Current Approaches to Antiarrhythmic Therapy in Heart Failure

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KEYWORDS

• Congestive heart failure • Antiarrhythmics • Atrial fibrillation • Rhythm control
• Ventricular tachycardia • Electrical storm • ICD shocks

KEY POINTS

- Atrial fibrillation (AF) is exceedingly common in patients with heart failure (HF), as they share common risk factors.
- Rate control is the cornerstone of treatment for AF in patients with HF; however, restoration of sinus rhythm should be considered when more than minimal symptoms are present.
- Although implantable cardioverter defibrillators (ICDs) protect against sudden cardiac arrest in patients with HF, many will present with ventricular tachycardia (VT) or ICD shocks.
- Antiarrhythmic drug therapy beyond beta-blocker therapy remains fundamental to the termination of acute VT and the prevention of ICD shocks.

INTRODUCTION

Antiarrhythmic drug therapy is used for 3 major purposes in patients with congestive heart failure (HF): maintenance of sinus rhythm (SR) in those with atrial fibrillation (AF), acute treatment of ventricular tachycardia (VT), and prevention of implantable cardioverter defibrillator (ICD) shocks. Management of arrhythmias in patients with HF requires nuance on the part of the provider. The efficacy of antiarrhythmic drugs must be balanced against its potential side effects and alternate therapies. Nevertheless, antiarrhythmic drug therapy retains a significant role in the chronic management of patients with HF.

SUPRAVENTRICULAR ARRHYTHMIA

Supraventricular tachycardia (SVT) is an arrhythmia that originates from the atria. The most common of these is AF. Other SVTs include atrial flutter, atrioventricular nodal reentrant tachycardia (AVNRT), atrioventricular reentrant tachycardia (AVRT), and atrial tachycardia. Typical atrial flutter (AFL), AVNRT, and AVRT are best treated with catheter ablation due to its high success rate and low risk of complications.[1] However, AF, atypical atrial flutter, and certain forms of atrial tachycardia often are treated first with medical therapy in the form of an antiarrhythmic drug. This review focuses on AF, the most prevalent atrial arrhythmia, which often is treated with antiarrhythmic drug therapy.

AF: EPIDEMIOLOGY AND PATHOPHYSIOLOGY

AF is the most common arrhythmia and is increasing in prevalence.[2] Current estimates are that AF affects 2.2 million people in the United States and it is projected that number will be approximately 15 million

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by 2050.[3] HF is one of the leading causes of death worldwide and its incidence is also increasing.[4,5] These companion epidemics have accelerated the need for management options for AF in this population.

Chronic HF results in structural remodeling that creates an ideal substrate for atrial fibrillation. There is a complex interplay among ultrastructural, electrophysiologic, and neurohormonal changes that promote the coexistence of AF in HF (Fig. 1)[6–9]:

- Persistent left atrial hypertension from poor left ventricular (LV) chamber compliance and function promotes interstitial fibrosis and decreased gap junction surface area
- Structural myocyte changes lead to a reduction of repolarizing potassium currents and consequently abnormal intracellular calcium handling
- A decline in electrical coupling between neighboring myocytes slows conduction within the myocardium
- Baseline pathophysiological activation of the sympathetic system
- HF medications may perturb electrolytes, which can influence further susceptibility to a proarrhythmic state

HF and AF share several risk factors, including coronary artery disease, diabetes mellitus, hypertension, obesity, and obstructive sleep apnea.[10] These contributing factors lead to a high prevalence of AF in HF, affecting 30% of all individuals with HF, including those with reduced or preserved ejection fraction.[11,12] In addition, there is

