Treatment Strategies for Atrial Fibrillation With Left Ventricular Systolic Dysfunction
— Meta-Analysis —

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Background: Atrial fibrillation (AF) frequently coexists with heart failure (HF) with reduced ejection fraction (EF). This meta-analysis compared AF control strategies, that is, rhythm vs. rate, and catheter ablation (CA) vs. anti-arrhythmic drugs (AAD) in patients with AF combined with HF.

Methods and Results: The MEDLINE, EMBASE, and CENTRAL databases were searched, and 13 articles from 11 randomized controlled trials with 5,256 patients were included in this meta-analysis. The outcomes were echocardiographic parameters (left ventricular EF, LVEF), left atrial (LA) size, and left ventricular end-systolic volume, LVESV), clinical outcomes (mortality, hospitalization, and thromboembolism), exercise capacity, and quality of life (QOL). In a random effects model, rhythm control was associated with higher LVEF, better exercise capacity, and better QOL than the rate control. When the 2 different rhythm control strategies were compared (CA vs. AAD), the CA group had significantly decreased LA size and LVESV, and improved LVEF and 6-min walk distance, but mortality, hospitalization, and thromboembolism rates were not different between the rhythm and rate control groups.

Conclusions: In AF combined with HF, even though mortality, hospitalization and thromboembolism rates were similar, a rhythm control strategy was superior to rate control in terms of improvement in LVEF, exercise capacity, and QOL. In particular, the CA group was superior to the AAD group for reversal of cardiac remodeling.

Key Words: Anti-arrhythmic drug; Atrial fibrillation; Catheter ablation; Heart failure; Meta-analysis
population would provide valuable data, but this has been done in only 1 RCT so far.\textsuperscript{11}

The aim of this meta-analysis was therefore to compare different treatment strategies for AF combined with HF. First, rhythm control was compared with rate control generally, and then an indirect comparison between CA and AAD relative to rate control strategy was conducted using the relevant RCT.

Methods

Search Strategy
This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and meta-Analyses (PRISMA) statement.\textsuperscript{13} All relevant studies from 1972 up to November 2017 in the MEDLINE, Embase, and the Cochrane Library (CENTRAL) databases were searched comprehensively using computer and manual searches. Searches and article reviews were performed by 2 independent investigators (J.A. and H.J.K.) and adjudicated by a third in the case of disagreement. Search terms used in each database are listed in Table S1.

Selection Criteria
The selected studies fulfilled all of the following criteria: (1) prospective RCT written in English; (2) participants diagnosed with AF combined with HF (LVEF <50%); (3) investigation of rate control vs. rhythm control irrespective of the method (AAD or CA); and (4) at least 1 of the following clinical outcomes: mortality, HF hospitalization, improvement of LVEF, exercise capacity, quality of life (QOL), left atrial (LA) size and LV end-systolic volume (ESV). The 2 investigators initially excluded papers that did not meet criteria based on the titles and abstracts; the full text of the remaining papers was then reviewed thoroughly to select the eligible studies (Figure 1).

Data Extraction and Outcome Measurement
Two independent investigators (J.A. and H.J.K.) extracted data and a third arbitrated any disagreement. Extracted data included the following: author, year of publication, study population, sex, mean LVEF, AF control strategy, follow-up period, drugs for rate or rhythm control, drug dosage, target heart rate, CA strategy, and outcome parameters. The corresponding author was sent an e-mail if required data were not reported. The primary clinical outcome was change in LVEF. The secondary outcomes of interest were echocardiography parameters including LA size and LV end-systolic volume (LVESV); clinical outcomes including mortality, hospitalization, and thromboembolism; exercise capacity measured with the 6-min walk distance (6MWD); and QOL defined using Minnesota Living with Heart Failure Questionnaire (MLHFQ) score. The MLHFQ is a self-administered questionnaire consisting of 21 items for patients with HF, representing different degrees from 0 (none) to 5 (very much), 5 being the worst. All outcome parameters were compared according to AF control strategy, that is, rhythm vs. rate control. In addition, studies using a different method for rhythm control were subdivided according to LVEF, LA size, LVESV, and 6MWD, and then differences between the AAD and CA groups were compared relative to the rate control group.

