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

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

3

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10

1 **Abstract**

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

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

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

14

## 1 **Introduction**

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

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

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

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

5

## 6 **Methods**

7 The present study was conducted in accordance to current guidelines, including the recent Preferred  
8 Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) amendment to the Quality  
9 of Reporting of Meta-analyses (QUOROM) statement<sup>16</sup>.

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

19 Retrieved citations were first screened independently by 2 reviewers (authors: M.A. and M.M.). If  
20 the citations were deemed potentially pertinent, they were then appraised as complete reports  
21 according to the following selection criteria: (i) human studies, (ii) published between 2002 and  
22 December 2014, (iii) investigating patients with impaired LV systolic function, defined as LVEF <  
23 50%, or with specific cardiomyopathies, undergoing AFCA. Exclusion criteria were: (i) non-human

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

4

## 5 **Search Results**

6 The first search identified 169 abstracts; among this group, 144 were excluded following  
7 application of the inclusion and exclusion criteria; 25 of them were finally selected and included, in  
8 particular 17 observational studies<sup>18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34</sup> 4 randomized controlled trials  
9 (RCTs)<sup>35,36,37,38</sup> and 4 meta-analyses<sup>39,40,41,42</sup>. Details concerning sample size and main findings for  
10 each of the studies considered are summarized in Table 1 and Table 2. The second search identified  
11 50 abstracts; among this group, 36 were excluded following application of the inclusion and  
12 exclusion criteria; 14 of them were finally selected, in particular one study including patients with  
13 tachycardiomyopathy (TCM)<sup>43</sup>, 8 studies including patients with hypertrophic cardiomyopathy  
14 (HCM)<sup>44,45,46,47,48,49,50,51</sup>, and 5 studies including patients with valvular cardiomyopathy<sup>52,53,54,55,56</sup>.

15

### 16 *Observational studies*

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



1 function<sup>19,20,21,24,25,26,27,28,29,30</sup>, quality of life, exercise tolerance<sup>18,19,20,27</sup>, mitral regurgitation<sup>28</sup> and  
2 reduction of heart failure hospitalizations<sup>33</sup>.

3

#### 4 *Randomized controlled trials*

5 The four available RCTs included 115 patients overall (Table 1). The control groups included  
6 patients undergoing atrioventricular node ablation and biventricular pacemaker implantation in the  
7 trial by Khan et al.<sup>35</sup>, while patients treated with optimal medical therapy and rate control  
8 management in the other three trials. Follow-up ranged from 6 to 10 months. Mean efficacy of  
9 AFCA in maintaining SR was 59% after the first procedure, raising up to 77% including the 31%  
10 patients undergoing redo procedures. All patients included underwent PV isolation, and 98%  
11 received additional left atrial lesions. Complications rate was 12%. Three of four studies found  
12 quality of life and functional improvement, respectively measured by 6-minute walking test  
13 (6MWT)<sup>35</sup> and peak VO<sub>2</sub> at cardiopulmonary exercise test<sup>37,38</sup>.

14

#### 15 *AFCA in patients with TCM*

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

20

#### 21 *AFCA in specific cardiomyopathies and valvular heart disease*

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

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

10

11

## 12 **Discussion**

### 13 *AFCA in CHF patients: past evidence and new perspectives*

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

1 electroanatomical substrate of these patients<sup>4</sup> seems not to impact the outcome of AFCA, although  
2 it is likely to be associated with the need of multiple procedures to maintain SR.

