

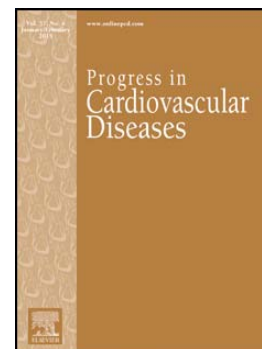
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Atrial Fibrillation and Heart Failure: Update 2015

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**Abstract:**

Heart failure (HF) and atrial fibrillation (AF) commonly coexist, adversely affect mortality, and impose a significant burden on healthcare resources. The presence of AF and HF portends a poor prognosis as well as an increased thromboembolic risk. In patients whose AF is symptomatic, rhythm restoration with either antiarrhythmic drugs or procedural therapies (*e.g.*, pulmonary vein isolation, either catheter-based or surgical) should be considered for symptom improvement, though a mortality benefit has yet to be demonstrated. Emerging evidence suggests that non-pharmacological treatment for AF (including catheter based ablation, hybrid surgical techniques, and atrioventricular node ablation with biventricular pacing) may be of value in improving HF patients' quality of life.

## Abbreviations:

6MWT-6-minute walk test

AADs-Anti-arrhythmia drugs

ACEIs-Angiotensin converting enzyme inhibitors

AF-Atrial fibrillation

ARBs-Angiotensin receptor blockers

BB–Beta blockade

BNP–Brain natriuretic peptide

CA–Catheter ablation

CHD–Coronary heart disease

CRT–Cardiac resynchronization therapy

CV–Cardiovascular

CVA–Cerebral vascular accident

HF–Heart failure

HFpEF–Heart failure preserved ejection fraction

HfrEF–Heart failure reduced ejection fraction

LV–Left ventricular

LVEF–Left ventricular ejection fraction

NOACs–Novel oral anticoagulants

NSR–Normal sinus rhythm

NYHA–New York Heart Association

OACs–Oral anticoagulants

PVI–Pulmonary vein isolation

QoL–Quality of life

STE–Systemic thromboembolism

VKAs–Vitamin K antagonists

ACCEPTED MANUSCRIPT

Atrial fibrillation (AF) is the most common sustained arrhythmia among adults. [1] Heart failure (HF) and AF often coexist. Each condition can promote the other, with an associated increase in morbidity and mortality. Together, their incidence and prevalence is on the rise, presenting a growing clinical and economic burden [2]. In order to provide optimal care, clinicians should remain abreast of relevant literature, guideline recommendations, and available therapies for their patients. In this article we review the complex relationship between AF and HF, with a focus on recent advances in management as well as emerging evidence.

### *Epidemiology of HF and AF*

Both AF and HF are common clinical entities. HF alone is a significant and growing epidemic, affecting nearly 5.7 million American adults. [2] The prevalence of AF is increasing as the population ages, currently affecting over 2 million people in the United States. [1] Collectively, AF and HF carry significant morbidity and mortality, while imposing a substantial adverse impact on healthcare resources. Overall, the estimated national annual cost of caring for patients with AF is approximately \$26 billion. [3] Likewise, HF hospital admissions account for over 6.5 million hospital days annually [4], and HF-related costs reach

an estimated \$34.4 billion each year. This total includes the cost of health care services, medications, and lost productivity. [5]

AF and HF often coexist, and when they do, they confer increased risk for hospitalization, portend lengthier inpatient stays, and increase overall morbidity and mortality. [6–10] Piccini *et al.* analyzed 27,829 HF admissions at 281 hospitals between 2006 and 2008, and found that pre-existing AF was associated with greater 3-year risks of all-cause mortality (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 readmission for stroke (HR: 1.20; 99% CI: 1.01–1.41), compared with no AF. There also was a greater hazard of mortality at one year among patients with new-onset AF (HR: 1.12; 99% CI 1.01–1.24) compared with no AF. [11]

