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Radiofrequency Ablation Versus Antiarrhythmic Drug Therapy for Atrial Fibrillation

Meta-Analysis of Quality of Life, Morbidity, and Mortality

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ABSTRACT

OBJECTIVES The aim of this study was to perform a collaborative meta-analysis of published and unpublished quality-of-life, morbidity, and mortality data from randomized controlled trial comparisons of radiofrequency ablation (RFA) and antiarrhythmic drug therapy (AAD) in symptomatic atrial fibrillation.

BACKGROUND RFA is superior to AAD in decreasing recurrences of atrial fibrillation, but the effects on other clinical outcomes are not well established.

METHODS The primary investigators of eligible randomized controlled trials were invited to contribute standardized outcome data. Random-effects summary estimates were calculated as standardized mean differences and risk ratios with 95% confidence intervals for continuous and binary outcomes, respectively. Fixed effects were used in subgroup analyses.

RESULTS Twelve randomized controlled trials (n = 1,707 patients) were included. RFA led to greater improvements in 4 36-Item Short Form Health Survey areas and the symptom frequency score from baseline to 3 months. In all quality-of-life metrics, there was a trend toward diminution of the differences between the 2 approaches with follow-up. There were 7 of 866 (5 in a study using phased RFA) and 0 of 704 strokes in the RFA and AAD arms, respectively ($p = 0.02$, Fisher exact test). Bleeding and mortality events were not significantly different between the 2 arms. There was high heterogeneity for hospitalizations, with decreased hospitalization risk with RFA when it was not first-line therapy (risk ratio: 0.34; 95% confidence interval: 0.24 to 0.46) and increased risk as first-line therapy (risk ratio: 1.22; 95% confidence interval: 1.03 to 1.45).

CONCLUSIONS RFA demonstrates an early but nonsustained superiority over AAD for the improvement of quality of life. There are no obvious differences in other clinical outcomes, and the periprocedural stroke risk is non-negligible. (J Am Coll Cardiol EP 2016;2:170–80) © 2016 by the American College of Cardiology Foundation.

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The optimal therapeutic approach for atrial fibrillation (AF) is still debated. A beneficial effect of radiofrequency ablation (RFA) on quality of life (QoL) has been suggested by several studies (1,2), but it is unclear whether the effect of RFA on QoL is sustained, because long-term follow-up data have been limited (3). Also, previous retrospective analyses have demonstrated conflicting results with regard to stroke and hospitalization risks with RFA and antiarrhythmic drug therapy (AAD) (4,5), and no randomized controlled trials (RCTs) have been sufficiently powered to address these issues. Finally, given the demonstrated superiority of RFA over AAD in rhythm control, and the potential ensuing decreased need for anticoagulation (6,7), long-term bleeding should theoretically be less frequent with an RFA strategy. However, this remains unproved.

Meta-analyses have demonstrated the superiority of RFA in maintaining sinus rhythm compared with AAD (8–16). However, only 1 study analyzed limited published QoL data in nonstandardized scales and demonstrated superiority of RFA, without addressing the longevity of this effect. Three meta-analyses assessed the safety of RFA and AAD and considered all adverse events related to the interventions collectively, ranging from minor events to death, without specifically focusing on clinically important outcomes such as stroke and bleeding (8,11,14). Only 1 meta-analysis synthesized limited published data from 3 RCTs on the risk for cardiovascular hospitalization and demonstrated favorable RFA effects (15). Also, a recent meta-analysis of 3 studies assessed the safety and effectiveness of RFA only as first-line treatment (16). No meta-analysis has been previously aimed at addressing specifically the long-term risks for stroke, bleeding, or death with RFA and AAD strategies.

We have therefore conducted a systematic review and meta-analysis of all published RCTs comparing RFA with AAD in paroxysmal or persistent AF with regard to QoL outcomes, hospitalization, stroke, bleeding, and mortality. We attempt to overcome the limitations imposed by the limited or nonstandardized published QoL and clinical event data by including unpublished primary trial data. Differences in AF recurrence were not within the scope of this study, because all previous meta-analyses have addressed this outcome convincingly (17).

ABBREVIATIONS AND ACRONYMS

AAD = antiarrhythmic drug therapy
AD = arcsine difference
AF = atrial fibrillation
CI = confidence interval
QoL = quality of life
RCT = randomized controlled trial
RFA = radiofrequency ablation
RR = risk ratio
SF36 = 36-Item Short Form Health Survey

METHODS

DATABASE SEARCH. Using the OVID search engine and the generic terms *atrial fibrillation*, *atrial flutter*, and *ablation*, 2 independent reviewers searched the MEDLINE, Embase, and Cochrane Central Register of Controlled Trials databases (limited to RCTs) without year or language restrictions (accessed March 18, 2015). We also searched ClinicalTrials.gov (accessed March 18, 2015) and the most recent major pertinent meetings (American College of Cardiology Scientific Sessions, American Heart Association Scientific Sessions, European Society of Cardiology Congress, Heart Rhythm, European Heart Rhythm Association/Cardiostim) for ongoing trials that were not yet published in journals. References of eligible papers were further scrutinized for additional eligible studies.

