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Article

Effectiveness and Safety of Warfarin Initiation in Older Hemodialysis Patients with Incident Atrial Fibrillation

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Summary

Background and objectives Although generally recommended in atrial fibrillation (AF) patients, the effectiveness and safety of oral anticoagulation in dialysis patients with AF is unknown.

Design, setting, participants, & measurements We assembled a cohort of older hemodialysis patients who initiated dialysis without prior record of AF and who had prescription drug benefits through three state-administered programs. The index event was a first hospitalization with diagnosed AF; patients with any recorded prior warfarin use were excluded. Eligible patients survived ≥30 days from discharge, and new warfarin use was recorded from prescription records during that 30-day window. Propensity-matched warfarin users and nonusers were compared using Cox regression. Outcomes included ischemic stroke, hemorrhagic stroke, and mortality.

Results Among 2313 patients with new AF who survived 30 days from discharge, 249 (10.8%) filled a prescription for warfarin. Comparing 237 warfarin users and 948 propensity-matched nonusers over 2287 person-years of follow-up, the occurrence of ischemic stroke was similar (HR = 0.92; 95% CI, 0.61 to 1.37), whereas warfarin users experienced twice the risk of hemorrhagic stroke (HR = 2.38; 95% CI, 1.15 to 4.96). The risks of stroke, gastrointestinal hemorrhage, and mortality did not differ between groups. As-treated analyses yielded similar findings, as did analyses restricted to patients with $CHADS_2$ scores ≥2.

Conclusions Although we confirmed association between warfarin use and hemorrhagic stroke in dialysis patients with AF, we found no association between warfarin use and ischemic stroke. Adequately powered randomized trials are required to conclusively determine the risks and benefits of the studied warfarin indication in hemodialysis patients.

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Introduction

Atrial fibrillation (AF) is an increasingly common condition among U.S. hemodialysis patients, with >10% having recurrent or permanent AF (1). The prevalence is particularly high among older patients: more than one-fifth of hemodialysis patients aged >75 years have AF. In the general population, it is widely recommended that most patients with AF who are at high risk for ischemic stroke receive long-term anticoagulation (2). Whether such recommendations should be adopted for the treatment of dialysis patients with AF is unclear. Dialysis patients experience four- to 10-fold higher rates of both ischemic and hemorrhagic stroke than demographically similar individuals in the general population (3), and thus an assessment of net benefits of warfarin may well differ among patients on renal replacement therapy.

Only a few existing studies have assessed the risks and benefits of warfarin in chronic dialysis patients (4–8). These studies are limited by their small sample sizes and/or analytical approaches. Most notably, rather than evaluating patients with incident AF who were newly started on warfarin therapy, these studies evaluated dialysis patients with pre-existing AF or prevalent warfarin users, a design that is particularly prone to bias in pharmacoepidemiological research (9). In this work, we conducted a careful pharmacoepidemiological analysis using a unique database of elderly patients who had comprehensive prescription drug coverage through generous state pharmaceutical benefit programs. We determined the associations among warfarin initiation (*versus* no warfarin use) and relevant ischemic and hemorrhagic outcomes in a cohort of older dialysis patients who were newly diagnosed with AF and warfarin naïve at the time.

Materials and Methods

Study Population

This study was conducted using healthcare claims data (1994 to 2006) from Medicare beneficiaries aged >65 years who received prescription coverage through one of three state-sponsored programs: New Jersey Medicaid, the New Jersey Pharmaceutical As-

sistance for the Aged and Disabled, and the Pennsylvania Pharmaceutical Contract for the Elderly. The latter two programs provided generous prescription drug coverage to their residents who did not qualify for Medicaid but who were still relatively indigent. Only patients with Medicare as the primary payor who participated in one of these prescription programs were retained. These patients' claims were augmented with additional information from the U.S. Renal Data System.

