

# Racial/Ethnic Disparities in Atrial Fibrillation Treatment and Outcomes among Dialysis Patients in the United States

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## ABSTRACT

**Background** Because stroke prevention is a major goal in the management of ESKD hemodialysis patients with atrial fibrillation, investigating racial/ethnic disparities in stroke among such patients is important to those who could benefit from strategies to maximize preventive measures.

**Methods** We used the United States Renal Data System to identify ESKD patients who initiated hemodialysis from 2006 to 2013 and then identified those with a subsequent atrial fibrillation diagnosis and Medicare Part A/B/D. Patients were followed for 1 year for all-cause stroke, mortality, prescription medications, and cardiovascular disease procedures. The survival mediational g-formula quantified the percentage of excess strokes attributable to lower use of atrial fibrillation treatments by race/ethnicity.

**Results** The study included 56,587 ESKD hemodialysis patients with atrial fibrillation. Black, white, Hispanic, and Asian patients accounted for 19%, 69%, 8%, and 3% of the population, respectively. Compared with white patients, black, Hispanic, or Asian patients were more likely to experience stroke (13%, 15%, and 16%, respectively) but less likely to fill a warfarin prescription (10%, 17%, and 28%, respectively). Warfarin prescription was associated with decreased stroke rates. Analyses suggested that equalizing the warfarin distribution to that in the white population would prevent 7%, 10%, and 12% of excess strokes among black, Hispanic, and Asian patients, respectively. We found no racial/ethnic disparities in all-cause mortality or use of cardiovascular disease procedures.

**Conclusions** Racial/ethnic disparities in all-cause stroke among hemodialysis patients with atrial fibrillation are partially mediated by lower use of anticoagulants among black, Hispanic, and Asian patients. The reasons for these disparities are unknown, but strategies to maximize stroke prevention in minority hemodialysis populations should be further investigated.

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Atrial fibrillation (AF) is the most common sustained arrhythmia observed in clinical practice.<sup>1</sup> The number of AF cases in the United States, estimated as approximately 6 million, is expected to double in the next decade, as the population ages and experiences higher rates of obesity, hypertension, coronary artery disease, and heart failure.<sup>2–5</sup> AF is associated with increased morbidity, especially related to stroke and mortality.<sup>6,7</sup> The risk

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of stroke, estimated using the congestive heart failure, hypertension, age, diabetes, previous stroke, Vascular disease, age, and sex category score (CHA<sub>2</sub>DS<sub>2</sub>-VASc) score,<sup>8</sup> can be dramatically reduced with the use of systemic anticoagulation.<sup>9–11</sup>

Patients with ESKD treated with hemodialysis (HD) are one of the few groups in which minority patients have better survival than white patients.<sup>12–14</sup> The reasons underlying this finding are unknown, but have been the subject of investigation for three decades.<sup>12,15,16</sup> Patients with ESKD are particularly prone to developing AF. The prevalence of AF in the ESKD population has increased over time (from 6% in 1996 to 17% in 2006).<sup>17</sup> The risk of stroke among patients initiating dialysis is approximately 6–10 times higher than in the general population, making prevention of stroke an important priority in the management of patients with ESKD and AF,<sup>18</sup> particularly considering the threat to quality of life that stroke entails.<sup>19,20</sup>

Several studies in the general AF population have evaluated barriers to stroke prevention and have observed higher stroke rates among minority racial/ethnic groups.<sup>21,22</sup> In the Medicare population, for example, blacks and Hispanics compared with whites had a higher hazard of stroke after being diagnosed with AF.<sup>21</sup> Similar racial/ethnic disparities in stroke rates have also been reported in patients with ESKD and AF.<sup>23</sup>

The potential causes of these racial/ethnic disparities in AF in patients with ESKD are multifactorial.<sup>24</sup> Poor access to care and reduced treatment with optimal medications are underlying reasons for suboptimal outcomes in racial/ethnic minority groups.<sup>25–27</sup> Reduced likelihood of treatment with anticoagulants among racial/ethnic minorities may contribute to their higher stroke and mortality rates.<sup>28,29</sup> Although studies evaluating the efficacy of oral anticoagulation in patients with ESKD and AF have shown mixed results,<sup>30,31</sup> interdisciplinary guidelines support use of oral anticoagulants in this population.<sup>32</sup> To our knowledge, no study has quantified the extent to which differential treatments contribute to racial/ethnic disparities in stroke outcomes among patients on dialysis with AF.

Elucidating the causes of racial/ethnic disparities, in particular those that are directly modifiable by physicians, remains a priority for the United States health care system. We used a causal inference mediation approach to measure racial/ethnic disparities in AF treatment and outcomes in a national ESKD registry.

## METHODS

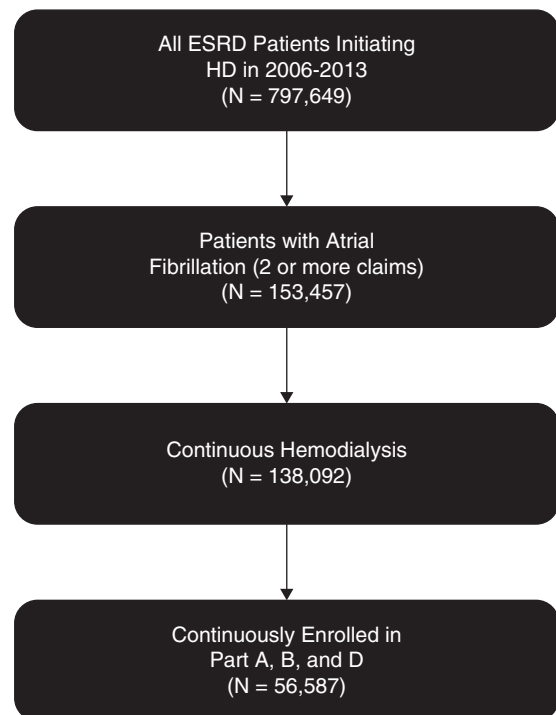
### Study Population

We conducted a retrospective cohort study using the United States Renal Data System (USRDS), including all patients who initiated HD as first ESKD modality between January 1, 2006 and December 31, 2013. We identified patients with a subsequent diagnosis of permanent, persistent, or recurrent paroxysmal AF using Medicare claims data. As previously,<sup>17,33</sup> AF was defined as having two diagnoses with International

### Significance Statement

Reduced likelihood of anticoagulant use among patients on hemodialysis with ESKD and atrial fibrillation may contribute to higher stroke rates, especially among racial/ethnic minority patients. In a retrospective cohort study, the authors identified patients with ESKD who initiated hemodialysis, determined which patients subsequently developed atrial fibrillation, and followed them for 1 year for all-cause stroke and other outcomes. Compared with white patients, racial/ethnic minority patients were more likely to experience stroke but less likely to fill a warfarin prescription. Additional analysis suggested that achieving warfarin distribution equal to that for white patients would prevent 7%, 10%, and 12% of excess strokes among black, Hispanic, and Asian patients, respectively. Identifying and addressing barriers to maximizing appropriate anticoagulation treatment may help reduce disparities in stroke among patients on hemodialysis with atrial fibrillation.

