Journal of Zhejiang University-SCIENCE B (Biomedicine & Biotechnology)
ISSN 1673-1581 (Print); ISSN 1862-1783 (Online)
www.jzus.zju.edu.cn; www.springerlink.com
E-mail: jzus@zju.edu.cn

# Effect of corticosteroids on atrial fibrillation after catheter ablation: a meta-analysis[#]

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Received Nov. 27, 2016; Revision accepted May 1, 2017; Crosschecked Dec. 24, 2017

**Abstract:** Objective: The purpose of this meta-analysis was to explore the effect of corticosteroids on atrial fibrillation (AF) following catheter ablation. Methods: We searched PubMed, Embase, and the Cochrane Central Register of Controlled Trials for published articles describing the effect of corticosteroids in preventing AF recurrence after catheter ablation. Data on study and patient were extracted. Risk ratios (RRs) and 95% confidence intervals (CIs) were calculated by use of a random-effect model, and *P* values of <0.05 were considered significant. Results: Two randomized controlled trials (RCTs) and three cohort studies involving 846 patients were included in this meta-analysis. Within one month of catheter ablation, corticosteroid use was associated with a declined risk of recurrence of AF in RCT (RR 0.57, 95% CI 0.39 to 0.85, *P*=0.005), but without significant effect in cohort studies (RR 1.01, 95% CI 0.79 to 1.30, *P*=0.94). After three months of catheter ablation, corticosteroids did not have a significant effect in the prevention of late recurrence of AF in either RCT (RR 0.78, 95% CI 0.38 to 1.59, *P*=0.49) or cohort studies (RR 0.96, 95% CI 0.70 to 1.31, *P*=0.78). Conclusions: Our meta-analysis suggested that periprocedural administration of corticosteroids of catheter ablation was associated with reduction of early but not late recurrence of AF.

**Key words:** Atrial fibrillation; Corticosteroids; Catheter ablation; Meta-analysis
https://doi.org/10.1631/jzus.B1600529 **CLC number:** R541.7

## 1 Introduction

Atrial fibrillation (AF) is the most common arrhythmia seen in clinical practice and is associated with many morbidities and mortalities, e.g. stroke and heart failure (Kannel et al., 1982; Lip et al., 2012; Roger et al., 2012). Catheter ablation has been one of the therapeutic modalities for the treatment of AF, especially symptomatic AF (Haïssaguerre et al., 1998). Studies of catheter ablation for AF have demonstrated that recovery from AF after a single procedure was 53.1% overall, 54.1% in paroxysmal AF, and 41.8% in persistent AF (Ganesan et al., 2013).

Several studies have indicated that inflammation may play a significant role in AF (Conway et al., 2004; Harada et al., 2015; Scridon et al., 2015; Gurses et al., 2016). Increased C-reactive protein (CRP) has proven to be a great risk factor for new-onset AF after acute myocardial infarction (Ren et al., 2015) or coronary artery bypass graft (Li et al., 2016). According to the Chronic Renal Insufficiency Cohort (CRIC) study, interleukin 6 (IL-6) was significantly associated in the presence of AF and new-onset AF (Amdur et al., 2016). Heat shock protein 27 (HSP27), IL-8, and tumor necrosis factor (TNF) are also known to be

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[#] Electronic supplementary materials: The online version of this article (https://doi.org/10.1631/jzus.B1600529) contains supplementary materials, which are available to authorized users
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involved in the pathogenesis of AF (Yang et al., 2007; Wu et al., 2008; Deng et al., 2011; Hu et al., 2012). Corticosteroids have also been shown to be efficient in anti-inflammation (Belvisi, 2004; Barnes, 2006; Coutinho and Chapman, 2011).

However, there has not yet been a systematic review or meta-analysis performed to evaluate the efficacy of corticosteroids in preventing recurrence of AF following catheter ablation. In this study, we aim to collect and summarize the available data on this topic.