Study Cohort

From the source population, we included all incident dialysis patients who were ≥66 years on their first ESRD service date. Patients were excluded if they had not been enrolled in one of the three prescription drug programs in the previous year or if they had had any Medicare claims with a diagnosis code for AF (International Classification of Diseases, 9th revision, ICD-9 code 427.31) before start of chronic dialysis. Patients were then followed for a first hospitalization with a primary or secondary discharge diagnosis of AF (index hospitalization); if patients had not had any claims for a filled prescription for warfarin before the index hospitalization and if they survived ≥30 days from their discharge date, they were enrolled in this study.

Exposure

The exposure of interest was initiation of warfarin anticoagulation immediately following discharge from these patients' index hospitalizations. From all prescription claims, we identified those patients as exposed who filled a prescription for warfarin within 30 days from their index hospitalization discharge (index date = 30 days after discharge from index hospitalization). Patients who did not fill such a prescription during that time window were considered unexposed. Primary analyses categorized patients as exposed or unexposed based on this first exposure ascertainment (intention to treat [ITT]). In secondary analyses, as-treated (AT) patients were considered continuously exposed if they refilled their warfarin prescription within 150% of the previously dispensed supply, which was usually 30 days; the first time they did not refill their warfarin prescription within 150% of the most recent supply (usually 45 days), they were censored. Correspondingly, AT analyses censored originally unexposed patients once they filled a first prescription for warfarin.

Outcomes

The outcomes of study were ischemic stroke (ICD-9: 433.x1, 434.x1, 436), hemorrhagic stroke (ICD-9: 430 to 432), a combined endpoint of any stroke, gastrointestinal bleed, and mortality from any cause. We used previously validated algorithms that had been shown to accurately ascertain these endpoints from healthcare claims (10–13).

Other Variables

We defined several other variables that were considered to be potential confounders of the associations among warfarin use and ischemic and hemorrhagic outcomes. We ascertained demographic information: age on index date, gender, and race (Caucasian *versus* non-Caucasian), as well as dialysis vintage on index date. Comorbid conditions were ascertained from both the Medical Evidence Report and from Medicare claims preceding by up to 1 year and including the index hospitalization. A comorbidity was considered present if noted on the Medical Evidence Report or if one inpatient or two outpatient encounters listed corresponding ICD-9 diagnosis codes. We created summary variables for the number of distinct medications used in the previous year, as well as the number of hospital days in the past year. We also ascertained certain frailty indicators, such as inability to ambulate or to transfer on the Medical Evidence Report and any previous nursing-home stay. The most recent erythropoietin dose and hematocrit were also recorded, as was the length of the index hospitalization. We also noted whether a prescription for a histamine-2-receptor blocker or a proton pump inhibitor was previously filled. Finally, we ascertained presence of any procedure codes reflecting peripheral vascular dialysis access creation or revision in the most recent 90 days before index.

Statistical Analyses

For all patients with a first hospitalization for AF who survived to index, we estimated the exposure propensity score for initiating warfarin treatment within 30 days of discharge using multivariable logistic regression and all defined variables. Each warfarin user was then closely matched on their propensity score to four nonusers of warfarin using a greedy match algorithm that identified the four closest neighbors on propensity score. The characteristics of warfarin users and matching nonusers were then tabulated using means and SD for continuous and counts and proportions for categorical data. Exposure groups were compared using standardized differences (14).

Cox proportional hazards regression was then used to study the associations among warfarin use and the first occurrence of each study outcome from the index date. In such time-to-event analyses, repeat events are not considered. Patients were only censored for end of database (December 31, 2006) in ITT analyses; AT analyses additionally censored patients at treatment cross-over as described above. We conducted one set of subgroup analyses of patients with a $CHADS_2$ score of ≥2, consummate with specific guideline recommendations supporting warfarin use (2). This work was approved by the institutional review boards of Brigham and Women's Hospital and Stanford University School of Medicine.

