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Original Article

ORIGINAL ARTICLE

Kidney function estimators for drug dose adjustment of direct oral anticoagulants in older adults with atrial fibrillation

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ABSTRACT

Background. The Cockcroft–Gault equation ($CrCl_{C\text{-}G}$) is recommended for dose adjustment of direct oral anticoagulant drugs (DOACs) to kidney function. We aimed to assess whether defining DOAC dose appropriateness according to various kidney function estimators changed the associations between dose appropriateness and adverse events in older adults with atrial fibrillation (AF).

Methods. Participants of the Berlin Initiative Study with AF and treated with DOACs were included. We investigated $CrCl_{C\text{-}G}$ and estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration and European Kidney Function Consortium equations based on creatinine and/or cystatin C. Marginal structural Cox models yielded confounder-adjusted hazard ratios for the risk of mortality, thromboembolism and bleeding associated with dose status.

Results. A total of 224 patients were included in the analysis (median age 87 years). Using $CrCl_{C\text{-}G}$, 154 (69%) had an appropriate dose of DOACs, 52 (23%) were underdosed and 18 (8%) were overdosed. During a 39-month median follow-up period, 109 (14.9/100 person-years) participants died, 25 (3.6/100 person-years) experienced thromboembolism and 60 (9.8/100 person-years) experienced bleeding. Dose status was not associated with mortality and thromboembolism, independent of the equation. Underdose status was associated with a lower risk of bleeding with all the equations compared with the appropriate dose group. In participants with discrepancies in dose status using $CrCl_{C\text{-}G}$ and eGFR equations, the occurrence of endpoints did not differ between participants having an appropriate dose using $CrCl_{C\text{-}G}$ or eGFR.

Conclusion. In older adults with AF, the association of DOAC dose status with adverse events did not differ when using $CrCl_{C\text{-}G}$ or eGFR. Our results suggest that eGFR equations are not inferior to $CrCl_{C\text{-}G}$ within this context.

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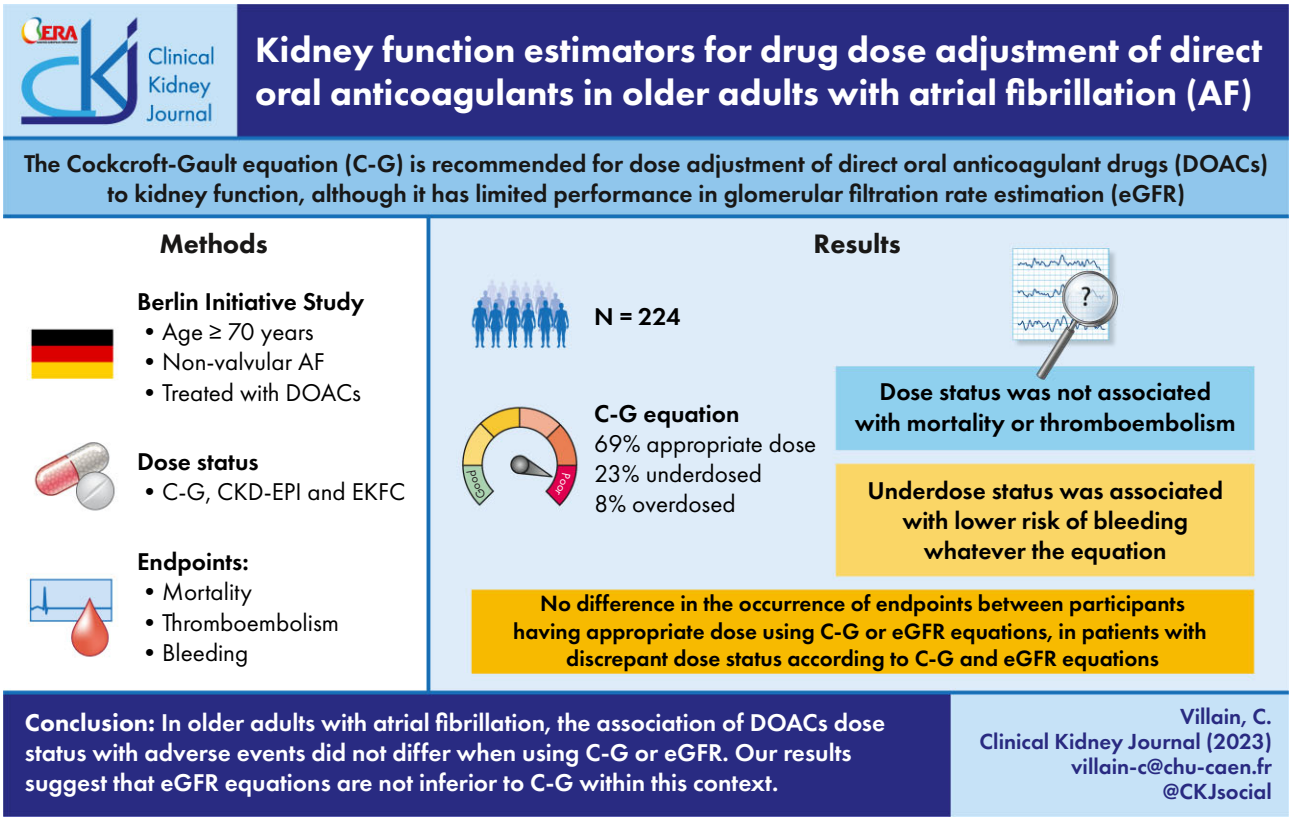
GRAPHICAL ABSTRACT



Keywords: atrial fibrillation, creatinine clearance, glomerular filtration rate, older adults, oral anticoagulant drug

INTRODUCTION

Direct oral anticoagulants (DOACs) are recommended as first-line therapy in non-valvular atrial fibrillation (NVAF) [1]. Dose adjustment is necessary when kidney function is reduced. Guidelines of the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) recommend the use of creatinine clearance estimated by the Cockcroft–Gault equation ($CrCl_{C\text{-}G}$) for this drug class [2, 3]. The $CrCl_{C\text{-}G}$ was used for drug dose adjustment for kidney function in the pivotal randomized controlled trials on DOACs in NVAF patients [4]. Several studies showed that the use of inappropriately dosed DOACs was associated with an increased risk of death [5–8], bleeding [9–12] and thromboembolism [10–12].

