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SYSTEMATIC REVIEW

Modernized Classification of Cardiac Antiarrhythmic Drugs

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BACKGROUND: Among his major cardiac electrophysiological contributions, Miles Vaughan Williams (1918–2016) provided a classification of antiarrhythmic drugs that remains central to their clinical use.

METHODS: We survey implications of subsequent discoveries concerning sarcolemmal, sarcoplasmic reticular, and cytosolic biomolecules, developing an expanded but pragmatic classification that encompasses approved and potential antiarrhythmic drugs on this centenary of his birth.

RESULTS: We first consider the range of pharmacological targets, tracking these through to cellular electrophysiological effects. We retain the original Vaughan Williams Classes I through IV but subcategorize these divisions in light of more recent developments, including the existence of Na^+ current components (for Class I), advances in autonomic (often G protein–mediated) signaling (for Class II), K^+ channel subspecies (for Class III), and novel molecular targets related to Ca^{2+} homeostasis (for Class IV). We introduce new classes based on additional targets, including channels involved in automaticity, mechanically sensitive ion channels, connexins controlling electrotonic cell coupling, and molecules underlying longer-term signaling processes affecting structural remodeling. Inclusion of this widened range of targets and their physiological sequelae provides a framework for a modernized classification of established antiarrhythmic drugs based on their pharmacological targets. The revised classification allows for the existence of multiple drug targets/actions and for adverse, sometimes actually proarrhythmic, effects. The new scheme also aids classification of novel drugs under investigation.

CONCLUSIONS: We emerge with a modernized classification preserving the simplicity of the original Vaughan Williams framework while aiding our understanding and clinical management of cardiac arrhythmic events and facilitating future developments in this area.

Key Words: anti-arrhythmia agents ■ arrhythmias, cardiac ■ homeostasis ■ ion channels

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Clinical Perspective

What Is New?

- We develop a modernized comprehensive classification of both established and potential antiarrhythmic drugs that preserves the basic simplicity of the widely accepted classic Vaughan Williams framework.
- This incorporates advances in our understanding made over the past half-century, covering all the major currently known classes of antiarrhythmic mechanisms

What Are the Clinical Implications?

- It will provide a valuable guide to our basic understanding of the principal and subsidiary categories of antiarrhythmic and proarrhythmic drug actions in terms of their electrophysiological actions on specific currently known and potential targets bearing on cardiac excitation.
- It will facilitate therapeutic decisions in current clinical practice and aid in the development of future novel antiarrhythmic drugs.

The year 2018 marks the centenary of the birth of Miles Vaughan Williams and provides an opportunity to revisit his electrophysiological and pharmacological contributions concerning cardiac arrhythmias. The classic work defined 4 major possible modes of action of antiarrhythmic drugs variously modifying Na^+, K^+, and Ca^{2+} channel function and intracellular mechanisms regulated by adrenergic activity. These insights provided the scientific basis for a landmark classification of antiarrhythmic drugs based on the actions of these drugs on cardiac action potential (AP) components and their relationship to arrhythmias.[1,2] This classification proved, and remains, central to clinical management. Thus, Class I drugs produce moderate (Ia), weak (Ib), or marked (Ic) Na^+ channel block and reduce AP phase 0 slope and overshoot while increasing, reducing, or conserving AP duration (APD) and effective refractory period (ERP), respectively.[3] Class II drugs, comprising β-adrenergic inhibitors, reduce sino-atrial node (SAN) pacing rates and slow atrioventricular node (AVN) AP conduction.[4] Vaughan Williams's pioneering studies of β-adrenergic inhibitors remain a mainstay of antiarrhythmic therapy.[5] Class III drugs, comprising K^+ channel blockers, delay AP phase 3 repolarization and lengthen ERP. Finally, Class IV drugs, comprising Ca^{2+} channel blockers, reduce heart rate and conduction, acting particularly on the SAN and AVN.[2]

APPROACHES TO DEVELOPMENTS OF NEW DRUG CLASSIFICATION SCHEMES: THE SICILIAN GAMBIT

A review article published simultaneously in *European Heart Journal* and *Circulation* in 1991 represents an important step in the integration of these developments into guidelines for antiarrhythmic drug therapy.[6] The meeting in Taormina, Sicily, sought to furnish opening moves toward new classifications of antiarrhythmic drug therapy, akin to the Queen's Gambit representing a particularly aggressive option in chess, and this new approach was called the Sicilian Gambit. This more complete and flexible framework adopted a pathophysiological foundation identifying vulnerable parameters reflecting electrophysiological properties or events with pharmacological modifications that would terminate or suppress the arrhythmia with minimal undesirable cardiac effects.[7–9] It correlated information on molecular targets, cellular mechanisms, functional targets, and clinical arrhythmias for individual drugs with similarities and differences in their effects, accommodating their multiple actions. Although not then seeking a completed formal classification system, it furnished an accurate and comprehensive updated analysis of antiarrhythmic drugs. Although this analysis increased our understanding of drug action, the revised approach has not won widespread acceptance by clinicians and educators, possibly owing to its inevitable complexity. The Sicilian Gambit requires detailed knowledge of cellular and molecular targets of drugs under consideration. This may have made it intimidating or impractical for regular clinical use.

MODERNIZED SCHEME BASED ON THE VAUGHAN WILLIAMS APPROACH

The Vaughan Williams scheme, for all its limitations in light of subsequent developments in the cardiac electrophysiological field, thus remains the most useful, clinically and pedagogically popular approach to categorizing antiarrhythmic drugs. Table 1 summarizes a pragmatic development and expansion of that original classification encompassing principal actions of both current and potential antiarrhythmic agents, retaining the original Classes I through IV as its central core (Table I in the online-only Data Supplement). We thereby address interests and requirements of current workers in the field, mainly citing major reviews rather than original research articles, emphasizing broad principles and generalizations. We first identify major pharmacological targets, whether specific membrane ion channels, transporters, cytosolic biomolecules, or regulators (Figure 1A) strategic to cardiac electrophysiological activity (Figure 1B). Most therapeutic agents either block

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Table 1. An Updated Classification of Current Antiarrhythmic Pharmacological Drugs

Class	Subclass	Pharmacological Targets	Electrophysiological Effects	Examples of Drugs	Major Clinical Applications	Corresponding Likely Therapeutic Mechanism(s)
HCN channel blockers						
0		HCN channel–mediated pacemaker current (I_f) block	Inhibition of I_f reducing SAN phase 4 pacemaker depolarization rate, thereby reducing heart rate; possible decreased AVN and Purkinje cell automaticity; increase in RR intervals[10–14]	Ivabradine	Stable angina and chronic heart failure with heart rate ≥70 bpm Potential new applications for tachyarrhythmias[15]	Reduction in SAN automaticity
Voltage-gated Na^+ channel blockers						
I	Ia	Nav1.5 open state; intermediate (τ≈1–10 seconds) dissociation kinetics; often concomitant K^+ channel block	Reduction in peak I_{Na}, AP generation, and $(dV/dt)_{max}$ with increased excitation threshold; slowing of AP conduction in atria, ventricles, and specialized ventricular conduction pathways; concomitant I_K block increasing APD and ERP; increase in QT intervals[16–23]	Quinidine, ajmaline, disopyramide	Supraventricular tachyarrhythmias, particularly recurrent atrial fibrillation; ventricular tachycardia, ventricular fibrillation (including SQTS and Brugada syndrome)[24–27]	Reduction in ectopic ventricular/atrial automaticity Reduction in accessory pathway conduction Increase in refractory period, decreasing reentrant tendency[16,28,29]
	Ib	Nav1.5 open state; rapid dissociation (τ≈0.1–1 second); I_{Na}; window current	Reduction in peak I_{Na}, AP generation and $(dV/dt)_{max}$ with increased excitation threshold; slowing of AP conduction in atria, ventricles, and specialized ventricular conduction pathways; shortening of APD and ERP in normal ventricular and Purkinje myocytes; prolongation of ERP and postrepolarization refractoriness with reduced window current in ischemic, partially depolarized cells Relatively little electrocardiographic effect; slight QTc shortening[16–23,30]	Lidocaine, mexiletine	Ventricular tachyarrhythmias (ventricular tachycardia, ventricular fibrillation), particularly after myocardial infarction[24,26]	Reduction in ectopic ventricular automaticity Reduction in DAD-induced triggered activity Reduced reentrant tendency by converting unidirectional to bidirectional block, particularly in ischemic, partially depolarized myocardium[16,28,29]
	Ic	Nav1.5 inactivated state; slow dissociation (τ>10 seconds)	Reduction in peak I_{Na}, AP generation and $(dV/dt)_{max}$ with increased excitation threshold; slowing of AP conduction in atria, ventricles, and specialized ventricular conduction pathways; reduced overall excitability; prolongation of APD at high heart rates; increase in QRS duration[16–23,30,31]	Propafenone, flecainide	Supraventricular tachyarrhythmias (atrial tachycardia, atrial flutter, atrial fibrillation, and tachycardias involving accessory pathways) Ventricular tachyarrhythmias resistant to other treatment in the absence of structural heart disease, premature ventricular contraction, catecholaminergic polymorphic ventricular tachycardia[24–27]	Reduction in ectopic ventricular/atrial automaticity Reduction in DAD-induced triggered activity Reduced reentrant tendency by converting unidirectional to bidirectional block Slowed conduction and reduced of excitability particularly at rapid heart rates blocking reentrant pathways showing depressed conduction[16,28,29]
	Id	Nav1.5 late current	Reduction in late Na^+ current (I_{NaL}), affecting AP recovery, refractoriness, repolarization reserve, and QT interval[22,32]	Ranolazine	Stable angina, ventricular tachycardia As a potential new class of drugs for the management of tachyarrhythmias	Decrease in AP recovery time Reduction in EAD-induced triggered activity

