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Association of Warfarin Initiation to Outcomes of Late-Stage Chronic Kidney Disease Patients with Incident Atrial Fibrillation

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COMPETENCY IN MEDICAL KNOWLEDGE: The clinical benefit of warfarin therapy for thromboprophylaxis after incident atrial fibrillation (AF) diagnosis in late-stage chronic kidney disease (CKD) patients transitioning to dialysis is unknown. Our results from a national cohort of veteran population suggest that warfarin use in advanced CKD is associated with higher risk of ischemic and bleeding events, but lower risk of mortality after end stage renal transition.

TRANSLATIONAL OUTLOOK: Future studies such as those comparing warfarin with newer oral anticoagulant agents are needed to more granularly define the net clinical benefit of anticoagulation therapy in advanced CKD patients with incident AF.

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Abstract

Objective: The clinical benefit of warfarin therapy for thromboprophylaxis after incident atrial fibrillation (AF) diagnosis in late-stage chronic kidney disease (CKD) patients transitioning to dialysis is unknown. The aim of this study was to examine the efficacy and safety of warfarin initiation following the diagnosis of AF in late-stage CKD patients transitioning to dialysis.

Methods: In this retrospective cohort analysis, the study population was a national cohort of 22,771 US veterans with incident end stage renal disease (ESRD) who developed incident AF prior to initiating renal replacement therapy. We examined the association of warfarin therapy following the diagnosis of incident AF with ischemic-cerebrovascular accidents (CVA) (ischemic stroke or transient ischemic attack), ischemic-CVA related hospitalization, major bleeding events (gastrointestinal or intracranial bleeding), bleeding event related hospitalizations and post-dialysis all-cause mortality in multivariable adjusted Cox regression analyses adjusting for demographic characteristics and comorbidities.

Results: The mean (SD) age of the cohort was 73.5±8.8 years, 13% were African American and the mean CHA2DS2-VASc score was 5.7±2.1. Among overall cohort, 6,682 (29.3%) patients were started on warfarin during the follow up period. The hazard ratios (95% confidence intervals) for ischemic-CVA, bleeding events and death for those started on warfarin were 1.23 (1.16 to 1.30), 1.36 (1.29 to 1.44), and 0.94 (0.90 to 0.97) compared with those who received no anticoagulation. Warfarin exposure was associated with higher risk for ischemic-CVA and bleeding event related hospitalizations also.

Conclusions: In late-stage CKD patients transitioning to dialysis, warfarin use was associated with higher risk of ischemic and bleeding events, but lower risk of mortality. Future studies such as those comparing warfarin with newer oral anticoagulant agents are needed to granularly define the net clinical benefit of anticoagulation therapy in advanced CKD patients with incident AF.

Graphical Abstract

Summary for use on social media (Twitter): The clinical benefit of warfarin therapy for thromboprophylaxis after incident atrial fibrillation (AF) diagnosis in late-stage chronic kidney disease (CKD) patients transitioning to dialysis is unknown. Our study from a national cohort of veteran population suggest that warfarin use in advanced CKD is associated with higher risk of ischemic and bleeding events, but lower risk of mortality after dialysis transition.

Condensed Abstract

The clinical benefit of warfarin therapy for thromboprophylaxis after incident atrial fibrillation (AF) diagnosis in late-stage chronic kidney disease (CKD) patients transitioning to dialysis is unknown. The present study from a national cohort of US veterans evaluates the efficacy and safety of warfarin initiation following the diagnosis of AF in late-stage CKD patients transitioning to dialysis. Our results suggest that warfarin use in advanced CKD is associated with higher risk of ischemic and bleeding events, but lower risk of mortality after end stage renal transition transition.

Keywords

Chronic Kidney Disease; Warfarin; Atrial fibrillation; Stroke; Bleeding

Introduction

Chronic kidney disease (CKD) affects 10% to 15% of the general population, and each year ~100,000 CKD patients transition to maintenance hemodialysis in the United States.[1] Warfarin has a proven benefit as a prophylactic therapy for preventing future embolic stroke events in the broader atrial fibrillation (AF) population with conflicting results from observational studies in both non-dialysis dependent (NDD) CKD and dialysis dependent population.[2–19] The management of thromboprophylaxis with anticoagulant agents in CKD patients is complex as these patients are also at higher risk of major bleeding. [8,15,17,20]

To the best of our knowledge, no literature exists describing whether warfarin treatment should be recommended in NDD-CKD patients transitioning to dialysis after incident AF. Therefore, we studied the effect of warfarin exposure after incident AF diagnosis on clinical outcomes of NDD-CKD patients transitioning to dialysis in a large nationally representative cohort of US veterans. We aimed to determine the association of warfarin exposure with measures of clinical safety (bleeding events), clinical effectiveness (ischemic-cerebrovascular accident [ischemic-CVA], death) in this population as compared to those not treated with warfarin.

