Atrial fibrillation in patients with systolic heart failure: pathophysiology mechanisms and management

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ABSTRACT Heart failure (HF) and atrial fibrillation (AF) demonstrate a constantly increasing prevalence during the 21st century worldwide, as a result of the aging population and the successful interventions of the clinical practice in the deterioration of adverse cardiovascular outcomes. HF and AF share common risk factors and pathophysiological mechanisms, creating the base of a constant interrelation. AF impairs systolic and diastolic function, resulting in the increasing incidence of HF, whereas the structural and neurohumoral changes in HF with preserved or reduced ejection fraction increase the possibility of the AF development. The temporal relationship of the development of either condition affects the diagnostic algorithms, the prognosis and the ideal therapeutic strategy that leads to euvolaemia, management of non-cardiovascular comorbidities, control of heart rate or restoration of sinus rate, ventricular synchronization, prevention of sudden death, stroke, embolism, or major bleeding and maintenance of a sustainable quality of life. The indicated treatment for the concomitant HF and AF includes rate or/and rhythm control as well as thromboembolism prophylaxis, while the progress in the understanding of their pathophysiological interdependence and the introduction of the genetic profiling, create new paths in the diagnosis, the prognosis and the prevention of these diseases.

Heart failure (HF) and atrial fibrillation (AF) have become epidemics of the 21st century, as a result of the increased longevity and the successful reduction of the cardiovascular (CV) mortality. The prevalence of both conditions is constantly rising, increasing significantly the cost of treatment to the healthcare systems worldwide. It is estimated that the incidence of AF (2%) is double compared to the last decade. AF is present in 0.12%–0.16% of those < 49 years of age, in 3.7%–4.2% of those aged 60–70 years, and in 10%–17% of those aged ≥ 80 years, occurring more frequently in males, with a male to female ratio of 1:2.1. By the year 2030 in Europe alone it is estimated that the patients with AF will be 14–17 million, with an annual number of 120–215,000 new cases, while the prevalence in the American population will be 12 million. HF affects approximately 1%–2% of adults in developed countries. Few individuals under 50 years of age are diagnosed with HF, whereas the prevalence in those aged 75 years or above is more than 10%. The prevalence of HF globally in AF individuals is 33% in patients with paroxysmal AF, 44% in those with persistent and 56% in those with permanent AF. Among the 5.8 million US adults with heart failure with reduced ejection fraction (HFrEF) or preserved EF (HFpEF), the prevalence of AF is up to 40%. It is clear that the combination of these two conditions will have a significant impact on healthcare and the management of cardiovascular (CV) disease as it is performed so far. The pathophysiology and risk factors for HF and AF are closely related and the coexistence of HF and AF affects elderly patients with a significant burden of comorbidities. The development of AF is connected with complex interactions that lead to impairment of systolic and diastolic function, that are not present in sinus rhythm (SR), resulting in a three-fold increased risk of HF incidence compared with SR. Conversely, the structural and neurohumoral changes in HF increase the possibility of the AF incidence both in HFrEF and in HFpEF. Previous studies have also demonstrated differences in atrial remodeling, prognosis and outcomes associated with AF development among the HF subtypes, with greater eccentric LA remodeling in HFrEF, and increased LA stiffness in HFpEF predis-
posing more evidently in AF.\textsuperscript{[19]} Regardless which condition develops first, their combined incidence is associated with a worse prognosis than either condition alone.\textsuperscript{[20–22]} Concerning the adverse outcomes that are associated with HF and AF, an important target of clinical studies is the development of effective therapies for these patients but also an arduous one as the so far applied treatments on either of these conditions alone are shown to be effective or provoke safety concerns in patients with HF and AF.\textsuperscript{[23, 24]}

**PATHOPHYSIOLOGY IN THE INTERDEPENDENCE OF AF AND HF**

HF and AF share common risk factors and pathophysiological pathways.\textsuperscript{[12]} There are several risk factors with a significant prognostic value to the development and management of these two cardiovascular diseases: age, alcohol, hypertension, obesity, diabetes mellitus, coronary artery disease, valvular heart disease, chronic kidney disease, B-type natriuretic peptide (BNP) and N-terminal pro hormone BNP (NT-proBNP), high sensitivity troponin T or I, sleep apnoea, tobacco use, genetic factors, anemia.\textsuperscript{[25–28]} In HF, neurohormonal imbalance and activation of the renin–angiotensin–aldosterone system (RAAS) leads to inappropriate physiological changes: increased filling pressures and afterload, increased left atrial strain and fibrosis, proarrhythmic remodeling and conduction abnormalities and finally development and maintenance of AF.\textsuperscript{[29–34]} Patients with HF also demonstrate dysregulated calcium handling and calcium overload, which can result in after-depolarizations and arrhythmias.\textsuperscript{[35]} In AF, loss of atrial systole impairs LV filling and can decrease cardiac output by up to 25\%, especially in patients with diastolic dysfunction.\textsuperscript{[36]} Irregular and/or rapid ventricular conduction in AF can lead to LV dysfunction or in some cases in a tachycardia-induced cardiomyopathy.\textsuperscript{[36, 37]} Restoration of sinus rhythm restores these maladaptations and even before contractility improves, a significant haemodynamic improvement occurs rapidly in patients with HF that undergo cardioversion.\textsuperscript{[38]}

