Journal of Cardiovascular Electrophysiology
Fellows Core Curriculum

Update on anti-arrhythmic drug pharmacology

Christopher L.-H. Huang[1-3*], Lin Wu[2,4], Kamalan Jeevaratnam[3] & Ming Lei[2,5*]

[1]Physiological Laboratory and Department of Biochemistry, University of Cambridge, Cambridge CB2 3EG; United Kingdom;
[2]Key Laboratory of Medical Electrophysiology of Ministry of Education, Institute of Cardiovascular Research, Southwest Medical University, Luzhou 646000, China
[3]Faculty of Health and Medical Sciences, University of Surrey, Guildford, GU2 7AL, United Kingdom
[4]Department of Cardiology, Peking University First Hospital, Beijing 100034, China
[5]Department of Pharmacology, University of Oxford, Oxford OX1 3QT, United Kingdom

Short title. Antiarrhythmic drugs

Key words. Anti-arrhythmic drugs, cardiac arrhythmias, Vaughan Williams, Sicilian gambit, Modernised Oxford Classification.

*corresponding authors: email: clh11@cam.ac.uk, phone +44 1223 333820 (CLLH); ming.lei@pharm.ox.uk; Tel: +44 1865271624 (ML)

Abstract

Cardiac arrhythmias constitute a major public health problem. Pharmacological intervention remains mainstay to their clinical management. This in turn depends upon systematic drug classification schemes relating their molecular, cellular and systems effects to clinical indications and therapeutic actions. This approach was first pioneered in the 1960s Vaughan Williams classification. Subsequent progress in cardiac electrophysiological understanding led to a lag between the fundamental science and its clinical translation, partly addressed by The Working Group of the European Society of Cardiology (1991), which however did not emerge with formal classifications. We here utilise the recent Revised Oxford Classification Scheme to review anti-arrhythmic drug pharmacology. We survey drugs and therapeutic targets offered by the more recently characterized ion channels, transporters, receptors, intracellular Ca^{2+} handling and cell signalling molecules. These are organised into their strategic roles in cardiac electrophysiological function. Following analysis of the arrhythmic process itself, we consider (a) pharmacological agents directly targeting membrane function, particularly the Na^{+} and K^{+} ion channels underlying depolarising and repolarising events in the cardiac action potential. (b) We also consider agents that modify autonomic activity that in turn affects both the membrane and (c) the Ca^{2+} homeostatic and excitation contraction coupling processes linking membrane excitation to contractile activation. Finally, we consider (d) drugs acting on more upstream energetic and structural remodelling processes currently the subject of clinical trials. Such systematic correlations of drug actions and arrhythmic mechanisms at different molecular to systems levels of cardiac function will facilitate current and future anti-arrhythmic therapy.

The clinical and preclinical background: Classifications of anti-arrhythmic drugs

Cardiac arrhythmias constitute a major public health problem causing ~3.7 million deaths worldwide and significant clinical morbidity [1]. Pharmacological intervention remains the mainstay of their management despite major progress in interventional including ablation and device therapy. Much of this was informed by systematic drug development and classification, the latter relating modes of molecular, cellular and systems actions to clinical indications and therapeutic effects. An early scheme classified then known anti-arrhythmic drugs and their actions on different components of the cardiac action potential [2,3]. Class I drugs reduced phase 0 slopes and overshoots, increasing, reducing or conserving AP durations (APD) and effective refractory periods (ERP) respectively through Na^+ channel block [4]. Class II drugs slowed sino-atrial node (SAN) pacing and atrioventricular node (AVN) action potential conduction through β-adrenergic inhibition [5,6]. Class III drugs delayed phase 3 repolarization and effective refractoriness by K^+ channel block. Finally, Class IV drugs reduced cardiac, particularly SAN and AVN, rate and conduction through L-type Ca^{2+} channel inhibition [3].

The resulting simple yet coherent and pragmatic working model for cardiomyocyte function, thus approached cardiac arrhythmia in terms of disrupted cardiac electrophysiological activation, correlating available therapies with then known arrhythmic targets (referenced in [7]). It found widespread usefulness in diagnostic analysis and therapeutic action, directly facilitating clinical management and drug development [8]. Subsequent progress has expanded our electrophysiological understanding of both normal and arrhythmic cardiac excitation and its underlying membrane ion channel, intracellular ion transport and receptor protein molecules [9,10], and offered numerous novel pharmacological and therapeutic targets [11]. Yet, management of clinical arrhythmias has often lagged progress in other cardiological areas and may not have optimally benefitted from these fundamental scientific advances. The latter may reflect unmet needs for classification of these wide-ranging findings coherently relating fundamental physiological mechanisms to clinical applications. This was partly attempted by the European Society of Cardiology [12] which however did not emerge with a formal drug classification scheme.

Revised classifications of pharmacological anti-arrhythmic targets: The Modernised Oxford Classification

A recent modernized classification grouped currently available approved and investigational new drugs through their known molecular, ion channel, transporter, receptor, intracellular Ca^{2+} homeostatic or cell signalling, targets (Fig. 1A). It devised a format accomplishing a simultaneous classification of their actions on strategic aspects of cardiac electrophysiological function (Fig. 1C). Of the latter processes, (a) the altered surface membrane excitability disrupting normal patterns of atrial or ventricular action potential generation involving one or more component ion channel processes (Fig. 2) constitutes the immediate source of arrhythmic phenomena. However, this interacts reciprocall**y** with *cytosolic processes* involving (b) autonomic modulation, itself acting on both (a) and (c) excitation contraction coupling. Drugs might also modify (d) more upstream energetic and remodelling structural processes often concerning cell signalling and intracellular metabolism, energetics and mitochondrial function, and fibrotic and inflammatory change (Fig. 1C).

Finally, it nevertheless remained possible to pragmatically retain the original Vaughan Williams classes I-IV [7], expanding these classes and adding additional drug categories to complete its representation of the subsequent biomedical advance. Together with the more concise representation emphasizing clinically accepted as opposed to investigational new drugs (Table 1; [13]), it thus represents a pragmatic modernization of the original Vaughan Williams approach. It retained but added to Vaughan-Williams Class I, recognising recently reported late Na^+ current (I_{NaL}) components and their importance in long QT syndrome type 3 (LQTS3). A broader Class II captures advances in our understanding of autonomic, G-protein signalling and an expanded Class III the many subsequently discovered K^+ channel subtypes. Class IV similarly encompasses recently demonstrated molecular targets and cellular physiological mechanisms related to Ca^{2+} homeostasis and excitation contraction coupling. Further new classes recognise discoveries in cardiac automaticity (Class 0), mechanically sensitive channels (Class V), cell-cell electrotonic coupling (Class VI), and physiological processes exerting longer term energetic changes and upstream structural remodelling (Class VII). This classification thus categorised both clinically acceptable and potential sites of drug

action relevant not only to current therapy but also future basic research and drug development.

Approved drugs, drugs under clinical trial and investigational new drugs in the modernized classification

This scheme thus updated current views on clinically used and potential anti-arrhythmic agents, facilitating classification of drugs under trial, and future developments of investigational new drugs. This article primarily concerns drugs either impacting current practice or under trial for possible future practice, listed in a shortened version [13] of the scheme in the original report [7] in Table 1. Thus, Table 1 indicates that most drugs in Classes 0, I, II, III and IV of the classification scheme are accepted in one or more of the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) and National Institute for Clinical Excellence (NICE) guidelines for management of patients with (a) ventricular arrhythmias and the prevention of sudden cardiac death [17], (b) atrial fibrillation [16] and (c) supraventricular tachycardia [18]. Table 1 also summarises their corresponding accepted therapeutic actions [6,19–21].

Of the remainder, ranolazine (Class Id), originally approved by the U.**S**. Food and Drug Administration for anti-anginal therapy, significantly reduced AF incidence in various clinical settings [22–24], including paroxysmal AF (HARMONY trial [25]). There are trials on use [28], and application in AF cardioversion [29] and comparisons against amiodarone [30,31] of the K1.5 channel mediated ultrarapid K^+ current (I_{Kur}) blocker vernakalant. Flecainide, normally considered part of class Ic, was trialled in relationship to management of catecholaminergic polymorphic ventricular tachycardia [32–34]. Although listed, clinical trials bearing on Kir6.2 (I_{KATP}) openers concern anginal rather than arrhythmia management. Table 1 is simplified in omitting the new classes V and VI as these only include investigational as opposed to clinically accepted drugs.

Finally, drugs in class VII are named in ACCF/AHA guidelines for management of heart failure [14] but not in ACCF/AHA guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death, atrial fibrillation and supraventricular tachycardia. However, there exist clinical trials testing all its drug

subcategories. Thus, a meta-analysis reported that both angiotensin-converting enzyme inhibitors (ACEIs), and angiotensin receptor inhibitors (ARBs) produced ~28% reductions in atrial fibrillation (AF) risk in patients with left ventricular (LV) dysfunction or hypertrophy [35]. Clinical trials reported decreased AF in postmyocardial infarction patients with LV dysfunction with trandolapril [36], and in patients with LV dysfunction with enalapril [37]. Ongoing clinical trials compared effects of telmisartan alone and in combination with ramipril (ONTARGET/TRANSCEND trial [38]), and clopidogrel with irbesartan in preventing vascular events (ACTIVE trial [39]). Of aldosterone receptor antagonists, a meta-analysis of 7 reported trials of spironolactone and epleronone demonstrated reduced episodes of ventricular premature complexes, and 21% and 72 % reductions in sudden cardiac death and ventricular tachycardia [40]. Clinical trials reported positive anti-arrhythmic effects of spironolactone in patients with [42,43] or without congestive heart failure [47] and of eplerenone in congestive heart failure due to idiopathic dilated or ischemic cardiomyopathy [45].

More preliminary evidence implicates omega-3 fatty acids in reducing incidence of AF ([48], but see also [49]), particularly following coronary artery bypass surgery [50]. Finally, a meta-analysis suggested that 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors reduced AF incidence in 3 of 3 trials [51]. Statins reduced recurrent AF in 62 retrospectively studied lone persistent AF (≥3 months) patients after direct current cardioversion [52]. It lowered rate of new AF development in prospectively studied coronary artery patients [53], and AF development by 23% in patients prospectively enrolled in the multicenter Guidant-sponsored Advancement Heart Failure Registry [54].

Electrophysiological pro-arrhythmic mechanisms as therapeutic targets

Arrhythmias are the result of abnormal sino-atrial (SA), AVN or Purkinje fibre automaticity, or pathological generation or conduction of excitation in atrial or ventricular cardiomyocytes. Sustained arrhythmia likely requires not only an initial trigger, but also arrhythmic substrate typically arising from re-entry of excitation from active into recovered previously active myocardial regions (Fig. 1B). It can take diverse forms in different cardiac regions each with distinct phenotypes. Successful therapeutic management of arrhythmias must therefore recognise this underlying mechanistic context bearing particularly upon cardiac action potential generation, recovery and/or its conduction [55].

