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Chapter 24

ANTIARRHYTHMIC DRUGS

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HISTORICAL PERSPECTIVE

The heart, and more specifically the heartbeat, has throughout history served as an indicator of well-being and disease, both to the physician and to the patient. Through one's own heartbeat, one can feel the physiologic manifestations of joy, thrills, fear, and passion; the rigors of a sprint or long-distance run; the instantaneous effects of medications, recreational drugs, or toxins; the adrenaline of a rollercoaster ride or a penalty shootout in a World Cup final. Although the complexities of the heart continue to humble the scientists and physicians who study it, the heart is unique in that, despite the complexity of its physiology and the richness of both visceral and romantic imagery associated with it, its function can be distilled down to that of a simple pump, the function and dysfunction of which we now understand a great deal (see Chapter 21). The history of development of pharmacologic agents to correct abnormalities in heart rhythm is, however, emblematic of drug development as a whole: major successes combined with paradoxes, damaging side effects, and the often frustrating intransigence of what would seem the most intuitive targets for antiarrhythmics—ion channels.[1,2]

In ancient Greek, Egyptian, and Chinese cultures, the pulse was recognized as a means to assess health, and for millennia it was the only measure of cardiac physiology and pathophysiology. In second-century Rome, Galen's work *De Pulsibus* became the first great treatise on the pulse as a window into human health and established Galen as the father of his discipline.[3] It was not for another 1500 years that the great physician, scientist, and naturalist William Harvey, of Folkstone in England, published his landmark (and then controversial) work *An Anatomical Exercise Concerning the Motion of the Heart and Blood in Animals*. This introduced the theory that blood circulates throughout the body, a hypothesis tested rigorously by Harvey with experiments on animals and the cadavers of executed criminals.[4] In the late 19th and early 20th centuries, Waller and Einthoven founded the field of electrocardiography, facilitating quantitative differential diagnoses of cardiac arrhythmias. This paved the way for modern cardiology and advances such

as Wolff, Parkinson, and White's neurocardiac theory, the discovery of atrial fibrillation, and the increasingly sophisticated molecular genotype-phenotype correlations from which we benefit today.[5,6]

These latter advances also owe much to the work of molecular geneticists in the 1990s whose Herculean efforts (before routine high-throughput sequencing) helped identify the mutant ion channel genes underlying inherited arrhythmias such as long QT syndrome, working hand-in-hand with cellular electrophysiologists and physicians to exemplify the bedside-to-bench model of modern molecular medicine. Having said this, β blockers, the first antiarrhythmics of the modern era, were developed in the later 1950s to early 1960s not with ion channels in mind, but were a by-product of Sir James W. Black's desire to create improved therapies for angina and essentially "to stop the effects of adrenaline on the heart" following the death of his father after a myocardial infarction. The resulting class II antiarrhythmic drug, propranolol, ushered in a new era of drug development and proved effective in therapy of disorders including angina, arrhythmia, and hypertension.[7]

Despite the vast array of imaging, molecular, and electrocardiographic diagnostic tools available to cardiologists and other physicians, measurement of the pulse will likely be central to routine examination of the cardiac and holistic health of individuals for the foreseeable future. Timely, rhythmic beating of the heart is essential for health. When the heart develops sustained nonrhythmic beating, generally termed *arrhythmia*, the consequences can range from mild (e.g., syncope) to lethal (sudden cardiac death). Cardiac arrhythmias are treated by surgical ablation, electronic pacemaker, cardioversion, pharmacologic agents, or a combination of these, depending on the location and nature of the causal factor. For example, in the case of ventricular fibrillation—a life-threatening, chaotic tachycardia—electrical defibrillation is required immediately to prevent sudden cardiac death. Whereas, in many cases of atrial fibrillation, there is an underlying structural defect in the atria that can be successfully treated using radio-frequency catheter ablation, for example, to prevent the aberrantly conducting area from being an arrhythmogenic focus.

This chapter focuses on antiarrhythmic medications as frequently encountered in the perioperative and critical care settings. These are a broad class of drugs, incorporating numerous structural classes and modes of action, that are used based on the suspected or known molecular etiology of the arrhythmia to be treated. Recent advances in the understanding of the molecular basis for generation of electrical currents in the heart, and also the genetic basis of many cardiac arrhythmias, have contributed to the development and use of antiarrhythmic drugs. Furthermore, these advances have demonstrated the basis for the proarrhythmic action of some drugs; paradoxically, even some drugs that are classified and used as antiarrhythmics.

To fully understand the mechanism of action of antiarrhythmic drugs, one must understand both the underlying cause of the arrhythmia, and the molecular target of the antiarrhythmic; these may or may not be the same entity. Accordingly, this chapter includes not only a description of the basic and clinical pharmacology of the major classes of cardiac arrhythmias, but also a discussion of the mechanistic underpinnings of these arrhythmias.

Table 24-1. Singh-Vaughan Williams Classification of Antiarrhythmic Agents

CLASS	MECHANISM OF ACTION	DRUGS
Ia	Na^+ channel blockade, prolonged repolarization	Procainamide, quinidine, disopyramide
Ib	Na^+ channel blockade, shortened repolarization	Lidocaine, mexiletine, phenytoin, tocainide
Ic	Na^+ channel blockade, repolarization unchanged	Encainide, flecainide, propafenone
II	Beta adrenoceptor antagonist	Esmolol, metoprolol, propranolol
III	Marked prolongation of repolarization	Amiodarone, bretylium, ibutilide, sotalol
IV	Calcium channel blockade	Diltiazem, verapamil

BASIC PHARMACOLOGY

Singh-Vaughan Williams Classification of Antiarrhythmic Drugs

Antiarrhythmic drugs include a wide range of structural and functional classes. While not perfect, a highly useful framework for their classification is that proposed by Singh and Vaughan Williams, usually referred to as the *Singh-Vaughan Williams (SVW) classification*. The SVW classification categorizes antiarrhythmic drugs into four classes (Table 24-1). Class I denotes sodium (Na^+) channel blocking activity, with resultant delay in phase 0 depolarization and/or altered action potential duration. Class II agents counteract the effects of endogenous catecholamines (in particular epinephrine and norepinephrine) by antagonism of β adrenergic receptors, and hence are known as β blockers or β antagonists. Class III antiarrhythmics prolong the action potential and refractory period, acting primarily by potassium (K^+) channel blockade. Class IV agents reduce heart rate, primarily by L-type calcium (Ca^{2+}) channel blockade, which slows conduction through the sinoatrial (SA) and atrioventricular (AV) nodes.[8,9] (For a more detailed discussion of cardiac electrophysiology and myocyte depolarization, see Chapter 20.)

The primary reason that the SVW classification is to some extent imperfect is that many, if not most, antiarrhythmic drugs exhibit physiologically significant actions in more than one of the four classes. Typically, the classification is based upon the action that was first described for each drug, which is generally but not necessarily the most therapeutically significant mechanism of action for all types of arrhythmia for which the drug is prescribed. This discrepancy can occur because of nonspecificity of the drug, or because major metabolites of the drug exhibit different activity to that of the drug itself. Furthermore, some important antiarrhythmic drugs, including digoxin and adenosine, do not fit primarily into any of the four classes. However, the SVW classification is still the most useful framework for describing antiarrhythmic drugs, especially if one considers the net effect of each drug rather than all its specific molecular targets. The clinical pharmacology of the major antiarrhythmic drugs is summarized in Table 24-2.

Table 24-2. Antiarrhythmic Drugs

CLASS	MECHANISM	SPECIFIC DRUGS	CLINICAL USES	ADVERSE EFFECTS
Ia	Na^+ channel block (intermediate kinetics); K^+ channel block; repolarization prolonged	Quinidine Procainamide Disopyramide	Ventricular arrhythmias Prevention of paroxysmal recurrent atrial fibrillation Conversion of atrial flutter and fibrillation (quinidine, procainamide) Maintenance of sinus rhythm after conversion of atrial flutter and fibrillation Wolff-Parkinson-White syndrome (procainamide)	QTP/torsades de pointes, nausea, diarrhea, hepatotoxicity, myelosuppression Lethal ventricular arrhythmias, QTP/torsades de pointes, hypotension Lupus-like syndrome, blood dyscrasias Proarrhythmic, torsades de pointes, negative inotropy Parasympatholytic
Ib	Na^+ channel block (fast kinetics); repolarization shortened	Lidocaine Tocainide Mexiletine	Ventricular tachycardia/ fibrillation (lidocaine) Atrial fibrillation	Seizure, tremor, confusion/ delirium Ataxia, tremor
Ic	Na^+ channel block (slow kinetics); no effect on repolarization	Flecainide Propafenone	Prevention of paroxysmal atrial fibrillation Recurrent tachyarrhythmias of abnormal conduction system Contraindicated immediately post-myocardial infarction	Proarrhythmic, heart failure Proarrhythmic, nausea
II	β blockade Propranolol also shows class I effect	Nonselective Propranolol Nadolol β1 selective Esmolol Metoprolol Atenolol Bisoprolol Nonselective β/α blockade Carvedilol Labetalol	Reduce myocardial infarction mortality Prevention of recurrence of tachyarrhythmias Rate control	Bradycardia, hypotension, fatigue, depression
III	K^+ channel block Sotalol is also a β blocker Amiodarone and dronedarone have Class I, II, and III activity	Sotalol Ibutilide Dofetilide Amiodarone Dronedarone Bretylium (no longer available in U.S.)	Wolff-Parkinson-White syndrome Ventricular tachycardia/ fibrillation (sotalol bretylium, amiodarone) Conversion of atrial flutter and fibrillation (ibutilide, sotalol, dofetilide, amiodarone) Maintenance of sinus rhythm after conversion of atrial flutter and fibrillation (sotalol, dofetilide, amiodarone, dronedarone)	Proarrhythmic, QTP/torsades de pointes, bradycardia, heart failure Proarrhythmic, QTP/torsades de pointes Proarrhythmic, QTP/torsades de pointes Hypotension, bradycardia Pulmonary, neurologic, hepatic, dermatologic, ophthalmic, thyroid Increased mortality with heart failure Nausea, vomiting, diarrhea Proarrhythmic, hypotension
IV	Ca^{2+} channel block	Dihydropyridine (selective vasodilators) Nifedipine, nicardipine, amlodipine, isradipine	Hypertension	
		Benzothiapine (less vasodilation; sinoatrial and atrioventricular node block)	Prevention of recurrent paroxysmal supraventricular tachycardia Reduce ventricular rate in atrial fibrillation	Bradycardia, hypotension, ankle swelling
		Diltiazem Phenylalkylamine (sinoatrial and atrioventricular node block)	Prevention of recurrent paroxysmal supraventricular tachycardia Reduce ventricular rate in atrial fibrillation	Bradycardia, hypotension, constipation
		Verapamil		
Other	Adenosine receptor activation	Adenosine	Supraventricular arrhythmias	
	Sodium pump inhibition	Digoxin	Heart failure, atrial fibrillation	Bradycardia, nausea, vomiting, visual disturbances
	Ca^{2+} channel block and other effects	Magnesium	Torsades de pointes	Hypotension, weakness

QTP, QT interval prolongation.

