JACC: ASIA VOL. 2, NO. 1, 2022

ORIGINAL RESEARCH

Different Renal Function Equations and Dosing of Direct Oral Anticoagulants in Atrial Fibrillation

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ABSTRACT

BACKGROUND Randomized trials of direct oral anticoagulants (DOACs) adopted the Cockcroft-Gault (CG) formula to calculate estimated glomerular filtration rate (eGFR) to determine the dosages of DOACs.

OBJECTIVES The authors aimed to investigate the agreements/disagreements of eGFRs calculated using different equations (CG, Modified Diet in Renal Disease [MDRD], and Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] formulas), and their impacts on the dosages of DOACs and clinical outcomes.

METHODS Medical data from a multicenter health care provider in Taiwan including 39,239 patients with atrial fibrillation were used. Among these patients, there were 11,185 and 2,323 patients treated with DOACs and warfarin, respectively.

RESULTS At the cutoff values of eGFR of <15, 15-50, and >50 mL/min, the agreements were 78% between MDRD and CG and 81% between CKD-EPI and CG. The disagreements among the different equations were largely due to overestimations, especially for patients aged >75 years and with a body weight of <50 kg (58.8% for MDRD and 50.9% for CKD-EPI). Among patients receiving DOACs whose dosages were defined as "on label" based on MDRD or CKD-EPI, only those whose dosages were "truly on label" based on CG were associated with a lower risk of major bleeding (adjusted HR: 0.34; 95% CI: 0.26-0.45) compared to warfarin.

CONCLUSIONS The adoptions of MDRD or CKD-EPI rather than CG would result in inappropriate dosing of DOACs (mainly overdosing), which would attenuate the advantages of DOACs compared to warfarin. The CG equation should be used as the gold standard to calculate eGFRs and guide the DOAC dosages. (JACC: Asia 2022;2:46–58) © 2022 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Atrial fibrillation (AF) is the most prevalent sustained cardiac arrhythmia in clinical practice, which significantly increases the risk of thromboembolism and mortality. Randomized controlled trials enrolling more than 70,000 patients have demonstrated that the direct oral anticoagulants (DOACs) (eg, dabigatran, rivaroxaban, apixaban, and edoxaban) showed noninferiority in efficacy and have a significantly lower risk of intracranial hemorrhage and major bleeding than dose-adjusted vitamin

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received June 1, 2021; revised manuscript received October 12, 2021, accepted November 2, 2021.

ISSN 2772-3747 https://doi.org/10.1016/j.jacasi.2021.11.006

K antagonists (eg, warfarin) in patients with nonvalvular AF.[1] Therefore, current guidelines recommend the prescriptions of DOACs in preference to warfarin in nonvalvular AF patients in most clinical scenarios,[2,3] and DOACs were increasingly used in daily practice.[4]

Of note, all DOACs require appropriate dosage adjustments based on each patient's renal function. Failure to appropriately reduce the dose may increase the risk of bleeding, and conversely, inappropriate dosage reduction of DOACs may decrease their effectiveness for stroke prevention. In all pivotal DOAC trials and international society guidelines, the Cockcroft-Gault (CG) formula, which considers a patient's age, sex, and body weight, was used to estimate the patient's renal function.[5] Different from the CG formula, information on body weight is not required to calculate estimated glomerular filtration rates (eGFRs) using the Modified Diet in Renal Disease (MDRD) or Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formulas.[6-8] Therefore, eGFRs based on the MRDR or CKD-EPI formulas are reported automatically in many laboratories and may be more user friendly and convenient for daily practice. However, data about the differences of eGFRs calculated by using different equations and the impacts on the dosage selections of DOACs and subsequent clinical outcomes are limited.

In the present study, we investigated the agreements/disagreements of eGFRs calculated using different equations (the MDRD or CKD-EPI formulas compared to the gold-standard CG formula) in Asian patients with AF. Second, we studied the impacts of using different equations on the dosages (underdosing, on-label dosing, or overdosing) of the DOACs used, and finally, clinical outcomes (mortality, major bleeding, and ischemic stroke/systemic embolism) compared to warfarin were assessed. The present comprehensive analysis aims to extend our previous brief report on this issue.[9]

METHODS

The study is based in part on data from the Chang Gung Research Database provided by Chang Gung Memorial Hospital (CGMH). We conducted the retrospective observational study by using patients' electronic data from the CGMH Medical System. The CGMH Medical System is composed of 3 major teaching hospitals and 4 tertiary care medical centers, and it is the largest health care provider in Taiwan. The personal information and identification number of each patient are encrypted and deidentified by using a consistent encrypting procedure; therefore, informed consent was waived for this study. Our study was approved by the Institutional Review Board of the Chang Gung Medical Foundation (201802075B0). Also, the study was adherent to the Declaration of Helsinki.

STUDY COHORT AND STUDY DESIGN. The flowchart of study design and patient enrollment is shown in Supplemental Figure 1. The CGMH medical database was retrospectively searched for patients aged ≥20 years in whom new-onset AF was diagnosed from July 1, 2001, to September 30, 2018 (n = 70,408) using the International Classification of Diseases (ICD)-9th Revision-Clinical Modification (ICD-9-CM) code (427.31) or ICD-10-CM code (I48). There were 39,239 patients whose body weight (BW) and serum creatinine (sCr) data were available within 6 months before AF was diagnosed. Among the 39,239 patients with AF, there were 11,185 and 2,323 patients with nonvalvular AF treated with DOACs and warfarin, respectively, after June 1, 2012. Among 11,185 patients with AF treated with DOACs, a total of 2,086; 5,041; 2,580; and 1,478 patients were treated with dabigatran, rivaroxaban, apixaban, and edoxaban, respectively. Information about important comorbid conditions of each individual was retrieved from the CGMH medical database based on the ICD-9-CM and ICD-10-CM codes (Supplemental Table 1) registered by the physicians responsible for the care of the patients. Patients were assumed to have no certain comorbidities if there were no corresponding ICD-9-CM and ICD-10-CM codes identified within the database before or at the same date as the diagnosis of AF.

