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The trend of change in catheter ablation versus antiarrhythmic drugs for the management of atrial fibrillation over time: a meta-analysis and meta-regression

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Abstract

Objective To evaluate the trend of change in the efficacy and safety of catheter ablation compared with antiarrhythmic drug therapy (ADT) for rhythm control in patients with atrial fibrillation (AF) over time. **Methods** The online databases PubMed and EMBASE were searched for relevant studies. STATA software (version 12.0) was used to perform the meta-analysis and meta-regression. **Results** Fifteen randomized controlled trials including 2249 patients with AF were identified. The pooled results showed that catheter ablation was associated with a 52% reduction in the risk of AF recurrence compared with ADT [risk ratio (RR) = 0.48, 95% confidence interval (CI): 0.40–0.57, I^2 = 70.7%). Subgroup analyses showed that catheter ablation exhibited less efficacy in studies after 2011 compared to studies before 2011 (RR = 0.61, 95% CI: 0.54–0.68, I^2 = 9.3% and RR = 0.34, 95% CI: 0.24–0.47, I^2 = 69.9%, respectively), and the safety outcome showed a 1.08-fold higher incidence of adverse events (14.2% *vs.* 7.3%; RR = 1.08, 95% CI: 1.04–1.13) in studies after 2011. **Conclusions** Catheter ablation appears to be superior to ADT for rhythm control. However, less efficacy and a higher rate of adverse events were observed in studies after 2011 compared to studies before 2011.

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Keywords: Antiarrhythmic drug therapy; Atrial fibrillation; Catheter ablation; Rhythm

1 Introduction

Atrial fibrillation (AF) is the most common type of cardiac arrhythmia in clinical practice, and it increases in prevalence with advancing age.[1] Furthermore, AF is also related to various clinical events, such as frequent hospitalizations, hemodynamic abnormalities and stroke, and results in significant morbidity and mortality.[2]

Rhythm control is a strategy for the management of AF, and it has the potential to restore and maintain sinus rhythm.[3] Antiarrhythmic drug therapy (ADT) and catheter ablation are commonly used strategies for rhythm control.[3] Currently, the guidelines suggest ADT as the first-line therapy when rhythm control is desired.[3,4] Nonetheless, the efficacy and safety of ADT remain an area of immense concern due to high rates of AF recurrence and long-term adverse drug reactions, which may mask the benefits of maintaining sinus rhythm.[5] Catheter ablation has been recognized as an alternative therapeutic modality for patients with AF refractory or intolerant to at least one class I or III antiarrhythmic medication in the recent guidelines.[3] Several clinical trials have compared the efficacy of ADT and catheter ablation on rhythm control in patients with AF.[6–10] However, there was a very confusing phenomenon in which early trials seemed to report higher success rates for catheter ablation than later studies.[6,7,10,11] Previous reviews that mainly included early studies also showed inconsistent results between catheter ablation and ADT, especially regarding the safety outcomes.[12,13] However, the different reports on efficacy and safety by early and later studies have not yet been completely investigated.

Therefore, we performed a systematic review and meta-analysis with more evidence from available randomized controlled trials (RCTs) to evaluate the trend of change in the efficacy and safety of catheter ablation compared with those of ADT for rhythm control in patients with AF over time.

2 Methods

2.1 Search strategy

The PubMed and EMBASE online databases were searched (up to March 12, 2017) to identify all publications associated with catheter ablation and ADT for rhythm con-

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trol in patients with AF. The following terms were used with proper logical connectors: "rhythm", "ablation", "antiarrhythmics", "amiodarone", "randomized", "randomised", "randomly" and "atrial fibrillation". Additionally, a manual search was performed by scanning the references of the identified articles to find studies that may have been missed by the electronic searches.

2.2 Study selection and data collection

The inclusion criteria of the present systematic review and meta-analysis were as follows: (1) the study must be a RCT; (2) patients were diagnosed with persistent or paroxysmal AF; (3) the studies compared ADT with catheter ablation techniques; and (4) relevant outcome data to be assessed in this systematic review and meta-analysis were reported in the article.

The article selection was performed strictly in compliance with the inclusion criteria. Two authors (LIU W and WU Q) independently assessed all potentially relevant studies. The selection process was carried out by crude screening of the title and abstract to exclude most of the irrelevant studies, and the full-texts of the remaining studies were examined twice to reach a final decision. A consensus was reached between the two screening authors on all eligible studies. Any discrepancies were resolved by discussion.

Two authors (LIU W and YANG XY) independently extracted all relevant information from eligible studies. A prespecified table containing the relevant items was used to help with data collection.

2.3 Endpoints

In the present systematic review and meta-analysis, efficacy and safety outcomes were analyzed to assess the differences of catheter ablation and ADT on rhythm control in patients with AF. The efficacy analysis was based on AF recurrence, and the safety outcome was based on complications and adverse events.

