Kidney Medicine

Oral Anticoagulant Initiation in Patients With Kidney Failure on Hemodialysis Newly Diagnosed With Atrial Fibrillation (2007-2020): An Observational Study of Trends and Disparities

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Rationale & Objective: Atrial fibrillation (AF) is common in patients with kidney failure on hemodialysis (HD), but few patients receive oral anticoagulant (OAC) treatment. Availability of direct-target OACs starting in 2010 may have induced greater OAC initiation, but this has not been systematically studied.

Study Design: Retrospective cohort study.

Setting & Participants: Using Medicare fee-for-service billing claims (2006-2020), we identified previously OAC-naïve HD patients newly-diagnosed with AF between January 1, 2007, and October 1, 2020.

Exposures: Calendar year; race/ethnicity.

Outcomes: OAC initiation within 90 days from AF diagnosis (any; specific agent).

Analytical Approach: We estimated initiation risk ratios for each calendar year compared with the referent cohort, 2007, using unadjusted and multivariable-adjusted modified Poisson regression. We also determined differences by racial/ethnic group in OAC initiation, as well as any changes in these disparities over time.

Results: Among 82,389 HD patients newly-diagnosed with AF, 20,002 (24.3%) initiated new OAC treatment within 90 days: 20.5% in 2007 and 34.1% in 2020. Direct-target OACs accounted for 81.0% of OAC initiations in 2020. Adjusted regression models estimated that OAC initiation remained essentially unchanged between 2007 and 2013, but thereafter increased toward a demographics-adjusted risk ratio of 1.61 (95% CI: 1.50-1.73) in 2020. Compared with non-Hispanic Whites, the rates of OAC initiation were 15% (95% CI, 12%-17%) lower among Black patients, 29% (95% CI, 24%-34%) lower among Asian patients, and 22% (95% CI, 19%-25%) lower among Hispanic patients. These disparities were not found to have differed across time ($P_{interaction}$ = 0.75).

Limitations: Lack of clinical detail to firmly establish contraindications to OAC initiation.

Conclusions: While rates of OAC initiation among patients on HD with newly-diagnosed AF increased in recent years, predominantly driven by increased use of apixaban, OAC initiation rates remained low, at 34% of patients in 2020. Compared with non-Hispanic White patients, OAC initiation remained consistently lower in patients of other race and ethnic groups.

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Atrial fibrillation/flutter (AF) is the most common sustained arrhythmia in the general population. Patients with AF experience poor health outcomes including higher mortality, excess rates of ischemic stroke, systemic thromboembolism, myocardial infarction, heart failure, and kidney disease, and incur higher health care costs.[1,2] AF is particularly common in patients with kidney failure undergoing long-term hemodialysis (KF_{HD}): 10.7% of prevalent US patients with KF_{HD} carried a confirmed diagnosis of AF in 2006, and both the incidence and prevalence of diagnosed AF have been increasing.[3,4] However, many more patients have either asymptomatic or undiagnosed AF. In a comprehensive study of patients with KF_{HD} in Vienna, Austria, where electrocardiograms were routinely obtained for all patients, the prevalence of AF was 26.5%.[5] When using loop recorders for at least 6 months in patients with KF_{HD}, the prevalence of AF, defined as at least 1 episode exceeding 6 minutes of duration, was 41%.[6]

Oral anticoagulation (OAC) using the vitamin K antagonist, warfarin, has long been shown to reduce the rates of ischemic stroke and mortality in suitable patients with AF (who did not have advanced chronic kidney disease or kidney failure).[7] The benefits from this intervention outweigh the excess bleeding risks that OAC confers, and international guidelines have issued strong recommendations in support of OAC in higher risk individuals with AF as indicated by the presence of certain risk factors.[8] Since 2010, newer OACs inhibiting specific targets in the coagulation cascade, namely the direct thrombin inhibitor, dabigatran, and the factor X inhibitors, rivaroxaban, apixaban, and edoxaban, have come to the US market. These direct-target oral anticoagulants (DOACs) were shown to be noninferior to warfarin use with respect to thromboembolic and bleeding risk. Hence, recent guidelines endorse the use of DOACs for stroke prevention in AF,[9] which have started to replace warfarin as the OAC of choice in many patients.[10]

PLAIN-LANGUAGE SUMMARY

Use of oral blood thinners (anticoagulants) in patients with kidney failure undergoing hemodialysis who have a common type of heart rhythm disorder (atrial fibrillation) used to be low. We studied whether the availability of a novel class of anticoagulants increased use of this treatment approach in recent years. We were also interested in identifying any differences in anticoagulant use between patients of different racial and ethnic backgrounds. We found that use of anticoagulants in patients newly diagnosed with the heart rhythm disorder almost doubled between 2007 and 2020. We also found that Asian, Black, and Hispanic patients were less likely than non-Hispanic Whites to receive anticoagulants. The reasons for these differences are unclear and require further study.

