REVIEW

Early drug development: assessment of proarrhythmic risk and cardiovascular safety

The age of repolarization cardiac toxicity

Robert M. Lester and Joy Olbertz
Cardiovascular Safety Services, Celerion Inc., Tempe, AZ, USA

ABSTRACT

Introduction: hERG assays and thorough ECG trials have been mandated since 2005 to evaluate the QT interval and potential proarrhythmic risk of new chemical entities. The high cost of these studies and the shortcomings inherent in these binary and limited approaches to drug evaluation have prompted regulators to search for more cost effective and mechanistic paradigms to assess drug liability as exemplified by the CIPA initiative and the exposure response ICH E14(R3) guidance document.

Areas covered: This review profiles the changing regulatory landscape as it pertains to early drug development and outlines the analyses that can be performed to characterize preclinical and early clinical cardiovascular risk.

Expert commentary: It is further acknowledged that the narrow focus on the QT interval needs to be expanded to include a more comprehensive evaluation of cardiovascular risk since unanticipated off target effects have led to the withdrawal of multiple drugs after they had been approved and marketed.

In 1988, prenylamine, a calcium channel blocking analog of amphetamine used for the treatment of angina, was the first drug to be withdrawn from the market due to QT prolongation and sudden cardiac death [1]. Thereafter, in 1990, the first case report was published showing an association between the anti-histamine terfenadine (Seldane) and Torsades de Pointes (TdP), a potentially fatal form of polymorphic ventricular tachycardia associated with a prolonged QT interval [2]. Prior to this event, TdP was known to occur with antiarrhythmic and cardiovascular medications but was not well documented with non-cardiovascular drugs. Over the next 7 years, other classes of agents including antibiotics and psychotropic drugs were linked to TdP and a number of these drugs were subsequently withdrawn from the market [1,3]. In response to these events, government regulators and the pharmaceutical industry realized that a more robust evaluation of arrhythmia risk was needed.

In 1997, the UK Committee for Proprietary Medicinal Products (CPMP) adopted a document entitled ‘Points to consider: the assessment of the potential for QT interval prolongation by non-cardiovascular medicinal products.’ [4] This document was drafted in response to multiple reports of non-antiarrhythmic drugs prolonging the QT interval on the electrocardiogram (ECG) resulting in TdP. This paper served as the template and forerunner for European, Canadian, Japanese, and US regulatory agencies to focus attention on the arrhythmic potential of noncardiac drugs previously deemed to be safe.

In 2001, Health Canada put forth the document ‘Assessment of the QT Prolongation Potential of Non Antiarrhythmic Drugs,’ although no specific testing protocol was recommended [5]. This was followed in 2005 by regulators from Europe, Japan, and the USA who finalized the tripartite International Conference on Harmonization (ICH) E14 and S7B guidance documents although they were not formally adopted in Japan until 2009 [6]. These guidelines were developed in an effort to characterize the effect of noncardiac drugs on cardiac repolarization prior to their approval. ICH E14 referred to the clinical evaluation of QT/QTC prolongation and proarrhythmic potential for non-antiarrhythmic drugs while ICH S7B described the preclinical evaluation of the potential for delayed ventricular repolarization (QT interval prolongation) by human pharmaceuticals. These documents mandated that virtually all new chemical entities (NCEs) that have systemic bioavailability undergo rigorous preclinical testing and subsequent clinical ECG evaluation in an integrated fashion so as to assess effects on QT prolongation and proarrhythmia risk. This same recommendation would also be applicable to approved drugs when a new dose or route of administration is planned or a different patient population is targeted. In contrast, regulatory agencies have suggested that thorough QT (TQT) studies are usually not applicable for orphan drugs, monoclonal antibodies or large biologic proteins which do not enter the cell and have little direct ion channel effects, and agents which are applied topically and may not be absorbed. Regulators also do not routinely require TQT trials for drug combinations where the individual components have previously been evaluated and did not demonstrate any QT liability. Finally, during the execution of TQT studies, compliance with good clinical practice (GCP) is necessary to ensure that data meets the regulatory standards for submission.

