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Review

Management of atrial fibrillation in patients with heart failure

Hans-Ruprecht Neuberger[1]*, Christian Mewis[1], Dirk J. van Veldhuisen[2], Ulrich Schotten[3], Isabelle C. van Gelder[2], Maurits A. Allessie[3], and Michael Böhm[1]

[1]*Klinik für Innere Medizin III, Kardiologie, Angiologie, und Internistische Intensivmedizin;, Universitätsklinikum des Saarlandes, D-66421 Homburg/Saar, Germany;* [2]*Department of Cardiology, University Medical Center Groningen, The Netherlands; and* [3]*Department of Physiology, Cardiovascular Research Institute Maastricht, Maastricht University, The Netherlands*

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Atrial fibrillation (AF) and chronic heart failure (CHF) are two major and even growing cardiovascular conditions that often coexist. However, few data are available to guide treatment of AF in patients with CHF. This review summarizes current literature concerning the following topics: (i) prognostic relevance of AF in patients with CHF, (ii) relevance and strategies of rhythm and rate control in patients with AF and CHF, and (iii) options for prevention of AF in patients with ventricular dysfunction. In conclusion, AF is associated with increased mortality in CHF patients. However, it is not clear whether there is a causal relationship. Emerging strategies to prevent the occurrence of AF are promising tools that might improve quality of life and survival in patients with CHF.

Introduction

Atrial fibrillation (AF) and chronic heart failure (CHF) are two major and even growing cardiovascular problems. Although precise data are lacking, the prevalence of both AF and CHF is estimated to be >1% of the general population and steeply increases with age:[1] While the prevalence of AF is <1% at an age below 60 years, about 8% at age 80 or older suffer from the arrhythmia. Correspondingly, the Framingham Heart Study found a CHF prevalence of 0.8% at age 50–59, increasing to 6.6% in men and 7.9% in women at age 80–89 years.[2] AF and CHF often coexist and may predispose to each other. In mild-to-moderate CHF (NYHA classes II–III), the AF prevalence is 10–15%, whereas in severe CHF (NYHA IV), AF is present in every second patient (*Figure 1*).[3]

Both systolic and diastolic dysfunction have been shown to be associated with an increased risk to develop AF.[4] They both can create a substrate of AF characterized by augmented atrial load, atrial dilatation, local conduction disturbances, and some degree of atrial fibrosis.[5–11] (Details on pathophysiology are beyond the scope of this article, for review see ref.[12]) On the other hand, AF can accelerate ventricular rate, thereby producing a tachycardiomyopathy in previously normal ventricles.[13–16] Besides, in patients with pre-existing CHF AF independently increases the risk for progressive ventricular dysfunction and exacerbation of heart failure symptoms.[17] This might be caused by a reduction in ventricular filling due to the irregular, rapid ventricular rate, and due to atrial contractile dysfunction.[18] Thus, the interrelations between AF and CHF could constitute a vicious cycle.[19] However, both conditions may be markers of a common pathophysiological substrate. According to data from the Framingham Heart Study, AF preceded CHF about as often as CHF preceded AF, and in one-fifth of subjects, AF and CHF were diagnosed for the first time on the same day.[20]

This review summarizes evidence concerning the following questions: (i) to what extent does AF increase morbidity and mortality in CHF? (ii) How important is restoration and maintenance of sinus rhythm in patients with CHF? (iii) What strategies are useful to maintain sinus rhythm or to control heart rate during AF? (iv) Which established CHF therapy can prevent the occurrence of AF? This paper has been designed as a narrative review without using formal meta-analytic techniques. A literature search of the PubMed Medline database was performed employing search terms appropriate for each section of the manuscript (e.g. 'atrial fibrillation AND heart failure AND beta blockers', limited to clinical trials and papers published in English). Papers reporting prospective data on large study populations were preferably selected. If these were not available, small studies and retrospective data were included. Furthermore, the reference lists of the current guidelines on heart failure and AF were analysed for studies relevant for each section.

* Corresponding author. Tel: +49 6841 162 3000; fax: +49 6841 162 3381.
E-mail address: h.neuberger@tiscali.de

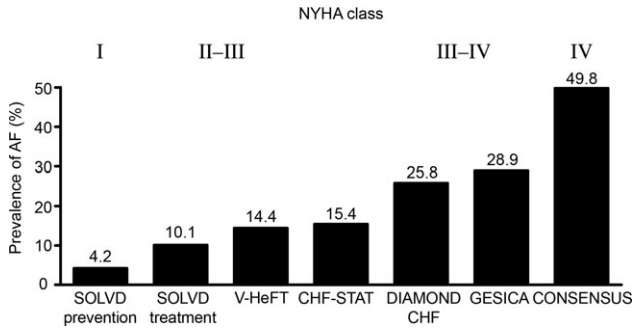

Figure 1 Prevalence of atrial fibrillation in several major CHF trials. See Maisel and Stevenson[3] for details.

