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CHAPTER 6:

Progression and mortality in patients with CKD attending outpatient nephrology clinics across Europe: A novel analytic approach

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Submitted

ABSTRACT

Background

The incidence of renal replacement therapy (RRT) varies across countries. Yet, little is known about the epidemiology of chronic kidney disease (CKD) outcomes. Our aim was to describe progression and mortality risk in CKD patients not on RRT attending outpatient nephrology clinics across Europe.

Method

We used individual data from nine CKD cohorts participating in the European CKD Burden Consortium. A joint model was used to estimate mean eGFR change 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).

Results

27,771 patients from five countries were included. The adjusted mean annual eGFR decline varied from 0.77 (95%CI 0.45-1.08) ml/min/1.73m^2 in the Belgium cohort to 2.43 (95%CI 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 (95%CI 0.11-0.43) in the London LACKABO cohort to 1.30 (95%CI 1.13-1.49) in the English CRISIS cohort.

Conclusion and Implications

Outcomes in CKD patients attending outpatient nephrology clinics varied markedly across European regions. Although eGFR decline showed minor variation, the most variation was observed in CKD mortality. Our results suggest that different healthcare organization systems are potentially associated with differences in outcome of CKD patients within Europe. These results can be used by policy makers to plan resources on a regional, national and European level.

INTRODUCTION

Chronic kidney disease (CKD) contributes substantially to global years of life lost (1), mainly through the increased risk of developing cardiovascular disease (CVD) (2) and progression to the need for renal replacement therapy (RRT) (3). For most patients however, the risk of cardiovascular death is much higher than the risk to develop end stage renal disease (ESRD) (3).

Several studies have shown that both CKD prevalence and RRT incidence vary across European regions and countries (4-8). Yet, little is known about the epidemiology of CKD progression. Studies from individual countries describing CKD progression in referred CKD patients have reported estimated glomerular filtration rate (eGFR) decline rates varying from 0.35 to 5.16 ml/min/1.73m^2/year (9, 10). Next to differences in the way progression is being expressed, comparison 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 (11). Importantly, as the rate of change in eGFR influences mortality risk (12), 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 (13, 14). The main advantage of this model, in the context of CKD progression, is its ability to correct for the measurement error in repeated eGFRs (14, 15). Another advantage is that it accounts for mortality risk when estimating eGFR decline (13, 16). Despite these clear advantages for studies investigating outcomes in CKD patients, joint models are currently underutilized within the nephrology literature (15, 17).

Previous studies have shown that pre-dialysis care can slow progression in patients with CKD and reduce mortality in ESRD patients (18). Moreover, it has been suggested that national healthcare system characteristics may influence outcomes in patients with CKD (19). Using a joint model to describe outcomes in CKD patients across regions and countries, may identify regions with overall slow CKD progression and/or low mortality, independent of well-known clinical risk factors. Such a comparison might help to identify health care system characteristics that are associated with improved population health. In addition, information regarding the mean eGFR decline over time can be used by policy makers to plan resources at the regional, national and European level.

The objective of this study was to describe CKD progression and mortality outcomes in CKD patients attending outpatient nephrology clinics. We used individual patient data from nine CKD cohorts in five European countries taking part in the European CKD Burden Consortium (4, 20). By means of a joint model, we combined a linear mixed model, to estimate mean annual eGFR change, and a Weibull survival model, estimating all-cause

mortality risk. Additionally, we determined mean annual eGFR change for subgroups based on age, sex and the presence of diabetes mellitus.

METHODS

Search strategy

We performed a literature search in PubMed to identify studies which could potentially contribute data on CKD progression in patients from outpatient nephrology clinics and were published between 2000 and the end of 2012. The following terms were used for this search: "Renal Insufficiency, Chronic"[Mesh] OR kidney (or renal) insufficienc*[tiab] OR kidney (or renal) dysfunction*[tiab] OR kidney (or renal) impairment[tiab] OR impaired kidney (or renal) function[tiab] OR decreased kidney (or renal) function[tiab] OR chronic (or renal) kidney[tiab] OR CKD[tiab] AND "Follow-Up Studies"[Mesh] OR progression[tiab] AND Cohort[Mesh] OR Cohort[tiab] progression[tiab] OR progression [Mesh] AND Glomerular filtration rate[tiab] OR *GFR[tiab] OR creatinin*[tiab] OR "Creatinine"[Mesh] OR proteinuria [Mesh] OR proteinuria[tiab] OR albuminuria[tiab] OR dipstick OR MDRD OR (Modification [tiab] AND diet [tiab] AND 'renal disease'[tiab]) OR ('Cockroft Gault' AND (equation OR formula)).

Study selection

Studies were included when carried out within CKD patients not on RRT attending 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 GFR estimation by serum creatinine-based equations, intervention trials and review articles. No language restrictions were applied. The search was done by one 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 (VS). 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 who 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 WHO criteria (46) and hypertension was defined as the use of antihypertensive medication or a systolic blood pressure of >=140mmHg or diastolic blood pressure of >=90mmHg. Obesity was defined as a body mass index (BMI) >=30 kg/m^2. We recoded the received PRD into eight main categories based on comparability of the individual cohort definitions.

Study cohorts provided information on 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. (47). GFR was estimated from serum creatinine measurements using the CKD-EPI equation (48). Baseline albuminuria was categorized into normoalbuminuria (ACR<30 mg/g, or PCR<150 mg/g or proteinuria<150 mg/24h), micro-albuminuria (ACR 30-300 mg/g, PCR 150-500 mg/g or proteinuria 150-500 mg/24h) or macroalbuminuria (ACR>300 mg/g, PCR >500mg/g or proteinuria>500 mg/24h) (11, 49).

Statistical analysis

We performed a joint model analysis combining a longitudinal (linear mixed) model with a Weibull survival model (13). By combining the longitudinal model with the survival model, the joint model accounts for mortality and reduces bias resulting from measurement error in eGFR (15). 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 event of interest and patients were right 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/1.73m^2 at the day of RRT start. Time was defined as time (in years) since first serum creatinine measured in outpatient nephrology care. The Italian PIRP cohort was chosen as reference category based on population size. We determined the mean annual eGFR change in ml/min/1.73m^2 and the hazard ratio for mortality (HR). To improve comparability of study cohorts, all studies were analyzed together, yet the results are presented by study. We could not present a HR for the CIC from Rome, as the CIC study did not provide data on follow up status. 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), + PRD (model 3), + diabetic, hypertensive and obesity status (model 4), + smoking (model 5). To evaluate the impact of ACEi/ARB use in the causal pathway between country 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 (< or >= 65 years), sex and presence of diabetes mellitus.

