Different rates of progression and mortality in patients with chronic kidney disease at outpatient nephrology clinics across Europe

Katharina Brück[1], Kitty J. Jager[1], Carmine Zoccali[2], Aminu K. Bello[3], Roberto Minutolo[4], Kyriakos Ioannou[5], Francis Verbeke[6], Henry Völzke[7], Johan Arnlöv[8], Daniela Leonardis[9], Pietro Manuel Ferraro[10], Hermann Brenner[11], Ben Caplin[12], Philip A. Kalra[13], Christoph Wanner[14], Alberto Martinez Castelao[15], Jose Luis Gorriz[16], Stein Hallan[17], Dietrich Rothenbacher[18], Dino Gibertoni[19], Luca De Nicola[4], Georg Heinze[20], Wim Van Biesen[6] and Vianda S. Stel[1]; on behalf of the European CKD Burden Consortium

[1]*ERA-EDTA Registry, Department of Medical Informatics, Academic Medical Center, Amsterdam Public Health Research Institute, Amsterdam, The Netherlands;* [2]*CNR-IFC, Clinical Epidemiology and Pathophysiology of Renal Diseases and Hypertension, Reggio Calabria, Italy;* [3]*Division of Nephrology and Immunology, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Canada;* [4]*Department of Nephrology, University of Campania "L. Vanvitelli", Naples, Italy;* [5]*Department of Nephrology, Nicosia General Hospital, Nicosia, Cyprus;* [6]*Renal Division, University Hospital Ghent, Ghent, Belgium;* [7]*Department of Clinical Epidemiology Research, University Medicine Greifswald, Greifswald, Germany;* [8]*Division of Family Medicine and Primary Care, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Huddinge, Sweden;* [9]*CNR-Institute of Clinical Physiology, Reggio Calabria, Italy;* [10]*Division of Nephrology, Fondazione Policlinico Universitario A. Gemelli, Università Cattolica del Sacro Cuore, Rome, Italy;* [11]*Division of Clinical Epidemiology and Aging Research, German Cancer Research Center/Network Aging Research, University of Heidelberg, Heidelberg, Germany;* [12]*Centre for Nephrology, University College London, London, UK;* [13]*Department of Renal Medicine, Salford Royal National Health Service Foundation Trust, Salford, UK;* [14]*Division of Nephrology, University Hospital Würzburg, Würzburg, Germany;* [15]*Department of Nephrology, Hospital Universitari de Bellvitge, Barcelona, Spain;* [16]*Department of Nephrology, Hospital Clínico Universitario INCLIVA, Departamento de Medicina, Valencia, Spain;* [17]*Department of Nephrology, St Olav Hospital/Faculty of Medicine, Norwegian University of Science and Technology, Norway;* [18]*Institute of Epidemiology and Medical Biometry, Ulm University, Ulm, Germany;* [19]*Department of Biomedical and Neuromotor Sciences, Unit of Hygiene and Biostatistics, University of Bologna, Bologna, Italy; and* [20]*Center for Medical Statistics, Informatics, and Intelligent Systems, Medical University of Vienna, Vienna, Austria*

The incidence of renal replacement therapy varies across countries. However, little is known about the epidemiology of chronic kidney disease (CKD) outcomes. Here we describe progression and mortality risk of patients with CKD but not on renal replacement therapy at outpatient nephrology clinics across Europe using individual data from nine CKD cohorts participating in the European CKD Burden Consortium. A joint model assessed the mean change in estimated glomerular filtration rate (eGFR) and mortality risk simultaneously, thereby accounting for mortality risk when estimating eGFR decline and vice versa, while also correcting for the measurement error in eGFR. Results were adjusted for important risk factors (baseline eGFR, age, sex, albuminuria, primary renal disease, diabetes, hypertension, obesity and smoking) in 27,771 patients from five countries. The adjusted mean annual eGFR decline varied from 0.77 (95% confidence interval 0.45, 1.08) ml/min/1.73m^2 in the Belgium cohort to 2.43 (2.11, 2.75) ml/min/1.73m^2 in the Spanish cohort. As compared to the Italian PIRP cohort, the adjusted mortality hazard ratio varied from 0.22 (0.11, 0.43) in the London LACKABO cohort to 1.30 (1.13, 1.49) in the English CRISIS cohort. These results suggest that the eGFR decline showed minor variation but mortality showed the most variation. Thus, different health care organization systems are potentially associated with differences in outcome of patients with CKD within Europe. These results can be used by policy makers to plan resources on a regional, national and European level.

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Correspondence: *Katharina Brück, ERA-EDTA Registry, Amsterdam Medical Center, Meibergdreef 9, 1100 DD Amsterdam, The Netherlands. E-mail: k.brueck@amc.uva.nl*

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Chronic kidney disease (CKD) is one of the fastest growing causes of death worldwide.[1] In stark contrast is the lack of novel treatment options for the management of CKD.[2] Current predialysis care can slow the progression in patients with CKD and reduce mortality in ESRD patients.[3] In addition, national health care system characteristics may influence outcomes in patients with CKD.[4]

Describing outcomes in CKD patients across regions and countries may identify regions with overall slow CKD

progression and/or low rates of mortality. Such a comparison may help to identify health care system characteristics that are associated with improved population health. Moreover, information regarding the decline of mean estimated glomerular filtration rate (eGFR) over time can be used by policy makers to plan resources at the regional, national, and European level.

Up to the present, little is known about the epidemiology of CKD progression. Studies from individual countries describing CKD progression in referred CKD patients have reported declines in the rates of eGFR varying from 0.35 to 5.16 ml/min per 1.73 m^2 per year.[5,6] Next to differences in the way progression is being expressed, comparisons of these studies is complicated by differences in baseline eGFR, albuminuria, primary renal disease (PRD), and presence of comorbidities, all factors that independently may influence the rate of CKD progression.[7] Importantly, as the rate of change in eGFR influences mortality risk,[8] mortality risk needs to be taken into account when describing eGFR change in CKD patients.

