Circulation: Arrhythmia and Electrophysiology

ORIGINAL ARTICLE

Catheter Ablation Versus Medical Therapy for Atrial Fibrillation

A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Zain Ul Abideen Asad, MD
Ali Yousif, MD
Muhammad Shahzeb Khan, MD
Sana M. Al-Khatib, MD
Stavros Stavrakis, MD, PhD

BACKGROUND: Despite the publication of several randomized clinical trials comparing catheter ablation (CA) with medical therapy (MT) in patients with atrial fibrillation (AF), the superiority of one strategy over another is still questioned by many. In this meta-analysis of randomized controlled trials, we compared the efficacy and safety of CA with MT for AF.

METHODS: We systematically searched MEDLINE, EMBASE, and other online sources for randomized controlled trials of AF patients that compared CA with MT. The primary outcome was all-cause mortality. Secondary outcomes included cardiovascular hospitalizations and recurrence of atrial arrhythmia. Subgroup analyses stratified by the presence of heart failure with reduced ejection fraction, type of AF, age, and sex were performed. Risk ratios (RRs) with 95% CIs were calculated using a random effects model, and Mantel-Haenszel method was used to pool RR.

RESULTS: Eighteen randomized controlled trials comprising 4464 patients (CA, n=2286; MT, n=2178) were included. CA resulted in a significant reduction in all-cause mortality (RR, 0.69; 95% CI, 0.54–0.88; *P*=0.003) that was driven by patients with AF and heart failure with reduced ejection fraction (RR, 0.52; 95% CI, 0.35–0.76; *P*=0.0009). CA resulted in significantly fewer cardiovascular hospitalizations (hazard ratio, 0.56; 95% CI, 0.39–0.81; *P*=0.002) and fewer recurrences of atrial arrhythmias (RR, 0.42; 95% CI, 0.33–0.53; *P*<0.00001). Subgroup analyses suggested that younger patients (age, <65 years) and men derived more benefit from CA compared with MT.

CONCLUSIONS: CA is associated with all-cause mortality benefit, that is driven by patients with AF and heart failure with reduced ejection fraction. CA reduces cardiovascular hospitalizations and recurrences of atrial arrhythmia for patients with AF. Younger patients and men appear to derive more benefit from CA.

VISUAL OVERVIEW: A visual overview is available for this article.

Key Words: atrial fibrillation ■ catheter ablation ■ humans ■ meta-analysis ■ randomized controlled trial

https://www.ahajournals.org/journal/circep

WHAT IS KNOWN?

- Multiple randomized controlled trials have shown that catheter ablation (CA) of atrial fibrillation (AF) is safe and superior to antiarrhythmic drugs in maintaining sinus rhythm and preventing recurrence of AF, and current guidelines recommend CA in symptomatic AF patients who are refractory or intolerant to antiarrhythmic drugs.
- The largest randomized controlled trial till date, CABANA (Catheter Ablation Versus Antiarrhythmic Drug Therapy) was recently published and showed that in patients with new or undertreated AF, there was no statistically significant benefit of CA versus medical therapy in the composite outcome of all-cause mortality, disabling stroke, serious bleeding, or cardiac arrest during a 5-year follow-up period.

WHAT THE STUDY ADDS?

- We undertook this meta-analysis of all published randomized controlled trials including CABANA to study the effect of CA versus medical therapy on all-cause mortality, cardiovascular hospitalizations, and recurrence of atrial arrhythmias. We performed subgroup analyses consisting of patients with heart failure with reduced ejection fraction versus nonheart failure, paroxysmal versus persistent AF, young (<65 years of age) versus old (≥65 years of age), hypertension versus no hypertension and men versus women.
- CA is associated with all-cause mortality benefit that is driven by patients with AF and heart failure with reduced ejection fraction. CA reduces cardiovascular hospitalizations and recurrences of atrial arrhythmia for patients with AF. Younger patients and men appear to derive more benefit from CA.

Atrial fibrillation (AF) is the most common clinically significant arrhythmia that is associated with considerable mortality, morbidity, and poor quality of life (QOL).[1] The lifetime risk for developing AF is 1 in 4 for middle-aged individuals, and the worldwide prevalence is estimated to be 33 million.[2–4] AF independently increases the risk of mortality by 2-fold in women and 1.5-fold in men.[5] The risk of ischemic stroke in patients with AF is increased by 5-fold, and 30% of all ischemic strokes are caused by AF.[6] Heart Failure (HF) occurs in more than one-third of individuals with AF, AF occurs in more than half of individuals with HF, and their coexistence carries a worse prognosis than either condition alone.[7,8] It is estimated that 10% to 40% of all patients with AF are hospitalized every year with incremental annual direct cost amounting to ≈$26 billion.[9–11]

Large randomized controlled trials (RCTs) in patients with AF failed to show benefit of rhythm control with antiarrhythmic drugs (AADs) as compared with rate control.[12–14] One explanation for the lack of benefit by AAD is their poor efficacy in maintaining normal sinus rhythm and the high rate of discontinuation given their side effects.[15–17]

Multiple RCTs have shown that catheter ablation (CA) of AF is safe and superior to AAD in maintaining sinus rhythm and preventing recurrence of AF.[18–24] Similarly, many RCTs consistently showed an improvement in left ventricular ejection fraction, QOL, and cardiovascular hospitalizations with CA as compared with medical therapy (MT).[25–28] In light of this evidence, the current guidelines recommend CA in symptomatic AF patients who are refractory or intolerant to AAD.[29] A recent meta-analysis of RCTs comparing CA versus MT showed survival benefit with CA only in HF with reduced ejection fraction (HFrEF) patients and reduced risk of cardiovascular hospitalization and recurrent arrhythmias in both HFrEF and non-HF patients.[30]

Since the publication of that meta-analysis, the largest RCT to date, namely, the CABANA (Catheter Ablation Versus Antiarrhythmic Drug Therapy) has been published.[31] CABANA showed that in patients with new or undertreated AF, there was no statistically significant benefit of CA versus MT in the composite outcome of all-cause mortality, disabling stroke, serious bleeding, or cardiac arrest over a 5-year follow-up period. The previous meta-analysis included 775 AF patients with HFrEF and 1497 AF patients without HF, whereas CABANA alone enrolled 2204 patients. An updated meta-analysis is necessary since CABANA had the potential to influence pooled results significantly because of its large sample size.

We undertook this meta-analysis of all published RCTs including CABANA to study the effect of CA versus MT on all-cause mortality, cardiovascular hospitalizations, and recurrence of atrial arrhythmias. Because individual trials are often underpowered to estimate effects in subgroups, an updated meta-analysis had the potential to improve power and precision of estimates in subgroup analyses. Therefore, we studied the effect of CA versus MT in subgroups consisting of patients with HFrEF versus non-HF, paroxysmal versus persistent AF, young (<65 years) versus old (≥65 years), hypertension versus no hypertension, and men versus women.

METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request. The Cochrane Collaboration guidelines were followed, and our results are reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses report.[32,33]

Data Sources and Search

Literature search was performed in PubMed/MEDLINE and EMBASE database up to November 2018. Independent searches were performed by 2 authors (Z.U.A.A. and A.Y.) using the following Medical Subject Headings: atrial fibrillation,

ablation, catheter ablation, radiofrequency ablation, cryoablation, and pulmonary vein isolation. Abstracts and presentations from all major cardiovascular conferences including www.hrsonline.org, www.acc.org, and www.clinicaltrials.gov were also searched. Abstracts were screened, and wherever necessary information was not available in the abstract, full articles and reference lists were reviewed. Details of PubMed search strategy algorithm are given (Data Supplement).

Study Selection

Two independent reviewers (Z.U.A.A. and A.Y.) screened the search results and included studies if they met the following inclusion criteria: (1) randomized controlled clinical trials of patients undergoing CA of AF; (2) comparison arm comprised of MT (rate control or AAD); (3) at least 1 outcome of interest was reported. We had no restriction on sample size, follow-up duration, or language.

Quality Assessment and Data Extraction

Two investigators (Z.U.A.A. and A.Y.) independently abstracted data from studies meeting inclusion criteria, and any disagreements were resolved by a third reviewer (S.S.). A structured data collection form was used to abstract the baseline characteristics of the study populations and outcomes of interest. In addition, we extracted data on outcomes in the following predefined subgroups: HFrEF versus non-HF, paroxysmal versus persistent AF, young (<65 years) versus old (≥65 years), males versus females, and hypertension versus no hypertension. The quality of included trials was assessed using previously published criteria.[34]

Outcome Measures

The primary outcome was all-cause mortality. The secondary outcomes included cardiovascular hospitalizations, recurrence of atrial arrhythmia, major bleeding, stroke, and a composite outcome of major adverse cardiac events (death, disabling stroke, major bleeding, cardiac arrest, or cardiovascular hospitalization).

Statistical Analysis

For all the included trials, including the CABANA trial, only outcomes reported according to the intention-to-treat principle were included in this analysis. The Mantel-Haenszel method for dichotomous data was used to calculate the 95% CIs and aggregated risk ratio (RR). All results were reported as RR with corresponding 95% CI, and statistical significance was considered for a 2-tailed P of <0.05. For 2 trials that reported primary composite outcome data using CIs for the hazard ratio (HR), we estimated the standard error of natural log of the HR.[26,35] The natural log of HR was pooled using the generic inverse variance method. A random effects approach was used since that accounts for any study heterogeneity.[36] A formal test of heterogeneity was conducted, and Q statistic was calculated. The proportion of total variability in the estimates due to between study variation was summarized with the I^2 index and its 95% CI.[37] Stepwise exclusion of 1 study at a time was used to perform a sensitivity analysis to determine the impact of an individual study on the outcomes. Data analysis was performed using the Review Manager (version 5.3; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

RESULTS

Our search for eligible studies is outlined in Figure 1. A total of 18 studies were included in the meta-analysis with a total of 4464 patients (CA, n=2286; MT, n=2178; Table I in the Data Supplement).[18–28,35,38–43] The baseline characteristics of the included studies are shown in the Table. Overall, the studies were of high quality with a low risk of bias (Figure I in the Data Supplement). The results of the sensitivity analysis are summarized (Table II in the Data Supplement).

