Treatment of Patients With Atrial Fibrillation and Heart Failure With Reduced Ejection Fraction

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ABSRACT: Atrial fibrillation (AF) and heart failure with reduced ejection fraction (HFrEF) frequently coexist, and each complicates the course and treatment of the other. Recent population-based studies have demonstrated that the 2 conditions together increase the risk of stroke, heart failure hospitalization, and all-cause mortality, especially soon after the clinical onset of AF. Guideline-directed pharmacological therapy for HFrEF is important; however, although there are various treatment modalities for AF, there is no clear consensus on how best to treat AF with concomitant HFrEF. This in-depth review discusses the available data for the treatment of AF in the setting of HFrEF, focuses on areas where more investigation is necessary, examines the clinical implications of randomized and observational clinical trials, and presents suggestions for individualized treatment strategies for specific patient groups.

Almost 2 decades ago, AF and heart failure (HF) were declared the "two new epidemics of cardiovascular disease."[1] Unfortunately, factors have led to steady growth rather than abatement of these intertwined conditions. The aging of the population, improvements in monitoring for more accurate detection of AF, and the epidemic of obesity in developed nations have led to a much higher-than-expected contemporary prevalence of AF.[2] Recent estimates project 12.1 million Americans will have AF and 8 million will have HF by 2030,[3,4] resulting in enormous healthcare expenditures and human suffering.

This international in-depth review will explore the pathophysiologic interconnection of AF and HFrEF, available AF therapy strategies, and data from randomized controlled trials to examine the impact of AF therapy. Special attention to limitations in our present knowledge and clinical recommendations in recognition of the absence of secure data will also be discussed.

ASSOCIATION BETWEEN AF AND HFREF

AF and HFrEF, at surface, share many fundamental predisposing risk factors, such as hypertension, diabetes mellitus, ischemic and valvular heart disease, and a predilection for increased incidence in the elderly, as well. Even more interesting is how AF and HFrEF collaborate to promote each other (Figure 1); deeper mechanistic understanding of these underlying pathways may eventually be helpful in disease prevention.

AF can facilitate the development of HFrEF by several mechanisms. The increase in resting heart rate shortens diastolic filling time that may result in a reduction in cardiac output. The irregular ventricular response results in a 25% reduction in car-

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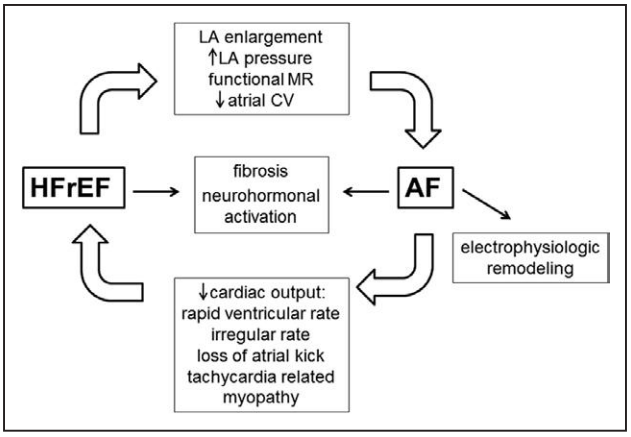

Figure 1. Known relationships between atrial fibrillation and heart failure that contribute to a vicious cycle.
AF indicates atrial fibrillation; CV, conduction velocity; HFrEF, heart failure with reduced ejection fraction; LA, left atrial; and MR, mitral regurgitation.

diac output[5,6] because filling during long cycles does not sufficiently compensate for the reduced filling in short cycles. The loss of atrial contribution to ventricular filling is also detrimental, at least conceptually. At issue is whether atria that are destined to fibrillate have already lost the potential for meaningful contractile function. It is theoretically possible that adaptation to AF may improve atrial reservoir and conduit function to compensate, but these functions may also deteriorate during AF, particularly in light of progressive atrial fibrosis.[7] In addition, AF-induced reduction in cardiac output leads to increases in plasma epinephrine and endothelin, augmenting the typical neurohormonal vasoconstrictor excess observed in HF.[8–10] AF can cause functional mitral annular enlargement with resultant mitral regurgitation, even in patients without structural heart disease.[11] Finally, AF may result in tachycardia-related cardiomyopathy, which in its full-blown form is related to rapid ventricular rates during AF and is reversible with appropriate rate control therapy.[12–14] Several observations suggest that a subtle form of tachycardia-related cardiomyopathy and a contribution of the hemodynamic effects described above are much more frequent, evidenced by improvement in left ventricular function after successful AF ablation, even in patients with reasonable rate control before ablation.[15,16]

HFrEF can promote the development of AF through structural, ultrastructural, and neuroendocrine processes. In human patients, HF exerts a prominent effect on atrial structure, with left atrial (LA) enlargement, increased LA pressure, and functional mitral regurgitation.[17] LA voltage abnormalities are recorded in patients with persistent AF which are most prominent in areas associated with high atrial stress.[18] The stress induced by structural changes, and the vasoconstrictive neurohormonal milieu of HF, as well, produce atrial fibrosis,[19,20] which has been shown to be ameliorated in animal models by angiotensin II–converting enzymes, and as other antifibrotic and anti-inflammatory agents, as well.[21–23] All these changes are not only profibrillatory, but cumulative and progressive.

IS AF AN INDEPENDENT RISK OF POOR OUTCOME IN HFREF?