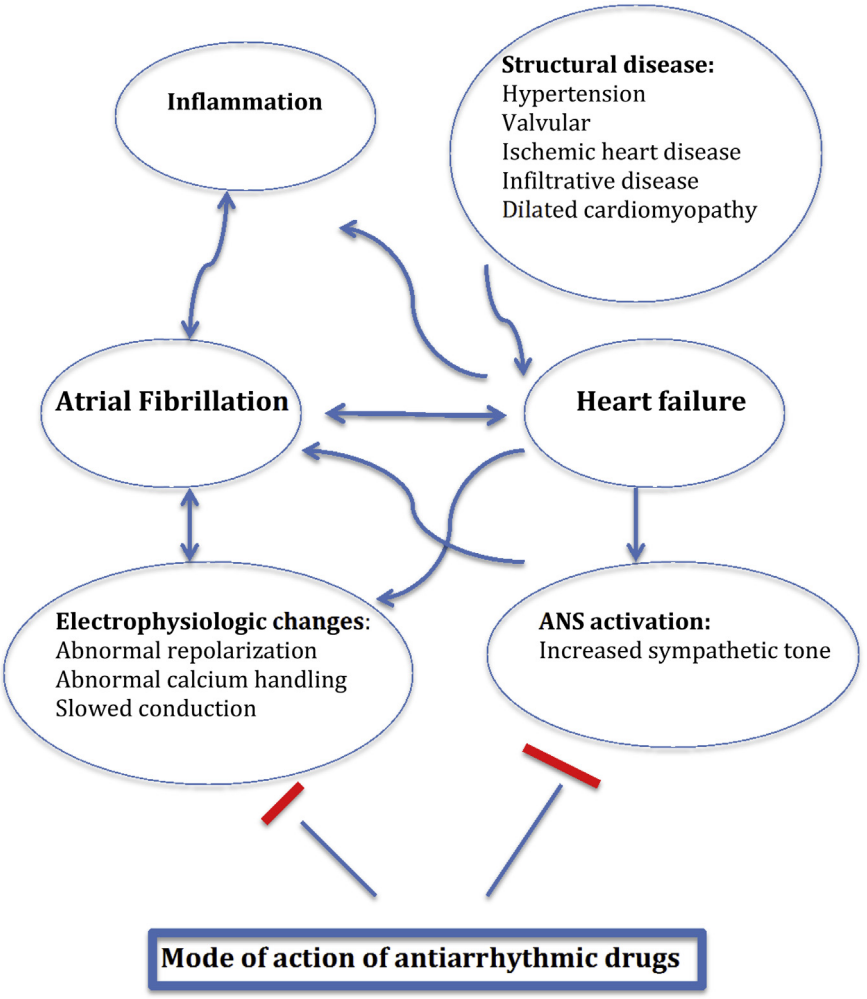

Fig. 1. There is a complex relationship between the multiple factors that promote the coexistence of AF in HF; antiarrhythmics can be used to target electrophysiologic changes and abnormal autonomics which promote AF. ANS, autonomic nervous system.

a direct relationship between the prevalence of AF and worsening HF class.[13] Thus, the treatment of AF in patients with HF may be an important step to prevent further worsening of HF symptoms leading to hospitalization or mortality.

Although many studies have shown that the presence of AF in patients with HF is associated with an adverse prognosis, it remains unclear whether targeting AF with a view to maintaining SR improves outcomes.[11,14–17]

ACUTE MANAGEMENT OF AF IN PATIENTS WITH HF

One-third of patients with HF with an acute exacerbation present in AF with rapid ventricular response, potentially precipitating an acute HF exacerbation.[14,18] Several aspects to the therapy of acute AF need to be considered:

- Atrioventricular (AV) nodal blockade has become the mainstay of therapy for rate control, as it limits how quickly rapid fibrillatory waves reach the ventricle
- Beta-adrenergic receptor blockers (beta-blockers), nondihydropyridine calcium channel blockers (CCBs), and digitalis glycosides prolong the refractoriness of the AV node and can be used for reducing ventricular rate[19]
- Analysis from the AFFIRM study demonstrated that beta-blockers were more effective than CCBs in the acute setting for rate control (70% vs 54%, respectively)[20]
- Additionally, CCBs have negative inotropic effect, and should be avoided in those with significant LV dysfunction
- Digitalis has a slower onset of action and is relatively ineffective in higher adrenergic states; should be avoided for acute rate control[2]
- Direct current cardioversion (DCCV) is the most effective method for conversion to SR, but clinicians must consider the risk of sedation (ie, stable patient with HF can be susceptible to drops in blood pressure)[21]
- Transesophageal echocardiogram (TEE) is necessary to rule out left atrial clot before DCCV if the AF episode has lasted more than 48 hours without concomitant anticoagulant therapy
- A TEE-guided cardioversion is equivalent to a standard approach of anticoagulation therapy 3 weeks before and 4 weeks after DCCV[22]

LONG-TERM MANAGEMENT OF AF IN PATIENTS WITH HF

A major treatment decision in the patient with HF with AF, is whether to pursue a rhythm control strategy over rate control for long-term management. Six major trials have been conducted to clarify the optimal treatment for AF (**Table 1**). Thus far, there is no compelling evidence that pharmacologic maintenance of SR leads to a better outcome as compared with rate control.[23–31]

However, it is noteworthy that quite a few limitations must be considered with these initial studies. A significant number of cross overs between strategy options, adverse effects of antiarrhythmic drugs, and general ineffectiveness of drugs used for rhythm control may have contributed to the lack of benefit seen with a rhythm-control strategy. In addition, therapy for stroke prophylaxis differed between treatment approaches and may have contributed to differences in outcome, biasing benefit toward the rate-control option.

Post hoc subgroup analyses from these large studies suggest a higher likelihood of survival in patients who were maintained in SR.[32–34] However, extrapolation of these data to the HF population is difficult because of the low number of patients with HF in the study sample. For example, in the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial, only 23% of the study population had HF.[26] A more contemporary study by the Atrial Fibrillation and Congestive Heart Failure Investigators (AF-CHF trial), focused solely on a population with HF (n = 1376).[31] However, this study also failed to show superiority of rhythm control over rate control with respect to cardiovascular mortality.

Improvement in left ventricular ejection fraction (LVEF), n-terminal pro-brain natriuretic protein, and quality of life has also been reported in smaller studies with rhythm control strategies.[33] However, these results have yet to be replicated in larger trials. Despite the lack of mortality benefit from the rhythm-controlling strategy with antiarrhythmic drug therapy in AF-CHF, there was no increased cost associated with the strategy.[35]

IS RHYTHM CONTROL EVER THE RIGHT ANSWER?

Frequently patients with HF have substantial symptoms while in AF as compared to when they are in SR. Significant benefit may be achieved with return of the left atrial contribution to stroke volume in certain patients with HF. Thus, rhythm restoration is generally considered acceptable when patients with HF exhibit more than minimal symptoms. Conversely, rate control is the backbone of therapy if symptomatology does not differ significantly between SR and AF.

