Treatment Considerations for a Dual Epidemic of Atrial Fibrillation and Heart Failure

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Abstract
Atrial fibrillation (AF) and heart failure (HF) have emerged as major cardiovascular epidemics in developed nations over the past decade. They share similar risk factors, seem to mutually accelerate progression and are associated with increased morbidity and mortality. Their relationship involves complex hemodynamic, neuro-hormonal, inflammatory and electrophysiologic mechanisms, which go beyond just mutual risk factors. This review focuses on updates in AF and HF with a hope of better understanding this relationship and the management of this complex duo.

Introduction
Burden of AF and HF
AF is the most common arrhythmia in clinical practice, accounting for approximately one-third of hospitalizations for cardiac rhythm disturbances. It has been estimated that 2.2 million people in America and 4.5 million in the European Union have paroxysmal or persistent AF. In an analysis of the Framingham Heart Study population including 3999 men and 4726 women, the investigators projected that the lifetime risk of developing AF was one in every four patients. The Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study projected that the prevalence of AF will increase 2.5-fold by the year 2050, affecting nearly 5.6 million Americans. The predicted future prevalence of AF was even greater in a community-based study by Miyasaka and colleagues. They observed that the age-adjusted incidence of AF increased by 12.6% over the period from 1980 to 2000. Recent data from Piccini and colleagues looking at Medicare beneficiaries from 1993-2007 suggested that the age- and sex-adjusted incidence of AF remained relatively stable over this time period. However, the prevalence of AF in this population has more than doubled from 41.1 per 1000 beneficiaries in 1993 to 85.8 per 1000 beneficiaries in 2007. The mean annual increase in prevalence was 5.0%.

AF is a major public health problem, with hospitalizations as the primary cost driver (52%), followed by drugs (23%), consultations (9%), further investigations (8%), loss of work (6%), and paramedical procedures (2%). During the past 20 years, there has been a 66% increase in hospital admissions for AF. Expenditures related to AF cost Medicare approximately $16 billion annually.

Heart failure affects approximately 5.7 million patients in the United States, and about 550 000 patients are diagnosed with new heart failure each year. Although the incidence of heart failure has remained stable over the past 50 years, the prevalence of heart failure in the United States has steadily increased. By the year 2030, it is predicted that an additional 3 million Americans will have HF, representing an astounding 25% increase from 2010. Heart failure is the primary reason for 12 to 15 million office visits and 6.5 million hospital days yearly. From 1990 to 1999, the annual number of hospitalizations increased from about 800 000 to over 1 million for heart failure as a primary diagnosis and from 2.4 to 3.6 million for heart failure as a primary or secondary diagnosis.

As a consequence, heart failure carries a significant economic burden on our society because it is the most common discharge diagnosis and because more Medicare dollars are spent for the diagnosis and treatment of heart failure than for any other diagnosis. In 2007, the American Heart Association estimated that $33 billion was spent on heart failure alone. Based on a policy statement from 2011, the American Heart Association projected that the annual direct cost of HF treatment in the United states is expected to increase from $24.7 billion in 2010 to $77.7 billion in 2030 while the loss of productivity (indirect cost) will increase from $9.7 billion to $17.4 billion over the
same time period.16

**Association Between AF and HF**

The association between AF and heart failure was appreciated almost a century ago.17 The reported prevalence of AF in modern heart failure series ranges from 13% to 27%,18-22 Among 1470 patients who developed either new AF or HF in the Framingham Heart Study, a total of 383 individuals (26%) developed both AF and heart failure.23 The prevalence of AF in patients with preexisting heart failure is associated with increasing heart failure severity. In chronic HF clinical trials, the prevalence of AF increases from 4% in functional class I patients24 to 50% in those with functional class IV,27 with class II-III patients in the intermediate range.19, 23, 25, 26 (Figure 1).

However, this association between new-onset AF, HF progression, and increased mortality does not prove causality. Although the causal relationship between the AF and HF has not been fully determined, their coexistence can be explained to some degree by the presence of common risk factors such as age, hypertension, diabetes, and obesity, as well as valvular, ischemic, and nonischemic structural heart disease.28 Exposure to these risk factors promotes development of atrial and ventricular structural and functional abnormalities through activation of several biologic pathways in concert including upregulation of neurohormonal signaling cascades, release of inflammatory mediators, programmed cell death, and fibrosis.29,30,31,37 Cardiac structural remodeling occurs in concert with electrophysiologic remodeling, both of which may contribute to atrial and ventricular rhythm disturbances, including AF.29 However, further studies are necessary to elucidate the exact mechanisms responsible for the association between AF and HF.