Whether AF is merely a marker for more advanced HF or an independent risk factor for increased mortality and hospitalization remains controversial. Most, but not all[24] randomized trials concluded that the increased mortality in patients who have HF with AF was negligible after adjusting for risk factors. A meta-analysis of legacy HF trials (randomized and observational) involving 53 969 patients in 16 studies demonstrated a significant adverse effect of the presence of AF in HF with preserved, and reduced ejection fraction, as well, but the effect was mild (adjusted odds ratio 1.40 in the randomized studies, 1.14 in the observational studies).[25] As we suggested in a prior review,[26] some of this confusion is caused by considering AF and HFrEF as generic entities, ie, without sufficient adjectives to distinguish different populations. The first-level adjectives include prevalent and incident for AF and HF with reduced or preserved left ventricular function (HFrEF and heart failure with preserved ejection fraction [HFpEF], respectively). In addition, the dose of AF (ventricular response, episode duration) and HFrEF (defined by functional status or ejection fraction) undoubtedly matters greatly. It is reasonable to suggest that rapid, incident AF would have more impact on a patient with class III to IV HFrEF than would rate-controlled persistent AF in a patient with class II HFrEF. This point is illustrated in a study by Pozzoli and colleagues, who did repeated hemodynamic studies on 28 patients (of 354 who had been evaluated for heart transplantation in sinus rhythm) soon after onset of AF.[27] Using patients as their own controls, with onset of AF functional class worsened (2.4±0.5–2.9±0.6), peak oxygen consumption decreased (16±5–11±5 mL/kg per min), cardiac output decreased (2.2±0.4–1.8±0.4), and mitral and tricuspid valve regurgitation increased. This resonates with the observation that mortality is increased with the onset of AF even in the general population, but levels off after 4 months.[28]

Several recent studies have clarified the impact of incident AF in patients with HF. A post hoc analysis of the MADIT II study (Multicenter Automatic Defibrillator Trial II), demonstrated that after adjustment for age, New York Heart Association class, renal function, and use of β-blocker, prevalent AF was not associated with mortality.[29] However, among 1007 patients in sinus rhythm at enrollment, 58 (6%) had ≥1 episodes of AF during follow-up. Patients with incident AF were older and had markers consistent with significantly more advanced structural

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heart disease. Nonetheless, multivariate Cox analysis demonstrated that new-onset AF had an increased risk of all-cause mortality (hazard ratio, 2.70) and HF hospitalization (hazard ratio, 2.05). A community-based study of 1664 patients with HF evaluated with risk of all-cause mortality in patients who developed AF before (prevalent) versus after(incident) the diagnosis of HF[30]; this study considered the clinical diagnosis of HF without distinction between HFpEF and HFrEF. In risk-adjusted models, in comparison with patients with HF and no AF, patients with prevalent and incident AF had a greater risk of all-cause mortality (hazard ratio, 1.22 and 2.29, respectively). A detailed analysis of AF timing on the prognosis of subtypes of HF was performed on 10 333 patients in the Framingham cohort (1980–2012),[31] strengthening the relationship between AF and HF demonstrated in a prior analysis.[32] Among 1737 individuals with new AF, 37% had HF. Patients with prevalent HFrEF and incident AF incurred a hazard ratio for all-cause mortality of 2.72, higher than those with HFpEF and those without HF (Figure 2).

The difference in impact of prevalent and incident AF is probably multifactorial. A population of patients with established AF may represent a preselected survivor group, with an artificially reduced risk of poor outcome in comparison with patients with new-onset AF. It may be that adaptive processes or improvements in rate control over time have an important impact. In the past, the ill-advised (in retrospect) use of class Ia antiarrhythmic drugs and less than judicious dose adjustment of warfarin at the onset of AF may have falsely inflated early risk in patients with new-onset AF.

In summary, AF and HFrEF commonly coexist, and incident AF has a profoundly negative effect on mortality and hospitalization in HFrEF. It would certainly appear that the optimal time for intervention in patients with HFrEF is early after AF onset.

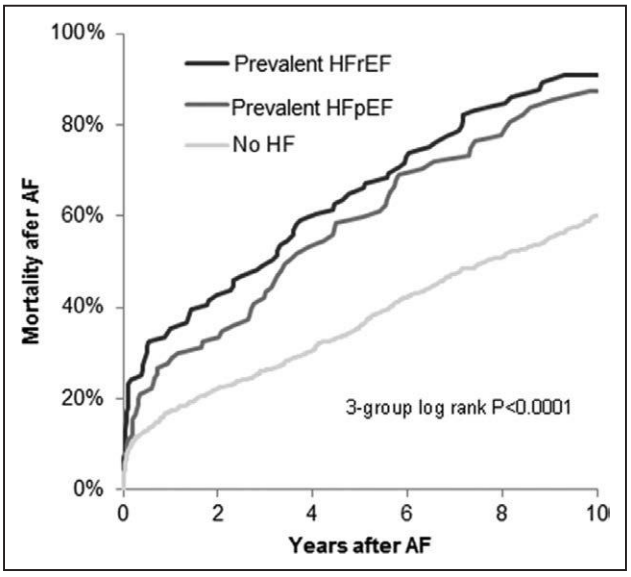

Figure 2. Incidence of all-cause mortality of new-onset atrial fibrillation stratified by heart failure status. New-onset AF has a marked effect on patients with both HFrEF and HFpEF, much greater than observed in patients without heart failure. AF indicates atrial fibrillation; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; and HFpEF, heart failure with preserved ejection fraction. Reprinted from Santhanakrishnan et al[31] with permission of the publisher. Copyright © 2016, American Heart Association, Inc.

MEDICAL MANAGEMENT OF AF AND HFREF

Guideline-Directed Medical Therapy for HFrEF

There is no compelling evidence to suggest that usual pharmacological therapy for the treatment of HFrEF would not naturally extend to patients with concomitant AF. Nonetheless, 1 meta-analysis suggested that β-blockers, the cornerstone of guideline-directed medical therapy, were not as helpful in patients with AF as those without.[33] However, in legacy pharmacological trials of HF therapy, patients with AF are typically older, have more comorbidities and longer duration of HF symptoms, all of which may dampen their response to interventions. This observation does demonstrate the lack of data regarding the specific effect of guideline-directed medical therapy for HFrEF for patients with AF. On the other hand, retrospective analyses of large randomized trials have demonstrated that angiotensin-converting enzyme inhibitors,[34,35] angiotensin II receptor blockers,[36,37] β-blockers,[38] and eplerenone[39] all reduce the rate of incident AF in patients with HFrEF.

