Catheter ablation for atrial fibrillation and risk of neurologic disease

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BACKGROUND Catheter ablation (CA) of atrial fibrillation (AF) has been proven to benefit patients with symptomatic AF and heart failure. However, the data on neurological outcomes including cerebrovascular accidents (CVA) and dementia remain controversial.

OBJECTIVE We aimed to determine the effect of CA on neurological events during long-term follow-up.

METHODS We performed a systematic review and meta-analysis of patients with AF who underwent CA of AF. The MEDLINE, EMBASE, and Web of Science databases were comprehensively searched from inception to January 2024. Studies that reported incidence of CVA and dementia in patients with AF were. Data from each study were combined by a random-effects model. The results were reported in risk ratios with 95% confidence intervals (CIs).

RESULTS A total of 29 studies and 379,993 patients (mean age 58 ± 4 years, 30% women) were included in the analysis. Mean follow-up was 36 ± 23 months (range 12–120 months). Patients who underwent CA of AF had a lower risk of developing CVA compared with medical management (odds ratio [OR] 0.54, 95% CI 0.42–0 69, I^2 = 91%). Moreover, the risk of dementia was lower in the CA group compared with medical management (OR 0.51, 95% CI 0.4–0.66, I^2 = 74%). The incidence of CVA in the CA group was 1% (95% CI 1%–2%, I^2 = 97%), and the incidence of dementia was 2% (95% CI 2%–8%, I^2 = 97%).

CONCLUSION CA of AF resulted in lower risk of CVA and dementia compared with medical management alone at long-term follow-up.

KEYWORDS Atrial fibrillation; Ablation; CVA; Outcomes; Dementia

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Introduction

Atrial fibrillation (AF) is the most common arrhythmia encountered today.[1] Over the years, a paradigm shift has occurred in the management of AF, with mounting evidence that rhythm control is superior to rate control.[1] This is especially true for catheter ablation (CA) in patients with symptomatic AF and heart failure, with data showing improvement in outcomes and quality of life. For neurologic outcomes, such as cerebrovascular accident (CVA) and dementia, however, the benefit of CA over medical management (MM) remains controversial and has warranted further investigation.[2,3]

Therefore, the aim of our study was to review the current literature and perform a meta-analysis to assess whether there is an overall beneficial effect of CA of AF on long-term neurological outcomes, such as CVA and dementia.

KEY FINDINGS

- Catheter ablation (CA) of atrial fibrillation (AF) resulted in lower risk of cerebrovascular accident compared with medical management alone at long-term follow-up.
- CA of AF resulted in lower risk of dementia compared with medical management alone at long-term follow-up.
- Prospective, randomized trials with larger sample sizes are needed to validate the efficacy of CA for AF in reducing risk of incident cerebrovascular accident and dementia across different patient populations and management strategies.

Methods

Literature review and search strategy

The protocol and selection criteria were performed in adherence to the guidelines of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement.[4] Studies were chosen for inclusion using the PICO format to identify studies performed on patients with AF (Population) that compared ablation (Intervention) with

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MM (Comparison) and assessed primary and secondary endpoints as described subsequently (Outcomes).

A systematic search was conducted using Ovid MEDLINE, EMBASE, and Web of Science for relevant literature reporting on CA vs MM for AF and consequent neurological outcomes. The search was not restricted by time, language or publication status. The systematic literature review was undertaken independently by 2 investigators (M.A. and N.T.) applying a search approach that incorporated the terms, provided in the Supplementary Data. Rayyan was used to accommodate the review. Any discrepancies between the investigators were resolved by the third investigator (J.D.). No language limitation was applied. This study was conducted by the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) and the 2020 PRISMA statement.[5] The Newcastle-Ottawa quality assessment scale was used to appraise the quality of the study for case-control studies and outcomes of interest for cohort studies.[6] The modified Newcastle-Ottawa scale was used for cross-sectional studies.[7] The risk of bias by the Cochrane Collaboration's tool was used for assessing risk of bias.

