



Long-term stroke rates after catheter ablation or antiarrhythmic drug therapy for atrial fibrillation: a meta-analysis of randomized trials

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Abstract

Background Atrial fibrillation (AF) is an independent risk factor for ischemic stroke and is associated with increased risk of death. Randomized studies suggest improved quality of life for patients with AF after successful catheter ablation compared to antiarrhythmic drug therapy. The value of ablation in long-term risk of ischemic stroke, however, has not been assessed. We conducted a meta-analysis to determine whether AF ablation reduces the long-term risk of stroke compared to antiarrhythmic drug therapy in randomized controlled trials. **Methods & Results** PubMed and the Cochrane Central Register were searched for randomized trials from January 1990 to December 2014 comparing AF catheter ablation to drug therapy. The results are reported as risk differences (RDs) and 95% CI. Thirteen trials were analyzed with 1097 patients treated by catheter ablation and 855 patients received antiarrhythmic drug therapy. Overall, seven patients (0.64%) in the catheter ablation group had ischemic stroke or transient ischemic attacks vs. two patients (0.23%) in the drug therapy group. No difference was shown in the rate of stroke or transient ischemic attack between ablation and drug therapy (RD: 0.003, 95% CI: -0.006 to 0.012, $P = 0.470$), and no evidence of heterogeneity was observed ($I^2 = 0$, $P = 0.981$). No potential publication bias was found. There was also no difference in mortality between the two groups (RD: -0.004, 95% CI: -0.014 to 0.006, $P = 0.472$). **Conclusions** This meta-analysis of randomized controlled trials showed similar rates of ischemic stroke or transient ischemic attack and death in AF patients undergoing catheter ablation compared to drug therapy. A larger prospective randomized trial to confirm this finding is warranted.

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Keywords: Atrial fibrillation; Antiarrhythmic drug; Catheter ablation; Death; Stroke

1 Introduction

Atrial fibrillation (AF) is a common arrhythmia, and its prevalence is increasing as the population ages and more individuals survive with cardiovascular disease.^[1] AF is the major cause of ischemic stroke and is moderately associated with increased mortality from stroke, heart failure, and cardiovascular disease.^[2] Stroke prevention, therefore, is a major goal for the management of AF.

Anticoagulation treatment has been shown to reduce AF related stroke. The use of anticoagulants is limited, however, due to poor patient compliance and increased risks for bleeding complications. Considering these factors contributing to an insufficient success rate for stroke prevention, other treatment strategies are urgently needed to reduce the clinical and economic burden of AF.^[3]

Rhythm control strategies have been proposed as a potential means to decrease stroke risk in AF patients. Antiarrhythmic drug treatment is the standard approach to patients with AF in the clinic, but adverse events commonly contribute to poor adherence. Mostly, the efficacy of antiarrhythmic drug therapy (ADT) is limited for there are high rates of AF recurrence even when ADT is used.^[4,5] Catheter ablation (CA) is currently more successful in maintaining sinus rhythm than antiarrhythmic drugs and has been proven superior to ADT in selected patients.^[6] Whether CA reduces AF related stroke and death rates, however, has not been systematically reviewed. In the current study, we performed a meta-analysis of randomized controlled trials to evaluate stroke and death rates caused by AF after ablation compared to drug therapy.

2 Methods

2.1 Search strategy

We conducted a systematic literature search of PubMed and the Cochrane Central Register of Controlled Trials cov-

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ering the period from January 1990 to December 2014 by using the following search terms: “randomized”, “ablation”, “atrial fibrillation”, and “antiarrhythmic” without language restrictions. Reference lists of the retrieved articles were also reviewed. We did not contact authors of the primary studies for additional information.

2.2 Selection criteria

Studies were included in this meta-analysis if they met the following criteria: (1) had a random study design; (2) the intervention group included patients ongoing catheter ablation compared with patients received antiarrhythmic drug therapy; and (3) the endpoint was non-procedure related thromboembolic stroke/transient ischemic attack. As catheter ablation is an invasive procedure with attendant potential risks, including procedural stroke, we recorded the dates of the all-cause and procedure-related events. We excluded trials if catheter ablation was used in both treatment groups and if surgery for AF was used. The methodological quality of selected studies was assessed using the Jadad scale.^[7]

2.3 Data extraction

The study was performed according to the QUOROM statement for high-quality meta-analyses.^[8] Information was recorded as follows: last name of the first author, year of publication, length of follow-up, mean age of study participants, sample size of each treatment, and number of end points in the intervention and control arms. In addition, left atrium size, left ventricular ejection fraction (LVEF), coronary artery disease (CAD), hypertension, CHADS2 score, anticoagulation time, and number of patient crossover to the CA arm in the ADT arm was also recorded.