Little is known, however, about longer-term trends in OAC utilization in patients with KF_{HD}, a population excluded from the pivotal placebo-controlled trials of warfarin and, decades later, the noninferiority trials comparing individual DOACs versus warfarin treatment. As a result, international guidelines give only tepid endorsements for warfarin use in patients with KF_{HD} and AF.[11] Several studies have shown only limited utilization of warfarin in the KF_{HD} population, and Black, Hispanic, and Asian patients were found to have even lower warfarin use than non-Hispanic White patients.[12-14] While not recommended for use in patients with KF_{HD} at the time, very limited use of dabigatran and rivaroxaban occurred in this population soon after their approval,[15] and following its market approval, apixaban seemed to have been adopted more briskly,[16] perhaps owing to a clear dosing recommendation for its use in patients with KF_{HD} in the January 30, 2014 version of its US package insert.[17]

We conducted this study to examine the trends in OAC use among patients with KF_{HD} and AF, with focus on overall OAC use as well as that of specific agents. First, we hypothesized that overall OAC use remained flat over time but increased after the introduction of apixaban's new label specifying dosing for patients with KF_{HD} in 2014. Second, we determined whether racial or ethnic differences existed in the selection of OAC type, warfarin versus DOAC, in the most recent years of available data. Third, if differences across racial and ethnic groups were found, we would examine whether differences among racial and ethnic groups in OAC initiation, reported during the pre-DOAC era,[14] had differed across the duration of the study.

METHODS

Study Population and Cohort Assembly

The US Renal Data System (www.USRDS.org) is the national registry of persons with kidney failure undergoing regular dialysis or living with a kidney transplant.[18] In addition to forms filled in by nephrologists, such as the Medical Evidence Report (CMS-2728), the USRDS contains final-action fee-for-service billing claims to Medicare for services covered through Parts A, B, and D (prescription drugs). The present study was nested in the USRDS, using standard analysis files covering the years 2006-2020.

We identified patients who were first diagnosed with AF between January 1, 2007 and October 1, 2020. Patients were considered as having AF if they had (a) an inpatient AF claim or (b) an outpatient AF claim followed by a second AF claim, either inpatient or outpatient, within 90 days. The date of the first AF diagnosis was designated as the AF (= index) date. Patients were considered as having incident (= newly diagnosed) AF if they had uninterrupted Medicare Part A and B coverage for 1 year prior to the AF index date and no AF diagnosis noted during that period. We further restricted the participants to AF patients with HD as their modality on the AF diagnosis date and excluded patients who had a history of valvular diseases prior to that date. We further restricted participants to patients who were active users of the Medicare Part D prescription drug benefit in both pre-AF period (from AF date −365 days to AF date −1 day) and post-AF period (from AF date to AF date +90 days), and who had no filled prescription for any OAC in the pre-AF period. Active users of the prescription drug benefit had continuous Medicare Part D coverage and ≥1 prescription filled in both the pre- and the post-AF periods.

Exposures

The exposure of interest was calendar time, specifically calendar year of incident AF. The secondary exposure, and effect modifier, of interest was reported racial group and Hispanic ethnicity, categorized into mutually exclusive groups of non-Hispanic White, Hispanic White, Black, Asian, and other race. Data on race and ethnicity in the USRDS are derived from the Medical Evidence Report (form CMS-2728), which asks about patient race and Hispanic ethnicity in 2 separate questions. Responses were presumed to be by self-report.

Outcomes

From Medicare Part D claims, we identified any filled prescriptions for an OAC: warfarin, and the DOACs, apixaban, dabigatran, rivaroxaban, and edoxaban. For incident (new) OAC use any filled prescription during the 90 days following the first AF diagnosis (= index) was assessed, and the earliest prescription during this time interval determined the specific type (warfarin vs DOAC) and agent.

Other Variables

From the Patients file in the USRDS we abstracted each person's age (on index date), sex, race, and Hispanic ethnicity. We defined presence of a low-income subsidy and dialysis vintage at the time of first AF diagnosis. We identified the presence of several comorbid conditions

using comorbid conditions reported through the Medical Evidence Report or as recorded in medical claims during the year preceding the index AF diagnosis, for which we used the Elixhauser Comorbidity Software (version 3.7) publicly available through the Health Care Utilization Project of the Agency for Healthcare Research and Quality (www.hcup-us.ahrq.gov). We calculated all patients' $CHADS_2$ score, a scoring system indicating estimated risk of ischemic stroke in persons with AF and recommended by international guidelines to determine candidacy for OAC initiation during the years studied.[11,19] We also calculated the CHA_2DS_2-VASc score, the use of which was recommended by guidelines starting in 2019.[9,20] We did not calculate bleeding risk scores, such as the HAS-BLED score,[21] because key clinical (laboratory and blood pressure) parameters required for the calculations are unavailable in a claims database.

Statistical Analysis

We calculated the proportion of patients initiated on an OAC relative to the total number of patients with KF_{HD} and newly diagnosed AF in each measurement period. We plotted the 90-day initiation risk from the index AF diagnosis of any OAC treatment and of each individual OAC across intervals of calendar time.

We evaluated trends over time by estimating risk ratios (RRs) of OAC initiation in each calendar year (categorical) compared with the year 2007 using modified Poisson regression.[22] The models were run without any adjustment, then with adjustment for age on index date (<50, 50-59, 60-69, 70-79, ≥80 years), sex, race/ethnicity, then additionally adjusted for several comorbid conditions. Then the models were repeated to estimate RRs of warfarin use over time. We also modeled the initiation of DOAC versus warfarin initiation among those initiating any OAC treatment.

Lastly, we tested if any trends were identified in overall OAC initiation difference by race or ethnic group. This was accomplished by including multiplicative interaction terms between calendar year (categorical) and race/ethnic group using a global −2 log likelihood test between the models that included versus excluded the interaction terms.

We repeated all analyses after restricting the cohort to patients with a $CHADS_2$-score of ≥2, since that was a recommended criterion for oral anticoagulant initiation in authoritative guidelines during the majority of time covered by this database.[11,19]

Statistical analyses were performed using SAS software (version 9.4, SAS Institute, Inc). An institutional review board at Baylor College of Medicine approved this study (protocol H-36408), which was conducted under a Data Use Agreement (2018-04a) for USRDS standard analytical files.

