

Impact of Heart Failure Type on Thromboembolic and Bleeding Risk in Patients With Atrial Fibrillation on Oral Anticoagulation



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Heart failure (HF) increases stroke risk in atrial fibrillation (AF) patients. Differential impact of HF category on thromboembolic and bleeding risk in AF patients on oral anticoagulation (OAC) is unknown. We used Medicare data for beneficiaries with new AF diagnosed between 2011 and 2013 to identify patients with HF with reduced ejection fraction (HFrEF), HF with preserved ejection fraction (HFpEF), and no HF. The primary endpoint of admission for ischemic stroke was evaluated using Cox proportional hazards regression models that controlled for patient demographics, comorbidities (including CHA₂DS₂-VASc and HASBLED scores), and OAC use as a time-dependent covariate. Secondary endpoints included all-cause mortality, admissions for gastrointestinal bleeding (GIB), intracranial hemorrhage (ICH), acute myocardial infarction (AMI), or HF. The 3 groups included 47840, 32360, and 718392 patients respectively. Patients with HFrEF and HFpEF had higher comorbidity burden, CHA₂DS₂-VASc and HASBLED scores compared with patients without HF. In multivariable analysis adjusting for patient comorbidities and OAC, HFrEF and HFpEF were associated with higher risk of ischemic stroke, HF and AMI compared with no HF. HFrEF was associated with higher all-cause mortality and HF-hospitalization risk compared with HFpEF. In conclusion, in AF patients, HFrEF and HFpEF are both associated with higher risk of ischemic stroke, HF and AMI admissions, even after adjusting for OAC use, compared with patients without HF. Published by Elsevier Inc. (Am J Cardiol 2019;123:1649–1653)

Heart failure (HF) is an important predisposing factor for atrial fibrillation (AF).¹ AF prevalence in HF with reduced ejection fraction (HFrEF) is up to 40%, and it is associated with worse outcomes including higher mortality, hospitalization and stroke rates.² Prevalence of AF is higher in HF with preserved ejection fraction (HFpEF) and can be up to 65%.³ While HFrEF is an established risk factor for stroke in AF, the evidence for impact of HFpEF on thromboembolic and bleeding risks is more scarce and conflicting. Congestive HF is assigned one point in common stroke risk scores such as CHA₂DS₂-VASc. However, there is not enough evidence to clarify in whether HFpEF carries the same risk as HFrEF in AF patients or not. Oral anticoagulation (OAC) is effective in reducing thromboembolic risk in AF patients with HFrEF but it comes with the burden of bleeding risk. Whether the

same stands true for patients with HFpEF is not well established. This study evaluates the impact of HFpEF on thromboembolic and bleeding outcomes in AF patients who are on OAC compared with patients with HFrEF and no HF.

Methods

We used linked data sources obtained from the Centers for Medicare and Medicaid Services (CMS) including: (1) Beneficiary Summary File Base and Chronic Conditions segments; (2) Inpatient (Part A) and Carrier (Part B) Standard Analytic Files for 2011 through 2013; (3) Pharmacy Drug Event (Part D) files for 2011–2013. The institutional review board of the University of Iowa approved this study.

We began by identifying Medicare patients who were ≥65 year old and were enrolled in CMS Part D prescription drug coverage and were newly diagnosed with AF between November 1, 2011 and October 31, 2013. New AF was defined based on previously published algorithms (i.e., one inpatient claim or two outpatient claims within 90 days with ICD-9-CM code 427.31 as primary or first secondary diagnosis).^{4,5} We classified our cohort into patients with systolic HF by ICD-9 code 428.2, diastolic HF by ICD-9 code 428.3 or patients with no HF. This classification was based on ICD-9 codes found in any claim during the study period before starting AF diagnosis.

We excluded patients who underwent open-heart surgery within 30 days before the initial AF diagnosis, to ensure that AF was not a post-surgical complication. In order to ensure that the intent of anticoagulation therapy was long-

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term prevention of stroke in patients with AF, we also excluded patients who underwent joint replacement surgery or were hospitalized for pulmonary embolism or deep vein thrombosis treatment during the 6 weeks before first anticoagulant prescription. Patients with mechanical heart valves were also excluded. The final sample included 798,592 patients with new AF diagnosis.