A relatively new statistical method, which enables simultaneous analysis of longitudinal and survival data, is the joint model.[9,10] The main advantage of this model, in the context of CKD progression, is its ability to correct for the measurement error in repeated eGFRs.[10,11] Another advantage is that it accounts for mortality risk when estimating GFR decline.[9,12] Despite these clear advantages for studies investigating outcomes in CKD patients, joint models are currently underused within the nephrology research.[11,13]

The objective of this study was to describe CKD progression and mortality outcomes in patients attending outpatient nephrology clinics. We used individual patient data from 9 CKD cohorts in 5 European countries taking part in the European CKD Burden Consortium.[14,15] Using a joint model, we combined a linear mixed model to estimate mean annual eGFR changes and a Weibull survival model to estimate all-cause mortality risk. Additionally, we determined mean annual eGFR changes for subgroups based on age, sex, and the presence of diabetes mellitus.

RESULTS

Study characteristics

We obtained data from 9 cohort studies,[16–22] followed in 5 European countries, including a total of 27,771 CKD patients not on renal replacement therapy (RRT), of which 25,702 patients (93%) had a baseline eGFR below 60 ml/min per 1.73 m^2. Of these patients, 18,126 had at least 2 creatinine measurements and were included in the main analysis. Inclusion and exclusion criteria for the cohorts are listed in Table 1. One cohort (Complesso Integrato Columbus [CIC]) did not have any exclusion criteria, 3 cohorts (Prevention of Renal Insufficiency Progression [PIRP], Chronic Renal Insufficiency Standards Implementation Study [CRISIS], London Arterial Calcification, Kidney and Bone Outcomes [LACKABO]) solely excluded patients with acute kidney injury or with RRT at first presentation, and the remaining cohorts had additional exclusion criteria in place. Table 1 additionally shows the type of access to nephrology care by cohort. Four cohorts applied an open access system (i.e., patients could visit a nephrologist without a referral from their general practitioner). In the other 5 cohorts, patients required a referral from their general practitioner prior to visiting the nephrologist (i.e., gatekeeper system).

Data extraction

All cohorts provided data for serum creatinine concentration, age, and sex. Eight cohorts provided data for the presence of comorbidities, baseline albuminuria, and PRD. Of the patients included in the main analysis, 34% had data available for either albuminuria or proteinuria. Tables 2 and 3 show baseline characteristics, and the availability of follow-up measurements of patients included in the main analysis (i.e., CKD stages 3 to 5 and $\geq$2 creatinine measurements). Supplementary Table S1 shows the characteristics of all included patients compared to those with only 1 creatinine measurement. Eight studies (89% of included studies) used isotope dilution mass spectrometry (IDMS) standardized creatinine measurements, of which 1 study used IDMS standardized creatinine methods in 79% of included patients.

CKD outcomes

We assessed CKD progression by using a joint model, simultaneously analyzing repeated measures of eGFR and mortality risk. As such, mortality risk was taken into account for the calculation of the mean annual eGFR decline, and conversely, eGFR decline was taken into account for calculating the mortality risk. Both crude results and results adjusted for baseline eGFR, age, sex, PRD, diabetes mellitus, hypertension, obesity, and smoking are presented. Adjustment for the presence of albuminuria and angiotensin-receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEi's) are presented in the Supplementary Tables S2, S3, S4, and S5.

Survival analysis

Figure 1 and Table 4 show the crude and adjusted mortality hazard ratios (HR) and their 95% confidence intervals (95% CI). The PIRP cohort served as the reference, based on population size. The crude HR varied from 0.08 (95% CI, 0.04 to 0.16) in the English LACKABO cohort to 1.0 in the reference population. The adjusted HR varied from 0.22 (95% CI, 0.11 to 0.43) in the LACKABO cohort to 1.30 (95% CI, 1.13 to 1.49) in the CRISIS cohort. Supplementary Table S2 presents the HR additionally adjusted for use of ACEi and ARB, indicating the impact of ACEi and ARB use in the causal pathway between cohort and CKD outcome. This HR ranged from 0.21 (95% CI, 0.11 to 0.41) in the LACKABO cohort to 1.11 (95% CI, 0.96 to 1.27) in the CRISIS cohort.

eGFR decline

Figure 1 and Table 5 show the crude and adjusted mean annual eGFR decline by study including the 95% CI. The crude mean eGFR decline varied from 0.30 (95% CI, +0.03 to 0.62 [+eGFR indicates increase instead of decline]) ml/min per 1.73 m^2 per year in the Italian CIC cohort to 2.36 (95%

Table 1 | Inclusion and exclusion criteria according to study and access to specialist nephrology care

Study	Country	Region	*N*	Inclusion criteria	Exclusion criteria	Inclusion period	Access to nephrologist
	Belgium	Ghent	557	All patients aged ≥18 yr Willing to participate in biobanking	Recent AKI (<3 mo) Recent acute CV event (<3 mo) Infection	2008–2012	Open access
	Cyprus	Nicosia	104	CKD patients (≥3 mo)	Malignancy Inflammation (<3 mo) Major CV event (i.e., stroke/MI/ acute IHD) (<3 mo)	2012–2013	Open access
CIC	Italy	Rome	3008	All consecutive patients with ≥1 creatinine measurements	None	2001–2015	Open access
MAURO	Italy	Multiple[a]	759	Age 18–75 yr ≥2 × creatinine >1.5 and <4.0 mg/dl (men) or >1.3 and <3.5 mg/dl (women) or albuminuria >30 mg/24 h ≥ 2 consecutive visits	AKI or rapidly evolving renal disease; transplant, pregnancy, cancer or disease in a terminal phase	2005–2008	Open access
PIRP	Italy	Emilia Romagna	18,244	All consecutive patients referred to nephrologist by primary care physicians	Subjects with RRT or AKI	2005–2015	Gatekeeper system
TABLE	Italy	Multiple[b]	1184	All consecutive patients with eGFR<60 ml/min per 1.73 m^2 (>3 mos)	Patients with acute kidney injury (<6 mo before first visit) Patients with first visit < 1 year	2000–2005	Gatekeeper system
PECERA	Spain	Valencia	995	CKD stage 4–5 not receiving dialysis Life expectancy >1 yr Informed consent	Kidney transplant, AKI, wasting disease, malignancy, incapacitating disease, or active infection/inflammation	2006–2009	Gatekeeper system
CRISIS	UK	Manchester	2649	10 < eGFR ≤60 ml/min per 1.73 m^2 Able to give written consent	AKI Previous RRT	2002–2013	Gatekeeper system
LACKABO	UK	London	271	serum creatinine >150 μmol/l (men) or >130 μmol/l (women) Able to give consent	Subjects with RRT or AKI	2006–2008	Gatekeeper system

