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Review

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Amiodarone and postoperative atrial fibrillation

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Abstract

New-onset postoperative atrial fibrillation (POAF) develops in 10%-50% of patients after cardiac surgery. In this review, we focus on risk factors associated with POAF and the different pharmacological strategies used for prophylaxis, with special attention to amiodarone. The use of amiodarone will be discussed both as a prophylactic regimen used before and following cardiac surgery, but also as a rhythm control treatment in patients who develop POAF. Finally, we conclude by reviewing gaps in the literature on amiodarone and further studies which could close these gaps.

Keywords: Amiodarone, atrial fibrillation, postoperative, cardiac surgery

INTRODUCTION

New-onset postoperative atrial fibrillation (POAF) may develop in 10%-50% of patients after cardiac surgery. The rate of occurrence is highly related to the primary cardiac pathology and certain co-morbidities[1]. The peak incidence is around days 2-4 postoperatively[2]. POAF is associated with increased morbidity and mortality as well as increased healthcare costs and resource utilization[3,4]. The mechanism of

POAF compared to preoperative persistent atrial fibrillation (PEAF) has recently been studied with noninvasive 3-dimensional beat-by-beat mapping using a 252-electrode vest[5]. This study has demonstrated that POAF and PEAF both involve rotor activity, but focal activity is much less common in POAF than PEAF. There are several well-established risk factors for POAF[6], which can broadly be divided into fixed risk factors and acute ones. Fixed risk factors include increasing age, with patients 60 years and older at higher risk[7-9]. Additionally, comorbidities including COPD, diabetes mellitus, and peripheral arterial disease increase the risk[8,10]. There are also acute risk factors that are related to the postoperative state. For example, blood transfusion has a dose-dependent relationship with POAF in patients undergoing cardiac surgery[11-13].

Prophylactic medications for post-operative atrial fibrillation

Several medications have been studied for prophylaxis of POAF. These include beta-blockers, angiotensin converting enzyme (ACE) inhibitors, statins, and anti-arrhythmic medications. Beta-blockers are well known to reduce POAF after cardiac surgery. The mechanism of POAF involves sympathetic activation, and therefore beta-blockers have been widely studied in its prevention. In a meta-analysis of thousands of patients included in randomized trials, beta-blockers were found to have an odds ratio of 0.33 for the prevention of POAF[14]. In fact, the 2006 American College of Cardiology/American Heart Association/European Society of Cardiology guidelines for the management of patients with atrial fibrillation have a class IA recommendation for the use of oral beta-blockers to prevent POAF[15].

There have been at least 8 randomized controlled trials of statins in cardiac surgery. In 2006 the ARMYDA-3 randomized trial of atorvastatin for reduction of POAF was published[16]. This trial enrolled 200 patients undergoing elective cardiac surgery with cardiopulmonary bypass and randomized them to 40 mg daily of atorvastatin or placebo starting 7 days before surgery. Atorvastatin was shown to have a 61% reduction in the incidence of POAF compared to placebo, and hospital stay was shortened by 0.6 days. In a meta-analysis from 2010, statins were found to be associated with a 43% risk reduction of POAF as well as shortened hospital stay, and starting statins earlier before surgery was found to be associated with a greater reduction in POAF[17]. In particular, there was a range of starting a statin 2 days to 28 days preoperatively, and meta-regression analysis of these trials had demonstrated that earlier initiation of a statin before surgery was linearly associated with a reduced incidence of POAF[17]. Interestingly, statin dose was not found to correlate with the magnitude of reduction in POAF.

