Evaluation of Toxicity for Heart Failure Therapeutics
Studying Effects on the QT Interval

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One of the most feared complications in medicine is sudden death caused by drug-induced proarrhythmia. Accordingly, concerted efforts have been made to define a drug's proarrhythmic potential before regulatory approval. Monitoring for QT prolongation is one such method. Patients with heart failure represent a particularly high-risk population for torsade de pointes because of structural and electric remodeling that impair repolarization reserve. However, these patients are frequently excluded from clinical trials. Preclinical models simulate some of the electric remodeling of heart failure and form an important part of safety evaluations during early drug development. Clinical programs usually include a thorough QT study, which attempts to find a small mean change in QTc that serves as a surrogate for the risk of torsade de pointes. The impairment of repolarization reserve in heart failure goes beyond QT prolongation, however, and other clinical methods of measuring this propensity may be necessary to obtain a complete picture of a drug's arrhythmic potential.

Heart failure (HF) is a common and serious affliction. HF is a listed diagnosis in as many as 65% to 70% of hospital admissions each year in the United States.[1] The prevalence of this disease continues to increase because of to a rise in coronary artery disease and diabetes incidence, an increase in the age of the population, and a reduction in the probability of sudden cardiac death (SCD) in HF with aggressive use of implantable cardioverter-defibrillators. The net result is a larger population of patients living longer with more comorbidities, and, as a corollary, more polypharmacy. HF has been recognized as one of several clinical risk factors for drug-induced proarrythmia.[2,3] Many classes of drugs have been shown to improve all-cause mortality in HF and have revolutionized both the treatment and prognosis of this condition. Although there is a need for continued development of drug treatments for HF, we must ensure that these treatments do not increase the risk for life-threatening arrhythmias.

Assessing this risk accurately, however, has proven challenging. Although antiarrhythmic drugs are understood to have proarrhythmic potential, it has only recently been understood that noncardiac drugs also carry such risk. The withdrawal of terfenadine (Seldane) from the market in 1998 due to several cases of torsade de pointes (TdP) markedly heightened awareness that such drugs can be cardiotoxic. Since then, numerous noncardiac drugs have been withdrawn from the market because of a TdP risk, including prenylamine, cisapride, and sparfloxacin. In a large sample of patients treated between 1995 and 2003, the use of QT-prolonging drugs in the general population was associated with a significantly increased risk of SCD.[4] In patients with coronary artery disease, the use of QT-prolonging drugs confers a higher risk of SCD, especially in patients with diabetes mellitus.[5] This has led to increased oversight by regulatory bodies. Concern about proarrhythmia has become the most common reason for drug nonapproval since the turn of the century.[6] The most important predictor of TdP is QT interval prolongation, and therefore TdP and drug-induced QT prolongation have become virtually synonymous.

There appear to be 3 components that are necessary for the genesis of TdP: lengthening of the cardiac action potential duration (APD), early afterdepolarizations (EAD), and transmural dispersion of repolarization allowing for propagation of the EAD and reentry.[7] Clinical risk factors for TdP, as described by Roden, include HF, which, in many ways, is an excellent example of how 1 or more of these requisite conditions can be met.[2]

This article will discuss the cellular basis for repolarization abnormalities in HF, the preclinical assessment of TdP risk including in vitro and in vivo models, clinical assessments including the thorough QT study, ideas for refinement of the process, and finally, examples of emerging HF treatments and how their liabilities are being assessed.

