

# Atrial Fibrillation Ablation – Benefits Beyond Symptom Reduction with a Focus on Patients with Heart Failure with Reduced Ejection Fraction

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Catheter ablation for atrial fibrillation (AF) has been regarded as a means for symptom control in patients with AF who are resistant to medical therapy. Recommendations in past USA and European guidelines for the management of patients with AF are based on that strategy. However, there are emerging data that catheter ablation for AF may have additional prognostic benefits for patients with AF beyond symptom reduction. Favourable effects of AF ablation on stroke, dementia and other outcomes have been reported. Recently, there has been growing evidence about AF ablation benefits in patients with AF and heart failure with reduced ejection fraction (HFrEF). In this article, seven randomised controlled trials, observational trials, as well as meta-analyses and reviews are described for AF ablation in patients with HFrEF. The results of these trials suggest that AF ablation has beneficial effects on all-cause mortality, hospitalisation for heart failure, improvement of left ventricular ejection fraction, quality of life, and functional capacity. These findings led to additional recommendations in a focused update of the USA guidelines for the management of patients with AF. Data on AF ablation in the subgroups of patients with heart failure with mid-range ejection fraction and preserved ejection fraction, however, are sparse. Robust randomised controlled trials on prognostic benefits of AF ablation in these subgroups are still needed to inform clinical practice.

## Keywords

Atrial fibrillation, catheter ablation, prognostic benefits, heart failure with reduced ejection fraction

**Disclosures:** Norbert Guettler, Kim Rajappan and Edward Nicol have nothing to disclose in relation to this article.

**Review Process:** Double-blind peer review.

**Compliance with Ethics:** This study involves a review of the literature and did not involve any studies with human or animal subjects performed by any of the authors.

**Authorship:** The named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship of this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval for the version to be published.

**Received:** 7 April 2019

**Accepted:** 29 May 2019

**Citation:** *European Journal of Arrhythmia & Electrophysiology*. 2019;5(1):30–8

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**Support:** No funding was received for the publication of this article.

Catheter ablation for atrial fibrillation (AF) is now a widely established treatment to prevent AF recurrence. Catheter ablation usually involves the isolation of the pulmonary veins, which is an adequate strategy in the majority of cases with paroxysmal AF. Persistent AF, however, often requires additional substrate modification.<sup>1–3</sup> Several strategies of substrate modification are under evaluation. While complex fractionated atrial electrograms and linear lesions have been abandoned as a consequence of the STAR AF II (Substrate and Trigger Ablation for Reduction of Atrial Fibrillation Trial-Part II) results,<sup>4</sup> the ablation of fibrotic areas, posterior wall isolation, and the ablation of non-pulmonary vein triggers show more promising results. The ablation results of rotational activity are still contradictory.<sup>3</sup> In many clinical trials, catheter ablation has proven superior over antiarrhythmic drug therapy for the maintenance of sinus rhythm and the improvement of quality of life.<sup>5–7</sup> In the latest guidelines for the management of AF, the European Society of Cardiology recommends catheter ablation in patients with symptomatic recurrences of AF on antiarrhythmic drug therapy for paroxysmal AF (class I, level of evidence A), and persistent AF (class IIa, level of evidence C).<sup>8</sup> In selected patients it should be considered as a first-line therapy to prevent recurrent AF to improve symptoms as an alternative to antiarrhythmic drug therapy, considering patient choice, benefit, and risk (class IIa, level of evidence B recommendation). Similar recommendations are given by the American Heart Association (AHA), the American College of Cardiology (ACC), and the Heart Rhythm Society (HRS) in their 2014 guidelines.<sup>9</sup>

Beyond improvement of symptoms and quality of life, several recent studies have demonstrated the prognostic benefit of catheter ablation for certain patient groups including reduced mortality and a reduction in hospitalisation. As a result of these trials, AHA, ACC and HRS added the recommendation in their 2019 focused update (of the 2014 guideline) that AF catheter ablation may be reasonable in selected patients with symptomatic AF and heart failure with reduced ejection fraction (HFrEF), to potentially lower mortality rates and reduce hospitalisation for heart failure (HF).<sup>10</sup>

In this article, recent clinical trials, meta-analyses, and reviews will be analysed to address whether catheter ablation for AF can have a prognostic benefit beyond symptom reduction in patients with HF. Different results for variable patient groups will be highlighted.

## Clinical trials

A number of clinical trials have tried to answer the question of whether AF ablation can demonstrate prognostic benefit beyond symptom reduction and improvement of quality of life. There have been several publications reporting favourable effects of catheter ablation on death, stroke, dementia and other outcomes in patients with AF in general.<sup>11,12</sup> An emerging number of clinical trials have analysed the effects of AF ablation in patients with HFrEF, while data concerning AF ablation in patients with heart failure with mid-range (HFmrEF) and preserved ejection fraction (HFpEF) is much sparser.<sup>13</sup>

### Catheter ablation of atrial fibrillation in patients not restricted to those with heart failure

Several trials on the outcome of catheter ablation for AF have been published including the general population with AF not restricted to HF.

#### RAAFT-1

The RAAFT-1 (Radiofrequency Ablation vs Antiarrhythmic Drugs as First-line Treatment of Symptomatic Atrial Fibrillation) trial was published in 2005 to determine whether pulmonary vein isolation (PVI) is feasible as first-line therapy for treating patients with symptomatic AF.<sup>14</sup> Patients were randomised to receive either PVI using radiofrequency energy (n=33) or antiarrhythmic drug treatment (n=37) with a 1-year follow-up. At the end of the follow-up period the results were significantly better in the PVI group. AF recurrences were lower (p<0.001), there were fewer hospitalisations (p<0.001), and quality of life was significantly better in the PVI group. The authors concluded that PVI appeared to be a feasible first-line approach for treating patients with symptomatic AF.