It should be noted, however, that a population of patients with systolic HF and atrial fibrillation

Table 1
Major trials comparing rate versus rhythm control strategy for atrial fibrillation

Trial, Year	Total No. of Patients	Patients with Heart Failure, %	Mean Age, y	Mean Follow-up, y	Rhythm Control Group	Rate Control Group	Outcomes
PIAF,[23,24] 2000	252	4	60.5	1	Amiodarone or DCCV	Diltiazem, BB, Digoxin or AVNA + PM	No significant differences in quality of life in patients in sinus rhythm or AF
AFFIRM,[26] 2002	4060	23	70	3.5	Amiodarone, sotalol, propafenone, procainamide	Digoxin, BB, Diltiazem, Verapamil	No significant differences in all-cause mortality; trend toward increased mortality with rhythm control
RACE,[28] 2002	522	50	68	2.3	Sotalol, flecainide, propafenone, amiodarone	Digoxin, CCB, BB	No significant differences in composite end point (cardiovascular death, CHF, embolic events, bleeding, pacemaker, severe adverse effects of AADs)
STAF,[29] 2003	200	56	65.8	1.6	Class I, sotalol, amiodarone	BB, Digoxin, CCB or AVNA + PM	No significant differences in composite end point (CPR, death, cerebrovascular and embolic events)
HOT CAFE,[30] 2004	205	46	60.8	1.7	Disopyramide, propafenone, sotalol, amiodarone	BB, CCB, Digoxin or AVNA + PM	No significant differences in composite end point (all-cause mortality, embolic events or major bleeding)
AF-CHF,[31] 2008	1376	100	66.5	3.1	Amiodarone, sotalol, dofetilide, or DCCV	BB, Digoxin or AVNA + PM	No significant differences in cardiovascular death

Abbreviations: AF, atrial fibrillation; AVNA, atrioventricular nodal ablation; BB, beta-blocker; CCB, calcium channel blocker; CHF, congestive heart failure; CPR, cardiopulmonary resuscitation; DCCV, direct current cardioversion; PM, pacemaker.
Data from Refs.[24,26,28–31]

(particularly rapid atrial fibrillation) may have developed HF directly as a result of atrial fibrillation.[36] When no other etiology is isolated, tachycardia-induced cardiomyopathy may be diagnosed. In this situation, rhythm control of atrial fibrillation is the preferred option with the goal of sustained rhythm control and resolution of the cardiomyopathy.[37]

MEDICAL THERAPY WITH RATE CONTROL: BETA-BLOCKERS, CALCIUM CHANNEL BLOCKERS, AND DIGOXIN

Beta-blockers, which also serve as evidenced-based treatment in systolic HF, are generally first-line for rate control via their effect on the AV node. As expected, a retrospective analysis of the US Carvedilol Heart Failure Trial established improved outcomes in patients with HF with concomitant AF who were in the treatment group.[38] Similar in their effect on the AV node, the *nondihydropyridine CCBs* (including verapamil and diltiazem) also are effective rate-controlling agents. As discussed previously, at optimal doses for ventricular rate control, CCBs are generally not tolerated in the low LVEF patients.[39]

Digoxin not only increases the refractory period, but also triggers vagal activation to slow the conduction of electrical impulses through the AV node. As mentioned previously, it is less effective in states of increased sympathetic tone, such as exercise or worsening HF.[2] However, digoxin does have a synergistic effect with beta-blockers as evidenced by the improvement in survival of patients' concomitantly on carvedilol and digoxin in a retrospective analysis of the US Carvedilol Heart Failure Trials.[38] Given the very narrow therapeutic window of digoxin, it is recommended that serum levels be maintained at less than 1.0 ng/mL.[40] In patients with HF with AF, digoxin may be considered as an adjuvant therapy.

HOW LOW TO GO?

The Lenient versus Strict Rate Control in Patients with Atrial Fibrillation study (RACE II) compared strict rate control (resting heart rate <80 beats per minute) versus lenient rate control (resting heart rate <110 beats per minute).[41] In a cohort of more than 600 patients with permanent atrial fibrillation, randomization to a lenient strategy was not inferior to a strict strategy in terms of cardiovascular mortality, malignant arrhythmias, and rate of hospitalizations during a 3-year follow-up.[41]

The RACE II study has noteworthy limitations when applying it to the HF population that must be appreciated. The population studied was relatively healthy, with only approximately 10% of patients having a history of HF hospitalization and only 15% with a known LVEF of 40% or less.[41] Nonetheless, even with limited data, lenient heart control is a practical initial approach. If symptoms continue despite more aggressive control of rate, then a rhythm-control strategy may be needed.

RHYTHM CONTROL

In the chronic setting, pharmacologic options for maintenance of SR in patients with HF are limited. Class I antiarrhythmics, sodium channel blockers, are contraindicated in HF, given their propensity to promote reentry in the structurally abnormal heart leading to VT.[42] The options for therapy in patients with HF and AF include dofetilide, amiodarone, and, to a lesser degree, sotalol and dronedarone (**Table 2**).

Dofetilide is a class III antiarrhythmic that induces potassium channel blockade (I_{Kr}). It is renally cleared and requires dosing based on creatinine clearance.[43] The Efficacy of Dofetilide in the Treatment of Atrial Fibrillation-Flutter in Patients with Reduced Left Ventricular Function (DIAMOND) substudy randomized 506 patients with AF or atrial flutter to either treatment with dofetilide or placebo.[34] Of note, this included a relatively high-risk population, with more than 50% having New York Heart Association (NYHA) class III or IV symptoms. Among 234 patients who achieved restoration of SR, patients were more likely to remain in SR at 1 year on dofetilide over placebo (79% vs 42%). Importantly, dofetilide's safety was proven in this cohort, with similar mortality between the treatment and placebo group. Interestingly, mortality was lower in patients who had SR restored and maintained, which was independent of therapy.[34] In general, dofetilide is considered more effective in the maintenance of SR than it is for cardioversion.[44]

Despite its efficacy, the use of dofetilide as an antiarrhythmic agent for AF in clinical practice has been limited.[45] This is largely due to the US Food and Drug Administration's (FDA's) mandatory requirement that initiation of this agent requires a minimum 72-hour in-hospital monitoring period. As a consequence of its potassium channel blocking effects, it carries a significant risk of torsades de pointes.[46] This effect is generally encountered within the first 3 days of initiation and thus close monitoring of the QT interval is necessary.[47]

