DOI: 10.24412/2311-1623-2026-49-5-18

Antiarrhythmic drugs: efficacy, safety, and rules of use

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The progress of invasive methods for treating cardiac arrhythmias is constrained by limited access to the arrhythmogenic substrate and its complexity, procedural risks, and the high prevalence of certain arrhythmias, which makes it impossible to perform invasive interventions for all patients in need within the context of modern healthcare. The selection and administration of antiarrhythmic therapy often pose a challenging task for practicing physicians.

Objective. The aim of this review is to provide up-to-date information on the mechanisms of action, efficacy, safety profiles, and treatment initiation strategies for available antiarrhythmic drugs (AADs).

Materials and methods. A literature search focusing on the clinical use of AADs was conducted in the Russian scientific electronic library eLibrary.ru and the PubMed biomedical research database to identify articles using the keywords: "antiarrhythmic drugs", "cardiac arrhythmias", "drug therapy", "efficacy", and "safety".

Results. Currently, AADs remain the preferred means for terminating and preventing most tachyarrhythmias; they can serve as a reserve therapy and often act as a useful adjunct to catheter ablation procedures or implantable cardioverter-defibrillator implantation. The prescription of AADs is aimed at achieving the primary goal — clinical efficacy. However, the narrow therapeutic range of AADs complicates their use in practice, requiring strict adherence to administration guidelines.

Conclusion. This review is based on the results of landmark scientific studies and recent clinical guidelines for the management of cardiac arrhythmias. The information contained herein is intended to achieve therapeutic goals without compromising patient safety.

Keywords: antiarrhythmic drugs, cardiac arrhythmias, drug therapy, efficacy, safety.

Conflict of interest: none declared.

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International Heart and Vascular Disease Journal. Volume 14, № 50, June 2026
ISSN: 2311-1623 (Print)
ISSN: 2311-1631 (Online)
http://www.heart-vdj.com

Received: 26.02.2026
Accepted: 04.05.2026

For citation: Kanorsky SG, Mamedov MN. Antiarrhythmic drugs: efficacy, safety, and rules of use. International Heart and Vascular Disease Journal. 2026;14(50): 4-15. DOI: 10.24412/2311-1623-2026-49-5-18

Introduction

Cardiac arrhythmias have a significant negative impact on the health of people worldwide. In recent decades, attempts have been made to find a radical solution to the problem of cardiac arrhythmias through invasive procedures. However, despite the success of invasive treatment with catheter ablation, issues regarding anatomical limitations for interventions, procedural risks, and arrhythmias with a complex myocardial substrate remain unresolved. Furthermore, the high prevalence of certain rhythm disorders limits the role of invasive treatments. For example, atrial fibrillation (AF), the most commonly diagnosed sustained arrhythmia, currently affects up to 7% of the adult population [1]. The need for its invasive treatment exceeds the capacity of healthcare systems in most regions. Even in countries with the most advanced medical care, currently only about 1% of patients with AF undergo catheter ablation. Moreover, according to forecasts, in the foreseeable future this figure will reach only 10% due to limited resources and the shortage of welltrained medical personnel to perform technically complex interventions [2].

For some patients, pharmacological treatment remains critically important, either because of ineffective ablation or for perioperative therapy. At least 50% of patients with AF after ablation of the arrhythmogenic substrate still require antiarrhythmic drugs (AADs). Due to the failure of the first procedure, a significant proportion of patients undergo repeat ablation, but even after that, AADs are still required in most cases [3]. Thus, in modern clinical practice, rhythm control in patients with AF often requires a combination of catheter ablation and AADs [4]. Similarly, in patients with implantable cardioverterdefibrillators (ICDs) and recurrent ventricular tachyarrhythmias (VT), AADs play a crucial preventive role. Arrhythmogenic channelopathies are generally not amenable to ablation, so they also require the use of AADs [5]. In addition, AADs are widely used in the emergency treatment of arrhythmias.

Materials and methods

A search of literature sources on the clinical use of AADs was conducted in the Russian scientific electronic library eLibrary.ru and the PubMed biomedical research database to identify articles using the keywords "antiarrhythmic drugs," "cardiac arrhythmias," "drug treatment," "efficacy," and "safety." During the screening of identified articles, preference was given to recent, highly cited Englishlanguage publications from journals with high impact factors, focusing on human studies and available in fulltext format. In addition, reference lists of suitable articles, including reviews, were examined for publications not previously identified. After excluding duplicates and articles that did not meet the inclusion criteria, 46 articles most relevant to the objectives of this literature review were selected for citation.