ESTIMATION OF RENAL FUNCTION (eGFR). The eGFR values were calculated using the CG (CG-eGFR), MDRD (MDRD-eGFR), and CKD-EPI (CKD-EPI-eGFR) formulas as follows[8,10,11]:

$$\mathrm{CG\ (mL/min)} = (140 - \mathrm{age}) \times \mathrm{BW} / (72 \times \mathrm{sCr}) \times (0.85 \text{ if female})$$

$$\mathrm{MDRD\ (mL/min)} = 175 \times \mathrm{sCr}^{-1.154} \times \mathrm{age}^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if Black})$$

$$\mathrm{CKD-EPI\ (mL/min)} = 141 \times \min[\mathrm{sCr}/(0.7 \text{ if female; } 0.9 \text{ if male}), 1]^{(-0.329 \text{ if female; } -0.411 \text{ if male})} \times \max[\mathrm{SCr}/(0.7 \text{ if female; } 0.9 \text{ if male}), 1]^{-1.209} \times 0.993 \times \mathrm{age} \times (1.018 \text{ if female}) \times (1.159 \text{ if Black})$$

DIFFERENCES AND AGREEMENTS/DISAGREEMENTS OF eGFR BY DIFFERENT EQUATIONS. The eGFRs calculated based on 3 kinds of equations and their differences were analyzed in different groups of patients categorized by different sCr levels, ages, and

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

aHR = adjusted HR

BW = body weight

CG formula = Cockcroft-Gault formula

CGMH = Chang Gung Memorial Hospital

CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration

DOAC = direct oral anticoagulant

eGFR = estimated glomerular filtration rate

ICD-9-CM = International Classification of Diseases-9th Revision-Clinical Modification

ICD-10-CM = International Classification of Diseases-10th Revision-Clinical Modification

IS/SE = ischemic stroke/systemic embolism

MDRD = Modified Diet in Renal Disease

sCr = serum creatinine

BWs. The percentages of agreements/disagreements (including underestimations and overestimations) of eGFRs using the MDRD or CKD-EPI formulas compared to the CG formula (the gold standard) were analyzed by categorizing patients into 3 groups according to their eGFRs (<15, 15-50, and ≥50 mL/min). The agreements were defined as the percentages of patients who were classified as the same groups of eGFRs (<15, 15-50, and >50 mL/min) calculated by "CG or MDRD" and "CG or CKD-EPI" formulas. Data about categorizing patients into 3 groups according to different cutoff values of eGFRs (<30, 30-50, and ≥50 mL/min) are reported in the supplemental material. We also analyzed the percentages and odds ratios (ORs) of agreements, underestimations, and overestimations of eGFR using the MDRD or CKD-EPI formulas compared to the CG equation in different groups of patients stratified by their ages and BWs.

ELIGIBILITY AND DOSAGE ADJUSTMENT OF DOACs. In the present study, patients treated with DOACs were defined as underdosing, on-label dosing, and overdosing generally based on the labeling of the Taiwan Food and Drug Administration as well as the dosage reduction criteria of pivotal DOAC randomized trials and recommendations of international society guidelines.[2,5,12-16] Detailed definitions were provided in our previous study.[17]

RISK OF CLINICAL EVENTS WITH ON-LABEL DOSING USING MDRD/CKD-EPI. For patients treated with DOACs who were defined as having on-label dosing based on the eGFRs calculated using the MDRD or CKD-EPI formulas, their dosages could be further categorized as "concordant" or "discordant (overdosing or underdosing)" by regarding the CG equation as the gold standard for the calculation of eGFRs. The concordance rates were defined as the percentages of patients whose dosages of DOACs were categorized as the same dosing groups (on-label dosing, underdosing, or overdosing) based on the eGFRs calculated using the different equations (the "CG or MDRD" and "CG or CKD-EPI" formulas). The risks of clinical outcomes in the concordant and discordant groups were compared to patients treated with warfarin. The clinical outcomes we reported were the occurrences of ischemic stroke/systemic embolism (IS/SE), major bleeding, or mortality and the composite endpoints of IS/SE, major bleeding, or mortality. The major bleeding events were defined as hospitalized events of intracranial hemorrhage, gastrointestinal bleeding, and other sites of critical bleeding. The composite adverse events were defined as the occurrence of IS/SE or major bleeding or death, whichever occurred first. All study outcomes were defined on the basis of the first discharge diagnosis to avoid misclassification. The ICD-9-CM and ICD-10-CM codes used to define the events are summarized in Supplemental Table 1. For each individual endpoint, we analyzed only the first-time hospitalization without multiple counting for patients who have repeated admissions.

STATISTICAL ANALYSIS. Data are presented as the mean ± SD for continuous variables and as proportions for categoric variables. The differences between continuous values were assessed using the unpaired 2-tailed Student's *t*-test or 1-way analysis of variance when the comparisons of 3 groups were performed. Differences between nominal variables were compared by the chi-square test. Logistic regression analysis was performed to report the ORs of agreements and overestimations of eGFR using different renal function formulas. The incidences of IS/SE, major bleeding, all-cause mortality, and composite adverse events were calculated by dividing the number of events by person-time at risk. The risk of adverse events was assessed using the Cox proportional hazards models. Statistical analyses were carried out using SPSS version 17.0 (IBM), and all statistical significances were set at $P < 0.05$.

RESULTS

The clinical characteristic of all patients with AF are shown in **Table 1**. The mean age of the study population was 71.1 ± 12.8 years, and 57% were men. The mean CHA_2DS_2-VASc and HAS-BLED scores were 2.58 ± 1.65 and 1.94 ± 1.33, respectively. The median sCr level was 1.03 mg/dL (interquartile range: 0.80-1.45 mg/dL). The mean eGFRs were 56.8 mL/min calculated by the CG, 69.7 mL/min by the MDRD, and 62.1 mL/min by the CKD-EPI equations.

DIFFERENCES AND AGREEMENTS/DISAGREEMENTS (OVERESTIMATIONS OR UNDERESTIMATIONS) OF eGFRs BY DIFFERENT EQUATIONS. The mean eGFRs and the differences among the 3 equations in different sCr strata are shown in **Figure 1**. Compared to the CG formula, the MDRD formula overestimated the eGFRs across a wide range of sCr levels, whereas the CKD-EPI formula overestimated the eGFRs only among strata with an sCr of <2.6 mg/dL. In the sCr strata of 1.20-1.29 mg/dL and 1.80-1.89 mg/dL among which CG-eGFRs were already below 50 mL/min and 30 mL/min, respectively, the eGFRs calculated by the MRDR or CKD-EPI formulas were still higher than 50 mL/min and 30 mL/min. When CG-eGFRs were lower than 15 mL/min at the sCr 3.50-3.59 mg/dL level, the MDRD-eGFRs and CKD-EPI-eGFRs were 15.9 and 14.1 mL/min, respectively.

TABLE 1 Baseline Characteristics of All Patients With Atrial Fibrillation (N = 39,239)

Age, y	71.1 ± 12.8
Age ≥75 y	17,651 (45.0)
Age 65-74 y	10,545 (26.9)
Male	22,385 (57.0)
Body weight, kg	63.2 ± 13.9
Body weight <50 kg	5,979 (15.2)
CHA_2DS_2-VASc score	2.58 ± 1.65
HAS-BLED score	1.94 ± 1.33
Comorbidities	
Hypertension	18,764 (47.8)
Diabetes mellitus	9,925 (25.3)
Heart failure	1,342 (3.4)
Prior stroke/TIA	2,593 (6.6)
Vascular diseases	1,477 (3.8)
COPD	9,086 (23.2)
Serum creatinine level, mg/dL	1.03 (0.80-1.45)
eGFR by CG equation, mL/min	56.8 ± 34.8
eGFR by MDRD equation, mL/min	69.7 ± 39.9
eGFR by CKD-EPI equation, mL/min	62.1 ± 29.4

