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Longitudinal kidney function trajectories predict major bleeding, hospitalization and death in patients with atrial fibrillation and chronic kidney disease

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ABSTRACT

Background: Chronic kidney disease (CKD), commonly described by estimated glomerular filtration rate (eGFR), is a frequent comorbidity in patients with atrial fibrillation (AF) and associated with thromboembolic and bleeding complications. Instead of single eGFR measurements, kidney function decline over time may better predict clinical outcomes but this has not been studied so far.
Methods: Patients with AF and stage 3/4 CKD were prospectively followed within a primary care electronic database from the United Kingdom (IMS-THIN). The associations between the longitudinal eGFR trajectory of these patients and stroke/systemic embolism, major bleeding, first hospitalization-for-any-cause, and death-from-any-cause were estimated with joint models of longitudinal and time-to-event data.
Results: 18,240 patients were included (median age 80.4 years, median CHA_2DS_2-VASc score 4). In 133,676 eGFR measurements (mean: 6 per patient) median "baseline" eGFR was 49 ml/min/1.73m^2 [41–55] and mean eGFR decline was 0.54 ml/min/1.73m^2/year (95%CI: 0.47–0.62). During follow-up (median 3.2 years; 50,841 patient-years at risk), 5-year cumulative incidence estimates were 9%, 3%, 32% and 76% for stroke/systemic embolism, major bleeding, hospitalization and death, respectively. In joint modeling, an accelerated decline in kidney function strongly predicted for a higher risk of major bleeding (hazard ratio [HR] 1.09 per ml/min/1.73m^2/year increase in eGFR decline), hospitalization (HR 1.06), and death-from-any-cause (HR 1.11; all $p < 0.05$), but not for stroke/systemic embolism (HR 0.97; $p = 0.239$).
Conclusions: Declining kidney function is a critical determinant of unfavourable outcomes in patients with AF and CKD. Longitudinal kidney function trajectories may enable a much more individualized prediction of adverse outcomes in this vulnerable patient population.

1. Introduction

Atrial fibrillation (AF) and chronic kidney disease (CKD) are frequently co-existing medical conditions in elderly patients [1]. The prevalence of AF patients aged 75 years or older is around 10%, and up to one-third have moderate-to-end stage CKD [2]. In a large cohort study, AF was present in 16.0% of patients with eGFR ≥45 ml/min per 1.73 m^2, rising to 20.4% of patients with more severe kidney impairment (eGFR <45 ml/min per 1.73 m2) [3].

While the clinical hallmark of AF is an increased risk for cardioembolic stroke, AF also is a strong risk factor for developing incident CKD and vice versa, suggesting that AF and CKD are inter-dependent [1,4]. In parallel, CKD increases the risk of stroke and mortality [5], which is much more pronounced in patients with pre-existing AF [6,7]. In an observational study of 132,372 AF patients, non-end stage CKD increased the risk for stroke or systemic embolism compared to patients without CKD (hazard ratio [HR] 1.5) and this risk increased with end stage CKD (HR 1.8) [8]. Furthermore, the adverse impact of CKD on bleeding risk can complicate the management of anticoagulation for stroke prevention in AF [8,9].

Thus, co-existing AF and CKD are highly interdependent processes which render elderly patients particularly vulnerable to adverse health outcomes. Previously published studies considered CKD as a "static"

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variable for predicting prognosis from a single ("baseline") point in time [10–12] but single measurements insufficiently reflect this increase in outcome risks, because kidney function represents a "dynamic" variable, which constantly changes over time [13]. This longitudinal change is influenced by aging, chronic comorbidities such as hypertension and diabetes mellitus, as well as by more transient intercurrent events such as cardiac decompensation or hypovolemia subsequent to diarrhea or infection. Therefore, the *longitudinal* change in kidney function over time may better reflect the prognosis of AF patients. However, the impact of faster or slower renal function decline on stroke, major bleeding, hospitalization, and death is poorly understood and data on the prognostic impact of accelerated kidney function loss on these outcomes in AF patients are lacking. Such data could help physicians to dynamically identify patients at increased risk for adverse events and thus may improve clinical management of this relevant patient population.