Classification of Disease–Ninth Revision–Clinical Modification codes for AF (427.3, 427.3x, where x can be any number), separated by  $\geq 14$  days but  $\leq 365$  days. This algorithm has been shown to have a positive predictive value of 96%.<sup>33</sup> We excluded patients who had a dialysis treatment modality switch; were transplanted; had interrupted Medicare Part A, B, or D coverage as primary payer between the date of HD initialization and the date of the second AF claim; or had missing sex or race/ethnicity data. Figure 1 presents a step-by-step diagram showing how the cohort was identified. Figure 2 presents a timeline depicting the temporality of dialysis initiation, AF confirmation, baseline variables, and measurement of mediators and outcomes.



**Figure 1.** Flow diagram showing exclusion criteria and cohort selection.

Study objectives were to: (1) analyze racial/ethnic disparities in 1-year all-cause stroke and mortality rates; (2) identify racial/ethnic disparities in AF treatment with prescription of medications and cardiovascular disease (CVD) procedures; (3) estimate the association of prescription of medications, CVD procedures with 1-year hazard of all-cause stroke and mortality; and (4) quantify the extent to which racial/ethnic disparities in 1-year all-cause stroke/mortality rates would be reduced if racial/ethnic disparities in beneficial treatments were eliminated.

## Measures

The exposure was race/ethnicity (black, Hispanic white, Asian, non-Hispanic white, other). We created the “other” race/ethnicity category from the following categories with small sample sizes: “American Indian/Alaskan Native” and “other/multiracial.” The date of the second AF diagnosis was used as the index date for AF diagnosis/confirmation. The primary outcome of interest was all-cause stroke during the 12 months after the index date (Supplemental Appendix A). Secondary outcomes included death, ischemic stroke, hemorrhagic stroke, gastrointestinal (GI) bleeding, and calciphylaxis during the 12 months after the index date.

The potential mediator(s) we considered were treatments received after the index date. Part D claims identified filled prescriptions of medications during the 12 months after the index date. Medications (Supplemental Appendix B) were those in the American Hospital Formulary Service classes of “Anticoagulants,” “Antiarrhythmics,” “Beta-Adrenergic Blocking Agents,” “Calcium Channel Blocking Agents,” “Coumadin Derivatives,” “Cardiotonic Agents,” “Platelet Aggregation Inhibitors,” “Direct Factor XA Inhibitors,” “Direct Thrombin Inhibitors,” and “Class III Antiarrhythmics.” Because some patients received medications before the index date, we created separate “baseline” dichotomous variables for each medication that indicated whether patients had filled a prescription between HD initiation and the index date.

We identified CVD procedures<sup>34,35</sup> during the 12 months after the index date using Healthcare Common Procedure

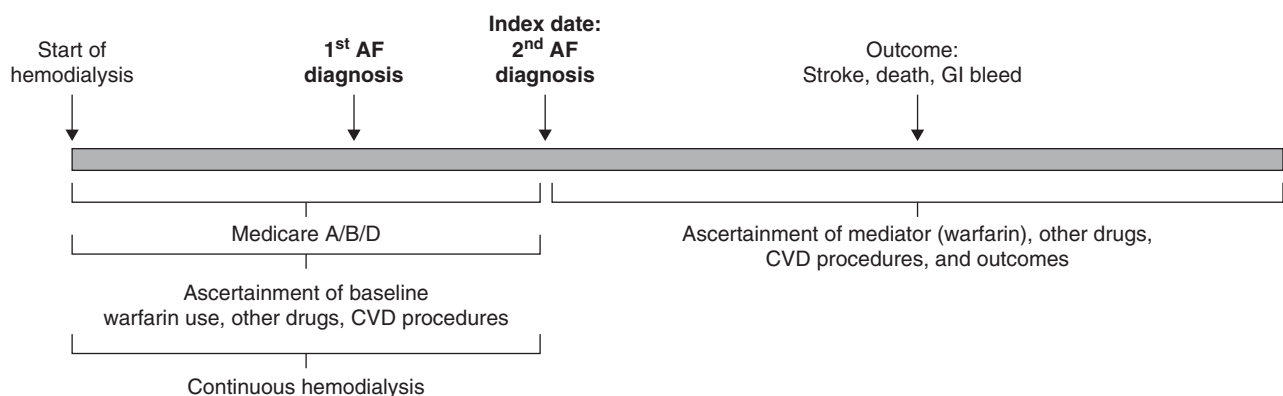
Coding System codes. We identified intracardiac catheter ablation,<sup>36</sup> electrical cardioversion,<sup>37</sup> surgical maze procedure,<sup>37</sup> placement of ambulatory event monitors,<sup>38</sup> and placement of implantable cardioverter-defibrillators (Supplemental Appendix C). We also created separate “baseline” dichotomous variables for each procedure.

Static covariates included sex, age, residential area, vintage, and household median income, assessed using ZIP-code level data from the US Census, as previously described.<sup>39</sup> Time-varying covariates included the CHA<sub>2</sub>DS<sub>2</sub>-VASc score,<sup>8,32</sup> Medicare dual eligibility, and comorbidities. The CHA<sub>2</sub>DS<sub>2</sub>-VASc score includes hypertension, heart failure, diabetes, vascular disease, sex, age, and history of stroke (between HD initiation and the index date). Studies among the general ESKD population have reported that the CHA<sub>2</sub>DS<sub>2</sub>-VASc score is useful in predicting ischemic stroke in patients with AF and ESKD undergoing dialysis, and has more predictive ability than the congestive heart failure, hypertension, age, diabetes, stroke score.<sup>40,41</sup> Comorbidities at HD initiation were ascertained from the Centers for Medicare and Medicaid Services Form 2728, and were measured during follow-up ( $\geq 1$  inpatient or  $\geq 2$  outpatient diagnoses). We identified variables that occurred before the index date as “baseline” covariates and those that occurred after the index date as potential mediating covariates (Figure 2).

## Statistical Analyses

Descriptive characteristics were summarized overall and by race/ethnicity. Our primary objective was to conduct time-varying mediation analyses to estimate the extent to which differential treatments by race/ethnicity mediate (*i.e.*, explain) racial/ethnic disparities in all-cause stroke rates (primary outcome). Before conducting mediation analyses, we executed several multivariable analyses to verify that the assumptions for mediation were met.

