

Atrial Fibrillation and Heart Failure Treatment Considerations for a Dual Epidemic

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Atrial fibrillation (AF) and heart failure have emerged as new cardiovascular epidemics over the last decade.¹ Heart failure affects ≈5 million patients in the United States, and >550 000 patients are diagnosed with new heart failure each year.² Although the incidence of heart failure remained stable over the past 50 years, the prevalence of heart failure in the United States has steadily increased. Heart failure is the primary reason for 12 to 15 million office visits and 6.5 million hospital days yearly.³ From 1990 to 1999, the annual number of hospitalizations increased from ≈800 000 to >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.⁴ The steadily increasing number of patients with heart failure is due partially to better treatment and “salvage” of patients with acute myocardial infarctions earlier in life.² 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.⁵ In 2007, the American Heart Association estimated that \$33 billion was spent on heart failure alone.⁶

AF is the most common arrhythmia in clinical practice, accounting for approximately one third of admissions resulting from cardiac rhythm disturbances. An estimated 2.3 million people in North America have AF. During the last 20 years, hospital admissions for AF have increased by 66% for a number of reasons, including the aging of the population, the rising prevalence of chronic heart disease, and more frequent diagnosis as a result of increased monitoring.⁷ The recent 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, an estimate based on the growing proportion of elderly individuals in the United States.⁸ The predicted future prevalence of AF was even greater in a community-based study by Miyasaka and colleagues.⁹ They observed that the age-adjusted incidence of AF increased by 12.6% over the period from 1980 to 2000. Assuming the rate of increase in incidence remains unabated and assuming that these incidence rates can be applied to the entire US population, the projected number of persons with AF in the United States could reach 15.9 million by 2050.

The Association Between AF and Heart Failure

The association between AF and heart failure was appreciated almost a century ago¹⁰; Paul Dudley White noted, “Since auricular fibrillation so often complicates very serious heart disease, its occurrence may precipitate heart failure or even death, unless successful therapy is quickly instituted.”¹¹ The reported prevalence of AF in modern heart failure series ranges from 13% to 27%.^{12–16} In the Framingham Heart Study, 1470 participants developed either new AF or heart failure between the years 1948 and 1995. Among these participants, a total of 383 individuals (26%) developed both AF and heart failure.¹⁷ Moreover, the prevalence of AF in patients with heart failure increased in parallel with the severity of the disease, ranging from 5% in patients with mild to 10% to 26% among patients with moderate up to 50% in patients with severe heart failure.¹⁸

Although the causative relationship between the 2 conditions 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. These factors are associated with myocardial cellular and extracellular alterations, electrophysiological and neurohormonal changes that combine to create an environment that predisposes the heart to both myocardial failure and AF.¹⁹

AF and Heart Failure: A Cause or a Consequence?

The pathophysiological relationship between AF and heart failure has been only partially elucidated and has therefore remained a subject of vibrant research. AF may facilitate the development or progression of heart failure in several ways (Figure 1). The increase in resting heart rate and the exaggerated heart rate response to exercise result in shorter diastolic filling time, leading to a reduction in cardiac output. This is further affected by the irregularity of the ventricular response: The reduction in left ventricular (LV) filling during short cycles is not completely compensated for by increased filling during longer cycles. The loss of effective atrial contractile function also contributes, even more importantly

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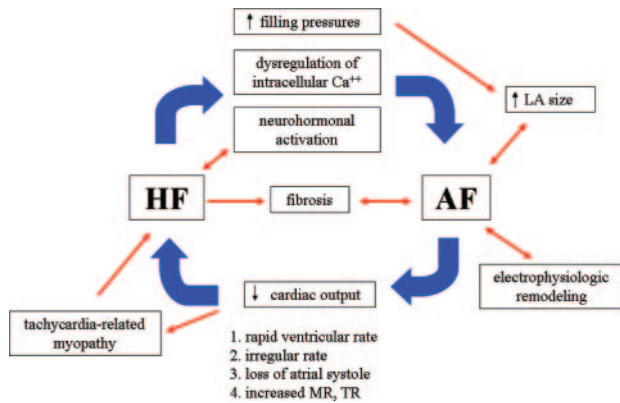


Figure 1. AF and heart failure (HF): a vicious pathophysiological cycle. LA indicates left atrial; MR, mitral regurgitation; and TR, tricuspid regurgitation.

in patients with diastolic dysfunction. In a prospective study of 344 patients with heart failure and sinus rhythm, the onset of AF was associated with highly significant worsening of the New York Heart Association (NYHA) functional class, peak oxygen consumption, and cardiac index, along with increased mitral and tricuspid regurgitation.²⁰ Restoration of sinus rhythm improves cardiac output, exercise capacity, and maximal oxygen consumption.²¹

AF is the most common cause of tachycardia-induced cardiomyopathy (Figure 2). The first case of tachycardia-induced cardiomyopathy was reported in 1913 in a young man with AF and a rapid ventricular rate who developed unexplained LV dilatation and heart failure.²² In 1937, a similar case was reported in which heart failure was reversed after restoration of sinus rhythm.²³ Whipple et al²⁴ provided the first experimental model for this condition, demonstrating that rapid and protracted atrial pacing led to low-output heart failure. Subsequent investigations have confirmed that persistent tachycardias can cause heart failure and that elimination of these arrhythmias reverses the hemodynamic and clinical manifestations associated with this syndrome.^{25–29} The mech-

anisms responsible for tachycardia-induced cardiomyopathy have not been fully elucidated; however, experiments in animal models suggest that myocardial ischemia, myocardial energy depletion, and abnormalities in calcium regulation all may contribute.³⁰ The incidence of tachycardia-induced cardiomyopathy is unknown; most reports have been small, retrospective series or case studies involving mostly patients with AF. Nevertheless, some component of tachycardia-induced myopathy is seen in 25% to 50% of those with LV dysfunction and AF.^{31–33} The detrimental effects of AF on heart failure also may derive from the antiarrhythmic therapy itself. Some antiarrhythmic drugs have negative inotropic effects, whereas others are associated with an increased proarrhythmic risk, especially in patients with structural heart disease.³⁴

Similarly, heart failure can increase the risk for the development of AF in several ways, including elevation of cardiac filling pressures, dysregulation of intracellular calcium, and autonomic and neuroendocrine dysfunction (Figure 1). Atrial stretch results in activation of stretch-activated ionic currents, leading to increased dispersion of refractoriness and alterations in anisotropic and conduction properties, facilitating AF.³⁵ Inhibition of these stretch-activated currents by gadolinium can reduce the susceptibility to AF in response to atrial pressure overload.³⁶ Heart failure has been associated with increased interstitial fibrosis.³⁷ This increase in fibrosis can lead to abnormal conduction through the atria, creating a substrate for AF in animal models.^{37–39} Dysregulation of intracellular calcium, an important feature in the pathophysiology of heart failure, also has been found to be associated with AF. The key regulators of intracellular calcium metabolism, the ryanodine receptor and the sarcoplasmic reticulum Ca²⁺-ATPase, are downregulated in AF.^{40,41} In addition, heart failure is characterized by neurohormonal activation, with elevated concentrations of catecholamine and angiotensin II; the degree of neurohormonal activation correlates with the severity of heart failure and has become a target of pharmacological inhibition. Interestingly, neurohormonal activation

