Antiarrhythmic Drugs
Risks and Benefits

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KEYWORDS

- Antiarrhythmic therapy • Cardiac action potential • Mechanisms of arrhythmia
- Practical approach to antiarrhythmics

KEY POINTS

- Antiarrhythmic drugs continue to have an important role in the management of atrial and ventricular arrhythmias.
- Most antiarrhythmic drugs have no proven mortality benefit when administered on a chronic basis, requiring a careful risk/benefit analysis.
- The side effects and proarrhythmic effects of antiarrhythmic drugs are distinct concepts and are critical to the risk/benefit analysis.
- Antiarrhythmic drugs can be safely used for symptomatic relief and prophylaxis of most cardiac arrhythmias.

INTRODUCTION

The narrow therapeutic window of antiarrhythmic drugs (AADs) and their potential for lethal proarrhythmia pose a unique clinical challenge without parallel in medical practice.[1] The therapeutic window of some of these medications overlaps significantly with their proarrhythmic effect. It is for this reason that the concept of *proarrhythmia* should be distinguished from that of a *side effect*. Side effects of AADs can be cardiac or extracardiac, but are due to mechanisms unrelated to their targeted ion channel. An example of a cardiac side effect of an AAD is the negative inotropic effect of disopyramide (Norpace), potentially exacerbating heart failure. Disopyramide also has extracardiac side effects resulting in constipation, dry mouth, and urinary retention because of its anticholinergic properties. However, it is its proarrhythmic effect of potentially causing torsades de pointes (TdP) that should be respected the most because such proarrhythmia can cause sudden cardiac arrest. Proarrhythmias occur primarily

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because of the effects on ion channels, not only at toxic levels but also at therapeutic levels. Drug-drug interactions can also alter the metabolism of an AAD or potentiate its effect, such that a previously therapeutic dose may become toxic. Because of their proarrhythmic effects, some AADs need to be started on an inpatient basis. For example, dofetilide can only be initiated on an inpatient basis (manufacturer recommendation and standard practice) with continuous telemetry monitoring and serial electrocardiograms to monitor the QT interval. Some cardiologists will initiate sotalol on an outpatient basis with close follow-up. With current ablation techniques, most atrial and ventricular arrhythmias can be potentially treated (cured or palliated) without the need for antiarrhythmic medications. However, atrial fibrillation and ventricular tachycardia (VT) in a structurally abnormal heart remain difficult to cure. In addition, not all patients are candidates for ablation. It is therefore often critical to weigh the risks and benefits of antiarrhythmic medications in such cases. Although primary care physicians will often defer to cardiologists or electrophysiologists for the management of AADs, it is nevertheless important for all clinicians to have a basic understanding of these powerful drugs. This understanding starts with cellular electrophysiology.

CARDIAC ACTION POTENTIAL

Fig. 1 demonstrates the action potential (AP) of a ventricular myocardial cell. There are some differences in AP phases and their slopes in other cardiac cells. However, ventricular myocardial cells are used as standard models because they contain all phases of an AP and are illustrative of the main concepts. The following is a simplified explanation of an AP.

Depolarization

From the resting membrane potential, any ion shift that makes the membrane more positive will result in depolarization: *Phase 0 in Fig. 1.* (ECG correlate: QRS interval)

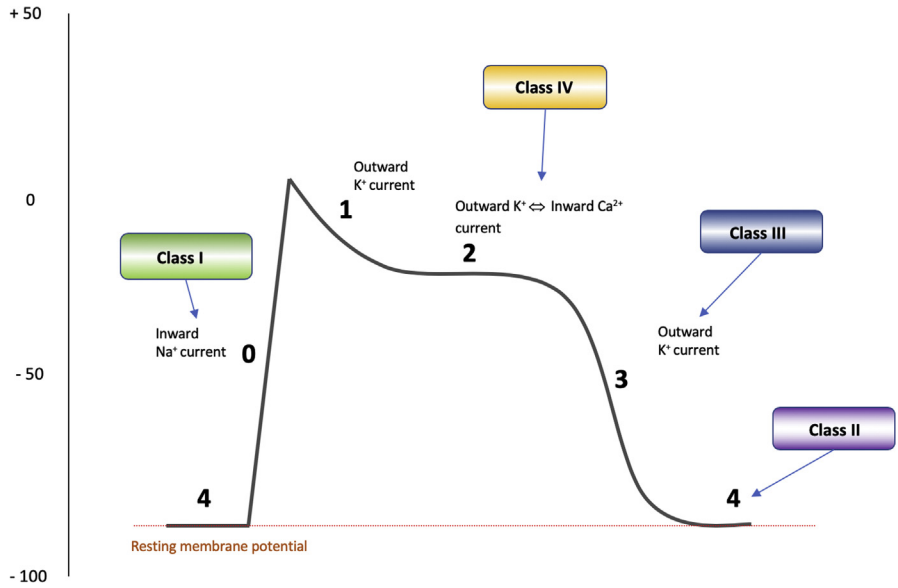

Fig. 1. Action potential in ventricular myocyte.

