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Original Article

Metoprolol versus low-dose sotalol for prevention of high-risk post coronary artery bypass grafting atrial fibrillation

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Abstract

Background: The optimal therapeutic strategy for high-risk postoperative atrial fibrillation (POAF) remains less well defined. Our objectives were to investigate the efficacy of prophylactic metoprolol versus low-dose sotalol regimens to prevent high-risk atrial fibrillation (AF) following coronary artery bypass surgery (CABG).

Methods: We assigned 113 consecutive patients referred for CABG to either metoprolol or low-dose sotalol regimen. The primary end-point was the frequency of POAF during the 6-week follow-up.

Results: Out of 113 patients enrolled, 52.2% % received metoprolol (n= 59) while 44.8% received sotalol (n= 54). The frequency of POAF at follow-up was significantly higher among the metoprolol group (59.3 % versus 50 %; P=0.017). The predictors of POAF were: age > 60 years (OR: 1.86 (1.01-4.41); P= 0.03), EF (OR: 2 (1.05-3.83); P= 0.02), and sotalol was protective against POAF (OR= 0.49%; (95% CI=0.25 -0.97); P=0.02). The length of hospital stay was significantly higher in the metoprolol group (7.5⍰1.3 % versus 6.1⍰1.2 days; P<0.001).

Conclusion: Prophylactic low-dose sotalol could be superior to metoprolol for the prophylaxis of POAF in high-risk patients. However, Larger prospective multicenter randomized trials are needed to confirm our findings.

KEYWORDS

Low-dose sotalol; Metoprolol; CABG; POAF; High-risk mitral valve replacement

Article History

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Introduction

Atrial fibrillation (AF) is the most frequent post-coronary artery bypass grafting (CABG) dysrhythmia. After CABG, the reported incidence of AF ranged from 20 to 40%, with dysrhythmia typically occurring between the second and fourth days [1-6].

Although these dysrhythmias are usually benign, it may result in longer hospital stay due to hemodynamic instability and thromboembolic events; consequently, healthcare costs are increased [2,4,7,8].

For prophylaxis against postoperative AF, according to the guidelines recommendations for routine prophylaxis, the use of β-blockers is considered as "class I, level of evidence; A," while for prophylaxis for high-risk patients, the use of amiodarone is considered as "class IIa, level of evidence: A). On the other hand, the use of sotalol is considered as "class IIb, level of evidence: B" [9], probably due to sotalol side effect profile.

Nystorom and colleagues [10] conducted a trial to compare sotalol to metoprolol in doses considered to provide equivalent Beta-blockade;

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the result was a higher prevalence of postoperative dysrhythmia in the sotalol prophylaxis arm. We hypothesized that a low-dose sotalol regimen could be superior to metoprolol in reducing the incidence of high-risk postoperative AF. Accordingly, this study aimed to investigate the efficacy of prophylactic metoprolol versus low-dose sotalol regimens to prevent high-risk atrial fibrillation following coronary artery bypass surgery.

Patients and Methods:

We conducted this study in the Departments of Cardiology and Cardiothoracic Surgery, Faculty of Medicine, Zagazig, and Cairo Universities. The study included 113 consecutive high-risk patients for postoperative AF (POAF) who had primary CABG from February 2018 to July 2020. The criteria for high-risk POAF were described before [11] and included one or more of the following: elder patients, large left atrium, and P-wave abnormality on ECG. Patients that were in sinus rhythm before the procedure and who were not on antiarrhythmic medications were included. Patients who had a concomitant operation, uncontrolled heart failure, low left ventricular ejection fraction (EF) (< 45%), cardiogenic shock, sustained ventricular tachyarrhythmia, end-stage renal disease, an implanted pacemaker, or with contraindications to β-blockers were excluded.

The patients were allocated to obtain either metoprolol 25-100 mg twice daily (Group A; n = 59) or low-dose sotalol 40 mg twice daily (Group B; n = 54), which was continuous for ten days after surgery. For new-onset AF during the study period, amiodarone oral and intravenous was given. The research complied with the Helsinki declaration [12] and was accepted by the participating centers' Medical Ethics Committee. All patients gave informed consent in writing.

