

Atrial Fibrillation as a Prognostic Indicator in Patients With Orthostatic Hypotension: Nationwide Inpatient Sample Analysis

Ahmed Brgdar^{a, f}, John Gharbin^a, Ahmad Awan^b, Richard Ogunti^c, Qasim Khurshid^a,
Mayar Hamad^d, Prafulla Mehrotra^e

Abstract

Background: Orthostatic hypotension and atrial fibrillation have common etiology and a bidirectional relationship with several cardiovascular conditions. Despite both conditions being highly prevalent in hospitalized patients, prior research has primarily evaluated adverse outcomes due to orthostatic hypotension and atrial fibrillation independent of each other. In this study, we aim to assess if the presence of atrial fibrillation exacerbates in-hospital outcomes of patients with orthostatic hypotension.

Methods: Adult patients hospitalized in 2019 with a primary diagnosis of orthostatic hypotension with or without pre-existing atrial fibrillation were identified using the International Classification of Diseases, Tenth Revision (ICD-10) code. The primary outcome of interest was in-patient mortality and cardiac arrest. Secondary outcomes of interest were the length of stay and total hospital charges. Adjusted and unadjusted analysis was performed on appropriate variables of interest.

Results: Among 10,630 hospitalizations with orthostatic hypotension, 2,987 (median (interquartile range (IQR)) age: 78.5 (68.5 - 88.5) years; 1,197 women (40.1%)) comprised the atrial fibrillation cohort. Mean Charlson comorbidity index was noted to be significantly higher in orthostatic hypotension and atrial fibrillation patients (mean (standard deviation (SD)): 3.1 (2.1) vs. 2.5 (2.1), $P < 0.001$). Compared to orthostatic hypotension patients without atrial fibrillation, the prevalence of congestive heart failure (1,263 (42.3%) vs. 1,367 (17.9%)), coronary artery disease (1,432 (47.9%) vs. 2,481 (32.5%)), history of percutaneous coronary intervention or graft (443 (14.83%) vs. 860 (11.3%)), chronic obstructive pulmonary disease

(644 (21.6%) vs. 1,131 (14.8%)), chronic kidney disease (1,182 (39.6%) vs. 2,216 (29.0%)), and hyperlipidemia (1,828 (61.2%) vs. 4,087 (53.5%)); all $P < 0.05$, were significantly higher in orthostatic hypotension patients with atrial fibrillation. Following multivariable analysis of orthostatic hypotension patients, atrial fibrillation was associated with 5.0 times greater odds for cardiac arrest (adjusted odds ratio (aOR) = 5.0 (95% confidence interval (CI): 1.4 - 18.2), $P = 0.014$), without increased risk of in-hospital mortality (aOR = 2.1 (95% CI: 0.9 - 5.0), $P = 0.090$).

Conclusions: Atrial fibrillation is an independent predictor for cardiac arrest but not in-hospital mortality in patients with orthostatic hypotension. The short- and long-term prognostic value of atrial fibrillation in orthostatic hypotension patients must be confirmed in future prospective trials to improve patient outcomes.

Keywords: Atrial fibrillation; Orthostatic hypotension; Cardiovascular; Hypertension

Introduction

Orthostatic hypotension (OH), a common manifestation of autonomic dysfunction, and atrial fibrillation (AF), the most common sustained arrhythmia, have shared risk factors such as advancing age, hypertension, and diabetes and are highly prevalent conditions. The prevalence of OH, defined as a drop in systolic blood pressure of at least 20 mm Hg or of at least 10 mm Hg in diastolic blood pressure within 3 min of standing up [1], is estimated to be around 5-6% among those aged 55 years or older [2, 3] although the prevalence of asymptomatic OH may be as high as 16% among those aged 65 years and older [4]. In 2004, OH caused 36 hospitalizations per 100,000 US adults with an in-hospital mortality rate of 0.9% [5]. On the other hand, AF currently affects about 6 million patients in the USA alone and accounts for more than 454,000 hospitalizations each year [6, 7].

