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Review Article

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Atrial Fibrillation in Heart Failure: a Therapeutic Challenge of Our Times

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ABSTRACT

Atrial fibrillation (AF) and heart failure (HF) are growing cardiovascular disease epidemics worldwide. There has been an exponential increase in the prevalence of AF and HF correlating with an increased burden of cardiac risk factors and improved survival rates in patients with structural heart disease. AF is associated with adverse prognostic outcomes in HF and is most evident in mild-to-moderate left ventricular (LV) dysfunction where the loss of "atrial kick" translates into poorer quality of life and increased mortality. In the absence of underlying structural heart disease, arrhythmia can independently contribute to the development of cardiomyopathy. Together, these 2 conditions carry a high risk of thromboembolism due to stasis, inflammation and cellular dysfunction. Stroke prevention with oral anticoagulation (OAC) remains a mainstay of treatment. Pharmacologic rate and rhythm control remain limited by variable efficacy, intolerance and adverse reactions. Catheter ablation for AF has resulted in a paradigm shift with evidence indicating superiority over medical therapy. While its therapeutic success is high for paroxysmal AF, it remains suboptimal in persistent AF. A better mechanistic understanding of AF as well as innovations in ablation technology may improve patient outcomes in the future. Refractory cases may benefit from atrioventricular junction ablation and biventricular pacing. The value of risk factor modification, especially with regard to obesity, sleep apnea, hypertension and diabetes, cannot be emphasized enough. Close interdisciplinary collaboration between HF specialists and electrophysiologists is an essential component of good long-term outcomes in this challenging population.

Keywords: Atrial fibrillation; Heart failure; Arrhythmias; Cardiomyopathy; Catheter ablation

INTRODUCTION

Atrial fibrillation (AF) and heart failure (HF) are cardiovascular disease epidemics that have grown worldwide in the past 2 decades.[1)] The underlying risk factors and pathophysiology are similar for the two conditions. AF is the most commonly diagnosed cardiac arrhythmia. Despite advances in care and available treatment options including catheter ablation, AF management continues to pose a therapeutic challenge. Nowhere is this more apparent than in patients with HF. While a growing body of epidemiological, clinical and experimental data has helped us understand the interrelationships between AF and HF and guide clinical

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management, several gaps in knowledge still exist. This review focuses on the epidemiology, pathophysiology, and management strategies for patients with AF and HF.

EPIDEMIOLOGY OF AF AND HF

The growing burden of risk factors such as hypertension, obesity, diabetes mellitus, ischemic heart disease, and untreated rheumatic heart disease in developing countries has contributed to the increased prevalence of both AF and HF.

Age is a major factor contributing to disease prevalence, as both AF and HF are disproportionately common in the elderly. The burden of this disease on healthcare system is therefore expected to increase in the future, with considerable implied healthcare cost, morbidity and mortality.[1-3] AF has an estimated prevalence of 1.0%–1.5% in developed countries. Within the United States, in 2001, an estimated 2.3 million people had AF and the figure is projected to increase 2.5-fold by 2050 according to the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study. Community-based studies looking at the age- and gender-adjusted incidence and prevalence of AF have reported an even higher estimated disease burden, with an incidence of 3.68 per 1,000 person-years and 12.1 million people affected by the year 2050.[4-8] Comparable or higher trends are reported elsewhere in the world.[3,7] AF confers higher mortality in both genders as shown by data from the Framingham Heart Study (odds ratio [OR], 1.5 in men and 1.9 in women),[9] although the incidence of AF is greater among men than women.[5]

Similarly, HF is a major public health problem affecting about 5.8 million patients in the United States and 23 million people worldwide. Approximately 550,000 new HF cases are diagnosed each year in North America. While the incidence of the disease has remained stable in recent years, the prevalence has increased given the improved survival rates of patients with ischemic heart disease.[10] This has translated into staggering healthcare costs associated with HF management. The American Heart Association reported that an estimated $33 billion was spent in the US on HF alone in 2007.[3] Survival rates have traditionally been reported as 50% at 5 years and 10% at 10 years following the initial diagnosis of HF. While there has been a modest improvement in survival since the development of angiotensin-converting enzyme inhibitors, the overall long-term mortality remains high.[10]

COMBINED PREVALENCE AND PROGNOSTIC IMPLICATIONS OF AF AND LEFT VENTRICULAR (LV) DYSFUNCTION: THE TIP OF THE ICEBERG

It is well-established that the combination of AF and HF has a worse prognosis than either of these conditions alone.[2,11] In a study published by Khazanie et al.[12] in 2008 that enrolled 27,829 Medicare beneficiaries with HF, those with pre-existing or new-onset AF had higher all-cause mortality compared to patients without AF. Furthermore, multivariate analysis revealed that pre-existing AF in HF patients increased the 3-year risk of all-cause mortality (hazard ratio [HR], 1.14; 99% confidence interval [CI], 1.08–1.20), all-cause readmission (HR, 1.09; 99% CI, 1.05–1.14), HF readmission (HR, 1.15; 99% CI, 1.08–1.21), and stroke readmission (HR, 1.20; 99% CI, 1.01–1.41). HF itself increases the risk of AF by 4.5- to 5.9-fold.[13,14] Large clinical trials of HF with reduced ejection fraction (HFrEF)

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patients demonstrated an increased prevalence of AF ranging from 10% in New York Heart Association (NYHA) class I to –50% in NYHA class IV patients.[5][13-15]

