Atrial Fibrillation in Heart Failure: An Innocent Bystander?

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Abstract: Heart failure (HF) and atrial fibrillation (AF) frequently coexist and each complicates the course of the other. The purpose of this review is to analyse the prognostic impact of AF in patients with HF and assess whether there is an advantage in targeting therapies towards the maintenance of sinus rhythm (SR) in this cohort of patients.

The presence of AF in patients with HF has been reported to be independently associated with an increase in mortality in many studies and this increased risk is observed in those with both preserved and impaired LV systolic function. The optimal strategy for targeting AF in patients with HF is unclear but recent randomised controlled studies indicate no significant prognostic advantage associated with a rhythm control strategy as compared to a rate control strategy. A number of small studies have investigated the role of both cardiac resynchronization therapy (CRT) and AF catheter ablation for the maintenance of conversion to SR in patients with HF with initial promising results although larger randomised controlled studies will need to be performed to define the role of these modalities in the treatment of this cohort and whether preliminary benefits observed in these studies translate to improvements in longer term prognosis. Finally, there has been a focus on modifying the arrhythmogenic atrial substrate and neurohormonal milieu by pharmacological means in order to prevent AF although it remains to be seen whether this approach proves to be efficacious with improvements in clinically relevant outcomes.

Keywords: Heart failure, atrial fibrillation, prognosis.

INTRODUCTION

Heart failure (HF) and atrial fibrillation (AF) are amongst the commonest cardiovascular conditions encountered in clinical practice and frequently coexist. Heart failure predicts the development of AF and conversely the presence of AF predicts the development of HF [1]. Heart failure prevalence has reached the proportions of a global epidemic with an estimated prevalence of 3-20 cases /1000 population rising to above 100 cases /1000 population in those aged over 65 years [2]. Similarly, the annual incidence of heart failure in middle aged men and women is 0.1-0.2 % rising steadily to 2-3 % in those aged above 85 years [2]. Extrapolating from available evidence, as many as 30 million people in Europe may have heart failure [3]. National Health and Nutrition Examination Survey (NHANES) data from 2005 to 2008 indicates that the prevalence of heart failure in Americans (over 20 years of age) is around 5.7 million. The lifetime likelihood of developing heart failure has been estimated as 1 in 5 and this risk rises with an ageing population. HF incidence approaches 10 per 1000 in above 65 year old group [4].

Atrial fibrillation is the most common sustained arrhythmia seen in clinical practice [5]. The Framingham as well as the Rotterdam studies estimate around 25% lifetime risk of developing AF. The prevalence of AF is estimated between 2.7 to 6.1 million in the United States. This is expected to rise to between 5.6 and 12 million [4]. The AnTicoagulation and Risk Factors In Atrial Fibrillation (ATRIA) study predicted that the prevalence will rise 2.5 times by 2050 [6]. The incidence rises steeply with age, rising to 17.4% in those above 85 years of age [7]. Similar to HF, AF also carries an enormous burden of morbidity, mortality and healthcare costs [8].

AF and HF frequently co-exist. The EuroHeart survey studied hospital admissions for heart failure in 24 European countries over a 6-week period in 10,701 patients and demonstrated that 34 % of patients had previous AF while 9% had new onset AF [9]. Whilst AF and HF frequently co-exist, it remains unclear as to whether the presence of chronic AF has a prognostic impact on outcomes in patients with HF. The purpose of this review is therefore to analyse the prognostic impact of AF in patients with HF and to assess whether there is an advantage in targeting therapies towards the maintenance of sinus rhythm in this cohort of patients.

EPIDEMIOLOGY

HF and AF share many common risk factors and frequently co-exist. For instance up to 20% with AF have HF and 5-50% with HF suffer with AF as well [1]. Factors such as hypertension, coronary atherosclerosis, diabetes mellitus, obesity and structural heart disease (ischaemic, nonischaemic, valvular) all predispose to HF as well as AF. Both increase exponentially with increasing age. Moreover, AF becomes more prevalent with worsening severity of HF. Thus
it can range from less than 10% in those with NYHA class 1 symptoms to 50% in those in NYHA class 4 [10]. According to the Acute Decompensated Heart Failure National Registry (ADHERE) around 30% of patients hospitalized for decompensated HF have AF [11] whilst the ALPHA study showed around 20-30% of NYHA class 2-3 patients had AF [12]. This compares to 50% patients with NYHA class 4 symptoms in the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) who had concomitant AF [10].

INTERPLAY BETWEEN AF AND HF

There is a complex inter-relationship between AF and HF. Each adversely affects and complicates the course of the other [13]. HF provides a substrate for the development of AF through a number of mechanisms such as atrial dilatation, fibrosis and electromechanical remodelling [13]. Neurohormonal activation and dysregulation of intracellular calcium may also play a role [14]. Similarly, AF predisposes to HF through a variety of mechanisms including tachycardia-related cardiomyopathy, loss of atrial kick, reducing ventricular diastolic filling time and functional mitral/tricuspid regurgitation [1]. The development of AF in HF may contribute to decompensation. For example, irregularity of the RR interval as seen in AF may affect haemodynamics adversely independent of the heart rate [15]. Pozzoli et al. studied the haemodynamic effects of new onset AF in heart failure patients. 344 patients with heart failure and sinus rhythm at baseline were prospectively followed up for the onset of AF. They showed that the onset of AF led to significant reduction in cardiac index, increased bi-atrial dimensions and functional atrioventricular valve regurgitation. This coincided with a decline in NYHA class as well as peak exercise oxygen consumption [16]. The pathophysiology of AF in CHF has previously been reviewed by Lubitz et al. and is beyond the scope of this review [8].

