Atrial fibrillation and heart failure: natural history and pharmacological treatment

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Abstract

Atrial fibrillation (AF) is the most common sustained arrhythmia. Congestive heart failure (CHF), an increasingly frequent cardiovascular disorder affecting millions of people world-wide, has become the most important risk factor of AF in developed countries, as a result of ageing populations. Approximately two thirds of patients with CHF are > 65 years of age and likely to have AF as a coexistent complication. Epidemiological surveys and large clinical trials in CHF provide strong evidence that AF is a marker of increased mortality. AF may compromise LV systolic function and worsen CHF through poor rate control, irregularity of ventricular response, and loss of atrial systolic activity. Furthermore, enhanced adrenergic stimulation in the setting of CHF facilitates AV conduction and promotes the progression of cardiomyopathy, and AF may worsen CHF as a consequence of the negative inotropic effects of drugs used to control the heart rate or rhythm, or of the proarrhythmic effects of drugs used to maintain sinus rhythm. This article reviews the putative mechanisms behind atrial remodelling due to long-standing AF, and the role of neuro-hormonal alterations in the atrial electrophysiologic and structural changes which facilitate its perpetuation. It also reviews and discusses various controlled trials of angiotensin-converting enzyme inhibitors and AT-1 receptor blockade in the perspective of AF treatment and prevention. Finally the role of specific antiarrhythmic drugs, the respective advantages and shortcomings of rate versus rhythm control in patients with AF and CHF, and the important issue of chronic anticoagulation are presented in the light of time-tested therapies, as well as new promising therapeutic approaches.

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Prevalence of atrial fibrillation and prognosis

Atrial fibrillation (AF) is the most common sustained arrhythmia, encountered in 1.5% of the population. It is estimated that 2.3 million Americans and probably a similar number of Europeans are affected by AF [1,2]. Projected data from the AnTicoagulation and Risk factors In Atrial fibrillation (ATRIA) study of adults enrolled in a large health care maintenance organisation in California indicate that the number of Americans with AF will increase to >5.6 million, i.e. 2.5-fold, in the next 50 years [1].

Congestive heart failure (CHF) is an increasingly frequent cardiovascular disorder that affects 15–20 million people worldwide. It has become the most important risk factor for AF in developed countries where, with the availability of superior therapeutic interventions, large populations of patients survive to old age with serious, though not life-threatening, heart disease. Approximately two thirds of patients with CHF are >65 years of age and likely to have AF as a coexistent complication. In the Framingham experience CHF increased the risk of AF 4.5-fold in men and 5.9-fold in women [3]. Common in elderly patients, diastolic ventricular dysfunction with a secondary increase in filling pressures mediates atrial remodelling and is associated with a 5.26-fold increased risk of AF development compared with normal diastolic function [4].

The EuroHeart Failure survey conducted in 2000–2001 in 24 countries in Europe has reported that up to 45% patients with CHF also presented with intermittent or established AF [5]. According to this survey, the overall prevalence of new onset AF in patients hospitalised for CHF is 13%, ranging from 8% to 36% in different European regions. The prevalence of AF generally depends on the severity of the underlying pathology, between 10% and 20% in mild to moderate CHF, and up to 50% in patients with more advanced disease (Fig. 1) [6]. Patients with CHF due to diastolic dysfunction have the same prevalence of AF as their counterparts with left ventricular (LV) systolic dysfunction. AF was present in 29.1% of patients with an ejection fraction >40% enrolled in the Candesartan in Heart Failure Assessment of Reduction in Mortality (CHARM)-Preserved trial, [7] and in 23.4% patients with an ejection fraction ≥50% who participated in the New York Heart Failure Consortium Registry [8].

A plethora of epidemiological surveys and large clinical trials in CHF provides strong evidence that AF is a marker of increased mortality. In the Framingham Study, the development of AF in patients with CHF was associated with a 2.7-fold increased risk of death in women and a 1.6-fold risk in men [9]. The Studies Of Left Ventricular Dysfunction (SOLVD) Treatment and Prevention

![Figure 1](https://academic.oup.com/europace/article-abstract/5/s1/S5/529990/529990)
trials reported a 1.34-fold greater risk of all-cause death conferred by AF, largely explained by and increased risk of death from progressive pump failure [10]. Middlekauff et al. [11] reported that AF was associated with a higher all-cause and sudden death mortality compared with sinus rhythm (48% vs 29%, and 31% vs 18%, respectively) in 390 patients with advanced CHF. These observations are consistent with those of the Danish Investigations of Arrhythmia and Mortality On Dofetilide (DIAMOND) study, in which the presence of AF was associated with a significantly lower survival in patients with CHF, and in patients with acute myocardial infarction and LV dysfunction [12]. Patients in AF had a 25% greater risk of death than patients in sinus rhythm. Similarly, in the Digitalis Investigation Group (DIG) study, the development of atrial tachyarrhythmias, predominantly AF, predicted a 2.5-fold greater risk of subsequent mortality and a 3-fold greater risk of hospitalisations for CHF [13].

It has been suggested that AF is independently associated with increased mortality rates only in patients with relatively preserved LV function, while in individuals with advanced disease, the relationship is more complicated and dependent on other variables [11,14]. In patients studied by Middlekauff et al. [11] AF did not further increase the risk in patients with a pulmonary capillary wedge pressure >16 mmHg. In the PRIME II study of ibopamine in 409 patients in New York Heart Association (NYHA) heart failure functional class III or IV, AF was no longer associated with an increased mortality after adjustment for age, LV ejection fraction, NYHA class, renal function, and blood pressure (risk ratio 0.86) [14]. Furthermore, in the Vasodilator in CHF Trials (V-HeFT), which included patients in NYHA functional class II or III, the presence of AF did not influence survival, though the follow-up was limited to 2 years and a placebo arm was absent in V-HeFT-II [15].