AF, HFrEF, and Anticoagulation

By definition, the presence of HF in an AF patient represents 1 point under the CHA2DS2-VASc scoring system. The European guidelines recommend an oral anticoagulant for any AF patient with a score of ≥1 with the exception of those whose only risk factor is female sex.[40] In the American guidelines, this recommendation is less prescriptive; a score of 1 allows no anticoagulation, aspirin, or an oral anticoagulant.[41] McMurray et al[42] evaluated the risk of stroke or systemic embolism attributable to HF in the ARISTOTLE trial (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation). The incidence of embolic events was highest in patients with HFrEF, intermediate for HFpEF, and lowest in patients without HF or reduced left ventricular (LV) function. Embolic events were less frequent in patients treated with apixaban in comparison with warfarin in each of the 3 groups. However, a systematic review and meta-analysis of trials comparing AF and HF attributable to reduced versus preserved ejection fraction found a similarly increased stroke rate in patients with HF who have reduced in comparison with preserved

ejection fraction.[43] An analysis of patients with symptomatic HF in the RE-LY trial (Randomized Evaluation of Long-term Anticoagulant Therapy) also observed that these patients had a higher annual embolic event rate than patients without HF.[44] The improved efficacy of dabigatran over warfarin on the occurrence of embolic events was consistent among those with and without HF and those with low or preserved ejection fraction. It is reasonable to support the recommendation to prescribe oral anticoagulants to patients with AF and HF irrespective of the presence of other risk factors.

Risk Factor Management for AF Control

In recent years, there has been an increasing focus on the relationship between AF and obesity, recently described as twin epidemics.[45] Epidemiological data have demonstrated that overweight and obese populations have a higher prevalence of AF and are more likely to progress from paroxysmal to persistent forms of the arrhythmia.[46–49] Similarly, epidemiological studies have also shown that weight change results in alteration of AF risk, suggesting this as an important treatment target.[47] Excess pericardial fat has been implicated as 1 possible mechanistic link between obesity and AF that no doubt is multifactorial.[50–52] Studies of weight loss have shown not only reductions in pericardial fat, but also accompanying reduction in atrial size, improvements in atrial mechanical function, and improvements in electrophysiological substrate.[53] These data indicate that atrial remodeling in response to obesity may in part be reversible. Recent clinical outcome studies have demonstrated the positive impact of weight loss on AF burden and progression. A randomized study of weight loss and risk factor management in AF patients with body mass index>27 and elevated waist circumference demonstrated a significant reduction in overall AF burden in the cohort who had risk factors aggressively managed in a specialized risk factor management clinic.[54] Observational studies have also demonstrated a highly significant reduction in AF recurrences following AF ablation in an overweight and obese cohort undergoing the same specialized risk factor management.[53,55] In particular, AF burden was specifically related to magnitude and maintenance of weight loss. A prospective randomized trial of risk factor management in AF ablation patients with body mass index>27 is ongoing, and, as yet, the role of weight loss in this population remains incompletely defined. It is also unclear to what extent improvements in AF burden are related directly to weight loss or to improvements in related risk factors such as hypertension, sleep apnea, diabetes mellitus, and increasing exercise.

Although numerous studies have demonstrated that the prevalence of HF is markedly increased in obesity, other studies have demonstrated that patients who are overweight or obese with HF have a better prognosis than their normal-weight counterparts: the so-called obesity paradox.[56–59] Although there are data demonstrating that weight loss can improve symptoms in patients with HF, there are no large studies that have demonstrated that weight loss can reduce clinical events and improve mortality in this population.[58] This therefore provides a note of caution and uncertainty when considering weight loss strategies in the obese patient with AF who also has HF. Further studies are required.

There is also emerging evidence that treatment of other risk factors including hypertension and obstructive sleep apnea may also be important for the long-term maintenance of sinus rhythm. Continuous positive airways pressure therapy in patients with obstructive sleep apnea has been shown to reduce the risk of postablation AF recurrence to the same level as patients without obstructive sleep apnea.[60,61] Conversely, ablation outcomes in patients with untreated obstructive sleep apnea were similar to patients who had not undergone ablation in the first place. There is also increasing evidence demonstrating the beneficial effects of antihypertensive therapies in reducing incident and recurrent AF in hypertensive patients with a focus on tighter systolic blood pressure control.[62–64] However, whether modification of risk factors reduces AF in a HF population is as yet unclear.

Strict or Lenient Pharmacological Rate Control in AF/HFrEF?

No single study has primarily addressed this question. The RACE II trial (Rate Control Efficacy in Permanent Atrial Fibrillation: A Comparison Between Lenient Versus Strict Rate Control II) randomly assigned patients with persistent AF to either lenient or strict heart rate control and found no difference in the primary composite end point of death from cardiovascular causes, hospitalization for HF, and stroke, systemic embolism, bleeding, and life-threatening arrhythmic events.[65] There was also no difference in symptoms. Importantly, however, there was no requirement for symptom severity as an inclusion criterion in the study and fully two-thirds of the patients in the study were entirely asymptomatic. In addition, the resting heart rate achieved in both groups only differed by 10 bpm as the mean resting heart rate of the lenient group was 85 bpm, well below the 110 bpm permitted in the study design.

A post hoc analysis of RACE II focused on those patients with AF and HF.[66] This was defined broadly and included both HFrEF (ejection fraction [EF]<40%) and HFpEF. Only a minority of patients had reduced EF. Similarly, there was no evidence of benefit in terms of cardiovascular morbidity and mortality, symptoms, or quality of life in the strict rate control group. In contrast, the Swedish Heart Failure Registry demonstrated that

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patients with AF-HF had greater mortality when resting heart rate was >100 bpm, and that the use of β-blockers was associated with improved survival.[67]

The American College of Cardiology/American Heart Association guidelines 2014 state that a "Lenient rate control strategy (resting heart rate <110 bpm) may be reasonable (but only) in asymptomatic patients and when LV systolic function is preserved."[41] (class IIB recommendation, level of evidence B). Although no prospective pharmacological study has addressed the common clinical scenario of the patient with persistent AF-congestive heart failure (CHF) who becomes symptomatic on minor exertion from an inappropriate increment in heart rate, insights may nevertheless be gained from the pace and ablate literature. As identified elsewhere in this article, this strategy results in significant symptom improvement and increments in LV function suggesting a significant component of tachycardia-mediated cardiomyopathy most apparent in the idiopathic dilated group.[68] For symptomatic patients with poor rate control, a lenient approach to heart rate control therefore seems inappropriate. For symptomatic patients in whom pharmacological rate control is either ineffective or associated with intolerable side effects, a pace and ablate strategy should be considered.

