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Atrial fibrillation in heart failure: drugs or ablation?

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Atrial fibrillation (AF) and heart failure (HF) frequently coexist and mutually exert negative influences with important clinical implications. Although there is evidence that restoring and maintaining sinus rhythm may have favourable clinical effects in patients with HF, there is no evidence of a survival benefit with pharmacological antiarrhythmic intervention compared with a heart rate control strategy. In these patients, transcatheter ablation (CA) of AF represents a procedure with an excellent safety profile in centres with expertise and a high volume of interventions. However, in the absence of definite evidence of benefit on major clinical end-points that can be generalized to the heterogeneous population with AF and HF, the option of CA should be discussed and shared with the patient, and mainly considered in patients with conditions that are associated with a greater prospect of clinical benefit, such as 'young' age (65–70 years), good health conditions and few or no comorbidities, recent onset of HF and AF (especially if with high heart rate), left atrial volume not excessively compromised (<55 mm in diameter), and without evidence of substantial fibrotic remodelling, left ventricular ejection fraction (LVEF) >25%, including HF with preserved EF (HFpEF).

Accordingly with the recent European guidelines on atrial fibrillation (AF),[1] transcatheter ablation (CA) of the pulmonary veins should be considered (class IIA) in selected patients with heart failure (HF) as an alternative or in combination with antiarrhythmic drugs on the basis of a shared decision-making process with the patient. The European guidelines on HF published in 2021[2] instead, while recognizing a similar class IIA indication for CA in patients with HF with reduced left ventricular ejection fraction (LVEF, HFrEF), subordinate its use to a lack of symptomatic improvement in patients without haemodynamic instability assigned to a rate control strategy, or failure of rhythm control with cardioversion and drugs in patients with haemodynamic instability assigned to a rhythm control strategy, thus reflecting the still insufficient indications to systematically prefer a rhythm control based strategies over heart rate control, and CA over drug therapy as antiarrhythmic strategy of choice. However, the guidelines[2] also underlines that although there is no evidence of survival benefit with pharmacological antiarrhythmic therapy in HF patients with AF, CA—which has shown greater efficacy in maintaining sinus rhythm, reducing the arrhythmic burden, and improving symptoms and quality of life compared with pharmacological antiarrhythmic therapy—failed to show consistent evidence of benefit on clinically important end-points such as mortality and hospitalization. Moreover, most of the currently available evidence of clinical benefit of CA derives from small studies including mostly young adults and highly selected participants.[3–7]

The 'Ablation versus amiodarone for treatment of persistent atrial fibrillation in patients with congestive heart failure and an implanted device: results from the AATAC multicenter randomized trial' (AATAC) study[3] is a multicentre, randomized, open-label, parallel study comparing CA with amiodarone antiarrhythmic therapy in 203 patients with HFrEF (LVEF <40%), history of persistent AF, and prior implantable cardiac defibrillator (ICD) or cardiac resynchronization therapy-defibrillator (CRT-D) implant. The primary end-point was the absence of sustained atrial arrhythmias at the 24 month follow-up, while secondary end-points were overall mortality, hospitalization for AF and HF during follow-up, and any changes in LVEF, plus

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other end-points related to quality of life. Of the 866 screened patients, 331 were eligible and only 203 of these were included (mean age 62 ± 10 years in the CA group and 60 ± 11 years in the amiodarone group), with a mean LVEF of 29 ± 5% and 30 ± 8%, respectively. CA was shown to be more effective in reducing arrhythmic burden, hospitalizations, and mortality than amiodarone, although event numbers were very small.

The 'Catheter ablation for atrial fibrillation with heart failure' (CASTLE-AF) trial[4] is a prospective, randomized-controlled, open-label, multicentre study conducted on patients with paroxysmal or persistent AF, with LVEF <35% and previous implantation of a Biotronik ICD or CRT, used for the detection of arrhythmias during the study. From a sample of 3013 patients, 363 were selected (mean age 64 years, 88% male, 70% with persistent AF) who, after a period of optimization of HF medical therapy, were randomized to CA vs. medical therapy; the use of antiarrhythmics was permitted in both groups. CA was associated with a significant reduction in the risk of death and/or worsening of HF [hazard ratio (HR) 0.62: 95% confidence interval (CI): 0.43–0.87] and overall mortality (HR 0.53; 95% CI: 0.32–0.86). It is interesting to note how the curve of mortality for all causes and for cardiovascular (CV) causes splits after 36 months from the procedure, while hospitalization for HF decreases after 10–12 months. These data could be attributed to a reduced incidence of AF tachy-cardiomyopathy whose deleterious effects in HF are well known. However, the results were not significant in patients aged >65 years, in those with advanced functional class, in diabetics, in those who were not on beta-blocker therapy, and in the group with LVEF <25%. Moreover, one of the major limitations of the CASTLE-AF study is certainly the limited generalization of these findings to the real-world patients with AF. In this regard, Noseworthy *et al.*[5] conducted a retrospective study using data contained in the OptumLabs Data Warehouse registry comprising 289 831 patients with AF and HF between 2008 and 2018, of whom 7465 had been treated with CA and 282 366 with medical therapy. Patients were divided into 3 subgroups based on their eligibility for the CASTLE-AF trial: (1) CASTLE-like patients, (2) patients who did not have exclusion criteria but did not meet the inclusion criteria, and (3) patients with at least one exclusion criterion. In CASTLE-like patients, which represented only 7.8% of the total, a clinical benefit of CA similar to that demonstrated in the CASTLE-AF study was actually found, particularly marked in patients <65 years, who represent a small minority of real-world AF patients. Furthermore, it should be noted that the low number of candidates for the procedure explains the difficulties encountered by the investigators during the screening, and this reinforces the idea that the CASTLE-AF results cannot be generalized to the entire population but only to a well-selected group of patients.

