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Renal Outcomes in Anticoagulated Patients With Atrial Fibrillation

Xiaoxi Yao, PhD,[a,b] Navdeep Tangri, MD, PhD,[c] Bernard J. Gersh, MB, ChB, DPhil,[d] Lindsey R. Sangaralingham, MPH,[a] Nilay D. Shah, PhD,[a,b,e] Karl A. Nath, MB, ChB,[f] Peter A. Noseworthy, MD[a,d]

ABSTRACT

BACKGROUND Lifelong oral anticoagulation, either with warfarin or a non-vitamin K antagonist oral anticoagulant (NOAC), is indicated for stroke prevention in most patients with atrial fibrillation (AF). Emerging evidence suggests that NOACs may be associated with better renal outcomes than warfarin.

OBJECTIVES This study aimed to compare 4 oral anticoagulant agents (apixaban, dabigatran, rivaroxaban, and warfarin) for their effects on 4 renal outcomes: ≥30% decline in estimated glomerular filtration rate (eGFR), doubling of the serum creatinine level, acute kidney injury (AKI), and kidney failure.

METHODS Using a large U.S. administrative database linked to laboratory results, the authors identified 9,769 patients with nonvalvular AF who started taking an oral anticoagulant agent between October 1, 2010 and April 30, 2016. Inverse probability of treatment weighting was used to balance more than 60 baseline characteristics among patients in the 4 drug cohorts. Cox proportional hazards regression was performed in the weighted population to compare oral anticoagulant agents.

RESULTS The cumulative risk at the end of 2 years for each outcome was 24.4%, 4.0%, 14.8%, and 1.7% for ≥30% decline in eGFR, doubling of serum creatinine, AKI, and kidney failure, respectively. When the 3 NOACs were pooled, they were associated with reduced risks of ≥30% decline in eGFR (hazard ratio [HR]: 0.77; 95% confidence interval [CI]: 0.66 to 0.89; $p < 0.001$), doubling of serum creatinine (HR: 0.62; 95% CI: 0.40 to 0.95; $p = 0.03$), and AKI (HR: 0.68; 95% CI: 0.58 to 0.81; $p < 0.001$) compared with warfarin. When comparing each NOAC with warfarin, dabigatran was associated with lower risks of ≥30% decline in eGFR and AKI; rivaroxaban was associated with lower risks of ≥30% decline in eGFR, doubling of serum creatinine, and AKI; however, apixaban did not have a statistically significant relationship with any of the renal outcomes.

CONCLUSIONS Renal function decline is common among patients with AF treated with oral anticoagulant agents. NOACs, particularly dabigatran and rivaroxaban, may be associated with lower risks of adverse renal outcomes than warfarin. (J Am Coll Cardiol 2017;70:2621–32) © 2017 by the American College of Cardiology Foundation.

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From the [a]Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery, Mayo Clinic, Rochester, Minnesota; [b]Division of Health Care Policy and Research, Department of Health Sciences Research, Mayo Clinic, Rochester, Minnesota; [c]Department of Medicine, Chronic Disease Innovation Center and University of Manitoba, Winnipeg, Manitoba, Canada; [d]Department of Cardiovascular Medicine, Mayo Clinic, Rochester, Minnesota; [e]OptumLabs, Cambridge, Massachusetts; and the [f]Division of Nephrology and Hypertension, Department of Internal Medicine, Mayo Clinic, Rochester, Minnesota. This study was funded by the Mayo Clinic Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery, which receives no industry funding. Dr. Gersh serves on the data and safety monitoring board for Janssen Research & Development, Mount Sinai St. Luke's, Boston Scientific, Teva, St. Jude Medical, Thrombosis Research Institute, Duke Clinical Research Institute, Kowa Research Institute, and Cardiovascular Research Foundation; and provides general consulting for Janssen Scientific Affairs (formerly known as Ortho-McNeil), Xenon Pharmaceuticals, and Sirtex Medical. Dr. Tangri has received a research grant from AstraZeneca; and has received honoraria from Otsuka. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

AKI = acute kidney injury

CKD = chronic kidney disease

eGFR = estimated glomerular filtration rate

HR = hazard ratio

INR = international normalized ratio

IPTW = inverse probability of treatment weighting

NOAC = non-vitamin K antagonist oral anticoagulant

For more than 5 decades, vitamin K antagonists, chiefly warfarin, were the only options for long-term oral anticoagulation in patients with atrial fibrillation (AF). Some warfarin-treated patients experience an accelerated progression of chronic kidney disease (CKD) and acute kidney injury (AKI) associated with excessive anticoagulation, so called warfarin-related nephropathy (1,2). Since 2010, 4 non-vitamin K antagonist oral anticoagulants (NOACs) have been approved and are now recommended in preference to warfarin for most patients with AF (3). Although the effects of NOACs on stroke and bleeding outcomes were extensively studied in randomized controlled trials and observational studies (4–8), their impact on renal function has been largely neglected.

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Emerging data suggest that NOACs may be associated with better preservation of renal function than warfarin. Recent post hoc analyses of the RE-LY (Randomized Evaluation of Long Term Anticoagulation Therapy) and 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) trials demonstrated a slower decline in estimated glomerular filtration rate (eGFR) among patients taking dabigatran or rivaroxaban in comparison with warfarin (9,10). This effect possibly reflects the differences in the pharmacological mechanisms of action. Warfarin inhibits the vitamin K–dependent protein matrix gamma-carboxyglutamic acid and thus may promote renovascular calcification and progressive nephropathy (11–13). In contrast, NOACs could be potentially protective because they inhibit factor Xa and thrombin, which have been demonstrated to be associated with vascular inflammation (14,15).

The nephroprotective effect of NOACs has remained largely speculative because no renal outcomes beyond eGFR decline were evaluated in the pivotal clinical trials, and some of the analyses were restricted to patients with long follow-up and could have underreported adverse renal outcomes as a result of early dropout (9,10). Only 1 observational study has compared dabigatran with warfarin for AKI, and it found a lower risk with dabigatran (16). As such, we aimed to compare 4 oral anticoagulant agents, including 3 NOACs (apixaban, dabigatran, and rivaroxaban) and warfarin, for 4 distinct and meaningful renal outcomes: ≥30% decline in eGFR, doubling of the serum creatinine level, AKI, and kidney failure.

METHODS

DATA SOURCE AND STUDY POPULATION. We conducted a retrospective cohort analysis using OptumLabs (Cambridge, Massachusetts) Data Warehouse, which contains privately insured and Medicare Advantage enrollees of all ages and races throughout the United States (17,18). We identified adult patients (≥18 years of age) with nonvalvular AF who started apixaban, dabigatran, rivaroxaban, or warfarin between October 1, 2010 and April 30, 2016. Patients were required to have at least 12 months of continuous enrollment in both medical and pharmacy insurance plans before treatment initiation (index date), defined as the baseline period. We limited our study to patients who had linked serum creatinine results at both baseline and follow-up. Patients with or without serum creatinine results documented in our data had similar sociodemographic and clinical characteristics (Online Table 1). We included only new users of oral anticoagulant agents and excluded warfarin-experienced patients, the so called new-user design (19), to minimize unmeasured confounding. We excluded patients with valvular AF (20), kidney failure, and other indications for NOAC use.