Presence of albuminuria is associated with CKD progression (11), but only a minority of included patients had baseline albuminuria data available. Since we could not fully correct for baseline albuminuria in the total population, we restricted the analysis to subjects with CKD stage 3 to 5 (i.e. eGFR<60 ml/min/1.73m^2) as subjects with CKD stage 1 and 2 will likely have some degree of albuminuria (11). 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 three sensitivity analyses: 1) including all subjects with available albuminuria data, to adjust for baseline albuminuria 2) subjects with at least three creatinine measurements (as compared to the required minimum of two measurements in the main analyses), which is recommended by KDIGO to reduce the influence of measurement error in eGFR (11) and 3) the joint model was run for the nine individual studies separately (as compared to the main analyses in which all studies were included into one model), to show the eGFR decline by cohort independent of the decline from other cohorts. The results of the sensitivity analyses are shown in the appendix. All analyses were performed in Stata/SE version 14. The "stjm" command was used for the joint model analysis (13).

RESULTS

Study characteristics

We obtained data from nine CKD cohort studies (21-27), followed in five European countries including a total of 27,771 patients not on RRT, of which 25,702 patients (93%) had a baseline eGFR below 60 ml/min/1.73m^2. Of these patients, 18,126 had at least two creatinine measurements and were included in the main analysis. The in- and exclusion criteria for participation of patients in these cohorts are listed in table 1. One cohort (CIC) did not have any exclusion criteria, three cohorts (PIRP, CRISIS, LACKABO) solely excluded patients with acute kidney injury (AKI) or with RRT at first presentation and the remaining cohorts had additional exclusion criteria such as recent cardiovascular (CV) events, malignancy or active infection. 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 nephrologist without a referral from their general practitioner) in the other five cohorts patients required a referral from their general practitioner prior to visiting the nephrologist (i.e. gatekeeper system).

Data extraction

All cohorts provided data on serum creatinine, age and sex. Eight cohorts provided data on the presence of comorbidities, baseline albuminuria and on PRD. Of the patients included in the main analysis 34% had data available on either albuminuria/proteinuria. Table 2 shows the baseline characteristics and availability of follow up measurements of patients included in the main analysis (i.e. CKD stage 3-5 and >=2 creatinine measurements). Eight studies (89%) used isotope dilution mass spectrometry (IDMS) standardized creatinine

Table 1: In- and exclusion criteria per study and access to specialist nephrology care.

Study	Country	Region	N	Inclusion criteria	Exclusion criteria	Enroll period	Access to specialist
	Belgium	Ghent	557	Willing to participate in biobanking	Recent AKI, acute CV event, Infection	2008-2012	open access
	Cyprus	Nicosia	104	CKD patients(>=3 m)	Malignancy , Inflammation, Major CV event (<3 m)	2012-2013	open access
CIC	Italy	Rome	3008	All consecutive patients with >=1 creatinine	None	2001-2015	open access
MAURO		Multiple [1]	759	Age 18-75 years >= 2 x creatinine >1.5 & <4.0 mg/dL (men) >1.3 & <3.5 mg/dL (women) albuminuria >30 mg/24 hours	AKI /rapidly evolving renal disease, transplant, pregnancy, cancer/terminal patients	2005-2008	open access
PIRP		Emilia Romagna	18244	All consecutive referred patients	Subjects with RRT or AKI	2005-2015	gatekeeper
TABLE		Multiple[2]	1184	All consecutive patients with eGFR<60 ml/min/1.73m^2 (>3 m)	Change in GFR >30% (<6m) First visit < 1 year	2000-2005	gatekeeper
PECERA	Spain	Valencia	995	CKD stage 4-5 not on dialysis Life expectancy >1 year Informed consent"	Kidney transplant, AKI, wasting disease, malignancy, incapacitating disease, active infection/inflammation	2006-2009	gatekeeper
CRISIS	UK	Manches-ter	2649	10 < eGFR ≤60 ml/min/1.73m^2	AKI, Previous RRT	2002-2013	gatekeeper
LACKABO		London	271	serum creatinine >150micromol/L (men) >130micromol/L (women)	Subjects with RRT or AKI	2006-2008	gatekeeper

N=number of patients included in study. AKI= acute kidney insufficiency, CV=cardiovascular. [1] MAURO patients included in 21 centers: 17 in Calabria, 3 in Sicily, 1 in Puglia and 1 in Sardinia. [2]TABLE patients included in 25 centers: the majority of these centers are located in south Italy, surrounding Naples and further south, 1 from Verona, 1 from Pisa, 1 from Chieti, 3 from Sicily. Open access= no referral by general practitioner (GP), gatekeeper= referral by GP required.

Table 2: Population characteristics by study.

Countries	**Belgium**	**Cyprus**	**Italy**				**Spain**	**UK**	
Studies	**Ghent**	**Nicosia**	**CIC**	**MAURO**	**PIRP**	**TABLE**	**PECERA**	**CRISIS**	**LACKABO**
N	403	70	1420	719	11277	1031	939	2049	218
Median age, years	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)
Males, %	61.0	71.4	58.6	59.1	64.6	57.3	60.4	61.6	72.0
Diabetes, %	35.7	60.0	36.6	34.9	36.6	26.8	35.9	32.3	20.2
Missing DM, %	*0.0*	*0.0*	*0.0*	*0.0*	*0.0*	*0.0*	*0.0*	*3.8*	*0.0*
Hypertension, %	48.4*	98.6	n/a	94.4	97.8	97.1	91.4	95.9	83.9
Missing HT, %	*0.0*	*0.0*	*100.0*	*0.0*	*0.0*	*0.0*	*0.0*	*0.0*	*0.0*
Obesity, %	34.8	61.4	n/a	31.9	24.0	25.7	30.9	n/a	26.4
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	n/a	12.5	9.5	9.5	11.3	12.6	13.8
Ex-smokers,%	40.5	25.7	n/a	37.1	41.7	22.9	34.0	53.4	30.7
Missing smoking, %	*2.0*	*0.0*	*100.0*	*0.0*	*29.1*	*0.0*	*0.0*	*4.1*	*0.0*
ARB use, %	n/a	75.7	n/a	41.2	37.5	25.2	55.0	26.5	40.8
ACEi use, %	n/a	48.6	n/a	65.7	40.8	52.6	33.0	43.4	50.9
Missing med, %	*100.0*	*0.0*	*100.0*	*5.6*	*0.0*	*0.0*	*0.0*	*0.9*	*0.0*

Table 2: (continued).

