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Research Article

Low-dose Amiodarone in Prophylaxis of Atrial Fibrillation After Isolated On-pump Coronary Artery Bypass Surgery in Patients with Risk Factors for the Development of Postoperative Atrial Fibrillation

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Abstract

Objective: Atrial fibrillation (AFib) is the most common arrhythmia complicating cardiac surgery and remains common despite improvements in surgical techniques and perioperative management. Due to its high risk for significant morbidity and mortality, AFib prophylaxis is very important to improve outcomes. The purpose of this study was to investigate the efficacy of lower-dose oral Amiodarone therapy protocol for the prevention of Postoperative Atrial fibrillation (POAF) in patient undergoing on-pump isolated Coronary Artery By-pass Grafting (CABG) with risk factors for the development of postoperative atrial fibrillation (POAF).

Methods: To investigate the role of lower - dose Amiodarone therapy for the prevention of POAF in high-risk patients, we conducted a prospective, randomized, placebo-controlled, single blind study. 120 male patients, aged 65 years and older and with EF≤40% who underwent elective and initial isolated CABG were enrolled in this study. Patient in the treatment group received oral Amiodarone, 2.4 g over 3 preoperative days, followed by 200 mg once daily regimen, for at least 6 days postoperatively.

Results: The incidence of POAF in the in the Amiodarone -treated group was significantly lower compared to the control group (18,3% vs 38,3% p = 0.015), with a Relative Risk of 0.48 times (95% CI: 0.26-0.89) and an estimated Number- Needed -to- Treat of 5 patients to prevent one additional case of POAF. The overall Intensive Care Unit (ICU) and hospital Length of stay (LOS) was significantly lower in the Amiodarone group compared to the control group (48 ± 9.1 vs 55 ± 15.4, p = 0.003 and 7.5 ± 0.99 vs 8.2 ± 1.4, p = 0.002, respectively). Patients who developed POAF in the Amiodarone group compared to the control group had a significant lower duration of Afib (18.2 ± 4.9 vs 36.6 ± 8.1, p = 0.001) and a significant lower ventricular rate (71.1 ± 2.7 vs 93.9 ± 8.6, p = 0.001).

Conclusion: Lower dose of oral Amiodarone therapy, resulted in effective for the prevention of POAF in the patient population aged 65 years and older, with EF≤40%, who underwent on-pump isolated elective CABG. This beneficial effect in the reduction of POAF incidence and duration is associated with significant shorter ICU and hospital LOS in the Amiodarone treated group and is achieved without adverse effects.

Keywords: Atrial Fibrillation; Post-op; Prevention; Cardiac Surgery; Amiodarone

Introduction

Atrial fibrillation (AFib) is the most common arrhythmia complicating cardiac surgery with no relevant decrease in incidence despite substantial improvements in surgical techniques and perioperative management. The reported incidence is between 10% and 50% [1-3].

Post-operative atrial fibrillation (POAF) typically develops within the first week after surgery. with a peak incidence between postoperative day 2 and 4 [1,2]. Different factors that can contribute to POAF range from perioperative use of catecholamines or increased sympathetic outflow from volume loss or anemia, metabolic alterations, such as hypo-/hyperglycemia and electrolyte disturbances. Moreover, inflammation, both systemic and local, may play a role in its pathogenesis.

Patients who develop postoperative atrial fibrillation are prone to prolonged hospitalization, increased length of stay (LOS) in the intensive care unit (ICU), [4,5] and increased risk of early and late mortality and morbidity [6].

Postoperative occurrence of AFib after isolated CABG is multifactorial and as such, several clinical and biochemical factors have been implicated as risk factors. These risk factors can be generally divided in intrinsic, patient related, mostly unmodifiable risk factors and transitory risk factors mainly related to intervention. The mostly identified risk factors included in the first group are: advanced age, decreased left ventricular function, prior history of AFib, congestive heart failure, left atrial enlargement, chronic obstructive pulmonary disease, thyroid dysfunction, diabetes. Meanwhile the mostly identified risk factors in the second group include postoperative withdrawal of β-adrenergic blockade, longer aortic cross clamping (AXC) and Cardiopulmonary bypass (CBP) time, myocardial ischemia and reperfusion, postoperative myocardial infarction, right coronary artery disease, local inflammatory reaction, metabolic disorder, excessive catecholamine, electrolyte imbalance, blood transfusion [2-4,7-13].

Older age is of particular importance as a risk factor for POAF development with a demonstrated higher risk in patients 60 years and older and with e 75% increase in the odds of developing POAF for each decade [7-11,14].

Prophylactic use of Amiodarone has been shown to decrease the incidence of POAF in deferent studies with different treatment protocols [14-17], Amiodarone blocks potassium currents that cause repolarization of the heart muscle during the third phase of the cardiac action potential. At times, it can be used to treat life threatening arrhythmias like ventricular arrhythmias. It is usually given when other medication was deemed unsuccessful in treating heart conditions.

A very appealing protocol that has shown efficacy lately is the low-dose protocol that consists of oral amiodarone 5 mg/kg/day for 6 days before and 6 days after surgery in a study that enrolled 150 patients that underwent CABG surgery [48].