Although OH [2, 3, 8-14] and AF [15] are both well-recognized risk factors for morbidity and mortality and have a bidirectional relationship with several cardiovascular conditions such as coronary heart disease, heart failure, myocardial infarction, venous thromboembolism (VTE), and stroke, the current literature largely considers AF and OH independently of each

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^aDepartment of Medicine, Howard University Hospital, Washington, DC, USA

^bCardiovascular Disease, Montefiore Medical Center, Bronx, NY, USA

^cDepartment of Medicine, Mayo Clinic Health System, Mankato, Minnesota, USA

^dFaculty of Science, University of Calgary, Calgary, AB, Canada

^eCardiovascular Disease, Howard University Hospital, Washington, DC, USA

^fCorresponding Author: Ahmed Brgdar, Department of Medicine, Howard University Hospital, Washington, DC, USA. Email: ABrgdar@huhosp.org

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other. Nevertheless, the intricate link between OH and AF has been emerging over the past decade. For instance, the Malmo Preventive Project demonstrated that OH is an independent risk factor of incident AF in middle-aged adults [13], while similar observations were reported from the Framingham Heart Study in older adults [16]. Moreover, several recent meta-analyses confirm the association between OH and increased risk of incident AF [12, 17], which might be partly due to the structural and hemodynamic heart remodeling seen with OH [18].

Similarly, the Irish Longitudinal Study on Ageing (TILDA) and a Chinese cohort study reported a higher OH occurrence among AF patients [19, 20]. In older adults, AF independently increases the risk of syncope and nonaccidental falls [21-23] and is likely to exacerbate the symptoms of OH and the need for hospitalization.

Despite the higher prevalence of OH [24] and AF [25] among hospitalized patients than in the general population, there is a paucity of studies reporting in-hospital outcomes of patients with concomitant OH and AF. In this retrospective cohort study, we aim to assess whether the presence of AF is an independent predictor of cardiac arrest and mortality in patients with OH using hospitalization records from the National Inpatient Sample (NIS) database.

Materials and Methods

Subjects

Patient hospitalization records for 2019 were retrieved from the NIS, the largest in-patient healthcare database in the USA, developed and maintained by the Healthcare Cost and Utilization Project (HCUP) under the sponsorship of the Agency for Healthcare Research and Quality. The details of the NIS database have been described previously [26].

Participants

In this study, patients aged 18 years or older hospitalized in 2019 with OH as the primary diagnosis were identified from the NIS database using the International Classification of Diseases, Tenth Revision (ICD-10) diagnosis code I95.1. The study sample was then categorized into OH patients with AF (ICD-10 = codes I48.20 and I48.91 corresponding to chronic AF and unspecified AF, respectively) and OH patients without AF. ICD10 code Z95.5 was used to identify patients with a history of coronary angioplasty or graft. We then compared in-hospital clinical outcomes between OH patients with AF and those without AF. Patient baseline characteristics included age, sex, race/ethnicity, household income, insurance type, and comorbidities. Hospital characteristics included hospital teaching status.

Outcomes

The primary outcomes of interest were in-patient mortality and in-hospital cardiac arrest. Secondary outcomes of interest were

the length of stay and total hospital charges.

Statistical analysis

We expressed continuous variables as median \pm interquartile range (IQR) and used *t*-tests or regression to compare differences between exposure and non-exposure group. Similarly, categorical variables were presented as percentages, and a Chi-squared test was used to compare the differences between the variables. All statistical tests were two-sided, and tests with *P* values of < 0.05 were considered significant. Multivariate logistic regression was used to adjust for comorbidities, hospital characteristics, and Charlson comorbidity index (CCI) [27]. Data were analyzed with Software for Statistics and Data Science (STATA V.14.2, Stata Corp 4905 Lakeway Drive, College Station, TX 77845, USA).

Institutional review board (IRB) statement

Howard University Hospital IRB exempted this study from full review because it was determined to be a non-human study. We have utilized anonymized data available from a public data repository. The study was conducted in compliance with the ethical standards of the responsible institution on human subjects as well as with the Helsinki Declaration.

Results

We identified 10,630 hospitalizations with the primary diagnosis of OH in 2019, 2,987 (28%) of whom had a concomitant diagnosis of AF (Table 1). OH patients with AF were older (78.5 (IQR: 68.5 - 88.5) vs. 71.6 (IQR: 57.6 - 85.6) years, $P < 0.001$) and predominantly male (1,790 (59.9%) vs. 4,019 (52.6%), $P < 0.001$) than patients without AF. While most of the patients in the two groups were White, the proportion was significantly higher (2,474 (87.5%) vs. 5,247 (76.5%), $P < 0.001$) in the AF group (Table 1). Similarly, Medicare was the primary insurer in both groups but with significantly more coverage among OH patients with AF than those without AF (2,632 (89.5%) vs. 5,745 (77.0%), $P < 0.001$) (Table 1). Nearly three-fourths of the patients were treated at a teaching hospital with no intergroup differences (Table 1). Also, patients' location was similar in the two groups (Table 1).

