

# Drug induced QT prolongation

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## Abstract

*The drug-induced QT prolongation predisposes to development of torsades de pointes (TdP) ventricular tachycardia and sudden death. The association between specific drug and development of TdP is difficult to document, therefore, QT prolongation is considered as a surrogate marker of the proarrhythmia risk. Most of the drugs prolong QT interval usually by blocking the potassium  $I_{Kr}$  current or altering trafficking of proteins forming the channel. Improved understanding of ion channel structure and kinetics and its role in repolarization has tremendous impact on understanding of the mechanisms of drug-induced QT prolongation and TdP. Proarrhythmia caused by a QT-prolonging drug occurs infrequently, and usually multiple factors need to operate to precipitate such an event including a combination of two or more drugs affecting the same pathway, hypokalemia, and possibly genetic predisposition. ECG provides unique opportunity to ensure safety of administered therapy. QT measurement is the most routine approach to a drug safety monitoring, however, there are many challenges related to methodology of measurements, accuracy of measurements, or optimal heart rate correction. Since drugs affecting repolarization not only prolong QT but also they alter T wave morphology, novel computerized methods quantifying these changes are being developed to assist physicians and drug manufacturers in monitoring safety of the drugs. The response of a patient to a drug is very individual and therefore an individualized system of drug administration and monitoring needs to be developed, which takes into account baseline QTc duration and its changes after a drug was introduced. (Cardiol J 2007; 14: 523–533)*

**Key words:** drug-induced QT prolongation, QT interval, torsade de pointes, long QT syndrome

## Introduction

A prolonged QT interval predisposes to the development of ventricular tachyarrhythmias such as torsades de pointes (TdP) and ventricular fibrillation, which could cause syncope, cardiac arrest,

or sudden cardiac death [1–4]. Drug-induced QT prolongation and TdP has been recognized as a side effect of many commonly used medications. The association between specific drug and development of TdP is difficult to document, therefore, QT prolongation is considered as a surrogate marker of the proarrhythmia risk. Some examples of QT-prolonging drugs are listed in Table 1 whereas an up-to-date information can be found at the website [www.qtdrugs.org](http://www.qtdrugs.org) supported by The Critical Path Institute and University of Arizona [5]. More single and combination drugs are being used as documented by 2.8 billion prescriptions filled in the US in the year 2000, averaging 10 prescription per every person in the United States [6]. The increasing incidence of polypharmacy in current clinical practice causes a need for further attention to side

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**Table 1.** Drugs that prolong the QT interval (for more complete listing please visit [www.qtdrugs.org](http://www.qtdrugs.org)).

Category	Drugs
Antihistamines	Astemizole, terfenadine
Anti-infectives	Amantadine, clarithromycin, chloroquine, erythromycin, grepafloxacin, moxifloxacin, pentamidine, sparfloxacin, trimethoprim-sulfamethoxazole
Antineoplastics	Tamoxifen
Antiarrhythmics	Quinidine, sotalol, procainamide, amiodarone, bretylium, disopyramide, flecainide, ibutilide, moricizine, tocainide, dofetilide
Antilipemic agents	Probucol
Calcium channel blockers	Bepridil
Diuretics	Indapamide
Gastrointestinal agents	Cisapride
Hormones	Fludrocortisone, vasopressin
Antidepressants	Amiripytyline, amoxapine, clomipramine, imipramine, nortriptyline, protriptyline
Antipsychotic	Chlorpromazine, haloperidol, perphenazine, quetiapine, risperidone, sertindole, thioridazine, ziprasidone, doxepin

effects of drugs and their interactions, possibly leading to adverse fatal events. Adverse drug reactions are responsible for significant morbidity and mortality, possibly accounting for up to an estimated 100,000 deaths annually [7, 8].

