45% were women, mean baseline eGFR was 44 mL/min/1.73 m^2 and median urine albumin:creatinine ratio was 52 mg/g. The incidence of all clinical events was greater and eGFR decline was faster with more advanced G- and A-stages. While baseline KDQOL and physical component measures were lower with more advanced G- and A-stage of CKD, changes in PROMs were inconsistently related to the baseline CKD stage. Groups formed on PROM trajectories were fairly distinct from existing CKD staging (observed agreement 60.6%) and were associated with the risk of ESKD, CVD, heart failure and death.

Conclusions. More advanced baseline CKD stage was associated with a higher risk of clinical events and faster eGFR decline, and was only weakly related to changes in patient-reported metrics over time.

Keywords: albuminuria, cardiovascular, CKD, ESKD, patient-centered outcome

INTRODUCTION

Patients with chronic kidney disease (CKD) are at risk for many adverse clinical outcomes, including end-stage kidney disease (ESKD), cardiovascular disease (CVD) and death [1, 2]. Patient-reported quality of life (QOL) and mental and physical well-being are likely also influenced by poor kidney function [3, 4]. The last decade has seen a shift in focus toward person-centered care and collection of self-reported health measures, with several studies demonstrating an association between low QOL and mortality in CKD, but there is limited understanding of the heterogeneity and evolution of patient experience as kidney disease progresses [5–7]. Characterizing the varying trajectories of CKD using longitudinal patient-reported outcome measures (PROMs) and clinical events could provide a framework for comparison with real-world experience, since PROMs are increasingly incorporated in medical care [8].

The Chronic Renal Insufficiency Cohort (CRIC) is a long-running study funded by the National Institute of Diabetes and Digestive and Kidney Diseases to study the causes and consequences of CKD among patients in the USA [9]. The goal of this study was to characterize the natural history of CKD in CRIC participants over up to 14 years of follow-up with respect to clinical events, trajectories in estimated glomerular filtration rate (eGFR) and changes in PROMs, including kidney disease QOL (KDQOL), and mental and physical well-being scores. As an exploratory approach, we also evaluated an unsupervised clustering approach based on longitudinal PROMs and compared group assignments with CKD staging at baseline. We hypothesized that those with a more advanced CKD stage would have more rapid decline in PROMs.

MATERIALS AND METHODS

Study population

This study population was enrolled from phase 1 of the CRIC Study, in which 3939 participants ages 21–74 years with

an eGFR between 20 and 70 mL/min/1.73 m^2 were recruited between 2003 and 2008 [9]. Exclusion criteria from the original study included a diagnosis of polycystic kidney disease and active immunosuppression for glomerulonephritis as well as cirrhosis, class III or IV heart failure, human immunodeficiency virus (HIV) infection, cancer and pregnancy. Participants were followed annually with study visits in which a variety of health measures were assessed through blood and urine laboratory tests as well as standardized questionnaires. Telephone calls spaced ~6 months apart were performed to provide updates on hospitalizations and important life events. For this study, the administrative censor date was December 2018. All participants provided written consent for this study.

Baseline characteristics

Baseline characteristics were assessed at the initial study visit and included demographics; body mass index [weight (kg) divided by height (m^2)]; history of CVD, diabetes mellitus or hypertension; and systolic and diastolic blood pressure. Three assessments of blood pressure were taken after 5 min of quiet rest using an aneroid sphygmomanometer. Hypertension was defined as systolic blood pressure $\geq$140 mmHg, diastolic blood pressure $\geq$90 mmHg and/or self-reported antihypertensive medication use. Diabetes was determined as at least one of the following: self-reported insulin or oral hypoglycemic medication, fasting blood glucose $\geq$126 mg/dL or a nonfasting level $\geq$200 mg/dL, or hemoglobin A1c $\geq$6.5%.

Assessment of kidney function

eGFR was calculated based on isotope dilution mass spectrometry–standardized serum creatinine measured using an enzymatic method (Orthos Vitros 950) and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. [10]. Albuminuria was assessed by radioimmunoassay using the 24-h urine sample collected at baseline. According to the Kidney Disease: Improving Global Outcomes (KDIGO) eGFR (G) and albuminuria (A) staging system, CKD was categorized into G-stage (G1: GFR $\geq$90 mL/min/1.73 m^2, G2: 60–89 mL/min/1.73 m^2, G3a: 45–59 mL/min/1.73 m^2, G3b: 30–44 mL/min/1.73 m^2, G4: 15–29 mL/min/1.73 m^2, G5: <15 mL/min/1.73 m^2) and A-stage [A1: albumin:creatinine ratio (ACR) <30 mg/g, A2: ACR 30–299 mg/g, A3: ACR $\geq$300 mg/g]; at the baseline assessment, stages G1/G2 and (separately) G4/G5 were combined due to low numbers. Serum creatinine was measured yearly at clinic visits.

Assessment of patient-reported outcomes over time

PROMs included scores from the KDQOL-36 questionnaires given at each clinic visit. The questionnaires consist of two parts: a disease-specific part to measure the three KDQOL domains and a generic part [the 12-item short form (SF-12)] to measure mental and physical health-related QOL. The disease-specific measures included a score for the burden of kidney disease (KDQOL Burden), a score for the effects of kidney disease (KDQOL effects) and a score for the symptoms of kidney disease (KDQOL symptoms) [11]. The generic SF-12 quantified physical well-being using the SF-12 physical component summary (PCS) score and mental well-being using the SF-12 mental component summary (MCS) score (Supplementary data, Appendix S1). All scores were provided on a scale of 0–100, where 100 represents the best possible health.

