Cardiac Safety Research Consortium Conference

Current challenges in the evaluation of cardiac safety during drug development: Translational medicine meets the Critical Path Initiative

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In October 2008, in a public forum organized by the Cardiac Safety Research Consortium and the Health and Environmental Sciences Institute, leaders from government, the pharmaceutical industry, and academia convened in Bethesda, MD, to discuss current challenges in evaluation of short- and long-term cardiovascular safety during drug development. The current paradigm for premarket evaluation of cardiac safety begins with preclinical animal modeling and progresses to clinical biomarker or biosignature assays. Preclinical evaluations have clear limitations but provide an important opportunity to identify safety hazards before administration of potential new drugs to human subjects. Discussants highlighted the need to identify, develop, and validate serum and electrocardiogram biomarkers indicative of early drug-induced myocardial toxicity and proarrhythmia. Specifically, experts identified a need to build consensus regarding the use and interpretation of troponin assays in preclinical evaluation of myocardial toxicity. With respect to proarrhythmia, the panel emphasized a need for better qualitative and quantitative biomarkers for arrhythmogenicity, including more streamlined human thorough QT study designs and a universal definition of the end of the T wave. Toward many of these ends, large shared data repositories and a more seamless integration of preclinical and clinical testing could facilitate the development of novel approaches to both cardiac safety biosignatures. In addition, more thorough and efficient early clinical studies could enable better estimates of cardiovascular risk and better inform phase II and phase III trial design. Participants also emphasized the importance of establishing formal guidelines for data standards and transparency in postmarketing surveillance. Priority pursuit of these consensus-based directions should facilitate both safer drugs and accelerated access to new drugs, as concomitant public health benefits. (Am Heart J 2009;158:317-26.)

Because of the potentially catastrophic nature of unanticipated "off-target" drug-related cardiovascular complications, cardiac safety is of paramount importance in contemporary drug development. In the US, cardiac safety is the leading cause for the drug discontinuation at all phases of development, including drug discovery, preclinical evaluation, clinical evaluation, and postmarket surveillance (Table I).[1,2] For both cardiac and noncardiac pharmaceuticals, cardiac safety concerns arise from a variety of drug-tissue interactions, including direct myocyte toxicity, QT and non–QT proarrhythmic changes, and other effects on vascular tone and injury (Table II). Efficient and sensitive evaluation of cardiac safety in the research and development of new molecular entities begins with preclinical in vitro and in vivo modeling and carries through all phases of human testing and postmarket use. In an era marked by increased public scrutiny, escalating industry costs, and limited resources at regulatory agencies, the need for efficient, yet safe drug development is more important than ever.[8]

The US Food and Drug Administration's (FDA) Critical Path Initiative emerged with the general recognition that both (1) the rising costs of drug development and (2) the decline in the number of new drugs approved in the United States are significant problems that threaten the public health. Cardiac safety evaluations of off-target drug effects in particular are generally expensive, time consuming, and contribute to the

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Table I. Leading reasons for drug withdrawal over the last 40 years[1,2]

Worldwide withdrawal (121 compounds)		US Withdrawal (95 compounds)	
Reason	**Percent**	**Reason**	**Percent**
Hepatotoxicity	26	Cardiovascular safety (proarrhythmia)	19 (12)
Hematologic toxicity	10	Neuropsychiatric effects	12
Cardiovascular safety	9	Hepatotoxicity	9
Dermatologic effects	6	Bone marrow toxicity	7
Carcinogenicity	6	Allergic reactions	6

Table II. FDA-Approved drugs withdrawn for cardiovascular safety concerns

Compound	Class	Reason for withdrawal	Year withdrawn
Astemizole[3]	Antihistamine	QT Proarrhythmia	1999
Cisapride[4]	Prokinetic agent	QT Proarrhythmia	2000
Ecainide[5]	Ic antiarrhythmic	Non-QT Proarrhythmia	1986
Flosequinan[6]	Vasodilator	Increased mortality	1992
Grepafloxacin[7]	Fluoroquinolone antibiotic	QT Proarrhythmia	1999[8]
Rofecoxib[9]	COX-2 inhibitor	Thrombotic risk	1999
Terfenadine[10]	Antihistamine	QT Proarrhythmia	1997
Terodiline[11]	Antimuscarinic	QT Proarrhythmia	1993
Valdecoxib[9]	COX-2 inhibitor	Thrombotic risk	2001

termination of many new molecular entities. Cardiac safety evaluation thus constitutes an area that fits the core mission of the FDA's Critical Path.

To help address the needs highlighted by the Critical Path, a dedicated effort was launched to create a transparent public-private partnership addressing cardiac safety evaluations, the Cardiac Safety Research Consortium (CSRC) (http://www.cardiac-safety.org). In addition, under the existing auspices of the nonprofit organization, the ILSI Health and Environmental Sciences Institute (HESI), a multisector Committee on Cardiac Safety was initiated in 2008. Both CSRC and HESI are nonprofit consortia that engage industry, academic, and government scientists in the collaborative identification and resolution of emerging issues in the science of pharmaceutical safety.

These consortia joined in the formulation of the "think-tank" meeting, which serves as the basis for this publication. The meeting engaged leaders from government, the pharmaceutical industry, and academia in Bethesda, MD, on October 5-6, 2008, to discuss current challenges in the nonclinical and clinical assessment and evaluation of cardiovascular safety during pharmaceutical development. The participants were challenged to discuss and offer solutions for gaps in translating cardiac safety assessment from preclinical modeling to clinical evaluation in the spirit of the Food and Drug Administration's Critical Pathway to New Medicinal Drugs initiative.[12] This publication represents a synthesis of the key areas of discussion and recommendations that emerged during the proceedings. The intention of this white paper is to summarize the think-tank discussions.

