

Rhythm versus rate control for atrial fibrillation in heart failure with preserved ejection fraction



Mohammed Al-Sadawi, MD,* Saadat Aleem, MD,* Faisal Aslam, MD,* Robin Jacobs, MD,* Gregg Stevens, MS,[†] Ibrahim Almasry, MD, FHRS,* Abhijeet Singh, MD, FHRS,* Roger Fan, MD, FHRS,* Eric Rashba, MD, FHRS*

From *Stony Brook Heart Institute, Stony Brook Medicine, Stony Brook, New York, and [†]Library Education and Clinical Services, University of Massachusetts, Worcester, Massachusetts.

BACKGROUND There are few prospective studies assessing the benefits of rhythm control of atrial fibrillation (AF) in patients with heart failure and preserved ejection fraction (HFpEF), which accounts for 50% of all heart failure patients.

OBJECTIVE Conduct a meta-analysis to assess the effects of rhythm control (ablation and/or antiarrhythmic medications) vs rate control on all-cause mortality in AF patients with HFpEF.

METHODS Databases were searched for studies reporting the effect of rhythm control vs rate control on mortality in patients with HFpEF (Ovid MEDLINE, EMBASE, Scopus, Web of Science, Google Scholar, and EBSCO CINAHL). The search was not restricted to time or publication status. The primary endpoint was all-cause mortality. The minimum duration of follow-up required for inclusion was 1 year.

RESULTS The literature search identified 1210 candidate studies; 5 studies and 16,825 patients were included. The study population

had 57% men with a mean age of 71 ± 2.5 years. Rhythm control for AF was associated with lower all-cause mortality (odds ratio 0.735, 95% confidence interval 0.665–0.813; $P < .001$) as compared to rate control.

CONCLUSION Rhythm control for AF in patients with HFpEF was associated with decreased all-cause mortality.

KEYWORDS Atrial fibrillation; Rhythm control; Rate control; Mortality; Heart failure with preserved ejection fraction; Hospitalization; Outcomes

(Heart Rhythm 0² 2022;3:520–525) © 2022 Heart Rhythm Society. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

Atrial fibrillation (AF) and heart failure (HF) are common comorbid conditions. AF is present in up to two-thirds of all patients with HF, with a higher prevalence in those with heart failure with preserved ejection fraction (HFpEF).¹ Both diseases share common risk factors, and the pathophysiology of each predisposes to development of the other in a synergistic manner.^{2,3} The incremental cost for AF management exceeds \$20 billion in the United States and is expected to increase.⁴ Both diseases cause significant morbidity and mortality, including stroke, hospitalization, and death. However, comorbid AF with HF is associated with worse outcomes than either disease in isolation.^{3,5,6}

Current practice guidelines provide limited information regarding whether patients with comorbid AF/HF should be treated with rhythm or rate control. American College of Cardiology guidelines differentiate between patients who develop AF after a diagnosis of HF and those that develop HF because of AF causing tachycardia-induced cardiomyopathy, and only

recommend rhythm control in the latter, as it is a reversible cause for HF.⁷ Heart Rhythm Society guidelines recommend catheter ablation in patients who are symptomatic and have failed medical therapy.⁸ These guidelines are still influenced by the landmark AFFIRM trial,⁹ which showed no survival benefit with rhythm control using antiarrhythmic drugs (AADs) and a trend toward higher mortality with rhythm control in HF patients.

The CASTLE-AF¹⁰ and the EAST-AFNET4¹¹ studies demonstrated significantly improved cardiovascular outcomes when employing an early rhythm control strategy. Subsequent subgroup analysis of this study reported improved outcomes with early rhythm control in patients with HF.¹² There are few prospective studies assessing the benefits of rhythm control in patients with HFpEF, which account for 50% of all HF patients.¹³ We conducted a meta-analysis to examine the effect of rhythm control on mortality in patients with AF and HFpEF.

Methods

Data search

The systematic review was conducted with a protocol in accordance with the Preferred Reporting of Items for

Address reprint requests and correspondence: Dr Eric Rashba, Stony Brook Heart Institute, Stony Brook Medicine, 101 Nicolls Rd, Stony Brook, NY 11794. E-mail address: Eric.Rashba@stonybrookmedicine.edu.

