Atrial Fibrillation in Congestive Heart Failure: Current Management

Noel G. Boyle, MD, PhD*, Kalyanam Shivkumar, MD, PhD

KEYWORDS
- Atrial fibrillation • Congestive heart failure
- Atrial remodeling • Antiarrhythmic drugs
- Catheter ablation

Atrial fibrillation (AF) and Congestive Heart Failure (CHF) are two commonly associated conditions and have been described as modern "epidemics" in cardiovascular disease by Braunwald[1] in the *New England Journal of Medicine* in 1997. Both conditions are increasingly common with age, with an estimated prevalence of 5.3 million people over age 20 years with CHF[2] and 2.2 million adults with AF in the United States.[3]

In the population-based Framingham Heart Study, each condition is associated with and increased risk of developing the other and each increases the mortality risk associated with the other. The cumulative incidence of first CHF in patients with AF was 15% at 5 years, whereas in patients with CHF, the cumulative incidence of AF was approximately 25% at 5 years.[4] The prevalence of AF is related to the extent of the left ventricular (LV) dysfunction, with AF occurring in about 10% of New York Heart Association (NYHA) functional class I/II heart failure and in to up to 50% of NYHA functional class IV patients in the large CHF trials.[5] In the Atrial fibrillation Follow-up and Investigation of Rhythm Management (AFFIRM) trial, which evaluated the management of AF in a general population of older patients with AF, 23% of patients had a history of CHF.[6]

MECHANISMS

There is a complex interplay between AF and CHF with heart failure predisposing to AF through atrial stretch and neurohormonal activation and AF promoting heart failure via fast irregular ventricular rates and loss atrio-ventricular (AV) synchrony (**Fig. 1**). AF results in loss of AV synchrony and a rapid and irregular ventricular response, which contribute to the development of CHF. In CHF, atrial volume and pressure overload contribute to the development of atrial enlargement, altered atrial refractory properties, and interstitial fibrosis, which then predispose to AF development.[5]

AF results in electrical, contractile, and structural remodeling of the atria (**Fig. 2**).[7] Both rapid atrial pacing and episodes of AF shorten the atrial refractory period, resulting in shorter wavelength, which allows more wavelets to coexist in the atrium supporting AF. This was the basis of the concept introduced by Allessie and coworkers that "atrial fibrillation begets atrial fibrillation." The ionic mechanisms underlying this process include reductions in the L-type calcium current and the transient outward potassium currents occurring over 1 to 2 days, resulting in shortening of the action potential and in contractile dysfunction. Within 1 week, signs of structural remodeling appear with changes in nuclear chromatin, and
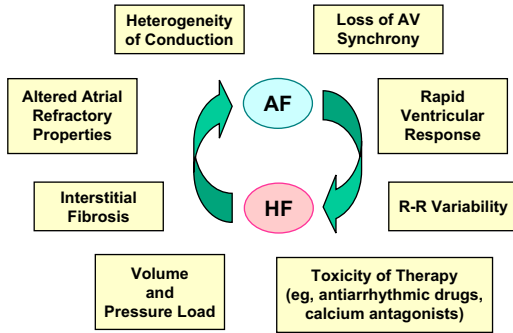
Fig. 1. Mechanisms involved in the interaction of AF and CHF. (*From* Maisel WH, Stevenson LW. Atrial fibrillation in heart failure: epidemiology, pathophysiology, and rationale for therapy. Am J Cardiol 2003;91(6A):2D–8D; with permission.)

by week 4, there is deceased connexin-40, sarcomere distortion, and accumulation of glycogen.

The work of Nattel and colleagues[8–10] has provided significant insights into the mechanisms of CHF-related AF. Using a model of ventricular high-rate pacing-induced CHF (240 beats per minute × 2 weeks in dogs), there was recovery of the ionic remodeling and contractile dysfunction in 4 weeks, but not of the structural remodeling or the ability to maintain AF.[11] This suggests that anatomic remodeling could be the primary factor contributing to AF in CHF. Angiotensin-converting enzyme (ACE) inhibitors can reduce CHF-associated atrial angiotensin II levels and attenuate this anatomic remodeling including atrial fibrosis and conduction abnormalities.[12] CHF-induced AF also resulted in atrial sarcoplasmic reticulum calcium overload and increased triggered activity.[13] The underlying mechanism was a reduction in ryanodine receptor and calsequestrin expression. In
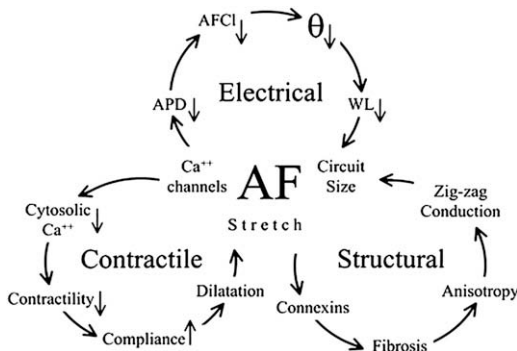

Fig. 2. Electrical, contractile, and structural remodeling in atrial fibrillation. (*From* Allessie M, Ausma J, Schotten U. Electrical, contractile and structural remodeling during atrial fibrillation. Cardiovasc Res 2002;54(2):230–46; with permission).

addition, there was decreased atrial contraction because of reductions in phosphorolated protein kinase A and myosin-binding protein kinase C. These changes in calcium handling and expression of contractile proteins provide a mechanistic link between atrial arrhythmias and atrial dysfunction seen in CHF.

CLINICAL MANAGEMENT OF ATRIAL FIBRILLATION IN CONGESTIVE HEART FAILURE PATIENTS

The most recent American College of Cardiology/American Heart Association/European Society of Cardiology (ACC/AHA/ESC) guidelines on the management of AF were published in 2006 and provide an extensive referenced document on the management of AF (**Fig. 3**).[14] When AF is initially suspected clinically, the diagnosis should be confirmed by electrocardiogram, Holter, or an event monitor. It is helpful, both in terms of treatment and prognosis, to classify it as paroxysmal (self-terminating episodes lasting <48 hours), persistent (not self-terminating and lasting from 48 hours to 6 months), and permanent or chronic (>6 months for which cardioversion has failed or has not been attempted). Often the clinical group to which a patient belongs will not be clear for a period of time, especially until cardioversion is attempted.

Optimal heart failure management with current state-of-the-art evidence-based therapy forms the basis of treatment in all heart failure patients with AF.[15] This includes ACE inhibitor or an angiotensin-receptor blocker (ARB) for all patients with maximum-tolerated doses of beta blockers. Diuretics, aldosterone antagonists, digoxin, and cardiac resynchronization therapy should be used as appropriate. It is noteworthy that these optimal heart failure therapies may also be beneficial in the treatment of AF as discussed below.

THERAPEUTIC APPROACH

The initial treatment approach to AF involves the standard approach targeting three different aspects of the condition: (1) risk assessment for thromboembolism and anticoagulation as appropriate, (2) ventricular rate control, and (3) assessment for conversion to and maintenance of sinus rhythm.

