The Egyptian Journal of Hospital Medicine (April 2024) Vol. 95, Page 2027- 2032

Postoperative Atrial Fibrillation Prevention in Patients Undergoing Coronary Artery Bypass Grafting by Using Perioperative HCN Channel Blockers and Selective Beta Blockers

Yousry Elsaied [1], Amany Ahmed Ibrahim [2], Mahmoud Mohamed Mahmoud Elbadawy [2]* and Eman Shafik Abd Elhameed Badr [1]

Departments of [1] Critical Care,

[2] Cardiothoracic Surgery Department, Faculty of Medicine, Benha University, Benha, Egypt.

*** Corresponding author:** Mahmoud Mohamed Mahmoud Elbadawy,

Email: docmohamed18@gmail.com, Phone: +201243117129

ABSTRACT

Background: Postoperative atrial fibrillation (AF) is commonly occurring following coronary artery bypass graft (CABG) surgery. Controversies are present regarding the superior medications that prevent AF.

Objective: To evaluate the efficacy of the perioperative use of bisoprolol and ivabradine versus bisoprolol alone as a prophylactic treatment in the prevention of postoperative AF in patients underwent elective CABG surgery.

Patients and Methods: This is a prospective interventional study included 50 adult patients who underwent elective CABG surgery. Patients were assessed for eligibility from Department of Cardiothoracic Surgery in Benha University Hospitals. Patients were randomly divided into two equal groups; Group I received both ivabradine (Procoralan®) and Bisoprolol (Concor®) and Group II received bisoprolol (Concor®) only. Both groups received their treatments 48 hours before surgery and continued one week postoperatively. Ethical approval and informed written consents were obtained.

Results: Postoperative prevention of postoperative atrial fibrillation in the combination therapy (Ivabradine plus bisoprolol) (group I) was more effective than bisoprolol given alone (group II). There was a statistically significant increase in the overall postoperative atrial fibrillation among patients in group II compared with group I (36% vs. 4%, respectively, P value=0.01).

Conclusion: Ivabradine is a safe and effective drug to be administered along with a beta blocker (Bisoprolol) perioperatively in patients undergoing CABG surgery in terms of reducing heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), intensive care unit (ICU) stay, and better postoperative echocardiographic data and significantly reducing the incidence of the overall postoperative atrial fibrillation.

Keywords: CABG; Atrial fibrillation; Ivabradine; Bisoprolol.

INTRODUCTION

Postoperative atrial fibrillation (POAF) emerges as the predominant arrhythmia subsequent to coronary artery bypass grafting (CABG). While traditionally perceived as a transient and innocuous sequel of CABG, contemporary research delineates a correlation between POAF and an augmented incidence of early mortality and morbidity. This includes complications such as cerebrovascular accidents, renal insufficiency, respiratory dysfunction, and extended stays in the intensive care unit [1,2].

Postoperative atrial fibrillation is diagnosed on the basis of irregular narrow complex tachycardia on an electrocardiogram considering absent P wave. If the postoperative atrial fibrillation untreated, the incidence of postoperative stroke would be increased [3].

Investigations into beta-adrenergic antagonists for the management of postoperative atrial fibrillation have yielded positive outcomes [4-7].

The perioperative administration of these pharmacologic agents has proven efficacious in mitigating the incidence of postoperative atrial fibrillation, extending beyond those patients undergoing solely CABG to include diverse cardiac surgical procedures. Nevertheless, the deployment of beta blockers, while beneficial in moderating heart rate, concurrently precipitates a reduction in blood pressure. This pharmacodynamic effect may pose a clinical challenge in numerous cases [8,9].

The hyperpolarization-activated, cyclic nucleotide-gated (HCN) channel blocker, ivabradine (Procoralan®), functions as a targeted inhibitor of the sinoatrial If current [10].

This pharmacological action facilitates a decrement in HR without exerting influence on blood pressure, intracardiac conduction pathways, ventricular repolarization, or myocardial contractility. Such specificity underscores its therapeutic potential in managing cardiac rhythm without the typical systemic side effects associated with other cardiotonic agents [11].

However, there is conflicting evidence regarding the recommended dose or combination treatment of ivabradine that is optimal for prevention of the postoperative atrial fibrillation [11-13].