#### *Pathophysiology of AF and HF*

AF and HF share several common risk factors and commonly occur together. [6–10,12–19]. The complex underlying mechanisms that lead to the development of AF in HF patients, and the converse relationship, have been partially described. In patients with HF, there is evidence to support structural, neurohormonal, and electrical atrial remodeling – each of which may encourage the development of AF. [20–26] The development of AF in HF appears to be a multifactorial process, including early atrial enlargement, conduction heterogeneity from intra-atrial fibrosis, ion channel dysregulation, and autonomic remodeling (see Figure1). [27–30]

This causative relationship also works in the opposite direction: AF can induce electrical and hemodynamic deterioration and can cause tachycardia-mediated cardiomyopathy, resulting in HF. [31–33] Through induction of a rapid ventricular response or altered diastolic ventricular function, AF also can cause HF symptoms even in patients with intact LV systolic function.

### *Anticoagulation*

The presence of AF in patients with HF increases the risk of stroke and systemic thromboembolism (STE) when compared to those without AF. [34] Likewise, AF can lead to left ventricular (LV) dysfunction, which in turn can compound the stroke risk. The risk of STE when HF is combined with AF is well described, and the clinical burden of STE events with regard to morbidity and mortality is substantial. [35] As described initially by the Framingham Heart Study investigators, the presence of HF carries a fourfold risk of STE events per year. [36] Other studies, including the Stroke Prevention in Atrial Fibrillation study (SPAF), have also demonstrated that LV dysfunction is a particularly significant independent risk factor for cerebral vascular accident (CVA.) [37–43]

Risk stratification schemes such as the CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores divide patients into low, intermediate, and high-risk groups and are invaluable in assessing the need for anticoagulation. [44–47] Recently



the American Heart Association/American College of Cardiology/Heart Rhythm Society AF guidelines have promoted the utility of the CHA<sub>2</sub>DS<sub>2</sub>-VASc over the CHADS<sub>2</sub> score to identify patients who are at truly low risk for STE events. [48] Additionally, the CHA<sub>2</sub>DS<sub>2</sub>-VASc score takes into consideration risk factors that were not previously accounted for (*i.e.*, female sex, age 65–75 years, vascular disease). [49] Patients at high stroke risk (*i.e.*, CHA<sub>2</sub>DS<sub>2</sub>-VASc  $\geq 2$ ) clearly benefit from anticoagulation with oral anticoagulants (OACs; either vitamin K antagonists [VKAs] or the novel oral anticoagulants [NOACs; see below]). Patients at intermediate risk (CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 1) are eligible for either aspirin alone or OAC therapy. [48] In AF patients with HF as their only risk factor, however, there is some evidence to suggest that therapy with OAC may be superior to aspirin alone (see below).

Recent data from smaller series of patients suggest that among intermediate–risk patients with AF, VKAs may be superior to antiplatelet agents alone for CVA protection, without a significant difference in major bleeding. [50] In a study of such patients, Gorin *et al.* reported a lower rate of CVA and mortality with VKA (RR=0.42, 95% CI 0.29–0.60,  $p < 0.0001$ ). [51] Overall, VKAs are to be superior to antiplatelet regimens in intermediate–risk patients, but this has not been specifically described in patients with HF. [52]

Importantly, the independent risk of stroke in patients with HF

complicating AF may be underestimated by commonly used risk stratification schemes. Specifically, similarly scored individual risk factors for STE events in AF do not imply exactly equivalent actual additional risk. [37–40, 53,54] Notably, in the Framingham Heart Study, HF carried a fourfold risk of STE events per year, whereas hypertension and coronary heart disease (CHD) implied only three times and twice the risk, respectively. [36] Thus, many experienced clinicians elect to anticoagulate patients with HF as their only CHA<sub>2</sub>DS<sub>2</sub>-VASc risk factor, using either VKA or a NOAC, if the bleeding risk is low. When making this decision, the HAS-BLED score can be utilized to assess the bleeding risk of anticoagulation. [55]

