Amiodarone after surgical ablation for atrial fibrillation: Is it really necessary? A prospective randomized controlled trial

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ABSTRACT

Objective: Prophylactic antiarrhythmic drug (AAD) treatment is a well-established practice after catheter ablation for atrial fibrillation (AF), but it is controversial after surgical ablation. This prospective randomized controlled trial examined whether amiodarone after surgical ablation reduced atrial arrhythmia recurrence within the first 3 months after surgery.

Methods: Ninety patients were randomized to receive ($n = 45$) or not receive ($n = 45$) amiodarone after surgical ablation. Rhythm status was ascertained via clinical follow-up and 72-hour continuous monitoring at 6 and 12 weeks, using Heart Rhythm Society guidelines. Primary outcome was defined as atrial arrhythmia recurrence, cardioversion, ablation, or crossover from no-amiodarone to amiodarone as a result of atrial arrhythmia during follow-up. An intention-to-treat approach was used.

Results: The 2 study groups were similar in traditional predictors for failure, including left atrium size (5.0 vs 5.1 cm, $P = .734$), median AF duration (23 vs 20 months, $P = .513$), and long-standing persistent AF (44% vs 33%, $P = .280$). The primary outcome occurred in 52% of the no-amiodarone group (23 of 44) and 19% of the amiodarone group (8 of 43; $P = .001$). Cumulative freedom from primary outcome was greater in the amiodarone group (81.4% vs 47.7%, $P < .001$). Amiodarone was discontinued in 18 patients randomized to amiodarone for side effects, bradycardia, or noncompliance.

Conclusions: Prophylactic amiodarone reduced early atrial arrhythmia recurrence. These results are consistent with catheter AF ablation findings and should inform recommendations for prophylactic class I/III AAD after surgical AF ablation, regardless of discharge rhythm status. As previously recommended, monitoring for side effects and amiodarone discontinuation by 3 months, for patients in sinus rhythm, is warranted.

Clinical Trial Registration: NCT01416935. (J Thorac Cardiovasc Surg 2016;151:798-803)

Freedom from atrial arrhythmia recurrence for the amiodarone and no-amiodarone groups.

Central Message

Short-term prophylactic AAD after surgical ablation is safe and effective with close monitoring. Guidelines in this area are needed.

Perspective

In a randomized controlled trial, prophylactic amiodarone reduced early atrial arrhythmia recurrence. These results are consistent with catheter AF ablation findings and should inform recommendations for prophylactic class I/III AAD after surgical AF ablation. Monitoring for side effects and amiodarone discontinuation by 3 months, for patients in sinus rhythm, remains warranted.

See Editorial Commentary page 804.

See Editorial page 298 in the February issue.

Atrial fibrillation (AF) is the most common cardiac rhythm disorder, affecting an estimated 6 million US adults.¹ Ablation of AF with either catheter-based or surgical techniques

is becoming increasingly common, and these techniques are performed in many major hospitals both nationally and throughout the world.²

Early recurrence of atrial arrhythmia is relatively common after ablation procedures for AF, even with the routine use of postoperative antiarrhythmic drugs (AADs).³⁻⁵ Most

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Abbreviations and Acronyms

AAD	= antiarrhythmic drug
AF	= atrial fibrillation
EuroSCORE	= European System for Cardiac Operative Risk Evaluation

of these early arrhythmias are transient and resolve within about 30 days.⁴ Recurrence of atrial arrhythmia in the post-operative course, however, has been found to be associated with late failure of catheter or surgical ablation.⁵⁻⁹ For this reason, to resume AAD treatment after catheter ablation for AF has become common practice, to prevent early recurrence.² The prophylactic use of AAD after surgical AF ablation, however, has been the subject of some debate.¹⁰⁻¹² To clarify the need for prophylactic AAD treatment after surgical ablation of AF, we conducted a prospective randomized controlled trial to determine whether amiodarone treatment after surgical ablation is effective in reducing the risk of early recurrence of atrial arrhythmia (≤ 3 months).

METHODS

This study was a prospective, randomized, controlled trial in which 90 patients were randomized to receive amiodarone ($n = 45$) or to not receive amiodarone ($n = 45$) for the first 3 months after surgical ablation for AF. The study was approved by our institutional review board (study no. 10.086), and all patients provided written informed consent. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Inclusion and exclusion criteria used for this study are listed in Table 1.