POORLY CONTROLLED AF AND TACHYCARDIA-MEDIATED CARDIOMYOPATHY

These data beg the question; why do some patients with LV dysfunction have improvements in EF but others have a deterioration in their EF in response to the ablate and right ventricular (RV) pace strategy. Although not entirely clear, this may relate in part to the nature of the underlying cardiomyopathy. In particular, those patients with LV dysfunction primarily on the basis of a tachycardia-mediated cardiomyopathy seem most likely to improve when rate is controlled with atrioventricular (AV) node ablation even in the presence of RV apical pacing only.[69] The prevalence of tachycardia-mediated cardiomyopathy in AF remains uncertain, but early studies of patients undergoing atrioventricular node ablation have suggested that tachycardia-mediated cardiomyopathy may be present to some degree in 25% to 50% of patients.[70,71] Other studies have demonstrated that patients with LV dysfunction and no late gadolinium enhancement on MRI show significantly more improvement in LV function following successful AF ablation than do patients who do have late gadolinium enhancement.[72]

INTERVENTIONAL MANAGEMENT OF AF IN HFREF: RATE CONTROL

AV node ablation was the original interventional procedure for patients with medically refractory AF with or without HF; for many years, AV node ablation with RV apical pacing was used in this population with good reported outcomes.

Improvement in LV Function With Ablate and RV Pace

Wood et al[68] performed a meta-analysis of 21 studies with a total of 1181 patients to clarify clinical outcomes and survival after AV node ablation and RV pacing in patients with medically refractory AF. The study demonstrated significant improvements in a range of measures including quality of life, exercise duration, and healthcare use. In addition, there was a significant improvement in EF across a population that included both patients with and without LV systolic dysfunction. Sudden death and total mortality rates were low at 1 year of follow-up. In a longer-term follow-up study, Ozcan et al[73] found no increase in mortality associated with an AV node ablation and RV pacing strategy.

LV Impairment as a Consequence of Chronic RV Pacing

Despite the improvements demonstrated in LV function in these earlier studies of patients with uncontrolled AF, more recent studies of patients with device indications but no AF have demonstrated that LV function may deteriorate under the influence of RV apical pacing.[74–77] RV apical pacing has been described to have adverse effects on myocardial metabolism and perfusion with negative impact on LV remodeling; the net effect is reduction in hemodynamic function associated with mechanical dyssynchrony.[78–80] Several clinical studies demonstrated that atrial-based pacing was superior to RV pacing for long-term risk of HF.[74,81,82] In view of the potential for long-term deleterious effects of RV pacing on LV systolic function, the approach of AV node ablation and RV pacing in patients with AF and HF has fallen into disrepute.

AV Node Ablation and Resynchronization Therapy

The advent of resynchronization therapy has facilitated a comparison of biventricular pacing with RV-only pacing in patients with reduced EF and heart block. In the BLOCK HF trial (Biventricular versus Right Ventricular Pacing in Heart Failure Patients with Atrioventricular Block), patients with AV block and reduced EF had improved outcomes when undergoing biventricular in comparison with RV-only pacing.[83]

In the context of improved outcomes with biventricular pacing, the PABA CHF study (Pulmonary Vein Antrum Isolation vs. AV Node Ablation with Bi-Ventricular Pacing for Treatment of AF in Patients with Congestive HF) randomly assigned patients with symptomatic, drug-resistant AF,

an EF of ≤40% or less, and New York Heart Association class II or III HF to undergo either pulmonary vein isolation (n=41) or AV node ablation with biventricular pacing (n=40).[84] At 6 months follow-up, patients who underwent AF ablation in comparison with to the biventricular pace and ablate strategy had a significant improvement in the composite primary end point of quality of life, LV function, and 6-minute walk. The follow-up in this study of only 6 months is particularly short when considering long-term recurrence rates after AF ablation in a HF population. Indeed, the long-term rate of sinus rhythm maintenance in AF ablation patients with HF is disappointing with multiple procedure success rate at 2 years of ≈60% in 1 study.[85] Furthermore, it is unclear whether those patients who underwent pace and ablate had poor AF rate control because this was not an inclusion criterion. Those patients with AF and good rate control might be expected to derive less symptomatic benefit from a pace and ablate approach.

A considerable body of literature exists demonstrating the clinical and possible mortality benefit of an ablate and biventricular pacing strategy in patients with AF and CHF. A systematic review of AV node ablation in cardiac resynchronization therapy (CRT) patients with AF and CHF evaluated outcomes in 768 patients.[86] This included 339 CRT patients who underwent AV nodal ablation and 429 CRT patients treated with medical therapy aimed at rate control alone. Compared with medical therapy, AV nodal ablation in CRT-AF patients was associated with significant reductions in all-cause mortality and cardiovascular mortality, and improvement in mean New York Heart Association functional class. Sohinki et al[87] compared outcomes between patients with nonischemic versus ischemic cardiomyopathy following AV node ablation and biventricular pacing in AF patients with rapid ventricular response rates. They observed a significant improvement in EF in the patients with dilated cardiomyopathy (11.2%) but no improvement in EF in the ischemic cardiomyopathy patients (0.5%). Heart failure hospitalizations were also significantly less in the dilated cardiomyopathy group than in the ischemic cardiomyopathy group. This study suggests that, in patients presenting with poorly controlled AF and an apparent dilated cardiomyopathy, a tachycardia-mediated reduction in EF may be an important factor. However, tachycardia-mediated cardiomyopathy is less likely to be an important factor in patients with impaired LV function attributable to coronary artery disease.

According to the 2012 American College of Cardiology Foundation/American Heart Association/Heart Rhythm Society Focused Update of the 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities, CRT can be useful in patients with AF and LVEF ≤35% on guideline-directed medical therapy if (a) the patient requires ventricular pacing or otherwise meets CRT criteria and (b) AV nodal ablation or pharmacological rate control will allow near 100% ventricular pacing with CRT.[88] This is a class IIA recommendation, level of evidence B.

