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Review

Catheter Ablation of Atrial Fibrillation in Patients With Heart Failure

A Meta-analysis of Randomized Controlled Trials

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Background: Atrial fibrillation (AF) and heart failure (HF) frequently coexist and are associated with increased morbidity and mortality risk.

Purpose: To compare benefits and harms between catheter ablation and drug therapy in adult patients with AF and HF.

Data Sources: ClinicalTrials.gov, PubMed, Web of Science (Clarivate Analytics), EBSCO Information Services, Cochrane Central Register of Controlled Trials, Google Scholar, and various scientific conference sessions from 1 January 2005 to 1 October 2018.

Study Selection: Randomized controlled trials (RCTs) published in English that had at least 6 months of follow-up and compared clinical outcomes of catheter ablation versus drug therapy in adults with AF and HF.

Data Extraction: 2 investigators independently extracted data and assessed study quality.

Data Synthesis: 6 RCTs involving 775 patients met inclusion criteria. Compared with drug therapy, AF ablation reduced all-cause mortality (9.0% vs. 17.6%; risk ratio [RR], 0.52 [95% CI, 0.33 to 0.81]) and HF hospitalizations (16.4% vs. 27.6%; RR, 0.60 [CI, 0.39 to 0.93]). Ablation improved left ventricular ejection fraction (LVEF) (mean difference, 6.95% [CI, 3.0% to 10.9%]), 6-minute walk test distance (mean difference, 20.93 m [CI, 5.91 to 35.95 m]), peak oxygen consumption (Vo_2max) (mean difference, 3.17 mL/kg per minute [CI, 1.26 to 5.07 mL/kg per minute]), and quality of life (mean difference in Minnesota Living with Heart Failure Questionnaire score, −9.02 points [CI, −19.75 to 1.71 points]). Serious adverse events were more common in the ablation groups, although differences between the ablation and drug therapy groups were not statistically significant (7.2% vs. 3.8%; RR, 1.68 [CI, 0.58 to 4.85]).

Limitation: Results driven primarily by 1 clinical trial, possible patient selection bias in the ablation group, lack of patient-level data, open-label trial designs, and heterogeneous follow-up length among trials.

Conclusion: Catheter ablation was superior to conventional drug therapy in improving all-cause mortality, HF hospitalizations, LVEF, 6-minute walk test distance, Vo_2max, and quality of life, with no statistically significant increase in serious adverse events.

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Atrial fibrillation (AF) is associated with thromboembolic stroke, systemic embolism, and decompensated heart failure (HF) requiring hospitalization, thereby imposing a substantial financial burden on the health care industry (1–3). The prevalence of AF in HF increases with HF severity: 5% in New York Heart Association (NYHA) class I to 50% in class IV HF (4). Together, AF and HF lead to atrial structural and electrical remodeling and progression of paroxysmal to persistent AF, perpetuating a vicious cycle of impaired left ventricular (LV) filling, contractility, and cardiac output (5).

Catheter ablation is an established therapeutic strategy for symptomatic, drug-refractory AF (6, 7). However, current guidelines support AF ablation with caution (class IIb recommendation) in patients with LV systolic dysfunction and HF with reduced ejection fraction (HF_REF) (6). Recent randomized controlled trials (RCTs) reported clinical improvements in mortality, HF hospitalizations, LV ejection fraction (LVEF), and quality of life in patients with HF_REF who have AF ablation (8–14). We performed a systematic review and meta-analysis of RCTs comparing the safety and efficacy of AF ablation versus drug therapy in patients with HF_REF.

Methods

We developed (on 12 September 2017) and followed a protocol for this systematic review and meta-analysis (**Supplement**, available at Annals.org).

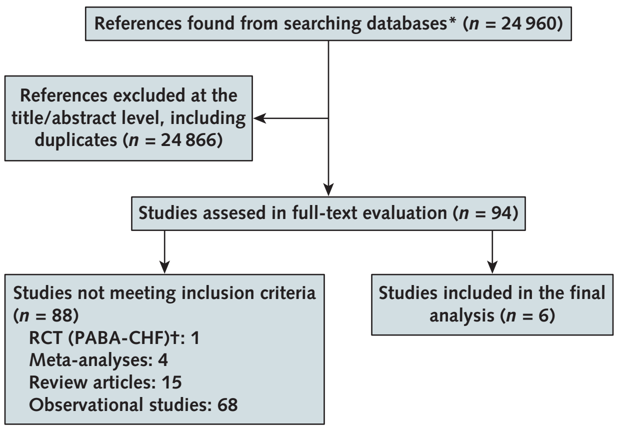
Data Sources and Searches

We searched (without language restrictions) ClinicalTrials.gov, PubMed, Web of Science (Clarivate Analytics), EBSCO Information Services, Cochrane Central Register of Controlled Trials, Google Scholar, and various major scientific conference sessions (held at American Heart Association, American College of Cardiology, European Society of Cardiology Congress, Heart Rhythm Society, and Cardiostim meetings) for abstracts and articles published between 1 January 2005 and 1 October 2018. Two investigators (M.K.T. and J.G.) independently performed searches including the following terms: *atrial fibrillation*, *catheter ablation*, *heart failure*, *left ventricular ejection fraction*, *hospital-*

See also:

Web-Only
Supplement

Figure 1. Evidence search and selection.



