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Does prophylactic low-dose amiodarone decrease the incidence of postoperative atrial fibrillation after coronary artery bypass graft surgery? A randomized controlled trial

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Abstract

Background: Postoperative atrial fibrillation (POAF) occurs within 1 to 5 days after coronary artery bypass grafting (CABG), with a peak occurrence on the second day. This research aimed to assess the role of dose-low amiodarone in the prevention of POAF after CABG.

Methods: This randomized controlled blind-single study was carried out on 150 patients undergoing elective CABG with sinus rhythm. Cases were randomized into two equal groups. The placebo group received matching placebo tablets. The amiodarone group received a prophylactic oral amiodarone 5 mg/kg/day for 6 days before and 6 days after surgery.

Results: The incidence of POAF was significantly lower in the amiodarone group compared to the placebo group (16% vs 33.3%, $P = 0.013$) with a relative risk of 0.48 times (95% confidence interval: 0.26–0.88). The onset of POAF, percent of patients responded to medication, and time elapsed to respond to medication were insignificantly different between both groups. The mean (± SD) of ICU stay was 2.51 ± 1.11 days in the amiodarone group versus 3.31 ± 1.83 days in the placebo group, and the mean (± SD) of hospital stay duration was 10 ± 1.99 days in the amiodarone group versus 12.72 ± 2.23 days in the placebo group. The length of ICU admission and hospital stay was significantly lower in the amiodarone group than in the placebo group ($P = 0.002$ and < 0.001, respectively).

Conclusions: Low-dose oral amiodarone was effective in POAF prevention after CABG with a lower length of ICU admission and hospital stay.

Trial registration: Pan African Clinical Trials Register PACTR202101651961317. Registered on 21 January 2021

Keywords: Atrial fibrillation, Prophylaxis, Amiodarone, CABG

Background

Postoperative atrial fibrillation (POAF) is the most frequent complication following cardiac surgeries, and it is still difficult to prevent, treat, or cure [1, 2]. The prevalence of POAF ranges between 20 and 40% in different studies, reflecting the differences in atrial fibrillation (AF) definition, monitoring, and screening [3]. POAF occurs within 1 to 5 days after coronary artery bypass grafting (CABG), with a peak occurrence on the second day [4].

POAF is related to higher mortality and morbidity, including increased intensive care unit (ICU) re-admission, persistent congestive heart failure, length of hospital stay, stroke, and overall cost [5].

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Several studies have searched for an efficient drug to prevent POAF. Many drugs were tried, including magnesium sulfate, beta-blockers, verapamil, quinidine, digoxin, and procainamide. However, the outcomes were not satisfactory [6, 7]. Also, these drugs have several side effects, and some drugs, such as beta-blockers, are not tolerable in patients with significant chronic lung illness and left ventricle dysfunction [8].

Amiodarone, a class III antiarrhythmic drug, expands the refractory time of ventricular and atrial muscle and AV nodes [9]. Additionally, amiodarone has a mild activity in beta- and calcium channel blocking [10]. Bradycardia and atrioventricular block are frequent side effects of amiodarone because of their calcium channel-blocking activity [11].

Amiodarone is commonly prescribed for many diseases in clinical practice due to its good antiarrhythmic effect [12, 13]. A few studies reported its usage as a prophylactic drug against POAF after CABG. This research aimed to assess the role of low-dose amiodarone in preventing POAF after CABG.

Methods

This randomized controlled single-blind study was carried out on 150 patients undergoing elective CABG with sinus rhythm from 1 December 2019 to 28 February 2022 in Cardiothoracic Surgery Department, a tertiary referral hospital established to manage heart diseases. The ethical committee of the Faculty of Medicine, Tanta University Hospital, Tanta, Egypt, has approved the study (approval code 33462/11/19). Then, registration was done on Pan African Clinical Trials Register (PACTR202101651961317). Before enrollment, informed written consent was taken from patients.