Assessment of clinical events over time

Participants were followed for the development of ESKD through biannual contact in which the date of initiation of renal replacement therapy was reported, supplemented by information from the US Renal Data System. Cardiovascular events were assessed at baseline as a history of myocardial infarction, cerebrovascular accident (both ischemic and hemorrhagic) and heart failure (based on the modified clinical Framingham criteria) and longitudinally by asking participants about intervening hospitalizations during biannual contact. Hospital records were then obtained and the first 30 discharge codes were abstracted and assessed for codes relevant to CVD. These charts were sent for centralized adjudicated review using event-specific guidelines by two physicians. Cardiovascular events captured during follow-up included myocardial infarction, cerebrovascular accident, heart failure and cardiovascular mortality [12]. Mortality was ascertained through reports from next of kin, retrieval of death certificates or obituaries, review of hospital records and linkage with the Social Security Death Master File.

Statistical analysis

Baseline characteristics were depicted across G-stage; P-values for trend were determined using linear regression and G-stage (1/2, 3, 4/5) as an ordinal variable. For the purpose of descriptive summaries, individual participant trajectories of decline in eGFR, the three KDQOL scores and the MCS and PCS scores were assessed using linear mixed models with random intercept and random slopes with G- and A-stage as both ordinal and categorical predictors using a complete case analysis (Supplementary data, Appendix S2). The cumulative incidence of clinical endpoints was assessed by baseline G- and A-stage, accounting for the competing event of mortality [13]; for mortality, cumulative incidence was assessed using the reciprocal of Kaplan–Meier curves. We also repeated analyses stratified by sex and the presence of diabetes at baseline. In exploratory analyses, we used an unsupervised clustering approach based on patient-reported outcomes over time to determine groups of patients using all baseline and follow-up data for the three KDQOL scores and the MCS and PCS scores [14]. This group-based multitrajectory approach, an extension of finite mixture modeling, estimates trajectories of indicators and classifies individuals into clusters based on similar trajectories in each of these domains. The number of groups was prespecified for ease of comparison with that of the risk-based staging system recommended by the KDIGO using baseline measures of eGFR and ACR. Comparisons were performed using observed agreement and a weighted kappa statistic [2]. The weighted kappa statistic represents the difference between observed and expected agreement, divided by 1, the expected agreement, with greater weighting to observed values that are farther apart (e.g. a high-risk classification and a low-risk classification). All

Table 1. Baseline characteristics of the CRIC by G-stage classified by baseline eGFR[a]

Characteristics	Overall	G1–2	G3a	G3b	G4–5
Patients, *n* (%)	3939	592 (15.0)	1190 (30.2)	1428 (36.3)	729 (18.5)
Age (years)	57.7 (11.0)	50.7 (10.9)	57.9 (10.1)	59.5 (10.7)	59.2 (10.9)
Black race, *n* (%)	1658 (42.1)	233 (39.4)	494 (41.5)	609 (42.6)	322 (44.2)
Hispanic ethnicity, *n* (%)	497 (12.6)	43 (7.3)	114 (9.6)	205 (14.4)	135 (18.5)
Female, *n* (%)	1778 (45.1)	267 (45.1)	487 (40.9)	672 (47.1)	352 (48.3)
Body mass index (kg/m^2)	32.1 (7.8)	31.5 (7.5)	32.1 (8.0)	32.4 (7.7)	31.8 (8.0)
Systolic blood pressure (mmHg)	128.5 (22.2)	122.3 (19.5)	126.7 (20.6)	130.4 (22.7)	132.7 (24.3)
Diastolic blood pressure (mmHg)	71.5 (12.8)	74.0 (12.8)	72.0 (12.5)	70.9 (12.7)	70.1 (13.4)
eGFR (CKD-EPI equation, mL/min/1.73 m^2)	44.3 (15.0)	69.5 (9.1)	51.7 (4.3)	37.8 (4.3)	24.6 (3.7)
Urine ACR (mg/g), median (IQR)	51.9 (8.7–458.8)	11.0 (4.4–77.3)	25.4 (6.5–200.5)	90.6 (12.9–641.0)	301.5 (46.4–1371.6)
Hemoglobin A1C (%)	6.7 (1.6)	6.3 (1.5)	6.6 (1.5)	6.8 (1.6)	6.7 (1.6)
Hypertension, *n* (%)	3391 (86.1)	391 (66.0)	1025 (86.1)	1297 (90.8)	678 (93.0)
Diabetes mellitus, *n* (%)	1908 (48.4)	186 (31.4)	530 (44.5)	777 (54.4)	415 (56.9)
CVD, *n* (%)	1316 (33.4)	104 (17.6)	371 (31.2)	540 (37.8)	301 (41.3)
KDQOL, burden of kidney disease (0–100 scale)	82.2 (23.7)	87.1 (21.5)	87.2 (20.4)	80.1 (24.1)	74.0 (26.7)
KDQOL, effect of kidney disease (0–100 scale)	89.1 (15.6)	91.6 (15.7)	91.7 (13.6)	88.2 (15.4)	84.8 (17.8)
KDQOL, symptoms of kidney disease (0–100 scale)	83.4 (14.8)	84.9 (15.7)	85.8 (13.6)	81.9 (15.3)	81.5 (14.4)
SF-12 MCS score	50.4 (10.5)	49.6 (10.5)	51.2 (10.4)	50.1 (10.4)	50.3 (10.8)
SF-12 PCS score	41.3 (11.5)	44.4 (11.9)	42.8 (11.3)	40.2 (11.4)	38.3 (10.8)

Values are presented as mean (SD) unless stated otherwise.
[a]All P for trend <0.05 with the exception of black race, body mass index and SF-12 MCS score.

analyses were performed with Stata SE 15 (StataCorp, College Station, TX, USA).