Two investigators (Ye LF and Zheng YR) independently extracted the data. We reviewed article titles and abstracts from the initial search and excluded those that did not meet the inclusion criteria. Articles included in the study were completely reviewed. If the same population was studied in more than one study, we included the study with the longest follow-up time. The primary end point was major thromboembolic events that were not considered to be related to the treatment (including stroke/transient ischemic attacks), and the secondary end point was all-cause mortality caused by AF itself. Any disagreements were resolved by discussion.

2.4 Statistical analysis

The measure of treatment effect for the end point was reported by risk difference with 95% CI. We assessed heterogeneity among studies using the I^2 index at 10% level of significance. Fixed-effect models were used to calculate the

combined risk difference and in sensitivity analyses. Potential publication bias was assessed using the Begg’s funnel plot and Egger’s regression test.^[9] Meta-regression models on stroke risk between the two groups using mean age in each study and a sensitivity analysis comparing risk of stroke by per protocol was performed to assess whether these factors would have affected the results. All analyses were performed by using STATA version 12.0.

The effect of different follow-up periods among different trials on the heterogeneity of the pooled results was assessed by repeating the analysis using the number of strokes per 1000 patient-year. Power analyses of individual studies and meta-analyses were all conducted by the software Power and Sample Size Calculation. All reported P values were two-sided, and $P < 0.05$ was determined as statistically significant.

3 Results

3.1 Study characteristics

The trial selection flow is shown in Figure 1. Thirteen randomized trials with 1952 patients were included in this review.^[10–22] The 13 trials were published between 2003 and 2014. Two trials were conducted at one center,^[10–17] whereas the rest of the trials were multicenter. One study included only patients with diabetes.^[14] One trial included patients with chronic AF,^[13] while four trials included patients with paroxysmal and persistent AF.^[10–12,14] All of these trials compared pulmonary vein isolation with antiarrhythmic drug therapy. Table 1 & 2 provides the baseline characteristics of the included studies. In most trials, the patients were followed for 12 months. There were no differences seen in patient characteristics. The mean age of enrolled patients was 57 ± 9 years for CA patients and 57 ± 11 years for ADT patients. The mean left atrial diameter among patients in CA group was 41.6 ± 5.7 mm, and in ADT group was 41.9 ± 5.9 mm. The mean left ventricular ejection fraction was $59\% \pm 8\%$ for CA patients and $59.3\% \pm 7.5\%$ for ADT patients. Many patients had a history of hypertension, although few had significant structural heart disease. Other co-morbidities such as cardiomyopathy or valvular heart disease were rare. The average value of CHADS2 score, mentioned in four studies, were comparable (0.6 ± 0.8 for CA patients and 0.7 ± 0.8 for ADT patients). As the data show, mean CHADS2 score, LVEF, left atrium size, and the percentages of coronary artery disease, diabetes were comparable between the two groups. Previous embolic events included transient ischemic events, stroke, pulmonary embolism, deep vein thrombosis and other peripheral embolism.