ELIGIBILITY OF STUDIES. We considered trials that randomly assigned patients with paroxysmal or persistent AF to any type of RFA versus AAD. Trials were eligible regardless of whether RFA was used as first-line therapy or not. Studies examining RFA versus AAD in patients with AF and heart failure were excluded because of the distinct QoL and overall prognostic characteristics of this patient population. We also excluded trials comparing the 2 modes of therapy following failure of previous ablation attempt, trials comparing different ablation techniques without medical management arms, trials evaluating RFA versus rate control, and trials comparing AAD with no AAD after ablation.

DATA COLLECTION AND ENDPOINTS OF INTEREST. For each eligible RCT, we documented general study

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and procedural characteristics. The risk for bias was assessed with the Cochrane risk for bias assessment tool (18). Blinding was considered adequate when it involved the outcome assessors, because blinding of patients or physicians is irrelevant because of the procedural nature of RFA (none of the trials performed sham ablation procedures).

Two investigators scrutinized the main publication and subsequent analyses of each trial for outcomes of interest per treatment arm: changes in QoL measures (19-21) and symptom frequency and severity scores (22,23) from baseline to 3-, 6-, and ≥9-month follow-up; hospitalization for any reason; stroke (excluding transient ischemic attacks); bleeding; and all-cause mortality. For continuous outcomes, we documented the mean change from baseline to follow-up after randomization to RFA or AAD and the standard deviation of the mean change. When outcome data were not available in published studies or were available in a format that precluded inclusion in meta-analysis, the primary investigators of the respective RCTs were invited to contribute such data using standardized spreadsheets.

STATISTICAL ANALYSIS. Using the mean changes of the QoL metric and symptom frequency and severity scores from randomization to follow-up and the respective SDs of mean changes per treatment arm, Hedges's g (24) standardized mean differences and their 95% confidence intervals (CIs) were calculated and synthesized. For categorical outcomes, the risk ratio (RR) was the metric of choice. For these outcomes, the longest available follow-up data per RCT were included in meta-analysis. Further details on the analysis are given in the Online Appendix.

For all outcomes, DerSimonian-Laird random-effect summary estimates were calculated and converted to Hartung-Knapp-Sidik-Jonkman random-effect estimates, which are more accurate, especially with a small number of studies (25). For binary outcomes, when there were zero counts, we used the arcsine method for meta-analysis and expressed the effect size as the arcsine difference (AD) (26). However, for outcomes with few or no events among most of the trials (stroke, bleeding, mortality), we preferred as the primary evaluation a pooled analysis using Fisher exact tests for the difference of total events in RFA and AAD groups (significance level set at 0.05). Fixed-effects models were used only in subgroup analyses when heterogeneity disappeared after splitting of the subgroups.

Heterogeneity was quantified with the I^2 statistic and its 95% CI (27,28). I^2 values >50% suggest the presence of significant heterogeneity. We did not perform funnel-plot asymmetry testing for small-study effects given the small number of studies (29). All analyses adhered to the intention-to-treat principle. Statistical analysis was performed in Stata version 12.0 (StataCorp LP, College Station, Texas). This meta-analysis was reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (30).

RESULTS

ELIGIBLE TRIALS. Of 567 studies, 57 were potentially eligible and scrutinized further. We identified 1 potentially eligible RCT currently recruiting patients (NCT00911508) and 1 completed study in patients with hypertrophic cardiomyopathy without any results available publicly or after communication with the primary investigators (NCT00821353). Ultimately, 14 reports of 12 RCTs met all inclusion criteria (12 primary trial publications [1,31-41], 1 report with additional detailed QoL data [42], and 1 report with longer follow-up data [3]) (Online Figure 1).

CHARACTERISTICS OF INCLUDED STUDIES. RFA consisted of pulmonary vein isolation with or without additional ablation methods in all trials. One trial (TTOP-AF [Tailored Treatment of Persistent Atrial Fibrillation]) used phased, multiarray electrodes for ablation of pulmonary veins and left atrial sites (39). In 3 trials (32,38,41), patients had never been treated with AAD (i.e., RFA was tested as first-line therapy). In general, AAD regimens were selected according to current guidelines (details shown in **Table 1**). None of the included trials was at high risk for bias in more than 1 of the evaluated areas. However, potential risks were frequently unclear (Online Table 1).

A total of 1,707 patients (RFA, n = 934; AAD, n = 773) were randomized (per trial median 142; interquartile range: 90 to 190). Four trials had mixed populations of paroxysmal and persistent AF, and 5 and 3 trials had only paroxysmal or persistent AF patients, respectively. Online Table 2 summarizes standard baseline patient characteristics per treatment arm.

The median percentage of patients requiring at least 1 repeat RFA procedure per trial was 19.5%, with a maximum of 47% in the MANTRA-PAF (Medical Antiarrhythmic Treatment or Radiofrequency Ablation in Paroxysmal Atrial Fibrillation) trial. After various follow-up periods, a total of 398 crossovers from AAD to RFA occurred among trials. By intention to treat, RFA was significantly more successful than AAD for arrhythmia control in all trials (**Table 2**).