CONTACT Robert M. Lester robert.lester@celerion.com Cardiovascular Safety Services, Celerion Inc., 2420 W. Baseline Road, Tempe, AZ 85283, USA © 2016 Informa UK Limited, trading as Taylor & Francis Group
The requirements for cardiac safety testing outlined in the ICH S7B preclinical guidance were in part based upon the knowledge that prolongation of phase III of the cardiac action potential (AP) is primarily responsible for QT prolongation. This prolongation, in turn, is usually related to alteration or blockade of various cation voltage-gated channels [7]. For example, prolongation of the AP can result from decreased inactivation of the inward Na⁺ or Ca²⁺ currents, increased activation of the Ca²⁺ current, inhibition of one or more of the outward K⁺ currents or altered potassium channel trafficking and protein synthesis [8] (Figure 1).

Foremost amongst these mechanisms is blockade of the rapidly activating delayed potassium rectifier current (I_{Kr}) which is encoded by the human ether-a-go-go gene hERG (now known as KCNH2). hERG inhibition was the proposed mechanism responsible for TdP and QT prolongation that led to the withdrawal of many non-cardiovascular drugs [9]. As such, hERG blockade became the focus of regulators and underlies the ICH S7B requirement that in vitro hERG and AP assays be performed on all NCEs. This data, in conjunction with mandatory in vivo QT and telemetry assessment in non-rodent animals, is then used to predict the compound’s effect on ventricular repolarization and arrhythmia risk in human subjects.

The ICH E14 guideline outlines the requirements for a thorough QT study which involves robust human ECG collection [6,10,11]. This is most often performed late in phase II or during phase III of drug development, when the clinical dose is understood and defined. Although a variety of adaptive study designs are now used, the traditional parallel or crossover designs are often still employed with four treatment arms: a placebo, a positive control (typically moxifloxacin), a therapeutic dose of the drug, and a supratherapeutic dose of the drug. ECGs and blood samples for pharmacodynamic (PD) and pharmacokinetic (PK) analysis are collected at baseline and on a time-matched basis in each treatment period and the influence of the compound under evaluation on the placebo corrected change from baseline is calculated at each time point. The threshold of regulatory concern for QTc prolongation is where the upper bound of the 95% one-sided confidence interval for the largest time matched mean effect of the drug on the QTc interval excludes 10 msec [6]. Values above 10 msec are deemed positive and will warrant further ECG evaluation in subsequent clinical trials but do not necessarily indicate that the drug is proarrhythmic or should be halted in development. Values below 10 msec are deemed negative which implies that there is no significant arrhythmia risk or need for augmented ECG testing beyond routine surveillance in subsequent studies.

1. Limitations of the TQT and hERG centric world

The utility and focus on the QT interval as a surrogate marker for TdP, although deeply ingrained, has been in question since ICH E14 and S7B guidance documents were initially issued. The positive predictive value of either QT prolongation or hERG blockade for TdP is relatively modest especially given the promiscuity of the hERG channel for compounds from diverse drug classes. For example, sodium pentobarbital, ranolazine, verapamil, and amiodarone are potent hERG blockers but are not viewed as torsadogenic and the latter two agents are actually known to be antiarrhythmic. This apparent paradox has been explained by multiple ion channel effects (MICE), particularly blockade of L-type calcium channels and/or the late Na⁺ current which modulate and mitigate arrhythmic risk by shortening the early phase of ventricular repolarization [12]. This is the basis for why verapamil, despite potent hERG block, shortens the J-T peak and QT intervals, reduces early after depolarizations (EADs), and lowers the incidence of TdP in experimental models. Conversely, there are drugs such as probucol, fluoxetine, arsenic, and pentamidine, which do not block hERG channels but are torsadogenic due to abnormal potassium channel protein synthesis or trafficking, thereby underscoring the lack of specificity of hERG channel block as a predictor of TdP [8,12,13]. Despite limitations in the predictive value of these markers, since the institution of the 2005 ICH guidelines, there have been no drugs approved which have subsequently been confirmed to be torsadogenic and the number of reports of TdP episodes for non-antiarrhythmic drugs has not increased [14]. However, even in light of this apparent success, there is concern about unintended consequences from these guidelines including premature termination of drug development for NCE’s based solely upon either the hERG assay or TQT study results. To this point, it has been estimated that as many as

![Figure 1](image_url)
20–60% of NCEs may demonstrate hERG blockade and up to 30% of NCEs have been abandoned solely due to the results of an hERG ion channel assay in which a high potency blocking agent was identified [15].