2.4 Evaluation of study quality and publication bias

The quality of the included studies was evaluated by the Jadad scale.[14] The Jadad scale consists of three items pertaining to descriptions of randomization (0–2 points), double blinding (0–2 points), and dropouts and withdrawals (0–1 point) for a total score of five, with a higher score indicating better quality. Trials scored 3 or greater were considered to be high quality.[14]

Publication bias was evaluated by Egger's tests. In addition, a funnel plot was generated to visually inspect the symmetry.

2.5 Data synthesis and statistical analysis

We separately conducted meta-analyses on the efficacy and safety of catheter ablation and ADT. The I^2 statistic was used to test statistical heterogeneity, with values > 50% representing important heterogeneity. A random-effects model was used to pool the effect sizes in all of the meta-analyses.

For the efficacy analysis, the risk ratio (RR) was calculated as the effect size. Subgroup analysis was performed to evaluate the efficacy of catheter ablation as a first- or second-line therapy. The role of study-level and aggregated individual-level parameters that might affect heterogeneity was assessed by meta-regression. The potential factors provided were types of AF (paroxysmal versus persistent), study design (single-center RCT versus multi-center RCT), intention-to-treat (ITT) analysis (ITT *vs*. non-ITT analysis studies), duration of follow-up (≤ 1 year *vs*. > 1 year), ablation approach [pulmonary vein isolation (PVI) only versus PVI + adjunctive ablation], year of publication (before 2011 versus after 2011) and electrical cardioversion during the blanking period. For the safety analysis, risk differences (RDs) were calculated to assess the differences in complications and adverse events between catheter ablation and ADT. Subgroup analyses were performed to compare studies before 2011 and studies after 2011.

The present systematic review and meta-analysis was performed in compliance with the recommendations of the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).[15] All meta-analyses in the present study were pooled in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0*.[16] All analyses were conducted using STATA software (version 12.0).

3 Results

Figure 1 details the study search and selection process. A total of 525 potential literature citations were identified through a systematic search. Finally, fifteen randomized trials with 2249 patients were included in this systematic review and meta-analysis.[6–11,17–25] Among these 15 trials, four were conducted at a single center,[7,18,22,25] while the remaining 11 trials were performed at multiple centers.[6,8–11,17,19–21,23,24] The year of publication of these trials ranged from 2003 to 2016, with 8 trials published before 2011 and 7 trials after 2011. Seven trials focused on patients with paroxysmal AF, five trials enrolled patients with persistent AF, and three trials included both paroxysmal and persistent AF patients. Adjunctive ablations, such as linear atrial lesions, and complex fractionated electrogram abla-

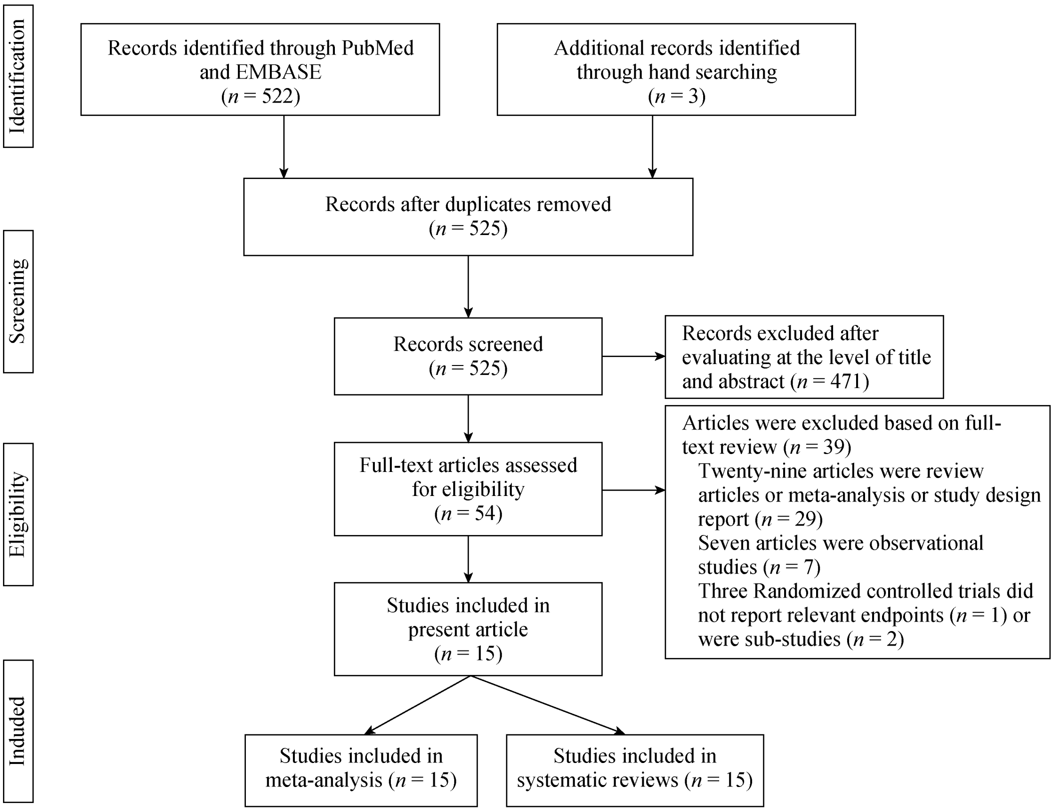

Figure 1. Flow chart of study selection.

tions were used in almost all the trials, depending on the investigators' decision, except for the earliest two trials.[11,25] The follow-up duration was 12 months or more in thirteen of the included trials, except for studies from Hummel, *et al*.[8] and Wilber, *et al.*[20] ITT analysis was used in 13 out of 15 trials. Tables 1 and 2 show the baseline characteristics of the included studies.

