

## Atrial Fibrillation and Heart Failure

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### Abstract

Atrial fibrillation is common in heart failure patients and is associated with increased mortality. Pharmacologic trials have not shown any survival benefit for a rhythm control over a rate control strategy. It has been suggested that sinus rhythm is associated with a survival benefit, but that the risks of antiarrhythmic drug treatment and poor efficacy offset the beneficial effect. Catheter ablation for atrial fibrillation can establish sinus rhythm without the risks of antiarrhythmic drug therapy. Data from randomized trials demonstrating a survival benefit for patients undergoing an ablation procedure for atrial fibrillation are still lacking. Ablation of the AV junction and permanent pacing remain a treatment alternative in otherwise refractory cases. Placement of a biventricular system may prevent or reduce negative consequences of chronic right ventricular pacing. Current objectives and options for treatment of atrial fibrillation in heart failure patients are reviewed.

**Keywords:** atrial fibrillation, heart failure, anticoagulation, antiarrhythmic drugs, ablation

### Introduction

Atrial fibrillation and heart failure are epidemics of contemporary cardiovascular medicine. In the US, more than 2 million people are suffering from atrial fibrillation and more than 5 million have heart failure.<sup>1-3</sup> Atrial fibrillation and heart failure often coexist, and patients with one condition, who subsequently develop the other, have an increased mortality.<sup>4</sup> Heart failure is associated with a 4.5 to 5.9-fold risk for atrial fibrillation.<sup>5</sup> The prevalence of atrial fibrillation increases with the severity of heart failure from  $\leq 5\%$  in patients with functional class NYHA I to nearly 50% in patients with functional class NYHA IV.<sup>6</sup> Approximately 40-50% of heart failure patients have preserved left ventricular function, which is often associated with older age, female gender and a history of hypertension.<sup>7-9</sup> In these patients, atrial fibrillation is even

more prevalent than in patients with reduced ejection fraction.<sup>7,9,10</sup>

Atrial fibrillation may lead to further hemodynamic deterioration in heart failure patients. An inappropriately fast or slow ventricular response, ventricular rhythm irregularity and loss of mechanical atrial function can have negative hemodynamic consequences and may elicit an increase in sympathetic tone.<sup>6,11,12</sup> A chronic fast ventricular response may lead to tachycardia-induced cardiomyopathy causing exacerbation or aggravation of heart failure.<sup>13</sup>

This article focuses on clinical management of atrial fibrillation in heart failure patients. Treatment options to prevent thromboembolism, control heart rate and maintain sinus rhythm will be discussed.

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## Anticoagulation

Data from the National Registry for Atrial Fibrillation suggest an overall stroke risk of 4.4% per year in patients with non-rheumatic atrial fibrillation aged 65 to 95 years. The annual stroke risk ranges from 1.9% in the absence of, to 18.2% per year in the presence of all of the following risk factors, recent congestive heart failure, history of hypertension, age  $\geq$  75 years, diabetes mellitus and prior stroke or history of prior thromboembolism.<sup>14</sup> Data from the Framingham Heart Study suggest that the risk of stroke is increased by 4.8-fold in atrial fibrillation and by 4.3-fold in heart failure. The presence of atrial fibrillation in patients with heart failure almost doubles the risk of stroke in men and triples the risk of stroke in women.<sup>15</sup> Recent meta-analyses showed, that dose-adjusted warfarin reduces the risk of stroke by 64% to 67%, but antiplatelet agents (i.e. aspirin and dipyridamole) are less effective, reducing stroke by only by 22%.<sup>16,17</sup> Heart failure and left ventricular ejection fraction  $\leq$  35% are both considered moderate risk factors for thromboembolic events in patients with atrial fibrillation. Anticoagulation with dose-adjusted warfarin should be maintained in all patients with heart failure and a history of atrial fibrillation unless contraindicated.<sup>18, 19</sup>

Data from the AFFIRM trial shows that major bleeding during anticoagulation with warfarin in patients at risk of stroke occurs in approximately 2% of patients per year. Congestive heart failure increases the risk of major bleeding by 43%. However, the rate of major bleeding in patients with atrial fibrillation at risk of stroke is usually lower than the expected rate of a thromboembolic event.<sup>20</sup> Thus, anticoagulation is still favored.