The prevalence of several comorbidities including congestive heart failure (1,263 (42.3%) vs. 1,367 (17.9%); $P < 0.001$), history of percutaneous coronary intervention (PCI) or graft (443 (14.8%) vs. 860 (11.3%); $P < 0.001$), coronary artery disease (1,432 (47.9%) vs. 2,481 (32.5%)), chronic obstructive pulmonary disease (COPD) (644 (21.6%) vs. 1,131 (14.8%); $P < 0.001$), chronic kidney disease (1,182 (39.6%) vs. 2,216 (29.0%); $P < 0.001$), and hyperlipidemia (1,828 (61.2%) vs. 4,087 (53.5%); $P < 0.001$) were significantly higher in OH patients with AF (Table 1). Furthermore, patients with OH and concomitant AF had higher mean CCI (3.1 (standard deviation (SD): 2.1) vs. 2.5 (SD: 2.1), $P < 0.001$). However, the prevalence

Table 1. Baseline Demographics, Comorbidities of Patients, Admitted for Orthostatic Hypotension (OH) With or Without Concomitant Atrial Fibrillation (AF)

Variables	OH with AF (n = 2,987)	OH without AF (n = 7,643)	P value
Age (mean ± SD)	78.5 ± 10	71.6 ± 14	< 0.001
Sex (n, %)			
Female	1,197 (40.1%)	3,624 (47.4%)	< 0.001
Male	1,790 (59.9%)	4,019 (52.6%)	
Race (n, %)			
White	2,474 (87.5%)	5,427 (76.5%)	< 0.001
Black	243 (8.6%)	1,149 (16.2%)	
Hispanic	111 (3.9%)	521 (7.3%)	
Type of insurance (n, %)			
Medicare	2,632 (90.0%)	5,745 (77.0%)	< 0.001
Medicaid	84 (2.9%)	611 (8.2%)	
Private insurance HMO	209 (7.1%)	953 (12.5%)	
Self-pay	14 (0.5%)	166 (2.2%)	
Comorbidities (n, %)			
Hypertension	905 (30.3%)	3,299 (43.2%)	< 0.001
Diabetes mellitus	1,133 (37.9%)	2,871 (37.6%)	0.725
Congestive heart failure	1,263 (42.3%)	1,367 (17.9%)	< 0.001
Coronary artery disease	1,432 (47.9%)	2,481 (32.5%)	< 0.001
History of PCI or graft	443 (14.8%)	860 (11.3%)	< 0.001
History of cardiac arrest	20 (0.7%)	32 (0.4%)	0.096
COPD	644 (21.6%)	1,131 (14.8%)	< 0.001
Chronic kidney disease	1,182 (39.6%)	2,216 (29.0%)	< 0.001
Obesity	331 (11.1%)	811 (10.6%)	0.482
Hyperlipidemia	1,828 (61.2%)	4,087 (53.5%)	< 0.001
ESRD	147 (4.9%)	314 (4.1%)	0.064
Alcohol use	103 (3.5%)	380 (5.0%)	0.001
Nicotine use	229 (7.7%)	951 (12.4%)	< 0.001
Charlson comorbidity index, (mean ± SD)	3.1 (2.1)	2.5 (2.1)	< 0.001
Hospital characteristics (n, %)			
Teaching hospital	2,194 (73.5%)	5,708 (74.7%)	0.191
Non-teaching hospital	793 (27.6%)	1,935 (25.3%)	
Median household income (n, %)			
\$1 - \$45,999	720 (24.4%)	2,148 (28.5%)	< 0.001
\$46,00 - \$58,999	738 (25.0%)	1,923 (25.6%)	
\$59,000 - \$78,999	761 (25.8%)	1,903 (25.3%)	
≥ \$79,000	731 (24.8%)	1,556 (20.7%)	
Patient location (n, %)			
Central counties of metropolitan areas > 1 million population	816 (27.4%)	2,268 (29.8%)	0.125
Fringe counties of metropolitan areas > 1 million population	829 (27.8%)	2,079 (27.3%)	
Counties in metro areas of 250,000 - 999,999 population	657 (22.0%)	1,595 (20.9%)	
Counties in metro areas of 50,000 - 249,999 population	279 (9.4%)	723 (9.5%)	
Micropolitan counties	225 (7.6%)	569 (7.5%)	
Not metropolitan or micropolitan counties	175 (5.9%)	383 (5.0%)	

SD: standard deviation; PCI: percutaneous coronary intervention; COPD: chronic obstructive pulmonary disease; ESRD: end-stage renal disease.