RESULTS

Baseline characteristics

There were 3939 participants included in the first phase of the CRIC Study. The mean age was 58 years [standard deviation (SD) 11]; 45.1% were female and 42.1% were African American (Table 1). The mean eGFR was 44 mL/min/1.73 m^2 (SD 15) and the median urine ACR was 51 mg/g [interquartile range (IQR) 87–459]. At baseline, the majority of participants had CKD Stage G3a or G3b (66.5%). Participants with a more advanced G-stage had lower KDQOL scores and lower PCS scores (P for trend <0.001 for all comparisons) but did not differ on MCS scores (P for trend = 0.8). Participants with diabetes had, on average, a higher prevalence of CVD at baseline, lower KDQOL and lower PCS and MCS scores than participants without diabetes, even within the same CKD G-stage (Supplementary data, Table S1). Male and female participants were generally similar (Supplementary data, Table S2).

PROMs and clinical events over time

Over a median follow-up of 11.5 years, PROMs worsened only slightly over time. Scaled to 100, the mean change per year in KDQOL burden was −0.65 [95% confidence interval (CI) −0.74 to −0.56], KDQOL effects were −0.47 (95% CI −0.53 to −0.41), KDQOL symptoms were −0.26 (95% CI −0.30 to −0.21), MCS score was −0.04 (95% CI −0.07 to −0.01) and PCS score was −0.34 (95% CI −0.37 to −30). However, there was substantial variation in these trajectories as well as that of eGFR decline (Supplementary data, Figure S1). The relationship between baseline G- and A-stage and change in PROMs over time was very small and statistically significant only for KDQOL burden [−0.15 (95% CI −0.25 to −0.05) faster change in score per year per higher G-stage; −0.47 (95% CI −0.59 to −0.36) faster change in score per year per higher A-stage) and for KDQOL effects for A-stage [−0.31 (95% CI −0.38 to −0.23) faster change in score per year] (Table 2). Survival free of CVD, heart failure, ESKD and death was markedly decreased with more advanced G- and A-stage (all log-rank P < 0.001) (Supplementary data, Figure S2). For example, at 5 years the cumulative incidence of CVD was 4% (15% if including disease present at baseline) in G1–2A1 CKD and 35% (57% if including disease present at baseline) in G4–5A3 CKD (Table 3). The 5-year cumulative incidence of ESKD was 0% (95% CI 0–1) in G1–2A1 CKD and 70% (95% CI 65–74) in G4–5A3 CKD and the incidence of death increased from 4% (95% CI 2–6) to 21% (95% CI 17–26) in the same groups of participants.

PROMs and clinical events over time, stratified by baseline diabetes status and sex

Patients with diabetes generally had a greater decline in PROMs over time compared with patients without diabetes (Supplementary data, Table S3). The greatest declines in eGFR were seen in patients with CKD A3, irrespective of G-stage, sex or diabetes status (Supplementary data, Table S4). The pattern of higher risk of clinical events with higher baseline G- and A-stage also persisted in stratified analysis. In particular, the risks of CVD and heart failure were much higher among those with diabetes than those without diabetes. Even participants with diabetes and G1–2A1 disease had a 6% cumulative incidence of CVD (>25% if including that present at baseline) at 5 years

Table 2. Differences in baseline and change in PROMs by G- and A-stage

PROM	Per higher G-stage, baseline		Per higher A-stage, baseline		Per higher G-stage, change/year		Per higher A-stage, change/year	
	β	P-value	β	P-value	β	P-value	β	P-value
KDQOL burden	−4.34	<0.001	−5.91	<0.001	−0.15	0.004	−0.47	<0.001
KDQOL effects	−2.32	<0.001	−3.18	<0.001	−0.06	0.06	−0.31	<0.001
KDQOL symptoms/problems	−1.56	<0.001	−1.28	<0.001	0.002	0.94	−0.03	0.31
SF-12 MCS	0.20	0.23	−1.03	<0.001	−0.01	0.70	0.01	0.56
SF-12 PCS	−2.10	<0.001	−0.90	<0.001	−0.01	0.79	−0.01	0.82

Trajectories were modeled using linear mixed models with random slopes and random intercepts, using G-stage (G1–2, G3a, G3b and G4–5) and A-stage (A1, A2 and A3) as ordinal variables.