The aim of this study was to evaluate the efficacy of the perioperative use of bisoprolol and ivabradine versus bisoprolol alone as a prophylactic treatment in the prevention of postoperative AF in patients underwent elective CABG surgery.

PATIENTS AND METHODS

This is a prospective interventional study that included 50 adult patients who underwent elective coronary artery bypass graft surgery. Patients were recruited and assessed for eligibility from Department of Cardiothoracic Surgery in Benha University Hospitals.

Received:13/12/2023
Accepted:13/02/2024

Inclusion criteria included: Adult patients aged >18 years old who were symptomatic for effort angina (stable angina). Patients eligible for elective surgical revascularization presented with angiographically confirmed significant coronary artery disease, characterized by a minimum of 50% stenosis in the left main coronary artery or over 70% stenosis in more than three substantial coronary arteries, or at least two substantial arteries inclusive of the proximal left anterior descending artery, with or without concurrent valve surgery. These individuals were not on any preoperative antiarrhythmic medications. Their cardiac parameters included a heart rate between >60 and <90 beats per minute, maintained in normal sinus rhythm, devoid of any electrocardiographic abnormalities such as ST-segment elevation or bundle branch block.

Exclusion criteria included patients with emergency CABG, atrial fibrillation or past history of atrial fibrillation, concomitant valve surgery or valvular heart diseases, preoperative heart rate of < 60 beats/minute, 2nd or 3rd degrees AV block, prior coronary artery bypass graft, abnormal renal function with creatinine level (>2 mg/dl), end stage renal disease (ESRD) on maintenance dialysis, patients on chronic amiodarone or digoxin therapy or with poor left ventricular function (Ejection fraction < 35 %), patients with known hypersensitivity to metoprolol or ivabradine.

METHODOLOGY

Patients were randomly divided into two equal groups; Group I included patients who received ivabradine (Procoralan®) and bisoprolol (Concor®) and Group II included patients who received bisoprolol (Concor®) only. Both groups received their treatments 48 hours before surgery and continued one week postoperatively. All patients were subjected to full history taking, thorough clinical examination, laboratory investigation, and ECG examination, pre and postoperatively.

Ethical considerations:

The study was done after being accepted by the Research Ethics Committee, Benha University. All patients provided written informed consents prior to their enrolment. The consent form explicitly outlined their agreement to participate in the study and for the publication of data, ensuring protection of their confidentiality and privacy. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical Analysis of Data

Statistical computations were executed employing SPSS v26 (IBM Inc., Chicago, IL, USA). Quantitative variables were articulated as mean ± standard deviation (SD), and range and were subjected to comparative analysis across distinct groups through the application of the unpaired Student's t-test. In contrast, qualitative attributes were elucidated in terms of frequency and proportion (%) and were subjected to scrutiny via the Chi-square or Fisher's exact test, depending on the appropriateness of conditions. A criterion for statistical significance was established at a two-tailed P value of less than 0.05.

RESULTS

There was no significant difference between the studied groups regarding demographic characteristics. There was no significant difference between the studied groups regarding the preoperative echocardiographic data **(Table 1)**.

Table 1: Demographic data and medical history of the studied groups:

		Group I (n=25)	Group II (n=25)	P value
Age (years)	**Mean ± SD**	54.88 ± 9.45	52.96 ± 8.74	0.299
	Range	39 – 69	40 - 67	
Sex	**Male**	16 (64%)	18 (72%)	0.544
	Female	9 (36%)	7 (28%)	
DM	**Yes**	16 (64%)	18 (72%)	0.544
	No	9 (36%)	7 (28%)	
Hypertension	**Yes**	15 (60%)	17 (68%)	0.556
	No	10 (40%)	8 (32%)	
Smoking	**Yes**	14 (56%)	16 (64%)	0.564
	No	11 (44%)	9 (36%)	
Hyperlipidemia	**Yes**	18 (72%)	19 (76%)	0.747
	No	7 (28%)	6 (24%)	
COPD	**Yes**	0 (0%)	1 (4%)	1
	No	25 (100%)	24 (96%)	

DM: diabetes mellitus; COPD: chronic obstructive pulmonary disease.

There was a statistically significant decrease in HR, SBP and DBP among patients in group I compared with group II **(Table 2)**.