Results

Potential roles of antiarrhythmic drugs in clinical practice

AADs are often an appropriate and, in many cases, the only therapy needed to treat cardiac arrhythmias, including as a means of acute termination, prevention of recurrences, and longterm management of patients who respond well to pharmacological therapy and prefer it over invasive procedures.

AADs are used as rescue therapy when other primary treatments, such as ablation or ICDs, are unavailable, poorly tolerated, associated with increased risk, contraindicated, or ineffective for preventing or terminating arrhythmic episodes.

AADs serve as a useful adjunct to other treatments, such as catheter ablation or ICDs, during waiting periods for procedures, in the perioperative phase, and subsequently, enhancing overall treatment efficacy.

Mechanisms of action of antiarrhythmic drugs

AADs are pharmacological agents designed to prevent or treat rhythm disorders by modulating the electri-

cal activity of the heart. Cardiac arrhythmias mainly arise through three key mechanisms: abnormal automaticity, triggered focal activity caused by early or delayed after depolarisations, and reentry. The latter mechanism is recognised as the most common and requires the existence of the following main factors for its manifestation. First, a trigger is needed to initiate reentry, which can be an ectopic impulse originating from some area of the heart. Second, a reentrant circuit is required, which is a pathway along which the electrical impulse circulates in cardiac tissue, maintaining the abnormal rhythm. This is facilitated by shortened refractoriness, slowed conduction (or a combination of both), and unidirectional block. In addition, sympathetic and parasympathetic influences on the electrical properties of the heart can either increase or decrease the likelihood of arrhythmia occurrence. These must be considered when selecting AADs in specific situations [6].

AADs exert their therapeutic effects by modulating the electrophysiological determinants of automaticity, triggered activity, and reentry. Class I AADs block sodium channels in cardiomyocyte membranes, reducing myocardial excitability and decreasing the likelihood of ectopic activity [7]. They may also prolong the effective refractory period (ERP) by delaying cardiomyocyte recovery after repolarisation. Some Class I AADs additionally prolong ERP by inhibiting the rapid component of the delayed rectifier potassium current (IKr) and other repolarising currents, leading to an increase in action potential duration. Such inhibition, which results in QT interval prolongation, is the main mechanism of action of Class III AADs [7]. Prolongation of ERP reduces the probability that trigger events will lead to the development of excitable tissue (arrhythmogenic substrate) and the occurrence of arrhythmia. This explains the role of AADs in preventing recurrences of supraventricular and ventricular arrhythmias. Class III AADs act primarily by inhibiting IKr, leading to increased action potential duration. As a result, ERP is prolonged, which prevents the stability of reentry and reduces the likelihood of sustained arrhythmias, justifying the use of Class I and III AADs for pharmacological cardioversion.

Class II AADs exert numerous indirect electrophysiological effects by reducing ßadrenoceptordependent phosphorylation of numerous ion channels, proteins involved in Ca^{2+} transport, and myofilament proteins. The resulting decrease in ryanodine receptor 2 activity, together with reduced Ltype calcium current, reduces the probability of early and delayed after depolarisations and, consequently, the likelihood of ectopic (triggered) activity [8]. Inhibition of β–adrenoceptormediated regulation of hyperpolarisationactivated and Ltype calcium channels reduces automaticity in sinoatrial node cells, justifying the use of Class II AADs for the treatment of sinus tachycardia [8]. Direct inhibition of Ltype calcium channels with Class IV AADs, or indirectly with Class II AADs, slows atrioventricular (AV) conduction, providing rate control during atrial arrhythmias. Thus, the main mechanisms of action of AADs are suppression of ectopic (triggered) activity (Class I and II), reduction of reentry probability (Class I and III), and modulation of impulse generation and conduction in the sinus and AV nodes (Class II and IV).

Importance of considering pharmacokinetics and genetic polymorphism in antiarrhythmic therapy

Most AADs have a narrow therapeutic range, which underscores the critical role of considering their pharmacokinetics in optimizing treatment outcomes. The pharmacokinetics of AADs, including aspects of intestinal absorption, firstpass hepatic metabolism, tissue distribution, and renal or hepatic elimination, are crucial for therapeutic efficacy and safety. Physicians must consider these factors, along with individual patient characteristics, to appropriately select antiarrhythmic therapy and reduce the likelihood of adverse treatment outcomes [9].