First, abnormal or altered action potential generation can arise from altered *automaticity* underlying spontaneous, rhythmic SAN, or AVN or purkinje tissue pacemaker activity. This could arise from altered slopes of the depolarisation processes triggering successive action potentials or altered maximum diastolic or resting potentials. Changes in *normal automaticity* typically reflect alterations in pacemaker potentials driven by inward HCN mediated I_f and other ionic currents following normal adrenergic or cholinergic SAN pacemaker stimulation or inhibition. *Abnormal automaticity* arises from spontaneous impulses generated in partially depolarised fibres in pathological circumstances; this can even involve normally non-automatic atrial and ventricular muscle. This causes an automatic, often tachycardic, firing distinct from the SAN activity, exemplified by ectopic atrial tachycardias, accelerated idioventricular rhythms and ventricular tachycardias.

Secondly, ***t****riggered activity* can be initiated by membrane potential afterdepolarisation events whose amplitude is sufficient to initiate regenerative Na^+ or Ca^{2+} channel excitation. *Early after-depolarisation* (EAD) events typically occur under bradycardic conditions, when altered balances of inward Na^+ or Ca^{2+} and outward K^+ current prolong the action potential. This permits Ca^{2+} current reactivation in turn triggering an extrasystolic action potential potentially leading to torsades de pointes. *Delayed after-depolarisation* (DAD) events following full action potential repolarisation result from transient inward currents, I_{ti}, resulting from enhanced electrogenic Na^+/Ca^{2+} exchange activity when this is increased by elevations in cytosolic Ca^{2+} concentrations due to abnormal diastolic SR Ca^{2+} release [11,56].

Thirdly, abnormal action potential *conduction slowing* can follow functional reductions in inward Na^+ current initiating the action potential and driving its propagation. It can also result from anatomical changes altering tissue electrical resistance compromising the local circuit currents taking place through connexin channels, and propagating the action potential. Either can involve either functionally or anatomically defined pathways [57]. Actual conduction block can be associated with heterogeneities in refractoriness and conduction in particular parts of such a circuit. These heterogeneities could be varying with time and previous impulse activation, or over anatomically or functionally consistent or defined paths. These often result in regions of unidirectional conduction block.

Altered action potential conduction is then often associated with a presence of *re-entrant substrate* perpetuating previously triggered arrhythmias [58]. Re-entry can also occur with

abnormal action potential recovery reflecting altered relationships between the time intervals between action potential recovery, refractoriness and repolarisation reserve. It has thus been associated with the presence of discrepancies between effective refractory periods and action potential recovery times as exemplified in LQT syndromes [56]. Either spatial heterogeneities, exemplified by transmural gradients, or temporal heterogeneities, most frequently manifest as alternans in these parameters, and would accentuate other pro-arrhythmic effects [11,59–61].

Pro-arrhythmic effects of isolated, decay or block of *impulse conduction* can also occur in the absence of re-entrant pathways. This is exemplified by the SA conduction block permitting escape of a supraventricular or ventricular focus then generating abnormal impulses. Similar phenomena could follow delayed or completely blocked AV conduction.

Therapeutic targets: Ion current excitation and the action potential propagation wavefront

The functional unit of excitable activity in the cardiomyocyte is the propagating action potential (Fig. 2). Typical action potential waveforms comprise rapid depolarising (phase 0), early repolarising (phase 1), brief atrial and prolonged ventricular plateaus (phase 2), late repolarisations (phase 3) and end in electrical diastole (phase 4). Phase 0 action potential initiation beginning this sequence of events requires inward Na^+ current activation (Fig. 2A); Ca^{2+} channel activation contributes to the phase 2 plateau contribution, and is more prominent in ventricular than atrial muscle and is considered in the next section. Action potential generation through the heart is initiated from *pacemaker activity* in the SAN which possesses a I_f current, for which a new drug Class 0 affecting such periodic generation of electrical activity and therefore heart rate has been introduced. Heart rate reduction also offers a therapeutic strategy to managing acute cardiac ischemia.

Of drugs directed at the *inward Na^+ current* responsible for the *depolarisation* phase 0 of the action potential, Class Ia drugs preferentially bind to the open state of the Nav1.5 Na^+ channel with a dissociation time constant of τ ~1-10 s. They thus inhibit AV conduction and increase the effective refractory period. They also exhibit a concomitant K^+ channel block which increases action potential duration. Together these properties reduce re-entrant tendency. Class Ib agents contrastingly bind preferentially to the inactivated state of the Na^+

channel from which they more rapidly dissociate over τ ~0.1 - 1.0 s. The latter minimises the duration of their actions within and through successive cardiac cycles. This explains their effectiveness in preventing arrhythmias in ventricular tissue, whose Na^+ channels remain inactive for the longest duration amongst cardiomyocyte types reflecting the duration of the action potential plateau. There they block Nav1.5 window current, shortening action potential duration and increasing effective refractory period. They are useful in cardiac ischaemic situations where there is Na^+ channel inactivation. Class Ic drugs bind to inactivated channels but dissociate slowly, over τ > 10 s. This results in a use-dependent channel block, particularly under conditions of high channel activation frequencies. They thus produce a generalised reduction in cardiac excitability with widespread effects, including slowing AV conduction, but do so whilst exerting little effect on action potential duration. Atrial Na^+ channels remain open for longer than in the ventricles, and so class Ia and Ic drugs have been used to prevent supraventricular arrhythmias [62].

Finally, the new Class Id recognises recently developed agents acting the late Na^+ current (I_{NaL}). These drugs are of potential importance for managing pro-arrhythmic situations under conditions of reduced repolarisation reserve as in long QT syndrome 3, and pathological bradycardic and ischaemic conditions, and cardiac failure. They shorten action potential recovery and increase refractoriness and repolarisation reserve [63].

Action potential *repolarisation* ultimately restoring the background resting potential is driven by a range of *outward K^+ currents* (Fig. 2B) [11,64]. An expanded class III reflects the considerable progress in our understanding of K^+ channel subtypes [64–68]. Thus, phase 0 depolarisation is rapidly terminated by transient outward Kv4.3 and Kv4.2-mediated I_{to} currents driving the early phase 1 action potential repolarisation. In atrial myocytes (Fig. 2C), the prominent I_{to} and the atrial-specific Kv1.5 (*KCNA5)* mediated ultra-rapid I_{Kur}, as well as the GIRK1 and GIRK4 mediated acetylcholine sensitive I_{KACh} together ensure the relatively shorter atrial action potentials. In ventricular myocytes (Fig. 2D), the Kv11.1 (HERG or *KCNH2)* mediated I_{Kr} rapidly activates with phase 0 action potential depolarisation, then rapidly inactivates over action potential phases 0–2 [69,70]. Phase 3 repolarisation then re-opens the channel driving outward phase 3 and early phase 4 currents that terminate the plateau. The more slowly activating Kv7.1 (*KCNQ1*) mediated I_{Ks} increases over phase 2 to become a major relatively persistent phase 3 K^+ conductance. The Kir2.1, Kir2.2 and Kir2.3 (*KCNJ2*, *KCNJ12* and *KCNJ4)* mediated inward rectifying I_{K1} reduces K^+ conductance at voltages >-

20 mV in phases 0-2. In contrast, it produces outward currents with repolarisation to <-40 mV late in phase 3, and stabilises phase 4 diastolic resting potentials. The latter are also stabilised by background $K_{2P}2.1$ (KCNK2, expressing K_{2P} currents), and the normally small ATP-sensitive Kir6.2 (*KCNJ11)* mediating I_{KATP}. However, the latter can be activated by reduced intracellular ATP levels [71]. Finally the effective refractory period extends beyond each action potential. This can increase with Na^+ channel inhibition delaying the point at which a critical proportion of Na^+ channels has recovered, or with action potential prolongation.

The new Class V of *mechanosensitive channel blockers* are selective for cation selective and a number of mechanosensitive ion channel types that include TRPC3 or TRPC6. However, they do not include currently clinically utilised drugs; their available exemplars are confined to investigational new drugs. The latter is also true for Class VI *gap junction modulators*, despite the importance of gap junction intercellular conductance between cardiomyocytes in cell-to-cell coupling. The latter is key to ventricular conduction, of central importance in the generation of re-entrant substrate. Thus, its underlying pro-arrhythmic action potential conduction slowing can result follow not only from compromised action potential activation due to reduced inward Na^+ current but also anatomical changes altering connexin (Cx)-dependent intercellular conductances [8].

Action potential depolarisation produces a coherent wave of excitation followed by refractoriness often propagating through often anisotropic gap junction connexin connections between successive SAN, atrial, AV, purkinje and endocardial and epicardial ventricular cardiomyocytes respectively, with detailed action potential waveforms varying with cell type. Thus atrial cells show shorter APs than ventricular cells, reflecting their large repolarising, transient outward voltage dependent and acetylcholine-sensitive K^+ currents (Fig. 2C, D) [57,61,72].

Therapeutic targets: Ca^{2+} homeostasis and excitation contraction coupling.

Figure 3 summarises recent reports suggesting reciprocal mechanistic relationships between the membrane excitation described above, and particular component excitation contraction coupling processes whose activation connects surface electrical activation to the initiation of mechanical activity. It thus represents the substantial progress made in understanding of this

area following Vaughan Williams's original studies. Thus, membrane excitation includes a depolarisation-induced Phase 2 activation of transverse tubular L-type Ca^{2+} current I_{CaL} in turn responsible for the action potential plateau phase. These Ca^{2+} currents also *feed-forward* to initiation of cardiac excitation contraction coupling. The resulting local elevations in cytosolic Ca^{2+}concentration trigger a Ca^{2+}-induced ryanodine receptor (RyR2) mediated sarcoplasmic reticular (SR) Ca^{2+} release, thereby synchronised to the membrane excitation events (Fig. 3c) [73,74]. The resulting elevated cytosolic Ca^{2+} concentrations result in the troponin mediated activation of mechanical activity. Termination of this Ca^{2+} release process normally takes place with membrane repolarisation. The cytosolic Ca^{2+} concentration is then returned to its resting level by both SR membrane Ca^{2+}-ATPase mediated Ca^{2+} re-uptake returning Ca^{2+} into the SR and the surface membrane Na^{+}-Ca^{2+} exchanger which expels Ca^{2+} from the cytosol into the extracellular space in return for extracellular Na^{+} entry [75]. Thus, the cycles of increase followed by restoration of cytosolic Ca^{2+} concentration are normally synchronised with membrane events associated with the action potential. The overall energetic cost is defrayed by metabolically dependent mitochondrial generation of cellular ATP [76].

