Catheter Ablation for Atrial Fibrillation in Heart Failure Patients
A Meta-Analysis of Randomized, Controlled Trials

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ABSTRACT

OBJECTIVES The objective of the study was to compare rate control versus atrial fibrillation (AF) catheter ablation strategies in patients with AF and heart failure (HF).

BACKGROUND Rhythm control with antiarrhythmic drugs (AADs) is not superior to rate control in patients with HF and AF, but AF ablation may be more successful at achieving rhythm control than are AADs. However, risks for both ablation and AADs are probably higher and success rates lower in patients with HF.

METHODS We conducted a meta-analysis of trials that randomized HF patients (left ventricular ejection fraction [LVEF] <50%) with AF to a rate control or AF catheter ablation strategy and reported changes in LVEF, quality of life, 6-min walk test, or peak oxygen consumption. Study quality and heterogeneity were assessed through the use of Jadad scores and Cochran’s Q statistics, respectively. Mantel-Haenszel relative risks and mean differences were calculated through the use of random effect models.

RESULTS Four trials (N = 224) met inclusion criteria; 82.5% (n = 185) had persistent AF. AF ablation was associated with an increase in LVEF (mean difference, 8.5%; 95% confidence interval [CI]: 6.4% to 10.7%; p < 0.001) compared with rate control. AF ablation was superior in improving quality of life by Minnesota Living With Heart Failure (MLWHF) questionnaire scores (mean difference, –11.9; 95% CI: –17.2 to 6.6; p < 0.001). Peak oxygen consumption and 6-min walk distance increased in AF ablation compared with rate-control patients (mean difference, 3.2; 95% CI: 1.1 to 5.3; p = 0.003; mean difference, 34.8; 95% CI: 2.9 to 66.7; p = 0.03, respectively). In the persistent AF subgroup, LVEF and MLWHF were significantly improved with AF ablation. Major adverse event rates (risk ratio: 1.3; 95% CI: 0.4 to 3.9; p = 0.64) were not significantly different. No significant heterogeneity was evident.

CONCLUSIONS In patients with HF and AF, AF catheter ablation is superior to rate control in improving LVEF, quality of life, and functional capacity. Before accepting a rate-control strategy in HF patients with persistent or drug-refractory AF, consideration should be given to AF ablation. (J Am Coll Cardiol EP 2015;1:200–9) © 2015 by the American College of Cardiology Foundation.
trial fibrillation (AF) and heart failure (HF) are 2 common cardiac conditions associated with substantial morbidity, mortality, and cost on health care systems (1-4). The 2 conditions frequently coexist, and each may promote the other. AF is present in up to 50% of patients with HF (5). AF in HF patients is associated with increased hospital stay, stroke, and mortality (6-8). This may be at least partially attributed to the hemodynamic effects of AF caused by loss of atrial contraction along with irregular and/or rapid ventricular rates, which can lead to left ventricular dysfunction and decreased cardiac output (9,10).

Rhythm control with anti-arrhythmic drugs (AADs) has failed to be superior to rate control in patients with HF and AF in terms of cardiovascular mortality or worsening of HF (11). The risk of adverse events associated with AADs and their limited efficacy in restoring sinus rhythm have triggered an increased interest in AF catheter ablation (12,13).

Several observational studies of AF catheter ablation in patients with HF have reported that maintenance of sinus rhythm by catheter ablation can significantly improve cardiac function (14-16).

The aim of our study was to determine if AF catheter ablation is superior to rate control in patients with AF and HF. We performed a meta-analysis of randomized, controlled trials that compared AF catheter ablation with rate control in patients with HF and AF.

METHODS

This meta-analysis of clinical trials was performed according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (17).

