Article:
Stamellou, E., Saritas, T., Froissart, M. et al. (6 more authors) (2024) Identifying individuals at risk of needing CKD associated medications in a European kidney disease cohort. BMC Nephrology, 25 (1). 60. ISSN 1471-2369

https://doi.org/10.1186/s12882-024-03497-y

BMC Nephrology

RESEARCH

Open Access

Identifying individuals at risk of needing CKD associated medications in a European kidney disease cohort

Eleni Stamellou[1,2*], Turgay Saritas[1], Marc Froissart[3], Florian Kronenberg[4], Peter Stenvinkel[5], David C. Wheeler[6], Kai-Uwe Eckardt[7], Jürgen Floege[1] and James Fotheringham[8,9]

Abstract

Background The consequences of chronic kidney disease (CKD) can be addressed with a range of pharmacotherapies primarily prescribed by nephrologists. More accurate information regarding future CKD-related pharmacotherapy requirements could guide clinical decisions including follow-up frequency.

Methods Following assignment to derivation and validation groups (2,1), variables predicting individually future use of vitamin D receptor agonists (VDRA), phosphate binders, erythropoiesis stimulating agents (ESAs) and iron were identified using logistic regression in a prospective cohort study containing demography, comorbidity, hospitalization, laboratory, and mortality data in patients with CKD stage G4/G5 across six European countries. Discriminative ability was measured using C-statistics, and predicted probability of medication use used to inform follow-up frequency.

Results A total of 2196 patients were included in the analysis. During a median follow-up of 735 days 648 initiated hemodialysis and 1548 did not. Combinations of age, diabetes status and iPTH, calcium, hemoglobin and serum albumin levels predicted the use of ESA, iron, phosphate binder or VDRA, with C-statistics of 0.70, 0.64, 0.73 and 0.63 in derivation cohorts respectively. Model performance in validation cohorts were similar. Sixteen percent of patients were predicted to have a likelihood of receiving any of these medications of less than 20%.

Conclusions In a multi-country CKD cohort, prediction of ESA and phosphate binder use over a two-year period can be made based on patient characteristics with the potential to reduce frequency of follow-up in individuals with low risk for requiring these medications.

Keywords CKD G4/G5, CKD-MBD, Renal anemia, ESAs, VDRA, Phosphate binders

*Correspondence:
Eleni Stamellou
stamellou.eleni@gmail.com
Full list of author information is available at the end of the article

Background

Chronic kidney disease (CKD) is a major public health problem associated with poor quality of life, and high morbidity and mortality rate [1]. Despite improvements in dialysis care, the mortality of patients treated by dialysis remains unacceptably high. Suboptimal care during CKD stages G4/CKD G5ND may contribute to this, as it has been shown that longer duration of specialized nephrology care prior to transition to chronic dialysis, is associated with significantly better outcomes [2, 3]. CKD care includes management for anemia and disturbances of bone mineral metabolism (CKD associated bone mineral disease; CKD-MBD). These conditions are common in patients with advanced CKD and are associated with adverse clinical outcomes, including cardiovascular events, protein energy wasting and death [4–9]. As anemia and CKD-MBD represent modifiable risk factors for cardiovascular and renal disease progression, early recognition and treatment represent a key task for nephrologists [10–14].

Recognizing individuals requiring CKD-related pharmacotherapy in the future helps the nephrologist identify a more severe CKD-phenotype requiring more intensive monitoring, management, or support than CKD severity stratification using eGFR alone. However, no predictive models exist to guide the need or intensity for CKD-related pharmacotherapy. Physicians must therefore make uninformed or inconsistent decisions about which patients to monitor more closely, risking delays in treatment in those who ultimately need a more intense nephrological care, or conducting unnecessary nephrological visits in those who do not need them. More targeted nephrological visits and treatments might reduce the burden of disease and save nephrology resources.

In this study we identified baseline patient characteristics and laboratory values to predict the need for traditionally nephrologist-led pharmacotherapy of renal anemia and CKD-MBD during follow-up, to inform predictive models which could support clinical decision-making. These models identified more severe CKD phenotypes, and conversely enable reduced follow-up frequency in milder CKD phenotypes.

Methods

Study population

The Analyzing Data, recognizing Excellence and Optimizing Outcomes (ARO) cohort III study contains anonymized longitudinal individual-level data for pre-hemodialysis patients (N = 2471) who received predialysis care in Fresenius Medical Care (FMC) facilities across six European countries (Italy; Czech Republic; Serbia; Bosnia; Slovak Republic and Russia) between 2012 and 2014 and who were followed until the end of 2016. Informed consent was obtained from all patients by FMC. Data on demography, comorbidity, laboratory, and outcomes such as dialysis, death and transplantation were captured prospectively in the FMC database. All local ethical and regulatory obligations concerning patient data for each of the 6 participating countries were met. The study has been approved by the institutional review board of the Medical University of Innsbruck (EK-Nr. 1339/2020). Follow-up commenced on the date of patients' first referral to an FMC unit until December 31, 2016. Chronic dialysis was defined as receiving hemodialysis for more than one month.