Genetic polymorphism can significantly affect drug responses, metabolism, and the risk of adverse effects [10]. The efficacy and safety of AADs vary considerably among individual patients due to genetic differences affecting their metabolism, transport, and pharmacodynamics. Genetically determined activity of cytochrome P450 isoenzymes CYP2D6 and CYP3A4 influences the biotransformation of AADs, especially drugs such as flecainide and propafenone, affecting blood drug concentrations and toxicity risk. Ion channel genes (e.g., SCN5A, KCNH2) affect AAD binding and may exert proarrhythmic effects; drug transporter genes (e.g., ABCB1, encoding Pglycoprotein) alter AAD absorption and distribution. Pharmacodynamic gene variants (e.g., ADRB1, CACNA1C) determine the body's response to AADs, which can significantly affect treatment efficacy. Certain genetic mutations,

such as those associated with long QT syndrome, increase the risk of druginduced arrhythmias such as polymorphic VT (torsades de pointes).

Classification of antiarrhythmic drugs

In the early 1970s, the thenknown AADs were grouped by Vaughan Williams and Singh into three classes based on their functional and electrophysiological effects: Class I drugs reduce myocardial excitability, Class II drugs (β-blockers) exert sympatholytic effects, and Class III drugs increase the duration of repolarisation [11]. The discovery of the antiarrhythmic potential of the calcium channel blocker verapamil led to the addition of Class IV AADs. Furthermore, the differential effects of individual Class I AADs on repolarisation duration, largely due to different binding and dissociation kinetics in the sodium channel, led to further subdivision into Classes Ia, Ib, and Ic. The practicality of this classification lies in the clinical significance of the pharmacological properties on which it is based, giving rise to electrophysiological effects, indications, and adverse effects characteristic of each AAD group [12]. However, subsequent studies showed that virtually all AADs act on multiple targets in cardiomyocytes, resulting in complex electrophysiological effects that are not identical in different clinical situations and are difficult to reflect in the Vaughan Williams classification [12]. Amiodarone is an example of an AAD with pronounced inhibitory effects on a number of ion channels; although traditionally classified as a Class III AAD, it affects sodium, potassium, and calcium channels, and also blocks α and ßadrenoceptors, thereby exhibiting properties of all four classes of the Vaughan Williams classification [13]. In addition, other substances with antiarrhythmic activity that do not fit into the Vaughan Williams classification have been identified, including magnesium sulfate for the treatment of torsades de pointes and the selective inhibitor of the sinus node If current, ivabradine, originally developed to reduce heart rate (HR) in patients with coronary heart disease (CHD), but also effective in treating inappropriate sinus tachycardia [14].

The limitations of the traditional Vaughan Williams classification have led to numerous attempts to refine the classification of AADs. In the early 1990s, the "Sicilian Gambit" was proposed to integrate the multiple mechanisms of action of AADs with their clinical effects [15]. However, the Sicilian Gambit did not replace the Vaughan Williams classification in everyday clinical practice. Subsequently, several extensions to the Vaughan Williams classification were proposed to cover emerging AADs and various compounds still in development and investigation. The latest and most extensive of these is the 2018 Oxford classification of AADs [16]. This classification expands Class I with a subclass Id, subdivides Classes II and III, expands Vaughan Williams Class IV, and adds Classes 0, V, VI, and VII. Meanwhile, most AADs used in practice belong to several subclasses due to their simultaneous blocking effects on different types of ion channels and on some elements of the new classes or subclasses. Table 1 presents a simplified Oxford classification of AADs, focusing on agents available in the Russian Federation.

The Oxford classification also includes other classes deliberately not presented in Table 1: IIb (isoprena-

Table 1. **Classification of Antiarrhythmic Drugs**

Class	Subclass	Mechanism of Action	Drugs
0		**Inhibition of If channels**	**Ivabradin**
Sodium channel blockers			
I	Ia	Openstate blockade (intermediate kinetics)	Procainamide
	Ib	Inactivatedstate blockade (fast kinetics)	Lidocaine
	Ic	Open/inactivatedstate blockade (slow kinetics)	Flecainide, propafenone
	Id	Late sodium current blockade	Ranolazine
Inhibitors of the autonomic nervous system			
II	IIa	β-Adrenoceptor antagonism	β_1-selective blockers: atenolol, bisoprolol, metoprolol; β_1- and β_2-blockers: propranolol, nadolol; β_1-, β_2- and α_1-blockers: carvedilol
Potassium channel blockers			
III	IIIa	Nonselective potassium channel blockers	Amiodarone, sotalol
Calcium channel blockers			
IV	IVa	Selective calcium channel blockers	Verapamil, diltiazem

line), IIc (atropine), IIIb (nicorandil), as well as classes IIIc, IVb, V, and VI, for which there are no AADs yet approved for clinical use. Class VII includes treatments for underlying cardiovascular pathology (angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, sacubitril/valsartan, mineralocorticoid receptor antagonists, sodiumglucose cotransporter 2 inhibitors, statins) [16].

