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Original Article

Chronic kidney disease classification according to different formulas and impact on adverse outcomes in patients with atrial fibrillation: A report from a prospective observational European registry

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ABSTRACT

Background: Chronic kidney disease (CKD) and atrial fibrillation (AF) often coexist, making accurate renal function estimation crucial, typically through equations calculating estimated glomerular filtration rate (eGFR) or creatinine clearance (CrCl).

Objective: To compare the concordance and predictive performance of different renal function estimation equations in a European cohort of AF patients.

Methods: We analyzed data from AF patients enrolled in a prospective observational European registry. Renal function was estimated using eight formulas: BIS-1, CG, CG-BSA, CKD-EPI, EKFC, FAS, LMR and MDRD. Concordance between formulas was assessed using weighted Cohen's Kappa, while Cox regression and receiver operating characteristic (ROC) curves evaluated their association with outcomes (composite of all-cause death, any coronary revascularization and any thromboembolism).

Results: We included 8,506 patients. CKD-EPI demonstrated good to excellent concordance with other formulas, with the lowest concordance with CG (K = 0.607; 95% CI, 0.595-0.618) and the highest with MDRD (K = 0.880; 95% CI, 0.873-0.887). The risk of adverse outcomes increased sharply when renal function dropped below 60 ml/min across all formulas. CG-BSA and CG formulas showed the best discriminative ability for predicting composite outcomes (AUC 0.660, 95% CI 0.644-0.677, and 0.661, 95% CI 0.644-0.678, respectively). Based on integrated discrimination improvement (IDI) analysis, compared to the CKD-EPI equation, the CG and CG-BSA formulas showed significant improvements in sensitivity of 0.9% and 1.1%, respectively

Conclusion: Equations for estimating renal function vary in concordance, with potential implications for drug prescription and predicting adverse events. CG and CG-BSA formulas showed superior performance in identifying patients at risk for adverse outcomes.

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1. Introduction

Atrial fibrillation (AF) has an increasing incidence and prevalence with an aging population, and is associated with adverse cardiovascular events, stroke in particular, that can result in significant morbidity and mortality [1–3].

Chronic kidney disease (CKD) is defined as abnormalities of kidney structure or function lasting more than 3 months with implications on health [4]. According to a meta-analysis of 100 studies, the global prevalence of CKD is 13.4% [5].

AF and CKD share many common risk factors, thus frequently coexisting in the same patient, particularly in the elderly age [6–8]. The interplay between these two conditions has been previously studied and significantly impact on adverse outcomes, increasing both thrombo-embolic and bleeding risk [9,10]. Furthermore, a precise estimation of renal function is crucial and mandatory in patients with AF who are candidates for treatment with direct oral anticoagulants [11–14].

The glomerular filtration rate (GFR) is widely accepted as the most reliable index for the estimation of kidney function. Many different formulas have been proposed and validated in the past years to provide an estimate of the GFR (eGFR) using the serum creatinine values [15].

Clinical Guidelines provided by KDIGO [15] (Kidney Disease: Improving Global Outcomes) group for the evaluation and management of CKD recommend the use of the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula for the estimation of GFR [16]. Conversely, the practical guidance on the use of direct oral anticoagulant (DOAC) advice the use of Cockcroft-Gault [17] (CG) equation for the kidney function evaluation, since it was the formula used in the randomized trials that validated DOACs in comparison with Vitamin K antagonists [12]. However, CG formula calculates the creatine clearance (CrCl), not the eGRF [17]. The landscape became even more intricated with the development of several other formulas and data from large scale cohorts regarding their performance in daily practice are needed.

The aim of this study is to assess the concordance between the different equations proposed for the estimation of renal function, and to assess their performance and their associations with long-term risk of adverse events at long-term.

2. Methods

2.1. Study design

We included AF patients derived from a European large, prospective, observational registry. Details on the study's design, baseline characteristics and primary results have been previously published [18–20]. Briefly, the registry enrolled consecutive adult patients with an ECG-documented diagnosis of AF in the 12 months before the enrolment.

Patients were enrolled in 250 centres across 27 countries between October 2013 and September 2016. The follow-up was pre-specified and has been conducted at 1 and 2 years. The study protocol was approved for each country and for ach enrolling site by the National Coordinators' main institutions. The study was performed according to the European Union Note for Guidance on Good Clinical Practice CPMP/ECH/135/95 and the Declaration of Helsinki.

At enrolment, the investigators collected data regarding baseline characteristics, demographics, previous medical history and reported them in a pre-specified electronic case report form. Baseline serum creatinine, sex, age and weight collected at baseline were used in this analysis to calculate the eGFR (or CrCl) according to different 8 formulas (details regarding the method of calculation and a brief outline on the advantages/disadvantages of different formulas are reported in Supplementary material):

- CKD-EPI [16];
- CG [17]
- CG adjusted for body surface area (CG-BSA) [21]
- Berlin Initiative Study (BIS-1) [22]
- Full Age Spectrum (FAS) [23]
- Liquidity Maintenance Ratio (LMR) [24]
- Modification of Diet in Renal Disease (MDRD) [25]
- European Kidney Function Consortium (EKFC) [26]

Using the proposed classification of the KDIGO, we categorized patients into 5 categories of CKD according to the eGFR estimated using the CKD-EPI formula: Stage I (eGFR ≥90 mL/min/1.73 m2); Stage II (eGFR between 89 and 60 mL/min/1.73 m2); Stage IIIa (eGFR between 59 and 45 mL/min/1.73 m2); Stage IIIb (eGFR be- tween 44 and 30 mL/min/1.73 m2); Stage IV/V (eGFR between <29 mL/min/1.73 m2). The last two categories (Stage IV/V) were considered together, due to low number of patients included in the Stage V (< 15 ml/min/1.73 m2).