All-Cause Mortality

Nine trials comprising 3576 patients reported all-cause mortality data during follow-up. A total of 96 (5.3%) events occurred among 1808 patients in the CA arm versus 140 (7.9%) events among 1768 patients in the MT arm. Based on the pooled estimate across the 9 studies, CA was associated with a statistically significant reduction in all-cause mortality compared with MT in patients with AF with low heterogeneity (RR, 0.69; 95% CI, 0.54–0.88; P=0.003; I^2=0%; P=0.64; Figure 2). Sensitivity analysis suggested that this result was driven by the CASTLE-AF trial (Catheter Ablation for Atrial Fibrillation With Heart Failure),[26] as overall significance was lost when this study was excluded from the analysis (Table II in the Data Supplement). Therefore, we advise caution when interpreting these results.

AF With HFrEF Versus AF Without HF

Four trials comprising 668 patients included patients with HFrEF. Notably, we did not include CABANA in this analysis because, in contrast to the rest of the studies, the term HF in CABANA referred to both HFrEF and HF with preserved ejection fraction. HFrEF-specific data were requested from the CABANA investigators but were not provided. A total of 33 (9.9%) events occurred among 333 patients in the CA arm versus 65 (19.4%) events among 335 patients in the MT arm. CA was associated with a statistically significant reduction in all-cause mortality compared with MT in AF patients with HFrEF with low heterogeneity (RR, 0.52; CI, 0.35–0.76; P=0.0009; I^2=0%; P=0.69; Figure 2). Sensitivity analyses showed that the statistical significance was maintained after serial exclusions of all trials except the CASTLE-AF trial (Table II in the Data Supplement).[26] On the contrary, in patients without HF, CA was not associated with a statistically significant reduction in all-cause mortality compared with MT (RR, 0.67; CI, 0.23–1.99; P=0.47; I^2=0%; P=0.81; Figure 2).

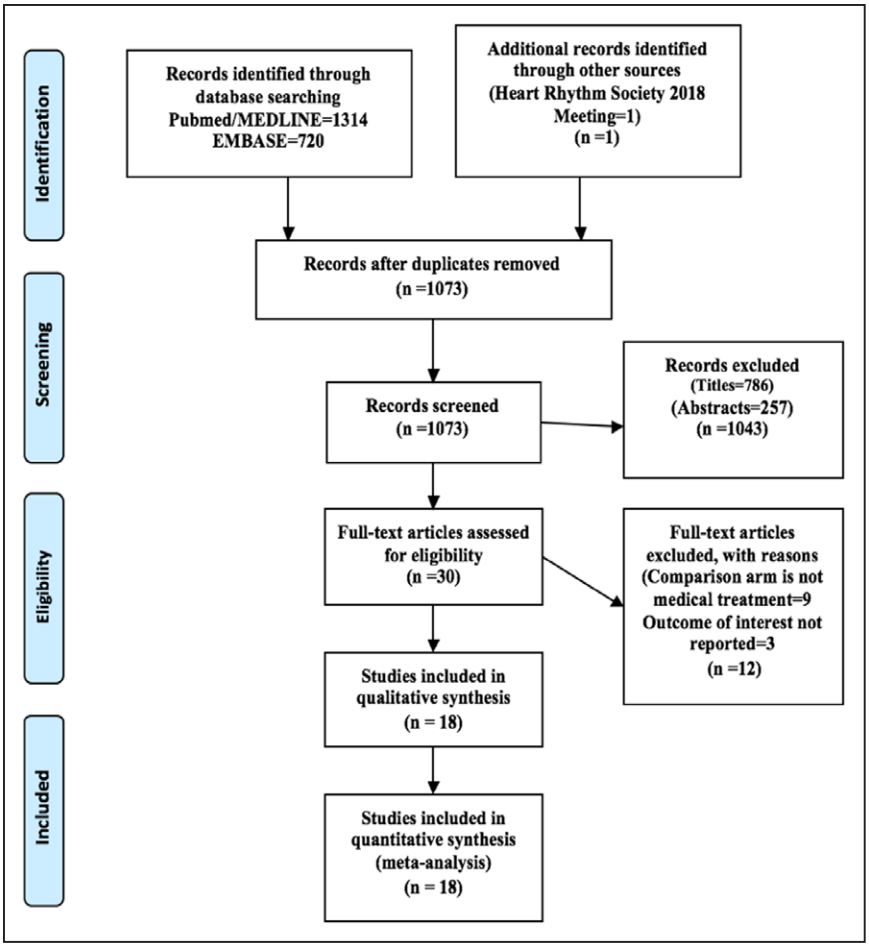

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart showing the search strategy. EMBASE indicates Excerpta Medica Database; and MEDLINE, Medical Literature Analysis and Retrieval System Online.

CA Versus AAD or Rate Control

Four trials compared CA with AAD in relation to the end point of all-cause mortality. Based on the pooled estimate across the 4 studies, CA had a significant mortality benefit compared with AAD with low heterogeneity (RR, 0.46; CI, 0.23–0.93; *P*=0.03; I^2=0%; *P*=0.82; Figure 2). This benefit was primarily driven by the AATAC trial (Ablation Versus Amiodarone for Treatment of Persistent Atrial; Fibrillation in Patients With Congestive Heart Failure and an Implanted Device), as suggested by the sensitivity analysis, which showed that the overall significance was lost when this study was excluded from the analysis. Based on the pooled estimate across 2 studies, CA did not reduce all-cause mortality compared with rate control (HR, 0.96; 95% CI, 0.10–8.95; *P*=0.97). These results should be interpreted with caution because there was only 1 event in each arm.

Cardiovascular Hospitalization

Seven trials reported the incidence of cardiovascular hospitalizations with CA versus MT. Compared with MT, CA decreased cardiovascular hospitalizations (HR, 0.56; CI, 0.39–0.81; *P*=0.002; I^2=78%; *P*=0.0001; Figure 3). No individual trial had a major impact on the pooled RR or the statistical significance based on sensitivity analysis. The benefit of CA versus MT in preventing cardiovascular hospitalizations was observed both in patients with HFrEF (RR, 0.62; CI, 0.47–0.82; *P*=0.0006; I^2=29%; *P*=0.25) and without HF (RR, 0.21; CI, 0.09–0.45; *P*<0.0001; Figure 3). In comparison to AAD, CA showed a statistically significant benefit in relation to cardiovascular hospitalizations (RR, 0.33; CI, 0.15–0.75; *P*=0.008; Figure 3).

Recurrence of Atrial Arrhythmia

Eighteen trials comprising 3500 patients reported recurrence of atrial arrhythmia during follow-up. CA was associated with a statistically significant reduction in recurrence of atrial arrhythmia compared with MT (RR, 0.42; 95% CI, 0.33–0.53; *P*<0.00001; Figure 4). The benefit of CA in preventing recurrence of atrial arrhythmia as compared with MT was observed both in patients with (RR, 0.40; 95% CI, 0.26–0.60; *P*<0.0001) and without HF (RR, 0.46; 95% CI, 0.35–0.60; *P*<0.00001; Figure 4).

Ten trials compared recurrence of atrial arrhythmia with CA versus rhythm control. Compared with MT, CA significantly reduced the recurrence of atrial arrhythmia (RR, 0.39; CI, 0.27–0.57; *P*<0.00001; Figure 4). Based on

Table. Baseline Characteristics of Patients

Study	Year	Groups	Sample, n	Age, y (Mean/ Median)	Male, %	Prior Embolic Events, %	DM, %	HTN, %	SIHD, %	LVEF, %	Type of AF: Paroxysmal/ Persistent, %	LAD, mm	ICM, %	Anticoagulation Strategy
A4 study	2008	RFA	53	50	85	2	2	22	19	63	100/0	39	6	Warfarin 1 mo before and 1 mo after procedure
		MT	59	52	83	12	3	31	24	66	100/0	40	10	
AATC study	2016	RFA	102	62	75		22	45			0/100	47	62	
		MT	101	60	73		24	48			0/100	48	65	
APAF	2006	RFA	99	55	70		5	56	7	60	100/0	40	2	Warfarin d/c after 6 wk if SR was maintained
		MT	99	57	65		4	57	4	61	100/0	38	2	
CABANA	2018	RFA	1108	68	63	14	25	80	19		42/58			Warfarin 46%
		MT	1096	67	63	14	25	82	20		43/57			Warfarin 39%
CAMERA-MRI	2017	RFA	33	59	94	6	12	39	100	35	28/72	48		100% on AC; unspecified type
		MT	33	62	88	0	15	36	100	35	24/76	47		
CAMTAF	2014	RFA	26	55	96	4						52	2	Warfarin 100%
		MT	24	60	96							50	3	
CASTLE-AF	2018	RFA	179	64	87		24	72	100	32	30/70	48		Warfarin at least 6 mo post-ablation
		MT	184	64	84		36	74	100	31	35/65	49		
Forleo et al	2009	RFA	35	63	57		100	63	46	55	46/54	44	20	Warfarin d/c 6 mo post-ablation
		MT	35	65	65		100	69	54	53	37/63	45	20	Warfarin throughout study period
Jones et al	2013	RFA	26	64	81							50	38	
		MT	26	62	92		22	45		29	0/100	46	37	
Krittayaphong et al	2003	RFA	15	55	73		7		13	64	73/27	39		Warfarin
		MT	15	49	53		20		13	62	60/40	40		
MacDonald	2010	RFA	22	62	77	9				16			50	Warfarin
		MT	19	64	79	11		3		20	0/100		47	
MANTRA-PAF	2012	RFA	146	56	68	4	4	29			100/0	40	4	Oral AC with INR 2–3
		MT	148	54	72	3	7	36			100/0	40	1	
Oral et al	2006	RFA	77	55	67				8	55	0/100	45	4	Warfarin
		MT	69	58	62				9	56	0/100	45	6	
RAAFT-2 study	2014	RFA	66	56	77	5	2	42		61	99/1	40	9	Warfarin
		MT	61	54	74	7	7	41		61	97/3	43	3	
SARA study	2014	RFA	98	55	78	6				61	0/100		3	
		MT	48	55	77	4				61	0/100		2	
Stabile et al	2006	RFA	68	62	54			53	63	59	62/38	46	4	
		MT	69	69	64			49	62	58	73/27	45	7	
Wazni et al	2005	RFA	33	53					25	53	97/3	41		
		MT	37	54					28	54	95/5	42		
Wilber et al	2010	RFA	106	56	69	2	10	49	10	62	100/0	40		
		MT	61	56	62	3	12	50	15	63	100/0	41		
Total		RFA	2286											
		MT	2178											