Technique:

The patients underwent CABG according to the standard surgical technique. Patients were continuously monitored up to the fifth postoperative day. After the patients shifted to the ward, they were also monitored using telemetry. All medical, hemodynamic, and surgical details were gathered, and an electrocardiogram (ECG) was reported 24-48 hours before surgery. A further ECG was recorded on days 0, 1, 2, 4, and 8 following operations and before discharging home. An apical and peripheral heart rate was checked at a 6-hour interval up to hospital discharge, and if AF was suspected, an additional 12-leads ECG was obtained. After hospital discharge, patients were followed every two weeks by their referring physician, and ECG was obtained each visit. At the end of the six-week follow-up period, all data were analyzed. Two cardiologists, who were blinded to other data, reviewed the ECG records.

The primary end-point was the frequency of the new-onset- POAF during the first 6-week follow-up. Secondary end-points were major adverse cardiovascular events (MACE) during the 6-weeks follow-up. Clinically significant AF episodes have been identified as symptomatic AF episodes at a rate of ≥ 120 beats/minute.

Statistical analysis:

The continuous variables were expressed as mean ± standard deviation (SD), while discrete variables were expressed as numbers and percentages. The differences in continuous variables were checked for statistical significance by t-test or Mann-Whitney test as appropriate. The differences in the discrete variables were checked for statistical significance with the X^2 test or Fisher exact test.

Univariable and multivariable logistic regression analysis was used to identify factors affecting the occurrence of POAF, and odds ratio (OR) and 95% confidence interval (CI) were reported.

All statistical comparisons were two-tailed, and a p-value of <0.05 was considered statistically significant. The statistical analysis was performed using SPSS 11 for windows (SPSS Inc., Chicago, Illinois, USA).

Results

The baseline, clinical, ECG, and echocardiographic variables are shown in Table 1. No statistically significant differences in age, gender, diabetes mellitus, hypertension, or in the

Table 1: Baseline characteristics of the study population. Values are presented as mean ± SD or n (%).

	Metoprelol group (n = 59)	Sotalol group (n = 54)	p value
I. Clinical variables			
Age (years)	61.5 ± 7	62.5±6	0.66
Male gender	53 (89.8)	49 (90.7)	0.87
Diabetes mellitus	12 (20.3)	11 (20.4)	0.99
Hypertension	30 (50.8)	27 (50)	0.92
Dyslipidemia	36 (61)	23 (42.6)	0.05
Current smokers	33 (55.9)	20 (37)	0.04
COPD	3 (5.1)	3 (5.6)	0.75
II. ECG variables			
p wave duration (ms)	118 ± 12	119 ± 11	0.46
III. ECHO variables			
EF	55 ± 17	58 ± 15	0.99
MR	6 (10.2)	5 (9.2)	0.87
LVH	5 (8.5)	4 (7.4)	0.88

AF = Atrial Fibrillation; EF% = Ejection Fraction; MR = Mitral Regurgitation; LVH = Left Ventricular Hypertrophy; COPD= Chronic obstructive pulmonary disease

criteria predicting high-risk POAF. On the other hand, the frequency of dyslipidemia was significantly higher among the metoprolol group, while the frequency of smoking was significantly higher among the sotalol group (p-value= 0.05 and 0.04), respectively.

Angiographic and operative variables are shown in Table 2. No statistically significant differences in the Euro-score, frequency of multivessel disease, reference vessel diameter, left internal mammary artery (LIMA) graft, vein graft, distal anastomosis, cardiopulmonary bypass, cardiopulmonary bypass time, endarterectomy, pericardial closure or aortic cross-clamp were found between the two groups. On the other hand, the frequency of two-vessel disease was significantly higher among the patients of the sotalol group (p-value= 0.02). The mean intubation time was significantly higher among the metoprolol group (p-value= 0.02; 0.008), respectively.

