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Review

The Era of Rhythm Control: A Review of the Epidemiology and Clinical Impact of Anti-Arrhythmic Medications in Atrial Fibrillation

Cicely Anne Dye *, Jamario Skeete, Asad Khan, Michael Dunleavy, Michael Dietrich, Annabelle Santos Volgman, Parikshit Sharma and Henry Huang

Division of Cardiology, Department of Internal Medicine, Rush University Medical Center, Chicago, IL 60612, USA
* Correspondence: cicely_a_dye@rush.edu; Tel.: +1-312-208-7388

Abstract: Atrial fibrillation has been described as a global epidemic with a three-fold increase in prevalence in the last 50 years. As the prevalence of atrial fibrillation continues to grow, multiple landmark trials have been designed to determine the best method to treat atrial fibrillation. Initial trials have stated that rate control was not inferior to rhythm control, however, as the efficacy of rhythm control of atrial fibrillation has improved, a benefit in rhythm control has been shown. Because of this trend towards increased rhythm control, more patients have been placed on anti-arrhythmic medications. This paper will review the epidemiology and clinical impact of the utilization of anti-arrhythmic medications. As we enter the era of rhythm control, increased awareness is needed regarding the monitoring and potential adverse events that can occur with these medications. Providers must balance the increased emphasis on rhythm control with the overall clinical impact on their patients due to drug-to-drug interactions and adverse effects that can occur with different co-morbidities. If the clinical momentum towards rhythm control continues, real-world data analysis will be needed to evaluate the clinical impact of the use, risk, and benefits of anti-arrhythmic medications.

Keywords: atrial fibrillation; anti-arrhythmics; rhythm control; rate control; arrhythmias

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1. Introduction

The increasing global burden of atrial fibrillation (AF) continues to be a major cause for concern due to the significant morbidity, mortality, and astounding economic impact attributable to this highly prevalent condition. To counter this surge in prevalence noted over the last five decades, there has been a valiant effort to identify the most effective strategies to prevent and manage AF [1]. While historically, the standard practice favored approaches aimed at controlling heart rates while in AF (rate control) over the pharmacologic restoration and maintenance of sinus rhythm (rhythm control) based on the findings of early clinical trials before catheter ablation techniques were available. In recent years, with improvements in technology and clinical outcome from catheter ablation, there has been a paradigm shift toward rhythm control [1,2].

Initial trials such as Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation Study (RACE) and Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM), have demonstrated rate control to be non-inferior to rhythm control [3,4]. In this context, providers often avoided the use of anti-arrhythmic drugs (AADs), which are often less well tolerated, require closer monitoring, and may be associated with several drug-to-drug interactions when compared to rate control agents. However, as the efficacy of rhythm control strategies for AF has improved with the introduction of catheter ablation in the last two decades [5–10], such as the Early Treatment of Atrial Fibrillation for Stroke Prevention Trial, Atrial Fibrillation Network (EAST-AFNET) has shown a possible benefit of earlier more aggressive pursuance of rhythm control [11–15]. This benefit of

rhythm control has been most pronounced in certain populations, such as those with heart failure with reduced ejection fraction (HFrEF), leading to an update in our current clinical guidelines [16–18]. This update to the consensus guidelines for the management of AF has led to an increase in rhythm control in patients with AF, including the increased use of AADs alone or in conjunction with catheter ablations.

Although clinically available choices for AADs for the treatment of AF have remained mostly unchanged in recent decades, the role of AADs has come to the forefront with an increased focus on rhythm control, and their use is now becoming more commonplace, particularly in select populations. At the same time, it is essential for prescribers of these agents to perform close patient monitoring, similar to those utilized in landmark trials, to mitigate complications associated with drug toxicities in real-world practice.

In this review, we will explore the clinical impact of recent trials on the utilization of AADs in the management of AF. We will examine key prescribing patterns of AADs for AF and discuss key prescribing considerations for each of the main AADs used in AF. Finally, we will discuss the proper use of these medications in special populations, such as those with inherited and acquired cardiomyopathies, persons requiring immunosuppressants and anti-retroviral medications, persons receiving chemotherapy and during pregnancy.

2. Methods

This review utilized electronic databases PubMed (NCBI), Embase (Ovid), Cochrane, and Google Scholar, which were searched for articles published until 31 January 2023. We included articles that were, but not limited to: Case-control, cohort, cross-sectional, prospective randomized clinical trials, systematic reviews, meta-analysis, and non-systematic reviews. We excluded non-English written articles and abstracts. All identified literature was reviewed by the senior editor (HH) to ensure clinical applicability and accuracy of the information utilized.

Given that the articles vary widely in their design, intervention, comparators, outcomes, and format no synthesis was utilized, and we utilized a non-systematic narrative review of the literature.