Table 2. Univariate and Multivariate Logistic Regression Analysis of Primary Outcomes of Patients With Orthostatic Hypotension and Concomitant Atrial Fibrillation

Outcomes	Univariate		Multivariate	
	Odds ratio (95% CI)	P value	Adjusted odds ratio (95% CI)	P value
In-hospital mortality	3.2 (1.5 - 6.9)	0.003	2.1 (0.9 - 5.0)	0.090
Cardiac arrest	7.7 (2.5 - 23.9)	< 0.001	5.0 (1.4 - 18.2)	0.014
LOS, mean in days	0.4	< 0.001	0.2	0.054
Total charges	\$1,877	0.016	\$1,536	0.074

CI: confidence interval; LOS: length of stay.

of hypertension (905 (30.3%) vs. 3,299 (43.2%), $P < 0.001$), alcohol use (103 (3.5%) vs. 380 (5.0%); $P < 0.001$), and nicotine use (229 (7.7%) vs. 951 (12.4%); $P < 0.001$) were significantly lower in OH patients with AF (Table 1). The prevalence of diabetes mellitus, obesity, end-stage renal disease, and previous history of cardiac arrest was similar in the two groups (Table 1).

In the univariate analysis, the risk of in-hospital mortality (odds ratio (OR) = 3.2 (95% confidence interval (CI): 1.5 - 6.9), $P = 0.003$) and cardiac arrest (OR = 7.7 (95% CI: 2.5 - 23.9), $P < 0.001$) were significantly higher in OH patients with AF with longer length of stay (0.4 days, $P < 0.001$) and higher total charges (\$1,877, $P = 0.016$) (Table 2). Although the risk of cardiac arrest remained significantly higher in OH patients with concomitant AF (adjusted odds ratio (aOR): 5.0 (95% CI: 1.4 - 18.2), $P = 0.014$) in the multivariate logistic regression analysis (Table 2), similar rates of in-hospital mortality (aOR: 2.1 (95% CI: 0.9 - 5.0), $P = 0.090$), length of stay (0.2 days, $P = 0.054$), and total charges (\$1,536, $P = 0.074$) were observed between the two groups.

Discussion

Earlier studies have reported an elevated risk of incident coronary events, stroke, AF, heart failure, and all-cause mortality among patients hospitalized for OH compared to non-OH hospitalizations [28, 29], although OH patients were examined independently of AF. However, not all studies support the notion that OH is predictive of adverse cardiovascular outcomes. The Last Evidences of Genetic Risk factors in the Aged (LEOGRA) Study, for instance, reported null associations between OH and cardiovascular events, including coronary events, heart failure, and arrhythmias after adjusting for confounders [30]. Comparably, Veronese et al showed that OH was only associated with higher non-cardiovascular disease (CVD) mortality but not with CVD mortality in older adults [31].

To our knowledge, this is the first study to examine the in-hospital outcomes of OH patients with pre-existing AF. We noted a disproportionately higher prevalence of several cardiovascular comorbidities such as congestive heart failure, history of coronary angioplasty or graft, COPD, chronic kidney disease, and hyperlipidemia in patients with concomitant diagnoses of OH and AF. Hence, we observed a higher mean comorbidity index in OH patients with AF. The higher prevalence of these comorbidities in patients hospitalized for OH is consistent with earlier

observations in middle-aged [28] or older adults [32]. However, it is noteworthy that patients with contaminant diagnoses of OH and AF in our study cohort had a significantly lower prevalence of hypertension, nicotine use, and alcohol use. Prior studies suggest that pre-arrest comorbidity score may be a key determinant of survival after an in-hospital cardiac arrest [33-35]. A study by Mankoo et al noted that while higher blood pressure is generally considered detrimental to cardiovascular or cerebrovascular outcomes, chronic hypertension necessitates higher pressure for the cerebral autoregulation of blood pressure, thereby increasing the risk of ischemia at lower blood pressure [36]. As a result, they observed an inverse relationship between blood pressure and mortality outcomes with increased mortality risks among patients with pre-existing OH and AF presenting with a transient ischemic attack [36].

It is, therefore, plausible that the lower prevalence of hypertension in our cohort of OH patients with AF prevents further exacerbation of mortality outcomes.

An earlier analysis of the NIS database demonstrated that the in-hospital mortality in patients hospitalized with AF-related complications consistently declined between 2000 and 2010 but with increased inflation-adjusted hospitalization costs [37]. While our analysis only included NIS data from 2019, the length and cost of hospitalization in OH patients with AF remained comparable to OH patients without AF.

Although the presence of AF in OH patients did not further exacerbate the length and cost of in-hospital care or mortality risk, we observed an increased risk of cardiac arrest among patients with concomitant OH and AF. To the best of our knowledge, the association between OH and cardiac arrest in either hospital or out-of-hospital settings has not been reported yet. However, consistent with our findings, a Swedish retrospective cohort study reported a positive association between AF and the occurrence of in-hospital cardiac arrest, albeit they did not explicitly recruit patients with concomitant OH diagnosis [38].