Patients with emergency CABG, CABG with valve surgery, re-do CABG, history of amiodarone allergy or toxicity, previous AF, chronic renal failure (serum creatinine level above 200 μmol/l), hypothyroidism, hyperthyroidism, and chronic amiodarone treatment were excluded.

Patients were allocated into two equal groups (group ratio 1:1): the placebo group received placebo tablets matching amiodarone tablets, and the amiodarone group received prophylactic oral amiodarone of 5 mg/kg/day, divided into two doses per day for 6 days before and 6 days after surgery. A single type of beta-blocker at a fixed dose was used to standardize the therapy to avoid outcome differences.

Randomization into two groups was performed by computer-generated random numbers and inserted into opaque concealed envelopes. Only participants were blinded.

To ensure consistency, all individuals were administered the same anesthesia. All operations were conducted using hypothermic cardiopulmonary bypass (cooling to 32 °C) with a single dose of cardioplegia solution (cold custodiol; Bretschneider's HTK Solution. Germany), a magnesium-free prime, and a membrane oxygenator [14].

Central venous pressure, invasive blood pressure, pulse oximetry, continuous electrocardiogram, and monitoring of central and peripheral temperature were performed intraoperatively. All operations were conducted in a single aortic clamping session. During and after surgery, repeated arterial blood samples were collected to measure blood gasses and potassium levels, which remained within normal ranges. Transit time flow measurement (TTFM) using a TTFM device was recorded 5 min after weaning from cardiopulmonary bypass to check the patency of grafts.

Continuous postoperative ECG monitoring was done for 6 days in the ICU and the ward by Mindray Datascope monitors. The rhythm was identified as AF when persistent P waves did not precede every QRS complex, and the ventricular rate was abnormal. If a patient developed POAF and persisted for 5 min or more, the patient was considered POAF.

When AF occurred, intravenous amiodarone was administered (150 mg bolus, 1 mg/min× 6 h, then 0.5 mg/min× 18 h) [15].

The primary outcome was the incidence of POAF, while the secondary outcomes were the safety and length of hospital and ICU stay. The adverse effects of amiodarone, including bradycardia and hypotension, were recorded.

Sample size calculation

G. power 3.1.9.2 (Universitat Kiel, Germany) was utilized for the sample size calculation. The following criteria determined the sample size: A previous study found that the incidence of AF was 25% with amiodarone and 53% with placebo [16], 0.05 α error and 90% power of the study to allocation ratio 1:1. Thirteen cases were added to each group to compensate for dropouts. Consequently, 75 patients were assigned to each group.

Statistical analysis

Data was entered into the computer and analyzed with SPSS v26 (IBM Inc., Chicago, IL, USA). Quantitative data were expressed as mean and standard deviation (SD) and were compared by an unpaired Student's test. Qualitative data were given as frequency and percentage (percent) and examined utilizing the chi-square test. Kaplan-Meier curve was used to show the onset of AF. Cox regression was used to estimate the hazard ratio. A two-tailed *P* value of 0.05 or less was regarded as statistically significant.

Results

In this study, 187 cases were evaluated for eligibility, 24 failed to meet the criteria, and 13 refused to join the trial. The remaining 150 cases were randomly allocated into two groups (75 cases in each). All allocated cases were followed up and analyzed statistically (Fig. 1).

Preoperative and intraoperative data were insignificantly different between both groups (Table 1).

The incidence of POAF in the amiodarone group was significantly lower than that in the placebo group (16% vs 33.3%, $P = 0.013$) with a relative risk of 0.48 (95% CI: 0.26–0.88). The onset of POAF, patients' response to medication, and elapsed time to respond to medication were insignificantly different between both groups (Table 2).

Postoperative ejection fraction was insignificantly different among the two groups (Table 2).

The length of ICU admission and hospital stay was significantly lower in the amiodarone group compared to the placebo group ($P = 0.002$ and < 0.001, respectively) (Table 2).