Blockade of hERG current can be evaluated using both direct and indirect assays of which the ‘gold standard’ is a direct assay voltage clamp technique using hERG transfected mammalian cells. The concentration of drug required to block 50% of hERG current (IC\textsubscript{50}) is determined from total and free drug concentration response curves. Redfern et al. viewed a 30-fold or greater difference between the IC\textsubscript{50} value and the therapeutic plasma concentration as the threshold for minimizing QT liability of a compound [16,17]. Alternatively, Gintant et al. have shown that a hERG safety margin of 45-fold between the IC\textsubscript{50} dose and the free plasma drug concentration predicts the absence of a QT effect >5 ms with a sensitivity of 64% and a specificity of 88%, highlighting the relative weakness of this assay for truly predicting QTc prolongation clinically [18]. Interpretation of these results is further complicated by the lack of standards for the hERG patch clamp assay and the associated variability of results observed between different laboratories which may be as high as a 20-fold difference in IC\textsubscript{50} values for a specific drug [19]. Further contributing to this weakness is that hERG current block is influenced by the type of mammalian cell line employed, the temperature of the experimental preparation, the configuration of the potassium channel which may be open or closed during testing, and the stimulation frequency and protocol used [20]. Moreover, the hERG channel assay will not capture effects of late appearing metabolites unless they are tested separately nor is its sensitivity sufficient to routinely detect outward slow channel potassium block (I\textsubscript{ks}) [21]. Finally, the hERG assay is an in vitro technique which cannot fully reflect human physiology especially when altered ion channel function may take hours to develop or may require a specific ionic milieu to manifest an abnormal response [22].

This lack of standards and specificity is not limited to the preclinical assessment of QTc prolongation. When evaluating QTc prolongation clinically, the methodology and technology used to measure the QT interval is not uniform. This lack of uniformity can complicate the interpretation of QTc results especially when comparing data between studies. To this point, a concern has been raised about the variability in the formulae that are employed for correcting the QT interval for heart rate [23]. Bazett’s formula has been shown to be inferior to Fredericia’s correction especially for measurements between individuals and within individuals. Therefore, all QT values should be reported with Fredericia’s correction as Bazett corrected data ‘is no longer warranted by regulators in all applications’ [24]. An additional and important concern has been raised when individual correction formulae (QTcI) are used since the heart rate correction method, the T wave amplitude, the range of heart rate variability, and the number of complexes analyzed can significantly impact QTc results when different correction equations are used [25]. Another clinical factor is that due to the low incidence of TdP, it is not possible to precisely determine the positive predictive power of the QTc study for this arrhythmia since these trials are only designed to identify whether prolongation in ventricular repolarization is present. Finally, although ICH E14 does provide relatively clear guidance for determining if a study is positive or negative based upon the 10 msc threshold of regulatory concern, it has been criticized as being too restrictive in its focus on the QT interval, too simplistic in that results are interpreted in a binary rather than graded fashion, and without a proven quantitative or mechanistic correlation to TdP risk.

Even with these known limitations of the hERG assay and the TQT study, since 2005 approximately 450 TQT trials have been conducted worldwide at a cost of 1.0–4.0 million dollars per study. It is acknowledged by regulators and industry that the time and resource expenditure for these studies is unacceptably high and that assessment of drug liability must be performed with a more cost effective and comprehensive paradigm. To this point, Bouvy et al. performed a pharmacoeconomic cost-effectiveness analysis of ICH E14’s recommendation of a TQT using a model of a prototype antipsychotic medication known to affect the QTc interval [26]. They suggested, given the high cost of the TQT study, the very low incidence of TdP and drug-mediated sudden death, and the absence of routine post-approval ECG monitoring of patients, that regulators should only consider a TQT when preclinical and early-phase studies raise a serious QTc liability concern. Last, the occurrence of TdP in the clinical setting is heavily influenced and may be amplified by numerous physiological conditions and drug interactions. In this regard, Zeltser et al. have shown that in 71% of cases of drug-related TdP two or more identifiable risk factors were concomitantly present (Table 1) [27]. The impact of these physiological conditions and drug interactions would not be fully vetted in a preclinical hERG assay or during conduct of a TQT trial further clouding the discussion about the role and positive predictive value of these studies in early drug development.