Follow-up, endpoints and adjustment variables

In the present analysis, patients with CKD stage 4/5 (eGFR < 30 ml/min/1.73m^2), being managed in healthcare systems where their first observation in the dataset represented their first assessment by a nephrologistwere included and were followed-up until they transitioned to chronic hemodialysis or until the end of follow-up (December 2016). Endpoints of interest were medication requirements when patients transitioned to chronic hemodialysis or at the end of follow-up: erythropoiesis stimulating agents (ESAs), iron (both oral and i.v), vitamin D receptor agonists (VDRA) and phosphate binders. Variables included demographic variables, including age (< 49; 50–60; 61–70; 71–80 and > 80 years old), sex (male; female), body mass index (BMI; underweight: < 18.5; normal range: 18.5–25, overweight: 25.01–30; obesity > 30 kg/m^2), smoking (former and current smokers; nonsmokers), country (Italy; Czech Republic; Serbia; Bosnia; Slovak Republic and Russia); and comorbid conditions (diabetes, clinical diagnosis of hypertension, cardiovascular disease, cancer and etiology of kidney disease). Comorbid conditions and medications were categorized as present or absent at the time of the first visit in an FMC unit. Serum laboratory variables included: hemoglobin (categorized as < 100; 100–120; > 120 g/l), serum phosphate (< 0.8; 0.8–1.49; ≥ 1.5 mmol/l), total calcium (< 2.1; 2.1–2.6; > 2.6 mmol/l), intact parathormone (iPTH) (< 149; 150–300; > 300 ng/l) and serum albumin (≤ 35 g/l; > 35). Medications recorded at the initial nephrology visit or when patients transition to hemodialysis or at the end of follow-up were ESAs, iron, VDRA, phosphate binders, diuretics, RAASi and antihypertensives. Glomerular filtration rate was estimated (eGFR) using the Chronic Kidney Disease Epidemiology (CKD-EPI) 2009 creatinine-based equation.

Through consensus among seven independent nephrologists and considering the absence of prior literature on this matter, participants with a than 20% for requiring these medications over the next 20 months risk should be classified as low-risk individuals.

Statistical analysis

Baseline patient characteristics were reported using descriptive statistics. Continuous variables were described using means and standard deviations or median and interquartile range; categorical data were reported as counts and frequencies. Intergroup comparisons were performed using the Pearson *chi-square test, Student's t-test.* Derivation and validation cohorts were assigned randomly with a 2:1 ratio. After excluding all patients receiving the relevant CKD-related pharmacotherapy (ESA, VDRA, phosphate binders), binary logistic regression analyses were employed on the derivation cohort to estimate the associations between baseline characteristics, and individually the future prescription of ESAs, iron (both oral and i.v), VDRA and phosphate binders. While cause-specific Cox models are commonly employed in time to event analyses, they are prone to overestimating risk when censoring for a competing risk (e.g. death) [15], and is recognized as a weakness of some widely adopted risk [16]. Patients who were already under treatment were excluded from the corresponding analysis. The reference values of covariates in our regression model were age: 71–80 years old, male gender, BMI 18.5–25 kg/m^2, non-smokers, diabetes mellitus as primary renal disease, hemoglobin 100–120 g/l, serum total albumin > 35 g/l, serum-calcium 2.1–2.6 mmol/l, serum-phosphate 0.8–1.5 mmol/l, iPTH < 150 ng/l. Backward selection was employed to retain predictive variables ($p < 0.05$) prior to the prediction of individual probabilities of each of the four CKD pharmacotherapies. For the evaluation of our predictive model's discrimination ability, we calculated C-statistics. We inputted the predictor variables into the model and obtained the predicted probabilities for each patient. Values over 0.7 were considered indicative for a good model. Finally, we ran the model to predict any requirement on the above-mentioned medications.

The formulae to calculate the predicted probability of starting treatment

$$F(x) = e^X / e^x + 1$$

Where X is estimated by summing the coefficients associated with the presence or absence of the predictor variables (full equations provided in supplemental materials).

Sensitivity analyses were performed excluding CKD5 patients, but resulted in inferior predictive performance and are not reported. Statistical analysis was performed using SPSS 28.0 and R version 4.1.0. A $p < 0.05$ was considered statistically significant.

