Modernized Classification of Cardiac Antiarrhythmic Drugs

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 Ca2+ 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.
STATE OF THE ART

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 Ca²⁺ 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 Ca²⁺ channel blockers, reduce heart rate and conduction, acting particularly on the SAN and AVN.²

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.

What Are the Clinical Implications?

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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 1 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...
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 | | | Ivabradine | Stable angina and chronic heart failure with heart rate >70 bpm | Decrease in SAN automaticity |
| | | | IVa | | | |
| | | | Reduction in late Na\(^+\) current | | | |
| | | | \(I_{Na}^{-}\) with increased excitation threshold; slowing of AP conduction in atria, ventricles, and specialized ventricular conduction pathways; concomitant \(I_f\) block increasing APD and ERP; increase in QT intervals | | | |
| | | | Quinidine, ajmaline, disopyramide | | | |
| | | | Supraventricular tachyarrhythmias, particularly recurrent atrial fibrillation; ventricular tachycardia, ventricular fibrillation (including SQTS and Brugada syndrome) | | | |
| | | | Reduction in ectopic ventricular/atrial automaticity | | | |
| | | | Reduction in accessory pathway conduction | | | |
| | | | Increase in refractory period, decreasing reentrant tendency | | | |
| | | | | | | |
| Voltage-gated Na\(^+\) channel blockers | | | | | | |
| I | Nav1.5 open state; intermediate \(=1–10\) seconds dissociation kinetics; often concomitant K\(^+\) channel block | Reduction in peak \(I_{Na}^{-}\), AP generation, and \(dV/dt\) \(\text{max}\) 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 | | Lidocaine, mexiletine | Ventricular tachyarrhythmias (ventricular tachycardia, ventricular fibrillation), particularly after myocardial infarction | | |
| | | | | | | |
| | | | | | | |
| Ic | Nav1.5 inactivated state; slow dissociation \(\geq 10\) seconds | Reduction in peak \(I_{Na}^{-}\), AP generation and \(dV/dt\) \(\text{max}\) 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 | | Propafenone, flecainide | Supraventricular tachyarrhythmias (atrial tachycardia, atrial flutter, atrial fibrillation, and tachycardias involving accessory pathways) | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |
| Id | Nav1.5 late current | Reduction in late Na\(^+\) current \(I_{Na}^{-}\), affecting AP recovery, refractoriness, repolarization reserve, and QT interval | | Ranolazine | Stable angina, ventricular tachycardia As a potential new class of drugs for the management of tachyarrhythmias | | |
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(Continued)
## Table 1. Continued