Anticoagulation

Although we do not have specific trials on anticoagulation in patients with AF and CHF, the major clinical trials on anticoagulation reported in the 1990s[16] included many patients with CHF—approximately 25% overall and 50% in the Danish
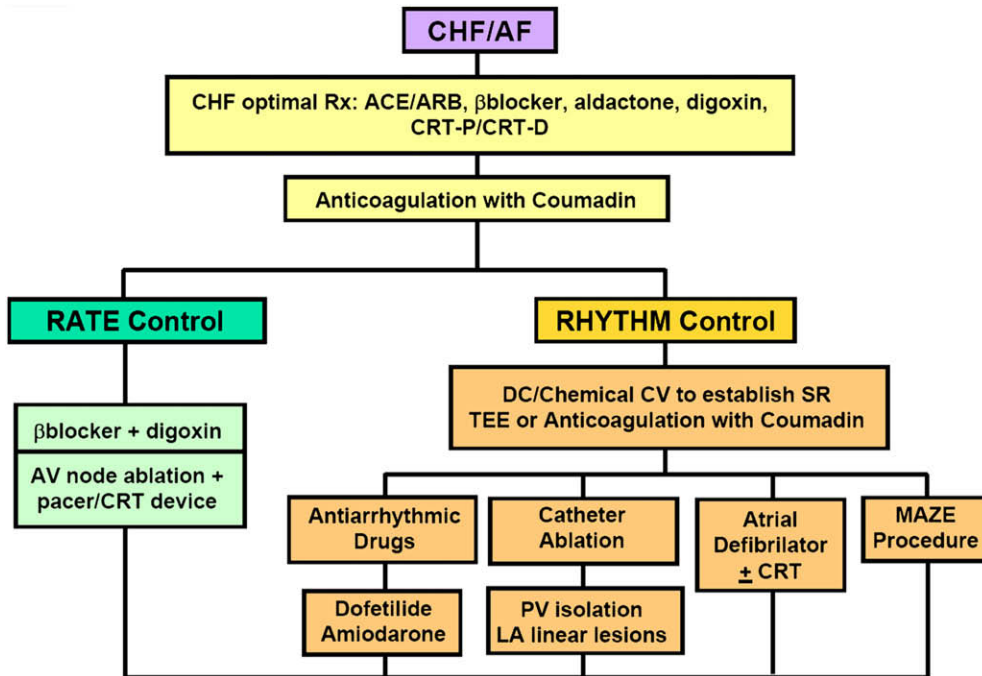
Fig. 3. Overview of the management of AF and CHF patients.

Atrial Fibrillation, Aspirin and Anticoagulant Therapy (AFASAK) trial. In the CHADS$_2$ (CHF, Hypertension, Age >75 years, Diabetes [each 1 point] and Stroke [2 points]) scoring system for stroke risk evaluation,[17] heart failure is assigned one point with an associated annual stroke risk of 2.8%; if the common associated conditions of hypertension and diabetes are added to CHF, yielding a total score of three, then the annual stroke rate is 5.9% (**Table 1**). The CHADS$_2$ score is

Table 1
Stroke risk in patients with nonvalvular atrial fibrillation not treated with anticoagulation according to CHADS$_2$ index

CHADS$_2$ Risk Criteria		Score
Prior stroke or transient ischemic attack		2
Age >75 yr		1
Hypertension		1
Diabetes mellitus		1
Heart failure		1
Patients (N = 1733)	Adjusted Stroke Rate (%/yr)* (95% CI)	CHADS$_2$ Score
120	1.9 (1.2 to 3.0)	0
463	2.8 (2.0 to 3.8)	1
523	4.0 (3.1 to 5.1)	2
337	5.9 (4.6 to 7.3)	3
220	8.5 (6.3 to 11.1)	4
65	12.5 (8.2 to 17.5)	5
5	18.2 (10.5 to 27.4)	6

Data from Fuster V, Ryden LE, Cannom DS, et al. ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation. Circulation 2006;114(7):e257–354.

a good predictor of stroke risk in clinical practice.[18] In an analysis of the Sudden Cardiac Death in Heart Failure trial population (class II or III CHF, ejection fraction (EF) ≤35%; no history of VT), the annual stroke rate was 1.7%.[19] In a meta-analysis of five major trials, Coumadin was associated with a 68% reduction in the stroke risk, whereas aspirin results in only a 21% reduction. The current American College of Chest Physicians guidelines classify CHF as a major risk factor for stroke and also recommend anticoagulation with coumadin.[20] Multiple clinical trials looking at other inhibitors of thrombin or factor Xa are ongoing.[21]

Nonpharmacologic approaches, such as left atrial appendage occluder devices ("watchman") currently are undergoing clinical trials for use in patients who cannot take Coumadin because of bleeding risks;[22] however, serious complications may also be associated with these devices.[23] It is worth remembering that only 65% of embolic strokes in patients with AF are thought to originate in the left atrial appendage, with the remainder caused by other mechanisms.[24]

Rate control

For acute rate control in a patient presenting with AF and rapid ventricular rate, in the setting of CHF, either an intravenous beta blocker or a calcium channel blocker such as diltiazem can be used to achieve short-term rate control.[25] In the chronic AF setting, the most effective drug therapy for rate control is a combination of a beta blocker and digoxin, already appropriate therapy in the heart failure setting. Carvedilol in combination with digoxin has also been shown to be superior to either carvedilol or digoxin alone.[26] In the AFFIRM and AF-CHF trials, effective rate control, defined as a heart rate less than 80 beats per minute at rest and less than 110 beats per minute with moderate exercise such as the 6-minute walk was achieved in more than 80% of patients assigned to this strategy by year 5 of follow-up.[27]

In approximately 5% of patients in the AFFIRM trial, rate control drug therapy was deemed ineffective, and AV node ablation and pacing was needed. Two trials have compared rate control drug therapy with AV node ablation and pacing. In an Australian trial of patients with chronic AF without CHF, there was no difference in exercise duration or ejection fraction at 12 months of follow-up; however, better rate control with exercise and quality-of-life measurements were found in the AV node ablation and pacer group.[28] In an Italian trial of patients with chronic AF with CHF (mean EF, 40%), there was no difference in exercise tolerance or measured EF at 1 year of follow-up, but the AV node ablation and pacer group

experience decreased symptoms of palpitations and dyspnea. In a meta-analysis of all six trials comparing AV junction ablation and pacer with pharmacologic therapy, there was no statistical difference in clinical outcomes including survival, stroke, hospitalization, functional class, EF, or exercise tolerance.[29]

There is much debate on whether chronic right ventricular pacing in itself can promote right ventricle (RV) dyssynchrony and possible worsen CHF.[30] Cardiac resynchronization therapy may provide improved outcomes when compared with RV pacing alone in the setting of AF and CHF.[31] In a nonrandomized trial of patients with permanent AF, AV node ablation, and RV pacing in whom class III-IV CHF developed, upgrading to biventricular pacing resulted in improvement in functional status and EF at 6 months' follow-up.[32] In the Post AV Nodal Ablation Evaluation (PAVE) trial, patients with AF and CHF (class II–III, mean EF 46%) undergoing AV nodal ablation were randomly assigned to either biventricular or right ventricular pacing.[33] At 6 months' follow-up, the biventricular pacing group has improved 6-minute walk and ejection fraction compared with the right ventricular pacing group, with most improvement seen in those with lower EF. In a meta-analysis looking at three available randomized trials of patients with AF treated with AV node ablation and randomly assigned to cardiac resynchronization therapy (CRT) versus RV pacing, the investigators found that CRT was associated with a statistically significant improvement in EF in two of the three trials and a trend toward reduced all-cause mortality.[29] Large-scale randomized trials are still needed to answer this question. Permanent para-Hisian pacing may offer another option to prevent development of ventricular dyssynchrony after AV node ablation in patients with permanent AF.[34]

Rhythm control—acute conversion

Direct current cardioversion with a biphasic shock is the most effective method to acutely establish sinus rhythm in a patient with AF, with initial success rates greater than 90%.[35] For pharmacologic cardioversion, digoxin is no better than placebo,[36] and although ibutilide is approximately 50% successful for acute conversion of AF, it is associated with a 5% risk of torsades de pointes in patients with CHF and is probably best avoided in this group except for possibly cardiac care unit settings.[37] Oral class I drugs, propafenone and flecainaide, used as a "pill in the pocket approach" are highly effective in acutely restoring sinus rhythm in a paroxysmal AF population without structural heart disease;[38] however, the use of class I drugs is contraindicated in CHF patients because of the risks of pro-arrhythmia.[39] Although amiodarone is

not usually considered a first choice drug for restoring sinus rhythm, when loaded intravenously and followed by a high-dose orally, it is approximately 60% effective in restoring sinus rhythm in 24 hours in a mixed group of paroxysmal and persistent patients with AF.[40] However, the efficacy of any drug used for chemical cardioversion will decrease depending on the duration of the AF.