Results

We identified 23,643 end-stage renal disease patients in the joint database of Medicare claims and prescription claims from the pharmaceutical benefit programs; 6880 had any hospitalization with a diagnosis code indicating AF. Of these, 2682 had AF before initiation of ESRD treatment. After excluding patients who had received warfarin before the index hospitalization and retaining patients who survived 30 days after discharge, our study cohort consisted of 2313 hemodialysis patients: 249 (10.8%) filled a prescription for warfarin within 30 days after discharge, and 2064 (89.2%) did not. Warfarin users tended to be younger than nonusers but were not different in their gender and race compositions (Table 1). Few comorbid

Table 1. Characteristics of dialysis patients hospitalized with incident atrial fibrillation, by warfarin use within 30 days after discharge

	Full Cohort				Propensity Score-matched Cohort (1:4)			
	Users (n = 249)	Nonusers (n = 2064)	P	Std. Diff. (%)	Users (n = 237)	Nonusers (n = 948)	P	Std. Diff. (%)
Age	68.6 (± 12.1)	70.1 (± 11.9)	0.06	12.5	68.9 (± 11.7)	68.9 (± 12.5)	0.99	0.0
Female gender	143 (57.4)	1186 (57.5)	0.99	0.2	139 (58.7)	538 (56.8)	0.60	1.8
Caucasian race (*versus* non-Caucasian)	169 (67.9)	1329 (64.4)	0.28	7.4	159 (67.1)	633 (66.8)	0.93	0.6
New Jersey *versus* Pennsylvania	180 (72.3)	1484 (71.9)	0.90	0.9	172 (72.6)	691 (72.9)	0.92	0.7
Dialysis vintage (years)	3.8 (± 3.6)	3.4 (± 3.7)	0.13	11.0	3.7 (± 3.4)	3.7 (± 3.7)	0.96	0.0
Hemodialysis *versus* peritoneal dialysis	237 (95.2)	1974 (95.6)	0.74	1.9	228 (96.2)	917 (96.7)	0.69	2.7
Diagnosed comorbid conditions								
coronary artery disease	115 (46.2)	1093 (53.0)	0.04	13.6	111 (46.8)	447 (47.2)	0.93	0.8
congestive heart failure	193 (77.5)	1545 (74.9)	0.36	6.1	184 (77.6)	722 (76.2)	0.63	3.3
peripheral artery vascular disease	109 (43.8)	822 (39.8)	0.23	8.1	101 (42.6)	395 (41.7)	0.79	1.8
cerebrovascular disease	57 (22.9)	487 (23.6)	0.80	1.7	55 (23.2)	213 (22.5)	0.81	1.7
hypertension	206 (82.7)	1666 (80.7)	0.44	5.2	196 (82.7)	778 (82.1)	0.82	1.6
diabetes	150 (60.2)	1219 (59.1)	0.72	2.2	143 (60.3)	566 (59.7)	0.86	1.2
chronic obstructive lung disease	70 (28.1)	595 (28.8)	0.81	1.6	66 (27.9)	252 (26.6)	0.69	2.9
malignancy	14 (5.6)	208 (10.1)	0.02	16.8	13 (5.5)	48 (5.1)	0.79	1.8
gastrointestinal bleed	17 (6.8)	334 (16.2)	<0.001	16.2	16 (6.8)	74 (7.8)	0.58	3.8
Recent vascular access surgery or revision	28 (11.2)	348 (16.9)	0.02	16.5	27 (11.4)	104 (11.0)	0.85	1.3
Length of stay, index hospitalization	11.4 (± 8.8)	12.2 (± 14.1)	0.21	6.8	11.3 (± 8.8)	11.3 (± 13.6)	0.97	0.0
Number of hospital days in prior year	12.8 (± 18.0)	20.7 (± 27.0)	<0.001	34.4	13.1 (± 18.2)	12.8 (± 16.7)	0.80	1.7
	25%: 0	25%: 0			25%: 0	25%: 0		
	50%: 6	50%: 12			50%: 6	50%: 7		
	75%: 18	75%: 29			75%: 20	75%: 19		
Number of different medications used in prior year	14.6 (± 8.9)	12.6 (± 10.4)	<0.001	20.7	14.3 (± 8.8)	13.9 (± 10.5)	0.50	4.1
	25%: 9	25%: 4			25%: 9	25%: 6		
	50%: 13	50%: 12			50%: 13	50%: 13		
	75%: 20	75%: 19			75%: 19	75%: 20		
Prior H_2 blocker or proton pump inhibitor use	123 (49.4)	980 (47.5)	0.57	3.8	115 (48.5)	461 (48.6)	0.98	0.2
Prior nursing home stay	35 (14.1)	374 (18.1)	0.11	10.9	33 (13.9)	127 (13.4)	0.83	1.5
Inability to ambulate	0	27 (1.3)	0.07	16.2	0	0	By design	
Inability to transfer	0	12 (0.6)	0.23	11.0	0	0	By design	
Most recent hematocrit value (%)	33.6 (± 4.4)	32.8 (± 4.6)	0.02	17.8	33.5 (± 4.4)	33.3 (± 4.5)	0.50	4.5
Total erythropoietin dose in prior month (in 1000 units)	88.6 (± 73.9)	85.8 (± 93.1)	0.59	3.3	89.1 (± 74.1)	85.0 (± 98.2)	0.49	4.7
	25%: 39.2	25%: 30.5			25%: 39.6	25%: 29.0		
	50%: 65.5	50%: 62.2			50%: 66.6	50%: 61.3		
	75%: 120.0	75%: 111.8			75%: 120.0	75%: 110.0		