Cases of life-threatening ventricular tachyarrhythmias and sudden death, associated with prescription drugs, have been reported since the 1960's, however this association was broadly recognized in the 1980's [9–13]. The first major series of quinidine-induced sudden deaths and subsequently the results of the CAST and SWORD trials brought further attention to the proarrhythmic effects of antiarrhythmic drugs [14]. In the early 1990's, the adverse effects of terfenadine (an antihistamine drug) brought much attention to the possibility of non-cardiac drugs being associated with torsade de pointes and sudden cardiac death [15]. The medical community and regulatory agencies (Food and Drug Administration; FDA in the USA) became more sensitive to the possibility that drugs causing QT prolongation might increase the risk of sudden death. Ultimately, terfenadine was withdrawn from the US market in 1998 after a reported 350 deaths attributed to the drug. Table 2 shows other drugs on which subsequent regulatory action was taken. This increasing awareness of drug-induced QT prolongation in the 1990's was also stemming from tremendous progress in research focused on the genetic background and mechanisms underlying congenital long QT syndrome (LQTS).

The magnitude of the problem related to drug-induced QT prolongation and sudden death might still be underappreciated. A recent study by De Bruin et al. [16] evaluated the associations between

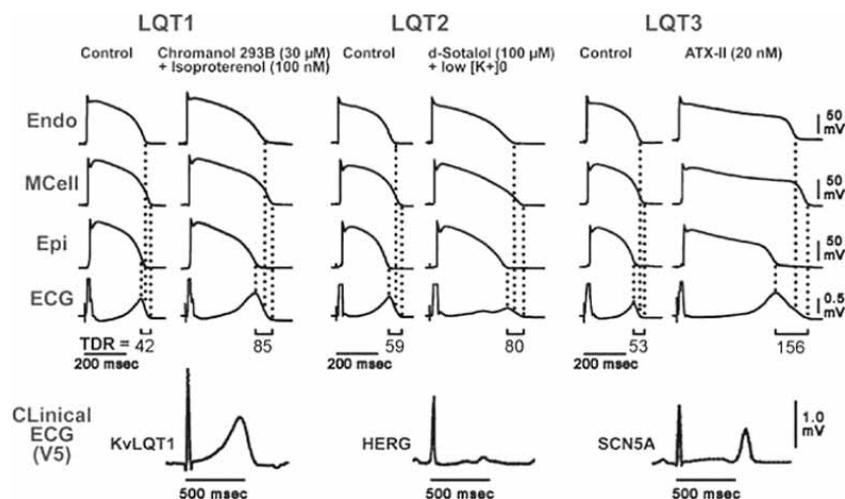
**Table 2.** Medications withdrawn due to torsades de pointes.

Drug	Class	Date withdrawn
Terfenadine	Antihistamine	1998
Sertindole	Antipsychotic	1998
Astemizole	Antihistamine	1999
Grepafloxacin	Antibiotic	1999
Cisapride	GI Prokinetic	2000

cardiac arrest and the number and dose of non-cardiac drugs known to have QT prolonging effect. Patients taking such drugs had a 2-fold increase in the risk of sudden death and this risk further increased with higher doses of the drug and with increased number of drugs. This study emphasizes the clinical importance of drug-induced arrhythmias especially in the setting of underlying cardiovascular disorders as well as the possible interaction of several drugs frequently taken without knowledge of their mutual impact.

### Lessons from congenital forms of long QT syndrome

The QT interval on an ECG is a reflection of electrical activity of the myocardium driven by the multiplicity of ion currents flowing across myocardial cell membranes through ion channels. During the last decade mutations in different genes encoding sodium and potassium ion channels have been found to cause the congenital LQTS, a familial



**Figure 1.** Transmembrane action potentials and transmural electrocardiograms in control and LQT1, LQT2, and LQT3 models of LQTS (arterially perfused canine left ventricular wedge preparations), and clinical ECG (lead V5) of patients with LQT1 (KvLQT1 defect), LQT2 (HERG defect), and LQT3 (SCN5A defect) syndromes. Isoproterenol plus chromanol 293B, an IKs blocker, d-sotalol plus low K<sup>+</sup>, and ATX-II, an agent that slows inactivation of late I<sub>Na</sub>, are used to mimic the LQT1, LQT2, and LQT3 syndromes, respectively; ECG — electrocardiogram; Endo — endocardial region; Epi — epicardial region; M — midmyocardial (from reference 20 with permission).

