Atrial Fibrillation in Heart Failure: Current Treatment of Patients With Remodeled Atria

Hans-Ruprecht Neuberger, MD, PhD, Jan-Christian Reil, MD, Oliver Adam, MD, Ulrich Laufs, MD, Christian Mewis, MD, and Michael Böhm, MD

Corresponding author
Hans-Ruprecht Neuberger, MD, PhD
Klinik für Innere Medizin III, Universitätsklinikum des Saarlandes, D-66421, Homburg/Saar, Germany.
E-mail: hr.neuberger@t-online.de

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Atrial fibrillation (AF) and chronic heart failure (CHF) can be caused by each other, and therefore constitute a vicious circle. The prevalence of both conditions is about 1% in industrialized countries and increases with age. Although mortality is increased in heart failure, the additional prognostic relevance of AF in these patients is less clear. AF in patients with CHF can worsen heart failure symptoms, cause complications (eg, stroke), and is difficult to treat. Thus, prevention of AF entirely is an important goal. This review summarizes recent data concerning prognostic relevance, treatment, and means of primary and secondary prevention of AF in patients with CHF.

Introduction

Atrial fibrillation (AF) and chronic heart failure (CHF) are interrelated conditions. The prevalence of AF increases with functional class (New York Heart Association [NYHA]) in patients with heart failure [1,2•]. AF abolishes atrial pump function and causes an irregular and often fast ventricular rhythm. This impairs ventricular filling, reduces cardiac output, and may cause or aggravate symptoms of heart failure. Furthermore, prolonged tachycardia due to AF can induce a so-called tachycardiomyopathy. Recent data suggest that tachycardiomyopathy is present in about one of seven patients submitted to a hospital who have symptoms of CHF with AF [3]. Conversely, systolic or diastolic impairment of ventricular function is associated with increased atrial pressure, thereby increasing atrial wall stress. This induces neurohumoral activation, atrial enlargement, and atrial fibrosis. Consequently, atrial conduction becomes locally disturbed and more heterogeneous. This, together with an increased atrial surface and/or mass, creates a substrate for the perpetuation of AF (Fig. 1) [4,5]. This review focuses on recent reports on pharmacologic and nonpharmacologic means to interrupting this vicious circle.

AF and the Risk of Death

There are conflicting data concerning the prognostic impact of AF in patients with heart failure. Some studies reported a statistically significant independent effect of prevalent AF on mortality rate, whereas most studies did not observe such an effect. Pai and Varadarajan [6] showed in 1931 patients undergoing echocardiography that the association of AF prevalence with an increased mortality rate was most pronounced in those with normal left ventricular (LV) systolic function, diminished with worsening LV function, and was absent in patients with severe LV dysfunction. Similar results were reported from the CHARM program, including 7599 patients with chronic symptomatic CHF and a broad range of ejection fractions (EFs). At baseline, 1148 patients (15%) had AF, which was associated with an increased risk of death [7]. In patients with preserved EF, AF was associated with a greater increase in all-cause mortality rate (hazard ratio [HR] 1.80) than in patients with low EF (EF ≤ 40%; HR 1.38). These data suggest that the impact of AF on prognosis is that the higher it is, the better the systolic LV function will be. However, the prognosis of patients with AF alone (ie, no concomitant heart disease or hypertension) is excellent according to a 30-year follow-up study in the Olmsted County population [8].

In a retrospective analysis of the COMET trial (3029 patients; NYHA II–IV; EF < 35%), AF on the baseline electrocardiogram was present in 600 patients and did not independently predict mortality in this β-blocker–treated population [9]. Interestingly, the occur-