Several mechanisms have been proposed which may explain the increased risk of cardiac arrest among patients with concomitant OH and AF. Autonomic nervous system dysregulation is thought to be central in the pathogenesis of OH [39], AF [40], and cardiac arrest [41]. Additionally, autonomic nervous system dysregulation may lead to arterial stiffness [42], a common pathophysiological change attributed to hypertension and aging. While arterial stiffness has been independently associated with OH [43] and AF [44], it may also potentially increase the risk of cardiac arrest [45]. It has been proposed

that the development of OH is secondary to autonomic nervous system dysregulation [17], and the development of AF occurs further downstream in the CVD continuum [17, 46]. Therefore, it is very likely that the presence of AF in OH patients indicates the severity of autonomic nervous system dysregulation to increase the risk of cardiac arrest.

Furthermore, studies suggest that although OH and AF may have shared etiology, they may have an additive detrimental effect on the cardiovascular remodeling and risk of cardiac arrest. For instance, echocardiographic assessments in OH patients show greater left atrial volume and left ventricular (LV) mass [47], while left atrial size progressively increases in AF patients independent of changes in LV size or function [48]. Patients with OH may also experience an orthostatic surge in catecholamine levels leading to ectopic ventricular tachycardia, premature ventricular contractions, and episodes of non-sustained ventricular tachycardia [49, 50], which in turn may precipitate into sustained ventricular tachycardia, ventricular fibrillation, primary cardiomyopathy, tachycardia-induced cardiomyopathy, and sudden cardiac death [51]. The concomitant presence of AF in OH patients further exacerbates the risk of ventricular tachycardia and sudden cardiac death as normal atrioventricular (AV) node conduction during AF is known to cause ventricular tachycardia and impaired LV function [52-54]. Similarly, pooled data from the prospective Cardiovascular Health Study (CHS) and the Atherosclerosis Risk in Communities (ARIC) Study show a moderately increased risk of VTE in older adults with OH [55], while thromboembolic complications in AF patients have been extensively reported by Rubart et al [56]. A recent meta-analysis by Noumegni et al shows that over 35% of deaths among VTE patients were attributable to cardiovascular deaths [57].

At least two previous meta-analyses show that AF is associated with a two-fold increased risk of sudden cardiac death and exacerbated risks of all-cause and cardiovascular mortality [58, 59]. However, several large prospective studies, including the Rotterdam Study [60], the Malmo Preventive Project [3], and the ARIC study [61], and a meta-analysis [9], show that OH increases the risk of all-cause mortality but not sudden cardiac death. Hence it is plausible that AF may introduce the additional risk of sudden cardiac death in patients with OH, which may have contributed to the increased risk of cardiac arrest observed in our study cohort.

Limitations

Our study has limitations. First, since many patients with OH are treated in an out-patient setting or do not seek medical treatment, our study population may have a selection bias. Moreover, there is a potential risk of selection bias by the non-random allocation of interventions, the risk of coding errors, and missing data that are inherent to any large database study. However, the NIS auditing process is well established, minimizing data inaccuracy issues. While unmeasured confounders may exist, they are expected to be evenly distributed among all groups. Second, the findings of this retrospective observational study are hypothesis-generating and need to be confirmed in future randomized control trials. Third, our findings

are limited to in-hospital setting, and long-term cardiovascular and mortality outcomes of patients with OH and AF remain unclear. Finally, the pharmacological treatment history of OH patients, especially anti-hypertensive medication, may affect hospital outcomes [62], and we were unable to account for this due to database limitations.

Conclusions

The findings of this study showed that AF is an independent predictor for cardiac arrest but not in-hospital mortality in patients with OH. Given that the survival to discharge after an in-hospital cardiac arrest is typically around 20% [35], our findings on an increased risk of cardiac arrest but not mortality in OH patients with AF suggest the involvement of additional factors which warrant further investigation.

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Conflict of Interest

None to declare.

Informed Consent

Patient consent was waived because the study utilized de-identified publicly available data.

Author Contributions

Ahmed Brgdar: conceptualization, methodology, writing - original draft preparation, and investigation. John Gharbin: data curation, formal analysis, and software. Ahmad Awan: conceptualization and visualization. Richard Ogunti: formal analysis. Qasim Khurshid: investigation. Mayar Hamad: formal analysis and supervision. Prafulla Mehrotra: supervision. All authors have read and agreed to the published version of the manuscript

Data Availability

The data utilized in this study can be found online at www.hcup-us.ahrq.gov (accessed on February 2, 2022).

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