Baseline eGFR in ml/min/1.73m²									
Mean CKD-EPI (SD)	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)
Baseline eGFR categories, %									
45-59	29.3	41.4	21.8	19.9	12.9	17.4	n/a	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
Albuminuria data, %									
normoalbuminuria	51.3	39.1	n/a	18.3	41.0	22.2	14.1	37.8	22.3
microalbuminuria	22.7	33.3	n/a	28.6	36.6	24.5	28.7	29.8	28.9
macroalbuminuria	26.0	27.5	n/a	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 (FU) data									
Median duration FU, years	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)
Start RRT, %	1.0	7.1	n/a	2.4	13.7	37.6	34.5	22.3	18.8
Mortality, %	6.5	5.7	n/a	4.5	20.7	13.4	15.4	27.5	4.6
Missing FU, %	*7.4*	*2.9*	*n/a*	*0.0*	*2.7*	*0.0*	*22.9*	*0.0*	*4.1*

*Hypertension in the Ghent cohort is based on blood pressure alone. DM=diabetes mellitus, BMI=Body mass index , Obesity= BMI>30kg/m², Normoalbuminuria=ACR<30 mg/g or PCR<150 mg/g or proteinuria<150 mg/24h; microalbuminuria: ACR 30-300 mg/g, PCR 150-500 mg/g or proteinuria 150-500 mg/24h; macroalbuminuria: ACR>300 mg/g, PCR >500mg/g or proteinuria>500 mg/24h

Table 2: (continued).

Countries	Belgium	Cyprus	Italy				Spain	UK	
Studies	**Ghent**	**Nicosia**	**CIC**	**MAURO**	**PIRP**	**TABLE**	**PECERA**	**CRISIS**	**LACKABO**
Primary renal disease (%)									
Vascular	27.7	22.9		12.0	59.7	25.0	40.9	25.3	6.1
Diabetic NP	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*

Vascular= Hypertensive + renovascular; NP= nephropathy; Glomerulonephritis= Glomerulonephritis + membranous nephropathy + IgA Nephropathy; Tubule-Interstitial= Pyelonephritis + interstitial + post renal.

measurements, of which one study used IDMS standardized creatinine methods in 79% of included patients.

CKD outcomes

We assessed CKD progression using a joint model, simultaneously analyzing repeated measures of eGFR progression 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. The results are presented both crude, with the inherent adjustment for baseline eGFR, and adjusted for baseline eGFR, age, sex, PRD, diabetes mellitus, hypertension, obesity and smoking. The adjustment for presence of albuminuria and ARB/ACEi use are presented in the appendix.

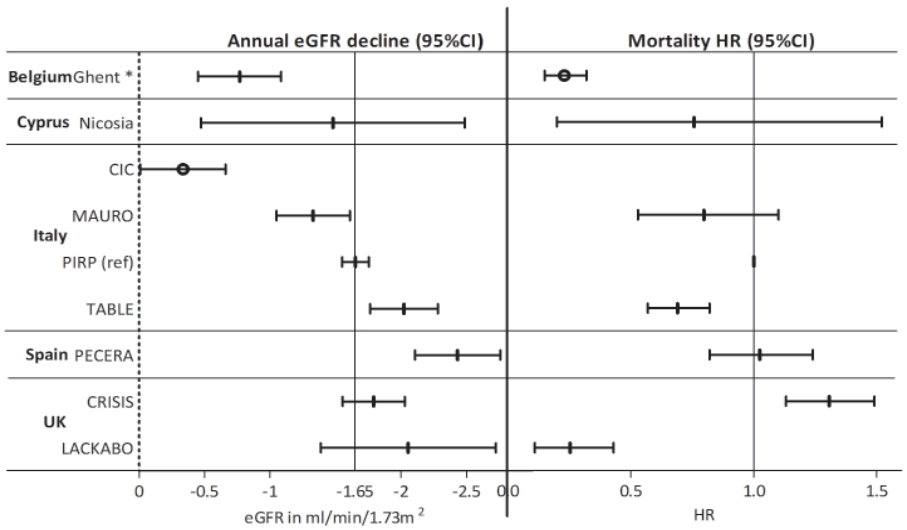
Survival analysis

Figure 1 and table 3 show the crude and adjusted mortality hazard ratios (HR) and their 95% confidence intervals (95% CI), where the PIRP cohort served as the reference (chosen based on population size). The crude HR varied from 0.08 (0.04-0.16) in the English LACKABO cohort to 1.0 in the reference population, the Italian PIRP cohort. The adjusted HR varied from 0.22 (95%CI 0.11-0.43) in the LACKABO cohort to 1.30 (95%CI 1.13-1.49) in the CRISIS cohort. The HR additionally adjusted for ACEi and ARB use, indicating the impact of ACEi/ARB use in the causal pathway between cohort and CKD outcome, is presented in table 1 of the appendix. It ranged from 0.21 (95%CI 0.11-0.41) in the LACKABO cohort to 1.11 (95%CI 0.96-1.27) in the CRISIS cohort.

eGFR decline

Figure 1 and table 4 show the crude and adjusted mean annual eGFR decline by study including the 95%CI. The adjusted mean annual eGFR decline varied from 0.77 (95%CI 0.45-1.08) ml/min/1.73m^2 in the Belgium cohort to 2.43 (95%CI 2.11-2.75) ml/min/1.73m^2 in the Spanish PECERA cohort. In appendix table 2, the eGFR decline additionally adjusted for ACEi and ARB use is shown, which ranged from 1.19 (95%CI 0.90-1.47) in the Italian MAURO cohort to 2.45 (95%CI 2.12-2.77) ml/min/1.73m^2 in the PECERA cohort.

