Why amiodarone failed to lower the rate of recurrence six months after catheter ablation for atrial fibrillation

K-H. Kuck* and E. Wissner

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This editorial refers to ‘Recurrence of arrhythmia following short-term oral AMIODarone after CAThereter ablation for atrial fibrillation: a double-blind, randomized, placebo-controlled study (AMIO-CAT trial)’1, by S. Darkner et al., on page 3356.

Recurrence of atrial fibrillation (AF) early after pulmonary vein isolation (PVI) is a common event.1 In terms of long-term outcome, the implications of recurrence of arrhythmia within the first months following ablation are thought to be different from arrhythmias occurring beyond the 3-month blanking period.1 Transient effects, such as a high catecholamine state, delayed maturation of ablative lesions and the inflammatory process caused by acute atrial tissue injury, may foster an early pro-arrhythmic milieu. Consequently, attempts to expose the patients to an early re-do ablation procedure should be weighed against the likelihood that these arrhythmias will subside spontaneously. Patients are frequently treated post-operatively with anti-arrhythmic medication that was previously ineffective. A randomized, prospective study demonstrated that the use of Class IC and Class III (excluding the use of amiodarone) anti-arrhythmic drugs, given for 6 weeks post-PVI in patients with a history of paroxysmal AF, reduced the rate of early recurrence of arrhythmia but had no effect on the recurrence rate after 6 months.2,3

The recurrence of arrhythmia following short-term oral AMIODarone after CAThereter ablation for atrial fibrillation: a double-blind, randomized, placebo-controlled study (AMIO-CAT) assessed the utility of amiodarone in the prevention of atrial tachyarrhythmias beyond the blanking period of 3 months. This was a prospective, randomized, double-blind study that allocated patients with paroxysmal or persistent AF (following first-time or repeat catheter ablation of AF) into receiving either 8 weeks of amiodarone or placebo. Follow-up was conducted at 1, 3 and 6 months, including a 12-lead surface ECG and a 3-day Holter monitor at 6–8 weeks and 6 months after the index ablation procedure. Additional monitoring was conducted if the patient reported symptoms suggestive of arrhythmia recurrence. The primary endpoint was any recurrence of symptomatic or asymptomatic atrial tachyarrhythmia (AF, atrial tachycardia or atrial flutter) lasting >30 seconds beyond the blanking period. Out of 212 patients randomized to amiodarone or placebo, 206 completed the follow-up period of 6 months. There was no statistically significant difference in the primary endpoint between the two groups (amiodarone: 42/107 patients (39%) vs. placebo: 48/99 patients (48%); P = 0.18). By contrast, amiodarone significantly reduced recurrence of atrial tachyarrhythmia during the blanking period (amiodarone: 37/108 patients (34%) vs. placebo: 55/104 patients (53%); P = 0.006). Additionally, in a multivariate analysis, recurrence of AF or atrial tachycardia during the 3-month blanking period predicted recurrence of atrial arrhythmia at 6-month follow-up. The authors concluded that the use of amiodarone for 8 weeks following catheter ablation of AF failed to demonstrate any effect on the recurrence of atrial tachyarrhythmias at 6-month follow-up, while its use lowered the number of arrhythmia-related hospital admissions and the need for cardioversion during the blanking period.

The study has several limitations that need to be addressed: first, the authors fail to mention the basis for the hypothesis on which the study was based. In other words, why would the use of amiodarone reduce the rate of recurrence at 6 months in patients with paroxysmal AF, if electrical pulmonary vein reconnection is the dominant mechanism of AF recurrence?4 Similarly, even in patients with long-standing, persistent AF, PV reconnection is found in the majority of cases during the re-do ablation procedure;5 hence, in paroxysmal and persistent AF, the predominant cause of recurrence of atrial arrhythmia, at any point in time during follow-up, is PV reconnection, which is unlikely to be altered by 8 weeks of amiodarone therapy, especially following cessation of the drug. Instead, different strategies to create durable PV isolation should be tested. It has been shown that ablation strategies concentrating on better lesion formation—such as contact force or loss of capture during pacing along the ablation.
line—are associated with lower recurrence rates following PV isolation.6,7 In an animal model, the term “AF begets AF” is based on electrical and anatomical remodelling, however, it has never been shown that “sinus rhythm begets sinus rhythm”, thereby facilitating reverse re-modelling.8 Amiodarone may exert a beneficial effect in patients with persistent AF; in whom the need for additional ablation of complex fractionated atrial electrograms (CFAE) indicates more extensive structural changes within the left atrium.

In order to test the effect of a select parameter on clinical outcome, the patient population should be kept homogeneous. The AMIO-CAT trial enrolled a heterogeneous patient population, including patients with paroxysmal and persistent AF. The outcome of catheter ablation in patients with persistent AF is variable. While persistent AF of less than a year’s duration may behave similarly to paroxysmal AF, long-standing persistent AF lasting more than a year may be the result of a left atrial disease process beyond the typical PV trigger.5 The latter group more commonly requires additional ablative strategies, such as CFAE ablation.5

A uniform ablative approach would be advisable, in order to assess the impact of amiodarone on clinical outcome. Patients in the present study were treated in two centres in Denmark, employing significant differences in their ablative strategy. In particular, failure to verify PV isolation by means of circular-mapping catheter recordings poses questions as to whether the PVs were truly isolated during the index procedure. In addition, no details are given in respect of those enrolled patients who had already undergone a catheter ablation procedure for the treatment of AF prior to inclusion in the trial. A patient with prior PVI and CFAE ablation would probably have a lower likelihood of PV reconnection, while a left atrial arrhythmogenic source outside the PVs may be a more likely mechanism for recurrence of arrhythmia.

In summary, recurrence of arrhythmia beyond 6 months after PVI is predominantly caused by PV reconnection. In this scenario, amiodarone or any other anti-arrhythmic agent is unlikely to permanently suppress recurrence of arrhythmia, while the preferred treatment strategy should aim for durable isolation of all reconducting PVs during a second ablation procedure.

References