TABLE 1 Characteristics of Eligible Randomized Controlled Trials Comparing Radiofrequency Ablation Versus Antiarrhythmic Drug Therapy for Atrial Fibrillation

Trial (Year)	Enrollment Period	Trial Type	Patient Population	Inclusion Criteria	RFA Arm	AAD Arm	n	Follow-Up (months)
RAAFT-2 (2014)	2006–2010	Multicenter	General	Symptomatic paroxysmal AF lasting >30 s (≤4 episodes within last 6 months); ≥1 ECG-documented episode; no previous AAD	PVI; optional LA lines, CTI, CFAE, GP ablation, SVC isolation	AAD per physician's discretion; doses according to HRS/EHRA/ECAS guidelines	127	24
SARA (2014)	2009–2011	Multicenter	General	Symptomatic persistent AF refractory to ≥1 class I or III AAD	PVI; optional CFAE and LA lines	AAD per physician's discretion according to 2012 ESC guidelines	146	12
TTOP-AF (2014)	2007–2010	Multicenter	General	Persistent AF; failed DCC and ≥1 class I or III AAD	PVI + CFAE ablation with phased RFA system	New AAD or new dosages of previously failed AAD	210	6
MANTRA-PAF (2012)	2005–2009	Multicenter	General	Symptomatic paroxysmal AF with ≥2 episodes in past 6 months lasting ≤7 days; no previous AAD	PVI + LA lines; optional mitral and tricuspid isthmuses lines	First-line class IC AAD, second-line class III AAD	294	24
ThermoCool AF (2010)	2004–2007	Multicenter	General	≥3 symptomatic paroxysmal AF episodes (≥1 episode verified by ECG) within the past 6 months, refractory to ≥1 AAD	PVI; optional LA lines, CFAE and CTI ablation	New AAD at provider's discretion, except amiodarone	167	12
Forleo et al. (2009)	2005–2006	Multicenter	Type 2 diabetes	Symptomatic paroxysmal or persistent AF for ≥6 months refractory to ≥1 class I–III AAD	PVI + CTI ablation; optional LA lines	Flecainide, propafenone, sotalol, amiodarone at maximum tolerable dose (single or combination therapy)	70	12
A4 (2008)	NA	Multicenter	General	Symptomatic, paroxysmal AF for ≥6 months with ≥2 episodes in past month	PVI + CTI ablation; optional LA lines	New AAD, per ACC/AHA/ESC 2006 guidelines	112	12
Oral et al. (2006)	2002–2004	Multicenter	General	Chronic AF >6-month duration without intervening spontaneous episodes of sinus rhythm and recurrent within 1 week after DCC	PVI + LA lines	DCC and amiodarone for 3 months	146	12
APAF (2006)	2006	Single center	General	Paroxysmal AF >6-month duration with ≥2 episodes in past 6 months	PVI + LA lines + CTI ablation	Amiodarone, flecainide, sotalol at maximum tolerable dose (single or combination therapy)	198	48
Stabile et al. (2006)	2002–2003	Multicenter	General	Paroxysmal or persistent AF, AAD intolerance or failure of ≥2 AAD	PVI + LA lines; as-needed CTI ablation	Amiodarone (preferentially) or class IC AAD	137	13
Wazni et al. (2005)	2001–2002	Multicenter	General	Monthly symptomatic paroxysmal or persistent AF for ≥3 months; no previous AAD	PVI	Flecainide, propafenone, sotalol at maximum tolerable dose (single or combination therapy)	70	12
Krittayaphong et al. (2003)	NA	Single center	General	Symptomatic paroxysmal or persistent AF of ≥6-month duration, failed ≥1 AAD, amiodarone-naive	PVI + LA lines + RA lines	Amiodarone	30	12

AAD = antiarrhythmic drug therapy; ACC = American College of Cardiology; AF = atrial fibrillation; A4 = Catheter Ablation Versus Antiarrhythmic Drugs for Atrial Fibrillation; AHA = American Heart Association; APAF = Ablation for Paroxysmal Atrial Fibrillation; CFAE = complex fractionated atrial electrogram; CTI = cavotricuspid isthmus; DCC = direct-current cardioversion; ECAS = European Cardiac Arrhythmia Society; ECG = electrocardiogram; EHRA = European Heart Rhythm Association; ESC = European Society of Cardiology; GP = ganglionated plexi; HRS = Heart Rhythm Society; LA = left atrial; MANTRA-PAF = Medical Antiarrhythmic Treatment or Radiofrequency Ablation in Paroxysmal Atrial Fibrillation; NA = not available; PVI = pulmonary vein isolation; RA = right atrial; RAAFT-2 = Radiofrequency Ablation Versus Antiarrhythmic Drugs as First-Line Treatment of Paroxysmal Atrial Fibrillation; RFA = radiofrequency ablation; SARA = Study of Ablation Versus Antiarrhythmic Drugs in Persistent Atrial Fibrillation; SVC = superior vena cava; ThermoCool AF = NAVISTAR THERMOCOOL Catheter for the Radiofrequency Ablation of Symptomatic Paroxysmal Atrial Fibrillation; TTOP-AF = Tailored Treatment of Persistent Atrial Fibrillation.