## 2 Methods

### 2.1 Search strategy

We searched PubMed, Embase, and Cochrane Central Register of Controlled Trials for articles describing the effect of corticosteroids in the prevention of AF recurrence following catheter ablation. The detailed search strategy is presented in the supplementary Data S1. To maximize the sensitivity of our search, we did not limit the language or study type for the initial extraction of the data.

### 2.2 Study selection

Two blind reviewers decided whether to include each study on the basis of predefined selection criteria. Studies were included in our meta-analysis if they met the following criteria: (1) randomized controlled trials (RCTs) or cohort study, (2) patients diagnosed as AF and undergoing catheter ablation, (3) comparison of corticosteroids with control, and (4) evaluation of AF recurrence as an end point. Any disagreement remaining following discussion was resolved by a third reviewer.

### 2.3 Data extraction

Two blind reviewers extracted the data in a predefined form. The following data were collected from each study: (1) publication data: the first author's name and year of publication; (2) study design; (3) characteristics of study population: sample size, age, gender, types of AF, and techniques of catheter ablation; (4) follow-up period and number of drop-outs; (5) treatment modality: corticosteroid type and dose; (6) endpoint measurement: definition of blanking periods, definition and detection methods of AF recurrence. Any disagreement remaining following discussion was resolved by a third reviewer.

### 2.4 Assessment of methodological quality

Two blind reviewers evaluated the methodological quality of each study using the Cochrane Collaboration's tool for assessing the risk of bias for RCTs and the Newcastle-Ottawa Scale for cohort studies (Table S1). Any disagreement remaining following discussion was resolved by a third reviewer.

### 2.5 Statistical analysis

We adopted pooled meta-analysis with the Mantel-Haenszel method and random-effects model. Data were expressed as risk ratios (RRs) with 95% confidence intervals (CIs). Heterogeneity between studies was quantified with the $I^2$ statistic, and an $I^2$ exceeding 50% was considered as a statistical heterogeneity. We used subgroup analysis based on study design (RCTs and cohort study). Statistical analysis was performed using Review Manager 5.3 software (available from The Cochrane Collaboration).

## 3 Results

### 3.1 Identification of studies

A search of the database yielded a total of 270 articles. Among these, 264 articles were excluded because they did not fulfill the study selection criteria by screening the title and abstract. We then screened the full-text of the remaining six potentially relevant articles. One article was further excluded due to its study design (case-control study). The remaining five articles were included in our meta-analysis (Fig. 1). Among these five articles, two were RCTs and the others were cohort studies.

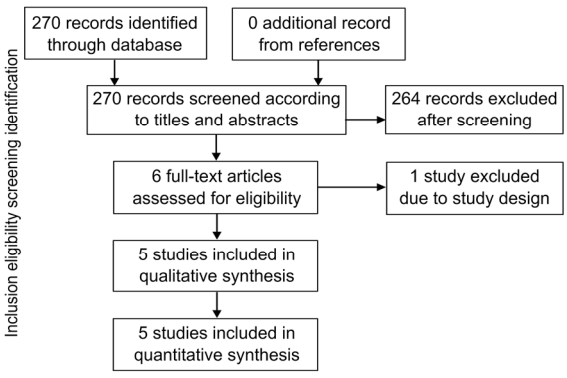


**Fig. 1 Study selection process**

### 3.2 Study and patient characteristics

In total, 846 patients (450 patients in the corticosteroid group, and 396 in the control group) were included in our meta-analysis. The detailed study characteristics are summarized in Table 1. The follow-up duration to detect AF recurrence after the catheter ablation ranged from 12 to 24 months. Three studies identified the blanking period as one month, and the other two studies as three months. The detailed patient characteristics are presented in Table 2. Two studies only enrolled paroxysmal AF. The detailed quality assessments of the included studies are listed in Table S1.