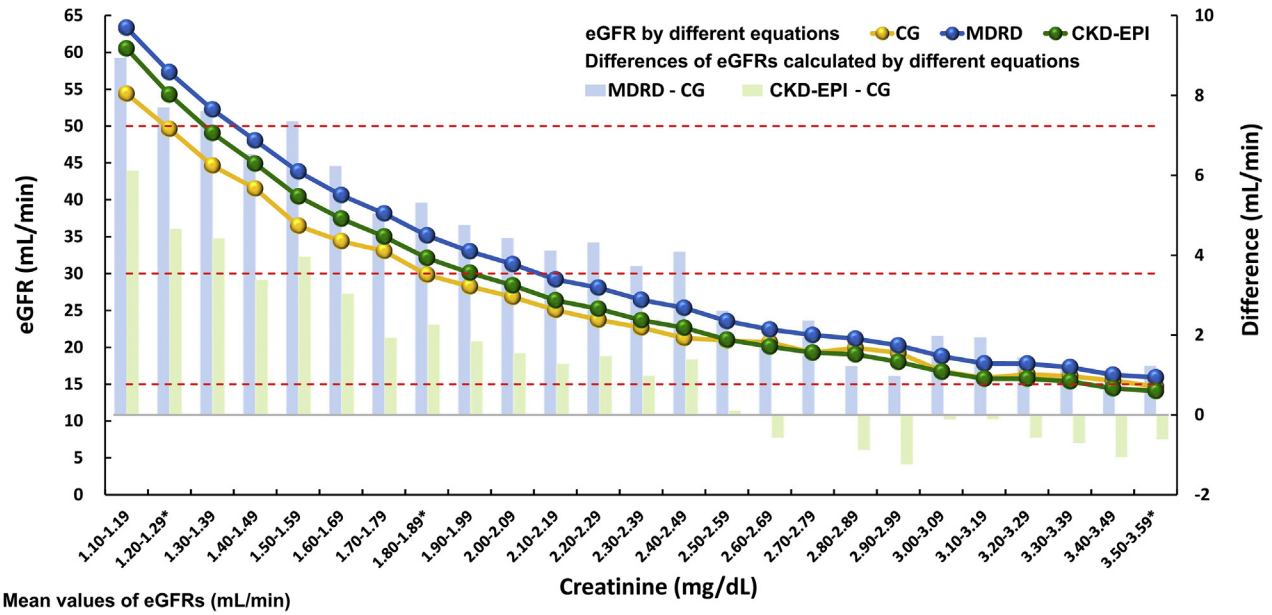
Values are mean ± SD, n (%), or median (interquartile range).

COPD = chronic obstructive pulmonary disease; TIA = transient ischemic attack; other abbreviations as in Figure 1.

At the cutoff values of eGFR of <15, 15-50, and ≥50 mL/min, the agreements were 78% between the MDRD and CG formulas and 81% between the CKD-EPI and CG formulas (Figure 2). The disagreements of different equations were largely due to overestimations (21% for the MDRD and 17% for the CKD-EPI formulas) (Figure 2). Data about the setting of cutoff values of eGFR of <30, 30-50, and ≥50 mL/min are shown in Supplemental Figure 2. The agreements were 73% between the MDRD and CG formulas and 77% between the CKD-EPI and CG formulas (Supplemental Figure 2).

Table 2 shows the percentages of disagreements/underestimations/overestimations and ORs for agreements and overestimations of eGFRs (<15, 15-50, and ≥50 mL/min) by the MDRD/CKD-EPI formulas compared to the CG formula in patients stratified by ages and BWs. For patients aged ≥75 years and with a BW of <50 kg, the percentages of overestimations were as high as 58.8% (MDRD vs CG) and 50.9% (CKD-EPI vs CG) with an OR for overestimations of 24.1 (95% CI: 22.0-26.2) for MDRD vs CG and 21.5 (95% CI: 19.6-23.5) for CKD-EPI vs CG compared to

FIGURE 1 Mean eGFRs and the Differences Among the 3 Equations in Different sCr Strata



Mean values of eGFRs (mL/min)

CG	54.4	49.6	44.6	41.5	36.5	34.4	33.1	29.8	28.3	26.8	25.1	23.7	22.7	21.3	20.9	20.7	19.3	19.9	19.3	16.8	15.8	16.3	16.1	15.5	14.7
MDRD	63.3	57.3	52.3	48.1	43.8	40.6	38.1	35.2	33.0	31.3	29.2	28.1	26.4	25.4	23.6	22.4	21.7	21.2	20.3	18.8	17.8	17.8	17.3	16.3	15.9
CKD-EPI	60.5	54.3	49.1	44.9	40.4	37.4	35.0	32.1	30.1	28.4	26.4	25.2	23.7	22.7	21.0	20.1	19.3	19.0	18.0	16.7	15.7	15.7	15.4	14.4	14.1

Compared to the CG formula, the MDRD equation overestimated the eGFRs across a wide range of sCr levels, whereas the CKD-EPI formula overestimated the eGFRs only among strata with an sCr of <2.6 mg/dL. In the sCr strata of 1.20-1.29 mg/dL and 1.80-1.89 mg/dL among which CG-eGFRs were already below 50 mL/min and 30 mL/min, respectively, the eGFRs calculated by the MRDR or CKD-EPI formulas were still higher than 50 mL/min and 30 mL/min. When CG-eGFRs were lower than 15 mL/min at the sCr 3.50-3.59 mg/dL stratum, the MDRD-eGFRs and CKD-EPI-eGFRs were 15.9 and 14.1 mL/min, respectively. *CG-eGFRs of <50, 30, or 15 mL/min. CG = Cockcroft-Gault; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; eGFR = estimated glomerular filtration rate; MDRD = Modified Diet in Renal Disease; sCr = serum creatinine.

FIGURE 2 Agreements of the MDRD, CKD-EPI, and CG Formulas for the Classifications of eGFR (<15, 15-50, and ≥50 mL/min)

	MDRD			
CG	<15	15-50	>50	Total
<15	2,999	698	1	3,698 (9%)
15-50	172	7,175	7,411	14,758 (38%)
>50	0	400	20,383	20,783 (53%)
Total	3,171 (8%)	8,273 (21%)	27,795 (71%)	39,239

Agreement = 78%; Under = 1%; Over = 21%

	CKD-EPI			
CG	<15	15-50	>50	Total
<15	3,222	476	0	3,698 (10%)
15-50	290	8,451	6,017	14,758 (37%)
>50	0	519	20,264	20,783 (53%)
Total	3,512 (9%)	9,446 (24%)	26,281 (67%)	39,239

Agreement = 81%; Under = 2%; Over = 17%

At the cutoff values of eGFR of <15, 15-50, and ≥50 mL/min, the agreements were 78% between the MDRD and CG formulas and 81% between the CKD-EPI and CG formulas. The disagreements of different equations were largely due to overestimations (21% for MDRD and 17% for CKD-EPI). Abbreviations as in Figure 1.

patients aged <75 years and with a BW of ≥50 kg. Results about the classifications of eGFRs as <30, 30-50, and ≥50 mL/min are shown in Supplemental Table 2.

