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Warfarin Use And the Risk Of Stroke, Bleeding, And Mortality In Older Adults On Dialysis With Incident Atrial Fibrillation

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Abstract

Aim—There is conflicting evidence regarding the safety and effectiveness of warfarin for atrial fibrillation (AF) treatment among older end-stage renal disease (ESRD) patients, and differences among subgroups are unclear.

Methods—Older dialysis patients who were newly diagnosed with AF (7/2007–12/2011) were identified in the United States Renal Data System. The adjusted hazard ratios (HR) of the outcomes (any stroke, ischemic stroke, major bleeding, severe gastrointestinal bleeding, and death)

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Contributions

Research idea and study design: JT, JBS, JZ, GCA, MMA; data acquisition: JT, SB, DLS; data analysis/interpretation: JT, JBS, JZ, GCA, MMA; statistical analysis: JT; supervision or mentorship: DLS, MMA. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. JT takes responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

by time-varying warfarin use were estimated using Cox regression accounting for the inverse probability of treatment weight.

Results—Among 5,765 older dialysis patients with incident AF, warfarin was associated with significantly increased risk of major bleeding (HR=1.50, 95% CI 1.33–1.68), but was not statistically associated with any stroke (HR=0.92, 95% CI 0.75–1.12), ischemic stroke (HR=0.88, 95%CI 0.70–1.11) or gastrointestinal bleeding (HR=1.03, 95% CI 0.80–1.32). Warfarin use was associated with a reduced risk of mortality (HR=0.72, 95%CI 0.65–0.80). The association between warfarin and major bleeding differed by sex (male: HR=1.29; 95%CI 1.08–1.55; female: HR=1.67; 95%CI 1.44–1.93; P-value for interaction=0.03).

Conclusion—Older ESRD patients with AF who were treated with warfarin had a no difference in stroke risk, lower mortality risk, but increased major bleeding risk. The bleeding risk associated with warfarin was greater among women than men. The risk/benefit ratio of warfarin may be less favorable among older women.

Keywords

atrial fibrillation; anticoagulants; end stage renal disease; warfarin; stroke

INTRODUCTION

Atrial fibrillation (AF) is common among patients with end stage renal disease (ESRD), reaching a prevalence as high as 32% among those aged 65 years or older with ESRD (1). Furthermore, the incidence of AF among older patients on dialysis increased from 11.3% in 1995 to 14.5% in 2007 (2). Patients on dialysis with AF have a 2-fold higher risk for mortality (3) and a 2- to 3-fold higher risk for stroke (4) compared to patients on dialysis without AF.

Warfarin has been used to prevent thrombotic cerebrovascular events in patients with AF without ESRD for decades (5). Despite abundant evidence supporting warfarin use in the general population with AF (6, 7), optimal anticoagulation in patients with ESRD and AF is not well defined because these patients are typically excluded from randomized controlled trials (8). Current evidence from observational studies offers conflicting results. In previous studies, warfarin treatment has been found to be associated with a reduced risk of stroke and mortality (9–12), with no statistically significant association with stroke and mortality, and an increased risk of stroke and mortality (13–17). Pooled estimates from recent meta-analyses of warfarin use among patients of all ages on dialysis with AF suggest that warfarin does not offer stroke and mortality risk reduction, but consistently increases bleeding risk (18–22). Due to recognized limitations of warfarin use such as frequent blood monitoring, food and drug restrictions, uncertain benefit for reducing stroke risk, and increase in bleeding risk, experts have raised concern about warfarin's safety and effectiveness in patients with AF undergoing dialysis (5, 8, 23–25).

The risks and benefits among older patients undergoing dialysis are less clear. Previous studies of warfarin in cohorts of older patients undergoing dialysis reported that warfarin use was not beneficial in reducing ischemic stroke or mortality risk (14, 15, 26). The bleeding

risk among older dialysis patients is unclear. Among older patients undergoing dialysis, warfarin may have differing risks and benefits by sex, age group, and race.

The main goal of this study was to quantify the risk and benefits of warfarin use with respect to stroke, bleeding, and mortality in a national cohort of older patients undergoing dialysis with incident AF. We also compared the impact of warfarin use on these outcomes among subgroups of patients with ESRD by sex, age group, and race. We reasoned that such information might be helpful, given that these basic patient and clinical characteristics could potentially be used to identify particular subpopulations with a distinct risk/benefit balance of warfarin treatment.

MATERIALS AND METHODS

Study population and data

We used the United States Renal Data System (USRDS), a national registry of patients with ESRD, to conduct our analysis. We identified a cohort of 9,784 older adults (aged ≥ 65 years) with ESRD who had an incident AF diagnosis (i.e. exclude pre-existing AF cases) from January 1, 2007 to December 31, 2011 based on 1 inpatient or 2 outpatient diagnosis codes within 30 days of each other indicating AF (International Classification of Diseases, Ninth Revision [ICD-9] code 427.31). We required patients to have uninterrupted Medicare Part A, B, and D coverage from 6 months before through 30 days after AF diagnosis. We excluded patients: 1) with valvular disease associated with AF in 6 months prior to AF diagnosis (n=3,039) (10); 2) who were not on dialysis at AF diagnosis (n=243); 3) warfarin prescription in 6 months prior to AF diagnosis (n=642); 4) with missing Medical Evidence Report (Centers for Medicare & Medicaid Services [CMS] form 2728) (n=84). We further excluded 11 patients who had kidney transplantation or died prior to AF discharge resulting in a final analytic sample of 5,765 patients.