### 3.3 Efficacy of corticosteroids for declining an early recurrence of AF (ERAF)

Pooled meta-analysis of the two RCTs shows that corticosteroid use is associated with a declined risk of AF recurrence within one month of catheter

**Table 1 Baseline characteristics of studies**

| Author, year | Study design | Ablation technique | Corticosteroids | Country | Date of enrollment | AF recurrence definition | Follow-up period (month) |
|---|---|---|---|---|---|---|---|
| Kim DR et al., 2015 | Prospective cohort | PVI with or without cavotricuspid isthmus ablation | Hydrocortisone 100 mg IV or methylprednisolone 125 mg IV | Korea | 2007–2012 | ERAF: AF>30 s within 3 months; LRAF: AF>30 s 3–12 months | 12 |
| Won et al., 2013 | Prospective cohort | PVI + cavotricuspid isthmus ablation | Hydrocortisone 100 mg IV | Korea | 2007–2010 | ERAF: AF>30 s within 1 month; LRAF: AF>30 s 1–12 months | 12 |
| Andrade et al., 2013 | Prospective cohort | PVI | Hydrocortisone 250 mg IV | Canada | Unclear | ERAF: AF>30 s within 3 months; LRAF: AF>30 s 3–12 months | 12 |
| Koyama et al., 2010 | RCT | PVI | Hydrocortisone 2 mg/kg IV; Prednisolone 0.5 mg/kg PO qd×3 d | Japan | 2007–2008 | ERAF: AF>30 s within 1 month; LRAF: AF>30 s at 14 months | 14 |
| Kim YR et al., 2015 | RCT | PVI with or without cavotricuspid isthmus ablation | Methylprednisolone 0.5 mg/kg IV qd×2 d; Ethylprednisolone 12 mg PO qd×4 d | Korea | 2010–2012 | ERAF: AF>30 s within 1 month; LRAF: AF>30 s 3–24 months | 24 |

PVI: pulmonary vein isolation; IV: intravenously; AF: atrial fibrillation; E/LRAF: early/late recurrence of atrial fibrillation; RCT: randomized controlled trial; PO: per os; qd: quaque die/every day

**Table 2 Baseline characteristics of patients**

| Study | *n* | Age (year) | PAF (%) | Stroke | Heart failure | Class Ic | Class III | ACEI/ ARB | β-Blockers | Statins | LA diameter (mm) | LVEF (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Kim DR et al., 2015 | 287 | 56±10 | 62 | 18 (6) | 10 (4) | 176 (61) | 92 (32) | 63 (22) | 44 (15) | 47 (16) | 42±6 | 61±6 |
| Won et al., 2013 | 209 | 55±11 | 51 | 14 (7) | 2 (3) | 70 (58) | 45 (38) | 30 (25) | 21 (18) | 18 (15) | 41±6 | 63±8 |
| Andrade et al., 2013 | 90 | 58±10 | 100 | | | | | | | | 38±6 | |
| Koyama et al., 2010 | 125 | 61±10 | 100 | | | 80 (64) | 56 (45) | 62 (50) | 56 (45) | 43 (34) | 38±7 | 64±9 |
| Kim YR et al., 2015 | 138 | 56±10 | 75 | 10 (7) | 11 (8) | 98 (71) | 23 (17) | | | | 42±6 | 60±7 |

Data are expressed as mean±standard deviation (SD) or number (percent), except for PAF. PAF: paroxysmal atrial fibrillation; ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; LA: left atrium; LVEF: left ventricle ejection fraction

ablation (RR 0.57, 95% CI 0.39 to 0.85, *P*=0.005; Fig. 2a). However, in cohort studies, corticosteroids do not show a significant effect in preventing AF recurrence within one month of catheter ablation (RR 1.01, 95% CI 0.79 to 1.30, *P*=0.94; Fig. 2b).

### 3.4 Efficacy of corticosteroids for late recurrence of AF (LRAF)

The pooled estimates of the two RCTs indicate that corticosteroids do not have a significant effect in the prevention of AF after three months of catheter ablation (RR 0.78, 95% CI 0.38 to 1.59, *P*=0.49; Fig. 3a). The analysis of three cohort studies shows a similar result (RR 0.96, 95% CI 0.70 to 1.31, *P*=0.78; Fig. 3b).