Clinical trials assessing the risk of STE events in AF have used various definitions for the diagnosis of HF. To date, clinical risk scores do not differentiate between clinical HF with preserved ejection fraction (HFpEF) and LV systolic dysfunction with or without HF symptoms. [44–46,48] Attempts have been made to correlate risk with the level of systolic dysfunction, but the results are mixed. [56–58] However, these data are confounded by inequalities in comorbid clinical factors that sway the results. From the best available evidence, it appears that there is no difference between HFpEF and LV systolic dysfunction in terms of CVA/STE risk. [57] Given the available evidence, we advise that the presence of clinical HF with evidence of either impaired LV systolic or diastolic function should imply to the clinician greater stroke risk than

when HF is absent, as has been suggested by Boos *et al.* [59]

The NOACs dabigatran, rivaroxaban, apixaban, and edoxaban, have recently become FDA approved for stroke prevention in nonvalvular AF, and are gaining widespread use. Data from the RE-LY and ARISTOTLE trials (examining dabigatran and apixaban, respectively) showed antithrombotic superiority, while ROCKET AF and ENGAGE AF-TIMI 48 (examining rivaroxaban and edoxaban, respectively) demonstrated noninferiority when compared to VKA. [60–63] Conveniently for the present review, these trials featured relatively large proportions of HF patients (32%–63%) with only small interstudy discrepancies in their criteria for the diagnosis of HF. Specifically, these trials included patients with current clinical HF, or  $\geq$  New York Heart Association (NYHA) II symptoms within 6 months of the enrollment, in their HF cohorts. However, LV ejection fraction (LVEF)  $<40\%$  qualified for systolic dysfunction in RE-LY and ARISTOTLE, while patients in ROCKET AF required LVEF  $<35\%$  for the diagnosis of HF. Of note, HF was not specifically defined in ENGAGE AF-TIMI 48.

Detailed subgroup analysis in the major NOAC trials showed similar benefit in the subgroups with HF with reduced LVEF (HfrEF) and HFpEF to what was found in the total study population. [60–62] For example, an analysis from ARISTOTLE compared patients with LV systolic dysfunction (LVEF  $<40\%$ ) to patients with HFpEF (LVEF  $>40\%$ ), and found no difference

in the risk of STE events in warfarin-treated patients, nor in subsequent reduction of risk with apixiban. [64]

The advantages of the NOACs over VKA include the convenience of a fixed therapeutic dose without obligatory monitoring. Of note, however, HF patients often demonstrate variable renal function, which may influence circulating levels of prescribed NOACs, although apixaban undergoes only ~30 % renal metabolism and is approved even in severe renal failure and dialysis patients. In such patients, however, caution with the use of many NOACs seems prudent. Potential drawbacks of NOACs are their relatively increased cost compared with VKA, and the present lack of a commercially available reversal agent. Warfarin remains an acceptable therapy for many patients, and may be the only option when NOACs are cost prohibitive.

For most patients, VKA is most effective when the INR is maintained between 2 and 3. Based on evidence from the ACTIVE A and W Trials, the INR must be maintained in this therapeutic range >65% of the time to achieve the therapeutic benefit of warfarin for prevention of embolization. [52, 65–66] Low scores on the novel risk tool SAME-TT<sub>2</sub>R<sub>2</sub> have been shown by Lip *et al.* to identify patients who will likely have a high time in therapeutic range, and hence may derive the most benefit from VKA. [67] Conversely, high SAME-TT<sub>2</sub>R<sub>2</sub> scores predict low TTR, perhaps favoring treatment with a NOAC.