Does atrial fibrillation increase mortality?

It is still a matter of debate whether AF is an independent predictor of mortality in patients with CHF. Some studies reported a statistically significant independent impact of prevalent AF on mortality, whereas others did not observe such an association (*Table 1*). On the basis of data available until 2002, van den Berg *et al*. described the concept that AF in the setting of severe CHF does not additionally affect mortality. In contrast, in patients with mild-to-moderate CHF, the presence of AF *per se* appeared to indicate an increased mortality risk.[21] This is supported by a recent analysis form the CHARM programme, including 7599 patients with chronic symptomatic CHF and a broad range of ejection fractions (EFs). At baseline, 1148 patients (15%) had AF, associated with an increased risk of mortality.[22] In patients with preserved EF, AF was associated with a greater increase in all-cause mortality (hazard ratio 1.80: 95% CI 1.46–2.21; $P < 0.001$) than in patients with low EF (EF $\leq$ 40%; HR 1.38: 95% CI 1.21–1.59; $P < 0.001$). In a retrospective analysis of the SOLVD trials (6797 patients), Dries *et al*.[23] reported that after multivariate analysis AF was significantly associated with all-cause mortality (HR 1.34: 96% CI 1.12–1.62; $P = 0.002$). This could largely be explained by an increased risk for progressive heart failure death. In the VALIANT trial, both current and prior AF were associated with an increased risk of death and major cardiovascular events during 3 years following an acute myocardial infarction [plus left ventricular (LV) systolic dysfunction and/or clinical CHF].[24] In contrast, the VHeFT I and II trials (including 1427 patients with mild-to-moderate CHF) did not show a significant difference in mortality between patients in sinus rhythm and AF.[25] Crijns *et al*.[26] prospectively evaluated 409 patients with moderate-to-severe chronic CHF. Overall mortality was higher in AF patients (RR 1.40, 95% CI 1.01–1.92; $P = 0.04$). However, after adjusting for important prognostic variables, this interaction was no longer detectable. In a study performed between 1985 and 1989, Stevenson *et al*.[27] observed that survival in patients with moderate-to-severe CHF and AF was lower compared with patients without AF. However, in a following study (performed between 1990 and 1993), the difference was smaller and not statistically significant. In this trial, the first-line anti-arrhythmic drug was amiodarone compared with class I drugs in the earlier study. Furthermore, an ACE-inhibitor (captopril) had been introduced into CHF therapy. Both, the less use of class I anti-arrhythmic drugs with potentially deleterious effects and the positive effects of ACE-inhibition may have reduced the impact of AF on mortality. In a retrospective analysis of the COMET trial (3029 patients, NYHA classes II–IV, EF < 35%), AF on the baseline ECG was present in 600 patients and was associated with an increased mortality. However, by multivariate analysis, AF no longer independently predicted mortality in this beta-blocker-treated population.[28] Interestingly, during follow-up, the occurrence of new AF was associated with a significantly increased risk of subsequent mortality, regardless of treatment allocation to metoprolol or carvedilol. A similar finding was reported from data of the Framingham Heart Study.[20] Conversely, in a community-based cohort of patients newly diagnosed with AF, the occurrence of CHF was associated with an increased mortality risk (hazard ratio 3.4: 95% CI 3.1–3.8; $P < 0.0001$).[29]

Rhythm control or rate control?

In patients with AF and CHF, achievement and maintenance of sinus rhythm ('rhythm control') has been presumed to be advantageous. This was based on the following theoretical benefits of sinus rhythm over AF: (i) regularization of the heartbeat improves haemodynamics, (ii) atrial contractile function is restored, further increasing cardiac output by improving ventricular filling, (iii) thrombo-embolic risk is reduced, (iv) tachycardiomyopathy is prevented or reversed, and (v) functional status and quality of life improve. Therefore, it is tempting to speculate that mortality, morbidity, and the need for hospitalization are reduced by a strategy aimed at achieving and maintaining sinus rhythm.

