

***The modernized classification of cardiac anti-arrhythmic drugs: its application to clinical practice***

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Short title: *Classification of anti-arrhythmic drugs.*

Key words: Miles Vaughan Williams, anti-arrhythmic drugs, cardiac arrhythmias, ion channels, Ca<sup>2+</sup> homeostasis.

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## *Abstract*

Cardiac arrhythmias pose a major public health problem and pharmacological intervention remains key to their therapy. The landmark Vaughan Williams (VW, 1970) classification utilizing known actions of then available anti-arrhythmic drugs (AADs) became and remains central to management, but requires revision in response to extensive subsequent advances. Our modernized antiarrhythmic drug (AAD) classification reflected and sought to facilitate such fundamental physiological and clinical development. We here respond to requests for an adaptation of our scheme specifically focussed at clinical practice. This adaptation: (1) improves accessibility of our original scheme to clinical practice, focussing on key AADs in clinical use rather than investigational new drugs (INDs) whilst still conserving and encompassing the classic VW scheme. We nevertheless (2) preserve a rational conceptual framework based on current understanding of the relevant electrophysiological events, their underlying cellular or molecular cardiomyocyte targets and the functional mechanisms they mediate. Additionally, (3) the adopted subclasses within each AAD class parallel clinical practice in including only subclasses containing established AADs, or approved potential off-label drugs, as opposed to those only including INDs. Finally, (4) the simplified scheme remains flexible, permitting drugs to be placed in multiple classes where required, and the future addition of classes and subclasses in the light of future investigations and clinical approvals. We thus derive from our comprehensive modernized AAD classification a more focussed and simpler scheme, for clinical use. This both modernizes but preserves the classic Vaughan Williams classification, and remains flexible accommodating for future developments.

(246 words)

## ***Anti-arrhythmic drug classification in clinical practice***

Cardiac arrhythmias pose a major public health problem and pharmacological intervention remains the mainstay of anti-arrhythmic therapy. Miles Vaughan Williams (VW) <sup>1,2</sup> had first proposed a landmark classification of cardiac anti-arrhythmic drugs based on their then established electrophysiological and pharmacological actions on cardiac action potential (AP) components and their relationship to arrhythmias<sup>1,2</sup>. Its effectiveness resulted in his approach becoming and remaining central to clinical management to the present. However, substantial subsequent progress in new therapeutic agents created requirements for revised classification schemes. In response to this we introduced in 2018 a modernized classification of antiarrhythmic drugs (AADs, Fig. 1A) in order to facilitate both clinical practice and drug discovery <sup>3</sup>. Given the desirability of enhancing its clinical usefulness, we here simplify that modernized scheme to a form specifically focussed at clinical practice. We have nevertheless continued to utilize its organization of drug classes and subclasses, as well as including some updates of subsequent progress in AAD development.

### ***A more focussed AAD classification***

First, ***a simplified classification should improve the accessibility of our scheme to clinical practice.*** We now focus on key drugs in clinical rather than investigational use. We emphasize that the drug classes in both this current 2025 and the initial 2018 versions (Fig. 1A) utilized, and encompassed drugs and drug targets within, the VW scheme (Fig. 1Ab), extended to include subsequently approved anti-arrhythmic (AAD)(Fig. 1Aa,b), potential off-label (Fig. 1Ad) and investigational new drugs (INDs) (Fig. 1Ac). Thus, the retained Class I contains drugs producing moderate (Ia), weak (Ib) or marked (Ic) Na<sup>+</sup> channel (Nav1.5) block. They reduce action potential (AP) phase 0 slope and overshoot, whilst respectively increasing, reducing or conserving AP durations (APD) and effective refractory periods (ERP)<sup>4</sup>. This was extended to include particular delayed Na<sup>+</sup> current ( $I_{NaL}$ ) components. Class II, originally grouping  $\beta$ -adrenergic inhibitors reducing sino-atrial node (SAN) pacing rates and slowing atrioventricular node (AVN) AP conduction<sup>4,5</sup>, was extended by incorporating the extensive advances in our understanding of autonomic, often G-protein-mediated, signalling. Extension of Class III comprising K<sup>+</sup> channel blockers delaying AP phase 3 repolarisation and lengthening ERP, reflected the more recent discoveries of numerous novel K<sup>+</sup> channel subspecies. Class IV, comprising Ca<sup>2+</sup> channel blockers, reducing cardiac rate and conduction, acting particularly on the SAN and AVN<sup>2</sup> was extended by major progress in our understanding of novel molecular targets related to Ca<sup>2+</sup> homeostasis.