Outcomes of the study

The primary outcome of the study is the relative risk of CVA in patients with AF who underwent CA vs MM alone. The secondary outcomes include the incidence of CVA in CA vs MM groups, as well as the incidence and relative risk of dementia in each group.

Data abstraction

A structured data collecting form was utilized to derive the following information from each study, including title, year of the study, name of the first author, publication year, country where the study was performed, and demographics and characteristic data of patients, including incidence of CVA and dementia. During the data extraction process, we excluded patients who were lost to follow-up or excluded in the final analysis.

Statistical analysis

Analyses were performed using R software version 3.6.3 (R Foundation for Statistical Computing). Adjusted point estimates from each included study were combined by the generic inverse variance approach of DerSimonian and Laird, which designated the weight of each study based on its variance.[8] Given the possibility of a between-study variance, we used a random-effects model rather than a fixed-effect model. Cochran's Q test and I^2 statistics were applied to determine between-study heterogeneity. A value of I^2 of 0% to 25% indicates insignificant heterogeneity, 26% to 50% low heterogeneity, 51% to 75% moderate heterogeneity, and 76% to 100% high heterogeneity.[9] Publication bias was assessed via the Egger test.[10] Sensitivity analysis was done by omitting one study at a time to evaluate the effect of each study.

For the primary outcomes, pooled odds ratios (Ors) were used to compare the risk of CVA between the CA and MM groups. For the secondary outcomes, the pooled incidence of CVA and dementia was calculated within each group. The pooled OR was used to compare risk of dementia between the CA and MM groups. There were some studies that reported these outcomes as median and range/interquartile range. Therefore, the median and range/interquartile range were converted to mean ± SD before performing our meta-analysis.[11,12]

Results

A total of 818 eligible studies were identified through a systematic search. Duplicate articles, case reports, correspondence, reviews, in vitro studies, and animal studies were excluded. A total of 46 studies remained for a full-length review. Seventeen studies were excluded from a full review due to the lack of outcomes of interest (Figure 1). Thus, the final analysis included 29 studies with 379,993 patients (19 studies observational, 10 randomized).[13–43] The literature retrieval, review, and selection process are illustrated in Figure 1. The characteristics and quality assessment of the included studies are presented in Table 1.

Risk of CVA after CA of AF vs MM

A total of 23 studies were included in the analysis with 204,837 patients. The odds of developing CVA were lower in the CA group (OR 0.54, 95% confidence interval [CI] 0.42–0.69, I^2 = 91%) (Figure 2). Subgroup analysis of the randomized studies (10 studies, n = 17,656 patients) showed a trend toward lower risk of CVA in the CA group but was not statistically significant (OR 0.64, 95% CI 0.31–1.33, I^2 = 0%) (Figure 3).

Incidence of CVA

A pooled incidence of CVA in 24 studies with 69,850 patients who underwent CA for AF was 1% (95% CI 1%–2%, I^2 = 97%). On the other hand, a pooled incidence of CVA in 28 studies with 16,6091 patients with MM was 2% (95% CI 1%–3%, I^2 = 100%) (Figures 4 and 5).

Risk of dementia after CA of AF vs MM

Six studies were included in the analysis. The analysis showed that risk of developing dementia was lower in the CA group (OR 0.51, 95% CI 0.4–0.66, I^2 = 74%) (Figure 6).

Discussion

Our analysis found that the risk of stroke was lower with AF patients who underwent CA as their treatment strategy compared with MM alone. However, a subgroup analysis of randomized studies did not show a statistically significant decreased risk of developing stroke in the CA group. The risk of developing dementia, however, did appear to be lower in the CA group compared with MM.