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Table 1. Continued

Class	Subclass	Pharmacological Targets	Electrophysiological Effects	Examples of Drugs	Major Clinical Applications	Corresponding Likely Therapeutic Mechanism(s)
Autonomic inhibitors and activators						
II	IIa	Nonselective β- and selective β1-adrenergic receptor inhibitors	Inhibition of adrenergically induced G_s protein-mediated effects of increased adenylyl kinase activity and $[cAMP]_i$ with effects including slowed SAN pacemaker rate caused by reduced I_f and I_{CaL}; increased AVN conduction time and refractoriness, and decreased SAN pacing and triggered activity resulting from reduced I_{CaL}; and reduced RyR2-mediated SR Ca^{2+} release and triggered activity; increase in RR and PR intervals[33]	Nonselective β inhibitors: carvedilol, propranolol, nadolol. Selective β1-adrenergic receptor inhibitors: atenolol, bisoprolol, betaxolol, celiprolol, esmolol, metoprolol	Sinus tachycardia or other types of tachycardic, including supraventricular (atrial fibrillation, atrial flutter, atrial tachycardia), arrhythmias Rate control of atrial fibrillation and ventricular tachyarrhythmias (ventricular tachycardia, premature ventricular contraction) Note: atenolol, propranolol, and nadolol also used in LQTS; nadolol used in catecholaminergic polymorphic ventricular tachycardia[24–27]	Reduction in SAN automaticity Reduction in AVN automaticity Reduction in ectopic ventricular/atrial automaticity Reduction in EAD-/DAD-induced triggered activity Reduced SAN reentry Reduction in AVN conduction terminating reentry[5,16,29]
	IIb	Nonselective β-adrenergic receptor activators	Activation of adrenergically induced G_s-protein effects of increasing adenylyl kinase activity and $[cAMP]_i$ (see entry above); decrease in RR and PR intervals[33]	Isoproterenol	Accelerating rates of ventricular escape rhythm in cases of complete atrioventricular block before definitive pacemaker implantation Acquired, often drug-related bradycardia-dependent torsades de pointes[34]	Increased escape ventricular automaticity Suppression of bradycardia-dependent EAD-related triggered activity[5,16,29]
	IIc	Muscarinic M_2 receptor inhibitors	Inhibition of supraventricular (SAN, atrial, AVN) muscarinic M_2 cholinergic receptors (see entry below); decreased RR and PR intervals[35–37]	Atropine, anisodamine, hyoscine, scopolamine	Mild or moderate symptomatic sinus bradycardia Supra-His, AVN, conduction block, eg, in vagal syncope or acute inferior myocardial infarction[34]	Increase in SAN automaticity Increase in AVN conduction[16,29]
	IId	Muscarinic M_2 receptor activators	Activation of supraventricular (SAN, atrial, AVN) muscarinic M_2 cholinergic receptors activates K_{ACh} channels, hyperpolarizing the SAN and shortening APDs in atrial and AVN tissue, and reduces $[cAMP]_i$ and therefore I_{CaL} and SAN I_f; inhibitory effects on adenylyl cyclase and cAMP activation, reducing its stimulatory effects on I_{CaL}, I_{Ks}, I_{Cl}, and I_{ti} in adrenergically activated ventricular tissue; increased RR and PR intervals[35–37]	Carbachol, pilocarpine, methacholine, digoxin	Sinus tachycardia or supraventricular tachyarrhythmias[24,27]	Reduction in SAN automaticity Reduced SAN reentry Reduction in AVN conduction, terminating reentry[16,29]
	IIe	Adenosine A_1 receptor activators	Activation of adenosine A_1 receptors in supraventricular tissue (SAN, atrial, AVN) activates G protein–coupled inward rectifying K^+ channels and I_{KAdo} current, hyperpolarizing the SAN and shortening APDs in atrial and AVN tissue, and reduces $[cAMP]_i$ and therefore I_{CaL} and SAN I_f; inhibitory effects on adenylyl cyclase and cAMP activation, reducing its stimulatory effects on I_{CaL}, I_{Ks}, I_{Cl}, and I_{ti} in adrenergically activated ventricular tissue; increased RR and increased PR intervals[38]	Adenosine, ATP; aminophylline acts as an adenosine receptor inhibitor	Acute termination of AVN tachycardia and cAMP-mediated triggered VTs Differentiation of sinus from atrial tachycardia[24,26,27,34]	Reduction in SAN automaticity Reduction in AVN conduction, terminating reentry Reduction in EAD-/DAD-induced triggered activity[16,29,39]

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Table 1. Continued

Class	Subclass	Pharmacological Targets	Electrophysiological Effects	Examples of Drugs	Major Clinical Applications	Corresponding Likely Therapeutic Mechanism(s)
K^+ channel blockers and openers						
III						
Voltage dependent K^+ channel blockers	IIIa	Nonselective K^+ channel blockers	Block of multiple K^+ channel targets resulting in prolonged atrial, Purkinje, and/or ventricular myocyte AP recovery, increased ERP, and reduced repolarization reserve; prolonged QT intervals[35,40,41]	Ambasilide, amiodarone, dronedarone	Ventricular tachycardia in patients without structural heart disease or with remote myocardial infarction; tachyarrhythmias with Wolff-Parkinson-White syndrome Atrial fibrillation with atrioventricular conduction via accessory pathway Ventricular fibrillation and premature ventricular contraction Tachyarrhythmias associated with supraventricular arrhythmias and atrial fibrillation[24–27]	Increase in AP recovery time Increase in refractory period, with decreased reentrant tendency Note: amiodarone also slows sinus node rate and atrioventricular conduction; see Table 2[16,29]
		Kv11.1 (HERG) channel–mediated rapid K^+ current (I_{Kr}) blockers	Prolonged atrial, Purkinje, and ventricular myocyte AP recovery, increased ERP, and reduced repolarization reserve; prolonged QT intervals[41]	Dofetilide, ibutilide, sotalol	Ventricular tachycardia in patients without structural heart disease or with remote myocardial infarction Tachyarrhythmias associated with Wolff-Parkinson-White syndrome Atrial fibrillation with atrioventricular conduction via accessory pathway, ventricular fibrillation, premature ventricular contraction Tachyarrhythmias associated with supraventricular arrhythmias and atrial fibrillation[24–27]	Increase in AP recovery time Increase in refractory period with decreased reentrant tendency[16,29,42]
		Kv7.1 channel–mediated, slow K^+ current (I_{Ks}) blockers	Prolonged atrial, Purkinje, and ventricular myocyte AP recovery, increased ERP, and reduced repolarization reserve; prolonged QT intervals[35,40,41,43]	No clinically approved drugs in use		Increase in AP recovery time Increase in refractory period with decreased reentrant tendency[16,29]
		Kv1.5 channel–mediated, ultrarapid K^+ current (I_{Kur}) blockers	Prolonged atrial AP recovery, increased ERP, and reduced repolarization reserve[35]	Vernakalant	Immediate conversion of atrial fibrillation	Atrium-specific actions: increase in AP recovery time and increase in refractory period with decreased reentrant tendency[29]
		$K_V1.4$ and $K_V4.2$ channel–mediated transient outward K^+ current (I_{to1}) blockers	Prolonged atrial, Purkinje, and ventricular myocyte AP recovery, increased ERP, and reduced repolarization reserve, particularly in subepicardial as opposed to subendocardial ventricular cardiomyocytes[35,41]	Blocker under regulatory review for the acute conversion of atrial fibrillation: tedisamil		Increase in AP recovery time; increase in refractory period, with decreased reentrant tendency[29]
Metabolically dependent K^+ channel openers	IIIb	Kir6.2 (I_{KATP}) openers	Opening of ATP-sensitive K^+ channels (I_{KATP}), shortening AP recovery, refractoriness, and repolarization reserve in all cardiomyocytes apart from SAN cells; shortened QT intervals[35,44,45]	Nicorandil, pinacidil	Nicorandil: treatment of stable angina (second line); pinacidil: investigational drug for the treatment of hypertension	Potential decrease in AP recovery time