## Pharmacologic Approach to Maintain Sinus Rhythm

In prior randomized trials (AFFIRM, RACE and STAF) comparing rhythm control and rate control with antiarrhythmic drugs, neither strategy demonstrated a survival benefit over the other.<sup>21-23</sup> The recently completed AF-CHF study addressed this issue specifically in heart failure patients. A total of 1,376 patients with heart failure symptoms, a left ventricular ejection fraction of  $\leq$  35% and at least one episode of atrial fibrillation within

6 months preceding enrollment were included. Mean left-ventricular ejection fraction was 27%; 31% of patients were in functional class NYHA III to IV and atrial fibrillation was persistent in 69% of patients. After a mean follow-up of 37 months, there was no difference between rate and rhythm control groups in the primary endpoint of cardiovascular mortality. Secondary outcomes including total mortality, worsening heart failure and stroke were also not different between groups.<sup>24, 25</sup> Patients included in these studies are likely different from those usually considered for catheter ablation of atrial fibrillation. It is conceivable, that patients with severe symptomatic episodes of atrial fibrillation would not have been considered as optimal participants. In the AFFIRM study, only patients of at least 65 years of age or with other risk factors for stroke or death could be enrolled.<sup>21</sup> The mean age of the participants in the AFFIRM, RACE, STAF and AF-CHF studies was 66 to 70 years.<sup>21-23, 25</sup> In contrast, the mean age of patients undergoing catheter ablation for atrial fibrillation was 60 years in a recent large multicenter registry.<sup>26</sup>

The AFFIRM, RACE and other studies have shown that maintenance of sinus rhythm is associated with improved survival and less hospitalizations, but in AFFIRM, antiarrhythmic drug use was associated with a worse outcome.<sup>27-30</sup> Thus, whether sinus rhythm is only a marker of less severe illness or causative for a better outcome remains controversial.<sup>27</sup>

In the absence of data clearly favoring one strategy over the other, therapy has to be individualized. Our practice is to consider rhythm control in patients with a first episode of persistent atrial fibrillation, for symptomatic paroxysms of atrial fibrillation, and when adequate rate control is difficult to achieve.<sup>31</sup>

Amiodarone or dofetilide, both class III antiarrhythmic drugs, are the major pharmacologic considerations for attempted maintenance of sinus rhythm in patients with heart failure.<sup>18</sup> Amiodarone was shown to be safe in heart failure patients in the CHF-STAT trial with a trend to a better survival in patients with non-ischemic cardiomyopathy.<sup>32</sup> In the SCD-HeFT trial, amiodarone did not significantly influence overall mortality, but subgroup analysis showed an increased mortality in patients with NYHA III heart failure. Whether this

result is biologically plausible was questioned by the authors of the study, but the findings do raise concern as to drug toxicity.<sup>33</sup> Amiodarone has a high efficacy in maintaining sinus rhythm, and it can safely be initiated in an outpatient setting.<sup>29</sup> Major concerns early during therapy include drug-induced bradycardia necessitating adjustment of concomitant drug therapy or pacemaker implantation in up to one third of the patients.<sup>34</sup> Noncardiac lung, liver, neurologic and thyroid toxicities are major concerns during long-term treatment. Amiodarone has to be discontinued in approximately 8% of patients per year due to extracardiac side effects.<sup>35</sup>

Dofetilide was shown to be relatively safe in heart failure patients, provided that several precautions are taken in its use.<sup>36</sup> In this patient group, it has efficacy in converting atrial fibrillation to sinus rhythm and maintaining sinus rhythm.<sup>30,36</sup> As an IKr blocker, dofetilide prolongs the QT interval. It caused torsade de pointes in approximately 3% of patients in the DIAMOND trial, even after dose-adjustment according to renal function and attention to following the QT interval. The peak increase in the QT interval was seen within the first 2 days, and 76% of cases of torsades de pointes occurred within the first 3 days of dofetilide therapy. In-hospital monitored initiation of dofetilide for 3 days is warranted.<sup>36</sup> ICDs may provide protection from death due to this arrhythmia. There is no head-to-head comparison of amiodarone and dofetilide in heart failure patients.

Sotalol is another class III antiarrhythmic drug that is an IKr blocker and also a non-selective beta-blocker. It may be considered as a therapeutic alternative. Data from the CTAF and SAFE-T trials show, that amiodarone is superior to sotalol in maintenance of sinus rhythm, but sotalol is still superior to placebo.<sup>37,38</sup> In patients with coronary artery disease, sotalol and amiodarone are similarly efficacious.<sup>38</sup> Of note, the minority of patients in both trials had abnormal left ventricular function.<sup>37,38</sup> Sotalol has a proarrhythmic potential similar to that of dofetilide. This effect may have been the cause of excess mortality that led to premature termination of the SWORD trial in which the d-isomer of sotalol was administered to patients with a history of prior myocardial infarction and an ejection fraction  $\leq$  40%.