The overall AF rate was significantly lower in the amiodarone group than in the placebo group ($P = 0.011$) with a hazard ratio of AF 0.414 times (95% CI: 0.21–0.815) in the amiodarone group than in the placebo group (Fig. 2).

The low-dose amiodarone treatment did not result in any significant adverse effects.

Discussion

Our results revealed that the prophylactic oral low-dose amiodarone administration in elective CABG decreased the incidence of POAF by about 50% compared to the controls.

We found that POAF occurred in only 16% of the amiodarone group compared to 33.3% in the placebo group, with maximum occurrence on the 2nd day postoperatively than on the third day postoperatively.

This was supported by Mitchell et al. [17], who determined whether oral administration of amiodarone perioperatively was an efficient and secure prophylactic drug for atrial tachyarrhythmia following heart operation (CABG and/or heart valve surgery). In their study, oral

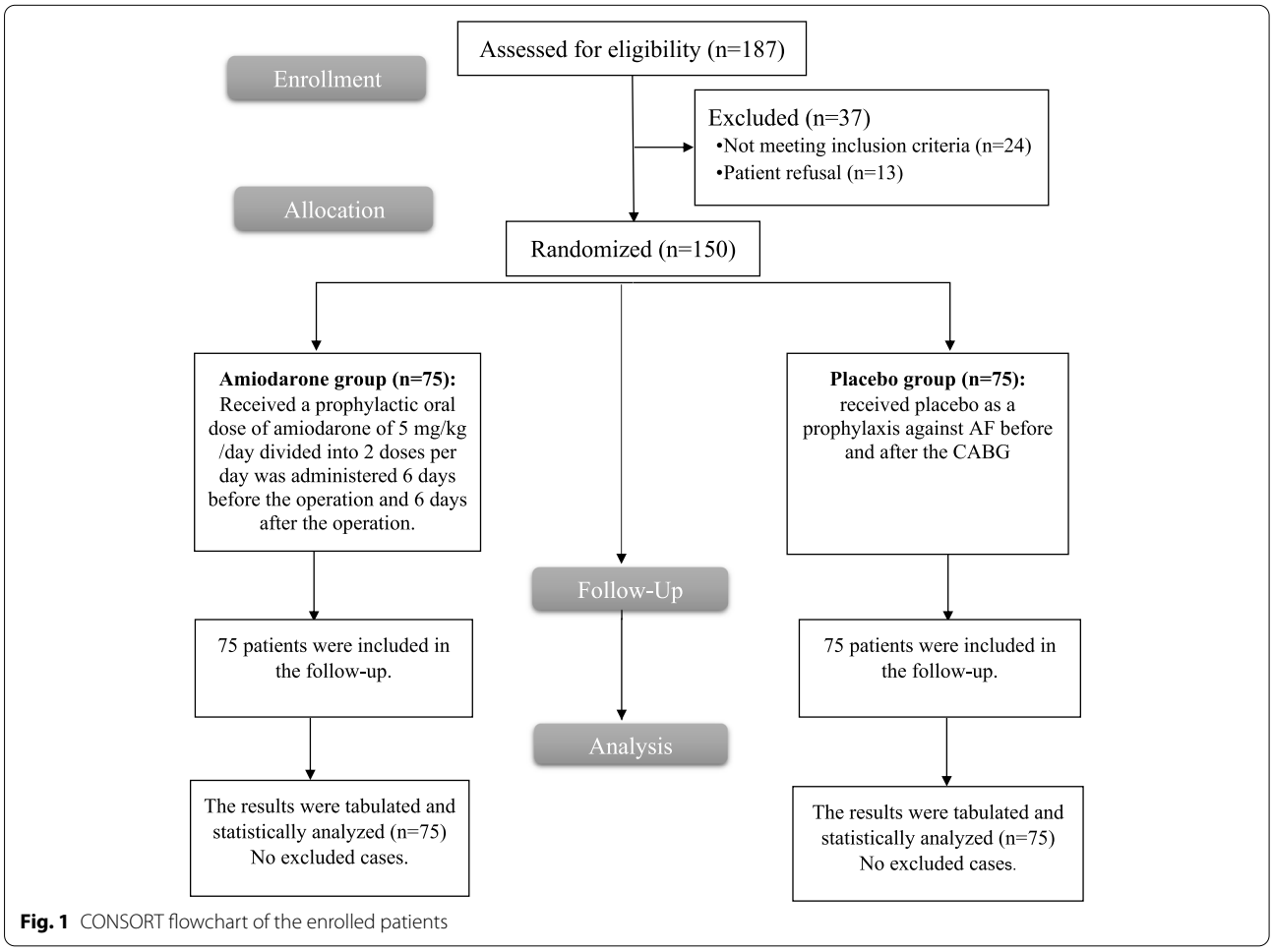

Fig. 1 CONSORT flowchart of the enrolled patients

Table 1 Distribution of preoperative and operative data in both groups ($n = 150$)

	Placebo group ($n = 75$)	Amiodarone group ($n = 75$)	*P* value
Age (years)	57.31 ± 6.85	57.76 ± 5.80	0.663
Gender			
Male	45 (60%)	42 (56%)	0.62
Female	30 (40%)	33 (44%)	
Hypertension	38 (50.7%)	34 (45.3%)	0.513
DM	34 (45.3%)	45 (60%)	0.072
Smoking	21 (28%)	19 (25.3%)	0.712
CCS > 3	53 (70.7%)	47 (62.7%)	0.299
NYHA > III	26 (34.7%)	24 (32%)	0.729
Previous MI	25 (33.3%)	24 (32%)	0.862
Obesity	9 (12%)	7 (9.3%)	0.597
