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Oral Anticoagulation and Cardiovascular Outcomes in Patients With Atrial Fibrillation and End-Stage Renal Disease

Sean D. Pokorney, MD, MHS,[a,b] Eric Black-Maier, MD,[a] Anne S. Hellkamp, MS,[b] Daniel J. Friedman, MD,[c] Sreekanth Vemulapalli, MD,[b] Christopher B. Granger, MD,[b] Laine Thomas, PhD,[b] Eric D. Peterson, MD, MPH,[b] Jonathan P. Piccini, Sr, MD, MHS[a,b]

ABSTRACT

BACKGROUND Atrial fibrillation (AF) is common in patients with end-stage renal disease (ESRD). The impact of oral anticoagulation (OAC) in ESRD patients is uncertain.

OBJECTIVES The purpose of this study was to describe patterns of OAC use in ESRD patients with AF and their associations with cardiovascular outcomes.

METHODS Using Medicare fee-for-service 5% claims data from 2007 to 2013, we analyzed treatment and outcomes in a cohort of patients with ESRD and AF. Prescription drug benefit information was used to determine the timing of OAC therapy. Cox proportional hazards modeling was used to compare outcomes including death, all-cause stroke, ischemic stroke, hemorrhagic stroke, and bleeding hospitalizations in ESRD patients treated with or without OAC.

RESULTS The cohort included 8,410 patients with AF and ESRD. A total of 3,043 (36.2%) patients were treated with OAC at some time during the study period. Propensity scores used to match 1,519 patients with AF and ESRD on OAC with 3,018 ESRD patients without OAC. Treatment with OAC was not associated with hospitalization for stroke (hazard ratio [HR]: 1.00; 95% confidence interval [CI]: 0.23 to 1.35; $p = 0.97$) or death (HR: 1.02; 95% CI: 0.94 to 1.10; $p = 0.62$). OAC was associated with an increased risk of hospitalization for bleeding (HR: 1.26; 95% CI: 1.09 to 1.46; $p = 0.0017$) and intracranial hemorrhage (HR: 1.30; 95% CI: 1.07 to 1.59; $p = 0.0094$).

CONCLUSIONS OAC utilization was low in patients with AF and ESRD. We found no association between OAC use and reduced risk of stroke or death. OAC use was associated with increased risks of hospitalization for bleeding or intracranial hemorrhage. Alternative stroke prevention strategies are needed in patients with ESRD and AF.
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From the [a]Duke Center for Atrial Fibrillation, Duke University Medical Center, Durham, North Carolina; [b]Duke Clinical Research Institute, Durham, North Carolina; and the [c]Division of Electrophysiology, Yale School of Medicine, New Haven, Connecticut. This project was supported by grant number U19HS021092 from the Agency for Healthcare Research and Quality. The content is solely the responsibility of the authors and does not necessarily represent the official views of the Agency for Healthcare Research and Quality. Additional funding was provided by the Duke Clinical Research Institute. Dr. Pokorney has received research grants from Boston Scientific, Janssen Pharmaceuticals, Bristol-Myers Squibb, Pfizer, and Gilead; has received consulting and research support from Bristol-Myers Squibb, Pfizer, Medtronic, Boston Scientific, and Janssen Pharmaceuticals; has received research support from the Food and Drug Administration; and has received Speakers Bureau support from Zoll. Dr. Friedman has received salary support from Boston Scientific and Abbott; has received consulting fees from Abbott and AtriCure; has received research support from Boston Scientific, Biosense Webster, and Abbott; and has received grants from Boston Scientific, Medtronic, Abbott, and Biotronik. Dr. Vemulapalli receives grants for clinical research from Abbott Vascular, Boston Scientific, National Institutes of Health, Patient Centered Outcomes Research Institute, Food and Drug Administration (NEST), American College of Cardiology, Society of Thoracic Surgeons; and serves as a consultant to Janssen, Boston Scientific, Heartflow, Baylabs (Caption Health), and the American College of Physicians. Dr. Granger has received funding support and/or honoraria from The Medicines Company, Pfizer, and AstraZeneca; and has been a consultant for Pfizer and AstraZeneca. Dr. Peterson has received grant support from the American College of Cardiology, the American Heart Association, and Janssen; and has served as a consultant for Bayer, Boehringer Ingelheim, Merck, Valeant, Sanofi, AstraZeneca, Janssen, Regeneron, and Genentech. Dr. Piccini has received grants for clinical research from Abbott, the American Heart Association, the Association for the Advancement of Medical Instrumentation, Bayer, Boston Scientific, and Philips; and has served as a consultant to Abbott, Allergan, ARCA Biopharma, Biotronik, Boston Scientific, LivaNova, Medtronic, Milestone, Myokardia, Sanofi, Philips, and Up-to-Date. 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

ESRD = end-stage renal disease

OAC = oral anticoagulant

Atrial fibrillation (AF) is more frequent in patients with impaired renal function and occurs in approximately 1 of 5 patients with end-stage renal disease (ESRD), likely due to shared risk factors including diabetes and hypertension (1). Chronic kidney disease is associated with an increased risk of ischemic stroke in patients with AF independent of traditional risk factors for stroke (2). Furthermore, the presence of AF complicates the management of ESRD. Patients with AF and ESRD require frequent vascular access, and are prone to bleeding complications, including intracranial hemorrhage, complicating the decision to initiate oral anticoagulation (OAC) (3).

Significant uncertainty remains regarding the risk-benefit of OAC in patients with ESRD and AF. Patients with AF and ESRD on warfarin spend less than one-half of their time with an international normalized ratio (INR) in the therapeutic range (TTR) (4). Maintenance of hemodialysis access requires frequent surgical and catheter-based interventions that often mandate interruption of OAC. There are conflicting data on the benefit of OAC on the risk of stroke in patients with AF and ESRD, with a large analysis from Denmark demonstrating reduced risk of ischemic stroke in patients with ESRD (5). Conversely, another analysis of AF and ESRD patients in the United States demonstrated a 2-fold increase in stroke in patients treated with warfarin (6). Although there are ongoing randomized trials of apixaban versus warfarin in patients with AF and ESRD, observational data suggest that dabigatran and rivaroxaban are associated with an increased risk for hospitalization and death due to bleeding relative to dose-adjusted warfarin in ESRD (7).