Developments in biostatistical research have brought forward so-called joint models of longitudinal and time-to-event data. These joint models can estimate the prognostic association between biomarker trajectories such as change in eGFR and time-to-event clinical outcomes such as hospitalizations. The models yield relative risks for clinical outcomes that may allow for more personalized treatment decisions. Here, we present a joint modeling study to quantify how renal decline over time impacts the risks of stroke, bleeding, hospitalization, and death in a real-world cohort of elderly patients with AF and CKD treated in the community setting.

2. Material and methods

2.1. Study population and design

Prospectively-collected, anonymized data from a validated longitudinal health records database, the IMS® The Health Improvement Network (IMS-THIN) were used for this study. IMS-THIN collects clinical, laboratory, and drug prescription data from primary care physicians in the United Kingdom (UK), and has been extensively used for observational epidemiology, pharmacoepidemiology, and clinical research [13,14]. Using UK Read diagnosis codes we identified all patients from IMS-THIN who had both a documented diagnosis of AF and stage 3/4 CKD at/or before August 31st, 2015 ("concomitant AF/CKD"). To limit survivorship bias and the inclusion of "prevalent" cases, patients with concomitant AF/CKD before January 1st, 2009 were not included, resulting in a population of n = 20,780 patients. The "baseline date" of each patient was defined as the first date at/or after January 1st, 2009, in which a concurrent diagnosis of AF and CKD stage 3/4 occurred for the first time, meaning the exact date on which a patient is first documented to have developed CKD stage 3/4 or vice versa. A total of 2540 patients (12%) were excluded according to pre-specified criteria (e.g. duplicate patients, missing or implausible eGFR values, follow-up <6 months), resulting in a study population of 18,240 subjects (Fig. S1). The CHA_2DS_2-VASc score and its items were constructed from comorbidity diagnosis codes that were documented prior to the baseline date. UK Read code lists for this analysis are available from the authors on request.

2.2. Ethics

As IMS-THIN collects exclusively anonymized data, neither an approval of an ethics committee nor consent from individual patients were required (in accordance with §3 of the German Federal Data Protection Act as well as pertinent regulations in the UK). However, we obtained full approval from the independent IMS Scientific Review Board (SRC 15THIN095).

2.3. Statistical methods

The statistical analysis was performed with Stata 15.0 (Windows version, Stata Corp., Houston, TX, USA). All statistical analyses were pre-specified, and executed in line with best-practice recommendations for joint modeling and the study of longitudinal eGFR data in patients with CKD [15]. Continuous variables were reported as medians and 25th–75th percentiles, whereas count data were summarized as absolute frequencies (%). The association between continuous and/or categorical variables were evaluated with rank-sum tests and χ^2-tests, respectively.

Time-to-first-clinical outcome (stroke/systemic embolism; major bleeding; first-after-baseline-hospitalization; and death-from-any-cause) was calculated, defined as the time to the first occurrence of each individual outcome after the baseline date. Patients who did not develop outcome events were censored at their time of death (except in time-to-death analysis) or at the time of last data entry in IMS-THIN databases.

The risk of death was quantified with 1-Kaplan-Meier estimators, whereas the risks of hospitalization, major bleeding, and stroke/systemic embolism were quantified with competing risk cumulative incidence estimators treating death-from-any-cause as a competing event of interest. The associations between baseline variables and the hazards of the 4 outcomes were modelled with Cox models (time-to-death) and Fine & Gray competing risk regression models (all three other outcomes).

The prognostic relationships between the three non-mortal outcomes and death were evaluated with unidirectional Semi-Markov Multistate Models.

The kidney function trajectory (defined as the annualized absolute change in the eGFR after baseline in ml/min/1.73m^2/year) was modelled with a joint model incorporating time-to-death in order to account for potentially informative censoring due to mortality.

Primary outcome of the study was the 1st derivative of the relationship between different eGFR trajectories and the *hazard rate* of the 4 clinical endpoints, reflecting the relative change in the hazard of a clinical endpoint for one unit increase in the rate of change of the eGFR.