Due to the limited performance of the $CrCl_{C\text{-}G}$ in determining the estimated glomerular filtration rate (eGFR), healthcare regulatory agencies recently proposed the use of eGFR equations for dose adjustment of other drug classes [13, 14]. In clinical routine, eGFR is based on serum creatinine, but combining serum creatinine with cystatin C leads to more accurate eGFRs [15, 16]. Recent studies found that patients having discrepancies in DOAC dose status according to the equations used (i.e. appropriate with the $CrCl_{C\text{-}G}$ and inappropriate with the eGFR equation, or vice versa) were exposed to higher risks of thromboembolism and bleeding than patients without discrepancies [17, 18]. One study in dabigatran users found that underdose determined using the $CrCl_{C\text{-}G}$ or Chronic Kidney Disease Epidemiology Collaboration eGFR ($eGFR_{CKD\text{-}EPI}$) equation was associated with a higher risk of thromboembolism as compared with appropriate dose, but overdose was associated with a higher risk of bleeding only when using the $CrCl_{C\text{-}G}$ [12]. However, to the best of our knowledge, this has not been studied in patients treated with other DOACs or using eGFR equations that include cystatin C.

Dose adjustment of DOACs is especially relevant in older adults, where the $CrCl_{C\text{-}G}$ has sometimes been shown to have poor performance [19]. The prevalence of NVAF and chronic kidney disease (CKD) dramatically increases in older age [20, 21]. Older adults are more prone to adverse drug reactions and oral anticoagulant drugs are among the most represented drugs in iatrogenic events [22]. Finally, an inappropriate dose of DOACs is frequent in older ages [5–9, 23], as are discrepancies in dose status of DOACs depending on kidney function estimators [12, 17, 24].

Using data from the Berlin Initiative Study (BIS), we aimed to assess whether defining dose appropriateness of DOACs according to various kidney function estimators (with or without cystatin C) modified the association between dose appropriateness and mortality, thromboembolism and bleeding in older adults with NVAF. We hypothesized that determination of the DOAC dose using eGFR equations would not be inferior to the use of the $CrCl_{C\text{-}G}$ in terms of association with endpoints.

MATERIALS AND METHODS

Study design and population

The BIS is a population-based prospective cohort study in Berlin, Germany, to evaluate kidney function in individuals ≥70 years of age. Criteria for study inclusion were age ≥70 years and membership at the statutory health insurance company Allgemeine Ortskrankenkasse (AOK) Nordost. Patients on dialysis, with kidney transplantation or with the highest level of care at baseline were excluded. All participants gave written informed consent before enrolment in the study. The study protocol was approved by the local ethics committee (EA2/009/08). Participants were followed up biennially until 2019. Detailed information on the design of the BIS is available in the Supplementary Methods and has been described elsewhere [25, 26].

In this analysis, we included BIS participants with a history of NVAF or flutter who were treated with DOACs on at least one follow-up visit and had a CHA2DS2-VASc ≥2 in men and ≥3 in women [1]. History of NVAF and flutter were defined using the German modification of the 10th revision of the International Classification of Diseases (ICD-10-GM) codes from the claims data (details in Supplementary Table 1). Participants were considered as having atrial fibrillation, flutter or valvular heart disease if they had at least one hospital or at least two ambulatory ICD-10-GM codes for the respective diagnosis before a follow-up visit. Participants were counted as being treated with DOACs if they had at least one dispensed prescription for apixaban, dabigatran, edoxaban or rivaroxaban in the 4 months before the study visit. We chose a 4-month period for its clinical relevance because a shorter period would have led to the exclusion of participants actually taking DOACs but who did not renew their prescription during that period, and a longer period would have led to the inclusion of participants who could have stopped taking DOACs before the follow-up visit.

Baseline data correspond to the first study visit where inclusion criteria were met. Participants were censored if they stopped taking DOACs between two follow-up visits (i.e. no prescription for DOACs in the 4-month period before the latter visit) and were then censored at the date of the latter visit, they died during follow-up or experienced a secondary endpoint or the end of the observation period (31/12/2021), whatever occurred first.

The primary endpoint was all-cause mortality. Death status was actively searched for biannually using both AOK data as well as official death certificates for all BIS participants. The secondary endpoints were hospitalization due to bleeding or thromboembolism, defined as stroke or transient ischaemic attack or systemic embolism, using at least one ICD-10-GM code based on hospital claims data (Supplementary Table 1).

Exposures

The type of DOAC and dose status were updated at each follow-up visit. The last prescription before the study visit was used to define DOAC dose. Appropriateness of the DOAC dose was assessed using EMA guidelines for dose adjustment of DOACs (details in Supplementary Table 2) [4]. Any participant with a higher dose than recommended according to the patient's characteristics or a contraindication to the considered DOAC use due to low kidney function was defined as overdosed. Any participant with a lower dose than expected for the respective DOAC according to the patient's characteristics was defined as underdosed. All others were defined as appropriately dosed.

Drug dose status was assessed using the $CrCl_{C\text{-}G}$[2], $eGFR_{CKD\text{-}EPI}$ [16] and the European Kidney Function Consortium ($eGFR_{EKFC}$) [15] equations (details in Supplementary Methods). For the two latter equations, we considered their versions based on serum creatinine ($eGFR_{CKD\text{-}EPIcr}$, $eGFR_{EKFCcr}$), serum cystatin C ($eGFR_{CKD\text{-}EPIcys}$, $eGFR_{EKFCcys}$ in its sex-specific version) and both biomarkers ($eGFR_{CKD\text{-}EPIcr\text{-}cys}$, $eGFR_{EKFCcr\text{-}cys}$). For drug dose adjustment, an eGFR expressed in ml/min is recommended by calculating the patient's individual body surface area (BSA) [13, 14]. The $eGFR_{CKD\text{-}EPI}$ and $eGFR_{EKFC}$ equations were thus expressed in ml/min after taking the estimated BSA using the Dubois equation into account. Kidney function and BSA were updated at each follow-up visit. Detailed information on other variables is available in the Supplementary Methods.

