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Nebivolol in preventing atrial fibrillation following coronary surgery in patients over 60 years of age

Nebivolol na prevenção da fibrilação atrial após a cirurgia coronária em pacientes acima de 60 anos de idade

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Abstract

Objective: Postoperative atrial fibrillation is a common complication after cardiac surgery, with an incidence as high as 20-50%. Increased age is associated with a significant increase in postoperative atrial fibrillation risk. This common complication is associated with higher morbidity and mortality rates. The aim of this study was to assess the efficacy of nebivolol in preventing atrial fibrillation following coronary artery bypass surgery in patients over 60 years of age.

Methods: In this prospective randomized study, 200 patients who were candidates for elective coronary artery bypass surgery were divided into two groups. The first group was administered with nebivolol and the second group was administered with metoprolol. Treatment was initiated four days prior to surgery, and patients were monitored for atrial fibrillation until discharge. Forty-one patients received 50 mg metoprolol succinate daily, which was initiated minimum 4 days before surgery.

Results: Demographic data were similar in both groups. The incidence of postoperative atrial fibrillation in both groups was similar, with no significant difference being identified [$n=20$ (20%); $n=18$ (18%), $P=0.718$; respectively]. There were not any mortality at both groups during study. Inotropic agent

requirement at ICU was similar for both groups [$n=12$ (12%), $n=18$ (18%), $P=0.32$].

Conclusion: We compared the effectiveness of nebivolol and metoprolol in decreasing the incidence of postoperative atrial fibrillation, and determined that nebivolol was as effective as metoprolol in preventing postoperative atrial fibrillation at patients. Nebivolol may be the drug of choice due to its effects, especially after elective coronary artery bypass surgery.

Descriptors: Coronary Artery Bypass. Atrial Fibrillation. Anti-Arrhythmia Agents. Drug Therapy.

Resumo

Objetivo: Pós-operatório fibrilação atrial é uma complicação comum após a cirurgia cardíaca, com uma incidência tão elevada quanto 20-50%. O aumento da idade está associado com elevação significativa no risco de pós-operatório da fibrilação atrial. Esta complicação comum é associada com taxas de morbidade e mortalidade. O objetivo deste estudo foi avaliar a eficácia do nebivolol na prevenção da fibrilação atrial após cirurgia de revascularização do miocárdio de pacientes acima de 60 anos de idade.

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Abbreviations, acronyms & symbols	
AF	Atrial fibrillation
CPB	Cardiopulmonary bypass
DVT	Deep vein thrombosis
ECG	Electrocardiogram
EuroSCORE	(European) System For Cardiac Operative Risk Evaluation Score
ICU	Intensive care unit
LMCA	Left main coronary artery
MI	Myocardial infarction
POAF	Postoperative atrial fibrillation

Métodos: Neste estudo prospectivo e randomizado, duzentos pacientes candidatos à cirurgia de revascularização do miocárdio foram divididos em dois grupos. O primeiro grupo foi administrado com nebivolol e o segundo grupo, com metoprolol. O tratamento foi iniciado quatro dias antes da cirurgia, e os pacientes foram monitorados para fibrilação atrial até a alta. Quarenta e um

pacientes receberam 50 mg de sucinato de metoprolol diário, que foi iniciado, no mínimo, 4 dias antes da cirurgia.

Resultados: Os dados demográficos foram semelhantes nos dois grupos. A incidência de fibrilação atrial pós-operatória em ambos os grupos foi semelhante, com nenhuma diferença significativa sendo identificado [n=20 (20%); n=18 (18%), $P=0,718$; respectivamente]. Não houve mortalidade em ambos os grupos durante o estudo. A necessidade de agente inotrópico em UTI foi semelhante nos dois grupos [n=12 pessoas (12%), n=18 (18%), $P=0,32$].

Conclusão: Nós comparamos a eficácia do nebivolol e metoprolol na diminuição da incidência de fibrilação atrial no pós-operatório, e verificamos que nebivolol foi tão eficaz como metoprolol na prevenção de fibrilação atrial no pós-operatório em pacientes. Nebivolol pode ser a droga de escolha devido aos seus efeitos, especialmente depois da cirurgia revascularização do miocárdio.

Descritores: Ponte de Artéria Coronária. Fibrilação Atrial. Antiarrítmicos. Quimioterapia.