3.1 The quality of included studies

Table 2 provides a detailed assessment of study quality. Notably, all included studies were open-label designs. Based on the Jadad score, 11 studies with a score of three were high quality, while the other four studies with a score of two were low quality.

3.2 AF recurrence

Fifteen studies compared AF recurrence between patients treated with catheter ablation and those treated with ADT. A total of 2249 patients were included in these studies, of which 1209 and 1040 patients were in the catheter ablation and ADT groups, respectively. The incidence of AF recurrence was 31.6% in patients who underwent catheter ablation and 63.0% in patients who underwent ADT. Catheter ablation was associated with a significantly lower risk of AF recurrence, as shown by the pooled results using a random-effects model [pooled RR = 0.48, 95% confidence interval (CI): 0.40–0.57, I^2=70.7%; Figure 2].

Subgroup analysis showed that there was a 50% reduction in the risk of AF recurrence in patients who underwent catheter ablation as a first-line therapy compared with patients who underwent ADT (pooled RR = 0.50, 95% CI: 0.34–0.75, I^2 = 72.3%). In addition, our meta-analysis revealed a 54% reduction in the risk of AF recurrence in patients who underwent catheter ablation as a second-line therapy (pooled RR = 0.46, 95% CI: 0.37–0.57, I^2 = 72.2%) compared to patients who underwent ADT.

3.2.1 Meta-regression

The I^2 test revealed significant heterogeneity among the studies. Therefore, we performed a meta-regression to explore the source of heterogeneity. Meta-regression showed that year of publication had a significant effect on the observed heterogeneity (P = 0.014, adjusted R^2 = 55.41%; Figure 3). There were eight studies published before 2011 and seven studies published after 2011.

In the studies before 2011, the rates of AF recurrence were 25.4% and 70.7% in the catheter ablation and ADT groups, respectively. The pooled result showed a 66%

Table 1. Baseline characteristics of the patients in the included studies.