#### RAAFT-2

The RAAFT-2 (Radiofrequency Ablation vs Antiarrhythmic Drugs as First-line Treatment of Paroxysmal Atrial Fibrillation) compared radiofrequency ablation with antiarrhythmic drugs (standard therapy) in treating patients with paroxysmal AF as a first-line therapy.<sup>15</sup> A total of 127 patients were enrolled; 61 were randomised to the antiarrhythmic drug group, 66 to the radiofrequency ablation group with a follow-up of 24 months each. The primary endpoint was the first documented atrial tachyarrhythmia of more than 30 seconds. Secondary endpoints included symptomatic recurrences of atrial tachyarrhythmia and quality of life. Forty-four patients (72.1%) in the antiarrhythmic drug group and 36 patients (54.5%) in the ablation group experienced the primary efficacy outcome (hazard ratio [HR] 0.56; 95% confidence interval [CI] 0.35–0.90; p=0.02). Among patients with paroxysmal AF without previous antiarrhythmic drug treatment, radiofrequency ablation resulted in a lower rate of recurrent atrial tachyarrhythmias at 2 years when compared with antiarrhythmic drugs. However, recurrence was frequent in both groups.

#### MANTRA-PAF

The MANTRA-PAF (Radiofrequency Ablation as Initial Therapy in Paroxysmal Atrial Fibrillation) trial compared radiofrequency ablation with antiarrhythmic drug therapy as first-line treatment in patients with paroxysmal AF.<sup>16</sup> A total of 294 patients without previous antiarrhythmic drug treatment were randomised to either radiofrequency ablation (n=146) or antiarrhythmic drug treatment (n=148). The authors found no significant difference between both groups in the cumulative burden of AF over a period of 2 years.

#### CABANA

The goal of the CABANA (Catheter Ablation versus Antiarrhythmic Drug Therapy for Atrial Fibrillation) trial was to compare the safety and efficacy of catheter ablation compared with drug therapy for the

treatment of patients with new-onset or untreated AF.<sup>17,18</sup> A total of 2,204 patients were randomised 1:1 for either catheter ablation (n=1,108) or drug therapy (n=1,096). Primary ablation was performed with standard techniques (PVI/wide area circumferential ablation). Ancillary ablation was added as needed. Drug therapy could be either for rate or rhythm control. The study details are listed in *Table 1*.

The full manuscript of the CABANA trial has not yet been published. So far, the results indicate that ablation is not superior to drug therapy for cardiovascular outcomes at 5 years among patients with new-onset or untreated AF requiring therapy, as the primary endpoint was missed in the intention-to-treat analysis. However, analysing secondary endpoints there was a significant reduction in death or cardiovascular hospitalisation with ablation, and a significant reduction in AF recurrence. The study also showed that ablation is a safe procedure, as the rate of adverse events was low. The main controversy, however, is caused by the fact that some electrophysiologists, including the principal investigator of this study, point to the positive results of a per protocol, or as-treated, analysis regarding the primary endpoint. They argue that the crossover rate in the study was comparatively high and that 27.5% of patients randomised to drug therapy were finally ablated, while 9.2% of patients randomised to the ablation arm did not undergo ablation.

Data for the primary endpoint based on treatment received in a per protocol analysis for ablation versus drug therapy showed a significant advantage for the ablation group with regard to all-cause mortality, death or cardiovascular hospitalisation. These findings may be considered hypothesis generating for further studies.

One of the caveats in this study is that the drug arm is quite heterogeneous, and it remains unclear if drug therapy for rhythm control would have been superior to a rate control strategy. Additionally, the trial is only single-blind. It is not blinded to the intervention received.

#### CAPTAF

The recently published CAPAF (Effect of Catheter Ablation vs Antiarrhythmic Medication on Quality of Life in Patients with Atrial Fibrillation) trial assessed quality of life with catheter ablation versus antiarrhythmic medication at 12 months in patients with AF.<sup>19</sup> A total of 155 patients aged 30–70 years with more than 6 months of AF and treatment failure with one antiarrhythmic drug or beta-blocker were enrolled in the study. They were randomised to catheter ablation (n=79) or previously untested antiarrhythmic drugs (n=76), with 4-year follow-up. The primary outcome was the General Health subscale score (Medical Outcomes Study 36-Item Short-Form Health Survey) at baseline and 12 months, assessed unblinded. Among patients with symptomatic AF despite use of antiarrhythmic medication, the improvement in quality of life at 12 months was greater for those treated with catheter ablation compared with antiarrhythmic medication. Although the study was limited by absence of blinding, catheter ablation may offer an advantage for quality of life.

### Catheter ablation of atrial fibrillation in patients with heart failure with reduced ejection fraction

There have been several observational studies evaluating the effect of catheter ablation for AF on left ventricular ejection fraction (LVEF) in patients with HF.<sup>20–39</sup> The median improvement of LVEF in the ablation group was 13%. In the nine studies consisting of patients with normal ejection fraction as a comparator arm,<sup>20–23,26,27,31,32,39</sup> the median improvement of LVEF was 12%.