**HF Induces AF**

HF remodeling adjustments predispose to the development and maintenance of atrial arrhythmias, and more specifically changes that lead to a decreased atrial refractory period, slowed atrial conduction, or increased heterogeneity of atrial repolarization take place.\textsuperscript{[39, 40]} These changes include hemodynamic, neurohormonal alterations, cellular and extracellular remodeling.\textsuperscript{[39, 40]} The increased atrial pressure and volume associated with the HF development may result in “tissue stretch” and further causing changes in atrial refractory properties and enhancing triggered activity.\textsuperscript{[41]} In a canine model atrial stretching reduced atrial refractory period, prolonged atrial conduction times, and increased frequency of spontaneous atrial arrhythmias.\textsuperscript{[42]} Atrial chamber enlargement and hypertrophy also act as arrhythmogenic mechanisms by increasing automaticity and heterogeneity of depolarization and repolarization.\textsuperscript{[43]} Moreover, the neurohormonal alterations that characterize the development of HF, affect the synthesis and degradation of the extracellular matrix, predisposing to the development of AF.\textsuperscript{[41, 43, 44]} For example, the activation of renin–angiotensin–aldosterone system (RAAS) induces extracellular matrix fibrosis,\textsuperscript{[31]} as a result of an increase in angiotensin II.\textsuperscript{[41]} The rapid atrial pacing in a HF-induced canine model resulted in extensive interstitial fibrosis\textsuperscript{[45]} which can further lead to heterogeneity of atrial repolarization as a result of the existence of areas of slow conduction contributing eventually to the development of AF.\textsuperscript{[39, 40, 45]} Angiotensin-converting enzyme inhibitors (ACEIs) seem to reduce the adverse changes in atrial conduction and the amount of atrial fibrosis observed in these canine models, while such changes are not observed with hydralazine and nitrates.\textsuperscript{[34]} The downregulation of atrial pacing normalizes the atrial functioning in canine models, atrial fibrosis and conduction abnormalities, however, continuous or rapid pacing predisposed to AF.\textsuperscript{[46]} Additionally, activation of the sympathetic nervous system, also can contribute to the development of AF by having an effect on atrial refractory properties.\textsuperscript{[41]} Experimental HF models induced by rapid pacing resulted in atrial ion channel remodeling, causing alterations of various ion currents within the myocardium,\textsuperscript{[39, 47]} with the most evident being the substantial increase in Na\(^+\)/Ca\(^{2+}\) exchanger current in the atrium\textsuperscript{[47, 48]} which could cause an increase in delayed afterde-
polarizations and triggered activity. The development of atrial premature beats promotes arrhythmogenesis and results in AF. Conduction velocity and atrial refractoriness could also be affected by other changes in the ion channels, such as reduced L-type Ca\(^{2+}\) current and reduced potassium currents, especially transient outward K\(^+\) current (I_{to}), and slow delayed rectifier current (I_{Ks}). Patients with HFrEF present with increased left atrial diameter, decreased left atrial function, and increased left atrial stiffness in comparison with healthy controls. Patients with HFrEF present with atrial remodeling and higher possibility of AF incidence. Despite the evidence of atrial ion channel remodeling occurring due to HF, the mechanisms that lead to arrhythmogenesis in humans remain theoretical.

**AF induces HF**

The development of AF may be initially associated with a decrease in cardiac output. Patients with severe HF and AF present with reduced stroke volume, cardiac output, peak oxygen consumption, and peak workload, in comparison with those with SR. Deregulation of atrioventricular synchrony can lead to impaired diastolic filling, reduced stroke volume, increased mean diastolic atrial pressure, and an approximately 20% reduction in cardiac output, as well as irregular ventricular response (R-R irregularity) occurring during AF may impair ventricular function and overall hemodynamic status. Irregular ventricular response results in decreased cardiac output, elevated right atrial pressure and pulmonary capillary wedge pressure independent of the rate. Chronic elevation in filling pressures may also lead to impairment of volume homeostasis and consecutively to fluid retention and further filling pressure elevation. AF also provokes cellular and extracellular remodeling, a significant predisposing factor to HF. Animal models of AF suggest that significant changes in ion channel function have an impact in atrial conduction and repolarization and can preserve the maintenance of AF. There is evidence that reduced L-type Ca\(^{2+}\) current is both a result of AF and essential to its maintenance. Changes in integral membrane ion channel proteins named connexins, responsible for cell-to-cell conduction and communication, have been reported in rapid pacing models of AF. Atrial natriuretic peptide levels are higher in patients with AF, the chronic atrial atrophy and fibrosis though lead to a gradual decrease in these levels. Patients with coexisting advanced HF and AF have higher levels of atrial natriuretic peptide and endothelin compared to individuals with HF and SR. These cellular and extracellular mechanisms in the maintenance of AF or contribution to HF, however, are still speculative. According to studies, left atrial fibrosis, stretch, and denervation, as well as the eventual downregulation of natriuretic peptides that occur in AF, can aggravate both HFrEF and HFrEF. However, other causal links between HF and AF likely differ between HF subtypes and they should be evaluated respectively. Neurohormonal activation is more intense in HFrEF subtype and may be amplified later by the rapid rate and irregularity of AF. In contrast, inflammation may be initially more relevant to the metabolic pathways that are associated with the development of HFrEF, but immune activation, however, increases according to the severity of the cardiac disease in both HFrEF and HFrEF. Tachycardiomyopathy is a type of cardiomyopathy that is a result of rapidly conducted AF. The development and resolution of tachycardiomyopathy caused by AF are linked with HFrEF due to the changes in LVEF, whereas there are no significant indicators considering HFrEF. HFpEF distinction and staging is complicated due to distinct phenotypes related to the existence or not of obesity and baseline venous congestion that lead in a variable way to further diastolic dysfunction, dyspnea, and hospitalizations.

The data occurring from studies on randomized hospital-based cohorts cannot often depict the connection between AF and HF. The association of AF with HFpEF and HFrEF was assessed in a large, community-based cohort, consisting of Framingham Heart Study participants with new-onset AF and/or HF between 1980 and 2012, targeting to the evaluation of the differences in the temporal associations between HFpEF and HFrEF events in relation to AF incidence, the chronicity of HF and AF and the risk of mortality among participants with various AF and HF subtypes. Among 1,737 individuals with new AF 37% had HF. Among 1,166 in-
Individuals with new HF, 57% had AF, most of them developing HF after AF onset. Prevalent AF had a stronger association with incident HFpEF (multivariable-adjusted hazard ratio [HR] = 2.34, 95% confidence interval [CI]: 1.48–3.70) compared to HFrEF (HR = 1.32, 95% CI: 0.83–2.10). Whereas, prevalent HF was associated with incident AF (HR = 2.18, 95% CI: 1.26–3.76). The presence of both AF and HF was related with higher mortality risk compared with a group of healthy individuals, particularly among those with new HFrEF and prevalent AF (HR = 2.72, 95% CI: 2.12–3.48) in comparison with new HFpEF and prevalent AF (HR = 1.83, 95% CI: 1.41–2.37). According to previous studies the incidence of HF after AF is nearly double that of stroke, indicating the need for future HF prevention strategies similarly to the way that stroke prevention strategies are applied after the development of AF. Another population-based study in the Olmsted County cohort examined the temporal relationship of AF and HFpEF. Similar to the results of the previous mentioned study, over half of individuals with HFpEF developed AF demonstrating a worse prognosis compared with those that developed AF prior to or concurrent with HFpEF presentation.

