Recent Advances in Antiarrhythmic drug therapy: A Review

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Abstract: Current antiarrhythmic drugs (AADs) are generally effective for the acute cardioversion of paroxysmal atrial fibrillation (AF), but their success in maintaining sinus rhythm over the long term is typically moderate. Additionally, the use of AADs is linked to an elevated risk of proarrhythmia, extracardiac side effects, and the worsening of coexisting conditions such as heart failure. Cardiac arrhythmias continue to be a leading cause of death and disability. Despite their moderate efficacy and potential for significant proarrhythmic side effects, antiarrhythmic drugs (AADs) remain a key component of current treatment strategies. However, due to a combination of conceptual, regulatory, and financial challenges, the development of new antiarrhythmic targets and agents has slowed considerably in recent decades. This review explores the critical conceptual factors involved in the development of new antiarrhythmic agents and provides an overview of the novel compounds and formulations that are currently undergoing clinical development.

Keywords: Abstract, Introduction, Conceptual Considerations (AAD) Development, Improved derivative of existing drug, Novel AAD formulation, Repurposing of approved drug, Conclusion, References.

INTRODUCTION

What is Arrhythmia : Arrhythmias, or irregular heart rhythms, occur when the heartbeat is too fast, too slow, or irregular. A heart rate above 100 beats per minute at rest is referred to as tachycardia, while a rate below 60 beats per minute is known as bradycardia. Some arrhythmias may not cause any symptoms, but when they do occur, individuals might experience palpitations or a sensation of skipped heartbeats. In more severe cases, symptoms can include dizziness, fainting, shortness of breath, chest pain, or a reduced level of consciousness. Although many arrhythmias are not life-threatening, some can lead to serious complications, including stroke, heart failure, or even sudden cardiac death.

Anti arrhythmic Drugs: Antiarrhythmic medications prevent and treat abnormal heartbeats. Problems with your heart's rhythm are caused by a disruption in the heart's electrical system.

1) Sodium channel blockers: Disopyramide, Quinidine Flecainide, Propafenone.
2) Beta blockers: Atenolol, Propanolol, Esmolol.
3) Potassium channel blocker: Amiodarone, Sotalol, Dronedarone.
4) Calcium channel blockers: Verapamil, Deltiazem.

Atrial fibrillation (AF) is the most common sustained arrhythmia, affecting approximately 2.3 million people in the United States. Advancing age is a significant risk factor for AF, and the prevalence of the condition is increasing rapidly due to the aging population. Among the two primary strategies for managing AF, rhythm control—aimed at restoring and maintaining sinus rhythm—is generally considered preferable to rate control, which focuses on managing the ventricular rate while the atria remain fibrillating. However, the current methods for rhythm control have notable limitations, as outlined below, making rate control a more suitable option in some cases, particularly for older patients with fewer AF-related symptoms.

Recent studies comparing rhythm control (which involves cardioversion followed by preventive treatment to avoid recurrence) with rate control have concluded that rhythm control is not superior to rate control. In fact, rhythm control has been found to be more costly and less convenient than rate control. Despite this, rhythm control remains a preferred approach for highly symptomatic patients, those with recent-onset AF, or younger individuals. The findings have, however, led to a shift away from rhythm control in patients who can tolerate the

arrhythmia, provided their ventricular rate is well-managed. It is likely that improvements in antiarrhythmic therapy—making it safer and more effective—could reverse this shift and lead to more widespread use of rhythm control.

