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Catheter ablation of atrial fibrillation in chronic heart failure: state of the art and future perspectives

Matteo Anselmino, MD PhD, Mario Matta, MD, Davide Castagno, MD, Carla Giustetto, MD, Fiorenzo Gaita, MD Prof.

Division of Cardiology, Department of Medical Sciences, ”Città della Salute e della Scienza” Hospital, University of Turin, Italy

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Abstract

Catheter ablation of atrial fibrillation (AFCA) is a widely recommended treatment for symptomatic AF patients refractory to pharmacological treatment. AFCA is becoming a therapeutic option also among patients with heart failure (CHF), on top of optimal medical treatment, being this arrhythmia related to a higher risk of death and/or symptom's worsening. In fact, in this setting, clinical evidences are continuously increasing.

The present systematic review pools all published experiences concerning AFCA among CHF patients, or patients with structural cardiomyopathies, in order to summarize procedural safety and efficacy in this specific population. Moreover, the effects of AFCA on functional class and quality of life and the different procedural protocols available are discussed.

The present work, therefore, attempts to provide an evidence based clinical perspective to optimize clinical indication and tailor procedural characteristics and endpoints to patients affected by CHF referred for AFCA.

Introduction

Atrial fibrillation (AF) and chronic heart failure (CHF) are two strictly related epidemics of modern cardiovascular medicine[1], as demonstrated by their increasing prevalence in the general population[2]. They share pathophysiological links, as CHF is related to AF occurrence through the increase of left ventricular (LV) filling pressures, left atrial dilation and fibrosis, that all lead to atrial structural and electrical remodeling[3,4]. On the other side AF increases the risk of developing CHF through the loss of atrial contraction, short and irregular cardiac cycles and uncontrolled heart rate secondary to the arrhythmia. This may ultimately lead to impaired ventricular filling, contractility and reduced cardiac output[5,6].

As AF can increase mortality in this population[7], the treatment of AF in patients with CHF plays a relevant role. In fact, rhythm control has recently proven beneficial in large observational cohorts, reporting longer survival[8], decreased incidence of stroke[9] and silent cerebral ischemic lesions[10], compared to rate control strategies. However, the optimal rhythm control option is still of concern, as the majority of antiarrhythmic drugs carry a high risk of adverse effects, such as pro-arrhythmias[11], negative inotropic effect potentially worsening heart failure status[12], and only amiodarone is permitted, but presents frequent extra-cardiac adverse effects[13,14]. Dronedarone, following the results of the Antiarrhythmic trial with DROnedarone in Moderate-to-severe congestive heart failure Evaluating morbidity DecreAse (ANDROMEDA)[15], is not recommended for patients with moderate to severe HF and should be avoided in patients with less-severe HF if appropriate alternatives exist[14].

Catheter ablation of AF (AFCA) is an established therapeutic option in patients symptomatic from AF despite adequate rate control and pharmacologic rhythm control[14]. Within the general population, to date, the safety and efficacy rates promoted this procedure to the first choice following one antiarrhythmic drug failure and, in selected patients, even the first option before drugs[14].

Its role within CHF patients, instead, is less well defined. Small randomized trials and observational studies, and recently a meta-analysis including up to 1,800 patients, have assessed the role of AFCA in CHF patients. The present systematic review aims to discuss patients' selection, safety, efficacy and clinical implications of AFCA in the setting of CHF.

Methods

The present study was conducted in accordance to current guidelines, including the recent Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) amendment to the Quality of Reporting of Meta-analyses (QUOROM) statement[16].

A systematic review was conducted to retrieve all published data concerning AFCA in patients with CHF. MEDLINE/PubMed and Cochrane database were searched for pertinent articles published in English from 2002 until January 2015, according to published recommendations[17]. The following terms: "atrial fibrillation" AND "catheter ablation" AND "heart failure" AND ("clinical trial" OR "meta-analysis" OR "observational study") were used to identify all the published articles referring to this specific patient population. Moreover, a second search was performed to identify published data concerning AFCA in patients with specific structural cardiomyopathies. The following terms: "atrial fibrillation" AND "catheter ablation" AND ("cardiomyopathy" OR "valvular") AND ("clinical trial" OR "meta-analysis" OR "observational study") were used.

Retrieved citations were first screened independently by 2 reviewers (authors: M.A. and M.M.). If the citations were deemed potentially pertinent, they were then appraised as complete reports according to the following selection criteria: (i) human studies, (ii) published between 2002 and December 2014, (iii) investigating patients with impaired LV systolic function, defined as LVEF < 50%, or with specific cardiomyopathies, undergoing AFCA. Exclusion criteria were: (i) non-human

setting, (ii) duplicate reporting (in which case the manuscript reporting the largest sample of patients was selected), (iii) studies including patients undergoing surgical or hybrid AF ablation, or (iv) studies without comprehensive follow-up description.

Search Results

The first search identified 169 abstracts; among this group, 144 were excluded following application of the inclusion and exclusion criteria; 25 of them were finally selected and included, in particular 17 observational studies[18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34] 4 randomized controlled trials (RCTs)[35,36,37,38] and 4 meta-analyses[39,40,41,42]. Details concerning sample size and main findings for each of the studies considered are summarized in Table 1 and Table 2. The second search identified 50 abstracts; among this group, 36 were excluded following application of the inclusion and exclusion criteria; 14 of them were finally selected, in particular one study including patients with tachycardiomyopathy (TCM)[43], 8 studies including patients with hypertrophic cardiomyopathy (HCM)[44,45,46,47,48,49,50,51], and 5 studies including patients with valvular cardiomyopathy[52,53,54,55,56].

Observational studies

As detailed in Table 1 observational studies included 1,253 patients. Follow-up ranged from 6 to 60 months. Mean efficacy of AFCA in maintaining sinus rhythm (SR) was 48% after the first procedure, raising up to 75% including the 32% of the patients undergoing a redo procedure. All the included patients underwent pulmonary veins (PV) isolation, and 55% received additional left atrial lesions: left isthmus line, roof line and complex fractioned atrial electrograms (CFAE) ablation. Complications rate was 4.3%. Several studies reported on improvement of LV systolic

function[19,20,21,24,25,26,27,28,29,30], quality of life, exercise tolerance[18,19,20,27], mitral regurgitation[28] and reduction of heart failure hospitalizations[33].

Randomized controlled trials

The four available RCTs included 115 patients overall (Table 1). The control groups included patients undergoing atrioventricular node ablation and biventricular pacemaker implantation in the trial by Khan et al.[35], while patients treated with optimal medical therapy and rate control management in the other three trials. Follow-up ranged from 6 to 10 months. Mean efficacy of AFCA in maintaining SR was 59% after the first procedure, raising up to 77% including the 31% patients undergoing redo procedures. All patients included underwent PV isolation, and 98% received additional left atrial lesions. Complications rate was 12%. Three of four studies found quality of life and functional improvement, respectively measured by 6-minute walking test (6MWT)[35] and peak VO2 at cardiopulmonary exercise test[37,38].