The uncertainty surrounding stroke prevention in ESRD and AF is reflected in the most recent KDIGO (Kidney Disease: Improving Global Outcomes) 2011 consensus statement on cardiovascular disease, which recommends against OAC in dialysis patients with AF (1). Given the uncertainty regarding the risks and benefits of OAC in patients with AF and ESRD, we sought to describe patterns of OAC in these high-risk patients. Moreover, we sought to evaluate the association of OAC use with cardiovascular outcomes in patients with AF and ESRD.

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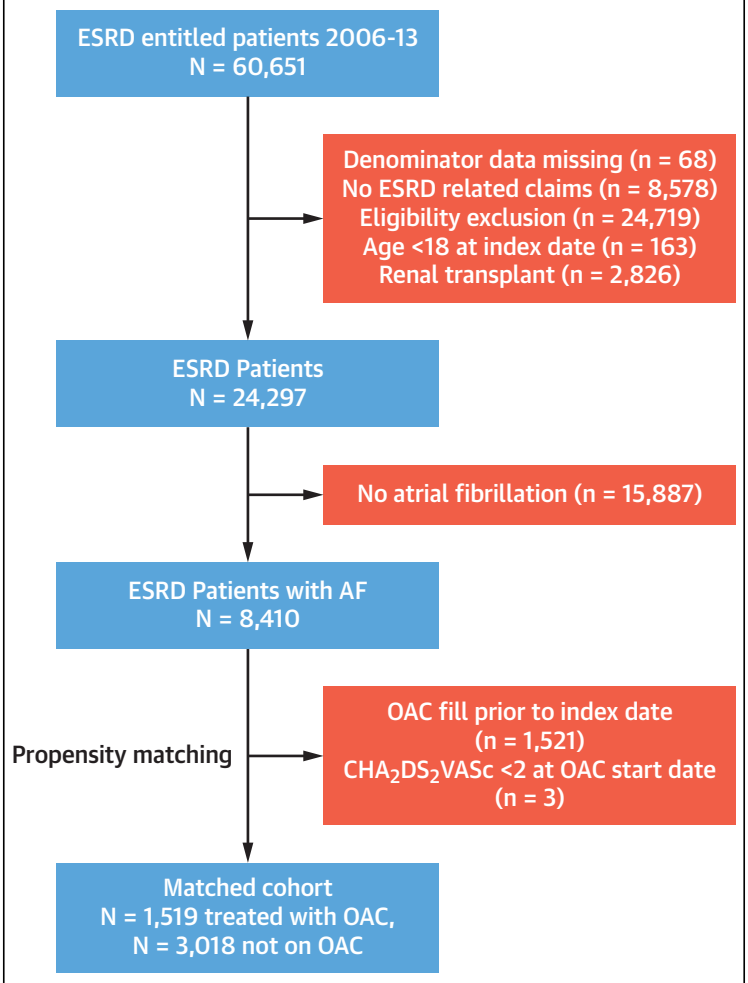
FIGURE 1 Study Flow Diagram



Study population was derived from a Medicare 5% fee-for-service sample. Exclusion criteria for not being designated ESRD included absence of ESRD-related claims, inconsistent demographic variables, lack of Medicare Part D enrollment, or absence of at least 1 year of Medicare FFS enrollment. Patients with AF were then identified using International Classification of Diseases-9th Edition-Clinical Modification diagnosis codes. Propensity matching was performed using a Cox proportional hazards model with each OAC patient matched by propensity score to the closest non-OAC patient. Each OAC patient was matched to 2 non-OAC patients, except for 20 OAC patients for whom a suitable second match could not be found. AF = atrial fibrillation; ESRD = end-stage renal disease; OAC = oral anticoagulant.

METHODS

DATA SOURCE. This study utilized the 5% sample of Medicare fee-for-service (FFS) beneficiaries from 2006 to 2013, including inpatient (Part A), outpatient (Part B), prescription drug (Part D), and denominator files. Data elements used were demographic and death data; enrollment in Medicare FFS Part A, Part B, and Part D; hospital admission and outpatient encounter dates; International Classification of Diseases-9th Edition-Clinical Modification (ICD-9-CM) diagnosis and procedure codes; Current Procedural Terminology codes; Healthcare Common Procedure Coding System codes; and date, amount, and medication type for prescription fills.

STUDY POPULATION. Medicare beneficiaries with ESRD (n = 60,651) were identified using the Entitlement Indicator, an annual variable that indicates the reason for entitlement to Medicare services (Figure 1). Patients under the age of 18 years were excluded (n = 163), as were those without ESRD-related claims (n = 8,578), with inconsistent sex or date of birth or death variables, or who resided outside of the United States (n = 68). Patients were also excluded if they were not enrolled in Medicare Part D (n = 15,423), did not have at least 1 year of Medicare fee-for-service (FFS) A and B eligibility (n = 9,320), or had undergone kidney transplantation (n = 2,826). Patients with AF were identified using the AF (427.31) and atrial flutter (427.2) ICD-9-CM diagnosis codes. To exclude patients with reversible forms of AF, patients were required to have at least 2 separate instances of AF or atrial flutter, at least 1 day apart, for inclusion in the AF group. Patients were designated to enter the analysis period on the index date, defined as the diagnosis of ESRD, diagnosis of AF, or eligibility for Medicare FFS A and B for 1 year, whichever came last. The analysis period extended from the index date until the date of death, renal transplantation, end of FFS A and B or Part D eligibility, or the end of the data period (December 31, 2013).

