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ANTIARRHYTHMIC DRUGS, THEIR RANGE OF APPLICATION AND ADVANTAGES OF MODERN ANTIARRHYTHMIC DRUGS

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Abstract. Arrhythmias of the heart continue to be a leading cause of death and disability. Despite their limited efficacy and the possibility of serious adverse proarrhythmic effects, antiarrhythmic medications (AADs) and antiarrhythmic agents continue to be a mainstay of modern cardiac arrhythmia treatment. The number of new antiarrhythmic targets and drugs in the development pipeline has significantly declined over the past few decades due to conceptual, regulatory, and economical factors. There are still a number of intriguing options, though, and there have been some exciting advancements in the repurposing and reformulation of already-approved medications for use in cardiac arrhythmia-related diseases. This review outlines new compounds and formulations currently in clinical development for the rhythm regulation of atrial fibrillation, examines the important conceptual issues for the development of new antiarrhythmic medications, and emphasizes the possibility of therapeutic repurposing. Lastly, the topic of future directions for AAD development is covered. These factors, along with a growing knowledge of the molecular mechanisms behind cardiac arrhythmias, contribute to a cautiously hopeful view of better pharmacological therapy options for individuals with cardiac arrhythmias.

Keywords. Cardiac arrhythmias, acute cardioversion, antiarrhythmic treatment, rhythm regulation, atrial fibrillation, therapeutic indications.

Introduction. Arrhythmias of the heart continue to be a leading cause of death and disability. In order to avoid arrhythmia recurrence (long-term maintenance of normal sinus rhythm) and/or terminate atrial and ventricular arrhythmias (acute cardioversion), antiarrhythmic medications (AADs) and antiarrhythmic agents are provided. AADs continue to be a mainstay of antiarrhythmic treatment, even in the face of major advancements in device and catheter ablation-based therapies for cardiac arrhythmias during the past few decades. For instance, a large retrospective countrywide study conducted in the United States found that the prescription rate of AADs nearly tripled between 2004 and 2016 [1-4]. Amiodarone, sotalol, flecainide, and dofetilide prescription rates rose, which was the primary cause of this increase. Similar findings were found in a statewide research conducted in Denmark, which

revealed that the usage of AADs increased by 16% over a 19-year period, primarily as a result of increased use of flecainide and amiodarone. Increased diagnosis rates of atrial arrhythmias, including atrial fibrillation (AF), the most prevalent cardiac arrhythmia in clinical practice, are the main cause of the higher prescription rates of AADs [5-9]. The obesity pandemic, an aging population, and a rise in the number of patients with chronic illnesses are all contributing factors to the rising incidence and prevalence of AF. But the rising diagnosis rates have also been attributed to the growing use of screening modalities and advancements in AF detection made possible by mobile health solutions. There is growing evidence that AF patients benefit from (early) antiarrhythmic medication to maintain and restore sinus rhythm (rhythm regulation). Nevertheless, there haven't been many new AADs developed recently, even though cardiac arrhythmias are becoming more common and AADs are essential for treating them [10-14]. The primary goal of the early AAD development initiatives in the 1970s and 1980s was to treat ventricular arrhythmias. However, the attention has switched increasingly to atrial arrhythmias, particularly AF, following the failures of the Cardiac Arrhythmia Suppression Trial (CAST) and Survival With Oral D-Sotalol (SWORD) trials, which revealed inferior outcomes in patients treated with AADs compared to placebo control. Although recent trials revealed a similar rate of adverse effects between AADs and ablation, with AADs showing a trend towards a lower rate of adverse effects, ventricular pro-arrhythmic side effects of novel AADs for rhythm control of AF have proven to be one of the hardest obstacles to overcome in AAD development. The pharmaceutical industry's main obstacles to the de novo development of AADs are the expensive and drawn-out preclinical development and extensive clinical trial processes, worries about drug safety, more regulatory barriers, and mounting pressure from generics on the economy [14-19]. Additionally, the development of AADs has probably been impeded by the initial success and clinical enthusiasm around the development of ablation therapy, which has dramatically reduced arrhythmia recurrence rates compared to currently available AADs. There are currently just a few new antiarrhythmic targets and therapies in the development pipeline. Their outcomes are encouraging, though, and there have been exciting advancements in the repurposing and reformulation of previously approved medications to new therapeutic indications and delivery systems, which offers patients with cardiac arrhythmias new hope for better pharmacological treatment options. The purpose of this study is to give an overview of current developments in pharmacological antiarrhythmic therapy for AF, including the repurposing and reformulation of previously approved drugs and agents, as well as insights into conceptual considerations for AAD development [7-13]. The focus is now on developing drugs that target the atrial electrical and structural remodeling associated with AF, which

is crucial for the maintenance and progression of the arrhythmia. Here, we give a summary of the main mechanisms underlying the pathophysiology of different types of AF, talk about new developments of AADs that take advantage of our current understanding of AF mechanisms, and critically evaluate the principles and future directions for AAD development as well as their potential to improve AF management. This is because the disease is becoming more and more recognized to be progressive [15-20].

