



## Systematic Review/Meta-analysis

# Health-Related Quality of Life in Patients With Atrial Fibrillation Treated With Catheter Ablation or Antiarrhythmic Drug Therapy: A Systematic Review and Meta-analysis

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## ABSTRACT

**Background:** Catheter ablation (CA) is performed in patients with atrial fibrillation (AF) to reduce symptoms and improve health-related quality of life (HRQL).

**Methods:** This systematic review and meta-analysis of randomized controlled trials (RCTs) evaluated CA of any energy modality compared with antiarrhythmic drugs (AADs) using inverse-variance random-effects models. We searched for RCTs reporting HRQL and AF-related symptoms at 3, 6, 12, 24, 48, and 60 months after treatment as well as the number of repeat ablations.

## RÉSUMÉ

**Contexte :** L'ablation par cathéter (AC) est réalisée chez les patients atteints de fibrillation auriculaire (FA) afin d'atténuer les symptômes et d'améliorer la qualité de vie liée à la santé (QVLS).

**Méthodologie :** Cette revue systématique et méta-analyse d'essais contrôlés à répartition aléatoire (ECRA) a permis d'évaluer l'AC, toutes modalités énergétiques confondues, comparativement aux agents antiarythmiques (AA) à l'aide de modèles à effets aléatoires à variance inverse. Nous avons recherché les ECRA qui faisaient état de la QVLS et des symptômes liés à la FA à 3, 6, 12, 24, 48 et 60

Atrial fibrillation (AF) is a common arrhythmia, affecting an estimated 1%-2% of the population worldwide.<sup>1</sup> The prevalence of AF increases with age, and the combined effects of aging and AF can be debilitating, particularly with respect to health-related quality of life (HRQL). HRQL is defined as “the

extent to which one's usual or expected physical, emotional and social well-being are affected by a medical condition or related treatment.”<sup>2</sup> Compared with age-matched healthy controls, patients with AF consistently report lower HRQL.<sup>3</sup> Furthermore, women more often report greater symptom burden and poorer HRQL, in comparison with men.<sup>4</sup>

The management of AF involves anticoagulation therapy to reduce the risk of stroke and medications that control rate or rhythm to decrease symptoms and improve HRQL.<sup>5</sup> Despite rate control being very effective in some individuals, many patients remain highly symptomatic.<sup>6</sup> To alleviate patient symptoms and improve HRQL, restoration and maintenance of sinus rhythm can be achieved with antiarrhythmic drugs (AADs).<sup>5</sup> However, these medications may be

Received for publication February 6, 2020. Accepted March 23, 2020.

**Ethics Statement:** Ethics approval not required for a meta-analysis of published trials.

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See page 294 for disclosure information.

**Results:** Of 15,878 records, we included 13 RCTs of CA vs AADs for the analyses of HRQL, 7 RCTs for the analyses of AF-related symptoms, and 13 RCTs for the number of repeat ablations. For the HRQL analyses at 3 months, there were significant increases in both the Physical Component Summary score (3 months' standardized mean difference = 0.58 [0.39-0.78];  $P < 0.00001$ ,  $I^2 = 6\%$ , 3 trials,  $n = 443$ ) and the Mental Component Summary score (3 months' standardized mean difference = 0.57 [0.37-0.77];  $P < 0.00001$ ,  $I^2 = 0\%$ , 3 trials,  $n = 443$ ), favouring CA over AADs. These differences were sustained at 12 months but not >24 months after randomization. Similar results were seen for AF-related symptoms. The number of repeat ablations and success rates after procedure varied considerably across trials.

**Conclusions:** Evidence from few trials suggests that CA improves physical and mental health and AF-related symptoms in the short term, but these benefits decrease with time. More trials, reporting both HRQL and AF-related symptoms, at consistent time points are needed to assess the effectiveness of CA for the treatment of AF.

associated with serious side effects<sup>7</sup> and have only modest efficacy at maintaining sinus rhythm over the long term.<sup>8</sup>

Catheter ablation (CA) is an alternative to pharmacologic therapies that have failed to control AF symptoms, particularly in those with paroxysmal AF (PAF).<sup>9</sup> The main driver for choosing this treatment option is the anticipated improvement in AF-related symptoms and HRQL. Numerous studies have shown the superiority of CA over AADs in reducing AF recurrence, with patients having larger overall improvements in HRQL scores compared with baseline, vs those treated with pharmacologic therapy.<sup>10-12</sup> Of note, across trials, only 2 trials<sup>13,14</sup> have compared between treatment differences (ie, HRQL scores in CA patients vs HRQL scores in AAD patients); in the recently published Catheter Ablation vs Antiarrhythmic Drug Therapy for Atrial Fibrillation (CABANA) trial, the mean Atrial Fibrillation Effect on Quality of Life (AFEQT) questionnaire summary score at 12 months was 5.3 points higher favouring radiofrequency ablation (RFA) over AADs.<sup>13</sup> As there is limited randomized controlled trial (RCT) evidence evaluating HRQL between CA and AADs, an updated synthesis of this literature is needed to inform quality treatment decisions.

## Methods

The study protocol and methods have been published previously.<sup>15</sup> Briefly, this systematic review and meta-analysis was conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions and reported following the Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) statement for meta-analysis in health care interventions<sup>16</sup> (PRISMA Checklist, [Supplemental Table S1](#)).

## Eligibility criteria

We included RCTs that evaluated CA of any energy modality (eg, cryoballoon ablation [CBA] or RFA) compared with AADs, irrespective of blinding, publication status, or

mois après le traitement et qui précisaient le nombre d'ablations répétées.

**Résultats :** À partir de 15 878 entrées, nous avons retenu 13 ECRA comparant l'AC à des AA pour l'analyse de la QVLS, 7 autres pour l'analyse des symptômes liés à la FA et 13 de plus aux fins de calcul du nombre d'ablations répétées. L'analyse de la QVLS à 3 mois indique une augmentation significative du score sommaire de la composante physique (différence moyenne normalisée à 3 mois = 0,58 [0,39-0,78];  $p < 0,00001$ ,  $I^2 = 6\%$ , 3 essais,  $n = 443$ ) et du score sommaire de la composante mentale (différence moyenne normalisée à 3 mois = 0,57 [0,37-0,77];  $p < 0,00001$ ,  $I^2 = 0\%$ , 3 essais,  $n = 443$ ), faisant pencher la balance en faveur de l'AC plutôt que des AA. Ces différences persistaient à 12 mois après la répartition aléatoire, mais pas aux moments d'évaluation ultérieurs (24, 48 et 60 mois). Des résultats similaires ont été observés au chapitre des symptômes liés à la FA. Le nombre d'ablations répétées et le taux de réussite postopératoire variaient considérablement d'un essai à l'autre.