AKI, acute kidney injury; CIC, Complesso Integrato Columbus; CKD, chronic kidney disease; CRISIS, Chronic Renal Insufficiency Standards Implementation Study; CV, cardiovascular; eGFR, estimated glomerular filtration rate; Gatekeeper, referral by general practitioner required; LACKABO, London Arterial Calcification, Kidney and Bone Outcomes; MAURO, multiple intervention and audit in renal diseases to optimize care; MI, myocardial infarction; *N*, total number of patients included in study; Open access, no referral by general practitioner required; PECERA, Proyecto de Estudio Colaborativo En pacientes con insuficiencia Renal Avanzada; PIRP, prevention of renal insufficiency progression; RRT, renal replacement therapy; TABLE, target blood pressure levels in CKD.
[a]MAURO patients included in 21 centers: 17 in Calabria, 3 in Sicily, 1 in Puglia, and 1 in Sardinia.
[b]TABLE patients included in 25 centers: most of these centers were located in southern Italy, surrounding Naples and further south, 1 from Verona, 1 from Pisa, 1 from Chieti, and 3 from Sicily.

CI, 2.04 to 2.68) ml/min per 1.73 m^2 per year in the Spanish PECERA cohort. The adjusted mean annual eGFR decline varied from 0.77 (95% CI, 0.45,1.08) ml/min per 1.73m^2 in the Belgium cohort to 2.43 (95% CI, 2.11,2.75) ml/min per 1.73m^2 in the PECERA cohort. Supplementary Table S3 shows the eGFR decline additionally adjusted for ACEi and ARB use; this ranged from 1.19 (95% CI, 0.90 to 1.47) in the Italian MAURO cohort to 2.45 (95% CI, 2.12 to 2.77) ml/min per 1.73m^2 in the PECERA cohort.

Table 6 presents the eGFR decline for the subgroups by age, sex, and presence of diabetes mellitus. The age group analysis showed faster eGFR decline in the younger aged group than in patients 65 years of age and older in all cohorts, except for the LACKABO cohort. In that cohort, there were no differences in eGFR decline between the 2 age groups. Overall eGFR decline was slower in females than in males. In patients with diabetes mellitus, mean annual eGFR decline was faster than in patients without diabetes mellitus in all cohorts.

We performed sensitivity analyses in 3 separate groups, for which the mean annual eGFR decline, including 95% CI, are all presented in the Supplementary Tables S4, S5, and S6. Supplementary Table S4 shows results for the patients with available baseline albuminuria measurements. Importantly, the correction for baseline albuminuria only slightly changed the rate of eGFR decline. Supplementary Table S5 shows the results for patients with at least 3 creatinine measurements. In Supplementary Table S6, we present the eGFR decline by cohort based on 9 separate models, in contrast to the main analysis in which all cohorts were analyzed in 1 model. Overall the results from the sensitivity subgroup analyses were in line with results of the main analysis.

DISCUSSION

In this prospective cohort analysis including individual data of 27,771 CKD patients from 5 European countries, outcomes in CKD patients varied significantly among European outpatient nephrology studies, while taking into account the effect of eGFR changes in mortality risk and vice versa. Variations in CKD outcomes persisted despite adjustment for factors associated with CKD progression, such as baseline

Table 2 | Population characteristics by study

Countries	Belgium	Cyprus	Italy				Spain	UK	
Studies	UZGhent	Nicosia	CIC	MAURO	PIRP	TABLE	PECERA	CRISIS	LACKABO
N	403	70	1420	719	1,1277	1,031	939	2,049	218
Median age yr (range)	69 (61–77)	72 (68–76)	74 (66–80)	65 (57–70)	74 (67–80)	69 (58–76)	73 (61–79)	67 (56–75)	61 (51–70)
% of Males	61.0	71.4	58.6	59.1	64.6	57.3	60.4	61.6	72.0
% with Diabetes	35.7	60.0	36.6	34.9	36.6	26.8	35.9	32.3	20.2
% of Missing DM	0.0	0.0	0.0	0.0	0.0	0.0	0.0	3.8	0.0
% with Hypertension[a]	48.4	98.6	NA	94.4	97.8	97.1	91.4	95.9	83.9
% of Missing HT	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0
% with Obesity	34.8	61.4	NA	31.9	24.0	25.7	30.9	NA	26.4
% with Missing BMI	0.2	0.0	100.0	0.3	0.0	0.0	0.1	100.0	7.8
Current smokers, %	11.9	24.3	NA	12.5	9.5	9.5	11.3	12.6	13.8
% of Ex–smokers	40.5	25.7	NA	37.1	41.7	22.9	34.0	53.4	30.7
% of Missing smokers	2.0	0.0	100.0	0.0	29.1	0.0	0.0	4.1	0.0
% using ACEi	NA	48.6	NA	65.7	40.8	52.6	33.0	43.4	50.9
% using ARBs	NA	75.7	NA	41.2	37.5	25.2	55.0	26.5	40.8
% Missing medication	100.0	0.0	100.0	5.6	0.0	0.0	0.0	0.9	0.0
% of PRD									
Vascular	27.7	22.9		12.0	59.7	25.0	40.9	25.3	6.1
Diabetic nephropathy	19.5	60.0		8.0	12.0	14.6	13.5	17.2	12.6
Glomerulonephritis	10.5	10.0		8.0	4.6	12.6	6.7	16.7	14.5
Tubule-interstitial	9.2	4.3		7.7	5.8	10.8	10.6	20.3	6.5
Polycystic kidney	3.0			7.4	3.2	5.5	4.6	5.2	9.8
Congenital	6.7			0.6	1.2	0.0			0.5
Other	12.0			3.5	0.6	10.2	12.2	15.3	31.8
Unknown	11.5	2.9		52.9	12.9	21.2	11.4		18.2
Missing PRD data	0.5	0.0	100.0	0.4	0.0	0.0	0.0	0.1	1.8