Methods

Study Population and Data Source

We retrospectively examined longitudinal data from the US Renal Dialysis System (USRDS) Transition of Care in Chronic Kidney Disease study,[21] a historic cohort study examining US veterans (n=102,477) who transitioned to renal replacement therapy from October 1, 2007 through March 31, 2015.[22,23] The study population was extracted from the Veterans Affairs (VA) Inpatient and Outpatient Medical SAS Datasets and from VA/ Centers for Medicare and Medicaid Services data using International Classification of Diseases, Ninth or Tenth Revisions diagnosis code (ICD-9 or ICD-10) diagnostic codes (MedPAR, Outpatient, Carrier and Inpatient files). We identified patients with an inpatient or outpatient ICD-9 code for AF or atrial flutter (n=37,390) (collectively referred to as AF in this study), as done previously.[24–28] The AF diagnosis date was used as the cohort entry date for our study. Incident non-valvular AF was defined as a new ICD 9-CM code for AF without such a diagnosis at the first encounter (excluding 9,017 patients with prevalent AF) and meeting all of the following criteria: a) no documented evidence indicating prescription of any of the following medications before the date of AF diagnosis: anticoagulant agents (warfarin, apixaban, dabigatran, rivaroxaban, edoxaban) and other rhythm conversion agents such as amiodarone, sotalol, digoxin, dofetilide, ibutilide, flecainide, propafenone, procainamide and quinidine (n= 3,608) and b) those with a diagnosis of valvular disease such as mitral stenosis and mechanical prosthetic valve (n=1,887). Any patient with a

prescription for newer oral anticoagulant agents during the follow-up period was also excluded (n=107). There were 22,771 patients who met these criteria and formed the final analytic cohort. A detailed description of cohort creation is shown in Figure 1.

Covariates

The patient characteristics at time of incident AF diagnosis, including age, sex, and self-identified race and ethnicity, were ascertained from the USRDS, VA, and CMS databases (Table 1). Preexisting comorbidities at the time of cohort entry were extracted from VA and CMS databases using ICD-9 and ICD-10 diagnostic and procedural codes and Current Procedural Terminology codes as guided by the Deyo Charlson Comorbidity Index (CCI) and CMS chronic conditions. Documentation of a diagnostic code within 3 years before AF diagnosis date during at least 1 inpatient visit or 2 outpatient visits was used to determine the presence of comorbidity, and otherwise were considered absent. The Charlson Comorbidity Index (CCI) was calculated without renal disease. We also calculated the CHA2DS2-VASc risk score using baseline comorbidity data.(8) Data related to baseline medication exposure were obtained from both CMS Medicare Part D and VA pharmacy dispensation records.(29) Patients who received at least one 30-day supply of these medications within 3 months of warfarin initiation (for the warfarin-exposed group) or date of AF diagnosis (for warfarin non-exposed group) were recorded as having been treated with these medications at baseline (Table 1).

Outcomes

The outcomes of interest were a) ischemic-CVA events (ischemic stroke or transient ischemic attack) b) ischemic-CVA-related hospitalization c) major bleeding events (hemorrhagic CVA, intracranial or GI bleeding events) d) major bleeding event related hospitalization e) all-cause mortality.

Exposure and Follow up period

Using both inpatient and outpatient medication data, warfarin prescription information was extracted using specific drug-class codes or names.(29) All patients were considered unexposed (i.e., without warfarin exposure) from the time of AF diagnosis until the start of warfarin treatment. We defined *de-novo* exposure as the initiation of warfarin following the diagnosis of incident AF. Patients who received a 30-day supply of warfarin with at least one refill were characterized as exposed to warfarin. Patients who were started on warfarin were considered warfarin exposed from the time of warfarin start date until date of outcome of interest (such as ischemic-CVA, major bleeding event, ischemic CVA related hospitalization, major bleeding event related hospitalization), death or date of last activity in VA system or date of administrative censoring (1st September 2015), whichever occurred first. As all patients transitioned to dialysis in our dataset, for the outcome of death the start of the follow up period was the date of first dialysis service instead of AF diagnosis date to control for immortal time bias, and then patients were followed until the date of death or last activity in VA network or date of administrative censoring (1st September 2015), whichever occurred earlier. All data on outcomes and censoring events were obtained from the USRDS, VA, and CMS datasets.

Statistical Analysis

Baseline patient characteristics are presented as the mean ± standard deviation (SD) or median [interquartile ranges) (IQR)] for continuous variables and as frequency (percentages) for categorical variables, as appropriate. Patients were compared between warfarin-exposed and non-exposed groups using chi-square test for categorical variables and student's t-test for continuous variables.

The exposure to warfarin was modeled in an "intention-to-treat" approach (with all *de novo* exposed patients kept in the treated group irrespective of subsequent discontinuation of warfarin). Given majority of incident non-valvular AF patients are not started on warfarin therapy at the time of AF diagnosis(30) and the outcomes of interest such as ischemic-CVA and bleeding events could have happened before warfarin exposure, we decided to model the exposure of warfarin initiation as a *time-dependant covariate*. The time between cohort entry (incident AF diagnosis date) and the start of warfarin therapy allocated to the unexposed group to avoid immortal time bias arising from the relevant follow-up period among patients treated with warfarin. (31) The comparison between warfarin exposed and untreated patients was performed with multivariable Cox regression analyses.