Patient characteristics

We ascertained patients' demographics, dialysis modality, geographic region, and comorbid conditions from the Medical Evidence Report (Centers for Medicare & Medicaid Services [CMS] form 2728) and all available Medicare inpatient claims data (i.e. from January 1, 1999 to AF diagnosis) using previously published ICD-9 based algorithms (27, 28) (Appendix Table 1). We ascertained history of medication use in the 6 months before AF diagnosis and concomitant use of antiplatelets and NSAIDs within 30 days of AF diagnosis from the Medicare prescription claims data.

Stroke and bleeding risk scores

We calculated the CHA_2DS_2-VASc (29) for stroke risk stratification and HAS-BLED (30) scores for bleeding risk stratification (Appendix Table 2). We modified the categorization of the CHA_2DS_2-VASc and HAS-BLED because the original categorization was not designed for older adults on dialysis. The original CHA_2DS_2-VASc categorizes low risk for score of 0, intermediate risk for score of 1, and high risk for score ≥ 2 (29). Our study population had a minimum CHA_2DS_2-VASc score of 1 due to age, so we refined the CHA_2DS_2-VASc categorization: low risk for score of 1, intermediate risk for score 2–3, and high risk for

score 4–8. The original HAS-BLED categorizes low risk for score 0, intermediate risk for score of 2–3, and high risk for score ≥ 3 (30). Our study population had a minimum HAS-BLED score of 2 due to age and abnormal kidney function and a maximum HAS-BLED score of 8 due to lack of international normalized ratio (INR). We refined the HAS-BLED categorization: intermediate risk for score 2–3, and high risk for score 4–8.

Warfarin use

We ascertained the date of each warfarin prescription and the days-supply using the Medicare Part D prescription drug events. We considered warfarin treatment as a time-varying exposure such that patients contributed person-time at risk to the untreated group and the treated group according to their warfarin prescription records. Patients were followed from the date of AF discharge (for those identified by inpatient claims) or the second AF diagnosis (for those identified by outpatient claims) until they developed the outcome of interest or the end of follow-up (December 31, 2011). We censored patients at death (for all outcomes other than mortality), kidney transplantation, loss of Medicare coverage, or the end of follow-up. Patients contributed person-time at risk to the untreated group before the date of their first warfarin prescription, and were considered treated after they started using warfarin until they discontinued treatment; if they re-started warfarin treatment, they contributed person-time at risk to the treated group until they discontinued treatment again. In our main analysis, we considered failure to fill a subsequent warfarin prescription within 30 days after their supply ran out as treatment discontinuation (10).

Stroke, bleeding, and mortality

The outcomes of interest were any stroke, ischemic stroke, major bleeding, gastrointestinal bleeding, and all-cause mortality. We defined: 1) any stroke as any inpatient diagnosis of ischemic stroke, cerebral thrombosis, cerebral ischemia and other cerebrovascular disease (31), 2) ischemic stroke as any inpatient diagnosis of ischemic stroke based on previously validated ICD-9 diagnosis (32), 3) major bleeding as any inpatient diagnosis of subarachnoid bleeding, intracerebral bleeding, gastrointestinal bleeding, hematuria, and hemorrhage not otherwise specified (27, 33), and 4) inpatient diagnosis of gastrointestinal bleeding based on the primary ICD-9 diagnosis codes (34) (Appendix Table 1). We ascertained the date of death and the cause of death from the Medical Evidence Report.

Statistical analysis

We evaluated the association of time-varying warfarin use and these outcomes using Cox proportional hazards models with robust standard errors adjusted for potential confounders such as demographics, dialysis characteristics, year of AF diagnosis, history of stroke/bleeding, concomitant use of NSAIDs or antiplatelet agents, comorbid conditions, and CHA_2DS_2-VASc and HAS-BLED risk categories. We checked the proportional-hazards assumption using the proportionality test based on Schoenfeld residuals.

To visualize the differences in outcomes between warfarin users and non-users, we first graphed the overall cumulative incidence of stroke outcomes, bleeding outcomes, and mortality by warfarin use, and compared the difference in these outcomes by warfarin use through log-rank tests. To account for confounding by indication or channeling bias (35), we

generated the stabilized inverse probability of treatment weight (IPTW) for warfarin use (i.e. any use of warfarin during the study follow up) as previously described (36, 37). The probability of being treated with warfarin was estimated using a logistic regression model that included all the potential confounders listed in Table 1. We then compared the measured covariates between warfarin users and nonusers before and after weighting using the standardized differences (38). We also checked the overlap of the IPTW graphically, and we truncated the weights that were outside of the range of complete overlap (i.e. lower than 0.8 or higher than 1.8). Using the weighted sample, we estimated hazard ratios (HR) and the corresponding 95% confidence intervals (95% CI) of these outcomes by warfarin using an adjusted Cox proportional hazards model and the competing risk model with robust standard errors.

Given the high mortality rate in older patients with ESRD, we conducted competing-risk regression using the Fine and Gray model based on a semiparametric subdistribution hazards model (39) for the stroke and bleeding outcomes. We considered death from causes other than the outcome of interest as a competing event since it precluded patients from developing stroke or bleeding.

