Title

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Comparison of Outcomes After Ablation of Atrial Fibrillation in Patients With Heart Failure with Preserved Versus Reduced Ejection Fraction

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ABSTRACT

Catheter ablation improves outcomes in atrial fibrillation (AF) patients with heart failure (HF) with reduced ejection fraction (HFrEF). We sought to evaluate the efficacy and safety of catheter ablation of AF in HF patients with a preserved ejection fraction (HFpEF). We performed a retrospective study of all patients who underwent de novo radiofrequency catheter ablation enrolled in the UC San Diego AF Ablation Registry. The primary outcome was recurrence of all atrial arrhythmias on or off antiarrhythmic drugs (AAD). Of 547 total patients, 51 (9.3%) had HFpEF, 40 (7.3%) had HFrEF, and 456 (83.4%) were without HF. There was no difference in recurrence of atrial arrhythmias on or off AAD [Adjusted Hazard Ratio (AHR) 1.92 (95% CI 0.97-3.83) for HFpEF versus HFrEF and AHR 0.90 (95% CI 0.59-1.39) for HFpEF versus no HF] or off AAD [AHR 1.96 (95% CI 0.99-3.90) for HFpEF versus HFrEF and AHR 1.14 (95% CI 0.74-1.77) for HFpEF versus no HF]. There was also no difference in rates of all-cause hospitalizations [AHR 1.80 (95% CI 0.97-3.33) for HFpEF versus HFrEF and AHR 2.05 (95% CI 1.30-3.23) for HFpEF versus no HF] or rates of all-cause mortality [AHR 0.53 (95% CI 0.05-6.11) for HFpEF versus HFrEF and AHR 2.46 (95% CI 0.34-17.92) for HFpEF versus no HF]. There were no significant differences in AAD use (p=0.176) or procedural complications between groups (p=0.980). In conclusion, there were no significant differences in arrhythmia-free survival between patients with HFpEF and HFrEF undergoing catheter ablation of AF.

Key words: catheter ablation, atrial fibrillation, heart failure with preserved ejection fraction

INTRODUCTION

Atrial fibrillation (AF) and heart failure (HF) are very prevalent and frequently co-exist, leading to increased morbidity and mortality relative to patients with either disease alone.[1,2] Given the potential adverse effects of pharmacologic antiarrhythmic therapy, especially in HF patients, and its inconsistent success at maintaining sinus rhythm, catheter ablation has emerged as a viable alternative for rhythm control of AF. Guidelines have been updated to recommend catheter ablation (CA) as a preferable alternative for AF in patients with HF with reduced ejection fraction (HFrEF) amidst evidence from several randomized controlled trials.[3-5] The role of CA in HF patients with a preserved ejection fraction (HFpEF) is less clear. The few retrospective and prospective analyses on CA in HFpEF have focused on symptomatic improvement and freedom from recurrent atrial arrhythmias, but data are lacking regarding hospitalization outcomes or mortality following CA.[6] Furthermore, one study did not include patients without HF as a comparator arm[7] and one study did not have any comparator arm.[8] Therefore, the objective of this study is to compare recurrence of AF, procedural complication rates, and all-cause hospitalizations and mortality after CA among AF patients with HFpEF, HFrEF and those without HF, focusing specifically on patients with HFpEF who have been less well-studied.

METHODS

This study was an observational, retrospective cohort study using data collected as part of the University of California, San Diego (UCSD) AF Ablation Registry and approved by the UCSD Institutional Review Board. The UCSD AF Ablation Registry was designed as a clinical registry of all patients undergoing left atrial ablation procedures for atrial arrhythmias at UCSD, a single academic center, as captured by a procedural database (Perminova, Inc, San Diego, CA) to collect patient, provider, and intra-procedural characteristics. All AF ablation procedures captured by the registry from October 2009 to March 2015 were linked to clinical encounters as recorded by the electronic medical record at UCSD Medical Center (Epic, Verona, WI). Patients with a prior AF ablation procedure were excluded (n=296). Data on baseline demographics, medical history, laboratory data, medications and cardiovascular implantable devices were collected as part of the UCSD AF Ablation Registry. Intra-procedural registry reports were reviewed to determine fluoroscopy and procedure times and ablation lesion sets.