Antiarrhythmic drugs (AADs) remain a cornerstone of treatment for arrhythmias. For instance, a large retrospective nationwide study in the USA found that the prescription rate of AADs nearly tripled between 2004 and 2016. This increase was primarily driven by a rise in the use of amiodarone, sotalol, flecainide, and dofetilide. A similar trend was observed in a Danish nationwide study, which reported a 16% increase in AAD use over a 19-year period, largely due to the increased prescription of amiodarone and flecainide. The initial development of antiarrhythmic drugs (AADs) in the 1970s and 1980s primarily focused on treating ventricular arrhythmias. However, following the negative results of the Cardiac Arrhythmia Suppression Trial (CAST) and the Survival With Oral D-Sotalol (SWORD) trial, which revealed worse outcomes in patients treated with AADs compared to a placebo, the focus shifted toward atrial arrhythmias, particularly atrial fibrillation (AF). Despite this shift, one of the biggest challenges in developing new AADs for AF rhythm control has been managing the ventricular proarrhythmic side effects. Recent trials, however, have shown that AADs have a comparable rate of adverse effects to ablation, with AADs even showing a slight trend towards fewer adverse outcomes.

This review aims to explore key conceptual factors in the development of antiarrhythmic drugs (AADs) and offer an overview of recent advancements in pharmacological therapy for atrial fibrillation (AF). It will also discuss the repurposing and reformulation of already approved drugs and agents as potential treatments for AF.

Conceptual Considerations for Antiarrhythmic Drug (AAD) Development :

(A) Multi-target Efects and Drug Combinations

An ideal antiarrhythmic drug (AAD) must meet several important criteria to be considered for clinical use, with safety being the primary concern. Cardiac proarrhythmic effects and extracardiac side effects present significant challenges in AAD development and must be carefully evaluated. Efforts have been made to selectively target ion channels that are primarily expressed in the atria, in order to reduce the risk of ventricular proarrhythmia. However, very few channels are truly selective for the atria, and disease-related remodeling can affect the regional expression of AAD targets, complicating the development of safer and more effective treatments. Ionic remodeling can negatively impact both the therapeutic efficacy and safety of antiarrhythmic drugs (AADs). If there is down-regulation of the primary therapeutic target in the atria, the drug's antiarrhythmic effect may be reduced. Conversely, up-regulation of the target in the ventricles can increase the risk of proarrhythmia. Additionally, most AADs do not act on a single ion channel; instead, they affect multiple ion currents and/or intracellular ion fluxes to varying degrees, further complicating the drug's efficacy and safety profile.

The multi-channel effects of antiarrhythmic drugs (AADs) can influence the risk of proarrhythmic and extracardiac side effects, depending on whether the combined effects of channel inhibition are synergistic or antagonistic. For instance, the combined inhibition of multiple repolarizing potassium channels can synergistically reduce the repolarization reserve, potentially increasing the risk of arrhythmias. In contrast, amiodarone's simultaneous inhibition of both depolarizing and repolarizing currents helps limit excessive rate-dependent repolarization prolongation, which contributes to its relatively low proarrhythmic potential compared to pure class III potassium channel blockers. Additionally, targeting multiple channels at once can enhance therapeutic efficacy, reduce the need for multiple drugs, and improve patient compliance and persistence. For example, the HARMONY trial demonstrated that combining midrange doses of oral ranolazine with reduced doses of dronedarone significantly reduced the atrial fibrillation burden in patients with paroxysmal AF, and was well tolerated.

(B) Drug Formulation and Route of Administration

Other important criteria that require consideration in the development of AADs are the chemical drug design, drug formulation and route of administration. Many cardiac ion channels are also expressed in the brain, where they play a crucial role in regulating the central nervous system. As a result, novel antiarrhythmic agents must be designed to prevent

them from crossing the protective blood-brain barrier, in order to avoid serious neurological side effects. Generally, oral drug formulations are preferred over other types of administration. Oral formulations tend to have higher patient compliance due to their convenience, and they are more cost-effective for large-scale production by the pharmaceutical industry. However, the bioavailability of orally administered drugs can be highly variable, influenced by shifts in physiochemical and metabolic processes that affect pharmacokinetics. Key factors such as intestinal metabolism, reverse transport in the gut, and first-pass hepatic metabolism significantly impact oral bioavailability. Furthermore, to achieve better therapeutic outcomes and reduce side effects, more targeted organ drug delivery should be considered, potentially through alternative routes of administration.