For the purpose of this analysis, we included patients with available data needed for the calculation of all the formulas. No other additional exclusion criteria were applied.

2.2. Follow-up and adverse outcomes

Patients enrolled in the registry completed a pre-specified follow-up at 1 and 2 years, after enrolment. Incidence of major adverse events were recorded by the investigator. For this analysis, we considered as primary outcome a composite of all-cause death, any coronary revascularization and any TE. All-cause death was also evaluated as a secondary endpoint.

2.3. Statistical analysis

Continuous variables were reported as median and interquartile range (IQR), and comparison between groups was performed using the Kruskal-Wallis test. Categorical variables were reported as counts and percentages and compared using the Chi-square.

We used weighted Cohen's kappa coefficient to assess the agreement in the classification of patients among different categories of CKD according to the different 8 formulas: in this case we considered Stage IV and V of CKD separated, to enhance a better comparison.

Concordance of classification was defined as follows: K <0.20 poor; 0.21-0.40 modest; 0.41-0.60 moderate; 0.61-0.80 good; >0.80 excellent. The results of the weighted Cohen's kappa were plotted in a heatmap.

To compare the predictive performance of the two scores, we used receiver operating characteristic (ROC) curves and calculated the area under the curve (AUC) with its 95% confidence intervals. Comparisons between the different AUC were estimated using the method proposed by DeLong and DeLong; CKD-EPI formula was used as reference for comparison. Additionally, as an exploratory analysis, we evaluated the discriminatory performance of each formula in predicting the occurrence of any TE event.

We used the method proposed by Pencina et al. to perform reclassification analyses. We calculated the integrated discrimination improvement (IDI), net reclassification improvement (NRI) and median improvement (MI) at 2-year follow-up. CKD-EPI formula was again used as reference.

Kaplan-Meier curves and their 95% CI were drafted to evaluate the cumulative survival curves for the outcomes of the study, and survival distributions were tested for difference across the groups with the log-rank test. Multivariable cox regression analysis was used to evaluate the association between the categories of CKD and adverse outcomes. Covariates included in the model included: age, sex, type of atrial fibrillation, oral anticoagulant therapy and EHRA class. We also included in the model the risk factors included in the CHA_2DS_2-VASc score [27]: hypertension, diabetes, heart failure, coronary artery disease or peripheral artery disease and a previous history of TE event.

Finally, we evaluated the association between eGFR (or CrCl when appropriate), calculated according to the 8 different formulas and modelled as a continuous non-linear variable, with the risk of outcomes using a restricted cubic spline with 3 knots and reference value set at 60 ml/min/1.73 m2. Results were reported as Hazard Ratio (HR) with 95% Confidence Interval (CI). A two-sided p-value <0.05 was considered statistically significant.

All analysis were performed using R 4.0.3 (R Core Team 2020, Vienna, Austria).

3. Results

3.1. Clinical characteristics of patients across different stages of CKD

Among the 11096 AF patients originally enrolled in the registry, a total of 8506 patients (median age 70.0 IQR 63.0-77.0, 41.3% female) had available data for calculating eGFR (or CrCl) with the 8 formulas and were included in the analysis. The clinical characteristics of included patients according to kidney function as expressed by eGFR according to CKD-EPI formula are shown in Table 1. At increasing level of renal impairment, there was a significant increase in the prevalence of the most common cardiac and non-cardiac comorbidities. Furthermore, patients with CKD were significantly more likely to present permanent AF, a higher EHRA class for AF-related symptoms and a profile with higher thromboembolic and bleeding risks. Conversely, the prescription of oral anticoagulant significantly decreased at the stages of increasing renal impairment. Of note, 74.8% of patients in CKD stage IV/V were treated with oral anticoagulants (OAC), with 15.2% of them being treated with DOACs.

3.2. Distribution of patients according to different formulas and concordance analysis

The distribution of patient population according to eGFR calculated with CKD-EPI equation is reported in Fig. 1. In our cohort, 34.7% of the patients were categorized as having CKD and 10.9% of them had a severe renal impairment (Stage IV/V).

All 8 formulas classified most patients as having a CKD stage II, with CG equation allocating to this stage of CKD the lowest percentage of patients (37.58%) and the EKFC formula the highest percentage (52.21%). Conversely, CG was the formula with the highest percentage of patients classified in the Stage I (30.19%), with LMR being the one with the lowest percentage (4.71%).

We compared the concordance in the categorization in CKD stages between the 8 different equations using Cohen's weighted K test. The results were plotted using a Heatmap (Fig. 2). Categorization using the CKD-EPI formula showed a good to excellent concordance with other equations: CG showed the lowest value of weighted K (K = 0.607, 95% confidence interval [CI], 0.595-0.618), while MDRD showed the best concordance with CKD-EPI (K = 0.880, 95% CI 0.873-0.887). The CG showed a good concordance only with CG-BSA, whilst only a moderate value of concordance was found with the other equations. The highest concordance was found between the BIS1 and FAS equation (K = 0.917, 95% CI 0.911-0.923).