Several other studies provided similar findings. In a *post-hoc* analysis of the 'Effect of Catheter Ablation vs. Antiarrhythmic Drug Therapy on Mortality, Stroke, Bleeding, and Cardiac Arrest Among Patients With Atrial Fibrillation' (CABANA) randomized clinical trial, including 778 patients with AF and HF with New York Heart Association (NYHA) class >2 (mean age 68 years, 63.5% > 65 years, 44.3% female, 9.3% with EF < 35%, and ~79% with LVEF ≥ 50%), randomized to CA vs. medical therapy.[8] Catheter ablation was significantly associated with a lower incidence of the composite end-point (death, stroke, severe bleeding, and cardiac arrest) compared with the medical therapy group (HR 0.64; 95% CI: 0.41–0.99), thus suggesting the possibility of an important clinical benefit also in patients with HFpEF. Accordingly, a marginally significant reduction in the composite end-point (CV mortality, stroke, hospitalization for worsening HF, and acute coronary syndrome) was also observed in patients undergoing CA compared with those treated with medical therapy in the pre-specified analysis of HF patients enroled in the 'Early rhythm control therapy in patients with atrial fibrillation and heart failure' (EAST-AFNET 4) trial.[9] In this trial, CA was performed on 140 of the 798 patients, and the authors point out that patients with HFpEF apparently benefit most from this strategy. Data derived from the Swedish Heart Failure Registry[10] also showed similar results. In a series of 434 patients undergoing CA and 868 non-ablated patients (mean age 67 years), the composite end-point (mortality from all causes and/or hospitalization for worsening HF) evaluated with the Cox model after propensity score matching was significantly reduced in patients undergoing CA (HR 0.78; 95% CI: 0.65–0.94), mainly due to a reduced incidence of hospitalizations for HF (HR 0.76; 95% CI: 0.61–0.93).

On the contrary, the recent results of the 'Randomized ablation-based rhythm-control vs. rate-control trial in patients with heart failure and atrial fibrillation' (RAFT-AF) study[11] do not seem to confirm these encouraging data. In this open-label, multicentre, randomized study, 411 patients (mean age 66.5 years, with a high burden of paroxysmal or persistent AF for less than 3 years, NYHA class II–III and high N-terminal pro-brain natriuretic peptide values) were assigned to a CA-based rhythm control strategy or to a heart rate control strategy. The primary composite end-point (overall mortality and acute HF events) was not significantly different in the two groups (HR 0.71; 95% CI: 0.49–1.03).

Overall, this recent evidence therefore seems to justify the current level of recommendation for CA in AF patients with HF, and underline the various critical issues that make it difficult to arrive, at the moment and probably also in the near future, at recommendations that can be generalized to the heterogeneous context of patients with AF. Although several recent meta-analyses[12,13] have demonstrated the superiority of CA over pharmacological antiarrhythmic therapy in maintaining sinus rhythm; reducing AF recurrence, all-cause mortality, and hospitalization for worsening HF; and improving LVEF, walking ability, and quality of life, these favourable data need to be considered in light of the limitations of the studies generating these conclusions within the meta-analyses. Firstly, there is a possible selection bias whereby randomized trials select patients who are younger and in better conditions than those in the real world, just as it is possible that in registries patients with better health conditions are more easily candidates for ablation, such as confirmed by studies that investigated the generalizability of clinical trials[5] and by an average age of patients enroled in randomized trials which is much younger than that of patients with AF in the real clinical world. The number of patients enroled in the trials was highly variable and the methods for documenting arrhythmic recurrences in the follow-up were different. Furthermore, additional ablative

procedures and the procedural changes that occurred during the time-frame of the studies may justify a certain heterogeneity of the results. Many studies were not blinded and therefore it is possible that post-ablation therapeutic strategies may have been influenced. Finally, there was considerable heterogeneity in the medical therapies employed in the non-ablation groups of the different studies, which makes interpretation of the results more difficult. Finally, some studies were stopped early for apparent futility, which does not exclude a possible long-term benefit.

In conclusion, for patients with HF and AF it should be emphasized that no randomized study has so far demonstrated any survival benefit with a pharmacological antiarrhythmic intervention compared with a heart rate control strategy.[14] Furthermore, the pharmacological options available for rhythm control are extremely limited in patients with HFrEF. Therefore, CA in patients with HF and AF represents an appealing and feasible procedure with an excellent safety profile in centres with a high volume of interventions and with adequate expertise, and with a potential clinical benefit for some patients. At the same time it must be critically taken into account that the studies conducted to date have also unequivocally demonstrated the limited efficacy of CA in long-term maintenance of sinus rhythm (although superior to drug therapy) and that not all patients with HF and AF derive the same benefit from CA despite the restoration of sinus rhythm.[5] Therefore, in the absence of definitive evidence of consistent major clinical benefit for the majority of AF patients with HF, at the moment it seems reasonable to conclude that the risk and/or benefit balance of CA should be discussed and shared with the patient, and that, at the moment, the option of CA should be mainly considered for patients with conditions that are associated with a greater prospect of clinical benefit, such as 'young' age (65–70 years), good health conditions, and few or no comorbidities, recent onset of HF and AF (especially if with high heart rate), left atrial volume not excessively compromised (<55 mm in diameter) and without evidence of substantial fibrotic remodelling, and with LVEF >25%, including patients with HFpEF.[15]

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Data availability

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