Table 1: Study details of the CABANA trial

Study design	Prospective, randomised, multicentre, open-label clinical trial
Study objective	The goal of the trial was to compare the safety and efficacy of catheter ablation compared with drug therapy for the treatment of patients with new-onset or untreated AF
Primary endpoint	Composite of total mortality, disabling stroke, serious bleeding or cardiac arrest
Secondary endpoints	<ul style="list-style-type: none"> <li>• Total mortality</li> <li>• Total mortality or CV hospitalisation</li> <li>• Total mortality, stroke or CV hospitalisation (for heart failure or acute ischaemic event)</li> <li>• CV death</li> <li>• CV death or disabling stroke</li> <li>• Arrhythmic death or cardiac arrest</li> <li>• Heart failure death</li> <li>• Exercise tolerance (6-minute walk test)</li> <li>• CV hospitalisation</li> <li>• Medical costs, resource utilisation and cost effectiveness</li> <li>• Quality of life</li> <li>• Composite adverse events</li> <li>• LA size, morphology, and function</li> </ul>
Sample size	2,204 patients (mean age 67.5 years, 37% females)
Inclusion criteria	<ul style="list-style-type: none"> <li>• Paroxysmal, persistent, or longstanding persistent patients with AF who warrant therapy</li> <li>• ≥65 years of age</li> <li>• &lt;65 years of age with ≥1 CVA/CV risk factor</li> <li>• Eligible for ablation</li> <li>• On ≥2 rhythm or rate control drugs</li> </ul>
Other salient features/ characteristics	<ul style="list-style-type: none"> <li>• Cardiomyopathy: 9%</li> <li>• Chronic heart failure: 15%</li> <li>• Prior CVA/TIA: 10%</li> <li>• Type of AF: paroxysmal: 43%, persistent 47%</li> <li>• Prior hospitalisation for AF: 39%</li> <li>• Crossover: ablation to drug: 9.2%, drug to ablation: 27.5%</li> </ul>
Follow-up	5 years
Principal findings	<p>The primary outcome, death, disabling stroke, serious bleeding, or cardiac arrest at 5 years for ablation versus drug therapy was 8.0% versus 9.2% (HR 0.86; 95% CI 0.65–1.15; p=0.3)</p> <ul style="list-style-type: none"> <li>• Death: 5.2% versus 6.1% for ablation versus drug therapy, p=0.38</li> <li>• Serious stroke: 0.3% versus 0.6% for ablation versus drug therapy, p=0.19</li> <li>• Primary endpoint based on treatment received (for ablation versus drug therapy): 7.0% versus 10.9%, p=0.006; all-cause mortality: 4.4% versus 7.5%, p=0.005; death or CV hospitalisation: 41.2% versus 74.9%, p=0.002</li> </ul> <p>Secondary outcomes:</p> <ul style="list-style-type: none"> <li>• Death or CV hospitalisation: 51.7% versus 58.1% for ablation versus drug therapy, HR 0.83; 95% CI 0.74–0.93; p=0.002</li> <li>• Time to first AF recurrence: HR 0.53; 95% CI 0.46–0.61; p&lt;0.0001</li> <li>• Pericardial effusion with ablation: 3.0%; ablation-related events: 1.8%</li> <li>• Recurrent AF for ablation versus drug therapy (HR 0.52; p&lt;0.001)</li> </ul>

AF = atrial fibrillation; CABANA = Catheter Ablation versus Antiarrhythmic Drug Therapy for Atrial Fibrillation; CI = confidence interval; CV = cardiovascular; CVA = cerebrovascular accident; HR = hazard ratio; LA = left atrium; TIA = transient ischaemic attack.

The seven randomised controlled trials<sup>40–46</sup> evaluating prognostic benefits of AF ablation in HFrEF patients are described in the following sections and summarised in Table 2. The most recently published of these randomised controlled trials, and potentially impactful, is the CASTLE-AF trial.

### CASTLE-AF

The CASTLE-AF (Catheter Ablation Versus Standard Conventional Treatment in Patients with Left Ventricular Dysfunction and Atrial Fibrillation) trial was published in 2018 by Marrouche et al.<sup>46</sup> It was an international, prospective, randomised, multicentre trial evaluating the effectiveness of catheter ablation for AF in patients with HF, comparing mortality and morbidity with a medical treatment control arm. A total of 398 patients from 33 sites in Europe, USA, and Australia were included. Inclusion criteria were symptomatic paroxysmal or persistent

AF; failure, intolerance or unwillingness to take antiarrhythmic drugs; left ventricular dysfunction with a LVEF ≤35% measured in the last 6 weeks prior to enrolment; New York Heart Association (NYHA) class ≥2; and an implantable cardioverter defibrillator (ICD) for primary or secondary prevention (with atrial sensing capabilities) or a cardiac resynchronisation therapy defibrillator (CRT-D) device, both with remote monitoring technology (Home Monitoring®, Biotronik SE & Co. KG, Berlin, Germany). The primary endpoint was all-cause mortality or worsening of HF requiring unplanned hospitalisation. Major secondary endpoints included event rates for cerebrovascular accidents, cardiovascular mortality, unplanned hospitalisation due to cardiovascular disease, all-cause hospitalisation, quality of life as evaluated by the Minnesota Living with Heart Failure (MLWHF) and the European Quality of Life 5 Dimensions (EuroQoL EQ-5D) questionnaires, and exercise tolerance evaluated by a 6-minute walk test.

**Table 2: Study characteristics of randomised controlled trials comparing catheter ablation for atrial fibrillation with different comparator arms in patients with heart failure with reduced ejection fraction**

Study (year)	N (CA/ comp. arm)	Type of AF	Mean follow-up (months)	Post-ablation heart rhythm assessment method	Ablation technique	Ablation strategy	Comp. arm	Primary endpoint	Result
Khan et al., 2008 <sup>40</sup>	81 (41/40)	Persistent 50%, paroxysmal 50%	6	Loop recorder	RF	PVI ± linear lesions and CFAE	AVN ablation + BiVpacing	Change in LVEF, 6MWT and MLWHF score	Improved LVEF, 6MWT and QoL score in PVI group (6-month f/u)
MacDonald et al., 2011 <sup>41</sup>	41 (22/19)	Persistent	6	24-h Holter monitor	RF	PVI ± linear lesions and CFAE ± CVTI (+ 3 months amiodarone)	Rate control with BB ± Dig	Change in LVEF	No difference in LVEF between groups; no difference in BNP, 6MWT or QoL (12-month f/u)
Jones et al., 2013 <sup>42</sup>	52 (26/26)	Persistent	12	48-h Holter monitor	RF	PVI ± linear lesions and CFAE ± CVTI	Rate control with BB ± Dig	Change in peak oxygen consumption	Improvement in exercise performance and BNP in ablation arm (12-month f/u)
Hunter et al., 2014 <sup>43</sup>	50 (26/24)	Persistent	6	48-h Holter monitor	RF	PVI with CFAE ± linear lesions ± CVTI	Rate control	Change in LVEF	Improved LVEF, better exercise performance and QoL score in ablation arm (12-month f/u)
Di Biase et al., 2016 <sup>44</sup>	203 (102/101)	Persistent	24	ICD/CRT-D	RF	PVI + LAPWI + SVCI + CFAE	Amiodarone	AF recurrence	Improved AF recurrence free survival, lower mortality and unplanned hospitalisations in ablation arm
Prabhu et al., 2017 <sup>45</sup>	66 (33/33)	Persistent	6	Loop recorder	RF CF	PVI + LAPWI	Rate control	Change in LVEF	Improved LVEF in ablation arm; those who were LGE negative had greater improvements in LVEF
Marrouche et al., 2018 <sup>46</sup>	363 (179/184)	Persistent 70%, paroxysmal 30%	38	ICD/CRT-D	Operator decision	PVI + operator decision	Rate or rhythm control	Mortality and heart failure hospitalisation	Improved primary composite end-point of mortality + HF hospitalisation in ablation arm