The random-allocation sequence was created with computer-generated random numbers, and blocked randomization of 10 patients in each block, to ensure balance in the treatment groups in case the study needed to be stopped early. Sequentially numbered opaque envelopes containing the treatment allocation were utilized to conceal the sequence. The random-allocation sequence was generated by the study statistician, and patients were enrolled and assigned to treatment groups by the research coordinator. Blinding was not used for this study.

All patients underwent surgery at the Inova Heart and Vascular Institute between January 2011 and December 2014. The Cox maze III/IV lesion set was utilized in all but 1 study patient.^{13,14} Patients in both groups received postoperative beta-blockers as standard of care, but this study investigated need for addition of amiodarone, a class III AAD, as standard of care for patients immediately after surgical AF ablation. Data collected in this study were merged with our local Society of Thoracic Surgeons database. All patients in this study were followed prospectively as part of our center's AF registry for surgical ablation patients. For patients with recurrences of atrial arrhythmias, recommendations for treatment course were made using our institutional clinical algorithm.¹⁵

Follow-up rhythm status was ascertained primarily via long-term monitoring at 6 and 12 weeks after surgery, using Heart Rhythm Society guidelines.² At the 6- and 12-week time points after surgery, patients wore CardioNet Dual Alert Afib Event Monitors (CardioNet, Malvern, Pa) that recorded for 48 to 72 hours (2-3 days). This methodology for rhythm status determination was more rigorous than standard clinical follow-up during the first 3 months after surgery, but it was important for this study to have increased ability to detect atrial arrhythmia recurrences. For the

rare times when patients could not wear the monitor, electrocardiograph or pacemaker interrogations were obtained from physician records for those time points. Most patients at 6 weeks (88%) and 12 weeks (84%) had rhythm status determined by long-term monitoring (CardioNet or pacemaker interrogation). In 3 patients who were randomized, no follow-up for rhythm status was obtained, including 2 patients who died before 6 weeks, and 1 patient who was lost to follow-up.

The primary outcome was defined as any of the following during the first 3 months after surgery: a recurrence of atrial arrhythmia (at 6- or 12-week follow-up monitoring); a requirement for cardioversion or catheter ablation for atrial arrhythmia; or crossover from the no-amiodarone to the amiodarone group for treatment of an atrial arrhythmia. Crossovers were defined as a patient who switched from the study group to which they were randomized into the other study group. Patients who were assigned to not receive amiodarone were allowed to be treated with a class I/III AAD (including amiodarone) if it was determined to be necessary for treatment of an atrial arrhythmia, and this switch was considered a crossover. Similarly, patients assigned to receive amiodarone were allowed to stop taking the medication if side effects or bradycardia occurred, and this switch was considered a crossover.

Statistical Analysis

Data were analyzed with an intention-to-treat approach in which patients were analyzed in the group to which they were randomized, regardless of crossover status. All analyses were conducted using SPSS, version 17.0 (SPSS, Inc, Chicago, Ill). Noninferiority analyses were originally planned for the primary rhythm outcome in this study, based on the hypothesis that the 2 treatment arms would not differ on rhythm status. Power analyses indicated a sample size of 186 patients ($n = 93$ per group) for the originally planned analyses.

However, midterm analyses were built into the protocol to assess the safety of the treatment arms. When these interim analyses were conducted, meaningful differences in the primary rhythm outcomes were noted, and analyses were shifted to a traditional superiority methodology, with the study protocol amended accordingly. In addition, the study was stopped at this point. Based on the results of the interim analyses presented here, there was no justification to continue the study given the significant differences in rhythm outcome.

Continuous data are presented as mean $\pm$ SD or median (interquartile range), and categorical data are presented as frequency (%), unless otherwise noted. Analyses comparing patient characteristics and outcomes by study group included the independent-samples *t* test or the Mann-Whitney *U* test for continuous variables; and χ^2 analysis or the Fisher exact test, for categorical variables.

Cumulative freedom from the primary outcome of AF recurrence was examined using Kaplan-Meier survival analysis. For multivariate analyses, logistic regression was used to examine whether receipt of amiodarone was an independent predictor for the primary outcome after adjustment for age, gender, EuroSCORE II (European System for Cardiac Operative Risk Evaluation), left atrium size, and duration of AF.

