

# Rechanneling the cardiac proarrhythmia safety paradigm: A meeting report from the Cardiac Safety Research Consortium

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This white paper provides a summary of a scientific proposal presented at a Cardiac Safety Research Consortium/Health and Environmental Sciences Institute/Food and Drug Administration–sponsored Think Tank, held at Food and Drug Administration's White Oak facilities, Silver Spring, MD, on July 23, 2013, with the intention of moving toward consensus on defining a new paradigm in the field of cardiac safety in which proarrhythmic risk would be primarily assessed using nonclinical in vitro human models based on solid mechanistic considerations of torsades de pointes proarrhythmia. This new paradigm would shift the emphasis from the present approach that strongly relies on QTc prolongation (a surrogate marker of proarrhythmia) and could obviate the clinical Thorough QT study during later drug development. These discussions represent current thinking and suggestions for furthering our knowledge and understanding of the public health case for adopting a new, integrated nonclinical in vitro/in silico paradigm, the Comprehensive In Vitro Proarrhythmia Assay, for the assessment of a candidate drug's proarrhythmic liability, and for developing a public-private collaborative program to characterize the data content, quality, and approaches required to assess proarrhythmic risk in the absence of a Thorough QT study. This paper seeks to encourage multistakeholder input regarding this initiative and does not represent regulatory guidance. (*Am Heart J* 2014;167:292-300.)

A Think Tank sponsored by Cardiac Safety Research Consortium (CSRC), Health and Environmental Sciences Institute (HESI), and Food and Drug Administration (FDA) was convened at FDA Headquarters on July 23, 2013, to discuss a potential new approach to assessing drug-induced proarrhythmic risk. The current safety testing paradigm is based primarily on the predictive link between drug-induced in vitro hERG channel blockade and in vivo/clinical QT interval prolongation and torsades de pointes (TdP). Prolongation of the QT interval has been considered as an initiating factor in clinical TdP. Although the current paradigm has largely eliminated new drugs entering the market with unanticipated

potential for torsade, it has important limitations and may have led to stopping the development of potentially valuable therapeutics. Therefore, a Comprehensive In vitro Proarrhythmia Assay (CiPA) was proposed as a new paradigm. It should be emphasized that the Think Tank was not designed to seek consensus endorsement of a fully defined and vetted new approach ready for immediate implementation. Rather, its goals were to suggest components of such a paradigm, identify weaknesses and areas for refinement, facilitate transparent stakeholder input and discussions, propose potential member organizations of a collaborative group to develop the specifics that would be needed, and consider the first pragmatic steps. These goals were accomplished, and such next steps are underway.

Based on the principles of the US FDA Critical Path Initiative, the CSRC<sup>1</sup> was created to facilitate collaborations among academicians, industry professionals, and regulators to develop consensus approaches addressing cardiac and vascular safety issues that can arise in the development of new medical products.<sup>2</sup> The HESI<sup>3</sup> is a nonprofit institution whose mission is to engage scientists from academia, government, and industry to identify and resolve global health and environmental issues, and is also a formal partner of FDA in developing improved approaches to regulatory sciences through public-private partnerships.

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This paper proposes a path forward toward a new safety testing paradigm of relevance to biopharmaceutical sponsors, scientists, clinicians, and regulatory authorities involved in the development of new molecular entities in the evaluation of potential proarrhythmia. The views expressed herein do not represent new regulatory policy.

## Executive summary

The present cardiac safety paradigm (ICH S7B non-clinical guidance<sup>4</sup> and E14 clinical guidance,<sup>5</sup> fully adopted in Europe, Japan, and North America) does not directly assess the end point of primary clinical concern, namely, ventricular proarrhythmia (ie, TdP): rather, it provides a regulatory framework for the detection of delayed ventricular repolarization as represented by the nonclinical focus on block of the repolarizing potassium ionic current that flows through the ion channel encoded by *hERG*, that is, the rapidly activating delayed rectifier potassium current  $I_{Kr}$ , and the clinical focus on QTc prolongation (a surrogate marker of proarrhythmia).

