

Original Article

Prophylactic amiodarone therapy following catheter ablation reduces early and very-late arrhythmia recurrences in atrial fibrillation patients: a systematic review and meta-analysis

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Received February 3, 2019; Accepted July 5, 2019; Epub August 15, 2019; Published August 30, 2019

Abstract: Background: Prophylactic amiodarone therapy following catheter ablation atrial fibrillation (AF) patients can be used to prevent arrhythmia recurrences, but the examples of this practice are still limited. Objective: The aim of this study was to perform a meta-analysis of published controlled trials comparing amiodarone therapy after catheter ablation with no amiodarone therapy in AF patients receiving catheter ablation. Recurrence of arrhythmia was set as primary outcome. Results: In total, five random controlled trials from Jan 1st, 2008 to Sep 1st, 2018 were included. Among 733 AF patients, 369 patients were treated with amiodarone and 369 patients served as a control group without concomitant amiodarone therapy. The follow-up duration ranged from 3 to 40 months following catheter ablation. Among amiodarone treated patients, the early recurrence of arrhythmia rate was 23.46% VS 40.23% in control patients ($P < 0.0001$). Although no significant difference was found during late follow-up (41.90% VS 46.72%, $P = 0.26$), the very late recurrence rate in amiodarone group (26.82%) was significantly lower than that in the control group (44.62%) ($P = 0.001$). Conclusions: Amiodarone therapy post catheter ablation could reduce both the early and very late recurrence of arrhythmias, although no significant difference was observed during late follow-up.

Keywords: Amiodarone, catheter ablation, arrhythmia recurrences, atrial fibrillation

Introduction

Atrial fibrillation (AF) still remains one of the major causes of stroke, sudden death, and cardiovascular morbidity in the world despite of substantial progress in the treatment [1]. It is estimated that about 20.9 million men and 12.6 million women have suffered from AF worldwide, and higher incidence and prevalence are observed in developed countries [2, 3]. AF is independently related to a 1.5-fold increased risk of all-cause mortality in men and a 2-fold increase risk in women, and approximately 31% AF patients are hospitalized each year [4].

An integrated management of AF may lead to improved outcomes, including acute rate and rhythm control, management of predisposing factors and mitigation of stroke risk [5, 6].

Although trials have shown that rhythm control along with rate control did not lead to improved outcomes compared to rate control alone [7-9], rhythm control therapy is still recommended in AF patients who remain symptomatic on regular rate control therapy [3]. Catheter ablation, primarily performed through isolation of the pulmonary vein, is considered as an effective therapeutic modality when antiarrhythmic drugs (AADs) therapy fails [10, 11], and it is considered that catheter ablation is more effective than AAD therapy in restoring of the sinus rhythm with similar complication rate [12]. However, both symptomatic and asymptomatic recurrences are common after catheter ablation [13, 14]. Since continuous rapid firing may result in shortened effective refractory periods and electric remodeling [15, 16], AAD therapy (most often amiodarone) after catheter ablation seems reasonable to reduce early AF recur-

Prophylactic amiodarone therapy in atrial fibrillation patients

rences, supported by a controlled trial where amiodarone delayed early AF recurrences compared with placebo [17], though more evidence from controlled trials is desirable.

One previous meta-analysis has assessed the effect of AAD therapy after catheter ablation [18], but due to inappropriate data extraction and limited number of involved trials, the precise role of amiodarone therapy was not clearly identified in this study. Hence, this study aimed to systematically review those randomized controlled trials regarding efficacy and safety of amiodarone post catheter ablation in atrial fibrillation patients.

Methods

Search strategy and selection criteria

For this meta-analysis, two investigators (Hong Wang and Yao Hu) performed a thorough electronic search independently through the Cochrane CENTRAL database, PubMed, EMBASE, Scopus and Web of Science (WOS) database from Jan 1st, 2008 to June 16th, 2018, without language restriction for randomized controlled clinical trials that assessed the efficacy of amiodarone on reducing arrhythmia recurrences after catheter ablation. Full search terms are provided:

“Atrial Fibrillation” [Mesh] or (Atrial Fibrillation) or (Atrial Fibrillations) or (Fibrillation, Atrial) or (Fibrillations, Atrial) or (Auricular Fibrillation) or (Auricular Fibrillations) or (Fibrillation, Auricular) or (Fibrillations, Auricular) or (Persistent Atrial Fibrillation) or (Atrial Fibrillation, Persistent) or (Atrial Fibrillations, Persistent) or (Fibrillation, Persistent Atrial) or (Fibrillations, Persistent Atrial) or (Persistent Atrial Fibrillations) or (Familial Atrial Fibrillation) or (Atrial Fibrillation, Familial) or (Atrial Fibrillations, Familial) or (Familial Atrial Fibrillations) or (Fibrillation, Familial Atrial) or (Fibrillations, Familial Atrial) or (Paroxysmal Atrial Fibrillation) or (Atrial Fibrillation, Paroxysmal) or (Atrial Fibrillations, Paroxysmal) or (Fibrillation, Paroxysmal Atrial) or (Fibrillations, Paroxysmal Atrial) or (Paroxysmal Atrial Fibrillations).