A recent opinion piece has suggested that AV node ablation and pacing as a rate control strategy should "be restricted until, and only if, it is absolutely necessary. Before doing so, catheter ablation of AF always should be considered."[89] Although we do not disagree with these statements, we also believe that some further qualification is necessary. In older patients with significant atrial enlargement, LV dysfunction, and comorbidities, consideration of AF ablation may be inappropriate for many. Indeed, many such patients are already in permanent AF at the time of referral. In these patients with ongoing symptoms because poor and varied rate control, and in the presence of drug side effects, excellent data exist demonstrating the considerable clinical benefits and safety of pacing and AV node ablation.

MANAGEMENT OF AF IN HFREF: RHYTHM CONTROL

It is clear that AF is associated with adverse outcomes in patients with HF, but the benefit of maintaining sinus rhythm in patients with both AF and HF has never been clearly established by large randomized trials.

Does Pharmacological Rhythm Control Improve Outcomes?

The 2 largest trials to evaluate the potential benefit of rhythm control over rate control in patients with HF are the AF-CHF trial (Atrial Fibrillation and Congestive Heart Failure)[54] and the DIAMOND-CHF trial (Danish Investigators of Arrhythmia and Mortality on Dofetilide in Congestive Heart Failure).[51] In AF-CHF[54] (n=1376) patients were randomly assigned to either rhythm control or rate control. More than 80% of the patients received amiodarone, and, after a median of 47 months, 73% of patients were in sinus rhythm in the rhythm control arm versus ≈35% in the rate control arm. There was no difference in cardiovascular mortality between the groups. In fact, hospitalizations for AF were significantly higher in the rhythm control arm (14% versus 9%, P=0.001). In DIAMOND-CHF,[51] 1518 patients were randomly assigned to dofetilide or placebo. At the end of follow-up, ≈65% of patients were in sinus rhythm in comparison with ≈30% in the placebo arm, and there was no difference in mortality. It should be noted that the comparison arm in DIAMOND was placebo and not a specific rate control strategy. Only 12% of patients were receiving β-blockers at baseline in DIAMOND as opposed to >80% in AF-CHF (both arms). So part of the reduction in hospitalization seen with dofetilide in DIAMOND may have been mediated by less than optimal rate control in the placebo arm.

Both studies performed a subanalysis comparing the outcome of patients in sinus rhythm in comparison with those patients that remained in AF.[58,81] Both substudies

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have the limitation of having only intermittent ECGs to assess whether a patient is in sinus or not. In the case of AF-CHF, a proportion of time in sinus rhythm was calculated based on the rhythm status of 2 consecutive ECGs. Neither rhythm control nor presence of sinus rhythm was associated with any benefit in cardiovascular mortality. There was not even any benefit of sinus rhythm for prevention of worsening HF. In contrast, the DIAMOND substudy[81] showed that patients who maintained sinus rhythm had lower mortality than those who did not (risk ratio, 0.44; 95% confidence interval, 0.30–0.64; $P<0.0001$) and also had lower rates of hospitalization for HF. Again, differences in the comparator arm (placebo versus rate control) may partially explain these results.

Unfortunately, antiarrhythmic options are limited in HFrEF patients. Current guidelines state that dofetilide and amiodarone are the only antiarrhythmic medications that can be used in patients with HFrEF.[41] Importantly, class I drugs and dronedarone are contraindicated in HFrEF patients. Although both dofetilide and amiodarone are safe and effective in HF patients, dofetilide requires hospital admission for dosing to avoid torsades de pointes, and amiodarone is associated with a high discontinuation rate.[90] Treatment with amiodarone has also been suggested to increase mortality from noncardiac causes,[91] although no increase in noncardiac mortality was seen in the amiodarone arm of AF-CHF. Toxicity from amiodarone could also potentially be mitigated by using the smallest effective dose. Even doses as small as 100 mg daily can prevent AF, so the dose of amiodarone should always be reevaluated and minimized when feasible.

It should also be added that neither AF-CHF nor DIAMOND had specific inclusion criteria that indicated symptomatic deterioration in response to AF development. Therefore, neither of these trials addressed the common clinical issue of the HF patient who decompensates with the development of persistent AF. For these patients, more aggressive attempts to maintain sinus rhythm, including catheter ablation, may be warranted. The 2016 European Society of Cardiology Guidelines for the management of AF state that "Rhythm control therapy is indicated for symptom improvement in patients with AF." (class I indication).[40] When the impact of AF is less certain, a trial of cardioversion accompanied by drugs to evaluate impact on clinical symptoms is 1 approach to determine which patients are likely to derive the most benefit from more aggressive attempts to maintain sinus rhythm.

CAN CATHETER ABLATION OF AF IN HF DO BETTER?

Although AF-CHF and DIAMOND create justified skepticism on whether maintaining sinus rhythm can improve outcomes in patients with AF and HF, their greatest limitation is in the limited ability of pharmacological therapy to maintain sinus rhythm. In both trials, sinus rhythm was seen in 65% to 70% of patients, and this was likely overestimated because none of these patients underwent any type of prolonged monitoring for AF beyond an ECG.[51,54] Furthermore, 30% to 35% of patients in the comparator group remained in sinus rhythm even without treatment, suggesting that antiarrhythmics had a limited benefit over placebo. Catheter ablation has emerged as an effective treatment for AF, and it may result in a freedom from AF recurrence 3 to 4 times greater than that of antiarrhythmics, particularly for patients who are resistant to antiarrhythmics.[41,56,74] Thus, there has been great interest in reevaluation of the benefits of sinus rhythm in HF by using catheter ablation as an alternative to antiarrhythmic drug therapy.