Amiodarone is a unique antiarrhythmic with multiple channel effects. It inhibits adrenergic stimulation (with alpha-blocking and beta-blocking properties) and blocks sodium, potassium, and calcium channels. Despite not being FDA approved for AF,

Table 2
Membrane active antiarrhythmic drugs

Vaughn-Williams Classification	Medication	Channel/Receptor Action*				Mechanism of Action	Side Effects	Comments
		Na	K	Alpha	Beta			
Ia	Procainamide	↓	↓	↓		• Slows conduction velocity • Increases refractoriness	• QT prolongation, TdP • Hypotension	• Monitor for hypotension • Contraindicated in impaired real function • Discontinue if QRS prolongation >50%
Ib	Lidocaine (intravenous) Mexiletine (oral)	↓				• Slows conduction velocity • Shortens refractoriness	• Drowsiness, visual disturbance, tinnitus • Seizure, obtundation (rare)	• Selectively acts on ischemic myocardium • Monitor concentration if using for >24 h
Ic	Flecainide	↓				• Slows conduction velocity	• Dizziness, headache, GI upset, blurred vision	• Contraindicated in CHD, significant LVH
	Sotalol		↓		↓	• Increases refractoriness • Blocks sympathetic activity • Decreases automaticity	• Dizziness, fatigue • QT prolongation, TdP • Bradycardia	• Monitor for QT prolongation (first 3 d) • Dose-related TdP • Renally cleared

III	Dofetilide		↓			• Increases refractoriness	• QT prolongations, TdP • Bradycardia	• Monitor for QT prolongation (first 3 d) • Dose-related TdP • Renally cleared • Contraindicated with verapamil, azoles, thiazide
	Azilimide		↓			• Increases refractoriness	• QT prolongation, TdP	• Not available in the US
	Amiodarone	↓	↓	↓	↓	• Long half-life • Slows conduction velocity • Increases refractoriness • Blocks sympathetic activity • Decreases automaticity	• Toxicity: thyroid, pulmonary, liver, GI, skin, eyes • Bradycardia • <0.5% TdP	• LFT, TFT every 6 mo • Ophthalmology annually • Monitor for symptoms: pulmonary, neurologic
	Dronedarone	↓	↓	↓	↓	• Short half-life • Slows conduction velocity • Increases refractoriness • Blocks sympathetic activity • Decreases automaticity	• Toxicity: less than amiodarone	• Avoid in NYHA class III/IV, severe systolic dysfunction • Contraindicated in persistent AF

Abbreviations: AF, atrial fibrillation; CHD, coronary heart disease; GI, gastrointestinal; LFT, liver function test; LVH, left ventricular hypertrophy; NYHA, New York Heart Association; TdP, Torsades de pointes; TFT, thyroid function test.

* Downward arrow denotes site of primary cardiac channel blockade.

amiodarone is the most commonly prescribed drug for AF.[45] Amiodarone has long been considered by cardiologists to be the most effective antiarrhythmic for the suppression of AF. It should be noted there are no head-to-head trials comparing amiodarone with dofetilide. The Canadian Trail of Atrial Fibrillation (CTAF) and the Amiodarone versus Sotalol for Atrial Fibrillation (SAFE-T) trial both demonstrated superiority of amiodarone in maintenance of SR at follow-up in comparison with sotalol.[48,49] The use of amiodarone has been documented in patients with HF with LVEF of 40% or less to confer a greater likelihood of conversion to SR over placebo. Furthermore, patients that reverted to SR with amiodarone had a lower total mortality than those who did not.[32]

The primary cardiovascular side effect of amiodarone in patients with HF is symptomatic sinus bradycardia, with a higher predominance of females requiring permanent pacemaker insertion.[50,51] While QT prolongation can occur given its potassium channel blockade properties, amiodarone very rarely induces torsades de pointes at less than 0.5%.[52]

Unfortunately, amiodarone is fraught with many noncardiac toxicities that require careful surveillance.[53] Hepatotoxicity ranging from low-level transaminase elevation to full out fulminant liver failure can occur. The pulmonary toxicity induced by amiodarone can manifest in numerous ways. Adult respiratory distress syndromes, acute hypersensitivity reactions with patchy infiltrates, solitary pulmonary nodules, and a chronic interstitial fibrosis are all reported in the literature.[54] Both hypo- or hyperthyroidism may also occur with use. Hypothyroidism, generally induced by a destructive thyroiditis phenomena, is more common.[55]

Sotalol blocks the same potassium current as dofetilide and is also renally cleared. The racemic d,l-sotalol formulation, which is the only available formulation in the United States, is also a nonselective beta blocker.[56] The Survival With Oral d-Sotalol (SWORD) investigators found that in survivors of myocardial infarctions with depressed ejection fractions, the use of d-sotalol was associated with higher mortality from ventricular arrhythmias.[57] Expert opinion suggest the use of sotalol only for those systolic HF patients with cardiac defibrillators in place. As discussed previously, sotalol is inferior to amiodarone for maintenance of SR when compared head-to-head.[49]

Dronedarone is a newer drug that was designed to mimic the antiarrhythmic effects of amiodarone but with a milder side effect profile. It was initially promising in the general AF population, as it was shown to be more effective over placebo in maintaining SR, but without the lung and thyroid effects seen with amiodarone.[58] However, the 2007 ANDROMEDA trial, which examined the use of dronedarone in symptomatic patients with HF (NYHA class III/IV) with severe LV dysfunction (LVEF <35%) tempered enthusiasm for its use in patients with HF. The trial was halted early because of a significant increase in death in the dronedarone group at a median follow-up of 2 months.[59] Consequently, current recommendations by the FDA are that dronedarone be avoided in patients with HF with recent decompensation or in those with advanced disease (NYHA class III/IV or severe systolic dysfunction of the left ventricle).