## 4 Discussion

Our meta-analysis based on two RCTs and three cohort studies indicated that perioperative administration

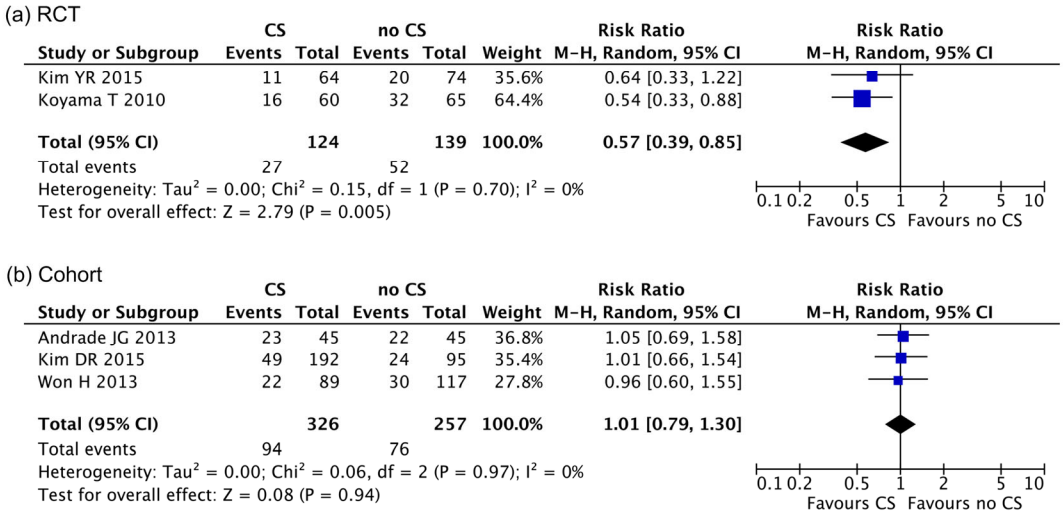


**Fig. 2 Efficacy of corticosteroids for early recurrence of AF**

(a) RCT studies: Kim YR et al., 2015; Koyama et al., 2010. (b) Cohort studies: Andrade et al., 2013; Kim DR et al., 2015; Won et al., 2013. RCT: randomized controlled trial; CI: confidence interval; CS: corticosteroid; M-H: Mantel-Haenszel method

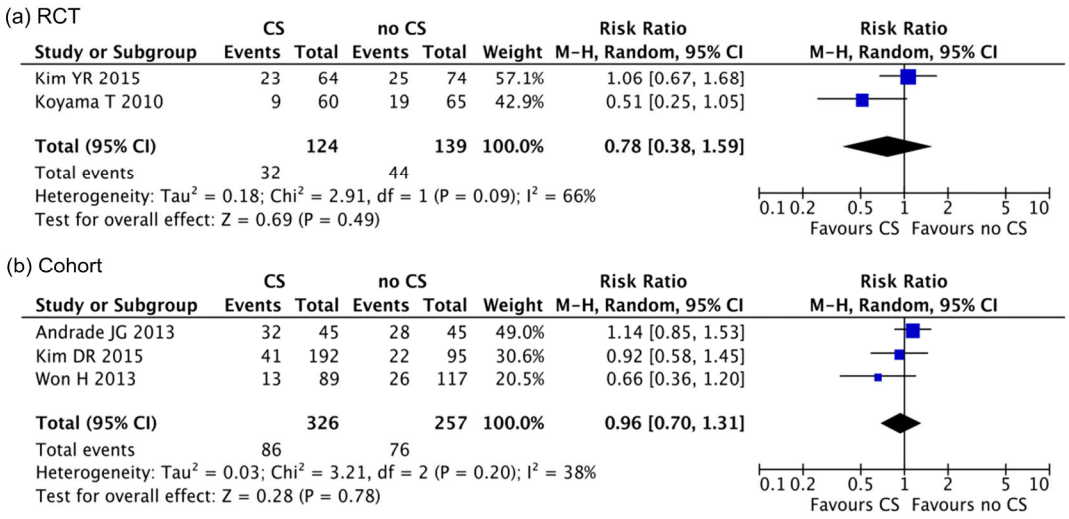


**Fig. 3 Efficacy of corticosteroids for late recurrence of AF**

(a) RCT studies: Kim YR et al., 2015; Koyama et al., 2010. (b) Cohort studies: Andrade et al., 2013; Kim DR et al., 2015; Won et al., 2013. RCT: randomized controlled trial; CI: confidence interval; CS: corticosteroid; M-H: Mantel-Haenszel method

