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REVIEW

An overview of drug-induced sodium channel blockade and changes in cardiac conduction: Implications for drug safety

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Abstract

The human voltage-gated sodium channel $Na_v1.5$ ($hNa_v1.5$/SCN5A) plays a critical role in the initiation and propagation of action potentials in cardiac myocytes, and its modulation by various drugs has significant implications for cardiac safety. Drug-dependent block of $Na_v1.5$ current (I_{Na}) can lead to significant alterations in cardiac electrophysiology, potentially resulting in conduction slowing and an increased risk of proarrhythmic events. This review aims to provide a comprehensive overview of the mechanisms by which various pharmacological agents interact with $Na_v1.5$, focusing on the molecular determinants of drug binding and the resultant electrophysiological effects. We discuss the structural features of $Na_v1.5$ that influence drug affinity and specificity. Special attention is given to the concept of state-dependent block, where drug binding is influenced by the conformational state of the channel, and its relevance to therapeutic efficacy and safety. The review also examines the clinical implications of I_{Na} block, highlighting case studies of drugs that have been associated with adverse cardiac events, and how the Vaughan-Williams Classification system has been employed to qualify "unsafe" sodium channel block. Furthermore, we explore the methodologies currently used to assess I_{Na} block in nonclinical and clinical settings, with the hope of providing a weight of evidence approach including in silico modeling, in vitro electrophysiological assays and in vivo cardiac safety studies for mitigating proarrhythmic risk early in drug discovery. This review underscores the importance of understanding $Na_v1.5$ pharmacology in the context of drug development and cardiac risk assessment.

Abbreviations: ECG, electrocardiogram; FAERS, FDA Adverse Event Reporting System; I_{Na}, $Na_v1.5$ current; HTS, high-throughput screening; ICH, International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use; PR/QRS/QT, deflections which comprise the electrocardiogram; QTc, heart rate-corrected QT interval; VCG, vectorcardiograms.

INTRODUCTION

Sudden cardiac death, primarily due to ventricular fibrillation, remains a leading cause of mortality. Unfortunately, antiarrhythmic drugs that block the human cardiac sodium channel ($Na_v1.5$/SCN5A), once believed to reduce the risk of sudden death in "at risk" individuals, are known to slow cardiac conduction leading to increased proarrhythmic risk. The Cardiac Arrhythmia Suppression Trials (CAST) have shown that antiarrhythmics (particularly sodium channel blockers) increase mortality and risk of sudden cardiac death in post-infarction patients.[1] Decades after CAST, there is still no consensus on safety assessment of novel sodium channel-blocking drugs.[2] In the general population, a significant increase in mortality is associated with each 10 ms prolongation in QRS duration of the electrocardiogram (ECG) – a measure of cardiac conduction.[3,4] In men, a QRS duration >110 ms led to ~2.5-fold increase in sudden cardiac death,[5] and significantly greater hazard ratio for mortality (HR > 3) with a QRS interval > 120 ms.[6,7] In addition, the arrhythmic risk associated with peak sodium current (I_{Na}) block is dependent on the presence and degree of structural heart disease, further complicating any translation of nonclinical findings and those in healthy human subjects.[1,8]

Cardiac conduction slowing can lead to the development of lethal arrhythmias and this property of novel drugs should be evaluated during drug development. However, unlike repolarization (i.e., the QT interval of the ECG), there is no standard risk assessment matrix for drug-induced conduction liability. Inward cardiac sodium channel current is the primary driver for the excitatory cardiac impulse, and channel kinetics contribute to the morphology of the resulting QRS complex. $Na_v1.5$ remains the second most prevalent target evaluated in early, nonclinical cardiac ion channel screening.[9] However, the number of marketed drugs exhibiting conduction slowing are dwarfed by agents that prolong the QT interval by blockade of the hERG encoded I_{Kr} channel ($hK_v11.1$) (Figure 1). This suggests that drugs with off-target sodium channel properties are not being developed due to "risk aversion" for QRS interval prolongation even though it may be potentially benign. Furthermore, there is uncertainty as to how well nonclinical results translate to clinical findings, making it difficult to provide a safety profile for new molecules in nonclinical development.

The kinetic properties of $Na_v1.5$ blockers are qualified by the Vaughan-Williams Classification system and considered "safe" (Class Ib) or "unsafe" (Class Ia/c); and yet, the kinetic properties of drugs are rarely investigated in nonclinical drug development. Current tools include ion channel electrophysiology methods, in silico modeling, nonclinical in vivo models, and an enhanced assessment of clinical ECGs all of which provide an opportunity to identify and successfully develop drugs that carry off-target I_{Na} ion channel blocking properties. This "weight of evidence" approach would qualify candidate molecules with little to no conduction slowing at sufficient multiples to the clinical therapeutic plasma concentration to be safe and not produce arrhythmias thereby supporting the clinical experience gained from the Vaughan-Williams classification. This review aims to contextualize the nonclinical/clinical/regulatory concerns associated with drug-induced conduction slowing and to provide a framework for de-risking pharmaceutical agents in drug development.

$NA_V1.5$ AND THE BIOPHYSICAL UNDERPINNING OF CONDUCTION

Cardiac conduction represents the transmission of electrical excitability throughout the heart. This wave of

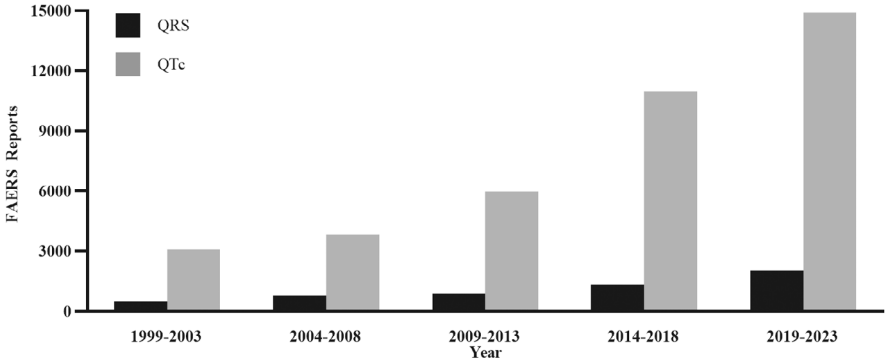

FIGURE 1 Incidence of QRS to QTc-TdP adverse events reported from 1999 to 2023 retrieved from the FDA Adverse Event Reporting System (FAERS) database shows 5508 versus 38,756 reports for QRS or QTc, respectively (duplicate reports were not removed). Search terms from 1999 to 2023 include: Electrocardiogram QRS complex prolonged, Electrocardiogram QRS complex abnormal, Electrocardiogram QRS complex abnormal, QRS axis abnormal; and for QTc: Electrocardiogram QT interval abnormal, Electrocardiogram QT prolonged, Long QT syndrome, Torsade de Pointes.

excitation results in coordinated contraction of cardiac muscle and pumping of blood. Depolarization is primarily driven by the movement of Na^+ ions via I_{Na} during Phase 0 of the myocyte action potential. The arrival of an excitatory (depolarizing) impulse through the Purkinje system to ventricular tissue results in the initial deflection of the QRS complex on the ECG. The time required for the excitatory wave to move through the ventricles is reflected in the width of the QRS complex. To initiate the action potential, the cellular Na^+ influx must be large and rapid to charge the membrane capacitance of the cardiac myocyte, which acts as a low pass filter to blunt rapid membrane potential changes.[10] The conduction velocity through the entire cardiac syncytium is determined by myocytes perpetuating this traveling electrical wavefront and cell-to-cell conduction.