A4 indicates Catheter Ablation Versus Antiarrhythmic Drugs for Atrial Fibrillation; AATAC, Ablation Versus Amiodarone for Treatment of Persistent Atrial Fibrillation in Patients With Congestive Heart Failure and an Implanted Device; AC, anticoagulation; AF, atrial fibrillation; APAF, A Randomized Trial of Circumferential Pulmonary Vein Ablation Versus Antiarrhythmic Drug Therapy; CAMERA-MRI, Catheter Ablation Versus Medical Rate Control in Atrial Fibrillation and Systolic Dysfunction; CAMTAF, A Randomized Controlled Trial of Catheter Ablation Versus Medical Treatment of Atrial Fibrillation in Heart Failure; CASTLE-AF, Catheter Ablation for Atrial Fibrillation With Heart Failure; Antiarrhythmic Drug Therapy in Paroxysmal Atrial Fibrillation; CABANA, Catheter Ablation Versus D/C, discontinued; DM, diabetes mellitus; HTN, hypertension; ICM, ischemic cardiomyopathy; INR, International Normalized Ratio; LAD, left atrial diameter; LVEF, left ventricular ejection fraction; MANTRA-PAF, Radiofrequency Ablation as Initial Therapy in Paroxysmal Atrial Fibrillation; MT, medical therapy; RAAFT-2, Radiofrequency Ablation Versus Antiarrhythmic Drugs as First-Line Treatment of Paroxysmal Atrial Fibrillation; RFA, radiofrequency ablation; SARA Study, Catheter Ablation vs Antiarrhythmic Drug Treatment of Persistent Atrial Fibrillation: A Multicentre, Randomized, Controlled Trial; SIHD, stable ischemic heart disease; and SR, sinus rhythm.

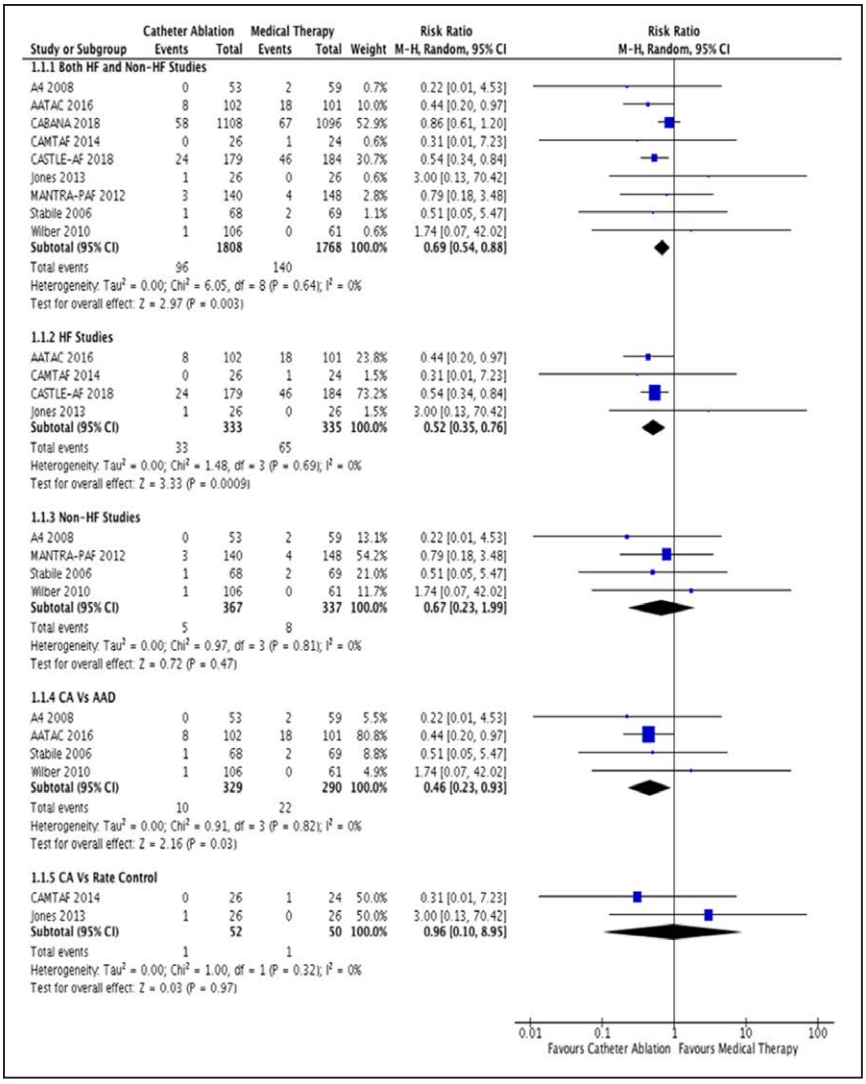

Figure 2. Forest plot showing primary outcome of all-cause mortality with catheter ablation vs medical therapy.
A4 indicates Catheter Ablation Versus Antiarrhythmic Drugs for Atrial Fibrillation; AAD, antiarrhythmic drugs; AATAC, Ablation Versus Amiodarone for Treatment of Persistent Atrial Fibrillation in Patients With Congestive Heart Failure and an Implanted Device; CA, catheter ablation; CABANA, Catheter Ablation Versus Antiarrhythmic Drug Therapy; CAMTAF, A Randomized Controlled Trial of Catheter Ablation Versus Medical Treatment of Atrial Fibrillation in Heart Failure; CASTLE-AF, Catheter Ablation for Atrial Fibrillation With Heart Failure; HF, heart failure; MANTRA-PAF, Radiofrequency Ablation as Initial Therapy in Paroxysmal Atrial Fibrillation; and M-H, Mantel Haenzel.

the pooled estimate across the 3 trials that compared the recurrence of atrial arrhythmia with CA versus rate control, there was a statistically significant reduction with CA (RR, 0.26; CI, 0.10–0.68; *P*=0.006; Figure 4). The benefit of CA compared with MT in reducing atrial arrhythmias during follow-up was consistent among patients with paroxysmal AF (RR, 0.44; CI, 0.27–0.72; *P*=0.001) and persistent AF (RR, 0.45; CI, 0.32–0.64; *P*<0.00001; Figure 4).

Stroke and Major Bleeding

Four trials reported the incidence of stroke with CA versus MT. Ten (0.68%) events occurred among 1459 patients in the CA arm, whereas 18 (1.23%) events occurred among 1452 patients in the MT arm. Based on the pooled estimate across the 4 trials, CA did not result in a statistically significant benefit as compared with MT in preventing stroke (RR, 0.56; CI, 0.26–1.22; *P*=0.14; I^2=0%; *P*=0.50; Figure 5). The incidence of major bleeding with CA versus MT was reported in 8 trials (Table III in the Data Supplement). Based on the pooled estimate across the 8 studies, there was no difference in the incidence of major bleeding with CA versus MT (RR, 1.55; CI, 0.83–2.91; *P*=0.17; I^2=7%; *P*=0.37; Figure 6). These results should be interpreted with caution because some of the included trials did not report the anticoagulation strategy during follow-up.

Subgroup Analysis

Given that risk stratification may improve selection of patients who are more likely to benefit from CA versus MT, we examined the effect of different clinical characteristics on the reported outcomes. Two trials reported outcomes stratified by age, sex, and hypertension[26,35] (Table IV in the Data Supplement). Specifically, CABANA reported subgroup analysis on the composite outcome of death, stroke, major bleeding, and cardiac arrest, whereas CASTLE-AF reported results for the composite outcome of death and HF hospitalizations. Even though the composite outcomes reported in each of these 2 trials were somewhat different, a significant percentage of the events of CABANA and CASTLE-AF were deaths, which is the common individual end point of the 2 composite end points used in the trials, allowing for pooling

