ndt
Nephrology Dialysis Transplantation

Chronic kidney disease progression and mortality risk profiles in Germany: results from the Chronic Kidney Disease Outcomes and Practice Patterns Study

Helmut Reichel[1], Jarcy Zee[2], Charlotte Tu[2], Eric Young[2], Ronald L. Pisoni[2], Bénédicte Stengel[3], Johannes Duttlinger[4], Gerhard Lonnemann[5], Bruce M. Robinson[2], Roberto Pecoits-Filho[2] and Danilo Fliser[6]

[1]Nephrological Center, Villingen-Schwenningen, Germany, [2]Arbor Research Collaborative for Health, Ann Arbor, MI, USA, [3]French National Institute of Health and Medical Research, Villejuif, France, [4]Deutsche Nierenzentren e.V., WiNe Institute, Düsseldorf, Germany, [5]Innere Medizin/Nephrologie, Eickenhof Dialyse, Langenhagen, Germany and [6]Internal Medicine - Nephrology and Hypertension, University Hospital of the Saarland, Homburg, Germany

Correspondence to: Helmut Reichel; E-mail: reichel@nephrologie-vs.de; Twitter handle: @pecoitsfilho

ABSTRACT

Background. Chronic kidney disease (CKD) progression among German patients in a representative setting has not been described previously. The Verband Deutsche Nierenzentren and Chronic Kidney Disease Outcomes and Practice Patterns Study established a longitudinal observational cohort among German CKD patients to research variations in patient care and outcomes in real-world nephrology practices.

Methods. A cohort of CKD Stages 3 (25%) and 4 (75%) patients was established from German nephrologist-run CKD clinics in 2013–16. Linear models were used to determine the estimated glomerular filtration rate (eGFR) slope during follow-up and Cox models were used to assess outcomes of end-stage kidney disease (ESKD) and death.

Results. A total of 1834 patients (median age 75 years, 58% male, 42% diabetics, median baseline eGFR 25 mL/min/1.73 m^2) were followed for a median of 29 months. More than 50% had slow or no decline and 17% declined $\geq$5 mL/min/1.73 m^2/year. After 4.5 years, the incidence of ESKD was 8% and of deaths without ESKD 16% among patients with eGFR $\geq$30 mL/min/1.73 m^2 and 37% and 19% for eGFR <30 mL/min/1.73 m^2. Adjusted models showed higher risks of ESKD or death for patients with worse kidney function at baseline, male sex, diabetes and higher blood pressure; a higher risk of ESKD with higher albuminuria; and a higher risk of death with older age or cardiovascular comorbidity.

Conclusions. Routine nephrology care of patients in Germany comprises mostly elderly patients, many with slow CKD progression. Identification of risk factors for CKD progression

and mortality may help guide resources by closer follow-up of high-risk patients.

Keywords: chronic kidney disease, CKD progression, mortality

INTRODUCTION

The worldwide disease and socio-economic burdens of chronic kidney disease (CKD) are very high. In recent years the importance of medical implications and socio-economic consequences related to the treatment of CKD patient groups has been increasingly recognized [1–3]. In Germany, the prevalence of end-stage kidney disease (ESKD) is ~950 patients per million population, and a survey-based study reported that 2.3% of the German population 18–79 years of age have an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 [4]; however, a higher prevalence in Germany was described in the European CKD Burden Consortium [5]. Such estimates have also been made for other countries and areas showing different prevalences of CKD [5, 6].

In addition to its socio-economic impact, CKD has been associated with unfavourable clinical outcomes. In addition to the high risk of progressing to ESKD, CKD is recognized as a major cardiovascular risk factor [7–9] and patients with impaired kidney function exhibit, depending on CKD stage, several-fold increased mortality risks [10]. Interestingly, a previous report based on the analysis of CKD patients identified from a large managed care organization in the USA found that the probability of death in patients from different CKD stages was >2-fold

higher compared with the probability of reaching ESKD, regardless of CKD stage [11]. Similar findings were reported in a cohort of patients from the international Chronic Kidney Disease Prognosis Consortium having eGFRs <30 mL/min/1.73 m^2 [12]. A similar analysis performed in specialized CKD care clinics in the real-world setting is lacking.

Relatively little is known about patients with CKD who do not advance to ESKD due to low progression rates or due to a fatal event before reaching ESKD. The objectives of this work were to study the natural history of CKD in a population followed in nephrology clinics in Germany, to examine the prevalence of variables associated with CKD progression and to describe clinical outcomes (death and ESKD) over a 4.5-year observation period [13].