Statistical analyses

Participants' characteristics were described using absolute and relative frequencies for categorical variables and mean ± standard deviation (SD) or median [1st–3rd quartiles (IQR)] for continuous variables, depending on the distribution. The association between the participants' characteristics and dose status according to the $CrCl_{C\text{-}G}$ was assessed using univariable multinomial logistic regression models.

The association between endpoints and dose status was assessed using marginal structural Cox models in order to account for changes in dose status over time [27, 28]. These models were chosen because they better control for the effects of time-varying confounders that are affected by prior treatment and allow for control for informative censoring compared with multivariate time-varying Cox models [27]. Detailed information on these models is available in the Supplementary Methods. Subgroup analyses were performed in participants taking apixaban or rivaroxaban and those with an $eGFR_{CKD\text{-}EPIcr}$ <60 ml/min/1.73 m^2, according to the current definition of CKD stages 3–5. Due to the small number of participants, we were unable to perform subgroup analyses in dabigatran and edoxaban users. Due to the low incidence rate of thromboembolism, we did no further subgroup analyses. In patients with discrepant dose status using the $CrCl_{C\text{-}G}$ and eGFR equations, we compared the occurrence of endpoints using the equation for which the dose status was considered appropriate. We used univariable logistic regression for this last analysis due to the small sample size.

Finally, we assessed the discrepancy in dose status according to indexed (i.e. expressed in ml/min/1.73 m^2) and de-indexed (i.e. expressed in ml/min) eGFR and investigated if the dose status based on the indexed eGFR was associated with the occurrence of the study endpoints.

Missing values were taken into account by computing multiple imputations using multiple chained equations, assuming that data were missing at random [29]. For each missing value, 20 imputations were computed, leading to 20 different databases. The results of the 20 databases were pooled according to Rubin's rules [30]. Statistical analyses were performed using R version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria). Effect estimates are presented alongside 95% confidence intervals (CIs). All analyses were performed in an exploratory manner and adjustment for multiple testing was not performed to avoid suppression of potential signals.

RESULTS

Study population

Among the 2069 participants of the BIS, 224 were included in the present analysis (flow diagram in Supplementary Fig.1). At baseline, the median age was 87 years and 115 (51%) participants were female. A total of 99 (44%) participants were treated with rivaroxaban, 86 (38%) with apixaban, 21 (9%) with edoxaban and 18 (8%) with dabigatran. Detailed characteristics of the study population are presented in Table 1.

Dose status according to patients' characteristics, drugs and kidney function estimators

When using the $CrCl_{C\text{-}G}$, 154 (69%) had appropriate dose status, 52 (23%) were underdosed and 18 (8%) were overdosed at baseline. Univariate associations between patients' characteristics and dose status are shown in Table 2 . Compared with patients with an appropriate dose, underdosed patients were significantly older and overdosed patients were more likely to be female, to have lower HAS-BLED scores, Charlson Comorbidity Index (CCI) and body mass index (BMI) and were less likely to have coronary artery disease. Dose status according to kidney function estimators and drugs are shown in Fig. 1. Appropriate dose status varied from 100% in dabigatran users to 58% in apixaban users (Fig. 1B). Underdose and overdose status were more frequently found in apixaban users (38%) and edoxaban users (19%), respectively. Proportions of patients with an appropriate dose ranged from 63% with the $eGFR_{CKD\text{-}EPIcr}$ to 69% with the $CrCl_{C\text{-}G}$ (Fig. 1A). Discrepancies in dose status when using the $CrCl_{C\text{-}G}$ or the other equations ranged from 7% (for $eGFR_{EKFCcr}$ and $eGFR_{EKFCcr\text{-}cys}$) to 13% (for $eGFR_{CKD\text{-}EPIcys}$ and $eGFR_{EKFCcys}$).

Association of dose status and endpoints

During a median follow-up of 39 months (IQR 28–58), of 224 participants, 109 (14.9/100 person-years) died, 60 (9.8/100 person-years) were hospitalized with a bleeding diagnosis and 25 (3.6/100 person-years) were hospitalized with a thromboembolism diagnosis. Fig. 2 shows the association of the endpoints with dose status according to the studied equations. Using marginal structural Cox models, dose status was not associated with the occurrence of death and thromboembolism, independent of the equation. Underdose status was associated with a lower risk of bleeding compared with the appropriate dose group, whereas overdose status was not associated with bleeding, whatever the equation used.

Subgroup analyses

In apixaban users, dose status was not significantly associated with death or bleeding (Supplementary Table 3). In rivaroxaban users, underdose using the $CrCl_{C\text{-}G}$ and $eGFR_{CKD\text{-}EPIcys}$ was associated with a significantly higher risk of death. Underdose using the $eGFR_{CKD\text{-}EPIcr}$ was associated with a significantly lower risk of bleeding as compared with the appropriate dose group, whereas the other associations were not statistically significant (Supplementary Table 4). In participants with an $eGFR_{CKD\text{-}EPIcr}$ <60 ml/min/1.73 m^2, underdose was associated with a lower risk of bleeding compared with the appropriate dose group, except when using the $CrCl_{C\text{-}G}$ (Supplementary Table 5).

In patients with discrepant dose status using the $CrCl_{C\text{-}G}$ and eGFR equations, we compared the occurrence of endpoints using the equation for which the dose status was considered appropriate (Fig. 3). No significant difference in endpoint occurrence was

Table 1: Characteristics of the study population at baseline (N = 224).