Cardiac conduction is a highly synchronized process due to the strong electrotonic coupling between myocytes; however, this coupling is reduced in many disease states (e.g., regional ischemia and subsequent fibrosis).[11] Weakly coupled cells can disrupt or slow conduction, produce heterogeneity of depolarization, and contribute to unidirectional block, all of which increase the potential for arrhythmias to develop.[12] When conduction is disrupted due to ischemia in one region, increased spatial dispersion of electrical activity may emerge as another proarrhythmic factor.[13,14] Acidosis, ischemia, chronic disease, or altered electrolyte homeostasis modifies electrotonic coupling and can lead to modulation of conduction. Additionally, pathology associated with the disease state may serve as an acute or chronic disruptor by promoting long-term ion channel, calcium, and anatomical remodeling.[15–17]

In humans, the pore forming α-subunits of the $Na_v1.5$ are encoded by nine genes, resulting in the expression of distinct isoforms ($Na_v1.1$–$Na_v1.9$).[18] $Na_v1.5$ is expressed primarily in heart and embryonic skeletal muscle; therefore, this review focuses solely on the contributions of this channel to cardiac electrophysiology.[19–21] The expression of multiple isoforms in different tissues is relevant when considering off-target drug effects because all currently available drugs that block $Na_v1.5$ have minimal isoform selectivity. Therefore, cardiac anti-arrhythmic drugs can alter Na channel activity in extra-cardiac tissue, which may affect cardiac function indirectly, as well as producing off-target non-cardiac toxicity. Likewise, Na^+ channel blockers for non-cardiac indications such as antiepileptics or local anesthetics may produce off-target cardiac toxicity due to sub-optimal selectivity against the Na^+ channel isoforms.

State-dependent block of the $Na_v1.5$ results in voltage- and/or frequency-dependence associated with drugs.[22–24] Hille and Hondeghem & Katzung concurrently, but independently, formulated the Modulated Receptor Hypothesis (MRH) to describe the effects of local anesthetics in nerve and cardiac muscle, respectively.[24,25] This theory postulates a conformational change in the channel as it transitions between open, closed, and inactive "states," causing a change in the drug binding properties in $Na_v1.5$. The Guarded Receptor Hypothesis (GRH) was later proposed to simplify the complex mathematics involved in the calculation of drug on-rate and off-rate constants.[26]

The MRH and GRH explain the voltage-dependence of recovery from drug block, which is slow in depolarized tissue compared to normal or highly polarized cells. Additionally, the kinetic properties of binding can have profound effects on drug-induced block of Na^+ current. Repetitive stimuli may cause accumulation of drug block due to the slow dissociation of drug from the high-affinity binding site. "Use-dependence" describes the increase in $Na_v1.5$ block associated with increased frequency of channel stimulation.[23] A combination of these state-dependent properties provides selectivity of drugs for different Na channel isoforms in different tissues and shapes the safety profile of the drug, a critical component in drug development.

HISTORY OF SODIUM CHANNEL BLOCKERS IN DRUG DISCOVERY

Antiarrhythmic drugs that reduce I_{Na} are classified by the Vaughan-Williams system as Class I agents.[27] At clinical doses, these drugs exhibit anesthetic properties, depress maximal rate of depolarization (MRD) and prolong the effective refractory period. Three subtypes of this classification were defined (Classes Ia, b, and c), which exhibit important differences in arrhythmogenic potential. Class Ib agents, such as lidocaine (a local anesthetic), are generally the least proarrhythmic because they produce little change in the MRD and QRS interval and may shorten QT interval during sinus rhythm. These drugs are often used in the acute management of ventricular arrhythmias. In contrast, Class Ia agents, such as quinidine, block Na^+ current and prolong action potential duration (APD) at relatively high therapeutic doses without depolarizing the membrane potential. Finally, Class Ic agents, such as flecainide, produce slowing of conduction and QRS widening without a significant prolongation of the APD or QT interval at clinical doses. In recent years, the evolution of these categories to include additional modes of block has been considered, preserving the simplicity of the original subclassification yet allowing for the existence of multiple drug targets or actions and consideration of proarrhythmic effects.[28]

The CAST trial was a randomized, multicenter, placebo-controlled clinical study designed to determine

whether, in patients with prior myocardial infarction (MI) and asymptomatic or minimally symptomatic ventricular ectopy (VE), the incidence of sudden cardiac death could be reduced by Class Ic antiarrhythmic drugs.[29] However, after <1 year of follow-up, the encainide and flecainide arms of the study were halted due to increased mortality compared to the placebo group. A subsequent study (CAST II), comparing moricizine to placebo, was also terminated prematurely due to excess mortality in the treatment arm.[30] Additional evidence in human and animal studies showed that Class I antiarrhythmic drugs may have proarrhythmic actions.[31–33] It was concluded that the use of cardiac $Na_v1.5$ blockers in post MI patients may suppress VE, but paradoxically increase sustained ventricular arrhythmias and mortality, and that delayed intramyocardial conduction in hearts with underlying disease promoted the formation of re-entrant circuits, despite a reduction in spontaneous triggers.[34] Unfortunately, the CAST findings confirmed the potential adverse effects of Class I antiarrhythmics that were previously postulated.[35,36]

Despite the CAST trial findings and acknowledged clinical risk, a significant number of drugs have been developed with both on- and off-target effects on the cardiac Na channel. In a contemporary analysis, we discovered a myriad of therapeutic areas reporting clinical observation of conduction slowing, that is, QRS prolongation, including, but not restricted to antiarrhythmics (Figure 2). One example is the development of tricyclic antidepressants (TCAs) in the 1950s, which largely replaced monoamine oxidase inhibitors for the treatment of depression. Most TCAs are potent $Na_v1.5$ blockers that may also block calcium channels.[37] TCA overdose is one of the most frequent causes of drug poisoning, and though initial symptoms are characterized by anticholinergic effects, the cardiac effects of $Na_v1.5$ block may be profound.[38] QRS prolongation serves as a marker for severe TCA overdose, such that QRS widening to >100 ms is predictive of seizures, while QRS > 160 ms is predictive of ventricular tachycardia.[39]