The mean eGFRs and the differences among 3 equations in different sCr strata for patients aged <75 and ≥75 years are shown in Figures 3A and 3B, respectively. Compared to the CG equation, the MDRD or CKD-EPI equation overestimated eGFRs for patients older than 75 years but not for those younger than 75 years. Similarly, the MDRD or CKD-EPI formulas overestimated eGFRs for patients having a BW lower than 50 kg (Figure 4A) but not for those whose BWs were higher than 50 kg (Figure 4B).

CONCORDANCE/DISCORDANCE (OVERDOSING OR UNDERDOSING) OF DOAC DOSAGES BASED ON eGFRs CALCULATED BY DIFFERENT EQUATIONS. Supplemental Table 3 shows the clinical characteristics of patients with AF treated with DOACs and patients whose dosages of DOACs were concordant or discordant between the MDRD/CG and CKD-EPI/CG formulas. Overall, there were 7.6% and 6.5% of patients treated with DOACs whose dosages were discordant between the MDRD/CG and CKD-EPI/CG formulas, respectively. The ages were older, and the BWs and eGFRs calculated by all equations were lower, in the discordant group than in the concordant group. The percentages of concordance and discordance of the dosages of each DOAC are shown in Figure 5. For the MDRD versus CG formula, the discordance rates were lowest for edoxaban (1%) and highest for rivaroxaban (13%) (Figure 5A). For the CKD-EPI versus CG formula, the discordance rates were 1% for edoxaban, 3% for apixaban, 5% for dabigatran, and 11% for rivaroxaban (Figure 5B).

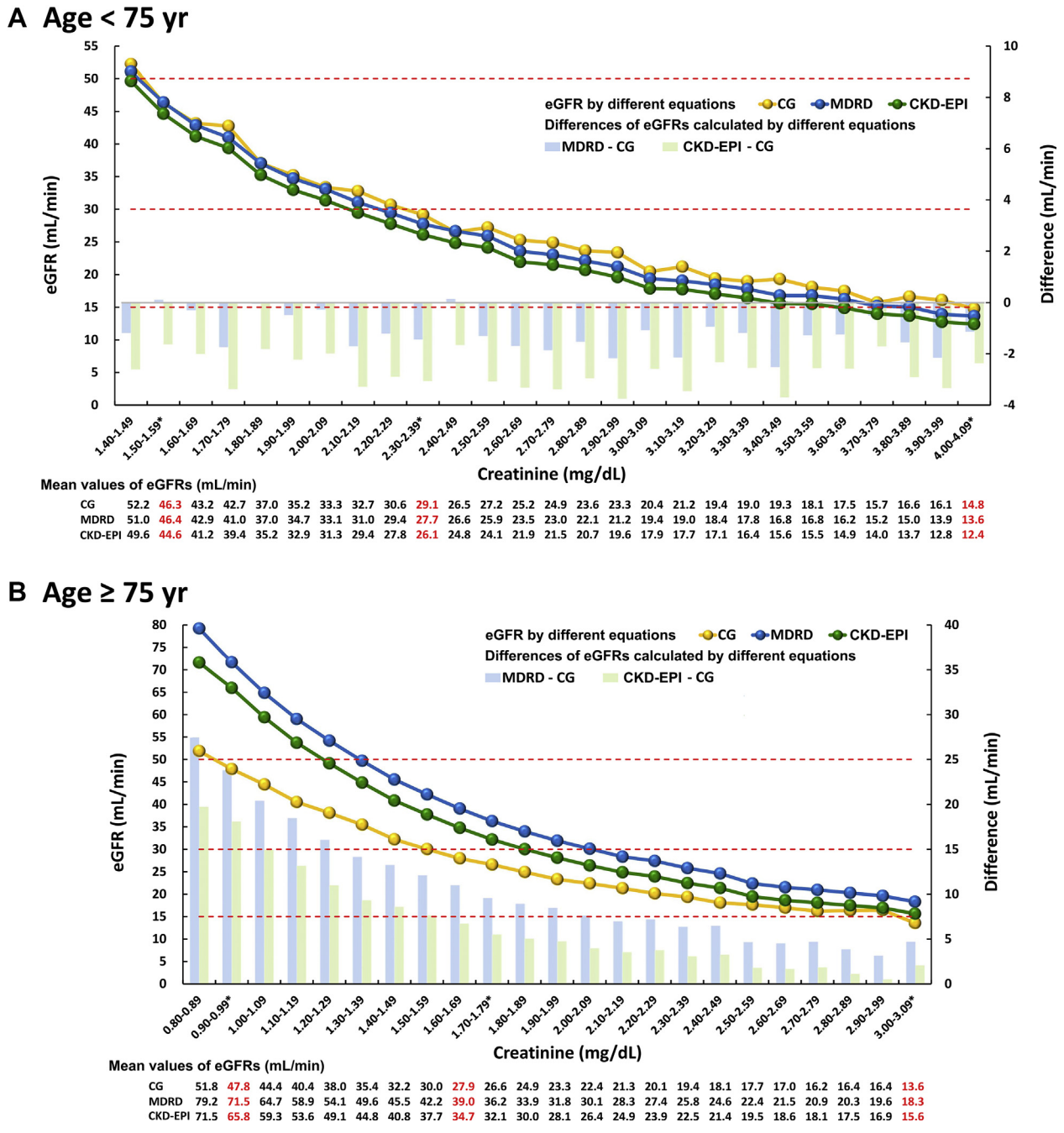
ON-LABEL DOSING USING THE MDRD OR CKD-EPI FORMULAS, OFF-LABEL DOSING BY THE CG FORMULA (GOLD STANDARD), AND CLINICAL OUTCOMES. Supplemental Table 4 shows the clinical characteristics of patients treated with warfarin and those treated with DOACs whose dosages were defined as on-label dosing based on MRDR-eGFRs

TABLE 2 Disagreements/Underestimations/Overestimations of eGFRs (<15, 15-50, and ≥50 mL/min) Using the MDRD or CKD-EPI Formulas Versus the CG Formula

Clinical Factors	n	Disagreement	Underestimation	Overestimation	OR (95% CI) for Overestimation	OR (95% CI) for Agreement
MDRD versus CG						
BW ≥50 kg and age <75 y	19,696	1,637 (8.3)	535 (2.7)	1,102 (5.6)	Reference	Reference
BW <50 kg	5,979	2,908 (48.6)	0 (0)	2,908 (48.6)	5.10 (4.81-5.41)	0.22 (0.21-0.24)
Age ≥75 y	17,651	6,540 (37.0)	37 (0.2)	6,503 (36.8)	7.25 (6.83-7.69)	0.19 (0.18-0.20)
BW <50 kg or age ≥75 y	15,456	4,642 (30.0)	37 (0.2)	4,605 (29.8)	7.16 (6.67-7.68)	0.21 (0.20-0.22)
BW <50 kg and age ≥75 y	4,087	2,403 (58.8)	0 (0)	2,403 (58.8)	24.10 (22.00-26.20)	0.06 (0.06-0.07)
CKD-EPI versus CG						
BW ≥50 kg and age <75 y	19,696	1,574 (8.0)	669 (3.4)	905 (4.6)	Reference	Reference
BW <50 kg	5,979	2,550 (42.7)	0 (0)	2,550 (42.7)	5.53 (5.20-5.88)	0.22 (0.21-0.24)
Age ≥75 y	17,651	5,257 (29.8)	140 (0.8)	5,117 (29.0)	6.00 (5.63-6.39)	0.25 (0.23-0.26)
BW <50 kg or age ≥75 y	15,456	3,649 (23.6)	140 (0.9)	3,509 (22.7)	6.10 (5.65-6.58)	0.28 (0.26-0.30)
BW <50 kg and age ≥75 y	4,087	2,079 (50.9)	0 (0)	2,079 (50.9)	21.50 (19.60-23.50)	0.08 (0.07-0.09)

Values are n (%) unless otherwise indicated.
BW = body weight; other abbreviations as in Figure 1.

