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Direct Oral Anticoagulants Versus Warfarin Across the Spectrum of Kidney Function: Patient-Level Network Meta-Analyses From COMBINE AF

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BACKGROUND: There is uncertainty surrounding the use of direct oral anticoagulants (DOACs) in patients with kidney dysfunction.

METHODS: Using the COMBINE AF (A Collaboration Between Multiple Institutions to Better Investigate Non-Vitamin K Antagonist Oral Anticoagulant Use in Atrial Fibrillation) database (data from RE-LY [Randomized Evaluation of Long-term Anticoagulation Therapy], ROCKET AF [Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation], ARISTOTLE [Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation], and ENGAGE AF-TIMI 48 [Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48]), we performed an individual patient-level network meta-analysis to evaluate the safety and efficacy of DOACs versus warfarin across continuous creatinine clearance (CrCl). A multivariable Cox model including treatment-by-CrCl interaction with random effects was fitted to estimate hazard ratios for paired treatment strategies (standard-dose DOAC, lower-dose DOAC, and warfarin). Outcomes included stroke and systemic embolism (S/SE), major bleeding, intracranial hemorrhage (ICH), and death.

RESULTS: Among 71 683 patients (mean age, 70.6±9.4 years; 37.3% female; median follow-up, 23.1 months), the mean CrCl was 75.5±30.5 mL/min. The incidence of S/SE, major bleeding, ICH, and death increased significantly with worsening kidney function. Across continuous CrCl values down to 25 mL/min, the hazard of major bleeding did not change for patients randomized to standard-dose DOACs compared with those randomized to warfarin ($P_{interaction}$=0.61). Compared with warfarin, standard-dose DOAC use resulted in a significantly lower hazard of ICH at CrCl values <122 mL/min, with a trend for increased safety with DOAC as CrCl decreased (6.2% decrease in hazard ratio per 10-mL/min decrease in CrCl; $P_{interaction}$=0.08). Compared with warfarin, standard-dose DOAC use resulted in a significantly lower hazard of S/SE with CrCl <87 mL/min, with a significant treatment-by-CrCl effect (4.8% decrease in hazard ratio per 10-mL/min decrease in CrCl; $P_{interaction}$=0.01). The hazard of death was significantly lower with standard-dose DOACs for patients with CrCl <77 mL/min, with a trend toward increasing benefit with lower CrCl (2.1% decrease in hazard ratio per 10-mL/min decrease in CrCl; $P_{interaction}$=0.08). Use of lower-dose rather than standard-dose DOACs was not associated with a significant difference in incident bleeding or ICH in patients with reduced kidney function but was associated with a higher incidence4 of death and S/SE.

CONCLUSIONS: Standard-dose DOACs are safer and more effective than warfarin down to a CrCl of at least 25 mL/min. Lower-dose DOACs do not significantly lower the incidence of bleeding or ICH compared with standard-dose DOACs but are associated with a higher incidence of S/SE and death. These findings support the use of standard-dose DOACs over warfarin in patients with kidney dysfunction.

Key Words: anticoagulants ■ atrial fibrillation ■ kidney

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Clinical Perspective

What Is New?

- As kidney function worsens (down to a creatinine clearance of at least 25 mL/min), patients derive a larger relative efficacy benefit from direct oral anticoagulants (DOACs) compared with warfarin in terms of the hazard of stroke and systemic embolism, with similar trends seen for death and intracranial hemorrhage.
- Patients with kidney dysfunction randomized to lower-dose DOACs did not have a significantly lower incidence of bleeding or intracranial hemorrhage compared with patients randomized to standard-dose DOACs but did have a higher incidence of death and thromboembolism.

What Are the Clinical Implications?

- The use of standard-dose DOACs is safer and more effective than warfarin down to a creatinine clearance of at least 25 mL/min.
- Inappropriate dose reduction of DOACs (eg, in patients with kidney dysfunction but not meeting clinical criteria for dose reduction) likely results in a higher risk of thromboembolism and death without reducing the risk of bleeding or intracranial hemorrhage.

Nonstandard Abbreviations and Acronyms

AF	atrial fibrillation
ARISTOTLE	Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation
AVERROES	A Phase III Study of Apixaban in Patients With Atrial Fibrillation
COMBINE AF	A Collaboration Between Multiple Institutions to Better Investigate Non-Vitamin K Antagonist Oral Anticoagulant Use in Atrial Fibrillation
CrCl	creatinine clearance
DOAC	direct oral anticoagulant
ENGAGE AF-TIMI 48	Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48
HR	hazard ratio
ICH	intracranial hemorrhage
RE-LY	Randomized Evaluation of Long-term Anticoagulation Therapy
ROCKET AF	Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation
S/SE	stroke and systemic embolism