Since 2000, five studies have been published comparing rhythm vs. rate control (PIAF, STAF, RACE, AFFIRM, HOT-CAFÉ; *Table 2*. For a detailed review, see Crijns[30]). None of them could demonstrate superiority of an approach aimed at rhythm control. AFFIRM (the largest of these studies) included 4060 patients. However, only 23% had a history of CHF.[31] The outcomes in CHF patients were similar with both treatment strategies, whereas in patients without CHF there was a trend toward lower mortality with rate control. Similarly, in a pre-defined analysis of the RACE study rate control was not inferior to rhythm control in 261 patients with mild-to-moderate CHF.[32] However, there was a trend for a higher mortality and major bleeding complications under rate control. Rhythm control was associated with excellent survival if sinus rhythm could be maintained. Similarly, in the AFFIRM study presence of sinus rhythm was associated with a considerably lower risk of death (HR 0.53: 95% CI 0.39–0.72; $P < 0.0001$).[33] According to a substudy from the DIAMOND trials in patients with AF and/or atrial flutter and an EF $\leq$ 35%, restoration of sinus rhythm was associated with a significant reduction in mortality.[34] Yet, sinus rhythm may be cause or just marker for a better prognosis. The important, ongoing AF-CHF trial will be the first study prospectively comparing rate vs. rhythm control in patients with CHF.[35]

Rate control in patients with atrial fibrillation and chronic heart failures

Adequate rate control has not been defined so far. In AFFIRM, the target level of rate control was a resting

Table 1 Analyses of large heart failure trials addressing the relative mortality risk of patients with atrial fibrillation at baseline

	Patients with AF/all patients included	Follow-up	EF (%)	NYHA class	BB (%)	ACE-I or ARB (%)	RR (95% CI)	*P*-value	Comments
CHARM[22]	478/7599	37.7 months	>40	II–IV	55	ACE-I: 20	1.80 (1.46–2.21)	<0.001	+ARB (candesartan) or placebo
	670/7599		≤40	II–IV	55	ACE-I: 55	1.38 (1.21–1.59)	<0.001	
SOLVD trials[23]	419/6517	33.4 months	≤35	I–IV	20	50	1.34 (1.12–1.62)	0.002	
VALIANT[24]	1812/14703	24.7 months	Mean: 34	NA	70	100	1.32 (1.20–1.45)	<0.0001	AMI; + CHF (clinical or radiological signs) and/or EF ≤ 35
V-HeFT[25]									LV dilation; or EF < 45% and V_{O_2max} < 25 mL/kg BW min
I	99/632	30 months	Mean: 30	NA	0	0	0.95[a]	0.81	
II	107/795	30 months	Mean: 30	NA	0	50	0.76[a]	0.18	
PRIME II[26]	84/409	41 months	<35	III–IV	10	95	0.86 (0.59–1.24)	n.s.[a]	
Stevenson *et al.*[27]	140/750	≥24 months	<40		0	60	1.12 (0.92–1.80)	n.s.[a]	
COMET[28]	600/3029	58 months	<35	II–IV	100	90	1.07 (0.92–1.24)	0.38	

BB, use of beta-blockers; ACE-I, ACE-inhibitors; ARB, angiotensin receptor blockers; CI, confidence interval; NA, no data available; RR, relative risk of all-cause mortality associated with baseline AF as assessed by multivariate analysis (Cox proportional hazards model).

[a]Confidence interval or *P*-value has not been reported.

heart rate ≤80 b.p.m. and a heart rate after exercise ≤110 b.p.m. The RACE study defined adequate rate control as resting heart rate ≤100 b.p.m. Interestingly, preliminary data from retrospective comparison showed no difference between lenient (RACE) and strict (AFFIRM) rate control.[36] According to an observational study in 77 patients with AF and severely reduced EF (mean EF: 23 ± 8%), a lower resting heart rate (<80 b.p.m.) at baseline may even be associated with a poorer prognosis.[37] From a clinical point of view, resting heart rate may not be sufficient to guide rate control. Treadmill exercise tests and 24 h Holter monitoring seem more reliable. Heart rates above 110 b.p.m., as well as excessive reductions in ventricular rate that could limit exercise tolerance, should be avoided. These issues will be further investigated by the RACE-II study.[38] To prevent tachycardia in patients with AF, the following strategies are currently available.