**Pathophysiology of this Association**

**Effect of Heart Failure and Diastolic Dysfunction (DD) on AF Development**

Heart failure is an independent risk factor for the development of AF. The development and stability of AF has been thought to be dependent on the production and maintenance of multiple re-entrant wavelets.32,33 HF enhances the production of these multiple wavelets through a combination of direct mechanical effects29 and production of a characteristic neurohormonal/cytokine milieu, which act to alter the atrial structure and its electrophysiological properties.38-41

In HF, the atria often become dilated as a consequence of the pressure and volume overload. This atrial dilation provides an increased area in which the wavelets can exist, increasing the number of wavelets34 and thus increasing the probability of AF development.35 Atrial dilation also results in the activation of stretch-activated ion channels, which alters the electrophysiological properties of the atria, producing heterogeneous shortening of the atrial refractory period, slowing of atrial conduction and spontaneous triggered activity.38, 39 HF has also been associated with increased interstitial fibrosis.40 This increase in fibrosis can lead to abnormal conduction through the atria, creating a substrate for AF in animal models.40-42 All these changes further encourage the development of multiple re-entrant wavelets and hence promote AF development.

The activation of the sympathetic nervous system,43 and the renin-angiotensin-aldosterone system (RAAS),44 as occurs in HF, acts to promote substrate changes within the atria that encourage the development of AF. In vitro studies have suggested that sustained sympathetic activation alters ion channel expression with reduction in IKs and ICaL45 and these reductions are known to be influential in the development of AF in the tachycardia-induced model of heart failure46 as they result in shortening of the atrial refractoriness, a process that stabilizes AF. The strong vasopressor action of angiotensin II can increase the cardiac afterload and left ventricular systolic stress, resulting in further atrial dilation and a propensity towards AF development. RAAS activation also promotes interstitial fibrosis of the atria, which acts to disrupt normal electrical conduction across the atria with the appearance of discrete areas of conduction slowing.47 Several large-scale HF trials of ACE inhibitors and angiotensin receptor blockers have shown reduction in the development of AF in treated patients compared to those on placebo.48-51 Recently, clinical studies using echo parameters have shown that
Although there is no data on literature examining the effect of AF on developing DD, the development of AF often heralds worsening of symptoms with deterioration in NYHA status, increased times to complete the 6-min walk test and reduced quality of life scores. One possible explanation for this symptomatic progression is the inherent effects of beat-to-beat variation on diastolic dysfunction. In animal studies performed on dogs long R-R intervals resulted in good LV relaxation and thus good subsequent contraction, while short R-R intervals resulted in poor relaxation and thus poor contractile function. However, studies in humans suggest that such an explanation is too simplistic and studies have shown a reduction in LV systolic and diastolic function with the onset of AF that was unrelated to rate control.

**Effect of AF on HF and DD**

AF can predispose to the development of HF or can result in clinical decompensation in those who already have HF. First of all, AF can lead to rapid ventricular activation rates, and persistently fast ventricular rates are known to produce HF in conditions such as tachycardia-induced cardiomyopathy. The precise molecular mechanisms underlying this condition have not been fully elucidated but are likely to involve a combination of cellular Ca\(^{2+}\) overload and longer-term adaption of the cell to this Ca\(^{2+}\) overload with depletion of the T-tubules, reduction in L-type Ca\(^{2+}\) channels and increase in Na\(^{+}\)–Ca\(^{2+}\) exchanger proteins. These adaptations reduce the net Ca\(^{2+}\) influx and thereby also reduce excitation–contraction coupling within the cell. Secondly, in AF, the loss of atrial contraction results in reduced active filling in diastole increasing reliance on active filling than in the normal heart, and this loss of active ventricular filling can lead to a reduction in cardiac output of about 20%. Finally, the irregularity of ventricular contraction in AF can in itself result in reduced cardiac output even when the rate of ventricular contraction is not increased. (Figure 2)

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**How AF affects Patients With HF and Vice-Versa?**