The prognostic implications of AF development in HF remain a controversial subject. Older trials such as the Vasodilator-Heart Failure Trial (V-HeFT) reported no difference in mortality between patients with mild-to-moderate HF in sinus rhythm (SR) or with the development of AF.[16][17] Retrospective analysis of the data from the Studies of Left Ventricular Dysfunction (SOLVD) trial looking at the association between AF and mortality showed that patients with LV dysfunction and AF at baseline had higher all-cause mortality and death from pump failure. The risk of arrhythmic death was the same when comparing patients with SR vs. AF. Compared to SR, patients with AF were older, more likely to be NYHA functional class III–IV and lower mean left ventricular ejection fraction (LVEF).[18] Similarly, results from the large randomized controlled trial of Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity (CHARM) indicated that baseline AF in patients with symptomatic HF conferred increased morbidity and mortality irrespective of ejection fraction (EF). Furthermore, the development of new-onset AF resulted in increased absolute risk for adverse cardiovascular outcomes in patients with HFrEF and greater relative risk of cardiovascular death and HF hospitalization in those with preserved LV function.[19]

An analysis of patients enrolled in the Danish Investigation of Arrhythmia and Mortality on Dofetilide (DIAMOND) trial revealed that 9.6% of the patients with HF and 2.9% of those with a recent myocardial infarction (MI) developed AF when followed for 42 months.[20] Of the 312 patients with LV dysfunction (LVEF <40%) post-MI included in the Cardiac Arrhythmias and Risk Stratification after Myocardial Infarction (CARISMA) study, 101 patients had AF detected via implantable cardiac monitors or devices in the study period. The authors reported the incidence to be highest in the two months following MI with a gradual decline and a stable incidence thereafter. The risk of major cardiovascular events was increased in patients with AF lasting ≥30 seconds (HR, 2.73; 95% CI, 1.35–5.50; p=0.005).[22] Similar results were reported with higher associated mortality rate in patients who developed AF with post-MI cardiac dysfunction in the Valsartan in Acute Myocardial Infarction (VALIANT) trial.[18][23] In summary, the reported occurrence of AF in the peri-infarct period with LV dysfunction ranges from 5%–21% and these patients tend to have higher mortality and stroke rates, both in-hospital and following discharge. However, limited data are available regarding whether a rate or rhythm control strategy in the peri-infarct period influences in-hospital and long-term outcomes.[21][23-25]

The impact of AF on mortality in HF patients seems to be more evident in patients with mild-to-moderate HF, while the effect on patients with more severe HF (LVEF <25%) seems to be limited.[17-26] Interestingly, evidence shows that new-onset AF carries a worse prognosis for HF patients than chronic AF. Patients who developed new-onset AF were older, mostly male and were at higher overall risk of cardiovascular mortality and HF hospitalization.[26][27] While age- and gender-adjusted data for baseline AF in HF patients failed to show an independent association with mortality in the Carvedilol Or Metoprolol European Trial (COMET) trial, subgroup analysis found new-onset AF to be independently associated with all-cause mortality.[28] In a survey of 10,701 hospitalized patients diagnosed with HF who were subdivided into baseline AF, without AF and developing AF during admission groups, patients who developed new-onset AF had longer in-hospital stays, higher morbidity, and a trend towards increased mortality.[29]

Bhatia et al.[32] used 10 years of US national registry data for HF patients to determine the effects of race on the prevalence and outcomes of the development of AF. Although there

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were no gender differences between the two groups (HF patients with and without AF), patients with AF and HF tended to be older, with higher in-hospital mortality. Moreover, after adjustment for demographic differences and co-morbidities, African Americans, Hispanics, Asians, and minority races were less likely to have AF than whites. There was, however, a significant racial difference in mortality associated with coexisting AF and HF; African Americans (24%), Hispanics (17%), Asians (13%), and whites (6%). Contrary to prior evidence, the authors concluded that while African American patients may have a lower overall prevalence of AF, mortality in these patients is much higher. This may be partially attributed to additional risk factors, such as uncontrolled hypertension, that are less commonly seen in whites when compared to other races. Furthermore, there is significant under-utilization of treatments such as cardioversion and catheter ablation in minority racial groups compared to white patients within US.[30-32]

Data from the Framingham Heart Study suggested the presence of worse outcomes and a higher probability of stroke in females with AF.[33] There was also a disproportionate distribution of traditional risk factors for AF with hypertension, HF, coronary and peripheral arterial disease and obesity being more common in African American and Hispanic women when compared to whites and Asians. HF with preserved ejection fraction (HFpEF), an independent risk factor for stroke in AF, is also more prevalent among elderly women.[34][35]

AF AND HFPEF

HFpEF makes up about half of the patient population diagnosed with HF. Recent evidence points to HFpEF being even more closely related to AF than HFrEF. The prevalence of AF in HFpEF is about 20%–40% and two-thirds of the patients may at some point have arrhythmia during the course of the disease.[36-39] AF seems to implicate a worse prognosis in patients with HFpEF than HFrEF.[37] Lam et al.[37] reported poorer exercise capacity, reduced peak VO_2, higher circulating N-terminal pro B-type natriuretic peptide (NT-proBNP) and left atrial enlargement in a small cohort of patients with HFpEF and AF when compared to those with SR. The investigators used both invasive and non-invasive measures and documented elevated filling pressures, shorter deceleration time and higher pulmonary capillary wedge and right atrial pressures in these patients. AF with HFpEF has been suggested to independently contribute to RV failure as well.[37-39] Therefore, based on current evidence, AF is a risk factor as well as a sequela of HF in both systolic and diastolic forms.