TABLE 2 Repeat Radiofrequency Ablation Procedures, Crossover, and Treatment Success Rates in the Radiofrequency Ablation and Antiarrhythmic Drug Therapy Arms

Trial (Year)	Number of Patients		Follow-Up (months)	Repeat RFA	Crossover*		Treatment Success‡	
	RFA	AAD			RFA to AAD	AAD to RFA	RFA	AAD
RAAFT-2 (2014)	66	61	24	10§ (15)	6 (9)	29† (48)	30 (45)	17 (28)
SARA (2014)	98	48	12	8 (8)	35 (36)	23 (48)	59 (60)	14 (30)
TTOP-AF (2014)	138	72	6	48 (35)	NA	43 (60)	77 (56)	19 (26)
MANTRA-PAF (2012)	146	148	24	69 (47)	13 (9)	54 (36)	124 (85)	105 (71)
ThermoCool AF (2010)	106	61	12	13 (12)	0 (0)	36 (59)	70 (66)	10 (16)
Forleo et al. (2009)	35	35	12	0 (0)	0 (0)	0 (0)	28 (80)	15 (43)
A4 (2008)	53	59	12	23 (43)	5 (9)	37 (63)	46 (87)	13 (22)
Oral et al. (2006)	77	69	12	25 (32)	1 (1)	53 (77)	57 (74)	40 (58)
APAF (2006)	99	99	48	27 (27)	NA	87 (88)	72 (73)	56 (57)
Stabile et al. (2006)	68	69	13	NA	NA	36 (52)	38 (56)	6 (9)
Wazni et al. (2005)	33	37	12	0 (0)	0 (0)	0 (0)	29 (88)	15 (41)
Krittayaphong et al. (2003)	15	15	12	0 (0)	NA	NA	12 (80)	6 (40)

Values are n (%). *By the end of follow-up; even after occurrence of the primary outcome. †Three patients underwent RFA during the blanking period. ‡According to each study's definition of treatment success. §One patient underwent repeat RFA during the blanking period.

Abbreviations as in Table 1.

CHANGES IN QoL. The published reports of 9 trials included 36-Item Short Form Health Survey (SF36) component and summary data (or the equivalent components of the Atrial Fibrillation-Quality of Life score), but their nonstandardized formats precluded inclusion in the meta-analysis. Therefore, standardized data (mean changes and the SD of the changes in the randomized groups) were provided by the investigators of 7 trials for meta-analysis. Compliance rates for completion of the QoL questionnaires are shown in Online Table 3.

By random effects, RFA was superior to AAD, with standardized mean differences demonstrating statistically significant and mostly moderate or large differences in SF36 component changes from baseline to 3-month follow-up: physical functioning, 0.48 (95% CI: 0.12 to 0.84); vitality, 0.66 (95% CI: 0.40 to 0.92), and role emotional, 0.43 (95% CI: 0.07 to 0.79). The difference in the mean change from baseline to 3-month follow-up was also significant for the mental component summary (0.43; 95% CI: 0.16 to 0.70), but not for the physical component summary (0.43; 95% CI: −0.08 to 0.94) (**Figure 1**).

In several SF36 individual components and summary scores, a trend toward a decrease in the effect of RFA was observed with increasing follow-up. The differences in QoL changes induced by RFA and AAD were no longer statistically significant at 6 months for role emotional, whereas differences for physical functioning, and the mental component summary were eliminated at ≥9-month follow-up.

