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Viewpoint

Replacing the thorough QT study: reflections of a baby in the bath water

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Current paradigm for assessing QT liability: evolution of a dilemma

Since its implementation in 2005, the E14 guidance 'Clinical Evaluation of QT/QT_c Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs' [1] promulgated by the International Conference on Harmonization (ICH) has elicited considerable dissatisfaction from many stakeholders at all levels.

The ICH E14 guideline sets out our current paradigm for regulatory assessment of potential pro-arrhythmic risk of drugs during their clinical development. It evolved from two earlier regulatory strategies, one from the European Medicines Agency (EMA) in 1997 [2] and the other (in a draft form) from Health Canada in 2001 [3], neither of which mandated a specific clinical trial dedicated to evaluating a drug effect on QT interval. The E14 guidance went much further and described a new type of clinical trial, which has come to be known as the 'Thorough QT Trial' (TQT), but more accurately described as the 'Thorough ECG Trial' (TET) since the trial evaluates parameters other than just the QT interval on the surface electrocardiogram (ECG). The TET is an unusual trial. It fits very awkwardly into our usual schema of drug development as it is in effect a phase I type trial that is usually performed well after other phase I trials have been completed, and sometimes as late as phase III or not infrequently, as part of a post-marketing commitment.

Before considering whether TET has proved to be an effective tool for early detection of an important safety signal during drug development, it is helpful to retrace the events that led to the ICH E14 guidance, and the birth of the TET. There are a number of reviews which already address this issue [4–6], but a brief summary is still in order. In essence, the TET was the ultimate outcome of proliferation during the 1980s and 1990s of drugs which were unexpectedly associated with sudden deaths during their post-marketing use. Most of these drugs were medications intended for relatively benign non-cardiac indications and were therefore removed from the market. Research quickly established that these episodes of sudden death were precipitated by an unusual form of ventricular tachycardia known as torsade de pointes (TdP), an arrhythmia that is typically preceded by prolongation of the QT interval as measured on the ECG. It was also soon determined that QT interval prolongation and TdP resulted from the ability of these drugs to block or inhibit the IKr channel, which is primarily responsible for conducting the major fraction of ventricular repolarizing outward current. Drug-induced QT prolongation is a pharmacological effect which one can readily measure by carefully recording and assessing ECGs. Not surprisingly, evidence of drug-induced QT prolongation came to be recognized as a valuable biomarker by which to identify new drugs that might be torsadogenic, leading to the use of QT interval in the TET as the key surrogate marker for identifying drugs with heightened clinical risk for TdP.

An appraisal of the current paradigm

Since its adoption in 2005 by the US Food and Drug Administration (FDA), EMA and Health Canada (Japan followed much later), the TET-based strategy outlined in ICH E14 (as well as the corresponding preclinical strategy recommended in the ICH S7B guideline [7]) has become the standard for investigating new chemical entities for their propensity to induce QT interval prolongation, and by inference TdP. Well over 250 such studies have been conducted to date [6]. The ICH E14 strategy, as it has developed over the past 8 years, has identified a number of drugs with clinically relevant QT-prolonging effect before their approval. A review of 163 TET studies, conducted in

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compliance with ICH E14 during 2005–2012, revealed 33 (20%) of them to be positive [8]. Many of these drugs have been approved, albeit some with very restricted labelling and even black box warnings, with instructions for prescribing physicians concerning appropriate patient selection and appropriate patient monitoring when utilizing these medications [1, 8–11].

It is perhaps too early to determine whether the E14 strategy constitutes a success in terms of reducing the clinical risk that really matters, the induction of TdP. This uncertainty is a natural corollary of the limitation of QT prolongation as an effective surrogate of the clinical risk of TdP. QT prolongation in and of itself has no adverse clinical consequences. Indeed, when adequately controlled, it may even be anti-arrhythmic and, therefore, beneficial. It is simply a surface manifestation of the underlying complex mechanisms which may ultimately lead to TdP. However, the relationship between prolongation of QT and induction of TdP is modulated by a wide variety of factors, both intrinsic (related to the drug itself) [12] and extrinsic (related to the patient) [13]. Not surprisingly, there are drugs which significantly lengthen the QT interval, but which do not induce TdP [14]. An example is ranolazine which blocks the IKr channel and therefore lengthens the QT interval [15], but which has not been reported to induce TdP. Ranolazine also blocks the late sodium current [16], and it is believed that this mitigates the proarrhythmic consequences of a prolonged QT interval that results from IKr channel blockade. Thus, while all drugs which induce TdP lengthen the QT interval, not all drugs which lengthen the QT interval induce TdP [17].