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Table 1. Continued

Class	Subclass	Pharmacological Targets	Electrophysiological Effects	Examples of Drugs	Major Clinical Applications	Corresponding Likely Therapeutic Mechanism(s)
Transmitter dependent K^+ channel blockers	IIIc	GIRK1 and GIRK4 (I_{KACh}) blockers	Inhibition of direct or G_i protein βγ-subunit–mediated activation of I_{KACh}, particularly in SAN, AVN, and atrial cells, prolonging APD and ERP and decreasing repolarization reserve[35,46]	Blocker under regulatory review for management of atrial fibrillation: BMS 914392		Reduction in SAN automaticity[47]
Ca^{2+} handling modulators						
IV						
Surface membrane Ca^{2+} channel blockers	IVa	Nonselective surface membrane Ca^{2+} channel blockers	Block of Ca^{2+} current (I_{Ca}), resulting in inhibition of SAN pacing, inhibition of AVN conduction, prolonged ERP, increased AP recovery time, increased refractory period, diminished repolarization reserve, and suppression of intracellular Ca^{2+} signaling; increased PR intervals[48,49]	Bepridil	Angina pectoris Potential management of supraventricular tachyarrhythmias[24,27]	Reduction in AVN conduction, terminating reentry Reduction in EAD-/DAD-induced triggered activity[5,16,29]
		$Ca_v1.2$ and $Ca_v1.3$ channel mediated L-type Ca^{2+} current (I_{CaL}) blockers	Block of Ca^{2+} current (I_{Ca}), resulting in inhibition of SAN pacing, inhibition of AVN conduction, prolonged ERP, increased AP recovery time, increased refractory period, diminished repolarization reserve, and suppression of intracellular Ca^{2+} signaling; increased PR intervals[48–50]	Phenylalkylamines (eg, verapamil), benzothiazepines (eg, diltiazem)	Supraventricular arrhythmias and ventricular tachycardia without structural heart disease Rate control of atrial fibrillation[24,26,27]	Reduction in AVN conduction, terminating reentry Reduction in EAD-/DAD-induced triggered activity[5,16,29]
		$Ca_v3.1$ channel mediated T-type Ca^{2+} current (I_{CaT}) blockers	Inhibition of SAN pacing, prolonged His-Purkinje phase 4 repolarization, absent from ventricular cells[49]	No clinically approved drugs in use		
Intracellular Ca^{2+} channel blockers	IVb	SR RyR2-Ca^{2+} channel blockers	Reduced SR Ca^{2+} release: reduced cytosolic and SR $[Ca^{2+}]$[31,33,48,51–54]	Flecainide, propafenone	Catecholaminergic polymorphic ventricular tachycardia	Reduction in DAD-induced triggered activity[5,16,29]
		IP_3R-Ca^{2+} channel blockers	Reduced atrial SR Ca^{2+} release; reduced cytosolic and SR $[Ca^{2+}]$[48]	No clinically approved drugs in use		
Sarcoplasmic reticular Ca^{2+}-ATPase activators	IVc	Sarcoplasmic reticular Ca^{2+} pump activators	Increased Ca^{2+}-ATPase activity, increased SR $[Ca^{2+}]$[33,48,53]	No clinically approved drugs in use		Reduction in DAD-induced triggered activity[5,16,29]
Surface membrane ion exchange inhibitors	IVd	Surface membrane ion exchanger (eg, SLC8A) inhibitors	Reduced Na^+-Ca^{2+} exchange reduces depolarization associated with rises in subsarcolemmal $[Ca^{2+}]$[48,53]	No clinically approved drugs in use		Reduction in EAD-/DAD-induced triggered activity[5,16,29]
Phosphokinase and phosphorylase inhibitors	IVe	Increased/decreased phosphorylation levels of cytosolic Ca^{2+} handling proteins	Includes CaMKII modulators: altered intracellular Ca^{2+} signaling[37,44,50,55–57]	No clinically approved drugs in use		Reduction in EAD-/DAD-induced triggered activity
Mechanosensitive channel blockers						
V		Transient receptor potential channel (TRPC3/TRPC6) blockers	Intracellular Ca^{2+} signaling[58]	Blocker under investigation: *N*-(p-amylcinnamoyl) anthranilic acid		Reduction in EAD-/DAD-induced triggered activity

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Table 1. Continued

Class	Subclass	Pharmacological Targets	Electrophysiological Effects	Examples of Drugs	Major Clinical Applications	Corresponding Likely Therapeutic Mechanism(s)
Gap junction channel blockers						
VI		Cx (Cx40, Cx43, Cx45) blockers	Reduced cell-cell coupling and AP propagation; Cx40: atria, AVN, ventricular conduction system; Cx43: atria and ventricles, distal conduction system; Cx45: SAN, AVN, conducting bundles[18,59]	Blocker under investigation: carbenoxolone		Reduction in ventricular/atrial conduction Reduction in accessory pathway conduction Reduction in AVN conduction
Upstream target modulators						
VII		Angiotensin-converting enzyme inhibitors	Electrophysiological and structural (fibrotic, hypertrophic, or inflammatory) remodeling[47,60,61]	Captopril, enalapril, delapril, ramipril, quinapril, perindopril, lisinopril, benazepril, imidapril, trandolapril, cilazapril	Management of hypertension, symptomatic heart failure Potential application reducing arrhythmic substrate[15,25]	Reduction of structural and electrophysiological remodeling changes that compromise AP conduction and increase reentrant tendency
		Angiotensin receptor blockers	Electrophysiological and structural (fibrotic, hypertrophic, or inflammatory) remodeling[47,60,61]	Losartan, candesartan, eprosartan, telmisartan, irbesartan, olmesartan, valsartan, saprisartan	Management of hypertension, symptomatic heart failure Potential application reducing arrhythmic substrate[15,25]	Reduction of structural and electrophysiological remodeling changes that compromise AP conduction and increase reentrant tendency
		Omega-3 fatty acids	Electrophysiological and structural (fibrotic, hypertrophic, or inflammatory) remodeling[60]	Omega-3 fatty acids: eicosapentaenoic acid, docosahexaenoic acid, docosapentaenoic acid	Post–myocardial infarct reduction of risk of cardiac death, myocardial infarct, stroke, and abnormal cardiac rhythms[26]	Reduction of structural and electrophysiological remodeling changes that compromise AP conduction and increase reentrant tendency
		Statins	Electrophysiological and structural (fibrotic, hypertrophic, or inflammatory) remodeling[60]	Statins	Post–myocardial infarct reduction of risk of cardiac death, myocardial infarct, stroke, and abnormal cardiac rhythms[25]	Reduction of structural and electrophysiological remodeling changes that compromise AP conduction and increase reentrant tendency

AP indicates action potential; APD, action potential duration; AVN, atrioventricular node; CaMKII, calcium/calmodulin kinase II; DAD, delayed afterdepolarization; EAD, early afterdepolarization; ERP, effective refractory period; HCN, hyperpolarization-activated cyclic nucleotide-gated; RyR2, ryanodine receptor 2; SAN, sino-atrial node; SQTS, short-QT syndrome; and SR, sarcoplasmic reticulum.

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or open specific ion channels or, in the case of particular signaling molecules and receptors, activate or inhibit the relevant pathway. We then summarize the corresponding principal electrophysiological effects of target modification, including actions progressively investigated at the level of single cells, particular cardiac regions, or the entire heart.[7–9] These are illustrated by clinically used drugs, their clinical indications, and likely therapeutic mechanisms of action, acknowledging their additional, often multiple, actions (Table 2), selecting these from the wide range of clinically approved available agents (Table II in the online-only Data Supplement) and, in some cases, the numerous investigational agents under development (Table III in the online-only Data Supplement).

