

## ORIGINAL PAPER

doi: 10.5455/medarh.2019.73.12-15

MED ARCH. 2019 FEB; 73(1): 12-15

RECEIVED: SEP 10, 2018 | ACCEPTED: NOV 15, 2018

<sup>1</sup>Heart Center BH Tuzla, Tuzla, Bosnia and Herzegovina<sup>2</sup>School of Medicine University of Belgrade, Serbia<sup>3</sup>Polyclinic Cardiocenter Sarajevo, Sarajevo, Bosnia and Herzegovina**Corresponding author:** Enes Osmanovic, MD, Msc, BH Heart Center, Tuzla, Bosnia and Herzegovina., ORCID ID:<http://www.orcid.org/0000-0002-7795-2363>. E-mail: osmanovic@bhsrce.ba.

# Pharmacological Prophylaxis of Atrial Fibrillation After Surgical Myocardial Revascularization

Enes Osmanovic<sup>1</sup>, Miodrag Ostojic<sup>2</sup>, Sevleta Avdic<sup>1</sup>, Samed Djedovic<sup>1</sup>, Adnan Delic<sup>3</sup>, Nedzad Kadric<sup>1</sup>, Amar Terzic<sup>1</sup>, Azra Avdic-Salihovic<sup>1</sup>**ABSTRACT**

**Introduction:** Postoperative Atrial Fibrillation (POAF) is associated with a higher rate of postoperative complications and mortality, as well as with longer hospitalization and increased treatment costs. We have designed and performed a randomized, trial of pharmacological prophylaxis in which the event of interest is POAF. **Aim:** The aim of this study is to reduce the risk of postoperative, complications associated with this arrhythmia. **Patients and methods:** We included 240 stable patients with a coronary heart disease, who were referred to elective surgical revascularization of the myocardium. The patients were assigned into three groups of 80 patients each: group A (BB, betablocker, comparator), group B (BB+ Amiodaron) and group C (BB + Rosuvastatin). The goal was to establish whether intervention by combination therapy was more useful than a comparator. **Results:** An event of interest (POAF) has occurred in 66 of the total 240 patients. Number of new POAF cases is the lowest in Group B, 14 (17.5%) compared to 25 (31.25%) new cases in the comparator group, and 27 new cases (33.75%) in group C. Absolute risk reduction was 13.75%, ≈14% less POAF in group B compared to comparator. Relative risk reduction was 56% (RR 0.56, p = 0.04). Number Needed to Treat was 7.27. In group C, 33.75% of patients developed POAF. Absolute risk was insignificantly higher in group C (2.5%, NS) compared to the comparator. The number needed to harm was high, 40. **Conclusion:** The results of our research show that prophylaxis of POAF with combined therapy BB + Amiodaron was the most efficient one.

**Keywords:** cardiac surgery, postoperative atrial fibrillation, amiodarone, prophylaxis.**1. INTRODUCTION**

Reported incidence of POAF is variable and ranges from 10 to 65%. This range is very wide because studies studying POAF after coronary surgery differ in basic pattern characteristics, type of surgery, detection methods, and POAF definitions. It is estimated that the incidence of POAF after cardiac surgery is 15-45% and increases to about 50% after the combined surgery (CABG + valve surgery) (1). POAF usually occurs on the second or third postoperative day, and less than 10% on the first postoperative day. Data from recent meta-analysis show that paroxysmal AF contributes to increased risk of stroke at an event rate similar to chronic AF. It is associated with a high incidence of thromboembolic complications, acute failure or worsening of chronic heart failure, stroke, prolonged stay in intensive care units (ICU) and length of total hospitalization, significantly higher postoperative treatment costs, and in the long run impair the quality of life (2, 3).

**2. AIM**

The aim of this study is to determine whether the preoperative administration of combined therapy of beta blocker+amiodarone and beta blocker+Rosuvastatin is more effective in the prophylaxis of postoperative atrial fibrillation than monotherapy with only beta blocker after coronary artery bypass surgery

**3. PATIENTS AND METHODS*****Design, randomization and implementation***

This is an event conditioned clinical trial of pharmacological prophylaxis in which the event of interest is POAF, and the aim is reducing the risk of postoperative, potentially dangerous complications associated with this arrhythmia. Event of interest: POAF has been verified by the 3 independent cardiologists, and is defined as an ECG recording of atrial fibrillation, with the duration of ECG strip of at least 30 seconds, or during ECG recording (if <30 seconds), whether only one or more ep-

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isodes of AF appeared and whether it was symptomatic or not. Detection of rhythm disturbance (POAF) was performed by continuous ECG telemetry and additional ECG recording in case of AF occurrence. Two ECGs were taken regularly during the day.