BMI, body mass index; DM, diabetes mellitus; glomerulonephritis, glomerulonephritis + membranous nephropathy + IgA nephropathy; NA, not applicable; obesity, BMI >30 kg/m^2; tubule-interstitial, pyelonephritis + interstitial + post renal; vascular, hypertensive + renovascular.
Median is presented with interquartile range in brackets.
[a]Hypertension in the UZGhent cohort is based on blood pressure alone.

eGFR, age, sex, presence of albuminuria, diabetes mellitus, hypertension, obesity, smoking, PRD, and medication used. The slowest adjusted eGFR decline was seen in the Belgian cohort. In addition, the mortality and initiation of RRT were very low in this cohort, suggesting that Belgian CKD patients had an excellent prognosis for both renal and overall survival.

Table 3 | Population characteristics by study; kidney function/damage and follow-up data

Countries	Belgium	Cyprus	Italy				Spain	UK	
Studies	UZGhent	Nicosia	CIC	MAURO	PIRP	TABLE	PECERA	CRISIS	LACKABO
Baseline eGFR in ml/min per 1.73m^2									
Mean (±SD) CKD-EPI	37.7 (11.5)	41.2 (11.3)	33.8 (12.3)	33.6 (12.0)	30.2 (11.9)	29.8 (13.8)	19.2 (5.4)	29.0 (13.3)	33.5 (13.5)
% of Baseline eGFR categories									
45–59	29.3	41.4	21.8	19.9	12.9	17.4	NA	15.2	24.3
30–44	43.2	40.0	35.7	39.5	35.6	28.3	2.0	28.0	33.9
15–29	25.3	15.7	40.8	34.9	41.5	38.1	72.9	40.9	33.0
<15	2.2	2.9	1.8	5.7	10.0	16.2	25.0	15.9	8.7
% with Albuminuria data									
Normoalbuminuria	51.3	39.1	NA	18.3	41.0	22.2	14.1	37.8	22.3
Microalbuminuria	22.7	33.3	NA	28.6	36.6	24.5	28.7	29.8	28.9
Macroalbuminuria	26.0	27.5	NA	53.1	22.4	53.2	57.2	32.4	48.8
Missing	4.7	1.4	100.0	9.5	92.8	0.0	5.6	7.9	44.5
Follow-up data									
Median (quartile range) creatinine measurements	16 (11–26)	4 (4–4)	3 (2–5)	7 (6–7)	4 (2–7)	4 (2–5)	5 (3–5)	4 (2–5)	5 (3–10)
Median duration follow-up, yr	5.7 (4.0–7.6)	3.0 (3.0–3.0)	0.5 (0.0–1.9)	3.0 (3.0–3.0)	2.4 (1.2–4.3)	4.2 (2.2–5.1)	2.5 (1.3–3.0)	3.2 (1.9–5.8)	5.2 (4.6–5.4)
Rate per 1,000 person yr at 1 year follow-up									
Mortality rate	7.5	14.4	NA	9.8	22.5	4.6	27.1	8.4	4.2
RRT rate	2.50	0.00	NA	5.6	33.5	63.3	159.4	53.7	8.4
% Missing follow-up	7.4	2.9	NA	0.0	2.7	0.0	22.9	0.0	4.1

NA, not available; normoalbuminuria, albumin creatinine ratio (ACR)<30 mg/g or protein creatinine ratio (PCR) <150 mg/g or proteinuria <150 mg/24 h; microalbuminuria: ACR 30–300 mg/g; PCR 150–500 mg/g or proteinuria 150–500 mg/24 h; macroalbuminuria: ACR> 300 mg/g; PCR >500 mg/g or proteinuria >500 mg/24 h.
Means are presented with SDs; medians are presented with interquartile ranges.

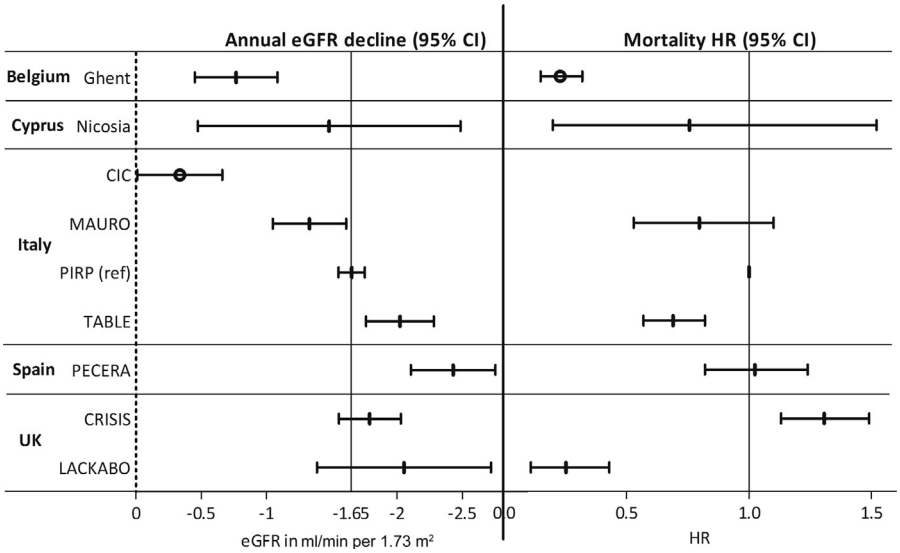

Figure 1 | Forest plot of adjusted mean annual eGFR decline in ml/min per 1.73 m^2 and adjusted mortality hazard ratio (HR) by study. The Italian PIRP cohort is the reference group. | = adjusted for baseline eGFR, age, sex, PRD, comorbidities, and smoking (model 5); Θ = only adjusted for age and sex. The hazard ratio for the Italian CIC cohort is not shown because they did not provide data for follow-up status. CI, confidence interval; CIC, Complesso Integrato Columbus; CRISIS, Chronic Renal Insufficiency Standards Implementation Study; eGFR, estimated glomerular filtration rate; LACKABO, London Arterial Calcification, Kidney and Bone Outcomes; MAURO, multiple intervention and audit in renal diseases to optimize care; PECERA, Proyecto de Estudio Colaborativo En pacientes con insuficiencia Renal Avanzada; PIRP, prevention of renal insufficiency progression; PRD, primary renal disease; TABLE, target blood pressure levels in CKD.