PROGNOSTIC IMPACT OF AF IN HF PATIENTS

A number of studies in patients with LV systolic dysfunction have shown that AF has an impact on prognosis. Retrospective analysis of the Studies Of Left Ventricular Dysfunction (SOLVD) by Dries et al. (involving 6517 patients with LVEF of less than 35%) showed that AF was associated with an increased risk for all-cause mortality in comparison to those in sinus rhythm (34% vs. 23%). This was applicable to asymptomatic as well as symptomatic patients and mainly attributable to an increased risk of pump failure deaths [17]. Similarly, the Candesartan in Heart FailureAssessment of Reduction in Mortality and Morbidity (CHARM) investigators showed an increased and independent effect of AF on cardiovascular outcomes in patients with either reduced or preserved LV systolic function [18]. Both the above retrospective analyses are, however, limited by the fact that data for these studies were derived from subgroup analysis. Prospective data from Stevenson et al. looked at the influence of AF on all-cause mortality in 390 patients with advanced systolic heart failure. They concluded that AF is an independent predictor of all-cause mortality (actuarial survival at 1 yr with AF 52% vs. 71% with sinus rhythm).

Interestingly, atrial fibrillation was associated with increased 1-year mortality only in patients with a pulmonary capillary wedge pressure lower than 16mmHg rather than the ones with higher filling pressures [19] suggesting that the relative risk of sudden death is highest in patients with relatively better ventricular function as compared to patients with more advanced ventricular dysfunction.

An adjusted meta-analysis of 16 studies (7 randomised trials and 9 observational studies) involving 53969 patients by Mamas et al. suggested worse prognosis with AF irrespective of systolic function [20]. They showed that AF has a deleterious effect on total mortality with an odds ratio of 1.40 (95% CI 1.32-1.48, P<0.0001) in randomised trials and an OR of 1.14 (95% CI 1.03-1.26, P<0.05) in observational studies. Ahmed et al. retrospectively studied an older population (mean age of 79 years) who had heart failure as the primary discharge diagnosis (no distinction was made between systolic and diastolic LV dysfunction). 4-year mortality rates and 30-day readmission rates were analysed. Multivariate analysis revealed a significant 52% increased risk of 4-year mortality but insignificant higher risk of readmission at 30 days [21].

Left ventricular diastolic dysfunction may also play an important role in patients with atrial fibrillation [1]. Not only does it predict the development of AF in HF but has also been connected with increased mortality [22]. Results from the CHARM study showed that although the absolute risk for all-cause mortality was highest in the low ejection fraction cohort, the relative increase in risk was highest in heart failure with preserved left ventricular ejection fraction cohort (HR 1.37, 95% CI 1.06 to 1.79) as compared to that with reduced ejection fraction (HR 1.22, 95% CI 1.04 to 1.43)[18].

There are a limited number of studies that assess new onset acute AF in patients with heart failure as an independent prognostic factor in comparison to those with chronic or paroxysmal AF. Borleffs et al. collected data on a prospective basis in patients receiving ICD implants. Those with chronic AF demonstrated twice the mortality as well as device discharge (both appropriate and inappropriate) than those in sinus rhythm. Paroxysmal or persistent AF, on the other hand, did not have increased mortality but thrice the inappropriate shocks [23]. Caldwell et al. interrogated ICDs of patients with severe heart failure. As many as 27% of patients previously thought to be in sinus rhythm were found to have silent episodes of paroxysmal AF. There was a trend towards increased mortality but not on thromboembolic events or hospital admissions [24]. Chamberlain et al. showed through their community study that there is a significant excess risk of all-cause mortality in patients with AF in HF as compared to those with HF without AF. Compared to patients in sinus rhythm, those with AF prior to HF had a 29% increased risk of death, while those who developed AF after HF had more than a 2-fold increased risk of death [25]. The EuroHeart Failure Failure survey showed that the increase in mortality with acute new onset of AF was higher than that in chronic AF (12% vs. 7%). This was possibly associated with more haemodynamic compromise with faster heart rates as well as a higher use of anti-arrhythmic agents as compared to those known to have AF in the past [9].
A number of studies have shown worse prognosis in HF patients with an ischaemic aetiology. The Valsartan in Acute Myocardial Infarction (VALIANT) study dealt with post myocardial infarction systolic impairment and the potential effect of previously known or new-onset AF on mortality in such patients. Mortality was increased at 3 years in both AF groups (those known to have chronic AF at baseline as well as those who developed new AF concomitantly with the myocardial infarction) [26]. Raunso et al. followed up participants of the Echocardiographic Heart of England Screening (ECHOES) study. A total of 2881 patients were followed up for 4 years. AF showed increased mortality risk only in patients with coronary artery disease (CAD) whilst it had no prognostic influence in those patients without an ischemic substrate [27]. Analysis of the Danish Investigations of Arrhythmia and Mortality on Dofetilide in Congestive Heart Failure (DIAMOND-HF) data had shown similar results in comparing ischaemic versus non ischaemic subsets [28]. When 3587 HF patients with and without ischaemic heart disease were followed for up to 8 years, there was a significant impact of AF on mortality in those with ischaemic heart disease [HR of 1.25 (95% CI: 1.09–1.42) and P < 0.001] as compared to those without ischaemic heart disease [HR of 1.01 (95% CI: 0.88–1.16) and P = 0.88]. It has been shown that AF is associated with reduced myocardial blood flow and increased coronary vascular resistance [29]. It is possible that presence of AF thus adds further ischaemic burden in such patients leading to a worse prognosis.