THE CAUSE OR THE EFFECT? THE PATHOPHYSIOLOGY OF AF AND HF

While there is evidence that AF and HF share common risk factors and tend to coexist, the exact causal relationship is not completely understood. Each disease condition induces structural, neuro-hormonal, and inflammatory changes that can predispose a patient to the other disease. The acute hemodynamic effects of AF are predominantly loss of atrial systole and ventricular chronotropic dysregulation. Loss of reservoir, conduit and booster function of the left atrium (LA) is likely a consequence of the atrial fibrosis secondary to increased wall stress, inflammatory cytokines and circulating neuro-hormonal factors seen in both HFrEF and HFpEF.[5][36] Upregulation of the renin-angiotensin-aldosterone system (RAAS) axis is thought to promote atrial fibrosis. Angiotensin II in particular has been shown to

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stimulate cardiac fibroblast proliferation. This acts synergistically with oxidative stress and cytokines such as interleukin-6 and tumor necrosis factor (TNF) to induce fibrosis. There exists an imbalance of the RAAS axis with LV dysfunction that promotes physiological maladaptation, increasing filling pressures and afterload. Stretching of the myocardium results in fibrosis and conduction abnormalities. This has been studied in humans and in animal models.[40-43] In patients with severely reduced EF (LVEF ≤ 35%), Sanders et al.[44] demonstrated an increased atrial effective refractory period (AERP), particularly in the lateral right atrium and distal coronary sinus, along with slowing of impulse conduction in areas of fibrosis. Other investigators found the atrial action potential (AP) to be prolonged, resting membrane potential (V_{max}) to be more depolarized and plateau phase amplitude to be smaller in right atrial cells in patients with HF. In a recent study, Workman et al.[46] demonstrated the conduction velocity and cellular AP maximum upstroke velocity in the atrium to be increased rather than reduced in HF. Animal studies have thus suggested that disorganization in refractoriness and conduction results in a predisposition to AF.[44-46]

CELLULAR BASIS OF AF IN HF

Dysregulation of intracellular calcium handling and sarcoplasmic calcium overload has been demonstrated in experimental animal models of HF. Prolonged AP is thought to mediate this process by increasing the calcium load and reducing inhibition of the sarcoplasmic calcium-ATPase pump. A marked decrease in the density and network of transverse T-tubules is also thought to be partially responsible for focal atrial arrhythmias in HF.[36][46-48]

Structural remodeling in the atrial myocardium with chronic elevated filling pressures and LV dysfunction has been shown to decrease expression of delayed rectifying potassium currents (I_{kur} and I_{Ks}) and upregulation of the Na^{2+}-Ca^{2+} exchange current. The combined effect is attenuation of the AP and can result in delay after depolarization leading to predisposition to atrial arrhythmias. Cellular studies in humans have also shown decreased acetylcholine sensitivity and acetylcholine-activated potassium current in the atrial myocardium of HF patients compared to controls.[35][43] Lugenbiel et al.[49] found that down regulation of atrial repolarizing K^+ channels (TREK-1) contributes to electrical remodeling with changes in the AERP. TREK-1 mRNA levels were reduced by 82% (left atrium) and 81% (right atrium) in chronic AF and HF when compared to SR patients. The investigators were able to replicate their findings in a porcine heart model of pacing induced AF and cardiomyopathy. Gene therapy with TREK-1 effectively increased TREK-1 levels and showed attenuation of prolonged AERP in animal models.

An increase in inflammatory cytokines, changes in TNF-α, transforming growth factor beta 1 (TGF-β1) expression, peroxisome proliferator-activated receptor-γ (PPAR-γ), increased number of $CD4^+$ cytotoxic T-cells with loss of CD28 within CD4 cells have all been implicated in the pathophysiology of AF and HF and could be potential therapeutic targets.[45-50]

AF: AN INDEPENDENT MEDIATOR OF CARDIOMYOPATHY

The hemodynamic effects of AF are both acute and chronic in nature. Particularly in HF patients, the loss of "atrial kick," changes in LA mechanics, loss of reservoir, conduit, and booster functions may impact patient functional status as well as adversely affecting

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outcomes. Loss of atrial systole decreases cardiac output by up to 25% and is of significance, particularly in diastolic dysfunction.[51)52)] Restoration of SR improves forward flow and contractility as evidenced by hemodynamic improvement in HF patients with rhythm control, both acute and long term.

Alternatively, persistent AF can lead to arrhythmia-induced cardiomyopathy (AIC), an important and potentially reversible entity of uncertain incidence that requires a high index of suspicion for diagnosis and an aggressive approach to management involving rhythm control strategies. The process is mediated by changes in cellular, and neuro-hormonal factors as well as extracellular remodeling. Resting tachycardia and increased HR with exercise as well as irregularities in ventricular rhythm result in alterations of myocardial gene and protein expression, calcium handling, and increased sympathetic discharge with detrimental effects on ventricular function.[5-52)]

BALANCING THE RISK OF STROKE AND ANTICOAGULATION

HF in itself represents an inflammatory hypercoagulable state with impaired flow, platelet and endothelial dysfunction, predisposing patients to both arterial and venous thrombosis. Its coexistence with AF multiplies this risk and the comparative outcomes are significantly worse when compared to those of patients with SR. The risk of stroke in patients with HF has been observed to increase manifold, from 18 per 1,000 persons with HF in the first year of diagnosis to 47.4 per 1,000 at 5 years.[53)] LA mechanical dysfunction and stasis predisposes HF patients to thrombus formation, particularly in the LA appendage (LAA). Contrary to the common belief that HFrEF is associated with increased stroke risk, a recent meta-analysis showed no difference in the risk of stroke between the two. Furthermore, the risk of thromboembolism is unrelated to the severity of LV dysfunction or NYHA functional class.[54-56)]

The $CHADS_2$-VASc scoring system is most commonly used to assess the risk of stroke and the choice of initiating anti-platelet vs. therapeutic anticoagulation is largely determined by weighing the benefit of treatment vs. the risk of bleeding. Both European and American Guidelines strongly recommend oral anticoagulation (OAC) for non-valvular AF and a $CHADS_2$-VASc score of 2 or more (**Figure 1**).[57-60)]

Risk factors	Recommended OAC therapy	
	ESC	ACC/AHA/HRS
CHADS2-Vasc 0	No antithrombotic therapy	No antithrombotic therapy
CHADS2-Vasc 1	NOAC >VKA	None vs. ASA vs. OAC
CHADS2-Vasc ≥2	NOAC >VKA	NOAC or VKA
Mechanical valve	VKA Target INR 2–3 (aortic value) Target INR 2.5–3.5 (mitral value)	

Figure 1. ESC and ACC/AHA/HRS guidelines for OAC therapy based on risk factors.
ACC = American College of Cardiology; AHA = American Heart Association; ASA = acetylsalicylic acid; ESC = European Society of Cardiology; HRS = Heart Rhythm Society; INR = international normalized ratio; NOAC = novel oral anticoagulant; OAC = oral anticoagulation; VKA = vitamin K antagonist.