PATIENT CHARACTERISTICS, TREATMENT, AND OUTCOMES. Baseline characteristics and comorbidities, including prior myocardial infarction, heart failure, coronary artery disease, hypertension, prior stroke/transient ischemic attack, peripheral arterial disease, chronic obstructive pulmonary disease, and diabetes mellitus (Supplemental Table 1) were determined using Medicare inpatient and outpatient claims in the health history period, defined as 1 year prior to the index date. Dialysis type (hemodialysis or peritoneal dialysis) and time of initiation of hemodialysis were also determined using inpatient and outpatient claims (Supplemental Table 2). To allow ascertainment of anticoagulation status, only patients enrolled in Medicare Part D for at least 1 year were included in the study population. Patients were considered to be in the OAC group if they had at least 1 prescription fill for apixaban, dabigatran, rivaroxaban, or warfarin during the analysis period. Persistence of OAC therapy was determined in patients at risk of stroke (CHA_2DS_2-VASc ≥2) by analyzing prescription fills in the period starting 9 months and ending 12 months after their first prescription fill. Patients were defined as remaining on OAC if they filled a prescription for the same type of OAC as the initial fill, switching anticoagulant if they filled a prescription for a different type of OAC than the first fill, and discontinuing if they did not fill an OAC prescription. We assessed outcomes including mortality, all-cause hospitalization, bleeding hospitalization, stroke or thromboembolic hospitalization, or

TABLE 1 Baseline Characteristics of ESRD Patients With and Without AF

	All ESRD Patients (N = 24,297)	Patients With AF (n = 8,410)	Patients Without AF (n = 15,887)	p Value
Demographics				
Age, yrs	65 (53-75)	71 (63-79)	60 (49-70)	<0.0001
Female	50.6 (12,300)	52.2 (4,386)	49.8 (7,914)	0.0005
Black race	35.9 (8,676)	28.7 (2,405)	39.7 (6,271)	<0.0001
Medical history				
Coronary artery disease	52.4 (12,740)	70.9 (5,962)	42.7 (6,778)	<0.0001
Prior MI	18.0 (4,369)	27.1 (2,277)	13.2 (2,092)	<0.0001
Congestive heart failure	54.1 (13,150)	74.0 (6,220)	43.6 (6,930)	<0.0001
Hypertension	93.4 (22,698)	97.2 (8,171)	91.4 (14,527)	<0.0001
Prior stroke or TIA	18.6 (4,514)	24.3 (2,042)	15.6 (2,472)	<0.0001
Diabetes	70.4 (17,109)	73.8 (6,207)	68.6 (10,902)	<0.0001
COPD	33.8 (8,214)	46.4 (3,905)	27.1 (4,309)	<0.0001

Values are median (interquartile range) or % (n).
AF = atrial fibrillation; COPD = chronic obstructive pulmonary disease; ESRD = end-stage renal disease; MI = myocardial infarction; TIA = transient ischemic attack.

TABLE 2 Baseline Characteristics of ESRD Patients With AF Overall and by Anticoagulant Use

	All ESRD AF Patients (N = 8,410)	Patients With OAC (n = 3,043)	Patients Without OAC (n = 5,367)	p Value
Demographics				
Age, yrs	71 (63-79)	70 (61-78)	72 (63-80)	<0.0001
Female	52.2 (4,386)	51.9 (1,579)	52.3 (2,807)	0.72
Black race	28.7 (2,405)	28.1 (854)	29.0 (1,551)	0.40
Medical history				
Coronary artery disease	70.9 (5,962)	69.4 (2,112)	71.7 (3,850)	0.024
Prior MI	27.1 (2,277)	24.3 (738)	28.7 (1,539)	<0.0001
Prior CABG	2.7 (228)	2.6 (78)	2.8 (150)	0.53
Congestive heart failure	74.0 (6,220)	73.6 (2,239)	74.2 (3,981)	0.55
Hypertension	97.2 (8,171)	96.7 (2,942)	97.4 (5,229)	0.047
Prior stroke or TIA	24.3 (2,042)	21.7 (659)	25.8 (1,383)	<0.0001
Diabetes	73.8 (6,207)	73.6 (2,239)	73.9 (3,968)	0.72
COPD	46.4 (3,905)	44.5 (1,353)	47.5 (2,552)	0.0064
Stroke and bleeding risk				
CHA_2DS_2-VASc score				
Median (IQR)	6 (4-7)	6 (4-7)	6 (4-7)	0.010
0 (low risk)	0.3 (22)	0.2 (7)	0.3 (15)	
1 (medium risk)	1.5 (122)	1.5 (47)	1.4 (75)	
2 or greater (high risk)	98.3 (8,266)	98.2 (2,989)	98.3 (5,277)	
Prior hospitalization for bleeding	8.0 (673)	6.0 (182)	9.1 (491)	<0.0001
ATRIA bleeding score				
Median (IQR)	8 (7-9)	8 (7-9)	8 (7-9)	<0.0001
0-3 (low risk)	0.7 (63)	0.5 (16)	0.9 (47)	
4 (medium risk)	5.8 (486)	6.6 (200)	5.3 (286)	
5 or greater (high risk)	93.5 (7,861)	92.9 (2,827)	93.8 (5,034)	

Values are median (interquartile range) or % (n).
CABG = coronary artery bypass grafting; IQR = interquartile range; other abbreviations as in Table 1.