Our modernized classification scheme then added four entirely distinct new drug classes reflecting additional drug targets. The latter included channels involved in sino-atrial node (SAN) automaticity (Class 0),

mechanically sensitive ion channels (Class V), connexins controlling electrotonic cell coupling (Class VI), and molecules underlying longer term signalling processes affecting structural remodelling (Class VII). The resulting more comprehensive listing included both approved drugs relevant to current clinical practice (Fig. 1Aabd) and INDs relevant only to drug discovery (Fig. 1Ac). In contrast, our first step in adapting our classification scheme defines two major categories, Classes I-IV and the new classes 0 and VII focussed on clinical practice, and Classes V and VI currently only containing INDs.

### *A mechanistic basis for classification*

Second, *the resulting simplified scheme nevertheless preserves a rational framework related to our understanding of arrhythmic pathophysiology*. Arrhythmic events arise from abnormalities in AP generation, recovery or refractoriness at the cellular, and in conduction at the systems level. Our revised categories (Fig. 1A) bear on on electrophysiological events (Fig. 1B) reflecting strategic cellular or molecular cardiomyocyte targets within a simple but nevertheless complete cellular model (Fig. 1C) underlying functional mechanisms for the abnormalities contributing to cardiac arrhythmogenesis (Fig. 1D). These form the basis of the systems level events in cardiac excitation beginning with its SAN initiation, and the consequent AP conduction through successive atrial, AV and Purkinje conducting tissue, and ventricular myocardium (Fig. 1B). The classes 0, I, III and IV respectively target surface hyperpolarisation-activated cyclic nucleotide-gated (HCN), voltage-sensitive  $\text{Na}^+$ , the different  $\text{K}^+$  channel species, and  $\text{Ca}^{2+}$  channels. These primarily mediate SAN pacing, cardiomyocyte excitation and its propagation through both conducting and contractile tissue, recovery from such excitation including refractoriness, and action potential plateau phases respectively. All these affect the stability of action potential kinetics or its propagation. Thus the  $\text{Na}^+$  channel initiates the excitation AP waveform and is an important determinant of its refractoriness, at the cellular level, and determines AP conduction velocity, at the tissue level. The  $\text{K}^+$  and  $\text{Ca}^{2+}$  channels importantly determine AP recovery quantified by its duration, APD, and thereby influence the effective refractory period, ERP, following excitation. Abnormalities in these features bear both on the initiation, through triggering events, and the maintenance of cardiac arrhythmia, through re-entrant excitation activity. Electrophysiological events thereby constitute the final common pathway through which arrhythmias occur. The remaining classes then address their modulating factors. Additional, Class IV targets trigger ryanodine receptor (RyR) mediated intracellularly stored  $\text{Ca}^{2+}$  release into the cytosol actually initiating cardiac mechanical activity, and its re uptake, and the regulatory effects of  $\text{Ca}^{2+}$  itself on the remaining processes. Class II targets modulate a large proportion of these functions through G-protein coupled mechanisms, often exogenously through sympathetic and parasympathetic autonomic actions. Class VII concerns upstream mechanisms modulating long term, but ultimately potentially arrhythmogenic, cardiac remodeling changes often involving pathological hypertrophic and fibrotic events, affecting the velocity and orderliness with which excitation is propagated.

