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Transcatheter Ablation of Atrial Fibrillation in Patients with Chronic Heart Failure

Antonio Di Monaco, Federico Quadrini,
Nicola Vitulano and Massimo Grimaldi

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Abstract

Atrial fibrillation (AF) is the most frequent of all cardiac arrhythmias and it is associated with an increased risk of stroke, systemic embolism and heart failure. Patients with AF have a twofold increased risk of death and fivefold increased risk of stroke compared with those without AF. In patients with heart failure (HF), AF ablation improves left ventricular (LV) function over short- and long-term follow-ups, especially compared with medical treatment. Furthermore, AF ablation in HF patients relates to a significant improvement in quality of life, functional class and exercise tolerance, possibly related to the improvement in LV function and hemodynamic status of the patients. Finally, data showed that restoration of sinus rhythm in this setting of patients reduced the incidence of stroke and death. In this review, we reported all the major data regarding atrial fibrillation therapy in patients with heart failure.

Keywords: atrial fibrillation ablation, heart failure, quality of life, left ventricular function, atrial fibrosis

1. Incidence and pathogenesis of atrial fibrillation in heart failure

Atrial fibrillation (AF) is defined as a cardiac arrhythmia characterized by the surface ECG showing 'absolutely' irregular RR intervals and absence of distinct P waves. Irregular atrial electrical activity, represented by the "f" waves, may be seen in some ECG leads, most often in lead V1, the "f-f" interval is variable and usually shorter than 200 ms [1]. An irregular pulse should always raise the suspicion of AF, but an ECG recording is necessary to diagnose AF [1].

From a clinical point of view, AF can be categorized into five subtypes based on the presentation and duration of the arrhythmia: (1) patient who presents with AF for the first time; (2) paroxysmal AF is self-terminating, usually within 48 h, but it may continue for up to 7 days; (3) persistent AF is present when an AF episode either lasts longer than 7 days or requires termination by cardioversion; (4) AF is considered as long-standing persistent when the arrhythmia has lasted for ≥ 1 year; (5) permanent AF, when the presence of the arrhythmia is accepted by the patient (and physician) and when it is decided to adopt a rate control strategy [1] (**Figure 1**).

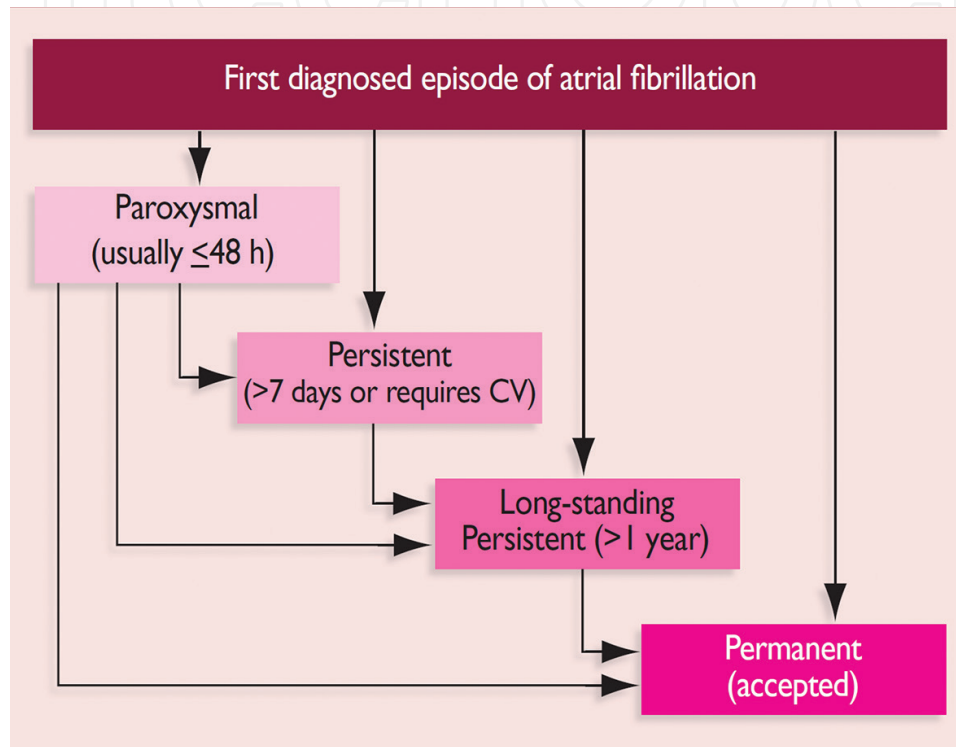


Figure 1. European Society of Cardiology guidelines for classification of atrial fibrillation [1].