TABLE 3 Characteristics That Are Associated With OAC Utilization (Propensity Model)

	HR (95% CI)	Wald Chi-Square	p Value
Age	0.87 (0.83–0.91) (per 10 yrs)	38.5706	<0.0001
Female	1.09 (0.98–1.21)	2.6999	0.1004
Black race	1.00 (0.90–1.13)	0.0063	0.9367
Region		5.1001 (3 df)	0.1646
Northeast vs. West	1.17 (0.98–1.41)		
Midwest vs. West	1.20 (1.01–1.43)		
South vs. West	1.11 (0.95–1.30)		
Time since AF diagnosis		0.3897 (3 df)	0.9424
<3 months vs. >9 months	1.02 (0.79–1.31)		
3–6 months vs. >9 months	1.09 (0.81–1.47)		
6–9 months vs. >9 months	1.01 (0.72–1.40)		
Time since ESRD diagnosis		5.4914 (3 df)	0.1392
<3 months vs. >9 months	0.90 (0.72–1.13)		
3–6 months vs. >9 months	1.18 (0.89–1.58)		
6–9 months vs. >9 months	1.01 (0.73–1.40)		
Dialysis type		1.8255 (2 df)	0.4014
Hemodialysis vs. none	1.02 (0.51–2.05)		
Peritoneal vs. none	0.77 (0.34–1.72)		
CAD	1.02 (0.89–1.18)	0.0997	0.7522
Prior MI	1.13 (1.00–1.29)	3.8372	0.0501
Prior CABG	1.40 (1.09–1.80)	6.8722	0.0088
Congestive heart failure	1.24 (1.06–1.45)	7.1502	0.0075
Hypertension	1.23 (0.55–2.76)	0.2484	0.6182
Stroke or TIA	1.03 (0.90–1.17)	0.1738	0.6768
Diabetes	0.99 (0.87–1.12)	0.0258	0.8723
COPD	1.00 (0.90–1.11)	0.0009	0.9755
Cancer	1.06 (0.93–1.20)	0.8273	0.3631
Dementia	0.75 (0.61–0.93)	7.0742	0.0078
Prior bleeding hospitalization	0.64 (0.51–0.81)	14.3654	0.0002
CHA_2DS_2-VASc high risk (≥2)	3.27 (1.04–10.33)	4.0891	0.0432
ATRIA score high risk (≥5)	1.36 (0.98–1.90)	3.3527	0.0671

Abbreviations as in Tables 1 and 2.

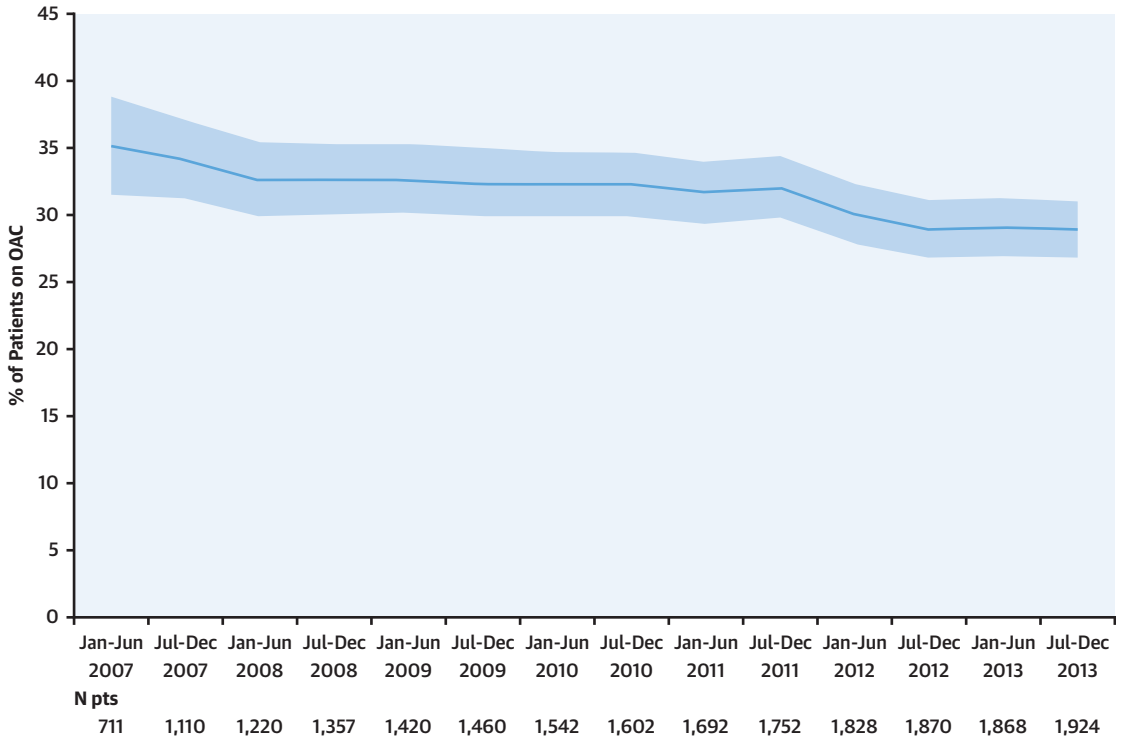
hospitalization for intracranial hemorrhage using primary diagnosis ICD-9-CM codes from inpatient claims data (Supplemental Table 3). Missing data were not present, with the exception of the "unknown" race category (<1% of patients), which was imputed as nonblack in modeling.

RISK SCORE CALCULATIONS. The CHA_2DS_2-VASc stroke risk score was calculated from age, sex, and comorbidity data, with 2 points for history of prior stroke/transient ischemic attack or age >75 years, and 1 point for heart failure/left ventricular dysfunction, hypertension, age >65 years, diabetes, peripheral vascular disease, and female sex (8). Patients were categorized by CHA_2DS_2-VASc as low (0 points), medium (1 point), or high risk for stroke (>2 points). ATRIA bleeding risk scores were calculated based on anemia (3 points), severe renal disease (3 points), age >75 years (2 points), any prior hemorrhage (1 point), or hypertension (1 point), with patients categorized as low risk (0 to 3 points), medium risk (4 points), or high risk for bleeding complications (>4 points) (9).