PABA-CHF = Pulmonary Vein Antrum Isolation vs. AV Node Ablation With Biventricular Pacing for Treatment of Atrial Fibrillation in Patients With Congestive Heart Failure; RCT = randomized controlled trial.
* ClinicalTrials.gov, PubMed, Web of Science (Clarivate Analytics), EBSCO Information Services, Cochrane Central Register of Controlled Trials, Google Scholar, and various scientific conference sessions from 1 January 2005 to 1 October 2018.
† PABA-CHF was excluded because it did not meet the exclusion criteria.

izations, *functional capacity*, *peak oxygen consumption*, and *quality of life*. Details regarding search strategies and filters are provided in the Supplement.

Study Selection and Outcomes

Two investigators (M.K.T. and J.G.) independently screened all titles and full-text versions of selected relevant RCTs to identify those that had at least 6 months of follow-up, included adults aged 18 years or older, compared AF ablation with standard drug therapy (rate or rhythm control medications) in patients with HF, and reported 1 or more clinical outcomes. Retrospective studies, studies with no comparative group, nonrandomized trials, case reports, editorials, reviews, expert opinion, and studies published in a language other than English were excluded.

Main outcomes of interest were all-cause mortality and HF hospitalization; change in LVEF; distance on the 6-minute walk test; peak oxygen consumption (V_{O_2}max); quality of life, assessed by the Minnesota Living with Heart Failure Questionnaire (MLHFQ); and AF recurrence. Harm outcomes were serious adverse events, including access site complications (femoral hematoma or bleeding, pseudoaneurysm, and groin infection), pericardial complications (with and without tamponade), HF, pulmonary vein stenosis, intracranial bleeding, and systemic thromboembolic events.

Data Extraction and Quality Appraisal

Two independent investigators (M.K.T. and J.G.) extracted data from the individual studies by using a standardized protocol and data extraction form (Supplement). Together, these investigators assessed the quality of individual studies by using the Cochrane Risk of Bias Tool (15).

Data Synthesis

Because previous studies found no differences in mortality or HF hospitalizations between rate and rhythm control drug therapies, we aggregated both approaches in the standard therapy group. We pooled outcomes of studies regardless of the follow-up length in each trial. We judged this strategy to be appropriate despite differences in study follow-up, because the effect of ablation diminishes over time.

Risk ratios (RRs) were used to pool differences in binary events, and mean differences were used to pool differences in continuous outcomes. We pooled within-group recurrence rates for the trials reporting AF-free survival and reported summaries on the basis of Freeman–Tukey double arcsine transformation (16). For binary outcomes and studies reporting a single proportion, an overall estimate with 95% CI was calculated by using a random-effects model with the Paule–Mandel method for estimating between-study variance τ^2. A random-effects model with the restricted maximum likelihood τ^2 estimator was used to calculate a pooled estimate for studies with continuous outcome data (17).

Because fewer than 10 studies were analyzed, the Hartung–Knapp small-sample adjustment was used (18). Treatment-group continuity correction was performed for studies with zero cell frequency. Between-study heterogeneity was assessed by using the τ^2 and I^2 statistics.

Sensitivity analyses were performed to assess the contribution of each study to the pooled estimate. Further sensitivity analysis included the PABA-CHF (Pulmonary Vein Antrum Isolation vs. AV Node Ablation With Biventricular Pacing for Treatment of Atrial Fibrillation in Patients With Congestive Heart Failure) study, which compared catheter ablation versus AV node ablation and cardiac resynchronization therapy in patients with AF and HF (13). The meta packages metabin, metacont, and metaprop were used to pool RRs, mean differences, and recurrence rates, respectively. All statistical analyses were performed with R, version 3.5.1 (The R Foundation for Statistical Computing).

Role of the Funding Source

The study received no funding.

RESULTS

Overview of Trials

Among 24 960 records identified, 6 trials met the inclusion criteria (Figure 1 and Supplement Figures 1 to 7, available at Annals.org) (8–12, 14). An additional trial, PABA-CHF, compared ablation with rate control, but the latter was achieved with AV junction ablation plus biventricular pacing, not medications; this trial was included only in the sensitivity analysis (13). We judged trials as having low risk of selection and attrition biases, as well as moderate risks of performance and detection biases due to open-label designs (Supplement Table 1, available at Annals.org). We judged risk of reporting bias as low for mortality and HF hospitalization outcomes and moderate for other outcomes.