The first assumption in order for mediation to be present is that the exposure (race/ethnicity) is associated with the outcome (1-year risk of stroke). We compared cumulative incidence rates of stroke within 1 year after the index date between



**Figure 2.** Study timeline depicting variables (including mediators and outcomes) were measured and shows the time period defined as baseline and follow-up.

ances/ethnicities using Kaplan–Meier curves in unadjusted analyses. We used Fine–Gray regression with death as a competing risk<sup>42</sup> to estimate the adjusted total effect of race/ethnicity on stroke within 1 year. Because we did not want to adjust for any mediators of race/ethnicity, we adjusted for baseline variables only (Figure 2).<sup>43,44</sup> Patients were followed from the index date for all-cause stroke and censored at 1 year after or the earliest date of death; dialysis modality switch; dialysis discontinuation; transplantation; loss of Part A, B, or D coverage; loss to follow-up; or kidney function recovery, whichever came first.

The second assumption of mediation is that the exposure (race/ethnicity) is associated with the mediator (treatments). We therefore used Kaplan–Meier curves and Fine–Gray regression with death as a competing risk to compare time to first filled prescription of medications and time to CVD procedures by race/ethnicity. Separate analyses were conducted for individual medications and CVD procedures. We adjusted for baseline variables only (Figure 2).<sup>43,44</sup> Patients were followed from the index date for the first filled prescription or CVD procedure and censored at 1 year after or the earliest date of death; dialysis modality switch; dialysis discontinuation; transplantation; stroke; loss of Part A, B, or D coverage; loss to follow-up; or kidney function recovery, whichever came first.

The third assumption is that the mediator (treatment) is associated with the outcome (all-cause stroke). We used Fine–Gray regression with death as a competing risk to estimate the adjusted association between prescription of medications and CVD procedures after the index date and 1-year hazard of stroke. Prescriptions of medications after the index date were treated as time-varying covariates, using the dates of prescription and the number of days supplied (assuming that patients took the drugs specified by the number of days supplied). CVD procedures were treated as time-varying covariates as well (set to 1 on all days after a CVD procedure). We created a dataset with one row for every person for each day of the follow-up period. Gaps between prescriptions were considered periods of not being exposed to drugs. We adjusted for all demographics, baseline medications, baseline CVD procedures, and time-varying covariates including all time-varying drugs and CVD procedures simultaneously in the same model. Follow-up time for stroke began on the index date. We censored at 1 year after or the earliest date of death; dialysis modality switch; dialysis discontinuation; transplantation; loss of Part A, B, or D coverage; loss to follow-up; or kidney function recovery, whichever came first.

After confirming that all three assumptions of mediation had been met (objectives 1–3), we conducted mediation analyses with time-varying mediators and confounders,<sup>45–47</sup> to quantify the extent to which racial/ethnic disparities in 1-year all-cause stroke rates would be reduced if racial/ethnic disparities in beneficial medications/CVD procedures were eliminated. We adjusted for all demographics, baseline medications, baseline CVD procedures, and time-varying

covariates. *A priori*, we considered the mediators to be treatments that were different among races/ethnicities (objective 2). We applied the survival mediational g-formula to conduct time-varying mediation analyses.<sup>45–47</sup>

The survival mediational g-formula was recently developed within the counterfactual framework of causal inference. It is the only method that can conduct mediation analyses for a survival outcome with time-varying mediators and confounders. It is an extension and adaptation of James Robins' g-formula,<sup>48</sup> which has been used often to estimate the causal effect of time-varying exposures in the presence of time-varying confounding.<sup>49–53</sup> The survival mediational g-formula is an appropriate method for the research design because patients initiate drugs and receive CVD procedures (the potential mediators) at different time points, and can be exposed to these treatments for various amounts of time (*i.e.*, treatments are not dichotomous yes/no variables).

As has been described, the survival mediational g-formula is a fully parametric, simulation-based algorithm.<sup>45,46</sup> It begins by partitioning the follow-up time into even, distinct time periods and specifying parametric regression models for the distribution of each time-varying mediator, confounder, and survival variable at each time point on the basis of former covariate values. Model parameters generated from these regression models are estimated using maximum likelihood and used to assign values to the mediator (counterfactual mediators) in order to generate two joint exposure-mediator hypothetical interventions employing Monte Carlo simulation. In our setting, the exposure is race/ethnicity, the mediator(s) is treatment, and the outcome is all-cause stroke. The survival mediational g-formula simulates what would have happened had all races/ethnicities received the same amount of treatment at the same time. It estimates the total effect, the interventional direct effect, and the interventional indirect effect, on both the risk difference and risk ratio scale. The interventional indirect effect represents the portion of the racial/ethnic disparity in excess strokes that would be reduced if an intervention equalized the medication/CVD procedure distributions in minority populations to the distribution in the white population.<sup>45–47</sup> The interventional direct effect is the portion of the total racial/ethnic disparity in excess strokes that would remain after the intervention equalized the treatment distributions.<sup>45–47</sup> Finally, the percentage mediated was calculated by dividing the interventional indirect effect by the interventional total effect.<sup>45–47</sup>

The survival mediational g-formula can be implemented using the mGFORMULA SAS macro, freely available for download.<sup>47</sup> We followed step-by-step instructions specified in the mGFORMULA SAS macro documentation<sup>47</sup> to conduct our analysis. First, we partitioned the follow-up period (from index date up until 1-year follow-up) into seven even time periods of 52 days each (the first two time periods are used as prebaseline periods to allow for lagged predictive models, per the suggestions of the documentation). Within each patient and time period, we estimated the total number of days

supplied for each drug (time-varying warfarin, time-varying  $\beta$ -blockers, *etc.*). We also identified all other time-varying confounders (CVD procedures, comorbidities, Medicaid dual eligibility, *etc.*) within each time period as well as an indicator of whether the patient had a stroke in that time period (stroke outcome at each time point). If a patient never experienced a stroke during follow-up, then they were assigned a 0 for all of their survival outcomes at all time points. If a patient did experience a stroke, then they were assigned a 1 at the earliest time period, and no data after were used for that individual. We specified outcome and predictor parametric models for all time-varying covariates according to their relevant functional form. Although parametric models for the baseline confounders as outcomes were not fit because they occurred before the index date, each baseline confounder was used as a predictor in all models as suggested by the mGFORMULA SAS documentation.

### Subgroup and Additional Analyses

Because novel oral anticoagulants (NOACs) were approved in 2011, we conducted a subgroup analysis among patients who were diagnosed with AF in 2011–2013 and used a combined warfarin/NOAC variable. Furthermore, we reported the unadjusted cumulative incidence rates of all-cause stroke by race/ethnicity and among minority races/ethnicities. We also reported 1-year excess stroke rates, which represent the overall racial/ethnic disparity in strokes (the unadjusted total effect). Finally, using the percentage mediated estimates, we reported the number of strokes on the rate scale that would be eliminated under the hypothetical intervention simulated with the mGFORMULA.