STATISTICAL ANALYSIS. Baseline characteristics of the ESRD patients with and without AF and patients with ESRD and AF with and without OAC were compared using Pearson chi-square tests for categorical variables and Wilcoxon rank sum tests for continuous variables. Temporal trends in OAC use over time in patients with ESRD were summarized by dividing each calendar year into 2 6-month intervals (January to June and July to December) and assessing prescription fills during each interval. The Mantel-Haenszel chi-square test was used to assess for a significant trend in OAC use.

To evaluate cardiovascular outcomes, we used the subset of patients who either had a new OAC prescription fill during the analysis period (no fill in prior 12 months) or did not have any OAC fills, and who were at high risk of stroke (CHA_2DS_2-VASc ≥2). Because patients who start taking an OAC may be different from patients who do not, we used propensity score methods to create a matched set of OAC and non-OAC patients. First, propensity scores were calculated using a Cox proportional hazards model, where "time to OAC" (days from index to first prescription fill) was the dependent variable and all predictors except sex and race were allowed to vary over time. Second, each OAC patient was matched on the day of their OAC fill to the non-OAC patient with the same dialysis type and the closest propensity score on that day (days from index date). OAC patients could be used as non-OAC patients before their OAC start date. Each OAC patient was matched to 2 non-OAC patients except for 20 OAC patients for whom a suitable second match could not be found. Thus, the cohort for this analysis had 1,519 OAC patients and 3,018 non-OAC patients. The quality of propensity matching was evaluated using standardized differences, defined as the absolute difference in means (or proportions) divided by the average SD. A standardized difference of <0.10 (10%) reflects good covariate balance between groups. All outcomes were assessed beginning on the day of the match. Absolute risk of relevant outcomes at 1 and 2 years were calculated by OAC status using Kaplan-Meier rates for mortality and cumulative incidence rates (with death as a competing risk) for hospitalization outcomes. A Cox model was used to evaluate the association of OAC use with mortality, and Fine and Gray models (with death as a competing risk) were used for hospitalization outcomes. All models were stratified on

FIGURE 2 Rates of Anticoagulation in Patients With ESRD



OAC use was ascertained by assessing prescription fills for apixaban, dabigatran, rivaroxaban, or warfarin during the analysis period. To assess persistence of OAC therapy, prescription fills in the period starting 9 months and ending 12 months after their first prescription fill were assessed. OAC = oral anticoagulant.

matched set, included all covariates from the propensity model as adjustment variables, and used robust covariance estimators to account for patients that are used more than once. Risk relationships are shown as hazard ratios (HRs) with 95% confidence intervals (CIs), along with p values; $p < 0.05$ was considered significant. All analyses were conducted using SAS version 9.4 or higher (SAS Institute, Cary, North Carolina).

RESULTS

BASELINE PATIENT CHARACTERISTICS. We identified a total of 24,927 ESRD patients during the study period, the majority of which (n = 21,944) were on hemodialysis. AF was highly prevalent, with 34.6% (n = 8,410) of ESRD patients having prevalent AF or incident AF. The baseline characteristics of ESRD patients with and without AF were markedly different with respect to age, sex, and comorbidities (Table 1). Compared with the general ESRD population, patients with AF were more likely to be older, male, and have more extensive medical comorbidities, including coronary artery disease, heart failure, hypertension, and diabetes (Table 1). The overall rate of $P2Y_{12}$ inhibitor use in the population at the time of matching was 15.9% (n = 721), including 16.4% of patients on OAC (n = 249) and 15.6% of patients not on OAC (n = 472).

TREATMENT PATTERNS. In patients with ESRD and AF at risk for stroke (CHA_2DS_2-VASc ≥2), 36.2% filled a prescription for an OAC at some point during the study period. Patients with ESRD and AF treated with OAC (n = 3,043) were younger and less likely than those not on anticoagulation (n = 5,367) to have been previously hospitalized for bleeding. Moreover, patients on OAC had lower rates of hypertension, coronary artery disease, prior stroke or transient ischemic attack, or prior myocardial infarction (Table 2). The vast majority of anticoagulated patients were treated with warfarin (n = 2,971), and <1% were treated with a direct acting oral anticoagulant (n = 46). Following initiation of OAC therapy, 33.8% of ESRD patients

TABLE 4 Variables Used in Propensity Model for OAC Use

Baseline Characteristics†	Pre-Match OAC (n = 1,522)	Pre-Match No OAC (n = 5,367)	Pre-Match Standardized Difference (%)	Matched 1:2 OAC* (n = 1,519)	Matched 1:2 No OAC (n = 3,018)†	Matched 1:2 Standardized Difference (%)
Age	69 (60–77)	69 (63–80)	24.9	70 (61–78)	70 (62–79)	6.3
Female	54 (825)	52 (2,807)	3.8	54 (825)	54 (1,638)	0.1
Black race	32 (481)	29 (1,551)	5.9	32 (480)	30 (917)	2.6
Southern region	44 (666)	45 (2,405)	2.1	44 (665)	45 (1,350)	1.9
Medical history‡						
CAD	76 (1,158)	80 (4,295)	9.5	82 (1,249)	82 (2,478)	0.3
Prior MI	22 (328)	25 (1,337)	8.0	24 (361)	25 (748)	2.4
Prior CABG	4 (64)	4 (193)	3.1	4 (67)	4 (135)	0.3
CHF	82 (1,248)	83 (4,472)	3.5	87 (1,323)	88 (2,648)	1.9
Hypertension	99 (1,511)	100 (5,345)	4.2	100 (1,513)	100 (3,010)	2.3
Stroke or TIA	16 (244)	21 (1,143)	13.5	20 (302)	21 (620)	1.6
Diabetes	77 (1,174)	77 (4,131)	0.4	79 (1,206)	79 (2,399)	0.2
COPD	50 (764)	55 (2,954)	9.7	57 (863)	57 (1,716)	0.1
Cancer	19 (294)	22 (1,195)	7.3	21 (319)	21 (623)	0.9
Dementia	5 (75)	9 (468)	15.1	7 (99)	6 (196)	0.1
Stroke and bleeding risk‡						
CHA_2DS_2-VASc high risk (≥2)	99 (1,510)	99 (5,328)	0.7	100 (1,519)	100 (3,018)	—§
Prior bleeding hospitalization	5 (74)	9 (472)	15.6	5 (79)	5 (162)	0.7
ATRIA score high risk (≥5)	96 (1,456)	97 (5,196)	6.0	98 (1,483)	98 (2,957)	2.4