The primary outcome was admissions for ischemic stroke. Secondary outcomes included admissions for gastrointestinal bleeding, other major intracranial or extracranial bleeding, acute myocardial infarction, or HF. Ischemic stroke was defined using algorithms described by Rothendler et al.⁶ and bleeding events were as defined by Suh et al.⁷ Relevant admissions were identified by the primary ICD-9-CM diagnosis on inpatient SAF claims for acute care stays (Appendix 1). Patient characteristics were derived from Inpatient and Carrier claims incurred during the 12 months before the first AF diagnosis. Stroke risk was represented using the CHA₂DS₂-VASc; this score ranges from 1 to 9 (higher risk associated with higher stroke risk) and is based on the presence of several risk factors including HF, hypertension, diabetes, previous stroke, advanced age, sex, and vascular disease.⁸ We calculated bleeding risk using the HAS-BLED score; this score ranges from 1 to 7 (higher risk associated with higher bleeding risk) and is based on the presence of several risk factors including hypertension, previous stroke, advanced age, renal disease, liver disease, concomitant use of medications that increase the risk of bleeding, and alcohol abuse.⁹ Additional patient characteristics included demographics, comorbid conditions, previous health services utilization, and overall illness burden. Demographics included age, gender, race, ethnicity, and dual Medicaid enrollment. We identified comorbid conditions based on definitions from the Elixhauser et al algorithm.¹⁰ We also identified additional comorbidities of importance to AF outcomes, including: other dysrhythmias (ICD-9-CM codes 427.X, excluding 427.3), cardiomyopathy (ICD9 codes 425.X), cardiac conduction disorder (e.g., bundle branch block; ICD9 codes 426.X), and previous implantable cardiac device (e.g., pacemaker and implantable defibrillator; ICD9 codes V45.01, V45.02). We identified previous stroke, previous pulmonary embolism or deep vein thrombosis, and previous gastrointestinal, intracranial, or other major extracranial bleeding using the same ICD9 algorithms as used for outcome definitions (Appendix 1). Indicators for the use of statins, prescription antiplatelets (e.g., clopidogrel), prescription nonsteroidal anti-inflammatory drugs (NSAIDs), proton pump inhibitors (PPI), beta blockers, calcium channel blockers, digoxin and other antiarrhythmic medications within 90 days of AF diagnosis were created.

The study cohort participants were categorized into HFrEF, HFpEF and no HF according to associated ICD-9 code. In each of these groups, continuous variables were reported as mean (standard deviation) or median (interquartile range) depending on the normality of data distribution. Categorical variables were reported as counts and percentages. We used chi-square test or one-way analysis of variance, as appropriate, to compare demographic variables, comorbid conditions, health care utilization, medication use among the 3 groups. Multivariable Cox proportional hazards regression were generated adjusting for differences in patient characteristics including age, sex, race, CHA₂DS₂-VASc score, HAS-

BLED score, history of cardiovascular, cerebrovascular, peripheral vascular, renal, liver disease, diabetes mellitus, hypertension, implantable device, and polypharmacy among the 3 groups. We also adjusted for oral anticoagulation use (Warfarin, Dabigatran and Rivaroxaban) as a time-dependent covariate. In these models, the dependent variables were time (in days) from anticoagulant initiation to a given event (e.g., admission for stroke or censoring). Censoring events included end of observation (December 31, 2013), or death. Analysis was performed using SAS. A p value <0.05 was considered statistically significant.

Results

Baseline characteristics of the study population are presented in Table 1. There was no difference between patients with HFpEF and HFrEF in mean CHA₂DS₂-VASc and HASBLED score. In addition, there was no difference in distribution of CHA₂DS₂-VASc scores between both groups (Table 1).