Ionic and Cellular Basis for Ventricular Repolarization Abnormalities in HF

The QT interval on the body surface represents 2 sequential ventricular electric events: ventricular depolarization (activation) that is marked by the QRS complex, and ventricular repolarization that starts with the J point and extends to the end of the T wave. Although ventricular activation time is relatively constant, ventricular repolarization is influenced by a variety of pathological conditions and drugs. It is generally accepted that ventricular repolarization time is largely determined by the repolarization of M cells, which reside in the

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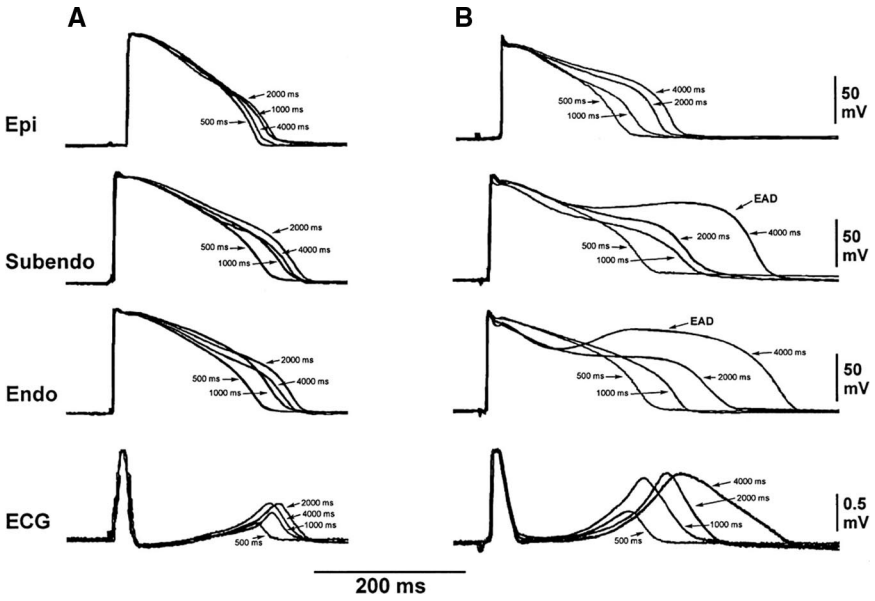

Figure 1. Transmural action potentials in the rabbit left ventricular hypertrophy renovascular model. A, Left ventricular hypertrophy (LVH) led to APD, along with EAD genesis in the subendocardium and endocardium. B, Graphic representation. Note that APD_{90} is longer at all transmural distances in the LVH model. Reprinted with permission.[17]

deep subendocardium,[8] and by M-cell electronic interaction with epicardial and endocardial layers.[9]

In HF, there are several changes at the myocyte level that tend to prolong repolarization time and facilitate reentry. This electric remodeling goes hand in hand with structural remodeling. As remodeling progresses, delayed ventricular repolarization manifests as a prolonged QT on the surface ECG. The risk of all-cause mortality in HF patients has been shown to triple in the presence of QT prolongation.[10,11]

The ionic changes that underlie ventricular repolarization abnormalities and that in turn give rise to arrhythmias in HF are complex. The most striking and consistent alteration is APD prolongation caused by the downregulation of several potassium currents responsible for repolarization. These include the inward rectifier K^+ current (I_{k1}), the transient outward K^+ current (I_{to}),[12] the slowly activating delayed rectifier K^+ current (I_{Ks}),[13] and the hERG channel mediating the rapidly activating delayed rectifier current (I_{Kr}).[14] Upregulation of the late sodium current (I_{Na}) also contributes importantly to QT prolongation and ventricular arrhythmias in HF.[15,16]

The second important component is EADs. In rabbits with HF (the renal vascular occlusion model), APD is prolonged in the subendocardium, leading to QT prolongation and the development of spontaneous EADs (Figure 1).[17] Similarly, in rabbits with HF after ligation of the left descending coronary artery, hypertrophied myocytes near the zone of infarction undergo electric remodeling in a fashion very similar to that in humans. When these animals are exposed to QT-prolonging drugs, there is an increase in spontaneous EADs attributable to impaired calcium handling eventuating in TdP.[18] Similarly, in a study using the canine AV block HF model, TdP occurred in 3 of 12 dogs, all of which had high-amplitude EADs, compared with no TdP in EAD-negative dogs.[19]