Values are median (interquartile range) or % (n). Baseline is the *index date* for pre-match and the *match day* for matched (*index date* = *last* of ESRD start, AF start, and 12 months FFS A and B and Part D; *match day* is days from index date to OAC start for the OAC patient in each pair). *Three OAC patients who were CHA_2DS_2-VASc = 0 or 1 at the time of their OAC start were omitted; hence, n is 3 less than for pre-match. †532 OAC patients were used as non-OAC patients in matches before their OAC start time. ‡Medical history and stroke and bleeding risk variables determined from claims in 12 months prior to baseline. §Patients were required to have CHA_2DS_2-VASc ≥2 at the time of match.

Abbreviations as in Tables 1 and 2.

TABLE 5 Unadjusted Risk of Relevant Outcomes Among Matched Cohort of ESRD Patients With AF by Anticoagulant Use

Event Risk*	OAC (n = 1,519)†	No OAC (n = 3,018)†
Death		
Total events	922	1,817
1-yr risk	33.9 (31.5–36.5)	34.2 (32.4–36.0)
2-yr risk	53.0 (50.2–55.8)	54.1 (52.1–56.1)
Hospital admission for any reason		
Total events	1,297	2,395
1-yr risk	79.2 (77.1–81.4)	72.7 (71.0–74.4)
2-yr risk	89.3 (87.7–91.0)	83.5 (82.0–85.0)
Hospital admission for bleeding		
Total events	230	375
1-yr risk	10.8 (9.3–12.6)	7.3 (6.4–8.4)
2-yr risk	14.5 (12.7–16.5)	11.5 (10.4–12.9)
Hospital admission for stroke or thromboembolic event		
Total events	117	211
1-yr risk	5.3 (4.2–6.6)	4.0 (3.3–4.8)
2-yr risk	7.3 (6.1–8.9)	6.3 (5.4–7.3)
Hospital admission for ICH‡		
Total events	129	198
1-yr risk	5.8 (4.7–7.1)	3.9 (3.2–4.7)
2-yr risk	7.8 (6.5–9.4)	6.0 (5.1–7.0)

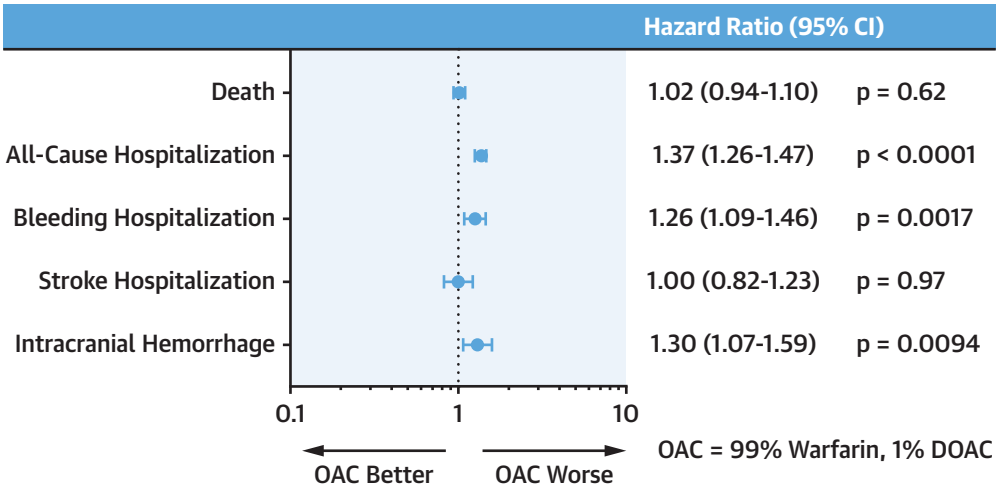
Values are % or median (interquartile range). *Kaplan-Meier for mortality; cumulative incidence (with death as competing risk) for admissions. †At time of match. ‡The number of ICH events is similar to that for all stroke events because they have overlapping definitions, but ICH is not a subset of stroke. It includes bleeding due to injury, while the stroke outcome does not.

ICH = intracranial hemorrhage.

with AF in our study cohort discontinued OAC within 12 months and 65.8% remained on OAC. Significant predictors of OAC initiation included heart failure, prior CABG, and CHA_2DS_2-VASc ≥2. Older patients and those with dementia or prior bleeding hospitalization were less likely to be treated with OAC (Table 3). Rates of anticoagulation in patients with ESRD and AF with CHA_2DS_2-VASc ≥2 decreased over the study period (p for trend <0.0001) (Figure 2).

OUTCOMES. The matched groups of OAC and non-OAC patients were well-balanced on sociodemographic and clinical characteristics (Table 4). The unadjusted 1- and 2- year rates of death, all-cause hospitalization, or hospitalization for bleeding, stroke, or intracranial hemorrhage are shown in Table 5. Treatment with OAC was not associated with a lower risk of hospitalization for stroke or thromboembolic events (adjusted HR: 1.00; 95% CI: 0.82 to 1.23; p = 0.97) or death (adjusted HR: 1.02; 95% CI: 0.94 to 1.10; p = 0.62). Patients with ESRD and AF treated with OAC were more likely to be hospitalized for bleeding (adjusted HR: 1.26; 95% CI: 1.09 to 1.46; p = 0.0017) or intracranial hemorrhage (adjusted HR: 1.30; 95% CI: 1.07 to 1.59; p = 0.0094) (Central Illustration). Cumulative incidence curves the propensity-matched cohort are shown in Figure 3.