Our approach retains but modifies Vaughan Williams Class I, adding a Class Id to include actions on recently reported late Na^+ current (I_{NaL}) components, recognizing their importance in long-QT syndrome (LQTS) type 3 (LQTS3). Class II conserves the β-adrenergic inhibitors but now captures subsequent advances in our understanding of autonomic, often G protein–mediated, signaling. Class III is expanded to take into account the large number of subsequently discovered K^+ channel species determining APD and subsequent refractoriness. Class IV now encompasses recently demonstrated and characterized molecu-

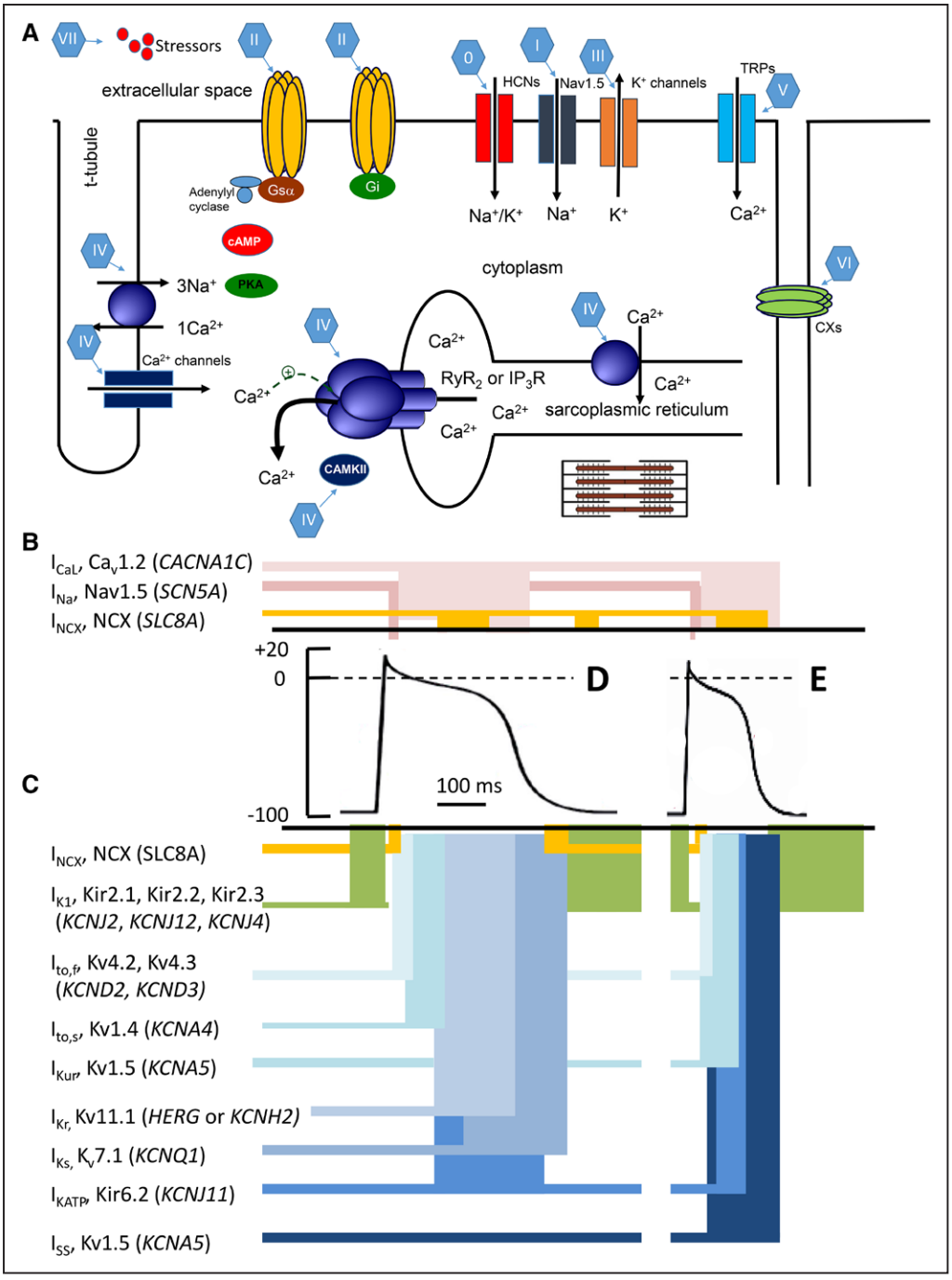


Figure 1. Surface and intracellular membrane ion channels, ion exchangers, transporters, and ionic pumps involved in cardiomyocyte electrophysiological excitation and activation.

A, Their grouping by pharmacological targets listed in Table 1. **B** through **E**, Activation and inactivation of ion channels, currents, underlying proteins, and encoding genes and their contributions to (**B**) inward depolarizing and (**C**) outward repolarizing currents bringing about cardiac action potentials (APs). Ventricular (**D**) and atrial (**E**) APs comprise rapid depolarizing (phase 0), early repolarizing (phase 1), brief (atrial) or prolonged (ventricular) phase 2 plateaus (phase 2), phase 3 repolarization, and phase 4 electric diastole. In these, inward Na^+ or Ca^{2+} currents drive phase 0 depolarization and Ca^{2+} current maintains the phase 2 plateau (**B**), and a range of outward K^+ currents (**C**) drive phase 1 and phase 3 repolarization. Phase 4 resting potential restoration is accompanied by a refractory period required for Na^+ channel recovery. The resulting wave of electric activity and refractoriness is propagated through successive sino-atrial node, atrial, atrioventricular, Purkinje, and endocardial and epicardial ventricular cardiomyocytes. CaMKII indicates calcium/calmodulin kinase II; Cx, connexin; G_i, inhibitory G protein; G_s, stimulatory G-protein; HCN, hyperpolarization-activated cyclic nucleotide-gated channel; Nav1.5, cardiac Na^+ channel protein; PKA, protein kinase A; RyR2, cardiac ryanodine receptor type 2; and TRP, transient receptor potential channel. Adapted from Huang[19] with permission. Copyright (c) 2017, American Physiological Society.

lar targets and cellular physiological mechanisms related to Ca^{2+} homeostasis. Further new classes reflect additional targets that have been identified since the original Vaughan Williams classification. They include cardiac automaticity (Class 0) and recently demonstrated drugs acting on mechanically sensitive channels (Class V) or medi-

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Table 2. Examples of Multiple Actions of Cardiac Electrophysiologically Active Drugs

Class	
0	HCN channel blockers[15,24–27]
Ivabradine	I_{Kr} antagonism and slowed atrioventricular conduction in addition to I_f antagonism
I	Voltage-gated Na^+ channel blockers[16,24–29]
Quinidine	I_{to}, I_{Kr}, I_{Ks}, I_{K1}, I_{KATP}, I_{Ca}, autonomic α-adrenergic, and cholinergic in addition to Class Ia antagonism
Disopyramide	I_{to}, I_{Kr}, I_{K1}, I_{KATP}, and cholinergic in addition to Class Ia antagonism; negative inotropic but no α- or β-adrenergic effects
Procainamide	I_{Kr}, I_{K1}, I_{KATP}, and autonomic ganglion in addition to Class Ia antagonism
Lidocaine	No I_K effects
Mexiletine	No I_K effects
Flecainide	I_{Kur}, I_{Kr}, I_{Ca} and RyR2 in addition to Class Ic antagonism
Encainide	I_{Kur} and I_{Kr} in addition to Class Ic antagonism
Propafenone	I_{Kur}, I_{Kr}, I_{Ca}, RyR2, autonomic β-adrenergic and vagal in addition to Class Ic antagonism
Ranolazine	I_{Kr} in addition to Class Ic antagonism
II	Autonomic inhibitors and activators[5,16,24–27,29]
Carteolol	Increased nitric oxide production in addition to Class IIa antagonism
Carvedilol	Possible antioxidant activity; I_{CaL}, RyR2-Ca^{2+} channel, and α_1-adrenergic in addition to Class IIa antagonism
Propranolol	I_{Na} in addition to Class IIa antagonism
Betaxolol	I_{CaL} in addition to Class IIb antagonism
Celiprolol	Increased nitric oxide production, partial β_2-adrenergic agonist, and weak α_2-adrenergic antagonist effects in addition to Class IIb antagonism
Nebivolol	Increased nitric oxide production in addition to Class IIb antagonism
III	K^+ channel blockers and openers[16,24–27,29,42]
Dofetilide	Often considered "pure" I_{Kr} blocker
Ibutilide	I_{Na} activation in addition to I_{Kr} antagonism
D/L-Sotalol	I_{to}, I_{K1}, and β-adrenergic in addition to I_{Kr} antagonism
Clofilium	I_{to} and I_{K1} in addition to I_{Kr} antagonism
Amiodarone	I_{Na}, I_{Ca}, I_{to}, I_{Ks}, I_{K1}, I_{KACh}, α- and β-adrenergic in addition to I_{Kr} antagonism; reduced automaticity
Dronedarone	I_{Ks} and β1-adrenergic in addition to I_{Kr} antagonism
Vernakalant	I_{NaL} in addition to I_{Kur} antagonism
Tedisamil	I_{Kr} and I_{KATP} in addition to I_{to} antagonism
Nicorandil	Nitrate action vasodilating vascular smooth muscle in addition to I_{KATP} antagonism
Rimakalim	Nitrate action vasodilating vascular smooth muscle in addition to I_{KATP} antagonism
(Lev) cromakalim	Nitrate action vasodilating vascular smooth muscle in addition to I_{KATP} antagonism
IV	Ca^{2+} handling modulators[5,16,24,26,27,29]
Verapamil	Vascular smooth muscle (tachycardic effects) in addition to cardiac I_{CaL} antagonism (bradycardic effects), reduced DADs
Diltiazem	Vascular smooth muscle (tachycardic effects) in addition to cardiac I_{CaL} antagonism (bradycardic effects), reduced DADs
Bepridil	Vascular smooth muscle (tachycardic effects) in addition to cardiac I_{CaL} antagonism (bradycardic effects), reduced DADs

DAD indicates delayed afterdepolarization; HCN, hyperpolarization-activated cyclic nucleotide-gated; and RyR2, ryanodine receptor 2.

ating electrotonic coupling between cells (new Class VI). Finally, a range of signaling processes exert longer-term effects on arrhythmic tendency through modifying structural remodeling (Class VII). These classification activities are now discussed briefly in turn.