Meanwhile low-dose protocols using a total of 2 g of amiodarone given over the first two postoperative days have shown modest to no efficacy [18,19]. The above listed studies [14-17] demonstrate beneficial effect of Amiodarone therapy in dosage higher than 3000 mg. European Society of Cardiology (ESC) guidelines for the diagnosis and management of atrial fibrillation in 2020, suggest that lower cumulative doses of amiodarone, <3000 mg, could be effective with less adverse effects [20]. Risks are substantial with high dose amiodarone like changes in heart rhythm and QT prolongation. Therefore, in medical settings, low dose amiodarone is usually preferred. Meanwhile although the proven efficacy, protocols investigating longer duration of treatment preoperatively [14,15], in daily practice, pose the risk of patients' treatment adherence interfering with the results.

This study is aimed to investigate the prophylactic effect of lower-dose Amiodarone, administered orally, initiating three days before surgery and continuing postoperatively, in patients who underwent initial elective isolated on pump Cardiac surgery and who are at Increased risk to develop POAF due to older age and decrease LV contractility. Amiodarone was administered in addition to B-blocker therapy in order to avoid adverse effect of b-blocker withdrawal. Especially in this subgroup of patients, due to limitations in use and dosage of Beta blocker, the expected beneficial effect of Amiodarone therapy was assumed to be relevant.

Methods

To investigate the role of lower - dose Amiodarone in the prevention of POAF in high-risk patients, we conducted a prospective, randomized, placebo-controlled, single blind study.

120 consecutive patients aged 65 years and older and with EF < = 40% who underwent elective and initial Isolated on-pump CABG operations in University Hospital Centre Mother Tereza (year, month, country) were enrolled in this study. We must note that the medical history of each patient was identified, and each case was confirmed.

Exclusion criteria included: history of atrial fibrillation, concomitant valve surgery, redo coronary artery surgery, emergency CABG, Heart rate less than 50/min, history of prolonged QT interval on amiodarone, history of amiodarone allergy or toxicity, chronic use of Amiodarone, thyroid dysfunctions, patients on hemodialysis.

Candidates that met the criteria were continuously enrolled and randomly divided in two equal groups. To produce the random numbers a randomizing computer program was used. All the patients were in sinus rhythm preoperatively.

For sample size calculation the following criteria were met: - Allocation ratio 1:1, 95% level of confidence, 90% power. The presumed Afib incidence in each group was 25% and 53% respectively, based on the results of a relevant previous study that showed efficacy of prophylactic Amiodarone treatment, given orally, initiated preoperatively [22].

The following formula is used for sample size calculation [24]:

$$n = (Z_{\alpha/2}+Z_{\beta})^2 * (p_1(1-p_1) + p_2(1-p_2))/(p_1-p_2)^2$$

Patients were assigned into two equal groups, the placebo and the amiodarone group. The patients of the Amiodarone group were administered 2.4 g oral Amiodarone, over 3 consecutive preoperative days, just before surgery, 400 mg twice daily, followed by 200 mg once daily postoperative regimen, up to the day of discharge, for at least 6 days. Patients in both groups, unless contraindicated, were under treatment with a B-blocker and additional conventional treatment of Heart failure with reduced ejection fraction (HFrEF): Angiotensin converting enzyme inhibitor (ACEi)/Angiotensin receptor blocker (ARB); Mineralocorticoid receptor antagonist (MRA). Amiodarone was administered in addition to the B-blockers, ACEi/ARBs, MRAs and Statins

The preoperative clinical characteristics of both groups are summarized in table 1 (Control group consists of patients with comorbidities that did not receive treatment with amiodarone post operatively).

Variables	Amiodarone n = 60(%)	Control n = 60(%)	P-value ƚ
Age	69.6 ± 3.4	70.0 ± 3.7	0.54*
Male sex	36 (60)	41(68.3)	0.34
Past history			
*Recent MI	28(46.6)	31(51.6)	0.58
Hypertension	48(80)	45(75)	0.51
Diabetes mellitus	19(31.6)	22(36.6)	0.56
Hypercholesterolemia	33(55)	38(63.3)	0.35
*COPD	9(15)	11(18,3)	0,62
*Moderate renal impairment	17(28.3)	19(31.7)	0.69
*Severe renal impairment	4(6.7)	5(8.3)	0.73
Nyha grade 3	34(56.6)	38(63.3)	0.46
Nyha grade 4	13(21.6)	10(16.6)	0.49
Perioperative drugs			

Beta-blockers	57(95)	58(96.6)	0.65
ACEi/ARBs	55(91.6)	53(88.3)	0.54
MRAs	53(88.3)	50(83.3)	0.43
Statins	59(98.3)	57(95)	0.31
Preoperative echo			
LVEF (%)	37.7 ± 2.6	37.4 ± 2,45	0.517*
*Moderate PHT	35(58.3)	33(55)	0.71
*Severe PHT	6(10)	9(15)	0.41
*RV dysfunction	24(40)	28(46.6)	0.46
*LA enlargement	33(55)	35(58.3)	0.71
Number of diseased vessels			
Single	2(3.3)	4(6.6)	0.40
Double	14(23.3)	11(18.3)	0.50
Triple	44 (73.3)	45(75)	0.83
LMT disease	15 (25)	19(31.6)	0.42
RCA disease	52(86.6)	50 (83,3)	0.61

Table 1: Preoperative characteristics of patients.

Values are presented as mean ± standard deviation or percent of patients.

ɫ Chi-square test, *t-test.

ACEi - Angiotensin Converting Enzyme Inhibitor; ARB - Angiotensin Receptor Blocker; COPD - Chronic Obstructive Pulmonary Disease; LA - Left Atrium; LMT - Left Main Trunk; LVEF - Left Ventricular Ejection fraction as calculated mainly by transthoracic echocardiography or cineangiography; MI - Myocardial Infarction; MRA - Mineralocorticoid Receptor Antagonist; Pts - Patients; RCA - Right Coronary Artery, RV - Right Ventricle.