The joint model was specified as follows: [1] Linear mixed model with random intercept and linear follow-up time and a random effect for follow-up time for the longitudinal component of eGFR trajectory, [2] Weibull proportional hazards model for the time to the 4 outcomes, [3] "1st derivative" specification of the association parameter α, and [4] an unstructured variance-covariance-matrix.

3. Results

3.1. Analysis at baseline

A total of 20,780 patients from 616 family medicine practices had a documented concurrent diagnosis of AF and stage 3/4 CKD in IMS-THIN between January 1st, 2009 and August 31st, 2015 (Table S1). Of these, 20,606 patients had a valid IMS-THIN exit date, which made them eligible for data extraction. Of these, 18,240 patients (88%) fulfilled our inclusion criteria (Fig. S1) and were incorporated in the analysis (Table 1), contributing a total of 133,694 eGFR measurements. Baseline characteristics were comparable between excluded and included patients (Table S2). The median duration from January 1st, 2009 to the baseline date (i.e. the date of concurrent AF and CKD) was 2.8 years [25th–75th percentile: 1.3–4.2]. At baseline, the mean age of the cohort was 80.4 years [standard deviation 74.6–85.5 years], the median CHA_2DS_2-VASc score was 4 [interquartile range (IQR) 3–5], and the median baseline eGFR was 49 ml/min/1.73m^2 [IQR 41–55 ml/min/1.73m^2].

3.2. Prospective analysis – clinical outcomes

Median follow-up was 3.2 years (50,841 patient-years at risk), with 75% of patients having at least 1.8 and 25% of the cohort having >4.6 years of follow-up, respectively. During follow-up, 1208 strokes/systemic embolisms, 334 major bleeding events, 3876 deaths and 11,891 first-after-baseline-hospitalizations occurred, translating into

Table 1
Baseline characteristics of the study population (n = 18,240). Continuous variables are summarized as medians [25th percentile (Q1) – 75th percentile (Q3)], whereas categorical variables are reported as absolute frequencies and percentages. N reports the number of patients with fully observed data for the respective variables.

Variable	Data available for n	Summary measure
Age (years)	18,240	80.4 [74.6–85.5]
BMI (kg/m^2)	17,604	27.6 [24.4–31.5]
median eGFR at or prior baseline	18,222	49 [41–55]
Female gender	18,240	9941 (55%)
CKD III/IV	18,240	18,240 (100%)
Atrial Fibrillation	18,240	18,240 (100%)
History of Stroke	18,240	3578 (20%)
History of Systemic Embolism	18,240	68 (0.4%)
History of Major Bleeding	18,240	776 (4%)
History of ACS	18,240	2088 (11%)
Peripheral artery disease	18,240	1401 (8%)
History of VTE	18,240	693 (4%)
Heart failure	18,240	3870 (21%)
Hypertension	18,240	11,498 (63%)
Diabetes mellitus	18,240	4364 (24%)
Liver disease	18,240	1101 (6%)
History of renal transplant	18,240	68 (0.4%)
Bleeding disposition	18,240	3138 (17%)
Clot disposition	18,240	18 (0.1%)
CHA_2DS_2-VASc score	18,240	4 [3–5]

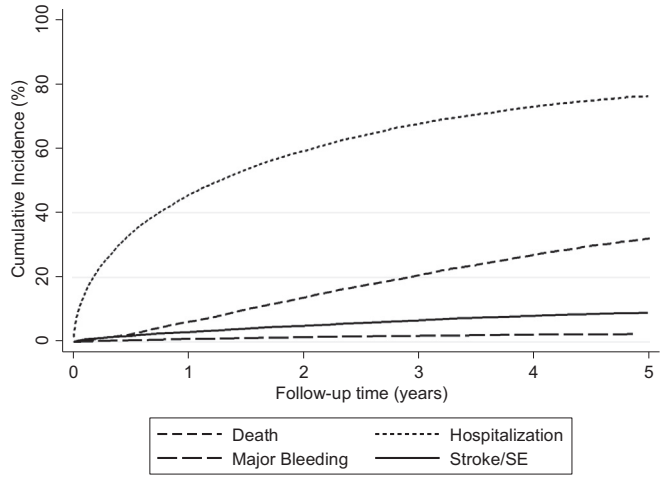

Fig. 1. Cumulative incidences of death, hospitalization, major bleeding, and stroke/systemic embolism in the analysis population (n = 18,240). Risk of death-from-any-cause was estimated with a 1-Kaplan-Meier estimator. The risks of all three other outcomes were quantified with Competing Risk Cumulative Incidence estimators, treating death-from-any-cause as a competing risk.