Beta-blockers

The ACC/AHA/ESC guidelines for the management of AF, and the ESC and ACC/AHA guidelines for the management of CHF, recommend beta-blockers generally in chronic AF to control heart rate.[39–41] According to rate control criteria of the AFFIRM trial, beta-blockers were the most effective drugs.[42] However, it is not clear from these data whether patients with and without CHF benefit in the same way. Because of the negative inotropic effects, intravenous beta-blockers should be administered cautiously in patients with CHF. According to a small study including seven patients with CHF (NYHA class III), a short-acting substance like esmolol in combination with digoxin might be advantageous and safe in acutely ill patients.[43] There is only one prospective, double-blind, placebo-controlled trial on the effect of beta-blockers in patients with AF and CHF. It included 47 patients and found an improved EF, symptom score, and rate control due to use of carvedilol in addition to digoxin.[44] However, follow-up was short and mortality was not addressed. A retrospective analysis of the US Carvedilol Heart Failure Trials Program found 136 patients with concomitant CHF and AF during the screening visit (84 assigned to carvedilol and 52 to placebo).[45] EF improved to a statistically greater degree in patients treated with carvedilol (from 23 to 33% with carvedilol and from 24 to 27% with placebo, $P = 0.001$). A trend toward a reduction in the combined end point of death or CHF hospitalization was also observed (19% in patients treated with placebo and 7% in patients on carvedilol; RR 0.35: 95% CI 0.12–1.02; $P = 0.055$). The MERIT-HF study included 3991 patients with CHF NYHA classes II–IV and EF ≤ 40%.[46] 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.[47] 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–IV, an EF ≤ 35%, and AF.[48] 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 (−8.8 ± 21.5 vs. 10.6 ± 12.4 b.p.m., $P = 0.02$). Furthermore, they found in the bisoprolol group 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 mmHg) by bisoprolol may be more deleterious in patients with AF than with sinus rhythm. On the other hand, AF in a patient with CHF may simply be a surrogate parameter of a more diseased heart or condition.

Non-dihydropyridine calcium channel antagonists

Because of their negative inotropic effects, calcium channel antagonists are in general regarded as inappropriate in CHF patients. However, there are some small trials indicating that short-term use of diltiazem in patients with AF and moderate-to-severe CHF may be safe and effective.[49–51]

Table 2 Clinical trials comparing rate control and rhythm control in patients with atrial fibrillation

	Patients	FU (years)	History of CHF (%)	Rate control (SR, %)	Rhythm control (SR, %)	Mortality rate/ rhythm control (%)	Ischaemic stroke rate/ rhythm control (%)	Hospitalization rate/ rhythm control (%)	Comments
PIAF[102]	252	1.0	N.A.	Diltiazem (10)	Amiodarone (56)	1.6/1.6	NA	24/69 $P = 0.001$	
STAF[103]	200	1.6	55.5	BB, NCA, DIG, or AVNA (0)	Class I or III AADs (23)	8/4	1/5	26/54 $P = 0.001$	Primary endpoint: death, stroke, embolism; $P = 0.99$
RACE[32,104]	522	2.3	50	BB, NCA, DIG (26)	Class I or III AADs (39)	7.0/6.8[a], n.s.	5.5/7.9[b], n.s.	5.4/3.8	Hospitalization: for CHF in patients with a history of CHF
AFFIRM[31]	4060	3.5	23.1	BB, NCA, DIG (34.6)	Class I or III AADs (62.6)	25.9/26.7 $P = 0.08$	5.5/7.1 $P = 0.79$	73.0/80.1 $P < 0.001$	
HOT-CAFÉ[105]	205	1.7	62	BB, NCA, DIG (N.A.)	Sotalol or class I AADs (63.5)	1/3 n.s.	0/3 n.s.	5/100 $P = 0.001$	

AADs, anti-arrhythmic drugs; AVNA, AV-nodal ablation or modification; BB, beta-blockers; DIG, digoxin; FU, mean follow-up; NA, no data available; NCA, non-dihydropyridine calcium channel antagonists; n.s., not statistically significant (*P*-values not available); SR, patients in sinus rhythm at study end or latest follow-up.
[a]Cardiovascular mortality.
[b]Thrombo-embolic complications.

Digitalis glycosides

The use of digoxin to control heart rate during rest in patients with CHF and AF is recommended according to the current ACC/AHA/ESC guidelines for the management of AF and the CHF guidelines.[39–41] Among other mechanisms, digoxin enhances vagal tone and may therefore be less effective at controlling the ventricular rate during exercise or increased sympathetic activity.[52] A rather small study in patients with CHF and AF suggested that the combination of digoxin and a beta-blocker (carvedilol) reduces symptoms, improves ventricular function, and leads to better ventricular rate control than either agent alone.[44] Adequate rate control at rest and exertion, as defined in the AFFIRM trial (mentioned earlier), was achieved with digoxin alone in 54% at 1 year vs. 81% with a beta-blocker (with or without digoxin) in patients with a history of CHF symptoms or an EF $< 40\%$.[42] It remains unclear whether digoxin affects mortality in patients with AF and CHF. Digoxin does not reduce mortality in patients with sinus rhythm and may be dangerous in women.[53,54] However, the combination of a beta-blocker with digoxin can allow the dose of each drug to be reduced. This may be advantageous with respect to their possible adverse effects. Recent data showed that digoxin use in AF is associated with increased levels of endothelial and platelet activation.[55] Whether this is associated with increased thrombo-embolic events has not yet been investigated.