Cardiotoxicity, troponin, and other biomarkers: where do they fit in drug development?

Drug-induced cardiac injury can be evaluated in a number of ways, including ex vivo pathologic examination, in vivo cardiac imaging, and serum biomarker evaluation. Across the spectrum of preclinical and clinical cardiac safety testing, highly specific serum markers have gained attention and interest for their potential to provide sensitive "early warning" of myocellular injury and death. There are many biomarkers of cardiotoxicity in various stages of maturity including natriuretic peptides (including B-type natriuretic peptide) and inflammatory markers such as interleukin-6, myeloperoxidase, and soluble CD40 ligand. Cardiac troponin assays in particular, because of their highly sensitive and specific correlation to acute myocyte injury, are considered a significant advance in the field, providing valuable information in the preclinical and clinical settings.[13,14]

Troponin in preclinical safety evaluations

Traditionally, preclinical evaluation of drug-related cardiac toxicity has included both functional assessments in single-dose studies and ex vivo morphologic evaluation with gross and light microscopic examinations in repeat-dose studies. Recognizing the translational challenges of such morphologic evaluation in human subjects, more recent attention has been given to exploiting serum biomarkers of cardiotoxicity as surrogates for direct examination of the heart for injury. Cardiac troponins have been the primary focus of this translational strategy and are believed to report similar pathobiological events in laboratory animal species and human patients. Complexities remain as a number of commercially available assay platforms have been developed that exhibit variable analytical performance across different laboratory species.[15]

Thus, although interest in preclinical troponin testing is widespread, significant uncertainty surrounding the interpretation and predictive utility of the data remains. As such, routine application of troponin monitoring in preclinical studies is controversial. Although prominent increases in troponin accompanied by morphologic evidence of cardiac injury imply clinically significant

risk, smaller or transient increases in serum troponin without a morphologic correlate present a conundrum for understanding true risk to patients, in both the short- and long-term. As such, the appropriate response to small newly detectable elevations in serum troponin in preclinical drug development is ill defined. Routine monitoring of serum troponin in preclinical animal models will remain a subject of debate until our experience with this biomarker allows us to interpret these data with greater confidence. Collaborative efforts to pool common databases of preclinical troponin data represent a significant opportunity to clarify the prognostic value of this biomarker and move the field forward.

Defining a universal threshold for increased troponin in preclinical drug development is complicated by analytical variability in cardiac troponin assays, variability in basal troponin levels among species, and heterogeneity in troponin responses among animal models. This dilemma is even more challenging when troponin increases occur in the absence of a morphologic correlate or occur in one species and not in another. Currently, troponin assays are applied more commonly in second-tier testing, where other lines of evidence create suspicion for or evidence of cardiotoxicity. At present, there are no FDA guidelines regarding the interpretation of troponin data in preclinical drug evaluation.

The following areas were identified as critical gaps in our understanding of preclinical troponin evaluation:

1. Lack of consensus and subsequent definition of troponin kinetics in several animal models of preclinical cardiotoxicity.
2. Lack of understanding and consensus regarding the long-term (human, clinical trial) implications of small troponin elevations in preclinical animal models.
3. Lack of a confirmatory/tier II strategy, in which troponin measurements in human subjects might be required only after primary evidence of cardiac myotoxicity is observed in animal models.

Clinical safety evaluations

Troponin serves as the gold standard for the detection of myocardial necrosis in the clinical practice of cardiology. However, what works well in one area of clinical medicine may not be directly transferable to the clinical development of novel pharmacologic agents. For instance, in contrast to the well-characterized prognostic significance of troponin elevation in acute coronary syndromes (ACS), the behavior of serum troponin in normal or nonischemic cardiac disease remains essentially unknown.[16] As troponin assays become more sensitive, the absence of reference data from normal populations leaves open questions regarding the specificity and optimal application of the biomarker's threshold level for identifying drug-induced cardiotoxicity. Similar to preclinical testing, the interpretation of troponin in clinical trials is further complicated by the wide technical variability across troponin assays with different performance characteristics. The development and subsequent analysis of both preclinical and clinical cardiac troponin data repositories could help characterize physiologic variability in serum troponin values, especially as troponin assays become more and more sensitive. For drug development, the use of a centralized reference laboratory with standard assay methodology was generally considered ideal. However, given the logistical challenges associated with such an approach, other designs using standardized troponin assays might also be considered for clinical trials.

In addition to questions about reference levels, the temporal course of troponin elevation outside of ACS in human subjects is poorly understood. As assays become more sensitive, thresholds based on the total area under the curve may prove to be more predictive than a single value at a single time point. To determine whether troponins have a role in routine cardiac safety evaluation, a better understanding of troponin kinetics in both healthy subjects and specific disease states is required before troponin area under the curve may be interpretable as a cardiac safety marker.