Improved derivatives of existing drugs :

The development of new antiarrhythmic drugs (AADs) often involves modifying molecules that have already shown efficacy in treating atrial fibrillation (AF). Many currently used AADs are derivatives of existing medications; for instance, flecainide and propafenone are both derived from procainamide and propranolol, respectively. A notable example of this approach is dronedarone, approved by the FDA in July 2009. Dronedarone is a derivative of amiodarone, but it lacks the iodine component believed to contribute to the multi-organ toxicity seen with amiodarone. Dronedarone has been shown to be significantly more effective than a placebo in maintaining sinus rhythm in AF patients, and it is largely free of extracardiac toxicity. Additionally, dronedarone possesses rate-control properties, and AADs with both rhythm-control and rate-control effects may become an important focus in the development of future antiarrhythmic therapies. The anti-AF efficacy of dronedarone, however, appears to be less effective than that of amiodarone. In the landmark ATHENA trial, a large, randomized, placebo-controlled study, dronedarone significantly reduced the incidence of cardiac hospitalizations and cardiovascular-related deaths in patients with atrial fibrillation. Among the participants, 21% had NYHA class II or III chronic heart failure, 12% had a left ventricular ejection fraction below 45%, and 60% had coronary artery disease. The use of dronedarone in ATHENA was associated with improvements in several comorbidities, including a reduced incidence of atrial fibrillation, stroke, acute coronary syndrome, and a decrease in blood pressure. These positive outcomes are likely interconnected, contributing to the reduction in cardiovascular-related hospitalizations and deaths. In another large trial, ANDROMEDA, dronedarone was associated with increased mortality in patients with severe heart failure and left ventricular (LV) systolic dysfunction (NYHA class III and IV). This was likely due to worsening of chronic heart failure. However, it remains unclear whether the increased mortality observed in the ANDROMEDA trial was directly related to dronedarone or to unrelated confounding factors. One hypothesis for the increase in mortality is the discontinuation of angiotensin-converting enzyme (ACE) inhibitors due to elevated serum creatinine levels, but this remains a topic of debate. Additionally, a potential negative inotropic effect of dronedarone, resulting from the inhibition of L-type calcium channels (ICa-L), may have contributed to the worsening of severe heart failure, leading to the observed increase in mortality.

Novel AAD Formulations :

Tabel 1: Reformulation of already approved drug

Sr.No.	Antiarrhythmic Drug	Original Formulation	Original Indication	Reformulation	Indication	Clinical Study
1.	Flecainide	Solution for intravenous injection or infusion and tablets	Prevention of both atrial and ventricular arrhythmias and cardioversion of recentonset AF in patients without known	Flecainide acetate inhalation solution	Acute cardioversion of recent-onset symptomatic AF	Phase 2 terminated NCT05039359 (RESTORE-1 study) Phase 3 completed NCT03539302 (INSTANT study

			relevant structural heart disease			
2.	Bisoprolol	Tablets	Hypertension	Bisoprolol transdermal patches	Prevention of AF postnon-cardiac surgery	Retrospective studies
3.	Amiodarone	Prevention of atrial and ventricular arrhythmias. Maintenance of sinus rhythm in patients with AF	Atrial and ventricular arrhythmias	Epicardial amiodarone-eluting bi-layered patches	Prevention of postoperative AF	Preclinical