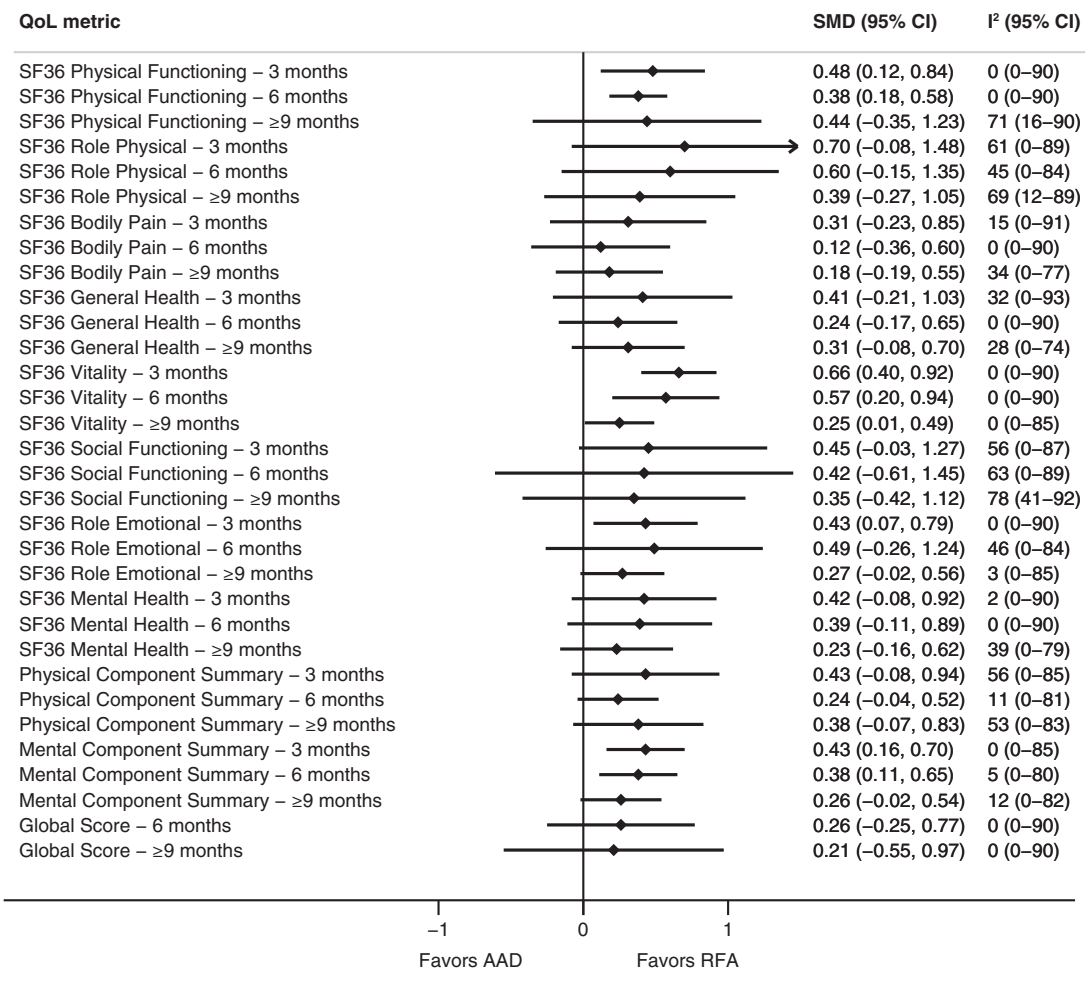
Two trials (SARA [Study of Ablation Versus Antiarrhythmic Drugs in Persistent Atrial Fibrillation] and RAAFT-2 [Radiofrequency Ablation Versus Antiarrhythmic Drugs as First-Line Treatment of Paroxysmal Atrial Fibrillation]) reported global QoL measures in different scales (Atrial Fibrillation-Quality of Life and EQ-5D tariff score, respectively). Data in standardized format were obtained from both trials. A meta-analysis of the global QoL scores revealed no differences between RFA and AAD at 6 and ≥9 months (**Figure 1**).

Online Figure 2 shows the studies included in the QoL meta-analyses and the respective individual study estimates.

CHANGES IN SYMPTOM FREQUENCY AND SEVERITY. Four trials had published data on symptom frequency and severity, and their investigators provided them in standardized format for inclusion in the meta-analysis. RFA led to larger improvement in symptom frequency at 3-month follow-up compared with AAD, with a standardized mean difference of −0.95 (95% CI: −1.69 to −0.21). This effect remained significant at 6-month follow-up, but not at ≥9-month follow-up. RFA also tended to confer larger symptom severity improvements, but the difference was not statistically significant. Again, we observed a trend toward equalization of the RFA and AAD effects with increasing follow-up in both the symptom frequency and severity scores (**Figure 2**; details in Online Figure 2).

RATES OF HOSPITALIZATION. Rates of hospitalization from 6 trials were analyzed (unpublished data from 3 trials). A total of 160 (34%) and 205 (48%) patients had ≥1 hospitalization in the RFA and AAD

FIGURE 1 **Summary Standardized Mean Difference (95% Confidence Interval) of the Effects of Radiofrequency Ablation and Antiarrhythmic Drug Therapy on Changes of 36-Item Short Form Health Survey Individual Components, 36-Item Short Form Health Survey Component Summaries, and Global Quality-of-Life Score From Baseline to 3-, 6-, and ≥9-Month Follow-Up**