The fastest adjusted eGFR decline was seen in the Spanish PECERA and the English LACKABO cohorts. The fast eGFR decline in the LACKABO cohort was in line with the rate of need for RRT and the low mortality in this cohort.

Previous studies have shown that younger age, male sex, and presence of diabetes mellitus are associated with more rapid CKD progression.[7,23,24] We have been able to confirm these associations, even after adjustment for several important predictors of CKD progression and mortality risk. This consistent effect of established risk factors suggests that the observed differences in CKD outcomes across CKD cohorts are due to other factors than age, sex, and diabetic status. Importantly, we are the first to show that the association between eGFR decline and these risk factors persists after adjustment for mortality risk.

Influence of selection criteria

Although we aimed to include comparable CKD cohorts, the exclusion criteria among the individual studies varied. This could have resulted in the selection of healthier patients in some studies compared to studies without additional exclusion criteria.

The Italian CIC cohort was the only unselected cohort, including all patients from the nephrology outpatient clinic. Although this cohort showed the slowest crude eGFR decline, we had insufficient information to fully compare these results with the other cohorts. Two cohorts, the Belgian and Cypriot cohorts, excluded patients with recent cardiovascular events. Given that cardiovascular death is the main cause of death in patients with CKD,[25] this selection may partly explain the low mortality HR observed of, respectively, 0.22 (95% CI, 0.15 to 0.32) and 0.55 (95% CI, 0.20 to 1.52). The Italian cohorts MAURO and TABLE excluded rapid loss in kidney function and recent acute kidney injury, respectively. This may have contributed to a relatively low mortality HR, as rapid eGFR decline is associated with an increased mortality risk.[8] The Spanish PECERA cohort showed a relatively rapid eGFR decline and high mortality and RRT initiation. This may in

Table 4 | Hazard ratio (95% CI) for mortality, with PIRP cohort as reference group

Country	Belgium	Cyprus	Italy				Spain	UK	
Study	Ghent	Nicosia	CIC	MAURO	PIRP	TABLE	PECERA	CRISIS	LACKABO
N	323	70	1,420	719	1,1277	103,100	939	2,049	218
Model 1	0.20 (0.14–0.30)	0.52 (0.19–1.44)	NA	0.30 (0.21–0.43)	ref.	0.42 (0.35–0.50)	0.76 (0.63–0.93)	0.77 (0.70–0.85)	0.08 (0.04–0.16)
Model 2	0.22 (0.15–0.32)	0.55 (0.20–1.52)	NA	0.74 (0.52–1.07)	ref.	0.63 (0.52–0.75)	0.93 (0.76–1.14)	1.21 (1.09–1.34)	0.20 (0.10–0.38)
Model 3	<Events	0.41 (0.15–1.10)	NA	0.73 (0.51–1.04)	ref.	0.68 (0.57–0.82)	1.34 (1.12–1.61)	1.29 (1.17–1.43)	0.20 (0.10–0.39)
Model 4	<Events	0.53 (0.19–1.45)	NA	0.75 (0.52–1.07)	ref.	0.66 (0.55–0.80)	0.99 (0.82–1.21)	1.34 (1.18–1.52)	0.21 (0.11–0.42)
Model 5	<Events	0.55 (0.20–1.52)	NA	0.76 (0.53–1.10)	ref.	0.68 (0.57–0.82)	1.01 (0.82–1.24)	1.30 (1.13–1.49)	0.22 (0.11–0.43)

CI, confidence interval; eGFR, estimated glomerular filtration rate; NA, not applicable; PRD, primary renal disease; RRT, renal replacement therapy.
Model 1, crude ([a]adjusted for baseline eGFR by use of random intercept); Model 2, age and sex adjusted; Model 3, 2 + RRT start; Model 4, 3 + PRD; Model 5, 4 + comorbidities (diabetes, hypertension and obesity); Model 6, 5 + smoking.

Table 5 | Mean annual eGFR decline (ml/min per 1.73 m^2 (95% CI,) by study

Country	Belgium	Cyprus	Italy				Spain	UK	
Study	Ghent	Nicosia	CIC	MAURO	PIRP	TABLE	PECERA	CRISIS	LACKABO
Model 1	0.76 (0.50–1.02)	1.86 (0.85–2.86)	0.30 (+0.03– 0.62)	1.41 (1.14–1.67)	1.71 (1.62–1.79)	2.04 (1.78–2.29)	2.36 (2.04–2.68)	2.00 (1.82–2.18)	2.36 (1.71–3.01)
Model 2	0.73 (0.47–0.99)	1.85 (0.85–2.86)	0.34 (0.01– 0.66)	1.29 (1.02–1.55)	1.71 (1.62–1.79)	1.99 (1.74–2.25)	2.40 (2.08–2.72)	1.85 (1.67–2.04)	2.13 (1.48–2.78)
Model 3	0.68 (0.42–0.94)	1.44 (0.45–2.43)	NA	1.33 (1.05–1.60)	1.66 (1.58–1.75)	1.99 (1.74–2.24)	2.42 (2.10–2.74)	1.80 (1.60–1.99)	2.02 (1.36–2.67)
Model 4	0.79 (0.48–1.09)	1.47 (0.48–2.46)	NA	1.30 (1.03–1.57)	1.66 (1.57–1.75)	1.99 (1.74–2.24)	2.41 (2.10–2.73)	1.70 (1.48–1.93)	2.03 (1.37–2.69)
Model 5	0.77 (0.45–1.08)	1.48 (0.47–2.49)	NA	1.33 (1.05–1.61)	1.65 (1.55–1.75)	2.02 (1.76–2.28)	2.43 (2.11–2.75)	1.79 (1.55–2.03)	2.05 (1.39–2.72)