AFCA in patients with TCM

Two studies (Table 1) selectively focused on patients with TCM, including 113 patients respectively with a follow-up of 6 and 18 months. AFCA efficacy at follow-up was 74%, and mean LV ejection fraction (LVEF) significantly improved form 35-40% to 54%. Of note, in both studies the presence of TCM was not related to increased risk of AF recurrences[29,43].

AFCA in specific cardiomyopathies and valvular heart disease

As listed in Table 2, 8 studies described the outcome of AFCA in HCM, including 242 patients with a follow-up ranging from 6 to 30 months. Mean efficacy after a first ablation procedure was 46%, improving to 71% including over 30% of the patients with a redo procedure. Of note, the majority of these studies, especially those reporting long-term follow-up, approached AF by extensive left atrial ablation including PV isolation, linear lesions and CFAE ablation.

Five studies reported the outcome of AFCA in patients with significant valvular cardiomyopathy, defined as at least moderate mitral or aortic regurgitation or stenosis or previous valvular surgery, including 259 patients followed for 11 to 54 months. Mean efficacy after a first ablation procedure was 49%, improving to 77% including the over 40% of patients undergoing redo procedures.

Discussion

AFCA in CHF patients: past evidence and new perspectives

The majority of available data are based on small observational single center studies, mainly retrospective. Overall the procedure envisaged PV isolation for all the patients. A large proportion of patients, according to the current knowledge of AF pathophysiology and the available tools[57], underwent additional linear lesions (e.g. the "7 scheme"[58], a lesion set including, besides PV isolation, a roof line connecting ipsilateral superior PVs and a mitral isthmus line connecting left inferior PV to the mitral annulus, or CFAE ablation[59]). The first studies reported encouraging results, showing favorable trends in AFCA efficacy (ranging from 70 to 80%). However, these results referred to a short (6-12 months) follow-up. Moreover, a relatively large number of repeated procedures (in around one third of the patients) was described. In general, the complex

electroanatomical substrate of these patients[4] seems not to impact the outcome of AFCA, although it is likely to be associated with the need of multiple procedures to maintain SR.

Four studies are characterized by long-term follow-up (more than 2 years)[23,28,30,33], showing lower efficacy rates after a single procedure (about 40-50%), raising significantly when including redo procedures. Of note, despite more procedures were performed per patient, complication rate was similar to previous studies.

Several studies reported improvement of quality of life and exercise capacity[18,19,20] following AFCA. Bunch et al.[33] are the only reporting long-term reduction of mortality and hospitalization for heart failure following AFCA compared to medical therapy. Although carrying limitations, such as the absence of follow-up pre-specified protocols, this finding surely warrants further attention and testing in RCTs.

Four short term RCTs have been performed on a limited population. These studies confirmed safety and efficacy of the procedure, except from MacDonald et al.[36] that reported lower success rates and no improvement in LVEF or exercise tolerance. However, it should be heeded that patients included in this study had advanced CHF, longer AF duration and a worse functional class (approximately 90% of the patients were in New York Heart Association functional class III) compared with the other 3 RCTs. In fact, in these trials, including patients with less severe CHF, LVEF, quality of life and exercise capacity improved significantly. Of note, complication rate was higher compared to observational studies: the reasons may be secondary to the high proportion of patients with advanced CHF compared to the other studies, often treated with extensive left atrial ablation, requiring longer procedural times and potential risk of complications. However, concerning SR restoration, there was no substantial difference between observational studies and the four RCTs. Among patients with CHF and underlying cardiomyopathy the procedure, may carry higher risks,

but, unless the patients are affected by advanced CHF and present with poor functional class, can result effective.

As summarized in Table 3 four meta-analyses have been published including the aforementioned studies. In the first two works, including maximum 800 patients[39,40], the Authors concluded that single AFCA in CHF patients is less effective than in patients without structural disease, but improves including redo procedures, without higher risks of complications; both analysis reported significant improvement in LVEF over follow-up. The third multi-center, collaborative meta-analysis, including more than 1,800 patients[41], reported, over a mean follow-up of 2 years, a similar improvement in LVEF, and particularly focused on the reduction in the proportion of patients with severely depressed LV function. This finding, previously reported by a single center study[60], is of paramount clinical importance since potentially confers to AFCA, on top of optimal medical treatment, the ability to reduce the proportion of patients further requiring implantation of cardioverter defibrillators. Of note, AFCA efficacy and safety were similar to the data reported in the long-term follow-up of general population studies[61,62]. Time to first AF diagnosis and heart failure diagnosis significantly related to AFCA outcome, highlighting the importance of prompt optimal treatment of both CHF and AF to achieve the best clinical benefit.

Eventually, within the general CHF population undergoing AFCA one small observational prospective study specifically investigated patients with preserved LVEF[34]. This study, including 74 patients with mean follow-up of 34 months, reported 27% efficacy after the first procedure, raised to 73% including redo procedures and antiarrhythmic drugs. All the patients underwent PV isolation, 59% linear ablation and 27% CFAE ablation, without major complications. Of note, LV diastolic function and systolic function measured with strain and strain rate improved only in patients maintaining stable SR. These finding are in accordance with a previous study by Tops et al.

showing a significant improvement of LV circumferential and longitudinal strain and strain rate after successful AFCA, which in contrast decrease in patients experiencing AF recurrence[63].

AFCA in patients with TCM

Two studies specifically focused on patients with TCM[29,43], and both agreed that TCM itself is not related to higher AF recurrence following AFCA. The same finding was reported in a long-term follow up sub-analysis by Anselmino et al.[28], highlighting the benefits of AFCA in this subset. Being the procedure performed after the failure of pharmacological rhythm or rate control strategies, effective SR restoration and consequent avoidance of uncontrolled high ventricular rates is pivotal in restoring normal LV function[64]. This subset of patients is, in fact, the most likely to recover normal LVEF following successful AFCA, and ablation, in this setting, proved to be superior to effective rate control in normalizing LV function[43]. In addition, being TCM a significant percentage of CHF patients referred to AFCA, achieving effective rhythm control may also be useful to confirm the etiology of LV dysfunction and avoid unnecessary long-term treatments.

AFCA in specific cardiomyopathies populations

Eight observational studies reported the outcome of AFCA among HCM patients[44,45,46,47,48,49,50,51]. Consistently, all studies reported low efficacy after a single ablation procedure, especially during long-term follow-up. However, the efficacy raised up to 70-80% including the over 30% redo procedures; the prevalence of extensive left atrial ablation, including linear lesions or CFAEs, was higher compared to the general CHF population (Figure 1). This finding reflects a complex substrate typical of this specific cardiomyopathy[65], characterized by severe left atrial enlargement. Being AF detrimental on both quality of life and prognosis of HCM patients[66], its effective

treatment warrants careful attention, and AFCA may be considered precociously to achieve rhythm control.

