SYSTEMATIC REVIEW

Amiodarone versus beta-blockers for the prevention of postoperative atrial fibrillation after cardiac surgery: An updated systematic review and meta-analysis of randomised controlled trials [version 1; peer review: awaiting peer review]

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First published: 25 May 2022, 11:569
https://doi.org/10.12688/f1000research.121598.1

Abstract

Background: Amiodarone and beta-blockers are widely used as prophylaxis for postoperative atrial fibrillation (AF). The current recommendations from society guidelines are inconclusive, leading to differing practices among physicians. This meta-analysis aimed to compare the efficacy of both agents in preventing postoperative AF after cardiac surgery.

Methods: We explored online medical databases, such as CINAHL, CENTRAL, MEDLINE, and EMBASE for randomised controlled trials (RCTs) comparing amiodarone and beta-blocker for prevention of AF after cardiac surgery. Outcomes analysed in this study were AF number of events and duration, hospital stay, and mean ventricular rate. Heterogeneity was assessed using the I² test, and publication bias was analysed using Egger's test.

Results: In total, eight RCTs comprising 1370 patients met the inclusion criteria. Pooled analysis showed that patients in both groups had no significant difference in both AF episodes (RR 0.83, 95% CI 0.66 to 1.04, p=0.10) and AF duration (SMD 0.46, 95% CI -1.14 to 2.05, p=0.57). Furthermore, secondary outcome analysis on mean ventricular rate and mean hospital length of stay in both groups showed no significant difference (MD -4.48, 95% CI -14.36 to 5.39, p=0.37 and MD 0.29, 95% CI -0.06 to 0.63, p=0.11, respectively).
Conclusions: Amiodarone and beta-blockers are equally effective in preventing postoperative atrial fibrillation after cardiac surgery, with no difference in AF episode and duration, mean ventricular rate, and hospital length of stay.

Keywords
Atrial fibrillation, cardiac surgery, amiodarone, beta-blockers
Introduction

Atrial fibrillation (AF) is a common complication after cardiac surgeries with incidence ranging from 10% to 65% despite the latest developments in both surgical and medical management. Postoperative AF could lead to prolonged intensive care unit (ICU) and hospital stay, resulting in increased cost. Although its mortality rate is low, it frequently induces hemodynamic disturbance and thromboembolic events. The hypothesized pathophysiology of postoperative AF is the interaction between acute surgery-related factors, including activated sympathetic nervous system and renin-angiotensin-aldosterone system, inflammation, trauma and oxidative stress, and underlying abnormal atrial substrate which induces electrical instability.

Pharmacological and non-pharmacological measures (e.g. atrial pacing) are used as strategies to prevent postoperative AF. Both beta-blockers and antiarrhythmics such as amiodarone could be used in postoperative AF prevention. Beta-blockers lower myocardial oxygen demand and ischemia events in the postoperative period by lessening the chronotropic and inotropic effects of catecholamine surge. Meanwhile, amiodarone prevents AF primarily by blocking potassium channels and through its anti-adrenergic effect, thus decreasing myocyte excitability, and preventing the re-entry mechanism and ectopic foci from causing an arrhythmia. Both drugs can be administered either orally or intravenously, although the latter route may be more effective. However, previous studies on the efficacy of these drugs provide conflicting results.

As a result, the gold standard regimen of postoperative AF prevention remains uncertain, resulting in varying practices and a high discontinuation rate, which might increase the patient’s risk of developing arrhythmias. Therefore, this study aims to compare the efficacy of these drugs in preventing postoperative AF.

Objectives

The objectives of this research are to compare the efficacy of amiodarone and beta-blockers in preventing postoperative AF after cardiac surgery.

Methods

We explored online medical databases, such as CINAHL, CENTRAL (Cochrane Library), MEDLINE (PubMed), and EMBASE (Science Direct), for a literature search from 11th January to 18th February 2022. The literature search process was performed using medical subject headings (MeSH) terms of (“coronary artery bypass graft”) AND (“amiodarone”) AND (“beta-blocker”). The search process was done according to the preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines (see Reporting guidelines). The literature searching and selection process were performed by all of the authors unfetteredly.

Eligibility criteria

A study was included if it met the following criteria: a study evaluating amiodarone and beta-blockers in patients who underwent cardiac surgery (coronary artery bypass grafting (CABG), valve repair/replacement, and both), available in full text, and written in English. Our exclusion criteria were studies which full text were not available, non-randomised studies, and studies with irrelevant outcomes. The evaluated effects should include the following parameters: AF number of events and duration, mean ventricular rate, and length of hospital stay.