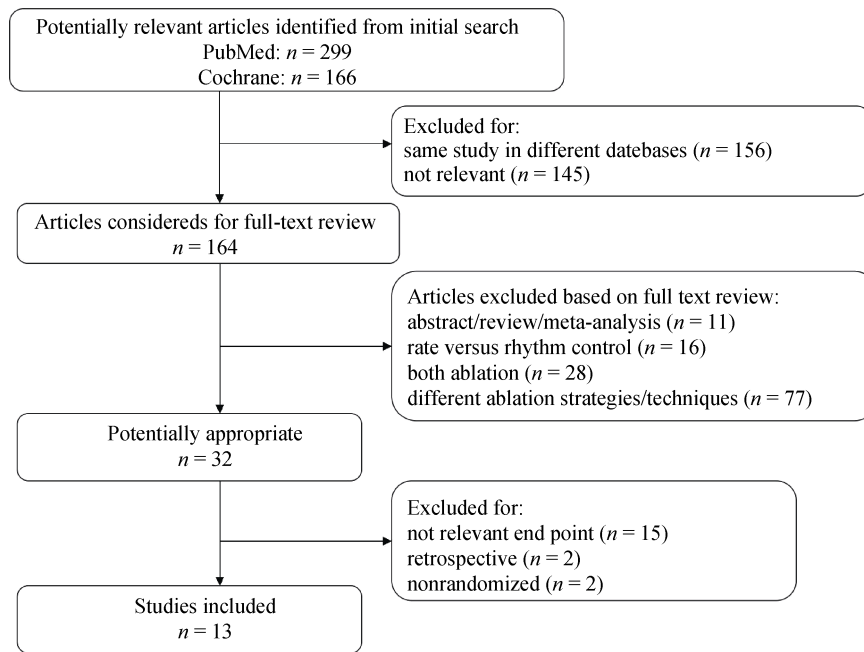


Figure 1. Flow diagram of studies included in the meta-analysis.

3.2 Drugs and technology

In the antiarrhythmic therapy arm, drugs included mainly class I and class III antiarrhythmic agents, either single or combination use, with the antiarrhythmic drug restricted to amiodarone in two of the trials.^[10,13] In the catheter ablation group, no one had received antiarrhythmic drug therapy before enrollment in three trials.^[11,18,22] In the remaining trials, CA was used in patients after at least one antiarrhythmic drug regimen had failed. The ablation technique

was pulmonary vein ablation combined with ablation of linear lesions in the left and right atria, ostia of the pulmonary veins, and cavotricuspid isthmus. The use of additional lesion ablations outside the pulmonary vein region was left to the discretion of the operator. Oral anticoagulation (international normalized ratio between 2 and 3) was required for at least three weeks before ablation in each trial, with a period ranging from 1 to 12 months after CA. In two studies, the period of anticoagulation use after CA was not noted.^[10,18]

Table 1. Study characteristics of the thirteen randomized trials included in the meta-analysis.

References	Publication year	Mean age (yr)		Randomized patients, n		Stroke/TIA, n		Death, n		Blanking period (weeks)	Follow-up (months)
		CA arm	ADT arm	CA arm	ADT arm	CA arm	ADT arm	CA arm	ADT arm		
Krittayaphong, <i>et al.</i> ^[10]	2003	55 ± 11	49 ± 15	15	15	0	0	0	0	NR	12
Wazni, <i>et al.</i> ^[11]	2005	53 ± 8	54 ± 8	33	37	0	0	0	0	8	12
Oral, <i>et al.</i> ^[13]	2006	55 ± 9	58 ± 8	77	69	0	0	1	0	12	12
Stabile, <i>et al.</i> ^[12]	2006	62 ± 9	62 ± 11	68	69	0	1	0	2	4	12
Jais, <i>et al.</i> ^[15]	2008	50 ± 11	52 ± 11	53	59	0	0	0	2	12	12
Forleo, <i>et al.</i> ^[14]	2009	63 ± 9	65 ± 7	35	35	0	0	0	0	5	12
Wilber, <i>et al.</i> ^[16]	2010	56 ± 9	56 ± 13	106	61	0	0	1	0	12	9
Pappone, <i>et al.</i> ^[17]	2011	55 ± 10	57 ± 10	99	99	0	0	0	0	6	48
Cosedis Nielsen, <i>et al.</i> ^[18]	2012	56 ± 9	54 ± 10	146	148	1	1	2	4	12	24
Packer, <i>et al.</i> ^[19]	2013	57 ± 9	56 ± 9	163	82	5	0	1	0	12	12
Mont, <i>et al.</i> ^[20]	2014	55 ± 9	55 ± 9	98	48	0	0	0	0	12	12
Hummel, <i>et al.</i> ^[21]	2014	60 ± 8	61 ± 8	138	72	1	0	0	0	NR	6
Morillo, <i>et al.</i> ^[22]	2014	56 ± 9	54 ± 12	66	61	0	0	0	0	12	24

Age is given as mean ± SD. ADT: antiarrhythmic drug therapy; CA: catheter ablation; NR: not reported; TIA: transient ischemic attack.

Table 2. Patient information for the included studies.