Although the present paradigm has largely eliminated the unanticipated discovery of new torsadogenic drugs entering the market, important limitations of the present approach include that block of  $I_{Kr}$  alone is often insufficient in predicting delayed repolarization (itself a surrogate marker of proarrhythmia); increases in the QTc interval are highly sensitive but not very specific for predicting ventricular proarrhythmia risk; and there are clinically important drugs that block  $I_{Kr}$  at therapeutic plasma concentrations that are not proarrhythmic. The bulk of the presentations and discussions, therefore, revolved around the following proposition:

*A new cardiac safety paradigm utilizing a novel array of nonclinical proarrhythmia assessments, combined with in silico predictive modelling of cellular electrophysiological effects, could make drug discovery and development efforts more efficient, move the major clinical/regulatory analysis concerning arrhythmogenic potential earlier in the drug discovery and development continuum, enhance the accuracy with which existing and/or new drugs are labelled relative to actual proarrhythmic risks, and increase the output of new chemical entities that benefit patients.*

The proposed paradigm, labeled the “Comprehensive *In vitro* Proarrhythmia Assay” (CiPA), is based on an established mechanistic understanding of TdP. To assess overall proarrhythmic risk, CiPA relies upon (a) characterization of electrophysiological effects of evolving or existing drugs on multiple human cardiac currents measured in heterologous expression systems, whose electrophysiological effects will then be integrated in silico by computer models reconstructing human cellular

ventricular electrophysiology, and (b) confirmation of the electrophysiological effects in a myocyte assay such as human induced pluripotent stem cell-derived cardiomyocytes. Evaluations of hemodynamic and electrocardiographic (ECG) effects from standard nonclinical cardiovascular in vivo studies (as described in ICH S7A and S7B) will remain part of the new paradigm, along with careful ECG assessment in phase 1 studies to evaluate a drug's effects on ECG intervals (QTc, PR, and QRS durations), atrioventricular conduction, and heart rate. These later studies would confirm that there were no unanticipated clinical ECG changes as compared with the nonclinical testing; if unanticipated changes are found, the reasons for the discrepancy would need to be understood.

With this new paradigm in place, the ICH S7B guideline<sup>4</sup> defining hERG as the primary ion channel of focus for proarrhythmia would need to be revised, and the Thorough QT (TQT) study described in ICH E14 guidelines<sup>5,6</sup> would no longer be a necessary component in drug development. Two years was proposed by the FDA as a timeframe for completion of confirmation and implementation of the proposed new paradigm.

## Background

### Regulatory history

In 2005, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)<sup>7</sup> released Guidelines S7B and E14 that currently govern the cardiac safety landscape. The S7B guideline provides a nonclinical testing strategy to evaluate the potential for human pharmaceuticals to affect cardiac electrophysiology, with specific attention focused on ventricular repolarization. The 2 highlighted biomarkers of particular interest are the repolarizing ionic current  $I_{Kr}$  and the QTc interval (the QT interval “corrected” for the effects of heart rate). The objectives for the nonclinical studies described in S7B include:

- Identify the potential of a drug molecule and its metabolites to delay ventricular repolarization;
- Relate the extent of the delayed ventricular repolarization to the concentration of the drug molecule and its metabolites;
- Elucidate the mechanism of action of the delayed ventricular repolarization;
- In conjunction with other relevant information, estimate the risk of delayed ventricular repolarization and QTc prolongation.

The guidance is narrowly focused on hERG current block and QTc prolongation, both of which are surrogates for proarrhythmia. Since its adoption and with evolving nonclinical and clinical data, it is now

appreciated that the effects of hERG current block may be modulated by multiple cardiac ion currents during repolarization and that hERG current block sometimes does not provide a meaningful indicator of proarrhythmic risk. Although not the focus of this paper, the cardiovascular safety community has also invested considerable effort in integrating the assessment of a range of structural and functional cardiovascular end points to ensure that nonarrhythmic risk factors are also considered.<sup>8</sup>

The ICH E14 Guidance (see Sager<sup>9</sup>) addresses clinical evaluation of QTc prolongation and the proarrhythmic potential of nonantiarrhythmic drugs. The document describes a dedicated clinical trial, the TQT study, designed to assess the degree to which a drug compound affects the QT duration. QTc prolongation reaching the level of regulatory concern generally leads to the requirement that extensive ECG evaluations be conducted in phase 3 trials (a sometimes formidable burden for further drug development), likely cautionary product labeling, which may adversely impact commercialization, and can cause significant challenges for smaller companies to develop novel compounds for licensing and further development to permit pharmacologic therapy for unmet medical needs. Results from those evaluations will factor into regulators' overall discussions on the favorability of the molecule's benefit-risk profile. See Stockbridge et al<sup>10</sup> and Turner et al<sup>11</sup> for detailed reviews of the current cardiac safety landscape.