Atrial fibrillation, the most frequent of all cardiac arrhythmias, is associated with an increased risk of stroke, systemic embolism (SE) and heart failure (HF). Patients with AF have a twofold increased risk of death and fivefold increased risk of stroke compared with those without AF [1–6].

Atrial fibrillation has multiple adverse clinical implications. The loss of atrial systole and the irregular, fast heart rate contribute to symptoms such as palpitations and reduced exercise tolerance and also predispose to the development of intracardiac thrombus and systemic thromboembolism. Atrial fibrillation can also cause tachycardia-mediated cardiomyopathy or worsening of preexisting heart failure [3].

Whereas anticoagulation treatment reduced the risk for stroke, large randomized trials failed to demonstrate any significant mortality benefit of a pharmacologically based rhythm control strategy even in patients with left ventricular dysfunction when compared with a rate control strategy [7–11].

This has led to a widespread belief that restoration of sinus rhythm (SR) does not improve prognosis. However, in-depth analysis of these trials demonstrated that the restoration of SR was associated with a 47% lower risk for death compared with continuing AF.

Besides having a good safety profile, catheter ablation therapy for AF has proved effective in establishing and maintaining SR. Induction of AF requires an initiating trigger and perpetuation occurs because triggering activity is sustained or because of the presence of a susceptible atrial substrate. Premature atrial ectopy has been shown to be the most frequent trigger for AF. Observations in patients with dual-chamber pacemakers revealed that 48% of AF episodes were triggered by premature atrial beats, 33% were preceded by bradycardia and 17% were sudden in onset [12]. Also, continuous cardiac monitoring in postoperative patients demonstrated that supraventricular premature beats induced AF in 72–100% of cases [13].

Endocardial mapping revealed that the origin of ectopic activity initiating AF is located inside the pulmonary veins (PV) in 89–94% of cases and that AF is most often triggered by repetitive focal PV discharges [14–18].

Catheter ablation targeting the fascicles, which connect the PVs to the left atrium, leads to electrical isolation of the PVs. Interestingly, after electrical isolation, up to 58% of PVs display slow, dissociated activity and some sustain ongoing tachycardia dissociated from the left atrium in SR, emphasizing the arrhythmogenic potential of these structures [19, 20].

Indeed, besides being triggers for AF, PVs can also be responsible for the perpetuation of AF. In a small series of patients who had irregular focal discharges initiating and perpetuating AF, foci at the ostium of PVs were found to be the drivers of sustained AF in 66%. Focal radiofrequency (RF) delivery targeting these foci eliminated AF in all these patients [21].

In addition, a spatial gradient in cycle length, with the PVs activating at a higher frequency than the nearest atrial tissue, has been found in some patients and this reinforces the role of PVs as AF perpetuators [22–25].

The involvement of the PVs in the maintenance of AF was further emphasized by the observation that PV isolation in paroxysmal AF led to a progressive increase in the AF cycle length, culminating in the termination of AF in 75% of patients. PV isolation rendered AF noninducible in 57% of patients and prevented relapse in 74% of patients [26]. These findings led to the venous wave hypothesis, postulating a role for PVs in maintenance of AF in most patients with paroxysmal AF [27]. Later, spectral analysis and dominant frequency mapping revealed that the dominant frequency and the highest dominant frequency were spatially distributed near the PVs in most of patients with paroxysmal AF [28]. Put together, these observations emphatically substantiate the role of PVs in the initiation and maintenance of nonpermanent forms of AF.