In contrast, other studies have shown no independent prognostic effect of AF. An analysis of the Carvedilol or Metoprolol European Trial (COMET) cohort by Svedberg et al. failed to demonstrate an independent prognostic influence when adjusted for other predictors of prognosis [30]. However one of the major limitations of this study was that the presence of AF was probably underestimated given that the criteria for diagnosing AF was limited to a single baseline ECG thus potentially missing future development of AF during the course of the study or the presence of paroxysmal AF. Correll et al. demonstrated that AF at baseline was associated with increased all-cause mortality and all-cause mortality/hospitalization. However, when adjusted for baseline covariates, it lost its independent prognostic impact on all-cause mortality and only retained it for the combined end point of all-cause mortality/hospitalization [31]. Again this may have missed the impact of paroxysmal AF. The study is underpowered due to small numbers and can only be regarded as hypothesis generating for new onset AF and its influence on long-term outcomes. Mahoney et al. showed that in patients with advanced heart failure referred for cardiac transplantation, AF was not associated with a reduced event free survival [32]. Instead, the prognosis for heart transplant population depends on the baseline resting heart rate irrespective of the presence of AF or sinus rhythm [33]. The severity and end-stage nature of heart failure in this cohort of patients, as well as the cross-sectional design of the study and small number of patients limits the applicability of these observations to a general HF population. Similarly, retrospective analysis of the Vasodilator-Heart Failure Trials (V-HEFT) in mild to moderate HF did not show AF as independent predictor of mortality [34]. Patients in AF in the study had higher LVEF than the ones in sinus rhythm and may have influenced the outcome. Japanese registry data for hospitalized patients showed that although AF is common in hospitalized patients, it did not influence long term outcomes independently [35]. This retrospective study did not cater for the impact of subsequent or recurrent AF and may have underestimated the prognostic effect. Prospective data from the Heart Failure Survey in Israel (HFSIS) showed an increased crude mortality rate in hospitalized patients both during index admission as well as at 1 and 4 years follow up. The survey, however, failed to prove an independent effect. The prognostic effect was largely explained by comorbidities [36]. Similarly, meta-analysis of 20 studies including 9 RCTs and 11 observational studies representing 32946 patients by Wasywich et al. demonstrated worse outcomes in those with AF when compared to sinus rhythm. It is unclear whether this was an independent effect or due to other prognostic variables such as age, comorbidities and HF severity [37]. The adjusted meta-analysis by Mamas et al. [20] has shown that the prognostic effect of AF on mortality persisted after multivariate adjustment.

**EFFECT OF VARIOUS THERAPEUTIC MODALITIES ON PROGNOSIS**

Whilst many of the studies outlined above have shown that the presence of AF in patients with HF is associated with an adverse prognosis, it remains unclear whether targeting AF with a view to maintaining sinus rhythm improves outcomes. AF management has received a great amount of interest over the years and a variety of therapeutic options have been developed to both optimise rate control and promote cardioversion/maintenance of sinus rhythm.

Pharmacological agents have long been the mainstay of AF management in HF. A number of trials have shown the benefit of ventricular rate control with beta-blockers and digoxin (as adjunct). A post-hoc retrospective analysis of the US Carvedilol HF trial was carried out looking specifically at a subgroup of patients who had AF at baseline. It not only demonstrated improved LV ejection fractions in the carvedilol group (as compared to placebo) but there was also a trend towards reduced combined end point of death/hospitalization [38]. The analysis of the same subgroup also showed similar survival in patients on carvedilol who were also on digoxin suggesting an added effect of the latter. Studies had already shown reduced hospitalization and improved symptom control with digoxin therapy [39]. Sub group analysis of the 600 AF patients in the COMET trial cohort showed a similar survival benefit with carvedilol [30]. The Digitalis Investigation Group (DIG) trial showed that although digoxin did not affect mortality in HF yet it reduced the number of hospitalizations. Ahmed et al. conducted a pre-specified 2-year post hoc analysis of DIG trial data specifically looking at patients with AF and HF. They showed a significant reduction in mortality as compared to placebo (27% vs. 33%) when higher risk heart failure patients with a LVEF of less than 25% and AF were considered [40].

The influence of pharmacological rhythm control of AF in HF has mainly been studied using amiodarone and dofetilide. Amiodarone is effective in maintaining sinus rhythm and has a neutral effect on survival in moderate/severe systolic dysfunction as shown in the Survival Trial of Antiar-
rhythmic Therapy in Congestive Heart Failure (CHF-STAT) and AF-CHF trials [41,42] but is associated with a significant long-term risk of adverse effects. 79% of patients prescribed dofetilide in DIAMOND trial remained in sinus rhythm. It reduced hospital admissions with heart failure [43]. The trial mainly looked at safety/efficacy in ischaemic systolic heart failure. However, there remains a risk of torsade de points (1.6%) even when initiated in hospital with close monitoring [43]. Dofetilide, however, is not available in Europe. Dronedarone is an iodine-free amiodarone derivative which has shown a promising adverse effect profile. ATHENA was a placebo-controlled, double blind study comparing dronedarone with placebo in atrial fibrillation. A post hoc analysis (in patients with stable HF with LVEF less than 40% and NYHA II/III symptoms) demonstrated reduced cardiovascular events (first cardiovascular hospitalization or death from any cause) [44]. However, AN-DROMEDA trial which studied the anti-arrhythmic dronedarone in patients with advanced heart failure (LVEF<35%) who had been recently hospitalized with new or worsening heart failure had to be terminated prematurely because dronedarone increased mortality in patients with severe heart failure. [45].