6MWT = 6-minute walk test; AF = atrial fibrillation; AVN = atrioventricular node; BB = beta blocker; BiVpacing = biventricular pacing; BNP = B-type natriuretic peptide; CA = catheter ablation; CF = contact force; CFAE = complex fractionated atrial electrogram; comp. arm = comparator arm; CRT-D = cardiac resynchronisation therapy defibrillation; CVTI = cavotricuspid isthmus; Dig = digitalis; f/u = follow-up; HF = heart failure; ICD = implantable cardioverter defibrillator; LAPWI = left atrial posterior wall isolation; LGE = late gadolinium enhancement; LVEF = left ventricular ejection fraction; MLWHF = Minnesota living with heart failure; N = number; PVI = pulmonary vein isolation; QoL = Quality of life; RF = radiofrequency; SVCI = superior vena cava isolation.

There were three key results of CASTLE-AF:

1. catheter ablation of AF in patients with HF was associated with a 38% reduction in death or hospitalisation for worsening HF;
2. catheter ablation of AF in patients with HF was associated with a 47% reduction in death from any cause; and
3. catheter ablation of AF in patients with HF was associated with a 44% reduction in hospitalisation for worsening HF.

CASTLE-AF is currently the most optimistic and robust trial indicating prognostic benefits of AF ablation. An overview over study details is given in Table 3. It is the first, large randomised study providing clinical evidence that ablation of AF improves hard outcome parameters in patients with HF. Catheter ablation for patients with HF and concomitant AF who fit the inclusion criteria of CASTLE-AF is now supported by robust evidence as a first-line therapy during the course of HF. The

results strongly indicate that catheter ablation of AF is a crucial element in managing advanced HF, alongside CRT and continuous remote monitoring. Limitations of the study include its relatively small and highly selected patient cohort and the lack of blinding.

#### AATAC

The AATAC (Ablation Versus Amiodarone for Treatment of Persistent Atrial Fibrillation in Patients With Congestive Heart Failure and an Implanted Device) trial, published by Di Biase et al., was designed to address whether AF ablation is superior to a pharmacological rhythm control strategy with amiodarone, with regards to AF-free survival in patients with symptomatic (NYHA II-III) HFrEF (LVEF ≤40%) and persistent AF.<sup>44</sup> AATAC was a multicentre, parallel-group, open-label, randomised controlled trial including 203 patients; 102 randomised to catheter ablation and 101 for amiodarone treatment. Inclusion criteria were age ≥18 years, persistent AF, dual chamber ICD or CRT-D in place, NYHA II-III, and LVEF ≤40%

Table 3: Study details of the CASTLE-AF trial

Study design	Prospective, randomised, multicentre, international
Study objective	Evaluation of the effectiveness of catheter ablation of atrial fibrillation in patients with heart failure on mortality and morbidity when compared to medical treatment
Primary endpoint	All-cause mortality or worsening of heart failure requiring unplanned hospitalisation
Major secondary endpoints	<ul style="list-style-type: none"> <li>• All-cause mortality</li> <li>• Worsening of heart failure requiring unplanned hospitalisation</li> <li>• Cerebrovascular accidents</li> <li>• Cardiovascular mortality</li> <li>• Unplanned hospitalisation due to cardiovascular reason</li> <li>• All-cause hospitalisation</li> <li>• Quality of Life: Minnesota Living with Heart Failure and EuroQoL EQ-5D</li> <li>• Exercise tolerance (6-minute walk test)</li> </ul>
Clinical sites	33 sites in Europe, USA and Australia
Sample size	398 patients
Main inclusion criteria	<ul style="list-style-type: none"> <li>• Symptomatic paroxysmal or persistent AF</li> <li>• Failure or intolerance of antiarrhythmic drug therapy or unwillingness to take antiarrhythmic drugs</li> <li>• Left ventricular dysfunction with LVEF <math>\leq</math>35 % (measured in the last 6 weeks prior to enrolment)</li> <li>• NYHA class <math>\geq</math>II</li> <li>• ICD for primary or secondary prevention with atrial sensing capabilities or CRT-D device, both with Home Monitoring<sup>®</sup> technology already implanted</li> </ul>
Main exclusion criteria	<ul style="list-style-type: none"> <li>• Documented left atrial diameter <math>&gt;</math>6 cm</li> <li>• Contraindication for chronic anticoagulation therapy or heparin</li> <li>• Previous left heart ablation procedure for atrial fibrillation</li> <li>• Acute coronary syndrome, cardiac surgery, angioplasty or stroke within 2 months prior to enrolment</li> <li>• Untreated hypothyroidism or hyperthyroidism</li> <li>• Listed for heart transplant</li> <li>• Cardiac assist device implanted</li> <li>• Planned cardiovascular intervention</li> </ul>
Follow-up	Follow-up visits at 3, 6, 12, 24, 36, 48 and 60 months after baseline (5 weeks after enrolment)
Key results	<ul style="list-style-type: none"> <li>• Catheter ablation of atrial fibrillation in patients with heart failure is associated with a significant 38% reduction in death or hospitalisation for worsening heart failure. HR 0.62 (95% CI 0.43–0.87); <math>p=0.007</math>; Log-rank test: <math>p=0.006</math></li> <li>• Catheter ablation of atrial fibrillation in patients with heart failure is associated with a significant 47% reduction in death from any cause. HR 0.53 (95% CI 0.32–0.86); <math>p=0.011</math>; Log-rank test: <math>p=0.009</math></li> <li>• Catheter ablation of atrial fibrillation in patients with heart failure is associated with a significant 44% reduction in hospitalisation for worsening heart failure. HR 0.56 (95% CI 0.37–0.83); <math>p=0.004</math>; Log-rank test: <math>p=0.004</math></li> </ul>