**Conclusions :** Les données probantes de quelques essais donnent à penser que l'AC améliore la santé physique et mentale ainsi que les symptômes liés à la FA à court terme, mais que ces bienfaits s'atténuent avec le temps. D'autres essais faisant état de la QVLS et des symptômes liés à la FA, à des moments d'évaluation constants, devront être réalisés pour évaluer l'efficacité réelle de l'AC dans le traitement de la FA.

language, in patients with persistent AF or PAF. Observational studies, RCTs that performed CA on other patient populations, atrial flutter, and ventricular tachycardia were excluded. Surgical AF ablation studies were beyond the scope of this review.

## Search strategy and study selection

A comprehensive search strategy was conducted from database inception to March 17, 2020, to identify published, in-press, and unpublished studies. Databases included Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR), Medical Literature Analysis and Retrieval System Online (MEDLINE), Cumulative Index of Nursing and Allied Health

### Strengths and Limitations:

- We performed a rigorous systematic review and meta-analysis of randomized controlled trials evaluating catheter ablation (CA) of any energy modality compared with antiarrhythmic drugs (AADs) in patients with atrial fibrillation (AF).
- Our study is one of very few to focus on patient-reported outcomes, including health-related quality of life (HRQL), AF-related symptoms, and the need for repeat ablations.
- Of the 13 RCTs comparing CA vs AADs and reporting HRQL outcomes, data from only 2 to 5 could be pooled at each time point due to inconsistencies in reported time points and variation in tools of HRQL assessment.
- There were not enough trials evaluating cryoballoon ablation (CBA) vs AADs to meta-analyze.

Literature (CINAHL), and Excerpta Medica database (EMBASE). The search strategy used a combination of keyword and database-specific subject headings for the following concepts: “atrial fibrillation,” “catheter ablation,” and “randomized controlled trial” (see [Supplemental Appendix](#) for example search strategy). We examined citations of included studies to identify additional studies not identified in the electronic search. Ongoing trials were identified using the World Health Organization International Clinical Trials Registry Platform and [ClinicalTrials.gov](#). We contacted experts to inquire about additional studies and unpublished data.

Three reviewers (K.S.A., T.A., and S.H.) independently examined the titles, abstracts, and full-text articles retrieved by the search. Studies were included for full-text review on the basis of agreement between 2 reviewers or when there was disagreement or uncertainty. Data from multiple reports of the same study were linked together and used to supplement information obtained from the primary report.

### Data extraction

After calibration exercises, 3 reviewers (K.S.A., T.A., and S.H.) used standardized forms to independently perform data extraction, in duplicate, with discrepancies resolved through consensus. In instances of missing or unclear information, study authors were contacted for clarification.

Data were abstracted from individual studies on the following variables: study location, duration of the trial, follow-up duration, blinding periods, study design, number of trial sites, inclusion/exclusion criteria, number of participants randomized, number of participants analysed, attrition, age, sex, type of AF, prior AAD therapy, type of CA, HRQL, AF-related symptoms, and number of repeat CA procedures.

Agreement between the 3 reviewers on study eligibility and risk of bias assessment was performed using the kappa statistic for inter-rater reliability.

### End points and subgroup analyses

The primary analyses evaluated whether CA or AADs improved patient HRQL measured by generic and/or disease-specific instruments in the acute phase (3-6 months after treatment) and long term (12-60 months after treatment). Secondary outcomes included the frequency and severity of AF-related symptoms in the acute phase and long term, as well as the number of repeat procedures needed to maintain sinus rhythm.

Planned subgroup analyses included (1) the effect of CA vs AADs in treatment naïve patients vs after failed AADs; (2) the effect of crossovers on HRQL (ie, patients randomized to AADs receiving CA later in the trial); (3) the effect of different CA modality (eg, cryoballoon or radiofrequency); and (4) differences in effects based on questionnaire type. Sensitivity analyses were planned to evaluate potential sources of bias resulting from variability in studies.

### Risk of bias and quality assessment

Risk of bias was assessed as “low risk,” “some risk of bias,” and “high risk of bias,” using the Cochrane Collaboration Risk of Bias 2.0 tool,<sup>17</sup> for the following measures: adequacy of sequence generation, adequacy of allocation concealment, adequacy of blinding for participants, study personnel and outcome assessors,

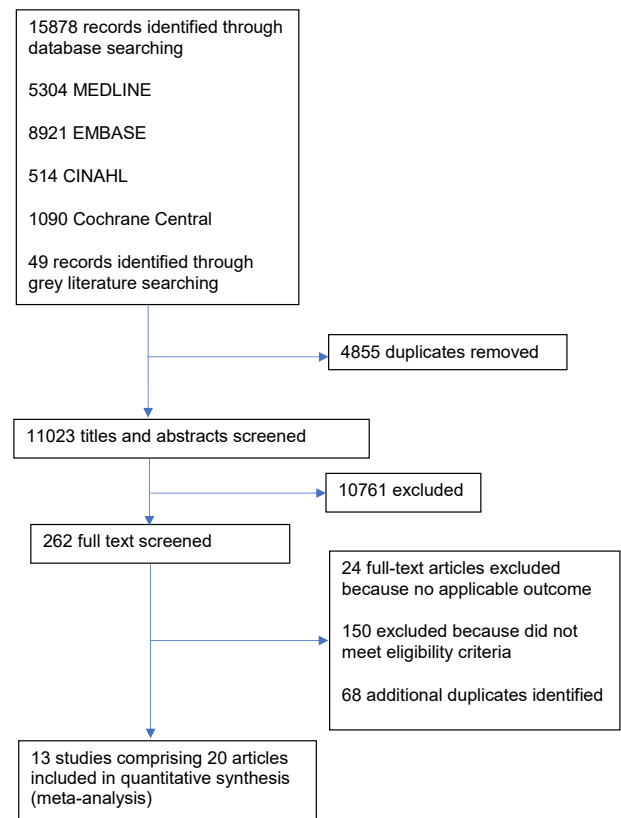
completeness of outcome data for each primary and secondary outcome, selective outcome reporting, and other potential sources of bias (ie, funding). Early stopping for benefit and observation of intention-to-treat principle were also assessed. Risk of bias tables were completed independently by the 3 reviewers (K.S.A., S.H., and T.A.) in pairs and compared for consensus.

GRADEpro GDT software (GRADEpro GDT: GRADEpro Guideline Development Tool [Software]. McMaster University, 2015 [developed by Evidence Prime, Inc.]. Available from [gradepro.org](#)) was used to generate Summary of Findings and Evidence Profile tables (K.S.A., M.H.M.). Confidence in effect estimates of the outcome measures were rated according to the quality of evidence using Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach for systematic reviews.<sup>18</sup> According to this approach, RCTs are ranked as high quality and downgraded for risk of bias, inconsistency, indirectness, imprecision, and publication bias. We planned on evaluating publication bias using funnel plots.