Although AF standard treatment in valvular cardiomyopathies is more commonly surgical[67], performed concomitantly to heart surgery, 5 studies (four observational and one RCT) reported the outcome of AFCA among patients with significant valvular disease. Three of them[53,55,56] included patients with prosthetic valves or previous percutaneous interventions for mitral rheumatic disease, reporting very low efficacy after a single procedure, raising up to 70% at a mean follow-up of 24 months including over 50% repeated procedures. Gu et al.[55] compared AFCA to surgical AF ablation, showing significantly better results for surgical ablation. This likely reflects the peculiar electroanatomical substrate of left atria determined by rheumatic heart disease[68], characterized by profound structural remodeling requiring extreme substrate modification to achieve stable SR. The two studies including patients with moderate aortic or mitral defects[52,54], instead, reported outcomes similar to the general population. This finding highlights the consequences on atrial substrate provided by a severe valvular disease or previous heart surgery compared to the minor atrial involvement present in lower degrees of valvular heart disease.

Procedural protocol: PV isolation alone or extensive atrial ablation?

The basis for extensive left atrial ablation lies in the pathophysiology of AF itself[69]: AF perpetuating in a left atrium with significant substrate modifications and advanced structural and electrical remodeling has historically been targeted by linear lesions[58,70]. However, linear lesions and CFAE ablation may increase the risk of iatrogenic atypical atrial re-entries (flutter) or atrial tachycardias if not transmural, incomplete, or not perfectly anchored to electrically inert structures[71], counterbalancing the benefit derived by extensive atrial substrate modification[72].

As illustrated in Figure 1, among the studies including unselected CHF patients, 55% of the patients underwent PV isolation alone, with a large heterogeneity among the studies (range 6-89%), resulting in SR maintenance comparable to the general non-CHF population. None of the observational studies was designed to compare the efficacy of different AFCA approaches. However, in the meta-analysis by Anselmino et al.[41], including the largest available population, there was no difference in AFCA outcome performing PV isolation alone compared to additional linear ablation.

Concerning specific cardiomyopathies, HCM and valvular cardiomyopathies have been approached by a much higher prevalence of left atrial linear lesions or CFAE, with only 37% of patients undergoing PV isolation alone. Even higher was the prevalence of linear lesions or CFAE among patients with severe or surgically corrected valvular disease, while patients with moderate valvular disease underwent more often PV isolation alone. This confirms once again the need of more aggressive substrate modification in cardiomyopathies with advanced left atrial substrate involvement. In patients with severe valvular cardiomyopathies, the ablation approach is in fact commonly surgical, and AFCA may play a role, perhaps as a hybrid approach, by completing the lesion set[73].

Despite this finding, however, extensive left atrial ablation strives to prove a net clinical benefit over PV isolation alone. CFAE ablation, for example, reported, after the introduction, minimally reproducible results and lower efficacy compared to traditional ablation protocols[74]. To date, rotors (areas of micro re-entries) and focal sources of high frequency activity have been proposed as new theoretically crucial targets for AF perpetuation[75]. However, although in non-CHF patients, the recent RADAR-AF trial[76], randomizing patients with both paroxysmal and persistent AF to PV isolation alone versus respectively rotor ablation alone and PV isolation with rotor ablation, showed no benefit, but longer procedural times and higher risk of complications, as potentially silent

cerebral ischemias[77], from assessing these targets. In accordance with these data, the Substrate and Trigger Ablation for Reduction of Atrial Fibrillation Part 2 (STAR AF 2) trial[78], comparing PV isolation alone to strategies adding non-pulmonary vein targets in patients with persistent AF, did not show significant differences in AF recurrence between these alternative approaches.

Clinical implications

First, AFCA is a safe procedure, and can be performed with low complications rate in patients with complex atrial substrate, comorbidities and frailty[62] such those with CHF. All the studies and meta-analyses are concordant with the data concerning general non-CHF population. In fact, technological innovations contribute to rise AFCA safety: new superirrigated catheters lead to a significant reduction of fluid administration during the procedure[79], particularly relevant among CHF patients. Moreover, magnetic resonance imaging plays an important role in correctly defining patients' anatomy[80], to avoid risks of access site related complications and to correctly map and target sites implicated in AF initiation and perpetuation[81]. However, due to the complexity of such patients, the suggestion is to refer to experienced, high volume Centers, also skilled to manage plausible complications.

Second, AFCA improves LV function over short and long term follow-up, especially compared to medical treatment. This finding is not surprising: interruption of the vicious circle between AF and CHF, restoration of regular cardiac cycles and normal atrial mechanical function are likely to slow or even interrupt the negative electrical and structural remodeling of the failing heart.

Third, AFCA relates to a significant improvement in quality of life, functional class and exercise tolerance, possibly related to the improvement of LV function and hemodynamic status of the patients. In general, shorter history of CHF and AF are both associated with improved outcome:

AFCA should be considered precociously to avoid progression of atrial substrate alteration. LA dimension is a marker of advanced substrate alteration, in fact patients with severe LA dilation present lower rate of SR maintenance. The absence of signs of advanced myocardial disease, such as late gadolinium enhancement at magnetic resonance or ischemic heart disease, are likely related to a significant improvement in LV function following SR restoration. Age, described as a predictor of outcome among the general population, despite not emerging independently related to AFCA outcome, resulted lower within the CHF patients included in the aforementioned studies compared to that of the general AFCA population. Finally, the role for new markers, as an advanced interatrial block or P wave duration[82] among patients with CHF and relevant cardiomyopathies warrant further investigation. Given this, patients with a low likelihood to benefit from AFCA, benefit from antiarrhythmic treatment by amiodarone. Careful monitoring of side effects (thyroid dysfunction, hepatic and corneal disorders or pneumonitis), is warranted, but their impact is reasonably limited. In fact, patients with advanced CHF, unstable hemodynamic parameters and poor functional class are less likely to take advantage from this procedure, in front of high procedural risks; in this setting AFCA should not be proposed to improve symptoms or prognosis.

Concerning the ideal AFCA protocol in this subset of patients, PV isolation alone seems to be sufficient in the majority of patients, at least for the first procedure, considering the potential arrhythmogenic “side effects” of extensive atrial ablation, reserving non-PV targets to repeated procedures for arrhythmic recurrences. To reduce the amount of redo procedures ablation tools innovation is needed to achieve safe, reproducible, and transmural PV isolation already after the first procedure. Only in the setting of specific, high risk subset populations such as HCM and severe valvular cardiomyopathies extensive left atrial ablation should be considered at first line to maintain SR. In facts, studies supporting PV isolation alone, such as STAR AF 2, include a very low

prevalence of patients with CHF, valvular cardiomyopathies or HCM, therefore, their results can not be translated to the present subset population without further investigation.