Figure 1: Forest plot of adjusted mean annual eGFR decline in ml/min/1.73m^2 and adjusted mortality hazard ratio by study.



The Italian PIRP cohort is the reference group. |= adjusted for baseline eGFR, age, sex, PRD, co-morbidities and smoking (model 5), Θ = only adjusted for age and sex. The hazard ratio for the Italian CIC cohort is not shown as they did not provide data on follow up status.

Table 5 presents the eGFR decline for the subgroups by age group, sex and presence of diabetes mellitus. The age group analysis showed faster eGFR decline in the younger age group as compared to patients older than 65 years in all cohorts, except the LACKABO cohort. In this cohort there was no difference in eGFR decline between the two age groups. Overall eGFR decline was slower in females as compared to males. In patients with diabetes mellitus, mean annual eGFR decline was faster as compared to patients without diabetes mellitus in all cohorts.

We performed sensitivity analysis in three separate groups, for which the mean annual eGFR decline including 95%CI are all presented in the appendix. Appendix table 3 shows the results for patients with available baseline albuminuria measurements. Importantly, the correction for baseline albuminuria only slightly changed the rate of eGFR decline. Appendix table 4 shows the results for patients with at least three creatinine measurements. In contrast to the main analysis, in which all cohorts were analyzed in one model, we additionally performed a joint model analysis for each cohort separately (appendix table 5), to show the eGFR decline independent of the other cohorts. Overall the results from the sensitivity subgroup analyses were in line with the results of the main analysis.

DISCUSSION

In this prospective cohort analysis including individual data of 27,771 CKD patients from five European countries, outcomes in CKD patients varied significantly between European outpatient nephrology studies, while taking into account the effect of eGFR change on mortality risk and vice versa. The variation in CKD outcomes persisted despite adjustment for other factors associated with CKD progression, such as baseline eGFR, age, sex, presence of albuminuria, diabetes mellitus, hypertension, obesity, smoking, PRD and medication use. The slowest eGFR decline was seen in the Belgium cohort. In addition, the mortality and initiation of RRT were very low in this cohort, suggesting that these Belgium CKD patients had an excellent prognosis for both renal and overall survival. The fastest eGFR decline was seen in the Spanish PECERA and the English LACKABO cohort. 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. The patients from the Spanish PECERA study had a relative high mortality and RRT initiation. However, since the PECERA cohort solely included CKD stage four and five, it is likely that this comparison is biased by the initial low eGFR as it is impossible to fully correct for baseline eGFR in this situation.

Previous studies have shown that younger age, male sex and the presence of diabetes mellitus are associated with more rapid CKD progression (11, 28, 29). Despite the adjustment for several important predictors of CKD progression and mortality risk, our results of the subgroup analysis confirm these associations. Our fully adjusted subgroup analysis revealed that younger patients had faster eGFR decline as compared to patients aged 65 years and older in all cohorts except for the English LACKABO cohort, were there was no difference between the age groups. Moreover, faster decline was present in males and diabetics as compared to females and patients without diabetes across all cohorts. 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.

Although we aimed to include comparable CKD cohorts, the exclusion criteria between the individual studies varied. This could have resulted in the selection of healthier patients in some studies compared to studies without additional exclusion criteria. Across studies with identical exclusion criteria the adjusted eGFR decline varied from 1.65 (95%CI 1.55-1.75) in the PIRP cohort to 2.05 (95%CI 1.39-2.72) ml/min/1.73m^2/year in the LACKABO cohort and the adjusted mortality rate varied from 0.22 (95%CI 0.11-0.43) in the LACKABO cohort to 1.30 (95%CI 1.13-1.49) in the CRISIS cohort.

As the cohorts are included from all over Europe it is likely that interregional differences have contributed to the observed differences in CKD outcomes. We will discuss the

Table 3: Hazard ratio (95%CI) for mortality with PIRP cohort as reference group.

Countries	Belgium	Cyprus	Italy				Spain	UK	
Studies	**Ghent**	**Nicosia**	**CIC**	**MAURO**	**PIRP**	**TABLE**	**PECERA**	**CRISIS**	**LACKABO**
N	323	70	1420	719	11277	1031	939	2049	218
model 1	0.20 (0.14-0.30)	0.52 (0.19-1.44)	n/a	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)	n/a	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)	n/a	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)	n/a	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)	n/a	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)

Table 4: Mean annual eGFR decline in ml/min/1.73 m² (95%CI) by study.

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)	n/a	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)	n/a	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)	n/a	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)

Model 1= Crude*(adjusted for baseline eGFR by use of random intercept)
Model 2= age & sex adjusted
Model 3= 2+PRD
Model 4= 3 +comorbidities (diabetes, hypertension and obesity)
Model 5= 4+ smoking

Table 5: Mean annual adjusted eGFR decline in ml/min/1.73 m² (95%CI) by subgroup.

Coun-tries	Belgium	Cyprus	Italy				Spain	UK	
Studies	**Ghent**	**Nicosia**	**CIC[1]**	**MAURO**	**PIRP**	**TABLE**	**PECERA**	**CRISIS**	**LACKABO**
<=65	0.88 (0.40-1.37)	1.85 (+1.10- -4.80)	n/a	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	0.84 (0.28-1.39)	1.20 (+1.92- -4.33)	n/a	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)	n/a	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)	n/a	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)

[1]The results for the CIC cohort are presented crude. All other results are adjusted for: baseline eGFR, age, sex, PRD, diabetes mellitus, hypertension, obesity and smoking status. . '+' eGFR increase instead of decline. DM= Diabetes mellitus.

possible influence of such factors starting with the regional population health, then the selection of patients who receive 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 (30). Hence it is likely that variation 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 Italy, for example, there is a distinct north-south economic and social disparity, in favor of the north, resulting in an overall better population health in northern compared to southern Italy (31). In contrast, the mortality rate in the TABLE study from southern Italy was relatively low as compared to the reference PIRP cohort from northern Italy. This counterintuitive association between regions with low socioeconomic status and CKD patients with low mortality could perhaps be the result of different barriers to either receive specialist nephrology care or adhere to their therapeutic prescriptions for socially deprived patients.