3.3. Follow-up and outcome

After a median follow-up of 729 days [IQR 664-745], a total of 1295 (15.2%) patients experienced an event of the primary composite outcome. Crude rates of outcome increased at increasing level of CKD (p for trend < 0.001, **Supplementary Table 1**). Consistently patients with more advanced CKD according to CKD-EPI formula showed a significantly lower cumulative survival free from the primary and secondary outcomes at Kaplan-Meier curves (Log Rank test, p <0.001, Fig. 3 **and Supplementary Figure 1**).

The results of the Cox regression analysis are presented in **Supplementary Figure 2**. All eight formulas demonstrated an increased hazard of adverse events for patients classified in Stage IV/V. However, only the CG formula showed a significant association with adverse outcomes across all CKD stages.

We also investigated the potential non-linear relationship between renal function, as estimated by the eight formulas, and adverse outcomes (Fig. 4). This analysis indicates that the risk of adverse outcomes

Table 1
Patients' clinical characteristics according to CKD stages.

	Stage I (n = 1304)	Stage II (n = 4253)	Stage IIIa (n = 1723)	Stage IIIb (n = 904)	Stage IV/V (n = 322)	P value
Age, median [IQR]	60.00 [53.00, 66.00]	69.00 [63.00, 76.00]	74.00 [67.50, 80.00]	77.00 [71.00, 83.00]	78.00 [72.00, 83.00]	<0.001
Female, N (%)	417 (32.0)	1628 (38.2)	814 (47.2)	488 (54.0)	171 (53.1)	<0.001
BMI, median [IQR]	27.70 [24.70, 31.40]	27.50 [24.80, 30.90]	27.50 [24.80, 31.20]	27.80 [24.70, 31.20]	27.30 [24.50, 30.90]	0.420
Type of AF, N (%)						<0.001
First diagnosed	265 (20.6)	754 (18.0)	253 (14.9)	125 (14.0)	44 (13.9)	
Paroxysmal	414 (32.1)	1146 (27.4)	403 (23.7)	180 (20.1)	82 (25.9)	
Persistent	296 (23.0)	929 (22.2)	349 (20.5)	156 (17.4)	35 (11.1)	
Long-persistent	64 (5.0)	185 (4.4)	76 (4.5)	33 (3.7)	9 (2.8)	
Permanent	249 (19.3)	1170 (28.0)	618 (36.4)	401 (44.8)	146 (46.2)	
Hypertension, N (%)	647 (50.3)	2577 (60.9)	1165 (68.1)	640 (71.2)	240 (75.2)	<0.001
Diabetes, N (%)	230 (17.7)	863 (20.3)	469 (27.3)	315 (35.1)	146 (45.6)	<0.001
Dyslipidemia, N (%)	466 (37.3)	1721 (41.6)	742 (44.3)	428 (48.5)	158 (50.2)	<0.001
Coronary artery disease, N (%)	245 (19.9)	1147 (28.4)	541 (33.5)	337 (40.4)	149 (49.7)	<0.001
Heart Failure, N (%)	348 (26.9)	1506 (35.5)	869 (50.9)	569 (63.6)	205 (63.9)	<0.001
LVEF, median [IQR]	57.00 [50.00, 62.00]	55.00 [45.00, 61.00]	55.00 [44.00, 60.00]	50.00 [40.00, 60.00]	49.00 [35.00, 57.00]	<0.001
Previous thromboembolic events, N (%)	86 (6.6)	506 (12.0)	223 (13.1)	140 (15.6)	56 (17.7)	<0.001
Malignancy (current/prior), N (%)	57 (4.4)	340 (8.0)	150 (8.8)	84 (9.4)	39 (12.2)	<0.001
Previous hemorragic events, N (%)	56 (4.3)	187 (4.4)	111 (6.5)	81 (9.1)	35 (10.9)	<0.001
Anemia, N (%)	48 (3.7)	171 (4.0)	109 (6.3)	107 (11.9)	72 (22.4)	<0.001
CHA_2DS_2VASc, median [IQR]	2.00 [1.00, 3.00]	3.00 [2.00, 4.00]	4.00 [3.00, 5.00]	4.00 [3.00, 5.00]	5.00 [4.00, 6.00]	<0.001
HAS-BLED, median [IQR]	1.00 [0.00, 2.00]	1.00 [1.00, 2.00]	2.00 [1.00, 2.00]	2.00 [2.00, 3.00]	3.00 [2.00, 3.00]	<0.001
EHRA class high, N (%)	796 (61.0)	2425 (56.9)	984 (57.1)	487 (53.9)	170 (52.8)	0.006
OAC, N (%)	1045 (80.2)	3762 (88.2)	1489 (86.5)	769 (85.2)	241 (74.8)	<0.001
Type of OAC, N (%)						<0.001
No	258 (19.8)	501 (11.8)	233 (13.5)	134 (14.8)	81 (25.2)	
VKA	557 (42.8)	2114 (49.6)	899 (52.2)	498 (55.1)	192 (59.6)	
DOAC	488 (37.4)	1648 (38.7)	590 (34.3)	271 (30.0)	49 (15.2)	

Legend AF, atrial fibrillation; BMI, body mass index; CG, Cockroft Gault; CKD, chronic kidney disease; CrCl, creatinine clearence; DOAC, direct oral anticoagulants; IQR, interquartile range; LVEF, left ventricular ejection fraction; N, number; OAC, oral anticoagulant; VKA, vitamin K antagonist.