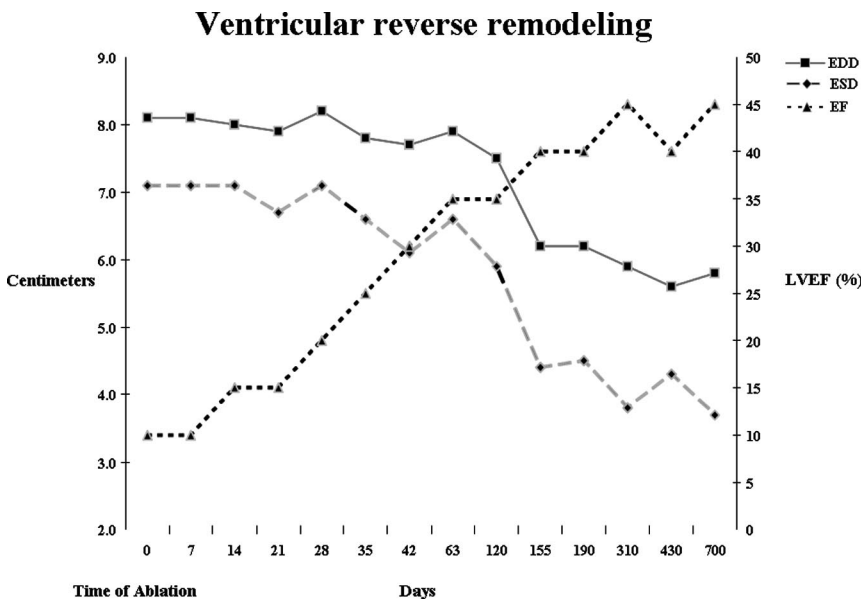


Figure 2. Ventricular reverse remodeling in an 18-year-old patient with unrecognized atrial tachycardia-induced cardiomyopathy. After atrial tachycardia ablation, a significant reduction in LV dimension was noted, corroborated by a gradual increase in LVEF from 12% to 45%. EDD indicates end-diastolic dimension; ESD, end-systolic dimension. Modified from Ilkanoff et al. Changes in ventricular dimensions and function during recovery of atrial tachycardia-induced cardiomyopathy treated with catheter ablation. *J Cardiovasc Electrophysiol.* 2007;18:1104–1106, with permission of the publisher. Copyright © 2007 Wiley-Blackwell.

Table. Prognostic Significance of AF in Patients With Heart Failure

Author/Substudy	Year	NYHA Class	Patients, n	AF, %	Follow-Up, y	Patients in SR, n	Patients With AF, n	P	Predictor
Middlekauff et al ¹²	1991	III–IV	395	19	1.5	29	48	0.0013	Yes
Carson et al ¹³									
V-HeFT I	1993	II–III	632	15	2.5	64	54	0.86	No
V-HeFT II		II–III	795	13	2.0	52	46	0.68	
Dries et al ⁴⁸ /SOLVD	1998	I–IV	6517	6	2.8	23	34	<0.001	Yes
Mahoney et al ¹⁴	1999	III–IV	234	27	1.1	16	23	0.21	No
Middlekauff et al ¹²									
1985–1989	1998	III–IV	359	20	2.0	45	61	0.002	Yes
1990–1993		III–IV	391	24	2.0	25	34	0.09	No
Mathew/DIG ^{45a}	2000	I–IV	7788	11	3.0	32	43	0.0001	Yes
Crijns/PRIME II ^{45b}	2000	III–IV	409	84	3.4	47	60	NS*	No
Køber/VALIANT	2006	I–IV	14703	15	3.0	20	37	<0.0001	Yes
Swedberg et al ⁵¹ /COMET	2005	II–IV	3029	20	5.0	37	42	NS	No*

SR indicates sinus rhythm; DIG, Digitalis Investigation Group; PRIME II, Prospective Randomized study of Ibopamine on Mortality and Efficacy.

*After adjustment for important prognostic variables.

also promotes structural remodeling and atrial fibrosis, thus altering atrial conduction properties and promoting AF.^{37,42}

AF: Independent Risk Factor or a Marker of Advanced Disease?

The prognostic significance of AF in patients with heart failure remains controversial because no consensus exists that AF is an independent risk factor of adverse outcome (the Table).^{13,43–45b} In the Framingham Heart Study, AF was associated with twice the cardiovascular mortality compared with sinus rhythm. However, the independent contribution of AF to mortality was not assessed.⁴⁶ 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.¹³ Two other relatively small studies also revealed no independent prognostic significance of AF in patients with heart failure.^{14,47} The results of these studies contrast with other, more recent, large heart failure trials. 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.⁴⁸ In the SOLVD registry data, the odds ratio for total mortality among heart failure patients with AF compared with patients in sinus rhythm was 1.81 ($P<0.0001$).⁴⁹ In the Valsartan in Acute Myocardial Infarction (VALIANT) trial of 14 703 patients with acute myocardial infarction complicated by heart failure, AF also was associated with greater long-term morbidity and mortality.⁵⁰ 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 heart failure hospitalization. However, after adjustment for other predictors of prognosis, AF was no longer an independent risk factor for mortality.⁵¹ Middlekauff et al¹² found that patients with advanced heart failure 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 heart failure compared with patients with severe heart failure, in whom the contribution of AF to further impairment in survival was limited. Similarly, Corell et al⁵² found that the presence of AF in outpatients with heart failure 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 al⁵³ 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 heart failure, and the independent effect of AF on mortality is inversely related to the severity of heart failure.

Although multicenter studies in patients with heart failure have provided valuable data on the importance of AF in this setting, it is critical to realize that AF was not the focus of these studies and that the data quality with respect to the presence of AF has not been adjudicated. In most of these trials, monitoring for the onset of AF or recurrence, in the absence of hospitalization, consists of ECGs at the study onset and scheduled visits. This approach lacks the power to detail the variety of ways AF affects patients.

Even taking this limitation into account, it is interesting that many studies have found that new-onset AF carries a particularly grave prognosis in patients with heart failure. Ahmed and Perry⁵⁴ found that among 944 elderly patients hospitalized with heart failure, the onset of new AF carried a significantly higher risk for death compared with patients with no AF or those with chronic AF (hazard ratio, 1.41; 95% confidence interval, 1.08 to 1.83). Over 80% of patients hospitalized with heart failure and found to have new-onset AF died within 4 years of discharge compared with only 61% to 66% in those without AF or with persistent AF. In a 21-year community-based cohort study of patients with

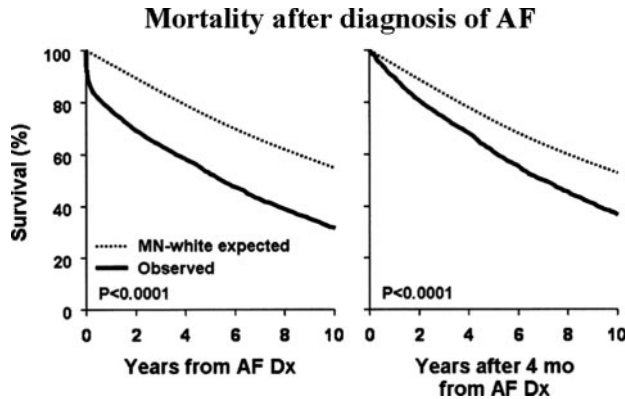


Figure 3. Survival of patients with AF compared with age- and gender-matched control subjects in a 21-year community-based study. Survival for the entire study population of patients diagnosed with first AF (left) and for the subgroup of survivors who lived beyond the first 4 months after the initial diagnosis (Dx) (right) compared with the age- and gender-matched general Minnesota population. Adapted from Miyasaka et al. Mortality trends in patients diagnosed with first atrial fibrillation: a 21-year community-based study. *J Am Coll Cardiol.* 2007;49:986–992, copyright © 2007, with permission from the American College of Cardiology.

