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Original Research

Clinical Associations with the differences in rivaroxaban dosing in patients with atrial fibrillation stratified by three renal function formulae

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Abstract

Background: Clinical trials used Cockcroft-Gault (CG) formula to calculate the estimated glomerular filtration rate (eGFR) in order to dose rivaroxaban for patients with atrial fibrillation (AF). **Objectives:** The aim of this study is to evaluate rivaroxaban dosing appropriateness in patients with AF with or without renal impairment based on the CG formula and other formulae, including Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation and the isotope dilution mass spectrometry (IDMS) traceable Modification of Diet in Renal Disease (MDRD) Study equation and the associated clinical outcomes. **Methodology:** A retrospective cohort study conducted at Sultan Qaboos University Hospital (SQUH) from 1st January 2016 to 31st December 2020, included all adult patients (≥ 18 years) treated with rivaroxaban for AF and followed up for one year after starting the treatment. **Results:** Based on the CG formula, the rivaroxaban dose was inappropriately prescribed in 27% of the patients (21% overdosed and 6% underdosed). Higher baseline creatinine (P=0.0014) and concurrent use of antiplatelet therapy (P<0.001) were associated with the tendency to rivaroxaban overdosing. Higher Body Mass Index (BMI) (P=0.002), female sex (P=0.032), and CKD (P=0.003) were associated with rivaroxaban underdosing. The degree of agreement between the renal function tests when comparing MDRD vs CG and CKD-EPI vs CG in terms of estimated glomerular filtration rate/creatine clearance (eGFR/CrCl) calculation was moderate (κ=0.46) and poor (κ=0.00), respectively, while, in terms of rivaroxaban dose appropriateness was almost perfect (κ=0.82) and substantial (κ=0.77). Clinical outcomes measured by stroke and bleeding events were not significantly different according to the appropriateness of the rivaroxaban dose. **Conclusion:** This study has shown a relatively high consistency with the gold standard in dosing rivaroxaban in AF patients using CG formula. Treatment efficiency and safety were not affected by the proportion of dose inappropriateness found in this cohort.

Keywords: atrial fibrillation; bleeding events; direct oral anticoagulant; medication appropriateness; renal function test; stroke events

INTRODUCTION

Atrial fibrillation (AF) is a growing epidemic as the most common cardiac arrhythmia recognized in clinical practice. It results in ineffective atrial contraction & thrombus formation, which increases the risk of systemic thromboembolism such as stroke. Recently, novel oral anticoagulants (NOACs) such as rivaroxaban are used for non-valvular AF to prevent thromboembolism.[1-4] Rivaroxaban is a direct factor Xa inhibitor; around 35% of its clearance is through the kidneys. Therefore, dose reduction is needed for patients with renal dysfunction to prevent adverse drug reactions (ADRs) such as bleeding with overdosing. In contrast, inappropriate underdosing can lead to a higher risk of stroke events.[3,5,6]

Clinical trials used Cockcroft-Gault (CG) formula to calculate the estimated glomerular filtration rate (eGFR) to dose rivaroxaban for patients with AF.[7,8] As a result, international guidelines approved rivaroxaban at a dose of 20 mg once daily for patients with non-valvular AF patients, and a reduced dose of 15 mg once daily for a patient with renal impairment when their calculated creatinine clearance (CrCl) drops below 50 mL/min to 15 ml/min and to avoid use if CrCl is < 15 ml/min.[3,9,10] This has proven to significantly prevent the 10-year risk of stroke events and reduce bleeding episodes associated with anticoagulation therapy in patients with AF.[7,8,11,12]

Given that rivaroxaban overdosing or underdosing when doses are not calculated based on the gold standard method using the CG formula, adverse clinical outcomes can occur, including; stroke and bleeding events. Therefore, we aim to evaluate the appropriateness of dose calculation of rivaroxaban in

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patients with AF with or without renal impairment based on the CG formula and other formulae (Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation and the isotope dilution mass spectrometry (IDMS) traceable Modification of Diet in Renal Disease (MDRD) Study equation) and the associated outcomes in terms of stroke and bleeding events.