Patients with a clinical diagnosis of heart failure were stratified into HFpEF versus HFrEF groups by LVEF as determined by transthoracic echocardiography before the index catheter ablation procedure. Patients with baseline LVEF $\geq$ 50% were designated as HFpEF while those with an LVEF $<$ 50% were designated as HFrEF. Those without a clinical diagnosis of heart failure compromised the third group for reference. Clinical outcomes were determined during all follow-up and included in-hospital adverse events, recurrence of atrial arrhythmia at final follow-up on or off

antiarrhythmic drugs (AAD) and off AAD, and all-cause hospitalizations and mortality. Arrhythmia recurrence was defined as AF, atrial flutter (AFL) or atrial tachycardia (AT) lasting >30 seconds on 12-lead ECG, ambulatory monitoring, or implantable device, as recommended by contemporary guidelines.[9] Patients who were continued on AAD after the 3-month blanking period were excluded from the analysis assessing recurrence of atrial arrhythmias off AAD.

Adverse events were recorded in the registry and included access site complications (i.e. bleeding, groin hematoma, pseudoaneurysm and arteriovenous fistula), cardiac perforation or tamponade, stroke or transient ischemic attack, pericarditis, myocardial infarction, atrioesophageal fistula, phrenic nerve paralysis and pulmonary vein stenosis. As part of the registry, follow-up arrhythmia monitoring was pre-specified and was recommended as a 12-lead ECG at each follow-up visit, along with routine ambulatory ECG monitoring (24-hour Holter monitor, extended ambulatory ECG monitoring, or event monitoring) in all patients at 6 months, 1 year and 2 years after ablation and additional ambulatory ECG monitoring to evaluate for arrhythmia recurrence in the presence of suggestive symptoms, which was consistent with consensus guidelines and updated consensus guidelines at the time of the registry.[9,10]

Informed consent was obtained prior to all ablation procedures. General anesthesia was used in all cases. Intravenous heparin was used to target an activated clotting time of 300-400 seconds. A transseptal puncture

was performed under direct visualization with intracardiac echocardiography. Pulmonary vein isolation was performed using segmental, circumferential, or both types of ablations at the discretion of the operator. Closed and open irrigated and non-contact and contact force sensing catheters were used at the discretion of the operator. Electroanatomic mapping systems were used in all cases ((CARTO™, Biosense-Webster Inc, Diamond Bar, CA) or Ensite™, St Jude Medical, Inc, Minneapolis, MN)). Pulmonary vein entrance and exit block were confirmed with use of a circular catheter, and adenosine and isoproterenol were administered at the operator's discretion. Additional lesion sets including cavotricuspid isthmus line, left atrial roof line, mitral isthmus line, coronary sinus ablation, and ablation of complex fractional atrial electrograms were performed at the discretion of the operator.

Continuous variables are presented by group as means ± standard deviation for normally distributed variables and as medians with 25^{th} and 75^{th} percentiles for variables that were not normally distributed. Comparison between all groups was done using the nonparametric Kruskal-Wallis tests. All possible comparisons among groups were performed using the Student *t* test if the data were normally distributed or the Wilcoxon rank sum test if the data were not normally distributed. Categorical variables were reported as count and percentage, with the χ^2 or Fisher exact test (expected cell counts<5) used for comparisons.

Recurrence of atrial arrhythmias at final follow up was analyzed using the Kaplan-Meier method with a 3-month blanking period and log-rank

significance testing. Unadjusted and adjusted Cox proportional hazards modeling was used to analyze recurrence of atrial arrhythmias with a 3-month blanking period, results are presented as hazard ratios (HR) with 95% confidence intervals (CI). Patients who were lost to follow-up were censored at the date of last known follow-up. Covariates included in the adjusted model are presented in **Table 1**, which were selected based on a clinically plausible association of the categorical predictor variable with recurrence of the primary outcome of recurrent atrial arrhythmias. Missing values were minimal and roughly equivalent between groups for all variables and were thus omitted. Analyses were performed using Stata 11 (StataCorp, LLC, College Station, TX) statistical software. A $p<0.05$ was considered statistically significant.