Table. Study Characteristics

Characteristic	PABA-CHF, 2008 (13)*	MacDonald et al, 2011 (12)	ARC-HF, 2013 (9)
Funding source	Ministry of Education, Youth, and Sports of the Czech Republic and St. Jude Medical	Chief Scientist Office of Scotland	NIHR Cardiovascular Biomedical Research Unit at the Royal Brompton and Harefield National Health Service Foundation Trust and Imperial College London
Mean age (SE), *y*†			
Ablation	60 ± 8	62 ± 6.7	64 ± 10
Drug therapy	61 ± 8	64.4 ± 8.2	62 ± 9
Patients, *n*			
Screened	177	366	101
Enrolled	81	41	52
Randomization	Ablation vs. AVJ ablation + CRT	Ablation vs. medical rate control	Ablation vs. medical rate control
Period of pharmacologic optimization	NR	3 mo	4-wk interval
Blinding adjudication	Unblinded to randomization and treatment	Image analysis done by blinded operators	Blinded to randomization
Primary end point	Change in LVEF, 6-min walk test distance, and MLHFQ score	Change in LVEF	Change in V_{O_2}max
Crossover, *n (%)*			
To ablation	None	None	None
To drug therapy	None	None	None
Total follow-up, *mo*	6	6	12
Types of medication, %			
Catheter ablation vs. ACEI/ARB			
Catheter ablation	NR	95	96
ACEI/ARB	NR	95	100
Catheter ablation vs. aldosterone antagonist			
Catheter ablation	NR	45	50
Aldosterone antagonist	NR	16	23
Catheter ablation vs. β-blockers			
Catheter ablation	NR	82	NR
β-Blockers	NR	95	NR
Catheter ablation vs. digoxin			
Catheter ablation	NR	55	62
Digoxin	NR	47	46
Catheter ablation vs. antiarrhythmics			
Catheter ablation	NR	NR	12
Antiarrhythmics	NR	NR	12
HF therapy, %‡			
Ablation	NA	74.2	79.4
Drug therapy	NA	68.4	72
Persistent AF, %	48	100	100
Codiagnosis of AF and HF, %	NA	NA	NA
Mean time since AF diagnosis (SE), *mo*	47.4 ± 31.2	54	51 ± 57
NYHA class	II and III	II and III	II and III
Nonischemic cardiomyopathy, %	29	51	67
Baseline LVEF, %	28	17.8	23
ICD/CRT, %	49.3	NA	27
Mean baseline 6-min walk test distance (SE), *m*	275 ± 49	334.6 ± 121.7	413.5 ± 93.5
Mean baseline V_{O_2}max (SE), *mL/kg per min*	NA	NA	17.25 ± 5.00
Mean baseline MLHFQ score (SE)	89.0 ± 11.5	57.5 ± 21.1	45.5 ± 22.0
Frequency of monitoring, *mo*	2, 3, and 6	3 and 6	3, 6, and 12
Monitoring method	ILR	24-h Holter	48-h Holter, CIED
Ablation strategy	PVI ± additional ablation	PVI ± additional ablation	PVI ± additional ablation
Ablation success with 1 procedure, %	68	40	68
Resolution of AF on follow-up, %			
Catheter ablation	88	50	88
Drug therapy	0	0	0

AATAC = Ablation versus Amiodarone for Treatment of Atrial Fibrillation in Patients with Congestive Heart Failure and an Implanted ICD; ACEI = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin-receptor blocker; ARC-HF = A Randomized Trial to Assess Catheter Ablation Versus Rate Control in the Management of Persistent Atrial Fibrillation in Chronic Heart Failure; AVJ = atrioventricular node junction; 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 versus Standard Conventional Therapy in Patients with Left Ventricular Dysfunction and Atrial Fibrillation; CIED = cardiac implantable electronic device; CRT = cardiac resynchronization therapy; HF = heart failure; ICD = implantable cardioverter-defibrillator; ILR = implantable loop recorder; IQR = interquartile range; LVEF = left ventricular ejection fraction; MLHFQ = Minnesota Living with Heart Failure Questionnaire; NA = not available; NIHR = National Institute for Health Research; NR = not reported; NYHA = New York Heart Association; PABA-CHF = Pulmonary Vein Antrum Isolation vs. AV Node Ablation With Biventricular Pacing for Treatment of Atrial Fibrillation in Patients With Congestive Heart Failure; PVI = pulmonary vein isolation; V_{O_2}max = peak oxygen consumption.
* This study was excluded from the primary pooled analysis.
† Unless otherwise indicated.
‡ Includes ACEIs/ARBs, β-blockers, and aldosterone antagonists.

Table–Continued

	CAMTAF, 2014 (11)	AATAC, 2016 (8)	CAMERA-MRI, 2017 (10)	CASTLE-AF, 2017 (14)
	British Heart Foundation grant	None	Investigator-initiated study	Biotronik
	55 ± 12	62 ± 10	69 ± 11	Median (IQR): 64 (56–71)
	60 ± 10	60 ± 11	62 ± 9.4	Median (IQR): 64 (56–73.5)
	390	331	301	3013
	50	203	66	363
	Ablation vs. medical rate control	Ablation vs. amiodarone	Ablation vs. medical rate control	Ablation vs. medical rhythm and rate control
	3 mo	3 mo	4 wk	5 wk
	Unblinded to randomization, blinded for measurement of LVEF	LVEF measurement was blinded	Blinded to randomization, unblinded to ablation procedure	Unblinded to randomization and treatment
	Change in LVEF	AF recurrence	Change in LVEF	All-cause death or HF hospitalization
	None	None	3 (4.5)	18 (9.8)
	None	None	None	28 (15.6)
	6–12	24	6	60
	NR	92	94	94
	NR	88	94	91
	NR	45	11	NR
	NR	50	16	NR
	NR	76	29	93
	NR	80	28	95
	NR	NR	NR	18
	NR	NR	NR	31
	NR	NR	8	32
	NR	NR	8	31
	NA	71.2	78	93.4
	NA	73	78	92
	100	100	100	67.5
	56	NA	68	NA
	NA	8.2 ± 3.6	NA	NA
	II and III	II and III	II, III, and IV	I–IV
	74	38	NA	53
	33	29	35	32
	NA	100	NA	100
	NA	349 ± 120	490 ± 139	NA
	20.8 ± 13.0	NA	NA	NA
	44.4 ± 89.0	51 ± 25	NA	NA
	1, 3, and 6	3, 6, 12, and 24	NA	3, 6, 12, 24, 36, 48, and 60
	48-h Holter	CIED	ILR	CIED
	PVI ± additional ablation	PVI ± additional ablation	PVI ± additional ablation	PVI ± additional ablation
	38	NA	56	NA
	81	70	NA	63.1
	0	34	0	21.7