METHODOLOGY

Study design, setting and population

This is a retrospective cohort study that included all adult patients (≥ 18 years old) treated with rivaroxaban for AF at Sultan Qaboos University Hospital (SQUH) from 1st January 2016 to 31st December 2020. All patients were followed-up for one year after the commencement of rivaroxaban. We excluded patients who lost follow-up, those with missing information (e.g., weight), and those who were anticoagulated for less than one year. Also, we excluded patients on antiplatelet therapy for any of the following indications: primary prevention, secondary prevention in patients with ischemic heart disease and patients on rivaroxaban 10 mg once daily.

Data collection

Data were retrieved from the hospital main information system (TrackCare). We gathered data on demographic data, including (age, sex, weight, and height), baseline characteristics data (hypertension, Diabetes Mellitus (DM),—chronic kidney disease (CKD) and ischemic heart disease (IHD)), data related to rivaroxaban dose, and information related to concurrent antiplatelet administration and indication. Renal function test was estimated using 3 formulas: eGFR by MDRD and CKP-EPI formulae, serum creatinine and calculated CrCl-by CG formula. The risk of major bleeding was estimated using Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly (HAS-BLED) score, and the risk of ischemic stroke was estimated using congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65 to 74 and sex category (female) (CHA_2DS_2-VASc) score. All patients were followed up for one year after initiation of rivaroxaban for one of the following outcomes: stroke, bleeding events and all-cause mortality.

Definitions

Dose appropriateness was defined based on the calculated renal function[9] and concurrent use of antiplatelets when indicated and classified into appropriate, overdosed or underdosed for all the three renal function formulae[13,14]. For patients with the calculated renal function of >50 ml/min, a rivaroxaban dose of 20 mg once daily alone or 15 mg once daily *combined with antiplatelet* was considered appropriate. In contrast, 20 mg once daily when *combined with antiplatelet* was considered overdosed, and 15 mg once daily *alone* was considered underdosed. For patients with calculated renal function between 50 to 15 ml/min, a rivaroxaban dose of 15 mg once daily *alone* was considered appropriate. In contrast, 15 mg once daily when *combined with antiplatelet* or 20 mg once daily *alone* were considered overdosed.[9,13,14]

The degree of agreement between the renal function tests using different formulae for eGFR/CrCl calculation was based on three categories for all the three renal function formulas, which are; >50 ml/min, between 50 to 15 ml/min, and <15 ml/min.

Sample size

A previous study by Mayer et al., 2018 showed that inappropriate dosing per patient's CrCl was recognized in 42% of patients on rivaroxaban;[15] similarly, Yao et al., 2017 showed that around 43% of patients with renal impermeant had NOAC overdose which led to higher risk for bleeding (the event rate for major bleeding was 11.29 and 5.06 per 100 person-years in the standard dose and reduced dose, respectively), while 13.3% was underdosed which led to a higher risk for stroke events (the event rate were 2.32 and 1.85 per 100 person-years in the standard dose and reduced dose respectively).[6] Therefore, we hypothesize that around 30% of our patients on rivaroxaban were inappropriately dosed on rivaroxaban, divided into 20% overdosing or 10% underdosing, which might lead to preventable outcomes if dosed on CG formula (bleeding or stroke), for which a sample size of 278 patients will be needed with a margin error of 5% and 95% confidence interval in an estimated population size of 2000 patients.