3. The Changing Epidemiology of Atrial Fibrillation

3.1. Epidemiology, Incidence, and Prevalence of Atrial Fibrillation

The increasing burden of AF has been a major concern. Epidemiologic studies estimated the worldwide prevalence of AF was estimated to approximately 37.5 million in 2017, with approximately 3 million new cases every year [19,20]. The incidence of AF was noted to be highest in the United States, Canada, Australia, and parts of Europe, while the lowest incidence was noted in Africa and the Middle East, with projections for this burden to increase in the future [21]. For instance, in the United States, it is projected that the prevalence of AF will more than double between the years 2010 and 2030 (5.2 million in 2010 to an estimated 12.1 million in 2030) [21]. Globally, age has the greatest contribution to the risk of the development of AF. However, its prevalence can vary based on gender, race, and a patient's co-morbidities. In the United States, the lifetime risk of AF is approximately 1 in 3 for White people and 1 in 5 for African American people, while increased socioeconomic status is associated with an increased risk of developing AF [21].

3.2. Atrial Fibrillation in Women of Child-Bearing Age & Pregnancy

The development of atrial fibrillation in women of childbearing age and during pregnancy is uncommon, although the incidence has been increasing over time. One study evaluating over 300,000 pregnancies at one medical center for the incidence of AF showed that at baseline in 42.3 per 100,000 pregnancies, the women had a pre-existing diagnosis of AF before the pregnancy (112 total pregnancies in 93 women). A meta-analysis that included 7 papers and over 300,000 pregnancies looked at the incidence of AF in those without structural heart disease, with structural heart disease, and recurrence of AF in those with a prior diagnosis. They found the incidence of AF during pregnancy was 0.3%

in women with no known structural heart disease, compared to 2.2% among women with known structural heart disease. Women who had known AF had a recurrence in 39.2% of pregnancies. As expected, pregnant women with prior structural heart disease had worse maternal outcomes compared to those without structural heart disease after their AF diagnosis [22].

4. The Impact of Atrial Fibrillation on Clinical Co-Morbidities

Several conditions accompany AF, many of which play a direct role in the pathogenesis and future development of AF. These co-morbidities include heart failure, hypertrophic cardiomyopathy, channelopathies, cardiac amyloidosis, human immunodeficiency virus (HIV), and malignancy. We will review the impact of these intrinsic factors and co-morbidities as they contribute to the overall burden of AF.

4.1. Heart Failure with Preserved and Reduced Ejection Fraction

Of these co-morbidities, heart failure has the greatest correlation with AF. This association has, been recognized for over seven decades, with Paul Dudley White (1886–1973) once declaring, "Since auricula fibrillation so often complicates very serious heart disease, its occurrence may precipitate heart failure or even death, unless successful therapy is instituted." Approximately 24% of patients diagnosed with congestive heart failure (CHF) had a prior diagnosis of AF or were found to have AF at the time of CHF diagnosis. The converse is also true, in which AF is strongly associated with a history of CHF or future development of CHF. In fact, 40% of patients with AF ultimately have a concomitant diagnosis of CHF [23,24]. According to a meta-analysis of 8 studies, patients with AF are 4.62 times more likely to be diagnosed with CHF compared to those without AF [25]. Moreover, patients with CHF are 4.5 to 6 times more likely to develop AF than patients without CHF [26]. In one city in the Netherlands, the incidence of CHF was 18.14 per 1000 person-years in residents with AF compared to just 2.91 per 1000 person-years in those without AF. In that population, incidence of heart failure with a reduced ejection fraction (HFrEF) is 12.75 per 1000 person-years, compared to 4.9 per 1000 person-years for heart failure with a preserved ejection fraction (HFpEF) [27]. Among Medicare beneficiaries in the United States, CHF is present in 51.4 percent of patients with AF 65 years old or over and 59.3% of patients under the age of 65 years [28]. Of patients with AF and HF, individuals with concomitant initial diagnosis tend to carry the best long-term prognosis for mortality [28].

4.2. Hypertrophic Cardiomyopathy

Another condition associated with AF is hypertrophic cardiomyopathy (HCM). AF has been found to occur in 18–22% of patients with hypertrophic cardiomyopathy. Patients with AF in this group also have increased mortality [29–31]. AF risk increases with age, as well as how long a patient has had HCM [32]. The incidence of AF in persons with HCM is around 2% per year and is 6 times more likely than in the age-matched general population [31,32].

4.3. Cardiac Amyloidosis

AF is commonly present in persons with cardiac amyloidosis, with a prevalence of up to 70% in patients with transthyretin cardiac amyloidosis. In this population, AF is associated with a higher risk of thromboembolism than persons with AF who do not have concomitant cardiac amyloidosis [33]. Comparatively, AF appears to be less strongly associated with sarcoidosis, with a prevalence of AF of 18% in patients with sarcoidosis and cardiac involvement [34].