*Recent MI - Within 90 days before operation; *COPD-long term use of corticosteroids and bronchodilators, *Moderate renal impairment-Creatinine clearance (CC) 50-85 ml/min *Severe renal impairment-CC < 50 ml/min *Moderate PHT - PA pressure 31–55 mmHg *Severe PHT-PA pressure 56 mmHg and above

*RV dysfunction – Tricuspid annular plane excursion (TAPSE)<17 mm and/or Peak systolic velocity of lateral tricuspid annulus in tissue Doppler imaging (PSV) < 9.5 cm/sec. *LA enlargement>34 ml/cm^2.

The same anesthesia and intraoperative protocol were applied in all patients.

All patients received premedication with midazolam and scopolamine. For the maintenance of anesthesia, we used mainly intravenous administration of Fentanyl, Sufentanil or Remifentanil and Propofol sometimes in combination with an inhalable agent such as Sevoflurane.

During Cardiopulmonary Bypass, aortic and right atrial 2-staged cannulation, systemic hypothermia (32°C), anterograde repeated blood cardioplegia, a membrane oxygenator and roller pump were used. Blood flow rate and systemic perfusion pressure were maintained greater than 2.5 L x m^2 x min and 50 mmHg, respectively.

After the surgical procedure accomplishment, patients were taken to the ICU and then transferred to the wards when their hemodynamic and respiratory functions were stable.

Continuous EKG and hemodynamic monitoring, repeated arterial blood sample for blood gasses and potassium levels analysis, were performed throughout the operation and during the intensive care stay.

After discharge from the intensive care unit, for an average of 7 days, a routine 12-lead electrocardiogram was obtained daily for all patients. Additional 12-lead ECG was obtained each time clinical observation suggested arrhythmias or if non-invasive EKG monitoring detected tachycardia or other arrhythmias.

Close monitoring of serum potassium, calcium and magnesium levels was performed to scrupulously avoid any imbalance. Potassium serum levels were kept ≥4 mmol/l, Magnesium levels ≥2 mg/dl.

The primary endpoint of the study was postoperative incidence of AF.

The secondary endpoints were ventricular rate at the onset of atrial fibrillation, presence of scale 3-4 Ehra symptoms, duration of atrial fibrillation, ICU and hospital LOS. Episodes of Amiodarone induced bradycardia and hypotension were registered as well.

Atrial fibrillation diagnosis was established according to the criteria of American Association for Thoracic Surgery (AATS) as well as European Society of Cardiology (ESC) and European Association for Cardio-Thoracic Surgery (EACTS) guidelines [20,21].

Intraoperative and postoperative characteristics of both groups are summarized in table 2.

Variables	Amiodaron n = 60(%)	Control n = 60(%)	P-value ɫ
Number of distal anastomoses	3.2 ± 0.9	3.3 ± 0.9	0.544*
Operation time (min)			
CPB	96.1 ± 22.9	100.8 ± 23,4	0.268*
Aortic cross-clamping	70.5 ± 20.7	73.9 ± 21.0	0.373*
Intraoperative inotropes	37(61,6)	39(65)	0.704
Blood transfusion	20 (33,3)	18(30)	0.695
Extubation time (hours)	4 ± 0.47	3,96 ± 0.61	0.688*
Incidence of postoperative AF	11(18.3)	23(38.3)	0.015
Time to the first episode of POAF (hours)	53.2 ± 15.7	37,3 ± 10.2	0.001*
Hospital stays (days after surgery)	7.5 ± 0.99	8.2 ± 1.4	0.002*
Hospital stays in pts with AFib	8.8 ± 0.75	9.7 ± 0.65	0.001*
LOS in ICU stay (hours after surgery)	48 ± 9.1	55 ± 15.4	0.003*
LOS in ICU in pts with Afib	64.2 ± 6.6	72.8 ± 9.1	0.009*
Duration of atrial fibrillation (hours)	18.2 ± 4.9	36.6 ± 8.1	0.001*
HR during AF	71.1 ± 2.7	93.9 ± 8.6	0.001*

Table 2: Intraoperative and postoperative characteristics of both groups

ɫ Chi-square test, *t-test.

A fib - Atrial Fibrillation; CPB - Cardiopulmonary Bypass; ESS - EHRA Symptom Scale; HR - Heart Rate; ICU - Intensive Care Unit; LOS - Length of Stay; Pts-Patients.

Onset of atrial fibrillation, persisting for greater than 15 minutes or in shorter duration but with clinical symptoms and hemodynamic deterioration, was considered as sufficient criteria for the initiation of treatment.

For the conversion of atrial fibrillation, in hemodynamically stable patients, intravenous amiodarone was administered as follows: 150 mg-300 intravenous over 20 min, followed by 1 mg/min for 6 h, followed by 0.5 mg/min for 18 h not exceeding 1200 mg/24 h until switched to oral therapy [20,25]. In all patients, sinus rhythm was restored within 48 hours.

Statistical analysis

The continuous quantitative variables are presented as mean ± standard deviation. Discrete variables are presented in absolute numbers and percentages. Pearson chi-square test is used to compare the proportions. Student's t-test was used to compare the means between two groups.

The independent contribution of the potential factors involved in the development of POAF was determined by using logistic regression analysis. Odds ratio (OR) and confidence interval (CI) 95% were calculated for each variable.

A p-value less than 5% was considered significant. The statistical analysis was performed using SPSS 25.0.