We used SAS version 9.4 to generate the analysis dataset. We employed the R packages *ggplot2*<sup>54</sup> and *timereg*<sup>55</sup> to generate Kaplan–Meier curves and fit Fine–Gray regression models for competing risks, respectively. We used the publicly available mGFORMULA SAS macro<sup>47</sup> to conduct separate mediation analyses for each minority race/ethnicity compared with whites.

## RESULTS

Tables 1 and 2 display descriptive characteristics of the study population, overall and by race/ethnicity. The study included 56,587 patients who met inclusion criteria. Black, white, Hispanic, Asian, and other patients accounted for 19%, 69%, 8%, 3%, and 1% of the study population, respectively. Approximately half of the patients were female. Patients aged  $\geq 65$  made up 86% of the population. The most common comorbidities in the population were hypertension (85%), diabetes (56%), congestive heart failure (51%), atherosclerotic heart disease (31%), and peripheral vascular disease (18%). The average CHA<sub>2</sub>DS<sub>2</sub>-VAsC score was  $4.1 \pm 1.4$ .

In bivariate analyses, white patients on HD were older, were less likely to be Medicaid dual eligible, and had shorter vintage than all other races/ethnicities. Blacks were more likely to be

female. The mean CHA<sub>2</sub>DS<sub>2</sub>-VAsC score did not vary by race/ethnicity.

### Primary Outcome: All-Cause Stroke

The Kaplan–Meier cumulative incidence plots show that black, Hispanic, Asian, and other patients were more likely to have a stroke within 1 year compared with white patients (log-rank  $P < 0.001$ ; Figure 3A). The cumulative incidence rates of 1-year all-cause stroke for white, black, Hispanic, Asian, and other patients were 8.4, 9.4, 9.7, 10.2, and 11.8 strokes per 100 person years, respectively. Table 3 displays hazard ratios (HRs) and 95% confidence intervals (95% CIs) for stroke by race/ethnicity. In adjusted analyses (model 2), black (HR, 1.13; 95% CI, 1.02 to 1.24), Hispanic (HR, 1.15; 95% CI, 1.01 to 1.30), and Asian (HR, 1.16; 95% CI, 1.02 to 1.35) patients had statistically significantly increased hazard of all-cause stroke compared with white patients.

Black, Asian, Hispanic, and other patients were less likely to be prescribed warfarin than white patients (Figure 3B;  $P < 0.001$ ). Asians were the most likely to be prescribed class III antiarrhythmics, blacks were the most likely to be prescribed calcium channel blockers, and whites were the most likely to be prescribed digoxin. Asian and Hispanic patients were the most likely to be prescribed platelet aggregation inhibitors.

White patients were most likely to have cardioversion (Figure 3C;  $P < 0.01$ ). Black patients were most likely to have catheter ablation. Asians were most likely to have ambulatory event monitors. Blacks and whites were the most likely to have an implantable cardioverter defibrillator. In adjusted analyses, however, the only medication or procedure that was statistically significantly different between races/ethnicities was prescription of warfarin (Table 4).

Table 5 displays the HRs and 95% CIs for stroke by medications/procedures after the index date. In the final model, adjusting for all potential confounders, prescription of warfarin (HR, 0.82; 95% CI, 0.71 to 0.94), calcium channel blockers (HR, 0.87; 95% CI, 0.77 to 0.99), beta blockers (HR, 0.78; 95% CI, 0.71 to 0.88 and class III antiarrhythmics (HR, 0.75; 95% CI, 0.69 to 0.83) after the index date were each statistically significantly associated with lower hazard of stroke. Ambulatory event monitors (HR, 0.60; 95% CI, 0.41 to 0.86) and implantable cardioverter defibrillators (HR, 0.61; 95% CI, 0.47 to 0.80) were statistically significantly associated with reduced stroke hazard.

Because the only racial/ethnic disparity in treatment was with respect to warfarin, we chose warfarin as the mediator in the effect decomposition analyses, and adjusted for all other medications and procedures as time-varying confounders. Figure 4 presents a directed acyclic graph depicting the primary causal relationships. Seven percent, 10%, and 12% of the racial/ethnic disparities in stroke were explained by racial/ethnic disparities in warfarin prescriptions among black, Hispanic, and Asian patients, respectively. This suggests that excess strokes among black, Hispanic, and Asian patients could be reduced by 7%, 10%, and 12%, respectively, if an intervention equalized

**Table 1.** Descriptive characteristics and outcomes of the incident HD population with AF, overall and by race/ethnicity, 2006–2013

Characteristic	Race/Ethnicity											
	Overall (n=56,587)		Black (n=10,561)		White (n=39,073)		Hispanic (n=4594)		Asian (n=1971)		Other (n=388)	
	N	%	N	%	N	%	N	%	N	%	N	%
Female sex	27,854	49.2	6281	59.5	18,204	46.6	2199	47.9	984	49.9	186	47.9
Age												
20–44	462	0.8	220	2.1	190	0.5	39	0.9	9	0.5	4	1.0
45–64	7559	13.4	2334	22.1	4299	11.0	703	15.3	160	8.1	63	16.2
65+	48,566	85.8	8007	75.8	34,584	88.5	3852	83.9	1802	91.4	321	82.7
Age (mean±SD)	69.3±12.2		65.4±12.3		71.5±11.6		68.2±11.7		71.5±11.8		64.0±12.5	
Residential												
Rural	11,002	19.4	1543	14.6	8848	22.6	392	8.5	53	2.7	166	42.8
Large metro	28,880	51.0	6411	60.7	17,938	45.9	2809	61.1	1594	80.9	128	33.0
Nonlarge metro	16,705	29.5	2607	24.7	12,287	31.5	1393	30.3	324	16.4	94	24.2
Household median income												
First quartile	12,543	22.2	2529	24.0	8310	21.3	1200	26.1	390	19.8	114	29.4
Second quartile	16,940	29.9	3554	33.7	11,255	28.8	1392	30.3	524	26.6	215	55.4
Third quartile	14,168	25.0	2567	24.3	9812	25.1	1215	26.5	543	27.6	31	8.0
Fourth quartile	12,936	22.9	1911	18.1	9696	24.8	787	17.1	514	26.1	28	7.2
Vintage												
1 yr	32,772	57.9	5306	50.2	24,021	61.5	2241	48.8	1013	51.4	191	49.2
2–3 yr	18,318	32.4	3701	35.0	12,107	31.0	1683	36.6	684	34.7	143	36.9
4+ yr	5497	9.7	1554	14.7	2945	7.5	670	14.6	274	13.9	54	13.9
Vintage (mean±SD)	1.8±1.4		2.0±1.5		1.7±1.3		2.1±1.7		2.0±1.8		2.0±2.1	
CHA <sub>2</sub> DS <sub>2</sub> -VASc (mean±SD)	4.1±1.4		4.1±1.3		4.1±1.4		4.1±1.4		4.2±1.4		4.2±1.6	
Medicaid dual eligible	21,485	38.0	6351	60.1	10,191	26.1	3242	70.6	1458	74.0	243	62.6
Stroke (1-yr)	3187	5.6	661	6.3	2060	5.3	294	6.4	142	7.2	30	7.7
Died (1-yr)	22,636	40.0	4153	39.3	1849	40.4	1849	40.3	710	36.0	155	40.0