The prognostic influence of AF in HF remains controversial, with some studies illustrating an independent adverse effect on mortality, whereas other studies show no significant effects. In a study involving the Framingham Heart Study participants, the combination of AF and HF carried a worse prognosis than subjects with HF or AF alone. The development of AF was associated with increased mortality [men: HR, 1.6; 95% CI, 1.2–2.1; women: HR, 2.7; 95% CI, 2.0–3.6]. However, the independent contribution of AF to mortality was not assessed. In the Vasodilator Heart Failure Trial (V-HeFT), the presence of AF was not associated with a worse outcome in 1427 patients with mild to moderate heart failure. In a retrospective analysis of the Studies of Left Ventricular Dysfunction (SOLVD) trial, which enrolled 6500 patients with LV ejection fraction (LVEF) <35%, baseline AF was an independent predictor for all-cause mortality, progressive pump failure, and the combined end point of death or hospitalization for heart failure. In the Valsartan
in Acute Myocardial Infarction (VALIANT) trial of 14703 patients with acute myocardial infarction complicated by HF, AF also was associated with greater long-term morbidity and mortality. In a retrospective analysis of the Carvedilol or Metoprolol European Trial (COMET), which included 3029 patients with LVEF ≤ 35%, baseline AF significantly increased the risk for death and HF hospitalization. However, after adjustment for other predictors of prognosis, AF was no longer an independent risk factor for mortality. Middlekauf et al found that patients with advanced HF and AF had significantly reduced 1-year survival compared with sinus rhythm patients. Moreover, AF seemed to be a stronger predictor of negative outcome in the subset of patients with mild to moderate HF compared with patients with severe HF, in whom the contribution of AF to further impairment in survival was limited. Similarly, Corell et al found that the presence of AF in outpatients with HF also was associated with increased morbidity and mortality and that AF was a stronger predictor of adverse outcome in patients with better cardiac function (LVEF >35%). In the Trandolapril Cardiac Evaluation (TRACE) study, Pedersen et al found that long-term mortality was increased in all subgroups of patients with AF except those with the most advanced disease (LVEF <25%). From these trials, it appears that AF serves as a negative prognostic marker in patients with systolic HF, and the independent effect of AF on mortality is inversely related to the severity of HF.

A recent study by the American Heart Association of 99 810 patients hospitalized with HF between 2005 and 2010 showed that AF was present in one third of HF cases and that AF was associated with adverse hospital outcomes, longer length of stay, and higher in-hospital death rates (4.0% versus 2.6%). Two recent meta-analyses have summarized the published literature on the risk of death in patients with HF with AF in comparison with those with HF alone. The results of these analyses show that the coexistence of AF in HF patients increases the odds of death from 14% to 40% in comparison with isolated HF. The meta-analysis by Mamas et al included 16 studies involving 53 969 patients and demonstrated the adverse prognosis associated with the presence of AF in patients with HF and systolic dysfunction but also suggested that in HF patients with preserved LV function, AF is associated with a two-fold increase in the risk of mortality compared with those in SR.

The findings of a recent community-based study involving 1664 individuals with HF showed not only that the presence of AF was associated with a 2-fold higher risk of death in comparison with those with HF alone, but also that patients with AF that develops after HF were at greater risk for dying than patients with preexisting AF at the time of HF diagnosis.

However, there are no large studies investigating the role of asymptomatic paroxysms of AF on HF cohorts. It is therefore unclear what effect if any paroxysmal AF might have on mortality outcome in patients with HF.

**Treatment of AF + HF**

**Rate Versus Rhythm Control of AF**

Rate control and rhythm control or rhythm restoration are the two options for management of AF. For over a decade there has been an ongoing debate about which of these strategies is better for management of AF in HF. The rhythm control strategy for asymptomatic patients with AF and HF had been considered to be advantageous based on the known deleterious effects of AF with respect to cardiovascular hemodynamics, thromboembolic risk, and quality of life. It was believed that AF with rapid ventricular response could lead to systolic HF, whereas restoration of sinus rhythm or
appropriate rate control can reverse this process. However, various studies over the past decade comparing the so-called rhythm to rate control strategies have failed to demonstrate superiority of a rhythm control in patients with AF with respect to major clinical endpoints. Several of these studies included patients with AF and HF (Table 1). However, given the relatively small number of patients with HF and AF included in many of the landmark rhythm vs. rate control trials, controversy still exists regarding whether patients with HF and AF respond better to rhythm restoration or ventricular rate control.