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Warfarin (a vitamin K antagonist) has been historically used for stroke prevention with a relative risk reduction of 64%. Since 2009, the Food and Drug Administration (FDA) has approved novel oral anticoagulants (NOACs) including dabigatran, rivaroxaban, apixaban, and edoxaban based on their respective clinical trials. Sub-group analysis from the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY), Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) (superiority), Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared to Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) and Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation (ENGAGE-AF) (non-inferiority) trials have shown them to be effective in HF patients with similar benefits in reduced and preserved EF. These trials had similar outcomes in patients with and without HF in terms of stroke prevention, systemic embolic events and reduced intracranial bleeding. The risk of gastrointestinal (GI) bleeding was higher in HF subgroups treated with NOACs except for in the ARISTOTLE trial, where the hazard ratios favored apixaban over warfarin in outcomes with the exception of GI bleeding in patients with HFpEF. A recent meta-analysis of 19,122 patients from NOAC trials showed that a single high NOAC dose reduced the risk of thromboembolism by an additional 14%, with a lower risk of major bleeding compared to warfarin.[58]

In patients with very high bleeding and thromboembolic risk, surgical or percutaneous LAA closure or exclusion should be considered. A success rate of 93%–100% has been reported for the LARIAT device (SentreHeart, Redwood City, CA, USA), with low reported adverse event rates, although its true safety has not been clearly defined. Transient ischemic attack (TIA), stroke, pericardial effusion, MI, LAA perforation, incomplete closure and leaks remain a concern.[61][62] Percutaneous closure of the LAA using the WATCHMAN™ device (Boston Scientific, Maple Grove, MN, USA) met the criteria for non-inferiority and superiority when compared to warfarin for preventing the combined outcomes of stroke, systemic embolism and cardiovascular death. The device has been approved for patients with a $CHADS_2$-VASc score of ≥3 with relative contraindications to long-term OAC. Long-term follow-up of this study population did not show any difference in the rates of all stroke or ischemic stroke between groups; however, the device group had fewer hemorrhagic strokes and cardiovascular deaths.[63] Ongoing follow-up will provide more information regarding long-term outcomes of patients receiving LAA closure with the WATCHMAN™ and similar devices.

MEDICAL THERAPY FOR AF IN HF: RATE OR RHYTHM CONTROL?

Despite growing evidence supporting rhythm control and early intervention to restore and maintain SR in patients with AF and HF, controversy still exists regarding the long-term benefits of these approaches. Subgroup analysis of the AF Follow-up Investigation of Rhythm Management (AFFIRM) and the Rate Control Versus Electrical Cardioversion for Persistent AF (RACE) trials suggested a potential survival benefit and decreased hospitalization in patients with LV dysfunction who were able to maintain SR. It was postulated that the patients maintaining SR may have been healthier. Moreover, only 23% of the patients included in the trial had HF and the benefit was offset by increased mortality associated with anti-arrhythmic therapy.[64][65] Guglin et al.[66] looked at HF symptoms in the different subgroups included in AFFIRM study to assess the impact of rate vs. rhythm control and found that stable SR was associated with the best functional status. Other trials including

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How to Treat Chronic Atrial Fibrillation (HOT CAFE), Strategies of Treatment of Atrial Fibrillation (STAF), and Pharmacological Intervention in Atrial Fibrillation (PIAF) also showed equivalent outcomes in terms of rate or rhythm control with the limitation that only 23%–64% patients assigned to rhythm control groups remained in SR.[17]

The Atrial Fibrillation and Congestive Heart Failure (AF-CHF) trial was the first prospective randomized trial to extend the findings of AFFIRM to patients with HF. It enrolled 1,376 patients with a mean of LVEF 27% that were randomized to rate control or rhythm control groups with amiodarone. A 3-year follow-up failed to show any benefit from the rhythm control strategy in HF. However, 15% of patients in the AF-CHF trial abandoned the initial treatment strategy to which they were assigned. Rhythm control was abandoned more frequently than rate control primarily due to treatment inefficacy. Moreover, 40% of patients in the rate control arm were in SR during follow-up. Interestingly, the subgroup analysis of the trial suggested ventricular arrhythmias in addition to worsening HF as the reason to switch to rhythm control. Failed rate or rhythm control with crossover did not affect cardiovascular or all-cause mortality. It has been argued that survival benefit may have been attenuated by the side effects of anti-arrhythmic therapy and the actual success rate of drug therapy to achieve rhythm control was lower than anticipated.[67]

RATE CONTROL

Generally, a resting heart rate of up to 80 beats per minute and up to 115 beats per minutes with exercise is an acceptable target for ventricular rate control in AF. Mobile telemetry has been recommended to objectively assess patients with AF-HF. Beta blockers have traditionally been used to control heart rate, particularly in HF patients, unless acutely decompensated, and are effective either alone or in combination with other agents in the majority of patients.[28][68] Rate control can be a difficult target to achieve particularly with exercise in real clinical practice. No drug class is uniformly effective and combination therapy or alternative management is required to alleviate symptoms.[69] The current guidelines strongly recommend beta-blockers in patients with HFrEF (class I, level of evidence A). While the patients who truly derive benefit from beta-blocker therapy are those who have HF and SR, there were no convincing studies to prove a similar derived benefit in AF-HF until recently. In subgroup analysis of AF-CHF patients with HFrEF and AF, beta-blockers were shown to decrease all-cause mortality by 28% regardless of the pattern of AF. The effect was more pronounced in individuals with higher AF burden.[70][71]