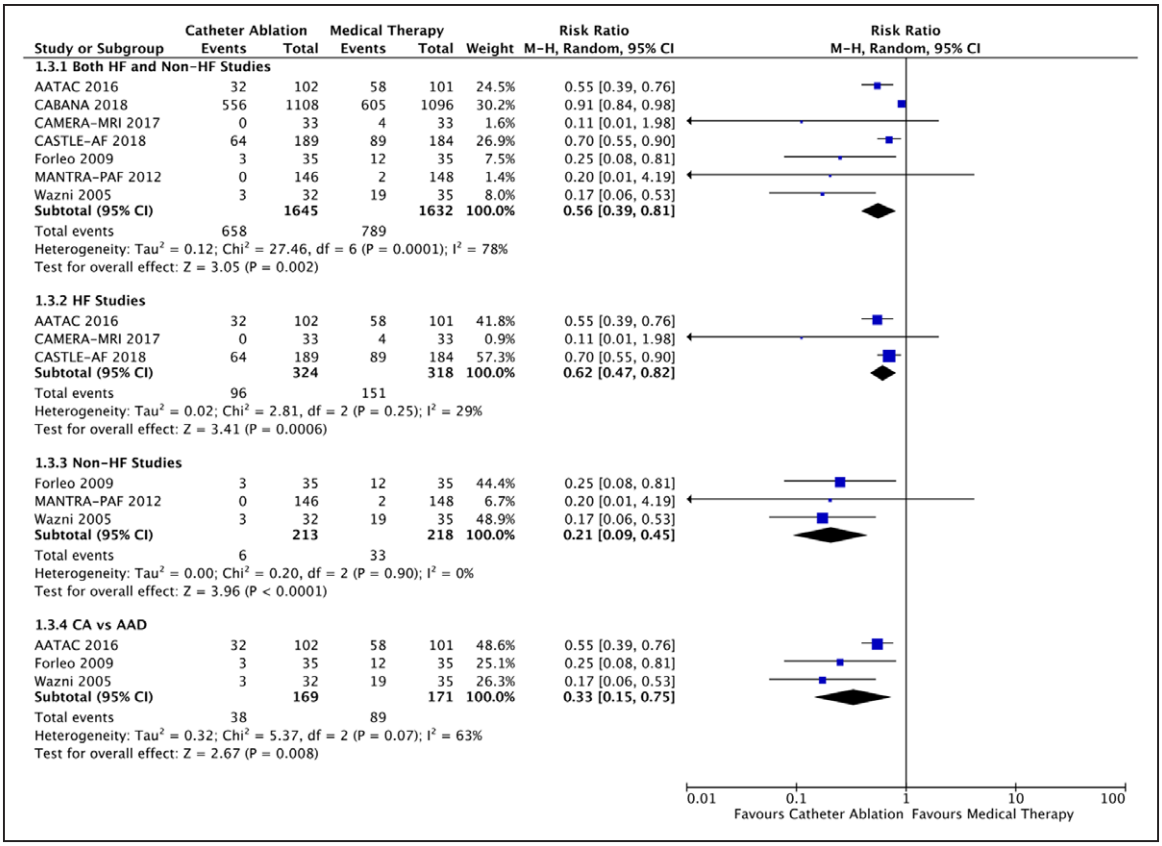

Figure 3. Forest plot showing secondary outcome of cardiovascular hospitalizations with catheter ablation vs medical therapy.
AAD indicates antiarrhythmic drugs; AATAC, Ablation Versus Amiodarone for Treatment of Persistent Atrial Fibrillation in Patients With Congestive Heart Failure and an Implanted Device; CA, catheter ablation; CABANA, Catheter Ablation Versus Antiarrhythmic Drug Therapy; CAMERA-MRI, Catheter Ablation Versus Medical Rate Control in Atrial Fibrillation and Systolic Dysfunction; CASTLE-AF, Catheter Ablation for Atrial Fibrillation With Heart Failure; HF, heart failure; MANTRA-PAF, Radiofrequency Ablation as Initial Therapy in Paroxysmal Atrial Fibrillation; and M-H, Mantel Haenzel.

of these outcomes. Nonetheless, given this limitation, we advise caution when interpreting these results.

There was a statistically significant benefit of CA in preventing the composite outcome among younger patients (age, <65 years; HR, 0.50; CI, 0.32–0.77; *P*=0.002; I^2=0%; *P*=0.86) but not among older patients (age, ≥65 years; HR, 0.93; CI, 0.67–1.28; *P*=0.66; I^2=31%; *P*=0.23; Figure 7). Interestingly, men (HR, 0.60; CI, 0.46–0.78; *P*=0.0002) but not women (HR, 0.97; CI, 0.62–1.53; *P*=0.91) derived a significant benefit from CA compared with MT (Figure 8). Patients with hypertension (HR, 0.75; 95% CI, 0.56–1.00; *P*=0.05) appear to derive more benefit from CA compared with MT, in comparison to those without hypertension (HR, 1.09; 95% CI, 0.33–3.61; *P*=0.89), although this result may be influenced by the small number of patients in the nonhypertension subgroup (n=525 versus 2041 in the hypertension subgroup; Figure 9).

DISCUSSION

Major Findings

In this meta-analysis, we have shown that in patients with AF, CA is associated with a mortality benefit (31% relative risk reduction) as compared with MT, that is driven by patients with AF and HFrEF (48% relative risk reduction). CA was also associated with reduction in cardiovascular hospitalizations and recurrence of atrial arrhythmias in both patients with paroxysmal and persistent AF. Our subgroup analysis suggested that men (40% relative risk reduction) and patients <65 years of age (50% relative risk reduction) may derive more benefit from CA. It should be noted that the mortality benefit in the overall population was driven by a single trial (CASTLE-AF) and, therefore, the results should be interpreted with caution.[26] Nonetheless, these results provide important clinical information to guide the decision to offer CA to selected patients with AF.

Comparison With Other Studies and Interpretation of Major Findings

The significant benefit of CA in patients with AF and HFrEF is in agreement with results of other studies that have not only shown a mortality benefit but also demonstrated improvement in QOL and left ventricular ejection fraction.[25,30,44,45] Possible mechanisms for these findings include an improvement in

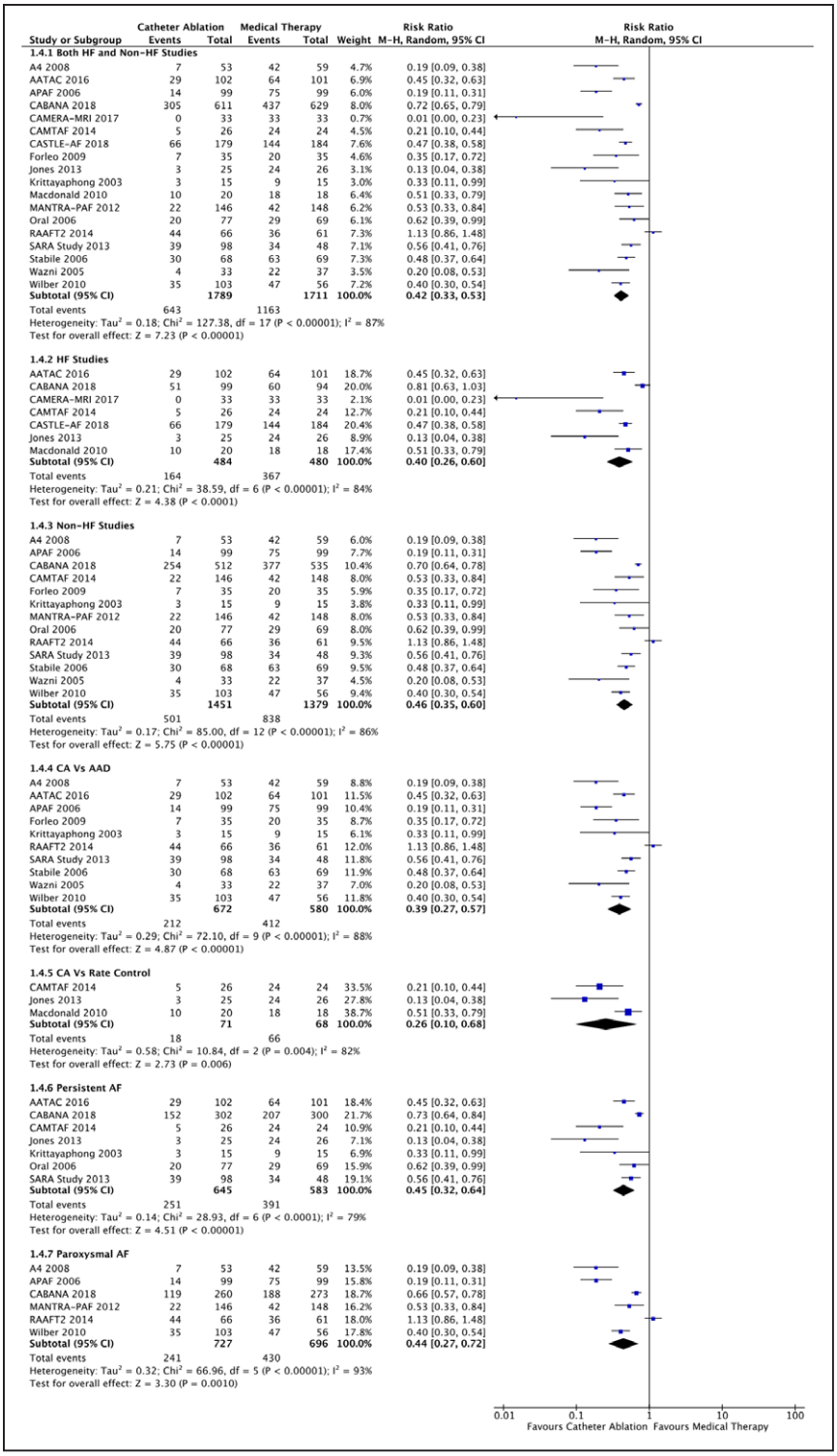

Figure 4. Forest plot showing secondary outcome of recurrence of atrial arrhythmia with catheter ablation vs medical therapy. A4 indicates Catheter Ablation Versus Antiarrhythmic Drugs for Atrial Fibrillation; AAD, antiarrhythmic drugs; AATAC, Ablation Versus Amiodarone for Treatment of Persistent Atrial Fibrillation in Patients With Congestive Heart Failure and an Implanted Device; AF, atrial fibrillation; APAF, A Randomized Trial of Circumferential Pulmonary Vein Ablation Versus Antiarrhythmic Drug Therapy in Paroxysmal Atrial Fibrillation; CA, catheter ablation; CABANA, Catheter Ablation Versus Antiarrhythmic Drug Therapy; CAMERA-MRI, Catheter Ablation Versus Medical Rate Control in Atrial Fibrillation and Systolic Dysfunction; CAMTAF, A Randomized Controlled Trial of Catheter Ablation Versus Medical Treatment of Atrial Fibrillation in Heart Failure; CASTLE-AF, Catheter Ablation for Atrial Fibrillation With Heart Failure; HF, heart failure; M-H, Mantel Haenzel; MANTRA-PAF, Radiofrequency Ablation as Initial Therapy in Paroxysmal Atrial Fibrillation; RAAFT-2, Radiofrequency Ablation Versus Antiarrhythmic Drugs as First-Line Treatment of Paroxysmal Atrial Fibrillation; and SARA Study, Catheter Ablation vs Antiarrhythmic Drug Treatment of Persistent Atrial Fibrillation: A Multicentre, Randomized, Controlled Trial.

cardiac hemodynamics by restoration of sinus rhythm because patients with HFrEF are more dependent on the atrial contraction for maintaining adequate cardiac output, as well as reduction in the incidence of tachycardia-mediated cardiomyopathy.[46] These results are clinically important because AF and HF coexist in a large number of patients with resultant significant morbidity and mortality.[8]