Data collection and statistical analysis

All authors were involved in data collection and worked independently. The main author collected the data manually from each author and any disagreement between authors were resolved through discussion. Included studies were examined using the EndNote 20 software for possible study duplication. Alternatively, this process can also be replicated using the Mendeley Reference Manager software. All statistical analysis was performed using STATA 17 software by StataCorp, California, USA, and Review Manager (RevMan) 5.4 software by Cochrane, Oxford, United Kingdom.

Data items

All eight studies investigated AF episodes, which we used as the primary outcome. Secondary outcomes were determined based on comparable outcomes reported among the studies (AF duration, mean ventricular rate, and mean length of hospital stay).

Study risk of bias assessment

Randomised study quality was assessed using the Cochrane Risk Index of Bias tools. All authors performed bias assessment independently and disagreements were resolved through discussion.
Effect measures
If the data extracted were binary outcomes, statistical calculation such as risk ratio (RR) or odds ratio (OR) would be selected. Meanwhile, if the data extracted were continuous outcomes, statistical calculation such as mean difference (MD) and standardized mean difference (SMD) would be chosen.

Synthesis methods
I² result would determine the heterogeneity test result. If the I² test result were less than fifty percent, a fixed-effect model would be selected since the heterogeneity was considered to be insignificant. Otherwise, a random-effect model would be chosen. All analyses used 95% of confidence intervals. P-value of less than 0.05 is considered to be statistically significant.

Reporting bias assessment
Reporting bias of each study was assessed using the assessed using the Cochrane Risk Index of Bias tools. Studies with high risk of reporting bias were not included in this study.

Certainty assessment
We used GRADE (grading of recommendations assessment, development and evaluation) approach to assess the certainty in the body of evidence. All authors performed the assessment independently, and disagreements between assessors were resolved through discussion between assessors.

Results
The article selection process was carried out according to PRISMA guidelines. Initial study searching resulted in 186 articles, which all were processed using the EndNote application for study duplication. According to our inclusion criteria, the remaining 155 studies were then assessed manually by all authors. As many as thirteen articles were further analysed for eligibility, resulting in eight studies¹⁻¹¹ analysed for final qualitative and quantitative analysis. The assessment of bias in the studies were conducted using Cochrane’s risk-of-bias tool, with the result listed in Table 1.

This study analysed four outcomes: number of AF episodes, AF duration, mean ventricular rate, and length of hospital stay. The authors, publication year, nation, sample size, mean age, surgery types, outcome, and follow up time were all extracted from the studies and presented in Table 2, while the treatment protocol details (type of drugs, dosage, timing, and duration of the treatment) of the included studies were elaborated in Table 3. AF episodes are presented in risk ratio (RR). AF duration is presented in standardized mean differences (SMD), and the secondary outcomes are presented in mean difference (MD). All analyses used 95% of confidence intervals. P-value of less than 0.05 is considered to be statistically significant.

AF episodes
A total of eight studies including 1370 participants met the inclusion criteria for the comparison of AF episode analysis. Pooled analysis in Figure 1 showed no significant difference in AF episodes between the amiodarone group and beta-blocker group (RR 0.83, 95% CI 0.66, 1.04, p=0.10).

AF duration
Three studies, including 384 participants, allocated into the amiodarone group (n=189) and beta-blocker group (n=195) compared the duration of AF. In accordance to the comparable risk of AF episode, pooled analysis in Figure 2 also showed no significant difference in terms of AF duration between both groups (SMD 0.46, 95% CI -1.1 to 2.05, p=0.57).

Mean ventricular rate
Mean ventricular rate comparison in Figure 3 was performed using fixed-effect model (I²=0%), resulting in not significant mean difference in mean ventricular rate comparison between both groups (MD -4.48, 95% CI -14.36 to 5.39, p=0.37).

Mean length of hospital stay
Four studies with 676 participants reported the difference in mean length of hospital stay. Figure 4 showed that there was no difference in mean length of hospital stay between both groups (MD 0.29, 95% CI -0.06 to 0.63, p=0.11).