MATERIALS AND METHODS

Study design and data collection

The Chronic Kidney Disease Outcomes and Practice Patterns Study (CKDopps) is an ongoing prospective cohort study of non-dialysis, advanced CKD patients in national samples of nephrology clinics in Brazil, France, Germany, Japan and the USA [13]. In Germany, data are collected by the Forschungsnetzwerk Deutsche Nierenzentren (FNDN Scientific Network of Germany Kidney Centers) Registry, a network designed to develop an evidence base and inform patients, doctors and policymakers about disease course and practice variation among advanced CKD patients under nephrology care [14]. Nephrology practices from the Verband Deutsche Nierenzentren (DN, Network of Germany Kidney Centers) were included in the study as a representative national sample of practices, guaranteed by stratification by geographic location and centre size. Consecutive individual patients treated in these clinics, with eGFR between 15 and 60 mL/min/1.73 m^2 at screening and who provided written consent, were enrolled in the study. The eGFR was calculated using the Modification of Diet in Renal Disease study equation, assuming serum creatinine measurements had not been calibrated to isotope dilution mass spectrometry. The frequency of visits to the clinic was defined according to the patients' characteristics, CKD stage and risk of progression. Patient follow-up continued after the onset of dialysis and until death or departure from nephrology care.

An electronic data collection system, Qualitätssicherung Nephrologie und Transplantation (QuaNT), was used to collect patient-level information. Data included demographic characteristics, comorbid conditions, medications, hospitalizations and laboratory values measured during routine clinical care. Data are assessed for data quality by study coordinators and transmitted quarterly from the DN to the CKDopps data coordinating centre in Ann Arbor, MI, USA, for inclusion in CKDopps. This study includes German patients enrolled from 2013 Quarter 1 through 2016 Quarter 2, with longitudinal data through 2018 Quarter 2. The study was conducted with adherence to the Declaration of Helsinki and received research ethics board approval from Ethical and Independent Review Services (study number 14004-05). Patient consent was obtained from study participants.

Independent variables

The primary cause of CKD was determined by the patient's attending physician and categorized using International Classification of Diseases, Tenth Revision (ICD-10) codes. Unspecified illness, unspecified immune disorder and unspecified kidney disorder were further grouped into an 'other' category for descriptive analyses. Comorbidities, including hypertension, diabetes and other cardiovascular conditions, were determined based on reported ICD-10 codes. For models assessing factors associated with outcomes (i) diabetes was treated as a three-category variable: diabetes as primary cause of CKD, diabetes as a comorbidity only, or neither (patients with other causes of CKD and without diabetes comorbidity) and (ii) heart failure, coronary artery disease, cerebrovascular disease and peripheral vascular disease were combined into a composite cardiovascular comorbidity indicator based on whether any of the individual comorbidities were present. Albuminuria, haemoglobin, parathyroid hormone, phosphate, calcium, blood pressure and body mass index were taken from the closest measurement to study entry ('baseline') within 1 year prior to the enrolment quarter. Albuminuria was categorized based on Kidney Disease Improving Global Outcomes (KDIGO) 2012 guidelines [15] using, in descending order of priority, spot urine albumin:creatinine ratio, spot urine protein:creatinine ratio, 24-h timed urine albumin, 24-h timed urine protein, or protein reagent strips. The 'severely increased' albuminuria category was also split into 'very high' and 'nephrotic range' (Table 1). Renin–angiotensin–aldosterone system inhibitor (RAASi) and statin prescriptions were recorded during the enrolment quarter.

Statistical analysis

Descriptive statistics were used to summarize demographic and clinical characteristics of patients at baseline, overall, and by eGFR at baseline. Individual patient-level linear models were used to estimate changes in eGFR over each patient's follow-up time. This analysis was restricted to 1571 patients with at least 6 months of eGFR data, which excluded 65 who reached ESKD before 6 months, 35 who died before 6 months and 163 lost to follow-up. Linearity of eGFR trajectories was assessed by calculating root mean squared error (RMSE) from each linear model. Cumulative incidences of ESKD, defined by dialysis or transplant, and death before ESKD were estimated separately by (i) eGFR at baseline ($\geq$30 versus <30 mL/min/1.73 m^2), (ii) eGFR at baseline and albuminuria category among patients with albuminuria data at baseline, (iii) eGFR at baseline and sex and (iv) eGFR at baseline and age tertiles (18–70, 71–78, 79–96 years). Cause-specific Cox models were used to assess associations between baseline patient characteristics and ESKD taking into account competing death events, while standard Cox models were used to assess associations between baseline patient characteristics and death, whether before or after ESKD. All models accounted for facility clustering with sandwich-type standard error estimates [16], were stratified by eGFR $\geq$30 versus <30 mL/min/1.73 m^2 at baseline, and further adjusted for baseline eGFR as a continuous variable. Effect modification between diabetes and albuminuria was assessed using a Wald test of the interaction term. The functional form for effects of continuous