The AF Follow-Up Investigation of Rhythm Management (AFFIRM) and the Rate Control Versus Electrical Cardioversion for Persistent AF (RACE) found that a rhythm control strategy provided no benefit and actually showed a trend toward harm in the general population of patients compared with rate control. Subsequent analyses have demonstrated a powerful benefit (hazard ratio, 0.5) of actually maintaining sinus rhythm as opposed to assignment to the rhythm control strategy, which seemed to be completely offset by the hazard of antiarrhythmic drug therapy (hazard ratio, 1.49). This response might be confounding because patients who were able to maintain sinus rhythm in AFFIRM may just be healthier than those who did not. Three other prospective randomized trials have compared rate and rhythm control. These studies include the How to Treat Chronic Atrial Fibrillation (HOT CAFE), Strategies of Treatment of Atrial Fibrillation (STAF), and Pharmacological Intervention in Atrial Fibrillation (PIAF) clinical trials. Each had similar results, showing equivalent outcomes in both arms. However, only 23% to 64% of patients assigned to rhythm control remained in sinus rhythm.

The issue of rate vs. rhythm control in patients with AF and HF was further addressed in the landmark Atrial Fibrillation in Congestive Heart Failure (AF-CHF) trial, which is the largest randomized control study to-date designed specifically to investigate whether rhythm control pharmacologic strategies impact mortality over rate control therapy in patients with AF and HF. On the basis of their observation that patients with AF and HF randomized to rhythm control were at equivalent risk for all of the major study endpoints, the study authors concluded that rhythm control should not be routinely recommended for asymptomatic patients with AF and HF. However, this study had various limitations and hence these findings should be accepted with caution. First, patients assigned to rate control were considered to be stable if they achieved adequate rate control both at rest and at low-level exercise, which may not necessarily be the case in “real-life” patients. Second, the benefit of sinus rhythm could have been counterbalanced by the harm of antiarrhythmic medications in a fashion similar to the AFFIRM study. Third, although the prevalence of sinus rhythm in the group assigned to rhythm control was as high as 80%, the actual percentage of patients free of AF after randomization may have been lower, reflecting a more traditional success rate of amiodarone in the range of 60% to 65%. One of the major and notable limitations of rhythm control among patients with AF and HF included in the aforementioned studies was the limited long-term efficacy of anti-arrhythmic drug therapy in these patients, (only 44% of participants remaining in sinus rhythm in DIAMOND, 51% in CHF- STAT and 58% in AF-CHF).

These findings suggest that although conversion to sinus rhythm is a positive prognostic sign in patients with HF and AF, the limited efficacy and toxicities of contemporary antiarrhythmic drugs in such patient’s limits the overall impact of the rhythm control strategy.

### Rate-Control Strategy

Optimal ventricular rate in patients with AF was thought to be 60 to 80 bpm at rest and 90 to 115 bpm during moderate exertion. It is important to note that adequate rate control cannot be determined by resting ECGs alone and should be assessed with 24-hour Holter monitors or by the evaluation of the chronotropic response during exercise. More recently, the adequacy of ventricular rate control in patients with AF and HF was assessed in the (Rate Control Efficacy in Permanent Atrial Fibrillation) trial that evaluated the potential benefits of strict (resting heart rate <80 bpm, heart rate <100 bpm during a 6-minute walk) versus lenient (resting heart rate <110 bpm) rate control in patients with permanent AF. Lenient rate control was found to be non-inferior to strict rate control in terms of 3-year estimated cumulative incidence of death from cardiovascular causes, hospitalization for HF, thromboembolic events, bleeding and life-threatening arrhythmias. However, in this study the mean ejection fraction (EF) was 52%; while the patients that had EF <40% were only 15% of the total subjects. Thus, no conclusions can be drawn regarding lenient or strict rate control in HF patients with permanent AF. Also, the long-term effects of a rapid heart rate response to AF on ventricular function were not studied and the study was inadequately powered to provide conclusive data on all clinically relevant differences in clinical outcomes between the 2 groups. The most recent American College of Cardiology Foundation/ American Heart Association/ Heart Rhythm Society (ACCF/AHA/HRS) guidelines state that strict rate control is not more beneficial than lenient rate control in patients with persistent AF and stable LV function, although uncontrolled tachycardia may over time be associated with a reversible decline in ventricular performance.