disorder characterized by QT prolongation and a propensity to ventricular tachyarrhythmias (usually torsades de pointes) frequently leading to sudden death at a young age. Identification of specific ion channel abnormalities causing QT prolongation in LQTS has increased our understanding of mechanisms related to myocardial electrophysiology and cardiac arrhythmias [4, 17, 18]. QT prolongation in LQTS could be caused by a decrease outflow of potassium ions (LQT1 — mutations of KCNQ1 gene, LQT5 — mutations of minK gene, both encoding the potassium channel for the I<sub>Ks</sub> current; LQT2 — mutations of HERG gene, LQT6 — mutations of MiRP1, both encoding the potassium channel for I<sub>Kr</sub> current) or by an increased inflow of sodium ions (LQT3 — mutations of the SCN5A sodium channel gene). Other forms of LQTS are very rare and they represent few disorders accompanied by QT prolongation, but importantly they confirm the mechanistic involvement of the ion channels and related proteins. The function of the rapidly activating delayed rectifier potassium current (I<sub>Kr</sub>), coded by the HERG gene, is most frequently affected by drugs inducing QT prolongation. However, not all medications that block I<sub>Kr</sub> are associated with TdP, which means that I<sub>Kr</sub> blockade and QT prolongation might not be sufficient to trigger TdP. QT prolongation must be accompanied by a significant increase in transmural dispersion of repolarization to create conditions suitable for the development of TdP. Calcium channel blockade by drugs may also cause QT prolon-

gation and lead to TdP, therefore compounds affecting those pathways must be considered as potentially proarrhythmic. There is also evidence for involvement of other ion channels (including cardiac sodium and chloride channels) in drug-induced cases of TdP. However, the majority of drugs rarely act on just one specific channel and the concomitant effect on different channels might ultimately govern lower or higher likelihood of drug-induced QT prolongation and TdP.

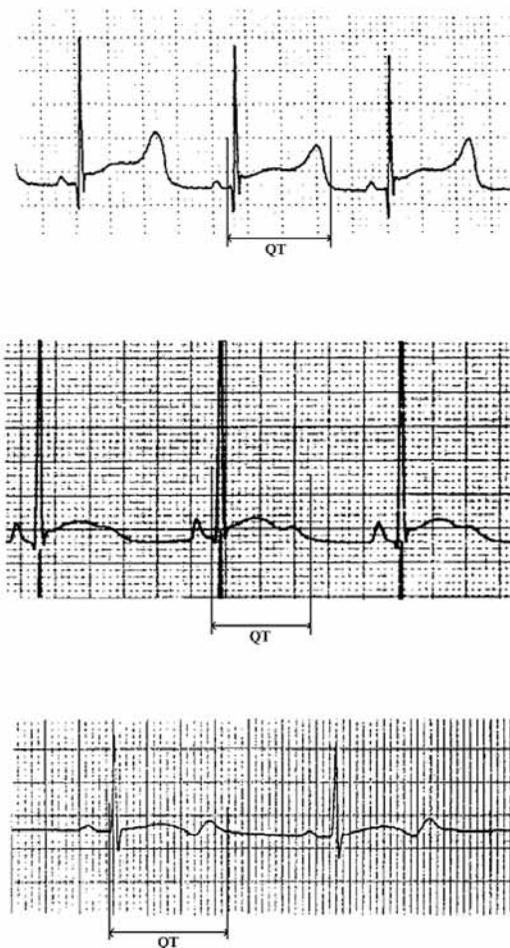
There are significant differences in repolarization in the various layers of the myocardium, with the epicardial cells having the shortest action potential duration, endocardial cells having an intermediate duration, and M cells having the longest action potential duration [19, 20]. QT duration on ECG represents the longest repolarization in the M cell zone. This physiologic transmural dispersion of repolarization usually does not lead to TdP. However, proarrhythmic states may arise as a result of specific gene mutations or actions of medications causing selective action potential prolongation in certain areas of the heart (usually M cells) that lead to increased transmural repolarization gradients (Fig. 1) [20]. This increased transmural gradient may contribute to reentrant arrhythmias leading to TdP. It is worth stressing that not all drugs prolonging repolarization cause TdP. For example, amiodarone is known to prolong QT duration, but since this drug is not increasing transmural heterogeneity of

repolarization (or it might decrease it), TdP is not observed in patients taking this drug. Similarly, novel compound ranolazine may increase QT duration but simultaneously decreases heterogeneity of repolarization. Interestingly both of these drugs are mild calcium and sodium channel blockers, which might contribute to a decreased propensity to proarrhythmias [21].