4.4. Channelopathies

AF has increased prevalence among patients with channelopathies. AF was documented in approximately 2% of patients with long QT syndrome who are younger than

50 years old, which is much higher than the expected 0.1% in the general population [35]. Among the total population of patients with Brugada Syndrome, the prevalence of AF has been estimated to be between 9 and 38% [36–41]. However, one study found 53% of patients with Type 1 pattern on electrocardiogram (ECG) had AF, whereas none of the patients with Type 2 or 3 patterns had AF [42]. Among patients with short QT syndrome, estimates of AF prevalence are quite variable. While some studies have noted a prevalence of AF as high as 70% among persons with short QT syndrome, more recent studies with larger cohorts suggest a lower prevalence of 18–41% [43].

4.5. Human Immunodeficiency Virus (HIV)

There is limited research into the association between HIV and AF. One systematic review recently showed the prevalence of AF and atrial flutter (AFL) to be between 2.0% and 5.13%, with an incidence rate of 3.6 per 1000 person-years. They also demonstrated that low CD4+ counts and high viral loads were predictive of AF or AFL [44].

4.6. Malignancies and Chemotherapeutics

In the Women's Health Study, a new diagnosis of AF is associated with a higher risk for cancer in the Women's Health Study. The incidence of cancer was 1.4 per 100 person-years after AF diagnosis, compared to 0.8 per 100 person-years in those without AF [45]. In the first 3 months after diagnosis of AF, the incidence of a new cancer diagnosis was 3 times higher. While this risk decreased after that, it remained significantly elevated compared to subjects without AF beyond one year of new AF diagnosis in that same study. While some of the increased risks may be due to bleeding after the initiation of anticoagulation or additional observation after the new diagnosis. Cancer therapies have also been associated with an increased risk of AF. For example, the incidence of ibrutinib-related AF is 25 per 100 person-years, with 38% of patients treated with this medication developing AF by 24 months. The incidence of AF with cisplatin is estimated to be 15–32% and is 10% with anthracyclines [46]. Tyrosine kinase inhibitor therapy may also increase proclivity for ventricular arrhythmias, though the mechanism for this genesis is unknown [47].

5. Clinical Impact of Recent Trials on the Utilization of Anti-Arrhythmic Drugs

5.1. Rate Control versus Rhythm Control

The current guidelines in AF management reflect the findings of several key trials which were conducted to compare rhythm versus rate control. Initial findings in these studies did not suggest a benefit to rhythm control over rate control [17]. However, the findings of more recent randomized control trials (RTCs) have suggested the benefit of an early rhythm strategy, particularly in select patients, such as those with HFrEF [48–57]. Understanding the landmark trials comparing rhythm control to rate control and how the results of these trials continue to shape our evolving knowledge of this subject is paramount.

The first randomized study to compare therapeutic strategies of rate control to rhythm control for AF was the Pharmacological intervention in Atrial Fibrillation (PIAF) study [49]. Specifically, this study looked at differences in symptoms related to AF between these treatment approaches. This landmark observational study consisted of 252 (125 in the rhythm control group and 127 in the rate control group) patients aged 18 to 75 years with a documented AF duration between 7 and 360 days and study participants were followed for 12 months. Notably, patients with New York Heart Association (NYHA) Class IV functional status, treatment with amiodarone within the 6 months of enrolment, and an average heart rate (HR) < 50 beats per minute (BPM) were excluded from this trial. Diltiazem was the first-line therapy for the rate control group, whereas amiodarone was the first-line therapy for the rhythm control group. Key endpoints assessed during each follow-up visit were changes in symptoms of palpitations, dyspnea, or dizziness compared to baseline. After a 52-week period of follow-up, there was no significant difference in terms of symptomatic improvement between the two groups ($p = 0.317$). At the end of the study, 56% of patients

in the rhythm group were in sinus rhythm compared to only 10% in the rate control group ($p < 0.001$). Furthermore, those patients treated with a rhythm control strategy showed an improved exercise tolerance (measured by the 6 Minute walk test) by the end of the study ($p = 0.008$). Patients treated with amiodarone were more likely to have side effects (47% vs. 64%; $p = 0.011$). Notably, the most common side effects of amiodarone were corneal depositions followed by thyroid problems and photosensitivity. Treatment was more likely to be stopped in the amiodarone group due to side effects ($p = 0.036$). Finally, there was a significant difference in hospitalizations driven primarily by rhythm-specific circumstances such as electrical cardioversion or amiodarone-associated related side effects ($p = 0.001$).