Amiodarone

The use of amiodarone in CHF patients to control heart rate during AF is regarded a second-line treatment according to the guidelines. Because of its possible adverse effects, it is recommended only when other measures are unsuccessful or contraindicated.[39,40] Amiodarone, given as an intravenous bolus, is relatively safe and more effective than digoxin for acute heart rate control.[56] It may especially be used in critically ill patients.[51] However, there are concerns about the safety of this drug in patients with CHF and concomitant beta-blockers and digitalis glycosides. In a small retrospective study, this combination had an increased risk of ventricular arrhythmia 3–48 h after initiation of amiodarone loading.[57]

Atrioventricular nodal ablation and ventricular pacing

Atrioventricular (AV) nodal ablation and ventricular pacing is a very efficient way to control heart rate. Patients with symptoms due to tachyarrhythmia or with tachycardiomyopathy most likely benefit from this therapeutic option.[15] Because AV nodal ablation causes lifelong pacemaker dependency, this approach should only be used if other means of rate control fail. In a meta-analysis published in 2000 and including 21 studies with a total of 1181 patients, Wood *et al*.[58] demonstrated a statistically significant improvement after ablation and pacing therapy in all outcome measures except fractional shortening that tended to be improved ($1.7 \pm 1.3\%$; $P = 0.08$, *Figure 2*). The calculated 1-year total and sudden death mortality rates after ablation and pacing therapy were comparable with medical therapy (6.3 and 2.0%, respectively). However, most patients included in this meta-analysis had normal or only slightly

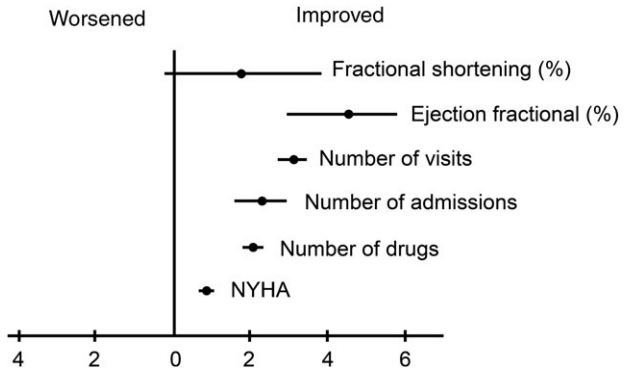

Figure 2 Data from a meta-analysis with a total of 1181 patients with symptomatic, medically refractory atrial fibrillation who underwent atrioventricular node ablation and pacing. Effects on left ventricular function, healthcare use, and New York Heart Association functional classification (effect sizes and 95% confidence intervals, $P < 0.001$ for all except fractional shortening ($P = 0.08$)). From Wood *et al.*[58]

reduced systolic LV function. Ozcan *et al.*[59] examined the 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 controls treated with drugs. In a study of patients with drug-refractory AF and LV dysfunction (EF $\leq$ 40%), near normalization of LVEF ($\geq$45%) occurred in 29% of study patients after AV nodal ablation and pacemaker implantation. This subset of patients showed a survival comparable to normal control subjects and probably reflects patients with at least some degree of tachycardiomyopathy.[15] However, because chronic right ventricular pacing may have adverse haemodynamic effects,[60–62] strategies to prevent pacing-induced asynchrony should be considered particularly in patients with CHF. Occhetta *et al.*[63] recently showed in a small trial (16 patients) that permanent para-Hisian pacing after AV node ablation can allow an improvement in functional and haemodynamic parameters compared with conventional right apical pacing. The OPSITE study compared LV and biventricular pacing with right ventricular pacing in patients with permanent AF treated with AV node ablation (EF: 38 $\pm$ 14%, NYHA class: 2.5 $\pm$ 0.5).[64] 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 favourable effect compared with RV pacing during the 3-month observation period. The authors therefore recommended that left or biventricular pacing (upgrading) should be considered only if right ventricular pacing after AV node ablation does not improve symptoms.[65] Yet, follow-up was only 3 months. This may be too short to detect relevant differences, since the PAVE study found an improvement in 6 min walk distance and a higher EF in patients receiving biventricular pacing compared with right ventricular pacing after AV nodal ablation.[66] In clinical practice, AV node ablation is performed more and more in AF patients with an indication for cardiac resynchronization therapy (CRT) to assure adequate biventricular pacing.