Reporting biases
All studies included in this meta-analysis are considered low risk of reporting bias.
<table>
<thead>
<tr>
<th></th>
<th>Random sequence generation</th>
<th>Allocation concealment</th>
<th>Blinding of participants and personnel</th>
<th>Blinding of outcome assessment</th>
<th>Incomplete outcome data</th>
<th>Selective reporting</th>
<th>Other bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bigdelian et al.</td>
<td>Low</td>
<td>Low</td>
<td>Unclear</td>
<td>Undear</td>
<td>Undear</td>
<td>Low</td>
<td>Undear</td>
</tr>
<tr>
<td>Halonen et al.</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
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<tr>
<td>Hassan et al.</td>
<td>Unclear</td>
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<tr>
<td>Kojuri et al.</td>
<td>Unclear</td>
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<td>Low</td>
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<tr>
<td>Mooss et al.</td>
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<td>Onk et al.</td>
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<tr>
<td>Sleilaty et al.</td>
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<td>High</td>
<td>High</td>
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<td>Low</td>
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<tr>
<td>Solomon et al.</td>
<td>Unclear</td>
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<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
</tr>
</tbody>
</table>
### Table 2. Characteristics of studies included in the meta-analysis.

<table>
<thead>
<tr>
<th>Study Author/Year/Country</th>
<th>Sample size</th>
<th>Mean age (years)</th>
<th>Surgery type</th>
<th>Outcomes</th>
<th>Follow-up time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone</td>
<td>Beta-blockers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bigdelian/2008/Iran</td>
<td>65</td>
<td>65</td>
<td>55</td>
<td>Elective CABG (on pump), valve surgery, CABG with valve surgery</td>
<td>Primary: AF incidence, number of AF episodes, ventricular rate, time to onset of AF, longest AF duration, LOS, ICU stay, complications</td>
</tr>
<tr>
<td>Halonen/2010/Finland</td>
<td>157</td>
<td>159</td>
<td>64.15</td>
<td>Elective CABG (on pump) with/without aortic valve surgery</td>
<td>Primary: AF incidence, time to onset of AF, ventricular rate, complications, death</td>
</tr>
<tr>
<td>Hassan/2013/India</td>
<td>20</td>
<td>30</td>
<td>47</td>
<td>Open heart surgery on cardiopulmonary bypass (repair of congenital defects, valve replacements)</td>
<td>Primary: AF Incidence, time to onset of AF, AF duration, ventricular rate, LOS, cost, complications, death</td>
</tr>
<tr>
<td>Kojuri/2009/Iran</td>
<td>80</td>
<td>80</td>
<td>59.75</td>
<td>Elective CABG (on pump)</td>
<td>Primary: AF incidence, correlation between risk factors and incidence of AF, 30-day mortality</td>
</tr>
<tr>
<td>Mooss/2004/USA</td>
<td>83</td>
<td>76</td>
<td>65</td>
<td>CABG (on pump), AVR, CABG with AVR</td>
<td>Primary: AF incidence, incidence of drug-related side effects, number of AF episodes, time to onset of AF, LOS, hemodynamic changes, use of vasoactive drugs, complications, death</td>
</tr>
<tr>
<td>Onk/2005/Turkey</td>
<td>122</td>
<td>129</td>
<td>57.65</td>
<td>CABG (on pump)</td>
<td>Primary: AF incidence, use of IABP, use of inotropic agents, LOS, ICU stay, hospital mortality, complications, survival rate</td>
</tr>
<tr>
<td>Sleilaty/2009/Lebanon</td>
<td>98</td>
<td>102</td>
<td>61.65</td>
<td>Elective CABG (on pump) with/without mitral valve repair</td>
<td>Primary: AF incidence, maximal ventricular rate, time to onset of AF, AF duration, AF recurrence, LOS, ICU stay, low cardiac output</td>
</tr>
<tr>
<td>Solomon/2001/USA</td>
<td>50</td>
<td>52</td>
<td>65.35</td>
<td>Elective CABG (on pump), valve surgery, CABG with valve surgery</td>
<td>Primary: AF incidence, time to onset of AF, number of AF episodes, AF duration, ventricular rate, LOS, ECG data, complications</td>
</tr>
</tbody>
</table>

CABG, coronary artery bypass surgery; AVR, aortic valve replacement; AF, atrial fibrillation; LOS, length of hospital stay; ICU, intensive care unit.
Table 3. Treatment protocol of the studies included in the meta-analysis.