References	Publi- cation year	LAD (mm)		LVEF (%)		CHADS2 score		AT (months)		HTN	SHD	CAD	PEE	Cross- over to CA(%)
		CA arm	ADT arm	CA arm	ADT arm	CA arm	ADT arm	CA arm	ADT arm					
Krittayaphong, <i>et al.</i> ^[10]	2003	39.6 ± 7.7	39.2 ± 7.1	63.7 ± 9.5	61.8 ± 8.8	NR	NR	NR	NR	NR	4/7	NR	0/0	NR
Wazni, <i>et al.</i> ^[11]	2005	41 ± 8	42 ± 7	53 ± 5	54 ± 6	NR	NR	3	12	8/10*	NR	NR	NR	NR
Oral, <i>et al.</i> ^[13]	2006	45 ± 6	45 ± 5	55 ± 7	56 ± 7	NR	NR	6	6	NR	6/6	3/4	0/0	77
Stabile, <i>et al.</i> ^[12]	2006	46 ± 5	45.4 ± 5.5	59.1 ± 6.7	57.9 ± 5.8	NR	NR	NR	NR	36/34	0/0	NR	NR	52
Jais, <i>et al.</i> ^[15]	2008	39.5 ± 5.6	40 ± 5.7	63.1 ± 11	65.6 ± 7.2	NR	NR	1	NR	11/18	10/14	NR	1/7	63
Forleo, <i>et al.</i> ^[14]	2009	44.3 ± 5.6	45.2 ± 5.2	54.6 ± 7.0	52.6 ± 8.6	NR	NR	6	12	22/24	16/19	7/7	5/3	NR
Wilber, <i>et al.</i> ^[16]	2010	40 ± 1.1	40 ± 1.5	62.3 ± 2	62.7 ± 2	NR	NR	3	NR	51/30	10/9	NR	2/2	59
Pappone, <i>et al.</i> ^[17]	2011	40 ± 6	38 ± 6	60 ± 8	61 ± 6	NR	NR	NR	NR	56/57	7/4	2/2	NR	42
Cosedis Nielsen, <i>et al.</i> ^[18]	2012	40 ± 6	40 ± 5	> 60	> 60	0.5 ± 0.8	0.6 ± 0.8	NR	NR	43/53	0/0	6/2	6/5	36
Packer, <i>et al.</i> ^[19]	2013	40 ± 5	41 ± 6	60 ± 6	61 ± 6	0.6 ± 0.7	0.6 ± 0.7	3	NR	67/37	NR	13/8	0/0	79
Mont, <i>et al.</i> ^[20]	2013	41.3 ± 4.6	42.7 ± 5.1	61.1 ± 8.8	60.8 ± 9.7	NR	NR	1	NR	46/19	NR	NR	4/2	48
Hummel, <i>et al.</i> ^[21]	2014	45 ± 5	46 ± 5	54.7 ± 7.1	54.9 ± 6.7	0.8 ± 0.8	0.8 ± 0.7	6	6	84/40	NR	28/12	0/0	60
Morillo, <i>et al.</i> ^[22]	2014	40 ± 5	43 ± 5	61.4 ± 4.8	60.8 ± 7.0	0.5 ± 0.7	0.7 ± 0.8	3	NR	28/25	0/0	6/2	3/4	43

Values are presented as mean ± SD. *mean combined data for structural heart disease and hypertension. The CHADS2 score is a measure of stroke risk in patients with atrial fibrillation, with scores ranging from 0 to 6. Higher scores indicate a greater risk. Congestive heart failure, hypertension, an age of 75 years or older, and diabetes mellitus were each assigned 1 point, and previous stroke or TIA was assigned 2 points. The score was calculated by summing all points for a given patient. ADT: antiarrhythmic drug therapy; AT: minimum anticoagulation time after ablation or antiarrhythmic drug therapy; CA: catheter ablation; CAD: coronary artery disease; LAD: left atrial diameter; LVEF: left ventricular ejection fraction; HTN: hypertension; NR: not reported; PEE: previous embolic events; SHD: structural heart disease; TIA: transient ischemic attack.

3.3 Follow-up and withdrawals

Before the study finished, 445 of a total 855 drug-treated patients crossed over to a CA procedure after failure or intolerance to ADT. A total of 23 in the CA arm and 26 in the ADT arm had previous embolic events. Ten patients were lost follow-up: four in the ablation arm and six in the AAD arm. There were also 32 withdrawals and 9 exclusions.