Results

Study population

Between April 1, 2012 and June 30, 2014, 2471 patients with eGFR < 30 ml/min/1.73m^2 were recruited. A total of 2196 patients were included in the present analysis. Patients who were transplanted during the pre-dialysis period (n = 9), with < 90 days of follow-up in the pre-dialysis period (n = 173), and who were received temporary dialysis (n = 93) were excluded, as medication requirements were unobserved or changed during follow-up. Of these, 648 patients (29.5%) transitioned to chronic hemodialysis and 1548 did not, while 334 died during a median of 735 days follow-up period (Fig. 1). Among enrolled patients, the mean age was 69 years, and 52% were women. Almost half of the patients had a history of hypertension and one third history of diabetes. Diabetic nephropathy followed by hypertensive nephropathy were

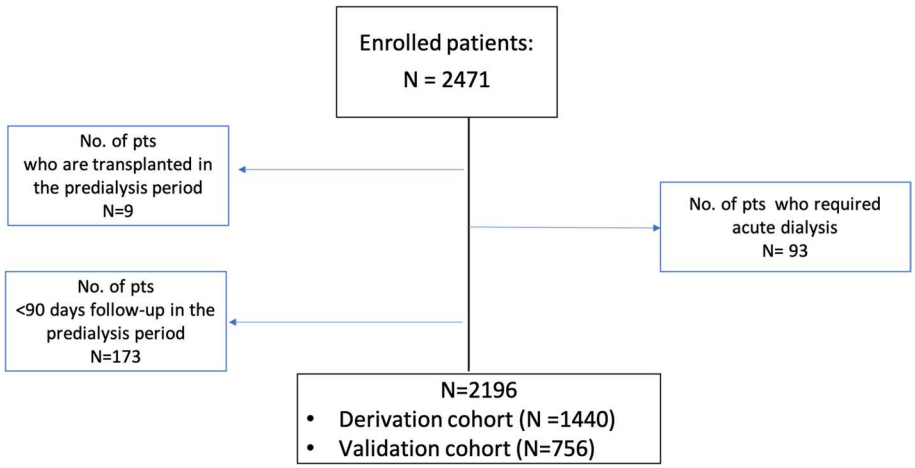

Fig. 1 Study flow chart

the most common causes of CKD. At baseline, eGFR was 18.6 ml/min/1.73m^2. Half of the patients were on a diuretic (51.7%) at referral and 33.7% were on RAASi. The characteristics of the derivation and validation groups are presented in Table 1. The two groups exhibited no significant differences and shared similar traits with the entire cohort. Patient already under treatment with CKD medications at referral displayed lower hemoglobin and eGFR, along with higher phosphate and iPTH (suppl. Table 1).

The association between phenotype, laboratory variables and medication requirements

Following backward selection, independently predictive variables of CKD medications are shown in Table 2. Significant predictors for the prescription of ESAs included VDRA and iron therapy already at referral, hemoglobin levels < 120 g/l and iPTH levels > 150 ng/l (Table 2). Regarding iron therapy, predictors included low eGFR at baseline and treatment with ESAs already at referral. Regarding the route of iron administration, most patients were receiving oral iron at baseline (13.9% oral vs 3.4% IV), with IV iron use increasing at the end of follow-up (15.3% vs 5.8%). In patients transitioning to hemodialysis, intravenous iron therapy was more frequent compared to those staying off hemodialysis (17.4% vs 10.8%). The predictors for prescription of phosphate binders during the follow-up (Table 2) included younger age, serum albumin concentration > 35 g/l, baseline iPTH levels > 150 ng/l and hemoglobin < 120 g/l. Lastly, the prescription of VDRA therapy was associated with a history of diabetes, baseline iPTH > 150 ng/l, serum albumin > 35 g/l, and abnormal calcium levels (≥ 2.6 mmol/L) (Table 2).

The prediction of future medication prescriptions

As depicted in Table 3, the discriminative performance varied across models. Regarding ESAs, both the derivation and validation cohorts exhibited good discrimination, with c-statistics of 0.70 and 0.73, respectively. Similar robustness was observed for phosphate binders, with c-statistics of 0.73 and 0.74, respectively. However, the c-statistics for both the validation and derivation cohorts displayed poor performance for iron and VDRA, yielding values of 0.64 (derivation), 0.63 (validation) and 0.66 (derivation), 0.69 (validation) respectively.

Model performance was assessed within specific patient groups: models for ESAs and iron exhibited a very good discrimination among patients with hemoglobin levels > 100 g/l at referral. Concerning phosphate binders, the c-statistic was 0.76 for patients with phosphate levels < 1.4 mmol/l at referral, and 0.59 for those with phosphate levels > 1.5 mmol/l (suppl. Table 2). Predictive factors for any CKD-related pharmacotherapy were also assessed, however, the model's performance was poor, with a c-statistic of 0.65 and 0.67 respectively (suppl. Table 3 and 4). In our study cohort of CKD G4/5 predialysis patients, these models identified 353 out of 2196 individuals as having a risk of less than 20% risk for any of these medications. Similarly, among CKD G4 patients, we found that 291 out of 1314 exhibited a risk of less than 20%.