KEY FINDINGS

- Heart failure with preserved ejection fraction (HFpEF) and atrial fibrillation (AF) are common comorbid diseases that are associated with poor outcomes.
- A rhythm control strategy for AF in HFpEF is associated with decreased mortality.
- Both catheter ablation and antiarrhythmic drugs were used for rhythm control in the analyzed studies.

Systematic reviews and Meta-Analyses (PRISMA) statement.¹⁴ A specialized librarian-tailored search strategy was used to systematically locate relevant articles. Searches were conducted in May 2021 using the following databases: Embase, Ovid Medline, CINAHL Plus with Full Text, Cochrane Central Register of Controlled Trials, Web of Science: Science Citation Index Expanded, and Latin American and Caribbean Health Sciences Literature (LILACS). Full search strategies and results for each database are available in [Supplemental Table 1](#). Additional relevant citations were located through Google Scholar. Citations were exported to

EndNote X9 (Clarivate, Philadelphia, PA) and uploaded to Rayyan (Rayyan QCRI, Qatar)¹⁵ after removal of duplicates.

Study selection

Studies were screened by 2 investigators (MA and RJ) independently at the level of title and abstract. Afterwards, full-length reports were evaluated for inclusion. The prespecified inclusion criteria were studies with at least 1 year of follow-up that reported all-cause mortality in patients with HFpEF and AF treated with rhythm control or rate control. Exclusion criteria were review articles, data reporting mortality without comparison between rate or rhythm control, concomitant HF with reduced ejection fraction, or publication in languages other than English. Any discrepancy was resolved by consensus. The year of publication, numbers of participants, and numbers of events/odds ratio (OR) were tabulated for eligible studies.¹⁶⁻²¹ The primary endpoint was all-cause mortality. Since data from Kelly and colleagues constitutes more than 75% of the population, the analysis was repeated after exclusion of this study. The analysis was also repeated after excluding the study by Kong and colleagues, since this was the only study that employed AADs as the exclusive method of rhythm control.