Table 3. Cumulative incidence and 95% CIs of new clinical outcomes at 5 years by KDIGO classification system at baseline in the CRIC participants

5-year heart failure	A1	A2	A3	5-year CVD	A1	A2	A3
G12	2% (1–3)	7% (3–13)	14% (7–23)	G12	4% (2–7)	9% (5–16)	25% (16–35)
G3a	3% (2–5)	8% (5–11)	13% (9–17)	G3a	9% (7–11)	14% (10–18)	24% (19–30)
G3b	5% (3–7)	12% (9–16)	16% (12–19)	G3b	12% (10–15)	22% (18–26)	28% (24–32)
G45	16% (11–23)	13% (9–18)	20% (16–25)	G45	26% (19–33)	21% (16–27)	35% (30–40)
5-year ESKD	**A1**	**A2**	**A3**	**5-year death**	**A1**	**A2**	**A3**
G12	0% (0–1)	3% (1–7)	7% (2–14)	G12	4% (2–6)	9% (5–15)	12% (6–20)
G3a	1% (0–2)	4% (2–7)	24% (18–29)	G3a	6% (4–8)	11% (8–15)	14% (10–19)
G3b	2% (1–4)	13% (10–16)	42% (38–46)	G3b	10% (8–13)	14% (10–17)	19% (16–23)
G45	13% (8–19)	31% (25–37)	70% (65–74)	G45	24% (17–31)	21% (16–27)	21% (17–26)

(Supplementary data, Table S4). By sex, risks of ESKD were higher in men than women; risks of new heart failure or CVD were similar (Supplementary data, Table S6).

Groups based on trajectories of patient-reported outcomes over time

When participants were classified into three groups by multitrajectory clustering of PROMs during follow-up (KDQOL scores, PCS and MCS scores) (Table 4), the lowest risk group contained 1423 participants and was characterized by fairly steady levels of patient-reported variables with the least impairment (Figure 1). The second group of 1602 participants had an intermediate level of impairment and the group of 914 participants constituted the group with the highest impairment. The most notable difference in groups was not differences in changes in PROMs over time, which appeared similar, but differences in PROMs at baseline. Baseline clinical characteristics were also different across the three groups, with the higher risk groups having lower eGFR, higher urine ACR and a higher prevalence of diabetes and CVD. Clinical outcomes in the three groups were consistent with the low-/medium-/high-risk classifications: the cumulative incidence of ESKD, CVD, heart failure and death was higher in the intermediate-risk group compared with the low-risk group, as well as the high-risk group compared with the intermediate-risk group (all log-rank $P < 0.001$) (Figure 2). A comparison of the classification using PROM trajectories with the current CKD staging system revealed differences in classification (observed agreement 60.6%, overall weighted kappa 0.15), with the high-risk group based on PROMs occurring in all G- and A-stages (Supplementary data, Figure S3).

DISCUSSION

This study of 3939 participants with CKD in a carefully phenotyped cohort followed up to 14 years characterized the natural history of disease, including clinical events, eGFR trajectories and PROMs, by baseline G- and A-stage. As expected, clinical events were strongly associated with more advanced disease. Somewhat surprisingly, G- and A-stage were most correlated with PROMs at baseline, with little association with change in PROMs over time. A clustering method based on trajectories of multiple PROMs over time showed a strong separation in risk of clinical events but distinct classification from G- and A-staging. The results provide the absolute risk of events in a CKD population and confirm the importance of both GFR and albuminuria across a wide range of clinical outcomes in patients with and without diabetes. They also suggest that PROMs represent a unique aspect of disease progression.

This study adds to the current literature by providing longitudinal assessment of PROMs over up to 14 years of follow-up. Other studies have suggested the importance of a single measure of QOL as a prognostic factor for morbidity and mortality in patients with advanced CKD as well as those requiring maintenance dialysis [7, 15, 16]. In our study of CRIC participants, baseline measures of mental and physical health were similar to other smaller studies of patients with advanced kidney disease [17, 18]. We found a clear cross-sectional relationship between G-stage and all baseline PROMs except for mental well-being, similar to a study of 220 patients with CKD [18]. Fewer studies have tracked longitudinal PROMs [19, 20]. Our finding that PROMs were relatively stable over time is consistent with some

Table 4. Baseline characteristics within three groups formed by unsupervised classification based on longitudinal trajectories of QOL and physical and mental health scores

Characteristics	Group 1	Group 2	Group 3
Patients, *n* (%)	914 (23.2)	1602 (40.7)	1423 (36.1)
Age (years)	56.4 (10.3)	59.1 (10.8)	56.9 (11.5)
Black race, *n* (%)	436 (47.7)	716 (44.7)	506 (35.6)
Hispanic ethnicity, *n* (%)	188 (20.6)	208 (13.0)	101 (7.1)
Female, *n* (%)	478 (52.3)	739 (46.1)	561 (39.4)
Body mass index (kg/m^2)	34.2 (8.8)	32.7 (8.0)	30.0 (6.2)
Systolic blood pressure (mmHg)	133.2 (23.7)	130.1 (22.6)	123.7 (19.7)
Diastolic blood pressure (mmHg)	72.5 (13.2)	70.7 (13.1)	71.9 (12.3)
eGFR (CKD-EPI equation, mL/min/1.73 m^2)	40.3 (14.9)	42.0 (14.0)	49.6 (14.7)
Urine ACR (mg/g), median (IQR)	197.3 (20.5–1246.4)	77.0 (11.8–461.4)	17.7 (5.7–178.5)
Hemoglobin A1C (%)	7.1 (1.8)	6.8 (1.6)	6.2 (1.3)
Hypertension, *n* (%)	830 (90.8)	1442 (90.0)	1119 (78.6)
Diabetes mellitus, *n* (%)	598 (65.4)	848 (52.9)	462 (32.5)
CVD, *n* (%)	427 (46.7)	610 (38.1)	279 (19.6)
Number of medications, median (IQR)	10.0 (7.0–13.0)	9.0 (6.0–12.0)	7.0 (5.0–10.0)
KDQOL burden of kidney disease (0–100 scale)	60.4 (26.7)	83.0 (21.0)	95.3 (11.4)
KDQOL effect of kidney disease (0–100 scale)	73.5 (20.6)	90.6 (11.4)	97.5 (4.9)
KDQOL symptoms of kidney disease (0–100 scale)	67.7 (15.7)	83.9 (10.9)	93.1 (7.8)
SF-12 MCS score	41.3 (11.1)	51.9 (9.4)	54.6 (7.4)
SF-12 PCS score	32.0 (9.2)	38.7 (10.4)	50.1 (7.1)