Results

As shown in table 1, there is no significant difference in preoperative characteristics between the two groups.

The incidence of postoperative AFib was 18.3% (11 patients) in the Amiodarone-treated group and 38.3% (23 patients) in the control group (p-value 0.015).

The incidence of POAF was significantly lower in the Amiodarone group compared to the control group (18.3% vs 38.3%, P = 0.015) with a Relative Risk (RR) of 0.48 times (95% CI: 0.26-0.89) and an estimated Number- Needed -to -Treat (NNT) of 5 patients to prevent one additional case of POAF.

Amiodarone administration did not induce severe bradycardia or hypotension in any of the treated patients.

A statistically significant difference was found between the two groups and between the two subgroups of patients who developed POAF regarding the time of AF onset, length of ICU stays, length of postoperative hospital stays, ventricular rate during AFib, duration of atrial fibrillation, symptoms due to AFib (Table 2).

Patient who developed POAF in the Amiodarone group compared to Control group had significant longer time of onset of AFib (53.2 ± 15.7 vs 37,3 ± 10.2 p = 0.001), significant lower duration of Afib (18.2 ± 4.9 vs 36.6 ± 8.1, p = 0.001), significant lower HR (71.1 ± 2.7 vs 93.9 ± 8.6, p = 0.001), significantly lower LOS in ICU (64.2 ± 6.6 vs 72.8 ± 9.1, p = 0.001) and significantly lower postoperative hospital stay (8.8 ± 0.75 vs 9.7 ± 0.65 p = 0.001). Significantly less patients in the treated group experienced grade 3-4 Ehra scale symptoms during AF compared to the control group (9% vs 9.7 ± 0.65, p = 0.009). The overall ICU and hospital LOS was significantly lower in the Amiodarone group compared to the control group (48 ± 9.1 vs 55 ± 15.4, p = 0.003 and 7.5 ± 0.99 vs 8.2 ± 1.4, p = 0.002, respectively) (Table 2).

Comparison of all patients with and without AFib to identify risk factors for POAF development was performed. Variables included in analyses were those with well-known clinical relevance (Table 3).

Variables	**A Fib(pos), n = 34 (%)**	**A Fib(neg), n = 86 (%)**	**P-value ǂ**
# Age	74.1 ± 2.96	68.1 ± 1.93	0.001*
# Pts ≥ 70y/o	31(91.2)	17(19.7)	0.001
Male sex	24(70.6)	53(61.6)	0.356
Past history			
#Recent MI	24(70.5)	35(40.7)	0.003
Hypertension	28(82)	65(75.6)	0.423
Diabetes mellitus	16(47)	25(29)	0.061
Hypercholesterolemia	24(70.5)	47(54.6)	0.109
#COPD	11(32.3)	9(10.5)	0.004
#Moderate renal impairment	15(44.1)	21(24.4)	0.033
#Severe renal impairment	6(17.6)	3(3.5)	0.008
NYHA grade 3	25(73.5)	47(54.6)	0.057
NYHA grade 4	9(26.5)	14(16.3)	0.201
Preoperative Echo			
#Ef value (%)	35.3 ± 2,7	38.4 ± 1.8	0.001*
#< = 35%	19(55.8)	11(12.8)	0.001
#Moderate PHT	25(73.5)	43(50.0)	0.019

#Severe PHT	9(26.5)	6(6.9)	0.004
#RV dysfunction	20(58.8)	32(37.2)	0.031
#La enlargement	25(73.5)	43(50.0)	0.019
Preoperative drugs			
Beta-blockers	31(91.2)	84(97.7)	0.108
ACEi, ARBs	32(94.1)	76(88.4)	0.344
MRAs	30(88.2)	73(84.9)	0.635
Statins	32(94.1)	78(90.7)	0.541
#Amiodaron	11(32.3)	49(56.9)	0.015
Number of diseased vessels			
Single	1(2.9)	5(5.8)	0.515
Double	7(20.6)	18(20.9)	0.966
Triple	26(76.4)	63(73.2)	0.717
LMT disease	11(32.3)	23(26.7)	0.539
RCA disease	30(88.2)	72(83.7)	0.532
Operation time (min)			
#CPB	87.8 ± 20.8	66.04 ± 17.5	0.001*
#Aortic cross-clamping	115.9 ± 22.7	91.5 ± 19.5	0.001*
Number of distal anastomoses	3.4 ± 0.9	3.2 ± 0.94	0.290*
#Intraoperative inotropes	29(85.3)	47(54.7)	0.017
#Blood transfusion	16(47.0)	22(25.6)	0.022
Hospital stay (days)	9.37 ± 0.8	7.26 ± 0.8	0.001*
ICU stay (hours)	70 ± 9.3	44.4 ± 4.4	0.001*

Table 3: Comparison of All Patients with and without Atrial Fibrillation.

ⱡ Chi-square test, *t-test.

Variables involved in the multivariate analysis.

Abbreviations correspond to those in Tables 1 and 2.

The independent contribution of the potential factors involved in the development of POAF was determined by using logistic regression analysis. All the variables that showed in univariate analysis (#Table 3) a significant correlation with the occurrence of Afib ($p < 0.05$) were included in the analyses. Odds ratio and CI 95% were calculated for each variable (Table 4).