Quality Assessment
The quality of the individual studies was assessed by the same independent investigators using the risk-of-bias tool in RevMan version 5.3 (Cochrane Collaboration, Oxford, UK). The 7 items assessed were random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective reporting; and other bias. Each RCT was scored using 3 grades: high; low; or uncertain risk of bias.
When the studies all assessed the same outcome but measured it in a different way, the standardized MD was used instead. The Mantel-Haenszel random effects model was used because of the small number of RCT and the clinical heterogeneity in this meta-analysis. Two-sided \( P < 0.05 \) was considered statistically significant. Specific approval was not required by the institutional review board.

**Figure 2.** Change in echocardiographic parameters: (A) left ventricular ejection fraction; (B) left atrial size; and (C) left ventricular end-systolic volume for (Upper columns) rhythm control by anti-arrhythmic drug (AAD) vs. rate control, and (Lower columns) rhythm control by radiofrequency catheter ablation (RFCA) vs. rate control.

**Statistical Analysis**

All statistical analysis was performed using RevMan version 5.3. Heterogeneity among studies was formally estimated using the \( I^2 \) statistic, which denotes significant heterogeneity when \( I^2 > 50\% \). Risk ratio (RR) with 95% CI were calculated for dichotomous outcome measures, and the mean difference (MD) with 95% CI was derived for continuous variables.
2,625 participants assigned to the rate control group were treated mainly with a β-blocker, non-dihydropyridine calcium channel blocker, or digoxin. HF was defined using either clinical symptoms in the New York Heart Association (NYHA) classification or LV systolic dysfunction on echocardiography, or both. Clinical outcomes in individual studies varied: mortality was assessed in 5 trials; hospitalization in 4 trials; thromboembolism in 3 trials; HF worsening in 3 trials; drug side-effects in 4 trials; changes in LVEF in 8 trials; LVESV in 4 trials; LA size in 4 trials; B-type natriuretic peptide level in 5 trials; rate requiring a pacemaker in 1 trial; NYHA class in 5 trials; peak oxygen consumption in 2 trials; 6MWD in 7 trials; and QOL in 8 trials. Mean follow-up period was 21.3 months.

Assessment of the risk of bias is shown in Figure S1. All but 2 trials attempted double-blind treatment. Overall, 67.0% of the bias items were rated as low risk.

Change in Echocardiography Parameters

Change in LVEF was analyzed in 7 trials (Figure 2A). Two compared LVEF between an AAD and a rate control group, whereas the other 5, between CA and a rate control group. LVEF increase was significantly greater in the for a meta-analysis.

Results

Literature Search

Figure 1 shows the study selection strategy. Of 3,479 articles retrieved in the database search, 3,399 were excluded based on title and abstract. The remaining 80 articles were reviewed as the full text for eligibility. Of these, 67 studies were excluded for the following reasons: 28 had irrelevant outcomes or topics, 4 lacked a rate-control group, 9 were duplicated or published as a full text later, and 26 were not designed as RCT. Finally, 13 articles from 11 trials were included in this meta-analysis.

Characteristics of Included Studies

The details of the 13 RCT included in the analysis are summarized in Table S2. Seven trials enrolled patients with only persistent AF, whereas the other 6 included both paroxysmal and persistent AF. Of a total of 5,256 patients, 2,631 (50.1%) were treated with a rhythm control strategy. SR restoration in the rhythm control group was attempted with either AAD (2,483, 94.4%) or CA (148, 5.6%). The

Figure 3. Change in clinical outcomes: (A) mortality; (B) hospitalization; and (C) thromboembolism in rate control vs. rhythm control.
All-cause or cardiovascular mortality did not differ between the AAD and rate control groups (all-cause mortality: RR, 1.12, \( P=0.36 \); cardiovascular mortality: RR, 0.94, \( P=0.24 \), Figure 3A). Similar rates were also seen for hospitalization (RR, 1.06, \( P=0.48 \), Figure 3B) and thromboembolism (RR, 1.14, \( P=0.55 \), Figure 3C) between the 2 different treatment strategy groups.

**Change in Exercise Capacity**

Data for 6MWD were available from 2 trials comparing AAD vs. rate control, and from 4 trials comparing CA vs. rate control. All available trials showed an improvement in 6MWD after treatment. Rhythm control had greater 6MWD improvement than rate control, regardless of the rhythm control strategy (6MWD MD, 28.60 m; 95% CI: 12.94–44.26, \( P<0.001 \), Figure 4A). In addition, the CA group showed a trend towards increased 6MWD compared with the AAD group (MD, 39.07 m vs. 12.05 m in the CA and AAD groups, respectively, \( I^2 =76.1\% \) between groups, \( P=0.02 \); Figure 4C).