ACE inhibitors have been suggested as a potential drug to reduce the incidence of atrial fibrillation, both in medical patients and after cardiac surgery. The mechanism by which ACE inhibitors reduce atrial fibrillation is thought to involve changes in cardiac structure and function, rather than direct anti-arrhythmic properties. In animal studies, ACE inhibitors and angiotensin receptor blockers (ARBs) have been found to prevent left atrial dilatation and atrial fibrosis[18]. Data on ACE inhibitors and ARBs from the randomized controlled atrial fibrillation suppression trials II and III (AFIST II and III) have been published[19]. AFIST II was a randomized trial evaluating the effect of amiodarone and atrial septal pacing on the incidence of POAF after coronary artery bypass grafting (CABG) and/or valvular surgery. AFIST III was a randomized trial evaluating the impact of aortic fat pad maintenance or removal on POAF in patients undergoing first-time CABG. In these two trials, 48.2% of 338 patients received an ACE inhibitor or ARB preoperatively. Analysis of these 338 patients has shown that preoperative use of an ACE inhibitor or ARB had an odds ratio of 0.71 for the development of POAF, but with a non-significant confidence interval[19]. A separate trial of irbesartan in 100 consecutive patients undergoing CABG randomized 50 patients to receive irbesartan for 5 days prior to surgery, and 50 to receive no irbesartan[20]. The incidence of POAF in the irbesartan group was 6% *vs.* 22% in the no irbesartan group, which was statistically significant. Therefore, this remains an unsolved issue. This lack of evidence combined with hesitation due to the risk of vasoplegia

further limit administration of ACE inhibitors or ARBs prior to cardiac surgery[21]. Following transcatheter aortic valve replacement (TAVR), renin-angiotensin system (RAS) inhibitors, including ACE inhibitors, ARBs, spironolactone, and eplerenone, have been shown to reduce the incidence of post-TAVR atrial fibrillation[22]. This data has emerged from a review of 2866 patients in the RASTAVI registry, a 10 institution multicenter registry of patients undergoing TAVR. These medications also reduced cerebrovascular events, readmissions, and cardiac mortality at 3 years. In the medical literature, a meta-analysis of 11 randomized controlled trials has shown that ACE inhibitors and ARBs reduced the incidence of atrial fibrillation by 28% in diverse populations: those with heart failure or hypertension, those who have undergone cardioversion for atrial fibrillation, and following myocardial infarction[18]. These benefits were found only in patients with left ventricular systolic dysfunction and left ventricular hypertrophy. These results suggest that ACE inhibitors could be used to improve the efficacy of cardioversion.

AMIODARONE

Amiodarone for post-operative atrial fibrillation

Amiodarone is one of the most widely used antiarrhythmic agents and is also commonly used for prophylaxis of POAF. Interestingly, amiodarone is approved by the Food and Drug Administration for the treatment of lethal ventricular arrhythmias, an approval which it gained in 1995, but not for the management of atrial fibrillation. However, it is safe and effective if used with a firm understanding of its unique pharmacokinetics as well as the potential for drug interactions and adverse events[23]. Amiodarone is an iodinated benzofuran derivative and a highly lipophilic drug with unpredictable pharmacokinetics. Although originally classified as a class III agent due to its ability to prolong refractoriness in cardiac regions and prevent/terminate re-entry, amiodarone shows antiarrhythmic properties in all four antiarrhythmic drug classes[24]. Specifically, amiodarone decreases conduction velocity by blocking sodium channels (Class I effect), antagonizes non-competitively α and β adrenergic receptors (class II effect), and also exerts a class IV antiarrhythmic effect by acting as a calcium channel blocker[25]. The consequences of these channel-blocking effects can be demonstrated electro-physiologically. Most importantly, potassium-channel blockade slows repolarization, causing an increase in the duration of the action potential and the refractoriness of cardiac tissue; this has the effect of prolonging the QT interval. In addition, amiodarone is also uniquely effective in preventing experimentally-induced atrial electrical remodeling[26]. Finally, dosing and route of administration have significant effects on the bioavailability and properties of amiodarone. During loading, the acute effects of intravenous amiodarone are predominately sodium channel, β-receptor, and calcium channel blockade. The class III effect is seen after completion of the loading dose because of the increased levels of the active metabolite, desethylamiodarone[27].