CI, confidence interval; CIC, Complesso Integrato Columbus; CRISIS, Chronic Renal Insufficiency Standards Implementation Study; eGFR, estimated glomerular filtration rate; LACKABO, London Arterial Calcification, Kidney and Bone Outcomes; MAURO, multiple intervention and audit in renal diseases to optimize care; NA, not applicable; PECERA, Proyecto de Estudio Colaborativo En pacientes con insuficiencia Renal Avanzada; PIRP, prevention of renal insufficiency progression; PRD, primary renal disease; TABLE, target blood pressure levels in CKD.
Model 1, crude (*adjusted for baseline eGFR by use of random intercept); Model 2, age and sex adjusted; Model 3, 2 + PRD; Model 4, 3 + comorbidities (diabetes, hypertension, and obesity); Model 5, 4 + smoking.

Table 6 | Mean annual adjusted eGFR decline (ml/min per 1.73 m^2; 95% CI) by subgroup

Country	Belgium	Cyprus	Italy				Spain	UK	
Study	Ghent	Nicosia	CIC[a]	MAURO	PIRP	TABLE	PECERA	CRISIS	LACKABO
≤65 yr	0.88 (0.40–1.37)	1.85 (+1.10– 4.80)	NA	1.44 (1.04–1.85)	1.88 (1.69–2.06)	2.32 (1.92–2.73)	3.02 (2.43–3.60)	2.17 (1.84–2.49)	2.05 (1.18–2.91)
>65 yr	0.84 (0.28–1.39)	1.20 (+1.92– 4.33)	NA	1.40 (0.86–1.94)	1.50 (1.07–1.58)	1.94 (1.42–2.46)	2.21 (1.52–2.90)	1.76 (1.37–2.14)	2.48 (1.15–3.80)
Female	0.26 (+0.10– 0.61)	1.55 (+0.29– 3.39)	+0.12 (+0.62– 0.38)	0.78 (0.36–1.20)	1.07 (0.92–1.22)	1.41 (1.02–1.80)	1.75 (1.27–2.23)	0.89 (0.56–1.21)	0.10 (+1.03– 1.23)
Male	1.00 (0.58–1.42)	1.49 (+0.67– 3.64)	0.57 (+0.08– 1.22)	1.21 (0.69–1.74)	1.23 (1.05–1.40)	1.92 (1.43–2.42)	2.29 (1.69–2.89)	1.03 (0.66–1.39)	2.47 (1.11–3.84)
Non-DM	0.60 (0.27–0.93)	1.29 (+0.20– 2.78)	NA	0.84 (0.51–1.17)	1.03 (0.91–1.15)	1.65 (1.36–2.44)	2.06 (1.67–2.44)	0.97 (0.70–1.24)	1.54 (0.81–2.27)
DM	1.07 (0.55–1.58)	1.63 (+0.32– 3.61)	NA	1.37 (0.82–1.92)	1.40 (1.20–1.59)	1.78 (1.22–2.34)	2.08 (1.46–2.69)	0.94 (0.54–1.33)	2.07 (0.40–3.74)

+eGFR, indicates increase instead of decline; CI, confidence interval; CIC, Complesso Integrato Columbus; CRISIS, Chronic Renal Insufficiency Standards Implementation Study; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; LACKABO, London Arterial Calcification, Kidney and Bone Outcomes; MAURO, multiple intervention and audit in renal diseases to optimize care; NA, not applicable; PECERA, Proyecto de Estudio Colaborativo En pacientes con insuficiencia Renal Avanzada; PIRP, prevention of renal insufficiency progression; PRD, primary renal disease; TABLE, target blood pressure levels in CKD.
[a]Results for the CIC cohort are presented as crude values. All other results are adjusted for: baseline eGFR, age, sex, PRD, diabetes mellitus, hypertension, obesity and smoking status.

part be explained by the sole inclusion of CKD stages 4 and 5, as it is impossible to fully correct for baseline eGFR in this situation.

The PIRP, CRISIS, and LACKABO cohorts had identical exclusion criteria and excluded patients solely on the basis of RRT or with acute kidney injury. Across these cohorts, the adjusted eGFR decline varied slightly from 1.65 (95% CI, 1.55 to 1.75) in the PIRP cohort to 2.05 (95% CI, 1.39 to 2.72) ml/min per 1.73m^2 per year in the LACKABO cohort. In contrast, there was a significant variation in the adjusted mortality rate, from 0.22 (95% CI, 0.11 to 0.43) in the LACKABO cohort to 1.30 (95% CI, 1.13 to 1.49) in the CRISIS cohort.

A recently published study by Bello *et al.*[26] showed large differences in CKD care and policy across European countries, such as the number of nephrologists, the existence/absence of referral guidelines, and in the provider payments for CKD care. As the cohorts are included from all over Europe, it is likely that inter-regional differences have contributed to the observed differences in CKD outcomes. We will discuss the possible influence of such factors starting with the regional population health, then the selection of patients who received specialist nephrology care, and finally the influence of the CKD management by the nephrologist.