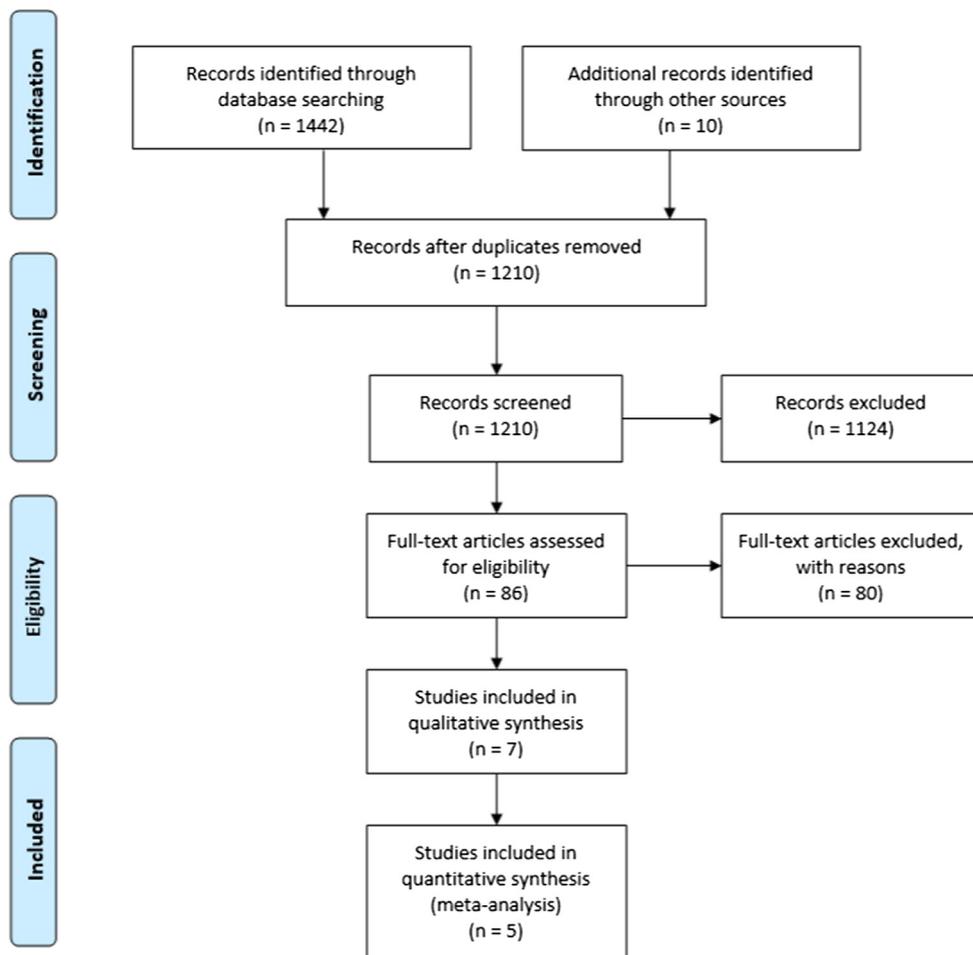


Figure 1 Preferred Reporting of Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart. Flow diagram depicts study selection for inclusion in the meta-analysis according to the PRISMA statement for reporting systematic reviews and meta-analyses.

Table 1 Demographic data of the included studies

Study	Rhythm group (event/total no.)	Rate group (event/total no.)	Type of rhythm control	Mean age (years)		Male (%)		Follow-up (months)		Mean EF (%)		HTN		DM		CHD		CVA	
				Rh	RA	Rh	RA	Rh	RA	Rh	RA	Rh	RA	Rh	RA	Rh	RA	Rh	RA
Kong et al (2010) ²¹	54/97	180/285	AAD	70	70	46	48	12	62	63	76	81	35	42	18	29	18	15	
Machino (2016) ²²	4/141	17/188	AAD/CA	70	70	67	67	28	64	64									
Rahman et al (2019) ¹⁸	5/85	9/95	AAD/CA	67	75	62	25	12											
Kelly et al (2019) ¹⁹	572/1857	5184/13,825	AAD/CA	81	83	34	34	12	58	58	83	81	36	36	48	45	17	19	
Zhang et al (2020) ²⁰	15/40	93/212	AAD/CA	73	79	45	42	12	61	61	75	85	30	36	15	16	2.5	22	

AAD = antiarrhythmic drugs; CA = catheter ablation; CHD = coronary heart disease; CVA = cerebrovascular accident; DM = diabetes mellitus; EF = ejection fraction; HTN = hypertension; RA = rate group; Rh = rhythm group.

Statistical analysis

Meta-analysis was performed using Comprehensive Meta-Analysis software, version 3 (Biostat, Englewood, NJ). We used a random-effects model to examine the association between rhythm vs rate control and outcomes and presented the results as an OR with 95% confidence interval (CI). The extent of heterogeneity was determined by I² (ranging from 0% to 100%). Statistical significance was considered with a *P* value < .05 and all tests were 2-sided. Funnel plot of standard error by log OR was applied to qualitatively assess publication bias.

Results

Literature search and study selection

The primary literature search identified 1210 potentially eligible studies. The process of study inclusion is illustrated in detail in Figure 1. MeSH words and databases used for systematic review are presented in Supplemental Table 1. A total of 1124 studies were excluded by screening the titles and abstracts. The remaining 86 articles were screened in full text for relevance. Five studies were eligible for meta-analysis for the outcome of all-cause mortality. Abstracts published with detailed information were included for 2 reasons: (1) it is recommended by the Agency for Healthcare Research and Quality (AHRQ), the Joanna Briggs Institute Reviewer's Manual, PRISMA for systematic review protocols (PRISMA-P)¹⁶; and (2) analysis with and without including such data resulted in similar outcomes.

Study, patient, and procedural characteristics

The study population of 16,825 patients was 57% men with a mean age of 71 ± 2.5 years and mean left ventricular ejection fraction 61% ± 7%. Table 1 summarizes the basic characteristics of the included studies.^{17–20,22,23} All 5 of the included studies were observational studies, and 4 studies used radio-frequency catheter ablation as the main intervention in the rhythm control arm. The studies did not stratify the results based on type of AF (paroxysmal vs persistent), duration of sinus rhythm maintenance, duration of AAD usage, and ablation techniques.

Association between rhythm control and mortality in patients with HFpEF and AF

Rhythm control for AF in patients with HFpEF was associated with lower all-cause mortality as compared to rate control (Figures 2 and 3; OR 0.735, 95% CI 0.665–0.813; *P* < .001). There was mild heterogeneity: *df* = 4 (*P* = .594), I² = 0; test for overall effect: *Z* = -6.7028 (*P* < .001). The analysis results were similar when Kelly and colleagues¹⁹ was excluded (OR 0.515, 95% CI 0.3–0.883; *P* = .01). The analysis results were also similar after removing the study that used AADs as the exclusive method of rhythm control (Kong and colleagues²¹: OR 0.538, 95% CI 0.325–0.892; *P* = .01).