These diverse drug actions converge on a defined set of distinct cellular and tissue electrophysiological end effects bearing on the respective cardiac properties of automaticity, AP generation, and AP conduction (Table 1, right column).[7] Changes in the automaticity responsible for spontaneous, rhythmic cardiac activity can arise from abnormalities in the repetitive SAN activity, depending on its pacemaker currents. It can also arise from subsidiary pacemaker formation in specialized conducting AVN or Purkinje fibers and from normally nonautomatic atrial and ventricular cardiomyocytes when they are depolarized by some pathological processes. In the case of triggered activity that generates ectopic APs, early afterdepolarization phenomena occur during late phase 2 or early phase 3 of often prolonged APs. The latter are particularly associated with prolonged clinical QT intervals observed under conditions of increased inward late Na^+, L-type Ca^{2+}, decreased repolarizing outward K^+ currents, or increased depolarizing Na^+/Ca^{2+} exchange current arising from spontaneous sarcoplasmic reticular (SR) Ca^{2+} release (Figure 1B). In contrast, delayed afterdepolarizations after full AP repolarization are associated with situations of intracellular Ca^{2+} overload, resulting in elevated SR Ca^{2+} or increased cytosolic Ca^{2+} sensitivity in the cardiac ryanodine receptor (RyR2). Either situation predisposes to spontaneous SR Ca^{2+} release. This increases cytosolic [Ca^{2+}], which in turn transiently increases inward depolarizing Na^+/Ca^{2+} exchange current.

These triggering events may produce persistent arrhythmia whether through their perpetuating further such events or through arrhythmic substrate facilitating reentry of excitation from active into recovered myocardial regions. This takes place in the presence of heterogeneities that generate obstacles to AP conduction, around which the AP circulates with slowed conduction velocities that may reflect altered ion channel or myocardial tissue electric properties. The result is a formation of multiple, heterogeneous pathways of impulse propagation between anatomically or functionally defined points in the heart.[62] Whereas an anatomic

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reentry of excitation takes place around a central inexcitable anatomic obstacle, a functional reentry of excitation involves a functional central obstacle. Reentrant excitation is also facilitated by abnormalities leading to heterogeneities in AP recovery arising from relative changes in ERP and APD, whether early (phase 2)[63–65] or late in the time course of AP repolarization.[19,23,66,67]

NEW CLASS 0 OF DRUGS ACTING ON SINO-ATRIAL AUTOMATICITY

Detailed characterizations of the properties of SAN cells postdated the original Vaughan Williams classification.[10] SAN cells are exceptional in showing automaticity under normal physiological conditions, with contributions from a "membrane clock" giving rise to a spontaneous diastolic depolarization described as the pacemaker potential. This is driven by a net inward current, to which the most important contribution may be the "funny current" (I_f) carried by hyperpolarization-activated cyclic nucleotide-gated channels, particularly during the initial phase of the diastolic depolarization.[12,14,68] The only currently clinically adopted Class 0 agent, ivabradine, is used to reduce heart rates in situations of inappropriate sinus tachycardia[69,70] or when sinus tachycardia accompanies cardiac failure.[71] It likely acts through hyperpolarization-activated cyclic nucleotide-gated channel block, with possible additional effects on intracellular Ca^{2+} cycling.[72] Future investigations may explore the extent to which diastolic depolarization is further augmented by deactivation of outward delayed rectifier K^+ current and activation of inward currents, including Na^+-dependent background current (I_{bNa}), T- and L-type Ca^{2+} currents (I_{CaL} and I_{CaT}),[73] and possibly sustained inward current (I_{st}). Inward voltage-dependent Na^+ current (I_{Na}) has also been recorded from SAN pacemaker cells, although it may be inactivated at the relatively positive potentials during the pacemaker potential in the SAN.[13,14] In addition, intracellular signaling involving SR Ca^{2+} stores, cellular cAMP levels, and consequent phosphorylation of their signaling proteins has recently been implicated in a "Ca^{2+} clock" in which spontaneous RyR2-mediated Ca^{2+} release enhances electrogenic Na^+/Ca^{2+} exchanger activity during both SAN[14,74,75] and Purkinje cell diastolic depolarization.[76]

EXTENSION OF VAUGHAN WILLIAMS CLASS I

Our revised classification system retains the 3 original Class I subcategories listing cardiac Na^+ channel ($Na_v1.5$) blockers.[16,30] However, it incorporates recent biophysical findings bearing on gating transitions regulated by voltage sensing components of Nav1.5 (Table 1).[77] Nav1.5 is preferentially expressed in atrial, Purkinje conducting, and ventricular as opposed to SAN and AVN cardiomyocytes. AP initiation then involves regenerative transitions from the resting state of Nav1.5 to its active state that permits the inward Na^+ current (I_{Na}), responsible for phase 0 rapid depolarization (Figure 2). The depolarization also causes the subsequent transition of Nav1.5 into an inactivated state, resulting in channel refractoriness. Channel recovery from the inactivated to the resting state then requires membrane repolarization and takes place over a finite time course.[17,22] Class Ia drugs subsequently proved to show concomitant effects on other, particularly K^+, channel species, with potential consequences for Class III actions related to late depolarizing events.[78] Nevertheless, we retain their original Class Ia subclassification as Na^+ channel blockers, with all drugs in Classes Ia through 1c reducing AP maximum upstroke rates $(dV/dt)_{max}$ and AP conduction in atria, ventricular, and conducting tissue despite different effects on APD (Figure 2).

Class Ia drugs preferentially bind to the open state of Nav1.5 with dissociation time constants (τ) of ≈1 to 10 seconds. They thus reduce AP conduction velocity and increase ERP. Concomitant K^+ channel block by Class Ia drugs also increases APD. Together, these properties reduce reentrant tendency. In contrast, Class Ib drugs bind preferentially to the Nav1.5 inactivated state from which they dissociate relatively rapidly with a τ of ≈0.1 to 1.0 second. This minimizes perturbations of processes in the remaining cardiac cycle and explains the effectiveness of Class 1b drugs in preventing arrhythmias, particularly in ventricular tissue, where Nav1.5 channels remain inactive for the longest duration. Class Ib drugs result in shortening of both APD and ERP in normal ventricular muscle and Purkinje cells[16] but cause prolongation of ERP and consequently prolongation of postrepolarization refractoriness in ischemic, partially depolarized, cells.[79] Class Ic drugs similarly bind to the inactivated Nav1.5, from which, however, they dissociate more slowly, over τ >10 seconds. Use-dependent channel block in Classes Ia through 1c arises from accumulation of blocked channels during repetitive stimulation at high frequencies and accordingly occurs to extents in the sequence Class Ic>Class Ia>Class Ib. This results in a generalized reduction in cardiac excitability with nonspecific and widespread effects. These include slowed AP conduction with increased APD at high heart rates and possible reductions in cardiac automaticity.[16]

These differing dissociation rates shown by Class Ia, Ib, and Ic agents also result in contrasting effects on AP conduction reflected in the associated normal and prolonged QRS durations, at least under conditions of normal cardiac rhythm. The different properties of Class I drug subgroups thus result in differing clinical effects, varying with the particular electrophysiological conditions underlying the targeted arrhythmias. The relatively slow dissociation of the Class Ic agent flecainide, from its binding to the inactivated state of Nav1.5, compromises AP initiation and conduction. Flecainide