Discussion

Our analysis provides a broad overview which patients to follow-up, aiming to reduce delays in treatment in those who ultimately need a more intense nephrological care. To our knowledge, this is the first study to describe the risk factors for initiation of CKD-related pharmacotherapy in pre-dialysis patients. Our aim is with the potential to inform clinical decisions around extending follow-up in individuals with low risk for requiring these medications.

The present study investigated risk factors for future medication use in a cohort of CKD4 patients, with a goal of predicting use of ESAs, iron (both oral and i.v), VDRA and phosphate binders. Age, history of diabetes, iPTH, hemoglobin, calcium and serum albumin levels predicted medication needs. The models showed varying prediction capabilities, which were best for ESAs and phosphate binders. A risk threshold of 20% was agreed to categorize low-risk patients needing these medications, identifying 353 such cases in the cohort.

Our findings shed light on several significant factors that influence the prescription of different medications, providing valuable insights for clinical practice and patient management. In our study, an association was observed between the baseline use of VDRA and increased iPTH levels and the prescription of ESAs. Indeed, several studies have found an association between CKD-MBD parameters and anemia [17, 18]. Together, these findings underscore the importance of monitoring and addressing CKD-MBD to reduce the need for ESAs [19–21].

The findings regarding phosphate binders were particularly intriguing. Older patients (> 60 years) were less likely to receive phosphate binders during follow-up. The relationship between age and serum phosphate levels in adults has been recognized for many years [22]. This age-related decline in serum phosphate levels has been attributed to changes in tubular phosphate reabsorption, which may, in turn, be explained by age-dependent alterations in tubular phosphate handling or in its hormonal regulators [23]. Additionally, another study observed a significant decrease in serum phosphorus levels with age in dialysis patients as well [24, 25]. One possible explanation is that relatively low caloric and protein intake is common among elderly HD patients. This observation

Table 1 Baseline characteristics

	Whole cohort (N = 2196)	Derivation cohort (N = 1440)	Validation cohort (N = 756)
Age at baseline (years)	69 ± 13	68.8 ± 13.2	69.2 ± 13.2
Gender			
Female	1138 (51.8)	745 (51.7)	393 (52.0)
Male	1058 (48.2)	695 (48.3)	363 (48.0)
Body mass index (kg/m^2)	29 ± 5.9	29 ± 5.8	29.1 ± 6.0
missing	*70 (3.2)*	*44 (3.0)*	*26 (3.4)*
Smoking status			
Nonsmoker	1140 (51.9)	761 (52.8)	379 (50.1)
Former	430 (19.6)	275 (19.1)	155 (20.5)
Current	215 (9.8)	141 (9.8)	74 (9.8)
Missing	411 (18.7)	263 (18.3)	148 (19.6)
History of cancer	106 (4.8)	70 (4.9)	36 (4.8)
History of CVD	492 (22.4)	338 (23.5)	154(20.4)
History of diabetes	*772 (35.2)*	*517 (35.9)*	255 (33.7)
History of hypertension	*1022 (46.5)*	*686 (47.6)*	336 (44.4)
Chronic kidney disease etiology			
Hypertensive nephropathy	46 (21.7)	331 (23.0)	145 (19.2)
Glomerulonephritis	146 (6.6)	91 (6.3)	55 (7.3)
Diabetic nephropathy	530 (24.1)	348 (24.2)	182 (24.1)
Tubulo-interstitial	347 (15.8)	224 (15.6)	123 (16.3)
Polycystic kidney disease	84 (3.8)	50 (3.5)	34 (4.5)
Miscellaneous/other	477 (21.7)	313 (21.7)	164 (21.7)
Missing	136 (6.2)	83 (5.8)	53 (7.0)
Country			
Italy	526 (24)	334 (23.2)	192 (25.4)
Czech Republic	706 (32.1)	465 (32.3)	241 (31.9)
Serbia	123 (5.6)	85 (5.9)	38 (5.0)
Bosnia	56 (2.5)	35 (2.4)	21 (2.8)
Slovak Republic	625 (28.5)	412 (28.6)	*213 (28.2)*
Russia	160 (7.3)	109 (7.6)	51 (6.7)
Iron at referral	385 (17.5)	251 (17.4)	134 (17.7)
ESA at referral	285 (13.0)	189 (13.1)	96 (12.7)
VDRA therapy at referral	611 (27.8)	401 (27.8)	210 (27.8)
Phosphate binders at referral	287 (13.1)	189 (13.1)	98 (13.0)
Amount of antihypertensives at referral			
0	989 (45.0)	646 (44.9)	343 (45.4)
1–2	1086 (49.5)	707 (49.1)	379 (50.1)
More than 3	121 (5.4)	87 (6.1)	34 (4.5)
RAASi at referral	739 (33.7)	484 (33.6)	255 (33.7)
Diuretic at referral	1133 (51.6)	756 (52.5)	377 (49.9)
Hemoglobin(g/l)	116 ± 16	116.2 ± 16	116.9 ± 16.8
Missing	*186 (8.5)*	*116 (8.0)*	*70 (9.3)*
Ferritin (μg/l)	276 (139, 524)	271 (142, 504)	280 (136,564)
Missing	822 (37.4)	544 (37.8)	*278 (36.8)*
Transferrin saturation (TSAT)	20.3 (15, 26)	20.0 (15, 26)	21(15, 27)
Missing	*1315 (60.0)*	*860 (60.0)*	*455 (60.2)*
Serum albumin (g/l)	40.6 ± 4.4	40.5 ± 4.5	40.6 ± 4.4
Missing	*482 (21.9)*	*308 (21.4)*	*174 (23.0)*
Total calcium (mmol/l)	2.3 ± 0.18	2.3 ± 0.18	2.3 ± 0.18