The cardiac myocyte in an equilibrium state is normally polarized between −80 and −95 mV.[2] While in phase 4, if the resting membrane potential is brought to threshold, a rapid influx of Na^+ ions flow into the cell via voltage-gated sodium-ion channels, generating phase 0 of the AP as demonstrated in Fig. 1.

Repolarization

After depolarization, any ion shifts that make the membrane more negative will result in repolarization. This includes phases 1, 2, and 3 (see Fig. 1). (ECG correlate: QT interval)

During phase 1 there is transient outward potassium current via I_{To} channels, which begins the repolarization process. The density of I_{To} channels is different between endocardium/epicardium and different chambers of the heart.

Phase 2 is characterized by a plateau (see Fig. 1). During this phase there is balance between outward current caused by late-activating calcium channels (L-type Ca channels) and inward potassium current, which results transiently in a net neutral membrane potential.

Phase 3 (see Fig. 1) is characterized by rapid repolarization caused by inward potassium currents (I_{Kr}, I_{Ks}). Toward the end of phase 3 there is activation of inward rectifying potassium current (I_{K1}), which brings the membrane potential close to the resting membrane potential.

Electrical Diastole

Phase 4 or resting membrane potential is maintained by I_{K1}. In the pacemaker cells (ie, the sinus node) there is spontaneous depolarization toward membrane threshold, resulting in AP generation. β-Blockers can reduce the slope of this phase.

ARRHYTHMIA MECHANISMS

There are 3 mechanisms for cardiac arrhythmias: Re-entry, abnormal automaticity, and triggered activity.

1. Re-entry is the by far most common mechanism of arrhythmia and does not require abnormal cellular electrophysiology. For re-entry to occur a propagating impulse needs to encounter an area of resistance—anatomic (due to scar) or functional (due to heterogeneity in electrophysiologic properties of the myocardium). In addition, there needs to be unidirectional block in one limb of the circuit (due to refractoriness) and propagation of the impulse along another limb (Fig. 2A). If the initially refractory limb of the circuit has recovered, the impulse can travel retrogradely along that limb. This circuit can perpetuate when the impulse returns to the original bifurcation point and finds the anterograde limb excitable again. This can result in circus movement tachycardia (re-entry) (Fig. 2B).
   - The spatial excitable gap is the amount of tissue that is available to be depolarized in a re-entry circuit.[3]
   - AADs that work by increasing refractoriness (class III) shorten the excitable gap and therefore increase the likelihood that a propagating impulse would find the tissue refractory and, therefore, unable to sustain a re-entrant tachyarrhythmia (Fig. 2C).[4,5]
   - Some AADs slow the conduction velocity by decreasing the slope of phase 0 of AP (class I, and especially class IC drugs), creating areas of slow conduction in the presence of an anatomic (scar) or a functional conduction barrier. This can also occur in healthy tissue, resulting in proarrhythmia with a mechanism of re-entry (Fig. 2D).[1]