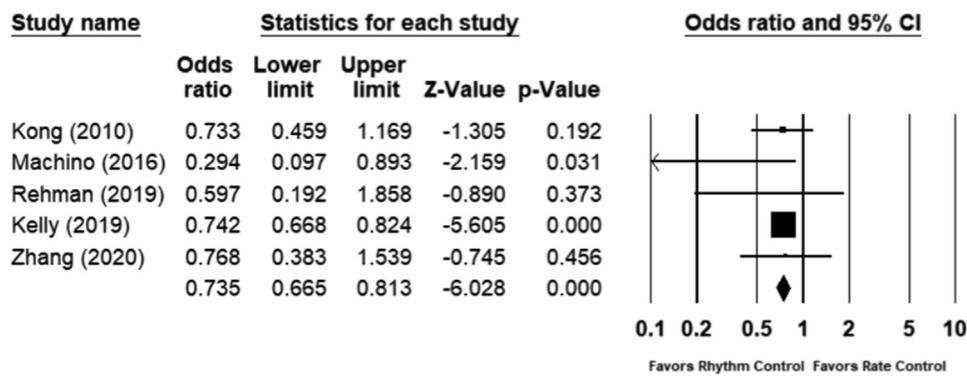


Figure 2 Forest plot demonstrating impact of rhythm control on long-term (>1 year) mortality in patients with heart failure with preserved ejection fraction (HFpEF) and atrial fibrillation. In HFpEF and atrial fibrillation, rhythm control was associated with improved all-cause mortality outcome (>1 year) compared to rate control (odds ratio 0.735, 95% confidence interval 0.665–0.813; $P < .001$). Heterogeneity: $df = 4$ ($P = .594$), $I^2 = 0$; test for overall effect: $Z = -6.7028$ ($P < .001$).

Discussion

The major finding of this study is that rhythm control in patients with HFpEF and AF was associated with a significant reduction in all-cause mortality. To our knowledge, this study is the first meta-analysis to report these findings. Catheter ablation was used as part of the rhythm control strategy in 4 of the 5 studies included in this meta-analysis. The results were still statistically significant with mild heterogeneity when we removed the only study that used AADs as the exclusive method of rhythm control.

Variability in the specific type of rhythm or rate control used in the individual studies may offer one explanation for the heterogeneity in outcomes. Kong and colleagues²¹ excluded patients in their analysis who underwent catheter ablation, and defined rhythm control as using class I or III antiarrhythmic medications. However, catheter ablation is a well-established rhythm control technique for treatment of symptomatic AF in patients that have failed drug therapy and is a class I recommendation for this cohort.^{8,24–27} The

procedure may be associated with fewer complications than antiarrhythmic medications, which have significant side-effect profiles and have been associated with a trend for increased mortality as compared to rate control medications.⁹ This hypothesis is supported by the results of the CASTLE-AF trial, which demonstrated a mortality benefit in HF with reduced ejection fraction patients randomized to catheter ablation as compared to standard medical therapy, which included rhythm control with antiarrhythmic medications.

Atrioventricular nodal ablation with implantation of a bi-ventricular pacemaker had a mortality benefit in the APAF-CRT mortality trial, which may indicate the benefit of maintaining a regular rhythm.²⁸ Saksena²⁹ performed subgroup analyses on patients with HFpEF and AF from the AFFIRM trial, finding no significant benefit for rhythm control over rate control in preventing HF progression or death. These conflicting observations are often attributed to (1) fewer effective methods for rhythm control in the past, using antiarrhythmic drugs with significant side-effect profiles; and (2)