Widely Used Antiarrhythmic Drugs Available in the Russian Federation

Class 0

Ivabradine

Ivabradine is a selective inhibitor of the If current, which carries a mixed Na^+/K^+ current and plays a key role in spontaneous diastolic depolarisation of the sinus node. By directly affecting this current, ivabradine reduces the rate of spontaneous depolarisation in the sinus node, thereby slowing the heart rate without significantly affecting myocardial contractility or AV conduction. Ivabradine may be used to reduce HR and symptoms in patients with inappropriate sinus tachycardia. However, ivabradine is not recommended for patients with paroxysmal AF, as it can provoke episodes of this arrhythmia [17].

Class Ia

Procainamide

Procainamide is a Class Ia AAD that inhibits sodium channels in cardiomyocyte membranes with high affinity for the open state and intermediate dissociation kinetics, and also blocks IKr. Collectively, these effects reduce excitability, prolong ERP and action potential duration, increasing refractoriness after repolarisation, and slow conduction. The halflife of procainamide is 34 hours. The drug is eliminated 50% by hepatic metabolism and 50% by renal excretion of unchanged drug. Procainamide is used for emergency cardioversion of monomorphic VT provided haemodynamics are stable. It is also used in patients with accessory AV connections and AF with preexcitation, slowing conduction through the accessory pathway and reducing the ventricular rate [2].

Class Ib

Lidocaine

Lidocaine is a Class Ib AAD that inhibits inactivated sodium channels with fast dissociation kinetics. Lidocaine reduces automaticity and triggered activity by decreasing the slope of phase 4 of the action potential and reducing ventricular myocardial excitability. The action potential duration under lidocaine is either unchanged or shortened. However, ERP may be prolonged due to increased postrepolarisation refractoriness resulting from sodium channel inhibition. After intravenous bolus administration, plasma lidocaine concentrations decline rapidly (halflife about 8 minutes) due to rapid distribution from plasma to peripheral tissues. Thereafter, the drug is eliminated by hepatic metabolism mediated by CYP3A4, with a halflife of about 2 hours. Mortality in myocardial infarction (MI) patients receiving lidocaine was higher, possibly due to a higher incidence of asystole and bradyarrhythmias, leading to abandonment of the previously widespread use of this AAD in such situations [2].

Class Ic

Flecainide and Propafenone

Flecainide and propafenone cause potent usedependent sodium channel blockade, reduce myocardial excitability, and slow conduction in rapidly responding cardiac tissues, exerting their greatest effects on the ventricles and the HisPurkinje system. They suppress ectopic automaticity, shorten the excitation period in Purkinje fibres, but prolong it in ventricular myocardium, and increase ventricular refractoriness by prolonging sodium channel reactivation. Flecainide and propafenone increase atrial action potential duration in a ratedependent manner, which may facilitate conversion of AF to sinus rhythm. In orthodromic and antidromic AV reentrant tachycardias, flecainide and propafenone slow conduction and increase antegrade and, especially, retrograde refractoriness in accessory pathways in a ratedependent manner. Flecainide also shortens the QT interval in patients with long QT syndrome type 3 and reduces arrhythmogenic Ca^{2+} release from the sarcoplasmic reticulum in patients with catecholaminergic polymorphic VT through blockade of ryanodine receptors in the myocardium [18]. Propafenone may serve as an alternative to flecainide in catecholaminergic polymorphic VT and exhibits moderate β-blocking activity at doses > 450 mg/day. Flecainide and propafenone have minimal haemodynamic effects in patients with normal left ventricular ejection fraction (LVEF) but reduce it in patients with LV dysfunction and heart failure (HF).

Flecainide and propafenone are recommended for cardioversion of AF to sinus rhythm and for longterm maintenance [19, 20], as well as to enhance the efficacy of direct current cardioversion and reduce the risk of early AF recurrence. In selected patients with significant symptoms and infrequent paroxysmal AF episodes, a single oral loading dose of flecainide or propafenone (the "pillinthepocket" approach) may be used to restore sinus rhythm, provided its safety has been previously established in hospital and anticoagulation guidelines are followed [21].

Intravenous flecainide or propafenone can terminate supraventricular tachycardias, including focal atrial tachycardia, AF with ventricular preexcitation, and AV nodal reentrant tachycardia, while oral formulations of these AADs prevent recurrences of these arrhythmias [22].