“Catheter Ablation” [Mesh] or (Catheter Ablation) or (Ablation, Catheter) or (Catheter Ablation, Transvenous) or (Transvenous Catheter Ablation) or (Ablation, Transvenous Catheter) or (Catheter Ablation, Electric) or

(Electrical Catheter Ablation) or (Catheter Ablation, Electrical) or (Ablation, Electrical Catheter) or (Electric Catheter Ablation) or (Ablation, Electric Catheter) or (Ablation, Transvenous Electric) or (Electric Ablation, Transvenous) or (Transvenous Electric Ablation) or (Ablation, Transvenous Electrical) or (Electrical Ablation, Transvenous) or (Transvenous Electrical Ablation) or (Catheter Ablation, Radiofrequency) or (Radiofrequency Catheter Ablation) or (Ablation, Radiofrequency Catheter) or (Catheter Ablation, Percutaneous) or (Percutaneous Catheter Ablation) or (Ablation, Percutaneous Catheter).

“Amiodarone” [Mesh] or Amiodarone or Amiodarona or “Amiodarone Hydrochloride” or “Hydrochloride, Amiodarone” or Amiohexal or Aratac or Tachyaron or Corbionax or Cordarone or Amiodarex or Trangorex or Kordaron or Cordarex or L-3428 or “L 3428” or L3428 or Ortacrone or Rytmarone or “SKF 33134-A” or “SKF 33134 A” or “SKF 33134A” or Amiobeta or Braxan.

1 AND 2 AND 3. Database searches were then supplemented by screening the references of relevant studies and other reviews. Chinese records were also translated into English.

Study selection and quality assessment

Studies were included if they were randomized control trials comparing amiodarone vs. control post catheter ablation in AF patients with outcomes of interest provided. Studies were excluded if the studies involved patients who are pregnant or younger than 18 years old. Observational, retrospective studies, case reports, and reviews were excluded. Studies involving surgical AF ablation and AV nodal ablation were also excluded.

Study quality was assessed according to the five-point scale outlined by Jadad [19].

Data analysis

Two investigators (Liu Yang and Lang Hong) extracted the data from included studies; a third investigator (Hengli Lai) resolved possible conflict when necessary. The follow-up included clinical assessment and regular monitoring with continuous Holter or other recording devices. The end point of arrhythmia recurrence was any documented atrial tachyarrhythmia, includ-

Prophylactic amiodarone therapy in atrial fibrillation patients

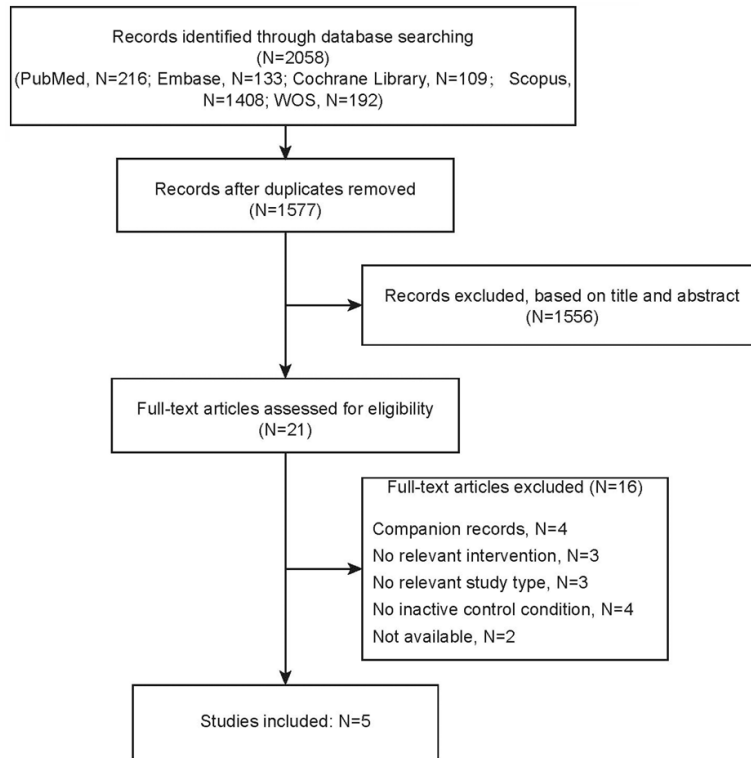


Figure 1. Information relevant to the literature search.

ing atrial AF, and atrial tachycardia lasting more than 30 seconds in all included studies. Recurrences were then categorized into early recurrence (within 3 months), late recurrence (more than 3 months and less than 12 months) and very late recurrence (more than 12 months) according to the time to recurrence.