LITERATURE REVIEW. Relevant studies were selected by searching PubMed, Medline, Embase, Central, ClinicalTrials.gov, The Cochrane Library, and ISI Web of Science (January 1980 to February 2015). The search was independently conducted by 2 investigators (S.A. and M.Q.). Search key terms were atrial fibrillation, persistent atrial fibrillation, pulmonary venous isolation, catheter ablation, heart failure, left ventricular dysfunction, impaired left ventricular systolic function, reduced left ventricular systolic function, low ejection fraction, heart failure with reduced ejection fraction, functional capacity, and quality of life. Bibliographies of retrieved studies were hand-searched to identify relevant studies.

SELECTION CRITERIA AND QUALITY ANALYSIS. Prospective randomized, controlled trials published in English that compared rate control with AF catheter ablation were included.

Trials that included patients with left ventricular ejection fraction (LVEF) <50%, randomized to a rate-control strategy or AF catheter ablation and that reported at least one of the studied outcomes, were included. Studies had to fulfill the following criteria for inclusion: 1) prospective randomized, controlled trial design; 2) patients enrolled with LVEF <50% and history of AF; 3) randomization to AF catheter ablation versus rate control (pharmacologic or atrioventricular [AV] node ablation with biventricular or right ventricular pacing); and 4) study follow-up of at least 6 months. Studies that used AADs as rhythm control or that did not report at least one outcome of interest were excluded.

Quality of the studies was assessed independently by 2 reviewers (S.A. and M.Q.). Jadad’s method was used to assess quality of the studies (18). The items assessed were blinding, randomization, and description of withdrawals or dropouts. All included studies had a quality score of 3. No studies attempted double-blinding. Therefore, weighting of the results was not performed.

DATA EXTRACTION AND OUTCOME MEASURES. Data were independently extracted by 2 investigators (S.A. and M.Q.), and discrepancies were resolved by unanimous consensus. Extracted data included number of patients in each intervention arm, characteristics of included patients, procedure characteristics, LVEF, quality-of-life parameters, and complications. Primary authors were contacted when data on studied outcomes were not reported.

The primary clinical endpoint was change in LVEF after 6 months. Secondary endpoints were Minnesota Living with Heart Failure (MLWHF) questionnaire scores, 6-min walk test distance, and peak oxygen consumption. Complications, adverse events, and deaths were also summarized.

Major adverse events were defined as death, intracranial hemorrhage, cardiac tamponade, pericardial effusion, pneumothorax, hemothorax, deep venous thrombosis or pulmonary embolism, sepsis, or pulmonary vein stenosis (>50%) requiring intervention. Procedural complications were defined as any complication that occurred in the 30-day postprocedural period. AF ablation was defined as pulmonary vein isolation with or without additional substrate modification and excluding AV junction ablation. Rate control was defined as the use of

ABBREVIATIONS AND ACRONYMS

AAD = anti-arrhythmic drug
AF = atrial fibrillation
HF = heart failure
LVEF = left ventricular ejection fraction
MLWHF = Minnesota Living With Heart Failure
NYHA = New York Heart Association
PVI = pulmonary vein isolation
pharmacological therapy or AV junction ablation for rate control.

**Statistical Analysis.** The results are presented as mean difference for continuous outcome measures with 95% confidence intervals (CIs). Random-effect models were used for all reported outcomes (19).

Heterogeneity among studies was assessed with the inconsistency index ($I^2$) statistic, which ranges from 0% to 100% and is defined as the percentage of the observed inter-trial variability that is due to heterogeneity rather than chance for each outcome ($I^2 > 60\%$ denotes significant heterogeneity) (20). Potential publication bias was evaluated by means of Begg’s funnel plot method (21).

To further detect any clinical heterogeneity, several sensitivity analyses were performed for the LVEF and MLWHF outcomes:

1. Trials including only patients with persistent AF were analyzed, excluding a trial that included patients with both persistent and paroxysmal AF.
2. Trials that used only pharmacologic rate control were analyzed, excluding a study that used AV node ablation with biventricular pacing as a rate-control strategy.
3. One trial assessed LVEF by means of 2 methods, with different results. Both results were used in a sensitivity analysis.
4. The LVEF for inclusion in 3 trials was < 40% and in 1 trial was < 50%. The trial with LVEF criterion of < 50% was excluded as a sensitivity analysis.
5. All trials had > 80% of patients free of AF after ablation, except 1 trial, which had > 50% of patients free of AF. This trial was excluded as a sensitivity analysis.