Excess in total mortality was driven by arrhythmic cardiac deaths. However, torsade de pointes were reported in only 0.2% of patients receiving sotalol.<sup>39</sup> The proarrhythmic effect of sotalol warrants in-hospital initiation of the drug.

The CAST trial showed an excess of mortality with use of class I antiarrhythmic drugs (sodium channel blockers, including flecainide) in patients with structural heart disease.<sup>40</sup> Heart failure patients may be prone to suffer from arrhythmogenic and cardiodepressant side effects of class I antiarrhythmic drugs. Accordingly, these drugs should be avoided in heart failure patients.<sup>19</sup>

### Non-Pharmacologic Approach to Maintain Sinus Rhythm

Over the last 20 years, surgical and catheter ablation techniques for treatment of atrial fibrillation have been developed and improved, with most of the trials in populations with no or little heart failure. The Cox maze III procedure, which was introduced into surgical treatment in 1988, is regarded as the gold standard for surgical treatment of atrial fibrillation. Long-term success in over 90% of patients, most of them off drugs, has been reported.<sup>41,42</sup> A review of recent publications on radiofrequency catheter ablation for atrial fibrillation shows consistently success rates in approximately 80% of patients, most of them off drugs, although more than one procedure is required in a significant number.<sup>43</sup> It is difficult to extrapolate these results for heart failure patients, since patients in these trials are selected to be reasonable ablation candidates, often with no or minimal structural heart disease. As for most therapies, lower success rates would be anticipated in patients with heart failure. Left atrial scarring, decreased left ventricular function, persistent atrial fibrillation and age were identified as predictors of procedural failure in catheter ablation for atrial fibrillation.<sup>44, 45</sup>

Surgical and catheter ablation procedures in patients with depressed left ventricular function were investigated in several recent studies. In a retrospective study of 37 patients with a left ventricular ejection fraction  $<$  55% (mean, 44%), who underwent a Cox maze procedure for paroxysmal and chronic atrial fibrillation and flutter, there was no perioperative mortality, and 3 patients required placement of a permanent pacemaker. During a

median follow-up of 48 months, atrial arrhythmias recurred in 4 patients. Mean left ventricular ejection fraction improved significantly to 54%. Improvement in functional capacity was noted in 56% of patients, deterioration of functional capacity was not observed.<sup>46</sup> Surgical risks are an important consideration. A recent review of 48 studies on surgical treatment of atrial fibrillation including the classical Cox maze III procedure, most performed with concomitant valve or bypass procedures, reported a 30-day mortality of 2 to 4%, major complications in 8% and the need for pacemaker implantation in 5 to 6% of cases.<sup>47</sup>

Hsu and coworkers studied 58 patients with congestive heart failure and a left ventricular ejection fraction < 45% (mean, 35%), who underwent radiofrequency catheter ablation for atrial fibrillation. One patient died 3 months after the procedure of heart failure. After a follow-up period of 12 months, 78% of patients remained in sinus rhythm, 69% off antiarrhythmic drugs. To achieve this result, a second procedure was required in 50% of patients. Success rates in a control group were 84% and 71%, respectively. Mean left ventricular ejection fraction improved to 56%, and left ventricular dimensions decreased. This translated into better functional capacity and quality of life. [48] Similar results were seen in another study on catheter ablation for atrial fibrillation, which included 90 patients with a reduced left ventricular ejection fraction of < 40% (mean, 36%). After a follow-up of 14 months, 73% of patients were free of atrial fibrillation, compared to 87% of patients in a control group. The increase in left ventricular ejection fraction to 41% was not significant, but quality of life improved significantly. In 22% of patients a second procedure was successful.<sup>45</sup> Major complications of catheter ablation for atrial fibrillation occur in 4 to 6% of patients, and it can be anticipated that heart failure patients will generally be at greater risk.<sup>26, 49</sup>