### Drawbacks of the current paradigm

From one important perspective, S7B and E14 have been successful: there have not been any withdrawals of marketed drugs for torsadogenic concerns since they were adopted. However, important limitations have been noted. Critically, increases in the QTc are highly sensitive but not very specific for predicting ventricular proarrhythmia risk. Thus, this paradigm may be inappropriately assigning TdP liability to some drugs. The degree of QTc prolongation, with the exception of pure  $I_{Kr}$  blockers, is largely drug specific, and the QTc can be prolonged by many factors not associated with proarrhythmia (eg, food, drugs, autonomic perturbations, glucose/insulin levels, circadian rhythms). S7B and E14 have had the unintended consequences of propagating an inaccurate understanding of the safety risk associated with  $I_{Kr}$  or QTc signals. The perception that detection of even a small effect on  $I_{Kr}$  or mild QTc prolongation will result in adverse regulatory and commercial implications during drug development has significantly impacted the pharmaceutical discovery pipeline.<sup>10,12</sup> Such findings may result in the de-emphasis of early drug candidates; redesign of chemical structures to address perceived safety concerns (possibly resulting in reduced efficacy or poorer pharmacokinetic profiles of subsequent drug candidates); inability of smaller companies to out-license or get funding for drugs that would overall have a positive

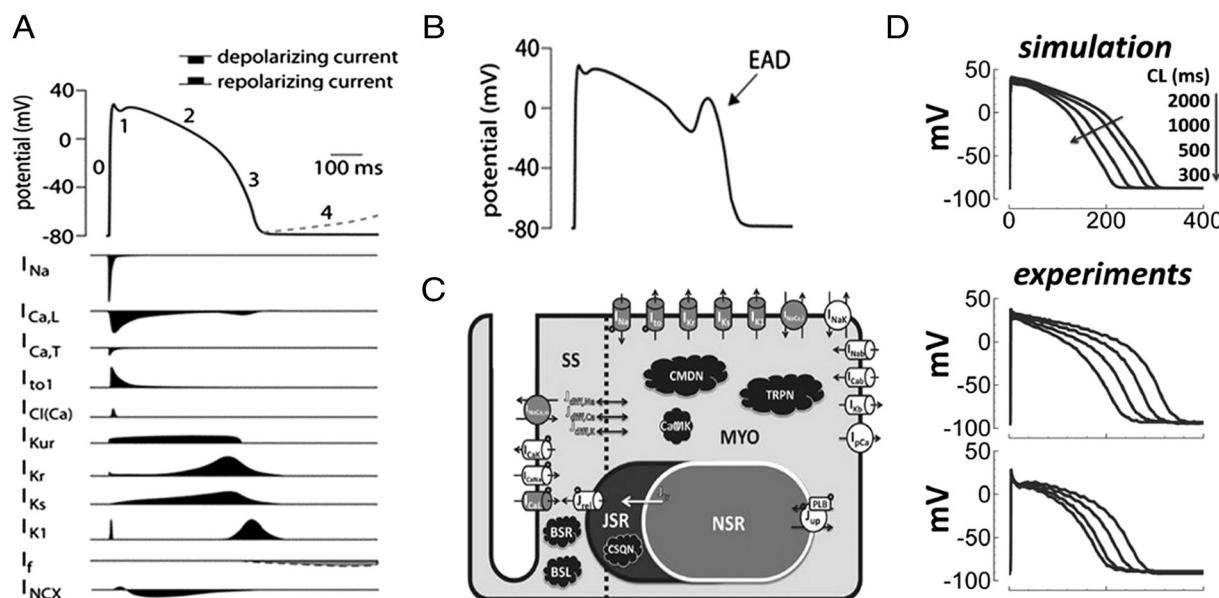
benefit-risk profile; and, occasionally, inappropriate discontinuation of entire development programs with potentially significant public health benefits. De Ponti<sup>12</sup> estimated that "as many as 60% of new molecular entities developed as potential therapeutic agents, when assayed for  $I_{Kr}$  blocking liability, test positive and are thus abandoned early in development."