The use of $Na_v1.5$ blockers for the termination and rhythm control in atrial fibrillation (AF) patients was once a promising avenue; however, their use in this condition is restricted by labeling warnings for patients at risk for $Na_v1.5$ inhibition-dependent CV complications.[40] Efforts to develop blockers of peak I_{Na}, such as vernakalant (Class III drug), for the therapeutic treatment of AF have raised concerns from regulators on: (1) the risk: benefit to patients and (2) potential adverse reactions that range from hypotension to mortality, all a consequence of on-target pharmacology (FDA: December 10, 2019, Meeting of the Cardiovascular and Renal Drugs Advisory Committee Meeting Announcement).[41–43] Recently, a revision in the product label for a marketed antiseizure medication, lamotrigine (Lamictal™), that included the in vitro classification of the drug displaying Class Ib-like properties elicited an editorial from "The International League Against Epilepsy"; emphasizing the need to better understand the impact of Na channel block on conduction for both cardiac and non-cardiac indications.[44,45]

REGULATORY FRAMEWORK: ICH GUIDELINES

Scientists have implemented drug development strategies based on principles described in the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) S7A and S7B guidance documents, that tailor validated in silico, in vitro, and in vivo nonclinical models conducted under Good Laboratory Practice (GLP) regulations to de-risk novel pharmaceutical agents from acute cardiovascular liabilities.[46,47] Although not specifically addressing conduction-related arrhythmias, the ICH S7A guidance describes several assays that may support first in human (FIH) trials, including radioligand binding assays, high-throughput ion channel screening assays (HTS), in vitro cell and cardiac tissue assays, and whole animal studies. In conscious, telemetered dogs and/or non-human primates (NHP), cardiac conduction is routinely assessed by evaluating QRS and PR intervals in single dose safety pharmacology and repeat dose toxicity studies. An important caveat is that these nonclinical studies are conducted in young healthy animals. While it has been established that cardiac conduction abnormalities are exacerbated in diseased tissue that sensitizes the heart to drug-mediated effects, validated animal disease models of conduction abnormalities may have limited utility in translation to healthy Phase I clinical trial subjects. Therefore, drug effects on $Na_v1.5$ channels are normally not investigated under pathophysiological conditions.

The focus of the ICH S7B guidance is almost entirely related to drug-induced hERG inhibition, QT prolongation, and repolarization-related arrhythmias. It does, however, describe the assessment of drug effects on ion channel currents, action potential and electrophysiological parameters in cardiac tissue, ECG effects in animals, and proarrhythmic effects. Drug effects on the QRS duration and conduction-related arrhythmias are likely detected in these studies.

In a recent survey conducted by the Safety Pharmacology Society (SPS, https://www.safetypharmacology.org/), 46% of respondents reported observing QRS prolongation in nonclinical cardiovascular safety studies either occasionally or frequently.[9] Several publications have shown

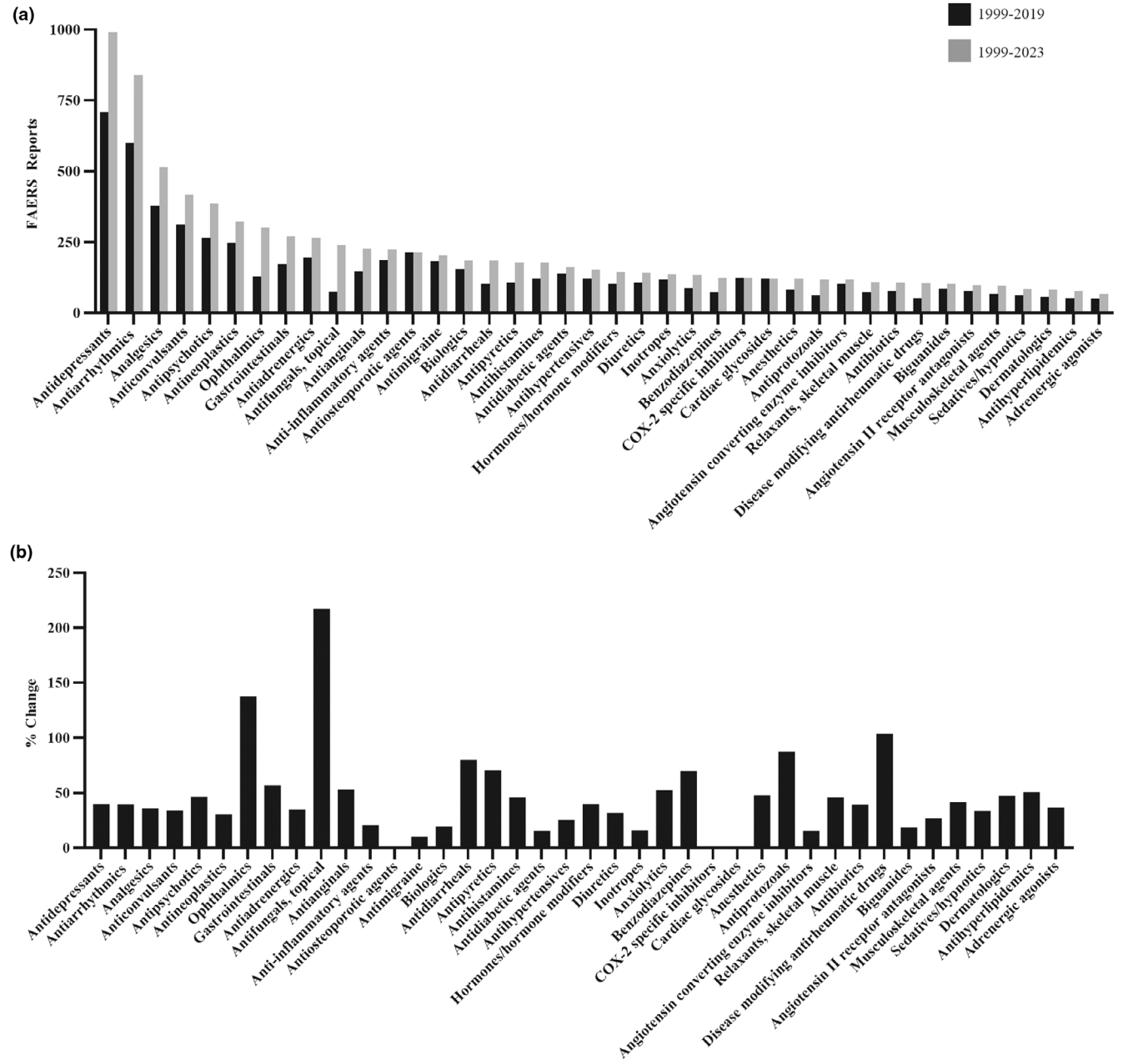

FIGURE 2 Various pharmacological drug classes that are reported to prolong the QRS interval of the ECG based on a search of the FDA AERS database. (a) Number of FAERS findings per drug class sorted from highest to lowest based on absolute cases from 1999 to 2023; (b) data shown as percent increase in findings in subsequent years 2019–2023.

that $Na_v1.5$ inhibition is detected during standard compound screening with some regularity with hit rates at approximately 13%[48] and in HTS I_{Na} patch clamp assays at approximately 26%.[49] Nonetheless, it is challenging to estimate the impact of QRS prolongation and conduction on drug development. Data available in PharmaPendium® (https://pharmapendium.com/; Elsevier) demonstrates the cases of QRS prolongation in nonclinical studies in the Drug Safety Data, as well as in humans as evidenced by a search within the FDA Adverse Event Reporting System (FAERS) (Figures 1 and 2).