The mechanisms by which AF varies among HF subtypes remain speculative. The similar risk of developing future AF in both individuals with HFpEF and HFrEF may reflect elevation in atrial pressures and remodeling in both types of HF. Melenovsky et al studied individuals with HF, and demonstrated that LA remodeling was distinct among HF subtypes: eccentric LA remodeling was observed in HFrEF, and greater LA stiffness occurred in HFpEF, suggesting that greater stiffness may contribute to greater AF burden seen in HFpEF. Other studies have supported that diastolic dysfunction, a precursor of HFpEF, is connected with the incidence of AF. This association may occur from the similar underlying mechanisms driving AF and HFpEF development, including myocardial inflammation and interstitial fibrosis.

**Tachycardia-induced cardiomyopathy**

Tachycardiomyopathy is a complication of AF, with a prevalence of 3%–25% in patients with atrial tachyarrhythmias. Among the mechanisms by which AF can beget HF the most notable is the reduction in ventricular function secondary to a rapid ventricular response. Experimental HF secondary to rapid pacing in animal models, demonstrated initially a reduction in cardiac output in the first 24 h, with a proceeding worsening of cardiac output and AF for up to 5 weeks. Suspension of pacing leads to an improvement of left ventricular ejection fraction (LVEF) within 24 h and a restoration to control levels within some weeks. Individual myocytes still presented abnormalities and there were indications for diastolic dysfunction even after 4 weeks following the recovery. The severity of the cardiomyopathy is found to be related to the duration and rate of pacing, e.g., an arrhythmic tachycardia occurring 10% to 15% of the day may impair ventricular function. There are multiple mechanisms suggested that contribute to this impairment: (1) myocardial energy depletion, including depletion of high-energy phosphates, such as adenosine triphosphate (ATP); (2) mitochondrial structural and functional abnormalities; (3) myocardial ischemia, even in patients with no prominent flow-limiting epicardial stenoses, including abnormal subendocardial to subepicardial flow ratios and impaired coronary flow reserve. Repeated or persistent rapid heart rates could result in ischemia, which even of mild severity could cause myocardial cell necrosis, myocardial stunning and reversible ventricular dysfunction, (4) abnormal calcium handling as it has been observed in experimental models presenting an abnormal calcium channel activity and abnormal sarcoplasmic reticulum calcium transport, however the exact mechanism of impairing LVEF is still not clear. There are also some hypotheses on decreased calcium sensitivity, abnormal excitation-contraction coupling, or altered calcium kinetics that could contribute to the worsening of ventricular function, and (5) cellular and extracellular matrix remodeling with evidence on the development of myocyte malalignment, myocyte loss, contractile dysfunction, and alteration of the basement membrane–myocyte interface to be associated with negative effects on mechanical contractile performance.

A clinically important fact regarding tachycardia-induced myopathy is that the control of ventricular rate can have significant results in cardiomyopathy,
leading even to its complete resolution in selected patients, as the possibility of complete, partial and nonexistent recovery is affected by variable factors such as the duration of the tachycardia and the coexistent cardiac disease. The quickest response in the restoration of ventricular rate is reported in the first weeks after the correction of tachycardia, presented with a ventricular improvement, followed by a period of slow improvement for up to 6 to 8 months. Resolution of chronic tachycardia improves symptoms, exercise capacity, and LVEF along with a marked reduction in the left ventricular end-systolic diameter. The detection of the tachycardia-induced ventricular dysfunction requires high index of suspicion, as the clinical evidence of progressive ventricular damage is not always sufficient to lead to the correct diagnosis. While the diagnosis could be considered in a patient with no history of cardiovascular diseases, who presents with new-onset HF in the setting of AF with rapid ventricular conduction, the primary exclusion of the other causes of ventricular dysfunction is most significant such as ischemia as well as other nonischaemic cardiomyopathy indicators (e.g., left ventricular hypertrophy, alcohol/drug use, infiltrative disorders, etc). Patients undergoing cardioversion with rapid AF at baseline showed normalization of atrial transport function within one week, restoration of left ventricular function and peak oxygen consumption was observed in weeks or months, indicating that the resolution of the cardiomyopathy is the key factor in the management. Similar findings have been reported in patients undergoing atioventricular junction ablation.

ATRIAL FIBRILLATION AND HEART FAILURE IN WOMEN

The coexistence of AF and HF may lead to poor cardiovascular outcomes. Preexisting AF was associated with a higher 3-year risk of all-cause mortality and hospital readmissions for stroke and HF in both men and women. A meta-analysis of 30 cohort studies demonstrated that AF is connected with a higher relative risk of cardiovascular and all-cause mortality, stroke, and HF in women compared with men. In AF participants in the Framingham Heart Study, the incidence of HF was associated with almost three times higher rates of mortality in both men and women. However, in HF subjects, the incidence of AF was associated with a 60% increase in mortality in men but a 170% increase in mortality in women. In the Women’s Health Study, of the 34,000 postmenopausal women who did not have history of cardiovascular disease at baseline, 1495 developed AF after a median follow-up of 20.6 years. Women with new-onset AF had a 9-fold higher risk of developing HF and eventually those who developed HF had a significant increase in all-cause mortality (HR = 1.83, 95% CI: 1.37–2.45) and cardiovascular mortality (HR = 2.87, 95% CI: 1.70–4.85). Modification of risk factors (smoking, obesity, hypertension, and diabetes) accounted for risk of HF in women with AF, may lower HF risk in women with AF.

