Original Article

Additional complex fractionated atrial electrogram ablation does not improve the outcomes of non-paroxysmal atrial fibrillation: A systematic review and meta-analysis of randomized controlled trials

Yoga Waranugraha a,b,*, Ardian Rizal a,b, Dion Setiawan b, Indra Jabbar Aziz b

a Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia
b Brawijaya Cardiovascular Research Center, Malang, Indonesia

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ABSTRACT

Background: Non-paroxysmal atrial fibrillation (AF) has a complex pathophysiological process. The standard catheter ablation approach is pulmonary vein isolation (PVI). The additional value of complex fractionated electrogram (CFAE) ablation is still unclear. We aimed to investigate the additional value of CFAE ablation for non-paroxysmal AF.

Methods: We performed a systematic review and meta-analysis of randomized controlled studies up to May 2020. Articles comparing pulmonary vein isolation (PVI) plus CFAE ablation and PVI alone for AF were obtained from the electronic scientific databases. The pooled mean difference (MD) and pooled risk ratio (RR) were assessed.

Results: A total of 8 randomized controlled trials (RCTs) including 1034 patients were involved. Following a single catheter ablation procedure, the presence of any atrial tachyarrhythmia (ATA) with or without the use of antiarrhythmic drugs (AADs) between both groups were not significantly different (RR = 1.1; 95% confidence interval [CI] = 0.97–1.24; p = 0.13). Similar results were also obtained for the presence of any ATA without the use of AADs (RR = 1.08; 95% CI = 0.96–1.22; p = 0.2). The additional CFAE ablation took longer procedure times (MD = 46.95 min; 95% CI = 38.27–55.63; p < 0.01) and fluoroscopy times (MD = 11.69 min; 95% CI = 8.54–14.83; p < 0.01).

Conclusion: Additional CFAE ablation failed to improve the outcomes of non-paroxysmal AF patients. It also requires a longer duration of procedure times and fluoroscopy times.

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1. Introduction

Atrial fibrillation (AF) is well known as the most common heart rhythm disorder encountered by the physician in daily clinical practice and is related to significant mortality, morbidity, and healthcare costs.1–2 Worldwide, the prevalence of AF is estimated to increase.3–5 AF could undergo the evolution from self-terminating short episodes (paroxysmal AF) to longer episodes (persistent AF or long-standing persistent AF), which require cardioversion for the conversion into sinus rhythm, or it can progress into the permanent AF.6–8 The evolution of AF is caused by the atrial remodeling caused by itself, the progression of the underlying heart disease, or both.9–10 Generally, the treatment approach for AF includes rhythm control, rate control, and prevention of thromboembolism. The conversion into sinus rhythm can be achieved through antiarrhythmic drugs (AADs) administration, electrical cardioversion, or catheter ablation.11–14 To date, several major cardiovascular associations give a class I recommendation for rhythm control using catheter ablation only for patients with recurrent paroxysmal AF who are refractory or intolerance to class I or III AADs, especially.11–13

Prior studies have demonstrated that pulmonary vein isolation (PVI) is effective in maintaining the sinus rhythm in 78 to 79.5% of paroxysmal paroxysmal AF patients at five years follow-up period.15–16 However, a study in persistent AF and long-standing persistent AF revealed that arrhythmia free survival at a one-year follow-up period was 66.7%.17 Non-paroxysmal AF that includes persistent AF, long-standing persistent AF, and permanent AF, has a more complex pathophysiological process than paroxysmal AF.8–10 This condition led to the need for an additional ablation strategy to...
modify the AF substrate, such as complex fractionated atrial electrogram (CFAE) and linear ablation. The additional value of CFAE ablation for AF is still unclear. We aimed to investigate whether the additional CFAE ablation could give the additional value for the rhythm control strategy in non-paroxysmal AF.

2. Methods

2.1. Study design

We performed a systematic review and meta-analysis study in May 2020 of published studies up to May 2020, according to the direction from Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines. Articles published in the electronic scientific database such as PubMed, ScienceDirect, Cochrane, ProQuest, and ClinicalTrials.gov were searched and identified based on the eligibility criteria. Eligible articles were processed and analyzed to determine the pooled mean difference (MD) for continuous data or pooled risk ratio (RR) for categorical data using a fixed-effect or random-effect analysis. We also assessed its corresponding 95% confidence interval (CI).