CA and CVA

The current state of the literature and our knowledge of the relationship between CVA and CA for AF is limited. There are mixed data regarding CVA outcomes after CA, resulting in little clarity on whether CA significantly and

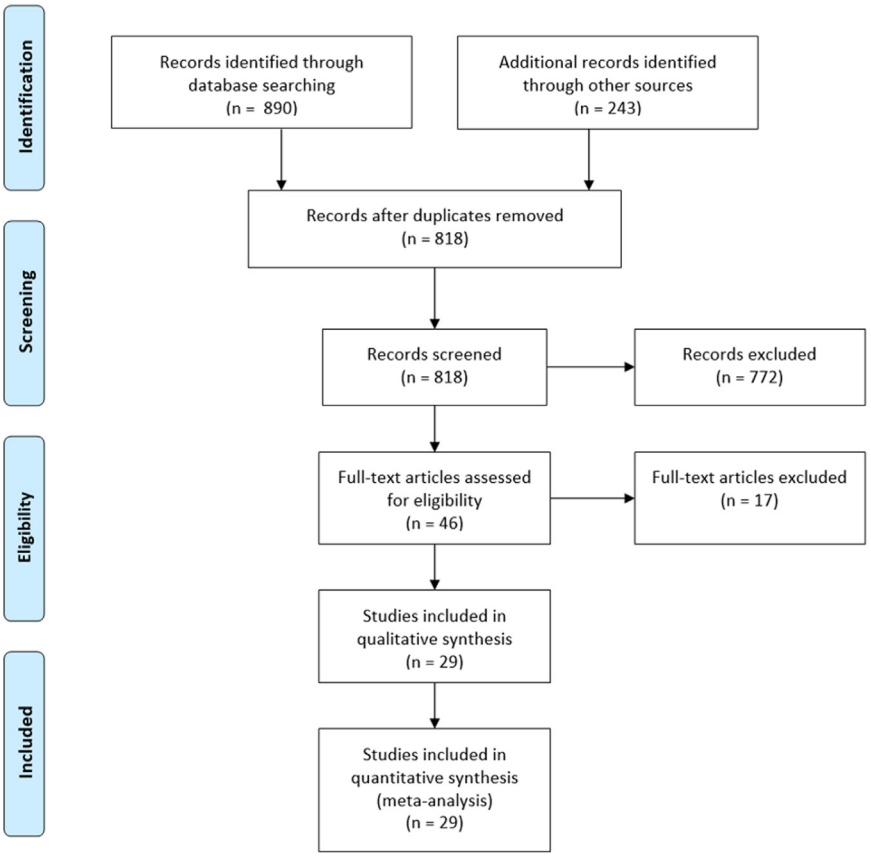

Figure 1 PRISMA flow chart. The flow diagram depicts study selection for inclusion in the meta-analysis according to the PRISMA statement for reporting systematic reviews and meta-analyses.

definitively reduces the risk of incident CVA.[11] As a result, the decision to continue long-term anticoagulation beyond the recommended 2 months after successful CA for AF remains controversial.[1,2] This is contrary to what we may expect with our pathophysiologic and mechanistic understanding of CVA in AF. There is, however, evidence that longer episodes of AF are associated with a higher risk of stroke.[45] Consequently, successful CA may reduce the overall burden of AF compared with medical treatment and, therefore, reduce risk of CVA.[46] This may not be true for all patients, however, due to the fact that CVA has multiple etiologic and associating factors, such as comorbidities and patient demographics. Currently, the advancement of AF ablation including new technologies such as pulsed field ablation, newer mapping systems, and new catheters will likely result in a higher success rate of the ablation, leading to lower burden of recurrent AF and longer time in sinus rhythm. This might lead to lower incidence of stroke. An up-to-date randomized trial will need to address the issue. On the other hand, the differences in the event rates between randomized controlled trials and observational studies might be explained by the smaller number of the included patients and they were not powered for CVA events.

CA and dementia

Studies have shown an association between AF and the development of dementia.[47] A large prospective study including 433,746 patients found that an earlier onset of AF was associated with subsequent dementia (hazard ratio 1.42, 95% CI 1.32–1.52).[48] Moreover, a report from the Home-Based Screening for Early Detection of Atrial Fibrillation in Primary Care Patients Aged 75 Years and Older (SCREEN-AF) trial revealed an association between AF and cognitive impairment.[3] There are multiple theories attempting to explain the relationship of AF and cognitive impairment, such as micro- vs macroembolic events, atrioventricular dyssynchrony leading to cerebral hypoperfusion, and others.[47] As CA is known to be the most effective method to maintain sinus rhythm, this strategy may theoretically provide more success in reducing the aforementioned deleterious neurocognitive effects of remaining in AF.[49] Therefore, CA for AF should result in reducing the risk of AF-related dementia. Our analysis was compatible with this theory. However, one must keep in mind that there are multiple factors that could lead to cognitive impairment. Patients with AF and dementia share many common features, especially old age, which could interfere with the result of studies.

