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Ivabradine can cause atrial fibrillation regardless of baseline left atrial size: A prospective study

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Abstract
Background: Ivabradine, a selective if current inhibitor, is widely used to reduce heart rate in patients with ischemic heart disease (IHD) and heart failure (HF). Atrial fibrillation (AF) is a known adverse effect of Ivabradine, but it remains unclear whether baseline left atrial (LA) size influences AF development. This study investigates the relationship between left atrial volume index (LAVI) and incidence of AF in patients treated with Ivabradine.
Methods: This prospective, observational study included 180 patients with HF or IHD receiving guideline-directed medical therapy, with 90 patients treated with Ivabradine and 90 as controls. Clinical and echocardiographic evaluations, including LAVI, LA size, and ejection fraction (EF), were performed. A 12-lead ECG was conducted weekly for the first four weeks and at 8 and 12 weeks to monitor AF development.
Results: No significant difference in AF incidence was found between Ivabradine and control groups (23.3% vs. 20.0%, p = 0.587). However, LAVI was considerably higher in Ivabradine group compared to controls (34.18±4.02 vs. 32.80 ±4.46 mL/m², p = 0.031). Within the Ivabradine group, no notable variations were observed between patients who developed AF and those who did not in terms of LAVI, EF, or CHA2DS2-VASc scores.
Conclusion: Ivabradine therapy showed no relationship with an elevated incidence of AF, irrespective of baseline LA size. Higher LAVI was linked to a greater AF incidence across the entire cohort, suggesting LA enlargement as a potential risk factor.

Keywords: Ivabradine, atrial fibrillation, left atrial volume index, heart failure, ischemic heart disease

Introduction
Ivabradine is a pharmacological agent designed to lower heart rate (HR) by specifically blocking the pacemaker current, a fundamental driver of spontaneous depolarization within the sinoatrial node, thereby regulating cardiac rhythm [1]. The European Medicines Agency (EMA) initially approved ivabradine in 2005 for patients with stable angina pectoris and normal sinus rhythm, particularly those who cannot tolerate or are unsuitable candidates for β-blocker therapy [2].
The results from BEAUTIFUL trial, released in 2010, broadened the therapeutic application of ivabradine, highlighting its benefit for individuals experiencing angina symptoms unresponsive to β-blockers and maintaining an HR above 70 beats per minute (bpm) [3]. Subsequently, in 2012, ivabradine gained further approval for managing chronic heart failure in patients with reduced systolic function, specifically those categorized under New York Heart Association (NYHA) classes II–IV, who remain in sinus rhythm with a HR exceeding 70 bpm. This recommendation was based on evidence from SHIFT trial, which emphasized ivabradine's efficacy when used in conjunction with standard heart failure treatments, such as β-blockers, or as an alternative option when β-blockers are either contraindicated or poorly tolerated [3, 4].
Ivabradine also exerts an influence on pulmonary venous myocardium, a tissue instrumental in triggering and sustaining AF due to its reliance on If current. This mechanism suggests that ivabradine may have an impact on AF risk. However, since AF is frequently observed in patients with preexisting HF or CAD, distinguishing AF incidence directly attributable to ivabradine from that linked to underlying cardiovascular conditions remains challenging [5, 6].

The objective of this study is to explore the association between LAVI and AF development in patients receiving ivabradine therapy over a 12-week period.

Patients and Methods

This prospective, observational study involved 180 patients referred to Misr University for Science and Technology Hospital and Ain Shams University Hospital between September 2020 and February 2021.The patients were undergoing treatment for HF or IHD with guideline-directed medical therapy. Informed consent was obtained in writing from all participants before their enrollment in the study. The Research Ethics Committee (REC) of Ain Shams University Faculty of Medicine (FWA 000017585) granted ethical approval for the study, which was conducted in strict compliance with institutional regulations and national ethical principles outlined in Declaration of Helsinki.

Study Population

A total of 180 patients were included in the study, chosen to provide an objective assessment based on previous trials such as Fasulto *et al*. [7] with 155 patients, Nerla *et al*. [8] with 61 patients, and Villano *et al*. [9] with 46 patients [3]. The participants suffered from either HF or IHD. Group I (Ivabradine group) consisted of 90 patients receiving guideline-directed medical therapy, including Ivabradine, after meeting the inclusion criteria. Group II (conventional group), which served as control group, also consisted of 90 patients receiving guideline-directed medical therapy but without Ivabradine. Both groups were comparable concerning sex, age, risk factors, and clinical status.