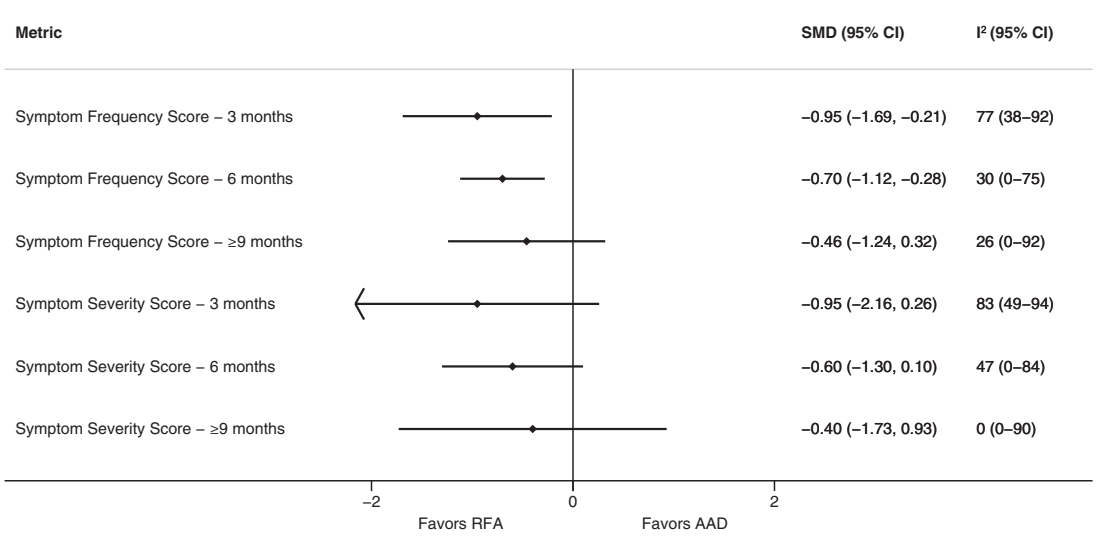
AAD = antiarrhythmic drug therapy; CI = confidence interval; RFA = radiofrequency ablation; SF36 = 36-Item Short Form Health Survey; SMD = standardized mean difference.

arms, respectively. Heterogeneity was large ($I^2 = 91\%$; 95% CI: 84% to 95%), and by random effects the summary RR was 0.50 (95% CI: 0.22 to 1.16) (Online Figure 3). The 2 trials in which RFA was tested as first-line treatment (RAAFT-2 and MANTRA-PAF) showed an increased risk for hospitalization with RFA (fixed-effects summary RR: 1.22; 95% CI: 1.03 to 1.45; $I^2 = 0\%$). On the contrary, RFA decreased hospitalizations in the remaining trials (RR: 0.34; 95% CI: 0.24 to 0.46; $I^2 = 0\%$ [95% CI: 0% to 85%]).

STROKE, BLEEDING, AND ALL-CAUSE MORTALITY. There were 7 strokes in the RFA arms and none in the control arms (follow-up 6 to 48 months among trials). Five of the RFA strokes were related to the ablation procedure (periprocedural stroke risk 0.3%), and 4 occurred in the TTOP-AF study, which used the phased RFA system (3 strokes happened within the first 5 procedures at 1 study site). By Fisher exact testing, RFA groups had significantly more strokes ($p = 0.02$). The summary AD by random effects was 0.05 (95% CI: −0.01 to 0.10; $I^2 = 0\%$ [95% CI: 0% to 60%]), but it should be noted that most trials had no events. Exclusion of the TTOP-AF trial from this analysis resulted in no difference in strokes between the 2 interventions ($p = 0.50$).

Eleven studies had available bleeding data with a total of 22 events, 13 in the RFA and 9 in the control arms. There was no significant difference between

FIGURE 2 Summary Standardized Mean Difference (95% Confidence Interval) of the Effects of Radiofrequency Ablation and Antiarrhythmic Drug Therapy on Changes of Symptom Frequency and Severity Scores From Baseline to 3-, 6-, and ≥9-Month Follow-Up



AAD = antiarrhythmic drug therapy; CI = confidence interval; RFA = radiofrequency ablation; SMD = standardized mean difference.

RFA and AAD (Fisher exact test in pooled analysis p = 0.83; random-effects AD 0.02; 95% CI: −0.02 to 0.06; I^2 = 0% [95% CI: 0% to 60%]). Ten events were related to the RFA procedure (absolute risk 0.7%) (**Figure 3**).

Fifteen (0.9%) deaths from any cause were recorded in 11 trials with available data (7 of 901 and 8 of 736 in RFA and AAD groups, respectively). Two of them were due to RFA-related periprocedural complications in a total of 1,591 procedures, including repeat RFA and crossovers (periprocedural mortality 0.13%). There was no discernible difference between RFA and AAD (Fisher exact p = 0.60; summary AD 0.01; 95% CI: −0.04 to 0.06; I^2 = 0% [95% CI: 0% to 60%]).