The **Table** summarizes the study characteristics, and **Supplement Table 2** (available at Annals.org) shows each trial's inclusion and exclusion criteria. The 6 trials enrolled 775 patients; 388 were randomly assigned to the AF ablation group and 387 to the standard therapy group. The mean age of patients in the trials ranged from 55 to 64 years. Ischemic cardiomyopathy was the predominant cause of HF. Five trials included patients with persistent AF (8–12). In CASTLE-AF (Catheter Ablation versus Standard Conventional Therapy in Patients with Left Ventricular Dysfunction and Atrial Fibrillation), 52% of patients had paroxysmal AF (14). The mean duration of persistent AF was longer than 12 months in all trials except AATAC (Ablation versus Amiodarone for Treatment of Atrial Fibrillation in Patients with Congestive Heart Failure and an Implanted ICD), in which it was 8.2 ± 3.6 months. The mean LVEF among the study populations was 28.3%. Four trials included patients with NYHA class II to III HF; CAMERA-MRI (Catheter Ablation Versus Medical Rate Control in Atrial Fibrillation and Systolic Dysfunction) and CASTLE-AF also included a minority of patients (1.3%) with NYHA class IV HF. Study follow-up ranged from 6 to 60 months.

Radiofrequency ablation catheters were used in all trials. Pulmonary vein isolation was the key ablation strategy in all studies, but in most patients, further ablation was done outside the pulmonary veins. In 4 trials, standard drug therapy consisted of rate control. Rhythm control with amiodarone was used exclusively in the AATAC trial, whereas CASTLE-AF used rate control in two thirds and rhythm control in one third of the cohort; most patients (approximately 90%) in the latter group received amiodarone.

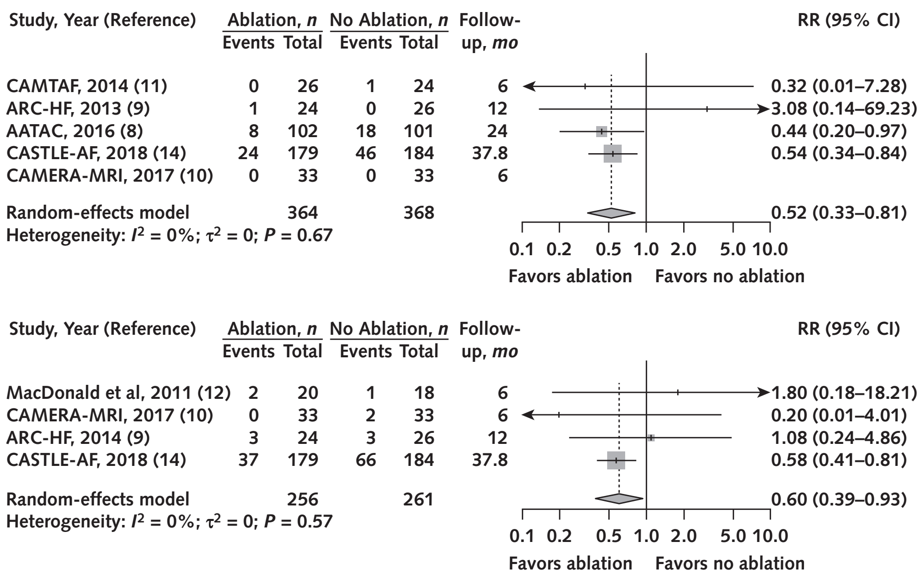
Outcomes

All-cause mortality and HF hospitalization data were available in 5 and 4 trials, respectively. Compared with standard drug therapy, AF ablation was associated with a greater reduction in all-cause mortality (9.0% vs. 17.6%; RR, 0.52 [95% CI, 0.33 to 0.81]) and HF hospitalizations (16.4% vs. 27.6%; RR, 0.60 [CI, 0.39 to 0.93]) (**Figure 2**). No statistically significant heterogeneity was observed (I^2 = 0%).

Changes in LVEF were assessed with echocardiography in 4 trials, cardiac magnetic resonance imaging in the study by MacDonald and colleagues (12), and both cardiac magnetic resonance imaging and echocardiography in CAMERA-MRI (10). Compared with the drug therapy groups, the AF ablation groups had a greater increase in LVEF (mean difference, 6.95% [CI, 3.0% to 10.9%]) (**Figure 3**, *top*). Although significant heterogeneity (I^2 = 94%) was observed, the improvement in LVEF with catheter ablation was observed across all trials.

Six-minute walk test results, available in 5 trials, showed improvements in the ablation groups relative to the standard therapy groups (mean difference, 20.93 m [CI, 5.91 to 35.95 m]) (**Figure 3**, *bottom*). The 2 trials with $\dot{V}O_2$max data showed improved values with ablation compared with standard therapy (mean difference, 3.17 mL/kg per minute [CI, 1.26 to 5.07 mL/kg per minute]) (**Figure 4**, *top*).

Figure 2. Forest plot of the decrease in all-cause mortality and HF hospitalization with catheter ablation compared with medical treatment for atrial fibrillation.