Statistical analysis

Statistical analyses were performed using STATA (version 14.3; College Station, TX, USA) and RevMan (version 5.3; The Nordic Cochrane Centre, Copenhagen, Denmark). Unless otherwise specified, statistically significant difference was set as a P value < 0.05 .

Results

Descriptive analyses of the studies

A thorough literature search turned to 2058 publications. The information relevant to the literature search is shown in **Figure 1**. Five studies were selected, and all were randomized (**Table 1**). Five studies included 733 patients from two single-center trials, a two-center trial and two multicenter trials (**Table 1**).

During early 3-month post-ablation, the overall recurrence of arrhythmia rate was 23.46% (61/260) in the amiodarone group VS 40.23% (103/256) in the control group (odds ratio 0.44, 95% CI 0.29-0.65, $P < 0.0001$; test for heterogeneity: $\chi^2 = 0.92$, $P = 0.63$, $I^2 = 0\%$) (**Figure 2**).

During late post-ablation follow-up, no significant difference was found between the two group as the rate of arrhythmia recurrence was 41.90% (106/253) in the amiodarone group VS 46.72% (114/244) in the control group (odds ratio 0.80, 95% CI 0.55-1.17, $P = 0.26$; test for heterogeneity: $\chi^2 = 1.10$, $P = 0.78$, $I^2 = 0\%$) (**Figure 3**).

It is worth noting that during very late follow-up that more than 12 months, the recurrence rate in amiodarone group is 26.82% (70/261) and that in control group is 44.62% (116/260) (odds ratio 0.43, 95% CI 0.25-0.72, $P = 0.001$; test for heterogeneity: $\chi^2 = 5.42$, $P = 0.14$, $I^2 = 45\%$) (**Figure 4**). This result indicated the promising prophylactic-effect of amiodarone in long term follow-up.

Discussions

Prophylactic AADs therapy after catheter ablation to ascertain freedom from arrhythmias is considered as a routine practice [25, 26], lack of forceful evidences rendered it a subject to debate. The results of our study revealed that prophylactic amiodarone is effective to prevent both early and very late recurrence of atrial arrhythmias after catheter ablation, even though the underlying mechanisms of early and very late recurrence may be quite different [27, 28].

The recently published 2017 HRS Expert Consensus Statement on Catheter Ablation and Surgical Ablation of Atrial Fibrillation have suggested that catheter ablation should be considered as the first-line therapy for patients with symptomatic paroxysmal or persistent AF

Prophylactic amiodarone therapy in atrial fibrillation patients

Table 1. Types of study design and general characteristics of enrolled studies

Studies	Location	Designs	Control (Age)	Gender (M/F)	Treatment (Age)	Gender (M/F)	Follow up (months)	Outcome measures	Jadad score
Wu, 2008 [20]	China	Single center prospective randomized	37 (53.6 ± 19.1)	29/8	37 (51.2 ± 17.7)	28/9	3/4/20+	ECG/HOLTER	3
Di Biase, 2012 [21]	America	Multicenter prospective randomized	52 (NA)	NA	53 (NA)	NA	6/24+	NA	3
Darkner, 2014 [22]	Denmark	Two-center double blinded randomized	104 (61 ± NA)	89/15	108 (62 ± NA)	87/21	3/6	PE/ECG	5
Mohanty, 2015 [23]	America	Multicenter prospective randomized	56 (62 ± 10)	38/18	56 (60 ± 11)	42/14	6/24+	ECG/HOLTER	5
Kettering, 2017 [24]	Germany	Single-center prospective randomized	115 (60.4 ± 11.3)	70/45	115 (61.9 ± 11.1)	67/48	3/12	ECG/HOLTER	5

Prophylactic amiodarone therapy in atrial fibrillation patients

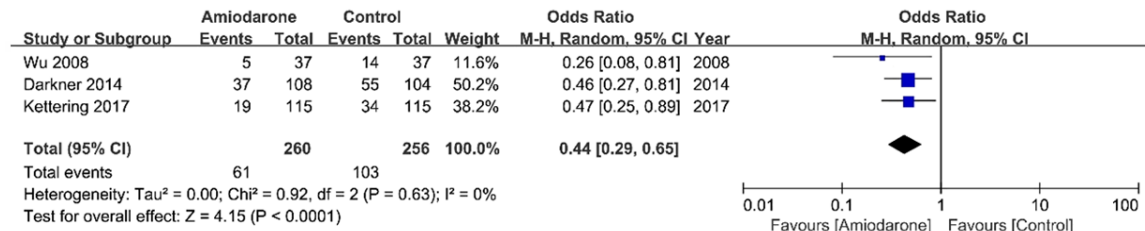


Figure 2. Overall effect of amiodarone therapy on early post-ablation outcome.