Although elimination of PV arrhythmogenicity has been highly effective for paroxysmal AF, it has modest efficacy for persistent AF suggesting that mechanisms beyond the PVs also contribute to perpetuation of AF in these patients. A number of ablation strategies have been proposed: linear ablation, ablation of complex fractionated atrial electrograms, ablation of intrinsic cardiac autonomies and ablation of rotors. Frequently these approaches are performed in combination, to target these substrate-related mechanisms beyond the PV arrhythmogenicity, particularly in patients with persistent AF [1].

In the setting of heart failure, the increased filling pressure of atrial and ventricle contributes to the electroanatomic disarrangement of the muscle fibers providing a substrate for reentry and imparts electrical heterogeneity and arrhythmogenicity to onset AF. Histological examinations of atrial tissue in patients with AF show patchy fibrosis, which may contribute to the nonhomogeneity of conduction. Atrial biopsies from patients undergone to cardiac surgery show increase in cell size, loss of sarcoplasmic reticulum and atrial myofibrils, changes in mitochondrial shape, accumulation of glycogen granules, alteration in connexin expression and increase in extracellular matrix [1]. A multicenter trial has demonstrated that atrial fibrosis, as estimated by magnetic resonance imaging (MRI), is independently associated with the likelihood of recurrent AF and in particular an extensive fibrosis caused a low success rate after catheter ablation [29]. Furthermore, recent studies showed that transmural conduction is the predominant mechanism of breakthrough during atrial fibrillation demonstrating the substrate complexity of this arrhythmia [30].

Heart failure increases the risk of AF, with the mechanism of the arrhythmia being multifactorial. Furthermore, AF is an independent risk factor for the development of heart failure and both conditions frequently coexist. Atrial fibrillation in patients with heart failure predisposes to episodes of worsening heart failure and increases the risk of thromboembolic events [1]. Hospitalizations due to AF account for one-third of all admissions for cardiac arrhythmias. Acute coronary syndrome, aggravation of heart failure, thromboembolic complications and acute arrhythmia management are the main causes. In 30% of patients with AF, it is possible to find HF with NYHA II-IV and at the same time, in 30–40% of heart failure patients, AF is found. Heart failure can be both a consequence of AF (e.g., tachycardiomyopathy or decompensation in acute onset AF) and a cause of the arrhythmia due to increased atrial pressure and volume overload, secondary valvular dysfunction, or chronic neurohumoral stimulation.

In the past decade, it showed an increase of the incidence of AF, above all in patients with HF. Many factors have contributed to these epidemiological changes; first of all, the new therapeutic approach to the cardiovascular disease and the following growing average age of patients. A recent comparison between two survey showed a significant increase in the incidence of AF in patients with HF between 38.4% in 2005 and 50.4% in 2013 [31]. Marked unexplained interregional variations in the occurrence of stroke and mortality suggest that factors other than clinical variables might be important [31]. Prevention of death from heart failure should be a major priority in the treatment of atrial fibrillation.

2. Pharmacological treatment of atrial fibrillation in heart failure

2.1. Rhythm control vs. rate control

The optimal resting ventricular rate in patients with AF and HF could be between 60 and 100 bpm [32–34]. Van Gelder et al. [35] suggested that a resting ventricular rate of up to 110 bpm might still be acceptable and 2016 ESC AF guidelines recommend this threshold as the target for rate control therapy [33, 36–40], but a lower rate for patients with HF may

be preferable (60–100 bpm). The optimal ventricular rate during exercise is also uncertain, but may be 110 bpm during light exercise [34].

Sinus rhythm, theoretically, offers physiological rate control, normal atrial activation and contraction, a normal sequence of atrioventricular (AV) conduction and AV valvular function and a regular rhythm.

Most clinical trials (PIAF, STAF, RACE, HOT CAFÉ, CABANA and AFFIRM) [1, 9–11, 41, 42] have reported no clear superiority of rhythm control. Furthermore, Crijns have reported that patients with AF and HF are unlikely to remain in sinus rhythm in the long-term and 2012 focus updated of ESC guidelines of the management of atrial fibrillation, that rhythm control should not be vigorously pursued in this clinical setting [1].