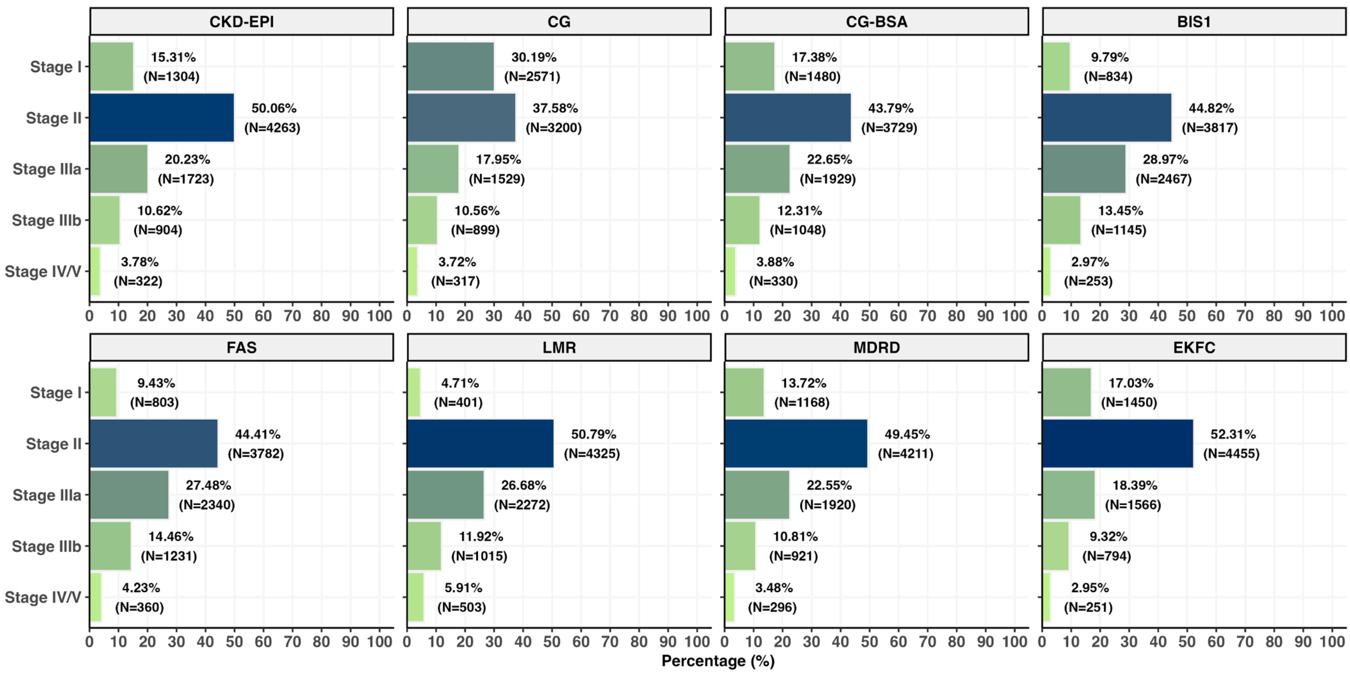

Fig. 1. Distribution of patients in different KDIGO stages according to the 8 different equations.
Legend. BIS-1, Berlin Initiative Study; CG, Cockcroft Gault; CG-BSA, adjusted for body surface area; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; EKFC, European Kidney Function Consortium; FAS, Full Age Spectrum; LMR, Liquidity Maintenance Ratio; MDRD, Modification of Diet in Renal Disease; N, number.

