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Anticoagulation and Clinical Outcomes in Heart Failure Patients With Atrial Fibrillation: Findings From the ADHERE Registry

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Abstract

The risks and benefits of anticoagulation for patients with both heart failure and atrial fibrillation are unclear. We hypothesized that anticoagulation was associated with improved clinical outcomes of heart failure patients with atrial fibrillation independent of other risk factors. We conducted a retrospective cohort study of clinical registry data linked to Medicare claims for new users of oral anticoagulation (warfarin) without contraindications, discharged home alive, and stratified by $CHADS_2$ score. Outcomes of interest were propensity score-adjusted estimates of the effects of warfarin at discharge on all-cause mortality, thromboembolic events, major adverse cardiovascular events, and bleeding events. Among 10,494 patients with heart failure and atrial fibrillation, the 2249 patients newly treated with warfarin had lower 1-year mortality (27.7% vs 39.3% for $CHADS_2$ score ≤ 3 [P < .001]; 31.6% vs 41.8% for $CHADS_2$ score > 3 [P < .001]) than patients not treated with warfarin. There was no significant difference in thromboembolic events, major adverse cardiovascular events, or bleeding events at 1 year. After multivariate adjustment, exposed individuals in both CHADS2 subgroups had lower adjusted 1-year mortality ($CHADS_2$ ≤ 3: hazard ratio, 0.78 [95% confidence interval, 0.69-0.89]; $CHADS_2$ > 3: 0.78 [0.66-0.93]). In conclusion, warfarin use in heart failure patients with atrial fibrillation was associated with improved survival at 1 year independent of baseline $CHADS_2$ score. However, there was no significant reduction in clinical events, such as thromboembolic or major adverse cardiovascular events at 1 year that might simply explain the survival benefit associated with warfarin.

Introduction

Heart failure patients with atrial fibrillation are at increased risk of adverse outcomes, including stroke and other thromboembolic events.[1,2] Accordingly, the 2009 focused update of the 2005 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines for chronic heart failure, the 2012 American College of Chest Physicians guidelines on antithrombotic therapy for atrial fibrillation,[3] and the 2006 Canadian Cardiovascular Society consensus conference recommendations on heart failure[4] recommend anticoagulation for patients with heart failure and atrial fibrillation in the absence of contraindications.[5] Use of warfarin at hospital discharge in all patients with heart failure and atrial fibrillation without contraindications is an individual performance measure in the 2005 ACC/AHA clinical performance measures for adults with heart failure.[6]

However, the 2006 ACC/AHA/European Society of Cardiology (ESC) guidelines for chronic atrial fibrillation and the 2012 update of the Canadian Cardiovascular Society atrial fibrillation guidelines recommend use of the $CHADS_2$ score, the most commonly used risk score for determining whether anticoagulation is warranted, to assess patient risk for adverse outcomes before initiating prophylaxis.[7,8] Thus, patients with heart failure, atrial fibrillation, and no other $CHADS_2$ risk factors could be managed with either aspirin or oral anticoagulation, according to the atrial fibrillation guidelines[9,10] These inconsistencies among the professional guidelines may contribute to the significant variations observed in the administration of anticoagulation in this patient population.[11,12]

Key Words:
Atrial Fibrillation, Heart Failure, Hemorrhage, Mortality; Thromboembolism, Warfarin

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Although warfarin reduces thromboembolic risk in the broad population of patients with atrial fibrillation,[13-15] it is unknown whether the same degree of benefit observed in randomized trials is conferred to patients with heart failure and atrial fibrillation independent of other risk factors. Furthermore, the degree to which the $CHADS_2$ score has the effect of stratifying an older, more high-risk population is not well understood. Using the Acute Decompensated Heart Failure National Registry (ADHERE) linked with Medicare inpatient claims, we examined associations between newly initiated anticoagulation and clinical outcomes of patients with heart failure and atrial fibrillation stratified by $CHADS_2$ score.

Material and Methods

Data Sources

Data for this study included the ADHERE registry and the 100% Medicare claims data from the US Centers for Medicare & Medicaid Services (CMS). ADHERE was an observational study established to study the characteristics, treatments, and inpatient outcomes of patients hospitalized with acute decompensated heart failure, which has been described previously .[16] Patients were eligible for ADHERE if they were 18 years or older and were admitted to an acute care hospital with a primary or secondary discharge diagnosis of heart failure. From January 2001 through March 2006, more than 300 community and academic centers in the United States participated and more than 185,000 patients were enrolled. The registry data included demographic characteristics, medical history, clinical presentation, laboratory tests, medical management, and health outcomes.