AF = atrial fibrillation; CASTLE = Catheter Ablation Versus Standard Conventional Treatment in Patients with Left Ventricular Dysfunction and Atrial Fibrillation; CI = confidence interval; CRT-D = cardiac resynchronisation therapy – defibrillator; HR = hazard ratio; ICD = implantable cardioverter defibrillator; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; QoL = quality of life.

within the last 6 months. The primary and secondary outcomes of this study were all in favour of a catheter ablation strategy. This included the primary endpoint of atrial arrhythmia-free survival at 2 years (71 patients in the ablation group [70.0%; 95% CI 60–78%] versus 34 patients in the control group [34.0%; 95% CI 25–44%];  $p<0.001$ ) and secondary outcomes including unplanned hospitalisation (32 [31.0%; 95% CI 20–41%] versus 58 [57.0%; 95% CI 51–69] [risk ratio (RR) 0.55; 95% CI 0.39–0.76; number needed to treat 3.8;  $p<0.001$ ]), death (8 [8.0%] versus 18 [18.0%; RR 0.44; 95% CI 0.20–0.96; number needed to treat 10;  $p=0.037$ ]), LVEF (change from baseline to follow-up, 8.1 [ $\pm$ 4] versus 4.0 [ $\pm$ 5];  $p=0.02$ ), 6-minute walk distance (change from baseline to follow-up, 22 [ $\pm$ 22] versus 10 [ $\pm$ 37];  $p=0.02$ ), and MLWHF (Minnesota Living with Heart Failure) Score (change from baseline to follow-up, 11 [ $\pm$ 19] versus 6 [ $\pm$ 17];  $p=0.04$ ).

One of the major criticisms, however, regarding these results is that this was a small, highly selected cohort and the trial was not designed to assess clinical outcomes like hospitalisation for HF and death, and that these results therefore require secondary validation with an appropriately powered study.

### CAMERA-MRI

The CAMERA-MRI (Catheter Ablation Versus Medical Rate Control in Atrial Fibrillation and Systolic Dysfunction) trial was a randomised clinical trial to evaluate medical rate control compared with catheter ablation for improvement of left ventricular systolic dysfunction in patients with AF and idiopathic cardiomyopathy (LVEF  $\leq$ 45%).<sup>45</sup> Sixty-eight patients were enrolled and cardiac magnetic resonance (CMR) was used to evaluate LVEF at baseline and 6 months after randomisation. At 6 months follow-up, LVEF normalised to  $\geq$ 50% in 58% of the catheter ablation group compared with only 9% in the medical rate control group. The authors concluded that catheter ablation is a promising strategy for improving LVEF in patients with AF and left ventricular systolic dysfunction and that catheter ablation may be superior to medical rate control in this cohort. It is likely that a significant proportion of patients with persistent AF and otherwise unexplained left ventricular systolic dysfunction have an under-recognised arrhythmia-related cardiomyopathy and efforts to restore sinus rhythm should be considered in selected patients.

## CAMTAF

The CAMTAF trial (Catheter Ablation Versus Medical Treatment of Atrial Fibrillation in Heart Failure) was published in 2014 by Hunter et al.<sup>43</sup> The authors compared the effect of a catheter ablation strategy with that of medical rate control in patients with persistent AF and HF. The primary endpoint was the difference between groups in LVEF at 6 months. Secondary endpoints included the percentage reduction in left ventricular end systolic volume,  $VO_2$  max, plasma B-type natriuretic peptide (BNP), NYHA class, MLWHF score, and 36-item Short-Form score (SF-36). The results demonstrated that a catheter ablation strategy in patients with persistent AF and HF resulted in improved left ventricular function, functional capacity, HF symptoms and quality of life compared with medical rate control, suggesting a beneficial effect of catheter ablation in treating selected patients with AF and HF.

## PABA-CHF

Khan et al. published the 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) trial in 2008.<sup>40</sup> In this prospective, multicentre, randomised, controlled trial, patients with symptomatic, drug-resistant AF, an LVEF of  $\leq 40\%$ , and HF NYHA class II or III, were assigned either to PVI or atrioventricular (AV) node ablation with biventricular pacing. The primary endpoint was a composite of LVEF, distance achieved on the 6-minute walk test, and MLWHF score. All criteria improved with PVI, with all three components demonstrating statistically significant improvements. For PVI as compared with AV node ablation with biventricular pacing, LVEF was significantly higher ( $35 \pm 9\%$  versus  $28 \pm 6\%$ ;  $p < 0.001$ ), the 6-minute walking distance significantly longer ( $340 \pm 49$  m versus  $297 \pm 36$  m;  $p < 0.001$ ), and the MLWHF scores significantly better ( $60 \pm 8$  versus  $82 \pm 14$ ;  $p < 0.001$ ). Thus, PVI was superior to AV node ablation and biventricular pacing in patients with HF who had drug-refractory AF.