RESULTS

A total of 547 patients underwent de novo radiofrequency CA during the study period with baseline characteristics summarized in **Table 1**. Of the analyzed cohort, 9% (n=51) had HFpEF, 7% (n=40) had HFrEF, and 83% (n=456) had no HF. Median (Q1, Q3) follow-up duration was 50.9 months (24.5, 62.3) in the HFpEF group, 24.2 months (8.2, 60.4) in the HFrEF group, and 31.3 months (9.2, 57.3) in the no HF group ($p = 0.027$).

Patients without HF were more likely to have paroxysmal AF relative to HFpEF and HFrEF patients ($p<0.001$ for both comparisons). HFpEF and HFrEF patients were more likely to have coronary artery disease or an ICD or

CRT-D implanted at baseline relative to those without HF and HFpEF patients were more likely to have COPD, OSA and ESRD (see **Table 1**).

Ablation characteristics are summarized in **Table 2**. Procedure times were significantly longer in the HFpEF group (277 minutes [229,331]; p=0.001) and HFrEF group (266 minutes [226, 300]; p=0.012) relative to patients without HF (240 minutes [200,282]). Additionally, fluoroscopy time was longer in the HFrEF group (84 minutes [67,99]; p=0.030) relative to patients without HF (73 minutes [58,90]). The types of additional ablations performed between groups were similar, with the exception that left atrial roof ablations were performed significantly more frequently in patients with HFpEF (36.0%; p=0.040) and HFrEF (46.2%; p=0.001) relative to those without HF (22.9%).

There were no statistically significant differences in any procedural complication between groups (**Table 2**). Recurrence of AF on or off AAD (72% in HFpEF versus 53% in HFrEF versus 63% in no HF at 5 years; log rank p=0.205) and off AAD (71% in HFpEF versus 34% in HFrEF versus 49% in no HF at 5 years; log rank p =0.053) was statistically similar between groups over all follow-up, with the exception that HFpEF patients had more recurrence off AAD relative to patients without HF **(Figure 1A and 1B)**. Patients were off AAD after CA in 32 (63%) patients with HFpEF, 20 (50%) with HFrEF, and 255 (56%) with no HF (p=0.096). Additionally, there were significantly more patients who underwent repeat ablations in the HFpEF group relative to the HFrEF group (51% v 28%; p=0.036).

All-cause hospitalizations over all follow-up were significantly more common in the HFpEF group (76%; log rank p<0.001) and HFrEF group (67%; log rank p=0.039) relative to patients without HF (55% at 5 years) **(Figure 2A)**. However, there was no difference in survival between all 3 groups (95% in HFpEF versus 87% in HFrEF versus 96% in no HF at 5 years; log rank p=0.604) **(Figure 2B)**.

Hazard ratios with multivariable adjustment for potential confounders and respective confidence intervals for recurrence of atrial arrhythmias and all-cause hospitalizations and mortality are summarized in **Table 3**. Although it did not reach statistical significance, there were trends towards increased recurrence of atrial arrhythmias on or off AAD in patients with HFpEF relative to those with HFrEF and in rates of all-cause hospitalizations in patients with HFpEF relative to those with HFrEF or no HF. Subgroup analysis grouped by AF type (paroxysmal versus persistent) showed significantly more recurrence of any atrial arrhythmia in HFpEF patients with persistent AF relative to both HFrEF patients and no HF patients both on or off AAD **(Figure 3)**.