The Mayo Clinic Institutional Review Board exempted this study from approval. Informed consent was not required because the study used preexisting, de-identified data.

BASELINE CHARACTERISTICS. We abstracted patients' serum creatinine results at baseline (i.e., within 1 year before the initiation of oral anticoagulant agents), including the date of treatment initiation. We used the serum creatinine result closest to the index date as the baseline value. We then calculated eGFR using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (21). We used physician, facility, and pharmacy claims to identify comorbidities and concomitant medication use. We also used laboratory results to assess a few biomarkers that may be important risk factors of renal outcomes, such as serum calcium, serum albumin, hemoglobin, uric acid, and serum phosphate. We did not include these biomarkers in the propensity score model, but both the values and the proportion of missing values were well balanced after IPTW (Online Table 2).

FOLLOW-UP. The follow-up started from the day after treatment initiation until the end of treatment, which was defined as the earliest date of the

following: discontinuation or switch of index medication, end of enrollment in health insurance plans, and end of the study period (i.e., April 30, 2016). A gap of maximum 30 days between treatment episodes was allowed (i.e., patients were considered to be receiving treatment as long as they had a refill of the same medication within 30 days of the end of the last treatment episode). This method was justified and used in our previous studies (8,22).

RENAL OUTCOMES. We assessed 4 renal outcomes: ≥30% decline in eGFR, doubling of the serum creatinine level, AKI, and kidney failure. Doubling of serum creatinine level is an endpoint accepted by the Food and Drug Administration for clinical trials of kidney disease progression. Because both kidney failure and doubling of creatinine levels are late events in CKD, we included 2 additional endpoints, ≥30% decline in eGFR and AKI, that occur more commonly and at earlier stages of kidney diseases, thus requiring smaller sample sizes and shorter follow-up to detect a meaningful difference in renal function change. We chose ≥30% decline in eGFR because in December 2012 the National Kidney Foundation and the Food and Drug Administration cosponsored a scientific workshop to determine whether alternative GFR-based endpoints could be used in clinical trials and concluded that a 30% to 40% decline in eGFR over 2 to 3 years may be an acceptable surrogate endpoint (23).

The 30% decline in eGFR and doubling of serum creatinine were defined as changes from baseline at any time point during follow-up. Because these 2 endpoints relied entirely on laboratory data, when examining these 2 outcomes, we censored patients at their last laboratory measurement. AKI was defined as a hospitalization or emergency department visit with a diagnosis code of AKI at the primary or secondary position, an approach validated in previous studies (24). Kidney failure was defined as eGFR lower than 15 ml/min per 1.73 m^2, having kidney transplant, or undergoing long-term dialysis (25).

We did not assess the mean change in eGFR because the average decline in eGFR was small, and a small fluctuation of eGFR is very common and may not necessarily lead to a severe adverse outcome.

STATISTICAL METHODS. We used propensity score and inverse probability of treatment weighting (IPTW) to minimize confounding. Specifically, we estimated propensity scores and weights by using generalized boosted models on the basis of 10,000 regression trees for optimal balance among the treatment populations (26). The weights were derived to obtain estimates representing population average treatment effects. The underlying propensity models included the demographics, comorbidities, and baseline medication use shown in **Table 1 and** Online Table 2. We also included the date of treatment initiation as a continuous variable in the model (i.e., the number of days from October 1, 2010 to the treatment initiation date) to account for the fact that patients initiating treatment early in the study period may have a longer follow-up. We evaluated the balance among treatment groups by comparing standardized mean differences of baseline covariates between 2 groups. Because we studied 4 drugs, for each baseline characteristic, there were 6 pairs of comparisons and 6 standardized mean differences. A baseline characteristic was considered balanced if the maximum standardized mean difference was <20% (26). We also used the Kolmogorov-Smirnov statistic to assess the equality of distribution of continuous variables and considered a Kolmogorov-Smirnov statistic >0.10 as signifying imbalance (26).

We calculated the event rates, plotted Kaplan-Meier curves, and estimated the cumulative risks at 6, 12, 18, and 24 months. We used Cox proportional hazards regression to compare treatments in the weighted population. Because some patients had very low or high weights, when performing weighted analyses, we trimmed the weights at the 1st and 99th percentiles (i.e., weights below or above the thresholds were set to the thresholds) (27). The proportional hazard assumption was tested on the basis of Schoenfeld residuals (28), and it was valid for all outcomes.

OTHER SENSITIVITY ANALYSES. First, the main analysis included only the treatment in the regression models. In the sensitivity analysis, we adjusted for age, sex, race, baseline eGFR, prior AKI, prior bleeding, peripheral artery disease, and digoxin, which were either important risk factors for renal outcomes or for baseline characteristics that had a standard mean difference >10%.

Second, because physicians and patients may discontinue or switch treatments when there are signs of renal function decline before the occurrence of an event, we performed a sensitivity analysis that did not censor at the switch or discontinuation (i.e., an intent-to-treat approach).

Third, because the oral anticoagulant agents may have different risks of stroke and major bleeding, it is possible that the different risks of renal outcome partially reflect the differences in the risks of stroke or major bleeding. Therefore, we conducted a sensitivity analysis excluding 387 patients who had a stroke or major bleeding event during follow-up.

TABLE 1 Baseline Characteristics (N = 9,769)