All statistical analyses were performed with the use of REVMAN software version 5.3. Two-tailed probability values of < 0.05 were considered significant.

**Results**

**Study Selection.** Of 1,144 papers originally retrieved by searching the databases, 4 met the inclusion criteria (Figure 1).

**Characteristics of Included Studies and Patients.** The 4 randomized, controlled trials (RCTs) were published between 2008 and 2014 and involved 224 patients (22-25). Three studies were conducted in Europe and one in both Europe and the United States. All trials were published in English.

The mean age of patients included in the trials ranged from 57 to 63 years. The proportion of men in the studies was 89%. Ischemic cardiomyopathy was the most common etiology for HF in the included patients. Three of the trials included patients with only persistent AF (23-25), whereas 1 trial included both paroxysmal and persistent AF (22). All but 39 of the included 224 patients had persistent AF. The mean duration of persistent AF was > 1 year. The mean LVEF of the included patients was 26.1%, and all patients had New York Heart Association (NYHA) functional classification of II or III. Further patient characteristics are listed in Table 1.

All of the included trials were of high quality ($\geq 3/5$) according to the Jadad quality assessment score. None of the included trials attempted double-blinding. Dropouts and withdrawals were described appropriately in the included trials. The blinding period ranged from 2 to 3 months. The percentage of patients requiring repeat procedures ranged from...
19.5% to 53.7%. Only 1 study had cross-over of patients, and intention-to-treat analysis was used (Table 2).

**OUTCOMES. LVEF.** Data for LVEF were available from all included trials. There was no significant heterogeneity ($I^2 = 0\%$) nor detectable publication bias. AF catheter ablation compared with rate control was associated with an 8.5% increase in LVEF at 6 to 12 months (mean difference, 8.53; 95% CI: 6.4 to 10.7; $p < 0.001$). The improvement in LVEF in the AF catheter ablation arm compared with rate control was evident in all of the included trials (Figure 2A).

**Quality of life and functional capacity measures.** Catheter ablation was superior to rate-control strategy in improving quality of life. Data on MLWHF were available from all the included trials. Across the included trials, there was no evidence of significant heterogeneity ($I^2 = 8\%$) or publication bias. There was a significant improvement in MLWHF questionnaire scores in the AF catheter ablation arm compared with rate control ($p < 0.001$).
scores in the AF catheter ablation intervention group versus that in the rate-control group (mean difference, -11.9; 95% CI: -17.2 to -6.6; p < 0.001) (Figure 2B).

Data on 6-min walk tests were available from three prospective clinical trials. Across the included trials, there was evidence of moderate heterogeneity ($I^2 = 45\%$). Significant improvement in performance on 6-min walk tests was observed in patients undergoing AF catheter ablation compared with a rate-control strategy (mean difference, 34.8; 95% CI: -17.2 to 83.3; p = 0.001). Sensitivity analyses. One trial included patients free of AF after ablation, whereas the other trials had >50% of patients free of AF after ablation. On exclusion of that trial (23), AF catheter ablation was still associated with significant improvements in LVEF (mean difference, 8.8; 95% CI: 6.3 to 11.3; p < 0.001) and MLWHF (mean difference, -13.8; 95% CI: -19.3 to 8.3; p < 0.001).

Procedural complications and adverse events. We were able to obtain previously unpublished data on complications and incorporate them into our analysis from 2 RCTs (23,24). Two strokes, 4 cardiac tamponades, and 1 pericardial effusion were seen in the AF catheter ablation, culminating in a procedural complication rate of 6.3%. Details of complications and adverse events are listed in Table 3.