Inclusion and Exclusion Criteria

Inclusion Criteria

Patients were included if they required Ivabradine as part of their treatment, whether for IHD or symptomatic HF. Patients in control group were matched to those in Ivabradine group based on age, sex, risk factors, and clinical condition.

Exclusion Criteria

Exclusion criteria included patients with a history of AF, conduction abnormalities (e.g., sick sinus syndrome, third-degree AV block, sinoatrial block), or acute decompensated HF. Patients with severe liver impairment (Ivabradine is contraindicated in Child-Pugh Class C), chronic renal disease requiring regular hemodialysis, sepsis, pregnancy, thyroid disorders, COVID-19 positivity, or those taking Cytochrome P450 3A4 inhibitors (e.g., erythromycin, ketoconazole) were also excluded. Additionally, patients with a resting HR of less than 70 beats per minute before initiating Ivabradine therapy and those with severe valvular heart disease were excluded.

Clinical Assessment and Investigations

A detailed medical history and thorough clinical examination were performed for all patients, gathering data on gender, age, weight, height, and smoking status. Blood pressure was measured using two office readings taken while the patient was seated and relaxed, with a three-minute interval between readings. A comprehensive cardiac assessment was performed. A comprehensive account of familial history of IHD was acquired, characterized by the CAD incidence in a first-degree male relative before the age of 55 or in a first-degree female relative before the age of 65. All patients underwent calculation of the CHA2DS2-VASc score.

Electrocardiogram (ECG) Monitoring

Surface ECG were performed on all patients. A 12-lead ECG was conducted weekly for the first four weeks, followed by assessments at 8 weeks and 12 weeks.

Laboratory Investigations

Routine laboratory tests were performed with special focus on serum creatinine, complete lipid profile, HbA1c, hemoglobin levels, thyroid function tests, and liver function tests.

Echocardiographic Assessment

To evaluate LVEF through Simpson's method, all patients underwent ECG-gated echocardiography. This technique relies on measuring end-systolic volume (ESV) and end-diastolic volume (EDV) from both apical 4-chamber and 2-chamber views. Additionally, LA size and LAVI were assessed, with these parameters similarly derived from apical four and two-chamber perspectives [10], excluding left atrial appendage (LAA) and pulmonary vein ostia during ventricular end-systole.

Treatment Protocol and Follow-Up

The cases in Ivabradine group were treated with a minimum dose of 5 mg twice daily, with a maximum dose of 7.5 mg twice daily, adjusted to achieve the target HR. All patients were subjected to the same clinical evaluations and monitoring. Both groups were followed up for at least 12 weeks. ECGs were conducted weekly for the first four weeks, then at two months and three months, to assess AF incidence. Patients were also educated to report any sensations of palpitations during the follow-up period.

Outcomes

The primary outcome was the incidence of AF and its correlation with Ivabradine therapy over a 12-week period. The secondary outcomes included the evaluation of echocardiographic parameters, such as LA size and volume, as well as LVEF, in both the Ivabradine and control groups.

Statistical analysis

The data were statistically summarized using mean ±SD, median with range, or frequencies and percentages, as appropriate. The Mann–Whitney U-test was used to compare numerical variables between the independent study groups. The Chi-square (χ^2) test was used for categorical data, including baseline characteristics, risk factors, and procedural parameters. Fisher's exact test was used when the expected frequency was below five. Statistical significance was determined with a p-value less than 0.05. All statistical analyses were conducted using SPSS version 26 (IBM, Armonk, New York, United States).

Results

No significant variations were observed in AF incidence between the Ivabradine group and the controls (P = 0.587), during the first month (P = 0.787), second month (P = 0.755), and third month (P = 0.387). Table 1.

Table 1: Comparison between the studied groups regarding AF and duration till AF

	Ivabradine group		Conventional group		Test value*	P-value
	No. 90	%	No. 90	%		
AF	21	23.3%	18	20.0%	0.295	0.587
Duration till AF						
1st month	8	8.9%	7	7.8%	0.073	0.787
2nd month	5	5.6%	6	6.7%	0.097	0.755
3rd month	8	8.9%	5	5.6%	0.746	0.387

*: Chi-square test, AF: atrial fibrillation.