Prior to dosing amiodarone, it is important to note the pharmacokinetics. Amiodarone has an oral bioavailability of 30%-50%, and the rate and extent of amiodarone absorption are increased when taken with food compared to the fasting state[28]. Amiodarone is metabolized in the liver. During loading, amiodarone passes through three phases of distribution: (1) central or vascular distribution occurs over approximately 24 h; (2) peripheral or solid organ distribution occurs over the next 7 days; and (3) deep or fat tissue distribution occurs over the subsequent 4 weeks. The full antiarrhythmic effect of amiodarone plateaus after 10 weeks of therapy[29], and the half-life of amiodarone is 55 days, resulting in significant residual effect after discontinuation[30]. For hemodynamically stable patients, the loading dose is initiated with intravenous amiodarone for better bioavailability: 150 mg intravenous bolus, followed by 1 mg/min for 6 h, followed by 0.5 mg/min for 18 h or until switched to oral therapy[31]. No dose adjustment is required for renal impairment. No specific guidelines exist for hepatic impairment; however, given the intermediate first-pass extraction through the liver, treatment may be initiated at a low-normal dose, with low maintenance dosing[32]. Similar loading strategies can be used for both atrial and ventricular arrhythmias. When amiodarone is used for rhythm control in atrial fibrillation, typical dosing is 200 mg daily[27], given after a

loading dose has been completed.

Amiodarone is an excellent choice for use in patients with structural heart disease or congestive heart failure[33], but there are also contraindications and side effects that should be considered. Contraindications to the use of amiodarone include severe sinus node dysfunction, including symptomatic sinus bradycardia, and advanced conduction system disease. A prolonged QT interval on amiodarone also represents a contraindication to its use, with different physicians choosing different intervals for discontinuation. Before choosing amiodarone for the treatment of atrial fibrillation, clinicians can consider other options, such as a trial of rate control agents. These agents have a lower risk profile than amiodarone, but their use depends on the clinical setting[33]. Amiodarone is associated with both cardiovascular and non-cardiovascular adverse events. The most frequent cardiovascular side effect is bradycardia, which is often dose-related, occurs more frequently in elderly patients than in younger patients, and can often be mitigated by dose reduction[34]. The conduction system should be monitored for QTc prolongation, but amiodarone is not generally associated with torsades de pointes (< 0.5%) as compared with other drugs that prolong the QT interval (e.g., sotalol and dofetilide)[23,35]. Clinical evidence of hypothyroidism occurs in up to 20% of patients taking amiodarone. This is likely because of interference with the iodothyronine deiodinases, which metabolize thyroid hormones[36]. Hypothyroidism is easily managed with levothyroxine and generally is not cause for discontinuing amiodarone. Thyrotropin levels should be checked in all patients at least every 6 months after initiation[37,38].

Pulmonary toxicity is one of the most serious complications of amiodarone use. It occurs in less than 3% of patients and is thought to be related to the total cumulative dosage[26], and therefore applies to chronic use rather than use in the postoperative period. Chronic amiodarone therapy should therefore be used cautiously in patients with preexisting pulmonary disease (e.g., severe asthma, chronic obstructive pulmonary disease) or those requiring oxygen therapy, as they are at higher risk of pulmonary toxicity[39]. The management of pulmonary toxicity involves discontinuation of therapy, supportive management, and potential corticosteroid administration for extreme cases[40]. Side effects resulting in discontinuation of therapy occur in 13%-18% of patients after 1 year[38].

Amiodarone is frequently used for the prevention and treatment of atrial fibrillation associated with cardiac surgery, including the maze procedure for the treatment of atrial fibrillation[33]. However, there are no major clinical trials that directly compare the use of amiodarone to beta-blocker alone. In addition, there have not been thorough studies on combinations of drugs such as ARBs with amiodarone. Emerging data suggest that combination therapy is more effective than either agent alone[26,41]. It is important to emphasize that the goal of a short 2-3 day course of amiodarone before surgery is to reduce the incidence of new-onset POAF, not to treat chronic atrial fibrillation. The increased efficacy of amiodarone in preventing new-onset POAF compared to treating chronic atrial fibrillation may arise from its action as a class I through IV antiarrhythmic, particularly its action as a beta-blocker (class II) and calcium channel blocker (class IV), as discussed above[25].