However, the processes involved in intracellular Ca^{2+} homeostasis can show pro-arrhythmic events independent of such surface membrane control. They can also actually exert potentially pro-arrhythmic *feed-back* effects on their initiating membrane events. First, altered Ca^{2+} channel function itself may predispose to initiation of pro-arrhythmic early after-depolarisation (EAD) phenomena late in phase 2 or early in phase 3 of the action potential particularly in the presence of action potential prolongation as might occur in long QT syndromes. These would in turn result in extrasystolic membrane excitation. Secondly, elevated sarcoplasmic Ca^{2+} concentrations resulting from increased Ca^{2+} channel or mechanosensitive channel activity, or RyR2 Ca^{2+} sensitivity, can themselves trigger propagating waves of spontaneous SR Ca^{2+} release asynchronous to the normal cycles of membrane excitation. These can lead to elevated cytosolic Ca^{2+} concentrations. The latter can result in increased electrogenic Na^{+}/Ca^{2+} exchange activity. This drives a depolarising transient inward current, I_{TI}. The latter may result in pro-arrhythmic delayed after-depolarisations (DADs) following full action potential repolarisation [75]. Thirdly, elevations in cytosolic Ca^{2+} concentration have been associated with downregulated longer-term Na^{+} channel expression and function compromising action potential conduction velocity [77].

Finally, the depolarising electrogenic effects of Na^+/Ca^{2+} exchange may contribute to SAN automaticity [78].

These recent advances have thus considerably broadened the range of potential therapeutic targets concerned with such Ca^{2+} homeostasis and its modulation. They hold future promise of agents directed at (a) surface membrane L and/or T-type Ca^{2+} channels, (b) intracellular RyR and inositol trisphosphate receptor- Ca^{2+} channels, (c) SR Ca^{2+}-ATPase activity, (d) ion exchange, particularly Na^+-Ca^{2+} exchange processes and (e) phosphorylation levels of cytosolic Ca^{2+} handling proteins, including CamKII inhibitors and P21 activated kinase 1 modulators. However, in this group, only Ca^{2+} channel blockers and one RyR2-blocker, flecainide, which has found recent use in monotherapy of catecholaminergic polymorphic ventricular tachycardia (CPVT) are currently clinically available.

Therapeutic targets: autonomic modulators

Figure 3b illustrates the various relationships between autonomic inputs and the processes outlined below in a retention and broadening of Vaughan Williams Class II beyond its originally listed sympathetic β-adrenergic effects. This reflects progress in understanding of the wide range of modulators acting upon the widely expressed cell surface membrane guanine nucleotide-binding protein (G-protein) coupled receptors (GPCRs). The latter have been successfully exploited in a variety of other therapeutic applications. Thus, in addition to the selective and non-selective adrenergic antagonists are adenosine receptor and cholinergic muscarinic receptor modulators [6], and a possibility of future potential targets amongst the ~150 remaining orphan GPCRs. The updated G-protein mechanisms have wide actions on both the excitation-contraction coupling and the surface membrane groups of functions.

First, β-adrenergic receptor activation produces multiple, inotropic, chronotropic and lusitropic effects upon cardiac function [73] through G_s-protein and adenylate cyclase activation increasing cytosolic cyclic 3'5'-adenosine monophosphate concentrations, $[cAMP]_i$. The latter promotes protein kinase A (PKA) mediated phosphorylation actions on a wide range of ion channels including the Nav1.5 Na^+ channel, Kv11.1 and Kv7.1 K^+ channel species mediating rapid and slow I_{Kr} and I_{Ks} K^+ currents, Cav1.2 and Cav1.3 L-type Ca^{2+} channels mediating I_{CaL} and the RyR2 SR Ca^{2+} release channel. cAMP also directly enhances HCN

channel and consequently pacemaker I_f current activity. Finally, exchange proteins directly activated by cAMP also likely trigger a pro-arrhythmic RyR2-mediated Ca^{2+} release [79].

Secondly, of further G-protein subtypes, Table 1 now incorporates drugs targeted at G_i protein mediated parasympathetic cholinergic muscarinic (M_2) or adenosine (A_1) receptor activation, conversely reducing membrane excitation. These actions occur in the SAN, AVN or atrial myocardium even in the absence, but in ventricular tissue only in the presence, of pre-existing adrenergic challenge. The G_i activation causes a G protein βγ subunit mediated opening of inward rectifying I_{KACh} or I_{KAdo} channels particularly in supraventricular tissue, through actions on their GIRK1 and GIRK4 components [65,80,81]. G_i activation also inhibits adenylyl cyclase reducing $[cAMP]_i$ and its associated increases in I_{CaL} and I_f. It may also upregulate protein phosphatase 2 (PP2A)-mediated dephosphorylation at PKA phosphorylation sites [82,83].

These updates prompt class II subclassifications of the clinically used nonselective and selective β1-adrenergic receptor inhibitors carvedilol propranolol and nadolol, and atenolol and bisoprolol respectively. To this are added the nonselective β-adrenergic receptor activators isoproterenol, reflecting the G_s-protein and adenylate cyclase modulation, and new subclasses also representing drugs acting through G_i protein.

Possible therapeutic targets: upstream modulators of energetic status and structural remodeling

Processes affecting long term cellular energetics and remodeling of tissue structure (Figs. 1d, 3d) contrast with the primary pre-occupation with the *acute* effects on specific ion channels in the original Vaughan Williams classification. Thus, rather than direct effects on arrhythmic processes, the drugs included in Class VII are normally indicated for cardiovascular conditions such as hypertension, coronary artery disease, and heart failure that do not primarily result in arrhythmias. Nevertheless, such specific conditions, and the general categories of changes related to oxidative stress as well as longer term structural. fibrotic, hypertrophic, inflammatory, changes upstream of the electrophysiological processes at the membrane level have been associated with atrial fibrillation [84–86].

Metabolic stress associated with cardiovascular conditions such as hypertrophic change, cardiac failure, and ischaemia-reperfusion [87–90], and biochemical conditions including obesity, insulin resistance and type 2 diabetes are thus accompanied by energetic, particularly mitochondrial, dysfunction [91–93]. The consequent destabilisation of inner membrane potentials required to drive the electron transport chain compromises ATP synthesis. ATP depletion or increased ADP increases sarcolemmal ATP-sensitive K^+ channel ($sarcK_{ATP}$) open probabilities [94]. This shortens action potential duration, potentially producing pro-arrhythmic re-entrant substrate [95,96], and hyperpolarises cell membrane potentials compromising cell excitability and action potential propagation [94].

Compromised mitochondrial function also increases reactive oxygen species (ROS)-induced ROS release; ROS exert a wide range of potentially arrhythmogenic channel actions bearing upon cell-cell coupling [97], action potential conduction [98], repolarisation [99], alternans [100], and Ca^{2+} -mediated triggers [90]. They decrease I_{Na} [98] and I_K [99], activate sarcolemmal K_{ATP} channels [101], modify Na^+ and L-type Ca^{2+} channel inactivation, increase I_{NaL} and oxidise RyR2. The latter results in an increased SR Ca^{2+} leak, altering intracellular Ca^{2+} cycling [76,90,102]. They also reduce Cx43 trafficking and function [94,103,104]..

Atrial fibrosis is a potential source of arrhythmic substrate leading to atrial fibrillation; fibrotic change also accompanies some Na^+ channelopathies [105,106]. A significant proportion of pharmacological agents that might influence this are known to act on the renin-angiotensin system. In the present context, rather than its immediate cardiovascular pressor effects, they likely relate to its effects on cardiac remodelling. Thus, angiotensin II, through angiotensin receptor-1 (AT1) may trigger fibroblast proliferation associated with increased transforming growth factor β (TGF-β) release. This promotes fibrotic and/or hypertrophic change which AT1 receptor antagonists are reported to reduce. Angiotensin II has also been reported to affect cardiac electrical activity including gap-junction mediated impulse propagation. Finally, AT1 receptor activation has been reported to upregulate ROS with inflammatory as well as mitochondrial effects. Preliminary evidence suggests that the currently available drugs listed including angiotensin-converting enzyme and angiotensin receptor blockers, aldosterone receptor antagonists, 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors (statins), and n-3 (ω-3) polyunsaturated fatty acids may reduce such structural and electrophysiological remodelling [85].

Further future upstream targets are likely to emerge. For example, the key cardiomyocyte regulator of ion channel activity, Ca^{2+} homeostasis and cardiac contractility [82,83,107], P21 activated kinase 1 (PAK1), has been reported to cardio-protect through signalling processes inhibiting maladaptive, pro-arrhythmic, hypertrophic remodelling and progression in cardiac failure [108]. This offers potential novel clinical therapeutic strategies [109,110].

Recapitulation

Cardiac arrhythmias constitute a major clinical problem, and pharmacological intervention remains the mainstay of their clinical management. Rational drug use relies on a fundamental understanding of drug modes of action through the cellular, systems, and clinical levels and clear correlations of these with their clinical indications and therapeutic actions. This thus further involves their systematic classification relating these scientific and clinical issues within a rational framework. This article surveys current clinically established anti-arrhythmic drugs in the light of pharmacological developments that followed the historic Vaughan Williams classification of such agents. It utilises the major progress in our understanding of cardiac electrophysiology, its contained mechanisms and its molecular and physiological basis in the large number of underlying membrane ion channel, intracellular ion transport and autonomic receptor and effector protein molecules underlying normal and abnormal cardiac function. It places these within a recently introduced classification scheme systematising their pharmacological targets in the light of recent biomedical advances. The latter in turn are grouped into categories of electrophysiological effects and their direct or indirect convergence upon their primary arrhythmic mechanisms. Such a systematic approach may facilitate current and future anti-arrhythmic therapy.

Conflicts of interest

None declared.

Acknowledgements

Our work is supported by the Medical Research Council (MR/M001288/1, CLHH, G10002647, G1002082, ML), the Wellcome Trust (105727/Z/14/Z), British Heart

Foundation (BHF) (PG/14/79/31102, and PG/15/12/31280 and BHF Centres for Research Excellence (CRE) at Cambridge, CLHH, PG/14/80/31106, PG/16/67/32340, PG/12/21/29473, PG/11/59/29004) and Oxford (ML) and the Chinese Natural Science Foundation (31171085: ML; 81930105, 81430098 and 81770325: LW).

References

1. Kuriachan V, Sumner G, Mitchell L. Sudden cardiac death. *Curr Probl Cardiol* 2017;**40**:133–200.

2. Vaughan Williams E. Classification of antiarrhythmic drugs. In: Sandoe E, Flensted-Jensen E, Olsen K, eds. *Symposium on Cardiac Arrhythmias* Elsinore, Denmark: Astra; 1970.