LAVI was notably higher in the Ivabradine group compared to the controls (34.18 ±4.02 vs. 32.80 ±4.46, respectively, P = 0.031). No notable variations were observed between the Ivabradine group and the controls regarding LA size (P = 0.298), EF (P = 0.490), and CHA2DS2-VASc score (P = 0.510). Table 2

Table 2: Comparison between the studied groups regarding echocardiographic findings and CHA2DS2-VASc score

		Ivabradine group	Conventional group	Test value	P-value
		No. = 90	No. = 90		
LAVI (mL/m^2)	Mean ±SD	34.18 ±4.02	32.80 ±4.46	-2.179•	0.031
	Range	25 – 41	22 – 40		
LA size Normal ≤28		9 (10.0%)	15 (16.7%)	3.679*	0.298
Mild enlargement: (29-33)		31 (34.4%)	37 (41.1%)		
Moderate enlargement: (34-39)		43 (47.8%)	33 (36.7%)		
Severe enlargement: ≥40		7 (7.8%)	5 (5.6%)		
EF (%)	Mean ±SD	47.03 ±12.37	45.62 ±14.91	-0.691•	0.490
	Range	20 – 75	15 – 70		
CHA2DS2-VASc score	Median (IQR)	2 (1 - 3)	3 (2 - 4)	-0.658ǂ	0.510
	Range	0 – 7	0 – 9		

*: Chi-square test; •: Independent t-test; ‡: Mann Whitney test, CHA2DS2-VASc: Congestive Heart Failure, Hypertension, Age ≥75 (doubled), Diabetes Mellitus, Prior Stroke or TIA or Thromboembolism (doubled), Vascular Disease, Age 65–74, Sex Category (Female), EF: ejection fraction, LAVI: left atrial volume index, SD: Standard Deviation, IQR: Interquartile Range.

The cases who developed AF were compared to those who did not in the Ivabradine group regarding echocardiographic findings and CHA2DS2-VASc score. No notable changes were observed between patients who developed AF and those who did not in group I regarding LAVI (P = 0.634), LA size (P = 0.794), EF (P = 0.082), and CHA2DS2-VASc score (P = 0.663). Table 3.

Table 3: Comparison between cases who developed AF and those who did not in group I regarding echocardiographic findings and CHA2DS2-VASc

		Non-AF	AF	Test value	P-value
		No. = 69	No. = 21		
LAVI (mL/m^2)	Mean ±SD	34.29 ±4.04	33.81 ±4.02	0.478•	0.634
	Range	26 – 41	25 – 40		
LA size: Normal		7 (10.1%)	2 (9.5%)	1.028*	0.794
LA size: (29-33) mild enlargement		22 (31.9%)	9 (42.9%)		
LA size: (34-39) moderate enlargement		34 (49.3%)	9 (42.9%)		
LA size: ≥40 Severe enlargement		6 (8.7%)	1 (4.8%)		
EF (%)	Mean ±SD	45.78 ±11.82	51.14 ±13.51	-1.759•	0.082
	Range	20 – 70	25 – 75		
CHA2DS2-VASc	Median (IQR)	2 (1 - 3)	2 (1 - 3)	-0.435ǂ	0.663
	Range	0 – 7	0 – 6		

*: Chi-square test; •: Independent t-test; ‡: Mann Whitney test, EF: Ejection Fraction, AF: Atrial Fibrillation, LAVI: Left Atrial Volume Index, SD: Standard Deviation, IQR: Interquartile Range.

Table 4: Comparison between cases who developed AF and those who did not in group II regarding echocardiographic findings and CHA2DS2-VASc score

		Non-AF	AF	Test value	P-value
		No. = 69	No. = 21		
LAVI (mL/m^2)	Mean ±SD	33.11 ±4.11	31.56 ±5.62	1.330•	0.187
	Range	24 – 40	22 – 39		
EF (%)	Mean ±SD	45.78 ±15.63	45.00 ±11.95	0.197•	0.844
	Range	15 – 70	29 – 63		
CHA2DS2-VASc score	Median (IQR)	3 (2 – 4)	2 (1 – 3)	-1.973ǂ	0.048
	Range	1 – 9	0 – 4		

*: Chi-square test; •: Independent t-test; ‡: Mann Whitney test, EF: Ejection Fraction, AF: Atrial Fibrillation, LAVI: Left Atrial Volume Index, SD: Standard Deviation, IQR: Interquartile Range.

The CHA2DS2-VASc score was significantly lower in patients who developed AF compared to those who did not in group II (2 [1–3] vs. 3 [2–4], P = 0.048). No notable variations were observed regarding LAVI (P = 0.187) and EF (P = 0.844). Table 4.