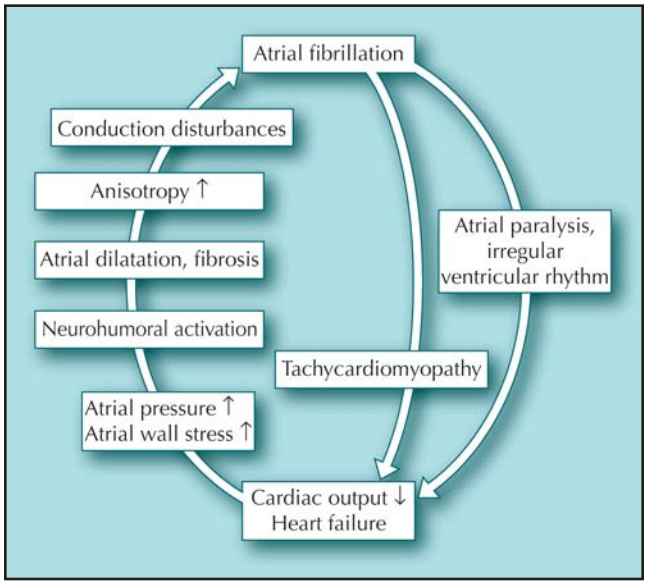

Figure 1. The interrelations between atrial fibrillation (AF) and heart failure are illustrated. AF reduces cardiac output and can cause or aggravate symptoms of congestive heart failure. Conversely, conditions associated with heart failure can create a substrate for the perpetuation of AF.

rence of new AF during follow-up was associated with a significantly increased risk of subsequent death, regardless of treatment allocation to metoprolol or carvedilol. Similarly, in a study of 1019 outpatients with heart failure due to LV systolic dysfunction, AF at baseline did not predict death after adjusting for baseline covariates [10]. Again, new-onset AF was independently associated with an increased risk of death.

Rhythm Versus Rate Control

In patients with AF and CHF, cardioversion and maintenance of sinus rhythm (rhythm control) theoretically should improve symptoms and survival compared with accepting AF and preventing tachycardiomyopathy (rate control). Reasons for this assumption are that 1) regularization of the heartbeat improves hemodynamics, 2) atrial contractile function is restored, further increasing cardiac output by improving ventricular filling, and 3) thromboembolic risk is reduced. So far, five studies have been published comparing strategies of rhythm versus rate control (PIAF, STAF, RACE, AFFIRM, and HOT-CAFE). However, none of these studies could prove superior in their approach to rhythm control.

Remarkably, in AFFIRM, only 23% of 4060 patients had a history of CHF, and their outcomes were similar with both treatment strategies [11]. Correspondingly, in a predefined analysis of RACE, rate control was not inferior to rhythm control in 261 patients with mild to moderate CHF [12]. However, there was a trend for higher mortality and major bleeding complications under rate control. Rhythm control was associated with excellent survival if sinus rhythm could be maintained. Similarly, in a substudy from the DIAMOND trials in patients with AF and/or atrial flutter and an EF of 35% or less, restoration of sinus rhythm was associated with a significantly lower mortality [13]. However, sinus rhythm may be a cause or just a marker for better prognosis. The first study that is prospectively comparing rate versus rhythm control in patients with CHF is the AF-CHF trial. Preliminary results were reported by Dr. Denis Roy at the American Heart Association (AHA) conference in 2007 [14]. The 1376 patients with CHF (NYHA class II–IV) and a left ventricular ejection fraction (LVEF) of 35% or less were randomly assigned to a strategy of rate control (β-blockers and/or digitalis) or rhythm control (electrical cardioversion plus antiarrhythmic drug therapy, primarily amiodarone). All patients received anticoagulation and optimal medical therapy for heart failure. After a mean follow-up of 37 months (minimum 2 years), 79% of patients were in sinus rhythm. Despite this remarkably high proportion of successful rhythm control, the occurrence of cardiovascular deaths was not different between the groups (primary end point, rhythm control, 26.7%; rate control, 25.2%; $P = 0.59$). Furthermore, total mortality, worsening CHF, and stroke (secondary end points) were similar between the two treatment arms. Thus, it appears that a rhythm control strategy in stable patients with CHF is not superior to a rate control strategy. However, data on quality of life have not yet been published. Furthermore, this study does not allow conclusions with respect to patients who are highly symptomatic if AF occurs because these are probably underrepresented in such a trial. An economic analysis of the data is being prepared.