newly diagnosed AF, the mortality risk was substantially higher within the first 4 months, with a hazard ratio of 9.62 (95% confidence interval, 8.93 to 10.32) compared with the hazard ratio of 1.66 (95% confidence interval, 1.59 to 1.73) thereafter (Figure 3).⁵⁵ In an analysis of COMET, new-onset AF, but not baseline AF, remained an independent predictor of all-cause mortality.⁵¹ Development of new AF was associated with increased mortality in the Framingham Heart Study as well.¹⁷ Pozzoli et al²⁰ prospectively studied patients with mild heart failure in sinus rhythm and found that the onset of AF was associated with a clinical and hemodynamic deterioration, predisposition to systemic thromboembolism, and overall poorer prognosis. The association between new-onset AF and heart failure progression is not evidence for a causative relationship and may simply be a marker for disease progression. Nonetheless, few plausible mechanisms may explain how new development of AF can lead to clinical and hemodynamic deterioration. First, the adequacy of rate control achieved either naturally over time or by medications is usually better than ventricular rates accompanying a new presentation of AF. Second, the potential to develop adverse effects to antiarrhythmic medications is highest during the initiation phase. Third, initiation of warfarin therapy, especially in elderly patients, carries considerable risk for both underanticoagulation and overanticoagulation despite adherence to well-established warfarin initiation protocols.⁵⁶ Fourth, development of new AF in a failing heart may pose a significant metabolic demand on the myocardial tissue until compensatory metabolic pathways are upregulated.

Therapeutic Considerations

Rate or Rhythm Control

AF with rapid ventricular response can lead to systolic heart failure, whereas restoration of sinus rhythm or appropriate rate control can reverse this process.⁵⁷ Controversy still exists

as to whether patients with heart failure respond better to rhythm restoration or ventricular rate control, commonly referred to as the issue of rhythm or 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.^{58,59} 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).⁶⁰ 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),⁶¹ Strategies of Treatment of Atrial Fibrillation (STAF),⁶² and Pharmacological Intervention in Atrial Fibrillation (PIAF)⁶³ 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.

Nevertheless, extrapolation from these studies to patients with heart failure should be done with caution. These studies included older patients or young patients with increased risk for stroke who were sufficiently tolerant of AF to be randomized. LV function was normal in 76% of AFFIRM patients, and only 9% had an NYHA functional class of II or greater. A separate large study of >1000 patients with heart failure and AF similarly demonstrated no benefit on overall mortality of rhythm compared with rate control.⁶⁴ The recently published Atrial Fibrillation and Congestive Heart Failure (AF-CHF) trial was the first prospective randomized study to examine the effect of rate versus rhythm control in a heart failure population.⁶⁵ A total of 1376 patients with AF and systolic heart failure (mean LVEF, 27%) were randomized to rhythm control (typically with amiodarone) versus rate control. After a mean follow-up of 3 years, the investigators found that rhythm control did not improve mortality, hospitalization resulting from heart failure exacerbation, or stroke compared with rate control. This study therefore extends the findings of the AFFIRM trial to patients with heart failure, in whom the theoretical benefit of rhythm control would seem to be higher. Clinicians should be cautious in their acceptance of the AF-CHF trial as the final and definitive study about the role of rate or rhythm control in patients with heart failure. 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%.⁶⁶

In addition, heart failure is caused by heterogeneous pathophysiological processes; hence, the hemodynamic effects of AF may be different in various forms of heart failure. It is plausible that the reduction in diastolic filling time (caused by elevation in heart rate) and the atrial contribution to LV filling is greater in patients with restrictive physiology such as patients with diastolic dysfunction. In theory, these patients may have a greater benefit from rhythm control. AF-CHF, however, studied only patients with systolic heart failure. Moreover, we currently know little about the characteristics of incident versus prevalent AF in AF-CHF, and it is possible that, similar to AFFIRM, only patients with relatively stable symptoms referable to AF were submitted to randomization.

Ventricular Rate Control

Optimal ventricular rate in patients with AF is 60 to 80 bpm at rest and 90 to 115 bpm during moderate exertion.⁶⁷ Therefore, 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. β -Blockers should be the first choice for rate control in patients with chronic heart failure and AF. β -Blockers may both control the ventricular response to AF and improve survival in patients with heart failure. A retrospective analysis of the US Carvedilol Heart Failure Trial demonstrated that carvedilol therapy improved outcome in patients with concomitant AF and heart failure.⁶⁸ A retrospective analysis of COMET demonstrated a survival benefit for carvedilol in patients with AF, similar to the larger trial.⁵¹ In acute AF with rapid ventricular response, the use of digoxin, which has a relatively slow onset of action, is likely to be ineffective. Moreover, digoxin slows ventricular response to AF through enhancement of vagal tone and therefore is less effective in states of increased sympathetic tone such as exercise or worsening heart failure. However, digoxin improves symptoms and reduces hospitalizations in patients with heart failure and exerts a synergistic effect with β -blockers.^{69–71} A retrospective analysis of the US Carvedilol Heart Failure Trials program demonstrated improved survival with carvedilol in patients also treated with digoxin.⁶⁸ Therefore, digoxin may be useful as an adjunct therapy to β -blockers in patients with AF and heart failure. Nondihydropyridine calcium channel blockers (including verapamil and diltiazem) also are effective rate-controlling agents. However, because of their negative inotropic effect, they may not be tolerated at doses required for optimal ventricular rate control, especially in patients with low LVEF.

Rhythm Restoration or Control

Although a variety of antiarrhythmic agents are available for the treatment of AF in patients with structurally normal hearts, patients with heart failure are particularly susceptible to side effects of some commonly used antiarrhythmic agents. The Cardiac Arrhythmia Suppression Trial (CAST) was a randomized, placebo-controlled study that examined the effect of class IC antiarrhythmic drugs on patients with ven-

tricular ectopy after myocardial infarction. This study showed that therapy with either flecainide or encainide was associated with increased mortality.^{72,73} The applicability of the CAST results to other populations (eg, those with chronic heart failure and no active ischemia) or other class IC antiarrhythmic drugs 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.

The cornerstone of antiarrhythmic therapy in patients with heart failure is amiodarone, sotalol, and dofetilide. Amiodarone is among the most effective antiarrhythmic agents for the suppression of AF. Amiodarone is a class III agent (potassium channel blocker) with some overlap functional activity of class I agents such as β -blockers and calcium channel blockers. Amiodarone appears to be safe and effective in patients with heart failure.⁷⁴ Despite its effectiveness, the use of amiodarone in patients with heart failure is associated with increased risk for symptomatic bradycardia requiring implantation of permanent pacemaker.⁷⁵

Dofetilide, a newer class III antiarrhythmic agent, also is commonly used to suppress AF. In the Danish Investigations of Arrhythmia and Mortality on Dofetilide (DIAMOND) congestive heart failure substudy, dofetilide was significantly more effective than placebo in restoring and maintaining sinus rhythm in patients with AF and heart failure.⁷⁶ In addition, dofetilide therapy was associated with reduced hospitalizations for heart failure. Therapy with dofetilide is usually initiated in the hospital with close monitoring of the QT interval and dosage adjustments in patients with impaired renal function. Nevertheless, even with careful monitoring, therapy with dofetilide has been associated with increased risk for torsades de pointes, particularly in elderly patients with heart failure.

Other, nonantiarrhythmic drug therapy has demonstrated effectiveness in reducing the incidence and recurrent rates of AF in the general population and in patients with heart failure. 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.^{77–80} 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 heart failure.^{81,82} 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 heart failure.