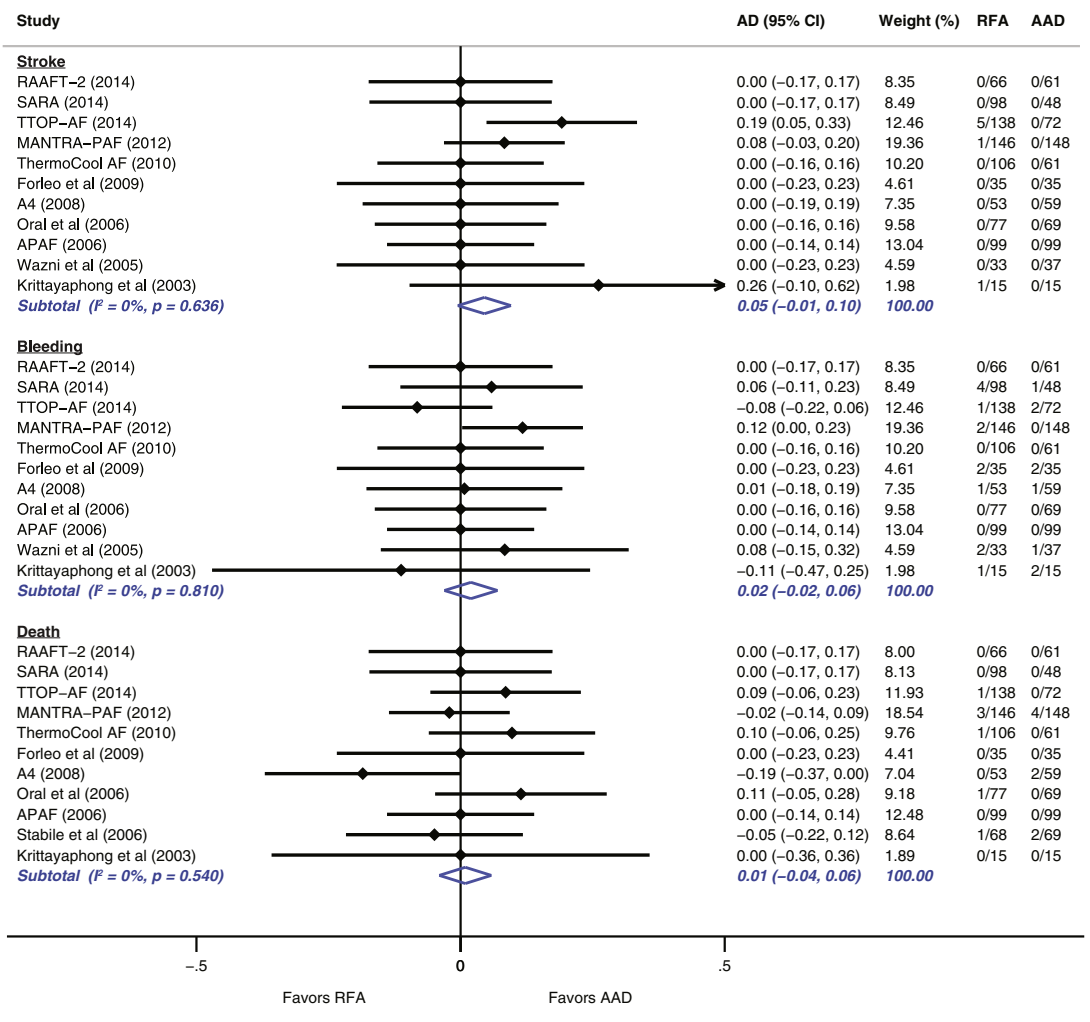
DISCUSSION

Our analysis indicates that ablation decreases symptoms and improves QoL, but this benefit appears to fade with time. Results on hospitalization rates are heterogeneous, with an increased risk with RFA when it is used as a first-line AF therapy (in 2 trials) and decreased risk when it is not used as a first-line therapy. Despite the decrease of AF recurrences and time spent in AF, RFA perhaps unsurprisingly did not reduce the risk for stroke. If anything, we documented an increased stroke risk with RFA, which was nevertheless driven by strokes in a single trial. Bleeding and mortality seem unaffected by the procedure compared with AAD.

Pulmonary vein isolation has been shown to lead to sustained improvements or even normalization of QoL more than 6 months to 2 years after ablation. As expected, this effect was more prominent among patients without recurrent AF (2,43). Herein, improvements in QoL and symptom burden were significantly better with ablation, but these differences shrank in magnitude with increasing follow-up and were not permanent treatment effects. The early superiority of RFA over AAD is likely a reflection of improved sinus rhythm maintenance, whereas a potential placebo effect of the more invasive RFA cannot be excluded. The trend toward equalization of efficacy with increasing follow-up could be due to the AF recurrences with both RFA and AAD and the fading of the placebo effect. An impact of crossovers (from AAD to RFA) also cannot be excluded. However, it should be noted that this phenomenon was consistent among trials with lower and higher crossover rates. Finally, QoL was assessed primarily with the SF36 questionnaire in the included trials, and even though it is used frequently for assessment of QoL in AF, it should be cautioned that the SF36 was not specifically developed for such patient populations.

Recent data suggest that ablative management of AF can improve health care utilization and expenditures and that it may not be costlier than AAD even when used as first-line therapy (44). A reduction in hospitalizations, a core metric of health care utilization, could have important socioeconomic consequences. In the United States, the total cost of nonvalvular AF was approximately $6.65 billion in 2005, and despite a static mean length of stay,

FIGURE 3 **Summary Arcsine Differences (95% Confidence Intervals) of the Effects of Radiofrequency Ablation and Antiarrhythmic Drug Therapy on Stroke, Bleeding, and All-Cause Mortality**



AAD = antiarrhythmic drug therapy; AD = arcsine difference; CI = confidence interval; RFA = radiofrequency ablation; SMD = standardized mean difference.

the cost of inpatient care increased between 2001 and 2010 (45). Our analysis of hospitalization data revealed large heterogeneity, with significantly different results in trials in which RFA was a first-line therapy for AF versus trials in which RFA was second- or subsequent-line therapy. This is likely a reflection of the fact that differences between RFA and AAD for AF recurrence may be less prominent when tested as first-line rather than subsequent-line treatments. Nevertheless, it should be noted that in many clinical fields the hospitalization rates may not square with serious outcomes such as mortality (46).