<table>
<thead>
<tr>
<th>Study Author/Year/Country</th>
<th>Amiodarone dosage</th>
<th>Beta-blockers dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bigdelian/2008/Iran</td>
<td>150 mg IV during 30 minutes after surgery, then continued with 150 mg/6 hours IV for 48 hours and followed by 400 mg/12 hour orally until hospital discharge</td>
<td>Immediately after surgery as 10 mg oral single dose, then continued with 10 mg/8 hours for 6 days</td>
</tr>
<tr>
<td>Halonen/2010/Finnland</td>
<td>15 mg/kg BW/day, IV, with maximum daily dose 1000 mg, started on first post-operative day, 15-21 hours post-surgery, continued for 48 hours</td>
<td>Metoprolol infusion IV 1 mg/hours for HR 60-70 bpm, 2 mg/hours for HR 70-80 bpm, or 3 mg/hours for HR &gt;80 bpm, started on first post-operative day, 15-21 hours post-surgery, continued for 48 hours</td>
</tr>
<tr>
<td>Hassan/2013/India</td>
<td>10 mg/kg BW/day orally, started 2 weeks before surgery and continued until hospital discharge</td>
<td>Metoprolol 25 mg/8 hours orally for HR 60-70 bpm, 50 mg/12 hours for HR 70-80 bpm, 50 mg/8 hours for HR &gt;80 bpm; started 2 weeks before surgery and continued until hospital discharge</td>
</tr>
<tr>
<td>Kojuri/2009/Iran</td>
<td>200 mg/12 hours orally, started 7 days before surgery until 5 days post-surgery</td>
<td>Propranolol 20 mg/12 hours orally, started 7 days before surgery until 5 days post-CABG</td>
</tr>
<tr>
<td>Mooss/2004/USA</td>
<td>15 mg/kg BW, IV, over 24 hours started at time of surgery, then switched to 200 mg/8 hours orally until 7 days</td>
<td>D,L-sotalol 80 mg orally, started 2 hours before surgery, then 80 mg/12 hours orally until 7 days</td>
</tr>
<tr>
<td>Onk/2005/Turkey</td>
<td>200 mg/8 hours orally, started 1 week before surgery and continued during post-operative period</td>
<td>Metoprolol 50 mg/12 hours orally, started 1 week before surgery and continued during post-operative period</td>
</tr>
<tr>
<td>Sleilaty/2009/Lebanon</td>
<td>15 mg/kg orally via gastric tube started on first day post-surgery, then 7mg/kg/day orally until hospital discharge; then 200 mg/day for one month</td>
<td>Bisoprolol 2.5 mg orally via gastric tube started on first day post-surgery; then 2 mg/12 hours continued indefinitely</td>
</tr>
<tr>
<td>Solomon/2001/USA</td>
<td>1 g/24 hours IV infusion for 48 hours, started within 3 hours post-surgery, continued with 400 mg/day orally until hospital discharge</td>
<td>Propranolol 1 mg/6 hour IV for 48 hours, started within 3 hours post-surgery, then 10 mg orally as test dose, then titrated to 20 mg/6 hours orally if HR remained &gt;60 bpm and BP &gt;100 mmHg, continued until hospital discharge</td>
</tr>
</tbody>
</table>

IV, intravenous; BW, body weight; HR, heart rate; BP, blood pressure.
Certainty of evidence

Assessment of evidence certainty for all outcomes in this meta-analysis resulted in moderate certainty.

Discussion

Postoperative AF remains the most common complication in cardiac surgery patients. The incidence varies depending on the procedure, occurring after around 30% of coronary artery bypass grafting (CABG) surgery, 40% of valve repair and replacement surgeries, and about 50% in combined cardiac procedures. According to the guideline by the American Heart Association/American College of Cardiology and the Heart Rhythm Society in 2014 on the management of AF, preoperative administration of amiodarone is recommended before cardiac surgery on patients with increased risk of developing postoperative AF (Class IIa, Level of Evidence A). Risk factors for developing postoperative AF include advanced age, male gender, previous history of AF, diabetes mellitus, and the presence of left atrial enlargement, which are similar to the characteristics of most patients undergoing cardiac surgery. On the other hand, the European Society of Cardiology (ESC), in their most recent guideline on diagnosis and management of AF, recommended routine perioperative administration of amiodarone or beta-blockers regardless of risk factor status (Class I, Level of Evidence A). Although the recent guidelines have signified the importance of therapeutic agents administration as a prophylaxis for postoperative AF, there is another issue on whether amiodarone or beta-blockers should be given for better outcomes.

In our meta-analysis comprising eight studies, there was no difference in postoperative AF episodes between the amiodarone and beta-blockers groups. This result supports the findings from a similar meta-analysis conducted in 2012. Furthermore, this study found no difference between both groups in duration of AF, hospital length of stay, and mean ventricular rate. It could be implied that both drugs are equally effective in preventing postoperative AF. Therefore, in clinical practice, it is more appropriate to make an individual decision for each case rather than to follow a prespecified general guideline.