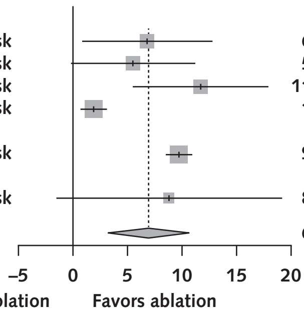


AATAC = Ablation versus Amiodarone for Treatment of Atrial Fibrillation in Patients with Congestive Heart Failure and an Implanted ICD; ARC-HF = A Randomized Trial to Assess Catheter Ablation Versus Rate Control in the Management of Persistent Atrial Fibrillation in Chronic Heart Failure; CAMERA-MRI = 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 versus Standard Conventional Therapy in Patients with Left Ventricular Dysfunction and Atrial Fibrillation; HF = heart failure; RR = risk ratio. **Top.** All-cause mortality. **Bottom.** HF hospitalization.

Figure 3. Forest plot of the improvement in LVEF and distance on the 6-minute walk test with catheter ablation versus medical treatment.

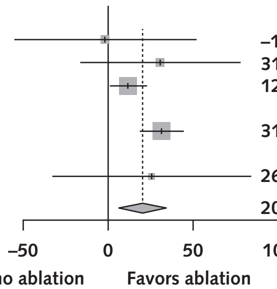
Study, Year (Reference)	Ablation Total, *n*	Ablation Mean, *n*	Ablation SD	No Ablation Total, *n*	No Ablation Mean, *n*	No Ablation SD	Comparison	RBA	Mean Difference (95% CI)
MacDonald, 2011 (12)	20	8.2	12.0	18	1.4	5.9	Ablation vs. rate control	Low risk	6.80 (0.88 to 12.72)
ARC-HF, 2013 (9)	24	10.9	11.5	26	5.4	8.5	Ablation vs. rate control	Low risk	5.50 (−0.14 to 11.14)
CAMTAF, 2014 (11)	26	8.1	12.5	24	−3.6	9.7	Ablation vs. rate control	Low risk	11.70 (5.52 to 17.88)
AATAC, 2016 (8)	102	8.1	4.0	101	6.2	5.0	Ablation vs. rate/rhythm control	Low risk	1.90 (0.65 to 3.15)
CASTLE-AF, 2018 (14)	51	8.7	1.9	37	−1.0	3.1	Ablation vs. rate/rhythm control	Low risk	9.70 (8.57 to 10.83)
CAMERA-MRI, 2017 (10)	33	17.7	10.8	33	8.9	v28.2	Ablation vs. rate control	Low risk	8.80 (−1.51 to 19.11)
Random-effects model	256			239					6.95 (3.00 to 10.90)

Heterogeneity: $I^2 = 94\%$; $\tau^2 = 12.1207$; $P < 0.01$



Study, Year (Reference)	Ablation Total, *n*	Ablation Mean, *n*	Ablation SD	No Ablation Total, *n*	No Ablation Mean, *n*	No Ablation SD	Comparison	RBA	Mean Difference (95% CI)
MacDonald, 2011 (12)	17	20.1	76.5	15	21.4	77.4	Ablation vs. rate control	Low risk	−1.30 (−54.75 to 52.15)
ARC-HF, 2013 (9)	26	21.0	103.7	26	−10.0	65.2	Ablation vs. rate control	Low risk	31.00 (−16.08 to 78.08)
AATAC, 2016 (8)	102	22.0	41.0	101	10.0	37.0	Ablation vs. rate/rhythm control	Low risk	12.00 (1.26 to 22.74)
CASTLE-AF, 2018 (14)	50	−6.9	26.7	35	−38.5	31.3	Ablation vs. rate/rhythm control	Low risk	31.60 (18.86 to 44.34)
CAMERA-MRI, 2017 (10)	33	55.0	114.5	33	29.0	125.5	Ablation vs. rate control	Low risk	26.00 (−31.96 to 83.96)
Random-effects model	228			210					20.93 (5.91 to 35.95)

Heterogeneity: $I^2 = 35\%$; $\tau^2 = 90.6227$; $P = 0.19$



AATAC = Ablation versus Amiodarone for Treatment of Atrial Fibrillation in Patients with Congestive Heart Failure and an Implanted ICD; ARC-HF = A Randomized Trial to Assess Catheter Ablation Versus Rate Control in the Management of Persistent Atrial Fibrillation in Chronic Heart Failure; 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 versus Standard Conventional Therapy in Patients with Left Ventricular Dysfunction and Atrial Fibrillation; LVEF = left ventricular ejection fraction RBA = risk-of-bias assessment. **Top.** Change in LVEF. **Bottom.** Change in 6-minute walk distance.

All 4 trials with quality-of-life outcomes showed that ablation improved MLHFQ scores, although the findings in 1 trial were not statistically significant. Overall, the improvement in MLHFQ scores observed in the AF ablation group relative to the drug therapy group was statistically significant (mean difference, −9.02 points [CI, −19.75 to 1.71 points]) (**Figure 4**, *bottom*).

Four trials reported AF-free survival, whereas CASTLE-AF and CAMERA-MRI reported percentage of AF burden on follow-up. In the former 4 trials, mean AF-free survival in the ablation groups was about 72% during follow-up; in contrast, only 22% of patients in the drug therapy groups were AF-free. **Figure 5**, *top*, which compares the pooled event rates for the 4 trials, shows a 66% reduction in AF recurrence with catheter ablation compared with drug therapy. The CASTLE-AF trial reported lower AF burden with catheter ablation (20% and 25% at 12- and 60-month follow-up, respectively) compared with drug therapy (50% and 65%). Likewise, CAMERA-MRI reported a mean AF burden at 6 months of 1.6% ± 5.0% in the AF ablation group, compared with 100% in the drug therapy group.