INTRODUCTION

Postoperative atrial fibrillation (POAF) is a commonly observed complication following cardiac surgery, with an incidence as high as 20-50% depending on the accepted definition of POAF and the methods used for detection^[1,2]. Increasing age in patients undergoing cardiac surgery is associated with a significant increase in POAF risk^[2,3]. This common complication contributes to higher morbidity and mortality rates among patients. Major outcomes associated with POAF include an increased incidence of stroke, longer hospitalization, increased hospital costs, and higher early and late mortality rates^[1,4,5].

Prophylactic treatment is recommended due to the high incidence of POAF, especially if risk factors are present. Effective preventive and treatment strategies are important for reducing the undesirable effects of this complication. It has been previously demonstrated in several studies that beta-blockers are effective agents for preventing POAF. Beta-blockers have also been recommended for POAF prophylaxis in several meta-analyses^[6,7]. Nebivolol is a selective beta-1 adrenergic receptor antagonist that differs from conventional beta-blockers in its ability to induce nitric oxide synthesis in the human endothelium. Teplakov et al.^[8] showed that nebivolol administration (1.25-5.0 mg/day) increased exercise tolerance, improved life quality, reduced IR index by 11.9%, and reduced triglyceride levels by 5.3% (which in turn lowered the risk of effects associated with diabetic atherogenic dyslipidemia).

In this prospective randomized study, we investigated the effectiveness of nebivolol and metoprolol in decreasing the incidence of POAF. Patients in this study were selected among individuals above 60 years of age, as age is a major risk factor for POAF. There are no other studies in the literature regarding the effects of nebivolol in preventing POAF.

METHODS

Following the approval of the Medical Faculty's Ethics Committee (Reference Number: 2009/145), and after written informed consents were obtained from the patients; 200 patients over 60 years of age with coronary artery disease, who had been admitted to our clinic for elective coronary artery bypass grafting surgery, were included into our study.

The study was performed according to a randomized, prospective, parallel-group, active controlled, open-label, single-blind study design. The patients were randomized into two groups, and the study procedures were carried out for a period of 4 days. All included patients were from an inpatient setting. Study subjects were randomly allocated into the NEB and MET treatment groups at the beginning of the study by using a random number generated by SAS.

The patients were not stratified according to race and sex during the randomization process, which led to an unequal distribution of males and females between the two groups. At the beginning of the study 100 subjects were recruited in each group. Due to the withdrawal of consent, lost to follow-up and missing values of some outcome variables, the final sample size was 100 in the NEB group and 100 in the MET group.

Group 1 was the nebivolol group, consisting of 100 patients (27 women and 73 men, mean age 67.2 ± 7.6), while Group 2 was the metoprolol group, also consisting of 100 patients (34 women and 67 men, mean age 68.4 ± 5.8). Patients who had previous beta-blocker or antiarrhythmic treatment, previous atrial fibrillation (AF), heart failure (ejection fraction $\leq 35\%$), sick sinus syndrome, atrioventricular block, permanent pacemaker, valvular surgery, peripheral vascular disease, hyperthyroidism, and emergency surgery were excluded from the study. In both groups, drugs use was started 4 days prior to surgery^[9].

Metoprolol was administered once daily at a dose of 50 mg, while nebivolol was administered once daily at a dose of 5 mg. Drug use was continued after extubation during the postoperative period. Dosages were adjusted according to the hemodynamic responses of the patients after coronary surgery. None of the patients withdrew from study due to the side effects of the drugs.

Data was collected at the time of hospitalization, during the first postoperative day, and at the time of discharge. The primary end point of the study was new-onset AF until discharge. None of the patients in both groups presented serious bradycardia or hypotension. Atrial fibrillation was diagnosed when 12-lead ECG showed rapid oscillations or fibrillatory *P* waves that varied in size, shape, and timing, and which were associated with irregular QRS complexes.

In this study, POAF was defined as AF of any duration during the postoperative period, with the AF diagnosis being based on the physician's assessments. All Holter and ECG data were evaluated by two blinded cardiologists, and AF diagnosis was confirmed with the observation of (i) absent *P* wave prior to QRS complex, and (ii) irregular ventricular rhythm that continued for more than 5 minutes. In the event that POAF was identified, no further evaluations were performed, and the patient was started on an administration of amiodarone at a 150 mg bolus dose, followed by administration at 15 mg/kg/24 h infusion. After sinus rhythm was achieved, the patient's treatment was continued with oral amiodarone administration for a period of 30 days, with a 800 mg/day dose being administered during week 1, a 600 mg/day dose during week 2, a 400 mg/day dose during week 3, and a 200 mg/day dose during week 4.