### *A more focussed listing of drug subclasses*

Thirdly, *the adopted subclasses within each AAD class parallel those available in clinical practice*. Our adaptation adopted only those subclasses containing AADs, or approved potential off-label drugs, whilst retaining subclasses with newly discovered AADs, as opposed to those only including INDs. Table 1 exemplifies established clinically utilized AADs in these subclasses. The new Class 0 contains a single subclass of drugs acting on hyperpolarisation-activated cyclic nucleotide-gated (HCN) channels, blocking  $I_f$  current, important in SAN pacemaking, particularly during the initial diastolic depolarisation<sup>6-8</sup>, and in SAN and AVN pacemaker cells. The HCN channel also occurs in ventricular Purkinje fibers and possibly other potentially spontaneously active cells. Its current single exemplar, ivabradine, is employed to reduce inappropriate sinus tachycardia<sup>9,10</sup>, or where sinus tachycardia accompanies heart failure<sup>11</sup>.

There are significant additional subclasses since the original VW classification in Class II, as this is broadened to encompass significant progress in cell surface membrane guanine nucleotide-binding protein (G-protein) coupled receptor (GPCR) physiology. Beyond updating the selective and nonselective sympathetic  $\beta$ -adrenergic agents, dependent upon adenylyl cyclase signaling, are further, including parasympathetic and adenosine ( $A_1$ ) receptor, targets.  $G_i$  activation liberating through its  $\beta\gamma$  subunits opens inward rectifying  $I_{K_{ACh}}$  or  $I_{K_{Ado}}$  channels particularly in supraventricular tissue, through acting on their GIRK1 and GIRK4 components<sup>12-14</sup>. It also inhibits adenylyl cyclase and therefore cAMP-associated increases in  $I_{CaL}$  and  $I_f$ . Parasympathetic cholinergic muscarinic ( $M_2$ ) or adenosine ( $A_1$ ) receptor activation<sup>15</sup> thereby reduces membrane excitation. It acts on SAN, AVN or atrial myocardium even in the absence, and on ventricular tissue only following, adrenergic-induced adenylyl cyclase activity. The corresponding drugs are then effective in SAN, atria or AVN tachycardias but only in adrenergically stimulated Purkinje or ventricular cells.

Expanded subclasses in Class III reflect extensive developments of novel clinical  $K^+$  channel blockers or openers. These include nonselective and selective  $Kv11.1$  (HERG;  $I_{Kr}$ ),  $Kv1.5$  ( $I_{Kur}$ ) and,  $Kv1.4$  and  $Kv4.2$ , ( $I_{to1}$ ) blockers as well as drugs opening metabolically-dependent ( $Kir6.2$ :  $I_{KATP}$ )  $K^+$  channels. Besides direct actions on their target channels, these could work via indirect effects. For example; dofetilide influences phosphoinositide 3-kinase signaling in turn inhibiting  $I_{Kr}$  and increases the prolonged  $I_{NaL}$ <sup>16,17</sup>. Even therapeutic amiodarone and dronedarone concentrations show diverse actions and complex therapeutic and toxicity profiles whilst remaining useful in managing atrial fibrillation. New Class IV subclasses reflect extensive findings subsequent to the VW classification bearing on the central importance of  $Ca^{2+}$  homeostasis in cardiac electrophysiological function and corresponding developments in drugs modulating  $Ca^{2+}$  handling. Besides the nonselective, there are the specific, phenylalkylamine, benzothiazepine, Cav1.2/Cav1.3, ( $I_{CaL}$ )-selective  $Ca^{2+}$  channel blockers. The class Ic agent flecainide and the class IIa agent carvedilol additionally

reduced RyR2-mediated SR  $\text{Ca}^{2+}$  release potentially applicable in catecholamine sensitive polymorphic VT (CPVT), either through reduced triggering activity, or reversing associated pro-arrhythmic reductions in  $I_{\text{Na}}$ <sup>18-20</sup>.