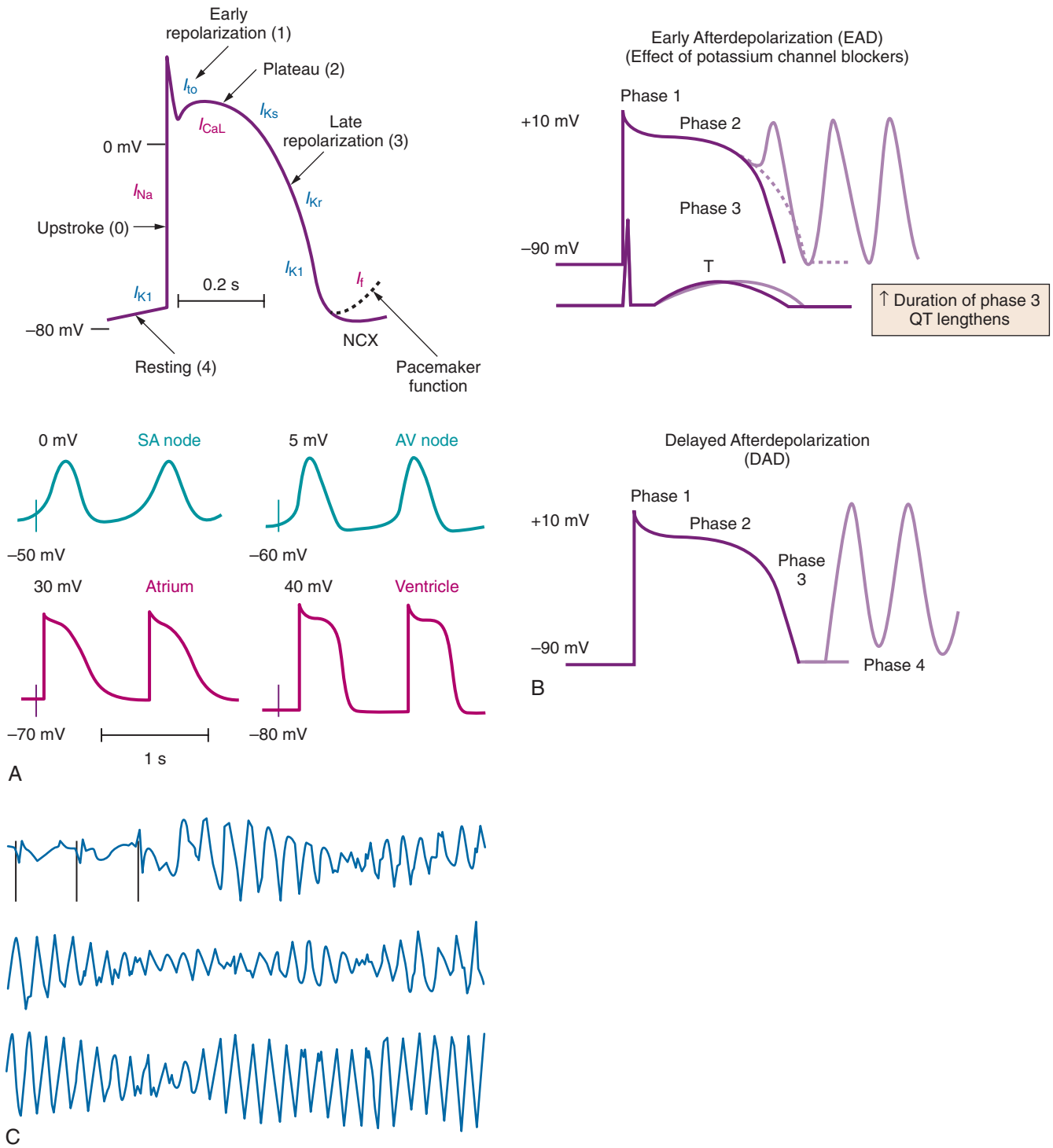

Figure 24-1 Cardiac action potentials and the electrocardiogram. **A,** *Upper,* a generic cardiac action potential illustrating the phases and major currents involved. NCX, sodium/calcium exchanger. *Lower,* comparison of nodal (SA, sinoatrial; AV, atrioventricular), atrial, and ventricular action potentials. **B,** *Upper,* ventricular action potential superimposed upon an electrocardiogram (ECG) showing the QT interval prolonging effects of potassium channel block and resultant early afterdepolarizations. *Lower,* delayed after-depolarizations. **C,** ECG showing torsades de pointes. *(Trace taken from Braunwald E, Zipes DP, Libby P, eds.* Heart Disease. *6th ed. Philadelphia: WB Saunders; 2001:868.)*

Sodium Channels and Class I Antiarrhythmic Drugs

Voltage-gated Na^+ (Na_v) channels open in response to cell membrane depolarization to permit influx of Na^+, further depolarizing the cell. The predominant Na_v channel in human cardiac electrophysiology is $Na_v1.5$, which is encoded by the *SCN5A* gene. In most cardiac myocytes, $Na_v1.5$ activation mediates the upstroke in phase 0 of the action potential, in which the membrane potential is depolarized from around –70 mV to +20 mV due to Na^+ influx (Figure 24-1, *A*). $Na_v1.5$, like other mammalian Na_v channels, inactivates rapidly, which together with the transient outward K^+ current, I_{to}, shapes the

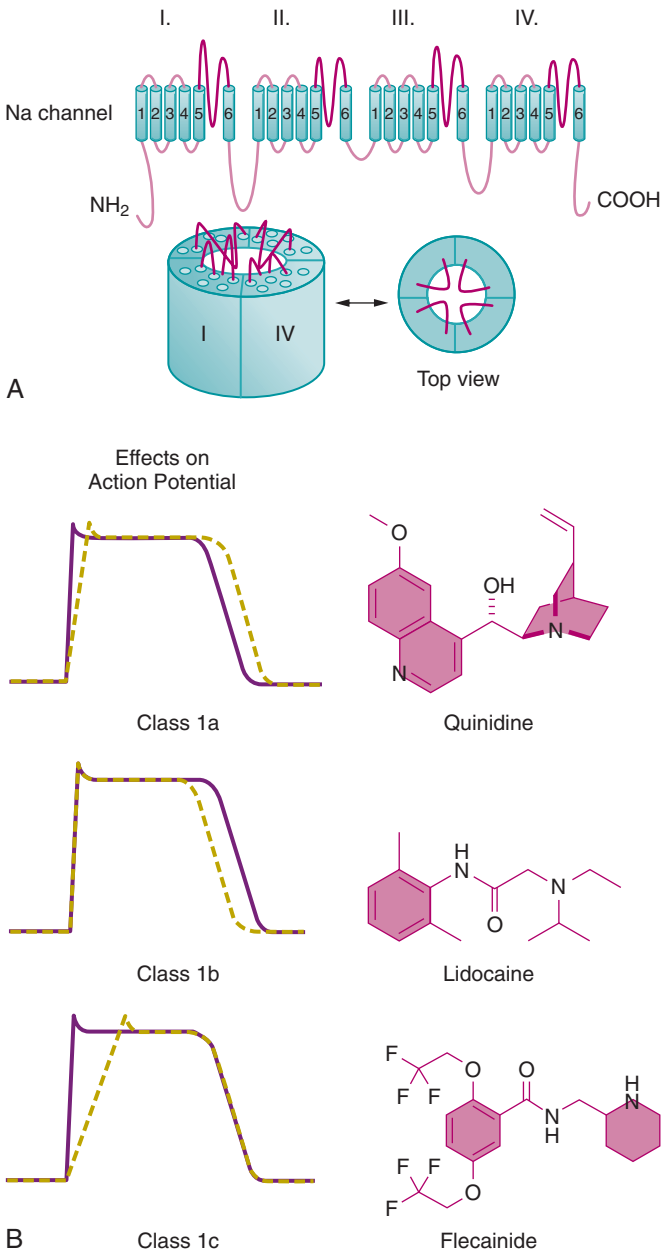

Figure 24-2 Sodium channels and the class I antiarrhythmics. **A,** Topology and subunit organization of the voltage-gated Na^+ (Na_v) channel α subunit. The 24-transmembrane segments form four homologous domains (I-IV) that fold to create the ion pore. **B,** *Left,* effects of class Ia, Ib, and Ic antiarrhythmics *(dotted lines)* on cardiac myocyte action potentials *(purple lines)*. *Right,* exemplar class Ia *(Quinidine)*, Ib *(Lidocaine)*, and Ic *(Flecainide)* antiarrhythmics.

notch in phase 1 at the beginning of the human cardiac myocyte action potential.[10]

Class I antiarrhythmics exhibit Na_v channel blocking activity. These drugs are often referred to as "membrane stabilizing agents" because by blocking cardiac Na_v channels, which mediate myocyte depolarization, they reduce cellular excitability. Na_v channels are composed of a 24-transmembrane-segment pore-forming α subunit that consists of four homologous domains (DI-DIV) also bears four voltage-sensing domains and one or more inactivation gates (Figure 24-2, *A*). The $Na_v1.5$ α subunits form cardiac ion channel complexes with single-transmembrane segment β subunits, encoded by the *SCNxB* genes, which modify $Na_v1.5$ function and pharmacology.[11]

Class I antiarrhythmic drugs are thought to bind in the inner pore vestibule of Na_v channels, with drugs from different structural classes including lidocaine, flecainide, and quinidine, and the anticonvulsant phenytoin, binding to an overlapping but nonidentical site influenced experimentally by mutations in the S6 transmembrane segment of domain IV.[12] Drugs in class I are subcategorized as Ia, Ib, or Ic depending on their effects on Na^+ channel conduction and resultant effects on action potentials in cardiac myocytes expressing the predominant cardiac form of Na_v channel, $Na_v1.5$ (see Figure 24-2, *B*).

$Na_v1.5$ is relatively insensitive to the canonical and lethal Na_v channel antagonist tetrodotoxin (TTX), a nerve toxin present, among other animal sources, in the nerves, skin, and gonads of the Japanese puffer fish, *Fugu rubripes*. *F. rubripes* is saddled with the dual distinction of having the shortest known genome of any vertebrate organism and being a delicacy in Japan that must be prepared by certified chefs in order to decrease the chances of lethal doses of TTX being ingested by adventurous diners. Compared to its effects on $Na_v1.5$, TTX acts with up to 10^3-fold higher potency on the predominantly neuronal Na_v channel subtypes $Na_v1.1$-1.3 *(SCN1A-3A)* and the skeletal muscle-expressed channel $Na_v1.4$ *(SCN4A)*.[13] TTX, nicknamed "zombie powder" because its paralysis- and coma-inducing effects have led to its use in voodoo ceremonies (it does not cross the blood-brain barrier; those ingesting sublethal doses are potentially conscious while paralyzed), is therefore not a useful antiarrhythmic (owing to its inefficacy and lethality at low doses). However, TTX prolongs the local anesthetic effect of bupivacaine when the two are coadministered.[14] A recent high-resolution x-ray crystallographic structure of an Na_v channel from *Arcobacter butzleri* has provided a first look at this class of proteins essential to function of nerve and muscle, and will likely enhance future class I antiarrhythmic development (see Chapter 17).[15]

β Receptors and Class II Antiarrhythmics

Class II antiarrhythmic drugs, also known as β blockers, antagonize the β adrenergic receptor (β receptor). This β blockade prevents activation of adenylyl cyclase and the consequent increase in intracellular cyclic adenosine monophosphate (cAMP), and thus also activation of its principal downstream target cAMP-dependent protein kinase (PKA), and the promotion of maximal myocardial performance that normally results from the enhancement of sympathetic nervous tone (Figure 24-3; see Chapters 12 and 13).