Therapy with β -blockers also was associated with reduced risk for AF. In a meta-analysis of 7 randomized, placebo-controlled trials including 11 952 patients with heart failure already taking angiotensin-converting enzyme inhibitors, β -blockers significantly reduced the incidence of new AF from 39 to 28 per 1000 patient-years (relative risk reduction, 27%).⁸³

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 heart failure.^{84,85} A recent meta-analysis of randomized trials with statins showed that their use was

associated with a significant decreased risk of AF compared with control subjects (odds ratio, 0.39; 95% confidence interval, 0.18 to 0.85, $p = 0.02$). Moreover, the benefit of statin therapy seemed more marked in secondary prevention of AF (odds ratio, 0.33) than for new-onset or postoperative AF (odds ratio, 0.60).⁸⁶

Ablation and Pacemaker Therapy

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 al⁸⁷ 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 $42 \pm 16\%$ to a mean of $50 \pm 14\%$ after a 2-year follow-up. In the subgroup of patients with heart failure, the degree of improvement was even greater ($32 \pm 9\%$ to $48 \pm 8\%$). Moreover, the NYHA functional class improved from 2.7 ± 0.6 to 1.4 ± 0.8 ($P < 0.001$).

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 heart failure 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 ($44 \pm 8\%$ versus $51 \pm 10\%$) and a higher NYHA functional class (1.7 ± 0.9 versus 1.4 ± 0.7) compared with the group assigned to AF ablation.⁸⁸

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.⁸⁹ Mechanical ventricular dyssynchrony is an established contributor to heart failure, and cardiac resynchronization therapy (CRT) has emerged as an effective device-based therapy to improve symptoms and mortality in patients.⁹⁰ This therapy also has proved to be effective in patients with heart failure and AF, although patients with AF show a milder degree of improvement with CRT compared with patients in sinus rhythm.⁹¹

The clinical efficacy of CRT also was assessed in patients with heart failure and AF with slow ventricular rate necessitating permanent ventricular pacing.⁹² Thirty-seven patients with NYHA class III heart failure underwent implantation of a biventricular pacemaker. This single-blind, randomized, controlled, crossover study compared clinical parameters during two 3-month treatment periods of conventional right ventricular and biventricular pacing. It showed that biventricular pacing improved peak oxygen uptake and exercise tolerance and reduced the number of hospitalizations for heart failure. An important issue remains whether CRT in patients with AF should be accompanied by AV nodal ablation to avoid inhibition of therapy by rapid intrinsic AV nodal conduction. A recent study compared the efficacy of CRT in patients with AF who underwent AV nodal ablation and

patients in whom rate control was achieved pharmacologically. This study showed that patients who underwent AV nodal ablation with CRT achieved significantly better symptomatic relief with improvement in their LV function, a benefit that was maintained for up to 4 years.⁹³ The effect of CRT on the incidence of new AF is still controversial. CRT can promote reverse remodeling of the left ventricle, reduce the degree of mitral regurgitation and left atrial stretching, and thus theoretically reduce the incidence of AF. However, the Cardiac Resynchronization in Heart Failure (CARE-HF) study did not demonstrate a reduction in the incidence of AF among patients randomized to CRT.⁹⁴

AF Ablation

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.⁶⁰ The effect of sinus rhythm on patients with heart failure 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.⁵⁸

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).^{95,96} Catheter ablation of AF also has been shown to be effective in patients with heart failure (Figure 5).^{97–100} In a prospective study of 58 patients with systolic heart failure, AF ablation resulted in significant improvement in LV function, exercise capacity, symptoms, and quality of life. After a mean follow-up of 1 year, 78% of the patients maintained sinus rhythm.⁹⁷ This important study demonstrated that curative ablation for AF offers the unique opportunity to retain the benefits of rhythm control without the detrimental effects of antiarrhythmic drugs. More recently, the Pulmonary-Vein Isolation for AF in Patients With Heart Failure (PABA-CHF)⁵⁵ demonstrated that a strategy of pulmonary vein isolation was superior to AV node ablation combined with biventricular pacing in patients with heart failure. Patients randomized to pulmonary vein isolation had a significantly higher mean LVEF (35% versus 28%), a longer distance on the walk test (340 versus 297 m), and a higher quality-of-life score.

Although AF ablation is a promising therapeutic intervention in patients with heart failure, several questions remain to be answered before this procedure is ready for prime time. First, improvement in LV function after AF ablation was more significant in patients who were inadequately rate controlled, suggesting that improvement was due partially to eliminating tachycardia-induced myopathy. The effect of AF

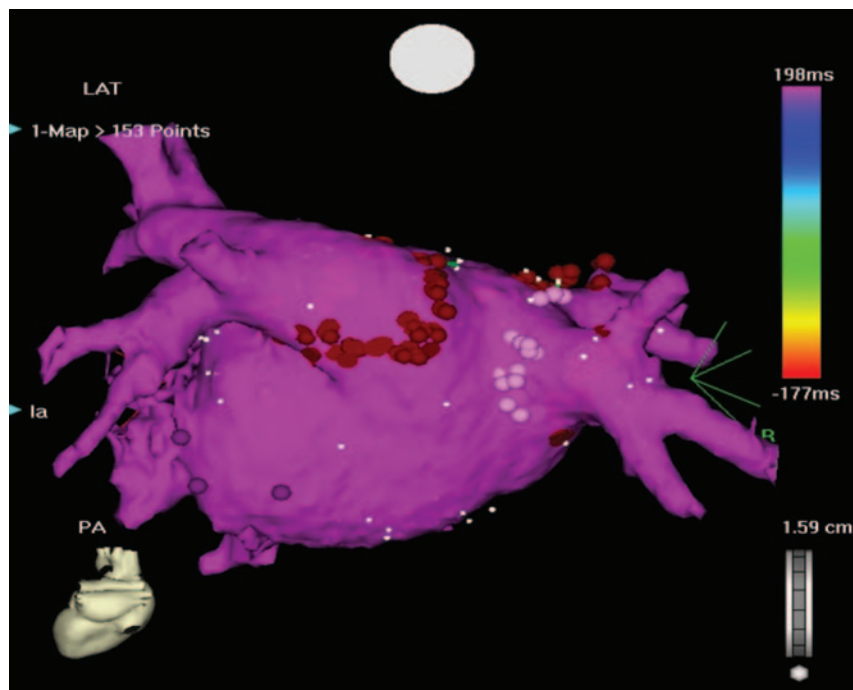


Figure 4. Pulmonary vein isolation using advanced imaging techniques. A pulmonary artery (PA) view of a computed tomography angiogram of the left atrium is shown. The images from the computed tomography angiogram are imported and registered into a 3-dimensional mapping system. This allows the operator to “drive” the ablation catheter within the context of the anatomic image of the left atrium. Individual ablation lesions are represented by red and pink icons; the pink icons represent low-power lesions over the area where the esophagus is in close contact with the posterior wall of the left atrium. The pulmonary veins are completely surrounded by ablation lesions, electrically isolating the pulmonary vein myocardial sleeves that provide the trigger beats that initiate episodes of atrial fibrillation.

ablation in patients with well-controlled heart rates requires further studies. Second, ablative procedures are associated with new scar formation, paradoxically augmenting interstitial fibrosis. This effect can potentially perpetuate the progression of AF and therefore requires further investigation. Finally, the cost-effectiveness of this procedure in patients with heart failure has not yet been studied.

Catheter ablation of AF is evolving rapidly, and newer techniques to integrate electroanatomic mapping with computed tomographic and magnetic resonance imaging into the ablation procedure will likely lead to further improvements in the efficacy and safety of this procedure.