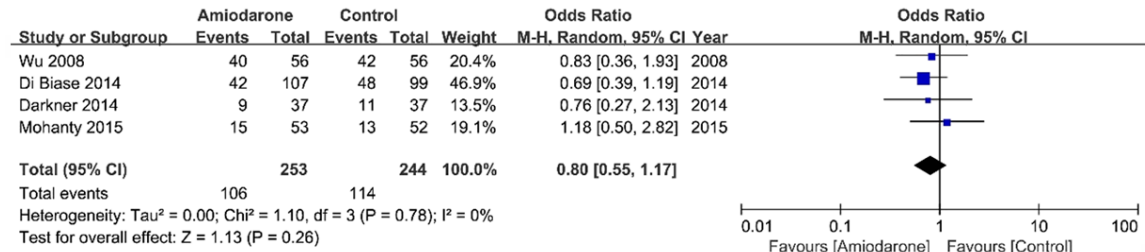


Figure 3. Overall effect of amiodarone therapy on late post-ablation outcome.

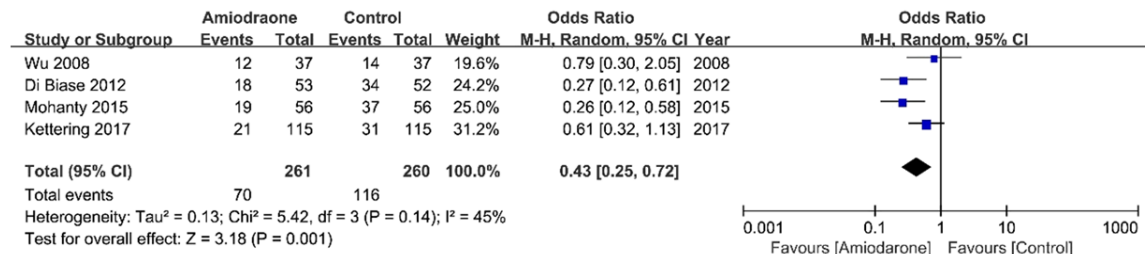


Figure 4. Overall effect of amiodarone therapy on very late post-ablation outcome.

[29]. Although its efficacy has been well established [30], catheter ablation still encounters with substantial risk of recurrences [25, 31, 32], including early recurrence (within 3 months), late recurrence (from 3 months to 1 year) and very late recurrence (more than 1 year) [29]. Because up to half of the early recurrences within weeks following the ablation may subside subsequently [27, 33], a 3-month blanking period after the procedure, during which re-intervention should be avoided, is recommended [34]. Nevertheless, it is noteworthy that early recurrence could predict late atrial arrhythmia recurrence [27, 35, 36] as well as increased morbidity and cost [37, 38]. Thus, it is still reasonable to initiate AADs therapy following catheter ablation to ascertain the restoration of sinus rhythm and finally better clinical outcome.

A previous meta-analysis has delineated that AADs therapy does not substantially reduce

recurrence after ablation [18]. However, this result is limited due to that only three trials were involved in amiodarone subgroup and the time to recurrence was not discussed. Thus, this study focused on amiodarone, which is proposed to be more effective than other AADs in prevention of atrial fibrillation recurrence [39], and tried to provide a more convincing result about AAD prophylactic therapy after catheter ablation.

Amiodarone constitutes one of the most effective AAD to maintain sinus rhythm acting as a potent alpha- and beta-receptor, and it could block sodium, potassium, and calcium channels [40]. As consequence of its several channel-blocking effects, amiodarone is shown to be effective in preventing atrial electrical remodeling [40], which may ensure the restoration of sinus rhythm and further beget sinus rhythm [41]. Therefore, prophylactic amioda-

rone therapy should be promising to prevent arrhythmias after ablation.

Moreover, other parameters besides of recurrence should be incorporated to gauge the clinical outcomes of catheter ablation. It has been suggested that occasional AF recurrences may not be considered as ablation failures if the frequency, duration or severity of the recurrences are markedly changed the procedure [34]. Therefore, hospitalization rate, quality of life, and other patient-reported outcomes should be taken into account in further studies. It has already shown that initiation of AAD therapy following intervention could result in a significant reduction in readmission [42].

In conclusion, this study inferred that amiodarone therapy post catheter ablation could reduce both the early and very late recurrence of arrhythmias, although more controlled trials are needed to provide convincing evidences restricted to specific type of AF.

Acknowledgements

All authors have read the final version of the manuscript and are in agreement for publication upon acceptance.

Disclosure of conflict of interest

None.

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Prophylactic amiodarone therapy in atrial fibrillation patients

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Prophylactic amiodarone therapy in atrial fibrillation patients

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