3. Vaughan Williams E. Classification of antidysrhythmic drugs. *Pharmacol Ther B* 1975;**1**:115–138.

4. Campbell TJ, Vaughan Williams EM. Voltage- and time-dependent depression of maximum rate of depolarisation of guinea-pig ventricular action potentials by two new antiarrhythmic drugs, flecainide and lorcainide. *Cardiovasc Res* 1983;**17**:251–258.

5. Dukes I, Vaughan Williams E. Effects of selective alpha 1-, alpha 2-, beta 1-and beta 2-adrenoceptor stimulation on potentials and contractions in the rabbit heart. *J Physiol* 1984;**355**:523–546.

6. Singh B. Beta-blockers and calcium channel blockers as anti-arrhythmic drugs. In: Zipes D, Jalife J, eds. *Cardiac Electrophysiology From Cell to Bedside* 4th ed. Philadelphia: Saunders; 2004. p. 918–931.

7. Lei M, Wu L, Terrar DA, Huang CLH. Modernized classification of cardiac antiarrhythmic drugs. *Circulation* 2018;**138**:1879–1896.

8. Antzelevitch C, Burashnikov A. Overview of basic mechanism of cardiac arrhythmia. *Card Electrophysiol Clin* 2011;**3**:23–45.

9. Carmeliet E, Vereecke J (Johan). Cardiac cellular electrophysiology. Kluwer Academic Publishers; 2002.

10. Gilmour RF, Zipes DP. Mechanisms of disease: New mechanisms of antiarrhythmic actions. *Nat Clin Pract Cardiovasc Med* 2004;**1**:37–41.

11. Huang CL-H. Murine models of cardiac arrhythmogenesis. *Physiol Rev* 2017;**97**:283–409.

12. Task force of the working group on arrhythmias The European Society of Cardiology. The Sicilian Gambit. A new approach to the classification of antiarrhythmic drugs based on their actions on arrhythmogenic mechanisms. *Circulation* 1991;**84**:1831–1851.

13. Lei M, Huang C-H. Cardiac arrhythmogenesis: a tale of two clocks. *Cardiovasc Res* 2019;**doi:10.109**.

14. Yancy C, Jessup M, Bozkurt B, Butler J, Casey D, Drazner M, Fonarow G, Geraci S, Horwich T, Januzzi J, Johnson M, Kasper E, Levy W, Masoudi F, McBride P, Murray J, Mitchell J, Peterson P, Riegel B, Sam F, Stevenson L, Tang W, Tsai E, Wilkoff B. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation* 2013;**128**:e240–e327.

15. NICE. Arrhythmias. Natl. Inst. Heal. Care Excell. 2014. p. https://bnf.nice.org.uk/treatment – summary/arrhythm.

16. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: Executive summary: A report of the American college of cardiology/American heart association task force on practice guidelines and the heart rhythm society. *J Am Coll Cardiol* 2014;**64**:2245–2280.

17. Al-Khatib SM, Stevenson WG, Ackerman MJ, Bryant WJ, Callans DJ, Curtis AB, Deal BJ, Dickfeld T, Field ME, Fonarow GC, Gillis AM, Hlatky MA, Granger CB, Hammill SC, Joglar JA, Kay GN, Matlock DD, Myerburg RJ, Page RL. 2017 AHA/ACC/HRS Guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Circulation* 2017;**pii: CIR.0**:doi: 10.1161/CIR.0000000000000548.

18. Page RL, Joglar JA, Caldwell MA, Calkins H, Conti JB, Deal BJ, Estes NAM, Field ME, Goldberger ZD, Hammill SC, Indik JH, Lindsay BD, Olshansky B, Russo AM, Shen W-K, Tracy CM, Al-Khatib SM. 2015 ACC/AHA/HRS Guideline for the management of adult patients with supraventricular tachycardia. *Circulation* 2015;**133**:e506–e574.

19. Gillis A. Class I anti-arrhythmic drugs: quinidine, procainamide, disopyramide, lidocaine, mexiletine, flecainide and propafenone. In: Zipes D, Jalife J, eds. *Cardiac Electrophysiology. From Cell to Bedside 4/e* 4th ed. Philadelphia: Saunders; 2004. p. 911–917.

20. Sampson K, Kass R. Anti-arrhythmic drugs. In: Brunton L, Chabner B, Knollman B, eds. *Goodman & Gilman's The Pharmaceutical basis of therapeutics 12/e* 12th ed. NY: McGrawHill; 2011. p. 815–848.

21. Roden D. Antiarrhythmic drugs. In: Brunton L, Knollman B, Hilal-Dandan R, eds. *Goodman and Gilman's The pharmacological basis of therapeutics 11th Ed* New York: McGrawHill; 2006. p. 899–932.

22. Gong M, Zhang Z, Fragakis N, Korantzopoulos P, Letsas KP, Li G, Yan GX, Liu T. Role of ranolazine in the prevention and treatment of atrial fibrillation: A meta-analysis of randomized clinical trials. *Hear Rhythm* 2017;**14**:3–11.

23. Rosa GM, Dorighi U, Ferrero S, Brunacci M, Bertero G, Brunelli C. Ranolazine for the treatment of Atrial fibrillation. *Expert Opin Investig Drugs* 2015;**24**:825–836.

24. Pulford BR, Kluger J. Ranolazine Therapy in Cardiac Arrhythmias. PACE - Pacing Clin. Electrophysiol. 2016. p. 1006–1015.

25. Reiffel JA, Camm AJ, Belardinelli L, Zeng D, Karwatowska-Prokopczuk E, Olmsted A, Zareba W, Rosero S, Kowey P. The HARMONY trial: Combined ranolazine and dronedarone in the management of paroxysmal atrial fibrillation: mechanistic and therapeutic synergism. *Circ Arrhythmia Electrophysiol* 2015;**8**:1048–1056.

26. DiMarco J. Adenosine and digoxin. In: Zipes D, Jalife J, eds. *Cardiac Electrophysiology. From Cell to Bedside 4/e* 4th ed. Philadelphia: Saunders; 2004. p. 942–949.

27. Smith T, Cain M. Class III Anti-arrhythmic drugs: amiodarone, ibutilide and sotalol. In: Zipes D, Jalife J, eds. *Cardiac Electrophysiology. From Cell to Bedside 4/e* 4th ed. Philadelphia: Saunders; 2004. p. 932–941.

28. Hall AJM, Mitchell ARJ. Introducing vernakalant into clinical practice. *Arrhythmia Electrophysiol Rev* 2019;**8**:70–74.

29. Tsuji Y, Dobrev D. Safety and efficacy of vernakalant for acute cardioversion of atrial fibrillation: an update. Vasc. Health Risk Manag. 2013. p. 165–175.

30. Camm AJ, Capucci A, Hohnloser SH, Torp-Pedersen C, Gelder IC Van, Mangal B, Beatch G. A randomized active-controlled study comparing the efficacy and safety of vernakalant to amiodarone in recent-onset atrial fibrillation. *J Am Coll Cardiol* 2011;**57**:313–321.

31. Simon A, Niederdoeckl J, Skyllouriotis E, Schuetz N, Herkner H, Weiser C, Laggner AN, Domanovits H, Spiel AO. Vernakalant is superior to ibutilide for achieving sinus rhythm in patients with recent-onset atrial fibrillation: A randomized controlled trial at the emergency department. *Europace* 2017;**19**:233–240.

32. Wang G, Zhao N, Zhong S, Wang Y, Li J. Safety and efficacy of flecainide for patients with catecholaminergic polymorphic ventricular tachycardia: A systematic review and meta-analysis. *Medicine (Baltimore)* 2019;**98**:e16961.

33. Kannankeril PJ, Fountain D, Roden DM, Knollmann BC, Moore JP, Cerrone M, Priori SG, Kertesz NJ, Ro PS, Batra AS, Kaufman ES, Fairbrother DL, Saarel EV, Etheridge SP, Kanter RJ, Carboni MP, Dzurik MV, Chen H, Ely EW. Efficacy of flecainide in the treatment of catecholaminergic polymorphic ventricular tachycardia a randomized clinical trial. *JAMA Cardiol* 2017;**2**:759–766.

34. Khoury A, Marai I, Suleiman M, Blich M, Lorber A, Gepstein L, Boulos M. Flecainide therapy suppresses exercise-induced ventricular arrhythmias in patients with CASQ2-associated catecholaminergic polymorphic ventricular tachycardia. *Hear Rhythm* 2013;**10**:1671–1675.

35. Healey JS, Baranchuk A, Crystal E. Prevention of atrial fibrillation with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. A meta-analysis. *ACC Curr J Rev* 2005;**14**:49–50.

36. Pedersen OD, Bagger H, Køber L, Torp-Pedersen C. Trandolapril reduces the incidence of atrial fibrillation after acute myocardial infarction in patients with left ventricular dysfunction. *Circulation* 1999;**100**:376–380.

37. Vermes E, Tardif JC, Bourassa MG, Racine N, Levesque S, White M, Guerra PG, Ducharme A. Enalapril decreases the incidence of atrial fibrillation in patients with left ventricular

dysfunction: Insight from the studies of left ventricular dysfunction (SOLVD) trials. *Circulation* 2003;**107**:2926–2931.

38. Zimmerman M, Unger T. Challenges in improving prognosis and therapy: The ongoing telmisartan alone and in combination with ramipril global end point trial programme. *Expert Opin Pharmacother* 2004;**5**:1201–1208.

39. Hohnloser SH, Connolly SJ. Combined antiplatelet therapy in atrial fibrillation: Review of the literature and future research avenues. *J Cardiovasc Electrophysiol* 2003;**14**:S60–S63.

40. Wei J, Ni J, Huang D, Chen M, Yan S, Peng Y. The effect of aldosterone antagonists for ventricular arrhythmia: A meta-analysis. *Clin Cardiol* 2010;**33**:572–577.

41. Barr CS, Lang CC, Hanson J, Arnott M, Kennedy N, Struthers AD. Effects of adding spironolactone to an angiotensin-converting enzyme inhibitor in chronic congestive heart failure secondary to coronary artery disease. *Am J Cardiol* 1995;**76**:1259–1265.

42. Gao X, Peng L, Adhikari CM, Lin J, Zuo Z. Spironolactone reduced arrhythmia and maintained magnesium homeostasis in patients with congestive heart failure. *J Card Fail* 2007;**13**:170–177.

43. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med* 1999;**341**:709–717.

44. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, Bittman R, Hurley S, Kleiman J, Gatlin M. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 2003;**348**:1309–1321.