Table 2: Postoperative vital signs of the studied groups:

		Group I (n=25)	Group II (n=25)	P value
HR (beats/min)	**Mean ± SD**	69.72 ± 7.66	74.28 ± 7.23	**0.035***
	Range	60 – 86	61 – 84	
SBP (mmHg)	**Mean ± SD**	126.4 ± 14.49	135.76 ± 16.52	**0.038***
	Range	97 – 146	115 – 171	
DBP (mmHg)	**Mean ± SD**	75.32 ± 8.02	80.68 ± 9.21	**0.033***
	Range	57 – 87	62 – 98	

HR: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; *: significant

There was no significant difference between the studied groups regarding the postoperative laboratory data **(Table 3)**.

Table 3: Postoperative laboratory data of the studied groups:

		Group I (n=25)	Group II (n=25)	P value
Hb (g/dl)	**Mean ± SD**	12.58 ± 0.93	12.98 ± 0.9	0.133
	Range	10.9 - 14.2	11.5 - 14.4	
Creatinine (mg/dl)	**Mean ± SD**	1.26 ± 0.25	1.18 ± 0.19	0.264
	Range	0.8 - 1.8	0.9 - 1.5	
HbA1c (%)	**Mean ± SD**	6.91 ± 0.99	6.78 ± 0.56	0.575
	Range	5.3 - 8.3	5.8 - 7.8	

Hb: hemoglobin; HbA1C: glycated hemoglobin.

There was a statistically significant decrease in LVEF among patients in group I compared with group II and a statistically significant increase in each of LVESD and LAVI among patients in group II compared with group I. Regarding MR grade, there was a statistically significant increase in MR grade 1 (48% vs. 20%) and grade 3 (12% vs. 4%) among patients in group II compared with group I respectively **(Table 4)**.

Table 4: Postoperative echocardiographic data of the studied groups:

		Group I (n=25)	Group II (n=25)	P value
LVEF (%)	**Mean ± SD**	49.44 ± 5.92	52.8 ± 5.21	**0.038***
	Range	40 – 59	44 - 62	
LVEDD (mm)	**Mean ± SD**	51.12 ± 3.09	52.52 ± 2.83	0.101
	Range	45 – 56	48 - 58	
LVESD (mm)	**Mean ± SD**	37.32 ± 3.51	39.32 ± 3.2	**0.04***
	Range	30 – 44	34 - 45	
LAVI (ml)	**Mean ± SD**	32.08 ± 2.9	34.16 ± 2.53	**0.009***
	Range	28 - 37	31 - 39	
MR grade	**0**	19 (76%)	10 (40%)	**0.035***
	1	5 (20%)	12 (48%)	
	2	0 (0%)	0 (0%)	
	3	1 (4%)	3 (12%)	

LVEF: left ventricular ejection fraction; LVEDD: left ventricular end diastolic diameter; LVESD: left ventricular end systolic diameter; LAVI: left atrial volume index; MR: mitral regurgitation; *: significant

There was a statistically significant increase in the overall postoperative atrial fibrillation among patients in group II compared with group I **(Table 5)**.

Table 5: Postoperative atrial fibrillation of the studied groups:

		Group I (n=25)	Group II (n=25)	P value
Overall	**Yes**	1 (4%)	9 (36%)	**0.010***
	No	24 (96%)	16 (64%)	
AF in day 1	**Yes**	0 (0%)	1 (4%)	1
	No	25 (100%)	24 (96%)	
AF in day 2	**Yes**	1 (4%)	7 (28%)	**0.048***
	No	24 (96%)	18 (72%)	
AF in days 3–5	**Yes**	0 (0%)	2 (8%)	0.489
	No	25 (100%)	23 (92%)	
AF in days 6–15	**Yes**	0 (0%)	1 (4%)	1
	No	25 (100%)	24 (96%)	
AF in days 16–30	**Yes**	0 (0%)	1 (4%)	1
	No	25 (100%)	24 (96%)	

AF: atrial fibrillation; *: significant

There was a statistically significant increase in ICU stay among patients in group II compared with group I **(Table 6)**.