## ARC-HF

Jones et al. published a randomised, open-label, blinded-endpoint clinical trial in 2013,<sup>42</sup> which compared catheter ablation with medical rate control for persistent AF in HF; it was called ARC-HF (Catheter Ablation Versus Rate Control in the Management of Persistent Atrial Fibrillation in Heart Failure) trial. Patients were followed up at 3, 6 and 12 months. The primary endpoint, peak  $VO_2$ , was defined at 12 months and also measured at 3 months. Secondary endpoints included quality of life, BNP, 6-minute walk distance, and ejection fraction. Results were analysed by intention-to-treat. Peak oxygen consumption significantly increased after catheter ablation compared with rate control (difference  $+3.07$  mL/kg/min; 95% CI 0.56–5.59;  $p = 0.018$ ). However, the change was not evident after 3 months. Catheter ablation improved the MLWHF score ( $p = 0.019$ ) and BNP ( $p = 0.045$ ) at 12 months.

## Other randomised controlled trials

Study results by MacDonald et al. published in 2011 were different from the promising results of the other trials. The aim of this study was to determine whether or not radiofrequency ablation (RFA) for persistent AF in patients with advanced HF leads to improvements in cardiac function.<sup>41</sup> Patients were randomised to radiofrequency ablation or continued medical rate control therapy. These results suggested that radiofrequency ablation did not improve LVEF measured by cardiac MRI compared with a medical rate control strategy. Radiofrequency ablation resulted in long-term restoration of sinus rhythm in only 50% of patients. It did improve radionuclide LVEF, but did not improve other secondary outcomes and was associated with a significant rate of serious complications.

## Meta-analyses and reviews

The seven previously mentioned randomised controlled trials have also been analysed in several meta-analyses and reviews.<sup>13,47–53</sup> Alturki et al.<sup>47</sup> summarised all seven trials (Khan et al.,<sup>40</sup> MacDonald et al.,<sup>41</sup> Jones et al.,<sup>42</sup> Hunter et al.,<sup>43</sup> Di Biase et al.,<sup>44</sup> Prabhu et al.,<sup>45</sup> and Marrouche et al.<sup>46</sup>). They found a significant reduction in mortality (RR 0.50; 95% CI 0.34–0.74;  $p = 0.0005$ ) and HF-related hospitalisations (RR 0.56; 95% CI 0.44–0.71;  $p < 0.0001$ ) in the ablation arm compared with medical therapy including antiarrhythmic drugs. Additionally, they found significant improvements in LVEF following catheter ablation (weighted mean difference 7.48; 95% CI 3.71–11.26;  $p < 0.0001$ ). All seven trials were also analysed by Briceño et al.,<sup>52</sup> Ruzieh et al.,<sup>49</sup> and Ma et al.<sup>53</sup> All found favourable effects of catheter ablation as compared to conventional treatment with regard to mortality, HF-related hospitalisations, improvement of LVEF, functional capacity, and quality of life. Turagam et al.,<sup>48</sup> Smer et al.,<sup>51</sup> and Elgendy et al.<sup>50</sup> analysed only six of the seven trials excluding the study by Khan et al., as the comparator arm of this study was AV node ablation and biventricular pacing instead of drug therapy. The results of these meta-analyses are listed in *Table 4*.

## Studies on catheter ablation of atrial fibrillation in patients with heart failure with mid-range or preserved ejection fraction

There have only been few studies regarding catheter ablation for AF in patients with HFmrEF or preserved ejection fraction (HFpEF). Cha et al. enrolled 368 patients in a prospective cohort study;<sup>29</sup> 157 with diastolic dysfunction (HFpEF), 111 with systolic dysfunction (HFrEF), and 100 patients in a control group with normal left ventricular function. After 1 year, there was no statistically significant difference in AF recurrence between patients with diastolic dysfunction and the control group. After 5 years, however, freedom from AF recurrence was about 40% in the diastolic dysfunction group and 65% in the control group, which was statistically significant. Thirty percent of patients with HFpEF showed at least one grade improvement in diastolic dysfunction and significant improvement in the physical components of the SF-36 questionnaire.

In 2013, Machino-Ohtsuka et al. published a study evaluating 74 patients with HFpEF undergoing catheter ablation for AF.<sup>54</sup> Average follow-up was 34 months. Drug-free success rate after one and multiple procedures was 27% and 45%, respectively. The success rate could be increased to 73% with pharmaceutical assistance. The study provided evidence in support of the safety and efficacy of catheter ablation on those patients; however, there was no comparator arm.

A recent retrospective study by Black-Maier et al. enrolled 97 patients with HFrEF and 133 patients with HFpEF who were evaluated after ablation.<sup>55</sup> The outcome of both patient groups was similar. There were no significant differences in procedure time, adverse events, arrhythmia recurrence, or functional improvement (Mayo AF Symptom Inventory and NYHA class).

## Discussion

These trial results show that in patients with AF and HFrEF the outcomes of catheter ablation compared to conventional treatment are superior with regard to all-cause mortality, hospitalisation for HF, improvement of LVEF, quality of life, and functional capacity, while complication rates are comparable between the two treatment strategies. Some of the earlier randomised controlled trials, however, included only small numbers of patients and were only adequately powered to assess surrogate end-points like LVEF, exercise capacity, and quality of life. Additionally, the ablation strategies in these trials were heterogeneous, and some of

**Table 4: Comparison of meta-analyses summarising randomised, controlled trials on catheter ablation of atrial fibrillation in patients with heart failure with reduced ejection fraction**