β Blockers are selective, in that they do not block other receptors, and specific, in that they do not antagonize cardiac stimulation and vasodilatation elicited by agents other than β agonists. All β blockers share the basic structure of β sympathomimetic side chain, which confers affinity for the receptor, along with an aromatic substituent, which determines potency; most are derivatives of the class-defining agent propranolol (see Figure 24-3, *B*). β Blockers are effective as antiarrhythmic agents because, by blocking the action of the sympathetic nervous system on the heart, they depress SA and AV node function, decrease conduction and automaticity, and prolong atrial refractory periods. β Blockers also reduce blood pressure, probably arising from a combination of reduced cardiac

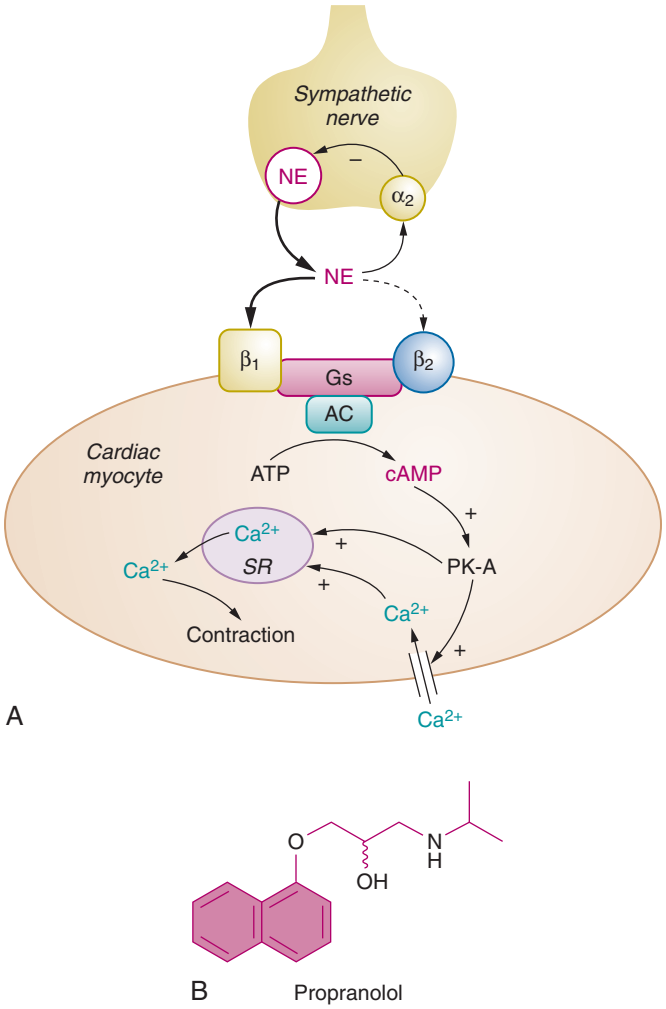

Figure 24-3 β-Adrenergic signaling and the class II antiarrhythmics. **A,** Schematic showing β-adrenergic signaling and its effects on cardiac function. *AC,* Adenylyl cyclase; *Gs,* G-stimulatory protein; *NE,* norepinephrine; *PK-A,* cAMP-dependent protein kinase; *SR,* sarcoplasmic reticulum. **B,** Structure of the canonical β blocker, propranolol.

output, renal renin release, and perhaps even effects within the central nervous system (see Chapter 23).[16,17] Inasmuch as an exaggerated increase in sympathetic tone typifies the deleterious reaction to congestive heart failure, β blockers, particularly the cardioselective ones, are used successfully also in the treatment of this ailment.[18] Propranolol is marketed as a *D,L*-racemic mixture (see Chapter 1 for a discussion of the pharmacologic implications of chirality), the reason being that the *L*-form is the β blocker while the *D*-form is a "membrane stabilizer," which adds antiarrhythmic effect to the β-blocking properties of the *L*-enantiomer.

Potassium Channels and Class III Antiarrhythmic Drugs

Class III antiarrhythmic drugs are defined by their ability to block K^+ channels. This activity increases action potential duration in cardiac myocytes and prolongs the refractory period, that is, extends the period during which the heart is refractory to premature electrical stimuli. Cardiac K^+ channels exhibit a much wider variety than other cardiac ion channels, the two most physiologically and therapeutically important families of K^+ channels in the heart, based on current understanding, being the voltage-gated K^+ (K_v) channels and inward rectifier potassium (K_{ir}) channels.[19,20] Channels in both these families are predominantly involved in the repolarization phases of the cardiac myocyte action potential, because both K_v and K_{ir} channels only pass inward K^+ currents when the cell membrane potential is negative to the K^+ equilibrium potential, which is around –80 mV under physiologic conditions.

K_v channels are each comprised of several subunit types. Similar to Na_v channels, the pore-forming α subunits of K_v channels are arranged in a 24-transmembrane-segment array forming an aqueous central pore with external voltage-sensing modules (Figure 24-4, *A*). However, in K_v channels, this is composed of a tetramer of noncovalently-linked α subunits (each subunit having six transmembrane segments) rather than one contiguous α subunit with four homologous six-segment domains as in Na_v and Ca_v channels. In K_v channel α subunits, the fourth transmembrane segment (S4) bears the basic residues that confer voltage sensitivity, while S6 lines the pore (see Figure 24-4, *A*). High-resolution X-ray crystallographic structures of bacterial and eukaryotic K_v channels have revolutionized the study of these ubiquitous and essential proteins, including current understanding of drug binding sites.[21,22]

The most important K_v α subunits in human ventricular repolarization are the *ether-à-go-go* related gene product (hERG; also named KCNH2) and KCNQ1. Tetramers of each of these coassemble with multiple single-transmembrane-domain ancillary or β subunits from the KCNE gene family. KCNQ1-KCNE1 complexes primarily generate the slowly activating I_{Ks} current; hERG-KCNE2 complexes generate I_{Kr}; and each of the five KCNE proteins probably regulates these and other α subunits in the heart too.[23-26] I_{Kr} and I_{Ks} are crucial to phase 3 repolarization (see Figure 24-1, *A*); therefore, blocking these currents delays ventricular repolarization, which can be proarrhythmic or antiarrhythmic depending on the disease state, and other genetic and environmental factors.[27] hERG is particularly sensitive to drug block by a wide range of drugs, owing to its bearing an unusual array of hydrophobic residues, not conserved among other K_v channels, in an internal pore cavity also predicted to be wider than in other K_v channels (see Figure 24-4, *B*).[28]

Inhibitors of K_v channels tend to bind in one of three distinct sites: the outer vestibule, the inner vestibule (drugs in these classes would be considered pore blockers), or on the voltage sensor, which is rarer among small molecules but is seen with some toxins from venomous animals, such as hanatoxin and SGTx from tarantula spiders.[29] The canonical inhibitors of hERG and KCNQ1 are E-4031 and Chromanol 293B, respectively, both of which bind in the inner vestibule and show relatively high specificity for their targets. Additionally, both drugs are sensitive to the presence of KCNE subunits in complex with the α subunits.[30] E-4031 will not be used in the future for antiarrhythmic therapy because pure hERG antagonists such as this cause dangerous repolarization delays. I_{Ks} inhibitors are still being considered because it might be therapeutically useful to counteract the upregulation of I_{Ks} during periods of high sympathetic activity associated with arrhythmia triggering. Other important K_v channel targets of class III antiarrhythmic drugs include the K_v4 α

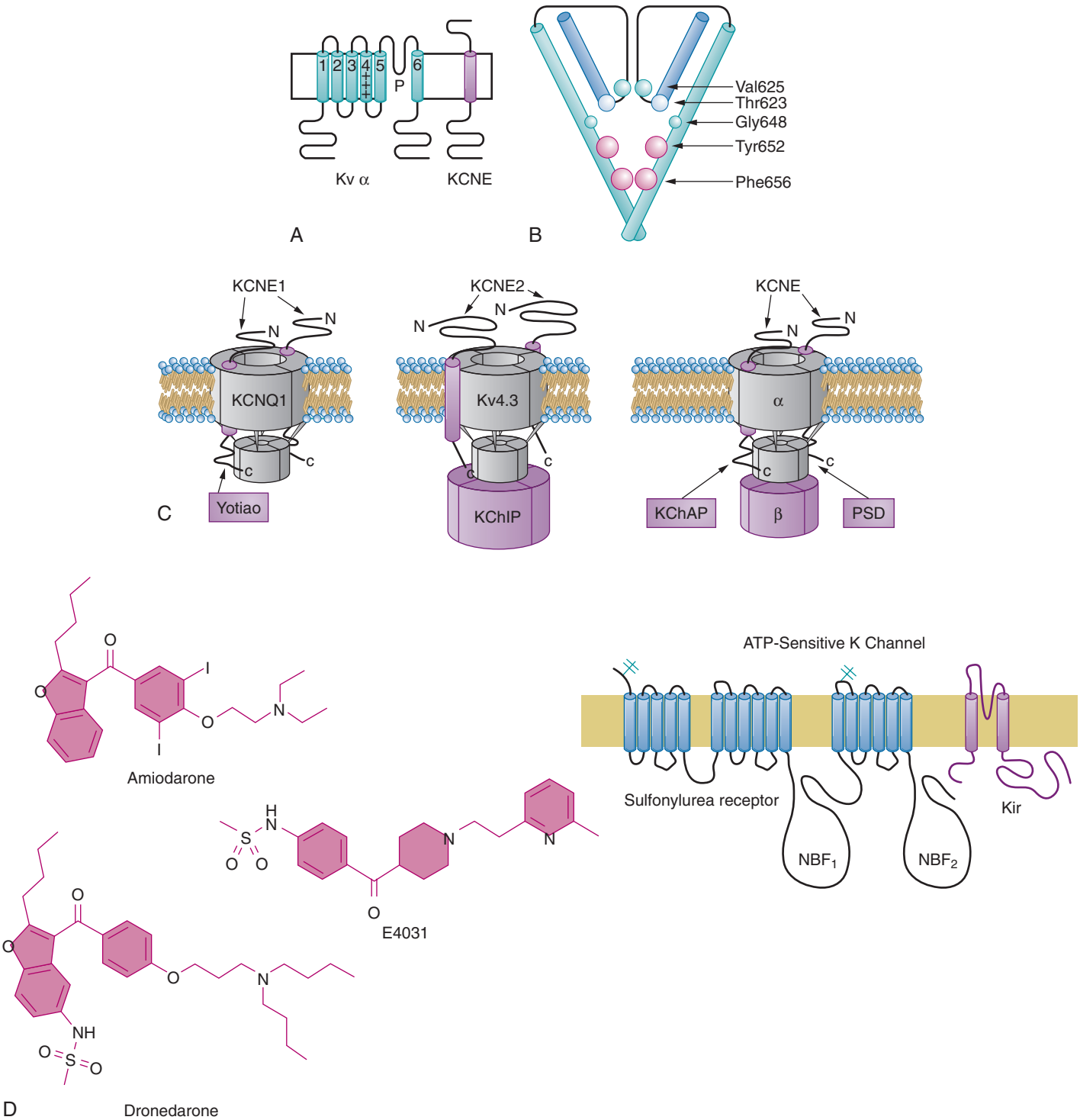

Figure 24-4 Potassium channels and the class III antiarrhythmics. **A,** Topology of a K_v α subunit and a KCNE β subunit. **B,** Left, drug binding site within the hERG K_v α subunit. Residues in red are crucial for binding of a variety of drugs, such as cisapride and terfenadine, and undergo π-bonding with the aromatic rings of methanesulfonanilides. Green and blue residues are less impactful on cisapride and terfenadine binding but important for methanesulfonanilide binding.[101] *Right,* structures of some class III antiarrhythmic drugs. **C,** Cartoons of some heteromeric K_v channels containing α subunits, and both transmembrane and cytoplasmic β subunits. **D,** Topology of a K_{ir} α subunit and an SUR subunit.

