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Association of Antiarrhythmic Drug Therapy with Syncope and Pacemaker Implantation with Arterial Fibrillation

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ABSTRACT

Background

Atrial fibrillation (AF) is a frequent cardiac arrhythmia and its treatment frequently requires the use of antiarrhythmic drugs (AAD). AAD therapy is designed to preserve sinus rhythm and regulate heart rate, but it does come with its dangers. To examine the relationship of antiarrhythmic drug therapy with syncope and pacemaker implantation in atrial fibrillation.

Methods

This study was a retrospective cohort analysis conducted at Hayatabad Medical Complex Peshawar, department of CRC, between 16th, May 2023 to 15th, April 2024. 'A total of 180 patients diagnosed with atrial fibrillation and treated with antiarrhythmic drugs were included in the study'. Inclusion criteria were patients aged 18 years or older with a diagnosis of atrial fibrillation confirmed by electrocardiography, starting oral antiarrhythmic drug therapy for either rhythm control (amiodarone) or rate control (beta-blockers) and a follow-up period of at least 6 months from the initiation. The study excluded patients with a history of pacemaker implantation or more than trivial structural heart disease and those under treatment for rhythm control of other types of arrhythmias. Demographic data, type of antiarrhythmic drug used, duration of therapy, and clinical outcomes were analyzed.

Results

The study enrolled 180 patients with atrial fibrillation, 'with a mean age of 68.5 ± 10.2 years; 112 (62.2%) were males and 68 (37.8%) were females'. The distribution of Body Mass Index was as follows: 10 (5.6%) were underweight, 72 (40.0%) were normal weight, 64 (35.6%) were overweight, and 34 (18.8%) were classified as obese. The 'logistic regression analysis indicated that the use of Class IC and Class III drugs was associated with a significantly increased risk of syncope, with adjusted odds ratios (ORs) of 2.5 (95% CI; 1.2-5.1, p = 0.01) and 2.1 (95% CI; 1.0-4.4, p = 0.04), respectively'.

Conclusion

This study highlights that the use of Class IC and Class III antiarrhythmic drugs is associated with syncope as a new factor leading to pacemaker implantation in patients suffering from atrial fibrillation

Keywords

Antiarrhythmic Drugs, Atrial Fibrillation, Syncope, Pacemaker Implantation.

INTRODUCTION

Atrial fibrillation (AF) represents the most common sustained cardiac arrhythmia affecting millions worldwide [1, 2]. The condition is defined by an irregular, and often fast heartbeat which can cause a range of complications including stroke or cardiac failure among others [3]. Management of AF generally includes restoration and maintenance of sinus rhythm with antiarrhythmic drugs (AADs) along with control of ventricular rate [4]. Nevertheless, treatment with AADs is not without risks of adverse effects including serious or life-threatening complications [5, 6].

One of the most characteristic drug-induced adverse events is syncope, defined as an abrupt and transient loss of consciousness due to insufficient cerebral blood flow [7]. Bradycardia, atrioventricular block and drug-induced tachyarrhythmias are common mechanisms [8]. The presence of syncope not only affects the quality of life but is also associated with a greater risk for falls and subsequently injury [9]. AAD therapy can also occasionally precipitate severe bradyarrhythmias or conduction disturbances requiring pacemaker implantation (PMI) [10]. Whether to implant a pacemaker is usually determined when the risk of symptomatic bradycardia/atrioventricular block outweighs its benefits with AAD therapy [11].

AAD use for AF has become common practice, 'but little is known about the relationship between AAD therapy and syncope with a need of pacemaker implantation' [12]. Deciphering such tangle connections is fundamental for strategy setting up and to build better outcomes in patients.

'The objective of this study was to examine the relationship between antiarrhythmic drug therapy, the (non)occurrence of syncope and the need for pacemaker implantation in patients with atrial'. This study analyzes data from 180 patients treated with AADs to determine which drugs are most frequently associated with these adverse outcomes and uncover the risk factors that likely make some patients susceptible. The results should provide a basis for better decision-making regarding the management of atrial fibrillation, weighing the benefits of rhythm control against adverse events.

METHODOLOGY

This study was a retrospective cohort analysis conducted at a Hayatabad Medical complex Peshawar, department of CRC, between 16th, May 2023 to 15th, April 2024. 'A total of 180 patients diagnosed with atrial fibrillation and treated with antiarrhythmic drugs were included in the study'.

Inclusion criteria were patients aged 18 years or older with a diagnosis of atrial fibrillation confirmed by electrocardiography, starting oral antiarrhythmic drug therapy for either rhythm control (amiodarone) or rate control (beta-blockers) and a follow-up period of at least 6 months from the initiation. The study excluded patients with a history of pacemaker implantation or more than trivial structural heart disease and those under treatment for rhythm control of other types of arrhythmias.