Variable	Value	Missing values, *n* (%)[a]
Sociodemographic variables		
Age (years), median (IQR)	87 (81–91)	
Female, *n* (%)	115 (51)	
Non-smoker, *n* (%)	114 (51)	3 (1)
Former smoker, *n* (%)	102 (45)	
Current smoker, *n* (%)	8 (4)	
Daily alcohol consumption, *n* (%)	14 (6)	2 (1)
Comorbidities, *n* (%)		
Hypertension	218 (97)	
Diabetes	69 (31)	13 (6)
Heart failure	173 (77)	
Coronary artery disease	167 (75)	
Peripheral artery disease	153 (68)	
Prior stroke or transient ischaemic attack	64 (29)	
Prior systemic embolism	14 (6)	
Prior bleeding event	157 (70)	
Bleeding predisposition	115 (51)	
Dementia	62 (28)	
Liver disease	57 (25)	
Cancer	14 (6)	2 (1)
CCI, median (IQR)	7 (5–10)	
CHA2DS2-VASc, median (IQR)	6 (5–7)	
HAS-BLED score, median (IQR)	3 (3–4)	
Nutritional and functional status		
Frailty status, *n* (%)		79 (35)
Non-frail, *n* (%)	43 (19)	
Pre-frail, *n* (%)	87 (39)	
Frail, *n* (%)	94 (42)	
History of falls, *n* (%)	45 (20)	
BMI (kg/m^2), median (IQR)	27 (25–30)	5 (2)
BSA (m^2), median ± SD	1.82 ± 0.18	5 (2)
Kidney function estimators, median (IQR)		
$CrCl_{C\text{-}G}$ (ml/min)	45 (36–60)	20 (9)
$eGFR_{CKD\text{-}EPIcr}$ (ml/min/1.73 m^2)	56 (41–68)	19 (8)
$eGFR_{CKD\text{-}EPIcys}$ (ml/min/1.73 m^2)	44 (32–57)	20 (9)
$eGFR_{CKD\text{-}EPIcr\text{-}cys}$ (ml/min/1.73 m^2)	48 (36–62)	20 (9)
$eGFR_{EKFCcr}$ (ml/min/1.73 m^2)	50 (37–60)	19 (8)
$eGFR_{EKFCcys}$ (ml/min/1.73 m^2)	46 (35–59)	20 (9)
$eGFR_{EKFCcr\text{-}cys}$ (ml/min/1.73 m^2)	47 (36–59)	20 (9)
Medication, *n* (%)		
Apixaban	86 (38)	
Dabigatran	18 (8)	
Edoxaban	21 (9)	
Rivaroxaban	99 (44)	
Antiplatelet agent	22 (10)	
NSAIDs	32 (14)	
DOAC prescription duration (years), median (IQR)	0.8 (0.3–1.4)	
Total number of drugs per patient, median (IQR)	7 (5–9)	

[a]The variables without any mention did not have missing values.
$CrCl_{C\text{-}G}$: creatinine clearance estimated by the Cockcroft-Gault equation; $eGFR_{CKD\text{-}EPI}$ and $eGFR_{EKFC}$: glomerular filtration rate estimation using the Chronic Kidney Disease Epidemiology Collaboration and European Kidney Function Consortium equations, based on serum creatinine (σ) and/or serum cystatin (cys); DOAC: direct oral anticoagulant drug; NSAIDs: non-steroidal anti-inflammatory drugs.

Table 2: Association between dose status according to the Cockcroft–Gault equation and patients' characteristics at baseline (N = 224).

	Appropriate dose (Ref) ($n = 154$)	Underdose ($n = 52$)		Overdose ($n = 18$)	
Variable	Value[a]	Value[a]	OR (95% CI)[b]	Value[a]	OR (95% CI)[b]
Age (years), median (IQR)	87 (81–90)	87 (82–91)	1.06 (1.01–1.11)[c]	88 (81–92)	0.99 (0.92–1.06)[c]
Sex					
Male	55	40	1	23	1
Female	45	60	1.46 (0.87–2.45)	77	2.56 (1.08–6.10)
Hypertension					
No	3	2	1	0	1
Yes	97	98	1.18 (0.30–4.68)	100	0.58 (0.11–2.95)
Diabetes					
No	70	63	1	79	1
Yes	30	37	1.02 (0.58–1.80)	21	0.97 (0.40–2.39)
Heart failure					
No	23	13	1	28	1
Yes	77	87	1.83 (0.91–3.68)	72	0.61 (0.26–1.44)
Coronary artery disease					
No	24	23	1	48	1
Yes	76	77	1.14 (0.63–2.06)	52	0.41 (0.18–0.91)
Peripheral artery disease					
No	32	29	1	37	1
Yes	68	71	1.42 (0.80–2.53)	63	0.65 (0.29–1.46)
Prior stroke or transient ischaemic attack					
No	71	68	1	88	1
Yes	29	32	0.97 (0.56–1.68)	11	0.35 (0.12–1.07)
Prior systemic embolism					
No	95	92	1	89	1
Yes	5	8	1.79 (0.71–4.51)	11	1.32 (0.28–6.13)
Prior bleeding event					
No	27	37	1	32	1
Yes	73	63	0.98 (0.56–1.71)	68	1.02 (0.42–2.47)
Bleeding predisposition					
No	48	46	1	65	1
Yes	52	54	1.46 (0.87–2.45)	35	0.69 (0.31–1.56)
Liver disease					
No	75	69	1	85	1
Yes	25	31	1.38 (0.77–2.46)	15	0.39 (0.11–1.45)
Dementia					
No	72	75	1	70	1
Yes	28	25	1.12 (0.63–1.99)	30	0.73 (0.27–1.98)
CHA2DS2-VASc score, median (IQR)	6 (5–7)	6 (5–7)	1.02 (0.58–1.80)[c]	5 (5–7)	0.97 (0.40–2.39)[c]
HAS-BLED score, median (IQR)	3 (3–4)	3 (3–4)	0.89 (0.70–1.12)[c]	3 (3–4)	0.64 (0.42–0.98)[c]
CCI	7 (4–10)	8 (6–11)	0.89 (0.71–1.12)[c]	5 (3–8)	0.65 (0.43–0.99)[c]
Frailty					
Non-frail	20	15	1	21	1
Pre-frail	42	31	1.11 (0.50–2.50)	35	0.85 (0.26–2.79)
Frail	38	53	2.01 (0.95–4.39)	45	1.40 (0.45–4.34)
History of falls					
No	81	78	1	77	1
Yes	19	22	1.10 (0.58–2.06)	23	1.18 (0.45–3.10)
BMI (kg/m^2), median (IQR)	27 (25–30)	28 (26–31)	1.00 (0.94–1.07)[c]	24 (22–28)	0.86 (0.76–0.97)[c]
$eGFR_{CKD\text{-}EPIcr}$ (ml/min/1.73 m^2), median (IQR)	58 (38–71)	58 (46–66)	1.07 (0.92–1.24)[d]	48 (41–54)	0.80 (0.63–1.02)[d]
Antiplatelet agent or NSAIDs use					
No	76	79	1	89	1
Yes	24	21	0.66 (0.34–1.28)	11	0.41 (0.12–1.43)
Total number of drugs, median (IQR)	7 (5–9)	7 (5–11)	1.05 (0.97–1.13)[c]	6 (4–8)	0.92 (0.81–1.05)[c]