2. The quest for alternative surrogates of QT liability

It has been established that AP prolongation in vitro does not necessarily equate to clinical prolongation of the QT interval and a prolonged QT interval does not correlate in an incremental linear fashion to the occurrence of TdP [29]. Moreover, QT prolongation viewed in isolation does not confer any de novo specific risk to a subject. As such, the regulatory focus on

| Table 1. Risk factors for torsades de pointes [28]. |
|-----------------|---------------------------------------------|
| QTc >500 msec   | Use of QT prolonging drug(s)                |
| Abnormal repolarization morphology on ECG: notching of T waves, long Tp-Tend |
| Underlying heart disease: cardiomyopathy, heart failure, or myocardial infarction |
| Bradycardia     | Premature contractions producing short-long-short cycles (short-term QT variability) |
| Hypokalemia     | Impaired hepatic clearance of drugs         |
| Hypomagnesemia  | Diuretic use                                |
| Advanced age    | Latent congenital LQTS polymorphisms       |
| Hypocalcemia    | Abnormal/reduced repolarization reserve     |
| Combinations of 2 or more risk factors |
hERG blockade and QT prolongation has fostered efforts to develop other surrogate markers and computational models to better predict arrhythmia risk of NCEs [30].

Electrophysiology studies suggest that Tdp likely originates in the Purkinje network and midmyocardial cells (M cells) and requires temporal and spatial heterogeneity of repolarization as a substrate. Additional factors which trigger Tdp include reduced repolarization reserve and the presence of EADs [31]. Bradycardia with premature beats that produce ‘short-long-short’ cycles are also thought to be contributing factors in the pathogenesis of Tdp. Computer modeling and research in animals have promoted the concept that triangulation of the AP (T), reverse use dependence (R), repolarization instability (I), and temporal dispersion of repolarization (D) or (TRIaD) in conjunction with QT prolongation and EADs are predictive of Tdp [32]. In fact, there have been no instances of drug-induced Tdp reported where all of these factors were absent.

Clinical ECG markers of TRIaD have been proposed including assessment of T wave morphology (T) where there may be flattening, lengthening, and notching, QT/RR slope (R) where AP duration increases with reduced heart rates, QT interval variability (I), and prolongation of the time from the peak of the T wave to the end of the T wave (Tp-Te) (D). However, these have not been well validated in large population-based human studies. The same pertains to the ratio of Tp-Te/QT which has been suggested by Yamaguchi et al. who claim that values above 0.28 are strongly associated with the risk of developing Tdp [33]. Similarly, in 30 patients with bradydysrhythmias and Tdp, Topilski and colleagues identified a prolonged Tp-Te of 117 msec as the best single predictor of Tdp [34]. The biomarker microvolt T wave alternans has been mentioned by other authors as a proarrhythmic risk factor although this is not routinely measured nor has it been validated [35]. More precise attention, measurement, and analysis of multiple ion channel effects centered on the PR interval as a reflection of calcium channel blockade and the QRS as a reflection of Na+ channel blockade when coupled with QT data has been shown to be superior to hERG block to clarify the arrhythmia liability of NCEs [36]. Isolated QT dispersion has also been postulated to be a surrogate for repolarization anisotropy although the sensitivity and specificity of this marker for arrhythmias is not well defined [37]. J-Tc peak measurement using vector magnitude plots [38] to assess late Na+ channel block and the early phase of ventricular repolarization, and T wave morphology including flattening, widening, and notching, are other ECG parameters which have garnered commercial and regulatory attention and may provide additional information about arrhythmia risk [39,40]. Finally, the use of Holter beat to beat interval analysis designed to evaluate QT drug effects independent of heart rate and autonomic changes is a promising approach to more precisely characterize the propensity for proarrrhythmia [23]. However, until the cellular basis for Tdp is precisely defined and it is extremely rare and almost never seen in clinical development, validated predictive surrogates for this rhythm will remain elusive.

