Impact of Atrial Fibrillation on Hospitalization Outcomes of Heart Failure in Patients ≥ 60 Years with Implantable Cardioverter Defibrillator

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The impact of atrial fibrillation (AF) on the hospitalization outcomes in patients ≥ 60 years of age with implantable cardioverter defibrillators (ICD) is not well studied. We queried the National Inpatient Sample database for all patients aged ≥ 60 who had a history of ICD placement, and were admitted with a primary diagnosis of heart failure (HF) during the years 2016-2017. Patients were stratified into 2 groups based on their history of AF. The primary outcome of the study was all-cause in-hospital mortality. Secondary outcomes included cardiogenic shock, myocardial infarction (MI), ventricular fibrillation (VF), stroke and acute kidney injury (AKI). The association between different age strata and outcomes was investigated. The hospitalization outcomes were modeled using logistic regression. A total of 178,045 patients were included, of whom 56.2% had AF. AF correlated with increased mortality (A-OR 1.22 (95% CI: 1.06-1.4), p=0.005), cardiogenic shock (A-OR 1.21 (95%CI: 1.08-1.36), p<0.001), AKI (A-OR 1.12 (95%CI: 1.06-1.17), p<0.001 and lower risk for MI (A-OR 0.79 (95% CI: 0.68-0.9), p<0.001. There was no correlation between AF and risk for VF or stroke. A significant correlation between AF and higher risk for mortality, cardiogenic shock and AKI was demonstrated in ages ≤ 75, ≤ 75, and ≤ 80 years, respectively. In contrast, a significant correlation between AF and lower risk for MI is only demonstrated at age > 70 years. We conclude that AF is an independent predictor for increased all-cause in-hospital mortality and cardiogenic shock. Such risk is influenced by age. **(Am J Cardiol 2021;152:94−98)**

Atrial fibrillation (AF) and heart failure (HF) are increasingly becoming more prevalent as the United States population over 60 is increasing.[1] They are frequently co-existing due to shared risk factors and the underlying or interrelated disease processes that promote and adversely contribute to one another in cyclical fashion.[2,3] The management of AF in advanced age, particularly in patients with heart failure who have implantable cardioverter-defibrillator (ICD), is complex as these patients are usually sicker, frailer, and have comorbidities.[4] While AF is generally considered a poor prognostic marker and is associated with a higher risk for stroke, there is some evidence that it can also result in a higher risk for mortality and inappropriate shocks in patients with ICD.[5,6] In this study, we aimed to investigate the impact of AF on outcomes of patients with ICD who were hospitalized with heart failure, utilizing a large sample database representative of the entire United States.

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See page 98 for disclosure information.

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Methods

This study was conducted using the publicly available National Inpatient Sample (NIS) of the Health Care Utilization Project (HCUP) sponsored by the Agency for Healthcare Research and Quality. Information about the registry has been previously described.[7]

All HF patients aged ≥ 60 who were diagnosed with a history of ICD placement, and were admitted with a primary diagnosis of HF during the years 2016 to 2017 were included (Supplement Table 1). Patients with history of ICD placement were identified using the International Classification of Diseases, Tenth Revision, Clinical Modification ICD-10th (Z95810). Elixhauser Comorbidity Index provided by the HCUP-NIS was used to estimate the prevalence of comorbidities in our sample. Patients were divided according to the presence or absence of AF into an AF and non-AF group. The primary objective of the study was to investigate the impact of AF on in-hospital mortality. Secondary outcomes included the risk for cardiogenic shock, myocardial infarction (MI), VF, stroke, and acute kidney injury. The association between different age strata and outcomes was investigated.