Beta-blockers are first-line agents for achieving rate control in

### Table 1: Rate versus Rhythm Control in AF and HF: Comparison of Major Trials

<table>
<thead>
<tr>
<th>Trials</th>
<th>STAF (74)</th>
<th>RACE (75)</th>
<th>AFFIRM (76)</th>
<th>HOT-CAFÉ (77)</th>
<th>AF-CHF (78)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients (n)</td>
<td>200</td>
<td>522</td>
<td>4060</td>
<td>205</td>
<td>1376</td>
</tr>
<tr>
<td>Number of HF patients (n, %)</td>
<td>27, 13.5</td>
<td>100, 19.2</td>
<td>939, 23.1</td>
<td>127, 62</td>
<td>1376, 100</td>
</tr>
<tr>
<td>Mean follow-up duration (years)</td>
<td>1.6</td>
<td>2.3</td>
<td>3.5</td>
<td>1.7</td>
<td>3.1</td>
</tr>
<tr>
<td>Mean Age (years)</td>
<td>65.8</td>
<td>68</td>
<td>69.7</td>
<td>61</td>
<td>67</td>
</tr>
<tr>
<td>Primary endpoint (Rhythm control, Rate control, p-value)</td>
<td>Composite of Death, Stroke/TIA, Systemic embolization and CPR (9%, 10%, 0.99)</td>
<td>Composite of CV death, HF, thromboembolic events, bleeding, PPM implantation, AAD adverse effects (22.6%, 17.2%, 0.11)</td>
<td>Overall Mortality (26.7%, 25.9%, 0.08)</td>
<td>Composite of Death, thromboembolic events, major bleeding (2%, 5.7%, 0.71)</td>
<td>CV mortality (27%, 25%, 0.53)</td>
</tr>
<tr>
<td>Incidence of HF during follow-up (%) (Rate/Rhythm control, p-value)</td>
<td>NA</td>
<td>4.5, 3.5, NS</td>
<td>2.7, 2.1, 0.58</td>
<td>NA</td>
<td>28, 31, 0.17*</td>
</tr>
</tbody>
</table>
AF and for reducing long-term morbidity and mortality in HF, especially among patients with severely reduced systolic function.\(^8^5\) Carvedilol therapy significantly improved the left ventricular EF and showed a trend toward a reduction in the combined end point of death or HF hospitalization in patients with concomitant AF and HF in a retrospective analysis of ‘US Carvedilol Heart Failure Trial’.\(^8^6\) Bisoprolol and Metoprolol succinate have also been shown to improve mortality among patients with HF.\(^8^7\) Labetalol has also demonstrated effectiveness for ventricular rate control in patients with AF\(^8^8\) while Nebivolol, has been shown as an effective and well-tolerated treatment for HF in elderly.\(^8^9\) Bucindolol was studied in the “Beta-Blocker Evaluation Of Survival” (BEST) trial\(^9^0\) and demonstrated a decrease in the incidence of AF in patients with HF. Non-dihydropyridine calcium channel blockers (verapamil and diltiazem) are effective rate controlling agents in AF, but their negative inotropic properties can worsen systolic HF.\(^9^1\) Some studies suggest that short term use of intravenous diltiazem in AF and moderate to severe HF may be safe and effective;\(^9^2, 9^3\) however, their safety in chronic heart rate control in patients with coexisting HF remains to be proven, and these agents are generally avoided in patients with severe HF.

Digoxin as monotherapy for AF rate-control is ineffective and usually not recommended. However, a retrospective analysis of the US Carvedilol Heart Failure Trials program demonstrated improved survival with carvedilol in patients also treated with digoxin.\(^9^4\) Also, a small study in patients with AF and HF suggested that the combination of digoxin and carvedilol reduces symptoms, improves ventricular function and leads to a better rate control than either agent alone.\(^9^5\) It remains unclear whether digoxin affects mortality in patients with AF and HF.\(^9^6\) Also, digoxin is not effective for heart rate reduction during exercise. Digoxin may thus be a helpful adjunctive agent for patients with AF and HF in whom rate-control is not adequately achieved with beta-blockers alone.

**Rhythm-Control Strategy**

Although a variety of antiarrhythmic agents are available for the treatment of AF in patients with structurally normal hearts, patients with HF are particularly susceptible to side effects of some commonly used antiarrhythmic agents. The Cardiac Arrhythmia Suppression Trial (CAST)\(^9^7\) was a randomized, placebo-controlled study that examined the effect of class IC antiarrhythmic drugs on patients with ventricular ectopy after myocardial infarction. This study showed that therapy with either flecainide or encainide was associated with increased mortality. The applicability of the CAST results to other populations (eg, those with chronic HF and no active ischemia) or other class IC antiarrhythmic drugs (AAD) such as propafenone is uncertain. However, currently, it is prudent to consider any class IC antiarrhythmic to have a significant risk in patients with structural heart disease.