The influence of potential confounders was analyzed by incremental adjustments based on *priori* considerations: unadjusted (model 1); age, sex, race/ethnicity (whites, African Americans, Hispanics, and others), marital status (married, divorced, single, and widowed) (model 2); model 2 plus comorbid conditions (hyperlipidemia, hypertension, diabetes, history of coronary artery disease, congestive heart failure, cerebrovascular disease, peripheral vascular disease, chronic pulmonary disease, dementia, depression, anemia, cancer, paraplegia and hemiplegia, AIDS/HIV, liver disease, peptic ulcer disease, history of gastrointestinal (GI) bleeding, history of other major bleeding, connective tissue disease, CCI, CHA2DS2-VASc score and medications (statins, non-statin lipid lowering agents, non aspirin anti-platelet agents, anti-arrhythmic, anti-anginals, calcium channel blockers, beta blockers, anti-depressants, potassium sparing diuretics, loop diuretics, renin angiotensin aldosterone system inhibitors, thiazides and anti-hypertensive vasodilator agents); model 3 plus blood/serum hemoglobin, systolic blood pressure, diastolic blood pressure and estimated glomerular filtration rate (eGFR) (model 4). Model 4 had high proportions of missing data (systolic blood pressure [~39%], diastolic blood pressure [30%], hemoglobin [~39%], eGFR [~36%]); therefore, we used model 3 as the main multivariable-adjusted model. We also performed the eGFR-stratified analysis to study the association of warfarin exposure with the outcomes. (e Table1 in supplement).

We performed different sensitivity analyses to test the robustness of our findings. As we did not have information regarding the type of AF (paroxysmal vs. persistent), we studied the association estimates depending on the number of times AF was documented during the longitudinal follow up (<3 vs. 3 times) (e Table 2 in supplement). We studied the associations of outcomes (ischemic-CVA, major bleeding events) with the warfarin initiation by performing separate analyses for pre and post -dialysis period (e Table 3 in supplement). To address confounding by indication of treatment an inverse probability of treatment weighted (IPTW) analysis was applied (e Table 4–7 in supplement). As many patients might obtain aspirin over the counter (that will not be captured in pharmacy prescription data), we

examined interactions and performed a subgroup analysis by aspirin exposure (eTable 8a–b). We examined the effect of warfarin exposure on ischemic-CVA in discrete time bins (0–7 days; 8–30 days; >30 days) after therapy initiation to differentiate the risk after warfarin initiation (early vs. late) (eTable 10)

Results are expressed as hazard ratios (HRs) for Cox regression analyses with 95% confidence intervals (CIs). P values are 2 sided and reported as significant at 0.05 for all analyses. All analyses were conducted using STATA MP, version 14 (STATA Corp LP) and SAS version 9.4 (SAS Institute Inc., Cary, NC). The institutional review board of Memphis VA Medical Center approved this study (IRB# 555872–15), and the participant written informed consent requirement was waived.

Results

The mean age of the study population was 73.50±8.8 years; the cohort was 21,729 (95.4%) male and 2,973 (13.1%) were African Americans. The mean time from AF diagnosis to dialysis initiation was 4.0± 3.8 years. 9,050 (39.7%) patients had a history of cerebrovascular disease, 5,268 (23.1%) patients had a history of GI bleeding and 2,512 (11.0%) patients had a history of other major bleeding events prior to the diagnosis of AF. The mean CCI and CHA2DS2-VASc risk score were 4.5±3.5 and 5.7±2.1 respectively. The mean eGFR was 35.8 ± 19.6 mL/min/1.73m^2, systolic blood pressure was 138.2 ± 23.0 mmHg, diastolic blood pressure was 70.7 ± 13.0 mmHg and blood/serum hemoglobin value was 12.5 ± 1.9 g/dL (Table 1).

During the follow-up period, 6,682 patients (29.3%) were started on warfarin treatment. For warfarin-exposed group, the median time from AF diagnosis to warfarin initiation was 2.4 years (0.4 to 5.0 years). Compared with AF patients without warfarin initiation, those started on warfarin treatment were younger and more likely to be African American, with lower prevalence of comorbidities, and with lower mean CCI and CHA2DS2-VASc scores. They were also more likely to be on statins, beta-blockers, renin-angiotensin system inhibitors, calcium channel blockers, antiarrhythmics and antiplatelet agents (Table 1).

Association of Warfarin Initiation with Cerebrovascular Accidents

The median follow-up period for the outcome of ischemic-CVA was 3.2 years (1.1 to 6.3 years) and ischemic-CVA hospitalization was 4.2 years (1.7 to 7.5 years). Patients who were started on warfarin had a lower crude ischemic-CVA rate compared with patients who were untreated (105.5; 95%CI, 100.7–110.6 vs. 107.3; 95%CI, 105.0–109.6 events per 1000 person-years) but higher ischemic-CVA related hospitalizations (61.4; 95%CI, 58.1–64.9 vs. 50.8; 95% CI, 49.3–52.3 events per 1000 person-years) (Table 2). In multivariable adjusted models, warfarin exposure was associated with higher ischemic-CVA events (HR= 1.23, 95%CI [1.16–1.30]) and higher risk for ischemic-CVA related hospitalizations (HR = 1.38, 95% CI [1.28 –1.48]) (Table 3). Similar results were observed when analysis was limited to pre-dialysis period and post-dialysis period (e Table 3). In IPTW analysis, warfarin exposure was associated with higher ischemic-CVA events (HR = 1.25, 95% CI [1.18– 1.32]) (e table 4). The analysis based on eGFR stratification (e Table1) and aspirin exposure also revealed similar results (e Table 8a–8b). We found higher risk of ischemic-CVA during 0–7 days (HR

= 4.03, 95% CI [0.83–19.53] and >30 days of warfarin exposure (HR = 1.24 [1.16– 1.31]) (e Table 10).