Table 1 (continued)

	Whole cohort (N = 2196)	Derivation cohort (N = 1440)	Validation cohort (N = 756)
Missing	*273 (12.4)*	*184 (12.8)*	*89 (11.8)*
Phosphate (mmol/l)	1.3 ± 0.29	1.3 ± 0.28	1.3 ± 0.3
Missing	*285 (13.0)*	*189 (13.0)*	*96 (12.7)*
iPTH (ng/l)	124 (72, 202)	125 (73, 201)	121 (72, 206)
Missing	*479 (21.8)*	*321 (22.3)*	158 (20.9)
eGFR (CKD-EPI)	18.6 ± 6.5	18.5 ± 6.5	18.8 ± 6.5
Missing	*243 (11.0)*	*156 (10.8)*	87 (11.5)
Days of follow-up	*735 (290, 1255)*	*733 (293, 1264)*	752 (283, 1237)

CVD Cardiovascular disease, *RAASi* Renin angiotensin aldosterone system inhibitors, *ESA* Erythropoesis Stimulating Agent, *VDRA* Vitamin D receptor agonists, *iPTH* intact parathormone, *HD* Hemodialysis

Data are expressed as mean ± SD or median, interquartile range as appropriate. Categorical variables are reported using n (%)

Table 2 Multivariate logistic regression of the risk of requiring CKD-related pharmacotherapy during the pre-dialysis period

	P value	OR[a] (95% CI)
Risk for requiring ESAs during the pre-dialysis period		
VDRA at referral	0.052	1.61 (0.99–2.60)
Iron at referral	0.042	1.85 (1.02–3.35)
eGFR at referral	0.026	0.95 (0.92–0.99)
Hemoglobin ref. < 100 g/l	0.053	2.24 (0.99–4.60)
Hemoglobin ref. 100- 120 g/l	0.040	2.18(1.28–3.71)
iPTH ref. > 150 ng/l	0.044	1.66(1.01–2.73)
Risk for requiring iron therapy during the pre-dialysis period		
eGFR ref. (CKD-EPI)	< 0.001	0.93 (0.89–0.97)
ESAs at referral	0.058	2.02 (0.98–4.17)
Risk for requiring phosphate binders during the pre-dialysis period		
Age > 80	0.03	0.20 (0.07–0.58)
Age 50–60	0.09	0.47 (0.18–1.15)
Age 61–70	0.08	0.33 (0.15–0.75)
Age 71–80	0.02	0.28 (0.13–0.64)
iPTH ref. > 150 ng/l	0.03	2.33 (1.33–4.04)
Hemoglobin ref. < 100 g/l	0.009	2.75 (1.29–5.86)
Hemoglobin ref. 100- 120 g/l	0.70	1.13 (0.6–2.09)
Serum albumin > 35 g/l	0.10	2.46 (1.29–5.86)
eGFR ref. (CKD-EPI)	0.05	0.93 (0.90–0.98)
Risk for requiring VDRA during the pre-dialysis period		
History of diabetes	0.025	1.55 (1.06–4.77)
Serum albumin > 35 g/l	0.016	2.40 (1.18–4.91)
Calcium < 2.1 mmol/l	0.189	1.54 (0.81–2.93)
Calcium > 2.6 mmol/l	0.040	2.27 (1.04–4.96)
iPTH > 150 ng/l	< 0.001	3.2 (2.15–4.77)