LAVI was significantly higher in patients who developed AF compared to those who did not (34.18 ±4.02 vs. 32.80 ±4.46, P = 0.031). No significant variations were observed regarding Ivabradine use (P = 0.587), EF (P = 0.490), and CHA2DS2-VASc score (P = 0.101). Table 5.

Table 5: Comparison between all of the patients who developed AF and all of the patients who did not from the entire cohort of patients regarding Ivabradine use, echocardiographic findings, and CHA2DS2-VASc score

		AF		Test value	P-value
		No	Yes		
		No. = 141	No. = 39		
Ivabradine	No	72 (51.1%)	18 (46.2%)	0.295*	0.587
	Yes	69 (48.9%)	21 (53.8%)		
LAVI	Mean ±SD	32.80 ±4.46	34.18 ±4.02	-2.179•	0.031
	Range	22 – 40	25 – 41		
EF	Mean ±SD	45.62 ±14.91	47.03 ±12.37	-0.691•	0.490
	Range	15 – 70	20 – 75		
CHADS2 VASc	Median (IQR)	3 (2 - 4)	2 (1 - 3)	-1.639‡	0.101
	Range	0 – 9	0 – 6		

*: Chi-square test; •: Independent t-test; ‡: Mann Whitney test, EF: Ejection Fraction, AF: Atrial Fibrillation, LAVI: Left Atrial Volume Index, SD: Standard Deviation, IQR: Interquartile Range.

Discussion

This observational case-control study found no statistically significant difference in age and gender between the two groups. The cases in the Ivabradine group had a mean age of 57.3 years, while it was 56.5 years for the controls. This finding aligns with Hassanin *et al.* [11], who reported a mean age range of 52.2 to 62.8 years in hospitalized HF patients across Egypt. However, it contrasts with Hosseini *et al.* [12], who reported global mean ages of 60.1 years for men and 63.2 years for women with IHD. The lower mean age in our study may be attributed to poorly controlled risk factors due to inadequate patient education and compliance [13].

Although gender distribution showed no significant difference, 81.1% of the Ivabradine group and 83.3% of the controls were male, consistent with global statistics indicating a higher incidence of heart disease in males [14]. While there were no notable variations in smoking, HTN, DM, dyslipidemia, family history of cardiac diseases, and BMI between the groups, a substantial proportion of patients in both groups were either active or former smokers (47.4% in the Ivabradine group and 52.2% in the controls). This is discordant with Oshunbade *et al.*'s findings [15], which showed that only 30% of patients with IHD in a black population in the US were either active or former smokers. This discrepancy may reflect Egypt's higher smoking rates [16].

The prevalence rates of hypertension (52.2% in the Ivabradine group and 45.6% in the controls) and diabetes mellitus (47.8% in the Ivabradine group and 37.8% in the controls) varied from findings reported in earlier studies. For example, the Framingham Heart Study [17] highlighted that 91% of individuals with heart failure had a history of hypertension. The lower prevalence of hypertension observed in this study might be attributed to the inclusion of patients with both ischemic heart disease and heart failure, as well as those with ischemic heart disease alone, potentially reflecting underdiagnosis due to inadequate follow-up before confirmation of the condition. On the other hand, the diabetes prevalence in our cohort aligns with previous research, which estimates that over 40% of hospitalized heart failure patients are affected by diabetes [18]. In addition, the significant rates of obesity and dyslipidemia in this study align with recognized risk factors for both CAD and HF [19].

Our results demonstrated no statistically significant variation in the occurrence of AF between the Ivabradine group and the controls. Similarly, there was no statistically significant difference between the two groups for the time to atrial fibrillation start at the 1st, 2nd, and 3rd months. Contrariwise, a meta-analysis conducted by Tanboğa *et al.* [5] reported an incidence of atrial fibrillation of 5.34% in individuals treated with Ivabradine and 4.56% in those given a placebo. The Ivabradine cohort demonstrated a significantly heightened occurrence of AF, with a 24% relative risk augmentation relative to placebo, both before (relative risk [RR]: 1.24, 95% confidence interval [CI]: 1.08-1.42, p = 0.003, I^2 = 53%) and after the exclusion of the comprehensive oral safety set (RR: 1.24, 95% CI: 1.06-1.44, p = 0.008).

Moreover, Martin *et al.* [3] established that Ivabradine administration was associated with an RR of AF of 1.15 (95% CI: 1.07-1.24, p = 0.0027) in a meta-analysis including 21,571 participants. The number needed to harm (NNH) for Ivabradine is predicted to be 208 (95% CI: 122-667) per year of treatment.