Lastly, increased bleeding risk with concomitant anti-platelet agents and OACs should be taken into consideration in patients with AF. In a retrospective analysis of 37,464 patients with HF and vascular disease, the addition of a single antiplatelet agent to VKA therapy was not found to enhance benefit in either thromboembolic (HR 0.91; 95% CI 0.73–1.12) or CHD risk (HR 1.11; 95% CI 0.96–1.28), but increased the frequency of bleeding (HR 1.31; 95% CI 1.09–1.57). [68]

#### *Rate control or rhythm control*

Thus far, randomized clinical trials have yet to demonstrate any mortality benefit from pharmacological rhythm control in patients with HF. Data from two large trials, including one exclusively examining HF patients, did not support benefit of a rhythm control strategy with regard to overall mortality and stroke risk. [69, 70] This was an unexpected finding, given data from registry populations and study subsets suggesting adverse outcomes with HF and prevalent AF. [6–9, 12, 16] Critics have argued that imperfect effectiveness of normal sinus rhythm (NSR) maintenance and adverse effects of current pharmacological therapy potentially limited benefit of rhythm control in these studies. [71]

The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial was the largest randomized trial to compare the rate-control and rhythm-control strategies. AFFIRM demonstrated

similar all-cause mortality at five years (24 vs. 21%,  $P=0.08$ ).

Supplementary analysis suggested that there was a gross mortality benefit to successful maintenance of NSR, but that effect was neutralized by an increase in mortality associated with antiarrhythmic drug (AAD) use. [72] Only 23% of patients in AFFIRM had clinical HF, so extrapolation of these findings to the HF population must be made with caution. [69]

The AF in Congestive Heart Failure (AF-CHF) trial was the most recent investigation comparing these two treatment strategies in HF patients specifically. The AF-CHF investigators randomized 1376 patients with systolic dysfunction and AF to rhythm control vs. rate control. There was no identified difference in overall survival, cardiovascular (CV) death, worsened HF, or stroke. [70] Unlike in AFFIRM, a post hoc analysis of AF-CHF failed to demonstrate any benefit to successful NSR maintenance, and use of antiarrhythmic agents was still associated with increased mortality. [73] The authors stressed that the mortality benefit of maintaining NSR is likely outweighed by the incomplete efficacy of, and adverse effects related to, current AADs. Arguably, the AAD-related increase in mortality in older trials could be accounted for by frequent use of Class I AADs, which may themselves increase mortality in some populations. However, patients in the AF-CHF trial instead received either amiodarone or dofetilide (Class III AADs) and still failed to demonstrate benefit. [70,74-76] Whether Class III drug toxicity was partly responsible for this finding is unclear at this time.

Given these data, AADs are primarily appropriate for symptom amelioration and improvement in quality of life (QoL), rather than for extension of life. Not surprisingly, many patients with HF have significant symptoms while in AF as compared to when they are in NSR. Because patients with HF may be more dependent on the left atrium's contribution to LV filling, they may benefit more from restoration of NSR than would their counterparts without HF. While large randomized studies such as AFFRIM and AF-CHF examined the endpoint of mortality (and failed to show a benefit), symptom relief was not studied specifically. [69,70] In contrast, the Randomized Controlled Study of Rate Versus Rhythm Control in Patients with Chronic Atrial Fibrillation and Heart Failure (CAFÉ-II) demonstrated in patients assigned to rhythm control not only improved QoL ( $p=0.019$ ), but also improved LV function ( $p=0.014$ ) and lower NT-pro Brain Natriuretic Peptide (BNP) levels ( $p=0.05$ ) at one year. [77] However, similar NYHA class and 6-minute walk test (6MWT) distance were observed whether a rate-control or rhythm-control strategy was pursued ( $p=NS$  for both). [77] The management strategy of NSR restoration with AADs is appropriate in HF patients with symptomatic AF.

Of the available AADs, only amiodarone and dofetilide are recommended in patients with LV dysfunction and/or clinical HF (see Table 1). [48] Amiodarone is the most effective AAD, but its potency is at best 60% at one year and its use carries a non-negligible risk of adverse

effects. [78,79] Dofetilide therapy is less effective, and its initiation requires a three-day hospitalization due to its potential to prolong the QT interval, which can lead to torsades de pointes in 0.8–3.3% of patients. [48, 80–81] Because dronedarone was associated with increased mortality in randomized hospitalized patients with advanced HF (NYHA III–IV), its trial in the HF population was terminated early. [82] Currently, dronedarone is not recommended for patients with advanced HF nor in patients with recent decompensated HF. [48]