Finally, three important drug-drug interactions deserve mention. First, QT prolongation due to lengthened repolarization from potassium channel blockade is a known side effect of amiodarone. This effect can be exacerbated by combining amiodarone with other drugs that prolong the QT interval[42]. Quinolones are one example, but digoxin is another medication that increases the risk of torsades de pointes in patients with long QT interval. In addition, antipsychotic agents including haloperidol, antidepressants such as fluoxetine, macrolide antibiotics, and methadone are common drugs that prolong QT interval[42]. Therefore obtaining a daily electrocardiogram to measure the QT interval is warranted in postoperative patients on

amiodarone. Second, adding amiodarone to a patient's home digoxin regimen can increase the level of digoxin, and dose adjustment of digoxin can be warranted. In fact, levels of digoxin can double in patients on amiodarone, and it is recommended to reduce the digoxin dose by 50% in patients on amiodarone[42]. Third, amiodarone increases the international normalized ratio in patients on warfarin, and warfarin dosing must be monitored and reduced[42].

Clinical trial data on amiodarone

There have been several randomized controlled trials examining oral amiodarone for prophylaxis of POAF [Table 1]. The first major randomized trial was performed at the University of Michigan in 1997, showing that amiodarone given 1 week before surgery at a dose of 600 mg daily, then 200 mg daily while in hospital and none on discharge, reduced the rate of POAF while in hospital from 53% to 25%, and reduced the rate of POAF after discharge from 12% to 2%[43]. The vast majority of operations were CABG, valve operations, or combined CABG-valve operations. 57% had a valve operation of some kind, contributing to a high baseline rate of POAF in the placebo group. For patients who experienced POAF, the average ventricular response rate was 112 bpm for the amiodarone group and 135 bpm for the placebo group. This trial was important for two reasons. First, hospital stay was reduced by 1.4 days in the amiodarone group, and the cost of hospitalization was reduced from $26,491 to $18,375. This cost reduction does not include the cost of the increased episodes of POAF after hospital discharge. Second, outpatient initiation of amiodarone proved safe, with no pro-arrhythmic side effects or serious adverse events such as symptomatic bradycardia.

The PAPABEAR (Prophylactic Oral Amiodarone for the Prevention of Arrhythmias that Begin Early after Revascularization, Valve Replacement, or Repair) trial in 2005 randomized 601 patients to placebo or oral amiodarone (10 mg/kg daily) for 6 days prior to surgery and for 7 days on and after the day of surgery, and found that the rate of atrial tachyarrhythmias was reduced from 29.5% to 16.1% by amiodarone[3]. Postoperative sustained ventricular tachyarrhythmias were less common (0.3% *vs.* 2.6%). Dosage reduction of amiodarone was required in 11.4% *vs.* 5.3% in the placebo group.

The second major randomized trial to examine preoperative oral amiodarone for prevention of POAF was the Atrial Fibrillation Suppression Trial (AFIST), published in 2001[44]. It examined 220 patients who were receiving beta-blockers preoperatively, and randomized them to receive amiodarone *vs.* placebo for 1 day before surgery (if more urgent surgery was required), or for 5 days before surgery. The dose of amiodarone was 1.6 g for one day or 600 mg daily before surgery if the patients had longer preoperative period. Amiodarone was then continued on the day of surgery, as well as for 4 days post-operatively. Over 75% of the patients in the study had an isolated CABG. The rate of POAF was reduced from 38% to 22.5% for patients in the amiodarone arm, time to the first episode of POAF was lengthened, and the average duration of POAF episodes was shorter. Rates of bradycardia were not different between amiodarone and placebo. None of the patients who started amiodarone 5 days before surgery required amiodarone discontinuation for side effects such as bradycardia, and these patients received amiodarone as well as a beta-blocker.