Variables	A Fib(pos), n = 34 (%)	AFib(neg), n = 86 (%)	OD	CI95%	P-value
Pts≥70y/o	31(91.2)	17(19.7)	2.16	1.906-7.203	0.001
Recent MI	24(70.5)	35(40.7)	3.03	1.294-7.105	0.011
COPD	11(32.3)	9(10.5)	1.2	1.111-5.083	0.006
EF< = 35%	19(55.8)	11(12.8)	2.01	1.134-5.551	<0.001
La enlargement	25(73.5)	43(50.0)	2.78	1.112-6.633	0.022
Aortic cross-clamping	115.9 ± 22.7	91.5 ± 19.5	1.45	1.010-3.648	0.032
Intraoperative inotropes	29(85.3)	47(54.7)	4.05	0.981-12.770	0.017
Amiodarone	11(32.4)	49(56.97)	2.7	1.201-6.387	0.017

Table 4: Results of binary logistic regression analysis. Correlation between Afib and identified independent variables.

Binary logistic regression analysis demonstrated a statistically significant correlation between the postoperative development of AFib and the age ≥70 years ($p < 0.001$), recent MI ($p = 0.011$), presence of COPD ($p = 0.006$), EF≤35 ($p < 0.001$), LA enlergement ($p = 0.022$), duration of Aortic cross-clamping ($p = 0.032$), Intraoperative use of Inotrops and Amiodarone therapy ($p = 0.017$).

According to our findings, it can be concluded that:

Patients with age 70 or over are 2.16 times more likely than those younger than 70 to develop POAF (OD = 2.16, CI95%: 1.91-7.20). Patients with recent MI are 3 times more likely than those without recent MI to develope POAF (OD = 3.03, CI95%: 1.29-7.11). Patients with COPD have a 20% increased risk to develope POAF than those without COPD (OD = 1.2, CI95%: 1.11-5.08). Patients with EF 35% or less are 2 times more likely to develop POAF than those with EF over 35% (OD = 2.01, CI95%: 1.13-5.55). Patients with LA enlargement are 2.8 times more likely to develop POAF than those without LA enlargement (OD = 2.78, CI95%: 1.11-6.63) .For every minute increase of AXC time there is a respective 45% increase in risk for POAF. (OD = 1.45, CI95%: 1.01-3.65). Pateints to whom Intraoperative inotrops were administered are 4 times more likely to develop Afib, compared with those without Inotrop use (OD = 4.05 CI 95% 0.981-12.770). Amiodarone treated patients are 2.7 times less likely to develop POAF than untreated patients (OD = 2.7, CI95%: 1.20-6.38).

Age 70 years and over, EF≤35%, longer AXC time, presence of COPD, presence of recent MI, the use of intraoperative inotropes and the absence of Amiodarone treatment were identified as independent risk factors for the development of POAF.

Discussion

New onset atrial fibrillation after isolated CABG is the most common arrhythmia observed postoperatively. The reported incidences of AF after CABG, ranged from 10% to 50% [1-3], with peak incidence between postoperative day 2 and 4 [1,2].

Recently the electrophysiological mechanism of POAF has been studied and compared to conventional persistent non-valvular atrial fibrillation (PNVAF). It has been demonstrated that the focal activity is much less common in POAF than PNVAF [23]. This finding might explain the fact why a proportion of POAF tends to be transitory and self-limited.

Anyway, increasing evidence shows that POAF carries a high risk for significant morbidity and mortality making mandatory the efforts for its prevention and treatment. POAF was demonstrated to be associated with two to four times: increased risk of postoperative stroke in short and long term [4], increased morbidity and hospital stay, increase in all-cause 30-day and 6-month mortality, increased long term cardiovascular mortality and all-cause mortality [4,10,22]. It should be expected that the adverse consequences of postoperative AF including hemodynamic instability, renal complications, infections, prolonged hospital stay are more pronounced in older patients with pre-existing LV dysfunction, which on the other hand are established risk factors for POAF development.

The adverse impact of post-operative atrial fibrillation on neurocognitive outcome after coronary artery bypass graft surgery is shown as well [50].

A wide variety of prophylactic strategies for the prevention of POAF have been evaluated. Well established evidence demonstrates that withdrawal of preoperative beta-blockers in the postoperative period doubles the risk of atrial fibrillation after CABG [29]. The mechanism of POAF involves sympathetic activation, and therefore in our practice, routine preoperative use and early postoperative initiation of B-blockers, to antagonize increased sympathetic activation, is considered a standard approach to reduce the risk of POAF after CABG.

The EACTS guidelines in 2006 [25] recommend several therapies for POAF prevention after cardiac surgery that include B-blockers, Amiodarone, Sotalol, Magnesium, Biatrial pacing. B-blockers are recommended as first line therapy that should routinely be used in all pts undergoing cardiac surgery, no matter when started, unless contraindicated (Grade A recommendation). Meanwhile Amiodarone is recommended for prophylaxis of AF in all patients undergoing cardiac surgery in whom b-blocker therapy is not possible. Amiodarone may also be used in addition to b-blocker therapy for prophylaxis of AF in high-risk patients with an acceptably low incidence of complications.

This Grade A recommendation of Amiodarone is based on Eleven Randomized Controlled Trials (RCTs) and one meta-analysis that were considered to represent the best evidence in this topic. Ten of these RCTs were included in this meta-analysis by Crystal., *et al.* [30] published in 2002, who reported a reduced incidence of AFib from 37% in control groups to 22.5% in the amiodarone groups, OR 0.48 (95% CI, 0.37 to 0.61), with a NNT of seven to prevent an additional case of AFib and an influence on LOS -0.91

day (95% CI, 1.59 to -0.23) Of note, the incidence of complications was low in all these RCTs except of one study by Butler., *et al*. [31], who found a significantly increased rate of bradycardias and pauses in Amiodarone group. Meanwhile the reported studies differ in their protocols with many of them continuing B-blocker use preoperatively.