Association of Warfarin Initiation with Major Bleeding Events

The median follow-up period for the outcome of major bleeding events was 2.8 years (IQR= 0.9 to 5.8) and bleeding event related hospitalization was 3.8 years (IQR= 1.5 to 7.1). Patients who were started on warfarin had a higher crude major bleeding event rate (144.7; 95%CI, 128.6 – 151.0 vs. 128.9; 95%CI, 126.3– 131.5 events per 1000 person-years) and higher major bleeding related hospitalizations (88.6; 95%CI, 84.4–93.0 vs. 66.4; 95%CI, 64.7–68.1 events per 1000 person-years) compared with patients who were untreated (Table 2). In multivariable adjusted models, warfarin exposure was associated with higher major bleeding events (HR= 1.36, 95%CI [1.29–1.44]) and higher risk for bleeding event related hospitalizations (HR = 1.56, 95% CI [1.47 –1.67]) (Table 3). Similar results were observed when analysis was limited to pre-dialysis period and post-dialysis period (e Table 3). In IPTW analysis also, warfarin exposure was associated with higher major bleeding events (HR = 1.34, 95% CI [1.27– 1.41]) (e Table 4). The analysis based on eGFR stratification (e Table1) and aspirin exposure also revealed similar results (e Table 8a–8b).

Association of Warfarin Initiation with Death

The median follow-up period post dialysis initiation for the outcome of death was 1.1 years (0.4 to 2.4 years). As shown in Table 2, patients who were started on warfarin had a lower crude all-cause mortality rate compared with patients who were untreated (460.9; 95%CI, 448.9–473.3 vs. 536.7; 95%CI, 527.6 – 545.9 events per 1000 person-years) (Table 3). In multivariable adjusted Cox regression analyses, warfarin exposure was associated with significantly lower risk of death (HR = 0.94, 95%CI [0.90 – 0.97]) (Table 3). In IPTW analysis also, warfarin exposure was associated with lower risk of death (HR = 0.89, 95% CI [0.86– 0.92]) (e Table 4). The analysis based on aspirin exposure revealed similar results (e Table 8a–b).

Discussion

This observational retrospective cohort study indicates that, in advanced CKD patients transitioning to dialysis, warfarin use is associated with higher risk of ischemic and bleeding events but lower risk of mortality. Till date, it is still unknown if thromboembolic and bleeding outcomes differ between patients with NDD-CKD who are started on warfarin therapy after incident AF while transitioning to dialysis, and those who are untreated. Our study examining a large national cohort of NDD-CKD patients provides new data highlighting the long-term outcomes of initiating warfarin therapy in incident AF patients with advanced NDD-CKD transitioning to dialysis.

The current clinical guidelines are controversial with respect to recommendations about use of warfarin in AF patients with end-stage renal disease (ESRD) or on dialysis.(10,32,33) With no randomized clinical trial studying this issue, observational studies in both ESRD and NDD-CKD patients have reported inconsistent results. (5–13,16,18,32–34) Recently Kumar et al. retrospectively examined 6,977 NDD-CKD patients (baseline GFR of <50

ml/min/1.73m^2) and incident AF in a large UK database and reported warfarin use to be associated with higher bleeding (HR = 2.42, 95%CI [1.44 to 4.05]) and higher stroke events (HR= 2.60, 95%CI [2.00 to 3.38]) over a follow up period of 1.4 years.(7) In a retrospective cohort analysis of 3,587 patients in a Danish registry, investigators reported an association of anticoagulants in NDD-CKD AF patients with increased bleeding risk (HR= 1.36, 95%CI [1.17 to 1.59]) without reducing strokes (HR= 0.84, 95%CI [0.69 to 1.01]).(15) Similar observations were seen in a Canadian population with use of warfarin providing no significant reduction in stroke events (HR= 1.10, 95%CI [0.78 to 1.56]) but increasing bleeding events (HR=1.42, 95%CI [1.04 to 1.93]).(18) In contrast, others have reported warfarin treatment to be associated with a significantly lower risk of all-cause mortality (16) and CVA events.(5) In ESRD population, some studies (13,34) reported warfarin use to be associated with a nearly two-fold increase in the risk of stroke events, while others (15) have shown warfarin use to be associated with a significant reduction in thromboembolic events (HR= 0.44, 95%CI [0.26 −0.74]). Garg et al. retrospectively studied 302 AF patients on chronic hemodialysis and reported lack of clinical benefit of warfarin use in reducing risk of ischemic stroke and mortality events.(2) Nochaiwong et al. in a meta-analysis of 14 studies found no clinical benefit of warfarin therapy for the outcomes of mortality and stroke/ thromboembolism and reported significantly increased risk of major bleeding among dialysis patients with AF.(12)