Criticisms of the current paradigm

In view of the foregoing, it is not surprising that since the release of the ICH E14 guidance, the TET has been the target of criticism.

First and the foremost is the concern that the ICH E14 guidance and the TET have made pharmaceutical companies and regulators too fixated on QT prolongation, a fixation which has led pharmaceutical companies to abandon the development of many drugs which block IKr only modestly during preclinical studies or which have demonstrated only a small increase in QT interval in early clinical trials [9, 18]. Medicinal chemists have also been busy designing candidate molecules which lack the off-target drug interaction with the hERG (human ether-a-go-go gene) channel, which is the alpha subunit of the IKr channel [18, 19] while, at the same time, attempting to find molecules with increasing efficacy through improved target specificity and selectivity. These two aims may often be mutually exclusive. Thus many new drugs are abandoned early in preclinical or phase I testing and do not reach phase III clinical trials. These drugs have never had the opportunity to demonstrate what might have been their clinically desirable effectiveness. Some of the drugs whose development has been halted early on due to QT concerns may have been breakthrough medications that are truly needed. Simply put, not enough right drugs, or perhaps some wrong drugs, are reaching the end of phase II and are undergoing a TET.

Furthermore, in view of binary outcome from the Intersection Union Test as recommended in ICH E14, the TET has come to be viewed as having 'pass or fail' categorization. It is common to hear of the fears generated by a drug's 'positive TET' and of serious questions being raised by the sponsor as to the viability or wisdom of continuing the development of the compound. However, we have only limited understanding of the relationship between the magnitude of a drug's QT_c effect and the actual clinical risk of TdP, and hardly any data on the reproducibility of the results of a TET. At the very outset, it was recognized by the E14 drafting group that a QT effect of 5–10 ms, as detected by a TET, was generally not a sign of the drug being potentially proarrhythmic. Instead, a breach of this threshold was intended to trigger further detailed scrutiny of its ECG effects during phase III trials, when the drug would be administered to larger group of patients with a range of co-morbidities and in receipt of co-medications [1]. Thus, the TET was presumed to provide a precise assessment of a drug's effect on the QT interval, which would then guide the ECG monitoring strategy during phase III clinical trials and after approval for marketing.

Another concern, which is not a trivial one for many small to medium sized companies, is the cost of running a TET, which typically is in the neighbourhood of 2–3 million dollars. Thus, this expensive trial is performed when all other healthy volunteer trials have been completed, and it yields only ECG safety data (in healthy volunteers). A TET may cost more than many of the other phase I trials combined and is typically conducted towards the end of phase II, when the tolerability, pharmacokinetics and the therapeutic dose for clinical use have been defined, a point at which the total expenditure on a new drug is still relatively modest compared with that of phase III trials. There are pharmacoeconomic simulations which suggest that a TET is not cost-effective in terms of the (clinical) return it produces [20]. Thus, from the point of view of a pharmaceutical company, a TET is expensive and a very inefficient use of scarce resources.

Proposals to replace the TET study

In response to the above well-argued concerns and dissatisfaction with TET, two broad strategies have recently been proposed for replacing it. The first proposal is to replace the TET by incorporating robust ECG monitoring during phase I single and multiple ascending dose (SAD/

MAD) studies whereas the second proposal is to replace the TET with a series of more extensive preclinical *in vitro* studies and computer modelling of the results from these studies.

Replacing a TET with an ECG-oriented SAD/MAD study would simply 'bolt on' additional intense ECG collection to the already pre-planned studies [21, 22]. Intuitively, this strategy ought to be much less expensive than performing a TET. These SAD/MAD studies offer an otherwise unparalleled opportunity to study the concentration–effect relationship for QT changes at a wide range of dosages. It is now widely acknowledged that understanding of the concentration–QT effect relationship provides a more effective approach to managing the risk (and risk/benefit) than the Intersection Union Test recommended by ICH E14 [22, 23].