Current guidelines indicate that chemical or electrical cardioversion may be undertaken after anticoagulation with Coumadin and a therapeutic International Normalized Ratio (INR) for approximately 1 month or after a negative transesophageal echocardiogram (TEE).[14] In the Assessment of Cardioversion using Transesophageal Echocardiography trial, 1222 patients were randomly assigned to either standard approach of anticoagulation with Coumadin for 1 month followed by cardioversion versus TEE and early cardioversion if negative for thrombus; at 8 weeks of follow-up, clinical outcomes for embolic events, and for restoration and maintenance of sinus rhythm were equivalent.[41] Approximately one quarter of the patients in this trial had a history of CHF and 15% were NYHA class III or IV. The *approach* of TEE followed by early cardioversion may be particularly useful for patients with AF and worsening CHF.

Rhythm control—maintenance of sinus rhythm
There are multiple studies in the literature comparing antiarrhythmic drug therapies for maintenance of sinus rhythm in patients with AF.[42] Three major trials reported in this decade make the overall findings clear. In the Canadian Trial of Atrial Fibrillation, Amiodarone was superior to sotalol or propafenone in the maintenance of sinus rhythm over a 5-year follow-up.[43] In the antiarrhythmic drug substudy of the AFFIRM trial[44] and the SAFE –T trial,[45] the results were similar. Overall amiodarone was approximately 70% effective in maintaining sinus rhythm and Sotalol or class I drugs approximately 40% effective at 1 year for patients with persistent AF. Amiodarone has also been shown not to increase mortality in patients with heart failure in the Grupo de Estudio de la Sobrevida en la Insuficienca Cardica en Argentina (GESICA) Trial[46] and Congestive Heart Failure—Survival Trial of Antiarrhythmic Therapy (CHF-STAT)[47] studies. The proarrhythmic effects of Sotalol and the class I drugs and the well-known organ toxic side effects of Amiodarone have propelled the search for new antiarrhythmic drugs.[39]

Dofetilide is a newer class III antiarrhythmic agent for the approved for the maintenance of sinus rhythm by the US Food and Drug Administration (FDA) in 1999. Dofetilide was evaluated specifically in heart failure patients (predominantly class II–III) in the Danish Investigators of Arrhythmia and Mortality on Dofetilide (DIAMOND)-CHF trial.[48] In a 3-year follow-up, there was no difference in survival rate between the dofetilide and placebo groups. Although dofetilide was poor at achieving chemical cardioversion (12% at 1 month), it was effective at maintaining sinus rhythm (approximately 75% at 1 year). There was a 3.3% incidence of torsades in the dofetilide group. This has led to the FDA current ''black box'' warning with dofetilide and the mandatory in hospital initiation by the manufacturer, limiting its utility compared with amiodarone. Interestingly dofetilide may be more effective in patients with persistent AF compared with those with paroxysmal AF.[49]

Dronedarone currently is an investigational drug for the treatment of AF. It has received much attention because it is a noniodinated derivative of amiodarone developed with the aim of reducing adverse effects while maintaining the efficacy of amiodarone. In addition, in a report of combined US (African American Trial of Dronedarone in Atrial Fibrillation) and European (European Trial of Dronedarone in Atrial Fibrillation) trials for non–heart failure patients with AF, dronedarone more than doubled the median time to recurrence of AF compared with placebo and was not associated with any increase in pulmonary, thyroid, or liver dysfunction at 12 months of follow-up.[50] In the A Trial of Dronedarone For Prevention Of Hospitalization in Patients with AF (ATHENA) trial, 4628 patients with paroxysmal AF were randomly assigned to dronedarone, 400 mg versus placebo; of note, 20% of patients had a history of class II or III CHF. The primary outcome of death or cardiovascular hospitalization was reduced by 24% and all-cause mortality by 16% with a mean follow-up of 1 year.[51] However, when used prophylactically in patients with class II–III heart failure in the Antiarrhythmic Trial in Heart Failure in the Antiarrhythmic Trial in Heart Failure (ANDROMEDA) study, dronedarone was associated with increased mortality primarily caused by worsening heart failure.[52] There was also an increase in renal insufficiency in the dronedarone group. The results of this trial have been widely debated—it has been suggested that the decrease or discontinuation of ACE inhibitors in patients who had worsening renal function may explain the increase in mortality rate from CHF in the treated group.[53]

RATE CONTROL VERSUS RHYTHM CONTROL
The AFFIRM and AF-CHF Trials

The definite AFFIRM trial compared rate control drug therapy with rhythm control drug therapy

(reflecting the standard drug therapy of the mid 1990s).[6] There was no difference in mortality or thromboembolic events between the two treatment groups. Four smaller rate control versus rhythm control trials—Pharmacologic Intervention in Atrial Fibrillation (PIAF),[54] Rate Control versus Electrical Cardioversion of Persistent Atrial Fibrillation (RACE),[55] Strategies of Treatment of Atrial Fibrillation (STAF),[56] and How to Treat Chronic Atrial Fibrillation (HOT CAFE)[57] looked at clinical endpoints only, and all showed no statistical difference between the defined clinical endpoints (Table 2).[58] It was notable in AFFIRM that at 5 years, 63% of the "rhythm control" group and 35% of the "rate control" group were in sinus rhythm; conversely, rate control as defined in the trial (heart rate, <80 at rest and <110 with moderate exercise), was successfully achieved in 70% to 80% of those assigned to this group.[27] This highlights a fundamental problem with all these studies—antiarrhythmic drugs are ineffective at actually achieving rhythm control, whereas AV nodal blocking drugs are relatively effective at achieving rate control. Hence, the trials are really comparing a rhythm control strategy with a rate control strategy, with the available drug therapy. Interestingly, only two variables in an AFFIRM subset analysis were possibly associated with a better outcome for rhythm control: age <65 years and CHF.

The Atrial Fibrillation and Congestive Heart Failure (AF-CHF) trial is a multicenter randomized trial comparing medical therapies for rhythm control versus rate control in a population with AF, EF less than 35%, and congestive heart failure (NYHA class II-IV) (Fig. 4).[59] A total of 1376 patients were randomly assigned to rate control (n = 694; beta blocker or digoxin or both) or rhythm control (n = 682; overwhelmingly, amiodarone was used), and followed up for a mean of 37 months. The average age was 67 years, 18% were women, 31% were NYHA class III or IV, and the mean EF was 27%. Fifty percent had been hospitalized previously for CHF, 31% had paroxysmal AF, 71% had persistent AF, and approximately 90% of patients in both groups received oral anticoagulation. A flow chart showing the design and outcomes of the trial is shown in Fig. 4. At follow-up visits, the prevalence of AF was approximately 60% in the rate control group and 20% to 30% in the rhythm control group over 4 years. In the rate control group, the target heart rate of less than 80 at rest and less than 110 during a 6-minute walk was achieved in approximately 85% of the patients studied during 3 years of follow-up.