Recent progress in understanding of ion channel structure and function has provided evidence for the mechanisms associated with HERG channel and IKr current abnormalities. Numerous medications cause QT prolongation by blocking I<sub>Kr</sub> due to their binding affinity to sites within the HERG channel cavity, some other may cause abnormal trafficking of proteins forming the channel from inside the cell towards the cellular membrane. Abnormal trafficking of channel proteins may result in a decreased number of channels in cellular membrane or expression of dysfunctional channels [22, 23]. Some of the proteins do not reach the membrane at all, and some reach them as imperfect, defective proteins that are not fully functional, therefore unable to pass the expected number of potassium ions through the pore of the channel. LQT2 patients as well as patients who never had a LQTS diagnosed but might have genetic polymorphism of HERG protein are particularly prone to developing QT prolongation due to drugs blocking this channel. Other individuals with normal function and structure of the channel who develop drug-induced QT prolongation might have affinity to experience an entrapment of the drug molecule within the pore of the channel causing decreased outward potassium current.

### QT Interval as a measure of ventricular repolarization

The QT interval is considered a practical measure of repolarization duration that could be obtained from routine ECG recordings. Despite this presumed simplicity, QT measurement remains a challenge both for clinicians and for specialized academic or commercial ECG core labs. Challenges relate to number of factors, but the most frequent difficulties consist of delineating the end of T wave when the T wave is flat, bifid, biphasic or overlapping on a U wave (Fig. 2) [24]. Identifying the end of the T wave and measurement of QT may lead to quite significant differences based on experience of the reader, as it was shown by Viskin et al. [25] who demonstrated that only about 40% of internists and 70% of cardiologists



**Figure 2.** Examples of complex repolarization patterns with identification of QT intervals (from reference 24 with permission).

were able to measure it properly in comparison to measurements done by a group of experts.

Clinicians rely on the QT interval measured usually in one lead (frequently limb lead II) of the standard 12-lead ECG, however, the time measured from the earliest Q wave onset in any lead to the latest offset of T wave in any lead is the most reliable reflection of repolarization duration in the myocardium. On any single standard 12-lead ECG, there may be differences in the QT interval in separate leads, referred to as QT dispersion [26]. QT dispersion is rarely used in the clinical arena due to its time-consuming nature, conceptual and methodological limitations, and poor reproducibility during manual measurements [26]. QT dispersion measurements should not be used as a standard tool in clinical practice or drug studies.

Evaluating the QT interval on serial ECGs (e.g., off and on drug) requires using the same leads to be compared between different ECG tracings. Since QT duration changes with heart rate, usually the

**Table 3.** QTc values by age and gender [34].

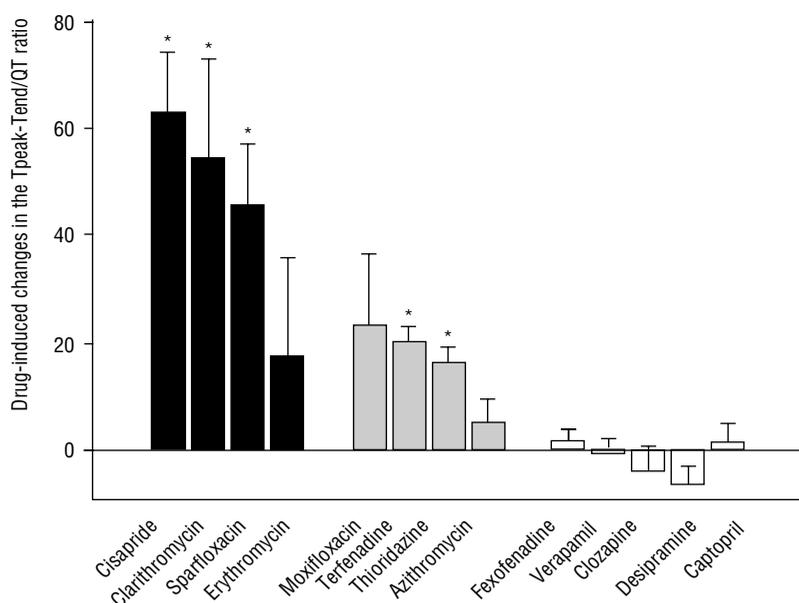
QTc value [s]	Children (1–15 years)	Men	Women
Normal	< 0.44	< 0.43	< 0.45
Borderline	0.44–0.46	0.43–0.45	0.45–0.46
Prolonged	> 0.46	> 0.45	> 0.46