The multiple risk factors that affect the possibility of concurrent development of HF and AF may cause changes in the structural and electrical properties of the heart and have different effects in men compared with women. Women have smaller hearts, higher resting left ventricular ejection fraction, longer baseline repolarization corrected QT intervals and the occurrence of coronary microvascular dysfunction is more frequent. Epidemiologic studies show that the lifetime risk of developing HFpEF was slightly higher for women, whereas, compared with women, men had a higher risk of developing HFrEF < 40%. In Framingham Heart Study, men had a higher incidence of HFrEF, but women had a similar incidence of HFpEF and HFrEF. In clinical studies, women have been found to develop HFpEF more often than men. Old age, hypertension, and sleep apnea are significant risk factors to the development of both AF and HFpEF.
utive AF patients hospitalized with heart failure developed AF before or at the same time as HF.\textsuperscript{194} Similarly, other population studies observed that between 59\% and 76\% of AF and HF patients develop AF before or simultaneously with HF.\textsuperscript{82, 95} Patients where the occurrence of AF was first had a better clinical profile and less adverse outcomes than patients with first occurrence of HF, as it is also described in a study by Chamberlain et al.\textsuperscript{82}

In ‘AF first’ patients, AF itself may trigger the development of HF through functional changes: an irregular and rapid rhythm, loss of atrioventricular synchrony, and loss of atrial transport, or structural changes such as gradual cellular and extracellular matrix remodelling in atria and ventricles.\textsuperscript{96–100} In the case of functional changes ventricular dysfunction may be reversible\textsuperscript{101}, an observation connecting this pathophysiology with the more benign prognosis that is associated with tachycardia-induced cardiomyopathy.\textsuperscript{94} The higher ejection fractions and more frequent presence of HFpEF imply that ‘AF first’ patients had significant diastolic HF.\textsuperscript{17, 67, 102} Interestingly, AF has been associated with a greater risk of major adverse events in patients with HFpEF than in patients with HFrEF.\textsuperscript{67, 102}

In ‘heart failure first’ patients, where severe structural remodeling than significant functional changes were predominant, a longer HF history is reported.\textsuperscript{94} ‘HF first’ patients with a history of ischaemic cardiomyopathy, developed AF late during the progress of the disease.\textsuperscript{94} An acute non-cardiac cause of the HF hospitalization was significantly more often present in ‘AF first’ patients implying that the development of HF was reversible after treatment of the precipitating cause, while the absence of an acute precipitating factor could connect the hospitalizations with a progression of the disease in ‘heart failure first’ patients. Additionally, the development of AF in patients with a long HF history could be a marker of progression of the underlying disease.\textsuperscript{82, 103–105} AF patients with HF seem to have less extensive underlying disease and a better outcome, while HF patients who develop AF have more severe underlying disease and increased risk of a worse outcome.\textsuperscript{106–108}

It is still uncertain whether AF is an independent contributor to a worse outcome in HF or whether it is a marker of severe disease. Wang et al. based on data from the Framingham study showed that prevalent HF adversely affected survival in patients developing AF, as it was linked with increased mortality, while prevalent AF was not associated with adverse survival in HF patients.\textsuperscript{82} On the contrary, in the Groningen study, AF first patients were not presenting with an event free prognosis, the reason of these changes can be probably attributed to the different patient populations and the HF definitions used.\textsuperscript{95}

**Mortality**

AF is connected with increased mortality in patients with underlying cardiac disease\textsuperscript{109} and patients with coexisting HF and AF have a worse prognosis.\textsuperscript{20, 110–112}

The SOLVD Prevention Trial and Treatment Trial studied 6,517 patients with HF, including 419 patients with AF, and a median follow up of almost 3 years.\textsuperscript{20} Patients with baseline AF had greater all-cause mortality than patients with baseline sinus rhythm (34\% vs. 23\%; \(P < 0.001\)), independent of age, LVEF, NYHA functional class, and medication use.\textsuperscript{20} The multivariate relative risk (RR) of death for patients with AF in comparison with those with sinus rhythm was 1.34 (1.12 to 1.62).\textsuperscript{20} Patients with AF also revealed a higher risk of death as a result of pump failure (16.8\% vs. 9.4\%, \(P < 0.001\), RR = 1.42 \([1.09 \text{ to } 1.85]\)), with no difference observed in the rate of arrhythmic death.\textsuperscript{20}

The Digitalis Investigations Group (DIG) trial demonstrated increased mortality rates among patients with supraventricular tachyarrhythmias.\textsuperscript{111} The trial included 7,788 HF patients with an average follow up of 38 months. Eight hundred and sixty patients (11.1\%) had supraventricular tachyarrhythmias, including those with AF, the prevalence of which demonstrated a greater risk of mortality (RR = 2.45 \([2.19 \text{ to } 2.74]\)) and a greater risk of hospitalization for HF complications (RR = 3.00 \([2.71 \text{ to } 3.33]\)).\textsuperscript{111}

Middlekauf, et al.\textsuperscript{112} evaluated 390 HF patients with NYHA functional class III–IV and mean LVEF of 0.19 between 1983 and 1990. A total of 75 patients (19.2\%) had AF and it was proven an independent predictor of sudden death and total mortality.\textsuperscript{112} Additionally, AF was found to be predictive among patients with a pulmonary capillary
wedge pressure < 16 mmHg on therapy and possibly a limited prognostic value reported in those with an elevated pulmonary capillary wedge pressure despite therapy.\cite{41}

Aronow, et al.\cite{110} studied 296 patients with a mean age > 80 years with prior myocardial infarction and HFpEF. The 6-month mortality was increased in patients with AF compared with those in sinus rhythm (11% vs. 2%; P < 0.001), suggesting that in patients with HF, AF is associated with increased mortality regardless of the preserved or reduced left ventricular ejection fraction.\cite{110}

In contrast to the results from the previous mentioned studies, the Vasodilator in Heart Failure Trial (V-HeFT) studied 1,427 HF patients for an average of 2.5 years with NYHA functional class II–III.\cite{113} The rates of sudden death and total mortality were not significantly increased in the 206 AF patients (14.4%) compared with those in sinus rhythm.\cite{113}

Crijns, et al.\cite{114} studied 409 HF patients with NYHA functional class III–IV and compared patients with baseline sinus rhythm to those with baseline AF (n = 84) in a mean follow-up of 3.4 years. Among the 203 patients (50%) that died, total mortality was higher in patients with AF compared to those with sinus rhythm (60% vs. 47%), but there were no significant differences in the mortality after adjusting for age, LVEF, NYHA functional class, renal function, and blood pressure concluding that AF had no significant prognostic value in the mortality of the patients with HF. Several other studies that enrolled < 250 patients did not reach the conclusion that AF was an independent predictor of mortality in patients with HF, as the small numbers of the individuals observed were not able to determine any small or moderate effects of AF on the total mortality.\cite{115–117}