The main purpose of this analytical manuscript is to provide a brief overview based on scientific research on antiarrhythmic drugs, their range of use and the benefits of modern antiarrhythmic drugs.

Characteristics of Antiarrhythmic drugs. The incidence of atrial fibrillation will double in frequency over the next 15 years due to population aging, so there is a need for more effective and safer antiarrhythmic drugs to treat the condition. Attempts to modify the most effective antiarrhythmic, amiodarone, have led to the development of other multichannel blockers, such as dronedarone, celivarone, and ATI-2042. Blockade of the ultra-rapid potassium rectifier current (IKur) and the acetylcholinedependent potassium current (IKAch), which exists only in atrial tissue, is more atrial-specific and, in theory, eliminates the risk of torsade de pointes. Vernakalant and other novel antiarrhythmics have been developed with this atrial-selective strategy in mind. Additionally being developed are the gap junction facilitation agent rotigaptide and another potassium channel-blocking drug, intravenous tedisamil [7-12].

The Vaughan-Williams (VW) categorization method is commonly used to classify antiarrhythmic drugs. Although some agents maintain characteristics from numerous classes, the approach groups the drugs based on their primary mode of action. There are four primary categories in the VW categorization, with some sources include a fifth (Tab 1.). Antiarrhythmic drugs are essential for treating a range of cardiac rhythm abnormalities, and the Vaughan-Williams system's categorization of them provides a foundation for comprehending their distinct modes of action. This exercise explores the updated Vaughan-Williams classification, providing insight into the most recent advancements in antiarrhythmic medication treatment. Since some pharmaceuticals have traits that span several groups, the four main categories—and possibly a fifth—help clinicians understand the complex qualities of these drugs. Depending on how severe the patient's illness is, participants examine the nuances of giving these drugs orally or intravenously. Indications, contraindications, pharmacology, adverse reactions, toxicity, monitoring parameters, and important interactions are all covered in the extensive curriculum [1-9]. With this knowledge, the interprofessional health team may ensure a

comprehensive approach to patient care by managing disorders for which antiarrhythmic medications are required.

Table 1. Classification of antiarrhythmic drugs by the Vaughan-Williams

№	Classes	Agents	Effects and application
1.	**Class Ia**	**Quinidine, procainamide, disopyramide**	Procainamide, disopyramide, and quinidine are examples of drugs. Because of their extended QTc interval, these sodium channel blockers are the most pro-arrhythmic; their usage is restricted because of this possibility. Quinidine is utilized as an alternative to implanted cardioverter-defibrillator insertion in certain patients with Brugada syndrome.
	Class Ib	**Lidocaine, mexiletine**	Causes sodium channels to become slightly blocked. Mexiletine and lidocaine are examples of drugs. The QTc interval is shortened by these medications, which are only effective for ventricular arrhythmias—particularly post-myocardial infarction VA—and ineffective for atrial arrhythmias. Mexiletine has been used to lessen recurring and ICD arrhythmias and shortens the QTc interval in long QT syndrome.
	Class Ic	**Allapinine,** **Propafenone**	These substances have little effect on the QT interval but cause a noticeable degree of sodium blockage. Propafenone and flecainide are examples of drugs. For individuals with symptomatic supraventricular tachycardia (SVT) who are not candidates for or choose not to receive catheter ablation, these medications make sense for continued

			treatment if they do not have structural or ischemic heart disease.
2.	**Class II**	**Carvidilole,** **Bysoprolole**	Beta-blockers are indicated for rate control in patients with paroxysmal, persistent, or permanent AF and atrial flutter. Oral beta-blockers are helpful for ongoing management in patients with symptomatic supraventricular tachycardia (SVT).
3.	**Class III**	**Amiodarone,** **Dronedarone,** **Dofetilide,** **Sotalol,** **Ibutilide**	Exerts sympatholytic, sodium, and calcium antagonistic properties that decrease AV and sinus node conduction. This drug is recommended in patients with AF to maintain sinus rhythm, especially those with left ventricular systolic dysfunction. Dronedarone reduces the hospitalization rate for atrial fibrillation in patients with sinus rhythm and a non-permanent AF history. However, the clinician should not prescribe dronedarone in patients with AF that cannot be converted into normal sinus rhythm (permanent AF). Only atrial arrhythmias are treated with dofetilide. For individuals with atrial fibrillation or atrial flutter, oral dofetilide is beneficial for acute pharmacological cardioversion. Class II and class II non-cardioselective beta-blockers and potassium channel blockers have similar effects to sotalol. As a result, physicians can treat supraventricular and ventricular arrhythmias with it. While sotalol can be used to prevent recurrent atrial fibrillation, it is ineffective at converting atrial fibrillation to sinus rhythm.