corrected QT (QTc) interval is computed. Many methods have been developed to correct the QT duration for heart rate (Bazett [27], Fridericia [28], Framingham [29], Hodges et al. [30], Rautaharju et al. [31], and Karjalainen et al. [32]), but by far the most commonly used is the formula developed by Bazett where  $QTc = QT/(RR^{1/2})$ . Usually the RR interval preceding the measured QT is used for this calculation, but the mean RR intervals from 3–5 consecutive beats may be averaged when there is an apparent sinus (or non-sinus) arrhythmia. Since most of ECG machines print heart rate for a 10-second period of recording, it is very useful to consider printed heart rate and convert it to mean RR interval for a given ECG, instead of using just one or few preceding beats. Correction formulae aim to adjust the QT interval to conditions seen during a heart rate of 60 beats per minute. This calculation will suffice for most clinical purposes since patients often have a resting heart rate in the range of 55–75 beats per minute. However, the Bazett's formula becomes less accurate underestimating repolarization duration at slow heart rates and overestimating at fast heart rates. Fridericia's formula performs better than Bazett's especially at faster heart rates and it is used most frequently in the drug approval process. Both Bazett's and Fridericia's formulae are exponential, trying to reflect the curvilinear QT-RR relationship observed in a wide range of heart rates. However, in the range of heart rate between 55–85 beats per minute the pattern of QT-RR relationship is frequently linear. This is why some linear formulae like the Framingham [29] equation seem to work quite well. Also, the formula by Rautaharju [31] is highly recommended especially when used with proper adjustment for female or male gender.

Another approach to deal with QT duration while avoiding mathematical heart rate corrections is to compare absolute QT duration at similar heart rates (so called RR bin method) [33]. This method is particularly useful when a long-term holter or bedside monitoring ECGs are available with sufficient number of beats spanning a wide range of heart rates.

Normal values of the QT interval are sex- and age-dependent with women and children having longer QTc duration than men (Table 3) [34]. These values are presented for Bazett's formula, which is the most popular heart rate correction used in clinical practice. It is worth stressing that normal values will be somewhat different when using other heart rate correction formulae. A different density of potassium ion channels in male *vs.* female myocardium, differential effects of estrogens and androgens on the QT interval, as well as heart rate seem to underlie this sex- and age-dependency of QT duration. It is worth emphasizing that phenotype-genotype correlations in LQTS patients indicate that LQTS carriers could have QTc as low as 0.42 s, therefore making the borderline category broader than previously expected [4, 18]. Bradycardia may especially lead to an underestimation of QT duration and simultaneously bradycardia is known to predispose to TdP.

There is no universal threshold for identifying significant drug-induced QTc prolongation, and each drug has to be analyzed on an individual basis. There is an agreement that a QTc prolongation by > 30 ms should raise concerns, and with greater concern when the QTc exceeds > 60 ms, especially if the QTc prolongs beyond 500 ms [35]. The analysis of the magnitude of QTc prolongation from baseline by a drug should be paralleled by evaluating the absolute value of the prolonged QTc. Again, there is no universal threshold but reported cases of drug-induced TdP indicate that almost all of them do occur in subjects with QTc > 500 ms. These observations are in agreement with data from congenital LQTS studies also showing that QTc > 500 ms is associated with a substantial increase in the risk of cardiac events [1–4]. The LQTS experience also indicates that the risk of cardiac events raises exponentially with QTc prolongation: for every 10ms increase in QTc there is a 5% increase in the risk of arrhythmic events [1]. A patient with QTc = 500 ms will have a 34% higher chance of developing arrhythmia than a subject with QTc = 440 ms ( $1.05^6 = 1.34$ ). Data from published reports on drug-induced TdP indicate that the majority of patients in whom ECG data were available had QTc in the



**Figure 3.** Maximal drug-induced change in Tpeak-Tend/QT ratio at concentrations < 100 fold of their free therapeutic plasma concentration. The black bars represent the compounds that resulted in significant QT prolongation accompanied by the development of EAD, R-on-T extrasystoles and TdP; the gray bars represent the compounds that led to a significant increase in the QT interval but without EAD and EAD-dependent phenomena; and the blank bars represent the negative compounds. The symbol of \* indicates  $p < 0.05$  when compared with the control value of the compound.

range of 500–600 ms [11, 13], confirming observations from the congenital LQTS and corresponding to current regulatory recommendations.