FIGURE 3 **Mean eGFRs and the Differences Among the 3 Equations in Patients Aged <75 and ≥75 years**

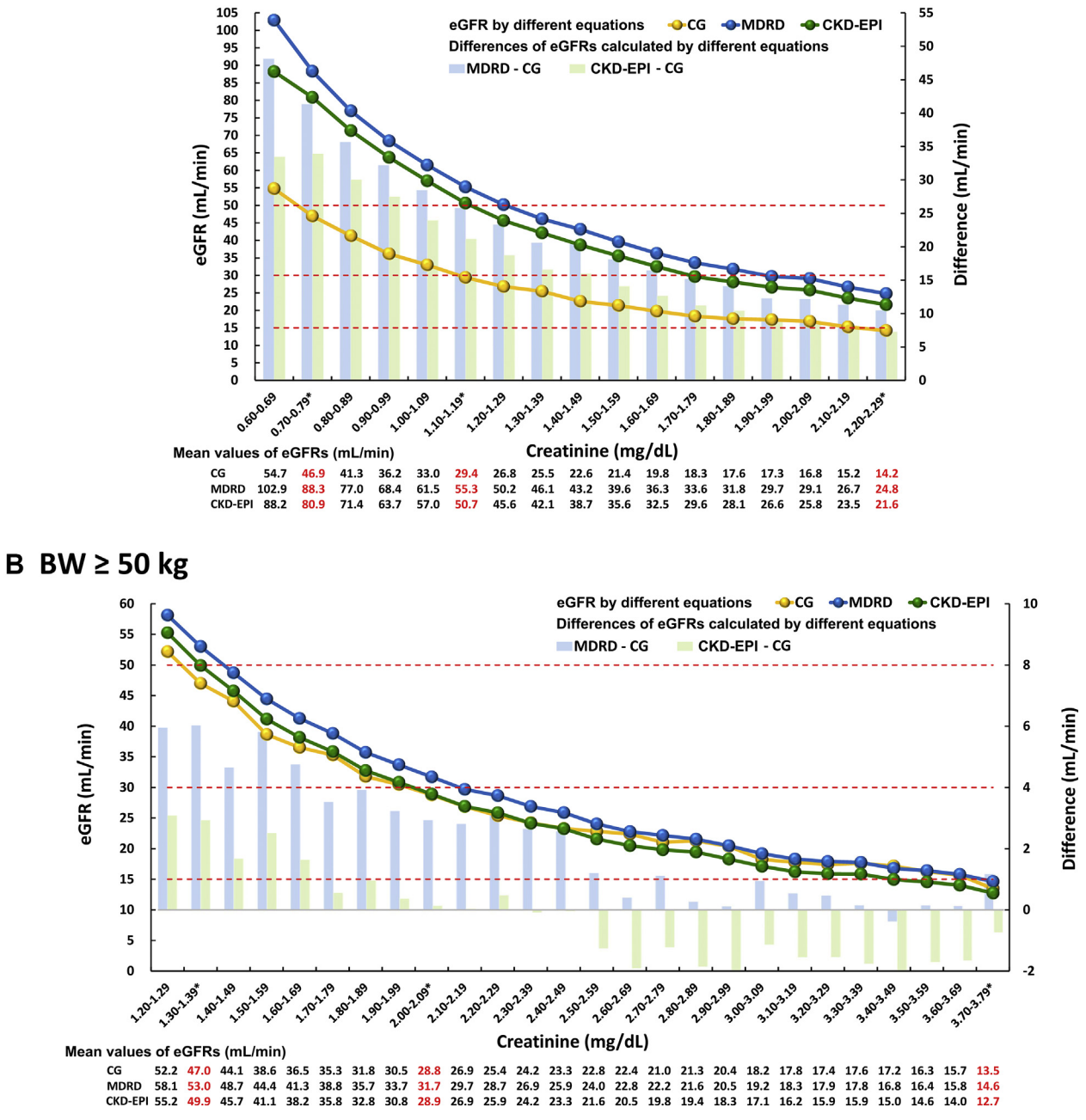


Compared to the CG equation, the MDRD or CKD-EPI formulas obviously overestimated eGFRs for **(B)** patients older than 75 years but not **(A)** those younger than 75 years. *CG-eGFRs of <50, 30, or 15 mL/min. Abbreviations as in Figure 1.

and CKD-EPI-eGFRs who were further categorized as having "concordance" or "discordance (overdosing or underdosing)" by regarding CG-eGFRs as the gold standard. The discordance rates were around 2.9% for MDRD vs CG and 2.7% for CKD-EPI vs CG, and most of the discordances were due to overdosing (90% for MDRD vs CG; 81% for CKE-EPI vs CG).

The median follow-up duration of patients was 18.6 months (interquartile range: 6.4-35.1 months).

FIGURE 4 Mean eGFRs and the Differences Among the 3 Equations in Patients With BWs of <50 and ≥50 kg



Compared to the CG equation, the MDRD or CKD-EPI formulas obviously overestimated eGFRs for **(A)** patients having a BW lower than 50 kg but not **(B)** those with a BW higher than 50 kg. *CG-eGFRs of <50 mL/min, 30 mL/min, or 15 mL/min. BW = body weight; other abbreviations as in Figure 1.