Taking in mind these considerations, the flow chart proposed by our group to guide the decision making process in patients with CHF and concomitant AF is summarized in Figure 2.

Future perspectives

AFCA is gaining a significant role in CHF treatment of patients with concomitant AF, as confirmed by the latest guidelines[14]. However, the following points remain of concern.

First of all, ablation protocol. PV isolation alone and/or additional non-PV targets, as in the general population, need to be tested in prospective randomized trials on CHF patients.

Second, AFCA safety greatly improved over the past years. Due to the widespread expansion of AFCA and increasing referral to the procedures, efforts should be made to further lower complications rate. For example, performing the procedure on anticoagulants has proved to minimize the risk of clinical and asymptomatic thromboembolic complications in the general population, and this should be tested in the CHF subset. In addition, radiation exposure reduction, favored by the new fluoroscopy-zero technologies[83], is warranted also in case of extensive ablation lesion sets.

Finally, few randomized controlled trials specifically investigating the role of AFCA in the setting of CHF are currently ongoing (e.g. Catheter Ablation versus Standard conventional treatment in patients with LV dysfunction and Atrial Fibrillation [CASTLE-AF][84], AF Management In Congestive heart failure with Ablation [AMICA], Ablation vs. Amiodarone for Treatment of Atrial Fibrillation in Patients with Congestive Heart Failure and an Implanted ICD/CRTD [AATAC-AF]).

In addition to assessing the impact of AFCA on symptoms, LV function and functional class, further studies are encouraged to define optimal timing of AFCA during the natural CHF course, and most of all, the impact of AFCA on hard outcomes, such as mortality and stroke incidence.

Reference

[1] Braunwald E. Shattuck Lecture: cardiovascular medicine at the term of the millennium: triumphs, concerns, and opportunities. *N Engl J Med* 1997;337:1360 –1369.

[2] Savelieva I, John Camm A. Atrial fibrillation and heart failure: natural history and pharmacological treatment. *Europace* 2004;5 Suppl 1:S5-19.

[3] Li D, Melnyk P, Feng J, **Errore. Solo documento principale.**, Petrecca K, Shrier A et al. Effects of experimental heart failure on atrial cellular and ionic electrophysiology. *Circulation* 2000; 101(22):2631-8.

[4] Sanders P, Morton JB, Davidson NC, Spence SJ, Vohra JK, Sparks PB et al. Electrical remodeling of the atria in congestive heart failure: electrophysiological and electroanatomic mapping in humans. *Circulation* 2003;108:1461-1468.

[5] Clark DM, Plumb VJ, Epstein AE, Kay GN. Hemodynamic effects of an irregular sequence of ventricular cycle lengths during atrial fibrillation. *J Am Coll Cardiol* 1997;30:1039 –1045.

[6] Naito M, David D, Michelson EL, Schaffenburg M, Dreifus LS. The hemodynamic consequence of cardiac arrhythmias: evaluation of the relative roles of abnormal atrioventricular sequencing, irregularity of ventricular rhythm and atrial fibrillation in a canine model. *Am Heart J* 1983;106:284-291.

[7] Wang TJ, Larson MG, Levy D, Vasan RS, Leip EP, Wolf PA 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.

[8] Ionescu-Ittu R, Abrahamowicz M, Jackevicius CA, Essebag V, Eisenberg MJ, Wynant W et al. Comparative effectiveness of rhythm control vs rate control drug treatment effect on mortality in patients with atrial fibrillation. *Arch Intern Med* 2012;172:997-1004.

[9] Tsadok MA, Jackevicius CA, Essebag V, Eisenberg MJ, Rahme E, Humphries KH et al. Rhythm versus rate control therapy and subsequent stroke or transient ischemic attack in patients with atrial fibrillation. *Circulation* 2012;126:2680-7.

[10] Gaita F, Corsinovi L, Anselmino M, Raimondo C, Pianelli M, Toso E et al. Prevalence of silent cerebral ischemia in paroxysmal and persistent atrial fibrillation and correlation with cognitive function. *J Am Coll Cardiol* 2013;62:1990-7.

[11] Corley SD, Epstein AE, DiMarco JP, Domanski MJ, Geller N, Greene HL et al; AFFIRM Investigators. Relationships between sinus rhythm, treatment, and survival in the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study. *Circulation* 2004; 109(12):1509-13.

[12] Ravid S, Podrid PJ, Lampert S, Lown B. Congestive heart failure induced by six of the newer antiarrhythmic drugs. *J Am Coll Cardiol* 1989;14:1326-30.

[13] Deedwania PC, Singh BN, Ellenbogen K, Fisher S, Fletcher R, Singh SN. Spontaneous conversion and maintenance of sinus rhythm by amiodarone in patients with heart failure and atrial fibrillation: observations from the veterans affairs congestive heart failure survival trial of antiarrhythmic therapy (CHF-STAT). The Department of Veterans Affairs CHF-STAT Investigators. *Circulation* 1998;98:2574-9.

[14] Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH et al; ESC Committee for Practice Guidelines (CPG). 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation.

Developed with the special contribution of the European Heart Rhythm Association. *Eur Heart J* 2012;33:2719-47.

[15] Kober L, Torp-Pedersen C, McMurray JJ, Gøtzsche O, Lévy S, Crijns H et al. Dronedarone Study Group. Increased mortality after dronedarone therapy for severe heart failure. *N Engl J Med* 2008;358:2678-2687.

[16] Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement BMJ 2009;339:b2535.

[17] Wilczynski NL, Haynes RB; for the Hedges Team. Developing optimal search strategies for detecting clinically sound prognostic studies in MEDLINE: an analytic survey. *BMC Med* 2004;2:23.

[18] Chen MS, Marrouche NF, Khaykin Y, Gillinov AM, Wazni O, Martin DO et al. Pulmonary vein isolation for the treatment of atrial fibrillation in patients with impaired systolic function. *J Am Coll Cardiol*. 2004;43:1004-1009.

[19] Hsu LF, Jaïs P, Sanders P, Garrigue S, Hocini M, Sacher F et al. Catheter ablation for atrial fibrillation in congestive heart failure. *N Engl J Med* 2004;351:2373-2383.

[20] Tondo C, Mantica M, Russo G, Avella A, De Luca L, Pappalardo A et al. Pulmonary vein vestibule ablation for the control of atrial fibrillation in patients with impaired left ventricular function. *Pacing Clin Electrophysiol* 2006;29:962-970.

[21] Gentlesk PJ, Sauer WH, Gerstenfeld EP, Lin D, Dixit S, Zado E et al. Reversal of left ventricular dysfunction following ablation of atrial fibrillation. *J Cardiovasc Electrophysiol* 2007;18:9-14.