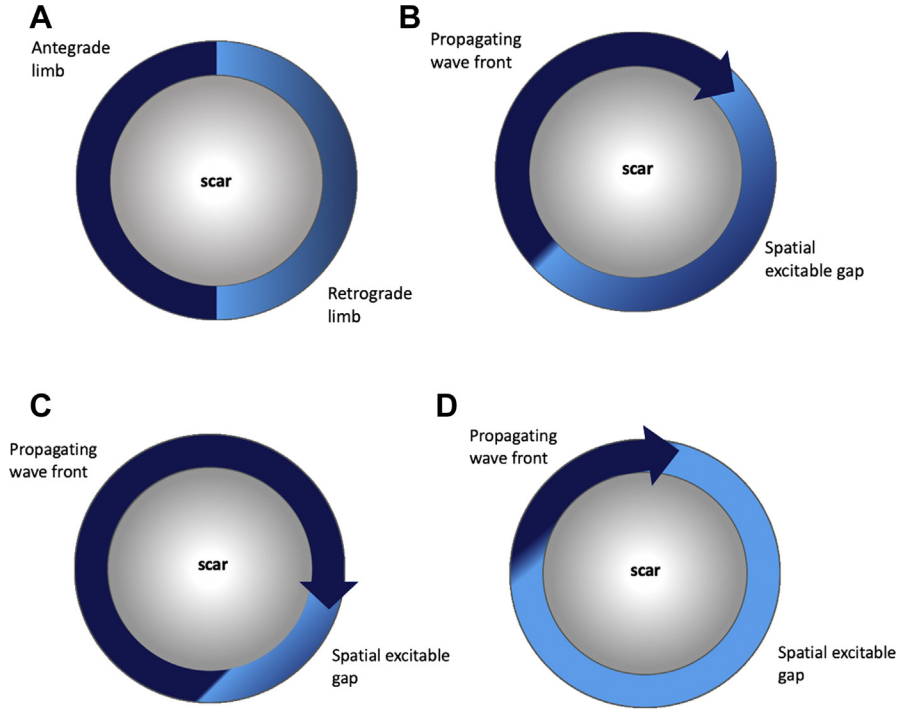

Fig. 2. Mechanism of action of antiarrhythmic drug in re-entry. (*A*) Re-entry substrate. (*B*) Schematic of re-entry mechanism. (*C*) Class III agents increase refractoriness and decrease excitable gap. (*D*) Class IC agents decrease conduction velocity and increase excitable gap.

2. Abnormal automaticity occurs when a group of cells gain the ability to spontaneously depolarize during electrical diastole (phase 4 of AP) and reach membrane threshold, resulting in an AP. Pacemaker cells of the heart (SA node, AV node, Purkinje cells) demonstrate this phenomenon inherently.[3] Pathologic examples of arrhythmias resulting from this mechanism include multifocal atrial tachycardia and some idiopathic VTs.
3. Triggered activity is due to afterdepolarizations, abnormal depolarizations that occur during the repolarization phase. If a cardiac cell reaches membrane threshold again, an extrasystole occurs. A tachyarrhythmia results when these extrasystoles perpetuate. There are 2 types of afterdepolarizations.
   - Early afterdepolarization, which occurs during phase 2 or 3 of AP. This mechanism is responsible for long QT-related arrhythmias such as polymorphic VT or TdP.
   - Late afterdepolarization occurs once the myocyte has been repolarized but before another AP would normally occur (early phase 4). This occurs because of intracellular calcium overload, resulting in ventricular premature beats that in turn can serve to trigger VT or ventricular fibrillation. This mechanism is involved in tachyarrhythmias seen during digoxin toxicity, catecholaminergic polymorphic ventricular tachycardia (CPVT), and ischemia-induced ventricular arrhythmias.[3]

CLASSIFICATION AND CLINICAL PEARLS

The modified Vaughan-Williams classification system of antiarrhythmic drugs is based on their primary effect on phases of AP and remains the most practical approach to understand their clinical use. However, many of these drugs can affect more than one type of ion channel, both at therapeutic doses and especially at toxic doses. This classification system does not include adenosine or digoxin despite their widespread use in the management of arrhythmias. Only the most commonly used AADs are discussed herein and only some clinical pearls are emphasized. The reader is referred to a more comprehensive discussion of these drugs. Although not part of the Vaughan-Williams classification, adenosine and digoxin have important roles in the treatment of arrhythmias and are also discussed below.

Class I: Sodium-Channel Blockers

These drugs affect phase 0 of AP, which results in prolongation of depolarization (widening of the QRS complex) and slowing of conduction. There are three subgroups according to their different pharmacokinetic properties.

IA: quinidine, procainamide, and disopyramide

Along with sodium-channel blocking properties, these drugs also have moderate potassium-channel blocking activity, which results in prolonged repolarization and long QTc ("The Sicilian Gambit"). Because of its I_{To} blocking properties, quinidine has a niche role in suppressing ventricular arrhythmias in Brugada syndrome.[6] These medications suppress myocardial contractility and therefore can result in exacerbation of congestive heart failure. Procainamide can be used in atrial fibrillation with rapid ventricular response in the setting of Wolf-Parkinson-White (WPW) syndrome. Its effects include termination of atrial fibrillation and slowing of conduction through the accessory pathway. *N*-Acetylprocainamide (NAPA; a metabolite of procainamide) can cause prolonged QT and TdP.[5] There are no large-scale outcome trials for these agents, and their effect on mortality is neutral at best. Their use is becoming very uncommon, as is their availability.