We followed HCUP NIS analytic guidelines and accounted for the complex survey design of the study data. Accordingly, we were able to obtain the national estimates for HF hospitalizations during the study period. Categorical and continuous variables were presented as percentages and median (with interquartile ranges) respectively and were compared using the standardized mean difference for effect

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size. Effect size is considered large, moderate, small, or trivial for values ≥ 0.5, 0.3 - 0.5, 0.1 - 0.3, and < 0.1, respectively.[8] The risk for Outcomes of hospitalization were estimated using logistic regression for binary outcomes. Potential patient-level factors including age, sex, race, and comorbid conditions as well as hospital-level factors including hospital size and teaching status were adjusted in the multivariable analysis. Effect modification of age was assessed by introducing interactions (age categories or continuous scale) in the models. Adjusted odds ratio (a-OR) was reported together with their 95% confidence intervals. Descriptive and analytic statistics were conducted using STATA 15 (Stata Corp). A p value <0.05 was considered significant.

Results

We included a total of 178,045 patients with a history of HF and ICD placed who were hospitalized for HF symptoms during the years 2016 to 2017. Table 1 summarizes the baseline characteristics of the study population. Patients with AF accounted for 56.2% of the total study population. Patients with AF were older with median age (75 vs 72 years, SMD=0.3) had less proportion of females (26.7% vs 32.3% SMD=0.1), higher proportions of white race (71.4% vs 57.4%, SMD=0.3) and had higher prevalence of anemia due to blood loss, valvular heart disease, hypothyroidism, chronic renal failure, and obstructive sleep apnea.

The rates of all-cause in-hospital mortality and complications are summarized in Table 2. Overall, patients with AF had higher rates of mortality (3.2% vs 2.4%, SMD=0.1) and acute kidney injury (33.6% vs 33.1%, SMD=0.1) There was a trivial difference in rates of cardiogenic shock, MI, VF, and stroke.

On multivariable analysis, AF was an independent predictor of increased mortality (Figure 1), cardiogenic shock, acute kidney injury, and lower MI (Figure 2). There was no correlation between AF and risk for VF and stroke. The age by AF interaction for predicting mortality and other endpoints are summarized in Figures 1 and 2. A significant correlation between AF and higher risk for mortality, cardiogenic shock and AKI is demonstrated at ages ≤ 75, ≤ 75, and ≤ 80 years, respectively. In contrast, a significant correlation between AF and lower risk for MI is only demonstrated at age > 70 years.

Discussion

The key findings in this study are: 1. AF is highly prevalent in hospitalized older patients with HF and ICDs. 2. AF is an independent predictor for increased all-cause in-hospital mortality and cardiogenic shock. 3. This increased risk for mortality and cardiogenic shock is age dependent, and counter-intuitively, risk decreases with advancing age and essentially becomes insignificant in patients older than 75 years. Perhaps this relationship can be explained by an increase in competing risks for mortality in older individuals.

Previous clinical trials have demonstrated that AF becomes more prevalent with worsening degree of New York Heart Association (NYHA), with up to 50% prevalence in NYHA class IV patients.[9] The landmark Framingham Heart Study was one of the first studies to report a link between AF, HF and increased mortality.[10] Since then, numerous studies have redemonstrated this association with overall worse outcomes. [11,12] Our study concurs with previous studies and further highlights the interaction