The values in parentheses represent percentages for categorical and standard deviations for continuous variables. Per requirement of the Centers for Medicare and Medicaid Services, cell counts ≤10 must not be reported, which is the reason why all patients of non-Caucasian race were collapsed into a single category. Because no patients with reported inability to ambulate or to transfer received warfarin, these patients were eliminated from consideration for propensity score estimation. Std. Diff., standardized difference; H_2, histamine-2-receptor.

conditions differed between users and nonusers; users were less likely to have cancer or cardiovascular disease. Warfarin users had filled prescriptions for more different medications in the past year than nonusers. The proportion of patients with a history of gastrointestinal bleed was markedly lower among warfarin users than nonusers (7% *versus* 16%), although prior use of gastroprotective medications did not differ. On multiple domains, there was indication that warfarin users were less frail: they had spent fewer days in the hospital in the past year and were less likely to have been in a nursing home, and none of them were noted on the Medical Evidence Report to be unable to transfer or ambulate.

Using all of the available information, but excluding all 29 patients who were unable to ambulate or transfer from consideration, we fit a multivariate logistic propensity score model. The c-statistic was 0.68, indicating that the collective information was moderately informative in predicting warfarin exposure. We then successfully 1:4 greedy-matched on propensity score 237 warfarin recipients with 948 unexposed patients. The characteristics of these patients are listed in Table 1 and illustrate that propensity matching successfully balanced all observed characteristics among warfarin users and nonusers as indicated by standardized differences of less than 5% for all characteristics.

The 1185 patients were followed for a total 2287 person-years. Important metrics of this study are detailed in Table 2. Comparing follow-up times from ITT and AT analyses illustrates that there was little new warfarin use beyond the index date among patients who did not receive warfarin within the first 30 days after discharge from the index admission. By contrast, approximately half the person-time was lost when censoring warfarin users following a period of nonrefill of their warfarin treatment.

Mortality from any cause exceeded 40 deaths per 100 person-years and did not differ among warfarin users and nonusers (hazard ratio [HR] = 1.06; 95% confidence interval [CI], 0.90 to 1.24). There were 7.7 ischemic strokes per 100 person-years of follow-up, again not different among warfarin users and nonusers (HR = 0.92; CI, 0.61 to 1.37). The rate of hemorrhagic stroke was 1.4 per 100 person-years, and warfarin recipients experienced more than twice the event rate compared with patients who did not receive warfarin (HR = 2.38; 95% CI, 1.15 to 4.96). For the composite endpoint of any stroke, ischemic or hemorrhagic, no association with warfarin exposure was found (Table 2). Finally, the risk of gastrointestinal bleed, which occurred at 13.5 events per 100 person-years did not differ by warfarin exposure status.

In general AT analyses were closely compatible with ITT analyses, albeit with wider confidence limits, indicating that treatment cross-over was noninformative with regard to the study endpoints. Analyses restricted to the 205 warfarin initiators with a $CHADS_2$ score of ≥ 2, and their matches indicated no departure from the overall results: a null association for ischemic stroke (HR = 0.86; 95%: 0.56 to 1.31) and a significant increase of hemorrhagic stroke risk (HR = 2.56; 95% CI, 1.16 to 5.65) with warfarin use.