Regional population health

In RRT patients, 26% of regional variation in mortality is explained by differences in general population mortality.[27] Hence, it is likely that variations in regional population health may also contribute to differences in both eGFR decline and mortality across CKD cohorts. We tried to reduce this influence by adjusting for the most important comorbidities, diabetes mellitus, hypertension, and obesity. As population health is determined by many more factors, it may still influence the results. In the 2 English cohorts, for example, the observed differences in mortality risk seemed to reflect previously reported differences in population health.[28,29] The adjusted mortality HR varied from 0.22 (95% CI, 0.11 to 0.43) in the London-based LACKABO study to 1.30 (95% CI, 1.13 to 1.49) in the CRISIS study. The CRISIS cohort is set in the northwest of England, where social deprivation and mortality are reportedly relatively high.[28] The population of London is ethnically diverse,[30] which corresponds to the high percentage of ethnic minorities (28%) in the LACKABO cohort. Previously, Barbour *et al.*[31] reported rapid eGFR decline rates and low mortality in Asian CKD patients compared to Caucasian CKD patients. Similarly, Dreyer *et al.*[32] reported faster eGFR decline in diabetic CKD patients in South Asian and black ethnic groups than in whites. Hence, it is possible that both the relatively fast eGFR decline and the low mortality risk in the LACKABO cohort can be in part contributed to the high percentage of ethnic minorities.

Access to specialist care

Apart from the selection of CKD patients through inclusion and exclusion criteria, there was an additional selection of patients determined by the organization of the regional health care system. Differences in access to specialist care will likely influence the overall health of the CKD population seen in outpatient nephrology clinics. In Belgium, the health system allows open access to specialist care (i.e., patients do not need a referral from a general practitioner).[33] Without a general practitioner's referral, there is no selection based on rate of eGFR decline or at-risk patients, and thus more healthy patients have access to a specialist's care. This may have contributed to the slow eGFR decline and low mortality we observed in the Belgian study. A slow eGFR decline was seen not only in the Belgian cohort but also in the other cohorts with open access (i.e., the Cypriot,[34] the CIC, and the MAURO cohorts).

In Italy, Spain, and England, access to specialists' care is in principle limited to patients with a referral from their general practitioner (i.e., the gatekeeper system).[35–37] Nonetheless, in 2005 in Italy, 56.8% of all visits made by specialists were privately paid by patients, although the proportion made among different specialties was quite variable.[36] Specific data for specialists' care in nephrology were not available. Among the Italian cohorts in the present study, PIRP and TABLE included only referred patients, whereas MAURO and CIC also allowed open access to patients. This might have contributed to the large variability in eGFR decline and mortality observed across these Italian cohorts.

In the English and Spanish cohorts, patients did need a referral to visit a nephrology specialist at an outpatient clinic, and both countries had referral criteria in place during (part of) the study enrollment period. In the United Kingdom, the Royal College of Physicians published referral criteria for CKD patients in 2005,[38] and in Spain, the Spanish Society of Nephrology published these criteria in 2008.[39] Overall, the national referral criteria are quite similar, and CKD patients with eGFR below 30 ml/min per 1.73 m^2 required referrals in both countries. This may perhaps partly explains the relative small variations in eGFR decline across the Spanish and English populations.

CKD management

CKD management can influence the rate of eGFR decline and mortality risk.[7,40] For instance, multiple studies have shown that treatment with ACEi and ARB therapy can reduce proteinuria, lower blood pressure, and slow CKD progression.[41,42] Consequently, the observed differences in baseline ACEi and ARB use, ranging from 25% to 75%, may have contributed to the differences in CKD progression. Importantly, we chose to focus on the results adjusted for everything but ACEi and ARB use, as treatment differences reflect current regional practice. Moreover, CKD management, for example, through ACEi and ARB medication is in the causal pathway between the baseline cohort eGFR and CKD outcomes. We only analyzed this to assess to what extent differences in CKD outcomes were mediated through ACEi and ARB use. The adjustment for ACEi and ARB use in our model slightly reduced eGFR decline in only 4 studies, indicating

that treatment differences with ACEi and ARB medication did not explain the variations in CKD progression.

Strengths and limitations

Our study has multiple strengths and limitations. The main strength of our study is the use of a sophisticated joint model analysis, which enabled us to account for the measurement error of eGFR. This is confirmed by the robustness of results in the sensitivity analyses, where we increased the minimum from 2 to 3 creatinine measurements. Moreover, the joint model corrects for the association between change in eGFR and mortality and the potential bias related to this association. One drawback of the model is the requirement of at least 2 creatinine measurements, thus excluding patients who dropped out early, which could have led to a selection bias. Other strengths of our study include the big sample size and adjustments for important factors including age, sex, baseline eGFR, albuminuria, PRD, and presence of diabetes, hypertension, and obesity, and smoking status and medication use. Although we did correct for baseline albuminuria, we did not assess change in albuminuria as only few cohorts provided repeated measurements of albuminuria. A limitation of any observational study is that no causative conclusions from the observed associations can be made. In addition, the results are based on CKD patients in nephrology outpatient clinics, and consequently, the results are not generalizable to undiagnosed CKD patients or CKD patients in primary care. Moreover, nephrology practice may vary per clinic and region, and therefore, the results should not be extrapolated to a national level. Finally, we did not collect ethnicity data from all cohorts, and differences in ethnicity might have influenced the observed CKD outcomes.

Conclusion

We observed clinically relevant variations in outcomes in CKD patients from outpatient nephrology clinics across European regions. Apart from the very slow decline in the Belgian cohort, adjusted mean annual eGFR decline varied only slightly across other cohorts. In contrast, we did find marked differences in mortality risk across the cohorts. This paper is a first step in identifying regional health care systems effective in preventing CKD progression and improving survival by monitoring CKD progression and mortality in CKD patients attending outpatient nephrology clinics across European regions.

METHODS

Search strategy

We performed a search of published studies in PubMed to identify studies which could contribute data for CKD progression in patients from outpatient nephrology clinics and were published between 2000 and the end of 2012. The full search terms are presented in Supplementary Appendix S1.

Study selection

Studies were included when carried out in CKD patients not undergoing RRT in an outpatient nephrology clinic within Europe and when creatinine follow-up measurements were available. We excluded studies with a sample size of less than 100 participants, studies not using eGFR based on serum creatinine equations, intervention trials, and review articles. No language restrictions were applied. The search was done by 1 investigator (KB). Any study that was judged relevant on the basis of its title was retrieved in abstract form, and if relevant, in full-text form. When eligibility was unclear this was resolved by discussion with another investigator (VSS). We extended our search by reviewing references from retrieved articles and review articles. Further studies and unpublished data were sought by communication with collaborators, nephrologists, and country representatives. Additionally, study groups were encouraged to join the European CKD Burden Consortium through a call in the newsletter of the 2012 European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) congress in Paris.