Preoperative EF (%)	49.63 ± 5.68	51.03 ± 6.53	0.163
Preoperative LA size (%)	3.68 ± 0.32	3.73 ± 0.29	0.317
Operative data			
Ischemic time (min)	61.19 ± 9.5	63.85 ± 8.16	0.067
Total bypass time (min)	97.59 ± 9.77	95.89 ± 8.47	0.259
Intraoperative inotropes	48 (64%)	46 (61.3%)	0.736
Number of grafts	2.60 ± 1.15	2.32 ± 0.82	0.089

Data presented as mean ± SD or frequency (%)

DM diabetes mellitus, *CCS* chronic coronary syndromes, *NYHA* New York Heart Association, *MI* myocardial infarction, *EF* ejection fraction, *LA* left atrium

Table 2 Outcomes in both groups

	Placebo group ($n = 75$)	Amiodarone group ($n = 75$)	*P* value
POAF	25 (33.3%)	12 (16%)	0.013*
Time of onset of POAF (days)	2.19 ± 0.87	2.32 ± 0.47	0.243
Patients responded to medication	12 (16%)	7 (9%)	0.22
Elapsed time to respond to medication (h)	15.77 ± 5.64	14.65 ± 3.14	0.135
Maximum ventricular rate	137.14 ± 7.21	135.25 ± 7.32	0.113
Postoperative EF (%)	43.06 ± 5.10	44.63 ± 5.81	0.081
ICU stay (days) (same)	3.31 ± 1.83	2.51 ± 1.11	0.002*
Hospital stay (days) (same)	12.72 ± 2.23	10 ± 1.99	< 0.001*

Data presented as mean ± SD or frequency (%)

AF atrial fibrillation, *POAF* postoperative atrial fibrillation, *ICU* intensive care unit, *EF* ejection fraction, *RR* Relative risk

*Significant *P* value < 0.05

amiodarone (10 mg/kg daily) was administered 6 days before operation through 6 days following operation (13 days). The atrial tachyarrhythmia occurred after surgery in a few amiodarone cases at 16.1% $P < 0.001$ with a peak rate in the 2nd day postoperatively.