Study	Year	Groups	*N*	Age, yrs	Male	HTN	Valvular disease	CHD	LAD, mm	LVEF	Follow-up (months)	Blanking period (weeks)	AF types
Di Biase L, *et al*.[17]	2016	CA	102	62 ± 10	77 (75%)	46 (45%)	NR	63 (62%)	47 ± 4.2	29% ± 5%	24	12	Persistent
		ADT	101	60 ± 11	74 (73%)	48 (48%)	NR	66 (65%)	48 ± 4.9	30% ± 8%			
Morillo CA, *et al*.[6]	2014	CA	66	56.3 ± 9.3	51 (77.3%)	28 (42.4%)	0%	6 (9.1%)	40 ± 5	61.4% ± 4.8%	24	12	Paroxysmal
		ADT	61	54.3 ± 11.7	45 (73.8%)	25 (41.0%)	0%	2 (3.3%)	43 ± 5	60.8% ± 7.0%			
Zhang XD, *et al*.[7]	2014	CA	101	59.9 ± 11.4	71 (70.3%)	52 (51.5%)	9 (8.9%)	11 (10.9%)	45.8 ± 6.3	57.9% ± 6.5%	24	12	Persistent
		ADT	100	58.4 ± 10.4	67 (67.0%)	48 (48.0%)	10 (10.0%)	13 (13.0%)	45.7 ± 6.0	57.5% ± 6.9%			
Jais P, *et al*.[10]	2008	CA	53	49.7 ± 10.7	45 (84.9)	11 (21.6%)	4 (7.5)	3 (5.7%)	39.5 ± 5.6	63.1% ± 11.0%	12	12	Paroxysmal
		ADT	59	52.4 ± 11.4	49 (83.1)	18 (30.5%)	5 (8.5)	6 (10.2%)	40.0 ± 5.7	65.6% ± 7.2%			
Mont L, *et al*.[9]	2014	CA	98	55 ± 9	76 (77.5%)	46 (46.9%)	3 (3.1%)	3 (3.1%)	41.3 ± 4.6	61.1% ± 8.8%	12	12	Persistent
		ADT	48	55 ± 9	37 (77.0%)	19 (39.5%)	1 (2.1%)	1 (2.1%)	42.7 ± 5.1	60.8% ± 9.7%			
Pokushalov E, *et al*[18]	2013	CA	77	57 ± 7	56 (72.7%)	24 (31%)	NR	8 (10%)	45 ± 7	57% ± 6%	36	12	Paroxysmal
		ADT	77	56 ± 7	59 (76.6%)	29 (38%)	NR	10 (13%)	46 ± 5	58% ± 5%			
Cosedis NJ, *et al*.[19]	2012	CA	146	56 ± 9	100 (68%)	43 (29%)	7 (5%)	6 (4%)	40 ± 6	> 60%**	24	12	Paroxysmal
		ADT	148	54 ± 10	106 (72%)	53 (36%)	15 (10%)	2 (1%)	40 ± 5	> 60%**			
Forleo GB, *et al*.[21]	2009	CA	35	63.2 ± 8.6	20 (57.1%)	22 (62.9%)	2 (5.7%)	7 (20.0%)	44.3 ± 5.6	54.6% ± 7.0%	12	5	Paroxysmal + Persistent
		ADT	35	64.8 ± 6.5	23 (65.7%)	24 (68.6%)	4 (11.4%)	7 (20.0%)	45.2 ± 5.2	52.6% ± 8.6%			
Pappone C, *et al*.[22]	2006	CA	99	55 ± 10	69 (70%)	55(56%)	3(3%)	2(2%)	40 ± 6	60% ± 8%	12	6	Paroxysmal
		ADT	99	57 ± 10	64 (65%)	56(57%)	1 (1%)	2(2%)	38 ± 6	61% ± 6%			
Oral H, *et al*.[23]	2006	CA	77	55 ± 9	67 (87%)	NR	1 (1.3%)	3(3.9%)	45 ± 6	55% ± 7%	12	12	Persistent
		ADT	69	58 ± 8	62 (90%)	NR	0 (0%)	4(5.8%)	45 ± 5	56% ± 7%			
Stabile G, *et al*.[24]	2006	CA	68	62.2 ± 9	37 (54.4%)	36 (52.9%)	3 (4.4%)	3 (4.4%)	46 ± 5	59.1% ± 6.7%	12	4	Paroxysmal + Persistent
		ADT	69	62.3 ± 10.7	44 (63.8%)	34 (49.3%)	2 (2.9%)	5 (7.2%)	45.4 ± 5.5	57.9% ± 5.8%			
Wazni OM, *et al*.[11]	2005	CA	33	53 ± 8	NR	8 (25%)*		NR	41(8)	53% ± 5%	12	8	Paroxysmal (97%)
		ADT	37	54 ± 8	NR	10 (28%)*		NR	42(7)	54% ± 6%			
Krittayaphong R, *et al*.[25]	2003	CA	15	55.3 ± 10.5	11 (73.3%)	4 (26.7%)	1 (6.7%)	1 (6.7%)	39.6 ± 7.7	63.7% ± 9.5%	12	NR	Paroxysmal + Persistent
		ADT	15	48.6 ± 15.4	8 (53.3%)	7 (46.7%)	0 (0%)	1 (6.7%)	39.2 ± 7.1	61.8% ± 8.8%			
Hummel J, *et al*.[8]	2014	CA	138	59.6 ± 8.3	115 (83.3%)	84 (60.9%)	7 (5.1%)	28 (20.3%)	45 ± 5	54.7% ± 7.1%	6	NR	Persistent
		ADT	72	60.7 ± 8.9	60 (83.3%)	40 (55.6%)	8 (11.1%)	12 (16.7%)	46 ± 5	54.9% ± 6.7%			
Wilber DJ, *et al*.[20]	2010	CA	106	55.5 ± 9	73 (68.9%)	51 (48.6%)	10 (9.5%)	NR	40 ± 1.1	62.3% ± 2%	9	12	Paroxysmal
		ADT	61	56.1 ± 13	38 (62%)	30 (50%)	9 (15%)	NR	40.5 ± 1.5	62.7% ± 2%			

ADT: antiarrhythmic drug therapy; AF: atrial fibrillation; CA: catheter ablation; CHD: coronary heart disease; EF: ejection fraction; HTN: hypertension; LAD: left atrial diameter; LVEF: left ventricular ejection fraction; NR: not reported. *Combined data for structural heart disease and hypertension. **Mean LVEF was not provided, all patients had an EF > 40% with majority having an EF > 60%.

reduction in AF recurrence in the catheter ablation group compared with the ADT group with significant heterogeneity (pooled RR = 0.34, 95% CI: 0.24–0.47, I^2 = 69.9%; Figure 4).

In studies after 2011, there was still a 39% reduction in the risk of AF recurrence following catheter ablation compared with that following ADT (pooled RR = 0.61, 95% CI: 0.54–0.68, I^2 = 9.3%). There was also nonsignificant between-study heterogeneity (I^2 = 9.3%, P = 0.358; Figure 4). The effect on AF recurrence was less apparent in studies after 2011 compared with studies before 2011.

The funnel plot and Egger's test did not reveal any presence of publication bias (P = 0.982).

3.3 Safety outcome

The incidence of complications and adverse events varied among studies, with the highest rate of complications and adverse events in the study by Krittayaphong, *et al*.[25]

Table 2. Characteristics and quality of the included studies.