3. Dawn of a new paradigm for drug cardiovascular liability

In light of the high cost and unfulfilled promise of clinical biomarkers to predict Tdp, regulatory focus has shifted to develop a more effective approach for arrhythmia assessment. These innovative efforts are designed to reduce the need for a TQT study and are currently centered on improving preclinical assays for evaluating arrhythmogenesis and clinically identifying arrhythmia risk utilizing exposure response analysis and intensive ECG QT assessment (IQT) in early-phase human studies.

A major clinical initiative in this direction was the pilot study presented and published by the Consortium for Innovation and Quality in Pharmaceutical Development and the Cardiac Safety Research Consortium (IQ-CSRC) [41]. They designed a two-dose single ascending dose (SAD)-like trial involving 20 subjects and six marketed drugs whose QT effects had been fully documented in previous TQT studies. Five ‘positive’ compounds were known to prolong the QT interval above the threshold of regulatory concern while one ‘negative’ agent was demonstrated to have no significant QT prolonging signal. ECGs were extracted at three pre-dose and 9 post-dose time points and up to ten 10 s ECG replicates were analyzed. The consortium hypothesized that by using concentration effect modeling in which IQT data are evaluated in conjunction with serial PK time points, they would be able to determine the exposure–response relationship and thus the propensity for a compound to prolong the QTc interval. The results of the study did confirm that this approach was able to replicate the previously documented TQT findings for each of the drugs and correctly characterize their effect on the QT interval. The IQ-CSRC and US FDA views this type of study as ‘an alternative’ or ‘option’ to the TQT trial which has the potential to enable sponsors to greatly decrease expenses and define QT liability earlier in drug development.

The IQ-CSRC acknowledges that this original study design does have a number of limitations including small sample size with more data variability and limited power to exclude minor QT effects, the unproven ability to extrapolate the findings to a large population, the absence of a positive control, and an incomplete block design. The drugs that were evaluated are not necessarily representative of the spectrum of compounds that may have less well-defined QT effects and chemical entities that impact autonomic function may not be accurately assessed with this model. While the researchers found that a linear relationship existed between drug concentration and QT interval measurements with the tested drugs (except for disopyramide), linearity may not be present with other compounds and would consequently necessitate analysis using an alternative nonlinear statistical model. Other concerns that have been voiced about this pioneering study are that, ‘concentration effect modeling and interpretation can be complicated when metabolites contribute to QT/QTc prolongation, when the drug affects multiple cardiac ion channels, or when there is a hysteresis effect due to delayed tissue penetration or there is interference with ion channel trafficking.’ [42] Finally, the reproducibility of this type of design should be confirmed in subsequent investigations particularly if less than ten ECG
replicates are analyzed, and the concordance with TQT trials regarding the incidence of false-positive and false-negative results needs to be established.

As a byproduct of the IQ-CSRC initiative, the ICH-E14 guidance was recently updated to include exposure response (PK/PD) modeling as a primary analysis modality in FIH studies as an option to performing a dedicated TQT study [43]. The essential elements of this type of analysis as recommended by the FDA’s Division of Cardiorenal Products are being written into a best practice document and include [44]:

- High-quality clinical conduct and ECG data collection
- A wide exposure margin of the test compound reflecting a worse case clinical scenario aiming for a concentration of 3–5 times higher than that which would be seen clinically
- Appropriate testing for linearity and hysteresis in the completed data set
- Prospectively specifying the modeling and statistical analysis plan and performing rigorous exposure response assessment
- Recruitment of at least 6 placebo-treated subjects in the study with typical cohort sizes of 6–9 subjects

The key component of this approach is to ensure that a sufficiently high drug exposure/concentration is achieved which is a multiple of the clinically relevant exposure or ‘worse case scenario.’ This may involve escalating the drug doses to levels beyond a supratherapeutic dose and require additional cohorts in SAD/MAD trials. In addition, the use of a positive control is not recommended as long as there is a placebo group and drug concentrations achieved are a multiple of the clinically relevant exposure. In addition, to mitigate against a false-negative study in cases where insufficient drug exposure occurs, method bias sensitivity (MBS) analysis [45] has been proposed by several stakeholders using the slope estimate of Bland–Altman plots as an indicator of potential bias. A bias severity <10 msec over a range of QTcF values was proposed as the threshold measure that would confer a <5% false-negative rate of drug-mediated QT prolongation.