#### **Study population**

The cohort of our study consisted of coronary heart disease patients of both sexes: men and women of the average age of 62 years, suffering from ischemic heart disease which was angio-graphically confirmed by coronary angiography, who were then referred to CABG. All respondents had a moderate risk for POAF. Seven to ten days before the operation the patients were informed by telephone of the day of hospitalization, and reminded that they start prehospital treatment with the allocated therapy. Then they were hospitalized and operated. During the operation and in the subsequent postoperative course, each patient was on a continuous ECG monitoring and visual telemetry by the staff on duty in order to register an occurrence of POAF.

#### **Operational approach or type of operation**

Access to the operating area was mostly a conventional, classical medium sternotomy. 229 (95.42%) patients were operated that way, while only 11 patients (4.58%) had a second, minimal invasive approach, the so-called MIDCAB, LAST operation only in the case of LIMA-LAD grafting. Two classical operational methods were developed: the first "On-pump" or the surgical intervention with the extra-corporeal circulation machine. The second operating technique is the so-called "Off-pump", performed without a 'heart-lung' device. When the latter technique is used, it is assumed that the patient will recover faster after surgery. In all the patients operated using On-pump technique, myocardial preservation was uniform for all and was done with the use of antegrade cold blood cardioplegia. Rapid cooling of the heart was achieved by the addition of a cold saline solution and ice in the pericardial cavity allowing a safe ischemic period (4 hours).

#### **Intervention (therapeutic regimen)**

This clinical study was analyzed according to the intention-to-treat principle (ITT). We investigated whether intervention by combination therapy was more useful than the treatment by comparator ("standard of treatment", BB). One group, treatment A (Bisoprolol, BB) received only selective BB Bisoprolol as a comparator monotherapy in an individual adjusted dose and this was a comparator group. Therapy was introduced pre-operatively for 7-10 days and lasted until discharge. The second group, treatment B (Bisoprolol+Amiodaron), received the combination therapy: selective beta-blocker (Bisoprolol in the individually adjusted dose)+ Amiodaron per os: Amiodaron was administered 7-10 days prior to surgery as an oral dose of 600 mg divided into three daily doses (Amiodaron tbl. a 200 mg x 3), and then, from the second postoperative day, orally at a dose of 400 mg divided into two daily doses (Amiodaron tbl. a 200 mg x 2) during the follow-up hospital stay. The third group, treatment C (Bisoprolol+Rosuvastatin) received the combination therapy: selective betablocker (Bisoprolol in an individualized dose)+Rosuvastatin in a single daily dose of 20 mg. The therapy was administered 7-10 days before surgery and lasted until discharge.

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#### **Statistical methods**

Statistical analysis was done using the application software "STATA" IC version 15". Continuous variables were presented with arithmetic mean and standard deviation or as real, positional mean: mod and median with interquartile range. Distribution of results of intermittent statistical series was expressed by absolute number (frequency) and relative representation (percentages). In order to determine the independence of categorical characteristics, we used a two-way Chi-square test of independence. For continuous variables normally distributed, we used the t-Student test for independent samples, and in the factorial diagrams of three-level variance analysis ANOVA test was used. For nonparametric data that do not have normal distribution, we used an alternative Mann-a sum-range test Whitney test as well as a Kruskal-Wallis variance analysis for comparing more than two groups. In the time-to-event analysis, the initial time in our research design (zero hour) was a time of arrival to the Intensive Care Unit (ICU) or the time recorded at the initial ECG. The dependent variable was time to event (hours), or follow-up hospital stay. If the respondent did not develop an event of interest until that moment, we considered it to be to the right censored observation, because it is quite possible that the event occurs after completion of hospital monitoring, but respondents were no longer observed. Using the Kaplan-Meier product limit curve and the Nelson Aalen estimator, we have approximated the function of experiencing events of interest and the function of cumulative risk, the current potential for the event to appear anyway. Test equality of survivor functions was performed using the Peto-Peto-Prentice equality test.