Our analysis showed an increased risk for stroke with RFA when all events were considered, often in causal relationship to the procedure. Interestingly, no strokes were seen in the control arms of all these trials. Studies suggest that periprocedural stroke can occur in about 0.5% of cases with RFA (47,48), similar to what was observed in this meta-analysis. We note that the clinically significant strokes documented in previous studies likely represent only a small fraction of all periprocedural cardioembolic events, as subclinical infarcts have been demonstrated with magnetic resonance imaging at an incidence of about 30% (49). It should be noted that 4 of the 6 periprocedural strokes in this meta-analysis originated from a single trial, TTOP-AF (39). When these events were excluded, the difference in stroke risk between RFA and AAD was not

different by random-effects meta-analysis or Fisher exact testing. TTOP-AF used the initial design of phased RFA, in which a multielectrode catheter is used to apply long contiguous left atrial lesions. There has been evidence of increased stroke rate with this approach (50). Although a system designed to decrease electrode interaction and char or bubble formation is approved for use in several parts of the world, phased RFA is not approved by the U.S. Food and Drug Administration, and its use has been experimental within the trial framework at U.S. sites.

Although stroke is the major feared complication of RFA, the benefits of post-ablation anticoagulation need to be weighed against the bleeding risk (6). Current consensus is that continued anticoagulation >2 months after successful ablation should be considered according to individual embolic and bleeding risk and patient preference (51). However, because of the high recurrence rates after RFA, long-term anticoagulation in patients with high pre-procedural embolic risk may be justified. Patients with low estimated embolic risks have less obvious indications for continued post-RFA anticoagulation. The bleeding risk was fairly similar in the 2 arms in this meta-analysis, but most bleeding events in the RFA arm were related to the procedure, and the risk was even higher than the risk for stroke in absolute magnitude. This emphasizes further the need to minimize procedure-related complications.

Mortality rates were not reduced by ablation therapy in the generally low-risk populations included herein. Perhaps follow-up of analyzed studies is not long enough to expose any effect on mortality. The reported in-hospital mortality with RFA is 0.06% to 0.3% and is due mainly to stroke, tamponade, atrioesophageal fistulae, and pneumonia (47,52). Our study detected a 0.13% periprocedural mortality risk with RFA, in accord with prior investigations.

STUDY LIMITATIONS. First, there were slight variations in the ablative techniques among trials. This may have resulted in different acute and long-term procedural success and complication rates, thereby possibly affecting the outcomes of interest (39). Similarly, AAD and anticoagulation regimens were not identical between trials, but all of them were based on current guideline recommendations.

Second, we did not have individual patient data on certain factors that could potentially influence QoL comparisons such as the number of repeat ablation procedures and AF burden before and after ablation. Also, crossover from AAD to RFA may have diluted the differences between the 2 interventions with increasing follow-up. Notably, populations with paroxysmal and permanent AF were included in the same analyses, but there were no obvious differences in effect estimates between studies with only paroxysmal or only permanent AF.

Finally, QoL is a subjective outcome, and therefore effects on QoL may be overestimated in unblended trials (53). Also, as with most meta-analyses of RCTs, the included populations are highly selected and do not necessarily represent typical real-world patients with AF.

CONCLUSIONS

RFA leads to greater QoL improvement and symptom alleviation in patients with AF, but these benefits appear to decrease with time, and the risk for periprocedural stroke is not negligible. A contribution of AAD-to-RFA crossovers to the diminution of the QoL effect cannot be entirely excluded. Although the outcomes of the invasive management of AF may continue to improve with the use of emerging technologies, such as contact-force sensing among others, large ongoing randomized studies, such as the CABANA (Catheter Ablation Versus Antiarrhythmic Drug Therapy for Atrial Fibrillation) trial, are needed to provide additional insights on the value of catheter ablation for the therapy of AF.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: RFA demonstrates an early but nonsustained superiority over AAD for the improvement of QoL. RFA has documented superiority in reducing AF recurrences and an overall trend toward a decrease in hospitalizations, but benefits for other hard patient outcomes are not obvious. In addition, the periprocedural risks, including stroke and bleeding, are nonnegligible. However, these may also depend on the specific ablation technique used and on operator experience.

TRANSLATIONAL OUTLOOK: Large well-powered RCTs with long follow-up are needed to clarify whether RFA is superior to AAD with regard to important patient outcomes with relatively infrequent events and whether the periprocedural risks are justified.

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APPENDIX For an expanded Methods section and supplemental tables and figures, please see the online version of this article.