	Before IPTW				After IPTW			
	Apixaban (N = 1,883)	Dabigatran (N = 1,216)	Rivaroxaban (N = 2,485)	Warfarin (N = 4,185)	Apixaban (N = 1,883)	Dabigatran (N = 1,216)	Rivaroxaban (N = 2,485)	Warfarin (N = 4,185)
Age, yrs	73.3 ± 10.1	69.0 ± 10.4	71.1 ± 10.3	74.3 ± 9.3	72.9 ± 19.1	72.1 ± 25.6	72.3 ± 18.3	73.2 ± 14.7
eGFR, ml/min per 1.73 m^2	66.2 ± 20.3	71.2 ± 18.7	70.9 ± 18.7	64.6 ± 20.3	67.6 ± 37.5	67.8 ± 49.0	69.0 ± 35.3	66.9 ± 29.7
CHA_2DS_2-VASc	4.1 ± 1.7	3.5 ± 1.7	3.7 ± 1.7	4.5 ± 1.7	4.0 ± 3.3	3.9 ± 4.4	3.9 ± 3.2	4.2 ± 2.5
HAS-BLED	2.5 ± 1.1	2.1 ± 1.1	2.3 ± 1.1	2.7 ± 1.1	2.4 ± 2.0	2.4 ± 2.7	2.4 ± 2.0	2.5 ± 1.6
Female	51.3	37.2	42.9	45.4	47.8	43.0	43.8	44.8
Non-Hispanic white	76.7	80.3	77.0	76.1	78.2	77.9	76.8	76.8
Medical history								
Heart failure	32.8	26.6	26.8	41.1	31.9	31.6	30.3	35.5
Hypertension	91.9	89.6	90.6	93.2	92.0	91.1	91.3	92.2
Hyperlipidemia	83.6	84.1	82.7	84.8	83.5	85.6	82.7	83.6
Diabetes mellitus	42.2	41.2	41.2	48.1	42.9	41.6	41.4	45.3
Thromboembolism*	15.3	14.1	12.0	20.1	14.5	17.2	14.1	17.2
Major bleeding	9.5	8.3	8.4	12.0	9.2	7.5	8.8	10.6
Myocardial infarction	12.2	10.6	12.4	17.1	12.4	12.1	13.4	15.0
Peripheral artery disease	8.4	5.4	6.6	11.0	9.2	6.3	7.1	9.2
Liver disease	5.1	4.4	4.6	5.6	4.6	4.9	4.5	5.3
Anemia	21.6	16.9	19.2	24.8	20.5	20.9	20.9	21.9
Proteinuria	7.2	6.5	6.1	8.1	7.4	6.2	6.7	7.6
Tubulointerstitial kidney diseases	3.0	2.8	2.3	3.2	3.2	2.7	2.5	3.1
AKI	13.3	7.0	8.8	17.0	12.5	10.5	10.8	13.4
Alcoholism	2.8	2.3	2.1	2.4	2.7	2.2	2.2	2.5
Obesity	30.5	30.9	31.4	26.9	31.7	28.7	30.6	28.6
Smoking	30.0	25.2	29.0	28.5	28.0	26.9	29.6	29.2
COPD	10.9	8.1	10.9	14.4	11.1	10.9	11.9	12.6
Falls	6.6	3.4	5.6	7.0	5.6	4.6	6.2	6.4
Depression	13.2	10.3	11.2	13.5	12.8	12.4	11.6	13.1
Other valvular heart disease (not qualifying as exclusion criteria)	43.5	38.0	39.0	43.1	41.7	39.4	41.0	41.8
Obstructive sleep apnea	16.8	20.2	16.7	14.6	16.6	16.8	15.6	15.1
Dementia	5.7	3.7	4.5	6.2	6.4	5.2	5.2	5.3
Cancer	20.4	20.5	19.6	21.4	19.6	20.3	20.3	20.6
Hypothyroidism	25.9	25.5	24.3	27.3	24.4	26.1	25.3	26.7
Thyrotoxicosis	2.8	3.8	2.5	2.6	3.0	2.8	2.4	2.5
Cardioversion	11.0	13.6	11.3	7.1	11.0	11.2	10.7	8.6
Ablation	1.4	3.2	1.8	1.1	1.4	1.5	1.7	1.3
Pacemaker/ICD	14.6	11.2	11.2	15.3	14.1	11.7	11.8	14.2

Values are mean ± SD or %. *Thromboembolism includes ischemic stroke, systemic embolism, and transient ischemic attack.

AKI = acute kidney injury; CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥75 years, age 65 to 74 years, stroke or transient ischemic attack or thromboembolism, vascular disease, diabetes, sex category (female); COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; HAS-BLED = hypertension, abnormal kidney and liver function, stroke, bleeding, labile international normalized ratio, elderly, drugs or alcohol; ICD = implantable cardioverter-defibrillator.

Fifth, we performed a sensitivity analysis by international normalized ratio (INR) of warfarin-treated patients. We divided these patients into 3 groups on the basis of their average INR (<2, 2 to 3, and >3) and compared patients in each group to patients taking NOACs. We used the mean INR instead of calculating time in therapeutic range because we wanted to identify patients who were overly anticoagulated, not just patients who had suboptimal warfarin control who could be either excessively or inadequately anticoagulated. This is because warfarin-related nephropathy occurs after an acute increase in INR (1,2). We also calculated the percentage of INR values below or above the therapeutic range and found that they were highly correlated with the mean INR.

Sixth, we used 2 pre-specified falsification endpoints, hospitalization related to pneumonia and fracture, to test for residual confounding (29,30). They are outcomes unlikely to differ as a result of using NOACs or warfarin, but they could be related to unmeasured health status, lifestyle factors, socioeconomic status, and other factors.

We conducted a number of other sensitivity analyses including censoring at the end of 2 years,

TABLE 2 Summary Results of Sensitivity Analyses

	HR (95% CI)					
	Main Results	Adjust for Baseline Characteristics*	Intent-to-Treat†	Exclude Stroke or Bleeding Events‡	Censor at 2 Years§	Death as Competing Risk‖
30% decline in eGFR						
Apixaban	0.88 (0.70–1.10)	0.89 (0.71–1.11)	0.98 (0.81–1.18)	0.91 (0.73–1.14)	0.85 (0.68–1.07)	0.91 (0.70–1.20)
Dabigatran	0.72 (0.56–0.93)	0.78 (0.60–1.01)	0.76 (0.62–0.93)	0.74 (0.57–0.96)	0.73 (0.56–0.95)	0.64 (0.48–0.87)
Rivaroxaban	0.73 (0.62–0.87)	0.79 (0.67–0.94)	0.88 (0.77–1.01)	0.73 (0.62–0.88)	0.73 (0.61–0.86)	0.72 (0.59–0.87)
Warfarin	Reference	Reference	Reference	Reference	Reference	Reference
Doubling of creatinine						
Apixaban	0.80 (0.41–1.56)	0.86 (0.41–1.81)	0.99 (0.60–1.61)	0.85 (0.43–1.70)	0.64 (0.34–1.20)	1.12 (0.51–2.46)
Dabigatran	0.64 (0.30–1.34)	0.68 (0.33–1.41)	0.58 (0.34–0.98)	0.71 (0.34–1.49)	0.67 (0.31–1.43)	0.67 (0.28–1.62)
Rivaroxaban	0.46 (0.28–0.75)	0.50 (0.30–0.83)	0.69 (0.48–0.98)	0.43 (0.25–0.74)	0.46 (0.27–0.76)	0.51 (0.28–0.94)
Warfarin	Reference	Reference	Reference	Reference	Reference	Reference
AKI						
Apixaban	0.84 (0.66–1.07)	0.86 (0.69–1.08)	0.89 (0.73–1.08)	0.89 (0.69–1.15)	0.83 (0.65–1.05)	0.82 (0.61–1.11)
Dabigatran	0.55 (0.40–0.77)	0.64 (0.46–0.90)	0.63 (0.50–0.78)	0.58 (0.40–0.82)	0.54 (0.38–0.76)	0.68 (0.48–0.96)
Rivaroxaban	0.69 (0.57–0.84)	0.81 (0.66–0.99)	0.76 (0.66–0.89)	0.66 (0.53–0.82)	0.67 (0.55–0.82)	0.70 (0.56–0.88)
Warfarin	Reference	Reference	Reference	Reference	Reference	Reference
Kidney failure						
Apixaban	1.02 (0.45–2.31)	1.09 (0.47–2.54)	0.93 (0.51–1.70)	1.11 (0.49–2.53)	1.05 (0.46–2.36)	1.31 (0.53–3.24)
Dabigatran	0.45 (0.13–1.59)	0.57 (0.17–1.92)	0.42 (0.18–0.97)	0.46 (0.12–1.80)	0.43 (0.11–1.68)	0.63 (0.18–2.27)
Rivaroxaban	0.63 (0.35–1.15)	0.82 (0.45–1.50)	0.68 (0.41–1.12)	0.66 (0.35–1.23)	0.65 (0.35–1.18)	0.66 (0.33–1.30)
Warfarin	Reference	Reference	Reference	Reference	Reference	Reference