## **4. RESULTS**

The results of our study show that POAF prophylaxis with combination therapy with BB +Amiodaron best reduced the frequency of POAF. In the group (treated with the previous standard, only BB), 25 patients or 31.25% had a newly developed side-effect (POAF), while 14 or 17.5% of the patients developed POAF in the second treated group (BB+Amiodaron combination). The risk ratio (RR) is 0.56 and is lower than " 1.0 " which suggests a protective effect or a reduction in risk in the BB+ Amiodaron group. In the BB+Amiodaron group, probability of POAF was 56% lower than in BB alone. The relative reduction risk was -0.2475 or 24.75%. Absolute risk reduction was 13.75% (95% CI: 0.62% -26.88%), so ≈14% less POAF was in combination treatment group (BB+Amiodaron) compared to the control group (BB).

Number Needed to Treat (NNT) was 7.27 patients, which also means that 1 out of 7 patients benefited from prophylaxis. In group C treated with combination BB+Rosuvastatin, a POAF developed in 27 patients or 33.75% compared to the group treated only BB (25 or 31.25%). The insignificantly higher absolute risk of 2.5% was in the BB+Rosuvastatin group (CI:-12.01 to 17.01%).

It means that the absolute increase in risk is not statistically significant.

This is accompanied by the calculated Number Needed to Harm (NNH) which is high, 40. This means that one of the 40 patients in this treatment group had an outcome which was negligibly worse in comparison with control. A POAF has developed in a total of 66 patients. The analyzed time at risk for all 66 patients who developed POAF was 3123 hours; the median time of the survival time is 45.25 h. (IQ range from 19.50 to 66.22 h), and the newer POAF was recorded at 21.13% with a range of 16.6–26.9%. The quantified number of new cases of POAF is the smallest in the treated BB + Amiodarone group and amounts to 14 patients, in the BB group we had 25 new cases and from the BB+Rosuvastatin group a total of 27 new cases.

The shortest total in-risk time was recorded in the group BB+Amiodarone and amounted to 1019 hours; the median time to develop the events in this group is greater than in the group treated with BB only, which amounts to 76.61 h. The minimum recorded time for the development of events in this group is 18.34h, the maximum is 125.65h, and the average is 72.78h. The maximum total time at risk was only BB in the control group and it was 1060 h. The median time to experience the event is 32.25 h. (42.40 h to 96.44 h). The mean value expressed as Mean for this group is 42.40 h, and the minimum recorded time is 9.21h. The total time at risk for the treated BB+Rosuva-statin group is 1043 h. It is also longer than the BB+Amiodarone group. The median time to appearance is higher than in the group with BB at 45.25 h, and the minimum recorded time for the development of events in this group is 8.15 h. The first patient to develop the event of interest was from this group. These are valuable data since the earlier occurrence of POAF is clinically potentially more dangerous because the patient in this short postoperative period is clinically most vulnerable to a number of threatening complications, as well as

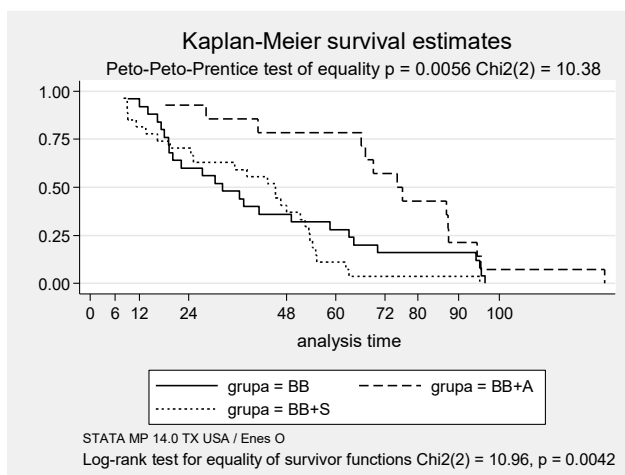


Figure 1. Cumulative function of hazards per type of treatment (Peto-Peto test).