Newer AADs including vernakalant, budiodarone, and adjuvant ranolazine (which was used with dronedarone in the HARMONY trial) are also being investigated, and may meet the promise of efficacy with improved safety. However, current trials examining these agents do not include patients with significant LV dysfunction. [83–86]

#### *Upstream Therapy for AF Prevention in HF*

Interest is burgeoning in primary prevention of AF in patients with LV dysfunction. Evidence for the utility of upstream (non-antiarrhythmic) therapy has emerged from observations in large clinical trials and experimental data. [87–89] These therapies treat the underlying condition while targeting substrates, such as atrial remodeling and fibrosis, that have been implicated in the development of AF. [27]



Therapy with angiotensin converting enzyme inhibitors (ACEi) and/or angiotensin receptor blockers (ARB) has been shown to prevent cardiac remodeling and fibrosis, and these drugs appear to be a reasonable and safe additive nonantiarrhythmic intervention. Retrospective analyses of large clinical trials have identified ACEi use among HF patients as an effective therapy in reducing the incidence of AF. [88,89] For example, a substudy of the Studies of Left Ventricular Dysfunction (SOLVD) trial demonstrated lower AF occurrence in patients treated with enalapril over 2.9 years (5.4% vs. 24% with placebo;  $P < 0.0001$ ). [89] As seen in the Valsartan Heart Failure Trial (Val-HeFT) and the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) study, ARBs also showed some benefit, but with more modest results. [90,91] In CHARM, for example, in which AF was a prespecified secondary endpoint, among 6379 patients with symptomatic HF, new onset AF was lower in the group treated with candesartan (5.6% vs. 6.7%;  $P = 0.048$ ). Thus, the 2014 AHA/ACC/HRS AF guidelines support ACEis or ARBs as reasonable therapy for primary prevention of AF in patients with HFrEF. [48] Interestingly, the efficacy of ARBs to prevent AF so far may be limited to patients with structural heart disease. Specifically, the Angiotensin II-Antagonist in Paroxysmal Atrial Fibrillation (ANTIPAF) trial randomized 430 patients without structural heart disease to either placebo or olmesartan, and found no difference ( $P = 0.77$ ) in AF burden during a 12-month follow-up period. [92]

Beta blockade (BB) may not be as useful for the treatment of HF in patients with AF as it is in patients in NSR. At present, major guidelines do recommend BB in patients with HF and AF (Class I, level of evidence A). [48] Additionally, robust trial data show convincingly that BB reduces morbidity and mortality among HF patients in general. [93–96] Although not specifically studied in the HF population, there was no previous signal of harm. However, two large meta-analyses recently suggested that the use of BB as standard therapy in concomitant AF and HF should be revisited. [97,98] Investigators from the  $\beta$ -blocker in Heart Failure Collaborative Group assessed trials involving a total of 18,254 patients (3,066 [17%] with AF), and found that BB led to a reduction in all-cause mortality in patients with NSR (HR 0.73; 95% CI 0.67–0.80;  $p < 0.001$ ), but not in patients with AF (HR 0.97; CI 0.83–1.14;  $p = 0.73$ ), when compared to placebo. [97] In a separate meta-analysis, Rienstra *et al.* had similar findings when examining trials totaling 8,680 patients with HF, of whom 1,677 had AF. In this meta-analysis, again BB showed significant reduction in mortality in patients in NSR (OR: 0.63; 95% CI 0.54–0.73) but not in patients with AF (OR 0.86; CI 0.66–1.13). [98] Likewise, in both analyses, BB was not associated with a reduction in HF hospitalizations among patients in AF. Interestingly, BB was associated with a 33% reduction in new onset AF (4% vs 6%, OR 0.67 [0.57–0.79]). [97] Additionally, a meta-analysis of seven large RCTs of BB found similar results: a reduced risk of AF (OR 0.73) among 11,952 patients with HF.