For drugs that do reach the market, cautionary product labeling can significantly impact the extent to which effective compounds with favorable benefit/risk relationships are prescribed by physicians or used by patients. The present paradigm likely leads to cautionary labeling when an observed QTc effect size is marginal, sometimes unlikely to be due to hERG current block and unlikely to result in a real proarrhythmic risk. With a more comprehensive set of mechanistic data via the CiPA paradigm, it may be possible to more specifically discern when a real proarrhythmic risk is present and provide relevant label cautions, while enhancing patient access to effective and safe products through more accurate labeling of *de minimis* risk products. Such an approach may also permit more tailored and more efficient risk management activities.

### Electrophysiological principles underlying CiPA

Drugs that prolong the QTc interval (often via block of the hERG current at therapeutic plasma concentrations) are not necessarily proarrhythmic; examples include ranolazine, phenobarbital, and tolterodine. Verapamil is a potent  $I_{Kr}$  blocker but does not cause QT prolongation (except possibly at very high intravenous exposures), likely due to its concomitant blockade of the calcium current.<sup>13</sup> Amiodarone is an example of a drug that causes marked QTc prolongation (not infrequently >550 ms) and only very rarely causes TdP. It is likely that drug effects on multiple calcium and sodium cardiac currents provide protection from proarrhythmia despite  $I_{Kr}$  block. The concept that block of non-hERG currents may mitigate proarrhythmic effects of hERG current block is not new, as combining block of repolarizing potassium current with either sodium- or calcium-channel block may reduce or reverse early after-depolarization (EAD) formation.<sup>14,15</sup> Indeed, a review of the potency of hERG current block (relative to clinical exposures) and TQT study results for 39 drugs demonstrated the need for additional (non- $I_{Kr}$ ) preclinical assays to assess the risk of QTc prolongation.<sup>16</sup> More recently, a logistic regression approach involving assessment of drug effects on 3 cardiac channels ( $I_{Kr}$  [Kv11.1], fast sodium [Nav1.5], and L-type calcium [Cav1.2]) showed a significant reduction in false-positive and false-negative classifications for 55 drugs from multiple classes (32 torsadogenic and 23 nontorsadogenic drugs) as compared with expectations based on  $I_{Kr}$  block alone.<sup>17</sup> Thus, block of  $I_{Kr}$  alone is occasionally insufficient in predicting delayed repolarization or proarrhythmic risk. Importantly, there are non-

**Figure 1**



Background elements of CiPA. **A**, Representative ventricular action potential (upper panel), along with multiple cardiac ion currents defining cardiac de-polarization and repolarization (lower panel). Up traces, outward (repolarizing) current such as hERG; down traces, inward (depolarizing current) such as sodium and calcium currents. **B**, An example of an early after depolarization (EAD), an abnormal electrical event during repolarization representing the underlying “trigger” for TdP. **C**, Schematic representation of elements of the O’Hara model of a human ventricular myocyte. Transmembrane ion channels represented as cylinders within the cell membrane. **D**, A comparison of computer reconstructed (labeled “simulation”, upper) and experimental recordings (labeled “experimental”, lower 2 panels) of epicardial ventricular action potentials at different stimulation rates. Panels **A** and **B** from Hoekstra et al<sup>32</sup>; panels C and D from O’Hara et al.<sup>30</sup>

hERG-dependent mechanisms responsible for TdP (eg, block of  $I_{Ks}$ , the slowly activating delayed rectifier potassium current, or enhancement of late sodium current linked to long QT [LQT] syndromes 1 and 3, respectively), which may lead to TdP, and concomitant block of both  $I_{Kr}$  and other repolarizing channels (eg,  $I_{Ks}$ ) could have additive/synergistic effects not appreciated by evaluating  $I_{Kr}$  block alone. Collectively, these studies demonstrate the need for considering drug effects on multiple cardiac currents when assessing proarrhythmic liabilities. Some companies are already screening multiple cardiac ion channels in drug discovery<sup>18</sup>; the proposed new regulatory paradigm would allow for better use of expanded data to directly inform decisions regarding cardiac safety.