*The sensitivity analysis adjusted for age, sex, race, baseline eGFR, prior AKI, heart failure, prior bleeding, peripheral artery disease, and digoxin in the final Cox proportional hazards regression models. They were either important risk factors for renal outcomes or baseline characteristics that had a standardized difference >10%. †The main analyses censored at the discontinuation or switch of the medications, whereas the intent-to-treat analyses censored at the end of enrollment in health insurance plans. ‡The sensitivity analysis excluded 387 patients who had a stroke or major bleeding during follow-up to examine whether the renal benefits were driven by the differences in efficacy or safety among drugs. §Because there were only 10% of patients remaining on treatment for more than 2 years, we performed a sensitivity analysis censoring at the end of 2 years. ‖We performed regression among 7,259 patients whose social security numbers were available so that we could link to the Social Security Death Master File. We considered death as a competing risk using the method of Fine and Gray.

CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 1.

using death as a competing risk, and comparing the drugs for mortality risk. We performed 7 subgroup analyses on the basis of age, sex, eGFR, diabetes at baseline, heart failure at baseline, CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years, age 65 to 74 years, stroke or transient ischemic attack or thromboembolism, vascular disease, diabetes, sex category [female]), and HAS-BLED (hypertension, abnormal kidney and liver function, stroke, bleeding, labile INR, elderly, drugs or alcohol) score. All analyses were conducted using SAS software version 9.4 (SAS Institute, Inc., Cary, North Carolina) and Stata version 14.1 (Stata Corp, College Station, Texas).

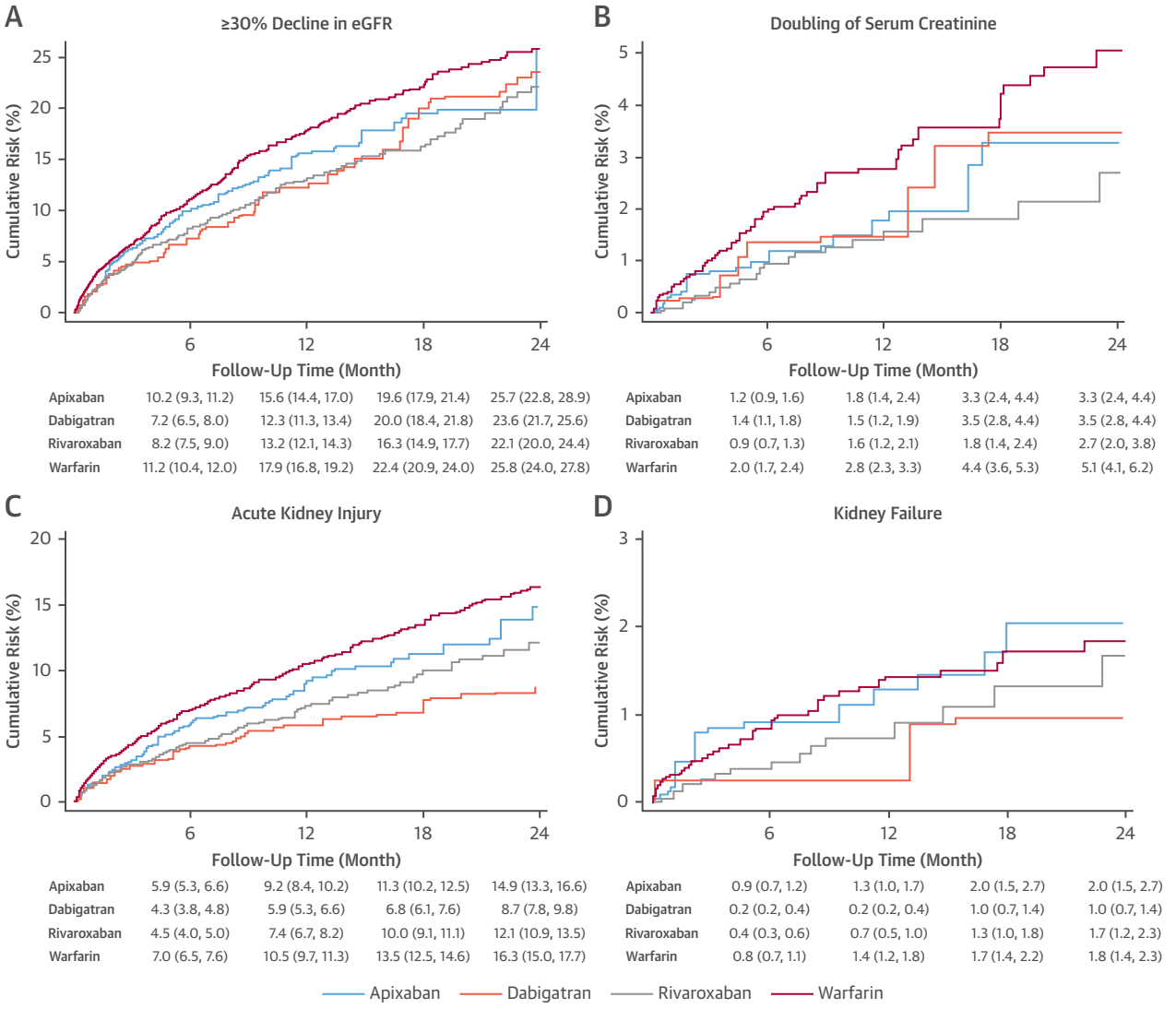
RESULTS

PATIENTS' CHARACTERISTICS. Our final cohort included 9,769 patients with an average on-treatment follow-up of 10.7 ± 9.9 months, during which an average of 2.5 ± 2.6 creatinine values were obtained. The follow-up time and the number of creatinine tests were largely similar among different drug cohorts after weighting (Online Table 3). The mean age was 72.6 ± 10.1 years. The mean eGFR at baseline was 67.3 ± 19.9 ml/min per 1.73 m^2.

All baseline characteristics were balanced after IPTW (**Table 1,** Online Table 2). The maximum standardized mean difference for most baseline characteristics was <10%. Age, baseline eGFR, heart failure, prior bleeding, peripheral artery disease, and digoxin use had a maximum standardized mean difference between 10.2% and 11.0% (Online Table 4). We conducted a sensitivity analysis including these characteristics in the final regression to address the small residual imbalance, and the results did not change (**Table 2**). All Kolmogorov-Smirnov statistics were <0.1, a finding suggesting no imbalance in the distribution of continuous variables.