Table 1 Baseline characteristics of the included studies.

Name	Year	Type	Follow-up (mo)	Age (y)	Male (%)	CA number	Control number
Akerström[13]	2024	Retrospective	54	61	70	3955	3955
Tseng[14]	2023	Retrospective	12	44	74	2146	50,452
Kawaji [15]	2022	Retrospective	64	66	75	537	537
Li[16]	2023	Retrospective	66	60	70	1561	66,826
Harrison[18]	2023	Retrospective	60	68	59	20,746	20,746
Zeitler[19]	2022	Retrospective	28	64	66	19,088	19,088
Kawaji[15]	2022	Retrospective	64	66	73	537	537
Kim[21]	2022	Retrospective	51	57	78	1629	1502
Yang[24]	2020	Retrospective	43	62	70	9185	18,770
Hsieh[25]	2020	Retrospective	108	54	70	787	787
Kim[26]	2020	Retrospective	52	60	74	5863	5863
Su[28]	2020	Retrospective	40	78	52	571	571
Iso[29]	2020	Retrospective	27	67	74	3451	2930
Freeman[30]	2020	Retrospective	24	64	67	535	535
Bunch[31]	2020	Retrospective	60	73	70	259	4272
Marrouche[32]	2018	RCT	38	64	85	179	184
Packer[33]	2019	RCT	48	68	63	1108	1096
Mansour[34]	2018	Retrospective	36	64	58	14,728	29,456
Srivatsa[35]	2018	Retrospective	43	68	72	4169	4169
Saliba[36]	2017	Retrospective	120	65	63	969	3772
Jarman[37]	2017	Retrospective	28	63	69	4991	4991
Friberg[38]	2016	Retrospective	53	60	74	2836	2836
Noseworthy[39]	2015	Retrospective	29	58	74	12,122	12,122
Hunter[40]	2014	RCT	6	67	95	26	24
Hummel[44]	2014	RCT	61	6		138	72
Packer[42]	2013	RCT	57	12		163	82
Nielsen[41]	2012	RCT	24	55	70	146	148
Cosedis Nielsen[41]	2012	RCT	26	24		146	148
Stabile[43]	2006	RCT	12	62		68	69

RCT = randomized controlled trial.