Pathophysiology

Haemodynamic and neurohormonal changes

AF may compromise LV systolic function and worsen CHF through poor rate control, irregularity of ventricular response, and loss of atrial systolic activity. Loss of atrioventricular (AV) synchrony is associated with impaired diastolic filling, reduced stroke volume, and elevated diastolic atrial pressure, resulting in an approximately 20% reduction in cardiac output [16]. An irregular ventricular response decreases cardiac output, increases right atrial pressure and pulmonary capillary wedge pressure independent of rate [17]. The reduced ventricular function triggers a cascade of neurohormonal changes, including the excessive production of circulating cateholamines and adrenergic stimulation, and activation of the rennin–angiotensin–aldosterone system [18,19]. Enhanced adrenergic stimulation in the setting of CHF facilitates AV conduction and promotes the progression of cardiomyopathy. Furthermore, AF may worsen CHF as a consequence of the negative inotropic effects of drugs used to control the heart rate or rhythm, or of the proarhythmogenic effects of drugs used to maintain sinus rhythm.

Although AF is more likely to precipitate CHF in the presence of underlying LV dysfunction or of a non-compliant hypertrophied heart, symptoms may also develop as a result of rapid and irregular ventricular activity in patients with little structural heart disease. The secondary development of LV dysfunction associated with significant ventricular dilatation and CHF is known as tachycardia-induced cardiomyopathy. It usually occurs with the persistent forms of AF, particularly with sustained ventricular rates >120 bpm. Mechanisms responsible for systolic and diastolic dysfunction in tachycardia-induced cardiomyopathy are likely to involve abnormal calcium handling, reduced stores of cellular energy, and abnormal utilisation of energy that lead to myocardial remodelling [20]. LV dysfunction caused by AF in the absence of significant heart disease may reverse completely after restoration of sinus rhythm or control of the ventricular rate.

Atrial remodelling

AF results from an advanced and complex pathophysiological process which promotes its triggers and forms its electrophysiological substrate. Sustained AF, in turn, causes electrophysiological and structural alterations of the atrial myocardium known as atrial remodelling, which further promotes arrhythmogenesis [21]. Early in the development of AF, tachycardia-induced calcium overload of atrial myocytes causes changes in gene expression which down-regulate the L-type calcium current. This results in shortening of the atrial effective refractory period to compensate for the calcium overload at the expense of a decrease in wavelength, promoting multiple re-entry [22]. Increased dispersion of refractoriness and a loss or reversal of rate adaptation of the effective refractory period are two other characteristics of electrophysiological remodelling that may further favour AF [22,23].
If AF persists, ultrastructural changes may occur, shifting atrial myocytes towards a more foetal phenotype, so-called dedifferentiation [24]. Atrial myocytes are increased in volume, with misaligned sarcomeres, loss of contractile elements, and accumulation of glycogen. Other changes involve gap-junctional remodelling with reduction in the expression of connexin Cx40 and Cx43 [25].

Experimental studies in a goat model suggest that electrophysiological and structural changes may lessen or reverse after restoration of sinus rhythm [26]. The atrial effective refractory period normalises within a few weeks though structural changes, such as the appearance of small, elongated mitochondria and loss of myofilament alignment, may persist for several months. More advanced changes include atrial hibernation, myolysis and hypertrophy, followed by irreversible fibrosis and cell death.

**Atrial stretch**

In the presence of CHF, the pathophysiology of AF is largely attributed to stretch caused by increased atrial pressure and volume [27]. Activation of stretch-mediated channels in the fibrillating atria enhances calcium binding to cellular myofilaments, generating calcium currents which produce delayed afterdepolarisations and triggered activity. In experimental models of cardio-myopathy-induced AF, the activity of the Na\(^+-\)Ca\(^{2+}\)-exchange current (NCX) is increased. The NCX exchanges intracellular Ca\(^{2+}\) accumulated in the cell during the action potential for extracellular Na\(^+\) ions at a rate 1:3. Thus, the NCX carries one net positive charge into the cell with each cycle, leading to delayed afterdepolarisations and triggered ectopic activity when NCX activity is enhanced. Because NCX regulates intracellular concentrations of free Ca\(^{2+}\) and Na\(^+\), it also modulates the action potential indirectly by way of influencing the activity of other Ca\(^{2+}\)- and/or Na\(^+\)-sensitive currents [28]. Atrial stretch is associated with slowing of conduction and increased dispersion of refractoriness, both of which favour re-entry. A blockade of stretch-activated channels by gadolinium impeded the initiation and maintenance of electrically induced AF and suppressed the occurrence of the spontaneous arrhythmia [29].

Moreover, atrial dilatation in the presence of CHF contributes to the formation of a substrate for AF by creating “a critical atrial mass” capable of supporting the sufficient number of re-entry wavelets necessary for maintenance of the arrhythmia.

It was recently shown that 85–95% of asymptomatic adults have extensions (“sleeves”) of atrial myocardium into the pulmonary veins [30]. These remnants of myocardial tissue may become active as a result of stretch and dilatation of the pulmonary veins, and produce spontaneous, rapid discharge, triggering AF leading to atrial remodelling. Studies in patients with “focal” AF have shown significant dilatation of the ostial and proximal portions of the pulmonary veins compared with control subjects [31]. Extensions of atrial myocardium in patients with AF also exhibit a significantly higher degree of hypertrophy, discontinuity, and fibrosis [30].