RENAL OUTCOMES. The crude event rates per 100 person-years for each outcome were 17.03 (95% confidence interval [CI]: 15.65 to 18.55), 2.33 (95% CI: 1.85 to 2.99), 8.50 (95% CI: 7.74 to 9.35), and 0.97 (95% CI: 0.71 to 1.36) for ≥30% decline in eGFR, doubling of serum creatinine, AKI, and kidney failure, respectively. The cumulative risk at the end of 2 years was 24.4% (95% CI: 22.5% to 26.4%), 4.0% (95% CI: 3.1% to 5.0%),

FIGURE 1 Cumulative Incidence of Renal Outcomes



Apixaban	10.2 (9.3, 11.2)	15.6 (14.4, 17.0)	19.6 (17.9, 21.4)	25.7 (22.8, 28.9)
Dabigatran	7.2 (6.5, 8.0)	12.3 (11.3, 13.4)	20.0 (18.4, 21.8)	23.6 (21.7, 25.6)
Rivaroxaban	8.2 (7.5, 9.0)	13.2 (12.1, 14.3)	16.3 (14.9, 17.7)	22.1 (20.0, 24.4)
Warfarin	11.2 (10.4, 12.0)	17.9 (16.8, 19.2)	22.4 (20.9, 24.0)	25.8 (24.0, 27.8)

Apixaban	1.2 (0.9, 1.6)	1.8 (1.4, 2.4)	3.3 (2.4, 4.4)	3.3 (2.4, 4.4)
Dabigatran	1.4 (1.1, 1.8)	1.5 (1.2, 1.9)	3.5 (2.8, 4.4)	3.5 (2.8, 4.4)
Rivaroxaban	0.9 (0.7, 1.3)	1.6 (1.2, 2.1)	1.8 (1.4, 2.4)	2.7 (2.0, 3.8)
Warfarin	2.0 (1.7, 2.4)	2.8 (2.3, 3.3)	4.4 (3.6, 5.3)	5.1 (4.1, 6.2)

Apixaban	5.9 (5.3, 6.6)	9.2 (8.4, 10.2)	11.3 (10.2, 12.5)	14.9 (13.3, 16.6)
Dabigatran	4.3 (3.8, 4.8)	5.9 (5.3, 6.6)	6.8 (6.1, 7.6)	8.7 (7.8, 9.8)
Rivaroxaban	4.5 (4.0, 5.0)	7.4 (6.7, 8.2)	10.0 (9.1, 11.1)	12.1 (10.9, 13.5)
Warfarin	7.0 (6.5, 7.6)	10.5 (9.7, 11.3)	13.5 (12.5, 14.6)	16.3 (15.0, 17.7)

Apixaban	0.9 (0.7, 1.2)	1.3 (1.0, 1.7)	2.0 (1.5, 2.7)	2.0 (1.5, 2.7)
Dabigatran	0.2 (0.2, 0.4)	0.2 (0.2, 0.4)	1.0 (0.7, 1.4)	1.0 (0.7, 1.4)
Rivaroxaban	0.4 (0.3, 0.6)	0.7 (0.5, 1.0)	1.3 (1.0, 1.8)	1.7 (1.2, 2.3)
Warfarin	0.8 (0.7, 1.1)	1.4 (1.2, 1.8)	1.7 (1.4, 2.2)	1.8 (1.4, 2.3)

(A to D) Kaplan-Meier cumulative incidence (%) and 95% confidence interval at 6, 12, 18, and 24 months by using inverse probability treatment weights. Dabigatran was associated with lower risks of ≥30% decline in estimated glomerular filtration rate (eGFR) and acute kidney injury; rivaroxaban was associated with lower risks of ≥30% decline in eGFR, doubling of serum creatinine, and acute kidney injury.

14.8% (95% CI: 13.5% to 16.1%), and 1.7% (95% CI: 1.3% to 2.2%) for ≥30% decline in eGFR, doubling of serum creatinine, AKI, and kidney failure, respectively, in the unweighted population. The Kaplan-Meier curves and cumulative risks by drugs after using IPTW are presented in **Figures 1A to 1D**.

When the 3 NOACs were pooled, they were associated with reduced risks of ≥30% decline in eGFR (hazard ratio [HR]: 0.77; 95% CI: 0.66 to 0.89), doubling of serum creatinine (HR: 0.62; 95% CI: 0.40 to 0.95), and AKI (HR: 0.68; 95% CI: 0.58 to 0.81) compared with warfarin. When comparing each NOAC with warfarin, dabigatran was associated with lower risks of ≥30% decline in eGFR (HR: 0.72; 95% CI: 0.56 to 0.93) and AKI (HR: 0.55; 95% CI: 0.40 to 0.77). Rivaroxaban was associated with lower risks of ≥30% decline in eGFR (HR: 0.73; 95% CI: 0.62 to 0.87), doubling of serum creatinine (HR: 0.46; 95% CI: 0.28 to 0.75), and AKI (HR: 0.69; 95% CI: 0.57 to 0.84). Apixaban was associated with a nonsignificant numerically lower risk of ≥30% decline in eGFR, doubling of serum creatinine, and AKI (**Table 3**).

TABLE 3 Number of Events, Event Rates per 100 Person-Years, and Hazard Ratios With 95% CIs

	No. of Events	Crude Event Rate (95% CI)	Weighted Event Rate (95% CI)	Hazard Ratio (95% CI)	p Value for Hazard Ratio
30% decline in eGFR					
Apixaban	166	19.40 (16.66–22.59)	18.31 (14.97–22.60)	0.88 (0.70–1.10)	0.25
Dabigatran	103	10.94 (9.02–13.28)	14.29 (11.24–18.43)	0.72 (0.56–0.93)	0.01
Rivaroxaban	208	14.63 (12.77–16.75)	15.10 (13.06–17.53)	0.73 (0.62–0.87)	<0.001
Warfarin	546	22.61 (20.79–24.59)	20.64 (18.79–22.71)	Reference	Reference
Doubling of creatinine					
Apixaban	20	2.23 (1.44–3.45)	2.54 (1.39–5.14)	0.80 (0.41–1.56)	0.51
Dabigatran	12	1.23 (0.70–2.16)	2.05 (1.03–4.70)	0.64 (0.30–1.34)	0.24
Rivaroxaban	21	1.40 (0.91–2.15)	1.47 (0.96–2.38)	0.46 (0.28–0.75)	<0.01
Warfarin	89	3.43 (2.78–4.22)	3.26 (2.62–4.12)	Reference	Reference
AKI					
Apixaban	131	9.87 (8.32–11.72)	9.38 (7.56–11.77)	0.84 (0.66–1.07)	0.16
Dabigatran	63	4.86 (3.80–6.22)	5.93 (4.36–8.26)	0.55 (0.40–0.77)	<0.001
Rivaroxaban	145	6.87 (5.84–8.09)	7.63 (6.44–9.09)	0.69 (0.57–0.84)	<0.001
Warfarin	441	12.63 (11.51–13.87)	11.15 (10.05–12.39)	Reference	Reference
Kidney failure					
Apixaban	13	0.96 (0.56–1.65)	1.33 (0.61–3.50)	1.02 (0.45–2.31)	0.95
Dabigatran	4	0.30 (0.11–0.80)	0.55 (0.14–3.77)	0.45 (0.13–1.59)	0.21
Rivaroxaban	14	0.64 (0.38–1.09)	0.80 (0.48–1.47)	0.63 (0.35–1.15)	0.13
Warfarin	58	1.58 (1.22–2.04)	1.28 (0.98–1.69)	Reference	Reference

Abbreviations as in Tables 1 and 2.

