



# Management of Atrial Fibrillation in Patients with Heart Failure: Time to Implement Ablation Control

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Published online: 21 February 2019  
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## Abstract

**Purpose of the Review** Atrial fibrillation (AF) in patients with heart failure and reduced systolic ejection fraction (HFrEF) is common and associated with increased morbidity and mortality, and managing AF in this population has been particularly challenging with sparse data regarding the optimal treatment strategy.

**Recent Findings** Recent data suggests that rhythm control with catheter ablation can be of particular benefit to patients with coexisting AF and HFrEF. Recent randomized control trials actually suggest that catheter ablation could potentially improve mortality in this particular patient population. This is in stark contrast to the current practice recommendations that reserve catheter ablation for symptomatic AF in the general population.

**Summary** In this paper, we will review the most current randomized controlled studies using catheter ablation in HFrEF patients with the hope to increase awareness of the potential mortality benefits the need for prioritization of catheter ablation in HFrEF patients in the next AF management guidelines.

**Keywords** Catheter ablation · Atrial fibrillation · Heart failure with reduced ejection fraction

## Abbreviations

AF	Atrial fibrillation	MLWHF	Minnesota Living with Heart Failure
HFrEF	Heart failure with reduced ejection fraction	ARC-HF	A randomized trial to assess catheter ablation versus rate control in the management of persistent atrial fibrillation in chronic heart failure
AAD	Antiarrhythmic drug	CAMTAF	Catheter ablation versus medical treatment of atrial fibrillation
LV	Left ventricular	AATAC	Ablation versus amiodarone for treatment of atrial fibrillation in patients with congestive heart failure and an implanted ICD/CRTD
DIAMOND-CHF	Danish Investigators of Arrhythmia and Mortality on Dofetilide in Congestive Heart Failure	NNT	Number needed to treat
PABA-CHF	Pulmonary Vein Antrum Isolation versus AV Node Ablation with Bi-Ventricular Pacing for Treatment of Atrial Fibrillation in Patients with Congestive Heart Failure	C A S T L E -AF	Catheter ablation versus standard conventional treatment in patients with left ventricular dysfunction and atrial fibrillation
NYHA	New York Heart Association		

This article is part of the Topical Collection on *Invasive Electrophysiology and Pacing*

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## Introduction

Atrial fibrillation (AF) is the most common arrhythmia and is responsible for significant morbidity, mortality, and healthcare costs [1–4]. In its early days, the mainstay of AF treatment included rhythm control additional to stroke prevention [5]. It was commonly believed that rhythm control of AF resulted in lower stroke rate, increased exercise tolerance, better quality of life, and increased survival. However, it was soon discovered that antiarrhythmic drugs (AADs) were not very effective

in maintaining sinus rhythm [6–8]. Several randomized controlled trials that followed showed that rhythm control with AADs had no mortality advantage over rate control [9, 10]. For this reason, rate and rhythm control are considered equally effective in the latest AF management guidelines [11–13].

AF often presents in patient with concomitant heart failure with reduced ejection fraction (HFrEF) [14, 15]. Coexisting AF and HFrEF leads higher rates of stroke, heart failure hospitalization, and death [16–18]. Traditionally, rhythm control with AADs have been limited in patients with HFrEF as most class I and class III agents are contraindicated.

Catheter ablation is an alternative means of rhythm control which is invaluable in HFrEF patients because it can potentially spare them from the serious side effects associated with AADs. There is growing evidence that catheter ablation of AF in HFrEF patients can improve left ventricular (LV) function, exercise tolerance, hospital admissions, and even mortality [19–21, 22•, 23, 24••]. Here, we will review the current evidence for rate control vs. catheter ablation in patients with AF and HFrEF.

## The Evidence for Rate Control

AF-CHF is the only large ( $n = 1376$ ) trial to assess rate vs. AAD rhythm control in patients with HFrEF (mean LV ejection fraction = 27%) [25]. In this trial, 695 patients were assigned to rate control (88% on beta blockers, 75% on digoxin, and 3% on calcium channel blockers) and 682 patients to aggressive rhythm control (82% amiodarone, 2% sotalol and < 1% dofetilide) for a follow-up period of 60 months. All patients had optimized heart failure therapy which included maximally tolerated doses of beta blocker, angiotensin-converting enzyme or angiotensin-receptor blocker, and aldosterone antagonist. Primary endpoint of death from any cause was assessed. After a median of 47 months, 73% maintained sinus rhythm in the rhythm control group vs. 35% in the rate control group. At 60 months, there was no difference in mortality between the groups.