RESULTS

Our cohort consisted of 82,389 patients with KF_{HD} and newly diagnosed non-valvular AF who met the inclusion and exclusion criteria and had no prior record of any OAC use in the pre-AF period (Fig 1). Table 1 shows the characteristics of all patients contributing to the analysis, as well as by consolidated time intervals. Median age was 68 years (interquartile range, 58-76), 47% were women, 34% were Black race, and 14% were Hispanic ethnicity. Among patients newly diagnosed with AF in 2007 and without prior OAC use, 20.5% newly initiated OAC within 90 days; only warfarin was available at the time (Fig 2). The proportion of patients with newly diagnosed AF who initiated OAC therapy remained roughly stable until 2013, with very little use of DOACs. Starting in 2014, the proportion of patients initiating OAC increased, mostly attributable to increasing adoption of apixaban. At the same time, use of warfarin began to decline. In 2020, the overall rate of OAC initiation in persons newly diagnosed with AF was 34.1%. Of the 1,433 patients filling a new OAC prescription in 2020, 274 (19.0%) initiated warfarin treatment, whereas 1,136 (78.7%) initiated apixaban and 23 (1.6%) initiated rivaroxaban. Formal regression analysis comparing annual OAC initiation rates to that in 2007 indicated that the overall annual rates of any OAC initiation did not significantly differ until 2014 but thereafter were found to increase monotonically each year and statistically significantly, reaching an RR of OAC initiation of 1.66 (95% confidence interval [CI], 1.55-1.79) in 2020 (Table 2). Multivariable adjustment for sociodemographic characteristics and dialysis vintage (RR, 1.61; 95% CI,

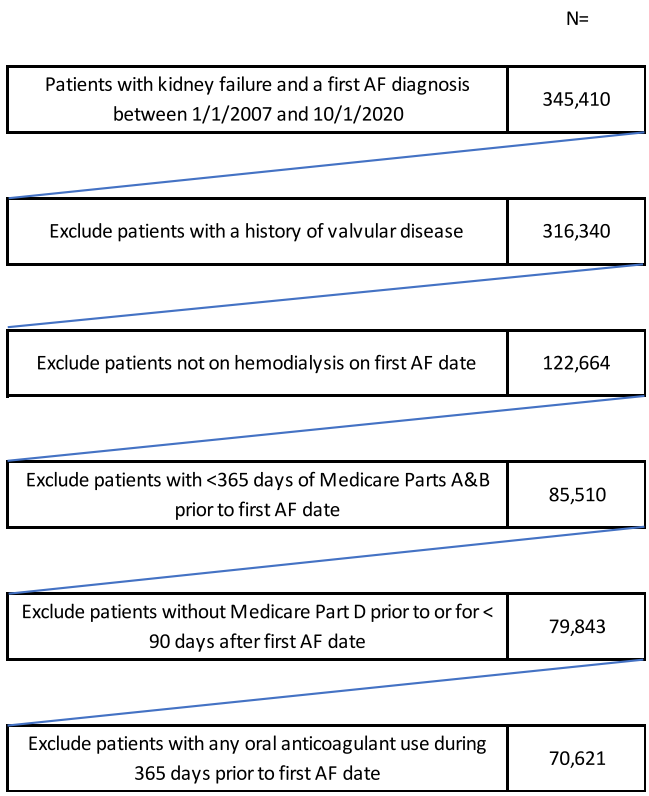

Figure 1. Flow chart of cohort assembly (patient counts). AF, atrial fibrillation.

Table 1. Characteristics of Patients With Newly Diagnosed Non-Valvular Atrial Fibrillation, by Era

	Overall (N = 82,389)	2007-2011 (N = 26,442)	2012-2016 (N = 32,603)	2017-2020 (N = 23,344)
Age on index date (y)	67.5 (58.1, 75.8)	67.4 (57.4, 76.1)	67.4 (58.0, 75.8)	67.7 (58.8, 75.7)
Female sex	38,467 (46.7%)	13,126 (49.6%)	15,015 (46.1%)	10,326 (44.2%)
Race/ethnicity				
Non-Hispanic White	37,474 (45.5%)	11,853 (44.8%)	14,656 (45.0%)	10,965 (47.0%)
Hispanic White	11,623 (14.1%)	3,691 (14.0%)	4,629 (14.2%)	3,303 (14.1%)
Black	27,905 (33.9%)	9,257 (35.0%)	11,226 (34.4%)	7,422 (31.8%)
Asian	3,321 (4.0%)	973 (3.7%)	1301 (4.0%)	1,047 (4.5%)
Other	2,066 (2.5%)	668 (2.5%)	791 (2.4%)	607 (2.6%)
Dialysis vintage (y)	3.7 (1.7, 6.6)	3.3 (1.5, 6.0)	3.8 (1.8, 6.7)	4.0 (1.9, 7.1)
Low income subsidy, %	57,277 (69.5%)	19,464 (73.6%)	22,408 (68.7%)	15,405 (66.0%)
Comorbid conditions				
Hypertension	81,075 (98.4%)	25,915 (98.0%)	32,094 (98.4%)	23,066 (98.8%)
Diabetes	58,881 (71.5%)	18,069 (68.3%)	23,492 (72.1%)	17,320 (74.2%)
Heart failure	50,327 (61.1%)	16,776 (63.4%)	19,687 (60.4%)	13,864 (59.4%)
Coronary artery disease	47,585 (57.8%)	15,782 (59.7%)	18,818 (57.7%)	12,985 (55.6%)
Peripheral vascular disease	34,782 (42.2%)	11,239 (42.5%)	13,760 (42.2%)	9,783 (41.9%)
Chronic lung disease	30,415 (36.9%)	9,825 (37.2%)	12,199 (37.4%)	8,391 (35.9%)
Cerebrovascular disease	22,895 (27.8%)	7,134 (27.0%)	9,200 (28.2%)	6,561 (28.1%)
Malignancy	10,517 (12.8%)	3,059 (11.6%)	4,198 (12.9%)	3,260 (14.0%)
Drug/alcohol use disorder	6,028 (7.3%)	1,570 (5.9%)	2,584 (7.9%)	1,874 (8.0%)
$CHADS_2$ score	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)	2.0 (2.0, 3.0)
$CHADS_2$ score ≥2	70,644 (85.7%)	23,718 (89.7%)	28,904 (88.7%)	18,022 (77.2%)
CHA_2DS_2-VASc score	5.0 (4.0, 6.0)	5.0 (4.0, 6.0)	5.0 (4.0, 6.0)	5.0 (4.0, 6.0)
CHA_2DS_2-VASc score ≥2	79,608 (96.6%)	25,453 (96.3%)	31,512 (96.7%)	22,643 (97.0%)