The postoperative, as well as 6-week follow-up variables, are shown in Table 2. No patient had death, stroke, heart failure (HF), angina, torsade de point, or high-grade atrioventricular (AV) block in the two groups. On the other hand, the frequency of AF at follow up and the length of hospital stay was significantly higher among the metoprolol group (p-value= 0.017 and 0.001), respectively.

Sotalol was more effective than metoprolol in prophylaxis against POAF (OR= 0.04, CI= 0.18-0.92). Univariable and multivariable model analysis for different variables predicting POAF is shown in Table 3. According to the multivariable model analysis, the predictors of POAF were: age, EF, and sotalol. Sotalol use was protective against POAF (OR= 0.49; 95% CI= 0.25 -0.97; P= 0.02).

Discussion

AF is the most frequent arrhythmia after CABG with a reported incidence between 20-40%; usually, its onset is between the second and fourth postoperative days [1,2,4-6].

Prevention of POAF reduces healthcare costs [8]. Sotalol is class III potent antiarrhythmic. Its use for prophylaxis for high-risk POAF is considered as class IIb (level of evidence = B) [9], probably due to the side-effect profile of sotalol. Our hypothesis of using low-dose sotalol to achieve prophylaxis but, at the same time, avoid its arrhythmia-related side effects was luckily effective.

Results of our study demonstrated that in the prevention of high-risk POAF, low-dose sotalol is more effective than metoprolol. The beneficial

Table 2: Angiographic, operative and postoperative variables of the study population. Values are presented as mean ± SD or n (%).

	Metoprelol group (n = 59)	Sotalol group (n = 54)	p value
I. Angiographic variables			
Euro score	4.2 ± 0.5	4.1 ± 0.6	0.96
Percent of 2 vessel disease	25 (42.4)	12 (22.2)	0.02
Percent of triple vessel disease	44 (74.5)	42 (77.8)	0.6
RVD	2.76 ± 0.6	2.93 ± 0.69	0.24
II. Operative variables			
LIMA graft	0.7 ± 0.5	0.7 ± 0.5	>0.99
Vein graft	2 ± 1	2 ± 1	>0.99
Distal anastomosis	3 ± 1	3 ± 1	>0.99
CPB	47 (79.7)	43 (79.6)	0.99
OPCAB	12 (20.3)	11 (20.4)	0.99
Extra corporeal bypass time	97 ± 22	96 ± 5	0.332
Aortic cross-clamp time (minutes)	57 ± 15	58 ± 16	0.34
Intubation time (hours)	22 ± 4	20 ± 4	0.008
Endarterectomy	3 (5.1)	3 (5.6)	0.75
Pericardial closure	18 (30.5)	17 (31.5)	0.91
AF	35 (59.3)	20 (37)	0.017
Hospital stay (days)	7.5 ± 1.3	6.1 ± 1.2	< 0.001

AF: Atrial fibrillation; RVD: Reference Vessel Diameter; LIMA: Left Internal Mammary Artery; OPCAG: Off-Pump Coronary Artery Bypass; CPB: cardiopulmonary bypass.

influence of sotalol can be because it is a beta-blocker drug with significant antiarrhythmic properties in class III. Several reports have examined the prevalence of POAF sotalol prophylaxis.

Burgess and coworkers [13] performed a meta-analysis of 14 studies involving 2,583 patients evaluating beta-blockers or placebo. It showed that sotalol was more beneficial than other beta-blockers or placebo in minimizing POAF. Sotalol tends, therefore, to provide substantial protection compared to remaining beta-blockers. However, in one clinical trial, a higher prevalence of postoperative brady arrhythmias was observed in the sotalol arm in doses where metoprolol was considered to provide the equivalent beta blockage effect. Several patients withdrew due to side effects from the sotalol arm, predominantly bradycardia, and hypotension [14].

The autonomic nervous system has been involved in the initiation and continuation of atrial

Table 3: Univariate versus multivariate model analysis for POAF and different variables predicting its occurrence.