Statistical analysis

All data had been analyzed using STATA, version 17.0 (Stata Corporation, College Station, Texas, USA). Descriptive statistics were used to summarize the demographic and clinical characteristics of the study patients. Categorical data were analyzed using the Chi-square test or Fisher's exact test. Continuous data between groups were compared using one-way analysis of Variance ANOVA for normally distributed variables or Kruskal–Wallis rank test for non-normally distributed variables. The significance level was set at 95% ($P \leq 0.05$) for all statistical tests. Univariate analysis was performed to identify factors associated with the variable (doses of rivaroxaban) and clinical outcomes (bleeding events or stroke) with (95% CIs, $P=0.05$). Scott's kappa (κ)[16] was used to assess the degree of agreement between the renal function tests using different formulae for GFR calculations and the difference in rivaroxaban dose appropriateness. The Scotts' κ values were interpreted using the following levels; poor agreement ($\kappa<0.01$), slight agreement ($\kappa=0.01–0.20$), fair agreement ($\kappa=0.21–0.40$), moderate agreement ($\kappa=0.41–0.60$), substantial agreement ($\kappa = 0.61–0.80$) and almost perfect agreement ($\kappa=0.81–1.00$).[17]

Ethical approval

The study was approved by the Medical and Research Ethics Committee at the College of Medicine and Health Sciences, Sultan Qaboos University, Muscat, Oman (MREC #2746; SQU-EC/103/2022; dated: 30th May 2022).

RESULTS

We screened 412 patients with AF on rivaroxaban, and only 221 patients met the inclusion criteria. The clinical, biochemical and treatment profiles of all included patients were summarized in Table 1. There were 119 female (53.9%), and the medium BMI

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Table 1. Clinical, biochemical and treatment profile of all included patients

Characteristic, ***n (%) unless specified otherwise***	**All n=221 (100%)**
Demographics	
Age, mean, years	67.0 (59.0-74.0)
Female	119 (53.9%)
Weight, IQR, Kg	72.6 (58.3-86.8)
Height, ±SD (m)	1.6 (0.1)
BMI, IQR, kg/m^2	28.2 (25.5-34.3)
Comorbidities:	
Hypertension	183 (82.8%)
Diabetes Mellitus	100 (45.3%)
Coronary Artery disease	78 (35.3%)
Chronic heart failure	78 (35.3%)
Chronic kidney disease	116 (52.5%)
Bleeding and thrombosis risk:	
CHA_2DS_2-VASc score, ±SD	3.7 (1.7)
HAS-BLED score, ±SD	1.8 (1.0)
Concurrent use of antiplatelets:	
Aspirin only	27 (12.2%)
Clopidogrel only	27 (12.2%)
Any antiplatelets or both	44 (19.0%)
Renal function tests:	
baseline Sr Creatinine, IQR, mmol/l	73 (59-89)
Kidney Function MDRD, IQR, ml/min/1.73 m^2	78 (62-90)
Kidney Function CKD-EPI, IQR, ml/min/1.73 m^2	91.6 (82.4-102.2)
Kidney Function CG, IQR, ml/min	89.5 (64.4-117.8)
Clinical outcomes:	
Intracranial haemorrhagic bleeding	0
Gastrointestinal bleeding	6 (2.7%)
Genitourinary bleeding	4 (1.8%)
Other source of bleeding	16 (7.2%)
All causes of bleeding	20 (9.1%)
Ischemic stroke or transient ischemic event	14 (6.3%)
Venous thromboembolism	3 (1.4 %)
All causes of arterial and venous thrombosis	16 (7.2%)
All cause of mortality	5 (1.3%)

IQR: interquartile range; BMI, Body Mass Index; SD, standard deviation; * Other source of bleeding includes; hematoma, gum bleeding, epistaxis, or vaginal bleeding.

was 28.2 kg/m^2. Hypertension (n=183,82.8%) was prevalent, followed by CKD (n=116,52.5%) and DM (n=100,45.3%). Among the cohort, 44 patients (19%) were concurrently treated with antiplatelets (aspirin, clopidogrel or both) in addition to rivaroxaban. In terms of health outcomes, 20 patients (9.1%) had bleeding complications, while 16 patients (7.2%) had a thromboembolic event (Table 1).

As shown in Table 2, the degree of agreement using Scotts' κ values between renal function tests in eGFR/CrCl calculation was moderate (κ =0.46) and poor (κ =0.00) when comparing MDRD *vs* CG and CKD-EPI *vs* CG, respectively. While the degree of agreement between renal function tests in terms of rivaroxaban dose appropriateness was almost perfect and substantial, with κ=0.82 and κ=0.77, when comparing MDRD *vs* CG and CKD-EPI *vs* CG, respectively.