However, a subgroup analysis of AFFIRM reported that rhythm control may be useful in patients with left ventricular dysfunction. In this study, patients with depressed left ventricular function benefited significantly from rhythm control compared to rate control. The presence of sinus rhythm was associated with a lower risk of death [43].

2.2. Practical approach to rate control

Rate control in AF is based mainly on pharmacological depression of conduction through the AV node. In the presence of HF, this requires careful dose titration and can result in symptomatic bradycardia requiring permanent pacing. Beta-blockers are the preferred drugs in combination with digoxin (adjunctive therapy), because they provide optimal rate control at rest and during exercise in this setting of patients [1]. The AFFIRM study showed during long-term follow-up that beta-blockers achieved optimal rate control in 58% of patients [44]. In a subgroup analysis, patients with a history of HF and left ventricular ejection fraction <40%, successful rate control was observed with beta-blocker, with or without digoxin in 81% and with digoxin alone in 54%, at 1-year follow-up.

Atrioventricular (AV) nodal ablation may be the treatment of choice in the presence of symptoms intolerable to higher rates, despite the use of rate slowing agents. Investigators compared pharmacological rate control vs. AV node ablation in 66 patients with CHF and AF [45]. In this randomized study, both treatment arms were associated with alleviation of symptoms and an increase in functional capacity. Patients treated with the “ablate and pace” strategy had fewer symptoms with no changes in cardiac performance and quality of life. This strategy was not associated with a reduction of mortality.

2.3. Practical approach to rhythm control

The potential of amiodarone to maintain sinus rhythm in patients with AF and HF has been repeatedly shown in observational and prospective randomized controlled studies.

In CTAF study, therapy with amiodarone reduced the incidence of recurrent AF by 57% when compared with sotalol and propafenone [46]. In the CHF-STAT study, patients treated with amiodarone, converted to sinus rhythm more frequently (31.3% vs. 7.7% on placebo) compared to placebo, experienced fewer recurrences of AF and were less likely to develop

new AF [47]. Amiodarone is a drug of choice for the management of AF associated with HF. In addition to its antiarrhythmic effects, it is useful in controlling ventricular rate response during recurrences [47].

Dronedarone is a drug similar to amiodarone, though is devoid of iodine with a theoretically safer adverse effect profile [1]. In the dronedarone atrial fibrillation study after electrical cardioversion (DAFNE) trial, dronedarone prolonged the mean interval to recurrence of AF by 55% compared with placebo, resulting in the spontaneous conversion to sinus rhythm in high percentage of patients. The results of the European trial in atrial fibrillation or flutter patients receiving dronedarone for the maintenance of sinus rhythm (EURIDIS) and American-Australian-African equivalent ADONIS showed that dronedarone was superior to placebo in the prevention of recurrent AF and effective in controlling the ventricular rate in over 1200 patients. However, the dronedarone in moderate to severe HF evaluating morbidity decrease (ANDROMEDA) study was stopped prematurely, as an interim safety analysis suggested an excess risk of death in patients on active treatment.

3. Ablation of atrial fibrillation in HF patients

Rhythm control with antiarrhythmic drugs has not been shown to confer benefit in randomized trials, neither in patients with HF nor in those without HF [7, 8]. The lack of benefits of antiarrhythmic drugs might reflect their poor (<50%) efficacy in maintaining sinus rhythm [8]. Conversely, ablative treatment in these patients can be highly effective in reducing morbidity and improving quality of life and functional capacity [7–9, 41–52]. However, patients with AF and left ventricular ejection fraction have more recurrences after a single procedure, thus requiring more repeat procedures, which increase costs and risks [53]. Recent studies [54–60] have demonstrated that nonpulmonary vein foci firing from the atrial chambers or other thoracic veins play an important role in initiating and maintaining AF in 3.2–62% of patients, depending on age, sex and comorbidities. Patients with HF usually have a more complex and diseased atrial substrate harboring more nonpulmonary vein foci, which could be responsible for the observed recurrence of AF or atrial tachyarrhythmia AT after pulmonary vein antrum isolation.