Other trials have corroborated these results. Another randomized trial of 110 patients undergoing coronary bypass randomized patients to placebo or amiodarone 600 mg given one day before surgery, and amiodarone 600 mg from days 2 to 7 after surgery[45]. Amiodarone was also given in the operating room (300 mg intravenous), followed by a continuous infusion of a total of 20 mg/kg over the first 24 h after surgery. Amiodarone was associated with a reduction in POAF (34% *vs.* 85%), reduction in intensive care unit stay (1.8 days *vs.* 2.4 days), and reduction in total hospital stay (11.3 days *vs.* 13.0 days). This trial also examined amiodarone levels, defining an effective level as a serum amiodarone level ≥ 0.7 μg/mL and serum desethylamiodarone level ≥ 0.4 μg/mL. In patients in the amiodarone group who maintained sinus rhythm

Table 1. Randomized trials of oral amiodarone as prophylaxis for POAF after cardiac surgery

Trial (year)	Number of patients	Regimen	Finding
Daoud *et al.*[43] (1997)	124	600 mg amiodarone *vs.* placebo × 7 days before surgery, then 200 mg daily *vs.* placebo until discharge	25% rate of POAF with amiodarone *vs.* 53% with placebo
Mitchell *et al.*[3], PAPABEAR[1] trial (2005)	601	Amiodarone 10 mg/kg daily × 13 days, starting 6 days before surgery, *vs.* placebo	16.1% rate of atrial tachyarrhythmias *vs.* 29.5% with placebo
Giri *et al.*[44], AFIST[2] trial (2001)	220	6-7 g total of amiodarone *vs.* placebo, starting 1 day or 5 days before surgery[3], given on day of surgery, and given after surgery for 4 days	22.5% rate of POAF with amiodarone *vs.* 38% with placebo
Budeus *et al.*[45] (2006)	110	Amiodarone 600 mg one day before surgery, 300 mg IV then 20 mg/kg total dose drip on day of surgery, then 600 mg daily days 2-7 after surgery, *vs.* placebo	34% rate of POAF with amiodarone *vs.* 85% with placebo

[1]Prophylactic Oral Amiodarone for the Prevention of Arrhythmias that Begin Early after Revascularization, Valve Replacement, or Repair (PAPABEAR). [2]Atrial Fibrillation Suppression Trial (AFIST). [3]Timing depended on the clinical requirement for surgery. POAF: Postoperative atrial fibrillation.

postoperatively, 74% had an effective amiodarone level. By contrast, in the patients in the amiodarone group who developed atrial fibrillation postoperatively, only 20% had an effective amiodarone level. Of note, patients with an effective level did not have any difference in baseline characteristics, including body mass index, compared to patients without an effective level.

Further trials have examined the use of intravenous amiodarone for prophylaxis of POAF [Table 2]. These trials have either started amiodarone in the operating room, shortly after reaching the intensive care unit, or on the first postoperative day. A trial published in 1999 consisted of 300 patients randomized to intravenous amiodarone (1 g/day for 2 days) or placebo, with a continuous amiodarone infusion started within three hours after reaching the intensive care unit[46]. Compared to oral regimens, this was a low-dose amiodarone regimen, and resulted in a more modest reduction in POAF from 47% in the placebo group to 35% in the amiodarone group ($P = 0.01$). By contrast, a similar low-dose randomized trial has not shown an effect. In a trial from 2010, 120 patients undergoing valvular operations were randomized to a loading dose of 300 mg of intravenous amiodarone in the operating room, followed by an infusion of 15 mg/kg per day for 2 days[47]. This totals 2.4 g of amiodarone in a 70 kg patient. This trial found that POAF occurred in 59.3% in the amiodarone group *vs.* 40% in the placebo group. This article has concluded that a 48 h infusion of amiodarone does not reduce the rate of POAF after valvular surgery.