45. Ramires FJA, Mansur A, Coelho O, Maranhão M, Gruppi CJ, Mady C, Ramires JAF. Effect of spironolactone on ventricular arrhythmias in congestive heart failure secondary to idiopathic dilated or to ischemic cardiomyopathy. *Am J Cardiol* 2000;**85**:1207–1211.

46. Hirsh BJ, Copeland-Halperin RS, Halperin JL. Fibrotic atrial cardiomyopathy, atrial fibrillation, and thromboembolism: mechanistic links and clinical inferences. *J Am Coll Cardiol* 2015;**65**:2239–2251.

47. Shah NC, Pringle SD, Donnan PT, Struthers AD. Spironolactone has antiarrhythmic activity in ischaemic cardiac patients without cardiac failure. *J Hypertens* 2007;**25**:2345–2351.

48. Mozaffarian D, Psaty BM, Rimm EB, Lemaitre RN, Burke GL, Lyles MF, Lefkowitz D, Siscovick DS. Fish intake and risk of incident atrial fibrillation. *Circulation* 2004;**110**:368–373.

49. Frost L, Vestergaard P. n-3 fatty acids consumed from fish and risk of atrial fibrillation or flutter: The Danish Diet, Cancer, and Health Study. *Am J Clin Nutr* 2005;**81**:50–54.

50. Calò L, Bianconi L, Colivicchi F, Lamberti F, Loricchio ML, Ruvo E De, Meo A, Pandozi C, Staibano M, Santini M. N-3 fatty acids for the prevention of atrial fibrillation after coronary artery bypass surgery: A randomized, controlled trial. *J Am Coll Cardiol* 2005;**45**:1723–1728.

51. Boos CJ, Anderson RA, Lip GYH. Is atrial fibrillation an inflammatory disorder? *Eur Heart J* 2006;**27**:136–149.

52. Siu CW, Lau CP, Tse HF. Prevention of atrial fibrillation recurrence by statin therapy in patients with lone atrial fibrillation after successful cardioversion. *Am J Cardiol* 2003;**92**:1343–1345.

53. Young-Xu Y, Jabbour S, Goldberg R, Blatt CM, Graboys T, Bilchik B, Ravid S. Usefulness of statin drugs in protecting against atrial fibrillation in patients with coronary artery disease. *Am J Cardiol* 2003;**92**:1379–1383.

54. Hanna IR, Heeke B, Bush H, Brosius L, King-Hageman D, Dudley SC, Beshai JF, Langberg JJ. Lipid-lowering drug use is associated with reduced prevalence of atrial fibrillation in patients with left ventricular systolic dysfunction. *Hear Rhythm* 2006;**3**:881–886.

55. Hoffman B, Rosen M. Cellular mechanisms for cardiac arrhythmias. *Circ Res* 1981;**49**:1–15.

56. Martin CA, Matthews GDK, Huang CL-H. Sudden cardiac death and inherited channelopathy: the basic electrophysiology of the myocyte and myocardium in ion channel disease. *Heart* 2012;**98**:536–543.

57. King J, Huang CL-H, Fraser JA. Determinants of myocardial conduction velocity: implications for arrhythmogenesis. *Front Physiol* 2013;**4**:154.

58. Spector P. Principles of cardiac electric propagation and their implications for re-entrant arrhythmias. *Circ Arrhythm Electrophysiol* 2013;**6**:655–661.

59. Sabir IN, Killeen MJ, Grace AA, Huang CL-H. Ventricular arrhythmogenesis: insights from murine models. *Prog Biophys Mol Biol* 2008;**98**:208–218.

60. Killeen MJ, Thomas G, Sabir IN, Grace AA, Huang CL-H. Mouse models of human arrhythmia syndromes. *Acta Physiol (Oxf)* 2008;**192**:455–469.

61. Kléber AG, Rudy Y. Basic mechanisms of cardiac impulse propagation and associated arrhythmias. *Physiol Rev* 2004;**84**:431–488.

62. Gillis A, Singh B, Smith T, Cain M, Kadish A, Weiberg K, Goldberger J. Pharmacologic Therapy. In: Zipes D, Jalife JJ, eds. *Cardiac Electrophysiology: From Cell to Bedside* 4th ed. Saunders; 2004. p. 911–965.

63. Belardinelli L, Giles W, Rajamani S, Karagueuzian H, Shryock J. Cardiac late Na+ current: Proarrhythmic effects, roles in long QT syndromes, and pathological relationship to CaMKII and oxidative stress. *Hear Rhythm* 2015;**12**:440–448.

64. Nerbonne JM, Kass RS. Molecular physiology of cardiac repolarization. *Physiol Rev* 2005;**85**:1205–1253.

65. Schmitt N, Grunnet M, Olesen S. Cardiac potassium channel subtypes: new roles in repolarization and arrhythmia. *Physiol Rev* 2014;**94**:609–653.

66. Tamargo J, Tamargo J, Caballero R, Caballero R, Gómez R, Gómez R, Valenzuela C, Valenzuela C, Delpón E, Delpón E. Pharmacology of cardiac potassium channels. *Cardiovasc Res* 2004;**62**:9–33.

67. Enyedi P, Czirjak G. Molecular background of leak K+ currents: two-pore domain potassium channels. *Physiol Rev* 2010;**90**:559–605.

68. Smith T, Cain M. Class III antiarrhythmic drugs: Amiodarone , ibutilide, and sotalol. In: Zipes D, Jalife J, eds. *Cardiac Electrophysiology From Cell to Bedside* 4th ed. Saunders Philadephia; 2004. p. 933–958.

69. Vandenberg JI, Perry MD, Perrin MJ, Mann SA, Ke Y, Hill AP. hERG K(+) channels: structure, function, and clinical significance. *Physiol Rev* 2012;**92**:1393–1478.

70. Sanguinetti MC, Tristani-Firouzi M. hERG potassium channels and cardiac arrhythmia. *Nature* 2006;**440**:463–469.

71. Foster MN, Coetzee WA. KATP Channels in the cardiovascular system. *Physiol Rev* 2016;**96**:177–252.

72. Amin AS, Tan HL, Wilde AAM. Cardiac ion channels in health and disease. *Hear Rhythm* 2010;**7**:117–126.

73. Bers DM. Cardiac excitation-contraction coupling. *Nature* 2002;**415**:198–205.

74. Bers DM. Excitation–contraction coupling and cardiac contractile force. 2nd ed. Dordrecht, The Netherlands: Kluwer Academic Publishers; 2001.

75. Bers DM. Calcium cycling and signaling in cardiac myocytes. *Annu Rev Physiol* 2008;**70**:23–49.

76. Brown DA, O'Rourke B. Cardiac mitochondria and arrhythmias. *Cardiovasc Res* 2010;**88**:241–249.

77. Zhang Y, Wu J, Jeevaratnam K, King JH, Guzadhur L, Ren X, Grace AA, Lei M, Huang CL-H, Fraser JA. Conduction slowing contributes to spontaneous ventricular arrhythmias in intrinsically active murine RyR2-P2328S hearts. *J Cardiovasc Electrophysiol* 2013;**24**:210–218.

78. Lakatta EG, Maltsev VA, Vinogradova TM. A coupled system of intracellular Ca(2+) clocks and surface membrane voltage clocks controls the timekeeping mechanism of the heart's pacemaker. *Circ Res* 2010;**106**:659–673.

79. Hothi SS, Gurung IS, Heathcote JC, Zhang Y, Booth SW, Skepper JN, Grace AA, Huang CL-H. Epac activation, altered calcium homeostasis and ventricular arrhythmogenesis in the murine heart. *Pflugers Arch* 2008;**457**:253–270.

80. Dascal N, Kahanovitch U. The Roles of Gβγ and Gα in Gating and Regulation of GIRK Channels. *Int Rev Neurobiol* 2015;**123**:27–85.

81. Lerman BB. Ventricular tachycardia: Mechanistic insights derived from adenosine. *Circ Arrhythmia Electrophysiol* 2015;**8**:483–491.

82. Wang Y, Tsui H, Bolton EL, Wang X, Huang CL-H, Solaro RJ, Ke Y, Lei M. Novel insights into mechanisms for Pak1-mediated regulation of cardiac Ca2+ homeostasis. *Front Physiol* 2015;**6**:76.

83. Ke Y, Lei M, Solaro RJ. Regulation of cardiac excitation and contraction by p21 activated kinase-1. *Prog Biophys Mol Biol* 2009;**98**:238–250.

84. Dobrev D, Nattel S. New antiarrhythmic drugs for treatment of atrial fibrillation. *Lancet* 2010;**375**:1212–1223.

85. Iwasaki Y, Nishida K, Kato T, Nattel S. Atrial fibrillation pathophysiology: implications for management. *Circulation* 2011;**124**:2264–2274.

86. Nattel S, Maguy A, Bouter S Le, Yeh Y-H. Arrhythmogenic ion-channel remodeling in the heart: heart failure, myocardial infarction, and atrial fibrillation. *Physiol Rev* 2007;**87**:425–456.

87. Belevych AE, Terentyev D, Terentyeva R, Ho HT, Gyorke I, Bonilla IM, Carnes C a., Billman GE, Györke S. Shortened Ca(2+) signaling refractoriness underlies cellular arrhythmogenesis in a postinfarction model of sudden cardiac death. *Circ Res* 2012;**110**:569–577.

88. Chouchani ET, Pell VR, Gaude E, Aksentijević D, Sundier SY, Robb EL, Logan A, Nadtochiy SM, Ord ENJ, Smith AC, Eyassu F, Shirley R, Hu C-H, Dare AJ, James AM, Rogatti S, Hartley RC, Eaton S, Costa ASH, Brookes PS, Davidson SM, Duchen MR, Saeb-Parsy K, Shattock MJ, Robinson AJ, Work LM, Frezza C, Krieg T, Murphy MP. Ischaemic accumulation of succinate controls reperfusion injury through mitochondrial ROS. *Nature* 2014;**515**:431–435.

89. Grivennikova VG, Kareyeva A V, Vinogradov AD. What are the sources of hydrogen peroxide production by heart mitochondria? *Biochim Biophys Acta* 2010;**1797**:939–944.

90. Terentyev D, Gyorke I, Belevych AE, Terentyeva R, Sridhar A, Nishijima Y, Blanco EC de, Khanna S, Sen CK, Cardounel AJ, Carnes CA, Györke S. Redox modification of ryanodine receptors contributes to sarcoplasmic reticulum Ca(2+) leak in chronic heart failure. *Circ Res* 2008;**103**:1466–1472.

91. Sato D, Xie L-H, Sovari A a, Tran DX, Morita N, Xie F, Karagueuzian H, Garfinkel A, Weiss JN, Qu Z. Synchronization of chaotic early afterdepolarizations in the genesis of cardiac arrhythmias. *Proc Natl Acad Sci U S A* 2009;**106**:2983–2988.