AV node modification by catheter ablation of inferior atrial inputs to the AV node slows ventricular rate and improves symptoms without the need of pacemaker implantation.[67,68] However, it is difficult to prevent complete AV block and simultaneously to ensure sufficient rate control. Therefore, this treatment option is rarely used. Alternatives like cell therapy to modify AV conduction are being developed at the preclinical level.[69]

Maintenance of sinus rhythm after cardioversion of atrial fibrillation in patients with chronic heart failure

Beta-blockers

So far, the role of beta-blockers in maintaining sinus rhythm after cardioversion in the presence of CHF has not been addressed specifically. Treating heart failure with beta-blockers might reduce atrial load and facilitate reversed atrial remodelling. Furthermore, chronic treatment with a beta-blocker is associated with a prolongation of the atrial action potential.[70] This could increase atrial wavelength and thereby exert anti-fibrillatory effects. Kühlkamp *et al.*[71] showed in 394 patients with normal LV systolic pump function that after cardioversion of AF metoprolol is more effective than placebo in maintaining sinus rhythm. Plewan *et al.*[72] observed in 128 patients with a mean EF of 41 $\pm$ 5% that bisoprolol and sotalol are equally effective in preventing AF recurrence, but there was no placebo group. Beta-blockers may also reduce new onset of AF. However, this was not an endpoint and not even analysed retrospectively in most large CHF survival trials. In COPERNICUS, 29 of 1156 patients on carvedilol vs. 52 of 1133 patients on placebo were hospitalized for atrial tachyarrhythmia, and AF was reported as adverse event in 1.9% of patients on placebo vs. 1.0% on carvedilol. Yet, these differences did not reach statistical significance ($0.05 < P < 0.10$).[73] *Post hoc* data from the CAPRICORN study (recent acute MI with LV systolic dysfunction) did show a significant reduction of AF incidence in patients receiving carvedilol vs. placebo.[74] Probably, most convincing data in patients with CHF come from a retrospective analysis of the MERIT-HF trial (NYHA classes II–IV, EF $\leq$ 40%). On the basis of ECG diagnosis, the risk of new onset AF was about halved in the metoprolol group (RR 0.53: 95% CI 0.37–0.76, $P = 0.0005$, *Figure 3*).[47]

Amiodarone and dofetilide

Patients with CHF carry an increased risk to develop ventricular arrhythmias and sudden death. Amiodarone and dofetilide are the only anti-arrhythmic agents recommended by the current guidelines for maintenance of sinus rhythm in patients with AF and CHF.[39–41] In the DIAMOND study, Torp-Pedersen *et al.* included 1518 patients with symptomatic CHF and severe LV dysfunction (EF < 35%). About 25% of these patients had AF at inclusion. They showed that dofetilide is more effective than placebo in converting to and maintaining sinus rhythm (hazard ratio for the recurrence of AF 0.35: 95% CI 0.22–0.57; $P < 0.001$). Dofetilide had no negative inotropic effects and did not affect mortality. Thus, it is regarded a relatively safe therapy in CHF. However, it has a very narrow therapeutic window. Initially, torsade de pointes occurred in 4.8% in the dofetilide group. This frequency could be reduced to 2.9% by adjusting the dose according to renal function and by continuous cardiac monitoring during the first 3 days of

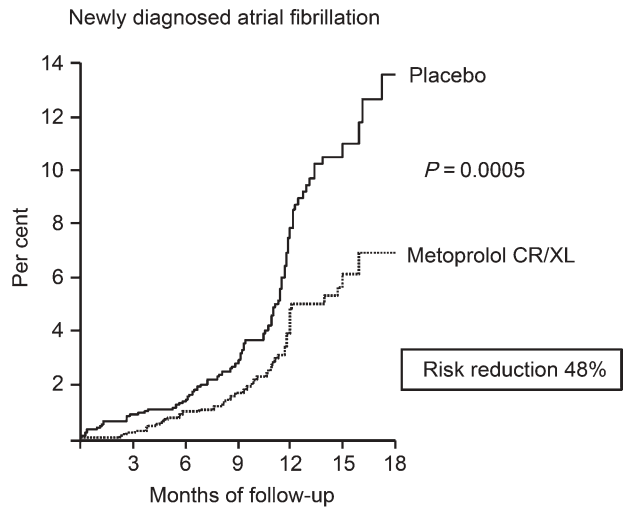

Figure 3 Retrospective data from the MERIT-HF study (from Van Veldhuisen *et al.*[47]): Kaplan–Meyer estimates of newly diagnosed atrial fibrillation during follow-up of patients in sinus rhythm at baseline. Atrial fibrillation was reported as an adverse event and/or defined from the follow-up ECG. Atrial fibrillation is counted only once in each patient.

treatment.[75] Therefore, the US Food and Drug Administration mandated in-hospital initiation of therapy. Dofetilide is not available in Europe. Amiodarone is regarded a safe drug in patients with CHF, too. Neither the rate of sudden death nor mortality was increased in 674 patients with CHF and an EF below 40%.[76] In a substudy of the CHF-STAT trial, amiodarone has been shown to be effective in converting to and stabilizing sinus rhythm. Of 667 patients with CHF, 103 (15%) had AF at baseline. Of these, 51 were randomized to amiodarone and 52 to placebo. Sixteen of 51 patients on amiodarone and four of 52 on placebo converted to sinus rhythm during the study ($P < 0.002$). Furthermore, in patients in sinus rhythm amiodarone prevented the occurrence of AF. During follow-up, 11 of 268 patients on amiodarone at baseline and 22 of 263 on placebo developed AF ($P < 0.005$).[77] However, relevant side effects including marked bradycardia in some patients limit the routine and long-term use of this drug.[78]