These reports from highly experienced centers with selected patients are promising, but controlled data confirming a prognostic benefit for patients undergoing these procedures are still lacking. The ongoing CABANA trial, which compares catheter ablation for atrial fibrillation with current state-of-the-art medical therapy, addresses this issue with a primary outcome measure of total mortality, but does not focus solely on a heart failure

population.<sup>50</sup> At present, catheter ablation for atrial fibrillation in heart failure is warranted in selected symptomatic patients with atrial fibrillation refractory to at least one antiarrhythmic drug. Surgical ablation for atrial fibrillation is usually considered for symptomatic patients undergoing other cardiac surgery, such as mitral valve repair. Patients may also be considered for surgical ablation, when they prefer a surgical approach, have failed one or more catheter ablation procedures or are not candidates for catheter ablation.<sup>18, 42</sup>

### Pharmacologic Control of Heart Rate

Atrial fibrillation with a fast ventricular response may have immediate adverse hemodynamic effects and places the patient at risk for tachycardia-mediated cardiomyopathy, particularly if the chronic heart rate exceeds 100 beats per minute.<sup>6,13</sup> Digoxin is recommended for rate control in patients with heart failure, but it slows atrioventricular conduction more effective at rest than during exercise. Beta-blockers are usually indicated in all symptomatic patients with systolic heart failure, but in heart failure initiation should be at a low dose followed by a gradual increase, because negative inotropic effects may cause fluid retention and worsening of heart failure. Combination of beta-blockers and digoxin may be more effective than beta-blockers alone. Amiodarone is an alternative for pharmacologic rate control in patients, where the abovementioned medications are contraindicated or fail, but it has a considerable potential of adverse drug effects and is usually avoided for rate control alone. Non-dihydropyridine calcium channel blockers verapamil and diltiazem slow heart rate during exercise, but should be avoided due to their negative inotropic effect, which increases the risk of exacerbation of heart failure.<sup>18, 19</sup>

Pharmacologic rate control with atrioventricular nodal blocking agents is chosen either as first line strategy or when attempts to establish and maintain sinus rhythm fail. Heart rate goals are 60 to 80 beats per minute at rest and 90 to 115 beats per minute during moderate exercise, but may vary according to patient age.<sup>18</sup>

### Non-pharmacologic Control of Heart Rate

Radiofrequency catheter ablation of the atrioven-

tricular junction and pacemaker placement may be warranted in medically refractory atrial fibrillation where sinus rhythm cannot be maintained and adequate rate control is not possible. Limitations of this approach include the persistent need for anticoagulation, loss of atrioventricular synchrony and pacemaker dependency.<sup>18</sup>

A meta-analysis of 21 studies showed, that ablation and pacing reduces symptoms and health-care use and improves left ventricular function, exercise duration and quality of life, with a one year total and sudden death mortality of 6.3% and 2.0%, respectively.<sup>51</sup>

However, right ventricular apical pacing may be detrimental by worsening heart failure and increasing mortality.<sup>52</sup> Right ventricular pacing induces electrical and mechanical dyssynchrony, which can adversely influence contraction and relaxation, ultimately causing unfavorable ventricular remodeling. It may be less well tolerated in patients with pre-existing systolic heart failure and mitral regurgitation.<sup>53, 54</sup> Consistent with this consideration is the observation that atrioventricular node ablation and permanent pacing for refractory atrial fibrillation leads to hemodynamic deterioration in certain patients. Ozcan and coworkers studied this approach in patients with left ventricular dysfunction with a mean left ventricular ejection fraction of 26% before the procedure.<sup>55</sup> Mean ejection fraction increased to 34% after ablation. The twenty-nine percent of patients with near normalization of the left ventricular ejection fraction to  $\geq 45\%$  had a survival comparable to that of normal subjects. However, the majority of patients had a persistent low ejection fraction and a poor prognosis with a mortality of 48% during a mean follow-up of 40 months.<sup>55</sup> In some patients with heart failure, ablation and pacing is followed by aggravation of mitral regurgitation.<sup>56</sup> Vanderheyden and coworkers found hemodynamic deterioration in 7% of patients undergoing ablation and pacing therapy, which was related to worsening mitral regurgitation. Of note, baseline echocardiograms in patients with hemodynamic deterioration showed left ventricular dilation and subnormal fractional shortening.<sup>57</sup>