As an extension of these prior studies, our core objective was to focus on advanced NDD-CKD patients transitioning to dialysis, and we found warfarin exposure to be associated with increased rate of bleeding and ischemic-CVA events, but with lower risk of all-cause deaths. The differences in our findings from the previous studies could be due to disparities in study sample size, temporal discordance (short term vs. long-term follow-up), type of AF (incident vs. prevalent), patient characteristics and severity of renal disease. We examined a population with advanced CKD with progressive decline in renal function. We decided to include patients with all CHA2DS2-VASc scores in our analysis without limiting to only those with higher scores, as advanced CKD patients were not included in the pivotal studies that established the use of risk-based anticoagulation prescription.(35) The lack of benefit of warfarin for stroke prevention and perhaps increased risk as seen in our study is plausibly multifactorial driven. First, the use of Vitamin K antagonist leading to accelerated vascular calcification predisposing patients to watershed vascular territory or lacunar infarcts has been previously reported.(8,17,18) Second, advanced CKD patients on warfarin have been shown to have poorer anticoagulation control with lower proportion of patients spending time in target international normalized ratio (INR) ranges (2 to 3) when compared to those with better renal function.(20) Hence the lack of benefit in CVA prevention with warfarin might simply be a reflection of inadequate anticoagulation causing failure in prevention of cardio-embolic strokes. Third, warfarin initiation has been reported to increase risk of stroke during the early treatment phase plausibly due to a transient hypercoagulable state as also observed by us. (36) Finally, our cohort represents an older age population, which has higher vascular calcification and atherosclerotic disease burden potentially making them prone to atherothrombotic stroke events rather than embolic stroke reducing the overall benefit of warfarin for stroke prevention in AF.

CKD patients have underlying platelet and coagulation disorders such as uremic thrombocyte function disorder, and a high prevalence of risk factors for bleeding such as hypertension and old age.(8) The use of anticoagulation in this background might augment the risk of bleeding. Additionally, post transition to dialysis; these patients require systemic anticoagulation with heparin to prevent clotting that may further increase the risk of bleeding. Warfarin related nephropathy has been described in CKD population that potentially can further compromise kidney function, compounding the risk of ischemic and bleeding events. (8,37) Reduced renal function in patients receiving warfarin has been shown to be associated with a higher incidence of over anticoagulation and greater risk for major hemorrhage. (20) We also speculate that reduced mortality could also be due to the protective effects of anticoagulation against cardiovascular events such as myocardial infarction and venous thromboembolic events, which in turn might decrease the mortality of advanced CKD patients.(38) The warfarin-exposed group was more likely to be on cardioprotective medications such as statins, beta-blockers and renin-angiotensin-aldosterone system inhibitor (RAASi), and while we did adjust for these in regression analysis, we cannot exclude the possibility of residual confounding. Although the association of warfarin exposure with the reduced mortality was statistically significant in our study, ~50% patients of our cohort died within one year of dialysis initiation. Previous studies have also shown that annualized mortality rate in the first 3–6 months of dialysis initiation is ~40%.(39) Hence it is vital to consider the limited life expectancy of this population when making treatment decisions.

Certain limitations merit consideration when interpreting our findings. We were not able to distinguish between paroxysmal and persistent AF. However, when we performed a subgroup analyses depending on the number of times AF was documented during longitudinal follow up, we observed similar results. The proportion of patients started on warfarin after incident AF diagnosis (~30%) was lower than expected and important clinical information, such as reasons of not starting warfarin treatment, is not available from the data source. However, a recent study found similar results and reported that nearly 60% of patients with AF were not receiving oral anticoagulation treatment and the median time to warfarin initiation from AF diagnosis (~2 years) was also comparable to that seen in our study.(30) This delay can possibly be from factors such as patient refusal or disinterest in warfarin therapy due to inconvenience of frequent monitoring and dose adjustment related to warfarin therapy, along with under-prescribing by providers due to concerns of patient compliance and warfarin associated bleeding complications in this high risk population. Most of our patients were male US veterans; hence, the results may not apply to women or patients from other geographic areas. As with all observational studies on drug effects, we cannot eliminate the possibility of unmeasured confounders and confounding by indication. (40) However, when we performed IPTW analyses, we found similar results. Our whole cohort transitioned to dialysis; hence we were not able to capture mortality events during the pre-dialysis period. Also since many advanced CKD patients do not transition to dialysis, the clinical applicability of our study findings may be limited. We were not able to analyze the warfarin treatment in a time dependent manner and taking into account factors such as warfarin discontinuation. We were not able to analyze the time in therapeutic INR range. Lastly, observational retrospective design of our study does not enable casual inferences.

Conclusions

This study revealed that warfarin use after incident AF diagnosis in advanced CKD is associated with higher risk of ischemic and bleeding events, but lower risk of mortality after ESRD transition. Future studies such as those comparing warfarin with newer oral anticoagulant agents are needed to granularly define the net clinical benefit of anticoagulation therapy in advanced CKD patients with incident AF.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding Sources:

Abbreviations and Acronyms

CKD	chronic kidney disease
AF	Atrial fibrillation
NDD	non-dialysis dependant
CVA	cerebrovascular accident
ICD-9 or ICD-10	International Classification of Diseases, Ninth or Tenth Revisions diagnosis code
CCI	Charlson Comorbidity Index
VA	Veterans Affairs
SD	Standard Deviation
IQR	Inter Quartile Range
CI	Confidence Interval
AIDS/HIV	Acquired Immunodeficiency Syndrome/ Human Immunodeficiency Virus
GI	Gastrointestinal
eGFR	estimated glomerular filtration rate
IPTW	inverse probability of treatment weighted

HR	Hazard Ratio
ESRD	End-stage renal disease
INR	International normalized ratio
RAASi	renin angiotensin-aldosterone system inhibitor