The debate of a Rate vs. Rhythm control strategy in patients with / without HF is controversial. A number of trials indicate no added benefit in terms of long term outcomes from rhythm control in comparison to rate control. These include the Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation (RACE)[46], the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AF-FIRM)[47], the How to Treat Chronic Atrial Fibrillation (HOT CAFE)[48], the Strategies of Treatment of Atrial Fibrillation (STAF)[49] and Pharmacological Intervention in Atrial Fibrillation (PIAF)[50]. These trials, however, were not exclusive to HF and the results may not necessarily be applicable to patients with heart failure. AF-CHF was a prospective trial in the HF population. 1376 patients with systolic heart failure were randomized to amiodarone or rate control respectively and followed up for 3 years for mortality, heart failure hospitalization and stroke [42]. It also arrived at similar results—there was no significant difference in death from cardiovascular cause in rhythm control patients as compared to rate control (27% vs. 25%). Secondary outcomes including death from any cause, stroke, worsening heart failure and composite of death from cardiovascular cause, stroke and worsening heart failure did not reveal any difference as well. However, the proportion of patients in the rhythm control arm who were truly free of AF was 80% (possibly 65% looking at the overall 3 year follow up visits as well as the 21% who crossed over to the rate control arm due to inability in maintaining sinus rhythm) [14]. A recent meta-analysis by Caldeira et al. analysed the 4 main RCTs of AF rate vs. rhythm control in heart failure incorporating 2486 patients. There was no significant difference in terms of mortality and stroke [51]. Registry on Cardiac Rhythm Disorders Assessing the Control of Atrial Fibrillation (RECORD-AF) was a community based prospective, multinational observational study that analysed data from 5171 patients of AF. It looked at real life experience in unselected patients with AF including those with and without HF [52]. It showed that outcomes in AF were not related to either a rate or rhythm control strategy. Conversely, Guglin et al. presented a post hoc analysis of the AFFIRM cohort looking at the rhythm control arm. Sinus rhythm was associated with fewer symptoms of HF (assessed by NYHA functional class) and improved functional status (assessed by 6-minute walk test) [53]. Also CHF-STAT subgroup analysis by Deedwania et al. showed that amiodarone therapy was more effective in converting AF to sinus rhythm as compared to placebo (31% vs. 8%). It not only prevented new onset AF throughout the course of the study but was also effective in maintaining a lower ventricular rate in those who did not convert into sinus rhythm. Importantly, Kaplan-Meier analysis of the survival curves for those who converted to SR with amiodarone as compared to those who did not showed significantly better survival [54]. Similar conclusions can be derived from DIAMOND trial [43] and the small CAFÉ-II study [55]. Again these are post hoc subgroup analyses and should be considered hypothesis generating rather than best available evidence. Kurita et al. argue in favour of rhythm control suggesting that overall prognosis in HF may improve provided without side effects of antiarrhythmic and catheter ablation complications [56].

A number of non-pharmacological modalities are in routine clinical use for the management of AF. Anti-arrhythmic drug therapy for the management of AF may in itself increase adverse cardiac events. AF-CHF trial patients who were in the rhythm control arm were more frequently hospitalized for dosage readjustment and cardioversion especially in the first year [42]. Furthermore, many patients are unable to achieve rhythm or rate control targets due to inadequacy of the drugs or side effects. Consequently, use of electrophysiological interventions to achieve this aim is increasing. AV nodal (AVN) ablation accompanied by a permanent pacemaker is often a last resort option for definitive AF rate control when medical therapy to achieve this has failed. This treatment strategy may only be of symptomatic benefit since AF is not eliminated and deleterious effects of A-V dysynchrony and loss of atrial transport still persist. While atrial lead placement and chronic atrial pacing has not shown any benefit in reducing AF recurrences, chronic RV pacing leads to progressive LV dysfunction due to inter-ventricular desynchronisation. As a result, upgrade to biventricular pacing has been suggested as a promising option provided it can be ensured that the device is pacing nearly 100% of the time for maximum benefit [57,58]. To date, a number of observational studies have shown improvement in LV function, reduction in mitral regurgitation and better exercise capacity with cardiac resynchronization therapy (CRT) in HF patients with AF [59–61]. For instance, the MUSTIC trial included 33 patients in AF, 29 (88%) of whom were programmed to biventricular pacing [59]. Similarly, registry data from Lue-dorff et al. looked at patients with severe heart failure incorporating 139 patients with AF vs. 445 in sinus rhythm. At 1 year follow up, CRT associated improvement of NYHA class and LV ejection fraction was similar in the two groups—albeit higher mortality in AF group (12% vs. 7%; OR 1.80; 95% confidence interval 0.95-3.4) [61]. The patient numbers, however, are limited. Therefore, in patients requiring AVN ablation and a permanent pacemaker, CRT should be the pacing option of choice. Conversely, CRT is less effective if adequate rate control cannot be achieved in AF and
in such cases AVN ablation can be very useful. AVERT-AF Trial [62] is currently underway to study the effect of AV junction ablation and CRT on patients with severely impaired LV systolic function and permanent AF looking at improvement in functional capacity. There is still a need for randomized, placebo-controlled trials looking at long term mortality data in patients with advanced heart failure.