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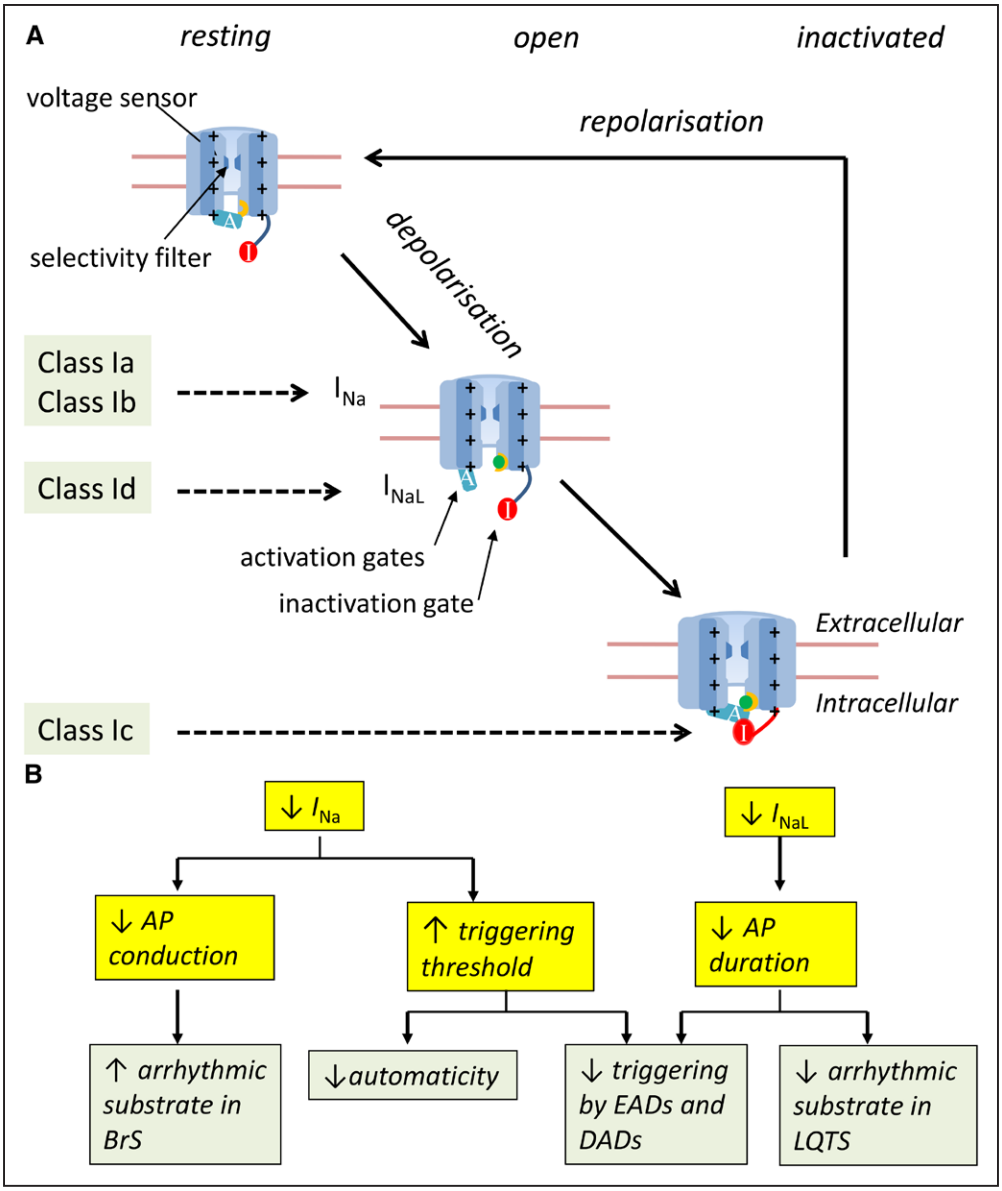


Figure 2. Relationships between biophysical actions of Class I drugs on cardiac Na^+ channel protein (Nav1.5) and their consequent electrophysiological antiarrhythmic and proarrhythmic effects.

A, Initial depolarization activates the Nav1.5 voltage sensor, in turn causing a transition from its resting, closed, to its open state, permitting extracellular Na^+ influx through the selectivity filter of the channel. The resulting regenerative depolarization results in slower transitions into an inactivated state, causing channel closure, from which recovery to the resting state requires membrane potential repolarization. The different Class Ia through Id drugs act at different stages in this reaction cycle and on differing early, I_{Na}, and late, I_{NaL}, Na^+ current components. This results in (**B**) differential actions on action potential (AP) conduction, triggering, and duration, with proarrhythmic or antiarrhythmic effects, depending on the background clinical conditions. BrS indicates Brugada syndrome; DAD, delayed afterdepolarization; EAD, early afterdepolarization; and LQTS, long-QT syndrome.

is thus antiarrhythmic, with the compromised AP recovery, gain of Na^+ channel function, and increased I_{NaL} in both clinical LQTS3 and genetically modified murine $Scn5a^{+/\Delta kpq}$ hearts experimentally modeling this condition.[23] In contrast, flecainaide was clinically proarrhythmic under conditions of compromised postinfarct AP generation and propagation (Table 3)[80] and the Brugada syndrome and in murine $Scn5a^{+/-}$ models that replicate its associated loss of Nav1.5 function and age-dependent fibrotic changes.[18–21] This also contrasts with the respective antiarrhythmic actions of the more rapidly dissociating Class Ia and Class Ib agents quinidine and lidocaine in situations of compromised AP generation and propagation. Quinidine is additionally proarrhythmic under conditions of prolonged AP recovery, at least partially reflecting its additional I_K-blocking effects. The different Class I actions also influence their clinical indications for arrhythmias affecting different regions of the heart. Finally, because atrial Nav1.5 channels remain open for longer than in the ventricles, Class Ia (exemplified in Table 1 by quinidine, ajmaline, and disopyramide) and Ic (exemplified

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Table 3. Examples of Common Proarrhythmic Actions of Antiarrhythmic Pharmacological Drugs

Class	Arrhythmia	Likely Mechanisms
0	Hyperpolarization-activated cyclic nucleotide-gated channel blockers[15]	
Ivabradine	Sinus bradycardia	Depressing sinus node automaticity by block of I_f
I	Voltage-gated Na^+ channel blockers[16,24–29]	
Quinidine	Torsades de pointes with prolonged QT interval; vagolytic effect with increase in ventricular rate in atrial flutter	EAD-related triggered activity Conduction slowing in the atrium with enhanced or unaltered atrioventricular conduction
Disopyramide	Torsades de pointes with prolonged QT interval	EAD-related triggered activity
Procainamide	Torsades de pointes with prolonged QT interval Ventricular tachycardia in the presence of ischemic heart disease	EAD-related triggered activity Conduction slowing in the ventricle
Flecainide	Increase in ventricular rate in atrial flutter Ventricular tachycardia in the presence of ischemic heart disease or old myocardial infarction	Conduction slowing in the atrium with enhanced or unaltered atrioventricular conduction Conduction slowing in the ventricle or myocardial scar areas
Propafenone	Increase in ventricular rate in atrial flutter Ventricular tachycardia in the presence of ischemic heart disease or old myocardial infarction Slowed sinus rate	Conduction slowing in the atrium with enhanced or unaltered atrioventricular conduction Conduction slowing in the ventricle or myocardial scar areas Depressing sinus node automaticity by block of I_f
II	Autonomic inhibitors and activators[5,16,24–27,29,34]	
β-Adrenergic receptor inhibitors	Sinus bradycardia; atrioventricular block Sinus tachycardia or other type of tachycardia	β-Blockade Upregulation of β-receptors with long-term therapy; β-blocker withdrawal
β-Adrenergic receptor activators	Sinus tachycardia, increased triggering activity	β-Receptor activation
M_2 receptor activators: carbachol, digoxin	Sinus bradycardia; atrioventricular block; ventricular tachycardia	Depression of SAN automaticity and atrioventricular node conduction Increase in vagal tone Increased delayed afterdepolarization–related triggered activity
M_2 receptor inhibitors: atropine	Exacerbated ventricular bradycardia and exacerbated effects of low atrioventricular block	Increased SAN automaticity and atrioventricular conduction despite persistent degenerative atrioventricular block at or below His bundle level
A_1 receptor activators: adenosine	Sinus bradycardia, sinus arrest, or atrioventricular block associated with adenosine terminating paroxysmal supraventricular tachycardia Frequent atrial or premature ventricular beats; atrial fibrillation	Depressing sinoatrial node automaticity and atrioventricular node conduction Unknown mechanism
III	K^+ channel blockers and openers[16,24–27,29]	
Dofetilide, ibutilide, D/L-sotalol	Torsades de pointes with prolonged QT interval	EAD-related triggered activity
IV	Ca^{2+} handling modulators[5,16,24,26,27,29]	
Ca^{2+} channel blockers eg, verapamil	Sinus bradycardia; atrioventricular block Increase in ventricular rate in patients with atrial fibrillation with Wolff-Parkinson-White syndrome	Depressing SAN automaticity and atrioventricular node conduction by block of Ca^{2+} channel; decreased accessory pathway

EAD indicates early afterdepolarization.

here by propafenone and flecainide) drugs are useful in preventing supraventricular arrhythmias.[30]

Finally, actions of drugs such as ranolazine, GS-458967, and F15845 in the new Class Id differ sharply from those in Classes Ia through 1c. They inhibit the relatively small but persistent late Na^+ current (I_{NaL}) that follows the principal rapidly inactivating I_{Na} decay and influences AP shape and duration. This increases in acquired or congenital proarrhythmic conditions, including hypoxia, heart failure, and LQTS3. These drugs thus shorten AP recovery and increase refractoriness and repolarization reserve. Both clinical and experimental reports suggest that they have potential antiarrhythmic effects in I_{NaL}-related arrhythmia.[32,81,82] Class Id effects may also contribute to multiple drug actions. This effect is found with mexiletine, originally placed in Class

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Ib, and makes it useful in management of not only LQTS3[78,83,84] but also Timothy syndrome, associated with L-type Ca^{2+} channel abnormality.[85]