[a]Categorical variables are described by their relative frequencies; continuous variables are described by their mean ± SD if they are normally distributed or by their median [1st-3rd quartiles] if they are not.

[b]Odds ratio (OR) and 95% confidence intervals (95%CI) computed using univariable multinomial logistic regression with participants with appropriate dose as the reference.

[c]For a 1-unit increment.

[d]For a 10-ml/min/1.73m^2 increment.

$eGFR_{CKD\text{-}EPIcr}$: estimated glomerular filtration rate using CKD-EPI creatinine, NSAIDs: non-steroidal anti-inflammatory agents.

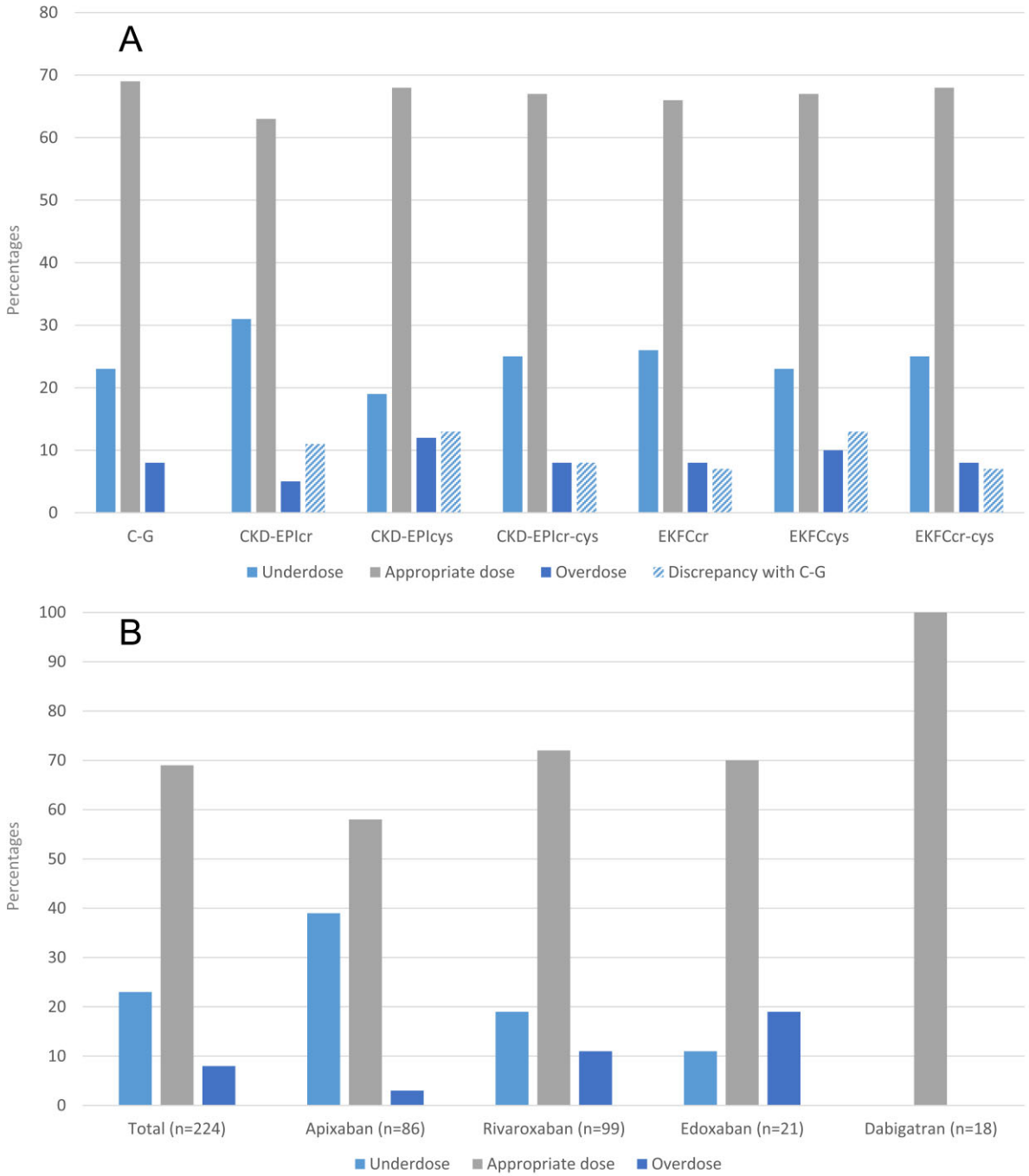


Figure 1: Dose status at baseline using various kidney function estimators **(A)** and Cockcroft–Gault according to drugs **(B)**. C-G: creatinine clearance estimated by the Cockcroft–Gault equation; CKD-EPI and EKFC: GFR estimation using the Chronic Kidney Disease Epidemiology Collaboration and European Kidney Function Consortium equations, based on serum creatinine (cr) and/or serum cystatin (cys).

found between participants having an appropriate dose using the $CrCl_{C\text{-}G}$ and eGFR equations.