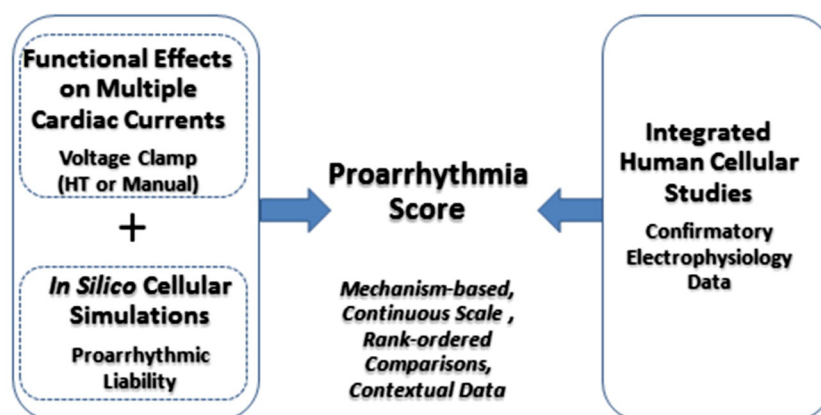
It is generally accepted that TdP is initiated by EADs (see Figure 1B and also the review by Kannankeril et al<sup>19</sup>). Early afterdepolarizations are slowly rising depolarizations that occur during the later phases of an action potential after the initial depolarization (termed the *triggering event*) that inscribes the slow second depolarizing upstroke (hence, the term *afterdepolarization*) that occurs before full repolarization (hence, an

“early”-afterdepolarization). If sufficiently large in amplitude and properly timed, EADs can trigger single or multiple premature ventricular depolarizations that may propagate throughout the ventricles. In the setting of enhanced dispersion of repolarization (as may occur with nonuniform drug-induced delayed repolarization) and sometimes coupled to rhythm disturbances, EAD-triggered responses may give rise to TdP. The Comprehensive In vitro Proarrhythmia Assay focuses on changes in processes underlying repolarization that enable EADs, the critical initiator of TdP proarrhythmia.

Outward potassium current, mostly  $I_{Kr}$ , promotes repolarization and suppresses re-excitation during the plateau of each action potential until terminal repolarization ensues with the subsequent contribution of  $I_{K1}$ . When repolarization is impaired, EADs can arise initiating triggered activity, for example, from the late inward sodium current, or L-type calcium window current. Whether such triggered activity occurs and the extent to which it occurs depend upon the dynamic balance of inward versus outward currents. Even fairly selective and complete  $I_{Kr}$  blockade does not lead immediately and universally to TdP or sudden death because triggered

Figure 2

### Comprehensive *In Vitro* Proarrhythmia Assay (CiPA)



Schematic of the elements of the CiPA. Abbreviations: *HT*, high throughput; *Manual*, manual patch voltage clamp.

activity does not ensue and normal propagation of electrical activity is preserved through the ventricles. Arrhythmias can only arise where this condition has somehow also become momentarily deranged, allowing the early activity on one part of the heart to affect another part with a delay, which then eventually makes its way back to the first area with enough of a delay to set up reentrant a loop or circuit. Although the exact circumstances that give rise to the conduction loop cannot be characterized in much detail, the vulnerability resulting from a drug's effects on various ion channels leading to triggered activity can be assessed with great precision.

### The comprehensive in vitro proarrhythmia assay

The CiPA approach uses automated, high-throughput methods and provides a more comprehensive assessment of ion channel-mediated proarrhythmic potential based upon knowledge of proarrhythmic mechanisms. This proposed mechanism-based approach includes evaluating drug effects on multiple cardiac ionic currents (inward and outward currents, thus, not limited to  $I_{Kr}$  or other repolarizing currents alone) and integrating these data using in silico modeling to reconstruct the ventricular action potential and evaluate the propensity for EADs and repolarization instability (discussed shortly). In addition, a confirmatory role for human stem cell-derived cardiomyocytes (providing an integrated response from an intact human-based physiologic system) is envisioned. The CiPA paradigm is presented schemat-

ically in Figure 2. It is important to note that it is not designed to reproduce arrhythmia but rather to directly assess risk liability based on mechanistic understanding of repolarization instability enabling the electrophysiological trigger for TdP proarrhythmia.