Initiation of guideline-directed medical therapy with beta-blockers, angiotensin receptor blockade, and aldosterone antagonists when indicated may be helpful in preventing AF onset in patients with HF.[10] Non-dihydropyridine calcium channel blockers can also provide effective rate control, but negative inotropic effects limit its use in HFrEF. In HFpEF, rate control with either calcium channel blockers or beta-blockers can help prolong diastolic filling with resultant increase in cardiac output, except for in very late stages of restrictive cardiomyopathy, where elevated heart rate is essential to maintaining flow.[10-35] Although conferring no mortality benefit, digoxin can be added to achieve rate control synergistically with atrioventricular nodal blocking agents for symptomatic improvement and reduced hospitalization in HF patients.[72] In patients where adequate rate control cannot be achieved despite medications and rhythm control is not considered, AV nodal ablation with permanent pacing can provide effective rate control.

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RHYTHM CONTROL

A rate control strategy alone may not sufficiently address AF-mediated cardiomyopathy or persistent symptoms. Rhythm control, whether achieved pharmacologically, with electrical cardioversion or catheter ablation, has been shown to achieve greater success in improving LV dysfunction with a resultant favorable impact on quality of life and survival.[65-67] Although limited in terms of the number of patients enrolled, the CAFÉ-II study provided evidence in support of rhythm control translating to improved quality of life (p=0.020) and improved LV function (p=0.014) in HF patients. The greatest benefit was observed in those maintaining SR at 1-year. Adjunctive therapy with amiodarone in addition to cardioversion was shown to restore and maintain SR at 1-year more successfully when compared to amiodarone alone (80% vs. 66%).[73]

LV dysfunction or structural heart disease limits the use of antiarrhythmic therapy options essentially to amiodarone and dofetilide. Each agent has its own safety issues and requires careful patient selection and monitoring. Amiodarone therapy, despite providing benefit in the form of rhythm control in HF patients, does increase the risk of symptomatic bradycardia in AF-HF in addition to a multitude of cardiac and non-cardiac adverse effects associated with long-term therapy.[74][75] Dofetilide is a pure class III anti-arrhythmic drug that is very effective in restoring and maintaining SR in HF patients. While the DIAMOND investigators demonstrated a neutral effect of the drug on mortality, dofetilide was shown to delay all-cause and CHF-related hospitalization. Additionally, the trial also demonstrated favorable outcomes of maintaining SR in both therapy and placebo groups. Close monitoring of renal function and QT intervals is required of patients during therapy.[76]

Renin-angiotensin system blockade has been shown to reduce the occurrence of AF in patients with HF in clinical and population-based studies.[19][23] RAAS blockade reduces fibrosis and remodeling in cardiac chambers with favorable effects. Pretreatment with angiotensin-converting-enzyme (ACE) inhibitors in patients undergoing catheter ablation for non-paroxysmal AF and LV dysfunction improved outcomes with a 49% relative risk reduction in AF recurrence and hospitalization.[77] Ranolazine (RN), an atrial-selective, late and fast sodium channel blocker is an established antianginal agent with a limited side effect profile. More recent experimental and clinical studies have drawn attention to its adjunctive role as an anti-arrhythmic, particularly in combination with amiodarone and dronedarone. Future studies will clarify its role as a monotherapy or in combination with other anti-arrhythmic agents.[78] **Figure 2** provides a synopsis of the management approach to patients with AF and HF based on the current American College of Cardiology (ACC) and European Society of Cardiology (ESC) guidelines.

NON-PHARMACOLOGIC TREATMENT OF AF IN LV DYSFUNCTION-CHOOSING THE RIGHT PATIENT AND PROCEDURE

A growing body of evidence supports a non-pharmacological rhythm control strategy with ablation, either percutaneously or through surgical intervention. Catheter-assisted pulmonary vein isolation (PVI) is superior to antiarrhythmic drug therapy as a second-line option for maintaining SR, improving LV function and physical activity and reducing