In multivariate analysis, HFpEF and HFrEF both were associated with higher risk for ischemic stroke compared with patients without HF (adjusted hazards ratio [aHR] 1.09, 95% confidence interval [CI] 1.03 to 1.16, p=0.005) and (aHR 1.08, 95% CI 1.03 to 1.14, p=0.004) respectively. There was no difference in risk of ischemic stroke between both HF groups after adjusting for demographics and comorbidities (aHR 1.01, 95% CI 0.93 to 1.08, p=0.88). There were no differences in risk of any hemorrhage or GI bleeding while on OAC among the 3 groups in different pairwise comparisons (Table 2). Furthermore, there was no significant difference in risk of intracranial hemorrhage between both HF categories while on OAC (aHR 1.16, 95% CI 0.95 to 1.42, p=0.14). In multivariate analysis, HFpEF and HFrEF both were associated with higher risk for myocardial infarction compared with patients without HF (aHR 1.13, 95% CI 1.06 to 1.21, p=0.0002) and (aHR 1.2, 95% CI 1.14 to 1.26, p < 0.001), respectively. There was no difference in risk of MI between both HF groups after adjusting for demographics and comorbidities (aHR 0.94, 95% CI 0.87 to 1.02, p=0.12). Patients with HFpEF had lower risk of HF admissions compared with HFrEF patients (aHR 0.89, 95% CI 0.86 to 0.92, p < 0.0001). There was higher risk of all-cause mortality in HFrEF patients compared with patients with no HF (aHR 1.1, 95% CI 1.08 to 1.13, p < 0.001). On the other hand, HFpEF was associated with lower risk of all-cause mortality compared with HFrEF (aHR 0.9, 95% CI 0.87 to 0.92, p < 0.001).

Discussion

In this large study using real world data from Medicare database, we assessed the differential impact of HF category in AF patients on risk of different thromboembolic and bleeding events while on OAC. We report several important findings. First, HFpEF patients had significantly higher ischemic stroke and acute myocardial infarction risk than patients with no HF and an equivalent risk to patients with HFrEF even after adjusting for important comorbidities and OAC use. Second, there were no difference in GI bleeding or any bleeding risks between both types of HF and patients with no HF. Third, patients with HFrEF had higher risk for HF hospitalization compared with patients

Table 1
Baseline characteristics of study population

Variable	HFrEF	HFpEF	No HF	p Value
N	47,840	32,360	718,392	
Age (year)	80	81	79	<0.001
Female	51%	69%	59%	<0.001
White	79%	82%	85%	<0.001
African American	11%	9%	6%	
Asian	3%	2%	2%	
Hispanic	7%	5%	5%	
Dual Medicaid coverage	39%	40%	29%	<0.001
CHA ₂ DS ₂ -VASc*	5.3	5.4	4.6	<0.001
Age >75	68%	74%	66%	<0.001
HASBLED*	3.5	3.4	2.8	<0.001
CHA ₂ DS ₂ -VASc score*				
1	0.1%	0.1%	2%	<0.001
2	0.8%	0.5%	7%	
3	3%	2%	14%	
4	9%	8%	21%	
5	21%	20%	20%	
6	24%	25%	17%	
7	20%	20%	12%	
8	16%	16%	6%	
9	7%	9%	2%	
Non-steroidals anti-inflammatory drugs	22%	24%	23%	<0.001
Clopidogrel	12%	8%	6%	<0.001
Statins	51%	47%	40%	<0.001
Calcium channel blockers	6%	11%	9%	<0.001
Beta-blockers	56%	51%	37%	<0.001
Amiodarone	9.4%	7.7%	7%	<0.001
Hypertension	92%	93%	84%	<0.001
Diabetes mellitus	53%	51%	36%	<0.001
Renal disease	50%	46%	21%	<0.001
Dialysis	5%	5%	2%	<0.001
Liver disease	9%	9%	6%	<0.001
Metastatic cancer	3%	4%	4%	0.001
Obesity (Body mass index \geq 30 kg/m ²)	18%	23%	11%	<0.001
Peripheral arterial disease	44%	43%	28%	<0.001
Chronic obstructive pulmonary disease	62%	64%	37%	<0.001
Prior stroke	22%	23%	18%	<0.001
Prior myocardial infarction	39%	24%	13%	<0.001
Coronary artery disease	76%	59%	40%	<0.001
Prior pacemaker	12%	7%	4%	<0.001
Prior ICD	13%	1%	1%	<0.001