Understanding of the pathogenesis underlying drug-induced cardiotoxicity remains limited. Specifically, accurate prediction of cardiotoxicity risk in human subjects based upon preclinical animal modeling remains elusive. This is particularly true for structural forms of cardiotoxicity. There is a need to improve the discrimination, calibration, and validation of preclinical models for the prediction of drug-related cardiac injury in clinical trials. Improvement of existing strategies and development of novel biomarker signatures should be a priority for all stakeholders in the drug-development process. Think-tank participants identified the following areas for focused research:

1. Development and analysis of shared clinical troponin data repositories.
2. Identification and validation of predictive models for the translation of preclinical troponin elevations and subsequent evidence of cardiac toxicity in clinical testing of candidate compounds.

Preclinical and clinical testing for QT proarrhythmia: How do they relate to one another and to risk of life-threatening arrhythmic events?

Long QT-mediated polymorphic ventricular tachycardia, or torsade de pointes, is a sudden and potentially lethal arrhythmia that has drawn attention as a cause for early termination of drug development and post-approval pharmaceutical withdrawal.[17] Cisapride and

terfenadine are two notable examples of drugs which were found to cause torsade de pointes after they were approved and in wide clinical use.[18,19] Unfortunately, the relationship between surrogate measures of action potential and QT interval prolongation and the clinical risk of torsade de pointes is complex and challenging. Generally speaking, agents that prolong the QT interval and cause torsade do so by creating heterogeneous repolarization across the myocardium. Heterogeneous repolarization of the myocardium facilitates the development of dynamic reentrant arrhythmias. However, there are numerous compounds which prolong the QT interval and action potential duration, yet carry an extremely low risk of torsade de pointes. Many of these drugs are used routinely in clinical medicine, including amiodarone, quietapine, and phenobarbital. Most recently, ranolazine, a drug with known QT-prolonging effects, was shown to be associated with a decreased incidence of ventricular arrhythmias after ACS despite significant lengthening of the action potential duration.[20] Currently, the FDA requires both preclinical and clinical evaluation of repolarization changes in the evaluation of most new molecular entities.

Preclinical QT-proarrhythmia testing

The International Conference on Harmonization (ICH) S7B guidelines[21] require preclinical studies to assess the risk of QT prolongation. The risk of QT prolongation is often assessed through in vitro *Human ether-a-go-go-related* gene product (hERG) testing. The hERG channel is responsible for the rapid component of the delayed rectifier potassium current (I_{Kr}) and is almost always the cause for drug-related acquired long QT syndrome. Unfortunately, testing for I_{Kr} inhibition is not sufficient. In addition, in vitro hERG-mediated action potential prolongation may not correlate with clinical risk for QT prolongation or, more specifically, torsade de pointes. Age and gender also play important roles in the risk of proarrhythmia.[22] On the other hand, several experts view preclinical hERG testing favorably. Preclinical hERG assays are especially helpful when there are several congeners available for potential clinical development. In these situations, preclinical hERG assays help by weeding out compounds with significant action potential prolongation. To improve the efficiency and value of QT investigation, better understanding of the relationship between preclinical assays and clinical effects is needed. Finally, more specific and predictive preclinical assays will enable better confidence and thus may obviate the need for clinical testing in specific scenarios.[23] Future work should focus on the following areas of need:

1. Development and validation of assays to assess non–hERG-mediated proarrhythmic potential of drugs.
2. Identification and validation of new surrogate markers for QT-mediated proarrhythmia such as triangulation, reverse use dependence, instability, and dispersion.[24]

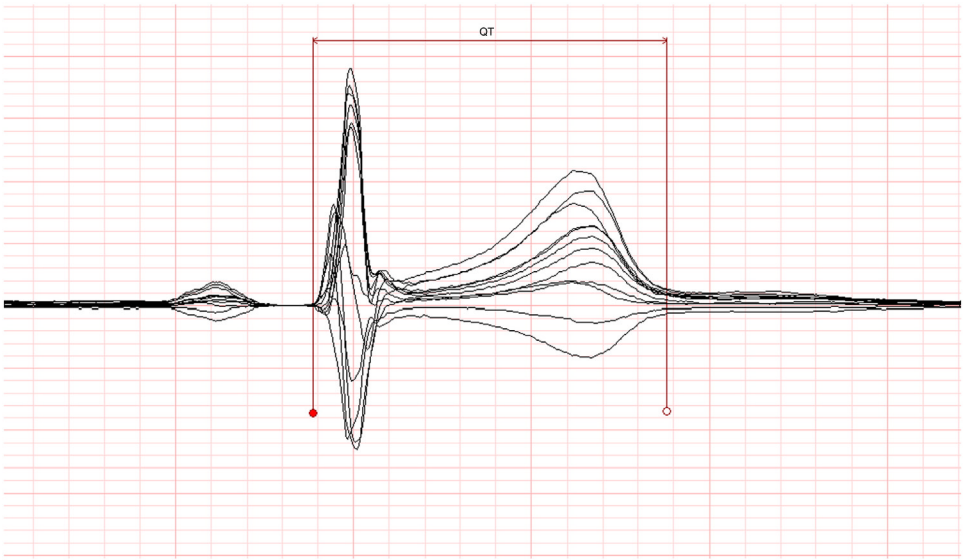
The thorough QT/QTc study

The ICH E14 Guideline codifies and establishes methodology for the thorough QT/QTc study (TQT). E14 recommends that all drugs should be evaluated with a TQT.[25] The goal of the TQT is to detect the degree of QT prolongation attributable to peak serum concentrations of either the active drug or its metabolites. To this end, healthy volunteers are given significant doses of investigational drug and the QT interval is measured using high-fidelity digital electrocardiograph (ECG) recordings (Figure 1). The TQT is generally designed to ensure an "assay sensitivity" of about 5 milliseconds changes in the QTc. To validate the assay sensitivity at such a low level, use of an active control (usually moxifloxacin) is required. Although a well-established regulatory standard, the TQT has several notable limitations, including different QT measurement techniques. Consequently, TQT results vary technically depending upon the methodology and the analytic software used.[26] In addition, although the TQT allows some quantification of cardiac repolarization, simple QTc does not specifically evaluate T-wave morphology or spatial dispersion, each of which has also been shown to correlate strongly with the occurrence of torsade de pointes.[27,28] The main drawbacks of the TQT thus include methodologic variability, limited specificity, and high cost.