2.2. Search strategy

Up to May 2020, articles comparing PVI plus CFAE ablation and PVI for AF were obtained from the electronic scientific database such as PubMed, ScienceDirect, Cochrane, ProQuest, and ClinicalTrials.gov. We used the following keywords: “non-paroxysmal atrial fibrillation” or “non-paroxysmal AF,” AND “catheter ablation,” AND “complex fractionated atrial electrogram” or “CFAE” AND “pulmonary vein isolation” or “PVI.” We also searched for potentially relevant information through the reference lists of all accessed papers.

2.3. Eligibility criteria

The inclusion criteria included: (1) studies comparing PVI versus PVI plus CFAE ablation for non-paroxysmal AF including persistent AF, long-standing persistent AF, or permanent AF; (2) the purpose of AF ablation was for rhythm control; (3) availability of the information about the procedure times, fluoroscopy times, or ablation times; (4) at least six months’ duration of follow-up; (5) availability of data about the arrhythmia detection method; (6) availability of the information about atrial tachyarrhythmia (ATA), AF, atrial flutter (AFL), or atrial tachycardia (AT) during the follow-up period; and (7) articles written in English. We excluded the articles which met the following criteria: (1) duplications; (2) review articles; (3) case reports; (4) editorials; (5) non-English language; (6) unavailable full-text; (7) incomparable approach in the treatment and control groups; (8) did not report the outcome of interest; (9) sub-study of the included studies (10) studies involved paroxysmal AF patients; or (11) non-RCT studies.

2.4. Exposure and outcome

The exposure variable was the CFAE ablation in addition to PVI. Therefore, patients were grouped into the “CFAE group” and “No CFAE group.” The primary outcome was the presence of any ATA, including AF, AFL, or AT, with or without the use of AADs following a single catheter ablation procedure. The secondary outcome of this study included: (1) the presence of any ATA including AF, AFL, or AT without the use of AADs following a single catheter ablation procedure; (2) repeat ablation procedure following a single catheter ablation procedure; (3) procedure-related complications; and also (4) procedure times and fluoroscopy times.

2.5. Quality of studies assessment and data extraction

The quality assessment of the collected randomized controlled trials (RCTs) was conducted using the modified Jadad scale. It is consists of 8 criteria with a range of values of 0–8. RCTs with a modified Jadad scale of 4–8 were considered as a high-quality study. This systematic review and meta-analysis study only included high-quality RCTs. Data about (1) the first author name; (2) acronym of the study; (3) year of publication; (4) design; (5) center involved; (6) type of AF; (7) ablation strategy; (8) CFAE ablation site; (9) CFAE detection method; (10) blanking period; (11) duration of follow-up period; (12) arrhythmia detection method; (13) primary endpoint; (14) definition of recurrent arrhythmia; (15) number of patients; (16) age; (17) gender; (18) valvular AF; (19) duration of AF; (20) left ventricular ejection fraction (LVEF); (21) anteroposterior diameter of left atrium (LA); (22) occurrence of ATA including AF, AFL, and AT with or without AADs; (23) repeat ablation procedure; (24) the use of AADs during follow up period; (25) procedure-related complications; (26) procedure times; and (27) fluoroscopy times were extracted from the included articles.

2.6. Statistical analysis

The statistical analysis process was carried out according to the standard guideline. Data were assessed for heterogeneity and potential publication bias before determining the conclusion. Q test was used to evaluate the presence of heterogeneity. We used the cut off value of p for heterogeneity (pHet) 0.1. In the presence of heterogeneity (pHet < 0.1), we used the random-effect analysis model. In contrast, in the absence of heterogeneity (pHet > 0.1), we used the fixed-effect analysis model. The existence of publication bias was evaluated using two methods, including funnel plot analysis and the Egger test. The presence of significant publication bias was identified if p Egger (pE) < 0.05. For categorical data, the pooled RR and 95% CI were measured using the Mantel-Haenszel statistical method. The inverse variance statistical method was used to measure the pooled MD and 95% CI for continuous data. Statistically significant was considered if a p-value < 0.05. Comprehensive Meta-Analysis version 3.0 (CMA, New Jersey, US) and Review Manager Version 5.3 (Cochrane, Copenhagen, Denmark) were used for the data analysis process.