In patients with left ventricular hypertrophy and cardiomyopathy, ventricular repolarization abnormalities related to dispersion of repolarization may manifest as increased beat-to-beat QT interval variability and T-wave alternans. This may be reflected on the surface ECG as a giant T-U wave occurring after long-short intervals when repolarization is maximally heterogeneous and intracellular calcium concentrations are at their highest.[20] In the rabbit HF model, beat-to-beat QT interval variability and T-wave alternans are the consequence of heterogeneous beat-to-beat changes in action potential duration across the ventricular wall.[21]

Clearly, cardiac remodeling in HF leads to ventricular repolarization changes that render the ventricle vulnerable to the development of TdP, particularly when exposed to QT-prolonging drugs. Thus, it is critical to carefully evaluate new agents in preclinical and clinical models to understand their propensity to cause TdP.

Preclinical Assessment of Drug-Induced QT Liability: Implication of HF

Regulatory guidelines recommend a battery of preclinical tests to assess proarrhythmic liability of all new chemical entities.

The extent of QT prolongation is not the sole determinant of the TdP risk. In addition, the actual incidence of TdP for noncardiac drugs is very low, between 1 in 10 000 to 1 in 100 000 patients. Terfenadine, removed from the US market in 1998, caused 1 episode of TdP for every 28 500 prescriptions.[22] Thus, only a small subset of patients are prone to develop TdP, and these patients may do so after years of exposure to the culprit drug.[2,23] Although there may be several pathological factors that reduce ventricular repolarization reserve and predispose humans to TdP, HF is clearly one of the most important.[17,24]

Drugs that might be used in HF patients therefore undergo careful scrutiny. Several models that mimic reduced ventricular repolarization reserve seen in HF have been developed for this purpose.[18,25] Several strategies have been adopted in drug development to understand proarrhythmic potential. An early test is assessing blockade of hERG, the ionic channel targeted by most QT prolonging agents. This includes measuring relative potency, which is the concentration at which at

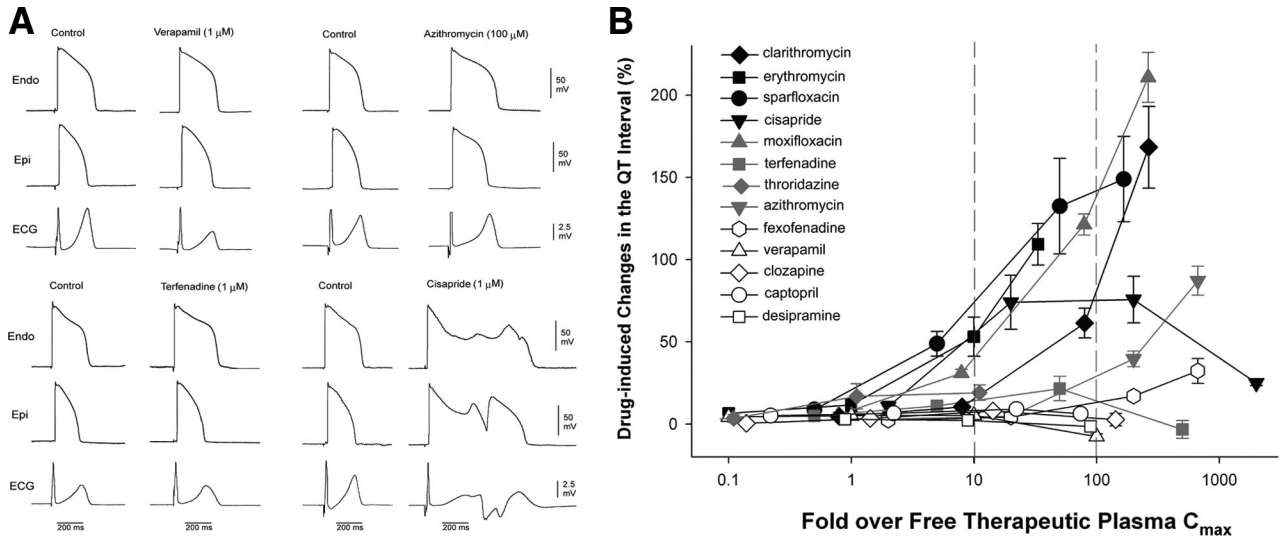

Figure 2. A, Arterially perfused rabbit left ventricular wedge preparation demonstrating prolongation of the QT interval, APD, and transmural gradient when exposed to representative drugs. B, Effect on the QT interval by a panel of known QT-prolonging drugs in increasing concentrations. Reprinted with permission from Elsevier.[30]