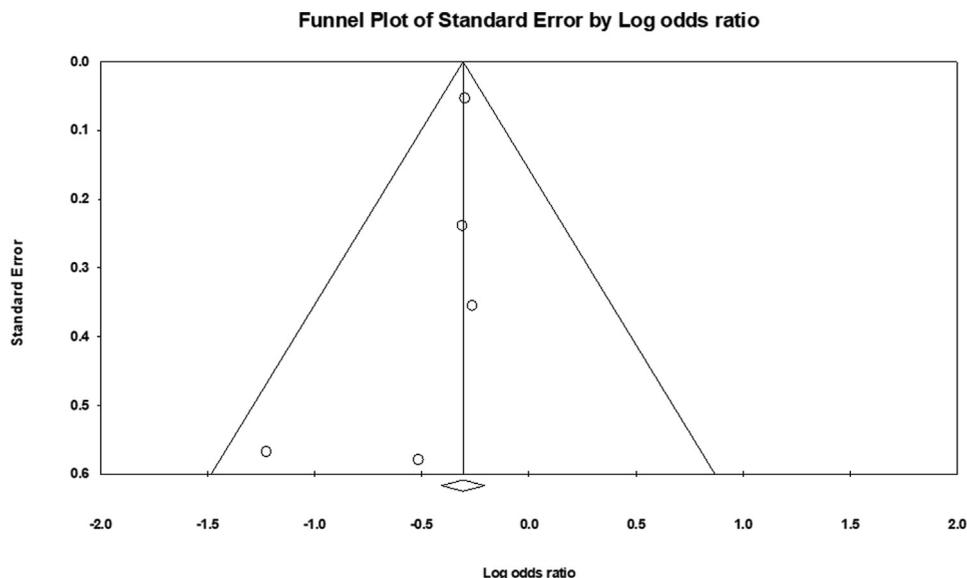


Figure 3 Forest plot standard error by log odds ratio.

inappropriate discontinuation of anticoagulation in rhythm-control patients in the past, leading to increased stroke and death, whereas more recent guidelines now recommend anticoagulation based on thromboembolic risk profile regardless of modality of arrhythmia management. Furthermore, older studies used symptom-triggered event monitoring, periodic electrocardiograms, or limited Holter monitoring, which has limited accuracy for AF assessment, compared to continuous mobile telemetry or cardiac implantable device monitoring.

Our findings are consistent with the known synergistic pathophysiology of AF and HFpEF. It is well known that AF and HF perpetuate one another.³ HFpEF is associated with neurohormonal dysfunction leading to atrial fibrosis and electrical remodeling, oxidative stress and inflammation, and calcium handling abnormalities in myocytes, all of which promote AF.²² A lack of atrial systole and tachycardia from AF potentiates the hemodynamic and neurohormonal dysfunction that promotes HFpEF. Therefore, attenuating AF burden by maintaining sinus rhythm may lead to improved HF in patients with HFpEF. The effect of rhythm control with catheter ablation is being tested in an ongoing trial, Ablation Versus Medical Management of Atrial Fibrillation in HFpEF (AMPERE) (NCT04282850), to test the difference on mortality and hospitalization.

Our analysis should be interpreted within the context of several limitations. The included studies are primarily observational, so unmeasurable confounders may have affected the results. There was heterogeneity in the study population, as well as definitions of what constituted rhythm or rate control. The studies also did not differentiate between using AAD and catheter ablation as the primary method for rhythm control, type and burden of AF, and duration of AF. Kelly and colleagues' study¹⁹ constitutes more than 75% of the population, but the analysis results were similar when this study was excluded. HFpEF has a complex and heterogeneous etiology and the studies included did not stratify or differentiate HFpEF etiology or whether amyloidosis was present.

Conclusion

In our systematic review and meta-analysis, rhythm control for AF in patients with HFpEF was associated with decreased all-cause long-term mortality as compared to rate control.

Funding Sources: The authors have no funding sources to disclose.

Disclosures: The authors have no conflicts of interest to disclose.

Authorship: All authors attest they meet the current ICMJE criteria for authorship.

Ethics Statement: The systematic review was conducted with a protocol in accordance with the Preferred Reporting of Items for Systematic reviews and Meta-Analyses (PRISMA) statement.

Appendix Supplementary data

Supplementary data associated with this article can be found in the online version at <https://doi.org/10.1016/j.hroo.2022.06.009>.

