Atrial Fibrillation in Congestive Heart Failure: Current Management

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

Atrial fibrillation (AF) and Congestive Heart Failure (CHF) are two commonly associated conditions and have been described as modern “epidemics” in cardiovascular disease by Braunwald1 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 CHF2 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 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...
by week 4, there is deceased connexin-40, sarcomerme distortion, and accumulation of glycogen.

The work of Nattel and colleagues 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 for 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. 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. CHF-induced AF also resulted in atrial sarcoplasmic reticulum calcium overload and increased triggered activity. The underlying mechanism was a reduction in ryanodine receptor and calsequestrin expression. In 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. 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. 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 included many patients with CHF—approximately 25% overall and 50% in the Danish
Atrial Fibrillation, Aspirin and Anticoagulant Therapy (AFASAK) trial. In the CHADS2 (CHF, Hypertension, Age >75 years, Diabetes [each 1 point] and Stroke [2 points]) scoring system for stroke risk evaluation, 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 CHADS2 score is

<table>
<thead>
<tr>
<th>CHADS2 Risk Criteria</th>
<th>Adjusted Stroke Rate (%/yr)* (95% CI)</th>
<th>CHADS2 Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior stroke or transient ischemic attack</td>
<td>1.9 (1.2 to 3.0)</td>
<td>0</td>
</tr>
<tr>
<td>Age &gt;75 yr</td>
<td>2.8 (2.0 to 3.8)</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4.0 (3.1 to 5.1)</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>5.9 (4.6 to 7.3)</td>
<td>3</td>
</tr>
<tr>
<td>Heart failure</td>
<td>8.5 (6.3 to 11.1)</td>
<td>4</td>
</tr>
<tr>
<td>Patients (N = 1733)</td>
<td>12.5 (8.2 to 17.5)</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>18.2 (10.5 to 27.4)</td>
<td>6</td>
</tr>
</tbody>
</table>

a good predictor of stroke risk in clinical practice. 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%. 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.

Multiple clinical trials looking at other inhibitors of thrombin or factor Xa are ongoing. 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.

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; however, serious complications may also be associated with these devices. 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.

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. 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. 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.

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 pacemaker group. 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 pacemaker 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.

There is much debate on whether chronic right ventricular pacing in itself can promote right ventricular (RV) dyssynchrony and possible worsen CHF. Cardiac resynchronization therapy may provide improved outcomes when compared with RV pacing alone in the setting of AF and CHF. 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. 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. 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. 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.

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%. For pharmacologic cardioversion, digoxin is no better than placebo, 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. Oral class I drugs, propafenone and flecainide, 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; however, the use of class I drugs is contraindicated in CHF patients because of the risks of pro-arrhythmia. 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. 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). 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. 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. 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. In the antiarrhythmic drug sub-study of the AFFIRM trial and the SAFE-T trial, 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 Insuficiencia Cardica en Argentina (GESICA) Trial and Congestive Heart Failure—Survival Trial of Antiarrhythmic Therapy (CHF-STAT) studies. The proarhythmic 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.

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. 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.

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. 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. 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. 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.

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). 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), Rate Control versus Electrical Cardioversion of Persistent Atrial Fibrillation (RACE), Strategies of Treatment of Atrial Fibrillation (STAF), and How to Treat Chronic Atrial Fibrillation (HOT CAFE) looked at clinical endpoints only, and all showed no statistical difference between the defined clinical endpoints (Table 2). 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. 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). 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>
<thead>
<tr>
<th>Table 2</th>
<th>Rate Control versus Rhythm Control Trials</th>
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<tbody>
<tr>
<td></td>
<td>PIAF</td>
</tr>
<tr>
<td>No.</td>
<td>252</td>
</tr>
<tr>
<td>Follow-up (range)</td>
<td>1 yr</td>
</tr>
<tr>
<td>Mean age (yr)</td>
<td>61.5</td>
</tr>
<tr>
<td>Duration of AF</td>
<td>&lt;360 d</td>
</tr>
<tr>
<td>Important inclusion criteria</td>
<td>Symptomatic patients</td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>Symptom improvement</td>
</tr>
<tr>
<td>Rhythm control</td>
<td>55.1%</td>
</tr>
<tr>
<td>Rate control</td>
<td>60.8%</td>
</tr>
<tr>
<td>P (primary end point)</td>
<td>0.317</td>
</tr>
</tbody>
</table>

^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.

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; an analysis of AFFIRM stratified by ejection fraction (<30%, 30%–39%, 40%–49%) 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. 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. 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).

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. 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 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. Interest has focused particularly on the ACE and ARB drugs based on analysis of results from heart failure studies. In the Trandolapril 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. 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).

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). 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).