D, L-sotalol

D, L-sotalol induces beta-blockade and exerts class III antiarrhythmic effects (prolongation of repolarization by blocking potassium channels). According to the SWORD trial, the class III effect (as exerted by d-sotalol) seems to be associated with increased mortality in patients with severely reduced systolic pump function (EF $\leq$ 40%) after myocardial infarction.[79] In a retrospective analysis derived from 22 clinical trials involving 3135 adult patients who received oral D, L-sotalol, a history of CHF was one of the factors most predictive of torsade de pointes ventricular tachyarrhythmia.[80] Therefore, D, L-sotalol should be avoided in patients with CHF.

Class I drugs

Class I anti-arrhythmic drugs such as propafenone or flecainide, though recommended to stabilize sinus rhythm in patients with lone AF, should not be used in patients with CHF due to their negative inotropic and potentially serious pro-arrhythmic effects. In a retrospective analysis from the SPAF trial, Flaker *et al.*[81] reported an increased mortality in patients with CHF taking class I anti-arrhythmic drugs even after excluding patients with documented ventricular arrhythmias. There was a relative risk of 3.3 for cardiac death (95% CI: 0.99–11.1, $P = 0.05$) and of 5.8 for arrhythmic death (95% CI 1.5–21.7; $P = 0.009$).

Non-pharmacological options

Catheter ablation

According to the current guidelines, catheter ablation to maintain sinus rhythm and prevent AF recurrences is regarded as a reasonable alternative to pharmacological therapy in symptomatic patients with little or no LA enlargement. Limited information is available regarding catheter ablation of AF in patients with CHF. A recent study from a highly experienced single-centre reported data on AF ablation in 58 patients with CHF and an EF $\leq$ 45%.[82] 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. Given the limited body of data and the complexity of the procedure, catheter ablation to treat AF in CHF patients cannot be generally recommended.

Surgery

Surgery, the so-called Cox-Maze procedure,[83] compartmentalizes both atria in order to reduce the atrial mass available to sustain AF. Restoration of sinus rhythm during long-term follow-up (3 months to 8 years) can be achieved in more than 90% without anti-arrhythmic medication.[84] The frequency of restoring atrial contraction varies in different series from 21 to 100%.[84,85] In patients with CHF, there are no prospective data on the role of surgery in maintaining sinus rhythm. One small retrospective trial reports beneficial effects of the Cox-Maze procedure on systolic function and functional status in patients with LV dysfunction.[86] However, because of the morbidity associated with the procedure, particularly in the presence of CHF, this option should be reserved for individual patients who also require valvular or coronary artery bypass surgery.

Heart failure therapy in patients with atrial fibrillation

This section discusses the therapeutics of CHF that do not directly act on cardiac electrophysiology but may have implications for the occurrence of AF in patients with CHF.

Renin–angiotensin–aldosterone system blockers

CHF is associated with an activation of the renin–angiotensin–aldosterone system (RAAS). Furthermore, it has been shown that ACE-inhibitors (CONSENSUS, SOLVD-T), angiotensin receptor blockers (Val-HeFT, CHARM), and aldosterone antagonists (RALES, EPHESUS) are beneficial in CHF patients.[87] In a dog model, it has been shown that an ACE-inhibitor (enalapril) attenuated the effects of CHF on atrial conduction, atrial fibrosis, and mean duration of induced AF episodes.[88] Accordingly, retrospective analysis from the TRACE study and the SOLVD trials indicated that ACE-inhibitors can reduce the occurrence of AF in patients

with LV dysfunction (*Figure 4*).[89,90] Moreover, irbesartan and enalapril can reduce the rate of AF recurrence after electrical cardioversion.[91,92] We have initiated a clinical trial testing the hypothesis that aldosterone blockade by eplerenone is able to reduce AF recurrences after cardioversion, too.

Diuretics

Diuretics and salt restriction are indicated in patients with current or prior symptoms of CHF and reduced LVEF who have evidence of fluid retention.[39] Diuretics can reduce atrial size and wall stress, and therefore may theoretically also reduce the occurrence, recurrence, and stability of AF.[9,93] In a clinical study of Gottdiener *et al.*, the effects of atenolol, captopril, clonidine, diltiazem, hydrochlorothiazide, and prazosin on left atrial size were investigated. Hydrochlorothiazide turned out to be most effective in reducing left atrial size in enlarged atria.[94] Anné *et al.*[95] showed in patients after radio frequency ablation of atrial flutter that the use of diuretics was significantly associated with less development of AF. However, almost all patients had normal systolic function. Whether the use of diuretics can prevent AF in patients with CHF has to be investigated.