In the two English cohorts, the observed differences in mortality risk did seem to reflect previously reported differences in population health (32, 33). The adjusted mortality hazard ratio varied from 0.22 (95%CI 0.11-0.43) in the London based LACKABO study to 1.30 (95%CI 1.13-1.49) in the CRISIS study. The CRISIS cohort is set in the North West of England, where social deprivation and mortality are reported to be relatively high (32). The population of London is ethnically diverse (34), which corresponds to the high percentage of ethnic minorities in the LACKABO cohort (28%). Previously, Barbour et al. reported rapid eGFR decline rates and low mortality in Asian CKD patients as compared to Caucasian CKD patients (35). Similarly, Dreyer et al. reported faster eGFR decline in diabetic CKD patients in South Asian and Black ethnicities as compared to whites (36). Hence, it is possible that both the relative 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 in- and exclusion criteria, there is 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 (37), i.e. patients do not need a referral from a general practitioner (GP). Without a GP referral, there is no selection based on rate of eGFR decline or at risk patients and thus more healthy patients have access to specialist care.

This may have contributed to the slow eGFR decline and low mortality we observed in the Belgium study. A slow eGFR decline was not only seen in the Belgium cohort, but also in the other cohorts with open access, i.e. the Cypriot (38), CIC and MAURO cohort.

In Italy, Spain and England, access to specialists care is in principle limited to patients with a referral from their general practitioner, i.e. gatekeeper system (31, 39, 40). 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 (31). Specific data for specialists care in nephrology are not available. Among the Italian cohorts in the present study, PIRP and TABLE included only referred patients, while MAURO and CIC also allowed open access to patients. This might have contributed to the large variability in eGFR decline and mortality observed in these Italian cohorts.

In the English and Spanish cohorts, patients did need a referral to visit specialist nephrology outpatient clinics and both countries had referral criteria in place during (part of) the study enrollment period. In the UK, the Royal College of Physicians published referral criteria for CKD patients in 2005 (41) and in Spain the Spanish Society of Nephrology published these in 2008 (42). Overall, the national referral criteria are quite similar and CKD patients with eGFR below 30 ml/min/1.73m^2 required referral in both countries. This may perhaps partly explain the relative small variation in eGFR decline across the Spanish and English populations. eGFR decline varied from 1.79 (95%CI 1.55-2.03) in the English CRISIS study to 2.43 (95%CI 2.11-2.75) ml/min/1.73m^2/year in the Spanish PECERA study.

CKD management

CKD management can influence the rate of eGFR decline and mortality risk (11, 43). For instance, multiple studies have shown that treatment with ACEi /ARB can reduce proteinuria, lower blood pressure and slow CKD progression (44, 45). Consequently, the observed difference in baseline ARB and ACEi 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 ARB/ACEi use, as treatment differences reflect current regional practice. Moreover, CKD management, for example through ARB/ACEI medication is in the causal pathway between study cohort and CKD outcome and we only analyzed this to assess to what extent differences in CKD outcomes were mediated through ARB/ACEi use. The adjustment for ACEi/ARB use in our model only slightly reduced eGFR decline in four studies and had no impact on the other studies, indicating that treatment differences with ACEi and ARB medication did not explain the variation 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 analysis of subjects with a minimum of three creatinine measurements, as compared to the required two measurements in the main analysis. Moreover, the joint model corrects for the association between change in eGFR and mortality and the potential bias related to this association. Other strengths of our study include the big sample size and various adjustments for several important factors including age, sex, baseline eGFR, albuminuria, PRD and presence of diabetes, hypertension and obesity, 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 measures of albuminuria. A limitation of any observational study is that no etiological 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 may have influenced the observed CKD outcomes.

CONCLUSION

We observed clinically relevant variation in outcomes in CKD patients from outpatient nephrology clinics across European regions. Apart from the very slow decline in the Belgium cohort, adjusted mean annual eGFR decline varied only slightly across the other cohorts. In contrast, we did find marked differences in mortality risk across the cohorts. Although we corrected for many important confounders, including albuminuria and comorbidity, it is likely that unmeasured confounders contributed to the observed mortality differences. This paper is a first step in identifying regional healthcare 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.

APPENDIX Table 1: Hazard ratio (95%CI) for mortality with PIRP cohort as reference group.

Countries	Belgium	Cyprus	Italy				Spain	UK	
Studies	Ghent	Nicosia	CIC	MAURO	PIRP	TABLE	PECERA	CRISIS	LACKABO
N	323	70	1420	719	11277	1031	939	2049	218
model 1	0.20 (0.14-0.30)	0.52 (0.19-1.44)	n/a	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)	n/a	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)	n/a	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)	n/a	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)	n/a	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)
model 6	n/a	0.58 (0.21-1.59)	n/a	0.78 (0.54-1.11)	ref.	0.61 (0.51-0.74)	1.01 (0.83-1.24)	1.11 (0.96-1.27)	0.21 (0.11-0.41)

n/a= not available, ref.=reference group, <events= too few events to present adjusted HR.
Model 1= Crude*(adjusted for baseline eGFR by use of random intercept)
Model 2= age & sex adjusted
Model 3= 2+ PRD
Model 4= 3 + comorbidities (diabetes, hypertension and obesity)
Model 5= 4+ smoking
Model 6= 5 + ARB/ACEi use

APPENDIX Table 2: Mean annual eGFR decline in ml/min/1.73 m² (95%CI) by study.