Table 1
Baseline characteristics of study population

	Atrial fibrillation		
	No (n= 77,970)	Yes (n=100,075)	SMD
Age (Years)	72.0 [66.0, 79.0]	75.0 [69.0, 82.0]	0.3
Women	32.3%	26.7%	0.1
Race			0.3
White	57.4%	71.4%	
Black	27.7%	18.1%	
Hispanic	9.9%	6.8%	
Elective admission	5.9%	5.7%	< 0.1
Deficiency anemias	28.4%	30.0%	< 0.1
Blood loss anemia	0.5%	0.9%	0.1
RA and vascular disease	3.9%	4.2%	< 0.1
Valvular heart disease	26.6%	35.2%	0.2
Chronic lung disease	43.1%	41.3%	< 0.1
Diabetes mellitus	54.5%	47.9%	0.1
Hypertension	71.1%	72.4%	< 0.1
Hypothyroidism	15.8%	21.9%	0.2
Alcohol abuse	2.2%	1.8%	< 0.1
Drug abuse	2.5%	1.1%	0.1
Liver disease	4.5%	4.9%	< 0.1
Chronic renal failure	56.6%	61.4%	0.1
Solid tumor	2.2%	2.3%	< 0.1
Metastatic cancer	0.8%	0.8%	< 0.1
Obesity	16.6%	17.7%	< 0.1
Peripheral vascular disease	13.8%	13.7%	< 0.1
Psychoses	1.5%	1.0%	< 0.1
Depression	10.2%	10.4%	< 0.1
Coronary artery disease	77.2%	75.3%	< 0.1
Hyperlipidemia	61.6%	61.2%	< 0.1
Tobacco use	1.5%	0.8%	0.1
Obstructive sleep apnea	16.3%	19.9%	0.1
Stroke	13.0%	14.2%	< 0.1
Median household income			0.2
0-25th percentile	37.6%	30.2%	
26th to 50th percentile	25.0%	25.8%	
51st to 75th percentile	22.1%	23.4%	
76th to 100th percentile	15.3%	20.6%	
Primary expected payer			0.1
Medicare	81.3%	85.7%	
Medicaid	6.2%	3.9%	
Private insurance	9.5%	8.1%	
Hospital bed size			< 0.1
Small	18.4%	17.8%	
Medium	28.9%	29.2%	
Large	52.7%	53.0%	
Hospital location and teaching status			0.1
Rural	9.1%	7.8%	
Urban nonteaching	25.1%	24.3%	
Urban teaching	65.7%	67.9%	

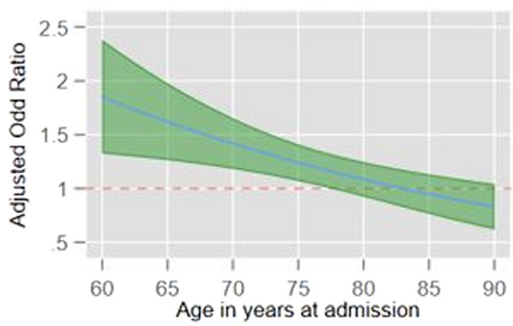
Data are presented as median (IQR) for continuous measures, and % for categorical measures. Abbreviations: SMD: Standardized mean differences for effect size.

Table 2
Risk for mortality and complications in patients with and without AF

	Univariable analysis			Multivariable analysis		
Variable	No AFn=77,970	AFn=100,075	SMD	Adjusted OR	95% CI	p value
Mortality	2.4%	3.2%	0.1	1.22	1.06-1.40	0.005
Cardiogenic shock	3.8%	4.6%	< 0.1	1.21	1.08-1.36	<0.001
Acute Myocardial Infarction	2.8%	2.1	< 0.1	0.79	0.68-0.90	<0.001
Ventricular fibrillation	3%	3.2%	< 0.1	1.04	0.91-1.19	0.56
Stroke	0.3%	0.3%	< 0.1	1.44	0.91-2.26	0.12
Acute Kidney Injury	33.1%	36.6%	0.1	1.12	1.06-1.17	<0.001

AF: Atrial fibrillation, SMD= Standardized mean difference (effect size).

Age by AF interaction for predicting Mortality



Age group	OR	95% CI	P value
All patients	**1.22**	**(1.06-1.40)**	**0.005**
60-65	1.72	(1.34-2.21)	<0.001
66-70	1.50	(1.25-1.81)	<0.001
71-75	1.31	(1.13-1.52)	<0.001
76-80	1.14	(0.99-1.33)	0.075
81-85	1.00	(0.83-1.21)	0.985
86-90	0.87	(0.68-1.12)	0.287

Figure 1. Age by AF interaction for predicting mortality.

between age, AF and risk for mortality and adverse outcomes.