IB: lidocaine and mexiletine

These drugs have higher affinity for inactivated sodium channels (depolarized state) and are therefore more effective with tachyarrhythmias (use-dependent pharmacokinetics). Lidocaine is more effective at ischemic sites and is therefore useful in treating ventricular arrhythmias associated with acute myocardial infarction. It is not used for prophylaxis of ventricular arrhythmias and has no role in the treatment of supraventricular tachycardia (SVT). Lidocaine levels are monitored closely because of its narrow therapeutic window. Extracardiac side effects include severe central nervous system toxicity including tonic-clonic seizures and altered mental status. Mexiletine is an oral medication that is structurally related to lidocaine and is used for prophylaxis of ventricular arrhythmias. It is used as an adjunct to class III antiarrhythmics (such as amiodarone) for treatment of refractory VT. It is rarely used as monotherapy and is associated with gastrointestinal and central nervous system side effects.[2]

IC: flecainide and propafenone

These drugs are powerful inhibitors of fast sodium channels, resulting in decreased slope of phase 0 of the AP. However, they can also inhibit the rapid repolarization current I_{Kr}, resulting in QRS widening and slowing of conduction through the His-Purkinje system. Propafenone also has some β-blocker effects. Seven percent of white patients have a genetic absence of a hepatic cytochrome enzyme (P-450 2D6) resulting

in slow metabolism of propafenone and, therefore, an increase of its β-blocker effect. Class IC antiarrhythmics show use-dependent pharmacokinetics. At faster heart rates there are more sodium channels in open or inactivated state, and these AADs have higher affinity for sodium channels in this state. As a result, monomorphic VT can occur at faster heart rates. It is prudent to conduct a stress test on patients started on these drugs to rule out this important proarrhythmic effect. This is also the mechanism by which atrial fibrillation can organize into a relatively slow atrial flutter (1C Flutter). Rapid conduction of the atrial flutter through the AV node in 1:1 fashion results in very fast ventricular activation with unusual intraventricular aberration (wide QRS complex), owing to propafenone's use-dependent kinetics and its effect on I_{Kr} channels. Therefore, these drugs should always be used in conjunction with AV nodal blockers to slow AV nodal conduction.[7] The CAST (Cardiac Arrhythmia Suppression Trial—flecainide) and CASH (Cardiac Arrest Study Hamburg—ropafenone) studies profoundly influenced the use of AADs by demonstrating increased mortality from these drugs owing to the proarrhythmic risk in patients with structural heart disease.[1,8] The proarrhythmia is due to their heterogenic electrical effects on healthy myocytes versus areas of scar or surrounding slow conduction, potentially setting up the substrate for ventricular re-entry (see **Fig. 2**C).[4] As a result of these studies, they are absolutely contraindicated in patients with coronary disease and a low left ventricular ejection fraction.

Class II

β-Blockers

The antiarrhythmic effect of β-blockers is more complicated than just their antiadrenergic effects. In acute myocardial infarction, the antiadrenergic effects result in decreased levels of cyclic AMP, reducing the risk of ventricular fibrillation. Catecholamines can potentiate arrhythmias via any of the 3 mechanisms described earlier in this article. β-blockers are generally effective in any tachyarrhythmia (SVT or VT) associated with increased sympathetic β-adrenergic tone. In patients with VT storm, that is, refractory to antiarrhythmics and ablation, sympathetic denervation to the heart via stellate ganglion blockade or bilateral cardiac sympathetic denervation via surgical approach can be effective and further provides evidence for the role of the sympathetic nervous system as a trigger for tachyarrhythmias.[9] β-Blockers depress activity of the SA node, AV node, and ectopic foci. They also increase AV node effective refractory period and can thus affect both anterograde and retrograde AV nodal conduction.

Class III

Potassium-channel blockers: amiodarone, dronedarone, sotalol, ibutilide, dofetilide

This class of medications blocks potassium channels and lengthens AP duration and effective refractory periods. The prolongation of the AP duration manifests on the surface ECG as a prolonged QT interval.

Amiodarone and sotalol are "mixed" class III agents because of their additional effects beyond potassium-channel blockade. Amiodarone has class I effects by inhibiting inactive sodium channels at high heart rates. It also noncompetitively binds at β-adrenergic receptors and even has some mild class IV effects. As remarkable as amiodarone is with its myriad of electrophysiologic effects, it is also remarkable for its many side effects and toxicities. The extracardiac side-effect profile is much higher than its risk of serious proarrhythmia. As a result, although the most effective antiarrhythmic available, amiodarone should be used with caution, especially in a young population. A meta-analysis of amiodarone trials established amiodarone as neutral