The great majority of patient in the rhythm control arm of AF-CHF were treated with amiodarone. In fact, pharmacological rhythm control for patients with coexisting HFrEF and AF is currently limited only to amiodarone and dofetilide. Currently, dofetilide is almost exclusively used in US. Other AADS including class Ic antiarrhythmics, sotalol, and dronedarone are contraindicated in patients with HFrEF [26–30]. Moreover, amiodarone use is associated with a high discontinuation rate and its use is suggested to be associated with increased non-cardiovascular death [31].

## The Evidence for Catheter Ablation: The Ablation Control

Several randomized controlled trials have assessed the efficacy of catheter ablation for rhythm control in patients with concomitant AF and HFrEF (Table 1). PABA-CHF compared pulmonary vein isolation ( $n = 41$ ) to atrioventricular node ablation followed by biventricular pacer implantation ( $n = 40$ ) for a follow-up period of 6 months [19]. Patients with LV ejection fraction < 40% and NYHA II or III were enrolled. The primary endpoint of the trial was improvement in the composite of ejection fraction, 6-min walk distance and Minnesota Living with Heart Failure (MLWHF) questionnaire. At the conclusion of the study, pulmonary vein isolation was found to be superior with respect to the primary end point.

In ARC-HF trial, catheter ablation ( $n = 26$ ) was compared to rate control ( $n = 26$ ) in patients with persistent AF and coexisting HFrEF (LV ejection fraction < 35%, NYHA II–IV). The primary endpoint of the study was improvement in peak oxygen consumption at 12 months [20]. The catheter ablation group enjoyed a significant improvement in the primary end point as well as significant improvements in their BNP and MLWHF scores. There was also a trend towards improving LV ejection fraction.

CAMTAF trial randomized patients with persistent AF and symptomatic heart failure (ejection fraction < 50%) to receive either catheter ablation ( $n = 26$ ) or rate control ( $n = 24$ ) [21]. The primary endpoint of an improvement in LV ejection fraction at 6 months was evaluated. Catheter ablation was found to result in a significant improvement in ejection fraction at the end of the study. Catheter ablation also correlated with improvement in secondary endpoints of peak oxygen consumption and MLWHF scores.

AATAC was the first trial to assess the effect of catheter ablation on all-cause mortality as an endpoint [22•]. Two hundred three patients with persistent AF and HFrEF (ejection fraction < 40%), NYHA II–III, and an implantable cardioverter defibrillator or cardiac resynchronization therapy defibrillator were included. One hundred two patients were randomized to catheter ablation and 101 to amiodarone therapy and followed for 2 years. The primary endpoint of the study was freedom from AF recurrence and the secondary endpoints were unplanned hospitalization and death. At the conclusion of the trial, catheter ablation was found to be superior to amiodarone for both the primary and the secondary endpoints. The rates of freedom from AF at 2 years were 70% vs. 34% for catheter ablation and amiodarone respectively. Catheter ablation also improved both unplanned hospitalization and all-cause mortality (NNT = 3.8 to prevent 1 unplanned hospitalization and NNT = 10 to prevent 1 death).

**Table 1** Landmark trials for catheter ablation of atrial fibrillation in patients with heart failure and reduced ejection fraction

Study	Sample Size	Catheter ablation arm (no.)	% Persistent AF	Comparator arm (no.)	Follow-up (mo)	Mean LV EF	Primary endpoint	Results
PABA-CHF [18]	81	PVI (41)	50	AV node ablation with biventricular pacing (40)	6	27 ± 8 vs 29 ± 7	Composite of ejection fraction, 6-min walk distance, and MLW/HF score	Catheter ablation was superior to AV nodal ablation and biventricular pacing.
MacDonald et al. [40]	41	PVI ± linear ablations ± CFAE ablation (22)	100	Rate control (19)	6	16.1 ± 7.1 vs 19.6 ± 5.5	Cardiac MRI ejection fraction	No significant difference between groups
ARC-HF [19]	52	PVI ± linear ablations ± CFAE ablation (26)	100	Rate control (26)	12	22 ± 8 vs 25 ± 7	Peak VO <sub>2</sub>	Improvement in peak VO <sub>2</sub> in the catheter ablation group compared to rate control
CAMTAF [20]	50	PVI ± linear ablations ± CFAE ablation (26)	100	Rate control (24)	12	31.8 ± 7.7 vs 33.7 ± 12.1	Left ventricular ejection fraction at 6 months	Improvement in left ventricular ejection fraction at 6 months in catheter ablation group
AATAC [21]	203	PVI ± posterior wall isolation ± CFAE ablation (102)	100	Amiodarone (101)	36	29 ± 5 vs 30 ± 8	Freedom from AF	Significant improvement in freedom from AF in the catheter ablation group
CAMERA-MRI [22]	68	PVI + posterior wall isolation (34)	100	Rate control (34)	6	32 ± 9.4 vs 34 ± 7.8	Left ventricular ejection fraction	Significant improvement in ejection fraction in catheter ablation group
CASTLE-AF [23]	363	PVI ± linear ablations ± CFAE ablation (179)	67	Medical rate or rhythm control (184)	60	32.5 vs 31.5	Death or heart failure hospitalization	Significant improvement in composite endpoint of death and heart failure hospitalization in catheter ablation group