		Postoperative atrial fibrillation		p value
		No POAF n=174	POAF n=66	
Age (yrs)	Median	63	63.5	0.499
	Q1-Q3	56-70	56-69	
Age categories	<50	5	2	0.277
	50-60	75	21	
	>60	94	43	
BMI (kg/m2)	Mean±SD	28.14±2.63	28.22±2.53	0.839
Sex (Male/Female)		119/55	41/25	0.358
Type of operation (On/Off pump)		128/36	50/15	0.854
CPB time (minute)		79 (70-88)	77 (65-94)	0.645
AoX time (minute)		53 (49-57)	52 (49-58)	0.540
ICU (days) Median (min-max)		1 (1-14)	2 (1-11)	0.0001
Hospital days Median (min-max)		9 (4-16)	10 (3-19)	0.0001

Table 1. Clinical characteristics of our sample

		Treatment			Total	
		BB	BB+Amiodaron	BB+Statin		
POAF	No	n	55	66	53	174
		%	68.75	82.50	66.25	72.50
	Yes	n	25	14	27	66
		%	31.25	17.50	33.75	27.50
Total	n	80	80	80	240	
	%	100	100	100	100	

n-absolute number and percentage. POAF-Postoperative atrial fibrillation; BB-beta blocker; BB+Amiodaron; BB+Statin. Pearson Chi-square  $\chi^2=6.14$ , df-2, p=0.046, Cramer's V 0.16. Fisher's 0.040.

Table 2. Incidence ratio of Postoperative atrial fibrillation.

those associated with POAF. With this subanalysis, we found that the cumulative hazard function has the least potential change and is best for the group treated with combination BB+Amiodaron (HR 3.82, HR 3.25, HR 3.89). By comparing the incidence in the treated groups, we established a marginally significant pearson-time rate for the POAF between the second and third groups of BB+Amiodarone and BB+Rosuvastatin, and this difference remained significant when we compared the incidence between the BB+Amiodaron treated group and the other two groups together. By analyzing the experience of events of interest it was clearly demonstrated that in the zero hour all respondents were expected to be in the sinus rhythm. The earliest recorded event of interest (POAF) occurred after 8 h. and 15 min. from group BB+Rosuvastatin, the next was after 9.21h. from group BB, and the longest time to event is 125.7h. he had a patient from the group combination therapy BB+Amio-daron. In the first 24 hours. in the sinus rhythm there were ≈70% of patients at risk (95% CI: 57.07-79.27).

**Length of hospitalization**

The average length of hospitalization was 9 days (minimum 3 and maximum 18 days), and the average length of stay in the intensive care unit (ICU) was 2 days (minimum 1, and maximum of 11 days). The average days (median, min-max) in ICU for patients in sinus rhythm was 1 day (1-14), while for patients with POAF was on average 2 days (1-11). The average length of hospitaliza-

tion for sinus rhythm patients was 9 days (4-16), and for patients with POAF 10 days (3-19), which in both cases was also statistically significant,  $p=0.0001$ .

## 5. DISCUSSION

According to the ESC recommendations, the prophylactic usage of BBs is recommended for the patients who are directed to cardiac surgery with moderate risk, except in cases when the BBs are contraindicated. In high-risk patients it is reasonable to use Amiodarone as prophylactic therapy (4). In a PAPABEAR study, the patients were randomized on either oral placebo or Amiodarone, starting with Amiodarone therapy 6 days before CABG and continuing it up to 6 days post-operatively. More than half of the patients in both groups (58.9% Amiodarone vs. 55.6% placebo) were treated pre-operatively with Beta blockers, this being very similar to our study. The Amiodarone therapy led to the reduction of POAF risk by 52% compared to the placebo (16.1% versus 29.5%,  $p<0.001$ ) while the outcome proportion of our research is 17.5% vs. 31.25%,  $p=0.047$  (5). A study (SPPAF) by Johann Auer et al. focusing on POAF prevention analyzed the effects of certain active oral regimens of pharmacotherapy compared to the placebo. In the group which was treated with Amiodarone plus Metoprolol, POAF incidence was significantly smaller than in the placebo group (30.2% vs 53.8%  $p=0.008$ ). POAF incidence in the group treated only with Metoprolol was similar to the incidence registered in the Placebo group (40.3% vs 53.8%,  $p=0.16$ ). Treatment with only metoprolol resulted in a trend of reduced risk of POAF. The study confirmed earlier guidelines which stated that the high risk patients require combination of drugs, rather than using BBs only (6).