Adverse Events

All trials reported percentages of patients with major adverse events (**Supplement Table 3**, available at Annals.org). The overall adverse event percentages were higher with ablation than drug therapy, although the difference was not statistically significant (7.2% vs. 3.8%, respectively; RR, 1.68 [CI, 0.58 to 4.85]) (**Figure 5**, *bottom*). The numerically higher complication rate observed with ablation was driven predominantly by a single trial—the study by McDonald and colleagues (12)—in which complications occurred in 6 of 20 patients (30%) in the ablation group (12).

Sensitivity Analysis

A sensitivity analysis was performed to investigate the significant heterogeneity observed among trials with regard to changes in LVEF. The CASTLE-AF study included patients with both persistent and paroxysmal AF, whereas the remaining studies included only those with persistent AF (14). After CASTLE-AF was excluded, significant heterogeneity remained (*P* for heterogeneity = 0.008; I^2 = 71%), as did the relative increase in LVEF with ablation (mean difference, 6.03% [CI, 1.13% to 10.92%]).

In CASTLE-AF and AATAC, patients in the standard therapy groups received antiarrhythmic drugs; in the other 4 studies, those in the standard therapy groups received rate-controlling medications only. After CASTLE-AF and AATAC were excluded, no significant heterogeneity (*P* for heterogeneity = 0.51; I^2 = 0%) was seen for changes in LVEF and the increase in mean LVEF with ablation remained (mean difference, 7.91% [CI, 3.30% to 12.52%]).

We also performed a sensitivity analysis with PABA-CHF added to the other 6 trials (**Supplement Figures 8** and **9**, available at Annals.org). Compared with patients receiving standard therapy, those in the AF ablation groups had larger reductions in mortality (RR, 0.52 [CI, 0.33 to 0.81]) and HF hospitalization (RR, 0.61 [CI, 0.41 to 0.91]) and greater improvements in mean LVEF (mean difference, 7.29% [CI, 4.06% to 10.52%]) and MLHFQ scores (−9.54 points [CI, −14.69 to −4.38 points]). Statistically significant heterogeneity remained for LVEF change (P for heterogeneity < 0.001; I^2 = 93%), whereas other measures exhibited no significant heterogeneity.

Discussion

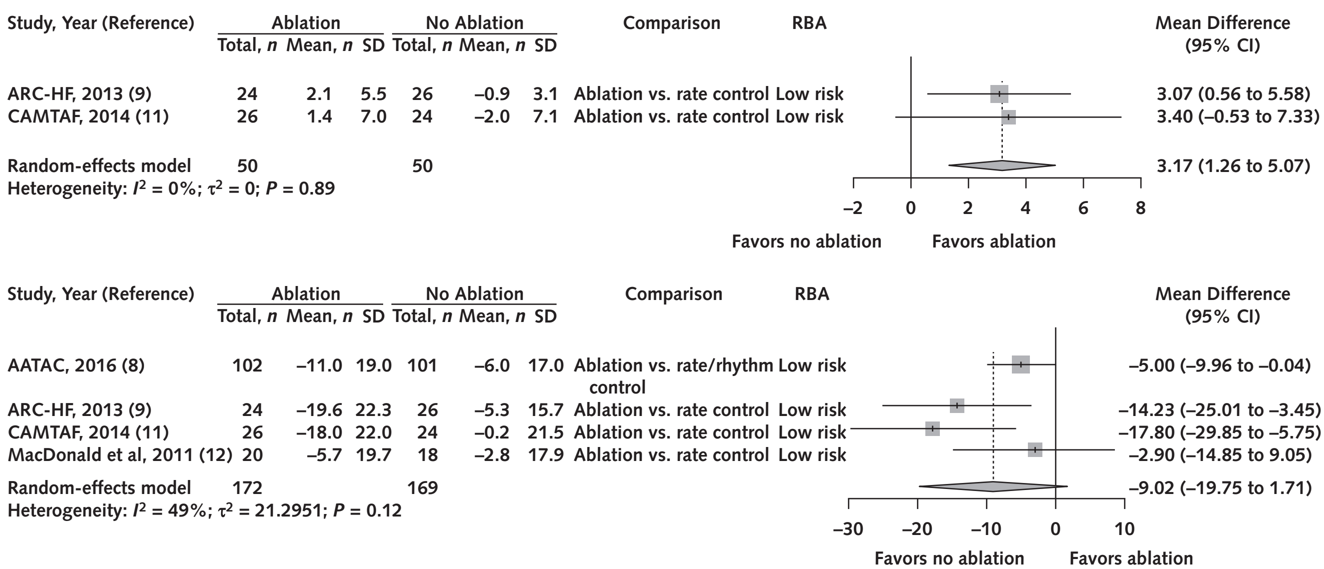
The main findings in this analysis are that AF catheter ablation in HF_REF was associated with reductions in all-cause mortality and HF hospitalizations and improvements in LVEF; quality of life; cardiopulmonary exercise capacity, estimated by VO_2max; and distance on the 6-minute walk test. A search between 2016 and 2018 in PubMed identified 4 other systematic reviews and meta-analyses that also found a decrease in all-cause mortality and HF hospitalizations with AF catheter ablation compared with medical therapy (19–22).