[99] In sum, therefore, the evidence suggests that BB can reduce the incidence of AF in HF patients, but they do not seem to be as effective in preventing major adverse CV outcomes in AF patients with chronic HFrEF. The authors have cited several plausible explanations for this differential effect of BB, including adverse impact of slow heart rate during AF, or that AF is simply a marker of a worse clinical condition in which improvement is more difficult to achieve. [97]

In patients with LVEF <35% and mild symptoms (NYHA II), the addition of the aldosterone blocker eplerenone to an optimal HF regimen demonstrated further reduction in new onset AF (HR 0.58, P=0.034).

[100] The utility of upstream therapy for the primary prevention of AF in patients with known LV dysfunction should not be disregarded. While further randomized data are needed, the experience with these now conventional HF therapies supports their role in primary prevention of AF in HF.

#### *Catheter-Based AF Ablation in HF*

In part due to the risks of AADs and its incomplete success in maintaining NSR, catheter-based ablation (CA) has emerged as a formidable therapeutic option in the management of AF. [101] Current data regarding CA support its safety, efficacy, and utility in alleviating symptoms and improving QoL. [102,103] However, whether CA reduces

all-cause mortality, stroke, and HF is still under investigation. [104]

Most patients included in CA trials are relatively young, with little co-morbidity, and normal to mildly reduced LVEF. [102] However, in two randomized controlled trials comparing CA to AAD, encouraging evidence showed clinical equivalence between these two therapies. These findings further support the recent American Heart Association/American College of Cardiology/Heart Rhythm Society Class IIa recommendation in favor of CA as first line therapy in patients with symptomatic paroxysmal AF, after considering the risks and benefits of AADs versus CA. Likewise, CA-based pulmonary vein isolation (PVI) is a Class I indication for CA when AF is refractory to therapy with at least one AAD. [48, 105–106] It should be noted that the latest CA guidelines do not distinguish patients with LV dysfunction from those without, but they do mention that recurrence rates and complication rates may be higher in the cardiomyopathic population. [48]

In nonrandomized studies of HF patients with AF, catheter-based PVI has demonstrated benefit, including improvements in CV function, exercise capacity, and QoL. [107–110] Reports vary from 73% to 87% success in maintaining NSR among HF patients at one year post-procedure. Additionally, post-PVI improvements in LV function have been noted. For example, in ARC-HF (A Randomized Trial to Assess Catheter Ablation Versus Rate Control in the Management of Persistent Atrial Fibrillation in Chronic Heart Failure), an open-label, blinded-endpoint

trial, 52 symptomatic AF patients with LVEF<35% were followed for 12 months after randomization to PVI vs. rate control. These investigators reported a success rate of 88% for maintaining NSR at one year in patients who underwent PVI. Following PVI, objective exercise performance improved, including peak oxygen consumption (+3.07 ml/kg/min, p=0.02). In addition, Minnesota symptom scores were improved, BNP was lower, and trends toward improved 6MWT (p=0.10) and LVEF (p=0.055) were demonstrated. [111] More recently, a single-center randomized trial, CAMTAF (Catheter Ablation Versus Medical Treatment of AF in Heart Failure), found that CA was effective in restoring NSR (81%) in selected patients with persistent AF and HF. Baseline LVEF was  $32\pm 8\%$  in the CA group and  $34\pm 12\%$  in the medical group. Investigators reported improved LV function at 6 months in the ablation group compared with the rate control group ( $40\pm 12\%$  vs.  $31\pm 13\%$ ; P=0.015), as well as improved functional capacity ( $22\pm 6$  vs.  $18\pm 6$  mL/kg per minute; P=0.014) and HF symptom scale score ( $24\pm 22$  vs.  $47\pm 22$ ; P=0.001). [112]

Clearly, CA is rapidly evolving at present, and improvements in the efficacy and safety of this procedure occur frequently. [113] Numerous studies have demonstrated the superiority of CA over medical therapy in maintaining NSR in structurally normal hearts. The initial experience suggests that these advantages may also extend to patients with HF – however at this time the number of randomized studies remains small.