We also tested whether the impact of warfarin on stroke outcomes, bleeding outcomes, and mortality differed by subgroups: sex, age (65 to < 75, 75 to < 85, or ≥ 85), race, and dialysis modality (hemodialysis or peritoneal dialysis) using multiplicative interaction terms in the Cox proportional hazards model with IPTW. However, there were few older peritoneal dialysis (3%) in this study, and these results should be interpreted with caution.

All statistical analyses were performed using Stata 14.0 (StataCorp, College Station, TX). Statistical significance was defined as 2-sided $P<0.05$.

Sensitivity analysis

For sensitivity analysis, we conducted an intention-to-treat analysis to assess the association of warfarin initiation (i.e. whether warfarin was initiated within 30 days of AF discharge) and stroke outcomes, bleeding outcomes, and mortality. In the multivariate analysis, we adjusted for potential confounders previously mentioned. We also conducted the analysis in the IPTW weighted sample and repeated the competing risk analysis.

RESULTS

Study population

Among the 5,765 older adults undergoing dialysis who were newly diagnosed with AF, 28.6% used warfarin during the study period. The study population had a median age of 74 years (interquartile range [IQR] 69–80 years) at the time of AF diagnosis and 96.7% were undergoing hemodialysis. Almost all patients (99.8%) had a CHA_2DS_2-VASc score ≥ 2 corresponding to intermediate or high stroke risk in both the ever use (28.6%) and never use (71.4%) groups. Half of the patients (49.5%) were categorized as being at intermediate and half (50.5%) at high risk of bleeding based on HAS-BLED scores. After applying the stabilized weight, all the observed patient characteristics were balanced (Table 1).

Warfarin use and stroke outcomes

We observed a total of 950 any stroke events for an incidence rate of 14.7 (95% CI: 13.9–15.7) per 100 person-years and 737 ischemic stroke events with a rate of 10.4 (95% CI: 9.6–11.1) per 100 person-years (Table 2). The Kaplan-Meier survival curve suggested that warfarin use was not statistically associated with any stroke event (log-rank test P=0.32; Figure 1a) or ischemic stroke (log-rank test P=0.17; Figure 1b). In the adjusted analysis using weighted sample, warfarin use was not independently associated with any stroke (HR=0.92, 95% CI: 0.75–1.12) or ischemic stroke (HR=0.88, 95% CI: 0.70–1.11) (Table 3). Results were consistent when using a competing risk analysis (any stroke HR=0.96, 95% CI: 0.79–1.17; ischemic stroke HR=0.93, 95% CI: 0.74–1.16). In the intention-to-treat analysis, warfarin initiation was not independently associated with any stroke (HR=0.90, 95% CI: 0.75–1.08) nor ischemic stroke (HR=0.88, 95% CI: 0.71–1.09) (Supplement Table 2).

Warfarin use and bleeding outcomes

We observed 1,966 major bleeding events for an incidence rate 33.9 (95% CI:32.4–35.4) per 100 person-years, and 506 gastrointestinal bleeding events with a rate of 6.9 (95% CI:6.3–7.6) per 100 person-years (Table 2). The Kaplan-Meier curve suggested that warfarin use was significantly associated with major bleeding (log-rank test P<0.001; Figure 1c), but not with gastrointestinal bleeding (log-rank test P=0.87; Figure 1d). In the adjusted analysis using weighted sample, warfarin use was independently associated with major bleeding (HR=1.50, 95% CI:1.33–1.68), but not with gastrointestinal bleeding (HR=1.03, 95% CI: 0.80–1.32) (Table 3). In the competing risk analysis, warfarin use was also independently associated with increased risk of major bleeding (HR=1.63, 95% CI: 1.45–1.83), but not with gastrointestinal bleeding (HR=1.13, 95% CI: 0.88–1.45). Similarly in the intention-to-treat analysis, warfarin initiation was associated with increased risk of major bleeding (HR=1.18, 95% CI: 1.05–1.33), but not associated with gastrointestinal bleeding (HR=1.10, 95% CI: 0.87–1.40) (Supplement Table 2).

Warfarin use and mortality

We observed 3,825 deaths for a mortality rate of 49.5 (95% CI: 48.0–51.1) per 100 person-years (Table 2). From the Kaplan-Meier curve, warfarin use was associated with significantly lower mortality risk (log-rank test P<0.001) (Figure 1e). Warfarin use was independently associated with significantly reduced risk of mortality (HR=0.72, 95% CI 0.65–0.80) (Table 3). Similar result was shown in the intention-to-treat analysis (HR=0.80, 95% CI: 0.73–0.88).

Differential effects of warfarin use

The association between warfarin use and any stroke, gastrointestinal bleeding, and mortality outcomes did not differ by age, sex, dialysis type, or race (all P>0.05) (Table 4). The association between warfarin and major bleeding only differed by sex (P-value for interaction=0.03). Warfarin use was associated with a 1.29-fold risk of major bleeding among men (95% CI: 1.08–1.55) and a 1.67-fold risk among women (95% CI: 1.44–1.93). The association between warfarin and ischemic stroke only differed by dialysis modality (P-value for interaction=0.02). Warfarin was not associated with ischemic stroke among older

patients on hemodialysis (HR=0.84, 95% CI 0.66–1.07) but associated with increased risk of ischemic stroke among those on peritoneal dialysis (HR=2.59, 95% CI: 1.06–6.32).