Conclusions

AF and heart failure have emerged as being among the most common cardiac disorders afflicting our society. They often occur together, and their combination is associated with increased morbidity and mortality compared with each dis-

order alone. AF and heart failure share common mechanisms and treatment strategies; consequently, therapies directed toward heart failure may protect the heart against the occurrence of AF. Although restoration of sinus rhythm in patients with heart failure 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. Recent advances in catheter-based ablative therapies for AF have been demonstrated to be effective in well-selected patients with heart failure, resulting in significant improvements in cardiac function, symptoms, and quality of life.

It will be years before sufficient data are generated to specifically guide practice when these 2 common disease processes intersect. Until that time, several concepts guide our care of these patients. It is clear that optimal pharmacological therapy for heart failure has a beneficial impact on the progression of AF. The impact of new AF in the setting of heart failure can be dramatic in individual patients, and it is possible that aggressive therapy to restore sinus rhythm during this window of opportunity may have lasting benefit. We typically recognize these patients by their relative youth (raising the possibility that tachycardia-related myopathy may be a sole cause of the recognized LV dysfunction) or the presence of severe symptoms referable to AF. In patients with new-onset and persistent AF, a test of cardioversion may be helpful to investigate whether sinus rhythm improves their symptoms of heart failure. When it is demonstrated to be important, maintenance of sinus rhythm by whatever means necessary seems reasonable in individual patients.

Disclosures

Dr Callans has received honoraria from Biosense Webster, St. Jude Medical, Boston Scientific, and Sanofi-Aventis. The other authors report no disclosures.

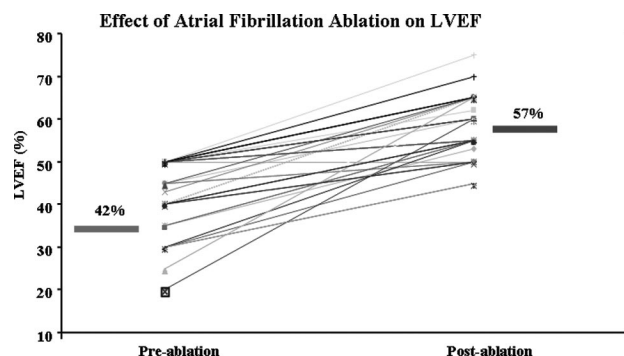


Figure 5. Effect of AF ablation on LVEF in 50 patients with idiopathic cardiomyopathy. All but 3 patients experienced an increase in LVEF, with the mean LVEF increasing from $42 \pm 9\%$ to $57 \pm 7\%$ ($P < 0.001$). Modified from Gentlesk et al,⁹⁸ with permission of the publisher. Copyright © 2007, Wiley-Blackwell.

References

- Braunwald E. Shattuck Lecture: cardiovascular medicine at the turn of the millennium: triumphs, concerns, and opportunities. *N Engl J Med*. 1997;337:1360–1369.
- Heart Disease and Stroke Statistics: 2005 Update. Dallas, Tex: American Heart Association; 2005.
- O'Connell JB, Bristow MR. Economic impact of heart failure in the United States: time for a different approach. *J Heart Lung Transplant*. 1994;13:S107–S112.
- Koelling TM, Chen RS, Lubwama RN, L'Italien GJ, Eagle KA. The expanding national burden of heart failure in the United States: the influence of heart failure in women. *Am Heart J*. 2004;147:74–78.
- Massie BM, Shah NB. Evolving trends in the epidemiologic factors of heart failure: rationale for preventive strategies and comprehensive disease management. *Am Heart J*. 1997;133:703–712.
- Heart disease and stroke statistics—2007 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation*. 2007;115:e69–e171.
- Friberg J, Buch P, Scharling H, Gadsbøhl N, Jensen GB. Rising rates of hospital admissions for atrial fibrillation. *Epidemiology*. 2003;14:666–672.
- Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, Singer DE. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *JAMA*. 2001;285:2370–2375.
- Miyasaka Y, Barnes ME, Gersh BJ, Cha SS, Bailey KR, Abhayaratna WP, Seward JB, Tsang TS. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. *Circulation*. 2006;114:119–125.
- Mackenzie J. *Diseases of the Heart*. 3rd ed. London, UK: Oxford Medical Publications; 1914.
- White PD. *Heart Disease*. New York, NY: The McMillan Co; 1937.
- Middlekauff HR, Stevenson WG, Stevenson LW. Prognostic significance of atrial fibrillation in advanced heart failure: a study of 390 patients. *Circulation*. 1991;84:40–48.
- Carson PE, Johnson GR, Dunkman WB, Fletcher RD, Farrell L, Cohn JN. The influence of atrial fibrillation on prognosis in mild to moderate heart failure: the V-HeFT Studies: the V-HeFT VA Cooperative Studies Group. *Circulation*. 1993;87(suppl):VI-102–VI-110.
- Mahoney P, Kimmel S, DeNofrio D, Wahl P, Loh E. Prognostic significance of atrial fibrillation in patients at a tertiary medical center referred for heart transplantation because of severe heart failure. *Am J Cardiol*. 1999;83:1544–1547.
- Senni M, Tribouilloy CM, Rodeheffer RJ, Jacobsen SJ, Evans JM, Bailey KR, Redfield MM. Congestive heart failure in the community: a study of all incident cases in Olmsted County, Minnesota, in 1991. *Circulation*. 1998;98:2282–2289.
- Deedwania PC, Singh BN, Ellenbogen K, Fisher S, Fletcher R, Singh SN. Spontaneous conversion and maintenance of sinus rhythm by amiodarone in patients with heart failure and atrial fibrillation: observations from the Veterans Affairs Congestive Heart Failure Survival Trial of Antiarrhythmic Therapy (CHF-STAT): the Department of Veterans Affairs CHF-STAT Investigators. *Circulation*. 1998;98:2574–2579.