3. Results

3.1. Eligible studies

A total of 442 articles were identified through PubMed, ScienceDirect, Cochrane, ProQuest, and ClinicalTrials.gov, while three articles were identified through reference lists of accessed full-text articles. Three hundred forty-one records were excluded because of duplications. We excluded 25 review articles, 17 case reports, 6 editorials, 9 articles written in a non-English language, and 10 articles without full-text availability during the initial screening. In further screening, 29 articles were excluded due to the following reasons: (1) incomparable approach in the treatment and control group (n = 11); (2) did not report the outcome of interest (n = 3); (3) sub-study of included studies (n = 4); (4) Involved paroxysmal AF patients (n = 8); and cohort studies (n = 3). In the end, 8 RCTs were included in this study. The flow diagram of the study selection process is shown in Fig. 1.

3.2. Baseline characteristics

All included studies have a modified Jadad scale ≥4, therefore considered as the high-quality study (Supplementary Table 1).
Baseline characteristics of the involved RCTs are summarized in Table 1. CFAE ablation on the LA was conducted in four studies,24,25,28,31 while CFAE ablation on both atria was also conducted in four studies.26,27,29,30 Most of the included studies used automatic CFAEs detection algorithm.24,25,27,28,30,31 The blanking period ranged from 2 to 3 months, and the mean follow-up period was at least 10 months. Ambulatory heart rhythm monitor devices were used to detect the episode of arrhythmia during follow up period.24

A total of 1034 patients with non-paroxysmal AF were included in our study. Additional CFAE ablation procedure was conducted in 607 patients in addition to the PVI with or without linear ablation. PVI with or without linear ablation was performed in 427 patients. All included studies were dominated by male patients, with the proportion of male patients ranged from 64.8 to 90%. The patients have the mean age ranged from 58 to 64.6 years old, and the mean duration of they had non-paroxysmal AF for was 3.6 to 9 years. The mean LA diameter was 42 to 48 mm, while the mean LVEF was 50.1 to 61.69%. The summary of baseline characteristics of the included patients is shown in Table 2.24

### 3.3. Heterogeneity and publication bias

The presence of heterogeneity was assessed using the Q-test. We did not find any heterogeneity in our meta-analysis, so we used the fixed-effect model to determine the correlation and effect estimation (Figs. 2, 3, and 4). From our analysis, the publication bias was present only in the analysis of procedure-related complications, which was supported by the asymmetrical funnel plot (Fig. 5) and pE = 0.02 (Table 3). The presence of heterogeneity and publication bias are summarized in Table 3 and Table 4.

### 3.4. Outcome

Following a single catheter ablation procedure, the presence of any ATA (RR = 1.1; 95%CI = 0.97–1.24; p = 0.13), AF (RR = 0.94; 95% CI = 0.79–1.22; p = 0.5), and AFL or AT (RR = 1.3; 95% CI = 0.92–1.82; p = 0.14) with or without the use of AADs between both groups were not significantly different (Fig. 2). The similar results were also obtained for the presence of any ATA (RR = 1.08; 95% CI = 0.96–1.22; p = 0.2), AF (RR = 0.97; 95% CI = 0.82–1.14; p = 0.68), AFL or AT (RR = 1.1; 95% CI = 0.76–1.6; p = 0.61), and repeat ablation procedure (RR = 1.17; 95% CI = 0.95–1.44; p = 0.14) without the use of AADs in between both groups (Fig. 3).