These differential association was not observed in the intention-to-treat analysis (Supplement Table 3). On the other hand, the association between warfarin initiation and all-cause mortality differed by sex, age group, race, and dialysis modality in the intention-to-treat analysis. Additionally, the younger age group (65 to <75 y) was associated with reduced risk of ischemic stroke (HR=0.76, 95% CI: 0.59–0.99) or any stroke (HR=0.73, 95% CI: 0.54–0.99), and increased risk of major bleeding (HR=1.21, 95% CI: 1.04–1.41); but the older age groups were not associated with these stroke or bleeding outcomes.

DISCUSSION

In this national study of older adults undergoing dialysis with incident AF, 15.5% of patients initiated warfarin therapy within 30 days of AF diagnosis and 46.8% of them discontinued its use after a median treatment length of 8.6 months (40). Warfarin use was associated with 0.72-fold lower risk of mortality, but associated with 1.50-fold higher risk of major bleeding. However, the risk of major bleeding differed for older men and women; warfarin use was associated with an increased risk of major bleeding for both men and women but a greater risk for among women. Warfarin use was not statistically associated with any stroke event or ischemic stroke among older patients on hemodialysis, but was associated with 2.59-fold increased risk of ischemic stroke among older patients on peritoneal dialysis.

To our knowledge, ours is one of only a few recent analyses examining the benefits and risks of warfarin among the older patients with AF and ESRD (14, 15, 26), and is the first study that assessed both the stroke and bleeding outcomes in the presence of the competing risk. In this study, we observed no association between warfarin use and any stroke or ischemic stroke, which was consistent with the results reported by previous cohort studies of patients on dialysis in the U.S. and Canada (10, 14, 15). A report by Shen et al. studied hemodialysis patients of all ages in the USRDS and reported no association between warfarin initiation and any stroke including stroke death or ischemic stroke in the intention-to-treat analysis, and marginal association (HR 0.68, 95% CI 0.47–0.99) in the as-treated analysis (10). Importantly, we extended these previous findings and tested for differential effects of warfarin on these outcomes through effect modification analysis by sex, age group, and race. We found that the impact of warfarin on major bleeding differ by sex. We also observed a difference in ischemic stroke risk by dialysis modality; however interpretation of the PD subgroup data should be cautioned since only a (41, 42) small minority of the study population (3%) had PD as their dialysis modality.

Similar to our analysis of bleeding outcomes, previous cohort studies reported significant association between warfarin use and major bleeding events (15, 43, 44). Our results on the lack of association between warfarin and gastrointestinal bleeding also corroborated previous studies including Shen et al. (10, 14). However, other studies reported lack of association between warfarin use and bleeding events among patients with ESRD (45). These studies reported < 50 bleeding events and < 100 warfarin users, so they might not have enough statistical power to detect significant association. Importantly, we identified

differences in the risk of major bleeding by sex which suggests that women may be at an increased risk of major bleeding while treated with warfarin.

We found that warfarin use significantly reduced the risk of mortality, and this result was consistent with previous reports (10, 11, 44, 46, 47). We extended these previous findings to older patients with AF who were undergoing dialysis. Other studies reported lack of association between warfarin use and mortality (3, 13, 14, 45, 47, 48) likely because warfarin use was parameterized as a time-fixed exposure, potentially introducing misclassification. As Genovesi et al. pointed out, it is necessary to consider the actual time of warfarin intake in the analysis for the protective effect of the drug to become evident (47). We accounted for the fact that warfarin users often discontinue or change their treatment at a high rate by defining warfarin use as a time-varying variable. Therefore, our findings may be more generalizable to older adults undergoing dialysis who may have complex oral anticoagulation treatment. While our study did not investigate the cause of death, other reports suggested that the reduction in mortality may be due to a reduction in cardiovascular death rather than stroke death (10, 47).

Our study has several limitations. First, we ascertained warfarin treatment status and duration from the prescription claim status, which might not reflect the true treatment compliance. Because of frequent dosage adjustment according to INR status, the days of supply on claims might not reflect the duration of medication consumption. We mitigated possible misclassification bias of exposure by defining warfarin treatment as a time-varying exposure to appropriately characterize treatment start and discontinuation. When we varied the length of the refill grace period, the results were consistent with our main findings. Because INR data is not available in our study, it is possible that patients discontinued warfarin therapy due to poor control of their INR (10). Previous research suggested that INR monitoring is often inadequate and high INR-variability was associated with increased risk of stroke and bleeding (13, 47, 49). We are not able to understand whether warfarin is associated with stroke and bleeding outcomes because of over- or under-dosing of warfarin or the effect of warfarin per se, so further investigation is required to discern the true effect of warfarin. While we adjusted for most patient characteristics that may confound the association between warfarin use and outcomes, we could not rule out biases due to residual confounding from unknown or unmeasured confounders including the use of over-the-counter aspirin or geriatric syndromes like frailty (50–53) because they were not available in this data. However, to account for differences in the older dialysis patients with AF who did and did not use warfarin we used IPTW to balance the populations on both observed and likely on unobserved differences (54). The stroke and bleeding outcomes were defined using diagnosis code, which may be subject to potential misclassification bias. This limitation is inherent in administrative claims analysis, and we used codes previously validated or published in the literature. The benefits of this study are the large sample size, the new user design of warfarin, and the identification of incident cases of AF among older dialysis patients.