of corticosteroids does not show any significant benefit in the prevention of LRAF. Although corticosteroid administration has a significant effect in reducing the risk of AF recurrence within one month of catheter ablation, there is not enough strong evidence that it could decrease the risk of AF recurrence after three months.

Inflammation is involved in the pathogenesis of AF recurrence. A previous study demonstrated that IL-6, an inflammatory factor, is an independent predictive factor of ERAF (hazard ratio (HR) 1.3) (Smit et al., 2012). Richter et al. (2012) screened the AF patients after pulmonary vein isolation (PVI) and indicated that increased CRP could predict ERAF within the first week of ablation. Letsas et al. (2009) also suggested that white blood cell count and CRP are significantly associated with LRAF after PVI with a mean follow-up period of 12.5 months.

Corticosteroids have been used for a long time in clinical practice as a means of preventing AF recurrence. In a double-blind RCT study for AF recurrence after cardioversion, Dernellis and Panaretou (2004) showed that methylprednisolone, 16 mg for four weeks and tapered to 4 mg for four months, could significantly reduce the incidence of AF recurrence when compared to a placebo group with a median follow-up of 23.65 months. Corticosteroids could also reduce the AF after cardiac surgery. In a meta-analysis of 3323 patients from 50 RCTs, Ho and Tan (2009) suggested that perioperative corticosteroid admission could significantly decrease the risk of AF after cardiac surgery (RR 0.74). However, recently, a large randomized trial dexamethasone for cardiac surgery (DECS) study failed to show the protective effect of intraoperative administration of dexamethasone against the incidence of AF following cardiac surgery (van Osch et al., 2015), which indicates that more updated meta-analysis may be needed to confirm whether corticosteroids could have a significant effect on new-onset AF or AF recurrence following cardiac surgery.

Koyama et al. (2010) first demonstrated that during a 14-month follow-up, corticosteroid administration during and after the catheter ablation could significantly reduce LRAF without any antiarrhythmic drugs. In the multivariable COX regression analysis, CRP and corticosteroid treatment were significant independent predictors of LRAF (CRP: HR 1.239; corticosteroid: HR 0.458). The results of this study are inconsistent with the prospective, randomized, single-blind study by Kim YR et al. (2015). During a mean 24.1-month follow-up period, methylprednisolone therapy could not decrease the incidence of LRAF significantly compared with the control group. Multi-regression analysis suggested that corticosteroid administration did not decrease the LRAF (Kim YR et al., 2015).

Differences in design, patient profile, definitions of LRAF, mean follow-up periods, and methods of arrhythmia monitoring could explain the contradictory results of these two RCT studies. The study by Kim YR et al. (2015) was a single-blind trial, while the study by Koyama et al. (2010) was a double-blind trial which could be more reliable for preventing bias. The study by Koyama et al. (2010) was focused on the recurrence of paroxysmal AF, whereas the study by Kim YR et al. (2015) included persistent AF, which usually has a high rate of recurrence of catheter ablation. The method to detect AF (24 h-Holter vs. 7 d-Holter) and follow-up periods (14 months vs. 24 months) may also affect the incidence of AF recurrence. Unsurprisingly, the incidence of AF recurrence was higher in the study performed by Kim YR et al. (2015).