Amiodarone is a class III anti-arrhythmic drug (AAD) with functional overlap with class I AADs, beta-blocker and calcium channel blocker drugs. Amiodarone is one of the most widely used rhythm control agents. It also appears to be the most effective agent for long-term maintenance of normal sinus rhythm in patients with AF with or without HF.\(^9^7, 10^0\) A sub-study of the CHF-STAT trial 23 which evaluated the long-term effects of amiodarone on morbidity and mortality in patients with HF and AF during a 4-year period.
showed that in patients with HF, amiodarone has a significant potential to spontaneously convert patients in AF to sinus rhythm and these patients had a lower mortality rate than those who do not. It also prevented the development of new-onset AF and significantly reduced the ventricular rate in those with persistent AF. On the basis of these and other findings, amiodarone remains a first-line agent for the acute conversion and maintenance of sinus rhythm in patients with AF and HF. However, the benefit of amiodarone must be weighed against its well-documented potential long-term adverse effects.101

Dronedarone is a multiclass AAD that has a superior safety profile and shorter half-life than amiodarone. Dronedarone has been shown to reduce the need for hospitalization and death in patients with AF.102 However, the ANDROMEDA study demonstrated increased cardiovascular mortality among patients with advanced and recently decompensated HF.103 In contrast, a post-hoc analysis of ATHENA study patients with AF and stable HF demonstrated that dronedarone did not increase mortality and showed a reduction of cardiovascular hospitalization or death similar to the overall population.104, 105 Dronedarone is therefore contraindicated in patients with NYHA class IV or unstable NYHA classes II and III HF. The most recently published PALLAS study, which was prematurely terminated, demonstrated that dronedarone increased rates of HF, stroke and death from cardiovascular causes in patients with permanent AF who were at risk for major vascular events, thus raising serious concerns about dronedarone's clinical utility in the future.106

Dofetilide, a class III AAD, has substantial evidence supporting its use in patients with AF and HF.25, 107, 108 A sub-study of the DIAMOND trial showed that although all-cause mortality was unaffected by dofetilide treatment, use of this AAD led to a significant reduction of hospitalization for HF.25 Although, Torsades de pointes developed in <1% of patients in the dofetilide treatment arm of the DIAMOND study, there was no significant difference in the total arrhythmic mortality between the dofetilide and placebo groups in patients with AF and severe LV dysfunction.109

Ibutilide is an intravenous class III AAD shown to have modest-to-high conversion rates with AF, particularly when administered within a few weeks of AF onset.109, 110 However, ibutilide infusion carries a 2-4% risk of precipitating polymorphic ventricular tachycardia and should be used cautiously among patients with AF and HF with decreased systolic function.

Sotalol is a class III AAD with strong beta-blocking effects. The SWORD trial, which involved prophylactic administration of D-sotalol to patients with severe LV dysfunction post myocardial infarction, was prematurely terminated as it demonstrated an increased cardiovascular mortality among those treated with sotalol.111 The SAFE-T trial demonstrated that as compared to amiodarone, sotalol has similar efficacy in converting persistent AF to sinus rhythm.97 However, with respect to maintenance of sinus rhythm Amiodarone was superior. However, SAFE-T excluded patients with NYHA class III or IV HF. On the basis of available data suggesting that HF patients treated with sotalol are vulnerable to increased rates of potentially life-threatening ventricular arrhythmias, sotalol is generally avoided in patients with AF and severe HF.82

Pharmacologic Agents and Prevention of AF and HF

There is data to suggest that drugs like renin angiotensin-aldosterone system inhibitors, 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors (statins), and omega-3 fatty acids can prevent the incidence of new or recurrent AF by targeting pathophysiological mechanisms that promote atrial structural or electrophysiological remodeling.