SESA Erythropoesis Stimulating Agent, *CVD* Cardiovascular disease, *iPTH* intact parathormone, *VDRA* Vitamin D receptor agonists

[a] Odds rations (OR) are computed through binary logistic regression. Reference groups were age < 49, Calcium between 2.1 and 2.6 mmol/l, Parathormone below 150 ng/l, Albumin < 35 g/l, Hemoglobin > 120 g/l

highlights the role of nutritional status in phosphate management. As expected, malnourished patients were more susceptible to having low phosphorus levels [26]. However, this discrepancy might also reflect age-related differences in treatment priorities or tolerability, warranting further investigation.

Table 3 C-statistic for the models predicting CKD-related pharmacotherapy

	Area	95% CIs
ESAs		
Derivation cohort	0.700	0.643–0.750
Validation cohort	0.728	0.652–0.803
Iron		
Derivation cohort	0.641	0.568–0.713
Validation cohort	0.630	0.545–0.715
Phosphate binders		
Derivation cohort	0.732	0.667–0.797
Validation cohort	0.741	0.663–0.819
VDRA		
Derivation cohort	0.659	0.619–0.716
Validation cohort	0.668	0.590–0.729

Given that diabetic patients are known to develop anemia earlier, regardless of the stage of CKD [14, 27], it was unexpected we did not find a significant association between diabetes and the risk of prescribing ESAs. However, patients with a history of diabetes at enrollment were more likely to be treated with VDRA during the follow-up. In a cohort of pre-dialysis patients, diabetes mellitus was associated with CKD-MBD, including higher calcium-phosphorus product throughout all stages of CKD, poorer vitamin D status and lower serum calcitriol levels [28].

We acknowledge that future use of CKD-specific medications is one of a number of factors a healthcare professional is considering when evaluating the follow-up requirements of a person with kidney disease including the risk of kidney failure. Variation in regional guidelines and the quality of care among the different countries cannot be excluded. However, the observation that laboratory parameters associated with renal anemia and CKD-MBD did not vary by clinically relevant amounts should be reassuring (suppl. Table 5).

A strength of our analysis is that we used routinely available laboratory data in patients with CKD, mirroring what a nephrologist would have available to them in clinical practice. The variables in our analysis were carefully considered to avoid anything estimated from future variable observations, or that may require additional analysis by the healthcare professional, such as eGFR slope, that may be not feasible in all clinical settings. Our cohort is unique and encompassed a large population from various European countries and health-care systems. Limitations include that our study was based on data generated from a single commercial kidney care provider, and therefore it could be considered less generalizable to other chronic kidney disease populations. It is important to note that approximately 10% of the cohort selected for analysis had missing data precluding their inclusion in our multivariable models, but less than recently reporting prognostic kidney disease research [16]. Missingness also precluded the inclusion of albuminuria in our analyses.

Our study offers valuable insights for policy and clinical practice in managing CKD patients. Patients at a lower risk, could benefit from an extended follow-up schedule. This approach not only conserves healthcare resources but also allows healthcare professionals to allocate more time and intensive care to patients who require immediate attention. By tailoring the frequency of follow-up appointments based on risk levels, healthcare systems can optimize resource utilization and improve patient outcomes. While our analysis provides valuable insights into predicting medication requirements in patients with advanced CKD, it is crucial to acknowledge the need for trials to validate the effectiveness and potential inferiority of the suggested approach.

Conclusions

Our study highlights the multifaceted nature of medication requirements in CKD patients. By identifying significant predictors for the initiation of specific pharmacotherapies, we provide a foundation for informed clinical decisions and policy development. With a holistic perspective, we aim to contribute to improved patient outcome and enhanced management of CKD-related complications.

Abbreviations

ARO	Recognizing Excellence and Optimizing Outcomes
CKD	Chronic kidney disease
VDRA	Vitamin D receptor agonists
ESAs	Erythropoiesis stimulating agents
CKD-MBD	CKD associated bone mineral disease
RAASi	Renin angiotensin aldosterone system inhibitors
BMI	Body mass index
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12882-024-03497-y.

Supplementary material 1.

Supplementary material 2.

Acknowledgements

The ARO CKD Research Initiative is a joint observational research commitment from Amgen and FMC, fully funded by Amgen (Europe) GmbH, Zug, Switzerland. The sponsors were responsible for data collection (FMC) and data management (FMC, Amgen).