The findings of our meta-analysis are not inconsistent with other anti-inflammatory drugs used in the prevention of AF recurrence after catheter ablation. Patel et al. (2009) conducted a nested case controlled analysis of 1500 AF patients who underwent catheter ablation. The result of this study suggested that patients treated with polyunsaturated fatty acid supplementation (PUFAS) showed a decreased incidence of ERAF and procedural failure with a mean follow-up period of 28 months. However, the meta-analysis showed that PUFAS was insufficient to reduce the incidence of AF following cardiac surgery, which indicates that the definite effect of PUFAS on AF after cardiac procedures may still be unclear. Another point that should be considered is that the administration of PUFAS took place during the entire follow-up period, while the corticosteroids were only used around the time of catheter ablation, which may affect the AF recurrence.

A RCT study performed by Deftereos et al. (2012), which included 170 AF patients who underwent catheter ablation, indicated that colchicine was an effective drug to prevent ERAF (blanking period three months) after PVI without antiarrhythmic drug therapy (odds ratio (OR) 0.38). It also showed that the

effect of colchicine in preventing ERAF was associated with decreasing inflammatory mediators (e.g. CRP and IL-6). Our meta-analysis of RCT studies also showed that corticosteroids could efficiently reduce the risk of ERAF after catheter ablation. Koyama et al. (2010) also suggested that corticosteroids could significantly lower the occurrence of ERAF. However, our meta-analysis of cohort studies failed to support this correlation. This may be due to potential confounding factors and various biases in these cohort studies. Further large randomized studies are needed to confirm the effect of corticosteroids on prevention of ERAF after catheter ablation.

Deftereos et al. (2014) also demonstrated that colchicine could reduce the LRAF in paroxysmal AF patient after a single PVI with a median follow-up period of 15 months (OR 0.46). However, the dosage of colchicine was 0.5 mg twice daily for three months after catheter ablation, while in our studies, the administration of low- or moderate-dose corticosteroids only lasted a few days. The difference in the course of treatment may have a long-term effect on AF recurrence.

There are several limitations of our analysis that should be noted. The major limitation is the heterogeneity of the included studies. Although these studies were of high quality, they may be susceptible to various biases. Firstly, different types of AF were described, and various definitions of ERAF and LRAF were used. Secondly, Andrade et al. (2013) did not mention the use of antiarrhythmic drugs, which may affect the results. Furthermore, various types and dosages of corticosteroids were used in these studies, which may also affect the findings. Finally, the incidence of AF recurrence after catheter ablation was dependent upon the type and frequency of monitoring techniques, which was also different in these studies. To overcome these heterogeneities, a large double-blind randomized study may be needed in the future.

## 5 Conclusions

Inflammation plays a critical role in the pathogenesis of AF development and recurrence. Corticosteroids have significant anti-inflammatory effects. However, our meta-analysis suggests that corticosteroid administration following catheter ablation is not significantly associated with a reduction in the LRAF. Corticosteroids may reduce the risk of ERAF, but there is not sufficient evidence of the effect on LRAF. Owing to potential confounding factors, further large and double-blind RCT studies are needed.

## Compliance with ethics guidelines

Sanjay JAISWAL, Xian-bao LIU, Qu-cheng WEI, Ying-hao SUN, Li-han WANG, Liu-guang SONG, Dan-dan YANG, and Jian-an WANG declare that they have no conflict of interest.

This article does not contain any studies with human or animal subjects performed by any of the authors.

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## List of electronic supplementary materials

Data S1 Searching strategy
Table S1 Quality assessment

## 中文概要

**题　目：皮质类固醇对导管消融术后心房颤动影响的荟萃分析**

**目　的：**探讨皮质类固醇对导管消融术后心房颤动（AF）的影响。

**创新点：**首个探讨皮质类固醇对导管消融术后 AF 影响的荟萃分析。

**方　法：**我们在 PubMed、Embase 和 Cochrane 对照试验中心注册库中搜索了描述皮质类固醇对预防导管消融后 AF 复发影响的文章，并提取了研究和患者的相关数据。使用随机效应模型计算风险比（RR）和 95%置信区间（CI），$P$<0.05 被认为具有统计学差异。

**结　论：**导管消融术围术期皮质类固醇的使用与 AF 早期复发减少相关，但与晚期复发无关。

**关键词：**心房颤动；皮质类固醇；导管消融术；荟萃分析