Unquestionably, additional prospective data describing CA-related mortality and morbidity in patients with LV dysfunction are needed. Ongoing clinical trials such as the Canadian RAFT AF (A Randomized Ablation-based Atrial Fibrillation Rhythm Control Versus Rate Control Trial in Patients With Heart Failure and High Burden Atrial Fibrillation) and the international CASTLE-AF (Catheter Ablation Versus Standard Conventional Treatment in Patients With Left Ventricular Dysfunction and Atrial Fibrillation) trials may help to fill this void. [104,114] At the present time, CA appears to be technically feasible in symptomatic patients with HF, without a significantly higher procedural complication rate than in patients without HF. [113] Catheter-based PVI may also improve LV performance, reduce symptoms, and improve QoL.

*Atrioventricular Node (AVN) Ablation and Pacing for Cardiac Resynchronization Therapy (CRT)*

Recently, CRT with subsequent radiofrequency ablation of the AVN has been shown to be effective in AF patients with a rapid ventricular response who are refractory to medical therapy (Class IIa recommendation). [115] Likewise, patients with persistent/permanent AF, an implanted CRT device, and suboptimal biventricular pacing also may benefit from AVN ablation. [116] By eliminating rapid intrinsic ventricular activation, AVN ablation in these HF patients may optimize synchronized biventricular activation. [117]

A recent meta-analysis, including data from 450 patients with concomitant HF and AF in three non-randomized trials, concluded that AVN ablation was associated with a reduction in all-cause mortality (RR 0.42,  $p < 0.001$ ) and CV mortality (RR 0.44,  $p = 0.008$ ). [118] However, long term outcome data suggest that for several outcome measures, PVI outperforms AV node ablation and pacing.[110] For instance, the Pulmonary Vein Isolation for AF in Patients with Heart Failure (PABA-CHF) trial showed that those randomized to PVI had a significantly higher mean LVEF (35% vs. 28%), better performance on the 6MWT (340 vs. 297 m), and a superior QoL score. [119] Additionally, another trial in elderly patients showed a higher incidence of new HF at 5 years in the ablate-and-pace group when compared to those who underwent AF ablation (53% vs. 24%). [120]

### *Surgical and Hybrid Therapy*

Surgical therapy of AF (*e.g.*, via the Cox Maze procedure) can result in high rates of freedom from arrhythmia (up to 93%) over an 8.5-year follow up period, with an operative mortality of 3%. [121, 122] Surgical PVI techniques using either radiofrequency ablation or cryoablation are less complicated than the full Maze procedure, and do not require an atriotomy nor additional time on cardiopulmonary bypass. [122] Procedural success with surgical PVI has been generally favorable but

variable (50–91%). [122] Current recommendations suggest standalone AF surgery in symptomatic AF patients who have failed medical management and prefer a surgical approach, or have failed one or more attempts at CA, or are not candidates for CA. [123]

A novel minimally invasive, hybrid epicardial and endocardial CA approach called the “Convergent” procedure shows promise. [124] The procedure circumvents sternal and/or thoracic incision by utilizing a sub-diaphragmatic endoscopic access to deliver epicardial CA lesions, and also uses simultaneous endocardial CA. While safety and efficacy of this procedure have been established in nonrandomized trials, there is a paucity of experience in HF patients. [124,125]

*Conclusion:*

Concomitant AF and HF consistently demonstrate a poor prognosis, increase hospitalization, and adversely affect mortality. While shared risk factors account for much of their frequent co-existence, HF can also cause AF, and vice versa. Certainly, HF begets AF via a complex interplay of atrial stretch, fibrosis, autonomic dysregulation and inflammation. Restoration of NSR with AADs can be effective in alleviating symptoms, but has failed to show a mortality benefit over rate control. Nevertheless, current AADs continue to have limited efficacy in NSR promotion, and CA has been shown to be superior to AADs in maintaining NSR. While



improvements in QoL and morbidity have been reported in HF patients, limited data exist regarding this population. Ongoing randomized multicenter studies examining mortality as well as HF outcomes with CA are currently underway. These data will hopefully clarify the utility of CA in patients with concomitant AF and HF. At the present time, the existence of symptoms when the patient is in AF is the primary indication for rhythm restoration over rate control. Lastly, novel risk characterization schemes and OACs are now accessible, and knowledge of their utility and limitations are necessary to optimize the care for patients with both AF and HF.