The prognostic significance of AF varies according to the clinical setting in which it occurs.\cite{112} AF in the absence of detectable cardiac disease is a relatively benign condition with excellent prognosis.\cite{118,119} In the Framingham Study in a population with adverse cardiac diseases, AF was associated with twice the cardiovascular mortality compared with patients with sinus rhythm.\cite{120} The presence of AF at the time of acute myocardial infarction is linked with a decrease in short- and long-term survival\cite{121–124}, whereas AF is not affecting the prognosis of acute myocardial infarction when other predictive factors are considered.\cite{19,10,11,14} In a study of more than 18,000 patients with coronary artery disease and varied ventricular function, AF was an independent risk factor for decreased survival, however with no separate analysis of the risk factors in the subgroups of HF.\cite{125} In studies of small populations of patients with idiopathic dilated cardiomyopathy, AF has been independently associated with decreased survival in some reports.\cite{126–130} In one study of 69 and another of 144 nonischemic dilated cardiomyopathy patients with LVEF < 0.50, AF was an indicator of decreased survival in univariate but not multivariate analysis.\cite{128,129} In a study of 110 idiopathic cardiomyopathy patients with LVEF < 0.55, AF was an independent predictor of sudden and HF deaths\cite{126} , whereas in studies of 111 and 169 patients with idiopathic dilated cardiomyopathy and mean LVEF = 0.30, AF was not associated with poor prognosis.\cite{131,132} Convert et al. studied 130 HF patients with mean LVEF = 0.30, where it was observed that AF was a good prognostic sign.\cite{130} Similarly, in a small population of advanced HF patients with a median LVEF 0.16 and a median pulmonary capillary wedge pressure = 25 mmHg, Keogh, et al. showed that AF was not a risk factor for decreased survival, without including however the patients with paroxysmal AF.\cite{112} A study on overall survival and sudden death was performed in 390 advanced HF patients, where coronary artery disease as a cause for HF was reported in 177 patients (45%) and nonischemic cardiomyopathy or valvular heart disease in 213 patients (55%), with a mean left ventricular ejection fraction of 0.19 ± 0.07, and a total of 75 patients (19%) were diagnosed with paroxysmal (26 patients) or chronic (49 patients) AF.\cite{112} AF was reported to be a significant marker for increased risk of death in HF patients with lower filling pressures on vasodilator and diuretic therapy, however an aggressive maintenance of SR was not associated with a reduction in this risk and remained unknown.\cite{112}

The discrepancies mentioned above can be summarized in the suggestion that, in patients with the most advanced ventricular dysfunction as it is presented by elevated pulmonary capillary wedge pressure on therapy, AF was not associated with further decrease in the survival rate, but in those with lower pulmonary capillary wedge pressure on
therapy, indicating a better ventricular function, AF was associated with a greater risk of sudden death.\textsuperscript{[112]}

The decreased survival in AF compared with sinus rhythm patients in those who achieved low pulmonary capillary wedge pressures but not in those whose pressures could not be lowered to that degree, may be revealing. It is assumed that any additional left ventricular impairment caused by the presence of AF is relatively insignificant in the patients with the most impaired ventricular function, whereas in patients with low pulmonary capillary wedge pressure and a relatively more favorable prognosis, the additional functional impairment may be important.\textsuperscript{[112]}

**Thromboembolic Events**

Another possible explanation for the decreased survival in AF is that it could increase the prevalence of fatal thromboembolic events. The embolic risk from AF may be further confounded by embolic events occurring from clots originating within the dilated ventricles.\textsuperscript{[112]} In addition, AF may contribute to the development of ventricular tachyarrhythmias in advanced HF by provoking dispersion of refractoriness within the ventricle via long-short sequences of ventricular depolarization, as it has been showed through electrophysiological studies.\textsuperscript{[133, 134]} Interestingly, sudden death risk rate was not decreased in paroxysmal AF patients comparing to those with chronic AF patients, indicating the role of AF in advanced HF as an indicator of underlying sinus node disease.\textsuperscript{[135]} Embolic risk may be highest soon after onset of AF or during reversion to sinus rhythm in patients with paroxysmal AF, indicating the adverse effect that the conversion in and out of AF may have in the embolism-associated sudden death in those patients.\textsuperscript{[136–141]}

The higher risk of stroke in patients with HFpEF than in those with HFrEF was investigated in the PRESERVE study (Atrial Fibrillation and Outcomes in Heart Failure With Preserved vs Reduced Left Ventricular Ejection Fraction)\textsuperscript{[22]} of 23,644 patients with a discharge diagnosis of congestive HF. In this study, 48.3\% of patients had a supplementary diagnosis of AF (9081 preexisting, 2348 incident). Patients with preexisting AF and HFpEF had a higher risk of stroke than HFrEF patients. Furthermore, patients with incident AF and HFpEF had the highest risk of stroke compared with patients with HFrEF or those with preexisting AF.\textsuperscript{[22]}

The Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist Trial (TOPCAT) found that the connection between incident AF and hospitalization was stronger in women than in men (63\% vs. 37\%) and in patients with AF, the estimated risk for all adverse cardiovascular events (hospitalization for stroke, death, HF, and cardiovascular death) were higher in women than in men.\textsuperscript{[142]}

The sub-study of Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial showed that, among patients with AF, women had a higher risk of stroke compared with men, even when treated with warfarin. In this study women spent more time outside or were below the therapeutic range and even those who maintained a score within the therapeutic range (≥ 66\%), they still had higher ischemic stroke rates than men ($P = 009$).\textsuperscript{[143]} These sex discrepancies were not observed in the use of novel anticoagulants. A metaanalysis evaluating the risk of stroke and major bleeding in male and female patients treated with warfarin compared with those treated with novel anticoagulants showed similar decreased risk of stroke in men and women, when they were treated with novel anticoagulants.\textsuperscript{[144]} Despite these results, the Practice INNovation And C linical Excellence (PINNACLE) Registry (2008–2014) reported that women with AF were significantly less likely to receive oral anticoagulants than men at all levels of the CHA2DS2- VASC risk evaluation score.\textsuperscript{[145]} The 2014 AF guidelines recommendation of using female sex as a risk factor may further increase the use of anticoagulants in women.\textsuperscript{[146]}