We also conducted analysis of the procedural aspects (Fig. 4). As we expected, the additional CFAE ablation took longer procedure times (MD = 46.95 min; 95% CI = 38.27–55.63; p < 0.01) and fluoroscopy times (MD = 11.69 min; 95% CI = 8.54–14.83; p < 0.01) (Fig. 4). The procedure-related complications between CFAE group and no CFAE group were not significantly different (RR = 1.49; 95% CI = 0.75–2.96; p = 0.26) (Fig. 3). It included
Table 1
Baseline characteristics of the involved randomized controlled trials.

| First author, year (Ref) | Design Type | Type of AF | Size, n | Ablation strategy | CFAE ablation site | CFAE detection method | CFAE definition | Blanking period | Follow up period | Arrhythmia detection method | Definition of recurrent arrhythmia |
|--------------------------|-------------|------------|--------|-------------------|-------------------|----------------------|----------------|----------------|----------------|-------------------------------|----------------------------------|
| Bassiouy, 2016 RCT-SC    | Persistent AF | 90         | PVAI + posterior wall and septum ablation | LA               | Automated cycle length between 50 and 120 ms, using automated electrographic analysis | 3 months           | 12 months       | Weekly follow-up telephone calls and trans-telephonic ECG transmissions (first 4–6 months) | AF, AFL or focal AT episode lasting >30 s after 3 months blanking period. |
| Dixit, 2012 RCT-SC       | Persistent AF | 156        | PVI     | PVI + non-PV trigger, PVI + CFAE, LA | Automated mean fractionation interval < 120 ms | 6 weeks           | 12 months       | At least 3 outpatient visits | Any symptomatic or asymptomatic AF or OAT episode that lasted ≥30 s |
| Elayi, 2008 RCT-MC       | Longstanding permanent AF | 144        | PVI-CPVA | PVI-PVAI, PVI-PVAI + CFAE atria | Visual atrial electrograms with fractionation and composed of 2 defects or more and/or with continuous activity of the baseline or Visual atrial electrograms with a cycle length < 120 ms | 2 months           | 16 months       | 12-lead ECG during outpatient visits | Episodes of AF/AT that lasted ≥1 min during the follow-up period |
| Elayi, 2011 RCT-SC       | Longstanding persistent AF | 98         | PVI-PVAI | PVI-PVAI + CFAE, No | Automated atrial electrograms with fractionation and composed of 2 defects or more and/or with continuous activity of the baseline or Automated atrial electrograms with a cycle length < 120 ms | 2 months           | 17.2 ± 5.2 months | Outpatients clinic visits with 48-h Holter monitor recording (3-month intervals for 1 year) | Any episode of AF at 48-h Holter monitor recording (3-month intervals for 1 year) |

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Oual. 2009 RCT: Persistent AF during PVAI

Any episode of AF or ATA lasting >30 s in duration beyond 12 weeks after ablation

Verma, 2015 RCT: Persistent AF

LA Automated CFAE mean of <120 ms

Clinical assessments: 12 AF lasting >30 s after ablation, ECG, and 24-h Holter—one ablation procedure

Transesophageal monitor recording (baseline or without the use of antiarrhythmic drugs); AF—atrial fibrillation; ATA—atrial tachyarrhythmia; AT—atrial tachycardia; CFAE—complex fractionated atrial electrogram; CPVA—circumferential pulmonary vein ablation; CPVI—circumferential pulmonary vein isolation; CFAE—complex fractionated atrial electrogram; CS—coronary sinus; LA—left atrium; MC—multicenter; OAT—organized atrial tachycardia; PVAI—pulmonary vein antrum isolation; PVI—pulmonary vein isolation; RCT—randomized controlled trial; SC—single center; ECG—electrocardiography; AADs—antiarrhythmic drugs; AF—atrial fibrillation; AT—atrial tachycardia; CFAE—complex fractionated atrial electrogram; CPVA—circumferential pulmonary vein ablation; CPVI—circumferential pulmonary vein isolation; LA—left atrium; MC—multicenter; OAT—organized atrial tachycardia; PVAI—pulmonary vein antrum isolation; PVI—pulmonary vein isolation; RCT—randomized controlled trial; SC—single center.
femoral access complications, stroke, pericardial tamponade, pulmonary vein stenosis, sinus node syndrome not requiring pacemaker, temporary respiratory arrest associated to anesthesia, and atrio-esophageal fistula.\textsuperscript{25,26,27,28,30} The analysis results of the procedural aspects are summarized in Tables 3 and 4.