| Class | Subclass | Pharmacological Targets | Electrophysiological Effects | Examples of Drugs | Major Clinical Applications | Corresponding Likely Therapeutic Mechanism(s) |
|-------|----------|--------------------------|-----------------------------|-------------------|---------------------------|---------------------------------------------|
| IIa   | Nonselective β- and selective β1-adrenergic receptor inhibitors | Inhibition of adrenergically induced G\(_\text{ protein-mediated effects of increased adenyl kinase activity and [cAMP], with effects including slowed SAN pacemaker rate caused by reduced I\(_{\text{CaL}}\), increased AVN conduction time and refactoriness, and decreased SAN pacing and triggered activity resulting from reduced I\(_{\text{CaL}}\), and reduced RyR2-mediated SR Ca\(^{2+}\) release and triggered activity, increase in RR and PR intervals\(^{13}\) | 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 | 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\(^{13,23}\) |
| IIb   | Nonselective β-adrenergic receptor activators | Activation of adrenergically induced G\(_\text{ protein effects of increasing adenyl kinase activity and [cAMP], (see entry above); decrease in RR and PR intervals\(^{23}\) | 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 points\(^{15}\) | Increased escape ventricular automaticity | Suppression of bradycardia-dependent EAD-related triggered activity | Reduction in SAN automaticity | Increase in AVN conduction\(^{12,23}\) |
| 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\(^{26-28}\) | Atropine, anisodamine, hyoscine, scopolamine | Mild or moderate symptomatic sinus bradycardia | Supra-His, AVN, conduction block, eg, in vagal syncope or acute inferior myocardial infarction\(^{16}\) | Increase in SAN automaticity | Increase in AVN conduction\(^{12,23}\) |
| II\(_d\) | Muscarinic M\(_{2}\) receptor activators | Activation of supraventricular (SAN, atrial, AVN) muscarinic M\(_{2}\) cholinergic receptors activates K\(_{\text{ATP}}\) channels, hyperpolarizing the SAN and shortening APDs in atrial and AVN tissue, and reduces [cAMP] and therefore I\(_{\text{CaL}}\), and SAN I\(_{\text{ATP}}\), inhibitory effects on adenyl cyclase and cAMP activation, reducing its stimulatory effects on I\(_{\text{CaL}}\), I\(_{\text{ATP}}\), and I\(_{\text{ATP}}\) in adrenergically activated ventricular tissue; increased RR and PR intervals\(^{26-28}\) | Carboclo, pilocarpine, methacholine, digoxin | Sinus tachycardia or supraventricular tachycardia\(^{24,27}\) | Reduction in SAN automaticity | Reduced SAN reentry | Reduction in AVN conduction, terminating reentry\(^{12,23}\) |
| IIIa  | Adenosine A\(_{1}\) receptor activators | Activation of adenosine A\(_{1}\) receptors in supraventricular tissue (SAN, atrial, AVN) activates G\(_\text{ protein-coupled inward rectifying K\(^{+}\) channels and I\(_{\text{ATP}}\) current, hyperpolarizing the SAN and shortening APDs in atrial and AVN tissue, and reduces [cAMP], and therefore I\(_{\text{CaL}}\), and SAN I\(_{\text{ATP}}\), inhibitory effects on adenyl cyclase and cAMP activation, reducing its stimulatory effects on I\(_{\text{CaL}}\), I\(_{\text{ATP}}\), and I\(_{\text{ATP}}\) in adrenergically activated ventricular tissue; increased RR and increased PR intervals\(^{26}\) | Adenosine, ATP; aminophylline acts as an adenosine receptor inhibitor | Acute termination of AVN tachycardia and cAMP-mediated triggered VFs | Differentiation of sinus from atrial tachycardia\(^{24,27,28}\) | Reduction in SAN automaticity | Reduction in AVN conduction, terminating reentry | Reduction in EAD-/DAD-induced triggered activity | Reduction in AVN conduction, terminating reentry | Reduction in EAD-/DAD-induced triggered activity\(^{12,23}\) |

(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 | 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 intervals²⁵,⁴⁰,⁴¹ | Ambisilide, 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 fibrillation²⁴–²⁷ | 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 2²⁶,²⁹ |
| 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 intervals³⁵,⁴⁰,⁴¹ | Ambisilide, amiodarone, dronedarone | 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 and premature ventricular contraction Tachyarrhythmias associated with supraventricular arrhythmias and atrial fibrillation²⁴–²⁷ | Increase in AP recovery time Increase in refractory period with decreased reentrant tendency²⁶,²⁹,⁴² |
| IIIb | Kir6.2 (Iₖᵣᵤₜ) openers | Opening of ATP-sensitive K⁺ channels (Iₖᵣᵤₜ), shortening AP recovery, refractoriness, and repolarization reserve in all cardiomyocytes apart from SAN cells; shortened QT intervals²⁴–²⁷,⁴¹ | Nicorandil, pinacidil | Nicorandil: treatment of stable angina (second line); pinacidil: investigational drug for the treatment of hypertension | Potential decrease in AP recovery time |
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 | IIc      | GIRK1 and GIRK4 (I_{GIRK}) blockers | Inhibition of direct or G protein  ß₂-subunit-mediated activation of I_{GIRK}, particularly in SAN, AVN, and atrial cells, prolonging APD and ERP and decreasing repolarization reserve⁵⁶,⁶⁶ | Blocker under regulatory review for management of atrial fibrillation: BMS 914392 | Reduction in SAN automaticity⁵⁷ |
| Ca²⁺ handling modulators     | IV       | Nonselective surface membrane Ca²⁺ channel blockers | Block of Ca²⁺ 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 Ca²⁺ signaling; increased PR intervals⁴⁶–⁵⁰ | Bepridil | Angina pectoris Potential management of supraventricular tachyarrhythmias²⁴,²⁷ Reduction in AVN conduction, terminating reentry Reduction in EAD-/DAD-induced triggered activity²⁴,²⁷ |
| Surface membrane Ca²⁺ channel blockers | IVa      | Surface membrane Ca²⁺ channel blockers | Block of Ca²⁺ 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 Ca²⁺ signaling; increased PR intervals⁴⁶–⁵⁰ | Phenyalkylamines (eg, verapamil), benzothiazepines (eg, diltiazem) | Supraventricular arrhythmias and ventricular tachycardia without structural heart disease Rate control of atrial fibrillation²⁴,²⁶,²⁷ |
| Intracellular Ca²⁺ channel blockers | IVb      | SR RyR2-Ca²⁺ channel blockers | Reduced SR Ca²⁺ release: reduced cytosolic and SR [Ca²⁺]³¹,³³,⁴⁶,⁵³ | Flecainide, propafenone | Catecholaminergic polymorphic ventricular tachycardia Reduction in DAD-induced triggered activity²⁴,²⁷ |
| Surface membrane ion exchange inhibitors | IVc      | Sarcoplasmic reticular Ca²⁺ ATPase activators | Increased Ca²⁺-ATPase activity, increased SR [Ca²⁺]³³,⁴⁸,⁵³ | No clinically approved drugs in use |
| Mechanosensitive channel blockers | V        | Transient receptor potential channel (TRPC3/TRPC6) blockers | Intracellular Ca²⁺ signaling¹⁸ Blocker under investigation: N-(p-amylcinnamoyl)anthranilic acid | Reduction in EAD-/DAD-induced triggered activity |