with respect to mortality and as low risk in regard to proarrhythmia, supporting its use in patients with congestive heart failure and cardiomyopathies.[10] Initiation of low-dose amiodarone in an outpatient setting for atrial arrhythmias is common. However, some experts recommend inpatient monitoring for initiation with large loading doses. Amiodarone is among the most widely prescribed AADs for both atrial and ventricular arrhythmias. As such, close monitoring for side effects is mandatory. Most side effects are related to the cumulative dose and can sometimes be reversible when the drug is discontinued. A complete discussion of the side effects of amiodarone is beyond the scope of this article. Amiodarone is capable of affecting virtually every organ system including the lungs (pulmonary fibrosis, acute respiratory distress syndrome), the thyroid gland (hypo- and hyperthyroidism), the gastrointestinal tract (liver, gastrointestinal distress), the eyes (corneal microdeposits, optic neuritis, photosensitivity), the skin (bluish discoloration), and the neurologic system (tremors). Although thyroid toxicity is more common, pulmonary toxicity is among the most feared complications of amiodarone therapy because it is often nonreversible and potentially fatal. Acute lung injury/acute respiratory distress syndrome and diffuse alveolar hemorrhage is rare but is associated with up to a 50% mortality rate. Risk factors for this include recent cardiothoracic surgery, high Fio_2 (fraction of inspired oxygen), and pulmonary angiography. The occurrence of severe, irreversible interstitial pulmonary fibrosis may be as high as 1.2%. It is related to the cumulative dose administered and the dose intensity. The overall mortality of interstitial pulmonary fibrosis is 9%. Milder forms of lung toxicity have been reported in the range of 4.2% to 17% of patients. For example, lipoid pneumonia, which is sometimes referred to as the "amiodarone effect," is mostly asymptomatic and recognized only by mild declines in lung diffusion capacity. This occurs as a result of the lipophilic moiety of amiodarone causing it to concentrate in organs with high lipid content (liver and lung).[11] Most of these conditions are reversible, and symptoms improve with drug withdrawal.

Dronedarone is a noniodinated congener of amiodarone used to maintain sinus rhythm in patients with atrial fibrillation. Because of the lack of iodine molecules, dronedarone has less pulmonary and thyroid toxicity. Like amiodarone, it primarily has class III effects but also has class II and IV effects. It is contraindicated in symptomatic heart failure or in permanent atrial fibrillation and should not be used as an agent for rate control.[12,13] It is not approved for the treatment of ventricular tachyarrhythmias. On the other hand, amiodarone is approved by the Food and Drug Administration for the treatment of life-threatening ventricular arrhythmias, but not for atrial tachyarrhythmias. Compared with other antiarrhythmic drugs, polymorphic VT (TdP) is less common with amiodarone and dronedarone, likely because of their homogeneous effect on all myocardial cells and channels.[4]

Sotalol (Betapace) has important class II effects in addition to its class III effects. At doses less than 160 mg/d, its class III effects are not evident. Ibutilide (an intravenous drug), dofetilide (Tikosyn), and sotalol demonstrate reverse-use dependence; their effect is more pronounced at lower heart rates, resulting in increased risk of TdP with sinus bradycardia. This is especially concerning in patients receiving sotalol because of its additional β-blocker effects. Because of the high risk of TdP from QT prolongation, dofetilide and sotalol should be initiated with in-hospital electrocardiographic QTc monitoring.[14] The proarrhythmic risk of dofetilide and sotalol increases with concomitant QT-prolonging medications or with renal dysfunction. Both drugs are renally excreted and can lead to fatal proarrhythmias if their use is continued in patients with acute renal failure. Dose-adjusted use in mild to moderate renal dysfunction is possible if creatinine is stable.

Class IV

The calcium-channel blockers verapamil and diltiazem are nondihydropyridine calcium-channel blockers. Their antiarrhythmic properties are achieved primarily through increasing the refractory period of the AV node, and are mainly used to control the ventricular rate during atrial fibrillation and for termination and prevention of SVTs dependent on the AV node. Calcium-channel blockers are contraindicated in heart failure with reduced ejection fraction. Verapamil is the drug of choice for idiopathic VT, Belhassen type.[15]

Digoxin

Digoxin blocks sodium-potassium ATPase, ultimately leading to increased intracellular calcium, which results in increased inotropy. It enhances vagal tone and results in inhibition of SA node and AV node. It has a narrow therapeutic window and can precipitate toxicity in the setting of renal dysfunction. The common manifestations of an increased level are nausea, vomiting, diarrhea, and changes in color vision. At toxic levels digoxin can cause paroxysmal atrial tachycardia with AV block, bidirectional VT, or high-degree AV block. Digoxin is considered safe in pregnancy and is widely used in pediatric patients with tachyarrhythmias.[16] The clinical uses of digoxin for the treatment of arrhythmias in adults has largely been supplanted by the use of β-blockers and calcium-channel blockers.