* There was no difference between patients with HFrEF and HFpEF in CHA₂DS₂-VASc or HASBLED scores.

with HFpEF. Last, HFrEF was associated with higher all-cause mortality compared with no HF and HFpEF, while there was no difference in risk of all-cause mortality between patients with HFpEF while on OAC and no HF.

The focus of commonly applied risk scores (CHADS₂, CHA₂DS₂-VASc, ATRIA)^{8,11} is the identification of patients at risk for stroke and systemic thromboembolism who would benefit from OAC. Although, all risk scores include history of HF as an important risk factor for thromboembolism, the definition of HF may differ and referred to recent decompensated HF, with some uncertainty whether HFpEF or asymptomatic systolic impairment should be included. Previous reports have questioned the role of HF history as an independent predictor of thromboembolic risk. An analysis of the Swedish Atrial Fibrillation cohort study, a nationwide cohort study of 182,678 subjects with a diagnosis of AF, suggested that history of HF was not an independent predictor of ischemic stroke or the composite

thromboembolism risk endpoint but was independent risk factor for major bleeding.¹² In contrast, analysis of the derivation and validations Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) cohorts confirmed the association of risk factors (including history of HF) included in the CHADS₂, CHA₂DS₂-VASc. Left ventricular systolic dysfunction has been previously associated with higher risk of stroke.¹³ The link between HFpEF and thromboembolic risk was established based on data from HF patients on antiplatelet agents enrolled in the ACTIVE A and W trials, in which no differences in the risk of stroke, transient ischemic attack, or systemic embolism between AF patients with HFpEF and HFrEF were found.¹⁴ These findings are in line with data from post-hoc analyses of clinical trials and other cohort studies.^{15,16} More recently, an analysis of a nationwide Swedish HF Registry of 41,446 patients with clinician-judged HF, linked with co-morbidities' and outcomes' data from the National Patient Registry demonstrated that

Table 2

Hazards ratio for risk of different outcomes in multivariate adjusted analysis with anticoagulant use as time-dependent covariate

	HR	95% CI	p Value
Stroke			
HFpEF vs. No HF	1.09	1.03-1.16	0.005
HFrEF vs. No HF	1.08	1.03-1.14	0.004
HFpEF vs. HFrEF	1.01	0.93-1.08	0.88
HF admissions			
HFpEF vs. No HF	1.65	1.61-1.70	<0.0001
HFrEF vs. No HF	1.86	1.82-1.90	<0.0001
HFpEF vs. HFrEF	0.89	0.86-0.92	<0.0001
Myocardial infarction			
HFpEF vs. No HF	1.13	1.06-1.21	0.0002
HFrEF vs. No HF	1.2	1.14-1.26	<0.0001
HFpEF vs. HFrEF	0.94	0.87-1.02	0.12
Gastrointestinal bleeding			
HFpEF vs. No HF	1.01	0.96-1.06	0.85
HFrEF vs. No HF	0.98	0.94-1.03	0.38
HFpEF vs. HFrEF	1.03	0.96-1.09	0.44
Intra-cranial hemorrhage			
HFpEF vs. No HF	0.95	0.81-1.10	0.5
HFrEF vs. No HF	0.81	0.71-0.93	0.003
HFpEF vs. HFrEF	1.16	0.95-1.42	0.14
Any hemorrhage			
HFpEF vs. No HF	1.01	0.97-1.06	0.2
HFrEF vs. No HF	0.97	0.94-1.02	0.2
HFpEF vs. HFrEF	1.04	0.98-1.10	0.15
All-cause mortality			
HFpEF vs. No HF	0.99	0.96-1.01	0.3
HFrEF vs. No HF	1.10	1.08-1.13	<0.001
HFpEF vs. HFrEF	0.90	0.87-0.92	<0.001