92. Kucharska-Newton AM, Couper DJ, Pankow JS, Prineas RJ, Rea TD, Sotoodehnia N, Chakravarti A, Folsom AR, Siscovick DS, Rosamond WD. Diabetes and the risk of sudden cardiac death, the Atherosclerosis Risk in Communities study. *Acta Diabetol* 2010;**47 Suppl 1**:161–168.

93. Vianna CR, Huntgeburth M, Coppari R, Choi CS, Lin J, Krauss S, Barbatelli G, Tzameli I, Kim Y-B, Cinti S, Shulman GI, Spiegelman BM, Lowell BB. Hypomorphic mutation of PGC-1beta causes mitochondrial dysfunction and liver insulin resistance. *Cell Metab* 2006;**4**:453–464.

94. Akar FG, O'Rourke B. Mitochondria are sources of metabolic sink and arrhythmias. *Pharmacol Ther* 2011;**131**:287–294.

95. Faivre JF, Findlay I. Action potential duration and activation of ATP-sensitive potassium current in isolated guinea-pig ventricular myocytes. *Biochim Biophys Acta* 1990;**1029**:167–172.

96. Fosset M, Weille JR De, Green RD, Schmid-Antomarchi H, Lazdunski M. Antidiabetic sulfonylureas control action potential properties in heart cells via high affinity receptors that are linked to ATP-dependent K+ channels. *J Biol Chem* 1988;**263**:7933–7936.

97. Smyth JW, Hong TT, Gao D, Vogan JM, Jensen BC, Fong TS, Simpson PC, Stainier DYR, Chi NC, Shaw RM. Limited forward trafficking of connexin 43 reduces cell-cell coupling in stressed human and mouse myocardium. *J Clin Invest* 2010;**120**:266–279.

98. Liu M, Liu H, Dudley SC. Reactive oxygen species originating from mitochondria regulate the cardiac sodium channel. *Circ Res* 2010;**107**:967–974.

99. Wang J, Wang H, Zhang Y, Gao H, Nattel S, Wang Z. Impairment of HERG K(+) channel function by tumor necrosis factor-alpha: role of reactive oxygen species as a mediator. *J BiolChem* 2004;**279**:13289–13292.

100. Belevych AE, Terentyev D, Viatchenko-Karpinski S, Terentyeva R, Sridhar A, Nishijima Y, Wilson LD, Cardounel AJ, Laurita KR, Carnes CA, Billman GE, Gyorke S. Redox modification of ryanodine receptors underlies calcium alternans in a canine model of sudden cardiac death. *Cardiovasc Res* 2009;**84**:387–395.

101. Weiss J, Lamp S, Shine K. Cellular K(+) loss and anion efflux during myocardial ischemia and metabolic inhibition. *Am J Physiol* 1989;**256**:H1165–H1175.

102. Bovo E, Lipsius SL, Zima A V. Reactive oxygen species contribute to the development of arrhythmogenic Ca^{2+} waves during β-adrenergic receptor stimulation in rabbit cardiomyocytes. *J Physiol* 2012;**590**:3291–3304.

103. Yang K-C, Kyle JW, Makielski JC, Dudley SC. Mechanisms of sudden cardiac death: oxidants and metabolism. *Circ Res* 2015;**116**:1937–1955.

104. Yang K-C, Bonini MG, Dudley SC. Mitochondria and arrhythmias. *Free Radic Biol Med* 2014;**71**:351–361.

105. Jeevaratnam K, Guzadhur L, Goh Y, Grace A, Huang CL-H. Sodium channel haploinsufficiency and structural change in ventricular arrhythmogenesis. *Acta Physiol* 2016;**216**:186–202.

106. Martin CA, Huang CL-H, Grace AA. Progressive Conduction Diseases. *Card Electrophysiol Clin North Am* 2010;**2**:509–519.

107. Wang Y, Tsui H, Ke Y, Shi Y, Li Y, Davies L, Cartwright EJ, Venetucci L, Zhang H, Terrar DA, Huang CL-H, Solaro RJ, Wang X, Lei M. Pak1 is required to maintain ventricular Ca(2+) homeostasis and electrophysiological stability through SERCA2a regulation in mice. *Circ Arrhythm Electrophysiol* 2014;**7**:938–948.

108. Tsui H, Zi M, Wang S, Chowdhury SK, Prehar S, Liang Q, Cartwright EJ, Lei M, Liu W, Wang X. Smad3 couples Pak1 with the antihypertrophic pathway through the E3 ubiquitin ligase, Fbxo32. *Hypertension* 2015;**66**:1176–1183.

109. Liu W, Zi M, Naumann R, Ulm S, Jin J, Taglieri DM, Prehar S, Gui J, Tsui H, Xiao R-P, Neyses L, Solaro RJ, Ke Y, Cartwright EJ, Lei M, Wang X. Pak1 as a novel therapeutic target for antihypertrophic treatment in the heart / clinical perspective. *Circulation* 2011;**124**:2702–2715.

110. Wang R, Wang Y, Lin WK, Zhang Y, Liu W, Huang K, Terrar DA, Solaro RJ, Wang X, Ke Y, Lei M. Inhibition of angiotensin II-induced cardiac hypertrophy and associated ventricular arrhythmias by a p21 activated kinase 1 bioactive peptide. *PLoS One* 2014;**9**:e101974.

Table 1. Current anti-arrrhythmic pharmacological drugs (after [7,13])

Class	Drug exemplars	Pharmacological targets	Clinical indications	Therapeutic action
0		***HCN channel blockers***		
	ivabradine	HCN channel mediated pacemaker current (I_f) inhibitor.	Stable angina and chronic cardiac failure with HR ≥ 70 bpm. Potential new applications for tachyarrhythmias [*ACCF/AHA/NICE guidelines* [14]]	Reduced SAN automaticity
I		***Voltage-gated Na^+ channel inhibitors***		
	quinidine, ajmaline, disopyramide	Nav1.5 open state; intermediate (τ~1-10 s) dissociation kinetics; often accompanying K^+ channel inhibition	Supraventricular tachyarrhythmias particularly recurrent AF. VT, VF (including SQTS and Brugada syndrome) [*ACCF/AHA/NICE guidelines* [15–18]**]**	Reduced ectopic ventricular/atrial automaticity and accessory pathway conduction. Increased refractory period, decreasing re-entrant tendency[19–21]
	lidocaine, mexiletine	Nav1.5 open state; rapid dissociation (τ~0.1-1.0 s).-I_{Na} window current	Ventricular tachyarrhythmias (VT, VF), particularly following myocardial infarction [*ACCF/AHA/NICE guidelines* [15,17]**]**.	Reduced ectopic ventricular automaticity, DAD-induced triggered activity, and re-entrant tendency by converting unidirectional to bidirectional block, particularly in ischaemic partially depolarised myocardium[19–21]
	propafenone, flecainide	Nav1.5 inactivated state; slow dissociation (τ>10 s).	Supraventricular tachyarrhythmias (AT, Af, AF and tachycardias involving accessory pathways). Ventricular tachyarrhythmias resistant to other treatment in the absence of structural heart disease, PVC, CPVT [*ACCF/AHA/NICE guidelines* [15–18]**]**	Reduced ectopic ventricular/atrial automaticity, DAD-induced triggered activity, and re-entrant tendency by converting unidirectional to bidirectional block. Slowed conduction and reduced excitability particularly at rapid heart rates blocking re-entrant pathways showing depressed conduction[19–21]
	ranolazine	Nav1.5 late I_{NaL} current.	Stable angina, VT. Potential new class of drugs for management of tachyarrhythmias, particularly in LQTS3. [*Clinical trials related to anti-arrhythmic effects* [22–25]]	Decreased AP recovery time and QT interval. Reduced EAD -induced triggered activity
II		***Autonomic inhibitors and activators***		

	Non selective, β-inhibitors: carvedilol, propranolol, nadolol Selective β1-adrenergic receptor inhibitors: atenolol, bisoprolol, betaxolol, celiprolol, esmolol, metoprolol	Non selective, β-, and selective β1-adrenergic receptor inhibitors	Sinus tachycardia or other types of tachycardic, including supraventricular (AF, Af, AT), arrhythmias. Rate control of AF, and ventricular tachyarrhythmias (VT, PVC). [note. Atenolol, propranolol and nadolol also used in LQTS; nadolol used in CPVT] [*ACCF/AHA/NICE guidelines* [15–18]**]**	Reduced SAN, AVN and ectopic ventricular/atrial automaticity. Reduced EAD/DAD-induced triggered activity, SAN re-entry, and AVN conduction terminating re-entry[6,20,21].
	isoproterenol	Nonselective β adrenergic receptor activators	Congenital or acquired (often drug-related) Torsades de Pointes VT [*ACCF/AHA/NICE guidelines* [15–18]**]**	Suppressed EAD related triggered activity[6,20,21].
	atropine, anisodamine, hyoscine, scopolamine	Muscarinic M_2 receptor inhibitors	Mild or modulate symptomatic sinus bradycardia or AVN conduction inhibition [*ACCF/AHA/NICE guidelines* [15,18]**].**	Increased SAN automaticity and AVN conduction[20,21]
	carbachol, pilocarpine, methacholine, digoxin	Muscarinic M_2 receptor activators	Sinus tachycardia or supraventricular tachyarrhythmias [*ACCF/AHA/NICE guidelines* [15,18]**].**	Reduced SAN automaticity, SAN re-entry, and AVN conduction terminating re-entry[20,21]
	adenosine, ATP. [note: aminophylline acts as an adenosine receptor inhibitor]	Adenosine A_1 receptor activators	Sinus tachycardia, supraventricular tachyarrhythmias, frequent atrial or premature ventricular beats, cAMP-mediated triggered VT [*ACCF/AHA/NICE guidelines* [15,17,18]**]**.	Reduced SAN automaticity, EAD/DAD-induced triggered activity, and AVN conduction, terminating re-entry[20,21,26]
III		***K^+ channel inhibitors and openers***		
	ambasilide, amiodarone, dronedarone	Nonselective K^+ channel inhibitors	VT in patients without structural heart disease, or with remote myocardial infarction, Tachyarrhythmias with WPW. AF with AV conduction via accessory pathway; VF and PVC; Tachyarrhythmias associated with supraventricular arrhythmias and AF [*ACCF/AHA/NICE guidelines* [15–18]**].**	Increased AP recovery time, and refractory period, decreasing re-entrant tendency. Note. Amiodarone also slows sinus node rate and AV conduction[20,21].
	dofetilide, ibutilide, sotalol	Kv11.1 (HERG) channel mediated rapid K^+ current (I_{Kr}) inhibitors	VT in patients without structural heart disease, or with remote myocardial infarction. Tachyarrhythmias associated with WPW syndrome. AF with AV conduction via accessory pathway, VF, PVC. Tachy-arrhythmias associated with supraventricular	Increased AP recovery time and refractory period, with decreased re-entrant tendency[20,21,27]