Overall, no statistically significant difference was found in the major adverse event rates between the AF catheter ablation (7.2%) versus the rate-control (4.6%) arms (RR: 1.3; 95% CI: 0.4 to 3.9; p = 0.64) (Figure 3A). On examining all reported adverse events, there was a trend toward more events in the AF catheter ablation (18.9%) compared with the rate-control arm (12.0%), but this did not reach statistical significance (RR: 1.6; 95% CI: 0.8 to 3.0; p = 0.17) (Figure 3B).

No difference in HF re-admissions was seen between the 2 treatment groups (RR: 1.4; 95% CI: 0.4 to 4.6; p = 0.56) (Figure 3C).

<table>
<thead>
<tr>
<th>TABLE 2 Intervention Characteristic</th>
<th>Khan et al. (22)</th>
<th>Jones et al. (24)</th>
<th>Macdonald et al. (23)</th>
<th>Hunter et al. (25)</th>
</tr>
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<tbody>
<tr>
<td>Blanking period, months</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Frequency of monitoring, months</td>
<td>2, 3, 6</td>
<td>2, 3, 6, 12</td>
<td>3, 6</td>
<td>1, 3, 6</td>
</tr>
<tr>
<td>Modality of assessing heart rhythm</td>
<td>Loop recorder</td>
<td>48-h Holter monitor</td>
<td>Existing implanted devices</td>
<td>48-h Holter monitor</td>
</tr>
<tr>
<td>AAD strategy after ablation</td>
<td>AAD for 2 months</td>
<td>AAD stopped after ablation</td>
<td>Amiodarone for 3 months</td>
<td>AAD stopped after ablation</td>
</tr>
<tr>
<td>No. of patients undergoing repeat procedures, n (%)</td>
<td>8 (19.5)</td>
<td>5 (20.1)</td>
<td>6 (30.0)</td>
<td>14 (53.7)</td>
</tr>
<tr>
<td>Cross-over</td>
<td>None</td>
<td>None</td>
<td>2†</td>
<td>None</td>
</tr>
<tr>
<td>Ablation strategy of AF</td>
<td>PVI ± Linear lesions and sources of complex fractionated electrograms</td>
<td>PVI ± Linear lesions ± left atrial complex fractionated electrograms ± Cardioversion and cavotricuspid isthmus ablation</td>
<td>PVI ± Linear lesions ± sources of complex fractionated electrograms ± Cardioversion ± cavotricuspid isthmus ablation</td>
<td>PVI with ablation of complex or fractionated electrograms ± Linear lesions ± Cavotricuspid isthmus ablation</td>
</tr>
<tr>
<td>Follow-up, months</td>
<td>6</td>
<td>12</td>
<td>6</td>
<td>6-12</td>
</tr>
</tbody>
</table>

*Only in the atrial fibrillation (AF) catheter ablation group. †One patient in the AF catheter ablation group and one patient in the rate-control group. Intention-to-treat analysis was used.

AAD = antiarrhythmic drug; PVI = pulmonary vein isolation.
DISCUSSION

We present the first meta-analysis of high-quality prospective, RCTs comparing AF catheter ablation versus rate-control strategies in patients with HF and AF.

Previous meta-analyses have relied mainly on data from observational studies in addition to a small number of RCTs (26–28). This resulted in heterogeneity that was highly significant, raising uncertainties about the consistency of the combined studies. The main outcomes studied were LVEF, B-type natriuretic peptide, and complications; all concluded improvements in LVEF of 11% to 13%. Through collaboration with primary investigators of the included RCTs, our current meta-analysis provides similar conclusions regarding improvement in LVEF in addition to new insight into subjective and objective quality-of-life measures and complication rates, including heart failure readmissions. It also provides conclusions that are based on a larger number of RCTs, culminating in results with trivial heterogeneity among the majority of reported outcomes, which suggests strong