Currently, most drug development programmes include hERG channel assays performed in heterologous expression systems or human derived myocytes and an *in vivo* study, typically in dogs. Purkinje fibre studies or papillary muscle assays and perfused wedge preparation studies are also performed [24]. The second proposal for replacing the TET, initiated by the FDA among others and referred to as the Comprehensive *In vitro* Pro-arrhythmia Assay (CIPA), calls for the use of *in vitro* ion channel studies followed by computer modelling of their results to predict a new drug's pro-arrhythmic potential. This proposal is based on mechanistic understanding of ventricular arrhythmias gained through investigations on over-expressed human cardiac ion channels, computer models of ventricular myocyte electrophysiology and isolated induced pluripotent stem cell-derived cardiomyocytes. The multiple ionic currents that influence the human ECG potentially include ICaL, IKr, IKs, IK1, INa(fast), and INa(late). *In silico* modelling, focusing on the propensity to manifest early after-depolarizations and increased proclivity of depolarization during phase 3 of repolarization, along with a complementary cell-based arm of CIPA, was proposed as a means to integrate the *in vitro* data into a prediction relevant to drug effects on human ventricular myocytes. There is a large literature-based dataset on the sensitivity and specificity of preclinical testing [25]. It is evident that depending on test conditions, the predictability of these tests can vary substantially. We have computed that in broad terms, sensitivity and specificity, respectively, average 50% and 85% for hERG studies, 30% and 93% for action potential duration (APD) studies and 68% and 85% for *in vivo* studies evaluating QT interval prolongation as the endpoint. For torsadogenesis as the endpoint, sensitivity and specificity, respectively, average 95% and 84% for hERG studies, 65% and 91% for APD studies and 100% and 100% for *in vivo* studies. In view of this, the bold CIPA proposal is somewhat surprising since hitherto, the ICH S7B guidance advocating essentially the same preclinical investigations of QT liability as CIPA has not received the recognition it should have.

Concerns with replacing the TET with an ECG-oriented SAD/MAD study

Concerns have been expressed that typical phase I studies have too few subjects receiving placebo, and that phase I studies generally do not employ a positive control with a known effect on QT interval in order to establish assay sensitivity. These concerns, however, can be readily overcome by relatively minor enhancement of the protocols [21]. The International Consortium for Innovation and Quality in Pharmaceutical Development (IQ) is a technically-focused organization of pharmaceutical and biotechnology companies with a mission of advancing science-based and scientifically-driven standards and regulations for pharmaceutical and biotechnology products worldwide. The IQ QT_c Working Group aims to explore innovative approaches to evaluating QT_c liability and risk assessment in early clinical drug development [26]. In collaboration with the Interdisciplinary QT Review Team of the FDA and the Cardiac Safety Research Consortium (CSRC), the IQ QT_c Working Group is developing a protocol for a phase I clinical research study designed to mimic the standard SAD/MAD studies in early clinical development that would test the positive and negative predictability of the concentration–QT_c response modelling in phase I for the outcome of the TET study. The study will include multiple currently marketed drugs from the FDA database of agents that have had a positive TET study. A protocol synopsis and approach to statistical analysis are reported to be nearly final. The protocol synopsis and statistical analysis approach will be agreed with the FDA and the study is expected to begin in the first half of 2014 [26]. However, since there is no information on how accurate and reproducible is the result of a TET study, there will inevitably be a question as to which result should be considered more reliable and accurate in the event that the estimates from the TET and the SAD/MAD studies differ. Reproducibility of a drug effect in a TET can be inferred from the reproducibility of the mean effect of a single oral dose of 400 mg moxifloxacin, so widely included as a positive control in TET studies. It has ranged from 7.7 ms to 15.8 ms across 13 crossover studies and from 9.7 ms to 16.7 ms across six parallel design studies, most conducted during 2004–2007 [27].

Concerns with replacing the TET with *in vitro* ion channel studies

The CIPA proposal and some of the specific details were discussed in July 2013 at a meeting sponsored by the FDA, CSRC and the Health and Environmental Sciences Institute (HESI) [28]. It did not attract unanimity and its acceptance was conditional, subject to the data package recommended and the novelty of the technologies involved [28].

Tentatively, July 2015 has been proposed by the FDA as a deadline for having a working preclinical assay in place [28]. Although this proposal has clear support from within the FDA, the position of other ICH member authorities is at present unclear. Unless all the regulatory authorities and the sponsors are in agreement, any lack of unanimity is likely to present a major dilemma, especially to the sponsors, since it undermines the fundamental spirit of the harmonization that underpins the ICH process. Sponsors may well find themselves having to meet divergent regulatory requirements, ICH E14-compliant TET studies for one region and the new preclinical package for another!

Philosophical and scientific bases of the two proposals

The philosophical and the scientific bases that underpin these two proposals for replacing the TET are quite different.