**Risk of Cognitive Decline in Patients with AF and HF**

Improved life quality of patients with cardiovascular diseases has led to a growing elderly population. This aging population, along with the increase in the prevalence of AF and HF will possibly lead to an increase in the number of patients presenting to their physicians with symptoms of cognitive decline and dementia.\textsuperscript{[147, 148]} AF has been linked to an increase in the risk of dementia and cognitive decline, but also to an increase in the risk of progres-
sion to dementia in individuals with mild cognitive impairment.149,150 This could be explained by the impaired atrial contraction, reduced cardiac output, low cerebral blood flow, “silent” or “mini” strokes that occur in AF patients, and increased expression of key molecules involved in the pathogenesis of Alzheimer’s disease.151,152 Sex differences in cognitive impairment have recently been reported in the Framingham Heart Study, where men with AF at baseline had worse performance in tests of abstract reasoning and executive function in comparison with women.153 Epidemiologic studies have also reported direct associations between exacerbation of HF and cognitive decline.150,154−156 There is too few or no literature regarding sex differences associated with cognitive decline and the presence of HF.165 Because of the clinical importance of HF and its adverse complications, it is imperative that standardized cognitive assessment tools should be used in clinical and research studies to evaluate cognitive functioning in the aging cardiac population.84

MANAGEMENT OF CONCOMITANT HF AND AF

Frequently in the clinical practice, clinicians often manage patients with combined HF and AF by focusing on therapeutic aspects that are evidence-based in one or the other of these conditions:

HF management targets: achievement of a good haemodynamic condition, less RAAS activation, deterioration of non-CV comorbidities, control of heart rate, RV-LV synchronization, prevention of sudden death and inotropic-mechanical support, keeping as a last option transplantation and mechanical support of circulation.12

AF management targets: prevention of stroke and embolism, control of rapid heart rate, deterioration of non-CV comorbidities, restoration of SR, prevention of HF, prevention of major bleeding.12 There is a cycle of interdependence between HF and AF and each makes the other more likely to occur, therefore a simple clinical mnemonic for the initial management of newly diagnosed concomitant HF and AF has been suggested. The CAN-TREAT HFrEF + AF algorithm clarifies the management of patients with concomitant HF and AF.12 The presence of haemodynamic instability should be managed with cardioversion (C). Anticoagulation (A) should be used to prevent thromboembolism, and diuretic therapy to normalize (N) fluid balance and symptoms of HF. Additional therapy should target (T) a heart rate < 110 beats/min and act antagonistically to RAAS (R). Finally, early (E) rhythm control in patients where rate control is not effective, and advanced (A) HF therapies should follow (e.g., cardiac resynchronization therapy), with effective treatment (T) of other coexisting CV disease, most importantly of ischaemia and hypertension.12

AF is the most common arrhythmia in HF regardless of the reduced LVEF development, as it increases the risk of embolism and the subsequent complications (particularly stroke) and may lead to further impairment of cardiac function, exacerbating the condition of HF.157 Incident HF in existing AF is associated with a more benign prognosis but new-onset AF in a patient with established HF is associated with a worse prognosis.158,159 Patients with chronic HF and permanent AF have worse prognosis than those in SR, although this group involves older patients with severe HF.158,159 Persistent ventricular rates > 150 beats/min may cause HFpEF that could be resolute with the use of rate control or rhythm correction (‘tachycardiomyopathy’).160,161 AF should be classified and managed according to the duration of the episodes, even when these cannot be fully determined and the possibility of previous undetected ones, (i.e., first diagnosed episode, paroxysmal, persistent, long-standing persistent or permanent).166

Moreover, in a HF patient presenting with AF, irrespective of LVEF, especially when a first episode of AF or paroxysmal AF is diagnosed, the following issues have to be taken into consideration157:

1. Possible correctable causes (e.g., hypothyroidism or hyperthyroidism, electrolyte disorders, uncontrolled hypertension, mitral valve disease).166,162
2. Compounding factors (e.g., recent surgery, chest infection or exacerbation of COPD/asthma, acute myocardial ischemia, alcohol binge).166,162
3. Evaluation of stroke risk the need of anticoagulation.166,162
4. Evaluation of ventricular rate and need for rate control.166,162
5. Evaluation of symptoms of HF and AF.166,162

Prevention of AF in patients with HF: Many treat-
ments for HF, including ACEIs, ARBs, beta-blockers and MRAs reduce the incidence of AF, but ivabradine may on the contrary increase it, as well as CRT is hardly effective in the incidence of AF. Amiodarone will reduce the incidence of AF, inducing pharmacological cardioversion, and leading to the maintenance of sinus rhythm in more patients after cardioversion and could be used to control symptoms in paroxysmal AF patients if beta-blockers fail to do so. Amiodarone should generally be restricted to < 6 months use in patients with paroxysmal or persistent AF to help preserve SR and reduce the high possibility of AF recurrence immediately after cardioversion. Dronedarone is contraindicated in patients with concomitant HF and AF.

Management of new-onset, rapid AF in patients with HF: If the patient has no distressing symptoms of HF, then treatment with oral beta-blockers may used to achieve ventricular rate control. For patients with marked congestion who are symptomatic at rest, initial treatment with oral or intravenous digoxin is preferred. For patients in haemodynamic instability, an intravenous bolus dose of digoxin or amiodarone should be carefully administered into a peripheral vein, however, where there is no certain venous access, amiodarone must not be given. Administration of amiodarone for a longer period should be done only by central or long-line venous access to avoid peripheral vein phlebitis. In patients with haemodynamic collapse, emergency electrical cardioversion is recommended.