NONPHARMACOLOGIC APPROACHES TO RHYTHM CONTROL

AV node ablation with biventricular pacemaker implantation has been shown in small trials to be effective in patients with HF with AF and rapid ventricular response that is refractory to medical therapy.[60] Manolis and colleagues[60] demonstrated a significant improvement in LVEF in a subgroup analysis of 30 patients with HF and atrial tachyarrhythmias who underwent an “ablate and pace” strategy. At 2-year follow-up, the LVEF improved from 32% $\pm$ 9% to 48% $\pm$ 8% and NYHA functional class also improved. A recent, larger systematic review of this approach was looked at in patients with HF with concomitant AF and cardiac resynchronization therapy. Ganesan and colleagues[61] pooled mortality data from 450 patients across 3 nonrandomized trials and showed that AV node ablation in patients with HF with AF was associated with a reduction in all-cause and cardiovascular mortality. Prospective, randomized controlled trials are needed to confirm these results.

AV nodal ablation with biventricular pacing was compared with pulmonary vein isolation (PVI) for benefit of HF status in 81 patients with drug-refractory AF and LVEF of 40% or less.[62] It was found that PVI was superior to AV node ablation with biventricular pacing in improvement of LVEF and quality of life assessed by the Minnesota Living with Heart Failure questionnaire. At 6 months, the LVEF had improved in the PVI group from 28% up to 35% ($P<.001$).[62]

Catheter ablation of atrial fibrillation is quickly becoming a promising new therapeutic intervention in symptomatic patients with HF when rate-control and antiarrhythmic drugs have failed. Radiofrequency ablation performs superiorly to antiarrhythmic drug therapy in the maintenance of SR.[63] Tondo and colleagues[64] reported a success rate of 88% for maintaining SR at 1 year in patients undergoing PVI with impaired LV function.

Catheter-based ablation strategies also appear to improve LVEF and quality of life while increasing

exertional tolerance in nonrandomized trials. The ARC-HF trial examined 52 symptomatic patients with HF with LVEF of 35% or less and randomly assigned them to a rate control strategy versus PVI. At 12 months, peak oxygen consumption and quality-of-life scores were appreciably improved.[65] Hsu and colleagues[66] found improvement in LV chamber size and mean LVEF from 35% to 56% in 58 patients with HF who underwent PVI.

The data for nonpharmacologic treatment of AF in HF continues to grow. The efficacy and safety of catheter-based procedures is also steadily improving.[67] However, the benefit of catheter ablation must be balanced with the procedural risk in patients with HF. Sufficient data are currently lacking to make strong recommendations regarding where in the therapeutic approach catheter ablation of AF should fall in patients with HF. The 2013 American College of Cardiology Foundation/American Heart Association HF guidelines give a IIB recommendation for ablation in patients with HF with persistent AF and the presence of disabling symptoms when antiarrhythmic therapy has failed.[39]

VENTRICULAR ARRHYTHMIAS IN HF

Sudden cardiac death (SCD) is a sudden, unexpected death caused by loss of heart function. Half of all the heart disease deaths, or more than 350,000 deaths annually, in the United States are due to SCD.[68,69] Life-threatening ventricular arrhythmias, including VT and ventricular fibrillation (VF) are responsible for most sudden deaths.[70] Ventricular arrhythmias occur with a much higher prevalence in those with HF with reduced ejection fraction (HFrEF). In fact, the primary mode of death in patients with NYHA I, II, or III HF is sudden death due to ventricular arrhythmia.[71]

MECHANISMS FOR VENTRICULAR ARRHYTHMIA AND ANTIARRHYTHMIC DRUG THERAPY IN HF

Multiple potential factors contribute to the development of ventricular arrhythmias in patients with HF (**Fig. 2**)[72,73]:

- Myocardial fibrosis leads to loss of cell-cell coupling, resulting in slowed electrical conduction and providing a substrate for reentry
- Abnormal triggered activity provides a focal mechanism for arrhythmia
- Repolarization of myocardial cells is altered due to disruption of outward potassium current
- Ventricular dilatation contributes to alterations in action potential refractoriness and conduction
- Sympathetic activation promotes abnormal automaticity and precipitates triggered activity
- Activation of the angiotensin system leads to electrolyte disturbance, promoting arrhythmia
- Subendocardial ischemia manifests as enhanced automaticity and regional alteration in conduction velocity and refractoriness, which are proarrhythmic
- Drugs commonly used in the treatment of HF, including inotropes, phosphodiesterase inhibitors, and digoxin can be proarrhythmic

Antiarrhythmic drugs have mechanistic effects, which counter those contributing to the genesis of ventricular arrhythmias (see **Table 2**). Drugs used for the treatment of ventricular arrhythmia include the following:

- Class Ia antiarrhythmics (eg, procainamide) slow conduction velocity and increase refractoriness
- Class Ib antiarrhythmics (eg, lidocaine, mexiletine) slow conduction velocity and shorten refractoriness, particularly in ischemic myocardium
- Class II antiarrhythmics (beta-blockers) block sympathetic activity and reduce conduction velocity
- Class III antiarrhythmics (sotalol, dofetilide, azimilide) increase refractoriness
- Amiodarone or dronedarone are drugs with combined effects that slow conduction velocity, block sympathetic activity, and increase refractoriness

The use of ICDs has revolutionized the care of the patient with HF. However, ICDs only provide a rescue therapy for ventricular arrhythmia and do not prevent the occurrence of arrhythmia. It has been well established that patients with HF with an ICD for primary prevention have a higher mortality risk if they receive a shock.[74] Furthermore, the anxiety and anguish that some patients experience from repeated shocks can be debilitating.[75] The fact that ICD shocks portend a poor prognosis in patients with HF,[74] and have profound psychological consequences, emphasizes the need to prevent and treat ventricular arrhythmias. In this role, antiarrhythmic drug therapy plays a pivotal role.