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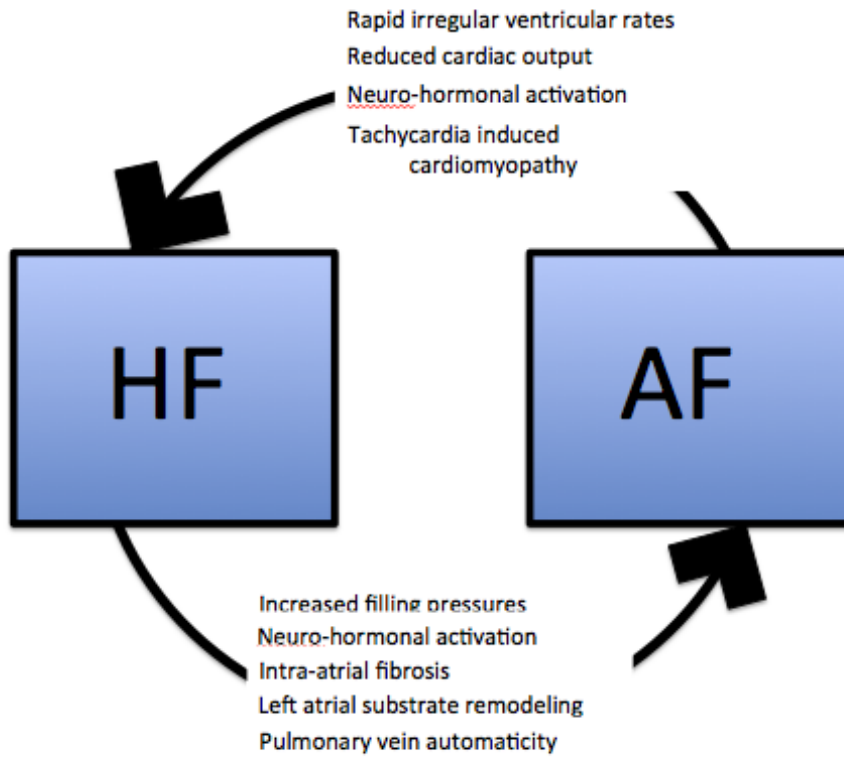
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**Figure 1: The interrelated pathophysiology of AF and HF**



ACCE



**Table 1: Antiarrhythmic Agents for Atrial Fibrillation in Heart Failure**

Agent	Dosing	Adverse Effects	Interactions
<b>Amiodarone</b>	100–200 mg. PO load 1.2 g- 1.8g/day until 10 g total.	•Hypo- or hyperthyroidism, retinal deposits, pulmonary fibrosis, hepatotoxicity	•Numerous; CYPs to cause drug interaction; Inhibits P-glycoprotein: ↑digoxin concentration
<b>Dofetilide</b>	125–500 mcg BID, based on renal function	•Prolonged QT interval, Torsades de Points (TDP), dizziness, diarrhea.	•Primary renal elimination *Avoid other QT interval–prolonging drugs; verapamil, HCTZ, cimetidine, ketoconazole, trimethoprim, prochlorperazine, and megestrol are contraindicated
<b>Dronedarone</b>	400 mg BID	•QT prolongation, hepatotoxicity, abdominal pain, HF exacerbation, bradycardia  <b><i>*Do not use in advanced HF, or with recent hospitalization</i></b>	•CYP3A, P-glycoprotein interactions; ↑concentrations of some statins, digoxin, dabigatran, other drugs

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