An additional effort to evaluate arrhythmia risk focuses on the preclinical evaluation of mechanisms leading to proarrhythmia. The Comprehensive in vitro Proarrhythmia Assay (CIPA) [46] (see Figure 2) initiative is taking a graded approach to preclinical drug arrhythmia liability unlike the current S7B preclinical assays which are typically interpreted in a binary manner as being either positive or negative. The CIPA initiative employs a mechanistic perspective on defining the pathogenesis of cardiac arrhythmias and builds upon the significant advancements during the past 10 years in computer technology, cardiomyocyte assays, and our understanding of ion channel pharmacology. It also is being driven by the recognition that the predictive value of current in vivo preclinical ECG assays is compromised by a number of factors including small sample size, absence of a positive control, the lack of standardization of ECG acquisition and reading methodology, and the difficulty interpreting results amongst different non-rodent species and extrapolating them to humans.

CIPA is being promulgated by thought leaders in academia, industry, and the FDA and involves four major elements in preclinical drug investigation. First, rather than focusing predominantly on IKr blockade, an ion channel working group has proposed more comprehensive in vitro voltage clamp studies of seven ion channels using high-throughput patch assays which affect the cardiac AP and influence proarrhythmic risk. The channels that are currently targeted include potassium (IKr, IKs, IKo, IK1), peak and late Na+ and Ca2+. A second component of the CIPA initiative, under development by the in silico working group, uses the O’Hara-Rudy computational model [47] of the human ventricular cardiomyocyte which is designed to reproduce the cellular electrophysiology of the compound and assess AP instability and proclivity to EADs using in silico modeling. A third in vivo piece of this approach under the auspices of the stem cell working group is the use of either human embryonic stem cell cardiomyocytes or human-induced pluripotent stem cell cardiomyocytes to confirm the findings of the in silico modeling. Last, the clinical translational working group has developed an FDA approved set of twenty-eight reference drugs categorized into low, medium, and high risk of proarrhythmia. This list of 28 drugs will then be used as a benchmark for grading the arrhythmia risk of the compound under evaluation by integrating the information derived from the ion channel, in silico and myocyte components of this paradigm. As such, the purpose of the CIPA initiative is to define and qualify the risk of proarrhythmia rather than focusing solely on the QT interval or attempting to induce TdP or other arrhythmias. It is also not intended to replace the need for in vivo telemetry studies in non-rodent species. This strategy will inevitably broaden the scope of arrhythmia focus to identify agents which may predispose to serious arrhythmias by mechanisms other than their effects on IKr and the QT interval.

By deploying the preclinical CIPA scheme in conjunction with IQT monitoring and exposure response analysis in early-phase clinical studies to assess a NCE’s arrhythmia liability, it is anticipated that the current recommendation to perform a TQT study on new small-molecule compounds will be dramatically reduced. In support of this perspective is acknowledgement by the FDA that a compelling case for a TQT waiver would be strongly considered if robust preclinical and clinical...
evaluation did not demonstrate any cardiac safety signals assuming that the drug exposure was a multiple of the clinically relevant exposure. Moreover, the adoption of this integrated approach may lead to lower drug development costs, potentially improve characterization of drug arrhythmia risk and commercialization opportunities, and enhance the ability to make early and informed go/no-go decisions. The expected timeline for completion of CiPA is by the end of 2017 although challenges to standardize, test, and validate the requisite technology and methodology may admittedly delay implementation. Finally, despite high-throughput assays, it remains to be determined what is the cost of the CiPA scheme, how will regulators interpret CiPA data when the findings are ambiguous, whether this approach will be recommended for development of all non-biologic NCEs or considered an optional undertaking, and what is the concordance and predictive power of CiPA results vis-a-vis early-phase human studies.