**Table 2** Ongoing clinical trials assessing utility of ablation in patients with concurrent HFrEF and AF

Trial name	Clinical trial identifier	Enrolment status	Description
AMICA	NCT00652522	Completed	Catheter ablation + ICD/CRT vs medical therapy + ICD/CRT in patients with persistent or long-standing persistent AF
CABANA	NCT00911508	Completed	Catheter ablation vs medical therapy in patients with either paroxysmal or persistent AF. Subgroup analysis will include patients with HFrEF
CONTRA-HF	NCT03062241	Recruiting	Cryoablation vs. medical therapy in patients with paroxysmal or persistent AF and HFrEF
CATCH-AF	NCT02686749	Recruiting	Catheter ablation vs. medical therapy in patients with HFrEF and newly diagnosed AF
RAFT-AF	NCT01420393	Active, not recruiting	Catheter ablation (pulmonary vein isolation with additional substrate modification) with or without adjunctive AADs vs. rate control in patients with heart failure and high AF burden

CAMERA-MRI enrolled randomized 68 patients with persistent AF and idiopathic cardiomyopathy (ejection fraction < 45%) where 34 patients were randomized to catheter ablation therapy and 34 patients to rate control [23]. All patients had a cardiac MRI prior to randomization and the extent of LV late gadolinium enhancement was measured. The primary endpoint was improvement in LV ejection fraction at 6 months which was reached by patients in the catheter ablation group. Interestingly, the study showed that the extent of LV late gadolinium enhancement can be used to predict catheter ablation response with absence of LV enhancement at baseline correlated with greater improvement in the ejection fraction at follow-up.

CASTLE-AF is the most recent and only randomized trial that studied the effect of catheter ablation on hard primary endpoints when compared to pharmacological treatment in patients with HFrEF [24••]. The trial enrolled patients with either paroxysmal or persistent AF, NYHA > II with LV ejection fraction < 35%, and an implantable cardioverter defibrillator or cardiac resynchronization therapy defibrillator. Patients were randomized to receive either catheter ablation or medical therapy. The medical therapy arm included both rate and rhythm control. Unlike previous trials, CASTLE-AF included composite of all-cause mortality or heart failure hospitalization as the primary endpoint. At 60 months, patients in the catheter ablation group had an absolute risk reduction of 18% for the primary endpoint with NNT = 6. They also had significantly improved rates of death, heart failure hospitalization, cardiovascular death, and cardiovascular hospitalization compared to the pharmacological therapy group. The LV ejection fraction also improved by 9% compared to

none in the medical therapy arm. Since the conclusion of CASTLE-AF, there have been multiple meta-analysis and retrospective studies examining efficacy of catheter ablation in HFrEF patients [32–38] with more studies currently underway (Table 2). These studies have invariably found catheter ablation to be superior to rate control in terms of symptoms, improvement in LV function, heart failure hospitalizations and mortality.

Although the exact underlying reason for superiority of catheter ablation over AADs for rhythm control of AF in patients with HFrEF is not understood, several explanations may be speculated. Catheter ablation is much more effective than AADs in sinus rhythm maintenance. In CASTLE-AF, ~65% of patients who underwent catheter ablation maintained sinus rhythm at 60 months. This was in contrast to 25% of patients on medical therapy. Secondly, catheter ablation significantly decreased AF burden in comparison to medical therapy (~25% vs. ~65%). Therefore, patients that do have AF recurrence spend less time in AF which may positively affect their hemodynamics and LV reverse remodeling. Lastly, AADs are associated with significant side effect which can counter the benefits of sinus rhythm maintenance as well as reduce compliance.

## Conclusions

Catheter ablation in patients with concomitant AF and HFrEF is safe and effective in reducing symptoms and improving mortality. Catheter ablation for sinus rhythm maintenance

should be considered strongly as part of routine heart failure management.

## Compliance with Ethical Standards

**Conflict of Interest** Alex Baher declares no conflict of interest.

Nassir Marrouche has received consulting fees and research support from Briotronic and Biosense Webster that are pertinent to this article.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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- randomized trial. *Circulation*. 2016;133(17):1637–44. <https://doi.org/10.1161/CIRCULATIONAHA.115.019406> **This study is a large prospective randomized controlled trial in patients with persistent atrial fibrillation and heart failure and reduced ejection fraction which compared freedom from atrial fibrillation in patients undergoing catheter ablation to amiodarone which is currently the most known effective antoarrhythmic therapy. In this study, mortality was included as a secondary endpoint.**
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