Compared to warfarin, patients treated with DOACs whose dosages were concordant between eGFRs calculated using the MDRD and CG formulas were associated with a lower risk of IS/SE (adjusted HR [aHR]: 0.78; 95% CI: 0.61-1.00), major bleeding (aHR: 0.34; 95% CI: 0.26-0.45), all-cause mortality (aHR: 0.43; 95% CI: 0.38-0.49), and IS/SE or major bleeding or mortality (aHR: 0.47; 95% CI: 0.42-0.52) after

FIGURE 5 Percentages of Concordance and Discordance of Dosages of Each DOAC With the Different Equations

A

Dabigatran

	MDRD		
CG	On label	Over	Total
On label	1,903	6	1,909 (92%)
Over	100	77	177 (8%)
Total	2,003 (96%)	83 (4%)	2,086

Concordance = 95%; Discordance = 5%

Rivaroxaban

	MDRD			
CG	Under	On label	Over	Total
Under	838	17	0	855 (17%)
On label	571	3,476	6	4,053 (80%)
Over	0	69	64	133 (3%)
Total	1,409 (28%)	3,562 (70%)	70 (2%)	5,041

Concordance = 87%; Discordance = 13%

Apixaban

	MDRD			
CG	Under	On label	Over	Total
Under	803	7	0	810 (31%)
On label	26	1,564	3	1,593 (62%)
Over	0	41	136	177 (7%)
Total	829 (32%)	1,612 (62%)	139 (5%)	2,580

Concordance = 97%; Discordance = 3%

Edoxaban

	MDRD			
CG	Under	On label	Over	Total
Under	228	0	0	228 (15%)
On label	0	999	0	999 (68%)
Over	0	6	245	251 (17%)
Total	228 (15%)	1,005 (68%)	245 (17%)	1,478

Concordance = 99%; Discordance = 1%

B

Dabigatran

	CKD-EPI		
CG	On label	Over	Total
On label	1,901	8	1,909 (92%)
Over	90	87	177 (8%)
Total	1,991 (95%)	95 (5%)	2,086

Concordance = 95%; Discordance = 5%

Rivaroxaban

	CKD-EPI			
CG	Under	On label	Over	Total
Under	824	31	0	855 (17%)
On label	454	3,589	10	4,053 (80%)
Over	0	60	73	133 (3%)
Total	1,278 (25%)	3,680 (73%)	83 (2%)	5,041

Concordance = 89%; Discordance = 11%

Apixaban

	CKD-EPI			
CG	Under	On label	Over	Total
Under	799	11	0	810 (31%)
On label	25	1,563	5	1,593 (62%)
Over	0	30	147	177 (7%)
Total	824 (32%)	1,604 (62%)	152 (6%)	2,580

Concordance = 97%; Discordance = 3%

Edoxaban

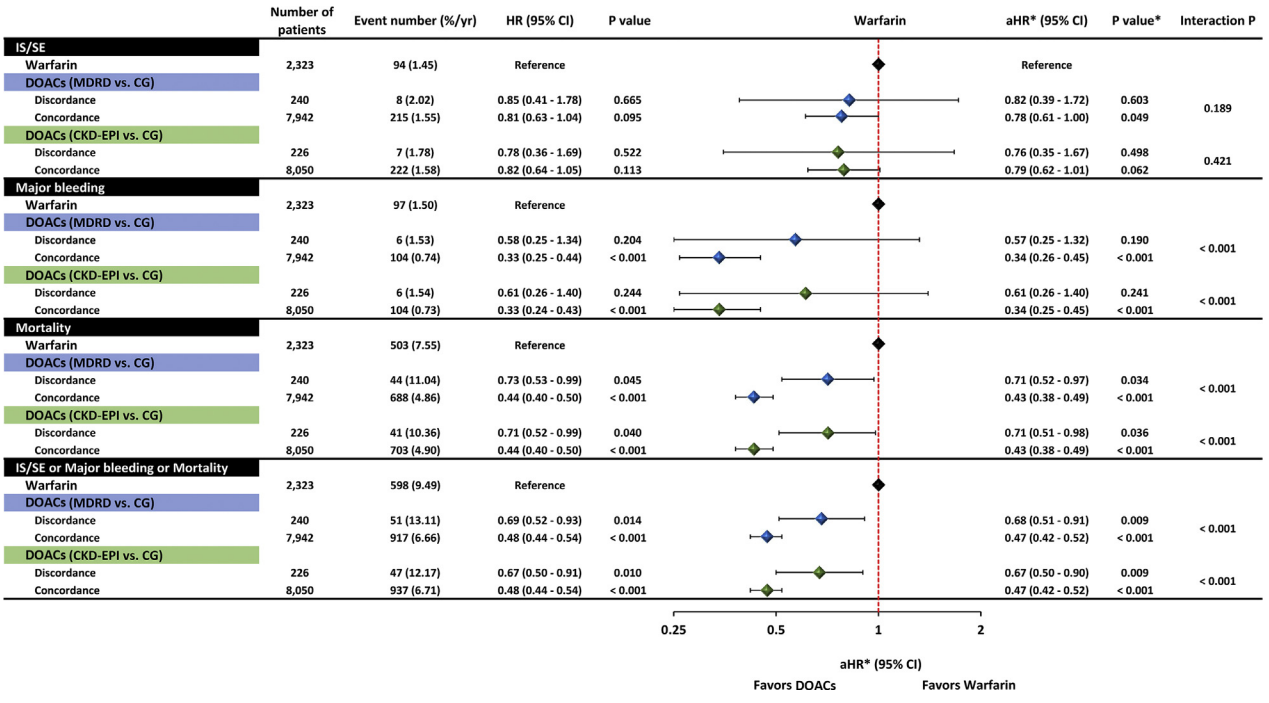
	CKD-EPI			
CG	Under	On label	Over	Total
Under	228	0	0	228 (15%)
On label	0	997	2	999 (68%)
Over	0	4	247	251 (17%)
Total	228 (15%)	1,001 (68%)	249 (17%)	1,478

Concordance = 99%; Discordance = 1%

Overall, there were 7.6% and 6.5% of patients treated with DOACs whose dosages were discordant between the MDRD/CG and CKD-EPI/CG formulas, respectively. **(A)** For the MDRD versus CG formulas, the discordance rates were lowest for edoxaban (1%) and highest for rivaroxaban (13%). **(B)** For the CKD-EPI versus CG formulas, the discordance rates were 1% for edoxaban, 3% for apixaban, 5% for dabigatran, and 11% for rivaroxaban. DOAC = direct oral anticoagulant; other abbreviations as in Figure 1.

adjustments for variables that were significantly different between the warfarin and DOAC groups in Supplemental Table 4, including age, sex, BW, CHA_2DS_2-VASc score, HAS-BLED score, chronic obstructive pulmonary disease, and sCr level (Figure 6). The risks of IS/SE (aHR: 0.82; 95% CI: 0.39-1.72) and major bleeding (aHR: 0.57; 95% CI: 0.25-1.32) were similar between patients receiving warfarin and

FIGURE 6 Risk of Clinical Outcomes for Patients Treated With DOACs Compared to Warfarin



Among patients receiving DOACs whose dosages were defined as on label based on the MDRD or CKD-EPI formulas, only those whose dosages were truly on label (concordance) based on the CG formula were associated with a lower risk of major bleeding compared to warfarin (interaction $P < 0.001$). *Adjusted for differences between the warfarin and DOAC groups, including age, sex, BW, CHA_2DS_2-VASc score, HAS-BLED score, chronic obstructive pulmonary disease, and sCr. aHR = adjusted HR; IS/SE = ischemic stroke/systemic embolism; other abbreviations as in Figures 1, 4, and 5.

patients treated with DOACs whose dosages were discordant between eGFRs calculated using the MDRD and CG formulas (Figure 6). A significant interaction *P* value (<0.001) was observed for risk of major bleeding. The results were generally similar when comparisons were performed between patients treated with warfarin and those treated with DOACs whose dosages were discordant or concordant between the CKD-EPI and CG formulas.