3.4 End points

A total of seven patients in the group that underwent CA (0.64%) and two patients in the ADT group (0.23%) had stroke or transient ischemic attack in the 13 trials. There was no difference in the rate of stroke or transient ischemic attack between the AF ablation and ADT therapy groups (Figure 2). Little evidence of heterogeneity was observed ($I^2 = 0$, $P = 0.981$), indicating the studies were very well-matched. The probability of potential publication bias existing among the 13 studies was estimated by Begg's funnel plots (Figure 3) and Egger's regression test ($P = 0.981$ with 95%CI: -1.030 to 1.054). This probability was very low.

Meta-regression models showed there was no statistical evidence for heterogeneity due to mean age ($P = 0.95$). We performed a sensitivity analysis comparing risk of stroke by

per protocol, no significant difference was shown between the two groups [risk differences (RD): 0.003, 95%CI: -0.006 to 0.012, $P = 0.475$]. A sensitivity analysis according to the follow-up years in the trials (trial follow up > 24 months vs. < 24 months), also did not reveal any influence of follow-up years on trial results (Table 3).

Similarly, no change was found in the effects of CA on stroke compared with ADT (4.6 vs. 1.5 per 1000 patient-years in stroke rates; RD: 0.002, 95% CI: -0.004 to 0.008) (Figure 4). The data were assessed by a power analysis with an alpha level of 0.05. The power of the meta-analysis with respect to stroke was 25.1%, using the risk of the medical therapy arm reported in this study. If there is a 50% reduction risk, 20,443 CA subjects with one control per case would be needed.

A total of 13 deaths were reported (five in the ablation arm and eight in the anti-arrhythmic drug arm). There was no difference in death rates between the ablation and anti-arrhythmic therapy groups (Figure 5). The risk difference of deaths in all trials between patients randomized to ablation and those randomized to ADT was -0.004 (95%CI: 0.014 to 0.006, $P = 0.472$), with no evidence for heterogeneity ($I^2 = 0$, $P = 0.953$).