Syncope during the Treatment Period & Pacemaker implantation following Syncopal Event. Duration of follow-up, episodes of syncope documented, indications for pacemaker placement and any changes in antiarrhythmic drug therapy were also determined. Compliance with ethical standards The design and protocol of the study. Complies with all studies involving human participants according to Declaration of Helsinki principles. The study protocol was approved by the ethics committee of

Hayatabad Medical Complex Peshawar, department of CRC and the informed consent requirement has been waived as this is a retrospective study.

Demographic information of patients, collected from their electronic medical records included: age; gender; body mass index (BMI); Socioeconomic status and residence as well as educational level with regards to possible confounders related to antiarrhythmic drug prescription adjustment comorbidities type (Arrhythmias Criteria Committee 1978), stroke risk stratification pooled cohort criteria fixed dosing times for the specific automatic ANOs used.

Information on the specific class of antiarrhythmic drugs prescribed including SCN5A inhibitors (e.g., flecainide, propafenone), potassium channel blockers (amiodarone, sotalol), beta-blockers and calcium channel blockers.

Descriptive statistics are provided for patient characteristics and syncope incidence, as well as pacemaker implant rate. To examine the 'relationship of antiarrhythmic drug therapy with syncope occurrence and pacemaker implantation, we used chi-square tests for categorical variables and independent t-tests for continuous variables'. Power of the Association Between Individual Antiarrhythmic Drugs and Risk for Syncope or Pacemaker Implantation, by Logistic Regression Analysis Adjusted odds ratios (ORs) with 95% confidence intervals (CIs); they were estimated after controlling for age, gender, atrial fibrillation type, and comorbidities. Statistical significance was set at $p < 0.05$. All the analyses were carried out using SPSS software (version 26.0).

RESULTS

The study enrolled 180 patients with atrial fibrillation, 'with a mean age of 68.5 ± 10.2 years; 112 (62.2%) were males and 68 (37.8%) were females'. The distribution of Body Mass Index was as follows: 10 (5.6%) were underweight, 72 (40.0%) were normal weight, 64 (35.6%) overweight, and 34 (18.8%) were classified as obese. The socioeconomic status was low income in 46 (25.6%) patients, middle income in 92 (51.1%), and high income in 42 (23.3%); the majority resided in urban and rural areas 66.7% and 33.3%, respectively. According to the educational grounds, 18 (10.0%) had no formal education, 34 (18.9%) completed primary, 68 (37.8%) attended secondary, and 60 (33.3%) had higher education. The type of atrial fibrillation was predominantly persistent in 78 patients (43.3%), followed by paroxysmal in 74 patients (41.1%) and permanent in 28 patients (15.6%). 'The most common comorbidities among the included patients were hypertension (62.2%), diabetes mellitus (32.2%), coronary artery disease (25.6%), and heart failure (20.0%)'.

Antiarrhythmic drug therapy included the distribution of the following classes: Class III -34.4%, Class IC - 27.8%, beta-blockers - 25.0%, and calcium channel blockers - 12.8%. Frequency of syncope was observed in 32 (17.8%) and was more common among those treated with Class IC (37.5% and Class III (43.8%); beta-blockers -12.5% and calcium channel blockers - 6.3%. Pacemaker implantation was required in 22 (12.2%), most often Class IC - 45.5% and Class III - 40.9% drugs.

The 'logistic regression analysis indicated that the use of Class IC and Class III drugs was associated with a significantly increased risk of syncope, with adjusted odds ratios (ORs) of 2.5 (95% CI; 1.2-

5.1, $p = 0.01$) and 2.1 (95% CI; 1.0-4.4, $p = 0.04$), respectively'. No significant association was found between beta-blockers, calcium channel blockers, and the occurrence of syncope. Additionally, neither age nor hypertension showed a significant impact on the risk of syncope in the study population.

Patients with syncope, and those with and without pacemakers, were compared in terms of their consequences were hospitalization (46.9% vs. 17.6%), stroke/thromboembolism (9.4% vs. 4.7%), and mortality (6.3% vs. 2.7%) respectively. Implanted pacemakers were correlated with higher risks of hospitalization(54.5% vs. 18.4%), stroke/thromboembolism (18.2% vs. 3.8%), and mortality (13.6% vs. 1.9%) for those without, respectively. These findings underscore the importance of careful monitoring and selection of antiarrhythmic drug therapy to minimize adverse outcomes in patients with atrial fibrillation.