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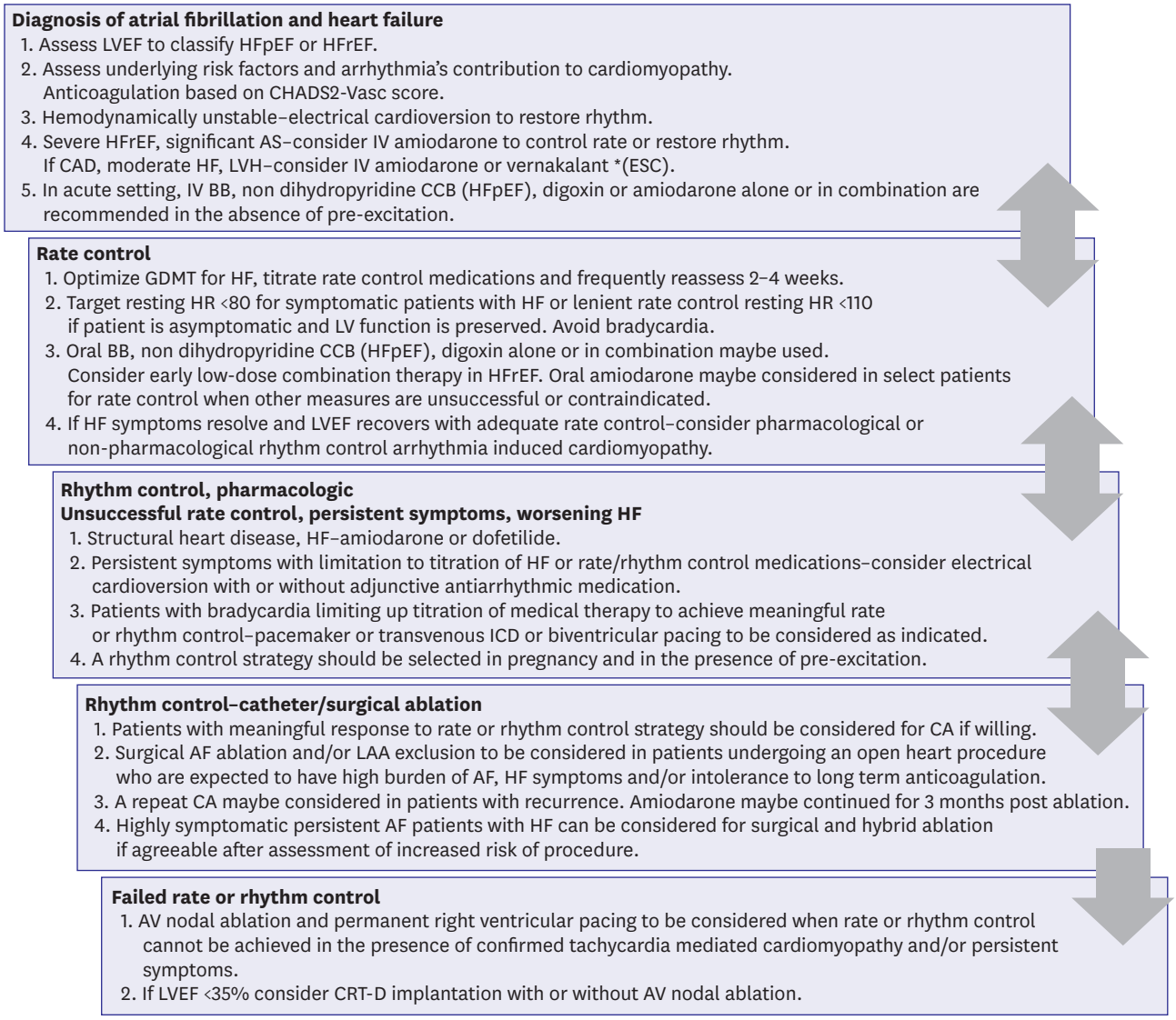

Figure 2. Management of patients with AF and HF based on current ACC and ESC guidelines.
ACC = American College of Cardiology; AF = atrial fibrillation; AS = Aortic Stenosis; AV = atrioventricular; BB = beta blockers; CA = catheter ablation; CAD = coronary artery disease; CCB = calcium channel blockers; CRT-D = cardiac resynchronization therapy defibrillator; ESC = European Society of Cardiology; GDMT = guideline-directed medical therapy; HF = heart failure; HFpEF = HF with preserved ejection fraction; HFrEF = HF with reduced ejection fraction; HR = heart rate; ICD = implantable cardioverter defibrillator; IV = intravenous; LAA = left atrial appendage; LVEF = left ventricular ejection fraction; LVH = left-ventricular hypertrophy.

hospitalization in symptomatic AF patients with or without HF. The Comparison of Pulmonary Vein Isolation Versus AV Nodal Ablation with Biventricular Pacing for Patients with Atrial Fibrillation and Congestive Heart Failure (PABA-CHF) study found PVI to be superior to AV node ablation and cardiac resynchronization therapy defibrillator (CRT-D) in terms of higher LVEF (35%±9% in the PVI group vs. 28%±6% in the AV node ablation group), quality of life and exercise capacity.[79] There was a mean absolute LVEF increase of 8%±8% in the PVI group compared to a decline of 1%±4% in the AV node ablation plus CRT-D group. Although studies have shown significant variability in terms of the efficacy of catheter ablation, especially in persistent AF, elimination of additional targets such as complex fractionated atrial electrograms and non-PV triggers in select patients may increase the success rate (**Table 1**).[80][81]

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Table 1. Synopsis of major completed trials of AF ablation in patients with HF

Trials (completed trials)	Inclusion criteria	No.	Intervention	Follow-up (months)	Primary outcomes	Results
Chen et al.[90]* (2004)	Symptomatic AF, failed AAD, study group LVEF <40%	94†	PVI±additional ablation/second procedure±CTI	14	Recurrence of AF, LVEF, QoL, complication rates	73% AF free survival at 14 months; 96% AF-free off AAD after second procedure in HFrEF patients, non-significant 5% increases LVEF, improved QoL
Gentlesk et al.[91]* (2007)	Symptomatic AF, failed AAD, study group LVEF <50%	67†	PVI±additional ablation (incl. non-PV triggers)	6	AF recurrence, LVEF, LAEF	14% mean improvement in LVEF when compared to controls at 6 months; 88% AF-free survival data up to 20 months
Khan et al.[79] (PABA-CHF, 2008)	Symptomatic drug-resistant AF, NYHA class II–III HF, LVEF <40%	81	PVI±additional ablation vs. AV nodal ablation with biventricular pacing	6	Composite of the LVEF, distance on the 6MWD and MLHFQ score	88% AF-free survival; superior QoL, functional status, and LVEF improvement as a composite end-point
MacDonald et al.[89] (2011)	Persistent AF, NYHA class II–IV HF, LVEF <35%	41	PVI±additional ablation vs. pharmacological rate control	6	Change in LVEF from baseline	50% AF-free survival; no difference in LVEF change, functional status, QoL, NT-proBNP, 15% serious complications
Jones et al.[88] (ARC-HF, 2013)	Persistent AF, NYHA class II–IV HF, LVEF <35%	52	PVI±additional ablation vs. pharmacological rate control	12	Peak VO_2 or functional capacity	88% AF-free survival; no difference in LVEF change; improved objective exercise performance, QoL, and BNP
Hunter et al.[87] (CAMTAF, 2014)	Persistent AF, NYHA class II–IV HF, LVEF <50%	50	PVI±additional ablation vs. pharmacological rate control	6	LVEF	81% AF free survival; superior QoL, functional capacity, and LVEF improvement
Di Biase et al.[82] (AATAC, 2016)	Persistent AF, LVEF ≤40% NYHA class II–III HF with dual chamber ICD or CRT-D	203	PVI±additional ablation (incl. non-PV triggers) vs. amiodarone	24	Freedom from AF, AFL, or AT >30 seconds	72% patients arrhythmia free in ablation group; improved LVEF, 6MWD and reduced MLHFQ score