### 4. Discussion

#### 4.1. Main findings and comparison with the previous studies

We performed a meta-analysis of 8 RCTs. During the 10 to 35 months mean follow-up period, the presence of any ATA, AF, and AFL or AT with or without the use of AADs after a single ablation procedure between the CFAE group and no CFAE group were not significantly different. Our results supported the results of the previous studies. However, those previous studies included both paroxysmal AF and non-paroxysmal AF patients.\textsuperscript{32,33} According to the included studies, our study differed from Providencia et al.\textsuperscript{33} which included cohort studies. Compared with a study from Kong et al.,\textsuperscript{32} which only included RCTs, we were able to add 6 RCTs to be included in our meta-analysis.\textsuperscript{24,25,27,28,30,31} We used a different method to extract data from the study conducted by Elayi et al.,\textsuperscript{25} where the patients were divided into three groups: CFAE ablation continued by pulmonary vein antrum isolation (PVAI) group, PVAI group, and circumferential pulmonary vein ablation (CPVA) group. The study of Kong et al. merged the PVAI group and the CPVA group as the control group.\textsuperscript{32} In this study, we needed to know the additional benefit of CFAE ablation for non-paroxysmal AF. Therefore, we only used the PVAI group as the control group.

The goal of our study was to determine whether CFAE ablation provided additional benefit for non-paroxysmal AF. The use of AADs after ablation could be the potential confounder. Therefore, we conducted the meta-analysis in patients who were not treated with AADs after a single ablation procedure. No significant difference was found in the presence of any ATA without the use of AADs after a single ablation procedure between the CFAE group and no CFAE group. Prior meta-analysis studies showed conflicting results. One study revealed that CFAE ablation did not provide additional value for non-paroxysmal AF patients,\textsuperscript{32} while another study revealed different result.\textsuperscript{35} Therefore, we identified the specific types of ATA that occurred after a single ablation procedure without AADs. No significant difference was also found in the presence of AF and AFL or AT without the use of AADs after a single ablation procedure between the CFAE group and the no CFAE group. The earlier studies did not provide the data about the specific types of ATA that occurred after a single ablation procedure without AADs.\textsuperscript{34,35} The need for repeat ablation procedure was also not different between both groups. Our result was not different from the earlier study on paroxysmal AF and non-paroxysmal AF.\textsuperscript{32}

Additional CFAE ablation was significantly correlated with increased duration of procedure times and fluoroscopy times. It was not different from the results of the previous meta-analysis.\textsuperscript{32,34,35} In our meta-analysis, CFAE was not correlated with an increase of procedure-related complications. Our findings in procedure-related complications should not be extrapolated. We found the potential of publication bias supported by the consistent result funnel plot analysis and the Egger test (Figs. 4 and 5, and Table 3).

#### 4.2. Non-paroxysmal AF and substrate modifying ablation

Electrical trigger, arrhythmogenic substrate, and modulating factors are essential factors in the pathogenesis of AF.\textsuperscript{36} Electrical triggers play a vital role in AF initiation, while modulating factors and arrhythmogenic substrate are responsible for its perpetuation or maintenance.\textsuperscript{37,38} In AF, most of the ectopic activities or electrical triggers are pulmonary veins origin. Ablation in those locations can prevent the recurrence of AF.\textsuperscript{39} Localized re-entry, rotors, and triggered activity were the underlying mechanisms in the focal ectopic activity induction.\textsuperscript{40,41} Modulating factors include atrial stretch, increased vagal tone, dispersion and shortening of the atrial refractory period, calcium load, inflammation, cardiovascular risk factors, or genetic predisposition.\textsuperscript{8,10,37} Anatomical remodeling (atrial dilatation, fibrosis, adipose tissue) and electrical remodeling (shortening of the action potential) are the arrhythmogenic substrates in AF.\textsuperscript{8,10,36,37} Paroxysmal AF shows a predominance of local electrical triggers, mainly pulmonary veins origin.\textsuperscript{12} Earlier studies revealed that the success rate of PVI ranged from 78 to 79.5%.\textsuperscript{15,16} In persistent AF, the success rate of PVI was lower, which finally permanent (non-paroxysmal), arrhythmogenic substrates (at the beginning functional and eventually become structural) predominates.\textsuperscript{10} In this meta-analysis, the structural changes in LA had already occurred because most all studies involved patients with large LA size.\textsuperscript{24,25,27,28,30} Anteroposterior LA diameter measured by echocardiography > 40 mm and >38 mm are considered large for male and female respectively.\textsuperscript{42} Earlier study in persistent AF showed the lower success rate of PVI, which was around 66.7%.\textsuperscript{17} Substrate modifying ablation approach, such as CFAE ablation, might be a solution to solve it.
4.3. The possible explanation for CFAE ablation did not give an additional benefit for non-paroxysmal AF