subunits that generate human ventricular I_{to}, (particularly active during phase 1 of the ventricular action potential), and $K_v1.5$, which generates the ultrarapidly activating K^+ current, I_{Kur}, important in atrial myocyte repolarization. K_v4 and $K_v1.5$ α subunits are also regulated by the KCNE subunits.[31,32] In addition, all the K_v channels discussed herein are regulated by a host of cytoplasmic β subunits and other regulatory proteins (see Figure 24-4, *C*), each of which can affect channel pharmacology either directly or indirectly, because changes in gating alter drug-binding kinetics.[30,33]

K_{ir} channels do not possess a voltage sensor, but exhibit inward rectification because they are inhibited at more

positive membrane potentials by intracellular constituents including Mg^{2+} and polyamines such as spermine. These channels are composed of a tetramer of α subunits, each with only two transmembrane segments, around a central, aqueous, K^+-selective pore (see Figure 24-4, *D*). The ventricular inward rectifier current I_{K1} is generated by $K_{ir}2$ family α subunits and contributes to stabilizing the cardiac potential, passing current at either end but less so when the myocyte is strongly depolarized (see Figure 24-1, *A*). The K_{ATP} channel, which also probably contributes to cardiac excitability, is an octamer of four $K_{ir}6$ α subunits and four membrane-spanning sulfonylurea receptor (SUR) subunits that render it ATP-sensitive.[19] A host of class III drugs, including amiodarone and dofetilide, inhibit K_{ir} channels by direct pore block within the inner vestibule.[34,35]

Calcium Channels and Class IV Antiarrhythmics

Class IV agents slow AV nodal conduction, primarily by L-type Ca^{2+} channel (LTCC) antagonism. LTCCs mediate the upstroke of nodal cell action potentials, unlike true atrial and ventricular myocyte action potentials in which the upstroke is mediated primarily by the faster activating and inactivating Na_v channel, $Na_v1.5$. Hence, nodal action potentials exhibit a much slower upstroke than that of typical atrial and ventricular myocytes (see Chapter 20). The transmembrane topology of voltage-gated Ca^{2+} channel (Ca_v) α subunits mirrors that of the Na_v channel α subunits: 24 transmembrane segments around an aqueous pore. LTCCs also incorporate a requisite array of ancillary subunits: the cytoplasmic β subunit, transmembrane δ and γ subunits, and extracellular α2 subunit (Figure 24-5, *A*). In cardiac muscle, the LTCC $Ca_v1.2$ α subunit is located in the T-tubules and is activated by cellular depolarization, via its voltage-sensing apparatus, which moves upon membrane depolarization and opens the discrete but connected pore. Ca^{2+} influx through $Ca_v1.2$, down the Ca^{2+} concentration gradient, helps depolarize the cell and increase cytosolic [Ca^{2+}] directly, but also indirectly by activating the sarcoplasmic reticulum-located ryanodine receptor (RyR2 in cardiac muscle) through Ca^{2+}-activated Ca^{2+} release. In skeletal muscle, the mechanism is somewhat different: $Ca_v1.1$ is mechanically linked to RyR1 and acts as the latter's voltage sensor. Thus in skeletal muscle, RyR1 is activated primarily by membrane depolarization, with the $Ca_v1.1$ S4 domains acting as the RyR1 voltage sensors (see Figure 24-5, *B*).[36,37]

Most clinically relevant Ca_v channel blockers are in one of three chemical classes: the dihydropyridines, which are not generally indicated for arrhythmias; the phenylalkylamines, exemplified by verapamil; and the benzothiazepines, exemplified by diltiazem.[38] Diltiazem and verapamil (see Figure 24-5, *C*) are thought to bind overlapping but distinct sites within the S6 segments of repeats III and IV, and the Ca^{2+} selectivity filter of the α1 subunit of the cardiac LTCC $Ca_v1.2$. [39-41]

CLINICAL PHARMACOLOGY

Categories of Arrhythmogenic Mechanisms

The mechanistic bases for most, if not all, arrhythmias can be placed in one of three categories. These are discussed with the most common modes of treatment.[42-47]

AUTOMATICITY

Arrhythmias in this category arise from changes to the normal process of automaticity essential for cardiac rhythm (see Figure 24-1). They can be further separated into two sub-categories:

Normal automaticity arrhythmias are those that elicit speeding or slowing of the heartbeat, initially at least maintaining regular beating, although this is lost at some point, for example, at extremely high heart rates, due to an intrinsic inability of ion channels to function rapidly enough in concert. Arrhythmias in this category include sinus tachycardia and ventricular tachycardia (both being an increased heart rate). *The most common pharmacologic treatment of sinus tachycardia and ventricular tachycardia is with β blockers (class II antiarrhythmics).*

Abnormal automaticity arrhythmias are those in which regular activity is lost immediately and involve spontaneous impulse formation in partially depolarized cells (membrane potentials in the range of −40 to −60 mV). Examples of arrhythmias that can fall into this category include ventricular tachycardias and ectopic atrial tachycardias in the subacute phase (within 48 hours) following myocardial infarction, exercise-induced idiopathic ventricular tachycardias, and catecholamine-sensitive idiopathic ventricular tachycardias. *The most common pharmacologic treatment of idiopathic rhythms and ectopic atrial tachycardias is with Ca^{2+} channel blockers (class IV antiarrhythmics).*

Sinus rhythm is regulated by pacemaker channels (i.e., hyperpolarization-activated, cyclic nucleotide-gated monovalent cation-nonselective channels known as *HCN*), and to a greater or lesser extent, Ca^{2+} oscillations. Hence, human HCN4 mutation is associated with sinus-mediated pathologic slowing of the heart rate (sinus bradycardia).

TRIGGERED

Triggered arrhythmias are those in which a mistimed beat occurs before the previous beat is complete (see Figure 24-1, *B*). The ion channels involved in orchestrating each cardiac myocyte action potential must work in concert to generate rhythmic contraction of the heart. Because the various classes of ion channel each have distinct gating kinetics and refractory periods, if one type of ion channel dysfunctions, it can act asynchronously with the others, potentially causing triggered arrhythmias. Triggered arrhythmias can be separated into two main classes:

Early after-depolarizations (EADs) occur when myocardial repolarization is delayed sufficiently that the next action potential in a given cardiac myocyte begins before that myocyte is fully repolarized. A common clinical consequence is the arrhythmia referred to as *torsades de pointes* (TdP). TdP is so named because it appears on the electrocardiogram (ECG) as a twisted ribbon due to the variance in magnitude of the voltages associated with each heartbeat (see Figure 24-1, *C*). TdP most often occurs because of pharmacologic inhibition of specific ventricular myocyte K^+ channels, which results in a delay in ventricular myocyte repolarization and consequent prolongation of the QT interval on the ECG. A number of drugs inhibit these channels and can lead to TdP, including a number of drugs commonly used in anesthesia; some of the major QT interval prolonging drugs are summarized in Table 24-3. The QT interval represents the time from the onset of ventricular depolarization to the end of

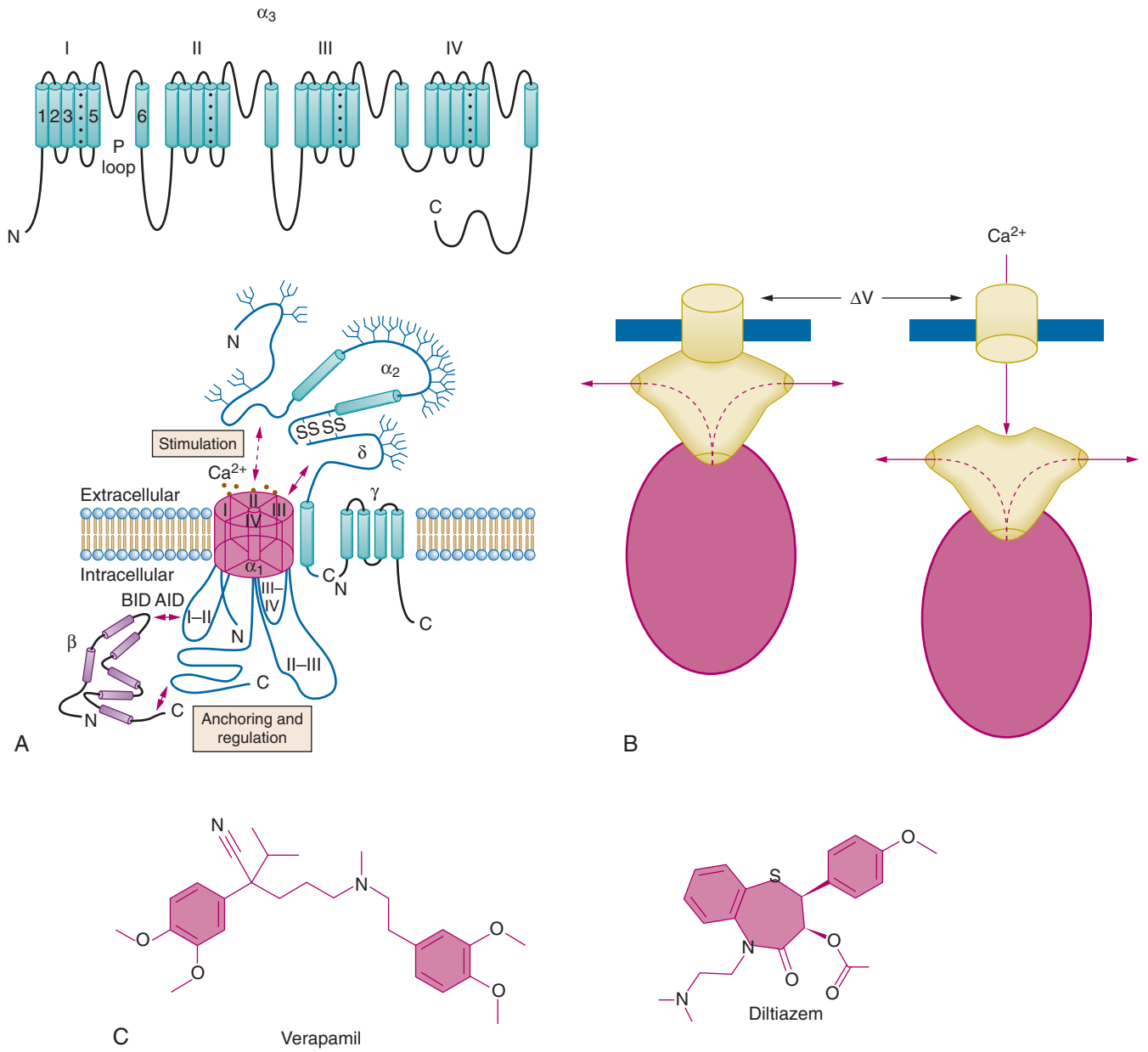

Figure 24-5 Calcium channels and the class IV antiarrhythmics. **A,** Upper, topology of a voltage-gated Ca^{2+} channel α subunit (Ca_v). Note similar structure to Na_v shown in Figure 24-2. *Lower,* heteromeric voltage-gated Ca^{2+} channel complex with $\alpha_2\delta$ accessory subunits. **B,** Juxtaposition of voltage-gated Ca^{2+} channel at the cell surface membrane *(blue)* and the SR-located ryanodine receptor in skeletal muscle *(left)* and cardiac muscle *(right)*. **C,** Structures of verapamil and diltiazem, key class IV antiarrhythmic drugs.