Note: Median (25^{th}, 75^{th} quartile) for continuous variables, count (percentage) for all other variables.

1.50-1.73) and, additionally, comorbid conditions (RR, 1.62; 95% CI, 1.51-1.74) did not materially change this observation. This development was mirrored by declining rates of warfarin initiation around the same time, which reached an adjusted RR of 0.31 (95% CI, 0.27-0.35) in 2020 relative to 2007 (Table S1).

Initiation of OAC during the entire observation period differed across racial and ethnic groups (Fig 3). After adjustment for patient sociodemographic characteristics and comorbid conditions, the rates of OAC initiation were 15% (95% CI, 12%-17%) lower among Black patients, 29% (95% CI, 24%-34%) lower among Asian patients, and 22% (95% CI, 19%-25%) lower among Hispanic White patients compared with non-Hispanic White patients (Table 2).

When comparing the characteristics of patients who initiated anticoagulation using a DOAC versus warfarin during 2017-2020, we identified few independent correlates (Table 3). More recent year of initiation was strongly associated with increased risks of OAC initiation using a DOAC. Age had a small inverse U-shaped relation with choice of OAC type wherein patients aged 50-59 (RR, 0.93; 95% CI, 0.87-1.00) had lower risks of initiating with a DOAC compared with those aged <50 years. Female patients (RR, 1.05; 95% CI, 1.01-1.09) had slightly higher risk of DOAC versus warfarin initiation compared with males. Black race (RR, 1.09; 95% CI, 1.04-1.13), Hispanic White race/ethnicity (RR, 1.13; 95% CI, 1.07-1.19), and Asian race patients (RR, 1.10; 95% CI, 1.01-1.19) had significantly higher risks of DOAC versus warfarin initiation compared with non-Hispanic White patients. None of the recorded comorbid conditions were associated with choice of OAC type. Overall, the concordance (*c*-) statistic of a corresponding logistic regression model including all available demographic and comorbidity information (but not calendar year) was 0.57 (95% CI, 0.56-0.59; model 1 in Table 3).

When formally testing for interaction between year of newly-diagnosed AF and racial/ethnic group on the risks of OAC initiation, however, no heterogeneity across the years for racial and ethnic groups was found ($P = 0.75$).

These findings were robust and nearly unchanged when restricting the study population to the 70,644 (85.7%) of patients who had a $CHADS_2$-score of ≥2 (Tables S2-S5; Figs S1-S2).

DISCUSSION

In a nationwide study of HD patients newly diagnosed with AF between 2007 and 2020, we confirmed that overall 90-day initiation of OAC was low but that a slight but meaningful uptick in new OAC prescriptions occurred in recent years. The increased use of OAC starting in 2014 coincided generally with the availability of DOACs and, specifically, a dosing recommendation for apixaban in "end-stage renal disease patients maintained with dialysis"