### Statistical analysis

We used inverse-variance random-effects models to compare treatment effects, incorporating for heterogeneity between studies. Data were pooled at consistent time points across studies, 3, 6, 12, 24, 48, and 60 months after treatment to measure differences between interventions.

Weighted mean differences were calculated for continuous outcomes measured on the same scale between studies and



**Figure 1.** Flow diagram of study selection.

**Table 1. Study characteristics**

+/Author, year	Country of recruitment	Multi or single centre	Total patients (n = 4093)	Number comparator patients	Number RFA patients	Comparators	Randomization	Prior treatment with AAD	HRQL instrument	AF-related symptoms instrument	HRQL	Symptoms	Duration of follow-up	Percentage with AF recurrence at end of FU comparator	Percentage with AF recurrence at end of FU RFA	Number of repeat ablations
Mark, 2019 <sup>13</sup>	USA, Australia, Canada, China, Czech Republic, Germany, Italy, Korea, Russia, UK	Multi	2204	1096	1108	CBA or RFA vs AADs	1:1	No	AFEQT SF-36	Mayo AF-Specific Symptom Inventory AFSS	✓	✓	5 y	69.5	49.9	215 (19.4)
Morillo, 2014 <sup>25</sup>	Canada, Germany, Czech Republic, USA, Italy	Multi	127	61	66	RFA vs AADs	1 to 1	No	EQ-5D	No	✓	N/A	2 y	72.1	54.5	10 (15.1)
Sohara, 2016 <sup>29</sup>	Japan	Multi	143	43	100	RFA vs AADs	2 to 1 (CA to AAD)	Yes	SF-36	No	✓	N/A	9 mo	95.3	41.0	Not reported
Pappone, 2011 <sup>28</sup>	Italy	Single	198	99	99	RFA vs AADs	1 to 1	Yes	SF-36	No	✓	N/A	4 y	87.9	27.3	27 (27.3)
Mont, 2014 <sup>24</sup>	Spain	Single	146	48	98	RFA vs AADs	2 to 1 (CA to AAD)	Yes	AF-QOL	No	✓	N/A	1 y	56.4	29.6	8 (8.2%)
Jais, 2008 <sup>10</sup>	USA, France, Switzerland	Multi	112	59	53	RFA vs AADs	1 to 1	Yes	SF-36	AF Symptom Frequency and Severity Checklist	✓	✓	1 y	77	11	23 (43.4)
Packer, 2013 <sup>27</sup>	USA, Canada	Multi	245	82	163	CBA vs AADs	2 to 1 (CA to AAD)	Yes	No	No	N/A	N/A	1 y	92.7	30.1	31 (19.0%)
Hummel, 2014 <sup>22</sup>	USA, the Netherlands	Multi	210	72	138	RFA vs AADs	2 to 1 (CA to AAD)	Yes	AF Symptom and QOL Surveys	AF Symptom and QOL Surveys	✓	✓	6 mo	73.6	44.2	48 (34.8%)
Reynolds, 2010 <sup>14</sup>	USA, Canada, Brazil, Italy, Czech Republic	Multi	159	56	103	RFA vs AADs	2 to 1 (CA to AAD)	Yes	SF-36	AF Symptom Frequency and Severity Checklist	✓	✓	9 mo	84	34	13 (12.6)
Wazni, 2005 <sup>11</sup>	Italy, Germany, USA	Multi	70	37	33	RFA vs AADs	1 to 1	No	SF-36	No	✓	N/A	1 y	63	13	4 (12.1%)
Nielsen, 2012 <sup>26</sup>	Denmark	Multi	294	146	148	RFA vs AADs	1 to 1	No	SF-36, EQ-5D	Arrhythmia Specific questionnaire in Tachycardia and Arrhythmia	✓	✓	5 y	29	14	58 (39.2%)
Krittayaphong, 2003 <sup>23</sup>	Thailand	Single	30	15	15	RFA vs AADs	1 to 1	Yes	SF-36	No	✓	✓	1 y	60	21.4	Not reported
Blomstrom-Lundqvist, 2019 <sup>21</sup>	Sweden, Finland	Multi	155	76	79	RFA or CBA vs AADs	1:1	Yes	SF-36	European Heart Rhythm Association Score	✓	✓	1 y	18.7	23	14 (18.7%)

AAD, antiarrhythmic drug; AF, atrial fibrillation; AFEQT, Atrial Fibrillation Effect on Quality of Life; AFSS, University of Toronto Atrial Fibrillation Severity Scale; CA, catheter ablation; CBA, cryoballoon ablation; EQ-5D, EuroQol-5 Dimensions; FU, follow-up; HRQL, health-related quality of life; RFA, radiofrequency ablation; SF-36, Short Form-36.