All racial/ethnic comparisons were very highly statistically significant ( $P<0.001$ ) except for the CHA<sub>2</sub>DS<sub>2</sub>-VASc, for which  $P=0.81$ .

the distribution and timing of filled warfarin prescriptions among patients belonging to these racial/ethnic groups to those of white patients.

**Secondary Outcomes: Mortality, Ischemic Stroke, Hemorrhagic Stroke, Calciphylaxis, and GI Bleeding**

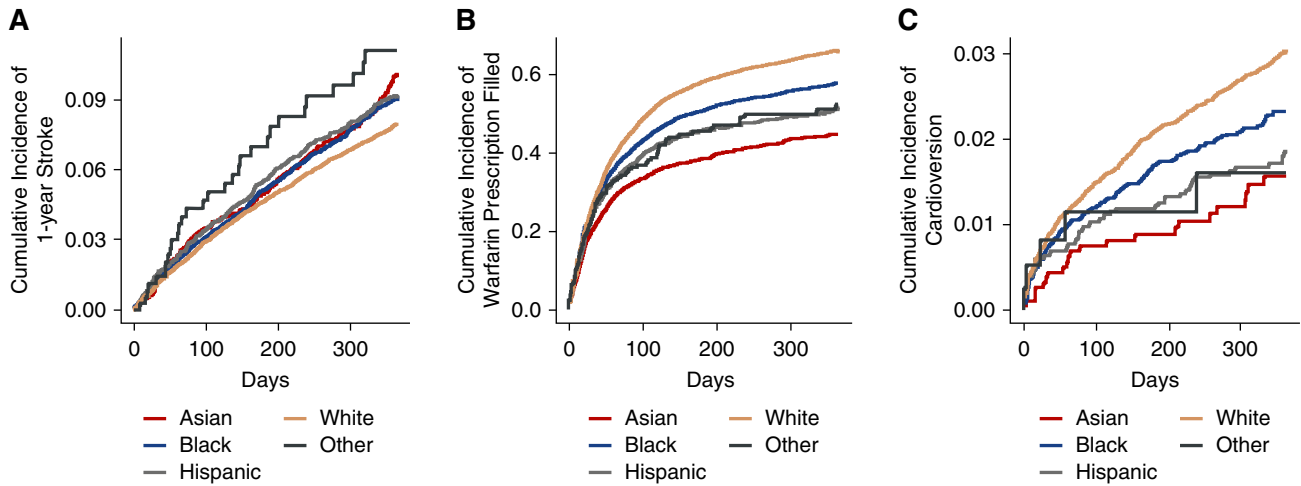
Table 6 reports the HRs and 95% CIs from separate regressions for mortality, ischemic stroke, hemorrhagic stroke,

calciphylaxis, and GI bleeding by race/ethnicity. In adjusted analyses, there were no statistically significant differences in mortality rates or GI bleeding between races/ethnicities. Blacks, Hispanics, and Asians were more likely to have an ischemic stroke compared with whites. Blacks were more likely to experience hemorrhagic stroke compared with whites. No other statistically significant racial/ethnic differences were observed.

**Table 2.** Comorbidities of the incident HD population with AF, overall and by race/ethnicity, 2006–2013

Comorbidity	Race/Ethnicity											
	Overall (n=56,587)		Black (n=10,561)		White (n=39,073)		Hispanic (n=4594)		Asian (n=1971)		Other (n=388)	
	N	%	N	%	N	%	N	%	N	%	N	%
Congestive heart failure	28,644	50.6	5276	50.0	20,217	51.8	2140	46.6	815	41.4	196	50.5
Cancer	5146	9.1	681	6.5	4111	10.5	232	5.1	96	4.9	26	6.7
Peripheral vascular disease	10,333	18.3	1567	14.8	7667	19.6	811	17.7	204	10.4	84	21.7
Cerebrovascular disease	7311	12.9	1700	16.1	4732	12.1	568	12.4	255	12.9	56	14.4
COPD	9223	16.3	1354	12.8	7224	18.5	448	9.8	148	7.5	49	12.6
Hypertension	48,131	85.1	9377	86.8	32,702	83.7	3986	86.8	1723	87.4	343	88.4
Current smoker	2385	4.2	527	5.0	1731	4.4	97	2.7	15	0.8	15	3.9
Atherosclerotic heart disease	17,344	30.7	2360	22.4	13,070	33.5	1254	27.3	516	26.2	144	37.1
Diabetes	31,541	55.7	6196	58.7	20,080	53.2	3111	67.7	1172	59.5	258	66.5

All racial/ethnic comparisons were very highly statistically significant ( $P<0.001$ ). COPD, chronic obstructive pulmonary disease.



**Figure 3.** Cumulative incidence plots by race/ethnicity. The x axis is the number of days and the y axis is the cumulative incidence. (A) Cumulative incidence of stroke by race/ethnicity. Black, Hispanic, Asian, and other patients had a higher incidence of stroke within 1 year. (B) Cumulative incidence of warfarin prescription filled by race/ethnicity. Black, Hispanic, Asian, and other patients had a lower incidence of warfarin filled prescriptions within 1 year. (C) Cumulative incidence of cardioversion by race/ethnicity. Black, Hispanic, Asian, and other patients had a lower incidence of cardioversion.

Table 7 reports the HRs and 95% CIs from separate regressions estimating associations between filled warfarin prescriptions and the secondary outcomes: mortality, ischemic stroke, hemorrhagic stroke, calciphylaxis, and GI bleeding. Warfarin was statistically significantly associated with reduced 1-year mortality and ischemic stroke risk, and was statistically significantly associated with increased 1-year hemorrhagic stroke risk and calciphylaxis. The association between warfarin and GI bleeding was not statistically significant. We conclude that there is lack of evidence to reject the null hypothesis of no effect.