H. Reichel et al.

Table 1. Baseline demographic and clinical characteristics

Characteristics	Overall	Baseline eGFR ≥30 mL/min/1.73 m²	Baseline eGFR <30 mL/min/1.73 m²
Patients, *n*	1834	486	1348
Age (years), median (IQR)	75 (67–80)	73 (64–78)	75 (68–81)
Male (%)	58	64	55
Body mass index[a] (kg/m²), mean (SD)	29 (6)	29 (5)	29 (6)
Primary cause of CKD[a,b] (%)			
Diabetes	30	25	32
Hypertensive renal disease	33	35	33
Glomerulonephritis	9	10	9
Hereditary disease	4	3	4
Tubulointerstitial disease	6	8	6
Other	17	20	16
Comorbidities (%)			
Diabetes[a]	42	39	42
Hypertension[a]	85	86	85
Heart failure[a]	13	9	14
Coronary artery disease[a]	28	29	28
Cerebrovascular disease[a]	11	12	11
Peripheral vascular disease[a]	20	16	21
eGFR (mL/min/1.73 m²), median (IQR)	25 (21–31)	40 (35–48)	23 (19–26)
Albuminuria[c] (%)			
Normal to mildly increased	19	27	16
Moderately increased	17	17	17
Very high	13	12	13
Nephrotic range	6	3	7
Missing	45	41	47
Haemoglobin[a] (g/dL), mean (SD)	12 (2)	13 (2)	12 (2)
Parathyroid hormone[d] (pg/mL), median (IQR)	103 (66–170)	70 (49–100)	118 (78–199)
Phosphate[e] (mg/dl), mean (SD)	3.69 (0.76)	3.30 (0.66)	3.83 (0.75)
Calcium[f] (mg/dl), mean (SD)	9.27 (0.63)	9.39 (0.53)	9.22 (0.65)
SBP[g] (mmHg), mean (SD)	139 (19)	136 (18)	139 (20)
DBP[g] (mmHg), mean (SD)	76 (11)	76 (11)	76 (11)
RAASi prescription[g] (%)	79	80	78
Statin prescription[g] (%)	52	56	51

[a]1–10% missing.
[b]According to attending physician.
[c]Albuminuria categories from KDIGO 2012 guidelines [15], where moderately increased is albumin 30–300 mg/day, albumin:creatinine ratio 30–300 mg/g, protein 150–500 mg/day, protein:creatinine ratio 150–500 mg/g or trace to 1+ protein reagent strip and severely increased is split into very high (albumin 300–2000 mg/day, albumin:creatinine ratio 300–2000 mg/g, protein 500–3000 mg/day, protein:creatinine ratio 500–3000 mg/g or 2+ protein reagent strip) and nephrotic range (higher than very high ranges).
[d]49% missing.
[e]Phosphate: mg/dL × 0.3229 = mmol/l.
[f]Calcium: mg/dL × 0.2495 = mmol/l.
[g]11–20% missing.