Flecainide and propafenone may be used for prevention and treatment of lifethreatening sustained VT episodes refractory to antiadrenergic drugs or ablation, or when these are not possible or undesirable. Combination therapy of flecainide/propafenone with amiodarone may be used in patients with frequent VT recurrences who have an ICD [23].

Flecainide/propafenone can cause monomorphic VT, have been associated with HF, cardiac arrest, and increased mortality in patients with prior MI and LV dysfunction [24, 25]. Therefore, their use in patients with CHD or stable angina pectoris should be avoided. There is controversy regarding the safety of flecainide in patients with stable angina without prior MI or ventricular dysfunction [26]. Prophylactic use of flecainide and propafenone is potentially dangerous in patients with congenital heart disease [27]. Flecainide and propafenone increase QRS duration, and if it widens by > 25% from baseline, dose reduction or discontinuation is recommended. These AADs are not recommended in patients with baseline QRS >120 ms due to risk of excessive conduction delay, especially in patients with left bundle branch block or bifascicular block.

Information on Russian Class Ic AADs (diethylaminopropionylethoxycarbonylaminophenothiazine, lappaconitine hydrobromide) is detailed in a separate review article [28].

Class Id
Ranolazine

Ranolazine is an antianginal agent that selectively inhibits sodium channels and IKr, prolonging atrial and, to a lesser extent, ventricular refractory periods [29]. Ranolazine does not slow intracardiac conduction, nor does it affect HR, myocardial contractility, or blood pressure. Offlabel use of ranolazine reduced the incidence of AF after cardiac surgery and after electrical cardioversion, and in patients with stable CHD was associated with prevention of arrhythmias and reduced mortality [30]. Combination of ranolazine and amiodarone may be effective in treating AF and VT refractory to other therapies. However, ranolazine requires careful monitoring due to the risk of QT interval prolongation, including from potential drug interactions.

Class IIa
β-Adrenoceptor blockers

Chronic autonomic dysfunction contributes to cardiac remodelling, including hypertrophy, apoptosis, and myocardial fibrosis. It also promotes the progression of cardiovascular diseases, indirectly creating an arrhythmogenic substrate in the heart. Moreover, acutely occurring autonomic imbalance is a wellrecognised trigger for cardiac rhythm disorders [8, 31]. In this context, the role of β-blockers in the treatment of cardiac arrhythmias is clear. Generally, β-blockers are divided into three generations: firstgeneration β-blockers (e.g., propranolol) have similar affinity for β1- and β2-adrenoceptors; secondgeneration β-blockers (e.g., atenolol, metoprolol, bisoprolol) have higher affinity for β1-adrenoceptors; thirdgeneration β-blockers possess additional α-blocking (e.g., carvedilol) or β3-stimulating (nebivolol) properties [8]. Most proarrhythmic effects of sympathetic stimulation are linked to β1-adrenoceptors. All β-blockers suppress sinus node automaticity (negative chronotropic effect), inhibit AV conduction (negative dromotropic effect), and reduce electrophysiological heterogeneity caused by heterogeneous autonomic innervation. With longterm use, they may help prevent proarrhythmic remodelling by reducing myocardial energy consumption and attenuating oxidative stress, partly due to their negative inotropic and chronotropic effects.

Owing to their negative dromotropic effect and rapid onset, β-blockers are firstline agents for ventricular rate control in AF [32]. In addition, β-blockers suppress ventricular ectopy, reduce the likelihood of VT, appropriate and inappropriate ICD shocks, and the risk of sudden cardiac death. Overall, they reduce

morbidity and mortality in a broad range of patients, including those with acute coronary syndromes, HF with reduced ejection fraction, long QT syndrome, and catecholaminergic polymorphic VT [5]. The prognostic benefit of β-blockers in patients with HF and sinus rhythm does not extend to similar patients with AF [33]. Perioperative β-blocker therapy is commonly used to prevent AF after cardiac surgery, but is not indicated for patients undergoing noncardiac surgery [32]. If shortacting, hepatically metabolized β-blockers are ineffective, switching to renally excreted β-blockers such as nadolol may be a more effective alternative.