Of the further, new drug classes, Class VII includes potential off-label drugs acting on and used to treat longer term upstream changes that have proven to exert pro-arrhythmic effects. These drugs were initially introduced for indications such as hypertension, coronary artery disease, and heart failure which are some of the most frequent causes of atrial fibrillation. Such upstream therapies were initially hypothesized to modify atrial substrate and prevent arrhythmogenic remodeling. The fibrotic change accompanying post-infarct healing has been associated with chronic scar-related arrhythmogenesis, pressure overload<sup>21</sup>, and to development of atrial fibrillation (AF)<sup>22-24</sup>. Experimental evidence suggests that renin-angiotensin-aldosterone inhibitors, omega-3 fatty acids and 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors (statins) prevent such electrophysiological and/or structural remodelling. Angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARB) may modify the atrial substrate underlying susceptibility to, or progression of, established, AF, in cardiac failure and hypertension. Statin therapy may be useful to prevent new-onset AF following coronary artery surgery<sup>22,24,25</sup>. However, large-scale clinical trials have failed to demonstrate efficacy of these upstream agents in primary or secondary prevention of atrial fibrillation, prompting AHA/ACC/HRS (2014) and ESC AF (2020) guidelines stating no benefit for AF prevention in patients without cardiovascular disease. Nevertheless, paralleling experimental reports<sup>26 27</sup>, recent clinical evidence suggests that sodium-glucose cotransporter-2 inhibitors (SGLT2i), reduced AF recurrences following ablation<sup>28</sup>, even if not its primary occurrence, in diabetes mellitus patients<sup>29</sup>. These add to their indications for diabetes mellitus and associated heart failure, and raise broader possibilities of future effective novel upstream therapies<sup>30</sup>.

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#### ***Possibilities for future developments in the AAD classification scheme***

Fourthly, ***in common with the initial modernized scheme, its simplified scheme remains flexible for future advances and developments.*** It allows addition of future classes and subclasses in the light of future IND investigations and approvals for clinical use. It also permits drugs to be accommodated in multiple classes where required. Between drug classes, increasing evidence demonstrates that significant numbers of existing AADs act on more than one target (Table 2 of ref<sup>3</sup>), with potentially positive or negative clinical implications (Table 3 of ref<sup>3</sup>). Within the original class Ia, quinidine's anti-arrhythmic effects in Brugada Syndrome, likely involves an additional  $I_{\text{to}}$  inhibition<sup>31</sup>. The latter reduces the transmural dispersion of ventricular repolarisation arising from higher epicardial than endocardial  $I_{\text{to}}$  expression. This shortens epicardial relative to endocardial

APD<sup>32-34</sup>. The class Ic agent flecainide and class IIa agent carvedilol additionally show Class IV effects reducing RyR2-mediated SR Ca<sup>2+</sup> release, potentially beneficial in CPVT, through reduced triggering activity, or reversed pro-arrhythmic reductions in  $I_{Na}$ <sup>18-20</sup>. Vernakalant, is flagged in Table 1 as an anti-arrhythmic Class III atrial  $I_{Kur}$  blocker restoring AF to sinus rhythm. But it also acts, albeit at higher IC<sub>50</sub>, on other,  $I_{KACH}$ ,  $I_{to}$  and  $I_{Kr}$ , K<sup>+</sup><sup>35</sup>, and Na<sup>+</sup> currents<sup>36</sup>. Similarly whereas orally administered amiodarone exerts a principal Class III inhibition of  $I_{Kr}$ , intravenous administration has been experimentally associated with Class I, II and IV effects<sup>37,38,39</sup>

Finally the scheme allows for the inclusion of off-label applications. For example, the  $I_{KATP}$  channel opener nicorandil is normally indicated for prophylaxis/treatment of stable angina associated with coronary artery microvascular disease, but has possible off-label applications in shortening QT interval<sup>40</sup>. Similarly, while originally indicated for management of chronic angina, ranolazine, whether in combination or as monotherapy, has proven effective at preventing atrial fibrillation<sup>41,42</sup>. Its action on  $I_{NaL}$  is also potentially useful when used in combination with other drugs such as dofetilide whose chronic use has been reported to increase such late currents with potential pro-arrhythmic effects<sup>43</sup>. This may prove potentially useful also in developing management protocols in emerging compounds. The Class III ibutilide whilst converting acute atrial flutter and fibrillation to sinus rhythm, and offering potential off label pre- and post-electrocardioversion applications has similarly been reported experimentally to similarly activate slow inward currents<sup>44</sup>.