ventricular repolarization; prolongation of this interval can indicate long QT syndrome, of which there are now many well-defined subtypes with distinct molecular etiologies. When sufficiently long delays in repolarization occur, Na_v channels can recover from their refractory period and open before repolarization is complete, leading to an EAD in phase 2, 3, or 4 of the ventricular or atrial action potential (see Figure 24-1, *B*). *The most common pharmacologic treatment of TdP is with magnesium sulphate, β blockers (class II antiarrhythmics), and/or Ca^{2+} channel blockers (class IV antiarrhythmics).*

Delayed after-depolarizations (DADs) classically occur in digitalis toxicity. Digitalis toxicity can occur through a variety of mechanisms, but all serve to raise intracellular Ca^{2+} concentration, generating a net depolarizing current that, together with the tendency of digitalis to increase vagal tone, leads to DADs (amongst other possible classes of arrhythmias). Unlike most EADs, DADs begin after repolarization, but before the next appropriately timed depolarization, that is, in phase 4 of the cardiac action potential (see Figure 24-1, *B*). *The most common pharmacologic treatment of DADs arising from digitalis toxicity is with Ca^{2+} channel blockers (class IV antiarrhythmics).*

CONDUCTION

Commonly arising from structural damage to the heart, but also from certain drug-ion channel interactions, localized

Table 24-3. Drugs Known to Prolong QT Interval

GENERIC NAME	CLASS	COMMENTS
Amiodarone	Antiarrhythmic	Females > males, TdP risk low
Arsenic trioxide	Anticancer	
Astemizole	Antihistamine	No longer available in U.S.
Bepridil	Antianginal	Females > males
Chloroquine	Antimalarial	
Chlorpromazine	Antipsychotic; antiemetic	
Cisapride	Gastrointestinal stimulant	No longer available in U.S.; available in Mexico
Citalopram	Antidepressant	
Clarithromycin	Antibiotic	
Disopyramide	Antiarrhythmic	Females > males
Dofetilide	Antiarrhythmic	
Domperidone	Antiemetic	Not available in U.S.
Droperidol	Sedative; antiemetic	
Erythromycin	Antibiotic; gastrointestinal stimulant	Females > males
Flecainide	Antiarrhythmic	
Halofantrine	Antimalarial	Females > males
Haloperidol	Antipsychotic	When given intravenously or at higher-than-recommended doses
Ibutilide	Antiarrhythmic	Females > males
Levomethadyl	Opioid agonist	Not available in U.S.
Mesoridazine	Antipsychotic	
Methadone	Opioid agonist	Females > males
Moxifloxacin	Antibiotic	
Ondansetron	Antiemetic	
Pentamidine	Antiinfective	Females > males
Pimozide	Antipsychotic	Females > males
Probucol	Antilipemic	No longer available in U.S.
Procainamide	Antiarrhythmic	
Quinidine	Antiarrhythmic	Females > males
Sevoflurane	Volatile anesthetic	
Sotalol	Antiarrhythmic	Females > males
Sparfloxacin	Antibiotic	
Terfenadine	Antihistamine	No longer available in U.S.
Thioridazine	Antipsychotic	
Vandetanib	Anticancer	

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slowed conduction within regions of the heart can cause re-entrant arrhythmias that can be categorized into two main types:

Reentrant circuits arise when one area of the heart contains a region of slowed ion conduction. When such regions occur, primarily due to the refractory period of Na_v channels arising from their rapid and extensive inactivation and its recovery, reentrant circuits are formed because normal conduction cannot proceed unidirectionally, but can proceed in a circle (Figure 24-6, *A*). They can be micro reentrant (involving a localized region within, e.g., one chamber of the heart) or macro reentrant, involving more than one chamber (see Figure 24-6, *B*). Such circuits are incompatible with normal cardiac rhythm because they disturb the (essentially) unidirectional wave of depolarization/repolarization required for normal contraction to occur. These types of circuits cause atrial flutter, and ventricular and supraventricular tachycardias. *Monomorphic ventricular tachycardia is treated with class Ia Na_v channel blockers or K^+ channel blockers (class III antiarrhythmics). AV node reentrant tachycardias (supraventricular tachycardia or SVAT), which arise from reentry in the region of the AV junction, are treated with Ca^{2+} channel blockers (class IV antiarrhythmics) or adenosine.*

Fibrillation occurs when many micro reentrant circuits span an entire chamber of the heart. This is a different situation from a single macro reentrant circuit and is typically classified (according to the chambers in which it is occurring) as atrial fibrillation or ventricular fibrillation. The substrate for atrial fibrillation is probably most commonly structural heart disease, and while it is typically not acutely dangerous, it requires treatment. This is partly because it suggests an underlying defect and partly because a significant risk in atrial fibrillation is the formation of atrial thrombi that can result in launching of systemic emboli when sinus rhythm is reestablished. Approximately 2 to 3 million people in the United States suffer from atrial fibrillation, the majority in the aging population, and this number is expected to rise as the population ages. Another common cause of atrial fibrillation is major surgery such as open heart surgery or lung resection, with the underlying mechanism not being entirely clear. Hyperthyroidism can also cause atrial fibrillation; return to euthyroidism abrogates the atrial fibrillation in the majority of cases. *Atrial fibrillation is most commonly treated with Na_v channel blockers (class Ia antiarrhythmics) or K^+ channel blockers (class III antiarrhythmics).*

Ventricular fibrillation, in contrast, is acutely life-threatening because the heart in ventricular fibrillation cannot pump blood effectively. An estimated 300,000 people in the United States die annually of sudden cardiac death, with ventricular fibrillation being among the most common lethal arrhythmias. Ventricular fibrillation must be rapidly treated (within minutes) using DC shock. Cardiopulmonary resuscitation (CPR) can be used to keep the brain alive until defibrillation is possible, but CPR cannot restore normal cardiac rhythm. *Amiodarone is the first-line antiarrhythmic drug clinically demonstrated to increase return of spontaneous circulation in refractory ventricular fibrillation and pulseless ventricular tachycardia unresponsive to CPR, defibrillation, and vasopressor therapy. If amiodarone is unavailable, lidocaine can be considered as a second line drug with less evidence of efficacy compared with amiodarone. Magnesium sulfate is used for TdP associated with a long QT interval.*

CLINICAL APPLICATION

Class I—Sodium Channel Blockers

CLASS Ia Na_V CHANNEL BLOCKERS

The class Ia antiarrhythmics block ion conduction through $Na_v1.5$, the principal cardiac Na^+ channel; this delays and reduces the magnitude of peak depolarization in cardiomyocytes, and thus prolongs the action potential. Refractoriness is also increased in that Na_v channels require a greater hyperpolarization and longer time to recover from inactivation in the presence of class Ia agents. These effects can be

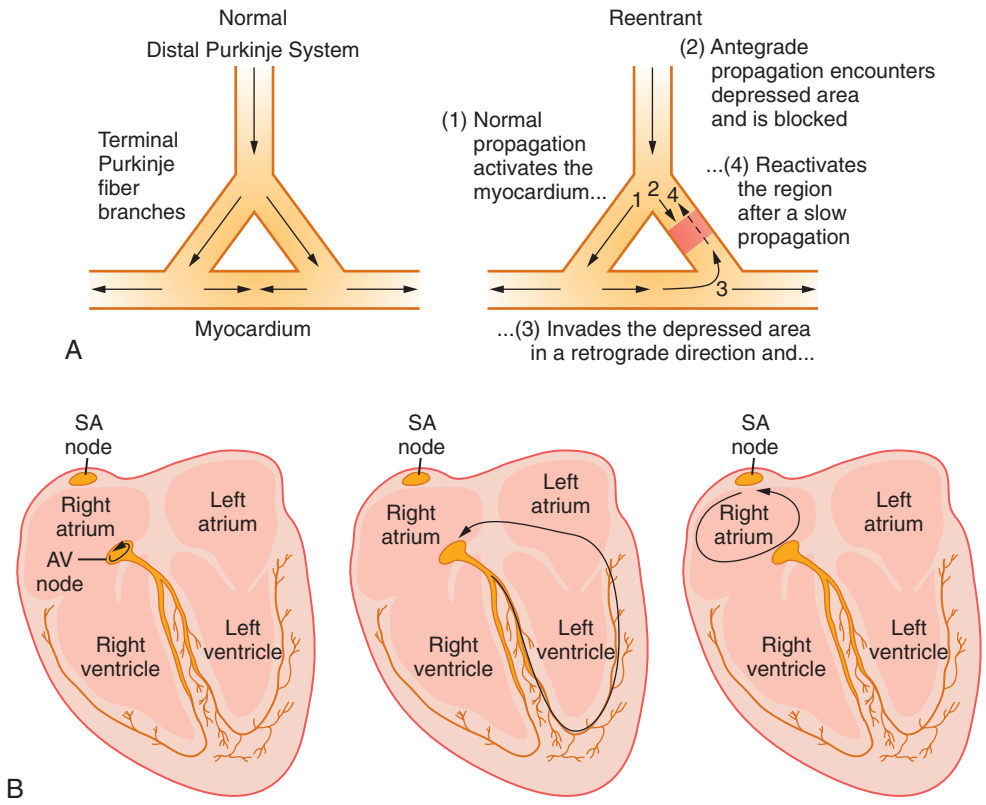

Figure 24-6 Reentrant circuits. **A,** Anatomy of a reentrant circuit. Depending on the relative speed of conduction and duration of refractory periods in two alternate longitudinal pathways, anterograde propagation can be blocked in one pathway whereas retrograde propagation progresses, creating a reentrant circuit. **B,** Examples of micro- and macro-reentrant circuits in the heart. *Left,* a micro-reentrant circuit in the AV node; *center,* a macro-reentrant circuit spanning the AV node and left atrium and ventricle; *right,* a micro-reentrant circuit in the right atrium.

therapeutic if the heart is beating too rapidly or in an uncoordinated fashion. Therefore, class Ia antiarrhythmics can be indicated for symptomatic premature ventricular beats, and ventricular and supraventricular tachyarrhythmias. They can also be used to prevent the acutely life-threatening condition ventricular fibrillation.

Quinidine exemplifies the advantages and potential drawbacks of class Ia antiarrhythmic drugs, and of the SVW classification itself. Aside from blocking $Na_v1.5$ channels in the activated state, which slows phase 0 depolarization (see Figure 24-2, *B*), quinidine also blocks certain voltage-gated K^+ channels, which in turn delays phase 3 repolarization and can in itself be proarrhythmic, prolonging the QT interval on the ECG (see Figure 24-1, *C*). It also widens the QRS complex through its effects on $Na_v1.5$. Quinidine can also decrease the slope of phase 4 depolarization in Purkinje fibers, thereby reducing automaticity. Because quinidine has antimuscarinic-based vagolytic properties that work against its direct action on the SA and AV nodes, it can actually increase conduction through these nodes. This presents problems because it can cause 1 : 1 conduction of atrial fibrillation, thereby increasing ventricular rate too. Thus, if used for atrial fibrillation, quinidine (and related class Ia agent, procainamide) must be accompanied by an AV node blocking agent to prevent this (e.g., class II or IV antiarrhythmics).