Although AVN ablation and pacemaker implantation is an effective rate control strategy it does not eliminate the burden of AF. Moreover, biventricular pacing is potentially associated with a number of procedural risks. Consequently, catheter ablation (particularly pulmonary vein isolation) has gained popularity in the management of AF. One non-randomized trial of patients in AF studied catheter ablation results in 58 patients with LVEF < 45% compared to similar number of patients without HF. It showed a significant improvement in LVEF (mean increase of 21%) post ablation. There was also a significant improvement in symptoms, quality of life and exercise capacity (assessed by NYHA class, SF-36 quality of life scores and bicycle-ergometer stress test respectively). However, there was a high recurrence of AF and 50% of the patients required a second procedure, although 79% of patients remained in sinus rhythm at 1 year. The study was, however, under-powered to look at mortality trends [63]. A number of other small non-randomized studies have shown promising improvements in LVEF and patient symptoms [64-66]. PABA CHF looked at pulmonary vein isolation (PVI) vs. AV Node ablation plus biventricular ICD [67]. This was a prospective, multicentre, randomized trial enrolling drug-refractory AF patients with LVEF of 40% or less and in NYHA II/III. 41 patients underwent PVI while 40 had AVN ablation along with biventricular ICD implantation. The primary end point was a composite of LVEF, 6 minute walk distance and Minnesota Living with Heart Failure score. PVI patients did better in all three components of the composite end point than the group who underwent AVN ablation and biventricular pacing. This data suggests that perhaps optimal rate control with a regular RR length is not enough on its own and eliminating AF to restore atrial transport and AV synchrony is equally important [56]. Dagres et al. recently presented a meta-analysis of trials of catheter ablation for AF in patients with moderate LV systolic dysfunction. 9 studies incorporating a total of 354 patients were analysed. Primary end point was change in ejection fraction while secondary end points were changes in exercise tolerance and quality of life post procedure. Catheter ablation led to improvement in LV systolic function. However, the extent of this benefit was quite heterogeneous and no survival data is available [68]. Clearly, definitely large, multicentre, randomized controlled trials are needed with longer follow up to guide clinical practice. Surgical ablation (variations of Cox Maze procedure) is an effective option available to those who are undergoing cardiac surgery for other reasons [69]. It has been shown to be safe and effective in heart failure [70].

Heart failure patients with AF represent a cohort at very high risk of thromboembolic events. Long-term oral anticoagulation is strongly indicated in AF and HF unless there are binding contraindications. ACCF/AHA/HRS recommend either aspirin or anticoagulation for patients with a CHADS2 score of 1 while ESC and CCS guidelines indicate anticoagulation for such patients in preference to aspirin. There is unanimous recommendation of anticoagulation with a CHADS2 score of 2 and above [71]. Warfarin therapy is often underutilized due to a variety of limitations including erratic INR control, need for monitoring blood levels as well as interactions with various drugs/food. More recently, a novel group of anticoagulants has been developed with the advantage of rapid onset of action, predictable therapeutic levels not requiring monitoring as well as reduced risk of intracranial bleeding while maintaining efficacy. There is a low likelihood of interactions with drugs and food. There is, however, the caveat of higher cost, unavailability of antidote and no validated lab marker of anticoagulant effect when deemed clinically important [72]. The two main classes of these novel anti-coagulants include direct thrombin inhibitors (dabigatran) and activated factor X inhibitors (apixaban, rivaroxaban, edoxaban). Dabigatran was approved by FDA in 2010 for non-valvular AF following the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial [73]. It showed that 150mg bd dose was superior in efficacy to warfarin while the lower 110 mg bd dose was at least non-inferior. Both had less risk of intracranial bleeding than warfarin. Dabigatran has been recommended as an alternative to warfarin in recent ESC as well as CCS guidelines as well [74,75]. ROCKET-AF (Rivaroxaban Once daily oral direct Factor Xa inhibition Compared with vitamin K antagonist for prevention of stroke and Embolism Trial in Atrial Fibrillation) studied once daily Rivaroxaban demonstrating non-inferiority to warfarin with reduced intracranial and similar rate of major bleeding [76]. ARISTOTLE (Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation) trial demonstrated efficacy and safety of apixaban on similar grounds [77].

Finally, there has been a focus on modifying the arrhythmogenic atrial substrate and neurohormonal milieu in order to prevent AF in heart failure patients. Limited data is available so far for statin therapy [78] and Renin-angiotensin-aldosterone system (RAAS) blockade [79,80]. In a recent meta-analysis of 8 RCTs incorporating 2323 patients, Bhuriya et al. looked at studies using ACE inhibitors or ARBs and containing data on outcomes of recurrent AF. They showed a significant reduction in recurrent AF in these patients (RR, 0.611; 95% CI, 0.441-0.847; P = .003). It should be pointed out, however, that the trials were not specifically designed to test this hypothesis and further large randomized controlled trials aimed a priori at the specific hypothesis are required [81].

CONCLUSIONS

In conclusion, HF and AF frequently co-exist and the presence of AF in patients with HF has been reported to be independently associated with an increase in mortality in many studies and this increased risk is observed in those with both preserved and impaired LV systolic function. Whilst many studies have shown that the presence of AF in HF patients is associated with an adverse prognosis, most studies that have targeted AF in patients with HF with a view to maintaining SR have shown no significant improvements in outcomes compared to those patients in which a rate control strategy has been adopted. A number of small trials have studied the role of AF catheter ablation results in pa-
patients with HF and have shown modest improvement in LVEF as well as significant improvement in symptoms, quality of life and exercise capacity although the utility of this modality of treatment needs to be further investigated in larger randomised controlled trials. Finally, there has been a focus on modifying the arrhythmogenic atrial substrate and neurohormonal milieu in order to prevent AF in heart failure patients although it remains to be seen whether this approach proves to be efficacious with improvements in clinically relevant outcomes.

CONFLICT OF INTEREST
The authors report no conflicts of interest.