(Continued)
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 importance in long-QT syndrome (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-

| Class | Subclass | Pharmacological Targets | Electrophysiological Effects | Examples of Drugs | Major Clinical Applications | Likely Therapeutic Mechanism(s) |
|-------|----------|------------------------|-------------------------------|-------------------|-----------------------------|----------------------------------|
| VI    | Gap junction channel blockers | 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 | Blocker under investigation: carbenoxolone | Reduction in ventricular/atrial conduction | |
| VII   | Upstream target modulators | Angiotensin-converting enzyme inhibitors | Electrophysiological and structural (fibrotic, hypertrophic, or inflammatory) remodeling | Captopril, enalapril, delapril, ramipril, quinapril, perindopril, lisinopril, benazepril,imidapril, trandolapril, cilazapril | Management of hypertension, symptomatic heart failure | Potential application reducing arrhythmic substrate |
|      |          | Angiotensin receptor blockers | Electrophysiological and structural (fibrotic, hypertrophic, or inflammatory) remodeling | Losartan, candesartan, eprosartan, telmisartan, irbesartan, olmesartan, valsartan, saprisartan | Management of hypertension, symptomatic heart failure | Potential application reducing arrhythmic substrate |
|      |          | Omega-3 fatty acids | Electrophysiological and structural (fibrotic, hypertrophic, or inflammatory) remodeling | 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 | Reduction of structural and electrophysiological remodeling changes that compromise AP conduction and increase reentrant tendency |
|      |          | Statins | Electrophysiological and structural (fibrotic, hypertrophic, or inflammatory) remodeling | Statins | Post–myocardial infarct reduction of risk of cardiac death, myocardial infarct, stroke, and abnormal cardiac rhythms | 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.

Our approach retains but modifies Vaughan Williams Classification 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-
lar targets and cellular physiological mechanisms related to Ca\textsuperscript{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-
Table 2. Examples of Multiple Actions of Cardiac Electrophysiologically Active Drugs

| Class | Drug | Actions |
|-------|------|---------|
| 0     | HCN channel blockers | L, C, K, and Na channels, Ca currents, and KATP channels |
| I     | Disopyramide | Na, Ca, and K channels, adrenergic and cholinergic receptors |
| II    | Diltiazem | Na, Ca, and K channels, adrenergic and cholinergic receptors |
| IIa   | Propranolol | Na, Ca, and K channels, adrenergic and cholinergic receptors |
| IIb   | Lorcainide | Na, Ca, and K channels, adrenergic and cholinergic receptors |
| III   | Lidocaine | Na, Ca, and K channels, adrenergic and cholinergic receptors |
| IV    | Verapamil | Na, Ca, and K channels, adrenergic and cholinergic receptors |

(Continued)
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) or late in the time course of AP repolarization.  