variables was checked by assessing effect estimates in centiles. Missing data for all independent variables in Cox models were multiply imputed by chained equations [17] and results from 20 imputed datasets were combined for the final analysis using Rubin's formula [18]. All statistical analyses were conducted using R software, version 3.4.0 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Of 1834 advanced CKD patients in the analysis, 486 had eGFR ≥30 mL/min/1.73 m² at study entry and 1348 had eGFR <30 mL/min/1.73 m². Over a median follow-up time of 29 [interquartile range (IQR) 13–51] months, 456 progressed to ESKD and 448 died, with 277 deaths prior to ESKD and 171 deaths after ESKD. The median age was 75 (IQR 67–80) years and the majority of patients were male (58%). The predominant primary cause of CKD according to attending physicians was hypertensive kidney disease (33%) followed by diabetes (30%) (Table 1). The proportion of patients with hypertensive kidney disease as the primary cause of CKD increased with increasing age, while the proportion of patients with glomerulonephritis decreased with increasing age (Supplementary data, Figure S1a). Many patients had diabetes (42%), hypertension (85%) and other cardiovascular comorbidities (47% with either heart failure, coronary artery disease, cerebrovascular disease or peripheral vascular disease). A higher proportion of patients who had diabetes (as the primary cause of CKD or as a comorbidity) had cardiovascular comorbidities compared with those without diabetes (Supplementary data, Figure S1 b). Among the patients with albumin measured at baseline [55% (n = 1004)], the majority had normal to mildly increased
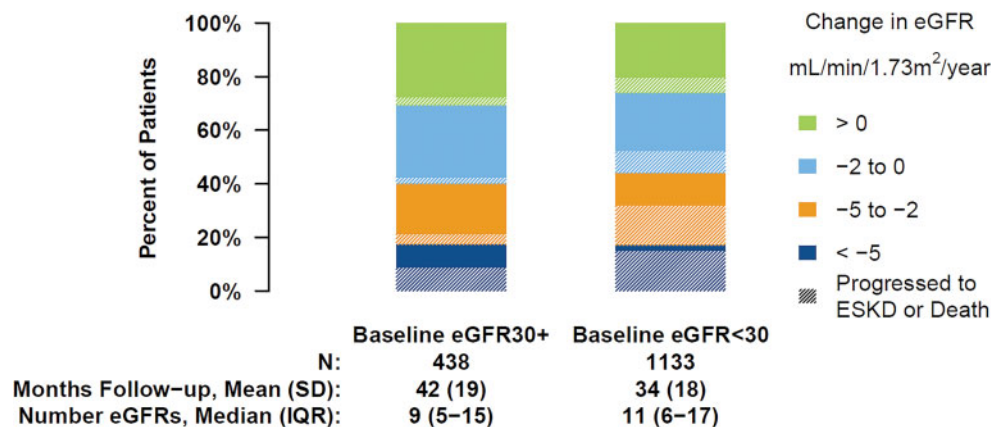
FIGURE 1: Yearly change in eGFR over the follow-up by eGFR at study entry. Analyses are restricted to patients with at least 6 months of eGFR data. Shading denotes the proportion in each category who progressed to ESKD or death during the study follow-up.
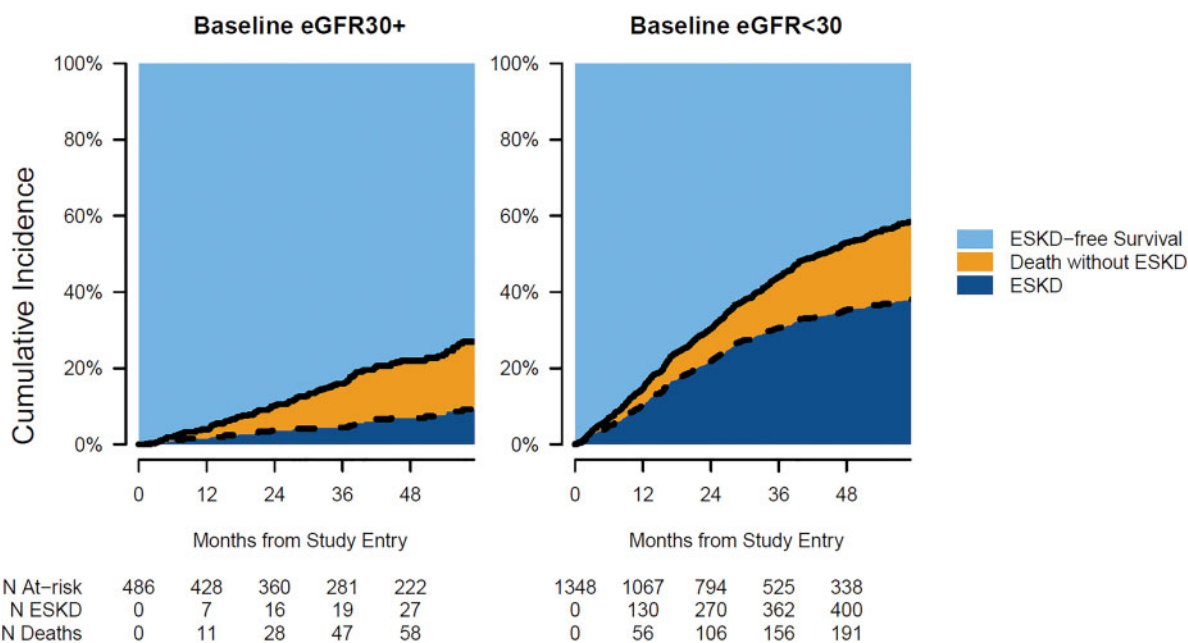

FIGURE 2: Cumulative incidence of ESKD, death without ESKD and ESKD-free survival by eGFR at study entry.

albuminuria, particularly among patients with eGFR $\geq$30 mL/min/1.73 m^2 at baseline. Many patients had a RAASi prescription at baseline (79%) and more than half had a statin prescription (52%).

Among patients with at least 6 months of follow-up, changes in eGFR were estimated over a mean follow-up time of 42 [standard deviation (SD) 19] months after baseline using a median number of eGFR measurements of 9 (IQR 5–15) among patients with eGFR $\geq$30 mL/min/1.73 m^2 at baseline and 34 (SD 18) months and 11 (IQR 6–17) eGFR measurements among patients with eGFR <30 mL/min/1.73 m^2 at baseline. The median time between visits was 3.0 (IQR 1.2–4.6) months among patients with eGFR $\geq$30 mL/min/1.73 m^2 at baseline and 2.3 (IQR 1.2–3.4) months among patients with eGFR <30 mL/min/1.73 m^2 at baseline. The median RMSE across patients was 2.1 (IQR 1.3–3.3) mL/min/1.73 m^2. The mean change in eGFR was −2.1 (SD 5.3) mL/min/1.73 m^2/year for the population as a whole, −2.3 (6.4) among patients with

Table 2. Cumulative incidences (%) of ESKD and death without ESKD by 4.5 years

Factor	ESKD		Death without ESKD	
	eGFR $\geq$30	eGFR <30	eGFR $\geq$30	eGFR <30
Overall	8	37	16	19
Albuminuria				
Normal to mildly increased	5	14	11	26
Moderately increased	3	22	16	21
Severely increased	17	56	13	13
Gender				
Male	12	45	15	18
Female	1	26	17	21
Age (years)				
18–70	8	43	7	9
71–78	10	38	16	17
79–96	5	28	32	32

Note that the cumulative incidence estimates for patients with baseline eGFR $\geq$30 mL/min/1.73 m^2 stratified by albuminuria, gender and age are based on small subsamples.