[22] Efremidis M, Sideris A, Xydonas S, Letsas KP, Alexanian IP, Manolatos D et al. Ablation of atrial fibrillation in patients with heart failure: reversal of atrial and ventricular remodelling. *Hellenic J Cardiol* 2008;49:19-25.

[23] Nademanee K, Schwab MC, Kosar EM, Karwecki M, Moran MD, Visessook N et al. Clinical outcomes of catheter substrate ablation for high-risk patients with atrial fibrillation. *J Am Coll Cardiol* 2008;51:843-849.

[24] Lutomsky BA, Rostock T, Koops A, Steven D, Müllerleile K, Servatius H et al. Catheter ablation of paroxysmal atrial fibrillation improves cardiac function: a prospective study on the impact of atrial fibrillation ablation on left ventricular function assessed by magnetic resonance imaging. *Europace* 2008;10:593-599.

[25] De Potter T, Berruezo A, Mont L, Matiello M, Tamborero D, Santibañez C et al. Left ventricular systolic dysfunction by itself does not influence outcome of atrial fibrillation ablation. *Europace* 2010;12:24-29.

[26] Choi AD, Hematpour K, Kukin M, Mittal S, Steinberg JS. Ablation vs medical therapy in the setting of symptomatic atrial fibrillation and left ventricular dysfunction. *Congest Heart Fail* 2010;16:10-14.

[27] Cha YM, Wokhlu A, Asirvatham SJ, Shen WK, Friedman PA, Munger TM et al. 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.

[28] Anselmino M, Grossi S, Scaglione M, Castagno D, Bianchi F, Senatore G et al. Long-term results of transcatheter atrial fibrillation ablation in patients with impaired left ventricular systolic function. *J Cardiovasc Electrophysiol* 2013;24:24-32

[29] Calvo N, Bisbal F, Guiu E, Ramos P, Nadal M, Tolosana JM et al. Impact of atrial fibrillation-induced tachycariomyopathy in patients undegoing pulmonary vein isolation. *Int J Cardiol* 2013;168:4093-4097.

[30] Nedios S, Sommer P, Dagres N, Kosiuk J, Arya A, Richter S et al. Long-term follow-up after atrial fibrillation ablation in patients with impaired left ventricular systolic function: the importance of rhythm and rate control. *Heart Rhythm* 2014;11:344-51.

[31] Kosiuk J, Nedios S, Darma A, Rolf S, Richter S, Arya A. Impact of single atrial fibrillation catheter ablation on implantable cardioverter defibrillator therapies in patients with ischaemic and non-ischaemic cardiomyopathies. *Europace* 2014;16:1322-6.

[32] Lobo TJ, Pachon CT, Pachon JC, Pachon EI, Pachon MZ, Pachon JC et al. Atrial Fibrillation Ablation in Systolic Dysfunction: Clinical and Echocardiographic Outcomes. *Arq Bras Cardiol* 2015;104(1):45-52.

[33] Bunch TJ, May HT, Bair TL, Jacobs V, Crandall BG, Cutler M et al. Five-year Outcomes of Catheter Ablation in Patients with Atrial Fibrillation and Left Ventricular Systolic Dysfunction. J Cardiovasc Electrophysiol 2015;26(4):363-70.

[34] Machino-Ohtsuka T, Seo Y, Ishizu T, Sugano A, Atsumi A, Yamamoto M et al. Efficacy, safety, and outcomes of catheter ablation of atrial fibrillation in patients with heart failure with preserved ejection fraction. *J Am Coll Cardiol* 2013;62:1857-65.

[35] Khan MN, Jaïs P, Cummings J, Di Biase L, Sanders P, Martin DO et al; PABA-CHF Investigators. Pulmonary-vein isolation for atrial fibrillation in patients with heart failure. *N Engl J Med* 2008;359:1778-1785.

[36] MacDonald MR, Connelly DT, Hawkins NM, Steedman T, Payne J, Shaw M et al. Radiofrequency ablation for persistent atrial fibrillation in patients with advanced heart failure and severe left ventricular systolic dysfunction: a randomised controlled trial. *Heart* 2011;97:740-747.

[37] Jones DG, Haldar SK, Hussain W, Sharma R, Francis DP, Rahman-Haley SL et al. A randomized trial to assess catheter ablation versus rate control in the management of persistent atrial fibrillation in heart failure. *J Am Coll Cardiol* 2013;61:1894-1903.

[38] Hunter RJ, Berriman TJ, Diab I, Kamdar R, Richmond L, Baker V et al. A randomized controlled trial of catheter ablation versus medical treatment of atrial fibrillation in heart failure (the CAMTAF trial). *Circ Arrhythm Electrophysiol* 2014;7:31-8.

[39] Wilton SB, Fundytus A, Ghali WA, Veenhuyzen GD, Quinn FR, Mitchell LB et al. Meta-analysis of the effectiveness and safety of catheter ablation of atrial fibrillation in patients with versus without left ventricular systolic dysfunction. *Am J Cardiol* 2010;106:1284-91.

[40] Dagres N, Varounis C, Gaspar T, Piorkowski C, Eitel C, Iliodromitis EK et al. Catheter ablation for atrial fibrillation in patients with left ventricular systolic dysfunction. A systematic review and meta-analysis. *J Card Fail* 2011;17:964-70.

[41] Anselmino M, Matta M, D'Ascenzo F, Bunch TJ, Schilling RJ, Hunter RJ et al. Catheter ablation of atrial fibrillation in patients with left ventricular systolic dysfunction: a systematic review and meta-analysis. *Circ Arrhythm Electrophysiol* 2014;7:1011-8

[42] Ganesan AN, Nandal S, Lüker J, Pathak RK, Mahajan R, Twomey D et al. Catheter Ablation of Atrial Fibrillation in Patients with Concomitant Left Ventricular Impairment: a Systematic Review of Efficacy and Effect on Ejection Fraction. *Heart Lung Circ* 2015;24(3):270-80

[43] Sairaku A, Nakano Y, Oda N, Uchimura Y, Tokuyama T, Kawazoe H et al. Incomplete cure of tachycardia-induced cardiomyopathy secondary to rapid atrial fibrillation by heart rate control without sinus conversion. *J Cardiovasc Electrophysiol* 2014;25:1037-43.

[44] Liu X, Ouyang F, Mavrakis H, Ma C, Dong J, Ernst S et al. Complete pulmonary vein isolation guided by three-dimensional electroanatomical mapping for the treatment of paroxysmal atrial fibrillation in patients with hypertrophic obstructive cardiomyopathy. *Europace* 2005;7:421-7.