Fox *et al.* [20] established a markedly elevated AF risk associated with Ivabradine (RR: 1.25, 95% CI: 1.10-1.42) in individuals with HRs over 70 bpm, which is inconsistent with our results. The study assessed the effects of emergent AF or bradycardia associated with Ivabradine on cardiovascular outcomes, documenting 754 instances of emergent AF throughout therapy (2.2% annually for Ivabradine vs to 1.5% annually for placebo). Additionally, Cammarano *et al.* [21] discovered that Ivabradine was linked to new-onset atrial fibrillation (odds ratio [OR]: 1.35, 95% CI: 1.19-1.53; $p < 0.001$). The variance in AF incidence between our research and existing literature may be ascribed to the reduced sample size and abbreviated follow-up period in our patient group. The current investigation demonstrated a substantially reduced LAVI in the controls vs to the Ivabradine group (p = 0.031). Nonetheless, no statistically notable variation was seen between the two groups for EF and CHA2DS2-VASc ratings. In the Ivabradine cohort, a comparison of individuals who developed AF and those who did not revealed no statistically significant variations in

LAVI, EF, or CHA2DS2-VASc scores. Likewise, in the controls, no statistically significant difference was seen between patients who developed AF and those who did not concerning LAVI, EF, or CHA2DS2-VASc scores.

These results contradict the research of Aksoy *et al.* [22], which indicated that higher CHA2DS2-VASc scores predicted the occurrence of AF in patients with STEMI. The divergence between our findings and theirs may stem from their research's sole emphasis on STEMI patients, whereas our analysis included patients with both IHD and HF. The limited sample size and short follow-up period in our investigation may have influenced the divergent outcomes.

The main objective of our study was to evaluate whether LAVI had an impact on the incidence of AF with Ivabradine use. While the Ivabradine group had a significantly larger LAVI compared to the controls, the overall incidence of AF between the two groups was not significantly different, despite a higher occurrence of AF in the Ivabradine group. Interestingly, within the Ivabradine group, those who developed AF had a smaller LAVI than those who did not, although the difference was not statistically significant. It is possible that with a larger sample size, this difference might have reached statistical significance.

To explore this further, we conducted an analysis on the entire patient population who developed AF from both groups (39 patients) and compared them to those who did not develop AF (141 patients). The aim was to determine if any correlations with AF development could be made, regardless of Ivabradine use. By increasing the AF patient count through this combined analysis, we found that LAVI was significantly larger among those who developed AF than among those who did not. This finding is consistent with Bratt *et al.* [23], who concluded that LA volume is an independent predictor of AF, as measured by chest CT. Their study specifically evaluated whether LA volume could be used as a predictor of AF occurrence.

The pathogenesis linking LA enlargement with AF has been attributed to the effects of chronic atrial stretch. This mechanical stress triggers the activation of multiple intracellular signaling cascades, leading to cellular hypertrophy, fibroblast proliferation, and the development of fibrotic tissue within the atrial myocardium. This electroanatomical substrate is characterized by increased non-uniform anisotropy and macroscopic slowing of conduction, which promotes the formation of reentrant circuits in the atria, facilitating AF development [24].

Based on our results and literature review, we believe it is crucial to encourage further research on risk factors and echocardiographic characteristics that may help predict which patients are at a higher risk of developing AF. Such research could guide the initiation of Ivabradine treatment more effectively.

One significant limitation of our study was the lack of existing literature on the relationship between Ivabradine use and AF in relation to LA size. While most studies agree that Ivabradine increases the incidence of AF, none have identified a specific parameter that could help physicians predict which patients are more likely to develop AF after starting Ivabradine. We hypothesized that baseline LA size might be a predictor of this adverse event. Although our results demonstrated a significant correlation between the LAVI and the incidence of AF, irrespective of Ivabradine use, we did not find a statistically significant difference between patients on Ivabradine and those who were not. However, this finding alone is not sufficient to disprove our hypothesis. Our study was limited by its short follow-up duration and the relatively small sample size. Therefore, larger studies with longer follow-up periods are needed to better assess the potential predictive role of LA size in the AF development in cases treated with Ivabradine.

Conclusion

In this study, ivabradine therapy did not demonstrate any association with an increased incidence of AF among patients with HF and/or IHD. Furthermore, no significant variation was observed in the time to AF onset at the conclusion of the first, second, or third month. Across the entire study cohort, elevated LAVI was linked to a higher AF incidence, independent of ivabradine administration.

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Declaration of interest statement: None to be declared.

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