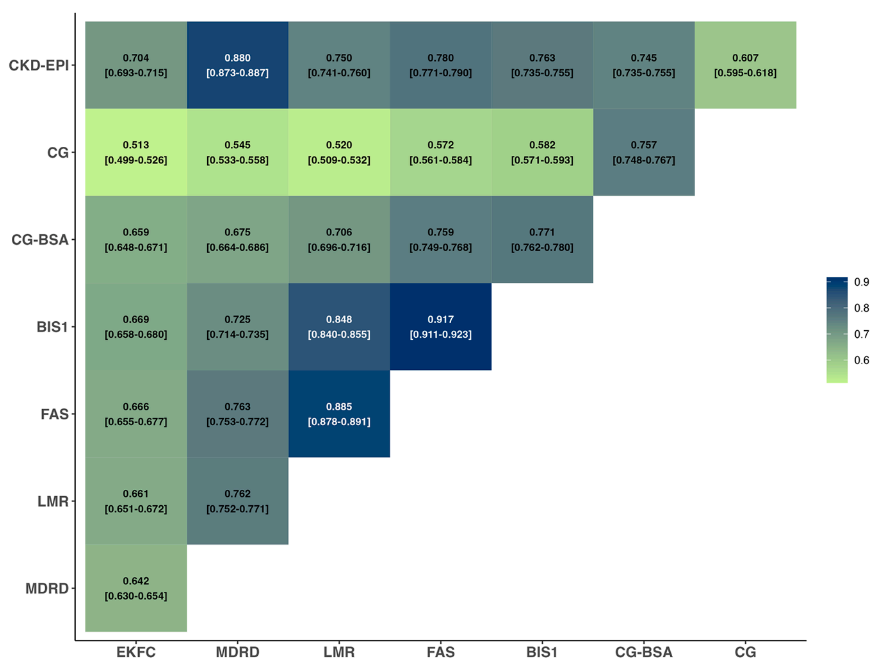

Fig. 2. Weighted Cohen's Kappa for concordance of classification of CKD according to 8 formulas.
Results are reported as K [95% CI]. Concordance was defined as follows: K <0.20 poor; 0.21-0.40 modest; 0.41-0.60 moderate; 0.61-0.80 good; >0.80 excellent.
Legend. BIS1 Berlin Initiative Study; CG, Cockcroft Gault; CG-BSA, Cockcroft Gault adjusted for body surface area; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; EKFC, European Kidney Function Consortium; FAS, Full Age Spectrum; LMR, Liquidity Maintenance Ratio; MDRD, Modification of Diet in Renal Disease.

increases exponentially when renal function falls below 60 ml/min. Conversely, for patients with eGFR (or CrCl) values ≥60 ml/min, the relationship plateaus, with a non-significant association observed for the CKD-EPI, BIS1, FAS, LMR, MDRD, and EKFC formulas. Only the CG and CG-BSA formulas showed a significant inverse association with adverse outcomes in patients with eGFR (or CrCl) ≥60 ml/min.

The secondary analysis, focusing on all-cause death, provided further validation of the findings from the main analysis. Specifically, this confirmed the increased risk of adverse outcomes observed for patients in CKD Stages IV/V across all eight formulas (**Supplementary Figures 3 and 4**).

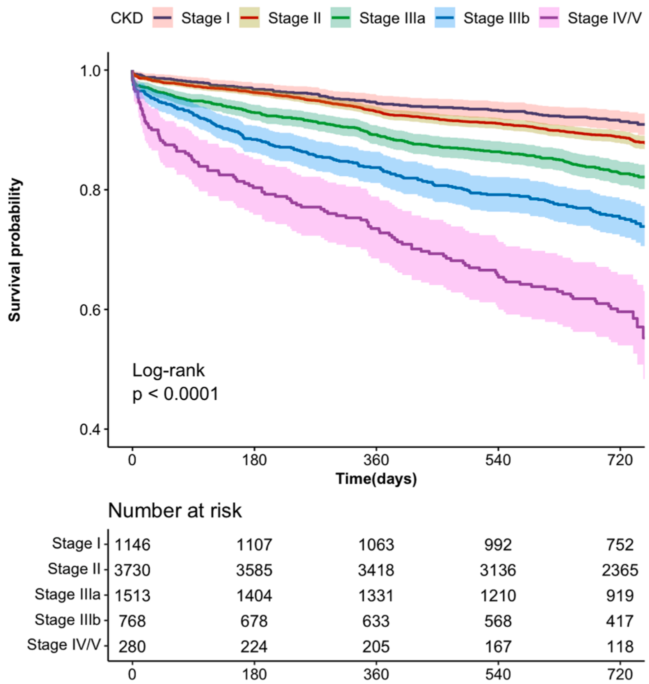

Fig. 3. Kaplan-Meier curves for primary composite outcome according to CKD stages.
Legend. CKD, chronic kidney disease.

3.4. Predictive and reclassification analysis

According to ROC curve analysis, the CG-BSA and CG formulas showed the best discriminant capability for predicting events of the composite outcome (Fig. 5 and **Supplementary Table 2**), with no significant difference between the two. Conversely, the MDRD equation showed the worst performance compared to the others. The CKD-EPI formula was statistically inferior to all other formulas except MDRD. Consistent results were found considering the secondary endpoint of all-cause death, with an overall better prediction of the event among across all the 8 formulas (Fig. 5).

The predictive performance of the different renal function formulas for any TE was overall limited (**Supplementary Figure 5**). Among the eight formulas tested, CKD-EPI and LMR demonstrated the highest, albeit modest, discriminative ability (AUC 0.562, 95% CI: 0.522–0.602 and 0.563, 95% CI: 0.524–0.603, respectively). No statistically significant differences were observed between the formulas in predicting TE events.

Based on integrated discrimination improvement (IDI) analysis, compared to the CKD-EPI equation, the CG and CG-BSA formulas showed significant improvements in sensitivity of 0.9% and 1.1%, respectively (Table 2). In contrast, the MDRD formula showed a significant reduction of -1.1% compared with CKD-EPI.

Using net reclassification improvement (NRI), there was a significant positive reclassification for CG and CG-BSA compared to CKD-EPI (11.3% and 16.3%, respectively), while the MDRD formula showed a negative reclassification of -22.0%. Overall, the median improvement (MI) in predictive ability for the CG and CG-BSA formulas was 0.9% and 1.2%, respectively, compared with CKD-EPI, whereas the MDRD formula resulted in a 0.9% reduction. All other formulas also showed significant positive reclassification compared with CKD-EPI in terms of MI (Table 2).