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

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

12 Four short term RCTs have been performed on a limited population. These studies confirmed safety  
13 and efficacy of the procedure, except from MacDonald et al.<sup>36</sup> that reported lower success rates and  
14 no improvement in LVEF or exercise tolerance. However, it should be heeded that patients included  
15 in this study had advanced CHF, longer AF duration and a worse functional class (approximately  
16 90% of the patients were in New York Heart Association functional class III) compared with the  
17 other 3 RCTs. In fact, in these trials, including patients with less severe CHF, LVEF, quality of life  
18 and exercise capacity improved significantly. Of note, complication rate was higher compared to  
19 observational studies: the reasons may be secondary to the high proportion of patients with  
20 advanced CHF compared to the other studies, often treated with extensive left atrial ablation,  
21 requiring longer procedural times and potential risk of complications. However, concerning SR  
22 restoration, there was no substantial difference between observational studies and the four RCTs.  
23 Among patients with CHF and underlying cardiomyopathy the procedure, may carry higher risks,

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

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

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

1 showing a significant improvement of LV circumferential and longitudinal strain and strain rate  
2 after successful AFCA, which in contrast decrease in patients experiencing AF recurrence<sup>63</sup>.

3

#### 4 *AFCA in patients with TCM*

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

15

#### 16 *AFCA in specific cardiomyopathies populations*

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

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

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

16

17 *Procedural protocol: PV isolation alone or extensive atrial ablation?*

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

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

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

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

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

5

### 6 *Clinical implications*

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

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

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



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

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

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

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

5

### 6 *Future perspectives*

7 AFCA is gaining a significant role in CHF treatment of patients with concomitant AF, as confirmed  
8 by the latest guidelines<sup>14</sup>. However, the following points remain of concern.

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

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

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

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

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

Author, Year (Ref)	N. pts	Age, years	Paroxys mal 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
<i>Observational studies</i>													
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
<i>Overall</i>	1253	58	19	2.3	41	57	32	-	48	32	75	+13%	-
<i>Randomized controlled trials</i>													
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 <sub>2</sub> , ↓ BNP vs. rate control
Hunter 2014 (38)	26	55	0	2.7	-	-	6	-	38	54	81	32→40	↑QoL, NYHA class peak VO <sub>2</sub> , ↓ BNP vs. rate control
<i>Overall</i>	115	60	12	2.7	-	-	8	-	59	31	77	+8%	-
<i>AFCA in patients with tachycardiomyopathy</i>													
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
<i>Overall</i>	113	56	11	-	-	-	12	-	73	-	74	+16%	-
<i>AFCA in patients with CHF with preserved LV ejection fraction</i>													
Machino- Ohtsuka 2013 (34)	74	65	31	2.2	-	15	34	-	27	68	73	-	LV strain and diastolic function improve in patients in SR

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



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

<i>Hypertrophic cardiomyopathy</i>											
Author, year ( <i>valvular cardiomyopathy subtype</i> )	N. patients	Age, years	Paroxysmal AF (%)	NYHA class	ICD/ CRT (%)	Follow- up (month s)	Follow-up after last (months)	Success single (%)	Success final (%)	Procedural characteristi cs	Complicatio ns (%)
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	-
<i>Overall</i>	242	56	52	1.9	46	18	-	46	71	-	2.
<i>Valvular cardiomyopathies</i>											
Khaykin, 2004 (52) ( <i>moderate mitral or aortic stenosis or regurgitation</i> )	102	64	37	1.4	-	11	-	83	93	PVI	3
Wang, 2009 (53) ( <i>Mitral or aortic prosthetic valves or previous mitral commissurotomy</i> )	51	48	0	-	-	12	-	51	67	PVI + CFAE	2
Miyazaki, 2010 (54) ( <i>moderate mitral or aortic stenosis or regurgitation</i> )	45	66	80	1.3	-	26	24	47	78	80% PVI, 20% PVI + 7 scheme	4.3

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

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

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1 **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

2

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



1 **Figure legends**

2 **Figure 1.** AFCA protocol according to underlying cardiomyopathies.

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

5

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

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

9 \* Dotted line refers to severe valvular cardiomyopathy and hypertrophic cardiomyopathy

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

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

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

17 ☒ As recommended in specific guidelines

18 AF: atrial fibrillation. CHF: chronic heart failure. ICD: implantable cardioverter defibrillator.

19 CRT: cardiac resynchronization therapy.