least 50% of the ion channel is inhibited. It is also important to understand the effects of a new drug on assorted ion channels or receptors that blunt or accentuate the drug's proarrhythmic potential. Finally, these models can help to design a drug with preferential effects on atrial repolarization currents, particularly important if the indication sought is atrial fibrillation.

Few of these models have been properly validated and therefore extrapolations to the clinical situation are hazardous. Regulators, though considering the data generated by these experiments, are likely to prefer clinical data for decision-making purposes. A major concern is that the effort to increase the sensitivity of preclinical tests using HF animal models may sacrifice the specificity of the tests, increasing the chance of false-positive outcomes.

We have recently developed an isolated arterially perfused rabbit ventricular wedge preparation that has been validated to be highly sensitive and specific with regard to TdP prediction.[26,27] Excellent predictive accuracy has been achieved in part by selecting an appropriate species and experimental preparation. The female rabbit left ventricle has a small I_{Ks}, making it particularly sensitive to QT-prolonging agents.[13] It bears a close resemblance to humans, particularly HF patients, with a reduced repolarization reserve.[28,29] This preparation also has a large ratio of QT signal over experimental noise. As shown in Figure 2, the response of the isolated arterially perfused rabbit ventricular wedge preparation is magnified, allowing discrimination of drugs with no QT effect from those with a weak effect on repolarization.[30]

Clinical Assessment of Drug-Induced QT Liability: The Thorough QT Study

The first regulatory schema for evaluating the effects of new drugs on repolarization was presented in a European Society of Cardiology (ESC) policy conference in 2000 (Figure 3).[31] The preclinical assessment of QT liability was to be followed by a number of clinical studies. The goal of the preclinical assessment was to identify compounds in a "worst case scenario," for example, in HF patients using supratherapeutic doses. Clinical phase I trials were to be performed in healthy volunteers including women who are at increased risk of TdP. Doses would be escalated with measurements of parent drug and metabolites at peak and trough, after steady-state levels of all active compounds (parent and metabolites) had been achieved. ECGs were to be obtained at baseline, at steady state, and following drug withdrawal. The ESC recommended manual QT measurements including comments on changes in T-wave morphology and U waves. The QT was to be measured in all leads for 3 to 5 beats and to be corrected for heart rate with nonlinear regression formulae including confidence intervals. QT dispersion measurement was not recommended. If the drug were judged safe in phase I and early phase II trials, at-risk groups would be enrolled, including HF patients, especially if the drug were to be used in these groups.

The International Conference on Harmonization document E14 reinforced these guidelines and established the industry standard for premarket QT assessment.[32] These guidelines recommend performing a thorough QT/QTc (TQT) study early in development. This study is required in the United States regardless of the outcomes of preclinical testing but may be waived in Europe if preclinical studies are negative.[33] Such a study is intended to be performed in healthy volunteers. Marked baseline QT prolongation, presence of risk factors for TdP (including heart failure), and concomitant use of medications known to prolong the QT interval are exclusion criteria. The threshold for regulatory concern is set at a maximal time-matched mean prolongation of QTc of 5 ms, which is derived almost exclusively from the data for terfenadine.[34] These studies should be randomized, blinded, and placebo- and positive-controlled, with either a parallel or crossover design (Figure 4). Crossover studies have the advantages of requiring fewer subjects and individual placebo subtraction, whereas parallel studies are required for the study of