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, a major risk factor for stroke and systemic embolism (S/SE), and an independent predictor of mortality. These risks are amplified by the presence of kidney dysfunction, which increases the risk of not only AF,[1] but also thromboembolic events, bleeding, and death in patients with AF.[2,3] Therefore, treatment decisions surrounding stroke prevention in patients with kidney dysfunction and AF are of critical importance. Direct oral anticoagulants (DOACs) are the first-line therapy for the prevention of stroke in AF according to randomized data from multiple trials demonstrating a similar or lower incidence of stroke with DOACs and a similar or lower risk of major bleeding compared with warfarin.[4–6] Currently, dabigatran is recommended for stroke prevention in AF for those with creatinine clearance (CrCl) >30 mL/min (with dose reduction for those with CrCl 15–30 mL/min). Edoxaban and rivaroxaban are recommended for those with CrCl >50 mL/min (with dose reduction for those with CrCl 15–50 mL/min), and apixaban is recommended for those with CrCl >25 mL/min (with dose adjustment for those meeting ≥2 clinical criteria [age, weight, and kidney function]).[7–10] Given that all DOACs are partially cleared renally, with renal clearance ranging from 27% (apixaban) to 80% (dabigatran), there are possible safety concerns for this population. As a result, DOACs are still less frequently used and are often underdosed in patients with kidney insufficiency.[11,12]

Although patients with CrCl as low as 25 to 30 mL/min were eligible for inclusion in the pivotal DOAC trials, relatively few patients with severely reduced kidney function were enrolled.[13–19] Subanalyses using smaller cohorts have supported the use of DOACs over warfarin in patients with reduced kidney function, although these analyses were limited by relatively small sample sizes.[17,20–22] Previous meta-analyses assessing the safety and efficacy of DOACs in patients with kidney dysfunction have been limited to traditional pair-wise, study-level, meta-analysis methodologies and the use of categorical CrCl cutoffs based on previously published summary data from each constituent trial.[23] Such pair-wise meta-analyses carry inherent limitations in the assessment of trials with multiple treatment arms, and study-level meta-analyses using aggregate published data are adversely affected by inconsistent follow-up time, absence of

individual time-to-event results, and inability to robustly evaluate for heterogeneity between trials. Network meta-analyses using individual patient data address these limitations. Network meta-analyses allow the simultaneous comparison of multiple treatments under the same model with robust estimation of heterogeneity across studies. Furthermore, individual patient data network meta-analyses: are not limited to the first event that occurred for a given patient (eg, a stroke or bleeding event, but not both); can reflect the time to first event for each adjudicated patient outcome; are able to account for inconsistent follow-up time across constituent trials; provide high statistical power; and allow robust analysis of continuous variables. Thus, a patient-level meta-analysis can provide a more accurate estimate of treatment effects.

The COMBINE AF (A Collaboration Between Multiple Institutions to Better Investigate Non-Vitamin K Antagonist Oral Anticoagulant Use in Atrial Fibrillation) database contains individual patient data from the pivotal randomized trials of DOACs versus warfarin in AF, including 24 396 patients with a CrCl <60 mL/min.[24] We used individual patient data from COMBINE AF to perform a network meta-analysis evaluating safety and efficacy outcomes of DOACs and warfarin across the continuous spectrum of kidney function (down to a CrCl of 25 mL/min), with a particular focus on patients with reduced kidney function, for whom hesitation to use DOACs may still exist.

METHODS

This analysis received local approval from the institutional review board. Due to data privacy restrictions, data from COMBINE AF are unable to be shared outside of the members of the COMBINE AF executive committee and their institutions. Participants consented to participate in each of the parent trials of this registry.

Analysis Design

The design and rationale of COMBINE AF have been described previously.[24] Briefly, COMBINE AF incorporated individual patient data from 77 282 deidentified patients from 5 pivotal randomized clinical trials comparing DOACs with warfarin or aspirin in patients with AF. For our analyses, we included all patients from RE-LY (Randomized Evaluation of Long-term Anticoagulation Therapy), ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation), ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation), and ENGAGE AF-TIMI 48 (Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48) who were randomized to warfarin or DOACs, yielding a cohort size of 71 683. Patients from AVERROES (A Phase III Study of Apixaban in Patients With Atrial Fibrillation; n=5599), which assessed apixaban versus aspirin, were not included in these analyses.

Patients were analyzed according to study drug randomization arm: standard-dose DOACs, lower-dose DOACs, or warfarin. These analyses were not affected by dose adjustment due to individual clinical characteristics such as age or weight. Standard-dose DOACs were defined as the standard dose used in ROCKET AF or ARISTOTLE (with trial protocol–specified dose adjustment based on age, weight, and kidney function) and as the DOAC randomization arm with the higher dosing regimen in RE-LY (150 mg of dabigatran twice daily) or ENGAGE AF-TIMI 48 (60 mg of edoxaban once daily or 30 mg once daily for patients meeting trial criteria for dose adjustment). Lower-dose DOACs were defined as the DOAC randomization arm with the lower dosing regimen in RE-LY (110 mg of dabigatran twice daily) or ENGAGE AF-TIMI 48 (30 mg of edoxaban once daily or 15 mg once daily for patients meeting trial criteria for dose adjustment).