Authors' contributions

Jürgen Floege, James Fotheringham, TS and ES designed the study; ES and James Fotheringham analyzed the data; ES wrote the paper. PS, DCW, FK, KUE, MF, Jürgen Floege, James Fotheringham designed AROiii study. Every step of

development of the project, from design and scientific conduct of the study, through interpretation of the data, to preparation, review, and approval of the manuscript, was led by authors who are also members of the ARO Steering Committee. Results and their interpretations were discussed by all members of the ARO Steering Committee at plenary meetings four times in year.

Funding
Open Access funding enabled and organized by Projekt DEAL. This research was supported by the clinical research unit InteraKD consortium CRU5011 (project number 445703531; E.S. and Jürgen Floege). E.S. is supported by a START grant (19/21 to E.S.) and by a clinician scientist-program of the Faculty of Medicine of the RWTH Aachen University. E.S. has received a research grant of the German Society of Nephrology (DGfN). This work was supported by ERK-NET.

Availability of data and materials
The datasets generated and /or analysed during the current study are not publicly available due to the conditions stated at the time of patient consent, but are available from thee corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
Fresenius Medical Care (Europe) collected and processed data in accordance with all applicable local ethical and regulatory obligations concerning patient data for each of the 6 participating countries and licensed the anonymous data to Amgen. Informed patient consent was obtained from all patients by Fresenius Medical Care (Europe).

Consent for publication
Not applicable.

Competing interests
Peter Stenvinkel: Advisory Boards and/or speaker honoraria for Astra Zeneca, Baxter Healthcare, Novo Nordisk, Vifor, Fresenius Medical Care, Invizius, Astellas, Glaxo Smith Beecham.
Jürgen Floege: has received consultancy and speaker honoraria from Alnylam, AstraZeneca, Boehringer, Calliditas, CSL-ViforNovartis, Omeros, Travere.
David C Wheeler: has received consultancy and speaker honoraria from Fresenius, Amgen, Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Glaxo-SmithKline, Gilead, Janssen, Mundipharma, Merck Sharp and Dohme, Tricida, Vifor, Zydus.
James Fotheringham: has received consultancy and speaker honoraria from Novartis, Fresenius and Boehringer Ingelheim. Grants from Vifor Pharma, Alnylam, Baxter Healthcare.
Kai-Uwe Eckardt: has received consultancy and / or speaker honoraria from Astra Zeneca, Bayer, Boehringer Ingelheim, Enyo, Fresenius Medical Care, Glaxo Smith Kline, Otsuka, Sanofi, Travere.
All other authors do not have conflict of interest.

Author details
[1]Division of Nephrology and Clinical Immunology, RWTH University of Aachen, Aachen, Germany. [2]Department of Nephrology, University Hospital of Ioannina, Ioannina, Greece. [3]Centre de Recherche Clinique (CRC), Lausanne University Hospital, Lausanne, Switzerland. [4]Department of Genetics, Institute of Genetic Epidemiology, Medical University of Innsbruck, Innsbruck, Austria. [5]Division of Renal Medicine, Department of Clinical Science, Intervention and Technology, Karolinska Institutet, Stockholm, Sweden. [6]Department of Renal Medicine, University College London, London, United Kingdom. [7]Department of Nephrology and Medical Intensive Care, Charité-Universitätsmedizin Berlin, Berlin, Germany. [8]Northern General Hospital, Sheffield Kidney Institute, Herries Road, Sheffield, South Yorkshire S5 7AU, United Kingdom. [9]School of Health and Related Research, University of Sheffield, Sheffield, United Kingdom.

Received: 9 December 2023 Accepted: 9 February 2024
Published online: 20 February 2024