How to Control Ventricular Rate in Patients With AF and CHF

Adequate rate control should prevent the development of tachycardiomyopathy and result in optimal functional status and quality of life. In practice, a 24-hour Holter recording probably best reflects actual heart rate and allows for diagnosing excessive tachycardia and/or bradycardia during daily life. However, adequate rate control has not yet been clearly defined. In the AFFIRM study, the target level of rate control was a resting heart rate of 80 bpm or less, and heart rate after exercise of 110 bpm or less. The RACE study defined adequate rate control as a resting heart rate of 100 bpm or less. Interestingly, preliminary data from a retrospective comparison showed no difference between lenient (RACE) and strict (AFFIRM) rate control. According to an observational study in 77 patients with AF and severely reduced EF (mean EF: 23%), a lower resting heart rate (< 80 bpm) at baseline may even be associated with a poorer prognosis [15]. However, we are not aware of a prospective trial aimed at answering this question in patients with AF and CHF.

β-Blockers

To control heart rate, β-blockers are generally recommended in chronic AF, whether CHF is present or not [16–18]. There is only one small, prospective, double-blind, placebo-controlled trial on the effect of β-blockers in patients with AF and CHF. It included 47 patients and found an improved EF, symptom score, and rate control due to β blockade in addition to digoxin [19]. However, follow-up was short and mortality was not addressed. The MERIT-HF study included 3991 patients with CHF NYHA II–IV and EF of 40% or less. Metoprolol significantly reduced the risk of death or heart transplantation by 32% compared with placebo. At baseline, 556 patients (13.9%) were in AF. Surprisingly, metoprolol had no effect on total or cardiovascular mortality in this subgroup [20]. Similarly, a post hoc analysis of the CIBIS II study showed that bisoprolol had no effect on mortality in patients with heart failure NYHA classes III to IV, an EF of 35% or less, and AF [21]. The authors speculated that the smaller reduction of heart rate by bisoprolol in patients with AF might explain this finding, although the difference was very small (2 bpm). Furthermore, in the bisoprolol group, they found a larger decrease in systolic blood pressure at 2 months in patients with AF who subsequently died. Thus, a too-pronounced decrease in blood pressure (> 10 mm Hg) by bisoprolol may be more deleterious in patients with AF than in sinus rhythm. Conversely, AF in a patient with CHF may simply be a surrogate parameter of a more diseased heart or condition.

Digitalis

Although these glycosides are recommended to control heart rate during rest in patients with AF and CHF, according to recent guidelines [16–18], there is concern that digoxin may be dangerous and increase mortality rate. Digoxin does not improve survival rates in patients with CHF and sinus rhythm and is potentially dangerous in women. Digoxin use in AF is associated with increased levels of endothelial and platelet activation [22]. However, the clinical relevance of this finding is not yet clear. Hallberg et al. [23] reported data from a Swedish registry on patients admitted to coronary care units. Twenty percent of 21,459 patients with AF, but without CHF, were discharged with digoxin. After adjustment by using a propensity score, a higher 1-year mortality rate was observed in this group compared with patients without digoxin (response rate [RR], 1.42; 95% CI, 1.29–1.56). Forty-six percent of 16,960 patients with AF and CHF received digoxin at discharge. After adjustment, 1-year mortality rate in this group of patients was the same, whether they were discharged with digoxin or not (RR, 1.00; 95% CI, 0.94–1.06). Similar results have been reported recently from SPORTIF III and V data [24]. After adjusting for covariates, all-cause mortality of patients with AF was increased for digitalis users (HR, 1.53; 95% CI, 1.22–1.92). This difference was not significant for the subgroup of patients with AF and LV dysfunction at baseline. Mortality was highest among digitalis users who were not receiving a β-blocker.

Among other mechanisms, digoxin enhances vagal tone and may therefore be less effective at controlling the ventricular rate during exercise or increased sympathetic activity. A small study in patients with CHF and AF suggested that the combination of digoxin and a β-blocker (carvedilol) reduces symptoms, improves ventricular function, and leads to better ventricular rate control than either agent alone [19]. Adequate rate control at rest and exertion, as defined in the AFFIRM trial, was achieved with digoxin alone in 54% at 1 year versus 81% with a β-blocker (with or without digoxin) in patients with a history of CHF symptoms or an EF of less than 40% [25].

In practice, we prefer a β-blocker as a first-line drug to control heart rate in patients with AF and CHF. The combination of a β-blocker with digoxin can allow the dose of each drug to be reduced. This may be advantageous with respect to their possible adverse effects.