Quinidine is also a notable antimalarial: It kills the schizont parasite of *Plasmodium falciparum* and gametocyte parasite stages of *Plasmodium* sp. Quinidine is associated with a number of contraindications and precautions aside from the AV conduction issues noted earlier: It can increase digoxin levels by decreasing renal and extrarenal clearance and can aggravate myasthenia gravis.[48]

Procainamide (only available in an intravenous formulation in the United States) is another important class Ia antiarrhythmic that can be used to treat atrial fibrillation in Wolff-Parkinson-White syndrome (WPWS). Other class Ia agents include ajmaline, lorajmaline, prajmaline, disopyramide, and sparteine.

CLASS Ib Na_v CHANNEL BLOCKERS

The class Ib antiarrhythmics have relatively little effect on conduction velocities and low proarrhythmic potential. They exhibit rapid Na_v channel binding kinetics and their main actions are to decrease the duration of the ventricular myocyte action potential and the refractory period (see Figure 24-2, *B*). Class Ib drugs have little effect on atrial myocyte action potentials, and therefore on atrial tissue, since they are, at baseline, relatively short compared to ventricular action potentials. Thus these drugs are primarily used to treat ventricular arrhythmias.[49]

Lidocaine (see Figure 24-2, *B*) is the archetypal class Ib antiarrhythmic. Like all class Ib drugs, its rapid binding and unbinding rates (endowing it with use-dependency or frequency-dependency) greatly diminish its effects at low

heart rates, and exaggerate its effects at high heart rates. Lidocaine selectively targets the open and inactivated states of $Na_v1.5$, with low affinity for the deactivated (closed or resting) state. For this reason, lidocaine and other class Ib drugs can be efficacious in the therapy of rapid heart rate conditions including ventricular tachycardia and ventricular fibrillation prevention, and also in cases of symptomatic premature ventricular beats. Other notable class Ib drugs include mexiletine (which is metabolized to lidocaine), phenytoin, and tocainide.[47]

CLASS Ic Na_V CHANNEL BLOCKERS

Class Ic antiarrhythmics exhibit relatively slow Na_v channel binding kinetics, and can be used to treat both atrial and ventricular arrhythmias. Drugs in this class are indicated for treatment of nonsustained ventricular tachycardias, but are contraindicated when there is underlying heart disease such as myocardial infarction or left ventricular hypertrophy.[50] Class Ic agents typically slow Na_v channel conduction, delaying the peak depolarization and somewhat prolonging the QT interval (see Figure 24-2, *B*).

Flecainide (see Figure 24-2, *B*), an important class Ic antiarrhythmic, displays little end-organ toxicity but can exhibit significant proarrhythmic effects. Interestingly, flecainide is now thought to also inhibit Ca^{2+} release from the cardiac sarcoplasmic reticulum Ca^{2+} release channel, ryanodine receptor 2 (RyR2), endowing it with therapeutic activity in individuals with catecholaminergic polymorphic ventricular tachycardia (CPVT).[51] The more well-recognized, class Ic action of flecainide confers its effectiveness in prevention of paroxysmal atrial fibrillation and flutter, paroxysmal supraventricular tachycardias, and sustained ventricular tachycardias.[52]

Class II—β Blockers

β-Adrenoceptor antagonists, also known as β blockers, are pharmacologic agents that competitively antagonize the β effects of catecholamines on the heart, blood vessels, bronchi, and so on (see Chapters 12 and 13). Propranolol was introduced in 1965 as the first therapeutically useful β blocker and more than 20 analogs are available today. They are used not only as antiarrhythmics, but also as antianginals and antihypertensives, in that they limit cardiac oxygen consumption and lower plasma renin activity. Depending on their relative β receptor affinities, β blockers are classified as nonselective (or "blanket" β blockers) when they block both β_1 and β_2 receptor subtypes like propranolol, or cardioselective (i.e., β1-selective), such as metoprolol, atenolol, and nebivolol. Third-generation β blockers endowed with vasodilating properties are also available, such as pindolol and carvedilol, which are therapeutically used in congestive heart failure.

Duration of action varies among the various analogs, esmolol being the shortest ($T_{1/2}$ ~9 minutes) and nadolol the longest-acting drug ($T_{1/2}$~24 hours), allowing once daily dosing. Lipid/water solubility of the various β blockers influences the route of elimination: the more lipid-soluble are eliminated primarily by the liver (e.g., propranolol and metoprolol), and the more water-soluble are eliminated primarily by the kidney (e.g., atenolol and nadolol). Thus hepatic cirrhosis and renal failure can prolong the action of lipid- and water-soluble β blockers, respectively.

Adverse effects of β blockers are due mainly to β_2-blocking effects. Among these, bronchospasm in patients with bronchial asthma or chronic obstructive pulmonary disease can cause severe dyspnea. Peripheral vasoconstriction can also occur with blockade of vascular β_2-receptors, as shown by a relatively rare worsening of symptoms of peripheral vascular disease (e.g., intermittent claudication, Raynaud phenomenon). Excessive β_1-blockade on the other hand can cause bradycardia, hypotension, and AV node conduction block.

β-Adrenoceptor stimulation enhances $I_{Ca\text{-}L}$ and $I_{Ca\text{-}T}$ currents and slows Ca^{2+} channel inactivation. It also increases sinus rate by increasing the I_f pacemaker current and increases Ca^{2+} storage in the SR leading to DAD (see Figure 24-1, *B*). By inhibiting all of these effects, β blockers exert an antiarrhythmic action that is particularly effective whenever sympathetic activity is increased, such as in stressful conditions, acute myocardial infarction, and CPR following cardiac arrest. Bradycardia and slowing of AV nodal conduction (prolongation of the PR interval) are typically observed. Therefore, β blockers are valuable in terminating reentrant arrhythmias that include the AV node, and also in controlling ventricular rate in atrial fibrillation or flutter.

Overall, β blockers are effective in treating or preventing arrhythmias that share as a common denominator increased sympathetic activity. These include paroxysmal atrial tachycardia due to exercise or emotion, exercise-induced ventricular arrhythmias, arrhythmias associated with pheochromocytoma, arrhythmias associated with myocardial infarction, and all the arrhythmias accompanied by angina or hypertension.[17,53]

Class III—Potassium Channel Blockers

K_v channels are the primary target for class III antiarrhythmics. By blocking K_v channels, class III agents prolong the action potential and, therefore, increase refractoriness (see Figure 4-4, *B*). These drugs can thus be highly efficacious in the treatment of a variety of tachyarrhythmias, both ventricular and atrial. One of the great paradoxes of arrhythmia therapy is that action potential prolongation can be either therapeutic or life-threatening depending on the nature of the genetic, electrical, and/or structural defect in the patient. While K_v channel blockade can help control dangerous tachycardia, it can also precipitate TdP due to its QT-prolonging effects; this in turn can lead to lethal ventricular fibrillation.

The problem with many class III agents is that they inhibit the hERG K_v channel (which generates I_{Kr} as explained earlier) in a reverse use-dependent manner that does not increase block with heart rate, but rather does the opposite. This impairs the crucial I_{Kr} repolarization current, delaying phase 3 repolarization, most aggressively in bradycardia and less so in tachycardia, which can lead to a dangerously proarrhythmic tendency.

Two significant advances in the field of class III antiarrhythmic development are overcoming these problems. The first advance is exemplified by amiodarone (see Figure 24-4, *B*), a drug that actually has actions in all four SVW classes, but the major therapeutic effect of which is thought to result from its class III effects.[54] The big advantage of amiodarone over earlier agents (although it was first described in 1961, it was only approved for use in the United States in 1985) is that

it inhibits both I_{Kr} and I_{Ks}. I_{Ks} is generated by a heteromer of the KCNQ1 K_v α subunit and most commonly the KCNE1 β subunit, and is the primary slow-activating component of the delayed rectifier K^+ current acting in phase 3 repolarization. I_{Ks} rises to prominence, in terms of its role in repolarization, at higher heart rates because KCNQ1-KCNE1 channels accumulate in the activated state, and conversely at these rates I_{Kr} is less effective at ventricular repolarization, hence the reverse use-dependence of "pure" I_{Kr} blockers. I_{Ks} probably acts as a safety factor, or repolarization reserve, to compensate for the relative impotency of I_{Kr} at high heart rates. Amiodarone, by blocking both I_{Kr} and I_{Ks}, exhibits a safer and more efficacious action on phase 3 repolarization. A related drug, dronedarone, lacks the iodine that is associated with some side effects of amiodarone, including skin photosensitivity and ocular abnormalities, and the former is therefore safer (although less efficacious) and still has the dual action of I_{Kr} and I_{Ks} antagonism, as does azimilide.[55-57] Azimilide, however, and tedisamil (which inhibits I_{Kr}, I_{to} and the ATP-sensitive inwardly rectifier K^+ current I_{KATP}) have proven marginally efficacious and also torsadogenic, leading to doubts about their ultimate usefulness in atrial fibrillation therapy.[58,59] Their key problem is that they do not present a big enough therapeutic window to reverse atrial tachyarrhythmias without causing an unsafe delay in ventricular repolarization; that is, they lack atrial specificity.

The majority of atrial fibrillation cases are linked to underlying disorders including structural heart disease, chronic alcohol use, hyperthyroidism, and pulmonary embolism. Most individuals with atrial fibrillation exhibit a chronic, sustained atrial arrhythmia, and the clinical manifestations range from palpitations to heart failure. Perhaps as many as a third of atrial fibrillation patients have "lone" atrial fibrillation, in which underlying heart or extracardiac disease is either occult or absent. Of these patients, some harbor ion channel mutations thought to be the substrate for atrial fibrillation. The KCNQ1 K_v channel gene is again involved. A key step in atrial fibrillation is thought to be shortening of the atrial effective refractory period; therefore, it is intuitive that, as with short QT syndrome, gain-of-function mutations in *KCNQ1* are linked to AF, in that they have the capacity to hasten repolarization. In addition, mutations in several members of the KCNE gene family of β subunits are associated with atrial fibrillation by increasing currents through the respective KCNQ1-KCNE channel complex.[60-62] Inherited mutations in *KCNA5*, which encodes the atrially expressed $K_v1.5$ potassium channel α subunit, also associate with AF. Nonchannel genes associated with AF include renin-angiotensin system genes, probably in combination with environmental agents that elevate blood pressure.[63,64]

Therapeutic approaches to AF involve not just lengthening of the atrial effective refractory period (pharmacologically or by electrical cardioversion), but also surgery to prevent recurrence and anticoagulation for stroke prevention. With respect to pharmacologic intervention to control the heart in atrial fibrillation, control of rhythm appears to offer no significant advantage in terms of mortality or stroke risk compared to controlling the rate, that is, returning the heart rate to somewhere between 60 and 100 beats per minute. However, rhythm control is desirable in newly diagnosed atrial fibrillation, and in other cases dictated by patient-specific factors,

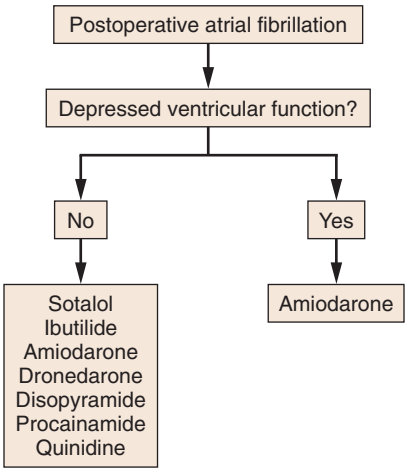

Figure 24-7 Rhythm control for postoperative atrial fibrillation. Given the side effect profile of amiodarone, it is generally reserved for use when other drugs are ineffective, contraindicated, or not well-tolerated. Dronedarone is contraindicated in patients with acutely decompensated heart failure. Sotalol may be used with caution in selected patients with mild to moderate reduction in left ventricular ejection fraction. *(Modified from Martinez EA, Bass EB, Zimetbaum P, et al. Control of rhythm: American College of Chest Physicians Guidelines for the prevention and management of postoperative atrial fibrillation after cardiac surgery.* Chest. *2005;128 [Suppl 2]:48S-55S.)*

and remains the strategy of choice. For pharmacologic rate control, β blockers and Ca^{2+} channel blockers are most often employed, whereas for pharmacologic rhythm control, Na^+ channel blockers or K^+ channel blockers are used. The pharmacologic control of postoperative atrial fibrillation is summarized in Figure 24-7.