5-year cumulative incidence estimates of 9%, 3%, 32% and 76%, respectively (Fig. 1, Table S3). Univariable baseline predictors of these outcomes are summarized in Tables S4 & S5. As indicated by their respective χ^2-statistics, the strongest baseline predictors were: higher age, a higher CHA_2DS_2-VASc score, and a lower eGFR for death; a higher CHA_2DS_2-VASc score, diabetes, and bleeding disposition for hospitalization; a prior history of major bleeding, liver disease, and a higher CHA_2DS_2-VASc score for major bleeding; and a prior history of stroke, a higher CHA_2DS_2-VASc score, and higher age for stroke/systemic embolism, respectively. Importantly, in this univariable analysis, a single baseline measurement of kidney function as represented by the eGFR predicted only for higher risks of death or hospitalization, but not for higher risks of major bleeding or stroke/systemic embolism, respectively.

3.3. Joint model assessment of mortality risk after an outcome event

The subsequent risk of death after experiencing either endpoint of hospitalization, major bleeding, or stroke/systemic embolism was substantial (Transition matrix in Table S6). In multistate modeling, the occurrence of these outcomes during follow-up independently predicted for an imminent increase in the risk of death, with hospitalization being the strongest predictor (Transition hazard ratio (THR) 4.3), followed by major bleeding (THR 2.5) and stroke/systemic embolism (THR 2.0) (Figs. S2–S4, Multistate models #1-#3 in Table S7, all $p < 0.0001$).

Patients with higher CHA_2DS_2-VASc scores had a higher risk for hospitalization without death and death without hospitalization, but also had higher risks of death after hospitalization. Similarly, a lower baseline eGFR and higher age increased transition risks towards death after hospitalization (Table S8), all of which was also reflected in higher state occupation probabilities according to increasing age and CHA_2DS_2-VASc score or decreasing baseline eGFR.

3.4. Joint model outcome risk assessment according to eGFR trajectory

A total of 133,676 eGFR measurements were available (mean: 6 measurements per patient; range: 1–124), and the median interval between first and last eGFR measurement was 1.9 years [25th–75th percentile: 0.8–3.3, range: 0–6.3]. In a joint model accounting for potential informative censoring due to mortality, the eGFR declined on average by 0.54 ml/min/1.73m^2/year (95%CI: 0.47–0.62, $p < 0.0001$; Fig. S5).

The crude eGFR trajectory over time differed in patients who were or were not hospitalized, or died compared to those who were alive during follow-up, whereas the crude eGFR trajectory did not significantly differ between patients who did and did not develop stroke/systemic embolism and/or major bleeding (Table 2). In detail, the eGFR decreased by 0.3 ml/min/1.73m^2/year in patients who remained alive during follow-up, but decreased by 1.3 ml/min/1.73m^2/year in patients who died during follow-up ($p < 0.0001$, Fig. S6). The eGFR decline was estimated at 0.3 ml/min/1.73m^2/year in patients who were never hospitalized during follow-up, and at 0.5 ml/min/1.73m^2/year in patients who were hospitalized at least once during follow-up ($p < 0.0001$, Fig. S7). The average annualized eGFR declines were not significantly different in patients who did and did not develop major bleeding and/or stroke/systemic embolism (Figs. S8 & S9).

3.5. Joint modeling of the eGFR trajectory and clinical outcomes

In joint modeling, the *rate of change* of the eGFR emerged as a strong adverse predictor of all outcomes except risk of stroke/systemic embolism (Table 3). In the joint model for death, acceleration of eGFR decline by 1 ml/min/1.73m^2/year was associated with a higher relative risk of death (HR = 1.11, 95%CI: 1.10–1.14, $p < 0.0001$), first hospitalization (HR 1.06; 1.04–1.08, $p < 0.0001$), and major bleeding (HR 1.09; 1.01–1.18, $p = 0.037$), respectively. In contrast, an accelerated decline in eGFR was not associated with higher risk of stroke/systemic embolism (corresponding HR per 1 ml/min/1.73m^2/year increase in eGFR decline = 0.97; 0.93–1.02, $p = 0.239$).