The strategy for replacing the TET with more intense phase I ECG testing would, admittedly, continue to rely on what is recognized as an imperfect biomarker (QT prolongation) as a surrogate for increased risk of ventricular pro-arrhythmia, albeit using a more effective approach of concentration–effect analysis rather than the Intersection Union Test as recommended for TET studies. It would use clinical methods similar to those used in a TET, but would do so as an addition to currently required phase I studies rather than in the context of an additional specific dedicated TET. Questions remain at present as to whether this strategy can accurately and cost-effectively replace the cost-ineffective TET for detecting drug-induced QT prolongation, but the test of such a hypothesis should be relatively straightforward.

In contrast, the proposal to replace the TET with a series of ion channel studies represents a far greater shift from the current paradigm, and would replace the use of QT interval as a biomarker with a completely different set of surrogate markers. It is unclear whether clinical evaluations, based on careful ECG assessment in phase I studies, would remain part of the new CIPA paradigm. It is true that computer modelling of *in vitro* data has enjoyed success recently [29–32]. However, the technologies involved are still evolving, and would need to be standardized, regulated and widely available before they are adopted to support sponsor and regulatory decisions. One challenge will be to reach a consensus on which specific elements should be included in the final assay suite. Not surprisingly, therefore, there is an ongoing discussion about exactly which ionic currents should be studied and in which cell type(s). A second challenge will be to validate the new suite and support its use instead of TET studies. It took years to standardize the ECG collection strategies, QT measurement methodologies and QT corrections, as well as the statistical analyses which constitute the current TET. It is not unreasonable to expect that it will likewise take time to standardize these novel technologies and the choice of which cell types should be used.

Arguments for replacing the TET with an ECG-oriented SAD/MAD study

The debate on whether, or how, to replace a TET will continue to rage in the immediate future but the protagonists of robust phase I ECG testing have advanced compelling arguments against replacing a TET exclusively with a series of preclinical tests. ECG trials performed *in vivo* in man are particularly useful because they allow us to evaluate drug effects in the very complex system of a human organism. The biomarker may be imperfect, but the system in which it is used, the clinical trial, allows for the interplay of many factors, including some which are, as yet, unknown to us. Clinical trials have surprised us when a metabolite that we did not anticipate or a previously unknown mechanism of action (often off-target) produces an unexpected result. Clinical trials let us test for effects that we do not understand or even anticipate. In contrast, relying on a small set of preclinical *in vitro* assays excludes many of the variables which are at play in living systems. Furthermore, early in drug development, when these preclinical assays would be performed, the clinical dose range of a new drug is unknown, and the human metabolites are not well characterized. In preclinical *in vitro* assays, there is a risk of completely overlooking other mechanisms of pro-arrhythmia. Although it is generally believed that direct hERG inhibition is the primary mechanism by which drugs give rise to ventricular pro-arrhythmia, there is now increasing recognition that indirect effects on ion channel trafficking may also produce TdP. Ion channels are macromolecules which are synthesized within the endoplasmic reticulum, undergo processing, migrate to the cell membrane, and undergo a life cycle ultimately leading to their degradation. Other components of the cell membrane, cytosol or extracellular matrix may interact with them and modulate their function. Patch clamp assays under very controlled conditions will not test these indirect modulators of ion channel behaviour. Furthermore, a single cell assay will not evaluate the effects of a drug on cell to cell coupling and other interactions which take place at the multicellular or systemic level. This paradigm shift to replacing a TET with a series of preclinical studies is particularly interesting since ICH E14 refers vaguely to how preclinical data may mitigate the need for conducting a TET but in practice, such a waiver has rarely, if ever, been granted. In contrast, waivers for a TET study have been granted for some drugs, based on the exclusion of a sig-

nificant QT effect in early phase clinical studies. The ICH E14 drafting group could have categorized drugs that need a TET on the basis of their hERG or IKr blocking properties (tests recommended in ICH S7B). Their decision, however, not to do so reflected their concern about reliance upon a preclinical assay for clinical decision making. This uncertainty led to the requirement to use drug-induced prolongation of the QT interval as the *in vivo* clinical biomarker to guide further drug development, regulatory decisions and when appropriate, labelling restrictions to mitigate the clinical risk of drug-induced pro-arrhythmia. It is true that ICH E14 guidance was a response to the events of the 1980s and 1990s, and made use of the scientific knowledge and technologies which were available or coming on line 10 to 15 years ago. We certainly now know more about drug-induced pro-arrhythmia than was known at that time, and the technologies for assessing the electrophysiologic effects of new drugs on a cellular and sub-cellular level have made tremendous strides. Nevertheless, it seems rather premature to assert that we fully understand all the factors which lead to drug-induced pro-arrhythmia and that we can fully predict the safety of new medications with a series of patch clamp studies and a novel software programme. It is also critical to make sure that we do not increase the rate of false positives, leading to the unnecessary termination of even more new drugs.