			arrhythmias and AF [*ACCF/AHA/NICE guidelines* [15–18]**.**	
	vernakalant	Kv1.5 channel mediated, ultra-rapid K^+ current (I_{Kur}) inhibitors	Acute conversion of AF. [*Clinical trials related to anti-arrhythmic effects:* [28–31]]	Increased atrial AP recovery time, and atrial refractory period, with decreased re-entrant tendency[20]
	nicorandil, pinacidil	Kir6.2 (I_{KATP}) openers	Nicorandil: treatment of stable angina (second-line). [note. Pinacidil: investigational drug for the treatment of hypertension]	Potentially decreased AP recovery time
IV		***Ca^{2+} handling modulators***		
	bepridil	Nonselective surface membrane Ca^{2+} channel inhibitors	Angina pectoris**.** Potential management of supraventricular tachyarrhythmias [*ACCF/AHA/NICE guidelines* [15,18]**]**	Reduced AVN conduction, terminating re-entry, and EAD/ DAD-induced triggered activity[6,20,21]
	phenylalkylamines (e.g. verapamil), benzothiazepines (e.g. diltiazem).	$Ca_v1.2$ and $Ca_v1.3$ channel mediated L-type Ca^{2+} current (I_{CaL}) inhibitors	Supraventricular arrhythmias and VT without structural heart disease. Rate control of AF [*ACCF/AHA/NICE guidelines* [15,17,18]**].**	Reduced AVN conduction, terminating re-entry, and EAD/ DAD-induced triggered activity[6,20,21]
	flecainide	SR RyR2-Ca^{2+} channel inhibitors	Catecholaminergic polymorphic ventricular tachycardia (CPVT). [*Clinical trials related to anti-arrhythmic effects*[32,33,34]]	Reduced DAD-induced triggered activity[6,20,21]
V		***Mechanosensitive channel inhibitors***		
	No clinically approved drugs in use.			
VI		***Gap junction channel inhibitors***		
	No clinically approved drugs in use.			
VII		***Upstream target modulators***		
	captopril, enalapril, delapril, ramipril, quinapril perindopril, lisinopril,benazepril, imidapril, trandolapril, cilazapril	Angiotensin-converting enzyme inhibitors (ACEIs)	Management of hypertension, symptomatic heart failure. Potential application reducing arrhythmic substrate. [*Clinical trials related to anti-arrhythmic effects*[35–37]**]**	Reduced structural and electrophysiological remodelling changes that compromise AP conduction and increase re-entrant tendency
	losartan, candesartan, eprosartan, telmisartan, irbesartan, olmesartan, valsartan, saprisartan	Angiotensin receptor inhibitors (ARBs)	Management of hypertension, symptomatic heart failure. Potential application reducing arrhythmic substrate. [*Clinical trials related to anti-arrhythmic effects*[35,38,39]]	Reduced structural and electrophysiological remodelling changes that compromise AP conduction and increase re-entrant tendency

eplerenone, spironolactone	Aldosterone receptor antagonists	Congestive cardiac failure. [*Clinical trials related to anti-arrhythmic effects*[40–47]]	Potential reduction of arrhythmic substrate, including reduced fibrosis. K^+ sparing diuretic effect.
omega-3 fatty acids: eicosapentaenoic acid (EHA), docosahexaenoic acid （DHA, docosapentaenoic acid (DPA)	Omega-3 fatty acids	Post myocardial infarct reduction of risk of cardiac death, myocardial infarct, stroke, and abnormal cardiac rhythms. [*Clinical trials related to anti-arrhythmic effects*[48–50]]	Reduced structural and electrophysiological remodelling changes that compromise AP conduction and increase re-entrant tendency
statins	3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors	Post myocardial infarct reduction of risk of cardiac death, myocardial infarct, stroke, and abnormal cardiac rhythms. [*Clinical trials related to anti-arrhythmic effects*[51–54]]	Reduced structural and electrophysiological remodelling changes that compromise AP conduction and increase re-entrant tendency

Notes

1. Of categories in the full classification [7], Classes V (Mechanosensitive channel inhibitors), VI (Gap junction channel inhibitors) and subclasses IIIc (Transmitter dependent K^+ channel inhibitors), IVc (Sarcoplasmic reticular Ca^{2+}-ATPase activators), IVd (Surface membrane ion exchange inhibitors) and IVe (Phosphokinase and phosphorylase inhibitors) include investigational but not clinically approved drugs and are not listed here. In Class III, nicorandil and pinacidil are approved drugs but not in use or clinical trials for anti-arrhythmic therapy. Class VII (Upstream target modulators) contains approved drugs not in current direct use for anti-arrhythmic therapy, but for which clinical trials for anti-arrhythmic actions are now available.

2. Abbreviations: AF, atrial fibrillation; Af, atrial flutter; AP, action potential; AT, atrial tachycardia; AV, atrioventricular; AVN; atrioventricular node; cAMP, cyclic 3',5'-adenosine monophosphate; CPVT, catecholaminergic polymorphic ventricular tachycardia; DAD, delayed afterdepolarisation; EAD, early afterdepolarisation; HCN, hyperpolarisation cyclic nucleotide activated channel; HR, heart rate; LQTS, long QT syndrome; PVC, premature ventricular contraction; SAN, sino-atrial node; SQTS, short QT syndrome; VF, ventricular fibrillation; VT, ventricular tachycardia; WPW, Wolf-Parkinson-White syndrome.

Figure legends

Figure 1. Modernised classification scheme [7,13] for currently available pharmacological agents directed at treatment of arrhythmia, with a correlation of the relevant classes (*A*) acting on either arrhythmic trigger or substrate [56] (*B*), to the cascade of their underlying cellular membrane and physiological processes (*Ca-d*) [11].

Figure 2. Membrane ion currents, listing their underlying proteins and encoding genes, underlying inward depolarising (*A*) or outward repolarising currents (*B*) producing the atrial (*C*) and ventricular (*D*) action potential, listing underlying membrane proteins and encoding genes [11].

Figure 3. Surface and intracellular membrane ion channels, ion exchangers, transporters, autonomic receptors and ionic pumps involved in cardiomyocyte physiological excitation and activation forming established or potential pharmacological targets underlying membrane (a) and autonomic signalling (b), excitation contraction coupling (c) and upstream energetic or structural remodelling targets (d). ACh: acetylcholine; Adr: adrenaline; cAMP: cyclic 3'5-adenosine monophosphate; Cx: connexin; G_i: inhibitory G protein; G_s stimulatory G-protein; HCN: hyperpolarisation-activated cyclic nucleotide-gated channel; MSC: mechanically sensitive channel; Na^+, K^+, $Ca^{2+}$and $Ca^{2+}/3Na^+$ fluxes through Nav1.5/Na^+, Kv/K^+, Cav/Ca^{2+} channel and Na^+/Ca^{2+} exchanger proteins; PKA: protein kinase A; RyR2: cardiac ryanodine receptor, type 2; SERCA: sarcoplasmic reticular Ca^{2+} ATPase.

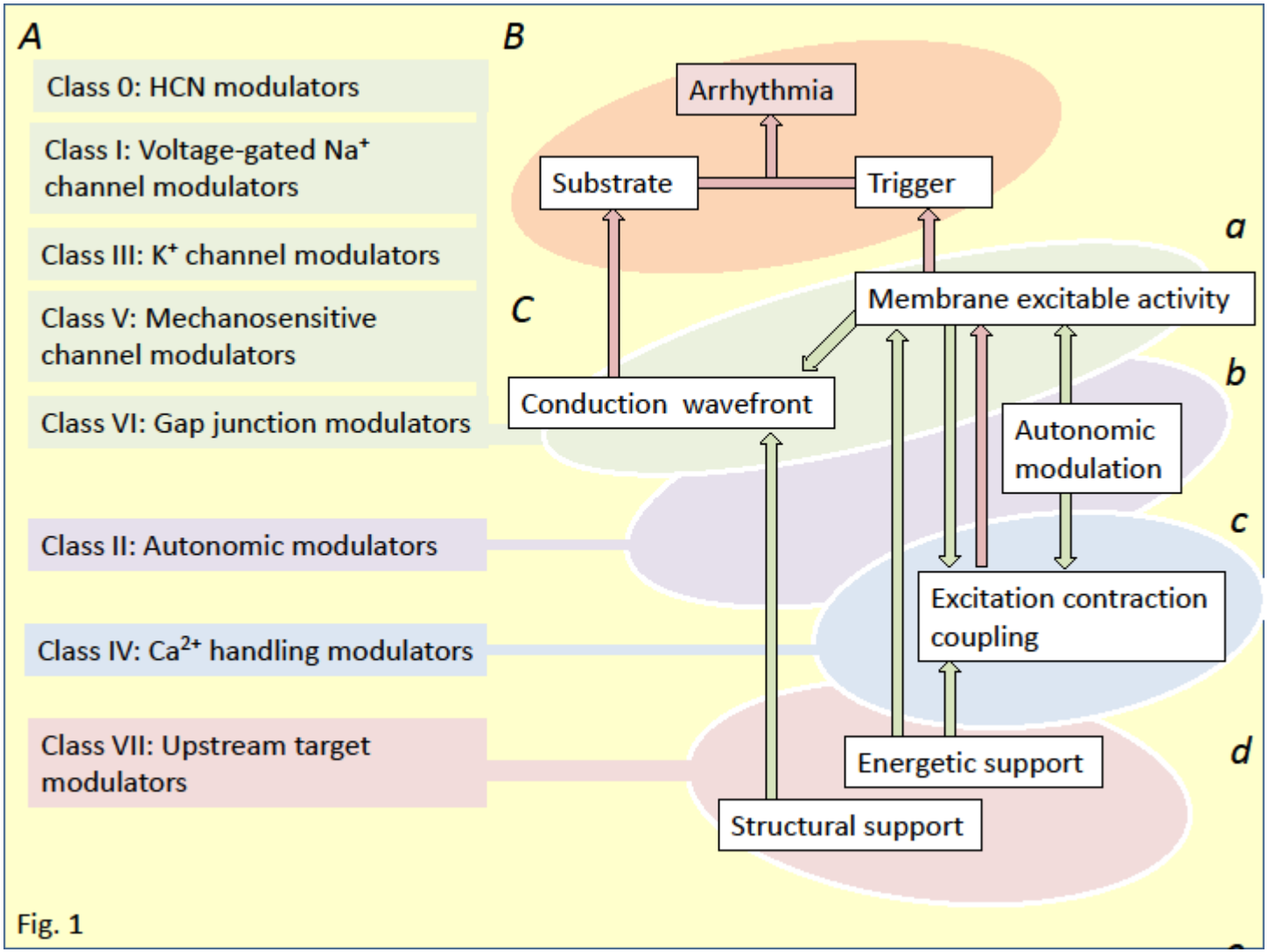
A
Class 0: HCN modulators
Class I: Voltage-gated Na+ channel modulators
Class III: K+ channel modulators
Class V: Mechanosensitive channel modulators
Class VI: Gap junction modulators
Class II: Autonomic modulators
Class IV: Ca2+ handling modulators
Class VII: Upstream target modulators
B
Arrhythmia
Substrate
Trigger
a
C
Membrane excitable activity
b
Conduction wavefront
Autonomic modulation
c
Excitation contraction coupling
Energetic support
d
Structural support