Beta-blockers should be the agent of choice for patients with multiple risk factors who are already receiving long-term beta-blockers, as abrupt discontinuation of beta-blockers before surgery is associated with two- to fivefold increased risk of developing postoperative AF. On the other hand, it might not be suitable for urgent patients without a history of prior use of the agent as it should be initiated two to seven days before surgery. Extra caution should also be taken when beta-blockers are administered to patients without a history of previous use, as some patients may develop bronchospasm. Another issue is choosing the preferred variant of beta-blocker. Carvedilol has shown an 18 to 20% higher reduction of postoperative AF than metoprolol, although the length of hospital stay was equal. A more recent type of beta-blocker is sotalol, which exhibits class III antiarrhythmic effects on top of typical beta-blocker features. Several studies have demonstrated the superiority of sotalol when compared to conventional beta-blockers to prevent postoperative AF, although the sotalol group developed more side effects such as bradycardia and hypotension.

Amiodarone, which plays a role in both rate control and rhythm control strategies, has been demonstrated to reduce the risk of postoperative AF by 12 to 51% when compared to placebo. It is equally effective when given in different
doses (low dose <3g), medium dose 3 – 5 g, and high dose > 5g), timing (pre/post operative), and through either routes (oral/IV). However, there is a rising concern regarding safety, as evidenced by a meta-analysis that reported an increased risk of hypotension, prolonged QT interval, and bradycardia in the amiodarone group when compared to placebo. Other extracardiac adverse effects from amiodarone include thyroid, hepatic, and pulmonary toxicities.

The emergence of alternative options for preventing postoperative AF, such as corticosteroids, colchicine, and statins may be considered in an individualised manner. Corticosteroids, for example, were demonstrated to further reduce the incidence of postoperative AF when combined with beta-blockers, although the length of hospital stay was not different. The overall use of corticosteroids is low due to the popular belief that they are associated with multiple risks. Nonetheless, although corticosteroids use is associated with increased risk of hyperglycaemia, several studies reported that administration of corticosteroids did not increase the risk of infection, bleeding, and stroke.

Longer AF duration (>24 h per week) is associated with a higher mortality risk. However, there is no evidence whether this is appropriate for postoperative AF. Longer AF duration is also associated with an increased risk of stroke, but there was not enough data in the studies included in this meta-analysis to assess either stroke or mortality as a secondary outcome.

Both amiodarone and beta-blockers have been widely utilised in the therapy of postoperative AF, with current evidence reporting comparable outcomes between both agents. Beta-blockers are one of the medications used in rate control strategy, while amiodarone plays a role in both rate control and rhythm control approaches. In the RACE II trial, patients set to a stricter limit [heart rate < 80 beats per minute (bpm)] were not associated with lower morbidity, mortality, and hospitalisation when compared to the more lenient group (heart rate <110 bpm). In postoperative AF, both rate control and rhythm control approaches have shown similar complication rates and equal days of hospitalisation.

There were a few notable limitations in this study. More recent studies investigated the use of less conventional drugs to prevent postoperative AF, resulting in a scarcity of newer trials comparing amiodarone and beta-blockers. It was not possible to examine the risk of bradycardia, hypotension, stroke, and mortality, which are commonly associated with atrial fibrillation, due to a lack of data. It should also be pointed out that in this study, we compared amiodarone with all types of beta-blockers, including sotalol. Each beta-blocker differs in properties, and some patients may benefit more from a specific type of beta-blockers but less from another.

Future research on specific population (e.g., diabetes, older age, previous history of AF) undergoing cardiac surgeries are needed to understand the efficacy and risk associated with each agent commonly used to prevent postoperative AF. Additionally, more studies investigating the efficacy and safety of emerging unconventional drugs as a first-line prophylaxis is required as existing studies have reported conflicting results.

Conclusions
Our meta-analysis showed that the use of either amiodarone or beta-blockers for the prevention of postoperative AF after cardiac surgery results in comparable AF episodes, duration, mean ventricular rate and hospital length of stay. The drug of choice for each patient should therefore be personalised based on the pre-existing medical conditions.

Data availability
Underlying data
All data underlying the results are available as part of the article and no additional source data are required.

Reporting guidelines

Data are available under the terms of the Creative Commons Zero “No rights reserved” data waiver (CC0 1.0 Public domain dedication).


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