The classes V and VI contain no AADs in current clinical use. Class V includes mechanosensitive channel blockers particularly transient receptor potential channels (TRPCs) such as TRPC3 or TRPC6. The heart expresses multiple TRPC subclasses exist in the heart whose functions are only now beginning to emerge. TRPCs are permeable to a range of cations, but their particular effects may primarily arise from Ca<sup>2+</sup> influx and consequent cardiomyocyte signalling, possibly through Ca<sup>2+</sup>-dependent regulatory proteins. Despite no AADs being currently approved, when available these could potentially be useful in suppressing abnormal ectopic or triggered activity in, and alleviating, pro-arrhythmic hypertrophic and fibrotic heart disease and cardiac failure<sup>45</sup>. INDs following this paradigm include ACA (N-(p-aminocinnamoyl)anthranilic acid)), GSK2332255B, GSK2833503A, Pyrazole-3 (Pyr3), GsMTx4, and SKF 96365. Similarly, still no AADs exist in Class VI directed at connexin-associated channels. However, AP conduction depends upon intercellular gap-junction conductances intervening between adjacent cardiomyocytes<sup>46</sup>. Connexin isoform Cx40 occurs in atrial myocytes, AVN and Purkinje conduction systems, Cx43 in atrial and ventricular myocytes and distal conduction tissue, and Cx45 in the SAN, AVN and Purkinje conducting system. Both hypertrophic and dilated

ventricular cardiomyopathies are associated with reduced and lateralised Cx43 expression<sup>47</sup>. Although there are no current approved drugs, connexin-blocking and -opening INDs under investigation, including carbenoxalone and the peptide analogue rotigaptide (ZP-123) hold promise, the latter potentially useful for atrial fibrillation.

Of possible new drug subclasses and individual new drugs within existing subclasses, new agents with *Class 0* actions, besides  $I_f$ -specific drugs, could act on other channels also contributing to SA pacing<sup>48, 7,49,50</sup>. New *Class II* agents could arise from the large numbers of additional, potentially participating, as yet unexplored GPCRs. In *Class III* there have already been significant advances in  $K^+$  channel targetting. In *Class IV*, the numerous relatively unexplored  $Ca^{2+}$  homeostatic targets include RyR2 and possibly inositol trisphosphate ( $IP_3$ ) receptor SR  $Ca^{2+}$  release channels<sup>51</sup>, PLN-regulated SR  $Ca^{2+}$ -ATPase (SERCA2a)<sup>52,53</sup>, sarcolemmal electrogenic  $Na^+/Ca^{2+}$  exchange<sup>15,54</sup> and  $Ca^{2+}$ -ATPase<sup>55</sup> transporters. These offer further cytosolic signaling targets, including PKA, PKC, calmodulin (CaM) and calcium/calmodulin kinase II (CaMKII)<sup>56-59</sup>, and their regulation by kinase-mediated phosphorylation and phosphatase-mediated dephosphorylation<sup>57,60-62</sup>. Besides their actions on contractile cells, intracellular  $Ca^{2+}$  and cAMP could modify RyR2 and  $Na^+$ - $Ca^{2+}$  exchanger driven “ $Ca^{2+}$  clock” contribute to SAN pacing<sup>7,63,64</sup>.”

## ***Conclusion***

We derive from our comprehensive modernized AAD classification a more focussed simpler scheme, similarly encompassing the classic Vaughan Williams classification. In addition to categorising therapeutically established drugs, their clinical indications, and their therapeutic mechanisms of action it retains flexibility for including future INDs as they become approved for clinical therapy.

## **ACKNOWLEDGEMENTS.**

Our work is supported by the British Heart Foundation (BHF) (PG/21/10512, PG/22/11217, PG/23/11479, and PG/19/59/34582 and the BHF Centre for Research Excellence (CRE) at Cambridge, CLHH, PG/14/80/31106, PG/16/67/32340, PG/12/21/29473, PG/11/59/29004 and the BHF CRE at Oxford, ML RE/18/3/34214).

## **CONFLICTS OF INTEREST**

None declared



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Tables.

Table 1. Drug exemplars within drug subclasses in the modernized classification of anti-arrhythmic drugs.