**Subgroup Analyses**

The results of the subgroup analyses were consistent with the main analysis. Using the combined warfarin/NOAC variable, racial/ethnic disparities in warfarin/NOAC were observed in adjusted analyses (blacks versus whites, HR, 0.91; 95% CI, 0.84 to 0.99; Hispanics versus whites, HR, 0.87; 95% CI, 0.80 to 0.96; Asians versus whites, HR, 0.85; 95% CI, 0.77 to 0.95). In time-varying analyses, prescription of warfarin/NOAC was associated with reduced stroke hazard (HR, 0.83;

95% CI, 0.70 to 0.98). Furthermore, descriptive analyses suggested that seven (black versus white), 13 (Hispanic versus white), 22 (Asian versus white), and 58 (other versus white) strokes per 10,000 person years would be eliminated among minority patients if they were exposed to warfarin as often as white patients (Table 8).

**DISCUSSION**

Among patients with ESKD and AF treated with HD, black, Hispanic, and Asian patients experienced increased risk of stroke compared with white patients. No such association was seen for 1-year risk of death. Racial/ethnic minority patients were less likely to fill prescriptions of oral anticoagulants after being diagnosed with AF compared with white patients, although prescription of warfarin after diagnosis of AF was associated with reduced risk of stroke within a year.

Mediation analyses suggest that excess strokes among black, Hispanic, and Asian patients with ESKD and AF on HD could be reduced by 7%, 10%, and 12%, respectively, if

**Table 3.** HRs and 95% CIs for 1-yr stroke by race/ethnicity among the incident HD population with AF, 2006–2013

Race/Ethnicity <sup>a</sup>	Sample Size	Number of Events	Model 1		Model 2	
			HR	95% CI	aHR	95% CI
Non-Hispanic white (ref.)	39,073	2060	1.00		1.00	
Black	10,561	661	1.13	1.04 to 1.23	1.13	1.02 to 1.24
Hispanic	4594	294	1.16	1.03 to 1.31	1.15	1.01 to 1.30
Asian	1971	142	1.23	1.04 to 1.46	1.16	1.02 to 1.35
Other	388	30	1.42	0.99 to 2.04	1.36	0.95 to 1.96

Model 1: Crude, unadjusted. Model 2: Adjusted for age, sex, vintage, baseline dual eligibility, residential area, median income, baseline comorbidities, baseline medications, and baseline CVD procedures. aHR, adjusted hazard ratio; ref., reference.

<sup>a</sup>Employed a competing-risks Cox model.

**Table 4.** HRs and 95% CIs for 1-yr hazard of warfarin filled prescription by race/ethnicity among the incident HD population with AF, 2006–2013

Race/Ethnicity <sup>a</sup>	aHR	95% CI
Non-Hispanic white (ref.)	1.00	
Black	0.90	0.87 to 0.93
Hispanic	0.83	0.79 to 0.87
Asian	0.72	0.67 to 0.79
Other	0.83	0.70 to 0.99

Model adjusted for age, sex, vintage, baseline dual eligibility, residential area, median income, baseline comorbidities, baseline medications, and baseline CVD procedures. aHR, adjusted hazard ratio; ref., reference.

<sup>a</sup>Employed a competing-risks Cox model.

an intervention equalized the distribution of filled warfarin prescriptions among patients belonging to these racial/ethnic groups to that of white patients. The results provide evidence that racial/ethnic minority groups have the highest stroke risk in this population, yet are less likely to be prescribed anticoagulation for stroke prevention. Thus, identification of the barriers to maximizing appropriate treatment with anticoagulation and developing interventions to address those barriers at the patient, practitioner, and/or system levels may provide avenues for reducing disparities in stroke morbidity among patients with ESKD and AF on HD.

Racial/ethnic disparities, defined by the National Institutes of Health as “differences in the incidence, prevalence, mortality, and burden of diseases and other adverse health conditions that exist among specific population groups,”<sup>56</sup> are complex barriers that can present challenges to health care systems striving to provide effective care to all. Similar to another study,<sup>23</sup> we report higher incidence of all-cause stroke among all minority subgroups, confirming racial/ethnic disparities in

AF outcomes. Furthermore, we found that black, Hispanic, and Asian patients were less likely to fill prescriptions of warfarin compared with white patients, which corroborates another USRDS study<sup>57</sup> and confirms racial/ethnic disparities in AF treatment.

Although they are important contributions, limitations of these two studies remain that they did not evaluate the association between warfarin and stroke, or examine whether differences in treatments between races/ethnicities contributed to the stroke differences between races/ethnicities. We address this important gap, and evaluate racial/ethnic disparities in AF treatment and outcomes among the ESKD population.

We provide evidence suggesting that prescription of warfarin is associated with reduced all-cause stroke rates among patients with AF and ESKD, as previously described.<sup>58,59</sup> Other studies, including several meta-analyses,<sup>30,31,60</sup> have reported no association between warfarin use and stroke rates among patients with AF and ESKD, calling into question the use of warfarin in the management of AF among patients with ESKD.

Differences in patient population and outcome definitions, and the analytic methods used, likely contribute to the discrepancies of these studies evaluating efficacy and safety of warfarin. For example, although some studies used one AF diagnosis, our study used a previously published algorithm that used two AF diagnoses to define a population with permanent, persistent, or recurrent paroxysmal AF.<sup>17</sup> Furthermore, our definition of all-cause stroke is broader than most studies, which focused on select types of ischemic and hemorrhagic strokes. Finally, most analyses did not account for time-varying prescriptions of warfarin or other AF treatments. Because patients with AF and ESKD are prescribed other

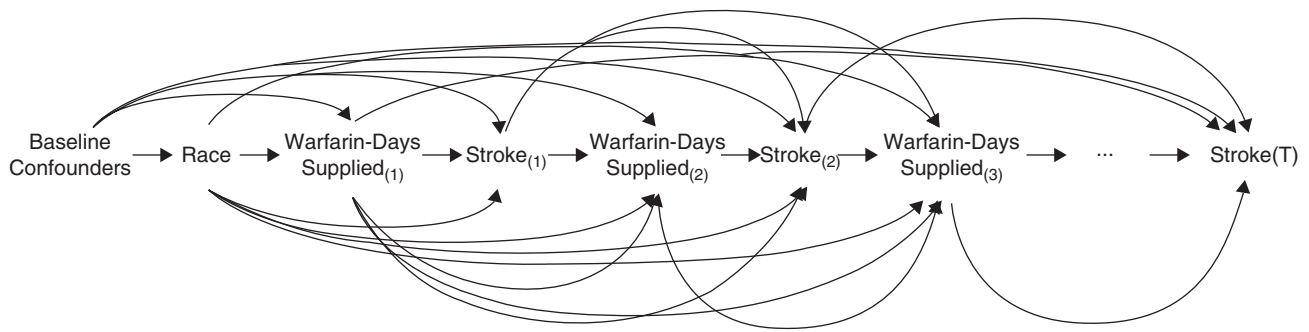
**Table 5.** HRs and 95% CIs for 1-yr stroke by drugs/procedures among the incident HD population with AF, 2006–2013