FIGURE 2 Changes in Functional Outcomes

(A) Change in left ventricular ejection fraction (LVEF). (B) Change in Minnesota Living With Heart Failure (MLWHF). (C) Change in 6-min walk test distance. (D) Change in peak oxygen consumption (VO2). Mean difference and 95% confidence intervals (CIs) in studies comparing atrial fibrillation catheter ablation with rate control in patients with heart failure. IV = inverse variance; SD = standard deviation.
homogeneity in clinical and methodological characteristics of the included RCTs. We sought evidence from RCTs in an attempt to limit the influence of selection bias and control for unmeasured confounders (29). We also targeted the specific patient population of HF with reduced LVEF and documented AF instead of including HF with preserved LVEF. At least 6 months of follow-up was chosen partially to control for differences in the use of AAD after AF catheter ablation (30).

A significant improvement in LVEF was seen with the AF catheter ablation strategy in comparison to the rate-control approaches. The trend in improvement of LVEF was evident among all of the included RCTs. Of note, 22% to 50% of patients were still in AF after AF catheter ablation, which suggests a role for reduction of AF burden rather than AF cure, leading to the aforementioned benefits. Another possibility is that patients may have had better follow-up and potentially better overall medical care in the AF catheter ablation group (30).

Several other observational studies have also shown improvement in LVEF in ablation compared with rate-control arms (14–16). This highlights the importance of preserving or restoring the atrial contribution to cardiac hemodynamics, because the AF catheter ablation rhythm control strategy provides additional benefits over simple control of rapid ventricular rate in patients with HF in AF.

Novel findings from this meta-analysis included the marked improvements in the quality of life, 6-min walk test performance, and peak VO2 in the AF catheter ablation group. The improvement in peak VO2 carries particular significance, given that it is a well-established prognostic indicator in HF with potential impact on survival and hospital stay (31–34). The change in distance walked on the 6-min walk test has also been established as an independent predictor of survival (35). In one of the trials in which half of patients in the AF catheter ablation remained in AF, there was no difference in the 6-min walk test outcome between the 2 groups (23). This trial led to the moderate heterogeneity observed of this outcome. Nevertheless, the improvements in quality of life observed despite similar HF re-admission rates between the 2 groups are consistent with the overall improvements observed in the 6-min walk test and peak VO2 (31). The concordant findings in these 3 outcomes provide both subjective and objective evidence for the benefits of catheter ablation for AF on quality of life.

Although the inconsistency index statistic measure of heterogeneity does not capture differences in methodology between AF ablation approaches (e.g., pulmonary vein isolation [PVI] and various substrate ablation approaches) as well as between rate-control approaches (e.g., AV nodal-blocking medications versus AV junction ablation), we performed sensitivity analyses, including repeating meta-analyses of LVEF and MLWHF without the 1 study that used AV junction ablation for rate control (22) and found similar results.

Catheter ablation is an invasive procedure, which may provide benefits but also carries well-known

<table>
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<tr>
<th>TABLE 3</th>
<th>Adverse Events</th>
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<tbody>
<tr>
<td>Complications</td>
<td>Khan et al. (22)</td>
</tr>
<tr>
<td>AF Catheter Ablation</td>
<td>Rate Control</td>
</tr>
<tr>
<td>Major</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>-</td>
</tr>
<tr>
<td>Stroke</td>
<td>-</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>-</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>-</td>
</tr>
<tr>
<td>Cardiac tamponade</td>
<td>-</td>
</tr>
<tr>
<td>Pericardial effusion</td>
<td>1</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>-</td>
</tr>
<tr>
<td>Minor</td>
<td></td>
</tr>
<tr>
<td>Pulmonary vein stenosis</td>
<td>2*</td>
</tr>
<tr>
<td>Temporary worsening of heart failure</td>
<td>1</td>
</tr>
<tr>
<td>Groin bleeding</td>
<td>3</td>
</tr>
<tr>
<td>Pocket hematoma</td>
<td>-</td>
</tr>
<tr>
<td>Chest infection</td>
<td>-</td>
</tr>
<tr>
<td>Ventricular lead dislodgment</td>
<td>-</td>
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</tbody>
</table>