Biventricular pacing

Patients with cardiac dyssynchrony, EF $\leq$ 35%, sinus rhythm, and NYHA functional class III or ambulatory class IV symptoms, despite optimal medical therapy, should receive CRT.[39] In these patients, biventricular pacing improves the blunted force–frequency relationship present during univentricular pacing.[96] This may contribute to the improvement in functional capacity. Very recent studies showed that this therapy option could be beneficial in patients with AF, too. In the case of a standard pacing indication biventricular pacing was beneficial even in the presence of AF.[97] In patients without standard pacing indication and permanent AF, CRT was beneficial only after AV nodal ablation.[98] Whether CRT reduces AF burden is at present unknown. In one study (CARE-CHF), new onset of AF in patients with sinus rhythm was not reduced by CRT.[99] In contrast, Hügl *et al.*[100] reported a gradual reduction in AF burden when CRT was started. Interestingly, in CARE-HF, CRT improved the outcome regardless of whether AF developed. However, none of these trials evaluated the effects of cardiac resynchronization on mortality in patients with AF and CHF.

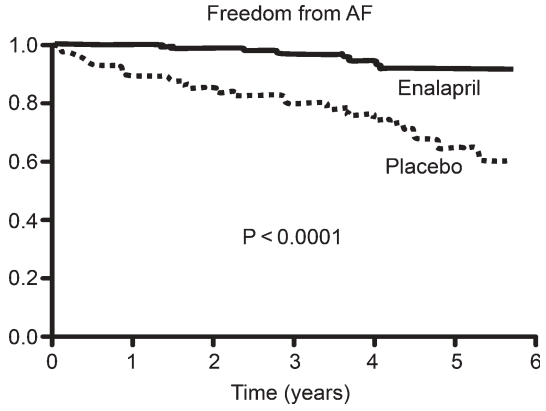

Figure 4 The Kaplan–Meier curves of percentage of patients remaining free of first occurrence of atrial fibrillation during 2.9 years of follow-up in 374 patients with depressed LV function (EF $\leq$ 35%) and sinus rhythm at baseline, randomly assigned to enalapril (solid line) or placebo (dotted line). From the SOLVD trials.[90]

Conclusions

At present, it is not clear whether AF is an independent risk factor or just a risk marker for increased mortality in patients with CHF and LV dysfunction. Furthermore, there are no prospective data showing that a strategy aimed at converting AF to sinus rhythm and preventing the recurrence of AF ('rhythm control') is superior to a strategy aimed at preventing tachycardia during AF ('rate control'). Therefore, the results from the ongoing CHF-Stat trial are of particular interest. For rate control, beta-blockers and digoxin can be used safely, and amiodarone is second choice. So far, even with beta-blockers, a reduction in mortality has not been shown in patients with AF and CHF, and prospective trials are needed. If these measures are ineffective, AV node ablation and ventricular pacing is an effective way to control heart rate. Probably, biventricular pacing is superior to right ventricular pacing. However, the long-term results with mortality as an endpoint are currently not available.

In the case of symptomatic AF, electrical cardioversion can be performed and sinus rhythm may be stabilized with beta-blockers. There is at least indirect evidence that these drugs can reduce the occurrence of AF in patients with CHF. Adequate heart failure therapy, e.g. with RAAS blockers, will probably increase the chance to maintain sinus rhythm and should be optimized before cardioversion. Additionally, amiodarone is safe and effective, if loaded before electrical cardioversion. Regarding the chronic use of this drug, side effects have to be considered. In severe heart failure and haemodynamic deterioration associated with AF, intravenous amiodarone and immediate electrical cardioversion may stabilize the patient.

Catheter ablation of AF is not a first-line option for therapy in CHF. Nevertheless, at experienced centres, this new approach may offer relevant symptomatic relief. Alternatively, in patients scheduled for open-heart surgery for other reasons, a surgical compartmentalization of the atria (Cox-Maze procedure) may be considered.

In the light of available data, prevention of AF occurrence in patients with CHF is the most important goal. It seems that beta-blockers, ACE-inhibitors, and angiotensin II receptor blockers are effective. Whether CRT (biventricular pacing) may prevent AF is unknown at present. Importantly, all patients with AF and CHF should receive anti-thrombotic therapy with warfarin (INR 2–3), unless individual circumstances seriously stand against it.[40,101]

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