NEW CLASS 0 OF DRUGS ACTING ON SINO-ATRIAL AUTOMATICITY

Detailed characterizations of the properties of SAN cells postdated the original Vaughan Williams classification. 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” ($I_{CaT}$) carried by hyperpolarization-activated cyclic nucleotide-gated channels, particularly during the initial phase of the diastolic depolarization. The only currently clinically adopted Class 0 agent, ivabradine, is used to reduce heart rates in situations of inappropriate sinus tachycardia or when sinus tachycardia accompanies cardiac failure. It likely acts through hyperpolarization-activated cyclic nucleotide-gated channel block, with possible additional effects on intracellular Ca$^{2+}$ cycling. 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 ($I_{NaP}$), T- and L-type Ca$^{2+}$ currents ($I_{CaL}$ and $I_{CaT}$), and possibly sustained inward current ($I_n$). 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. 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 and Purkinje cell diastolic depolarization.

EXTENSION OF VAUGHAN WILLIAMS CLASS I

Our revised classification system retains the 3 original Class I subcategories listing cardiac Na$^+$ channel (Na1.5) blockers. However, it incorporates recent biophysical findings bearing on gating transitions regulated by voltage sensing components of Nav1.5 (Table 1). 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. 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. Nevertheless, we retain their original Class Ia subclassification as Na$^+$ channel blockers, with all drugs in Classes Ia through Ic 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 ($\tau$) of $\approx$ 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 $\tau$ of $\approx$ 0.1 to 1.0 second. This minimizes perturbations of processes in the remaining cardiac cycle and explains the effectiveness of Class Ib 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 but cause prolongation of ERP and consequently prolongation of postrepolarization refractoriness in ischemic, partially depolarized, cells. Class Ic drugs similarly bind to the inactivated Nav1.5, from which, however, they dissociate more slowly, over $\tau$ $>\approx$ 10 seconds. Use-dependent channel block in Classes Ia through Ic arises from accumulation of blocked channels during repetitive stimulation at high frequencies and accordingly occurs to extents in the sequence Class Ic $>$ Class Ib $>$ Class Ia. 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.
is thus antiarrhythmic, with the compromised AP recovery, gain of Na$^+$ channel function, and increased $I_{\text{NaL}}$ in both clinical LQTS3 and genetically modified murine Scn5a$^{+/\Delta kpq}$ hearts experimentally modeling this condition. In contrast, flecainide was clinically proarrhythmic under conditions of compromised postinfarct AP generation and propagation (Table 3$^{20}$ and the Brugada syndrome and in murine Scn5a$^{+/\Delta kpq}$ 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 Ib (exemplified...
here by propafenone and flecainide) drugs are useful in preventing supraventricular arrhythmias. 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 proarhythmic 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

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

| Class | Arrhythmia | Likely Mechanisms |
|-------|------------|-------------------|
| 0     | Hyperpolarization-activated cyclic nucleotide-gated channel blockers | Depressing sinus node automaticity by block of I_{f} |
| I     | 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 | EAD-related triggered activity |
|      | 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 | 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 inhibitors | 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 | Torsades de pointes with prolonged QT interval | EAD-related triggered activity |
| IV    | Ca2+ handling modulators | 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 Ca2+ channel; decreased accessory pathway |

EAD indicates early afterdepolarization.
Ca\textsuperscript{2+} entry and SR Ca\textsuperscript{2+} release and their consequent (selective), indicated in a wide range of tachyarrhythmias, with carvedilol and propranolol (nonselective) and atenolol (selective), but not the detailed mechanisms of β-adrenergic receptor activation through increased cytosolic [cAMP] after successive G\textsubscript{protein}–protein and adenylate cyclase activation. The increased [cAMP] activates protein kinase A, which phosphorylates a wide range of ion channels, including Nav1.5, the K\textsuperscript{+} channel species Kv11.1, Kv7.1 (mediating the rapid and slow K\textsuperscript{+} currents, I\textsubscript{sc} and I\textsubscript{s} respectively), Cav1.2, and Cav1.3 (mediating L-type Ca\textsuperscript{2+} currents), and RyR2. cAMP also exerts a direct influence on hyperpolarization-activated cyclic nucleotide-gated channel activity and consequently on the pacemaking I\textsubscript{f}. Finally, exchange proteins directly activated by cAMP have been reported to trigger RyR2-mediated Ca\textsuperscript{2+} release.\textsuperscript{19}