AF was progressively more common with increasing ejection fraction and the risk of death, HF hospitalization, and stroke were similarly increased in HFrEF and HFpEF.³ Finally, a meta-analysis of cohort studies and post-hoc analysis of randomized clinical trials including 54,587 patients with AF (approximately 50% of patients were on OAC) suggested significantly higher all-cause mortality in AF patients with HFrEF compared with HFpEF, but similar stroke risk and HF hospitalization rates.¹⁷ Our analysis builds upon currently available evidence as it indicates that HFrEF and HFpEF patients on OAC carry significantly higher risk of stroke and acute myocardial infarction compared with AF patients without HF on OAC. Therefore, the presence of any HF subtype should be considered an independent thromboembolic risk factor and taken into account when estimating thromboembolic risk in patients with AF. Interestingly, our analysis found higher all-cause mortality among patients with HFrEF compared with HFpEF and no HF. A potential explanation for these findings is potential misclassification of patients with symptomatic AF, but without true HF, as HFpEF. In the presence of AF symptoms of HF may be present, echocardiographic diagnosis of diastolic dysfunction can be challenging, and natriuretic peptide levels can be increased. Finally, the absence of substantial differences in the bleeding risk among the 3 study groups confirms the results of previous studies which did not identify left ventricular dysfunction or history of HF as important independent risk factors of bleeding.¹⁸

Our study has several strengths including the large number of AF patients from a real world setting, and the fact that we adjusted for several comorbidities including CHA₂DS₂-VASc and HASBLED scores in our analysis. However, there are some limitations that need to be outlined. First, we did not have information on EF of individual patients. HF was classified based on ICD-9 codes for diastolic and systolic heart failure. Thus, there is a possibility that some patients were misclassified. However, we believe that such misclassification would be nondifferential. Furthermore, in a previous meta-analysis including 19 studies (2 studies from Medicare), overall specificity was $\geq 95\%$ and positive predictive value was $\geq 87\%$ for the same ICD-9 codes we used in our study.¹⁹ Second, there is always the possibility of residual confounding from unmeasured factors in analysis of this administrative database. Third, because our study cohort was derived from Medicare database, all of our patients were older than 65 years, which might limit external validity of results to younger patients. Fourth, we lacked granular details such as type of AF (paroxysmal vs persistent vs permanent), clinical symptoms, INR levels, and time in therapeutic range in warfarin users. Last, our classification was based on ICD-9 codes, which relies on the accuracy of coding by treating physicians.

In conclusion, HFrEF and HFpEF are associated with similar risk of stroke and myocardial infarction in the setting of AF and the risk is higher than that of patients without HF in spite of OAC.

Disclosures

The authors do not have any conflicts of interest or financial disclosures.

Appendix. 1

ICD-9-CM Diagnosis codes for adverse outcomes associated with AF:

Previously described algorithms were used to identify ischemic stroke, intracranial hemorrhage and other hemorrhage events. The estimated positive predictive values of the proposed definitions are 95% for ischemic stroke, 76% for intracranial hemorrhage and 88% for major bleeding.²⁰

Ischemic stroke

- With mention of cerebral infarction 433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, 434.91
- other cerebral ischemic event 436.x

Major hemorrhage

- Intracranial hemorrhage 430.X, 431.X, 432.X (may also include trauma codes 852.0X, 852.2X 852.4X, 853.0)
- Gastrointestinal hemorrhage 455.2, 455.5, 455.8, 456.0, 456.2, 459.0, 530.7, 530.8, 531.0-531.6, 532.0 – 532.6, 533.0-533.6, 534.0-534.6, 535.01, 535.11, 535.21, 535.31, 535.41, 535.51, 535.61, 537.8, 562.02, 562.03, 562.12, 562.13, , 568.81, 569.3, 569.85, 569.3, 578.0, 578.1, 578.9
- Other major bleeding 423.0X, 593.81, 599.7X, 623.8X, 626.2X, 626.2X, 719.1X, 786.3X, 784.7X, 784.8X,

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