Some discussions regarding the components of CiPA are captured as follows:

#### 1. Functional effects on multiple cardiac currents

This core in vitro strategy involves studying drug effects on functional human cardiac currents in heterologous expression systems and integrating this information using in silico approaches. It is well known that multiple time- and voltage-dependent currents define the cardiac action potential (see Figure 1A). Knowledge gleaned from inherited LQT syndromes and drug-induced proarrhythmia strongly suggests that outward (repolarizing) and inward (depolarizing) currents must both be considered to understand proarrhythmia.  $I_{Kr}$ , which is associated with LQT2, for example, represents only 1 of multiple potassium and sodium currents that, when mutated or absent, are associated with LQT and proarrhythmia. Studies of acquired LQT syndromes and proarrhythmia demonstrate that fast inward sodium current and enhanced inward current (carried by late  $I_{Na}$  or reactivation of calcium current during the action potential plateau) are also involved in proarrhythmia. Thus, a more comprehensive in vitro set of ion current assays could conceivably explore  $I_{Kr}$ ,  $I_{Ks}$ , and  $IK1$  as well as  $I_{NaFast}$ ,  $I_{NaLate}$ , and  $ICaL$  for drug effects. The

specific currents to be evaluated to generate a sufficiently sensitive and predictive data set will need to be discussed further by work streams that will be initiated in the near future.

To facilitate the use of voltage clamp studies for unbiased and standardized decision making in arrhythmia evaluation, it will be necessary to develop consensus on best practices and/or standardization of protocols, positive/negative controls, and experimental conditions. This effort will reduce variability, allow comparisons across assays and laboratories, and move toward more uniform data quality for purposes of regulatory decision making in the CiPA context. Although it would be expected that potency of current block (based on  $IC_{50}$  values) would be of key importance, further characteristics of block (such as voltage- and time-dependent characteristics) might be critical for some currents; comparing *in silico* studies incorporating conductance block models with those incorporating kinetics of drug block and unblock will guide future discussions.<sup>20</sup> Advances in the capabilities and adoption of higher throughput automated voltage clamp patch platforms will facilitate more efficient data collection of multiple currents.<sup>20-24</sup> Using higher throughput automated patch techniques would also provide sufficient sample size and statistical power to facilitate parameterization of subsequent *in silico* reconstruction efforts and to determine  $IC_{50}$  values and other characteristics of block as deemed necessary to provide reliable, reproducible characterization of integrated electrophysiological effects.

## II. Repolarization instability assessed from *in silico* reconstruction of ventricular action potentials

A second component of CiPA uses *in silico* models to integrate the effects of compounds on multiple cardiac currents and reconstruct ventricular electrical activity. Electrophysiological models have been used since the pioneering work of Hodgkin and Huxley to reconstruct neuronal excitability of squid giant axons based on contributions of overlapping voltage- and time-dependent sodium and potassium currents. In the CiPA paradigm, voltage-clamp data describing a drug's effects on multiple ionic currents would be used to support *in silico*-based reconstructions of effects on ventricular repolarization not easily understood from characterization of effects on any one individual ionic current.

It is envisioned that the *in silico* reconstructions would not only provide information on drug effects related to the ability of the action potential to be re-excited during phase 3 repolarization but also on the likelihood of generating EADs and exploring additional candidate parameters associated with instability of cellular repolarization, including changes in plateau resistance, calcium current reactivation, and enhanced late sodium current. A scoring system may be devised in which proarrhythmic scores based on repolarization instability would be

determined for a training set of compounds affecting multiple cardiac ion channels and associated with TdP as well as those not linked to proarrhythmia. This continuous scoring system could then be used to rank order risk of TdP proarrhythmia, along with consideration of context (eg, therapeutic concentration, plasma protein binding). In support of the use of “integrating” *in silico* models, 1 recent study using *in silico* modeling to measure action potential prolongation demonstrated that drug effects across 3 human ion channels (Kv11.1, Nav1.5, CaV1.2) provided improved prediction of TdP risk compared with IKr block alone.<sup>25</sup> Numerous studies have described the general utility of the *in silico* reconstruction approach in evaluating overall proarrhythmic risk.<sup>17,25-29</sup>