CURRENT METHODOLOGIES FOR NONCLINICAL ASSESSMENT OF $NA_V1.5$ BLOCK

The nonclinical assessment of conduction liability utilizes the framework outlined in regulatory guidance documents, with the intention of identifying hazards early in the drug development process. The nonclinical development strategy for off-target $Na_v1.5$ blockade is based on knowledge of the actions of local anesthetics, antiarrhythmics and anticonvulsants, coupled with advances in predictive modeling

and structural analysis.[50,51] Because endpoints from early exploratory studies are surrogates for conduction slowing and arrhythmia, considerable flexibility exists in models/technologies/methods to appropriately identify the hazard—often increasing in complexity and physiological relevance as development compounds transition to clinical candidates.

Most in vitro secondary pharmacology panels include $Na_v1.x$ displacement binding assays derived from rat brain preparations, which may have limited applicability to cardiac $Na_v1.5$. HTS cellular electrophysiology assays on automated platforms are now commonly utilized for screening purposes, while manual patch-clamp provides more detailed mechanistic data including the characterization of state- and use-dependent binding.[52–55] The advantage of these platforms is that they utilize human cardiac ion channels, as compared to binding studies.

While a link between reduced $Na_v1.5$ conductance and delayed cardiac conduction is well established, translation from nonclinical in vitro and in vivo models to clinical end points has been challenging across assays and models. The I_{Na} patch clamp assay results strongly correlate with QRS prolongation in the ex vivo Langendorff preparation (guinea pig) and clinical QRS prolongation, with greatest sensitivity and specificity at 20% channel inhibition.[49] Prolongation is related to exposure, pacing frequency/heart rate, and is exaggerated for a Class Ic drug (flecainide) versus a Class Ib drug (mexiletine) across species.[56] Flecainide significantly prolonged QRS in the rabbit wedge preparation and conscious rat and dog studies at concentrations approximately 10- and 20-fold, respectively, below I_{Na} potency (IC_{50}).[56] Further, modulation of pacing rate allows for characterization of frequency-dependent QRS prolongation which is a hallmark of Na^+ channel block and conduction slowing.[57] QRS prolongation in humans is also predicted and achieved by drug exposures significantly lower than the $Na_v1.5$ potency (IC_{50}), substantiating that <10% inhibition of current is sufficient to produce conduction slowing.[54,58] In contrast, exposures that prolong the QRS interval in humans produce much smaller changes in the dog QRS interval, suggesting a species-dependent difference that should be considered when interpreting nonclinical study data. Regardless of these challenges, detection limits in drug-induced changes in QRS duration on the order of 1–2 msec have been reported based on historical power analysis in nonclinical species and can be detected using in vivo non-rodent telemetry study methods.[59]

While these in vitro and in vivo methodologies may appear to provide a comprehensive toolbox for assessing conduction slowing, several limitations exist: (1) binding assay are usually performed in non-cardiac tissue such as rat brain which do not contain the $Na_v1.5$ channel isoform (2) high-throughput automated patch clamp assays are not designed to characterize state-dependence of drug block, (3) ex vivo assays may exhibit species/tissue specific pharmacology and not accurately reflect effects in humans, and (4) in vivo ECG studies in animals at resting heart rates may not identify drugs which exhibit Class Ib-like rate-dependent activity. Discussions of challenges and best practices in the published literature include surveys,[60] original data and analyses,[51–55,61,62] reviews[50,51] and commentary.[62] Considering the reported high hit rates for $Na_v1.5$ inhibition,[61] which approach those for hERG inhibition, there remains a need for better understanding of the translatability of nonclinical signals to clinically relevant adverse events.[50–55,60–62]

CLINICAL ASSESSMENT OF $NA_V1.5$ BLOCK DURING DRUG DEVELOPMENT

Clinical QRS prolongation may be identified in a dedicated Thorough QT/QTc (TQT) trial, as described in the ICH E14 guidance, since these studies are also powered to detect small changes in the QRS duration and PR interval, in addition to QT/QTc.[63] Such studies are generally performed in healthy volunteers and require centralized collection of replicate ECGs at 10–12 timepoints following dosing.[64] It is also possible to detect QRS prolongation in Phase I ascending dose studies by using concentration-QRS modeling, using the same standards for ECG and PK collection, ECG analysis, and concentration-effect modeling that are used in a TQT trial.[65] In general, drug-induced $Na_v1.5$ block produces QRS prolongation with a linear relationship to drug plasma concentration.[66]

The ECG collection devices used in modern clinical trials generally provide interval duration measurements, including QRS, which are performed on a superimposed global median beat or the vector magnitude lead. In contrast, nonclinical ECG measurements are generally performed on a single lead (usually lead II), even when multiple leads are recorded. The precision of the measurement is affected by the acquisition sampling rate, filtering of the digital signal, the magnification at which measurements are performed, and by the use of paper versus digital ECG records.[67] In general, a sampling frequency of 500 Hz or above is sufficient for precise measurements of QRS duration. Filtering may smooth out the QRS onset or offset, and therefore, should be avoided.[68] High magnification of digital files is preferred for very precise QRS duration measurements, just as for measurement of the QT interval. Ultimately, to detect small QRS increases, large numbers of ECGs must be collected and analyzed.

When measuring QRS duration in animals, species-specific characteristics should also be considered. While

canines and NHPs have ECG morphologies relatively comparable to humans, minipigs tend to have deep S-waves, which affects the QRS interval duration and is associated with greater inter-individual variability in this species,[69] whereas rats typically have low-amplitude S-waves. These variations in QRS complex result from species specific differences in their cardiac ion channel profile.[70]

A "WEIGHT OF EVIDENCE" APPROACH FOR $NA_V1.5$ SAFETY PROFILING

Cardiac $Na_v1.5$ blockade does not always translate to meaningful conduction slowing, but when apparent, can lead to increased proarrhythmic potential and sudden death; therefore, it is important we develop a framework for prediction of clinical risk when off-target pharmacology is suspected or observed. Because of the synergistic effects of multiple risk factors including background pathology in the patient, designing a safety pharmacology strategy to predict conduction liability is challenging. To adequately assess the hazard, we propose a "weight of evidence" approach anchored in rigorous biophysical characterization using validated assays, modeling of drug effects in a setting of healthy and diseased myocardium using both computational and in vitro assays, along with novel approaches to nonclinical and clinical ECG analysis (Figure 3). One might envision implementation as reflexive to an early screening hit against $Na_v1.5$ or follow-up to conduction slowing in later stage in vivo studies. In either case, the hazard would be weighed against other developability and quality criteria, including the therapeutic area and unmet patient need.