SUBGROUP AND SENSITIVITY ANALYSES. Warfarin-treated patients whose average INR was >3 had much higher rates of eGFR decline of at least 30%, doubling of serum creatinine, and AKI. However, in comparison with warfarin-treated patients whose mean INR was <2 or 2 to 3, NOACs may still be associated with lower risks (**Table 4, Figure 2**).

There were, in general, no statistically significant interactions in most subgroup analyses (Online Figures 1 to 4). We conducted numerous sensitivity analyses, and the results support our main findings (**Table 2,** Online Tables 5 and 6).

TABLE 4 Sensitivity Analysis by Mean INR of Warfarin-Treated Patients, Hazard Ratio, and 95% CI Comparing a NOAC With Warfarin*

	HR (95% CI)		
	Subtherapeutic Warfarin Comparison by Mean INR <2, N = 6,301	Therapeutic Warfarin Comparison by Mean INR 2-3, N = 6,778	Supratherapeutic Warfarin Comparison by Mean INR >3, N = 5,888
30% decline in eGFR			
Apixaban	0.93 (0.67–1.29)	0.99 (0.76–1.29)	0.61† (0.41–0.92)
Dabigatran	0.82 (0.56–1.19)	0.84 (0.61–1.14)	0.53‡ (0.34–0.84)
Rivaroxaban	0.77 (0.58–1.04)	0.80 (0.64–1.01)	0.52§ (0.35–0.76)
Warfarin	Reference	Reference	Reference
Doubling of creatinine			
Apixaban	0.76 (0.32–1.79)	0.91 (0.42–1.96)	0.40 (0.15–1.08)
Dabigatran	0.73 (0.28–1.86)	0.76 (0.34–1.72)	0.38 (0.13–1.11)
Rivaroxaban	0.44† (0.21–0.93)	0.50† (0.27–0.93)	0.24‡ (0.10–0.59)
Warfarin	Reference	Reference	Reference
AKI			
Apixaban	0.98 (0.68–1.41)	0.91 (0.68–1.21)	0.81 (0.51–1.26)
Dabigatran	0.62† (0.39–0.99)	0.56‡ (0.38–0.82)	0.49‡ (0.29–0.84)
Rivaroxaban	0.83 (0.59–1.17)	0.74† (0.57–0.96)	0.65 (0.43–1.00)
Warfarin	Reference	Reference	Reference
Kidney failure			
Apixaban	1.48 (0.48–4.55)	0.85 (0.34–2.10)	1.47 (0.45–4.82)
Dabigatran	0.83 (0.18–3.77)	0.38 (0.10–1.40)	0.81 (0.18–3.72)
Rivaroxaban	0.87 (0.33–2.27)	0.46† (0.22–0.94)	0.86 (0.31–2.39)
Warfarin	Reference	Reference	Reference

*Inverse probability weights were recalculated in each of the 3 cohorts: 1) all NOAC-treated patients and warfarin-treated patients with mean INR <2; 2) all NOAC-treated patients and warfarin-treated patients with mean INR 2 to 3; and 3) all NOAC-treated patients and warfarin-treated patients with mean INR >3. †$p < 0.05$. ‡$p < 0.01$. §$p < 0.001$.

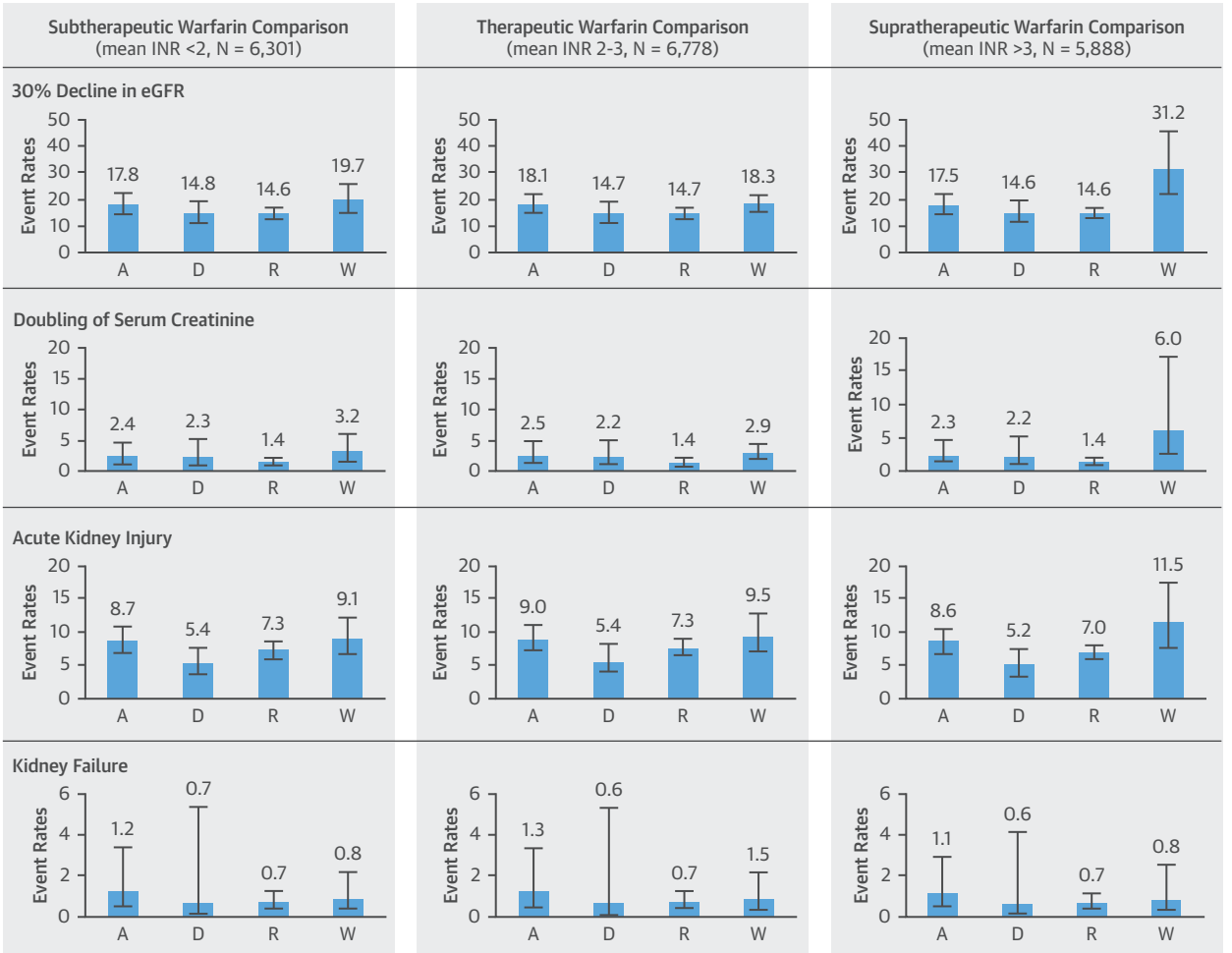
INR = international normalized ratio; NOAC = non-vitamin K antagonist anticoagulant; other abbreviations as in Tables 1 and 2.