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REFERENCES
[1] Caldwell JC, Mamas MA. Heart failure, diastolic dysfunction and atrial fibrillation: mechanistic insight of a complex interrelationship. Heart Fail Rev 2012; 17(1):27-33.
[2] McMurray JJ, Stewart S. Epidemiology, aetiology, and prognosis of heart failure. Heart 2000; 83(5): 596-602.
[3] McMurray JJ, Petrie MC, Murdoch DR, Davie AP. Clinical epidemiology of heart failure: public and private health burden. Eur Heart J 1998; 19 Suppl P: P-96.
[4] Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics-2012 update: a report from the American Heart Association. Circulation 2012; 125(1): e2-e220.
[5] Kannel WB, Benjamin EJ. Status of the epidemiology of atrial fibrillation. Med clin North Am 2008; 92(1): 17-40, ix.
[6] 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 J Am Med Assoc 2001; 285(18): 2370-5.
[7] Murphy NF, Simpson CR, Jhund PS, Stewart S, Kirkpatrick M, Chalmers J, et al. A national survey of the prevalence, incidence, primary care burden and treatment of atrial fibrillation in Scotland. Heart 2007; 93(5): 606-12.
[8] Lubitz SA, Benjamin EJ, Ellinor PT. Atrial fibrillation in congestive heart failure. Heart Fail Clin 2010; 6(2): 187-200.
[9] Rivero-Ayerza M, Scholte Op Reimer W, Lenzen M, et al. New-onset atrial fibrillation is an independent predictor of in-hospital mortality in hospitalized heart failure patients: results of the Euro-Heart Failure Survey. Eur Heart J 2008; 29(13): 1618-24.
[10] Maisel WH, Stevenson LW. Atrial fibrillation in heart failure: epidemiology, pathophysiology, and rationale for therapy. J Am Cardiol 2003; 91(6A): 2D-8D.
[11] Adams KF, Jr, Fonarow GC, Emerman CL, et al. Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). Am Heart J 2005; 149(2): 209-16.
[12] De Ferranti GM, Klersy C, Ferrero P, et al. Atrial fibrillation in heart failure patients: prevalence in daily practice and effect on the severity of symptoms. Data from the ALPHA study registry. Eur J Heart Fail 2007; 9(5): 502-9.
[13] Decdewania PC, Lardizabal JA. Atrial fibrillation in heart failure: a comprehensive review. Am J Med 2010; 123(3): 198-204.
[14] Anter E, Jessup M, Callans DJ. Atrial fibrillation and heart failure: treatment considerations for a dual epidemic. Circulation 2009; 119(18): 2516-25.
[15] Clark DM, Plumb VJ, Epstein AE, Kay GN. Hemodynamic effects of an irregular sequence of ventricular cycle lengths during atrial fibrillation. J Am Coll Cardiol 1997; 30(4): 1039-45.
[16] Pozzoli M, Cioffi G, Traversi E, Pinna GD, Cobelli F, Tavazzi L. Predictors of primary atrial fibrillation and concomitant clinical and hemodynamic changes in patients with chronic heart failure: a prospective study in 344 patients with baseline sinus rhythm. J Am Coll Cardiol 1998; 32(1): 197-204.
[17] Dries DL, Exner DV, Gersh BJ, Domanski MJ, Waclawiw MA, Stevenson LW. Atrial fibrillation is associated with an increased risk for mortality and heart failure progression in patients with asymptomatic and symptomatic left ventricular systolic dysfunction: a retrospective analysis of the SOLVD trials. Studies of Left Ventricular Dysfunction. J Am Coll Cardiol1998; 32(3): 695-703.
[18] Olsson LG, Swedberg K, Ducharme A, et al. Atrial fibrillation and risk of clinical events in chronic heart failure with and without left ventricular systolic dysfunction: results from the Candesartan in Heart Failure-Assessment of Reduction in Mortality and morbidity (CHARM) program. J Am Coll Cardiol 2006; 47(10): 1077-2004.
[19] Middlekauff HR, Stevenson WG, Stevenson LW. Prognostic significance of atrial fibrillation in advanced heart failure. A study of 390 patients. Circulation 1991; 84(1): 40-8.
[20] Mamas MA, Caldwell JC, Chacko S, Garratt CJ, Fath-Ordoubadi F, Neyes L. A meta-analysis of the prognostic significance of atrial fibrillation in chronic heart failure. Eur J Heart Fail 2009; 11(7): 676-83.
[21] Ahmed A, Thornton P, Perry GJ, Allman RM, DeLong JF. Impact of atrial fibrillation on mortality and readmission in older adults hospitalized with heart failure. Eur J Heart Fail 2004; 6(4): 421-6.
[22] Sherazi S, Zareba W. Diastolic heart failure: predictors of mortality. Cardioj 2011; 18(3): 222-32.
[23] Borleffs Cj, van Rees JB, van Welsenes GH, et al. Prognostic importance of atrial fibrillation in implantable cardioverter-defibrillator patients. J Am Coll Cardiol 2010; 55(9): 879-85.
[24] Caldwell JC, Contractor H, Petkar S, et al. Atrial fibrillation is under-recognized in chronic heart failure: insights from a heart failure cohort treated with cardiac resynchronization therapy. Europace 2009; 11(10): 1295-300.
[25] Chamberlain AM, Redfield MM, Alonso A, Weston SA, Roger VL. Atrial fibrillation and mortality in heart failure: a community study. Circulation Heart Fail. 2011; 4(6): 740-6.
[26] Kober L, Swedberg K, McMurray JJ, et al. Previously known and newly diagnosed atrial fibrillation: a major risk indicator after a myocardial infarction complicated by heart failure or left ventricular dysfunction. Eur J Heart Fail 2006; 8(6): 591-8.
[27] Raunso J, Pedersen OD, Dominguez H, et al. Atrial fibrillation in heart failure is associated with an increased risk of death only in patients with ischaemic heart disease. Eur J Heart Fail 2010; 12(7): 692-7.
[28] Pedersen OD, Sondergaard P, Nielsen T, et al. Atrial fibrillation, ischaemic heart disease, and the risk of death in patients with heart failure. Eur J Heart 2006; 27(23): 2866-2876.
[29] Range FT, Schafer M, Acil T, et al. Impaired myocardial perfusion and perfusion reserve associated with increased coronary resistance in persistent idiopathic atrial fibrillation. Eur J Heart J 2007; 28(18): 2223-30.
[30] Swedberg K, Olsson LG, Charlesworth A, et al. Prognostic relevance of atrial fibrillation in patients with chronic heart failure on long-term treatment with beta-blockers: results from COMET. Eur Heart J 2005; 26(13): 1303-8.
[31] Corell P, Gustafsson F, Schö M, Markenward J, Nielsen T, Hildebrandt P. Prevalence and prognostic significance of atrial fibrillation in outpatients with heart failure due to left ventricular systolic dysfunction. Eur J Heart Fail 2007; 9(3): 258-65.
[32] Mahoney P, Kimmel S, DeNofrio D, Wahl P, Loh E. Prognostic significance of atrial fibrillation in patients at a tertiary medical center referred for heart transplantation because of severe heart failure. Am J Cardiol 1999; 83(11): 1544-7.
[33] Rewinski K, Wizner B, Fedyk-Lukasik M, et al. Epidemiology and management of coexisting heart failure and atrial fibrillation in an outpatient setting. Polskie Archiwum Medycyny Wewntrznej. 2011; 12(11): 392-9.
[34] Carson PE, Johnson GR, Dunkman WB, Fletcher RD, Farrell L, Cohn JN. The influence of atrial fibrillation on prognosis in mild to moderate heart failure. The V-HeFT Studies. The V-HeFT VA Cooperative Studies Group. Circulation 1993; 87(6): 676 Suppl 1:VI102-10.
[35] Hamaguchi S, Yokoshiki H, Kinugawa S, et al. Effects of atrial fibrillation on long-term outcomes in patients hospitalized for heart failure in Japan: a report from the Japanese Cardiac Registry of...
Heart Failure in Cardiology (JCARE-CARD). Circ J 2009; 73(11): 2084-90.