Countries	Belgium	Cyprus	Italy				Spain	UK	
Studies	**Ghent**	**Nicosia**	**CIC**	**MAURO**	**PIRP**	**TABLE**	**PECERA**	**CRISIS**	**LACKABO**
N	323	70	1420	719	11277	1031	939	2049	218
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)	n/a	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)	n/a	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)	n/a	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)
model 6	n/a	1.42 (0.44-2.41)	n/a	1.19 (0.90-1.47)	1.58 (1.48-1.69)	2.02 (1.76-2.29)	2.45 (2.12-2.77)	1.78 (1.53-2.03)	1.96 (1.29-2.62)

Model 1= Crude*(adjusted for baseline eGFR by use of random intercept)
Model 2= age & sex adjusted
Model 3= 2+ PRD
Model 4= 3 + comorbidities (diabetes, hypertension and obesity)
Model 5= 4+ smoking
Model 6= 5 + ARB/ACEi use

APPENDIX Table 3:Mean annual eGFR decline in ml/min/1.73 m² (including 95% confidence interval) by study. All subjects with available baseline albuminuria measurement, irrespective of initial CKD stage or number of creatinine measurements.

Countries	Belgium	Cyprus	Italy				Spain	UK	
Studies	**Ghent**	**Nicosia**	**CIC**	**MAURO**	**PIRP**	**TABLE**	**PECERA**	**CRISIS**	**LACKABO**
N	437	103		677	881	1076	886	1995	134
model 1	0.88 (0.49-1.27)	2.42 (1.42-3.42)	n/a	1.37 (0.96-1.79)	0.92 (0.61-1.24)	1.99 (1.59-2.39)	2.32 (1.85-2.79)	1.93 (1.57-2.30)	1.91 (1.01-2.82)
model 2	0.87 (0.47-1.26)	2.46 (1.46-3.46)	n/a	1.37 (0.95-1.79)	0.99 (0.68-1.31)	2.06 (1.65-2.47)	2.48 (2.00-2.95)	1.95 (1.58-2.31)	1.92 (1.04-2.80)
model 3	1.04 (0.66-1.43)	2.62 (1.63-3.61)	n/a	1.30 (0.89-1.71)	1.09 (0.89-1.40)	2.01 (1.61-2.41)	2.27 (1.80-2.74)	2.03 (1.67-2.39)	1.72 (0.85-2.59)
model 4a	1.01 (0.63-1.39)	2.36 (1.37-3.35)	n/a	1.28 (0.86-1.71)	1.04 (0.73-1.35)	2.01 (1.62-2.40)	2.29 (1.83-2.76)	2.03 (1.67-2.39)	1.73 (0.86-2.60)
model 5a	1.08 (0.66-1.50)	2.45 (1.47-3.43)	n/a	1.26 (0.83-1.68)	1.02 (0.71-1.34)	2.01 (1.61-2.40)	2.28 (1.82-2.75)	1.97 (1.56-2.38)	1.78 (0.91-2.65)
model 6a	1.04 (0.58-1.49)	2.39 (1.40-3.38)	n/a	1.25 (0.80-1.70)	0.92 (0.56-1.27)	2.00 (1.57-2.43)	2.28 (1.79-2.77)	1.99 (1.55-2.43)	1.76 (0.87-2.64)
model 7a	n/a	2.26 (1.28-3.24)	n/a	1.13 (0.66-1.60)	0.86 (0.48-1.23)	2.04 (1.59-2.48)	2.34 (1.84-2.83)	1.95 (1.47-2.44)	1.71 (0.82-2.60)

Model 1= Crude*(adjusted for baseline eGFR by use of random intercept)
Model 2= age & sex adjusted
Model 3= age, sex & albuminuria
Model 4a= age, sex, albuminuria & PRD
Model 5a= age, sex, albuminuria, PRD and comorbidities (diabetes, hypertension and obesity)
Model 6a= age, sex, albuminuria, PRD, comorbidities & smoking
Model 7a= age, sex, albuminuria, PRD, comorbidities, smoking & ARB/ACEi use

APPENDIX table 4: Mean annual eGFR decline in ml/min/1.73 m² (95%CI) by study. Only included subject with minimum of 3 creatinine measurements.

Countries	Belgium	Cyprus	Italy				Spain	UK	
Studies	**Ghent**	**Nicosia**	**CIC**	**MAURO**	**PIRP**	**TABLE**	**PECERA**	**CRISIS**	**LACKABO**
Model 1	0.76 (0.50-1.02)	1.78 (0.77-2.78)	0.38 (0.06-0.70)	1.39 (1.13-1.65)	1.58 (1.50-1.66)	2.06 (1.80-2.31)	2.33 (2.01-2.64)	1.89 (1.71-2.07)	2.33 (1.68-2.98)
Model 2	0.73 (0.47-0.99)	1.82 (0.82-2.83)	0.43 (0.11-0.76)	1.25 (0.99-1.52)	1.61 (1.53-1.69)	1.99 (1.74-2.25)	2.37 (2.05-2.69)	1.74 (1.56-1.93)	2.08 (1.43-2.73)
Model 4b	0.69 (0.43- 0.95)	1.39 (0.40-2.38)	n/a	1.30 (1.03-1.57)	1.62 (1.54-1.70)	2.00 (1.75-2.25)	2.43 (2.11-2.74)	1.72 (1.53-1.91)	1.96 (1.30-2.62)
Model 5b	0.82 (0.51- 1.12)	1.42 (0.42-2.41)	n/a	1.27 (1.00-1.54)	1.59 (1.51-1.68)	2.01 (1.75-2.26)	2.41 (2.09-2.72)	1.62 (1.39-1.84)	1.82 (1.16-2.47)
Model 6b	0.80 (0.49- 1.11)	1.43 (0.42-2.44)	n/a	1.29 (1.01-1.57)	1.57 (1.47-1.67)	2.04 (1.78-2.30)	2.41 (2.09-2.74)	1.70 (1.46-1.93)	1.85 (1.19-2.52)
Model 7b	n/a	1.37 (0.38-2.35)	n/a	1.21 (0.87-1.44)	1.52 (1.42-1.62)	2.03 (1.77-2.29)	2.43 (2.11-2.75)	1.71 (1.46-1.96)	1.70 (1.05-2.36)

Model 1= Crude*(adjusted for baseline eGFR by use of random intercept)
Model 2= age & sex adjusted
Model 4b= age, sex, & PRD
Model 5b= age, sex, PRD and comorbidities (diabetes, hypertension and obesity)
Model 6b= age, sex, PRD and comorbidities & smoking
Model 7b= age, sex, PRD, comorbidities, smoking & ARB/ACEi use