Three additional trials, including intravenous amiodarone, used a larger dose and have shown a larger absolute reduction in POAF. A randomized study from Turkey also demonstrated the value of preoperative amiodarone[48]. 241 patients scheduled for coronary bypass were randomized to one of three groups. Group 1 received 100 mg of metoprolol preoperatively, then 1 mg intravenous digoxin on the day of operation, then oral digoxin (0.25 mg) and metoprolol (100 mg) postoperatively. Group 2 received a total of 3.45 g of amiodarone, with 1.2 g given intravenously starting on completion of the operation with a 300 mg bolus, then 450 mg amiodarone the next day intravenously, then 600 mg daily for three days. Group 3 received no antiarrhythmic prophylaxis. The rates of POAF were 16.8% in Group 1, 8.3% in Group 2, and 33.6% in Group 3. Two of 72 patients in Group 2 had amiodarone stopped for atrioventricular block. Next, a trial from Denmark published in 2007 randomized 250 patients undergoing coronary bypass to amiodarone or placebo[49]. Amiodarone was given as 300 mg intravenously over 20 min on the first postoperative day, followed by an oral dose of 600 mg twice daily for the first 5 postoperative days. The risk of POAF was reduced from 26% to 11%. Of patients with POAF, 43% were symptomatic in the amiodarone group *vs.* 84% in the placebo group. This concords with earlier observations that patients who develop POAF after amiodarone administration are less tachycardic[43]. Finally, a trial from 2003 randomized 157

Table 2. Randomized trials of intravenous amiodarone as prophylaxis for POAF after cardiac surgery

Trial (year)	Number of patients	Regimen	Finding
Guarnieri *et al.*[46] (1999)	300	IV[1] amiodarone 1 g/day for 2 days *vs.* placebo, starting immediately after surgery	35% rate of POAF with amiodarone *vs.* 47% with placebo
Beaulieu *et al.*[47] (2010)	250	IV amiodarone 300 mg in the operating room, followed by 15 mg/kg per day infusion for 2 days, or placebo	59.3% rate of POAF with amiodarone *vs.* 40% with placebo
Tokmakoglu *et al.*[48] (2002)	241	Group 1: metoprolol preoperatively, digoxin intraoperatively, and metoprolol and digoxin postoperatively Group 2: amiodarone started in the operating room and continued postoperatively (3.45 g total) Group 3: no antiarrhythmic prophylaxis	16.8% rate of POAF in Group 1, 8.3% in Group 2, and 33.6% in Group 3
Zebis *et al.*[49] (2007)	250	IV amiodarone 300 mg on the first postoperative day, then 600 mg of oral amiodarone twice daily for 5 days, or placebo	11% rate of POAF with amiodarone *vs.* 26% with placebo
Yagdi *et al.*[50] (2003)	157	IV amiodarone 10 mg/kg per day for 2 days, then oral amiodarone 600 mg per day for 5 days, 400 mg per day for 5 days, then 200 mg per day for 20 days, or placebo	10.4% rate of POAF with amiodarone *vs.* 25% with placebo

[1]IV is intravenous. POAF: Postoperative atrial fibrillation.

patients undergoing elective coronary bypass to placebo or intravenous amiodarone 10 mg/kg per day for 2 days, started within 2 h of intensive care unit arrival[50]. This was followed with oral amiodarone 600 mg daily for 5 days, 400 mg daily for 5 days, and 200 mg daily for 20 days. The rate of POAF was 10.4% with amiodarone and 25% with placebo. Once again, the maximum ventricular rate during atrial fibrillation was 105.9 with amiodarone and 126 with placebo. Hospital stay was 1.0 day shorter with amiodarone. A higher rate of postoperative hypotension was observed with amiodarone (10.4% *vs.* 5%), but this was not significant. Amiodarone was discontinued in 5.2% of patients owing to bradycardia less than 60 beats per minute or a corrected QT interval > 440 ms, although this is quite a low threshold in corrected QT interval for discontinuation. None of these patients had POAF, and bradycardia resolved after discontinuation.