Chronic stretch and calcium overload during rapid atrial activity are likely to induce sustained proteolysis and a loss of contractile elements leading to atrial myopathy. CHF therefore favours AF by both creating a structural substrate for atrial re-entry and producing a functional basis for atrial ectopic activity that can trigger re-entry.

**Role of angiotensin II**

Atrial stretch results in an increased local synthesis of angiotensin II. Angiotensin-converting enzyme and angiotensin II levels are elevated in fibrillating atrial tissue [32,33]. Subsequently, stimulation of angiotensin II type 1 (AT-1) receptors initiates a cascade of phosphorylation processes that activate a family of mitogen-activated protein kinases (MAP kinases). MAP kinases promote atrial myocyte hypertrophy, fibroblast proliferation, accumulation of collagen, and apoptosis, further contributing to structural remodelling (Fig. 2) [34]. The three best-defined angiotensin II-dependent MAP kinases include extracellular signal-regulated protein kinases 1 and 2, c-Jun N-terminal kinase,
and p38 MAP kinase. The latter two are also activated by atrial stretch. When occurring in the presence of preexisting atrial fibrosis, common in CHF, AF itself increases the amount of collagen accumulation, thus closing the vicious circle.

Angiotensin II also modifies atrial electrophysiology by indirect effects on ion channels. Stimulation of AT-1 receptors activates phospholipase C leading to inositol-1,4,5-triphosphate (IP3)-mediated release of calcium from the sarcoplasmic reticulum [35]. Protein kinase C phosphorylates L-type calcium channels, which results in increased calcium influx, and is also implicated in the reduction of the transient outward potassium current (Ito) and the delayed rectifier potassium current (IK) promoting increased dispersion of refractoriness.

**Angiotensin-converting enzyme inhibitors and AT-1 receptor blockers**

**Experimental evidence**

Angiotensin-converting enzyme (ACE) inhibition and AT-1 receptor blockade may prevent or delay the development of AF in patients with CHF by unloading the left atrium, i.e., by lowering intratral pressure and wall stress, reducing mitral regurgitation, and preventing left atrial dilatation. Furthermore, experimental evidence suggests that the beneficial effects of ACE inhibitors and AT-1 receptor blockers are not confined to their haemodynamic effects. AT-1 receptor blockers may also act by reducing the activation of AT-1-dependent MAP kinases, thus preventing cellular hypertrophy and fibrosis. Importantly, they do not block and can upregulate “protective” AT-2 receptors, the activation of which inhibits MAP kinases through activation of different phosphatases thus exerting antiproliferative effects [36]. Indeed, the altered expression of angiotensin II receptors with down-regulation of AT-1 and up-regulation of AT-2 receptors has been observed in tissue samples obtained from the right atrium in patients with AF, suggesting an adaptive mechanism aimed at preventing further accumulation of collagen [37]. Immunohistological analysis of left atrial tissue has shown AT-1 up-regulation consistent with the pathophysiological mechanism of atrial remodelling [38]. AT-1 receptor blockers and ACE inhibitors also prevent increased bradykinin degradation mediated by the angiotensin-converting enzyme in fibrillating atrial tissue which may contribute to degenerative changes associated with AF [34].

In experimental CHF or rapid atrial pacing models of AF, both ACE inhibitors and AT-1 receptor blockers have been shown to prevent electrical remodelling and reduce interstitial fibrosis [33,39]. The beneficial effects on atrial electrical and structural remodelling of angiotensin II inhibition are independent of intra-atrial pressures [31,40]. A reduction in atrial fibrosis has only been observed with the ACE inhibitor enalapril, despite a similar or even greater decrease in left atrial pressure with the combination of hydralazine and isosorbide [33]. In a canine model, oral candesartan administered 1 week before, and 5 weeks during, rapid atrial pacing prevented to some extent the shortening of the atrial effective refractory period and slowing of intra-atrial conduction, and decreased the inducibility and duration of AF (Fig. 3) [39].

![Figure 3](https://academic.oup.com/europace/article-abstract/5/s1/55/529990/bysl.png)
Clinical trials

The TRAndolapril Cardiac Evaluation (TRACE) study was the first large randomised trial to report a lower incidence of new cases of AF by ACE inhibition in 1746 patients with acute myocardial infarction and LV dysfunction. In this study, treatment with trandolapril was associated with a 55% relative reduction in risk of developing AF during 2–4 years of follow-up, compared with placebo (2.8% vs 5.3%) [41]. Although AF was not a pre-specified endpoint and no fully satisfactory explanation was offered, the TRACE study has drawn attention to the potential role of ACE inhibitors in the prevention of atrial arrhythmias.

Following the TRACE report and new experimental evidence, Canadian investigators from the Montreal Heart Institute, presented a retrospective analysis of their cohort of 374 participants in the SOLVD Prevention and Treatment studies (Table 1, Fig. 4) [42]. Treatment with enalapril reduced the risk of AF by 78% compared with placebo. The effect was even greater in patients with better preserved LV function, and therefore potentially reversible myocardial changes, who were enrolled in the SOLVD Prevention arm. Furthermore, the rapidly diverging Kaplan–Meier curves suggested that enalapril may have a beneficial effect on electrical remodelling. Adding the AT-1 receptor blocker, valsartan, to ACE inhibition (93%) and beta-adrenergic blockade (35%), theValsartan in CHF Trial (Val-HeFT) investigators reported a 35% relative reduction in the incidence of AF (from 7.86% to 5.27%) compared with placebo in 5010 patients with symptomatic CHF during 23 months of follow-up [43]. Furthermore, in the Val-HeFT study, the presence of AF increased the risk of all-cause mortality by 64%. However, as in the case of TRACE and SOLVD, the Val-HeFT AF sub-study was analysed retrospectively, and AF was detected from electrocardiographic data and adverse event reports.