At present, the TQT is the cornerstone for the evaluation of QT prolongation as a marker of proarrhythmic safety. The FDA prefers a crossover design with positive and negative controls. The TQT does not work well for drugs dosed to the maximal tolerated dose or for those drugs that are too toxic to administer to normal volunteers (such as most oncology drugs). The TQT could be improved by better consensus on optimal methods for QT correction in the setting of autonomic effects and elevated heart rate.[29] In addition, there is a need for validation of positive controls in different drug classes (eg, neuroleptics), rather than solitary reliance on moxifloxacin. Reliable automated QT analysis and innovative designs might improve assay sensitivity, efficiency, and cost-effectiveness.[30]

Critics of the TQT study emphasize that, despite the sensitivity of the TQT study, its lack of specificity remains a major challenge for risk assessment in new drug development. Verapamil, amiodarone, and ranolazine are all examples of compounds that prolong the QT but have almost no actual clinical proarrhythmic risk. Some experts argue that, although the TQT is a helpful predictive tool, the true test of a drug's proarrhythmic risk is extensive and careful postmarketing surveillance. A "negative" TQT does not guarantee drug safety. Similarly, a "positive" TQT does not mean a drug will cause proarrhythmia in the clinical setting. Although the TQT should remain a part of

Figure 1



Electrocardiogram QT overlay. During TQT study, the QT interval is measured using high-fidelity digital ECG recordings. Thorough QT/QTc studies exhibit heterogeneity owing to varying methods of determining the end of the T wave.

drug safety evaluation, there are several areas where further research and clarification are needed. Short-term goals for the improvement of proarrhythmia risk assessment include:

1. Using the CSRC ECG data warehouse or other public domain large ECG databases that include positive controls and evaluate the performance characteristics of assays for alternative biomarkers, including those for T-wave alternans, T-wave volumetric analysis, and T-wave vectorcardiography.
2. Developing a consensus definition for measurement of the end of the T wave. Until there is a consensus definition, continued heterogeneity will persist in QT quantification.

Preclinical and clinical evaluation of non-QT proarrhythmia

QT prolongation is not the only mechanism by which drugs can cause proarrhythmia. Several notable examples of non–QT-mediated proarrhythmia include ventricular tachycardia precipitated by Vaughan-Williams class Ic agents (eg, flecainide toxicity), methylxanthine-induced atrial fibrillation, sinus node dysfunction after β-blocker therapy, and the multiple triggered arrhythmias which can be seen in the setting of digitalis toxicity.[5,31,32] The mechanisms surrounding non-QT proarrhythmia are diverse and complex. Thorough investigation and evaluation of potential non-QT proarrhythmia require in vitro and in vivo models, in addition to thorough clinical study. However, assays for non-QT proarrhythmia are not sufficiently developed or validated for most clinical development and regulatory decisions. For example, the degree to which QRS prolongation is associated with a specific risk of ventricular proarrhythmia, or the degree to which PR prolongation will lead to atrioventricular block, is not well defined. To make preclinical evaluation more efficient, the data need to be robust with clearly interpretable findings. This is a continuing challenge, as the relationships between non-QT pharmacodynamics and risk thresholds are poorly defined.

Some experts advocate the development of a "thorough electrocardiographic study," designed to capture small degrees of change in any electrocardiographic parameter, including the PR interval, QRS duration, and wavelet morphology. However, such "thorough ECG" studies were generally considered premature for widespread use, as their results will be difficult to interpret until definitive relationships between electrocardiographic findings and clinical outcomes can be established.

Strong interest was also voiced for an accurate pharmacodynamic marker for drugs that increase the susceptibility to atrial fibrillation. Given the increasing prevalence of atrial fibrillation, a reliable marker of atrial fibrillation proarrhythmia was recognized as a critical need for future drug development.

In summary, although preclinical models may be useful to characterize broader aspects of a given drug's electrophysiologic profile, the translation of such

characterizations into human proarrhythmic risk is still poorly defined. An additional consideration in the complexities of translation from preclinical to clinical evaluation of proarrhythmia is the interaction between drug and substrate, for example, complexities related to patient diversity. It is now well appreciated that many cases of proarrhythmia are due to otherwise silent gene mutations and diminished repolarization reserve.[33,34] Variability in autonomic tone or other "brain-heart" connections may not be well reproduced in animal models.

An important step forward in drug development and drug safety will be the identification of those individuals who might be more susceptible to the proarrhythmic effects of a compound.[35] For example, it is likely that there are subsets of patients who can take cisapride safely without risk of torsade de pointes. Just as likely is the possibility that some patients can safely take flecainide or other antiarrhythmic drugs in the presence of structural heart disease, whereas, for others, such pharmacotherapy may have life-threatening consequences.