The lack of survival benefit of CA in AF patients without HF can perhaps be explained by the low event rates. Based on the event rates in trials that included AF without HF patients, it is estimated that it will take a trial with at least 6000 patients to demonstrate a mortality benefit with CA even if such a benefit exists. CABANA enrolled 2204 patients in >100 centers worldwide, and it took ≈9 years to complete, which makes the feasibil-

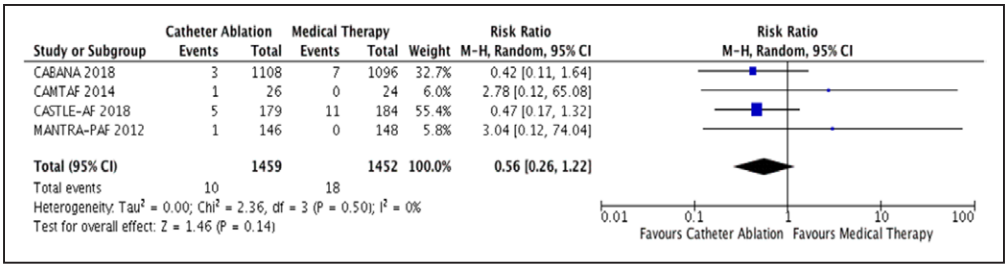

Figure 5. Forest plot showing secondary outcome of stroke with catheter ablation vs medical therapy.
CABANA indicates Catheter Ablation Versus Antiarrhythmic Drug Therapy; CAMTAF, A Randomized Controlled Trial of Catheter Ablation Versus Medical Treatment of Atrial Fibrillation in Heart Failure; CASTLE-AF, Catheter Ablation for Atrial Fibrillation With Heart Failure; MANTRA-PAF, Radiofrequency Ablation as Initial Therapy in Paroxysmal Atrial Fibrillation; and M-H, Mantel Haenzel.

ity of a trial with 6000 sample size highly doubtful.[47] The reduction in cardiovascular hospitalizations and atrial arrhythmia recurrence with CA in patients with or without HF is clinically significant as these are end points that affect patients' QOL and have important economic implications.[48,49]

While these findings add to the growing body of evidence favoring CA, careful attention should be given to identify patients who are most likely to derive benefit from CA. Our analysis sheds some light on patient selection for CA and suggests that patients <65 years of age derive more benefit from CA. This can possibly be explained by the high burden of comorbidities and procedural complications in older patients.[50] Our results challenge observational studies that have suggested comparable outcomes between young and old patients undergoing CA and underscore the importance of interpreting those studies with caution because of their small sample size and the effect of confounding and selection bias.[51–53]

There can be multiple explanations for why women did not appear to derive benefit from CA. Women are referred for CA later than men at which point they may have a larger left atrial size that may impact the effectiveness of the procedure and they have higher procedural complications.[54,55] In addition, our results may be explained by the underrepresentation of women in RCTs of AF CA. There is some evidence that suggests that despite a more complex preablation course, the outcomes of CA in women are comparable to those of men.[56] Therefore, we suggest that our finding of potential lack of benefit from CA in women be interpreted with caution and in fact form the basis for enrolling more women in future CA trials. Beyond age and sex, other risk stratification tools have been proposed to identify patients that will have good long-term success with CA. The CAMERA-MRI trial (Catheter Ablation Versus Medical Rate Control in Atrial Fibrillation and Systolic Dysfunction) included in our analysis showed that absence of late gadolinium enhancement predicted an improvement in left ventricular ejection fraction post-CA.[25] The ongoing DECAAF-II trial (Delayed Enhancement MRI-Guided Ablation Versus Conventional Catheter Ablation of Atrial Fibrillation) will be able to provide more data on improving outcomes with CA by targeting atrial fibrosis detected by late gadolinium enhancement magnetic resonance imaging.[57]

Implications for Future Research

Selecting patients for CA who will likely derive greater benefit with minimal side effects should be our goal. Future trials of CA should focus on developing risk stratification tools that can help in patient selection. More trials of CA in HF with preserved ejection fraction are needed because

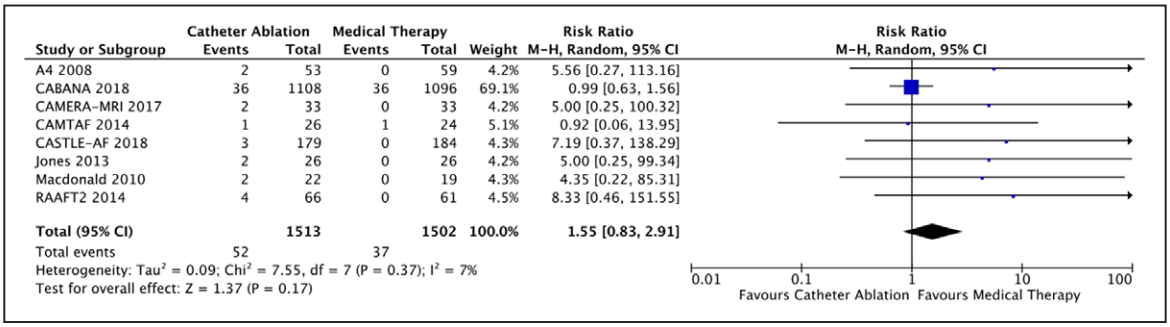

Figure 6. Forest plot showing secondary outcome of major bleeding with catheter ablation vs medical therapy.
A4 indicates Catheter Ablation Versus Antiarrhythmic Drugs for Atrial Fibrillation; CABANA, Catheter Ablation Versus Antiarrhythmic Drug Therapy; CAMERA-MRI, Catheter Ablation Versus Medical Rate Control in Atrial Fibrillation and Systolic Dysfunction; CAMTAF, A Randomized Controlled Trial of Catheter Ablation Versus Medical Treatment of Atrial Fibrillation in Heart Failure; CASTLE-AF, Catheter Ablation for Atrial Fibrillation With Heart Failure; M-H, Mantel Haenzel; and RAAFT-2, Radiofrequency Ablation Versus Antiarrhythmic Drugs as First-Line Treatment of Paroxysmal Atrial Fibrillation.

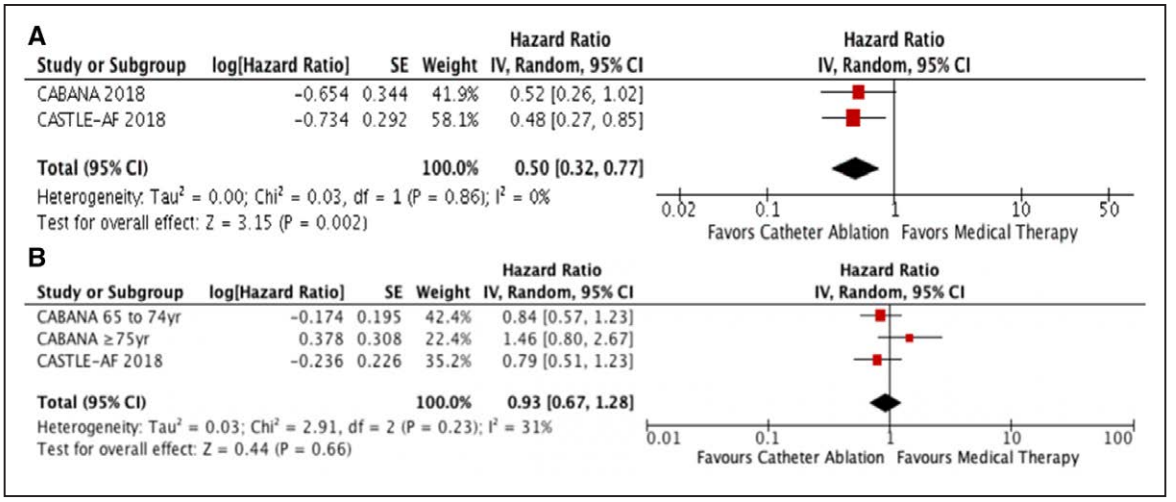

Figure 7. Forest plot showing composite outcome of death, stroke, major bleeding, cardiac hospitalization, and cardiac arrest with catheter ablation vs medical therapy.
A, Age <65 y; (**B**) age ≥65 y. CABANA indicates Catheter Ablation Versus Antiarrhythmic Drug Therapy; and CASTLE-AF, Catheter Ablation for Atrial Fibrillation With Heart Failure.

we do not know whether the benefits of CA observed in HFrEF patients still apply to patients with HF with preserved ejection fraction. Limited observational data suggest that the outcomes of HFrEF and HF with preserved ejection fraction patients undergoing CA are not different.[58,59]

Most of CA trials focused on recurrence of atrial arrhythmia as the primary end point and defined as an episode of AF lasting >30 seconds in a binary fashion. However, it is increasingly recognized that the burden of AF, measured either as percentage time in AF, number of AF episodes, duration of the longest AF episode, or AF density is a more clinically relevant parameter, which should be explored as an end point in CA trials.[60] Moreover, since methods for detection of AF have improved remarkably in the last decade with the availability of noninvasive remote monitoring devices, monitoring AF burden might be more feasible and informative. Current guidelines recommend CA in patients with symptomatic AF.[29,61] However, in light of recent evidence that even asymptomatic patients may derive benefit from CA with regard to QOL and exercise capacity, future RCTs should evaluate the effect of CA in this patient population.[49,62]

Clinical Implications

The benefits of CA for AF in HFrEF patients have been consistently shown for over a decade now; however, the uptake of this procedure by clinicians in practice has been