**Table 2. Patient characteristics**

Author	Male (%)		Mean age of comparator patients		Mean age of RFA patients		Weighted age	PAF (%)	Persistent AF (%)	Failed AADs (%)		DM (%)	CAD/MI (%)	LA size (cm) RFA	LA size (cm) comparator	Mean LVEF (SD) (SD)	Mean LVEF (SD) comparator	Mean weighted LVEF (SD)	Mean weighted LVEF (SD)
	63	75.6	67 ± 2.9	54.3 ± 11.7	67.3 ± 2.9	55.3 ± 10.4				42.9	47.3								
Mark <sup>13</sup>	63	75.6	67 ± 2.9	54.3 ± 11.7	67.3 ± 2.9	55.3 ± 10.4	42.9	47.3	38.6	61.4	80.6	25.5	19.2	NR	NR	NR	NR	NR	NR
Morillo <sup>25</sup>	75.6	56.3 ± 9	54.3 ± 11.7	54.3 ± 11.7	55.3 ± 10.4	97.6	2.4	42.5	41.7	3.9	6.3	3.9	6.3	4.0 (0.5)	4.3 (0.5)	61.4 (4.8)	60.8 (7.0)	61.1 (5.9)	61.1 (5.9)
Sohara <sup>29</sup>	80.4	58.8 ± 10.4	61 ± 10	59.3 ± 10.3	59.3 ± 10.3	100.0	0.0	75.5	52.4	4.9	3.5	4.9	3.5	3.8 (0.6)	3.8 (0.5)	66.7 (6.1)	66.5 (6.5)	66.6 (6.4)	66.6 (6.4)
Pappone <sup>28</sup>	67.2	55 ± 10	57 ± 10	56 ± 10	56 ± 10	100.0	0.0	100.0	0.0	56.1	4.5	2.0	2.0	4.0 (0.6)	4.0 (0.6)	60 (8)	61 (6)	60.5 (7)	60.5 (7)
Mont <sup>24</sup>	77.4	55 ± 9	55 ± 9	55 ± 9	55 ± 9	0.0	100.0	100.0	0.0	44.5	NR	NR	NR	4.1 (0.5)	4.3 (0.5)	61.1 (8.8)	60.8 (9.7)	60.9 (9.4)	60.9 (9.4)
Jais <sup>0</sup>	83.9	49.7 ± 10.7	52.4 ± 11.4	52.4 ± 11.4	50 ± 11	100.0	0.0	100.0	0.0	25.9	2.7	NR	NR	3.9 (0.6)	4.0 (0.6)	63.1 (11)	65.6 (7.2)	64.3 (9.2)	64.3 (9.2)
Packer <sup>27</sup>	77.1	57 ± 9	56 ± 9	56 ± 9	56.3 ± 9	100.0	0.0	100.0	0.0	42.4	7.3	8.6	8.6	4.0 (0.5)	4.1 (0.6)	61 (6)	60 (6)	60.3 (6)	60.3 (6)
Hummel <sup>22</sup>	83.3	59.6 ± 8.3	60.7 ± 8.9	60.7 ± 8.9	60.3 ± 8.7	0.0	100.0	65.7	34.3	59.0	14.3	19.0	19.0	4.5 (0.5)	4.6 (0.5)	54.7 (7.1)	54.9 (6.7)	54.8 (6.8)	54.8 (6.8)
Reynolds <sup>14</sup>	66.5	55.8 ± 1.8	56.1 ± 3.2	56.1 ± 3.2	55.9 ± 2.3	100.0	0.0	100.0	0.0	48.5	10.2	NR	NR	4.0 (0.1)	4.0 (0.1)	62.3 (2)	62.7 (2)	62.6 (2)	62.6 (2)
Wazni <sup>11</sup>	NA	53 ± 8	54 ± 8	54 ± 8	54 ± 8	95.7	4.3	0.0	100.0	NR	NR	NR	NR	NR	NR	53 (50)	54 (6)	53.5 (5.5)	53.5 (5.5)
Nielsen <sup>26</sup>	70.1	56 ± 9	54 ± 10	54 ± 10	55 ± 10	100.0	0.0	0.0	100.0	32.7	5.4	2.7	2.7	4.0 (0.6)	4.0 (0.5)	NR	NR	NR	NR
Kritvayaphong <sup>23</sup>	63.3	55.3 ± 10.5	48.6 ± 15.4	48.6 ± 15.4	51.9 ± 13	70.0	30.0	60.0	40.0	36.7	13.3	6.7	6.7	4.0 (0.7)	3.9 (0.7)	63.7 (9.5)	61.8 (8.8)	62.7 (9.2)	62.7 (9.2)
Blomstrom-Lundqvist <sup>21</sup>	77.4	55.8 ± 10.6	56.3 ± 8.9	56.3 ± 8.9	56.0 ± 9.8	72.9	27.1	100.0	0.0	38.7	3.9	3.2	3.2	4.2 (0.6)	4.2 (0.5)	56.2 (7.2)	56.1 (7.7)	56.1 (7.4)	56.1 (7.4)

AAD, antiarrhythmic drug; AF, atrial fibrillation; CAD, coronary artery disease; comparator, antiarrhythmic drugs; DM, diabetes mellitus; HTN, hypertension; LA, left atrial; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NR, not reported; PAF, paroxysmal atrial fibrillation; RFA, radiofrequency ablation; SD, standard deviation.

standardized mean differences (SMD) were calculated for continuous outcomes measured on different scales between studies. When the data were unavailable numerically, we used approximations based on graphic output. For studies reporting only means and interquartile ranges, means and standard deviations were estimated.<sup>19</sup> Point estimates with 95% confidence intervals are reported.

Studies were evaluated for clinical heterogeneity using the  $\chi^2$  test for homogeneity with an alpha = 0.10 and the  $I^2$  statistic to quantify inconsistency.<sup>20</sup> We considered  $I^2$  values of 0%-40% as not important, 30%-60% as moderate heterogeneity, and 75%-100% as considerable heterogeneity.<sup>20</sup> Review Manager (RevMan) Version 5.3.5 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, 2014) software was used to enter and analyse the study data.

**Results**

**Literature search and study selection**

We identified 15,878 records. After removing duplicates, 11,023 records were screened by title and abstract ( $K = 0.74$ ), 262 full-text articles were assessed for eligibility ( $K = 0.87$ ), and 13 studies<sup>10,11,13,14,21-29</sup> comprising 20 articles were included (Fig. 1).

**Study characteristics**

A total of 4093 patients were included in the 13 studies, ranging from 30 to 2204 patients. Most studies were from Europe and North America, and all were published between 2003 and 2019. Table 1 summarizes the study characteristics of the included studies.

**Patient characteristics**

Patients were predominantly male (73.8%), with a weighted mean age of 56.3 ± 8.8, and had mostly PAF (42.9%-100%). Over two-thirds had failed ≥1 AADs. Rates of cardiac risk factors ranged from 2.0% to 80.6%, whereas LA size and LVEF were consistent across studies (Table 2).

**Risk of bias**

Most trials had low risk of bias for 5 of 7 categories (Supplemental Fig. S1); however, almost all trials were at high risk of bias because of lack of blinding of both participants and personnel for outcome assessment.

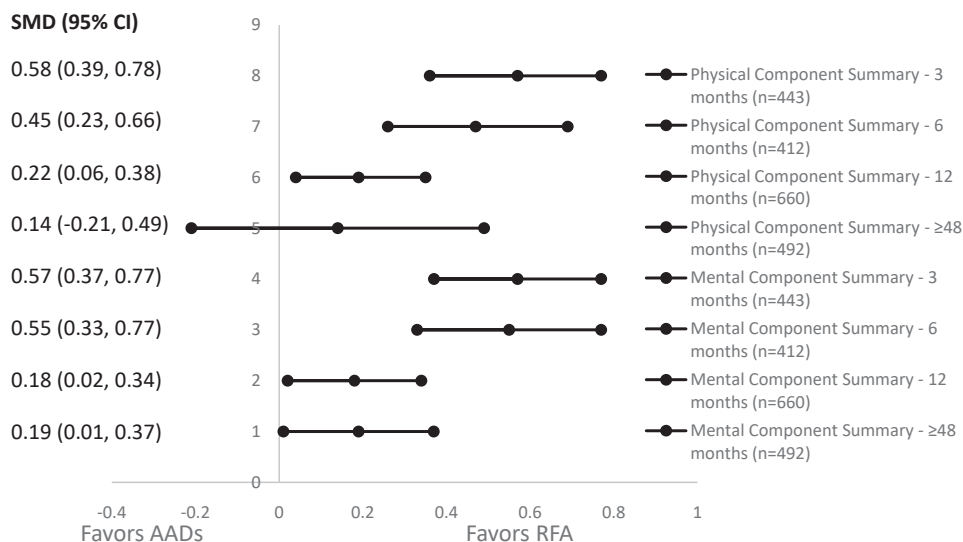
**Quality of evidence**

Because of concerns with risk of bias and imprecision, evidence for HRQL and symptoms were downgraded from high to “low.” The GRADE summary of quality evaluation for the HRQL outcomes and AF-related symptoms is presented in Supplemental Table S2.