RESULTS

No significant differences were found between the 2 groups in preoperative patient characteristics (Table 2), including age (63.8 vs 63.4 years, $P = .832$); ejection fraction (55.2% vs 54.4%, $P = .729$); EuroSCORE II (2.4% vs 2.9%, $P = .332$), and proportion of women (27% vs 29%, $P = .814$). No differences were found between the amiodarone and no-amiodarone groups in traditional predictors for failure of surgical AF ablation, including left atrium size (5.0 vs 5.1 cm, $P = .734$); median duration of AF (23 vs

TABLE 1. Inclusion and exclusion criteria

Characteristics and criteria
Inclusion
Age ≥ 18 y
Persistent or long-standing persistent AF, according to HRS guidelines
Candidate to undergo the Cox maze procedure for AF
Left ventricular ejection fraction $\geq 30\%$
Normally would be prescribed amiodarone as an AAD after surgical ablation
Able and willing to provide written informed consent
Able and willing to comply with all study requirements including attending follow-up visits
Life expectancy of ≥ 1 y
Exclusion
Emergent cardiac surgery (eg, cardiogenic shock)
Previous attempts at ablation procedure or other AF operation, including surgical or catheter ablation
NYHA class IV heart failure
Documented myocardial infarction within 6 wk before study enrollment
Accessory-pathways disorder (eg, Wolff-Parkinson-White syndrome)
Carotid artery stenosis $>80\%$
Current diagnosis of active systemic infection
Pregnant, planning to become pregnant within 12-14 mo, or lactating
Preoperative intra-aortic balloon pump or intravenous inotropes
Renal failure requiring dialysis
Hepatic failure
Taking antiarrhythmic drug therapy for ventricular arrhythmia
Known connective tissue disorder
Previous or current therapy that could compromise tissue integrity, including thoracic radiation, chemotherapy, or long-term oral or injected steroids
Intravenous drug and/or alcohol abuse
Participation in concomitant research studies of investigational products

AF, Atrial fibrillation; HRS, Heart Rhythm Society; AAD, antiarrhythmic drugs; NYHA, New York Heart Association.

20 months, $P = .513$); proportion with long-standing persistent AF (44% vs 33%, $P = .280$); and proportion with a minimally invasive approach (36% vs 27%, $P = .362$).

Study-Group Crossovers

The proportion of patients who crossed over to the other group was identical for the amiodarone and no-amiodarone groups (40% vs 40%, $P > .999$; Figure 1). The mean time to crossover did not differ between the groups either (13 days vs 11 days, $P = .451$).

In 18 (40%) patients who had been randomized to the amiodarone group, amiodarone was discontinued, due to side effects ($n = 6$; rash, nausea, jaundice, blurred vision, elevated values on liver function test, medication interaction); bradycardia ($n = 9$); or noncompliance ($n = 3$). Discontinuation occurred in-hospital for 9 of these patients, and after discharge for the other 9. In this group of 18 patients, only 1 experienced the primary outcome. This patient had an atrial arrhythmia of >30 seconds but <5 minutes, at 6 weeks and 12 weeks after surgery, as detected by long-term monitoring. The reason for amiodarone to be

TABLE 2. Patient characteristics

Characteristic	No amiodarone (n = 45)	Amiodarone (n = 45)	P
Age (y)	63.4 $\pm$ 10.1	63.8 $\pm$ 10.7	.832
Female	13 (29)	12 (27)	.814
Ejection fraction (%)	54.4 $\pm$ 9.6	55.2 $\pm$ 11.6	.729
Congestive heart failure	12 (27)	10 (22)	.624
Diabetes	3 (7)	8 (18)	.108
Body mass index	27.8 $\pm$ 5.6	30.0 $\pm$ 7.1	.113
Hypertension	30 (67)	27 (60)	.512
Peripheral vascular disease	4 (9)	1 (2)	.361
Previous cerebrovascular accident	2 (4)	2 (4)	$>.999$
Chronic pulmonary disease	11 (24)	9 (20)	.612
Left atrium size (cm)	5.1 $\pm$ 0.9	5.0 $\pm$ 0.9	.734
Duration of AF (mo)	20 (3-52)	23 (7-59)	.513
Long-standing persistent AF type	15 (33)	20 (44)	.280
EuroSCORE II (%)	2.9 $\pm$ 3.5	2.4 $\pm$ 1.8	.332
Minimally invasive approach	12 (27)	16 (36)	.362
Concomitant procedure	38 (84)	35 (78)	.419
Type of concomitant surgery			
Mitral valve	27 (60)	23 (51)	.396
Aortic valve	8 (18)	9 (20)	.788
Coronary artery bypass	8 (18)	6 (13)	.561

Data are presented as frequency (%), mean $\pm$ SD, or median (interquartile range). EuroSCORE, European System for Cardiac Operative Risk Evaluation; AF, atrial fibrillation.

discontinued in this patient was bradycardia; discontinuation happened during the hospital stay, and the patient was in sinus rhythm during the hospital stay and at discharge.