The primary outcome—cardiovascular mortality—was 27% in the rhythm control group and 25% in the rate control group (hazard ratio [HR], 1.06; confidence interval [CI]: 0.86–1.30; P value

Table 2
Rate Control versus Rhythm Control Trials

	PIAF	STAF	RACE	AFFIRM
No.	252	200	522	4060
Follow-up (range)	1 yr	19.6 mo (0-36)	2.3 yr	3.5 yr (3.5–6)
Mean age (yr)	61.5	65.8	68	69.7
Duration of AF	<360 d	<2 yr	<1 yr	<6 mo
Important inclusion criteria	Symptomatic patients	Moderate risk of AF recurrence	1–2 previous DCC within 2 years	High risk of AF recurrence
Primary endpoint	Symptom improvement	Composite[a]	Composite[b]	Overall mortality
Rhythm control	55.1%	10%	22.6%	23.8% (at 5 yr)
Rate control	60.8%	9%	17.2%	21.8% (at 5 yr)
P (primary end point)	0.317	0.99	0.11	0.08

[a] Combination death, stroke, or transient ischemic attack, cardiopulmonary resuscitation, or systemic embolism.
[b] Death from cardiovascular causes, heart failure, thromboembolic complications, bleeding, implantation of a pacemaker, or severe adverse effects of anti-arrhythmic drugs.
   Abbreviation: DCC, direct current cardioversion.
   Data from Fuster V, Ryden LE, Cannom DS, et al. ACC/AHA/ESC 2006 Guidelines for Management of Patients with Atrial Fibrillation. Circulation 2006:114(7):e257–354; and Chung MK. Randomized trials of rate control versus rhythm control for atrial fibrillation. Journal of Interventional Cardiac Electrophysiology 2004;10:45–53.
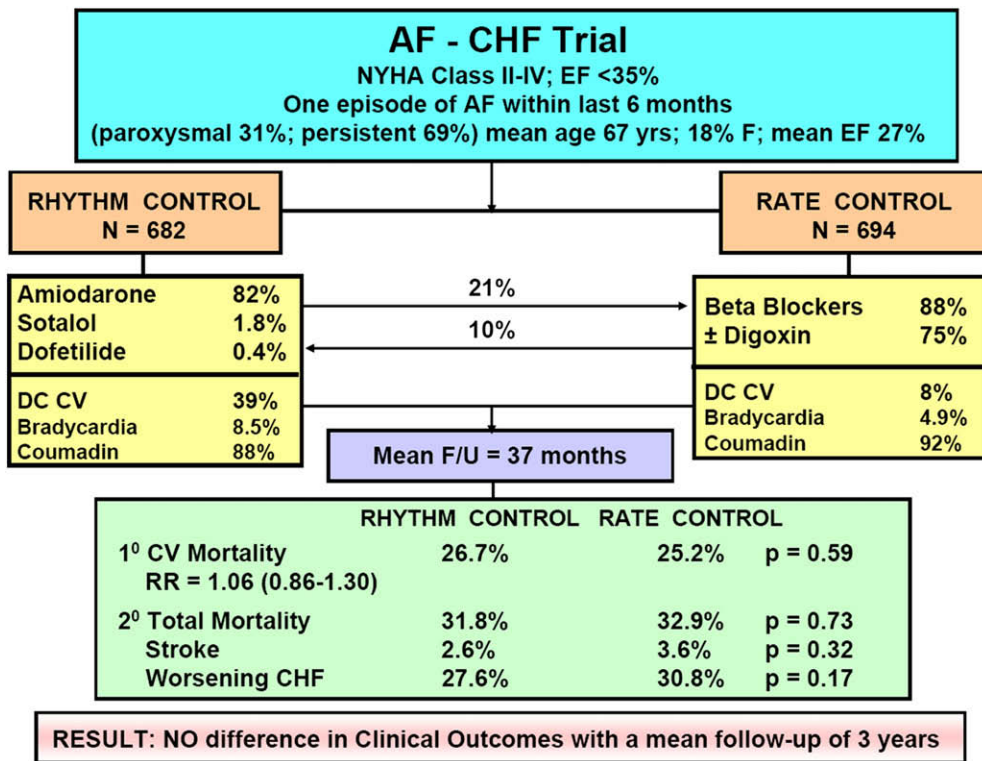
Fig. 4. Flow chart shows design and results of AF-CHF trial.

not significant). Secondary outcomes including all-cause mortality, stroke, and worsening heart failure were the same in both groups. This result mirrors the findings of the main AFFIRM trial;[6] an analysis of AFFIRM stratified by ejection fraction (<30%, 30%–39%, 40%–49%)[60] and other rate-versus-rhythm control trials, showed no survival or clinical advantage for a rhythm control strategy.

Several explanations have been suggested for these findings.[59,61] First antiarrhythmic drugs, even amiodarone, are ineffective at maintaining sinus rhythm (0~30% relapse rate), and up to 40% of patients in the rate control group were in sinus rhythm at some time during the follow-up; hence, a greater difference in the prevalence of sinus rhythm between the two groups may have been necessary to show a reduction in mortality with rhythm control. Second, it is possible that any benefit achieved in maintaining sinus rhythm was counterbalanced by the harmful effect of antiarrhythmic drugs. Third, radiofrequency (RF) ablation was not used in this trial as a treatment option for AF, which offers the possibility of achieving sinus rhythm without the toxicities of antiarrhythmic drugs. Fourth, at the end of the trial recruitment in June 2005, only 16% of the patients had received an implantable cardioverter defibrillator (ICD) implant, based on standard care

approached in that period; this could have influenced outcomes because approximately one third of all deaths in the trial were presumed associated with arrhythmia. It is also possible that AF may be a marker of an overall poor prognosis and not independently associated with survival.

SINUS RHYTHM AND SURVIVAL

There are some intriguing pointers that sinus rhythm, if achievable without drug toxicity or procedure or device complications, is a marker for improved survival. An analysis of the CHF-STAT study found that patients with AF and CHF treated with Amiodarone who converted to and remained in sinus rhythm had an improved survival rate.[62] In a substudy of the DIAMOND trials, for patients with ejection fraction less than 35%, the maintenance of sinus rhythm at 1 year was associated with a significant reduction in mortality, either with dofetilide or placebo (relative risk [RR] = 0.44).[63] An analysis of the AFFIRM trial outcomes found that sinus rhythm (HR = 0.54) and warfarin use (HR = 0.47) were associated with increased survival.[64] It remains to be confirmed in future randomized trials if newer therapies that can maintain sinus rhythm without toxicities will prove superior to rate control therapy.