In our meta-analysis, there were several reasons for CFAE ablation did not give an additional benefit for non-paroxysmal AF. First, in some studies, the CFAE detection method was conducted using an automatic CFAE detection algorithm, while other studies used direct visual inspection. Although the automatic mapping systems were used, there were differences in their set up and algorithms for defining and classifying fractionated electrograms. The heterogenous CFAE definition, different CFAEs detection algorithm among studies, or direct visual inspection could be the potential confounder. Second, the location of the CFAE ablation site also could be the possible confounder. CFAE ablation was conducted in LA and both atria.

Fourth, an additional CFAE ablation is associated with the wider area of scar tissues. It could be seen using cardiac magnetic resonance (CMR) with the late-gadolinium enhancement (LGE). Previous studies revealed that poor scar formation was associated with recurrent ATA after catheter ablation procedure for AF.

4.4. Strengths and limitations

There were several strengths of our study. First, our meta-analysis represents the largest pooled analysis of RCTs of the additional value of CFAE ablation for non-paroxysmal AF to the best of our knowledge. Second, we provided the data about the
A. Atrial tachyarrhythmia without antiarrhythmic drugs

| Study or Subgroup | CFAE Events | No CFAE Events | Total Events | Risk Ratio M-H, Fixed, 95% CI | Risk Ratio M-H, Fixed, 95% CI |
|-------------------|-------------|----------------|--------------|-------------------------------|-------------------------------|
| Bassouy, 2016     | 31          | 44             | 30           | 46                            | 1.08 [0.81, 1.44]              |
| Dixit, 2011       | 36          | 51             | 28           | 55                            | 1.29 [1.01, 1.60]              |
| Elayi, 2008       | 19          | 49             | 29           | 48                            | 0.96 [0.77, 1.23]              |
| Oral, 2009        | 32          | 50             | 31           | 50                            | 1.03 [0.76, 1.39]              |
| Verma, 2015       | 163         | 244            | 63           | 61                            | 1.13 [0.90, 1.42]              |
| Wong, 2015        | 40          | 65             | 34           | 65                            | 1.18 [0.87, 1.62]              |
| **Total (95% CI)**| **503**     | **325**        | **100.0%**   | **1.08 [0.96, 1.22]**         |                               |

Total events: 321 of 188
Heterogeneity: Chi² = 8.69, df = 5 (P = 0.11); I² = 44%
Test for overall effect: Z = 1.27 (P = 0.20)

B. Atrial Fibrillation without antiarrhythmic drugs

| Study or Subgroup | CFAE Events | No CFAE Events | Total Events | Risk Ratio M-H, Fixed, 95% CI | Risk Ratio M-H, Fixed, 95% CI |
|-------------------|-------------|----------------|--------------|-------------------------------|-------------------------------|
| Bassouy, 2016     | 16          | 44             | 18           | 46                            | 12.2% [5.55, 1.65]            |
| Dixit, 2011       | 26          | 51             | 32           | 55                            | 21.4% [11.92, 4.2]            |
| Elayi, 2008       | 8           | 49             | 15           | 48                            | 10.5% [3.24, 1.12]            |
| Oral, 2009        | 26          | 50             | 29           | 50                            | 20.2% [0.63, 1.28]            |
| Verma, 2015       | 154         | 244            | 32           | 61                            | 35.6% [0.93, 1.56]            |
| **Total (95% CI)**| **438**     | **260**        | **100.0%**   | **0.97 [0.82, 1.14]**         |                               |

Total events: 230 of 126
Heterogeneity: Chi² = 5.79, df = 4 (P = 0.22); I² = 31%
Test for overall effect: Z = 0.41 (P = 0.68)