Based on the CG formula for renal function, the rivaroxaban dose was inappropriately prescribed in 60 patients (27.1%), including 14 patients (6.3%) who were underdosed and 46 patients (20.8%) who were overdosed (Table 3). Higher baseline creatinine (P=0.0014) and concurrent use of antiplatelet therapy (P<0.001) were associated with the tendency to rivaroxaban overdosing. On the other hand, higher BMI (P=0.002), female sex (P=0.032), and CKD (P=0.003) were associated with rivaroxaban underdosing.

Regarding relevant health outcomes, there were no statistically significant differences in the occurrence of death, bleeding, and thromboembolic events between the three groups (Table 3).

DISCUSSION

In the current study, we showed relatively high consistency with the gold standard in dosing rivaroxaban in AF patients using the CG formula. Also, using Scotts' κ test, when comparing the calculation of eGFR/CrCl with the gold standard CG formula, the level of agreement was moderate with MDRD and poor with CKD-EPI. Nevertheless, when compared with the CG formula, we demonstrated an almost perfect and substantial agreement in rivaroxaban dosing between the other renal test formulae (MDRD and CKD-EPI, respectively). Furthermore, treatment efficacy and safety measured by stroke and bleeding events were not associated with dosing inappropriateness.

Most of our prescriptions were appropriately dosed based on the CG formula (73%), in which 21% were overdosed, and only 6% were underdosed; this finding contradicts other studies.[6,15,18,19] A German study, for example, showed that in clinical practice, rivaroxaban was underdosed in 52% of the patients, which is frequently incoherent with the trial labelling.[19] Another retrospective Saudi study showed that 42% of rivaroxaban prescriptions had inappropriate doses, and 83% were underdosed.[15] In clinical practice, HAS-BLED score and patient's age might be considered when dosing rivaroxaban. However, in this cohort, we considered in the classification of dose appropriateness the concurrent use of antiplatelet,[14] as we had a small proportion of major stroke in patients with cerebral small vessel disease (CSVD) or patients post percutaneous coronary intervention **(**PCI).[13,14,20,21] Adding to that, we believe that dose appropriateness might be affected by the high quality of clinical pharmacists working in our institution (SQUH), where clinical pharmacists work with various multidisciplinary care teams to ensure issuing the most appropriate prescription for hospitalized and non-hospitalized patients by practising pharmaceutical interventions based. They have proven a high proportion of dose changes based on gold standard guidelines with a high acceptance rate by the treating physicians.[22]

Table 2. Degree of agreement between renal function tests (MDRD, CKD-EPI and CG) in terms of eGFR/CrCl calculation and rivaroxaban dose appropriateness

Renal function test	Degree of agreement (%)	Kappa (*κ*)	Type of agreement	*P* value
eGFR/CrCl calculation				
MDRD *vs* CG	90.50%	0.46	Moderate agreement	<0.001
CKD-EPI *vs* CG	88.68%	0.00	Poor agreement	<0.001
Dose appropriateness				
MDRD *vs* CG	92.76%	0.82	Almost perfect agreement	<0.001
CKD-EPI *vs* CG	90.50%	0.77	Substantial agreement	<0.001

The Scotts' *κ* values interpreted using the following levels; poor agreement (*κ* < 0.01), slight agreement (*κ* = 0.01–0.20), fair agreement (*κ* = 0.21–0.40), moderate agreement (*κ* = 0.41–0.60), substantial agreement (*κ* = 0.61–0.80) and almost perfect agreement (*κ* = 0.81–1.00)

Table 3. Univariate analysis to identify factors for dose inappropriateness based on CG formula and its associations with clinical outcomes (measured by bleeding and stroke events)