The 100% Medicare claims data include inpatient claims files and the corresponding denominator files from 2000 through 2007. The inpatient files contain institutional claims for facility costs covered under Medicare Part A, as well as beneficiary, physician, and hospital identifiers, admission and discharge dates, and diagnosis and procedure codes. The carrier files contain noninstitutional provider claims for services covered under Medicare Part B. The corresponding denominator files include encrypted beneficiary identifiers, dates of birth, sex, race/ethnicity, dates of death, and information about program eligibility and enrollment.

To obtain information about outcomes, we linked the ADHERE hospitalization data to the Medicare inpatient claims using several indirect identifiers: hospital identifier, admission date, discharge date, patient sex, and either birth date or month and year of birth, as previously described.[17] Combinations of these identifiers are almost completely unique, enabling identification of registry hospitals and registry hospitalizations in the Medicare claims data. The ADHERE patient subset used for linking included reported admissions of patients 65 years or older with complete data on the identifiers listed above. Medicare inpatient records used for linking included all hospitalizations of patients 65 years or older with an associated heart failure diagnosis in any position on the inpatient claim (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] diagnosis code 402.x1, 404.x1, 404.x3, or 428.x).

Study Population

The study population included patients 65 years or older who had an ADHERE admission that linked to fee-for-service Medicare claims data. If multiple hospitalizations were linked for a patient, we used the earliest hospitalization. Eligible patients had atrial fibrillation indicated in their medical history, were discharged home alive, had no history of anticoagulation use at admission, and had no contraindications for warfarin. To ensure prior claims history, we required eligible patients to have at least 6 months of continuous enrollment in fee-for-service Medicare.

Drug Exposure

The exposure of interest was oral anticoagulation at discharge in patients who had not previously received anticoagulation. We defined anticoagulation as documentation of a warfarin prescription at the time of discharge in the discharge medications reported to the ADHERE registry.

Outcomes

The outcomes of interest included all-cause mortality, thromboembolic events, major adverse cardiovascular events, and bleeding events. All outcomes were defined based on Medicare data. For the primary treatment comparison, the period of follow-up for all events was 1 year after discharge from the ADHERE hospitalization. We determined all-cause mortality from death dates recorded in the Medicare denominator files. Thromboembolic events included nonhemorrhagic stroke or transient ischemic attack (ICD-9-CM diagnosis codes 433.x-437.x) [18], peripheral vascular disease (444.x), or deep vein thrombosis, pulmonary embolism, or other venous thrombosis (415.1x, 451.1x, 451.2, 451.81, 451.9, 452.x, 453.x)[19] listed as the primary diagnosis on a subsequent inpatient Medicare claim. Major adverse cardiovascular events included incident myocardial infarction (410.x1) and incident stroke (433.x, 434.x) listed as the primary diagnosis on a subsequent inpatient Medicare claim. Bleeding events included gastrointestinal bleeding (ICD-9-CM procedure code 44.4x for control of hemorrhage and suture of ulcer of stomach or duodenum,[20] esophageal bleeding (ICD-9-CM diagnosis code 530.82), ulcer (531.0x, 531.2x, 531.4x, 531.6x, 532.0x, 532.2x, 532.4x, 532.6x, 533.0x, 533.2x, 533.4x, 533.6x, 534.0x, 534.2x, 534.4x, 534.6x), gastritis and duodenitis with hemorrhage (535.x1), bleeding of stomach or duodenum due to vascular abnormalities (537.83, 537.84), bleeding of intestine to due to vascular abnormalities (569.85, 569.86), rectum (569.3x), unspecified gastrointestinal hemorrhage (578.x), and cerebrovascular hemorrhage (430.x, 431.x, 432.x). For patients who did not experience an event, we defined a censoring date as the earliest of either the end of follow-up or the date when the patient enrolled in a Medicare managed care plan.