Beyond the difference in symptom control across treatment strategies, the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) sought to compare rate versus rhythm control on overall mortality [5]. A total of 4060 patients with recurrent AF, at least 65 years of age, and with at least one risk factor for stroke were enrolled in this study. Two-thousand and twenty-seven (2027) patients were randomized to the rate-control group and 2033 to the rhythm-control group. Patients in the rhythm control strategy were treated with one of several different anti-arrhythmic drugs depending on the discretion of the treating physician. Patients in the rate control group were given either beta-blockers, verapamil, diltiazem, digitalis, or a combination of these drugs. There was no statistical difference between the two treatment groups at baseline with regards to age, sex, left ventricular ejection fraction (LVEF), and the predominant cardiac diagnosis. After a follow-up period of five years, there was no difference between the two groups in the primary end point of mortality [HR: 1.15 (95% CI 0.99 to 1.34); $p = 0.08$]. The rate of the composite end point of death, disabling stroke, disabling anoxic brain injury, major bleeding, and cardiac arrest were also similar between the two groups ($p = 0.33$). The most used AAD for rhythm control was amiodarone (62.8%), while the most used drug for rate control with digitalis (70.6%). By the end of the study, 62.6% of patients in the rhythm control group were in sinus rhythm at 5-year follow-up compared to only 34.6% in the rate control group. One criticism of this study was that patients who maintained successful rhythm control could have their anticoagulation stopped. This possibly introduced bias in the stroke and death outcomes as this led towards less use of anticoagulation in the rhythm control group.

Another key landmark study is the Rate Control versus Electrical Cardioversion for persistent atrial fibrillation (RACE) study. This was the first study to evaluate the synergistic effects of AADs on the efficacy of synchronized direct current cardioversions for the purpose of rhythm control [4]. The RACE study randomized 522 patients with persistent atrial fibrillation to a rate control strategy or a rhythm control strategy. Patients in the rhythm control strategy were cardioverted and then treated with sotalol, flecainide, and amiodarone. Rate control was achieved with the administration of digitalis, a non-dihydropyridine calcium-channel blocker, and beta-blocker, alone or in combination. The target resting heart rate in the rate control arm was less than 100 beats per minute. There was no significant difference between the two groups with regards to age, sex, LVEF, valvular disease, history of coronary artery disease (CAD) myocardial infraction (MI) or indexed left atrial (LA) volume. The primary end point was a composite of death from cardiovascular causes, heart failure, thromboembolic complications, bleeding, implantation of a pacemaker, and severe adverse effects of drugs. After a mean follow-up of 2.3 years, the primary end point occurred in 44 of the 256 patients in the rate-control group (17.2%) and in 60 of the 266 patients in the rhythm-control group (22.6%) [HR 0.73 (90% CI 0.53 to 1.01; $p = 0.11$). Severe adverse effects of anti-arrhythmic drugs occurred mainly in the rhythm-control group: Seven patients had sick sinus syndrome or atrioventricular block, three had torsade de pointes or ventricular fibrillation, one had rapid, hemodynamically significant atrioventricular conduction during flutter, and one had drug-induced heart failure.

Another key study comparing rhythm control to rate control was the Strategies of Treatment of Atrial Fibrillation (STAF) trial [51]. In this multi-center study, 200 patients were

randomized to either a rate control or a rhythm control strategy (100 patients per group) [38]. Patients in the rhythm control group were to undergo electrical cardioversion and be given prophylaxis with either class I AAD, amiodarone, or sotalol. Patients in the rate control group were treated with beta-blockers, digitalis, calcium channel blockers, or underwent AVN modifications with or without a pacemaker. Both groups were anticoagulated based on established guidelines. After a mean follow-up of 19.6 months, there was no significant difference in the primary end point of a combination of death, stroke or TIA, systemic embolization, and CPR (5.54%/year vs. 6.09%/year; $p = 0.99$). After three years, only 23% of patients in the rhythm control group maintained sinus rhythm despite up to 4 potential cardioversions. Furthermore, 18 primary end points occurred in atrial fibrillation, with only 1 occurring during sinus rhythm ($p = 0.049$). At first glance, the findings of this study may suggest that rhythm control failed to demonstrate superiority due to the inability to achieve long-term maintenance of sinus rhythm. However, when taking into consideration the findings of the AFFIRM trial in which 73.3% of patients demonstrated long-term maintenance of sinus rhythm at three years and there was still a failure to demonstrate the superiority of maintenance of sinus rhythm over rate control.