Outcomes

Outcome definitions in COMBINE AF have been described previously.[24] All outcomes were adjudicated in each of the constituent trials, which used a time-to-first-event design. Efficacy outcomes included S/SE and all-cause mortality. Safety outcomes included intracranial hemorrhage (ICH) and major bleeding as defined by the International Society on Thrombosis and Haemostasis, which includes fatal bleeding, symptomatic bleeding in a critical area or organ system, a fall in hemoglobin concentration >2 g/dL, or transfusion of ≥2 U of whole blood or packed red blood cells.[25] Two composite outcomes were analyzed: the composite of major bleeding and death, and the composite of major bleeding, death, and S/SE.

Study Population

For efficacy outcomes, the intention-to-treat population was used. To account for different follow-up durations across trials and to set a comparable follow-up duration in these network meta-analyses, subjects were censored when <10% were at risk in each individual study.[24] For safety and composite outcomes, the safety population was used as defined by each of the individual trials but typically included participants who received at least 1 dose of a study drug and were followed up for events occurring between the date the participant began treatment with the study drug and up to 2 days after the participant discontinued study drug.

Statistical Analyses

The Cockcroft-Gault equation was used to calculate CrCl. Primary analyses were conducted across the continuous spectrum of CrCl. We additionally prespecified categorical CrCl groups at baseline as follows: <30, 30 to 44, 45 to 59, 60 to 89, and ≥90 mL/min. These groups were used to describe baseline characteristics and raw event rates.

To understand whether CrCl is associated with event incidence and treatment effects, we first assessed raw event incidence per 100 patient-years by categorical CrCl. To assess the impact of kidney function on event rates continuously, a quasi-Poisson regression model including continuous CrCl values and logarithm of event time (follow-up time if censored) as offset was fitted to estimate the event rates with respect to each outcome. The quasi-Poisson model was used due to the

overdispersion of the outcomes. We considered linear and nonlinear associations between CrCl and outcomes. For nonlinear associations, we considered a cubic spline with 3 knots and a linear piecewise model with 1 or 3 knots. The model assuming a linear CrCl-by-outcome relationship was selected because it has the lowest quasi–Akaike information criterion for all outcomes. We plotted the event rates per 100 patient-years by decreasing CrCl values and presented the change in event rate per 10-mL/min CrCl decrease.

We performed a patient-level network meta-analysis to evaluate treatment effects across continuous CrCl values. A multivariable-stratified Cox proportional hazard model including a treatment-by-CrCl interaction was fitted to estimate hazard ratios (HRs) for pairs of treatment strategies with respect to each outcome. The model allows random effects on treatment effect coefficients to account for heterogeneity across trials. We did not add random effects on the CrCl or treatment-by-CrCl interaction because doing so did not improve model fit according to the Akaike information criterion. We considered continuous and categorical CrCl in 2 separate fitted quasi-Poisson models. Cox models assuming linear and nonlinear associations between CrCl and outcomes were fitted when CrCl was used continuously. For nonlinear associations, we considered a cubic spline model with 3 knots and a linear piecewise model with 1 or 3 knots. In Cox regression models, nonlinear associations were not observed, and results from linear models were selected on the basis of goodness-of-fit assessment with the Akaike information criterion. In addition, proportional hazard assumptions were assessed with the Schoenfeld residuals test[26] and graphical assessment of Kaplan-Meier curves in each trial.[27] To assess whether treatment effects differ across continuous kidney function, we presented change in HR per 10-mL/min CrCl decrease with statistical significance assessed by the treatment-by-CrCl interaction. Between-study heterogeneity of the treatment effect was assumed to differ by treatment comparison and quantified by the SD of random effects. All analyses were conducted with the coxme (version 2.2) and survival (version 3.3) packages in R version 4.2.0 (The R Foundation).[28]

RESULTS

Baseline Characteristics

Baseline characteristics of 71 683 patients by CrCl category and overall are presented in Table 1. Lower-CrCl groups tended to include patients of older age, female sex, lower body weight, and previous diagnoses of heart failure, coronary artery disease, and bleeding. Patients in lower-CrCl groups also tended to have higher CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥ 75 [doubled], diabetes, stroke [doubled], vascular disease, age 65 to 74 and sex category [female]) scores, be more likely to use antiplatelet agents, and have permanent or persistent AF versus paroxysmal AF. Median follow-up time was 23.1 months across all trials. Table S1 provides a brief list of patient demographics and median follow-up in individual trials.

Overall Event Incidence by CrCl

Among all patients in the pooled data set (n=71 683), the incidence of major bleeding, ICH, S/SE, and death significantly increased with decreasing kidney function (Figure 1; Table S2).

Hazard of Major Bleeding Events by Continuous CrCl

Across the spectrum of continuous kidney function, patients randomized to standard-dose DOACs compared with those randomized to warfarin had numerically lower hazards of bleeding at all CrCl values, although this was not statistically significant. There was no significant treatment-by-CrCl interaction for the hazard of major bleeding for standard-dose DOACs versus warfarin (Figure 2; Table 2).