Population Stratification

We derived $CHADS_2$ scores from the ADHERE registry using the algorithm described by Gage et al .[1] Specifically, we added 1 point each for the presence of heart failure, history of hypertension, age 75 years or older, and history of diabetes mellitus, and we added 2 points for history of stroke or transient ischemic attack. By definition, all patients in the study had a $CHADS_2$ score of at least 1, because all were admitted to the hospital with heart failure. In addition, a majority of Medicare beneficiaries in the analysis would likely have a $CHADS_2$ score of 2 because of age greater than 75 years. As a result, we defined the subgroups of interest as patients with $CHADS_2$ score ≤ 3 and those with $CHADS_2$ score > 3.

Covariatess

For population comparisons and the predictive models, we used variables from ADHERE and each patient's prior claims history. ADHERE data included demographic characteristics (age, sex,

race), medical history (chronic obstructive pulmonary disease, chronic renal insufficiency, coronary artery disease, diabetes mellitus, hyperlipidemia, hypertension, myocardial infarction, peripheral vascular disease, stroke or transient ischemic attack), initial evaluation (dyspnea, ejection fraction, fatigue, rales), initial vital signs (arrhythmia, heart rate, systolic blood pressure), laboratory test results (creatinine, hemoglobin, sodium), other admission and discharge medications (angiotensin-converting enzyme [ACE] inhibitor or angiotensin receptor blocker [ARB], aspirin, β-blocker, clopidogrel, diuretic, lipid-lowering agent), and length of the index hospitalization. Prior claims data included the number of previous hospitalizations and previous diagnoses of either gastrointestinal bleeding or hemorrhagic stroke (as defined above).

Statistical Analysis

We describe the baseline characteristics of the study population and therapies received, stratified by $CHADS_2$ score, as frequencies with percentages for categorical variables and as means with SDs for continuous variables. We compared these variables between treatment groups using $\chi 2$ tests for categorical variables and Wilcoxon rank sum tests for continuous variables.

To describe the observed outcomes, we present observed event rates for each treatment group by $CHADS_2$ score. For mortality, we used the Kaplan-Meier method to estimate the cumulative incidence of mortality at 1 year after discharge and log-rank tests to assess differences in mortality between groups. For the other end points, we estimated cumulative incidence at 1 year after discharge based on the cumulative incidence function, which accounts for the competing risk of mortality. We used the Gray test to assess differences between groups on these outcomes.

To control for confounding, we used estimates weighted by the inverse probability of treatment to assess relationships between treatment and outcomes. We calculated the weight on the basis of the propensity score, which is the probability of a patient receiving the treatment he or she actually received, conditional on observed covariates.[21] We derived these propensity scores by fitting a logistic regression model with treatment as the dependent variable and all of the baseline characteristics as the independent variables, including baseline patient characteristics, admission and in-hospital therapies, medical history, initial clinical evaluation, initial vital signs, laboratory test results, and the prior claims history variables described above. To verify the balance between the treatment groups after weighting, we again compared the baseline characteristics of each group. We used standardized differences to assess the balance of covariates between treatment groups.[22] Finally, we estimated the relationship between treatment and each outcome of interest by fitting 3 Cox proportional hazard models: (1) an unadjusted model with the treatment indicator as the sole independent variable; (2) an inverse probability-weighted model; and (3) an inverse probability-weighted model adjusted for