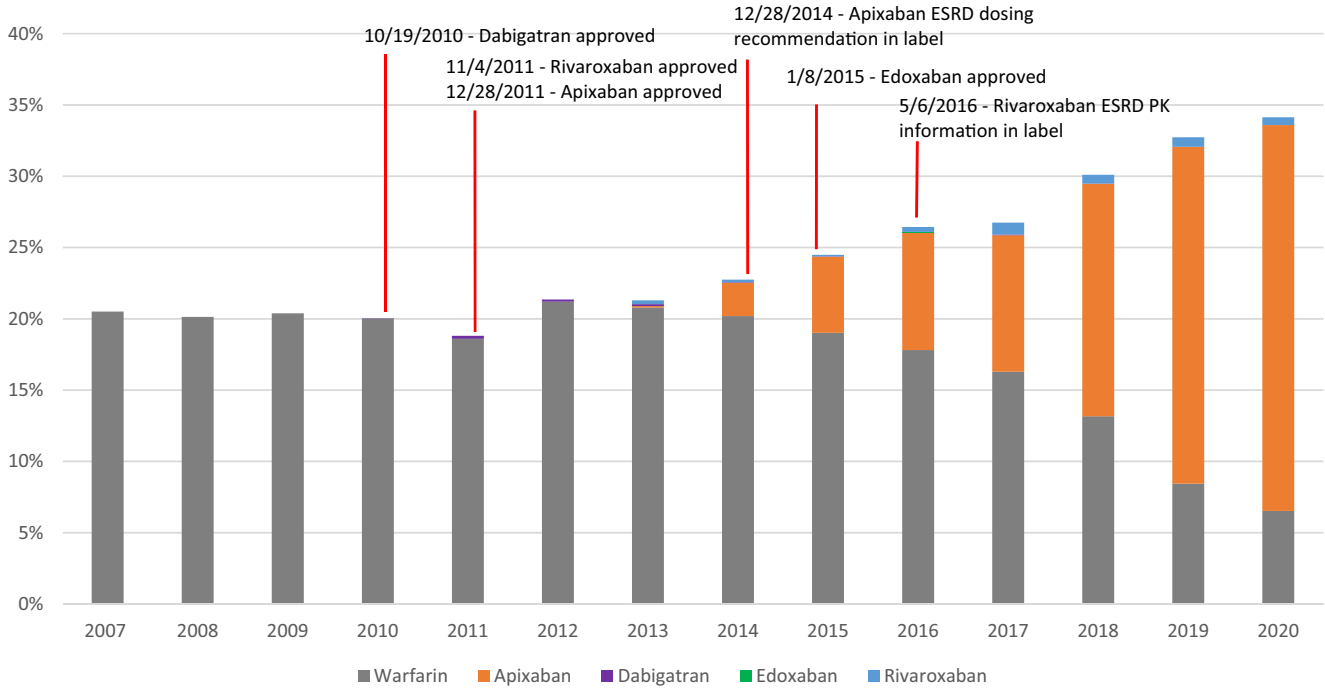

Figure 2. Trends in the initiation of oral anticoagulants within 90 days from newly diagnosed atrial fibrillation in persons with kidney failure on hemodialysis, 2007-2018. ESRD, end-stage renal disease (terminology used in product label; corresponds to patient-centric terminology of kidney failure on hemodialysis used in this report); PK, pharmacokinetic.

in its January 2014 revision to the label.[17] Since then, apixaban appears to have both replaced some use of warfarin as well as expanded overall OAC use by over 60% compared with historic levels, although the proportion of patients starting OAC following a new diagnosis of AF in 2020 remained low at 34%. Unfortunately, while we found that racial minorities were more likely than non-Hispanic White patients to be prescribed a DOAC over warfarin between 2017 and 2020, the racial disparities previously documented in the warfarin era remained unaffected by the introduction of these new therapeutic options.[14] Other than demographic characteristics, such as age, sex, and racial/ethnic group, comorbid conditions were not associated with the choice of OAC, and the overall *c*-statistic from the model was 0.57, close to the fair flip of a coin ($c = 0.5$), thus indicating that factors other than patient characteristics, eg, physician biases or patient preferences, may drive the choice between warfarin and DOAC initiation.

AF is exceedingly common in patients with KF_{HD}; however, it is unclear whether there is a net benefit in this population associated with anticoagulation. A recent study using implanted loop recorders to study the arrhythmia burden in patients on HD showed that more than one-third of these patients had episodes of AF that exceeded 6 minutes in duration.[23] Even when using less sensitive tests, such as a routine electrocardiograms, more than one-quarter of patients with KF_{HD} were found to have AF.[5] Thus, clinicians are challenged by what to do with this information.

One important consideration when diagnosing a patient on HD with AF is whether to initiate OAC to reduce the risk of ischemic stroke in these patients. However, the evidence supporting an OAC strategy in these patients is weak. Whereas in the general population the evidence is clear that suitable patients at sufficient risk for ischemic stroke, as indicated by stroke risk scores ($CHADS_2$ or CHA_2DS_2-VASc), should undergo OAC,[9,11] it is not clear that there is a net benefit of OAC in persons with kidney failure, who were excluded from pivotal trials of vitamin K antagonists or DOACs. Concerns are rooted in the high prevalence of bleeding events and that the net benefit may be diminished in these patients or OAC may not be favorable overall. As a result, the use of OAC in persons with KF_{HD} who develop AF has been shown to be low. It was 11% in older HD patients with newly-diagnosed AF in New Jersey and Pennsylvania (1994-2006)[24] and 15% in older US patients initiating dialysis and with new AF diagnoses between 2007-2011.[25] These 2 studies differed from the present one in that the window of ascertainment for warfarin initiation was 30 days rather than 90 days from first AF diagnosis, which may explain the lower proportion of OAC initiation observed. In a Canadian provincial system, with universal health care and prescription drug coverage for older adults, the warfarin initiation rate was substantially higher, at 46%, although it appears that persons undergoing peritoneal dialysis and, perhaps, patients with acute kidney injury requiring dialysis may have been included in that study.[26]

Table 2. Annual Relative Rates of Oral Anticoagulant Initiation Among Patients on Hemodialysis With Newly Diagnosed Atrial Fibrillation, 2007 (Referent) to 2020