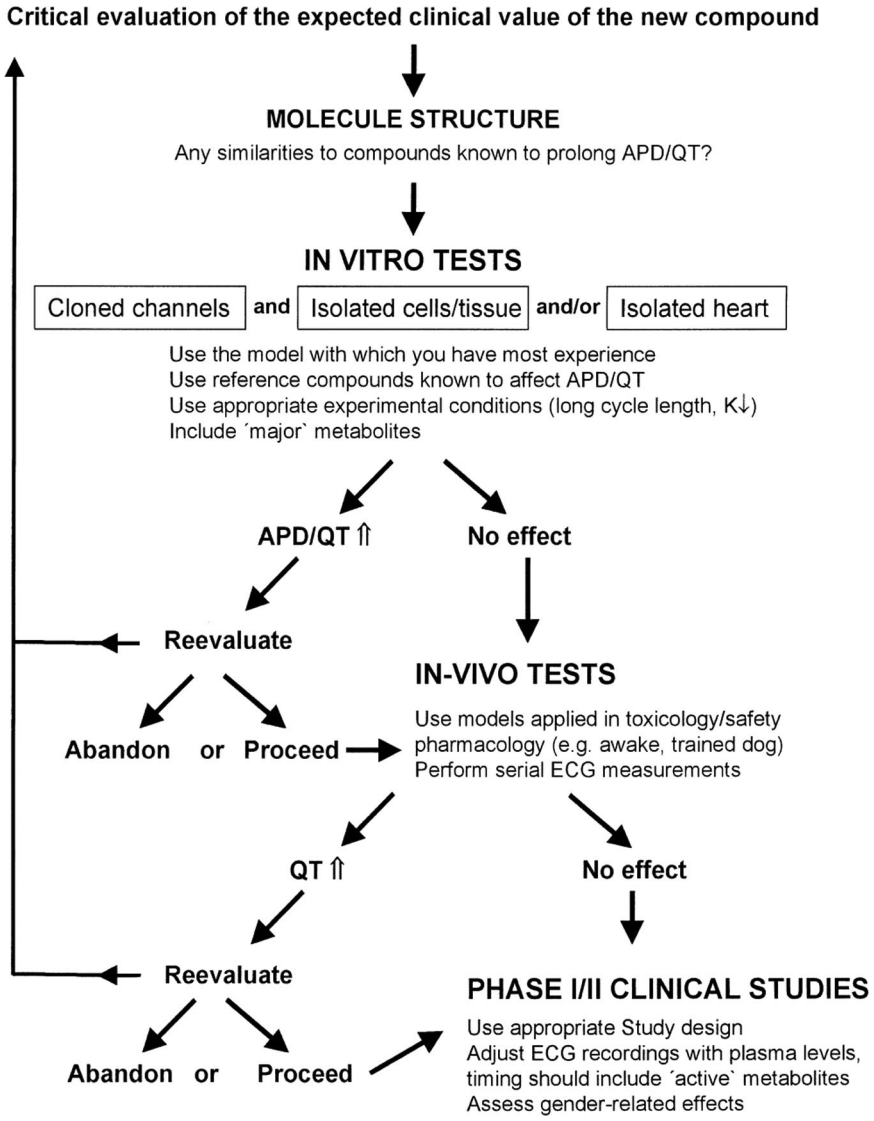

Figure 3. ESC-proposed algorithm for evaluating QT effects of drugs in development. Reprinted with permission from.[31]

drugs with longer half-lives.[35] The positive control for the TQT study is an agent known to prolong the mean QTc by at least 5 ms, usually moxifloxacin.

Currently the QT interval is analyzed using a semiautomated technique in which each interval is examined by a technician before a physician overread. Automated reading has obvious advantages in facilitating the process and reducing costs. Several systems for computerized QT analysis are in development and are undergoing proper validation.[36,37]

Dose selection is a key factor in the success of a TQT study. For drugs that are extensively metabolized, such as through the cytochrome P450 system (such as terfenadine), and particularly if the metabolite is electrophysiologically active, it may be necessary to study ECG effects under conditions of maximum inhibition or with doses that permit a replication of the maximum effect of parent and metabolite, even in patients who are organ-impaired.