Dose status using indexed equations

Discrepancies in dose status defined by indexed versus de-indexed eGFR varied by 3% for $eGFR_{CKD\text{-}EPIcr}$ to 9% for $eGFR_{EKFCcr\text{-}cys}$ (Supplementary Fig. 2). Discrepancies in dose status defined by indexed eGFR and $CrCl_{C\text{-}G}$ varied by 9% for $eGFR_{EKFCcr}$ to 16% for $eGFR_{CKD\text{-}EPIcys}$ and $eGFR_{EKFCcys}$. The association of endpoints with dose status using indexed eGFR was similar to de-indexed eGFR. However, underdose status was not associated with a lower risk of bleeding when using cystatin C–based $eGFR_{CKD\text{-}EPIcys}$ and $eGFR_{EKFCcys}$ (Supplementary Table 6).

DISCUSSION

In this population of older adults with NVAF, DOAC dose adjustment was appropriate in the majority of patients, with discrepancies in dose status according to the considered drugs

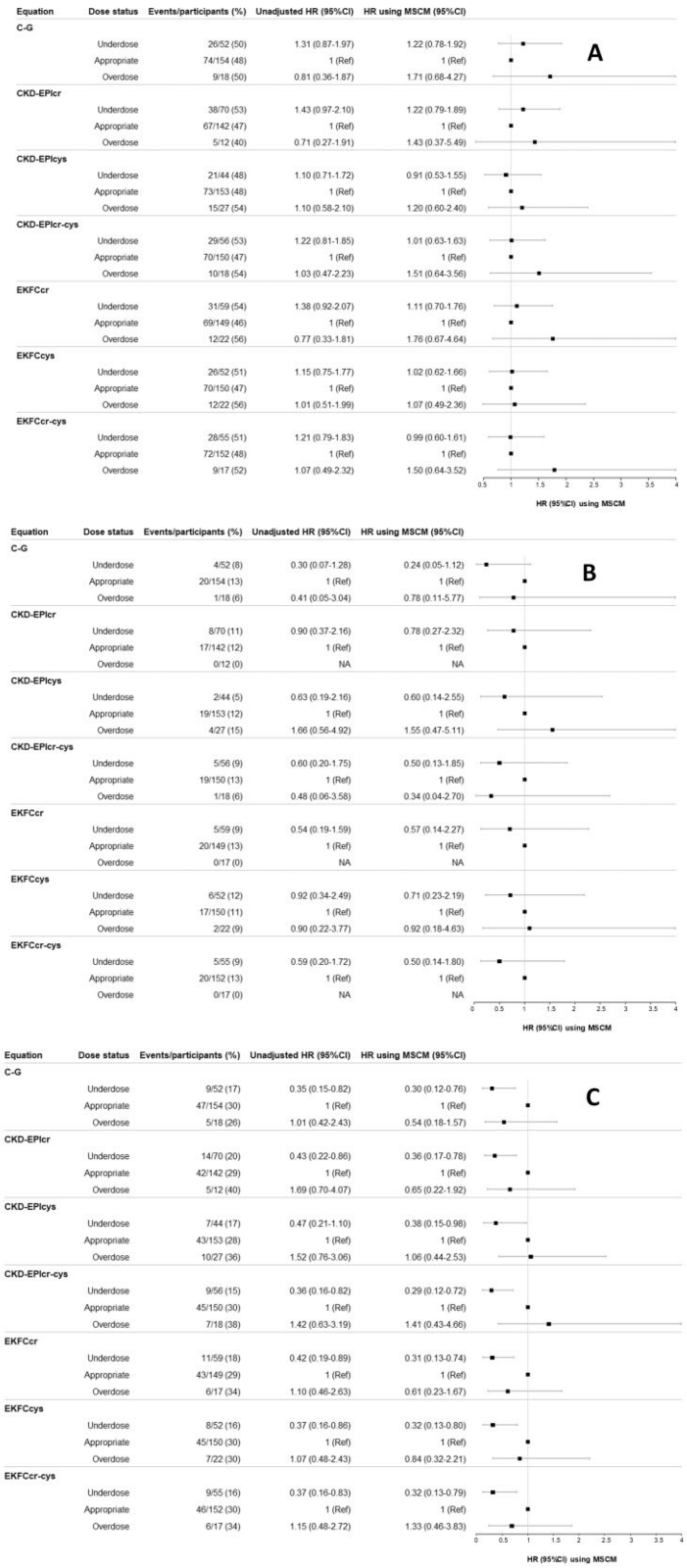


Figure 2: Association between dose status and **(A)** mortality, **(B)** thromboembolism and **(C)** bleeding according to various kidney function estimators. Sums of events and sample size can slightly differ between estimators due to the multiple imputation process. C-G: creatinine clearance estimated by the Cockcroft–Gault equation; CKD-EPI and EKFC: GFR estimation using the Chronic Kidney Disease Epidemiology Collaboration and European Kidney Function Consortium equations, based on serum creatinine (cr) and/or serum cystatin (cys).

