Abstract
AF and heart failure with reduced ejection fraction (HFrEF) frequently coexist. Catheter ablation is an increasingly utilised treatment strategy for patients with AF and can be safely performed and is effective in achieving sinus rhythm for patients with HFrEF. Successful ablation may result in improved LV function, clinical heart failure status, quality of life and possibly even mortality. This review summarises the literature analysing efficacy, safety and outcomes of AF ablation for patients with HFrEF.

Keywords
Atrial fibrillation, cardiomyopathy, catheter ablation, heart failure, outcomes

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Medical Therapy for AF in Heart Failure with Reduced Ejection Fraction Patients
Guidelines recommend the use of beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, aldosterone antagonists and, more recently, angiotensin receptor-neprilysin inhibitors as medical therapy for patients with symptomatic HFrEF, and these medications are associated with improved mortality. Patients with AF and HFrEF have a significantly higher risk of stroke or systemic embolism, as well as overall mortality compared with patients with both AF and HFrEF with preserved ejection fraction (HFD/E) or without HF. As such, the presence of HF merits one point with the CHADS2 and CHA2DS2-VASc risk scores and thus oral anticoagulation is usually recommended for stroke prophylaxis, as per guidelines.

Beta-blockers
Beta-blockers have long been considered the cornerstone of HF therapy in patients with reduced LVEF. However, the beneficial effect of these medications in patients with HFrEF appears to be mitigated by the coexistence of AF. Studies have suggested that the survival benefit with beta-blockers in HFrEF is limited only to those patients who are in sinus rhythm. Large meta-analyses assessing thousands of patients from clinical trials comparing beta-blockers and placebo in patients with HFrEF and sinus rhythm with AF have shown that beta-blockers significantly reduce both all-cause mortality and cardiovascular hospitalisations in patients in sinus rhythm but not AF, despite similar degrees of ventricular rate reduction in both groups.

Anti-arrhythmic Drugs
Due to potential for pro-arrhythmia, the choice of anti-arrhythmic drugs for AF is limited to amiodarone and dofetilide in patients with HFrEF, as per the 2014 American Heart Association/American College of Cardiology/Heart Rhythm Society guidelines. Dronedarone is contraindicated in patients with New York Heart Association (NYHA) class III–IV HF or severe LV dysfunction (LVEF <40 %) as its use has been associated with increased early mortality due to HF worsening.
Treatment

Figure 1: Ablation Lesion Set for Circumferential Pulmonary Vein Isolation

Posterior (A) and anterior (B) projections of the left atrium on the 3-dimensional electroanatomical map showing circular ablation lesions delivered around both sets of pulmonary veins (pink, red and blue circles). The smaller yellow and orange circles in (B) are sites where pacing resulted in diaphragmatic stimulation, delineating the course of the right phrenic nerve.

Vaughan–Williams classification class lc agents have negative inotropic effects and should thus be avoided in patients with HFrEF. Sotalol should also be avoided in patients with HFpEF due to increased likelihood of torsades de pointes, particularly in patients with concomitant renal failure. Dofetilide was studied in the Danish Investigations of Arrhythmia and Mortality on Dofetilide in Congestive Heart Failure (DIAMOND-CHF) trial, which randomised 1,518 patients with HF and LV dysfunction to dofetilide versus placebo. The study showed that dofetilide was more effective in converting AF to sinus rhythm and maintaining sinus rhythm compared with placebo and dofetilide reduced the risk of HF hospitalisation (RR 0.75, 95% CI [0.63–0.89]). Although there was no overall difference in mortality compared with placebo among all patients, a post hoc analysis suggested significant reduction in mortality among patients with normal baseline QTc treated with dofetilide compared with patients randomised to placebo. Amiodarone is the most effective anti-arrhythmic drug (AAD) to maintain sinus rhythm, but is also associated with several side effects with long-term use including multiple organ toxicities that may as a result actually increase likelihood of non-cardiac mortality, as was suggested by the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT), which included patients with NYHA class III HF. The Atrial Fibrillation and Congestive Heart Failure (AF-CHF) trial randomised 1,376 patients to rate control versus rhythm control (>80% with amiodarone) and showed that rhythm control was associated with an increased rate of hospitalisation and no mortality benefit.