Class IIIa

Amiodarone

Amiodarone inhibits a broad spectrum of ion channels and receptors, including IKr, sodium and calcium channels, as well as α and ßadrenoceptors, possessing properties of all four originally proposed AAD classes [34]. As a result, it increases the duration of repolarisation (mainly through IKr inhibition) and slows conduction velocity by blocking sodium channels. Intravenous amiodarone predominantly slows ventricular conduction, causes less repolarisation prolongation, has a minor effect on HR, and exerts a more pronounced antiadrenergic effect [35]. Amiodarone has a delayed onset of action (antiarrhythmic effect stabilizes after 10 weeks of therapy) and a very long halflife (30100 days). To accelerate onset, intravenous administration and high oral loading doses are used. The initial dose may be 600 mg daily for four weeks, followed by a maintenance dose usually 100200 mg daily. Elimination is mainly via the liver and biliary tract, with almost no renal excretion [36].

Amiodarone is considered the most effective AAD currently available. Its efficacy and relatively low proarrhythmic risk are likely due to complex interactions between multiple molecular targets, leading, for example, to increased repolarisation duration without increasing repolarisation dispersion or the risk of early after depolarisations [37]. Amiodarone is one of the few AADs approved for use in patients with HF; it is used to suppress ventricular arrhythmias, to prevent VT recurrences terminated by appropriate ICD shocks, and is a firstline drug for the treatment of ventricular fibrillation [36]. Amiodarone is widely used for cardioversion of AF and subsequent longterm maintenance of sinus rhythm, being more effective than other AADs (sinus rhythm maintained at 1 year in >⅔ of patients) [32]. Amiodarone is also used for the prevention and treatment of perioperative AF in cardiac surgery [32]. The negative dromotropic effect of amiodarone may be useful for rate control in addition to β-blockers and digoxin in patients with AF, including in acute situations with haemodynamic instability [32].

Compared with other Class III AADs, amiodarone has a relatively low proarrhythmic risk, with an incidence of druginduced torsades de pointes of <1% despite QT prolongation. Therefore, amiodarone therapy may be safely continued in patients with QTc prolongation up to 550 ms, provided there are no additional risk factors such as bradycardia, electrolyte imbalance, or concomitant use of other QTprolonging drugs. At the same time, amiodarone use is limited by its potentially serious extracardiac toxicity [38]. Despite significant toxicity, amiodarone remains the most commonly prescribed AAD. In a US insurance database, it accounted for about half of all AAD prescriptions [39]. This is likely due to the high prevalence of CHD and HF in patients with supraventricular and ventricular arrhythmias; in these settings, many other AADs are contraindicated because of their increased proarrhythmic potential.

Sotalol

Sotalol is a racemic mixture of two isomers: D and Lsotalol. Lsotalol is a nonselective β-blocker with minor Class III AAD effects, while Dsotalol primarily blocks IKr. At low doses (e.g., ⩽160 mg/day), racemic sotalol mainly exerts β-blocking (Class II) effects. At doses >160 mg/day, with increasing dose, D,Lsotalol provides both ßblocking and increasing Class III antiarrhythmic effects. Sotalol slows heart rate, prolongs ERP (QT interval), and increases refractoriness throughout the heart, especially at lower HR. In the AV node, it slows conduction and prolongs the refractory period, but does not affect conduction velocity in fastresponse tissues. In patients with baseline reduced LVEF, sotalol may reduce cardiac output and precipitate HF [40].

Sotalol is less effective than amiodarone in maintaining sinus rhythm after cardioversion of AF/atrial flutter (AFL) in patients with normal left ventricular function, stable CHD, or valvular heart disease. However, it may enhance the efficacy of direct current cardioversion [41, 42]. A dose of 80 mg twice daily

may be sufficient for AF prevention, but higher doses may be needed if recurrences occur. Sotalol reduces ventricular rate during AF, but is ineffective for cardioversion of AF [32]. In patients with ICDs and ischaemic or nonischaemic VT recurring despite β-blockers, sotalol reduced the frequency of recurrent sustained VT/ventricular fibrillation, but did not improve survival [43]. After MI, longterm Dsotalol therapy significantly reduced the risk of reinfarction but not sudden cardiac death [44]. Sotalol may be used in idiopathic right ventricular outflow tract VT with severe symptoms or haemodynamic compromise. It may also be used in patients with long QT syndrome when ICDs are contraindicated or refused, or with a family history of sudden cardiac death [41]. Sotalol prolongs QT interval and dosedependently increases the risk of torsades de pointes from 0.3 to 2%, especially with renal impairment and HF [40, 41]. Sotalol is not recommended for patients with less severe arrhythmias (ventricular ectopy, nonsustained VT) even if symptomatic, and may be used for longterm therapy only with careful monitoring of QT interval, potassium levels, and creatinine clearance [5].