In addition, 18 (40%) patients who had been randomized to the no-amiodarone group crossed over to amiodarone for treatment of an atrial arrhythmia. All of these patients experienced the primary endpoint—recurrence of atrial arrhythmia—which necessitated use of amiodarone and crossover out of their randomized treatment group.

Rhythm Outcome

The no-amiodarone group was similar to the amiodarone group in the percentage of patients discharged after surgery with atrial arrhythmia (7% vs 7%, $P > .999$). The primary composite outcome of AF recurrence occurred in 52% of the no-amiodarone group (23 of 44 patients) and 19% of the amiodarone group (8 of 43 patients; $P = .001$). Cumulative freedom from AF recurrence during the first 3 months after surgery was significantly greater in the amiodarone group than in the no-amiodarone group (81.4% vs 47.7%; log rank = 13.1; $P < .001$; Figure 2).

In multivariate analyses adjusting for relevant clinical factors, patients in the amiodarone group were found to have significantly reduced odds for the primary outcome,

FIGURE 1. CONSORT flow diagram depicting progression of patients in the study.

compared with those in the no-amiodarone group (odds ratio, 0.19; 95% confidence interval: 0.07-0.52; $P = .001$). At 6 weeks, 90% of patients in sinus rhythm were classified using long-term monitoring; at 12 weeks, 84% of the patients in sinus rhythm were classified using long-term monitoring. An analysis that removed any rhythm status not verified by long-term monitoring additionally found that the primary composite outcome of AF recurrence occurred more often in the no-amiodarone group (55%; 22 of 40 patients), compared with the amiodarone group (22%; 8 of 37 patients; $P = .003$).

Clinical Outcomes

The study groups were similar with regard to operative outcomes as defined by the Society of Thoracic Surgeons. The amiodarone and no-amiodarone groups had similar incidences of the following: prolonged ventilation, >24 hours (9% vs 4%; $P = .677$); pneumonia (0% vs 2%, $P > .999$); reoperation for bleeding (0% vs 2%, $P > .999$); renal failure (0% vs 2%, $P > .999$); and new pacemaker implantation (4% vs 2%, $P > .999$). The median length of stay in the

hospital was similar for the amiodarone and no-amiodarone groups (6 [3-8] vs 7 [4-9] days; $P = .495$). Operative mortality within 30 days (2% vs 2%; $P > .999$) and readmission within 30 days (9% vs 16%; $P = .334$) were similar for the amiodarone and no-amiodarone groups. No patients in either group experienced a stroke and/or transient ischemic attack in the hospital.

No strokes occurred during the first 12 weeks of follow-up after surgery. No differences were found between the amiodarone and no-amiodarone groups in the percentage of patients with major bleeding events during 12 weeks of follow-up (0% vs 2%; $P > .999$). The 1 bleeding event was a subdural hematoma in a patient who was on anticoagulation medication at the time of the bleeding event. No follow-up catheter ablations were required during the first 12 weeks after surgery, and no difference was found between the amiodarone and no-amiodarone groups in patients with electrical cardioversions during 12 weeks of follow-up (13% vs 18%; $P = .561$). In addition, the mean time to cardioversion did not differ (1.0 months vs 1.2 months; $P = .648$).

FIGURE 2. Freedom from atrial arrhythmia recurrence for amiodarone and no-amiodarone groups. *CI*, Confidence interval.