Table 6: ICU and hospital stay of the studied groups:

		Group I (n=25)	Group II (n=25)	P value
ICU stay (h)	**Mean ± SD**	18.28 ± 2.44	24.24 ± 3.17	**<0.001***
	Range	15 – 23	19 - 30	
Hospital stay (days)	**Mean ± SD**	6.12 ± 1.24	6.12 ± 1.42	1
	Range	4 – 9	4 - 8	

ICU: intensive care unit; *: significant

DISCUSSION

Regarding the assessment of vital parameters, the current study elucidated that, preoperatively, there were no statistically significant variances between Group I and Group II with respect to HR, SBP, and DBP. Postoperatively, however, there emerged a statistically significant augmentation in HR (74.28 ± 7.23 bpm vs. 69.72 ± 7.66 bpm), SBP (135.76 ± 16.52 mmHg vs. 126.4 ± 14.49 mmHg), and DBP (80.68 ± 9.21 mmHg vs. 75.32 ± 8.02 mmHg) observed within Group II as compared to Group I respectively.

These observations are congruent with the findings from **Bhatt *et al.*,** who conducted an investigation involving 150 patients stratified into three therapeutic cohorts. Group I was administered ivabradine (5 mg), Group II received metoprolol (25 mg), and Group III was treated with a combination of ivabradine (5 mg) and metoprolol (25 mg). The results indicated that the decrement in HR was most pronounced in the combination therapy group, followed by the ivabradine-only group, and least in the metoprolol-only group. Additionally, the reductions in systolic, diastolic, and mean arterial pressures were most substantial in the combination therapy group, subsequently in the metoprolol group, and least in the Ivabradine group [11].

Additionally, **Tekin *et al.*** conducted a study comprising 174 patients who were subjects to CABG, segregating them into two distinct groups; Group I (n=90), which was administered ivabradine, and Group M (n=84), which received metoprolol from pre-surgical administration through to the tenth postoperative day. The findings from this study reported that ivabradine substantially reduced HR and significantly enhanced surgical comfort during the operative procedure [13].

Regarding the echocardiographic data, the present study revealed that preoperatively, LVEF was not significantly different between group I and group II, however, postoperatively there was a statistically significant decrease in LVEF among patients in group I compared with group II (49.44 ± 5.92 vs. 52.8 ± 5.21%, respectively). Preoperatively, LVESD was not significantly different between group I and group II, however, postoperatively, there was a statistically significant decrease in LVESD among patients in group I compared with group II (37.32 ± 3.51 vs. 39.32 ± 3.2 mm, respectively). Preoperatively, LAVI was not significantly different between group I and group II, however, postoperatively, there was a statistically significant decrease in LAVI among patients in group I compared with group II (32.08 ± 2.9 vs. 34.16 ± 2.53 ml, respectively). Regarding MR grade, there was a statistically significant increase in MR grade 1 (48% vs. 20%) and grade 3 (12% vs. 4%) among patients in group II compared with group I respectively.

Such findings are in agreement with **Abdel-Salam and Nammas,** study on 740 consecutive patients scheduled for elective CABG reported that

postoperative left ventricular ejection fraction was higher among patients received bisoprolol alone compared with patients received ivabradine alone or patients in the combination group. Furthermore, there was a statistically significant increase in MR grade 0 among the combination group compared with patients received ivabradine alone or those received beta blockers. However, in contrary with the present findings, the postoperative left ventricular end systolic dimension was significantly higher in the combination group (Ivabradine plus beta blockers) compared with patients received ivabradine alone or those received beta blockers alone [14].

A further investigation by **Nguyen and Le,** revealed that the synergistic regimen comprising ivabradine, and low-dose beta-blocker therapy was correlated with a substantial diminution in HR alongside an enhanced ejection fraction, thereby substantiating both the efficacy and safety of this therapeutic approach. After a two-month period, a marked reduction in the mean resting heart rate was observed, decreasing from 78.6 ± 9.3 bpm at baseline to 65.1 ± 6.5 bpm. Additionally, a notable increase in ejection fraction was documented, rising from 56.7 ± 9.3% to 57.9 ± 8.7% [15].

Conversely, a prospective, randomized investigation by **Marazia *et al.*** involved patients undergoing cardiac rehabilitation subsequent to recent CABG. Participants were allocated to either a regimen of ivabradine 5 mg BID combined with standard medical therapy including bisoprolol 1.25 mg QD (combination group, n = 38), or standard medical therapy with bisoprolol dosed between 2.5 to 3.75 mg QD (bisoprolol group, n = 43). Results indicated a significant improvement in LVEF within the combination group, escalating from 57% ± 3% at admission to 62% ± 4% at discharge, and reaching 66% ± 3% at three months. Conversely, LVEF remained relatively stable in the bisoprolol group, documented at 57% ± 3% at admission, 59% ± 4% at discharge, and 59% ± 3% at three months [16].