Observational Studies

To date, most of the data assessing catheter ablation of AF in HFrEF patients have come from small nonrandomized, single-center studies with very limited follow-up. Table 1 summarizes all the nonrandomized studies published to date.[15,16,85,92–108] Most of these studies were quite small (<100 patients), but consistently demonstrated significant improvements in EF following successful ablation (average +13%). This improvement is very substantial given that angiotensin-converting enzyme inhibitors and other pharmacological therapies in HF demonstrated EF changes closer to 5% and yet were associated with mortality reduction. Furthermore, most of these patients had a history of persistent AF. Four of these studies also demonstrated improvements in quality of life and functional capacity,[15,92,93,99] and one showed that inappropriate shocks from an implantable cardioverter defibrillator could be reduced.[102] There are obviously some very important limitations to these data. Only 1 study reported on a reduction in mortality and hospitalization in comparison with matched controls,[108] but none of these trials were sufficiently powered to show a reduction in hard end points like death. Although the average follow-up duration was >2.5 years, many studies followed patients for only 6 to 16 months. Importantly, the freedom from AF in these patients was poor after 1 procedure (48%), and about one-third of these patients required repeat ablation, which is quite consistent with data of other studies in persistent AF.[109,110] After repeated ablation, the reported freedom from AF was 75%, but routine monitoring for AF postablation was limited, so these results may be an overestimate of success. Studies were also split according to the technique of ablation, with about half using pulmonary vein isolation (PVI) and the other half using PVI plus some adjuvant ablation. Most importantly, the majority of these patients had nonischemic dilated cardiomyopathy. Ischemic cardiomyopa-

Table 1. Summary of Observational Studies of Catheter Ablation of Atrial Fibrillation in Patients With Heart Failure

	Sample Size	Age, y	NICM, %	Comparator Arm	LVEF	Follow-Up, mo	Single-Procedure Success, %	Multiprocedure Success, %	LVEF Improvement, %	Other Comments
Chen 2004[92]	377 (94)	56	20	Normal EF controls	36	14	52	73	+5	QoL improved
Hsu 2004[15]	116 (58)	56	55	Normal EF controls	35	12	50	78	+22	QoL, exercise capacity, LVD improved
Tondo 2006[93]	105 (40)	57	45	Normal EF controls	33	14	55	87	+13	QoL, exercise capacity improved
Gentlesk 2007[16]	366 (67)	54	82	Normal EF controls	42	20	55	86	+14	
Efremidis 2008[94]	13 (13)	54	62	None	36	9	62	NA	+16	LVD improved
Nademanee 2008[95]	129 (129)	67	NA	None	31	27	58	79	+10	
Lutomsky 2008[96]	70 (18)	56	83	Normal EF controls	41	6	50	NA	+10	
De Potter 2010[97]	72 (36)	52	50	Normal EF controls	41	16	50	64	+8	
Choi 2010[98]	30 (15)	56	67	HF treated medically	37	16	46	73	+13	
Cha 2011[99]	368 (111)	55	87	Normal EF and diastolic dysfunction controls	35	13	NA	75	+21	5-y success of ablation dropped to 33%
Anselmino 2013[85]	196 (196)	60	40	None	40	46	45	62	+10	LVD and MR improved
Calvo 2013[100]	658 (97)	53	63% were tachy-induced cardiomyopathy	Normal EF controls	40	6	70	83	+12	
Nedios 2014[101]	138 (69)	60	51	Normal EF controls	31	28	40	65	+15	
Kosiuk 2014[102]	73 (73)	59	59	None	37	40	37	NA	+4	Reduction in ICD therapies
Lobo 2015[103]	31 (31)	60	61	None	45	20	51	77	+14	
Bunch 2015[104]	2403 (267)	66	41	Matched low EF, no ablation, low EF no AF	27	60	39	NA	+16	Reduction in death and hospitalization
Rillig 2015[105]	80 (80)	62	65 (41% were tachy-induced cardiomyopathy)	None	35	72	35	57	+21	
Kato 2016[106]	18 (18)	55	44	None	26	21	11	61	+11	
Yanagisawa 2016[107]	54 (54)	60	78 (59% were tachy-induced cardiomyopathy)	None	39	6	9	35	+10	BNP levels significantly reduced
Ullah 2016[108]	1273 (171)	58	67	Normal EF controls	34	43	26	65	+12	Multicenter registry, reduced cardiac death

AF indicates atrial fibrillation; BNP, brain natriuretic peptide; EF, ejection fraction; HF, heart failure; ICD, implantable cardioverter defibrillator; LVD, left ventricular dimensions; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; NA, not available; NICM, nonischemic cardiomyopathy; QoL, quality of life; and tachy, tachycardia.

thy is overwhelmingly a more common cause for HFrEF in the developed world, so there is clearly a selection bias in the profile of these patients. It is likely that many of these patients had concomitant tachycardia-induced cardiomyopathy, explaining the dramatic improvement in EF. It is therefore far from clear that equivalent results would be obtained in other populations with HF.

One of the largest and the only multicenter observational study was recently published, which nicely illustrates the data from observational studies.[108] It included 1273 patients but only 171 had HF with the others as matched controls. Patients were quite young (mean age, 58 years), and almost two-thirds had persistent or long-standing persistent AF. Mean EF was 37%, and over two-thirds had nonischemic dilated cardiomyopathy. Single procedure freedom from AF was low (25.7%) and multiprocedure AF freedom was only 65%. After a follow-up of 3.6 years, New York Heart Association class improved by 1 point, and EF improved from 34% to 46% (median, 10 months postablation). The composite of death, cardiac death, and stroke was reduced by successful ablation in the HF group, although this was driven almost entirely by cardiac death. However, only 72% of patients were on a β-blocker and 84% on an angiotensin-converting enzyme inhibitor preablation, which are low given that these patients had HFrEF. In patients with persistent AF, HFrEF patients required more repeat procedures than patients without HF (mean, 2.05 procedures/patient) and >20% required >2 procedures. The complication rate from ablation was relatively high at 5%, with 2.5% tamponade and nearly 1% stroke/transient ischemic attack. Finally, it is interesting that those with ischemic cardiomyopathy had significantly lower improvement in EF (less than half) than those with dilated cardiomyopathy.