Variable	Model 1		Model 2		Model 3	
	HR	95% CI	aHR	95% CI	aHR	95% CI
<b>Drugs<sup>a</sup></b>						
Warfarin	0.70	0.65 to 0.76	0.72	0.66 to 0.77	0.82	0.71 to 0.94
Calcium channel blockers	0.91	0.83 to 1.00	0.89	0.81 to 0.99	0.87	0.77 to 0.99
β-blockers	0.62	0.58 to 0.67	0.61	0.57 to 0.66	0.78	0.71 to 0.88
Platelet aggregation inhibitors	0.92	0.84 to 1.01	0.92	0.83 to 1.00	0.96	0.85 to 1.06
Class III	0.69	0.63 to 0.76	0.69	0.63 to 0.75	0.75	0.69 to 0.83
Digoxin	0.93	0.83 to 1.03	0.92	0.83 to 1.03	0.96	0.87 to 1.07
NOACs	0.90	0.51 to 1.59	0.89	0.50 to 1.56	0.89	0.50 to 1.56
<b>Procedures</b>						
Cardioversion	0.99	0.77 to 1.30	1.05	0.81 to 1.37	1.10	0.84 to 1.43
Catheter ablation	1.17	0.76 to 1.80	1.24	0.80 to 1.91	1.28	0.83 to 1.98
Surgical maze	0.79	0.30 to 2.11	0.85	0.32 to 2.26	0.90	0.34 to 2.39
Ambulatory event monitor	0.55	0.38 to 0.79	0.55	0.38 to 0.81	0.60	0.41 to 0.86
Defibrillator	0.56	0.43 to 0.73	0.60	0.46 to 0.79	0.61	0.47 to 0.80

Model 1: Crude, unadjusted. Model 2: Adjusted for age, sex, race/ethnicity, dual eligibility, residential area, vintage, and median income. Model 3: Model 2+CHA<sub>2</sub>DS<sub>2</sub>-VASC+baseline and time-varying comorbidities (congestive heart failure, cancer, peripheral vascular disease, cerebrovascular disease, COPD, hypertension, current smoker status, atherosclerotic heart disease, diabetes, AIDS)+baseline and time-varying medications+baseline and time-varying procedures. aHR, adjusted hazard ratio. COPD, chronic obstructive pulmonary disease.

<sup>a</sup>Employed a competing-risks Cox model.





**Figure 4.** Directed acyclic graph showing relevant causal relationships for the time-varying mediation analysis. The exposure is race/ethnicity and warfarin is a time-varying mediator. The outcome is 1-year all-cause stroke. Time-varying confounders were omitted from this directed acyclic graph, but were adjusted for in the analysis. Stroke(T), stroke at time T.

medications, the confounding effects of these prescriptions were accounted for in this study to give a more unbiased estimate.

Although randomized, controlled trials in the general AF population have shown clear benefits of anticoagulation, these studies have excluded patients treated with HD, resulting in a lack of conclusive evidence supporting anticoagulation use in this population. Anticoagulation may pose considerable safety concerns among patients on HD in particular, because they are at a higher risk of bleeding and thrombosis. Our study provides evidence that warfarin is associated with decreased risk of all-cause stroke, mortality, and ischemic strokes, but its prescription is also associated with increase in the risk of hemorrhagic strokes. Ischemic strokes in this study, however, were more common than hemorrhagic strokes. It may not be surprising that the lack of conclusive evidence regarding the efficacy and safety associated with warfarin among patients on HD has led to inconsistent prescription patterns, which may explain why some providers prescribe this drug less often in some racial/ethnic groups. However, all-cause stroke is an important outcome relevant to patients. Given that all types of strokes have debilitating effects, we believe that using all-cause stroke as the primary outcome in our study is appropriate, especially considering that we have presented separate analyses for different types of strokes as secondary outcomes. Although our study alone does not provide conclusive evidence of warfarin efficacy, it remains an important contribution

given that the relevant randomized, controlled trials may never be conducted among patients on HD.

We believe that this is the first study to adopt a causal inference mediation framework to estimate the extent to which racial/ethnic disparities in warfarin prescription contribute to racial/ethnic disparities in all-cause stroke rates among patients with ESKD and AF. For each race/ethnicity compared with whites, the survival mediational g-formula decomposed the interventional total effect of race/ethnicity on stroke and quantified how much of it was explained by racial/ethnic differences in treatment patterns. We concluded that 7%, 10%, and 12% of excess strokes among black, Hispanic, and Asian patients could be prevented if the warfarin prescription distributions in these groups were equalized to those in the white population. These estimates have a direct, clinical interpretation, because they provide a simulation of what the outcomes would be if physicians and the health care system intervened to equalize the warfarin distribution among races/ethnicities. Physicians and other practitioners can modify their prescription patterns to address the racial/ethnic disparities in stroke incidence in patients with ESKD on HD, suggesting that they may be the individuals who could implement interventions most readily.

Racial/ethnic disparities in outcomes have been previously identified in Medicare beneficiaries,<sup>61,62</sup> patients with CKD,<sup>63</sup> patients with ESKD who receive transplants,<sup>64–66</sup> and patients receiving HD,<sup>67–69</sup> including in the administration of

**Table 6.** HRs and 95% CIs for 1-yr mortality, ischemic stroke, hemorrhagic stroke, calciphylaxis, and GI bleeding by race/ethnicity among the incident HD population with AF, 2006–2013

Race/Ethnicity <sup>a</sup>	Mortality		Ischemic Stroke		Hemorrhagic Stroke		Calciphylaxis		GI Bleeding	
	aHR	95% CI	aHR	95% CI	aHR	95% CI	aHR	95% CI	aHR	95% CI
Non-Hispanic white (ref.)	1.00		1.00		1.00		1.00		1.00	
Black	1.01	0.98 to 1.05	1.39	1.11 to 1.74	1.21	1.07 to 1.35	0.91	0.75 to 1.28	1.17	0.87 to 1.61
Hispanic	1.01	0.96 to 1.06	1.80	1.36 to 2.38	1.08	0.91 to 1.27	0.72	0.49 to 1.09	1.07	0.94 to 1.24
Asian	0.89	0.76 to 1.04	2.37	1.67 to 3.36	0.94	0.74 to 1.20	0.68	0.32 to 1.11	0.96	0.75 to 1.30
Other	1.00	0.85 to 1.17	2.13	0.99 to 4.53	1.36	0.95 to 1.96	0.80	0.37 to 1.43	1.45	0.96 to 2.02

Models adjusted for age, sex, vintage, baseline dual eligibility, residential area, median income, baseline comorbidities, baseline medications, and baseline CVD procedures. aHR, adjusted hazard ratio; ref., reference.