Table 1: Baseline Characteristics of the Study Population

Characteristic	$CHADS_2$ Score ≤ 3 (n = 7023)			$CHADS_2$ Score > 3 (n = 3471)		
	No Warfarin (n = 5429)	Warfarin (n = 1594)	P Value	No Warfarin (n = 2816)	Warfarin (n = 655)	P Value
Age, mean (SD), y	81.2 (8.3)	77.8 (7.5)	< .001	82.1 (6.5)	80.3 (6.1)	< .001
Male, No. (%)	2388 (44.0)	770 (48.3)	.002	1121 (39.8)	316 (48.2)	< .001
Race, No. (%)			.41			.03
Black	425 (7.8)	119 (7.5)		252 (8.9)	45 (6.9)	
White	4661 (85.9)	1360 (85.3)		2341 (83.1)	572 (87.3)	
Other/unknown	343 (6.3)	115 (7.2)		223 (7.9)	38 (5.8)	
Medical history, No. (%)						
Bleeding event in the previous 6 months	153 (2.8)	25 (1.6)	.005	94 (3.3)	5 (0.8)	< .001
Chronic renal insufficiency	1482 (27.3)	373 (23.4)	.002	1004 (35.7)	187 (28.5)	.001
Coronary artery disease	3282 (60.5)	881 (55.3)	< .001	1826 (64.8)	422 (64.4)	.84
Diabetes mellitus	1115 (20.5)	337 (21.1)	.60	1895 (67.3)	449 (68.5)	.54
Hypertension	3597 (66.3)	1071 (67.2)	.49	2490 (88.4)	596 (91.0)	.06
Myocardial infarction	1623 (29.9)	413 (25.9)	.002	912 (32.4)	210 (32.1)	.87
Peripheral vascular disease	848 (15.6)	247 (15.5)	.90	640 (22.7)	157 (24.0)	.50
Stroke or transient ischemic attack	24 (0.4)	10 (0.6)	.35	1567 (55.6)	345 (52.7)	.168
Laboratory test results, No. (%)						
Ejection fraction < 35%	1793 (33.0)	577 (36.2)	< .001	782 (27.8)	218 (33.3)	.002
Hemoglobin < 9 g/dL	262 (4.8)	39 (2.4)	< .001	157 (5.6)	20 (3.1)	< .001
Discharge medications, No. (%)						
ACE inhibitor or ARB	3078 (56.7)	1003 (62.9)	< .001	1656 (58.8)	406 (62.0)	.14
Aspirin	3034 (55.9)	573 (35.9)	< .001	1615 (57.4)	250 (38.2)	< .001
β-Blocker	3010 (55.4)	1000 (62.7)	< .001	1671 (59.3)	419 (64.0)	.03
Clopidogrel	836 (15.4)	76 (4.8)	< .001	681 (24.2)	48 (7.3)	< .001
Diuretic	4140 (76.3)	1213 (76.1)	.90	2123 (75.4)	509 (77.7)	.21
Lipid-lowering agent	1453 (26.8)	516 (32.4)	< .001	951 (33.8)	242 (36.9)	.12

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

discharge medications and length of stay. Significance tests and confidence intervals for estimates from all models were based on robust standard errors to account for the clustering of patients by hospital. We report hazard ratios and 95% confidence intervals for all estimated associations. We used α = .05 to determine statistical significance. To assess the potential for unmeasured confounding, we conducted a sensitivity analysis to examine the association between treatment and hip fracture, an outcome unrelated to treatment but related to overall health status. We identified hip fracture events by ICD-9-CM diagnosis code 820.xx listed as the primary diagnosis on a subsequent inpatient claim. [23]

We used SAS version 9.2 (SAS Institute Inc, Cary, North Carolina) for all analyses. The institutional review board of the Duke University Health System approved the study.

Results

The study population included 10,494 patients admitted to 272 hospitals between 2001 and 2006. Of these, 7023 patients (66.9%) had a $CHADS_2$ score ≤ 3 and 3471 (33.1%) had a $CHADS_2$ score > 3. Table 1 presents the baseline characteristics of the study population. The study population consisted largely of older white patients. Slightly more women than men had a $CHADS_2$ score ≤ 3. Overall, 2249 patients (21.4%) received warfarin at discharge. Among new users, 1594 patients (70.9%) had a $CHADS_2$ score ≤ 3. Compared with patients with a $CHADS_2$ score ≤ 3 who did not receive warfarin, new users with a $CHADS_2$ score ≤ 3 were slightly younger and more likely to be men.

In addition to the comorbid conditions accounted for by the $CHADS_2$ score, new users of warfarin were less likely to have coronary artery disease, a history of myocardial infarction, and chronic renal insufficiency. New users with a $CHADS_2$ score > 3 (29.1% of all warfarin users in this study population) were slightly younger and were more likely to be men, compared with patients with a CHADS2 score > 3 who did not receive warfarin. They were less likely to have chronic renal insufficiency but otherwise had similar rates of comorbid conditions. Regardless of $CHADS_2$ score, patients discharged with warfarin were more likely to have severe left ventricular dysfunction. They were less likely to have anemia (ie, hemoglobin < 9 g/dL) or a history of bleeding. Use of medications for heart failure—ACE inhibitors, β-blockers, and diuretics—was similar between patients who did or did not receive warfarin. However, patients treated with warfarin were less likely to also receive antiplatelet therapy, such as aspirin or clopidogrel.