Adenosine

Adenosine opens adenosine-sensitive inward rectifier potassium channels, resulting in inhibition of the sinus and AV node. Adenosine also shortens the atrial refractory period heterogeneously across atrial myocardium and therefore can trigger atrial fibrillation in as many as 10% of patients who receive it.[17] Because it has a mild effect on ventricular myocardium, ventricular ectopy can also be seen immediately following administration. Patients with active bronchospasm may experience severe and persistent bronchoconstriction. Adenosine should not be given to patients with reactive airway disease. Patients who have undergone autologous heart transplantation have a hypersensitivity to adenosine and should not receive adenosine in doses in excess of 3 mg or even at all. Its transient effect on the AV node makes it an ideal choice for treatment of SVT, including SVT associated with WPW syndrome. However, it is absolutely contraindicated in patients with WPW and atrial fibrillation (pre-excited atrial fibrillation) because it can potentially lead to more rapid conduction of atrial fibrillation to the ventricles via the accessory pathway by selectively inhibiting the AV node, resulting in ventricular fibrillation. Adenosine can be safely given to pregnant patients.

ANTIARRHYTHMICS IN CLINICAL PRACTICE

With the advancement of ablation therapy, the need for AADs has certainly waned. For most SVTs, atrial flutter, and idiopathic VT in structurally normal hearts, ablation is often offered as first-line therapy because the cure rates are extremely high. For atrial fibrillation or VT in ischemic or nonischemic cardiomyopathies, ablation is usually offered as second-line therapy after failure of at least one AAD. AADs still have an important role in the management of acute arrhythmias when a patient is not a candidate for ablation, when ablation is not successful, or when the patient prefers a more conservative approach. Based on the preceding discussion, the decision to initiate an AAD requires careful consideration of the risks and benefits. In some cases, the desire to treat an arrhythmia is based on symptom relief rather than expected mortality benefit. With the exception of β-blockers none of the antiarrhythmic medications

can claim a mortality benefit. For example, in patients with minimally symptomatic atrial fibrillation and adequate rate control, the chronic use of amiodarone may not be justified. If an AAD is to be prescribed chronically, a complete discussion highlighting toxicities and proarrhythmic risks should be carried out with the patient. The approach to the use of AADs in atrial fibrillation is now discussed in more depth.

The most important factors to consider in choosing an AAD are as follows.

Arrhythmia Origin and Mechanism

The origin and mechanism of the arrhythmia being treated is important in selecting an AAD. If the arrhythmia is supraventricular in origin such as SVT, SVT associated with WPW syndrome, atrial fibrillation, atrial flutter, or atrial tachycardia, the choice of AAD (depending on acuity of arrhythmia, presence or absence of structural heart disease, and patient comorbidities) include a wide range of options (**Table 1**). If the arrhythmia is ventricular in origin such as monomorphic VT, polymorphic VT, ventricular fibrillation, or frequent PVCs, the choice of AADs might include procainamide, quinidine, lidocaine, mexiletine, sotalol, and amiodarone. (see **Table 1**).[18] In some cases the origin of the arrhythmia may be known but not the mechanism (re-entry versus triggered versus enhanced automaticity). Specific AADs may be the drug of choice for specific arrhythmias with known mechanisms. Flecainide has a niche role in CPVT in combination with β-blockers. CPVT is an inherited disorder that results in mutations affecting proteins that regulate intracellular calcium levels in cardiac muscle cells, resulting in calcium overload and ventricular arrhythmias in a structurally normal heart that lead to sudden cardiac death. Ibutilide is the drug of choice in atrial fibrillation with WPW syndrome (pre-excited atrial fibrillation). Adenosine, β-blockers and calcium-channel blockers have a role in treatment of some idiopathic VTs (VT in a structurally normal heart): adenosine in outflow tract VT, β-blockers in outflow tract VT and CPVT, and verapamil in fascicular VT.[19]

Arrhythmia Acuity and Chronicity

The pattern of occurrence, acuity, and chronicity of the arrhythmia also play a role in AAD selection. Electrical cardioversion is the treatment of choice for symptomatic,

Table 1
Medications by arrhythmia type

	Atrial Arrhythmias	Ventricular Arrhythmias
Adenosine	Yes	Idiopathic VT
Digoxin	Yes	No
β-Blocker (II)	Yes	Idiopathic VT
Calcium-channel blockers (IV)	Yes	Idiopathic VT
Procainamide, quinidine (IA)	Yes	Yes
Disopyramide (IA)	Yes	No
Lidocaine, mexiletine (IB)	No	Yes
Flecainide (IC)	Yes	Flecainide in CPVT
Propafenone (IC)	Yes	No
Dofetilide, ibutilide (III)	Yes	No
Sotalol, amiodarone (III)	Yes	Yes

Abbreviation: CPVT, catecholaminergic polymorphic ventricular tachycardia.

unstable patients with VT or SVT. Table 2 describes the AADs that can be used in intravenous and oral forms.