Fig. 1

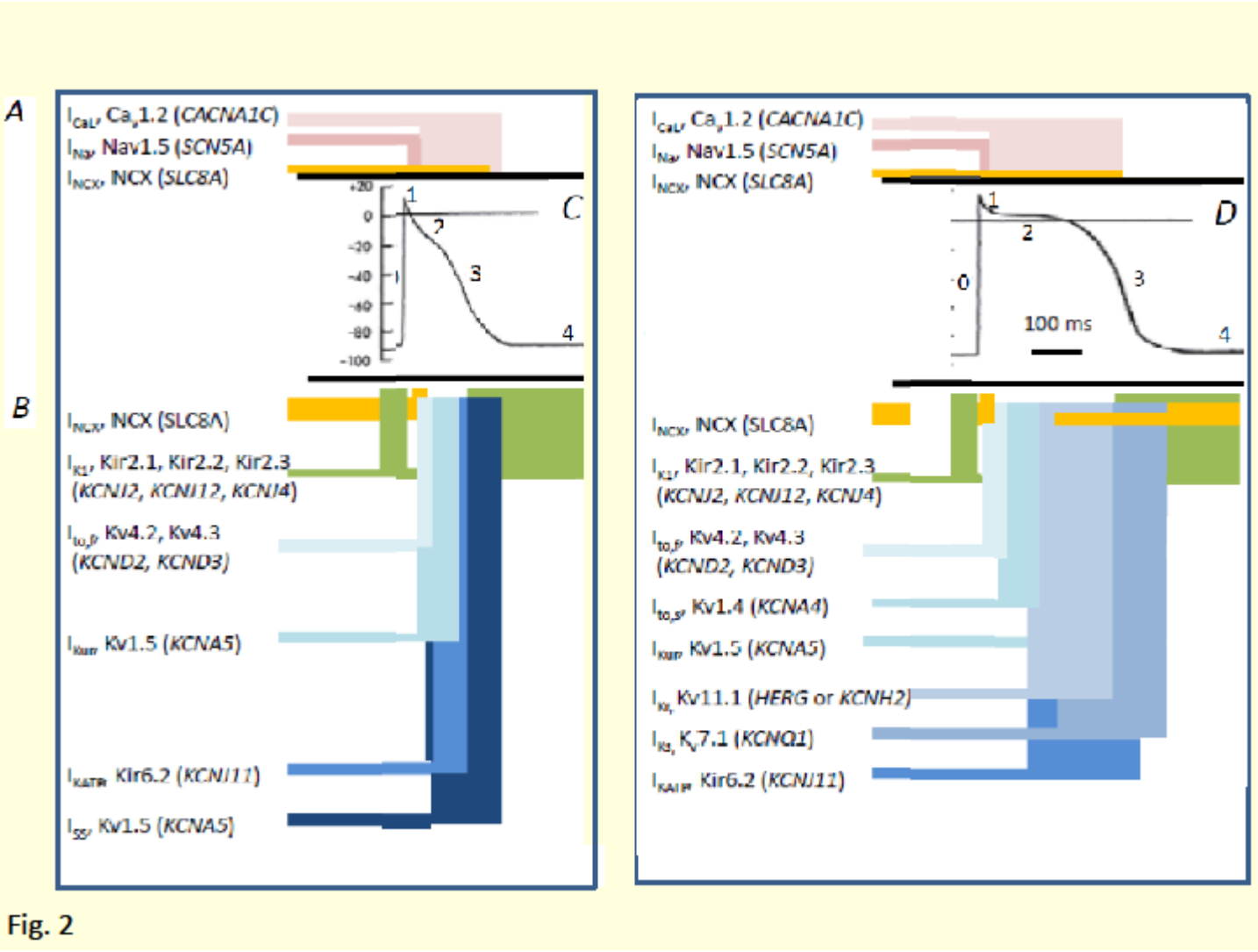
A
B
I_{CaL}, $Ca_v1.2$ (*CACNA1C*)
I_{Na}, Nav1.5 (*SCN5A*)
I_{NCX}, NCX (*SLC8A*)
+20
0
-20
-40
-60
-80
-100
1
2
3
4
C
I_{NCX}, NCX (SLC8A)
I_{K1}, Kir2.1, Kir2.2, Kir2.3
(*KCNJ2, KCNJ12, KCNJ4*)
$I_{to,f}$, Kv4.2, Kv4.3
(*KCND2, KCND3*)
I_{Kur}, Kv1.5 (*KCNA5*)
I_{KATP}, Kir6.2 (*KCNJ11*)
I_{SS}, Kv1.5 (*KCNA5*)
I_{CaL}, $Ca_v1.2$ (*CACNA1C*)
I_{Na}, Nav1.5 (*SCN5A*)
I_{NCX}, NCX (*SLC8A*)
1
2
3
4
0
100 ms
D
I_{NCX}, NCX (SLC8A)
I_{K1}, Kir2.1, Kir2.2, Kir2.3
(*KCNJ2, KCNJ12, KCNJ4*)
$I_{to,f}$, Kv4.2, Kv4.3
(*KCND2, KCND3*)
$I_{to,s}$, Kv1.4 (*KCNA4*)
I_{Kur}, Kv1.5 (*KCNA5*)
I_{Kr}, Kv11.1 (*HERG* or *KCNH2*)
I_{Ks}, $K_v7.1$ (*KCNQ1*)
I_{KATP}, Kir6.2 (*KCNJ11*)

Fig. 2

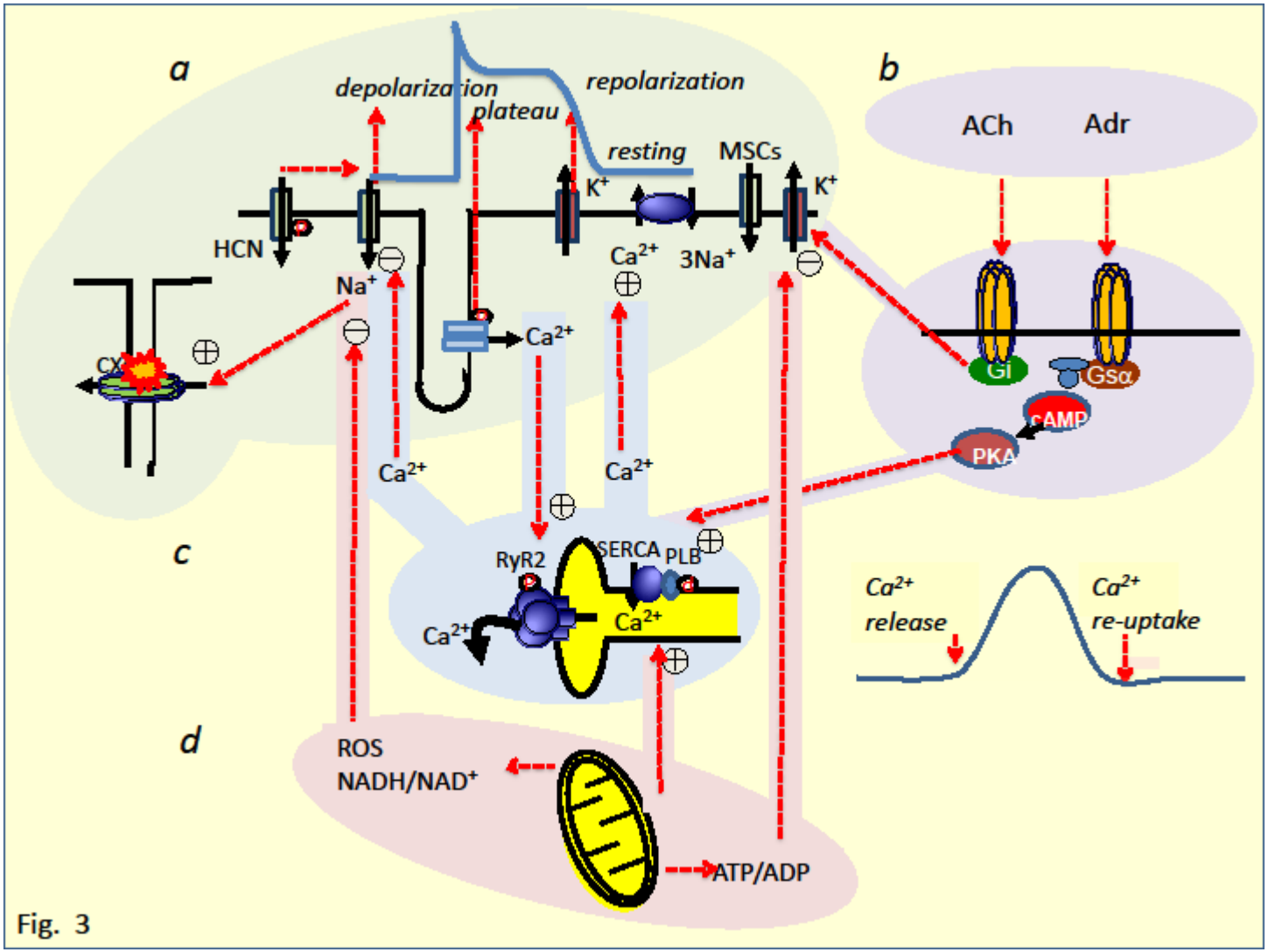
a
depolarization
plateau
repolarization
resting
MSCs
HCN
K+
K+
Ca2+
3Na+
Na+
Ca2+
CX
Ca2+
Ca2+
b
ACh
Adr
Gi
Gsα
cAMP
PKA
c
RyR2
SERCA
PLB
Ca2+
Ca2+
Ca2+
release
Ca2+
re-uptake
d
ROS
NADH/NAD+
ATP/ADP

Fig. 3