Patients with AF are at higher risk for ventricular tachyarrhythmia (VT) and VF. [13,14] Previous studies have investigated the link between AF and VT/VF in ICD recipients shedding further light on this distinct association. Stein et al. investigated the incidence of VT/VF events being preceded by paroxysmal AF or atrial tachycardia (AT) in dual-chamber ICD recipients for secondary prevention of sudden cardiac death. Of the spontaneous VT/VF episodes included, 8.6% were preceded by a paroxysm of AF/AT and during follow-up of patients who had a VT/VF episode, they found that 20.3% had experienced at least one dual atrial-ventricular tachycardia episode. In the current study, AF had no significant association with the risk for ventricular arrhythmia. However, our findings were limited to in-hospital events following hospitalization for HF and no long-term follow up data was obtained.

Patients with HF are at higher risk for AKI through multiple factors including decreased cardiac output, use of diuretics and renin−angiotensin-aldosterone system blockade. In patients with HF, the presence of AKI is linked to a higher risk of mortality and adverse outcomes.[15,16] The risk is even higher in patients with advanced age and in the presence of underlying chronic kidney disease and other comorbidities.[17] In our study, we found that AF is strongly correlated with a higher risk of AKI. The risk of AKI imposed by AF decreases with advanced age and no significant difference in risk of AKI between patients with and without AF at age above 80 years.

In patients with established risk for MI, as in this study's patient population, AF has less contribution to the occurrence of MI when compared to healthier patients.[18] The risk for thromboembolic complications including risk for stroke and MI has been shown to be decreased with the use of anticoagulation. [19,20,21] This might explain the negative correlation between AF and risk for MI as seen in our study.

This study has some limitations. The NIS is an administrative database and is prone to coding and /or misclassification bias and under-reporting of chronic conditions. In the absence of radiological and echocardiography data it was not possible to measure the ejection fraction for patients. In a patient population with AF and ICDs, antiarrhythmic drugs may play a role in preventing as well as promoting ventricular arrhythmias. Since the NIS database does not provide medications, the role of antiarrhythmic drugs cannot be ascertained. The study was limited to in-hospital events and re-admission data as well as long-term follow up was not obtained due to the limitations of the database.

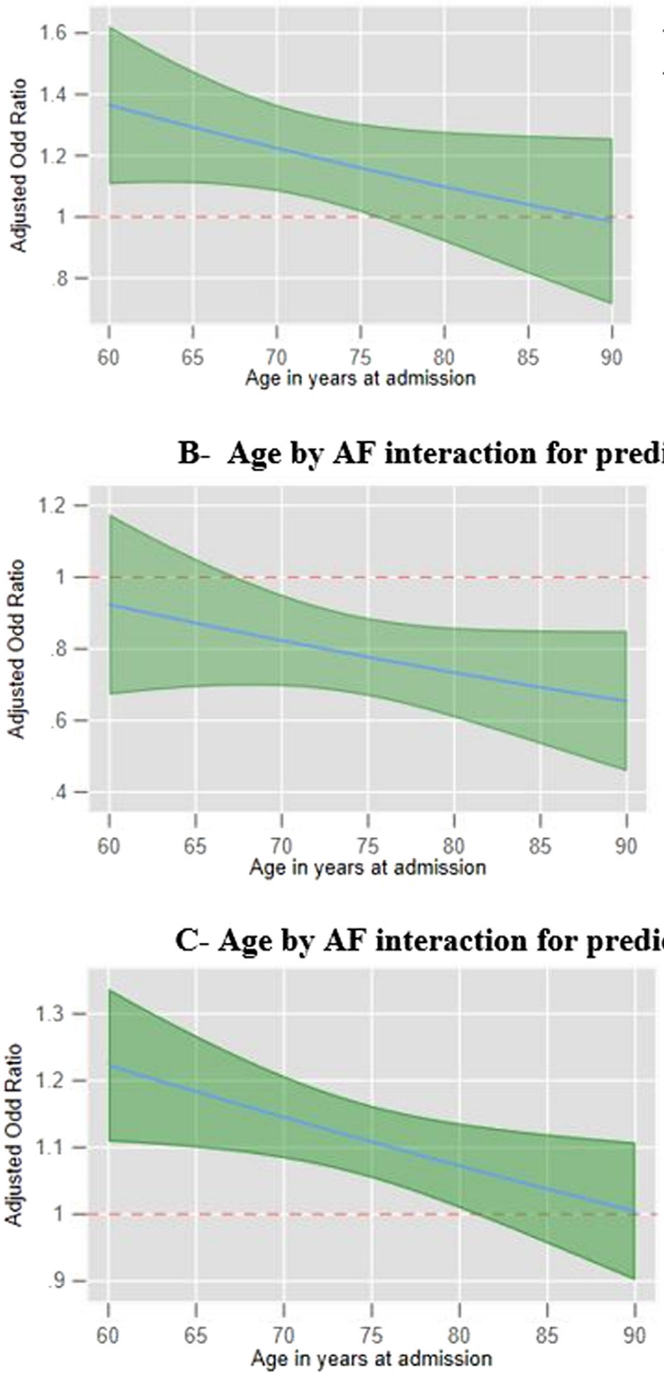
The primary strength of this study is the availability of a large sample representative of the entire United States population. Our analysis focused on patients with advanced age and analyzed the age interaction with the study outcomes. Confounding bias was mitigated by performing a multivariable analysis with adjustment for patients' demographics, chronic conditions and socioeconomic factors and hospital characteristics available within the registry.