Catheter Ablation for AF in Heart Failure with Reduced Ejection Fraction

Maintenence of sinus rhythm has been associated with improved mortality and decreased all-cause and heart failure hospitalisations in patients with AF and HFpEF. However, the optimal strategy for rhythm control remains controversial. Since the efficacy of AADS remains suboptimal in patients with HFpEF, catheter ablation has become an increasingly utilised treatment strategy. The decision of whether to perform catheter ablation in patients with HFpEF should be individualised, weighing the potential long-term benefits of successful ablation against the risks of intra-procedural complications. Importantly, certain individual patient characteristics such as larger left atrial volume may predict AF recurrence after ablation. There is a growing body of literature supporting AF ablation for patients with HFpEF, with a large number of retrospective observational studies and several randomised controlled trials in addition to many meta-analyses. Based on these data, the 2017 Heart Rhythm Society/European Heart Rhythm Association/European Cardiac Arrhythmia Society/Asia Pacific Heart Rhythm Society/Latin American Society of Cardiac Stimulation and Electrophysiology expert consensus statement on AF ablation recommends that it is reasonable to use similar indications for AF ablation in selected patients with HF as for patients without HF (class IIa, level of evidence B-R). The optimal ablation strategy for patients with HFpEF remains controversial. Achievement of electrical pulmonary vein isolation (PVI) (Figure 1) should be performed for all AF ablations (class I, level of evidence A) and may be adequate especially in patients with paroxysmal AF. However, especially among patients with non-paroxysmal forms of AF, the benefit additional ablation with lesions sets such as empirical linear ablation, posterior wall isolation and targeting of non-pulmonary vein triggers, complex fractionated atrial electrograms or rotors remains unclear. Prior prospective studies (in non-HFrEF patients) have not shown benefit of additional empirical linear ablation or targeting of complex fractionated atrial electrograms on top of PVI alone in patients with non-paroxysmal AF.

Observational Studies of AF Ablation in Heart Failure with Reduced Ejection Fraction

There have been numerous retrospective observational studies examining outcomes of catheter ablation for AF in patients with HFpEF. Although most these studies are single-centre experiences with relatively small (<100 patients) sample sizes, ablation has been shown to be relatively safe in patients with HFpEF and successful ablation has in general been associated with improved LVEF, improved quality of life and functional capacity. Table 1 summarises the findings of these observational studies.

Prospective Randomised Controlled Trials of AF Ablation in Heart Failure with Reduced Ejection Fraction

Most randomised controlled trials have demonstrated overall benefit with ablation. However, there has been one notable exception: a study by MacDonald et al. published in 2011 randomised 41 patients with persistent AF and HFpEF (LVEF ≤40%, NYHA class II–III) to AF ablation versus medical therapy and found no difference in LVEF improvement, N-terminal pro-brain natriuretic peptide level, 6-minute walk distance or quality of life. Importantly, in this study, only 50% of patients remained in sinus rhythm at 6 months and there was a 15% complication rate in the ablation group.

Khan et al. randomised 81 patients with HFpEF (LVEF ≤40% and NYHA class II–III) to AF ablation versus AV nodal ablation and biventricular pacing and showed that at 6 months, those randomised to AF ablation had improved questionnaire scores, longer 6-minute walk distance and higher LVEF.