FROM ELECTRICAL TO STRUCTURAL THERAPY
Role of Nonantiarrhythmic Drugs

As the poor results and unacceptable side effects of current antiarrhythmic drugs used to treat AF have become more apparent in the last decade, interest has moved to the role of other drug therapies. Basic studies on the role of ACE inhibitors and ARBs in reversing atrial remodeling have provided a basis to evaluate these drugs as AF therapies in humans.[65] Interest has focused particularly on the ACE and ARB drugs based on analysis of results from heart failure studies. In the Trandopril Cardiac Evaluation (TRACE) trial, the ACE inhibitor trandolapril reduced the incidence of AF from 5.3% to 2.8% (RR = 0.45) in post–myocardial infarction patients.[66] An analysis of the Studies of Left Ventricular Dysfunction (SOLVD) trials database found that enalapril treatment was associated with a 5.4% risk of AF compared with a 24% risk in the treatment group (HR = 0.22).[67]

When enalapril was added to amiodarone in patients with persistent AF after cardioversion, the maintenance of sinus rhythm was improved compared with amiodarone therapy alone (74% versus 57% at 9 months of follow-up).[68] A meta-analysis looking at the available mostly retrospective studies to 2005 found that ACE inhibitors were associated with a relative risk of 0.78, and ARBs were associated with a relative risk of 0.71 for the development or recurrence of AF (**Table 3**).[69]

Table 3
Meta-analysis of the effects of ACE inhibitors and ARBs in AF prevention

Study	Treatment n/N	Control n/N	RR (95%CI Random)	Weight %	RR (95%CI Random)
01 ACE inhibitor					
Van Den Berg	2/7	7/11		1.7	0.45[0.13,1.57]
SOL VD	10/186	45/188		4.8	0.22[0.12,0.43]
TRACE	22/790	42/787		6.6	0.52[0.31,0.87]
Ueng	18/70	32/75		7.0	0.60[0.37,0.97]
CAPP	117/5492	135/5493		11.4	0.87[0.68,1.11]
STOPH2	200/2205	357/4409		13.0	1.12[0.95,1.32]
GISSI	665/8865	721/8846		14.0	0.92[0.83,1.02]
Subtotal(95%CI)	1034/17615	1339/19809		58.7	0.72[0.56,0.93]
Test for heterogeneity chi-Square = 32.58 df = 6 P<.00001					
Test for overall effect z = -2.53 P = .01					
02 ARB					
Madrid	9/79	22/75		4.3	0.39[0.19,0.79]
ValHeFT	116/2209	173/2200		11.8	0.67[0.53,0.84]
Charm	179/2769	216/2749		12.5	0.82[0.68,1.00]
LIFE	179/4417	252/4387		12.6	0.71[0.59,0.85]
Subtotal(95%CI)	483/9474	663/9411		41.3	0.71[0.60,0.84]
Test for heterogeneity chi-Square = 5.25 df = 3 p = 0.15					
Test for overall effect z = -4.12 p = 0.00004					
Total(95%CI)	1517/27089	2002/29220		100.0	0.72[0.60,0.85]
Test for heterogeneity chi-Square = 48.50 df = 10 p< 0.00001					
Test for overall effect z = -3.74 p = 0.0002					

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                    .1   .2         1      5   10
                    Favours treatment    Favours control
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From Healey JS, Baranchuk A, Crystal E, et al. Prevention of atrial fibrillation with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers a meta-analysis. J Am Coll Cardiol 2005;45(11):1832–9; with permission.

More recent studies, however, have shown less impressive results. In the Heart Outcomes Prevention Trial (HOPE), use of the ACE inhibitor ramipril was not associated with any reduction in the incidence of AF in patients without systolic dysfunction, although the incidence of AF was low at 5%.[70] In a single-center, double-blind randomized study, treatment with the ARB candesartan for 6 weeks before and 6 months after electrical cardioversion of persistent AF had no effect on the recurrence of AF.[71] Large ongoing randomized trials such as the ACTIVE-I trial[72] should provide more reliable information on the role of ACE and ARBs in AF treatment. The role of nonantiarrhythmic drugs such as statins, fish oil, and anti-inflammatory agents continues to be investigated actively.[73,74] This represents a paradigm shift in the treatment of AF from electrical to structural therapy (**Fig. 5**);[75,76] however, the precise role of these therapies in clinical practice remains to be established.

NONPHARMACOLOGIC THERAPY
Cardiac Resynchronization Therapy

Biventricular pacing has emerged in the last decade as an additional treatment for patients with advanced CHF, left bundle branch block (LBBB), and EF less than 35% refractory to medical therapy. Large clinical trials in patients with sinus rhythm have shown clinical benefit in approximately two thirds of patients implanted.[77,78]

Although there are randomized trials specifically for CHF patients with AF, information is available from several smaller trials and substudies. In the Multisite Stimulation in Cardiomyopathy (MUSTIC) trial, a crossover substudy of patients with chronic AF (n = 45) and class III CHF, biventricular pacing resulted in improved clinical outcomes and decreased hospitalizations.[79] Approximately 60% of the patients required AV node ablation to ensure ventricular pacing. In a prospective multicenter study comparing permanent AF patients (n = 1620) with sinus rhythm patients treated with CRT (n = 511), both groups had significant improvement in clinical parameters.[80] However, within the AF group, only those who underwent AV node ablation (n = 114) had a significant increase in ejection fraction and exercise tolerance. The authors of the study emphasized the importance of AV node ablation for optimal results in patients with permanent AF and CHF undergoing a CRT device implant in this study as well as in a recent study in which they also showed improved survival CHF patients with AF treated with CRT.[81] However, another single-center, prospective study comparing CRT in patients with AF (n = 86) and sinus rhythm (n = 209) showed significant and comparable clinical endpoint improvements in both groups, without the need for AV node ablation in the AF patients.[82] A randomized trial is again awaited.[83]

Conversely, it is of interest to ask if CRT prevents development of AF in patients with CHF. In

Multiple pathways leading to atrial remodelling that predisposes the atria to atrial fibrillation
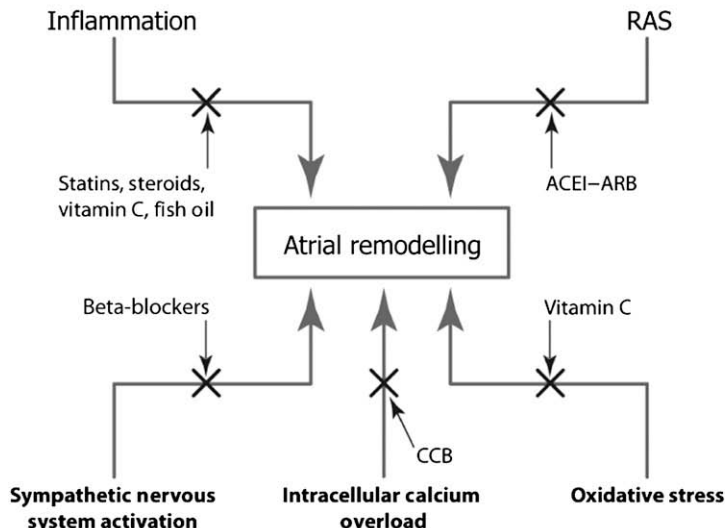
Dorian, P. et al. Eur Heart J Suppl 2008 10:H11-31H; doi:10.1093/eurheartj/sun033

Fig. 5. Proposed mechanisms for nonantiarrhythmic drugs in AF (*From* Dorian P, Singh BN. Upstream therapies to prevent atrial fibrillation. European Heart Journal Supplements 2008; 10(Supplement H):H11–H31; with permission.)