ECG and 12-lead ECG were needed to confirm the 12-lead ECG findings. Patients who developed AF were treated with a standard protocol of anticoagulation and amiodarone. None of patients who developed AF required electrical cardioversion. All of the patients were discharged from the hospital with a sinus rhythm.

Statistical analysis

Data were analyzed using the Statistical Package for Social Sciences 16.0 (SPSS 16.0) for Windows (SPSS Inc., Chicago, IL). Data for patient characteristics and outcomes were expressed either as percentage of total or as mean±SD. The independent samples *t*-test was used for normally distributed continuous variables (expressed as mean±SD), while the Pearson chi-square, Yates' corrected chi-square and Fisher's exact tests were used for categorical variables, where applicable. The Mann Whitney U test was used for continuous variables such as age, BMI and EuroSCORE, which were not normally distributed. The results were assessed within 95% confidence, and a value of *P*<0.05 was considered as statistically significant.

Surgical Procedure

Patients were placed under general anesthesia, and conventional median sternotomy was performed. Each patient underwent on-pump coronary artery bypass grafting surgery,

and cardiopulmonary bypass was established by cannulating the ascending aorta and right atrium. Heparin (3 mg/kg) was administered for anticoagulation. Activated clotting time was maintained for longer than 450 seconds, and a roller pump and non-pulsatile flow (2.4 L/m²/min) were used.

The body was cooled to a core temperature between 32°C and 34°C when performing distal anastomosis, and the body was rewarmed to 36°C before weaning from cardiopulmonary bypass. Cold blood cardioplegia was delivered intermittently via antegrade and retrograde routes throughout the procedure. A final dose of "hot-shot" cardioplegia was delivered intermittently via antegrade and retrograde routes throughout the procedure. A final dose of "hot-shot" cardioplegia was administered immediately before the aorta was unclamped. An epicardial temporary pacemaker lead (FLEXON 3-0 temporary cardiac pacing lead, Syneture, Covidien, US) was placed on the right ventricle. Details of the surgical techniques used for complete revascularization solely by means of arterial grafts have been previously described^[10].

The same protocol was applied for each case in which radial artery was used. Radial-artery harvesting was carried out simultaneously with left internal thoracic artery harvesting. Saphenous veins were harvested using conventional methods. The choice of graft material was left to the surgeon, but certain protocols were followed. Left internal thoracic artery was generally used as a graft for the left anterior descending artery; radial artery and saphenous vein graft conduits were used mainly to bypass vessels other than the left anterior descending artery; and only radial artery conduits were used to bypass vessels other than the left anterior descending artery in case they exhibited more than 70% stenosis.

Outcome parameters

A prospective study was performed for the relevant pre-operative, intraoperative and postoperative data of the study group. The specific pre- and intraoperative data obtained from each patient included the following: age and gender, history of hypertension, diabetes, smoking, obesity, hyperlipidemia, body surface area and body mass index (BMI), history of myocardial infarction (MI), the presence of unstable angina, prior percutaneous transluminal coronary angioplasty, the presence of carotid artery disease, left ventricular ejection fraction, the presence of left main coronary artery (LMCA) disease, additive EuroSCORE and the extent of coronary disease.

The postoperative data that was collected included the number of grafts per operation, the graft types that were used (i.e., left internal mammary artery, radial artery or saphenous vein grafts), the cardiopulmonary bypass time, the aortic cross-clamp time, the mechanical ventilation time, the requirement for inotropic or intra-aortic balloon pump support, presence of infection, re-exploration for bleeding or cardiac tamponade, the duration of stay in the intensive care unit (ICU), overall duration of hospital stay, and hospital mortality (defined as

death in the first 30 days after coronary artery bypass grafting surgery). We further employed data regarding study design, baseline patient data, administered treatment and POAF incidence by entering them to an Excel spreadsheet that was standardized. POAF incidence was considered as the study's primary outcome.

RESULTS

Two hundred patients (100 patients per group) were included into this study. The pre-operative demographic characteristics of the patients are summarized in Table 1 and Table 2. The mean age of the patients was 67.2 ± 7.6 years in Group 1, and 68.4 ± 5.8 years in Group 2.