### T wave morphology

Observations from ECG analyses in patients with congenital LQTS demonstrated that specific genetic forms of LQTS might be associated with distinctive T wave morphology [36]. LQT1, associated with a loss of function of the  $I_{Ks}$  current, is usually manifested by a broad based T wave. LQT2, associated with a loss of function in the  $I_{Kr}$  current, frequently features low amplitude and notched T waves. LQT3, associated with a gain of function of the  $I_{Na}$  current, is manifested by remote peaked T waves. These clinical findings were subsequently confirmed in the experimental setting of drug-induced forms of LQT1 produced by chromanol, LQT2 by D-Sotalol, and LQT3 by ATXII with a differential ECG recorded from the surface of canine perfused wedge preparations [20]. These experiments also documented the presence and importance of transmural dispersion of action potential duration for precipitating reentry ventricular tachyarrhythmias (Fig. 1). Since the peak of the recorded T wave coincided with the end of repolarization in the

epicardium and the end of the T wave with the end of repolarization in the M cell zone, measurement of the Tpeak–Tend duration and its ratio to QT interval was proposed to reflect transmural dispersion, at least in the experimental setting. As recently demonstrated by Liu et al. [37] this approach identified extremely effectively in laboratory conditions drugs prone to induce TdP. Figure 3 shows drug-induced changes in the Tpeak-Tend/QT ratio for drugs known to cause QT prolongation and TdP in comparison to drugs with no such effect. These findings provide the foundation for applying T wave morphology for identifying patients prone to developing TdP.

There are conflicting results regarding the predictive value of Tpeak–Tend in the clinical setting. The Tpeak–Tend duration recorded from body surface ECG is not yet proven to measure heterogeneity of repolarization since the surface ECG is reflecting a multitude of currents in the whole myocardium not just localized differences in duration of repolarization. Recent studies support Tpeak–Tend interval as an index of transmural dispersion and vulnerability. Yamaguchi et al. [38] observed that that Tpeak–Tend is more effective than QTc as a predictor of TdP in patients with acquired LQTS. In patients with hypertrophic cardiomyopathy, Shimizu et al. [39] demonstrated that Tpeak–Tend predicts sudden

cardiac death. More studies are needed evaluating the association between T<sub>peak</sub>–T<sub>end</sub> duration and cardiac events in various patient populations.

T wave morphology is affected by drugs and as frequently seen the T wave becomes flatter and broader (Fig. 1), and these visual characteristics could be quantified by computerized methods in digital or digitized ECGs [40, 41]. Computerized ECG parameters reflecting drug-induced changes in repolarization include T wave amplitude, slopes of left and right arms of the T wave, early and late duration of T wave components as well as notching. In addition, the analyses of T wave loop morphology might provide additional information regarding the presence of baseline or drug-induced alterations that might predispose to TdP. These novel computerized methods might replace or at least complement standard QT measurements methods both in a drug testing setting as well as for clinical cardiac monitoring when evaluating safety of administered drugs.

#### Drug-induced torsades de pointes: Multiple hit hypothesis

Frequently-prescribed drugs including erythromycin, tamoxifen, or haloperidol affect I<sub>Kr</sub> kinetics, however, they rarely cause QT prolongation and life-threatening arrhythmias. Susceptibility to drug-induced QT prolongation and TdP is multifactorial and a combination of several factors is needed for arrhythmia to occur (Table 4). Most likely genetic variations (not obligatory mutations causing LQTS) in genes encoding the function of ion channels operate as a key factor underlying susceptibility to drug-induced QT prolongation and TdP [42, 43]. Variations (polymorphisms) in genes encoding ion channels may cause an increased sensitivity of these