Table 4
RF ablation of AF in CHF studies

Study (Yr)	n	Baseline, EF (%)	Paroxysmal or Persistent AF, %	Procedure (Second Procedure)	Complications Rate	Follow-Up (mo)	Increase in EF	%SR at 1 yr (+AAD)
Chen et al.[91] (2004)	94	<40	67	PVI, LA abl. (22%)	3.1%			69% (78%)
Hsu et al.[92] (2004)	58	35	15	PVI, LA abl. (50%)	3%	12	+21%	69% (78%)
PABA-CHF (2006)	39	28	55	PVI	—	6	+8%	72% (90%)
Gentlesk et al.[93] (2007)	67	42	100	PVI (60%)	—	20	+14%	57% (86%)
Efremidis et al.[94] (2008)	13	35	77	PVI, LA abl.	0	9	+22.5	62% (—)
Lutomsky et al.[95] (2008)	18	41	100	PVI	—	6	+10%	50% (—)

Abbreviations: abl, ablation; LA, left atrial ablation; PVI, pulmonary vein isolation.

the Cardiac Resynchronization in Heart Failure Study (CARE-HF) trial[78] (n = 813), CRT did not result in any difference in the incidence of AF (approx. 15%) at 30 months of follow-up. CRT improved the clinical outcomes regardless of whether AF occurred.[84] We[85] and others[86] have found that patients with CHF who respond to CRT have shorter duration of AF, a lower likelihood of persistent AF, and evidence of reverse atrial remodeling. In the first reported randomized trial of an algorithm for AF prevention with atrial overdrive pacing in patients receiving CRT, no benefit was seen.[87]

Catheter Ablation

Since it was first described in 1998,[88] catheter ablation targeting pulmonary vein isolation for the treatment of AF has developed at a rapid rate.[89] Currently reported success rates average 70% to 90% at 1 year in maintaining sinus rhythm for persistent and paroxysmal AF; however, serious complications can arise.[90] A total of 6 nonrandomized studies (**Table 4**) have been reported. Five studies[91–95] have compared the outcomes of RF ablation in patients with AF, decreased EF, and history of CHF with those in non-CHF control patients. Although these are single-center studies with only small numbers of patients, the percentage of patients in SR at 1 year and the complication rates are consistent with the results for AF ablation in non-CHF patients. There was a consistent improvement in EF and decrease in the need for antiarrhythmic drugs. In one study,[92] patients with inadequate rate control before ablation had the most marked improvement in EF (86% of patients classified as inadequate rate control had an increase of >20% in EF), suggesting the role of tachycardia-mediated cardiomyopathy in CHF patients with AF may be much more significant than previously appreciated. One study, the Pulmonary Vein Antral Isolation versus Atrioventricular Node Ablation with Biventricular Pacing for the Treatment of AF in patients with CHF (PABA-CHF) trial, reported in abstract form,[96] compared pulmonary vein isolation (PVI) with atrioventricular node (AVN) node ablation and biventricular pacing in patients with AF and CHF (EF < 40%). The PVI approach resulted in significant improvement in EF and 6-minute walk test not seen in the AVN ablation and pacing group.

It remains to be shown in a multicenter, randomized trial that RF ablation is truly superior to antiarrhythmic drug (AAD) therapy as some single center studies have found.[97] In a recent meta-analysis of six trails, mostly single center, RF ablation reduced the risk of recurrence of AF at 1 year by 65% compared with antiarrhythmic drugs.[98] This would suggest that the next "AFFIRM" type study should use RF ablation as the rhythm control approach, although the ablation techniques need to be refined and standardized further before a large-scale multicenter trial could be undertaken.

SUMMARY

AF and CHF are common conditions, and each predisposes to the development of the other. Basic research using animal models of the two conditions continues to yield insights that may improve therapies. The AFFIRM and AF-CHF trials have shown no clinical benefits from the use of antiarrhythmic drugs to achieve sinus rhythm. Only dofetilide and amiodarone have been shown to be mortality neutral in CHF patients with AF. The role of medical therapies aimed at the underlying structural changes in AF continues to be a subject of ongoing studies. CRT is an effective therapy in appropriately selected patients with both SR and AF. Catheter ablation is now emerging as a potential alternative to antiarrhythmic drug therapy, but large randomized trials will be needed to assess its role.

REFERENCES

1. Braunwald E. Shattuck lecture–cardiovascular medicine at the turn of the millennium: triumphs, concerns, and opportunities. N Engl J Med 1997; 337(19):1360–9.
2. Heart and stroke facts 2008.
3. Go AS, Hylek EM, Phillips KA, et al. 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(18):2370–5.
4. Wang TJ, Larson MG, Levy D, et al. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart study. Circulation 2003;107(23):2920–5.
5. Maisel WH, Stevenson LW. Atrial fibrillation in heart failure: epidemiology, pathophysiology, and rationale for therapy. Am J Cardiol 2003;91(6A):2D–8D.
6. Wyse DG, Waldo AL, DiMarco JP, et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. N Engl J Med 2002;347(23): 1825–33.
7. Allessie M, Ausma J, Schotten U. Electrical, contractile and structural remodeling during atrial fibrillation. Cardiovasc Res 2002;54(2):230–46.
8. Nattel S. New ideas about atrial fibrillation 50 years on. Nature 2002;415(6868):219–26.

9. Nattel S, Shiroshita-Takeshita A, Brundel BJ, et al. Mechanisms of atrial fibrillation: lessons from animal models. Prog Cardiovasc Dis;48(1):9–28.

10. Nattel S, Opie LH. Controversies in atrial fibrillation. Lancet 2006;367(9506):262–72.

11. Cha TJ, Ehrlich JR, Zhang L, et al. Dissociation between ionic remodeling and ability to sustain atrial fibrillation during recovery from experimental congestive heart failure. Circulation 2004;109(3): 412–8.

12. Li D, Shinagawa K, Pang L, et al. Effects of angiotensin-converting enzyme inhibition on the development of the atrial fibrillation substrate in dogs with ventricular tachypacing-induced congestive heart failure. Circulation 2001;104(21):2608–14.

13. Yeh Y-H, Wakili R, Qi X-Y, et al. Calcium handling abnormalities underlying atrial arrhythmogenesis and contractile dysfunction in dogs with congestive heart failure. Circ Arrhythm Electrophysiol 2008;1(2): 93–102.

14. Fuster V, Ryden LE, Cannom DS, et al. ACC/AHA/ ESC 2006 Guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the management of patients with atrial fibrillation): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. Circulation 2006;114(7):e257–354.

15. Hunt SA, Abraham WT, Chin MH, et al. ACC/AHA 2005 Guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the evaluation and management of heart failure): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society. Circulation 2005;112(12): e154–235.

16. Hart RG, Benavente O, McBride R, et al. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. Ann Intern Med 1999; 131(7):492–501.

17. van Walraven C, Hart RG, Wells GA, et al. A clinical prediction rule to identify patients with atrial fibrillation and a low risk for stroke while taking aspirin. Arch Intern Med 2003;163(8):936–43.

18. Rietbrock S, Heeley E, Plumb J, et al. Chronic atrial fibrillation: incidence, prevalence, and prediction of stroke using the Congestive heart failure, Hypertension, Age > 75, Diabetes mellitus, and prior Stroke or transient ischemic attack (CHADS2) risk stratification scheme. Am Heart J 2008;156(1):57–64.

19. Freudenberger RS, Hellkamp AS, Halperin JL, et al. Risk of thromboembolism in heart failure: an analysis from the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT). Circulation 2007;115(20):2637–41.

20. Singer DE, Albers GW, Dalen JE, et al. Antithrombotic therapy in atrial fibrillation: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th edition). Chest 2008; 133(6 Suppl):546S–92S.

21. Connolly SJ, Eikelboom J, O'Donnell M, et al. Challenges of establishing new antithrombotic therapies in atrial fibrillation. Circulation 2007; 116(4):449–55.

22. Sick PB, Schuler G, Hauptmann KE, et al. Initial worldwide experience with the WATCHMAN left atrial appendage system for stroke prevention in atrial fibrillation. J Am Coll Cardiol 2007;49(13):1490–5.

23. Stollberger C, Schneider B, Finsterer J. Serious complications from dislocation of a Watchman left atrial appendage occluder. J Cardiovasc Electrophysiol 2007;18(8):880–1.