References

- Zakeri R, Chamberlain AM, Roger VL, Redfield MM. Temporal relationship and prognostic significance of atrial fibrillation in heart failure patients with preserved ejection fraction: a community-based study. *Circulation* 2013;128:1085–1093.
- Patel RB, Vaduganathan M, Shah SJ, Butler J. Atrial fibrillation in heart failure with preserved ejection fraction: insights into mechanisms and therapeutics. *Pharmacol Ther* 2017;176:32–39.
- Mamas MA, Caldwell JC, Chacko S, Garratt CJ, Fath-Ordoubadi F, Neyses L. A meta-analysis of the prognostic significance of atrial fibrillation in chronic heart failure. *Eur J Heart Fail* 2009;11:676–683.
- Kim MH, Johnston SS, Chu B-C, Dalal MR, Schulman KL. Estimation of total incremental health care costs in patients with atrial fibrillation in the United States. *Circ Cardiovasc Qual Outcomes* 2011;4:313–320.
- Stewart S, Hart CL, Hole DJ, McMurray JJV. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. *Am J Med* 2002;113:359–364.
- Wang TJ, Larson MG, Levy D, et al. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. *Circulation* 2003;107:2920–2925.
- Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013;62:e147–e239.
- January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol* 2014;64:e1–e76.
- Wyse DG, Waldo AL, DiMarco JP, et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med* 2002;347:1825–1833.
- Marrouche NF, Brachmann J, Andresen D, et al. Catheter ablation for atrial fibrillation with heart failure. *N Engl J Med* 2018;378:417–427.
- Kirchhof P, Camm AJ, Goette A, et al. Early rhythm-control therapy in patients with atrial fibrillation. *N Engl J Med* 2020;383:1305–1316.
- Rillig A, Magnussen C, Ozga A-K, et al. Early rhythm control therapy in patients with atrial fibrillation and heart failure. *Circulation* 2021;144:845–858.
- Oktay AA, Rich JD, Shah SJ. The emerging epidemic of heart failure with preserved ejection fraction. *Curr Heart Fail Rep* 2013;10:401–410.
- Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009;339:b2535.
- Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan—a web and mobile app for systematic reviews. *Syst Rev* 2016;5:210.
- Scherer RW, Saldanha JJ. How should systematic reviewers handle conference abstracts? A view from the trenches. *Syst Rev* 2019;8:264.
- Machino-Ohtsuka T, Seo Y, Ishizu T, et al. Relationships between maintenance of sinus rhythm and clinical outcomes in patients with heart failure with preserved ejection fraction and atrial fibrillation. *J Cardiol* 2019;74:235–244.
- Rahman A, Hasani A, Moussa O, et al. Efficacy of catheter ablation of atrial fibrillation in heart failure with preserved ejection fraction. *J Card Fail* 2019;25:S84–S85.
- Kelly JP, DeVore AD, Wu J, et al. Rhythm control versus rate control in patients with atrial fibrillation and heart failure with preserved ejection fraction: insights from Get With The Guidelines-Heart Failure. *J Am Heart Assoc* 2019;8:e011560.
- Zhang P, Chamberlain AM, Hodge DO, et al. Outcomes of incident atrial fibrillation in heart failure with preserved or reduced ejection fraction: a community-based study. *J Cardiovasc Electrophysiol* 2020;31:2275–2283.
- Kong MH, Shaw LK, O'Connor C, Califf RM, Blazing MA, Al-Khatib SM. Is rhythm-control superior to rate-control in patients with atrial fibrillation and diastolic heart failure? *Ann Noninvasive Electrocardiol* 2010;15:209–217.
- Machino T. The impact of rhythm control by catheter ablation on reduction of heart failure hospitalization in patients with HFPEF and AF. *Eur Heart J* 2016;37:599–983.
- Fukui A, Tanino T, Yamaguchi T, et al. Catheter ablation of atrial fibrillation reduces heart failure rehospitalization in patients with heart failure with preserved ejection fraction. *J Cardiovasc Electrophysiol* 2020;31:682–688.
- Cosedis Nielsen J, Mortensen LS, Hansen PS. Radiofrequency ablation as initial therapy in paroxysmal atrial fibrillation. *N Engl J Med* 2013;368:478–479.
- Fuster V, Rydén LE, Cannom DS, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation—executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation). *J Am Coll Cardiol* 2006;48:854–906.

26. 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.
27. 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;293:2634–2640.
28. Brignole M, Pentimalli F, Palmisano P, et al. AV junction ablation and cardiac resynchronization for patients with permanent atrial fibrillation and narrow QRS: the APAF-CRT mortality trial. *Eur Heart J* 2021;42:4731–4739.
29. Saksena S. Rate and rhythm control strategies in atrial fibrillation patients with heart failure and preserved or reduced left ventricular ejection fraction: An affirm substudy. *Heart Rhythm* 2017;14:S94–S143.