Hazard of ICH by CrCl

Patients randomized to standard-dose DOACs had a significantly lower hazard of ICH compared with patients randomized to warfarin at any CrCl <122 mL/min, with a trend toward a positive treatment-by-CrCl interaction such that patients tended to derive a greater relative benefit from standard-dose DOACs versus warfarin as kidney function worsened (HR decreases by 6.2% [0.7%–12.6%] for every 10-mL/min decrease in CrCl; *P*=0.08; Figure 2; Table 2).

Hazard of S/SE by CrCl

Patients randomized to standard-dose DOACs had a significantly lower hazard of S/SE than those randomized to warfarin at any CrCl <87 mL/min. A significant treatment-by-CrCl interaction was noted for the hazard of S/SE with standard-dose DOACs compared with warfarin such that patients derived a greater benefit from standard-dose DOACs with decreasing kidney function (HR decreases by 4.8% [1.3%–8.1%] for every 10-mL/min decrease in CrCl; *P*=0.01; Figure 2; Table 2).

Mortality Hazards by CrCl

The hazard of death was significantly lower for patients randomized to standard-dose DOACs compared with those randomized to warfarin at any CrCl <77 mL/min, with a trend toward increasing benefit from standard-dose DOAC as kidney function decreased (HR decreases by 2.1% [−0.3% to 4.4%] for every 10-mL/min decrease in CrCl; *P*=0.08; Figure 2; Table 2).

Hazard of Composite End Points by CrCl

Patients randomized to standard-dose DOACs compared with those randomized to warfarin had a significantly

Table 1. Baseline Demographics by CrCl Category

	CrCl category, mL/min					Overall (n=71 683)
	<30 (n=510)	30–44 (n=8409)	45–59 (n=15 477)	60–89 (n=28 891)	≥90 (n=18 277)	
Female, n (%)	335 (65.7)	4721 (56.1)	7118 (46.0)	10 068 (34.8)	4425 (24.2)	26 715 (37.3)
Age, y	80.2 (6.8)	78.5 (6.6)	75.3 (6.8)	70.6 (7.7)	62.6 (8.7)	70.6 (9.4)
CrCl, mL/min	26.6 (3.0)	38.7 (4.1)	52.7 (4.3)	73.5 (8.5)	116.1 (26.7)	75.5 (30.5)
BMI, kg/m^2	23.6 (4.4)	25.2 (4.4)	26.7 (4.4)	28.9 (4.7)	33.6 (6.4)	29.2 (5.9)
Weight, kg	59.9 (13.3)	66.3 (13.3)	72.9 (13.6)	82.5 (14.7)	101.5 (20.3)	83.2 (20.0)
Smoking, n (%)	190 (37.3)	2984 (35.5)	6104 (39.4)	12 659 (43.8)	9283 (50.8)	31 265 (43.6)
Diabetes, n (%)	129 (25.3)	2118 (25.2)	4212 (27.2)	8607 (29.8)	6996 (38.3)	22 087 (30.8)
Stroke, n (%)	129 (25.3)	2517 (29.9)	4737 (30.6)	8376 (29.0)	4361 (23.9)	20 147 (28.1)
Previous VKA use, n (%)	310 (60.8)	5433 (64.6)	10 328 (66.7)	19 698 (68.2)	13 056 (71.4)	48 892 (68.2)
Antiplatelet use, n (%)	196 (38.4)	3168 (37.7)	5711 (36.9)	10 142 (35.1)	6213 (34.0)	25 464 (35.5)
CHA_2DS_2-VASc score	4.9 (1.4)	4.8 (1.4)	4.5 (1.4)	3.9 (1.5)	3.2 (1.4)	4.0 (1.5)
AF type, n (%)						
Paroxysmal	89 (17.5)	1880 (22.4)	3574 (23.1)	6870 (23.8)	4174 (22.8)	16 609 (23.2)
Persistent/permanent	421 (82.5)	6526 (77.6)	11 903 (76.9)	22 015 (76.2)	14 098 (77.1)	55 059 (76.8)
Coronary disease, n (%)	201 (39.4)	2753 (32.7)	5037 (32.5)	9137 (31.6)	5513 (30.2)	22 674 (31.6)
Hypertension, n (%)	444 (87.1)	7285 (86.6)	13 465 (87.0)	25 191 (87.2)	16 380 (89.6)	62 863 (87.7)
Heart failure, n (%)	271 (53.1)	4107 (48.8)	6884 (44.5)	12 750 (44.1)	9231 (50.5)	33 276 (46.4)
Previous GIB, n (%)	23 (4.5)	320 (3.8)	506 (3.3)	750 (2.6)	429 (2.3)	2030 (2.8)
Previous non-GIB, n (%)	55 (10.8)	500 (5.9)	861 (5.6)	1517 (5.3)	1049 (5.7)	3989 (5.6)

CrCl calculated at baseline with the Cockcroft-Gault formula. Frequencies are shown as number (percentage); continuous variables are shown as mean (SD) except for CHA_2DS_2-VASc score, which is shown as mean (SD).