[36] Shotan A, Garty M, Blondhein DS, et al. Atrial fibrillation and long-term prognosis in patients hospitalized for heart failure: results from heart failure survey in Israel (HFSIS). Eur Heart J 2010; 31(3): 309-17.

[37] Waznisewich CA, Pope AJ, Somaratne J, Poppe KK, Whalley GA, Doughy RN. Atrial fibrillation and the risk of death in patients with heart failure: a literature-based meta-analysis. Int Med J 2010; 40(5): 498-501.

[38] Rich MW, McSherry F, Williford WO, Yusuf S. Effect of age on mortality, hospitalizations and response to digoxin in patients with heart failure: the DIG study. J Am Coll Cardiol 2001; 38(3): 806-13.

[39] Ahmed A, Rich MW, Love TE, et al. Digoxin and reduction in mortality and hospitalization in heart failure patients: a randomized controlled trial. Ann Intern Med 2002; 137(1): 40-50.

[40] 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. New Engl J Med 1995; 333(2): 77-82.

[41] Roy D, Talajic M, Nattel S, et al. Rhythm control versus rate control for atrial fibrillation and heart failure. New Eng J Med 2008; 358(25): 2678-77.

[42] Pedersen OD, Bagger H, Keller N, Marchant B, Kober L, Torp-Pedersen C. Efficacy of dofetilide in the treatment of atrial fibrillation-flutter in patients with reduced left ventricular function: a Danish investigation of arrhythmia and mortality on dofetilide (diadom) substudy. Circulation 2001; 104(3): 292-6.

[43] Hohnloser SH, Crijns HJ, van Eickels M, et al. Randomized trial of rate control versus rhythm control in patients with persistent atrial fibrillation: the Strategies of Treatment of Atrial Fibrillation (STAF) study. J Am Coll Cardiol 2003; 41(14): 1717-21.

[44] Kober L, Torp-Pedersen C, McMurray JJ, et al. Increased mortality after dofetilide therapy for severe heart failure. New Eng J Med 2008; 358(25): 2678-87.

[45] Van Gelder IC, Hagens VE, Bosker HA, et al. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. Results of the HOT CAFE Polish Study. Kardiologia polska 2003; 59(7): 1-16.

[46] Caldeira D, David C, Sampao C. Rate vs rhythm control in patients with atrial fibrillation and heart failure: a systematic review and meta-analysis of randomised controlled trials. Eur J Int Med 2011; 22(5): 448-55.

[47] Camm AJ, Breithardt G, Crijns H, et al. Real-life observations of clinical outcomes with rhythm- and rate-control therapies for atrial fibrillation RECORDAF (Registry on Cardiac Rhythm Disorders Assessing the Control of Atrial Fibrillation). J Am Coll Cardiol 2011; 58(5): 493-501.

[48] Guglin M, Chen R, Curtis AB. Sinus rhythm is associated with fewer heart failure symptoms: insights from the AFFIRM trial. Heart rhythm 2010; 7(5): 596-601.