EXTENSION OF VAUGHAN WILLIAMS CLASS II

We similarly retain the Vaughan Williams Class II but extend its coverage beyond an updated range of sympathetic β-adrenergic effects to further include parasympathetic targets.[5] This thereby provides more complete coverage of autonomic effects as a whole, including actions through cell surface membrane guanine nucleotide-binding protein (G-protein)–coupled receptors. First, Vaughan Williams would have been aware of the end effects but not the detailed mechanisms of β-adrenergic receptor activation through increased cytosolic $[cAMP]_i$ after successive G_s-protein and adenylate cyclase activation. The increased $[cAMP]_i$ activates protein kinase A, which phosphorylates a wide range of ion channels, including Nav1.5, the K^+ channel species Kv11.1, Kv7.1 (mediating the rapid and slow K^+ currents, I_{Kr} and I_{Ks} respectively), Cav1.2, and Cav1.3 (mediating L-type Ca^{2+} currents), and RyR2. cAMP also exerts a direct influence on hyperpolarization-activated cyclic nucleotide-gated channel activity and consequently on the pacemaking I_f. Finally, exchange proteins directly activated by cAMP have been reported to trigger RyR2-mediated Ca^{2+} release.[19]

These actions together produce multiple inotropic, chronotropic, and lusitropic effects on cardiac function.[33,53] Table 1 places the clinically used nonselective and selective β_1-adrenergic receptor inhibitors carvedilol and propranolol (nonselective) and atenolol (selective), indicated in a wide range of tachyarrhythmias, in Class IIa. These often act through inhibiting Ca^{2+} entry and SR Ca^{2+} release and their consequent proarrhythmic early afterdepolarization– or delayed afterdepolarization–induced triggered activity. The classification also places nonselective β-adrenergic receptor activators, exemplified by isoproterenol, in Class IIb. The latter contrastingly activate Ca^{2+} entry and SR Ca^{2+} release, potentially accentuating proarrhythmic early afterdepolarization–induced triggered activity. However, their chronotropic effects usefully accelerate rates of ventricular escape rhythm in the management of complete atrioventricular block before pacemaker implantation.[34] Such acceleration of depressed heart rates and relief of prolonged postextrasystolic pauses may additionally suppress bradycardia-dependent early afterdepolarizations. Isoproterenol thus exerts antiarrhythmic effects in bradycardia-dependent, drug- or atrioventricular block–related, and possibly congenital LQTS type 2– and LQTS3-related torsades de pointes but proarrhythmic effects in adrenergic dependent or LQTS type 1–related torsades de pointes.[86]

Second, of the large range of further G-protein subtypes, G_i proteins mediate parasympathetic cholinergic muscarinic (M_2) or adenosine (A_1) receptor activation. Their activation and inhibition reduce and increase membrane excitation, respectively, particularly under conditions of preexisting adenylyl cyclase activity, affecting chronotropic and conduction function. Table 1 introduces M_2 inhibitors in the new Class IIc, exemplified by atropine, indicated for relieving sinus bradycardia and supra-His (Table 1), although not degenerative, atrioventricular block at or below the His bundle level (Table 3). Table 1 also illustrates drugs inhibiting G_i exemplified by carbachol and adenosine in new Classes IId and IIe, respectively, while bearing in mind the brief period of intravenous adenosine action and its tendency to produce atrial fibrillation.[87] It also cites an action of aminophylline in adenosine receptor block, useful to treat bradycardia associated with sinus node dysfunction.[88] The latter actions take place in the SAN, AVN, or atrial myocardium even in the absence of sympathetic stimulation but in ventricular tissue take place only after adrenergic activation. Thus, drugs activating G_i are normally effective in SAN, atria, or AVN tachycardias but are effective only in adrenergically stimulated Purkinje or ventricular cells. G_i activation opens inward rectifying I_{KACh} or I_{KAdo} channels mediated by βγ subunits of the G protein, particularly in supraventricular tissue, through actions on their GIRK1 and GIRK4 components.[35,89,90] G_i activation also inhibits adenylyl cyclase, which reduces $[cAMP]_i$; therefore cAMP-associated increases in I_{CaL} and I_f. G_i activation may also upregulate protein phosphatase 2–mediated dephosphorylation at protein kinase A phosphorylation sites on inwardly rectifying K^+ channels, L-type Ca^{2+} channels, RyR2s, phospholamban, troponin subunit cardiac troponin I, and cardiac-type myosin-binding protein C.[36,37] Finally, ≈150 of the large number of additional potential G protein–coupled receptors remain orphan receptors that might offer potential therapeutic targets.

EXTENSION OF VAUGHAN WILLIAMS CLASS III

Much progress has also followed the original Vaughan Williams classification[42] resulting from increased knowledge of K^+ channel subtypes. More is also known about the α and auxiliary β subunits, selective localization of K^+ channels in particular cardiac regions, and roles of these channels in AP recovery and membrane potential stabilization (Figure 1B and Table 1).[35,41] After phase 0 depolarization, complex components of transient inward current (I_{to}) contribute to early rapid phase 1 AP repolarization. These include rapidly activating and inactivating Kv4.3- and Kv4.2-mediated fast inactivating $I_{to,f}$ and Kv1.4-mediated and slowly inactivating $I_{to,s}$, which become activated at potentials of >−30 mV. Atrial myocytes show particu-

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larly prominent I_{to}, and an atrium-specific Kv1.5 (*KCNA5)* mediates ultrarapid I_{Kur}. In addition, there is a 6-fold greater expression of GIRK1 and GIRK4 proteins that mediate I_{KACh}. These multiple K channel contributions together result in the shorter atrial compared with ventricular APs. Kv11.1 (HERG or *KCNH2*) mediating I_{Kr} rapidly activates with phase 0 AP depolarization but then rapidly inactivates over AP phases 0 to 2. The onset of phase 3 repolarization reverses this inactivation, reopening the channel leading to outward phase 3 and early phase 4 currents terminating the AP plateau. The channel responsible for I_{Kr} is more greatly expressed in human ventricular than atrial cardiomyocytes and in left than right canine atrial cardiomyocytes. In contrast, Kv7.1 (*KCNQ1*) mediating I_{Ks} requires depolarization to a more positive potential for activation, which then takes place relatively slowly. I_{Ks} increases over phase 2 to become a major phase 3 K^+ conductance that barely inactivates. It is expressed uniformly in canine atria but at a higher density in epicardial and endocardial cells than M cells and in right ventricular than left ventricular M cells with possible implications for proarrhythmic LQTS.[40,43] Inward rectifying I_{K1}, mediated by Kir2.1, Kir2.2, and Kir2.3 (*KCNJ2*, *KCNJ12*, and *KCNJ4*), reflects reductions in K^+ conductance at membrane potentials more depolarized than ≈–20 mV, as occurs in phases 0 to 2 of the AP. This reduces the net depolarizing inward currents required to maintain the AP plateau phase. In contrast, the K^+ conductance becomes greater when the AP recovers to membrane potentials more hyperpolarized than ≈–40 mV. This results in the increased K^+ outward current, which in turn facilitates late phase 3 AP repolarization. This channel also stabilizes phase 4 diastolic resting potentials. It occurs at a higher density in human ventricular than atrial myocytes.

Finally, the metabolically dependent I_{KATP} is normally small but is activated by reduced intracellular ATP levels when it results in triangulation of AP waveforms.[44] The $K_{2P}2.1$ (*KCNK2*, expressing K_{2P} currents) and the ATP-sensitive Kir6.2 (*KCNJ11)* mediating I_{KATP} show little time or voltage dependence but contribute background currents regulating resting membrane potentials and cell excitability.