1. Future collaborative efforts should define pharmacogenomic risk factors for proarrhythmia to tailor cardiac safety to individual patients.
2. There is a pressing need for pharmacodynamic markers for drugs that increase the risk of atrial fibrillation.
3. Development of consensus surveillance algorithms for the identification of atrial fibrillation as an adverse event in clinical trials and postmarketing surveillance.

Biologics and large molecules: how to evaluate proarrhythmia and myotoxicity when a thorough QT study cannot be performed

Because of the size of most biologics, such as antibodies or other large molecule therapeutics (usually >140,000 d), cardiotoxicity resulting from direct hERG channel blockade is generally not a concern.[23] As a result, their off-target electrophysiologic liabilities are limited and there is low risk for QT-mediated proarrhythmia. Known exceptions include scorpion toxin, which can bind the outer pore of the hERG channel, and oxytocin, which has been reported to prolong the QTc.[36,37] Although access to the intracellular pore is not likely for large molecules, there remain means for affecting the potassium current by interference with gene expression or the insertion of the protein into the membrane ion channel.[38] Overall, the risk of QT prolongation is sufficiently low that a standard ICH E14–type TQT study is not necessary in the development and evaluation of monoclonal antibodies, and a similar rationale can be raised for other large molecules.[39] Biologics are not specifically mentioned or explicitly excluded in ICH E14 recommendations. Some authorities have called for the development of better preclinical assays with high negative predictive value. In cases where preclinical models demonstrate action potential prolongation, formal clinical testing with a TQT could be required. However, in large molecules, the relationship between peak serum concentration and nonsteric QT effects is not straightforward. For example, decreased I_{to} expression is only observed after 24 to 48 hours of exposure to recombinant TNF-α.[40]

A review of >170 protein therapeutics approved in the US highlights that no biologics have been withdrawn from the market because of proarrhythmia. Biologics are fairly specific in their pharmacologic action.[41] Taken together, the available evidence suggests that the risk for QT-mediated proarrhythmia is low and that the cardiac safety evaluation of large molecules or biologics should focus on the potential for myocardial toxicity or impaired contractility.[23] The case of trastuzumab, a recombinant antibody used in adjuvant treatment of advanced breast cancer, is illustrative of this point. Trastuzumab-mediated ErbB2 blockade causes cardiomyotoxicity that can lead to potentially reversible LV dysfunction.[42]

In some instances, more extensive evaluation of biologics and large molecules may be required. These instances might include identification of class effects, secondary effects that might target the myocardium, and "bystander" toxicity due to the underlying disease state (eg, sarcoidosis). There is no regulatory guidance to monitor cardiotoxicity in clinical trials of large molecules and biologics; however, moving forward, there is a great need for consensus, especially with respect to:

1. Appropriate surveillance for myotoxicity and impaired contractility.
2. Development of alternative QT assays for use in safety evaluation of large molecules and biologics.

Do we need "thorough" blood pressure, heart rate, platelet, and lipid studies?

Preclinical safety evaluations are heavily influenced by the ICH S7B guidelines.[21] Despite the fact that most preclinical evaluations go beyond the S7B guidelines, some aspects of preclinical cardiovascular risk assessment could be improved to provide a more inclusive evaluation of overall cardiac function.

Preclinical cardiovascular safety assessment generally includes a defined cardiovascular safety study performed before the onset of clinical testing. These studies include an evaluation of blood pressure, heart rate, and simple telemetry in nonrestrained animals receiving single doses of varying concentration of an experimental drug. In addition, a minimal ECG evaluation is often done in restrained animals at the conclusion of dosing in repeat-dose nonrodent studies. The sensitivity for telemetered

models to detect acute drug-induced changes in cardiac function is considered good and readily translates to human patients.[43] Alternatively, the ECG evaluation in restrained animals is predominately used to assess changes in heart rate and prominent changes in the ECG. Consequently, the functional evaluation in repeat-dose studies is relatively insensitive and, importantly, lacks assessment of blood pressure.

Serum lipids and platelet counts are routinely performed in repeat-dose, rodent, and nonrodent studies of varying length. Although changes in total lipids may have clinical relevance, it is important to remember that lipoprotein profiles in some laboratory animal species vary significantly from human patients. Notably, rodents are considered HDL-predominant species in contrast to the LDL predominance of nonhuman primates and human patients. Also, laboratory animals are generally not susceptible to atherosclerosis—a significant cardiovascular risk factor in target patient populations. In addition to platelet quantitation, repeat dose studies in rodents and nonrodents frequently include assessment of coagulation. The totality of these assessments is likely a better reflection of prothrombotic risk than platelet quantification alone. The addition of more functional evaluations, including an assessment of blood pressure as well as identification and application of more predictive animal models for structural cardiotoxicity, would be a positive step toward improved preclinical evaluation.