4. The shift from cardiac to cardiovascular safety

Over the past 20 years, multiple drugs which had been approved and marketed were subsequently withdrawn because of significant morbidity and mortality due to unanticipated and profound off-target effects on the cardiovascular system (Table 2).

<table>
<thead>
<tr>
<th>Indication</th>
<th>Drug</th>
<th>Off-target effect</th>
<th>Date withdrawn</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute myelogenous leukemia</td>
<td>Gemtuzumab ozogamicin(Mylotarg)</td>
<td>Veno-occlusive disease</td>
<td>2010</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Gatixofloxin (Tequin)</td>
<td>Prolonged QT interval, arrhythmias</td>
<td>2006</td>
</tr>
<tr>
<td>Antifibrinolytic</td>
<td>Aprotinin(Trasylo)</td>
<td>Heart failure, stroke</td>
<td>2008</td>
</tr>
<tr>
<td>Antihistamine</td>
<td>Terfenadine(Seldane)</td>
<td>Prolonged QT interval, arrhythmias</td>
<td>1998</td>
</tr>
<tr>
<td>Antipsychotic</td>
<td>Atestizole(Hismanal)</td>
<td>Prolonged QT interval, arrhythmias</td>
<td>1999</td>
</tr>
<tr>
<td>Appetite suppressant</td>
<td>Sibutramine(Meridia)</td>
<td>Heart attack, stroke, death</td>
<td>2010</td>
</tr>
<tr>
<td>Arthritis/analgesia</td>
<td>Rofecoxib(Vioxx)</td>
<td>Heart attack, stroke, death</td>
<td>2004</td>
</tr>
<tr>
<td>Bladder incontinence</td>
<td>Terodiline(Micturin)</td>
<td>Prolonged QT interval, arrhythmias</td>
<td>1991</td>
</tr>
<tr>
<td>Gastrointestinal reflux</td>
<td>Cesapride(Propulsid)</td>
<td>Prolonged QT interval, arrhythmias</td>
<td>2000</td>
</tr>
<tr>
<td>Irritable bowel syndrome</td>
<td>Tegaserid(Zelnorm)</td>
<td>Heart attack, stroke, angina</td>
<td>2007</td>
</tr>
<tr>
<td>Obesity</td>
<td>Dexfenfluramine(Redux)</td>
<td>Cardiac valve dysfunction, pulmonary hypertension</td>
<td>1997</td>
</tr>
<tr>
<td>Opioid analgesic</td>
<td>Propoxyphene(Darvone/Darvocet)</td>
<td>Prolonged QT interval, arrhythmias</td>
<td>2010</td>
</tr>
<tr>
<td>Opioid dependence</td>
<td>Levomethadyl acetate(Orlaam)</td>
<td>Prolonged QT interval, arrhythmias</td>
<td>2003</td>
</tr>
<tr>
<td>Parkinson’s disease</td>
<td>Pergolide(Permax)</td>
<td>Cardiac valve dysfunction</td>
<td>2007</td>
</tr>
</tbody>
</table>

Table 2. Representative drug classes and agents which have been withdrawn due to off-target cardiovascular effects.

ICH E14 and ICH S7B have fulfilled the short-term goal of preventing non-antiarrhythmic drugs that are torsadogenic from coming to market. However, it is now evident that the limited focus on QT liability may have prevented compounds with favorable clinical characteristics from further development, being approved by regulators, or having been appropriately labeled with black-box warnings. In addition, this approach has arguably created a narrow view of cardiovascular safety that is dominated by discussions of QT prolongation which is known to have significant shortcomings as a biomarker for arrhythmia risk [56]. Moreover, given the resource intensive, high cost of TQT trials, and their limited positive predictive value for arrhythmias, stakeholders are seeking to develop a more cost effective and qualitative mechanistic characterization of a drug’s liability based upon enhanced understanding of ion channel pharmacology and advances in