Discussion

In a cohort of older and relatively indigent dialysis patients who were hospitalized with a new diagnosis of AF, we found that initiation of warfarin treatment did not provide any measurable benefit for the prevention of ischemic stroke and increased the risk of hemorrhagic stroke. We obtained these findings from a study that carefully incorporated key pharmacoepidemiological principles, use of an inception cohort (incident AF) and using a new user design (initiation of warfarin treatment in close temporality to incident AF) (9) and propensity score matching as a means to maximize internal validity in a setting of rare outcomes (15,16).

Our findings differ from those observed in a recent study of 1671 patients who already had AF when starting hemodialysis with a national dialysis provider and survived 90 days from initiation (7). In that study, the risk of any stroke was double among pre-existing users of warfarin compared with otherwise similar patients who did not use warfarin at initiation of dialysis (propensity-matched HR = 2.00; 95% CI, 1.32 to 3.04). When focusing on hemorrhagic stroke, the HR was 2.22 (95% CI, 1.01 to 4.91), very compatible with our findings. However, somewhat implausibly, that study also reported almost a doubling in ischemic stroke (HR = 1.81; 95% CI, 1.12 to 2.92) with warfarin use, which suggests the presence of residual confounding by indication or inaccurate outcome ascertainment. Our own data indicate no association between warfarin and the risk of ischemic stroke with the estimate of association (HR = 0.92) on the "expected" side of the null value.

Another recent analysis used the Dialysis Outcomes and Practice Patterns Study to assess the outcomes of hemodialysis patients with AF, by warfarin exposure (8). Warfarin use was associated with increased stroke risk among patients over 75 years of age (HR = 2.17; 95% CI, 1.04 to 4.53) but not in patients younger than 75 years. There are several concerns with this analysis, which was admittedly not the main focus of the report. The potential problems included overfitting of the age-specific multivariate models, which had only between 35 and 61 stroke outcomes; inability to distinguish between ischemic and hemorrhagic stroke; and enrollment of patients with pre-existing AF and with prevalent warfarin treatment.

In addition to these two larger studies, there are at least three smaller studies with conflicting results: two studies of 61 and 127 hemodialysis patients with atrial fibrillation found no association with stroke risk (4,6). A third study had only remote warfarin information available and reported an overall survival benefit among past warfarin users compared with past nonusers (5).

In an attempt to also study nonstroke sequelae of oral anticoagulation, we found that the risk of gastrointestinal bleed did not differ between warfarin users and nonusers. Gastroprotective medication use was already high at almost 50% in both groups before the index hospitalization in our cohort, and an additional 20% of patients in the AT cohort initiated such treatment after discharge and before an event. Our finding is compatible with a detailed study of potential risk factors for gastrointestinal bleed in dialysis patients, where no association with anticoagulant use was identified (17).

Table 2. Number of patients, follow-up time, number of events, and incidence rates for all study outcomes, by warfarin use