Clinical evaluations of cardiovascular safety tend to focus on acute drug effects. Increased analysis and scrutiny of chronic drug effects would similarly improve clinical evaluations. Ambulatory blood pressure monitoring provides a tool with great potential value. Not only does ambulatory blood pressure monitoring provide a better quantification of blood pressure effects, but it can also provide important qualitative information. For example, loss of the nocturnal dip has been associated with adverse outcomes, such as in the case of cyclosporine.[44,45] However, with better quantification of chronic drug-related blood pressure effects, new questions emerge, such as redefining what constitutes boundaries for unacceptable blood pressure elevation. Increases as little as 2 to 3 mm Hg have been associated with increased mortality; however, the magnitude of blood pressure elevation would have to be considered in the light of the overall benefit of a drug intended for chronic administration. For example, moderate blood pressure elevation is tolerated in the case of immunosuppressive agents (such as cyclosporine) that are essential for organ transplantation. Future advances in cardiac safety evaluation have several areas of need to be addressed:

1. Should "thorough" ambulatory blood pressure studies use a positive control? If so, what agents would be permissible in a young healthy phase I volunteer population?
2. Routine evaluation of cardiovascular risk for both patients (eg, Framingham risk score) and new drugs (eg, an as yet to be developed cardiovascular clinical risk score, based on changes in blood pressure, platelet reactivity, and lipid biology) would be of great value in future preclinical and clinical investigation.

Risks and benefits of developing drugs with safety signals

The Critical Path Initiative highlighted the decline of new drugs entering clinical practice in the face of escalating costs and enormous commitment of resources by the pharmaceutical industry.[12] In light of this investment-return mismatch, some attention has been focused on whether or not the development of some new drugs may have been terminated prematurely owing to preclinical safety signals before they had a chance to be fully evaluated for clinical relevance. Unfortunately, there is a paucity of published data on the subsequent evaluation and development of drugs with suboptimal early risk-benefit profiles.

Decisions to continue the development of compounds with potential safety signals are a function of both scientific and financial considerations. These decisions are unique to each compound and the specific safety concern. There are many challenges in this area, including the translation of biologic safety signals from preclinical animal models to human subjects. No doubt there are differences between animals and human patients, but a significant part of what we know about human biology and pathobiology comes from animal studies. Within the context of the level of unmet medical need and market size addressed by a new compound, cardiac safety factors that influence the fate of a compound include preclinical safety data, the predictive value of the preclinical model, the strength or magnitude of the safety signal, relative promise of the compound compared to others in the organization's pipeline, competitor molecules already in the marketplace, and willingness to absorb possible failures.

As part of reducing the number of potentially viable drugs that may be inappropriately abandoned during development, a number of participants called for further discussion and consensus around the characterization of potential preclinical cardiac safety signals. At the present time, there is a great deal of variability within and across industry, academia, and government regarding the measurement and definition of cardiotoxicity (both preclinically and clinically) and how such toxicity is calculated into developmental risk assessments is also highly variable. Specifically, a multiagency consensus should be reached on:

1. Which clinical risks require routine, formal assessment, and what degree of deviation from normal in clinical evaluation should be considered "significant"?

2. What are the most relevant preclinical models to predict either short- or long-term cardiovascular liabilities in patients and which end points should be used to evaluate these risks?

Examples of challenging cardiovascular safety signals include a 15-millisecond prolongation of the QTc, second-degree type I atrioventricular conduction block, nonsustained ventricular tachycardia, vascular injury, and platelet dysfunction. Complicating the picture is the strong emotional response many of these findings elicit, especially from noncardiovascular specialists. Continued drug evaluation after an adverse signal has been observed should focus on the potential impact on individual patient safety. To answer this question, human data are necessary. Therefore, special consideration must be given to how the safety concern will be handled in first-in-human protocols and subsequent trial design. This is where a robust, sensitive, and relevant biomarker strategy can serve a vital role in the transition from preclinical to clinical risk assessment.

Finally, investigators need to examine carefully the risk-benefit ratio, to ensure that further commitment of resources is justified. Part of examining the risk-benefit ratio will, of course, direct the focus back on the individual patient. Can the toxicity be predicted based upon clinical characteristics or a genetic or other laboratory assay? What is the mortality risk of the condition being treated relative to the mortality risk of the drug in question? Ultimately, final answers will only be achieved in large, phase III trials or extensive postmarketing surveillance. The recent example of blood pressure elevation observed with torcetrapib or the excessive risk of rhabdomyolysis observed with cerivastatin highlights these points.[46,47] All stakeholders need to remember that many landmark, paradigm changing medications, including propranolol (heart block), captopril (agranulocytosis), and amiodarone, had significant cardiac safety concerns surfacing during their development.[48-50] In addition, many drugs with preclinical signals of cardiotoxicity have not demonstrated pathologic cardiac effects in clinical practice. Informed study design and interpretation of available data, paired with vigilance, are what is ultimately required to bring these challenging, yet promising, drugs to the bedside.

Future directions

The current paradigm for evaluating clinical safety begins with preclinical animal modeling and progresses to clinical biomarker assays. "Thorough" studies of high-leverage surrogate markers for important clinical outcomes (such as blood pressure) and targeted, specific clinical biomarkers with a proven correlation with end-organ toxicity are needed. Just as the relationship between structure and receptor affinity is important in medicinal chemistry, the relationship between preclinical biosignatures, clinical risk assessment, and long-term outcomes is crucial in the evaluation of cardiovascular drug safety.

One goal of the Critical Path Initiative is to improve both the quality and the efficiency of drug safety evaluation. Thus the evaluative improvements being sought must, by definition, lead to refined efficiency and cost savings, since their ultimate success will be judged by how well they lead to safe, cost-effective, and timely drug delivery. Concrete steps to improve the infrastructure and processes of drug development are needed. However, more information will not necessarily lead to better information. Common, shared data repositories that are available for analysis by a range of expert stakeholders are needed to enable novel techniques in the identification and interpretation of biosignatures. The ability to evaluate aggregated data and common experiences is critical to avoid repeated mistakes and to benefit from the collective knowledge that has been generated across the field. Concomitantly, efforts to develop consensus definitions, techniques, and standards for cardiac safety evaluation are widely seen as the most likely next steps toward better drug development in the future.