In conclusion, warfarin use was not statistically associated with any stroke, ischemic stroke, or gastrointestinal bleeding, but associated with a significantly increased risk of major bleeding and decreased risk of mortality among older patients on dialysis with incident AF.

Warfarin use had a differential effect on major bleeding; while both men and women were at risk of major bleeding while using warfarin, the risk was greater among older women. Our findings provide some evidence in favor of warfarin use among older patients on dialysis with AF due to significant improvement in survival, but the lack of stroke reduction and increased bleeding risk should be taken into consideration. Physicians should balance the risks of bleeding and potential mortality benefit when initiating warfarin among older patients on dialysis who are newly diagnosed with AF.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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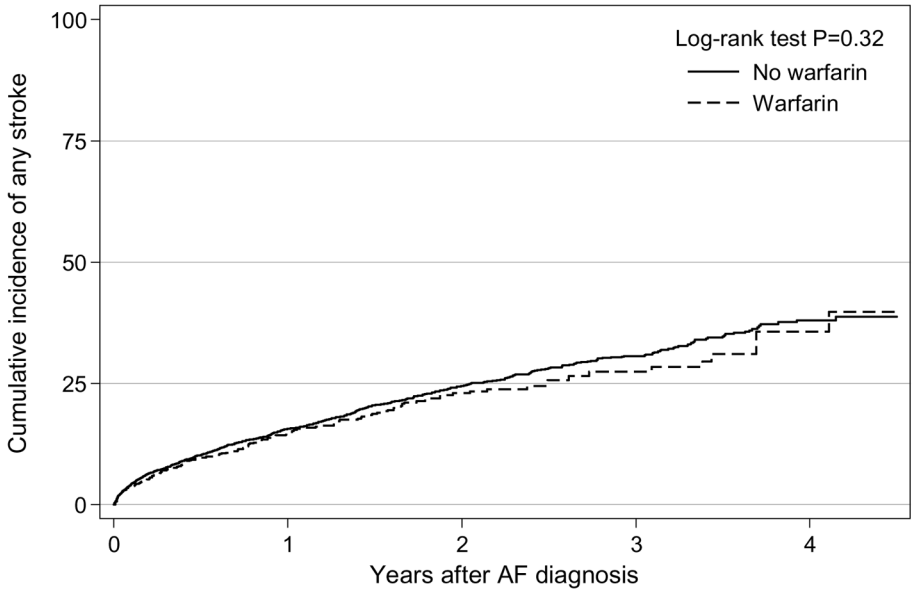
Figure 1a.



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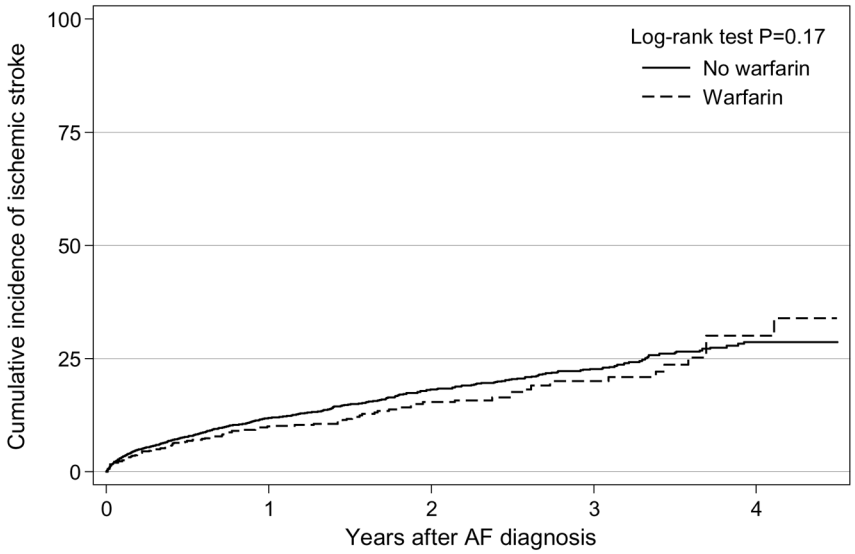

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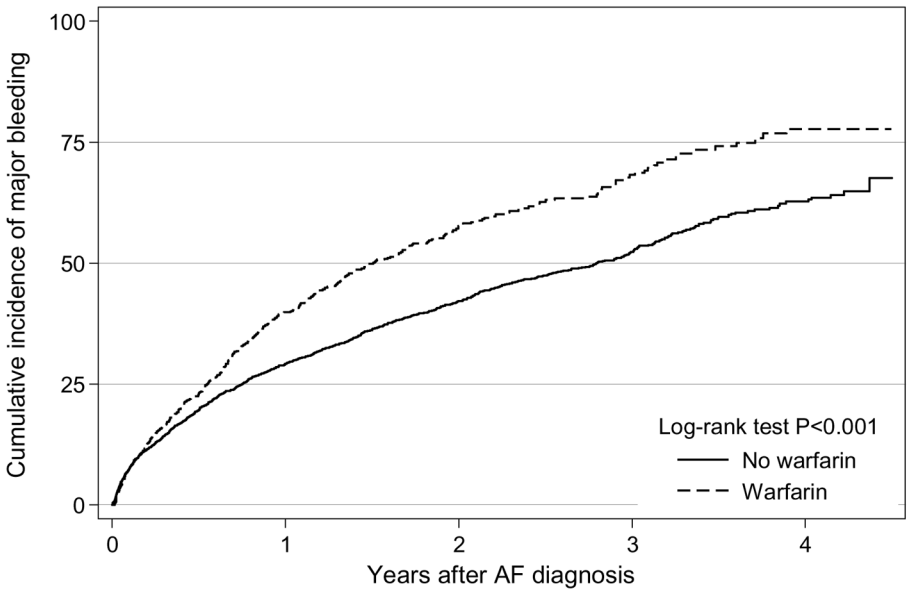