Publication bias was not evaluated using a funnel plot, as < 10 studies were included for each outcome.<sup>17</sup>

**Outcome analyses**

For the HRQL analyses, 2 studies assessed it with tools other than the Short Form-36 (SF-36) survey.<sup>22,24</sup> In the AF-QOL, the physical and psychological components were analysed together with the SF-36 physical and mental component



**Figure 2.** Physical and Mental Component Summary scores at 3, 6, 12, and ≥48 months: as measured by the SF-36 (0-100). A positive change from baseline (right axis) to follow-up indicates an improvement in HRQL, whereas a negative change (left axis) indicates a worsening of HRQL. AAD, antiarrhythmic drug; CI, confidence interval; HRQL, health-related quality of life; RFA, radiofrequency ablation; SF-36, Short Form-36; SMD, standardized mean difference.

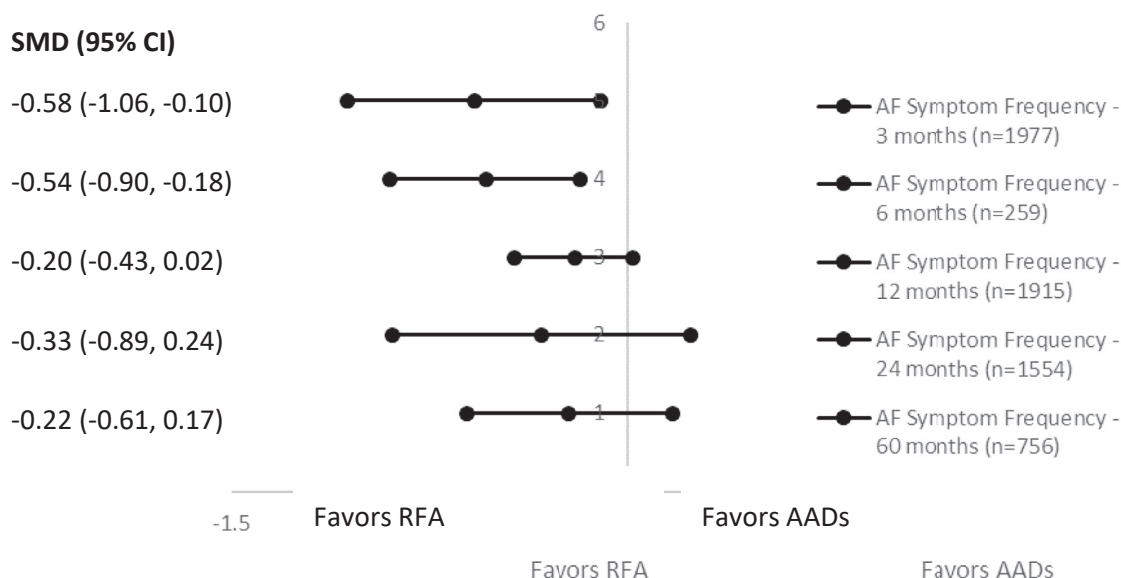
scores, respectively. For the AF symptom and QOL surveys, the physical and mental scores were analysed together with the SF-36 physical and mental component scores, respectively.

Key analyses are shown in Figures 2-4. Individual forest plots for each outcome, by follow-up time point, can be found in Supplemental Figures S2-S14.

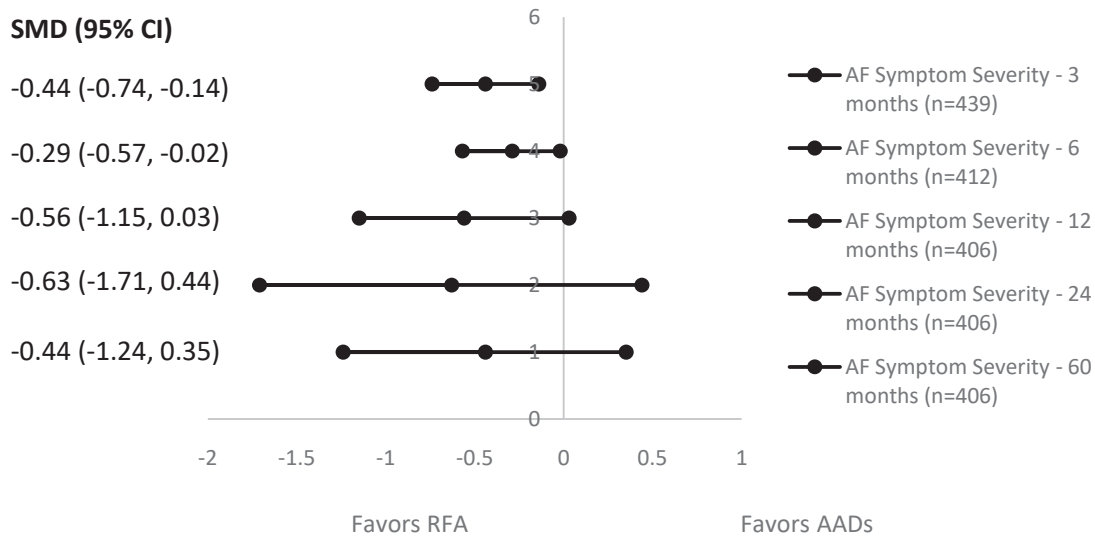
Of the 13 RCTs comparing CA performed with RFA energy vs AADs and reporting HRQL outcomes, data from only 2-5 studies could be pooled at each time point due to inconsistencies in reported time points and variation in tools

of HRQL assessment. There were not enough trials evaluating CBA vs AADs that reported patient HRQL to meta-analyse.