Despite the findings of these initial studies, the question persisted as to whether rhythm control could be more beneficial in select populations, in which maintenance of normal sinus rhythm might be more critical, such as those with heart failure. One key study seeking to answer this question was the Atrial Fibrillation and Congestive Heart Failure (AF-CHF) trial, which compared the two treatment strategies in patients with AF and symptomatic HFrEF (EF < 35%). The primary outcome was the time to death from cardiovascular causes. A total of 1376 patients were enrolled and randomized to a rhythm control group or a rate control group and were followed for a mean of 37 months. Patients in the rhythm control group underwent cardioversion and were then treated medically with amiodarone, sotalol, or dofetilide. Therapies for rate control included beta-blockers or digitalis to achieve a target HR of <80 BPM during a resting 12 lead ECG. If the target HR was not achieved, then patients could undergo ANV ablation with pacemaker implantation. There was no significant difference between the two groups at baseline with regards to background heart failure GDMT, anticoagulation, LA dimensions, or LVEF. After follow-up, there was no difference in mortality between the treatment arms, 27% of patients in the rhythm-control group died from cardiovascular causes compared with 25% in the rate-control group [HR 1.06 (95% CI 0.86 to 1.30); $p = 0.59$].

In the last few years, early intervention with rhythm control in AF with AAD has shown promising results in reducing adverse cardiovascular outcomes [57]. ATHENA was a double-blind, randomized, placebo-controlled trial that sought to assess hospitalization due to cardiovascular events or death in patients with AF. In total, 4628 were randomly assigned to either dronedarone versus placebo and followed for a mean of 21 months. Patients included in the trial had paroxysmal or persistent AF or atrial flutter within 6 months before randomization and met >1 CHADS2 risk factors, LVEF < 40%, or LA enlargement. After follow-up, there was a reduction in the primary endpoint seen with the use of dronedarone compared to placebo [HR 0.76 (95% CI 0.69 to 0.84); $p < 0.001$] [48]. There were no significant differences between the two groups for any of the baseline characteristics, including age, sex, LVEF, or incidence of hypertension. Dronedarone was discontinued in 30.2% of patients, mostly due to treatment-adverse events, including bradycardia, QT prolongation, diarrhea, nausea, or rash. There was one case of torsades de pointes in a 66-year-old female receiving dronedarone.

These recent trials support rhythm control as a potentially important strategy in the early stages of AF. A sub-analysis of the CASTLE-AF trial examined 210 patients treated pharmacologically with AAD (n = 60) and patients treated with rate control (n = 150). Over a median follow-up of 3.4 years, there was no difference in the primary composite endpoint of mortality and CHF admission (HR 0.99; 95% confidence interval 0.62 to 1.60; $p = 0.97$). Patients in the rhythm control group were less likely to be on BB therapy (88.3% vs. 97.9%; $p = 0.004$) or digitalis (13.3% vs. 36.8%; $p < 0.001$) [58].

5.2. Rhythm Control for Quality of Life

The Japanese Rhythm Management Trial for Atrial Fibrillation (J-RHYTHM) built upon prior studies by including those patients who were underrepresented in prior studies including patients who were younger and without risk factors for stroke, those who had paroxysmal AF, and those who had symptoms that were considered severe [52]. Another novel aspect of this trial was that in addition to the end points of morbidity and mortality, this study also emphasized patient-reported experience and perception of AF-specific disability. A total of 823 patients with PAF were followed for a mean period of 578 days. The primary endpoint occurred in 64 patients (15.3%) assigned to rhythm control and in 89 patients (22.0%) to rate control (p = 0.0128). This was driven by the patients' desire to move to the alternate treatment strategy because of physical/psychological disability caused by their current treatment regimen. There were no significant differences between the groups in the total occurrences of mortality, embolism, major bleeding, and heart failure. Patients in the rhythm control group did show significant improvement in AF-specific quality of life scores compared to patients in the rate control group.

Overall, few differences in end points were observed between rate and rhythm control strategies in these early comparison trials. This results in providers defaulting to a rate control strategy. Current registries suggest that 75–85% of patients are not treated with a rhythm control strategy [53]. Sinus rhythm maintenance was higher in patients receiving rhythm control therapy, but as previously discussed, long-term achievement of normal sinus rhythm did necessarily portend a better outcome. Importantly, these studies consistently showed that simple rate control was associated with fewer hospitalizations, likely due to the necessary monitoring during drug dose titration and the higher likelihood of re-admissions associated with AADs. In general, rates of stroke, systemic embolization, and major bleeding also did not differ between treatment strategies. Prior studies have demonstrated that quality of life (QoL) is significantly impaired in patients with AF compared with that of the general population and control groups [54,55]. Despite this, one major limitation of the existing literature is the lack of objective measures on QoL scores associated with AF as well as methodological weaknesses, such as small sample size, short-term follow-up, or the use of generic rather than AF-specific tools to assess QoL [59,60].

5.3. Catheter Ablation Used Alone or in Conjunction with AAD

The introduction of catheter ablation as an option for rhythm control has greatly impacted the use of AAD in atrial fibrillation. Catheter ablation has been shown to be more efficacious than AAD use, with a 70% arrhythmia-free survival compared to rates of 50% in our most efficacious AAD in paroxysmal atrial fibrillation [59].