ANTIARRHYTHMIC DRUG THERAPY FOR PRIMARY PROPHYLAXIS OF VENTRICULAR ARRHYTHMIA IN PATIENTS WITH HF

Ventricular arrhythmias claim a significant number of lives of patients with HFrEF. Thus, many of the antiarrhythmic drugs (AAD) have been studied for

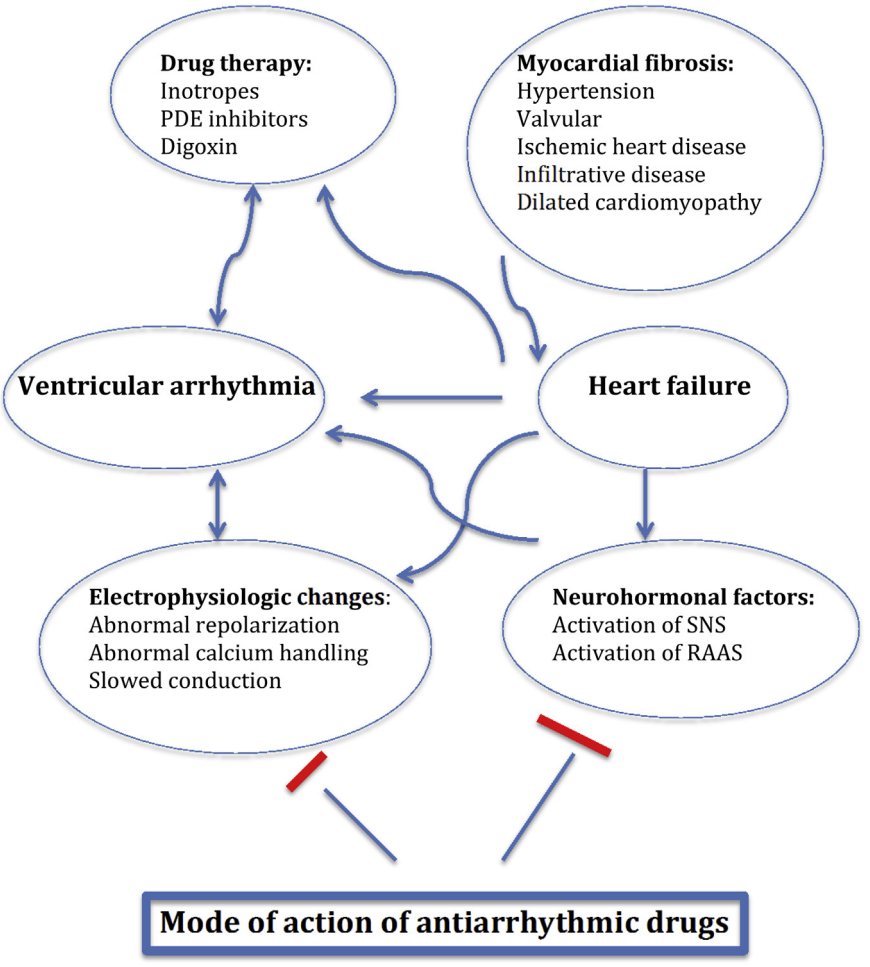

Fig. 2. HF induces neurohormonal activation, structural remodeling, and electrophysiologic changes, all of which can stimulate ventricular arrhythmias. Furthermore, certain drug therapy used in HF can also contribute to a proarrhythmic state. PDE, phosphodiesterase inhibitors; RAAS, renin-angiotensin-aldosterone system; SNS, sympathetic nervous system.

the primary prophylaxis of ventricular arrhythmias, including the following:

Beta-blockers

- Metoprolol (MERIT-HF) and Bisoprolol (CIBIS-II), both lipophilic and highly β1 selective beta-blockers, have been shown to reduce the risk for sudden cardiac death by 41% and 44%, respectively.[71,76]
- Carvedilol is a nonselective β1, β2, and α blocker. The US Carvedilol Heart Failure Study group[77] showed the benefit of carvedilol in reducing the risk of VT/VF in patients with HF.

Sotalol

- Sotalol was studied in the SWORD trial.[60] The d-sotalol was compared with placebo in 3121 patients with LVEF of 40% or less and recent (6–42 days) myocardial infarction (MI) or symptomatic congestive heart failure (CHF) in the setting of a remote (≥42 days) MI. The trial was terminated prematurely because all-cause mortality (5.0% vs 3.1%) and arrhythmic death (3.6% vs 2.0%) were significantly higher with sotalol as compared with placebo.