Meta-Analyses

There have been 5 meta-analyses performed of the observational trials on AF ablation in HF.[111–115] A range of 8 to 26 studies was evaluated with 354 to 1838 patients included. The single-procedure success rate of ablation ranges from 36% to 73% and the multiprocedure success ranges from 54% to 82%. Complications occurred in 4% to 7% of patients. The net improvement in EF was 11% to 13%. In 1 analysis, they found that the presence of coronary disease resulted in no improvement in EF.[112] Another analysis[114] also showed a net improvement in exercise capacity and quality of life. The most recent analysis showed that 55% of HF patients undergoing ablation in the studies received PVI alone, whereas the remaining patients received PVI plus substrate modification.[115] The majority of those receiving substrate modification received the so-called 7 scheme, whereas the remaining (<10%) received ablation of complex electrograms.

Randomized Trials

To date, there have only been 5 randomized trials assessing efficacy of AF ablation in HF patients (Table 2).[84,116–119] In contrast to the observational studies, all the patients received optimal HF medical therapy. However, with the exception of the recently published AATAC trial (Ablation vs. Amiodarone for Treatment of Atrial Fibrillation in Patients With Congestive Heart Failure and Implanted ICD/CRTD),[119] all included a very small number of patients. There is also some variability in the trial designs because 3 studies compared ablation with rate control,[116–118] 1 with AV nodal ablation and biventricular pacing,[84] and 1 with amiodarone.[119] Given this mixed picture, it is difficult to make any definitive conclusions on the benefits of catheter ablation.

Of the 3 studies comparing ablation with rate control, 2 demonstrated substantial improvement in EF as was seen in the observational studies.[117,118] They also went further by documenting a quantitative improvement in functional capacity through a significant improvement in peak oxygen consumption (+3–4 mL/kg per min) and the Minnesota HF quality-of-life score. In both studies, the freedom from AF achieved through ablation was impressive with 88% in ARC-AF[117] and 81% in Hunter et al[118] after ≥1 procedures and a low complication rate with 2 tamponades, 1 stroke, and no procedural deaths in both studies combined. More than two-thirds of the patients had a nonischemic etiology for HF. Follow-up was limited to 12 months in ARC-HF[117] and 6 months for Hunter et al,[118] and in the latter, the success rate for ablation decreased from 81% to 73% at 12 months, but analyses were only performed at 6 months. The third study failed to show any benefit to AF ablation in HF.[116] There was no improvement in EF as measured by cardiac MRI, 6-minute walk distance, or quality of life. Importantly, about half of the patients in this study had ischemic cardiomyopathy and less than one-third had dilated cardiomyopathy. The freedom from AF was also lower (50% at 1 year) with a high rate of major complications (15%). From these studies, it is clear that the HF population chosen, the success rate of ablation, and duration of follow-up can all have substantial impacts on trial results.

Rate control may not be the ideal comparator for many patients because the patients seeking ablation are often those believed to be very symptomatic from their AF. To date, only 1 study has compared ablation with another interventional strategy: AV nodal ablation and biventricular pacing.[84] This very small study showed substantial EF, quality-of-life, and 6-minute walk improvements associated with ablation, but follow-up was limited to 6 months. So the question of whether ablation would compare favorably with such alternative intervention remains an open question.

The recently published AATAC trial is the largest randomized trial of AF ablation in HFrEF (n=203) and is unique in many respects.[119] First, the comparator arm was attempted rhythm control with amiodarone. Sec-

Table 2. Summary of Randomized Trials of Catheter Ablation of Atrial Fibrillation in Patients With Heart Failure

	Sample Size	Age, y	NICM, %	Comparator Arm	LVEF, %	Follow-Up, mo	Single-Procedure Success, %	Multiprocedure Success, %	LVEF Improvement, %	Other Comments
Khan 2008[84]	81 (41)	60	27	AV nodal ablation + BIV pacing	27	6	68	88	+8	Improved 6MHW and Minnesota score
MacDonald 2011[116]	41 (22)	62	37	Medical rate control	36	12	40	50	+4	No difference vs rate control, high complication rate
Jones 2013[117]	52 (26)	63	73	Medical rate control	22	12	68	88	+11	Minnesota score, BNP, and peak oxygen consumption improved
Hunter 2014[118]	366 (67)	54	82	Medical rate control	42	20	38	81	+8	Minnesota score and peak oxygen consumption improved
Di Biase 2016[119]	203 (102)	62	38	Amiodarone	29	24	—	70	+8	1.4 procedures per patient, 6MHW, Minnesota score, hospitalization and death improved by ablation

6MHW indicates 6-minute hall walk; AV, atrioventricular; BIV, biventricular; BNP, brain natriuretic peptide; LVEF, left ventricular ejection fraction; and NICM, nonischemic cardiomyopathy.

ond, patients were followed up for 24 months. Third, the primary end point was recurrence of AF and not changes in EF or functional capacity. The freedom from AF achieved by ablation was impressive (70%) in comparison with amiodarone (34%). Unplanned hospitalization was also reduced by 45%, and even mortality declined by 56%, although these were secondary end points with very small numbers of actual events. Minnesota score, 6-minute walk test, and EF all significantly improved as well, but the mean change in EF was 8.1% for the ablation group, substantially less than reported for the observational studies. This may be related to the fact that the majority of patients (62%) had ischemic cardiomyopathy rather than dilated cardiomyopathy.

Unaddressed Questions

Although the results of AATAC are encouraging, we must exercise caution in interpreting secondary end points, and there remain several key, unaddressed questions in this field. First, do we know which technique of AF ablation is best? Most of the trials to date have used PVI in combination with additional linear and substrate modification (complex electrograms). Since the publication of STAR AF 2 (Substrate and Trigger Ablation for Reduction of Atrial Fibrillation Trial Part II),[109] the role of linear and complex electrogram ablation has been questioned, but it is still unclear if PVI alone can adequately treat persistent or long-standing persistent AF. The role of additional rotor and scar-based ablation also remains unclear.[120,121] Second, will the benefits of ablation apply to all subgroups of HF patients? Those with tachycardia-induced and dilated cardiomyopathy may be best suited to improve with the elimination of AF, but how much benefit can we expect in patients with ischemic cardiomyopathy and HFpEF? Patients with HFpEF, in particular, are often older, are predominantly female, and have multiple comorbidities.[122] Trials of ablation have rarely addressed the efficacy of