These actions together produce multiple inotropic, chronotropic, and lusitropic effects on cardiac function.\textsuperscript{33,53} Table 1 places the clinically used nonselective and selective β\textsubscript{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\textsuperscript{2+} entry and SR Ca\textsuperscript{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\textsuperscript{2+} entry and SR Ca\textsuperscript{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.\textsuperscript{64} 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 LQT53-related torsades de pointes but proarrhythmic effects in adrenergic dependent or LQTS type 1–related torsades de pointes.\textsuperscript{86}

Second, of the large range of further G-protein subtypes, G\textsubscript{i} proteins mediate parasympathetic cholinergic muscarinic (M\textsubscript{j}) or adenosine (A\textsubscript{1}) receptor activation. Their activation and inhibition reduce and increase membrane excitation, respectively, particularly under conditions of preexisting adenyl cyclase activity, affecting chronotropic and conduction function. Table 1 introduces M\textsubscript{i} 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\textsubscript{i} exemplified by carbachol and adenosine in new Classes IIId and IIe, respectively, while bearing in mind the brief period of intravenous adenosine action and its tendency to produce atrial fibrillation.\textsuperscript{87} It also cites an action of aminophylline in adenosine receptor block, useful to treat bradycardia associated with sinus node dysfunction.\textsuperscript{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\textsubscript{i} are normally effective in SAN, atria, or AVN tachycardias but are effective only in adrenergically stimulated Purkinje or ventricular cells. G\textsubscript{i} activation opens inward rectifying I\textsubscript{Ks} and I\textsubscript{Ado} channels mediated by β\textsubscript{2} subunits of the G protein, particularly in supraventricular tissue, through actions on their GIRK1 and GIRK4 components.\textsuperscript{35,89,90} G\textsubscript{i} activation also inhibits adenylyl cyclase, which reduces [cAMP]; therefore cAMP-associated increases in I\textsubscript{CAch} and I\textsubscript{Ado} channels may also upregulate protein phosphatase 2–mediated dephosphorylation at protein kinase A phosphorylation sites on inwardly rectifying K\textsuperscript{+} channels, L-type Ca\textsuperscript{2+} channels, RyR2s, phospholamban, troponin subunit cardiac troponin I, and cardiac-type myosin-binding protein C.\textsuperscript{36,37} Finally, \approx 150 of the large number of additional potential G–protein–coupled receptors remain orphan receptors that might offer potential therapeutic targets.
larly prominent \( I_{Kr} \) and an atrium-specific \( \text{Kv}1.5 \) (KCNA5) mediates ultrarapid \( I_{Kur} \). In addition, there is a 6-fold greater expression of GIRK1 and GIRK4 proteins that mediate \( I_{KATP} \). These multiple K channel contributions together result in the shorter atrial compared with ventricular APs. \( \text{Kv}11.1 \) (HERG or KCNHI2) 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, \( \text{Kv}7.1 \) (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+ conductive Kir6.2 (\( \text{KCNJ11} \)) mediating \( I_{K_{ATP}} \), Kir2.1, Kir2.2, and Kir2.3 (transmitter-dependent (GIRK1 and GIRK4: pinacidil; Class IIIb) and investigational drugs blocking sotalol) \( I_{Kv11.1} \), \( I_{Kv1.5} \) (\( \text{KCNA5} \)) mediating \( I_{Kur} \); vernakalant), and \( I_{KV4.2} \), (\( \text{KCNQ1} \)) mediating \( I_{K_{ATP}} \). These multiple K channel contributions together result in the shorter atrial compared with ventricular APs. \( \text{Kv}11.1 \) (HERG or \( \text{KCNH2} \)) mediating \( I_{K_{ATP}} \) and \( I_{K_{UR}} \) mediate ultrarapid and long-lasting inward K+ currents, respectively, but contribute background currents regulating resting membrane potentials and cell excitability.