A) Flecainide: Flecainide is a sodium channel blocker that is approved for the prevention of both atrial and ventricular arrhythmias, as well as for the cardioversion of recent-onset atrial fibrillation (AF) in patients without significant structural heart disease. The rate of successful cardioversion with intravenous flecainide ranges from 51% to 55%. Additionally, a high-dose oral form of flecainide is available as part of the "pill-in-the-pocket" approach, offering a more convenient method for pharmacological cardioversion. More recently, an inhaled formulation of flecainide acetate has been developed. This new administration method aims to achieve higher and faster plasma concentrations, providing a potentially more effective approach to acute pharmacological cardioversion compared to the oral form. A recent dose-escalation study explored the feasibility, tolerability, and efficacy of inhaled flecainide acetate in doses of 30, 60, 90, and 120 mg for cardioversion in patients with recent-onset atrial fibrillation (AF). The conversion rates were found to be dose-dependent and closely correlated with plasma concentrations. Patients who received the highest dose, resulting in a plasma concentration greater than 200 ng/mL, had a cardioversion success rate of 50% within 90 minutes. This rate is similar to those observed with oral and intravenous flecainide administration. Administering flecainide through oral inhalation could offer a safe and effective alternative to intravenous or pill-in-the-pocket approaches, potentially reducing the need for hospital admissions in AF patients.

B) Bisoprolol: Bisoprolol is a selective β1-receptor blocker commonly prescribed for managing hypertension. In a retrospective study involving 61 patients undergoing non-cardiac surgery who were treated with bisoprolol transdermal patches, 77% of patients reverted to sinus rhythm within 24 hours after developing postoperative atrial fibrillation (AF). However, the main limitation of this study was the absence of a control group, which made it difficult to confirm whether the high cardioversion rate was partly due to spontaneous cardioversion in some patients. In another retrospective study examining the incidence of postoperative atrial fibrillation (AF) between orally administered bisoprolol and bisoprolol transdermal patches in patients undergoing cardiac surgery, researchers found that only 24% of patients treated with transdermal patches developed AF, compared to 46% of those receiving oral bisoprolol. Both studies were retrospective and involved a relatively small number of patients. As a result, further validation is needed to determine whether bisoprolol patches could be a viable therapeutic option for preventing postoperative AF.

C) Amiodarone: Amiodarone is currently the most effective antiarrhythmic drug (AAD) available, with both oral and intravenous formulations. While still in the preclinical phase, the epicardial application of amiodarone-eluting patches presents an innovative approach for targeted drug delivery, particularly in patients at risk of developing postoperative atrial fibrillation (AF). Targeted drug delivery could potentially allow for the achievement of therapeutic amiodarone levels directly in the atrial tissue, reducing systemic exposure and, consequently, minimizing the wide range of extracardiac side effects associated with the drug. In studies conducted on goats, the epicardial application of bi-layered amiodarone-eluting patches led to an

extended effective refractory period, prolonged conduction time, and a decreased susceptibility to burst pacing-induced atrial arrhythmias for up to 28 days after the patches were implanted. However, additional clinical trials in patients undergoing open-heart surgery are necessary to assess the full antiarrhythmic effectiveness of this approach.

Repurposing of Approved Agents:

Tabel 2: Repurposing of already approved drugs :

Sr.No.	Drug	Target	Original Indication	Repurposed Indication	Clinical Study
1	Doxapram	TASK-1 channels	Respiratory stimulant in patients with moderate to severe ventilatory failure and in patients with COPD	Cardioversion of paroxysmal or persistent, non-valvular AF	Phase 2 ongoing
2	Canakinumab	Monoclonal IL-1β antibody	Atherosclerosis	The recurrence rate of AF after electrical cardioversion of patients with persistent AF	Phase 2 terminated NCT01805960 (CONVERT-AF study)
3	Colchicine	NLRP3 infammasome inhibitor through microtubule-disrupting properties	Gout and Mediterranean feve	Atherosclerosis, pericarditis, HF, MI, and postoperative AF	Phase 2 and 3 ongoing trials
4	Metformin	5′AMP-activated kinase activator	Diabetes	Upstream therapy in AF	Phase 2 and 3 ongoing trials