Table 2
Changes in the eGFR over time in patients with AF & stage 3/4 CKD who did or did not develop 4 clinical outcomes during follow-up (n = 18,240). Patients who died and/or were hospitalized experienced significantly accelerated eGFR declines over time than patients without these events. The overall eGFR trajectory did not appear to significantly differ between patients did or did not experience major bleeding and/or stroke/systemic embolism. All results are from joint models of longitudinal and time-to-event data. Death was considered for the time-to-event submodel in all 4 analyses, so that the eGFR trajectory is fully adjusted for potential informative censoring by death. The 4 clinical outcomes were treated as explanatory variables in the longitudinal submodel by fitting an interaction between outcome status and the eGFR trajectory.

eGFR model	Change in eGFR/year (95%CI, p)		
	No event	Event	Difference
Death	−0.3 ml/min/1.73m^2/year (−0.3-(−0.2), $p < 0.0001$)	−1.3 ml/min/1.73m^2/year (−1.5-(−1.2), $p < 0.0001$)	1.1 ml/min/1.73m^2/year (0.9–1.3, $p < 0.0001$)
Hospitalization	−0.3 ml/min/1.73m^2/year (−0.4-(−0.1), $p < 0.0001$)	−0.5 ml/min/1.73m^2/year (−0.6-(−0.4), $p = 0.003$)	0.2 ml/min/1.73m^2/year (0.1–0.4, $p < 0.0001$)
Major Bleeding	−0.4 ml/min/1.73m^2/year (−0.5-(−0.4), $p < 0.0001$)	−0.6 ml/min/1.73m^2/year (−1.1-(−0.2), $p = 0.010$)	0.2 ml/min/1.73m^2/year (−0.7–0.3, $p = 0.409$)
Stroke/systemic embolism	−0.5 ml/min/1.73m^2/year (−0.5-(−0.4), $p < 0.0001$)	−0.1 ml/min/1.73m^2/year (−0.5–0.3, $p = 0.558$)	0.4 ml/min/1.73m^2/year (0.0–0.7, $p = 0.069$)

Table 3
Joint models for the primary endpoint (quantification of the prognostic association between the eGFR changes over time and the 4 clinical outcomes death, hospitalization, major bleeding, and stroke/systemic embolism (a "1st derivative" specification of α, reflecting the relative change in the hazard ratio of clinical outcomes per unit of accelerated eGFR decline per year).

Specification of α	"1st derivative" specification of α (i.e. primary endpoint)		
Interpretation of α	α-fold relative change in the hazard of clinical outcomes per unit of eGFR decline acceleration		
Clinical Outcome	α	95%CI	p
Death	1.11	1.10–1.14	<0.0001
Hospitalization	1.06	1.04–1.08	<0.0001
Major bleeding	1.09	1.01–1.18	0.037
Stroke/systemic embolism	0.97	0.93–1.02	0.239

4. Discussion

In this observational cohort study, we examined the relationship between changes in kidney function over time and the risks of death, hospitalization, major bleeding, and stroke/systemic embolism in 18,240 elderly patients with AF and CKD stage 3/4 who contributed >133,000 eGFR measurements over time. While AF and CKD are known to be interdependent processes [1,4], the association between longitudinal trajectories rather than single-point-in-time measurements of kidney function and adverse clinical outcomes have not been explored before. By using joint models, we could confirm that patients who had accelerated kidney function decline experienced higher rates of hospitalization, major bleeding, and death. In contrast, neither the baseline eGFR nor the longitudinal eGFR trajectory identified patients at higher risk of stroke/systemic embolism. Our pre-specified selection of mortality, hospitalization, major bleeding, and stroke/systemic embolism as the clinical outcomes for this study in patients with AF and CKD stages 3/4 was justified, since our multi-state model demonstrated that the occurrence of all three non-mortal outcomes (hospitalization, major bleeding, and stroke/systemic embolism) predicted for an immediate increase in the risk of death in this high-risk population.