DISCUSSION

In this retrospective cohort study, there appears to be no significant differences in safety and efficacy of CA in patients with HFpEF, HFrEF, and those without HF. Patients with HFpEF and HFrEF had longer procedure times compared to those without HF, but complication rates were low and without significant differences across groups. There were no significant differences

in recurrence of atrial arrhythmias, regardless of AAD use, between all three groups up to 5 years, with the exception that HFrEF patients had less recurrence of atrial arrhythmias on or off AADs relative to those without HF. Furthermore, in a sub-analysis looking at paroxysmal and persistent AF, there was significantly more recurrence of atrial arrhythmias on or off AAD in HFpEF patients with persistent AF relative to HFrEF and no HF patients. However, both of these differences may be a consequence of the shorter follow-up in the HFrEF group and not reflective of a true difference. Alternatively, the atrial arrhythmias in the HFrEF population may be primarily driven by the reduced systolic function, which has been shown to improve following catheter ablation, [11] and AF may cause more symptoms in patients with HFpEF, resulting in more detected recurrence and repeat ablations.

These findings are significant as options for pharmacologic rhythm control are limited in patients with structural heart disease.[12] While ablation of AF in HFrEF patients has been shown to effectively maintain sinus rhythm, improve left ventricular ejection fraction, exercise capacity, and quality of life and reduce hospitalization and mortality rates,[11] it is unclear if these benefits extend to HFpEF patients.

Both systolic and diastolic left ventricular dysfunction result in elevated left ventricular end diastolic pressure which causes increased left atrial filling pressures.[13] This in turn increases atrial wall stress, consequently affecting the renin angiotensin system,[14] calcium handling,[15] pro-fibrotic[16] and

proinflammatory pathways,[17] all of which promote electrical and structural remodeling.[18]

Despite these distinct changes, results from previous studies are mixed. While Cha et al. showed that patients with diastolic dysfunction were more likely to maintain sinus rhythm at one year relative to those with systolic dysfunction, this difference was no longer significant at 5 years.[19] Black-Meier et al. found no difference in freedom from AF after ablation in HFpEF and HFrEF groups. However, they also found no significant difference in recurrence rates between groups and by type of AF in a sub-analysis comparing paroxysmal and persistent AF.[7] Vecchio et al. found that freedom from AF following ablation was less in HFpEF patients relative to the general population, but similar to those with HFrEF.[20] In a subgroup analysis by Jayanna et al., recurrence of AF at 3 months and 1 year were similar between HFpEF and HFrEF patients.[21]

None of the previous studies compared hospitalizations and mortality between HFpEF and HFrEF patients who underwent ablation for AF. While patients without HF had significantly less hospitalizations relative to those with HFpEF, this is expected given the increased morbidity and mortality HF incurs and would likely have also been observed in the HFrEF group had median follow-up duration been equivalent.[22] This is supported by the fact that there were no differences in all-cause hospitalizations when comparing HFpEF to HFrEF. Furthermore, HFpEF patients did not have increased all-cause mortality relative to those with HFrEF and no HF. This is significant, as

prior to ablation, patients with AF and HFpEF suffer from greater morbidity and mortality relative to those with AF and HFrEF or no HF, which is likely a result of the increased dependence on left atrial function in HFpEF.[23-27]

There are some limitations to interpreting the data presented in this study. First, the generalizability may be limited given that this study involved a single-center and is a retrospective study. Second, given the numerically small number of HF patients, a lack in significant difference between groups may reflect a type II error and not a lack of a true difference. Third, there is no consensus definition for the clinical classification of HFpEF or for the precise ejection fraction cutoff to distinguish HFpEF from HFrEF.[28-30] Although patients with an ejection fraction of 40% to 50% represent an intermediate group, they were included in the HFrEF group, as in prior studies, since they are often treated with goal-directed medical therapy similar to that used in patients with HFrEF.[30] Fourth, groups differed in terms of comorbidities, with HFpEF patients having more COPD, OSA and ESRD. This may significantly affect rates of all-cause hospitalization. Fifth, there was no standardized duration of monitoring for AF recurrence as it was left to the discretion of the clinician. However, at the minimum, guideline based recommendations were followed in all cases.[9] Patients with HF may be more symptomatic when they are not in sinus rhythm, potentially resulting in less detection of asymptomatic AF in patients without HF. Sixth, the analysis looking at recurrence of atrial arrhythmias off AAD is at risk of selection bias given that the patients chosen to be taken off AAD may have been inherently

different (such as having a lower AF burden prior to ablation or less subjective symptoms of AF).