[45] Kilicaslan F, Verma A, Saad E, Themistoclakis S, Bonso A, Raviele A et al. Efficacy of catheter ablation of atrial fibrillation in patients with hypertrophic obstructive cardiomyopathy. *Heart Rhythm* 2006;3:275-80.

[46] Di Donna P, Olivotto I, Delcrè SD, Caponi D, Scaglione M, Nault I et al. Efficacy of catheter ablation for atrial fibrillation in hypertrophic cardiomyopathy: impact of age, atrial remodelling, and disease progression. *Europace* 2010;12:347-55.

[47] Bunch TJ, Munger TM, Friedman PA, Asirvatham SJ, Brady PA, Cha YM et al. Substrate and procedural predictors of outcomes after catheter ablation for atrial fibrillation in patients with hypertrophic cardiomyopathy. *J Cardiovasc Electrophysiol* 2008;19:1009-14.

[48] Derejko P, Polańska M, Chojnowska L, Michałowska I, Wójcik A, Piotrowicz E et al. Catheter ablation of atrial fibrillation in patients with hypertrophic cardiomyopathy: atrial fibrillation type determines the success rate. *Kardiol Pol* 2013;71:17-24.

[49] Santangeli P, Di Biase L, Themistoclakis S, Raviele A, Schweikert RA, Lakkireddy D et al. Catheter ablation of atrial fibrillation in hypertrophic cardiomyopathy: long-term outcomes and mechanisms of arrhythmia recurrence. *Circ Arrhythm Electrophysiol* 2013;6:1089-94.

[50] Müssigbrodt A, Kosiuk J, Koutalas E, Pastromas S, Dagres N, Darma A et al. Results of catheter ablation of atrial fibrillation in hypertrophied hearts - Comparison between primary and secondary hypertrophy. *J Cardiol* 2015; 65(6):474-8.

[51] Okamatsu H, Ohara T, Kanzaki H, Nakajima I, Miyamoto K, Okamura H et al. Impact of Left Ventricular Diastolic Dysfunction on Outcome of Catheter Ablation for Atrial Fibrillation in Patients With Hypertrophic Cardiomyopathy. *Circ J* 2015;79(2):419-24.

[52] Khaykin Y, Marrouche NF, Saliba W, Schweikert R, Bash D, Chen MS et al. Pulmonary vein antrum isolation for treatment of atrial fibrillation in patients with valvular heart disease or prior open heart surgery. *Heart Rhythm* 2004;1:33-9.

[53] Wang X, Liu X, Shi H, Gu J, Sun Y, Zhou L et al. Heart rhythm disorders and pacemakers: Pulmonary vein isolation combined with substrate modification for persistent atrial fibrillation treatment in patients with valvular heart diseases. *Heart* 2009;95:1773-83.

[54] Miyazaki S, Kuwahara T, Kobori A, Takahashi Y, Takei A, Sato A et al. Catheter ablation of atrial fibrillation in patients with valvular heart disease: long-term follow-up results. *J Cardiovasc Electrophysiol* 2010;21:1193-8.

[55] Gu J, Liu X, Jiang WF, Li F, Zhao L, Zhou L et al. Comparison of catheter ablation and surgical ablation in patients with long-standing persistent atrial fibrillation and rheumatic heart disease: a four-year follow-up study. *Int J Cardiol* 2013;168:5372-7.

[56] Derejko P, Walczak F, Chmielak Z, Romanowska I, Wójcik A, Bilińska M et al. Catheter ablation of complex left atrial arrhythmias in patients after percutaneous or surgical mitral valve procedures. *Kardiol Pol* 2013;71:818-26.

[57] Anselmino M, D'Ascenzo F, Amoroso G, Ferraris F, Gaita F. History of transcatheter atrial fibrillation ablation. *J Cardiovasc Med* 2012;13:1-8.

[58] Gaita F, Caponi D, Scaglione M, Montefusco A, Corleto A, Di Monte F et al. Long-term clinical results of 2 different ablation strategies in patients with paroxysmal and persistent atrial fibrillation. *Circ Arrhythm Electrophysiol* 2008;1:269-75.

[59] Nademanee K, McKenzie J, Kosar E, Schwab M, Sunsaneewitayakul B, Vasavakul Tet al. A new approach for catheter ablation of atrial fibrillation: mapping of electrophysiologic substrate. *J Am Coll Cardiol* 2004;43:2044 –53.

[60] Bortone A, Boveda S, Pasquié JL, Pujadas-Berthault P, Marijon E, Appetiti A et al. Sinus rhythm restoration by catheter ablation in patients with long-lasting atrial fibrillation and congestive heart failure: impact of the left ventricular ejection fraction improvement on the implantable cardioverter defibrillator insertion indication. *Europace* 2009;11:1018-23.

[61] Ganesan AN, Shipp NJ, Brooks AG, Kuklik P, Lau DH, Lim HS et al. Long-term Outcomes of Catheter Ablation of Atrial Fibrillation: A Systematic Review and Meta-analysis. *J Am Heart Assoc* 2013;2:e004549.

[62] Stabile G, Bertaglia E, Pappone A, Themistoclakis S, Tondo C, Calzolari V et al. Low incidence of permanent complications during catheter ablation for atrial fibrillation using open-irrigated catheters: a multicentre registry. *Europace* 2014;16:1154-9.

[63] Tops LF, Den Uijl DW, Delgado V, Marsan NA, Zeppenfeld K, Holman E et al. Long-term improvement in left ventricular strain after successful catheter ablation for atrial fibrillation in patients with preserved left ventricular systolic function. *Circ Arrhythm Electrophysiol* 2009;2:249-57.

[64] Gupta S, Figueredo VM. Tachycardia mediated cardiomyopathy: pathophysiology, mechanisms, clinical features and management. *Int J Cardiol* 2014;172:40-6.

[65] Maron BJ, Haas TS, Maron MS, Lesser JR, Browning JA, Chan RH et al. Left atrial remodeling in hypertrophic cardiomyopathy and susceptibility markers for atrial fibrillation identified by cardiovascular magnetic resonance. *Am J Cardiol* 2014;113:1394-400.

[66] Maron BJ, Ommen SR, Semsarian C, Spirito P, Olivotto I, Maron MS. Hypertrophic cardiomyopathy: present and future, with translation into contemporary cardiovascular medicine. *J Am Coll Cardiol* 2014;64:83-99.

[67] Calkins H, Kuck KH, Cappato R, Brugada J, Camm AJ, Chen SA et al. 2012 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design. *Europace* 2012;14:528-606.

[68] Sharma S, Sharma G, Hote M, Devagourou V, Kesari V, Arava S et al. Light and electron microscopic features of surgically excised left atrial appendage in rheumatic heart disease patients with atrial fibrillation and sinus rhythm. *Cardiovasc Pathol* 2014;23:319-26.