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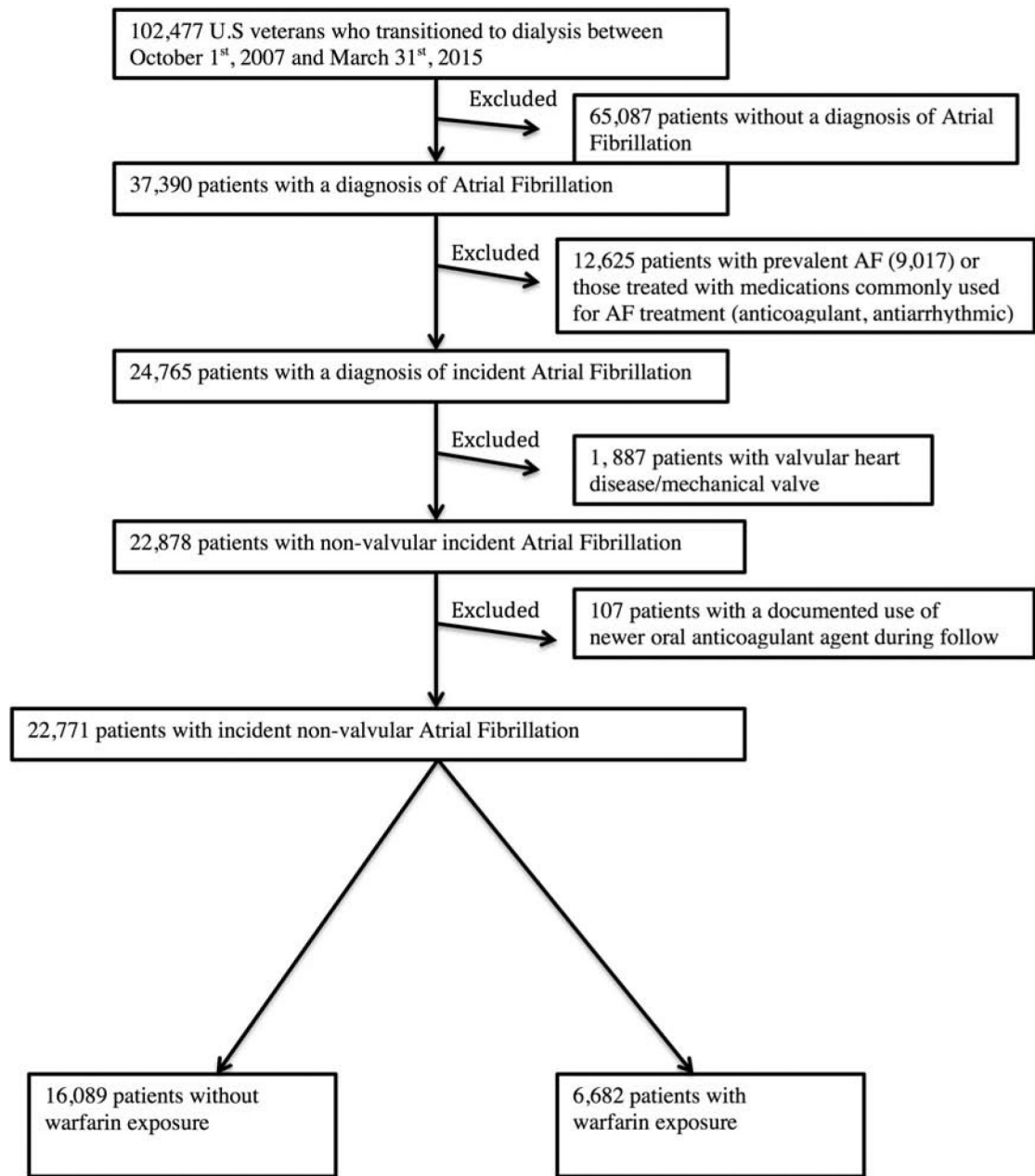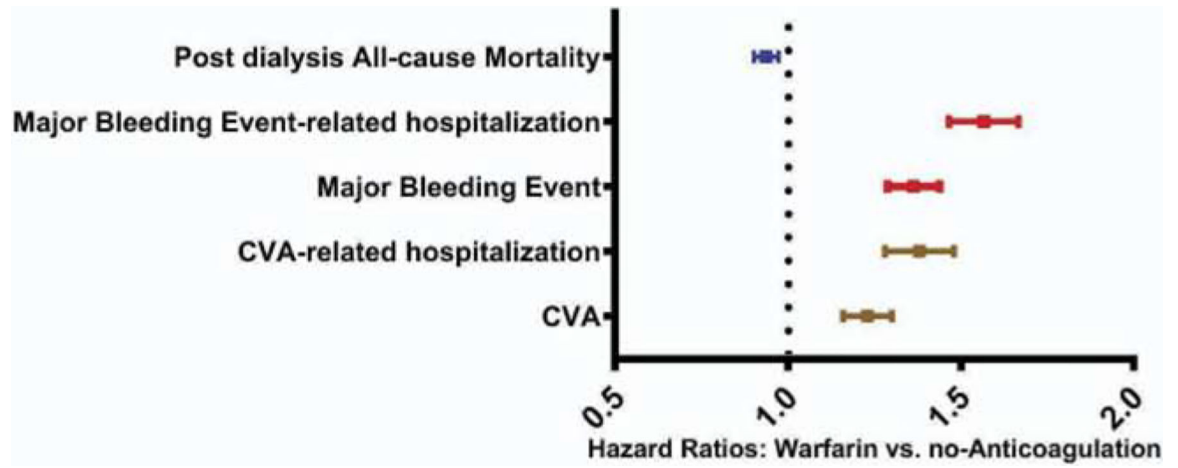**Figure 1.**
Flow chart of patient selection

CENTRAL ILLUSTRATION:
Warfarin Use for Atrial Fibrillation in Advanced Chronic Kidney Disease: Hazard Ratios
CVA, ischemic cerebrovascular accident (ischemic stroke or transient ischemic attack)

Table 1.