4. Discussion

The main findings of our analysis are as follows: i) the majority of patients with AF are classified as having renal impairment according to 8 different formulas, with the majority of them having Stage II CKD; ii) the concordance in the classification of AF patients was variable across formulas, with CG showing only a modest concordance with the others; iii) nonetheless, CG and CG-BSA showed the best discrimination ability for the prediction of adverse events; iv) a reduction of renal function below 60 ml/min was associated with an exponential increase of the risk of adverse events according to all the formulas.

The finding that the majority of patients AF are classified as having renal impairment across all eight formulas underscores the strong link between AF and CKD. This association may be explained by several

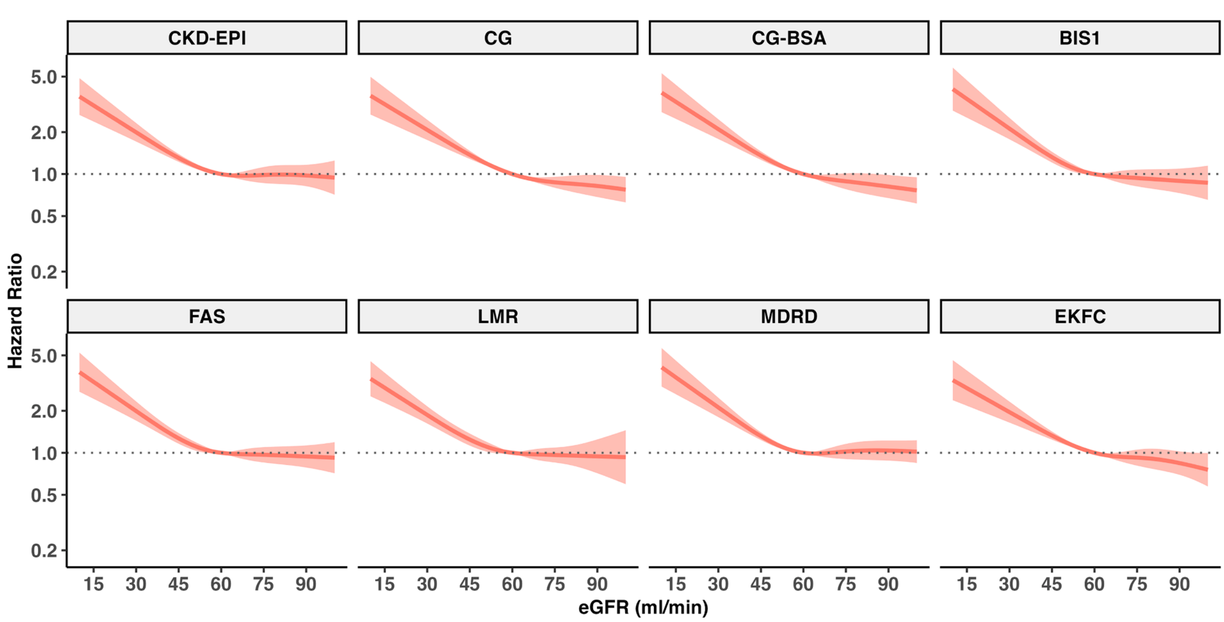

Fig. 4. Spline curves expressing the non-linear association between eGFR (or CrCl) and composite outcome.
Legend. BIS1 Berlin Initiative Study; CG, Cockcroft Gault; CG-BSA, Cockcroft Gault adjusted for body surface area; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; EKFC, European Kidney Function Consortium; FAS, Full Age Spectrum; LMR, Liquidity Maintenance Ratio; MDRD, Modification of Diet in Renal Disease.