APPENDIX table 5: Mean annual eGFR decline in ml/min/1.73 m² (95%CI), CKD stage 3-5 analyzed separate by study

Countries	Belgium	Cyprus	Italy				Spain	UK	
Studies	**Ghent**	**Nicosia**	**CIC[1]**	**MAURO**	**PIRP**	**TABLE**	**PECERA**	**CRISIS**	**LACKABO**
Model 1	0.79 (0.53- 1.04)	1.98 (0.85-3.11)	0.61 (0.25-0.97)	1.37 (1.08-1.66)	1.64 (1.56-1.73)	1.81 (1.48-2.14)	3.10 (2.71-3.49)	2.00 (1.80-2.20)	2.52 (1.54-3.50)
Model 2	0.83 (0.57-1.08)	2.23 (1.04-3.42)	0.64 (0.28-1.00)	1.36 (0.99-1.73)	1.60 (1.51-1.68)	1.84 (1.49-2.19)	3.24 (2.84-3.64)	1.75 (1.51-1.99)	2.14 (0.91-3.37)
Model 4b	0.78 (0.50-1.06)	0.78 (+0.94- -2.50)	n/a	1.29 (0.80-1.77)	1.66 (1.58-1.75)	1.98 (1.69-2.26)	3.35 (2.94-3.76)	1.72 (1.47-1.97)	3.71 (1.33-6.08)
Model 5b	0.90 (0.54-1.25)	1.30 (+0.07- -2.67)	n/a	1.26 (0.77-1.75)	1.66 (1.57-1.75)	2.17 (1.89-2.44)	3.23 (2.82-3.64)	1.69 (1.43-1.95)	3.82 (1.40-6.23)
Model 6b	0.87 (0.51-1.23)	1.23 (+0.20- -2.65)	n/a	1.28 (0.79-1.77)	1.64 (1.53-1.74)	n/a	3.24 (2.83-3.65)	1.68 (1.42-1.94)	3.87 (1.48-6.27)

[1]The results for the CIC cohort are results of initial model as no events available to run adjustment for mortality risk. '+' eGFR increase instead of decline.

Model 1= Crude*(adjusted for baseline eGFR by use of random intercept)
Model 2= age & sex adjusted
Model 4b= age, sex, & PRD
Model 5b= age, sex, PRD and comorbidities (diabetes, hypertension and obesity)
Model 6b= age, sex, PRD and comorbidities & smoking

REFERENCES

1. Collaborators GMCoD. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015;385(9963):117-71.
2. Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, de Jong PE, et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a colla borative meta-analysis. Lancet. 2010;375(9731):2073-81.
3. Gansevoort RT, Correa-Rotter R, Hemmelgarn BR, Jafar TH, Heerspink HJ, Mann JF, et al. Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention. Lancet. 2013;382(9889):339-52.
4. Bruck K, Stel VS, Gambaro G, Hallan S, Volzke H, Arnlov J, et al. CKD Prevalence Varies across the European General Population. Journal of the American Society of Nephrology: JASN. 2015.
5. De Nicola L, Zoccali C. Chronic kidney disease prevalence in the general popula-tion: heterogeneity and concerns. Nephrol Dial Transplant. 2016;31(3):331-5.
6. Pippias M, Jager KJ, Kramer A, Leivestad T, Sanchez MB, Caskey FJ, et al. The changing trends and outcomes in renal replacement therapy: data from the ERA-EDTA Registry. Nephrol Dial Transplant. 2016;31(5):831-41.
7. Aitken GR, Roderick PJ, Fraser S, Mindell JS, O'Donoghue D, Day J, et al. Change in prevalence of chronic kidney disease in England over time: comparison of nationally representative cross-sectional surveys from 2003 to 2010. BMJ open. 2014;4(9):e005480.
8. Girndt M, Trocchi P, Scheidt-Nave C, Markau S, Stang A. The Prevalence of Renal Failure. Deutsches Arzteblatt international. 2016;113(6):85-91.
9. Jones C, Roderick P, Harris S, Rogerson M. Decline in kidney function before and after nephrology referral and the effect on survival in moderate to advanced chronic kidney disease. Nephrol Dial Transplant. 2006;21(8):2133-43.
10. de Goeij MC, Liem M, de Jager DJ, Voormolen N, Sijpkens YW, Rotmans JI, et al. Proteinuria as a risk marker for the progression of chronic kidney disease in patients on predialysis care and the role of angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker treatment. Nephron Clinical practice. 2012;121(1-2):c73-82.
11. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney IntSuppl. 2013;3.
12. Naimark DM, Grams ME, Matsushita K, Black C, Drion I, Fox CS, et al. Past Decline Versus Current eGFR and Subsequent Mortality Risk. Journal of the American Society of Nephrology : JASN. 2015.
13. Crowther MJ, Abrams KR, Lambert PC. Flexible parametric joint modelling of longitudinal and survival data. Statistics in medicine. 2012;31(30):4456-71.
14. Wulfsohn MS, Tsiatis AA. A joint model for survival and longitudinal data measured with error. Biometrics. 1997;53(1):330-9.
15. Asar O, Ritchie J, Kalra PA, Diggle PJ. Joint modelling of repeated measurement and time-to-event data: an introductory tutorial. International journal of epidemiology. 2015;44(1):334-44.
16. Vonesh EF, Greene T, Schluchter MD. Shared parameter models for the joint analysis of longitudinal data and event times. Statistics in medicine. 2006;25(1):143-63.
17. Boucquemont J, Heinze G, Jager KJ, Oberbauer R, Leffondre K. Regression methods for investigating risk factors of chronic kidney disease outcomes: the state of the art. BMC nephrology. 2014;15:45.
18. Powe NR. Early referral in chronic kidney disease: an enormous opportunity for prevention. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2003;41(2):505-7.
19. Hallan SI, Ovrehus MA, Romundstad S, Rifkin D, Langhammer A, Stevens PE, et al. Long-term trends in the prevalence of chronic kidney disease and the influence of cardiovascular risk factors in Norway. Kidney international. 2016.
20. Bruck K, Jager KJ, Dounousi E, Kainz A, Nitsch D, Arnlov J, et al. Methodology used in studies reporting chronic kidney disease prevalence: a systematic literature review. Nephrol Dial Transplant. 2016;31(4):680.
21. D'Hoore E, Neirynck N, Schepers E, Vanholder R, Verbeke F, Van Thielen M, et al. Chronic kidney disease progression is mainly associated with non-recovery of acute kidney injury. Journal of nephrology. 2015;28(6):709-16.
22. Stel VS, Ioannou K, Bruck K, Dounousi E, Pappas K, Siamopoulos KC, et al. Longitudinal association of body mass index and waist circumference with left ventricular mass in hypertensive predialysis chronic kidney disease patients. Nephrol Dial Transplant. 2013;28 Suppl 4:iv136-45.
23. Leonardis D, Mallamaci F, Enia G, Postorino M, Tripepi G, Zoccali C. The MAURO study: baseline characteristics and compliance with guidelines targets. Journal of nephrology. 2012;25(6):1081-90.
24. Gibertoni D, Mandreoli M, Rucci P, Fantini MP, Rigotti A, Scarpioni R, et al. Excess mortality attributable to chronic kidney disease. Results from the PIRP project. Journal of nephrology. 2015.
25. De Nicola L, Minutolo R, Chiodini P, Borrelli S, Zoccali C, Postorino M, et al. The effect of increasing age on the prognosis of non-dialysis patients with chronic kidney disease receiving stable nephrology care. Kidney international. 2012; 82(4): 482-8.
26. Hoefield RA, Kalra PA, Baker P, Lane B, New JP, O'Donoghue DJ, et al. Factors associated with kidney disease progression and mortality in a referred