In the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study, the incidence of new onset AF was 8.2 per 1000 person-years in the losartan-treated group, compared with 11.7 person-years in the group of patients assigned to atenolol therapy, a 30% relative risk reduction [44]. AF was not a pre-specified endpoint and new cases were not continuously sensed. Furthermore, patients with CHF or LV ejection fraction (EF) <40% were not enrolled into the study.

Clinical evidence in support of the therapeutic effects of AT-1 receptor blockade has recently been presented in the first prospective study of irbesartan in patients with persistent AF referred for electrical cardioversion [45]. The study was open-label with no placebo arm, irbesartan was added to amiodarone, and asymptomatic recurrences of AF were not monitored. Furthermore, there were incidental differences between the irbesartan and non-irbesartan arms. Patients randomly assigned to therapy with amiodarone had undergone a greater number of previous cardioversion attempts. In the irbesartan group, more patients were treated with beta-adrenergic blockers or calcium antagonists, which may also have affected the outcome of cardioversion and the incidence of recurrent AF during follow-up. However, patients treated with irbesartan and amiodarone combined had fewer symptomatic recurrences of AF than those who received amiodarone alone (20% vs 44%) during 1 year of follow-up, a 75% relative risk reduction.

In a similarly designed study, 70 patients treated with amiodarone and enalapril showed a trend towards a lower rate of AF recurrences within 2 min after electrical cardioversion (4.3% vs 14.7%) and had a higher probability of remaining in sinus rhythm at a median follow-up of 270 days (74.3% vs 57.3%) than 75 patients treated with amiodarone alone [46]. The patients enroled in that study had a mean LVEF of 50% and were in NYHA heart failure functional class I or II.

The preliminary results from the CHARM studies of 5518 patients with CHF who did not have AF at enrolment (72.6% of the total CHARM population) show that treatment with candesartan is associated with a 19% reduction in relative risk of developing AF compared with placebo (6.5% vs 7.9%) [47]. It is noteworthy that this therapeutic effect was consistent among the three components of the trial, including CHARM-Preserved, in patients with diastolic dysfunction and preserved systolic function.

These observations suggest that ACE inhibitors and AT-1 receptor blockers may effectively prevent or delay atrial remodelling in patients with AF, including in absence of conventional indications, such as heart failure, hypertension or myocardial infarction. The ongoing AF Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE) study will investigate the effects of irbesartan on atrial remodelling and the incidence of recurrent AF in approximately 10,000 patients at risk of stroke, though not systematically in need of AT-1 receptor blockade. This multicentre, prospective, partial factorial, randomised, double-blind, placebo-controlled, superiority trial of irbesartan will test (1) whether irbesartan reduces the risk of arrhythmia recurrences in

S10 I. Savelieva, A. John Camm
<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>Patients (n)</th>
<th>Pathology</th>
<th>Treatment assignment</th>
<th>Follow-up</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRACE [41]</td>
<td>Retrospective analysis of a non-pre-specified variable; AF detected at 3-month follow-up visits</td>
<td>1749</td>
<td>Acute MI and LV dysfunction, EF ≤ 0.36</td>
<td>Trandolapril vs placebo</td>
<td>4 years</td>
<td>Incidence of AF is 2.8% in the ACEI arm vs 5.3% in the placebo arm (RR 0.45; 9% CI 0.26–0.76)</td>
</tr>
<tr>
<td>SOLVD [42]</td>
<td>Retrospective analysis of a non-pre-specified variable from a single centre; AF detected at 4-month follow-up visits</td>
<td>391</td>
<td>Asymptomatic LV dysfunction, EF ≤ 0.35, or overt HF</td>
<td>Enalapril vs placebo</td>
<td>2.9 years</td>
<td>Incidence of AF 5.4% in the ACEI arm vs 24% in the placebo arm (RR 0.22; 95% CI 0.11–0.44) Patients without HF benefit more (AF 3.2% in the ACEI group, 24.6% in the placebo group)</td>
</tr>
<tr>
<td>Val-HeFT [43]</td>
<td>Retrospective analysis of a non-pre-specified variable; AF detected on ECG or from adverse event reports</td>
<td>5010</td>
<td>Symptomatic HF, EF &lt; 0.40</td>
<td>Valsartan vs placebo</td>
<td>23 months</td>
<td>Incidence of AF in the ARB arm 5.27% vs 7.86% (RR 0.65; 95% CI 0.52–0.82)</td>
</tr>
<tr>
<td>LIFE [44]</td>
<td>Retrospective analysis of a non-pre-specified variable</td>
<td>9193</td>
<td>Hypertension, LV hypertrophy, and sinus rhythm at inclusion</td>
<td>Losartan vs atenolol</td>
<td>4.9 years</td>
<td>Incidence of AF is 8.2/1000 in the ARB arm vs 11.7/1000 person-years in the BB arm (RR 0.70; 95% CI 0.58–0.85)</td>
</tr>
<tr>
<td>Hernandez-Madrid et al. [45]</td>
<td>Prospective, randomised, open-label</td>
<td>154</td>
<td>AF post-cardioversion</td>
<td>Irbesartan + amiodarone vs amiodarone alone</td>
<td>254 days</td>
<td>Free from AF recurrence 79.52% in the ARB arm vs 55.91% in the no ARB arm (RR 0.35; 95% CI 0.12–0.46) Free from AF recurrence at 4 weeks 84.3% in the ACEI arm vs 61.3% in the no ACEI arm (RR 0.69; 95% CI 0.11–0.87) Free from AF recurrence at the end of follow-up 74.3% in the ACEI arm vs 57.3% in the no ACEI arm Immediate AF recurrence 4.3% in the ACEI arm vs 14.7% in the no ACEI arm</td>
</tr>
<tr>
<td>Ueng et al. [46]</td>
<td>Prospective, randomised, open-label</td>
<td>145</td>
<td>AF post-cardioversion</td>
<td>Enalapril + amiodarone vs amiodarone alone</td>
<td>270 days</td>
<td>Free from AF recurrence at 4 weeks 84.3% in the ACEI arm vs 61.3% in the no ACEI arm (RR 0.69; 95% CI 0.11–0.87) Free from AF recurrence at the end of follow-up 74.3% in the ACEI arm vs 57.3% in the no ACEI arm Immediate AF recurrence 4.3% in the ACEI arm vs 14.7% in the no ACEI arm</td>
</tr>
<tr>
<td>CHARM [47]</td>
<td>Prospective, randomised, double-blind, AF is a pre-specified endpoint</td>
<td>5518</td>
<td>HF, LVEF ≤ 0.40, or diastolic LV dysfunction, LVEF &gt; 0.40, no AF at inclusion</td>
<td>Candesartan vs placebo</td>
<td>38 months</td>
<td>Incidence of AF in the ARB arm 6.5% vs 7.9% in the placebo arm (RR 0.81; 95% CI 0.66–1.00)</td>
</tr>
</tbody>
</table>