Regarding the incidence of postoperative atrial fibrillation of the studied groups, the present study revealed that there was a statistically significant increase in the overall postoperative atrial fibrillation among patients in group II compared with group I (36% vs. 4%, respectively, P value=0.01).

These observations concur with those reported by **Virmani *et al.***, who found that postoperatively in the ICU, the control group—administered conventional antianginal treatments including beta blockers preoperatively—exhibited three instances of sinus tachycardia (ST) and one of combined supraventricular tachycardia (SVT) and AF. Conversely, in the cohort receiving a regimen of ivabradine 5 mg twice daily alongside the usual antianginal medications and beta blockers for three days prior to surgery, only one patient demonstrated occurrences of ST, SVT, AF, and VT [12].

Additionally, a research investigation by **Iliuta and Rac-Albu,** encompassing 527 individuals subjected to CABG, demonstrated that the incidence of postoperative AF and other arrhythmic events during the hospital stay was notably reduced in the cohort receiving a dual therapeutic approach involving metoprolol in conjunction with ivabradine, as opposed to the groups treated singularly with either ivabradine or metoprolol [17].

In a similar vein, a study by **Abdel-Salam and Nammas,** which included 740 consecutive patients undergoing elective CABG, reported that the integration of ivabradine with beta blockers during the perioperative phase was correlated with a reduced incidence of AF at a 30-day follow-up, in comparison to the administration of either pharmacologic agent singly. Specifically, the AF incidence was 4.2% in the group receiving combined ivabradine and bisoprolol 5 mg, versus 12.2% in those administered only bisoprolol 5 mg, and 15.5% in the cohort treated solely with ivabradine [14].

Correspondingly, a meta-analysis by **Aly *et al.*** illustrated that ivabradine significantly enhances ventricular rate, heart rate, and maintenance of sinus rhythm in cases of atrial fibrillation, with minimal or absent adverse effects. Furthermore, these findings suggest that the concomitant use of ivabradine with other medications more effectively improves ventricular rate and sustains sinus rhythm compared to its solitary use [18].

Conversely, an investigation by **Tekin *et al.*,** which encompassed 174 patients undergoing CABG, indicated that ivabradine did not significantly lower the incidence of AF compared to metoprolol. In the postoperative phase, AF was documented in 7 patients (7.7%) in the ivabradine group and in 10 patients (11.9%) in the metoprolol group, revealing a statistically insignificant difference between the two cohorts [13].

Regarding the ICU and hospital stay of the studied groups, the present study revealed a statistically significant increase in ICU stay among patients in group II compared with group I (24.24 ± 3.17 vs. 18.28 ± 2.44 h, respectively, P value<0.001). Meanwhile, there was no statistically significant difference between the studied groups regarding hospital stay duration.

These outcomes align with the findings from **Bhatt *et al.*,** who analyzed 150 patients randomly allocated into three therapeutic cohorts. Group I was administered ivabradine (5 mg), Group II received metoprolol (25 mg), and Group III was prescribed a combination of ivabradine (5 mg) and metoprolol (25 mg). The study demonstrated no significant variation in total hospitalization duration across all treatment groups. Contrary to the current findings, the length of ICU stay also did not exhibit significant differences among the groups studied. The mean ICU duration, longer than that observed in our study, averaged 3.7 ±

0.5 days, whereas the mean total hospital stay was 7.3 ± 1.2 days, statistically consistent across the groups [11]. Similarly, **Tekin *et al.,*** involving 174 CABG patients, reported no significant differences in the duration of hospital and ICU stays between the ivabradine and metoprolol groups[13].

This study is subject to certain limitations. Primarily, it was conducted at a single center and involved a comparatively limited number of participants.

CONCLUSION

Ivabradine is a safe and effective drug to be administered along with a beta blocker (Bisoprolol) perioperatively in patients undergoing CABG surgery in terms of reducing HR, SBP, DBP, ICU stay, and better postoperative echocardiographic data and significantly reducing the incidence of the overall postoperative atrial fibrillation.