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>RR (95% CI Random)</th>
<th>Weight % (95% CI Random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 ACE inhibitor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Van Den Berg</td>
<td>2/7</td>
<td>7/11</td>
<td>1.7</td>
<td>0.45[0.13,1.57]</td>
</tr>
<tr>
<td>SOL VD</td>
<td>10/186</td>
<td>45/188</td>
<td>4.8</td>
<td>0.22[0.12,0.43]</td>
</tr>
<tr>
<td>TRACE</td>
<td>22/790</td>
<td>42/787</td>
<td>6.6</td>
<td>0.52[0.31,0.87]</td>
</tr>
<tr>
<td>Ueng</td>
<td>18/70</td>
<td>32/75</td>
<td>7.0</td>
<td>0.60[0.37,0.97]</td>
</tr>
<tr>
<td>CAPP</td>
<td>117/5492</td>
<td>135/5493</td>
<td>11.4</td>
<td>0.87[0.68,1.11]</td>
</tr>
<tr>
<td>STOPH2</td>
<td>200/2205</td>
<td>357/4409</td>
<td>13.0</td>
<td>1.12[0.95,1.32]</td>
</tr>
<tr>
<td>GISSI</td>
<td>665/8865</td>
<td>721/8846</td>
<td>14.0</td>
<td>0.92[0.83,1.02]</td>
</tr>
<tr>
<td>Subtotal(95% CI)</td>
<td>1034/17615</td>
<td>1339/19809</td>
<td>58.7</td>
<td>0.72[0.56,0.93]</td>
</tr>
<tr>
<td>Test for heterogeneity chi-Square = 32.58 df = 6 P = .00001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect z = -2.53 P = .01</td>
<td></td>
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<td></td>
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</tr>
</tbody>
</table>

| 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 |

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%. 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. Large ongoing randomized trials such as the ACTIVE-I trial 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. This represents a paradigm shift in the treatment of AF from electrical to structural therapy 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. 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. 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. 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. 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. A randomized trial is again awaited.

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

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

<table>
<thead>
<tr>
<th>Study (Yr)</th>
<th>n</th>
<th>Baseline, EF (%)</th>
<th>Paroxysmal or Persistent AF, %</th>
<th>Procedure (Second Procedure)</th>
<th>Complications Rate</th>
<th>Follow-Up (mo)</th>
<th>Increase in EF</th>
<th>%SR at 1 yr (+ AAD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen et al.¹⁹¹ (2004)</td>
<td>94</td>
<td>&lt;40</td>
<td>67</td>
<td>PVI, LA abl. (22%)</td>
<td>3.1%</td>
<td>69</td>
<td>62%</td>
<td>69% (78%)</td>
</tr>
<tr>
<td>Hsu et al.²⁰² (2004)</td>
<td>58</td>
<td>35</td>
<td>15</td>
<td>PVI, LA abl. (50%)</td>
<td>3%</td>
<td>12</td>
<td>22%</td>
<td>69% (78%)</td>
</tr>
<tr>
<td>PABA-CHF (2006)</td>
<td>39</td>
<td>28</td>
<td>55</td>
<td>PVI</td>
<td>—</td>
<td>6</td>
<td>8%</td>
<td>72% (90%)</td>
</tr>
<tr>
<td>Gentlesk et al.³¹³ (2007)</td>
<td>67</td>
<td>42</td>
<td>100</td>
<td>PVI (60%)</td>
<td>—</td>
<td>20</td>
<td>14%</td>
<td>57% (86%)</td>
</tr>
<tr>
<td>Efremidis et al.³¹⁴ (2008)</td>
<td>13</td>
<td>35</td>
<td>77</td>
<td>PVI, LA abl.</td>
<td>0</td>
<td>9</td>
<td>22.5%</td>
<td>62% (—)</td>
</tr>
<tr>
<td>Lutomsky et al.³¹⁵ (2008)</td>
<td>18</td>
<td>41</td>
<td>100</td>
<td>PVI</td>
<td>—</td>
<td>6</td>
<td>10%</td>
<td>50% (—)</td>
</tr>
</tbody>
</table>

*Abbreviations: abl, ablation; LA, left atrial ablation; PVI, pulmonary vein isolation.*
the Cardiac Resynchronization in Heart Failure Study (CARE-HF) trial\(^7\) (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.\(^8\) We\(^8\) and others\(^9\) 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.\(^8\)

**Catheter Ablation**

Since it was first described in 1998,\(^8\) catheter ablation targeting pulmonary vein isolation for the treatment of AF has developed at a rapid rate.\(^8\) 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.\(^9\) A total of 6 nonrandomized studies (Table 4) have been reported. Five studies\(^9\) 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,\(^9\) 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,\(^9\) 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.\(^9\) In a recent meta-analysis of six trials, mostly single center, RF ablation reduced the risk of recurrence of AF at 1 year by 65% compared with antiarrhythmic drugs.\(^9\) 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.

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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


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