Values presented as mean (SD) unless stated otherwise.

but not all studies, which differ in selection and severity of disease in participants [21–23]. Meuleman *et al.* [20] used latent class growth models to classify patient-reported outcome trajectories in 396 patients referred for predialysis care (mean eGFR 16 mL/min/1.73 m^2) and found that groups separated primarily on baseline levels, similar to our study. Da Silva-Gane *et al.* [24] evaluated mental health and physical health scores over 3 years in 170 patients with advanced CKD (late-stage G4 or G5 disease) and showed little change over time. One possible explanation for the stability of PROMs is that the KDQOL and physical and mental component measures are insensitive to significant changes in individual patient experience. Another is that most of the significant decline in patient QOL occurred prior to enrollment in the studies. Additional studies are required to determine if there are interventions that can improve QOL and well-being in patients with CKD.

This study provides long-term absolute risks of a wide range of outcomes, both clinical and patient reported, that are experienced by patients with CKD [25]. The high incidence of CVD among participants with diabetes—even among those in the KDIGO-defined low-risk category—suggests that clinical management of this population should strongly emphasize risk factor reduction, including blood pressure control, lipid management and smoking cessation [26]. That eGFR decline was fastest among those with higher albuminuria underscores the idea that patients with A3 represent a high-risk group; angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and consideration of specific medications such as sodium glucose cotransporter-2 inhibitors or glucagon-like peptide-1 receptor agonists in patient with diabetes have been shown to reduce CKD endpoints in similar patients in clinical trials [27–30]. Finally, with one in five patients with CKD G4–5A3 dying by 5 years, the results confirm that advanced CKD has an extremely high rate of mortality, even in a cohort of research participants, emphasizing the pressing need for effective therapy and advanced care planning.

The difference in baseline functionality by baseline eGFR was striking. At enrollment, patients with lower eGFR already had lower physical well-being than those with preserved kidney function, as has been observed previously [23, 31]. Poor physical function has been associated with subsequent morbidity and mortality in populations receiving maintenance dialysis [32–35], thus regular exercise and preventative efforts to combat frailty and maintain physical well-being may be of particular relevance in the CKD population, with early intervention being most effective. Since counseling on physical activity by nephrologists is low, and routine assessment of physical function is not standard, large gains may be achievable with greater provider appreciation of the importance of physical well-being [36, 37].

A novel aspect of this study was the use of PROMs—KDQOL, physical well-being and mental well-being—to group participants into clusters using an unsupervised clustering algorithm. The three groups based on trajectories showed a large separation in risk of clinical events, providing a measure of construct validity to the unsupervised approach. The only slight agreement of the clusters with that of baseline G- and A-stages suggests that patient-reported outcomes provide a unique aspect of risk of future clinical events in a population with CKD. A previous study used an unbiased approach to CKD classification, but instead of patient-centered measures, it used laboratory trajectories and did not compare groups to existing staging systems or concomitant risk of clinical outcomes [38].

The strengths of this study include a study population of carefully phenotyped patients with CKD followed for up to 14 years. Clinical outcomes were rigorously collected and adjudicated. However, some weaknesses must also be mentioned. Although the CRIC Study has one of the largest cohorts of CKD patients available, it is a research cohort, with a younger population than the average patient with CKD. Studies suggest that