AF indicates atrial fibrillation; BMI, body mass index; CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥ 75 (doubled), diabetes, stroke (doubled), vascular disease, age 65 to 74 and sex category (female); CrCl, creatinine clearance; GIB, gastrointestinal bleed; and VKA, vitamin K antagonist.

lower hazard of composite of bleeding or death when CrCl was between 42 and 109 mL/min and a significantly lower hazard of a composite of bleeding, death, or S/SE when CrCl was between 30 and 96 mL/min. However, there was no significant interaction by CrCl for the hazard of either composite for patients randomized to standard-dose DOACs compared with those randomized to warfarin (Table 2).

Hazard of Events by Continuous CrCl in Patients Randomized to Lower-Dose DOAC Compared With Those Randomized to Warfarin or Standard-Dose DOAC

Patients randomized to lower-dose DOACs compared with those randomized to warfarin had a significantly lower hazard of bleeding across all CrCl values >35 mL/min and a lower risk of death for CrCl values >56 mL/min. Similarly, a lower hazard of ICH was seen with lower-dose DOACs compared with warfarin for all CrCl values without any significant interaction-by-CrCl effect. There was no CrCl value for which lower-dose DOACs had a significantly different hazard of S/SE (Table 2; Figure S1).

Patients randomized to lower-dose DOACs compared with those randomized to standard-dose DOACs had a lower hazard of bleeding with CrCl values between 77 and 140 mL/min and a lower hazard of ICH with CrCl between 47 and 106 mL/min. However, these patients had a significantly higher hazard of death for CrCl values between 30 and 42 mL/min and of S/SE with CrCl values of 30 to 98 mL/min. No significant treatment-by-CrCl effect was observed for the hazard of bleeding, ICH, or S/SE for patients randomized to lower-dose DOAC compared with those randomized to either warfarin or standard-dose DOACs. Patients randomized to lower-dose DOACs also had a significant increase in the hazard of death with worsening kidney function compared with those randomized to either warfarin (HR increases 3.5% [0.3%–6.9%] for every 10-mL/min decrease in CrCl; P=0.03) or standard-dose DOACs (HR increases 5.8% [2.4%–9.2%] for every 10-mL/min decrease in CrCl; P=0.001; Table 2; Figure S1).

HR of Events by Categorical CrCl

Similar results were found when hazards of major bleeding, ICH, S/SE, and death were assessed through Cox modeling across CrCl categories (Table S3). For