One study contributed over half of all patients.<sup>13</sup> We performed a sensitivity analysis by removing this study’s data from all applicable outcomes (see Supplemental Fig. S15). Most outcomes did not change with the exception of the EuroQol-5 Dimension (EQ-5D) scales at 12 months, Mental Health at 12 months, and AF symptom frequency at 3 months, which all went from slightly favouring RFA to demonstrating no difference between treatments. Interestingly, AF symptom severity at



**Figure 3.** AF-symptom frequency at 3, 6, 12, 24, and 60 months: AF-symptom frequency as measured by the AF Symptom Frequency and Severity Checklist and the University of Toronto Atrial Fibrillation Severity Scale. A negative change (left axis) between baseline and follow-up indicates an improvement in symptoms, whereas a positive change (right axis) indicates a worsening of symptoms. AAD, antiarrhythmic drug; AF, atrial fibrillation; CI, confidence interval; RFA, radiofrequency ablation; SMD, standardized mean difference.



**Figure 4.** AF-symptom severity at 3, 6, 12, 24, and 60 months: AF-symptom severity as measured by the University of Toronto Atrial Fibrillation Severity Scale and AF Symptom Frequency and Severity Checklist (AFSS). A negative change (**left axis**) between baseline and follow-up indicates an improvement in symptoms, whereas a positive change (**right axis**) indicates a worsening of symptoms. AAD, antiarrhythmic drug; AF, atrial fibrillation; CI, confidence interval; RFA, radiofrequency ablation; SMD, standardized mean difference.

6 months and General Health at 12 months both showed a stronger association favouring RFA over AADs with the removal of CABANA data.

Two trials<sup>13,21</sup> combined RFA and CBA in their CA strategy and did not report the data separately. We first pooled both studies to see if their effects were similar (see [Supplemental Fig. S16](#)) before pooling them with the other study data.

### RFA vs AADs

In the RFA vs AAD analyses, RFA in the acute phase (3-6 months) was associated with a significant increase in both the Physical Component Summary (PCS) score (3 months' SMD = 0.58 [0.39-0.78];  $P < 0.00001$ ,  $I^2 = 6\%$ , 3 trials,  $n = 443$ ) (6 months' SMD = 0.45 [0.23-0.66];  $P < 0.0001$ ,  $I^2 = 0\%$ ; 3 trials,  $n = 412$ ) and the Mental Component Summary (MCS) score (3 months' SMD = 0.57 [0.37-0.77];  $P < 0.00001$ ;  $I^2 = 0\%$ , 3 trials,  $n = 443$ ) (6 months' SMD = 0.55 [0.33-0.77];  $P = 0.00001$ ,  $I^2 = 0\%$ , 3 trials,  $n = 412$ ) at 3 and 6 months ([Fig. 2](#)) in comparison with AADs. At 12 months, both the PCS and MCS scores still showed a significantly greater improvement favouring RFA over AADs ([Supplemental Figs. S2 and S3](#)). Only 1 trial reported PCS and MCS summary scores at 24 months preventing meta-analysis at this time point.<sup>30</sup> By 48 months after intervention, no differences in PCS scores were observed between treatment strategies; however, a very small statistically significant difference favouring RFA over AADs was seen in the MCS scores ([Supplemental Figs. S2 and S3](#)).

For all 8 SF-36 subscales, some improvements in HRQL were observed in the initial 6-12 months after CA ([Supplemental Figs. S7-S14](#)); however, the results were not consistent across subscales or time points. Long-term improvements were observed favouring RFA in comparison with AADs in 6 of 8 SF-36 subscales including General Health, Physical Functioning, Bodily Pain, Mental Health, Social

Functioning, and Vitality ([Supplemental Figs. S8, S10-S12, and S14](#)).

Because of the small number of trials measuring HRQL at each time point, we were only able to perform the following subgroup analyses: (1) the effect of CA vs AADs on HRQL in treatment naïve patients and (2) the effect on HRQL on AAD patients crossing over to CA. Of the 4 trials comparing CA vs AADs as first-line treatment,<sup>11,13,25,26</sup> we were able to pool HRQL data from 3 of these trials at 12 months after treatment that assess the impact of CA vs AADs on treatment naïve patients with AF.<sup>15,25,26</sup> After 12 months, there was no difference in HRQL scores between treatment groups, as measured using the EQ-5D (MD = 0.02 [-0.00, 0.04];  $P = 0.18$ , 3 trials,  $n = 2172$ ) ([Supplemental Fig. S4](#)).

Three trials reported summary HRQL data without crossovers and only at 3 months after randomization.<sup>10,14,22</sup> At 3 months, there were significant increases in both the PCS and MCS summary scores favouring CA performed with RFA energy vs AADs ([Supplemental Figs. S2 and S3](#)).

For AF-related symptoms, significant decreases in symptom frequency were observed acutely (3-6 months), favouring CA performed with RFA vs AADs ([Fig. 3](#)) and diminished by 12 months. Similar results were seen for AF symptom severity ([Fig. 4](#)).

The number of repeat ablations varied significantly between trials, from 4 (12.1%) to 215 (19.4%) as did the percentage of patients with AF recurrence (11%-54.5% in the RFA arm) ([Table 1](#)). As most studies did not report the exact timing of when these repeat ablations occurred, we were not able to determine their sequencing in relation to AF symptom recurrence. Drug-related side effects and lack of efficacy were the most common reasons why patients with AF discontinued treatment or crossed over to the CA arm where permitted. Side effects ranged from bradycardia, thyrotoxicosis, sexual dysfunction, and gastrointestinal effects to stroke and pulmonary vein stenosis.

## Discussion

We performed a meta-analysis evaluating whether CA or AADs improved HRQL, AF-related symptoms, and the number of repeat ablations needed to maintain sinus rhythm. Our analyses demonstrated that CA performed with RFA energy improves both HRQL and AF-related symptoms in the acute phase (3-6 months); however, these results were not consistently observed in long term (12-60 months). The number of repeat ablations needed, as well as the percentage of patients with AF recurrence at the end of follow-up, varied significantly between trials.

Our results corroborate with a previously published meta-analysis from Siontis et al.,<sup>31</sup> who evaluated published and unpublished HRQL data from RCTs of CA performed with RFA energy vs AADs for symptomatic AF. They found that CA demonstrated significant improvements in 3 of 8 SF-36 subscales and the MCS summary score, 3 months after procedure, but these effects diminished by 6 months.<sup>31</sup> We also observed that CA demonstrated significant improvements in the PCS and MCS scores and 8 of 8 SF-36 subscales in the 3 months after procedure compared with AADs, but these effects were only sustained in the long term in 5 of 8 subscales.