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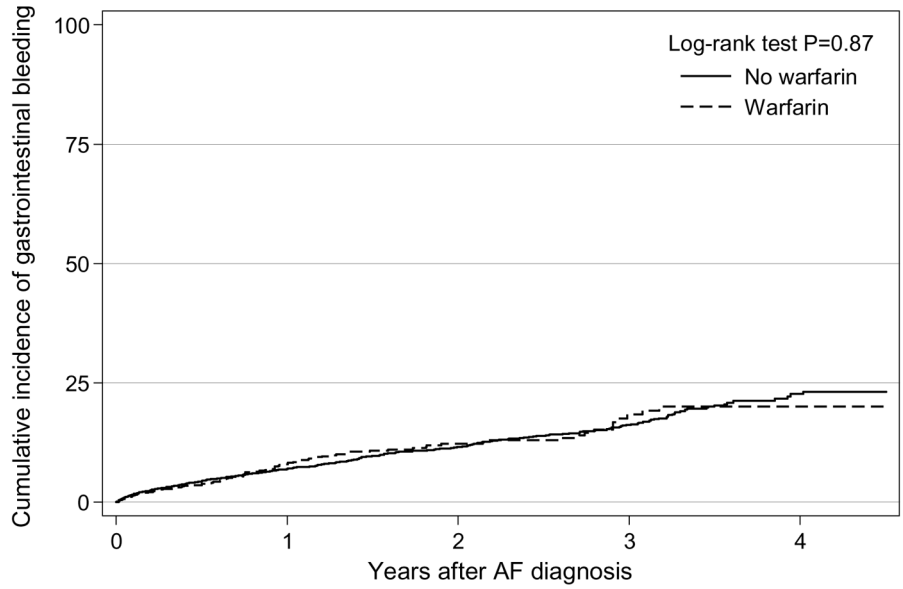

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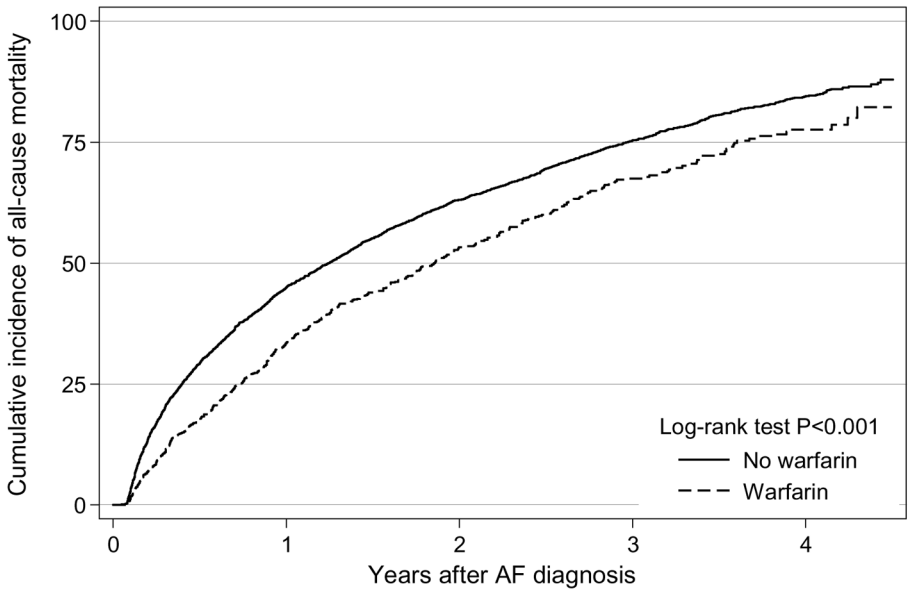

Figure 1.

Figure 1a. Cumulative incidence of any stroke by warfarin use among older patients (≥ 65 years) undergoing dialysis with newly diagnosed atrial fibrillation

Figure 1b. Cumulative incidence of ischemic stroke by warfarin use among older patients (≥ 65 years) undergoing dialysis with newly diagnosed atrial fibrillation

Figure 1c. Cumulative incidence of major bleeding by warfarin use among older patients (≥ 65 years) undergoing dialysis with newly diagnosed atrial fibrillation

Figure 1d. Cumulative incidence of gastrointestinal bleeding by warfarin use among older patients (≥ 65 years) undergoing dialysis with newly diagnosed atrial fibrillation

Figure 1e. Cumulative incidence of all-cause mortality by warfarin use among older patients (≥ 65 years) undergoing dialysis with newly diagnosed atrial fibrillation

Table 1

Patient characteristics before and after inverse probability treatment weighting (IPTW).