With a mean age of 80.4 years, our study population reflects a common and clinically challenging cohort. Since age is associated with stroke, major bleeding, hospitalization, death and renal decline, the decision in favor of or against anticoagulation for stroke prevention in AF is often difficult and higher age as well as impaired renal function are commonly observed reasons for withholding anticoagulation [16,17]. Furthermore, especially elderly patients are vulnerable to acute kidney injury from hypovolaemia or infections, causing acute renal impairment, which sometimes is followed by slow restauration of kidney function. Especially in this challenging clinical situation, the use of an eGFR trajectory (instead of single eGFR measurements) may be helpful to better predict the individual dynamics of thromboembolic and bleeding risks. Our results provide important insights into the clinical biology of kidney disease progression and adverse health outcomes in the setting of concomitant AF. They indicate that prospective longitudinal monitoring of kidney function (or a retrospective evaluation of longitudinally collected eGFR values from previous healthcare encounters) may represent a new avenue of personalized risk assessment with potential to improve the clinical management of elderly patients with comorbid AF and CKD.

In prognostic studies of kidney function and health outcomes, the eGFR may be treated (a) as a single measurement at baseline, which can be easily implemented in standard time-to-event analysis models, (b) as a longitudinal string of measurements over time, which can be implemented in joint models under the so-called "current parameter" specification of the association parameter α, and (c) as a longitudinal trajectory of measurements, which can be implemented in joint models under the so-called "1st derivative" specification of the association parameter α. We selected the 1st derivative specification as our primary endpoint, because it represents the impact of the "rate of change in eGFR" on outcome rather than a single measurement in time or a string of measurements over time. Clinically, this concept is likely the most meaningful implementation of eGFR as a prognostic biomarker. This assertion is further supported by the fact that CKD is a chronic illness that is often aggravated by intercurrent acute-on-chronic declines in kidney function. The relevance of a joint modeling approach for identifying patients with AF and CKD at risk for complications is particularly evident when looking at our results for major bleeding. Here, neither a single eGFR measurement (Table S5) nor a string of longitudinal eGFR measurements (Table 3, Fig. S8) predicted for this important complication. In contrast, the eGFR trajectory as represented by the *rate of change* in eGFR (Table S5) predicted an increased risk for major bleeding. This demonstrates how prognostic information contained in dynamic changes of a biomarker over time can successfully be used for clinical outcome prediction. This is especially important, since available risk scores (such as HAS-BLED) are helpful to describe the bleeding risk of a certain population but perform poorly in risk prediction for individual patients.

On the other hand, whether addition of kidney function data to the CHA_2DS_2-VASc score can improve the prognostic potential of this stroke/SE risk stratification score in an ongoing debate. [18] Our current data do not support this concept, as neither a single eGFR measurement at baseline nor the eGFR trajectory predicted for a higher risk of stroke/SE in the subgroup of patients with AF and moderate-stage CKD 3/4.

How can our data impact clinical care? Obviously, single eGFR measurements are insufficient for adequate risk assessments. Therefore, clinicians should consider to take a closer look at the deterioration of renal function over time (i.e. in recent years), which includes the task to check and document eGFR regularly. For example, not all patients with an eGFR of 35 ml/min in a single measurement may carry similar risks for outcomes. A patient with chronically impaired but stable renal function at eGFR 35 ml/min may benefit from a more aggressive antithrombotic treatment to reduce the risk of stroke without an unacceptable increase in bleeding complications. In contrast, another patient with an eGFR 35 ml/min but a rapid decline over time (for example from 55 to 35 ml/min over 2 years) may be at much higher risk for bleeding, hospitalization or death. Such patients may benefit less from a more aggressive antithrombotic treatment, carry higher bleeding risks and may require a dedicated search for the reasons behind the accelerated renal decline. Further studies are needed to identify trigger points for action in AF patients with an acceleration of renal function loss.