Study	Year	Group	ITT analysis	Study design	Ablation approach	ECV during blanking period	Jadad score			
							Randomi-sation	double blinding	Dropo-uts	Total*
Di Biase L, *et al*.[17]	2016	CA ADT	Yes	Multicenter	PVI+liner ablation	Yes	2	0	1	3
Morillo CA, *et al*.[6]	2014	CA ADT	Yes	Multicenter	PVI+lnerablation+CFAE	Yes	2	0	1	3
Zhang XD, *et al*.[7]	2014	CA ADT	Yes	Single center	PVI+linerablation+CFAE	No	2	0	1	3
Jais P, *et al*. [10]	2008	CA ADT	Yes	Multicenter	PVI+liner ablation	No	1	0	1	2
Mont L, *et al*. [9]	2014	CA ADT	Yes	Multicenter	PVI+linerablation+CFAE	Yes	2	0	1	3
Pokushalov E, *et al*.[18]	2013	CA ADT	Yes	Single center	PVI+liner ablation	No	2	0	1	3
Cosedis NJ, *et al*.[19]	2012	CA ADT	Yes	Multicenter	PVI+liner ablation	No	2	0	1	3
Forleo GB, *et al*.[21]	2009	CA ADT	Yes	Multicenter	PVI+liner ablation	No	2	0	1	3
Pappone C, *et al*. [22]	2006	CA ADT	Yes	Single center	PVI+liner ablation	No	1	0	1	2
Oral H, *et al*.[23]	2006	CA ADT	Yes	Multicenter	PVI+liner ablation	Yes	2	0	1	3
Stabile G, *et al*.[24]	2006	CA ADT	Yes	Multicenter	PVI+liner ablation	Yes	2	0	1	3
Wazni OM, *et al*.[11]	2005	CA ADT	No	Multicenter	PVI	No	2	0	1	3
Krittayaphong R, *et al*.[25]	2003	CA ADT	Yes	Single center	PVI	Yes	1	0	1	2
Hummel J, *et al*[8]	2014	CA ADT	Yes	Multicenter	PVI+linerablation+CFAE	No	1	0	1	2
Wilber DJ, *et al*.[20]	2010	CA ADT	No	Multicenter	PVI+linerablation+CFAE	No	2	0	1	3

*The Jadad scale scores a maximum of five, with a higher score indicating better quality. Trials scored 3 or more are considered to be high-quality. ADT: antiarrhythmic drug therapy; CA: catheter ablation; CFAE: complex fractionated atrial electrograms; ECV: electrical cardioversion; ITT: intention-to-treat; PVI: circumferential pulmonary-vein isolation.

Table 3. Summary of the quality of life.

Study	Assessment scale	Outcomes
Di Biase L, *et al*.[17]	Minnesota Living with Heart Failure Questionnaire	Ablation improved QoL
Morillo CA, *et al*.[6]	EQ-5D score	Improvement of QoL was not significantly different between catheter ablation and AADs.
Zhang XD, *et al*.[7]	SF-36	QoL was significantly higher for catheter ablation.
Jais P, *et al*.[10]	SF-36	QoL was significantly higher in the ablation group.
Mont L, *et al*.[9]	AF-QoL questionnaire	There were no statistically significant differences between arms on the AF-QoL scores.
Cosedis NJ, *et al*.[19]	SF-36	The SF-36 physical-component summary score improved more over time in the ablation group than in the drug-therapy group.
Forleo GB, *et al*.[21]	SF-36	In the catheter ablation group, a significant improvement in QoL scores as compared with AADs group was observed.
Wazni OM, *et al*.[11]	SF-36	The improvement in QoL of patients in the catheter ablation group was significantly better than the improvement in the AADs group.
Krittayaphong, *et al*.[25]	SF-36	Catheter ablation results in a significant improvement in QoL, whereas amiodarone had no significant effect on QoL.
Wilber DJ, *et al*.[20]	SF-36	Mean QoL scores improved significantly in patients treated by catheter ablation compared with AADs at3 months

AF-QoL questionnaire: atrial fibrillation quality of life questionnaire; QoL: quality of life; SF-36: the medical outcomes study short-form36 health survey.