DISCUSSION

Using a large, heterogeneous cohort of patients treated in routine clinical practice, we found that renal function decline is common among patients with AF treated with oral anticoagulant agents. Approximately 1 in 4 patients had at least a 30% decline in eGFR, and 1 in 7 had an episode of AKI within 2 years (**Central Illustration**). In comparison with warfarin, treatment with NOACs was related to lower risks of ≥30% decline in eGFR, doubling of serum creatinine, and AKI. The risk of kidney failure was also numerically lower in patients treated with NOACs compared with warfarin, but this was not statistically significant.

Our study has 3 important implications for practice. First, regardless of treatment with warfarin or

FIGURE 2 Sensitivity Analyses by Mean INR in Warfarin-Treated Patients, Event Rates per 100 Person-Years

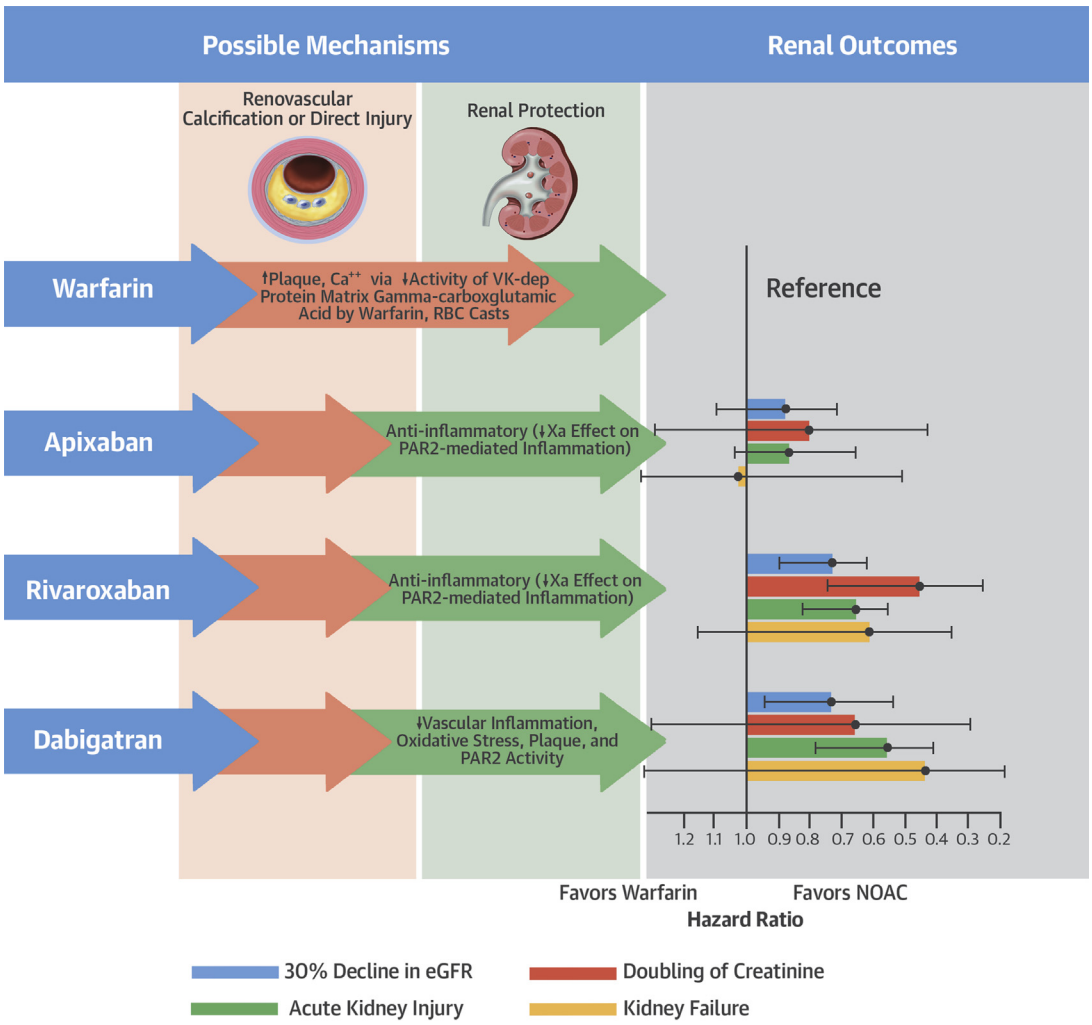


Risks of adverse renal outcomes were particularly high in warfarin-treated patients with supratherapeutic international normalized ratio (INR). Inverse probability weights were recalculated in each of the 3 cohorts: 1) all non-vitamin K antagonist oral anticoagulant (NOAC)-treated patients and warfarin-treated patients with mean INR <2; 2) all NOAC-treated patients and warfarin-treated patients with mean INR 2 to 3; and 3) all NOAC-treated patients and warfarin-treated patients with mean INR >3. A = apixaban; D = dabigatran; eGFR = estimated glomerular filtration rate; R = rivaroxaban; W = warfarin.

NOACs, renal function decline is very common. Maintaining adequate renal function is particularly important in patients with AF treated with oral anticoagulant agents because worsening renal function has been shown to increase the risks of both stroke and bleeding further (31,32). Moreover, adjusting therapies (e.g., reducing NOAC dose or switching therapies) may be needed if patients' renal function declines significantly. As such, our findings underscore the need for periodic monitoring of renal function and comprehensive efforts to prevent and treat progressive CKD.

Second, when choosing an oral anticoagulant agent, the impact of the drug on subsequent renal function may need to be considered. Despite guideline recommendations (3), currently warfarin is still used in more than one-half of anticoagulated patients (33). Our study on kidney outcomes provided another piece of evidence that will help clinicians and patients weigh the benefits and risks of NOACs versus warfarin. These data may shift the tipping point in many patients because some kidney outcomes (e.g., 30% decline in eGFR and AKI) are often more common than stroke and major bleeding. Regarding which NOAC to choose, unlike dabigatran and rivaroxaban, apixaban was not statistically significantly associated with lower risks of adverse renal outcomes. The lack of a significant relationship when

CENTRAL ILLUSTRATION **Renal Outcomes Associated With the Various Oral Anticoagulant Agents: Possible Mechanisms and Outcomes**



Yao, X. et al. J Am Coll Cardiol. 2017;70(21):2621–32.