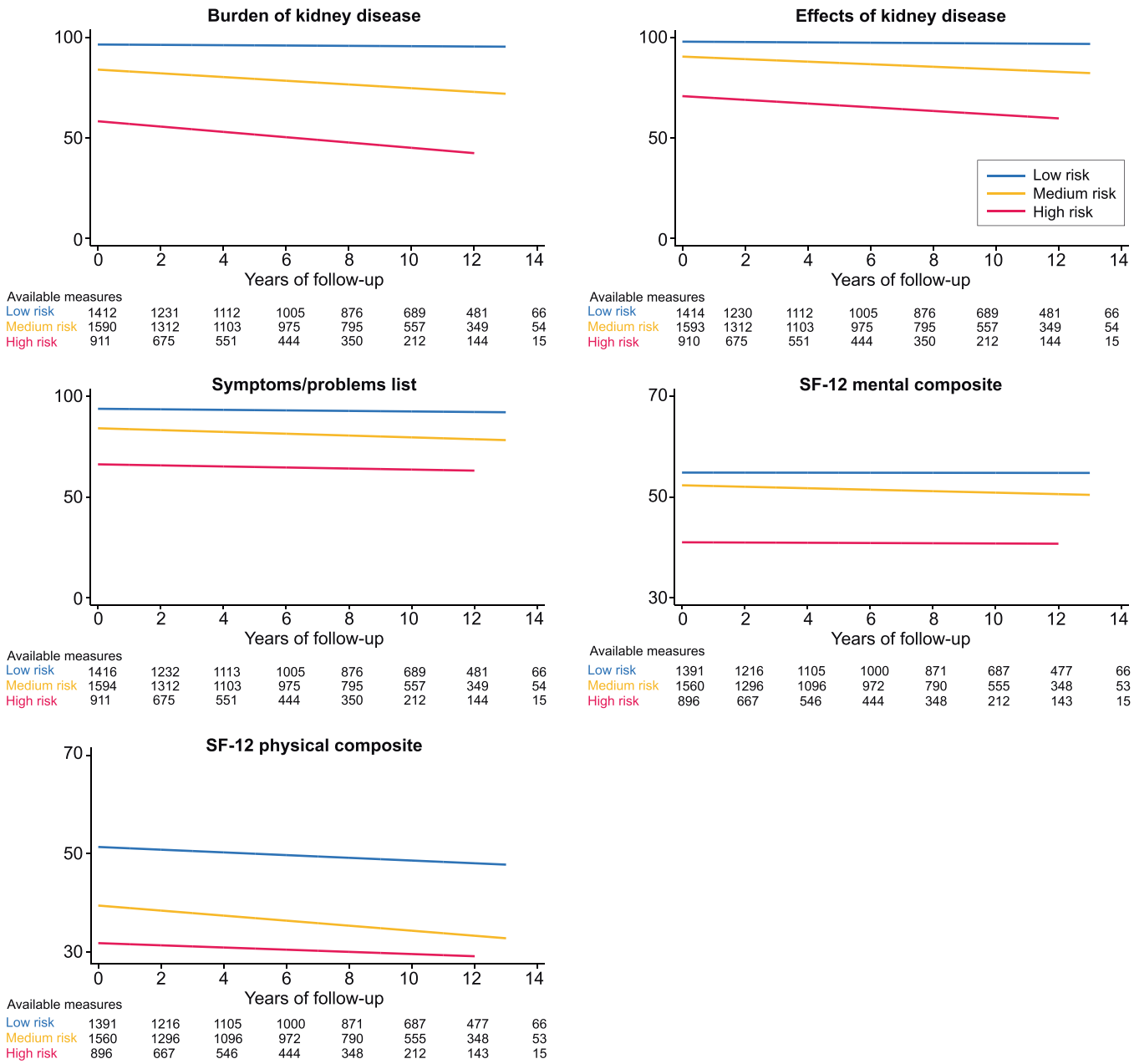


FIGURE 1: Mean trajectories of patient-centered outcomes over time according to groups assigned through clustering of CRIC participants based on longitudinal trajectories of KDQOL, physical well-being and mental well-being scores. Trajectories are plotted using linear mixed models with random slopes and intercepts, extending until <10% of the original participants remain.

research cohorts have lower rates of mortality and CVD than the equivalent CKD population seen in clinical practice, thus our estimates for CVD and death may be conservative [25, 39]. Second, our estimates are stratified by G- and A-stage, providing a population rather than an individual average estimate. Third, the unsupervised approach to clustering was employed as a proof of concept to evaluate whether patient-reported outcomes could be considered another axis of CKD. The method uses longitudinal data and thus is not used to classify participants at a single point in time, such as an office visit. We did not test whether the addition of PROMs as assessed in routine clinical care may aid in the prediction of key clinical outcomes.

In summary, this study provides information on clinical and patient-reported outcomes in the CRIC Study, one of the most carefully phenotyped cohorts of patients with CKD in the world. It reinforces the observation that, in addition to the widely appreciated risk of ESKD, the risk of mortality associated with advanced CKD is high and that CVD is very common. In addition, it suggests that PROMs represent a unique axis of CKD trajectory. The findings underscore the need for a comprehensive, patient-centered approach to CKD care that includes risk factor reduction, administration of known effective therapies and interventions to maintain and improve physical well-being.

SUPPLEMENTARY DATA

Supplementary data are available at ndt online.