Baseline patient characteristics by Warfarin Exposure status

		Overall	Warfarin-Exposure		P-value
			No	Yes	
		N= 22,771	N= 16,089	N= 6,682	
Age	Mean (SD), y 95% CI	73.5 (8.8) 73.4 to 73.6	74.3 (8.7) 74.2 to 74.5	71.4 (8.7) 71.2 to 71.6	<0.001
Sex	Males	21,729(95.4%)	15,311(95.2%)	6,418(96.1%)	0.004
Race					0.076
	Whites	19,228(84.4%)	13,598(84.5%)	5,630(84.3%)	
	Blacks	2,973(13.1%)	2,068(12.9%)	905(13.5%)	
	Others	569(2.5%)	422(2.6%)	147(2.2%)	
Ethnicity	Hispanic	775(3.4%)	548(3.4%)	227(3.4%)	0.973
Marital Status					<0.001
	Married	14,393(68.5%)	10,187(69.4%)	4,206(66.5%)	
	Single	878(4.2%)	626(4.3%)	252(4.0%)	
	Divorced	2,966(14.1%)	1,924(13.1%)	1,042(16.5%)	
	Widowed	2,782 (13.2%)	1,952(13.3%)	830(13.1%)	
Comorbidities					
	Hyperlipidemia	14,000(61.5%)	10,434(64.9%)	3,566(53.4%)	<0.001
	Hypertension	17,999(79.0%)	13,256(82.4%)	4,743(71.0%)	<0.001
	Diabetes	13,672(60.0%)	9,833(61.1%)	3,839(57.5%)	<0.001
	Coronary artery disease	12,864(56.5%)	9,651(60.0%)	3,213(48.1%)	<0.001
	Congestive Heart Failure	11,988(52.7%)	8,788(54.6%)	3,200(47.9%)	<0.001
	Cerebrovascular Disease	9,050(39.7%)	7,028(43.7%)	2,022(30.3%)	<0.001
	Peripheral vascular Disease	9,940(43.7%)	7,603(47.3%)	2,337(35.0%)	<0.001
	Chronic Pulmonary Disease	9,882(43.4%)	7,444(46.3%)	2,438(36.5%)	<0.001
	Dementia	2,163(9.5%)	1,830(11.4%)	333(5.0%)	<0.001
	Depression	3,424(15.0%)	2,723(16.9%)	701(10.5%)	<0.001
	Anemia	9,531(41.9%)	7,503(46.6%)	2,028(30.4%)	<0.001
	Cancer	6,179(27.1%)	4,860(30.2%)	1,319(19.7%)	<0.001
	Paraplegia and Hemiplegia	993(4.4%)	796(5.0%)	197(3.0)	<0.001
	AIDS/HIV	137(0.6%)	111(0.7%)	26(0.4%)	<0.001
	Liver Disease	3,962(17.4%)	3,189(19.8%)	773(11.6%)	<0.001
	Peptic Ulcer Disease	1,990(8.7%)	1,600(9.9%)	390(5.8%)	<0.001
	History of GI bleed	5,268 (23.1%)	4,197 (26.1%)	1,071(16.0%)	<0.001
	History of other Major bleeding	2,512 (11.0%)	1,985(12.3%)	527(7.9%)	<0.001
	Connective Tissue Disease	2,868(12.6%)	2,362(14.7%)	506(7.6%)	<0.001
Medications					
	Statin	7,425(32.6%)	3,643(22.6%)	3,782(56.6%)	<0.001