Next, we review briefly a study of rate versus rhythm control for POAF[51]. In this study, 523 patients were randomized to either rate control or rhythm control for POAF, with findings showing a similar length of hospitalization and a rate of cerebrovascular thromboembolic events less than 1% per patient-month in both groups, although more patients in the rhythm control arm were in sinus rhythm at 60 days. However, 26.7% of patients in the rate control group received amiodarone or underwent cardioversion, and 23.8% of patients in the rhythm control group did not complete a full course of amiodarone mostly due to side effects. The rate of amiodarone discontinuation due to side effects seems high compared with anecdotal clinical practice. Overall, the rate of nonadherence makes the two treatment groups difficult to compare, the baseline rate of thromboembolic events was very low, and the trial demonstrates the challenges of performing randomized trials in this space. Nonetheless, both groups received amiodarone, and this shows the ubiquity of its use.

Finally, it is important to note that rates of POAF are similar with on-pump CABG and off-pump CABG. In a retrospective review of 1836 patients undergoing CABG, POAF occurred in 18.3% of on-pump CABG patients and 19.3% of off-pump CABG patients[52]. In both groups, the peak incidence was between the second and third postoperative days. Similarly, in an analysis of the Randomized On Versus Off Bypass trial of on-pump *vs.* off-pump CABG, POAF occurred in 25.4% of on-pump CABG patients and 27% of off-pump CABG patients[53]. As a result, prophylaxis is warranted for all CABG patients.

Protocols for use of amiodarone to prevent postoperative atrial fibrillation

The various trials reviewed use different doses and durations of amiodarone, and many protocols are effective. Some protocols use oral amiodarone before surgery, while others start amiodarone on the day of surgery. Of note, low-dose protocols using a total of 2 g of amiodarone given over the first two postoperative days have shown none to low reduction in POAF[46,47]. Therefore, amiodarone must be started preoperatively to have the greatest benefit. Rates of 10% for POAF have been achieved in trials with adequate prophylactic regimens that involve the administration of a large enough amount of amiodarone. These amounts are well tolerated, with very low rates of bradyarrthythmias in all trials.

Amongst the authors of the current paper, protocols are as follows. Many use a 2 to 3-day course of oral amiodarone at a dose of 400 mg twice daily before surgery. This is followed by a longer course of 8 days postoperatively, ranging from 200 mg to 400 mg daily. Another protocol is a 5 to 7-day course of oral amiodarone at a dose of 200 mg daily before surgery. This is followed by 400 mg daily until discharge. If POAF develops, a load of 400 mg three times daily is given, followed by a 4-week taper. To summarize, it is important to select a regimen that provides enough preoperative amiodarone to provide a measurable reduction in POAF.

Knowledge gaps and future directions

There are several gaps in our current understanding of amiodarone use for POAF. While the pharmacokinetics of intravenous amiodarone are well described, the clinical efficacy of intravenous amiodarone boluses for POAF, compared to oral administration of amiodarone, have not been studied in a trial setting. It also remains unclear how many boluses to give an individual patient. The safety of intravenous amiodarone boluses is also a point of contention. Intravenous amiodarone is dissolved in polysorbate 80, a solvent that is a known vasodilator and a negative inotrope[54]. The negative inotrope properties of polysorbate 80, also known as Tween 80, were reported in dogs in 1982, where severe declines in left ventricular dP/dt for over 30 min after administration were observed[54]. It is known that vasodilatation occurs from an intrinsic vasorelaxant effect, as well as histamine release triggered by polysorbate 80[55]. These effects may be decreased by lowering the rate of infusion[55]. Evidence for the role of polysorbate 80 has recently been provided by a study that compared blood pressure in patients after administration of amiodarone dissolved in polysorbate 80 (120 patients), to blood pressure in patients after administration of amiodarone dissolved in a new solvent cyclodextrin (40 patients)[56]. Patients received these formulations based on a rate of amiodarone of 1 mg/min for 6 h, followed by 0.5 mg/min for 18 h There was both a significant decrease in blood pressure as well as increased requirement for fluid boluses to treat hypotension in the polysorbate 80 group. These findings were also reported in dog studies in which amiodarone in polysorbate 80 decreased aortic pressure, cardiac output, and cardiac contractility[57]. These findings were also noted after administration of polysorbate 80 alone, but not after administration of the cyclodextrin solvent. This helps to explain why 15% to 26% of patients receiving intravenous amiodarone have hypotension[57]. These studies explain the common observation of hypotension with intravenous amiodarone boluses, but the overall safety of these boluses, as well as which patients should be receiving them, remains unknown. Further, it is not established whether or not amiodarone drips are more efficacious than oral amiodarone dosing for the management of POAF.