[69] Allessie M, Ausma J, Schotten U. Electrical, contractile and structural remodeling during atrial fibrillation. *Cardiovasc Res* 2002;54:230-246.

[70] Knecht S, Hocini M, Wright M, Lellouche N, O'Neill MD, Matsuo S et al. left atrial linear lesions are required for successful treatment of persistent atrial fibrillation. *Eur Heart J* 2008;29:2359-2366.

[71] Sawhney N, Anousheh R, Chen W, Feld GK. Circumferential pulmonary vein ablation with additional linear ablation results in an increased incidence of left atrial flutter compared with segmental pulmonary vein isolation as an initial approach to ablation of paroxysmal atrial fibrillation. *Circ Arrhythm Electrophysiol* 2010;3:243-248.

[72] Tamborero D, Mont L, Berruezo A, Matiello M, Benito B, Sitges M et al. Left atrial posterior wall isolation does not improve the outcome of circumferential pulmonary vein ablation for atrial fibrillation: a prospective randomized study. *Circ Arrhythm Electrophysiol* 2009;2:35-40.

[73] Gaita F, Ebrille E, Scaglione M, Caponi D, Garberoglio L, Vivalda L et al. Very long-term results of surgical and transcatheter ablation of long-standing persistent atrial fibrillation. *Ann Thorac Surg* 2013;96:1273-8.

[74] Oral H, Chugh A, Good E, Wimmer A, Dey S, Gadeela N et al. Radiofrequency catheter ablation of chronic atrial fibrillation guided by complex electrograms. *Circulation* 2007;115:2606-12.

[75] Swarup V, Baykaner T, Rostamian A, Daubert JP, Hummel J, Krummen DE et al. Stability of Rotors and Focal Sources for Human Atrial Fibrillation: Focal Impulse and Rotor Mapping (FIRM) of AF Sources and Fibrillatory Conduction. *J Cardiovasc Electrophysiol* 2014;25:1284-92

[76] Atienza F, Almendral J, Ormaetxe JM, Moya A, Martínez-Alday JD, Hernández-Madrid A et al; RADAR-AF Investigators. Comparison of Radiofrequency Catheter Ablation of Drivers and Circumferential Pulmonary Vein Isolation in Atrial Fibrillation: A Noninferiority Randomized Multicenter RADAR-AF Trial. *J Am Coll Cardiol* 2014;64:2455-67

[77] Anselmino M, Gaita F. Unresolved issues in transcatheter atrial fibrillation ablation: silent cerebrovascular ischemias. *J Cardiovasc Electrophysiol* 2013;24:129-31

[78] Verma A, Jiang CY, Betts TR, Chen J, Deisenhofer I, Mantovan R et al; STAR AF II Investigators. Approaches to catheter ablation for persistent atrial fibrillation. *N Engl J Med* 2015;372:1812-22.

[79] Bertaglia E, Fassini G, Anselmino M, Stabile G, Grandinetti G, De Simone A et al. Comparison of ThermoCool® Surround Flow catheter versus ThermoCool® catheter in achieving persistent electrical isolation of pulmonary veins: a pilot study. *J Cardiovasc Electrophysiol* 2013;24:269-73.

[80] Anselmino M, Ferraris F, Cerrato N, Barbero U, Scaglione M, Gaita F. Left persistent superior vena cava and paroxysmal atrial fibrillation: the role of selective radio-frequency transcatheter ablation. *J Cardiovasc Med (Hagerstown)* 2014;15:647-52.

[81] Anselmino M, Blandino A, Beninati S, Rovera C, Boffano C, Belletti M et al. Morphologic analysis of left atrial anatomy by magnetic resonance angiography in patients with atrial fibrillation: a large single center experience. *J Cardiovasc Electrophysiol* 2011;22:1-7.

[82] Enriquez A, Sarrias A, Villuendas R, Ali FS, Conde D, Hopman WM, Redfearn DP, Michael K, Simpson C, De Luna AB, Bayés-Genís A, Baranchuk A. New-onset atrial fibrillation after cavotricuspid isthmus ablation: identification of advanced interatrial block is key. *Europace* 2015 Feb 10. pii: euu379.

[83] Anselmino M, Sillano D, Casolati D, Ferraris F, Scaglione M, Gaita F. A new electrophysiology era: zero fluoroscopy. *J Cardiovasc Med (Hagerstown)* 2013;14:221-7.

[84] Marrouche NF, Brachmann J; CASTLE-AF Steering Committee. Catheter ablation versus standard conventional treatment in patients with left ventricular dysfunction and atrial fibrillation (CASTLE-AF) - study design. *Pacing Clin Electrophysiol* 2009; 32:987-94.

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Table 1. Observational studies and randomized controlled trials focusing on AFCA in CHF patients. Unweighted means are indicated as rough summary of each section.

Author, Year (Ref)	N. pts	Age, years	Paroxysmal AF (%)	NYHA class	ICD/ CRT (%)	Pts on AADs (%)	Summary of findings						
							F-U, months	F-U after last, months	Success single (%)	Redo (%)	Success final (%)	LVEF (%)	Other parameters
Observational studies													
Chen 2004 (18)	94	57	51	2.8	32	-	14	-	52	22	73	36→41	↑QoL
Hsu 2004 (19)	58	56	9	2.3	-	78	-	12	28	50	78	35→56	↑LVD, QoL, exercise capacity and NYHA
Tondo 2006 (20)	40	57	25	2.8	-	100	14	-	55	33	87	33→47	↑exercise capacity and QoL
Gentlesk 2007 (21)	67	54	70	-	-	-	6	-	55	31	86	42→56	-
Efremidis 2007 (22)	13	54	0	-	-	-	9	-	62	-	62	36→52	-
Nademanee 2008 (23)	129	67	40	-	-	-	-	27	-	21	79	30→37	-

Lutomsky 2008 (24)	18	-	100	-	-	61	6	-	50	-	-	41→52	-
De Potter 2010 (25)	36	52	39	-	-	55	16	-	50	31	69	41→58	-
Choi 2010 (26)	15	56	67	1.7	7	73	16	-	47	27	73	37→50	-
Cha 2011 (27)	111	55	28	-	-	67	12	-	-	-	76	35→56	↑QoL
Anselmino 2013 (28)	196	60	22	2.1	-	50	46	27	45	30	62	40→50	↑NYHA and mitral regurgitation
Calvo 2013 (29)	36	52	24	-	-	-	6		70	31	83	41→48	-
Nedios 2014 (30)	69	61	33	2.4	26	4	28	-	40	46	65	33→48	-
Kosiuk 2014 (31)	73	59	32	-	100	25	12	-	37	30	-	37→41	↓ ICD shocks
Lobo 2014 (32)	31	60	7	2.2	-	-	20	-	-	26	77	44→59	-
Bunch 2015 (33)	267	66	-	-	-	-	60	-	39	-	-	27→42	↓ death and CHF hospitalization vs. AF,