Patient characteristics	Before IPTW			After IPTW		
	Warfarin Use (n = 1,651)	No use (n = 4,114)	Standardized difference	Warfarin Use	No use	Standardized difference
Demographics						
Age at AF diagnosis, mean (year)	73.9	75.1	−0.180	74.4	74.7	−0.043
Female sex, %	56.4	57.0	−0.011	57.0	56.8	0.003
Non-white, %	35.6	37.9	−0.048	37.3	37.3	−0.001
Hispanic, %	19.0	18.8	0.003	18.6	18.8	−0.006
Year of AF diagnosis, %						
2007	24.7	22.8	0.042	23.8	23.4	0.009
2008	28.0	26.8	0.027	26.8	27.0	−0.004
2009	21.6	20.8	0.020	21.4	21.0	0.011
2010	17.6	17.9	−0.010	17.8	17.9	−0.001
2011	8.2	11.7	−0.116	10.1	10.7	−0.020
Dialysis vintage, mean (year)	4.3	4.5	−0.054	4.4	4.4	−0.004
Modality, %						
Hemodialysis	96.0	96.9	−0.049	96.2	96.6	−0.020
Peritoneal dialysis	4.0	3.1	0.049	3.8	3.4	0.020
Geographic region, %						
Northeast	19.2	16.9	0.059	18.1	17.6	0.013
Midwest	23.4	20.0	0.081	21.6	21.0	0.015
South	41.6	45.1	−0.072	43.6	44.2	−0.011
West	15.9	17.9	−0.054	16.7	17.3	−0.015
History of medication use, %						
Anticoagulant agent	0.8	0.6	0.028	0.7	0.6	0.009
Antiplatelet agent	25.9	25.1	0.017	25.8	25.3	0.011
Beta-Blocker	43.7	43.6	0.002	43.6	43.6	−0.000
Calcium channel blocker	48.2	47.3	0.018	47.6	47.6	0.001
Calcium acetate	31.6	31.8	−0.005	31.7	31.7	−0.000
Central acting agonist	15.7	16.6	−0.024	16.2	16.4	−0.003

Patient characteristics	Before IPTW			After IPTW		
	Warfarin Use (n = 1,651)	No use (n = 4,114)	Standardized difference	Warfarin Use	No use	Standardized difference
Diuretic	20.5	20.4	0.002	20.1	20.4	−0.009
Lipid-lowering agent, nonstatin	8.0	7.9	0.004	8.1	7.9	0.007
Nitrate	23.1	23.5	−0.011	23.9	23.5	0.008
NSAID	8.7	9.3	−0.021	8.7	9.0	−0.012
PPI or H2-blocker	45.4	48.8	−0.068	47.0	47.8	−0.018
Sevelamer	43.3	42.6	0.015	43.2	42.8	0.008
Statin	47.7	45.3	0.048	46.7	46.1	0.013
History of comorbid conditions, %						
Alcohol dependence	0.8	0.8	−0.004	0.8	0.8	0.001
Tobacco use	10.2	13.0	−0.086	12.1	12.2	−0.006
Concomitant use of antiplatelets or NSAIDs	15.6	16.0	−0.013	15.8	15.9	−0.002
Cancer (excl. non-melanoma skin cancer)	14.5	16.1	−0.045	14.9	15.6	−0.020
Cerebrovascular disease	18.9	22.6	−0.092	21.0	21.6	−0.015
Ischemic heart disease	63.5	67.5	−0.082	65.9	66.4	−0.010
Diabetes mellitus	68.2	73.0	−0.105	70.7	71.6	−0.020
Congestive heart failure	64.9	70.6	−0.121	68.2	69.0	−0.018
Hypertension	98.1	98.8	−0.058	98.4	98.6	−0.017
Liver disease	5.5	8.8	−0.130	7.3	7.8	−0.021
Myocardial infarction	11.4	17.8	−0.180	14.8	16.0	−0.034
Peripheral vascular disease	39.1	43.4	−0.088	41.9	42.2	−0.006
Pulmonary disease	33.3	37.9	−0.098	35.2	36.6	−0.029
Stroke/TIA/TE history	11.0	14.1	−0.094	13.0	13.3	−0.008
Bleeding history	22.5	32.5	−0.224	27.7	29.6	−0.042
Risk Scores, %						
CHA2DS2-VASc						
Low	0.2	0.2	0.003	0.2	0.2	−0.003
Intermediate	18.7	14.3	0.119	16.3	15.5	0.021
High	81.2	85.6	−0.118	83.5	84.3	−0.021
HAS-BLED						
Intermediate	56.3	46.4	0.199	51.0	49.3	0.035

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Patient characteristics	Before IPTW			After IPTW		
	Warfarin Use (n = 1,651)	No use (n = 4,114)	Standardized difference	Warfarin Use	No use	Standardized difference
High	43.7	53.6	−0.199	49.0	50.7	−0.035

IPTW was used to balance the observed baseline characteristics in order to account for potential confounding bias. Standardized difference was a balance assessment that compares the difference in means of the observed covariates.

Table 2

Time-varying analysis: Incidence rate of stroke outcomes, bleeding outcomes, and all-cause mortality among older dialysis patients (≥65 years) with newly diagnosed atrial fibrillation. Incidence rates were unadjusted.