The definition of a negative TQT study is one in which the single-sided 95% confidence interval for the largest time-matched placebo-subtracted mean effect of the drug on the QTc interval excludes 10 ms. There are 2 possible interpretations of "largest time-matched mean": either largest change from baseline or worst of all time points. The latter is more likely to be biased toward a positive result; therefore, the largest change from baseline is most often used.

There are no specific recommendations about which QT correction formula to use, although an individualized correction is most frequently used. ECGs should be measured by designated skilled readers at a centralized ECG laboratory. The interreader and intrareader variability should be established. U waves are to be excluded from the QT interval measurement. Significant end points include clinical adverse events such as syncope, an absolute QTc prolongation >500 ms, and changes from the baseline of >60 ms. Genotyping for subclinical LQTS when marked QT prolongation occurs is recommended though most often unrevealing.

A negative thorough QT study obviates intensive monitoring during subsequent clinical development because drugs causing less than 5-ms changes in mean QTc are unlikely to cause TdP. Customary ECG monitoring, such as obtaining a

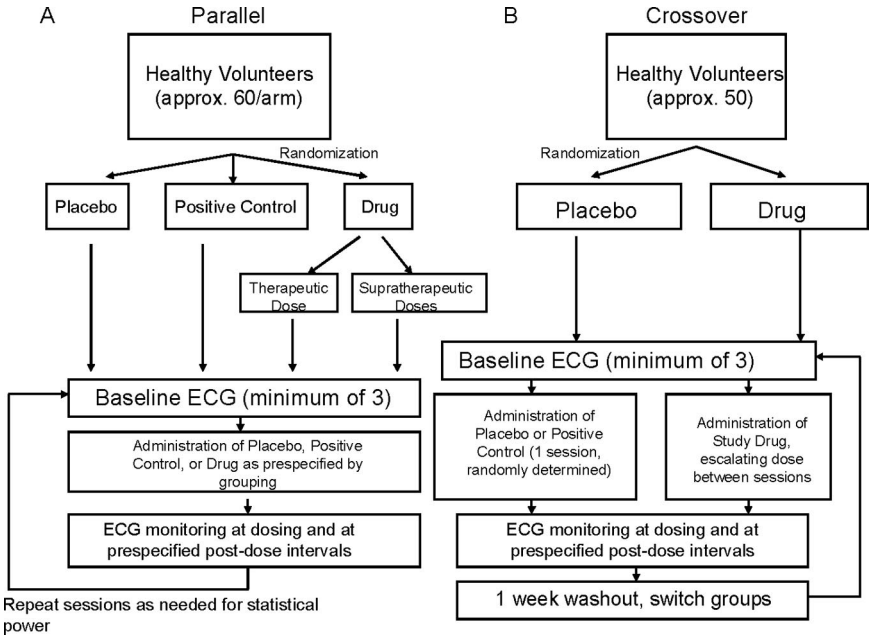

Figure 4. Schematic of representative design of thorough QT study. The parallel design (A) is used primarily for drugs with long half-lives, active metabolites, or tachyphylaxis at high doses, but the preferred method is the crossover (B). The doses used as well as the magnitude of dose escalation are determined by Phase I single ascending dose or multiple ascending dose studies. Often, thorough QT studies use only a single supratherapeutic dose arm. Statistical power increases with the number of sessions performed, but there is no fixed requirement.

single ECG at the time of dosing or only if an adverse event occurs, is the rule. Given the high sensitivity of TQT studies, it does not seem reasonable that minor ECG changes observed after a negative TQT should in and of themselves be grounds for subsequent denial of drug approval. Such changes might be indicative of a patient-specific or disease-specific effect, however, which could necessitate further study. A positive study necessitates more intensive safety monitoring, and testing of patients with additional risk factors for TdP, including those with heart failure.