The \( I_{K_{ATP}} \) channel blockers (Class IIIa), including nonselective (ambisilide, amiodarone) and selective (\( \text{HERG} \); \( \text{Kv}11.1 \), \( \text{Kv}12.1 \) (\( \text{KCNR2} \), \( \text{KCNR12} \), and \( \text{KCNR4} \)), reflects reductions in K+ conductance at more depolarized potentials than \( \approx -20 \text{ mV} \), 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 \( \approx -40 \text{ mV} \). 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 \( I_{K_{ATP}} \) is normally small but is activated by reduced intracellular ATP levels when it results in triangulation of AP waveforms. The \( I_{K_{ATP}} \) channel blockers (Class IIIa), including nonselective (ambisilide, amiodarone) and selective (\( \text{HERG} \); \( \text{Kv}11.1 \), \( \text{Kv}12.1 \) (\( \text{KCNR2} \), \( \text{KCNR12} \), and \( \text{KCNR4} \)), reflects reductions in K+ conductance at more depolarized potentials than \( \approx -20 \text{ mV} \), 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 \( \approx -40 \text{ mV} \). 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.

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 \( I_{Kr} \). 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 \( I_{Kr} \), which results in the normally shorter epicardial relative to endocardial APDs. 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.

**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 Ca2+ entry through specific Ca2+ channels. Here, we have extended Class IV to include drugs with a variety of actions that can be described as Ca2+ handling modulators. The L-type voltage-gated Ca2+ current (\( I_{CaL} \)) emerges with about an initial cytosolic [Ca2+] elevation that triggers the Ca2+-induced release of SR Ca2+ by intracellular RyR2 Ca2+ release channels. The resulting further elevations of cytosolic [Ca2+] in turn drive contractile activation. An inositol triphosphate (IP3)–triggered Ca2+ release that has been implicated in atrial arrhythmia may also exist.

After AP recovery, cytosolic Ca2+ is returned to resting levels by Ca2+ transport from cytosol to SR lumen by phospholamban-regulated SR Ca2+-ATPase and from cytosol to extracellular space by plasma membrane Ca2+-ATPase and by surface membrane ion exchangers, particularly sarcolemmal Na+/Ca2+ exchange. These Ca2+-Ca2+ exchange involves electrogenic entry of 3 Na+ for each Ca2+ extruded. Depending on the membrane potential and submembrane [Ca2+] that determine the driving forces on Na+ and Ca2+ fluxes, this can exert depolarizing effects. Activity in a significant proportion of these membrane and cytosolic signaling and Ca2+ transport molecules is altered by kinase-mediated phosphorylation and phosphatase-mediated dephosphorylation. These opposing processes are in turn modified by cytosolic, often Ca2+-sensing, signaling molecules also offering potential pharmacological targets. Besides protein...
kinases A and C, these include calmodulin and calcium/calmodulin kinase II. Modifications in 1 or more of these processes in turn altering cytosolic [Ca\(^{2+}\)] have been implicated in both atrial and ventricular clinical arrhythmias. In particular, Na\(^+/Ca\(^{2+}\) exchange exerts electrogenic effects that can increase to become potentially proarrhythmic with cellular Ca\(^{2+}\) overload.

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\(_{\text{CaL}}\))–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\(_{\text{Na}}\). 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 and istaroxime 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) (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. 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. Accordingly, inhibition of TRPC-mediating Ca\(^{2+}\) influx could potentially both exert direct arrhythmogenic effects and attenuate replacement fibrosis after cardiomyocyte death. Such an approach is being explored with a number of investigational drugs, including ACA [N-(p-amylcinnamoyl)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. 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.

### 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, and the development of atrial fibrillation. It also accompanies some Na\(^{+}\) channelopathies. 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**

The online-only Data Supplement is available with this article at https://www.ahajournals.org/doi/suppl/10.1161/circulationaha.118.035455.

**Correspondence**

Ming Lei, BM, MSc, DPhil, Department of Pharmacology, University of Oxford, Mansfield Rd, Oxford OX1 3QT, United Kingdom. Email ming.lei@pharm.ox.ac.uk or Christopher L.-H. Huang, MA, BMBCh, DM, DSc, PhD, MD, ScD, Physiological Laboratory, University of Cambridge, Cambridge CB2 3EG, United Kingdom. Email chl11@cam.ac.uk.

**Affiliations**

Department of Pharmacology, University of Oxford, United Kingdom (M.L., D.A.T.). Department of Cardiology, Peking University First Hospital, Beijing, China (L.W.). Physiological Laboratory (C.L.-H.) and Department of Biochemistry (C.L.-H.H.). University of Cambridge, United Kingdom. Key Laboratory of Medical Electrophysiology of the Ministry of Education and Institute of Cardiovascular Research, Southwest Medical University, Luzhou, China (M.L., L.W.).

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