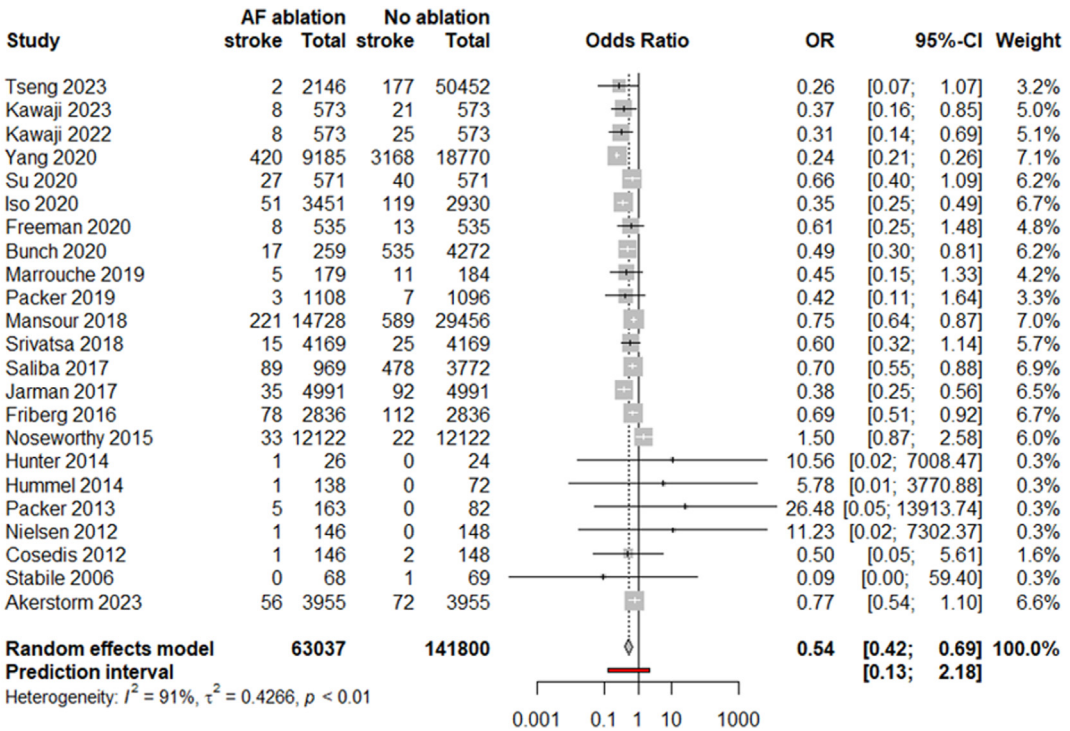

Figure 2 Association of catheter ablation vs medication and stroke in long-term follow-up. AF = atrial fibrillation; CI = confidence interval; OR = odds ratio.

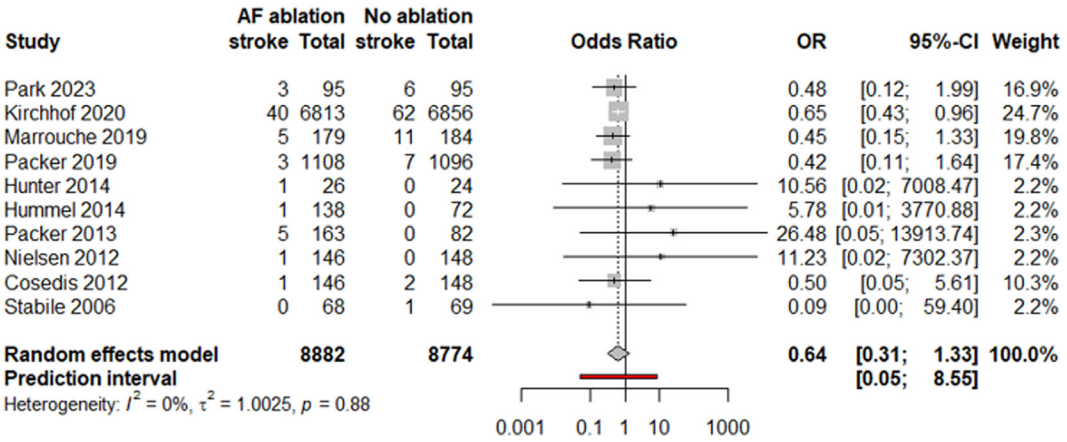

Figure 3 Association of catheter ablation vs medication and stroke in long-term follow-up in randomized controlled trials. AF = atrial fibrillation; CI = confidence interval; OR = odds ratio.

Limitations

Our study provides a comprehensive analysis and risk assessment of long-term neurological outcomes in AF patients after CA vs MM. However, it should be interpreted in the context of meta-analysis limitations. There is suspected heterogeneity between studies with respect to the study population: age, sex, comorbidities, and other unidentified risk factors. Moreover, the types of studies included are mixed, as with some observational studies, and therefore unmeasurable confounders may have affected the outcomes. Timing of the events in relation to intervention, duration of AF, and burden were not reported in most of the included studies.