Preclinical evaluations have clear limitations but provide an irreplaceable opportunity to identify safety hazards before administration of potential new drugs to human subjects. Similarly, more thorough and efficient early clinical studies will enable better estimates of cardiovascular safety and better inform phase II and phase III trial design. Ultimately, these innovations should serve as a common goal, which will benefit all parties, vis-à-vis safer drugs and accelerated public health benefits.

Consensus goals

1. Identify, develop, and validate specific clinical biomarkers indicative of early drug-induced myocardial toxicity.
2. Build consensus regarding the use and interpretation of troponin assays in preclinical evaluation of myocardial toxicity.
3. Encourage and promote preclinical data repositories to enable data sharing and foster collaborative interpretation and analysis of relevant end points for cardiac safety assessment.
4. Identify better qualitative and quantitative biomarkers for arrhythmogenicity.
5. Streamline the thorough QT study and develop a consensus definition of the end of the T wave.
6. Use the CSRC ECG warehouse or other similar public domain data repositories to develop more sensitive and specific diagnostic alternatives to the thorough QT and ECG-related safety assessment.
7. Establish formal guidelines for data standards and transparency in postmarketing surveillance.

Disclosures

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References

1. Fung M, Thorton A, Mybeck K, et al. Evaluation of the characteristics of safety withdrawal of prescription drugs from worldwide pharmaceuticals markets — 1960 to 1999. Drug Inf J 2001;35: 293-317.
2. Stephens M. Introduction. In: Talbot J, Waller P, editors. Stephens' Detection of New Adverse Drug Reactions. 5th ed. Maiden (MA): John Wiley and Sons, Ltd.; 2004. p. 1-91.
3. Astemizole: voluntary withdrawal: Janssen, USA. WHO Pharmaceuticals Newsletter; 1999 (07 and 08).
4. Henney JE. Withdrawal of troglitazone and cisapride. JAMA 2000; 283:2228.
5. The 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;321:406-12.
6. Packer M, Rouleau J, Swedberg K, et al. Effect of flosequinan on survival in chronic heart failure: preliminary results of the PROFILE trial. Circulation 1993;88(Suppl I):I-301.
7. Owens ÂJ, Robert ÂC, Ambrose Paul ÂG. Antimicrobial safety: focus on fluoroquinolones. Clin Infect Dis 2005;41:S144-57.
8. Garber AM. An uncertain future for cardiovascular drug development? N Engl J Med 2009;360:1169-71.
9. Sun SX, Lee KY, Bertram CT, et al. Withdrawal of COX-2 selective inhibitors rofecoxib and valdecoxib: impact on NSAID and gastroprotective drug prescribing and utilization. Curr Med Res Opin 2007;23:1859-66.
10. FDA announces plan to halt marketing of terfenadine. Am J Health Syst Pharm 1997;54:342-.
11. Shah R. Withdrawal of terodiline: a tale of two toxicities. In: Mann R, Andrews E, editors. Pharmacovigilance. London: John Wiley and Sons, Ltd.; 2002.
12. Pitts PJ. FDA and the critical path to twenty-first-century medicine. J Med Philos 2008;33:515-23.
13. O'Brien PJ, Dameron GW, Beck ML, et al. Cardiac troponin T is a sensitive, specific biomarker of cardiac injury in laboratory animals. Lab Anim Sci 1997;47:486-95.
14. O'Brien PJ. Cardiac troponin is the most effective translational safety biomarker for myocardial injury in cardiotoxicity. Toxicology 2008; 245:206-18.
15. Apple FS, Murakami MM, Ler R, et al. Analytical characteristics of commercial cardiac troponin I and T immunoassays in serum from rats, dogs, and monkeys with induced acute myocardial injury. Clin Chem 2008;54:1982-9.
16. Jaffe A. Elevations in cardiac troponin measurements: false false-positives. Cardiovasc Toxicol 2001;1:87-92.
17. Roden DM. Drug-induced prolongation of the QT interval. N Engl J Med 2004;350:1013-22.
18. Drolet B, Khalifa M, Daleau P, et al. Block of the rapid component of the delayed rectifier potassium current by the prokinetic agent cisapride underlies drug-related lengthening of the QT interval. Circulation 1998;97:204-10.
19. Monahan BP, Ferguson CL, Killeavy ES, et al. Torsades de pointes occurring in association with terfenadine use. JAMA 1990;264: 2788-90.
20. Scirica BM, Morrow DA, Hod H, et al. Effect of ranolazine, an antianginal agent with novel electrophysiological properties, on the incidence of arrhythmias in patients with non ST-segment elevation acute coronary syndrome: results from the Metabolic Efficiency With Ranolazine for Less Ischemia in Non ST-Elevation Acute Coronary Syndrome Thrombolysis in Myocardial Infarction 36 (MERLIN-TIMI 36) Randomized Controlled Trial. Circulation 2007;116:1647-52.
21. Cavero I, Crumb W. ICH S7B draft guideline on the non-clinical strategy for testing delayed cardiac repolarisation risk of drugs: a critical analysis. Ex Opin Drug Saf 2005;4:509-30.
22. Lehmann MH, Hardy S, Archibald D, et al. Sex difference in risk of torsade de pointes with D,L-sotalol. Circulation 1996;94:2535-41.
23. Vargas HM, Bass AS, Breidenbach A, et al. Scientific review and recommendations on preclinical cardiovascular safety evaluation of biologics. J Pharmacol Toxicol Methods 2008;58: 72-6.
24. Shah RR, Hondeghem LM. Refining detection of drug-induced proarrhythmia: QT interval and TRIaD. Heart Rhythm 2005;2:758-72.
25. Food and Drug Administration, HHS. International conference on harmonisation; guidance on E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs; availability. Notice. Fed Regist 2005;70: 61134-5.
26. Kligfield P, Hancock EW, Helfenbein ED, et al. Relation of QT interval measurements to evolving automated algorithms from different manufacturers of electrocardiographs. Am J Cardiol 2006;98:88-92.
27. Couderc JP, McNitt S, Hyrien O, et al. Improving the detection of subtle *I*(Kr)-inhibition: assessing electrocardiographic abnormalities of repolarization induced by moxifloxacin. Drug Saf 2008;31:249-60.
28. Couderc J-P, Zhou M, Sarapa N, et al. Investigating the effect of sotalol on the repolarization intervals in healthy young individuals. J Electrocardiol [in press], Corrected proof.
29. Malik M. Problems of heart rate correction in assessment of drug-induced QT interval prolongation. J Cardiovasc Electrophysiol 2001; 12:411-20.
30. Marek M, Hnatkova K, Batchvarov V, et al. Sample size, power calculations, and their implications for the cost of thorough studies of drug induced QT interval prolongation. Pacing Clin Electrophysiol 2004;27:1659-69.
31. Piccini J, Zaas A. Cases from the Osler Medical Service at Johns Hopkins University. Am J Med 2003;115:70-1.
32. Varriale P, Ramaprasad S. Aminophylline induced atrial fibrillation. Pacing Clin Electrophysiol 1993;16:1953-5.
33. Lehtonen A, Fodstad H, Laitinen-Forsblom P, et al. Further evidence of inherited long QT syndrome gene mutations in antiarrhythmic drug-associated torsades de pointes. Heart Rhythm 2007;4:603-7.
34. Yang P, Kanki H, Drolet B, et al. Allelic variants in long-QT disease genes in patients with drug-associated torsades de pointes. Circulation 2002;105:1943-8.
35. Lord PG, Papoian T. Genomics and drug toxicity. Science 2004;306: 575.