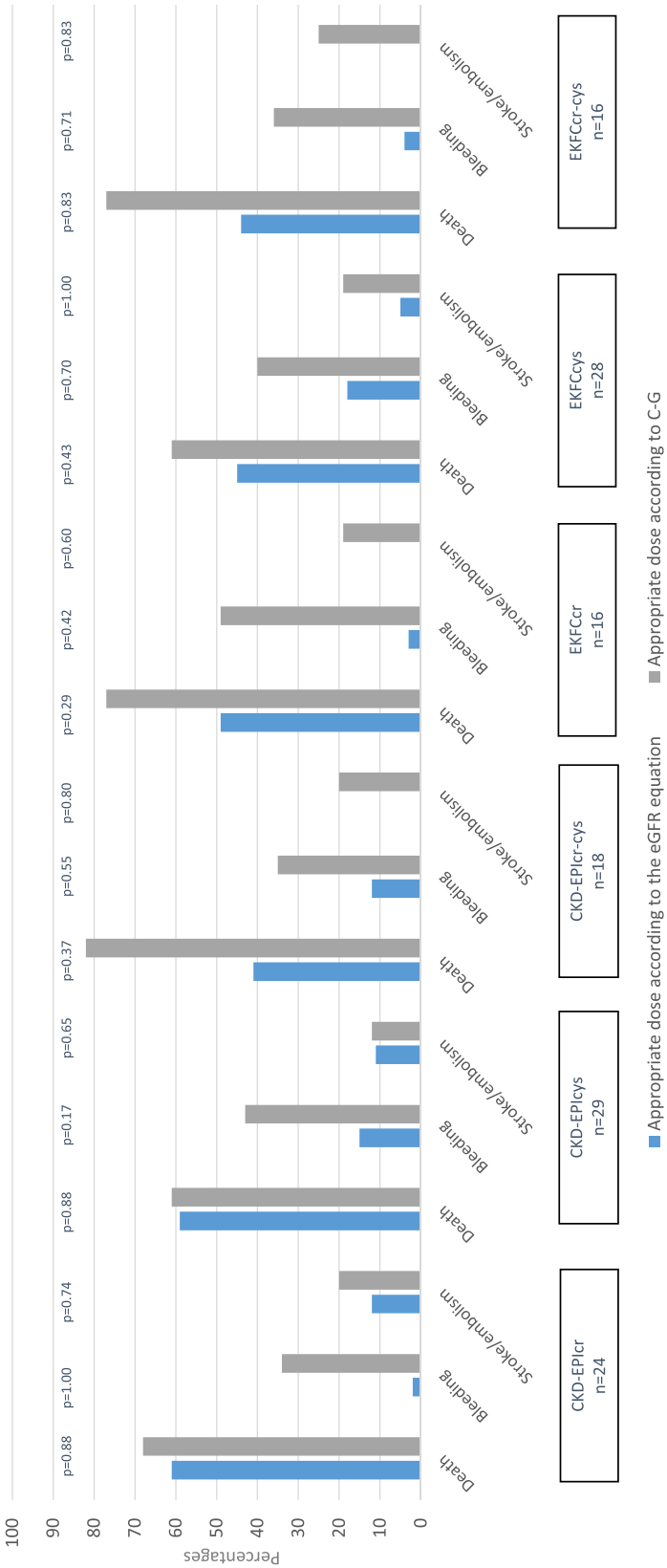


Figure 3: Comparison of endpoint occurrence in patients with discrepancies in dose status according to the Cockcroft–Gault equation and eGFR. These participants are represented by the striped bars in Fig. 1A. P-values were obtained using univariable logistic regression models; CKD-EPI and EKFC: GFR estimation using the Chronic Kidney Disease Epidemiology Collaboration and European Kidney Function Consortium equations, based on serum creatinine (cr) and/or serum cystatin (cys).

and kidney function estimators. Drug dose appropriateness was not associated with the occurrence of death and thromboembolism, no matter which kidney function estimator or underlying biomarker was used. The underdose group experienced fewer bleeding events with all the studied equations, but the overdose group did not experience a higher risk of bleeding.

Underdose status was more frequent than overdose status, as previously reported [5, 7–10]. The 69% of participants with an appropriate dose of DOACs was consistent with previous studies, which reported ranges from 63% to 87% [5, 7, 9, 10, 23, 31, 32]. However, dose appropriateness varied widely according to the considered drug. Previous studies found conflicting results about the most frequently underdosed and overdosed DOACs [7, 10, 23, 31, 32]. This discrepancy is likely to reflect various prescription practices and guidelines across countries, as well as differences in study population regarding kidney function. All dabigatran users were on appropriate drug doses at baseline. This could be explained by the small number of dabigatran users ($n = 18$), including only one patient with a medically indicated highest dose (i.e. 150 mg twice daily) and none with CKD stage 4 or 5.

Older age was the only factor significantly associated with the underdose status. Female sex, lower BMI, lower HAS-BLED score and lower CCI were significantly associated with overdose status. Older age, female sex and lower BMI have already been shown to be associated with an inappropriate dose of DOACs [5–10, 23]. Previous reports found conflicting results for the association between CCI and DOAC dose status [6, 9, 23]. Our results suggest that having a history of coronary artery disease was associated with a lower probability of being in the overdose group. Several studies found that cardiology follow-up was associated with an appropriate dose of DOACs [5, 33]. As patients with coronary artery disease are more likely to benefit from regular cardiology visits, this could explain this result.

Inappropriate dose status was not associated with mortality and thromboembolism. Whereas there was a lack of statistical power for the overdose group and the thromboembolism analysis with a high risk of type II error, this was unlikely the case for the mortality and bleeding analyses for the comparison of the appropriate and underdose groups. Previous studies that demonstrated increased mortality in patients with an inappropriate dose status included younger populations [5–8], which could explain the difference in results. It is possible that in a very old population with a high prevalence of multimorbidity and polypharmacy, the appropriateness of a single drug dose adjustment could be associated with bleeding or thromboembolism but not mortality. Underdose status was associated with a lower bleeding risk compared with the appropriate group, reconfirming former findings [7].