Financial support and sponsorship: Nil.
Conflict of interest: Nil.

REFERENCES

1. **Tzoumas A, Nagraj S, Tasoudis P *et al.* (2022)**: Atrial fibrillation following coronary artery bypass graft: Where do we stand? Cardiovasc Revasc Med., 40:172-9.
2. **Benedetto U, Gaudino MF, Dimagli A *et al.* (2020)**: Postoperative atrial fibrillation and long-term risk of stroke after isolated coronary artery bypass graft surgery. Circulation, 142:1320-9.
3. **Oraii A, Masoudkabir F, Pashang M *et al.* (2022)**: Effect of postoperative atrial fibrillation on early and mid-term outcomes of coronary artery bypass graft surgery. Eur J Cardiothorac Surg., 62:15-9.
4. **Kim S, Hwang H, Choi J *et al.* (2020)**: The impact of beta-blocker use on postoperative atrial fibrillation after aortic valve replacement. Journal of Thoracic Disease, 12:2545.
5. **Francisco A, Awata W, Lima TS *et al.* (2023)**: Three generation β-blockers for atrial fibrillation treatment. Current Hypertension Reviews, 19:34-41.
6. **Rezaei Y, Peighambari M, Naghshbandi S *et al.* (2020)**: Postoperative atrial fibrillation following cardiac surgery: from pathogenesis to potential therapies. American Journal of Cardiovascular Drugs, 20:19-49.
7. **Chooriyil N, Jayakumar T, Palappallil D (2021)**: Post-operative atrial fibrillation in off pump coronary artery bypass graft: association with medication. International Journal of Research in Medical Sciences, 9:1.
8. **Badem S, Pekcolaklar A (2023)**: Inflammatory prognostic index predicts new-onset atrial fibrillation and mortality after on-pump coronary artery bypass grafting. Revista da Associação Médica Brasileira, 69:28385.
9. **Watson M, Bennett M, Hamilton C *et al.* (2022)**: Rate vs rhythm: beta blockers and antiarrhythmics as pharmacological options for the treatment of postoperative atrial fibrillation. British Journal of Cardiac Nursing, 17:1-7.
10. **Sartiani L, Mannaioni G, Masi A *et al.* (2017)**: The hyperpolarization-activated cyclic nucleotide-gated channels: from biophysics to pharmacology of a unique family of ion channels. Pharmacol Rev., 69:354-95.
11. **Bhatt P, Bhavsar N, Naik D *et al.* (2021)**: Comparative effectiveness of metoprolol, ivabradine, and its combination in the management of inappropriate sinus tachycardia in coronary artery bypass graft patients. Indian J Pharmacol., 53:264-9.
12. **Virmani S, Mallik I, Mohire VB *et al.* (2023)**: Effect of preoperative ivabradine on hemodynamics during elective off-pump CABG. Ann Card Anaesth., 26:260-7.
13. **Tekin E, Yeşiltaş M, Haberal İ (2022)**: Short-term results of ivabradine versus metoprolol: The effects on atrial fibrillation in patients undergoing off-pump coronary artery bypass grafting. Braz J Cardiovasc Surg., 37:857-65.
14. **Abdel-Salam Z, Nammas W (2016)**: Atrial fibrillation after coronary artery bypass surgery: Can ivabradine reduce its occurrence? J Cardiovasc Electrophysiol., 27:670-6.
15. **Nguyen P, Le P (2021)**: Effect of ivabradine in combination with beta-blockers on heart rate, angina pectoris, and left ventricular function in patients with coronary artery diseases after percutaneous coronary intervention. A nonrandomized single arm trial. World Heart Journal, 13:361-9.
16. **Marazia S, Urso L, Contini M *et al.* (2015)**: The role of ivabradine in cardiac rehabilitation in patients with recent coronary artery bypass graft. J Cardiovasc Pharmacol Ther., 20:547-53.
17. **Iliuta L, Rac-Albu M (2014)**: Ivabradine versus beta-blockers in patients with conduction abnormalities or left ventricular dysfunction undergoing cardiac surgery. Cardiol Ther., 3:13-26.
18. **Aly Y, Beshir S, Gillani S (2023)**: Efficacy and safety of ivabradine in arrhythmias: A systematic review. Pharmacy Practice, 21: 1886-3655.