In conclusion, catheter ablation of AF appears safe and effective in patients with HF, regardless of the presence of systolic or diastolic left ventricular dysfunction. There were no significant differences in recurrence of atrial arrhythmias and rates of procedural complications, all-cause hospitalizations and mortality between patients with HFpEF and HFrEF.

REFERENCES

1. Mountantonakis SE, Grau-Sepulveda MV, Bhatt DL, Hernandez AF, Peterson ED, Fonarow GC. Presence of atrial fibrillation is independently associated with adverse outcomes in patients hospitalized with heart failure: an analysis of get with the guidelines-heart failure. *Circulation Heart failure* 2012;5:191-201.

2. Wang TJ, Larson MG, Levy D, Vasan RS, Leip EP, Wolf PA, D'Agostino RB, Murabito JM, Kannel WB, Benjamin EJ. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. *Circulation* 2003;107:2920-2925.

3. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC, Jr., Ellinor PT, Ezekowitz MD, Field ME, Furie KL, Heidenreich PA, Murray KT, Shea JB, Tracy CM, Yancy CW. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation. *Circulation* 2019:CIR0000000000000665.

4. Marrouche NF, Brachmann J, Andresen D, Siebels J, Boersma L, Jordaens L, Merkely B, Pokushalov E, Sanders P, Proff J, Schunkert H, Christ H, Vogt J, Bansch D, Investigators C-A. Catheter Ablation for Atrial Fibrillation with Heart Failure. *N Engl J Med* 2018;378:417-427.

5. Prabhu S, Taylor AJ, Costello BT, Kaye DM, McLellan AJA, Voskoboinik A, Sugumar H, Lockwood SM, Stokes MB, Pathik B, Nalliah CJ, Wong GR, Azzopardi SM, Gutman SJ, Lee G, Layland J, Mariani JA, Ling LH, Kalman

JM, Kistler PM. Catheter Ablation Versus Medical Rate Control in Atrial Fibrillation and Systolic Dysfunction: The CAMERA-MRI Study. *J Am Coll Cardiol* 2017;70:1949-1961.

6. Aldaas OM, Malladi CL, Hsu JC. Atrial fibrillation in patients with heart failure with preserved ejection fraction. *Current opinion in cardiology* 2020.

7. Black-Maier E, Ren X, Steinberg BA, Green CL, Barnett AS, Rosa NS, Al-Khatib SM, Atwater BD, Daubert JP, Frazier-Mills C, Grant AO, Hegland DD, Jackson KP, Jackson LR, Koontz JI, Lewis RK, Sun AY, Thomas KL, Bahnson TD, Piccini JP. Catheter ablation of atrial fibrillation in patients with heart failure and preserved ejection fraction. *Heart Rhythm* 2018;15:651-657.

8. Machino-Ohtsuka T, Seo Y, Ishizu T, Sugano A, Atsumi A, Yamamoto M, Kawamura R, Machino T, Kuroki K, Yamasaki H, Igarashi M, Sekiguchi Y, Aonuma K. Efficacy, safety, and outcomes of catheter ablation of atrial fibrillation in patients with heart failure with preserved ejection fraction. *J Am Coll Cardiol* 2013;62:1857-1865.

9. Calkins H, Hindricks G, Cappato R, Kim YH, Saad EB, Aguinaga L, Akar JG, Badhwar V, Brugada J, Camm J, Chen PS, Chen SA, Chung MK, Nielsen JC, Curtis AB, Davies DW, Day JD, d'Avila A, de Groot N, Di Biase L, Duytschaever M, Edgerton JR, Ellenbogen KA, Ellinor PT, Ernst S, Fenelon G, Gerstenfeld EP, Haines DE, Haissaguerre M, Helm RH, Hylek E, Jackman WM, Jalife J, Kalman JM, Kautzner J, Kottkamp H, Kuck

KH, Kumagai K, Lee R, Lewalter T, Lindsay BD, Macle L, Mansour M, Marchlinski FE, Michaud GF, Nakagawa H, Natale A, Nattel S, Okumura K, Packer D, Pokushalov E, Reynolds MR, Sanders P, Scanavacca M, Schilling R, Tondo C, Tsao HM, Verma A, Wilber DJ, Yamane T. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation: Executive summary. *Journal of arrhythmia* 2017;33:369-409.

10. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC, Jr., Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW, American College of Cardiology/American Heart Association Task Force on Practice G. 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:e1-76.

11. Aldaas OM, Malladi CL, Hsu JC. Catheter Ablation of Atrial Fibrillation in Patients With Heart Failure. *Am J Cardiol* 2019;123:187-195.

12. Pedersen OD, Bagger H, Keller N, Marchant B, Kober L, Torp-Pedersen C. Efficacy of dofetilide in the treatment of atrial fibrillation-flutter in patients with reduced left ventricular function: a Danish investigations of arrhythmia and mortality on dofetilide (diamond) substudy. *Circulation* 2001;104:292-296.

13. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Kober L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Ronnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A, Task Force for the D, Treatment of A, Chronic Heart Failure of the European Society of C, Bax JJ, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windecker S, McDonagh T, Sechtem U, Bonet LA, Avraamides P, Ben Lamin HA, Brignole M, Coca A, Cowburn P, Dargie H, Elliott P, Flachskampf FA, Guida GF, Hardman S, Iung B, Merkely B, Mueller C, Nanas JN, Nielsen OW, Orn S, Parissis JT, Ponikowski P, Guidelines ESCCfP. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *European journal of heart failure* 2012;14:803-869.

14. Liang F, Gardner DG. Autocrine/paracrine determinants of strain-activated brain natriuretic peptide gene expression in cultured cardiac myocytes. *J Biol Chem* 1998;273:14612-14619.

15. Leistad E, Aksnes G, Verburg E, Christensen G. Atrial contractile dysfunction after short-term atrial fibrillation is reduced by verapamil but increased by BAY K8644. *Circulation* 1996;93:1747-1754.

16. Mayyas F, Niebauer M, Zurick A, Barnard J, Gillinov AM, Chung MK, Van Wagoner DR. Association of left atrial endothelin-1 with atrial rhythm, size, and fibrosis in patients with structural heart disease. *Circ Arrhythm Electrophysiol* 2010;3:369-379.

17. De Jong AM, Maass AH, Oberdorf-Maass SU, Van Veldhuisen DJ, Van Gilst WH, Van Gelder IC. Mechanisms of atrial structural changes caused by stretch occurring before and during early atrial fibrillation. *Cardiovascular research* 2011;89:754-765.

18. Ling LH, Kistler PM, Kalman JM, Schilling RJ, Hunter RJ. Comorbidity of atrial fibrillation and heart failure. *Nature reviews Cardiology* 2016;13:131-147.

19. Cha YM, Wokhlu A, Asirvatham SJ, Shen WK, Friedman PA, Munger TM, Oh JK, Monahan KH, Haroldson JM, Hodge DO, Herges RM, Hammill SC, Packer DL. Success of ablation for atrial fibrillation in isolated left ventricular diastolic dysfunction: a comparison to systolic dysfunction and normal ventricular function. *Circ Arrhythm Electrophysiol* 2011;4:724-732.

20. Vecchio N, Ripa L, Orosco A, Tomas L, Mondragon I, Acosta A, Talavera L, Rivera S, Albina G, Diez M, Scazzuso F. Atrial Fibrillation in Heart Failure Patients with Preserved or Reduced Ejection Fraction.

Prognostic significance of Rhythm control strategy with Catheter Ablation. *J Atr Fibrillation* 2019;11:2128.

21. Jayanna MB, Mohsen A, Inampudi C, Alvarez P, Giudici MC, Briasoulis A. Procedural Outcomes of Patients With Heart Failure Undergoing Catheter Ablation of Atrial Fibrillation. *American journal of therapeutics* 2019;26:e333-e338.

22. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Jr., Colvin MM, Drazner MH, Filippatos GS, Fonarow GC, Givertz MM, Hollenberg SM, Lindenfeld J, Masoudi FA, McBride PE, Peterson PN, Stevenson LW, Westlake C. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Journal of cardiac failure* 2017;23:628-651.

23. Melenovsky V, Hwang SJ, Redfield MM, Zakeri R, Lin G, Borlaug BA. Left atrial remodeling and function in advanced heart failure with preserved or reduced ejection fraction. *Circulation Heart failure* 2015;8:295-303.

24. Olsson LG, Swedberg K, Ducharme A, Granger CB, Michelson EL, McMurray JJ, Puu M, Yusuf S, Pfeffer MA, Investigators C. Atrial fibrillation and risk of clinical events in chronic heart failure with and without left ventricular systolic dysfunction: results from the

Candesartan in Heart failure-Assessment of Reduction in Mortality and morbidity (CHARM) program. *J Am Coll Cardiol* 2006;47:1997-2004.

25. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. *N Engl J Med* 2006;355:251-259.

26. Santos AB, Roca GQ, Claggett B, Sweitzer NK, Shah SJ, Anand IS, Fang JC, Zile MR, Pitt B, Solomon SD, Shah AM. Prognostic Relevance of Left Atrial Dysfunction in Heart Failure With Preserved Ejection Fraction. *Circulation Heart failure* 2016;9:e002763.

27. von Roeder M, Rommel KP, Kowallick JT, Blazek S, Besler C, Fengler K, Lotz J, Hasenfuss G, Lucke C, Gutberlet M, Schuler G, Schuster A, Lurz P. Influence of Left Atrial Function on Exercise Capacity and Left Ventricular Function in Patients With Heart Failure and Preserved Ejection Fraction. *Circulation Cardiovascular imaging* 2017;10.

28. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ, Chamber Quantification Writing G, American Society of Echocardiography's G, Standards C, European Association of E. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology.

Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography 2005;18:1440-1463.

29. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P, Authors/Task Force M, Document R. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *European journal of heart failure* 2016;18:891-975.

30. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Jr., Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL, American College of Cardiology F, American Heart Association Task Force on Practice G. 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:e147-239.

FIGURE LEGENDS

Figure 1: Kaplan-Meier plots of A) long-term recurrence of atrial arrhythmias on or off antiarrhythmic drugs (excluding a 3-month post-procedural blanking period), and B) long-term recurrence of atrial arrhythmias off antiarrhythmic drugs. Patients with heart failure with preserved ejection fraction, heart failure with reduced ejection fraction and no heart failure are compared. Abbreviations: AAD=antiarrhythmic drug; AF=atrial fibrillation; HF=heart failure; HFpEF=heart failure with preserved ejection fraction; HFrEF=heart failure with reduced ejection fractioon

Figure 2: Kaplan-Meier plots of A) long-term rate of all-cause hospitalizations and B) long-term rate of all-cause mortality. Patients with heart failure with preserved ejection fraction, heart failure with reduced ejection fraction

and no heart failure are compared.

Abbreviations: HF=heart failure; HFpEF=heart failure with preserved ejection fraction; HFrEF=heart failure with reduced ejection fraction.

Figure 3: Freedom from atrial arrhythmias by atrial fibrillation subtype over all follow-up. Patients with heart failure with preserved ejection fraction, heart failure with reduced ejection fraction and no heart failure are compared. A) Freedom from atrial arrhythmias on or off antiarrhythmic drugs in patients with persistent atrial fibrillation and B) freedom from atrial arrhythmias on or off antiarrhythmic drugs in patients with paroxysmal atrial fibrillation. P-values that are presented have been adjusted with a multivariable regression models using the covariates listed in Table 1.

Abbreviations: AAD = antiarrhythmic drug; AF = atrial fibrillation; AFL = atrial flutter; AT = atrial tachycardia; HF=heart failure; HFpEF=heart failure with preserved ejection fraction; HFrEF=heart failure with reduced ejection fraction.

*P<0.05 for HFpEF compared with no HF

†P<0.05 for HFrEF compared with no HF

‡P<0.05 for HFpEF compared with HFrEF