C. Atrial Flutter or atrial tachycardia without antiarrhythmic drugs

| Study or Subgroup | CFAE Events | No CFAE Events | Total Events | Risk Ratio M-H, Fixed, 95% CI | Risk Ratio M-H, Fixed, 95% CI |
|-------------------|-------------|----------------|--------------|-------------------------------|-------------------------------|
| Bassouy, 2016     | 15          | 44             | 12           | 46                            | 28.6% [0.69, 2.47]            |
| Dixit, 2011       | 9           | 51             | 7            | 55                            | 16.4% [0.56, 3.45]            |
| Elayi, 2008       | 11          | 49             | 14           | 48                            | 34.5% [0.39, 1.52]            |
| Oral, 2009        | 6           | 50             | 2            | 50                            | 4.9% [0.64, 14.16]            |
| Verma, 2015       | 9           | 244            | 4            | 61                            | 15.6% [0.18, 1.77]            |
| **Total (95% CI)**| **438**     | **260**        | **100.0%**   | **1.10 [0.76, 1.60]**         |                               |

Total events: 50 of 39
Heterogeneity: Chi² = 4.61, df = 4 (P = 0.34); I² = 11%
Test for overall effect: Z = 0.51 (P = 0.61)

D. Repeat ablation procedure

| Study or Subgroup | CFAE Events | No CFAE Events | Total Events | Risk Ratio M-H, Fixed, 95% CI | Risk Ratio M-H, Fixed, 95% CI |
|-------------------|-------------|----------------|--------------|-------------------------------|-------------------------------|
| Bassouy, 2016     | 14          | 44             | 12           | 46                            | 11.0% [0.64, 2.34]            |
| Dixit, 2011       | 24          | 51             | 14           | 55                            | 12.6% [1.08, 3.17]            |
| Elayi, 2008       | 10          | 49             | 12           | 48                            | 11.3% [0.39, 1.71]            |
| Oral, 2009        | 17          | 50             | 18           | 50                            | 16.8% [0.55, 1.61]            |
| Verma, 2015       | 63          | 244            | 13           | 61                            | 19.4% [0.72, 2.05]            |
| Wong, 2015        | 54          | 65             | 31           | 65                            | 28.9% [0.78, 1.55]            |
| **Total (95% CI)**| **503**     | **325**        | **100.0%**   | **1.17 [0.95, 1.44]**         |                               |

Total events: 162 of 100
Heterogeneity: Chi² = 4.48, df = 5 (P = 0.48); I² = 0%
Test for overall effect: Z = 1.46 (P = 0.14)

Fig. 3. Atrial tachyarrhythmia (A), atrial fibrillation (B), atrial flutter or atrial tachycardia (C), and repeat ablation procedure (D) after single catheter ablation procedure without antiarrhythmic drugs. CI – confidence interval; CFAE – complex fractionated atrial electrogram; M–H – Mantel-Haenszel.
recurrent ATA, including AF, AFL, or AT, after a single catheter ablation procedure. Third, arrhythmia detection following a single catheter ablation was conducted using ambulatory heart rhythm monitors in all studies. In addition to those strengths, our study also had several limitations. First, as well as other meta-analysis studies, the possibility of publication bias cannot be avoided. To overcome

### A. Procedure times

| Study or Subgroup | CFAE Mean SD Total | No CFAE Mean SD Total | Mean Difference IV, Fixed, 95% CI | Mean Difference IV, Fixed, 95% CI |
|-------------------|-------------------|---------------------|-----------------------------------|-----------------------------------|
| Bassiouny, 2016   | 273 76 44          | 231 72 46           | 42.00 [11.39, 72.61]              |                                  |
| Dixit, 2011       | 384 99 51          | 356 85 55           | 28.00 [7.25, 63.25]               |                                  |
| Elsayy, 2008      | 239 102 49         | 183 91 48           | 56.00 [17.55, 94.45]              |                                  |
| Kim, 2017         | 244.91 53.14 54   | 219.54 60.7 54      | 25.37 [5.85, 46.89]               |                                  |
| Verma, 2015       | 229 83 244         | 167 55 61           | 25.2% [20.5, 33.1]                |                                  |
| Wong, 2015        | 201 35 65          | 152 45 65           | 49.00 [25.1, 68.0]                |                                  |
| **Total (95% CI)** | **507** | **329** | **100.0%** | **46.95 [38.27, 55.63]** |