The favorable outcomes reported with catheter ablation probably were driven mostly by a reduction in AF burden and an improvement in LVEF. Improved LVEF was observed with catheter ablation in all 6 trials, with a mean increase of 7%. To appreciate how substantial this improvement is, note that treatment with angiotensin-converting enzyme inhibitors, which also has a mortality benefit, results in a 5% LVEF improvement in patients with HF_REF (23). In addition, our pooled analysis of 4 trials showed greater AF-free survival with catheter ablation, and analysis of 2 other trials showed substantial reductions in AF burden with ablation. These results provide additional support to the notion that AF itself is an important cause of LV systolic dysfunction independent of tachycardia, because most patients had robust rate control during follow-up.

Ablation therapy improved distance on the 6-minute walk test and VO_2max. Studies have shown that both are independent predictors of survival in persons with HF (24, 25). In addition to increased LVEF, improvements in walk distance and oxygen consumption are plausible contributors to the reduction in mortality and HF hospitalization. These results are consistent and concordant among the trials, with the exception of the study by MacDonald and colleagues (12), which did not demonstrate any significant differences in 6-minute walk test distance or MLHFQ scores between groups. This may be attributable to both the suboptimal AF ablation outcomes in restoring sinus rhythm (50%) and the higher-than-expected complication rates in this early trial of AF ablation in HF (12).

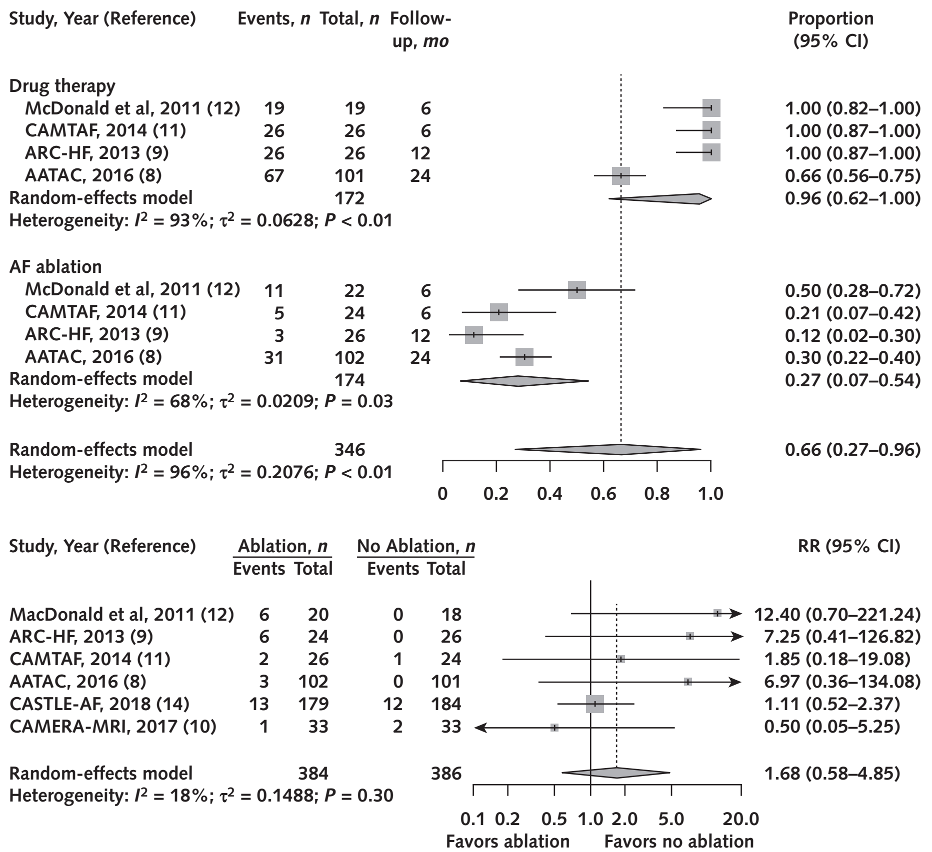
An important challenge in interpreting these data is the difficulty in determining the temporal relationship between AF and HF. Data from the Framingham Heart Study from 1980 to 2012 demonstrated that among persons with a diagnosis of new-onset AF, a codiagno-

Figure 4. Forest plot demonstrating improvement in VO_2max and mean difference in quality of life with catheter ablation versus medical treatment.



AATAC = Ablation versus Amiodarone for Treatment of Atrial Fibrillation in Patients with Congestive Heart Failure and an Implanted ICD; ARC-HF = A Randomized Trial to Assess Catheter Ablation Versus Rate Control in the Management of Persistent Atrial Fibrillation in Chronic Heart Failure; CAMTAF = A Randomized Controlled Trial of Catheter Ablation Versus Medical Treatment of Atrial Fibrillation in Heart Failure; RBA = risk-of-bias assesment; VO_2max = peak oxygen consumption. **Top.** Mean difference in VO_2max. **Bottom.** Mean difference in quality of life.

Figure 5. Forest plot demonstrating decreased AF recurrence with no difference in complications with catheter ablation versus medical treatment.