													no ablation
Overall	1253	58	19	2.3	41	57	32	-	48	32	75	+13%	-
Randomized controlled trials													
Khan 2008 (35)	41	60	49	-	-	100	6	-	71	20	88	27→35	↑QoL and 6MWT distance vs. AV node ablation
MacDonald 2010 (36)	22	62	0	2.9	-	0	10	-	-	30	50	36→41	QoL and 6MWT: no difference vs. medical treatment
Jones 2013 (37)	26	64	0	2.4	15	12	10	-	69	19	88	21→32	↑QoL and peak VO_2, ↓ BNP vs. rate control
Hunter 2014 (38)	26	55	0	2.7	-	-	6	-	38	54	81	32→40	↑QoL, NYHA class peak VO_2, ↓ BNP vs. rate control
Overall	115	60	12	2.7	-	-	8	-	59	31	77	+8%	-
AFCA in patients with tachycardiomyopathy													
Calvo 2013 (29)	61	52	22	-	-	-	6	-	73	-	80	40→54	TCM doesn't relate to AF recurrence

Sairaku 2014 (43)	52	61	0	-	-	-	18	-	-	-	67	35→54	↑ LVEF improvement in patients in SR; TCM doesn't relate to AF recurrence
Overall	113	56	11	-	-	-	12	-	73	-	74	+16%	-
AFCA in patients with CHF with preserved LV ejection fraction													
Machino-Ohtsuka 2013 (34)	74	65	31	2.2	-	15	34	-	27	68	73	-	LV strain and diastolic function improve in patients in SR

AFCA: catheter ablation of atrial fibrillation. CHF: chronic heart failure. AF: atrial fibrillation. FU: follow-up. LVEF: left ventricular ejection fraction. QoL: quality of life. LVD: left ventricular diameter. ICD: implantable cardioverter defibrillator. 6MWT: 6-minute walking test. TCM: tachycardiomyopathy. SR: sinus rhythm.

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Table 2. Observational studies concerning AFCA in specific subset cardiomyopathies. Unweighted means are reported as rough summary of each section.

Hypertrophic cardiomyopathy											
Author, year *(valvular cardiomyopathy subtype)*	N. patients	Age, years	Paroxysmal AF (%)	NYHA class	ICD/ CRT (%)	Follow-up (months)	Follow-up after last (months)	Success single (%)	Success final (%)	Procedural characteristics	Complications (%)
Liu, 2005 (44)	4	57	100	2.0	50	6	-	75	100	PVI	0
Kilicaslan, 2006 (45)	27	55	52	-	-	12	9	52	70	PVI	0
Bunch, 2008 (46)	33	51	64	-	-	30	-	-	74	24% PVI; 76% PVI + 7 scheme	12
Di Donna, 2010 (47)	61	54	57	2.0	28	40	29	28	67	PVI + 7 scheme	0
Derejko, 2013 (48)	30	49	47	1.8	53	22	12	33	53	42% PVI, 58% PVI + 7 scheme + CFAE	0
Santangeli, 2013	43	59	28	1.9	63	15	-	49	94	PVI + 7 scheme +	0

(49)										CFAE	
Mussigbrodt, 2014 (50)	22	57	45	-	36	-	-	41	54	68% PVI, 32% PVI + 7 scheme	5
Okamatsu, 2014 (51)	22	65	23	-	-	21	21	45	59	PVI	-
Overall	242	56	52	1.9	46	18	-	46	71	-	2.
Valvular cardiomyopathies											
Khaykin, 2004 (52) *(moderate mitral or aortic stenosis or regurgitation)*	102	64	37	1.4	-	11	-	83	93	PVI	3
Wang, 2009 (53) *(Mitral or aortic prosthetic valves or previous mitral commissurotomy)*	51	48	0	-	-	12	-	51	67	PVI + CFAE	2
Miyazaki, 2010 (54) *(moderate mitral or aortic stenosis or regurgitation)*	45	66	80	1.3	-	26	24	47	78	80% PVI, 20% PVI + 7 scheme	4.3

Gu, 2010 (55) *(Rheumatic heart disease 6 months after valvular surgery)*	47	55	0	-	-	54	-	32	79	57% PVI + CFAE + 7 scheme; 33% PVI + CFAE; 10% PVI alone	4
Derejko, 2014 (56) *(Previous mitral valve surgery or percutaneous mitral commissurotomy)*	14	55	29	-	-	23	-	36	71	93% PVI + CFAE + 7 scheme; 7% PVI alone	0
Overall	259	58	29	-	-	25	-	49	77	-	2.2

AFCA: atrial fibrillation catheter ablation. PVI: pulmonary vein isolation. CFAE: complex fractioned atrial electrograms.

Table 3. Meta-analyses of published studies on AFCA in CHF patients.

	N. studies	N. patients	Success single (%)	Success final (%)	Complications (%)	LVEF improvement	Other findings
Wilton, 2010 (38)	8	483	45-73	69-96	4.8	+11%	-
Dagres, 2011 (39)	9	354	-	-	6.7	+11%	CAD relates to no LVEF improvement
Anselmino, 2014 (40)	26	1,838	36-44	54-67	4.2	+13%	↓NT-proBNP and patients with LVEF<35%; time to first AF and CHF diagnosis relate to recurrences
Ganesan, 2014 (41)	19	914	56	82	5.5	+13%	Improvement in exercise capacity and QoL

AFCA: atrial fibrillation catheter ablation. CHF: chronic heart failure. LVEF: left ventricular ejection fraction. CAD: coronary artery disease. QoL: quality of life.

Figure legends

Figure 1. AFCA protocol according to underlying cardiomyopathies.

AFCA: atrial fibrillation catheter ablation. CHF: chronic heart failure. HCMP: hypertrophic cardiomyopathy. CFAE: complex fractioned atrial electrograms.

Figure 2. Proposed flow-chart for AF management in patients with concomitant CHF.

¶ Heart failure defined as the presence of structural cardiomyopathy with left ventricular ejection fraction <50% and symptoms of heart failure (NYHA class > I)

* Dotted line refers to severe valvular cardiomyopathy and hypertrophic cardiomyopathy

Long-standing persistent AF should be approached as persistent AF, except in case of severe left atrial dilation (volume > 150 ml)

‡ Dronedarone may be considered in the absence of valuable alternatives in stable (NYHA class I-II) CHF patients

§ Catheter ablation as first line therapy for patients with paroxysmal AF and favorable baseline characteristics (left atrial dimension, short AF and CHF history) and for those intolerant to or rejecting antiarrhythmic drug therapy

¤ As recommended in specific guidelines

AF: atrial fibrillation. CHF: chronic heart failure. ICD: implantable cardioverter defibrillator. CRT: cardiac resynchronization therapy.