Building on the legacy of TET standards

Whichever of the above two strategies is adopted in an effort to replace a TET, a greater concern is the fear of risking all of one's eggs in a single basket – either robust ECG testing in phase I clinical studies or a series of preclinical ion channel studies. There is a risk of losing sight of the real concern during drug development which is whether a drug will induce a pro-arrhythmia, and not whether it will prolong QT or whether the IC_{50} for IKr block is above or below a certain threshold. A more desirable strategy for the next 5 to 10 years seems to be to investigate whether more extensive phase I electrocardiographic testing can differentiate drugs which produce slight QT prolongation and are likely pro-arrhythmic from those which produce slight QT prolongation without being pro-arrhythmic. We believe this goal is attainable by a combination of modified SAD/MAD studies, incorporating robust ECG monitoring and concentration–response modelling, as has often been reported [21, 33–36], and the use of novel preclinical biomarkers and already available models of pro-arrhythmia [14, 37–39]. Such a strategy would also allow the continued investigation of other biomarkers for the risk of TdP, such as evaluation of changes in T-wave morphology or other ECG markers.

Currently, only a properly designed TET or a positive early phase clinical study at therapeutic doses is acceptable to regulatory authorities as adequate evidence of characterization of a drug's effect on the QT prolongation, and by inference, of the risk of TdP. However, comparison of the results of population prediction of QT_c prolongation with the available TET results and evaluation of concentration–response models suggest that phase I/II studies are eminently capable of assessing a new drug's QT liability [22, 36, 40]. It is not our intention to pre-empt more scholarly deliberations on which strategy is the most appropriate to identify the clinical risk of torsadogenesis. However, given that the clinical use of a drug that affects cardiac repolarization typically relies on baseline and serial post-therapy monitoring of a patient's QT interval, it seems that a careful assessment of its potential to change the QT interval will still be required during its development. A strategy that merits further consideration is a step-wise approach, consisting of utilizing the findings from preclinical studies and QT interval evaluation and concentration–effect (QT) assessment in early phase clinical studies to exclude those molecules for which TET studies may not be required. In contrast to the current practice of accepting evidence from early phase clinical pharmacology studies only if the drug is documented to prolong the QT interval, evidence from these studies should also be equally acceptable when the drug is found to lack an effect on QT interval, thereby mitigating the need for a TET study. A TET should only be required when the preclinical and early phase clinical trials data collectively are inconclusive or ambiguous. This approach can be used until we have either a well characterized and reliable preclinical package or a robust, well characterized methodology for QT evaluation in early phase studies that can be used for completely replacing the TET.

When considering a wholesale replacement of TET with other strategies which exclude robust clinical evaluation of ECGs, the old expression, '*let's not throw out the baby with the bath water*' springs to mind. There is a wide consensus that a vast majority of TdP events are preceded by ECG evidence of QT prolongation, any disagreement being related only to a mean effect that may be a forerunner of a torsadogenic potential. The TET and the entire strategy of ECG assessment of new drugs for QT prolongation has set standards which could be applied to other, more cost-effective approaches to assessing the QT liability of a new drug and to determining its clinical risk of inducing TdP. We should seek to build upon the successes of ICH E14 and reduce its negative effects, rather than scrap the whole strategy altogether in favour of hitherto unproven *in vitro* assays. Perhaps more interesting is the observation that if robust ECG testing during phase I studies becomes the option of choice for replacing the TET, we will have gone full circle and come back to the draft strategy originally proposed by Health Canada way back in 2001!

Competing Interests

All authors have completed the Unified Competing Interest Form at http://www.icmje.org/coi_disclosure.pdf which is available on request from the corresponding author and declare no support from any organization for the submitted work. All the three authors have financial relationships with organizations that might have an interest in the submitted work. RRS was formerly the EU Topic Leader, representing the EU at ICH E14 Working Group and is now the Director of his own consultancy firm which provides services related to the conduct, analysis and interpretation of thorough QT studies and early phase clinical pharmacology studies to pharmaceutical companies. JM and RBK are currently Chief Cardiac Consultant to and paid employee as Chief Medical Officer of, respectively, eResearch Technology, Philadelphia, USA, a company which also provides services related to the conduct, analysis and interpretation of thorough QT studies and early phase clinical pharmacology studies to pharmaceutical companies. Apart from the above, the three authors declare no other relationships or activities that could appear to have influenced the submitted work.

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