		Overall	Warfarin-Exposure		P-value
			No	**Yes**	
		N= 22,771	**N= 16,089**	**N= 6,682**	
	Non statin lipid lowering agents	1,392(6.1%)	724(4.5%)	668(10.0%)	<0.001
	Non Aspirin-antiplatelet agents	1,660(7.3%)	901(5.6%)	759(11.4%)	<0.001
	Antiarrhythmics	1,044(4.6%)	91(0.6%)	953(14.3%)	<0.001
	Anti-anginals	2,730(12.0%)	1,245(7.7%)	1,485(22.2%)	<0.001
	Calcium channel blocker	5,961 (26.2%)	3,174 (19.7%)	2,787(41.7%)	<0.001
	Beta blockers	8,081 (35.5%)	3,659 (22.7%)	4,422(66.2%)	<0.001
	RAASi	6,073(26.7%)	3,040(18.9%)	3,033(45.4%)	<0.001
	Antihypertensive vasodilator agents	1,875(8.2%)	926(5.8%)	949(14.2%)	<0.001
	Potassium sparing diuretics	951(4.2%)	386(2.4%)	565(8.5%)	<0.001
	Loop diuretics	6,478(28.5%)	2,953(18.4%)	3,525(52.8%)	<0.001
	Thiazides	1,896(8.3%)	983(6.1%)	913(13.7%)	<0.001
	Antidepressants	2,661(11.7%)	1,315(8.2%)	1,346(20.1%)	<0.001
	NSAIDs	17(0.1%)	13(0.1%)	4(0.1%)	0.60
					<0.001
Systolic Blood pressure, in mm Hg		138.2(23.0) (137.8–138.6)	138.7(22.8) (138.3–139.1)	137.2(23.2) (136.5–137.8)	<0.001
Diastolic Blood pressure, in mm Hg		70.7 (13.0) (70.5–70.9)	70.4(12.9) (70.1–70.6)	71.3(13.1) (70.9–71.6)	<0.001
Hemoglobin, g/dL		12.5 (1.9) 12.5–12.5	12.4(1.9) 12.4–12.4	12.8(1.9) 12.7–12.8	<0.001
eGFR, mL/min/1.73 m^2		35.8 (19.6) (35.5–36.1)	34.8 (19.5) (34.4 – 35.2)	37.8 (19.7) (37.3– 38.3)	<0.001
Charlson Comorbidity		4.5 (3.5) 4.4 to 4.5	4.8 (3.7) 4.8 to 4.9	3.5 (3.0) 3.4 to 3.6	<0.001
Index, Mean (SD) 95% CI					
CHA2DS2-VASc score Mean (SD) 95% CI		5.7 (2.1) 5.7 to 5.8	6.0 (2.0) 6.0 to 6.0	5.1 (2.1) 5.19 to 5.2	<0.001
AF diagnosis to dialysis initiation, years Mean (SD) 95% CI		4.0 (3.8) 4.0 to 4.1	3.7(3.7) 3.6 to 3.7	5.0 (3.8) 4.9 to 5.1	<0.001

SD, standard deviation; CI, confidence interval; RAASi, renin angiotensin aldosterone inhibitors; NSAIDs, Non steroidal anti inflammatory drugs

Table 2.

Outcomes depending on exposure to warfarin (based on patient-time in each risk group)

Outcome of Interest	Overall	No-Warfarin Exposure	Warfarin Exposure
	1000 patient years	1000 patient years	1000 patient years
	[95% CI]	[95% CI]	[95% CI]
Cerebrovascular Accident	107.0 (100.7 – 110.6)	107.3(105.0–109.6)	105.5(100.7–110.6)
Cerebrovascular Accident-hospitalization	52.7(51.4–54.0)	50.8(49.3–52.3)	61.4(58.1–64.9)
Major Bleeding Event	131.5 (129.1 – 134.0)	128.9(126.3–131.5)	144.7(128.6–151.0)
Major Bleeding event-hospitalization	70.3(68.7–71.9)	66.4(64.7–68.1)	88.6(84.4–93.0)
All-cause mortality	512.1(504.8–519.5)	536.7(527.6–545.9)	460.9(448.9–473.3)

CI, confidence interval

-Cerebrovascular accident defined as ischemic stroke or transient ischemic attack

-Major bleeding event defined as hemorrhagic stroke or intracranial bleeding or gastrointestinal bleeding event

Table 3.

Association of Warfarin Exposure with Outcomes in Time Varying Covariate Cox Regression model analyses.

Outcome	Model 1		Model 2		Model 3		Model 4	
	no-warfarin	Warfarin exposed	no-warfarin	Warfarin exposed	no-warfarin	Warfarin exposed	no-warfarin	Warfarin exposed
CVA, Hazard ratio (95% CI)	Ref	1.10 (1.04–1.17)	Ref	1.13(1.07–1.19)	Ref	1.23(1.16–1.30)	Ref	1.23(1.15–1.32)
CVA-hospitalization, Hazard ratio (95% CI)	Ref	1.26(1.18–1.34)	Ref	1.29(1.20–1.38)	Ref	1.38(1.28–1.48)	Ref	1.33(1.221.46)
Major Bleeding Event, Hazard ratio (95% CI)	Ref	1.27 (1.211.33)	Ref	1.28 (1.22 to 1.35)	Ref	1.36(1.291.44)	Ref	1.34(1.251.43)
Major Bleeding Event-Hospitalization, Hazard ratio (95% CI)	Ref	1.47 (1.391.56)	Ref	1.50(1.41–1.59)	Ref	1.56(1.47–1.67)	Ref	1.49(1.381.61)
All-cause post dialysis mortality, Hazard ratio (95% CI)	Ref	0.87(0.84–0.90)	Ref	0.92(0.90–0.96)	Ref	0.94(0.90–0.97)	Ref	0.93 (0.890.98)

Ref, reference; CVA, cerebrovascular accident; CI, confidence interval

Model 1- unadjusted

Model 2- adjusted for age, sex, race, ethnicity, marital status

Model 3- adjusted for age, sex, race, ethnicity, marital status, comorbidities, chadvasc score, Charlson comorbidity index and medications

Model 4- adjusted for age, sex, race, ethnicity, marital status, comorbidities, chadvasc score, Charlson comorbidity index, medications, systolic and diastolic blood pressures, serum/blood hemoglobin values and estimated glomerular filtration rates