			Ibutilide is indicated for AF or atrial flutter only
4.	**Class IV**	**diltiazem, verapamil**	Diltiazem and verapamil are non-dihydropyridine calcium channel blockers that slow conduction through the AV node and decrease conduction velocity. They are useful for controlling ventricular rate in both acute and chronic atrial fibrillation and atrial flutter. They can be used to treat hemodynamically stable patients with focal, multifocal, and SVT atrial tachycardias in the short term.
5.	**Other Antiarrhythmic Drugs**	**Adenosine**	Adenosine helps diagnose and terminate SVT due to either atrioventricular nodal reentrant tachycardia (AVNRT) or orthodromic atrioventricular reentrant tachycardia (AVRT). This drug may also be utilized diagnostically; adenosine helps unmask atrial flutter or atrial tachycardia (AT). Adenosine is also helpful in terminating the focal AT of a triggered mechanism and differentiating focal AT from AVNRT and AVRT.
		Digoxin	In patients with AF and heart failure, digoxin is not often the first-line treatment for ventricular rate control; instead, a combination of digoxin with a beta-blocker or non-dihydropyridine calcium channel blocker is an acceptable rate control alternative.

Conceptual Considerations for Antiarrhythmic Drug (AAD) Development. Multi-target Effects and Drug Combinations An ideal AAD must meet a number of criteria before it can be made clinically available, the most important of which is safety. When developing AADs, cardiac pro-arrhythmic effects and extracardiac side effects present significant challenges that must be carefully evaluated. A lot of work has been done to target ion channels that are selectively expressed in the atria in order to lower the risk of ventricular pro-

arrhythmia; however, the regional expression of AAD targets can be differentially affected by disease-related remodeling. Both treatment efficacy and safety may be adversely affected by this ionic remodeling (because of the increased risk of pro-arrhythmia due to up-regulation in the ventricles). Furthermore, most AADs target numerous membrane ion currents and/or intracellular ion fluxes to varying degrees rather than just one ion channel. Depending on if the multi-channel block impact is antagonistic or synergistic, this multi-channel action can alter the risk of pro-arrhythmic and extra-cardiac adverse effects. For instance, amiodarone's simultaneous inhibition of depolarizing and repolarizing currents limits excessive reverse rate-dependent repolarization prolongation in comparison to pure class III potassium channel blockers, while the combined inhibition of multiple repolarizing potassium channels can synergistically reduce repolarization reserve. A polypill consisting of aspirin, ramipril, and atorvastatin was compared to standard therapy in the SECURE research, which included patients who had experienced a myocardial infarction in the preceding six months. According to the study, patients who took the polypill had a far decreased chance of experiencing serious adverse cardiovascular events, such as cardiovascular mortality, nonfatal ischemic stroke, or urgent revascularization. Higher patient compliance was another outcome of the polypill method, underscoring the potential to combine already available treatments to lower polypharmacy, boost compliance, and, hopefully, boost efficacy. Nevertheless, the combination of AADs to enhance long-term rhythm regulation has not been thoroughly assessed, with the exception of the HARMONY trial. Lastly, it should be mentioned that patients with AF frequently experience negative medication-drug interactions with various pharmacological therapy, which may be made worse by drug combinations.

Several cardiac ion channels are also expressed in the brain, where they play a crucial role in regulating the central nervous system. Therefore, novel antiarrhythmic agents must be designed in a way that prevents them from passing the protective blood-brain barrier in order to avoid serious neurological side effects. In general, oral drug formulations are preferred over other types of formulations. Other important criteria that must be taken into consideration in the development of AADs include the chemical drug design, drug formulation, and route of administration. When compared to alternative routes of administration, oral formulations have a greater patient compliance rate because they are more convenient for patients. Additionally, because oral formulations are more cost-effective for the pharmaceutical industry, they can be readily translated to large-scale production. However, changes in the physiochemical and metabolic processes that determine pharmacokinetics can cause oral bioavailability to vary greatly. The first-pass hepatic metabolism, intestinal metabolism, and reverse transport in the gut

are important factors that significantly impact the bioavailability of medications taken orally. In order to improve therapeutic results and minimize adverse effects, alternate routes of administration should be explored for more focused organ medication delivery. Examples are provided below for local cardiac injections, nasal delivery, and other modes of administration.