Another later meta-analysis published in 2006 by Burgess., *et al*. concluded that all five commonly tested interventions, B-blockers, Amiodarone, Sotalol, Magnesium, and atrial pacing, were effective in preventing POAF [29]. Interestingly the effect of B-blocker resulted less than previously demonstrated. It was shown that more than the beneficial effect of B-blocker in reducing the incidence of POAF, is the B-blocker withdrawal that increased the risk of POAF development. Meanwhile results from 18 included trials, that have evaluated Amiodarone for the prevention of POAF with a variety of dosing strategies, demonstrated that Amiodarone reduced AFib incidence from 33.2% in the control group to 19.8% (OR 0.48, 95% CI 0.40-0.57). A significant reduction of VT or VF from 5.2% in the control groups to 2.2% in the amiodarone groups (OR = 0.45, 95% CI: 0.29-0.69) was also observed. The reported adverse effect was the increased incidence of bradycardia in the Amiodarone group (OR = 1.66, 95% CI: 1.73-2.47).

Atrial fibrillation guidelines of Canadian Cardiovascular Society in 2010 recognize the beneficial effect of Beta-blockers, Amiodarone, and intravenous Magnesium therapy in the prevention of POAF while the quality of evidence supporting biatrial pacing and sotalol is considered low, with greater adverse profile in case of Sotalol usage [32].

It is strongly recommended that there be a continuation of b-blocker therapy throughout perioperative procedure in patents who have been receiving b-blockers before cardiac surgery in the absence of the development of a new contraindication. Meanwhile initiation of B-blockers just before or immediately after the operative procedure in the patients who have not been receiving a blocker before cardiac surgery, is only suggested.

It is also strongly recommended to consider prophylactic therapy with amiodarone, before or after cardiac surgery, to prevent postoperative AFib in patients who have a contraindication to B-blocker therapy. The Quality of Evidence under this recommendation is considered high.

This recommendation is mainly based in two meta-analyses. The first being the above-mentioned meta-analysis by Burgess., *et al*. published in 2006 [29]. The other one published in 2006 by Bagshaw SM., *et al*. with 19 placebo controlled RCTs included, that demonstrated similar beneficial effect of Amiodarone in prevention of POAF. (OR = 0.50, 95% CI: 0.43-0.59, P < .0001). Amiodarone therapy was also associated with significant reduction in postoperative ventricular tachyarrhythmias (OR 0.39, 95% CI 0.26-0.58, P <.001), postoperative neurologic events (OR 0.53, 95% CI 0.30-0.92, P = .02), post surgery hospital LOS (0.6 days: 95% CI 0.4-0.8 days, P < .0001), and a reduction in hospital costs [33].

About the optimal timing of Amiodarone therapy initiation, these guidelines underline the results of another meta-analysis by Buckley MS., *et al*. published in 2007 that showed no statistically significant difference in the prevention of postoperative AFib (P = .86) between preoperative, intraoperative or postoperative therapy initiation [34].

These guidelines propose two Amiodarone administration regimens based on two different studies. One, preoperative oral amiodarone 10 mg/kg/d, beginning at day 6 before surgery up to day 6 post surgery [14] and the second, postoperative amiodarone 900-1200 mg intravenously over 24 hrs beginning within 6 hrs of surgery, then 400 mg PO tid each of the next 4 days [17].

A more recent meta-analyses by Arsenault KA., *et al*. published in 2013 [35] that investigated all interventions for preventing post-operative atrial fibrillation in patients undergoing heart surgery also showed that Amiodarone administration was associated with a significant reduction in post-operative atrial fibrillation in the treatment group (19.4%) compared with the control group (33.3%) (OR 0.43; 95% CI 0.34 to 0.54; I2 = 63%;) In this review, were included thirty-three studies, with a total of 5402 participants. Approximately in half of the studies amiodarone administration was initiated pre-operatively and half post-operatively, with variations in Amiodarone dosing regimens and administration route.

Finally, 2020 ESC guidelines recommend perioperative Amiodarone or b-blocker therapy for the prevention of postoperative AF after cardiac surgery [20]. This class I recommendation is based on A level of evidence [36].

In these guidelines it is proclaimed that Amiodarone is the most frequently used drug for prevention of perioperative AFib [37].

These guidelines underline data coming from one meta-analysis, showing that amiodarone (oral or i. V.), and beta-blockers were equally effective in reducing POAF (risk ratio 0.77, 95% confidence interval 0.55 to 1.06, P = 0.11) [38], and one randomized, placebo-controlled pilot study demonstrating that combination was better than beta-blockers alone. In this study patients receiving combination therapy (amiodarone plus metoprolol) a had a significantly lower frequency of AFib, with an absolute difference, 23.6% vs placebo (OR, 0.37, 95% CI, 0.18 to 0.77, P <.01) while treatment with metoprolol alone was associated with a 13.5% absolute reduction of AF (P = .16; OR, 0.58 (0.29 to 1.17 vs placebo) [36].

In these guidelines, it is suggested as well that lower cumulative doses of amiodarone (< 3000mg) could be effective, with the advantage of fewer adverse effects [20].

It has been shown that Amiodarone has a distinctive property in preventing experimentally induced atrial electrical remodeling [39]. It is, as well, an excellent choice for use in patients with structural heart disease or congestive heart failure [20].