36. Hill AP, Sunde M, Campbell TJ, et al. Mechanism of block of the hERG K^+ channel by the scorpion toxin CnErg1. Biophys J 2007;92: 3915-29.
37. Charbit B, Funck-Brentano C, Samain E, et al. QT interval prolongation after oxytocin bolus during surgical induced abortion. Clin Pharmacol Ther 2004;76:359-64.
38. Cordes JS, Sun Z, Lloyd DB, et al. Pentamidine reduces hERG expression to prolong the QT interval. Br J Pharmacol 2005;145:15-23.
39. Mascelli MA, Zhou H, Sweet R, et al. Molecular, biologic, and pharmacokinetic properties of monoclonal antibodies: impact of these parameters on early clinical development. J Clin Pharmacol 2007;47: 553-65.
40. Fernández-Velasco M, Ruiz-Hurtado G, Hurtado O, et al. TNF-alpha downregulates transient outward potassium current in rat ventricular myocytes through iNOS overexpression and oxidant species generation. Am J Physiol Heart Circ Physiol 2007;293:H238-45.
41. Giezen TJ, Mantel-Teeuwisse AK, Straus SM, et al. Safety-related regulatory actions for biologicals approved in the United States and the European Union. JAMA 2008;300:1887-96.
42. Grazette LP, Boecker W, Matsui T, et al. Inhibition of ErbB2 causes mitochondrial dysfunction in cardiomyocytes: implications for herceptin-induced cardiomyopathy. J Am Coll Cardiol 2004;44: 2231-8.
43. Lynch III JJ, Wilson AW, Hernandez LE, et al. Dose response effects of sotalol on cardiovascular function in conscious, freely moving cynomolgus monkeys. Br J Pharmacol 2008;154: 1439-45.
44. Haydar AA, Covic A, Jayawardene S, et al. Insights from ambulatory blood pressure monitoring: diagnosis of hypertension and diurnal blood pressure in renal transplant recipients. Transplantation 2004; 77:849-53.
45. Toprak A, Koc M, Tezcan H, et al. Night-time blood pressure load is associated with higher left ventricular mass index in renal transplant recipients. J Hum Hypertens 2003;17:239-44.
46. Barter PJ, Caulfield M, Eriksson M, et al. Effects of torcetrapib in patients at high risk for coronary events. N Engl J Med 2007;357:2109-22.
47. Ahmad SR. Adverse drug event monitoring at the Food and Drug Administration. J Gen Intern Med 2003;18:57-60.
48. Kalantzis N, Gabriel P, Mouzas J, et al. Acute amiodarone-induced hepatitis. Hepatogastroenterology 1991;38:71-4.
49. Kantelip JP, Duchene-Marullaz P, Delaigue-Fabry R, et al. Comparison of the effects of propranolol, pindolol, oxprenolol and acebutolol on atrioventricular conduction in unanaesthetized dogs. Br J Clin Pharmacol 1982;13(Suppl 2):159S-66S.
50. Weber MA. Safety issues during antihypertensive treatment with angiotensin converting enzyme inhibitors. Am J Med 1988;84:16-23.