ACEI = angiotensin-converting enzyme inhibitors; AF = atrial fibrillation; ARB = angiotensin receptor blockers; BB = beta-adrenergic blocker; EF = ejection fraction; HF = heart failure; LV = left ventricle; MI = myocardial infarction; RR = relative risk; CI = confidence interval.
patients with paroxysmal AF, (2) whether it limits the progression of paroxysmal AF to a permanent form, and (3) whether irbesartan reduces the size of the left atrium, thereby reducing the left atrial volume load. Recurrences of AF will be documented by transtelephonic monitoring twice a week, irrespective of symptoms, for the first 4 months. Later transtelephonic recordings will be obtained between months 18 and 20 of follow-up. Atrial remodelling will be ascertained by echocardiography at baseline, 24 months, and completion of the study. The study is designed to detect a 25% reduction in AF recurrences with an 80% power.

Rhythm control vs rate control

Special considerations in CHF

Sinus rhythm, theoretically, offers physiological rate control, normal atrial activation and contraction, a normal sequence of AV conduction and AV valvular function, and a regular rhythm. Four European clinical trials (PIAF, STAF, RACE, and HOT CAFE) [48–51], and the North American Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial [52], have specifically addressed this important question. All trials report no clear superiority of rhythm control. There was a general trend towards higher survival and fewer major adverse cardiovascular events, such as thromboembolism, torsades de pointes, and hospital admissions for management of AF or CHF with rate as opposed to rhythm control. Explanations for the poorer results in patients assigned to the rhythm control strategy have been discussed in detail elsewhere [53]. In brief, they seem largely attributable to the study designs, patient selections, inability to achieve adequate rhythm control, and the underuse of anticoagulation once the patient was believed to be in sinus rhythm. Furthermore, there have been reports [54] that patients with AF and CHF are unlikely to remain in sinus rhythm in the long-term and, until recently, it was the consensus, reflected in current ACC/AHA/ESC guidelines on management of AF, that rhythm control should not be vigorously pursued in this clinical setting [55].
However, a subgroup analysis of AFFIRM, the largest study, designed to assess total mortality, revealed a benefit conferred by rhythm control in patients with CHF or LV dysfunction. While the overall survival of patients with normal LV systolic function was not influenced by the treatment strategy, patients with depressed LV function benefited significantly from restoration and maintenance of sinus rhythm compared with patients who had been assigned to rate control. Furthermore, the "on-treatment" analysis of AFFIRM showed that presence of sinus rhythm predicted a considerably lower risk of death (hazard ratio 0.53, 99% confidence intervals 0.39, 0.72; *P* < 0.0001) [56].

The primary objective of the ongoing Atrial Fibrillation and Congestive Heart Failure (AF-CHF) trial is to determine whether restoring and maintaining sinus rhythm significantly reduces cardiovascular mortality compared with a rate-control strategy in patients with AF and CHF [57]. AF-CHF is a prospective trial including 109 enroling centres in Canada, the United States, South America, Europe, and Israel. The nearly 1500 participants in NYHA heart failure functional classes II—IV, with LVEF <35% and persistent AF, will be randomly assigned to rhythm control with electrical cardioversion + amiodarone or other class III agents, or rate control with beta-adrenergic blockers, digoxin, or AV node ablation. Cardiovascular mortality is the primary endpoint, which will be analysed according to the intention-to-treat principle. The study is powered to detect a 25% reduction in mortality with rhythm control assuming an 18.75% 2-year cardiovascular mortality in the rate-control arm. The minimum follow-up will be 2 years.

**Practical approach to rate control**

It is generally assumed that to compensate for loss of atrial contribution, the ventricular rate during AF should be approximately 10—20% faster than the corresponding rate during sinus rhythm. Current ACC/AHA/ESC guidelines consider the ventricular rate controlled when the ventricular response ranges between 60 and 80 bpm at rest, and between 90 and 115 bpm during moderate exercise [55]. No systematic study has validated these criteria, and these recommendations may be flawed for several reasons, including the absence of atrial mechanical activity, altered cardiac haemodynamics from irregular ventricular contractions, or misdirected clinical endpoint of ventricular rate instead of symptomatology. The absence of chronotropic incompetence and prevention of prominent irregularity are important elements for effective ventricular rate control.