24. Hart RG, Halperin JL. Atrial fibrillation and stroke: concepts and controversies. Stroke 2001;32(3): 803–8.

25. Demircan C, Cikriklar HI, Engindeniz Z, et al. Comparison of the effectiveness of intravenous diltiazem and metoprolol in the management of rapid ventricular rate in atrial fibrillation. Emerg Med J 2005; 22(6):411–4.

26. Khand AU, Rankin AC, Martin W, et al. Carvedilol alone or in combination with digoxin for the management of atrial fibrillation in patients with heart failure? J Am Coll Cardiol 2003;42(11):1944–51.

27. Olshansky B, Rosenfeld LE, Warner AL, et al. The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study: approaches to control rate in atrial fibrillation. J Am Coll Cardiol 2004; 43(7):1201–8.

28. Weerasooriya R, Davis M, Powell A, et al. The Australian Intervention Randomized Control of Rate in Atrial Fibrillation Trial (AIRCRAFT). J Am Coll Cardiol 2003;41(10):1697–702.

29. Bradley DJ, Shen WK. Atrioventricular junction ablation combined with either right ventricular pacing or cardiac resynchronization therapy for atrial fibrillation: the need for large-scale randomized trials. Heart Rhythm 2007;4(2):224–32.

30. McGavigan AD, Mond HG. Selective site ventricular pacing. Curr Opin Cardiol 2006;21(1):7–14.

31. Koneru JN, Steinberg JS. Cardiac resynchronization therapy in the setting of permanent atrial fibrillation and heart failure. Curr Opin Cardiol 2008;23(1): 9–15.

32. Valls-Bertault V, Fatemi M, Gilard M, et al. Assessment of upgrading to biventricular pacing in patients with right ventricular pacing and congestive heart failure after atrioventricular junctional ablation for

chronic atrial fibrillation. Europace 2004;6(5): 438–43.

33. Doshi RN, Daoud EG, Fellows C, et al. Left ventricular-based cardiac stimulation post AV nodal ablation evaluation (the PAVE study). J Cardiovasc Electrophysiol 2005;16(11):1160–5.

34. Occhetta E, Bortnik M, Magnani A, et al. Prevention of ventricular desynchronization by permanent para-Hisian pacing after atrioventricular node ablation in chronic atrial fibrillation: a crossover, blinded, randomized study versus apical right ventricular pacing. J Am Coll Cardiol 2006;47(10):1938–45.

35. Mittal S, Ayati S, Stein KM, et al. Transthoracic cardioversion of atrial fibrillation: comparison of rectilinear biphasic versus damped sine wave monophasic shocks. Circulation 2000;101(11):1282–7.

36. Intravenous digoxin in acute atrial fibrillation. Results of a randomized, placebo-controlled multicentre trial in 239 patients. The Digitalis in Acute Atrial Fibrillation (DAAF) Trial Group. Eur Heart J 1997;18(4): 649–54.

37. Volgman AS, Carberry PA, Stambler B, et al. Conversion efficacy and safety of intravenous ibutilide compared with intravenous procainamide in patients with atrial flutter or fibrillation. J Am Coll Cardiol 1998;31(6):1414–9.

38. Alboni P, Botto GL, Baldi N, et al. Outpatient treatment of recent-onset atrial fibrillation with the "pill-in-the-pocket" approach. N Engl J Med 2004; 351(23):2384–91.

39. Camm AJ. Safety considerations in the pharmacological management of atrial fibrillation. Int J Cardiol 2008;127(3):299–306.

40. Vardas PE, Kochiadakis GE, Igoumenidis NE, et al. Amiodarone as a first-choice drug for restoring sinus rhythm in patients with atrial fibrillation: a randomized, controlled study. Chest 2000;117(6):1538–45.

41. Klein AL, Grimm RA, Murray RD, et al. Use of transesophageal echocardiography to guide cardioversion in patients with atrial fibrillation. N Engl J Med 2001;344(19):1411–20.

42. Khand AU, Rankin AC, Kaye GC, et al. Systematic review of the management of atrial fibrillation in patients with heart failure. Eur Heart J 2000;21(8):614–32.

43. Roy D, Talajic M, Dorian P, et al. Amiodarone to prevent recurrence of atrial fibrillation. Canadian Trial of Atrial Fibrillation Investigators. N Engl J Med 2000; 342(13):913–20.

44. Maintenance of sinus rhythm in patients with atrial fibrillation: an AFFIRM substudy of the first antiarrhythmic drug. J Am Coll Cardiol 2003;42(1):20–9.

45. Singh BN, Singh SN, Reda DJ, et al. Amiodarone versus sotalol for atrial fibrillation. N Engl J Med 2005;352(18):1861–72.

46. Doval HC, Nul DR, Grancelli HO, et al. Randomised trial of low-dose amiodarone in severe congestive heart failure. Grupo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina (GESICA). Lancet 1994;344(8921):493–8.

47. Singh SN, Fletcher RD, Fisher SG, et al. Amiodarone in patients with congestive heart failure and asymptomatic ventricular arrhythmia. Survival trial of antiarrhythmic therapy in congestive heart failure. N Engl J Med 1995;333(2):77–82.

48. Torp-Pedersen C, Moller M, Bloch-Thomsen PE, et al. Dofetilide in patients with congestive heart failure and left ventricular dysfunction. Danish Investigations of Arrhythmia and Mortality on Dofetilide Study Group. N Engl J Med. 1999;341(12): 857–65.

49. Banchs JE, Wolbrette DL, Samii SM, et al. Efficacy and safety of dofetilide in patients with atrial fibrillation and atrial flutter. J Interv Card Electrophysiol 2008;23:111–5.

50. Singh BN, Connolly SJ, Crijns HJ, et al. Dronedarone for maintenance of sinus rhythm in atrial fibrillation or flutter. N Engl J Med 2007;357(10):987–99.

51. Hohnloser SH, Connolly SJ, Crijns HJ, et al. Rationale and design of ATHENA: a placebo-controlled, double-blind, parallel arm trial to assess the efficacy of dronedarone 400 mg bid for the prevention of cardiovascular hospitalization or death from any cause in patients with atrial fibrillation/atrial flutter. J Cardiovasc Electrophysiol 2008;19(1):69–73.

52. Kober L, Torp-Pedersen C, McMurray JJ, et al. Increased mortality after dronedarone therapy for severe heart failure. N Engl J Med 2008;358(25):2678–87.

53. Ezekowitz MD. Maintaining sinus rhythm–making treatment better than the disease. N Engl J Med 2007;357(10):1039–41.

54. 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(9244):1789–94.

55. Van Gelder IC, Hagens VE, Bosker HA, et al. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. N Engl J Med 2002;347(23):1834–40.

56. Carlsson J, Miketic S, Windeler J, et al. 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(10):1690–6.

57. Opolski G, Torbicki A, Kosior DA, et al. 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(2):476–86.

58. Chung MK. Randomized trials of rate vs. rhythm control for atrial fibrillation. J Interv Card Electrophysiol 2004;10(Suppl 1):45–53.

59. Roy D, Talajic M, Nattel S, et al. Rhythm control versus rate control for atrial fibrillation and heart failure. N Engl J Med 2008;358(25):2667–77.

60. Freudenberger RS, Wilson AC, Kostis JB. Comparison of rate versus rhythm control for atrial fibrillation in patients with left ventricular dysfunction (from the AFFIRM Study). Am J Cardiol 2007;100(2):247–52.