H. Reichel *et al.*

Table 3. Factors associated with time to ESKD and death

Factor	ESKD (456 events)		Death (448 events)	
	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)
Age (per 5 years)	0.92 (0.89–0.96)	0.96 (0.92–1.00)	1.29 (1.22–1.37)	1.31 (1.23–1.39)
Male	2.30 (1.86–2.83)	1.95 (1.54–2.46)	1.43 (1.17–1.74)	1.48 (1.18–1.86)
Body mass index (per 5 kg/m^2)	0.85 (0.78–0.94)	0.92 (0.83–1.02)	0.88 (0.80–0.98)	0.93 (0.84–1.02)
Diabetes				
As primary cause of CKD	1.72 (1.39–2.14)	1.49 (1.18–1.88)	1.65 (1.33–2.05)	1.58 (1.27–1.96)
As comorbidity only	1.59 (1.17–2.16)	1.57 (1.14–2.15)	1.26 (0.93–1.70)	1.30 (0.96–1.77)
Neither	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Other comorbidities				
Hypertension	0.93 (0.70–1.22)	0.86 (0.64–1.15)	1.01 (0.75–1.37)	1.06 (0.78–1.44)
Composite cardiovascular	1.10 (0.89–1.37)	1.19 (0.95–1.48)	1.58 (1.28–1.94)	1.58 (1.28–1.96)
Baseline eGFR (per mL/min/1.73 m^2)	0.87 (0.85–0.89)	0.90 (0.88–0.92)	0.93 (0.91–0.94)	0.95 (0.93–0.97)
SBP (per 10 mmHg)	1.11 (1.04–1.18)	1.07 (1.00–1.15)	0.97 (0.91–1.04)	0.97 (0.91–1.04)
DBP (per 10 mmHg)	0.96 (0.86–1.08)	0.99 (0.87–1.12)	1.14 (1.01–1.28)	1.19 (1.06–1.34)
Albuminuria				
Normal to mildly increased		1 (ref)		1 (ref)
Moderately increased		1.20 (0.81–1.77)		0.94 (0.68–1.29)
Very high		2.16 (1.50–3.12)		1.06 (0.76–1.47)
Nephrotic range		4.22 (2.70–6.62)		1.05 (0.68–1.63)
Haemoglobin (per g/dL)		0.87 (0.81–0.93)		0.89 (0.83–0.95)
Parathyroid hormone (per 10 pg/mL)		1.01 (1.00–1.02)		1.02 (1.01–1.03)
Phosphate (per mg/dL)[a]		1.10 (0.94–1.30)		1.10 (0.94–1.29)
Calcium (per mg/dL)[b]		0.94 (0.78–1.14)		0.97 (0.81–1.17)

Model 1 includes all demographic and clinical variables listed except for albuminuria and other lab values. Model 2 additionally includes albuminuria and lab values. Results were similar when treatments (RAASi, statins) were included in the models. SBP and DBP were only moderately correlated (P = 0.506). All models were stratified by eGFR ≥30 versus eGFR <30 ml/min/1.73 m^2 at study entry.
[a]Phosphate: mg/dL × 0.3229 = mmol/l.
[b]Calcium: mg/dL × 0.2495 = mmol/l.

eGFR ≥30 at baseline and −2.0 (4.8) among patients with eGFR <30. More than half had slow or no decline (>−2 mL/min/1.73 m^2/year) in eGFR. The prevalence of slow or no decline was 60% among patients with eGFR ≥30 mL/min/1.73 m^2 at baseline and 56% among patients with eGFR <30 mL/min/1.73 m^2 at baseline (Figure 1). About 25% of patients displayed a moderate eGFR decline (eGFR slope between −5 to −2 mL/min/1.73 m^2/year) and 17% had a steep decline (eGFR slope <−5 mL/min/1.73 m^2/year) during the study follow-up. Patients who were fast progressors (i.e. eGFR slope ≤−2 mL/min/1.73 m^2/year) were younger and a greater proportion were male compared with patients who were slow progressors or had no decline (eGFR slope >2 mL/min/1.73 m^2/year) (Supplementary data, Table S1). A greater proportion of fast progressors than slow/non-progressors had glomerulonephritis (14% versus 7%) and more severe albuminuria, while a smaller proportion had hypertension (25% versus 40%) as the primary cause of CKD. Fast progressors also had slightly higher mean systolic blood pressure (SBP) than slow/non-progressors (140 versus 137 mmHg).