[49] Guglin M, Chen R, Curtis AB. Sinus rhythm is associated with fewer heart failure symptoms: insights from the AFFIRM trial. Heart rhythm 2010; 7(5): 596-601.

[50] Deedwania PC, Singh BN, Ellenbogen K, Fisher S, Fletcher R, Singh SN. 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.

[51] Shelton RJ, Clark AL, Goode K, et al. A randomised, controlled study of rate versus rhythm control in patients with chronic atrial fibrillation and heart failure: (CARE-II Study). Heart 2009; 95(11): 924-30.

[52] Kuntz T, Motoki K, Yasuoka R, et al. Rhythm control should be better for the management of patients with atrial fibrillation and heart failure--rhythm control vs. rate control: which is better in the management of atrial fibrillation? (Rhythm-side). Circ J 2011; 75(4): 979-85.

[53] Leon AR, Greenberg JM, Kanuru N, et al. Cardiac resynchronization in patients with congestive heart failure and chronic atrial fibrillation: effect of biventricular pacing on heart failure and long-term right ventricular pacing. J Am Coll Cardiol 2002; 39(8): 1258-63.

[54] Walls-Bertault V, Fatemi M, Gilard M, Penney PY, Etienne Y, Blane JJ. 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.

[55] Hohnloser SH, Crijns HJ, van Eickels M, et al. Comparative assessment of rate, left, and biventricular pacing in patients with permanent atrial fibrillation. Eur Heart J 2005; 26(7): 712-22.

[56] Luedorf G, Grove R, Kowalski M, Woffl E, Thale J, Kranig W. Impact of chronic atrial fibrillation in patients with severe heart failure and indication for CRT: data of two registries with 711 patients (1999-2006 and 2007-6/2008). Herz Elektrophys 2011; 22(4): 226-32.

[57] Hamdan MH, Freedman RA, Gilbert EM, Dimarco JP, Ellenbogen KA, Page RL. Atrioventricular junction ablation followed by rate control was associated with better heart failure and atrial fibrillation (AVERvation-ATF) study design. Pacing clin electrophysiol 2006; 29(10): 1081-8.

[58] Eo J, Jais P, Sanders P, et al. Catheter ablation for atrial fibrillation in congestive heart failure. New Eng J Med 2004; 351(23): 2373-83.

[59] Tondo C, Mantica M, Russo G, et al. Pulmonary vein vestibule ablation for the control of atrial fibrillation in patients with impaired left ventricular function. Pacing clin electrophysiol 2006; 29(9): 962-70.

[60] 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.

[61] Gentlesk DJ, Sauer WH, Gerstenfeld EP, et al. Comparison of left ventricular dysfunction improving biventricular pacing of atrial fibrillation. J Cardiovasc Electrophysiol 2007; 18(1): 9-14.

[62] Khan MN, Jais P, Cummings J, et al. Pulmonary-vein isolation for atrial fibrillation in patients with heart failure. New Eng J Med 2008; 359(17): 1778-85.

[63] Dagres N, Varounis C, Gaspar T, et al. Catheter ablation for atrial fibrillation in patients with left ventricular systolic dysfunction. A systematic review and meta-analysis. J Card Fail 2011; 17(11): 964-70.

[64] Khargi K, Hutton BA, Lemke B, Deneke T. Surgical treatment of atrial fibrillation: a systematic review. Eur J Cardiothorac 2005; 27(2): 258-65.

[65] Ad N, Henry L, Hunt S. The impact of surgical ablation in patients with low ejection fraction, heart failure, and atrial fibrillation. Eur J Cardiothorac 2011; 40(1): 70-6.

[66] Wasmert K, Eckardt L. Management of atrial fibrillation around the world: a comparison of current ACC/AHA/HRCS, CESC, and ESC guidelines. Europace 2011; 13(10): 1368-74.

[67] Tzes S, Andrikopoulos G. Novel anticoagulants for atrial fibrillation: a critical appraisal. Angiology 2012; 63(3): 164-70.
Atrial Fibrillation of the European Society of Cardiology (ESC). Eur Heart J 2010; 31(19): 2369-429.

[75] Cairns JA, Connolly S, McMurry S, Stephenson M, Talajic M. Canadian Cardiovascular Society atrial fibrillation guidelines 2010: prevention of stroke and systemic thromboembolism in atrial fibrillation and flutter. Can J Cardiol 2011; 27(1): 74-90.

[76] Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. New Engl J Med 2011; 365(10): 883-91.

[77] Lopes RD, Alexander JH, Al-Khatib SM, et al. Apixaban for reduction in stroke and other Thromboembolic events in atrial fibrillation (ARISTOTLE) trial: design and rationale. Am Heart J 2010; 159(3): 331-9.

[78] Savelieva I, Camm AJ. Statins and atrial fibrillation: do we need a further study? Exp Rev Cardiovasc Ther 2011; 9(7): 801-4.

[79] Savelieva I, Kakouros N, Kourliouros A, Camm AJ. Upstream therapies for management of atrial fibrillation: review of clinical evidence and implications for European Society of Cardiology guidelines. Part I: primary prevention. Europace 2011; 13(3): 308-28.

[80] Savelieva I, Kakouros N, Kourliouros A, Camm AJ. Upstream therapies for management of atrial fibrillation: review of clinical evidence and implications for European Society of Cardiology guidelines. Part II: secondary prevention. Europace 2011; 13(5): 610-25.

[81] Bhuriya R, Singh M, Sethi A, et al. Prevention of recurrent atrial fibrillation with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers: a systematic review and meta-analysis of randomized trials. J Cardiovasc Pharm 2011; 16(2): 178-84.