Amiodarone

Amiodarone, given as an intravenous bolus, is relatively safe and more effective than digoxin for heart rate control [26]. Negative inotropic effects are less pronounced than in β-blockers given intravenously. Therefore, amiodarone may be used, particularly in critically ill patients. However, amiodarone can result in cardioversion to sinus rhythm. This may be a problem in the presence of an atrial thrombus or in the case that an atrial thrombus has not been excluded (effective anticoagulation for < 3 weeks with no transesophageal echocardiography). Due to its possible adverse effects, the use of amiodarone in CHF patients to control heart rate during AF is regarded as a second-line treatment and is recommended only when other measures are unsuccessful or contraindicated [16,17]. The risk and benefit have to be considered on an individual basis.

Atrioventricular nodal ablation and ventricular pacing

Patients with symptoms or cardiomyopathy due to tachyarrhythmia or refractory to drug treatment will most likely benefit from atrioventricular (AV) nodal ablation. Because it causes lifelong pacemaker dependency, this approach should only be used if other means of rate control fail. Ozcan et al. [27] examined long-term survival after AV nodal ablation and pacemaker implantation. In a subgroup analysis of 115 patients with AF and CHF, they did not find a significant survival difference compared with 58 matched controls treated with drugs. However, chronic right ventricular (RV) pacing causes adverse ventricular remodeling [28]. Therefore, pacing strategies avoiding asynchrony should be considered, particularly in patients with CHF. Occhetta et al. [29] recently demonstrated in a small trial (16 patients) that permanent para-Hisian pacing after AV node ablation can allow improvement in functional and hemodynamic parameters compared

with conventional right apical pacing. The OPSITE study compared LV and biventricular pacing with RV pacing in patients with permanent AF treated with AV node ablation (EF, 38 ± 14%; NYHA class, 2.5 ± 0.5) [30]. Rhythm regularization achieved with this approach improved quality of life and exercise capacity with all modes of pacing. Surprisingly, LV and biventricular pacing provided modest or no additional favorable effects compared with RV pacing during the 3-month observation period. However, follow-up was only conducted for 3 months. This may be too short to detect relevant differences because at 6 months after AV nodal ablation, the PAVE study found an improvement in 6-minute walk distance and a higher EF in patients receiving biventricular pacing compared with RV pacing [31]. Whether or not AV node ablation is a prerequisite for success in AF patients with an indication for cardiac resynchronization therapy (CRT) will be discussed.

Primary and Secondary Prevention of AF in Patients with CHF

Amiodarone and dofetilide

Because class I antiarrhythmic drugs and sotalol are associated with an increased risk of death in patients with CHF, these drugs must not be used to maintain sinus rhythm. The only antiarrhythmic drugs that do not increase mortality rate in patients with AF and CHF are amiodarone and dofetilide. In the DIAMOND study, 1518 patients with symptomatic CHF and severe LV dysfunction (EF < 35%) were included. About 25% of these patients had AF at inclusion. Dofetilide was more effective than placebo in converting to and maintaining sinus rhythm (HR for the recurrence of AF, 0.35; $P < 0.001$) [32]. Because torsade de pointes occurred in 3.3% in the dofetilide group, the United States Food and Drug Administration (FDA) mandated in-hospital initiation of therapy. Dofetilide is not available in Europe. Amiodarone has been shown to convert AF to sinus rhythm and to prevent the recurrence and occurrence of arrhythmia in patients with CHF, although data are limited. Of 667 patients included in the CHF-STAT trial, 103 (15%) had AF at baseline. Of these, 51 were randomly assigned to amiodarone and 52 to placebo. Sixteen of 51 patients (31%) on amiodarone and 4 of 52 on placebo (8%) converted to sinus rhythm during the study ($P < 0.002$). Furthermore, amiodarone reduced the occurrence of AF in patients in sinus rhythm [33]. Relevant cardiac and extracardiac side effects limit the routine use of this drug.

Can optimal heart failure therapy prevent AF?