After 4.5 years of follow-up, the cumulative incidence of ESKD was 8% among patients with a baseline eGFR ≥30 mL/min/1.73 m^2 and 37% among patients starting the study with eGFR <30 mL/min/1.73 m^2. The cumulative incidence of death reached 16 and 19% for patients with eGFR ≥30 and <30 mL/min/1.73 m^2, respectively (Figure 2). The cumulative incidence of ESKD differed substantially by albuminuria at baseline (Supplementary data, Figure S2), sex (Supplementary data,

Figure S3) and age (Supplementary data, Figure S4). Among patients with normal to mildly increased albuminuria or moderately increased albuminuria and a baseline eGFR <30 mL/min/1.73 m^2, the cumulative incidence of ESKD after 4.5 years of follow-up was <22% (Table 2). However, at the same baseline eGFR level, patients with severely increased albuminuria (very high and nephrotic range) presented a cumulative 56% incidence of ESKD. Male and female patients with baseline eGFR <30 mL/min/1.73 m^2 had a 45 and 26% incidence of ESKD, respectively. Patients up to age 70, between 70 and 78 and >78 years with baseline eGFR <30 mL/min/1.73 m^2 had cumulative incidences of ESKD of 43, 38 and 28%, respectively. While patients with baseline eGFR <30 mL/min/1.73 m^2 up to age 78 years had higher cumulative incidences of ESKD compared with mortality, patients with baseline eGFR ≥30 mL/min/1.73 m^2 and patients >78 years old had higher cumulative incidences of death compared with ESKD.

Adjusted for all demographic and clinical variables, males had estimated hazards of ESKD that were 95% higher than females {hazard ratio [HR] 1.95 [95% confidence interval (CI) 1.54–2.46]} (Table 3). Compared with patients without diabetes, patients with diabetes as a primary cause of CKD had 1.49 (95% CI 1.18–1.88) times higher hazards of ESKD and patients with diabetes as a comorbidity had 1.57 (95% CI 1.14–2.15) times higher hazards of ESKD. Patients with the composite cardiovascular comorbidity had 1.19 (95% CI 0.95–1.48) times the hazards of ESKD compared with patients without cardiovascular comorbidity, although the 95% CI was wide. For every

10 mmHg higher SBP, hazards of ESKD increased by 7% [HR 1.07 (95% CI 1.00–1.15)]. We note that when SBP was split into categories of <110, 110–140, 140–160 and >160 mmHg, the effect was somewhat linear: HRs for each category with SBP <110 mmHg as the reference group were 1.17, 1.47 and 1.92, respectively. Patients with more albuminuria at baseline had increased hazards of ESKD, with those in the nephrotic range at the highest risk. We did not find evidence of effect modification between diabetes and albuminuria for ESKD (P = 0.997).

Males also had higher hazards of death than females [HR 1.48 (95% CI 1.18–1.86) in the fully adjusted model]. Patients with diabetes as the primary cause of CKD had the highest hazards of death, followed closely by those with diabetes as a comorbidity compared with patients without diabetes. Patients with a cardiovascular comorbidity had higher hazards of death than those without any cardiovascular comorbidities. For every 10 mmHg higher diastolic blood pressure (DBP), the hazard of death increased by nearly 20% [HR 1.19 (95% CI 1.06–1.34)]. We note that when DBP was split into categories of <60, 60–75, 74–90 and >90 mmHg, the effect was somewhat linear: HRs for each category with DBP <60 mmHg as the reference group were 1.06, 1.28 and 1.93, respectively. We did not find evidence of effect modification between diabetes and albuminuria for death (P = 0.990).

DISCUSSION

In this study we describe the clinical and demographic characteristics of a representative German cohort of patients with advanced kidney disease under nephrology care and report risk factors and the incidence of kidney disease progression and mortality in this country. Interestingly, despite the high comorbid profile of the population of this cohort, we observed that a high proportion of patients did not reach ESKD and mortality endpoints, which is somewhat different from previous findings in different cohorts [19].

The CKD patient cohort described in this article is part of the international CKDopps project and was recruited in Germany in nephrology centres of the DN, where more than half of the non-dialysis outpatient CKD population is treated and followed. We sought to establish a representative real-world cohort of nephrology-referred CKD patients by randomly selecting the participating centres, stratified by centre size and geographic location, and by including consecutive consenting patients into the registry until the recruiting goal of a centre was achieved. This procedure resulted in a fairly representative selection of CKD patients with advanced kidney disease. Preliminary descriptive data of a larger, unselected CKD patient group from our database were previously published [14]. The recruiting procedure resulted in a cohort of mostly elderly patients with predominantly hypertensive/vascular and diabetic kidney disease. As expected, primary kidney disease diagnoses differed considerably among age groups, and patients carried a high burden of comorbidities, especially diabetes and cardiovascular diseases.

The population included in this study differs in some aspects from the German Chronic Kidney Disease (GCKD) cohort [20]. Patients in the GCKD cohort were younger, with a mean age at baseline of 60 (SD 12) years; however, a similar patient population was described in the German Care for Home cohort. Also, mean eGFR at baseline was 47 mL/min/1.73 m^2 in the GCKD cohort, as compared with a median eGFR of 25 mL/min/1.73 m^2 in this study. It is likely that these differences result from different selection criteria, and the combination of the two studies may yield complementing information to describe the patient population and treatment of CKD patients followed in nephrology clinics in Germany.