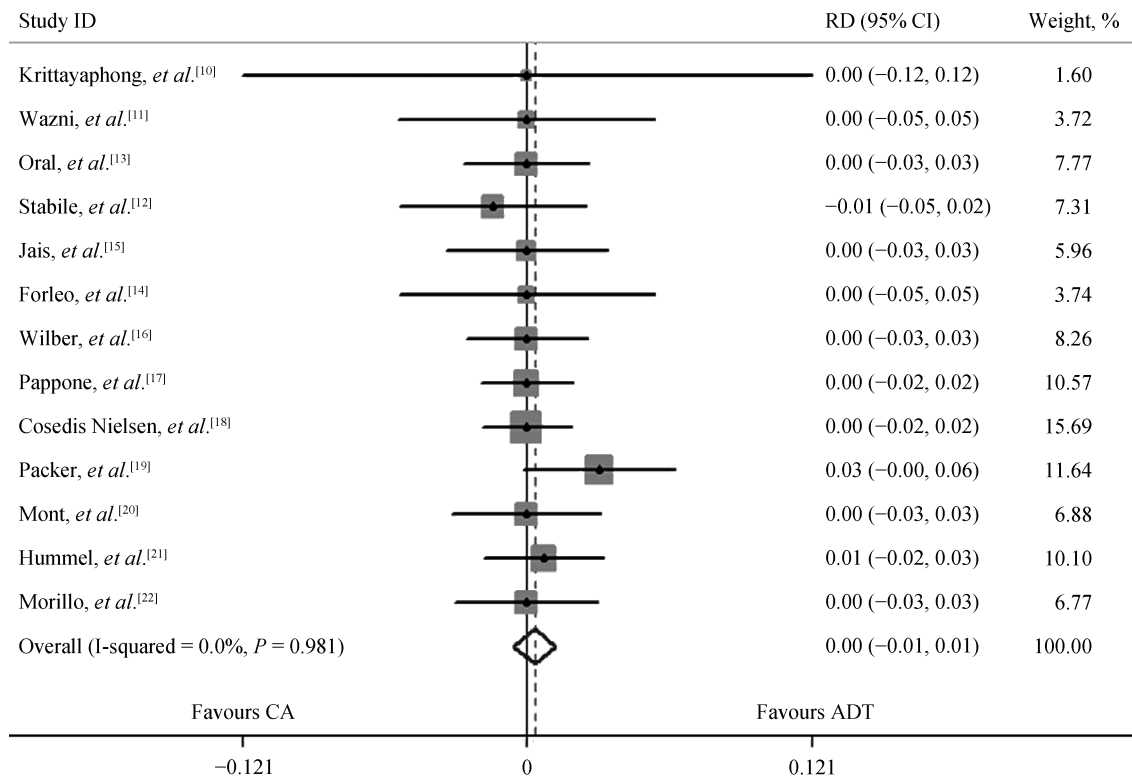


Figure 2. Strokes/transient ischemic attacks during follow-up in patients randomized to ablation versus drug therapy with RDs and 95% CIs. Heterogeneity chi-squared = 4.15 (d.f. = 12), $P = 0.981$; I-squared (variation in RD attributable to heterogeneity) = 0.0; Test of RD = 0, $Z = 0.72$, $P = 0.470$. ADT: antiarrhythmic drug therapy; CA: catheter ablation; RD: risk differences.

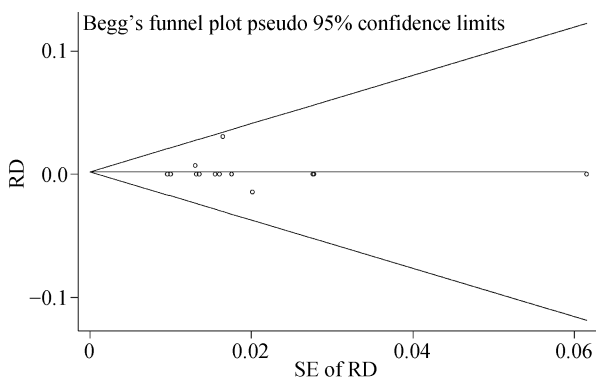


Figure 3. Begg's funnel plot of all studies included in the meta-analysis, with pseudo 95% confidence limits. The risk difference for each study was plotted against SE of RD. The absence of asymmetry indicates that there was no publication bias. RD: risk differences.

4 Discussion

The goal of this study was to conduct a meta-analysis to determine whether AF ablation reduces the long-term risk of stroke compared to anti-arrhythmic drug therapy in randomized controlled trials. To our knowledge, this is to date

the first meta-analysis to compare CA to ADT for the risk of stroke and mortality induced by AF.

Several observational research studies have suggested that AF ablation strategy may associate with lower stroke and death rates compared to drug therapy.^[23-25] It also has been shown that the patients had long-term stroke rates similar to patients without atrial fibrillation in several studies.^[26,27] One previous meta-analysis of eight randomized trials reported no significant difference between the two arms for death or stroke,^[28] although, all these studies recorded all-cause events. Clearly, there are risks of stroke associated with ablation or drugs, the dilemma whether CA could reduce stroke rate of AF was still unsolved.

Table 3. Sensitivity analysis according to the follow-up time of randomized studies.

	No. of Patient studies number	Stroke (RD with 95% CI)	P	P heterogeneity
Total	13	1952	0.003 (-0.006-0.012)	0.470 0.981
Long follow-up (> 24 months)	3	619	0.000 (-0.013-0.014)	0.995 1.000
Short follow-up (< 24 months)	10	1333	0.005 (-0.007-0.016)	0.415 0.916

CI: confidence interval; RD: risk difference.