While the Comprehensive in vitro Proarrhythmia Assay (CiPA) paradigm has served as a model for assessment of repolarization risk, a more diligent approach might benefit the characterization of conduction liability.[71] For example, understanding the complex biophysics of state-dependent block requires a more sophisticated voltage protocol than the Milne's dynamic pulse-protocol or step-protocols proposed in CiPA. Liu et al. (2003) investigated the state-dependent block of flecainide and lidocaine using protocols that stimulate the channel with rapid pre-pulses or sustained depolarization followed by a protocol allowing for quantification of channel recovery and inactivated state block - biophysical properties that define the Vaughan-Williams classification of Na^+ channel blockers.[72] Although these conditions seem non-physiological, depolarization of the myocardium is known to occur post-MI and is associated with risk of conduction slowing in the presence of $Na_v1.5$ blockers.

The in vivo non-rodent study described by the ICH S7A/B guidelines is a valuable component of the nonclinical

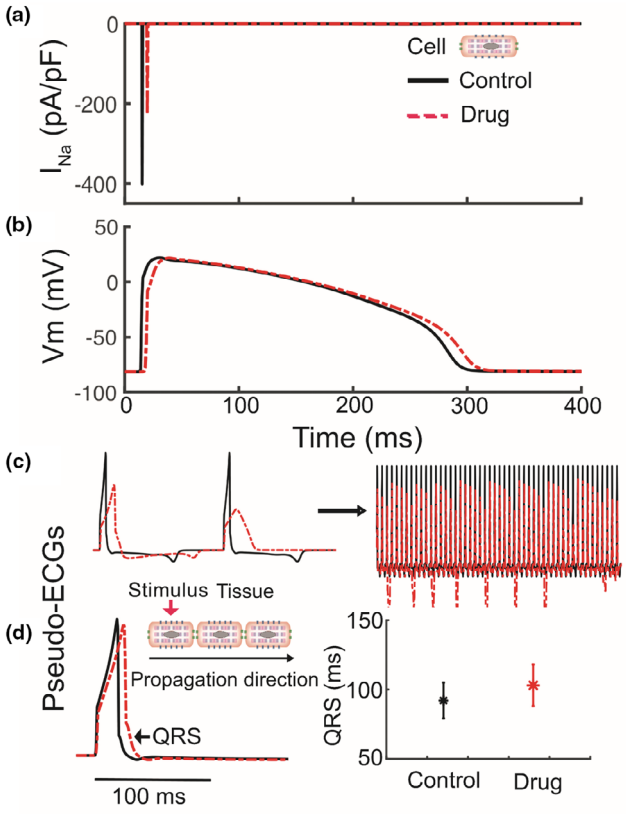

FIGURE 3 The effect of cardiac $Na_v1.5$ channel blockade on cardiac electrophysiology. The top two panels (I_{Na} and resting membrane potential (V_m)) show the predicted effects of $Na_v1.5$ reduction (red) on I_{Na} (a) compared to control (black) during a simulated human O'Hara-Rudy ventricular cardiac action potential (b). The lower two panels show the effect of substantial $Na_v1.5$ reduction on the simulated electrogram in a human virtual tissue representation (c) on an expanded and compressed time-course. (d) The effect of $Na_v1.5$ reduction on QRS width is shown (red) compared to control (black) and quantified in the lower right graph.

risk assessment thought to complement or supersede any in vitro findings. These are often conducted late in nonclinical development in support of regulatory review enabling "First in Human" clinical trials. While studies in non-rodents are conducted in freely moving, conscious dogs, or NHPs, the data are limited to a range of resting heart rates under normal sinus rhythm and "unstressed" conditions, which may not inform on complex state-dependent $Na_v1.5$ block. Conversely, rodent species including rats and mice may be suited to investigate conduction slowing (PR/QRS prolongation) and their higher heart rates may enable interrogation of frequency-dependent $Na_v1.5$ block, complexities of comparison across nonclinical species and human translation remain challenging.[73] While the linear translation of these findings to humans may be tenuous, inducing the rapid heart rate in non-rodents would require resource-intensive means such as surgical implantation of

a pacemaker, external cardio-stimulation, or pharmacological intervention.

A more thorough analysis of the ECG might prove valuable in characterizing $Na_v1.5$ block in vivo. QRS amplitude may also be altered by $Na_v1.5$ block, but relatively little has been published in the clinical literature about the effects of $Na_v1.5$ blockers on QRS amplitude other than the use of signal averaged ECGs to evaluate late potentials.[74,75] Alternatively, the use of vectorcardiograms (VCG), a measure of the cardiac wavefront vector of the ECG, identified conduction slowing independent of changes in repolarization and have proven a sensitive biomarker of Brugada Syndrome.[76] Unfortunately, these complex analyses require a modified or full 12-lead ECG acquisition, which may exceed the standard study design and resource in nonclinical studies.

And finally, computational modeling of the structural interactions of drugs and ion channels may permit predictions across multiple time and space scales, including effects on cardiac rhythm. These predictions could then be tested experimentally and/or validated by clinical data.[77,78] In silico modeling of cardiac $Na_v1.5$ biophysics was incorporated in the O'Hara Rudy model employed by CiPA, yet the impact of pharmacology on peak I_{Na} and conduction was not emphasized.[79–81]

Incorporation of the voltage- and drug-dependent changes in channel conformation can be used to predict drug binding, and the subsequent effect on conduction.[82,83] Figure 3 illustrates the computational integration of both cellular and tissue effects on conduction. Additionally, by incorporating effects of beat rate on action potential upstroke and the contribution of accessory proteins on $Na_v1.5$ pharmacology, as well as the impact of ischemic damage, a framework for modeling drug-induced conduction slowing is feasible.[84–87]

ADDITIONAL CONSIDERATIONS

While $Na_v1.5$ channels are the primary drivers of the excitatory impulse and cardiac conduction, additional ion channels may play an important role particularly in the setting of ischemia, infarct or heart failure disease states.[88] Gap junctions facilitate intercellular conduction to form the myocardial syncytium and have been associated with drug-dependent QRS widening.[89,90] Drugs may also indirectly alter cardiac current by affecting post-translational processing or trafficking of ion channels.[91] Finally, mutations in multiple proteins that interact with cardiac Na^+ channels have been shown to alter channel function and result in cardiac disease.[92] However, none of these effects can be determined from electrophysiological assays in heterologous systems, and in vivo safety pharmacology studies may not provide accurate assessments. Discussion of these processes is beyond the scope of this review but should be considered when evaluating the proarrhythmic potential of new therapeutic agents.