- Wang TJ, Larson MG, Levy D, Vasan RS, Leip EP, Wolf PA, D'Agostino RB, Murabito JM, Kannel WB, Benjamin EJ. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. *Circulation*. 2003;107:2920–2925.
- Maisel WH, Stevenson LW. Atrial fibrillation in heart failure: epidemiology, pathophysiology, and rationale for therapy. *Am J Cardiol*. 2003;91:2D–8D.
- Kareti KR, Chiong JR, Hsu SS, Miller AB. Congestive heart failure and atrial fibrillation: rhythm versus rate control. *J Card Fail*. 2005;11:164–172.
- Pozzoli M, Cioffi G, Traversi E, Pinna GD, Cobelli F, Tavazzi L. Predictors of primary atrial fibrillation and concomitant clinical and hemodynamic changes in patients with chronic heart failure: a prospective study in 344 patients with baseline sinus rhythm. *J Am Coll Cardiol*. 1998;32:197–204.
- Gosselink AT, Crijns HJ, van den Berg MP, van den Broek SA, Hillege H, Landsman ML, Lie KI. Functional capacity before and after cardioversion of atrial fibrillation: a controlled study. *Br Heart J*. 1994;72:161–166.
- Gossage AM, Braxton JA. On auricular fibrillation. *QJM*. 1913;6:435–440.
- Brill IC. Auricular fibrillation with congestive failure and no other evidence of organic heart disease. *Am Heart J*. 1937;13:175–182.
- Whipple GH, Sheffield LT, Woodman EG, Theophilis C, Friedman S. Reversible congestive heart failure due to chronic rapid stimulation of the normal heart. *Proc N Engl Cardiovasc Soc*. 1962;20:39–40.
- Zupan I, Rakovec P, Budihna N, Breclj A, Kozelj M. Tachycardia induced cardiomyopathy in dogs: relation between chronic supraventricular and chronic ventricular tachycardia. *Int J Cardiol*. 1996;56:75–81.
- Armstrong PW, Stopps TP, Ford SE, de Bold AJ. Rapid ventricular pacing in the dog: pathophysiologic studies of heart failure. *Circulation*. 1986;74:1075–1084.
- Wilson JR, Douglas P, Hickey WF, Lanoce V, Ferraro N, Muhammad A, Reichel N. Experimental congestive heart failure produced by rapid ventricular pacing in the dog: cardiac effects. *Circulation*. 1987;75:857–867.
- Zipes DP. Atrial fibrillation: a tachycardia-induced atrial cardiomyopathy. *Circulation*. 1997;95:562–564.
- Van Gelder IC, Crijns HJ, Blanksma PK, Landsman ML, Posma JL, Van Den Berg MP, Meijler FL, Lie KI. Time course of hemodynamic changes and improvement of exercise tolerance after cardioversion of chronic atrial fibrillation unassociated with cardiac valve disease. *Am J Cardiol*. 1993;72:560–566.
- Shinbane JS, Wood MA, Jensen DN, Ellenbogen KA, Fitzpatrick AP, Scheinman MM. Tachycardia-induced cardiomyopathy: a review of animal models and clinical studies. *J Am Coll Cardiol*. 1997;29:709–715.
- Luchsinger JA, Steinberg JS. Resolution of cardiomyopathy after ablation of atrial flutter. *J Am Coll Cardiol*. 1998;32:205–210.
- Redfield MM, Kay GN, Jenkins LS, Mianulli M, Jensen DN, Ellenbogen KA. Tachycardia-related cardiomyopathy: a common cause of ventricular dysfunction in patients with atrial fibrillation referred for atrioventricular ablation. *Mayo Clin Proc*. 2000;75:790–795.
- Edner M, Caidahl K, Bergfeldt L, Darpo B, Edvardsson N, Rosenqvist M. Prospective study of left ventricular function after radiofrequency ablation of atrioventricular junction in patients with atrial fibrillation. *Br Heart J*. 1995;74:261–267.
- Hohnloser SH, Singh BN. Proarrhythmia with class III antiarrhythmic drugs: definition, electrophysiologic mechanisms, incidence, predisposing factors, and clinical implications. *J Cardiovasc Electrophysiol*. 1995;920–936.
- Solti F, Vecsey T, Kékesi V, Juhász-Nagy A. The effect of atrial dilatation on the genesis of atrial arrhythmias. *Cardiovasc Res*. 1989;23:882–886.
- Bode F, Katchman A, Woosley RL, Franz MR. Gadolinium decreases stretch-induced vulnerability to atrial fibrillation. *Circulation*. 2000;101:2200–2205.
- Li D, Fareh S, Leung TK, Nattel S. Promotion of atrial fibrillation by heart failure in dogs: atrial remodeling of a different sort. *Circulation*. 1999;100:87–95.
- Guerra JM, Everett TH 4th, Lee KW, Wilson E, Olgin JE. Effects of the gap junction modifier rotigaptide (ZP123) on atrial conduction and vulnerability to atrial fibrillation. *Circulation*. 2006;114:110–118.
- Lee KW, Everett TH 4th, Rahmutala D, Guerra JM, Wilson E, Ding C, Olgin JE. Pifenidone prevents the development of a vulnerable substrate for atrial fibrillation in a canine model of heart failure. *Circulation*. 2006;114:1703–1712.
- Beuckelmann DJ, Näbauer M, Erdmann E. Intracellular calcium handling in isolated ventricular myocytes from patients with terminal heart failure. *Circulation*. 1992;85:1046–1055.
- Ohkusa T, Ueyama T, Yamada J, Yano M, Fujumura Y, Esato K, Matsuzaki M. Alterations in cardiac sarcoplasmic reticulum Ca^{2+} regulatory proteins in the atrial tissue of patients with chronic atrial fibrillation. *J Am Coll Cardiol*. 1999;34:255–263.
- Cha YM, Dzeja PP, Shen WK, Jahangir A, Hart CY, Terzic A, Redfield MM. Failing atrial myocardium: energetic deficits accompany structural remodeling and electrical instability. *Am J Physiol Heart Circ Physiol*. 2003;284:H1313–H1320.
- Stevenson WG, Stevenson LW, Middlekauff HR, Fonarow GC, Hamilton MA, Woo MA, Saxon LA, Natterson PD, Steimle A, Walden JA, Tilles JH. Improving survival for patients with atrial fibrillation and advanced heart failure. *J Am Coll Cardiol*. 1996;28:1458–1463.
- Deleted in proof.