4.1. Expert commentary and five-year view

Antidiabetic agents have been shown to have important off-target effects on nitric oxide-mediated endothelial function as measured by flow-mediated dilation that may presage systemic hypertension and atherosclerosis [54]. Increased thrombogenicity due to thromboxane effects on platelet aggregation leading to stroke and heart attack assessed by platelet aggregometry has been controversially linked to cyclooxgenase-2 inhibitors prompting more intense scrutiny of this class of agents including the withdrawal of rofecoxib(Vioxx) from the market in 2004 [55]. As such, it is incumbent during early drug development to consider broadening the scope of evaluation beyond the ECG assessment of QT prolongation to include a more comprehensive characterization of cardiovascular safety.
computer modeling and stem cell technology. Ultimately, a more robust preclinical paradigm as outlined in the CiPA initiative paired with an IQT early-phase clinical study with exposure response analysis would provide a more comprehensive strategy to assess cardiac safety and offer the opportunity to apply for a TQT waiver.

However, despite the aforementioned limitations, the TQT still has relevance and will likely remain an important option to clarify risk particularly when preclinical and early clinical results are ambiguous or discordant. In addition, there are valuable elements and lessons learned from the cumulative TQT experience which are being incorporated into the newly proposed regulatory scheme. Amongst these are more efficient and cost-effective study designs, expanded testing of multiple ion channel effects and better in vitro assays, more sophisticated in vivo cell preparations using stem cell-derived cardiac myocytes, continuous digital recordings, and acquisition of triplicate ECGs at key PK time points in FIH studies, and the needed focus to standardize assay methodology and technology. Thus, until a new comprehensive guidance document is drafted by regulators and is formally adopted by industry, the TQT should still be considered an integral undertaking particularly for NDA applications which are scheduled to be filed within the next several years. Equally important in drug development programs and to complement arrhythmia risk assessment, the observation that off-target effects of drugs may be clinically deleterious should promote efforts to fully characterize a compound’s cardiovascular liability beyond measurement of hERG block, cardiac APs, and the QT interval, utilizing a complementary suite of serum biomarkers, ECG monitoring and cardiac imaging modalities.

**Key issues**

- ICH E14 and S7B have been successful in preventing torsadogenic drugs from coming to market
- hERG assays and the QT interval have shortcomings in their positive predictive value for Torsades de pointes and proarrhythmic risk
- Torsades de pointes typically occurs in association with multiple risk factors
- Surrogate markers for Torsades de pointes will remain elusive given the very low incidence of this event in preclinical and clinical trials and the incomplete understanding of its pathogenesis
- The TQT trial is a resource intensive binary approach to arrhythmia risk and needs to be replaced by a mechanistic and graded assessment of drug proarrhythmia liability
- Intensive ECG monitoring with exposure response analysis in early phase drug development along with a more robust preclinical assessment as detailed in the CiPA initiative may reduce the need for TQT studies
- A positive control is no longer routinely recommended for early phase intensive ECG studies if the drug concentration achieved is a multiple of the clinically relevant exposure AND there are are sufficient subjects administered placebo
- Comprehensive cardiovascular risk assessment should be routinely considered in early drug development to fully characterize a compound’s liability

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**References**

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.


**Excellent overall review of the impact of drugs on ventricular repolarization.**


**The definitive guidance document regarding QT interval prolongation with non-antiarhythmic drugs.**


**Outstanding general review about the Thorough QT study by a key opinion leader in the field.**


**Outstanding overall review of drug development and implications regarding cardiac repolarization.**


**Excellent overall review of the topic by leading authorities.**


**Comprehensive basic review of the subject.**


19. • A good scientific summary of the role and science behind hERG testing in early drug development.
38. Johannsen L. How sponsors could implement new ECG biomarker approaches. Presentation at joint FDA/CSRC meeting; 2016 Apr 6; Washington, DC.
• Comprehensive review by regulatory experts in the field.
• The landmark study by the regulatory and CSRC consortium supporting an alternative to TQT studies.
43. E14 Implementation Working Group ICH E14 Guideline. The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs questions & answers (R3); 2015 Dec 10.
• Update on the new proarrhythmia CIPA paradigm by the key opinion leaders in the field.
• Good general review of preclinical cardiovascular risk assessment.