Moreover, Daoud et al. [18] used oral amiodarone as a preventive medication for valvular and CABG surgery. POAF was presented in 25% (16 of 64 patients) of the amiodarone group and 53% of the placebo group (32 of 60 patients). In Daoud et al.'s study, 40% (26 of 64 patients) of cases are receiving amiodarone with beta-blockers; however, the incidence of AF among amiodarone-treated patients taking beta-blockers was not significantly different from that of amiodarone-treated patients not taking beta-blockers ($P = 0.76$). So, the use of beta-blockers did not influence the prevalence of AF in their study. While in our study, a single type of beta-blocker at a fixed dose was used to standardize the therapy.

Since many patients require urgent CABG, other studies have administered amiodarone intravenously. Hohnloser et al. [15] studied 77 patients after heart surgery in a placebo-controlled study of IV amiodarone as prophylaxis against AF. The total IV dose of 4.5 g was

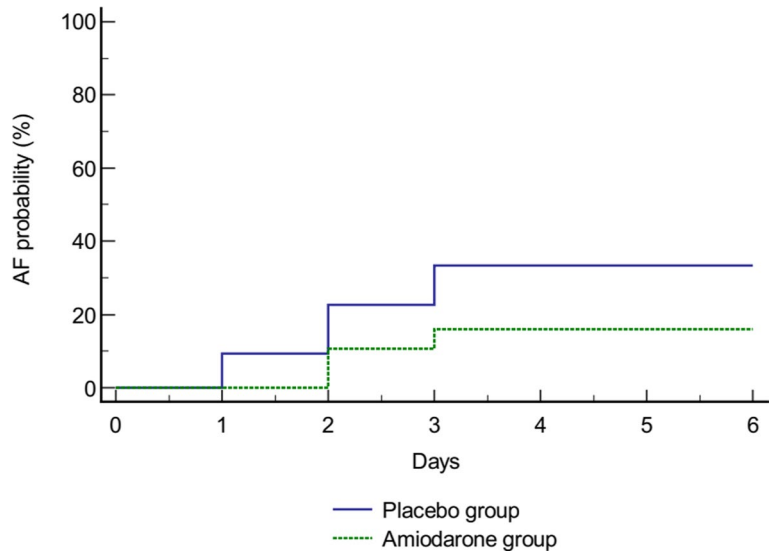

Fig. 2 Kaplan-Meier curve of cumulative incidence of atrial fibrillation

administered, and infusion started following the end of the surgery and significantly decreased the occurrence of AF. However, 18% stopped amiodarone due to adverse effects and concluded the incidence of AF (5% vs 21% in the control group; $P < 0.05$).

In contrast with our results, Redle et al. [19] compared oral amiodarone with a placebo to prevent POAF after CABG. Cases were administered 2 g of amiodarone or placebo in separate doses 1 to 4 days before the operation and 400 mg daily for 7 days after the operation. POAF was presented in 24.7% of cases obtaining amiodarone and 32.8% of cases taking placebo but with an insignificant change between both groups. This difference might be due to their inclusion of all patients referred for CABG, not only elective but also emergent cases which were excluded from our study. Additionally, blocker therapy was not controlled as cases in the placebo group more frequently applied these medications before the operation, which may affect the occurrence of POAF.

In disagreement with our study, Maras et al. [20] determined the effectiveness of one loading dose (1200 mg) of amiodarone 1 day before the operation, continued by a maintained dose (200 mg) each day for the subsequent week after CABG and found that the rate of POAF was lower in amiodarone cases (19.5%) than in placebo (21.2%) with no significant difference between both groups. While their study had two limitations related to AF, one was that b-blocker treatment was not effectively managed. Cases in the placebo group who more frequently applied these medications before operation (P-value = 0.032) influence the incidence of AF. The second limitation was in the follow-up of the patients after the operation as they did not perform continuous ECG monitoring except on the 1st day following the operation. It is conceivable that some occurrences of AF were not identified, and the length of AF episodes was overestimated. In this study, continuous monitoring of ECG for six postoperative days. Also, our dose strategy may give a higher total dose effect by lengthening the duration of orally given rather than administering a relatively large dose in a short hospitalization time.