DISCUSSION

In this prospective randomized controlled trial, we examined the effectiveness of amiodarone in reducing the risk of early recurrence of atrial arrhythmia after surgical ablation for AF. Patients were randomly assigned to receive either amiodarone or no amiodarone after their procedure. Patients who were randomized to not receive any postoperative amiodarone were significantly more likely to have recurrence of atrial arrhythmia in the hospital and during the first 3 months after their procedure. Our results suggest that the effectiveness of prophylactic amiodarone after surgical ablation is comparable to that of prophylactic AAD after catheter ablation of AF.⁴

Treatment with AADs is commonly resumed after AF catheter ablation to reduce early recurrence of atrial arrhythmias.^{4,16} The rationale for this approach is based on the recognition that sustained AF leads to atrial tissue remodeling that in turn supports the continued maintenance of AF.^{17–19} In addition, several studies have reported an association between early recurrence of atrial arrhythmias and later recurrence of arrhythmias.^{5,7,8}

Although the general agreement is that early recurrence of arrhythmias during the so-called “blanking period” or “therapy stabilization period” after AF ablation does not necessarily indicate treatment failure, these early recurrences may nevertheless be associated with increased morbidity, cost,

and negative psychological effects.^{4,20} Management of early recurrences varies among institutions and ranges from conservative approaches to repeat catheter and/or surgical AF ablation procedures.^{8,21,22} Because early recurrence of atrial arrhythmia has been found to be predictive of later recurrence of atrial arrhythmia, AAD treatment is typically resumed after catheter AF ablation.^{2,5–9} The appropriate use of AAD after surgical ablation, however, is less clear. Further research on the use of prophylactic AAD after surgical ablation should focus on the efficacy of this strategy, to not only prevent early recurrence of atrial arrhythmias, but also reduce the risk of surgical ablation failure.

Limitations

A potential limitation of our study is that recurrence of atrial arrhythmia during the first 3 months after surgery was not continuously monitored with an insertable cardiac monitor. We have found, however, that the use of this type of device, and sometimes even longer-term Holter monitoring, is not feasible in the current health care environment, in which reimbursement for such devices is often challenging. Because continuous monitoring was not used, episodes of atrial arrhythmia may have occurred between the specified time points that were not captured, although most patients did undergo long-term Holter monitoring to determine rhythm status.

In addition, a potential source of bias may have been created when patients were discharged from the rigorously controlled clinical environment of the hospital into the care of various cardiologists and physicians, as well as their own self-management. In standard practice, however, the pre- and post-discharge environments are likely to be similar, and these results can be generalized to patients with a standard postoperative clinical course that is managed outside of the hospital.

Finally, some results from this study, particularly perioperative morbidity, may have been affected by reduced power, owing to the relatively small sample size and the low incidence of these outcomes. However, sufficient observed power was achieved for the primary endpoint of atrial arrhythmia recurrence. Although substantial previous evidence indicating advantages of using amiodarone is in line with the results of this study, future larger-scale trials would be beneficial to confirm these findings.

CONCLUSIONS

In this study, patients were followed using our comprehensive follow-up program with the addition of 6- and 12-week, long-term monitoring, to enhance our ability to detect asymptomatic atrial arrhythmias. Future studies should additionally focus on the efficacy of AAD in only treating patients who have recurrence of atrial arrhythmia, and compare the outcomes with those of patients who were treated all along with class I/III AAD. The most important concern in treating patients with amiodarone is associated side effects. However, treatment for a very short period of time (3 months) with close monitoring has been shown to be safe and effective. Our results in this prospective randomized controlled study indicate the need for recommendations regarding prophylactic class I/III AAD in patients undergoing surgical AF ablation, with close monitoring for side effects and AAD discontinuation by 3 months for those in sinus rhythm.

Conflict of Interest Statement

Dr Niv Ad is a consultant and a member of the speaker's bureau for Medtronic, Inc and AtriCure; a proctor for Sorin Group; and co-owner of Left Atrial Appendage Occlusion, LLC. The other authors have nothing to disclose with regard to commercial support.