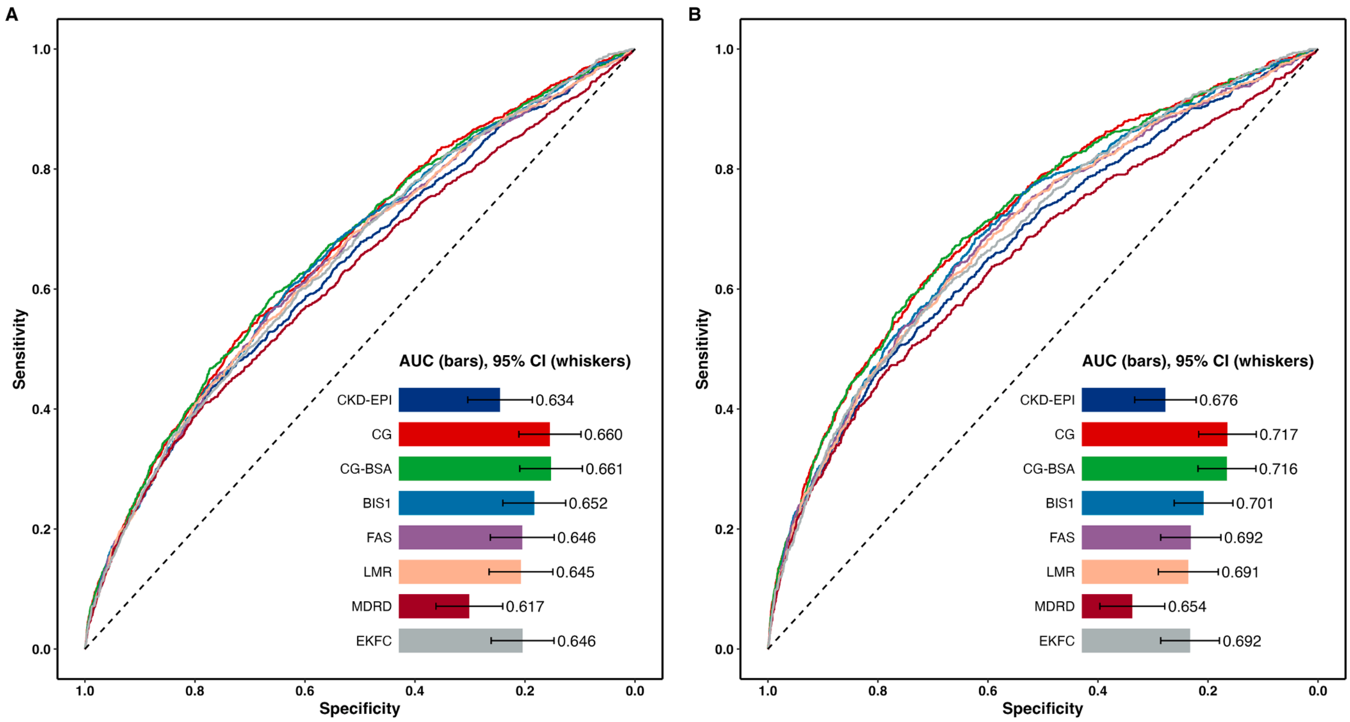

Fig. 5. Area under the curve for prediction of adverse events for different equations. Panel A composite outcome of All-cause death and MACEs, Panel B All-cause death.
Legend. AUC, area under the curve; BIS1 Berlin Initiative Study; CI, confidence interval; CG, Cockcroft Gault; CG-BSA, Cockcroft Gault adjusted for body surface area; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; EKFC, European Kidney Function Consortium; FAS, Full Age Spectrum; LMR, Liquidity Maintenance Ratio; MDRD, Modification of Diet in Renal Disease.

Table 2
Reclassification analysis for the composite outcome.

Formula	IDI	95% CI	P value	NRI	95% CI	P value	MI	95% CI	P value
CKD-EPI	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
CG	0.009	0.002/0.015	0.020	0.113	0.049/0.16	<0.001	0.009	0.005/0.015	<0.001
CG-BSA	0.011	0.007/0.016	<0.001	0.163	0.098/0.209	<0.001	0.012	0.007/0.018	<0.001
BIS1	0.005	0.002/0.008	0.007	0.125	0.045/0.181	0.007	0.005	0.002/0.009	0.007
FAS	0.002	0.000/0.004	0.166	0.055	-0.007/0.125	0.066	0.003	0.000/0.005	0.047
LMR	0.005	0.003/0.006	<0.001	0.184	0.141/0.219	<0.001	0.004	0.003/0.005	<0.001
MDRD	-0.011	-0.014/-0.009	<0.001	-0.220	-0.253/-0.189	<0.001	-0.009	-0.012/-0.007	<0.001
EKFC	0.004	0.000/0.008	0.020	-0.002	-0.051/0.058	0.977	0.006	0.003/0.009	<0.001

Legend. BIS-1, Berlin Initiative Study; CG, Cockcroft Gault; CG-BSA, adjusted for body surface area; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; EKFC, European Kidney Function Consortium; FAS, Full Age Spectrum; IDI, integrated discrimination improvement; LMR, Liquidity Maintenance Ratio; MDRD, Modification of Diet in Renal Disease; MI, median improvement; NRI, net reclassification improvement.

factors, including shared risk factors such as hypertension, diabetes, and aging [28–30], as well as the pathophysiological interplay where CKD can lead to structural and electrical remodelling of the heart [31], predisposing patients to AF, while AF itself may contribute to worsening renal function through mechanisms like reduced cardiac output and renal perfusion [32]. Previous studies have consistently demonstrated this bidirectional relationship between AF and CKD, highlighting how the presence of one condition often exacerbates the other [6,33,34]. Previous analyses showed that also a mildly reduced renal function (e.g. <90 ml/min) is associated with an increased risk of incident AF [35]. In our study, we extended this understanding by analyzing eight different formulas for estimating renal function, and remarkably, all were concordant in classifying the majority of AF patients as having renal impairment.

However, the degree of concordance between the formulas varied. The CG formula, for instance, showed only modest concordance with the others, potentially due to its reliance on body weight and lack of standardization to BSA. In contrast, the CKD-EPI formula demonstrated high concordance with the MDRD formula, both of which are commonly used in clinical practice. These results are consistent with those of a previous analysis by Malavasi et al. [36], conducted among patients admitted to the Cardiology Division of a single centre in Italy (whether with AF or not). Similarly, a previous analysis by Boriani et al. [37] showed comparable results when considering AF patients, with a weighted kappa of 0.892 between the MDRD and CKD-EPI formulas. The strong concordance between the MDRD and CKD-EPI formulas may be explained by their similar approaches to estimating renal function. Both formulas incorporate serum creatinine, age, and sex, but CKD-EPI is considered more accurate, particularly at higher levels of kidney function [15]. However, they share methodological similarities that likely contribute to their alignment in classifying patients across different stages of CKD (Supplementary Material).