Current heart failure therapy includes β-blockers, ACE inhibitors (ACE-Is) or angiotensin receptor blockers (ARBs), and aldosterone antagonists [34]. Boldt et al. [35] studied 148 patients with an LVEF of 45% or less who underwent electrical cardioversion of AF. They found that the extent of CHF therapy predicts maintenance of sinus rhythm for 24 hours after cardioversion of AF. Only 29% of patients who were not receiving any of these drugs versus 93% of patients receiving β-blockers plus ACE-I/ARB plus aldosterone antagonists were in sinus rhythm for at least 24 hours ($P < 0.001$).

In animal models and clinical studies, it has been shown that ACE-I attenuates the effects of CHF on atrial conduction, atrial fibrosis, and AF stability [36]. Accordingly, retrospective analyses from the TRACE study, the SOLVD trials, CHARM, and Val-HEFT indicated that ACE-I and ABR can reduce the occurrence of AF in patients with LV dysfunction. In contrast, in patients without systolic dysfunction, these drugs cannot prevent the arrhythmia [37•].

β-blocker treatment in heart failure might reduce atrial load, thereby reducing atrial structural remodeling. Furthermore, chronic treatment with a β-blocker may reverse atrial electrical remodeling by prolonging the action potential duration [38]. This could increase atrial wavelength and exert antifibrillatory effects. Whether β-blockers are effective in primary prevention of AF was not an endpoint and was not even analyzed retrospectively in most large CHF survival trials. A recent meta-analysis including 11,952 patients with heart failure showed that β-blockers added to ACE-I treatment can further reduce the incidence of AF from 39 to 28 per 1000 patient-years (RR, 0.73; 95% CI, 0.62–0.86; $P < 0.001$) [39•]. All studies except the SENIORS study showed the same trend. The SENIORS study used nebivolol, included older patients (> 70 years) and patients with diastolic heart failure, and had a high prevalence of AF at baseline (35% vs 11%–15% in the other trials). One or more of these factors may be responsible for the absence of an effect on AF occurrence.

Statins

Data from the ADVANCENT registry of 25,268 patients with systolic LV dysfunction (EF ≤ 40%) showed that the use of lipid-lowering drugs (LLDs) is associated with a reduced prevalence of AF in patients with CHF, independent of the lipid profile [40•]. In probably the vast majority, the LLD was a 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor (statin); however, fibrates were also used. The association of LLD use with a reduced prevalence of AF remained significant after multivariate analysis (OR 0.69; 95% CI, 0.64–0.74), and the reduction was larger than that of ACE-I/ARB or β-blockers. Accordingly, Adabag et al. [41] reported that the incidence of AF was reduced in patients with coronary artery disease and CHF receiving statin treatment (HR, 0.57; 95% CI, 0.33–1.00; $P = 0.04$). Mechanistically, statin treatment may attenuate CHF-induced atrial structural remodeling. In a dog model of CHF, simvastatin reduced the stability of induced AF, and attenuated atrial conduction disturbances and fibrosis [42]. Inhibition of Rac1 and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity by statins may have antiar-

rhythmic effects [43]. However, prospective clinical trials are needed before the general use of HMG-CoA reductase inhibitors to prevent AF in CHF can be discussed.

Nonpharmacologic options

Ablation techniques

Although catheter ablation of paroxysmal AF in highly symptomatic patients without structural heart disease is becoming a routine procedure, limited experience is available regarding patients with CHF. A study from a highly experienced single center reported data on AF ablation in 58 patients with CHF and an EF of 45% or less [44]. The authors demonstrated that this approach can significantly improve cardiac function, symptoms, exercise capacity, and quality of life even in patients with coexisting heart disease. However, the study lacks a control group of patients with CHF without ablation, and the mean follow-up was only 12 months. Similar results were reported from other groups [45–47]. Considering the limited data and the complexity of the procedure, catheter ablation to treat AF in CHF patients cannot be generally recommended. In patients with AF and LV systolic dysfunction, surgical AF ablation can also result in improved systolic pump function [48,49]. Because data are even more limited than for the percutaneous approach, the procedure should be restricted to patients who require valvular or coronary artery bypass surgery.