The PAVE study compared conventional right ventricular with biventricular pacing in patients

undergoing atrioventricular node ablation for the management of atrial fibrillation.<sup>58</sup> Biventricular pacing was associated with improvement in functional capacity at 6 months. Left ventricular ejection fraction remained unchanged after implantation of a biventricular system in contrast to right ventricular pacing, where a slight but significant decline in ejection fraction was observed. Patients with a baseline ejection fraction of  $\leq 45\%$  or NYHA functional class II / III symptoms had a greater improvement in functional capacity than patients with normal left ventricular function or class I symptoms.<sup>58</sup> In another study of patients with severe heart failure after atrioventricular node ablation and right ventricular pacing for management of chronic atrial fibrillation, upgrade to a biventricular system was followed by improvement in left ventricular dimensions and function, and quality of life and a decrease in hospitalizations.<sup>59</sup> The HOBIPACE study compared bi-ventricular to right ventricular pacing for 3 months in a randomized cross-over design trial in 30 patients. Biventricular pacing was superior to conventional right ventricular pacing with regard to left ventricular function, exercise capacity and quality of life in patients with left ventricular dysfunction and standard indication for pacemaker implantation.<sup>60</sup>

Accordingly, implantation of a biventricular pacemaker is a reasonable consideration for patients who are undergoing atrioventricular node ablation for drug-refractory atrial fibrillation with heart failure or depressed left ventricular function. An upgrade to a biventricular system should be contemplated in patients with persistent heart failure, who have undergone atrioventricular junctional ablation and have only right ventricular pacing.<sup>18</sup>

Polymorphic ventricular tachycardia, ventricular fibrillation and sudden death were not uncommonly observed early after ablation of the atrioventricular junction and pacemaker implantation. These complications occurred in 6% of cases in a larger study of Geelen and coworkers. Ventricular arrhythmias mostly occurred during slow ventricular escape rhythms or slow pacing rates of  $\leq 60$  beats per minute. Bradycardia and pacing-related prolongation of repolarization, change in ventricular activation, increased dispersion of re-

polarization, increased sympathetic tone and individual factors like heart failure, hypokalemia and female gender may increase the vulnerability to these arrhythmias. Pacing at 90 beats per minute for 1 to 3 months after the procedure appears to prevent this complication.<sup>61, 62</sup>

The recently completed PABA CHF trial compared catheter ablation for atrial fibrillation with atrioventricular node ablation and biventricular pacing. Preliminary results showed a significantly greater ejection fraction in the catheter ablation group at 6 months post procedure.<sup>63</sup>

### Prevention of Atrial Fibrillation in Heart Failure

Perhaps the best way to deal with atrial fibrillation and its negative consequences is through prevention. Angiotensin converting enzyme inhibitors, angiotensin receptor blockers and beta-blockers belong to the standard pharmacologic armamentarium for treatment of heart failure.<sup>19</sup> There is strong evidence of participation of the renin-angiotensin system in electrical and structural atrial remodeling, involved in the pathogenesis of atrial fibrillation.<sup>64</sup> Both angiotensin converting enzyme inhibitors and angiotensin receptor blockers reduce atrial fibrillation in patients with heart failure or hypertension, as supported by meta-analysis.<sup>65</sup> The benefit was similar between these two classes of drugs and greatest in patients with heart failure with a 44% relative risk reduction.<sup>65</sup> A recent meta-analysis on the efficacy of beta-blockers in heart failure trials showed a significant prevention of atrial fibrillation by use of beta-blockers with a 27% relative risk reduction.<sup>66</sup>

The protective effect of cardiac resynchronization therapy is still unclear. Although a small study showed a significantly lower incidence of atrial fibrillation in patients with cardiac resynchronization therapy, data from the CARE-HF study did not support this hypothesis.<sup>67, 68</sup>

### Conclusions

Atrial fibrillation is common in heart failure. Patients with one condition who subsequently develop the other have an increased mortality. Treatment has to be individualized in these complex patients

and the risks and benefits of the different therapeutic options carefully considered. Anticoagulation and rate control are crucial in all patients with atrial fibrillation and heart failure. Pharmacologic rhythm control offers no survival benefit over rate control, and may be used in selected symptomatic patients. Catheter ablation of atrial fibrillation in selected patients can be successful, but also has risks. Atrioventricular node ablation and placement of a biventricular pacemaker for drug-refractory atrial fibrillation is an option when rate control and sinus rhythm can not be maintained. The important question, of whether catheter ablation for atrial fibrillation has the potential to prolong life, is still unresolved. The answer may have substantial impact on our approach to treat atrial fibrillation in the future.

### Disclosures

None to disclose in context of current subject matter.

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