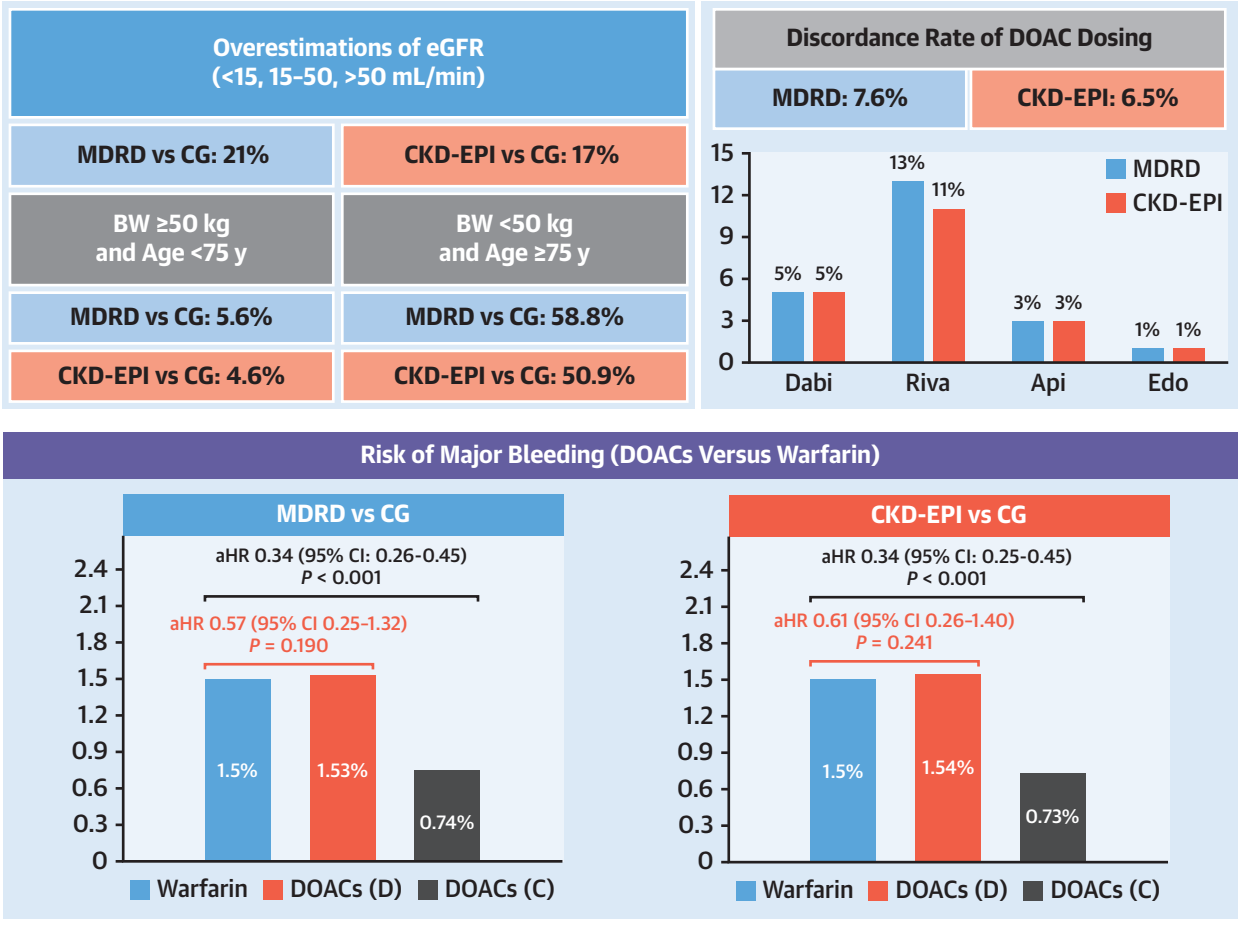
DISCUSSION

In the present study, we investigated the differences of eGFRs calculated using different equations and the impacts on the dosages of DOACs and clinical outcomes. Our principal findings are as follows:

- Compared to the CG equation, the MDRD and CKD-EPI formulas would overestimate eGFRs in a considerable percentages of patients with AF (21% for the MDRD formula and 17% for the CKD-EPI formula), especially for patients aged ≥75 years and with BWs of <50 kg (58.8% for the MDRD formula and 50.9% for the CKD-EPI formula).
- For patients treated with DOACs, approximately 7.6% (MDRD formula) and 6.5% (CKD-EPI formula) of them had dosages of DOACs that were discordant compared to those calculated with CG equation.
- Among patients receiving DOACs whose dosages were defined as on-label based on the MDRD or CKD-EPI formula, only those whose dosages were truly on-label based on the CG formula were associated with a lower risk of major bleeding compared to warfarin (Central Illustration).

DIFFERENCES OF eGFRs AMONG DIFFERENT RENAL EQUATIONS. There were several studies that investigated the differences of eGFRs using different equations among patients with AF.[18-21] However, these studies enrolled only several hundred patients, which may not be able to show the broad spectrum of patients with AF. Although the studies performed by Manzano-Fernández et al[18] and Pérez Cabeza et al[19] showed that non-CG methods tended to more frequently overestimate eGFRs than the CG equation, the study performed by Andrade et al[21] showed an

CENTRAL ILLUSTRATION **Overestimations of Estimated Glomerular Filtration Rate, Discordance Rate of Direct Oral Anticoagulant Dosing, and Risk of Major Bleeding**



Chan, Y.-H. et al. JACC: Asia. 2022;2(1):46–58.

Compared to the CG equation, the MDRD and CKD-EPI formulas would overestimate eGFRs in a considerable percentages of patients with atrial fibrillation (21% for MDRD and 17% for CKD-EPI), especially for patients aged ≥75 years and with a BW of <50 kg (58.8% for MDRD and 50.9% for CKD-EPI). For patients treated with DOACs, approximately 7.6% (MDRD) and 6.5% (CKD-EPI) of them had dosages of DOACs that were discordant compared to the CG equation (5% for dabigatran [Dabi], 11%-13% for rivaroxaban [Riva], 3% for apixaban [Api], and 1% for edoxaban [Edo]). Only patients whose dosages of DOACs were truly on label based on the CG formula were associated with a lower risk of major bleeding compared to warfarin. aHR = adjusted hazard ratio; BW = body weight; CG = Cockcroft-Gault; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; DOAC = direct oral anticoagulant; eGFR = estimated glomerular filtration rate; MDRD = Modified Diet in Renal Disease.

opposite conclusion. In the latter study, which enrolled 831 patients with AF, the MDRD-eGFRs and CKD-EPI-eGFRs misclassified 36.2% and 35.8% of patients with respect to DOAC dosing compared to CG-eGFRs, respectively.[21] The misclassification resulted in undertreatment (eg, inappropriate dose reduction: 26.9% MDRD and 28.8% CKD-EPI) and, to a lesser extent, overtreatment (eg, inappropriate use of standard dose: 9.3% MDRD and 7.0% CKD-EPI). These conflicting results would result in more confusion over the optimal method to assess eGFR.