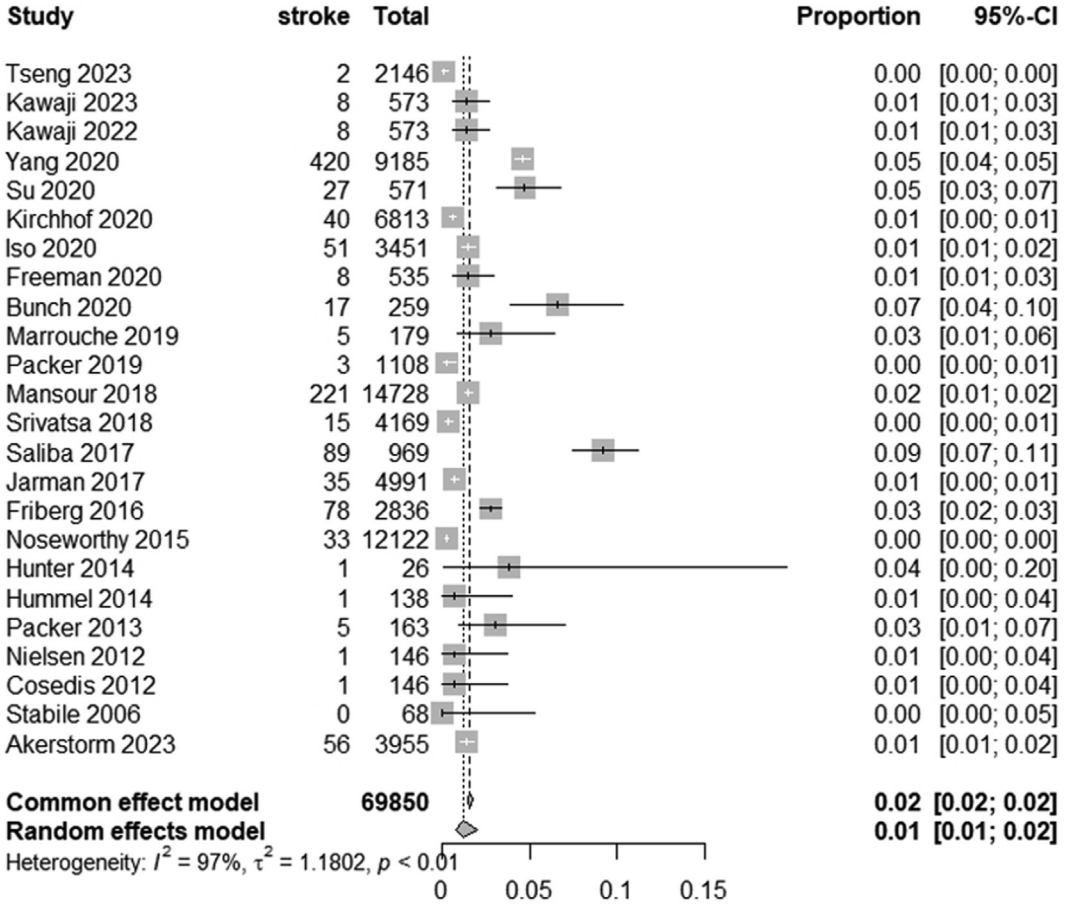

Figure 4 Incidence of stroke in patients underwent catheter ablation. CI = confidence interval.