In our analysis, the FAS and BIS 1 formulas exhibited the highest concordance with each other, suggesting their utility in providing reliable estimates of renal function across diverse patient populations. This variability in concordance highlights the importance of considering multiple formulas when assessing renal function in patients with AF, particularly given the implications for clinical decision-making.

Crucially, our findings also revealed an exponential increase in the risk of adverse events when the estimated glomerular filtration rate (eGFR) fell below 60 ml/min, consistent across all eight formulas. This pattern underscores the significance of renal impairment as a critical risk factor for adverse events in AF patients [37]. The exponential rise in risk below this threshold suggests that even moderate declines in kidney function can substantially worsen outcomes, potentially due to the combined burden of reduced renal clearance, increased cardiovascular stress, and the challenges of managing anticoagulation in this population [38] . This finding aligns with previous research, which has similarly reported heightened risks in CKD patients with AF, particularly as renal function deteriorates [9]. The consistent results across different formulas in our study reinforce the robustness of this association and highlight the importance of early identification and management of renal impairment to mitigate the risk of adverse events in AF patients.

Finally, when it comes to predicting adverse events, our analysis found that the CG and CG-BSA formulas outperformed all others, showing the highest discrimination ability. This finding is particularly important given that anticoagulation decisions in clinical practice are based on the CG formula as recommended by clinical guidelines and consensus globally [11,39,40]. The superior performance of these formulas may therefore reflect their alignment with the criteria used to assess stroke and bleeding risks in AF patients, making them more sensitive to the nuances of renal function that are critical in anticoagulation management. Nonetheless, it is well recognized that achieving precise predictive tools in AF is challenging, whether for thromboembolic events or bleeding risks, and our results are consistent with the broader difficulties seen across various predictive tools used in this clinical setting [41].

While the differences in AUC between CG, CG-BSA, and the other formulas were statistically significant, it's important to note that the absolute differences in AUC values were relatively small. This suggests that, although CG and CG-BSA may have a slight edge in predictive accuracy, the clinical significance of this difference might be limited. In practical terms, this means that while CG-based formulas are preferred for certain clinical decisions, such as anticoagulation, the other formulas still provide valuable and nearly equivalent information for assessing renal function and associated risks in AF patients. Therefore, while CG and CG-BSA may guide specific therapeutic decisions, the overall predictive capacity across different formulas remains robust, reinforcing the importance of comprehensive renal function assessment in managing AF.

CKD, like other comorbid conditions such as obesity, chronic obstructive pulmonary disease, peripheral artery disease, and heart failure, significantly worsens outcomes in patients with AF [42–45] . The clustering of these conditions further amplifies the risk, making it essential to adopt an integrated management approach [46–48]. Addressing CKD alongside these other comorbidities is crucial to improving prognosis and tailoring treatment strategies for AF patients, ensuring that both cardiovascular and renal health are optimally managed in an evidence-based manner [49]. In the future, artificial intelligence tools are expected to play a pivotal role in risk stratification and the management of patients with AF and CKD [50]. Ongoing studies are currently exploring the potential of these technologies to enhance clinical decision-making and improve outcomes in this complex patient population [51].

4.1. Study limitations

This study has several limitations that should be acknowledged. Firstly, the retrospective nature of the analysis inherently limits the ability to establish causality and may introduce biases related to the collection and interpretation of data. Secondly, the study was conducted exclusively in a European population, which limits the generalizability of the findings to other populations, particularly those of Asian descent, who may have different genetic and environmental risk profiles. Finally, despite comprehensive adjustments for known confounders, the possibility of residual confounding cannot be entirely excluded, which may impact the study's conclusions regarding the relationship between renal function, as estimated by different formulas, and adverse outcomes in patients with AF.

5. Conclusions

Our study underscores that AF and CKD frequently coexist in patients with AF, as assessed by various equations for estimating renal function. The concordance between the CG formula and other formulas is only moderate, which could have implications for OAC prescription. Nonetheless, renal function estimation using the CG and CG-BSA formulas showed the best discriminative performance for predicting adverse events.

Declaration of competing interest

GB reported small speaker fees from Bayer, Boehringer Ingelheim, Boston, Daiichi Sankyo, Janssen, and Sanofi outside of the submitted work. GB is the Principal Investigator of the ARISTOTELES project (Applying ARtificial Intelligence to define clinical trajectorieS for personalized predicTiOn and early deTEction of comorbidity and muLtimorbidity pattErnS) that received funding from the European Union within the Horizon 2020 research and innovation program (Grant N. 101080189).

GFR reports consultancy for Boehringer Ingelheim and an educational grant from Anthos, outside the submitted work. No fees are directly received personally;

MP is national leader of the AFFIRMO project on multimorbidity in AF, which has received funding from the European Union's Horizon 2020 research and innovation program under grant agreement No 899871;

GYHL is a consultant and speaker for BMS/Pfizer, Boehringer Ingelheim, Anthos and Daiichi-Sankyo. No fees are received personally. GYHL is a NIHR Senior Investigator and co-principal investigator of the AFFIRMO project on multimorbidity in AF, which has received funding from the European Union's Horizon 2020 research and innovation program under grant agreement No 899871.

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Supplementary materials

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