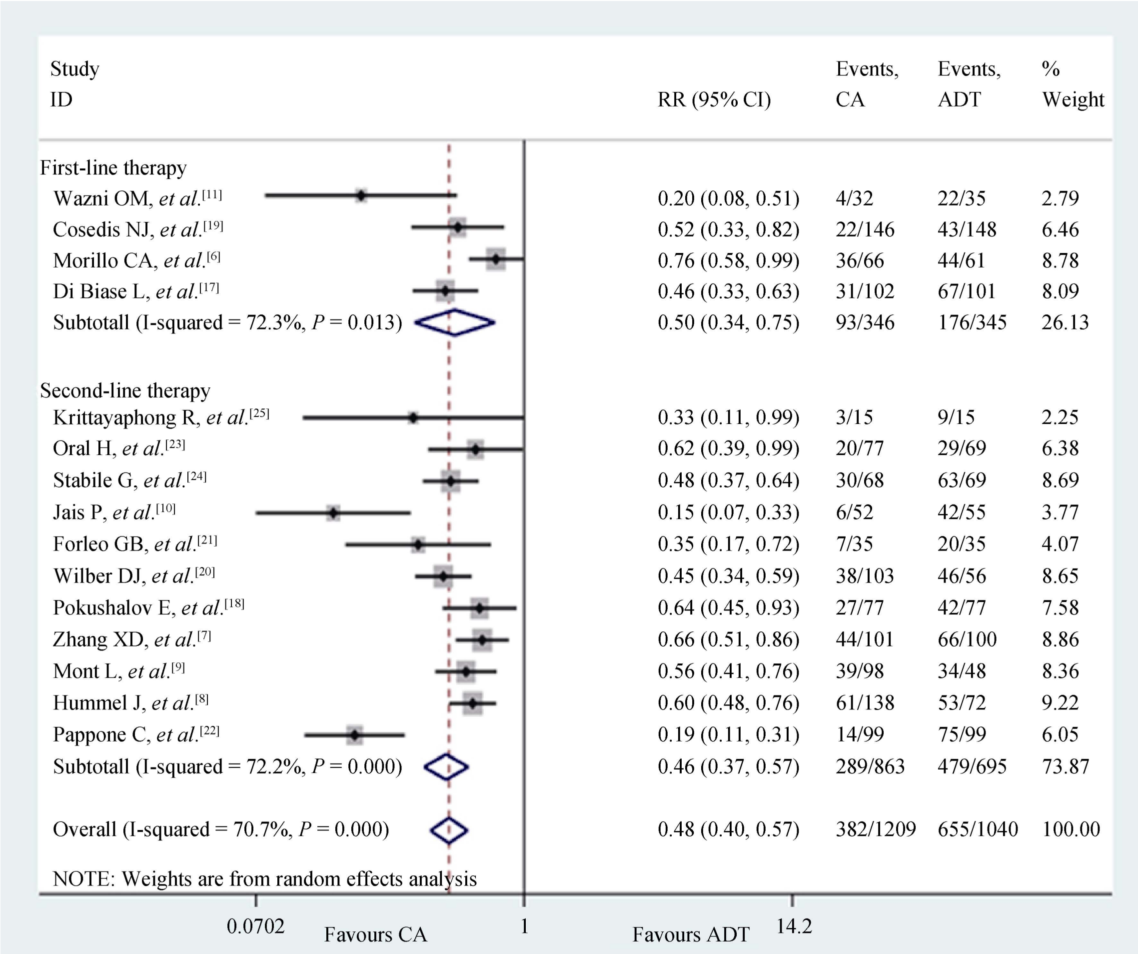

Figure 2. The pooled outcome of AF recurrence. Subgroup analysis was performed based on catheter ablation as a first- or second-line therapy. ADT: antiarrhythmic drug therapy; AF: atrial fibrillation; CA: catheter ablation.

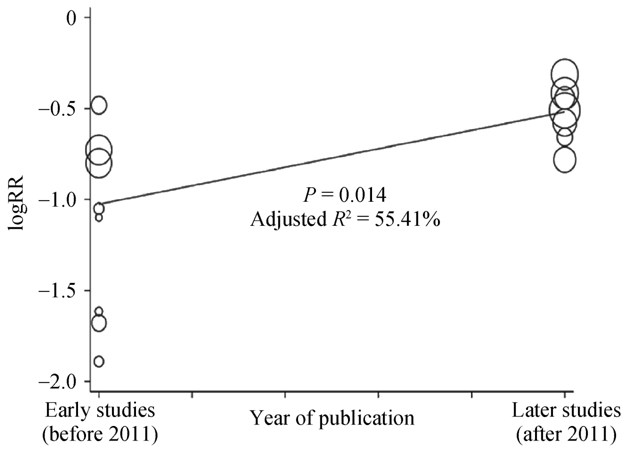

Figure 3. Meta-regression of included studies based on the year of publication.

Pooled data did not indicate any significant difference in the incidence of complications and adverse events between the ablation group and the ADT group (RD = –0.00, 95% CI: –0.04 to 0.04; Figure 5). Notably, sensitivity analysis indicated a 1.08-fold increase in the incidence of complications and adverse events in patients who underwent catheter ablation in studies after 2011 when compared with studies before 2011 (14.2% *vs*. 7.3%, RR = 1.08, 95% CI: 1.04–1.13).

4 Discussion

In the present systematic review and meta-analysis, a total of 15 RCTs with 2249 patients were included. Our result showed that compared with ADT, catheter ablation was associated with a 52% reduction in the recurrence of AF. This result was stable when catheter ablation was considered both as a first- and second-line therapy. Notably, the efficacy was less apparent in studies after 2011, with a 1.08-fold higher rate of adverse events compared to studies before 2011. This difference might indicate that the efficacy was exaggerated and that the adverse events were overlooked among patients who underwent catheter ablation in studies before 2011.