CKD population. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2010;56(6):1072-81.
27. Caplin B, Nitsch D, Gill H, Hoefield R, Blackwell S, MacKenzie D, et al. Circulating methylarginine levels and the decline in renal function in patients with chronic kidney disease are modulated by DDAH1 polymorphisms. Kidney International. 2010;77(5):459-67.
28. Eriksen BO, Tomtum J, Ingebretsen OC. Predictors of declining glomerular filtration rate in a population-based chronic kidney disease cohort. Nephron Clinical practice. 2010;115(1):c41-50.
29. 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. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2008;52(4):661-71.
30. van Dijk PC, Zwinderman AH, Dekker FW, Schon S, Stel VS, Finne P, et al. Effect of general population mortality on the north-south mortality gradient in patients on replacement therapy in Europe. Kidney international. 2007;71(1):53-9.
31. Ferre F, de Belvis AG, Valerio L, Longhi S, Lazzari A, Fattore G, et al. Italy: health system review. Health systems in transition. 2014;16(4):1-168.
32. Eames M, Ben-Shlomo Y, Marmot MG. Social deprivation and premature mortality: regional comparison across England. BMJ (Clinical research ed). 1993;307(6912):1097-102.
33. Udayaraj UP, Ben-Shlomo Y, Roderick P, Casula A, Ansell D, Tomson CR, et al. Socio-economic status, ethnicity and geographical variations in acceptance rates for renal replacement therapy in England and Wales: an ecological study. Journal of epidemiology and community health. 2010;64(6):535-41.
34. White E. Ethnicity and National Identity in England and Wales: 2011. In: Statistics OfN, editor. 2012.
35. Barbour SJ, Er L, Djurdjev O, Karim M, Levin A. Differences in progression of CKD and mortality amongst Caucasian, Oriental Asian and South Asian CKD patients. Nephrol Dial Transplant. 2010;25(11):3663-72.
36. Dreyer G, Hull S, Mathur R, Chesser A, Yaqoob MM. Progression of chronic kidney disease in a multi-ethnic community cohort of patients with diabetes mellitus. Diabetic medicine : a journal of the British Diabetic Association. 2013;30(8):956-63.
37. Gerkens S, Merkur S. Belgium: Health system review. Health systems in transition. 2010;12(5):1-266, xxv.
38. Theodorou M, Charalambous C, Petrou C, Cylus J. Cyprus health system review. Health systems in transition. 2012;14(6):1-128.
39. Boyle S. United Kingdom (England): Health system review. Health systems in transition. 2011;13(1):1-483, xix-xx.

40. Garcia-Armesto S, Begona Abadia-Taira M, Duran A, Hernandez-Quevedo C, Bernal-Delgado E. Spain: Health system review. Health systems in transition. 2010;12(4):1-295, xix-xx.
41. Burden R, Tomson C. Identification, management and referral of adults with chronic kidney disease: concise guidelines. Clinical medicine (London, England). 2005;5(6):635-42.
42. Gorostidi M, Santamaria R, Alcazar R, Fernandez-Fresnedo G, Galceran JM, Goicoechea M, et al. Spanish Society of Nephrology document on KDIGO guidelines for the assessment and treatment of chronic kidney disease. Nefrologia : publicacion oficial de la Sociedad Espanola Nefrologia. 2014;34(3):302-16.
43. Su X, Zhang L, Lv J, Wang J, Hou W, Xie X, et al. Effect of Statins on Kidney Disease Outcomes: A Systematic Review and Meta-analysis. American journal of kidney diseases. 2016;67(6):881-92.
44. Molnar MZ, Kalantar-Zadeh K, Lott EH, Lu JL, Malakauskas SM, Ma JZ, et al. Angiotensin-converting enzyme inhibitor, angiotensin receptor blocker use, and mortality in patients with chronic kidney disease. Journal of the American College of Cardiology. 2014;63(7):650-8.
45. Ripley E. Complementary effects of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in slowing the progression of chronic kidney disease. American heart journal. 2009;157(6 Suppl):S7-s16.
46. Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia. Geneva Switzerland: World Health Organization, 2006.
47. Levey AS, Coresh J, Greene T, Marsh J, Stevens LA, Kusek JW, et al. Expressing the Modification of Diet in Renal Disease Study equation for estimating glomerular filtration rate with standardized serum creatinine values. Clinical chemistry. 2007;53(4):766-72.
48. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, III, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604-12.
49. Moody WE, Chue CD, Inston NG, Edwards NC, Steeds RP, Ferro CJ, et al. Understanding the effects of chronic kidney disease on cardiovascular risk: are there lessons to be learnt from healthy kidney donors? Journal of human hypertension. 2012;26(3):141-8.