ablation in these patient groups, but limited data have suggested that these patients may be prone to higher rates of procedural complication.[123] Only select centers with high expertise and long experience can deliver AF ablation in these patients with reasonably low complication rates. Even if benefit can be demonstrated in a small trial, will operators ultimately take higher-risk patients for invasive treatment routinely and will these patients accept this option? Third, we need to have the most relevant comparator arms against which catheter ablation can be compared. Rate control is the current standard of care for many of these patients, but if trials fail to show a benefit for ablation, can we identify subgroups for whom ablation may be more relevant? There will always be a subset in whom rate control fails to control AF symptoms and improve HF. A better comparison arm for these patients may be alternative intervention such as antiarrhythmic therapy or AV nodal ablation and resynchronization. Last, will ablation be a cost-effective solution for HF patients? Ablation may out-perform medical therapy in the short term (1–2 years),[114] but we do not know if procedural success can be maintained in the long term as HF progresses and the substrate evolves. If patients require ongoing intervention, or if the efficacy of intervention falls over time, a short-term benefit may not be sufficient to justify the upfront cost of ≥1 ablations. It is not clear whether freedom from AF recurrence will be as durable in HF patients who have continuously progressing ventricular and atrial substrates. Ultimately, we need a variety of adequately powered, randomized trials with hard end points such as hospitalization and mortality. These trials must also have adequate follow-up to address whether ablation can achieve a reasonable freedom from AF over the long term. The ongoing trials in this area are summarized in Table 3 according to a search of Clinicaltrials.gov. Beyond these trials, CABANA (Catheter Ablation Versus Anti-arrhythmic Drug Therapy for Atrial Fibrillation Trial; NCT00911508) may also provide some valuable data on the performance of AF ablation in higher-risk patients, many of whom will also have concomitant HF.

CONCLUSIONS

In summary, the relationship between AF and HFrEF is clear. It is also apparent that, in many patients, AF causes symptomatic deterioration and may be associ-

Table 3. Ongoing Randomized Trials of Catheter Ablation of Atrial Fibrillation in Patients With Heart Failure

Trial	Clinicaltrials.gov Registration	Sample Size	Multicenter	Population	Comparator Arm	Primary End Point	Follow-Up, mo	Anticipated Completion	Other Comments
CASTLE AF	NCT00643188	420	Yes	Any AF type, LVEF <35%	Medical treatment – sinus rhythm encouraged	All-cause mortality or HF hospitalization	Minimum 3 y	September 2019	
RAFT AF	NCT01420393	600	Yes	Any type of AF, HF of any type (preserved or impaired EF)	Medical or interventional rate control	All-cause mortality or HF hospitalization >24 h	Minimum 2 y	2018–19	Stratified for HF with preserved and impaired EF
AFARC-LVF	NCT02509754	180	Yes	Persistent AF, LVEF <35%,	Medical or interventional rate control	Improvement of LVEF >35%, NYHA class >II	1 y	December 2017	
CATCH AF	NCT02686749	220	?	LVEF 25%–35%	Medical rate or rhythm control	First hospitalization for HF or recurrence of AF or cardioversion	1 y	February 2019	
AMICA	NCT00652522	216	Yes	ICD or CRT-D, any AF type, LVEF <35%	Medical rate or rhythm control	LVEF by echo	1 y	December 2016	

AF indicates atrial fibrillation; AFARC-LVF, Atrial Fibrillation Ablation Compared to Rate Control Strategy in Patients With Impaired Left Ventricular Function; AMICA, Atrial Fibrillation Management in Congestive Heart Failure With Ablation; CASTLE AF, Catheter Ablation Versus Standard Conventional Treatment in Patients With Left Ventricular Dysfunction and Atrial Fibrillation; CATCH AF, Catheter Ablation vs. Medical Therapy in Congested Hearts With AF; CRT-D, cardiac resynchronization therapy defibrillator; echo, echocardiography; EF, ejection fraction; HF, heart failure; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; and RAFT-AF, Rhythm Control - Catheter Ablation With or Without Anti-arrhythmic Drug Control of Maintaining Sinus Rhythm Versus Rate Control With Medical Therapy and/or Atrio-ventricular Junction Ablation and Pacemaker Treatment for Atrial Fibrillation.

ated with increased mortality. The difficulty is in identifying those patients in whom AF is simply a coexisting condition and those in whom AF is a major contributor to quality of life, ventricular function, and long-term mortality. Although clinical trials are no doubt the gold standard for evaluating treatments and strategies for treatment of AF in HFrEF patients, they can never fully address the need for an individualized approach. For patients who deteriorate early after the onset of AF despite adequate rate control, it is logical that an aggressive approach to rhythm control would be warranted. For those in whom the relationship between AF and symptoms of HF is less clear, a trial of sinus rhythm by performing cardioversion with or without concomitant antiarrhythmic therapy may help to assess whether the patient feels better and whether structural parameters like EF improve. For all patients, oral anticoagulation, lifestyle modifications, and optimization of guideline-directed medical therapy are a must. Rate control should also be broadly applied, even if rhythm control is the final goal. Although RACE II has suggested that lenient rate control may be as good as stricter rate control,[124] there were very few patients in that study with HFrEF and trials like AF-CHF used much stricter definitions of rate control. Therefore, guidelines continue to suggest that stricter rate control in HF patients, particularly those with reduced EF, is preferred.[40,41] Finally, interventional approaches should be considered in HFrEF patients. Catheter ablation is an emerging and potentially promising therapy for HF patients in whom lasting rhythm control is desired. Ablation may reduce the morbidity associated with long-term treatment with antiarrhythmic agents such as amiodarone. AV nodal ablation with resynchronization therapy should also not be overlooked, particularly for patients who may not be good candidates for catheter ablation (large left atrium, older age, multiple comorbidities) and in whom strict rate control may not be achieved through pharmacological treatment alone. With the imminent release of several clinical trial results in the near future, we can look forward to a further refinement in how we approach the treatment of patients with HF and concomitant AF.

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FOOTNOTES

Circulation is available at http://circ.ahajournals.org.

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