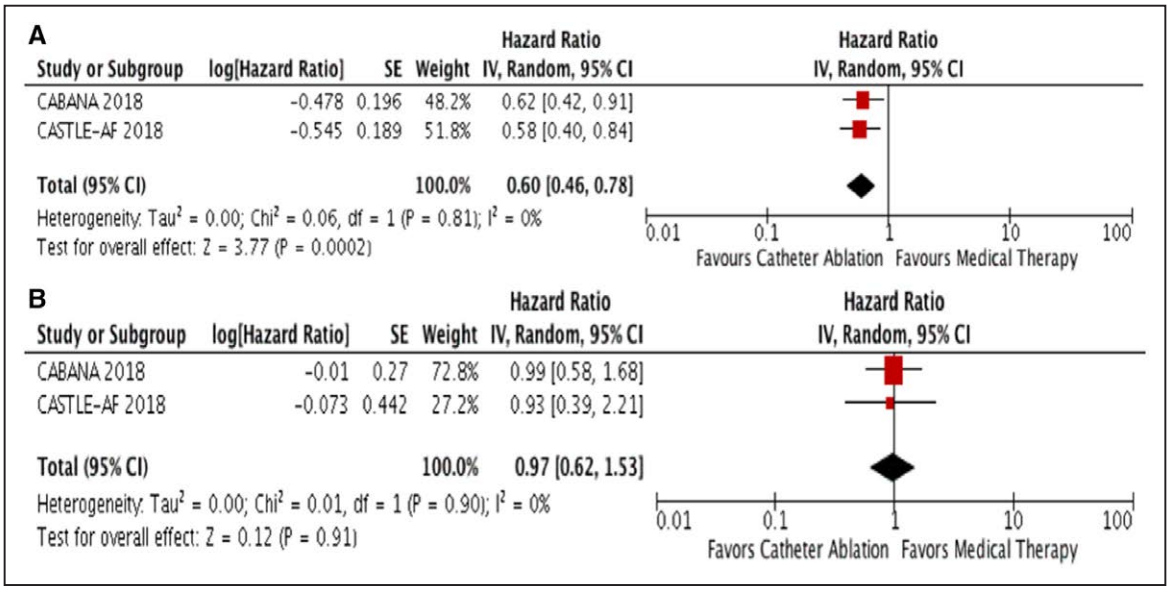

Figure 8. Forest plot showing composite outcome of death, stroke, major bleeding, cardiac hospitalization, and cardiac arrest with catheter ablation vs medical therapy.
A, Men; (**B**) women. CABANA indicates Catheter Ablation Versus Antiarrhythmic Drug Therapy; and CASTLE-AF, Catheter Ablation for Atrial Fibrillation With Heart Failure.

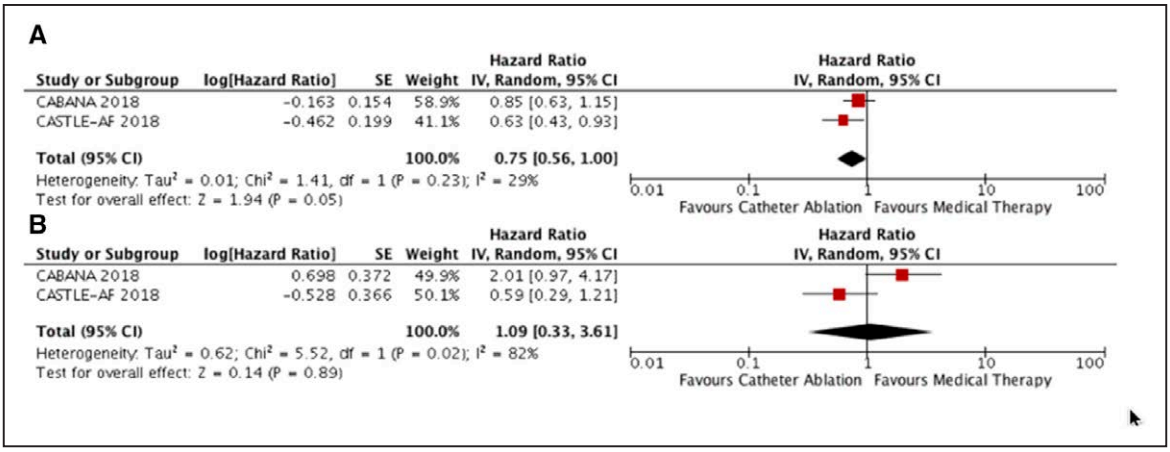

Figure 9. Forest plot showing composite outcome of death, stroke, major bleeding, cardiac hospitalization, and cardiac arrest with catheter ablation vs medical therapy.
A, Hypertension; (**B**) no hypertension. CABANA indicates Catheter Ablation Versus Antiarrhythmic Drug Therapy; and CASTLE-AF, Catheter Ablation for Atrial Fibrillation With Heart Failure.

slow. In a large ambulatory cardiology database from the United States, the predominant treatment offered to patients with AF and HFrEF who appeared to be good candidates for CA was rate control, followed by AAD (29%), and only 9% received CA.[63] We suggest that in light of our findings, CA should be offered to patients with AF and HFrEF early, especially if they are young (<65 years).

Limitations

Our study has a few limitations. Although these results were based on high-quality evidence from multiple RCTs with adequate follow-up and low risk of bias, most of the CA procedures in the included trials were performed in large centers by experienced operators, which may limit the generalizability of these findings. Individual patient data were not available to us, and we were limited by use of available summary data from published studies. Patients had variable background and comparison pharmacological therapies, different duration of AF before CA, and inconsistent follow-up durations, which had the potential to confound our results. However, there was no heterogeneity in the majority of our reported outcomes, suggesting consistency in the results of the included trials. Stratification of outcomes by age and sex in a nonrandom fashion between CA and MT had the potential to affect outcomes because of imbalanced baseline characteristics. However, the large sample size and the randomized study design in included studies likely balanced known and unknown confounders.

Conclusions

In patients with AF, CA is associated with all-cause mortality benefit compared with MT, that is driven by patients with AF and HFrEF. CA is safe and reduces cardiovascular hospitalizations and recurrences of atrial arrhythmias for different groups of patients with AF (paroxysmal and persistent AF). Men and patients <65 years of age appear to derive the highest benefit from CA.

ARTICLE INFORMATION

Received March 20, 2019; accepted June 11, 2019.
The Data Supplement is available at https://www.ahajournals.org/doi/suppl/10.1161/CIRCEP.119.007414.

Correspondence

Stavros Stavrakis, MD, PhD, University of Oklahoma Health Sciences Centre, 800 Stanton L. Young Blvd, AAT 5400, Oklahoma City, OK 73104. Email stavros-stavrakis@ouhsc.edu

Affiliations

Cardiovascular Disease Section, University of Oklahoma Health Sciences Center (Z.U.A.A., A.Y., S.S.). Internal Medicine, John H. Stroger, Jr. Hospital of Cook County, Chicago, IL (M.S.K.). Duke Clinical Research Institute, Durham, NC (S.M.A.-K.).

Disclosures

None.

REFERENCES

1. Thrall G, Lane D, Carroll D, Lip GY. Quality of life in patients with atrial fibrillation: a systematic review. *Am J Med*. 2006;119:448.e1–448.e19. doi: 10.1016/j.amjmed.2005.10.057
2. Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ, Gillum RF, Kim YH, McAnulty JH Jr, Zheng ZJ, Forouzanfar MH, Naghavi M, Mensah GA, Ezzati M, Murray CJ. Worldwide epidemiology of atrial fibrillation: a global burden of disease 2010 study. *Circulation*. 2014;129:837–847. doi: 10.1161/CIRCULATIONAHA.113.005119
3. Colilla S, Crow A, Petkun W, Singer DE, Simon T, Liu X. Estimates of current and future incidence and prevalence of atrial fibrillation in the U.S. adult population. *Am J Cardiol*. 2013;112:1142–1147. doi: 10.1016/j.amjcard.2013.05.063
4. Lloyd-Jones DM, Wang TJ, Leip EP, Larson MG, Levy D, Vasan RS, D'Agostino RB, Massaro JM, Beiser A, Wolf PA, Benjamin EJ. Lifetime risk for development of atrial fibrillation: the framingham heart study. *Circulation*. 2004;110:1042–1046. doi: 10.1161/01.CIR.0000140263.20897.42

5. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham heart study. *Circulation*. 1998;98:946–952. doi: 10.1161/01.cir.98.10.946
6. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham study. *Stroke*. 1991;22:983–988.
7. Wang TJ, Larson MG, Levy D, Vasan RS, Leip EP, Wolf PA, D'Agostino RB, Murabito JM, Kannel WB, Benjamin EJ. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham heart study. *Circulation*. 2003;107:2920–2925. doi: 10.1161/01.CIR.0000072767.89944.6E
8. Santhanakrishnan R, Wang N, Larson MG, Magnani JW, McManus DD, Lubitz SA, Ellinor PT, Cheng S, Vasan RS, Lee DS, Wang TJ, Levy D, Benjamin EJ, Ho JE. Atrial fibrillation begets heart failure and vice versa: temporal associations and differences in preserved versus reduced ejection fraction. *Circulation*. 2016;133:484–492. doi: 10.1161/CIRCULATIONAHA.115.018614
9. Rozen G, Hosseini SM, Kaadan MI, Biton Y, Heist EK, Vangel M, Mansour MC, Ruskin JN. Emergency department visits for atrial fibrillation in the united states: trends in admission rates and economic burden from 2007 to 2014. *J Am Heart Assoc*. 2018;7:e009024. doi: 10.1161/JAHA.118.009024
10. Steinberg BA, Kim S, Fonarow GC, Thomas L, Ansell J, Kowey PR, Mahaffey KW, Gersh BJ, Hylek E, Naccarelli G, Go AS, Reiffel J, Chang P, Peterson ED, Piccini JP. Drivers of hospitalization for patients with atrial fibrillation: results from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF). *Am Heart J*. 2014;167:735.e2–742.e2. doi: 10.1016/j.ahj.2014.02.003
11. Coyne KS, Paramore C, Grandy S, Mercader M, Reynolds M, Zimetbaum P. Assessing the direct costs of treating nonvalvular atrial fibrillation in the United States. *Value Health*. 2006;9:348–356. doi: 10.1111/j.1524-4733.2006.00124.x
12. Van Gelder IC, Hagens VE, Bosker HA, Kingma JH, Kamp O, Kingma T, Said SA, Darmanata JI, Timmermans AJ, Tijssen JG, Crijns HJ; Rate Control Versus Electrical Cardioversion for Persistent Atrial Fibrillation Study Group. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. *N Engl J Med*. 2002;347:1834–1840. doi: 10.1056/NEJMoa021375
13. de Denus S, Sanoski CA, Carlsson J, Opolski G, Spinler SA. Rate vs rhythm control in patients with atrial fibrillation: a meta-analysis. *Arch Intern Med*. 2005;165:258–262. doi: 10.1001/archinte.165.3.258
14. Wyse DG, Waldo AL, DiMarco JP, Domanski MJ, Rosenberg Y, Schron EB, Kellen JC, Greene HL, Mickel MC, Dalquist JE, Corley SD; Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) Investigators. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med*. 2002;347:1825–1833. doi: 10.1056/NEJMoa021328
15. Zarembski DG, Nolan PE Jr, Slack MK, Caruso AC. Treatment of resistant atrial fibrillation. A meta-analysis comparing amiodarone and flecainide. *Arch Intern Med*. 1995;155:1885–1891.
16. Israel CW, Grönefeld G, Ehrlich JR, Li YG, Hohnloser SH. Long-term risk of recurrent atrial fibrillation as documented by an implantable monitoring device: implications for optimal patient care. *J Am Coll Cardiol*. 2004;43:47–52. doi: 10.1016/j.jacc.2003.08.027
17. Falk RH. Is rate control or rhythm control preferable in patients with atrial fibrillation? rate control is preferable to rhythm control in the majority of patients with atrial fibrillation. *Circulation*. 2005;111:3141–3150; discussion 3157. doi: 10.1161/CIRCULATIONAHA.104.485565
18. Pappone C, Augello G, Sala S, Gugliotta F, Vicedomini G, Gulletta S, Paglino G, Mazzone P, Sora N, Greiss I, Santagostino A, LiVolsi L, Pappone N, Radinovic A, Manguso F, Santinelli V. A randomized trial of circumferential pulmonary vein ablation versus antiarrhythmic drug therapy in paroxysmal atrial fibrillation: the APAF study. *J Am Coll Cardiol*. 2006;48:2340–2347. doi: 10.1016/j.jacc.2006.08.037
19. Jaïs P, Cauchemez B, Macle L, Daoud E, Khairy P, Subbiah R, Hocini M, Extramiana F, Sacher F, Bordachar P, Klein G, Weerasooriya R, Clémenty J, Haïssaguerre M. Catheter ablation versus antiarrhythmic drugs for atrial fibrillation: the A4 study. *Circulation*. 2008;118:2498–2505. doi: 10.1161/CIRCULATIONAHA.108.772582
20. Wilber DJ, Pappone C, Neuzil P, De Paola A, Marchlinski F, Natale A, Macle L, Daoud EG, Calkins H, Hall B, Reddy V, Augello G, Reynolds MR, Vinekar C, Liu CY, Berry SM, Berry DA; ThermoCool AF Trial Investigators. Comparison of antiarrhythmic drug therapy and radiofrequency catheter ablation in patients with paroxysmal atrial fibrillation: a randomized controlled trial. *JAMA*. 2010;303:333–340. doi: 10.1001/jama.2009.2029
21. Stabile G, Bertaglia E, Senatore G, De Simone A, Zoppo F, Donnici G, Turco P, Pascotto P, Fazzari M, Vitale DF. Catheter ablation treatment in patients with drug-refractory atrial fibrillation: a prospective, multi-centre, randomized, controlled study (catheter ablation for the cure of atrial fibrillation study). *Eur Heart J*. 2006;27:216–221. doi: 10.1093/eurheartj/ehi583
22. Krittayaphong R, Raungrattanaamporn O, Bhuripanyo K, Sriratanasathavorn C, Pooranawattanakul S, Punlee K, Kangkagate C. A randomized clinical trial of the efficacy of radiofrequency catheter ablation and amiodarone in the treatment of symptomatic atrial fibrillation. *J Med Assoc Thai*. 2003;86(suppl 1):S8–S16.
23. Forleo GB, Mantica M, De Luca L, Leo R, Santini L, Panigada S, De Sanctis V, Pappalardo A, Laurenzi F, Avella A, Casella M, Dello Russo A, Romeo F, Pelargonio G, Tondo C. Catheter ablation of atrial fibrillation in patients with diabetes mellitus type 2: results from a randomized study comparing pulmonary vein isolation versus antiarrhythmic drug therapy. *J Cardiovasc Electrophysiol*. 2009;20:22–28. doi: 10.1111/j.1540-8167.2008.01275.x
24. Mont L, Bisbal F, Hernández-Madrid A, Pérez-Castellano N, Viñolas X, Arenal A, Arribas F, Fernández-Lozano I, Bodegas A, Cobos A, Matía R, Pérez-Villacastín J, Guerra JM, Ávila P, López-Gil M, Castro V, Arana JI, Brugada J; SARA Investigators. Catheter ablation vs. antiarrhythmic drug treatment of persistent atrial fibrillation: a multicentre, randomized, controlled trial (SARA study). *Eur Heart J*. 2014;35:501–507. doi: 10.1093/eurheartj/eht457
25. Prabhu S, Taylor AJ, Costello BT, Kaye DM, McLellan AJA, Voskoboinik A, Sugumar H, Lockwood SM, Stokes MB, Pathik B, Nalliah CJ, Wong GR, Azzopardi SM, Gutman SJ, Lee G, Layland J, Mariani JA, Ling LH, Kalman JM, Kistler PM. Catheter ablation versus medical rate control in atrial fibrillation and systolic dysfunction: the CAMERA-MRI study. *J Am Coll Cardiol*. 2017;70:1949–1961. doi: 10.1016/j.jacc.2017.08.041
26. Marrouche NF, Brachmann J, Andresen D, Siebels J, Boersma L, Jordaens L, Merkely B, Pokushalov E, Sanders P, Proff J, Schunkert H, Christ H, Vogt J, Bänsch D; CASTLE-AF Investigators. Catheter ablation for atrial fibrillation with heart failure. *N Engl J Med*. 2018;378:417–427. doi: 10.1056/NEJMoa1707855
27. Jones DG, Haldar SK, Hussain W, Sharma R, Francis DP, Rahman-Haley SL, McDonagh TA, Underwood SR, Markides V, Wong T. A randomized trial to assess catheter ablation versus rate control in the management of persistent atrial fibrillation in heart failure. *J Am Coll Cardiol*. 2013;61:1894–1903. doi: 10.1016/j.jacc.2013.01.069
28. Hunter RJ, Berriman TJ, Diab I, Kamdar R, Richmond L, Baker V, Goromonzi F, Sawhney V, Duncan E, Page SP, Ullah W, Unsworth B, Mayet J, Dhinoja M, Earley MJ, Sporton S, Schilling RJ. A randomized controlled trial of catheter ablation versus medical treatment of atrial fibrillation in heart failure (the CAMTAF trial). *Circ Arrhythm Electrophysiol*. 2014;7:31–38. doi: 10.1161/CIRCEP.113.000806
29. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW; ACC/AHA Task Force Members. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. *Circulation*. 2014;130:2071–2104. doi: 10.1161/CIR.0000000000000040
30. Khan SU, Rahman H, Talluri S, Kaluski E. The clinical benefits and mortality reduction associated with catheter ablation in subjects with atrial fibrillation: a systematic review and meta-analysis. *JACC Clin Electrophysiol*. 2018;4:626–635. doi: 10.1016/j.jacep.2018.03.003
31. Packer DL, Mark DB, Robb RA, Monahan KH, Bahnson TD, Poole JE, Noseworthy PA, Rosenberg YD, Jeffries N, Mitchell LB, Flaker GC, Pokushalov E, Romanov A, Bunch TJ, Noelker G, Ardashev A, Revishvili A, Wilber DJ, Cappato R, Kuck KH, Hindricks G, Davies DW, Kowey PR, Naccarelli GV, Reiffel JA, Piccini JP, Silverstein AP, Al-Khalidi HR, Lee KL; CABANA Investigators. Effect of catheter ablation vs antiarrhythmic drug therapy on mortality, stroke, bleeding, and cardiac arrest among patients with atrial fibrillation: the CABANA randomized clinical trial. *JAMA*. 2019;321:1261–1274. doi: 10.1001/jama.2019.0693
32. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med*. 2009;151:264,W64–269, W64. doi: 10.7326/0003-4819-151-4-200908180-00135
33. Higgins JPT, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions,* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. https://training.cochrane.org/handbook.
34. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA; Cochrane Bias Methods Group;

Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928. doi: 10.1136/bmj.d5928
35. Packer DL. Catheter ablation vs. antiarrhythmic drug therapy for atrial fibrillation: the results of the CABANA multicenter international randomized clinical trial. In: Heart Rhythm Society Scientific Session; May 10, 2018; Boston, MA.
36. DerSimonian R, Kacker R. Random-effects model for meta-analysis of clinical trials: an update. *Contemp Clin Trials*. 2007;28:105–114. doi: 10.1016/j.cct.2006.04.004
37. Huedo-Medina TB, Sánchez-Meca J, Marín-Martínez F, Botella J. Assessing heterogeneity in meta-analysis: Q statistic or I2 index? *Psychol Methods*. 2006;11:193–206. doi: 10.1037/1082-989X.11.2.193
38. Di Biase L, Mohanty P, Mohanty S, Santangeli P, Trivedi C, Lakkireddy D, Reddy M, Jais P, Themistoclakis S, Dello Russo A, Casella M, Pelargonio G, Narducci ML, Schweikert R, Neuzil P, Sanchez J, Horton R, Beheiry S, Hongo R, Hao S, Rossillo A, Forleo G, Tondo C, Burkhardt JD, Haissaguerre M, Natale A. Ablation versus amiodarone for treatment of persistent atrial fibrillation in patients with congestive heart failure and an implanted device: results from the AATAC multicenter randomized trial. *Circulation*. 2016;133:1637–1644. doi: 10.1161/CIRCULATIONAHA.115.019406
39. Morillo CA, Verma A, Connolly SJ, Kuck KH, Nair GM, Champagne J, Sterns LD, Beresh H, Healey JS, Natale A; RAAFT-2 Investigators. Radiofrequency Ablation vs Antiarrhythmic Drugs as First-Line Treatment of Paroxysmal Atrial Fibrillation (RAAFT-2): a randomized trial. *JAMA*. 2014;311:692–700. doi: 10.1001/jama.2014.467
40. Cosedis Nielsen J, Johannessen A, Raatikainen P, Hindricks G, Walfridsson H, Kongstad O, Pehrson S, Englund A, Hartikainen J, Mortensen LS, Hansen PS. Radiofrequency ablation as initial therapy in paroxysmal atrial fibrillation. *N Engl J Med*. 2012;367:1587–1595. doi: 10.1056/NEJMoa1113566
41. MacDonald MR, Connelly DT, Hawkins NM, Steedman T, Payne J, Shaw M, Denvir M, Bhagra S, Small S, Martin W, McMurray JJ, Petrie MC. Radiofrequency ablation for persistent atrial fibrillation in patients with advanced heart failure and severe left ventricular systolic dysfunction: a randomised controlled trial. *Heart*. 2011;97:740–747. doi: 10.1136/hrt.2010.207340
42. Oral H, Pappone C, Chugh A, Good E, Bogun F, Pelosi F Jr, Bates ER, Lehmann MH, Vicedomini G, Augello G, Agricola E, Sala S, Santinelli V, Morady F. Circumferential pulmonary-vein ablation for chronic atrial fibrillation. *N Engl J Med*. 2006;354:934–941. doi: 10.1056/NEJMoa050955
43. Wazni OM, Marrouche NF, Martin DO, Verma A, Bhargava M, Saliba W, Bash D, Schweikert R, Brachmann J, Gunther J, Gutleben K, Pisano E, Potenza D, Fanelli R, Raviele A, Themistoclakis S, Rossillo A, Bonso A, Natale A. Radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of symptomatic atrial fibrillation: a randomized trial. *JAMA*. 2005;293:2634–2640. doi: 10.1001/jama.293.21.2634
44. Al Halabi S, Qintar M, Hussein A, Alraies MC, Jones DG, Wong T, MacDonald MR, Petrie MC, Cantillon D, Tarakji KG, Kanj M, Bhargava M, Varma N, Baranowski B, Wilkoff BL, Wazni O, Callahan T, Saliba W, Chung MK. Catheter ablation for atrial fibrillation in heart failure patients: a meta-analysis of randomized controlled trials. *JACC Clin Electrophysiol*. 2015;1:200–209. doi: 10.1016/j.jacep.2015.02.018
45. Kieny JR, Sacrez A, Facello A, Arbogast R, Bareiss P, Roul G, Demangeat JL, Brunot B, Constantinesco A. Increase in radionuclide left ventricular ejection fraction after cardioversion of chronic atrial fibrillation in idiopathic dilated cardiomyopathy. *Eur Heart J*. 1992;13:1290–1295. doi: 10.1093/oxfordjournals.eurheartj.a060351
46. Redfield MM, Kay GN, Jenkins LS, Mianulli M, Jensen DN, Ellenbogen KA. Tachycardia-related cardiomyopathy: a common cause of ventricular dysfunction in patients with atrial fibrillation referred for atrioventricular ablation. *Mayo Clin Proc*. 2000;75:790–795. doi: 10.4065/75.8.790
47. Packer DL, Mark DB, Robb RA, Monahan KH, Bahnson TD, Moretz K, Poole JE, Mascette A, Rosenberg Y, Jeffries N, Al-Khalidi HR, Lee KL; CABANA Investigators. Catheter ablation versus antiarrhythmic arug therapy for atrial fibrillation (CABANA) trial: study rationale and design. *Am Heart J*. 2018;199:192–199. doi: 10.1016/j.ahj.2018.02.015
48. Nisar MU, Munir MB, Sharbaugh MS, Thoma FW, Althouse AD, Saba S. Trends in atrial fibrillation hospitalizations in the united states: a report using data from the National Hospital Discharge Survey. *Indian Pacing Electrophysiol J*. 2018;18:6–12. doi: 10.1016/j.ipej.2017.07.010
49. Mohanty S, Santangeli P, Mohanty P, Di Biase L, Holcomb S, Trivedi C, Bai R, Burkhardt D, Hongo R, Hao S, Beheiry S, Santoro F, Forleo G, Gallinghouse JG, Horton R, Sanchez JE, Bailey S, Hranitzky PM, Zagrodzky J, Natale A. Catheter ablation of asymptomatic longstanding persistent atrial fibrillation: impact on quality of life, exercise performance, arrhythmia perception, and arrhythmia-free survival. *J Cardiovasc Electrophysiol*. 2014;25:1057–1064. doi: 10.1111/jce.12467
50. Moser JM, Willems S, Andresen D, Brachmann J, Eckardt L, Hoffmann E, Kuck KH, Lewalter T, Schumacher B, Spitzer SG, Hochadel M, Senges J, Hoffmann BA. Complication rates of catheter ablation of atrial fibrillation in patients aged ≥75 years versus <75 years-results from the german ablation registry. *J Cardiovasc Electrophysiol*. 2017;28:258–265. doi: 10.1111/jce.13142
51. Nademanee K, Amnueypol M, Lee F, Drew CM, Suwannasri W, Schwab MC, Veerakul G. Benefits and risks of catheter ablation in elderly patients with atrial fibrillation. *Heart Rhythm*. 2015;12:44–51. doi: 10.1016/j.hrthm.2014.09.049
52. Lioni L, Letsas KP, Efremidis M, Vlachos K, Giannopoulos G, Kareliotis V, Deftereos S, Sideris A. Catheter ablation of atrial fibrillation in the elderly. *J Geriatr Cardiol*. 2014;11:291–295. doi: 10.11909/j.issn.1671-5411.2014.04.003
53. Metzner I, Wissner E, Tilz RR, Rillig A, Mathew S, Schmidt B, Chun J, Wohlmuth P, Deiss S, Lemes C, Maurer T, Fink T, Heeger C, Ouyang F, Kuck KH, Metzner A. Ablation of atrial fibrillation in patients ≥75 years: long-term clinical outcome and safety. *Europace*. 2016;18:543–549. doi: 10.1093/europace/euv229
54. Spragg DD, Dalal D, Cheema A, Scherr D, Chilukuri K, Cheng A, Henrikson CA, Marine JE, Berger RD, Dong J, Calkins H. Complications of catheter ablation for atrial fibrillation: incidence and predictors. *J Cardiovasc Electrophysiol*. 2008;19:627–631. doi: 10.1111/j.1540-8167.2008.01181.x
55. Kaiser DW, Fan J, Schmitt S, Than CT, Ullal AJ, Piccini JP, Heidenreich PA, Turakhia MP. Gender differences in clinical outcomes after catheter ablation of atrial fibrillation. *JACC Clin Electrophysiol*. 2016;2:703–710. doi: 10.1016/j.jacep.2016.04.014
56. Forleo GB, Tondo C, De Luca L, Dello Russo A, Casella M, De Sanctis V, Clementi F, Fagundes RL, Leo R, Romeo F, Mantica M. Gender-related differences in catheter ablation of atrial fibrillation. *Europace*. 2007;9:613–620. doi: 10.1093/europace/eum144
57. Marrouche NF. Efficacy of delayed enhancement MRI-guided ablation vs conventional catheter ablation of atrial fibrillation (DECAAFII). 2016–2020. https://clinicaltrials.gov/ct2/show/NCT02529319.
58. Black-Maier E, Ren X, Steinberg BA, Green CL, Barnett AS, Rosa NS, Al-Khatib SM, Atwater BD, Daubert JP, Frazier-Mills C, Grant AO, Hegland DD, Jackson KP, Jackson LR, Koontz JI, Lewis RK, Sun AY, Thomas KL, Bahnson TD, Piccini JP. Catheter ablation of atrial fibrillation in patients with heart failure and preserved ejection fraction. *Heart Rhythm*. 2018;15:651–657. doi: 10.1016/j.hrthm.2017.12.001
59. Machino-Ohtsuka T, Seo Y, Ishizu T, Sugano A, Atsumi A, Yamamoto M, Kawamura R, Machino T, Kuroki K, Yamasaki H, Igarashi M, Sekiguchi Y, Aonuma K. Efficacy, safety, and outcomes of catheter ablation of atrial fibrillation in patients with heart failure with preserved ejection fraction. *J Am Coll Cardiol*. 2013;62:1857–1865. doi: 10.1016/j.jacc.2013.07.020
60. Chen LY, Chung MK, Allen LA, Ezekowitz M, Furie KL, McCabe P, Noseworthy PA, Perez MV, Turakhia MP; American Heart Association Council on Clinical Cardiology; Council on Cardiovascular and Stroke Nursing; Council on Quality of Care and Outcomes Research; and Stroke Council. Atrial Fibrillation burden: moving beyond atrial fibrillation as a binary entity: a scientific statement from the American Heart Association. *Circulation*. 2018;137:e623–e644. doi: 10.1161/CIR.0000000000000568
61. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P; ESC Scientific Document Group. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J*. 2016;37:2893–2962. doi: 10.1093/eurheartj/ehw210
62. Fiala M, Wichterle D, Bulková V, Sknouril L, Nevralová R, Toman O, Dorda M, Januska J, Spinar J. A prospective evaluation of haemodynamics, functional status, and quality of life after radiofrequency catheter ablation of long-standing persistent atrial fibrillation. *Europace*. 2014;16:15–25. doi: 10.1093/europace/eut161
63. Mathew JS, Marzec LN, Kennedy KF, Jones PG, Varosy PD, Masoudi FA, Maddox TM, Allen LA. Atrial fibrillation in heart failure US ambulatory cardiology practices and the potential for uptake of catheter ablation: an National Cardiovascular Data Registry (NCDR((R)) Research to Practice (R2P) project. *J Am Heart Assoc*. 2017;6:e005273. doi: 10.1161/JAHA.116.005273