Characteristic, ***n (%) unless specified otherwise***	**All n=221 (100%)**	**Under dosing n=14 (6.3%)**	**Appropriate dosing n=161 (72.9%)**	**Overdosing n=46 (20.8%)**	***P***
Age, IQR, years	67.0 (59.0-74.0)	70 (65-74)	67 (57-74)	69.0 (64.0-.75.0)	0.101
Female	119 (53.9%)	9 (64.3%)	93 (57.8%)	17 (37.0%)	**0.032**
Weight, IQR, Kg	72.6 (58.3-86.8)	75.5 (63-92)	75.6 (61.9-87.0)	63.4 (52.4-78.3)	**0.036**
BMI, IQR, kg/m^2	28.2 (25.5-34.3)	30.1 (28.5-37.6)	29.0 (26.4-35.0)	26.4 (22.6-28.4)	**0.002**
Chronic kidney disease	116 (52.5%)	12 (85.7%)	74 (46.0%)	30 (65.2%)	**0.003**
Baseline serum creatinine, IQR, mmol/l	73 (59-89)	82.5 (63-113)	70.0 (57.0-87.0)	83.5 (69.0-107)	**0.001**
CHA_2DS_2-VASc score ±SD	3.7 (1.7)	3.8 (1.1)	3.5 (1.7)	4.6 (1.6)	0.168
HAS-BLED score ±SD	1.8 (1.0)	1.6 (0.5)	1.6 (0.9)	2.7 (0.9)	0.058
Aspirin	27 (12.2%)	0	5 (3.1%)	22 (47.8%)	**<0.001**
Clopidogrel	27 (12.2%)	0	6 (3.7%)	21 (45.7%)	**<0.001**
Antiplatelets	44 (19.0%)	0	9 (5.6%)	35 (76.1%)	**<0.001**
Intracranial haemorrhagic bleeding	0	0	0	0	-
Gastrointestinal bleeding	6 (2.7%)	0	4 (2.5%)	2 (4.4%)	0.742
Genitourinary bleeding	4 (1.8%)	1 (7.1%)	3 (1.9%)	0	0.259
Other source of bleeding*	16 (7.2%)	1 (7.1%)	9 (5.6%)	6 (13.0%)	0.192
All causes of bleeding	20 (9.1%)	2 (14.3%)	12 (7.5%)	6 (13.0%)	0.300
Ischemic stroke or transient ischemic event	14 (6.3%)	1 (7.1%)	7 (4.4%)	6 (13.0%)	0.107
Venous thromboembolism	3 (1.4%)	1 (7.1%)	2 (1.2%)	0	0.281
All causes of arterial and venous thrombosis	16 (7.2%)	2 (14.3%)	8 (5.0%)	6 (13.0%)	0.074
All cause of mortality	5 (1.3%)	0	4 (2.5%)	1 (2.2%)	1.000

IQR: interquartile range; SD, standard deviation; * Other source of bleeding includes; hematoma, gum bleeding, epistaxis, or vaginal bleeding.

In our study, the degree of agreement using Scotts' *κ* values between renal function tests in terms of eGFR/CrCl calculation was moderate (*κ* =0.46; degree of agreement 90.5%) and poor (*κ* =0.00; degree of agreement 88.6%) when comparing MDRD *vs* CG and CKD-EPI *vs* CG, respectively. Our results are comparable to the recent study in Taiwan published in 2021, which represented 78% agreement with MDRD and 81% with CKD-EPI when compared with the CG formula.[23] In another study published in Canada, Jason and his colleagues stated that the agreement between MDRD and CG formulae in rivaroxaban dosing was 63%, with a similar agreement percentage when comparing CKD-EPI with CG.[18] These findings suggest that MDRD and CKD-EPI formulae may fail to correctly classify patients who are candidates for dose adjustment,[23] resulting in overdosing mainly as shown in our cohort and possibility has a relation to high baseline serum creatinine (*P*=0.001).