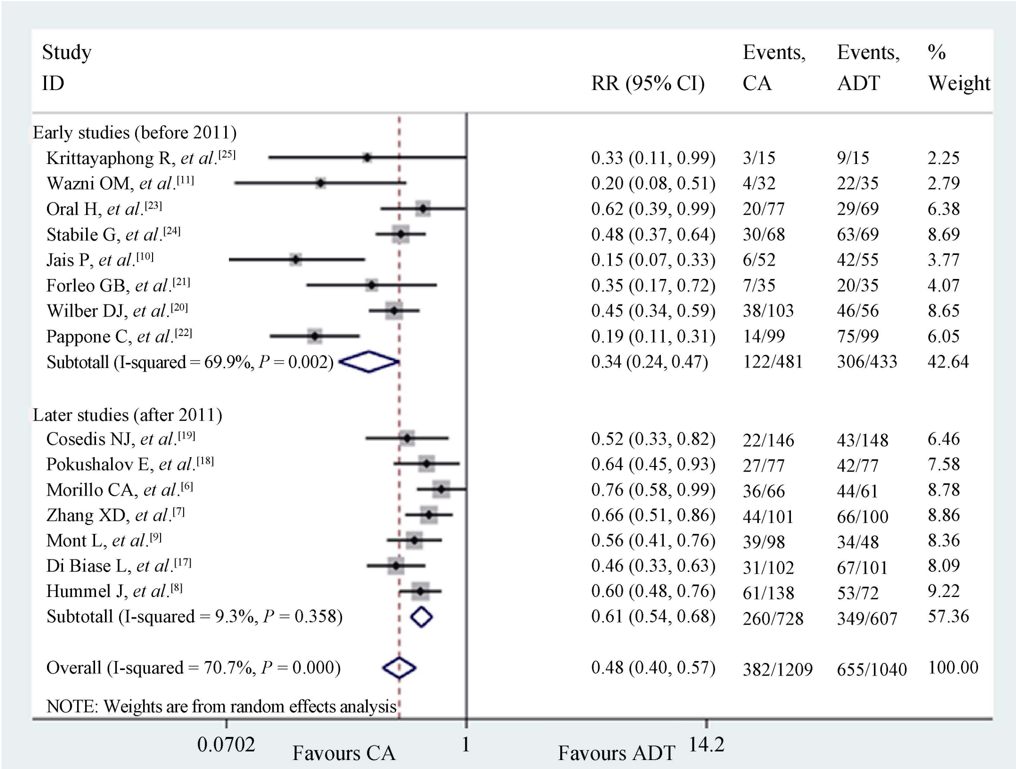

Figure 4. The pooled outcome of AF recurrence. Subgroup analysis based on the year of publication. ADT: antiarrhythmic drug therapy; AF: atrial fibrillation; CA: catheter ablation.

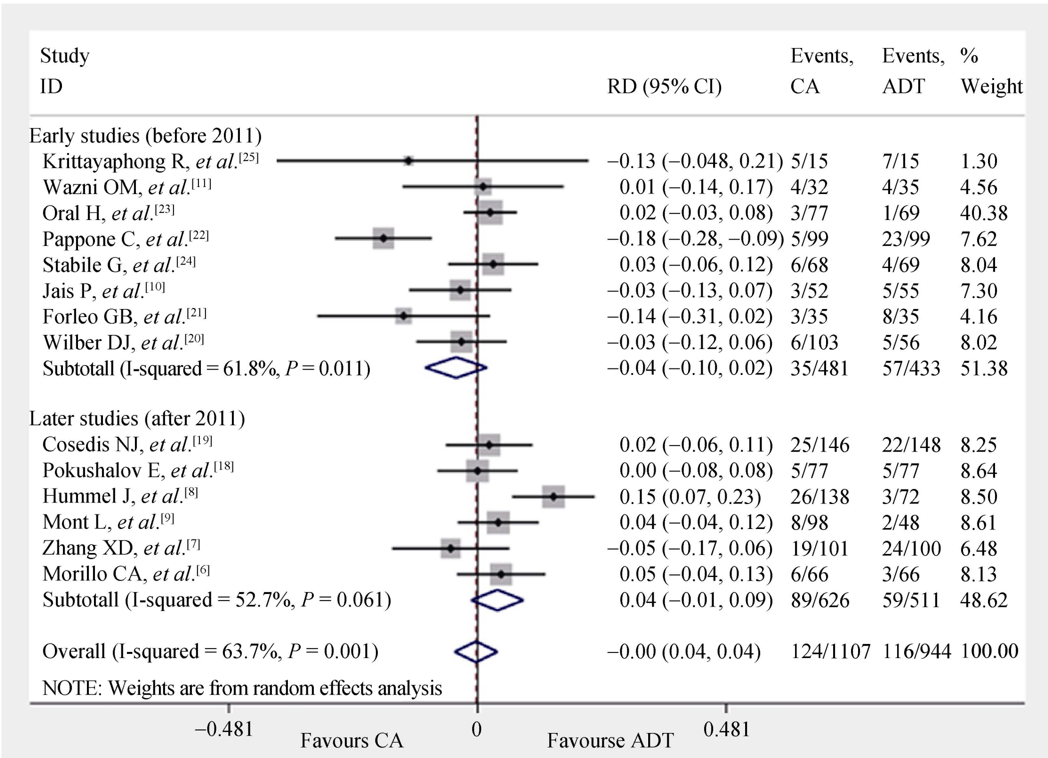

Figure 5. The pooled outcome of complications and adverse events between catheter ablation and ADT groups. Subgroup analysis was performed based on the year of publication. ADT: antiarrhythmic drug therapy; CA: catheter ablation.