One of the main goals of this study was to analyse risk factors for CKD progression. Aligned with previous reports in different cohorts, we observed that factors independently associated with faster progression in our cohort were worse kidney function at baseline, male sex, diabetes mellitus both as a renal diagnosis and as a comorbidity, higher SBP and higher albuminuria. These findings are consistent with previously published reports [7, 21–29]. In addition, we aimed to identify rates and risk factors for mortality in the same population, which were male sex, diabetes mellitus both as a renal diagnosis and comorbidity, lower baseline eGFR, composite cardiovascular comorbidity and higher DBP. These risk factors are in line with previously published reports [30–32].

The overall mean annual eGFR decline was in general relatively low (−2.1 mL/min/1.73 m^2/year). More than half of patients with longer follow-up had slow or no decline in eGFR. In addition, only 17% had a steep decline during the study follow-up. Patients with a moderate or steep decline in eGFR were younger and a greater proportion were male compared with patients with slow or no decline—the latter having a lower proportion of diabetes and hypertension as a cause of CKD. Potential reasons for the lower rates of CKD progression to ESKD observed in the present cohort include the fact that all patients were followed by nephrologists in specialized CKD clinics, and therefore the treatment rates (including the high prevalence of prescription of RAASis and other renoprotective strategies) could differ from those observed in more general care clinics. Also, the targets for the management of CKD-specific risk factors are potentially more stringent in nephrology care compared with general practices.

Another important and novel finding of this study relates to the risk of ESKD in competition with the mortality risk. ESKD risk was considerably higher than mortality risk before reaching ESKD (37% versus 19%) only in the subgroup of patients starting follow-up at eGFR <30 mL/min/1.73 m^2. On the other hand, mortality risk exceeded the incidence of ESKD (32% versus 28%) in the subgroup of patients between 79 and 96 years of age. These findings contrast with the proportionally higher mortality rates (compared with ESKD) among advanced CKD patients reported in other studies [10, 11, 21, 26, 33]. The reasons for this discrepancy remain speculative, but this is observed in general population cohorts where low GFR may not always reflect true CKD. Possibly, different practice patterns, different patient characteristics, different underlying population mortality and different socio-economic conditions with respect

H. Reichel *et al.*

to access to medical treatment of patients account for these differences.

This study has the following weaknesses: (i) the smoking status of patients is not known; (ii) quantitation of proteinuria could only be done categorically for many patients and was missing in 45% of patients; (iii) availability of blood pressure data was limited and (iv) while most clinic visits were likely scheduled during a previous visit with frequency of visits defined based on comorbidities, CKD stage and risk of progression, specific reasons for variable frequency of eGFR measurements are unknown. However, there are many strengths, including the patient selection process, which resulted in a representative CKD patient cohort and the relatively long observation time with a high number of follow-up visits, allowing the identification of risk factors for kidney and mortality outcomes.

In summary, routine care of nephrology-referred patients in Germany comprises mostly elderly patients and patients with hypertensive/diabetic kidney disease. While mortality risk was significantly higher than ESKD risk only in elderly patients, the risk of ESKD was significantly higher than mortality in the group of patients with eGFR <30 mL/min/1.73 m^2. The identification of local risk factors for CKD progression may help to guide nephrological resources by closer follow-up of patients with higher risk. CKD progression varied largely among the patient population, and a large proportion of patients displayed low CKD progression rates.

SUPPLEMENTARY DATA

Supplementary data are available at ndt online.

AUTHORS' CONTRIBUTIONS

J.Z., G.L., D.F., H.R., J.D., C.T., B.R., E.Y., R.P. and R.P.F were responsible for conception or design, analysis and interpretation of data or both. J.Z., G.L., D.F., H.R., J.D., B.R., E.Y., R.P. and R.P.F. were responsible for drafting the article or revising it. J.Z., H.R., B.R., E.Y., R.P. and R.P.F. provided intellectual content of critical importance to the work described. J.Z., D.F., H.R., J.D., B.S., E.Y., R.P. and B.R. were responsible for final approval of the version to be published.

CONFLICT OF INTEREST STATEMENT

J.D., D.F., B.S. and G. L have no conflicts of interest to declare. J.Z., R.L.P., B.M.R. and C.T. are employees of Arbor Research Collaborative for Health, which administers the Dialysis Outcomes and Practice Patterns Study (DOPPS). R.P.-F. reports personal fees from AstraZeneca, Akebia and Novo Nordisk outside the submitted work. E.Y. reports partial support from the Center for Medicare and Medicaid Services and the DOPPS. H.R. reports personal fees from Hexal, Vifor, Amgen and Otsuka outside the submitted work. The results presented in this article have not been published previously in whole or part, except in abstract format.