Cardiac resynchronization

Recent studies have shown that biventricular pacing in patients with cardiac dyssynchrony, low EF, and NYHA classes III to IV could be an effective therapy in patients who also have AF. In case of a standard pacing indication, CRT was beneficial even in the presence of AF [50]. In patients with permanent AF and without standard pacing indication, there are conflicting data on whether it is necessary to ablate the AV junction to maximize CRT delivery. Gasparini et al. [51] reported an increase of EF and improved exercise tolerance after AV junction ablation only. Furthermore, they showed that long-term overall survival with CRT plus AV junction ablation is better compared with CRT alone and comparable to patients in sinus rhythm [52]. However, these were observational data. Delnoy et al. [53] and Khadjooi et al. [54] showed the same symptomatic and prognostic benefit of CRT in patients with AF and without AV junction ablation compared with patients in sinus rhythm. Prospective randomized studies are needed to resolve this issue.

Meanwhile, the individual decision to ablate or not to ablate the AV junction may be based on the actual frequency of CRT delivery and side effects of AV nodal–blocking agents. Whether CRT is "antifibrillatory" is unknown at present. In the CARE-CHF trial, new onset of AF in patients with sinus rhythm was not reduced by CRT [55]. However, in the control group, there was no implanted device to monitor atrial rhythm. Therefore, AF detection was more likely in the CRT group. Nevertheless, others similarly reported no effect of CRT of AF burden, although CRT might have delayed onset of new AF [56]. Hügl et al. [57] found a gradual reduction of AF burden when CRT was started. This was supported by Yannopoulos et al. [58], who noted a decrease in number and duration of atrial tachyarrhythmia episodes 1 year after starting CRT compared with 3 months before CRT.

Conclusions

The worse the systolic pump function, the lower seems to be the impact of AF on survival in patients with CHF. In stable patients with AF and CHF, a strategy of ventricular rate control is not inferior compared with a rhythm control strategy based on amiodarone. Rate control is best achieved by β-blockers, and digoxin may be added. However, relevant symptoms of AF may necessitate cardioversion and a strategy to maintain sinus rhythm (rhythm control). If amiodarone cannot be used, AF ablation is an option in experienced centers. Primary prevention of AF in patients with CHF is probably best achieved by optimal heart failure therapy, including ACE-I/ARB, β-blockers, and possibly aldosterone antagonists. CRT seems to improve symptoms and survival in patients with severe heart failure symptoms and ventricular asynchrony even in the presence of AF. To maximize CRT delivery, an ablation of the AV node may be necessary. It is likely that CRT can reduce the frequency and duration of atrial tachyarrhythmia episodes. Notably, effective oral anticoagulation (international normalized ratio, 2–3) can prevent thromboembolic complications in patients with AF and CHF, and thus it is an important determinant of survival and quality of life.

Clinical Trial Acronyms

AF-CHF—Atrial Fibrillation and Congestive Heart Failure; ADVANCENT—National Registry of Advance Heart Health; AFFIRM—Atrial Fibrillation Follow-up Investigation of Rhythm Management; CARE-HF—Cardiac Resynchronization–Heart Failure; CHARM—Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity; CHF-STAT—Congestive Heart Failure: Survival Trial of Antiarrhythmic Therapy; CIBIS II—Cardiac Insufficiency Bisoprolol Study II; COMET—Carvedilol or Metoprolol European Trial; DIAMOND—Danish Investigations of Arrhythmia and Mortality on Dofetilide; HOT CAFE—How To Treat Chronic Atrial Fibrillation; MERIT-HF—Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure; OPSITE—Optimal Pacing Site; PAVE—Post AV Node Ablation Evaluation; PIAF—Pharmacologic Intervention in Atrial Fibrillation; RACE—A Comparison of Rate Control and Rhythm Control in Patients with Recurrent Persistent Atrial Fibrillation; SENIORS—Study of the Effects of Nebivolol Intervention

on Outcomes and Rehospitalization in Seniors with Heart Failure; SOLVD—Study of LV Dysfunction; SPORTIF III—Stroke Prevention Using Oral Thrombin Inhibition in Atrial Fibrillation; STAF—Strategies of Treatment of Atrial Fibrillation; TRACE—Trandolapril Cardiac Evaluation; Val-HEFT—Valsartan Heart Failure Trial.

Disclosures

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