As shown in Table 2, patients treated with warfarin had lower unadjusted mortality at 1 year independent of $CHADS_2$ score. There was no significant difference in unadjusted thromboembolic events, major adverse cardiovascular events, or bleeding events at 1 year. Table 3 shows the unadjusted and inverse probability-weighted hazard ratios for associations between warfarin at discharge and 1-year events. After accounting for underlying observed differences between the treatment groups, the difference in all-cause mortality between exposed and unexposed patients remained statistically significant at 1 year (Figure). There were no significant differences in thromboembolic events, major adverse cardiovascular events, or bleeding events at 1 year in the unadjusted or inverse probability-weighted analyses among patients prescribed warfarin at discharge, regardless of $CHADS_2$ score. In the sensitivity analysis examining the association between warfarin prescription and 1-year hip fracture rate, there was no significant difference in either the unadjusted or the inverse probability-weighted analyses among patients who were prescribed warfarin at discharge, regardless of $CHADS_2$ score (Table 4).

Table 2: Cumulative Incidence of Outcomes at 1 Year*

Outcome	$CHADS_2$ Score ≤ 3 (n = 7023)			$CHADS_2$ Score > 3 (n = 3471)		
	No Warfarin (n = 5429)	Warfarin (n = 1594)	P Value	No Warfarin (n = 2816)	Warfarin (n = 655)	P Value
All-cause mortality	2123 (39.3)	438 (27.7)	< .001	1169 (41.8)	205 (31.6)	< .001
Thromboembolic events	271 (5.0)	78 (4.9)	.88	160 (5.7)	47 (7.2)	.15
Major adverse cardiovascular events	317 (5.9)	82 (5.2)	.28	216 (7.7)	44 (6.8)	.41
Bleeding events	212 (3.9)	71 (4.5)	.31	110 (3.9)	28 (4.3)	.67

*Values are expressed as number of patients (unadjusted cumulative incidence per 100 patients at risk).

Discussion

Heart failure and atrial fibrillation are common conditions and frequently coexist in older patients. Our analysis is among the largest to examine associations between anticoagulation and outcomes in older patients with concomitant heart failure and atrial fibrillation, stratified by $CHADS_2$ score. The ability to link detailed patient level-data from ADHERE, a large nationwide registry of heart failure hospitalizations, with Medicare data provides a view of real-

Table 3: Hazard Ratios of Outcomes at 1 Year

CHADS2 Score	Outcome	Unadjusted		Inverse-Weighted		Inverse-Weighted and Adjusted	
		HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value
≤ 3 (n = 7023)	All-cause mortality	0.65 (0.58-0.72)	< .001	0.76 (0.67-0.86)	< .001	0.78 (0.69-0.89)	< .001
	Thromboembolic events	0.90 (0.70-1.15)	.39	0.94 (0.71-1.25)	0.692	0.94 (0.70-1.26)	.68
	Major adverse cardiovascular events	0.80 (0.63-1.01)	.06	0.87 (0.66-1.15)	0.319	0.93 (0.71-1.22)	.62
	Bleeding events	1.04 (0.79-1.38)	.77	1.33 (0.96-1.84)	0.083	1.33 (0.95-1.87)	.10
> 3 (n = 3471)	All-cause mortality	0.70 (0.61-0.80)	< .001	0.79 (0.67-0.94)	0.008	0.78 (0.66-0.93)	.004
	Thromboembolic events	1.17 (0.83-1.66)	.36	1.16 (0.78-1.72)	0.457	1.17 (0.81-1.68)	.42
	Major adverse cardiovascular events	0.81 (0.59-1.11)	.19	0.78 (0.55-1.10)	0.159	0.82 (0.58-1.17)	.28
	Bleeding events	1.01 (0.64-1.59)	.97	1.10 (0.65-1.85)	0.719	1.10 (0.64-1.90)	.72

Abbreviations: CI, confidence interval; HR, hazard ratio.

Table 4: Sensitivity Analysis of Hazard Ratios of Hip Fracture at 1 Year

$CHADS_2$ Score	Outcome	Unadjusted		Inverse-Weighted		Inverse-Weighted and Adjusted	
		HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value
≤ 3 (n = 7023)	Hip fracture	0.79 (0.51-1.24)	.30	1.25 (0.70-2.20)	.45	1.36 (0.76-2.41)	.30
> 3 (n = 3471)	Hip fracture	0.59 (0.31-1.15)	.12	0.88 (0.43-1.80)	.73	0.86 (0.41-1.83)	.71

Abbreviations: CI, confidence interval; HR, hazard ratio.