Interestingly, in both the above-mentioned studies, advanced age and low weight were the main contributors to the disagreement.[18,23] In our study, we showed that obesity, female sex, and CKD were associated with underdosing. In contrast, higher baseline serum creatinine, concurrent use of antiplatelets were associated with overdosing. Unlike the CG formula, the MDRD and CKD-EPI do not take into account patients' weight, for which obese patients might be underdosed if the renal function was calculated using MDRD or CKD-EPI for dose guidance.[24] Real-world studies have shown a significant difference in NOACs dosing using eGFR

with MDRD or CKD-EPI formulae compared to the CG formula that led to either underdosing or overdosing of rivaroxaban in AF patients.[25] When we defined dose appropriateness as mentioned above, we took into account the concurrent use of antiplatelets. As suggested by the PIONEER AF-PCI trial starting dose of rivaroxaban is 15 mg once daily for CrCl > 50 ml/min when combined with antiplatelets for AF patients post PCI to reduce events of bleeding.[14] However, it was not practised before 2018 and is probably not being practised by neurology physicians when using antiplatelets with rivaroxaban for CSVD patients with AF, which might be the reason behind the high proportion of overdose in this group of patients in our cohort.[26]

We found an almost perfect and substantial degree of agreement between renal function tests regarding rivaroxaban dose appropriateness when comparing MDRD *vs* CG and CKD-EPI *vs* CG, with κ=0.82 and κ=0.77, respectively. In addition, it contributed to the small number of underdosed or overdosed prescriptions, given the wide range for dose adjustments in which a renal function falls, as described by the international guidelines and classified into three categories; >50 ml/min, between 50 to 15 ml/min and <15 ml/min.[3,9,10]

We demonstrated that treatment efficacy and safety measured by stroke and bleeding events were not associated with dosing inappropriateness. While an observational, retrospective cohort from the Korean National Health Insurance Service compared rivaroxaban 20 mg once daily versus 15 mg once daily in 10392 patients with AF and found that in patients with CrCl ≥50 mL/min, rivaroxaban 20 mg once daily showed higher prevention of stroke and higher major bleeding events compared to 15 mg once daily in patients with CrCl between 50 to 60 ml/min using the CG formula.[27] Another study from the US retrieved a sizeable administrative database from 2010 to 2015, which was before the PIONEER AF-PCI trial,[14] found that 43.0% of rivaroxaban prescriptions were potentially overdosed, which was associated with worse safety but no benefit in effectiveness in sever CKD patients.[6] Although the disagreements between the formulae were significant in terms of renal function calculation but not in terms of dose appropriateness, however, the clinical associations with that are still lacking evidence. Therefore, GC remains the gold standard in dosing rivaroxaban.[18,23] However, our results should be cautiously used due to the low sample size.

This study had a few limitations. First, the retrospective nature of the study design limits its finding. Second, the cohort did not meet the calculated sample size, due to lost follow-up and missing information. Third, we captured data on outcomes only from SQUH, without considering other private, regional, or peripheral hospitals that could influence the results.

CONCLUSION

We showed relatively high consistency with the gold standard in the dosing of rivaroxaban in AF patients using the CG formula. Although there was a poor to moderate degree of agreement between renal function tests in terms of eGFR/CrCl calculation, there was an almost perfect and substantial agreement on the dosing of rivaroxaban. According to our cohort, using the CG formula for dose appropriateness, treatment safety and efficacy measured by stroke and bleeding events were not affected by dose inappropriateness. Our results should be used cautiously due to study limitations, and larger powered studies are warranted to correlate our results.

CONFLICTS OF INTERESTS

All authors declared no conflicts of interest.

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All authors declared that there was no financial support received from any organization.

AUTHORSHIP CONTRIBUTION

Juhaina Salim Al-Maqbali: Conceptualization, proposal writing, data collection sheet design, data collection accuracy checking, and manuscript writing and editing; Abdullah M. Al Alawi: Methodology, data analysis, and overall manuscript review; Marai Al-Adawi: Data collection; Zubida Al-Falahi: Manuscript writing; Asia Al-Azizi: Contributed to data collection; Kholoud Al Badi: Contributed to data collection; Mohammed Al Rawahi: Conceptualization, follow up on data collection, and overall manuscript review.

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