Data extraction

Eligible study groups that agreed to participate were asked to send a limited anonymized dataset with individual patient data including baseline characteristics and follow-up measurement of serum creatinine and (if available) albuminuria/proteinuria measurements. We excluded in-patient serum creatinine measurements and measurements after the start of RRT.

Diabetes mellitus was defined according to the 2006 World Health Organization criteria,[43] and hypertension was defined as the use of antihypertensive medication or a systolic blood pressure of $\geq$140 mm HG or diastolic blood pressure of $\geq$90 mm Hg. Obesity was defined as a body mass index $\geq$30 kg/m^2. We recoded the received PRD into 8 main categories based on comparability of the individual cohort definitions.

Study cohorts provided information for the creatinine assay method used, the use of IDMS calibration, and if any changes in methods occurred during follow-up. None of the laboratories changed the creatinine assay method during the follow-up period. Serum creatinine results from non–IDMS-calibrated creatinine measurement methods were reduced by 5% as suggested by Levey *et al.*[44] We used the CKD-EPI equation to estimate GFR.[45] Baseline albuminuria was divided into normoalbuminuria (albumin creatinine ratio <30 mg/g, or protein creatinine ratio <150 mg/g, or proteinuria <150 mg/24 h), microalbuminuria (albumin creatinine ratio 30 to 300 mg/g, protein creatinine ratio 150 to 500 mg/g, or proteinuria 150 to 500 mg/24 h) or macroalbuminuria (albumin creatinine ratio >300 mg/g, protein creatinine ratio >500mg/g, or proteinuria >500 mg/24 h).[7,46]

Statistical analysis

We performed a joint model analysis combining a longitudinal (linear mixed) model with a Weibull survival model.[9] By combining the longitudinal model with the survival model, the joint model accounted for mortality and reduced bias resulting from measurement error in eGFR.[11] The latter method leads to an estimation of the underlying error-free eGFR.

The longitudinal part of the model estimates the rate of change in eGFR over time, taking into account the varying number and spacing of eGFR measurements as well as the variable follow-up duration for each subject. In the survival model, death was the outcome, and patients were censored when lost to follow-up or at initiation of RRT. We added a penalty for initiation of RRT by imputing an eGFR of 5 ml/min per 1.73 m^2 at the day of RRT initiation. Time was defined in years since the first serum creatinine measured in outpatient

nephrology care. The Italian PIRP cohort was chosen as the reference category based on population size. We determined the mean eGFR change in ml/min per 1.73m^2 per year and the HR for mortality. To improve comparability of study cohorts, all studies were analyzed together, but the results are presented by study. The analysis was performed "crude" including only the inherent adjustment for baseline eGFR (model 1) and adjusted for the following potential confounders: age, sex (model 2), plus PRD (model 3), plus diabetic, hypertensive, and obesity status (model 4), plus smoking (model 5). To evaluate the impact of ACEi and ARB use in the causal pathway between baseline cohort eGFR and CKD outcomes, we added this variable into the model (model 6). All potential confounders were entered in the survival submodel as covariates and in the longitudinal model as both covariate main effects and interactions with time. In addition, eGFR decline was also presented by, a priori defined, subgroups based on age group (±65 years of age), sex, and presence of diabetes mellitus. In Supplementary Appendix S1, a more extensive explanation of the joint model can be found, including 2 tables with the parameters of both the longitudinal and the survival models.

Presence of albuminuria is associated with CKD progression,[7] but baseline albuminuria data were only partly available. Because we could not fully correct for baseline albuminuria in the total population, we restricted the main analysis to subjects with CKD stages 3 to 5 (i.e., eGFR <60 ml/min per 1.73m^2), as subjects with CKD stages 1 and 2 will likely have some degree of albuminuria.[7] Moreover, this restriction improved comparability of the CKD cohorts as they differed with regard to percentage of patients per CKD stage. In total, we performed 4 sensitivity analyses: (i) only subjects with available albuminuria data, to adjust for baseline albuminuria; (ii) subjects with at least 3 creatinine measurements (in the main analysis the required minimum was 2), which is recommended by Kidney Disease: Improving Global Outcomes to reduce the influence of measurement error in eGFR[7]; (iii) the joint model was run for the 9 individual studies separately (as compared to the main analyses in which all studies were included in 1 model), to show the eGFR decline by cohort independent of the decline from other cohorts; and (iv) the model without a penalty for RRT, using only the original, last eGFR value. The results of the sensitivity analyses are shown in Supplementary Table S4, S5, S6, and S7. All analyses were performed in Stata/SE version 14 software (College Station, TX). The "stjm" command was used for the joint model analysis.[9]

DISCLOSURE

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SUPPLEMENTARY MATERIAL

Table S1. Population characteristics by number of creatinine measurements.
Table S2. Hazard ratio (95% CI) for mortality with PIRP cohort as reference group.
Table S3. Mean annual eGFR decline in ml/min per 1.73 m^2 (95% CI) by study.
Table S4. Mean annual eGFR decline in ml/min per 1.73 m^2 (including 95% CI) by study. All subjects with available baseline albuminuria measurement, regardless of initial CKD stage or number of creatinine measurements.
Table S5. Mean annual eGFR decline in ml/min per 1.73 m^2 (95% CI) by study. Only subject with minimum of 3 creatinine measurements were included.
Table S6. Mean annual eGFR decline in ml/min per 1.73 m^2 (95% CI), CKD stages 3–5 were analyzed separately by study.
Table S7. Mean annual eGFR decline in ml/min per 1.73 m^2 (95% CI), CKD stages 3–5 with and without penalty eGFR for RRT initiation.
Appendix 1: Search terms and joint model explanation (word document).
Supplementary material is linked to the online version of the paper at www.kidney-international.org.

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