world postdischarge outcomes in Medicare beneficiaries with heart failure and atrial fibrillation. We found that warfarin was infrequently initiated in patients with both heart failure and atrial fibrillation. Warfarin initiation was associated with improved 1-year survival, and this finding was independent of stroke risk as measured by the $CHADS_2$ score. There was no significant reduction in clinical events, such as thromboembolic or major adverse cardiovascular events at 1 year that might simply explain the survival benefit associated with warfarin. Insufficient event rates and residual confounding may partially explain similarities in clinical event rates. Nevertheless, the observed reduction in 1-year mortality warrants additional studies to determine whether anticoagulation therapy reduces mortality in patients with heart failure and atrial fibrillation independent of potentially unmeasured confounding in these observational data.

Although heart failure and atrial fibrillation each are present in 9% of patients older than 80 years, and although up to 50% of patients with heart failure also have atrial fibrillation, the coexistence of heart failure and atrial fibrillation is often overlooked.[24-26] Elderly patients with both heart failure and atrial fibrillation are often excluded from randomized trials. Moreover, previous trials have focused on reductions in thromboembolic events but have not necessarily examined whether there is a mortality benefit related to anticoagulation in this patient population. Post hoc subgroup analyses of several large heart failure trials are also inconsistent with respect to these clinical end points. Half of these analyses suggested that patients with both heart failure and atrial fibrillation have a greater likelihood of thromboembolic events, whereas the other half found no differences in event rates between heart failure patients with and without atrial fibrillation.[2,27-30] Other post hoc analyses have found an association between warfarin use and improved survival in those with atrial fibrillation alone but no statistically significant benefit in the subgroup of patients with heart failure and atrial fibrillation.[31]

Inconsistency in professional guidelines may reflect uncertainty about thromboembolic risk in patients with heart failure and atrial fibrillation, as well as uncertainty about the benefit of anticoagulation therapy in these patients. The ACC/AHA guidelines for heart failure include a class IA recommendation for anticoagulation therapy in patients with heart failure and atrial fibrillation, stating that "anticoagulation should be maintained in all patients with heart failure and a history of atrial fibrillation regardless of whether sinus rhythm is achieved, because of the high rate of silent recurrence of atrial fibrillation with its attendant embolic risk, unless a contraindication exists" .[5] However, the ACC/AHA/ESC 2006 guidelines for atrial fibrillation include a class IA recommendation for anticoagulation with a vitamin K antagonist in patients with more than 1 moderate risk factor, including "age 75 years or greater, hypertension, heart failure, impaired LV systolic function (ejection fraction 35% or less or fractional shorting less than 25%), and diabetes mellitus".[8]

Contemporary clinical decision making about anticoagulation extends beyond evaluating thromboembolic risk and incorporates an evaluation of bleeding risk to determine the net clinical benefit of anticoagulation. Our data predate the emergence of newer risk scores, such as the CHA_2DS_2-VASc and HAS-BLED scores, which can be used to refine both stroke risk and bleeding risk in this patient population. The 2012 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure and the 2010 ESC guidelines for the management of atrial fibrillation recommend a preference for oral anticoagulation in patients with a CHA_2DS_2-VASc score of 1 and a firm indication for oral anticoagulation in patients with a CHA_2DS_2-VASc score of 2 or greater.[9,10] The ESC guidelines for atrial fibrillation also suggest that the HAS-BLED score should be considered in the assessment of bleeding risk. Regardless of thromboembolic risk as determined in this high-risk population using the $CHADS_2$ score, we found that anticoagulation use was associated with significantly lower mortality rates, including fatal thromboembolic and bleeding