Outcome	Comparison group, by treatment status	Number of events	Follow-up time (person-years)	Incidence rate (per 100 person-years, 95% CI)
Stroke-related outcomes				
Any stroke	No warfarin	826	5,780.4	14.3 (13.3–15.3)
	Warfarin	124	1,086.8	11.4 (9.6–13.6)
Ischemic stroke	No warfarin	644	5,975.6	10.8 (10.0–11.6)
	Warfarin	93	1,132.9	8.2 (6.7–10.0)
Bleeding-related outcomes				
Major bleeding	No warfarin	1,559	4,829.6	32.3 (30.7–33.9)
	Warfarin	407	975.7	41.7 (37.8–46.0)
Gastrointestinal bleeding	No warfarin	426	6,074.8	7.0 (6.4–7.7)
	Warfarin	80	1,230.3	6.5 (5.2–8.1)
All-cause mortality	No warfarin	3,349	6440.2	52.0 (50.3–53.8)
	Warfarin	476	1287.5	37.0 (33.8–40.4)

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Table 3

Time-varying analysis: Association of warfarin use with stroke outcomes, bleeding outcomes, and all-cause mortality among older adults (≥ 65 years) undergoing dialysis with newly diagnosed atrial fibrillation (N = 5,765)

Outcome	Unadjusted HR (HR, 95% CI)	Adjusted* HR in multivariate analysis (HR, 95% CI)	Adjusted* HR in IPTW weighted sample (HR, 95% CI)	HR after accounting for the competing risk of mortality in IPTW weighted sample (HR, 95% CI)
Stroke-related outcomes				
Any stroke	0.86 (0.71–1.04)	0.91 (0.75–1.10)	0.92 (0.75–1.12)	0.96 (0.79–1.17)
Ischemic stroke	0.82 (0.66–1.03)	0.87 (0.70–1.09)	0.88 (0.70–1.11)	0.93 (0.74–1.16)
Bleeding-related outcomes				
Major bleeding	1.38 (1.23–1.54) *	1.48 (1.32–1.66) *	1.50 (1.33–1.68) *	1.63 (1.45–1.83) *
Gastrointestinal bleeding	0.98 (0.77–1.25)	1.05 (0.82–1.34)	1.03 (0.80–1.32)	1.13 (0.88–1.45)
All-cause mortality	0.69 (0.62–0.76) *	0.72 (0.65–0.79) *	0.72 (0.65–0.80) *	-

* P-value for effect modification statistically significant < 0.05.

Adjusted for age category, sex, race, ethnicity, year of AF diagnosis, region, dialysis modality, dialysis vintage, alcohol dependence, tobacco use, concomitant use of antiplatelets or NSAIDs, cancer (excl. non-melanoma skin cancer), cerebrovascular disease, ischemic heart disease, diabetes mellitus, congestive heart failure, hypertension, liver disease, myocardial infarction, peripheral vascular disease, pulmonary disease, stroke/TIA/TE history, bleeding history, CHA2DS2-VASc score category, HAS-BLED score category

Table 4

Time-varying analysis: Warfarin use and stroke outcomes, bleeding outcomes, and all-cause mortality by sex, age, race and dialysis modality among older adults (≥ 65 years) undergoing dialysis with newly diagnosed atrial fibrillation

	Any stroke	Ischemic stroke	Major bleeding	Gastrointestinal bleeding	All-cause Mortality
	HR, 95% CI	HR, 95% CI	HR, 95% CI	HR, 95% CI	HR, 95% CI
Sex					
Male (n=2,491)	0.80 (0.57–1.11)	0.74 (0.50–1.08)	1.29 (1.08–1.55) *	1.06 (0.74–1.54)	0.72 (0.62–0.84)
Female (n=3,274)	0.98 (0.77–1.26)	0.97 (0.73–1.29)	1.67 (1.44–1.93) *	1.00 (0.70–1.41)	0.72 (0.63–0.83)
Age category					
65 to < 75 y (n=3,062)	0.96 (0.74–1.25)	0.89 (0.66–1.20)	1.47 (1.27–1.71)	0.97 (0.70–1.35)	0.73 (0.64–0.84)
75 to <85 y (n=2,157)	0.88 (0.64–1.22)	0.88 (0.61–1.28)	1.52 (1.25–1.84)	1.09 (0.71–1.66)	0.68 (0.57–0.80)
≥ 85 y (n=546)	0.74 (0.31–1.77)	0.82 (0.31–2.12)	1.57 (1.01–2.45)	1.24 (0.46–3.30)	0.85 (0.60–1.21)
Race					
White (n=3,617)	0.87 (0.67–1.12)	0.86 (0.64–1.16)	1.59 (1.38–1.83)	0.99 (0.72–1.35)	0.74 (0.65–0.84)
Non-white (n=2,148)	1.00 (0.73–1.35)	0.92 (0.65–1.30)	1.36 (1.11–1.65)	1.10 (0.72–1.67)	0.69 (0.57–0.83)
Modality					
Hemodialysis (n=5,572)	0.89 (0.73–1.09)	0.84 (0.66–1.07) *	1.49 (1.33–1.68)	1.03 (0.80–1.33)	0.72 (0.65–0.80)
Peritoneal dialysis (n=193)	1.93 (0.82–4.50)	2.59 (1.06–6.32) *	1.60 (0.89–2.88)	1.07 (0.31–3.62)	0.66 (0.40–1.10)

* P-value for effect modification statistically significant < 0.05.

Analysis was based on the adjusted Cox regression analysis in the IPTW weighted sample.