Outcome	Analysis	Exposure Group	Number of Patients	Follow-up Time (years)			Number of Events	Incidence Rate (per 100 person-years)	Hazard Ratio (95% CI)
				Mean	SD	Median			
Mortality	ITT	Warfarin	237	1.78	1.71	1.17	181	42.9	1.06 (0.90 to 1.24)
		No warfarin	948	1.97	2.00	1.36	750	40.2	
	AT	Warfarin	237	0.87	0.97	0.52	80	38.8	1.05 (0.83 to 1.33)
		No warfarin	948	1.84	1.92	1.20	585	33.5	
Ischemic stroke	ITT	Warfarin	237	1.66	1.67	1.01	29	7.4	0.92 (0.61 to 1.37)
		No warfarin	948	1.83	1.93	1.20	135	7.8	
	AT	Warfarin	237	0.83	0.92	0.50	18	9.2	1.03 (0.62 to 1.70)
		No warfarin	948	1.71	1.85	1.05	121	7.5	
Hemorrhagic stroke	ITT	Warfarin	237	1.77	1.71	1.17	11	2.6	2.38 (1.15 to 4.96)
		No warfarin	948	1.95	1.98	1.35	21	1.1	
	AT	Warfarin	237	0.87	0.97	0.52	[a]	2.9	2.63 (1.01 to 6.88)
		No warfarin	948	1.82	1.91	1.19	19	1.1	
Any stroke	ITT	Warfarin	237	1.65	1.66	1.01	38	9.7	1.08 (0.76 to 1.55)
		No warfarin	948	1.81	1.91	1.19	150	8.7	
	AT	Warfarin	237	0.82	0.92	0.50	23	11.8	1.31 (0.77 to 1.89)
		No warfarin	948	1.69	1.83	1.05	134	8.4	
Gastrointestinal hemorrhage	ITT	Warfarin	237	1.51	1.56	0.97	48	13.4	0.96 (0.70 to 1.31)
		No warfarin	948	1.67	1.78	1.07	216	13.6	
	AT	Warfarin	237	0.82	0.92	0.50	27	13.9	0.90 (0.60 to 1.35)
		No warfarin	948	1.56	1.70	0.99	205	13.9	

CI, confidence interval; HR, hazard ratio; ITT, intention to treat; AT, as treated.

[a]Per requirement of the Centers for Medicare and Medicaid Services, cell counts ≤10 must not be reported. Hazard ratios estimated from propensity score-matched sets of four unexposed for each exposed patient.

Our study also has certain limitations, which include unavailability of laboratory measurements including coagulation metrics; reliance on administrative claims data for the ascertainment of comorbid conditions, medication use, and outcomes; the potential for residual confounding by unobserved characteristics; and use of a regional cohort of patients in New Jersey and Pennsylvania who were in the lower half of the income distribution among dialysis patients in the two states. In addition, we studied patients whose first coded AF diagnosis occurred in the context of a hospitalization; generalizability of these findings to patients first diagnosed as outpatients and not admitted is uncertain. We also do not know whether patients used acetylsalicylic acid for thrombosis prophylaxis, because this drug is cheaply available over the counter and not recorded in medication claims. These potential limitations need to be weighed in light of the strengths of this study. We sought to identify hemodialysis patients who experienced a first hospitalization with AF, thus capturing the specific event that should trigger a treatment decision regarding anticoagulation. We excluded any patients who had used warfarin before, at least during the year before the index hospitalization, thus likely observing patients who initiated warfarin because of the specific indication of stroke prevention from AF. Our approach should have enabled us to remove patients who initiated warfarin for prevention of vascular access thrombosis, a questionable and non-evidence-based practice that certainly indicates particularly high-risk patients. We ascertained several stroke risk factors and other prognostic factors that were then subjected to propensity score estimation and used for successful matching of similar warfarin users and nonusers. A potential strength rather than limitation is the fact that the available information was only of limited use to predict whether a patient would receive warfarin after diagnosis of AF, perhaps reflecting the clinical uncertainty that providers experience in this specific clinical scenario. Finally, an important strength is the availability of pharmacy claims that precisely recorded whether a patient filled a prescription for warfarin. Such claims are the closest that we can observe actual drug taking behavior and are preferred over recorded medications from medical records in dialysis units, which are likely subject to recall and other reporting biases.

From this careful analysis of hemodialysis patients who experienced a first hospitalized episode of AF, we observed an increased risk of hemorrhagic stroke, whereas no association was found between warfarin use and ischemic stroke. This study did not possess the power to give a tight estimate of net benefits *versus* risks from a strategy that uses warfarin compared with one that does not. Our findings have face validity, however, with the risk of hemorrhagic stroke being associated with warfarin use, and the estimate of association indicating the possibility that warfarin reduces the risk of ischemic stroke. The new availability of prescription data through Medicare Part D claims facilitates larger observational comparative effectiveness studies among in the ESRD population. Although such analyses have the capacity to address this question with increased power, it seems reasonable and ethical to propose a randomized trial to settle this important question of whether hemodialysis patients with AF should receive oral anticoagulation.

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Disclosures

None.

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