In a recent study, Zhao et al. [61] demonstrated that patients with left ventricular ejection fraction more often presented nonpulmonary vein triggers than in patients with normal ejection fraction; in patients with the long-term procedural outcome of pulmonary vein isolation ablation alone remain unsatisfactory with a 32.2% single-procedure success rate, whereas pulmonary vein isolation plus nonpulmonary vein triggers ablation significantly increases the success rate to 75.0%, which is comparable with the success rate of pulmonary vein isolation alone in patients with normal ejection fraction (75.0% vs. 81.7%).

Patients with low ejection fraction and paroxysmal atrial fibrillation had a higher prevalence of nonpulmonary vein triggers than patients with normal ejection fraction (69.1% vs. 26.6%). Many investigators [54–60] have addressed the importance of nonpulmonary vein triggers

for atrial fibrillation initiation and the reported incidence of nonpulmonary vein triggers in paroxysmal atrial fibrillation.

The basis for extensive left atrial ablation lies in the pathophysiology of atrial fibrillation itself [62]: atrial fibrillation perpetuating in a left atrium with significant substrate modifications and advanced structural and electrical remodeling has historically been targeted by linear lesions [63]. 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, counterbalancing the benefit derived by extensive atrial substrate modification [64].

Among the studies reporting AF ablation in patients with HF, 55% of the patients underwent PV isolation alone, with a large heterogeneity among studies (6–89%). None of the observational studies were designed to compare the efficacy of different AF ablation approaches. However, in the meta-analysis by Anselmino et al. [65] including the largest available population, there was no difference in AF ablation outcome, performing PV isolation alone when compared with additional linear ablation. Moreover, no data compared the different techniques to perform AF ablation (radiofrequency, cryoablation, laser, rotors and surgery) in patients with HF. Finally, recent data reported a higher success rate after AF ablation with a hybrid approach (percutaneous and surgical), but no data were published regarding patients with HF [1].

Larger randomized studies are needed to understand the optimal procedural protocol to adopt in patient with HF and symptomatic AF.

3.1. Paroxysmal vs. persistent atrial fibrillation ablation in heart failure

Several studies have suggested that catheter ablation of AF in the context of HF is relatively safe reporting that the complication rate was not different from that in patients with structurally normal hearts [7, 48–53, 65–85]. The success rate for catheter ablation of paroxysmal AF was similar in HF patients compared with non-HF patients (70–80%), whereas the success rate for persistent AF was markedly worse. In randomized studies, the success rate following a single procedure has been reported at 38–68%, rising to 50–88% after repeated procedures (2 or 3) at 6–12 months [52, 79–81]. Ullah et al [84] published an international multicenter registry from seven centers for patients with HF undergoing AF ablation (**Figure 2**). In this study with 1273 patients (171 with HF and 1102 without HF) and a median follow up of 3.1 years, the final procedure success rate was no different from paroxysmal AF (78.7% vs. 85.7%, $p = 0.186$), but significantly different for persistent AF (57.3% vs. 75.8%, $p < 0001$).

However, despite a lower success rate in patients with HF ablated for persistent AF, Zhu et al. [85] published a meta-analysis of three randomized controlled trials showing a significant improvement of LVEF (6.22%) and reduction of NYHA class and Minnesota living with heart failure questionnaires scores in patients with HF ablated for persistent AF compared with the medical rate control.