References

- Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ, et al. Heart disease and stroke statistics—2014 update: a report from the American Heart Association. *Circulation*. 2014;129:e28-292.
- Calkins H, Kuck KH, Cappato R, Brugada J, Camm AJ, Chen SA, et al. 2012 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design. *J Interv Card Electrophysiol*. 2012;33:171-257.
- Bertaglia E, Stabile G, Senatore G, Zoppo F, Turco P, Amellone C, et al. Predictive value of early atrial tachyarrhythmias recurrence after circumferential anatomical pulmonary vein ablation. *Pacing Clin Electrophysiol*. 2005;28:366-71.
- Altman RK, Proietti R, Barrett CD, Paoletti Perini A, Santangeli P, Danik SB, et al. Management of refractory atrial fibrillation post surgical ablation. *Ann Cardiothorac Surg*. 2014;3:91-7.
- Lee SH, Tai CT, Hsieh MH, Tsai CF, Lin YK, Tsao HM, et al. Predictors of early and late recurrence of atrial fibrillation after catheter ablation of paroxysmal atrial fibrillation. *J Interv Card Electrophysiol*. 2004;10:221-6.
- Ad N, Henry L, Holmes SD, Stone LE, Hunt S. The association between early atrial arrhythmia and long-term return to sinus rhythm for patients following the Cox maze procedure for atrial fibrillation. *Eur J Cardiothorac Surg*. 2013;44:295-300; discussion, 300-1.
- Arya A, Hindricks G, Sommer P, Huo Y, Bollmann A, Gaspar T, et al. Long-term results and the predictors of outcome of catheter ablation of atrial fibrillation using steerable sheath catheter navigation after single procedure in 674 patients. *Europace*. 2010;12:173-80.
- Lellouche N, Jais P, Nault I, Wright M, Bevilacqua M, Knecht S, et al. Early recurrences after atrial fibrillation ablation: prognostic value and effect of early re-ablation. *J Cardiovasc Electrophysiol*. 2008;19:599-605.
- Maroto LC, Camero M, Silva JA, Cobiella J, Perez-Castellano N, Reguillo F, et al. Early recurrence is a predictor of late failure in surgical ablation of atrial fibrillation. *Interact Cardiovasc Thorac Surg*. 2011;12:681-6.
- Ott MC, Khor A, Leventhal JP, Paterick TE, Burger CD. Pulmonary toxicity in patients receiving low-dose amiodarone. *Chest*. 2003;123:646-51.
- Roy D, Talajic M, Dorian P, Connolly S, Eisenberg MJ, Green M, et al. Amiodarone to prevent recurrence of atrial fibrillation. Canadian Trial of Atrial Fibrillation Investigators. *N Engl J Med*. 2000;342:913-20.
- Lafuente-Lafuente C, Mouly S, Longas-Tejero MA, Mahe I, Bergmann JF. Antiarrhythmic drugs for maintaining sinus rhythm after cardioversion of atrial fibrillation: a systematic review of randomized controlled trials. *Arch Intern Med*. 2006;166:719-28.
- Cox JL, Schuessler RB, D'Agostino HJ Jr, Stone CM, Chang BC, Cain ME, et al. The surgical treatment of atrial fibrillation. III. Development of a definitive surgical procedure. *J Thorac Cardiovasc Surg*. 1991;101:569-83.
- Cox JL. The surgical treatment of atrial fibrillation. IV. Surgical technique. *J Thorac Cardiovasc Surg*. 1991;101:584-92.
- Ad N, Henry L, Hunt S, Stone L. The implementation of a comprehensive clinical protocol improves long-term success after surgical treatment of atrial fibrillation. *J Thorac Cardiovasc Surg*. 2010;139:1146-52.
- Roux JF, Zado E, Callans DJ, Garcia F, Lin D, Marchlinski FE, et al. Antiarrhythmics after ablation of atrial fibrillation (5A Study). *Circulation*. 2009;120:1036-40.
- Wijffels MC, Kirchhof CJ, Dorland R, Allesie MA. Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats. *Circulation*. 1995;92:1954-68.
- Nattel S, Harada M. Atrial remodeling and atrial fibrillation: recent advances and translational perspectives. *J Am Coll Cardiol*. 2014;63:2335-45.
- Xu Y, Sharma D, Li G, Liu Y. Atrial remodeling: new pathophysiological mechanism of atrial fibrillation. *Med Hypotheses*. 2013;80:53-6.
- Eitel C, Husser D, Hindricks G, Fruhauf M, Hilbert S, Arya A, et al. Performance of an implantable automatic atrial fibrillation detection device: impact of software adjustments and relevance of manual episode analysis. *Europace*. 2011;13:480-5.
- Leong-Sit P, Roux JF, Zado E, Callans DJ, Garcia F, Lin D, et al. Antiarrhythmics after ablation of atrial fibrillation (5A Study): six-month follow-up study. *Circ Arrhythm Electrophysiol*. 2011;4:11-4.
- Themistoclakis S, Schweikert RA, Saliba WI, Bonso A, Rossillo A, Bader G, et al. Clinical predictors and relationship between early and late atrial tachyarrhythmias after pulmonary vein antrum isolation. *Heart Rhythm*. 2008;5:679-85.

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