Amiodarone

- In the EMIAT trial, amiodarone in comparison with placebo resulted in a 35% reduction in arrhythmic death (P = .05) in survivors of myocardial infarction with an EF 40% or less; however, there was no significant difference in all-cause or cardiac mortality.[78,79]

- The Grupo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina (GESICA) study showed a nonsignificant risk reduction (27%; $P = .16$) of sudden death with amiodarone as compared with placebo in severe HF.[80]
- Amiodarone did not reduce mortality compared with placebo in the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT),[81] which looked at patients with an LVEF of 35% or less and NYHA II or III HF.
- A meta-analysis of 15 randomized controlled trials examining the use of amiodarone versus placebo/control for the prevention of SCD in 8522 patients showed that there was a 1.5% absolute risk reduction in all-cause mortality that was not statistically significant ($P = .093$).[82]

Dronedarone

- The Antiarrhythmic Trial with Dronedarone in Moderate-to-Severe Congestive Heart Failure Evaluating Morbidity Decrease (ANDROMEDA)[59] evaluated patients with NYHA class III or IV symptoms and EF of 35% or less. The trial was terminated early due to a significantly higher mortality rate with dronedarone treatment (8.1%) as compared with placebo (3.8%).

Dofetilide

- The DIAMOND-MI trial enrolled 1510 patients within 2 to 7 days of an acute MI with an EF of 35% or less. Patients were randomly assigned to receive either dofetilide (n = 749) or placebo (n = 761).[83] There was no difference in arrhythmic death or mortality.
- The DIAMOND-CHF trial consisted of patients with LVEF of 35% or less who were hospitalized for new or worsening CHF within 7 days.[47] Dofetilide use did not result in a significant difference in SCD or mortality.

Azimilide

- Azimilide is a newer class III AAD that is currently available only in Europe.
- Azimilide Post-Infarct Survival Evaluation (ALIVE)[84] trial looked at 3717 patients after an MI with an EF between 15% and 35% who were randomized to azimilide or placebo. No significant difference was found in arrhythmic deaths or mortality.

Several studies have shown that *beta-blockers* remain among the very few AADs that reduce the incidence of SCD and prolong survival. Once patients are treated with evidence-based therapies for HF, evidence suggests that there is no role for other antiarrhythmic drug therapy in the primary prevention of ventricular arrhythmias.

ACUTE MANAGEMENT OF UNSTABLE VENTRICULAR ARRHYTHMIA IN PATIENTS WITH HF

Management of acute ventricular arrhythmia in patients with HF is challenging and requires an approach tailored to the underlying cause. Acute management of the hemodynamically unstable patient is according to the algorithm outlined by Advanced Cardiovascular Life Support (ACLS) guidelines, including cardiopulmonary resuscitation, defibrillation, a vasoactive agent (epinephrine or vasopressin), and/or amiodarone. Following acute resuscitation, the management should shift to determining and correcting the underlying instigator. This may range from volume overload/acute on chronic decompensation, ischemia, electrolyte imbalances, or other causative factors.

MANAGEMENT OF STABLE VENTRICULAR ARRHYTHMIA IN PATIENTS WITH HF

In the hemodynamically stable patient with VT, acute management may include sedation with synchronized cardioversion or infusion of procainamide, lidocaine, or amiodarone.

Before treatment, careful consideration must be given to distinguishing the presenting rhythm as VT versus SVT with aberrant conduction or much more rarely a preexcited tachycardia. This should be done by careful examination of the 12-lead electrocardiogram during tachycardia in combination with the clinical context. In the patients with HF, because VT is more prevalent, this should be the presumed diagnosis unless proven otherwise.

Once the diagnosis of VT is made, efforts should be made to terminate the VT. Sedation with cardioversion can be considered a primary option. However, antiarrhythmic agents are often used.

Procainamide is a class Ia antiarrhythmic agent that blocks fast sodium channels in addition to being a potent potassium channel blocker. The parent compound primarily blocks sodium channels, whereas its metabolite, N-acetylprocainamide, blocks potassium channels. The potassium channel blocking effect of N-acetylprocainamide is likely the primary mode for its high rate of VT termination.[85,86] Because of its potassium channel blocking effect, procainamide can be proarrhythmic (torsade de pointes), particularly in those with impaired renal function. Procainamide is typically given as a slow load of 10 to 15 mg/kg or until VT terminates, followed by an infusion of 1 to 4 mg per minute. Due to its alpha-blocking

properties, procainamide can cause hypotension.[87] Procainamide should be used cautiously in the patient with HF.

Lidocaine is a class Ib antiarrhythmic agent, which preferentially blocks inactivated sodium channels. Conditions that enhance the utility of lidocaine are more prevalent with ischemic VT. In other situations, lidocaine may not be as effective as procainamide.[86] Lidocaine is given as a load of 1.0 to 1.5 mg/kg that can be repeated at a dose of 0.5 to 0.75 mg/kg followed by a continuous infusion of 1 to 4 mg/min. The primary side effects to watch for are neurologic (visual disturbances, confusion, drowsiness, seizures).

Although amiodarone is frequently used in the acute treatment of stable VT, it is not ideal for acute cardioversion. Amiodarone blocks fast sodium channels in a fashion similar to lidocaine, in addition to having beta-blocker and calcium-channel blocker properties. However, its effect on ventricular refractoriness may take weeks to develop.[88,89] Thus, amiodarone is more effective as a long-term agent to prevent recurrent arrhythmia. Fortunately, amiodarone has minimal negative inotropic effects and rarely is proarrhythmic.

Recurrent ventricular arrhythmia, including electrical storm, defined as 3 or more events in 24 hours, may require further therapy including multiple antiarrhythmic agents, nonpharmacologic treatment, such as rapid pacing, radiofrequency ablation, deep sedation, and in extreme circumstances, temporary mechanical circulatory support or heart transplantation.