Class IVa

Verapamil and diltiazem

Verapamil and diltiazem block cardiac calcium channels, reduce HR and cardiac contractility, slow conduction and prolong refractoriness in the AV node, suppress abnormal automaticity in depolarised cells, and inhibit triggered activity caused by early after depolarisations [45]. They do not affect excitability, conduction velocity, or refractoriness in atrial, ventricular, or His-Purkinje myocardium. Verapamil and diltiazem should be used with caution in patients with LV dysfunction or those taking β-blockers, as HR and cardiac contractility may decrease sharply.

Owing to their AV nodedepressant effects, diltiazem and verapamil are recommended for ventricular rate control in patients with AF/AFL without ventricular preexcitation. They may be used alone or in combination with digoxin [32].

Verapamil and diltiazem are recommended for rate control in haemodynamically stable patients with supraventricular tachycardias such as focal or multifocal atrial tachycardia, inappropriate sinus tachycardia, AFL, macroreentrant atrial tachycardias, AV nodal reentrant tachycardia, and AV reentrant tachycardias without preexcitation [22].

Verapamil is recommended for idiopathic fascicular left ventricular tachycardia, in patients with symptomatic papillary muscle tachycardia, and for mitral and tricuspid annular VT [5].

Verapamil and diltiazem are contraindicated in patients with hypotension or HF with reduced LVEF, haemodynamic instability, and also in AF with ventricular preexcitation, as they may accelerate the ventricular response. Verapamil and diltiazem may cause marked haemodynamic deterioration in patients with widecomplex tachycardia of unknown origin [2].

Verapamil, compared with diltiazem, exerts greater negative inotropic and chronotropic effects, making it more effective in AF and supraventricular tachycardias; it more often causes bradycardia, worsens HF, and leads to constipation due to effects on gastrointestinal smooth muscle, and may reduce bronchospasm. Diltiazem is better tolerated and less constipating, but more often causes pedal oedema than verapamil. It is preferred in patients requiring milder heart rate or blood pressure control.

Prescribing Guidelines for Antiarrhythmic Drugs

Prescribing AADs requires thoughtful, safetyoriented actions to achieve optimal outcomes with minimal risks. This implies responsible consideration of underlying and comorbid conditions, careful monitoring, and patient education.

Treatment of the underlying disease – CHD – involves lipidlowering therapy, adequate ßblockade, myocardial revascularization when indicated, and elimination of arrhythmiaprecipitating factors such as electrolyte imbalance. Patients with HF are recommended therapy according to phenotype: with reduced ejection fraction, β-blockers, mineralocorticoid receptor antagonists, angiotensinconverting enzyme inhibitors or sacubitril/valsartan, and sodiumglucose cotransporter 2 inhibitors (dapagliflozin, empagliflozin) are prescribed; the latter play a central role in preserved ejection fraction [46].

Baseline ECG, echocardiography, assessment of renal and hepatic function, and complete blood count and biochemical tests (lipid profile, glucose, electrolytes) are recommended. When prescribing amiodarone, baseline thyroid function tests, chest X-ray, pulmonary function tests (with diffusing capacity assessment), and slitlamp ophthalmoscopy should be performed. Patients starting Class Ic AADs

Table 2. **Recommended Investigations at Initial Assessment and During Followup of Patients Receiving AADs [2]**

Investigation	Parameter	Frequency of Assessment	Toxicity Assessment
AADs other than amiodarone			
ECG	Heart rhythm, PR interval, QTc interval, QRS complex	Baseline and soon after initiation or dose adjustment (1–2 days for Class Ia AADs, sotalol) and periodically (e.g., every 6 months)	QT prolongation (Class Ia and III); QRS widening (Class Ic); Proarrhythmia (e.g., AFL with Class Ic); Bradycardia / bundle branch block / AV block
Echocardiography	Ventricular function	Baseline and if change is suspected	Systolic dysfunction (contraindication for Class Ic and IV)
Blood tests and serum electrolytes	GFR, serum K^+, Mg^{2+}	Baseline and periodically (e.g., every 6 months)	Reduced drug elimination; risk of arrhythmia
Liver function	ALT, AST, total bilirubin	Baseline and periodically (e.g., every 6 months)	Reduced drug elimination
Exercise test	QRS complex at peak exercise, myocardial ischaemia	Consider during Class Ic therapy	QRS widening on exercise
Amiodarone			
ECG	Heart rhythm, PR interval, QTc, QRS	Baseline, after full loading (1–3 months), annually	QT prolongation, proarrhythmia (e.g., in WPW syndrome), bradycardia or AV block
Echocardiography	Ventricular function	Baseline and if change is suspected	Systolic dysfunction
Serum electrolytes	K+, Mg^{2+}	Baseline and every 6 months	Risk of arrhythmia
Liver function	ALT, AST, total bilirubin	Baseline and every 6 months	Hepatotoxicity
Thyroid function	TSH, free T_4, free T_3	Baseline and every 6 months	Hypothyroidism or hyperthyroidism
Pulmonary function	Chest Xray and pulmonary function tests (diffusing capacity)	Baseline and every	Interstitial lung disease
Ophthalmic examination	Slitlamp corneal examination and ophthalmoscopy	Baseline and every	Corneal microdeposits and, rarely, optic neuropathy