*Mild asymptomatic pulmonary vein stenosis that did not require intervention. †Death occurred 11 months after ablation from progressive worsening of heart failure and end-stage lung disease.
risks, such as stroke, pericardial tamponade, pericarditis, bleeding, pulmonary stenosis, atrio-esophageal fistula, and even death, risks that may be even higher in a population with HF. The AF catheter ablation peri-procedural major complication rate in this study was 6.3%. Despite the structural changes seen in patients with reduced LVEF, the reported AF catheter ablation complication rate in this meta-analysis is comparable to, though perhaps slightly higher than, AF catheter ablation complication rates reported in a large prospective study (5.2%) and a recent meta-analysis in patients with structurally normal hearts (2.7% to 3.5%) (36,37). The trend toward higher adverse event rates compared with the rate-control group (p = 0.17) suggests there may be a price paid for improving the other outcomes measured in this study. Given the overall low adverse event rates, our study was probably under-powered to detect statistically significant differences in adverse events. These risks are put in context to the rate-control adverse event rates in this study of 12.5% in the pharmacological rate-control studies and 10% in the study using AV node ablation and biventricular pacing. Cross-over occurred in one trial in only 2 patients, making it less likely that cross-overs can explain the comparability in the incidence of major complications. It is perhaps more plausible that AF ablation was associated with relatively low rates of major adverse event complications, such as death or stroke (<1%), in these studies (38).

The majority (82.5%) of patients in the current study had persistent AF; therefore, results may not be easily extrapolated to a population with paroxysmal AF. However, this high proportion of patients with persistent AF, as well as the sensitivity analyses demonstrating similar efficacy of AF catheter...
ablation compared with rate control for persistent AF, supports attempting an AF catheter ablation approach in this population despite persistence of AF. In current clinical practice, patients with HF and persistent AF may be more readily relegated to a rate-control approach. Our findings suggest that significant additional benefit might be achieved by pursuing a rhythm control approach with the use of AF catheter ablation. A well-designed, adequately powered, RCT seems warranted to provide further data on safety, efficacy, survival, and functional capacity outcomes associated with catheter ablation in patients with HF and AF. Subanalyses of patients with AF and HF in the ongoing CABANA trial of AF ablation versus antiarrhythmic drug use will also be of interest.

**STUDY LIMITATIONS.** First, patients were only followed up to 1 year, therefore limiting the assessment of long-term outcomes. Second, the number of patients included in these RCTs remains small. Thus, the included RCTs were not powered to assess hard outcomes, such as mortality. Third, there may have been bias in selecting healthier patients, who were suitable candidates for an invasive strategy, for these randomized trials. A fourth limitation is the fact that the power of funnel plots in detecting publication bias increases with the inclusion of more studies; however, we were limited by the available trials in the literature. Nevertheless, the mean LVEF of patients was <35% in all studies, NYHA functional class was predominantly 2 to 3, and complication and adverse event rates were at the higher end of that reported in the literature, which suggests that these patients might be representative of a HF population at large. Last, PVI alone was not used in the majority of cases; after PVI, additional atrial substrate modification was used to varying degrees in each study. However, these approaches reflect contemporary local practice for catheter ablation of persistent AF.

**CONCLUSIONS**

An AF catheter ablation strategy in patients with AF and HF results in improved LV function, functional capacity, HF symptoms, and quality of life compared with a rate-control strategy. Patients with HF may be at higher risk of complications with interventional approaches for both rhythm and rate-control strategies. However, our analyses suggest that before accepting a rate-control strategy in HF patients with persistent or drug-refractory AF, an individualized approach should be pursued, including consideration to performing AF catheter ablation in appropriately selected patients.

**REFERENCES**


KEY WORDS atrial fibrillation, catheter ablation, heart failure, pulmonary vein isolation