Some limitations and strengths of the current study need to be addressed. Despite prospective data collection during routine care, healthcare database analyses carry a considerable risk of bias due to missing data, entry errors or censored or selective data entry, miscoding or under-reporting of outcomes. For instance, we cannot rule out that the rate of major bleeding events was underestimated because our finding of 3% event rate over 5 years is considerably lower than the rates reported in recent randomized trials or prospective AF registries in which major bleeding data are prospectively collected and centrally adjudicated [9,19,20]. Furthermore, our data on stroke events did not allow us to discriminate between ischaemic and haemorrhagic strokes. Thus, intracranial hemorrhages may also have been coded as stroke. We did not include type or dosage of antithrombotic/anticoagulant therapy in our model, since in retrospective data analyses only prescription data are documented whereas compliance, adherence, treatment interruption or discontinuations are insufficiently captured, but much more relevant. Since interaction between renal function, renal decline and prescription patterns are likely, much more granular data would be needed to include treatments effects into the statistical models. We are aware that antithrombotic treatments may have a direct causal relationship to outcome rates of stroke, bleeding, hospitalization and death and the lack of granular data is definitely a major limitation and further

(ideally prospective) studies are warranted. Finally, it is in the nature of such databases to be designed on a regional or national level and, here, we addressed our study question using prospectively collected data from outpatients treated in the UK primary care setting. Therefore, findings of our outcome analyses may not be generalizable to other healthcare systems.

On the other hand, the large sample size of our cohort, the considerable duration of follow-up and the large number of eGFR measurements and events over time are a significant strength of our analysis. Moreover, our selection criteria only excluded a small proportion of patients from the original dataset, and the baseline characteristics of in- and excluded patients were comparable. We applied appropriate measures to limit the impact of survivor bias and the inclusion of "prevalent" cases by excluding patients with a long history of concurrent AF/CKD.

Joint modeling allowed us to incorporate mortality in our longitudinal eGFR analysis, thus greatly reducing the potential for informative censoring which often applies to longitudinal kidney function analyses. Mortality was also included as a competing event in the estimation of non-mortal outcome risks. [13] The overall eGFR decline of roughly 0.5 ml/min/1.73m^2/year in our study is also broadly consistent with previously published cohorts in this field, as are the confirmed prognostic associations of the CHA_2DS_2-VASc score with stroke and non-stroke-related endpoints.

We consider this study as the first proof-of-principle that eGFR trajectory based joint model predictions may be an important concept for advancing personalized care and clinical management of patients with AF & CKD, with relevance for the global community of primary care physicians, internists, nephrologists, and cardiologists. Future studies should evaluate if implementation of biomarker trajectories (such as a continuous import of updated eGFR values) into "dynamic" clinical prediction models can be used for "real-time" risk predictions of adverse clinical outcomes that may then be used by treating physicians to improve care.

5. Conclusion

This observational study using joint models of longitudinal and time-to-event data demonstrates that accelerated kidney disease progression predicts the risks of death, hospitalization and major bleeding, but not stroke/systemic embolism. Our data illustrate the potential for a novel concept of risk assessment of clinical outcomes based on kidney function trajectories which could better help to personalize the clinical management of AF patients with stage 3/4 CKD.

Disclosures

FP: honoraria for lectures and consultancy from Eli Lilly, Daiichi Sankyo, Roche, MSD Oncology. CA: honoraria from Sanofi, Pfizer/BMS, Daiichi Sankyo, Boehringer Ingelheim, Bayer. RK: honoraria for consultancy, lectures and research support from AstraZeneca, Bayer AG, Berlin-Chemie Menarini, Daiichi Sankyo, Sanofi, Servier. JBW: honoraria and institutional research support from Bayer, Boehringer-Ingelheim, Daiichi Sankyo, Janssen, Pfizer, Portola.

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Author contributions

Conceived and designed the study: JBW; RK; FP. Performed statistical analyses: FP. Interpreted the results: all authors. Wrote the first draft of the manuscript: FP; JBW. Critical revision of the first draft of the manuscript: all authors. Contributed to the writing of the final manuscript: all authors. Agree with the manuscript's results and conclusions: all authors. ICMJE criteria for authorship read and met: all authors.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.01.089.

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