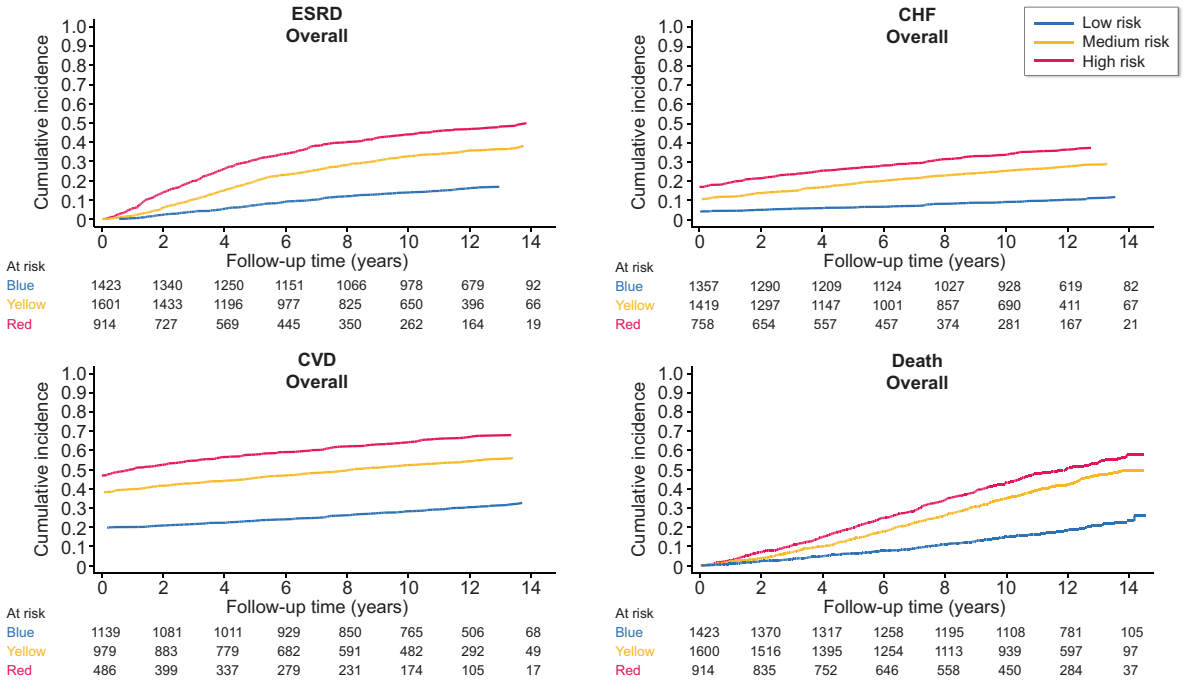


FIGURE 2: Cumulative incidence of clinical outcomes (prevalent and incident events) among three groups of CRIC participants formed using longitudinal trajectories of KDQOL, physical well-being and mental well-being scores. Cumulative incidence curves estimated taking into account the competing event of death truncated on the last event.

FUNDING

Funding for the CRIC Study was obtained under a cooperative agreement from the National Institute of Diabetes and Digestive and Kidney Diseases (U01DK060990, U01DK060984, U01DK061022, U01DK061021, U01DK061028, U01DK060980, U01DK060963 and U01DK060902). In addition, this work was supported in part by the Perelman School of Medicine at the University of Pennsylvania (Clinical and Translational Science Award NIH/NCATS UL1TR000003), Johns Hopkins University (UL1 TR-000424), University of Maryland (GCRC M01 RR-16500), Clinical and Translational Science Collaborative of Cleveland (UL1TR000439) from the National Center for Advancing Translational Sciences (NCATS) component of the National Institutes of Health and the NIH Roadmap for Medical Research, Michigan Institute for Clinical and Health Research (UL1TR000433), University of Illinois at Chicago (CTSA UL1RR029879), Tulane COBRE for Clinical and Translational Research in Cardiometabolic Diseases (P20 GM109036) and Kaiser Permanente (NIH/NCRR UCSF-CTSI UL1 RR-024131).

CONFLICT OF INTEREST STATEMENT

The authors have no relevant conflicts of interest.

(See related article by Amir *et al.* Trajectories of quality of life in chronic kidney disease: a novel perspective of disease progression. *Nephrol Dial Transplant* 2021; 36: 1563–1565)

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the NIDDK Central Repository upon request.

REFERENCES

1. Astor BC, Matsushita K, Gansevoort RT *et al.* Lower estimated glomerular filtration rate and higher albuminuria are associated with mortality and end-stage renal disease. A collaborative meta-analysis of kidney disease population cohorts. *Kidney Int* 2011; 79: 1331–1340
2. Kidney Disease: Improving Global Outcomes CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int Suppl* 2013; 3: 1–150
3. Weldring T, Smith SM. Patient-reported outcomes (PROs) and patient-reported outcome measures (PROMs). *Health Serv Insights* 2013; 6: 61–68
4. Abdel-Kader K, Unruh ML, Weisbord SD. Symptom burden, depression, and quality of life in chronic and end-stage kidney disease. *Clin J Am Soc Nephrol* 2009; 4: 1057–1064
5. Finkelstein FO, Wuerth D, Finkelstein SH. Health related quality of life and the CKD patient: challenges for the nephrology community. *Kidney Int* 2009; 76: 946–952
6. Thong MS, Kaptein AA, Benyamini Y *et al.* Association between a self-rated health question and mortality in young and old dialysis patients: a cohort study. *Am J Kidney Dis* 2008; 52: 111–117
7. Grincenkov FR, Fernandes N, Pereira Bdos S *et al.* Impact of baseline health-related quality of life scores on survival of incident patients on peritoneal dialysis: a cohort study. *Nephron* 2015; 129: 97–103
8. Aiyegbusi OL, Kyte D, Cockwell P *et al.* Patient and clinician perspectives on electronic patient-reported outcome measures in the management of advanced CKD: a qualitative study. *Am J Kidney Dis* 2019; 74: 167–178
9. Feldman HI, Appel LJ, Chertow GM *et al.* The Chronic Renal Insufficiency Cohort (CRIC) Study: design and methods. *J Am Soc Nephrol* 2003; 14(7 Suppl 2): S148–S153