The more extensive group of clinical Class III agents now includes wider ranges of voltage-dependent K^+ channel blockers (Class IIIa), including nonselective (ambasilide, amiodarone) and selective (HERG; I_{Kr}; dofetilide, ibutilide, sotalol) Kv11.1, Kv1.5 (I_{Kur}; vernakalant), and $K_V1.4$ and $K_V4.2$, (I_{to1}: tedisamil) blockers, as well as important drugs opening metabolically dependent (Kir6.2: I_{KATP}: nicorandil, pinacidil; Class IIIb) and investigational drugs blocking transmitter-dependent (GIRK1 and GIRK4: I_{KACh}; BMS 914392; Class IIIc) K^+ channels. These may act directly on the channels concerned or involve further indirect effects such as those exemplified by the inhibitory actions of dofetilide on phosphoinositide 3-kinase signaling, in turn inhibiting I_{Kr} and increasing I_{NaL}.[91,92] In addition, a number of agents with multiple actions are included here (Table 2). Amiodarone and dronedarone show diverse actions even at therapeutic concentrations and complex therapeutic and toxicity profiles but find widespread use in managing atrial fibrillation (Table 2). Finally, the significant K^+ channel and therefore Class III actions demonstrated for the original Class Ia agents have been recognized. Thus, although quinidine was originally placed in Class I, its clinical antiarrhythmic effects in Brugada syndrome probably include inhibition of I_{to}.[63] It has been suggested that this involves reductions in the transmural dispersions of ventricular repolarization that arise from the greater epicardial than endocardial expression of I_{to}, which results in the normally shorter epicardial relative to endocardial APDs.[23,64,66] Further examples of agents with such multiple actions are listed in Table 2. Finally, K^+ itself influences K^+ channel permeabilities with important effects on resting membrane potential stability and APD.[23]

EXTENSION OF VAUGHAN WILLIAMS CLASS IV

Much recent physiological progress has broadened the range of drugs included as Vaughan Williams Class IV drugs, originally defined as drugs blocking Ca^{2+} entry through specific Ca^{2+} channels. Here, we have extended Class IV to include drugs with a variety of actions that can be described as Ca^{2+} handling modulators. The L-type voltage-gated Ca^{2+} current (I_{CaL}) emerges with roles in both atrial and ventricular cardiomyocyte function and in AP conduction in the AVN. It thus both contributes to the ventricular and atrial AP plateau phases and initiates excitation-contraction coupling. I_{CaL} brings about an initial cytosolic [Ca^{2+}] elevation that triggers the Ca^{2+}-induced release of SR Ca^{2+} by intracellular RyR2 Ca^{2+} release channels. The resulting further elevations of cytosolic [Ca^{2+}] in turn drive contractile activation. An inositol trisphosphate (IP_3)–triggered Ca^{2+} release that has been implicated in atrial arrhythmia may also exist.

After AP recovery, cytosolic [Ca^{2+}] is returned to resting levels by Ca^{2+} transport from cytosol to SR lumen by phospholamban-regulated SR Ca^{2+}-ATPase[33] and from cytosol to extracellular space by plasma membrane Ca^{2+}-ATPase and by surface membrane ion exchangers, particularly sarcolemmal Na^+/Ca^{2+} exchange.[53] Of these, Na^+/Ca^{2+} exchange involves electrogenic entry of 3 Na^+ for each Ca^{2+} extruded. Depending on the membrane potential and submembrane [Ca^{2+}] that determine the driving forces on Na^+ and Ca^{2+} fluxes, this can exert depolarizing effects.

Activity in a significant proportion of these membrane and cytosolic signaling and Ca^{2+} transport molecules is altered by kinase-mediated phosphorylation and phosphatase-mediated dephosphorylation.[55,56] These opposing processes are in turn modified by cytosolic, often Ca^{2+}-sensing, signaling molecules also offering potential pharmacological targets. Besides protein

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kinases A and C, these include calmodulin and calcium/calmodulin kinase II.[44,50,56,57] Modifications in 1 or more of these processes in turn altering cytosolic [Ca^{2+}] have been implicated in both atrial and ventricular clinical arrhythmias.[51,52] In particular, Na^+/Ca^{2+} exchange exerts electrogenic effects that can increase to become potentially proarrhythmic with cellular Ca^{2+} overload.[5,48]

The central importance of Ca^{2+} homeostasis to cardiac electrophysiological activity with extensive findings after the original Vaughan Williams classification accounts for a wide range of potential applications directed at clinical arrhythmia (Table 1). Besides nonselective (bepridil) and Cav1.2/Cav1.3 (I_{CaL})–selective (verapamil, diltiazem) Ca^{2+} channel blockers (Class IVa), Mg^{2+}, although not strictly falling within the category of a drug, also exerts Ca^{2+} channel blocking and membrane stabilizing effects, with applications in treatment of torsades de pointes. In recent reports, the Class Ic agent flecainide and the Class IIa agent carvedilol show additional Class IVb actions in reducing RyR2-mediated SR Ca^{2+} release. This proved potentially applicable in the management of catecholamine-sensitive polymorphic ventricular tachycardia, whether through reduced triggering activity or reversing associated proarrhythmic reductions in I_{Na}.[93–95] Possible clinical applications of decreasing cardiac myosin heavy chain– or SR Ca^{2+} reuptake–related ATPase activity (Class IVc) have prompted explorations of the investigational new drugs MYK-461[96] and istaroxime[97] in hypertrophic cardiomyopathy and cardiac failure, respectively. Possible applications will also likely emerge from drugs modifying Na^+/Ca^{2+} exchange (Class IVd) and phosphorylation of proteins involving Ca^{2+} homeostasis, including calcium/calmodulin kinase II (Class IVe)[98] (Table III in the online-only Data Supplement).

NEW CLASS V OF DRUGS ACTING ON MECHANOSENSITIVE CHANNELS

Class V is introduced to include mechanosensitive channel blockers. These are selective for cation-selective and mechanosensitive ion channels, particularly transient receptor potential channels (TRPCs) such as TRPC3 or TRPC6. Multiple subclasses of TRPCs exist in the heart, although their functions are only now beginning to emerge. They potentially suppress abnormal ectopic or triggered activity in cardiac conditions such as cardiac hypertrophy and heart failure.[58] A TRPC subclass may regulate the cardiac hypertrophic response. Although TRPCs allow permeation by a range of different cations, their specific biological functions have generally been attributed to Ca^{2+} influx, resulting in signaling within local domains, direct interactions with Ca^{2+}-dependent regulatory proteins, or regulation of cardiac fibroblastic Ca^{2+} signals in arrhythmic hypertrophic and fibrotic heart disease and cardiac failure.[58] Accordingly, inhibition of TRPC-mediated Ca^{2+} influx could potentially both exert direct antiarrhythmic effects and attenuate replacement fibrosis after cardiomyocyte death. Such an approach is being explored with a number of investigational drugs, including ACA [*N*-(p-amylcinnamoy)anthranilic acid], GSK2332255B, GSK2833503A, pyrazole-3, GsMTx4, and SKF 96365 (Table III in the online-only Data Supplement).

NEW CLASS VI OF DRUGS ACTING ON CONNEXIN-ASSOCIATED CHANNELS

AP conduction depends on intercellular local circuit current spread involving gap-junction conductances containing apposed connexin (Cx) hemichannels electrically connecting the intracellular spaces of adjacent cardiomyocytes.[62] This possible therapeutic direction is being investigated with both Cx-blocking and -opening agents, exemplified by carbenoxalone and the peptide analog rotigaptide (ZP-123), respectively, the latter in connection with potential treatments for atrial fibrillation (Table III in the online-only Data Supplement). Of cardiac Cx isoforms, Cx40 occurs in atrial myocytes, AVN, and the Purkinje conduction system. Cx43 occurs in both atrial and ventricular myocytes and the distal conduction system. Cx45 occurs mainly in the SAN, AVN, and Purkinje conducting system. Blocking gap junction conductance or expression, depending on circumstances, can enhance or reduce arrhythmogenicity. Changes in gap junction function can accompany alterations in other AP conduction determinants such as fibrotic change or other remodeling processes in which these are accompanied by altered excitability. Plasticity reducing and lateralizing Cx43 expression occurs in both hypertrophic and dilated ventricular cardiomyopathies.[18,59]

NEW CLASS VII OF DRUGS ACTING ON UPSTREAM MODULATORY TARGETS

The introduction of a Class VII results from the need to encompass tissue structure remodeling processes and their consequently longer-term changes that contrast with the primary preoccupation with the short-term effects of particular drugs on specific ion channels in the original Vaughan Williams classification. In addition, molecular mechanisms influencing longer-term changes upstream of the electrophysiological processes also constitute novel potential therapeutic targets. Fibrotic change is an important accompaniment to postinfarct healing, potentially leading to chronic scar-related arrhythmogenesis, pressure overload,[99] and the development of atrial fibrillation.[47,60,61] It also accompanies some Na^+ channelopathies.[18] Experimental studies have demonstrated that renin-angiotensin-aldosterone inhibitors, omega-3 fatty acids, and statins prevent such electrophysiological and/or structural remodeling.

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These drugs are already available for indications such as hypertension, coronary artery disease, and heart failure, which are some of the most frequent causes of atrial fibrillation. Angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers may be useful in modifying the atrial substrate for primary or secondary prevention, reducing susceptibility to or progression of established atrial fibrillation in the presence of cardiac failure and hypertension. Statin therapy may be useful for the primary prevention of new-onset atrial fibrillation after coronary artery surgery.[25,60,61]

RECAPITULATION

The revised classification of antiarrhythmic drugs presented here summarizes current views of their electrophysiological effects, which are categorized as principal (Table 1), subsidiary (Table 2), and proarrhythmic (Table 3). It represents a pragmatic development of the Vaughan Williams classification (Table I in the online-only Data Supplement). The revised scheme is consistent with clinical actions of therapeutically established drugs (Table 1 and Table II in the online-only Data Supplement) and provides a classification framework for studies of new drugs under investigation (exemplified in Table III in the online-only Data Supplement).

ARTICLE INFORMATION

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Disclosures

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