Future Directions. In contrast to the substantial amount of evidence required for approval of a novel pharmacological agent, the clinical excitement of technological advancements and shifting patterns of medical practice, along with relatively lenient device legislation, allowed patients in Europe to quickly and continuously access new device-based therapies. However, this development also led to the approval of new devices without direct clinical trial evidence to show whether the manufacturer could provide evidence that the new device was similar to an already approved device. But compared to what has been the case thus far, the new European medical device legislation, which went into full force in May 2021, may alter the industrial development of device therapies and maybe decrease the number of approvals based on the principle of equivalency. It is possible that this will rekindle interest in the creation of new AADs [7-11]. Furthermore, there is evidence of socioeconomic disparities in the use of rhythm-control therapies, especially ablation, in AF patients. This implies that, in addition to stepping up our efforts to develop new AADs, ensuring that they are widely available to all patients should be a key goal for the future. In contrast to ventricular fibrillation, AF does not pose an immediate threat to life. Anti-fibrotic therapy has long been a popular strategy for stopping or even reversing the course of heart disorders and arrhythmias. However, the development of anti-fibrotic medications has been hampered by the challenges of addressing the intricate mechanism of pro-fibrotic signaling. The renin-angiotensin-aldosterone system (RAAS) and the NLRP3-inflammasome are promising targets that may help lessen fibrotic remodeling in people. When developing novel antiarrhythmic medications, the complexity of atrial arrhythmias and the reality that patients are very varied, old, and comorbid necessitate careful selection and design of therapeutically relevant and measurable outcomes in the clinical trials [2-9].

Discussion. Cardiology specialty nurses are essential for monitoring patients on antiarrhythmic medications because they are trained to identify adverse events, understand treatment goals, and communicate any concerns to the specialist or other clinicians; the pharmacist can also be a board-certified cardiology specialist and help with agent selection, ongoing monitoring, checking for drug interactions, and keeping in touch with the prescriber. However, primary care physicians, nurses, and pharmacists are responsible for monitoring patients on antiarrhythmic medications, which are not benign [1,4,5,7,11]. Examples of interprofessional team dynamics that

can lead to positive outcomes for patients include the need for all members of the interprofessional team to promptly document their findings in the patient's medical record and notify other members of any changes in the patient's condition, potential drug interactions or adverse effects, and signs of therapeutic failure. Doing so will allow all members of the team to have access to the same patient data and enable the implementation of appropriate corrective measures [9-12]. In the updated Vaughn-Williams classification, every agent has unique adverse effect profiles that need to be monitored on an individual basis. The doctor ought to consult a cardiologist if there is any uncertainty regarding the medicine. The management of arrhythmias like atrial fibrillation heavily relies on nurses and other allied health providers. In order to effectively manage atrial fibrillation, the European Society of Cardiology (2016) recommends collaborative care. ESC guidelines also urge pursuing a patient-centered, interdisciplinary team approach to enhance treatment outcomes [17-20]. Over the past few decades, there has been a decrease in the development of new antiarrhythmic drugs; however, despite the advancements in ablation therapy, there is still a need for arrhythmia management, and recent large clinical trials have shown that antiarrhythmic drugs are sufficiently effective and safe. While there are currently only a few new drugs in the development pipeline, their initial results seem promising, and some may eventually reach the clinical setting. Crucially, the repurposing and reformulating of already approved drugs to novel therapeutic indications, along with new and ideally atrial-selective delivery methods, provide new opportunities for the development of novel antiarrhythmic therapies that could help lower the morbidity and mortality associated with cardiac arrhythmias and improve the quality of life for millions of patients [11-18].

Conclusions. Over the past few decades, there has been a decrease in the development of new antiarrhythmic drugs; however, despite the advancements in ablation therapy, there is still a need for arrhythmia management, and recent large clinical trials have shown that antiarrhythmic drugs are sufficiently effective and safe.

While there are currently only a few new drugs in the development pipeline, their initial results seem promising, and some may eventually reach the clinical setting. Crucially, the repurposing and reformulating of already approved drugs to novel therapeutic indications, along with new and ideally atrial-selective delivery methods, provide new opportunities for the development of novel antiarrhythmic therapies that could help lower the morbidity and mortality associated with cardiac arrhythmias and improve the quality of life for millions of patients.

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