The STICS presented by Zhe Zheng et al. has given recent evidence on the effects of perioperative statin therapy on post-operative complications. Concomitant therapy with BBs was given to 84.7% patients in the treated group and to 83.6% patients in the placebo group. With regards to that, their placebo group matched our BB group, which was our comparator. Their group treated with rosuvastatin matched our group of combined treatment BB+S. Authors Zhe Zhang et al. reported that rosuvastatin was not connected to the lower incidence of POAF compared with the placebo (7).

### Limitations

The research is not a RCT with total blindness control, the comparator is an original tablet, not placebo. This clinical trial was analyzed according to the "intent for treatment" principle, and the basic principle of the purpose of treatment is that research participants should be analyzed in groups in which they were randomized regardless of whether they received or observed specific therapeutic interventions. There was no verification of therapeutic compliance, therefore the restriction of this study is an uncertain therapeutic compliance in the pre-operative application of the assigned treatment. The reason for weaker compliance is partly in late reporting, i.e., calling for surgery without sufficient time to carry out prophylaxis. Some patients were waiting for the term of

the surgery for several months. Also, patients came to the surgery consecutively, which is not a random schedule, so it is quite possible that the more ill patients had a priority. Activities related to the detection, understanding and assessment of undesirable effects of drugs or other problems related to their use were not in the focus of this research, and the data are too modest for more serious analysis. We also did not use a continuous holter monitoring to detect events of interest. Future research should take into account and elaborate models of better prehospital therapeutic compliance and more precise detection of rhythm disorders.

## 6. CONCLUSION

Combination therapy with BB+Amiodarone significantly reduces the incidence of POAF in the population of patients undergoing isolated CABG. Combination therapy with BB+Amiodarone also reduced the appearance of "early" AF. The time to develop the POAF in the group treated with BB+Amiodarone combination is the longest, and peak incidence is shifted from the second to the third postoperative day when the patient is clinically significantly more stable. The length of hospitalization is significantly longer in patients who develop POAF, including a longer stay in the intensive care unit, and also considerably higher costs of treatment are associated with this group of patients.

- Author's contribution: E.O. gave substantial contribution to the conception or design of the work and in the acquisition, analysis and interpretation of data for the work. M.O., S.A., S.D., A.D., N.K., A.T. and A.A. had role in drafting the work and revising it critically for important intellectual content. Each authors gave final approval of the version to be published and they agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
- Conflicts of interest: There are no conflicts of interest.
- Financial support and sponsorship: None.

## REFERENCES

1. Suresh G Nair. Atrial fibrillation after cardiac surgery. *Ann Card Anaesth*. 2010; 13: 3.
2. Patel D, Gillinov MA, Natale A. Atrial Fibrillation after Cardiac Surgery: Where are we now? *Indian Pacing Electrophysiol J*. 2008; 8: 281-291.
3. Reynolds MR, Essebag V, Zimetbaum P, Cohen DJ. Healthcare resource utilization and costs associated with recurrent episodes of atrial fibrillation: the FRACTAL registry. *J Cardiovasc Electrophysiol*. 2007; 18: 628-633.
4. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Europace*; 2016; 18.
5. Mitchell LB, Exner D V, Wyse DG, Connolly CJ, Prystai GD, Bayes AJ, et al. Prophylactic Oral Amiodarone for the Prevention of Arrhythmias that Begin Early After Revascularization, Valve Replacement, or Repair: PAPABEAR: a randomized controlled trial. *Jama J Am Med Assoc*. 2005; 294: 3093-3100.
6. Auer J, Weber T, Berent R, Puschmann R, Hartl P, Ng CK, et al. A comparison between oral antiarrhythmic drugs in the prevention of atrial fibrillation after cardiac surgery: the pilot study of prevention of postoperative atrial fibrillation (SPPAF), a randomized, placebo-controlled trial. *Am Heart J*. 2004 Apr; 147(4): 636-643.
7. Zheng Z, Jayaram R, Jiang L, Emberson J, Zhao Y, Li Q, et al. Perioperative Rosuvastatin in Cardiac Surgery. *N Engl J Med*. 2016 May 5; 374(18): 1744-1753.