Our results differ, likely because they included RCTs comparing CA with or without subsequent AADs after procedure. We focused solely on the effect of CA itself without the addition of AADs after blanking, to evaluate the effect of each treatment method separately. This may explain why we found more HRQL differences favouring CA in the acute phase, whereas Siontis et al. did not. We also included the recently published CABANA trial<sup>13</sup> that contributed substantial weight in meta-analysis of HRQL due to their large patient population, thus driving the overall effects to favour CA. The mixed patient populations of the included trials could be another reason for why CA only showed improvement in HRQL and symptom burden in the acute phase. Most RCTs included patients with AF who had already failed AADs and only 4 of the RCTs studied treatment naïve patients, with 3 of these measuring HRQL at the same time point, 12 months after CA using the EQ-5D.<sup>13,25,26</sup> When meta-analysed, no differences were observed between treatment strategies. More trials comparing CA vs AADs in naïve individuals are needed to definitively assess their treatment-related impact on HRQL and AF symptoms.

Results from Siontis et al.'s meta-analysis, and ours, raise an important question as to why the HRQL-related effects of CA do not seem to be maintained in the long term. One explanation relates to the current limitations of generic HRQL surveys, which measure overall "global change" compared with baseline status.<sup>32</sup> Generic HRQL surveys are effective in assessing general levels of HRQL in a variety of patient populations, but they lack specificity to distinguish between different disease states.<sup>33</sup> Another issue is the short timeframe for HRQL measurement, with most asking about HRQL and symptoms in the 4 weeks before their administration. This short recall timeframe, combined with infrequent administration, limits the utility of these instruments to detect more temporally nuanced changes in the clinical status of patients with AF. It may be that a longer-term impact on HRQL, if present, is not being detected by virtue of insensitive measurement bias.

Several AF-specific tools have come into widespread use in the past few years.<sup>34,35</sup> Their additive value lies with their frequent capture of experiences of patients with AF and they assess domains that are relevant and exclusive to AF, thereby increasing their sensitivity to HRQL changes.<sup>36</sup> Only 3 of 13 RCTs we found measured HRQL using an AF-specific survey and all at differing time points. Future RCTs of CA should use AF-specific HRQL instruments at standardized time points to assess the impact of CA as a treatment option for patients with AF.

The potential "placebo" effect of the more invasive CA over AADs cannot be discounted for the initial improvement of HRQL and AF-related symptoms. As an example, in the ORBITA trial, percutaneous coronary intervention was compared head to head with a sham procedure, and despite percutaneous coronary intervention-improving haemodynamic and imaging indices, it did not improve exercise time or symptoms.<sup>37</sup> An apparent benefit of CA over AADs is not surprising, given the considerable interventional nature of the procedure. An RCT using a placebo design would help tease out the real effects of the procedure itself.

Perhaps the most important question is, despite the increased emphasis on patient-reported outcomes in AF, only a minority of trials collect and report HRQL, with very few using AF-specific instruments.<sup>38</sup> The recently published CAPTAF trial<sup>21</sup> was the first that we have seen to measure HRQL as its primary outcome, with freedom from AF recurrence and AF burden collected as secondary outcomes. More broadly, Steinberg et al.<sup>38</sup> measured how frequently patient-reported outcomes were collected in registered clinical trials of patients with AF over a 19-year period. Of 1709 registered studies, only 14% included patient-reported outcomes, with most describing HRQL outcomes using generic rather than disease specific tools. This echoes our own findings, as we were only able to pool data from 2 to 5 trials for each HRQL outcome data due to inconsistencies in reported time points and variation in tools of HRQL assessment. Most notably, this highlights the lack of attention paid by the scientific community to outcome measurements that are most relevant to patients. Future AF trials should collect and publish HRQL outcomes at consistent time points so that patients and clinicians can decide on the best treatment options.

## Limitations

The RCTs included in these analyses had differing follow-up periods, AAD and anticoagulation regimens, and AF definitions. We could only analyse data at the study level and not at the patient-level data.

Patient crossovers may have diluted the differences between treatments. Given that most of the RCTs allowed crossovers to varying degrees at differing time points, it is likely a big contributor to the equalization in HRQL and symptoms reported between groups over time.

Another source of bias is that a third of patients (34.1%; 1398 of 4093) had failed  $\geq 1$  AADs before treatment. It is possible that AAD failures were not randomized in the same proportion as treatment naïve patients, thus leading to a bias favouring RFA over AADs.

The SF-36 PCS, MCS, and 8 subscale scores were not available across similar time points, limiting the amount of



data to pool for analysis. We were not able to evaluate the benefit of CBA vs RFA, as only 2 of 4 trials comparing these had HRQL data and at different time points.

## Conclusions

There is low-quality evidence from few RCTs suggesting that CA performed with RFA is more effective in improving short-term physical and mental health than AAD therapy in patients with AF with prior failed AAD treatment. However, these benefits decrease over time such that patients who received AAD therapy show an improvement in both physical and mental health, whereas patients who received CA generally remain consistent in their HRQL scores. Similar results were seen for AF-related symptom frequency and severity. There is a need for more trials reporting HRQL and AF-related symptoms at consistent time points to definitively assess the effectiveness of CA for the treatment of patients with AF.

## Acknowledgements

K.S.A. is the guarantor. K.S.A., S.L.C., and M.H.M. developed the study concept and design. L.B. developed and performed the search strategy in conjunction with K.S.A. K.S.A., T.A., S.H., and M.H.M. contributed to the development of the selection criteria, the risk of bias assessment, and data extraction criteria. J.C.V. provided statistical expertise. P.D., J.S.H., and J.G.A. provided content expertise. All authors provided feedback and approved the final manuscript.

## Funding Sources

K.S.A. was funded by an EB Eastburn Post-Doctoral Fellowship. J.G.A. is supported by a Michael Smith Foundation for Health Research Scholar Award. This meta-analysis was funded by a Canadian Arrhythmia Network (CANet) CHAT Discovery Award. The study funder had no involvement in the preparation, conduct, or writing of this manuscript.

## Disclosures

P.D., J.S.H., J.G.A., and S.L.C. are Network Investigators of the Cardiac Arrhythmia Network of Canada (CANet), as part of the Networks of Centres of Excellence (NCE). K.S.A. is Chair of the CANet Training and Education Committee and receives salary support from a CANet Program grant. P.D. is supported by a CANet Program grant. J.S.H. received grants from Medtronic and Abbott (formerly St Jude Medical). J.G.A. reports grants from Medtronic.