In our study, we demonstrated that the MDRD and CKD-EPI formulas would overestimate eGFRs in a considerable percentages of patients with AF (21% for the MDRD and 17% for the CKD-EPI formula) but would underestimate eGFRs in only approximately 1% (MDRD) and 2% (CKD-EPI) of the AF population. Our results were concordant with those reported by Manzano-Fernández et al and Pérez Cabeza et al.[18,19] However, compared to previously published studies,[18-21] we enrolled a much larger number of patients with AF (n = 39,239) and reported the

differences of eGFRs by different equations in wide ranges of sCr, ages, and BWs.

We showed that age and BW were important factors significantly associated with the agreements/disagreements among the different equations. In our prior report, MDRD-eGFRs and CKD-EPI-eGFRs tended to overestimate CG-eGFRs for patients aged ≥75 years or with BWs of <50 kg.[9] In the present study, we further demonstrated that for patients aged <75 years and with BWs of ≥50 kg, the percentages of disagreements were only 8.3% for the MDRD vs CG formulas and 8% for the CKD-EPI vs CG formulas. On the contrary, for patients aged ≥75 years and with BWs of <50 kg, the percentages of overestimations were as high as 58.8% (MDRD vs CG) and 50.9% (CKD-EPI vs CG). Because a low BW was significantly associated with the possibility of overestimations, the difference of the mean BWs of the population in our study (63.2 kg) and that in the study by Andrade et al[21] (80.1 kg) could partly explain the discrepancies of the results. Our findings highlight the importance of the adoption of the CG equation rather than MDRD and CKE-EPI formulas to calculate eGFRs, especially for elderly patients and those with and low BW.

IMPACT OF DIFFERENT EQUATIONS FOR eGFRs ON DOAC DOSAGES AND CLINICAL OUTCOMES. Although the rates of the misclassifications of eGFRs were 21% for the MDRD and 17% for the CKD-EPI formulas compared to the CG formula, the discordance rates of the dosages of DOACs were only 7.6% for the MDRD and 6.5% for the CKD-EPI formulas in our DOAC cohort. There were 2 reasons that could possibly explain this gap. First, renal function is not the only criterion for dosage reductions of DOACs, except for rivaroxaban. Indeed, the highest discordance rate of dosages was observed for rivaroxaban (11%-13%) in our study. Second, DOACs at a reduced dosages even for patients who did not fit the dosage reduction criteria are commonly used in daily practice in Asia.[22] Therefore, off-label low-dose DOACs would be categorized as "underdosing" for all renal equations.

In our previous brief report, we showed the impacts of the adoptions of the MDRD or CKD-EPI formulas rather than the CG equation for the determinations of dosages of DOACs on the risk of IS/SE and major bleeding.[9] In the present study, we further reported the impacts of the adoptions of different renal equations on the risks of more clinical outcomes. Among patients treated with DOACs whose dosages were defined as on-label dosing based on non-CG equations, the discordance rates were approximately 2.9% for the MDRD vs CG equations and 2.7% for the CKD-EPI vs CG equations, and most of the discordances were due to overdosing (90% for the MDRD vs CG equations and 81% for the CKE-EPI vs CG equations). Compared to warfarin, only patients whose dosages were truly on label based on the CG formula were associated with a lower risk of major bleeding. Our findings suggest that the CG equation should be used as the gold standard for the calculation of eGFR to guide the optimal dosages of DOACs.

STUDY LIMITATIONS. First, it was a retrospective analysis of the electronic medical record database, and there was no universal and prespecified algorithm for the measurements of sCr levels in patients with AF. Therefore, whether our findings were consistent among patients whose data for sCr level were not available was unclear. Also, patients experiencing adverse events that occurred outside the CGMH Medical System would not be recorded, and this is a common limitation of studies based on electronic health records. Second, although the baseline differences of warfarin and DOACs were adjusted using multivariable Cox regression analysis, some unmeasured confounders may still exist. Third, we investigated only Taiwanese patients with AF, and whether our findings could be generalized to other populations is uncertain. Because White AF patients were heavier than Asian patients with AF, the overestimations of eGFRs with the MDRD and CKD-EPI equations may be less evident among non-Asians. Finally, although the discordance of eGFRs calculated using different renal equations existed in clinical practice, the real impacts of this discordance on the dosing of DOACs are less prominent. However, our results support the use of the CG equation to calculate eGFRs to determine the dose of DOACs, as adopted in pivotal randomized trials.

CONCLUSIONS

The adoption of the MDRD or CKD-EPI rather than the CG formula would result in inappropriate dosing of DOACs (mainly overdosing), which would attenuate the advantages of DOACs compared to warfarin. Therefore, the CG equation should be used as the gold standard for the calculation of eGFR to guide the DOAC dosages.

ACKNOWLEDGMENTS The authors thank and wish to acknowledge the statistical assistance and support of the Maintenance Project of the Center for Big Data

Analytics and Statistics (grant CLRPG3D0045) at Chang Gung Memorial Hospital for study design and monitoring, data analysis, and interpretation. The interpretation and conclusions contained herein do not represent the position of Chang Gung Memorial Hospital.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

This work was supported in part by grants from the Ministry of Science and Technology (MOST107-2314-B-075-062-MY3 and MOST110-2314-B-075-059), Taipei Veterans General Hospital (V108B-015, V108B-027, V108C-090, V109C-042, and V109C-186), Research Foundation of Cardiovascular Medicine, and Szu-Yuan Research Foundation of Internal Medicine, Taipei, Taiwan. This study was supported by grant 105-2628-B-182A-003-MY3 from the Ministry of Science and Technology and grants CMRPG3E1681, CMRPG3E1682, CMRPG3E1683, and CORPG3G0351 from Chang Gung Memorial Hospital, Linkou, Taiwan. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Compared to the CG equation, the MDRD and CKD-EPI formulas would overestimate eGFRs in a considerable percentage of patients with AF (21% for MDRD and 17% for CKD-EPI), especially for patients aged ≥75 years and with BWs of <50 kg (58.8% for MDRD and 50.9% for CKD-EPI).

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: For patients with AF treated with DOACs, approximately 7.6% (MDRD) and 6.5% (CKD-EPI) had dosages of DOACs that were discordant compared to the CG equation. Only patients whose dosages of DOACs were truly on label based on the CG formula were associated with a lower risk of major bleeding compared to warfarin.

TRANSLATIONAL OUTLOOK: The CG equation should be used as the gold standard for the calculation of eGFR to guide DOAC dosages, as used in pivotal randomized trials.

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KEY WORDS atrial fibrillation, CKD-EPI, Cockcroft-Gault (CG) formula, eGFRs, MDRD

APPENDIX For supplemental tables and figures, please see the online version of this paper.