Although sub-group data suggest that SR is associated with improved outcomes in patients with HF (including all-cause survival), clinical trials have not resulted in superiority of either a rate or rhythm-control strategy and provided that SR is difficult to maintain particularly in patients with HF. For example, in the AF-CHF trial, there was no difference in CV death, all-cause mortality and exacerbation of HF, when comparing a rate vs. rhythm-control strategy in patients with HFrEF and NYHA classes II–IV (HR = 1.06, 95% CI: 0.86–1.30, P = 0.59). A suggestion, according to which rhythm control has failed to improve survival in clinical trials, is the limited efficacy and adverse effects of available treatments, or already irreversible cumulative effects of AF. On the other hand, in studies of AF catheter ablation, restoration of SR is associated with improved left ventricular function (an average 11% LVEF increase). Despite the lack of clear evidence in the improvement of CV outcomes, patients with AF and HF who manage to maintain SR for a longer time, demonstrate less severe functional impairment (NYHA class III symptoms in 27% patients with SR vs. 35% with rhythm disturbances, P < 0.0001). Based on these and other data, rhythm-control therapy is applied on those patients who experience AF-related symptoms or exacerbation of HF despite sufficient rate control.

Rate control: An evaluation of ventricular rate control from the radial pulse is not ideal, especially in HF patients, as ventricular activation may not always generate a palpable pulse. Rate control should be evaluated electrocardiographically. A wearable device evaluates the ventricular rate during rest, exercise and sleep, but there is no clear evidence yet of the value of routine monitoring. Implanted devices such as pacemakers, CRT or ICDs can also be used to assess ventricular rate control. The optimal rest ventricular rate in patients with AF and HF is uncertain but should be between 60-100 beats/min. One trial suggested that a ventricular rates at rest of up to 110 beats/min might still be acceptable and the 2016 ESC AF guidelines recommended this threshold as the target for rate control therapy, although a lower rate for patients with HF may be more preferable. Ventricular rates < 70 beats/min are associated with a worse prognosis and this may be the reason why beta-blockers administered in guideline-target doses failed to reduce morbidity or mortality in patients with HFrEF and AF and may also explain the association between digoxin and adverse outcomes that are mentioned in some observational studies of AF. The optimal ventricular rate during exercise is not clarified, but may be < 110 beats/min during light exercise. Beta-blockers, digoxin and their combination may be useful in the control of the ventricular rate. Although there is no clear optimal approach, beta-blockers appear safe as the first-line treatment even if it is not clarified that they reduce morbidity and mortality in patients with AF. At the acute phase of AF beta-blockers reduce ventricular rate during periods of activity or a high sympathetic
...considered instead of the standard used RV pacing. For patients with HFrEF, CRT should be considered and additionally if the patient has moderate to severe HF symptoms with an ICD indication, AV node ablation with implantation of CRT-D may be a preferred option. The use of class I antiarrhythmic agents and dronedarone is associated with an increased risk in morbidity and mortality in patients with HF and AF and therefore should be avoided. Amiodarone can result in restoration of SR in some patients with chronic AF, may reduce symptomatic paroxysms of AF and will help the maintenance of SR after spontaneous or electrical cardioversion. The continuous administration of amiodarone should be regularly reviewed and justified. The safe and efficient application of catheter ablation in the atria and pulmonary veins (PV) as a rhythm control strategy in HF is not yet clarified, except for tachycardia induced cardiomyopathy. One small study reported that AF ablation was superior to AV node ablation and CRT in patients with AF and a resting ventricular rate < 100–110 beats/min. However, in patients with a fast ventricular rate and refractory symptoms, AV node ablation may be considered and additionally if the patient has moderate to severe HF symptoms with an ICD indication, AV node ablation with implantation of CRT-D may be a preferred option. Rhythm control: In patients with chronic HF, a rhythm control strategy (including pharmacological or electrical cardioversion) has not been shown to be more beneficial than a rate control strategy in reducing mortality or morbidity. Urgent cardioversion has an indication only if the AF is life threatening, otherwise both HF and ventricular rate should be controlled before cardioversion is applied. A rhythm control strategy is probably preferable in patients that are supplementary diagnosed with a reversible secondary cause of AF (e.g., hyperthyroidism) or an obvious precipitant (e.g., current pneumonia) and in seriously symptomatic patients due to AF post the best combination of rate control and HF therapy administration. The use of class I antiarrhythmic agents and dronedarone is associated with an increased risk in morbidity and mortality in patients with HF and AF and therefore should be avoided. Amiodarone can result in restoration of SR in some patients with chronic AF, may reduce symptomatic paroxysms of AF and will help the maintenance of SR after spontaneous or electrical cardioversion. The continuous administration of amiodarone should be regularly reviewed and justified. The safe and efficient application of catheter ablation in the atria and pulmonary veins (PV) as a rhythm control strategy in HF is not yet clarified, except for tachycardia induced cardiomyopathy. One small study reported that AF ablation was superior to AV node ablation and CRT. Another study, including 203 patients with persistent AF, HF and an ICD or CRT device, reported that AF ablation was superior to amiodarone in the SR restoration, and this was associated with fewer hospitalizations for HF outcomes and lower mortality. Two small studies of AF ablation compared with rate control showed controversial results in procedural complications and success in improving symp-
A meta-analysis including 914 patients reported an encouraging success rate of PV isolation ablation for AF in patients with LV dysfunction, improving LVEF and functional capacity.\[212\] The American College of Cardiology/American Heart Association Task Force on Practice Guidelines and guidelines from the Heart Rhythm Society recommend antiarrhythmic therapy for possible pharmacologic cardioversion.\[146\] However, studies have reported an increase in torsades de pointes, especially when the used medications increased corrected QT intervals, in women compared with men with antiarrhythmic drugs.\[213, 214\] The presence of HF is another risk factor for increased possibility of developing proarrhythmia. In a 2-year analysis from the AF registry, where the administration of antiarrhythmic drug therapy was similar in men (28.6%) and women (28.9%), women were less likely to undergo electrical cardioversion (26.7% vs. 32.4%), less likely to be referred for AF ablation (4.9% vs. 5.9%), less likely to receive beta-blocker therapy, more likely to be on digoxin (24.6% vs. 22.6%) and more likely to undergo AV node ablation for rate control of AF (2.9% vs. 1.7%).\[215\] At the time of the ablation women were older and are referred for the procedure later than men\[216, 217\] demonstrating a higher procedural complication rate than men.\[218\] Possible anatomic differences may be the cause of sex differences in the discrepancies occurring in the outcomes of ablation (smaller female heart, greater duration of AF, greater prevalence of nonparoxysmal forms of AF, and higher bleeding complication rates in women compared with men).\[219, 220\] The Catheter Ablation for Atrial Fibrillation with Heart Failure (CASTLE-AF) study studied patients with AF and HFrEF that they were randomized to medical therapy or catheter ablation and had a median follow-up of 37.8 months. Compared with medical therapy, catheter ablation led to a significantly lower rate of all-cause mortality or hospitalization for adverse HF outcomes.\[221\] Supplementary data from the FIRE AND ICE (radiofrequency vs cryoballoon-based therapy) trial of catheter ablation for AF showed that female sex had an almost 40% increase in the risk of atrial arrhythmia recurrence and cardiovascular rehospitalization after catheter ablation for AF, indicating the probable need for better monitoring for women to decrease the risk of arrhythmia recurrence after cardioversion.\[222\]