Heterogeneity: Chi² = 8.28, df = 5 (P = 0.14); I² = 40%
Test for overall effect: Z = 10.60 (P < 0.0000001)

### B. Fluoroscopy times

| Study or Subgroup | CFAE Mean SD Total | No CFAE Mean SD Total | Mean Difference IV, Fixed, 95% CI | Mean Difference IV, Fixed, 95% CI |
|-------------------|-------------------|---------------------|-----------------------------------|-----------------------------------|
| Dixit, 2011       | 110 37 51         | 103 35 55           | 7.00 [6.74, 20.74]                |                                  |
| Elsayy, 2008      | 94 27 49          | 76.9 21 48          | 17.10 [7.46, 26.71]               |                                  |
| Elsayy, 2011      | 71 22 50          | 59 18 48            | 15.7% [11.2, 20.3]                |                                  |
| Verma, 2015       | 42 21 244         | 29 16 61            | 13.00 [8.20, 17.80]               |                                  |
| Wong, 2015        | 47 22 65          | 39 13 65            | 8.00 [1.79, 14.21]                |                                  |
| **Total (95% CI)** | **459** | **277** | **100.0%** | **11.69 [8.54, 14.83]** |

Heterogeneity: Chi² = 3.31, df = 4 (P = 0.51); I² = 0%
Test for overall effect: Z = 7.29 (P < 0.0000001)

### C. Procedure related complications

| Study or Subgroup | No CFAE Events Total | CFAE Events Total | Weight | Risk Ratio M−H Fixed, 95% CI | Risk Ratio M−H Fixed, 95% CI |
|-------------------|----------------------|-------------------|--------|-----------------------------|-----------------------------|
| Dixit, 2011       | 3 51                 | 1 55              | 7.8%   | 3.24 [0.35, 30.11]          |                             |
| Elsayy, 2008      | 3 49                 | 1 48              | 8.2%   | 2.94 [0.32, 27.27]          |                             |
| Elsayy, 2011      | 3 50                 | 1 48              | 8.2%   | 2.88 [0.31, 26.74]          |                             |
| Kim, 2017         | 5 54                 | 3 54              | 24.2%  | 1.67 [0.42, 6.63]           |                             |
| Verma, 2015       | 11 244               | 4 61              | 51.6%  | 0.69 [0.23, 2.08]           |                             |
| **Total (95% CI)** | **448** | **266** | **100.0%** | **1.49 [0.75, 2.96]** |

Heterogeneity: Chi² = 3.05, df = 4 (P = 0.55); I² = 0%
Test for overall effect: Z = 1.13 (P = 0.26)

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**Fig. 4.** Procedure times (A), fluoroscopy times (B), and procedure-related complications (C). CI = confidence interval; CFAE = complex fractionated atrial electrogram; IV = inverse variance; M−H = Mantel-Haenszel.

**Fig. 5.** Funnel-plot analysis. Funnel-plot analysis showing asymmetrical funnel plot for procedure-related complications.
that problem, we used two methods mentioned above to identify any publication bias. The publication bias was found only in procedure-related complications. Second, the published experience on our outcomes. That is the standard issue in performing a meta-analysis. Fourth, the CFAE detection method widely varied among the included studies. The diversity in methodology could affect the analysis results. However, our results likely reflect current real-world clinical practice highlighting the absence of a clear CFAE definition. The last, the differences in the extent or location of CFAE ablation might influence the outcomes.

5. Conclusion

Our meta-analysis of RCTs revealed that additional CFAE ablation failed to improve the outcomes of non-paroxysmal AF patients. It also requires a longer duration of procedure times and fluoroscopy times. The universal definition of CFAE has to be established. Further multicenter RCTs with large homogenous participants and a more extended follow-up period are required to provide high-quality evidence about the benefit of additional CFAE ablation for patients with non-paroxysmal AF.

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Authors contributions

Idea/concept: YW. Design: YW. Control/supervision: AR. Data collection/processing: YW/DS/IJA. Extraction/Analysis/interpretation: YW/DS/IJA. Literature review: YW/AR/DS/IJA. Writing the article: YW/AR. Critical review: YW/AR. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

Declaration of competing interest

All authors declared that there is no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijhj.2020.11.004.

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