45. Keogh AM, Baron DW, Hickie JB. Prognostic guides in patients with idiopathic or ischemic dilated cardiomyopathy assessed for cardiac transplantation. *Am J Cardiol*. 1990;65:903–908.
- 45a. The Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. *N Engl J Med*. 1997;336:525–533.
- 45b. Crijns HJ, Tjeerdsma G, de Kam PJ, Boomsma F, van Gelder IC, van den Berg MP, van Veldhuisen DJ. Prognostic value of the presence and development of atrial fibrillation in patients with advanced chronic heart failure. *Eur Heart J*. 2000;21:1238–1245.
46. Kannel WB, Abbott RD, Savage DD, McNamara PM. Epidemiologic features of chronic atrial fibrillation: the Framingham study. *N Engl J Med*. 1982;306:1018–1022.
47. Crijns HJ, Van den Berg MP, Van Gelder IC, Van Veldhuisen DJ. Management of atrial fibrillation in the setting of heart failure. *Eur Heart J*. 1997;18(suppl C):C45–C49.
48. Dries DL, Exner DV, Gersh BJ, Domanski MJ, Waclawiw MA, Stevenson LW. Atrial fibrillation is associated with an increased risk for mortality and heart failure progression in patients with asymptomatic and symptomatic left ventricular systolic dysfunction: a retrospective analysis of the SOLVD trials: Studies of Left Ventricular Dysfunction. *J Am Coll Cardiol*. 1998;32:695–703.
49. *Heart and Stroke Statistics Update*. Dallas, Tex: American Heart Association; 2001.
50. Køber L, Swedberg K, McMurray JJ, Pfeffer MA, Velazquez EJ, Diaz R, Maggioni AP, Mareev V, Opolski G, Van de Werf F, Zannad F, Ertl G, Solomon SD, Zelenkofske S, Rouleau JL, Leimberger JD, Califf RM. Previously known and newly diagnosed atrial fibrillation: a major risk indicator after a myocardial infarction complicated by heart failure or left ventricular dysfunction. *Eur J Heart Fail*. 2006;8:591–598.
51. Swedberg K, Olsson LG, Charlesworth A, Cleland J, Hanrath P, Komajda M, Metra M, Torp-Pedersen C, Poole-Wilson P. Prognostic relevance of atrial fibrillation in patients with chronic heart failure on long-term treatment with beta-blockers: results from COMET. *Eur Heart J*. 2005;26:1303–1308.
52. Corell P, Gustafsson F, Schou M, Markenvard J, Nielsen T, Hildebrandt P. Prevalence and prognostic significance of atrial fibrillation in outpatients with heart failure due to left ventricular systolic dysfunction. *Eur J Heart Fail*. 2007;9:258–265.
53. Pedersen OD, Bagger H, Køber L, Torp-Pedersen C, for the TRACE Study Group. Impact of congestive heart failure and left ventricular systolic function on the prognostic significance of atrial fibrillation and atrial flutter following acute myocardial infarction. *Int J Cardiol*. 2005;100:65–71.
54. Ahmed A, Perry GJ. Incident atrial fibrillation and mortality in older adults with heart failure. *Eur J Heart Fail*. 2005;7:1118–1121.
55. Khan MN, Jaïs P, Cummings J, Di Biase L, Sanders P, Martin DO, Kautzner J, Hao S, Themistoclakis S, Fanelli R, Potenza D, Massaro R, Wazni O, Schweikert R, Saliba W, Wang P, Al-Ahmad A, Beheiry S, Santarelli P, Starling RC, Dello Russo A, Pelargonio G, Brachmann J, Schibgilla V, Bonso A, Casella M, Raviele A, Haïssaguerre M, Natale A, for the PABA-CHF Investigators. Pulmonary-vein isolation for atrial fibrillation in patients with heart failure. *N Engl J Med*. 2008;359:1778–1785.
56. Roberts GW, Helboe T, Nielsen CB, Gallus AS, Jensen I, Cosh DG, Eaton VS. Assessment of an age-adjusted warfarin initiation protocol. *Ann Pharmacother*. 2003;37:799–803.
57. Grogan M, Smith HC, Gersh BJ, Wood DL. Left ventricular dysfunction due to atrial fibrillation in patients initially believed to have idiopathic dilated cardiomyopathy. *Am J Cardiol*. 1992;15:1570–1573.
58. Wyse DG, Waldo AL, DiMarco JP, Domanski MJ, Rosenberg Y, Schron EB, Kellen JC, Greene HL, Mickel MC, Dalquist JE, Corley SD, for the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Investigators. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med*. 2002;347:1825–1833.
59. Van Gelder IC, Hagens VE, Bosker HA, Kingma JH, Kamp O, Kingma T, Said SA, Darmanata JI, Timmermans AJ, Tijssen JG, Crijns HJ, for the Rate Control Versus Electrical Cardioversion for Persistent Atrial Fibrillation Study Group. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. *N Engl J Med*. 2002;347:1834–1840.
60. Corley SD, Epstein AE, DiMarco JP, Domanski MJ, Geller N, Greene HL, Josephson RA, Kellen JC, Klein RC, Krahn AD, Mickel M, Mitchell LB, Nelson JD, Rosenberg Y, Schron E, Shemanski L, Waldo AL, Wyse DG, for the AFFIRM Investigators. Relationships between sinus rhythm, treatment, and survival in the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) Study. *Circulation*. 2004;109:1509–1513.
61. Opolski G, Torbicki A, Kosior DA, Szulc M, Wozakowska-Kaplon B, Kolodziej P, Achremczyk P, for the Investigators of the Polish How to Treat Chronic Atrial Fibrillation Study. Rate control vs rhythm control in patients with nonvalvular persistent atrial fibrillation: the results of the Polish How to Treat Chronic Atrial Fibrillation (HOT CAFE) Study. *Chest*. 2004;126:476–486.
62. Carlsson J, Miketic S, Windeler J, Cuneo A, Haun S, Micus S, Walter S, Tebbe U, for the STAF Investigators. Randomized trial of rate-control versus rhythm-control in persistent atrial fibrillation: the Strategies of Treatment of Atrial Fibrillation (STAF) study. *J Am Coll Cardiol*. 2003;41:1690–1696.
63. Hohnloser SH, Kuck KH, Lilienthal J. Rhythm or rate control in atrial fibrillation: Pharmacological Intervention in Atrial Fibrillation (PIAF): a randomised trial. *Lancet*. 2000;356:1789–1794.
64. Al-Khatib SM, Shaw LK, Lee KL, O'Connor C, Califf RM. Is rhythm control superior to rate control in patients with atrial fibrillation and congestive heart failure? *Am J Cardiol*. 2004;94:797–800.
65. Roy D, Talajic M, Nattel S, Wyse DG, Dorian P, Lee KL, Bourassa MG, Arnold JM, Buxton AE, Camm AJ, Connolly SJ, Dubuc M, Ducharme A, Guerra PG, Hohnloser SH, Lambert J, Le Heuzey JY, O'Hara G, Pedersen OD, Rouleau JL, Singh BN, Stevenson LW, Stevenson WG, Thibault B, Waldo AL, for the Atrial Fibrillation and Congestive Heart Failure Investigators. Rhythm control versus rate control for atrial fibrillation and heart failure. *N Engl J Med*. 2008;358:2667–2677.
66. Humphries KH, Kerr CR, Steinbuch M, Dorian P, for the Canadian Registry of Atrial Fibrillation Investigators. Limitations to antiarrhythmic drug use in patients with atrial fibrillation. *CMAJ*. 2004;171:741–745.
67. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation. *Circulation*. 2006;114:e257–e354.
68. Joglar JA, Acosta AP, Shusterman NH, Ramaswamy K, Kowal RC, Barbera SJ, Hamdan MH, Page RL. Effect of carvedilol on survival and hemodynamics in patients with atrial fibrillation and left ventricular dysfunction: retrospective analysis of the US Carvedilol Heart Failure Trials Program. *Am Heart J*. 2001;142:498–501.
69. Rich MW, McSherry F, Williford WO, Yusuf S, for the Digitalis Investigation Group. Effect of age on mortality, hospitalizations and response to digoxin in patients with heart failure: the DIG study. *J Am Coll Cardiol*. 2001;38:806–813.
70. Yusuf S. Digoxin in heart failure: results of the recent Digoxin Investigation Group trial in the context of other treatments for heart failure. *Eur Heart J*. 1997;18:1685–1688.
71. Farshi R, Kistner D, Sarma JS, Longmate JA, Singh BN. Ventricular rate control in chronic atrial fibrillation during daily activity and programmed exercise: a crossover open-label study of five drug regimens. *J Am Coll Cardiol*. 1999;33:304–310.
72. Echt DS, Liebson PR, Mitchell LB, Peters RW, Obias-Manno D, Barker AH, Arensberg D, Baker A, Friedman L, Greene HL, Huthier ML, Richardson DW, the CAST Investigators. Mortality and morbidity in patients receiving encainide, flecainide, or placebo: the Cardiac Arrhythmia Suppression Trial. *N Engl J Med*. 1991;324:781–788.
73. Gottlieb SS, Kucin ML, Medina N, Yushak M, Packer M. Comparative hemodynamic effects of procainamide, tocainide, and encainide in severe chronic heart failure. *Circulation*. 1990;81:860–864.
74. Roy D, Talajic M, Dorian P, Connolly S, Eisenberg MJ, Green M, Kus T, Lambert J, Dubuc M, Gagné P, Nattel S, Thibault B. Amiodarone to prevent recurrence of atrial fibrillation: Canadian Trial of Atrial Fibrillation. *N Engl J Med*. 2000;342:913–920.
75. Weinfeld MS, Drazner MH, Stevenson WG, Stevenson LW. Early outcome of initiating amiodarone for atrial fibrillation in advanced heart failure. *J Heart Lung Transplant*. 2000;19:638–643.
76. Pedersen OD, Bagger H, Keller N, Marchant B, Køber L, Torp-Pedersen C. Efficacy of dofetilide in the treatment of atrial fibrillation-flutter in patients with reduced left ventricular function: a Danish Investigations of Arrhythmia and Mortality on Dofetilide (DIAMOND) substudy. *Circulation*. 2001;104:292–296.
77. Burstein B, Nattel S. Atrial fibrosis: mechanisms and clinical relevance in atrial fibrillation. *J Am Coll Cardiol*. 2008;51:802–809.
78. Pedersen OD, Bagger H, Køber L, Torp-Pedersen C. Trandolapril reduces the incidence of atrial fibrillation after acute myocardial