Jones et al. randomised 52 patients with LVEF ≤35% and persistent AF to ablation versus rate control. Overall, 88% of patients in the ablation group were in sinus rhythm at the end of the study (68% single procedure success). The primary endpoint of peak oxygen consumption was significantly higher in the ablation group. Furthermore, significant improvements in Minnesota score and B-type natriuretic peptide (BNP) level were seen in the ablation group as well as a non-significant trend towards benefit in 6-minute walk distance and LVEF.
AF ablation for HFrEF

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those randomised to ablation had 81% freedom from recurrent AF off AADs and improved LVEF, peak oxygen consumption and Minnesota score compared with the rate control arm. In the Ablation versus Amiodarone for Treatment of Persistent Atrial Fibrillation in Patients with Congestive Heart Failure and an Implanted Device (AATAC) trial, Di Biase et al. randomised 203 patients with persistent AF, dual-chamber or biventricular implantable cardioverter defibrillator (ICD) and HFrEF (LVEF ≤40% and NYHA class II–III) to ablation versus amiodarone. The primary endpoint was AF recurrence and secondary endpoints were all-cause mortality and unplanned hospitalisations. Despite a wide range of single-procedure success rates between centres (29–61%), those randomised to ablation were more likely to be in sinus rhythm after single and multiple procedures. Over 2 years of follow-up, the ablation group had lower rates of hospitalisation (31 versus 57%, p<0.001) and mortality (8 versus 18%, p=0.037) compared with those randomised to amiodarone. In the Catheter Ablation versus Medical Rate Control in Atrial Fibrillation and Systolic Dysfunction (CAMERA-MRI) trial, Prabhu et al. randomised 68 patients with persistent AF and LVEF ≤45% to ablation versus rate control and found that the ablation group were more likely to have improved LVEF. They also demonstrated that absence of late gadolinium enhancement on pre-procedural MRI predicted greater improvement in LVEF and normalization of LVEF at 6 months. Catheter Ablation versus Standard Conventional Treatment in Patients with Left Ventricular Dysfunction and Atrial Fibrillation (CASTLE-AF) is the most recent randomised controlled trial, where patients with paroxysmal or persistent AF (LVEF <35%) and ICD (with home monitoring capability) were randomised to either ablation or conventional medical therapy for

### Table 1: Summary of Observational Studies of AF Ablation in Patients with Heart Failure with Reduced Ejection Fraction (HFrEF)

| Study          | Sample size (ablation group) | Comparison arm | Mean LVEF (%) | Follow-up (months) | Single procedure success (%) | Multiple procedure success (%) | Improvement in LVEF (%) | Other comments                        |
|----------------|-------------------------------|----------------|---------------|--------------------|-----------------------------|-------------------------------|-------------------------|---------------------------------------|
| Chen 2004†*    | 377 (94)                      | Normal LVEF controls | 36            | 14                | 52                          | 73                           | +5                     | Improved QOL                          |
| Hsu 2004†*     | 116 (58)                      | Normal LVEF controls | 35            | 12                | 50                          | 78                           | +22                    | Improved QOL, exercise capacity, LV dimensions |
| Tondo 2006‡    | 105 (40)                      | Normal LVEF controls | 33            | 14                | 55                          | 87                           | +13                    | Improved QOL                          |
| Gentlesk 2007‡ | 366 (67)                      | Normal LVEF controls | 42            | 20                | 55                          | 86                           | +14                    |                                      |
| Efremidis 2008‡ | 13 (13)                       | –               | 36            | 9                 | 62                          | –                            | +16                    | Improved LV dimensions                 |
| Nadamanee 2008‡ | 129 (129)                     | –               | 31            | 27                | 58                          | 79                           | +10                    |                                      |
| Lutomsky 2008‡ | 70 (18)                       | Normal LVEF controls | 41            | 6                 | 50                          | –                            | +10                    |                                      |
| De Potter 2010‡ | 72 (36)                       | Normal LVEF controls | 41            | 16                | 50                          | 64                           | +8                     |                                      |
| Choi 2010‡     | 30 (15)                       | HF treated medically | 37            | 16                | 46                          | 73                           | +13                    |                                      |
| Cha 2011‡      | 368 (111)                     | Normal LVEF, diastolic dysfunction controls | 35            | 13                | –                            | 75                           | +21                    |                                      |
| Anselmino 2013‡ | 196 (196)                     | –               | 40            | 46                | 45                          | 62                           | +10                    | Improved LV dimensions and mitral regurgitation |
| Calvo 2013‡    | 658 (97)                      | Normal LVEF controls | 40            | 6                 | 70                          | 83                           | +12                    |                                      |
| Nedmos 2014‡   | 138 (69)                      | Normal LVEF controls | 31            | 28                | 40                          | 65                           | +15                    |                                      |
| Kosiuk 2014‡   | 73 (73)                       | –               | 37            | 40                | 37                          | –                            | +4                     | Reduction in ICD therapies             |
| Lobo 2015‡     | 31 (31)                       | –               | 45            | 20                | 51                          | 77                           | +14                    |                                      |
| Bunch 2015‡    | 2403 (267)                    | Matched HFrEF with AF but ablation; and HFrEF with no AF | 27            | 60                | 39                          | –                            | +16                    | Reduction in death and hospitalisation |
| Rillig 2015‡   | 80 (80)                       | –               | 35            | 72                | 35                          | 57                           | +21                    |                                      |
| Kato 2016‡     | 18 (18)                       | –               | 26            | 21                | 11                          | 61                           | +11                    |                                      |
| Yanagisawa 2016† | 54 (54)                      | –               | 39            | 6                 | 65                          | 65                           | +10                    | Reduction in BNP                      |
| Ullah 2016‡    | 1273 (171)                    | Normal LVEF controls | 34            | 43                | 26                          | 65                           | +12                    | Reduction in cardiac death             |