1. Doxapram : The two-pore-domain potassium (K2P) channels are among the newest therapeutic targets identified for atrial fibrillation (AF). K2P channels represent a large family of potassium channels that generate an immediate and persistent ‘leak’ current. TASK-1 (K2P3.1) channels, which are primarily expressed in atrial tissue, show increased expression and activity in patients with AF. This makes them a promising atrial-specific target for potential AF therapies. Doxapram is a potent inhibitor of TASK-1 channels. Historically, it has been used as a respiratory stimulant for patients with moderate to severe ventilatory failure and those with chronic obstructive pulmonary disease (COPD). However, its use for these indications has declined due to the development of alternative pharmacological treatments. Preclinical studies in pigs have demonstrated the antiarrhythmic potential of doxapram. Currently, it is being investigated for its role in cardioversion of paroxysmal or persistent non-valvular atrial fibrillation (AF) in the ongoing DOxapram Conversion TO Sinus Rhythm (DOCTOS-Trial) (EudraCT No: 2018-002978-17).
2. Canakinumab : Growing evidence highlights the significant role of inflammation in atrial fibrillation (AF). Inflammatory biomarkers in the serum have been found to correlate with low atrial voltages in patients with AF. Similarly, COVID-19 infection has been linked to the development of AF, and in turn, AF is recognized as a risk factor for major adverse cardiovascular events in patients with COVID-19. Recent studies have reported increased cardiomyocyte-specific activation of the NLRP3 inflammasome in patients with atrial fibrillation (AF), as well as in those who develop postoperative AF, highlighting the NLRP3 inflammasome as a potential novel target for AF. However, there are currently no drugs in development aimed at inhibiting the NLRP3 inflammasome specifically for AF prevention. Despite this, targeting the downstream effects of NLRP3 activation remains a possible approach. Canakinumab, a monoclonal antibody against IL-1β, has been shown to reduce major cardiac events in patients with atherosclerosis in the CANTOS trial (The Canakinumab Anti-Inflammatory Thrombosis Outcome Study). The potential effects of

canakinumab on AF were explored in the small pilot trial CONVERT-AF, which assessed AF recurrence following electrical cardioversion in patients with persistent AF treated with either canakinumab or a placebo. At six months, the recurrence rate of AF was 77% in the placebo group and 36% in the canakinumab group. However, this difference did not reach conventional statistical significance, likely due to the small sample size of the study.

3. Colchicine : Colchicine is a well-established drug that has been used for decades to treat gout and familial Mediterranean fever. Due to its ability to disrupt microtubules, colchicine can inhibit the assembly and activation of the NLRP3 inflammasome. When used in low doses, colchicine has been shown to be safe, and its therapeutic applications in the cardiovascular field have expanded to include conditions such as atherosclerosis, pericarditis, heart failure, and myocardial infarction. Moreover, colchicine has been explored as an antiarrhythmic drug (AAD). Specifically, it has been tested for preventing postoperative atrial fibrillation (AF) after open-heart surgery and catheter ablation. While some studies have reported positive outcomes, others have failed to replicate these findings. Currently, four clinical trials are underway to investigate colchicine's antiarrhythmic potential in AF patients.
4. Metformin : Metformin is an oral antidiabetic drug that activates 5′-adenosine monophosphate-activated kinase (AMPK). Observational studies have shown that metformin use is linked to a lower risk of atrial fibrillation (AF) compared to other oral antidiabetic medications, such as sulfonylureas. In a mouse model of bleomycin-induced lung fibrosis, metformin's anti-fibrotic properties were clearly demonstrated. However, it is still uncertain whether these effects extend to cardiac fibrosis. In a recent transcriptomics-based network medicine analysis, metformin was identified as a promising candidate for atrial fibrillation (AF) therapy. This analysis, which involved drug-gene signatures and functional studies in human induced pluripotent stem cell-derived cardiomyocytes, suggested that metformin may reduce the risk of AF compared to standard antidiabetic treatments.

CONCLUSION

Study of Antiarrhythmic drug give us deep knowledge about therapy. Here the New formulation of drug useful to patients with great effect and less side effect. Few changes in the drug structure and give the increase in activity of drug with overcome the adverse effect.

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