The best *in silico* cellular model(s) for reconstructions would have to be selected and then made available (in a standardized format) to users to provide meaningful ranking of proarrhythmia across different laboratories or, alternatively, be made available on a centralized cloud-based resource for all to use. Candidate models include the O'Hara and Rudy model,<sup>30</sup> schematically illustrated in Figure 1C, with simulation results shown in Figure 1D. Recent studies have modeled drug effects using simple “conductance block” models, in which the amount of current is simply scaled back and effects on repolarization measured. It is not yet known whether other more sophisticated models that include additional block characteristics, discrete channel subunits, and more complex kinetics, for example, would provide significant improvement in proarrhythmic assessment. However, methodological work for high-throughput evaluation of kinetics has begun.<sup>20</sup>

## III. Effects on human ventricular myocytes

Finally, it is proposed that myocytes, likely using human stem cell-derived cardiomyocytes, be used to provide a cell-based integrated electrophysiological drug response and the adequacy of the voltage-clamp data that went into the *in silico* reconstruction. The isolation and propagation of human-induced pluripotent stem cells (hiPSCs) and hiPSC-derived cardiomyocytes have provided a useful source of cells for applications in drug discovery and cardiotoxicity screening.<sup>31</sup>

Voltage clamp studies of hiPSC-derived cardiomyocytes have demonstrated the presence of currents expected of adult ventricular myocytes<sup>23,32</sup> and effects on repolarization consistent with human responses.<sup>32,33</sup> However, some studies have shown a relative immaturity of these preparations compared with adult human myocytes.<sup>34,35</sup> Until isolated cardiac myocytes more closely resemble myocytes derived from the human heart, they may still play a role in CiPA in confirming the adequacy of findings from *in silico* reconstructions. There is potential utility of cardiac stem cells to replace other proarrhythmia testing approaches once fully mature stem cells expressing all

the currents in the same densities as human myocytes are developed.

A critical assessment of present practices and data obtained from stem cell-derived cardiomyocytes will be necessary in defining the most appropriate methodologies. As these platforms are relatively new, nonvalidated, and rapidly evolving, there is a need to characterize them more fully and build consensus on their ability to provide consistent data across laboratories and methods. The selection of stem cell-derived cardiomyocytes and experimental conditions will need to be rigorously defined (a not unexpected occurrence for a relatively new *in vitro* preparation), allowing for subsequent standardization for use in CiPA.

### Advantages of the proposed paradigm

The new paradigm addresses many of the concerns related to the current approach. Importantly, it focuses on the real issue, that is, assessment of potential ventricular proarrhythmia risk via a mechanistically robust set of input data instead of correlated surrogates (hERG and QTc prolongation). One advantage is that drugs that effect hERG current or prolong the QTc interval would be assessed for their potential to enhance vulnerability to disrupt repolarization (not simply delay repolarization), and agents that could have real beneficial impacts on public health would not be prematurely discontinued due to an effect on a nonideal surrogate.

The paradigm would also move the mainstay of the assessment of proarrhythmic risk to the discovery stage of development, permitting its use in candidate selection as well as preventing the current common scenario in which a QTc signal is discovered in phase 2 that results in drug discontinuation after a large financial and resource investment. The CiPA paradigm is also unlikely to be binary: instead, a graduation of risk scale can be used that would permit improved benefit/risk assessments as some proarrhythmic risk may be acceptable for some drugs (eg, serious oncologic diseases<sup>36</sup>) but not for others (eg, allergic rhinitis). Lastly, utilization of the new approach would be expected to permit the relabeling of compounds that currently have QTc warnings but are found to have a low proarrhythmic risk.

### Role of phase 1 ECG evaluation

Electrocardiographic evaluation and the careful assessment of drug effects on ECG intervals (PR, QRS, QT), heart rate, and QT morphology will be used to demonstrate that there are no effects in humans that were not predicted based on the nonclinical evaluation. Any discrepancies would need to be understood. However, the finding of QTc prolongation in phase 1 in a molecule shown to have a low risk of proarrhythmia

based on CiPA would be anticipated to result in labeling that is devoid of risks concerning proarrhythmia, unless new findings during development of actual proarrhythmia were seen. Phase 1 ECG evaluation remains an important tool to assess cardiovascular safety and will provide an opportunity to determine if drugs have meaningful effects on other ECG indices, such as atrioventricular nodal or ventricular conduction.