## References

1. Camm AJ, Kirchhof P, Lip GY, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Europace* 2010;12:1360-420.
2. Fairclough D. *Design and Analysis of Quality of Life Studies in Clinical Trials*. Boca Raton, FL: Chapman and Hall/CRC, 2010.
3. 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.e1-19.
4. Reynolds MR, Lavelle T, Essebag V, Cohen DJ, Zimetbaum P. Influence of age, sex, and atrial fibrillation recurrence on quality of life outcomes in a population of patients with new-onset atrial fibrillation: the Fibrillation Registry Assessing Costs, Therapies, Adverse events and Lifestyle (FRACTAL) study. *Am Heart J* 2006;152:1097-103.
5. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* 2016;37:2893-962.
6. Kirchhof P, Ammentorp B, Darius H, et al. Management of atrial fibrillation in seven European countries after the publication of the 2010 ESC Guidelines on atrial fibrillation: primary results of the PREvention of F thromboembolic events—European Registry in Atrial Fibrillation (PREFER in AF). *Europace* 2014;16:6-14.
7. Shi LZ, Heng R, Liu SM, Leng FY. Effect of catheter ablation versus antiarrhythmic drugs on atrial fibrillation: a meta-analysis of randomized controlled trials. *Exp Ther Med* 2015;10:816-22.
8. Piccini JP, Lopes RD, Kong MH, et al. Pulmonary vein isolation for the maintenance of sinus rhythm in patients with atrial fibrillation: a meta-analysis of randomized, controlled trials. *Circ Arrhythm Electrophysiol* 2009;2:626-33.
9. Andrade JG, Verma A, Mitchell LB, et al. 2018 focused update of the Canadian Cardiovascular Society Guidelines for the management of atrial fibrillation. *Can J Cardiol* 2018;34:1371-92.
10. Jais P, Cauchemez B, Macle L, et al. Catheter ablation versus antiarrhythmic drugs for atrial fibrillation: the A4 study. *Circulation* 2008;118:2498-505.
11. Wazni OM, Marrouche NF, Martin DO, et al. Radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of symptomatic atrial fibrillation: a randomized trial. *JAMA* 2005;293:2634-40.
12. Wilber DJ, Pappone C, Neuzil P, et al. Comparison of antiarrhythmic drug therapy and radiofrequency catheter ablation in patients with paroxysmal atrial fibrillation: a randomized controlled trial. *JAMA* 2010;303:333-40.
13. Mark DB, Anstrom KJ, Sheng S, et al. Effect of catheter ablation vs medical therapy on quality of life among patients with atrial fibrillation: The CABANA Randomized Clinical Trial. *JAMA* 2019;321:1275-85.
14. Reynolds MR, Walczak J, White SA, Cohen DJ, Wilber DJ. Improvements in symptoms and quality of life in patients with paroxysmal atrial fibrillation treated with radiofrequency catheter ablation versus antiarrhythmic drugs. *Circ Cardiovasc Qual Outcomes* 2010;3:615-23.
15. Allan KS, Henry S, Aves T, et al. Comparison of health-related quality of life in patients with atrial fibrillation treated with catheter ablation or antiarrhythmic drug therapy: a systematic review and meta-analysis protocol. *BMJ Open* 2017;7:e017577.
16. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;6:e1000097.
17. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928.
18. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924-6.

19. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol* 2005;5:13.
20. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21:1539-58.
21. Blomstrom-Lundqvist C, Gizurarson S, Schwieler J, et al. Effect of catheter ablation vs antiarrhythmic medication on quality of life in patients with atrial fibrillation: The CAPTAF Randomized Clinical Trial. *JAMA* 2019;321:1059-68.
22. Hummel J, Michaud G, Hoyt R, et al. Phased RF ablation in persistent atrial fibrillation. *Heart Rhythm* 2014;11:202-9.
23. Krittayaphong R, Raungrattanaamporn O, Bhuripanyo K, et al. 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):S8-16.
24. Mont L, Bisbal F, Hernandez-Madrid A, et al. Catheter ablation vs. antiarrhythmic drug treatment of persistent atrial fibrillation: a multicentre, randomized, controlled trial (SARA study). *Eur Heart J* 2014;35:501-7.
25. Morillo CA, Verma A, Connolly SJ, et al. Radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of paroxysmal atrial fibrillation (RAAFT-2): a randomized trial. *JAMA* 2014;311:692-700.
26. Nielsen JC, Johannessen A, Raatikainen P, et al. Radiofrequency ablation as initial therapy in paroxysmal atrial fibrillation. *N Engl J Med* 2012;367:1587-95.
27. Packer DL, Kowal RC, Wheelan KR, et al. Cryoballoon ablation of pulmonary veins for paroxysmal atrial fibrillation: first results of the North American Arctic Front (STOP AF) pivotal trial. *J Am Coll Cardiol* 2013;61:1713-23.
28. Pappone C, Vicedomini G, Augello G, et al. Radiofrequency catheter ablation and antiarrhythmic drug therapy: a prospective, randomized, 4-year follow-up trial: the APAF study. *Circ Arrhythm Electrophysiol* 2011;4:808-14.
29. Sahara H, Ohe T, Okumura K, et al. HotBalloon ablation of the pulmonary veins for paroxysmal AF: a multicenter randomized trial in Japan. *J Am Coll Cardiol* 2016;68:2747.
30. Nielsen JC, Johannessen A, Raatikainen P, et al. Long-term efficacy of catheter ablation as first-line therapy for paroxysmal atrial fibrillation: 5-year outcome in a randomised clinical trial. *Heart* 2017;103:368-76.
31. Siontis KC, Ioannidis JP, Katritsis GD, et al. Radiofrequency ablation versus antiarrhythmic drug therapy for atrial fibrillation. *JACC Clin Electrophysiol* 2016;2:170-80.
32. Dorian P, Burk C, Mullin CM, et al. Interpreting changes in quality of life in atrial fibrillation: how much change is meaningful? *Am Heart J* 2013;166:381-387.e388.
33. Heidt ST, Kratz A, Najarian K, et al. Symptoms in atrial fibrillation: a contemporary review and future directions. *J Atr Fibrillation* 2016;9:1422.
34. Dorian P, Guerra PG, Kerr CR, et al. Validation of a new simple scale to measure symptoms in atrial fibrillation: the Canadian Cardiovascular Society Severity in Atrial Fibrillation scale. *Circ Arrhythm Electrophysiol* 2009;2:218-24.
35. Spertus J, Dorian P, Bubien R, et al. Development and validation of the Atrial Fibrillation Effect on Quality-of-Life (AFEQT) Questionnaire in patients with atrial fibrillation. *Circ Arrhythm Electrophysiol* 2011;4:15-25.
36. Aliot E, Botto GL, Crijns HJ, Kirchhof P. Quality of life in patients with atrial fibrillation: how to assess it and how to improve it. *Europace* 2014;16:787-96.
37. Al-Lamee R, Thompson D, Dehbi HM, et al. Percutaneous coronary intervention in stable angina (ORBITA): a double-blind, randomised controlled trial. *Lancet* 2018;391:31-40.
38. Steinberg BA, Dorian P, Anstrom KJ, et al. Patient-reported outcomes in atrial fibrillation research: results of a Clinicaltrials.gov analysis. *JACC Clin Electrophysiol* 2019;5:599-605.

### Supplementary Material

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