	Briceño et al., 2018 <sup>52</sup>	Ma et al., 2018 <sup>53</sup>	Alturki et al., 2019 <sup>47</sup>	Ruzieh et al., 2019 <sup>49</sup>	Elgendy et al., 2018 <sup>50</sup>	Smer et al., 2018 <sup>51</sup>	Turagam et al., 2019 <sup>48</sup>
Trials included [Ref]	[40–46]	[40–46]	[40–46]	[40–46]	[41–46]	[41–46]	[41–46]
All-cause mortality	OR 0.46; CI 0.29 to 0.72; p=0.0007	RR 0.52; CI 0.35 to 0.76; p=0.0009	RR 0.50; CI 0.34 to 0.74; p=0.0005	OR 0.49; CI 0.31 to 0.77; p=0.002	RR 0.50; CI 0.34 to 0.74; p<0.0001	OR 0.46; CI 0.29 to 0.73; p=0.0009	RR 0.52; CI 0.33 to 0.81
Heart failure related hospitalisation	–	RR 0.58; CI 0.46 to 0.66; p<0.00001	RR 0.56; CI 0.44 to 0.71; p<0.0001	OR 0.43; CI 0.29 to 0.64; p<0.001	RR 0.58; CI 0.41 to 0.81; p=0.002	OR 0.43; CI 0.30 to 0.62; p<0.00001	RR 0.60; CI 0.39 to 0.93
Cerebrovascular accident	–	RR 0.56; CI 0.23 to 1.36; p=0.20	–	–	–	OR 0.49; CI 0.18–1.35; p=0.17	–
Change in LVEF	SMD 0.68; CI 0.28 to 1.08; p=0.0009	MD 7.57; CI 3.72 to 11.41; p=0.0001	WMD 7.48; CI 3.71 to 11.26; p<0.0001	MD 6.8%; CI 3.5 to 10.1; p<0.001	SMD 2.58; CI 0.88 to 4.27; p=0.003	MD 5.93; CI 3.59 to 8.27; p<0.00001	MD 6.95%; CI 3.0 to 10.9%
6-minute walk test [m]	SMD 0.51; CI 0.13 to 0.90; p=0.008	MD 26.67; CI 12.07 to 41.27; p=0.62; p=0.0003	WMD 30.15; CI 10.47 to 49.84; p<0.0001	MD 29.3; CI 11.8 to 46.8; p=0.001	–	MD 24.65; CI 11.18 to 38.12; p=0.0003 (versus rate control)	MD 20.93; CI 5.91 to 35.95
Quality of life (MLWHF questionnaire)	SMD -0.69; CI -1.29 to -0.09; p=0.02	MD -9.49; CI -14.64 to -4.34; p=0.0003	WMD -9.53; CI -14.67 to -4.38; p<0.0001	MD -12.1; CI -20.9 to -3.3; p=0.007	SMD -0.40; CI -0.65 to -0.14; p=0.002	MD -9.01; CI -15.56 to -2.45; p=0.007	MD -9.02; CI -19.75 to 1.71
Functional capacity (peak VO <sub>2</sub> )	–	MD 3.16; CI 1.09 to 5.23; p=0.003	–	–	–	MD 3.16; CI 1.04 to 5.29; p=0.004	MD 3.17; CI 1.26 to 5.07
NYHA class	–	MD -0.74; CI -0.83 to -0.64; p<0.00001	–	–	–	–	–
Adverse events	OR 1.13; CI 0.58 to 2.20; p=0.71	–	7.3%; CI 3.4 to 11.3%	–	7.3%; CI 3.4 to 11.3%	OR 1.18; CI 0.44 to 3.15; p=0.75	RR 1.68; CI 0.58 to 4.85

The meta-analyses by Briceño et al.,<sup>52</sup> Ma et al.,<sup>53</sup> Alturki et al.,<sup>47</sup> and Ruzieh et al.<sup>49</sup> analysed all seven trials by Khan et al.,<sup>40</sup> MacDonald et al.,<sup>41</sup> Jones et al.,<sup>42</sup> Hunter et al.,<sup>43</sup> Di Biase et al.,<sup>44</sup> Prabhu et al.,<sup>45</sup> and Marrouche et al.<sup>46</sup> The meta-analyses by Elgendy et al.,<sup>50</sup> Smer et al.,<sup>51</sup> and Turagam et al.<sup>48</sup> excluded the study by Khan, as the comparator arm in this study was not medical therapy but atrioventricular nodal ablation plus biventricular pacing. There was a significant benefit in the ablation arm concerning all-cause mortality, hospitalisation for heart failure, left ventricular ejection fraction, 6-minute walk test, quality of life, peak oxygen consumption and NYHA class. On the other hand, numbers of cerebrovascular accidents and adverse events did not significantly differ.

CI = confidence interval (95%); LVEF = left ventricular ejection fraction; m = metres; MD = mean difference; MLWHF = Minnesota Living With Heart Failure; NYHA = New York Heart Association; OR = odds ratio; Ref = reference; RR = risk ratio; SMD = standard mean difference; VO<sub>2</sub> = oxygen consumption; WMD = weighted mean difference.

them have already been abandoned.<sup>3</sup> While PVI is still the cornerstone of catheter ablation for paroxysmal and persistent AF and left posterior wall isolation has shown promising results, routine ablation of complex fractionated atrial electrograms and linear lesion formation are no longer used since the disappointing results of STAR AF II and other trials.<sup>4,56,57</sup> The most important trial in this context is probably CASTLE-AF, published in 2018, which assessed the impact of AF ablation on mortality and HF progression rates. Overall, the findings of these trials seem understandable as patients with HF carry an increased risk of AF, while AF is a risk factor for the development of HF. More than half of patients with HF have AF, and one in three patients with AF develops HF.<sup>58</sup> These frequently coexisting conditions are among the most common cardiovascular diagnoses associated with hospital admission, morbidity, and mortality.<sup>59</sup>

These data resulted in a new recommendation in the 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: 'AF catheter ablation may be reasonable in selected patients with symptomatic AF and HF with reduced left ventricular (LV) ejection fraction (HFREF) to potentially lower mortality rate and reduce hospitalization for HF' (IIB indication).<sup>10</sup> This indication clearly exceeds mere symptom control in this selected group of patients. It does not mention a previous ICD or CRT-D

implantation. The latter, however, was an inclusion criterion of AATAC and CASTLE-AF. In clinical practice, AF ablation in patients with HFREF is often performed before the implantation of an ICD or CRT-D, because device implantation may no longer be indicated in case of an improved LVEF after the ablation.