Limitations of the TQT and Future Directions for Proarrhythmic Risk Assessment in HF Patients

The results of a thorough QT study can be difficult to reproduce and are not easily applicable to the HF population. Detecting a difference of 10 ms or less on a standard 12-lead ECG is challenging even for experienced readers. Neither the ESC nor the International Conference on Harmonization has recommended computerized readings, although there are new technologies in development that might make that practical.

The finding of an increased mean QT prolongation implies either potentially significant prolongation in many subjects, or a wide variation in prolongation with grossly unequal distribution of risk. Therefore, a categorical analysis is important to determine how risk is distributed and for what reason. Unfortunately, it is statistically difficult to determine a 95% confidence interval for time-matched means. Most commonly, intersection-union tests are used, but these tests tend to have lower power than TQT studies and this may bias toward a positive test result. Also, the statistical assumptions underlying intersection-union tests may be invalid in an HF population.[38]

As originally stated by the ESC, drugs that may be used in HF must be assessed for their proarrhythmic risk in a HF population. Additionally, proper correction of the QT is vital when the drug being tested affects autonomic tone, as many HF drugs do. Typical correction formulas tend overcorrect at higher heart rates, leading to a falsely prolonged QTc.[33,39] This was demonstrated in the TQT results for vardenafil and alfuzosin. Both drugs had borderline-positive TQT when the Fridericia correction formula was used but negative results with individualized heart rate correction.[40,41] This problem was also evident in the case of a new gadolinium contrast agent used for cardiac MRI, gadobutrol, which had a minimally positive thorough QT study with conventional correction but a negative study when the QT was corrected with individualized QT/R-R hysteresis.[42] Also, changes in autonomic tone may be more proarrhythmic in HF patients compared with healthy volunteers. Electric remodeling leads to an increase in steepness of APD restitution curves during increased sympathetic stimulation, which in turn leads to dynamic wave instability, further loss of repolarization reserve, and therefore arrhythmic risk.[43] This underscores the need for proper, reproducible QT correction.

In attempting to clinically establish the proarrhythmic potential of a new drug in HF patients, it would be useful to be able to assess electric stability noninvasively. The QT interval, as we have discussed, is an important parameter, particularly when markedly prolonged. The QT/R-R slope, peak QTc, number of beats with QTc >500 ms, and variance about the mean may add predictive power.[44] Other methods include heart rate variability, late potentials on signal-averaged ECG, QT dispersion, T-wave alternans, time to inscribe the second half of the T wave (T_{peak}-T_{end}), and beat-to-beat variability of repolarization.[45,46,47,48,49,50]

Although these tests have the potential to provide a more comprehensive assessment of repolarization reserve, validation is essential. A common failing of currently existing noninvasive assays of electric stability is high specificity for predicting fatal arrhythmias but low sensitivity. Conversely, preclinical models and TQT studies tend to be more sensitive at the expense of specificity. Therefore, a potential future

Table. Summary of Details Regarding Selected HF Therapeutics in Development and Their Effects on the QT Interval