**Table 4.** Factors associated with increased risk of QT prolongation and torsades de pointes.

Prolonged QTc
Female sex
Advanced age
Bradycardia
Hypokalemia
Hypomagnesemia
Congestive heart failure (low EF)
Cardiac arrhythmias
Combinations of drugs (ion channel blockers, cytochrome P450 enzymes inhibitors)
Genetic polymorphisms of gene coding cardiac ion channels or enzymes in liver metabolising drugs

channels to drugs blocking I<sub>Kr</sub>. Recent studies focused on the associations between genetic polymorphisms and QT duration provided proof of the concept of potential importance of genetic predisposition to QT prolongation in the general population. The KORA study [44] indicated that NOS1AP polymorphism could be associated with a 7-millisecond average increase in QT duration. The Framingham study [45] identified a 3-millisecond difference associated with another yet underinvestigated genetic variation in the KVN2 gene. It is worth stressing that terfenadine, which was withdrawn from the market based on a series of sudden deaths, caused a 6-millisecond increase in QT duration on average. Therefore, the range of genetically determined variation in general population is comparable to a threshold used by the FDA for drug approval.

Polymorphisms in genes encoding enzymes metabolizing drugs may increase serum levels of drugs to excessive levels blocking the channel [42]. Borderline prolonged QT duration might be the phenotypic expression of such polymorphisms and therefore it is worth paying attention to a baseline ECG when prescribing drugs that could block I<sub>Kr</sub> or could interfere with metabolism of drugs blocking potassium currents. The field of pharmacogenomics is still in its infancy but there is growing evidence that genetic make-up might be critical for drug-induced QT prolongation.

Women account for 70% of cases of drug-induced QT prolongation and TdP indicating that sex-related differences in repolarization duration might predispose women to proarrhythmias [20]. Older age and pre-existing heart disease (contributing to downregulation of potassium channels) are additional factors increasing susceptibility to QT prolongation and proarrhythmia. Bradycardia, whether spontaneous or drug-induced, also contributes to a proarrhythmic response due to an increased heterogeneity of repolarization during slow heart rates. Electrolyte abnormalities including hypokalemia and hypomagnesemia might also predispose to QT prolongation and TdP.

Concomitant use of several drugs sharing the same metabolic pathway, such as the major cytochrome P450 (CYP) enzyme systems, is likely to augment individual drug levels and may increase the risk of arrhythmias beyond that seen when the medications are used alone [46]. Drugs including terfenadine and astemizol were removed from the market mainly because when prescribed with P450 inhibitors like ketoconazole or macrolide antibiotics they may result in QT prolongation and fatal arrhythmias. The use of two or more I<sub>Kr</sub> blockers simultaneously (e.g., erythromycin and pimozide)

**Table 5.** QT and torsades de pointes safety steps in drug development process.

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<i>In vitro</i> screening of the drug and its metabolite for effects on ion channels (IKr) and action potential duration
Screening of the drug and its metabolites for altered repolarization and proarrhythmia in animal studies
Clinical phase I/II studies with protocols incorporating arrhythmia and QT monitoring
Thorough QT studies (if needed)
Clinical studies/trials evaluating risk-benefit ratio of the drug
Postmarketing studies detecting risk of cardiac events

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may also lead to substantial QT prolongation and subsequent arrhythmias.

The multiple hit hypothesis emphasizes the fact that rarely one of the above factors is sufficient to cause drug-induced QT prolongation. Usually, a combination of several above mentioned factors must coincide to precipitate drug-induced TdP. Again, QT prolongation is a precipitating factor when it is accompanied by transmural dispersion of repolarization predisposing to reentry arrhythmias. Unfortunately there are no proven clinical ECG methods to evaluate the magnitude of such heterogeneity. QT dispersion failed to serve as such a marker. Based on ECGs from perfused wedge preparations, there is emerging evidence that T wave morphology and Tpeak–Tend duration might provide clinically useful information regarding heterogeneity of repolarization in the myocardium and propensity to TdP.

### Improving safety of administering drugs

The response of a patient to a drug is very individual and therefore an individualized system of drug administration and monitoring needs to be developed, which takes into account baseline QTc duration and its changes after a drug is introduced. Pharmacogenomics is a promising field, however, its clinical application is still a decade or two away. Therefore, current efforts need to focus on clinical evaluation and the ECG as a diagnostic and monitoring tool available to every physician. Since drug-induced QT prolongation and TdP are more likely to occur in prone individuals (Table 5), patients need to be evaluated regarding baseline probability of developing drug-induced arrhythmia. Young healthy patients occasionally taking erythromycin are very unlikely to develop QT prolongation and TdP. However, the same erythromycin given to a 70-year old female with moderate heart failure taking diuretics (thus with risk of hypokalemia) and taking an antipsychotic drug (with some QT prolonging effect) might lead to an unfortunate combination of factors leading to proarrhythmia and sudden death. The first