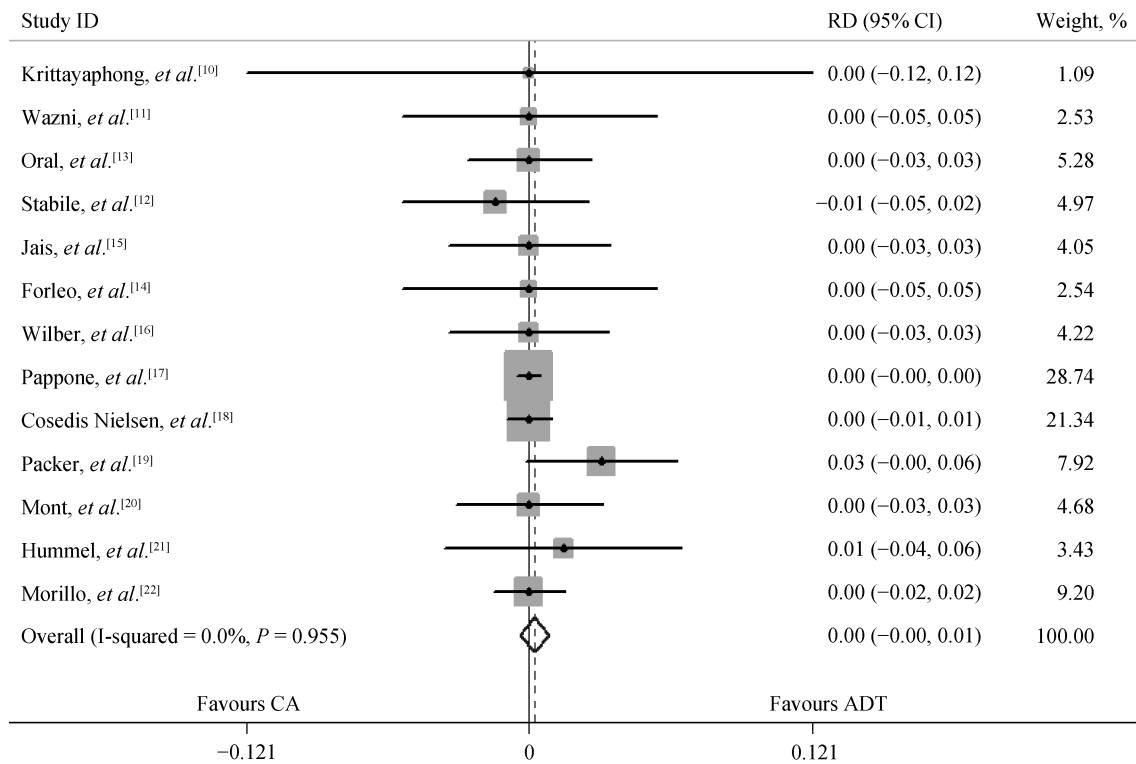


Figure 4. Strokes/transient ischemic attacks per patient-year follow up in patients randomized to ablation versus drug therapy with RDs and 95% CIs. ADT: antiarrhythmic drug therapy; CA: catheter ablation; RD: risk differences.