- Re-entry SVTs can occur in an episodic pattern ranging from rare events to weekly or even daily episodes. For rare episodes, β-blockers or calcium-channel blockers can be prescribed as needed for acute termination as an outpatient. Along with adenosine, they can also be given on an intravenous basis for acute termination in an inpatient or emergency room setting. They can also be taken on a daily basis for prophylaxis against frequent episodes. Clinical judgment and a discussion with the patient are needed to decide when to initiate daily therapy, mostly dependent on the patient's quality of life.
- Intravenous β-blockers and intravenous calcium-channel blockers are often used for rate control in the setting of atrial tachyarrhythmias such as atrial fibrillation and atrial tachycardia. β-Blockers also blunt sympathetic response and can decrease the slope of phase 4 of the AP, which decreases automaticity and can potentially facilitate termination of atrial tachycardia and atrial fibrillation.
- Adenosine has a very short half-life (<10 s) as it is rapidly absorbed by red blood cells and vascular endothelium and metabolized very quickly. As a result, adenosine is only used acutely in the setting of narrow complex regular tachycardia. It can be both diagnostic and therapeutic. There are also rare adenosine-sensitive, idiopathic VTs. The effect of adenosine can be potentiated by pretreatment with β-blockers or calcium-channel blockers.
- Ibutilide is only available in intravenous formulation and is used to chemically cardiovert atrial fibrillation or flutter. However, it requires close telemetry monitoring for 4 hours immediately following administration given the risk of QT prolongation and TdP.[14] Pretreatment with ibutilide can facilitate electrical cardioversion.
- Intravenous amiodarone, procainamide, and lidocaine can be used for treatment of VT. Intravenous amiodarone and procainamide can also be used in the acute management of atrial fibrillation.
- Oral digoxin is used less commonly because of its limited efficacy and the availability of better alternatives. However, it can be modestly effective in the setting of atrial fibrillation with rapid ventricular rate in hospitalized patients with severe cardiomyopathy, hypotension, and normal renal function. Chronic outpatient administration of digoxin for rate control of atrial fibrillation is only modestly effective for patients in a resting state.

Table 2
Medications by acuity

Acute Use (Intravenous)	Chronic Use (Oral)
Adenosine	
Digoxin	Digoxin
β-Blockers	β-Blockers
CCBs	CCBs
Procainamide (IA)	Quinidine (IA), disopyramide (IA)
Lidocaine (IB)	Mexiletine (IB) Flecainide (IC), propafenone (IC)
Ibutilide (III), amiodarone (III)	Sotalol (III), dofetilide (III), amiodarone (III)

Abbreviation: CCBs, calcium-channel blockers.

Structural Heart Disease

Structural heart disease is one of the most important determinants for AAD selection. For the purposes of AAD selection, structural heart disease is defined as the presence of coronary artery disease, significant cardiomyopathy, or any condition that causes myocardial fibrosis and scar (eg, sarcoid, hypertrophic cardiomyopathy, arrhythmogenic right ventricular dysplasia). The proarrhythmic potential of AADs is greater in patients with structural heart disease. Class IC AADs in particular are contraindicated in the presence of structural heart disease, especially coronary artery disease.[1] An ischemic workup is advisable before starting a class IC AAD in patients with multiple risk factors for coronary disease and in whom occult ischemia could be present.

Clinical Factors and Drug Monitoring

Comorbidities, concurrent medication use, and age also have an important impact on selection of AADs. The most critical comorbid conditions to be considered are chronic or acute kidney disease, liver function abnormalities, and chronic lung conditions. These conditions increase the risk of proarrhythmia and side effects.

- *Renal failure*. Digoxin, dofetilide, ibutilide, sotalol, and procainamide are renally cleared from the body and therefore cannot be used in patients with renal failure. In the presence of mild to moderate but stable renal dysfunction, dofetilide and sotalol may be given with dose adjustments. However, these patients often develop electrolyte abnormalities, which can potentiate the proarrhythmic risk of AADs. Close and frequent monitoring is required.
- *Hepatic dysfunction*. AADs that cannot be used in liver failure are amiodarone, procainamide, lidocaine, propafenone, flecainide, and disopyramide.
- *Heart failure* with reduced ejection fraction is an important comorbidity to consider when choosing an AAD. Patients with heart failure frequently experience both atrial and ventricular arrhythmias.
  - Class IA AADs (procainamide, quinidine, and disopyramide) suppress myocardial contractility and are contraindicated in heart failure.
  - Dronedarone is contraindicated in patients with New York Heart Association functional class II or, worse, congestive heart failure.
  - Calcium-channel blockers such as diltiazem and verapamil are also contraindicated in heart failure with reduced ejection fraction.
- Because many AADs are either metabolized by or inhibit cytochrome P450 enzymes in the liver, it is important to review a patient's medications and the interaction with AADs. For example, amiodarone interaction with warfarin results in increased serum concentration of warfarin and requires warfarin dose reduction to achieve the desired therapeutic level.