Beta-blocker therapy is an important adjunctive therapy to any membrane-active antiarrhythmic in both the acute and chronic management of ventricular arrhythmia. Clearly, as discussed previously, there are beneficial effects of beta-blocker therapy in preventing recurrent ventricular arrhythmia. Furthermore, beta-blocker therapy is a fundamental component of medical therapy in patients with HF. However, beta-blocker therapy is also beneficial in acute management of ventricular arrhythmia. Blocking sympathetic activity with a beta-blocker or stellate ganglion blockade not only decreases the propensity for ventricular arrhythmia but also increases the VF threshold.[90]

ANTIARRHYTHMIC DRUGS FOR SECONDARY PREVENTION OF ICD SHOCKS

The use of ICDs in patients with HF has revolutionized their care and successfully extended the length of high-quality, high-functioning life for our patients with HF. However, although ICDs prevent sudden death, many patients will suffer ICD shocks, some with a relatively high frequency. Thus, we have moved from an era of ICD implantation to an era of shock reduction.

Shock reduction strategies encompass several approaches, including the following:

- Aggressive use of antitachycardia pacing (ATP)
- Device programming to withhold unnecessary shocks from SVT or nonsustained ventricular arrhythmias
- Drug-based or catheter-based therapy to prevent the occurrence of ventricular arrhythmias

In this role, antiarrhythmic drug therapy has a pivotal role in the secondary prevention of ICD shocks in patients with HF.

As described previously, *beta-blockers* should be a cornerstone of management for patients with HF. They are also effective in the reduction of ICD shocks. In a substudy of the Multicenter Automatic Defibrillator Implantation Trial (MADIT-II) evaluating the benefit of ICDs in primary prevention of SCD, patients who received beta-blockers had a 52% reduction in ventricular arrhythmic requiring ICD shock.[91]

Sotalol was studied for the prevention of ICD shock in a double-blind, prospective, multicenter trial by Pacifico and colleagues.[92] In this study, 302 patients were randomized to receive racemic d,l-sotalol or placebo and were followed for 12 months. Sotalol was associated with a 48% reduction in risk of mortality or first shock. This included a reduction in both inappropriate and appropriate shock. Those on sotalol were more likely to be bradycardic and have QT prolongation but there was only 1 case of torsade de point.[92]

Azimilide is a novel class III antiarrhythmic drug, currently available only in Europe. Azimilide blocks both the rapid and slow delayed rectifier potassium currents, unlike other class III antiarrhythmics (which block only the rapid rectifier potassium current). Azimilide has been shown to be effective in reducing ICD shocks in multiple studies. A pilot study of 172 patients by Singer and colleagues[93] demonstrated a 69% reduction in the relative risk of appropriate ICD shocks or antitachycardia pacing at 1 year. The larger Shock Inhibition Evaluation with Azimilide (SHIELD) study randomized 633 ICD patients to placebo, azimilide 75 mg, or azimilide 125 mg. At 1-year follow-up, the primary end point of all-cause ICD shock or ATP was reduced by 57% for the 75-mg dose and 47% for the 125-mg dose. The secondary end point of appropriate ICD shock or ATP was reduced by 48% for the 75-mg dose and 62% for the 125-mg dose. Adverse events with azimilide

were low, including QT prolongation with torsade de point in 5 patients and reversible neutropenia in 1 patient. Further investigation with azimilide is awaited.[93]

Amiodarone remains the most efficacious and safe of the antiarrhythmic drugs for ICD shock prevention. The Optimal Pharmacologic Therapy in Cardioverter Defibrillator Patients (OPTIC) study compared the efficacy of beta-blocker alone, sotalol, or beta-blocker with amiodarone for the prevention of ICD shocks.[94] In this randomized controlled trial of 412 patients, at 1-year follow-up, amiodarone with beta-blocker reduced the risk of appropriate or inappropriate ICD shock by 73% compared with beta-blocker alone and by 57% compared with sotalol. However, adverse pulmonary, thyroid, and bradycardic events were more common with amiodarone compared with other therapies.[94]

OTHER EFFECTS OF ANTIARRHYTHMIC DRUG THERAPY IN ICD PATIENTS

Importantly, the use of antiarrhythmic drug therapy can have an effect on defibrillation and pacing thresholds. In general, class I agents (procainamide, lidocaine, mexiletine) and amiodarone can increase defibrillation and pacing threshold. On the other hand, class III agents (sotalol, dofetilide) can lower thresholds. In a substudy of the OPTIC trial, amiodarone led to a small 1.29-J increase in defibrillation threshold, whereas sotalol was associated with a 0.89-J reduction in defibrillation threshold and beta-blocker was associated with a 1.67-J reduction in threshold. In patients with a high defibrillation threshold and a low safety margin with ICD output, defibrillation threshold testing may be required in certain circumstances.[95]

It should also be noted that antiarrhythmic drugs can prolong the cycle length of ventricular arrhythmias. This can be problematic, as detection algorithms may need to be adjusted so that slow VT is appropriately detected after antiarrhythmic drug loading. Additionally, slow ventricular rhythms may become more resistant to therapy, as the excitable gap of the arrhythmia circuit widens.

SUMMARY

Structural remodeling, underlying neurohormonal activation, and concomitant drug therapies in patients with HF all create an ideal substrate for both atrial and ventricular arrhythmias. Although they commonly coexist, the presence of AF or VT in the HF patient adversely affects mortality. Beta-blockers remain the ideal treatment for rate control in the patient with AF and for both prevention and suppression of VT. Although antiarrhythmics can be proarrhythmic and have significant toxicities, when used cautiously, they can have an important role in the treatment of the patient with chronic HF. In patients with HF who remain persistently symptomatic despite adequate rate control, certain antiarrhythmics can be helpful for restoration of SR. Furthermore, their utility in the acute termination of ventricular arrhythmias and in the secondary prevention of ICD shocks has been well established.

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