### Confirmation efforts

The transformational approach used in CiPA is based on a mechanistic understanding of the integrated effects on multiple ionic currents linked to a well-established trigger for proarrhythmia (EAD repolarization instability) with confirmation provided by human integrated cellular studies.

The CiPA approach is an atypical nonclinical assay that is not based on binary discrimination obtained from a complex, integrated, but poorly understood biological system (ie, QT prolongation). What is envisioned is a nonbinary output in which proarrhythmic risk is associated with a score based on a continuous scale calibrated against a test set of clinical drugs affecting different ion channels with and without recognized proarrhythmic risk. Although the precise number of drugs with known characteristics that is necessary to define a spectrum of response remains to be determined, 12 might seem a reasonable starting point.

### Next steps and pathway forward

Input will be required from industry, academia, and governmental (regulatory) agencies regarding the development, confirmation, and implementation of CiPA. Various consortia and professional organizations will be essential in providing their collective experience and expertise. The Cardiac Safety Research Consortium could contribute toward consideration of translation of this *in vitro*-based approach to clinical findings. The Safety Pharmacology Society is another organization that could contribute their considerable expertise regarding early *in vitro* screening of ionic channels and translation of these effects. It is also expected that HESI would be a central contributor. As a nonprofit scientific organization, it has public-private partnerships to address human and environmental science issues: members include a wide range of academic institutions, corporate sponsors, government agencies, and scientific committees. Importantly, it has a solid track record of working on nonclinical cardiovascular safety issues, including Proarrhythmia and Cardiac Stem Cells Working Groups. Its proarrhythmia committee currently has representation from >50 industry, academic, and governmental participants. All organizations mentioned here were represented at this meeting.

## Concluding comments

Much experience and understanding has been gained since the adoption and implementation of present nonclinical and clinical guidelines focusing on proarrhythmic risk. Given our present knowledge of mechanisms responsible for TdP, the ability to evaluate drug effects on human cardiac ion channels, successes in *in silico* modeling of human ventricular electrical activity, and the evolving use of stem cell-derived human cardiac myocytes, it is our obligation to provide a more comprehensive evaluation of the actual proarrhythmic risk of a compound than is presently provided by S7B and E14. The goal of CiPA is not to generate unnecessary (and more burdensome) data sets to reflect available technology. Rather, its goal is to engineer a new, efficient, predictive paradigm positioned earlier in drug discovery that is based on well-established proarrhythmic mechanisms and that increases the efficiency of drug development, enhances the accuracy of drug labeling relative to potential torsadogenic effects, and reduces the premature discontinuation of drugs with real potential to improve the public health. It is important that the new paradigm is predictive of proarrhythmia, and with confirmation/qualification, the CiPA paradigm provides such an opportunity. Although this effort (and ICH E14) is focused on TdP, the envisioned ion channel screening will also reveal the potential for drugs to cause ventricular arrhythmias via other mechanisms, such as reducing the fast inward sodium current.<sup>37</sup>

Further collaborative efforts will be necessary to attain these goals, with the ultimate goal of ensuring more efficient discovery and development of safe therapeutics. Although discussions at the Think Tank adopted a necessary and helpful reductionist approach by considering these steps in turn and considering their advantages, limitations, and current feasibility, subsequent discussions will need to address the integration of selected assays and applications into a final risk assessment package that, as far as possible, will be integrative, interactive, and seamless.

## Disclosures

Philip T. Sager, MD, has a stock ownership in Merck and Aegerion. He is not a member of any speakers' bureaus and has declared no research funding. He is a safety consultant (member of DSMB, CV end point committee, consultant, or advisory board) to Shire Pharmaceuticals, Theravance, Lilly, Milestone, Medtronic, Aerpio, SK Science, Zalicus, Orexo, Viamet, SNBL, Biomedical Systems, iCardiac, Baxter, Celgene, Labrys, and Mitsubishi. He is a member of the FDA Cardiovascular and Renal Drugs Advisory Committee and the CSRC Executive Committee.

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