may undergo an exercise test to assess QRS widening during exertion or detect subclinical myocardial ischaemia (Table 2).

When prescribing AADs, especially intravenously, it is essential to monitor blood pressure regularly, as these drugs may cause vasodilation and hypotension. Careful control of infusion rate is recommended to ensure adequate peak plasma concentration and avoid hypotension. The physician should remain with the patient during administration.

ECG parameters for monitoring/ observation during AAD infusion [2]

- Atrial rate, atrial cycle length (in AFL)
- Bradycardia
- Enhanced AV conduction, 1:1 AV conduction
- Unexpected AV block (Class Ic and III AADs)
- Termination of AF or AFL
- Signs of sinus node dysfunction upon termination of AF/AFL
- QRS widening and aberrant conduction (Class Ic AADs)
- QT prolongation (Class Ia and III AADs)
- Brugada pattern on ECG in right precordial leads (Class I AADs)
- Torsades de pointes and other ventricular arrhythmias.

Outpatient initiation of therapy is more convenient but requires appropriate monitoring using tools such as smartwatches, transtelephonic devices, or other patientactivated ECG recording methods. Any abnormalities detected on wearable electronic devices should prompt a confirmatory 12-lead ECG. The choice between inpatient and outpatient initiation is primarily based on safety considerations (Table 3).

In women and patients over 65 years of age, sotalol should be initiated on an outpatient basis only under close supervision and in the absence of other risk factors. Patients should be informed of symptoms to watch for, the need to avoid certain medications, and the importance of regular followup visits. Sotalol should be initiated in hospital when QTc is ⩾ 450 ms (500 ms with intraventricular conduction delay), HR ⩽60 bpm, or specific risk factors are present (e.g., structural heart disease and renal dysfunction). Hospitalisation is required if QT prolongation occurs or sinus rhythm is not confirmed (risk of sick sinus syndrome or bradycardic pauses). In cases of high proarrhythmic risk (torsades de pointes, syncope, cardiac arrest), inpatient observation is required.

Table 3. **AADs Recommended for Outpatient or Inpatient Initiation [2]**

AAD	In AF		In Sinus Rhythm	
	Inpatient	Outpatient	Inpatient	Outpatient
Class Ia	+		+	
Class Ib			+	+1
Class Ic	+1	+2	+1	+2
Sotalol	+		+	+3
Amiodarone	+1	+2	+1	+2

Notes. [1] – when sinus node function is uncertain or there is a risk of 1:1 AV block;
[2] – when there is potential risk of sinus node dysfunction or AV conduction disturbances;
[3] – when there are no risk markers for AF/AFL and sinus rhythm is present.

To ensure safety and adherence, patients should be educated to recognise potential adverse effects, including palpitations or (pre)syncope during exercise or at rest, which may indicate proarrhythmia. Patients should be informed about possible fooddrug interactions and interactions between QTprolonging drugs.

At each visit, adherence to therapy should be assessed, and risk factors for proarrhythmia should be carefully reviewed. Such a systematic approach ensures effective AAD therapy, allowing therapeutic goals to be achieved without compromising patient safety.

Conclusion

AADs remain a cornerstone of modern therapy for cardiac arrhythmias, despite their modest efficacy and potential for toxic and proarrhythmic effects. Antiarrhythmic drug therapy has traditionally been directed at modulating the generation or propagation of action potentials in the heart using agents acting on membrane ion channels. However, the narrow therapeutic range of AADs complicates their clinical use. For effective and safe treatment of cardiac arrhythmias with AADs, it is necessary to understand the main mechanisms underlying various rhythm disorders, identify the underlying cardiac pathology, consider the pharmacokinetics and antiarrhythmic properties of each individual AAD, adhere to established prescribing guidelines, and carefully monitor the results of pharmacotherapy. Such a comprehensive approach will enable effective and safe medical treatment of cardiac rhythm disorders.

Conflict of interest: none declared.

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