	Model 1	Model 2	Model 3
Calendar year			
2007	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)
2008	0.98 (0.91-1.06)	0.97 (0.90-1.05)	0.97 (0.90-1.05)
2009	0.99 (0.92-1.08)	0.98 (0.91-1.06)	0.98 (0.91-1.06)
2010	0.98 (0.90-1.06)	0.96 (0.89-1.04)	0.97 (0.90-1.05)
2011	0.92 (0.85-0.99)	0.91 (0.84-0.98)	0.92 (0.85-0.99)
2012	1.04 (0.97-1.12)	1.03 (0.95-1.11)	1.02 (0.95-1.10)
2013	1.04 (0.96-1.12)	1.02 (0.95-1.10)	1.03 (0.96-1.11)
2014	1.11 (1.03-1.19)	1.08 (1.01-1.16)	1.10 (1.03-1.19)
2015	1.19 (1.11-1.28)	1.16 (1.08-1.25)	1.18 (1.10-1.27)
2016	1.29 (1.20-1.38)	1.25 (1.16-1.34)	1.27 (1.18-1.36)
2017	1.30 (1.22-1.40)	1.26 (1.18-1.36)	1.28 (1.19-1.37)
2018	1.47 (1.37-1.57)	1.42 (1.33-1.52)	1.44 (1.34-1.54)
2019	1.60 (1.49-1.71)	1.54 (1.44-1.65)	1.56 (1.46-1.67)
2020	1.66 (1.55-1.79)	1.61 (1.50-1.73)	1.62 (1.51-1.74)
Age on index date (y)			
<50		1.0 (Referent)	1.0 (Referent)
50-59		1.16 (1.11-1.22)	1.20 (1.14-1.26)
60-69		1.19 (1.13-1.24)	1.24 (1.18-1.30)
70-79		1.17 (1.11-1.23)	1.22 (1.16-1.28)
80 or older		0.97 (0.92-1.02)	1.00 (0.95-1.06)
Female sex		0.97 (0.95-0.99)	0.96 (0.94-0.98)
Race/ethnicity			
Non-Hispanic White		1.0 (Referent)	1.0 (Referent)
Hispanic White		0.79 (0.76-0.82)	0.78 (0.75-0.81)
Black		0.85 (0.83-0.88)	0.85 (0.83-0.88)
Asian		0.75 (0.70-0.80)	0.71 (0.66-0.76)
Other		0.80 (0.73-0.87)	0.79 (0.72-0.86)
Dialysis vintage (y)			
<1		1.0 (Referent)	1.0 (Referent)
1 to <3		0.99 (0.95-1.03)	0.97 (0.93-1.00)
3 to <5		1.00 (0.96-1.04)	0.97 (0.93-1.01)
≥5		1.03 (0.99-1.07)	0.98 (0.95-1.02)
Low income subsidy, %		0.88 (0.86-0.91)	0.91 (0.88-0.93)
Comorbid conditions			
Hypertension			0.97 (0.89-1.06)
Diabetes			1.00 (0.98-1.03)
Heart failure			0.96 (0.93-0.99)
Coronary artery disease			0.92 (0.90-0.95)
Peripheral vascular disease			0.90 (0.87-0.92)
Chronic lung disease			0.93 (0.91-0.96)
Cerebrovascular disease			0.88 (0.85-0.90)
Malignancy			0.92 (0.88-0.95)
Drug/alcohol use disorder			0.75 (0.71-0.79)

Another reason for historically low OAC initiation rates in patients with KF_{HD} may have been the concern of accelerated vascular calcification arising from vitamin K deficiency or therapeutic antagonism.[27] This consideration is particularly relevant in the setting of HD, where calcification is a hallmark feature of the near-ubiquitous kidney failure complication, secondary hyperparathyroidism, and where vitamin K levels are low even absent vitamin K antagonist treatment. Hence, the introduction of OAC agents that do not act on the vitamin K axis, but more specifically target individual coagulation cascade components, such as factor II (thrombin) or factor Xa, would provide a welcome addition to the therapeutic toolbox in patients with advanced kidney disease or kidney failure. Unfortunately, patients with kidney failure, including those on dialysis, were systematically excluded from the pivotal trials that compared DOACs to warfarin. Furthermore, post-marketing trials that specifically focused on the