References

1. Levin A, Tonelli M, Bonventre J, et al. Global kidney health 2017 and beyond: a roadmap for closing gaps in care, research, and policy. Lancet. 2017;390(10105):1888–917.
2. Saran RST, Shahinian V, et al. Earlier pre-ESRD care throughout the U.S is associated with better survival for dialysis patients in their first year of ESRD. J Am Soc Nephrol. 2007;18:299A.
3. De Nicola L, Chiodini P, Zoccali C, et al. Prognosis of CKD patients receiving outpatient nephrology care in Italy. Clin J Am Soc Nephrol. 2011;6(10):2421–8.
4. Besarab A, Levin A. Defining a renal anemia management period. Am J Kidney Dis. 2000;36(6 Suppl 3):S13-23.
5. Bello AK, Alrukhaimi M, Ashuntantang GE, et al. Complications of chronic kidney disease: current state, knowledge gaps, and strategy for action. Kidney Int Suppl (2011). 2017;7(2):122–9.
6. Couser WG, Remuzzi G, Mendis S, et al. The contribution of chronic kidney disease to the global burden of major noncommunicable diseases. Kidney Int. 2011;80(12):1258–70.
7. Lee GH, Benner D, Regidor DL, et al. Impact of kidney bone disease and its management on survival of patients on dialysis. J Ren Nutr. 2007;17(1):38–44.
8. Kestenbaum B, Sampson JN, Rudser KD, et al. Serum phosphate levels and mortality risk among people with chronic kidney disease. J Am Soc Nephrol. 2005;16(2):520–8.
9. Eddington H, Hoefield R, Sinha S, et al. Serum phosphate and mortality in patients with chronic kidney disease. Clin J Am Soc Nephrol. 2010;5(12):2251–7.
10. Palmer SC, Hayen A, Macaskill P, et al. Serum levels of phosphorus, parathyroid hormone, and calcium and risks of death and cardiovascular disease in individuals with chronic kidney disease: a systematic review and meta-analysis. JAMA. 2011;305(11):1119–27.
11. Schwarz S, Trivedi BK, Kalantar-Zadeh K, et al. Association of disorders in mineral metabolism with progression of chronic kidney disease. Clin J Am Soc Nephrol. 2006;1(4):825–31.
12. Bhuriya R, Li S, Chen SC, et al. Plasma parathyroid hormone level and prevalent cardiovascular disease in CKD stages 3 and 4: an analysis from the Kidney Early Evaluation Program (KEEP). Am J Kidney Dis. 2009;53(4 Suppl 4):S3-10.
13. Voormolen N, Noordzij M, Grootendorst DC, et al. High plasma phosphate as a risk factor for decline in renal function and mortality in pre-dialysis patients. Nephrol Dial Transplant. 2007;22(10):2909–16.
14. Bellasi A, Mandreoli M, Baldrati L, et al. Chronic kidney disease progression and outcome according to serum phosphorus in mild-to-moderate kidney dysfunction. Clin J Am Soc Nephrol. 2011;6(4):883–91.
15. Noordzij M, Leffondre K, van Stralen KJ, et al. When do we need competing risks methods for survival analysis in nephrology? Nephrol Dial Transplant. 2013;28(11):2670–7.
16. Ramspek CL, Evans M, Wanner C, et al. Kidney failure prediction models: a comprehensive external validation study in patients with advanced CKD. J Am Soc Nephrol. 2021;32(5):1174–86.
17. Komaba H, Fukagawa M. The role of FGF23 in CKD–with or without Klotho. Nat Rev Nephrol. 2012;8(8):484–90.
18. Jablonski KL, Chonchol M, Pierce GL, et al. 25-Hydroxyvitamin D deficiency is associated with inflammation-linked vascular endothelial dysfunction in middle-aged and older adults. Hypertension. 2011;57(1):63–9.
19. Lin CL, Hung CC, Yang CT, et al. Improved anemia and reduced erythropoietin need by medical or surgical intervention of secondary hyperparathyroidism in hemodialysis patients. Ren Fail. 2004;26(3):289–95.
20. Rault R, Magnone M. The effect of parathyroidectomy on hematocrit and erythropoietin dose in patients on hemodialysis. ASAIO J. 1996;42(5):M901-903.
21. Battistella M, Richardson RM, Bargman JM, et al. Improved parathyroid hormone control by cinacalcet is associated with reduction in darbepoetin requirement in patients with end-stage renal disease. Clin Nephrol. 2011;76(2):99–103.
22. Keating FR Jr, Jones JD, Elveback LR, et al. The relation of age and sex to distribution of values in healthy adults of serum calcium, inorganic phosphorus, magnesium, alkaline phosphatase, total proteins, albumin, and blood urea. J Lab Clin Med. 1969;73(5):825–34.

23. Cirillo M, Ciacci C, De Santo NG. Age, renal tubular phosphate reabsorption, and serum phosphate levels in adults. N Engl J Med. 2008;359(8):864–6.
24. Avila M, Prado MDC, Cuevas-Budhart MA, et al. Reduced phosphorus is associated with older age and hypoalbuminemia. Risk factors for all-cause mortality in peritoneal dialysis patients. Front Nutr. 2023;10:1094256.
25. Lorenzo Sellares V, Torres RA. Management of hyperphosphataemia in dialysis patients: role of phosphate binders in the elderly. Drugs Aging. 2004;21(3):153–65.
26. Gutierrez OM. Contextual poverty, nutrition, and chronic kidney disease. Adv Chronic Kidney Dis. 2015;22(1):31–8.
27. Astor BC, Muntner P, Levin A, et al. Association of kidney function with anemia: the third National Health and nutrition examination survey (1988–1994). Arch Intern Med. 2002;162(12):1401–8.
28. Glendenning P, Chew GT, Seymour HM, et al. Serum 25-hydroxyvitamin D levels in vitamin D-insufficient hip fracture patients after supplementation with ergocalciferol and cholecalciferol. Bone. 2009;45(5):870–5.

Publisher's Note