We demonstrated that the period of ICU stay and postoperative hospital stay were significantly lowered in the amiodarone group in comparison to the placebo. This is mainly due to the increased incidence of POAF in the placebo rather than in the amiodarone group, leading to hemodynamic instability and prolonging the period of ICU and hospital stay.

This study's low-dose amiodarone regimen did not result in any significant adverse effects. In addition, the low risk of complications in the amiodarone group supports the findings of earlier investigations [21, 22].

This low dose of short-term oral amiodarone is enough to control heart dysrhythmias and did not reduce the left ventricular ejection fraction. It bypasses some IV medication constraints.

Limitations

Our trial was a single-center study; this may hinder the generalizability of our findings. Moreover, long-term case results were not included in our trial.

Conclusions

Prophylactic low-dose oral amiodarone was effective in the prevention of POAF after CABG with a lower length of ICU admission and hospital stay.

Abbreviations

AF: Atrial fibrillation; CABG: Coronary artery bypass grafting; CCS: Chronic coronary syndromes; DM: Diabetes mellitus; ECG: Electrocardiogram; ICU: Intensive care unit; MI: Myocardial infarction; NYHA: New York Heart Association; POAF: Postoperative atrial fibrillation; RR: Relative risk; SD: Standard deviation; TTFM: Transit time flow measurement.

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Authors' contributions

MA, AS, and AG conceived and supervised the study. AM and AA were responsible for the data collection. MA and AG analyzed and interpreted the data. All authors provided comments on the manuscript at various stages of development. All authors read and approved the final manuscript.

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Availability of data and materials

Data and materials are available on a reasonable request from the authors.

Declarations

Ethics approval and consent to participate

The ethical committee of the Faculty of Medicine, Tanta University Hospital, Tanta, Egypt, has approved the study. Before enrollment, informed written consent was taken from the patients.

Consent for publication

All authors give their consent for publication in the journal.

Competing interests

The authors declare that they have no competing interests.