<sup>a</sup>Employed a competing-risks Cox model.

**Table 7.** HRs and 95% CIs for 1-yr mortality, ischemic stroke, hemorrhagic stroke, calciphylaxis, and GI bleeding by warfarin among the incident HD population with AF, 2006–2013

Variable	Mortality <sup>a</sup>		Ischemic		Hemorrhagic		Calciphylaxis		GI Bleeding	
	aHR	95% CI	aHR	95% CI	aHR	95% CI	aHR	95% CI	aHR	95% CI
Warfarin	0.81	0.72 to 0.91	0.79	0.66 to 0.95	1.22	1.03 to 1.46	1.49	1.05 to 1.91	1.12	0.94 to 1.36

Adjusted for age, sex, race/ethnicity, dual eligibility, residential area, vintage, median income+CHA<sub>2</sub>DS<sub>2</sub>-VASc+baseline and time-varying comorbidities (congestive heart failure, cancer, peripheral vascular disease, cerebrovascular disease, COPD, hypertension, current smoker status, atherosclerotic heart disease, diabetes, AIDS)+baseline and time-varying medications+baseline and time-varying procedures. aHR, adjusted hazard ratio. COPD, chronic obstructive pulmonary disease.

<sup>a</sup>Employed a competing-risks Cox model with time-varying covariates.

erythropoietin.<sup>70,71</sup> We speculate that systemic factors in the health care system may contribute to these disparities to some degree. Although the causes of racial/ethnic disparities are complex and often difficult to modify by a physician, factors such as implicit bias, poor communication, and physician stereotyping can be addressed more directly. For example, the reasons for geographic and racial differences in stroke study<sup>72</sup> reported that blacks were one-third as likely as whites to be aware of having AF. Researchers hypothesized that this could be due to lack of physician–patient education, or perhaps higher rates of undiagnosed AF, because AF can be asymptomatic. Another study among the general AF population<sup>20</sup> identified “implicit racial bias, lack of awareness of racial/ethnic disparities in AF stroke risk, and lack of effective multicultural awareness and training” as consistent barriers to optimal stroke prevention. Genetic differences in susceptibility to bleeding events induced by anticoagulation have been reported and may be associated with lower use of these agents.<sup>73–77</sup>

**Limitations**

This is an observational study and causal relationships cannot necessarily be inferred, especially with respect to warfarin efficacy, which has yet to be evaluated in a randomized, controlled trial among patients on HD. Although time-varying mediation accounted for bias induced by time-varying confounding, the survival mediational g-formula is subject to potential violation of the confounding assumptions, and is prone to

model misspecification. Given that sensitivity analyses have yet to be developed for time-varying mediation analyses, we have not been able to evaluate to what extent these assumptions would have to be violated in order to explain away the results. Accordingly, we adjusted for a comprehensive set of covariates that are used in standard USRDS studies. Furthermore, the study design resulted in the generation of a selected population, characterized by relatively high age and low proportion of black patients, which is different from the overall ESKD population. In order to identify medications, procedures, and stroke diagnoses, we needed to define a population with continuous Medicare coverage. Our results therefore cannot be generalized to patients with ESKD with other sources of insurance coverage. Additionally, we were not able to ascertain interim international normalized ratio values (or other measures of adherence) or dose of heparin during dialysis, an inherent limitation of Medicare claims data. Finally, because we have no way of knowing whether patients actually took their drugs, we are assuming that patients who filled a prescription were exposed to the drug on an intention-to-treat basis. Nevertheless, the results of this study have important implications for future research, which may influence clinical practice.

We have applied modern causal inference methods to assess the potential role of oral anticoagulants in explaining racial/ethnic disparities in stroke among patients with ESKD and AF while accounting for the complex time-varying relationships with other drugs and treatments. Similar methods can be used to evaluate what other factors may mediate racial/ethnic disparities in this high-risk population. Furthermore, our results contribute to the greater discussion regarding the role of oral anticoagulation in patients with AF and ESKD. The study supports efforts to develop approaches regarding appropriate prescription of such medications among the ESKD population, and to promote optimal treatment in this high-risk patient population. Consideration of population health initiatives may help change physician behavior to be attuned to racial/ethnic disparities, ensure optimal treatment in these groups, and reduce unjust and unfair differences in patient management by race/ethnicity.

**Table 8.** Unadjusted 1-yr all-cause stroke rates, excess risk percentage difference, and excess stroke prevention rates under hypothetical interventions that equalize warfarin distributions

Race/ Ethnicity	1-Yr All-Cause Stroke Rate (Per 100 Person Yr)	Excess Risk Percentage Difference (Per 100 Person Yr)	Excess Strokes Preventable (Per 10,000 Person Yr)
Non-Hispanic white (ref.)	8.4	(Ref)	
Black	9.4	1.0	7
Hispanic	9.7	1.3	13
Asian	10.2	1.8	22
Other	11.8	3.4	58

Ref., reference.

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Dr. Waddy, Dr. Solomon, Dr. Becerra, Dr. Ward, Dr. Chan, Dr. Fwu, Dr. Norton, Dr. Eggers, Dr. Abbott, and Dr. Kimmel designed the study. Dr. Becerra analyzed the data. Dr. Waddy, Dr. Solomon, Dr. Becerra, Dr. Ward, Dr. Chan, Dr. Fwu, Dr. Norton, Dr. Eggers, Dr. Abbott, and Dr. Kimmel interpreted the analysis. Dr. Waddy, Dr. Solomon, Dr. Becerra, Dr. Ward, Dr. Chan, Dr. Fwu, Dr. Norton, Dr. Eggers, Dr. Abbott, and Dr. Kimmel drafted and revised the paper. All authors approved the final version of the manuscript.

## DISCLOSURES

The opinions expressed are those of the authors and do not necessarily reflect those of the National Institute of Diabetes, Digestive and Kidney Diseases, the National Institutes of Health, the Department of Health and Human Services or the Government of the United States.

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## SUPPLEMENTAL MATERIAL

This article contains the following supplemental material online at <http://jasn.asnjournals.org/lookup/suppl/doi:10.1681/ASN.2019050543/-DCSupplemental>.

Supplemental Appendix A. ICD-9-CM diagnostic codes to identify stroke.

Supplemental Appendix B. Medications.

Supplemental Appendix C. HCPCS codes for cardiovascular disease procedures.

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