This introduces the second significant recent advance in class III antiarrhythmic development. The dependency of the human heart for hERG-mediated ventricular repolarization is problematic in an increasingly medicated population owing to the predilection of hERG for nonspecific drug block. In addition, hERG protein folding (part of the process that ensures that hERG channels reach the cell surface and pass K^+ ions) is highly sensitive to both drugs and inherited single amino acid substitutions. This incredibly unfortunate combination of circumstances is due in part to the fact that, for the majority of human evolution, drugs have not been an environmental factor and thus have not impacted natural selection.[65]

However, nature has provided a fortuitous solution to the hERG targeting conundrum. In human atrium, the ultrarapidly activating K_v current, I_{Kur}, is generated by the $K_v1.5$ (gene name *KCNA5*) K_v channel α subunit, but $K_v1.5$ is not significantly functionally expressed in human ventricles. Pharmacologic inhibition of $K_v1.5$ can lengthen the atrial refractory period enough to be of therapeutic benefit in AF. Crucially, because it does not contribute to ventricular repolarization, specific $K_v1.5$ inhibition does not delay ventricular repolarization and therefore is not torsadogenic.

There are some caveats vis-à-vis $K_v1.5$ blockers. While Kv1.5 is in a different α subunit subfamily, it has been difficult to develop selective $K_v1.5$ antagonists that do not also inhibit hERG therapeutic concentrations. Interestingly, the most

promising $K_v1.5$-blocking class III agents appear to be the less specific drugs that block $K_v1.5$, hERG, $K_v4.3$ (which generates to in human heart), and $Na_v1.5$. These drugs, exemplified by AVE0118 and RSD1235, inhibit $K_v1.5$ more effectively than the other channels, and the hERG block appears to be "balanced" by $Na_v1.5$ block (thus both ventricular repolarization and depolarization). Furthermore, $Na_v1.5$ inhibition by AVE0118 is use-dependent and therefore more efficacious the faster the atrium is fibrillating. In summary, as with many antiarrhythmics, nonspecificity can be tolerated and can even be desirable, depending on the targets and their location, the nature of the action on those targets, and the relative affinity for each target.[66-69]

Class IV—Calcium Channel Blockers

The class IV antiarrhythmics block voltage-gated Ca^{2+} channels, the primary target with respect to arrhythmias being the cardiac LTCC, $Ca_v1.2$. While in atrial and ventricular myocytes the primary role of Ca^{2+} is signaling in muscular excitation-contraction coupling, in nodal cells its primary role is electrical conduction of a depolarizing signal. By lowering ventricular myocyte intracellular [Ca^{2+}], some class IV antiarrhythmics decrease the force of contraction of the heart, an effect referred to as *negative inotropy*. By slowing conduction through nodal cells, some class IV drugs reduce the heart rate, an effect referred to as *negative chronotropy* (see Chapter 21).

The dihydropyridines (e.g., nifedipine) are used to treat increased systemic vascular resistance but are not generally indicated for arrhythmias. The phenylalkylamines, exemplified by verapamil, are relatively myocardial-specific and cause negative inotropy with minimal vasodilation or reflex tachycardia. Verapamil is indicated for angina, with two probable main modes of action: dilatation of the main coronary arteries and arterioles, inhibiting coronary vasospasm, and reduction of oxygen utilization via unloading of the heart achieved by relaxing the peripheral arterioles. As an antiarrhythmic, verapamil is highly effective at slowing ventricular contraction rate in patients with atrial flutter or atrial fibrillation because it slows AV node conduction in a rate-dependent manner. This rate dependence also accounts for the fact that verapamil generally is much less effective at reducing already normal AV conduction rates—a desirable property—although it can occasionally induce AV node block in the absence of preexisting conduction defects. Verapamil is effective in reducing the frequency of episodes of paroxysmal supraventricular tachycardia, but can also induce ventricular fibrillation in patients with atrial flutter or fibrillation and a coexisting AV accessory pathway.[70-72]

The benzothiazepines, exemplified by diltiazem, exhibit myocardial specificity intermediate between the dihydropyridines and phenylalkylamines. Diltiazem causes excitation-contraction uncoupling, relaxation of coronary vascular smooth muscle and dilatation of coronary arteries, but has relatively modest negative inotropic effects. Diltiazem is typically prescribed for angina and hypertension, and is quite effective in lowering blood pressure in hypertensive individuals, with little effect on normotensives. It is also reportedly as effective as verapamil in the treatment of supraventricular tachycardias, and is also indicated for atrial flutter and atrial fibrillation. Its negative dromotropic effect (slowing of conduction through the AV node) reduces oxygen consumption by increasing the time required for each heartbeat.[73,74] The rational selection of drugs for controlling heart rate is summarized in Figure 24-8.

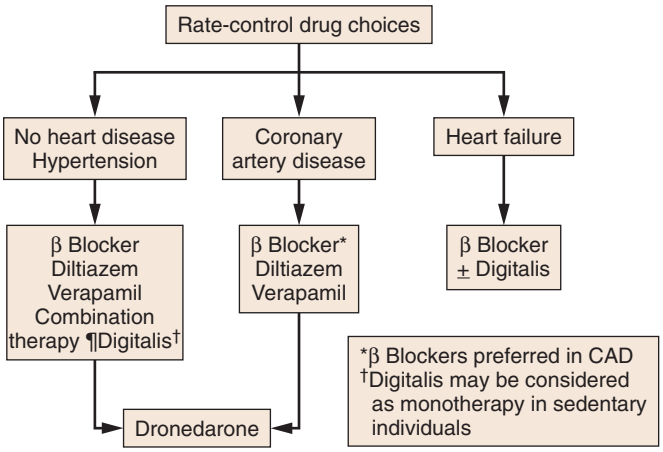

Figure 24-8 Selection of rate-control drug therapy is based on the presence or absence of underlying heart disease and other comorbidities. Combination therapy might be required. *CAD,* Coronary artery disease. *(Modified from Gillis AM, Verma A, Talajic M, et al. Canadian Cardiovascular Society Atrial Fibrillation Guidelines 2010: rate and rhythm management.* Can J Cardiol. *2011;27:47-59.)*

EMERGING DEVELOPMENTS

Molecular Genetics of Arrhythmias

A combination of molecular genetics, recombinant DNA technology and physiologic techniques are revealing the secrets of many cardiac arrhythmias; intuitively, the majority of the genes linked thus far to abnormal cardiac rhythm are those that express ion channel proteins.[27] Many of these same ion channels are targets for clinically important antiarrhythmic and proarrhythmic drugs. An understanding of the precise molecular basis for an individual's arrhythmia can remove some of the uncertainty about how best to treat the arrhythmia, and facilitates genetic or other forms of testing of family members, permitting early diagnosis and preventive measures to avoid potentially lethal cardiac events.

LONG QT SYNDROME

A delay in ventricular myocyte repolarization can prolong the QT interval on the ECG and lead to TdP and even ventricular fibrillation. The most common inherited causes of this phenomenon are loss-of-function mutations in ventricular, voltage-gated K_v channels, which are primarily responsible for ventricular myocyte repolarization by virtue of K^+ efflux to restore a negative membrane potential (see Figure 24-1, *A*). Around 45% of individuals diagnosed with inherited long QT syndrome (LQTS) whose DNA has been sequenced have loss-of-function mutations in the *KCNQ1* gene. *KCNQ1* encodes the K_v channel pore-forming (α) subunit of the same name. *KCNQ1* mutations underlie long QT syndrome type 1 (LQT1), which is further divided into the autosomal dominant Romano Ward syndrome (RWS) and the recessive

cardioauditory Jervell Lange-Nielsen syndrome (JLNS). Individuals with loss-of-function mutations in both KCNQ1 alleles (i.e., JLNS) exhibit both LQTS and profound sensorineural deafness. KCNQ1, in protein complexes with KCNE1, a single-transmembrane segment ancillary (β) subunit, generates the slowly activating ventricular repolarization current, I_{Ks}.[75]

I_{Ks} is important for phase 3 repolarization in the ventricular action potential, particularly when the dominant ventricular repolarization K^+ current, I_{Kr} (see later), is compromised, or during sustained exercise or other prolonged sympathetic activation. The KCNQ1-KCNE1 potassium channel is also expressed in the inner ear, where it is responsible for K^+ secretion into the endolymph (hence the deafness in JLNS). Individuals with KCNE1 mutations (1%-2% of sequenced LQTS cases) are classified as having LQT5; they exhibit RWS or JLNS with similar symptoms as LQT1 patients, indicating the KCNE1 β subunit is important for I_{Ks}.

I_{Kr} is generated by the human *ether-à-go-go* related gene product (hERG), the voltage-gated K^+ channel α subunit encoded by the *KCNH2* gene, probably in complexes with the KCNE2 β subunit and perhaps others. *KCNH2* loss-of-function mutations (LQT2) account for ~40% of known LQTS cases, *KCNE2* mutations (LQT6) ~1%.

The third most commonly linked LQTS gene is *SCN5A*, which encodes the $Na_v1.5$ cardiac voltage-gated Na^+ channel that underlies the upstroke in phase 0 of the cardiac myocyte action potential (see Figures 24-1, *A* and 24-2). $Na_v1.5$, like all voltage-gated Na^+ channels, inactivates rapidly, which together with the transient outward K^+ current, I_{to}, cause the notch at the beginning of the human ventricular myocyte action potential. Gain-of-function mutations in *SCN5A*, particularly those that increase Na^+ influx during phases 2-3 when the majority of $Na_v1.5$ channels are normally inactivated, delay repolarization because they produce persistent depolarizing force (Na^+ influx). *SCN5A* mutations account for 5% to 10% of LQTS cases and are categorized as LQT3. $Na_v1.5$ is an important antiarrhythmic target, with many drugs known to alter its inactivation kinetics.[76,77]

The remaining molecularly defined inherited LQTS cases are relatively rarer and are spread among other genes encoding K^+ channel subunits, Ca^{2+} channel subunits, and channel-associated proteins.