CONCLUSION

A renewed emphasis on conduction abnormalities is important to overall drug safety and risk assessment. Furthermore, the subclassification of cardiac $Na_v1.5$ blockers can inform relative "safety" based upon an understanding of historical compounds that define these subclasses. An integrated risk assessment from nonclinical in vitro and in vivo safety studies together with additional computational models may provide additional kinetic data to enhance our ability to define drug activity and ultimately predict patient risk. In this context, understanding and defining the translation of drug-induced effects on Na channel pharmacology from in vitro ion channel block to in vivo QRS prolongation, and subsequent translation to clinical outcomes should be prioritized.[58,87] Moreover, it may be possible to mitigate the risk of $Na_v1.5$ blocking drugs by utilizing novel technologies from automated patch clamp assays to hiPSC-CM platforms and complex mathematical modeling to incorporate additional human and disease-specific co-factors that may exacerbate Na channel pharmacological effects of new drugs.

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CONFLICT OF INTEREST STATEMENT

The authors declared no competing interests for this work, other than their employment in commercial biopharmaceutical companies, academic institutions, or contract research organizations (CROs). No information is presented in this paper that advocates for or promotes commercial products from any of our organizations.

DISCLAIMER

The opinions presented here are those of the authors. No official support or endorsement by the US FDA and participating companies is intended or should be inferred.

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REFERENCES

1. Echt DS, Liebson PR, Mitchell LB, et al. Mortality and morbidity in patients receiving encainide, flecainide, or placebo. The Cardiac Arrhythmia Suppression Trial. *N Engl J Med*. 1991;324:781-788.
2. Lu HR, Rohrbacher J, Vlaminckx E, Van Ammel K, Yan GX, Gallacher DJ. Predicting drug-induced slowing of conduction and pro-arrhythmia: identifying the 'bad' sodium current blockers. *Br J Pharmacol*. 2010;160:60-76.
3. Badheka AO, Singh V, Patel NJ, et al. QRS duration on electrocardiography and cardiovascular mortality (from the National Health and Nutrition Examination Survey-III). *Am J Cardiol*. 2013;112:671-677.
4. Desai AD, Yaw TS, Yamazaki T, Kaykha A, Chun S, Froelicher VF. Prognostic significance of quantitative QRS duration. *Am J Med*. 2006;119:600-606.
5. Kurl S, Makikallio TH, Rautaharju P, Kiviniemi V, Laukkanen JA. Duration of QRS complex in resting electrocardiogram is a predictor of sudden cardiac death in men. *Circulation*. 2012;125:2588-2594.
6. Bongioanni S, Bianchi F, Migliardi A, et al. Relation of QRS duration to mortality in a community-based cohort with hypertrophic cardiomyopathy. *Am J Cardiol*. 2007;100:503-506.
7. Shenkman HJ, Pampati V, Khandelwal AK, et al. Congestive heart failure and QRS duration: establishing prognosis study. *Chest*. 2002;122:528-534.
8. Akiyama T, Pawitan Y, Greenberg H, Kuo CS, Reynolds-Haertle RA. Increased risk of death and cardiac arrest from encainide and flecainide in patients after non-Q-wave acute myocardial infarction in the Cardiac Arrhythmia Suppression Trial. CAST Investigators. *Am J Cardiol*. 1991;68:1551-1555.
9. Authier S, Abernathy MM, Correll K, et al. An industry survey with focus on cardiovascular safety pharmacology study design and data interpretation. *Int J Toxicol*. 2020;39:274-293.
10. De Simone SA, Moyle S, Buccarello A, Dellenbach C, Kucera JP, Rohr S. The role of membrane capacitance in cardiac impulse conduction: an optogenetic study with non-excitable cells coupled to cardiomyocytes. *Front Physiol*. 2020;11:194.
11. Zlochiver S, Muñoz V, Vikstrom KL, Taffet SM, Berenfeld O, Jalife J. Electrotonic myofibroblast-to-myocyte coupling increases propensity to reentrant arrhythmias in two-dimensional cardiac monolayers. *Biophys J*. 2008;95:4469-4480.
12. Kumar R, Joyner RW. Calcium currents of ventricular cell pairs during action potential conduction. *Am J Physiol*. 1995;268:H2476-H2486.
13. Qu Z, Karagueuzian HS, Garfinkel A, Weiss JN. Effects of Na(+) channel and cell coupling abnormalities on vulnerability to reentry: a simulation study. *Am J Physiol Heart Circ Physiol*. 2004;286:H1310-H1321.
14. Nguyen TP, Xie Y, Garfinkel A, Qu Z, Weiss JN. Arrhythmogenic consequences of myofibroblast-myocyte coupling. *Cardiovasc Res*. 2012;93:242-251.
15. Cabo C, Boyden PA. Electrical remodeling of the epicardial border zone in the canine infarcted heart: a computational analysis. *Am J Physiol Heart Circ Physiol*. 2003;284:H372-H384.
16. Cabo C, Boyden PA. Heterogeneous gap junction remodeling stabilizes reentrant circuits in the epicardial border zone of the healing canine infarct: a computational study. *Am J Physiol Heart Circ Physiol*. 2006;291:H2606-H2616.
17. Cabo C, Yao J, Boyden PA, et al. Heterogeneous gap junction remodeling in reentrant circuits in the epicardial border zone of the healing canine infarct. *Cardiovasc Res*. 2006;72:241-249.
18. Catterall WA, Goldin AL, Waxman SG. Voltage-gated sodium channnels (version 2019.4) in the IUPHAR/BPS guide to pharmacology database. IUPHAR/BPS Guide to Pharmacology CITE. 2019 2019.
19. Holm H, Gudbjartsson DF, Arnar DO, et al. Several common variants modulate heart rate, PR interval and QRS duration. *Nat Genet*. 2010;42:117-122.
20. Coppini R, Ferrantini C. NaV1.8: a novel contributor to cardiac arrhythmogenesis in heart failure. *Cardiovasc Res*. 2018;114:1691-1693.
21. Paludan-Muller C, Larsen S, Ahlberg G, et al. Clinical implications of SCN10A loss-of-function variants in 169 610 exomes representing the general population. *Circ Genom Precis Med*. 2022;15:e003574.
22. Strichartz GR. The inhibition of sodium currents in myelinated nerve by quaternary derivatives of lidocaine. *J Gen Physiol*. 1973;62:37-57.
23. Courtney KR. Mechanism of frequency-dependent inhibition of sodium currents in frog myelinated nerve by the lidocaine derivative GEA. *J Pharmacol Exp Ther*. 1975;195:225-236.
24. Hille B. Local anesthetics: hydrophilic and hydrophobic pathways for the drug-receptor reaction. *J Gen Physiol*. 1977;69:497-515.
25. Hondeghem LM, Katzung BG. Time- and voltage-dependent interactions of antiarrhythmic drugs with cardiac sodium channels. *Biochim Biophys Acta*. 1977;472:373-398.
26. Starmer CF, Courtney KR. Modeling ion channel blockade at guarded binding sites: application to tertiary drugs. *Am J Physiol*. 1986;251:H848-H856.
27. Vaughan Williams EM. A classification of antiarrhythmic actions reassessed after a decade of new drugs. *J Clin Pharmacol*. 1984;24:129-147.