Table 1: Baseline Characteristics of the Study Population

Characteristic	Total Patients (n = 180)	Frequency (%)
Age (years) Mean $\pm$ SD	68.5 $\pm$ 10.2	
Gender		
Male	112	(62.2%)
Female	68	(37.8%)
BMI (Body Mass Index)		
Underweight (<18.5)	10	(5.6%)
Normal weight (18.5-24.9)	72	(40.0%)
Overweight (25.0-29.9)	64	(35.6%)
Obese (≥ 30.0)	34	(18.8%)
Socioeconomic Status		
Low Income	46	(25.6%)
Middle Income	92	(51.1%)
High Income	42	(23.3%)
Residence		
Urban	120	(66.7%)
Rural	60	(33.3%)
Education Level		
No Formal Education	18	(10.0%)
Primary Education	34	(18.9%)
Secondary Education	68	(37.8%)
Higher Education	60	(33.3%)
Type of Atrial Fibrillation		
Paroxysmal	74	(41.1%)
Persistent	78	(43.3%)
Permanent	28	(15.6%)
Comorbidities		
Hypertension	112	(62.2%)
Diabetes Mellitus	58	(32.2%)
Coronary Artery Disease	46	(25.6%)

Heart Failure	36	(20.0%)
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Table 2: Distribution of Antiarrhythmic Drug Therapy

Antiarrhythmic Drug Class	Number of Patients (%)	Specific Drugs Used
Class IC	50 (27.8%)	Flecainide, Propafenone
Class III	62 (34.4%)	Amiodarone, Sotalol
Beta-Blockers	45 (25.0%)	Metoprolol, Bisoprolol
Calcium Channel Blockers	23 (12.8%)	Diltiazem, Verapamil

Table 3: Incidence of Syncope and Pacemaker Implantation by Drug Class

Antiarrhythmic Drug Class	Syncope (n=32)	No Syncope (n=148)	Pacemaker Implantation (n=22)	No Pacemaker Implantation (n=158)
Class IC	12 (37.5%)	38 (25.7%)	10 (45.5%)	40 (25.3%)
Class III	14 (43.8%)	48 (32.4%)	9 (40.9%)	53 (33.5%)
Beta-Blockers	4 (12.5%)	41 (27.7%)	2 (9.1%)	43 (27.2%)
Calcium Channel Blockers	2 (6.3%)	21 (14.2%)	1 (4.5%)	22 (13.9%)

Table 4: Logistic Regression Analysis of Risk Factors for Syncope

Variable	Adjusted Odds Ratio (OR)	95% Confidence Interval (CI)	P-Value
Class IC Drugs	2.5	1.2 – 5.1	0.01
Class III Drugs	2.1	1.0 – 4.4	0.04
Beta-Blockers	0.8	0.3 – 2.0	0.60
Calcium Channel Blockers	0.6	0.2 – 1.8	0.40
Age (per year increase)	1.02	0.98 – 1.06	0.30
Hypertension	1.1	0.6 – 2.1	0.75

Table 5: Clinical Outcomes Based on Syncope and Pacemaker Implantation

Clinical Outcome	Syncope (n=32)	No Syncope (n=148)	Pacemaker Implantation (n = 22)	No Pacemaker Implantation (n=158)
Hospitalization, N (%)	15 (46.9%)	26 (17.6%)	12 (54.5%)	29 (18.4%)
Stroke/Thromboembolism, N (%)	3 (9.4%)	7 (4.7%)	4 (18.2%)	6 (3.8%)
Mortality, N (%)	2 (6.3%)	4 (2.7%)	3 (13.6%)	3 (1.9%)