CENTRAL ILLUSTRATION **Adjusted Outcomes Among Matched End-Stage Renal Disease-Atrial Fibrillation Patients by Anticoagulant Use at 2 Years**



Pokorney, S.D. et al. J Am Coll Cardiol. 2020;75(11):1299–308.

Absolute risk at 2 years was calculated by OAC status using Kaplan-Meier rates for mortality and cumulative incidence rate hospitalization outcomes. The association of OAC use with mortality was evaluated using a Cox proportional hazards model. Hospitalization outcomes (intracranial hemorrhage, bleeding, and stroke) were assessed using Fine and Gray models (with death as a competing risk). Risk relationships are shown as hazard ratios (HRs) with 95% confidence intervals (CIs), along with p values; $p < 0.05$ was considered significant. The HRs are depicted on the horizontal axis in log-scale. All models were stratified on matched set, included all covariates from the propensity model as adjustment variables, and used robust covariance estimators to account for patients that are used more than once.

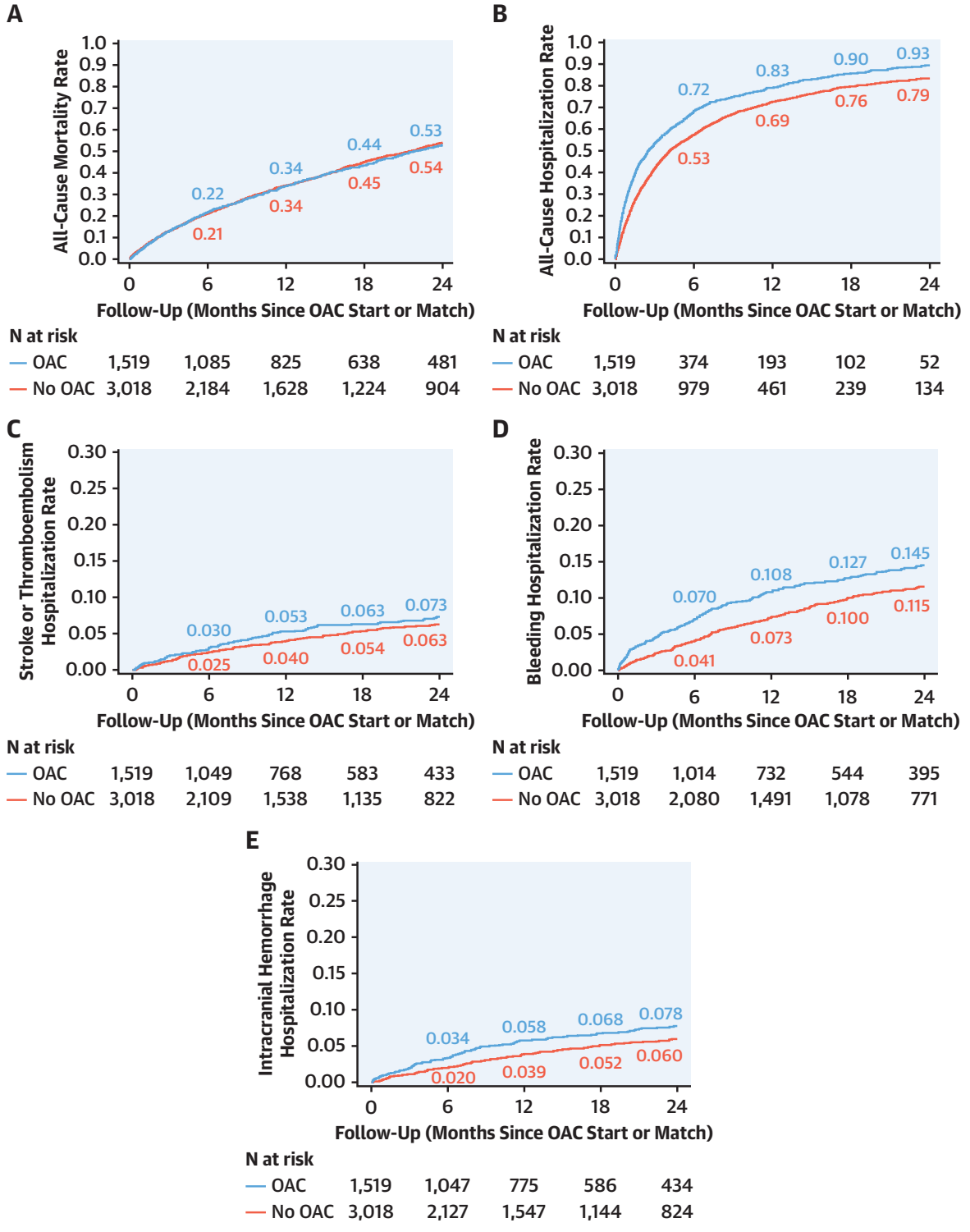
DISCUSSION

In this nationwide analysis of patients with ESRD and AF, we found that 1 of 3 patients with ESRD had AF. Patients with ESRD and concomitant AF were older and had more comorbid illness than those without AF. Only 1 of 3 patients with AF, ESRD, and a CHA_2DS_2-VASc ≥2 were treated with OAC. However, there was no evidence of an association between OAC therapy and lower risk of stroke. Finally, approximately one-third of patients with ESRD and AF who were treated with OAC discontinued therapy at 1 year, and patients treated with OAC experienced an increased risk for all-cause bleeding and intracranial hemorrhage.