28. Lei M, Wu L, Terrar DA, Huang CL. Modernized classification of cardiac antiarrhythmic drugs. *Circulation*. 2018;138:1879-1896.
29. Cardiac Arrhythmia Suppression Trial (CAST) Investigators. Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. *N Engl J Med*. 1989;321:406-412.
30. Cardiac Arrhythmia Suppression Trial II Investigators. Effect of the antiarrhythmic agent moricizine on survival after myocardial infarction. *N Engl J Med*. 1992;327:227-233.
31. el-Sherif N. Experimental models of reentry, antiarrhythmic, and proarrhythmic actions of drugs. Complexities galore! *Circulation*. 1991;84:1871-1875.
32. Starmer CF, Lastra AA, Nesterenko VV, Grant AO. Proarrhythmic response to sodium channel blockade. Theoretical model and numerical experiments. *Circulation*. 1991;84:1364-1377.
33. Velebit V, Podrid P, Lown B, Cohen BH, Graboys TB. Aggravation and provocation of ventricular arrhythmias by antiarrhythmic drugs. *Circulation*. 1982;65:886-894.
34. Pratt CM, Brater DC, Harrell FE Jr, et al. Clinical and regulatory implications of the cardiac arrhythmia suppression trial. *Am J Cardiol*. 1990;65:103-105.
35. Hondeghem LM. Antiarrhythmic agents: modulated receptor applications. *Circulation*. 1987;75:514-520.
36. Tamargo J, Valenzuela C, Delpon E. New insights into the pharmacology of sodium channel blockers. *Eur Heart J*. 1992;13(Suppl F):2-13.
37. Pancrazio JJ, Kamatchi GL, Roscoe AK, Lynch C 3rd. Inhibition of neuronal Na+ channels by antidepressant drugs. *J Pharmacol Exp Ther*. 1998;284:208-214.
38. Kerr GW, McGuffie AC, Wilkie S. Tricyclic antidepressant overdose: a review. *Emerg Med J*. 2001;18:236-241.
39. Boehnert MT, Lovejoy FH Jr. Value of the QRS duration versus the serum drug level in predicting seizures and ventricular arrhythmias after an acute overdose of tricyclic antidepressants. *N Engl J Med*. 1985;313:474-479.
40. Humphries KH, Kerr CR, Steinbuch M, Dorian P, Canadian Registry of Atrial Fibrillation investigators. Limitations to antiarrhythmic drug use in patients with atrial fibrillation. *CMAJ*. 2004;171:741-745.
41. Kowey PR, Dorian P, Mitchell LB, et al. Vernakalant hydrochloride for the rapid conversion of atrial fibrillation after cardiac surgery: a randomized, double-blind, placebo-controlled trial. *Circ Arrhythm Electrophysiol*. 2009;2:652-659.
42. Roy D, Pratt CM, Torp-Pedersen C, et al. Vernakalant hydrochloride for rapid conversion of atrial fibrillation: a phase 3, randomized, placebo-controlled trial. *Circulation*. 2008;117:1518-1525.
43. Fedida D. Vernakalant (RSD1235): a novel, atrial-selective antifibrillatory agent. *Expert Opin Investig Drugs*. 2007;16:519-532.
44. French JA, Perucca E, Sander JW, et al. FDA safety warning on the cardiac effects of lamotrigine: an advisory from the ad hoc ILAE/AES Task Force. *Epilepsy Curr*. 2021;6:45-48.
45. Ingleby-Talecki L, van Dijkman SC, Oosterholt SP, et al. Cardiac sodium channel inhibition by lamotrigine: in vitro characterization and clinical implications. *Clin Transl Sci*. 2022;15:1978-1989.
46. Food and Drug Administration, HHS. International Conference on Harmonisation; guidance on S7A safety pharmacology studies for human pharmaceuticals; availability. *Fed Regist*. 2001;66:36791-36792.
47. Food and Drug Administration, HHS. International Conference on Harmonisation; guidance on S7B nonclinical evaluation of the potential for delayed ventricular repolarization (QT interval prolongation) by human pharmaceuticals; availability. *Fed Regist*. 2005;70:61133-61134.
48. Zhang H, Zou B, Du F, Xu K, Li M. Reporting sodium channel activity using calcium flux: pharmacological promiscuity of cardiac Nav1.5. *Mol Pharmacol*. 2015;87:207-217.
49. Jenkinson S, Bassyouni A, Cordes J, et al. Cardiac sodium channel antagonism – translation of preclinical in vitro assays to clinical QRS prolongation. *J Pharmacol Toxicol Methods*. 2018;89:9-18.
50. Bagal SK, Marron BE, Owen RM, Storer RI, Swain NA. Voltage gated sodium channels as drug discovery targets. *Channels (Austin)*. 2015;9:360-366.
51. Yekkirala AS, Roberson DP, Bean BP, Woolf CJ. Breaking barriers to novel analgesic drug development. *Nat Rev Drug Discov*. 2017;16:545-564.
52. Cao X, Lee YT, Holmqvist M, et al. Cardiac ion channel safety profiling on the IonWorks Quattro automated patch clamp system. *Assay Drug Dev Technol*. 2010;8:766-780.
53. Penniman JR, Kim DC, Salata JJ, Imredy JP. Assessing use-dependent inhibition of the cardiac Na(+/−) current (I(Na)) in the PatchXpress automated patch clamp. *J Pharmacol Toxicol Methods*. 2010;62:107-118.
54. Harmer AR, Valentin JP, Pollard CE. On the relationship between block of the cardiac Na^+ channel and drug-induced prolongation of the QRS complex. *Br J Pharmacol*. 2011;164:260-273.
55. Morissette P, Nishida M, Trepakova E, et al. The anesthetized guinea pig: an effective early cardiovascular derisking and lead optimization model. *J Pharmacol Toxicol Methods*. 2013;68:137-149.
56. Heath BM, Cui Y, Worton S, et al. Translation of flecainide- and mexiletine-induced cardiac sodium channel inhibition and ventricular conduction slowing from nonclinical models to clinical. *J Pharmacol Toxicol Methods*. 2011;63:258-268.
57. Cros C, Skinner M, Moors J, Lainee P, Valentin JP. Detecting drug-induced prolongation of the QRS complex: new insights for cardiac safety assessment. *Toxicol Appl Pharmacol*. 2012;265:200-208.
58. Bergenholm L, Parkinson J, Mettetal J, Evans ND, Chappell MJ, Collins T. Predicting QRS and PR interval prolongations in humans using nonclinical data. *Br J Pharmacol*. 2017;174:3268-3283.
59. Baublits J, Vargas HM, Engwall MJ. The in vivo QTc core assay: an evaluation of QTc variability, detection sensitivity and implications for the improvement of conscious dog and non-human primate telemetry studies. *J Pharmacol Toxicol Methods*. 2021;109:107067.
60. Authier S, Pugsley MK, Koerner JE, et al. Proarrhythmia liability assessment and the Comprehensive in Vitro Proarrhythmia Assay (CiPA): an industry survey on current practice. *J Pharmacol Toxicol Methods*. 2017;86:34-43.
61. Lounkine E, Keiser MJ, Whitebread S, et al. Large-scale prediction and testing of drug activity on side-effect targets. *Nature*. 2012;486:361-367.
62. Sedwick C. Sodium ion unlocks understanding of channel blockade. *J Gen Physiol*. 2017;149:405.
63. International Conference on Harmonisation. E14: the Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-antiarrhythmic Drugs (Step 4). 2015.