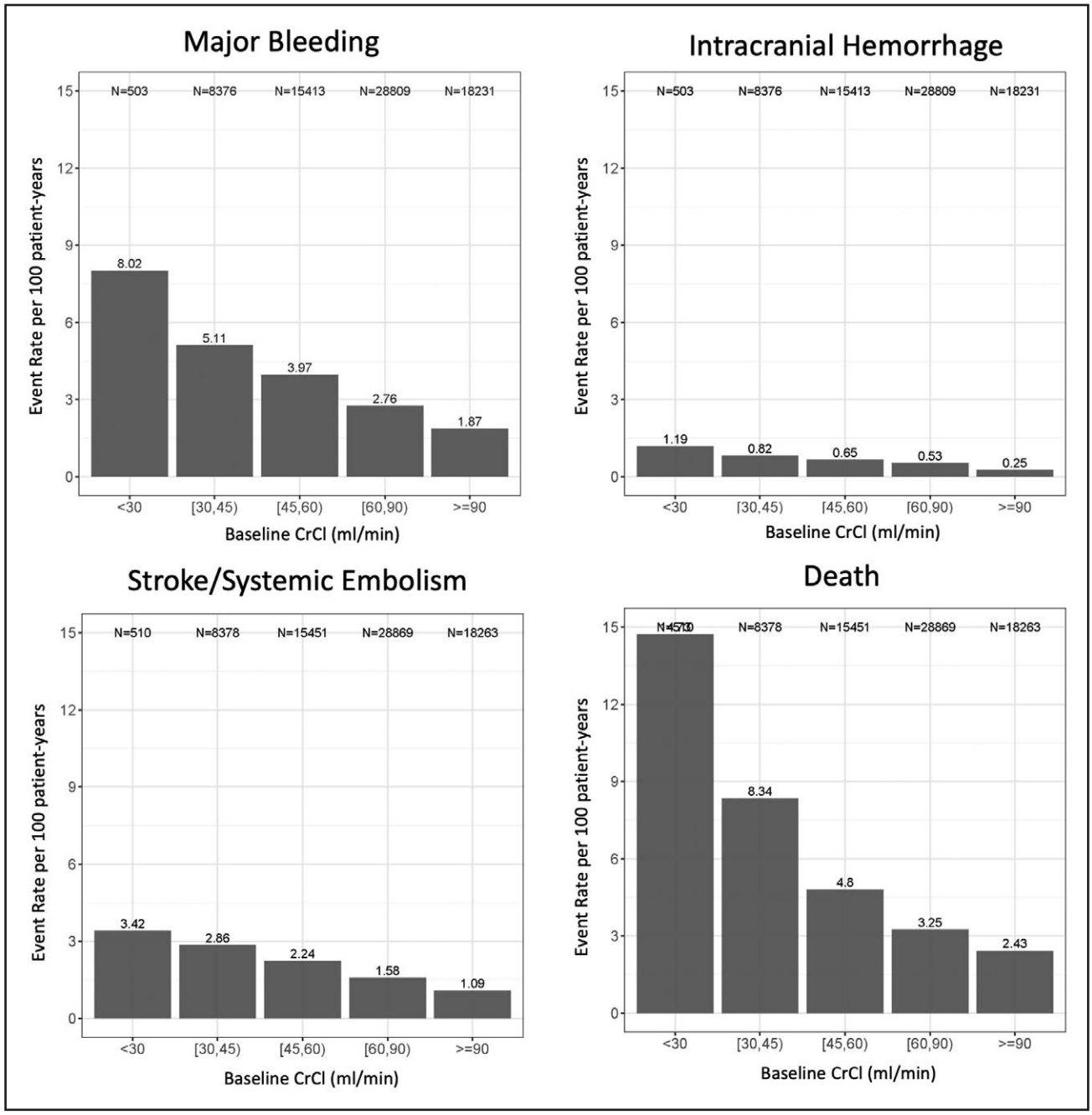

Figure 1. Raw event by category.
Shown per 100 person-years. **A**, Major bleeding. **B**, Intracranial hemorrhage. **C**, Stroke. **D**, Mortality. CrCl indicates creatinine clearance.

patients randomized to standard-dose DOACs compared with those randomized to warfarin, the hazards of major bleeding, ICH, S/SE, and death were numerically lower for each CrCl category <90 mL/min. This was statistically significant for CrCl values between 30 and 89 mL/min for ICH and S/SE and between 30 and 59 mL/min for death. In Cox regression models, little or no between-study heterogeneity was observed for all outcomes, with an SD of random effects close to 0 (Table S4).

DISCUSSION

In this network meta-analysis of 71 683 patients randomized in the pivotal trials of anticoagulation in AF, we found that the benefits of DOACs over warfarin are retained in patients with reduced kidney function. In a Cox model analysis, patients with reduced CrCl randomized to standard-dose DOACs compared with those randomized to warfarin had lower hazards of ICH, S/SE, and death, with no difference in bleeding down to a CrCl of at least 25