- infarction in patients with left ventricular dysfunction. *Circulation*. 1999;100:376–380.
79. Madrid AH, Bueno MG, Rebollo JM, Marín I, Peña G, Bernal E, Rodriguez A, Cano L, Cano JM, Cabeza P, Moro C. Use of irbesartan to maintain sinus rhythm in patients with long-lasting persistent atrial fibrillation: a prospective and randomized study. *Circulation*. 2002;106:331–336.
 80. Vermes E, Tardif JC, Bourassa MG, Racine N, Levesque S, White M, Guerra PG, Ducharme A. Enalapril decreases the incidence of atrial fibrillation in patients with left ventricular dysfunction: insight from the Studies of Left Ventricular Dysfunction (SOLVD) trials. *Circulation*. 2003;107:2926–2931.
 81. Maggioni AP, Latini R, Carson PE, Singh SN, Barlera S, Glazer R, Masson S, Cerè E, Tognoni G, Cohn JN, for the Val-HeFT Investigators. Valsartan reduces the incidence of atrial fibrillation in patients with heart failure: results from the Valsartan Heart Failure Trial (Val-HeFT). *Am Heart J*. 2005;149:548–557.
 82. Ducharme A, Swedberg K, Pfeffer MA, Cohen-Solal A, Granger CB, Maggioni AP, Michelson EL, McMurray JJ, Olsson L, Rouleau JL, Young JB, Olofsson B, Puu M, Yusuf S, for the CHARM Investigators. Prevention of atrial fibrillation in patients with symptomatic chronic heart failure by candesartan in the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) program. *Am Heart J*. 2006;152:86–92.
 83. Nasr IA, Bouzamondo A, Hulot JS, Dubourg O, Le Heuzey JY, Lechat P. Prevention of atrial fibrillation onset by beta-blocker treatment in heart failure: a meta-analysis. *Eur Heart J*. 2007;28:457–462.
 84. Young-Xu Y, Jabbour S, Goldberg R, Blatt CM, Graboyes T, Bilchik B, Ravid S. Usefulness of statin drugs in protecting against atrial fibrillation in patients with coronary artery disease. *Am J Cardiol*. 2003;92:1379–1383.
 85. Shiroshita-Takeshita A, Brundel BJ, Burstein B, Leung TK, Mitamura H, Ogawa S, Nattel S. Effects of simvastatin on the development of the atrial fibrillation substrate in dogs with congestive heart failure. *Cardiovasc Res*. 2007;74:75–84.
 86. Fauchier L, Pierre B, de Labriolle A, Grimard C, Zannad N, Babuty D. Antiarrhythmic effect of statin therapy and atrial fibrillation: a meta-analysis of randomized controlled trials. *J Am Coll Cardiol*. 2008;51:828–835.
 87. Manolis AG, Katsivas AG, Lazaris EE, Vassilopoulos CV, Louvros NE. Ventricular performance and quality of life in patients who underwent radiofrequency AV junction ablation and permanent pacemaker implantation due to medically refractory atrial tachyarrhythmias. *J Interv Card Electrophysiol*. 1998;2:71–76.
 88. Hsieh MH, Tai CT, Lee SH, Tsao HM, Lin YK, Huang JL, Chan P, Chen YJ, Kuo JY, Tuan TC, Hsu TL, Kong CW, Chang SL, Chen SA. Catheter ablation of atrial fibrillation versus atrioventricular junction ablation plus pacing therapy for elderly patients with medically refractory paroxysmal atrial fibrillation. *J Cardiovasc Electrophysiol*. 2005;16:457–461.
 89. O'Keefe JH Jr, Abuissa H, Jones PG, Thompson RC, Bateman TM, McGhie AI, Ramza BM, Steinhaus DM. Effect of chronic right ventricular apical pacing on left ventricular function. *Am J Cardiol*. 2005;95:771–773.
 90. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L, for the Cardiac Resynchronization–Heart Failure (CARE-HF) Study Investigators. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med*. 2005;352:1539–1549.
 91. Molhoek SG, Bax JJ, Bleeker GB, Boersma E, van Erven L, Steendijk P, van der Wall EE, Schalij MJ. Comparison of response to cardiac resynchronization therapy in patients with sinus rhythm versus chronic atrial fibrillation. *Am J Cardiol*. 2004;94:1506–1509.
 92. Leclercq C, Walker S, Linde C, Clementy J, Marshall AJ, Ritter P, Djiane P, Mabo P, Levy T, Gadler F, Bailleul C, Daubert JC. Comparative effects of permanent biventricular and right-univentricular pacing in heart failure patients with chronic atrial fibrillation. *Eur Heart J*. 2002;23:1780–1787.
 93. Gasparini M, Auricchio A, Regoli F, Fantoni C, Kawabata M, Galimberti P, Pini D, Ceriotti C, Gronda E, Klersy C, Fratini S, Klein HH. Four-year efficacy of cardiac resynchronization therapy on exercise tolerance and disease progression: the importance of performing atrioventricular junction ablation in patients with atrial fibrillation. *J Am Coll Cardiol*. 2006;48:734–743.
 94. Hoppe UC, Casares JM, Eiskjaer H, Hagemann A, Cleland JG, Freemantle N, Erdmann E. Effect of cardiac resynchronization on the incidence of atrial fibrillation in patients with severe heart failure. *Circulation*. 2006;114:18–25.
 95. Haïssaguerre M, Jaïs P, Shah DC, Takahashi A, Hocini M, Quiniou G, Garrigue S, Le Mouroux A, Le Métayer P, Clémenty J. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *N Engl J Med*. 1998;339:659–666.
 96. Haïssaguerre M, Shah DC, Jaïs P, Hocini M, Yamane T, Deisenhofer I, Chauvin M, Garrigue S, Clémenty J. Electrophysiologic breakthroughs from the left atrium to the pulmonary veins. *Circulation*. 2000;20:2463–2465.
 97. Hsu LF, Jaïs P, Sanders P, Garrigue S, Hocini M, Sacher F, Takahashi Y, Rotter M, Pasquié JL, Scavée C, Bordachar P, Clémenty J, Haïssaguerre M. Catheter ablation for atrial fibrillation in congestive heart failure. *N Engl J Med*. 2004;351:2373–2383.
 98. Gentles PJ, Sauer WH, Gerstenfeld EP, Lin D, Dixit S, Zado E, Callans D, Marchlinski FE. Reversal of left ventricular dysfunction following ablation of atrial fibrillation. *J Cardiovasc Electrophysiol*. 2007;18:9–14.
 99. Tondo C, Mantica M, Russo G, Avella A, De Luca L, Pappalardo A, Fagundes RL, Picchio E, Laurenzi F, Piazza V, Bisceglia I. Pulmonary vein vestibule ablation for the control of atrial fibrillation in patients with impaired left ventricular function. *Pacing Clin Electrophysiol*. 2006;29:962–970.
 100. Chen MS, Marrouche NF, Khaykin Y, Gillinov AM, Wazni O, Martin DO, Rossillo A, Verma A, Cummings J, Erciyes D, Saad E, Bhargava M, Bash D, Schweikert R, Burkhardt D, Williams-Andrews M, Perez-Lugones A, Abdul-Karim A, Saliba W, Natale A. Pulmonary vein isolation for the treatment of atrial fibrillation in patients with impaired systolic function. *J Am Coll Cardiol*. 2004;43:1004–1009.

KEY WORDS: arrhythmia ■ atrial fibrillation ■ heart failure