ATRIAL FIBRILLATION

Atrial fibrillation is one of the most commonly encountered arrhythmias. Its varied presentations and associated comorbidities make it an ideal arrhythmia on which to apply the concepts presented in this article. Virtually all of the antiarrhythmic medications discussed in this article (except lidocaine, mexiletine, and adenosine) have been used in some capacity or another for the management of atrial fibrillation. The pattern of atrial fibrillation occurrence, the severity of symptoms, the associated comorbidities, and the presence or absence of structural heart disease are all factors to be taken into account when selecting an AAD. **Fig. 3** presents an algorithm for drug selection based on these factors. If there is no structural heart disease, first-line

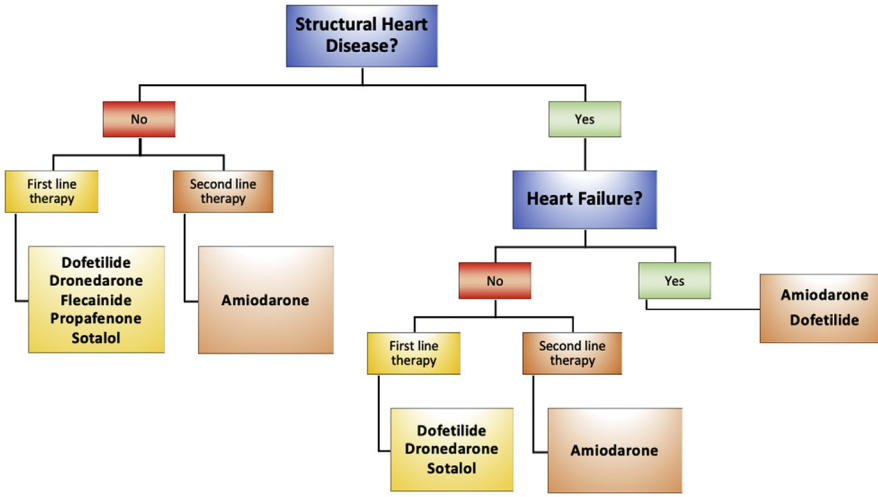

Fig. 3. Approach to selection of antiarrhythmic therapy in atrial fibrillation. (*Modified from* January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2014;64:e1–76.)

antiarrhythmic therapy includes class III antiarrhythmics (except amiodarone) and class IC antiarrhythmics. Amiodarone is considered a second-line agent because of its side-effect profile. However, if the patient has other comorbidities such as renal failure, amiodarone may be the only appropriate choice. Chronic administration of any of these medications assumes a significant atrial fibrillation burden with symptoms. Nonpharmacologic therapies should also be considered. Propafenone and flecainide can be used as a "pill-in-the-pocket" approach. When the patient experiences a persistent episode of atrial fibrillation, they can be used for the acute cardioversion to sinus rhythm in the outpatient setting. If a patient has structural heart disease, the class IC antiarrhythmics are contraindicated.[20] In patients with rare (once a year) episodes and concurrent structural heart disease with congestive heart disease, periodic electrical cardioversion may be preferable to antiarrhythmic drugs. Finally, if the frequency of atrial fibrillation increases, dofetilide and amiodarone are the only suitable pharmacologic options because sotalol and dronedarone have been shown to increase mortality in patients with heart failure.[13,21]

SUMMARY

Despite the widespread availability and effectiveness of radiofrequency ablation, antiarrhythmic medications will continue to have an important role in the treatment of atrial and ventricular arrhythmias. Understanding arrhythmia mechanisms and the mechanism of action of antiarrhythmic drugs is the first step in being able to appropriately select an AAD. The Vaughan-Williams classification remains the most clinically practical method to classify antiarrhythmic medications. Recognizing the proarrhythmic potential and side-effect profile of each of the AADs is critical for their safe use. Shared decision-making practices and close clinical monitoring of patients is required. Because both atrial and ventricular arrhythmias have similar mechanisms, multiple AADs can be used for both. Individualized therapy based on the acuity of arrhythmia,

the presence of underlying structural heart disease, the patient's comorbidities, and side-effect profile of the AAD dictate the choice. It is apparent from this discussion that the principle of "do no harm" is the overarching theme when using AADs. There are no data to confer a mortality benefit with the chronic use of AADs (except β-blockers). Their use can only be justified if they provide symptomatic relief without adverse effects.

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