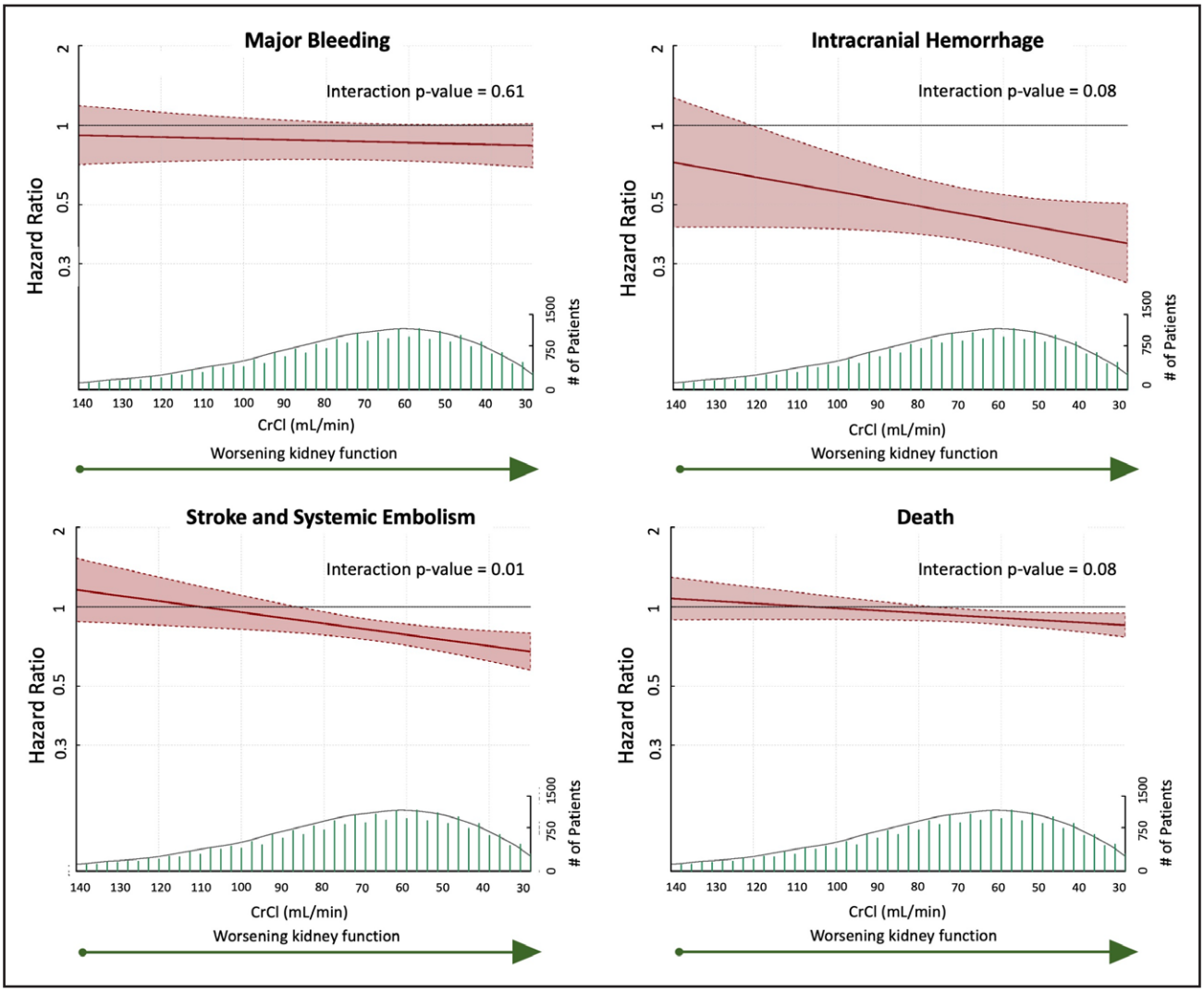

Figure 2. HRs for standard-dose DOACs vs warfarin across CrCl.
Hazard ratio (HR) and 95% CI from Cox models shown in red (**left**, *y* axis), with population at each creatinine clearance (CrCl) value shown in green directly below (**right**, *y* axis). Cox models assume linear associations between CrCl and each outcome. HR>1 favors warfarin; HR<1 favors standard-dose direct oral anticoagulant (DOAC). $P_{interaction}$ value represents significance of the treatment-by-CrCl effect.

mL/min. Furthermore, patients with low CrCl randomized to standard-dose DOACs compared with those randomized to lower-dose DOACs had a significantly lower hazard of S/SE and death without a significantly increased hazard of bleeding or ICH. There was no CrCl value for which standard-dose DOAC use resulted in a higher risk of bleeding, ICH, S/SE, or death than warfarin.

There was a significant treatment-by-CrCl interaction such that there was a greater relative reduction in risk of S/SE with standard-dose DOACs compared with warfarin, with nonsignificant trends toward greater benefit with standard-dose DOACs over warfarin seen for reduction in risk of ICH and death with worsening kidney function. More important than any CrCl cutoff, these findings suggest that beyond DOACs being as safe and effective as warfarin in patients with diminished kidney function, the benefits of DOACs over warfarin are actually amplified as kidney function worsens, with increasing efficacy and a trend toward greater safety.

Despite concerns about safety with the use of drugs that are in part eliminated renally, these results are reassuring, and show that the safety of DOACs is preserved and their efficacy is even greater in patients with impaired kidney function, down to a CrCl of at least 25 mL/min. We did not appreciate significant heterogeneity between trials despite the varying renal clearance of different DOACs. These results suggest that DOACs are safer and more effective than warfarin at lower CrCl and that the benefits of DOACs over warfarin may in fact be amplified in patients with poor kidney function. Our findings are consistent with previous subanalyses from individual trials that have demonstrated preserved safety and efficacy of dabigatran,[1] apixaban,[2] edoxaban,[3] and

Table 2. Treatment-by-CrCl Interaction for HR of Event by Study Drug Randomization

Interaction by treatment with CrCl		$P_{interaction}$ value
Major bleeding		
SD DOAC vs warfarin	Decrease 0.7% (−2.1%, 3.4%)	0.61
LD DOAC vs warfarin	Increase 2.6% (−1.7%, 7.1%)	0.24
LD DOAC vs SD DOAC	Increase 3.4% (−1.0%, 8.0%)	0.14
ICH		
SD DOAC vs warfarin	Decrease 6.2% (−0.7%, 12.6%)	0.08
LD DOAC vs warfarin	Decrease 3.4% (−9.0%, 14.3%)	0.57
LD DOAC vs SD DOAC	Increase 3.0% (−9.2%, 16.9%)	0.65
S/SE		
SD DOAC vs warfarin	Decrease 4.8% (1.3%, 8.1%)	0.01
LD DOAC vs warfarin	Decrease 2.1% (−2.3%, 6.2%)	0.34
LD DOAC vs SD DOAC	Increase 2.8% (−1.6%, 7.4%)	0.21
Death		
SD DOAC vs warfarin	Decrease 2.1% (−0.3%, 4.4%)	0.08
LD DOAC vs warfarin	Increase 3.5% (0.3%, 6.9%)	0.03
LD DOAC vs SD DOAC	Increase 5.8% (2.4%, 9.2%)	0.001
Composite of major bleeding and death		
SD DOAC vs warfarin	Increase 0.3% (−1.9%, 2.6%)	0.78
LD DOAC vs warfarin	Increase 3.4% (0.0%, 6.9%)	0.05
LD DOAC vs SD DOAC	Increase 3.1% (−0.3%, 6.6%)	0.08
Composite of major bleeding, S/SE, and death		
SD DOAC vs warfarin	Decrease 0.9% (−1.1%, 2.9%)	0.36
LD DOAC vs warfarin	Increase 1.7% (−1.2%, 4.7%)	0.24
LD DOAC vs SD DOAC	Increase 2.7% (−0.3%, 5.7%)	0.07

HR change rate shown for every 10-mL/min decrease in CrCl with 95% CIs.