Catheter ablation has been shown to improve freedom from AF in patients who could not be treated with the use of AAD and meanwhile their toxicity is avoided.\[223\] Accordingly, the use of catheter ablation has been increased in clinical practice and it is associated with positive CV outcomes.\[224\] Observational data suggest that in patients with AF and HF, LVEF improved by 11.1% after ablation (95% CI: 7.1–15.2).\[179\] The higher recurrence rates of AF after catheter ablation led to the suggestion that further ablation procedures are about to be needed.\[225–227\] The PABA-CHF pilot study compared a rate-control approach with AV node ablation and CRT, vs. AF catheter ablation in 81 patients with drug-refractory AF and mild-to-moderate HF. In the ablation group, 71% of the patients maintained SR without AAD, had better HF-related quality of life, better 6-min walk times, and greater improvement in LVEF.\[174\] The Ablation vs. Amiodarone for Treatment of Atrial Fibrillation in Patients with Congestive Heart Failure and an Implanted ICD/CRTD trial suggested promising results for catheter ablation in this patient group along with a greater maintenance of SR.\[228\] While the most beneficial ablation method is yet not clear, more trials are conducted in order to speculate the actual CV improvement that ablation leads in, for patients with AF and HF.\[12\] As long as percutaneous ablation has still limitations in patients with advanced forms of AF, there are emerging alternative approaches, including both surgical ablation and hybrid ablation.\[12\] More traditional surgical ablation, like the Cox-Maze procedure, has a role particularly in patients with symptomatic AF that are undergoing surgery for valvular disease or revascularization.\[229\] Some primary data show that in AF patients with concomitant HF, Cox-Maze procedures may be effective and safe in the patients with an LVEF < 40% and symptomatic HF with a maintenance of SR > 80% in a 6-month follow-up.\[230\]

Cardiac resynchronization therapy: CRT decreases mortality and prevents hospitalizations in patients with symptomatic HF, LVEF ≤ 35%, and QRS duration ≥ 120 ms.\[231\] Between 25% and 50% of patients that present for CRT have AF, although patients with AF are not well represented in random-
ized clinical trials of CRT. At the moment, CRT is a class IIa recommended therapy in patients with HF and AF. Loss of AV synchrony and rapid ventricular rates in AF may impair the beneficial effect of CRT and small studies have suggested that a better outcome can be achieved with a concomitant AV node ablation. Although response rates are lower in patients with AF, CRT should still be pursued in appropriate patients, where any attempt in the restoration of rate control is absolutely essential. It is important to ensure that biventricular pacing is as close to 100% as possible and keep the number of inappropriate shocks to the minimum.

Thromboembolism prophylaxis: Anticoagulation should be administrated in patients with HF and AF and the balance of benefit and risk of bleeding using CHA2DS2-VASc and HAS-BLED risk assessment scores should be evaluated according to the ESC guidelines for AF. A substantial proportion of patients with HF will have both benefit and risk scores ≥ 3, indicating that the prescription of an oral anticoagulant should be carefully planned and that regular reassessment is required. NOACs are preferred for HF patients with non-valvular AF, as they seem to be at least similarly effective and even safer (less intracranial haemorrhage) in patients with HF than in subjects without HF compared to the use of Vitamin K antagonists. However, there are concerns regarding the safety of NOACs in older patients with HF and poor renal function. In patients with HF and AF who have mechanical heart valves or at least moderate mitral stenosis, only oral vitamin K antagonists are indicated for the prevention of thromboembolic stroke. The dabi-gatran should administer in a reduced dose of 110 mg twice daily when creatinine clearance is 30–49 mL/min, rivaroxaban should be reduced to 15 mg daily and edoxaban to 30 mg daily when creatinine clearance is 30–50 mL/min and apixaban to 2.5 mg twice daily if a patient has two or more of the following factors: age ≥80 years, serum creatinine ≥ 1.5 mg/dL or body weight ≤ 60 kg. Finally, a left atrial occlusion device could be considered in a patient with AF as an alternative to an oral anticoagulant, when the patients are concerned to be at high-risk of both thromboembolism and bleeding in order to avoid the risk of haemorrhage due to the use of anticoagulation treatment.

CONCLUSION

As the number of patients with AF and HF continues to rise, it is evident that the treatment of these conditions should necessarily extend beyond their presence with adverse symptoms and CV of moderate prognosis. Research efforts should focus basically on prevention that involves a wider range of CV disease caused by AF and HF and not only tachycardiomyopathy. The aging population and the increasing prevalence of CV events requires more effective approaches to AF prevention and treatment in patients with HF and HF prevention and treatment in patients with AF. To that end, a better understanding of the common pathophysiology that AF and HF share and of the mechanisms that create an underlying predisposition to AF in patients with HF and to HF in patients with AF, and their role to clinically significant outcomes, is of utmost importance. This understanding applies to both HFpEF and HFrEF, regardless of the way that they may be related with AF. The identification of high-risk subgroups of patients with AF or HF for screening and prevention and the best algorithms for early detection of these conditions is also very important. In addition, understanding of the symptom burden in AF versus HF and define the best approach to apply this knowledge in patient-based management may improve the use of various treatments, enhance the available clinical data in the research on their efficacy and safety and lead to new prospects in the combination of routine clinical practice with genetic profiling, introducing the biology of the cell in the management of concomitant HF and AF.

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