Inhibition of the renin-angiotensin-aldosterone system attenuates atrial electric remodeling and fibrosis, processes that are associated with an increased risk for development of AF.112-114 Clinical studies have demonstrated that renin-angiotensin-aldosterone system blockade with angiotensin receptor-1 blockers can reduce the incidence and recurrence rates of AF in patients with HF.49,50,51 In the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) study, treatment with candesartan reduced the incidence of AF in a large, broadly based population with HF. However, the recently published Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE-I) study, which evaluated the effect of irbesartan on cardiovascular outcomes in 9016 patients with AF, demonstrated that the irbesartan treatment among patients with intermittent AF who were in sinus rhythm at enrollment had no effect on rates of AF recurrence.115 Similarly, the GISSI-AF study did not demonstrate a significant reduction in the occurrence of new-onset or recurrent AF events in patients with HF or LV hypertrophy randomized to receive valsartan.116 However, the ACTIVE-I trial did show that in patients with AF, the addition of irbesartan significantly reduced HF hospitalization rates. These findings are consistent with the results of a trial of angiotensin receptor blockers in patients with a low EF117 and with the results of the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) Preservation trial involving patients with a normal EF and HF. However, ACTIVE I results differ from those of the Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (TRANSCEND),118 Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR)120 and Irbesartan in Heart Failure with Preserved Ejection Fraction (I- PRESERVE) study;121 all of which showed no benefit of additional angiotensin receptor blockers with respect to HF.

Therapy with beta-blockers has also been associated with reduced risk for AF. In the BEST trial, use of Bucindolol in patients with HF was associated with a decrease in incidence of AF.90 In a meta-analysis of 7 randomized, placebo-controlled trials including 11 952 patients with HF already taking angiotensin-converting enzyme inhibitors, beta-blockers significantly reduced the incidence of new AF from 39 to 28 per 1000 patient-years (relative risk reduction, 27%).122 Recent studies suggest that 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statin) therapy may reduce the incidence and recurrence of AF in patients with HF.123, 124 However, a recent meta-analysis evaluating 22 trials of statin agents showed no significant reduction in the rates of AF among individuals randomized to receive statin agents.125

Several epidemiological and experimental studies suggest that n-3 polyunsaturated fatty acids (PUFA) may exert antiarrhythmogenic or antiarrhythmic effects. The Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto Miocardico-Heart Failure (GISSI-HF) trial demonstrated a small benefit of n-3 PUFA administration with respect to reducing cardiovascular mortality in patients with HF (of whom 20% had concomitant AF). 126 However, the role of n-3 PUFA in preventing AF has been controversial. A meta-analysis of 10 randomized controlled trials evaluating the role of n-3 PUFA for AF demonstrated that there were no significant benefits.
of n-3 PUFA supplementation for AF prevention. Also, a recent randomized control trial by Kowey et al demonstrated no clinically significant benefit from this agent in prevention of recurrent AF.

Device-Based and Ablative Therapies for AF and HF

In patients with symptomatic AF and rapid ventricular response refractory to pharmacological therapy, radiofrequency atrioventricular (AV) nodal ablation with subsequent pacemaker placement can improve cardiac performance. Manolis et al showed that in 46 patients with atrial tachyarrhythmias and rapid ventricular response refractory to medical therapy who underwent AV nodal ablation with placement of a permanent pacemaker, the LVEF improved from a mean of 42% to a mean of 50% after a 2-year follow-up. In the subgroup of patients with HF, the degree of improvement was even greater (32% to 48%). Moreover, the NYHA functional class improved from 2.7 to 1.4.

However, long-term outcomes of the “ablate and pace” strategy have been less favorable. In a study of 71 elderly patients with pharmacologically refractory AF assigned to either AV nodal ablation with pacing or AF ablation, AV nodal ablation with pacing was associated with a higher incidence of new HF compared with ablation of the AF after 5 years of follow-up (53% versus 24%). AV node ablation with pacing resulted in a significantly lower LVEF (45 versus 51) and a higher NYHA functional class (1.7 versus 1.4) compared with the group assigned to AF ablation.

A large body of evidence has emerged recently that underscores the harmful effects of long-term right ventricular pacing. LV dyssynchrony imposed by right ventricular pacing can lead to LV remodeling with dilatation and decreases in LVEF. Mechanical ventricular dyssynchrony is an established contributor to HF, and cardiac resynchronization therapy (CRT) has emerged as an effective device-based therapy to improve symptoms and mortality in patients. CRT, through its salutary benefits on hemodynamic function and cardiac remodeling, has also been theorized to reduce the incidence of AF. However, in the Cardiac Resynchronization in Heart Failure Study (CARE-HF) trial, randomization to CRT did not result in any reduction in the incidence rates of AF at 30-months of follow-up. It must be noted that approximately 10% of patients enrolled in CARE-HF who had been classified as having “permanent” AF converted to sinus rhythm after implantation with CRT. Patients with AF and HF who undergo biventricular pacemaker or ICD implantation remain less likely to respond to CRT, perhaps due to low rates of biventricular pacing. A recent analysis showed that AF patients who underwent AV node ablation and CRT implantation had significantly improved EFs, exercise tolerance, and decreased hospitalizations as compared to patients with AF and HF who underwent biventricular ICD implantation alone.