The low rate of OAC utilization in patients with AF and ESRD is not surprising considering there are several studies that have demonstrated an increased risk for stroke in patients with ESRD treated with OAC (6,10–13). There is some evidence to suggest that warfarin may confer net clinical harm in patients with ESRD by acceleration of vascular calcification (1). Patients in the United States with ESRD treated with warfarin spend <50% of their time within the therapeutic range (4,14). Such poor INR control likely contributes to an increased risk of stroke, systemic embolism, and major bleeding episodes for patients with ESRD on warfarin (15). The low therapeutic persistence of OAC in patients with ESRD and AF may reflect bleeding events associated with anticoagulation in patients on hemodialysis, who require vascular access 3 times weekly. The 33.8% rate of therapy discontinuation in our analysis is similar to the findings of Tan et al. (16), who found a 46.8% rate of warfarin discontinuation in an analysis of the U.S. Renal Data System.

Importantly, our findings contrast with the results of a Danish study including 1,142 patients with ESRD on hemodialysis, in which warfarin was associated with lower risk of all-cause mortality in patients with a CHA_2DS_2-VASc ≥2 (17). There may be important differences between ESRD patients in the United States and Denmark, including a lower TTR in U.S. ESRD patients. Moreover, 98.3% (n = 8,266) of ESRD patients with AF in our cohort had a CHA_2DS_2-VASc ≥2 vs. 78.6% (n = 898) in the Danish cohort.

FIGURE 3 Cumulative Incidence Curves for Propensity-Matched Outcomes



The 24-month cumulative incidence curves for relevant outcomes including **(A)** all-cause mortality, **(B)** all-cause hospitalization, **(C)** stroke or thromboembolic hospitalization, **(D)** bleeding hospitalization, and **(E)** intracranial hemorrhage. OAC = oral anticoagulant.

Overall, 74.0% (n = 6,220) of patients with AF and ESRD had HF in our cohort, whereas only 19% (n = 222) of the Danish cohort had HF (17). Considering that our results are from a larger cohort of U.S. Medicare patients, they are likely more generalizable to U.S. clinical practice. Furthermore, our results are strengthened by findings from a smaller Medicare claims analysis of OAC comparing 237 patients treated with warfarin and 948 propensity-matched patients with AF and ESRD not on warfarin (10). Winkelmayer et al. (10) similarly found no effect of warfarin on ischemic stroke (HR: 0.92; 95% CI: 0.61 to 137) and an increased risk of hemorrhagic stroke (HR: 2.38; 95% CI: 1.15 to 4.96) in patients with AF and ESRD treated with warfarin (10). Interestingly, stroke event rates in both OAC and non-OAC treated patients were lower than might be expected considering a median CHA_2DS_2-VASc score of 6 (5.3% and 4.0%, respectively). A nationwide study from Taiwan similarly found that stroke rates were lower in ESRD patients than predicted according to CHA_2DS_2-VASc score, possibly due to the competing risk of in-hospital death (18). These lower event rates have implications for the design of future clinical trials in similar populations.

Alternative therapeutic strategies to prevent ischemic stroke in patients with ESRD and AF are needed. Although observational data have suggested that apixaban is associated with lower risk of bleeding and similar risk of stroke or systemic embolism when compared with warfarin (19), prospective randomized trials comparing apixaban with warfarin in patients with AF and ESRD are ongoing. Left atrial appendage occlusion (LAAO) has a potentially favorable risk profile for ESRD patients, considering that this therapy does not require long-term anticoagulation. The PROTECT-AF (Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation) study found LAAO therapy to be noninferior to warfarin with respect to a primary endpoint of stroke, systemic embolism, and cardiovascular or unexplained death (rate ratio: 0.62; 95% CI: 0.35 to 1.25) (20). Rates of hemorrhagic stroke were particularly low in patients treated with LAAO compared with warfarin (relative risk: 0.09; 95% CI: 0.00 to 0.45) (19). Although observational data suggest that LAA occlusion may be a feasible strategy in ESRD patients, prospective randomized clinical trials are needed (21).

STUDY LIMITATIONS. Because our analysis is based on administrative claims data for determination of outcomes and comorbidities, it is possible that unmeasured confounders such as over-the-counter medication use (e.g., aspirin) may have affected our results. Information about TTR and adherence to warfarin therapy in patients prescribed OAC were not available from Medicare claims data. Furthermore, the analysis does not include socioeconomic information (such as income or education level), certain clinical variables (blood pressure, weight), or information regarding smoking and alcohol use. Although no trials of direct-acting oral anticoagulants in hemodialysis patients have been completed, the limited number of patients treated with direct-acting oral anticoagulants in our cohort limits any analysis of these agents or their impact on clinical outcomes in patients with AF and ESRD.

CONCLUSIONS

In a large propensity-matched analysis of U.S. patients with ESRD and AF, we found that OAC use was not associated with a reduction in risk of ischemic stroke. AF patients with ESRD treated with OAC were more likely to be hospitalized for bleeding or intracranial hemorrhage. Prevention of stroke in patients with AF and ESRD represents a major unmet clinical need, and prospective studies of alternative treatment strategies, including left atrial appendage occlusion, are needed.

ADDRESS FOR CORRESPONDENCE: Dr. Jonathan P. Piccini, Sr., Electrophysiology Section, Duke University Medical Center, P.O. Box 17969, Durham, North Carolina 27710. E-mail: jonathan.piccini@duke.edu. Twitter: @JonPicciniSr.

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL OUTCOMES: Patients with AF and ESRD are at increased risk of thromboembolic and bleeding complications. Observational studies of oral vitamin K antagonist therapy have reported conflicting effects on mortality, thrombotic, and bleeding events in these patients.

TRANSLATIONAL OUTLOOK: Further investigation is needed to establish the safety and efficacy of target-specific oral anticoagulants and left atrial appendage occlusion in these patients.

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KEY WORDS anticoagulation, atrial fibrillation, bleeding, end-stage renal disease, stroke

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