*BNP = B-type natriuretic peptide; ICD = implantable cardioverter defibrillator; LVEF = left ventricular ejection fraction; QOL = quality of life. Adapted and modified, with permission, from Verma et al. 25

for HFrEF

TABLE 1: Summary of Observational Studies of AF Ablation in Patients with Heart Failure with Reduced Ejection Fraction (HFrEF)
The primary endpoint was a composite of all-cause mortality and unplanned hospitalisation for worsening HF. Over median follow-up of 37.8 months, those randomised to ablation were significantly less likely to experience the composite primary endpoint (28.5 % versus 44.6; HR 0.62, 95 % CI [0.43–0.87]; p=0.007) than controls. Those in the ablation group were also less likely to meet the secondary endpoints of all-cause mortality (13.4 % versus 25 %; HR 0.53, 95 % CI [0.32–0.86]; p=0.011) or HF hospitalisation (20.7 % versus 35.9 %; HR 0.56, 95 % CI [0.37–0.83]; p=0.004) than controls.

Table 2 summarises the major randomised controlled trials comparing catheter ablation with medical therapy.

### Meta-analyses of AF Ablation in Heart Failure with Reduced Ejection Fraction

A number of meta-analyses have examined the benefit, efficacy and safety of catheter ablation for patients with HFrEF, all of which have suggested AF ablation to be safe, effective and beneficial in this patient population. Anselmino et al. pooled data for 1,838 patients from 26 studies (randomised controlled trials, clinical trials and observational studies) and found that over mean follow-up of 23 months, there was a 4.2 % complication rate and 60 % of patients maintained sinus rhythm over long-term follow-up. AF ablation resulted in significant improvement in LVEF (13 %) and reduction in BNP (620 pg/ml). Wilton et al. included eight studies of 1,851 patients in their meta-analysis comparing efficacy and safety of AF ablation in patients with reduced versus normal left ventricular systolic function. Freedom from recurrent AF after a single procedure was achieved in 28–55 % of patients with HFrEF, although allowing for multiple procedures, this number increased to 64–96 % (mean 1.4 procedures). There was no difference in rates of complications between groups and there was an 11 % improvement in LVEF in patients in the HFrEF group after AF ablation.

### Conclusion

Significant interplay exists between AF and HFrEF. Catheter ablation can be safely performed and is effective in maintaining sinus rhythm in patients with HFrEF, although multiple ablations may be necessary to achieve long-term freedom from AF. Successful ablation may result in improved LV function, clinical heart failure status and quality of life, as evidenced by lower BNP levels and improved peak oxygen consumption, Minnesota score and 6-minute walk distance. As such, AF ablation should be considered as an adjunctive treatment strategy for patients with HFrEF.
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