EAST-AFNET included patients who also underwent an AF ablation. A total of 1395 were assigned to an early rhythm control strategy, of which 270 underwent catheter ablation. There were no significant clinical or demographic differences between the two groups at baseline. The primary outcome was a composite of death from any cause, stroke, or prespecified serious adverse events arising from complications of rhythm-control therapy. The trial was stopped early due to an early demonstrated benefit in the rhythm control group [HR 0.79 (95% CI 0.66 to 0.95); p = 0.005] [61]. This effect was consistent even after adjustment for relevant covariates. The number of nights spent in the hospital did not differ significantly between the groups (5.8 + 21.9 and 5.1 + 15.5 days per year; p = 0.23). Serious adverse events related to rhythm control therapy were more common in the rhythm control group but were relatively infrequent. During the five-year follow-up period, such events occurred in 68 patients (4.9%) assigned to early rhythm control and 19 patients (1.4%) assigned to usual care.

Although catheter ablation is more effective than AAD there is still a subset of patients that have recurrent atrial fibrillation despite catheter ablation that are highly symptomatic and require a second ablation. In patients with recurrent atrial fibrillation, trial data

suggests that the hybrid method of utilizing both AAD and catheter ablation significantly reduces the recurrence of atrial tachy-arrhythmias in the first year after PVI [59].

6. Prescribing Considerations for Anti-Arrhythmic Drugs

The use of anti-arrhythmic drugs (AADs) continues to see increased use in the management of atrial fibrillation. This aligns with not only the increasing prevalence that has been noted in atrial fibrillation but an increased emphasis on rhythm control in the last decades. This was demonstrated in a recent study using clinical informatics data, examining the trends in the use of AADs in the United States between 2004–2016, which showed an increase in AADs for AF and atrial flutter (AFL) from 345 to 979 per 100,000 patients. Driving this increase was the use of amiodarone, sotalol, flecainide, and dofetilide [60]. Notably, during this period, there was a decrease in quinidine and disopyramide, a trend that had continued from the preceding decade [60,61].

While there are several AADs of various levels of efficacy in achieving rhythm control in AF, numerous factors influence which drug is used in which clinical situation. For instance, certain co-morbidities, such as structural heart disease, renal impairment, or underlying lung or thyroid disease may limit which agent is used. Additionally, special attention to drug-to-drug interactions and the need for dose adjustment should be noted (Table 1).

For instance, congestive heart failure (CHF) poses a particular challenge for the use of AADs in the management of atrial fibrillation. This is largely because the CHF may function to act as a pro-arrhythmic state, which can be worsened by several AADs, leading to poor clinical outcomes. Specifically, CHF may lead to impaired calcium handling, up-regulation of adrenergic receptors, and impaired function of voltage-dependent potassium channels, which may potentiate the pro-arrhythmic state of many AADs [62–69]. Furthermore, based on the inferences from landmark studies such as the Cardiac Arrhythmia Suppression Trial (CAST), which included post-myocardial infarction patients with high PVC burden in the era prior to wide-spread percutaneous coronary revascularization, class Ic agents such as flecainide were associated with increased mortality, this agent is contraindicated in the setting of CHF or coronary artery disease [63–66]. However, recently, numerous studies have subsequently demonstrated a favorable safety profile of class 1C drugs administered to patients with stable CAD [64–67]. Randomized clinical trials have demonstrated increased mortality with the use sotalol and dronedarone in the setting of heart failure, thereby, limiting the use of these drugs in this population [70,71]. In individuals with CHF, for whom rhythm control is desired, dofetilide, or amiodarone may be a reasonable option, though this is not reflected in current AF guidelines [16,17].

Another key consideration is the impact of co-morbidities on the pharmacokinetic properties of the various AADs (Table 1). Notably, renal impairment may lead to decreased clearance of select AADs, such as the case for flecainide, sotalol, dofetilide, and dronedarone, prompting the need for dose adjustment in mild cases of kidney disease or avoidance in more advanced stages of chronic kidney disease [72]. Similarly, propafenone, which undergoes hepatic clearance, is contraindicated in individuals with liver disease and has rarely been associated with acute liver failure [73].

Table 1. Drug-to-drug interactions.