The discrepancies in drug dose status using the $CrCl_{C\text{-}G}$ and eGFR equations ranged from 7 to 13%, with higher discrepancies when using equations solely based on serum cystatin C. The discrepancy in dose status between the $CrCl_{C\text{-}G}$ and $eGFR_{CKD\text{-}EPIcr}$ (in ml/min) has been reported to range from 7 to 9% [12, 24, 34]. The low rate of discrepancies could explain why the association with endpoints did not differ according to the respective equations. Our results suggest that eGFR equations based on serum creatinine and/or cystatin C are not inferior to the $CrCl_{C\text{-}G}$ in this context.

Our results differ from those obtained in dabigatran users showing a stronger association between dose status and bleeding when using the $CrCl_{C\text{-}G}$ as compared with the $eGFR_{CKD\text{-}EPIcr}$ [12]. However, we were unable to perform a subgroup analysis in dabigatran users and we cannot rule out that the results may differ according to the studied DOACs. We showed that being underdosed was associated with an increased risk of death and a decreased risk of bleeding in rivaroxaban users with several equations. In contrast, drug dose status was not associated with adverse events in apixaban users. This discrepancy in results between these two drugs could be explained by the lower rate of these events in apixaban users as compared with rivaroxaban users. Furthermore, renal clearance of apixaban is lower than that of rivaroxaban, which could partly explain why dose status was not associated with bleeding or mortality [4].

Patients with discrepancies in dose status are of great interest to study performances of kidney function estimators in drug dose adjustment. In a recent study, Chan *et al.* [17] reported a similar bleeding risk between vitamin K antagonist users and patients with discrepancies in dose status according to the $CrCl_{C\text{-}G}$ and $eGFR_{CKD\text{-}EPIcr}$, with appropriate dose according to the $eGFR_{CKD\text{-}EPIcr}$. The authors concluded that their results suggest that the $CrCl_{C\text{-}G}$ should be used as the gold standard for drug dose adjustment of DOACs, but no comparison was performed in patients with discrepancies in dose status with appropriate dose according to the $CrCl_{C\text{-}G}$. In our study, the association with endpoints did not significantly differ in patients with a discrepancy in dose status between the $CrCl_{C\text{-}G}$ and other equations, according to the equation for which the dose was appropriate. However, it should be noted that in patients for whom the dose was appropriate according to the $CrCl_{C\text{-}G}$, the occurrence of endpoints was at least as high compared with patients with an appropriate dose according to other estimators, which could suggest that there is no disadvantage in using eGFR equations in these patients.

Using indexed equations (i.e. expressed in ml/min/1.73m^2), the discrepancies between eGFR and $CrCl_{C\text{-}G}$ were slightly higher (9–16%) than when using de-indexed equations. De-indexed eGFR has been proven to increase the correlation between the $CrCl_{C\text{-}G}$ and eGFR and to improve performances of eGFR in drug dose adjustment, which could explain these results [35, 36]. If discrepancies between de-indexed and indexed equations were low (3–9%), it is likely that they occurred in patients with extremely low or high body weight. It would have been of great interest to do analyses stratified by body weight, but unfortunately the respective sample sizes were too small. For now, physicians should be advised to take BSA into account when using eGFR for drug dose adjustment, as recommended by current guidelines [13, 14].

Our study has several strengths. This is the first study assessing the impact of DOAC dose adjustment by kidney function using recent equations also including cystatin C. Given the paucity of clinical evidence on kidney function estimators for drug dose adjustment, which contrasts with the growing literature on equations to estimate GFR, our results could help physicians who daily face the issue of adapting drug dose to kidney function. The BIS detailed phenotyping including individual claims data allowed us to consider many confounders by computing marginal structural Cox models.

We must also acknowledge some limitations. First, the small sample size of the study did not allow us to study subgroups properly, such as patients with overdose status, edoxaban and dabigatran users, patients with extreme body weights and patients with discrepancies in dose status according to the studied equations. The prevalence of atrial fibrillation ranges from 12 to 18% in people >80 years of age in Europe [37], but we included 11% of the BIS participants. The low inclusion rate was mainly because the BIS was initiated in 2010, when the DOACs

started to be available in Germany but were not recommended as first-line therapy yet. Indeed, most participants were included in 2014 and later. Second, we did not have measured GFR to compare with the $CrCl_{C\text{-}G}$ and eGFR. Third, secondary endpoints were based on hospitalization diagnoses and we could not control their accuracy. Also, whereas thromboembolism is probably mainly treated in hospital, we may have missed less severe bleeding managed outside the hospital. Fourth, the definition of DOAC exposure could have led to biased results. We did not focus exclusively on new users, which could have excluded participants who had stopped taking DOACs due to adverse events before the inclusion. However, more than half of the participants at baseline were taking DOACs for <1 year. To further limit this bias, DOAC prescription duration was considered in our models. Dose status and DOAC use was only assessed at each follow-up visit, but medication could have been discontinued between visits. Also, our database did not include information on drug adherence. Fifth, as we focused on DOAC use in older adults with NVAF, our conclusions regarding drug dose adjustment for kidney function cannot necessarily be extrapolated to other drug classes in younger individuals.

CONCLUSION

The association between adverse events and DOAC dose adjustment according to the $CrCl_{C\text{-}G}$ and eGFR equations did not differ in older adults with NVAF. Our results suggest that eGFR equations based on serum creatinine and/or cystatin C are not inferior to the $CrCl_{C\text{-}G}$ within this context. Future studies including a larger number of older participants, with discrepant dose status and focusing on other drug classes are important.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

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AUTHORS' CONTRIBUTIONS

C.V. was responsible for statistical analysis and writing the first draft of the manuscript. All authors were responsible for study concept and design, interpretation of data, significant contributions and final approval of the manuscript.

DATA AVAILABILITY STATEMENT

The data underlying this article cannot be shared publicly to protect the privacy of individuals who participated in the study. The data will be shared upon reasonable request to the corresponding author.

CONFLICT OF INTEREST STATEMENT

N.E. received fees from Bayer AG Leverkusen as a member of an editorial advisory board outside the submitted work. E.S. received a research grant from Bayer unrelated to the topic of the article and receives a stipend from the National Kidney Foundation. The other authors declare no conflicts of interests.

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