**Change in QOL**

Five trials investigated QOL measured by MLHFQ score. Rhythm control group showed a significantly greater improvement in QOL than the rate control group, regardless of strategy (MD, 7.95%; 95% CI: 5.53–10.37, \( P<0.001 \)). The CA group showed a trend towards greater LV functional improvement than the AAD group (MD, 9.27% vs. 5.23% in the CA and AAD group, respectively, \( I^2 =74.8\% \) between groups, \( P=0.05 \)).

There were also differences between the 2 treatment strategies in LA size and LVESV (Figure 2B, C). Between the rate and rhythm control groups, the change in LVESV favored rhythm control strategy, whereas that in LA size was not different significantly. When the 2 different rhythm control strategies (CA vs. AAD) were compared, however, the CA group was superior to the AAD group, with regard to reduction in LA size (MD, –1.37 vs. –0.16 in the CA and AAD group, respectively, \( I^2 =81.2\% \) between groups, \( P=0.02 \); Figure 2C).

**Change in Clinical Outcomes**

Mortality, hospitalization, and thromboembolism were evaluated in 6, 4, and 3 trials, respectively (Figure 3). All studies compared AAD and rate control groups. There was a significant heterogeneity among studies regarding all-cause mortality and hospitalization.

All-cause or cardiovascular mortality did not differ between the AAD and rate control groups (all-cause mortality: RR, 1.12, \( P=0.36 \); cardiovascular mortality: RR, 0.94, \( P=0.24 \), Figure 3A). Similar rates were also seen for hospitalization (RR, 1.06, \( P=0.48 \), Figure 3B) and thromboembolism (RR, 1.14, \( P=0.55 \), Figure 3C) between the 2 different treatment strategy groups.
The rhythm control group had a significant improvement in QOL, compared with the rate control group (MD, -12.65; 95% CI: -19.68 to -5.61, P<0.001, Figure 4B).

Discussion

This meta-analysis involved 13 RCT and compared different AF management strategies for AF combined with HF with reduced EF. Rhythm control did not reduce the rate of mortality, hospitalization, or thromboembolism, but improvement in LV function, exercise capacity, and QOL was greater with rhythm control than with rate control. In addition, when AAD and CA groups were compared indirectly against the rate control group, the CA group had greater reduction in LA size and LVESV, improvement in LVEF, and exercise capacity.

The preference between rhythm and rate control strategies for AF has been investigated in several meta-analyses. These analyses also assessed 2 different approaches, but did not compare CA with AAD. In addition, separate analyses on HF exclusively were lacking, or were based on observational studies and a small number of RCT. All the patients in the present updated meta-analysis had AF combined with HF, and only RCT were included, to compare rate vs. rhythm control according to rhythm control strategy. Given that there was a lack of RCT directly comparing AAD and CA in the same population, we compared the CA and AAD groups indirectly relative to the rate control group.

AF has been thought to influence cardiac performance as a result of adverse hemodynamics due to loss of atrial kick, which limits ventricular filling, aggravating presystolic mitral regurgitation and leading to an excessive tachycardic ventricular response. A prolonged, rapid ventricular rate >100 beats/min probably leads to tachycardia-induced cardiomyopathy and/or an exacerbation of HF. Aortic valve opening fails in 15% of beats at the fast average rate, affecting net coronary perfusion. Therefore, rate control is a fundamental treatment option for AF combined with HF. In contrast, the irregular ventricular response in AF per se worsens cardiac performance in HF subjects at elevated heart rate. Beat-to-beat variability in cycle length would affect diastolic filling time, resulting in a 12–15% reduction in cardiac output. The present meta-analysis noted greater improvement in LVEF with rhythm control than with rate control, and with CA than with AAD. This suggests the importance of preserving the atrial contribution to cardiac function, reducing AF triggers or substrates, and maintaining longer SR duration.