Rate control in AF is based mainly on pharmacological depression of conduction through the AV node. In the presence of CHF, this requires careful dose titration and, not infrequently, incurs a risk of symptomatic bradycardia and need for permanent pacing. Preference is given to beta-adrenergic blockers, usually in combination with digoxin, as they are more likely to provide adequate rate control at rest and during exercise and because of their overall therapeutic effects in patients with CHF [55]. In the AFFIRM sub-study, long-term rate control was achieved with beta-adrenergic blockers alone in 58%, and combined with digoxin in 70% of patients [58]. In a subgroup with a history of CHF and LVEF <40%, successful rate control was observed with a beta-adrenergic blocker with or without digoxin in 81% and with digoxin alone in 54% at 1 year.

However, the beneficial effects of beta-adrenergic blockade do not eliminate the need for digoxin therapy in patients with CHF and AF. A retrospective analysis of the US carvedilol study demonstrated a greater survival benefit of carvedilol in patients with CHF treated with digoxin, although the proportion of patients with AF was small [59]. In a group of 47 patients with predominantly NYHA heart failure functional class II, the combination of carvedilol and digoxin was superior to either digoxin or carvedilol alone in controlling the ventricular rate and reducing symptoms [60]. Withdrawal of digoxin in patients treated with carvedilol was generally deleterious, suggesting that both an enhanced vagal tone and a reduced sympathetic activity are important in controlling AF associated with CHF. The sympatholytic effects of digoxin may be synergistic with those of a beta-adrenergic blocker. In 88 patients in NYHA functional class III studied in Armenia, the combination of digoxin and bisoprolol was superior to either drug alone in controlling ventricular rates both at rest and during exercise, improving symptoms and increasing the distance covered during a 6-min walk [61]. LVEF also increased by nearly 15%.

Until very recently, the most effective rate-control strategy has not been supported by data from randomised clinical trials. AV node ablation may be the treatment of choice in the presence of symptoms intolerable despite rate slowing agents. Brignole et al. [62] reported the results of a randomised controlled study comparing pharmacological rate control vs AV node ablation for AF in 66 patients with CHF. Alleviation of symptoms and an
increase in functional capacity were observed with both treatment strategies. Patients assigned to the "ablate and pace" strategy had fewer symptoms, especially palpitations and exertional dyspnea, though there was no difference in changes in quality of life or cardiac performance. The "ablate and pace" strategy also did not prevent the progression of CHF, and the overall mortality was similar in both treatment groups. However, during subsequent follow-up, 10 patients randomised to pharmacological rate control (30%) crossed over to ablative therapy. The Australian Interventional Randomised Control of Rate in AF Trial (AIRCRAFT), which focused predominantly on the effects of pharmacological rate control vs AV node ablation on LV function, found no difference between the two strategies, but reported an 18% relative risk reduction in symptoms at 1 year in the group randomised to ablation and pacing [63].

Specific antiarrhythmic therapy

Beta-adrenergic blockade

Beta-adrenergic blockers are modestly effective in preventing recurrences of AF and are mainly used for rate control. In the Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN) study of almost 2000 patients with myocardial infarction and LV dysfunction, carvedilol reduced the risk of developing AF by nearly two thirds, probably contributing to the overall beneficial effect conferred by beta-adrenergic blockade on prognosis [64]. The survival benefit of carvedilol was similar in CHF patients with and without AF in the US Carvedilol study [59]. However, the subgroup analysis of the Cardiac Insufficiency Bisoprolol Study II (CIBIS II) showed that bisoprolol reduced all-cause mortality in patients with sinus rhythm (relative risk 0.58) but had no beneficial effects in patients presenting with AF (relative risk 1.16) [65]. These discordant results may be explained by different patient populations and different pharmacological properties of the beta-adrenergic blockers used in these trials.

Amiodarone and dronedarone

The potential of amiodarone to maintain sinus rhythm in patients with AF and CHF has been repeatedly shown in observational and prospective, randomised, controlled studies. In the Canadian Trial of Atrial Fibrillation (CTAF), therapy with amiodarone reduced the incidence of recurrent AF by 57% compared with sotalol and propafenone [66]. In the Congestive Heart Failure Survival Trial of Antiarrhythmic Therapy (CHF-STAT), patients treated with amiodarone converted to sinus rhythm more frequently (31.3% vs 7.7% on placebo), had fewer recurrences of AF, and were less likely to develop new AF (Table 2) [67]. Given its neutral effect on all-cause mortality, amiodarone is a drug of choice for the management of AF associated with CHF. In addition to its antiarrhythmic effects, it is effective in controlling the ventricular rate during recurrences. In the CHF-STAT study, amiodarone reduced both the mean and maximum ventricular rates by 14–22%.