Class	Medication	Route	Typical Dosing	Anti-Arrhythmic Dose Adjustments	Drug-Drug Interactions and Medication Adjustments	Clinical Contraindications
IA	Disopyramide	PO	100–400 every 8–12 h, maximum dose, 800 mg/24 h	Reduce dose in renal or hepatic dysfunction	Use with caution with inhibitors and inducers of CYP3A4. This includes non-dihydropyridine calcium channel blockers, ketoconazole, macrolide antibiotics, protease inhibitors, grapefruit juice, rifampin, phenobarbital, and phenytoin. Coadministration with beta-blockers can cause hypotension and even death. Avoid coadministration with anticholinergic medications in the elderly. Coadministration with mavacamten can decrease serum concentration of disopyramide.	Narrow-angle glaucoma
IA	Procainamide	IV or PO	IV: 10–17 mg/kg at 20–50 mg/min load. Maintenance dose 1–4 mg/min. PO (sustained release) 500–1250 mg q6h		Use with caution with medications that inhibit cationic tubular secretion (levofloxacin, trimethoprim), especially in baseline CKD present.	QT Interval
IC	Flecainide	PO	50–100 mg twice a day, maximum dose 300–400 mg/d, can give 200 mg PO daily slow release	Discontinue if QRS widens > 25% above baseline, new LBBB, or QRS > 120 ms	Coadministration with CYP2D6 inhibitors increases plasma concentrations by 16–28%. Coadministration with amiodarone raises concentration by approximately 50%. Coadministration with sotalol causes hypotension that is generally not seen with other BBs. Coadministration with mavacamten can decrease metabolism of mavacamten.	Coronary disease, CrCl < 35 mL/min/1.73 m^2
IC	Propafenone	PO	150–300 every 8 h or sustained release 225–425 twice a day	Discontinue if QRS widens > 25% above baseline, new LBBB, or QRS > 120 ms	Increases concentrations of digoxin and warfarin (INR typically increases 25%). Can increase beta-blocker concentrations. Coadministration with CYP2D6 inhibitors can increase plasma concentrations, including severe drug reactions when coadministered with CYP2D6 inhibiting antidepressants. Increases digoxin concentrations by approximately 60%. Coadministration with mavacamten can decrease serum concentration of Propafenone.	Coronary disease, severe renal or liver disease, asthma

Table 1. *Cont.*

Class	Medication	Route	Typical Dosing	Anti-Arrhythmic Dose Adjustments	Drug-Drug Interactions and Medication Adjustments	Clinical Contraindications
III	Dofetilide	PO	Renally dosed: CrCL > 60 (500 μg twice a day), CrCl 40–60 (250 μg twice a day), CrCl 20–39 (125 μg twice a day)		HCTZ, Verapamil, cimetidine, ketoconazole, trimethoprim, prochlorperazine, dolutegravir, and megestrol are absolute contraindications. Discontinue amiodarone at least 3 months before initiation, though in patients with and ICD can consider as little as 7 days. Stop dofetilide 48 h before amiodarone load. Administer strong CYP3A4 inhibitors with caution. Tyrosine kinase inhibitors, particularly vandetanib and nilotinib, Arsenic, anthracyclines, and panobinostat, can prolong the QT interval. Coadministration with mavacamten can decrease serum concentration of dofetilide.	QT interval
III	Dronedarone	PO	400 mg every 12 h	Discontinue if QTC > 500 ms or >60 ms increase	Use with caution with CYP3A4 inhibitors (non-dihydropyridine calcium channel blockers, dabigatran, ketoconazole, macrolide antibiotics, protease inhibitors, grapefruit juice). Use with caution with CYP3A4 inducers (e.g., rifampin, phenobarbital, phenytoin). Recommend decrease beta-blocker and digoxin dose with coadministration doses. It can increase concentrations of some statins, sirolimus, and tacrolimus. Tyrosine kinase inhibitors, particularly vandetanib and nilotinib, Arsenic, anthracyclines, and panobinostat, can prolong the QT interval. Coadministration with mavacamten leads to increased mavamectin doses.	CrCl < 30 mL/min
III	Sotalol	IV or PO	IV: 75 mg every 12 h. PO 80–160 mg every 12 h. Can increase dose every 72 h. Maximum dose 320 mg every 12 h	Discontinue if QTC > 500 ms or >60 ms increase	Tyrosine kinase inhibitors, particularly vandetanib and nilotinib, Arsenic, anthracyclines, and panobinostat, can prolong the QT interval. Administering with food or antacids can decrease plasma concentrations, though the clinical significance is unclear	Significant LVH, CrCl < 30 mL/min, long QT, asthma, hypokalemia
III	Ibutilide	IV only	1 mg intravenous over 10 min, repeat after 10 min if necessary		Recommend a minimum of 4 h after ibutilide administration prior to administration of Class IA or Class III anti-arrhythmic agents due to risk of precipitating ventricular arrhythmias	QT interval