64. Darpo B. The thorough QT/QTc study 4 years after the implementation of the ICH E14 guidance. *Br J Pharmacol*. 2010;159:49-57.
65. Darpo B, Benson C, Dota C, et al. Results from the IQ-CSRC prospective study support replacement of the thorough QT study by QT assessment in the early clinical phase. *Clin Pharmacol Ther*. 2015;97:326-335.
66. Sällström J, Al-Saffar A, Pehrson R. Pharmacokinetic-pharmacodynamic modeling of QRS-prolongation by flecainide: heart rate-dependent effects during sinus rhythm in conscious telemetered dogs. *J Pharmacol Toxicol Methods*. 2014;69:24-29.
67. Pizzuti GP, Cifaldi S, Nolfe G. Digital sampling rate and ECG analysis. *J Biomed Eng*. 1985;7:247-250.
68. Kligfield P, Gettes LS, Bailey JJ, et al. Recommendations for the standardization and interpretation of the electrocardiogram: part I: the electrocardiogram and its technology a scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society endorsed by the International Society for Computerized Electrocardiology. *J Am Coll Cardiol*. 2007;49:1109-1127.
69. Authier S, Gervais J, Fournier S, Gauvin D, Maghezzi S, Troncy E. Cardiovascular and respiratory safety pharmacology in Gottingen minipigs: pharmacological characterization. *J Pharmacol Toxicol Methods*. 2011;64:53-59.
70. Accardi MV, Troncy E, Abtout S, Ascah A, Maghezzi S, Authier S. Rat cardiovascular telemetry: marginal distribution applied to positive control drugs. *J Pharmacol Toxicol Methods*. 2016;81:120-127.
71. Fermini B, Hancox JC, Abi-Gerges N, et al. A new perspective in the field of cardiac safety testing through the comprehensive in vitro proarrhythmia assay paradigm. *J Biomol Screen*. 2016;21:1-11.
72. Liu H, Atkins J, Kass RS. Common molecular determinants of flecainide and lidocaine block of heart Na+ channels: evidence from experiments with neutral and quaternary flecainide analogues. *J Gen Physiol*. 2003;121:199-214.
73. Regan CP, Cresswell HK, Zhang R, Lynch JJ. Novel method to assess cardiac electrophysiology in the rat: characterization of standard ion channel blockers. *J Cardiovasc Pharmacol*. 2005;46:68-75.
74. Goedel-Meinen L, Hofmann M, Schmidt G, Barthel P, Baedeker W, Blömer H. Effect of class I anti-arrhythmia agents on the signal-averaged ECG. *Herz*. 1988;13:188-196.
75. Lombardi F, Finocchiaro ML, Dalla Vecchia L, et al. Effects of mexiletine, propafenone and flecainide on signal-averaged electrocardiogram. *Eur Heart J*. 1992;13:517-525.
76. Postema PG, van Dessel PF, Kors JA, et al. Local depolarization abnormalities are the dominant pathophysiologic mechanism for type 1 electrocardiogram in brugada syndrome a study of electrocardiograms, vectorcardiograms, and body surface potential maps during ajmaline provocation. *J Am Coll Cardiol*. 2010;55:789-797.
77. Yang PC, DeMarco KR, Aghasafari P, et al. A computational pipeline to predict cardiotoxicity: from the atom to the rhythm. *Circ Res*. 2020;126:947-964.
78. Li Z, Mirams GR, Yoshinaga T, et al. General principles for the validation of proarrhythmia risk prediction models: an extension of the CiPA in silico strategy. *Clin Pharmacol Ther*. 2020;107:102-111.
79. O'Hara T, Virag L, Varro A, Rudy Y. Simulation of the undiseased human cardiac ventricular action potential: model formulation and experimental validation. *PLoS Comput Biol*. 2011;7:e1002061.
80. Dutta S, Chang KC, Beattie KA, et al. Optimization of an in silico cardiac cell model for proarrhythmia risk assessment. *Front Physiol*. 2017;8:616.
81. Li Z, Dutta S, Sheng J, et al. Improving the in silico assessment of proarrhythmia risk by combining hERG (human Ether-a-go-go-Related Gene) channel-drug binding kinetics and multichannel pharmacology. *Circ Arrhythm Electrophysiol*. 2017;10:e004628.
82. Ahmed M, Jalily Hasani H, Ganesan A, Houghton M, Barakat K. Modeling the human Nav1.5 sodium channel: structural and mechanistic insights of ion permeation and drug blockade. *Drug des Devel Ther*. 2017;11:2301-2324.
83. Moreno JD, Zhu W, Mangold K, Chung W, Silva JR. A molecularly detailed NaV1.5 model reveals a new class I antiarrhythmic target. *JACC Basic Transl Sci*. 2019;4:736-751.
84. Yuan L, Koivumaki JT, Liang B, et al. Investigations of the Navbeta1b sodium channel subunit in human ventricle; functional characterization of the H162P Brugada syndrome mutant. *Am J Physiol Heart Circ Physiol*. 2014;306:H1204-H1212.
85. Zhu W, Wang W, Angsutararux P, et al. Modulation of the effects of class-Ib antiarrhythmics on cardiac NaV1.5-encoded channels by accessory NaVbeta subunits. *JCI Insight*. 2021;6:e143092.
86. Moreno JD, Zhu ZI, Yang PC, et al. A computational model to predict the effects of class I anti-arrhythmic drugs on ventricular rhythms. *Sci Transl Med*. 2011;3:98ra83.
87. Shaw RM, Rudy Y. Ionic mechanisms of propagation in cardiac tissue. Roles of the sodium and L-type calcium currents during reduced excitability and decreased gap junction coupling. *Circ Res*. 1997;81:727-741.
88. Decker KF, Rudy Y. Ionic mechanisms of electrophysiological heterogeneity and conduction block in the infarct border zone. *Am J Physiol Heart Circ Physiol*. 2010;299:H1588-H1597.
89. Caillier B, Pilote S, Castonguay A, et al. QRS widening and QT prolongation under bupropion: a unique cardiac electrophysiological profile. *Fundam Clin Pharmacol*. 2012;26:599-608.
90. Curry SC, Kashani JS, LoVecchio F, Holubek W. Intraventricular conduction delay after bupropion overdose. *J Emerg Med*. 2005;29:299-305.
91. Marionneau C, Abriel H. Regulation of the cardiac Na+ channel NaV1.5 by post-translational modifications. *J Mol Cell Cardiol*. 2015;82:36-47.
92. Kyle JW, Makielski JC. Diseases caused by mutations in Nav1.5 interacting proteins. *Card Electrophysiol Clin*. 2014;6:797-809.

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