<b>Class 0</b> <i>Pacemaker channel blockers</i>	<b>HCN channel blockers:</b> <i>ivabradine</i>
<b>Class I: Na<sup>+</sup> channel blockers</b>	<b>Ia:</b> quinidine, procainamide, disopyramide, ajmaline, hydroquinidine <b>Ib:</b> lidocaine, mexiletine, phenytoin <b>Ic:</b> flecainide, propafenone, moricizine* <b>Id:</b> <i>ranolazine</i>
<b>Class II: G-protein signaling modulators</b>	<b>Nonselective β1 blockers:</b> propranolol, nadolol, carvedilol <b>Selective β1 blockers:</b> metoprolol, bisoprolol, esmolol, atenolol <b>β Activators:</b> isoproterenol, adrenaline <b>Adenosine receptor activators:</b> adenosine <b>M receptor inhibitors:</b> atropine
<b>Class III: K<sup>+</sup> channel modulators</b>	<b>Nonselective K<sup>+</sup> channel blockers:</b> amiodarone, dronedarone <b>K<sub>v</sub>11.1 (HERG; I<sub>Kr</sub>) blockers:</b> dofetilide, d/l-sotalol, ibutilide‡ <b>K<sub>v</sub>1.5 (I<sub>Kur</sub>) blockers:</b> vernakalant† <b>K<sub>v</sub>1.4 and K<sub>v</sub>4.2 (I<sub>to1</sub>) blockers:</b> quinidine <b>Kir6.2 (Metabolically dependent K<sup>+</sup> channel) activators:</b> <i>nicorandil</i> †, <i>pinacidil</i> ‡
<b>Class IV: Ca<sup>2+</sup> handling modulators</b>	<b>Nonselective Ca<sup>2+</sup> channel blockers:</b> bepridil <b>Ca<sub>v</sub>1.2 and Ca<sub>v</sub>1.3 (L-type Ca<sup>2+</sup> channel) blockers:</b> phenylalkylamines (e.g. verapamil); benzothiazepines (e.g. diltiazem) <b>RyR2 (ryanodine receptor) blockers:</b> flecainide, carvedilol, <i>dantrolene</i>
<b>Class V: Mechanosensitive channel blockers</b>	No approved drugs
<b>Class VI: Gap junction channel blockers</b>	No approved drugs
<b>Class VII: Upstream target modulators</b>	<b>Angiotensin-converting enzyme inhibitors:</b> <i>captopril, enalapril, ramipril, lisinopril, quinapril</i> <b>Angiotensin receptor blockers:</b> <i>losartan, valsartan, telmisartan, irbesartan, olmesartan, candesartan</i> <b>Omega-3 fatty acids:</b> <i>eicosapentaenoic acid (EHA), docosahexaenoic acid (DHA), docosapentaenoic acid (DPA)</i> <b>3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors:</b> <i>statins</i> <b>Sodium-glucose cotransporter-2 inhibitors:</b> <i>dapagliflozin, empagliflozin, canagliflozin</i>

Italic text: off-label drugs approved for use in other clinical conditions. † denotes: available in UK NICE/BNF, Europe and range of other countries but not USA FDA. ‡ denotes: available in the USA but not the UK. \* denotes: not available in the UK (BNF/NICE) and USA(USP/FDA); still in use in Peoples Republic of China.

## FIGURE LEGENDS

Figure 1. The modernized classification scheme for anti-arrhythmic drugs (AADs). (A) Its clinical adaptation in terms of established AADs (a), including drugs classifiable within the Vaughan Williams scheme (b), investigational new drugs (c) and potential off label drugs (d). Correlations of the classification schemes with: (B) electrophysiological events reflecting sino-atrial node (SAN), atrial, Purkinje conducting and ventricular APs producing a propagated wave of electrical activity through their respective cardiomyocytes. (C) biomolecular targets including ionic currents, intracellular signaling, and autonomic modulating events. (D) Underlying component physiological processes underlying cardiomyocyte activation including surface membrane  $I_{Na}$ ,  $I_K$ ,  $I_{Ca}$ ,  $Na^+$ ,  $K^+$  and  $Ca^{2+}$  currents; NCX,  $Na^+/Ca^{2+}$  exchange, and intracellular cAMP: cyclic 3'5-adenosine monophosphate; PKA: protein kinase A; RyR2: cardiac ryanodine receptor, type 2, signaling. SR, sarcoplasmic reticulum