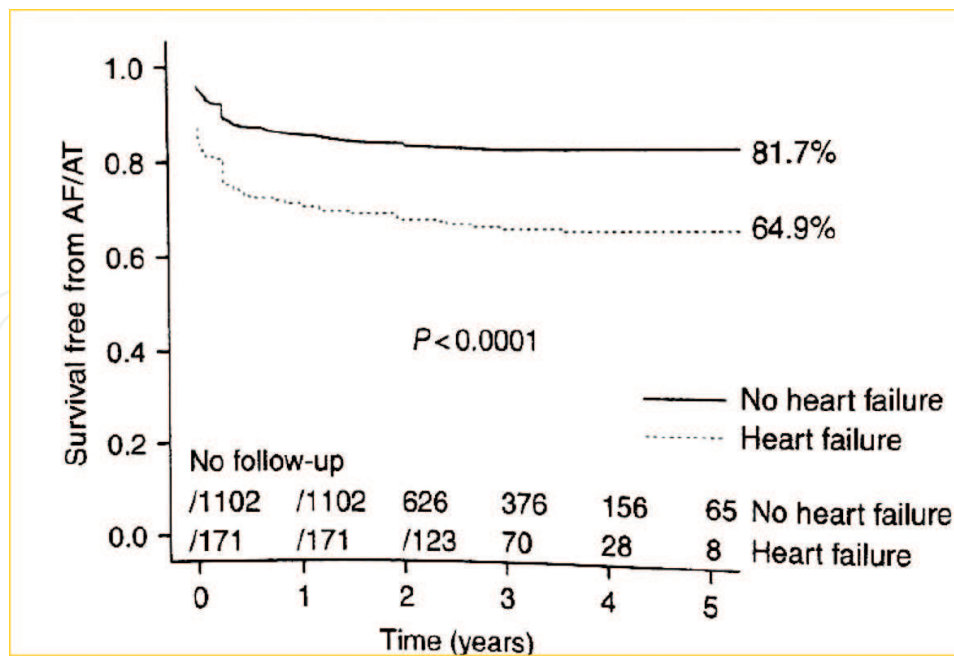


Figure 2. Freedom from atrial fibrillation and atrial flutter after ablation in patients with and without heart failure [84].

The lower success rate for catheter ablation for persistent AF in the HF group is likely multifactorial. Both HF and the conditions leading to HF increase the left atrial pressure and wall stress that causes progressive mitral regurgitation, which further impacts on left atrial pressure and remodeling. The result of these factors is more scarred and remodeled atria, which are more inclined to support AF.

3.2. Improvement in left ventricular function and heart failure

3.2.1. Symptoms after atrial fibrillation ablation

Atrial fibrillation ablations have been shown to improve the LV function during short- and long-term follow-up, when compared to medical therapy. Several meta-analyses regarding the usefulness of AF ablation in HF patients have been published [53, 65, 82, 83, 85]. In the first two works, including maximum 800 patients, the authors concluded that single AF ablation procedure in HF patients is less effective in patients without structural disease, but improves including redo procedures, obtaining a significant improvement in LV ejection fraction over follow-up [53, 82]. The third multicenter, collaborative meta-analysis, including more than 1800 patients [65], reported over a mean follow-up of 2 years a significant improvement in LV ejection fraction and a reduction in the proportion of patients with severely depressed LV function. This finding is very important since potentially confers to ablation the ability to reduce the proportion of patients requiring implantation of cardioverter defibrillators. Moreover, the authors reported that time to first AF diagnosis and heart failure diagnosis was significantly related to ablation outcome, highlighting the importance of prompt optimal treatment of both HF and AF to achieve the best clinical benefit.

Ganesan et al. [83], furthermore, reported meta-analyses including more than 900 patients with HF-ablated for AF showing a LVEF improvement of 13%.

Ullah et al [84] in their multicentric registry reported a significant LV ejection fraction increasing from 34.4 ± 9 to $45.8 \pm 12.8\%$ ($p < 0.001$).

One small observational prospective study specifically investigated patients with preserved LVEF [75]. This study, including 73 patients with a mean follow-up of 34 months, reported 27% efficacy after the first procedure which further raised to 73% with redo procedures and antiarrhythmic drugs. On note, LV diastolic function and systolic function measured with strain and strain rate improved only in patients maintaining stable sinus rhythm.

Moreover, data reported that effective sinus rhythm restoration after AF ablation was useful to improve LVEF in patients with tachycardiomyopathy [48, 65].

Furthermore, AF ablation in HF patients relates to a significant improvement in quality of life, functional class and exercise tolerance, which possibly relates to the improvement in LV function and hemodynamic status of the patients. In general, shorter history of HF and AF is both associated with improved outcome: AF ablation in HF patients should be considered precociously to avoid progression of atrial substrate alteration. Left atrial dimension is a marker of advanced substrate alteration; in fact, patients with severe LA dilation present lower rate of sinus rhythm maintenance.