There were no significant differences between the groups with respect to gender distribution; the prevalence of chronic obstructive pulmonary disease; the frequency of previous percutaneous transluminal coronary angioplasty; the prevalence of hypertension, obesity (body mass index, $\geq 30 \text{ kg/m}^2$), hyperlipidemia, smoking, diabetes mellitus, unstable angina, or LMCA disease; the ratio of patients with a history of MI; or the ratio of patients with carotid artery disease. There were also no statistical differences between the groups with respect to the mean number of diseased vessels, the mean left ventricular ejection fraction, or the EuroSCORE.

Intraoperative and postoperative data that were collected included the number of grafts per operation, the types of grafts used (for example, left internal thoracic artery, radial artery, and venous grafts), the cardiopulmonary bypass (CPB) time, and the aortic cross-clamp time. Data collected regarding the postoperative outcomes included the mechanical ventilation time; the requirement for inotropic or intra-aortic balloon pump support; the development of atrial fibrillation or infective complications; the re-exploration for bleeding or cardiac tamponade; and the occurrence of major pleural effusions, superficial or deep-wound infections, and deep vein thrombosis (DVT).

With regards to inotrope usage, hypoxemia and low cardiac output, no statistically significant differences were observed between the two groups. Similarly, there was also no statistically significant difference between Group 1 and Group 2 in any of the types of data described above (Table 3).

Group I and Group II had similar durations of stay in the intensive care unit (2.6 ± 0.7 vs. 2.5 ± 0.9 days, respectively; $P=0.559$), durations of overall hospital stay (7.1 ± 1.4 vs. 7.4 ± 2.2 days, respectively; $P=0.388$) and ventilation times (7.3 ± 2.5 vs. 7.2 ± 2.9 hours, respectively; $P=0.794$), with no significant differences being identified between the two groups. In addition, no perioperative deaths occurred in any of these two groups.

There was no significant difference in the incidence of POAF between Group I and Group II (20% vs. 18%, respectively; $P=0.718$). The incidence of inotropic agent requirement at ICU were also similar in both groups (12% in Group I vs. 18% in Group II, $P=0.32$) (Table 4).

Table 1. Preoperative demographic data.

	Group 1 Nebivolol	Group 2 Metoprolol	P-Value
N	100	100	
Mean Age	67.2 ± 7.6	68.4 ± 5.8	0.21
Gender (Female)	27 (27%)	34 (34%)	0.36
Previous MI	43 (43%)	46 (46%)	0.67
Diabetes Mellitus	31 (31%)	28 (28%)	0.64
Hypertension	25 (25%)	33 (33%)	0.21
Smoking	52 (52%)	45 (45%)	0.39
COPD	14 (14%)	8 (8%)	0.25
Hypercholesterolemia	58 (58%)	66 (66%)	0.24
Obesity	25 (25%)	24 (24%)	0.9
Renal Dysfunction	0 (0%)	2 (2%)	0.49
BMI	26.9 ± 4.1	26.6 ± 4.4	0.574
EuroSCORE	3.55 ± 2.02	4.1 ± 2.28	0.072
BSA	1.78 ± 0.16	1.75 ± 0.16	0.274

COPD=Chronic Obstructive Pulmonary Disease; BMI=Body Mass Index; BSA=Body Surface Area

Table 2. Preoperative demographic data (cardiac).

	Group 1 Nebivolol	Group 2 Metoprolol	P-Value
Number of Diseased Vessels			
One Vessel	8 (8%)	8 (8%)	1.000
Two Vessel	45 (47%)	50 (50%)	0.479
Three Vessel	47 (47%)	42 (42%)	0.477
LMCA disease	6 (6%)	8 (8%)	0.78
Right Coronary Disease	66 (66%)	71 (71%)	0.44
Carotid artery disease	10 (10%)	5 (5%)	0.28
Previous PTCA	13 (13%)	22 (22%)	0.13
Ejection fraction	50.2 ± 8.1	50.9 ± 8.6	0.533
New MI	6 (6%)	17 (17%)	0.027
Unstable Angina	13 (13%)	21 (21%)	0.19

LMCA=Left Main coronary Artery Disease; PTCA=Percutaneous Transluminal Coronary Angioplasty; MI=Myocardial Infarction

Table 3. Operative data.