Data adapted and republished with permission from Ling et al.[5]
6MWD = 6 minute walk distance; AATAC = Ablation vs. Amiodarone for Treatment of Atrial Fibrillation in Patients with Congestive Heart Failure and an Implanted ICD/CRT-D; AF = atrial fibrillation; AFL = atrial flutter; ARC-HF = Catheter Ablation Versus Medical Rate Control for Atrial Fibrillation in Patients with Heart Failure; AT = atrial tachycardia; AV = atrioventricular; BNP = B-type natriuretic peptide; CAMTAF = Catheter Ablation Versus Medical Treatment of AF in Heart Failure; CRT-D = cardiac resynchronization therapy defibrillator; CTI = cavotricuspid isthmus; HF = heart failure; HFrEF = HF with reduced ejection fraction; ICD = implantable cardioverter defibrillator; incl. = fibrillation including; LAEF = left atrial ejection fraction; LVEF = left ventricular ejection fraction; MLHFQ = Minnesota Living with Heart Failure Questionnaire; NT-proBNP = N-terminal pro B-type natriuretic peptide; NYHA = New York Heart Association; PABA-CHF = Comparison of Pulmonary Vein Isolation Versus AV Nodal Ablation with Biventricular Pacing for Patients with Atrial Fibrillation and Congestive Heart Failure; PV = pulmonary vein; PVI = pulmonary vein isolation; QoL = Quality of life.
*Cohort study, †Number of patients in the reduced EF group.

The Ablation vs. Amiodarone for Treatment of Atrial Fibrillation in Patients with Congestive Heart Failure and an Implanted ICD/CRT-D (AATAC) trial was the first multicenter randomized trial in HF patients with persistent AF undergoing catheter ablation. The trial found a 45% risk reduction in hospitalization during a 2-year follow-up period and reduced mortality (8%) in HF patients undergoing ablation when compared to amiodarone therapy (18%). Amiodarone was significantly more likely to fail when compared to catheter ablation, despite single procedural success rates ranging from 29%–61% at different centers.[82] Other trials including the Catheter Ablation Versus Medical Rate Control for Atrial Fibrillation in Patients with Heart Failure (ARC-HF) and Catheter Ablation Versus Medical Treatment of AF in Heart Failure (CAMTAF) trials provided similar evidence (**Table 1**). While encouraging in many aspects, the available data still raise a number of questions with regard to the factors affecting procedural outcomes.

A multicenter registry evaluating 1,273 patients with AF (171 with HF and 1,102 without HF) showed that the procedural success rate of catheter ablation was similar for paroxysmal AF irrespective of HF status (78.7% vs. 85.7%, p=0.186) whereas patients with persistent AF and HF had a lower success rate with ablation than persistent AF patients without HF (57.3% vs. 75.8%, p<0.001). HF independently predicted recurrent arrhythmia and AF recurrence in this cohort and was associated with a higher rate of stroke and death (HR, 8.33; CI, 1.86–37.7; p=0.001).[80] In another study of 720 consecutive patients with preserved EF (>50%) and HFrEF (LVEF <35%), ablation of non-pulmonary vein (PV) triggers in patients with reduced

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Table 2. Catheter ablation of AF in HF trials in progress

Trials (trials in progress)	Inclusion criteria	No.	Intervention	Follow-up (years)	Primary outcomes	Results
Moreno et al.[84] (CABANA, May 2009–June 2018)	AF in high risk groups defined as one or more of the following age >65 years, HTN, DM, HF, previous stroke/TIA or systemic embolism, atherosclerotic vascular disease, or LA dilatation	2,200	Catheter ablation vs. medical treatment with rate control or rhythm control	5	Composite of all-cause mortality, stroke or serious bleeding	NA
ClinicalTrials.gov (US)[85] (RAFT-AF, Aug 2011–Sept 2019)	High burden AF, NYHA class II–IV HF, LVEF <45% or ≥45%	1,000	Catheter-ablation-based AF rhythm control versus medical rate control±AV nodal ablation and pacemaker implantation	5	Composite of all-cause mortality and worsening HF	NA
Marrouche et al.[86] (CASTLE-AF, Jan 2009–April 2019)	Symptomatic drug-resistant AF, NYHA class II–III HF, LVEF <35%, dual-chamber or biventricular ICD with home-monitoring capability	420	AF ablation within 48 hours of baseline assessment vs. conventional treatment	≥3	Composite of all-cause mortality and worsening HF	NA

Data adapted and republished with permission from Ling et al.[5]
AF = atrial fibrillation; AV = atrioventricular; CABANA = Catheter Ablation Versus Antiarrhythmic Drug Therapy for Atrial Fibrillation; CASTLE-AF = Catheter Ablation Versus Standard Conventional Treatment in Patients with Left Ventricular Dysfunction and Atrial Fibrillation; DM = diabetes mellitus; HF = heart failure; HTN = hypertension; ICD = implantable cardioverter defibrillator; LA = left atrium; LVEF = left ventricular ejection fraction; NA = not applicable; NYHA = New York Heart Association; RAFT-AF = Randomized Ablation-Based Atrial Fibrillation Rhythm Control Vs. RATE Control Trial in Patients with Heart Failure and High Burden Atrial Fibrillation; TIA = transient ischemic attack.