10. Levey AS, Stevens LA, Schmid CH *et al.*A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009; 150: 604–612
11. Hays RD, Kallich JD, Mapes DL *et al.* Development of the Kidney Disease Quality of Life (KDQOL) Instrument. *Qual Life Res* 1994; 3: 329–338
12. Ho KK, Anderson KM, Kannel WB *et al.* Survival after the onset of congestive heart failure in Framingham Heart Study subjects. *Circulation* 1993; 88: 107–115
13. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999; 94: 496–509
14. Nagin DS, Jones BL, Passos VL *et al.* Group-based multi-trajectory modeling. *Stat Methods Med Res* 2018; 27: 2015–2023
15. Grove BE, Schougaard LM, Hjollund NH *et al.* Self-rated health, quality of life and appetite as predictors of initiation of dialysis and mortality in patients with chronic kidney disease stages 4–5: a prospective cohort study. *BMC Res Notes* 2018; 11: 371
16. Ducharlet K, Sundararajan V, Philip J *et al.* Patient-reported outcome measures and their utility in the management of patients with advanced chronic kidney disease. *Nephrology (Carlton)* 2019; 24: 814–818
17. Abdel-Kader K, Myaskovsky L, Karpov I *et al.* Individual quality of life in chronic kidney disease: influence of age and dialysis modality. *Clin J Am Soc Nephrol* 2009; 4: 711–718
18. Ware JE, Richardson MM, Meyer KB *et al.* Improving CKD-specific patient-reported measures of health-related quality of life. *J Am Soc Nephrol* 2019; 30: 664–677
19. de Goeij MCM, Ocak G, Rotmans JI *et al.* Course of symptoms and health-related quality of life during specialized pre-dialysis care. *PLoS One* 2014; 9: e93069
20. Meuleman Y, Chilcot J, Dekker FW *et al.* Health-related quality of life trajectories during predialysis care and associated illness perceptions. *Health Psychol* 2017; 36: 1083–1091
21. Mujais SK, Story K, Brouillette J *et al.* Health-related quality of life in CKD patients: correlates and evolution over time. *Clin J Am Soc Nephrol* 2009; 4: 1293–1301
22. Revicki DA, Brown RE, Feeny DH *et al.* Health-related quality of life associated with recombinant human erythropoietin therapy for predialysis chronic renal disease patients. *Am J Kidney Dis* 1995; 25: 548–554
23. Gorodetskaya I, Zenios S, McCulloch CE *et al.* Health-related quality of life and estimates of utility in chronic kidney disease. *Kidney Int* 2005; 68: 2801–2808
24. Da Silva-Gane M, Wellsted D, Greenshields H *et al.* Quality of life and survival in patients with advanced kidney failure managed conservatively or by dialysis. *Clin J Am Soc Nephrol* 2012; 7: 2002–2009
25. Eckardt KU, Bansal N, Coresh J *et al.* Improving the prognosis of patients with severely decreased glomerular filtration rate (CKD G4+): conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int* 2018; 93: 1281–1292
26. Arnett DK, Blumenthal RS, Albert MA *et al.* ACC/AHA guideline on the primary prevention of cardiovascular disease. *Circulation* 2019; 140: e596–e646
27. Perkovic V, Jardine MJ, Neal B *et al.* Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med* 2019; 380: 2295–2306.
28. Agodoa LY, Appel L, Bakris GL *et al.* Effect of ramipril vs amlodipine on renal outcomes in hypertensive nephrosclerosis: a randomized controlled trial. *JAMA* 2001; 285: 2719–2728
29. Tuttle KR, Lakshmanan MC, Rayner B *et al.* Dulaglutide versus insulin glargine in patients with type 2 diabetes and moderate-to-severe chronic kidney disease (AWARD-7): a multicentre, open-label, randomised trial. *Lancet Diab Endocrinol* 2018; 6: 605–617
30. Gerstein HC, Colhoun HM, Dagenais GR *et al.* Dulaglutide and renal outcomes in type 2 diabetes: an exploratory analysis of the REWIND randomised, placebo-controlled trial. *Lancet* 2019; 394: 131–138
31. Painter P, Marcus RL. Assessing physical function and physical activity in patients with CKD. *Clin J Am Soc Nephrol* 2013; 8: 861–872
32. O'Hare AM, Tawney K, Bacchetti P *et al.* Decreased survival among sedentary patients undergoing dialysis: results from the dialysis morbidity and mortality study wave 2. *Am J Kidney Dis* 2003; 41: 447–454
33. Sietsema KE, Amato A, Adler SG *et al.* Exercise capacity as a predictor of survival among ambulatory patients with end-stage renal disease. *Kidney Int* 2004; 65: 719–724
34. Mapes DL, Lopes AA, Satayathum S *et al.* Health-related quality of life as a predictor of mortality and hospitalization: the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Kidney Int* 2003; 64: 339–349
35. Stack AG, Molony DA, Rives T *et al.* Association of physical activity with mortality in the US dialysis population. *Am J Kidney Dis* 2005; 45: 690–701
36. Delgado C, Johansen KL. Deficient counseling on physical activity among nephrologists. *Nephron Clin Pract* 2010; 116: c330–c336
37. Koufaki P, Mercer T. Assessment and monitoring of physical function for people with CKD. *Adv Chronic Kidney Dis* 2009; 16: 410–419
38. Burckhardt P, Nagin DS, Padman R. Multi-trajectory models of chronic kidney disease progression. *AMIA Annu Symp Proc* 2016; 2016: 1737–1746
39. Grams ME, Sang Y, Ballew SH *et al.* Predicting timing of clinical outcomes in patients with chronic kidney disease and severely decreased glomerular filtration rate. *Kidney Int* 2018; 93: 1442–1451

Received: 6.1.2020; Editorial decision: 2.10.2020