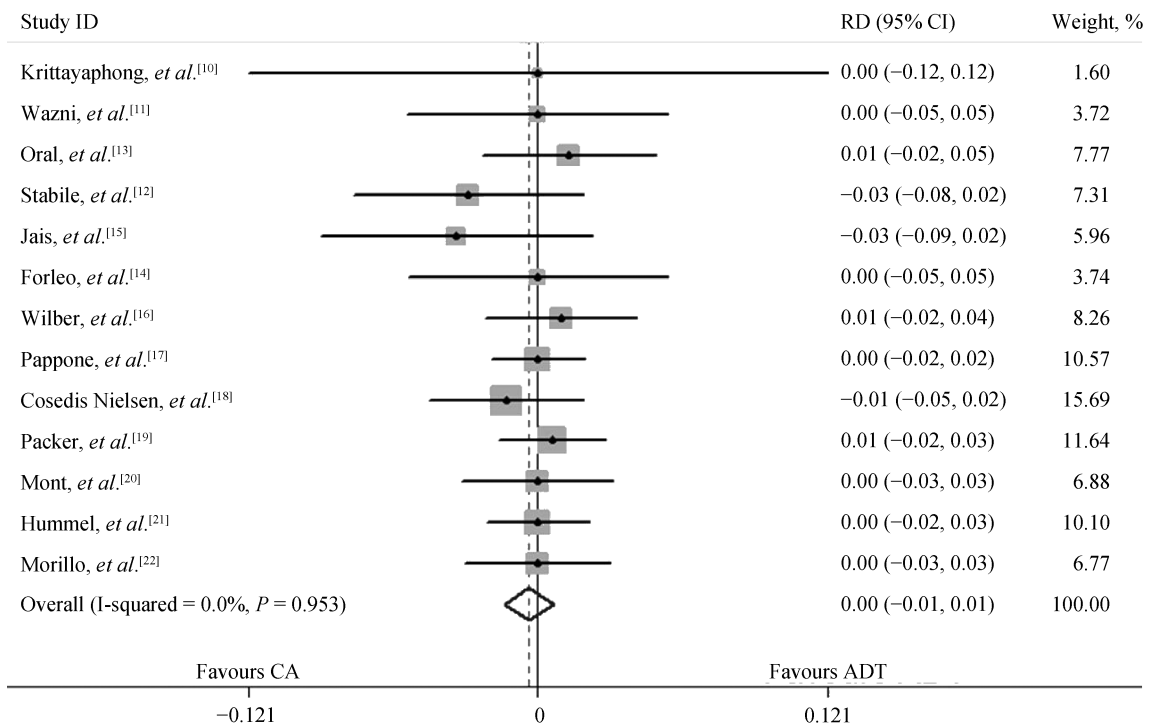


Figure 5. Deaths during follow-up in patients randomized to ablation versus drug therapy with RD and 95% CI. Heterogeneity chi-squared = 5.16 (d.f. = 12), P = 0.953; I-squared (variation in RD attributable to heterogeneity) = 0.0; Test of RD = 0, Z = 0.72, P = 0.472. ADT: antiarrhythmic drug therapy; CA: catheter ablation; RD: risk differences.

The potential risk of stroke in patients with AF in the two groups with like age, sex, hypertension, vascular disease, and prior stroke or TIA are matched well, as shown on following tables. Stroke is an uncommon complication of ablation or drugs, while still having great impact on our rare end events. To find out the direct effect of ablation on stroke risk of AF, we recorded events directly induced by AF itself, and excluded events that were due to the procedure or drugs used. The major finding was that the two groups had similar rates of stroke and death, indicating homogeneous responses. This result differs from a previously reported effect.^[5] Our results provide insight into rhythm control treatment strategies, including ablative interventions that may not reduce the stroke rate on the basis that catheter ablation was more effective than drug therapy in maintaining sinus rhythm. In this meta-analysis, the power was < 80%. These findings indicate that there is not enough evidence on the relative effects between catheter ablation and anti-arrhythmic drugs. Because stroke and death were rare study events, our findings provide strong rationale for a larger multi-center randomized prospective study.

The analysis included studies which differed in the types of AF, different definition of procedure-related or device-related adverse events, previous embolism events, definition for procedure-related events, the use of ADT in the CA arm, and the time to anticoagulation before and after ablation. All of these factors were considered for potential influence on the pooled effect estimate. The patients included in the trials were mostly younger and may not reflect that typical age seen in patients with AF. Of note, there was minimal evidence of structural heart disease, the left atrial diameter was < 50 mm, a mean CHAD2S scores < 1, and there was well-preserved systolic function with normal ejection fraction (LVEF > 50%) in this cohort. Thus, our results may not apply to other populations of patients, including very elderly patients or patients with underlying structural heart disease or more severe heart disease. The effect of CA on this patient population will require further investigation.

4.1 Study limitations

There were several clear strengths of the current meta-analysis. These strengths include the absence of heterogeneity between the groups and the low probability of publication bias. Despite these strengths, there are a few limitations that should be considered. Most importantly, 445 of the total 855 drug-treated patients (52%) crossed over to a CA procedure after failure or intolerance to ADT before the end of the follow-up, and the significant crossover rate in the ADT arm may contribute to the results that both groups had similar stroke rates. Second, the total sample size of this meta-

analysis may have been insufficient to detect significant differences between groups. More definitive evidence on the effect of ablation on AF on the clinical end-points of stroke and mortality will be provided by several on-going multi-center RCTs.^[29,30] Finally, there was a relatively short follow-up period of 12 months or less with few outcome data beyond one year. The follow-up period is a possible contributor to the lack of statistical difference observed. Indeed, in one study,^[31] the stroke/TIA regression models showed statistically significant different rates of events between cohorts that emerged after the first year of follow-up. A more prolonged follow-up period in a randomized trial may reveal differences not observed in the current study.

4.2 Conclusions

In conclusion, our analysis revealed similar rates of stroke or transient ischemic attack in patients treated by catheter ablation or anti-arrhythmic drugs for atrial fibrillation. While catheter ablation did not reduce the rates of stroke or death compared to drug therapy, a large-scale clinical research trial to confirm these findings is warranted.

Acknowledgments

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