LA remodeling is the principal pathophysiologic mechanism underlying AF. Certain conditions such as inflammation, ischemia, and dilation make the LA vulnerable to AF, which results from both structural remodeling and complex ionic and electrical remodeling at the cellular level. LA remodeling acts as both the substrate and trigger to initiate and maintain AF; moreover, remodeling induces heterogeneous refractoriness. As a consequence, a susceptible environment, that is, multiple-circuit re-entry, is created and perpetuates AF. CA targets the trigger or substrate to restore SR. A reduction in LA size after ablation has been demonstrated in patients with symptomatic, isolated AF. A notable finding in the present meta-analysis was that LA reverse remodeling was shown exclusively in CA, but not in AAD. It is to be noted that CA was superior to AAD even though the majority of patients assigned to the rhythm control group were on AAD, and only 5.6% received CA.

Another finding related to cardiac reverse remodeling was a reduction in LVESV in the CA group. LV performance is an important factor predicting post-ablation outcome. Both systolic and diastolic dysfunction recover, leading to ventricular volume reduction after SR conversion by CA. In the present study, exercise capacity measured using 6MWD improved significantly in the CA group, and probably reflected structural as well as functional recovery. AF is associated with compromised exercise tolerance in chronic HF, and clinical data indicate that restoration of SR by ablation improves exercise capacity, cardiac function, and QOL.

Despite these echocardiographic and functional improvements, this study found that the rhythm control strategy did not lead to improvement in mortality, hospitalization, or thromboembolism. Because none of the included RCT comparing CA and rate control reported these end-points, rhythm control with only AAD was compared to rate control strategy in the present study. One of the reasons why AAD did not show superiority to rate control could be the low SR conversion rate. The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial, the first RCT comparing rhythm control by AAD vs. rate control in AF, preferred rate control to rhythm control. The most important limitation in that trial, however, was the extremely low SR maintenance rate in the rhythm control group. On-treatment subanalysis of the AFFIRM trial showed that SR was an important determinant of survival outcome. Trials included in the present meta-analysis reported SR maintenance rates widely ranging from 51% to 88%, which would explain the neutral results regarding clinical outcome in the present study.

Another concern is the adverse effect of AAD. Several studies demonstrated an increased risk of death after adjustment for the presence of SR, and the benefits of AAD were offset by their adverse effects. Moreover, AAD did not adequately restore SR; therefore, interest in CA has increased. Investigators of the Ablation vs. Amiodarone for Treatment of persistent Atrial fibrillation in patients with Congestive heart failure and an implanted device (AATAC) trial directly compared CA with amiodarone therapy in patients with AF and HF. That study showed a significantly longer AF-free period and reduced hospitalization and mortality rates in the CA group. No other RCT so far has compared CA and AAD regarding these points in the same population, therefore meta-analysis could not be performed. Instead, the present meta-analysis conducted an indirect comparison between CA and AAD, and better cardiac function in the CA group seemed to support the result of the AATAC trial.

The recently published Catheter Ablation vs. Standard conventional Therapy in patients with LEFT ventricular dysfunction and Atrial Fibrillation (CASTLE-AF) trial reported lower rates of death and hospitalization for HF in CA compared with medical therapy. That RCT, however, was excluded from the present meta-analysis because they did not compare different AF management strategies (rhythm vs. rate control), but compared CA with medical therapy (either rate or rhythm control) to prove the superiority of CA over pharmacological treatment.

Study Limitations

There are several limitations in this study. First, this...
meta-analysis compared rhythm vs. rate control strategies. A considerable number in the rate control group, however, had restoration of SR, and many in the rhythm control group did not maintain SR. Second, some variability in trial design such as AF type, follow-up duration or detailed inclusion criteria, and differences in therapeutic regimen between rate control strategies as well as between CA approaches limited appropriate comparison. Third, a sensitivity analysis was not performed due to the limited number of studies. The results from ongoing, highly-qualified large trials will be available in the near future, and are expected to provide more valuable data.

Conclusions

This updated meta-analysis compared different treatment strategies for AF combined with HF, that is, direct comparison between rhythm vs. rate control and indirect comparison between CA vs. AAD relative to rate control strategy. Even though mortality, hospitalization, and thromboembolism rates were similar, rhythm control showed greater improvement in LVEF, exercise capacity, and QOL. In particular, the CA group was superior to the AAD group in terms of reverse cardiac remodeling.

Acknowledgment

This work was supported by clinical research grant from Pusan National University Hospital in 2017.

Disclosures

The authors declare no conflicts of interest.

References


Supplementary Files

Supplementary File 1

- Figure S1. Assessment of the risk of bias.
- Table S1. Database search strategy
- Table S2. RCT in the meta-analysis: study characteristics (n=13)

Please find supplementary file(s):