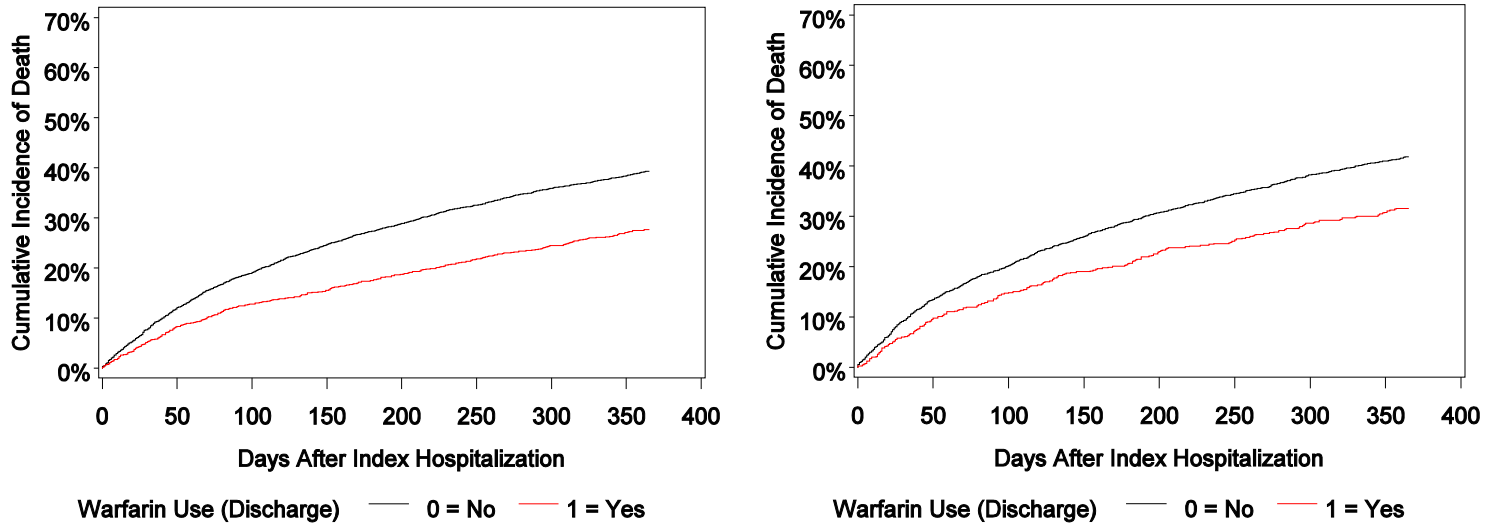

Figure 1: Cumulative Incidence of 1-Year Mortality
Panel A: Patients with CHADS2 score ≤ 3 (hazard ratio, 0.78; 95% confidence interval, 0.69-0.89; P < .001).
Panel B: Patients with CHADS2 score > 3 (hazard ratio, 0.78; 95% confidence interval, 0.66-0.93; P = .004).

events. The emergence of novel oral anticoagulants that do not require monitoring and are associated with less intracranial bleeding may increase the proportion of patients considered appropriate to treat.[32-34]

Our study has some limitations. We observed that warfarin use in patients with heart failure and atrial fibrillation independent of $CHADS_2$ score was associated with improved survival at 1 year, but we found no significant differences in thromboembolic events, major adverse cardiovascular events, or bleeding events to explain the impact on survival. Cause of death was not available, limiting our ability to explore this finding. Event rates in our study population were comparatively lower than those observed in other studies. For example, in the Swedish Atrial Fibrillation cohort study, a thromboembolic event rate of 12.3 per 100 years was observed among patients with a $CHADS_2$ score greater than 3.[35] The low clinical event rates in this study may have been insufficient for discerning statistically significant differences. In addition, treatment differences among the subgroups may explain similarities in clinical event rates. Antiplatelet agents were more frequently prescribed in patients who were not prescribed warfarin and may have contributed to a bleeding event rate comparable to that seen in patients prescribed warfarin. Similarities in clinical event rates may also be a result of residual and unmeasured confounding for which we could not adjust. Several clinical variables that are likely to be associated with anticoagulation use and clinical outcomes were not available, including anticoagulation adherence, anticoagulation control, symptom severity, body mass index, and frailty. We also could not account for socioeconomic status, education level, and health literacy. However, our sensitivity analysis of an outcome unrelated to treatment but related to overall health status, hip fracture rate at 1 year, suggests that treatment exposure was not biased. The use of administrative claims is subject to incomplete claims, coding errors, omissions, and unobserved factors that may influence outcomes. In addition, the data were restricted to patients 65 years and older in the ADHERE registry and the majority of patients in this analysis were 75 years or older, a risk factor in the $CHADS_2$ score. This limited our ability to generalize the findings to the broader population of patients with atrial fibrillation and heart failure.

Conclusions:

Warfarin use in patients with heart failure and atrial fibrillation was associated with improved survival at 1 year independent of $CHADS_2$ score. These observational findings raise important questions that will require randomized controlled trials to provide answers. Additional studies are needed to determine whether anticoagulation therapy reduces mortality in patients with heart failure and atrial fibrillation independent of potentially unmeasured confounding in observational data.

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