CrCl indicates creatinine clearance; DOAC, direct oral anticoagulant; HR, hazard ratio; ICH, intracranial hemorrhage; LD, lower dose; SD, standard dose; and S/SE, stroke and systemic embolism.

rivaroxaban.[4] These findings are of particular importance given the observed increased risk of S/SE, bleeding, ICH, and death with decreased kidney function, which we noted in our results, and has been reported previously as well, including estimates that the risk of S/SE increases by 7% with every 10-mL/min decrease in CrCl.[1–6] Because patients with reduced kidney function are at higher risk for complications related to both AF and anticoagulation, the safety and efficacy benefits seen with DOACs compared with warfarin are even more important.

These results also suggest that it is inappropriate, and even dangerous, to reduce DOAC dose with kidney dysfunction unless the patient meets prespecified criteria for dose reduction; doing so may result in a higher incidence of stroke and death without providing any safety benefit in terms of bleeding or ICH. Patients in RE-LY and ENGAGE AF-TIMI 48 were randomized to standard-dose DOACs, lower-dose DOACs, or warfarin. This is different from the criteria for dose adjustment used in ARISTOTLE, ROCKET, and ENGAGE AF-TIMI 48, which was not random, and was instead based on patient criteria, including age, body weight, and creatinine. Our analysis stratified patients on the basis of their randomized DOAC dosing strategy (standard versus low), not trial-specific dose adjustments made for kidney clearance or other nonrandomized patient factors. Our findings show that at reduced levels of kidney function (lower than ≈45 mL/min), patients randomized to lower-dose DOACs had significantly higher hazards of both death and S/SE, with no significant difference in risk of bleeding or ICH compared with those randomized to standard-dose DOACs. Furthermore, we find that there was a significant interaction of kidney function on the hazard of death for patients randomized to lower-dose DOACs compared with those randomized to warfarin and standard-dose DOACs such that lower-dose DOACs actually became more dangerous (ie, were associated with a significantly higher hazard of death) with decreasing kidney function.

These findings are consistent with a previous, smaller secondary analysis of patients with 0 versus 1 dose reduction criterion in ARISTOTLE, all of whom received

either warfarin or standard-dose apixaban without any dose reduction (because they met 1 but not 2 criteria for dose reduction).[29] Importantly, the authors found no difference in the HR for patients with 0 versus 1 dose reduction criterion for any outcome, nor did they find a significant difference based on type of dose reduction criteria (weight, age, or kidney function). Taken together with our findings, these results strongly suggest that there is no role for dose reduction in patients who do not meet criteria, and that standard-dose DOACs maintain a safety profile comparable to that of lower-dose DOACs while simultaneously preventing more strokes and deaths. This is of critical importance because patients with kidney dysfunction who do not meet criteria for dose reduction of their DOACs are frequently underdosed in an attempt to reduce the risk of bleeding or other complications from anticoagulation.

Limitations and Strengths

There are limitations to our work. Our analyses were conducted with baseline CrCl, and we did not account for changes in CrCl over time. Because of natural variation in CrCl, patients with baseline CrCl as low as 11 mL/min were included in our analysis, although patients were eligible for inclusion in the individual AF DOAC trials only down to a CrCl of 25 mL/min (in the case of ROCKET AF and RE-LY) to 30 mL/min (ENGAGE AF TIMI-48, and ARISTOTLE). Therefore, there were relatively few events at the lowest values (<25 mL/min) of CrCl. However, this analysis still represents the largest examination of anticoagulation across kidney function in patients with AF randomized to DOACs versus warfarin. Furthermore, our analysis shows linear trends toward greater, not diminishing, benefit with decreasing kidney function. CrCl is by nature an estimated measure of kidney function. There is also variation between DOACs in degree of kidney clearance. Despite this, little heterogeneity was seen between trials for HRs or interaction-by-CrCl treatment effects.

Strengths of these analyses include that they were performed on the largest and highest-quality set of randomized data available for AF anticoagulation and were performed with the use of individual patient data in a patient-level meta-analysis. Furthermore, these analyses were conducted with kidney function as a continuous variable rather than being limited to categorical analyses.

CONCLUSIONS

We found that standard dosing strategies with DOACs are safer and more effective than warfarin in patients with kidney dysfunction down to a CrCl of at least 25 mL/min, with additional evidence that patients derive a greater relative benefit from standard-dose DOACs over both warfarin and lower-dose DOACs with decreasing kidney function. Furthermore, we found that for patients with the worst kidney function (down to a CrCl of 25 mL/min), use of lower-dose rather than standard-dose DOACs was associated with a higher risk of S/SE and death without any significant reduction in incidence of major bleeding or ICH. Taken together, these results support the use of DOACs over warfarin down to a CrCl of at least 25 mL/min and emphasize the importance of prescribing guideline-supported doses of DOACs in the prevention of S/SE.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S4

Figure S1

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