In conclusion, we found that that AF is independently associated with increase mortality based on parameters assessed. Age has a significant interaction and modifies

A- Age by AF interaction for predicting Cardiogenic Shock

B- Age by AF interaction for predicting Myocardial Infraction

C- Age by AF interaction for predicting Acute kidney Injury



A- Age by AF interaction for predicting Cardiogenic Shock

Age group	OR	95% CI	P value
All Patients	**1.21**	**1.08-1.36**	**<0.001**
60-65	1.27	1.07-1.51	0.01
66-70	1.23	1.09-1.40	0.00
71-75	1.19	1.06-1.34	0.00
76-80	1.16	1.00-1.35	0.05
81-85	1.12	0.91-1.38	0.27
86-90	1.09	0.83-1.43	0.54

B- Age by AF interaction for predicting Myocardial Infraction

Age group	OR	95% CI	P value
All Patients	**0.79**	**0.68-0.90**	**<0.001**
60-65	0.93	0.73-1.18	0.56
66-70	0.86	0.73-1.03	0.11
71-75	0.80	0.70-0.93	<0.001
76-80	0.75	0.64-0.88	<0.001
81-85	0.69	0.56-0.87	<0.001
86-90	0.65	0.48-0.87	<0.001

C- Age by AF interaction for predicting Acute kidney Injury

Age group	OR	95% CI	P value
All Patients	**1.12**	**1.06-1.17**	**<0.001**
60-65	1.19	1.10-1.29	<0.001
66-70	1.16	1.09-1.23	<0.001
71-75	1.13	1.08-1.19	<0.001
76-80	1.10	1.04-1.17	<0.001
81-85	1.08	1.00-1.16	0.06
86-90	1.05	0.95-1.16	0.36

Figure 2. Age by AF interaction for predicting secondary outcomes.

the AF related risk of in-hospital mortality, cardiogenic shock, and thromboembolic complications in HF patients with ICDs. Further studies are needed to investigate the age-related factors including echocardiographic variables and type of medications, especially antiarrhythmic drugs and anticoagulants, which can influence this association.

Authors contribution

AA: Conceptualization, Methodology, Resources, Formal analysis, Visualization, Writing, review & eiditing.

AE, AO, HA: Writing - review & editing.

MA: Formal analysis, review & editing

AV: Supervision, Methodology, Writing review & editing.

Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2021.04.016.

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