SHORT QT SYNDROME

Shortening of the QT interval, indicating premature ventricular repolarization, can also be pathogenic, further illustrating the importance of timely electrical activity in the heart. The majority of sequenced short QT syndrome (SQTS) cases are, intuitively, associated with *KCNQ1* or *KCNH2* gain-of-function mutations. SQT1 is associated with *KCNH2* mutation; SQT2 with *KCNQ1;* and the inward rectifier K^+ channel gene *KCNJ2* with SQT3. SQTS is characterized by a corrected QT interval (QTc) of less than 300 ms, and manifests as palpitations, syncope, and sudden cardiac death; patients with a QTc of up to 330 ms are also diagnosed with SQTS if they have had an arrhythmic event such as ventricular fibrillation, syncope or resuscitated sudden cardiac death. Also associated with an increased risk of both atrial and ventricular fibrillation, SQTS has been found to respond to hydroquinidine, whereas class IC and III antiarrhythmics were unable to prolong the QT interval in this context. However, the current therapy of choice is an implantable cardioverter-defibrillator (ICD).[78-80]

BRUGADA SYNDROME

In contrast to the long and short QT syndromes, the majority of sequenced Brugada syndrome (BrS) cases (perhaps representing 30% of all BrS cases) have been linked to loss-of-function mutations in the *SCN5A* voltage-gated Na^+ channel gene that encodes $Na_v1.5$. BrS is an autosomal dominant, idiopathic form of ventricular fibrillation that manifests on the ECG as persistent ST-segment elevation in the right precordial leads, together with complete or incomplete right bundle branch block. BrS patients are strongly predisposed to life-threatening ventricular fibrillation even with a structurally normal heart, and BrS was recently found to be clinically and genetically the same disorder as sudden unexplained nocturnal death syndrome (SUNDS/SUDS) described in Southeast Asia, where BrS is endemic and is often mistaken for a supernatural curse by poorly educated people.

In BrS patients, the transient outward K^+ current that forms a notch at the start of the ventricular action potential is inadequately balanced by the voltage-gated Na^+ current due to loss of function in $Na_v1.5$, which is considered a trigger for ventricular tachycardia and fibrillation. Accordingly, a gain-of-function mutation in the KCNE3 β subunit, which regulates the K^+ channel underlying I_{to} ($K_v4.3$), was also recently associated with BrS. An ICD is again the treatment of choice for BrS patients, but quinidine can be used to inhibit I_{to}, and isoproterenol and cilostazol can bolster the voltage-gated Ca^{2+} current to the same end, that is, reduction of the action potential notch that provides a substrate for potentially catastrophic ventricular micro-reentry circuits.[81,82]

OTHER INHERITED ARRHYTHMIA SYNDROMES

Other inherited arrhythmia syndromes include cardiac conduction disease, Wolff-Parkinson-White syndrome (WPWS), catecholaminergic polymorphic ventricular tachycardia (CPVT), and various sinus node disorders.[75,83]

Lev-Lenègre syndrome, a progressive cardiac conduction disease, has been linked to SCN5A loss-of-function gene variants, and is characterized by slowed conduction, pathologic slowing of cardiac rhythm, and conduction system fibrosis. A pacemaker or ICD is the most common therapeutic strategy, although pharmacologic intervention can also be indicated.

WPWS, in its rare familial form, is linked to mutations in the *PRKAG2* gene, which encodes the γ2 regulatory subunit of AMP-activated protein kinase (AMPK), but in the sporadic form of the disease this gene is rarely implicated. Other genetic associations include mitochondrial DNA mutations and, in association with hypertrophic cardiomyopathy, *TNNI3* and *MYBPC3* gene variants.[84,85] WPWS manifests as supraventricular arrhythmias associated with palpitations, and preexcitation and syncope. WPWS is caused by an abnormal accessory electrical circuit that is present at birth (known as "the bundle of Kent"), and surgical ablation of this pathway is almost always successful in eliminating the cause and symptoms of WPWS. However, the marginally less-effective but much less invasive measure of radiofrequency catheter ablation is now typically employed in WPWS.[86,87]

CPVT is observed clinically as exercise- or emotional stress-induced syncope and sudden cardiac death, and on the

body-surface ECG as bidirectional or polymorphic ventricular tachycardia. Two genes involved in excitation-contraction coupling have been linked to CPVT: *RyR2* (which encodes the cardiac ryanodine receptor, a sarcoplasmic reticulum Ca^{2+} release channel) and *CASQ2* (encoding calsequestrin, which stores releasable Ca^{2+} within the sarcoplasmic reticulum). Increased RyR2 activity or decreased calsequestrin expression generates spontaneous Ca^{2+} transients and DADs. CPVT is treated with β blockers, ICD, and/or other antiarrhythmic medications.

Sinus rhythm is dictated by hyperpolarization-activated, cyclic-nucleotide gated monovalent cation channels known as HCN or pacemaker channels (and to a greater or lesser extent, Ca^{2+} oscillations, a matter of current debate). Hence, HCN4 mutation is associated with sinus-mediated pathologic slowing of the heart rate (sinus bradycardia). *SCN5A* sodium channel gene mutations have been linked to sick sinus syndrome, and atrial standstill—which is also associated with a loss-of-function sequence variant in the gene encoding connexin 43 (Cx43), a transmembrane protein that forms gap junctions important to intercellular coupling.

hERG Drug Interactions

I_{Kr} is the dominant phase 3 repolarization current (see Figure 24-1, *A*), and by an evolutionary quirk, the hERG α subunit has a propensity for inhibition by a wide range of otherwise potentially clinically useful drugs (see Figure 24-4). This unfortunate situation has led drug regulatory agencies including the FDA to mandate that all potential new medications, and current medications linked to increased sudden death or QT prolongation, are subjected to time-consuming and expensive testing for potential hERG antagonism and QT prolongation in experimental preparations including canine Purkinje fibers, which are part of the specialized conduction system of the heart that rapidly conducts signals from the atrial-ventricular node (AV node) to the ventricles. Indeed, hERG safety concerns have spawned an industry in their own right, with companies being formed the major directive of which is to facilitate hERG safety testing via product development or outsourcing of cellular electrophysiology.[88] QT prolongation and TdP thought to result from block of cardiac hERG channels has resulted in withdrawal of drugs for a variety of indications. Between 1997 and 2001, ten prescription drugs were withdrawn from the U.S. market, four because of links to increased incidence of TdP: the antihistamines Seldane (terfenadine) and Hismanal (astemizole), the heartburn medication Propulsid (cisapride monohydrate), and the antibiotic grepafloxacin.

Interestingly, some medications (e.g., Trisenox [arsenic trioxide], a last-resort treatment for acute promyelocytic leukemia), and the majority of LQTS-linked *KCNH2* mutations, are now known to reduce I_{Kr} because of hERG misfolding and/or mistrafficking, rather than impaired conduction or gating of channels at the plasma membrane as was first thought. It remains to be seen whether this holds for other cardiac ion channels, but it is clinically relevant because it will influence the therapeutic strategies used to repair I_{Kr} in these cases: Small molecules have been identified that fix LQTS-associated mutant hERG channels, probably by creating nucleation points to aid channel folding.[89-92] Future antiarrhythmics could even be targeted toward enhancing "normal" hERG trafficking to overcome other repolarization deficiencies.

Gene Therapy Guided by Molecular Genetics of Inherited Arrhythmias

An interesting experimental approach to treatment of arrhythmias is to introduce genes that regulate cardiac rhythm based on their ability to regulate specific ion channels. Three examples stand out in the literature; it should be noted that gene therapy is currently only in experimental and trial phases owing to an array of side effects, not specific to the introduced gene but rather to the delivery method, often a virus.

In the first example, researchers have exploited the ability of the KCNE3 K^+ channel β subunit to accelerate ventricular repolarization by increasing current through the KCNQ1 K_v α subunit. In the heart, KCNQ1-KCNE1 normally generates the slowly activating I_{Ks} repolarizing current. However, in the colon, KCNQ1 complexes with KCNE3, a subunit that locks the KCNQ1 voltage sensor (and thus pore) open, producing a constitutively active yet K^+-selective channel that regulates cAMP-stimulated chloride secretion in vivo.[93,94] When KCNE3 was introduced into guinea-pig ventricular cavity by injection of adenovirus containing the *KCNE3* gene, the result was a shortening of the action potential and a reduction in QT interval, stemming from the resultant increase in KCNQ1 current (which would have been especially marked at negative voltages, where KCNQ1-KCNE1 is typically closed).[95]

Second, introduction of HCN channel genes into quiescent ventricular myocytes shows promise for converting them into pacemaker cells. HCN expression endows them with automaticity, the ability to fire spontaneously, because HCN channels open in response to hyperpolarization and initiate depolarization.[96,97]

Third, a natural polymorphism (Q9E) in the KCNE2 ancillary subunit that regulates the hERG K_v α subunit, increases the sensitivity of hERG-KCNE2 channels to block by the macrolide antibiotic clarithromycin. The polymorphism was discovered in an African-American woman with ventricular fibrillation precipitated by clarithromycin, and was later found to be present in 3% of African Americans but absent in Caucasian Americans. This finding was exciting because it uncovered a pharmacogenomic mechanism for increased susceptibility to adverse effects for a significant fraction of a specific ethnic group. However, it was also utilized ingeniously to engineer experimentally chamber-specificity to erythromycin susceptibility with therapeutic goals in mind. Thus, viral introduction of Q9E-KCNE2 into porcine atrium rendered hERG channels within the atrium several-fold more susceptible to block by clarithromycin than their ventricular, wild-type hERG-KCNE2 counterparts. Clarithromycin was found to selectively prolong the atrial refractory period in these pigs without significantly affecting ventricular action potentials, exploiting the increased sensitivity of the mutant KCNE2-containing atrial channels.[25,98-100]

Future work will build upon all these discoveries to create bench-to-bedside medicine that utilizes each patient's own molecular lesion to tailor highly patient- and target-specific, bespoke gene- and stem-cell-related therapies.

KEY POINTS

- Antiarrhythmic drugs are organized into the Singh-Vaughan Williams classification, which is a useful framework for categorizing by primary mode of action.
- Most antiarrhythmics can be classified into more than one of the four categories. Amiodarone, one of the most efficacious, falls into all four classes.
- Class I antiarrhythmics block voltage-gated Na^+ channels and are subcategorized into Ia, Ib, and Ic depending on their binding kinetics, which dictate their effects on cardiac myocyte action potentials. They are used for ventricular arrhythmias, but are currently less commonly used because of potential proarrhythmic effects.
- Class II antiarrhythmics block β adrenergic signaling and slow heart rate. Sinus tachycardia and ventricular tachycardia are treated with β blockers.
- Class III antiarrhythmics block K^+ channels, prolonging the cardiac myocyte action potential and refractory period. They are used for conversion and prevention of atrial fibrillation/flutter, and in the case of amiodarone in the treatment of ventricular tachycardia/fibrillation.
- Class IV antiarrhythmics block Ca^{2+} channels, slowing nodal conduction and reducing intracellular [Ca^{2+}], without eliminating sympathetic regulation. Ca^{2+} channel blockers are used for treatment of idiopathic rhythms, ectopic atrial tachycardias, and atrioventricular nodal reentrant supraventricular tachycardias.
- Atrial fibrillation is most commonly treated with Na^+ channel blockers (Class 1a) or K^+ channel blockers (class III).
- A number of drugs from a variety of drug classes often used in anesthesia, as well as certain channel mutations, can predispose to torsades de pointes by blocking specific K^+ channels and prolonging the QT interval. This is usually treated with intravenous magnesium.

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