These gaps in understanding provide avenues for further study. We would propose a randomized trial in which patients are randomized to intravenous amiodarone drips or oral amiodarone regimens for new-onset POAF. We would propose a further study in which patients are randomized to various amounts of 150 mg boluses of amiodarone for POAF, with outcomes to be studied including not only duration of the atrial fibrillation episode, but also other parameters such as hypotension and requirement for cessation of intravenous infusion. A more widely available formulation of amiodarone dissolved in cyclodextrin could

Table 3. Summary of recommendations

Practice	Recommendation
Preoperative amiodarone	400 mg PO bid × 3 days before surgery; if longer period before surgery, can give 200 mg PO daily × 5-7 days
Postoperative amiodarone	400 mg PO daily until discharge, then stopped on discharge, if no POAF. If POAF develops, load with 400 PO tid × 3 days, then a 4-week taper.
Cardioversion	We would recommend for a patient in POAF for more than 24 h, provided there are no contraindications or concerns regarding conscious sedation
Intraoperative blood transfusion	We recommend a threshold level of Hg < 6.0 g/dL with at least one of the following: mixed venous saturation ≤ 55, elevated lactate > 2.2 mmol/L, elevated base excess > -3, low bicarbonate < 22 mmol/L[58]
Postoperative blood transfusion	We recommend a threshold level of Hg < 7.0 g/dL with at least one of the following: increased oxygen requirement, hypotension, end-organ dysfunction, elevated lactate > 2.2 mmol/L, or ongoing bleeding[58]

POAF: Postoperative atrial fibrillation.

provide a solution to this long-standing issue.

To summarize, the benefits of prophylaxis against POAF with amiodarone are clear. Trials consistently demonstrate a reduction in intensive care length of stay and overall hospital stay. There is a reduction in the fraction of patients who are symptomatic when having an episode POAF, and there is a measurable reduction in heart rate during episodes of POAF. Traditional objections to prophylactic regimens of amiodarone, such as side effects when starting amiodarone in the outpatient setting, have not borne out in clinical trials. These trials all show very low rates of discontinuation of amiodarone when used for prophylaxis. The most successful reductions in POAF appear to occur when amiodarone is started before the time of cardiac surgery. Whether or not to use intravenous or oral amiodarone in the immediate postoperative period seems less important in terms of reduction in POAF, but the use of oral amiodarone may afford hemodynamic benefits.

Finally, limiting POAF is an effort that requires not only medication prophylaxis, but also improvements in perioperative care. For instance, blood transfusion is now known to increase the rate of POAF[11-13], and a restrictive transfusion policy could lead to a reduction in POAF. For example, it is known that inflammation plays a role in the development of POAF, and that red blood cell transfusion increases plasma levels of inflammatory markers. In particular, red blood cell administration has been shown to increase plasma levels of bactericidal permeability increasing protein and interleukin-6 in patients undergoing cardiac surgery[13]. As a result, many programs have undertaken a program to reduce blood transfusion in an effort to minimize not only renal failure and respiratory failure, but also in an attempt to reduce the incidence of POAF.

CONCLUSION

Multiple medications can be used to reduce the incidence of POAF, including statins, beta-blockers, and amiodarone. We provide an example of a protocol to reduce POAF in [Table 3]. Institutional protocols that combine medication prophylaxis with perioperative care protocols limiting blood transfusion are likely to produce the lowest possible rate of POAF and provide multiple opportunities for reducing the incidence of POAF.

DECLARATIONS

Authors' contributions

Contributed to the writing of the manuscript: Waterford SD, Ad M, Ad N, Santore LA, Spellman C, Prescher L

Contributed to the outline of the manuscript: Ad N, Waterford SD
Contributed to the conception of the study: Ad N

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All authors declared that there are no conflicts of interest.

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Not applicable.

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