Name of Drug	Class	Mechanism of Action	TQT Results	Notes
Sitaxsentan	Endothelin ET_A antagonist	Reduces pulmonary vasoconstriction, theoretical improvement in diastolic dysfunction.[52]	Negative TQT.[53]	Approved for pulmonary arterial hypertension in Canada.[53]
				Increases treadmill time on Naughton protocol for patients with HF with preserved ejection fraction. [52]
Istaroxime (PST-2744)	Luso-inotrope	Inhibits cardiac Na^+/K^+ ATPase to increase calcium availability and stimulates SERCA 2a to promote reuptake of calcium for relaxation.[54]	Shortens QT.[55]	Currently in phase III clinical trials.
Omecantiv mecarbil (CK-1827452)	Inotrope	Calcium-independent inotrope, direct activator of myosin.[56]	No clinical data.	Prolongs ejection time[57] without increasing myocardial O_2 demand or dp/dt.[58]
Levosimendan	calcium sensitizer	Binds to calcium-bound troponin C, stabilizing it and increasing half-life. Also vasodilates by opening ATP-sensitive calcium channels.[59]	Mild QTc prolongation, no proarrhythmia.[60]	Possible survival benefit vs conventional inotropes, [62,63]although not borne out in larger trials.[64]
			Increases mean APD_{50} by 9 to 17 ms and mean APD_{90} by 5 to 15 ms in healthy volunteers.[61]	More brain natriuretic peptide lowering than dobutamine.[65]
				Improves weaning from bridge-to-recovery ventricular assist device after cardiotomy.[66]
Ularitide (ANP 95–126)	Human urodilatin (ANP family) analog[67]	Increases diuresis via inhibition of cGMP in distal tubule and collecting duct.	No TQT performed (May G, MD, unpublished data, 2009).	Safety demonstrated in decompensated HF patients.[68]
				Inhibits remodeling after infarction, [69]possible synergy with PDE-5 inhibitors.[70]
Lixivaptan (OPC-21268)	Oral V2 vasopressin antagonist[71]	Blocks V2 receptors in collecting duct, enhancing free water clearance.[72]	Completed in October 2008, results pending.[73]	Related drugs conivaptan[74] and tolvaptan[75] both had negative TQT.
Naxifylline (BG9719, CVT-124)	Adenosine A_1 antagonist	Enhances diuresis by dilating renal afferent arterioles and inhibiting sodium reabsorption in the proximal and distal tubules.[76]	No published data.	Natriuresis equivalent to furosemide but without reduction in glomerular filtration rate.[77]

approach for new drugs developed for HF patients might be to follow a preclinical study with a focused clinical analysis of the drug's total effect on repolarization in HF patients. This would not necessarily obviate the need for a TQT study but might provide added assurance of safety before embarking on costly pivotal clinical trials.

HF Drugs in Development

There are several promising therapies for HF[51] currently undergoing the development process, including TQT studies. Examples are presented in the Table.[52–77] These therapies attempt to achieve benefit in HF including fluid reduction and enhanced contractility, using novel mechanisms that could reduce the tendencies to proarrhythmia. Because these drugs are in early stages of development, most of the current data come from animal models. The preclinical data are generally favorable with regard to their electrophysiological effects.[78,79]

The clinical data available for these drugs have been promising. Sitaxsentan (Thelin) had a negative TQT study and is currently approved in Canada for the treatment of pulmonary arterial hypertension.[53] This drug may eventually be used primarily in patients with heart failure with preserved ejection fraction.[54] Istaroxime underwent a TQT study that demonstrated shortening of the QT interval not associated with ventricular ectopy, ventricular fibrillation, or untoward hemodynamic effects.[54] Omecantiv mecarbil (CK-1827452) also shortened the QT interval in phase I trials[56] and was subsequently shown to be safe in patients with ischemic cardiomyopathy in phase II trials.[80] Levosimendan slightly increased QTc, with a modest increases in APD_{50} and APD_{90} in healthy volunteers and a small increase in nonsustained ventricular tachycardia in HF patients.[61,81] Its overall proarrhythmic risk is likely to be low but must be defined.

Conclusion

Preservation of safety is the prime directive in the use of all medications. As our patients age, the number of

comorbidities increases and polypharmacy becomes more common, medication toxicity will become more commonplace. There is no more serious adverse drug event than death. Nonetheless, while preserving drug safety, we should not lose sight of the importance of novel, therapies to improve patients' symptoms and quality of life. A proper evaluation of the proarrhythmic potential of new therapeutics, in particular their effects on the QT interval, is especially critical in the HF population. The mechanism of TdP has been elegantly described, but it remains hard to predict. Because HF is uniquely associated with impaired repolarization reserve, all new therapeutics targeting heart failure patients require careful testing. Although we have several promising testing modalities for predicting the risk of proarrhythmia, each must be properly validated. The availability of better safety testing will enhance the development of HF drugs and ultimately lead to better patient outcomes.

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KEY WORDS: heart failure ■ torsade de pointes ■ drugs ■ ion channels ■ electrocardiography

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