	Group 1 Nebivolol	Group 2 Metoprolol	P-value
N	100	100	
Preoperative Mortality	0	0	1
Complete arterial revascularization	3 (3%)	1 (1%)	0.62
LIMA usage	96 (96%)	95 (95%)	0.733
Radial Artery usage	7 (7%)	4 (4%)	0.352
Mean distal bypass number	2.40 ± 0.67	2.38 ± 0.69	0.835
Cross-clamp time (min)	64.6 ± 16.5	62.6 ± 15.7	0.423
Perfusion time (min)	74.7 ± 17.6	74.2 ± 16.9	0.838

LIMA=Left Internal Mammalian artery

Table 4. Postoperative data.

	Group 1 Nebivolol	Group 2 Metoprolol	P-value
Requirement for Inotropes	11 (11%)	22 (22%)	0.057
IABP	0 (0%)	1 (1%)	1.000
Ventilation time (hours)	7.3 ± 2.5	7.2 ± 2.9	0.794
ICU stay (days)	2.6 ± 0.7	2.5 ± 0.9	0.559
Surgical site infection	1 (1%)	1 (1%)	1.000
Re-exploration for bleeding or tamponade	3 (3%)	1 (1%)	0.62
Pleural effusion	3 (3%)	0 (0%)	0.24
DVT	1 (1%)	1 (1%)	1.000
Atrial Fibrillation	20 (20%)	18 (18%)	0.718
Inotrope requirement in ICU	12 (12%)	18 (18%)	0.32
Hospital Stay (days)	7.1 ± 1.4	7.4 ± 2.2	0.388

IABP=Intra-aortic Balloon Pump; ICU=Intensive Care Unit; DVT=Deep Vein Thrombosis

DISCUSSION

The aim of this study was to investigate the effectiveness of nebivolol in the prophylaxis of postoperative atrial fibrillation (POAF) by comparing it with metoprolol, a medication whose effectiveness against atrial fibrillation is well-documented. Based on the study results, we identified no significant difference between nebivolol and metoprolol with regards to the effectiveness of POAF prophylaxis. POAF is observed in nearly 30% of patients who undergo isolated coronary artery bypass (CABG) surgery. This ratio increases to nearly 40% if replacement or repair of valves is performed during surgery, and to 50% in case combined procedures are performed. Considering that the age average of populations undergoing cardiac surgery is gradually increasing, and that the incidence of POAF is positively correlated with age, it is likely that these percentages will increase in the future.

In most cases, POAF develops between the 2nd and 4th days that immediately follow surgery, with the highest incidence being observed on the 2nd day. The onset of POAF occurs before the 4th postoperative day in 70% of cases, and before the 6th postoperative day in 94% of cases^[11].

POAF often manifests itself as a transient condition that is tolerated by most patients. However, POAF also has the potential to cause serious complications or even be fatal in certain patients – especially older patients and patients with certain ventricular dysfunctions^[12] and mortality^[13]. POAF was previously described as a potential cause of significant morbidity^[14] that can lead to further postoperative complications such as thromboembolism^[15], hemodynamic problems^[16], ventricular dysrhythmias^[17], and even to iatrogenetic effects due to inappropriate diagnosis and treatment of POAF.

Moreover, POAF is known to increase nearly three times the incidence of perioperative stroke^[13-17]. In a study conducted by Almassi et al. on 3855 cardiac surgery patients^[14], it was

observed that POAF led to a nearly two-fold increase in the hospital mortality and the 6-month mortality of patients. Increasing age is the most significant contributing factor to the risk of POAF^[11,13,14]. Matthew et al.^[18] determined in a recently conducted study that the incidence of POAF increased by nearly 75% for every decade of age, and that all patients above the age of 70 were at a high risk of POAF.

Other factors that also increase the risk of POAF include previous episodes of AF, lower left ventricular ejection fraction, left atrial enlargement, valvular heart surgery, chronic obstructive pulmonary disease, chronic renal failure, diabetes mellitus, and rheumatic heart diseases^[13,17,18]. Recent studies have also suggested that obesity may be associated with a higher incidence of POAF in both patients with and without previous cardiac surgeries^[19,20].

A variety of factors appear to be involved in the etiology of POAF, although the mechanistic relationship between these factors and POAF development has not yet been clearly identified. Several mechanisms that are potentially involved in POAF pathogenesis include pericardial inflammation, excessive catecholamine production, postoperative autonomic imbalance, and interstitial fluid mobilization. These factors may adversely affect atrial refractoriness and slow atrial conduction. The multiple re-entry wavelets caused by the dispersion of atrial refractoriness appear to be the underlying mechanism for the development of POAF^[21].