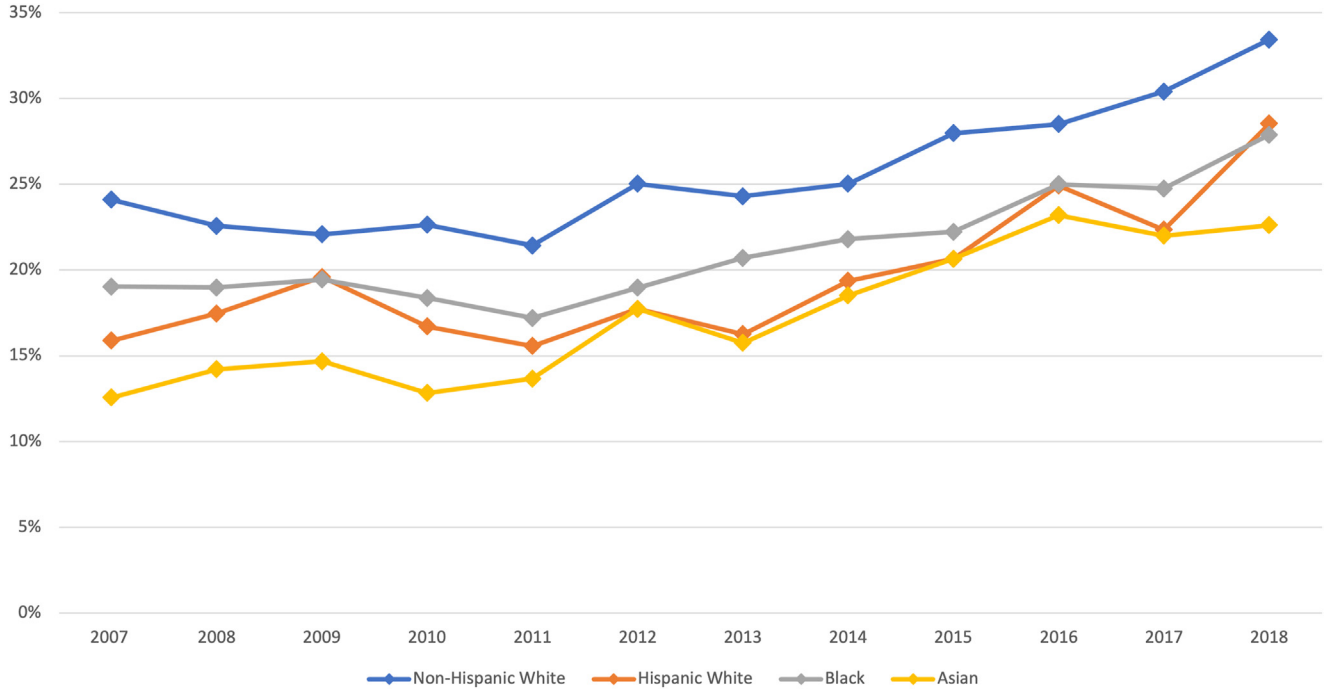

Figure 3. Trends by racial and ethnic group in the initiation of oral anticoagulation within 90 days from newly diagnosed atrial fibrillation in persons with kidney failure on hemodialysis, 2007-2020.

HD population, such as the US-based Renal Hemodialysis Patients Allocated Apixaban Versus Warfarin in Atrial Fibrillation (RENAL-AF; NCT02942407) trial or the German A Safety Study Assessing Oral Anticoagulation With Apixaban Versus Vitamin-K Antagonists in Patients With Atrial Fibrillation and End-Stage Kidney Disease on Chronic Hemodialysis Treatment (AXADIA; NCT02933697) enrolled poorly and did not provide conclusive evidence informing practice.[28,29] However, some observational, non-experimental findings from the early years of DOAC availability in the US HD population provide some reason for optimism. When comparing new users of apixaban with new users of warfarin, the rates of hemorrhagic outcomes were lower in patients initiating apixaban.[30] While the time to stroke or thromboembolic event or death was similar between the groups overall, persons who used the full 5 mg twice daily dose did have reduced rates of a thromboembolic event or mortality compared with those initiating OAC using warfarin.[30] However, the relevant question on whether OAC, using warfarin or DOAC, improves outcomes compared to a strategy of no OAC, remains uncertain, with 2 well-designed observational studies failing to demonstrate benefit from warfarin and from apixaban initiation, respectively, compared with no OAC initiation in persons with KF_{HD} with new AF.[25,31] The expert panel of the 2019 AHA/ACC/HRS guideline update on the management of AF issued the following modified statement, "[…] it might be reasonable to prescribe warfarin (INR 2.0 to 3.0) or apixaban for oral anticoagulation […]."[9] The impact of this revised guideline on OAC or, specifically, apixaban uptake cannot be identified in the present study, which ended follow-up just a year after this guideline update was published.

Racial and ethnic differences in OAC use in patients with AF on hemodialysis have been reported from an earlier era, 2006-2013. Compared with non-Hispanic White patients, Black, Hispanic, and Asian patients had lower hazards by 10%, 17%, and 28%, respectively, for the time to fill a warfarin prescription in the year following a second AF diagnosis.[14] In the general population-based Get With The Guidelines-Atrial Fibrillation Registry (2014-2020), 81.1% of patients hospitalized with AF were prescribed an OAC at discharge; 74.1% of those received a DOAC. Black patients were 25% less likely to be prescribed an OAC at discharge compared with White patients, whereas there were no significant differences for Hispanic and Asian patients. These Black versus White race disparities were more pronounced for DOAC prescription (−27%) than for warfarin prescription (−16%).[32] The root causes of these differences in treatment behavior, both in patients on dialysis and the more general population with AF, are poorly understood and warrant more detailed investigation, including qualitative studies of diverse patients and their potential prescribers. Overattribution of (bleeding) risk in minority patients with adverse clinical and socioeconomic factors may play a role; by contrast, Black and Hispanic patients have higher rates of stroke and other thromboembolic events and hence have the potential

Table 3. Risk Ratios of Oral Anticoagulant Choice, Direct-Target Oral Anticoagulant Versus Warfarin, Among Patients on Hemodialysis With Newly Diagnosed Atrial Fibrillation, 2017-2020