However, when interpreting the results of the meta-analysis, we should note that there were obvious differences in the following factors among the studies. First, the types of AF were different among the 15 included trials: seven trials focused on patients with paroxysmal AF, five trials enrolled patients with persistent AF, and three trials included both paroxysmal and persistent AF patients. In addition, the study by Di Biase, *et al*.[17] included persistent AF patients with congestive heart failure. Some studies reported that both catheter ablation and ADT were more effective for paroxysmal AF than for persistent AF.[26–28] Therefore, the types of AF might influence the results of our meta-analysis. Second, the ablation methods were diverse among studies. All the trials used PVI as the endpoint of the ablation procedure. However, there were differences in adjunctive ablation strategies (linear lines and sources of complex fractionated electrograms). Several studies have shown that adjunctive ablation strategies might affect the efficacy of ablation,[29,30] but recently, a large RCT indicated that there was no difference in the rate of AF recurrence when either linear ablation or complex fractionated electrogram ablation was performed in addition to PVI.[31] Therefore, the impact of ablation strategies has not been completely and systematically evaluated. Third, catheter ablation was performed as a first-line therapy in four trials and as a second-line therapy in 11 trials. Currently, catheter ablation is recommended by guidelines as a second-line therapy for patients with AF after treatment with at least one antiarrhythmic drug has failed.[3,4] At present, no study has directly compared first-line therapy with second-line therapy. An indirect comparison from a recent meta-analysis showed comparable results between first-line therapy and second-line therapy.[13] In the present meta-analysis, we also performed subgroup analyses to compare the different effects of catheter ablation treated as a first- or second-line therapy. The pooled data showed that catheter ablation as both a first- and second-line therapy was associated with a lower incidence of AF recurrence compared with ADT. In addition, different study designs and statistical analyses were used in the included studies (single-center versus multicenter studies, ITT analysis versus non-ITT analysis). These differences among studies might also impact the results. However, their influence cannot be completely and quantitatively evaluated in the present study.

These abovementioned differences were reflected in the present study as significant heterogeneity among studies. Therefore, we performed a meta-regression to explore the source of heterogeneity. Meta-regression did not reveal any significant effect from the types of AF, ablation strategies, study design, indication and ITT analysis on the observed heterogeneity (data not shown). However, the year of publication was observed to significantly affect heterogeneity. In studies after 2011, the heterogeneity was nonsignificant. Pooled results showed that studies after 2011 seemed to exhibit less efficacy with an increased trend of adverse events compared to early studies before 2011. The reasons for the differences between studies before and after 2011 were unclear. The possible reasons may be as follows: (1) as the recognition on catheter ablation was more and more sober, the nocebo effects were gradually decreased.[32] Similar to renal denervation, the early studies showed better results than the later studies.[32] A sham control trial may be required to further verify the result. (2) the supervision and study designs improved and more cases of recurrent AF, complications and adverse events were adjudicated in the later studies. In the present study, studies before 2011 showed an AF recurrent rate of 25.4% among patients who underwent catheter ablation, whereas studies after 2011 showed an AF recurrent rate of 35.7%. The rate of AF recurrence after ablation from studies after 2011 is closer to 40%–50%, as reported in a recent study.[31] These differences between early and later studies reflect advanced awareness of catheter ablation and reveal that catheter ablation is not as effective as previously thought. The actual efficacy and safety of catheter ablation still requires verification by double-blinded RCTs.

4.1 Limitations

Although our study included only prospective RCTs, there were also some important limitations. (1) The present systematic review and meta-analysis included studies that differed in the types of AF evaluated as well as antiarrhythmic drugs, catheter ablation approaches, definitions of AF recurrence, study designs, indications and the methods of surveillance used. These factors may have had an impact on the pooled effect estimate. (2) In most of the included studies, the adherence to ADT is unclear. Medication adherence is known as a critical factor that affects treatment outcomes. This may have influenced the results of our analyses but cannot be systematically evaluated. (3) In all the included trials, no sham procedures were used. Placebo and nocebo effects from catheter ablation and ADT may affect the results of the present study. A recent editorial by Ozeke *et al*.[32] raised the question and systematically elaborated the theory regarding placebo and nocebo effects from catheter ablation of AF;[32] and (4) the inherent limitations of meta-analyses cannot be ignored, such as publication bias. Although no obvious publication bias was observed from the funnel plot and Egger's test, bias cannot be ruled out entirely.

4.2 Conclusions

Catheter ablation may be superior for rhythm control, as it is not associated with increased complications and adverse events compared with ADT. Subgroup analyses indicated stable results when catheter ablation was considered both as a first- and second-line therapy. Subgroup analyses showed that studies after 2011 with non-significant heterogeneity also showed a lower risk of AF recurrence in the catheter ablation group, but the effect appeared to be smaller than that in studies before 2011. Future high-quality, large-sample trials with sham control groups are required to verify these findings.

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