In particular, Ullah et al. [84] reported a reduction in NYHA class from 2.3 ± 0.7 at baseline to 1.5 ± 0.8 at follow up. This was the first study to examine specifically the impact of maintaining sinus rhythm on rates of stroke and death after catheter ablation of AF patients with HF showing that restoration of sinus rhythm reduced the incidence of stroke and death (**Figure 3**).

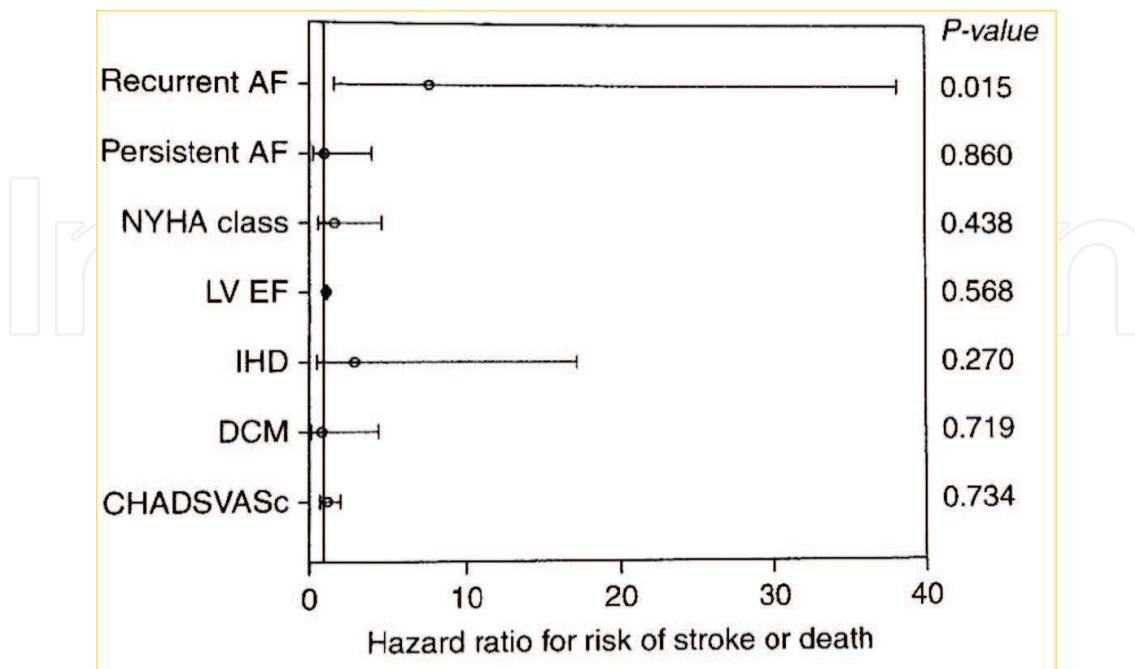


Figure 3. Factors predicting stroke and death in patients with heart failure [84].

3.3. Indications for transcatheter ablation of atrial fibrillation in patients with heart failure

Within the general population, the safety and efficacy rates of AF ablation promoted this procedure to the first choice following one antiarrhythmic drug failure and in selected patients, even the first option before drugs [1]. Its role within HF, instead, is less well defined due to small randomized trials and observational studies [48–53, 65–85]. The revised European recommendations for antiarrhythmic drug therapy leave amiodarone as the only available antiarrhythmic agent in this setting [1]. In patients who suffer from symptomatic AF recurrences on amiodarone therapy, catheter ablation remains as the sole choice for rhythm control therapy [1] (**Figure 4**). In the last guidelines, AF ablation is indicated in symptomatic patients with reduced ejection fraction in order to improve symptoms and cardiac function (class IIa, level of evidence C) [36].