Dronedarone is an investigational agent with multiple electrophysiological effects similar to amiodarone, though is devoid of iodine and is believed to have a safer adverse effects profile. Several randomised studies have examined the

| Table 2 | Efficacy of amiodarone, dofetilide and azimilide in patients with AF and CHF |
|---------|---------------------------------|-----------------|-----------------|
| CHF–STAT study | DIAMOND study | ALIVE study |
| Active drug | Amiodarone | Dofetilide | Azimilide |
| Patients (overall n) | 667 | 3028 | 3381 |
| Patients with AF at baseline (n) | 103 (15.4%) | 506 (16.7%) | 93 (2.8%) |
| Patients who converted to sinus rhythm during follow-up (%) | | | |
| Placebo (%) | 7.7 | 33.5 | 6 |
| Active drug (%) | 33.5 | 59.4 | 34 |
| Active drug efficacy (%) | 23.7 | 25.9 | 28 |
| Patients who developed new AF during follow-up (%) | | | |
| Placebo (%) | 8 | 6.55a | 1.15 |
| Active drug (%) | 4 | 1.98a | 0.49 |
| Active drug efficacy (%) | 4 | 4.57a | 0.66 |

Adapted from Ref. [72].

a Data from the DIAMOND–CHF study.
efficacy of dronedarone in different populations of patients with AF. In the Dronedarone Atrial Fibrillation (DAFNE) trial which enrolled 199 patients, dronedarone, 800 mg daily, prolonged the mean interval to recurrence of AF by 55% compared with placebo [68]. Spontaneous conversion to sinus rhythm was dose-dependent and occurred in 5.8%–14.8% of patients treated with dronedarone compared with 3.1% of patients treated with placebo. Like amiodarone, dronedarone controlled the ventricular rate during AF recurrences. The preliminary results of the EURopean trial in atrial fibrillation or flutter patients receiving Dronedarone for the maintenance of Sinus rhythm (EURIDIS) and its American–Australian–African equivalent ADONIS showed that dronedarone was superior to placebo in the prevention of recurrent AF and effective in controlling the ventricular rate in over 1200 patients (unpublished data). These efficacy and safety trials were not designed to assess mortality and excluded patients with prominent LV dysfunction. However, the Antiarrhythmic trial with Dronedarone in Moderate to severe CHF Evaluating Morbidity Decrease (ANDROMEDA) study was stopped prematurely after the enrolment of 627 patients, out of the 1000 planned, as an interim safety analysis suggested an excess risk of death in patients on active treatment.

Dofetilide and azimilide

Dofetilide is considered a relatively safe and effective class III antiarrhythmic drug for the treatment of AF associated with advanced underlying heart disease. In the DIAMOND studies in over 3000 patients with symptomatic CHF, or myocardial infarction and LV dysfunction, dofetilide, 500 μg twice daily, compared with placebo, increased the likelihood of remaining in sinus rhythm at 1 year significantly (79% vs 42%) and prevented the occurrence of new cases of AF (1.98% vs 6.55%) [12]. It is also noteworthy that restoration and maintenance of sinus rhythm was associated with a significant survival benefit.

Azimilide, which is in its final phase of clinical development, is effective in the prevention of recurrent AF. A meta-analysis of four randomised, controlled dose-efficacy studies in 1380 patients showed that the two highest drug doses (100 and 125 mg/day) prolonged the time to symptomatic recurrences of AF significantly (hazard ratios 1.34 and 1.32, respectively) [69]. Patients with a history of coronary artery disease or CHF had a significantly greater treatment effect from azimilide than those with other underlying cardiovascular diseases (hazard ratio 1.49–1.86).

The Azimilide post-Infarct survival Evaluation (ALIVE) trial reported a lower incidence of new cases of AF and a clear trend towards higher conversion rates in the azimilide arm compared with placebo (26.8% vs 10.8%) in over 3000 high-risk patients with recent myocardial infarctions, depressed ventricular function, and decreased heart rate variability [70]. As in the DIAMOND study, patients in AF had a 50% greater risk of death from CHF or sudden death than patients in sinus rhythm, even after adjustment for age, hypertension, CHF, NYHA functional class, treatment with beta-adrenergic blockers and ACE inhibitors. Azimilide had a neutral effect on all-cause mortality, including patients with an LVEF <20% [71]. However, the efficacy of azimilide is modest and limited to patients with structural heart disease.

Experimental antiarrhythmic agents

Experimental antiarrhythmic agents targeting specific pathophysiological mechanisms of AF associated with CHF are in development [72]. Stretch-activated ion channels may play an important role in arrhythmogenesis in the presence of CHF, suggesting that the pharmacological blockade of stretch-activated channels may prevent the occurrence of AF. Such agents, e.g., GsMtx4, may be particularly effective under conditions of increased atrial pressure or volume.

Structural remodelling of cardiac gap junctions can result from alterations in connexin transport and/or connexin protein synthesis or degradation under conditions of atrial stretch and prolonged periods of AF [73]. Antiarrhythmic peptide (AAP), first isolated from the bovine atria in 1980, modifies the electrophysiological properties of the myocardium without exerting direct effects on ion channels and action potential duration. Synthesized in 1994, AAP10 increases the conductivity gap junctions and improves intracellular coupling by activation of protein kinase C via G-protein and enhanced phosphorylation of connexin 43 [74,75]. However, the use of endogenous AAP and synthetic derivatives has been hindered by instability and a very short half-life. Newer gap junction modifiers with prolonged action, such as ZP123 (GAP-486), are under investigation.

Increased Ca²⁺ influx via the cardiac Na⁺/Ca²⁺ exchanger can lead to increased intracellular calcium concentrations. KB-R7943 is an isothiourea derivative which selectively inhibits the reverse mode of the Na⁺/Ca²⁺ exchanger. In a rapid atrial pacing canine model of AF, KB-R7943 prevented
the shortening of the atrial refractory period but had no effect on ventricular refractoriness [76]. The agent also possesses Na\(^+\), L-type Ca\(^{2+}\), and K\(^+\) ion currents blocking properties, including the ultra-rapid delayed rectifier current (I\(_{Kur}\)) which is specific for the atrial myocardium. At least two other drugs that prevent Na\(^+\) and Ca\(^{2+}\) overload, the benzothiazolamine R56865 and the methylenephenoxydioxy-derivative CP060S, have been described.