AATAC = Ablation versus Amiodarone for Treatment of Atrial Fibrillation in Patients with Congestive Heart Failure and an Implanted ICD; AF = atrial fibrillation; ARC-HF = A Randomized Trial to Assess Catheter Ablation Versus Rate Control in the Management of Persistent Atrial Fibrillation in Chronic Heart Failure; 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 versus Standard Conventional Therapy in Patients with Left Ventricular Dysfunction and Atrial Fibrillation; RR = risk ratio. **Top.** AF recurrence between both groups on the basis of Freeman–Tukey arcsine tranformation. **Bottom.** Safety of catheter ablation versus drug therapy.

sis of HF was noted in 37%, suggesting that a primary tachycardiomyopathy may have at least partly contributed to the LV dysfunction. Likewise, among patients with new-onset HF, 57% had a codiagnosis of AF. In addition, among persons with HF diagnosed after AF, HF with preserved ejection fraction subsequently developed in 50% and HF_REF in 40% (3). Among the studies included in the meta-analysis, a codiagnosis of AF and HF was reported in 2 studies: CAMTAF (A Randomized Controlled Trial of Catheter Ablation Versus Medical Treatment of Atrial Fibrillation in Heart Failure) (in 56% of patients) and CAMERA-MRI (in 68% of patients). However, in most trials (5 of 6), time since AF diagnosis exceeded 12 months, with the exception of AATAC (8.5 ± 3.65 months), suggesting an integral role of persistent and long-standing persistent AF (despite rate control) in HF_REF (8, 10, 11). Recent data from CAMERA-MRI demonstrate that the absence of ventricular fibrosis on cardiac magnetic resonance imaging predicted greater improvements in absolute LVEF (+10.7%; P = 0.0069) and LVEF normalization at 6 months (73% vs. 29%; P = 0.0093) with AF ablation. These data echo previous findings and are consistent with our pooled analysis (10, 26).

The major adverse event rates observed in our pooled analysis were 7.2% in the AF ablation group and 3.8% in the standard therapy group (**Supplement Table 3**, available at Annals.org). Despite these complications with AF ablation (which were not statistically significantly different between groups), the long-term benefits in all-cause mortality, HF hospitalizations, and overall clinical outcomes must be weighed in clinical decision making.

Currently, 4 RCTs of AF catheter ablation in HF are under way. RAFT-AF (Randomized Ablation-based AF Rhythm Control vs. Rate Control Trial in Patients With HF and High Burden AF; ClinicalTrials.gov: NCT01420393) is randomly assigning patients with HF_REF or HF with preserved ejection fraction to receive catheter ablation or rate control with drugs or AV junction ablation. The primary end point is all-cause mortality or HF hospitalization, and the estimated completion date is June 2020. CATCH-AF (Catheter Ablation vs. Medical Therapy in Congested Hearts With AF; ClinicalTrials.gov: NCT02686749) is investigating catheter ablation versus antiarrhythmic drugs in patients with HF_REF. The primary end point is HF hospitalization, and the estimated completion date is December 2019. AFARC-LVF (AF Ablation Compared to Rate Control Strategy in Patients With Recently Diagnosed Impaired LV Function; ClinicalTrials.gov: NCT02509754) is comparing AF ablation with medical rate control in patients with recently diagnosed HF_REF (<6 months previously). The primary end point is improvement in LVEF or NYHA class. The study was estimated to have been completed in December 2017, and its current status is unknown. AMICA (AF Management in Congestive HF With Ablation; ClinicalTrials.gov: NCT00652522) randomly assigned patients with persistent AF and HF_REF to receive catheter ablation or antiarrhythmic drugs. The primary end point is LVEF change. Enrollment was completed in July 2017, and results are pending.

Several limitations merit mention. First, despite the inclusion of 6 RCTs, the results of our meta-analysis were driven primarily by the largest trial—CASTLE-AF. However, the beneficial outcomes of catheter ablation in HF_REF were consistent across all clinical trials. Second, patient selection bias remains a major factor, because patients selected for a randomized catheter ablation trial may be "healthier" than those who are receiving only medical management. Of note, the patients included in this meta-analysis were relatively young (aged 55 to 64 years). Extrapolating these outcomes to elderly patients with HF may be problematic. Although the ratio of total patients eligible for enrollment to enrolled patients was 5:1, this proportion is consistent with that of other RCTs involving interventional procedures. Also, differences in the types of adverse events between 2 study groups are expected when comparing an invasive strategy, such as catheter ablation, with drug therapy. Third, because patients and physicians were not blinded to treatment assignment, medical care and follow-up may have differed after ablation, further affecting results. Fourth, most studies in the pooled analysis had limited follow-up, and the possibility remains that the significant benefit observed with catheter ablation may diminish on long-term follow up. However, it should be noted that CASTLE-AF reported outcomes out to 5 years, and the Kaplan–Meier curves revealed that as time progressed, the mortality and HF hospitalization curves continued to diverge. Fifth, the heterogeneity in LVEF improvement among the various studies may have been the result of including patients with both ischemic and nonischemic cardiomyopathy as well as differences in the treatment of underlying HF. Finally, patient-level data are not available for more detailed analyses, and reporting biases were possible for some outcomes.

Despite the study's limitations, we conclude that compared with standard drug therapy, catheter ablation of AF in patients with HF_REF reduces all-cause mortality and HF hospitalization and improves LVEF, functional capacity, and quality of life.

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Reproducible Research Statement: *Study protocol:* See the Supplement. *Statistical code:* Available from Dr. Reddy (e-mail, vivek.reddy@mountsinai.org). *Data set:* Not applicable.

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