Amiodarone is classified as a class III Antiarrhythmic drug (AAD) that prevents or terminates re-entry by prolonging refractoriness in cardiac regions through blocking several different types of K^+ channel [40]. Anyway, it possesses additional antiarrhythmic properties of the three other antiarrhythmic drug classes. Amiodarone exerts Class I effect by blocking sodium channels that reduces conduction velocity, Class II effect by antagonizing non-competitively α and β adrenergic receptors and Class IV antiarrhythmic effect by acting as a calcium channel blocker [41]. Considering his special pharmacokinetics properties, dosing and route of administration have significant role on the bioavailability and effects of amiodarone. The immediate effects of intravenous amiodarone loading are mainly due to β-receptor, calcium and sodium channel blockade. The class III effect, that is property of the active metabolite desethylamiodarone and depends on its levels, is achieved after completion of the loading dose [42].

Amiodarone is associated with both cardiovascular and non-cardiovascular adverse events; the majority being related to the doze and duration of drug exposure. The most frequent cardiovascular side effect is bradycardia that can be attenuated by dose reduction [43]. Other less frequent cardiovascular side effect is hypotension and atrioventricular block mainly manifested with intravenous loading administrations [20]. QTc prolongation, due to the potassium-channel blockade, is common and might be an early manifestation in intravenous loading, but rarely associated with torsades de pointes (< 0.5%) [20].

Amiodarone might cause hyper or hypothyroidism, the latter occurring in up to 20% of patients taking amiodarone, generally being easily managed with no need for amiodarone discontinuation [44]. Meanwhile, pulmonary toxicity which is one of the most serious complications of amiodarone use, occurs < 3% of patients and is related to the total cumulative dosage [24].

Since the first major randomized trial performed in 1997 by Daoud., *et al*. [51], showing that Amiodarone given 1 week before cardiac surgery (CABG, Valve, CABG-Valve operations) at a dose of 600 mg daily, followed by 200 mg postoperative daily dose during hospital stay, reduced the rate of hospital POAF from 53% to 25%, and reduced the rate of POAF after discharge from 12% to 2%, various other trials have investigated the beneficial role of oral Amiodarone therapy [14-16].

There was a consistency in demonstrating Amiodarone therapy's significant efficacy for the prevention of POAF (29.5% placebo group vs 16.1% amiodarone group [14]; 38% placebo group vs 22.5% amiodarone group [15]; 85% placebo group vs. 34% amiodarone group [16]) along with a reduction of AFib duration, ventricular response rate during Afib, Hospital LOS, with no or low reported adverse effect and no required therapy discontinuation [14-16]. This beneficial effect was observed throughout different age groups, different cardiac interventions, with or without concomitant use of B-blockers [14] and in preselected patients with higher risk for POAF development [16]. In one study dosage reductions of blinded therapy were more common in amiodarone patients than in placebo patients (11.4% vs 5.3) [14]. A significant reduction of postoperative sustained ventricular tachyarrhythmias rates by amiodarone (0.3% vs. 2.6%). was reported as well [14].

As mentioned above actual evidence finds no superiority of a certain timing of Amiodarone therapy initiation or administration route [34]. Beneficial effect of Amiodarone in POAF prevention along with reduced Hospital LOS, was also reported in studies where amiodarone therapy was initiated intravenously in the operating room or early after intervention followed by a period of Amiodarone therapy given orally [17,45].

Actual evidence also shows that total amiodarone dosage of 3000 mg or higher may be more effective than lower doses in reducing the rate of postoperative atrial fibrillation after cardiac surgery. In fact, in two low-dose protocols using a total Amiodarone dose of 2 g, given intravenously over the first two postoperative days, one resulted in a more modest reduction of POAF incidence, compared with other protocols, from 47% in the placebo group to 35% in the amiodarone group [18] the other showed no significant reduction in POAF [19].

Hence, we see that there is a large body of data that demonstrates the benefits and cost-effectiveness of Amiodarone therapy in POAF prophylaxis with trials consistently demonstrating a reduction in intensive care and overall hospital LOS, with very low rates of adverse side effects that would mandate discontinuation of amiodarone when used for prophylaxis. Anyway, oral use of amiodarone can afford hemodynamic benefits.

It should be underlined that the goal of a short treatment course of amiodarone in cardiac surgery, is not to treat chronic AFib, but to prevent the new-onset POAF that has a deleterious impact in the patient's morbidity and mortality. This is especially true in the subsets of older patients, with reduced ejection fraction and other co morbidities which are risk factors for the development of POAF. This beneficial effect of amiodarone, in the case of POAF, is achieved from its Class I through IV antiarrhythmic properties, particularly due to its action as a beta-blocker and calcium channel blocker.

As previously mentioned, several factors have been implicated as risk factors for the development of POAF. These risk factors can be generally divided into patient related unmodifiable risk factors and transitory risk factors mainly related to intervention [2-4,7-13].

The most recent meta-analysis that studied the clinical risk factors for postoperative atrial fibrillation among patients after cardiac surgery is published in 2019 by Yamashita K., *et al*. [12], and included 24 studies published from 2001 to May 2017, with a total number of 36,834 subjects. It was shown that standardized mean difference (SMD) between POAF and non-POAF groups was significantly different for age (0.55, 95% CI: 0.47-0.63), left atrial diameter (0.45, 95%CI: 0.15-0.75), and left ventricular ejection fraction (0.30; 95% CI: 0.14-0.47). The pooled odds ratios (ORs) demonstrated that heart failure (1.56: 1.31-1.96), chronic obstructive pulmonary disease (1.36: 1.13-1.64), hypertension (1.29: 1.12-1.48), and myocardial infarction (1.18: 1.05-1.34) were significant predictors of POAF incidence.