	Univariable analysis		Multivariable analysis	
	OR (95% CI)	**P**	**OR (95% CI)**	**P**
Age ≥ 60	3.25 (1.32-8.09)	0.004	1.86 (1.01-4.41)	0.03
Sotalol use	0.4 (0.18-0.92)	0.017	0.49 (0.25-0.97)	0.02
LV ejection fraction	2.73 (1.17-6.4)	0.001	2 (1.05-3.83)	0.02
HTN	2.7 (1.17-6.29)	0.01	-	
P wave abnormality	2.18 (0.93-5.1)	0.04	-	

HTN: hypertension; LV: left ventricle; HTN: hypertension; POAF: postoperative atrial fibrillation

fibrillation. Fibrillation has been seen, to begin with, as an episode of a rapid extrasystole [15]. The proposed causes were the incidence of a single ectopic focus whose impulse discharge frequency was so fast that consistent atrial excitation was no longer probable. Triggered activity or enhanced automaticity may be the mechanisms that cause the phenomenon of POAF in setting an increased sympathetic state or high catecholamine level. Sympathetic activation often decreases atrial refractoriness in a nonuniform way that facilitates the continuation of atrial fibrillation [16].

In most cases, suggesting the role of sympathetic stimulation is evident in atrial fibrillation occurring for the first time shortly following CABG and indicates that the provocative stimuli will not arise any longer [17].

Our protocol regimen of giving the prophylaxis medications starting on the day of the surgery, maintained for ten days postoperatively, was suitable in the prevention of POAF because the dysrhythmia usually starting between the second and fourth postoperative days [6]. To avoid the marked pro-arrhythmic side effects reported in the survival with oral D-sotalol trial (SWORD) [18], sotalol was given at a low-dose regimen and for ten days only.

Weber and colleagues [19] proposed that the use of low-dose sotalol in patients during CABG should be limited in the first nine days following the operation. Our protocol to identify the preoperative risk stratification of surgical patients for the occurrence of post-CABG AF was previously described [11]; their variables were validated by several other studies [3,4,20-23]. The use of antiarrhythmic prophylaxis in high-risk situations increases the cost-effectiveness and safety of antiarrhythmic [24].

A previous randomized clinical trial had tested the efficiency of sotalol versus metoprolol in preventing high-risk POAF following CABG. This study demonstrated the superiority of sotalol over metoprolol in the prevention of POAF. Unlike other studies, Parrika and associates examined sotalol's ability to prolong repolarization even in modest doses suggesting a specific class III effect of sotalol is present [25].

Low to moderate doses of sotalol is effective in preventing POAF following CABG. Furthermore, sotalol is especially effective in high-risk subgroup [25]. Our results demonstrated no differences between the two groups in MACE except longer hospital stay length among the metoprolol group. The longer hospital stay is most probably due to the higher frequency of POAF noticed among the same group (metoprolol group) that mandated extension of admission. Our findings of prolonged hospital stay among metoprolol arm agreed with Pfisterer and coworkers' study [22]. A double-blinded placebo-controlled clinical randomized trial in patients undergoing CABG, where the low-dose sotalol reduced the AF rate to 26%, together with a reduced hospital stay in the sotalol arm.

Auer and associates [26] further investigated the relative effects of sotalol, metoprolol, amiodarone plus metoprolol versus placebo through a randomized, double-blinded trial in patients undergoing CABG. Again, they reported a significantly longer hospital stay in those who had POAF compared to those with no POAF.

Limitations:

Firstly, the present study has a low sample size. Secondly, a 6-week period is a relatively short follow-up period; a longer follow-up duration is needed to detect MACE. Thirdly, AF definition, and the method of its detection (using Holter device) is not used, definitely affected the reported incidence, which may be lower than that reported by other studies. Fourthly, it tested only the low-dose sotalol. Testing moderate dose sotalol that may lead to further reduction of POAF in that high-risk group is still needed. Finally, the POAF risk stratification score used in this study needs further testing on a wide-scale basis. However, this was beyond the scope of our current study.

Conclusion

Prophylactic low-dose sotalol could be superior to metoprolol for the prophylaxis of POAF in high-risk patients. However, Larger prospective multicenter randomized trials are needed to confirm our findings.

Conflict of interest: Authors declare no conflict of interest.

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