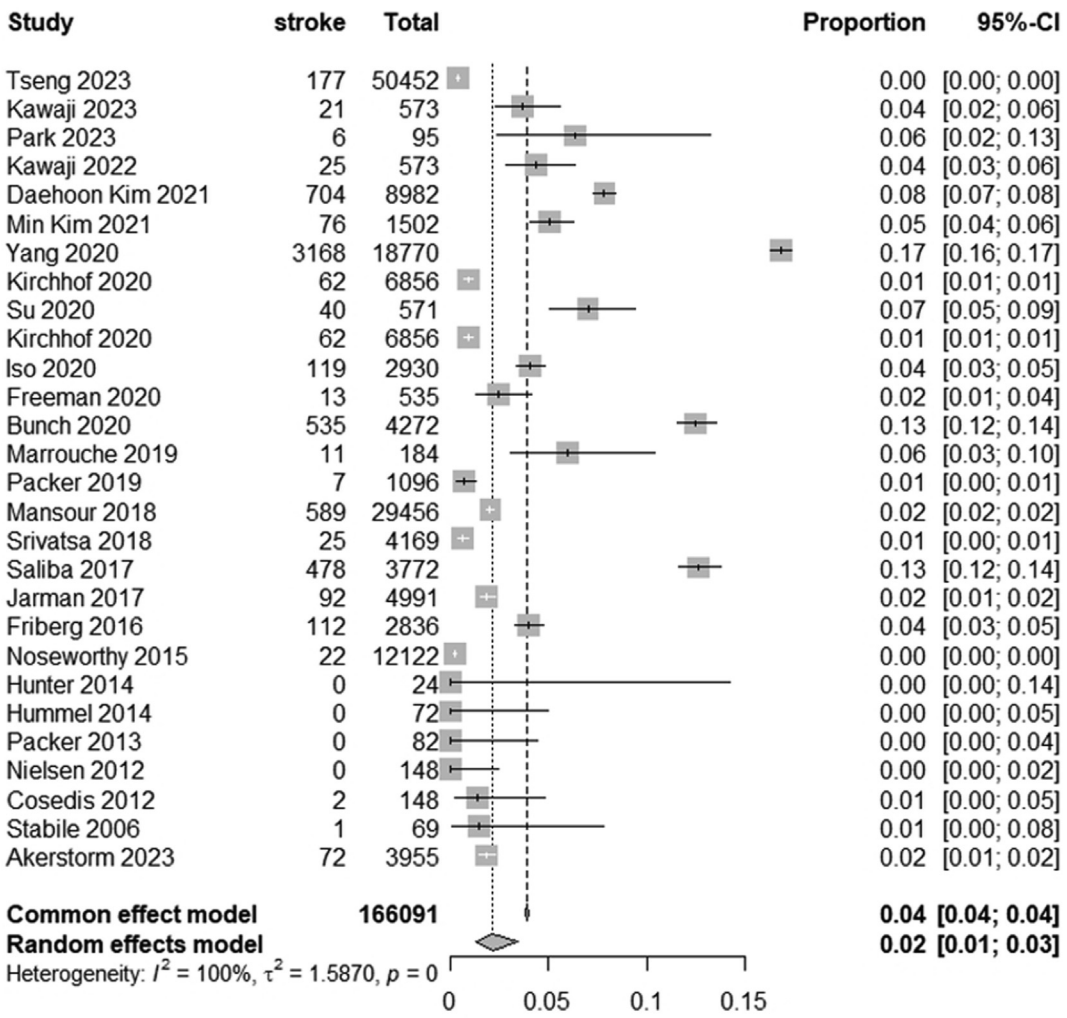

Figure 5 Incidence of stroke in patients underwent medical therapy. CI = confidence interval.

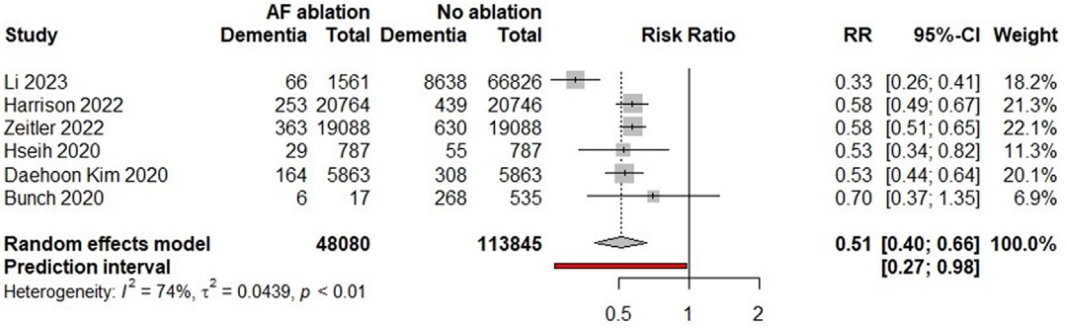

Figure 6 Association of catheter ablation vs medication and dementia in long-term follow-up. CI = confidence interval; RR = risk ratio.

Prospective, randomized trials with larger sample sizes are needed to validate the efficacy of CA for AF in reducing risk of incident CVA and dementia across different patient populations and management strategies.

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Ethics Statement: The systematic review was conducted with a protocol in accordance with the Preferred Reporting of Items for Systematic reviews and Meta-Analyses (PRISMA) statement.

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