recommendation is to determine pre-treatment probability of such incident based on known clinical factors (Table 3). Secondly, a baseline ECG needs to be recorded to determine whether the patient does not present with baseline QT prolongation which could be related to genetic predisposition, underlying disease process, or drugs currently being taken. QTc should be evaluated based on manual measurements, not relying on, but also not neglecting automatic printouts of QTc by ECG machines. ECGs should be repeated in a period reflecting maximum plasma concentrations of the drug and the QT should be measured using the same methodology as it was done for baseline ECGs. In case of significant QTc prolongation by 60 ms or above 500 ms, treatment should be stopped or the combination of drugs modified to diminish the risk of cardiac events. The proposed model is not routinely exercised with exception for some prespecified conditions and drugs (for example in atrial fibrillation patients receiving dofetilide) but would most likely result in a significant decrease of sudden death cases, otherwise attributed to underlying diseases and older age. Large studies are needed to determine the effectiveness of active ECG monitoring of prone patients taking cardiac and non-cardiac QT prolonging drugs.

### Drug testing

In parallel to individualized safety measures, regulatory agencies and pharmaceutical companies are increasingly sensitive to ensure safety of existing and new compounds entering the market (Table 6) [47–50]. Postmarketing studies brought to attention drug-induced cases of sudden death and they remain (together with phase III clinical trials) an important source of information regarding the safety of a given drug. However, both pharmaceutical companies and regulatory agencies are eager to determine the potential for QT prolonging or torsadogenic properties of a drug at an early stage of its development. Starting with the preclinical stage of investigations, the effects of a drug on  $I_{Kr}$  currents *in vitro* are tested with and without metabolic

**Table 6.** Clinical (bedside) approach to improving safety of administered drugs.

Evaluate baseline probability of developing drug-induced arrhythmia by considering factors predisposing to QT prolongation and TdP (age, gender, comorbidities, drug interactions)
Record baseline ECG to measure QTc
Repeat ECG and measure QTc at the time point reflecting maximum and/or steady state plasma concentrations of the drug
In case of significant QTc prolongation by 60 ms from baseline or if QTc is above 500 ms, treatment should be stopped or the combination of drugs modified to diminish the risk of cardiac events

inhibitors, and next in laboratory animals where measuring QT is possible. Phase I and phase II clinical studies are the next important sources of data regarding the effect of the tested drug on QT duration, heart rate, and T wave morphology. In the case of the majority of compounds these tests do not reveal significant drug-induced repolarization changes and drugs can proceed to further phases of development and approval. However, a number of drugs might have some QT prolonging properties and depending on the magnitude of effects and the risk-benefit ratio, the drugs might require stopping the development or further testing in a so called Thorough QT Study. The Thorough QT Study consists of careful monitoring of ECG parameters during administration of a tested drug (timing of ECG follows dynamics of plasma concentration) and during administration of moxifloxacin, an antibiotic with known QT prolonging effect considered as positive control (to validate the ability of the ECG core lab to detect the expected repolarization changes). Drugs with QT prolongation showing upper confidence intervals below 10 ms do not raise concerns regarding their QT-related safety whereas drugs causing QT prolongation exceeding this threshold might require additional safety measures during the next phases of development, possibly requiring specific warning labeling about the QT prolonging effect, or may not be recommended for entering the market.

### Summary

In conclusion, the cardiac safety of existing and novel drugs is of growing concern for patients, physicians, health service systems, as well as drug manufacturers. Improved understanding of mechanisms through which various medications might cause abnormalities in repolarization with consequent susceptibility to ventricular arrhythmias helps develop safer drugs, provides a foundation for more robust ECG monitoring, and leads to safer utilization of new compounds. Novel computerized approaches for monitoring drug safety aim to provide

more sensitive monitoring tools for early detection of repolarization changes. There is tremendous need for broader clinical use of safety precautions when administering drugs and their combinations to individual patients. Educating patients and physicians as well as frequent implementation of ECG monitoring might decrease beyond expectancies the risk of sudden death in the general population.

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