In a meta-analysis performed recently by Crystal et al.^[22], it was observed that, within the scope of 28 trials conducted with 4074 subjects, beta-blocker drugs demonstrated the highest magnitude of effect with an odds ratio (OR) of 0.3, and a 95% confidence interval (CI) of 0.26 to 0.49. In the meta-analysis of Burgess et al.^[23], the authors reported that the use of beta-blocker drugs lead to a reduction in the incidence of POAF.

According to the American College of Cardiology/American Heart Association and the European Society of Cardiology Guidelines for AF; pre-operative or early postoperative administration of beta-blockers for preventing AF after coronary artery bypass grafting surgery in patients without contraindications is a class-I indication, with an evidence level of A^[24].

Nebivolol is a third generation selective beta-1 adrenergic receptor antagonist that differs from conventional beta-blockers in its ability to induce nitric oxide synthesis in the endothelium^[25]. The endothelium produces nitric oxide, which is a well-known vasodilator. Nebivolol has a high beta-1 adrenergic receptor selectivity, and can be used safely in patients with reduced cardiac functions.

There are numerous studies discussing other properties of Nebivolol; however, based on our review of the literature, we believe that our study was the first to investigate the prophylactic use of nebivolol for POAF after coronary artery bypass surgery.

Metoprolol is an important drug that was approved by the FDA in 1978. We chose metoprolol for comparison with

nebivolol due to its safety and common use. Metoprolol has been used for the prevention and treatment of postoperative AF for decades. Thus, in this study we aimed to investigate the effectiveness of nebivolol in the prophylaxis of POAF by comparing it with metoprolol

Radial arterial graft vasospasm is one of the most problematic complications following cardiac surgery. As mentioned before, nebivolol possesses a potent vasodilator effect on radial artery graft, and can increase the lumen diameter and protect the graft^[26].

Furthermore, nebivolol is also known to improve sleep parameters, which contributes positively to the patients' life quality^[27]. Disturbance of normal sleep, in particular, may cause tiredness and lead to depression. This is most important for postoperative patients, who are emotionally vulnerable after surgery. Owing to its electrophysiological properties, and in a manner similar to other beta-blockers; nebivolol has the effect of increasing the ventricular fibrillation threshold.

This effect allows nebivolol to reduce ventricular arrhythmia or drug-induced cardiomyopathy in various animal models. Nebivolol is also known to reduce the QT dispersions, which are associated with the risk of developing arrhythmias, and P-wave dispersions, which are associated with the risk of developing atrial fibrillation^[28]. We believe that the results we obtained for nebivolol in our study – which were not significantly different than those for metoprolol – were ultimately the result of the effects and mechanisms described above.

Previous experiments on ischemia and reperfusion injury^[29] have also demonstrated the preventive and protective effects of nebivolol. In addition, it was shown that the administration of nebivolol in humans increased tolerance during exercise (in comparison to atenolol), as well as the time required for the onset of angina^[30]. Nebivolol was also demonstrated to have a consistent effect in increasing coronary flow among individuals with ischemic and nonischemic heart diseases, which is believed to engender a decrease in the ischemic threshold of these individuals^[31].

We believe that these effects that counter the damages associated with ischemia and ischemia-reperfusion will also allow nebivolol to be effective in the prevention and treatment of POAF. For ethical reasons, and also due to the relatively low number of patients in our study groups, we did not to include into the study design a control group without beta-blocker treatment. Unlike metoprolol, nebivolol does not have an IV form, which also represents a disadvantage.

CONCLUSION

Metoprolol is a well-known and commonly preferred drug for the prevention of POAF. In this study, Nebivolol was determined to be as effective as metoprolol. Thus, it is possible to use nebivolol effectively for prophylaxis of POAF. Moreover, nebivolol's characteristic properties may also result in additional benefits for elderly patients. Due to the limitations of

this study; well-planned prospective and randomized studies with larger groups that evaluate other properties and features of nebivolol will be necessary to gain further information. The contribution of such studies on the body of knowledge regarding nebivolol's effects will be significant.

Authors' roles & responsibilities

NE	Analysis and/or interpretation of data, statistical analysis, final approval of manuscript
MK	Final approval of manuscript, conception and study design, conduct of operations, and/or experiments
KD	Study design, conduct of operations, and/or experiments
OMD	Analysis and/or interpretation of data, statistical analysis, final approval of the manuscript, conception and study design, conduct of operations, and/or experiments
BB	Conception and design of the study

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