Table 1. *Cont.*

Class	Medication	Route	Typical Dosing	Anti-Arrhythmic Dose Adjustments	Drug-Drug Interactions and Medication Adjustments	Clinical Contraindications
III	Amiodarone	PO or IV	IV load 10 g over 7–10 d, then 200–400 mg/d. IV: 150–300 mg bolus, then 1 mg/min infusion for 6 h followed by 0.5 mg/min for 18 h.	Dose reduce load in the setting of bradycardia or QT prolongation. Maintenance dose of 400 mg/d recommended if treating ventricular tachycardia	Inhibits metabolism of most statins leading to statin toxicity. Reduce simvastatin max dose to 20 mg/d and lovastatin to 40 mg/d when coadministered with amiodarone. Amiodarone increases cyclosporine concentration 2-fold. Requires decreased warfarin dose by 25–40% depending on the daily amiodarone dose. Amiodarone increases plasma colchicine, macrolide antibiotics, and systemic azole antifungals. Amiodarone increases procainamide concentration (consider a decrease in procainamide by 20–30% prophylactically when starting amiodarone). Should not use amiodarone with sofosbuvir-based hepatitis C treatments—serious cases of bradycardia, causing PPM placement, and even death, have been reported. Coadministration with mavacamten leads to increased mavamectin doses.	Manifest Hyperthyroidism

Toxicity Monitoring

Side effects and drug toxicity are commonly associated with many AADs. To mitigate the significant potential for toxicities associated with AADs when used in AF management, close monitoring becomes key. This becomes of paramount importance for individuals treated with amiodarone, for whom close monitoring of thyroid, pulmonary, hepatic function, as well as visual disturbance, is key. As is the case with amiodarone, significant side effects (both cardiac and non-cardiac) can be encountered with most AADs, and close attention should be paid to the monitoring for these (Table 2). Although side effects of amiodarone are typically thought to be long-term in nature due consequence of cumulative toxicity, acute pulmonary toxicity has been reported, and a single-center study of elderly patients (age > 60) and preserved LV systolic function demonstrated amiodarone use was associated with higher in-hospital and 100-day all-cause mortality after hospitalization for AF in comparison to propensity-matched control group, not on amiodarone [74,75].

Table 2. Common toxicities associated with anti-arrhythmic drugs used for atrial fibrillation.

Anti-Arrhythmic Drugs Cardiovascular and Non-Cardiovascular Toxicities		
Anti-Arrhythmic Drug	**Noncardiovascular Toxicity**	**Cardiovascular Toxicity**
Class Ia		
Procainamide (pre-excited AF)	Hypotension, drug-induced lupus, agranulocytosis	Torsades de Pointes
Disopyramide	Anticholinergic (Urinary retention, contraindicated for narrow-angle glaucoma, dry mouth, constipation, blurry vision), hypoglycemia	Negative inotropic effects, torsades de pointes, and QRS widening
Class Ic		
Propafenone	Metallic taste, dizziness, worsening of reactive airway disease, GI upset	Bradycardia, atrial flutter with 1:1 conduction, ventricular tachycardia-CAD with infarct, may unmask Brugada-type ST elevation, QRS widening
Flecainide	Dizziness, headache, visual blurring, paresthesias, interstitial lung disease	Bradycardia, atrial flutter with 1:1 conduction, ventricular tachycardia- CAD with infarct, may unmask Brugada-type ST elevation, QRS widening
Class III		
Sotalol	Bronchospasm, hypotension, lightheadedness, fatigue	Bradycardia, torsades de pointes, negative inotropic effects
Dofetilide, US only	None	Torsades de pointes
Amiodarone	Increase in serum creatinine, Thrombophlebitis (IV), Pulmonary (acute hypersensitivity pneumonitis, chronic interstitial infiltrates), hepatitis, thyroid (hypothyroidism or hyperthyroidism), photosensitivity, blue-gray skin discoloration with chronic high dose, nausea, ataxia, tremor, alopecia, peripheral neuropathy, corneal deposits	Sinus bradycardia, torsades de pointes (rare)
Ibutilide (intravenous)	Nausea	Torsades de pointes
Dronedarone	Anorexia, nausea, hepatotoxicity, increase in serum creatinine	Bradycardia, torsades de pointes (rare), should not be used in patients with a history of heart failure or with permanent AF

7. Conclusions

Over the last few decades, atrial fibrillation has become ubiquitous with a significant impact on society regarding healthcare expenditure, morbidity, and mortality. Since the era of catheter ablation, recent evidence-based literature has an emphasis on utilizing rhythm control early in the disease course. Although pulmonary vein catheter ablation is becoming the mainstay of rhythm control, AADs are increasingly used in clinical practice and remain a key element in obtaining and maintaining sinus rhythm in many patients.

Understanding the clinical impact of recent trials on the utilization of AADs in the management of AF is paramount to knowing when rhythm control is appropriate and which method should be used. This article focused on the epidemiology of atrial fibrillation and AADs, the appropriate prescribing of AADs for AF, and the key prescribing considerations for each of the main AADs used in AF.

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