Although recent studies, including RACE, AFFIRM, and AF-CHF, suggest an equivalent outcome for pharmacological rhythm or rate control, new evidence from the AFFIRM investigators showed that the presence of sinus rhythm was associated with significantly improved survival. The effect of sinus rhythm on patients with HF remains to be determined, and we hope that further analysis from AF-CHF will help to clarify this question. It is conceivable, however, that benefits of rhythm control are counterbalanced by the lack of effective antiarrhythmic agents, coupled with their significant adverse effects. Moreover, sinus rhythm was maintained in only 63% of patients in the rhythm control arm of AFFIRM at 5 years. This highlights the difficulty of rhythm control with currently available antiarrhythmic agents and the need for effective therapy to maintain sinus rhythm while minimizing toxicity.

One of the promising therapeutic options for AF may therefore be a curative catheter ablation. The observation that AF could be initiated by ectopic beats originating in the pulmonary veins sparked new interest in catheter-based techniques to isolate the pulmonary veins from the surrounding left atrium (Figure 4). Catheter

Figure 5: AF ablation and improvement in LVEF in patients with idiopathic cardiomyopathy

All but 3 patients experienced an increase in LVEF, with the mean LVEF increasing from 42±9% to 57±7% (P<0.001). Modified from Gentlesk et al, J Cardiovasc Electrophysiol. 2007; 18:9 –14. Permission obtained from the publisher. Copyright © 2007, Wiley-Blackwell
Ablation of AF has also been shown to be effective in patients with HF (Figure 5). Five studies143-147 have specifically focused on the benefit of catheter-based AF ablation among patients with AF and HF. These studies have shown that catheter-based AF ablation significantly improved the cardiac function, symptom burden, exercise capacity, and quality of life of patients with AF and HF. The Pulmonary vein Antral isolation versus AV node ablation with Biventricular pacing for the treatment of AF in patients with CHF (PABA-CHF) trial148 demonstrated that pulmonary vein isolation resulted in significant improvement in EF and 6-minute walk distance as compared to AV nodal ablation and biventricular pacemaker implantation. On the basis of these data, the 2011 ACCF/AHA/HRS guidelines now recommend considering catheter-based AF ablation for the treatment of symptomatic, paroxysmal AF in patients with significant left atrial dilatation or with significant LV dysfunction.84

The Cox maze surgical procedure involves placing multiple incisions within the left and right atrial myocardium, with the intention of interrupting potential reentry and isolating AF triggers. The Cox-maze procedure has excellent long-term efficacy, with nearly 90% of treated patients remaining in sinus rhythm at 10 years. Although it is usually avoided in patients with HF, the Cox-maze operation has been shown to be safe and effective for rhythm control of AF.149,150 Although the full “cut and sew” Cox maze procedure (with lesions created by surgical incision) is now rarely performed due to its complexity, variants of this procedure are in widespread use, typically utilizing either cryo- or radiofrequency energy to create ablative lesions.

Conclusions:

AF and HF share common mechanisms and treatment strategies; consequently, therapies directed toward HF may protect the heart against the occurrence of AF. Although restoration of sinus rhythm in patients with HF may offer hemodynamic and clinical benefits, recent clinical trials have failed to demonstrate the clinical advantage of sinus rhythm over optimal rate control. The deleterious effects of currently available antiarrhythmic drugs, coupled with their low efficacy, may blunt the potential benefit of sinus restoration. A variety of therapies, including drugs, devices, and ablation procedures, are available to aid in the management of symptomatic and asymptomatic patients with both AF and HF. Recent advances in catheter-based ablative therapies for AF have been demonstrated to be effective in well-selected patients with HF, resulting in significant improvements in cardiac function, symptoms, and quality of life.

Along with further advances in pharmacotherapy and catheter-based ablative therapies, more trials comparing ablation with medical therapy in patients with AF and HF are needed before a standardized therapy for patients with AF and HF can be recommended. Based on the available therapies outlined above, it is fair to say that an individualized approach is a better strategy and might help improve symptoms and prognosis for patients with AF and HF.

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