Older age is of particular importance as a risk factor for POAF development [7-12] with a 75% increase in the odds of developing POAF for each decade shown in one study [10] and with a significant older age of patient who developed POAF vs those who did not, shown in another study (66.1 ± 11.5 years vs 58.7 ± 13.5 years, P < .0001) [5].

In our daily clinical practice, we have identified age 65 and above as an independent risk factor for POAF development. In one study investigating Amiodarone efficacy in POAF prevention also through different age groups, a cut off from 65 y/o was used to divide two age groups that pose different risk [14]. A risk stratification algorithm, for preventive treatment initiation in patients 65yo and older with an additional risk factor, is proposed by one author as well [49].

The European Association of Cardiothoracic Surgery (EACTS) guidelines, for the treatment and prevention of POAF published in 2006 recommend that Off-pump CABG reduces the incidence of AFib compared with conventional (on-pump) CABG with a grade A evidence based on level 1a and level 1b studies [25]. More recent evidence shows similar rates of POAF with on-pump CABG and off-pump CABG [26], but longer cross clamp time is demonstrated as a risk factor for POAF development (RR, 1.3; P = 0.001) [7].

There is a rationale under the conviction that CPB is a risk factor for POAF development. During CABG with CBP, cardioplegic perfusion is intermittently discontinued for distal anastomosis construction. This might lead to myocardial ischemic injury and ischemic reperfusion injury-induced atrial/ventricular arrhythmias. Cardioplegia content and its pattern of administration, duration of CPB, duration of AXC, insufficient right atrial protection with consecutive atrial infarction are added risk factors related to CPB [28].

Evidence further supports beneficial effect of Amiodarone and B blockers combination [15,17,30,36] and suggests that combination therapy, even with less confirmed medication in the prevention of POAF, is more effective than either agent alone [39]. On the other hand, studies investigating anti arrhythmic properties of non-antiarrhythmic drugs like Statins and ACEi/ARBs in POAF prevention have shown significant efficacy of statin therapy [46] and modest effect of ACEi//ARBs [47].

Our study demonstrated a significant reduction of POAF in the in the Amiodarone-treated group compared with control group (18.3% vs 38.3% p = 0.015), with a RR of 0.48 times (95% CI: 0.26-0.89) and an estimated NNT of 5 patients to prevent one additional case of POAF.

This significant beneficial effect in the prevention of POAF is achieved with administration of lower dose Amiodarone, given orally, started three days before surgery and continuing for 6 days post-surgery. A total Amiodarone dose of 3600 mg, 2400 mg in preoperative period and 1200 mg in postoperative period is administered. Despite suggestions for lower (< 3000 mg) cumulative dose protocols to avoid adverse events [20], to the best of our knowledge the two lowest Amiodarone dosage protocols that have demonstrated efficacy are oral amiodarone 5 mg/kg/day for 6 days before and 6 days after surgery [48] in 150 patients that underwent CABG surgery and continuous infusion protocol initiated at the time of induction of anesthesia, for 96 hours with a total dose 4200 mg in 80 patients that underwent transthoracic esophagectomy.

In our study this significant beneficial effect of lower Amiodarone dose protocol is achieved in preselected patients with higher risk for development of POAF due to older age, decreased LV function and on -pump CABG surgery.

POAF was significantly prevented by Amiodarone, without significant adverse effect. No case of significant bradycardia or hypotension was reported, and no interruption of Amiodarone therapy was needed. We sidestepped incorporation of intravenous administration of Amiodarone in our protocol to avoid any hemodynamic deterioration attributed mainly to its calcium channel blocker effect, especially in the subset of patients with decreased LV contractility.

Amiodaron was used in addition to conventional HF therapy unless contraindications, in combination with B-blockers with well-established evidence for the prevention of POAF and ACEi/ARB, MRAs and Statins all medications discussed as non-arrhythmic drug with antiarrhythmic properties. Although no significant correlation between these drugs and POAF prevention was found in our study, evidence suggests, as mentioned above, superiority of combination compared to monotherapy.

Prevention of POAF, especially in the population of patients with LV systolic dysfunction, which on the other hand is a risk factor for POAF development, is crucial due to the detrimental hemodynamic consequences of AFib in these patients. Meanwhile Amiodarone is an excellent choice for patients with decreased LV contractility, while there are limited possibilities in B-blocker dose increase when needed. Thereby, the described beneficial effect in this category of patients is more than relevant.

In our study, absence of Amiodarone therapy resulted as an independent risk factor for the development of POAF. Other identified risk factors were recent MI, COPD, Left Atrial enlargement, duration of Ao Cross-Clamping, intraoperative use of Inotropes. Age 70 years and above and EF≤ 35% pose an additional risk for POAF development and both were found to be independent risk factors as well.

Conclusion

In conclusion, lower cumulative dose of oral Amiodarone therapy, resulted effective for the prevention of POAF in the patient population aged 65 years and older, with EF≤40%, who underwent on-pump isolated elective CABG. This beneficial effect in the reduction of POAF incidence and duration is associated with significant shorter ICU and hospital LOS in the Amiodarone treated group and is achieved without adverse effects.

The patient population sample size of the study is relatively small, which is a limitation of this study. Larger randomized controlled studies are needed to evaluate the lowest efficacious Amiodarone dose and the optimal therapy duration needed for POAF prevention in patients with risk factors for POAF development.

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