**Anticoagulation for AF**

The absence of organised mechanical contraction of fibrillating atria, with a consequent increase in atrial pressure, atrial stretch and dilatation due to multiple pathophysiological mechanisms compensating for a reduced cardiac output, generate conditions for blood stasis and thrombus formation. Abnormalities of haemostasis, endothelial function, and platelet activation often associated with AF further increase the risk of thromboembolic events [77].

CHF itself, in the absence of AF, confers an increased risk of thromboembolism. The incidence of systemic thromboembolic accidents in CHF ranges from 0.9 to 5.5 events per 100 patient-years [78]. The Vasodilator in Heart Failure Trials (V-HeFT) I and II, in patients with NYHA functional class II or III, reported overall embolic event rates of 2.5 and 2.3 per 100 patient-years, respectively [15]. This risk is greater in presence of AF.

Anticoagulation is now imperative in a majority of patients with AF (Table 3) [79]. A meta-analysis of pooled data from five large randomised clinical trials of oral anticoagulation for the primary prevention, and one for the secondary prevention of thromboembolic events in patients with non-rheumatic AF, showed a 61% risk reduction in strokes with warfarin adjusted to a target INR between 2.0 and 3.0, compared with placebo, and a 36% risk reduction compared with aspirin [80].

Three independent models have been developed to grade the risk of stroke associated with AF, including one in 1994 by the Atrial Fibrillation Investigators and supported by the pooled analysis of five primary prevention trials of warfarin [81], and another in 1998 by the Stroke Prevention in Atrial Fibrillation (SPAF) Investigators, based on the results of SPAF I—III studies [82]. In 2001, the American College of Chest Physicians published recommendations for anticoagulation in chronic (permanent or persistent) AF based on stratification of risk for stroke as high (> 7%), intermediate (2.5%) and low (1%) [83]. All three models include CHF and LV dysfunction as factors associated with a high risk of stroke and systemic thromboembolism. The Atrial Fibrillation Investigators reported that the annual risk of stroke was 1.3% in patients without underlying cardiovascular disease and increased to 3.6% in the presence of CHF. The subsequent analysis of echocardiograms in three studies by the Atrial Fibrillation Investigators showed that moderate-to-severe LV dysfunction was associated with a 2.5-fold greater risk of stroke [84]. In the SPAF trials, recent CHF or an LV fractional shortening ≤25% was pre-specified thromboembolic risk factors. A report from the ATRIA study has shown that the presence of CHF and a history of ischaemic cardiovascular events are the strongest predictors of warfarin use in ambulatory patients with AF (adjusted odds ratio 1.63 and 2.55, respectively) [85].

### Table 3  Annual risk of stroke and recommendations for anticoagulation in AF

<table>
<thead>
<tr>
<th>Annual risk of stroke</th>
<th>Risk factors</th>
<th>Recommendations(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (1%)</td>
<td>Age &lt; 65 years and no major risk factors (prior stroke, TIA, systemic thromboembolism, hypertension, HF, LVEF &lt; 0.50)</td>
<td>Aspirin: 227 (132–2500)</td>
</tr>
<tr>
<td>Low moderate (1.5%)</td>
<td>Age 65–74 years and no major risk factors</td>
<td>Aspirin: 152 (88–1667)(^b)</td>
</tr>
<tr>
<td>High moderate (2.5%)</td>
<td>Age 65–74 years, no major risk factors but either diabetes mellitus or coronary artery disease</td>
<td>Warfarin: 32 (28–42)</td>
</tr>
<tr>
<td>High (6%)</td>
<td>Age &lt; 75 years and either hypertension, HF or LVEF &lt; 0.50; or age ≥ 75 years in the absence of other risk factors</td>
<td>Warfarin: 14 (12–17)</td>
</tr>
<tr>
<td>Very high (10%)</td>
<td>Age ≥ 75 years and either hypertension, HF or LVEF &lt; 0.50; or any age and prior stroke, TIA, or systemic thromboembolism</td>
<td>Warfarin: 8 (7–10)</td>
</tr>
</tbody>
</table>

HF = heart failure; LVEF = left ventricular ejection fraction; TIA = transient ischaemic attack. Adapted from Ref.[80].

\(^a\) Number of patients treated to prevent one stroke in 2 years.

\(^b\) With warfarin, number to treat is 54 (46–69).
Conclusions

AF and CHF are two growing epidemics of the third millennium which often intersect, as the general population is ageing and better therapies have been implemented for the management of previously fatal heart diseases. Many clinical trials have addressed different aspects of treatment of patients with either pathology but few have focussed on the management of patients with both diseases combined. The multifactorial aetiology of CHF and AF suggests the need for a multidimensional approach targeted at different pathophysiological mechanisms. Retrospective analyses of large-scale randomised trials and small observational and controlled studies have shown that AT-1 receptor blockers and ACE inhibitors are effective in the prevention of new onset or recurrent AF. New antiarrhythmic agents are being developed and tested that may favourably influence the survival of patients with AF and CHF. Understanding the mechanisms underlying AF has led to the rapid development of non-pharmacological treatment alternatives, including various catheter ablation techniques, such as pulmonary vein isolation and ablation of atrial flutter that may trigger fibrillation. New implantable pacemakers and defibrillators incorporate cardiac resynchronisation therapy and some also feature continuous monitoring and defibrillators incorporate cardiac resynchronisation therapy and some also feature continuous surveillance and detection of AF and atrial-paced therapies aimed at prevention and/or termination of the arrhythmia. Identification of genes associated with familial dilated cardiomyopathy, progressive sinus node disease and conduction disorder, AF, and stroke may expose several possible targets for the prevention or cure of genetically determined arrhythmias.

References


Atrial fibrillation and heart failure