REFERENCES

1. Hsu CY, Iribarren C, McCulloch CE et al. Risk factors for end-stage renal disease: 25-year follow-up. Arch Intern Med 2009; 169: 342–350
2. Eckardt KU, Coresh J, Devuyst O et al. Evolving importance of kidney disease: from subspecialty to global health burden. Lancet 2013; 382: 158–169
3. Xie Y, Bowe B, Mokdad AH et al. Analysis of the global burden of disease study highlights the global, regional and national trends of chronic kidney disease from 1990–2016. Kidney Int 2018; 94: 567–581
4. Girndt M, Trocchi P, Scheidt-Nave C et al. The prevalence of renal failure. Results from the German Health Interview and Examination Survey for Adults, 2008–2011 (DEGS1). Dtsch Arztebl Int 2016; 113: 85–91
5. Brück K, Stel VS, Gambaro G et al. CKD prevalence varies across the European general population. J Am Soc Nephrol 2016; 27: 2135–2147
6. McCullough K, Sharma P, Ali T et al. Measuring the population burden of chronic kidney disease: a systematic literature review of the estimated prevalence of impaired kidney function. Nephrol Dial Transplant 2012; 27: 1812–1821
7. Levey AS, De Jong PE, Coresh J et al. The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. Kidney Int 2011; 80: 17–28
8. Gansevoort RT, Correa-Rotter R, Hemmelgarn BR et al. Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention. Lancet 2013; 382: 339–352
9. Thomas B, Matsushita K, Abate KH et al. Global cardiovascular and renal outcomes of reduced GFR. J Am Soc Nephrol 2017; 28: 2167–2179
10. Go AS, Chertow GM, Fan D et al. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 2004; 351: 1296–1305
11. Keith DS, Nichols GA, Gullion CM et al. Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. Arch Intern Med 2004; 164: 659–663
12. 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
13. Mariani L, Stengel B, Combe C et al. The CKD Outcomes and Practice Patterns Study (CKDopps): rationale and methods. Am J Kidney Dis 2016; 68: 402–413
14. Kleophas W, Bieber B, Robinson BM et al. Implementation and first results of a German chronic kidney disease registry. Clin Nephrol 2013; 79: 184–191
15. 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
16. Lin DY, Wei LJ. The robust inference for the Cox proportional hazards model. J Am Stat Assoc 1989; 84: 1074–1078
17. van Buuren S, Groothuis-Oudshoorn K. Mice: multivariate imputation by chained equations in R. J Stat Softw 2011; 45: 1–67
18. Little RJA, Rubin DB. Statistical Analysis with Missing Data. New York: Wiley, 1987.
19. 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
20. Titze S, Schmid M, Köttgen A et al. Disease burden and risk profile in referred patients with moderate chronic kidney disease: composition of the German Chronic Kidney Disease (GCKD) cohort. Nephrol Dial Transplant 2015; 30: 441–451

21. O'Hare AM, Choi AL, Bertental B *et al.* Age affects outcome in chronic kidney disease. *J Am Soc Nephrol* 2007; 18: 2758–2765

22. Levin A, Djurdjev O, Beaulieu M, Er L. Variability and risk factors for kidney disease progression and death following attainment of stage 4 CKD in a referred cohort. *Am J Kidney Dis* 2008; 52: 661–671

23. Eriksen BO, Tomtum J, Ingebretsen OC. Predictors of declining glomerular filtration rate in a population-based chronic kidney disease cohort. *Nephron Clin Pract* 2010; 115: c41–c50

24. Borrelli S, Leonardis D, Minutolo R *et al.* Epidemiology of CKD regression in patients under nephrology care. *PLoS One* 2015; 10: e0140138

25. Denker M, Boyle S, Anderson AH *et al.* Chronic Renal Insufficiency Cohort Study (CRIC): overview and summary of selected findings. *Clin J Am Soc Nephrol* 2015; 10: 2073–2083

26. Lundström UH, Gasparini A, Bellocco R *et al.* Low renal replacement therapy incidence among slowly progressing elderly chronic kidney disease patients referred to nephrology care: an observational study. *BMC Nephrol* 2017; 18: 59–68

27. Tsai CW, Ting IW, Yeh HC *et al.* Longitudinal change in estimated eGFR among CKD patients: a 10 year follow-up study of an integrated kidney disease program in Taiwan. *PLoS One* 2017; 12: e0173843

28. Inaguma D, Imai E, Takeuchi A *et al.* Risk factors for CKD progression in Japanese patients: findings from the Chronic Kidney Disease Japan Cohort (CKD-JAC) study. *Clin Exp Nephrol* 2017; 21: 446–456

29. Tanaka K, Watanabe T, Takeuchi A *et al.* Cardiovascular events and death in Japanese patients with chronic kidney disease. *Kidney Int* 2017; 91: 227–234

30. Shlipak MG, Katz R, Kestenbaum B *et al.* Clinical and subclinical cardiovascular disease and kidney function decline in the elderly. *Atherosclerosis* 2009; 204: 298–303

31. Nitsch D, Grams M, Sang Y *et al.* Associations of estimated glomerular filtration rate and albuminuria with mortality and renal failure by sex. A meta analysis. *BMJ* 2013; 346: f324

32. Coresh J, Turin TC, Matsushita K *et al.* Decline in estimated glomerular filtration rate and subsequent risk of end-stage renal disease and mortality. *JAMA* 2014; 311: 2518–2531

33. Conway B, Webster A, Ramsay G *et al.* Predicting mortality and uptake of renal replacement therapy in in patients with stage 4 chronic kidney disease. *Nephrol Dial Transplant* 2009; 24: 1930–1937

H. Reichel *et al.*