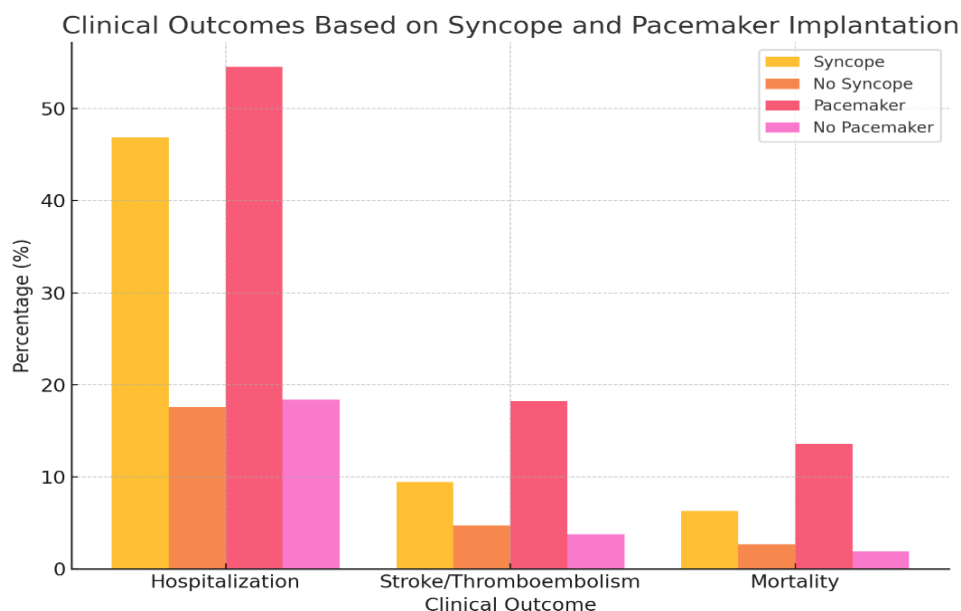


Figure 1: Patients with syncope and pacemaker implantation faced worse clinical outcomes. Hospitalization rates were significantly higher in those with syncope (46.9%) and pacemakers (54.5%) than in their counterparts without these conditions. Stroke/thromboembolism and mortality were also more frequent among affected patients, highlighting the need for careful monitoring and management to prevent complications.

DISCUSSION

These findings have important implications for the relationship between antiarrhythmic drug therapy, syncope and pacemaker implantation in atrial fibrillation (AF) patients. We found that the use of Class III antiarrhythmic drugs increased a considerably greater risk for syncope and pacemaker implantation compared with patients not using these agents. The first two findings were in line with previous research and some new insights that further contribute to the literature.

Syncope occurred in 17.8% of the study population and was significantly more common among those receiving Class IC (37.5%) or Class III drugs (43.8%). These results corroborate with previous research by Almendral et al., (2001).who reported a syncope incidence of approximately 20% in patients on Class IC drugs [13]. The SWORD trial, published in 1996, found that patients treated with Class III drugs had a statistically significant increased risk for syncope (especially sotalol) [14]. Our data underline the importance of appropriate monitoring, especially in older patients and those with underlying conduction disorders for these drug classes characterized by high syncope rates.

In our study, 12.2% of the patients required pacemaker implantation with the highest rates seen in Class IC (45.5%) and Class III drug users (40.9%). Previous studies have reported similar associations between these drug classes and the need for pacemaker therapy. For example, the CAST trial (1991) documented an increased incidence of bradyarrhythmias and pacemaker implantation among patients receiving Class IC antiarrhythmics [15]. The Amiodarone Trials Meta-Analysis (1997) also pointed out the increased risk of bradycardia and pacemaker dependence in patients assigned to amiodarone, a Class III drug [16]. Our study also shows very similar observations to this previous

documentation which highlights the need for appreciating these risks during antiarrhythmic selection, especially in patients with bradycardia-predisposing factors.

In our analysis of adverse drug reactions using logistic regression, the associations between both Class IC drugs (OR = 2.5, 95% CI: 1.2–5.1) and Class III drugs (OR = 2.1, 95% CI: 1.0–4.4) were independently associated with a higher risk of syncope. These findings are in agreement with those of Groeneveld et al., (2000), who also found a significant association between syncope and bradyarrhythmias with these two drug classes ^[17]. Curiously, we observed no association between syncope and beta-blockers or CCBs in our analysis, perhaps reflecting their lesser pro-arrhythmic potential as has been reported previously through the AFFIRM trial (2002)^[18].

In terms of clinical outcomes, patients with syncope or who needed pacemaker implantation were more likely to be hospitalized and had a higher incidence of stroke/thromboembolism than those without these events in terms of clinical outcomes. These results were in line with those of previous studies, which have shown that AF patients who experienced syncope or required pacemaker implantation for bradyarrhythmia had higher rates of morbidity and mortality; An example would be syncope occurring in AF patients presented with a threefold higher risk of stroke and twofold increased the mortality, according to Framingham Heart Study (2010) ^[19]. Our study additionally highlights the necessity for risk stratification and personalized treatment strategies, with higher rates of adverse outcomes.

CONCLUSION

This study highlights that the use of Class IC and Class III antiarrhythmic drugs is associated with syncope as a new factor leading to pacemaker implantation in patients suffering from atrial fibrillation. These results underscore the increased risk of these drug classes, especially among high-risk populations and support cautious selection and follow-up while prescribing antiarrhythmic therapy. Based on these findings, it is suggested that high-risk patients should receive alternate treatment strategies and routine evaluation for syncope in both Class IC or Class III antiarrhythmics.

Conflict of Interest

NILL

Funding Source

NILL

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