Contrasting evidence to the favourable results of AF ablation in patients with HFREF, however, was published by Roy et al. in 2008.<sup>60</sup> In their multicentre, randomised Atrial Fibrillation in Congestive Heart Failure trial they compared rhythm control with rate control in patients with a LVEF of ≤35%, symptoms of congestive HF, and a history of AF. The primary outcome was the time to death from cardiovascular causes. Rhythm control was mainly achieved by electrical cardioversion and drug therapy with amiodarone, sotalol and dofetilide, rate control with beta-blockers and digitalis. AV nodal ablation and pacemaker therapy were recommended for patients who did not meet the rate-control targets with drug therapy. In this study, rhythm control did not reduce the rate of death from cardiovascular causes, as compared with a rate-control strategy.

According to current guidelines, patients with HF are classified as those with reduced (HFREF, LVEF <40%), mid-range (HFmrEF, LVEF

40–49%), and preserved (HFpEF, LVEF  $\geq$ 50%) ejection fraction.<sup>61</sup> Data on long-term outcomes after catheter ablation for AF in patients with HFmrEF or HFpEF are sparse. Recently, Zafrir et al.<sup>62</sup> investigated long-term implications of AF compared to sinus rhythm in patients with all three categories of HF. They analysed data from the observational, prospective, HF long-term registry of the European Society of Cardiology. A total of 14,964 patients with HF were enrolled. The prevalence of AF was 27% in HFrEF, 29% in HFmrEF, and 39% in HFpEF. This increasing prevalence of AF in patients with less systolic dysfunction seems to be counterintuitive at first glance. It can be explained by the physiological milieu associated with HFpEF with elevated filling pressure and myocardial fibrosis, which probably increases the risk of AF.<sup>59</sup> After multivariate adjustment, the HR of AF for HF hospitalisations was 1.036 in HFrEF (95% CI 0.888–1.208;  $p=0.652$ ), 1.430 in HFmrEF (95% CI 1.087–1.882;  $p=0.011$ ), and 1.487 in HFpEF (95% CI 1.195–1.851;  $p<0.001$ ). For combined all-cause death or HF hospitalisations, HR was 0.957 for HFrEF (95% CI 0.843–1.087;  $p=0.502$ ), 1.302 for HFmrEF (95% CI 1.055–1.608;  $p=0.014$ ), and 1.365 for HFpEF (95% CI 1.152–1.619;  $p<0.001$ ). In patients with HFrEF, AF was not associated with worse outcomes in those with either an acute or a chronic presentation of HF. The authors concluded that the prevalence of AF increases with increasing ejection fraction. Its association with worse cardiovascular outcomes remained significant in patients with HFpEF and HFmrEF, but not in those with HFrEF. Despite these observations, no pharmacological or device-based therapies have been consistently shown to offer meaningful improvements in hard clinical outcomes in HFpEF.<sup>59</sup> The recently published CASTLE-AF trial was limited to patients with an ejection fraction  $\leq$ 35%.<sup>46</sup> But if AF has a larger adverse impact on patients with HFpEF and HFmrEF than on those with HFrEF, a durable restoration of sinus rhythm could confer an even larger benefit in HFpEF patients.

Despite limitations in the study by Zafrir et al., and conflicting results of other trials showing similar prognostic relevance of AF in all three categories of patients with AF,<sup>63</sup> AF treatment in the subgroup of HFpEF seems to be a promising therapeutic target. Thus, more randomised controlled trials on AF ablation for patients with HFmrEF and HFpEF will be needed in the future. The CABANA trial, the full manuscript of which has not yet been published, and which included patients with all

categories of HF, did not meet the primary endpoint of a composite of total mortality, disabling stroke, serious bleeding, or cardiac arrest in the intention-to-treat analysis indicating that ablation is not superior to drug therapy for cardiovascular outcomes at 5 years among patients with new-onset or untreated AF requiring therapy. The positive outcome of a per protocol analysis, which purists would strictly reject, could serve at least as hypothesis-generating for further trials.

Some clinical trials on AF ablation are currently ongoing. The CONTRA-HF (Ablation of Atrial Fibrillation in Heart Failure Patients; ClinicalTrials.gov identifier NCT03062241) trial will investigate the impact of cryoablation in patients with HF and implanted ICD or CRT-D. Whilst the AMICA (Atrial Fibrillation Management in Congestive Heart Failure With Ablation; ClinicalTrials.gov identifier NCT00652522) trial will investigate whether PVI alone in patients with persistent AF or longstanding persistent AF improves outcomes compared with best medical therapy. Finally, the RAFT-AF (Randomised Ablation-based Atrial Fibrillation Rhythm Control Trial in Patients with Heart Failure and High Burden Atrial Fibrillation; ClinicalTrials.gov identifier NCT01420393) trial will assess the cost-effectiveness of an ablation strategy in patients with HF as well as assess hard endpoints including all-cause mortality; with patients stratified according to reduced or preserved ejection fraction.

## Conclusion

In previous guidelines, catheter ablation for AF was regarded as predominantly a means for symptom reduction. The favourable effects of AF ablation on stroke, dementia, and other outcomes in patients with AF have been observed in many studies. Emerging data suggest that catheter ablation for AF, especially in the group of patients with HFrEF, has beneficial effects on mortality, hospitalisation for HF, improvement of LVEF, quality of life, and functional capacity, even in those with only mild HF symptoms and no obvious symptoms from the AF itself. The procedure of catheter ablation seems to be safe, as adverse events in the ablation and conventional treatment arms of most trials do not differ significantly. In contrast to the subgroup of HF patients with reduced ejection fraction, there is a lack of data regarding the prognostic benefit of catheter ablation for AF in the subgroups of HFmrEF and HFpEF. Randomised controlled trials to answer that question will be needed in the future. □

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