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References

1. Li Z, Han H, Liu Y (2019) Colchicine for prevention of postoperative atrial fibrillation following cardiac surgery. Int J Clin Exp Med 12:1344–1354
2. Dmour B-A, Miftode R-S, Iliescu Halitchi D et al (2021) Latest insights into mechanisms behind atrial cardiomyopathy: it is not always about ventricular function. Diagnostics (Basel, Switzerland) 11:449–453. https://doi.org/10.3390/diagnostics11030449
3. Dobrev D, Aguilar M, Heijman J et al (2019) Postoperative atrial fibrillation: mechanisms, manifestations and management. Nat Rev Cardiol 16:417–436. https://doi.org/10.1038/s41569-019-0166-5
4. Ghurram A, Krishna N, Bhaskaran R et al (2020) Patients who develop post-operative atrial fibrillation have reduced survival after off-pump coronary artery bypass grafting. Indian J Thorac Cardiovasc S 36:6–13. https://doi.org/10.1007/s12055-019-00844-9
5. Mangi AR, Zia K, Ali TA et al (2019) Postoperative atrial fibrillation among patients undergoing isolated coronary artery bypass grafting. Cureus 11:4333–4336. https://doi.org/10.7759/cureus.4333
6. Cook RC, Humphries KH, Gin K et al (2009) Prophylactic intravenous magnesium sulphate in addition to oral {beta}-blockade does not prevent atrial arrhythmias after coronary artery or valvular heart surgery: a randomized, controlled trial. Circulation 120:S163–S169. https://doi.org/10.1161/circulationaha.108.841221
7. Kamali A, Yavari S, Yazdi B et al (2021) Prophylactic effect of Amiodarone and in combination with Vitamin C in reducing atrial fibrillation after coronary artery bypass. Eur J Transl Myol 31:8991–8993. https://doi.org/10.4081/ejtm.2021.8991
8. Dézsi CA, Szentes V (2017) The real role of β-blockers in daily cardiovascular therapy. Am J Cardiovasc Drugs. 17:361–373. https://doi.org/10.1007/s40256-017-0221-8
9. Ji Y, Takanari H, Qile M et al (2017) Class III antiarrhythmic drugs amiodarone and dronedarone impair K(IR) 2.1 backward trafficking. J Cell Mol Med 21:2514–2523. https://doi.org/10.1111/jcmm.13172
10. Esmail M, Nilufa D, Majid G-E et al (2015) Prophylactic effect of amiodarone in atrial fibrillation after coronary artery bypass surgery; a double-blind randomized controlled clinical trial. J Cardiovasc Dis Res 6:12–17
11. Kim HL, Seo JB, Chung WY et al (2014) The incidence and predictors of overall adverse effects caused by low dose amiodarone in real-world clinical practice. Korean J Intern Med 29:588–596. https://doi.org/10.3904/kjim.2014.29.5.588
12. Goldschlager N, Epstein AE, Naccarelli G et al (2000) Practical guidelines for clinicians who treat patients with amiodarone. Arch Intern Med 160:1741–1748. https://doi.org/10.1001/archinte.160.12.1741
13. Trohman RG, Sharma PS, McAninch EA et al (2019) Amiodarone and thyroid physiology, pathophysiology, diagnosis and management. Trends Cardiovasc Med 29:285–295. https://doi.org/10.1016/j.tcm.2018.09.005
14. Edelman JJ, Seco M, Dunne B et al (2013) Custodiol for myocardial protection and preservation: a systematic review. Ann Cardiothorac Surg 2:717–728. https://doi.org/10.3978/j.issn.2225-319X.2013.11.10
15. Samuels LE, Holmes EC, Samuels FL (2005) Selective use of amiodarone and early cardioversion for postoperative atrial fibrillation. Ann Thorac Surg 79:113–116
16. Naqvi S, Hussain SA (2008) Amiodarone prophylaxis for atrial fibrillation after coronary artery bypass grafting. PAFMJ 58:125–131
17. Mitchell LB, Exner DV, Wyse DG et al (2005) Prophylactic oral amiodarone for the prevention of arrhythmias that begin early after revascularization, valve replacement, or repair: PAPABEAR: a randomized controlled trial. JAMA 294:3093–3100. https://doi.org/10.1001/jama.294.24.3093
18. Daoud EG, Strickberger SA, Man KC et al (1997) Preoperative amiodarone as prophylaxis against atrial fibrillation after heart surgery. N Engl J Med 337:1785–1791. https://doi.org/10.1056/nejm199712183372501
19. Redle JD, Khurana S, Marzan R et al (1999) Prophylactic oral amiodarone compared with placebo for prevention of atrial fibrillation after coronary artery bypass surgery. Am Heart J 138:144–150. https://doi.org/10.1016/s0002-8703(99)70260-7
20. Maraš D, Bošković SD, Popović Z et al (2001) Single-day loading dose of oral amiodarone for the prevention of new-onset atrial fibrillation after coronary artery bypass surgery. Am Heart J 141:5–12
21. Nicklas JM, McKenna WJ, Stewart RA et al (1991) Prospective, double-blind, placebo-controlled trial of low-dose amiodarone in patients with severe heart failure and asymptomatic frequent ventricular ectopy. Am Heart J 122:1016–1021. https://doi.org/10.1016/0002-8703(91)90466-u
22. Lévy S, Lauribe P, Dolla E et al (1992) A randomized comparison of external and internal cardioversion of chronic atrial fibrillation. Circulation 86:1415–1420. https://doi.org/10.1161/01.cir.86.5.1415

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