NOACs, particularly dabigatran and rivaroxaban, were associated with lower risks of adverse renal outcomes than warfarin, possibly because of the differences in pharmacological mechanisms of action. Hazard ratios were calculated comparing each NOAC with warfarin by using inverse probability treatment weights. eGFR = estimated glomerular filtration rate; NOAC = non-vitamin K antagonist oral anticoagulant; PAR2 = protease-activated receptor 2; RBC = red blood cell; VK = vitamin K.

comparing apixaban with warfarin was consistent with the subanalysis of ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation), which showed a small but greater decline in eGFR with apixaban than with warfarin (31). However, this could also reflect a lack of statistical power in apixaban-treated patients, and the hazard ratios for apixaban were all lower than 1 except for kidney failure. Future studies are needed to examine whether the impact on renal function decline is a medication-specific effect. However, this finding does not suggest that dabigatran and rivaroxaban should be used in preference to apixaban. In our previous head-to-head comparison among the 3 NOACs, apixaban was related to a lower risk of major bleeding but a similar risk of stroke (22). Furthermore, in phase III trials, apixaban was the only drug demonstrating a statistically significant

reduction in all-cause mortality compared with warfarin, a finding consistent with our sensitivity analysis on mortality (Online Table 5).

Third, our findings by INR suggested that warfarin-treated patients with supratherapeutic INRs had a much higher risk of adverse renal outcomes, a finding that is consistent with previous studies reporting warfarin-related nephropathy in patients with INR >3 (1,2). The renal benefits of NOACs appeared to be more evident in comparison with these patients. In recent years, point-of-care testing has become increasingly used to monitor INR, which could potentially improve the outcome in warfarin-treated patients. However, as observed in our study, in most cases, NOACs may still be associated with a lower (or numerically lower) risk of renal outcomes when compared with warfarin-treated patients with subtherapeutic or therapeutic INRs. This observation suggests that differential renal outcomes are not attributable solely to poor INR control with warfarin and that off-target effects of these agents may be at play.

The strength of our study includes its large sample of nearly 10,000 patients with AF treated in diverse clinical practice settings who had linked insurance claims and laboratory results. Most administrative claims databases do not have the ability to link to laboratory data and thus are not able to assess the change in creatinine or eGFR (16). Registries or electronic health records have laboratory data, but they may not have a large number of NOAC-treated patients, and the patient populations are more selective (34,35). Furthermore, many registries and electronic health records do not have linkage to claims data and can measure only whether a drug is prescribed by physicians, but not whether a drug is filled and refilled by patients. This issue is problematic considering the notoriously poor adherence to oral anticoagulant agents (36). The availability of pharmacy claims in our database allowed us to assess drug exposure more accurately.

The richness of the data allowed us to examine multiple kidney outcomes. It was very important to assess multiple kidney outcomes in this hypothesis-generating study because the consistency of results across a variety of kidney outcomes supported the robustness of our findings. Although examining multiple outcomes could raise the concern of multiple testing, because of the large sample size, the statistically significant results would remain significant even if we corrected the significance level using the most conservative method (37).

STUDY LIMITATIONS. First, despite careful adjustment using IPTW, our study may still be subject to residual confounding. However, the treatment groups were balanced on more than 60 dimensions, and the test of falsification endpoints provided some reassurance that there is no substantial residual confounding. Furthermore, our findings are consistent with the subanalyses of RE-LY and ROCKET AF that found a slower eGFR decline with dabigatran and rivaroxaban than with warfarin (9,10), as well as with a recent study from a Taiwanese national database, which demonstrated a lower risk of AKI with dabigatran than with warfarin (16). The broadly similar findings across a variety of patient populations, time periods, and methodologies provide reassuring data and will motivate the inclusion of renal outcomes in future AF trials. However, it is important to be circumspect in the interpretation of these observational data, and we stress that unless rigorous, prospective clinical trials confirm these findings, the potential lower risk of renal outcomes with NOACs remains speculative.

Second, in our studies, the serum creatinine level is not tested at a pre-specified time interval for every patient; thus, inevitably, patients who had more frequent testing were those with worsening renal function. We examined the frequency of creatinine tests among treatment arms. Although warfarin-treated patients on average received more tests than NOAC-treated patients (2.66 vs. 2.40 tests), the difference was small. Furthermore, for the eGFR and serum creatinine endpoints, we censored at patients' last creatinine tests.

Third, the average on-treatment follow-up was short, only 10.7 ± 9.9 months. Such length and variability of on-treatment follow-up time are commonly seen in studies of oral anticoagulant agents that use real-world data, particularly in the United States. A number of recent NOAC studies using a variety of data sources reported a mean follow-up of 6 months or less (38–45). The short follow-up is mostly the result of the poor medication persistence in routine practice (36), rather than an intrinsic limitation of the data sources. In fact, our patients on average continuously enrolled in health insurance plans for 6.2 ± 3.8 years and had 10.2 ± 8.1 creatinine results. Thus, the short on-treatment time simply reflected the treatment pattern in practice and does not necessarily limit the generalizability of our results. We conducted sensitivity analyses using an "intent-to-treat" approach, which followed patients until the end of insurance enrollment, and the results remained largely the same (**Table 4**).

Last, given the small number of events, we were not able to detect a difference in kidney failure. Because our data are de-identified, we were not able to link it to the U.S. Renal Data System to confirm the

cases for end-stage renal disease, and it is not uncommon for patients to switch to Medicare fee-for-service insurance once they initiate renal replacement therapy. However, for these patients, we should still have captured their substantial decline in eGFR and eGFR <15 ml/min per 1.73 m^2 before they changed insurance.

CONCLUSIONS

Renal function decline is common among patients with AF treated with oral anticoagulant agents. This observation underscores the need for periodic monitoring and comprehensive efforts to prevent and treat progressive CKD. NOACs may be associated with lower risks of adverse renal outcomes than warfarin. When choosing which oral anticoagulant agents to use, the potential differential effect on subsequent renal function may need to be taken into consideration, but the potential renal benefit of NOACs will need to be confirmed in future clinical trials.

ADDRESS FOR CORRESPONDENCE: Dr. Xiaoxi Yao, Mayo Clinic, 200 First Street Southwest, Rochester, Minnesota 55905. E-mail: yao.xiaoxi@mayo.edu.

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Patients with AF face a greater risk of adverse renal outcomes when anticoagulated with warfarin than target-specific agents, particularly dabigatran and rivaroxaban, and warfarin-related nephropathy is more likely to occur in those with supratherapeutic anticoagulation.

TRANSLATIONAL OUTLOOK: Further studies are needed to confirm the mechanisms responsible for warfarin-related nephropathy and identify patients most likely to develop this complication of therapy.

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KEY WORDS acute kidney injury, apixaban, chronic kidney disease, dabigatran, kidney failure, rivaroxaban

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