	Unadjusted Models	Model 1	Model 2
Calendar year			
2017	1.0 (Referent)		1.0 (Referent)
2018	1.44 (1.34-1.54)		1.44 (1.34-1.54)
2019	1.90 (1.78-2.03)		1.90 (1.78-2.02)
2020	2.07 (1.94-2.21)		2.07 (1.94-2.21)
Age on index date (y)			
<50	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)
50-59	0.91 (0.85-0.98)	0.91 (0.85-0.98)	0.93 (0.87-1.00)
60-69	0.91 (0.85-0.97)	0.93 (0.87-1.00)	0.95 (0.89-1.01)
70-79	0.93 (0.87-0.99)	0.99 (0.92-1.06)	1.00 (0.93-1.07)
80 or older	1.01 (0.94-1.09)	1.08 (1.00-1.17)	1.08 (1.00-1.16)
Female sex	1.07 (1.03-1.11)	1.04 (1.00-1.09)	1.05 (1.01-1.09)
Race/ethnicity			
Non-Hispanic White	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)
Hispanic White	1.16 (1.10-1.22)	1.13 (1.07-1.19)	1.13 (1.07-1.19)
Black	1.11 (1.07-1.16)	1.09 (1.04-1.14)	1.09 (1.04-1.13)
Asian	1.17 (1.08-1.27)	1.12 (1.03-1.22)	1.10 (1.01-1.19)
Other	1.00 (0.88-1.14)	0.98 (0.86-1.12)	0.98 (0.86-1.11)
Dialysis vintage (y)			
<1	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)
1 to <3	1.06 (1.00-1.13)	1.05 (0.98-1.11)	1.04 (0.98-1.10)
3 to <5	1.10 (1.03-1.17)	1.07 (1.00-1.14)	1.06 (1.00-1.13)
≥5	1.07 (1.01-1.14)	1.03 (0.97-1.10)	1.03 (0.97-1.09)
Low income subsidy, %	1.12 (1.08-1.16)	1.11 (1.06-1.16)	1.11 (1.07-1.16)
Comorbid conditions			
Hypertension	1.03 (0.88-1.21)	1.03 (0.88-1.21)	0.99 (0.86-1.15)
Diabetes	1.00 (0.96-1.04)	0.99 (0.95-1.03)	0.98 (0.94-1.02)
Heart failure	1.00 (0.96-1.04)	1.00 (0.96-1.04)	0.99 (0.96-1.03)
Coronary artery disease	0.97 (0.93-1.00)	0.98 (0.94-1.02)	0.99 (0.95-1.03)
Peripheral vascular disease	0.98 (0.94-1.01)	0.98 (0.94-1.02)	1.00 (0.96-1.03)
Chronic lung disease	0.99 (0.96-1.03)	1.01 (0.97-1.05)	1.01 (0.97-1.05)
Cerebrovascular disease	1.02 (0.98-1.06)	1.02 (0.98-1.06)	1.02 (0.98-1.06)
Malignancy	0.98 (0.93-1.03)	0.99 (0.94-1.05)	0.99 (0.94-1.04)
Drug/alcohol use disorder	0.96 (0.89-1.04)	0.96 (0.89-1.04)	0.96 (0.89-1.03)

Note: Unadjusted means that each characteristic (continuous, dichotomous, or categorical) was modeled separately. Models 1 and 2 include the variables in their respective column. When fitting identical logistic regression models to assess model discrimination, the *c* statistic for Model 1 was 0.57 (95% CI, 0.56-0.59) and for Model 2 was 0.71 (95% CI, 0.69-0.72).
Abbreviations: CI, confidence interval.

to derive greater benefit from OAC treatment. Difference in insurance status should not play a role in the population we have studied because all patients were required to have Medicare Part D prescription drug coverage.

Certain limitations of this study need to be considered. We restricted this analysis to patients with KF_{HD}. Patients undergoing peritoneal dialysis have different risks for developing AF[33] and may have a different benefit–risk profile, thus warranting separate study. We cannot be certain that OAC was initiated for AF versus a different indication. However, by anchoring the OAC ascertainment at a new AF diagnosis and limiting the window to the subsequent 90 days, we attempted to maximize the likelihood that OAC was for stroke prevention after AF (temporality criterion). Although we aimed to identify racial differences in OAC use, and any difference over time, we did not design this study to explain which factors may potentially contribute to these disparities. Thus, we did not include any potential patient- or community-level mediators of these racial differences in our models. Providing insights into the latter would require a different study approach, including qualitative studies of patients and potential OAC prescribers.

In conclusion, starting from historically very low rates of OAC initiation in persons with KF_{HD} with newly diagnosed AF, there was a meaningful uptick in recent years, mostly driven by increased use of apixaban. However, only one-third of patients with newly diagnosed AF and a qualifying $CHADS_2$ score were initiated on OAC as recently as 2020. Even lower rates of OAC initiation in minority groups, relative to non-Hispanic White patients, were

unaffected by the new therapeutic option offered by DOACs, and these disparities previously described during the warfarin years persisted into the most recent years of observation. Further evidence informing the safety and efficacy of OAC, in particular DOACs, in persons with KF_{HD} is warranted as is investigation on the underlying causes giving rise to ongoing racial disparities in OAC initiation.

SUPPLEMENTARY MATERIALS

Supplementary File (PDF)

Figure S1. Trends in the Initiation of Oral Anticoagulants Within 90 Days From Newly Diagnosed Atrial Fibrillation Among Patients on Hemodialysis and $CHADS_2$ Score ≥2, 2007-2020.

Figure S2. Trends by Racial and Ethnic Group in the Initiation of Oral Anticoagulation Within 90 Days From Newly Diagnosed Atrial Fibrillation Among Patients on Hemodialysis and $CHADS_2$ Score ≥2, 2007-2020.

Table S1. Risk Ratios of Warfarin Initiation Among Patients on Hemodialysis With Newly Diagnosed Atrial Fibrillation, 2007 (Referent) to 2020.

Table S2. Characteristics of Patients With Newly Diagnosed Non-Valvular Atrial Fibrillation and $CHADS_2$ Score ≥2, by Era.

Table S3. Risk Ratios of Oral Anticoagulant Initiation Among Patients on Hemodialysis With Newly Diagnosed Atrial Fibrillation and $CHADS_2$ Score ≥2, 2007 (Referent) to 2020.

Table S4. Risk Ratios of Oral Anticoagulant Choice, Direct-Target Oral Anticoagulant Versus Warfarin, Among Patients on Hemodialysis With Newly Diagnosed Atrial Fibrillation and $CHADS_2$ Score ≥2, 2017-2020.

Table S5. Risk Ratios of Warfarin Initiation Among Patients on Hemodialysis With Newly Diagnosed Atrial Fibrillation and $CHADS_2$ Score ≥2, 2007 (Referent) to 2020.

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