EF correlated with a higher success rate (75% vs. 32.2%). In the same study, low LVEF and non-PV triggers were shown to be independent predictors of AF recurrence in multivariate analysis.[81]

Al Halabi et al.[83] conducted a meta-analysis of 224 patients with HF included in catheter ablation trials for AF and reported outcomes in terms of LVEF, quality of life, HF admissions and complication rates. A significant improvement in LV function, exercise capacity and quality of life was demonstrated in the catheter ablation group. The peri-procedural major complication rate in this study was 6.3% and was considered acceptable in comparison to the adverse reactions encountered with antiarrhythmic therapy and AV nodal ablation. Future trials such as the Catheter Ablation Versus Antiarrhythmic Drug Therapy for Atrial Fibrillation (CABANA) trial will provide further data on the safety and efficacy of catheter ablation in high-risk patients (**Table 2**).[83][84]

Catheter ablation in patients with failed medical therapy and HFpEF has been studied on a limited basis as well. Observational data suggested a success rate of up to 73% with catheter ablation in these patients, but long-term maintenance of SR often required multiple procedures and the addition of anti-arrhythmic agents.[35]

As technology evolves and our understanding of the mechanisms of persistent AF in HF improves, ablation of AF in HF patients will likely become more successful in terms of its utility, cost-effectiveness and safety.

HYBRID AND SURGICAL ABLATION

Traditional "cut and sew" Cox Maze surgery was the only available treatment for AF until the advent of percutaneous catheter ablation. Surgical maze combined with LAA exclusion is primarily reserved for patients already undergoing cardiac surgery. Both European and American guidelines recommend surgical ablation and/or LAA excision in patients undergoing open-heart procedures when the expected burden of atrial arrhythmia and thromboembolic risk is high (class IIa). In a systematic review commissioned for the 2016 ESC guidelines, concomitant AF surgery resulted in an increased arrhythmia-free interval,

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with no effect on mortality (adjusted OR, 1.00; 95% CI, 0.83–1.20), but with a greater need for pacemaker implantation (adjusted OR, 1.26; 95% CI, 1.07–1.49).[59]

Stand-alone surgical PVI is effective for paroxysmal AF while persistent AF may be treated more successfully with additional lesion sets. A minimally invasive thoracoscopic approach with intraoperative mapping has been developed for a select group of high risk and/or symptomatic AF patients who are not candidates for conventional therapy.[59][60] The Atrial Fibrillation Catheter Ablation Versus Surgical Ablation Treatment (FAST) trial randomized 129 patients to catheter or surgical ablation. Patients had LA dilatation (>4.0 cm), predominantly paroxysmal AF or failed prior catheter ablation. Surgical ablation was found to be more effective, but with a higher complication rate.[92] One- or 2-step convergent AF ablation with minimally invasive surgical access to achieve PV and posterior wall isolation followed by endocardial ablation to consolidate lesions has been employed across the globe, particularly in persistent symptomatic AF ablation patients. The success rate reported for persistent AF is variable, ranging from 50%–80% based on pooled data, with a major complication rate of 7%.[93] Some investigators also believe the procedure offers no additional benefit when compared to extensive endocardial ablation. Ongoing and future trials are expected to provide more clarification.[94]

"ABLATE AND PACE": AV NODAL ABLATION AND CARDIAC RESYNCHRONIZATION THERAPY (CRT)

AV nodal ablation and permanent pacing is a last resort to achieve AV synchrony in patients with AF and HF who fail all other attempts at rate or rhythm control. Many of these patients undergoing AV nodal ablation will require CRT implantation. CRT is an established therapeutic option for a select group of patients with severe LV dysfunction and a wide QRS who fail to respond to optimal medical therapy for HF. Improvement in cardiac function, restoration of atrioventricular and interventricular synchrony and LA mechanics with CRT has been shown to correlate with a lower incidence of AF.[95] AF occurrence in patients with HF who receive a CRT device results in loss of derived resynchronization benefit with a higher rate of non-responders (35% with AF vs. 28% without AF, p=0.001).[96] A large percentage of patients with AF and HF who receive CRT-D will require AV node ablation for adequate resynchronization.[99]

A meta-analysis of 450 patients with concomitant HF and AF from 3 non-randomized trials concluded that AV nodal ablation was associated with reductions in all-cause mortality (risk ratio [RR], 0.42; p<0.001) and cardiovascular mortality (RR, 0.44; p=0.008).[97] Although an initial improvement in symptoms of HF, LV function, and NYHA functional class was shown by Manolis et al.[98] after ablation of the AV node and right ventricular permanent pacemaker implantation, long-term outcomes have not been favorable when compared to patients who underwent PVI for AF.[82] The clinical outcomes of patients with AF, AV node ablation and biventricular pacing were similar to those with cardiac resynchronization and normal SR.[99]

CONCLUSION

AF and HF have emerged as a complex, growing epidemic, with significant cardiovascular morbidity and mortality. The two entities are similar, yet distinct with regard to risk factors, pathophysiology and progression. These conditions can exacerbate one another and their combination leads to increased patient morbidity and mortality and a consequent adverse

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impact on healthcare utilization. In patients with AF and HF, in addition to anticoagulation and standard HF therapy, it is extremely important to institute aggressive attempts at rate and/or rhythm control, as a proportion of these patients will have AF-mediated HF and cardiomyopathy, which can be partially or completely reversed. With limited options in terms of medical therapy in achieving successful control of AF in HF, rhythm control by catheter ablation has potential towards favorable outcomes in this patient population. Thus, there has been a shift towards seeking early intervention with catheter ablation to restore SR. The value of lifestyle and risk factor modification, especially control of obesity, sleep apnea, hypertension and diabetes, among others, on outcomes cannot be emphasized enough. A great deal of work needs to be done still to define the optimal pharmacologic and/or interventional therapy for patients with AF and HF. Close interdisciplinary collaboration between HF specialists and electrophysiologists is essential to achieve good long-term outcomes in this challenging population.

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