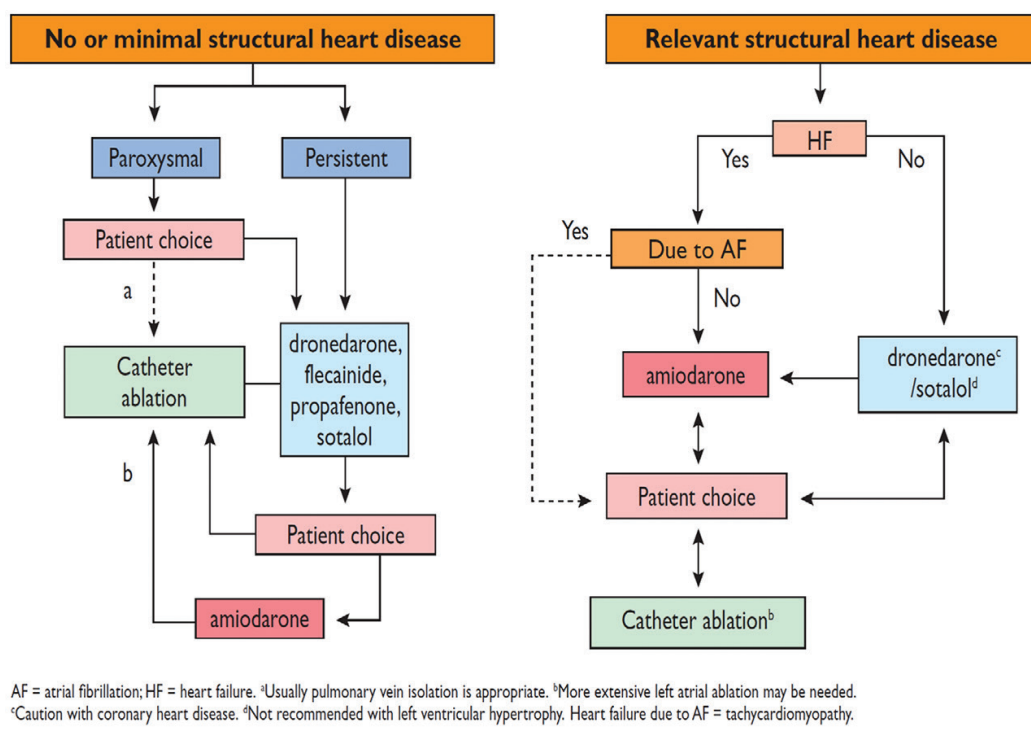


Figure 4. European Society of Cardiology guidelines for atrial fibrillation ablation [1].

3.4. Catheter ablation of atrial fibrillation in specific cardiomyopathies populations

Some observational studies reported the outcome of AF ablation among patients with hypertrophic [65, 83, 86, 88]. 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 and the prevalence of extensive left atrial ablation, including linear lesions or CFAEs, which was higher when compared with the general HF population. This finding reflects a complex substrate typical of this specific cardiomyopathy, characterized by severe left atrial enlargement. Being AF detrimental on both the quality of life and prognosis of HCM patients, its effective treatment warrants careful attention and ablation may be considered precociously to achieve rhythm control.

Moreover, although AF standard treatment in valvular cardiomyopathies is more commonly surgical, performed concomitantly to heart surgery, some studies reported the outcome of AF ablation among patients with significant valvular disease. Two studies, including patients with prosthetic valves or previous percutaneous intervention for mitral rheumatic disease, reported a very low efficacy after a single procedure, raising up to 70% at a mean follow-up of 24 months including over 50% repeated procedures [87, 88]. Other two studies including patients with moderate aortic or mitral defects, instead, reported outcomes similar to the general population [87, 89].

3.5. Future perspectives

Catheter ablation of AF is gaining a significant role in HF treatment of patients with concomitant AF, as confirmed by the latest ESC guidelines. However, the following points remains of concern. First of all, pulmonary vein isolation alone and/or additional non-PV targets, as in the general population, need to be tested in prospective randomized trials on HF patients.

Further studies, moreover, should define the optimal timing to perform AF ablation in these patients to increase the success rate and reduce mortality.

In the future, technological innovations may contribute to rise AF ablation safety, for example, new irrigated catheters able to significantly reduce the fluid administration during procedure, particularly relevant among HF patients.

Finally, due to the complexity of this procedure, the suggestion is to refer to experienced, high volume centers, also skilled to manage plausible complications.

Author details

Antonio Di Monaco, Federico Quadrini, Nicola Vitulano and Massimo Grimaldi*

*Address all correspondence to: fiatric@hotmail.com

Department of Cardiology, Hospital "F. Miulli", Bari, Italy

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