61. Cain ME, Curtis AB. Rhythm control in atrial fibrillation–one setback after another. N Engl J Med 2008;358(25):2725–7.

62. Deedwania PC, Singh BN, Ellenbogen K, et al. 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(23):2574–9.

63. Pedersen OD, Brendorp B, Elming H, et al. Does conversion and prevention of atrial fibrillation enhance survival in patients with left ventricular dysfunction? Evidence from the Danish Investigations of Arrhythmia and Mortality ON Dofetilide/(DIAMOND) study. Card Electrophysiol Rev 2003;7(3): 220–4.

64. Corley SD, Epstein AE, DiMarco JP, et al. Relationships between sinus rhythm, treatment, and survival in the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) study. Circulation 2004;109(12):1509–13.

65. Ehrlich JR, Hohnloser SH, Nattel S. Role of angiotensin system and effects of its inhibition in atrial fibrillation: clinical and experimental evidence. Eur Heart J 2006;27(5):512–8.

66. Pedersen OD, Bagger H, Kober L, et al. Trandolapril reduces the incidence of atrial fibrillation after acute myocardial infarction in patients with left ventricular dysfunction. Circulation 1999;100(4):376–80.

67. Vermes E, Tardif JC, Bourassa MG, et al. 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(23):2926–31.

68. Ueng KC, Tsai TP, Yu WC, et al. Use of enalapril to facilitate sinus rhythm maintenance after external cardioversion of long-standing persistent atrial fibrillation. Results of a prospective and controlled study. Eur Heart J 2003;24(23):2090–8.

69. Healey JS, Baranchuk A, Crystal E, et al. Prevention of atrial fibrillation with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: a meta-analysis. J Am Coll Cardiol 2005; 45(11):1832–9.

70. Salehian O, Healey J, Stambler B, et al. Impact of ramipril on the incidence of atrial fibrillation: results of the Heart Outcomes Prevention Evaluation study. Am Heart J 2007;154(3):448–53.

71. Tveit A, Grundvold I, Olufsen M, et al. Candesartan in the prevention of relapsing atrial fibrillation. Int J Cardiol 2007;120(1):85–91.

72. Connolly S, Yusuf S, Budaj A, et al. Rationale and design of ACTIVE: the atrial fibrillation clopidogrel trial with irbesartan for prevention of vascular events. Am Heart J 2006;151(6):1187–93.

73. Murray KT, Mace LC, Yang Z. Nonantiarrhythmic drug therapy for atrial fibrillation. Heart Rhythm 2007;4(3 Suppl):S88–90.

74. Burstein B, Nattel S. Atrial structural remodeling as an antiarrhythmic target. J Cardiovasc Pharmacol 2008;52(1):4–10.

75. Heidbuchel H. A paradigm shift in treatment for atrial fibrillation: from electrical to structural therapy? Eur Heart J 2003;24(23):2077–8.

76. Dorian P, Singh BN. Upstream therapies to prevent atrial fibrillation. Eur Heart J Suppl 2008;10(Suppl H): H11–31.

77. Bristow MR, Saxon LA, Boehmer J, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med 2004;350(21):2140–50.

78. Cleland JG, Daubert JC, Erdmann E, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med 2005;352(15): 1539–49.

79. Leclercq C, Walker S, Linde C, et al. Comparative effects of permanent biventricular and right-univentricular pacing in heart failure patients with chronic atrial fibrillation. Eur Heart J 2002;23(22):1780–7.

80. Gasparini M, Auricchio A, Regoli F, et al. 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(4):734–43.

81. Gasparini M, Auricchio A, Metra M, et al. Long-term survival in patients undergoing cardiac resynchronization therapy: the importance of performing atrioventricular junction ablation in patients with permanent atrial fibrillation. Eur Heart J 2008; 29(13):1644–52.

82. Khadjooi K, Foley PW, Chalil S, et al. Long-term effects of cardiac resynchronisation therapy in patients with atrial fibrillation. Heart 2008;94(7):879–83.

83. Steinberg JS. Desperately seeking a randomized clinical trial of resynchronization therapy for patients with heart failure and atrial fibrillation. J Am Coll Cardiol 2006;48(4):744–6.

84. Hoppe UC, Casares JM, Eiskjaer H, et al. Effect of cardiac resynchronization on the incidence of atrial fibrillation in patients with severe heart failure. Circulation 2006;114(1):18–25.

85. Lellouche N, De Diego C, Vaseghi M, et al. Cardiac resynchronization therapy response is associated with shorter duration of atrial fibrillation. Pacing Clin Electrophysiol 2007;30(11):1363–8.

86. Yannopoulos D, Lurie KG, Sakaguchi S, et al. Reduced atrial tachyarrhythmia susceptibility after

upgrade of conventional implanted pulse generator to cardiac resynchronization therapy in patients with heart failure. J Am Coll Cardiol 2007;50(13):1246–51.

87. Padeletti L, Muto C, Maounis T, et al. Atrial fibrillation in recipients of cardiac resynchronization therapy device: 1-year results of the randomized MASCOT trial. Am Heart J 2008;156(3):520–6.

88. Haissaguerre M, Jais P, Shah DC, et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N Engl J Med 1998;339(10):659–66.

89. Calkins H, Brugada J, Packer DL, et al. HRS/EHRA/ ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: recommendations for personnel, policy, procedures and follow-up. A report of the Heart Rhythm Society (HRS) task force on catheter and surgical ablation of atrial fibrillation. Heart Rhythm 2007;4(6):816–61.

90. Spragg DD, Dalal D, Cheema A, et al. Complications of catheter ablation for atrial fibrillation: incidence and predictors. J Cardiovasc Electrophysiol 2008; 19(6):627–31.

91. Chen MS, Marrouche NF, Khaykin Y, et al. Pulmonary vein isolation for the treatment of atrial fibrillation in patients with impaired systolic function. J Am Coll Cardiol 2004;43(6):1004–9.

92. Hsu LF, Jais P, Sanders P, et al. Catheter ablation for atrial fibrillation in congestive heart failure. N Engl J Med 2004;351(23):2373–83.

93. Gentlesk PJ, Sauer WH, Gerstenfeld EP, et al. Reversal of left ventricular dysfunction following ablation of atrial fibrillation. J Cardiovasc Electrophysiol 2007;18(1):9–14.

94. Efremidis M, Sideris A, Xydonas S, et al. Ablation of atrial fibrillation in patients with heart failure: reversal of atrial and ventricular remodelling. Hellenic J Cardiol 2008;49(1):19–25.

95. Lutomsky BA, Rostock T, Koops A, et al. Catheter ablation of paroxysmal atrial fibrillation improves cardiac function: a prospective study on the impact of atrial fibrillation ablation on left ventricular function assessed by magnetic resonance imaging. Europace 2008;10(5):593–9.

96. Cleland JG, Coletta AP, Abdellah AT, et al. Clinical trials update from the American Heart Association 2006: OAT, SALT 1 and 2, MAGIC, ABCD, PABA-CHF, IMPROVE-CHF, and percutaneous mitral annuloplasty. Eur J Heart Fail 2007;9(1):92–7.

97. Pappone C, Augello G, Sala S, et al. A randomized trial of circumferential pulmonary vein ablation versus antiarrhythmic drug therapy in paroxysmal atrial fibrillation: the APAF Study. J Am Coll Cardiol 2006; 48(11):2340–7.

98. Nair GM, Nery PB, Diwakaramenon S, et al. A systematic review of randomized trials comparing radiofrequency ablation with antiarrhythmic medications in patients with atrial fibrillation. J Cardiovasc Electrophysiol September 3, 2008 [Epub ahead of print].